Supporting information for:

Doxorubicin and Aclarubicin: Shuffling Anthracycline Glycans for Improved Anti-Cancer Agents

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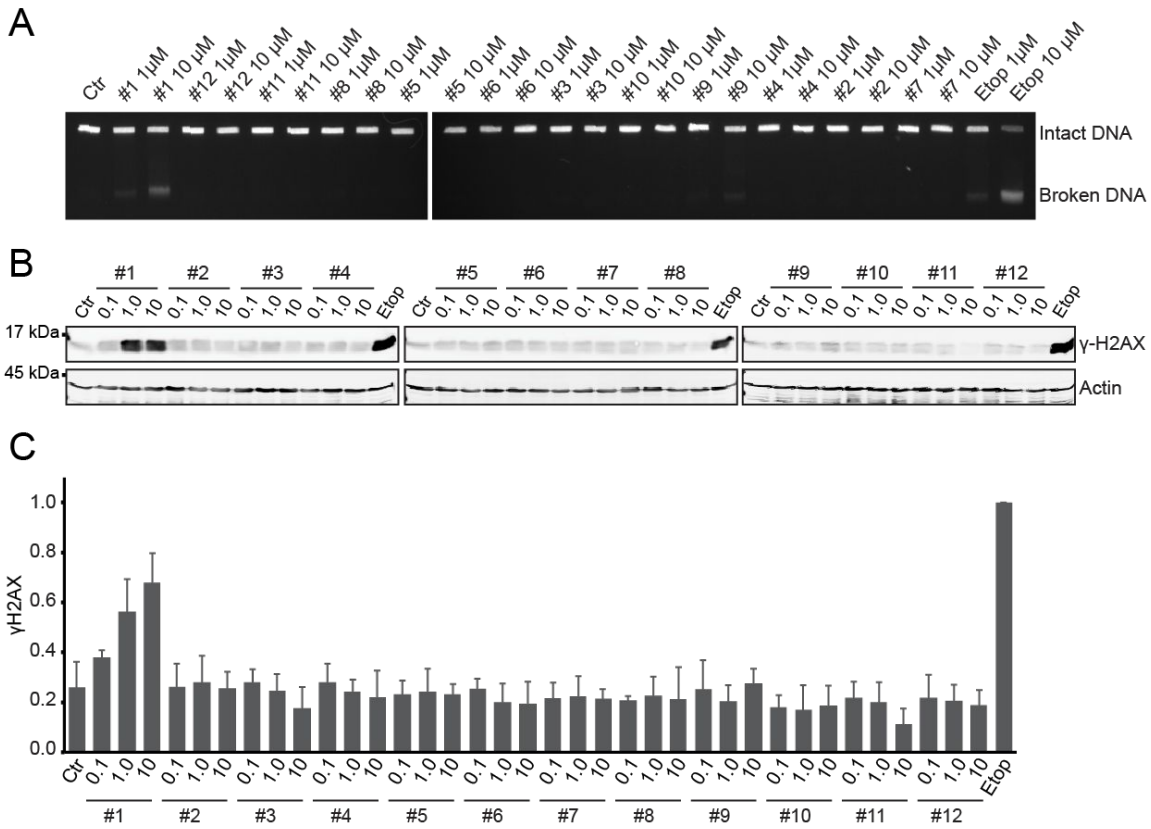
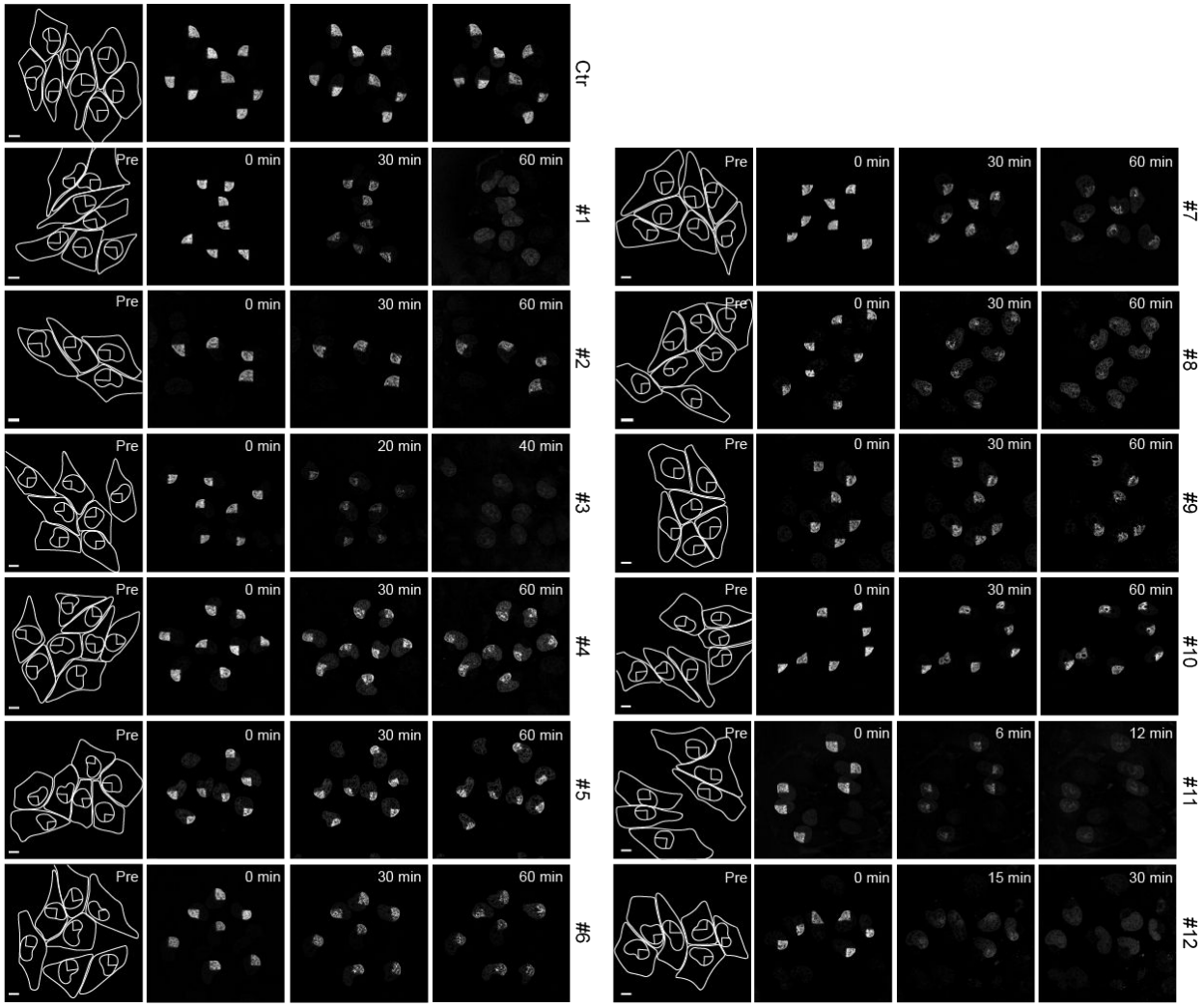


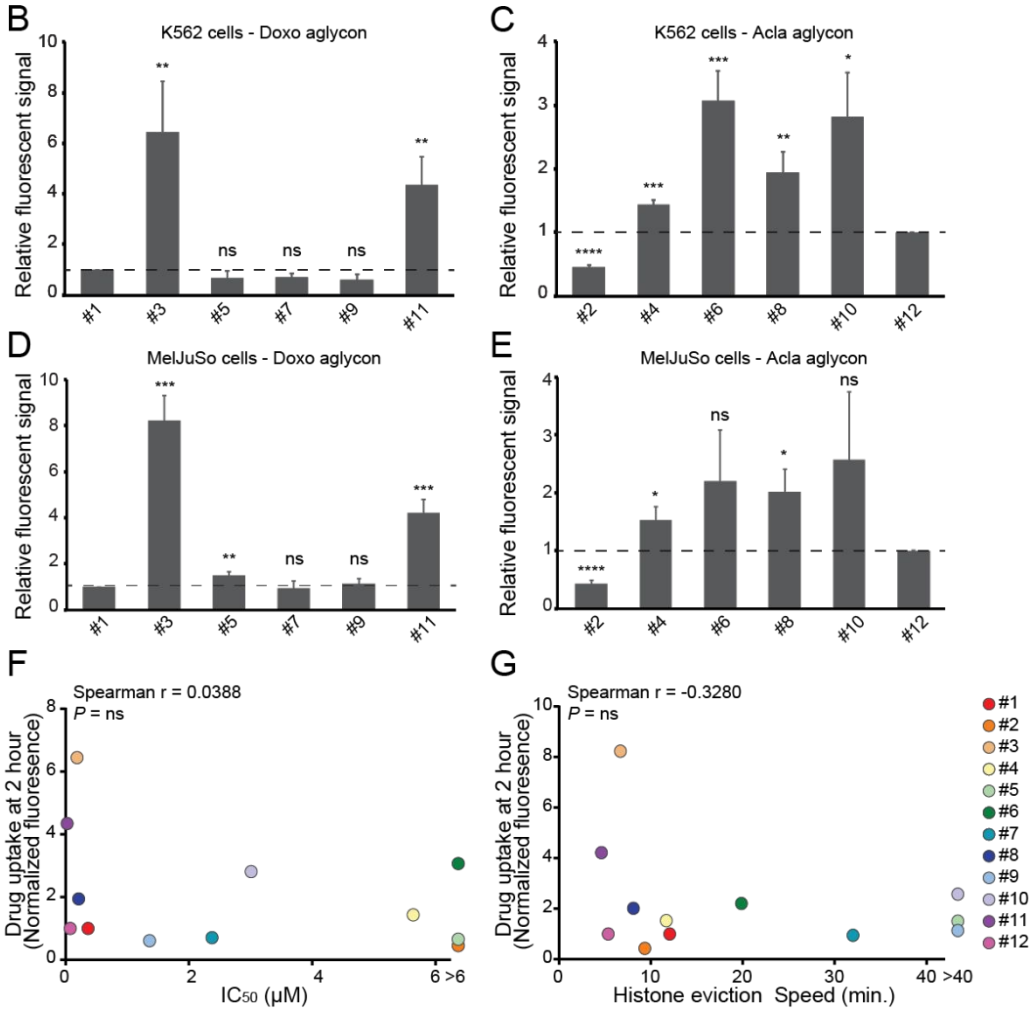
A: Figure S1. Evaluation of DNA break capacity of the hybrid structures. (A) K562 cells were treated for two hours with the indicated compound and concentration and DNA double strand breaks were analysed by CFGE. The position of intact and broken DNA is indicated. (B) K562 cells were treated for two hours with the indicated concentration of the various hybrid structures. γH2AX levels were visualized by Western blot. Actin was used as a loading control. (C) Quantification of the γH2AX signal normalized to actin. Results are presented as mean ± SD of three independent experiments.



B: Figure S2. Chromatin damage activity of the doxorubicin/aclarubicin hybrid structures. Histone eviction was measured by time-lapse confocal microscopy. Photo-activated GFP-H2A was monitored for one hour after administration of 10uM of the indicated compounds. Lines in the left panel define the cytoplasm, nucleus and the activated region of the nucleus before treatment. Scale bar, 10μm.

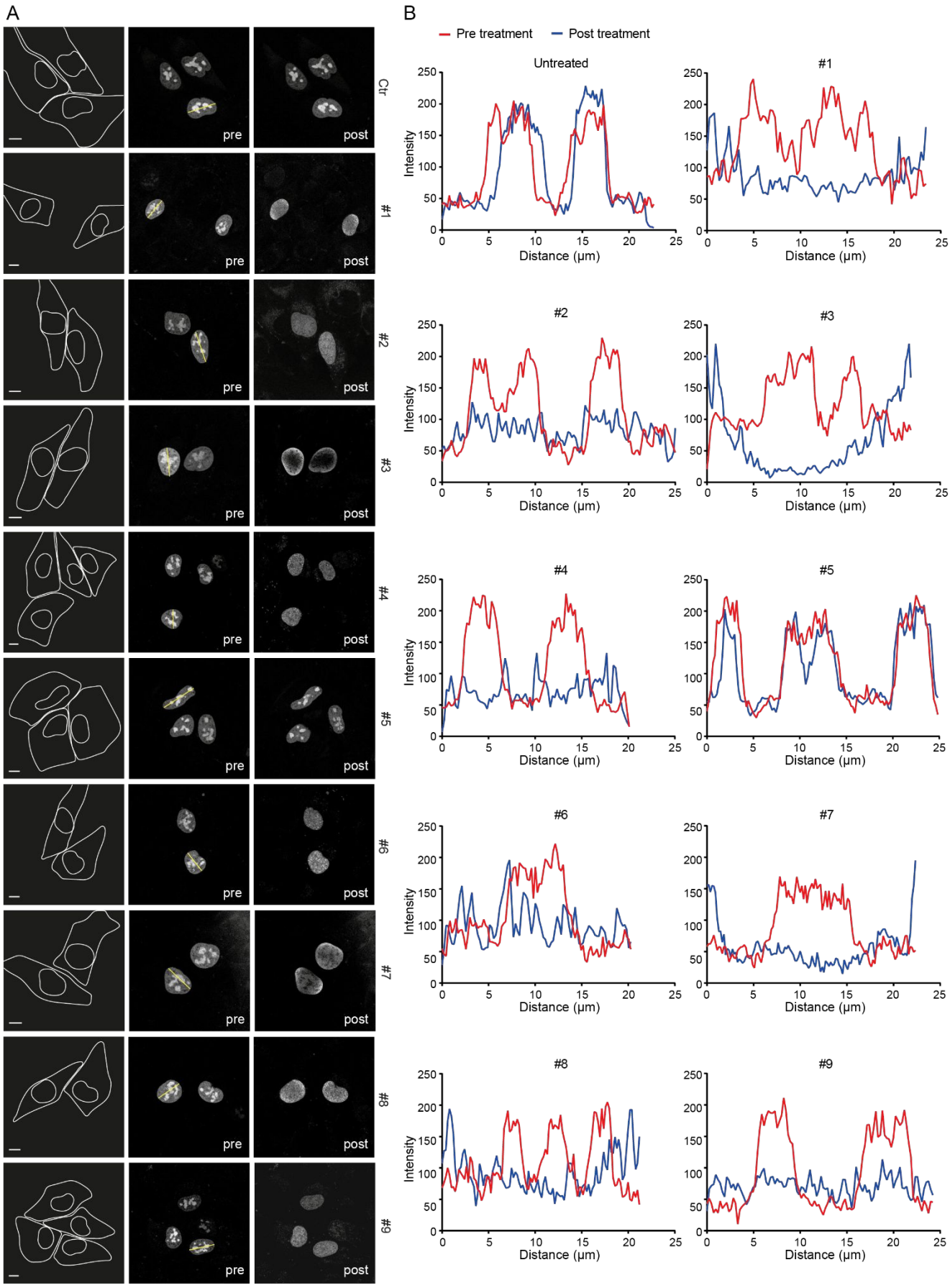
A

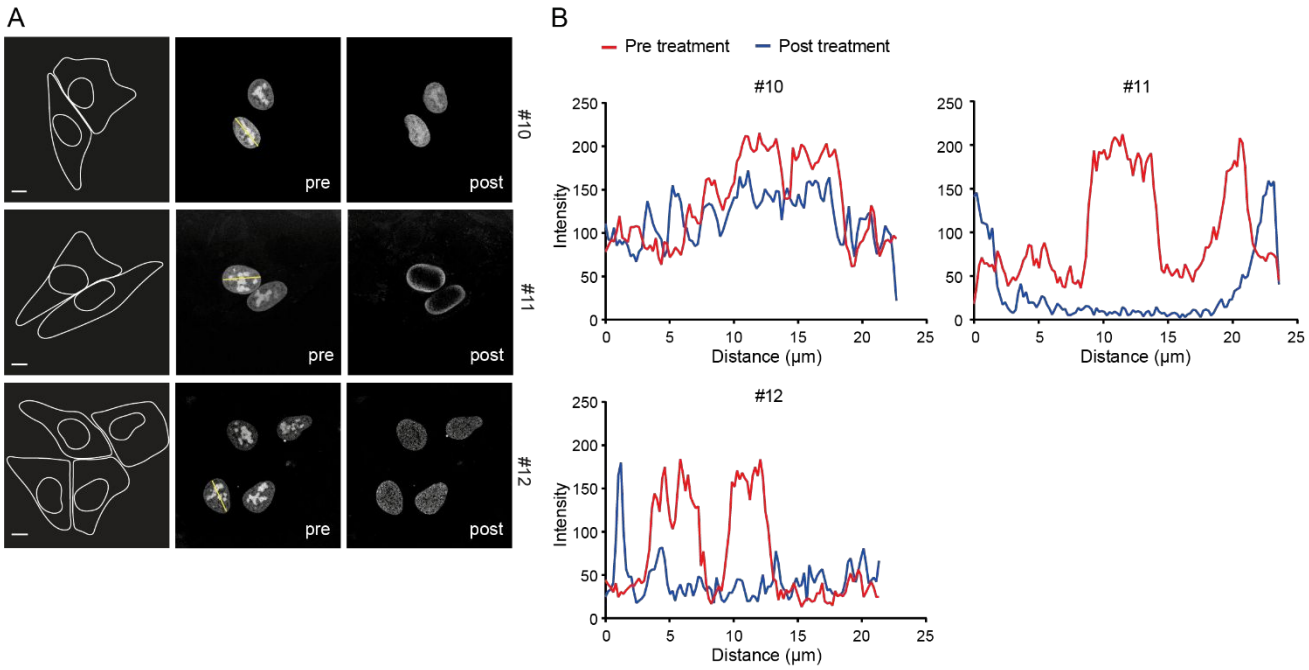
Compound	IC_{50}	$\frac{IC_{50}[\#]}{IC_{50}[Doxo]}$	$\frac{IC_{50}[\#]}{IC_{50}[Acla]}$
#1	0.362	1.000	4.751
#2	N.D.	N.D.	N.D.
#3	0.186	0.515	2.446
#4	5.633	15.569	73.963
#5	N.D.	N.D.	N.D.
#6	N.D.	N.D.	N.D.
#7	2.407	6.653	31.605
#8	0.211	0.583	2.769
#9	1.405	3.883	18.448
#10	3.035	8.389	39.850
#11	0.026	0.073	0.346
#12	0.076	0.211	1.000



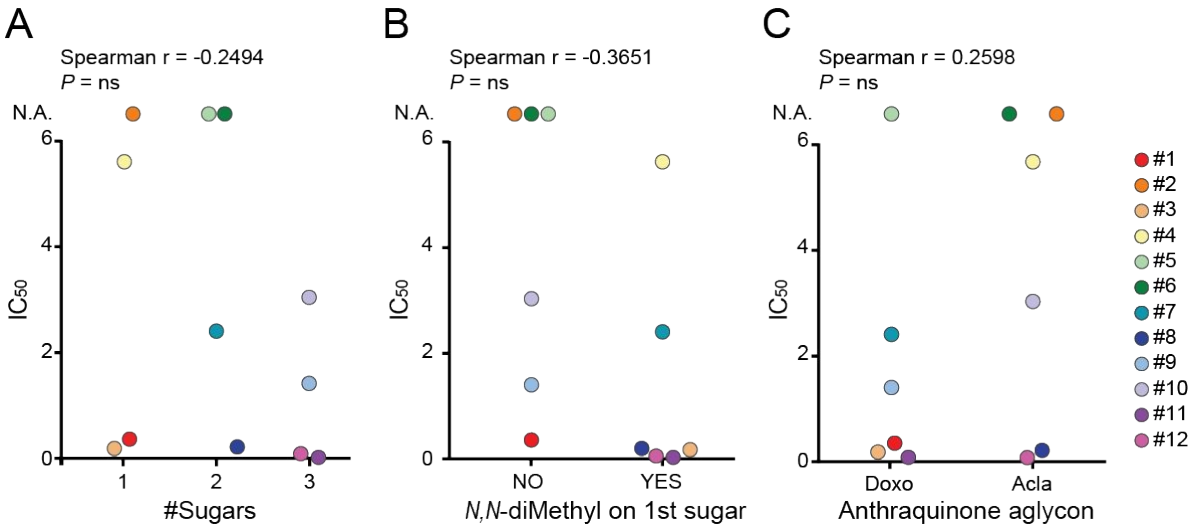
C: Figure S3. Evaluation of various hybrid structures uptake. (A) IC_{50} values in μM of the various hybrid structures for K562 cells. Last panels list the IC_{50} ratio from the indicated compound in relation to doxorubicin (Doxo, **1**) or aclarubicin (Acla, **12**). N.D. = Not detected. (B - E) The cellular drug uptake was measured. K562 (B and C) or MelJuSo (D and E) cells were treated for two hours with 1μM of the indicated compound. Cells were washed, fixed and the autofluorescence of the compounds were quantified by flow cytometry. Data is shown as mean ± SD from three independent experiments. Fluorescent intensity was normalized to doxorubicin (**1**) for the hybrid structures containing the doxorubicin aglycon (B and D), or to aclarubicin (**12**) for structures containing the aclarubicin aglycon (C and E). Dotted line indicated the signal of the parental drug doxorubicin and aclarubicin. Two-tailed t-test; ns, not significant; *P < 0.05; **P < 0.01; ***P < 0.001; ****P<0.0001. (F) The drug uptake (normalized fluorescent intensity at two hours) in K562 cells versus the IC_{50} in K562 cells is plotted.

Two-tailed Spearman correlation, ns; not significant. (G) The drug uptake (normalized fluorescent intensity at two hours) in MelJuSo cells versus histone eviction speed (time at which 25% of the initial signal is reduced) in MelJuSo cells is plotted. Two-tailed Spearman correlation, ns; not significant.


A
B
Pre treatment
Post treatment
Ctr.
#1
#2
#3
#4
#5
#6
#7
#8
#9
pre
post
Untreated
Intensity
Distance (μm)

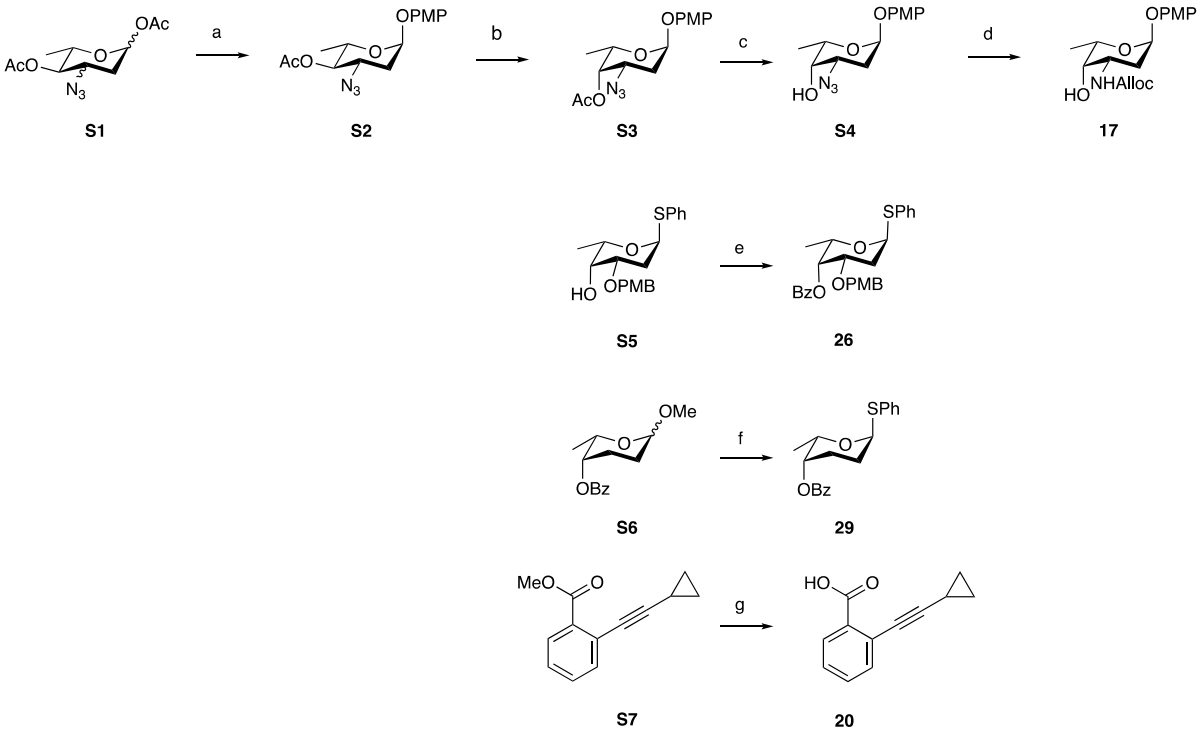


D: Figure S4. Topo IIα targeting by the doxorubicin/aclarubicin hybrid structures. MelJuSo cells transiently expressed with GFP-tagged TopoIIα. (A) Cells are treated for 15 minutes with 10µM of the indicated compounds and followed over time. Lines in the left panel define the cytoplasm and nucleus. Stills from time-laps experiment, before (pre) and after (post) treatment are shown. Scale bar, 10µm. (B) Pixel plot of the GFP signal pre and post treatment with the indicated compounds. Fractional distance is plotted as fluorescence over distance of yellow line as marked in A.



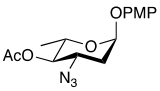
E: Figure S5. Correlating cytotoxicity with anthracycline structural features. (A) IC_{50} values versus the number of sugars of the doxorubicin/aclarubicin hybrid structures is plotted. (B) IC_{50} values versus the presence of a *N,N*-diMethylated sugar in the doxorubicin/aclarubicin hybrid structures is plotted. (C) IC_{50} values versus the parental tetracycline aglycon of the doxorubicin/aclarubicin hybrid structures is plotted. Two-tailed Spearman correlation, ns; not significant.

F: Synthesis of monosaccharide building blocks **17, 26** and **29** and accompanying NMR data



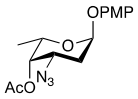
Scheme S1. Reagents and conditions: (a) *p*-methoxyphenol, TMSOTf, DCM, 0°C, 50%; (b) 1) NaOMe, MeOH, 100%, 2**)** Tf_2O, pyr., DCM, 0°C; 3) KOAc, 18-crown-6, DMF, 92% over 2 steps; (c) NaOMe, MeOH, 90%; (d) polymer-bound PPh_3, THF/H_2O, then Alloc-OSu, 89%; (e) BzCl, pyr., DCM, 82%; (f) PhSH, $BF_3.OEt_2$, DCM, -78°C → -15°C, 80%, 1.2:1 α:β; (g) NaOH, THF/H_2O

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-rhamnopyranoside (S2)**



Mixture **S1**[1] (11.6 g, 45.0 mmol) and *p*-methoxyphenol (8.38 g, 67.5 mmol, 1.5 eq) were coevaporated thrice with toluene and subsequently dissolved in DCM (225 mL). Activated 4Å molecular sieves were added, and the mixture was allowed to stir for 30 minutes. Thereafter, TMSOTf (2.44 mL, 13.5 mmol, 0.3 eq) was added at 0°C and the mixture was stirred for a further 4 hours at that temperature. It was then filtered into sat. aq. $NaHCO_3$, after which the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (7:93 EtOAc:pentane) gave the title compound as a white solid (7.20 g, 22.4 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.92 (m, 2H), 6.92 – 6.78 (m, 2H), 5.47 (d, *J* = 2.7 Hz, 1H), 4.75 (t, *J* = 9.8 Hz, 1H), 4.07 (ddd, *J* = 12.3, 9.9, 5.0 Hz, 1H), 3.93 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.77 (s, 3H), 2.36 (ddd, *J* = 13.3, 4.9, 1.1 Hz, 1H), 2.14 (s, 3H), 1.86 (td, *J* = 12.9, 3.5 Hz, 1H), 1.13 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 155.0, 150.4, 117.6, 114.7, 95.5, 76.8, 75.5, 66.7, 57.6, 55.7, 35.5, 20.9, 17.6. HRMS: $[M + Na]^+$: calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

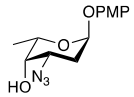
***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (S3)**



To a solution of **S2** (7.20 g, 22.4 mmol) in MeOH was added NaOMe (242 mg, 4.48 mmol, 0.2 eq) and the mixture was allowed to stir over 3 days. It was then neutralized by addition of Amberlite IR120 (H^+ form), filtered off and concentrated *in vacuo* to give the alcohol as a yellow oil (6.26 g, 22.4 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.94 (m, 2H), 6.88 – 6.79 (m, 2H), 5.47 (d, *J* = 2.8 Hz, 1H), 3.96 (ddd, *J* = 12.2, 9.5, 4.9 Hz, 1H), 3.83 (dq, *J* = 9.3, 6.2 Hz, 1H), 3.78 (s, 3H), 3.22 (td, *J* = 9.4, 4.1 Hz, 1H), 2.36 (ddd, *J* = 13.2, 4.9, 1.1 Hz, 1H), 2.26 (d, *J* = 4.2 Hz, 1H), 1.85 (td, *J* = 12.7, 3.5 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 150.6, 117.7, 114.7, 95.8, 76.8, 76.1, 68.5, 60.4, 55.8, 35.3, 17.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4$; 302.1111; found 302.1118.

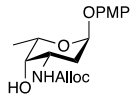
To a solution of the above compound (18.09 g, 64.8 mmol) in DCM (250 mL) and pyridine (25 mL), triflic anhydride (13.5 mL, 77.8 mmol, 1.2 eq) was added at 0°C. The mixture was allowed to stir for 1 hour, after which it was poured into 1M HCl solution. This was then extracted with DCM twice, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude triflate and 18-crown-6 (20.5 g, 77.8 mmol, 1.2 eq) were coevaporated thrice with toluene and dissolved in DMF (250 mL). To this was added KOAc (7.6 g, 77.8 mmol, 1.2 eq) and the mixture was stirred for 1 hour. It was then diluted with EtOAc and washed with H_2O five times and brine. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 - 7:93 EtOAc:pentane) gave the title compound as a yellow solid (19.2 g, 59.8 mmol, 92% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.91 (m, 2H), 6.91 – 6.75 (m, 2H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.22 (d, *J* = 2.5 Hz, 1H), 4.14 (q, *J* = 6.2 Hz, 1H), 4.05 (ddd, *J* = 12.3, 5.1, 3.0 Hz, 1H), 3.78 (s, 3H), 2.28 – 2.07 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.0, 150.7, 117.6, 114.8, 96.3, 76.8, 70.2, 66.0, 55.8, 54.6, 29.9, 20.9, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (S4)**



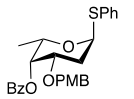
S3 (19.2 g, 59.8 mmol) was dissolved in MeOH (300 mL), to which NaOMe (650 mg, 12.0 mmol, 0.2 eq) was added. After stirring overnight, it was neutralized by addition of acetic acid and concentrated *in vacuo*. Column chromatography (15:85 - 30:70 EtOAc:pentane) gave the title compound as a light yellow solid (15.00 g, 53.7 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.92 (m, 2H), 6.92 – 6.79 (m, 2H), 5.55 (d, *J* = 3.0 Hz, 1H), 4.06 (q, *J* = 5.1 Hz, 1H), 4.01 (ddd, *J* = 12.3, 5.1, 2.8 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 3.1 Hz, 1H), 2.21 (td, *J* = 12.7, 3.6 Hz, 1H), 2.11 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.03 (d, *J* = 4.3 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 150.8, 117.6, 114.7, 96.2, 76.8, 69.8, 66.7, 57.1, 55.8, 29.0, 16.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4Na$; 302.1111; found 302.1118.

***p*-Methoxyphenyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (17)**



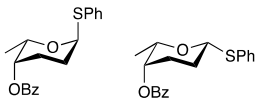
To a solution of **S4** (838 mg, 3.00 mmol) in THF/H_2O (10:1 v/v, 16.5 mL) was added polymer-bound triphenylphosphine (3 mmol/g, 2.00g, 3 eq) and the mixture was stirred for 4 nights. To this mixture were then added $NaHCO_3$ (504 mg, 6 mmol, 2 eq), H_2O (10 mL) and finally *N*-(allyloxycarbonyloxy)succinimide (956 mg, 4.8 mmol, 1.6 eq). After stirring for 3 hours, it was partitioned between EtOAc and H_2O, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70:1– 40:60:1 EtOAc:pentane:Et_3N) gave the title compound as a white solid (904 mg, 2.67 mmol, 89% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.91 (m, 2H), 6.91 – 6.74 (m, 2H), 5.94 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1H), 5.48 (d, *J* = 3.4 Hz, 1H), 5.41 – 5.29 (m, 1H), 5.29 – 5.16 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.39 – 4.22 (m, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 1H), 2.08 (ddt, *J* = 13.2, 5.0, 1.1 Hz, 1H), 194 (bs, 1H), 1.87 (td, *J* = 12.9, 3.7 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 154.8, 150.9, 132.9, 118.0, 117.6, 114.7, 96.2, 77.5, 77.2, 76.8, 70.0, 65.8, 55.8, 47.1, 30.8, 16.9. HRMS: $[M + Na]^+$ calculated for $C_{17}H_{23}NO_6Na$ 360.1423; found 360.1416.

Phenyl 4-*O*-benzoyl-2-deoxy-1-thio-α-L-fucopyranoside (26)



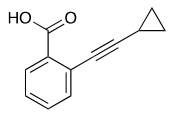
To a solution of **S5**[2] (10.7 g, 29.8 mmol) in pyridine (150 mL) and DCM (30 mL) was added benzoyl chloride (11.3 mL, 89.4 mmol, 3 eq). After stirring overnight, MeOH was added to quench and the mixture was concentrated *in vacuo*. Column chromatography (4:96 – 5:95 EtOAc:pentane) gave the title compound as a light yellow solid (11.3 g, 24.3 mmol, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.07 (m, 2H), 7.63 – 7.51 (m, 1H), 7.51 – 7.35 (m, 4H), 7.35 – 7.17 (m, 5H), 6.89 – 6.77 (m, 2H), 5.80 (d, *J* = 5.6 Hz, 1H), 5.62 (d, *J* = 2.9 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.01 (ddd, *J* = 12.3, 4.8, 2.9 Hz, 1H), 3.78 (s, 3H), 2.60 – 2.44 (m, 1H), 2.15 (ddt, *J* = 13.5, 4.9, 1.2 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 133.2, 131.2, 130.0, 129.6, 129.1, 128.5, 127.3, 114.0, 84.6, 72.1, 70.1, 69.5, 66.4, 55.4, 32.6, 17.0. HRMS: $(M + Na)^+$ calculated for $C_{27}H_{28}O_5SNa$ 487.1555, found 487.1552.

Phenyl 4-*O*-benzoyl-2,3-dideoxy-1-thio-α,β-L-fucopyranoside (29)

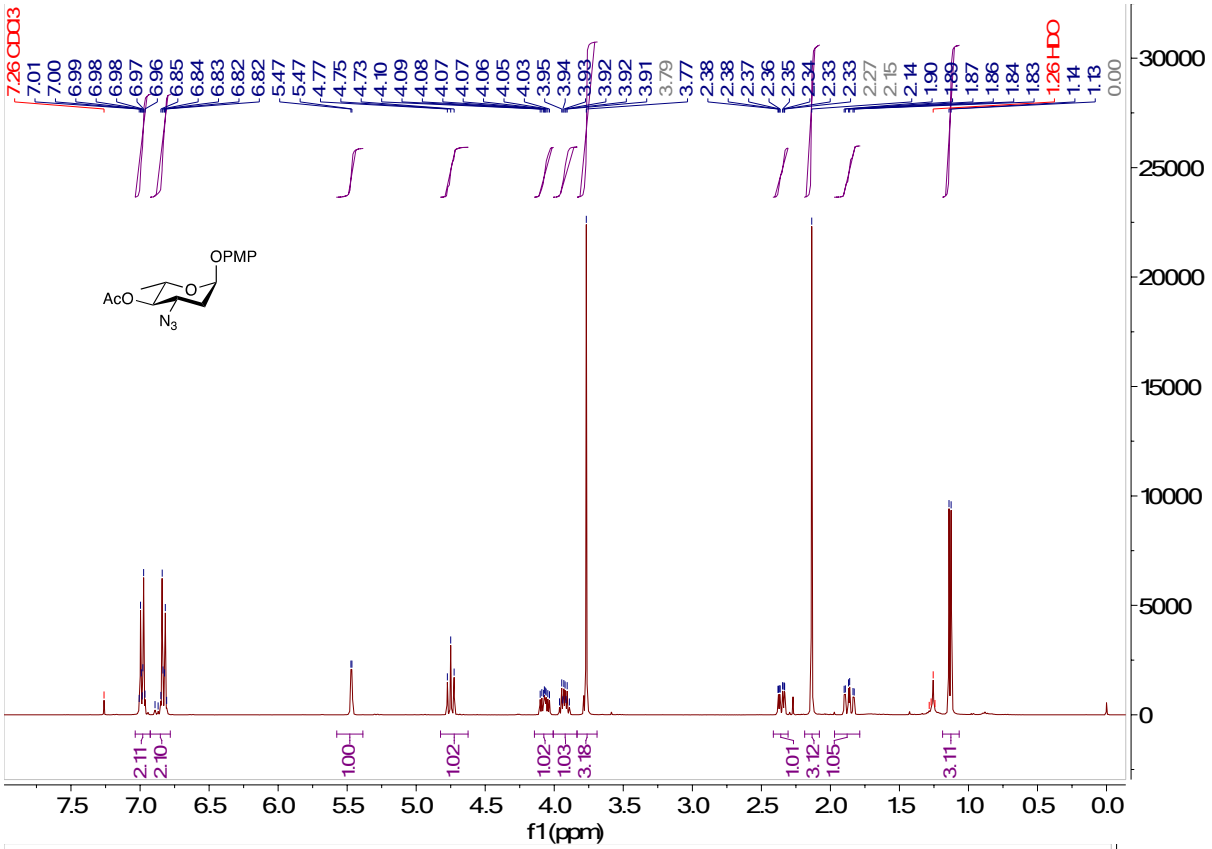


To a solution of **S6**[3] (3.05 g, 12.2 mmol) in DCM (60 mL) at -78°C were added thiophenol (1.30 mL, 12.7 mmol, 1.04 eq) and $BF_3 \cdot OEt_2$ (3.75 mL, 30.5 mmol, 2.5 eq) dropwise. The mixture was allowed to warm up to -15°C over 4 hours, after which it was poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:98 – 10:90 EtOAc:pentane) gave the α-anomer and the β-anomers as clear oils (3.19 g, 9.71 mmol, 80%, α:β 1.2:1). Analytical data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 8.03 (m, 2H), 7.66 – 7.55 (m, 1H), 7.55 – 7.39 (m, 4H), 7.39 – 7.16 (m, 4H), 5.73 (d, *J* = 5.3 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.61 (qd, *J* = 6.6, 1.5 Hz, 1H), 2.44 (tt, *J* = 13.8, 5.1 Hz, 1H), 2.17 (tdd, *J* = 13.7, 4.4, 2.9 Hz, 1H), 2.13 – 2.00 (m, 1H), 1.87 (dt, *J* = 14.2, 3.5 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.44, 133.25, 131.12, 129.86, 129.05, 128.59, 126.99, 84.98, 69.96, 66.35, 25.65, 24.77, 17.27. HRMS: $(M + Na)^+$ calculated for $C_{19}H_{20}O_3SNa$ 351.10254; found 351.10250.

