Diversity-Oriented Library Synthesis from Steviol and Isosteviol-Derived Scaffolds

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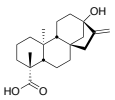
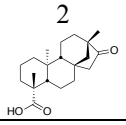
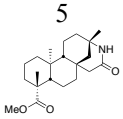
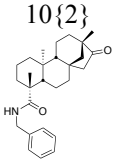
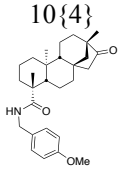
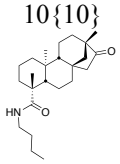
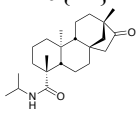
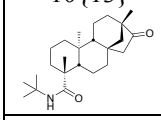
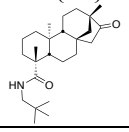
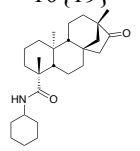
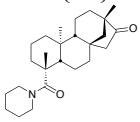
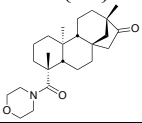
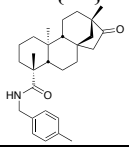
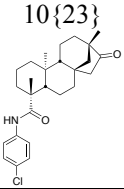
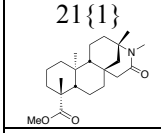
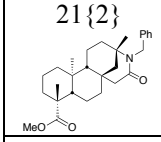
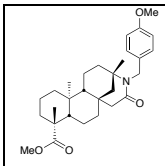
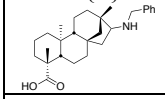
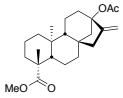
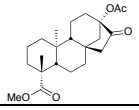
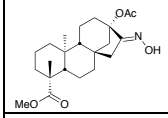
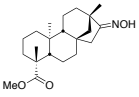
Supporting Information

Contents

Table S1. Complete current activity table of isosteviol and steviol analogs from PubChem

Compound	PubChem ID	Assay ID	BioAssay	Activity (if given)	
				Assay Type	Result or Value (μM)
1 	9905087	602438	uHTS identification of modulators of interaction between CendR and NRP-1 using fluorescence polarization assay	Primary screen	active
2 	42601320	652104	qHTS of TDP-43 inhibitors	Confirmatory	IC_{50}[A] 19.953
5 	42601318	720706	HTS for bacterial rRNA inhibitors measured in microorganism-based system	Primary screen	active
10{2} 	42601330	540271	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium falciparum HSP40-mediated toxicity measured in whole organism system	Confirmatory	AbsAC[C] 1.427
		686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 18.356
		652041	Cell-based secondary assay to test the inhibitory activity of small molecule on Plasmodium falciparum (HB3 strain) survival in red blood cells measured in cell-based system	Confirmatory	AbsAC 21.72
		652047	Cell-based secondary assay to test the inhibitory activity of small molecule on Plasmodium falciparum (3D7 strain) survival in red blood cells measured in cell-based system	Confirmatory	AbsAC 30.22
		2825	uHTS Luminescent assay for indentification of inhibitors of NALP3 in yeast	Primary screen	active
		435006	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay	Primary screen	active
		504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active
10{4} 	42601335	624417	qHTS of GLP-1 receptor inverse agonists	Confirmatory	EC_{50} 10
		624466	Fluorescence-based cell-based primary HTS assay to identify antagonists of human TAAR1	Primary screen	active
		2825	uHTS Luminescent assay for indentification of inhibitors of NALP3 in yeast	Primary screen	active
		504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active
10{10} 	42601331	488784	Single concentration confirmation of inhibitors of NALP3 in yeast using Caspase-1-ASC counter screen	Primary screen	active
		2685	qHTS assay for lipid storage modulators in drosophila S3 cells	Confirmatory	EC_{50} 0.651
		2825	uHTS Luminescent assay for indentification of inhibitors of NALP3 in yeast	Primary screen	active
		463195	uHTS identification of small molecule inhibitors of tim10 yeast via a luminescent assay	Primary screen	active
		435006	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay	Primary screen	active

		488794	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay-retest	Primary screen	active
10{11} 	42601329	2825	uHTS luminescent assay for indentification of inhibitors of NALP3 in yeast	Primary screen	active
		488784	Single concentration confirmation of inhibitors of NALP3 in yeast using Caspase-1-ASC counter screen	Primary screen	active
		488794	Single concentration confirmation of uHTS for the identification of inhibitors of NALP3 in yeast using a luminescent assay-retest	Primary screen	active
10{13} 	42601326	2825	uHTS luminescent assay for indentification of inhibitors of NALP3 in yeast	Primary screen	active
10{14} 	42601334	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 23.109
10{19} 	42601327	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 23.109
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 18.356
		602438	uHTS identification of modulators of interactions between CendR and NRP-1 using fluorescence polarization assay	Primary screen	active
10{20} 	42601332	602123	Fluorescence polarization-based primary biochemical HTS assay to identify inhibitors of E. coli DNA-binding ATP-dependent protease La (eLon)	Primary screen	active
		624169	Luminescence-based cell-based primary HTS assay to identify agonists of the mouse HTR2A	Primary screen	active
10{21} 	42601333	652048	qHTS of D3 dopamine receptor agonist	Primary screen	active
		652051	qHTS of D3 dopamine receptor potentiators	Primary screen	active
10{22} 	42601336	504582	*In vivo*-based yeast HTS to detect compounds rescuing yeast growth/survival of Plasmodium falciparum HSP40-mediated toxicity measured in whole organism system	Primary screen	active
10{23} 	42601328	602438	uHTS identification of modulators of interactions between CendR and NRP-1 using fluorescence oolarization assay	Primary screen	active
21{1} 	42601319	-	Inconclusive data in 7 assays and inactive in 417 assays	Primary screen	inactive
21{2} 	53299290	-	N/A	N/A	N/A
21{4}	42601337	624132	Shn3: Dual-Go Shn3RL cells measured in cell-based system	Confirmatory	$AC_{50}{}^{D}$ 10.58

		624133	Schnurri-3 Inhibitors: specific inducers of adult bone formation measured in cell-based system	Confirmatory	AC_{50} 8.16
		504832	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 48 hr incubation	Confirmatory	IC_{50} 1.651
		504834	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 96 hr incubation	Confirmatory	IC_{50} 1.472
		504444	Nrf2 qHTS screen for inhibitors	Confirmatory	IC_{50} 14.581
		651820	qHTS assay for inhibitors of hepatitis C virus	Confirmatory	IC_{50} 12.589
		686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 6.513
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 11.582
		743417	Schnurri-3 inhibitors: specific inducers of adult bone formation measured in cell-based system	Confirmatory	AC_{50} 8.16
22{2} 	42601325	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 20.596
24 	42601321	588850	uHTS identification of cystic fibrosis induced NFkb inhibitors in a fluorescence assay	Primary screen	active
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 18.356
		602438	uHTS identification of modulators of interactions between CendR and NRP-1 using fluorescence polarization assay	Primary screen	active
25 	42601322	686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 20.596
		624466	Fluorescence-based cell-based primary HTS assay to identify antagonists of human TAAR1	Primary screen	active
26 	42601323	686978	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 16.360
		686979	qHTS for inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50} 16.360
27 	42601324	686978	qHTS of inhibitors of human TDP1: qHTS in cells in absence of CPT	Confirmatory	EC_{50}^{B} 20.596
		463212	uHTS identification of small molecule inhibitors of tim23-1 yeast via a luminescent assay	Primary screen	active
		463218	Single concentration confirmation of small molecule inhibitors of tim23-1 yeast via a luminescent assay	Primary screen	active

[A] IC_{50}= concentration of an inhibitor required for 50% inhibition of maximum control response

[B] EC_{50}= concentration of an agonist required to produce 50% maximum (effective) response

[C] AbsAC= Absolute active concentration with compounds below 10 μM to be considered active hits

[D] AC_{50}= concentration required to elicit a 50% response in an *in vitro* assay

Calculations of Drug-like Properties

We sought to determine the potential drug-like qualities of these compounds by calculating parameters beyond the Lipinski's "rule of five."[1] Walters and coworkers previously analyzed over 415,000 molecules reported in the *Journal of Medicinal Chemistry* from 1959 to 2009.[2] In their investigation, they identified the eight important properties for all drugs or drug-like molecules to be molecular weight (MW), cLogP, total polar surface area (TPSA), rotatable bonds, hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), complexity, and fraction of sp^3 carbons (Fsp3). From this information, Hergenrother and coworkers established the importance for compounds to have higher Fsp3 values, from 0 to 1, and lower cLogP values, lower than 5 units, in order to be developed into drugs.[3] The Fsp3 value pertains to the number of sp^3-hybridized carbon atoms in a compound divided by the sum of carbon atoms, and this value has been associated with lower melting points as well as enhanced aqueous solubility.[4] They calculated four main parameters: Fsp3, cLogP, number of stereocenters, and Tanimoto similarity coefficients of their compounds compared to a 150,000-member ChemBridge collection. In our case, we compared our library to the ChemBridge CombiSet and the Maybridge Diversity Set of compounds, which contain 30,000 and about 54,000 compounds, respectively. We expected this would offer insight in to the diversity of our libraries relative to two commercially-available libraries.

We employed Pipeline Pilot to calculate ALogP values,[5] the number of stereocenters, and the Fsp3 ratio.[6] While our compounds have an average cLogP of 4.63 (Figure S1), the Hergenrother group reported an average cLogP of 2.90.[3] The ChemBridge and MayBridge library sets that we chose for comparison had an average cLogP value of 3.11 and 3.04, respectively. With such a lipophilic core scaffold, we endeavored to create less lipophilic compounds by adding various substituents and hydrophilic groups that would lower cLogP values. Our Fsp3 calculations (Figure S2) yielded an average of 0.79, while the ChemBridge and MayBridge libraries have average Fsp3 values of 0.45 and 0.22, respectively.

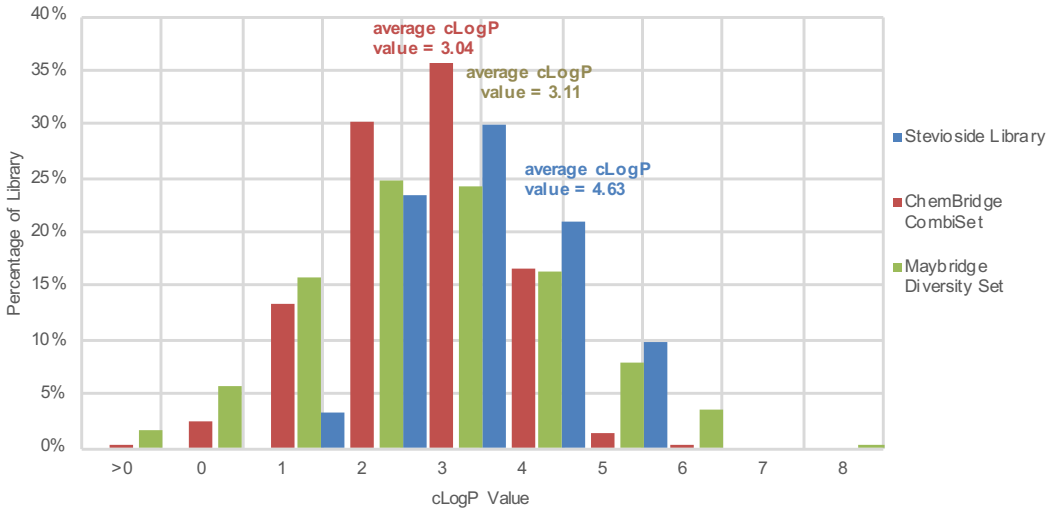


Figure S1. cLogP values of stevioside library vs commercial library sets.