***ortho*-Cyclopropylethynylbenzoic acid (20)**



A solution of **S7**[4] in THF (5 mL/mmol) and 1M NaOH (5 mL/mmol) was stirred at 50°C for 8 hours. It was then poured into 1M HCl (6 mL/mmol) and extracted with DCM 3x. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The title acid thus obtained was used without further purification, due to its instability. Spectral data of the purified compound was in accordance with that of literary precedence.[5]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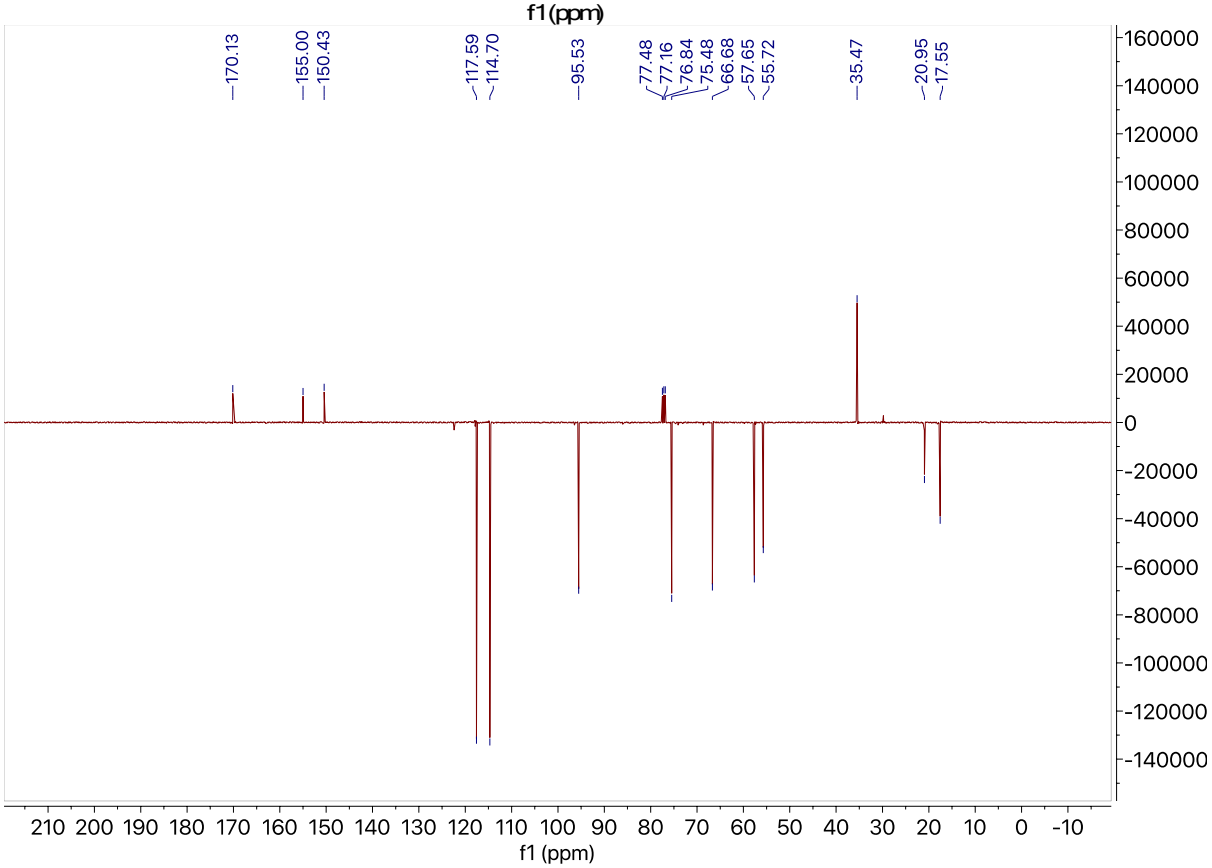
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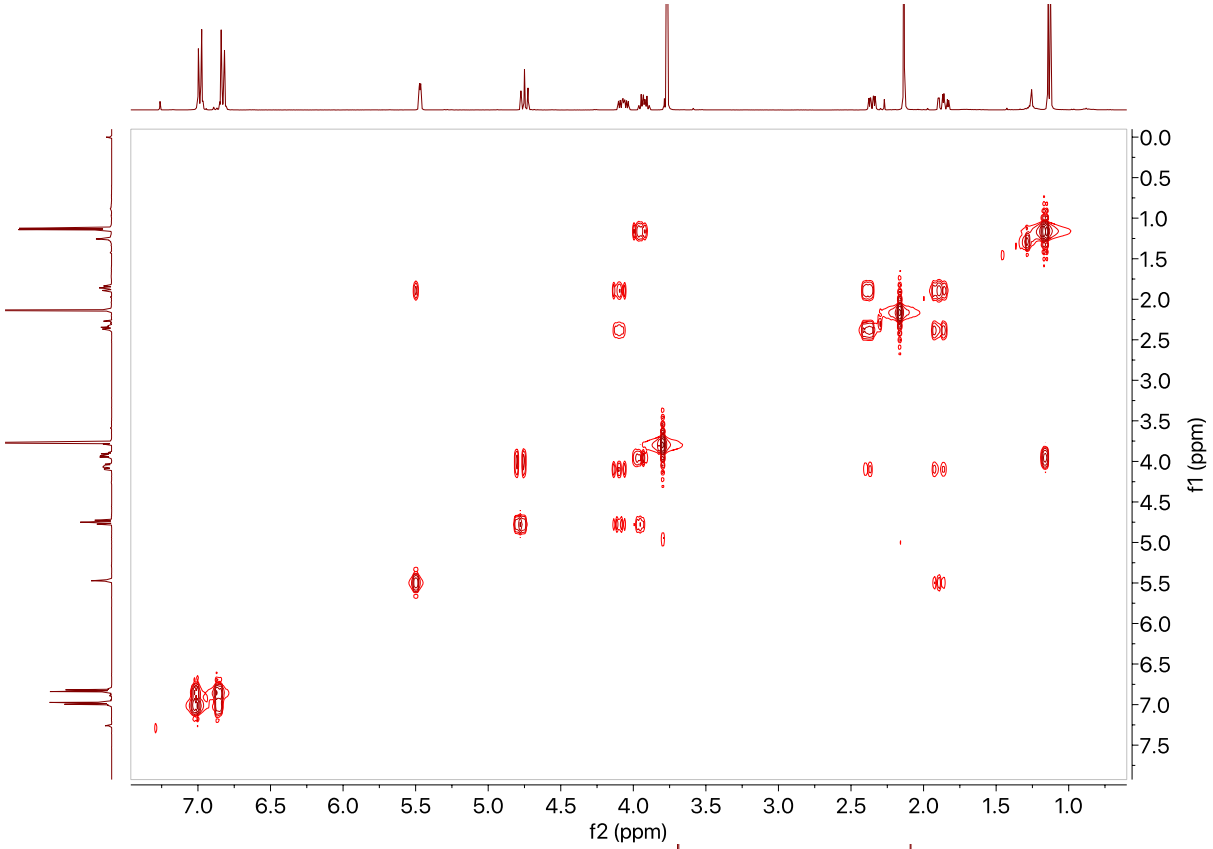
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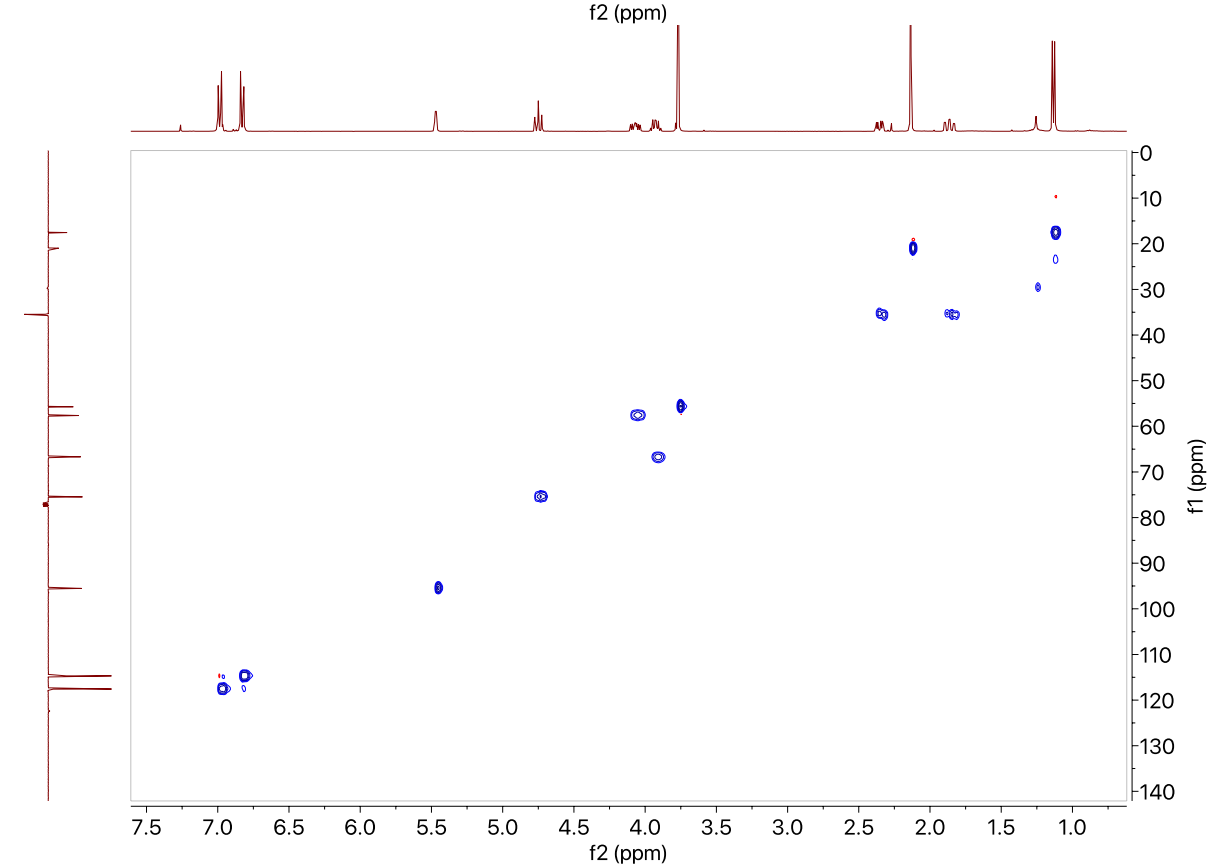
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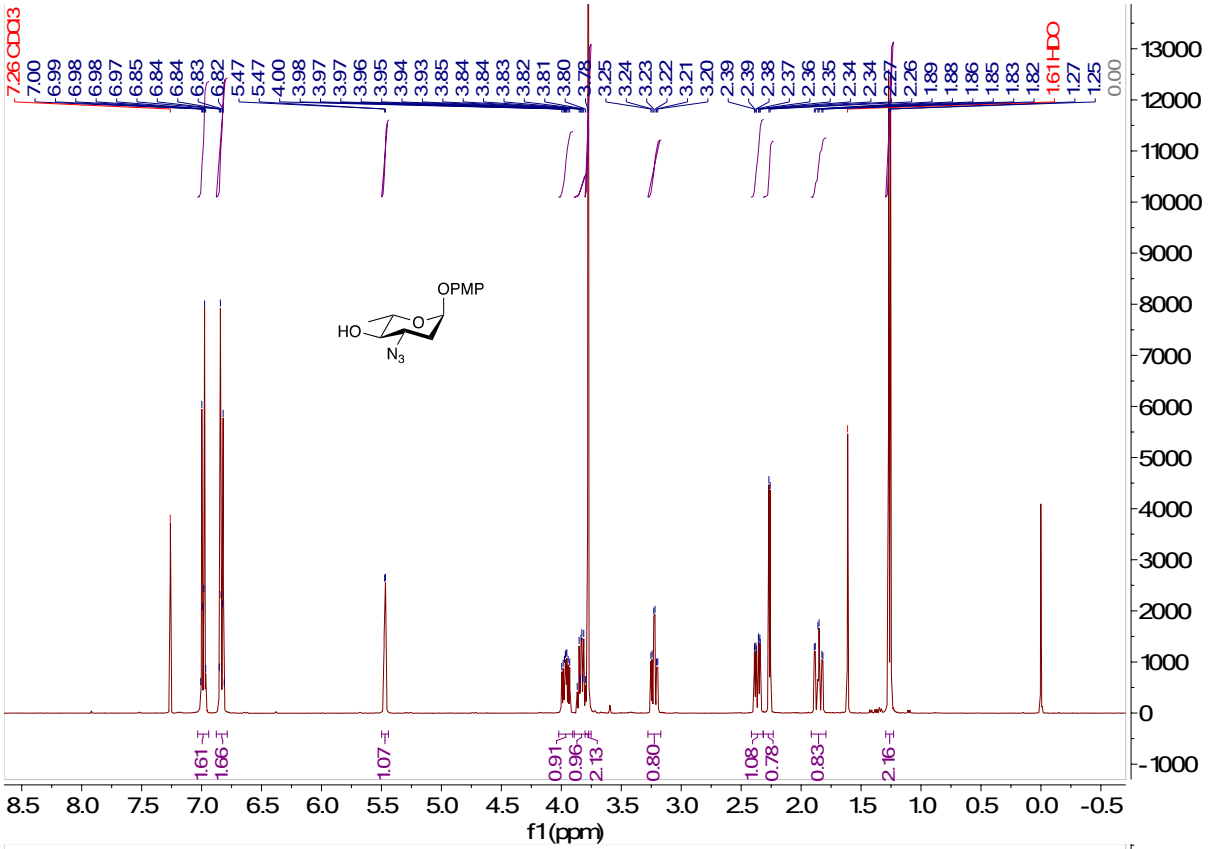
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HO
O
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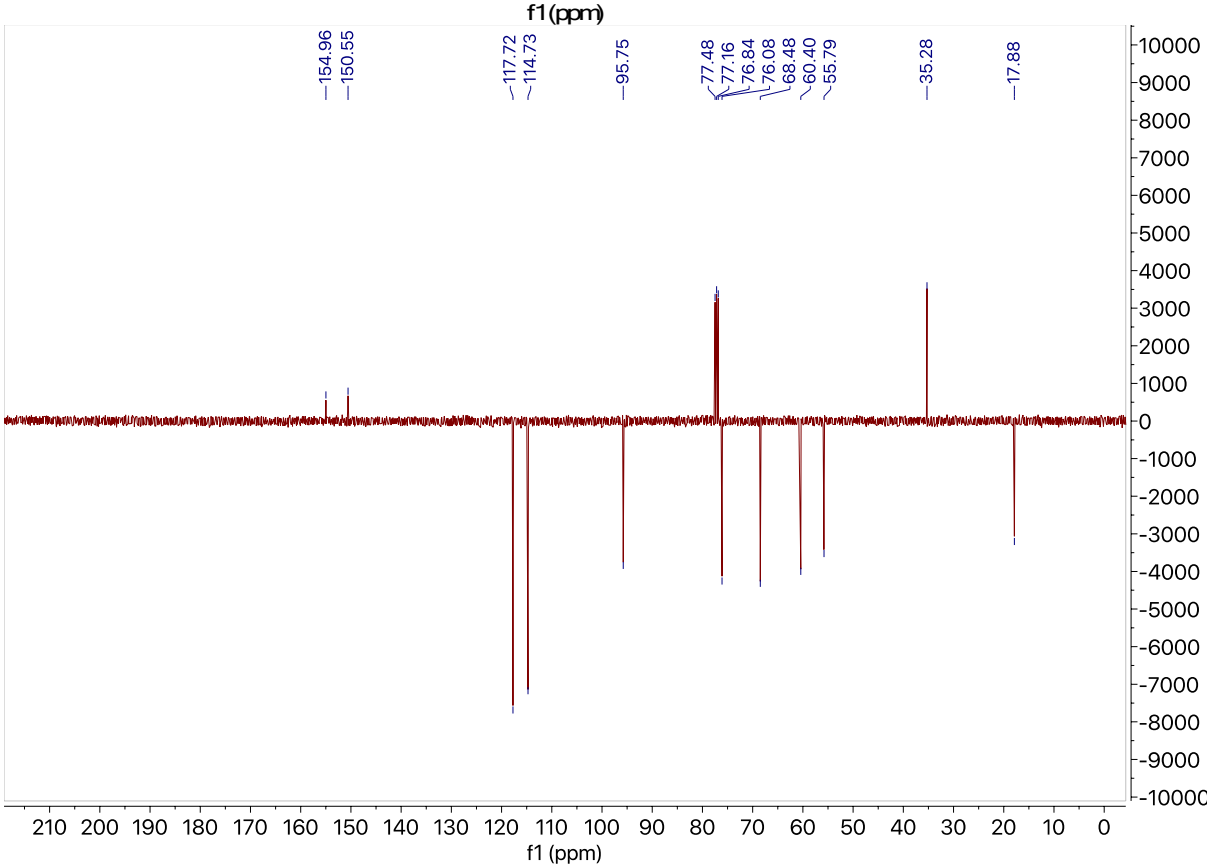
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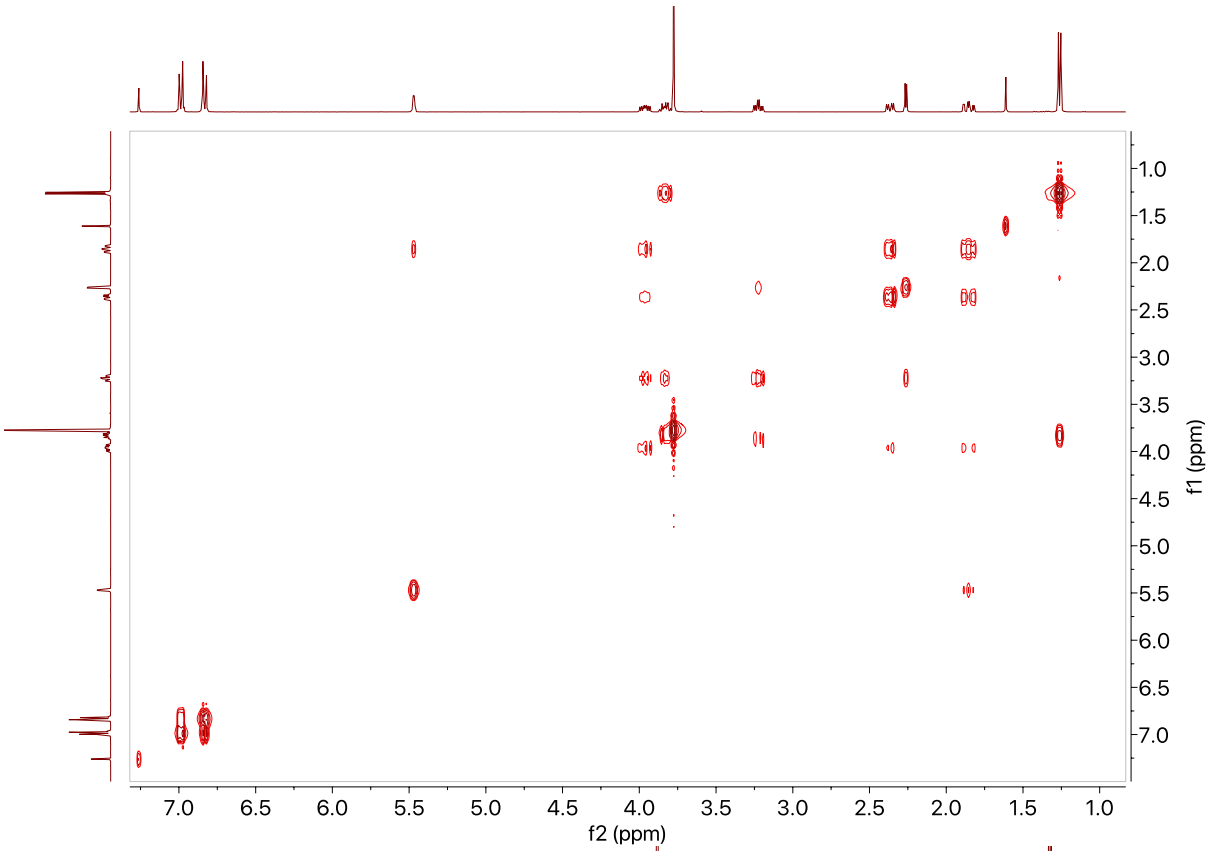
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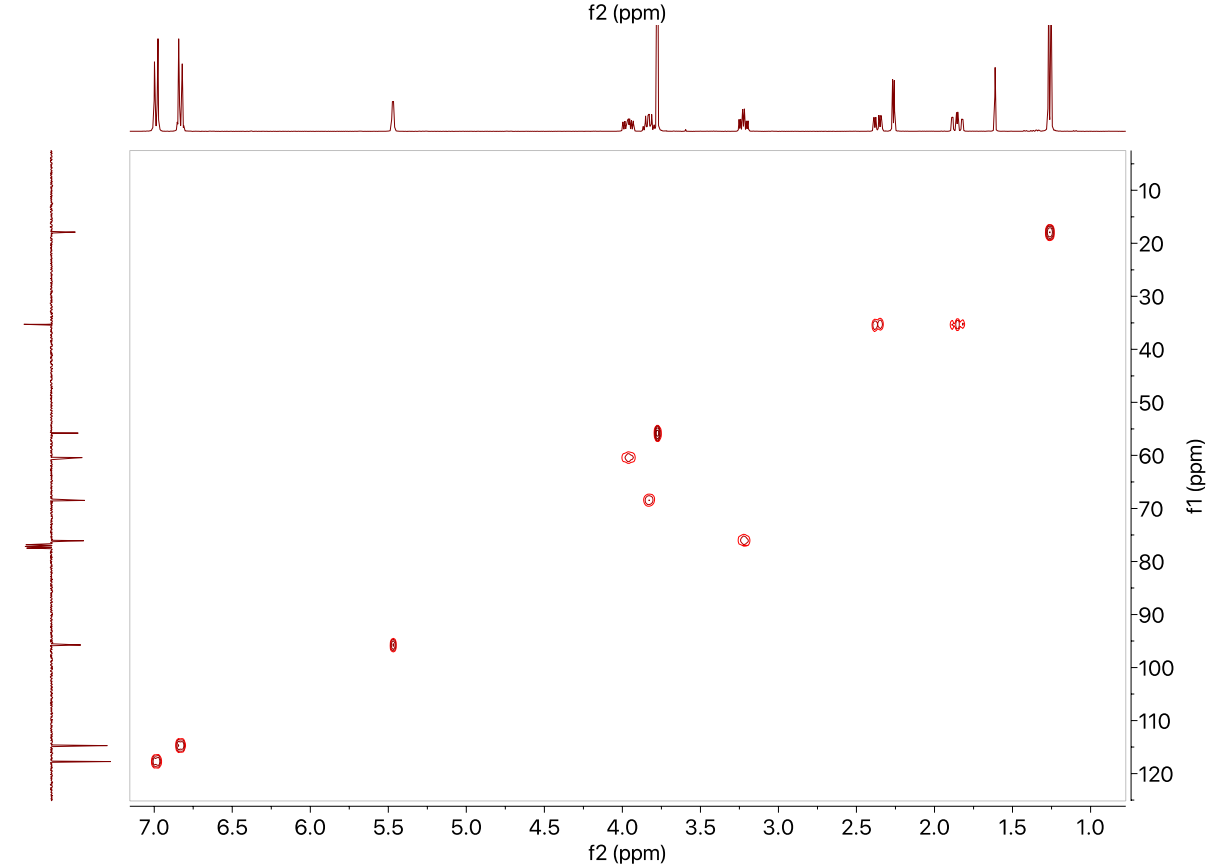
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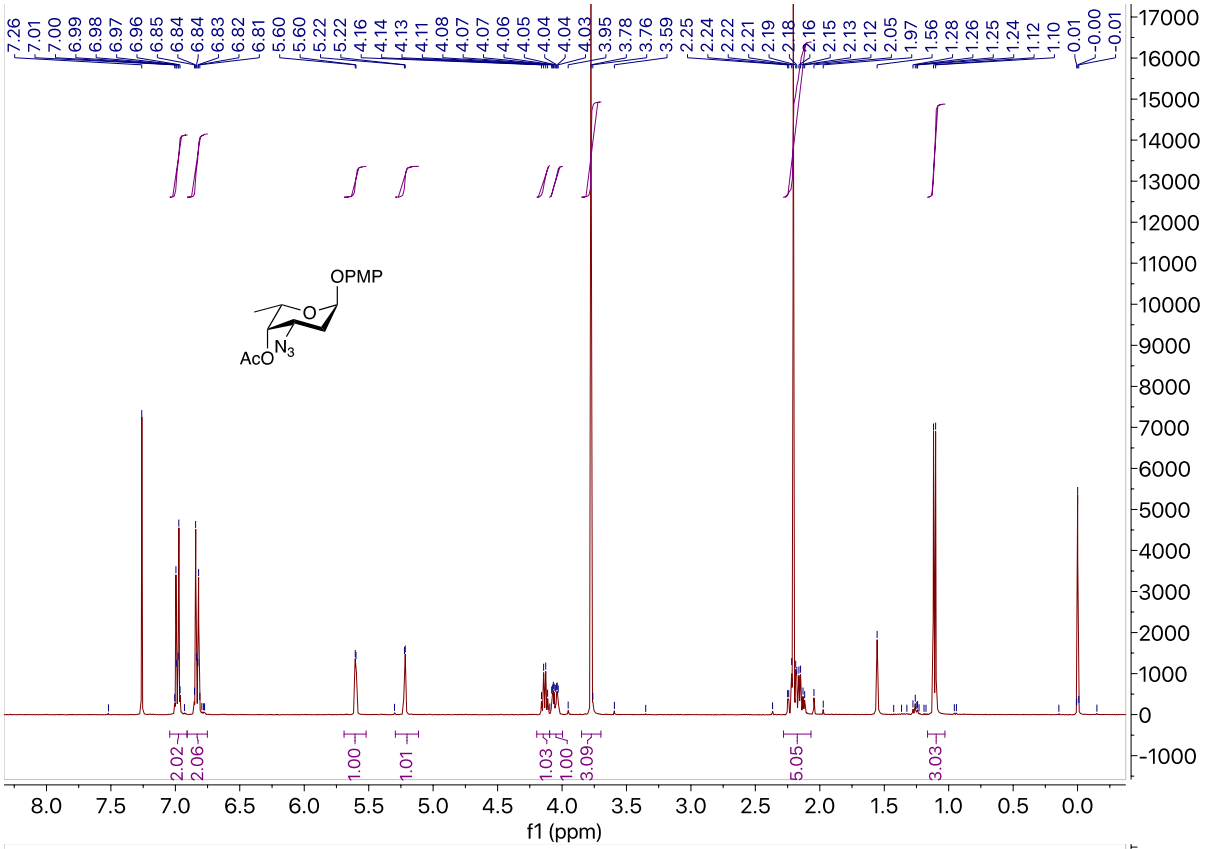
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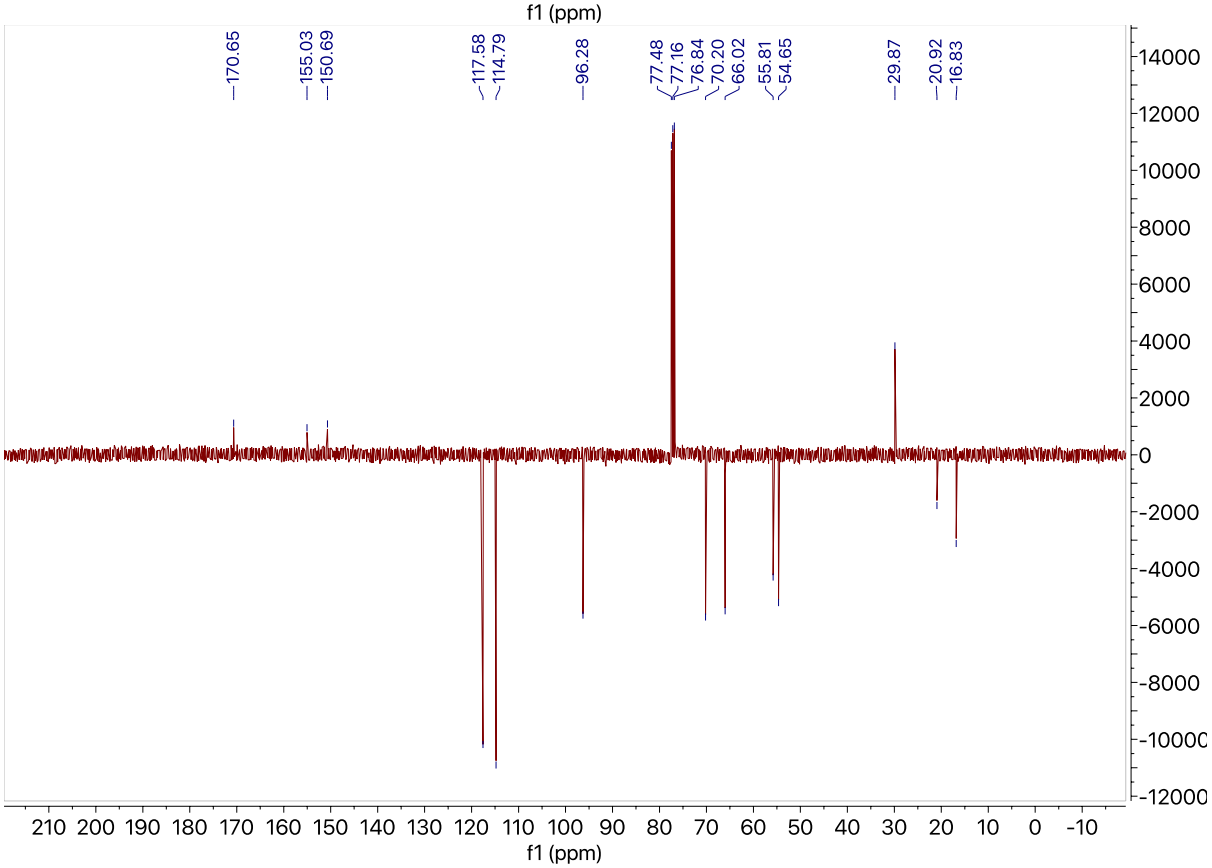
f1 (ppm)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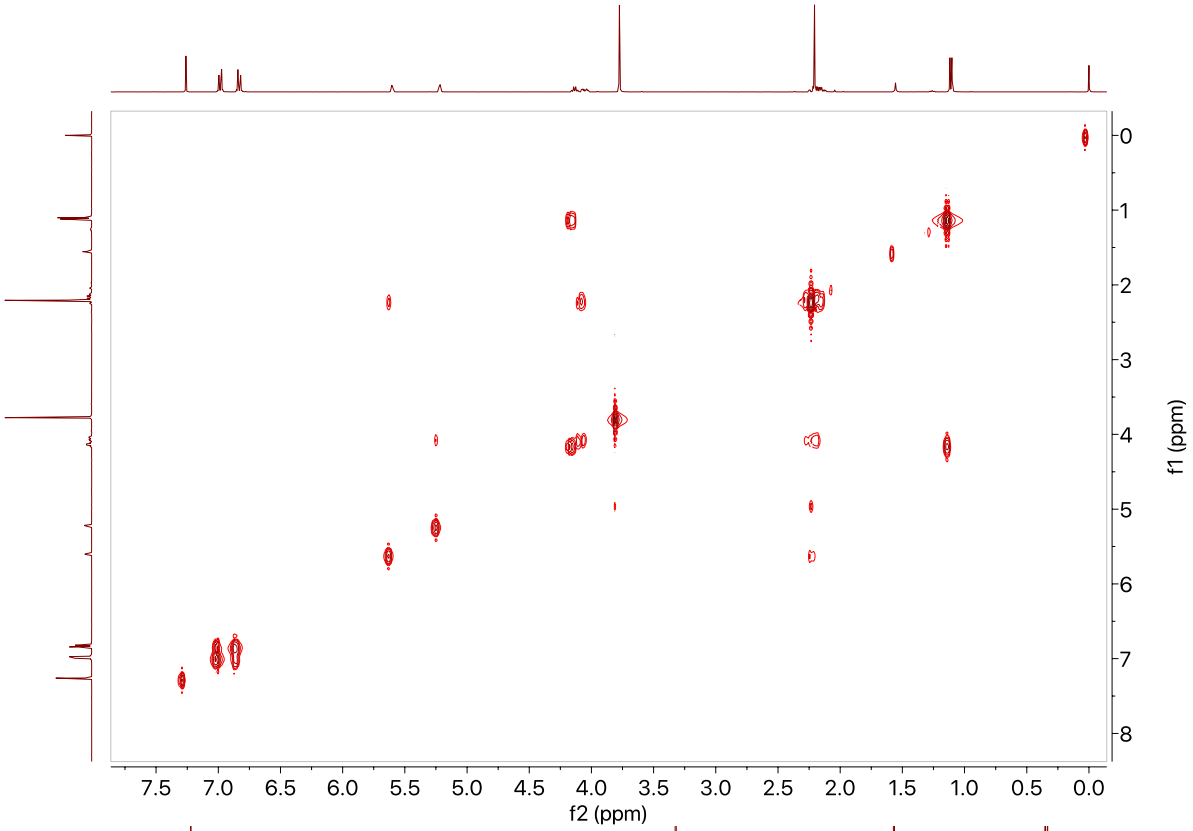
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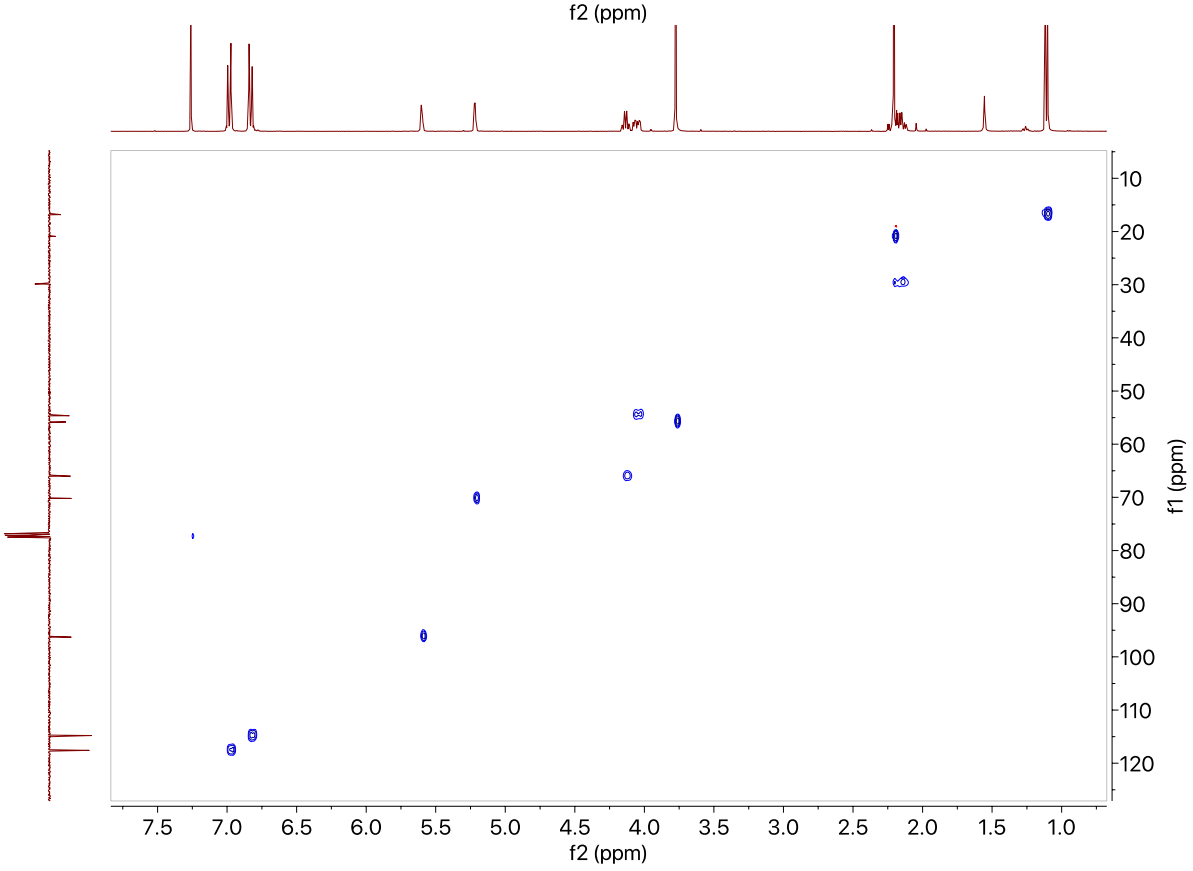
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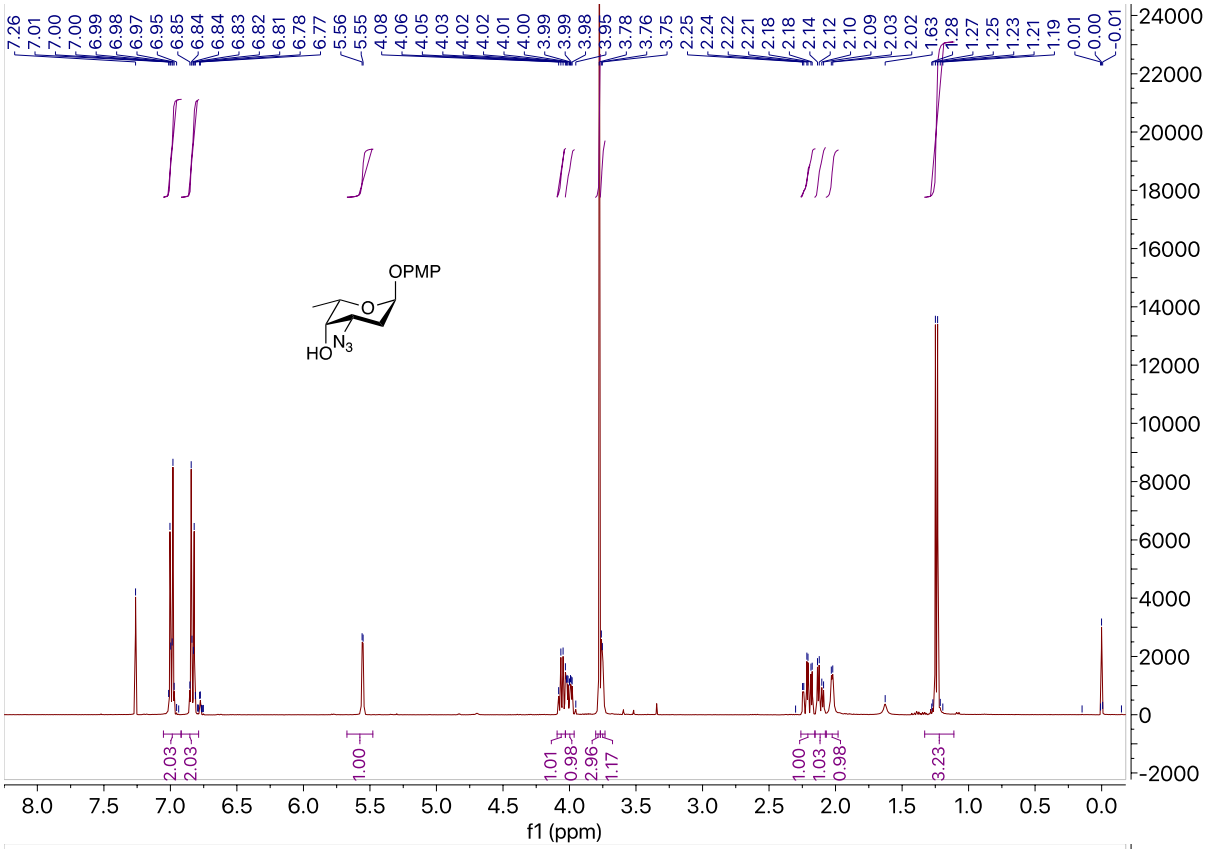
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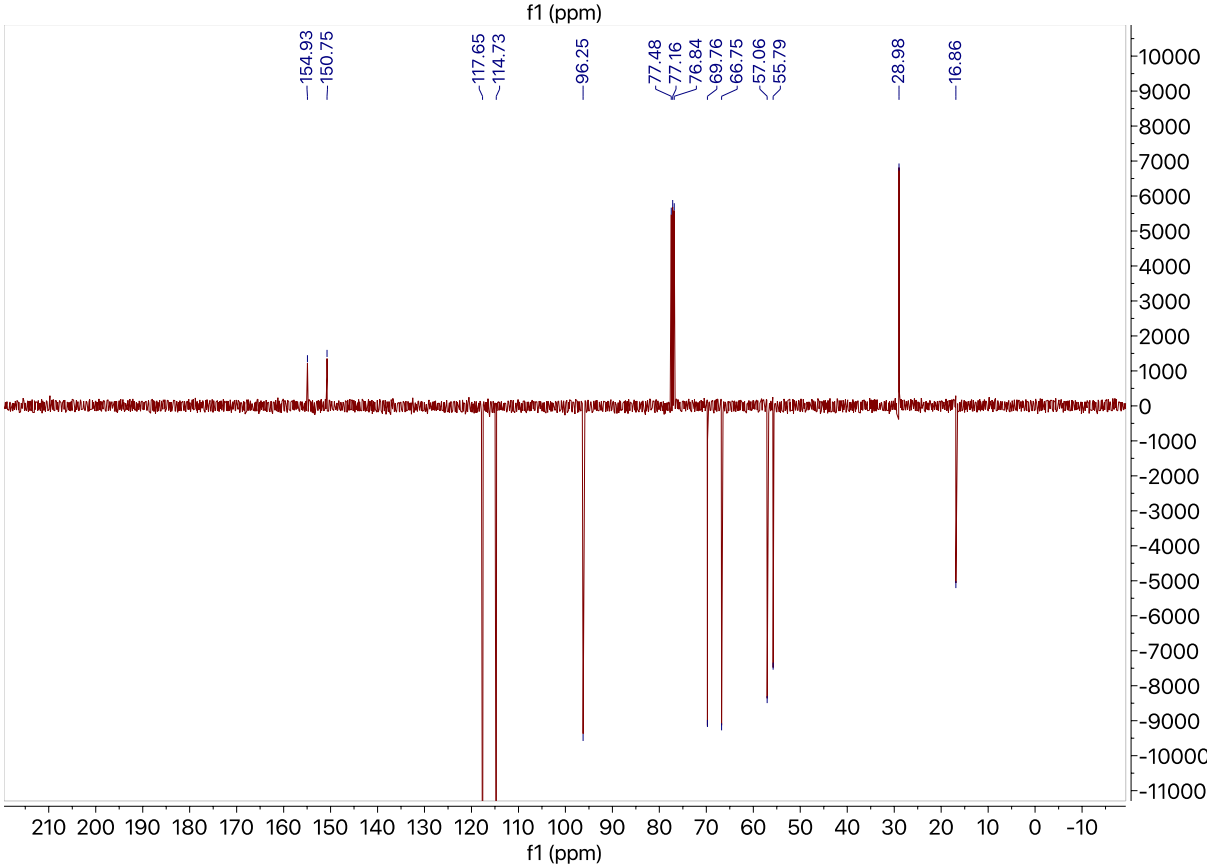
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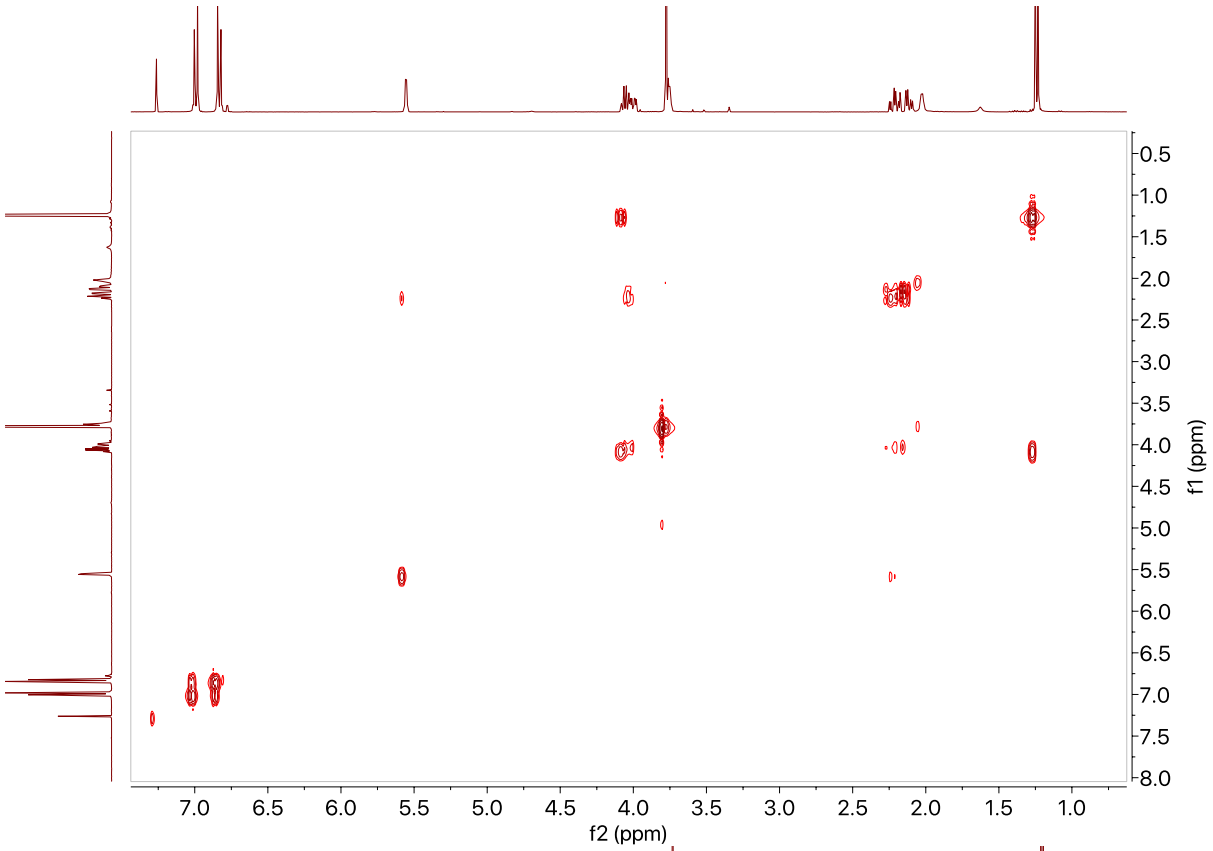
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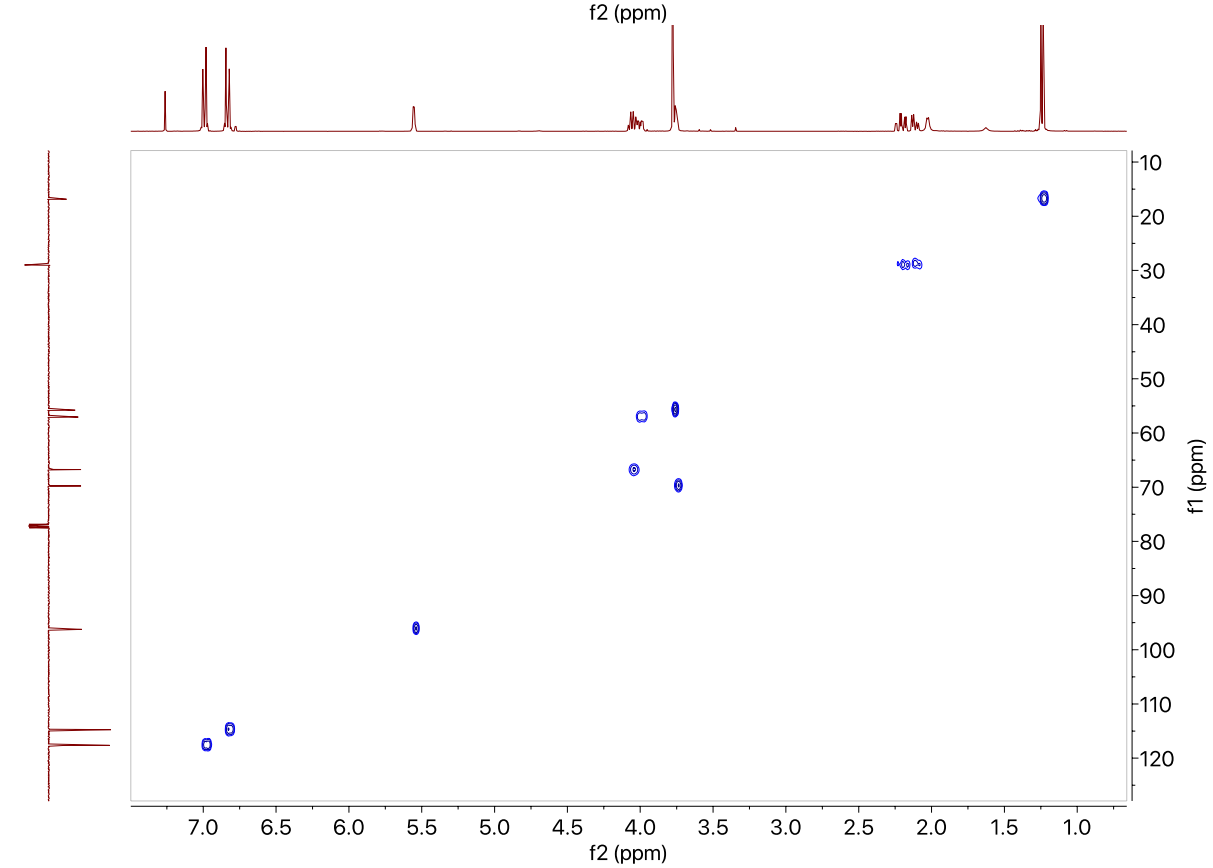
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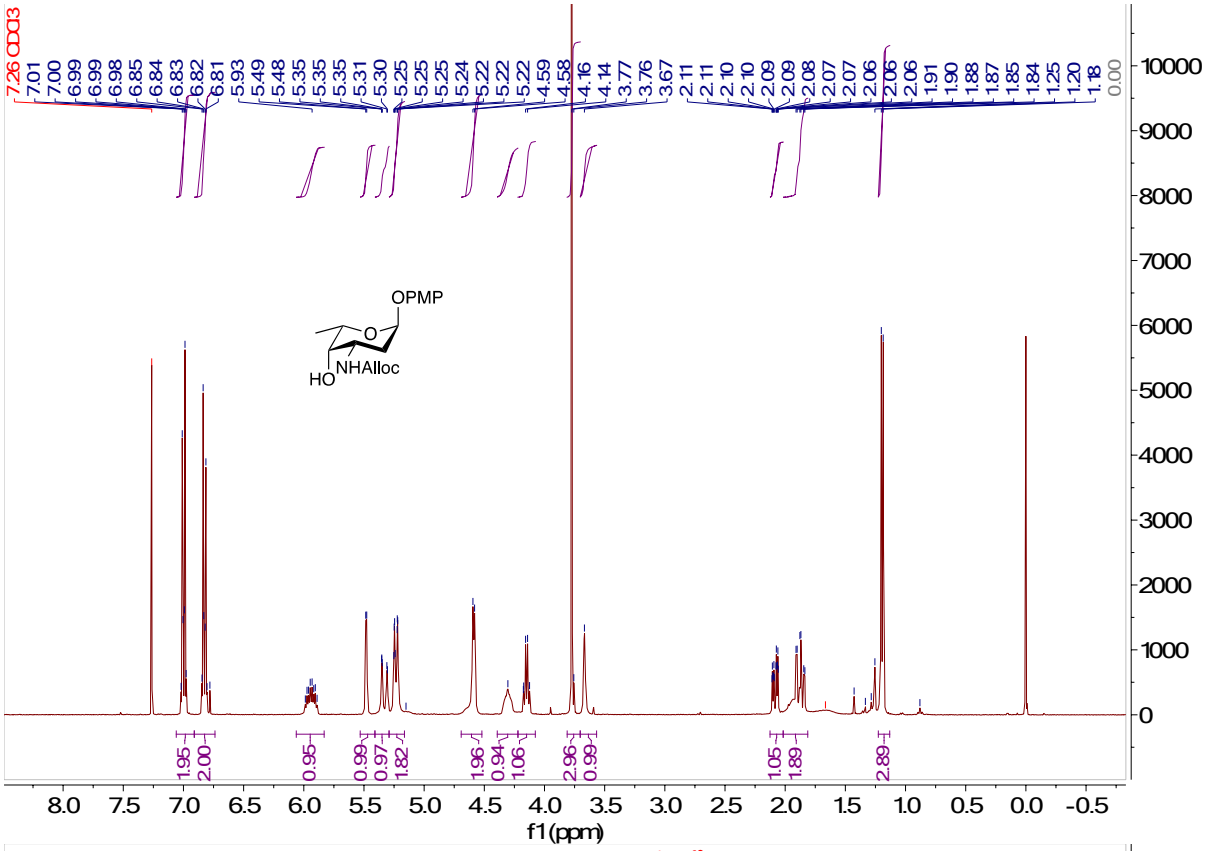
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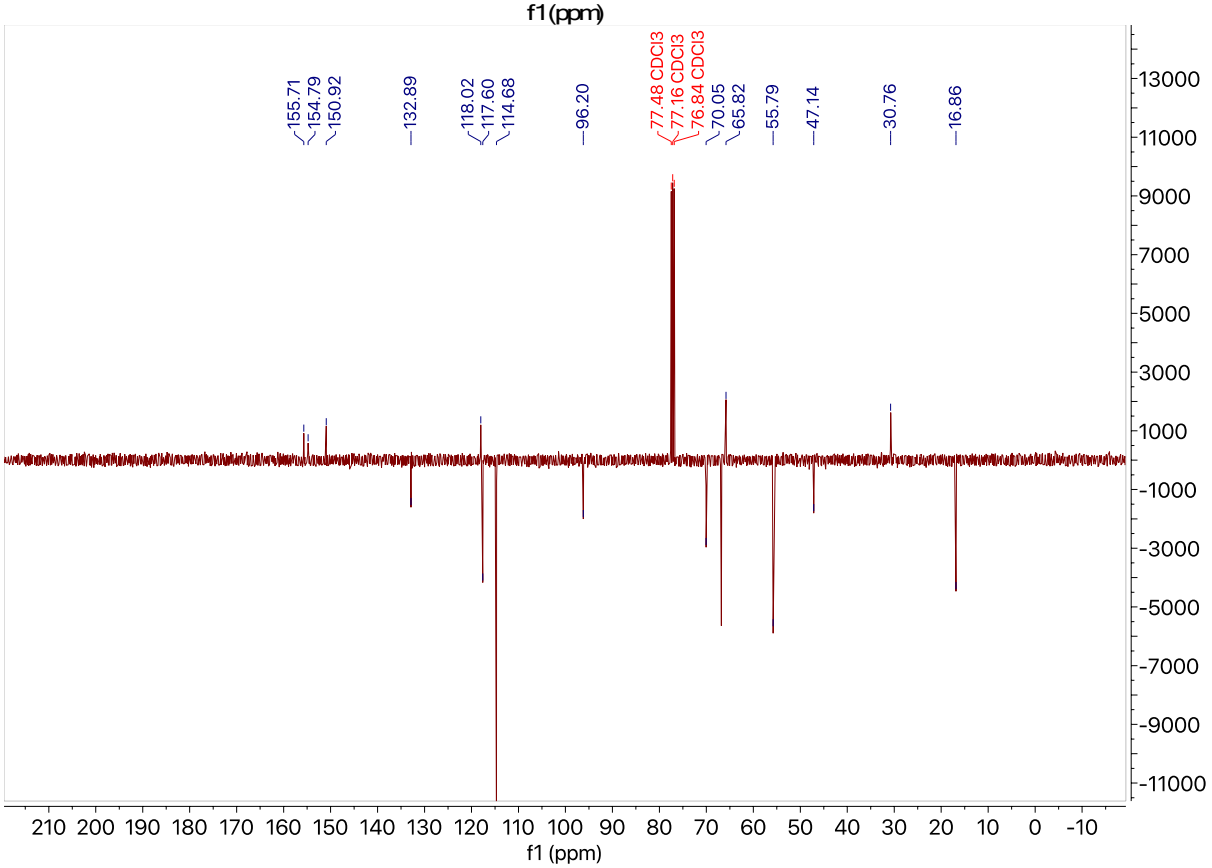
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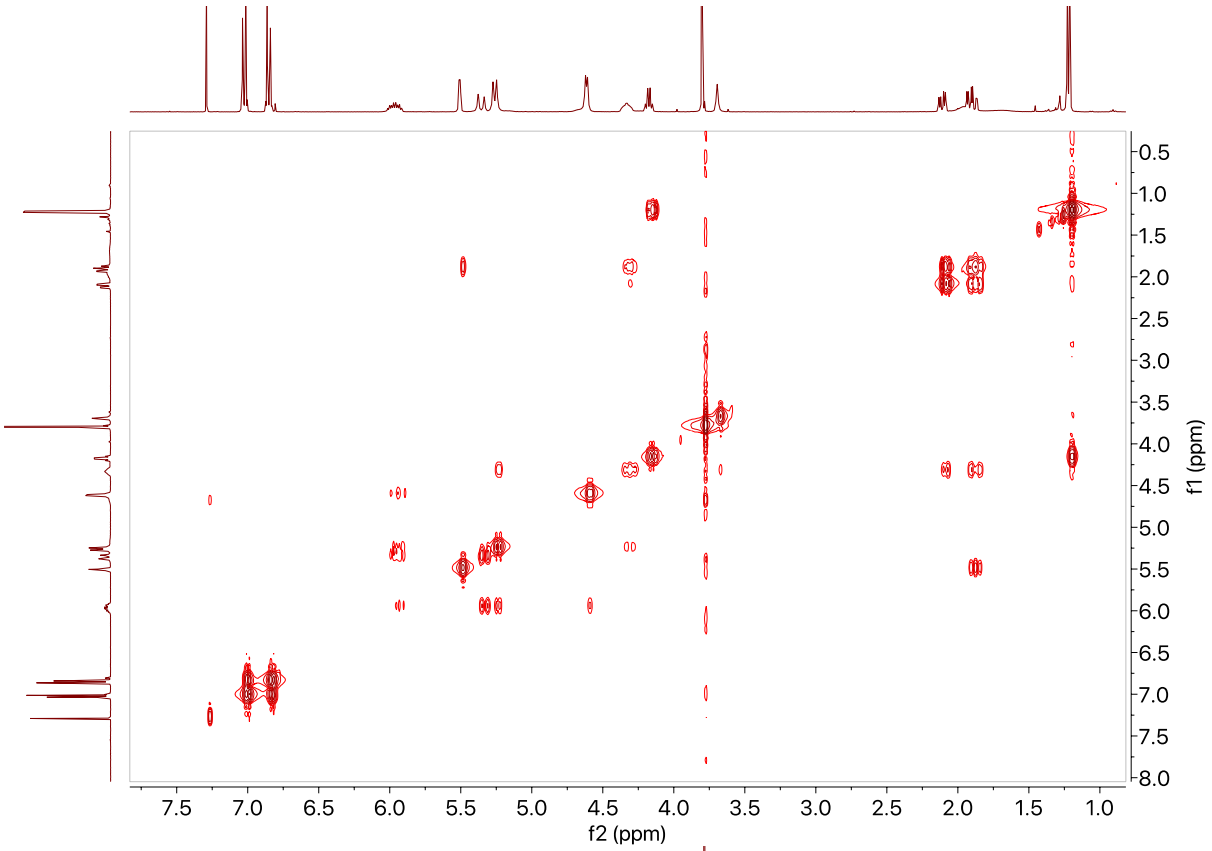
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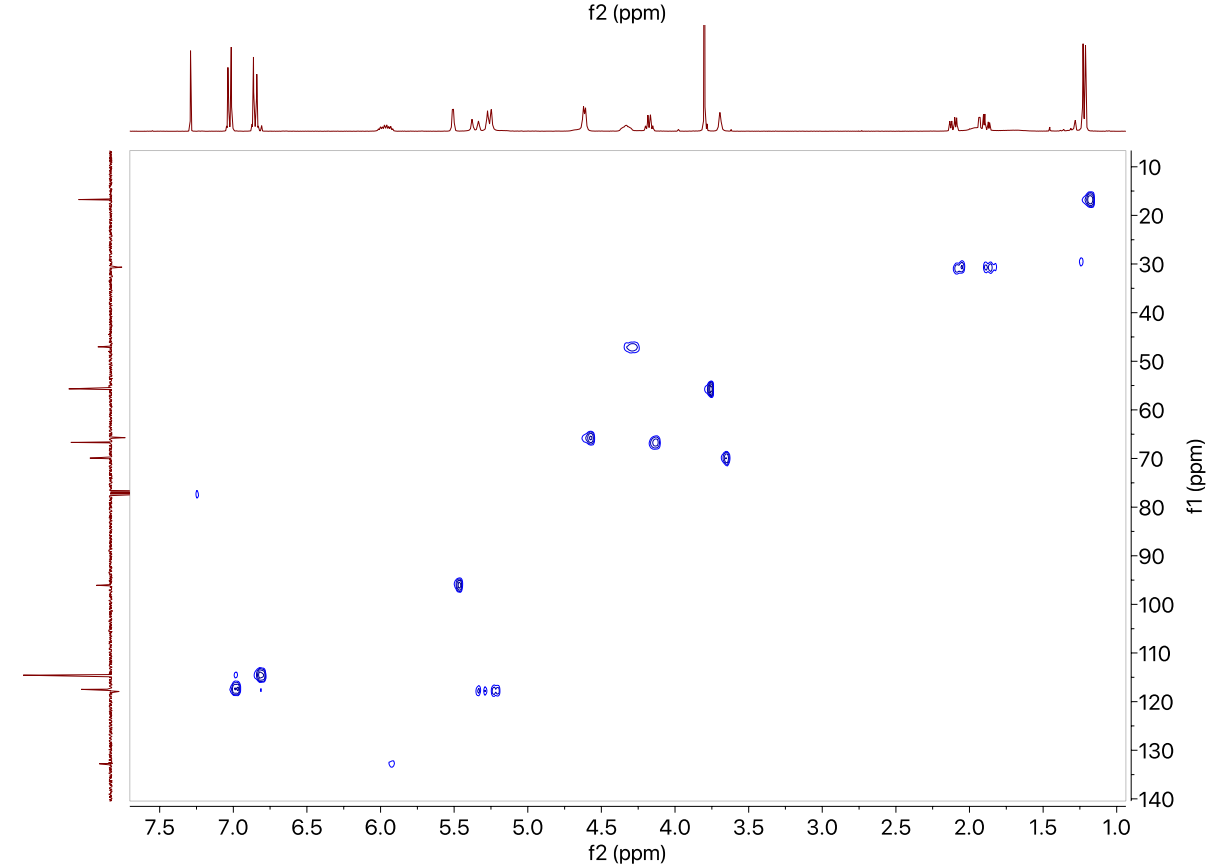
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1.0
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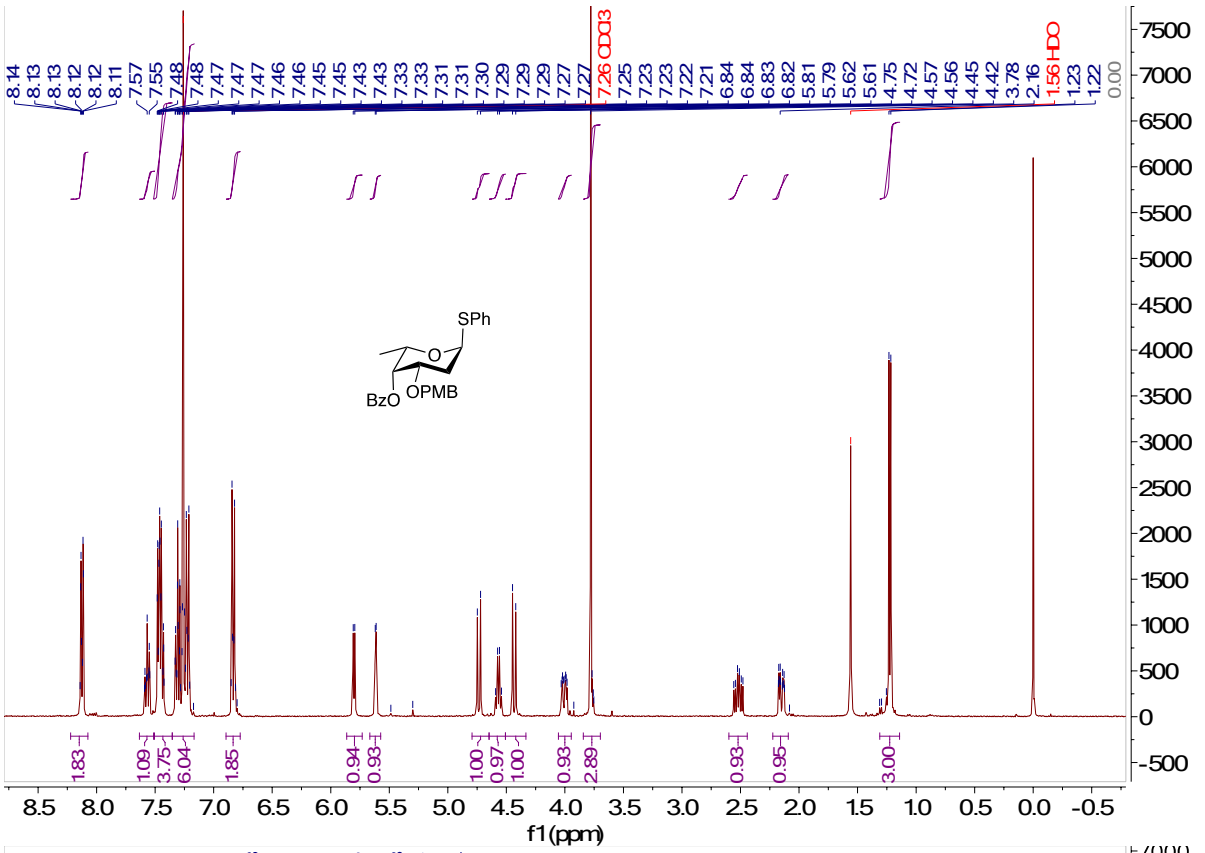
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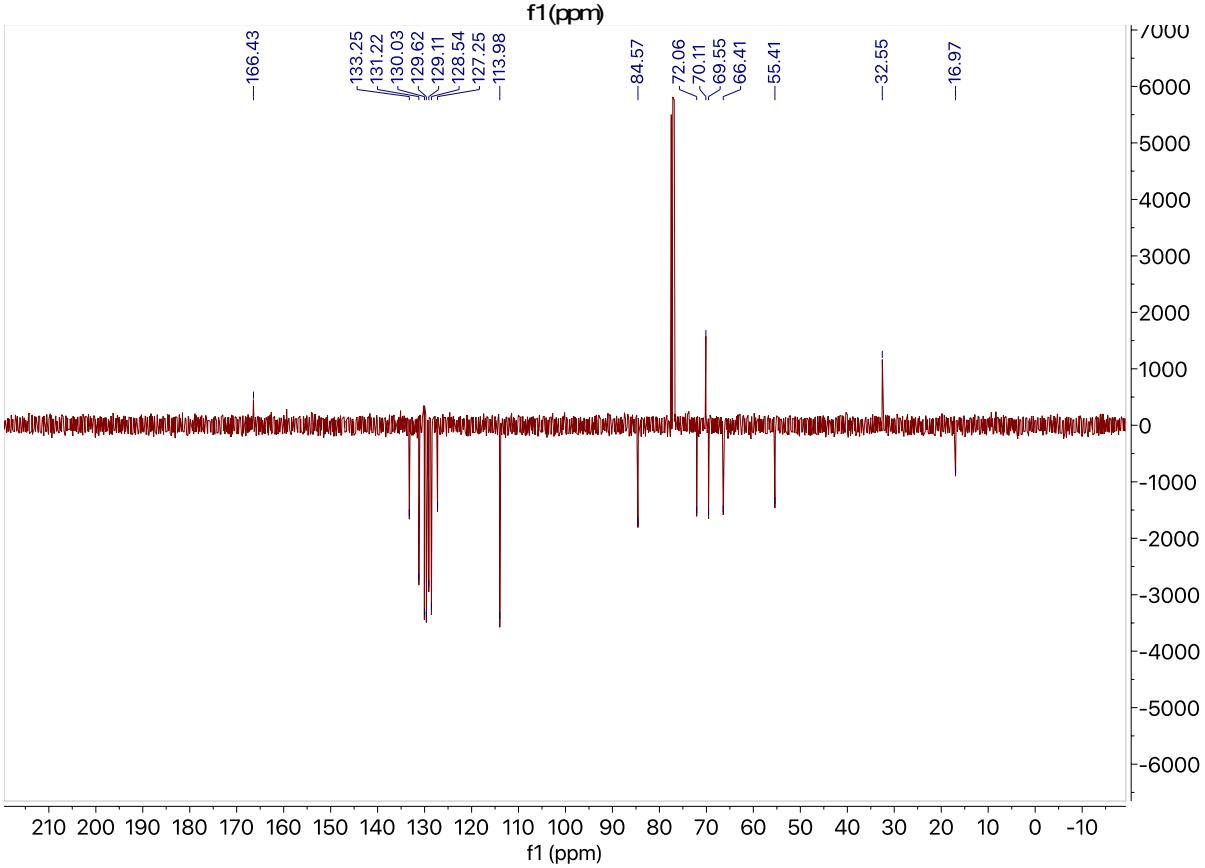
BzO
OPMB
f1 (ppm)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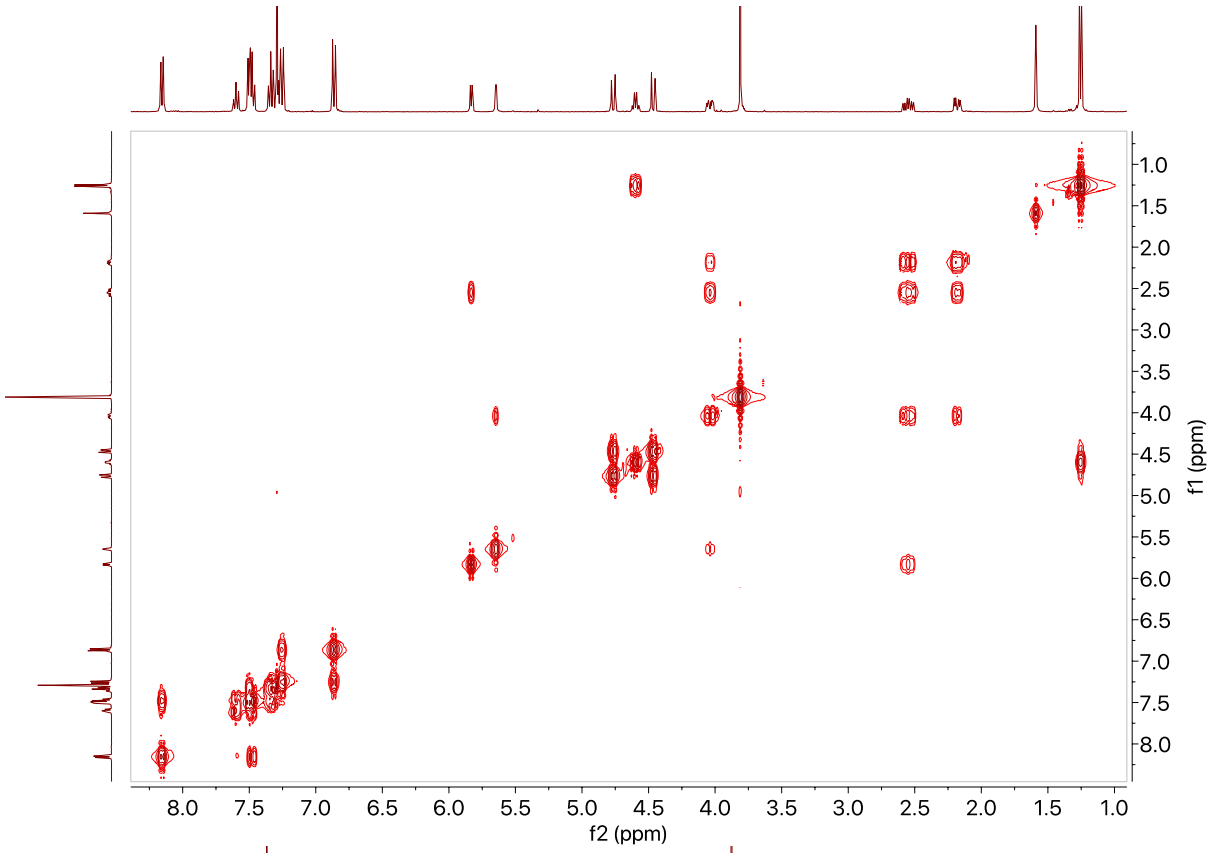
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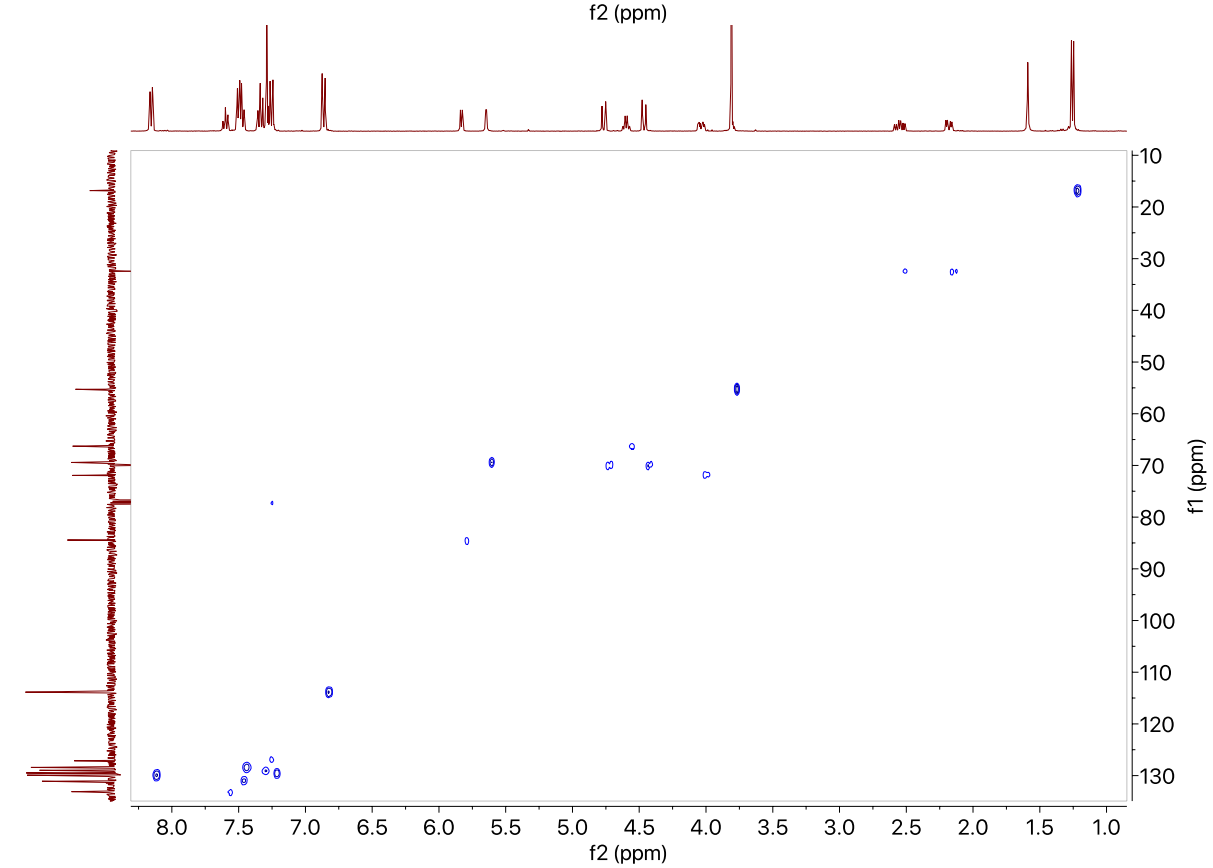
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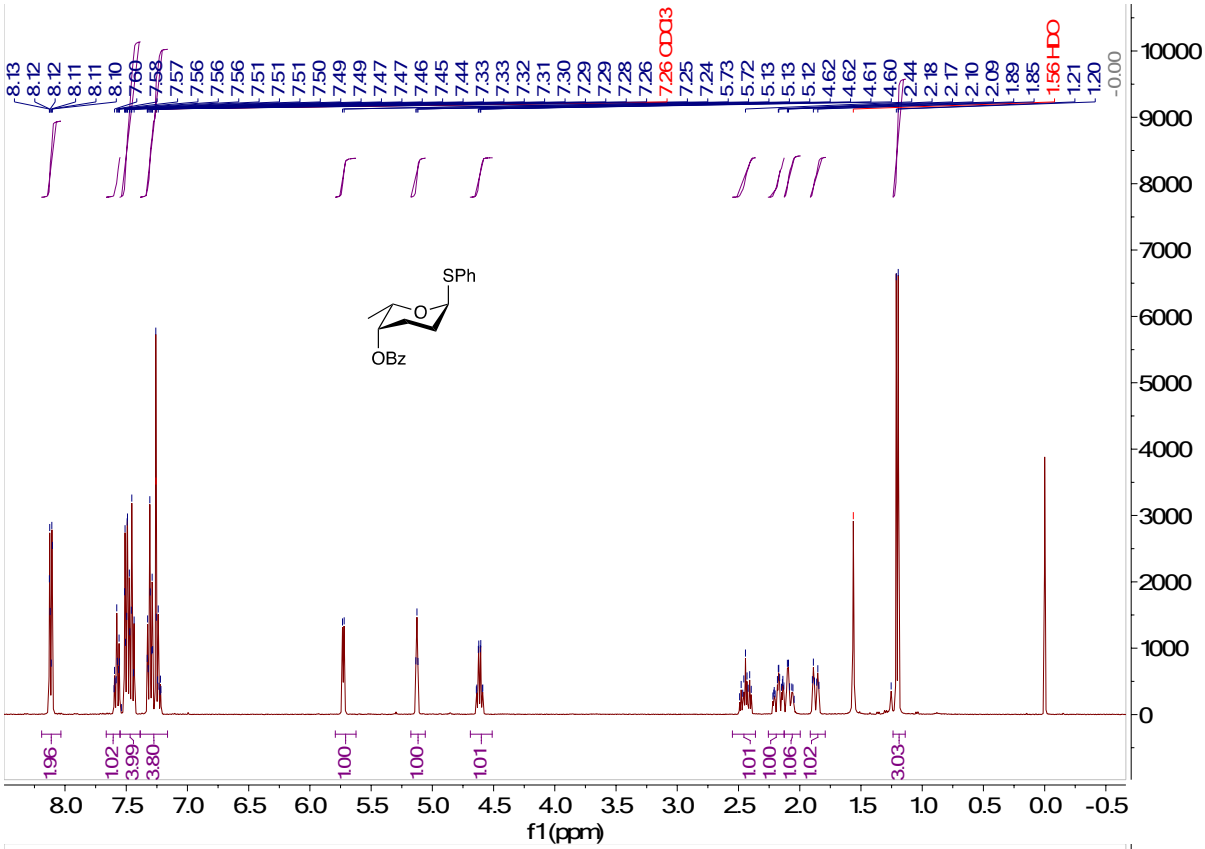
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OBz
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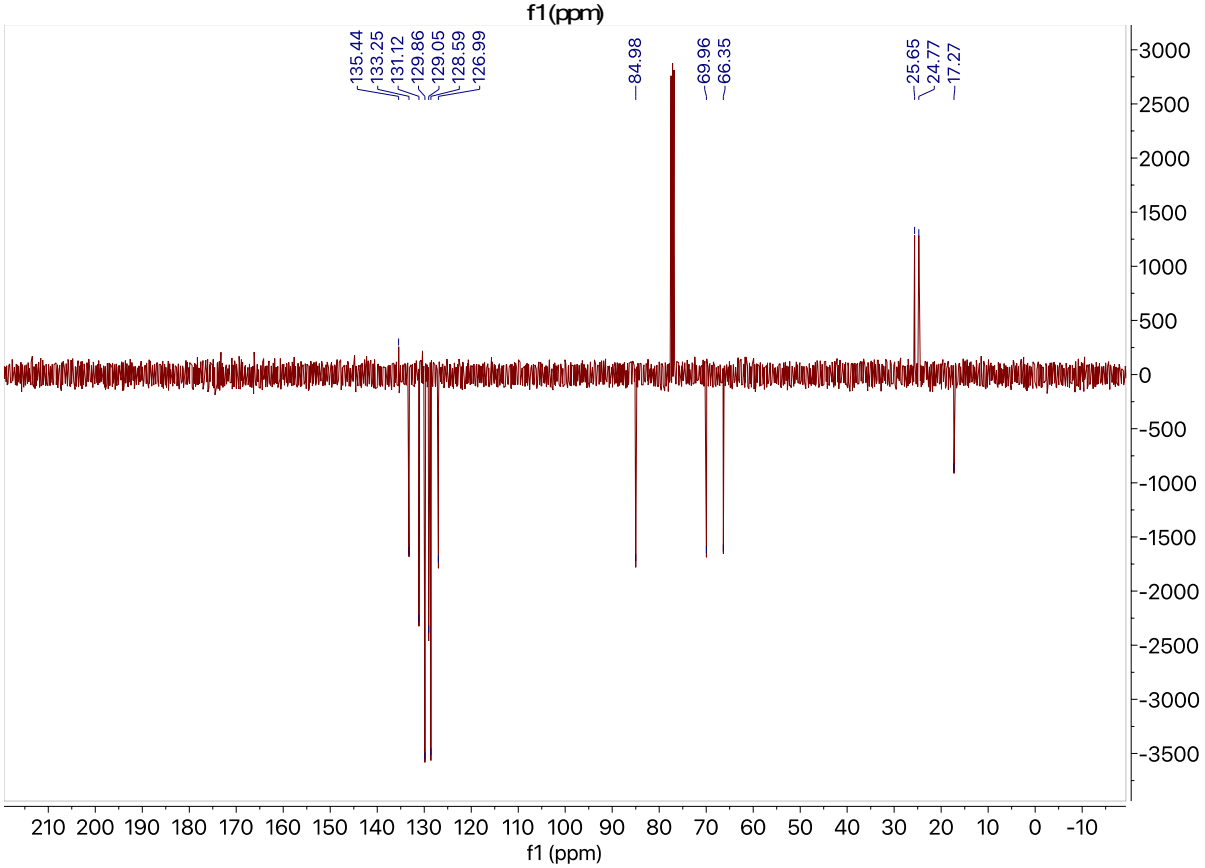
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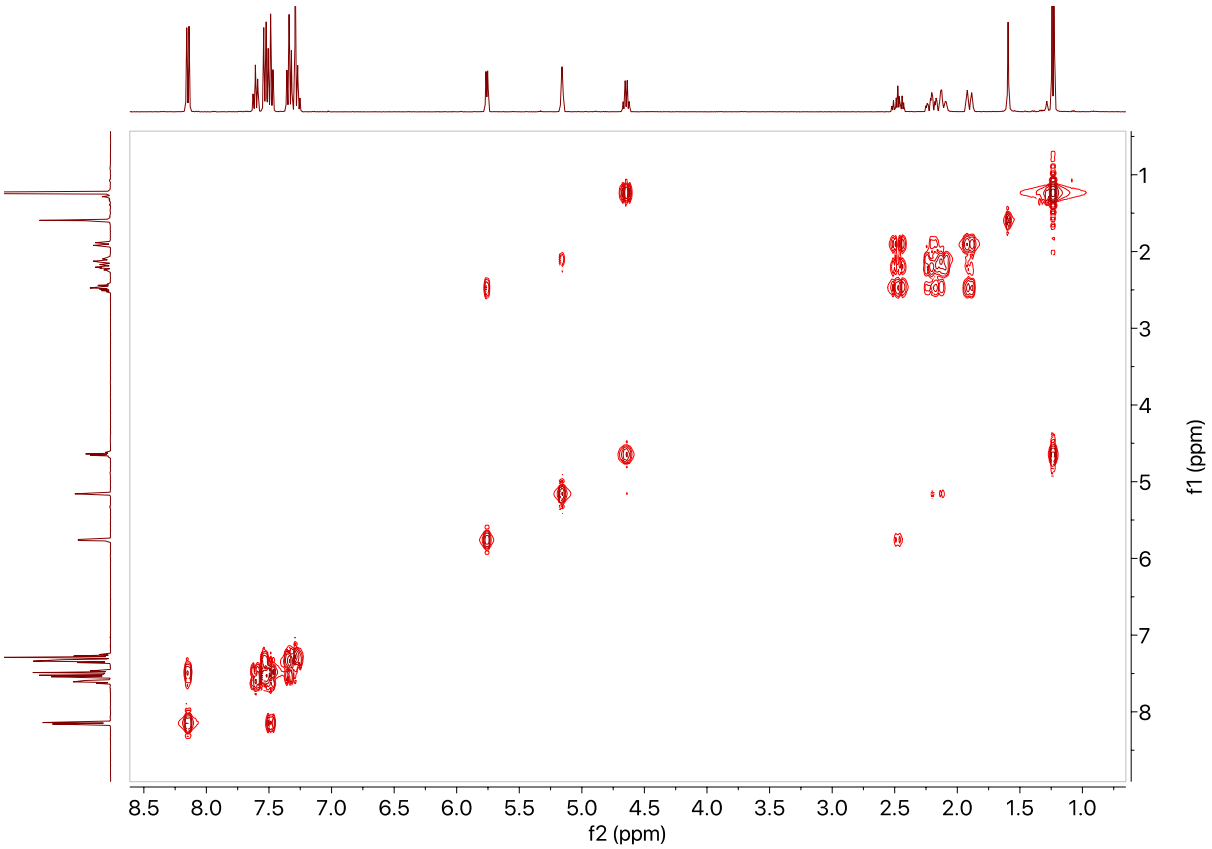
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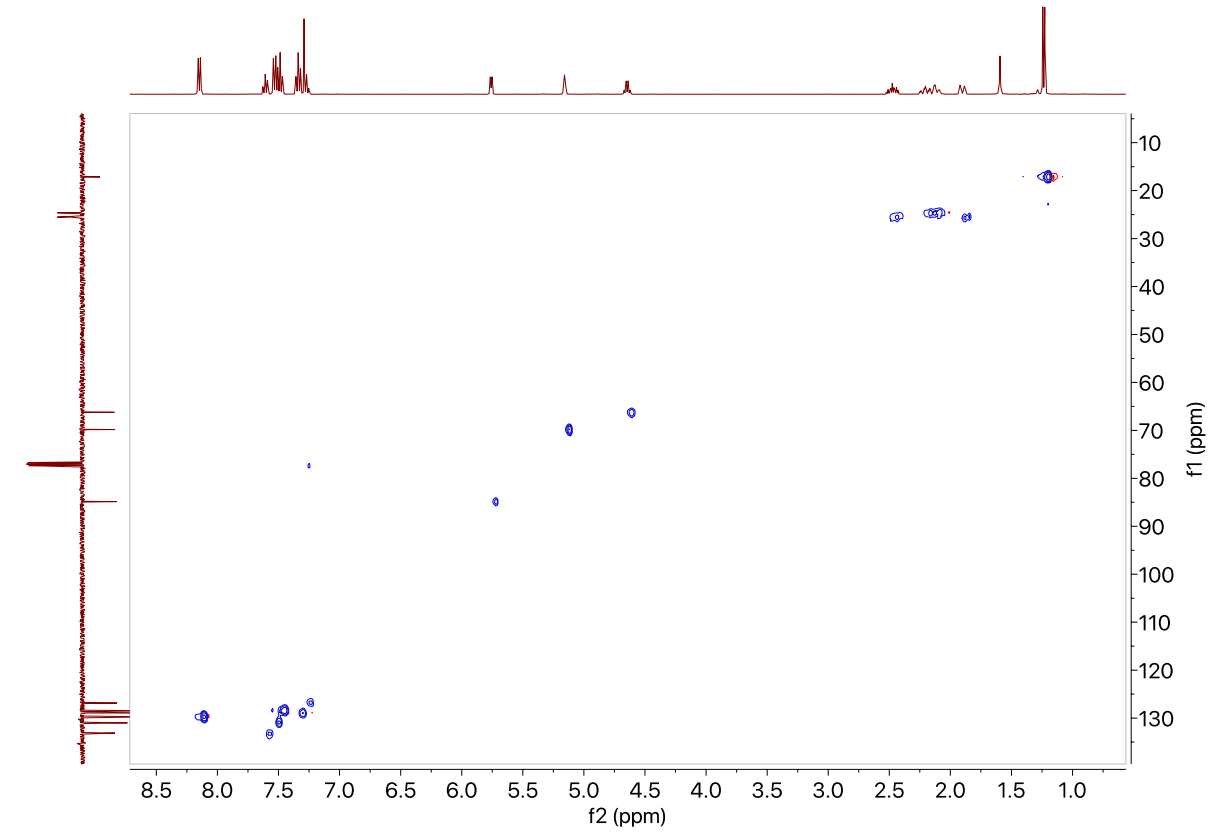
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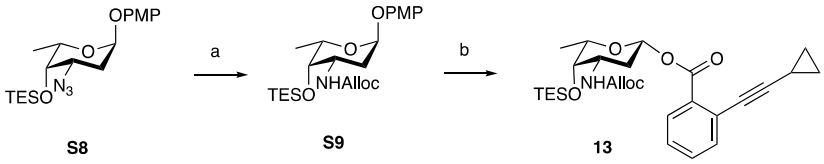
G: Additional info on the synthesis of anthracycline monosaccharides **2** and **4** and accompanying NMR data

The synthesis of **3** is described in (1) Qiao, X.; Zanden, S. Y. van der; Wander, D. P. A.; Borràs, D. M.; Song, J.-Y.; Li, X.; Duikeren, S. van; Gils, N. van; Rutten, A.; Herwaarden, T. van; Tellingen, O. van; Giacomelli, E.; Bellin, M.; Orlova, V.; Tertoolen, L. G. J.; Gerhardt, S.; Akkermans, J. J.; Bakker, J. M.; Zuur, C. L.; Pang, B.; Smits, A. M.; Mummery, C. L.; Smit, L.; Arens, R.; Li, J.; Overkleeft, H. S.; Neefjes, J. Uncoupling DNA Damage from Chromatin Damage to Detoxify Doxorubicin. *Proc. Natl. Acad. Sci.* **2020**, doi/10.1073/pnas.1922072117.

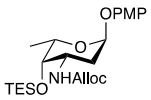
Synthesis of 13



S8 **S9** **13**

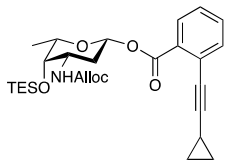
Scheme S2. Reagents and conditions: (a) (1) polymer-bound PPh_3, THF/H_2O (10:1, v/v), (2) Alloc-Cl, pyr. DCM, 88% over 2 steps; (b) **20**, EDCI.HCl, DIPEA, DMAP, CH_2Cl_2, 73% over 2 steps;

***p*-Methoxyphenyl-3-N-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (S9)**

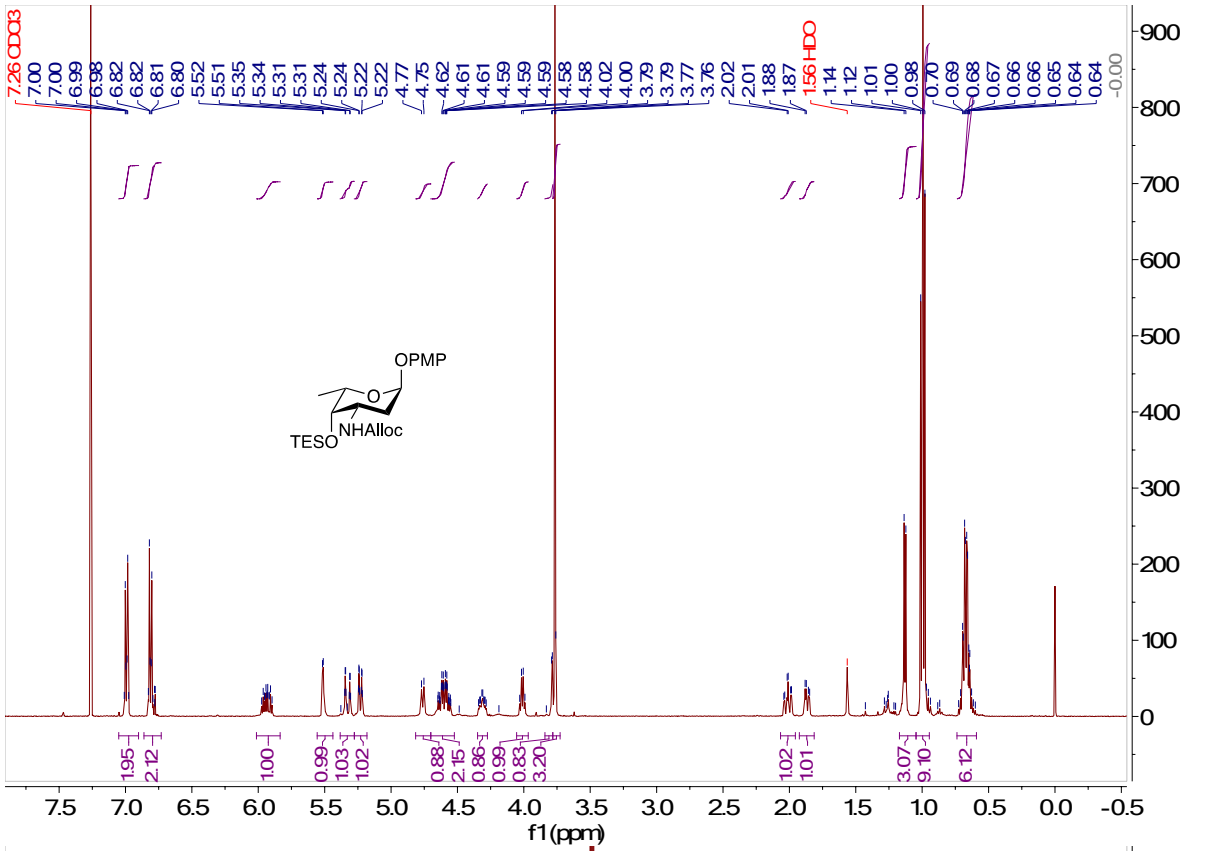


To a solution of **S8**[6] (862 mg, 2.19 mmol) in THF/H_2O (80 mL, 10:1 v/v) was added polymer-bound PPh_3 (1.46 g, 4.38 mmol, 2 eq) and the mixture was stirred overnight at 50 °C. Then, an additional portion of polymer-bound PPh_3 (0.73 g, 2.19 mmol, 1 eq) and the mixture was stirred an additional night at 50 °C. It was then filtered off and concentrated *in vacuo*. The resulting amine was dissolved in DCM (15.7 mL) to which pyridine (0.53 mL, 6.57 mmol, 3 eq) and allyl chloroformate (0.35 mL, 3.29 mmol, 1.5 eq) were added at -20 °C. After stirring at that temperature for 15 minutes, the reaction was allowed to warm up to RT, and poured into sat. aq. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 – 10:90 EtOAc:pentane) gave the title compound as a yellow oil (870 mg, 1.93 mmol, 88% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.05 – 6.90 (m, 2H), 6.86 – 6.73 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.51 (d, *J* = 2.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.76 (d, *J* = 9.1 Hz, 1H), 4.60 (qdt, *J* = 13.4, 5.8, 1.5 Hz, 2H), 4.35 – 4.27 (m, 1H), 4.01 (q, *J* = 6.5 Hz, 1H), 3.79 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.01 (td, *J* = 12.7, 3.5 Hz, 1H), 1.86 (dd, *J* = 12.5, 4.4 Hz, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.67 (qd, *J* = 7.9, 3.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 154.6, 151.1, 133.0, 117.8, 117.5, 114.7, 96.2, 71.4, 67.4, 65.7, 55.8, 47.5, 30.6, 17.7, 7.2, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{23}H_{37}NO_6SiNa$: 474.2288; found 474.2288.