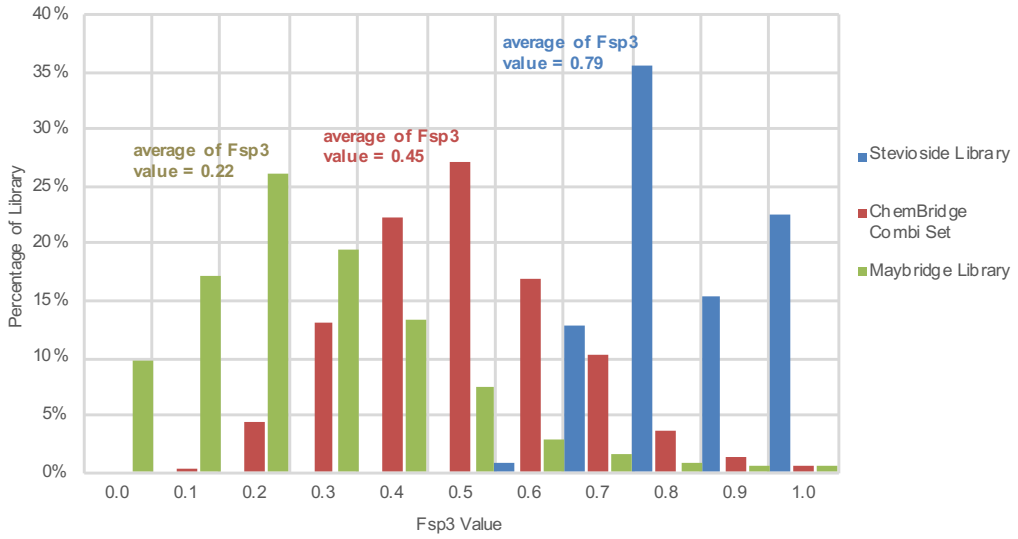


Figure S2. Fsp3 values of stevioside library vs commercial library sets.

The number of stereocenters in a compound can correlate to its structural complexity; on average, the structures in our compound library contained six stereocenters (Figure S3), while the ChemBridge and Maybridge libraries both have zero averages. Interestingly, Hergenrother's library of compounds had an average of 5.17 stereocenters.[3] The majority of the compounds in the commercial libraries contain aromatic rings and aryl group substitutions and this largely accounts for their lack of stereocenters. Our compounds as well as those in the compound library of Hergenrother's group appear to be more structurally complex with a greater number of stereocenters because they are natural product analogs. ChemBridge and Maybridge compound libraries contain compounds without or few stereocenters, because these compounds are typically less complex and therefore, relatively easier to synthesize.[7]

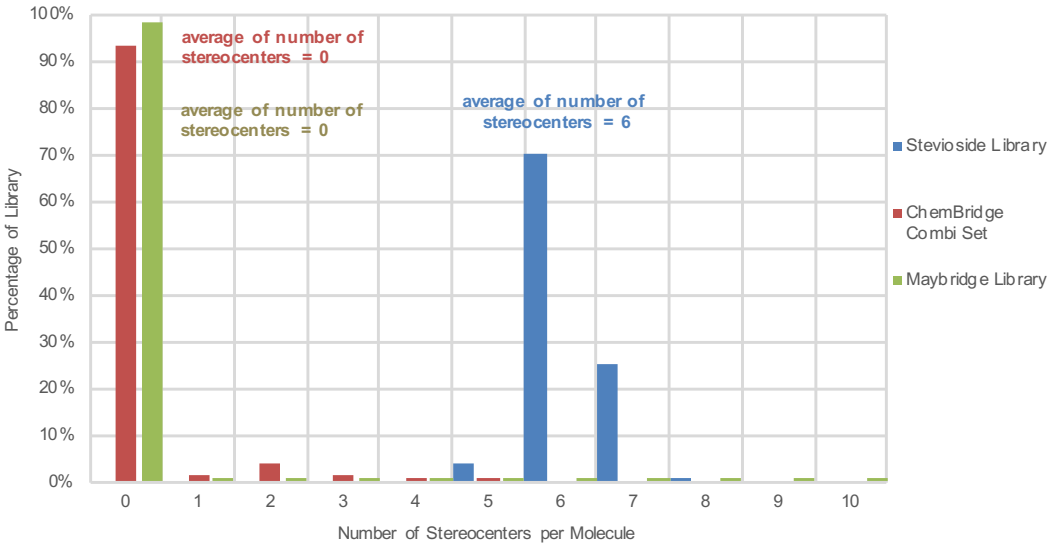


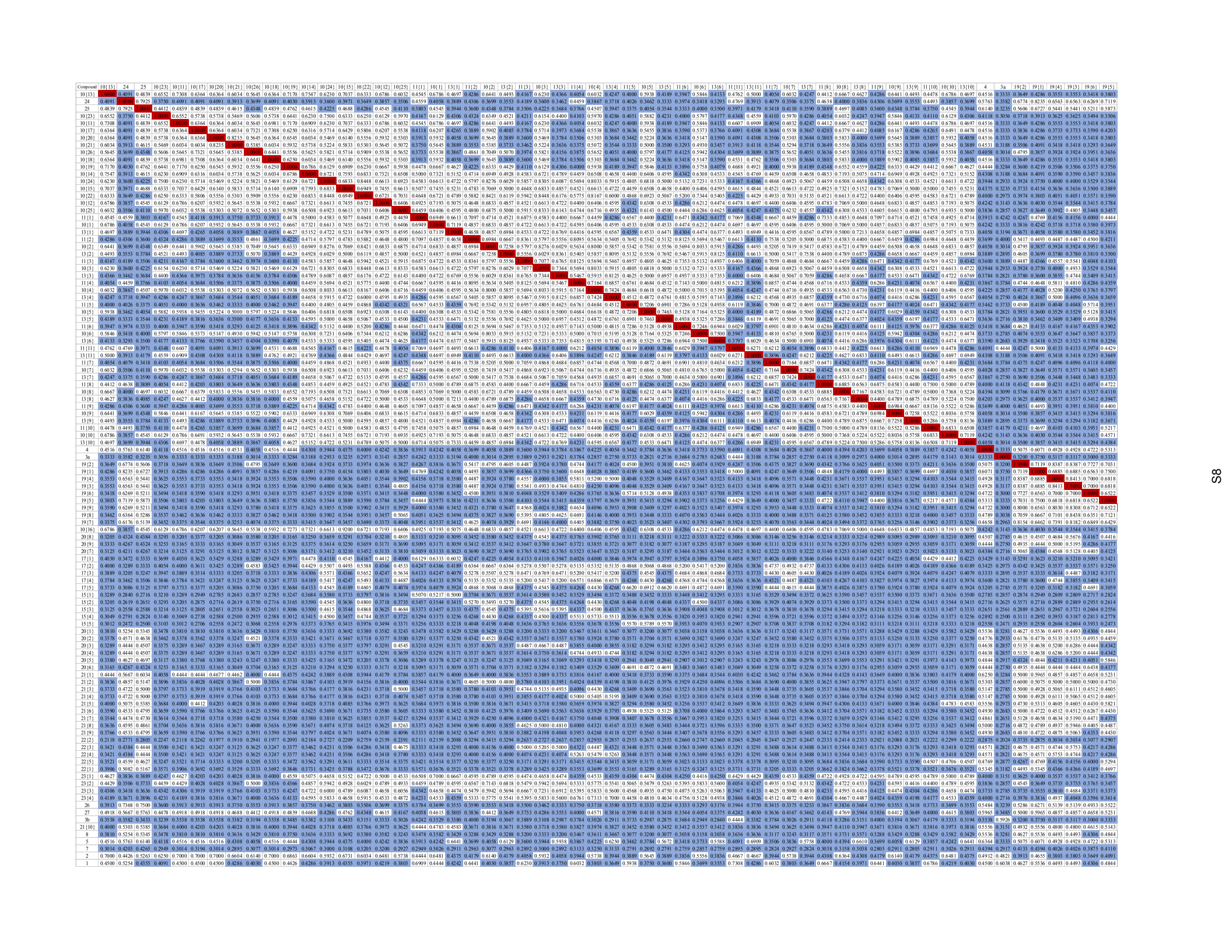
Figure S3. Number of stereocenters in stevioside library vs commercial library sets.

Furthermore, similarity coefficients were generated (Tanimoto, ECFP_4) to determine the structural similarity between the compounds in our libraries. These values are graphed in a matrix format in Chart S1 to allow visualization of the pairwise similarity of the compounds. That is an intersection of a column and a row contains the calculated similarity between the compounds in the row and column. Low scores (blue) indicate a relatively high level of difference between the structures, while high scores (red) indicate very similar (0.700< ratio <1.00) or the identical structure (coefficient = 1.00) when a compound is compared to itself. Low (blue) pairwise similarity is desired in a diverse library. The calculated average similarity between compounds in the library was 0.44. Over half, or 63%, of the complete steviol and isosteviol analog library compounds had similarities below 0.44, represented in Chart S1 as indicated by the blue cells in Chart S1. A detailed analysis is shown in Table S2.

Cmpd	24	25	11{1}	10{1}	13{1}	11{5}	10{5}	13{5}	19{2}	17{2}	15{2}	20{3}	20{5}	21{3}	21{5}	22{3}	22{5}	23{1}	26	27	8	5	7	2	1
24	1.000	0.792	0.456	0.406	0.389	0.403	0.346	0.333	0.677	0.329	0.262	0.444	0.463	0.472	0.507	0.438	0.456	0.384	0.737	0.567	0.525	0.576	0.420	0.443	0.525
25	0.792	1.000	0.380	0.455	0.394	0.338	0.405	0.354	0.561	0.333	0.265	0.451	0.470	0.500	0.538	0.444	0.463	0.389	0.750	0.576	0.534	0.614	0.426	0.526	0.435
11{1}	0.456	0.380	1.000	0.695	0.661	0.657	0.440	0.423	0.427	0.425	0.346	0.321	0.329	0.346	0.368	0.333	0.342	0.651	0.378	0.406	0.348	0.391	0.295	0.444	0.691
10{1}	0.406	0.455	0.695	1.000	0.712	0.453	0.631	0.453	0.382	0.437	0.354	0.329	0.338	0.372	0.397	0.342	0.351	0.700	0.370	0.462	0.358	0.424	0.303	0.648	0.444
13{1}	0.389	0.394	0.661	0.712	1.000	0.436	0.453	0.647	0.367	0.419	0.341	0.317	0.325	0.358	0.382	0.329	0.338	0.667	0.355	0.380	0.343	0.644	0.291	0.438	0.424
11{5}	0.403	0.338	0.657	0.453	0.436	1.000	0.721	0.690	0.450	0.487	0.405	0.318	0.294	0.341	0.329	0.345	0.306	0.430	0.337	0.359	0.308	0.346	0.279	0.389	0.594
10{5}	0.346	0.405	0.440	0.631	0.453	0.721	1.000	0.746	0.395	0.507	0.420	0.329	0.305	0.369	0.358	0.357	0.317	0.447	0.333	0.411	0.320	0.378	0.289	0.565	0.375
13{5}	0.333	0.354	0.423	0.453	0.647	0.690	0.746	1.000	0.381	0.487	0.405	0.318	0.294	0.356	0.345	0.345	0.306	0.430	0.321	0.342	0.308	0.567	0.279	0.389	0.360
19{2}	0.677	0.561	0.427	0.382	0.367	0.450	0.395	0.381	1.000	0.434	0.357	0.514	0.432	0.500	0.473	0.468	0.427	0.363	0.529	0.500	0.463	0.507	0.413	0.391	0.463
17{2}	0.329	0.333	0.425	0.437	0.419	0.487	0.507	0.487	0.434	1.000	0.521	0.453	0.411	0.354	0.325	0.507	0.425	0.413	0.316	0.338	0.583	0.342	0.288	0.368	0.357
15{2}	0.262	0.265	0.346	0.354	0.341	0.405	0.420	0.405	0.357	0.521	1.000	0.281	0.241	0.289	0.261	0.322	0.253	0.337	0.253	0.268	0.250	0.272	0.662	0.289	0.282
20{3}	0.444	0.451	0.321	0.329	0.317	0.318	0.329	0.318	0.514	0.453	0.281	1.000	0.656	0.583	0.434	0.712	0.529	0.313	0.427	0.457	0.581	0.464	0.395	0.352	0.342
20{5}	0.463	0.470	0.329	0.338	0.325	0.294	0.305	0.294	0.432	0.411	0.241	0.656	1.000	0.421	0.537	0.529	0.683	0.321	0.443	0.477	0.643	0.484	0.389	0.364	0.353
21{3}	0.472	0.500	0.346	0.372	0.358	0.341	0.369	0.356	0.500	0.354	0.289	0.583	0.421	1.000	0.682	0.575	0.416	0.461	0.453	0.486	0.449	0.515	0.403	0.400	0.370
21{5}	0.507	0.538	0.368	0.397	0.382	0.329	0.358	0.345	0.473	0.325	0.261	0.434	0.537	0.682	1.000	0.429	0.529	0.493	0.486	0.523	0.484	0.556	0.411	0.431	0.397
22{3}	0.438	0.444	0.333	0.342	0.329	0.345	0.357	0.345	0.468	0.507	0.322	0.712	0.529	0.575	0.429	1.000	0.662	0.325	0.421	0.451	0.571	0.457	0.390	0.347	0.338
22{5}	0.456	0.463	0.342	0.351	0.338	0.306	0.317	0.306	0.427	0.425	0.253	0.529	0.683	0.416	0.529	0.662	1.000	0.333	0.437	0.470	0.632	0.477	0.384	0.358	0.348
23{1}	0.384	0.389	0.651	0.700	0.667	0.430	0.447	0.430	0.363	0.413	0.337	0.313	0.321	0.461	0.493	0.325	0.333	1.000	0.351	0.375	0.338	0.400	0.288	0.431	0.418
26	0.737	0.750	0.378	0.370	0.355	0.337	0.333	0.321	0.529	0.316	0.253	0.427	0.443	0.453	0.486	0.421	0.437	0.351	1.000	0.732	0.500	0.548	0.403	0.444	0.431
27	0.567	0.576	0.406	0.462	0.380	0.359	0.411	0.342	0.500	0.338	0.268	0.457	0.477	0.486	0.523	0.451	0.470	0.375	0.732	1.000	0.544	0.596	0.433	0.564	0.467
8	0.525	0.534	0.348	0.358	0.343	0.308	0.320	0.308	0.463	0.583	0.250	0.581	0.643	0.449	0.484	0.571	0.632	0.338	0.500	0.544	1.000	0.554	0.415	0.414	0.400
5	0.576	0.614	0.391	0.424	0.644	0.346	0.378	0.567	0.507	0.342	0.272	0.464	0.484	0.515	0.556	0.457	0.477	0.400	0.548	0.596	0.554	1.000	0.439	0.491	0.450
7	0.420	0.426	0.295	0.303	0.291	0.279	0.289	0.279	0.413	0.288	0.662	0.395	0.389	0.403	0.411	0.390	0.384	0.288	0.403	0.433	0.415	0.439	1.000	0.324	0.314
2	0.443	0.526	0.444	0.648	0.438	0.389	0.565	0.389	0.391	0.368	0.289	0.352	0.364	0.400	0.431	0.347	0.358	0.431	0.444	0.564	0.414	0.491	0.324	1.000	0.640
1	0.525	0.435	0.691	0.444	0.424	0.594	0.375	0.360	0.463	0.357	0.282	0.342	0.353	0.370	0.397	0.338	0.348	0.418	0.431	0.467	0.400	0.450	0.314	0.640	1.000

Chart S1. A representative chart of the pairwise similarity for the steviol and isosteviol library compounds described herein. Red indicates similarity coefficient of 1.0 (identical) and Blue indicates pairwise structural comparison with similarities less than the average pairwise similarity for the entire library.

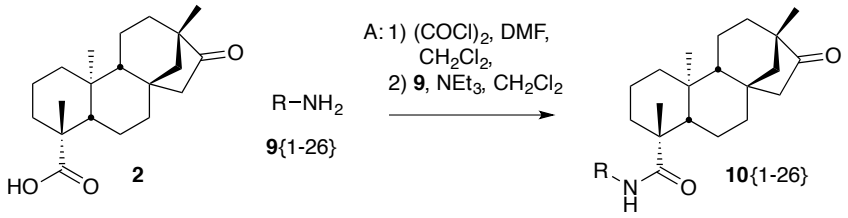
Table S2. Similarity coefficients for Stevioside compound libraries



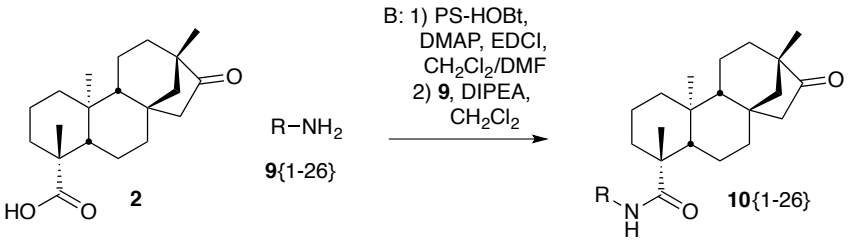
Experimental Details and Compound Characterization.

General Methods. Unless otherwise noted, all reactions were carried out open to air with reagent grade solvents. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light or cerium molybdate stain followed by heating. High-resolution mass spectral data were acquired utilizing the electrospray ionization technique. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature at 400 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 77.16 ppm). The data are reported as follows: chemical shift on the δ scale in ppm, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Solvent abbreviations: tetrahydrofuran (THF), dimethylformamide (DMF), Hex (hexanes), methyl tert.-butyl ether (MTBE). Steviol and steviol methyl ester data were in agreement with previous reports.[1]

Syntheses of compounds **21{1}**, **21{2}**, and **24-27** were reported by us before.[8]

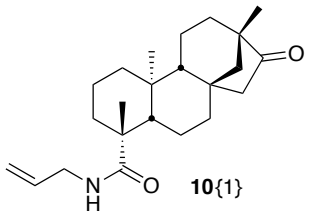


Standard procedure for the solution phase amide bond formation (Scheme 2, A). To an oven-dried reaction flask under nitrogen at 0 °C (ice bath), was added DMF (37 μL, 0.47 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) followed by oxalyl chloride (41 μL, 0.47 mmol, 1.5 equiv). The ice bath was removed and the mixture was allowed to stir at room temperature for 1 h. Then the reaction flask was cooled to 0 °C (ice bath) and isosteviol (**2**, 100 mg, 0.31 mmol) and Et_3N (130 μL, 0.47 mmol, 3 equiv) in CH_2Cl_2 (1.0 mL) were added. After stirring for 5 min, allylamine (**9{1}**, 1 mL, 13.4 mmol) was added and the mixture was stirred for 2 h. (For all reactions 1mL of the amine was added). Then the mixture was loaded onto a 20-mL silica gel plug in a 70-mL column and eluted with dry THF. The solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL), and methylisocyanate polystyrene resin was added. The mixture was shaken for 20 h and was then loaded onto a 20-mL silica gel plug in a 70-mL column and eluted with ethyl acetate (40 mL). The solvent was removed and the residues was purified using column chromatography on silica gel with 10% EtOAc:Hex as the eluent to provide the allyl amide product **10{1}** in 47% yield.



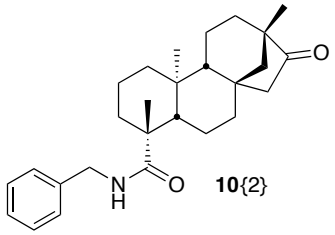
Standard procedure for solid phase amide bond formation (Scheme 2, B). To a flame-dry reaction vial of isosteviol (**2**, 100.0 mg, 0.318 mmol, 1.0 equiv) in CH_2Cl_2/DMF (4:1) was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (15.5 mg, 0.127

mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resin was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of allylamine (**9{1}**, 15.5 μL, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. Column chromatography on silica gel with 20% EtOAc:Hex as the eluent gave amide product **10{1}** in 43 mg (38% yield).



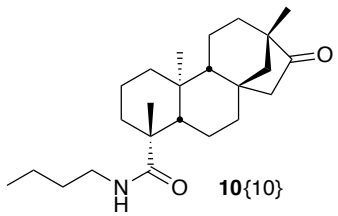
10{1}

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Allyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (10{1}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 – 5.70 (m, 1H), 5.62 (s, 1H), 5.09 (dd, *J* = 23.1, 13.7 Hz, 2H), 3.79 (t, *J* = 5.1 Hz, 2H), 2.58 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.03 - 1.85 (m, 2H), 1.73 (d, *J* = 18.5 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.55 – 1.41 (m, 4H), 1.43 – 1.33 (m, 3H), 1.21 – 1.13 (m, 2H), 1.13 (s, 3H), 1.10 – 1.02 (m, 1H), 0.91 (s, 3H), 0.87 (d, *J* = 4.5 Hz, 1H), 0.71 (s, 3H), 0.66 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.6, 176.4, 134.4, 116.6, 57.5, 57.2, 54.7, 54.2, 48.7, 48.4, 43.7, 41.9, 41.7, 40.2, 39.5, 38.1, 37.3, 30.2, 22.2, 20.3, 19.9, 19.2, 13.6; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{36}NO_2$ 358.2668, found 358; $[\alpha]_D^{23}$ –80.7 (*c* 0.950, $CHCl_3$).



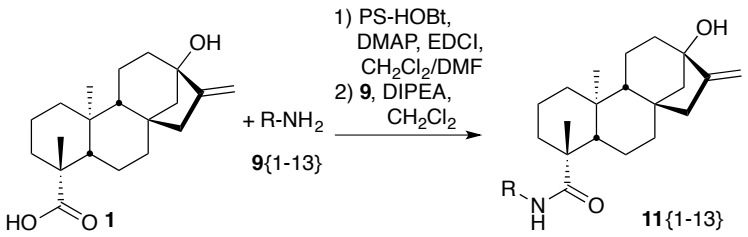
10{2}

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Benzyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (10{2}). Pale yellow solid; mp 68-69 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.25 (m, 5H), 5.86 (t, *J* = 4.9 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 2H), 2.62 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.06 – 1.90 (m, 2H), 1.83 – 1.63 (m, 6H), 1.59 – 1.32 (m, 7H), 1.27 – 1.22 (m, 1H), 1.21 (s, 3H), 1.18 – 1.12 (m, 2H), 0.96 (s, 3H), 0.95 – 0.79 (m, 1H), 0.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.4, 176.4, 138.5, 128.9, 128.7, 128.0, 127.5, 127.5, 57.6, 54.7, 54.3, 48.7, 48.4, 43.7, 41.7, 40.2, 39.5, 38.1, 38.1, 37.3, 30.2, 22.2, 22.2, 20.3, 19.9, 19.2, 13.6; LRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{37}NO_2Na$ 430.2824, found 430.4; $[\alpha]_D^{23}$ –44.0 (*c* 1.00, $CHCl_3$).