***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-β-L-fucopyranoside (13)**



Prepared according to General Procedure A and B from **S9** (225 mg, 0.500 mmol), to give after column chromatography (5:95 – 30:70 EtOAc:pentane) gave the title compound as a clear oil (158 mg, 0.308 mmol, 61% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.2, 5.7 Hz, 1H), 6.01 – 5.84 (m, 2H), 5.40 – 5.17 (m, 2H), 4.84 (d, *J* = 9.1 Hz, 1H), 4.59 (qdt, *J* = 13.3, 5.8, 1.5 Hz, 2H), 3.93 (qd, *J* = 9.0, 2.7 Hz, 1H), 3.78 – 3.62 (m, 2H), 2.00 – 1.87 (m, 2H), 1.51 (tt, *J* = 7.2, 5.8 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.82 (m, 4H), 0.67 (qd, *J* = 7.8, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 155.4, 134.3, 132.8, 132.0, 130.9, 127.0, 125.2, 117.9, 99.8, 93.4, 74.6, 73.1, 70.3, 65.8, 50.8, 31.1, 17.6, 9.0, 7.2, 5.4, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2444; found 536.2449.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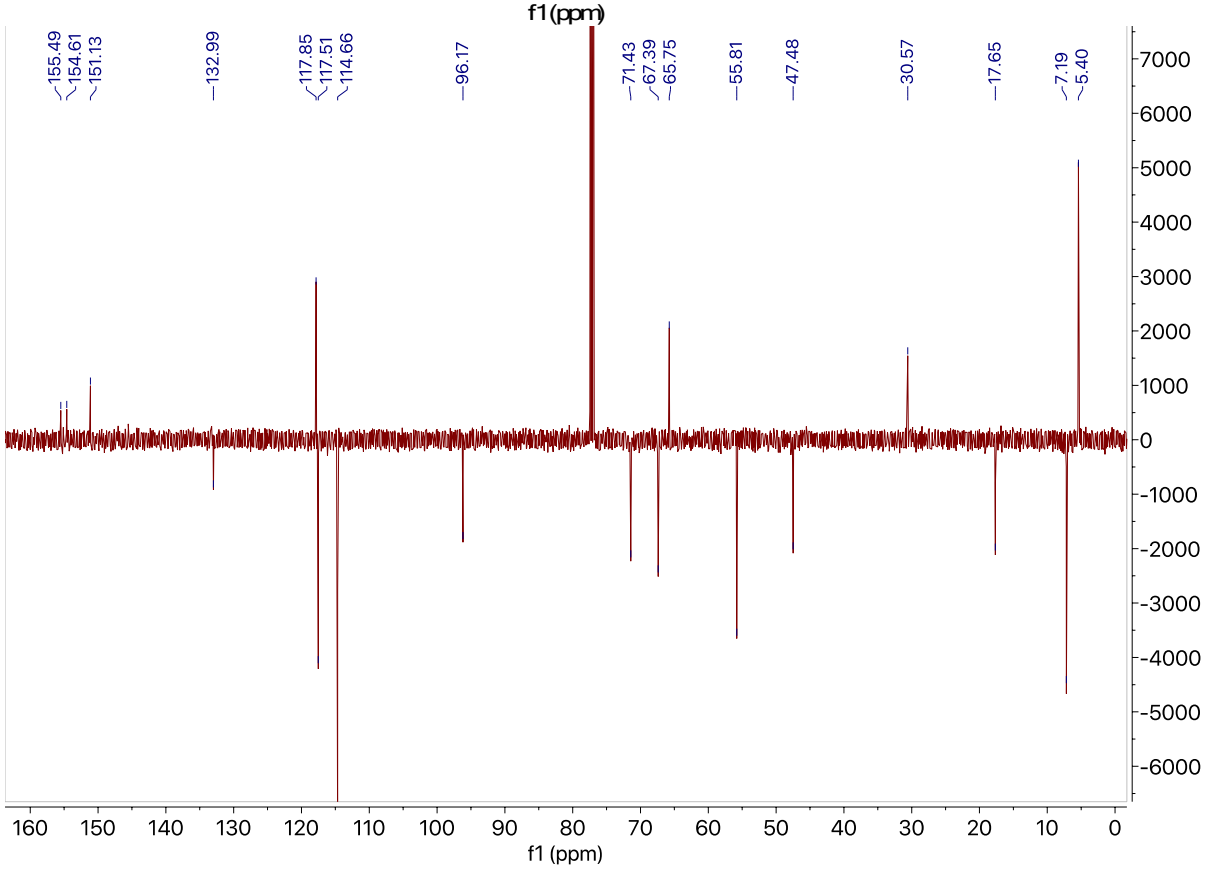
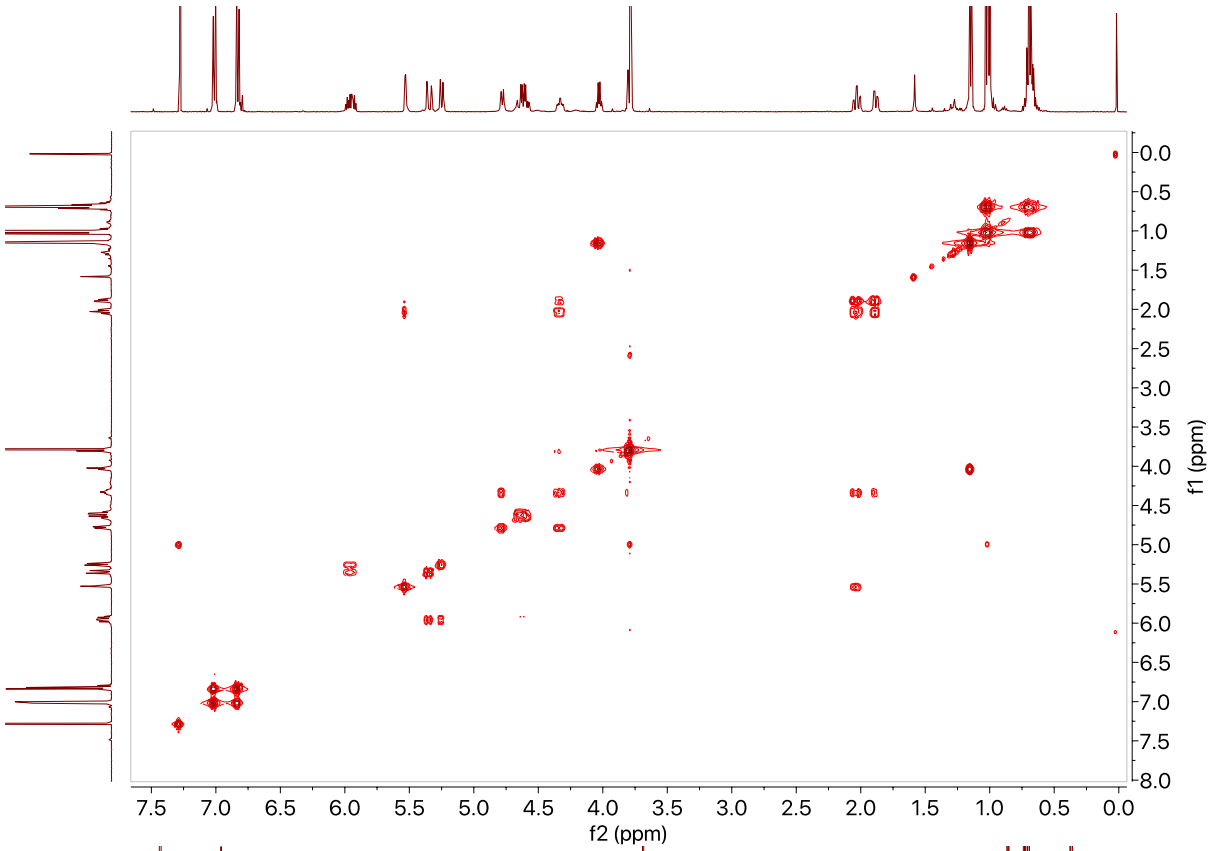

f1 (ppm)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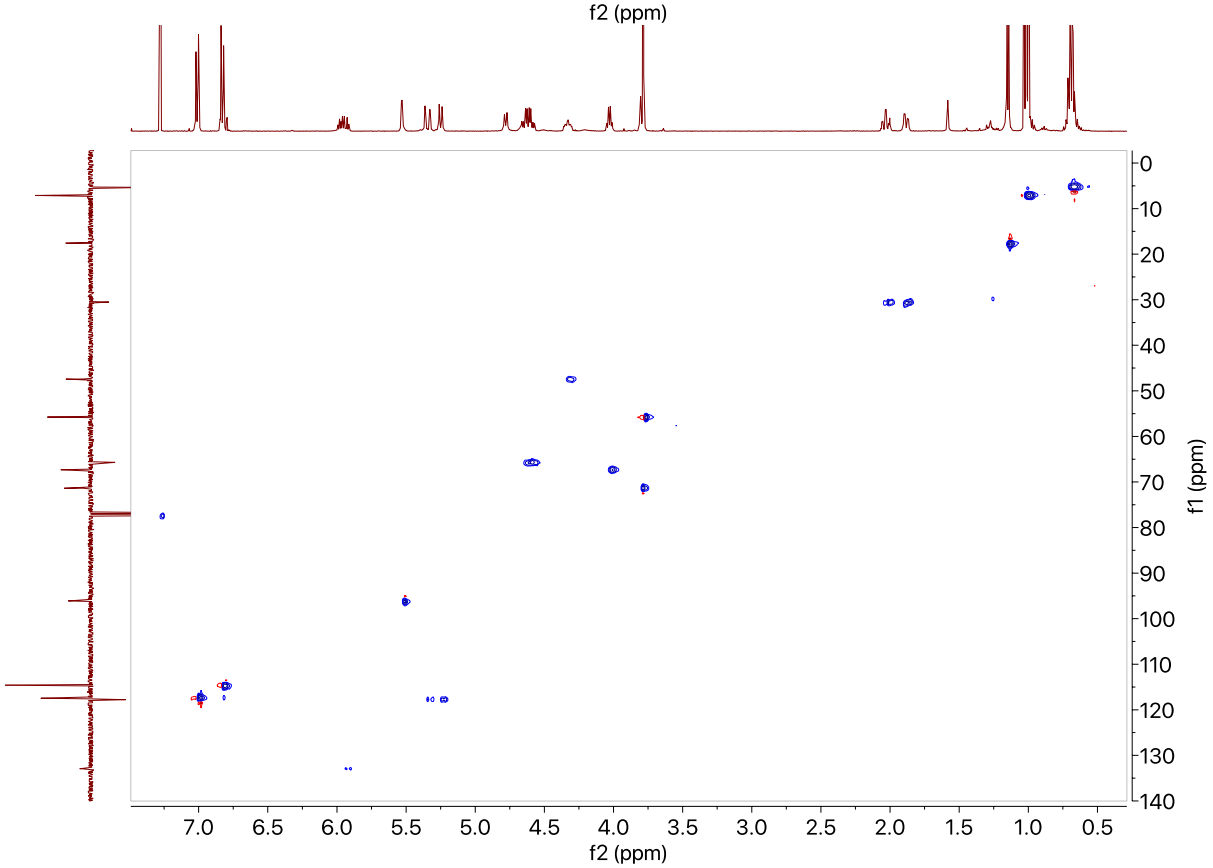
f1 (ppm)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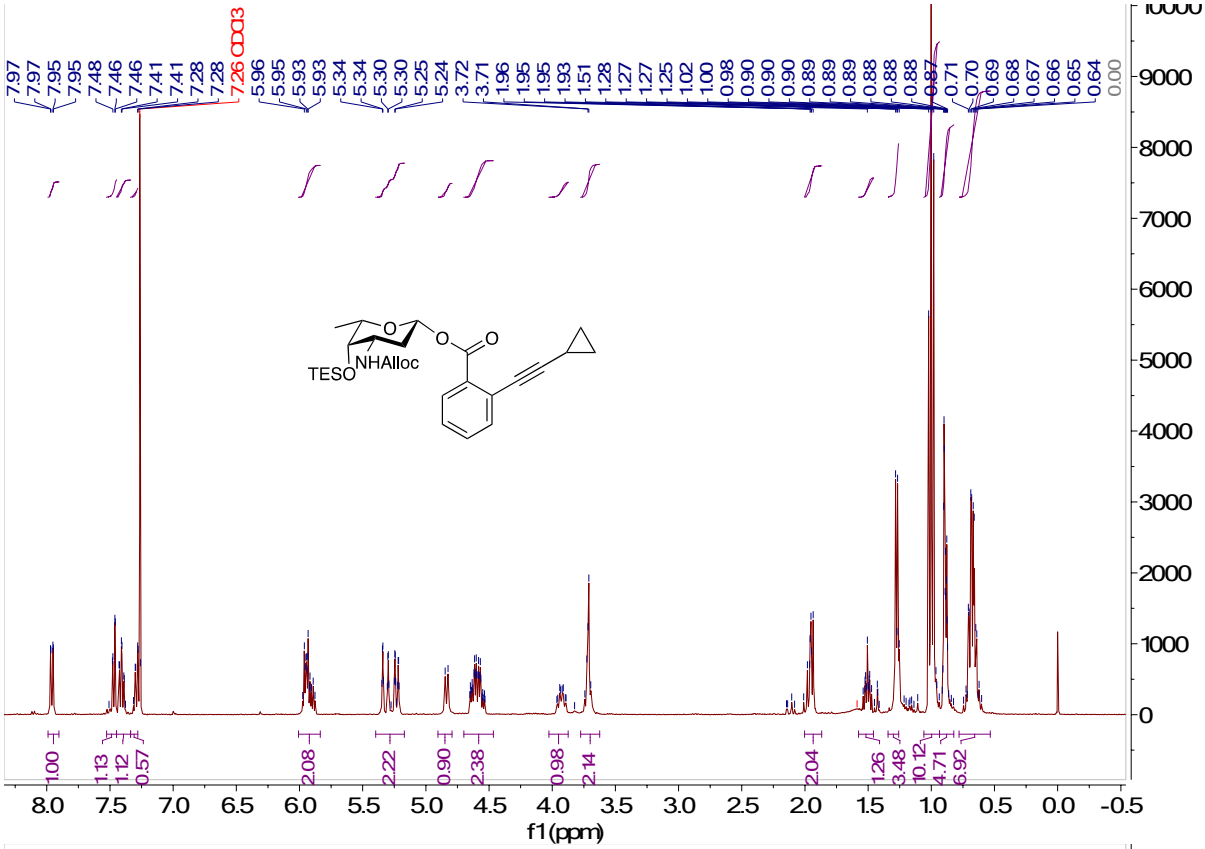
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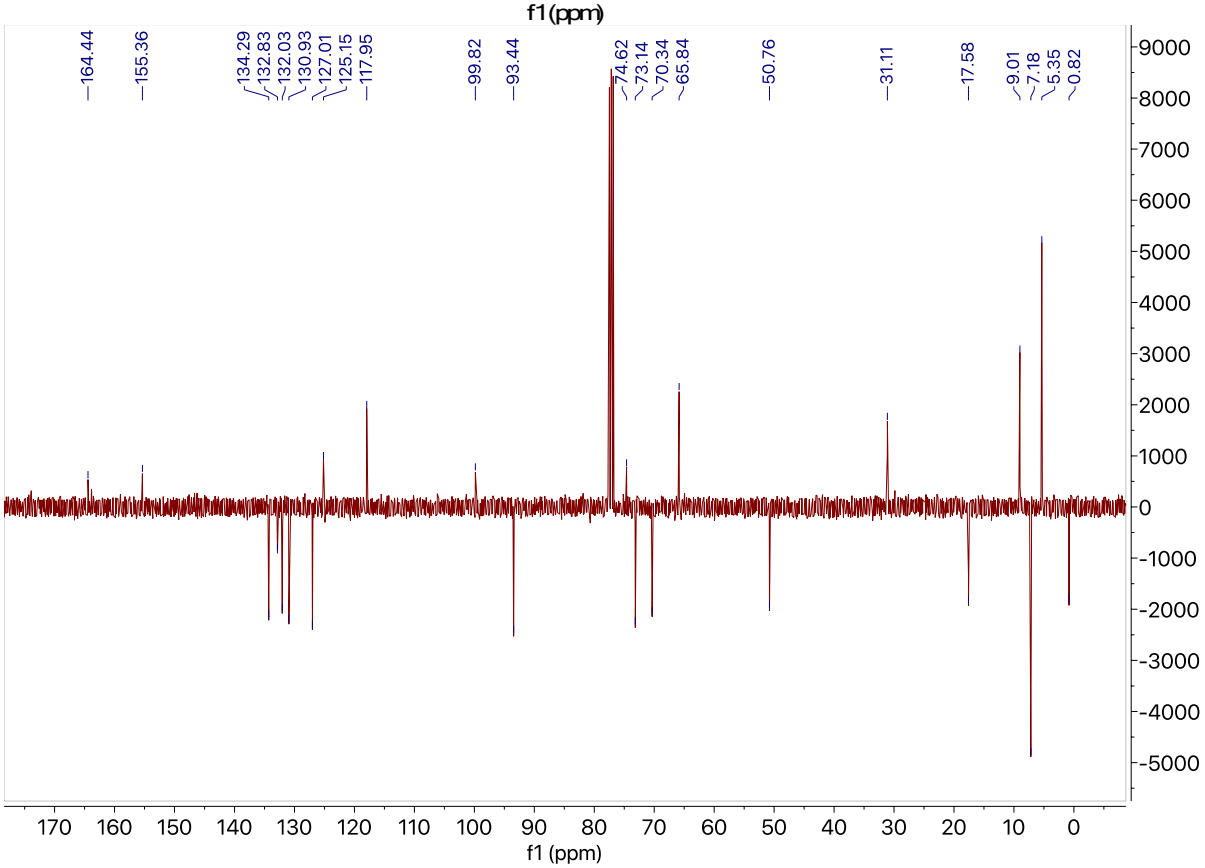
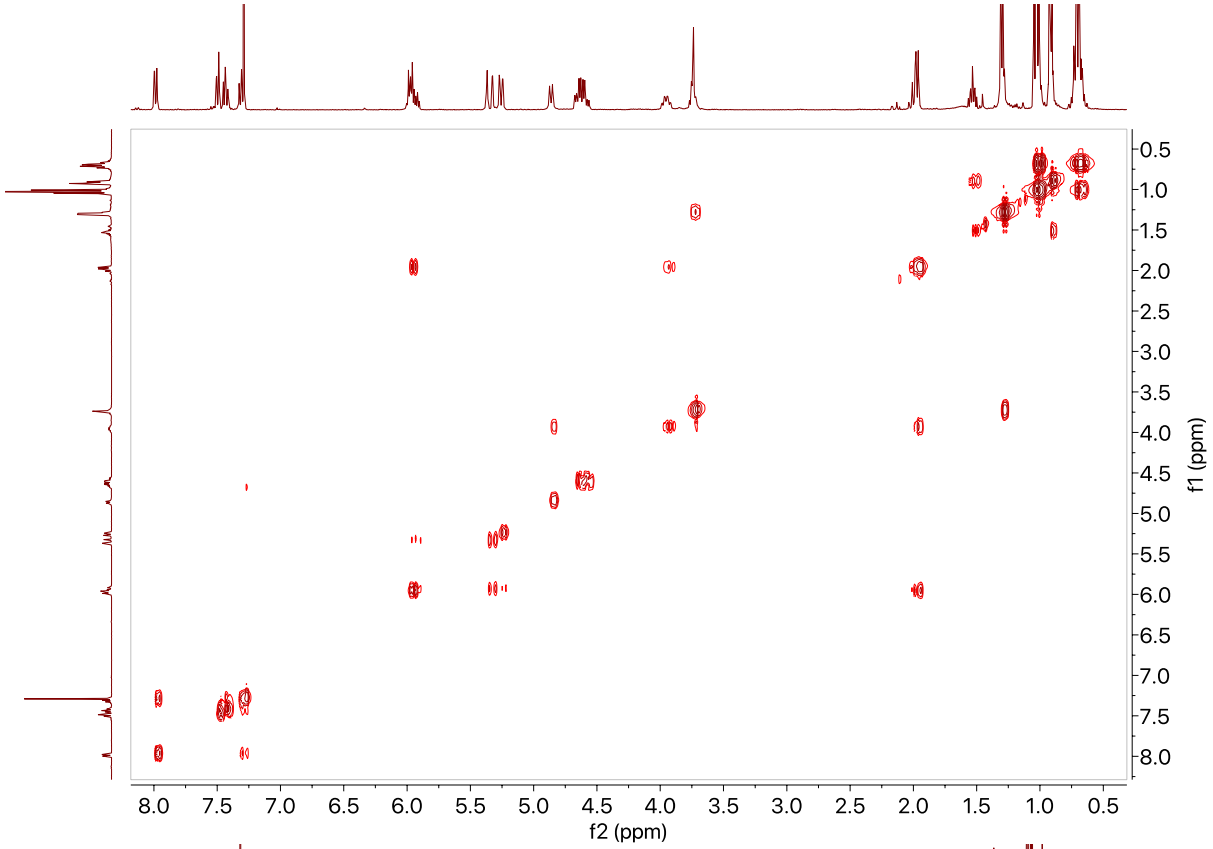
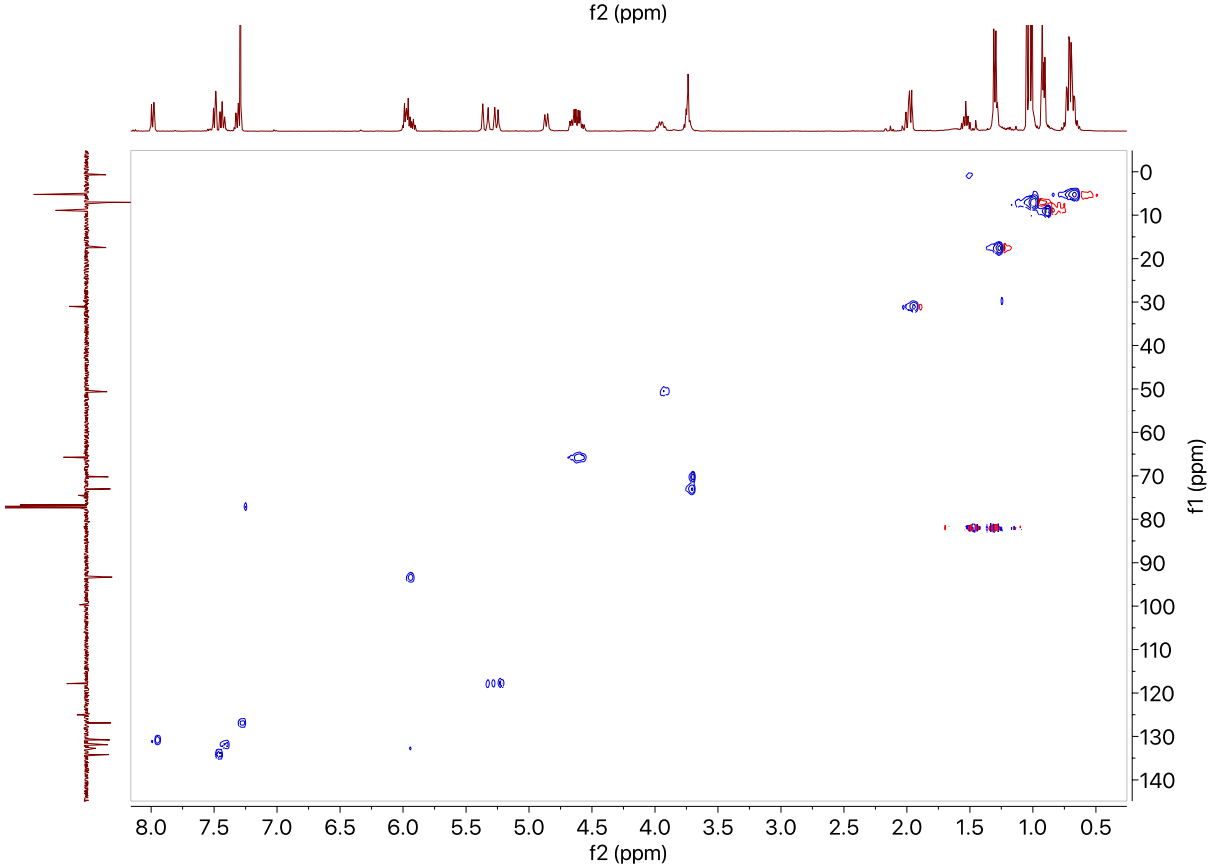
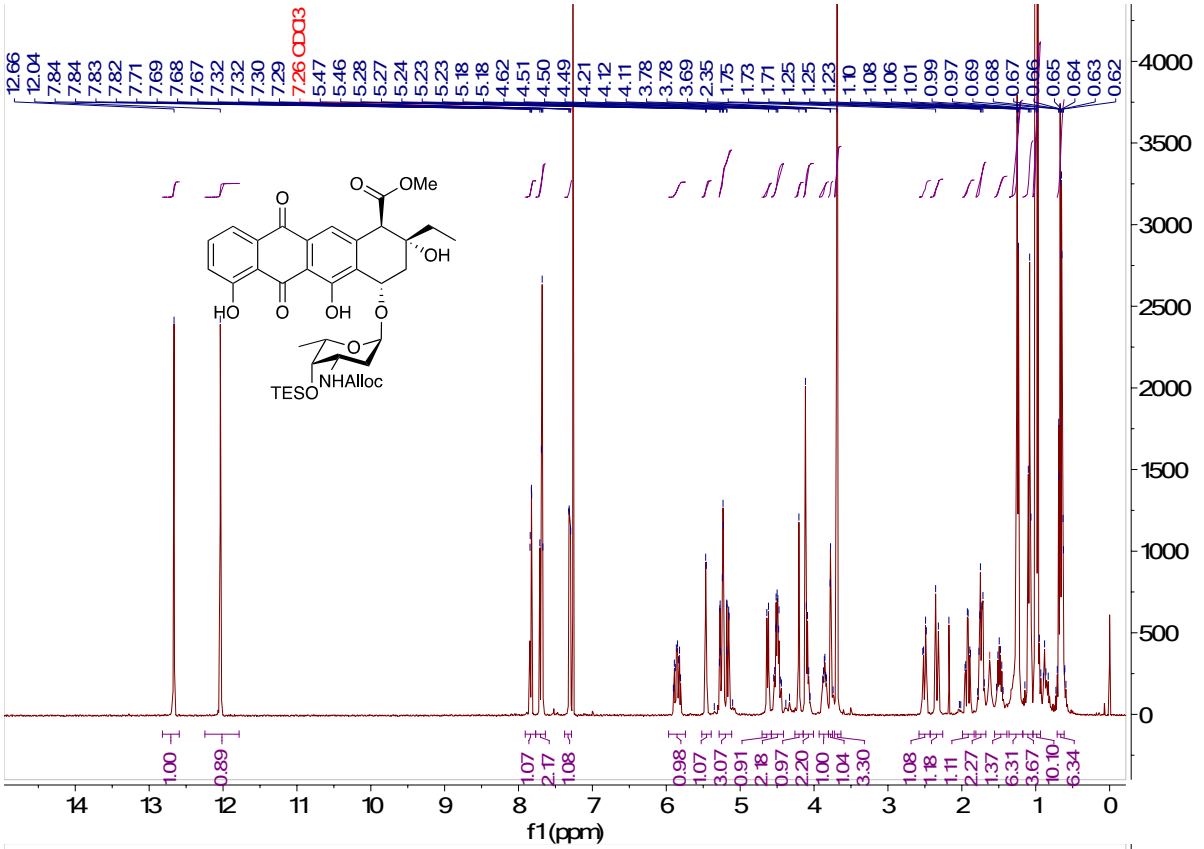
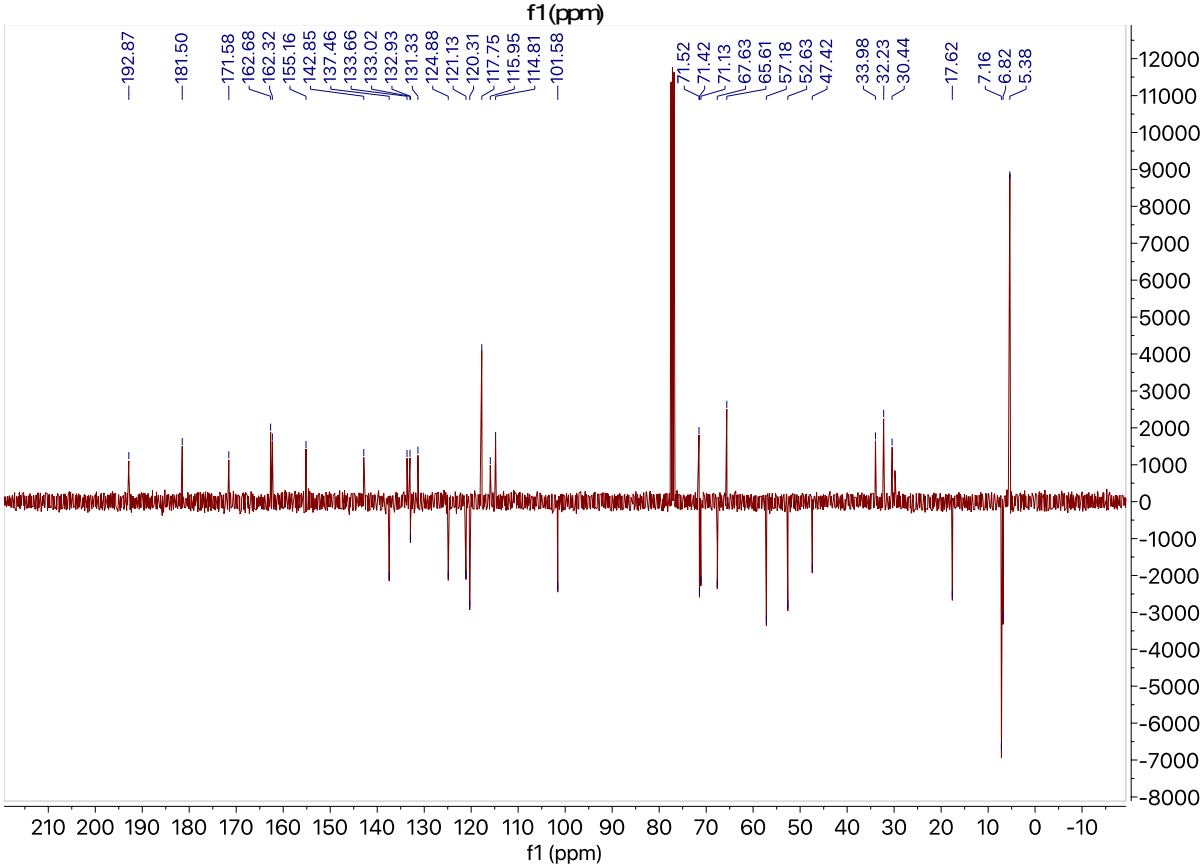
4.71
6.92
f1 (ppm)

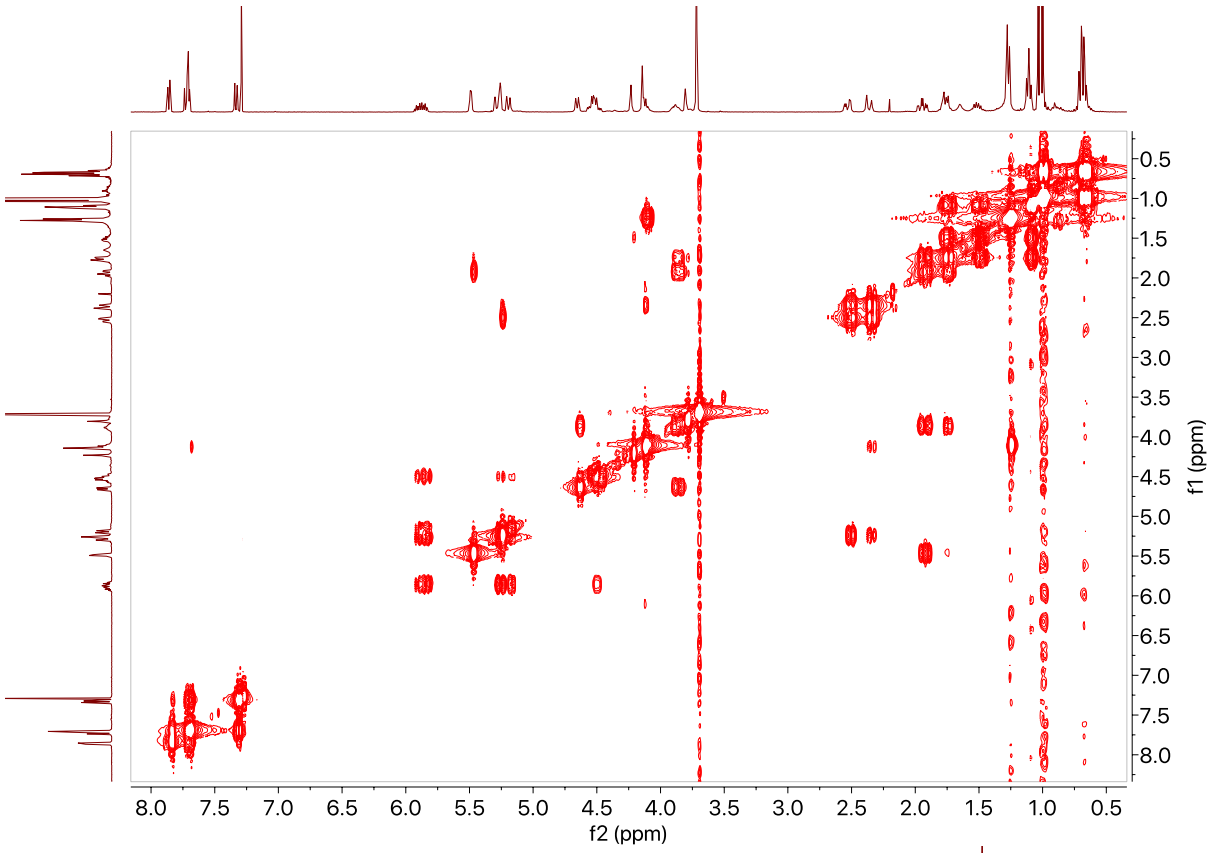

164.44
155.36
134.29
132.83
132.03
130.93
127.01
125.15
117.95
99.82
93.44
74.62
73.14
70.34
65.84
50.76
31.11
17.58
9.01
7.18
5.35
0.82
f1 (ppm)

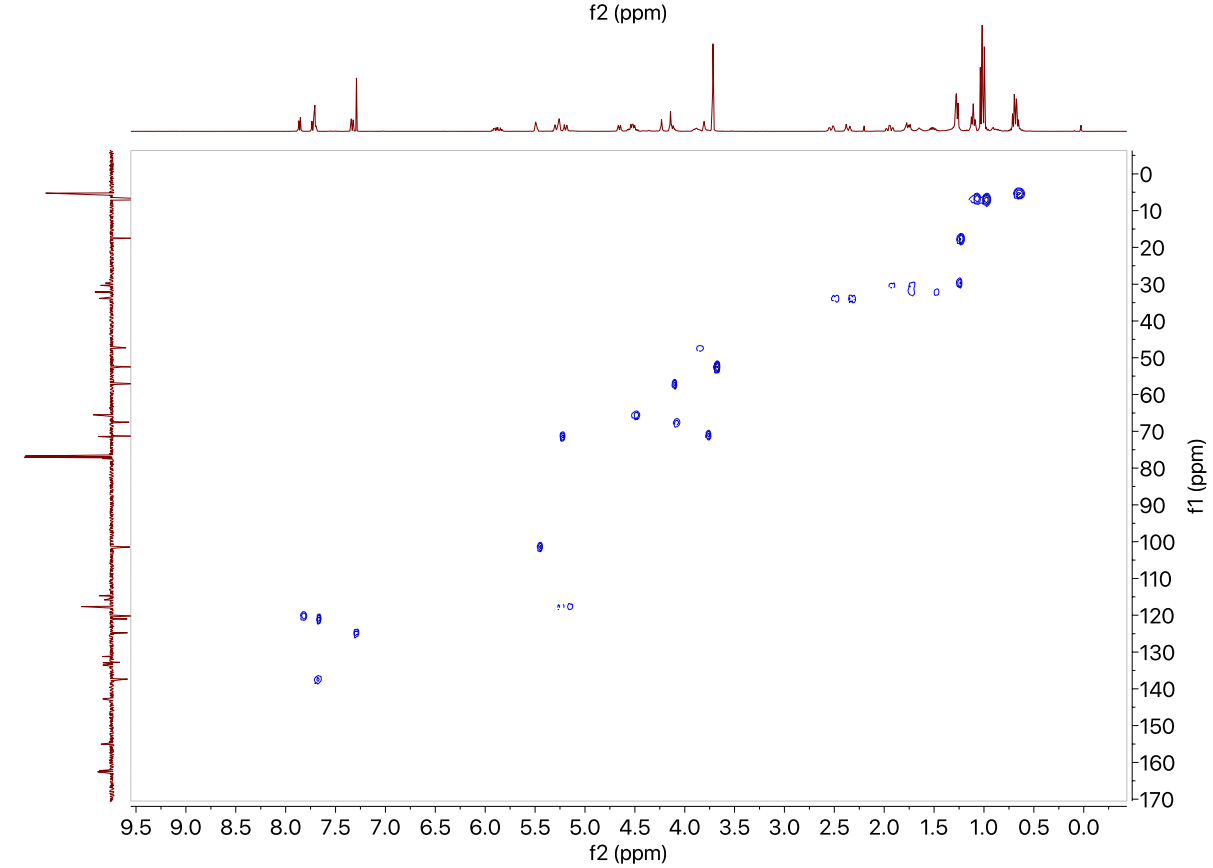

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

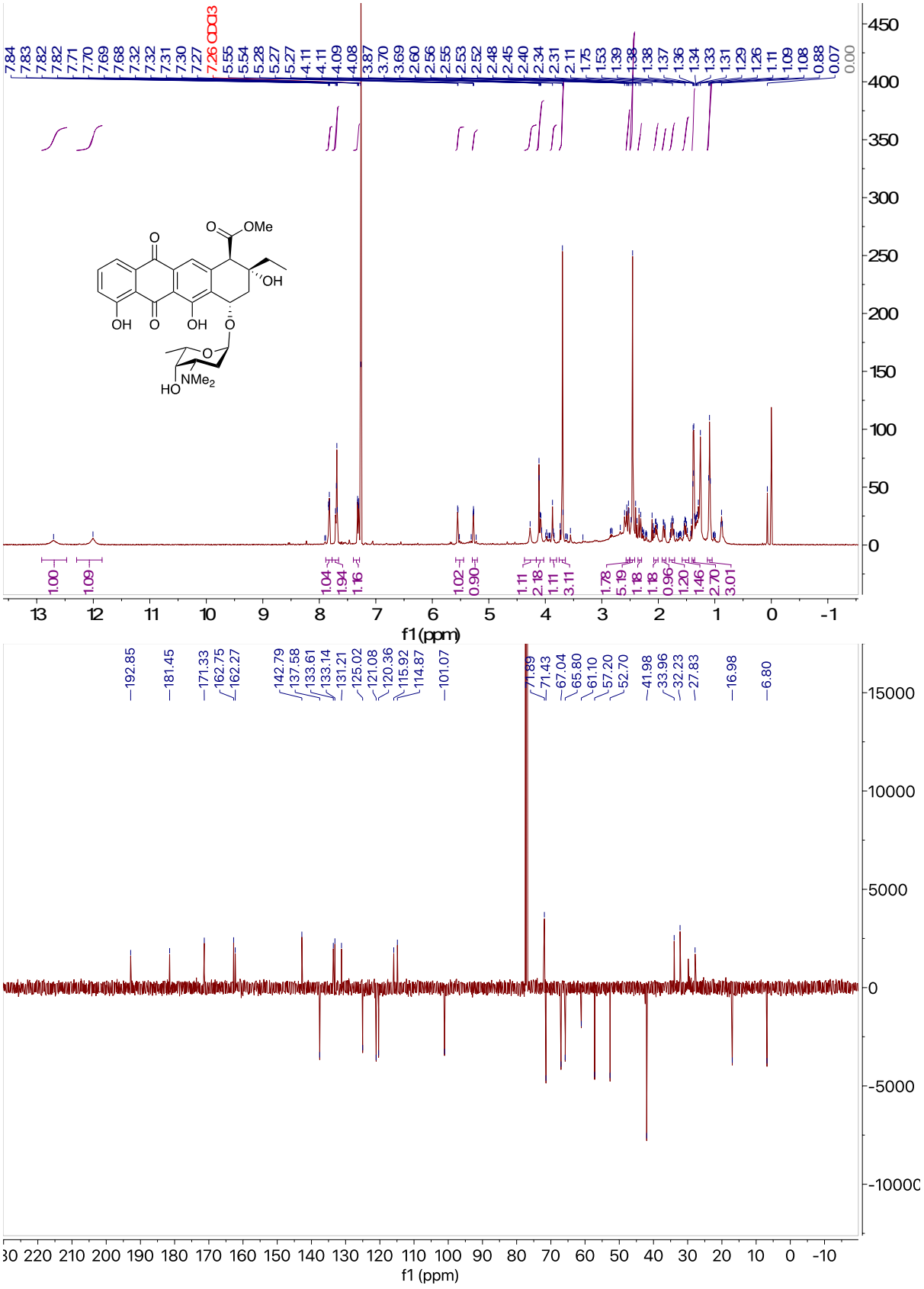

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

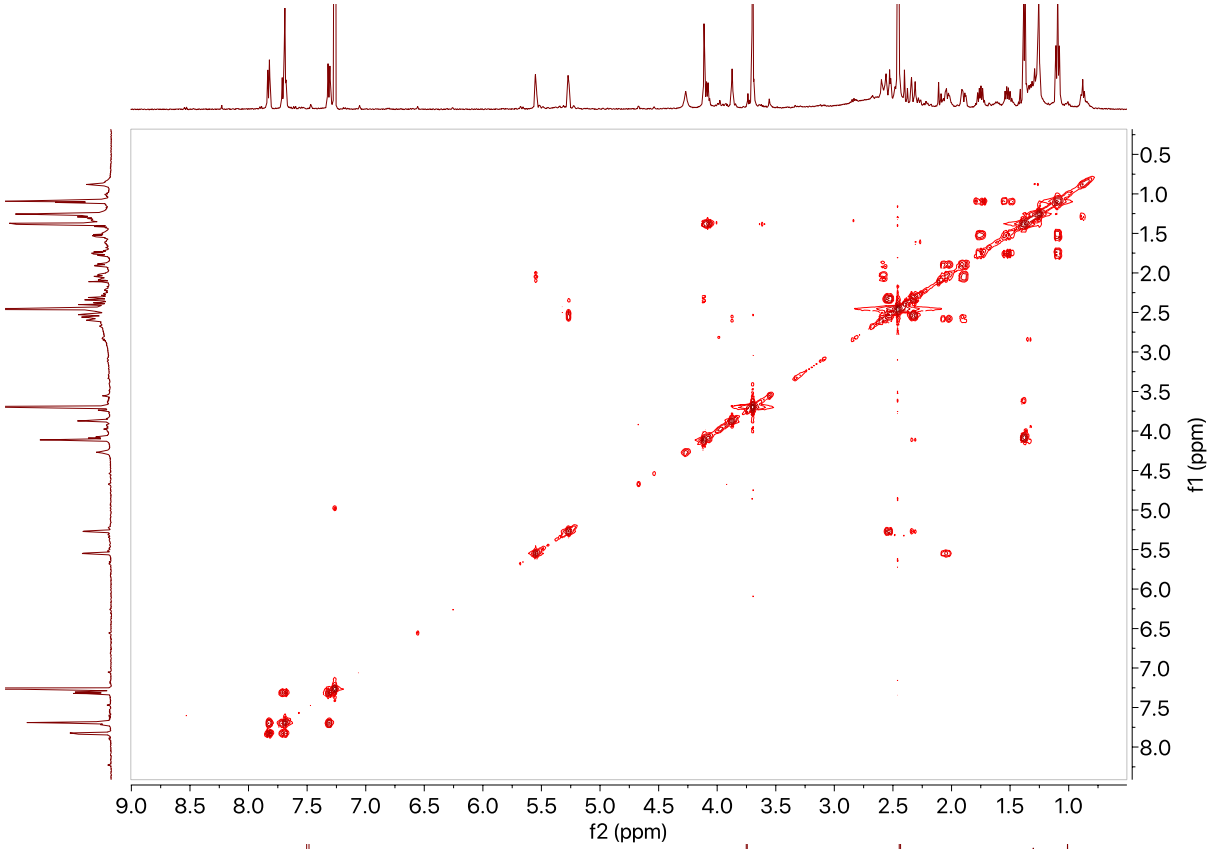

12.66
12.04
7.84
7.84
7.83
7.82
7.71
7.69
7.68
7.67
7.32
7.32
7.30
7.29
7.26 CDCl3
5.47
5.46
5.28
5.27
5.24
5.23
5.23
5.18
5.18
4.62
4.51
4.50
4.49
4.21
4.12
4.11
3.78
3.78
3.69
2.35
1.75
1.73
1.71
1.25
1.25
1.23
1.10
1.08
1.06
1.01
0.99
0.97
0.69
0.68
0.67
0.66
0.65
0.64
0.63
0.62
OMe
OH
HO
OH
TESO
NHAlloc
1.00
0.89
1.07
2.17
1.08
0.98
1.07
3.07
0.91
2.18
0.97
2.20
1.00
1.04
3.30
1.08
1.18
1.11
2.27
1.37
6.31
3.67
10.10
6.34
f1 (ppm)

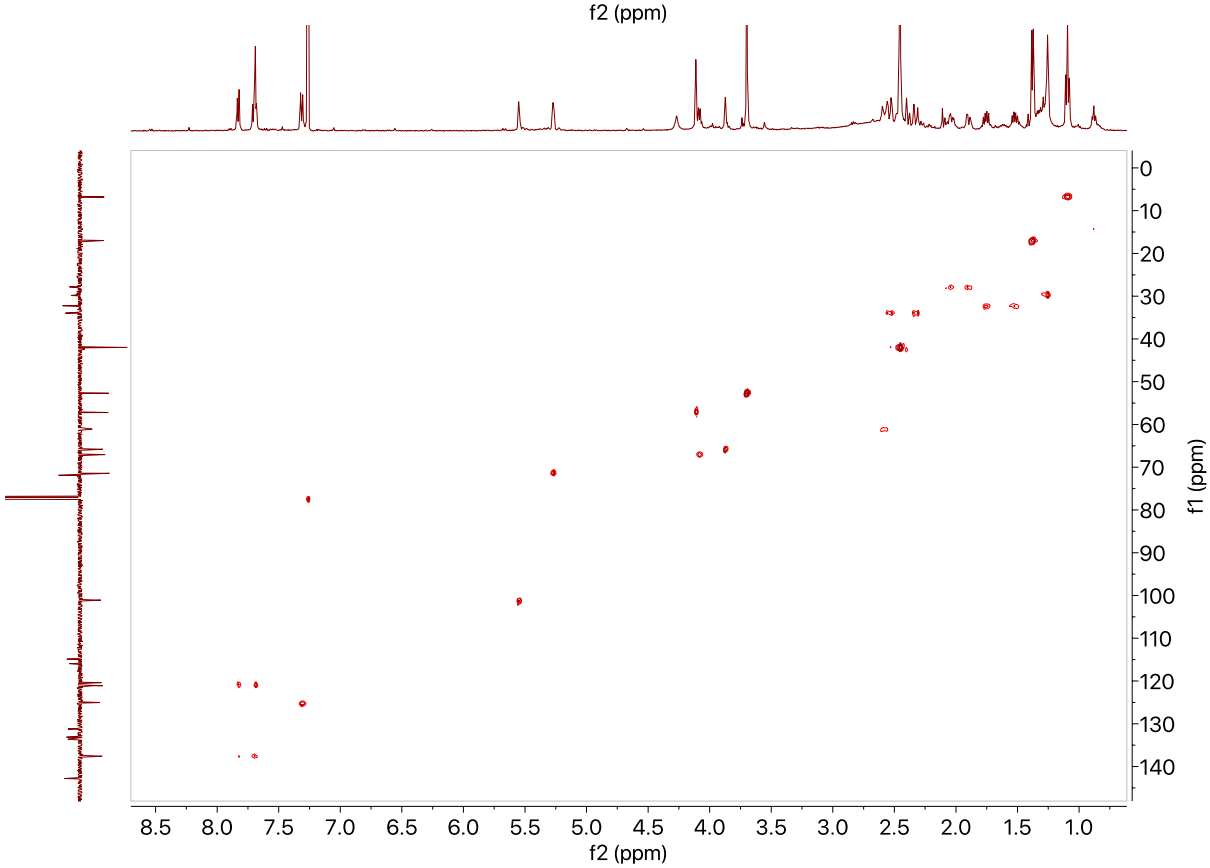

192.87
181.50
171.58
162.68
162.32
155.16
142.85
137.46
133.66
133.02
132.93
131.33
124.88
121.13
120.31
117.75
115.95
114.81
101.58
71.52
71.42
71.13
67.63
65.61
57.18
52.63
47.42
33.98
32.23
30.44
17.62
7.16
6.82
5.38
f1 (ppm)

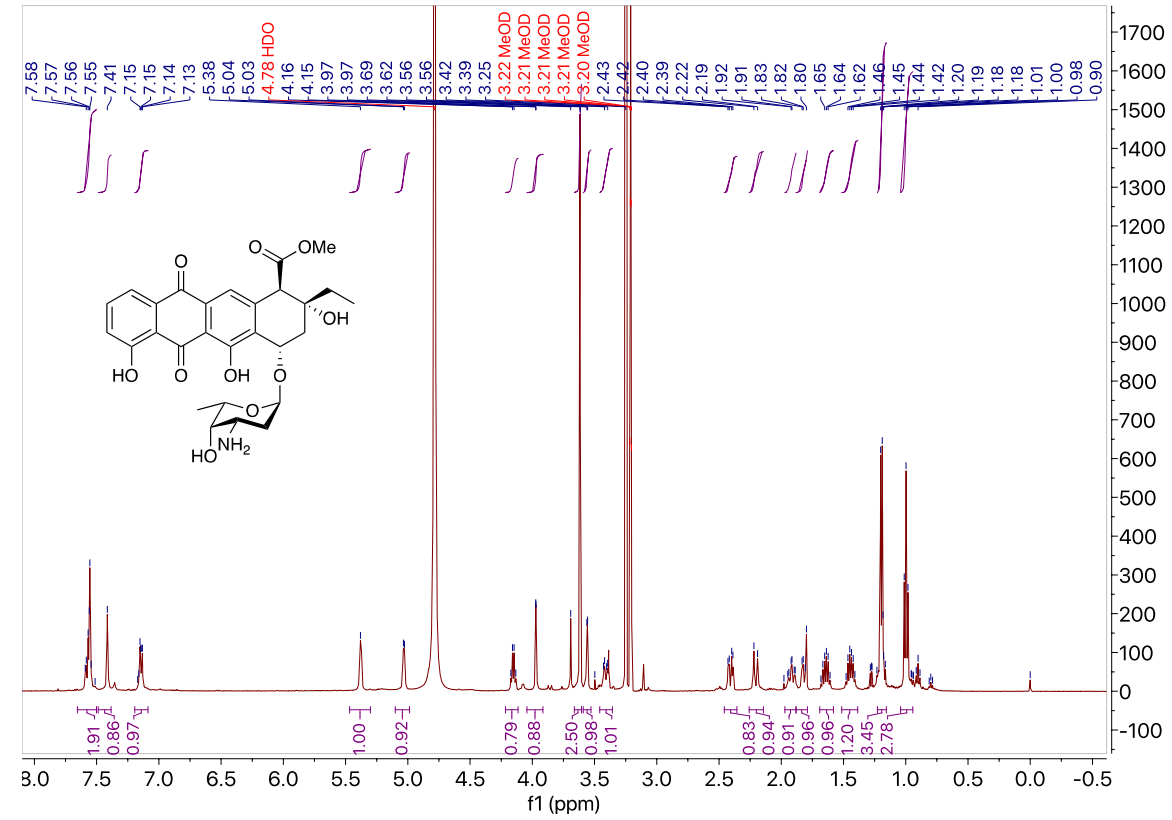

f2 (ppm)
f1 (ppm)

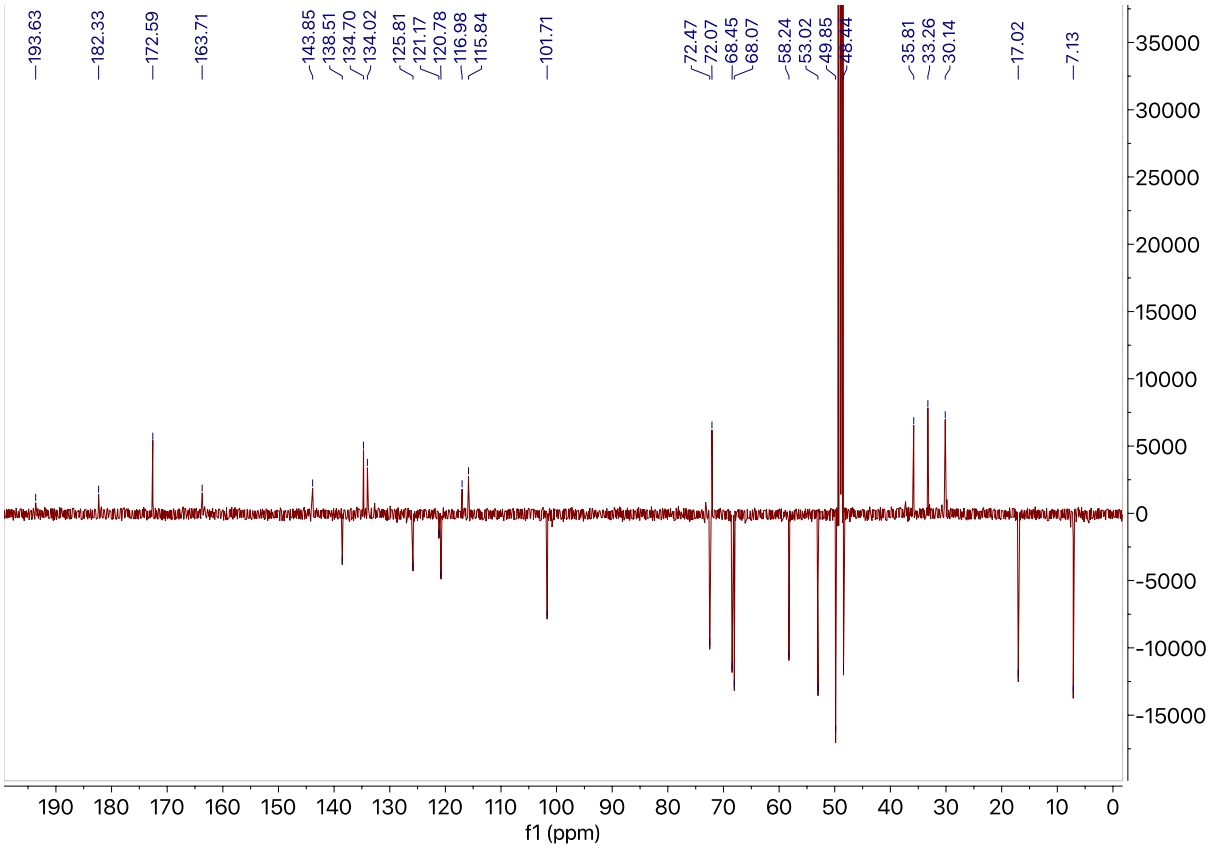

f2 (ppm)
f1 (ppm)

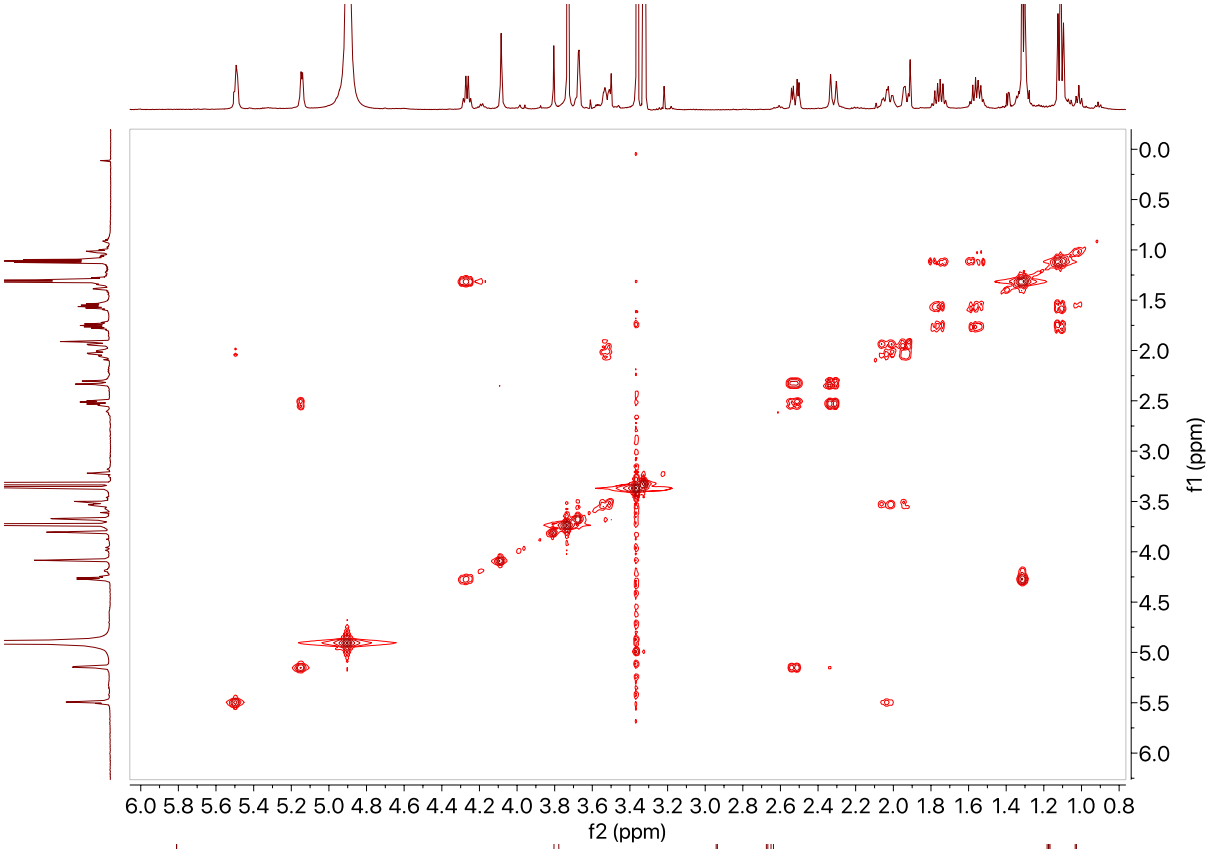

7.84 7.83 7.82 7.82 7.71 7.70 7.69 7.68 7.32 7.32 7.31 7.30 7.27 7.26 CDCl3 5.55 5.54 5.28 5.27 5.27 4.11 4.11 4.09 4.08 3.87 3.70 3.69 2.60 2.56 2.55 2.53 2.52 2.48 2.45 2.40 2.34 2.31 2.11 1.75 1.53 1.39 1.38 1.38 1.37 1.36 1.34 1.33 1.31 1.29 1.26 1.11 1.09 1.08 0.88 0.07 0.00
O
OMe
OH
OH
O
OH
O
O
HO
NMe2
1.00 1.09 1.04 1.94 1.16 1.02 0.90 1.11 2.18 1.11 3.11 1.78 5.19 1.18 1.18 0.96 1.20 1.46 2.70 3.01
f1 (ppm)
192.85 181.45 171.33 162.75 162.27 142.79 137.58 133.61 133.14 131.21 125.02 121.08 120.36 115.92 114.87 101.07 71.89 71.43 67.04 65.80 61.10 57.20 52.70 41.98 33.96 32.23 27.83 16.98 6.80
f1 (ppm)

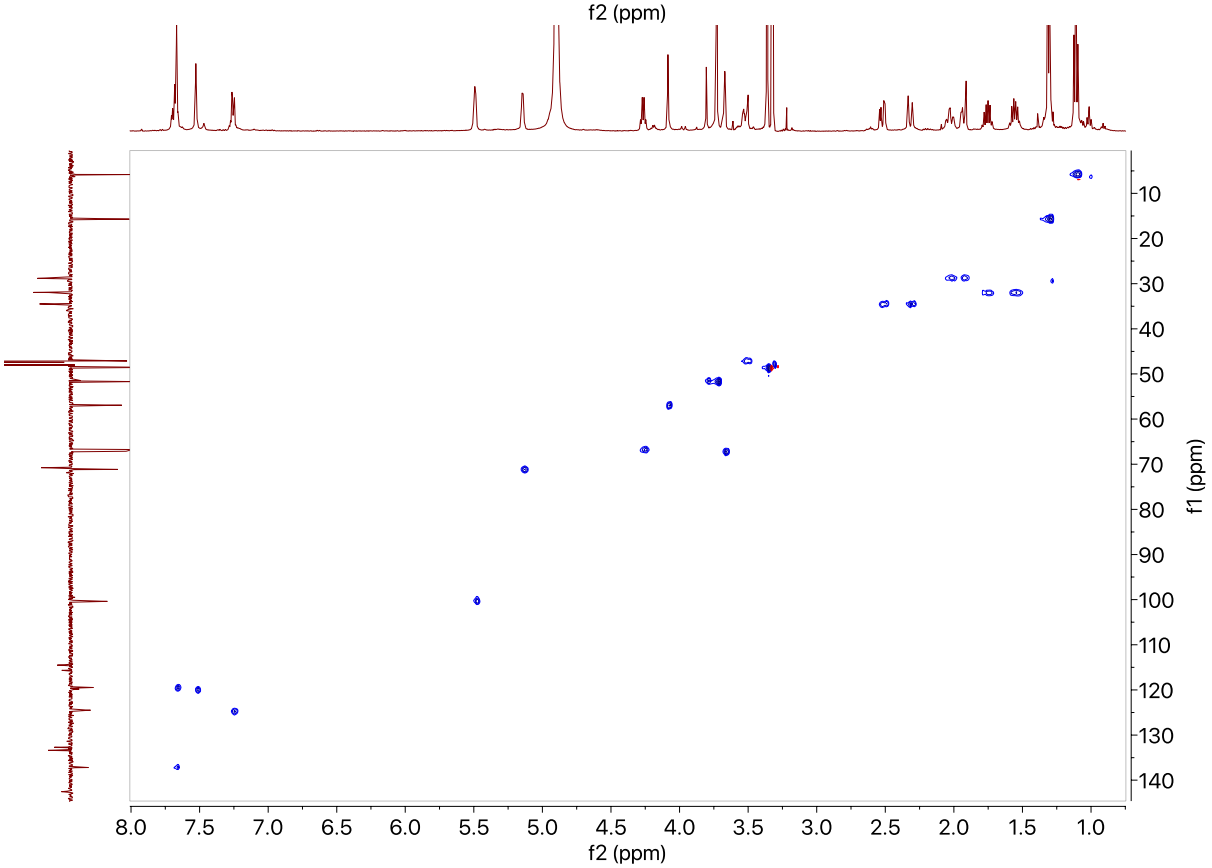

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)


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
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)


7.58 7.57 7.56 7.55 7.41 7.15 7.15 7.14 7.13 5.38 5.04 5.03 4.78 HDO 4.16 4.15 3.97 3.97 3.69 3.62 3.56 3.56 3.42 3.39 3.25 3.22 MeOD 3.21 MeOD 3.21 MeOD 3.21 MeOD 3.20 MeOD 2.43 2.42 2.40 2.39 2.22 2.19 1.92 1.91 1.83 1.82 1.80 1.65 1.64 1.62 1.46 1.45 1.44 1.42 1.20 1.19 1.18 1.18 1.01 1.00 0.98 0.90
1.91 0.86 0.97 1.00 0.92 0.79 0.88 2.50 0.98 1.01 0.83 0.94 0.91 0.96 0.96 1.20 3.45 2.78
f1 (ppm)

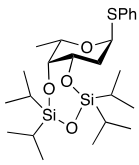

193.63 182.33 172.59 163.71 143.85 138.51 134.70 134.02 125.81 121.17 120.78 116.98 115.84 101.71 72.47 72.07 68.45 68.07 58.24 53.02 49.85 48.44 35.81 33.26 30.14 17.02 7.13
f1 (ppm)


0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)

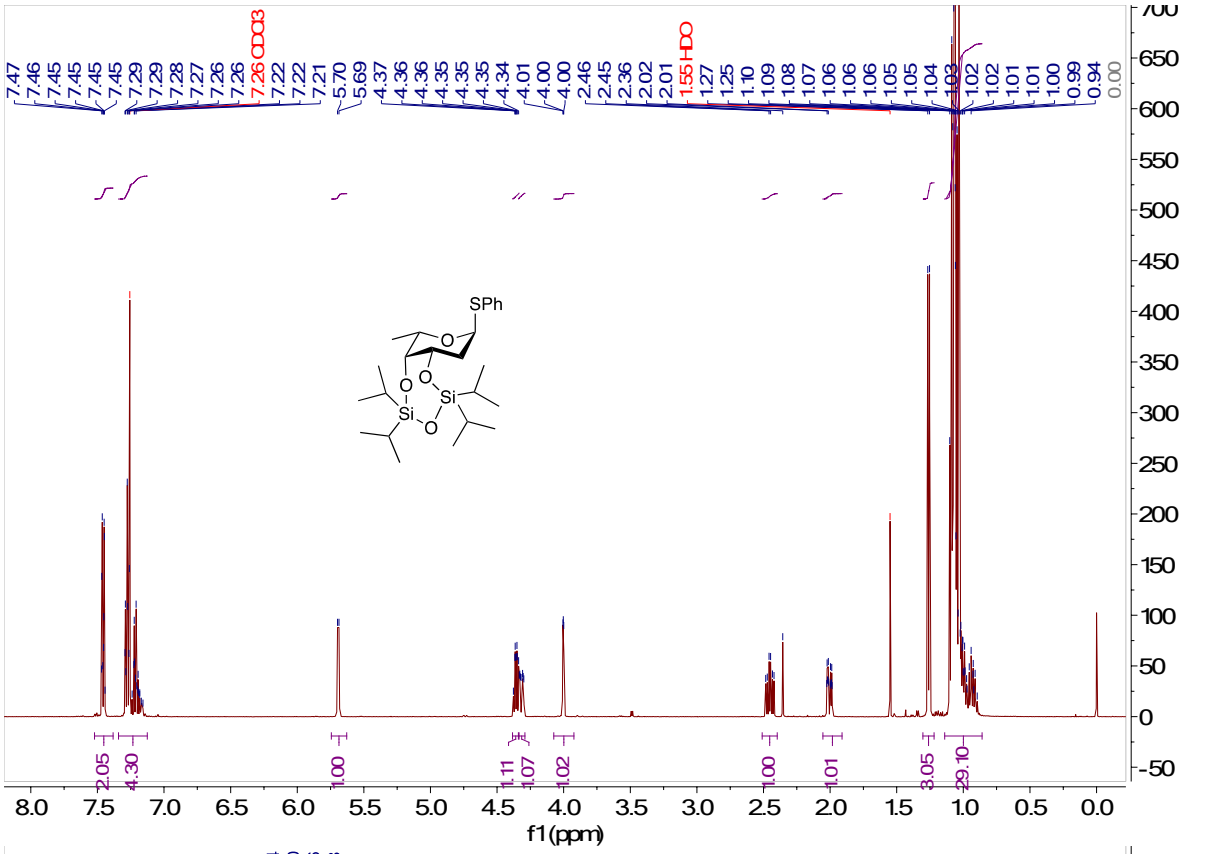

10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)

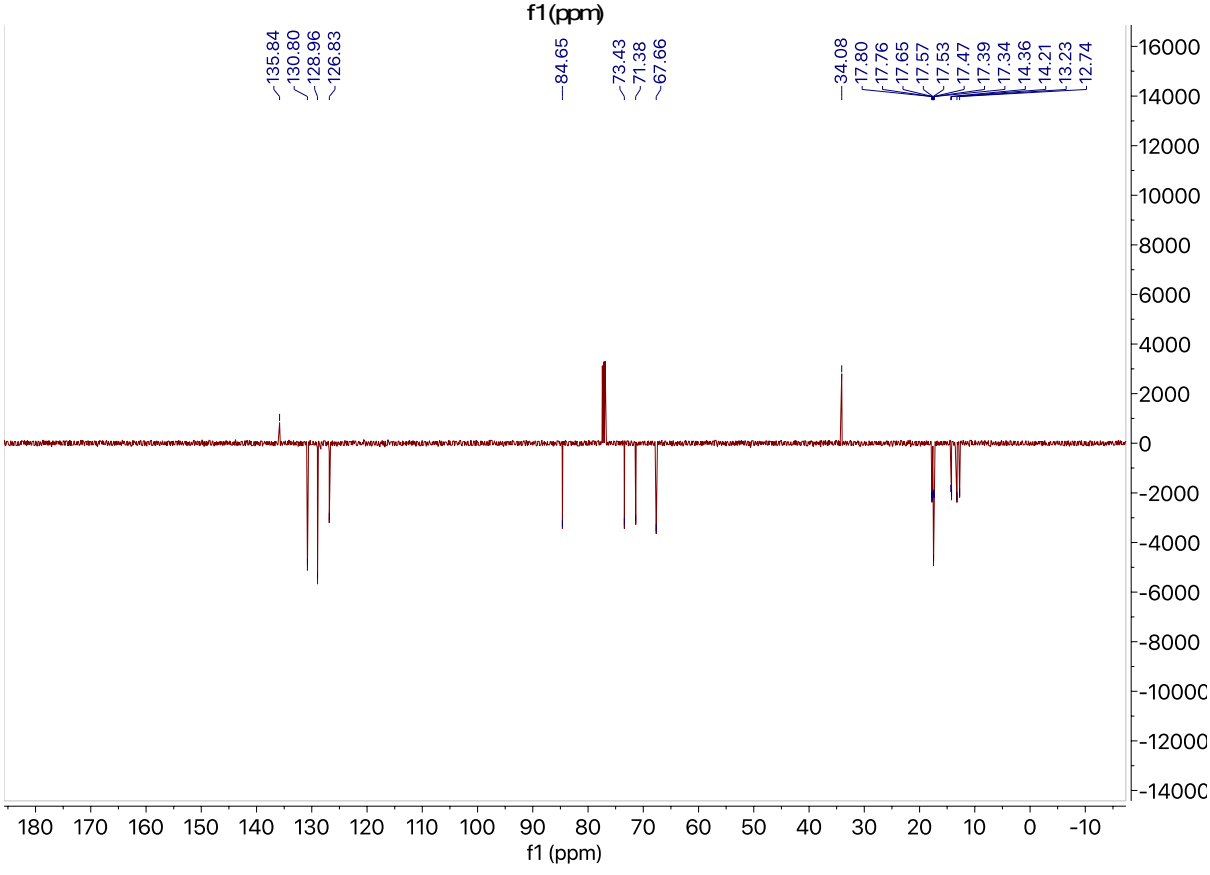
H: Additional info on the synthesis of anthracycline disaccharides **5**, **6**, **7** and **8** and accompanying NMR data