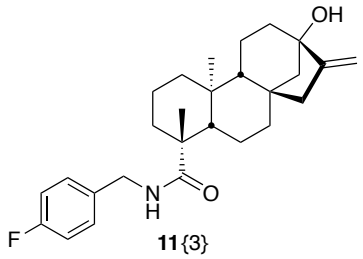


10{10}

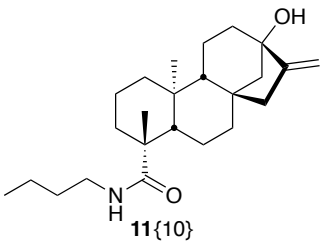
(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Butyl-4,9,11b-trimethyl-8-oxotetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (10{1}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H), 3.21 (dt, *J* = 11.8, 6.7 Hz, 2H), 2.65 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.01 (d, *J* = 14.3 Hz, 1H), 1.95 (d, *J* = 13.3 Hz, 1H), 1.77 (dd, *J* = 19.9, 14.1 Hz, 4H), 1.71 – 1.65 (m, 2H), 1.63 – 1.57 (m, 1H), 1.56 – 1.52 (m, 1H), 1.51 – 1.45 (m, 4H), 1.40 (dd, *J* = 11.8, 3.7 Hz, 1H), 1.37 – 1.30 (m, 3H), 1.25 – 1.18 (m, 2H), 1.17 (s, 3H), 1.16 – 1.09 (m, 2H), 0.97 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 4H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.4, 176.5, 57.6, 54.8, 54.3, 48.7, 48.4, 43.6, 41.8, 40.2, 39.5, 39.2, 38.2, 38.1, 37.3, 31.5, 30.2, 22.3, 20.3, 20.3, 19.9, 19.2, 13.8, 13.5; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –32.2 (*c* 0.500, $CHCl_3$).



Standard procedure for solid-phase bond formation of steviol amide analogs **11{1-13}** (Scheme 3). To a solution of steviol (**1**, 100 mg, 0.318 mmol, 1.00 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.213 mmol, 0.670 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of 4-flurobenzylamine (**9{3}**, 27.5 mg, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica gel with 20% EtOAc:Hex to furnish the amide **11{3}**.

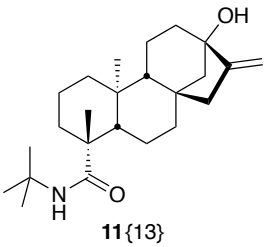


(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-(4-Fluorobenzyl)-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (11{3}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.70 (dd, *J* = 8.5, 5.7 Hz, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 4.82 (d, *J* = 67.5 Hz, 2H), 4.69 (s, 2H), 2.13 – 1.93 (m, 4H), 1.88 – 1.63 (m, 6H), 1.58 – 1.22 (m, 5H), 1.20 – 1.16 (m, 1H), 1.11 (s, 3H), 1.08 – 0.97 (m, 3H), 0.88 (d, *J* = 7.9 Hz, 1H), 0.79 (s, 3H), 0.75 (dd, *J* = 12.7, 3.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 160.6, 156.0, 130.1, 129.6, 129.4, 115.6, 115.4, 103.0, 80.2, 64.2, 57.4, 53.7, 47.4, 46.9, 43.8, 42.9, 41.7, 40.9, 39.4, 38.2, 30.1, 23.0, 22.4, 20.4, 19.3, 15.7; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{37}FNO_2$ 426.2730, found 426; $[\alpha]_D^{23}$ –84.0 (*c* 0.451, $CHCl_3$).



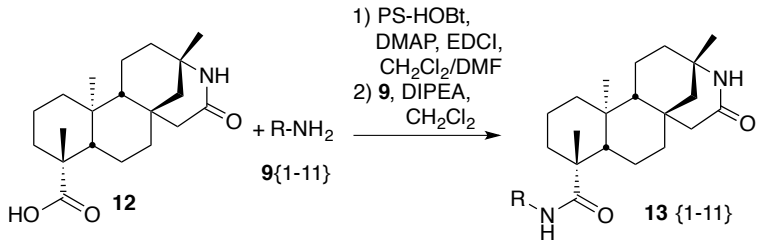
11{10}

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-Butyl-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (11{10). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 5.58 (s, 1H), 4.88 (d, *J* = 68.1 Hz, 2H), 3.20 (dt, *J* = 12.2, 6.8 Hz, 2H), 2.90 (d, *J* = 30.2 Hz, 1H), 2.18 (d, *J* = 17.0 Hz, 1H), 2.14 – 2.09 (m, 1H), 2.07 – 2.00 (m, 2H), 1.89 (dd, *J* = 21.7, 5.2 Hz, 3H), 1.82 – 1.71 (m, 3H), 1.63 – 1.51 (m, 2H), 1.51 – 1.43 (m, 4H), 1.42 – 1.30 (m, 3H), 1.26 (d, *J* = 10.8 Hz, 1H), 1.13 (s, 3H), 1.10 – 0.99 (m, 2H), 0.94 – 0.90 (m, 3H), 0.89 (s, 3H), 0.86 – 0.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 156.1, 102.9, 80.2, 57.3, 53.8, 47.4, 46.9, 43.7, 41.7, 41.6, 41.1, 39.4, 39.3, 39.2, 38.3, 31.5, 30.1, 22.4, 20.5, 20.3, 19.4, 15.6, 13.8; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –77.5 (*c* 1.00, $CHCl_3$).



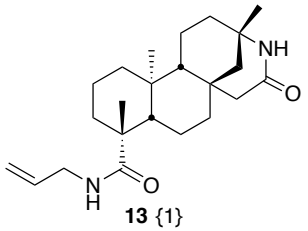
11{13}

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-*N*-(*tert*-Butyl)-9-hydroxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (11{13}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 4.88 (d, *J* = 66.6 Hz, 2H), 2.94 (s, 1H), 2.18 (d, *J* = 19.5 Hz, 1H), 2.10 (d, *J* = 17.2 Hz, 1H), 1.99 (d, *J* = 13.6 Hz, 1H), 1.91 – 1.84 (m, 4H), 1.82 – 1.73 (m, 4H), 1.60 – 1.50 (m, 2H), 1.49 – 1.37 (m, 3H), 1.33 (s, 3H), 1.31 (s, 6H), 1.27 (dd, *J* = 14.7, 3.6 Hz, 1H), 1.12 (s, 3H), 1.08 – 0.98 (m, 2H), 0.95 (s, 3H), 0.82 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.7, 156.1, 102.9, 80.2, 57.2, 53.8, 50.7, 47.4, 46.9, 44.1, 41.7, 41.6, 41.2, 39.5, 39.3, 38.5, 30.2, 28.8, 28.7, 28.7, 22.5, 20.5, 19.3, 15.9; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.2981, found 374.3; $[\alpha]_D^{23}$ –102.1 (*c* 0.750, $CHCl_3$).



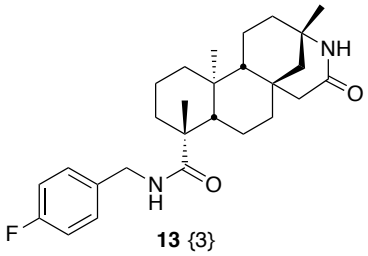
Standard procedure for solid-phase bond formation of isosteviol lactam **13{1-11}** from previously reported **12**[2] (Scheme 3). To a solution of lactam **12** (100 mg, 0.333 mmol, 1.00 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.223 mmol, 0.670 equiv), 4-dimethylaminopyridine (58.0 μL, 0.333 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (155 mg, 1.00 mmol, 3.0 equiv). The reaction mixture was shaken

slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of allylamine (**9{1}**, 29.1 mg, 0.220 mmol, 0.70 equiv) and diisopropylethylamine (58.0 μL, 0.333 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica gel with 20% EtOAc:Hex to furnish the amide **13{1}**.



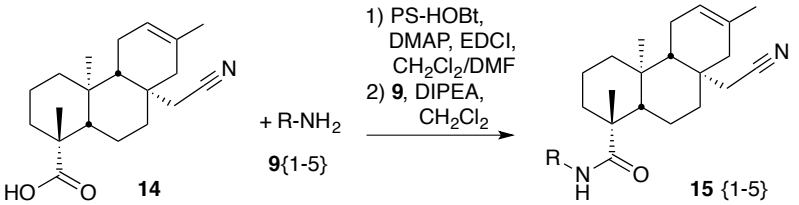
13 {1}

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-Allyl-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide (13{1}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 – 5.80 (m, 1H), 5.66 (s, 1H), 5.22 – 5.13 (m, 2H), 3.92 – 3.79 (m, 2H), 2.92 (d, *J* = 29.2 Hz, 1H), 2.52 (ddd, *J* = 52.5, 16.6, 2.1 Hz, 1H), 2.20 – 1.70 (m, 8H), 1.59 (s, 6H), 1.53 – 1.23 (m, 4H), 1.20 (s, 3H), 1.19 – 1.08 (m, 3H), 0.90 (dd, *J* = 13.6, 3.8 Hz, 1H), 0.80 – 0.71 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 134.5, 131.4, 120.0, 116.8, 57.9, 52.0, 45.9, 43.8, 42.1, 40.3, 39.5, 38.1, 37.6, 35.4, 33.2, 30.2, 23.4, 22.4, 20.5, 20.1, 19.4, 14.0; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{36}O_2N_2Na$ 395.2777, found 395.2680; $[\alpha]_D^{23}$ –10.3 (*c* 1.20, $CHCl_3$).

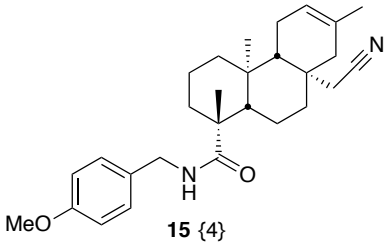


13 {3}

(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-(4-Fluorobenzyl)-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide (13{3}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (m, 1H), 7.25 – 7.22 (m, 1H), 7.03 – 6.97 (m, 2H), 6.51 (t, *J* = 6.0 Hz, 1H), 4.56 (dd, *J* = 15.0, 6.5 Hz, 1H), 4.49 – 4.33 (m, 2H), 3.10 (d, *J* = 17.6 Hz, 1H), 2.40 (d, *J* = 12.1 Hz, 1H), 2.31 (d, *J* = 17.8 Hz, 1H), 2.17 (d, *J* = 13.4 Hz, 1H), 1.92 – 1.83 (m, 3H), 1.78 (d, *J* = 13.2 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.64 – 1.56 (m, 2H), 1.51 – 1.42 (m, 1H), 1.39 (s, 3H), 1.36 – 1.28 (m, 2H), 1.25 (s, 3H), 1.22 – 1.15 (m, 1H), 1.13 –1.04 (m, 2H), 1.02 – 0.93 (m, 2H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 176.1, 171.0, 161.1, 129.5, 129.5, 115.7, 115.5, 77.3, 77.0, 76.7, 59.5, 57.3, 56.6, 51.2, 43.7, 43.6, 42.8, 42.0, 39.8, 38.0, 37.7, 37.5, 35.0, 28.8, 26.1, 19.5, 19.1, 18.9, 13.8; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{38}FN_2O_2$ 441.2339, found 441; $[\alpha]_D^{23}$ 19.2 (*c* 1.00, $CHCl_3$).