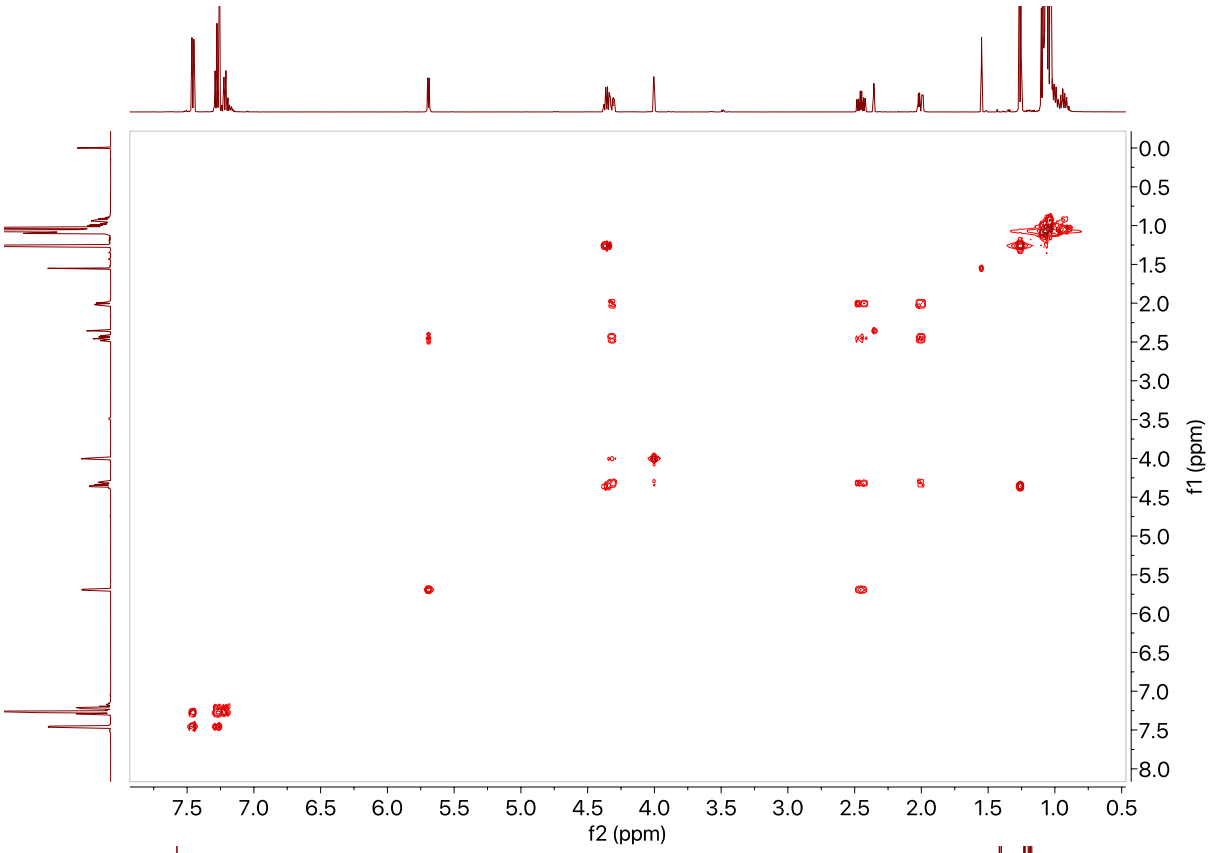
Phenyl 2-deoxy-3,4-tetraisopropyldisiloxyl-1-thio-α-L-fucopyranoside (18)

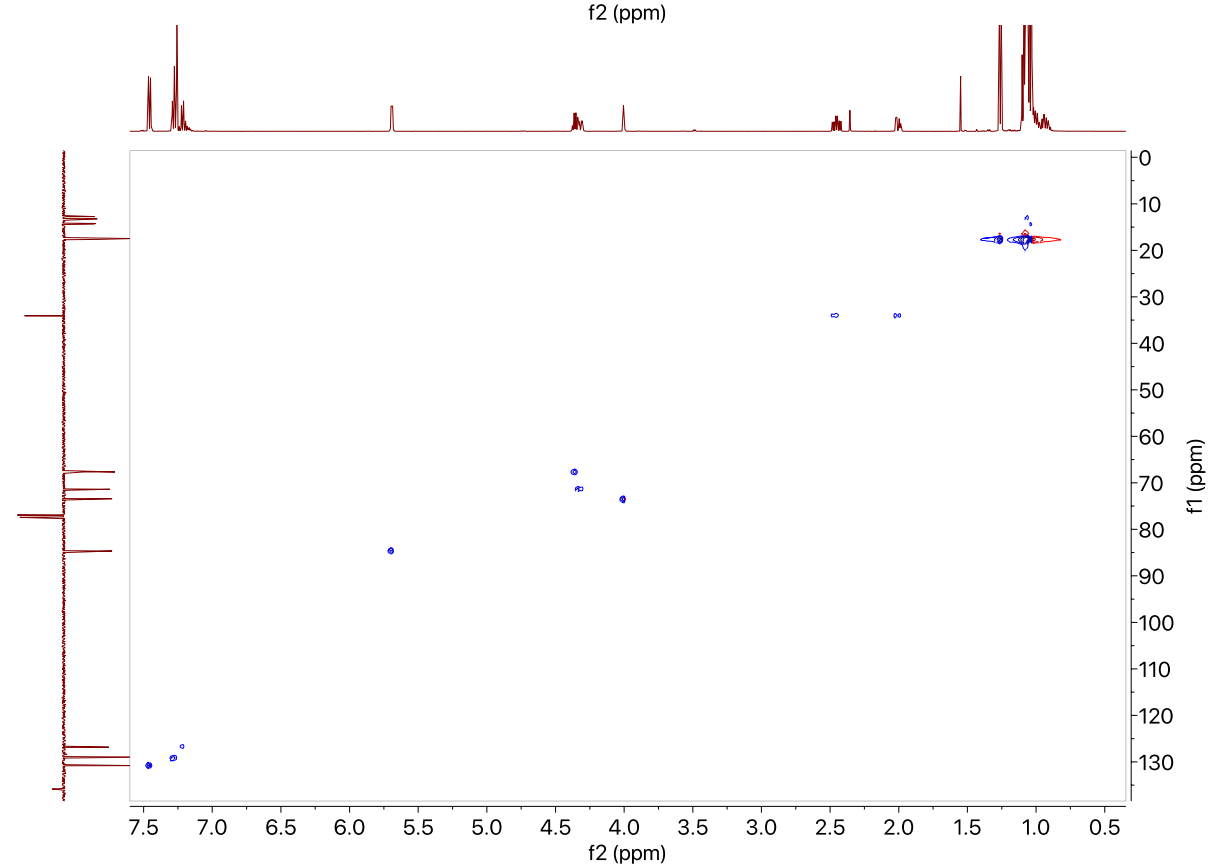


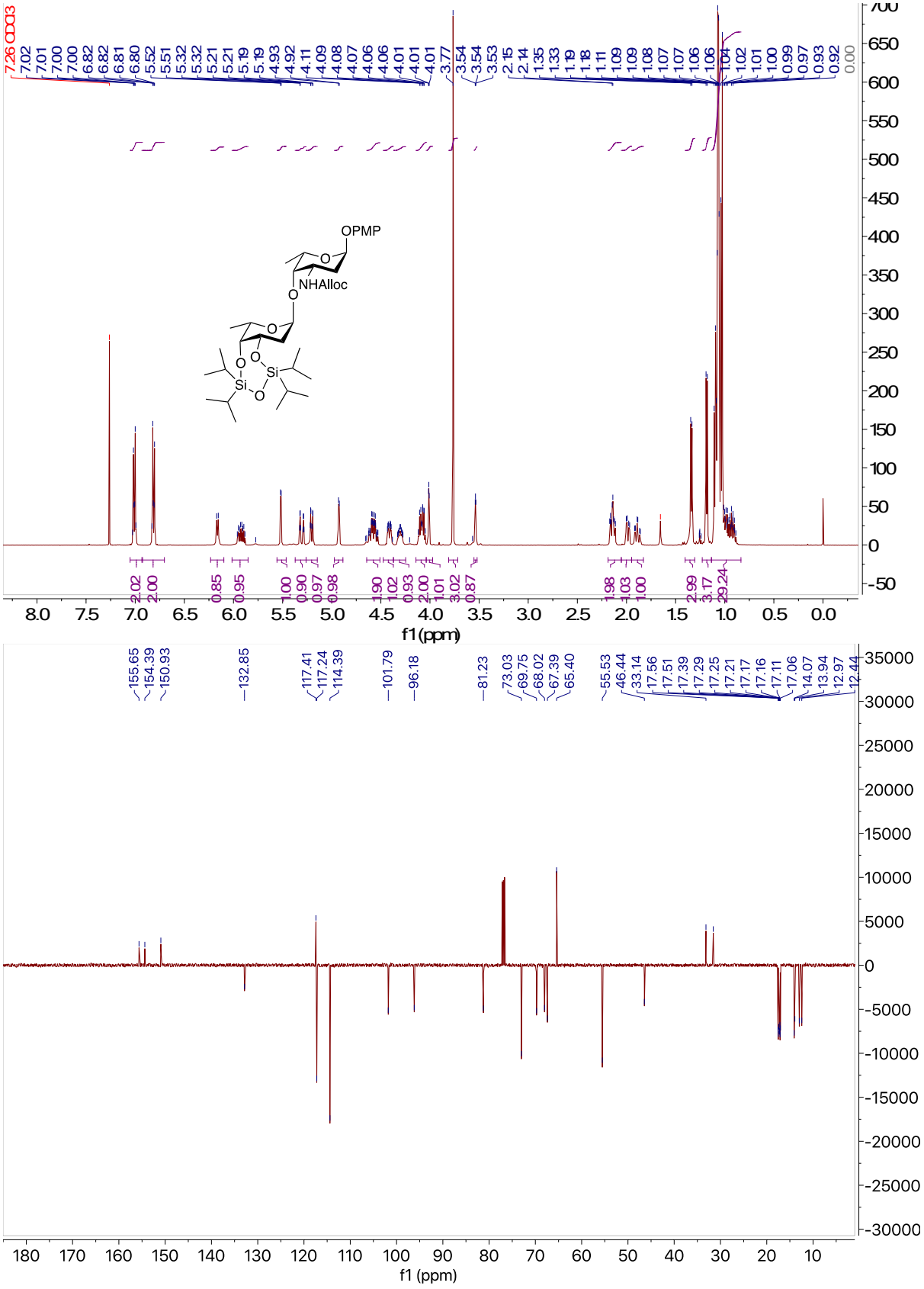
A solution of phenyl 2-deoxy-1-thio-α-L-fucopyranoside [2] (6.35 g, 19.6 mmol) and NaOMe (cat. amount) in MeOH (200 mL) was stirred overnight. It was then quenched by addition of Amberlite IR120 (H^+ form), filtered and concentrated *in vacuo* to give the intermediate diol. To a solution of this diol in pyridine (100 mL) was added tetraisopropyldisiloxane dichloride (8.3 mL, 25.5 mmol, 1.3 eq) and the resulting mixture was stirred overnight. It was then poured into Et_2O, washed with H_2O thrice and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:96 – 8:92 toluene:pentane) gave the title compound as a colourless oil (6.36 g, 13.2 mmol, 67%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.38 (m, 2H), 7.34 – 7.13 (m, 3H), 5.69 (d, *J* = 5.6 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.34 – 4.29 (m, 1H), 4.07 – 3.92 (m, 1H), 2.45 (td, *J* = 12.7, 5.8 Hz, 1H), 2.00 (ddt, *J* = 13.0, 4.6, 1.1 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.14 – 0.86 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 130.8, 129.0, 126.8, 84.6, 73.4, 71.4, 67.7, 34.1, 17.8, 17.8, 17.7, 17.6, 17.5, 17.5, 17.4, 17.3, 14.4, 14.2, 13.2, 12.7. HRMS: $[M + Na]^+$ calculated for $C_{24}H_{42}O_4SSi_2Na$ 505.2240; found 505.2238.

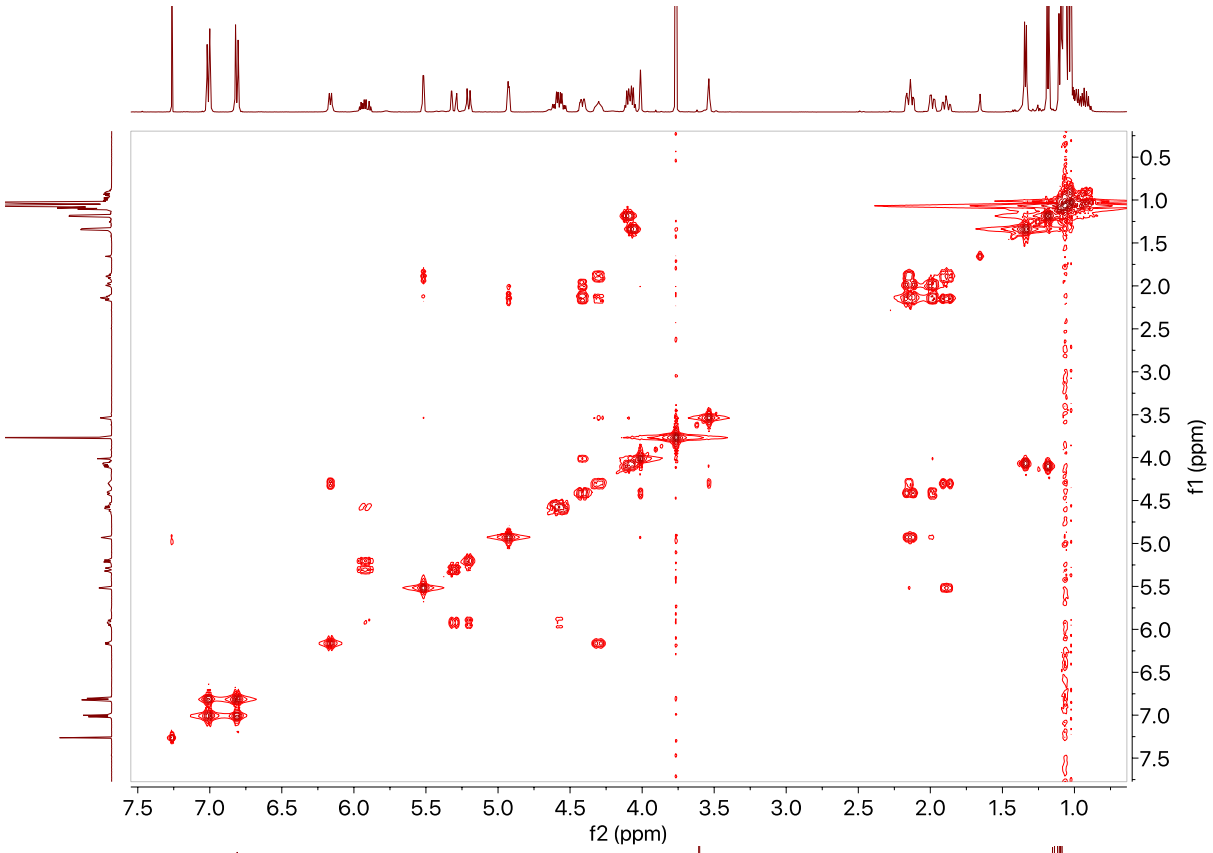

SPh
O
O
O
Si
Si
O
f1 (ppm)

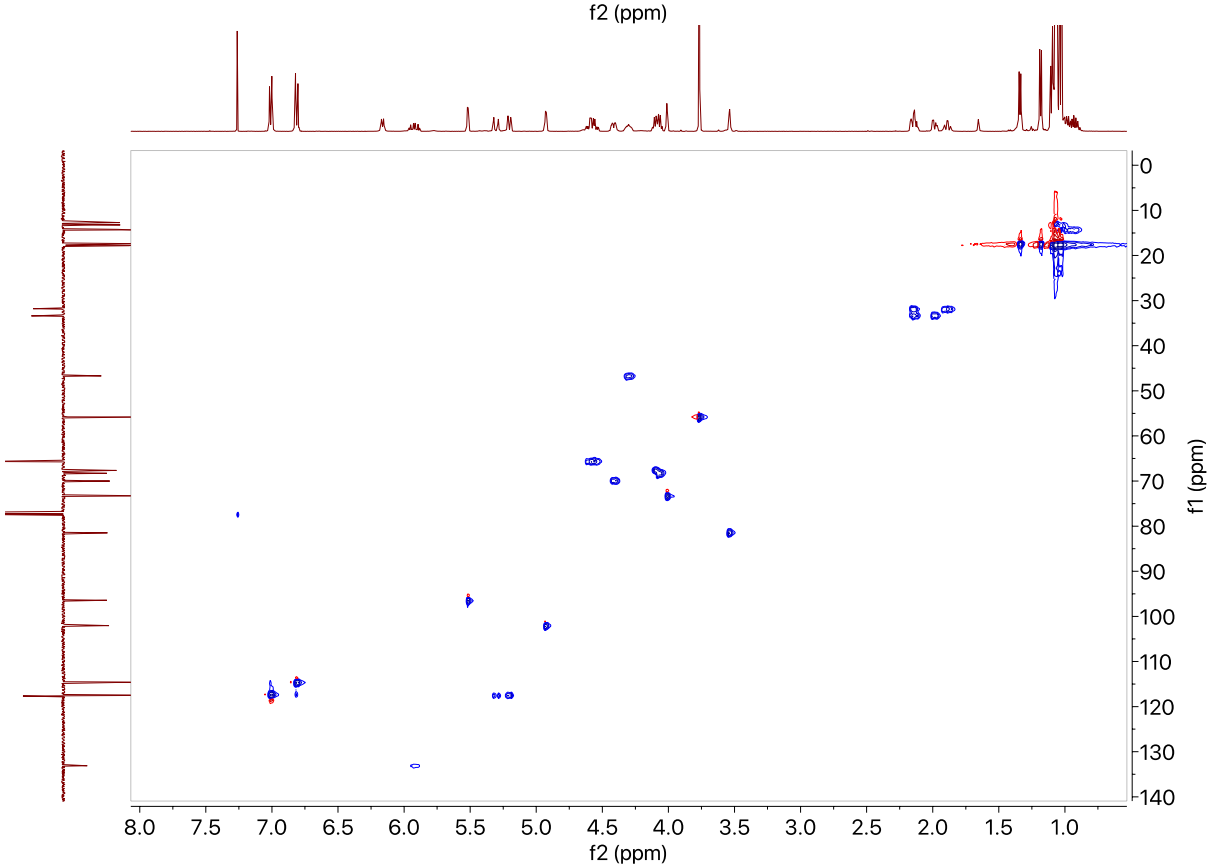

f1 (ppm)

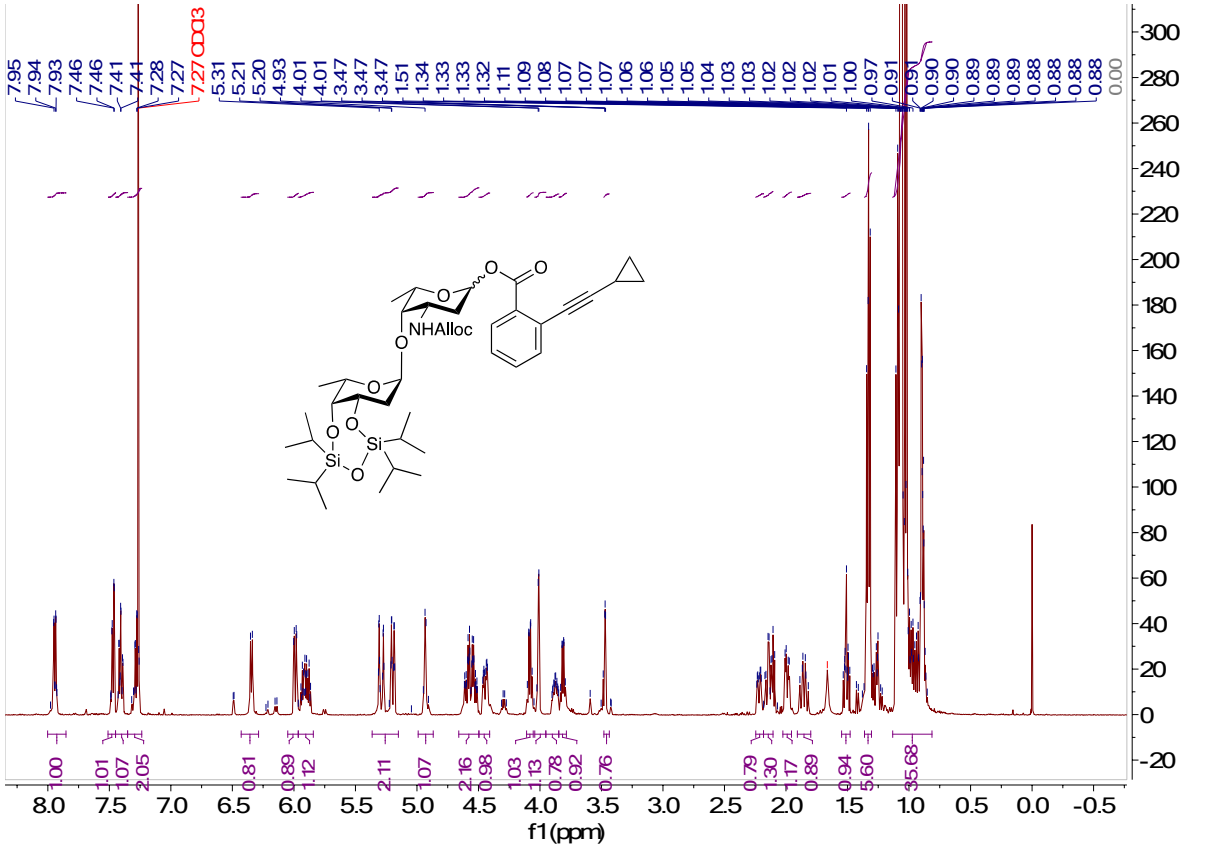

0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

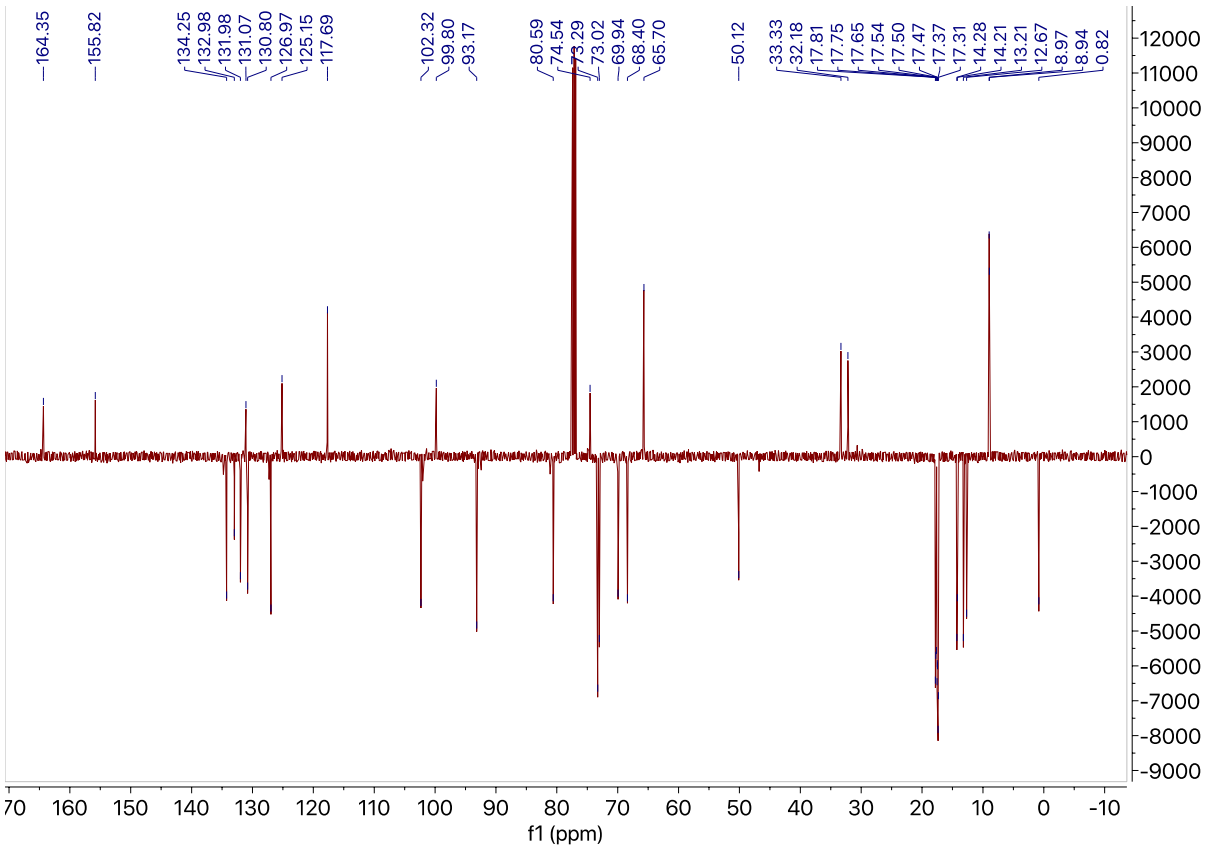

0
10
20
30
40
50
60
70
80
90
100
110
120
130
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

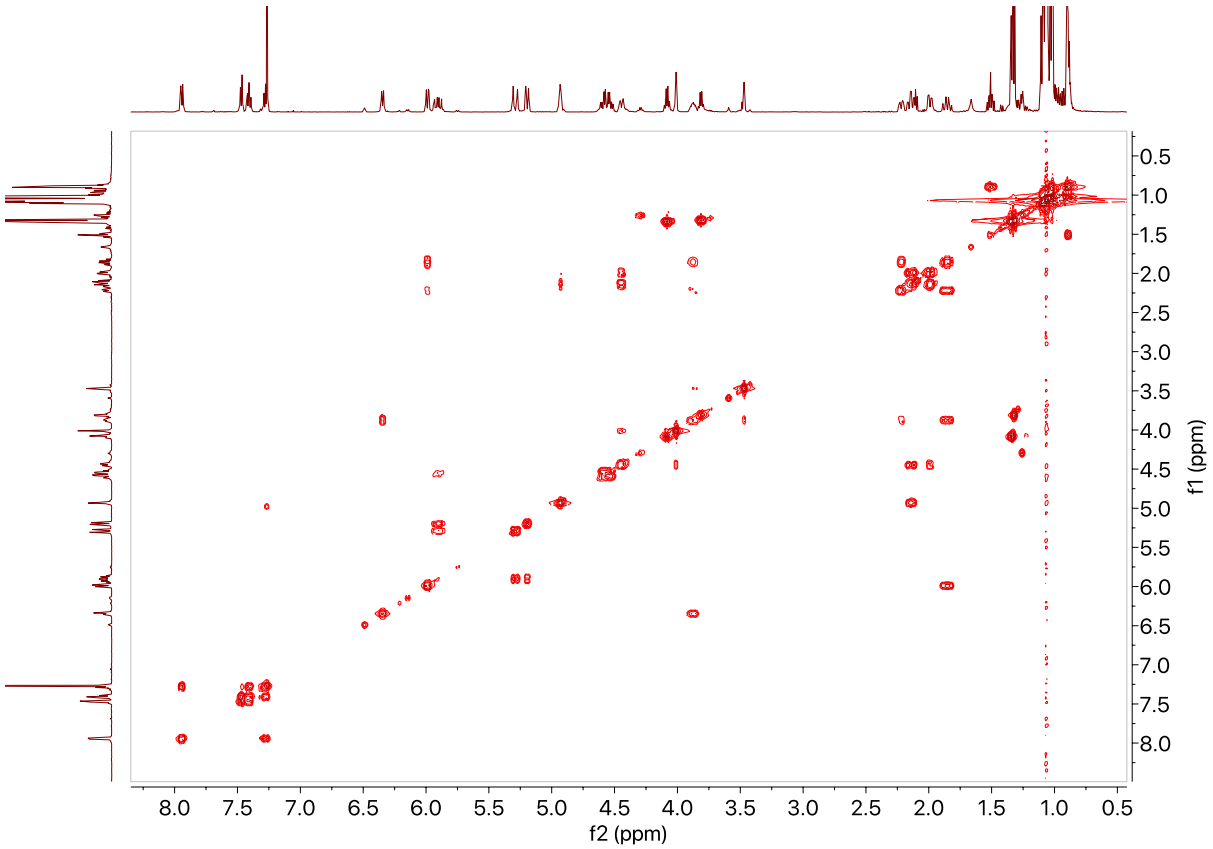

OPMP
NHAlloc
O
Si
f1 (ppm)

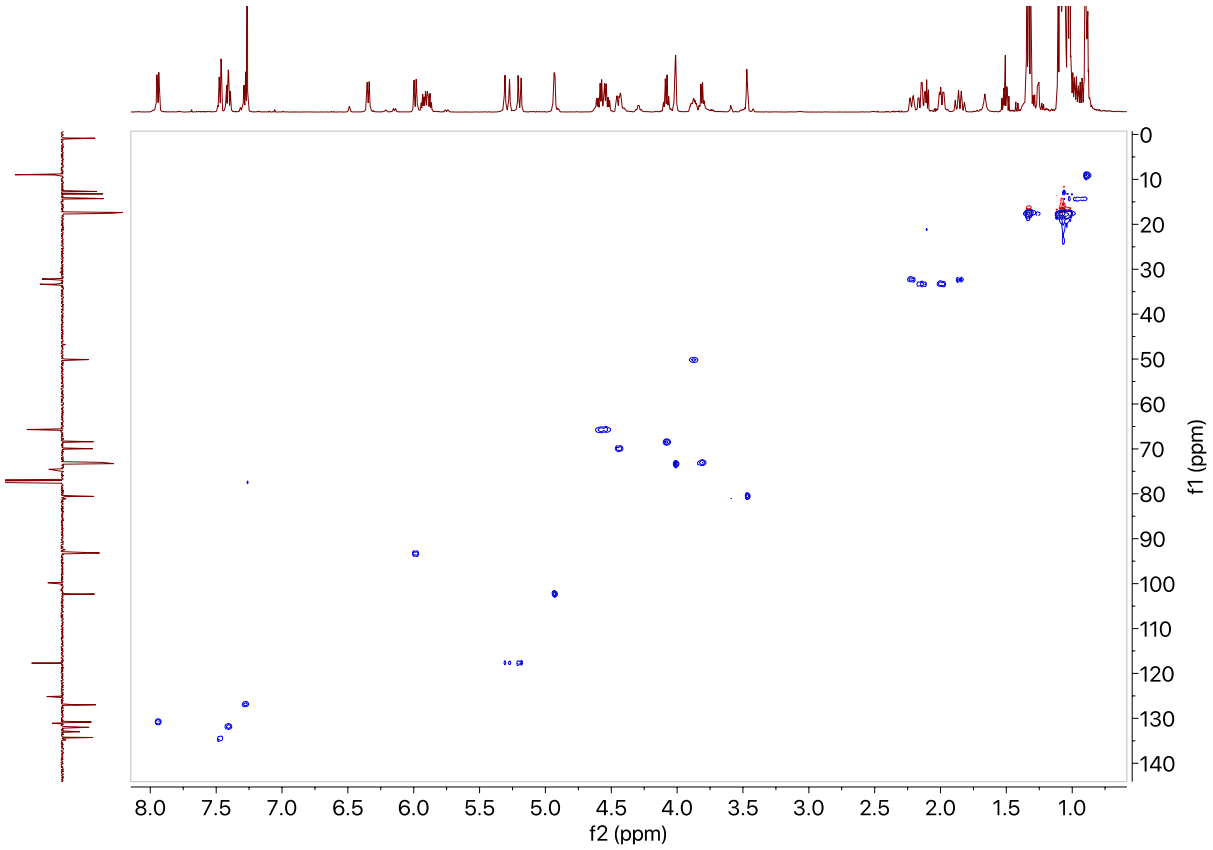

f2 (ppm)
f1 (ppm)

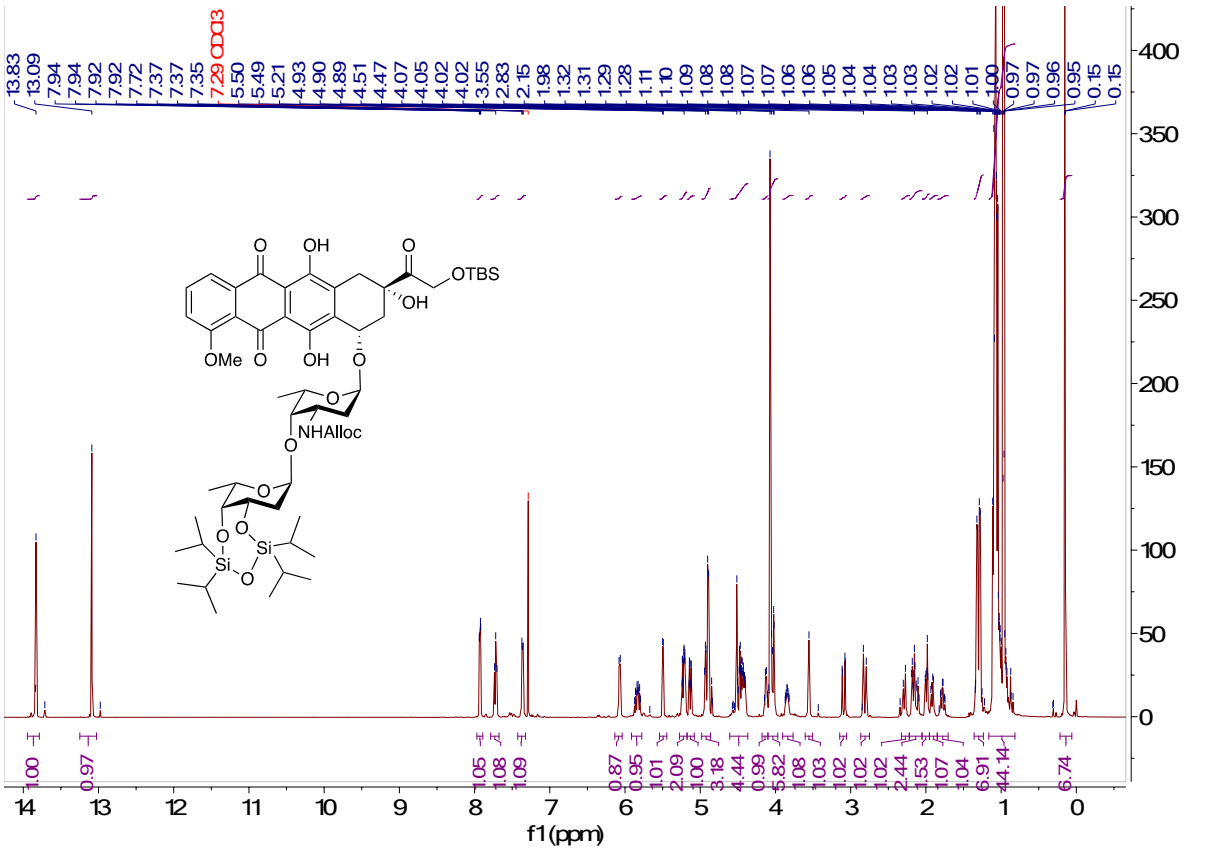

f2 (ppm)
f1 (ppm)

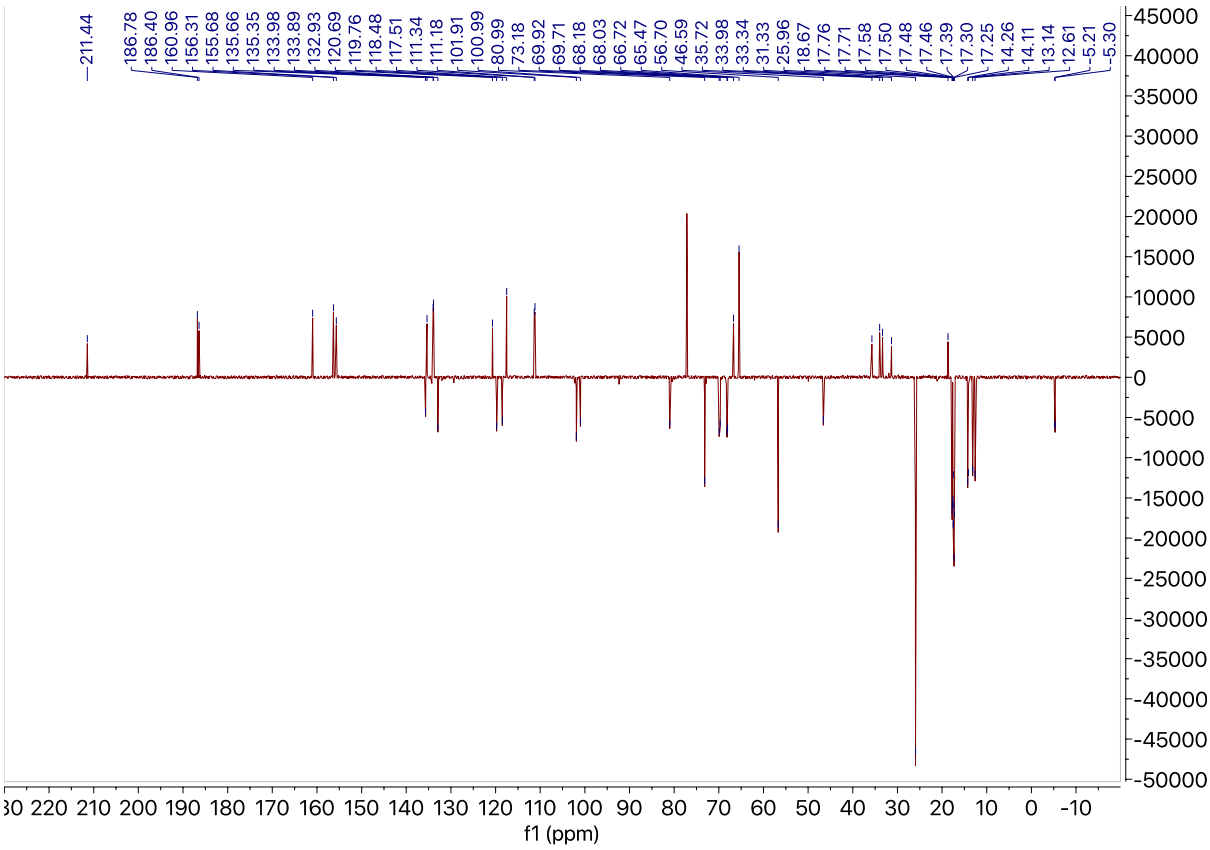

NHAlloc
Si
Si
f1 (ppm)

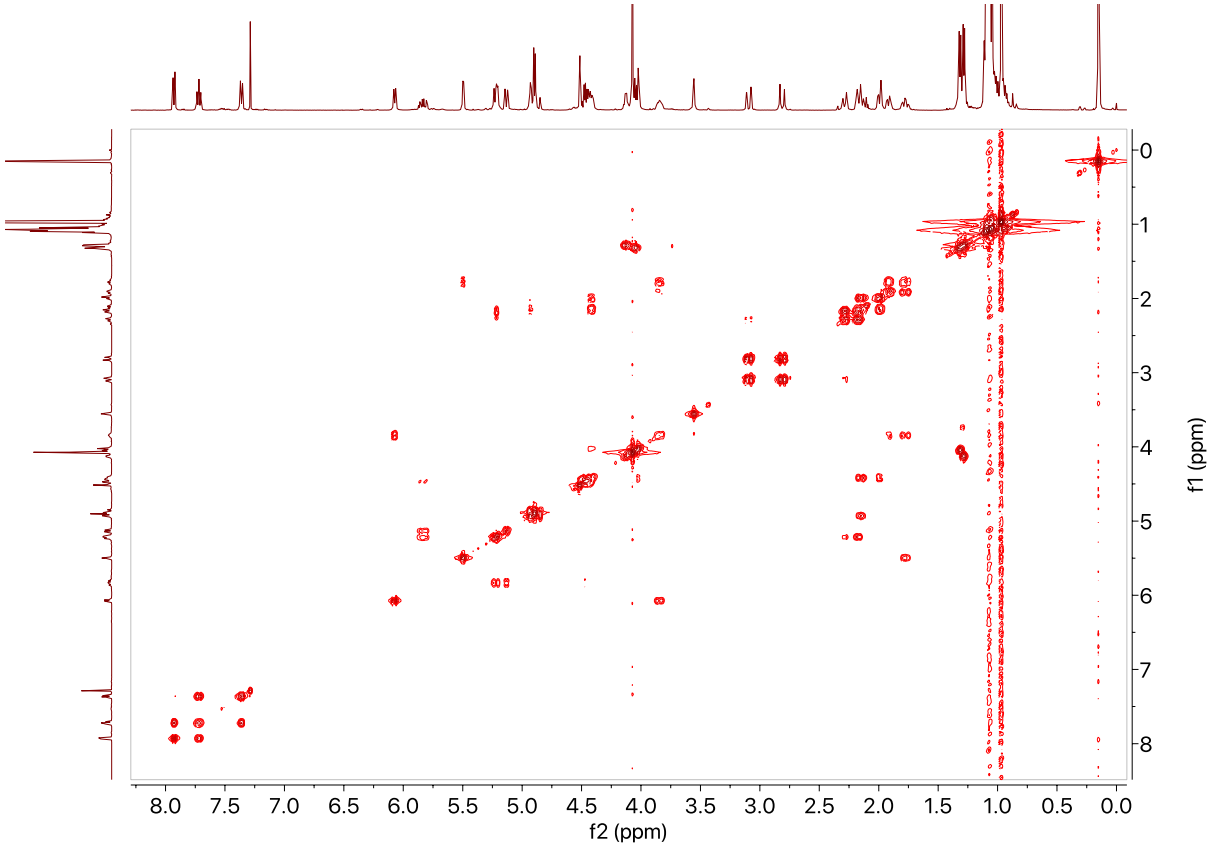

f1 (ppm)

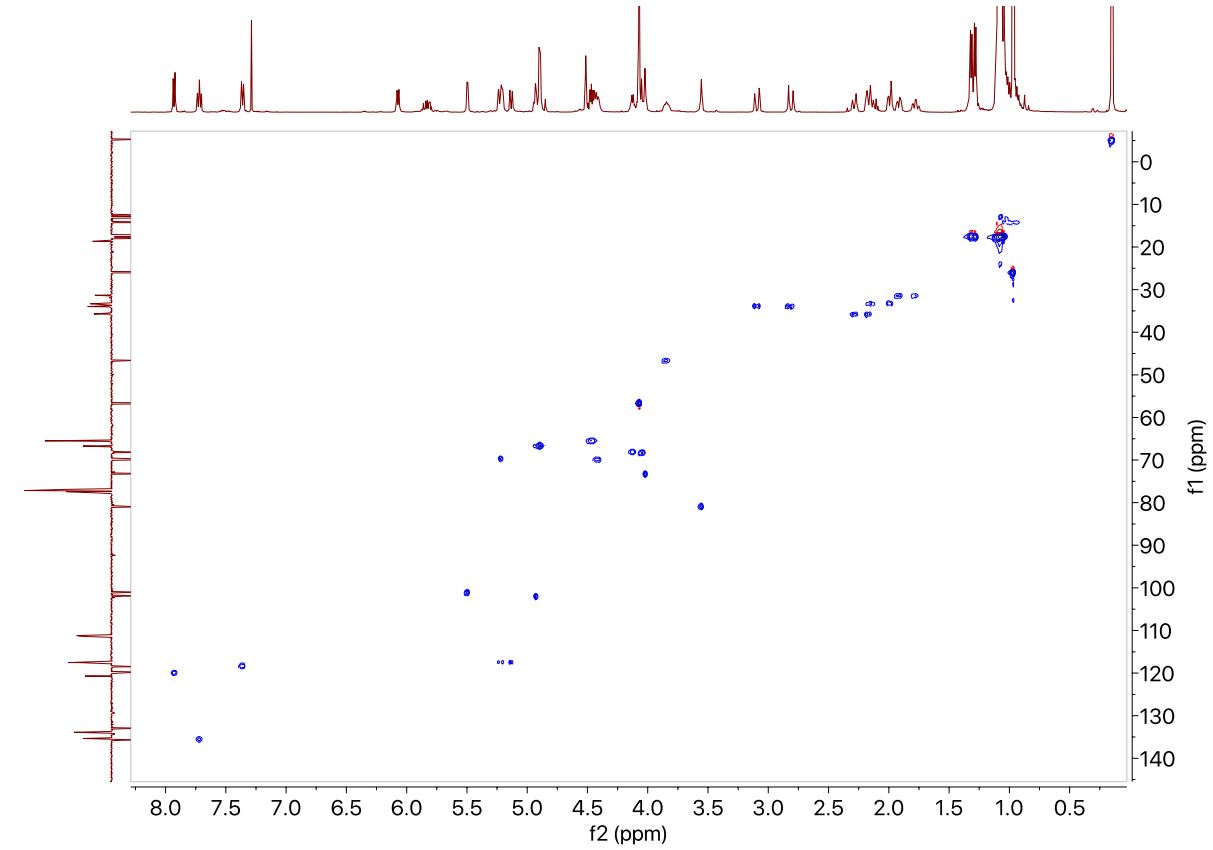

f2 (ppm)
f1 (ppm)

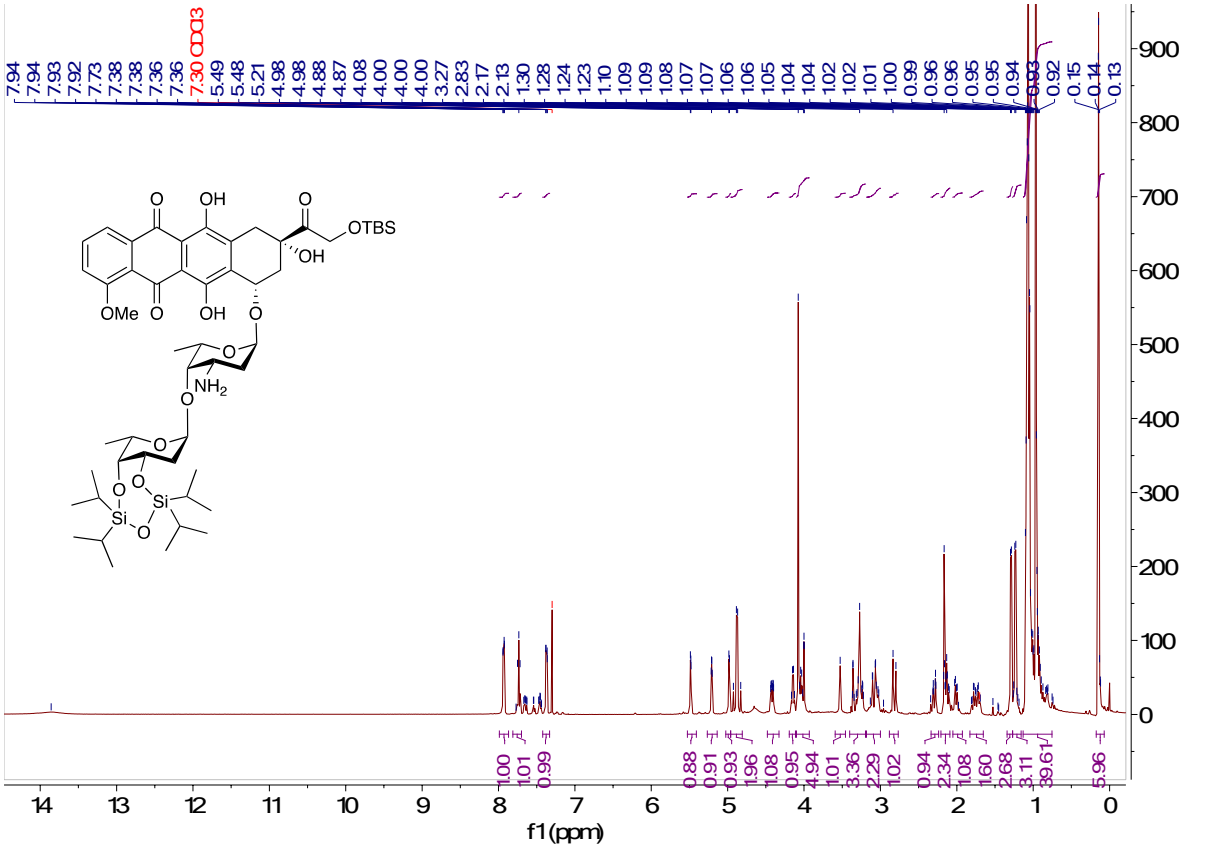

f2 (ppm)
f1 (ppm)

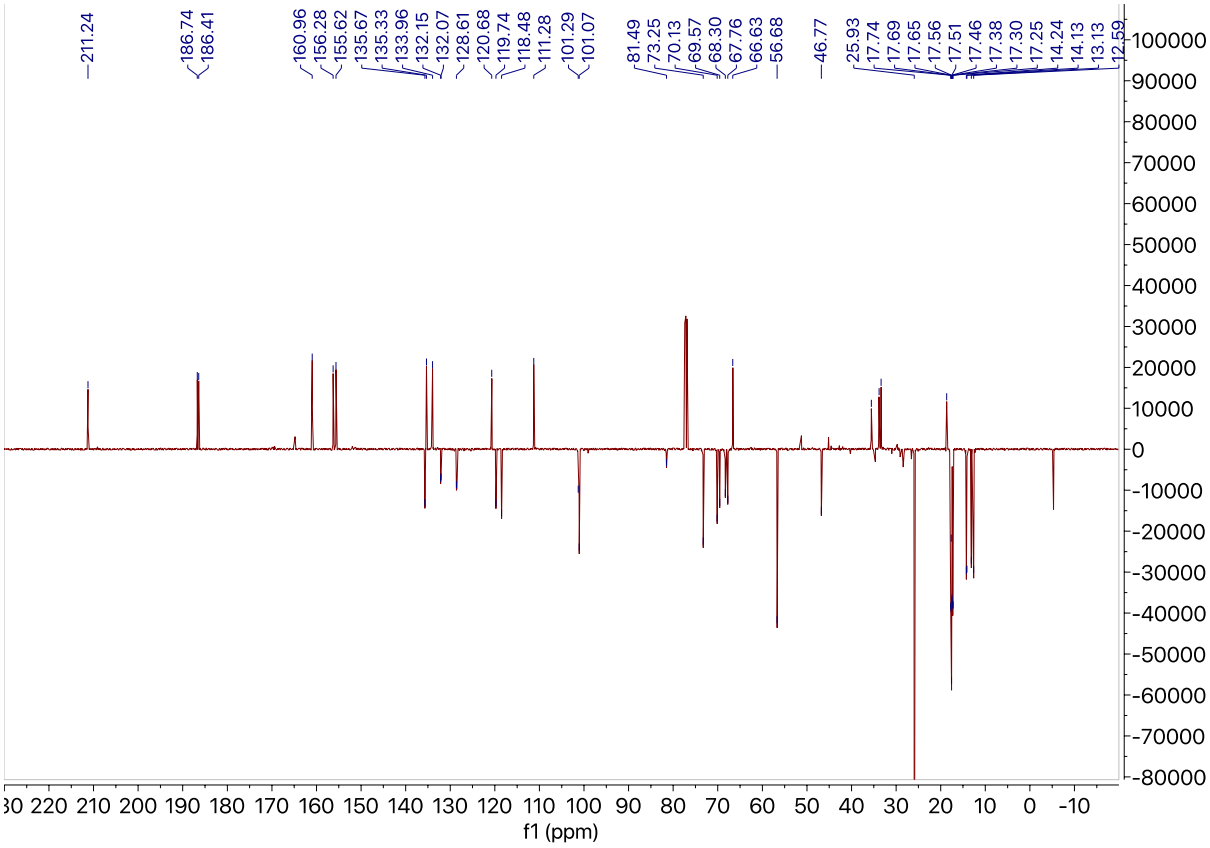

OTBS
OH
OMe
NHAlloc
f1 (ppm)

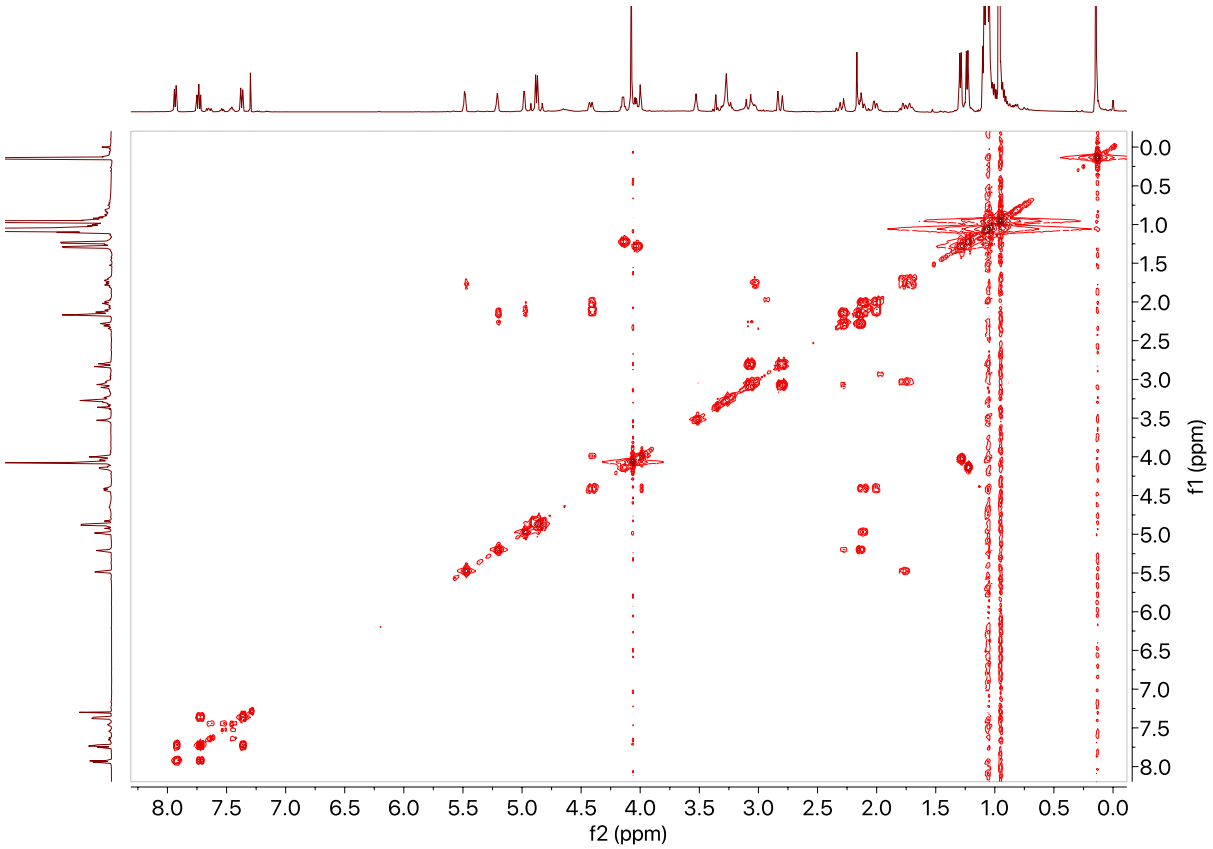

f1 (ppm)

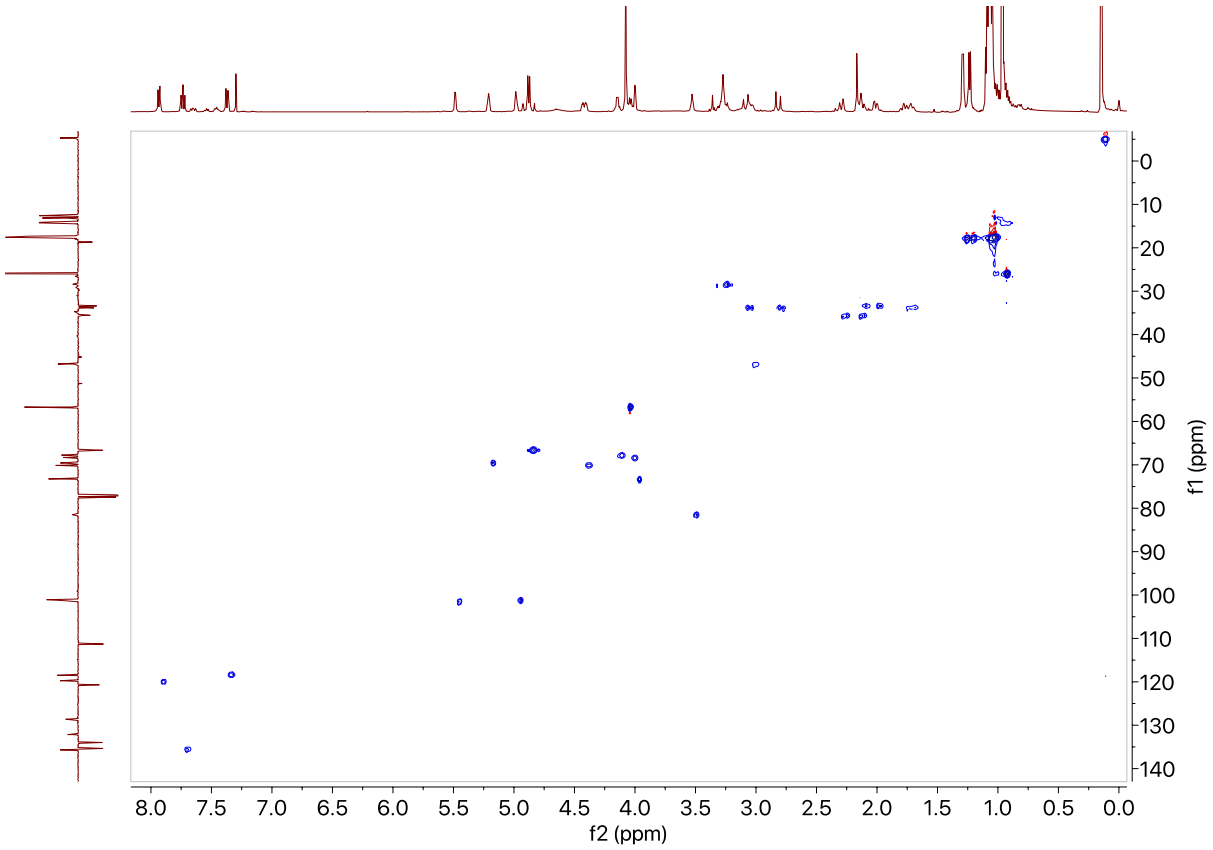

0
1
2
3
4
5
6
7
8
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)

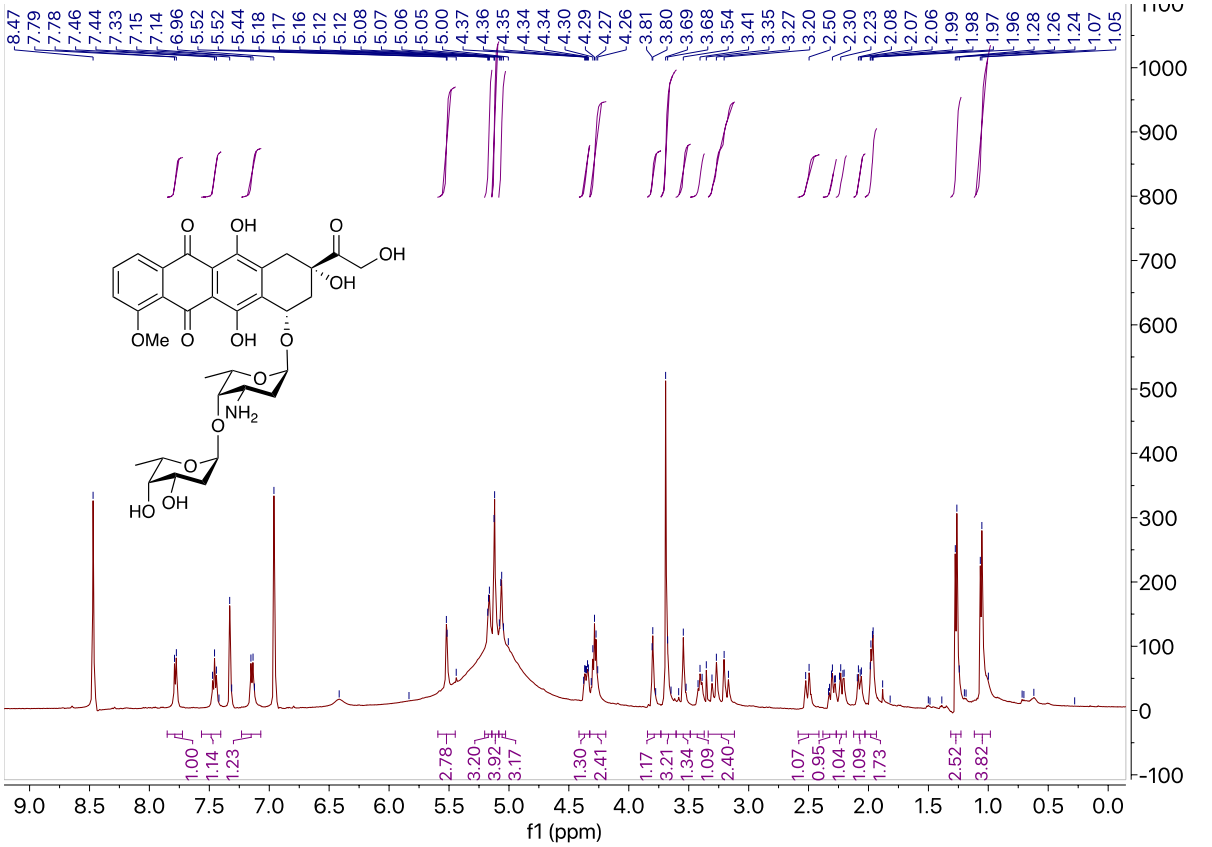

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

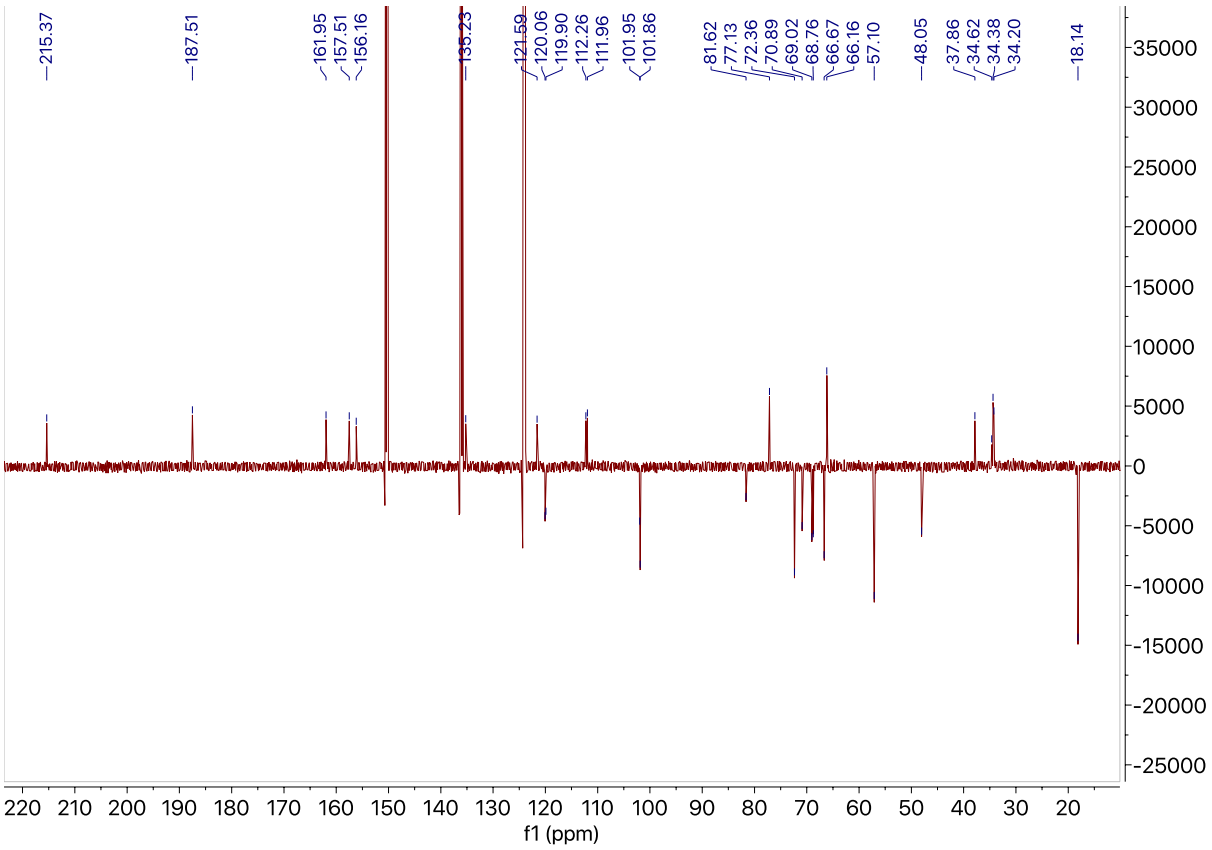

OH
O
OTBS
OH
OMe
O
OH
O
O
NH2
O
O
O
O
Si
Si
O
f1 (ppm)

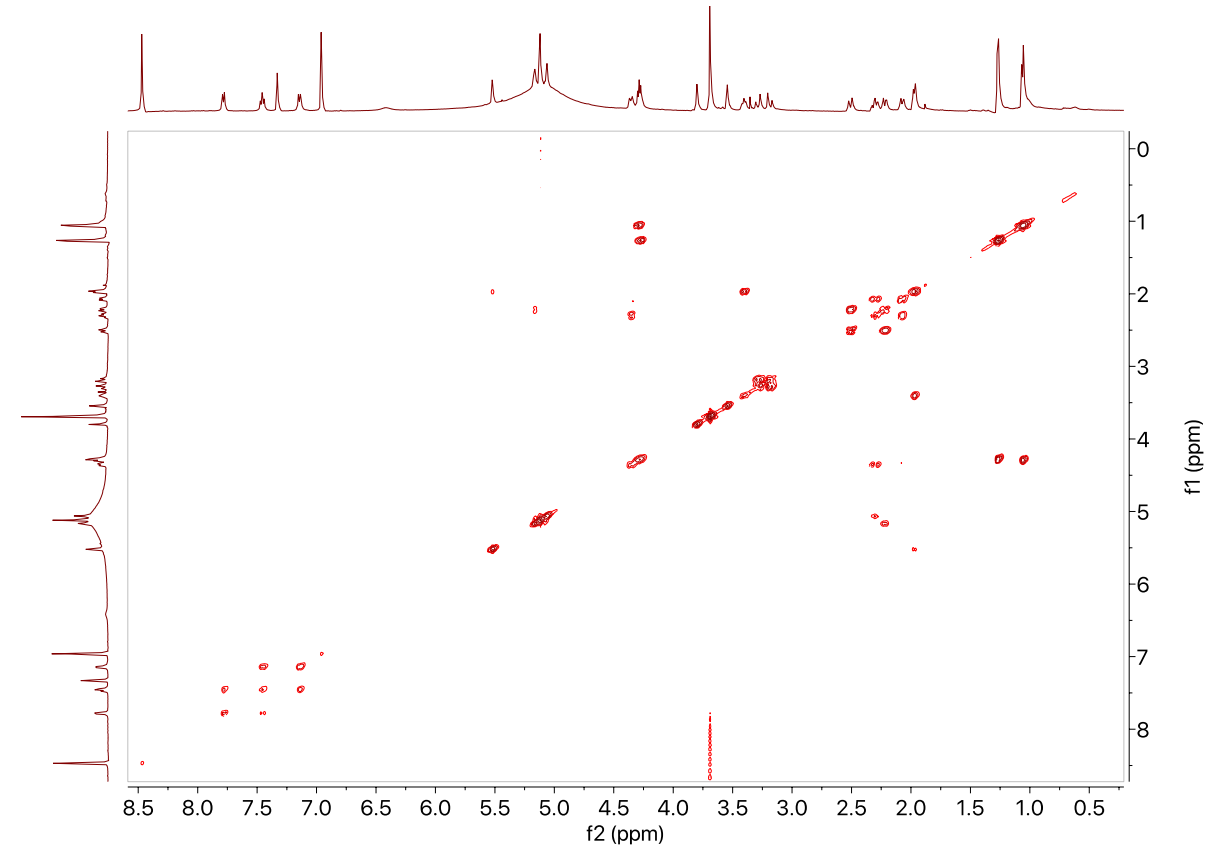

f1 (ppm)