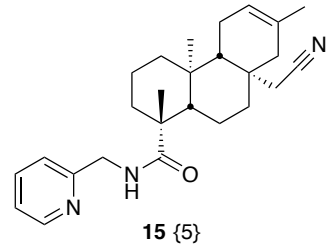


Standard procedure for amide bond formation of **15**{1-5} from **14**. To a flame-dried reaction flask of the nitrile acid **14** (1.0 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of amine **9** (0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica gel with 20% EtOAc:Hex to furnish the amide **15**.



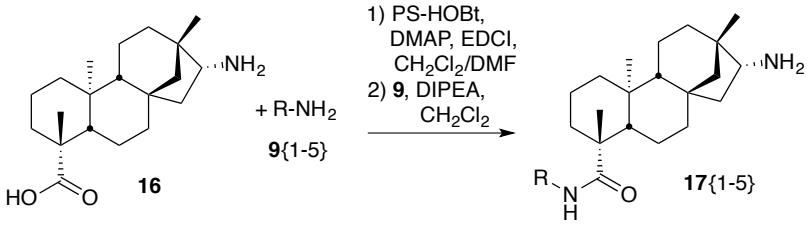
15 {4}

(1*R*,4a*S*,4b*R*,8a*R*,10a*S*)-*N*-Benzyl-8a-(cyanomethyl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxamide (15{4}). Pale yellow crystals; mp 63 – 64 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.69 (s, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 2.98 (dd, *J* = 19.0, 2.5 Hz, 1H), 2.17 (d, *J* = 13.1 Hz, 1H), 2.01 (s, 3H), 2.05 – 1.96 (m, 1H), 1.90 – 1.66 (m, 4H), 1.61 (d, *J* = 13.6 Hz, 2H), 1.51 – 1.38 (m, 4H), 1.28 (s, 1H), 1.23 (s, 3H), 1.09 (s, 3H), 1.01 (td, *J* = 13.5, 3.8 Hz, 1H), 0.93 – 0.87 (m, 1H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 170.6, 170.0, 159.2, 130.4, 129.4, 129.4, 114.2, 114.2, 77.5, 77.2, 76.8, 57.3, 56.4, 55.5, 55.1, 44.0, 43.7, 43.4, 40.8, 40.1, 39.6, 38.4, 37.2, 29.2, 23.4, 22.3, 21.7, 20.6, 19.1, 13.6; LRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{38}N_2O_2$ 434.2933, found 457.3; $[\alpha]_D^{23}$ 3.60 (*c* 0.600, $CHCl_3$).

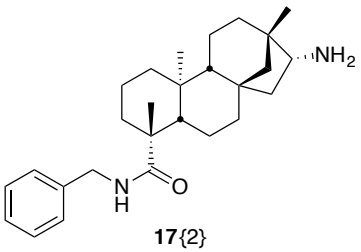


15 {5}

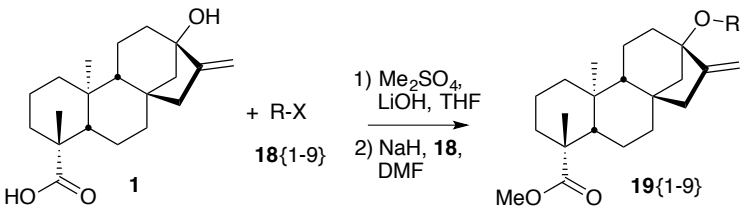
(1*R*,4a*S*,4b*R*,10a*S*)-8a-(Cyanomethyl)-1,4a,7-trimethyl-*N*-(pyridin-2-ylmethyl)-1,2,3,4,4a,4b,5,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxamide (15{5}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 4.5 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.11 (s, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 4.53 (tdd, *J* = 16.5, 11.7, 4.7 Hz, 2H), 2.78 – 2.53 (m, 1H), 2.49 – 2.29 (m, 1H), 2.26 – 2.12 (m, 2H), 2.12 – 1.92 (m, 5H), 1.87 – 1.77 (m, 1H), 1.75 – 1.69 (m, 1H), 1.66 (s, 3H), 1.58 – 1.49 (m, 1H), 1.35 – 1.27 (m, 1H), 1.23 (s, 3H), 1.22 – 1.12 (m, 3H), 0.92 (dt, *J* = 16.0, 8.2 Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ176.6, 156.4, 149.0, 136.7, 131.2, 122.4, 122.3, 119.9, 119.0, 57.7, 51.7, 45.7, 44.4, 43.7, 40.2, 39.4, 37.9, 37.4, 35.3, 29.9, 23.3, 22.2, 20.2, 19.9, 19.1, 13.5; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{35}N_3ONa$ 428.2780, found 428.3; $[\alpha]_D^{23}$ –34.0 (*c* 1.00, $CHCl_3$).



Standard procedure for the amide bond formation for amine **17**{1-5} from previously reported **16**.[9] To a flame-dried reaction flask of the amine **16** (1.0 equiv) in CH_2Cl_2/DMF (4:1) in a flame-dry reaction vial, was added PS-hydroxybenzotriazole (PS-HOBt, 1.00 mmol/g, 0.67 equiv), 4-dimethylaminopyridine (55.4 μL, 0.318 mmol, 0.40 equiv), and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (148 mg, 0.954 mmol, 3.0 equiv). The reaction mixture was shaken slowly for 24 h and then filtered. The resins were washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice to remove excess acid. Then, the resin was added to a solution of amine **9** (0.220 mmol, 0.70 equiv) and diisopropylethylamine (55.4 μL, 0.318 mmol, 1.0 equiv) in CH_2Cl_2 and shaken slowly for another 24 h. The mixture was filtered again was washed with MeOH (5 mL) and CH_2Cl_2 (5 mL) thrice before the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica gel with 5% MeOH: CH_2Cl_2 to furnish the amide **17**.

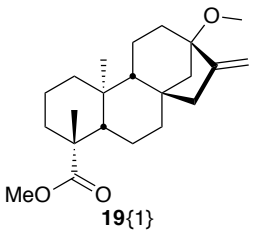


(4*R*,4a*S*,6a*R*,8*R*,9*S*,11a*R*,11b*S*)-8-Amino-*N*-benzyl-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxamide (17{2}). Oil;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.83 (m, 1H), 7.36 (d, *J* = 6.8 Hz, 2H), 7.34 - 7.30 (m, 3H), 4.53 (d, *J* = 6.2 Hz, 2H), 2.18 (d, *J* = 13.9 Hz, 1H), 1.94 – 1.78 (m, 4H), 1.76 - 1.71 (m, 3H), 1.69 – 1.58 (m, 3H), 1.49 – 1.41 (m, 3H), 1.40 – 1.33 (m, 2H), 1.30 – 1.26 (m, 1H), 1.25 (s, 3H), 1.17 – 1.12 (m, 1H), 1.11 – 1.01 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 1H), 0.93 (s, 3H), 0.92 – 0.85 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.3, 159.9, 136.9, 128.8, 128.8, 127.9, 127.9, 57.6, 56.9, 56.0, 55.6, 43.8, 43.6, 42.6, 42.0, 41.3, 40.5, 39.9, 38.2, 37.8, 33.9, 29.0, 24.8, 21.6, 20.7, 18.8, 13.5; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{40}N_2O$ 408.3141, found 409; $[\alpha]_D^{23}$ –5.25 (*c* 0.750, $CHCl_3$).



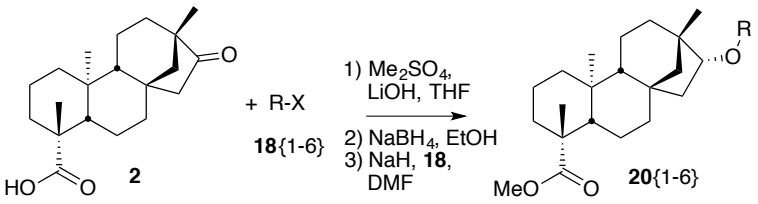
Steviol Methyl Ester.[3] To a solution of steviol (**1**, 10 g, 32 mmol) in THF (50 mL) in a 500-mL round-bottomed flask at room temperature was added $LiOH•H_2O$ (1.5 g, 34 mmol). The reaction stirred at room temperature for 1 h under nitrogen, then Me_2SO_4 (3.3 mL, 35 mmol) was added slowly, and the reaction vessel was fitted with a reflux condenser. The reaction was refluxed for 18 h at 80 ºC. Once the reaction cooled to room temperature, the off-white precipitate was collected via filtration to furnish steviol methyl

ester (7.6 g, 73%) as off-white crystals. mp 117-118 °C (Lit 113-115 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (d, J = 64.0 Hz, 2H), 3.66 (s, 3H), 2.28 – 2.04 (m, 4H), 1.93 – 1.73 (m, 7H), 1.62 – 1.40 (m, 5H), 1.33 – 1.26 (m, 1H), 1.19 (s, 3H), 1.10 – 0.93 (m, 3H), 0.85 (s, 3H), 0.82 – 0.75 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 156.0, 102.9, 80.3, 56.9, 53.8, 51.2, 47.4, 46.9, 43.8, 41.6, 41.3, 40.7, 39.4, 39.2, 38.0, 28.7, 21.9, 20.4, 19.1, 15.3. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{32}O_3Na$ 355.2249, found 355.2080; $[\alpha]_D^{23}$ –191.3 (*c* 1.00, $CHCl_3$).



19{1}

Methyl (4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-9-Methoxy-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (19{1}). To a solution of steviol methyl ester (100 mg, 0.318 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dry reaction vial was added slowly via cannula a solution of sodium hydride (38.3 mg in 60% dispersion in oil, 0.954 mmol, 3.0 equiv) in dry DMF (5 mL). Then, methyl iodide (90.3 mg, 0.636 mmol, 2.0 equiv) was added to the reaction flask and the mixture was allowed to stir for 2 h at ambient temperature. The reaction was quenched with MTBE and the organic phase was washed successively with water. The aqueous phase was extracted with MTBE and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel with 20% EtOAc:Hex yielded the product **19**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (d, *J* = 6.1 Hz, 2H), 3.64 (s, 3H), 3.22 (s, 3H), 2.18 (d, *J* = 13.2 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.89 – 1.80 (m, 4H), 1.79 – 1.71 (m, 3H), 1.69 – 1.58 (m, 1H), 1.57 – 1.49 (m, 2H), 1.48 – 1.40 (m, 3H), 1.17 (s, 3H), 1.07 – 0.94 (m, 3H), 0.82 (s, 3H), 0.85 – 0.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 151.0, 103.7, 85.2, 57.0, 54.0, 51.2, 50.1, 48.1, 43.8, 41.7, 41.5, 40.7, 40.0, 39.3, 38.8, 38.0, 28.7, 21.9, 20.2, 19.1, 15.3, LRMS (ES) (*m*/*z*): $[M+CH_2O_2]^+$ calcd for $C_{22}H_{34}O_3$ 390.2508, found 390.3; $[\alpha]_D^{23}$ –93.5 (*c* 0.800, $CHCl_3$).