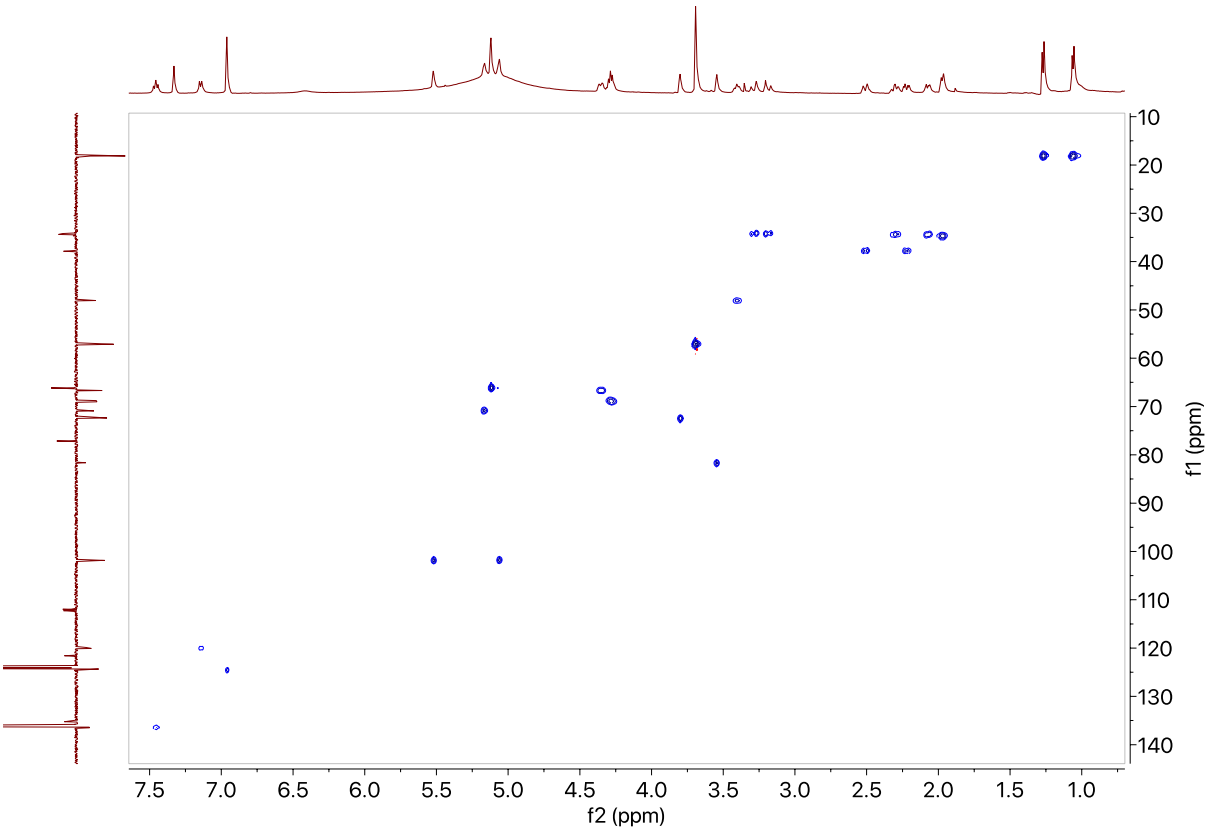

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)

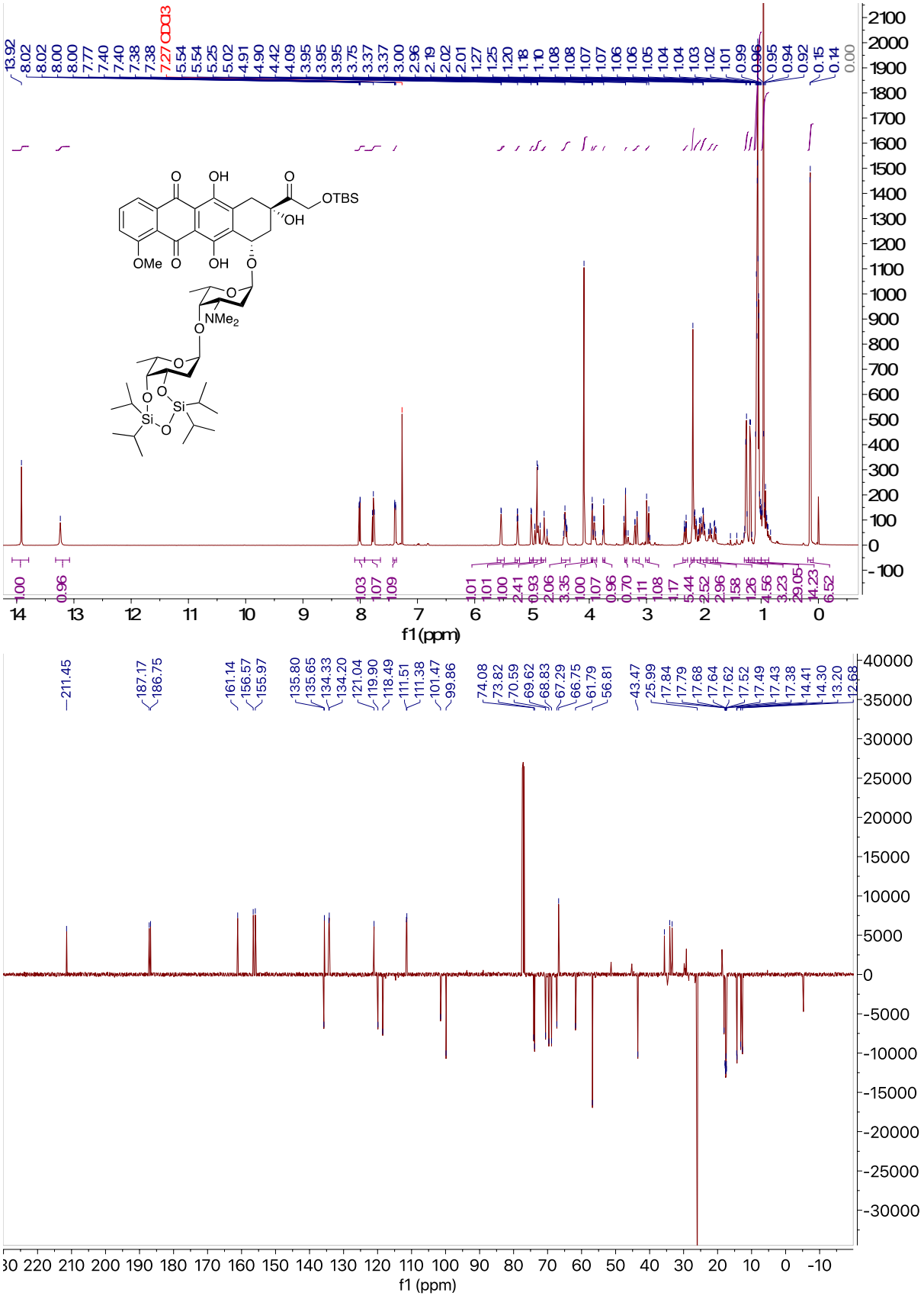

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

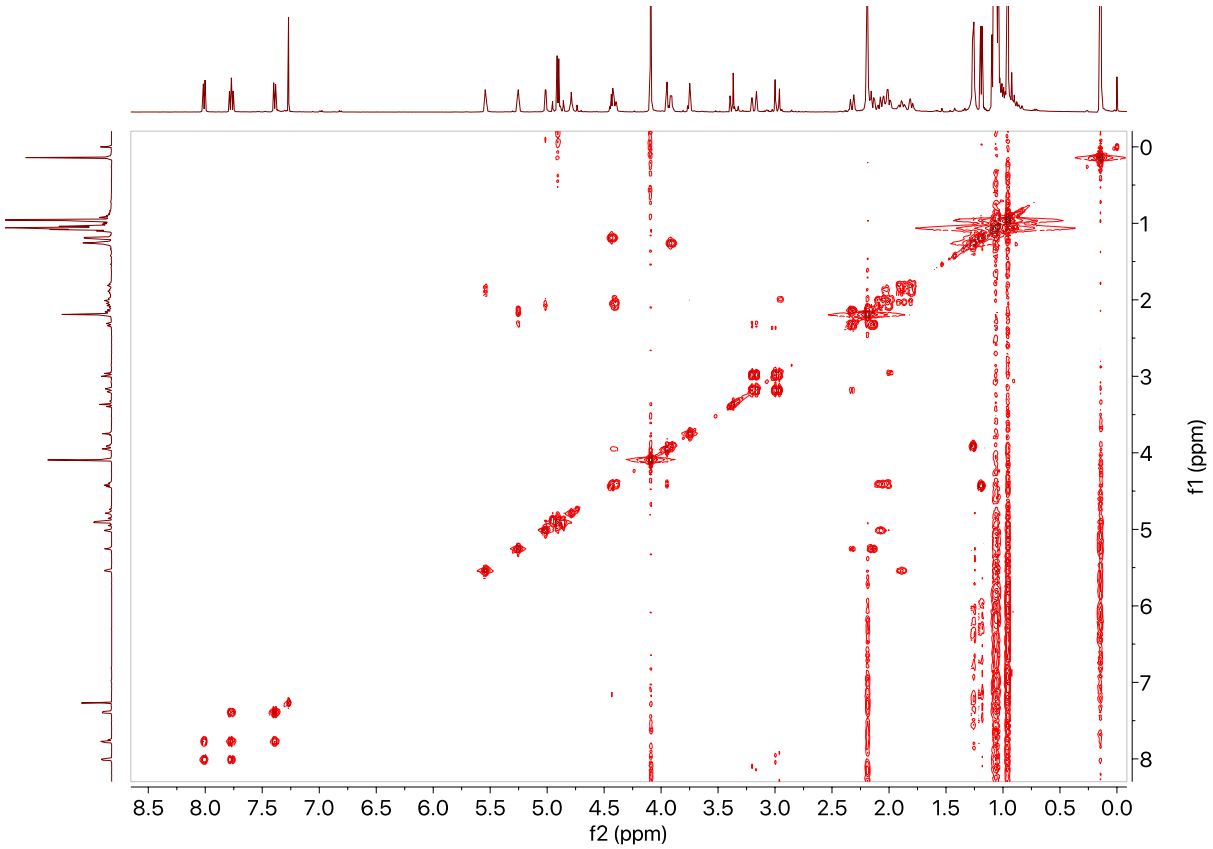

8.47 7.79 7.78 7.46 7.44 7.33 7.15 7.14 6.96 5.52 5.52 5.44 5.18 5.17 5.16 5.12 5.12 5.08 5.07 5.06 5.05 5.00 4.37 4.36 4.35 4.34 4.34 4.30 4.29 4.27 4.26 3.81 3.80 3.69 3.68 3.54 3.41 3.35 3.27 3.20 2.50 2.30 2.23 2.08 2.07 2.06 1.99 1.98 1.97 1.96 1.28 1.26 1.24 1.07 1.05
OH
O
OH
OMe
O
OH
O
NH2
HO
OH
1.00 1.14 1.23 2.78 3.20 3.92 3.17 1.30 2.41 1.17 3.21 1.34 1.09 2.40 1.07 0.95 1.04 1.09 1.73 2.52 3.82
f1 (ppm)

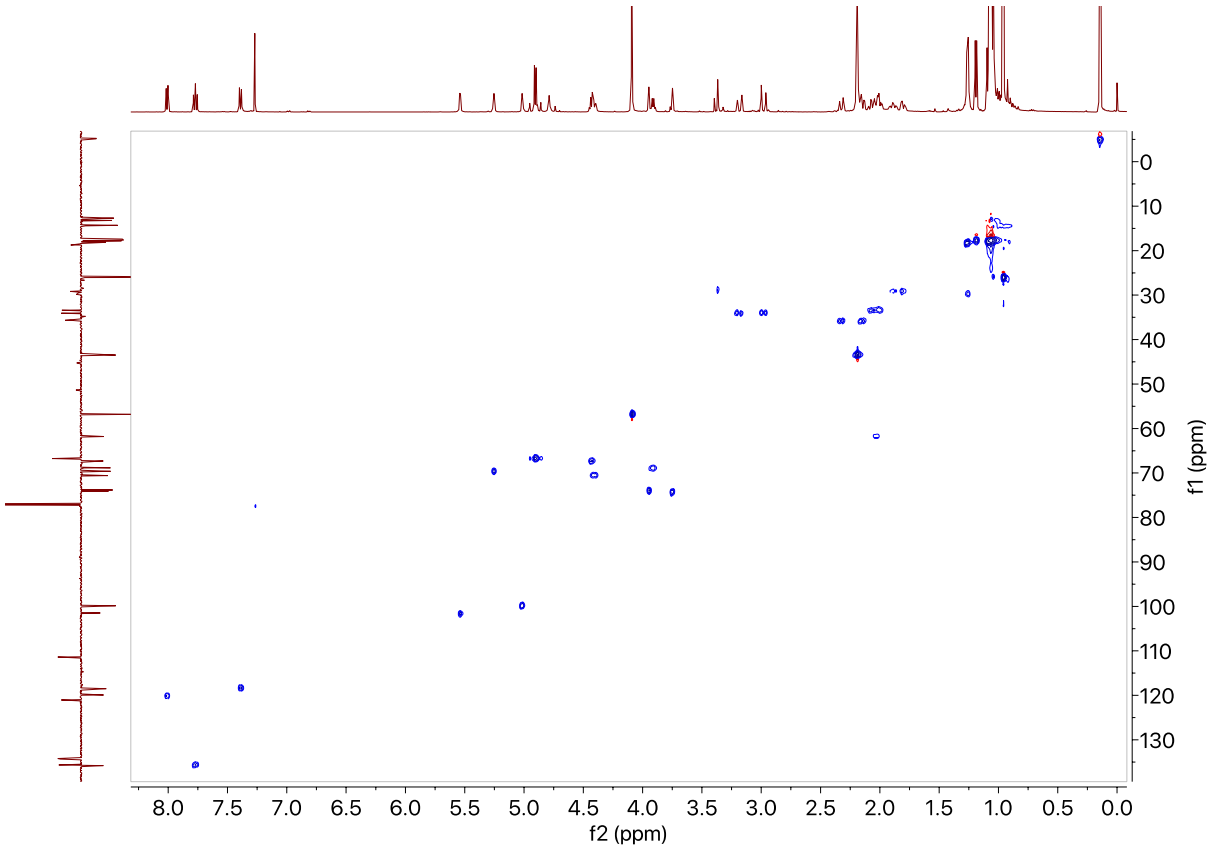

215.37 187.51 161.95 157.51 156.16 135.23 121.59 120.06 119.90 112.26 111.96 101.95 101.86 81.62 77.13 72.36 70.89 69.02 68.76 66.67 66.16 57.10 48.05 37.86 34.62 34.38 34.20 18.14
f1 (ppm)

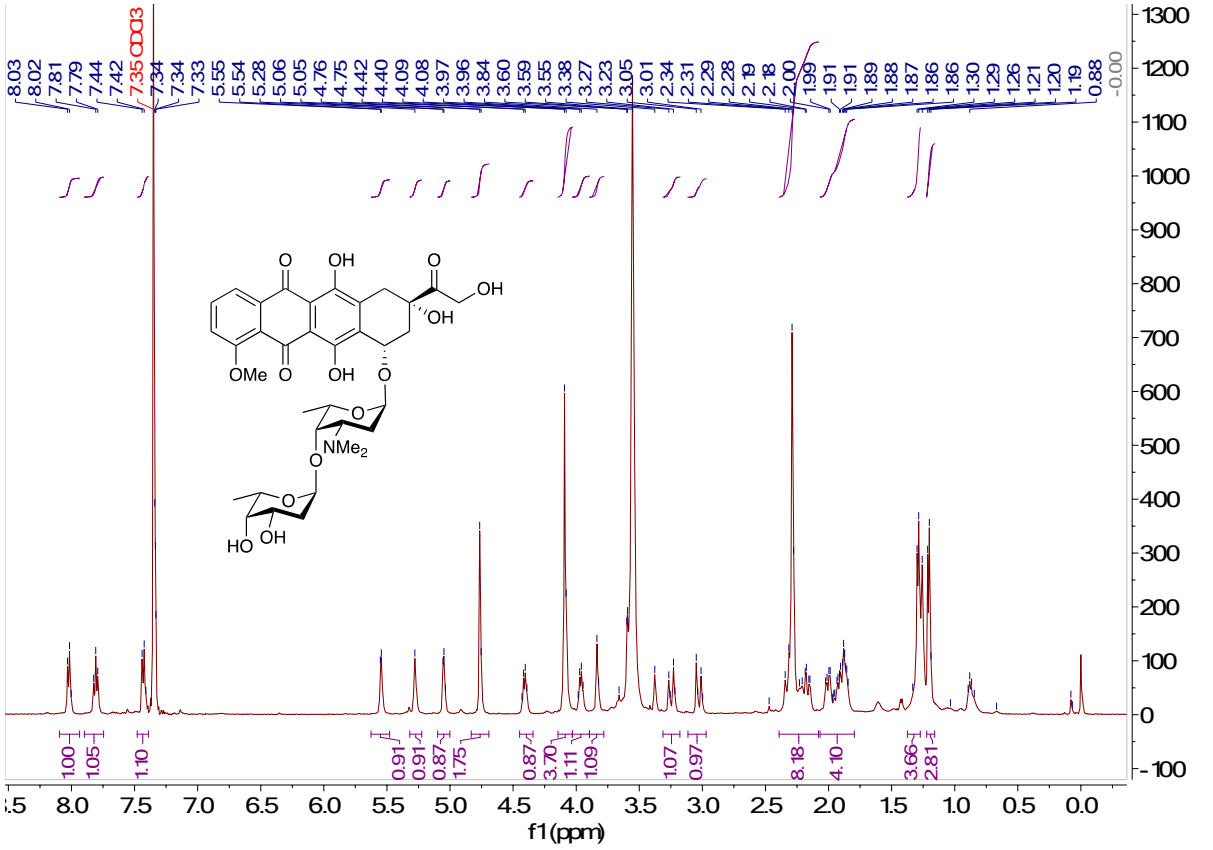

f1 (ppm)
f2 (ppm)

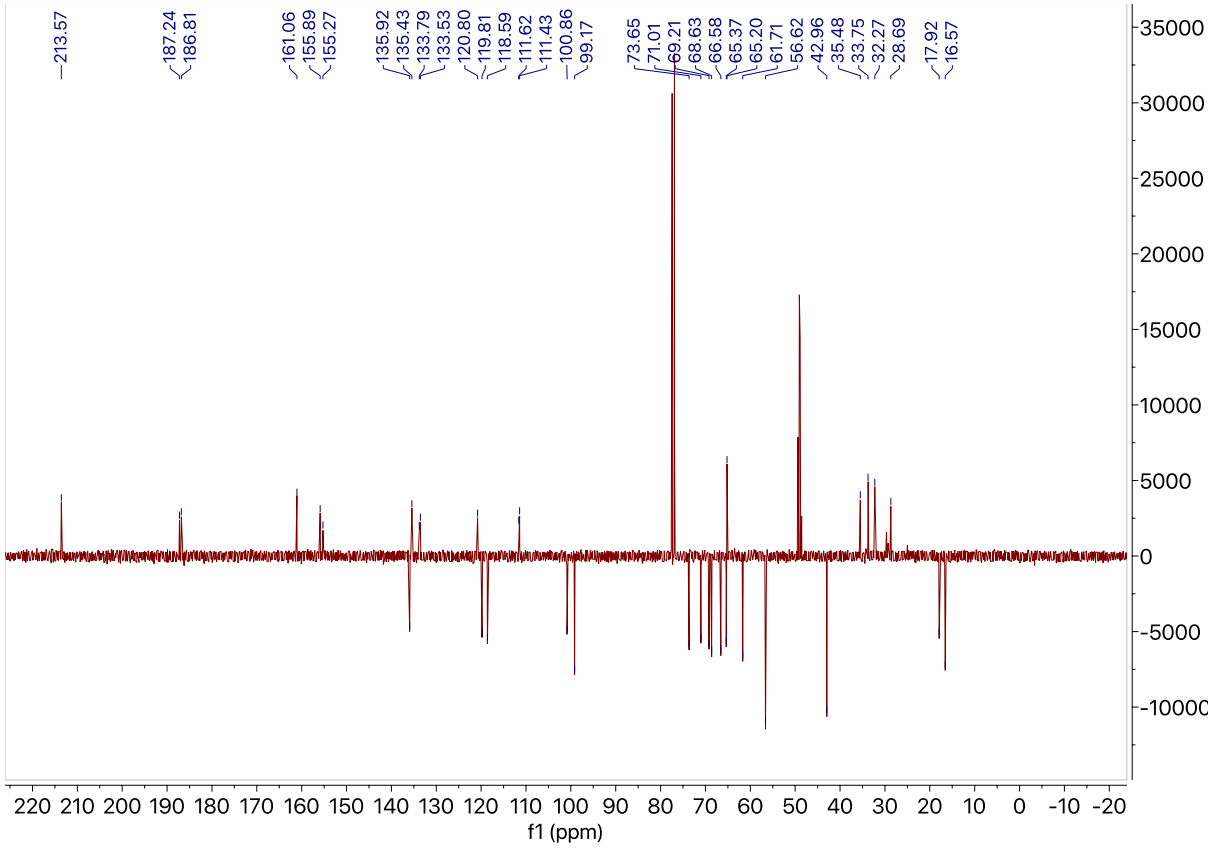

f1 (ppm)
f2 (ppm)

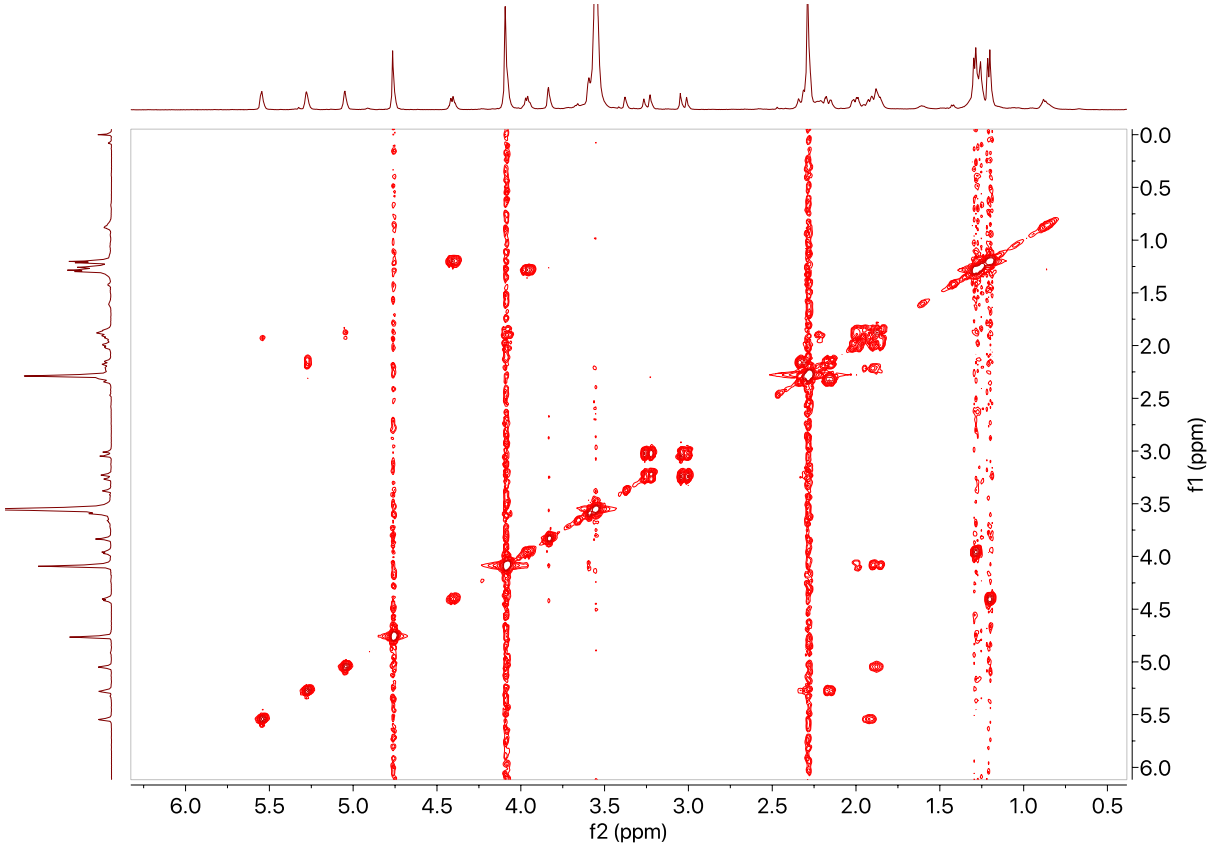

f1 (ppm)
f1 (ppm)

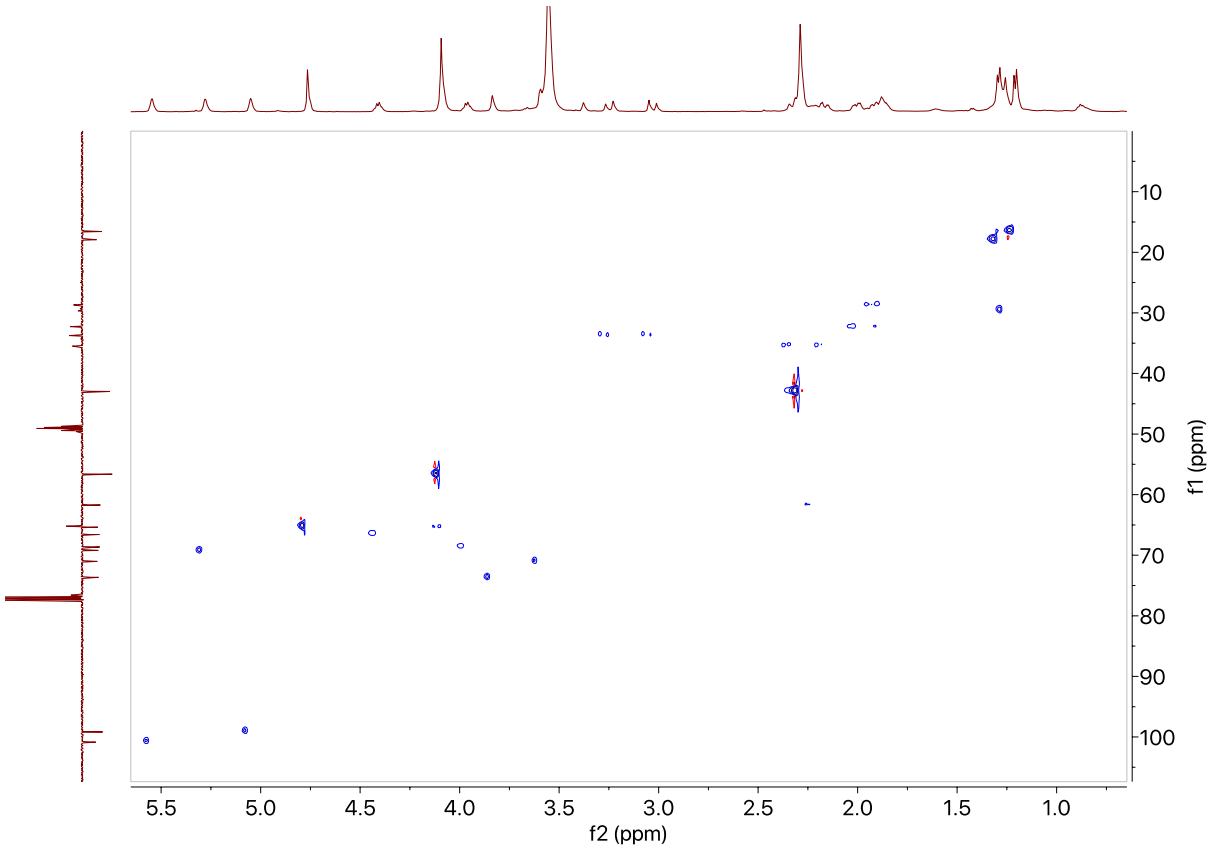

f1 (ppm)
f2 (ppm)

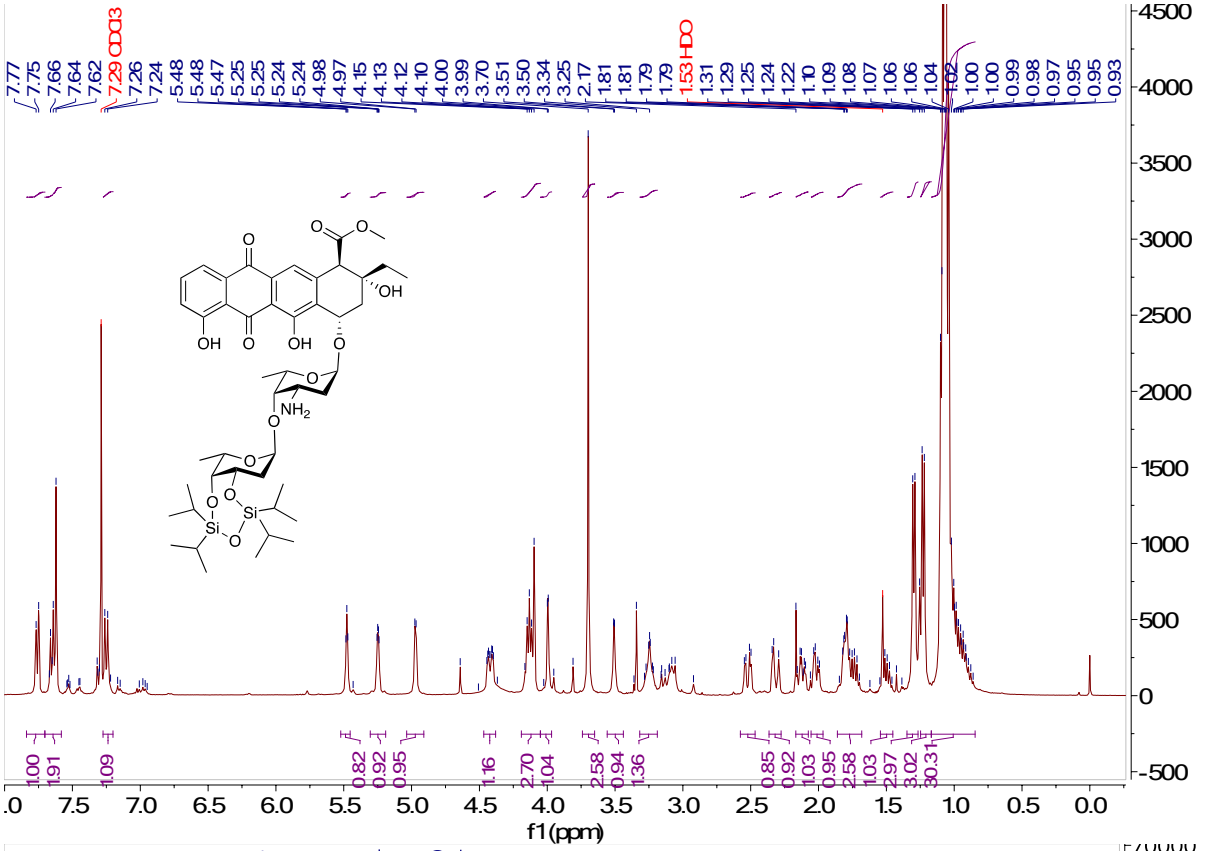

f1 (ppm)
f2 (ppm)

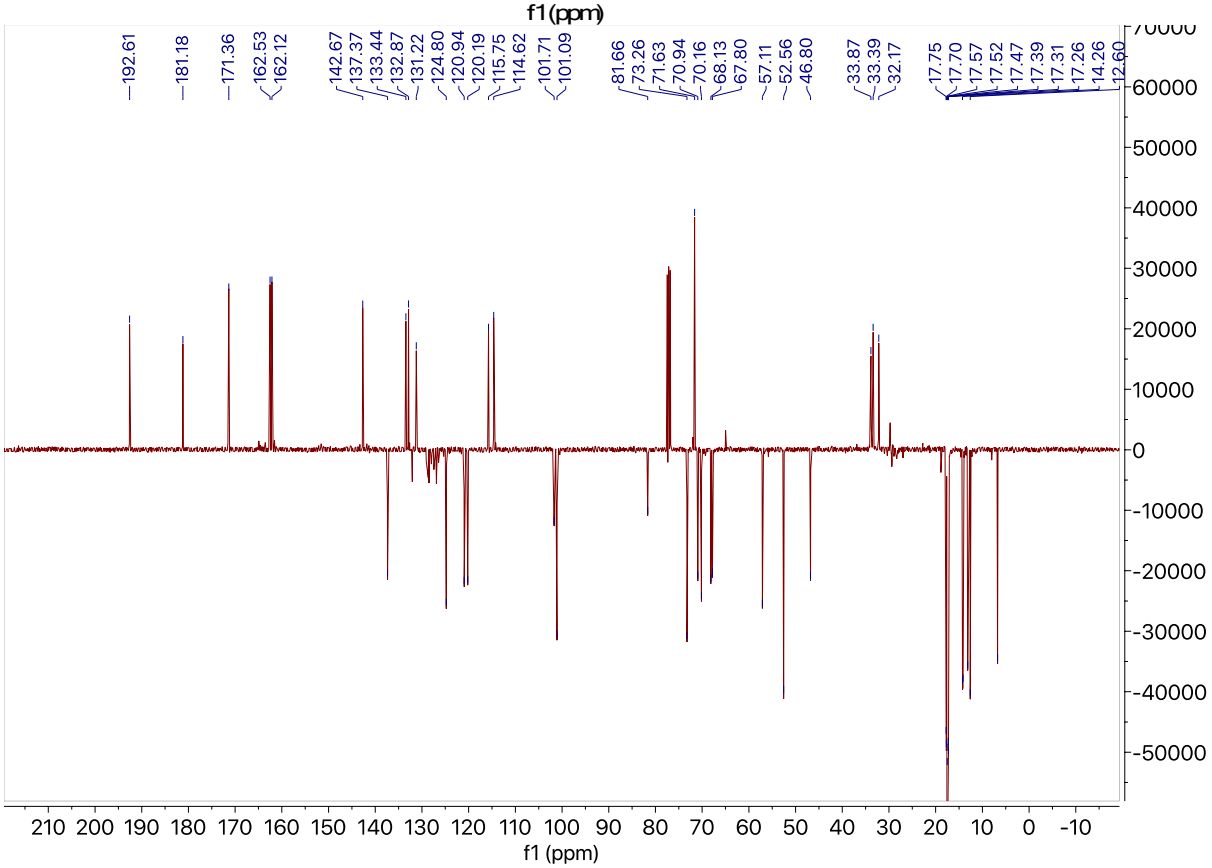

8.03 8.02 7.81 7.79 7.44 7.42 7.35 7.34 7.34 7.33 5.55 5.54 5.28 5.06 5.05 4.76 4.75 4.42 4.40 4.09 4.08 3.97 3.96 3.84 3.60 3.59 3.55 3.38 3.27 3.23 3.05 3.01 2.34 2.31 2.29 2.28 2.19 2.18 2.00 1.99 1.91 1.89 1.88 1.87 1.86 1.86 1.30 1.29 1.26 1.21 1.20 1.19 0.88 -0.00
1.00 1.05 1.10 0.91 0.91 0.87 1.75 0.87 3.70 1.11 1.09 1.07 0.97 8.18 4.10 3.66 2.81
f1 (ppm)

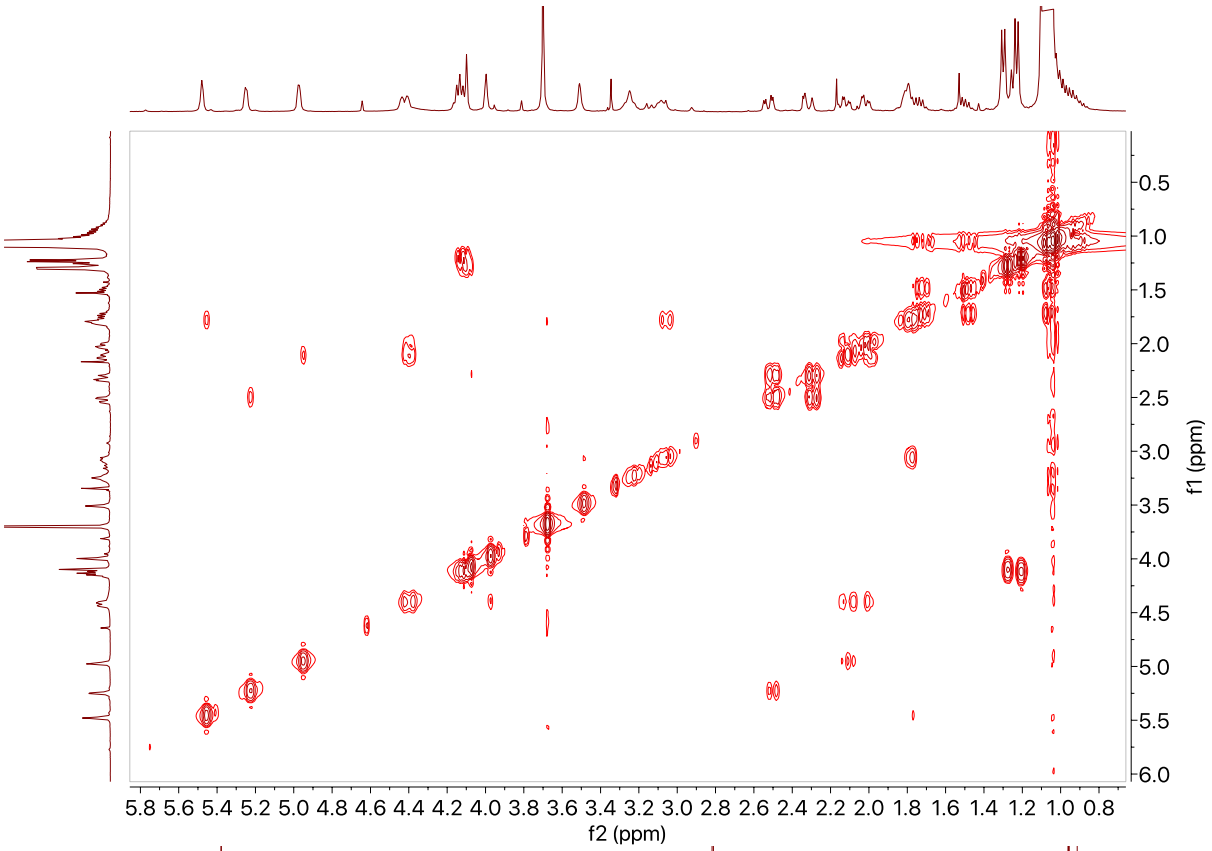

213.57 187.24 186.81 161.06 155.89 155.27 135.92 135.43 133.79 133.53 120.80 119.81 118.59 111.62 111.43 100.86 99.17 73.65 71.01 69.21 68.63 66.58 65.37 65.20 61.71 56.62 42.96 35.48 33.75 32.27 28.69 17.92 16.57
f1 (ppm)

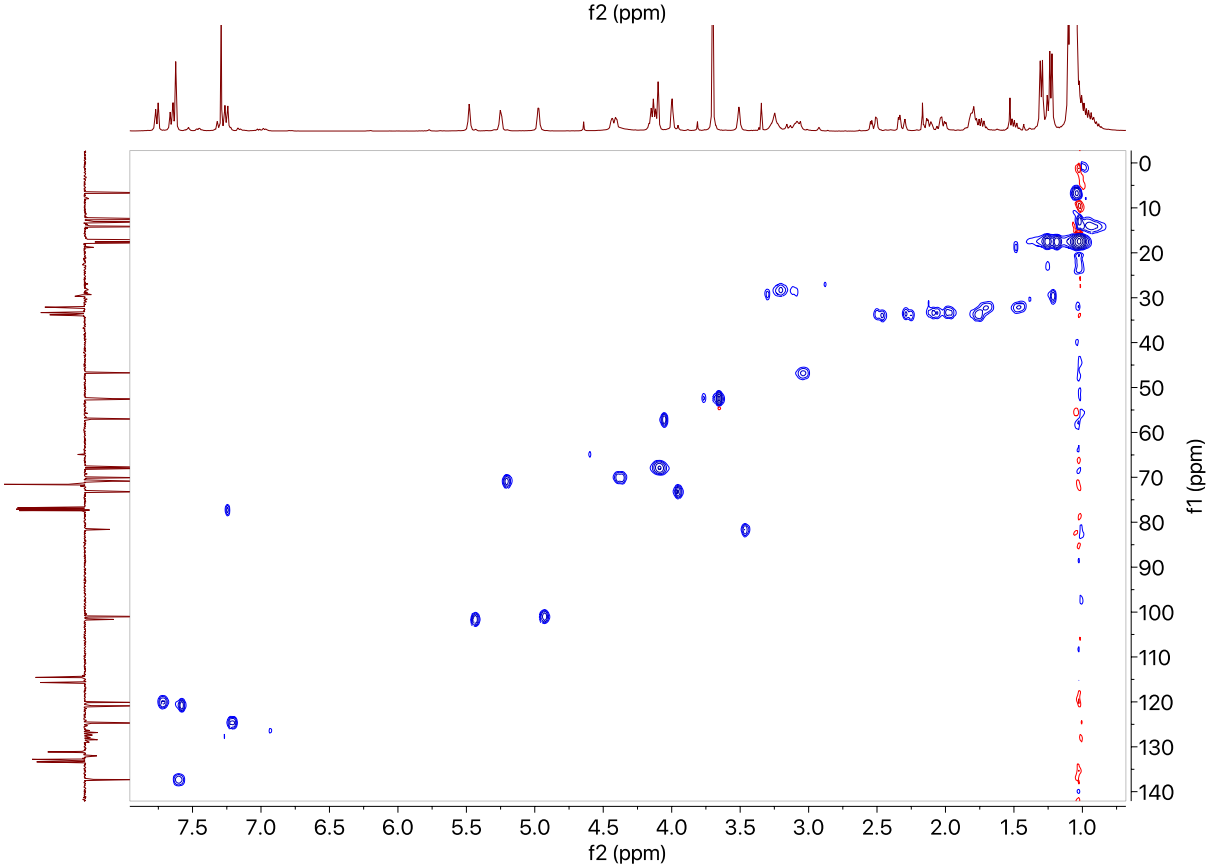

f2 (ppm)
f1 (ppm)

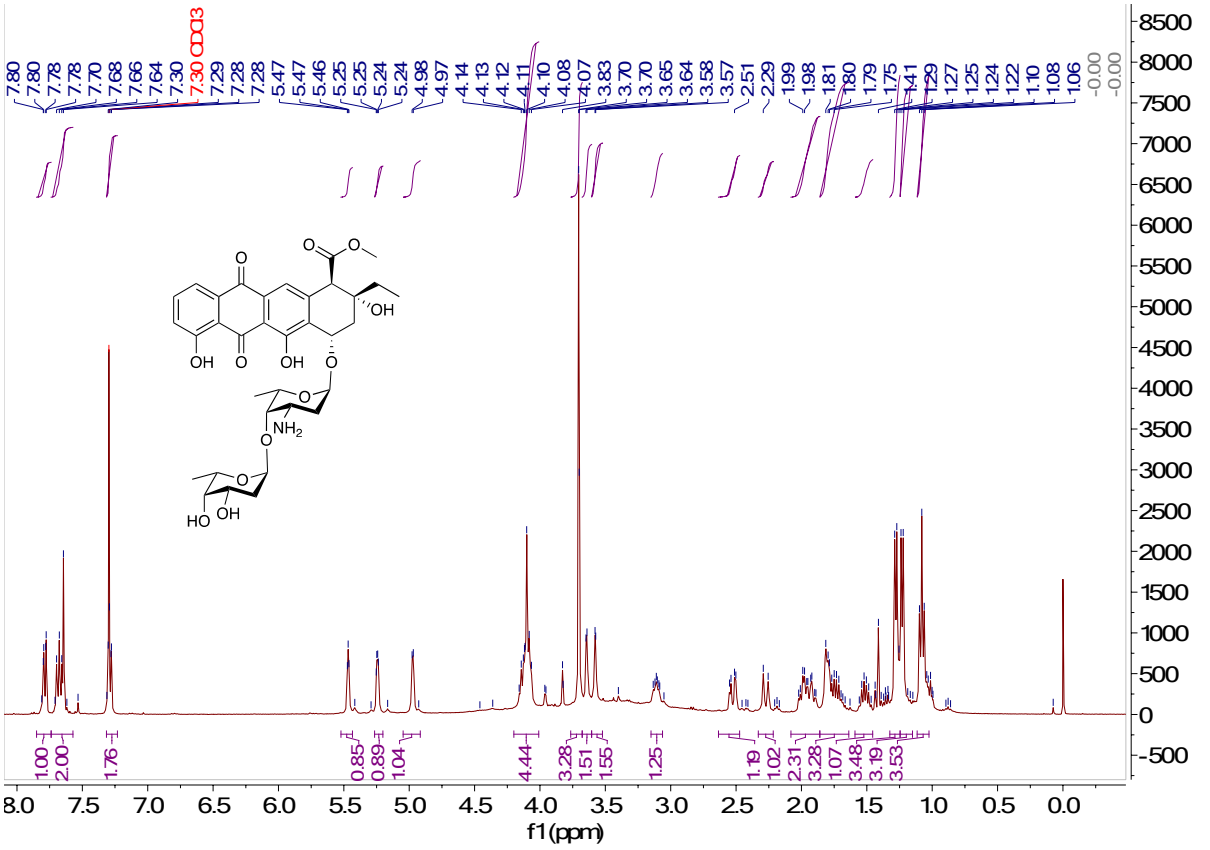

f2 (ppm)
f1 (ppm)

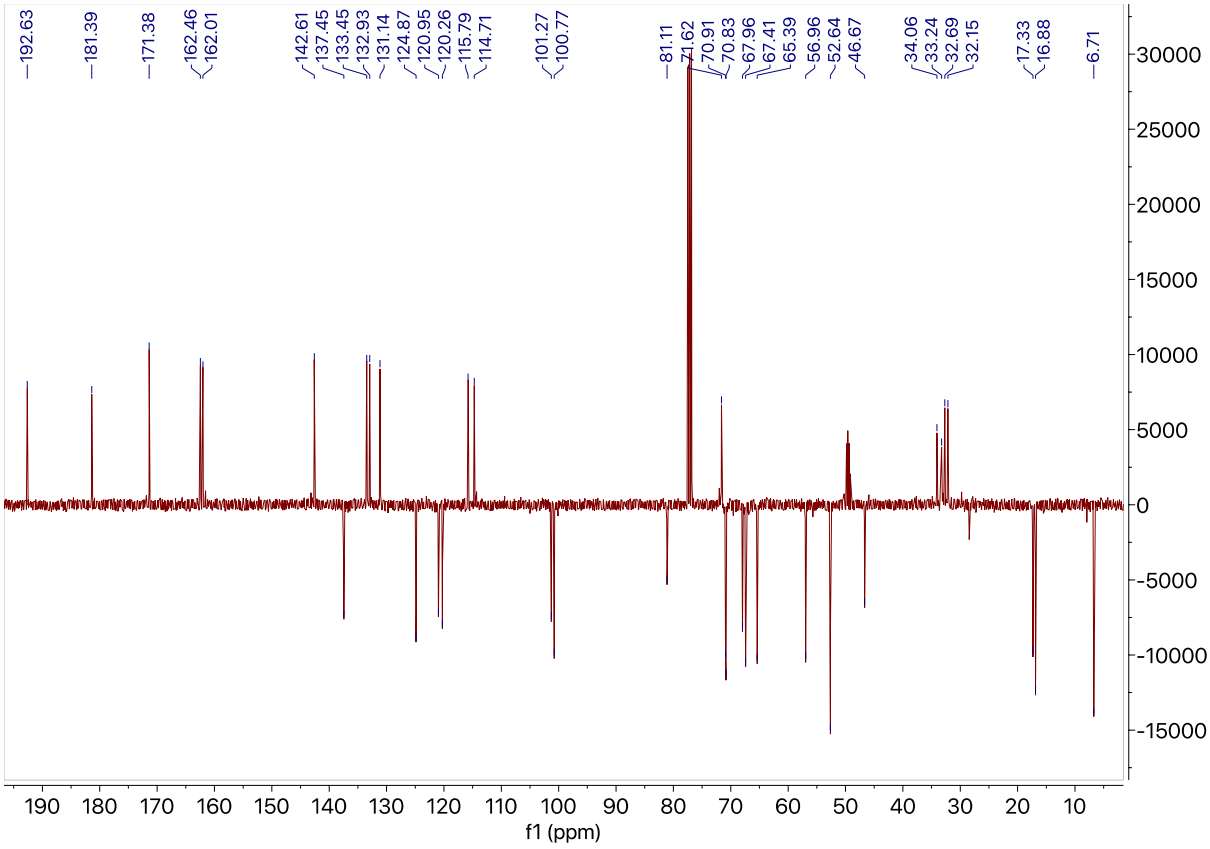

7.77 7.75 7.66 7.64 7.62 7.29 CDCl3 7.26 7.24 5.48 5.48 5.47 5.25 5.25 5.24 5.24 4.98 4.97 4.15 4.13 4.12 4.10 4.00 3.99 3.70 3.51 3.50 3.34 3.25 2.17 1.81 1.81 1.79 1.79 1.53 HDO 1.31 1.29 1.25 1.24 1.22 1.10 1.09 1.08 1.07 1.06 1.06 1.04 1.02 1.00 1.00 0.99 0.98 0.97 0.95 0.95 0.93
OH
O
OH
O
OH
O
O
O
NH2
O
O
O
Si
Si
O
O
1.00 1.91 1.09 0.82 0.92 0.95 1.16 2.70 1.04 2.58 0.94 1.36 0.85 0.92 1.03 0.95 2.58 1.03 2.97 3.02 30.31
f1 (ppm)

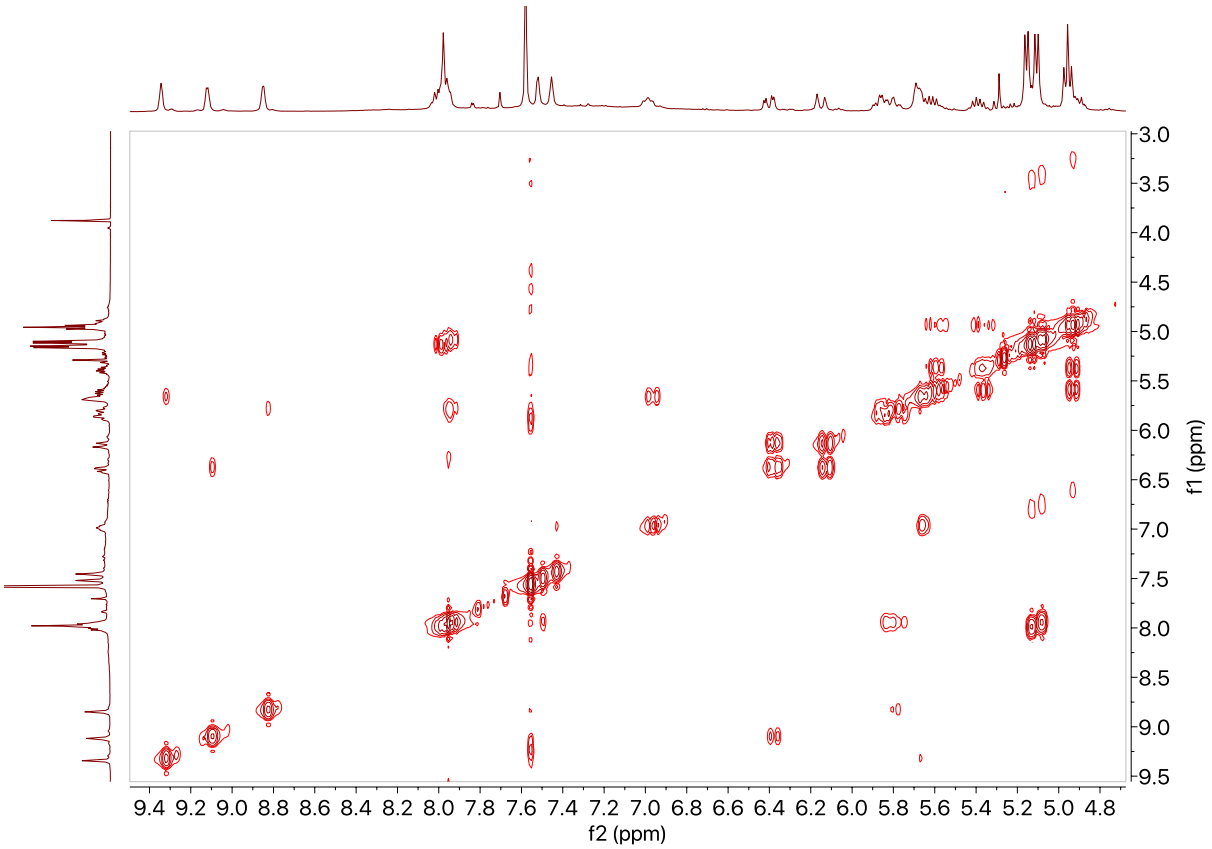

192.61 181.18 171.36 162.53 162.12 142.67 137.37 133.44 132.87 131.22 124.80 120.94 120.19 115.75 114.62 101.71 101.09 81.66 73.26 71.63 70.94 70.16 68.13 67.80 57.11 52.56 46.80 33.87 33.39 32.17 17.75 17.70 17.57 17.52 17.47 17.39 17.31 17.26 14.26 12.60
f1 (ppm)

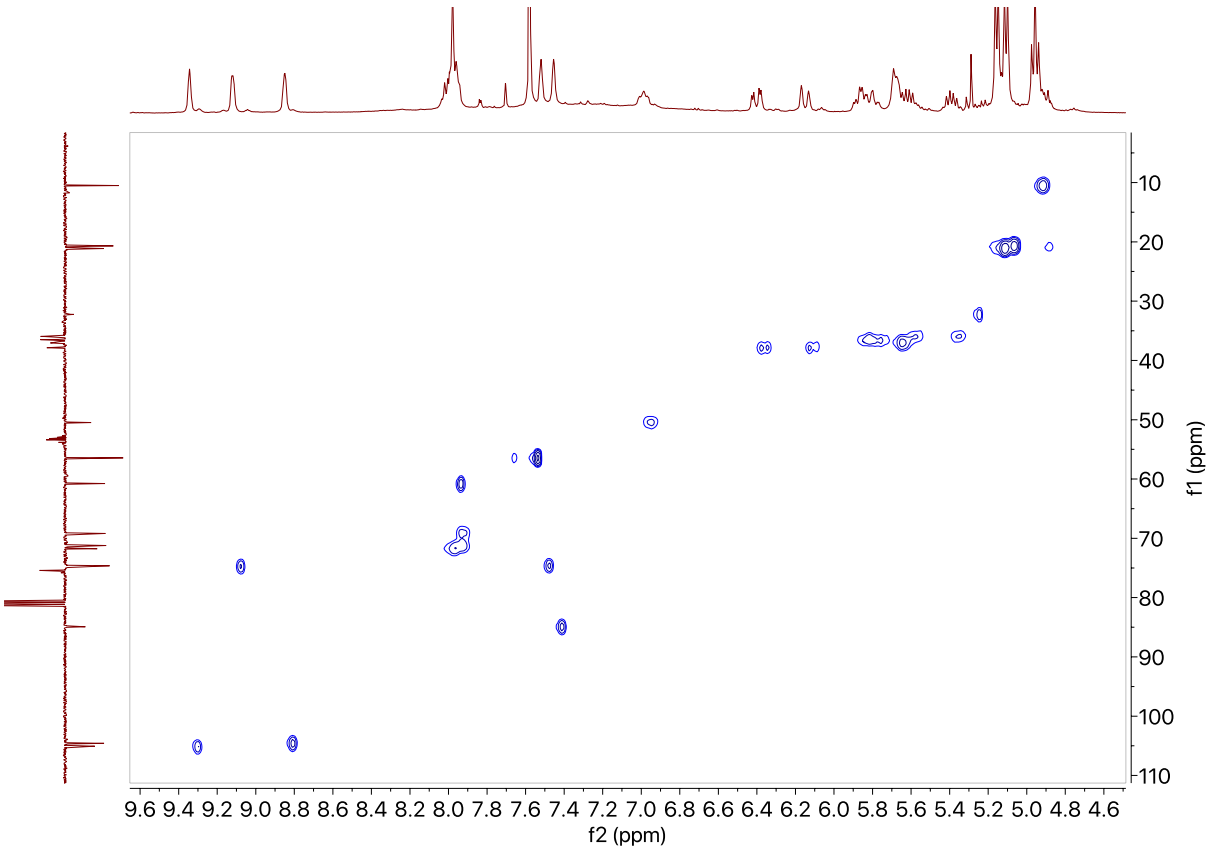

5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
f1 (ppm)

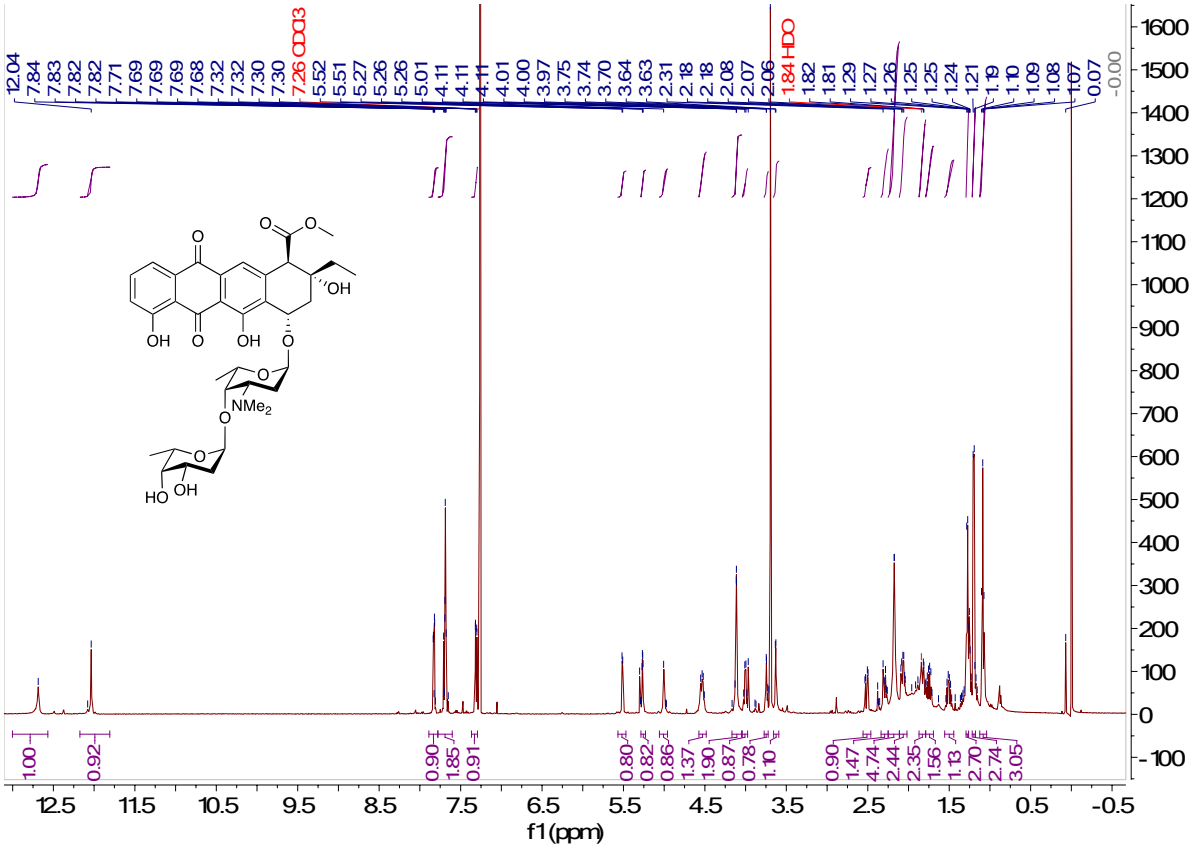

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

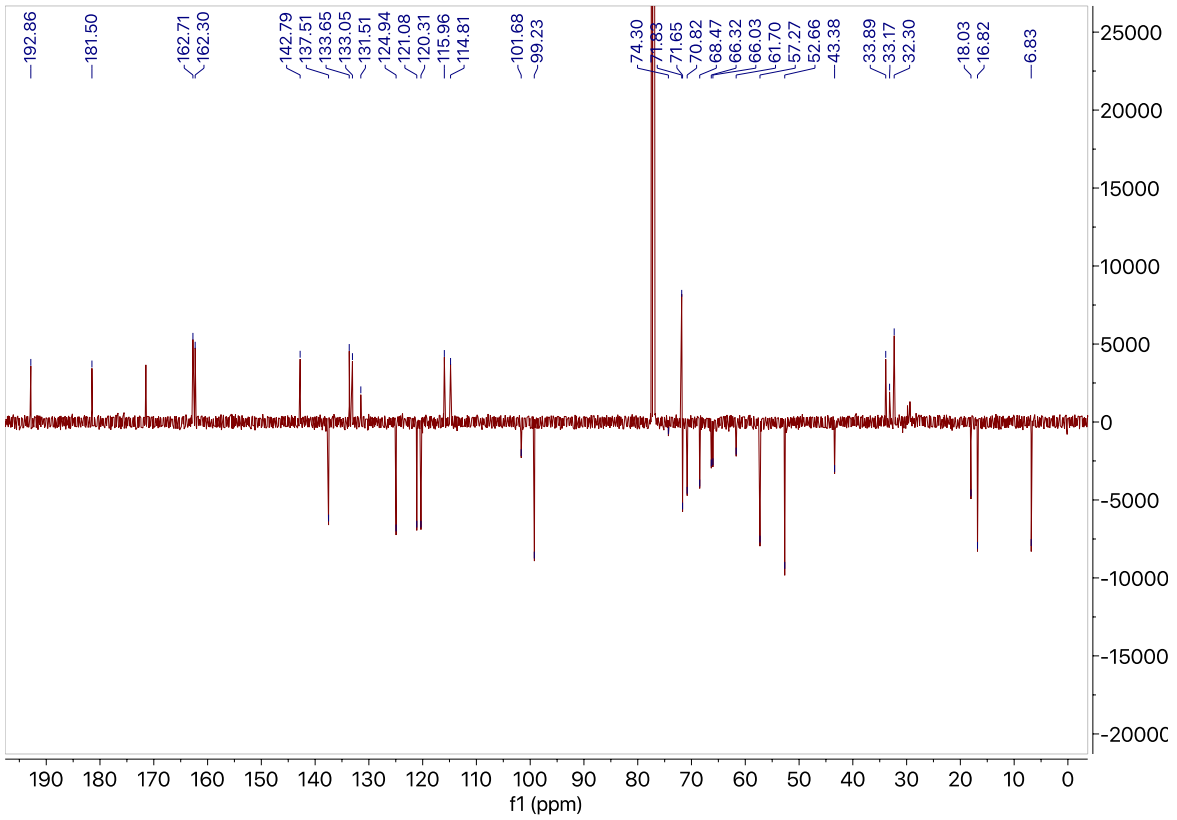

f1 (ppm)

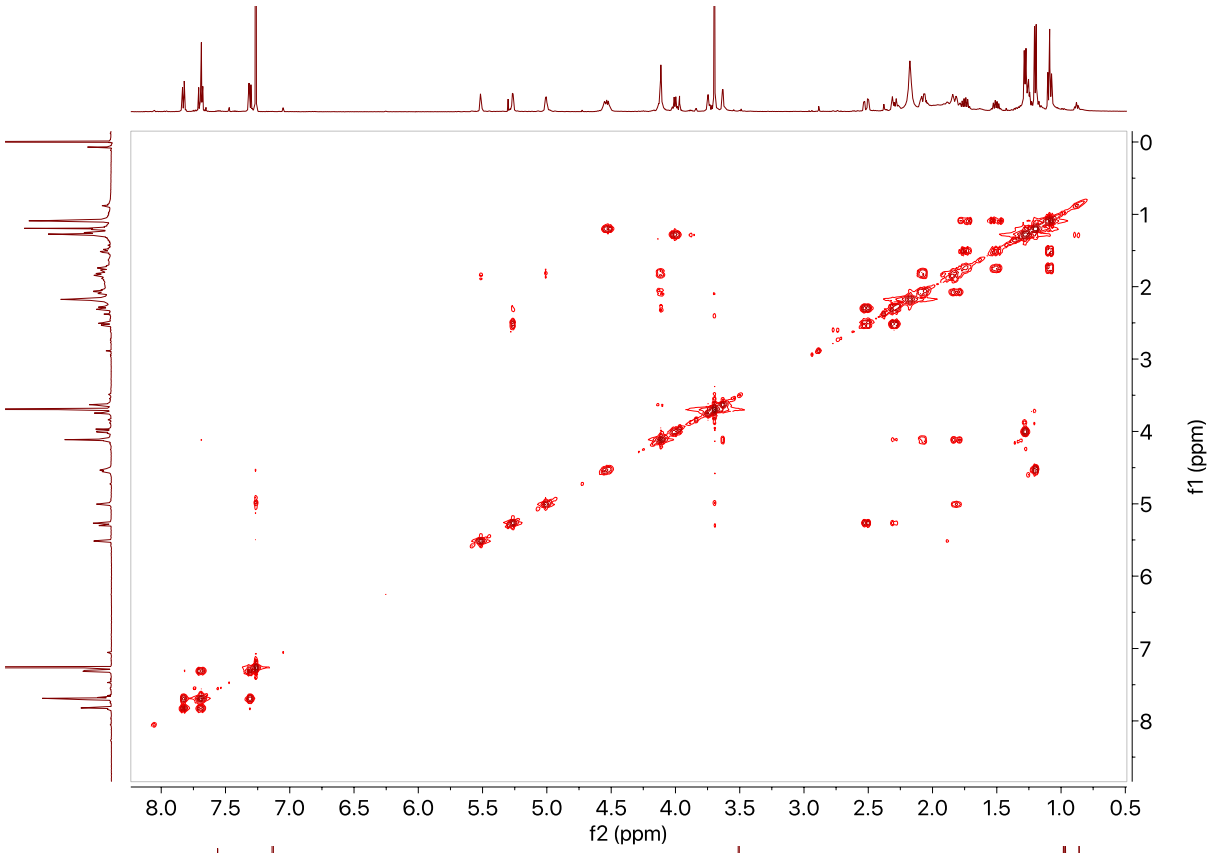

f1 (ppm)

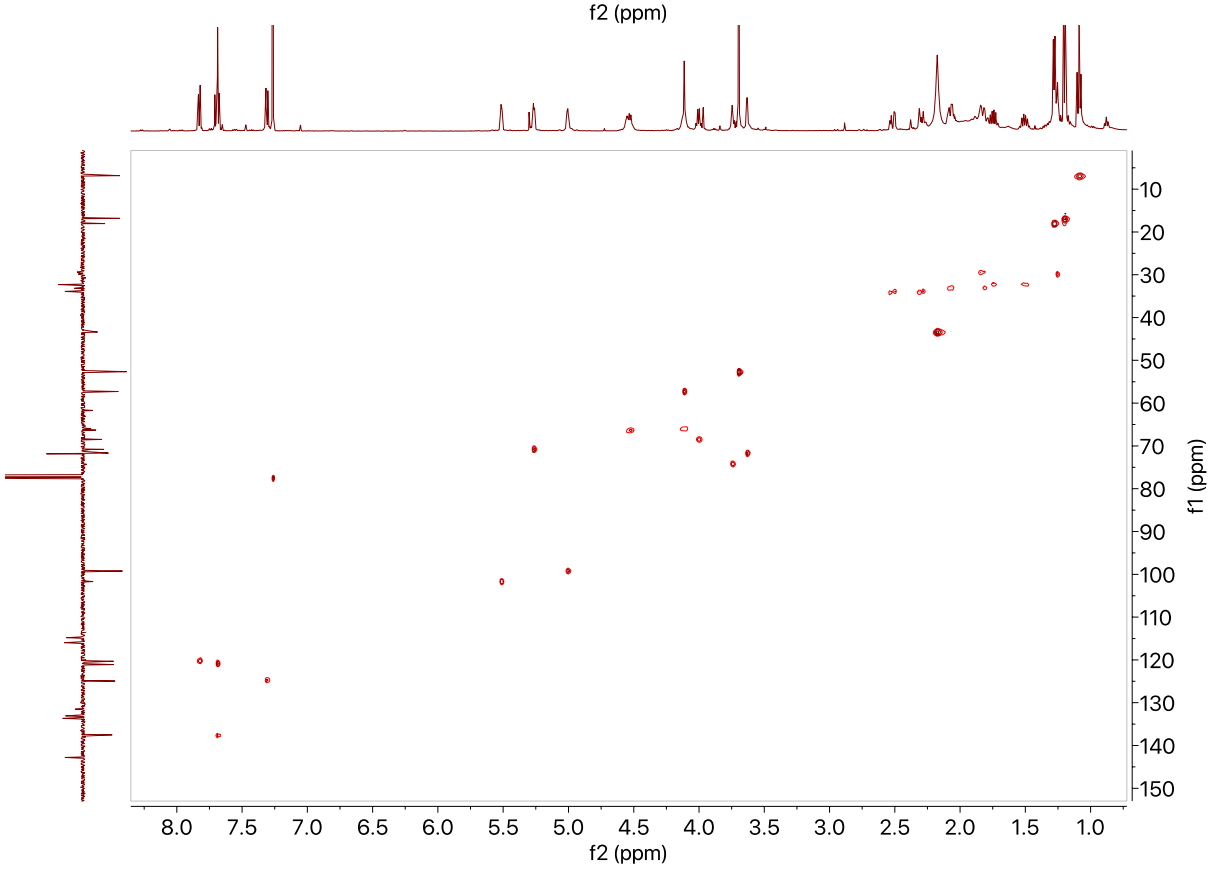

3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
f1 (ppm)
9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8
f2 (ppm)


10
20
30
40
50
60
70
80
90
100
110
f1 (ppm)
9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6
f2 (ppm)

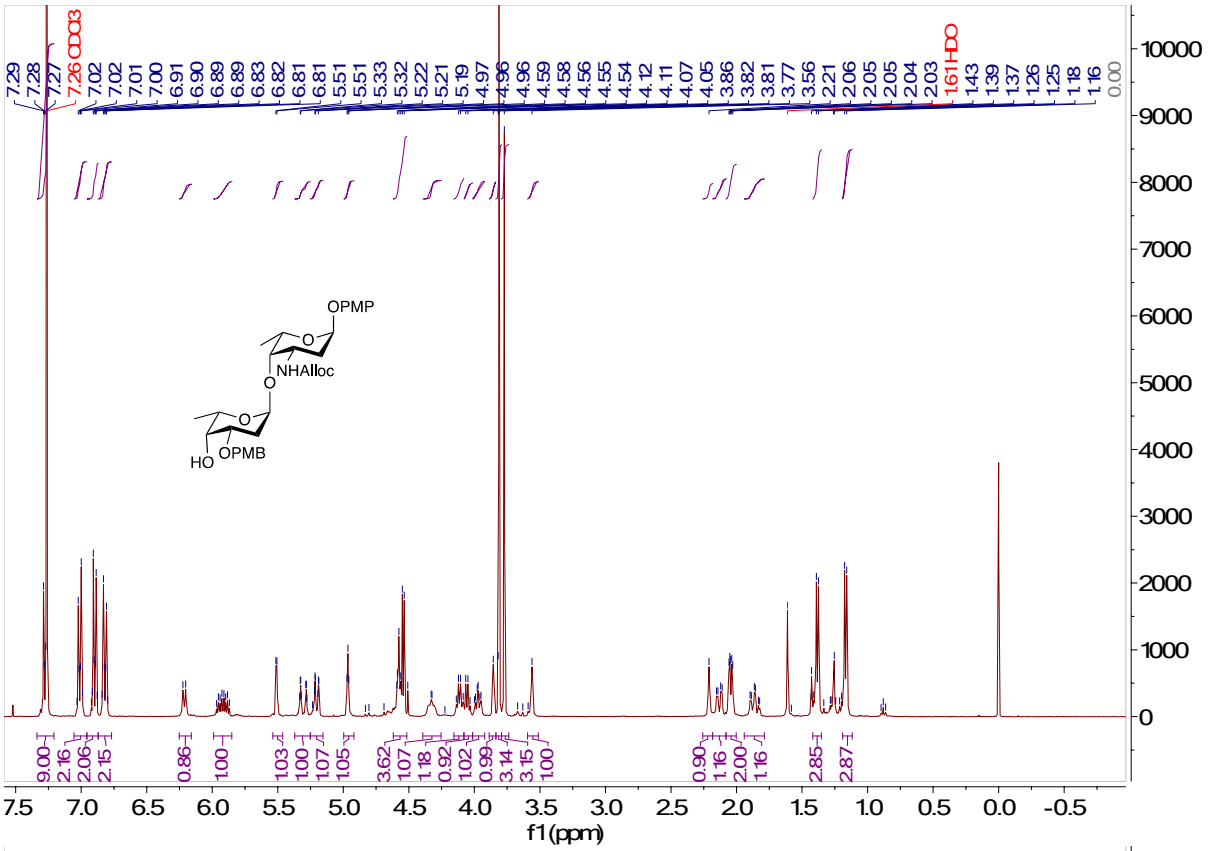

f1 (ppm)

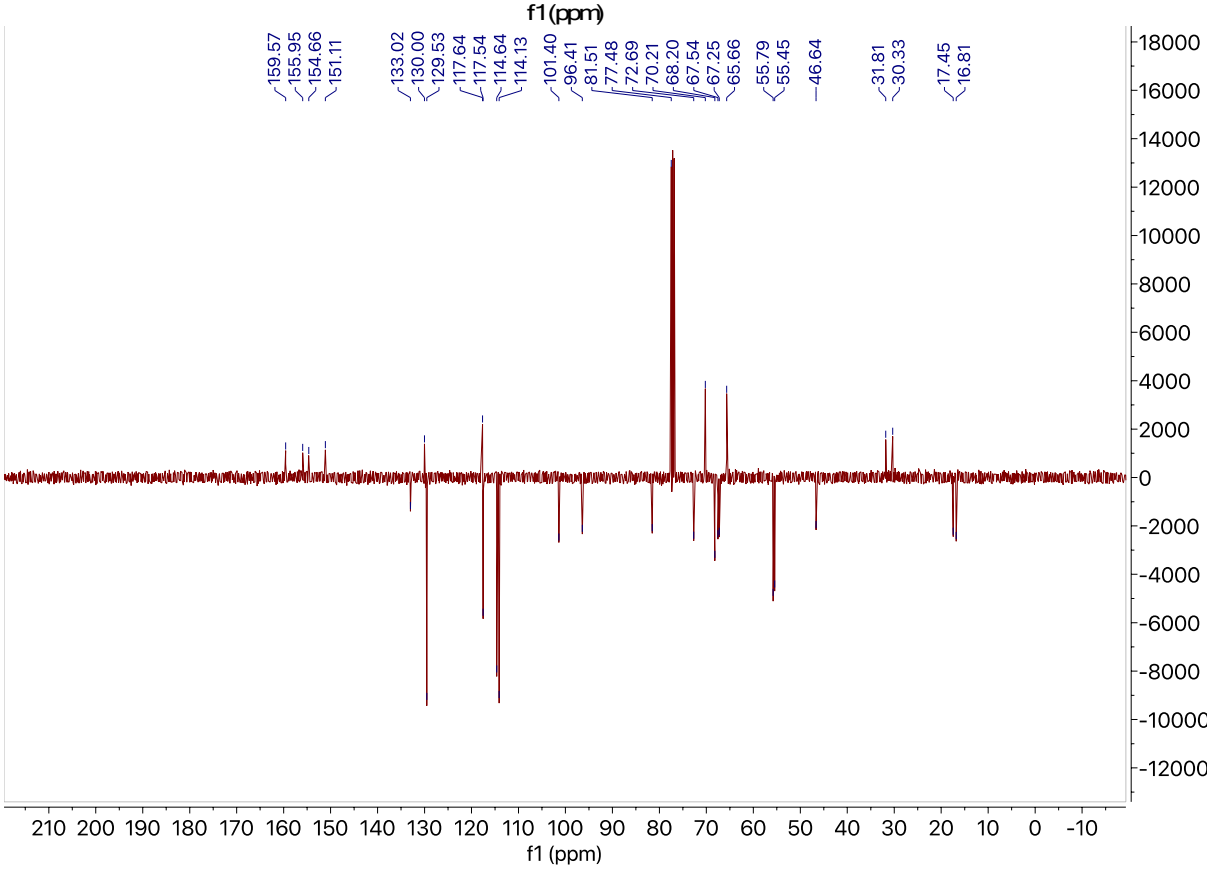

f1 (ppm)

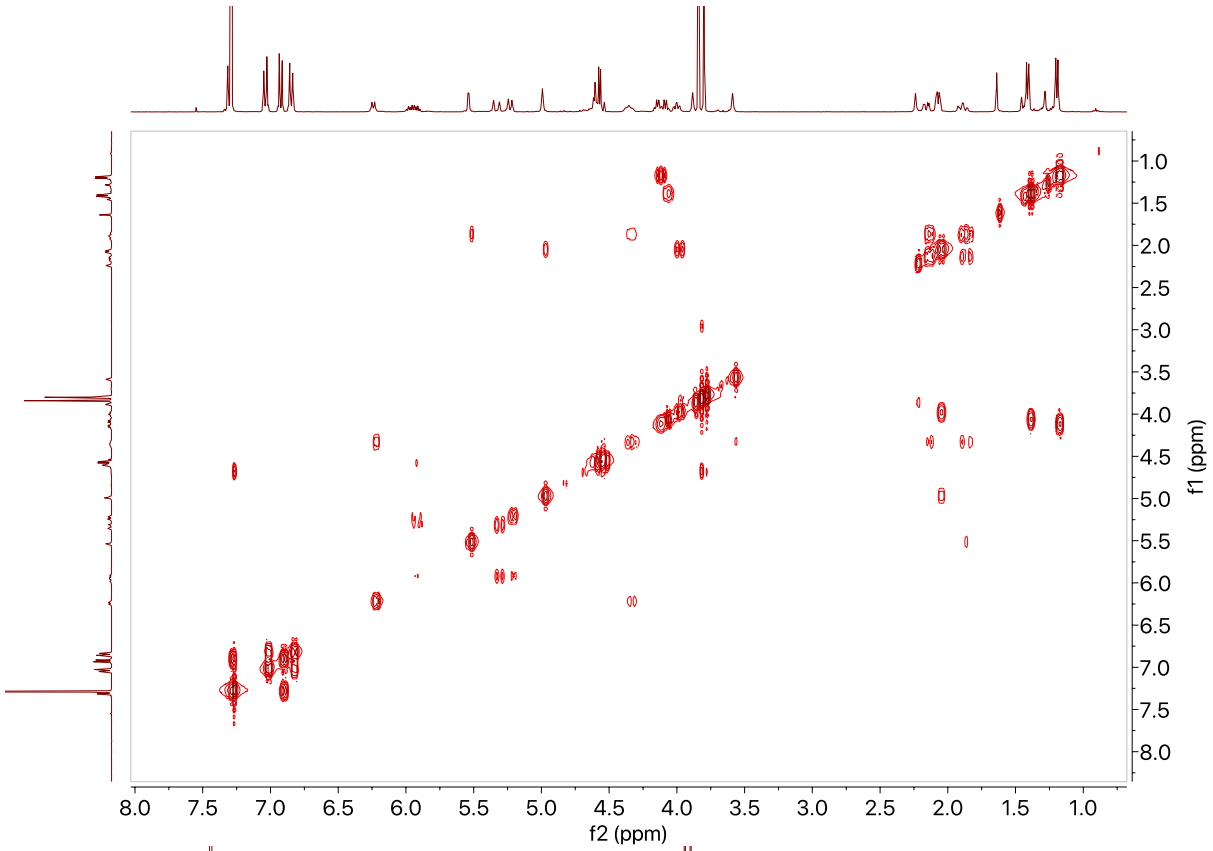

0
1
2
3
4
5
6
7
8
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

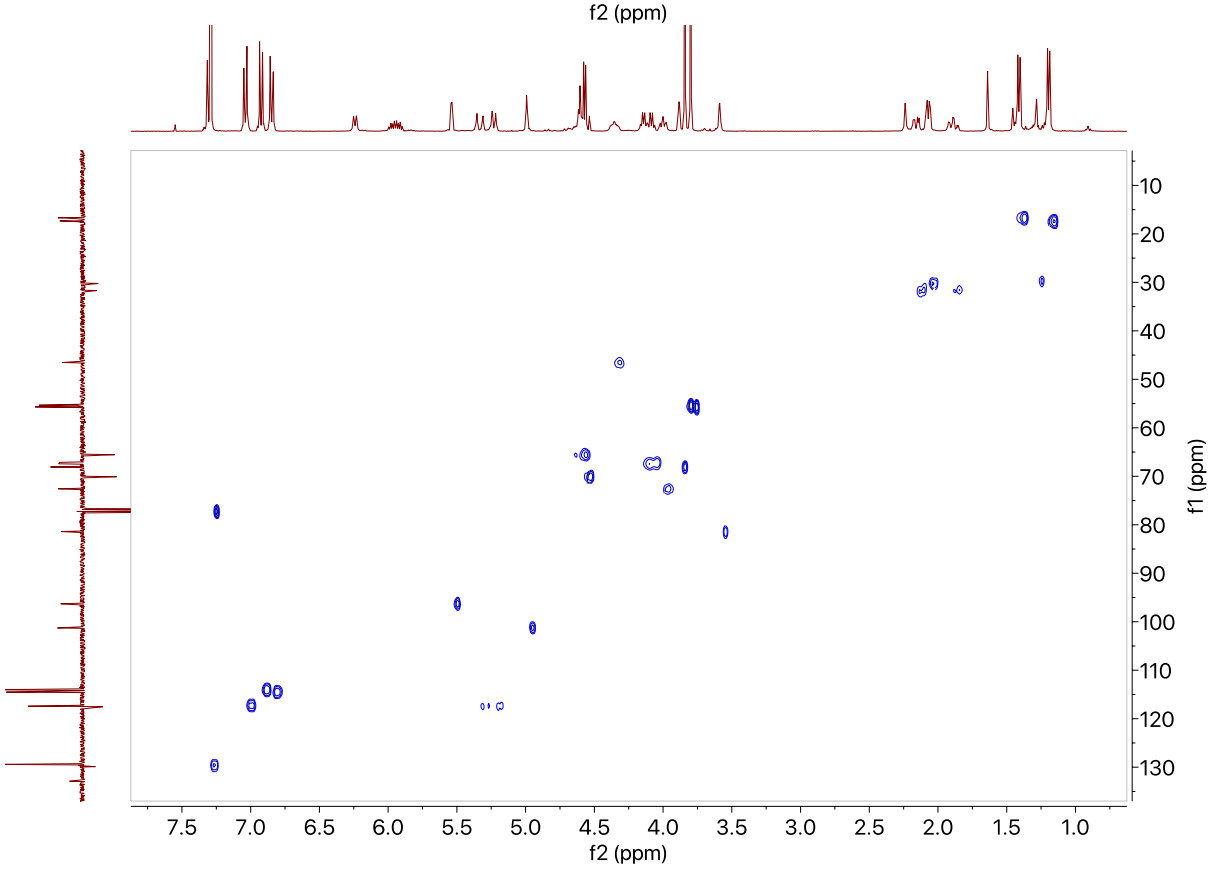

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

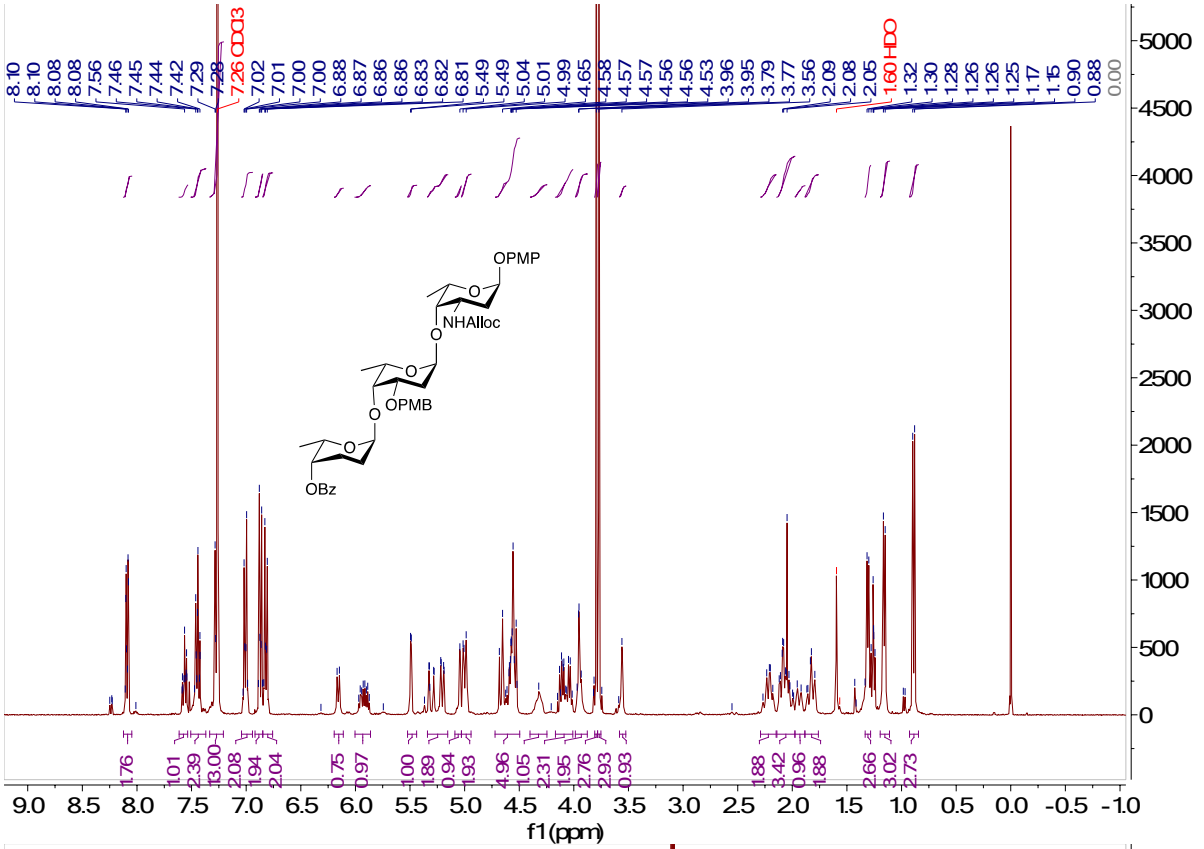
I: NMR data accompanying the synthesis of anthracycline trisaccharides **9**, **10** and **11**

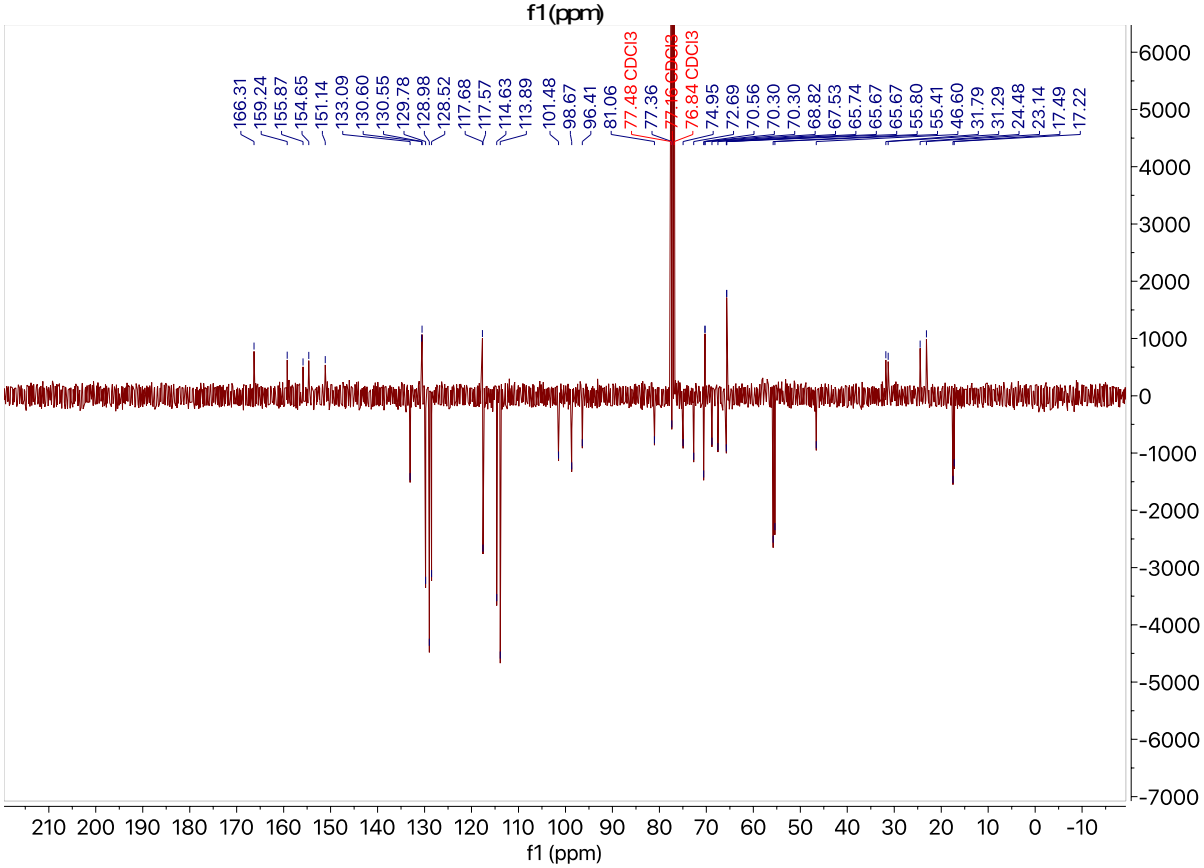


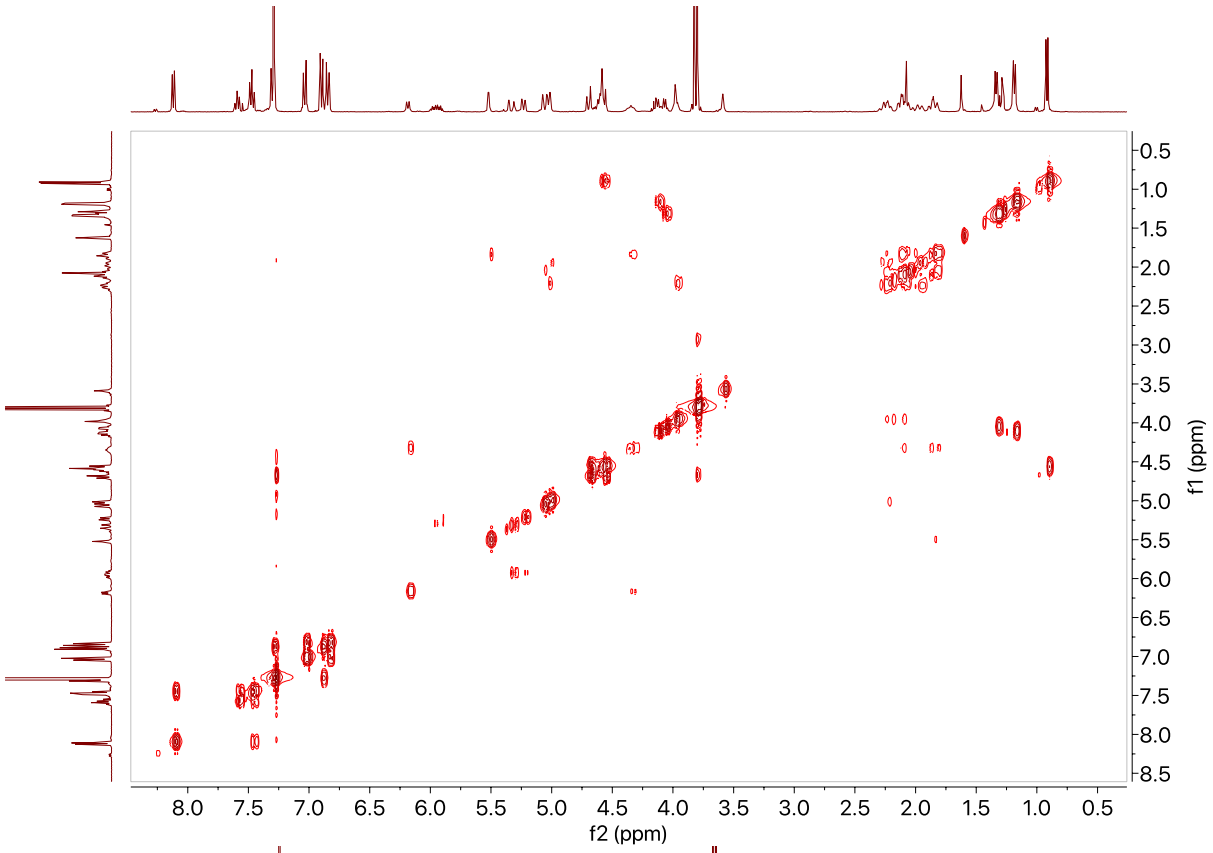


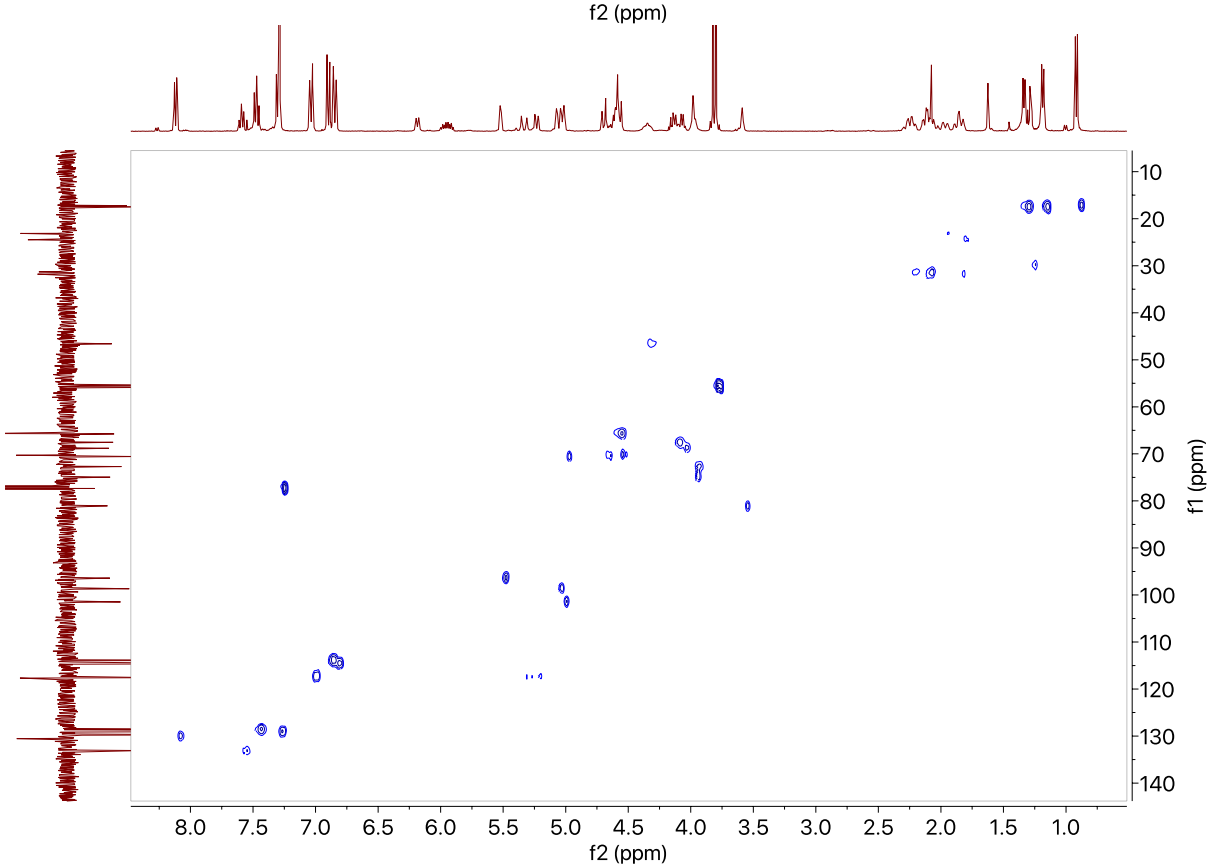

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)

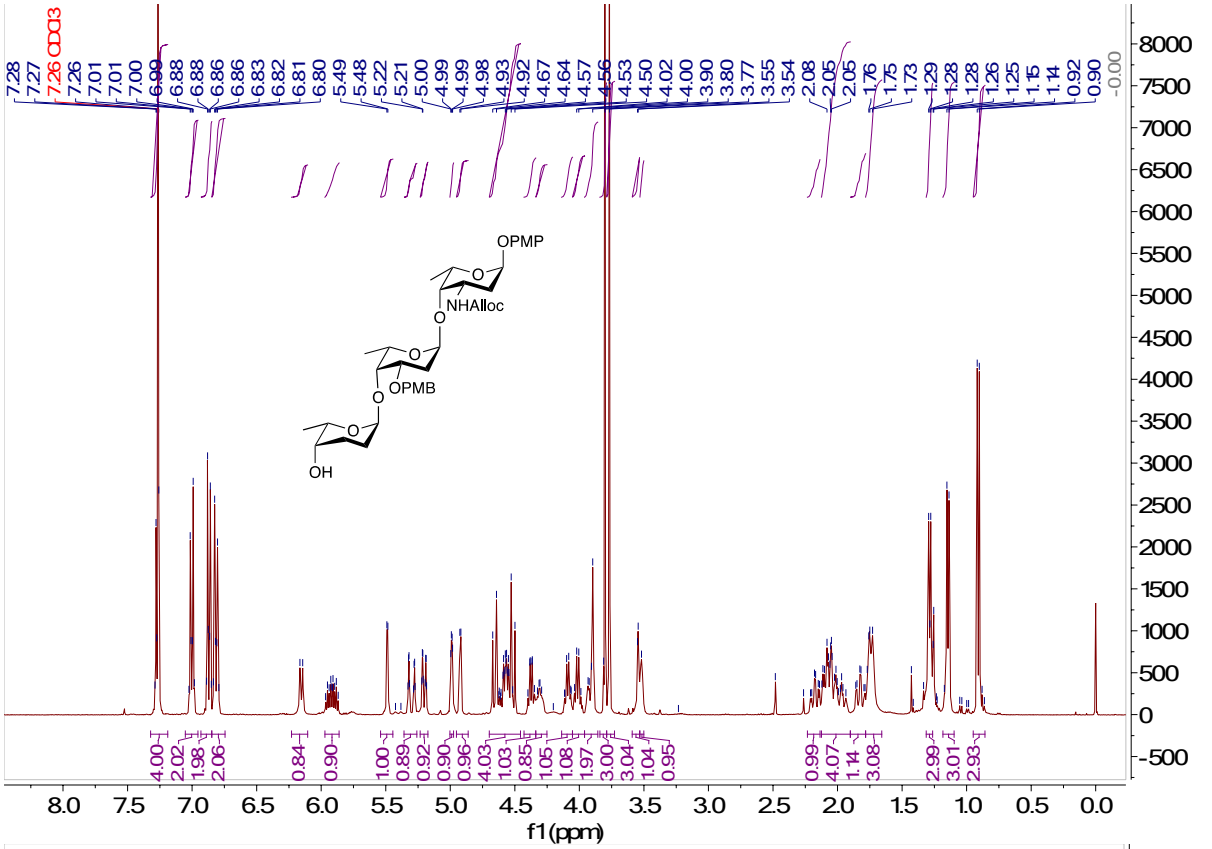

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130
f1 (ppm)

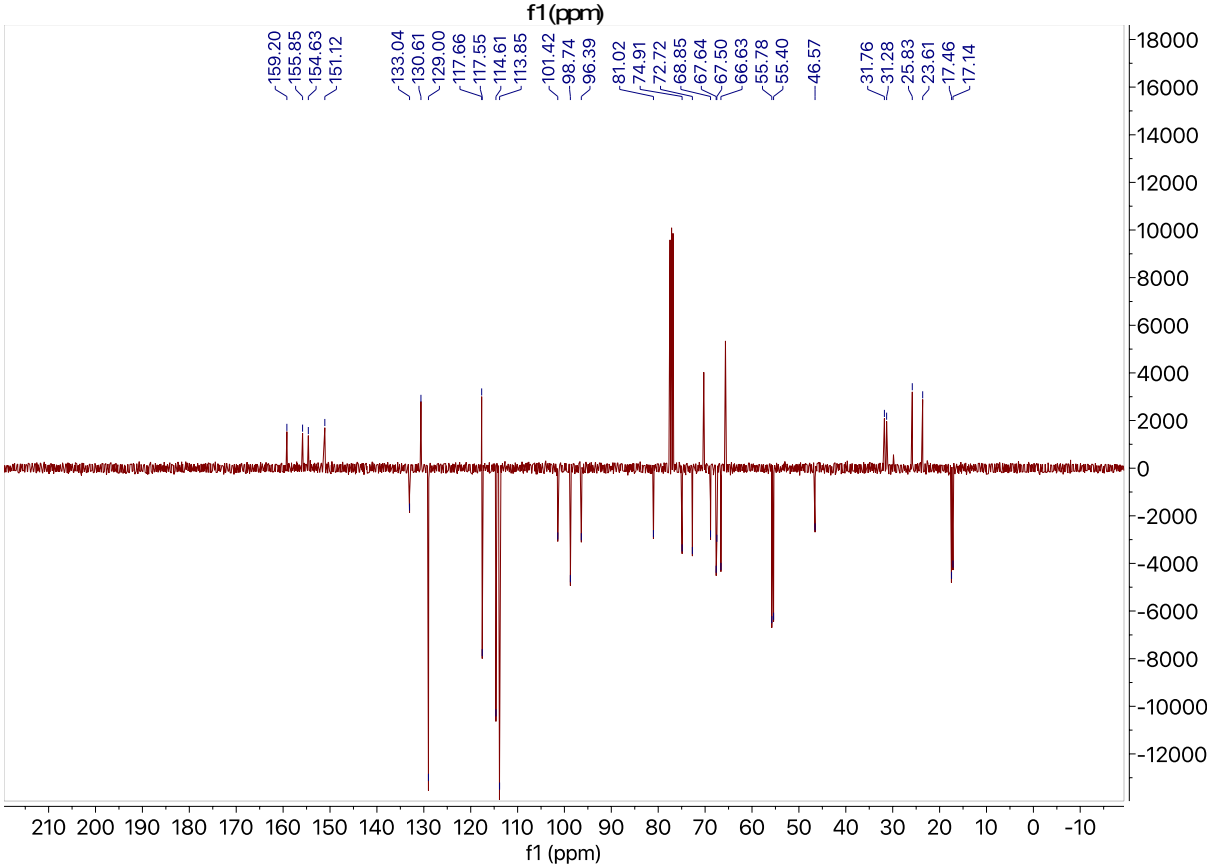

OPMP
NHAlloc
OPMB
OBz
f1 (ppm)

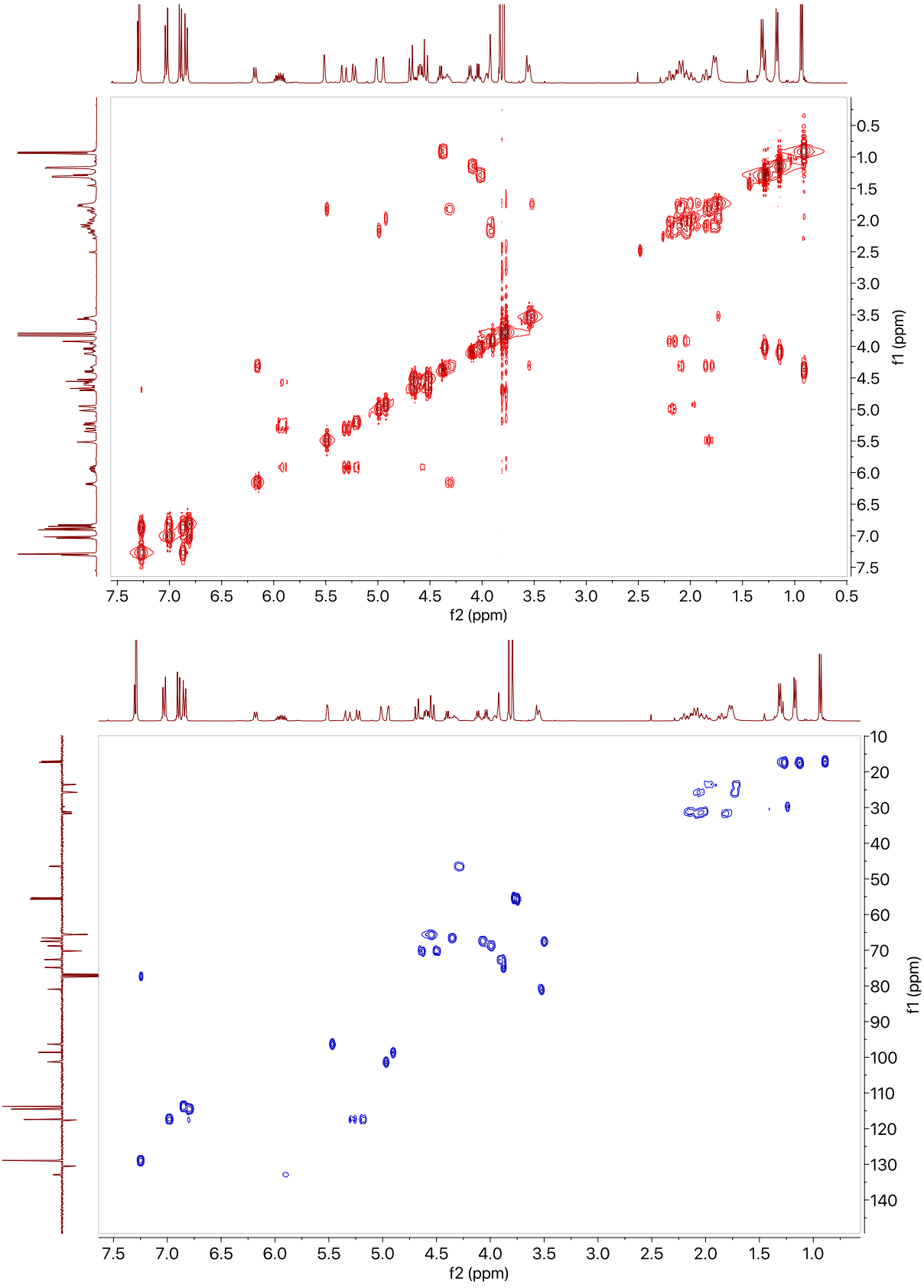

f1 (ppm)

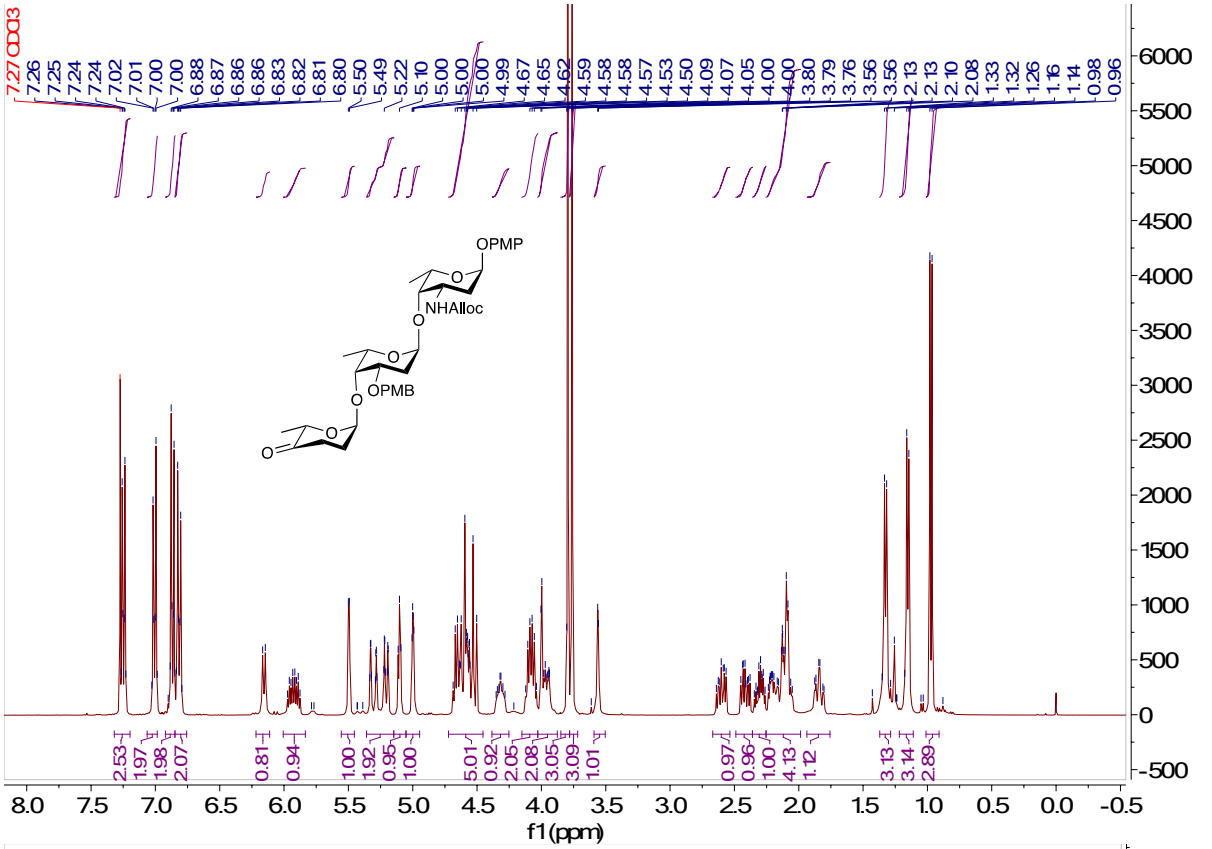

f2 (ppm)
f1 (ppm)

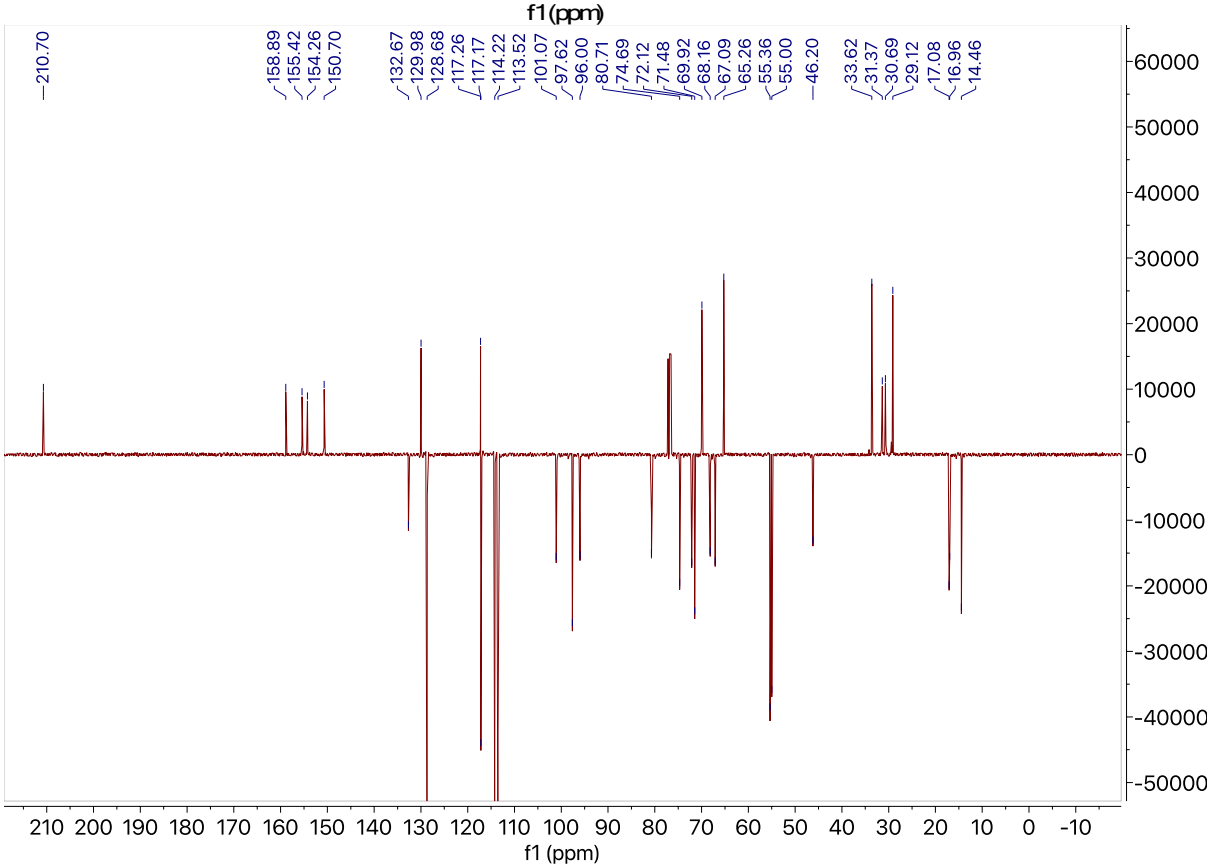

f2 (ppm)
f1 (ppm)

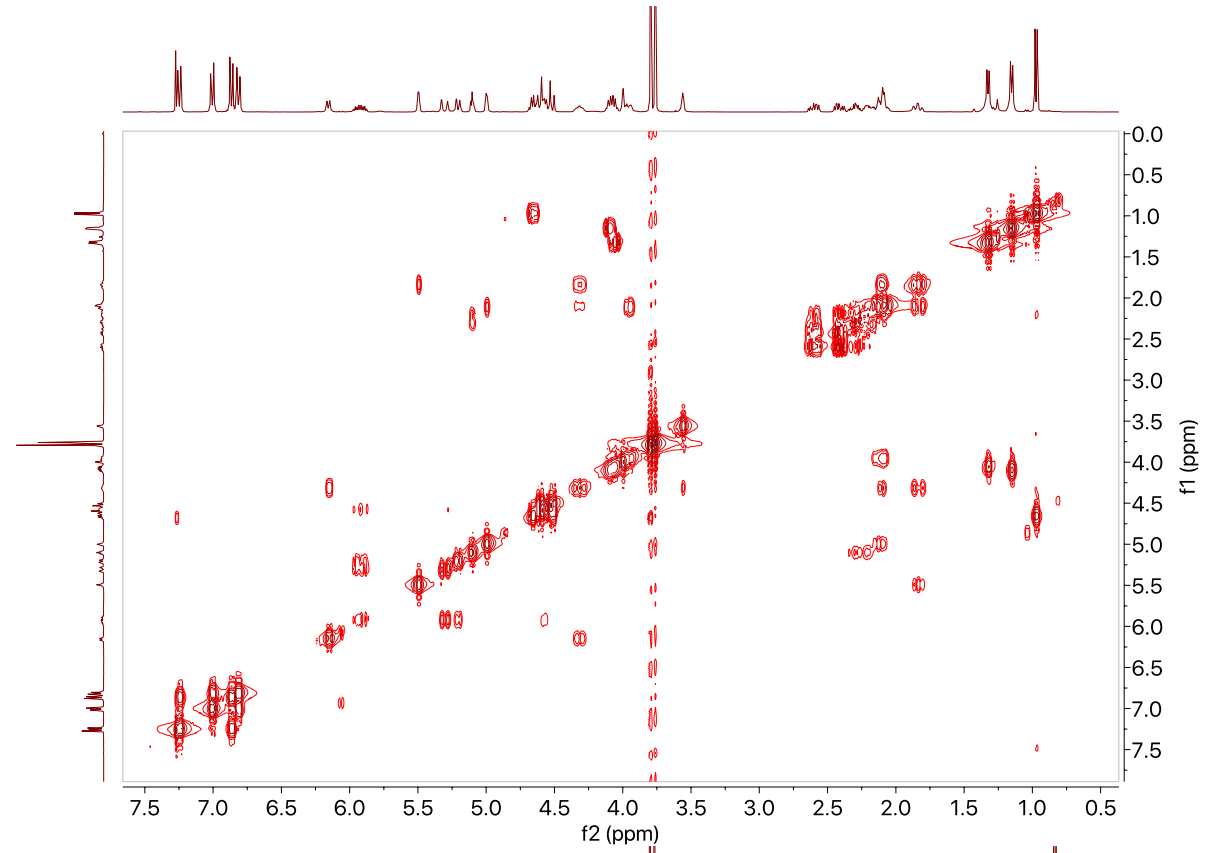

OPMP
NHAlloc
OPMB
OH
f1 (ppm)

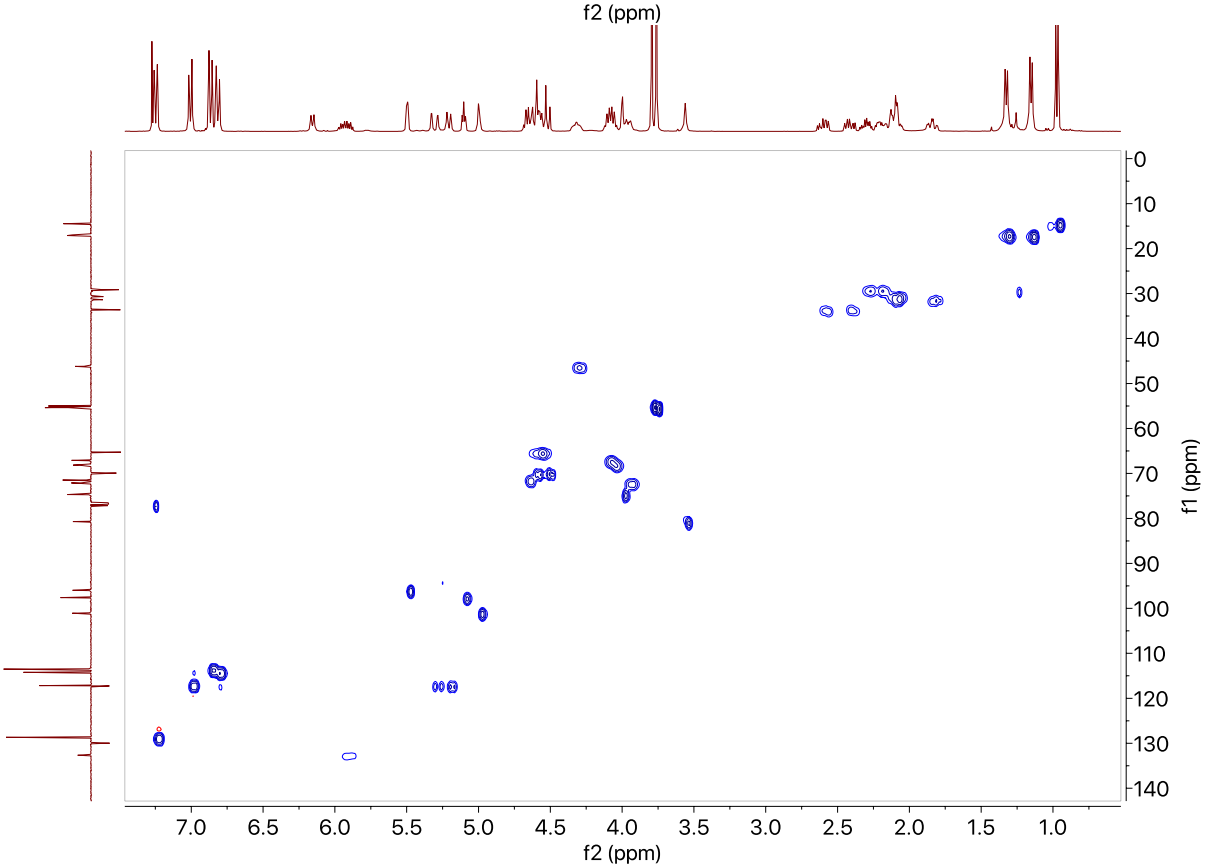

f1 (ppm)

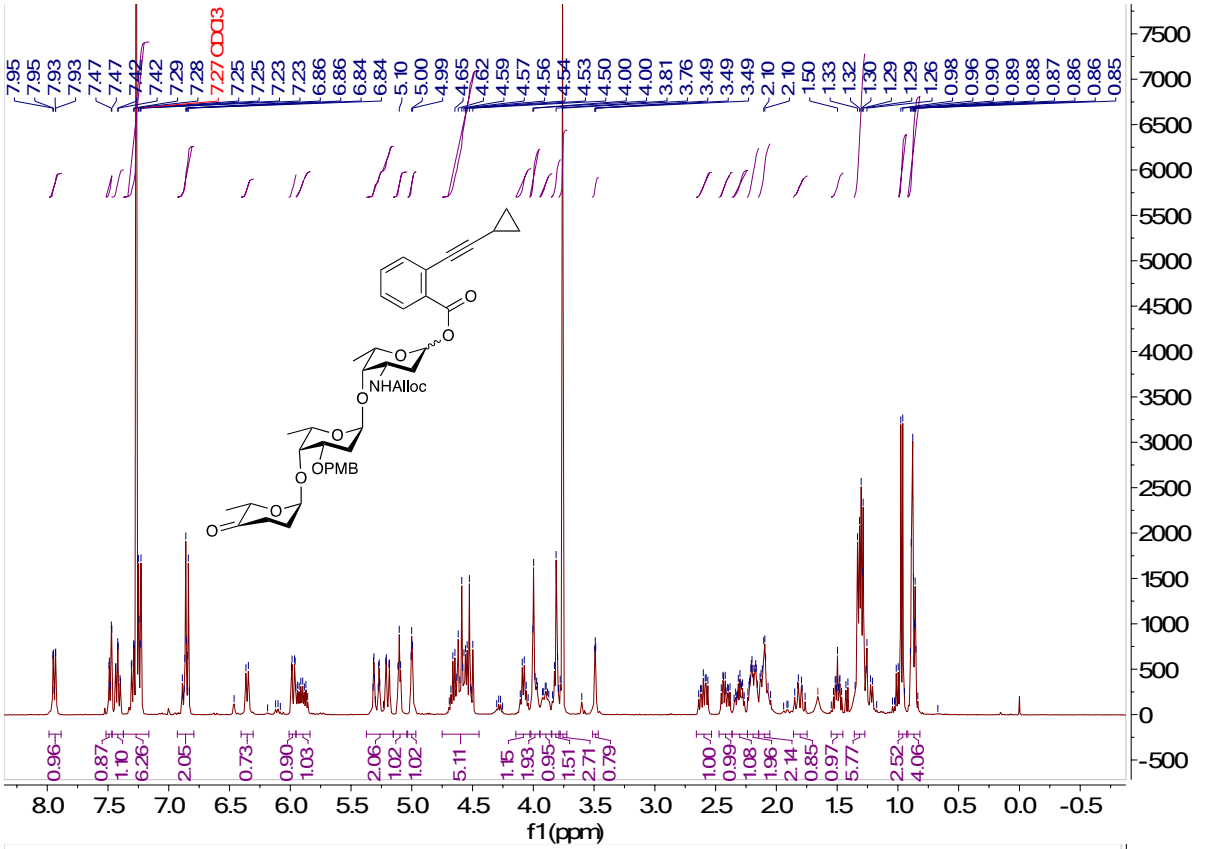

f2 (ppm)
f1 (ppm)
f2 (ppm)
f1 (ppm)

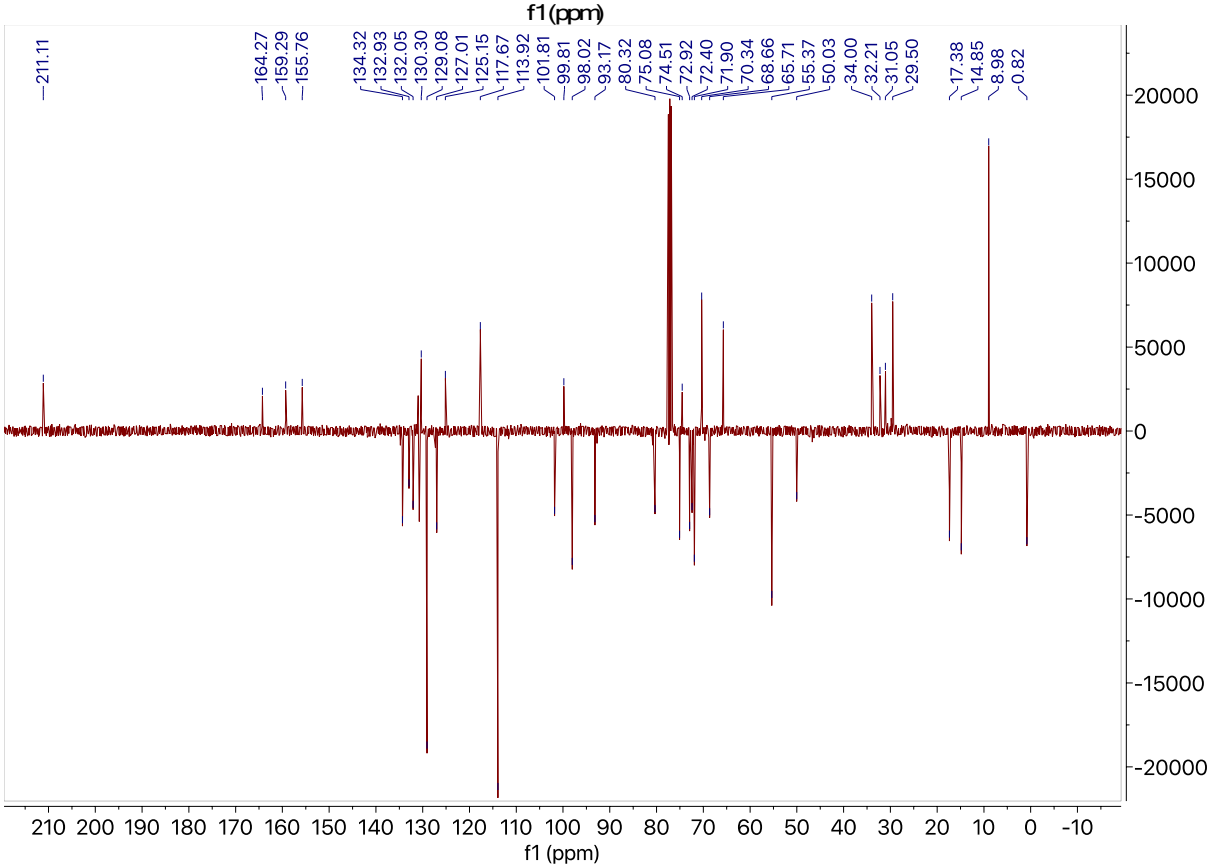

OPMP
NHAlloc
OPMB
f1 (ppm)

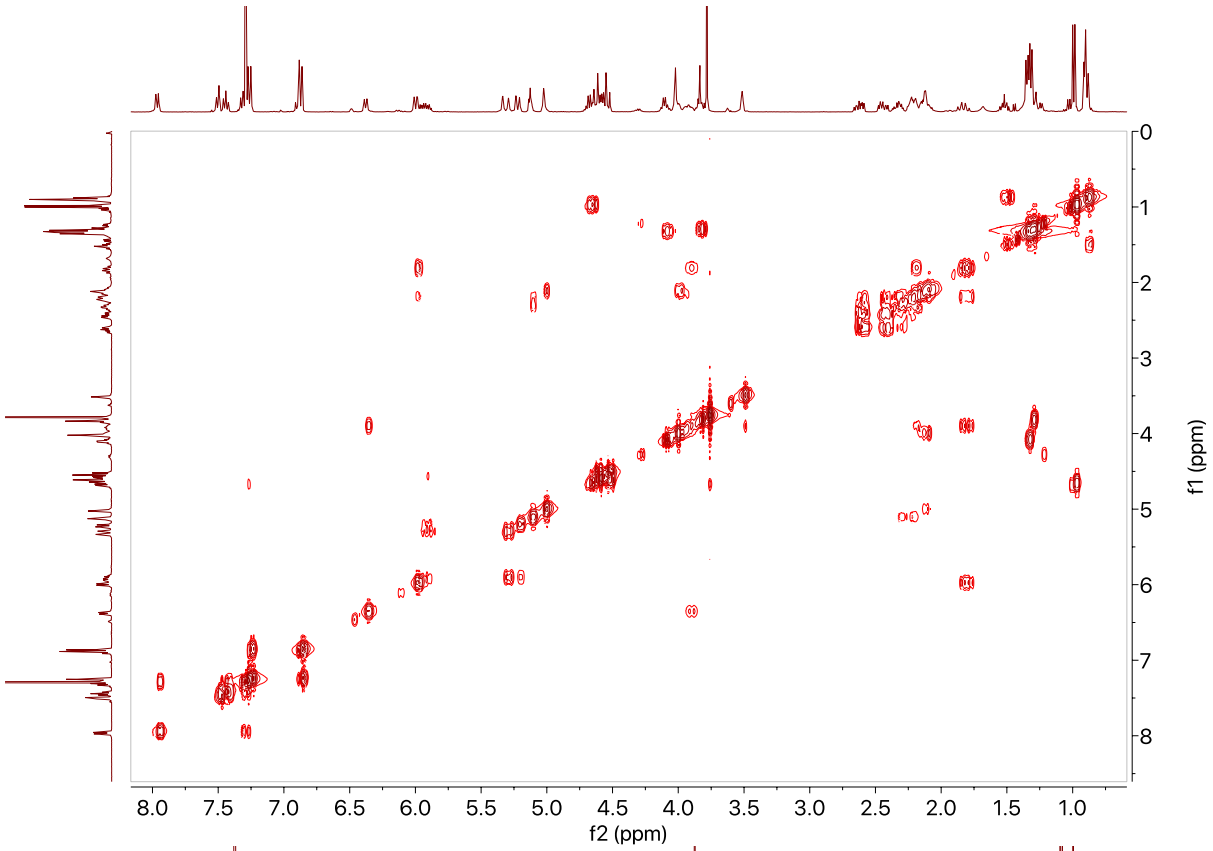

f1 (ppm)

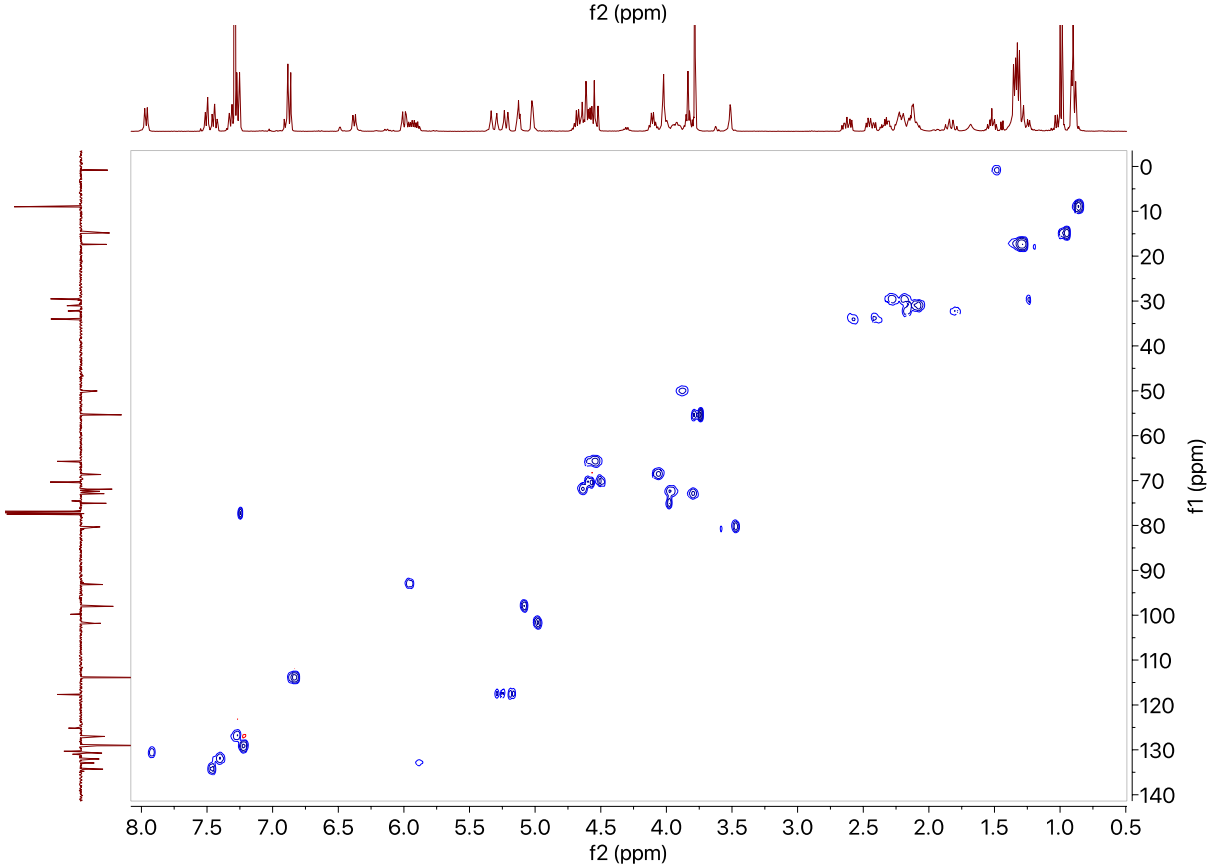

0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

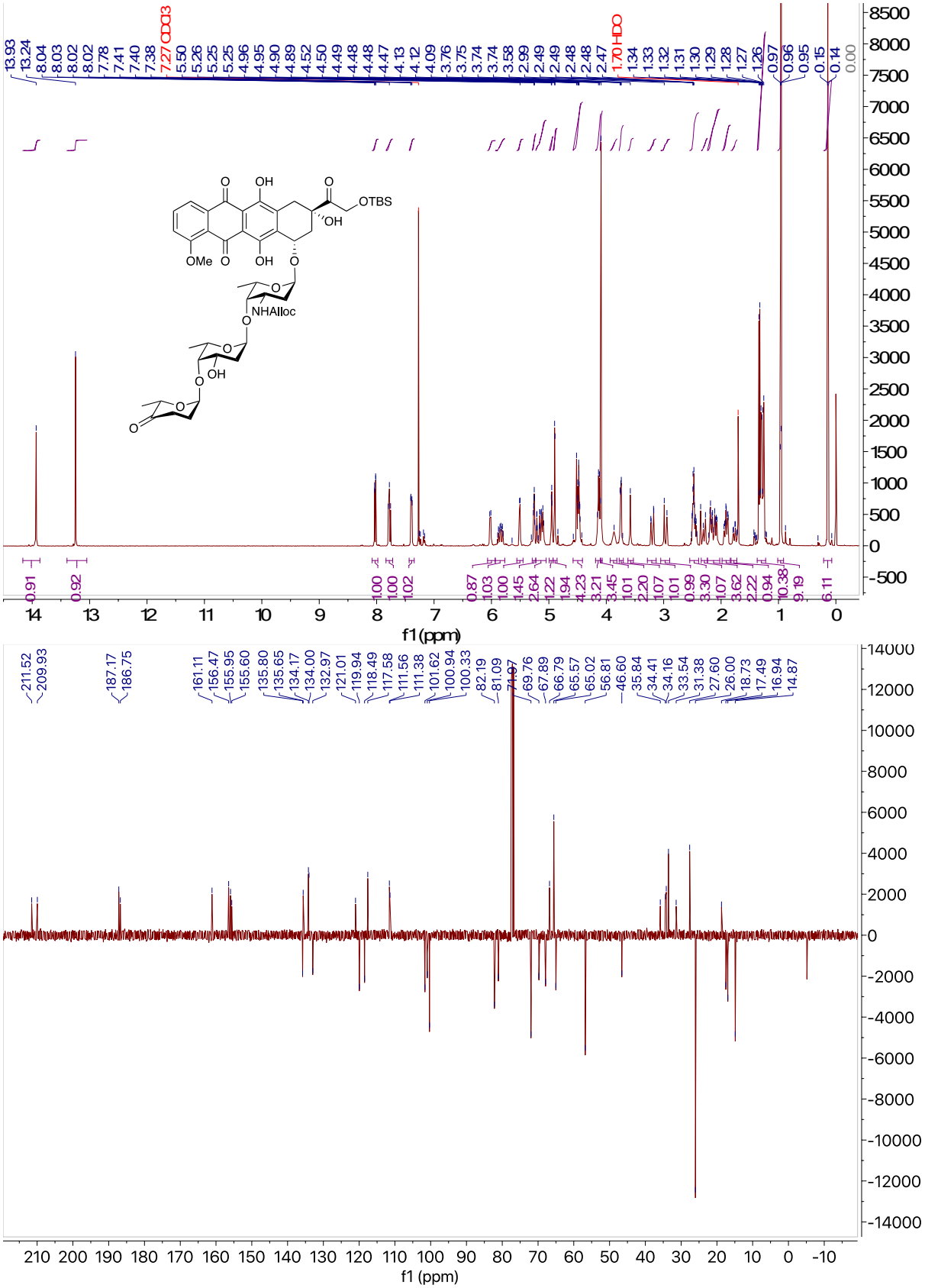

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)