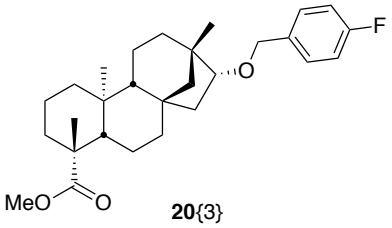


Isosteviol methyl ester.[8] To a flame-dried 500 mL round-bottomed flask was added isosteviol (**2**, 20 g, 63 mmol) and dry THF (120 mL). Upon dissolution, $LiOH•H_2O$ (2.9 g, 68 mmol) was added and the reaction stirred for 1 h at room temperature under an atmosphere of nitrogen. Me_2SO_4 (6.5 mL, 69 mmol) was slowly added, then a reflux condenser was fitted to the flask and the temperature was raised to 80 °C for 18 h. The colorless precipitate was then recovered through filtration. The cake was washed repeatedly with Et_2O and then concentrated *in vacuo* to furnish isosteviol methyl ester (18.3 g, 88%). The reaction was quenched with 10% NaOH and then washed with brine and dried over $MgSO_4$. R_f = 0.3 (Hex:EtOAc 9:1); white crystals; mp 200-202 ºC (Lit 202-203 ºC)[1]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.62 (dd, *J* = 18.6, 3.8 Hz, 1H), 2.18 (d, *J* = 13.3 Hz, 1H), 1.89 (dd, *J* = 13.6, 2.9 Hz, 1H), 1.74-1.85 (m, 2H), 1.57-1.74 (m, 5H), 1.52 (ddd, *J* = 17.8, 12.5, 3.3 Hz, 2H), 1.33-1.45 (m, 3H), 1.19-1.30 (m, 2H), 1.19 (s, 3H), 1.10-1.16 (m, 1H), 0.99-1.06 (m, 1H), 0.97 (s, 3H), 0.92 (dd, *J* = 13.2, 4.2 Hz, 1H), 0.68 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 222.4, 177.8, 57.0, 54.7, 54.3, 51.2, 48.7, 48.5, 48.4, 43.8, 41.5, 39.8, 39.4, 37.9, 37.3, 28.8, 21.7, 20.3, 19.9, 18.9, 13.2; IR (film) 2952, 1744, 1720, 1452, 1240, 1175, 1153 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{32}O_3Na$ 355.2244; found 355.2234; $[\alpha]_D^{23}$–82.2 (*c* 1.00, $CHCl_3$); reported $[\alpha]_D^{25}$–69.0 (*c* 1.02, $CHCl_3$).[8]

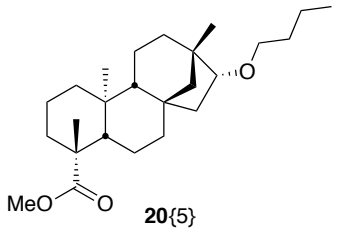
Reduction of isosteviol methyl ester.[10] To a solution of the isosteviol methyl ester (1.00 g, 3.00 mmol) in MeOH (25 mL) at 0 °C (ice bath), was slowly added $NaBH_4$ (134 mg, 3.55 mmol). The reaction mixture was stirred for 1 h at 0 °C (ice bath), and then the solvent was evaporated under reduced pressure, followed by dilution with water and extraction with MTBE. Evaporation of the solvent and purification of the product on a silica gel column using 10% EtOAc:Hex gave the hydroxyl methyl ester (450 mg, 45%) as a white crystals. Mp 169-171 ºC (Lit 163-166 ºC)[11]; ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (dd, J = 10.6, 4.6 Hz, 1H), 3.42 (s, 3H), 1.96 (d, J = 13.4 Hz, 1H), 1.73 (s, 1H), 1.68 – 1.47 (m, 6H), 1.45 – 1.27 (m, 4H), 1.24 – 0.97 (m, 4H), 0.96 (s, 3H), 0.86 – 0.75 (m, 4H), 0.70 (s, 3H), 0.69 – 0.61 (m, 1H), 0.52 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 80.4, 57.1, 55.8, 55.2, 51.1, 43.7, 42.8, 42.0, 42.0, 41.7, 39.9, 38.0, 38.0, 33.7, 28.9, 24.9, 21.7, 20.4, 18.9, 13.1. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{34}O_3Na$ 357.2406, found 357.2398; $[\alpha]_D^{23}$ –57.1 (*c* 0.833, $CHCl_3$).

Standard procedure for the synthesis of **20**{1-6}. To a solution of the above hydroxyl methyl ester (100 mg, 0.345 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dry reaction vial was added slowly via cannula a solution of sodium hydride (38.3 mg in 60% dispersion in oil, 0.954 mmol, 3.0 equiv) in dry DMF (5 mL). Then, methyl iodide (90.3 mg, 0.636 mmol, 2.0 equiv) was added to the reaction flask and the mixture was allowed to stir for 2 h at ambient temperature. The reaction was quenched with MTBE and the organic phase was washed successively with water. The aqueous phase was extracted with MTBE and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel with 20% EtOAc:Hex yielded the product **20**.



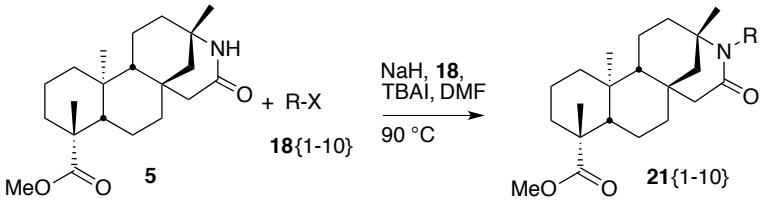
20{3}

Methyl (4*R*,4a*S*,6a*R*,8*S*,9*S*,11a*R*,11b*S*)-8-((4-Fluorobenzyl)oxy)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (20{3}). White crystals; mp 151-152 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.45 (dd, 2H), 3.63 (s, 3H), 3.54 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.17 (d, *J* = 13.3 Hz, 1H), 1.96 – 1.79 (m, 4H), 1.76 – 1.62 (m, 3H), 1.59 – 1.53 (m, 2H), 1.50 – 1.36 (m, 3H), 1.33 – 1.24 (m, 2H), 1.17 (s, 3H), 1.06 – 0.96 (m, 4H), 0.93 (s, 3H), 0.91 – 0.83 (m, 1H), 0.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3, 135.3, 129.0, 128.9, 115.9, 115.2, 115.0, 87.0, 71.3, 57.3, 56.0, 55.5, 51.3, 43.9, 42.4, 42.2, 42.0, 40.3, 40.0, 38.2, 38.1, 34.5, 29.0, 25.6, 21.9, 20.6, 19.1, 13.3; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{39}O_3FNa$ 465.2883, found 465.2795; $[\alpha]_D^{23}$–103.7 (*c* 0.655, $CHCl_3$).

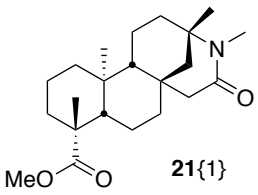


20{5}

Methyl (4R,4aS,6aR,8R,9S,11aR,11bS)-8-Butoxy-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (20{5}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.53 – 3.43 (m, 1H), 3.43 – 3.31 (m, 2H), 2.17 (d, *J* = 13.0 Hz, 1H), 1.89 – 1.84 (m, 2H), 1.83 – 1.77 (m, 3H), 1.72 – 1.66 (m, 2H), 1.64 – 1.56 (m, 3H), 1.51 (dd, *J* = 12.2, 6.1 Hz, 3H), 1.44 – 1.37 (m, 4H), 1.32 – 1.24 (m, 2H), 1.21 (d, *J* = 4.7 Hz, 1H), 1.18 (s, 3H), 1.12 – 1.03 (m, 2H), 1.02 – 0.97 (m, 2H), 0.94 (s, 3H), 0.92 – 0.83 (m, 2H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 87.3, 69.9, 57.3, 56.0, 55.5, 51.1, 43.8, 42.2, 42.0, 40.5, 39.9, 38.1, 38.0, 34.4, 32.3, 28.9, 25.6, 21.8, 21.7, 20.4, 19.5, 19.0, 14.0, 13.1; HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{42}O_3Na$ 413.3134, found 413.2998; $[\alpha]_D^{23}$ –42.8 (*c* 0.850, $CHCl_3$).



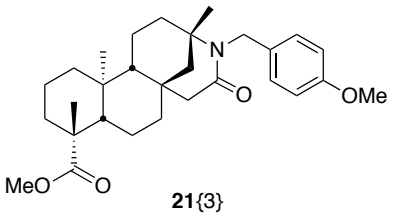
Standard procedure for *N*-alkylation of known lactam **5** to form **21(1-10}**.[8] To a solution of the lactam methyl ester **5** (100 mg, 0.347 mmol, 1.0 equiv) in DMF (5 mL) in a flame-dried reaction flask, was added sodium hydride (3.0 equiv, pre-washed with hexanes), alkyl halide **18** (5.0 equiv) and a catalytic amount of tetrabutylammonium iodide (TBAI, 10 mol%). The reaction flask was heated to 90 °C, stirred overnight and then the reaction was carefully quenched with water (2 mL). The organic layer was then washed with brine and the aqueous layers were re-extracted with Et_2O (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the Et_2O was removed under reduced pressure, while a centrifugal evaporator was used to remove the DMF to furnish alkylated lactam methyl ester **21**. Column chromatography on silica gel with 5% MeOH:CH_2Cl_2 gave the substituted-lactam products.



21{1}

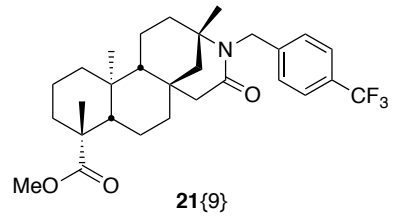
(3*S*,8a*S*,9*R*,12a*S*,12b*R*)-Methyl 3,4,9,12a-Tetramethyl-5-oxotetradecahydro-1*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (21{1}). Yellow solid; mp 168-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3H), 2.98 (dd, *J* = 18.3, 2.9 Hz, 1H), 2.84 (s, 3H), 2.16 (d, *J* = 13.3 Hz, 1 H), 2.04 (d, *J* = 18.3 Hz, 1H), 1.95 – 1.22 (m, 2H), 1.83 – 1.66 (m, 3H), 1.65 – 1.54 (m, 2H), 1.51 (dt, *J* = 12.9, 3.2, 3.2 Hz, 1H), 1.48 – 1.37 (m, 1H), 1.30 (dd, *J* = 12.8, 2.9 Hz, 1H), 1.25 (s, 3H), 1.21 (d, *J* = 13.0, 3.8 Hz, 1H), 1.16 (s, 3H), 1.16 – 0.93 (m, 4H), 0.92 – 0.78 (m, 2H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 171.9, 57.4, 56.8, 55.3, 51.1, 51.0, 44.3, 43.7, 41.0, 39.9, 38.0, 37.8, 35.7, 33.9, 28.5,

27.4, 26.8, 19.7, 18.8, 18.7, 13.5; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{36}NO_3$ 362.2695; found 362.2677; $[\alpha]_D^{23}$ 18.9 (*c* 0.800, $CHCl_3$).