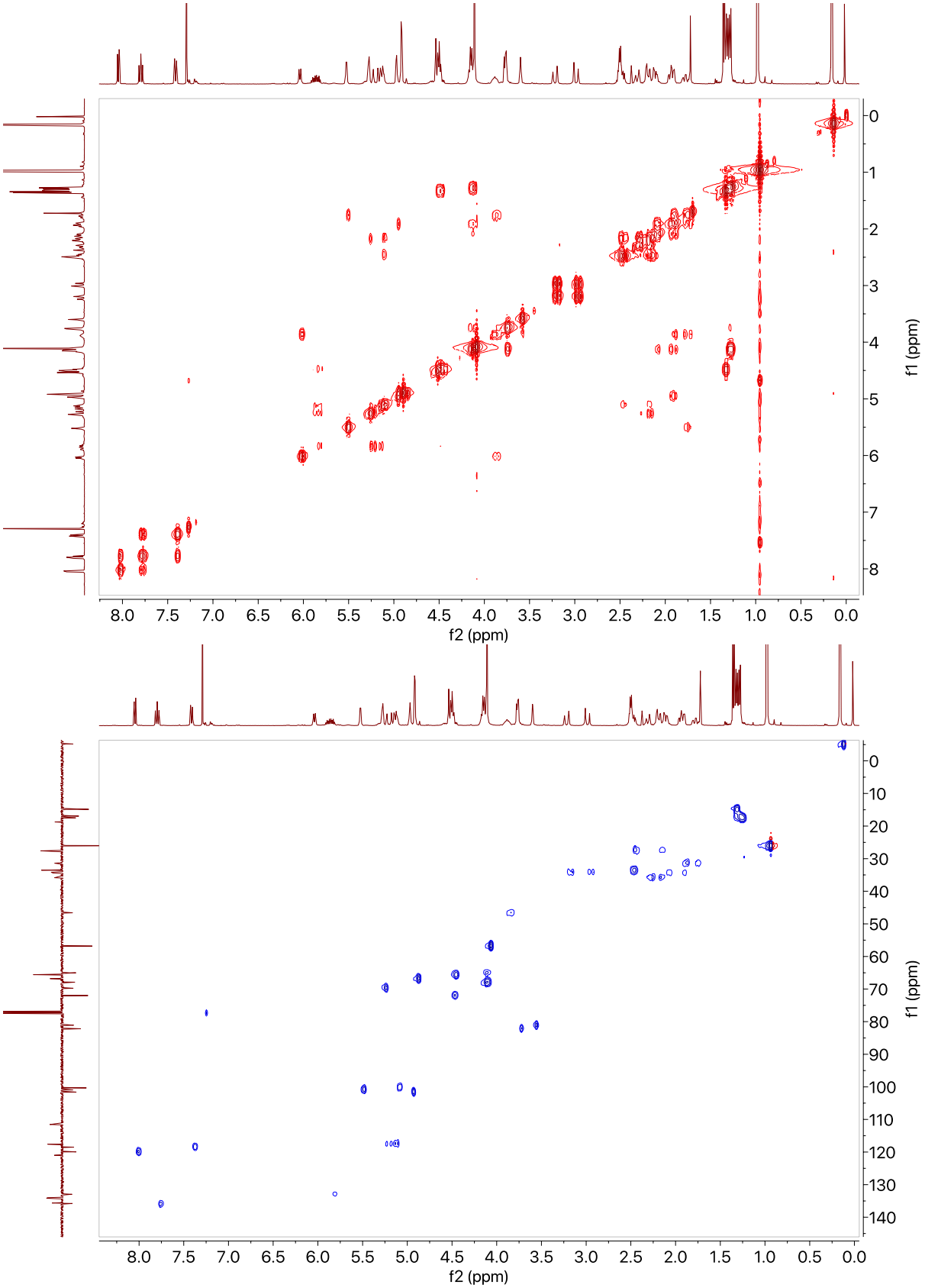

NHAlloc
OPMB
f1 (ppm)

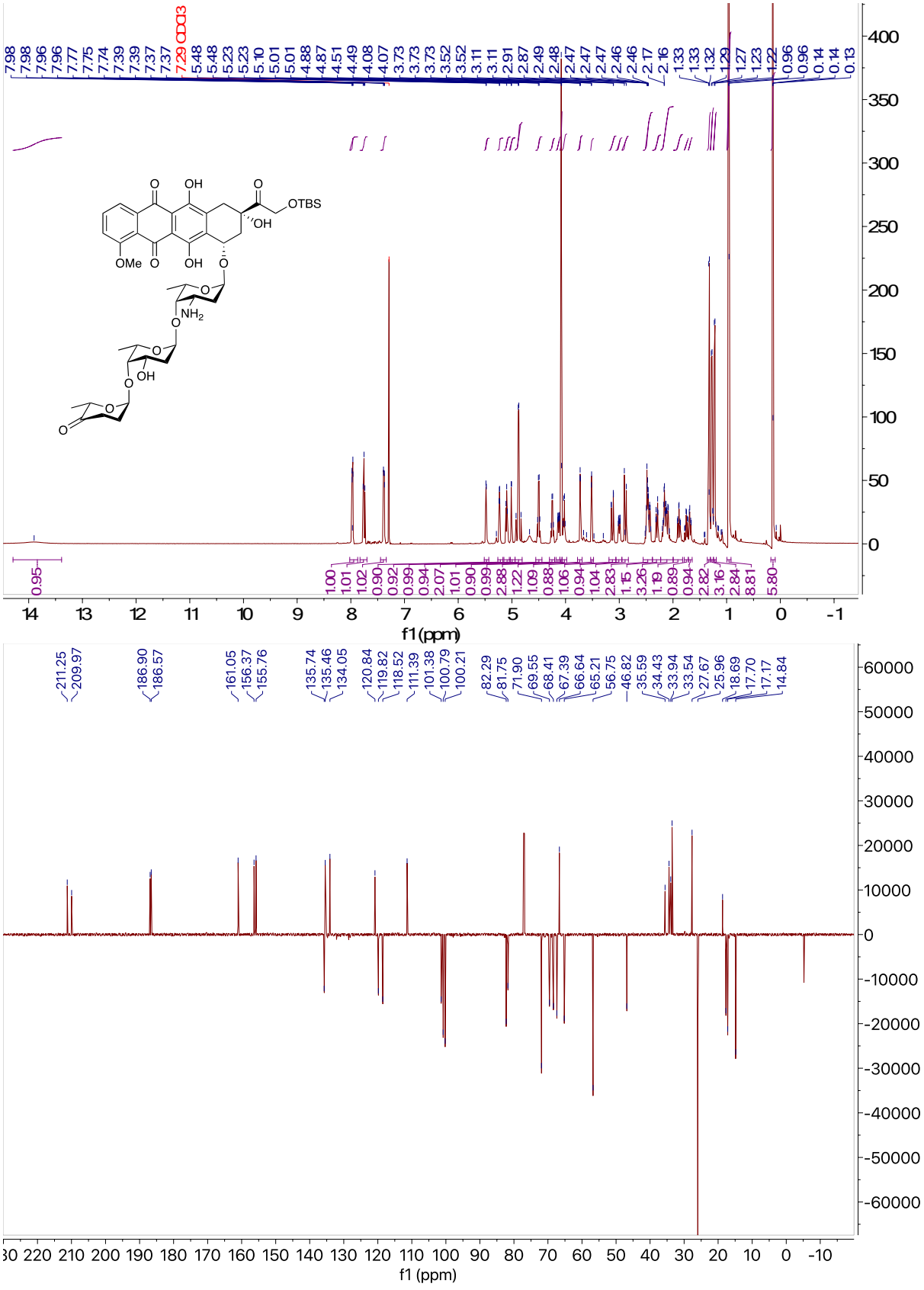

f1 (ppm)

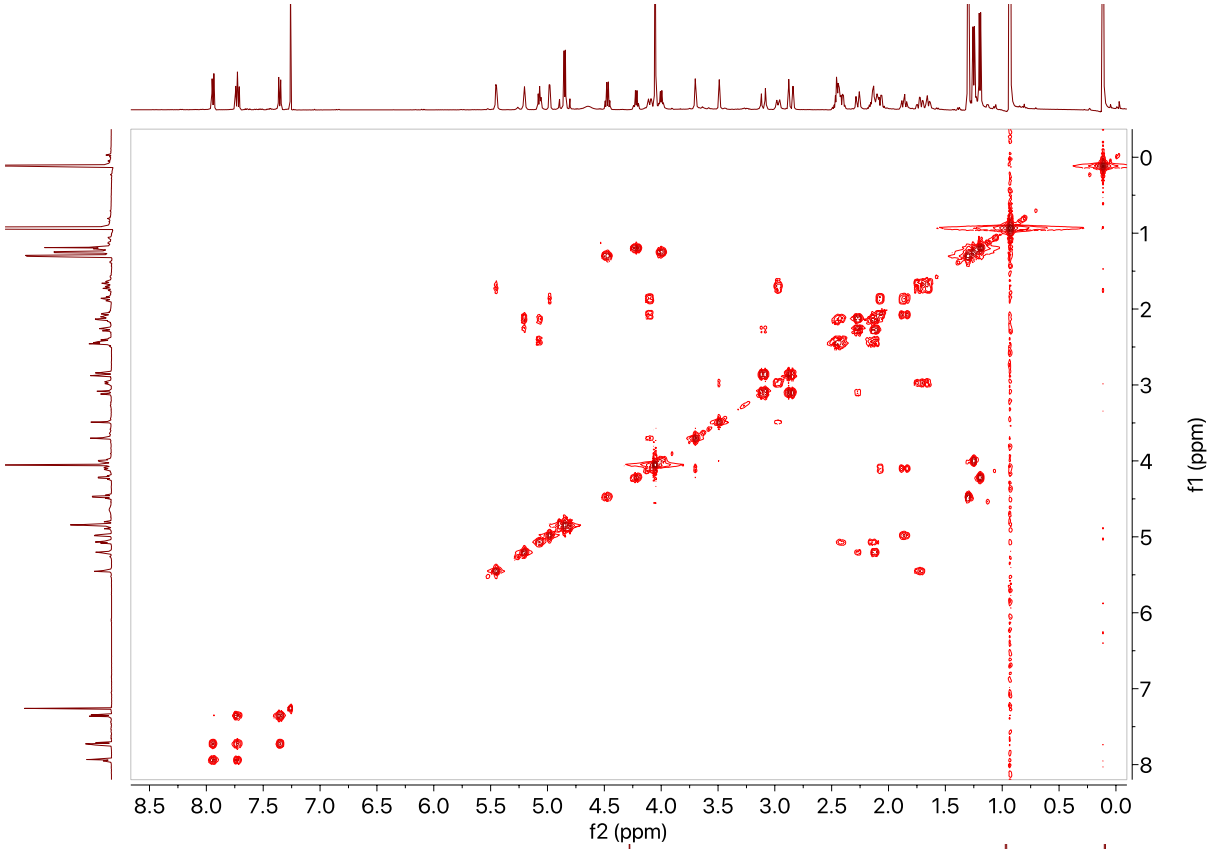

0
1
2
3
4
5
6
7
8
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

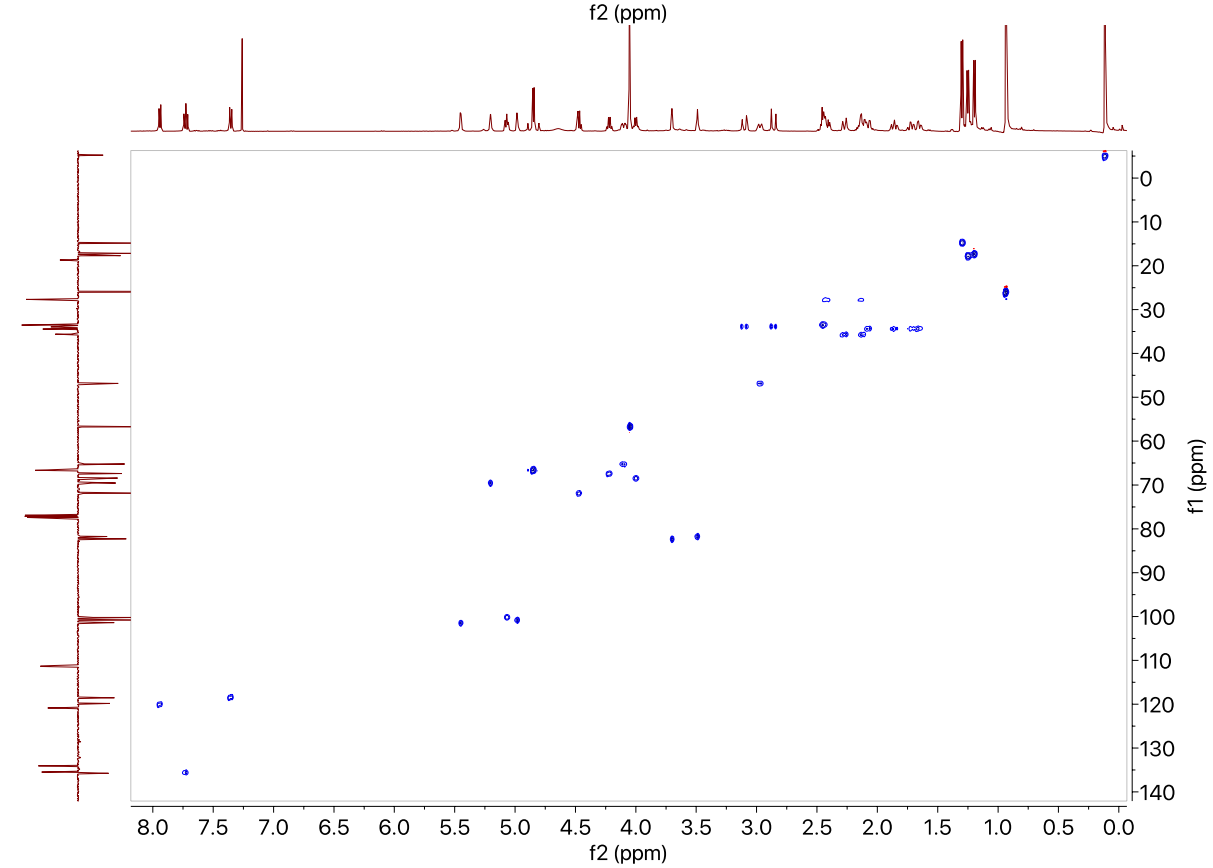

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

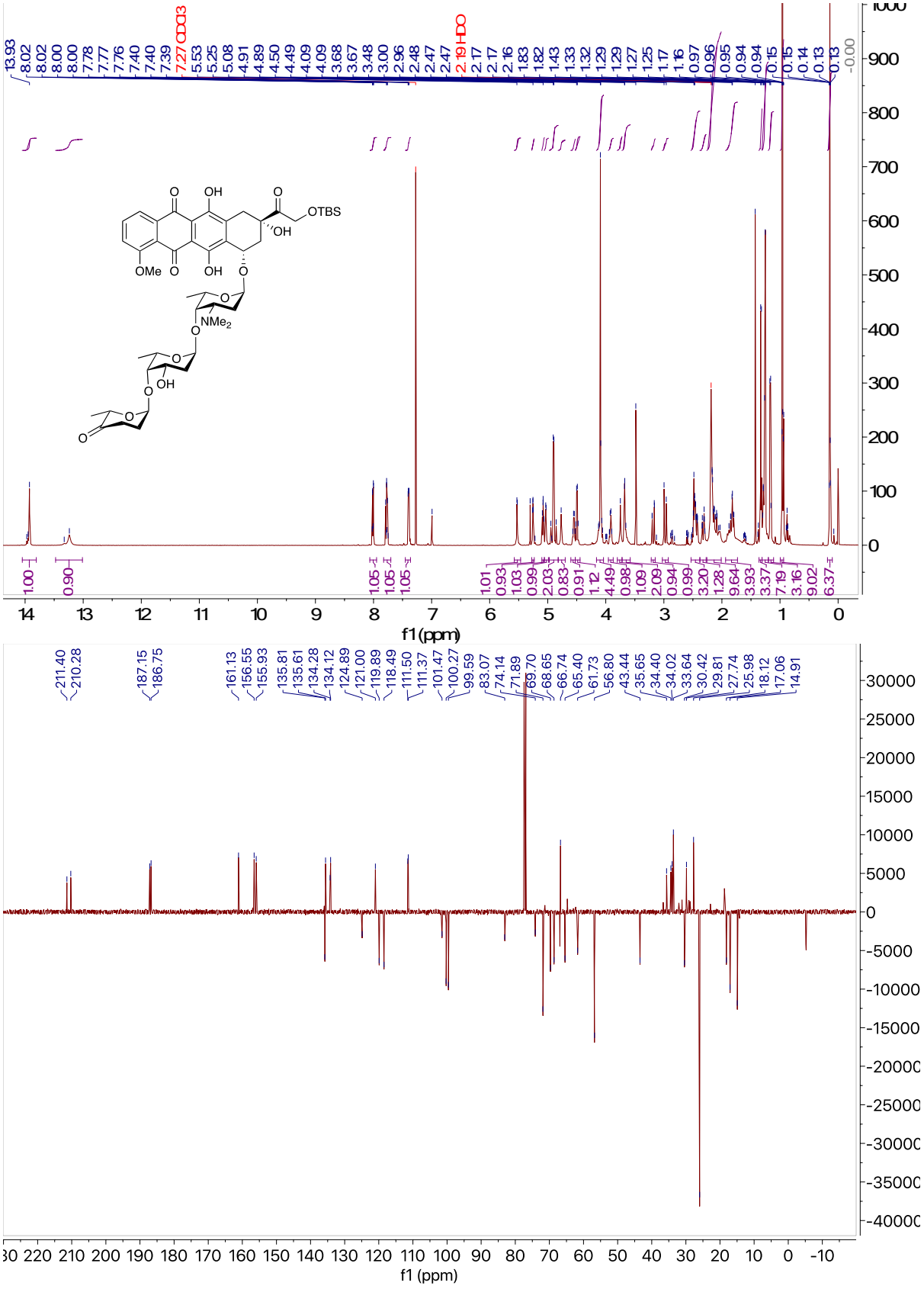

OTBS
OH
OMe
NHAlloc
f1 (ppm)
f1 (ppm)

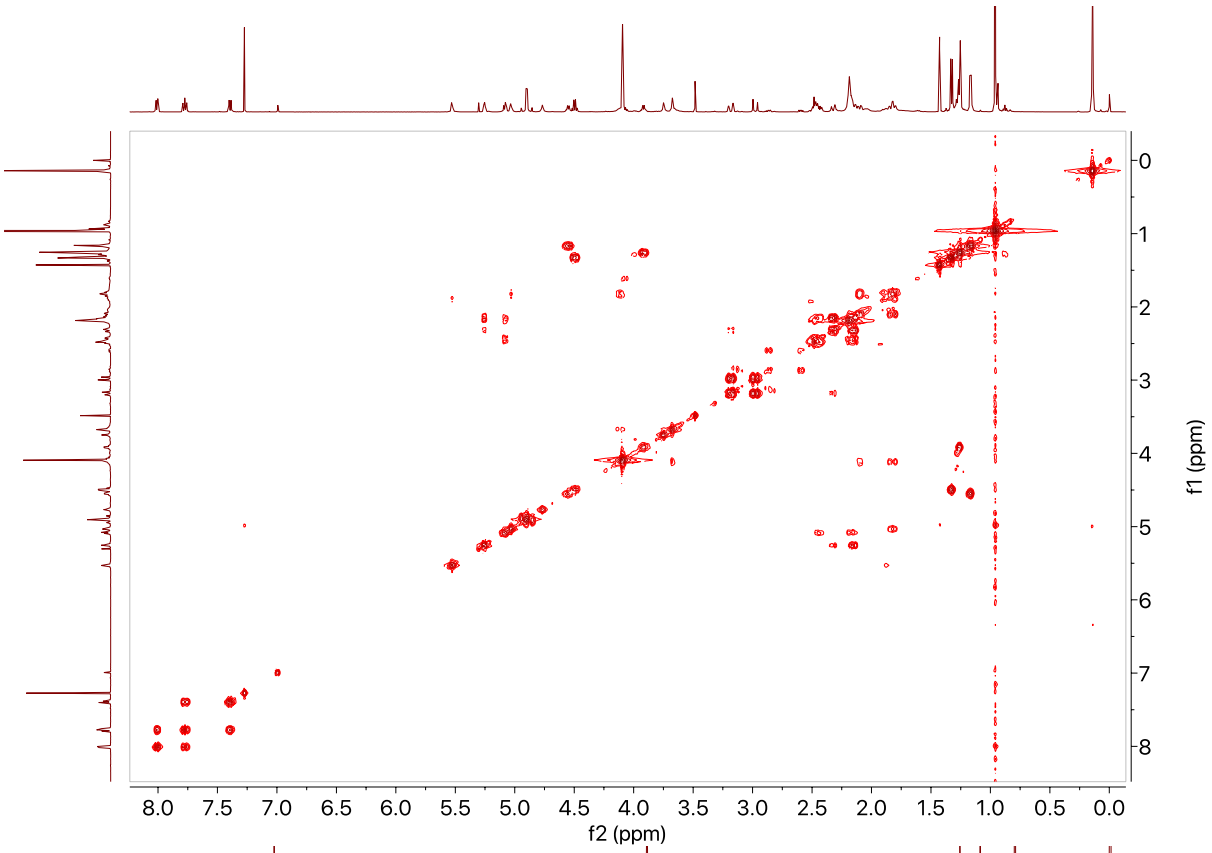

f2 (ppm)
f1 (ppm)
f2 (ppm)
f1 (ppm)

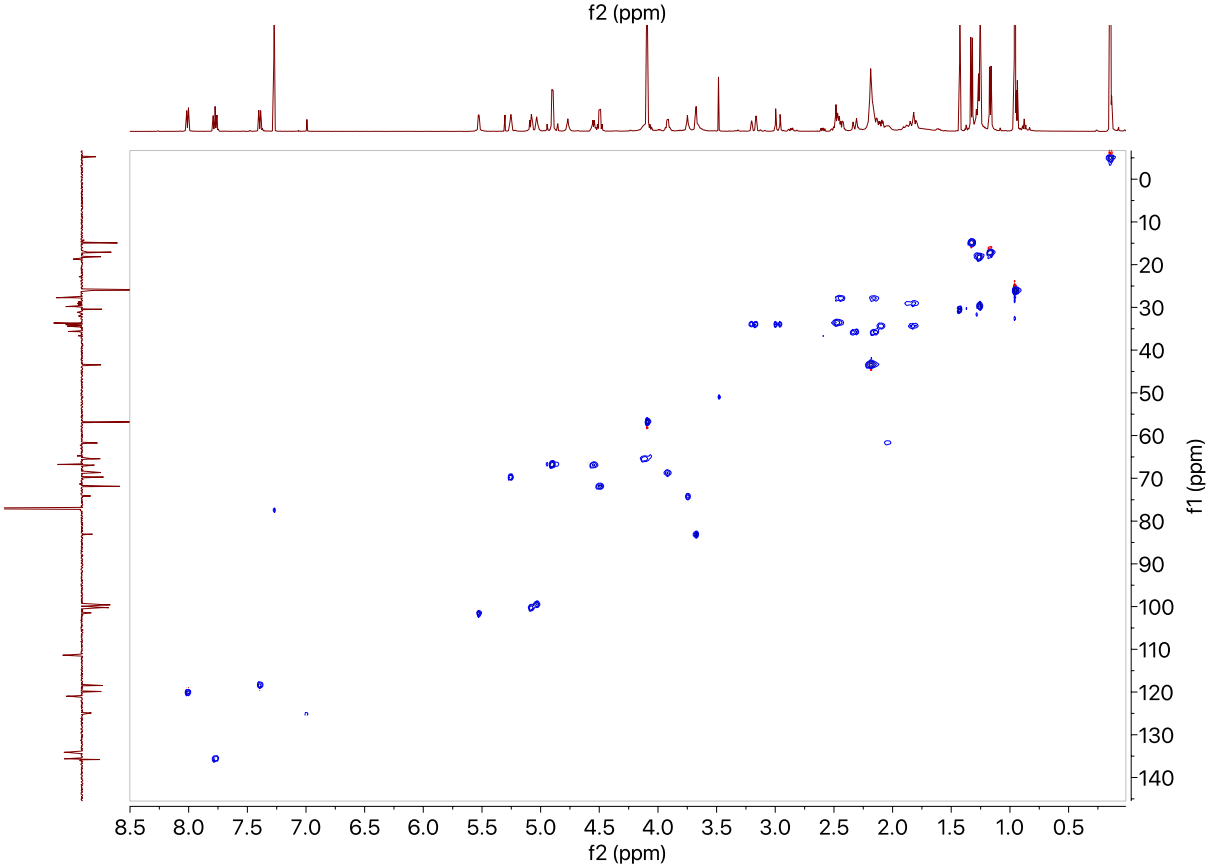

7.98 7.98 7.96 7.96 7.77 7.75 7.74 7.39 7.39 7.37 7.37 7.29 CDCl3 5.48 5.48 5.23 5.23 5.10 5.01 5.01 4.88 4.87 4.51 4.49 4.08 4.07 3.73 3.73 3.73 3.52 3.52 3.11 3.11 2.91 2.87 2.49 2.48 2.47 2.47 2.47 2.46 2.46 2.17 2.16 1.33 1.33 1.32 1.29 1.27 1.23 1.22 0.96 0.96 0.14 0.14 0.13
O OH O OTBS OH OMe O OH O O NH2 O O OH O O O O
0.95 1.00 1.01 1.02 0.90 0.92 0.99 0.94 2.07 1.01 0.90 0.99 2.88 1.22 1.09 0.88 1.06 0.94 1.04 2.83 1.15 3.26 1.19 0.89 0.94 2.82 3.16 2.84 8.81 5.80
f1 (ppm)
211.25 209.97 186.90 186.57 161.05 156.37 155.76 135.74 135.46 134.05 120.84 119.82 118.52 111.39 101.38 100.79 100.21 82.29 81.75 71.90 69.55 68.41 67.39 66.64 65.21 56.75 46.82 35.59 34.43 33.94 33.54 27.67 25.96 18.69 17.70 17.17 14.84
f1 (ppm)

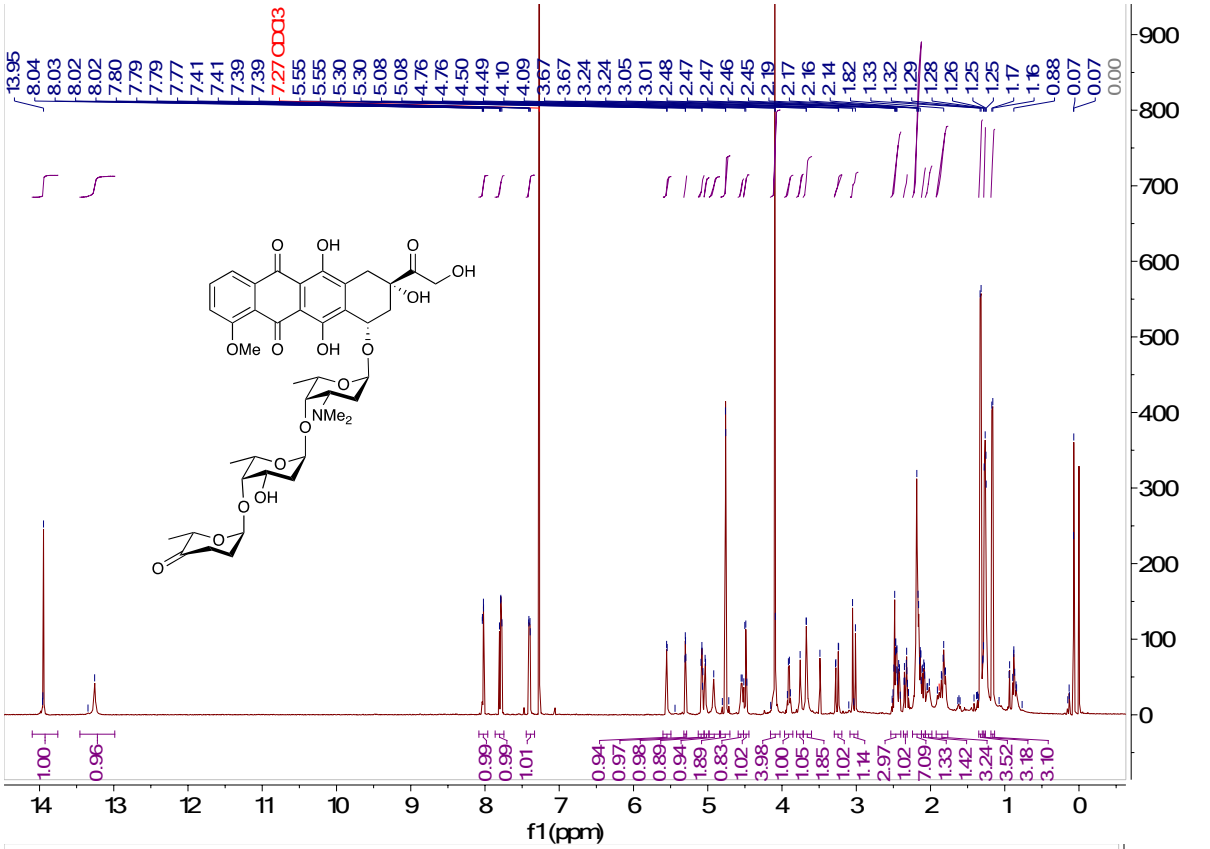

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 1 2 3 4 5 6 7 8
f1 (ppm)

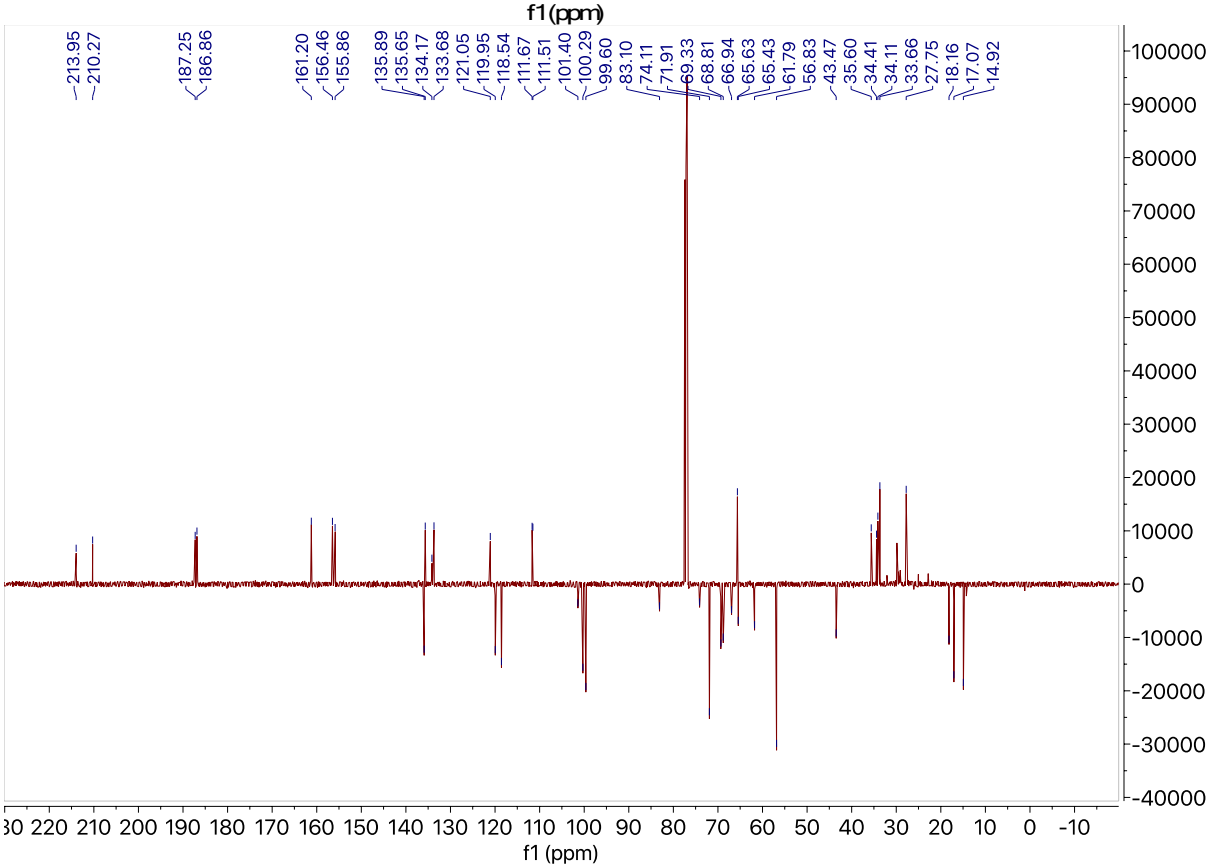

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

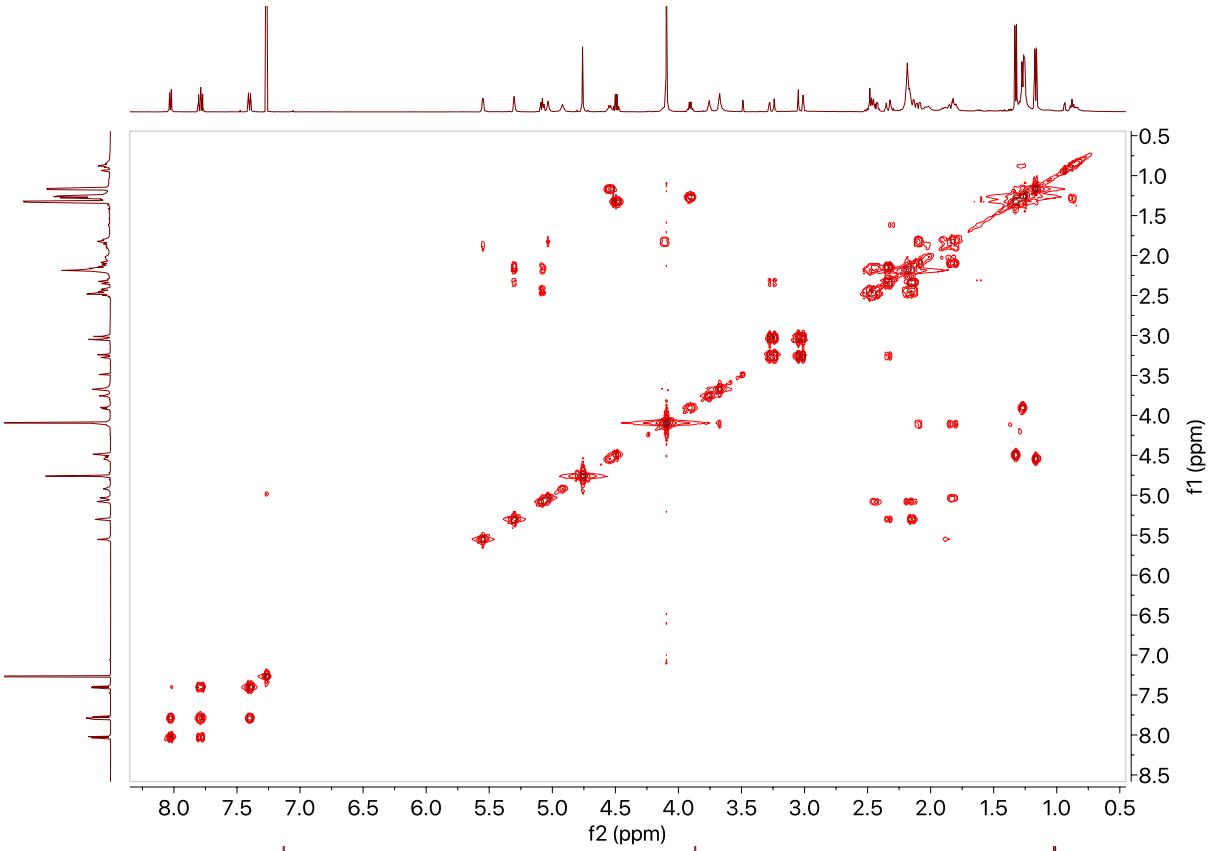

OTBS
OH
OMe
NMe2
f1 (ppm)
f1 (ppm)

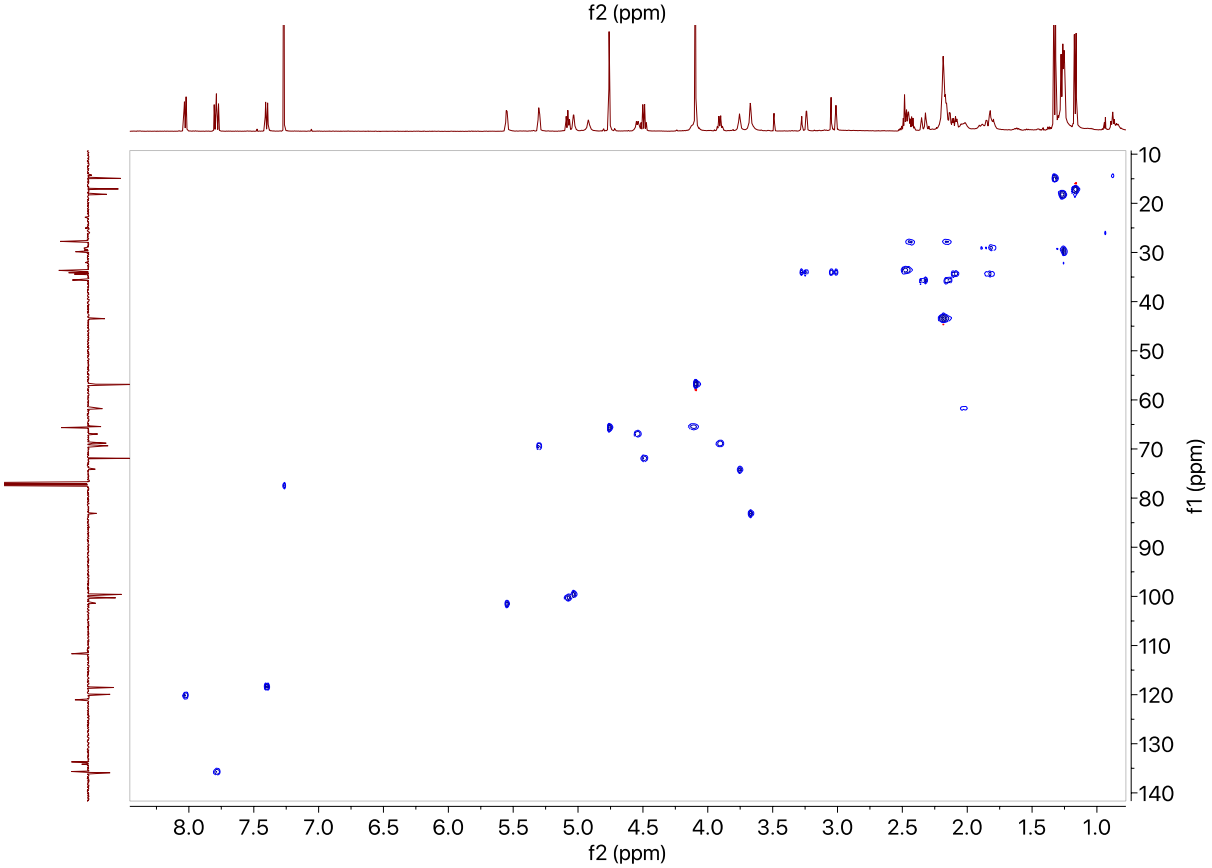

f1 (ppm)
f2 (ppm)

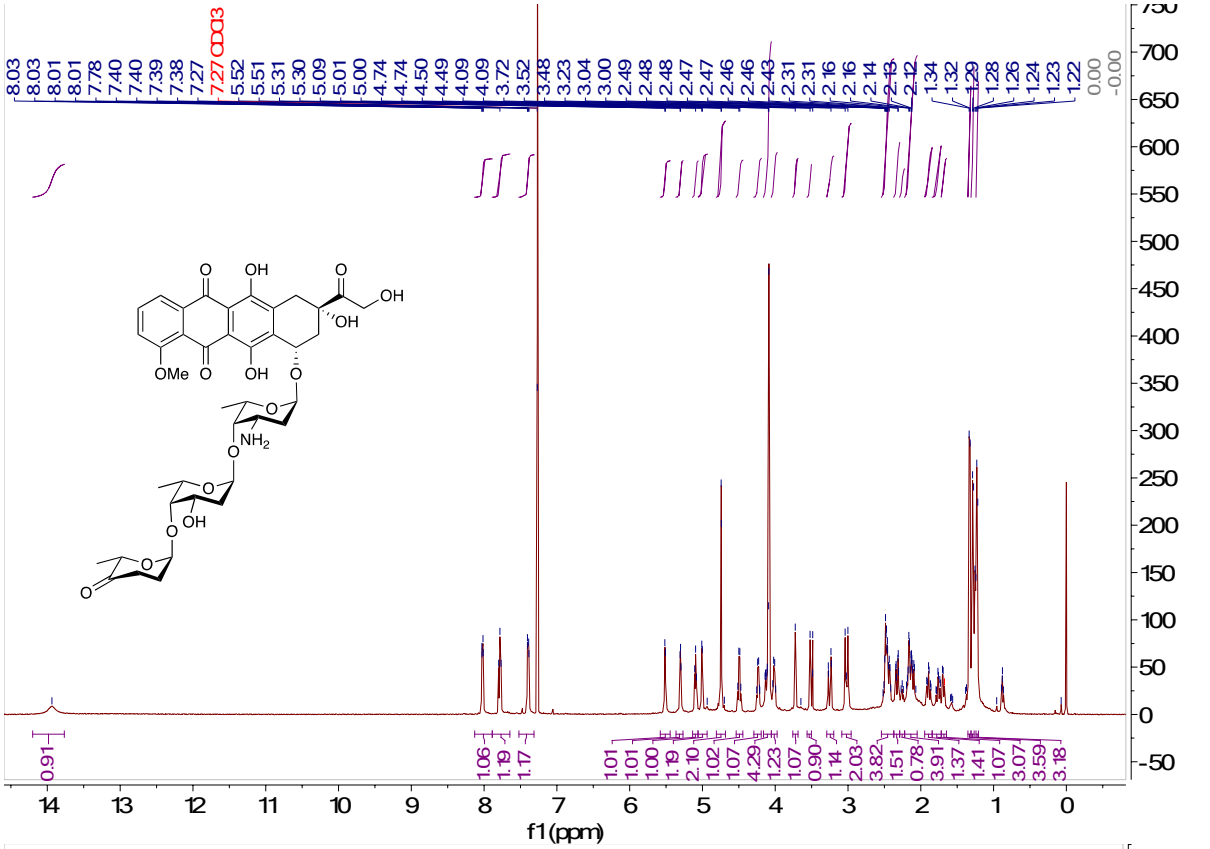

f1 (ppm)
f2 (ppm)

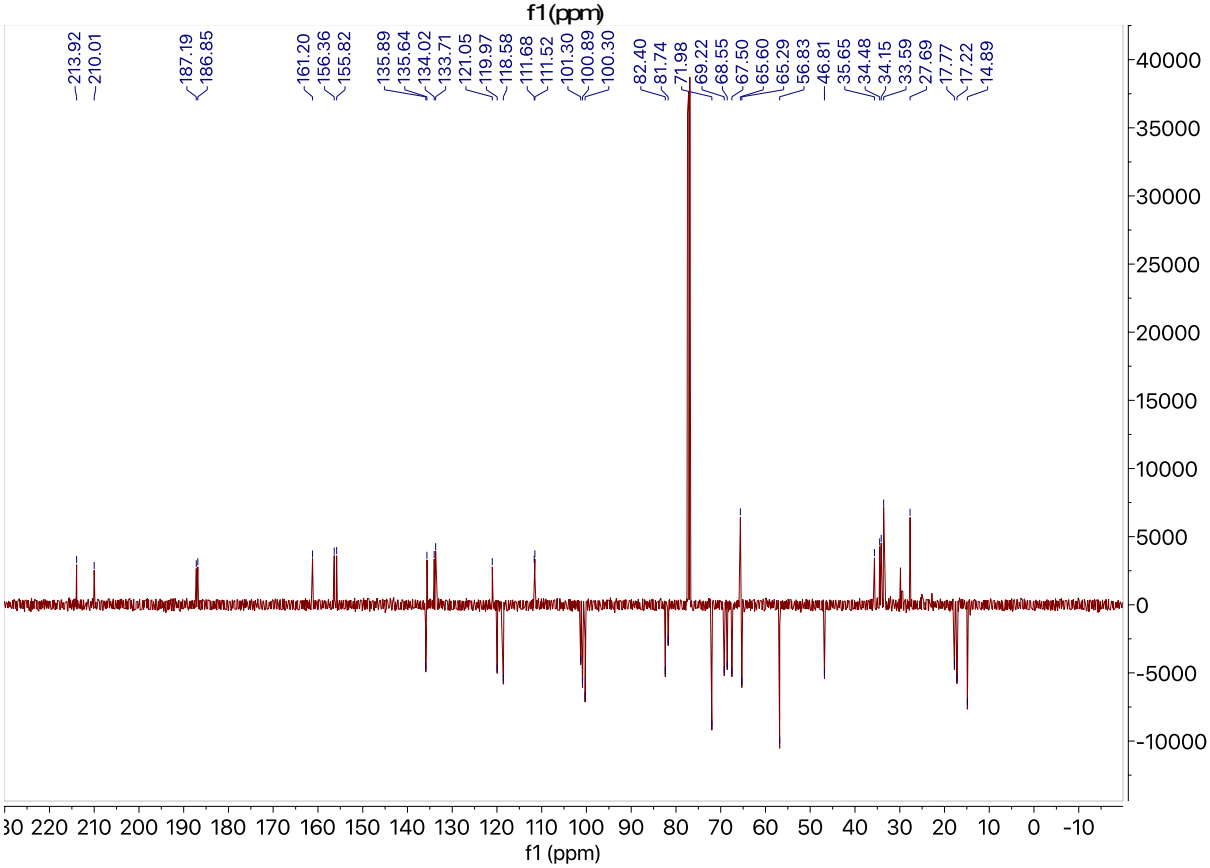

13.95
8.04
8.03
8.02
8.02
7.80
7.79
7.79
7.77
7.41
7.41
7.39
7.39
7.27 CDCl3
5.55
5.55
5.30
5.30
5.08
5.08
4.76
4.76
4.50
4.49
4.10
4.09
3.67
3.67
3.24
3.24
3.05
3.01
2.48
2.47
2.47
2.46
2.45
2.19
2.17
2.16
2.14
1.82
1.33
1.32
1.29
1.28
1.26
1.25
1.25
1.17
1.16
0.88
0.07
0.07
0.00
OH
O
OH
OH
OMe
O
OH
O
NMe2
O
O
OH
O
O
O
1.00
0.96
0.99
0.99
1.01
0.94
0.97
0.98
0.89
0.94
1.89
0.83
1.02
3.98
1.00
1.05
1.85
1.02
1.14
2.97
1.02
7.09
1.33
1.42
3.24
3.52
3.18
3.10
f1 (ppm)

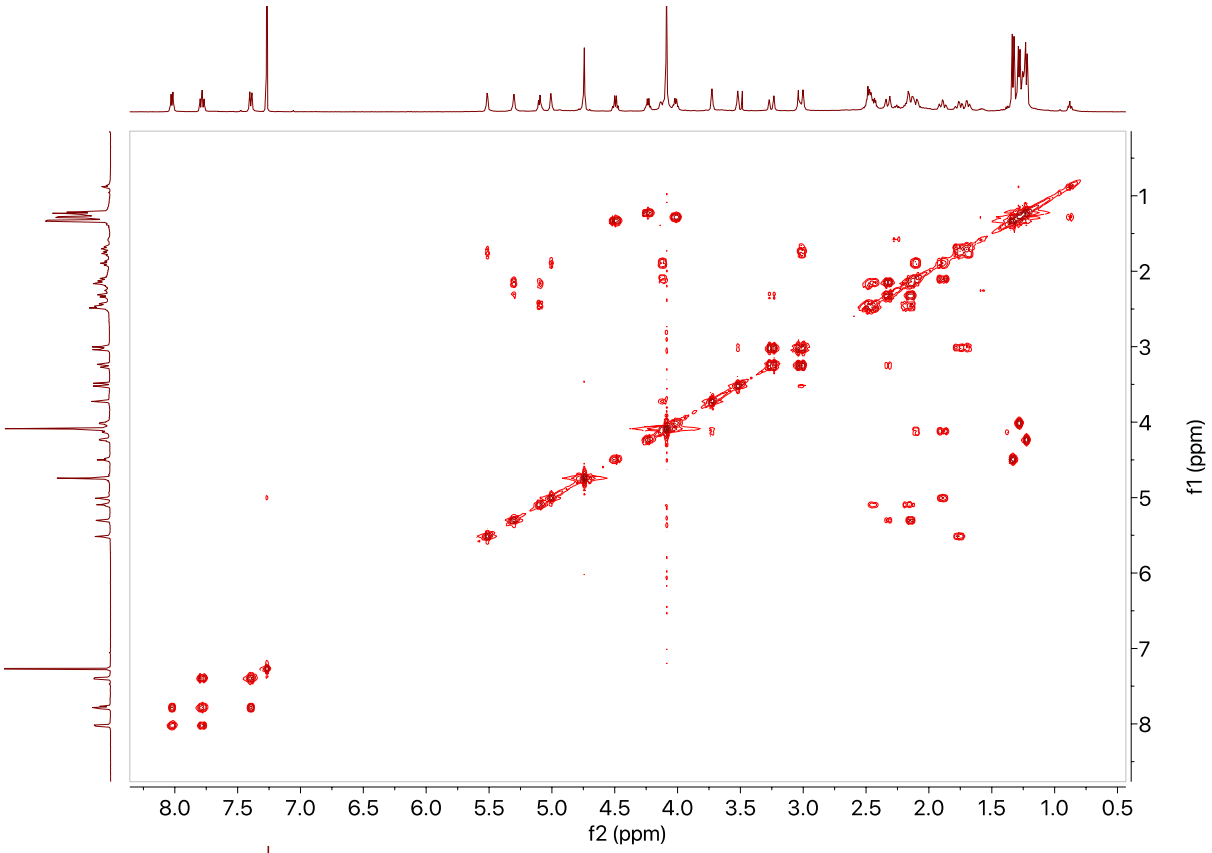

213.95
210.27
187.25
186.86
161.20
156.46
155.86
135.89
135.65
134.17
133.68
121.05
119.95
118.54
111.67
111.51
101.40
100.29
99.60
83.10
74.11
71.91
69.33
68.81
66.94
65.63
65.43
61.79
56.83
43.47
35.60
34.41
34.11
33.66
27.75
18.16
17.07
14.92
f1 (ppm)

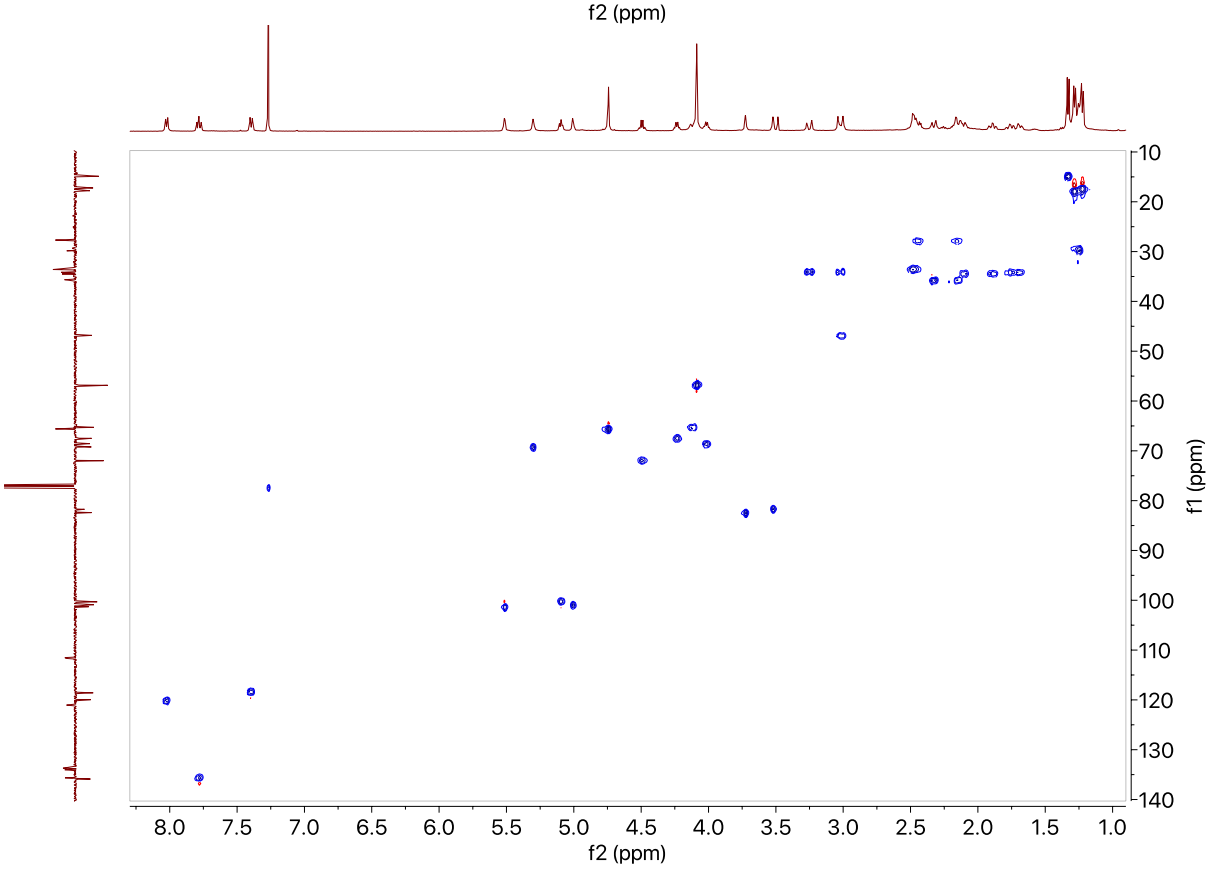

f1 (ppm)
f2 (ppm)

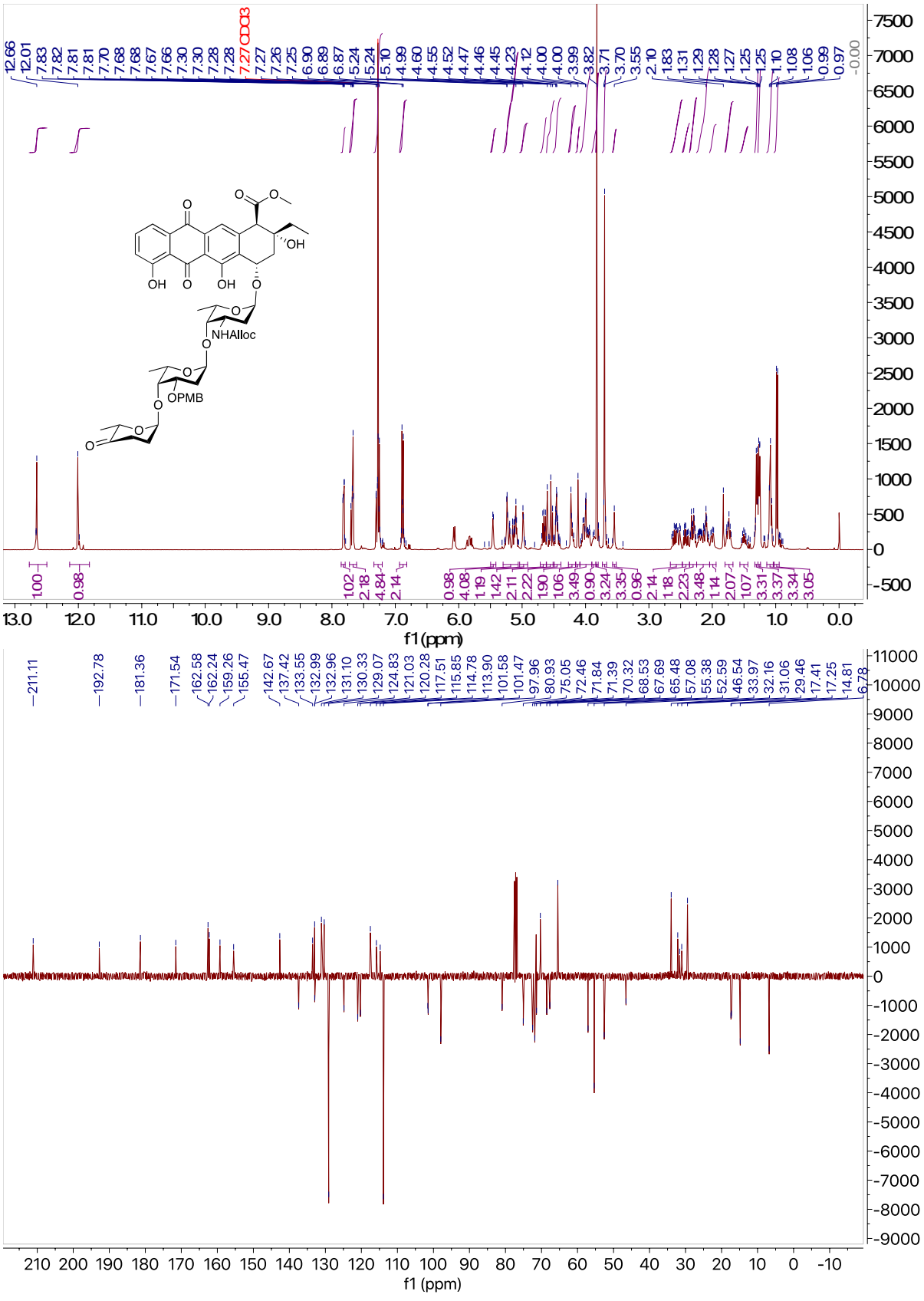

f1 (ppm)
f2 (ppm)

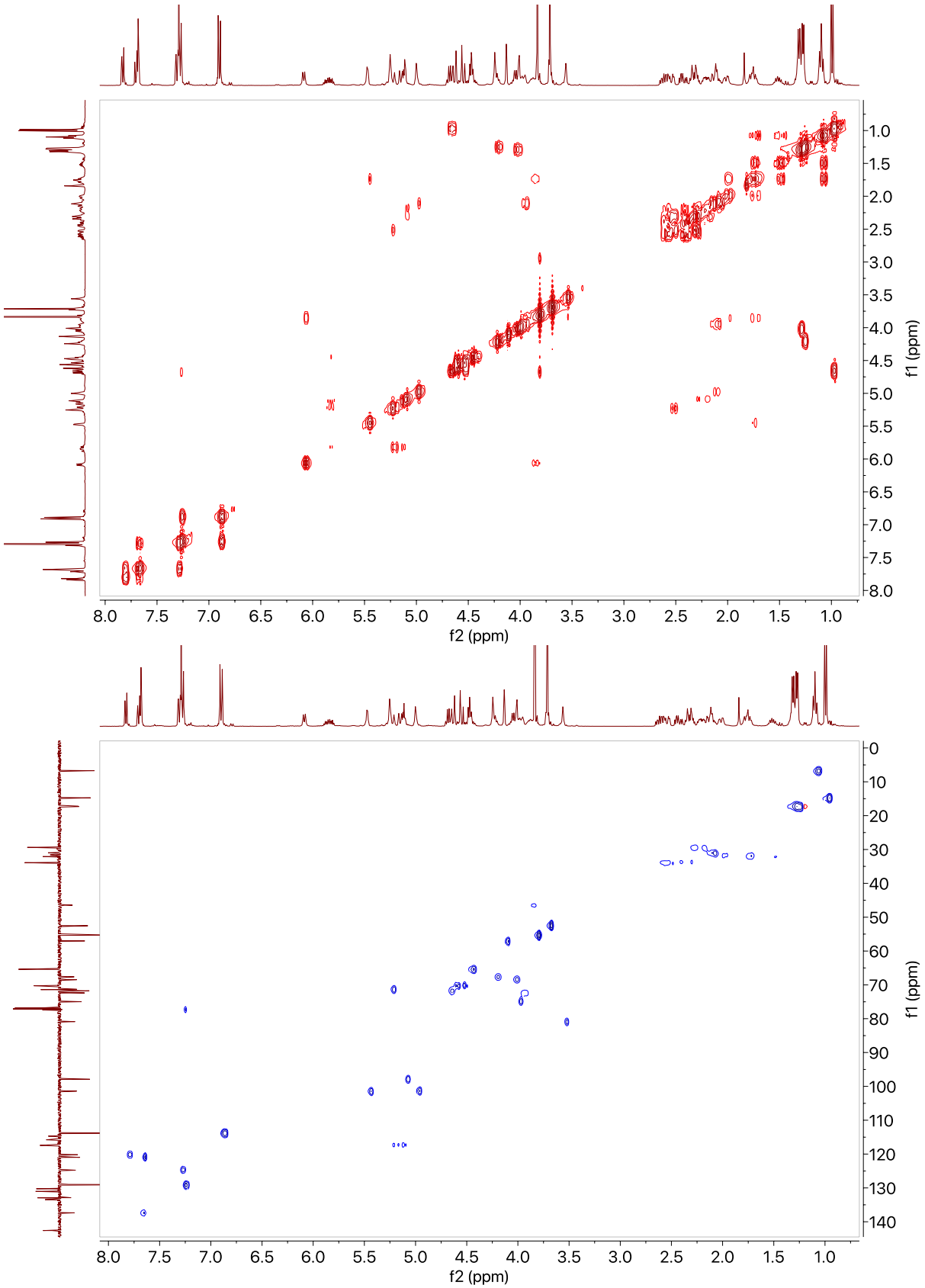

f1 (ppm)

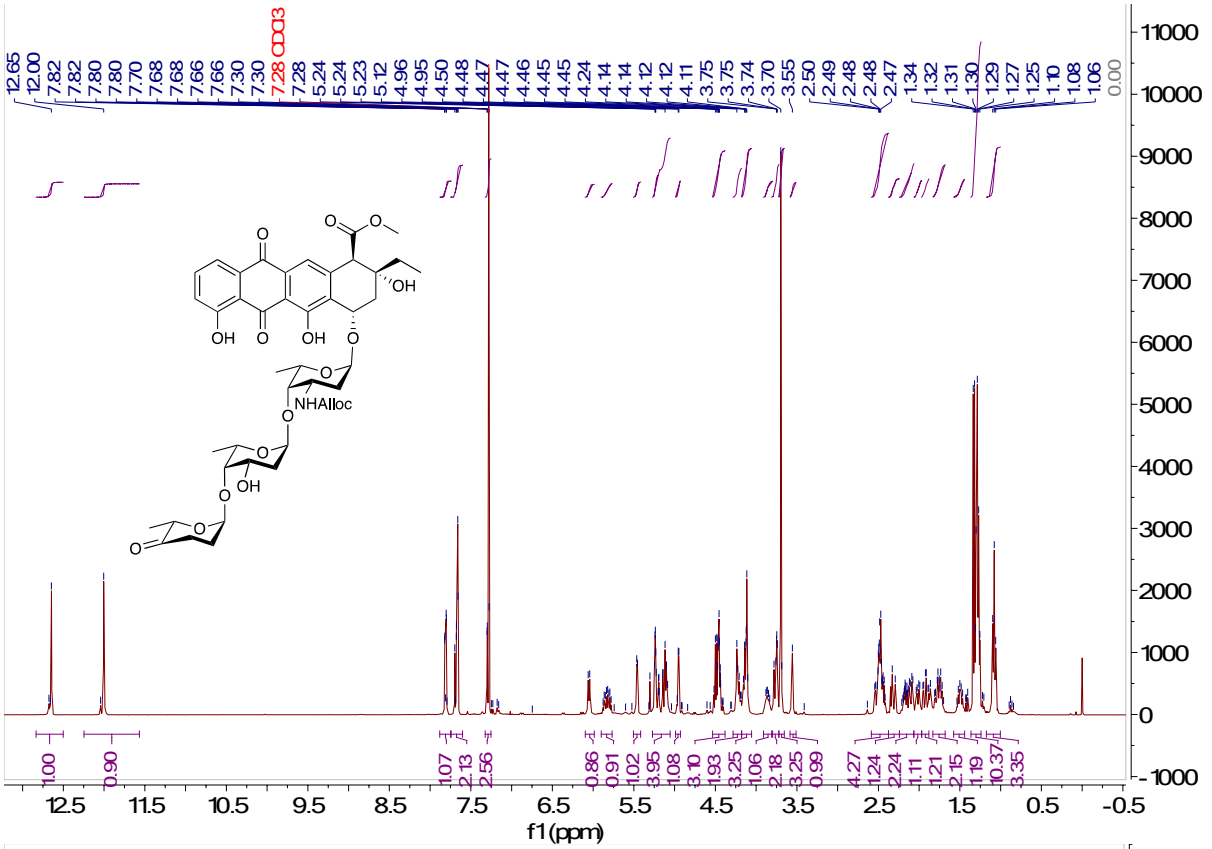

f1 (ppm)