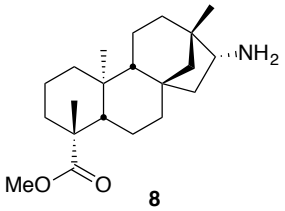
21{3}

Methyl (3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-4-(4-Methoxybenzyl)-3,9,12a-trimethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (21{3}). Pale yellow solid; mp 151-152 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.07 (dd, *J* = 18.4, 2.7 Hz, 1H), 2.16 (d, *J* = 18.2 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.81 – 1.72 (m, 4H), 1.67 (dd, *J* = 13.0, 2.8 Hz, 1H), 1.54 (dd, *J* = 12.9, 3.1 Hz, 2H), 1.48 – 1.39 (m, 1H), 1.31 – 1.19 (m, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.12 – 0.95 (m, 3H), 0.90 – 0.79 (m, 2H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 177.8, 172.3, 158.3, 132.1, 128.3 (2C), 113.7 (2C), 57.5, 56.9, 56.4, 55.2, 51.7, 51.2, 44.3, 44.0, 43.8, 41.2, 40.0, 38.0, 37.8, 37.1, 34.1, 28.6, 28.1, 19.8, 18.9, 18.6, 13.7; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{29}H_{42}NO_4$ 468.3036, found 468.3; $[\alpha]_D^{23}$ –15.6 (*c* 1.00, $CHCl_3$).



21{9}

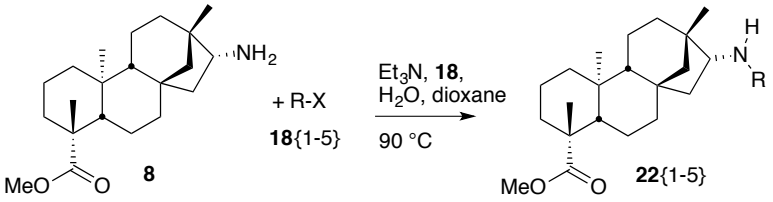
Methyl (3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-3,9,12a-Trimethyl-5-oxo-4-(4-(trifluoromethyl)benzyl)tetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxylate (21{9}). Lightly yellow solid; mp 151-152 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.08 (d, *J* = 16.2 Hz, 1H), 4.15 (d, *J* = 16.1 Hz, 1H), 3.64 (s, 3H), 3.09 (dd, *J* = 18.2, 2.5 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.91 – 1.75 (m, 5H), 1.71 (dd, *J* = 13.1, 2.5 Hz, 1H), 1.64 – 1.55 (m, 2H), 1.45 (d, *J* = 13.7 Hz, 1H), 1.36 – 1.29 (m, 1H), 1.27 – 1.20 (m, 2H), 1.18 (s, 3H), 1.17 – 1.11 (m, 1H), 1.10 (s, 3H), 1.08 – 0.96 (m, 2H), 0.94 – 0.84 (m, 2H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 172.7, 144.0, 127.1, 127.1, 127.1, 125.4, 125.3, 125.3, 57.4, 56.8, 56.6, 51.5, 51.2, 44.5, 44.2, 43.8, 41.1, 40.0, 38.0, 37.8, 36.9, 34.1, 28.6, 28.0, 19.7, 18.9, 18.6, 13.7; LRMS (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{29}H_{38}F_3NO_3$ 505.2814, found 506.4; $[\alpha]_D^{23}$ –36.6 (*c* 0.905, $CHCl_3$).



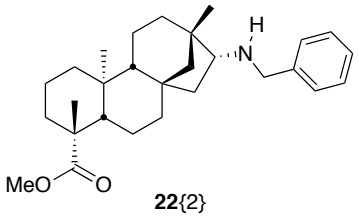
8

Methyl (4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-8-Amino-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta [*a*]naphthalene-4-carboxylate (8).[12] To a solution of methyl

(4*R*,4a*S*,6a*R*,9*S*,11a*R*,11b*S*)-8-(hydroxyimino)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate[1] (348 mg, 1.00 mmol, 1.0 equiv) in MeOH, cooled to 0 °C (ice bath), was added sodium borohydride (189 mg, 5.0 equiv) then molybdenum (VI) oxide (216 mg, 1.5 equiv). The reaction was stirred at room temperature overnight. The next day the reaction was filtered, and then the solvent was evaporated. The resulting residue was treated with aqueous KOH (20%) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and then concentrated *in vacuo*. Column chromatography on silica gel with 5% MeOH/ CH_2Cl_2 provided amine **8** in 20% yield as an off-white solid. mp: 255-258 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.12 (dd, *J* = 10.6, 6.7 Hz, 1H), 2.13 (d, *J* = 13.2 Hz, 1H), 1.86 – 1.49 (m, 10H), 1.42 – 1.25 (m, 4H), 1.26 – 1.21 (m, 1H), 1.14 (s, 3H), 1.11 – 1.01 (m, 2H), 1.00 (s, 3H), 0.99 – 0.92 (m, 2H), 0.88 – 0.78 (m, 2H), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 77.0, 76.7, 59.6, 57.0, 56.0, 55.6, 51.1, 43.7, 42.4, 41.2, 41.1, 39.7, 39.0, 38.0, 38.0, 33.0, 28.8, 24.6, 21.6, 20.2, 18.8, 12.9; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{36}NO_2$ 334.2688, found 334.2747; $[\alpha]_D^{23}$ –153.1 (*c* 1.00, $CHCl_3$).

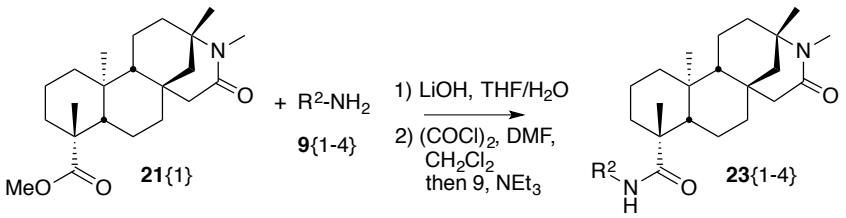


Standard procedure for *N*-alkylation of amine **8** for the synthesis of **22{1-5}**. To a flame-dried reaction flask of the amine **8** (100 mg, 0.333 mmol, 1.0 equiv) and triethylamine (1.5 equiv) in a 1,4-dioxane-water mixed solvent (1:1, 6 mL), the alkyl halide (**18**, 1.0 equiv) was added. The reaction flask was heated to 90 °C and allowed to stir for one day. The reaction mixture was quenched with EtOAc and the organic layer was washed with saturated aqueous NH_4Cl. The organic layer was then washed with brine and the aqueous layers were extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude alkylated amine product **22**. Purification was done by column chromatography on silica gel with 5% MeOH: CH_2Cl_2.

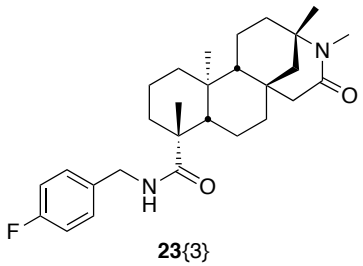


22{2}

Methyl (4*R*,4a*S*,6a*R*,8*R*,9*S*,11a*R*,11b*S*)-8-(Benzylamino)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (22{2}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 4H), 7.29 – 7.25 (m, 1H), 3.80 (q, *J* = 46.0, 13.4, 12.4 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 1H), 2.77 (dd, *J* = 10.6, 5.4 Hz, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 1.86 – 1.80 (m, 2H), 1.74 (d, *J* = 13.5 Hz, 3H), 1.64 – 1.59 (m, 3H), 1.57 – 1.51 (m, 2H), 1.46 – 1.40 (m, 1H), 1.38 – 1.31 (m, 2H), 1.19 (s, 3H), 1.10 – 1.04 (m, 2H), 1.03 – 0.98 (m, 3H), 0.92 (s, 3H), 0.90 – 0.86 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 141.4, 128.3, 128.2, 128.0, 128.0, 126.7, 66.2, 57.3, 57.0, 55.9, 53.2, 51.1, 43.8, 42.4, 41.8, 41.6, 41.2, 40.0, 38.1, 38.1, 34.3, 28.9, 25.6, 21.8, 20.7, 19.0, 13.3; HRMS (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{28}H_{41}NO_2$ 423.3137, found 424.3; $[\alpha]_D^{23}$ –58.5 (*c* 1.00, $CHCl_3$).



Standard procedure for amide bond formation lactam ester **23**{1-4} from **21**{1}. To a solution of *N*-methyl lactam ester **21**{1} (1.00 g, 2.77 mmol) in THF/H_2O (1:1, 10 mL) in a round-bottom flask was added LiOH (1M aq. 5 mL) at room temperature. The reaction was heated to reflux and stirred overnight. Then, it was cooled to room temperature and quenched with HCl (1M aq.) to pH 4. The resultant mixture was extracted with EtOAc and the combined organic layers were washed with brined and dried over $MgSO_4$. The acid was carried on without further purification. To an oven-dried reaction flask under nitrogen at 0 °C (ice bath), was added DMF (37 µL, 0.47 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) followed by oxalyl chloride (41 µL, 0.47 mmol, 1.5 equiv). The ice bath was removed and the mixture was allowed to stir at room temperature for 1 h. Then the reaction flask was cooled to 0 °C (ice bath) and N-methyl lactam acid (108 mg, 0.31 mmol) and Et_3N (130 µL, 0.47 mmol, 3 equiv) in CH_2Cl_2 (1.0 mL) were added. After stirring for 5 min, amine **9** (1 mL) was added and the mixture was stirred for 2 h. Then, the solvent was removed and the reaction was purified using column chromatography on silica gel with 10%->20% EtOAc:Hex as the eluent to provide the substituted lactam amide product **23**.



(3*S*,6a*R*,8a*S*,9*R*,12a*S*,12b*R*)-*N*-(4-Fluorobenzyl)-3,4,9,12a-tetramethyl-5-oxotetradecahydro-2*H*-3,6a-methanonaphtho[2,1-*d*]azocine-9-carboxamide(23{3}). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 8.3, 5.4 Hz, 2H), 7.00 (t, *J* = 8.5 Hz, 2H), 5.20 (d, *J* = 15.4 Hz, 1H), 4.67 (s, 1H), 4.44 (d, *J* = 15.4 Hz, 1H), 3.63 (s, 3H), 2.15 (dd, *J* = 23.4, 13.3 Hz, 2H), 1.87 – 1.72 (m, 2H), 1.70 (s, 3H), 1.67 – 1.56 (m, 3H), 1.55 – 1.44 (m, 2H), 1.42 – 1.32 (m, 3H), 1.30 (s, 3H), 1.28 – 1.18 (m, 2H), 1.15 (s, 3H), 1.11 – 0.89 (m, 4H), 0.87 (dd, *J* = 13.0, 3.8 Hz, 1H), 0.78 (td, *J* = 13.4, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 177.4, 133.8, 129.1, 129.0, 116.1, 115.9, 96.4, 58.7, 56.9, 56.2, 51.3, 51.2, 43.7, 43.1, 39.5, 39.3, 37.7, 37.3, 37.2, 35.4, 28.9, 25.2, 19.2, 19.2, 19.0, 14.2, 12.9; LRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{40}FN_2O_2$ 455.2996, found 455; $[\alpha]_D^{23}$ –74.3 (*c* 0.450, $CHCl_3$).