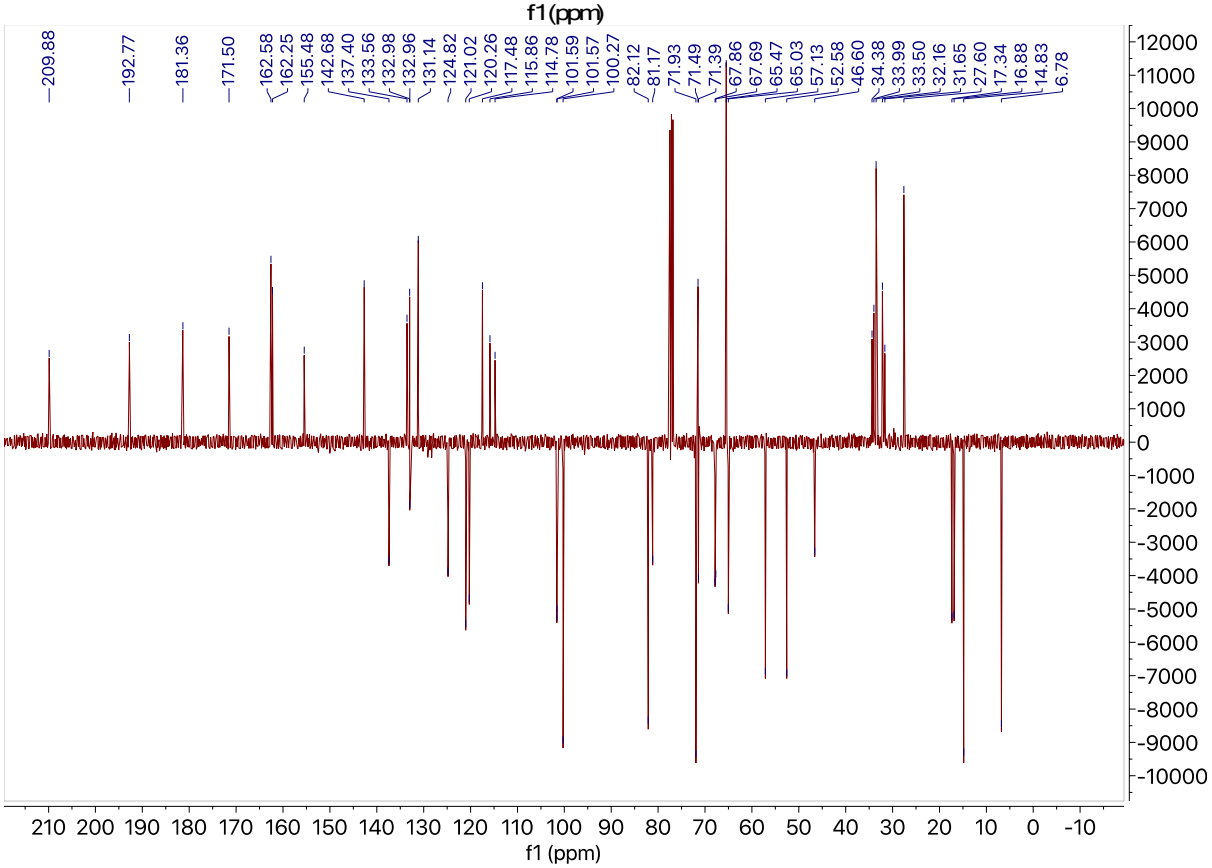

f1 (ppm)
f2 (ppm)

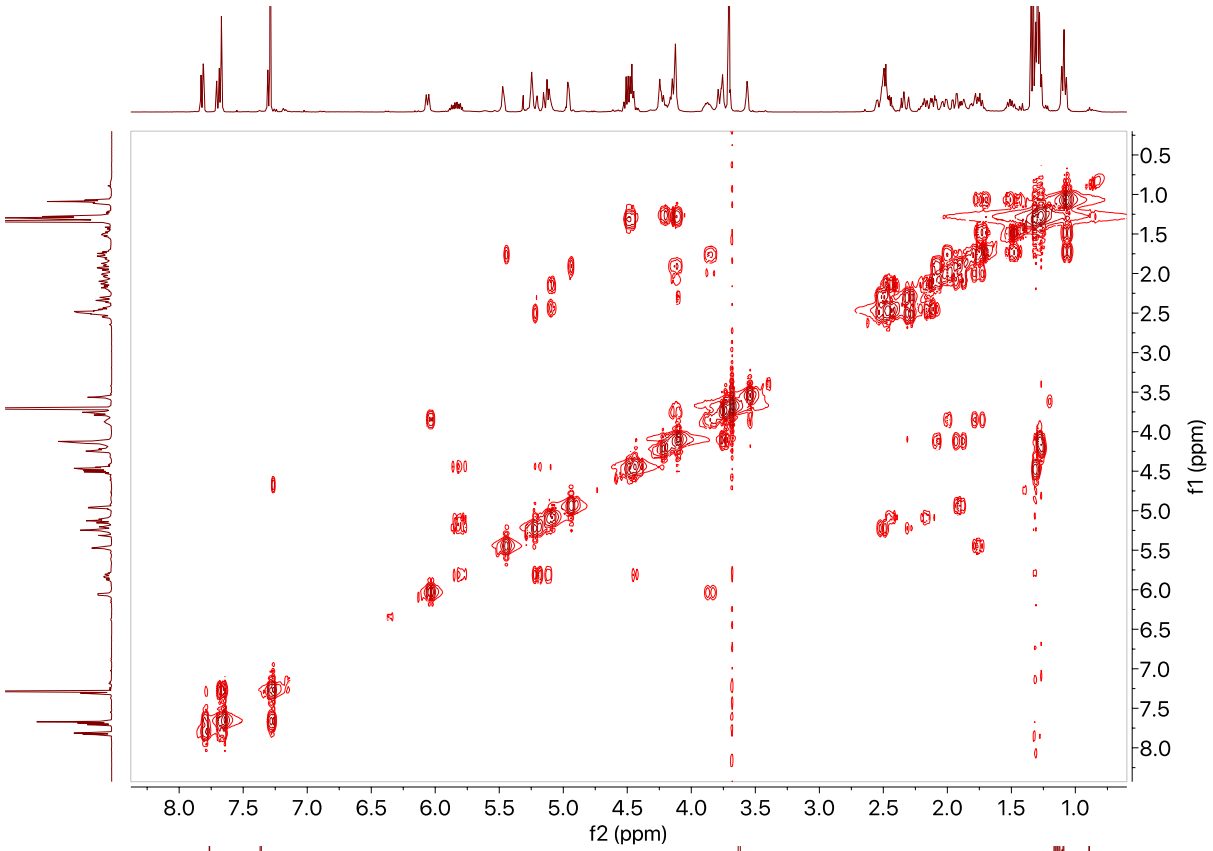

f1 (ppm)
f2 (ppm)

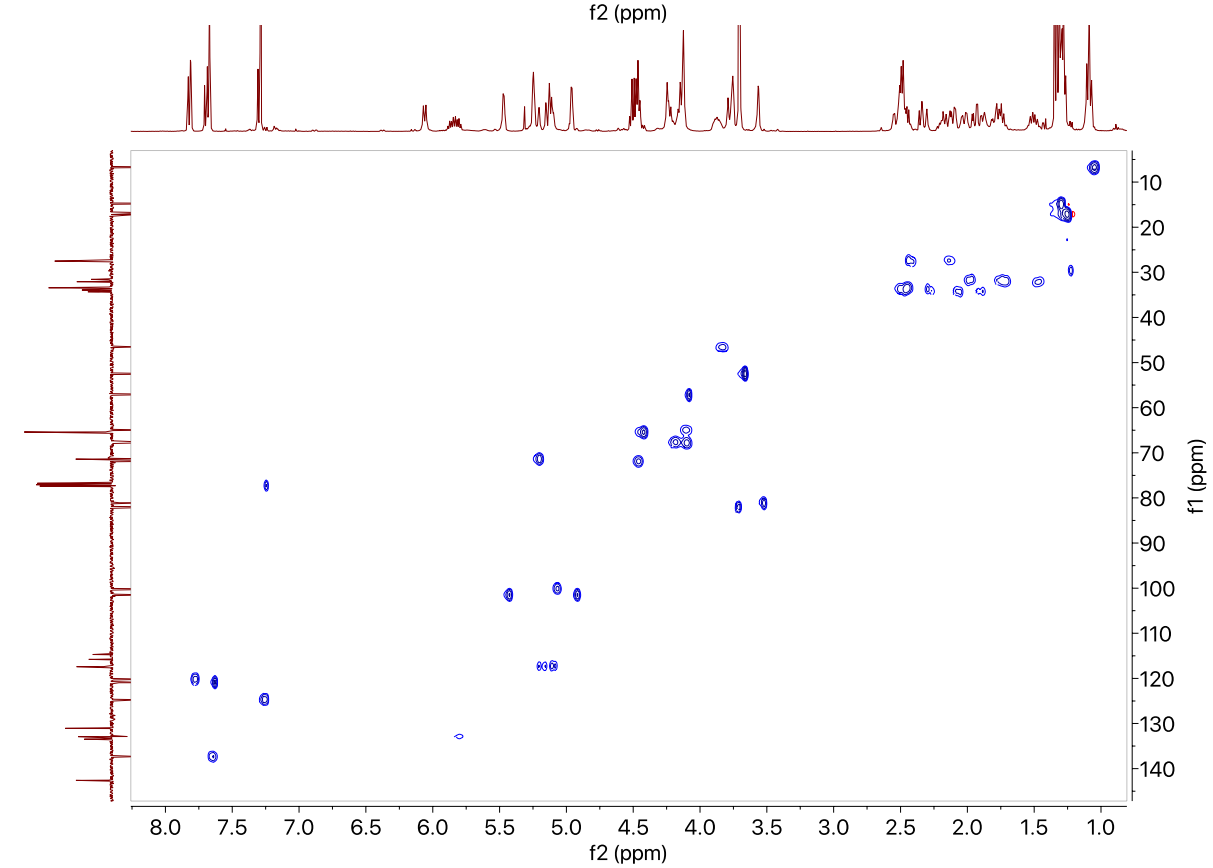

f1 (ppm)
f1 (ppm)

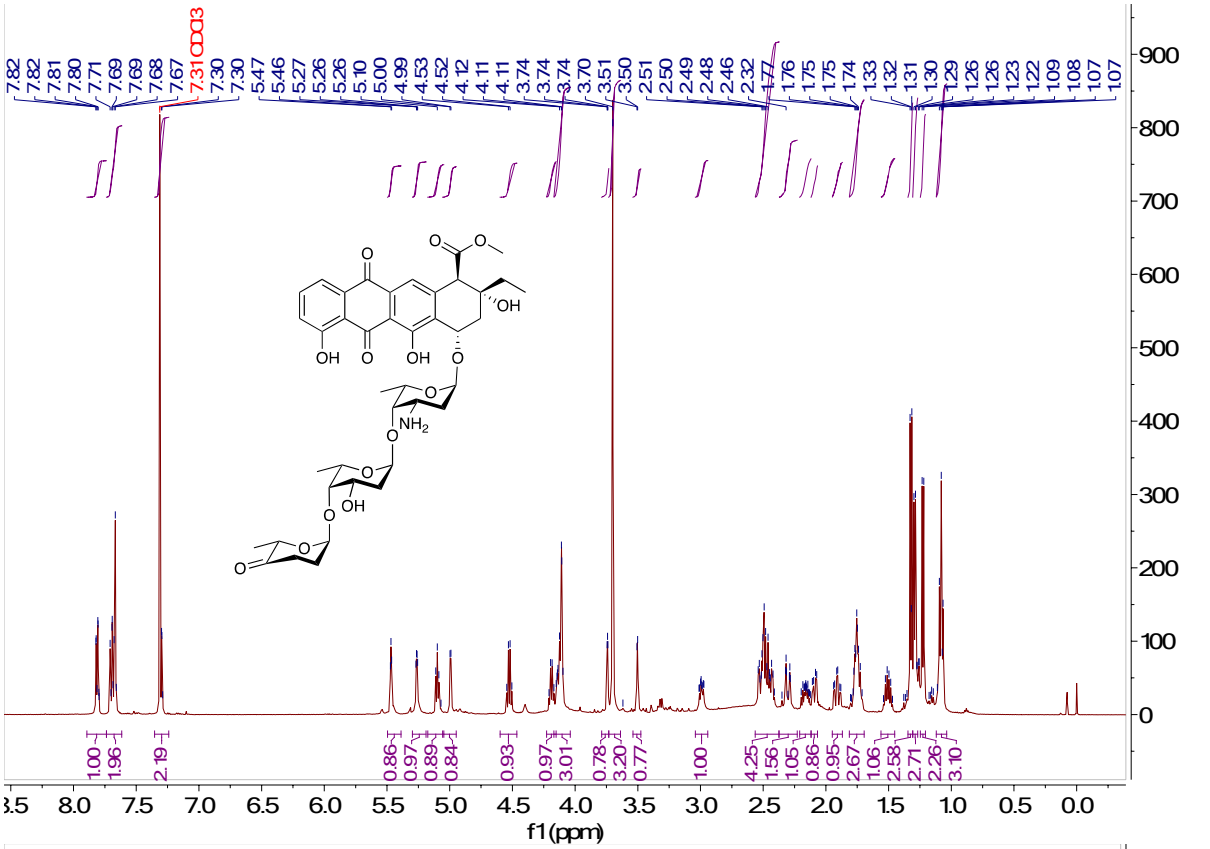

f2 (ppm)
f1 (ppm)
f2 (ppm)
f1 (ppm)

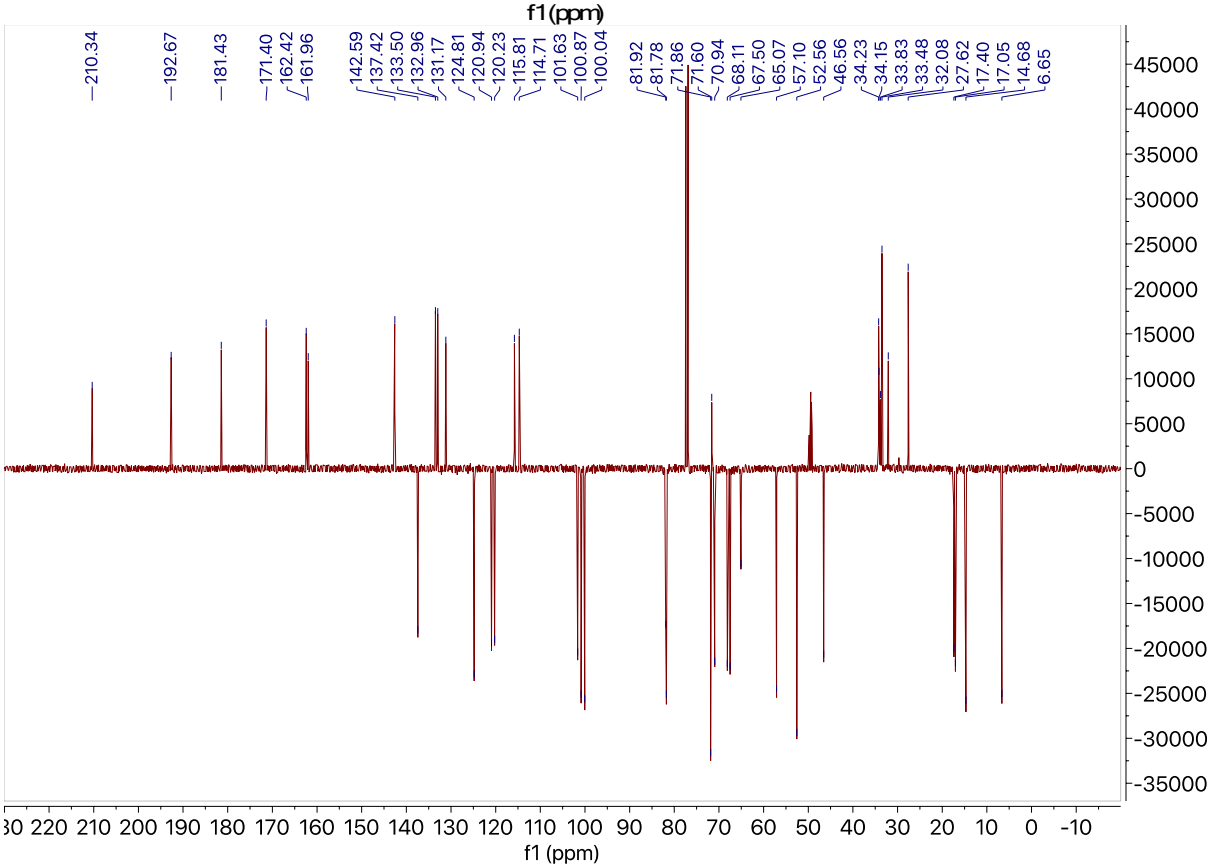

12.65 12.00 7.82 7.82 7.80 7.80 7.70 7.68 7.68 7.66 7.66 7.30 7.30 7.28 CDCl3 7.28 5.24 5.24 5.23 5.12 4.96 4.95 4.50 4.48 4.47 4.47 4.46 4.45 4.45 4.24 4.14 4.14 4.12 4.12 4.11 3.75 3.75 3.74 3.70 3.55 2.50 2.49 2.48 2.48 2.47 1.34 1.32 1.31 1.30 1.29 1.27 1.25 1.10 1.08 1.06 0.00
OH
OH
O
OH
O
O
O
O
O
NHAlloc
O
O
OH
O
O
O
1.00 0.90 1.07 2.13 2.56 0.86 0.91 1.02 3.95 1.08 3.10 1.93 3.25 1.06 2.18 3.25 0.99 4.27 1.24 2.24 1.11 1.21 2.15 1.19 10.37 3.35
f1 (ppm)

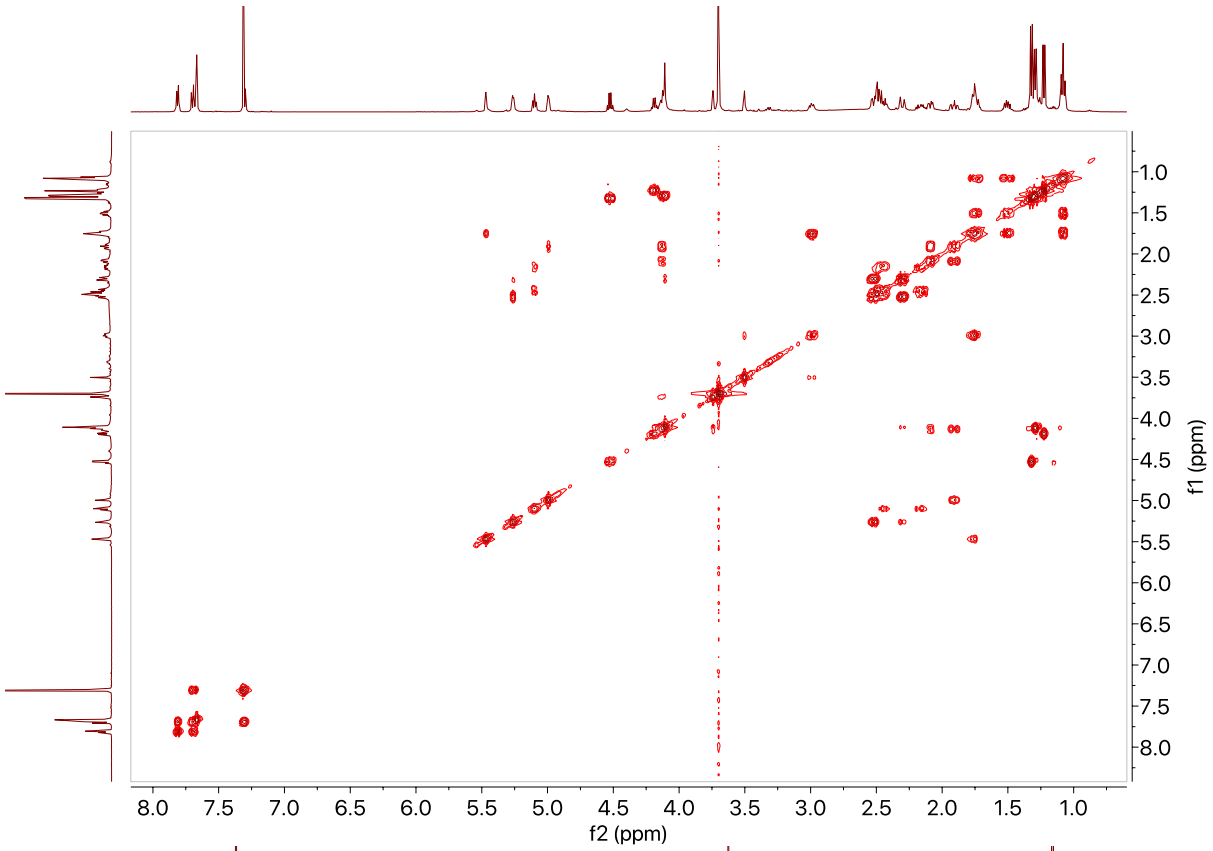

209.88 192.77 181.36 171.50 162.58 162.25 155.48 142.68 137.40 133.56 132.98 132.96 131.14 124.82 121.02 120.26 117.48 115.86 114.78 101.59 101.57 100.27 82.12 81.17 71.93 71.49 71.39 67.86 67.69 65.47 65.03 57.13 52.58 46.60 34.38 33.99 33.50 32.16 31.65 27.60 17.34 16.88 14.83 6.78
f1 (ppm)

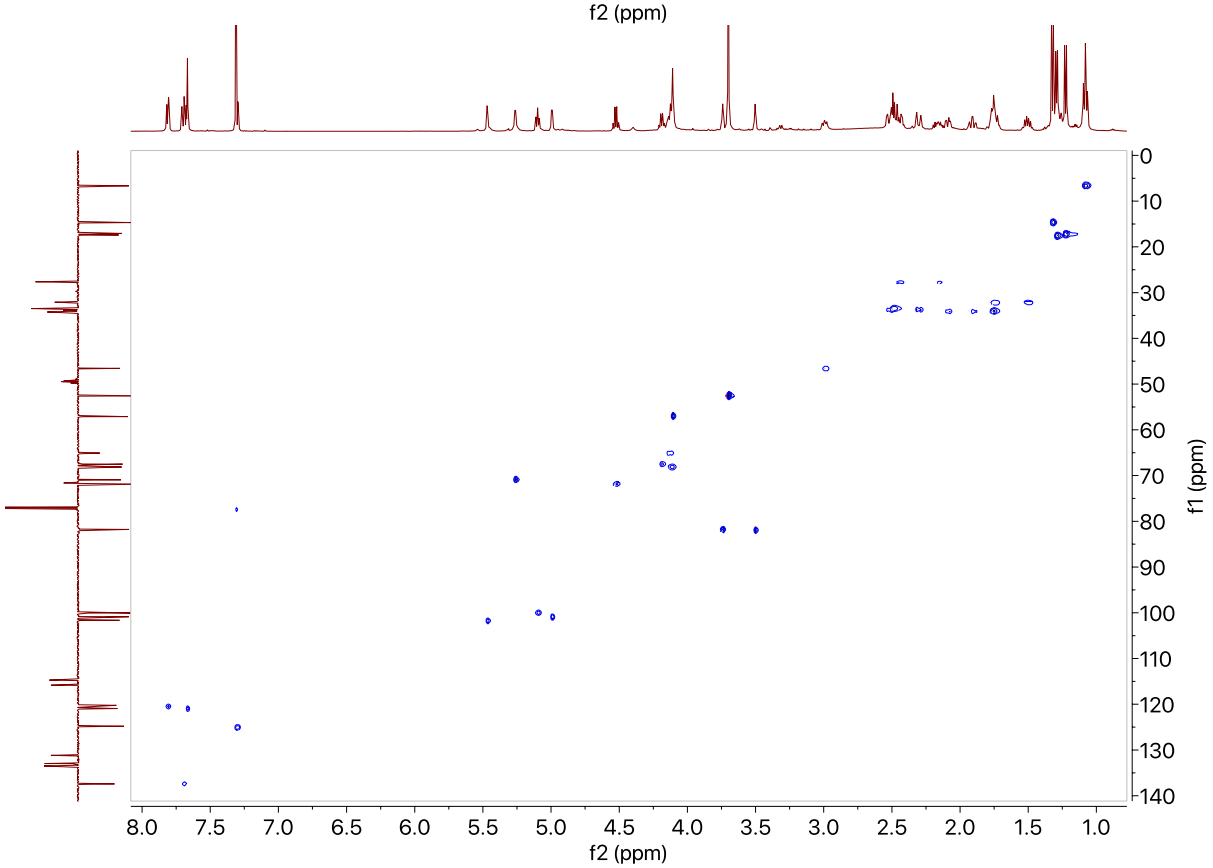

f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)


7.82
7.82
7.81
7.80
7.71
7.69
7.69
7.68
7.67
7.31
7.30
7.30
5.47
5.46
5.27
5.26
5.26
5.10
5.00
4.99
4.53
4.52
4.12
4.11
4.11
3.74
3.74
3.70
3.51
3.50
2.51
2.50
2.49
2.48
2.46
2.32
1.77
1.76
1.75
1.75
1.74
1.33
1.32
1.31
1.30
1.29
1.26
1.26
1.23
1.22
1.09
1.08
1.07
1.07
OH
O
O
OH
O
OH
O
NH2
O
O
OH
O
O
O
1.00
1.96
2.19
0.86
0.97
0.89
0.84
0.93
0.97
3.01
0.78
3.20
0.77
1.00
4.25
1.56
1.05
0.86
0.95
2.67
1.06
2.58
2.71
2.26
3.10
f1 (ppm)

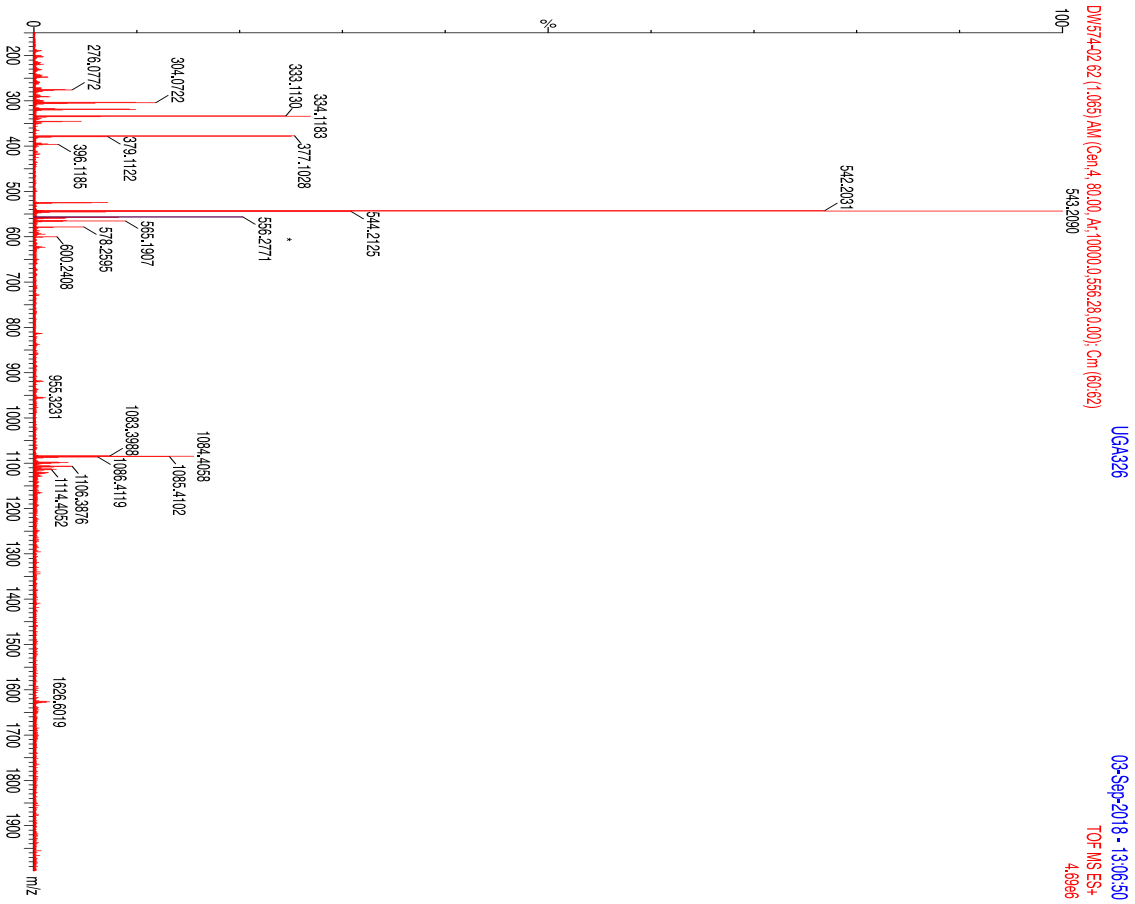

210.34
192.67
181.43
171.40
162.42
161.96
142.59
137.42
133.50
132.96
131.17
124.81
120.94
120.23
115.81
114.71
101.63
100.87
100.04
81.92
81.78
71.86
71.60
70.94
68.11
67.50
65.07
57.10
52.56
46.56
34.23
34.15
33.83
33.48
32.08
27.62
17.40
17.05
14.68
6.65
f1 (ppm)


f2 (ppm)
f1 (ppm)

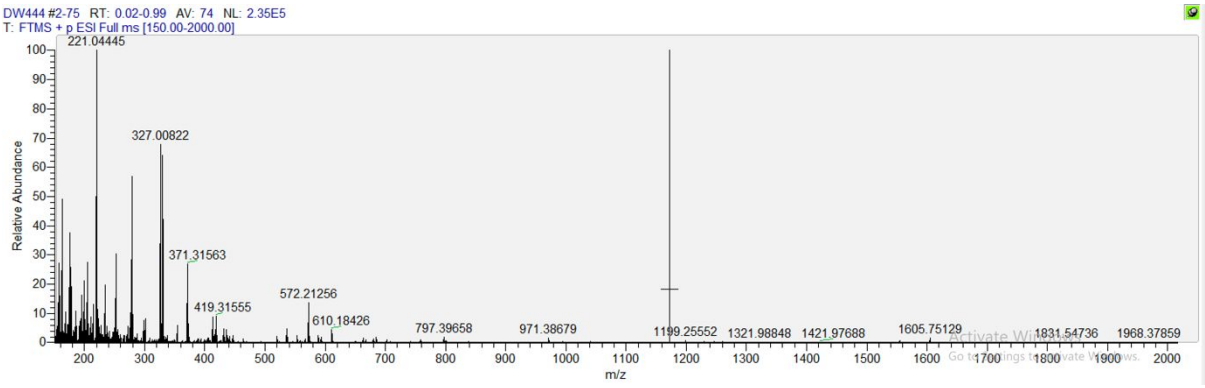

f2 (ppm)
f1 (ppm)

J: HRMS data of compounds **2-11**

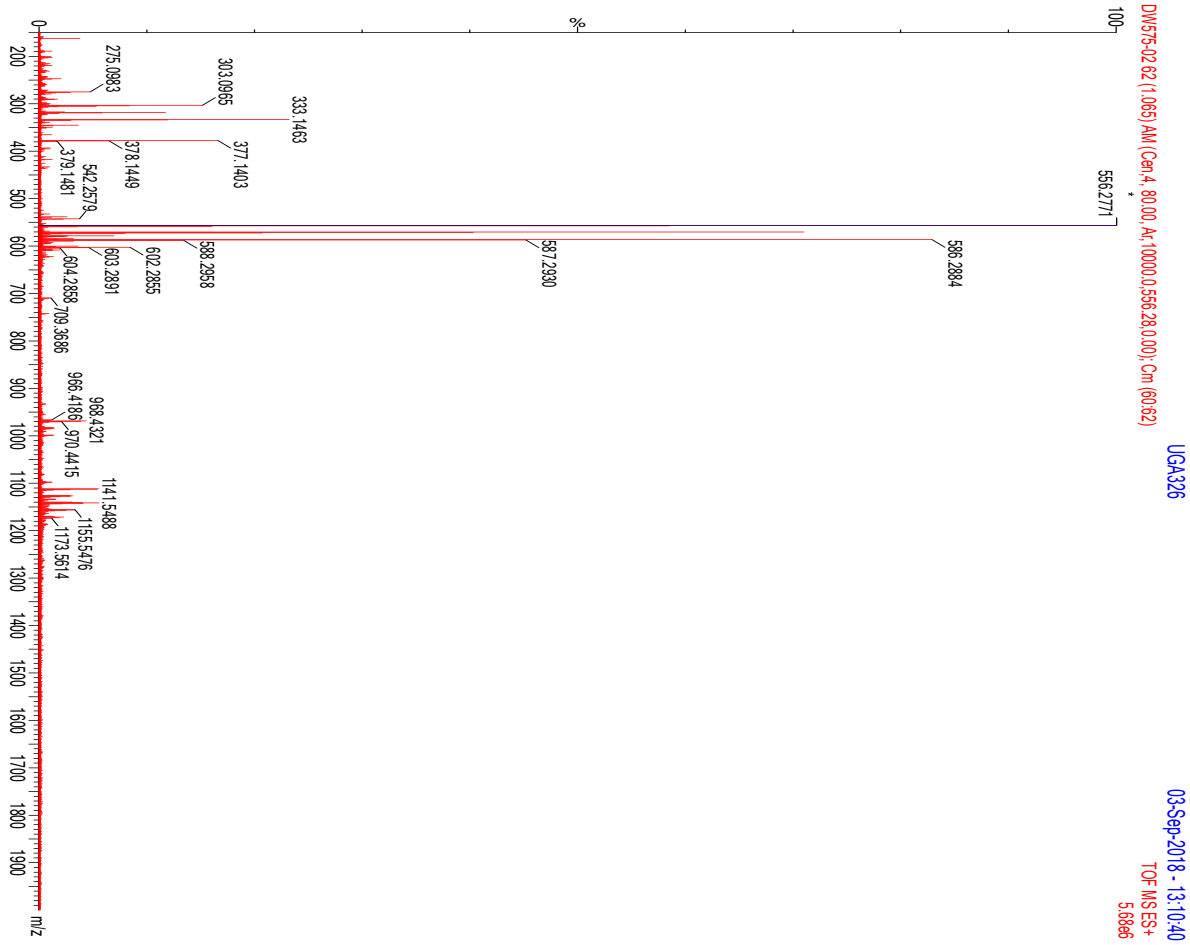
Compound 2



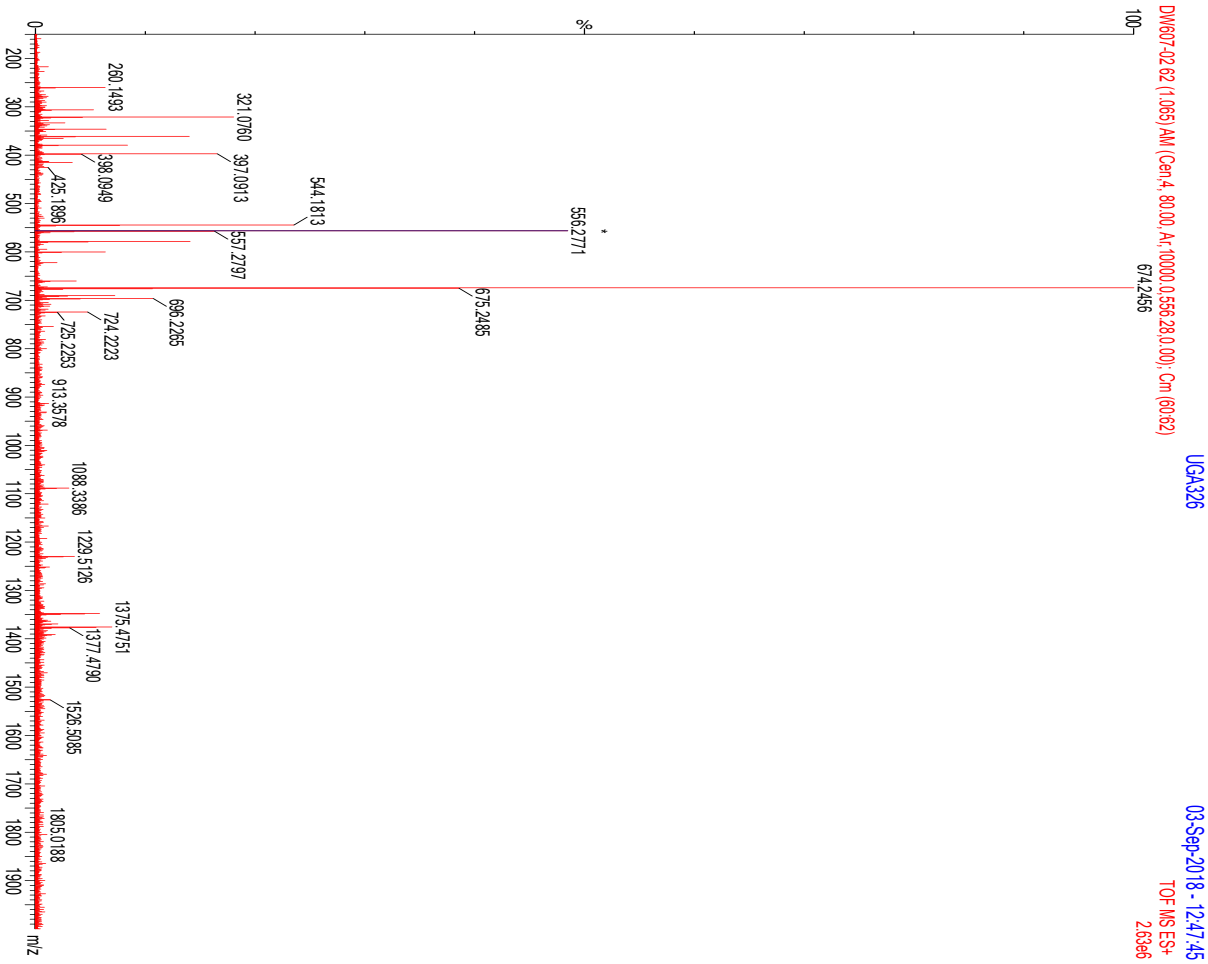
Compound 3



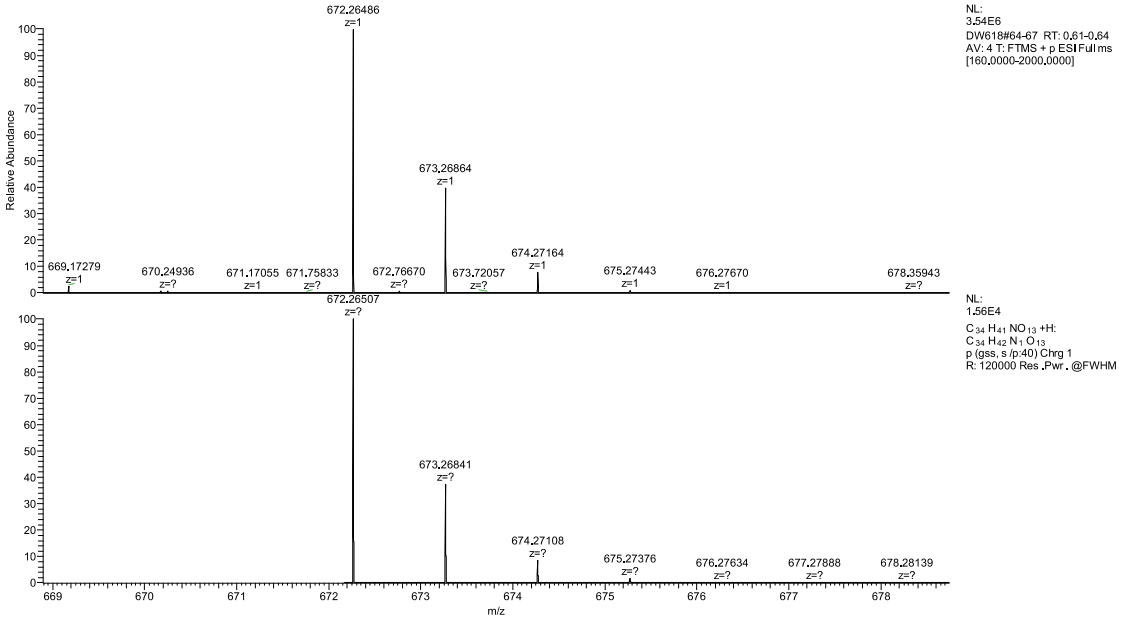
Compound 4


DW575-02 62 (1.065) AM (Cen,4, 80.00, Ar,10000.0,556.28,0.00); Cm (60:62)
UGA326
03-Sep-2018 - 13:10:40
TOF MS ES+
5.68e6
100
%
0
556.2771
586.2884
587.2930
588.2953
602.2855
603.2891
604.2853
709.3686
966.4186
968.4321
970.4415
1114.5488
1155.5476
1173.5614
275.0883
303.0965
333.1463
377.1403
378.1449
379.1481
542.2579
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

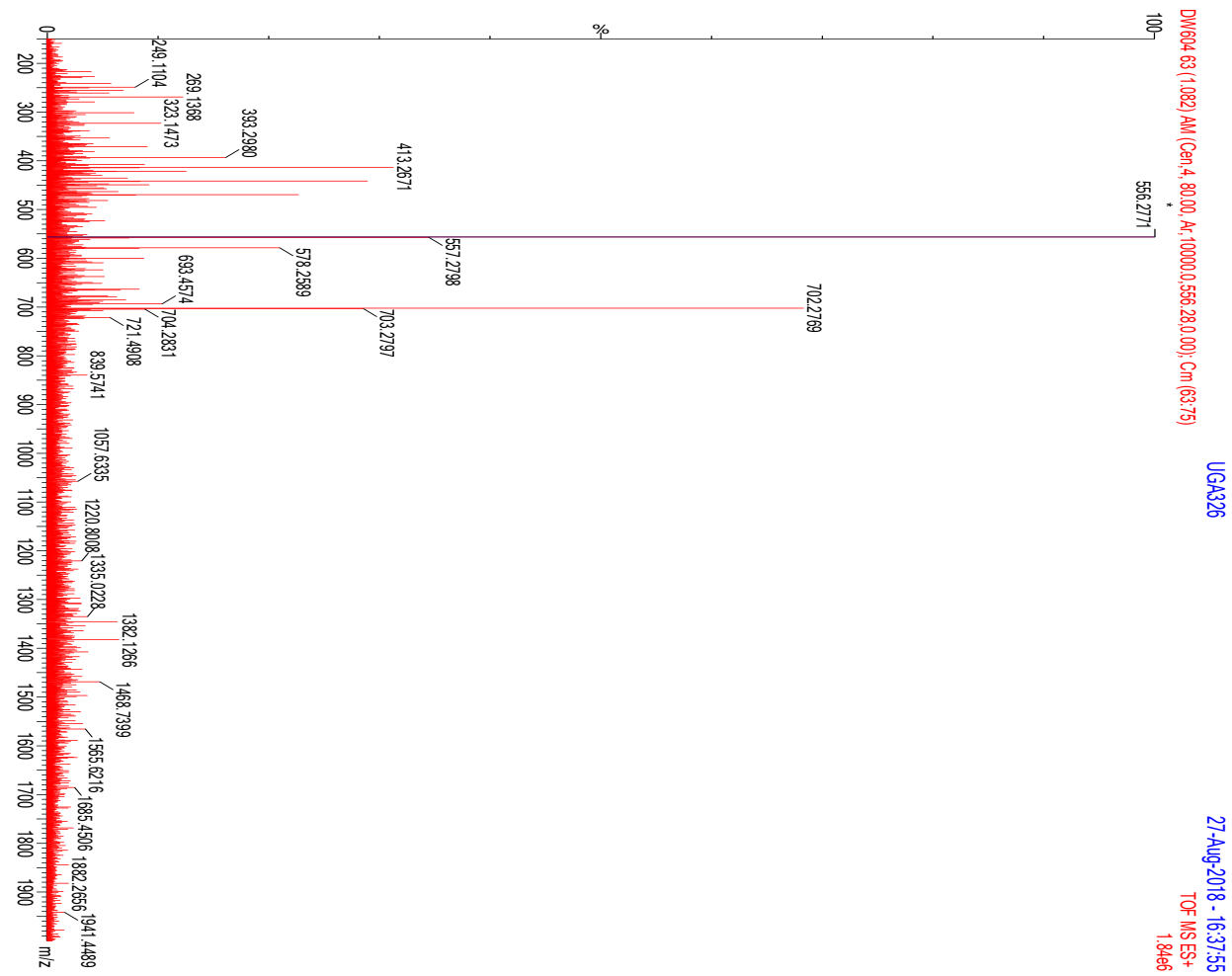
Compound 5


DW607-02 62 (1.065) AM (Cen,4, 80.00, Ar,10000.0,556.28,0.00); Cm (60:62)
UGA326
03-Sep-2018 - 12:47:45
TOF MS ES+
2.53e6
100
%
0
200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900
m/z
260.1493
321.0760
397.0913
398.0949
425.1896
544.1813
556.2771
557.2797
674.2456
675.2485
696.2265
724.2223
725.2253
913.3578
1088.3386
1229.5126
1375.4751
1377.4790
1526.5085
1805.0188

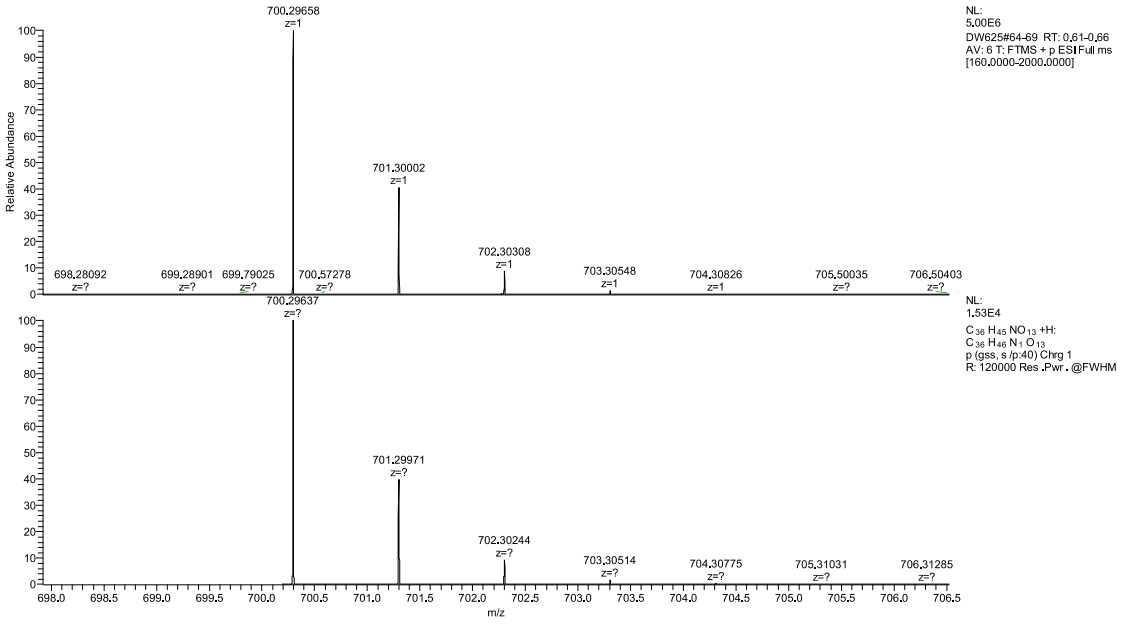
Compound 6


672.26486
z=1
673.26864
z=1
674.27164
z=1
669.17279
z=1
670.24936
z=?
671.17055
z=1
671.75833
z=?
672.76670
z=?
673.72057
z=?
675.27443
z=1
676.27670
z=1
678.35943
z=?
Relative Abundance
NL:
3.54E6
DW618#64-67 RT: 0.61-0.64
AV: 4 T: FTMS + p ESI Full ms
[160.0000-2000.0000]
672.26507
z=?
673.26841
z=?
674.27108
z=?
675.27376
z=?
676.27634
z=?
677.27888
z=?
678.28139
z=?
NL:
1.56E4
C34 H41 NO13 +H:
C34 H42 N1 O13
p (gss, s /p:40) Chrg 1
R: 120000 Res .Pwr . @FWHM
m/z

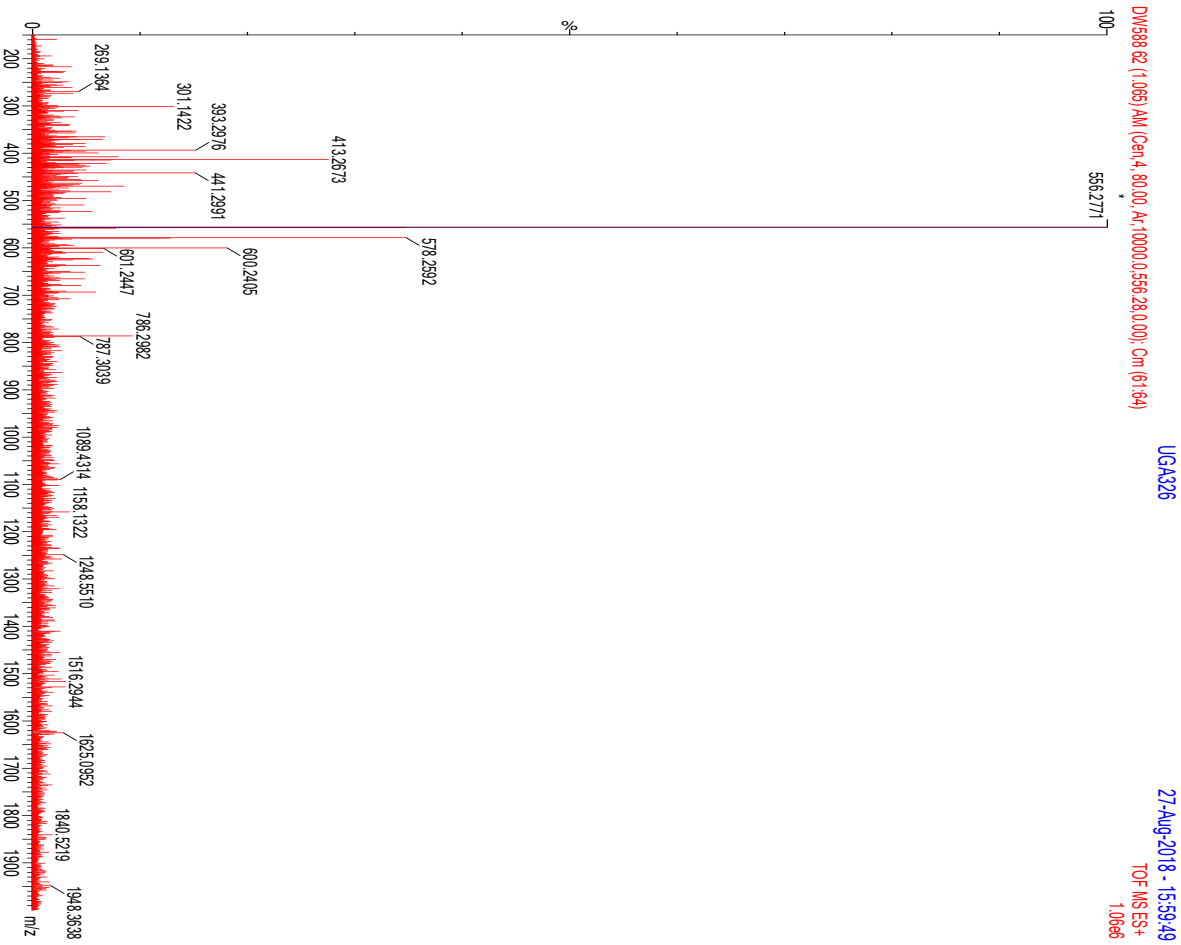
Compound 7


DW604 63 (1.082) AM (Cen,4, 80.00, Ar, 10000.0, 556.28, 0.00); Cm (63:75)
UGA326
27-Aug-2018 - 16:37:55
TOF MS ES+
1.84e6
100
%
0
556.2771
557.2798
702.2769
413.2671
578.2589
703.2797
693.4574
704.2831
721.4908
839.5741
1057.6335
1220.8008
1335.0228
1382.1266
1468.7399
1565.6216
1685.4506
1882.2656
1941.4489
249.1104
269.1368
323.1473
393.2980
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

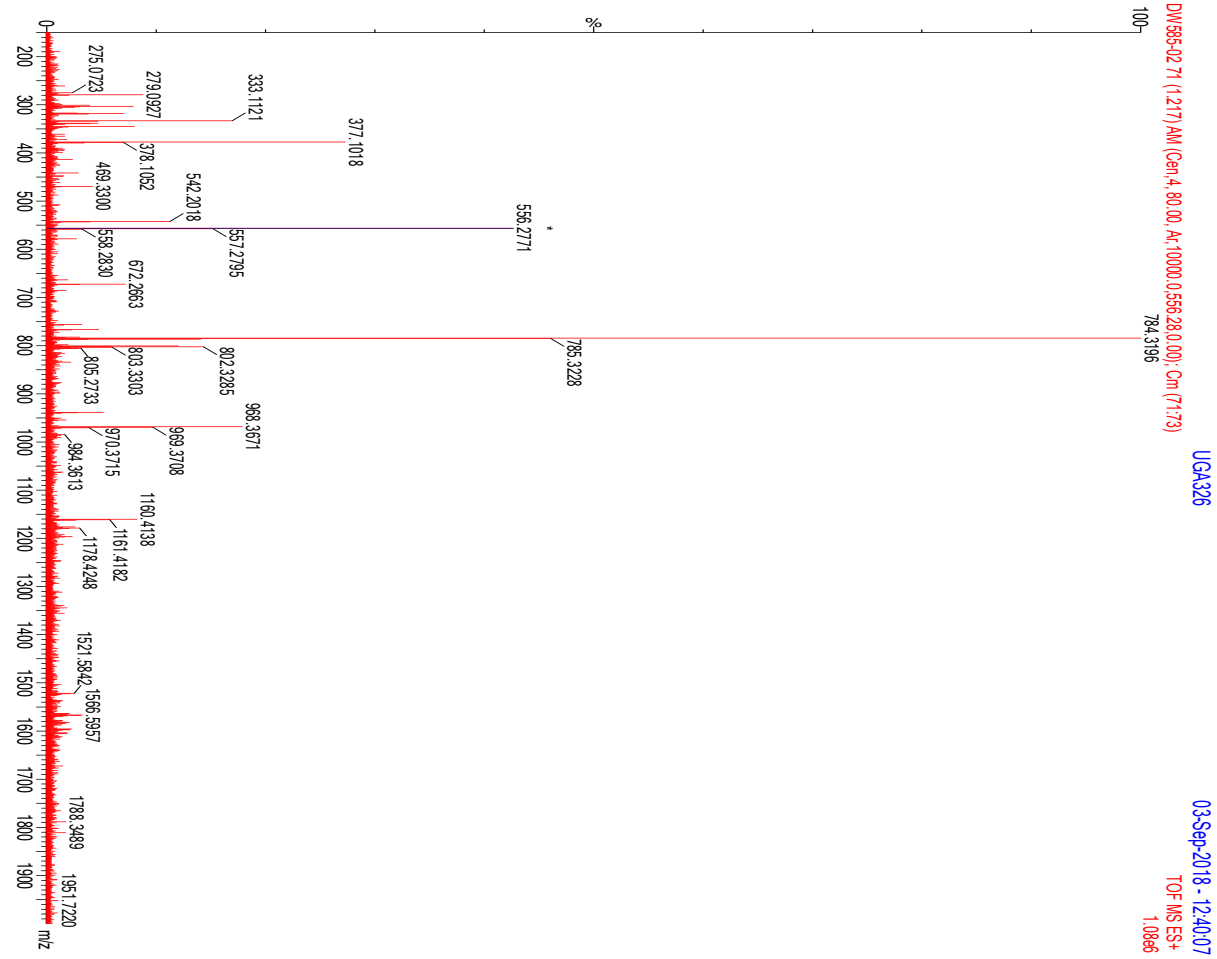
Compound 8


NL:
5.00E6
DW625#64-69 RT: 0,61-0,66
AV: 6 T: FTMS + p ESI Full ms
[160.0000-2000.0000]
700.29658
z=1
701.30002
z=1
702.30308
z=1
698.28092
z=?
699.28901
z=?
699.79025
z=?
700.57278
z=?
703.30548
z=1
704.30826
z=1
705.50035
z=?
706.50403
z=?
Relative Abundance
NL:
1.53E4
C36 H45 NO13 +H:
C36 H46 N1 O13
p (gss, s /p:40) Chrg 1
R: 120000 Res .Pwr . @FWHM
700.29637
z=?
701.29971
z=?
702.30244
z=?
703.30514
z=?
704.30775
z=?
705.31031
z=?
706.31285
z=?
m/z

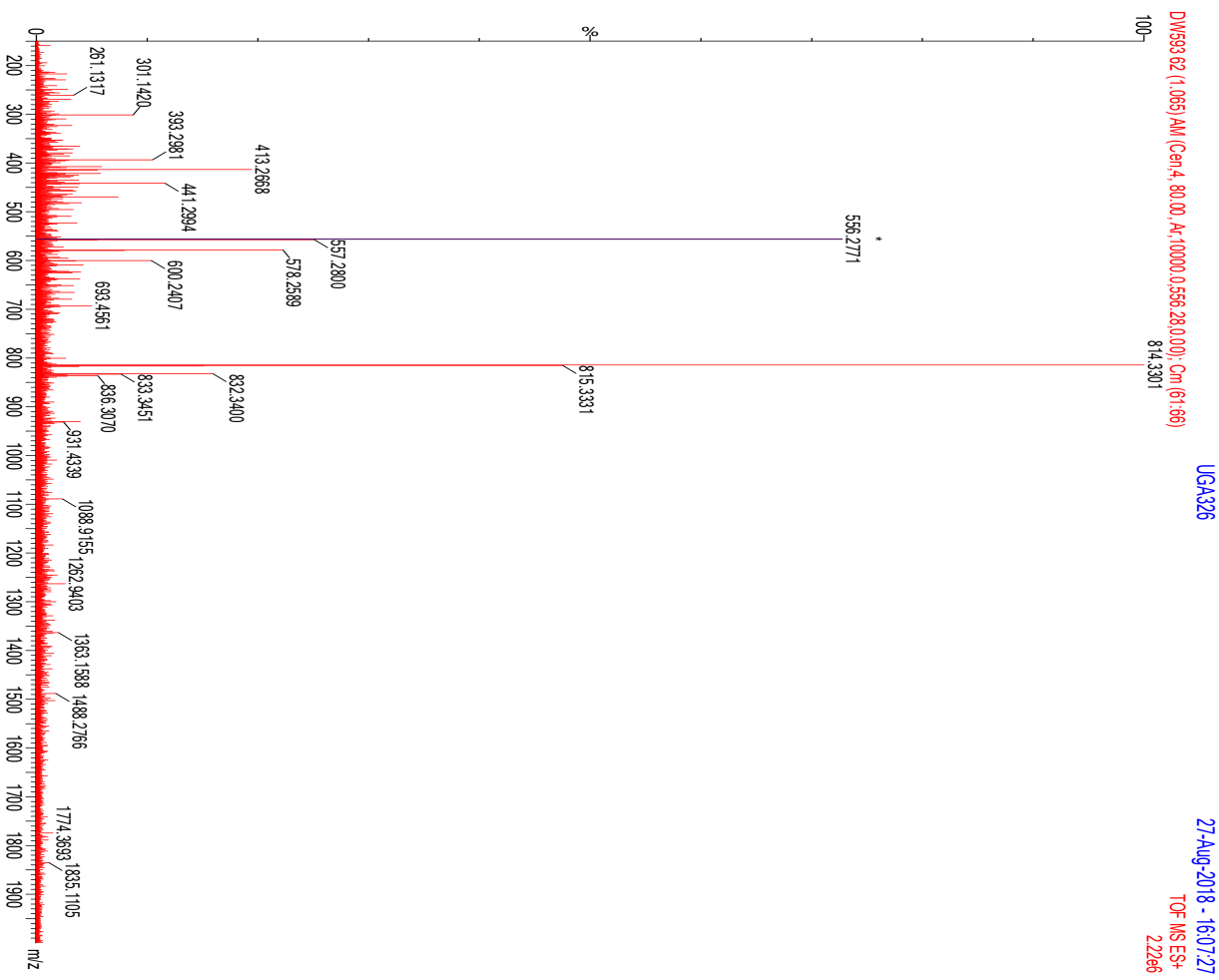
Compound 9


DW588 82 (1.065) AM (Cen,4, 80.00, Ar,10000.0,556.28,0.00); Cm (61:64)
UGA326
27-Aug-2018 - 15:59:49
TOF MS ES+
1.06e6
100
%
0
556.2771
578.2592
600.2405
601.2447
786.2982
787.3039
413.2673
441.2991
393.2976
301.1422
269.1364
1089.4314
1158.1322
1248.5510
1516.2944
1625.0952
1840.5219
1948.3638
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

Compound 10

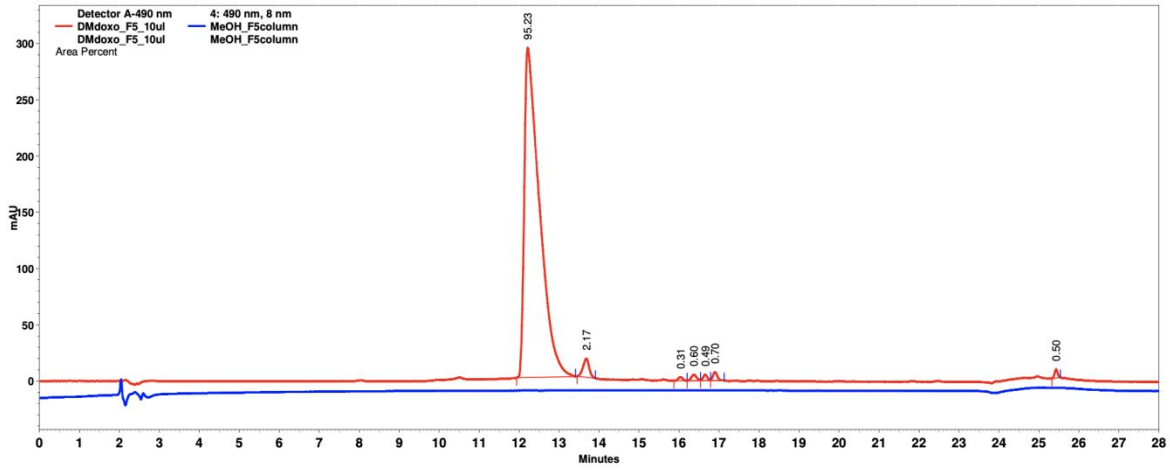

DW585-02 71 (1.217) AM (Cen,4, 80.00, Ar,10000.0,556.28,0.00); Cm (71:73)
UGA326
03-Sep-2018 - 12:40:07
TOF MS ES+
1.08e6
100
%
0
784.3196
785.3228
556.2771
377.1018
333.1121
279.0927
275.0723
378.1052
469.3300
542.2018
557.2795
558.2830
672.2663
802.3285
803.3303
805.2733
968.3671
969.3708
970.3715
984.3613
1160.4138
1161.4182
1178.4248
1521.5842
1566.5957
1788.3489
1951.7220
200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900
m/z

Compound 11


DW593 62 (1.065) AM (Cen,4, 80.00, Ar,10000.0,556.28,0.00); Cm (61:66)
UGA326
27-Aug-2018 - 16:07:27
TOF MS ES+
2.22e6
100
%
0
556.2771
814.3301
815.3331
261.1317
301.1420
393.2981
413.2668
441.2994
557.2800
578.2589
600.2407
693.4561
832.3400
833.3451
836.3070
931.4339
1088.9155
1262.9403
1363.1588
1488.2766
1774.3693
1835.1105
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

K: HPLC traces of (lead compounds) 3, 8 and 11

Compound 3:



Column description:
Phenomenex Kinetex® F5 2.6µm 100 Å, LC Column 100 x 4.6 mm (cat no. 00D-4723-E0)
Blank run (MeOH) in blue

Flow rate: 0.5 mL/min; with following gradient elution:

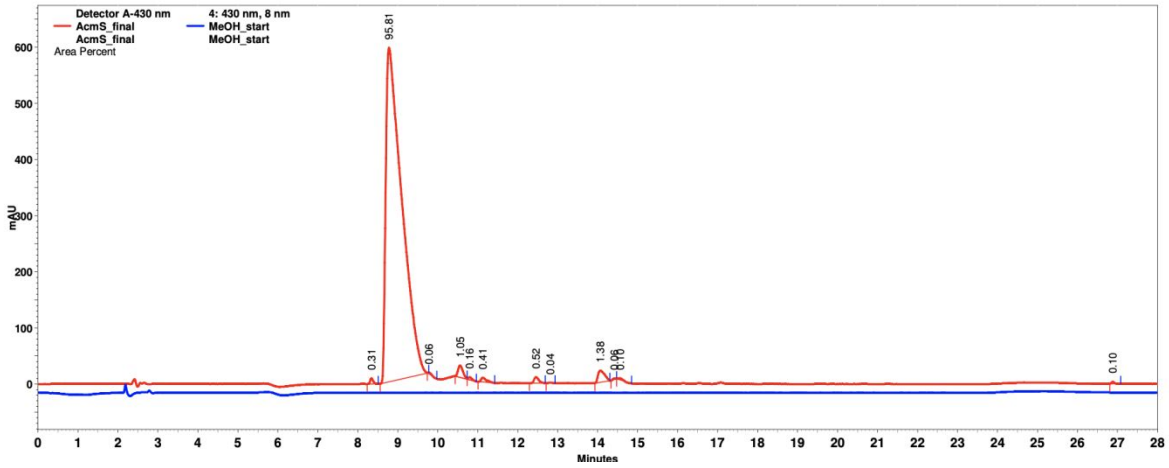
time (min)	B%
0.1	15
19	40
20	100
24	100
24.1	15
28	15

Buffer used for elution:
Buffer A:

45 % ammonium acetate solution
5% ACN
50% MQ

Buffer B:
100% ACN

Compound 8:



Column description:
Phenomenex Kinetex® 2.6 µm C18 100 Å, LC Column 100 x 4.6 mm (cat no. 00D-4462-E0)
Blank run (MeOH) in blue

Flow rate: 0.5 mL/min; with following gradient elution:

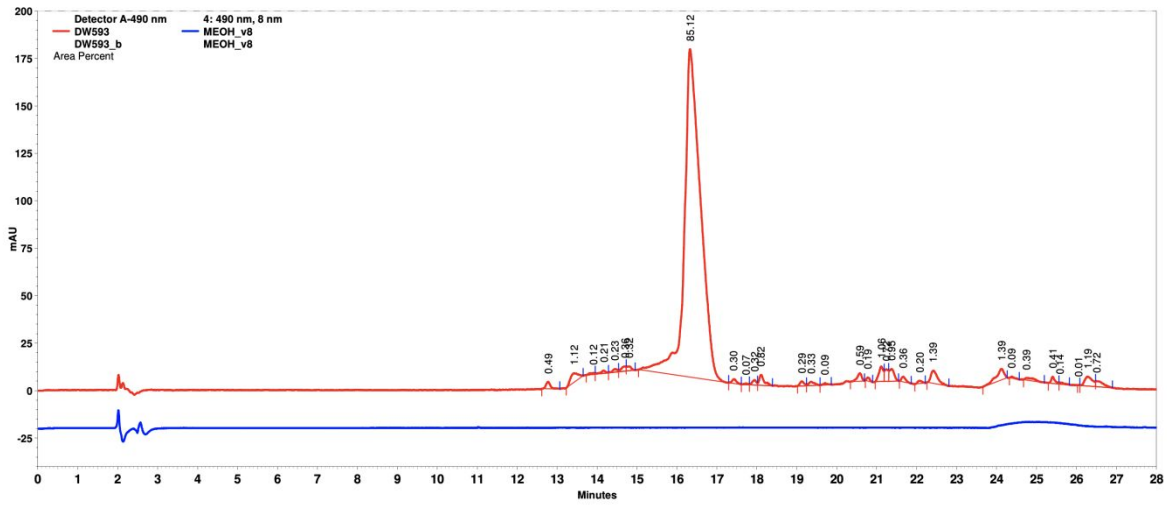
time (min)	B%
0.1	0
0.5	30
1.5	33
4.0	37
19.0	50
20	100
24	100
24.1	0
28	0

Buffer used for elution:
Buffer A:

45 % ammonium acetate solution
5% ACN
50% MQ

Buffer B:
100% ACN

Compound 11:



Column description:
Phenomenex Kinetex® F5 2.6µm 100 Å, LC Column 100 x 4.6 mm (cat no. 00D-4723-E0)
Blank run (MeOH) in blue

Flow rate: 0.5 mL/min; with following gradient elution:

time (min)	B%
0.1	15
19	40
20	100
24	100
24.1	15
28	15

Buffer used for elution:
Buffer A:

45 % ammonium acetate solution
5% ACN
50% MQ

Buffer B:
100% ACN

L: References

1. Fan, E., Shi, W. & Lowary, T. L. Synthesis of Daunorubicin Analogues Containing Truncated Aromatic Cores and Unnatural Monosaccharide Residues. *J. Org. Chem.* **72**, 2917–2928 (2007).
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3. Shi, W., Coleman, R. S. & Lowary, T. L. Synthesis and DNA-binding affinity studies of glycosylated intercalators designed as functional mimics of the anthracycline antibiotics. *Org. Biomol. Chem.* **7**, 3709–3722 (2009).
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5. Hashmi, A. S. K. *et al.* On Homogeneous Gold/Palladium Catalytic Systems. *Adv. Synth. Catal.* **354**, 133–147 (2012).
6. Qiao, X. *et al.* Uncoupling DNA damage from chromatin damage to detoxify doxorubicin. *Proc. Natl. Acad. Sci.* **117**, 15182–15192 (2020).