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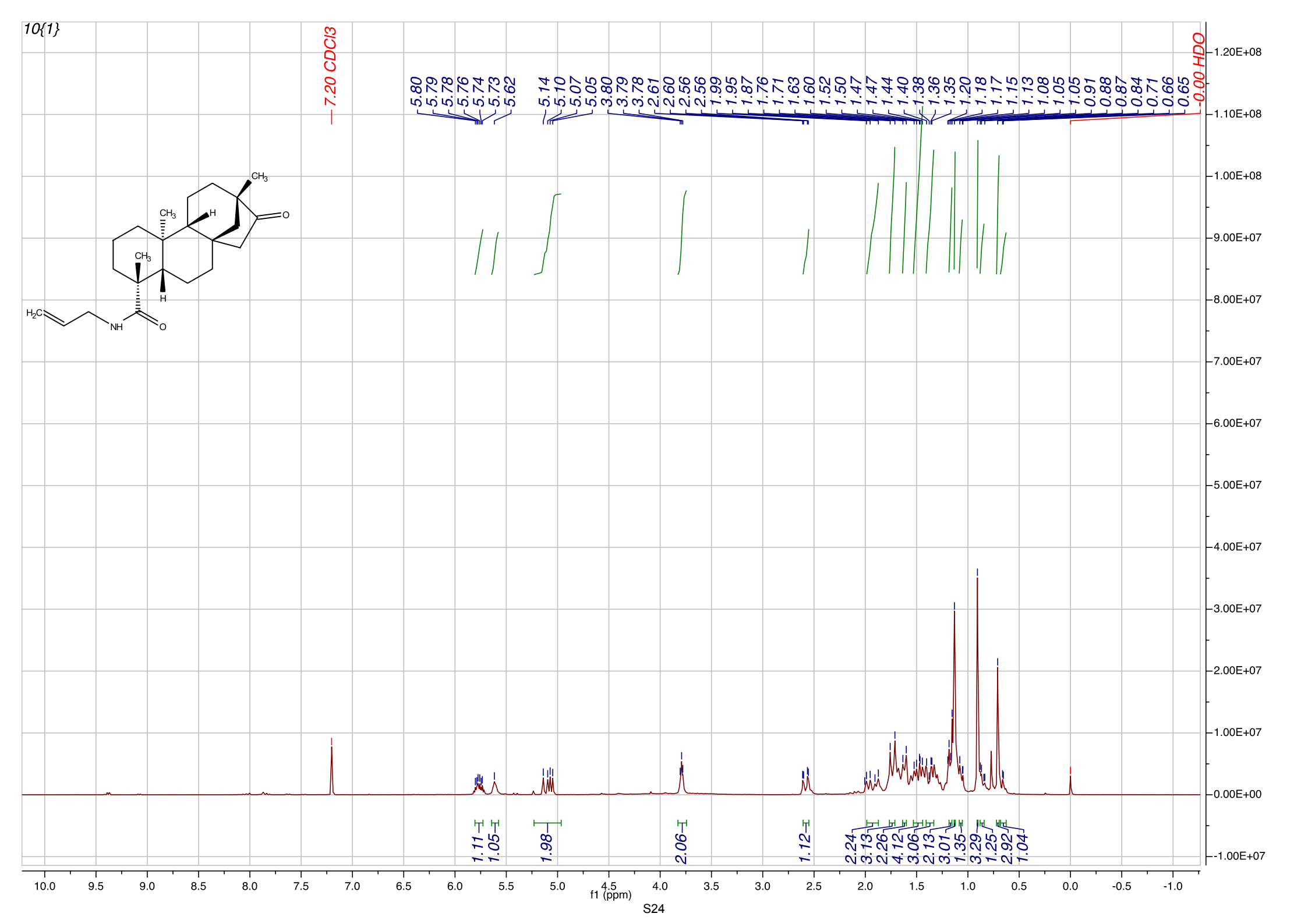
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0.00 HDO
5.80 5.79 5.78 5.76 5.74 5.73 5.62
5.14 5.10 5.07 5.05
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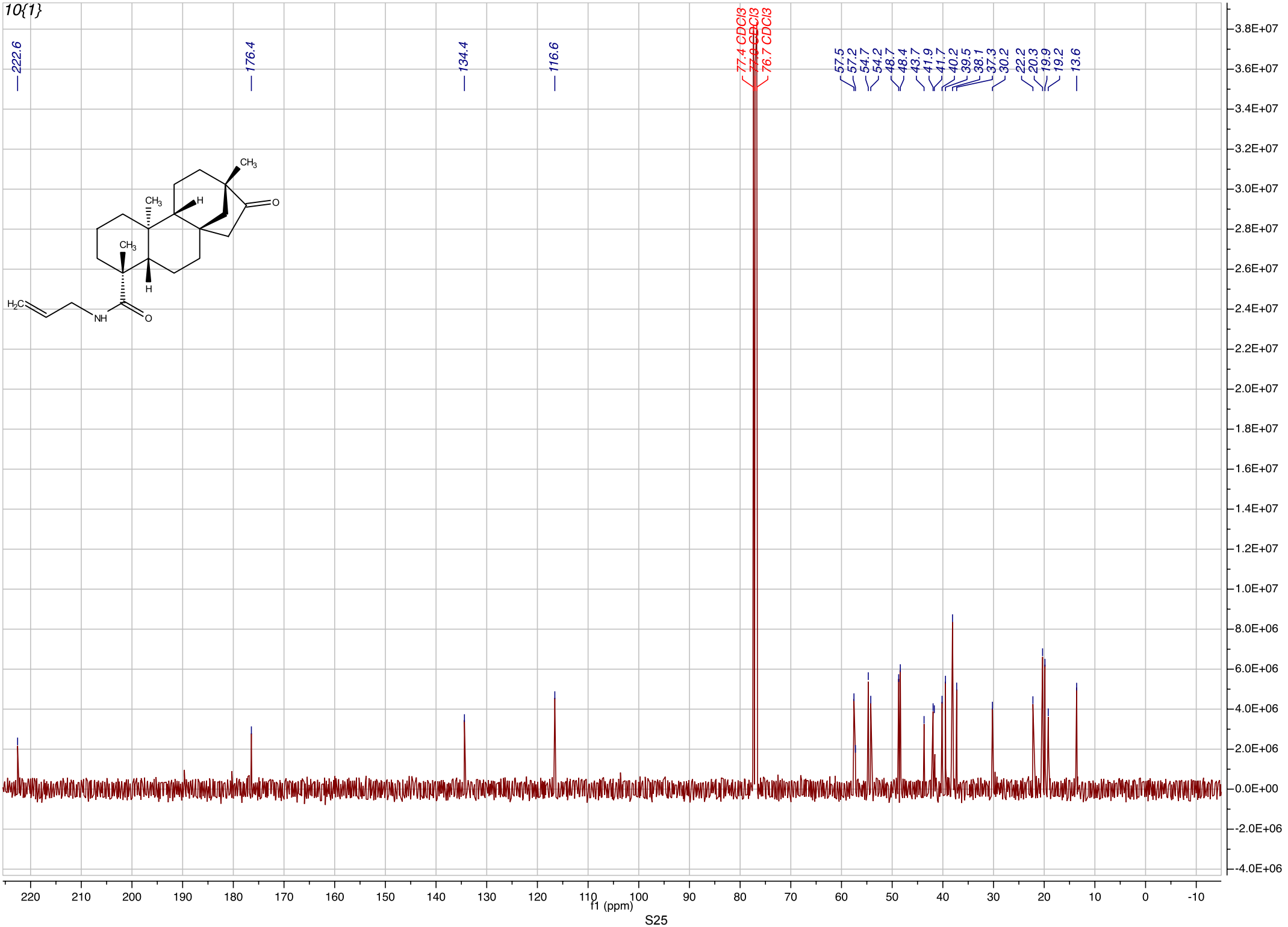
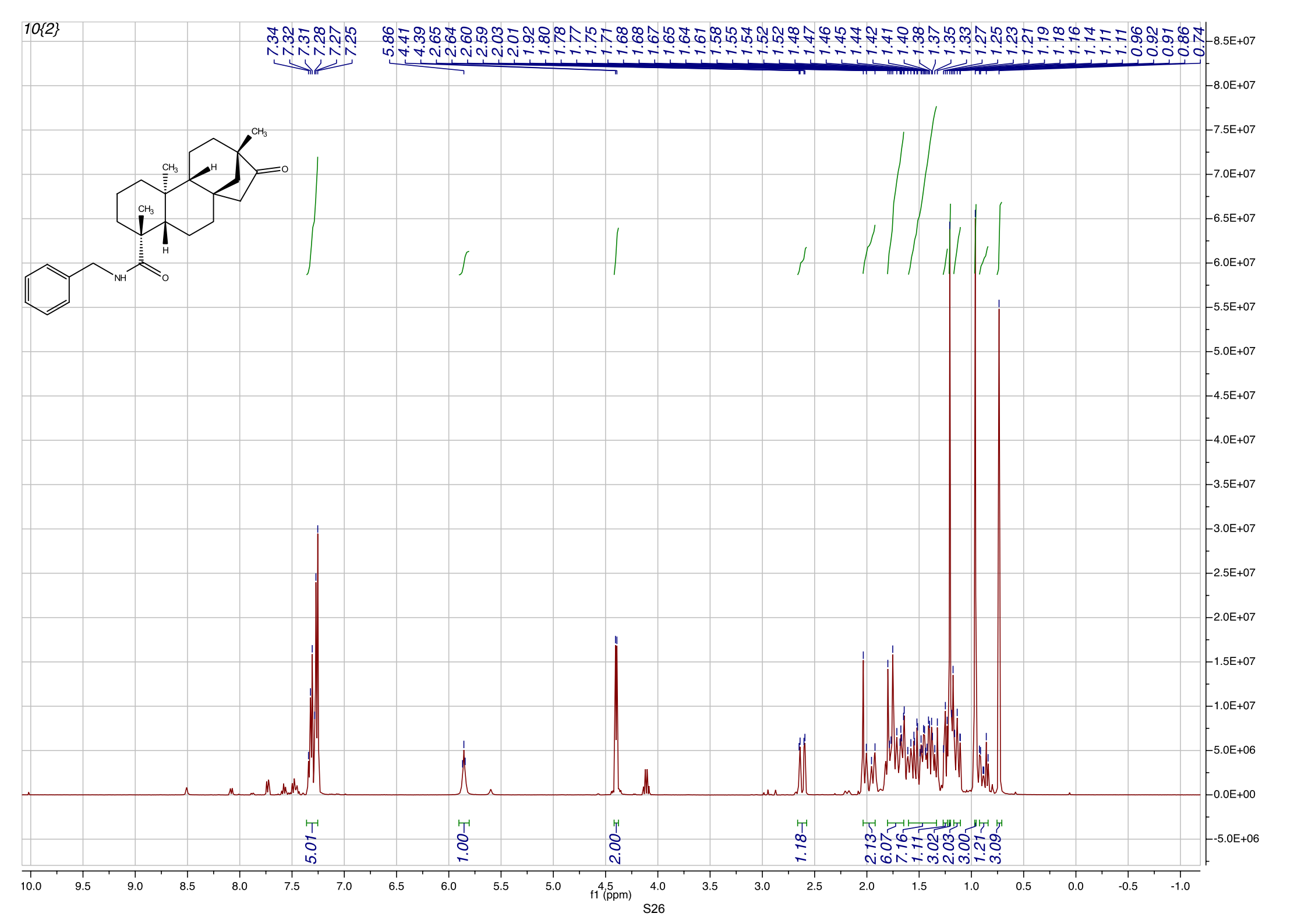
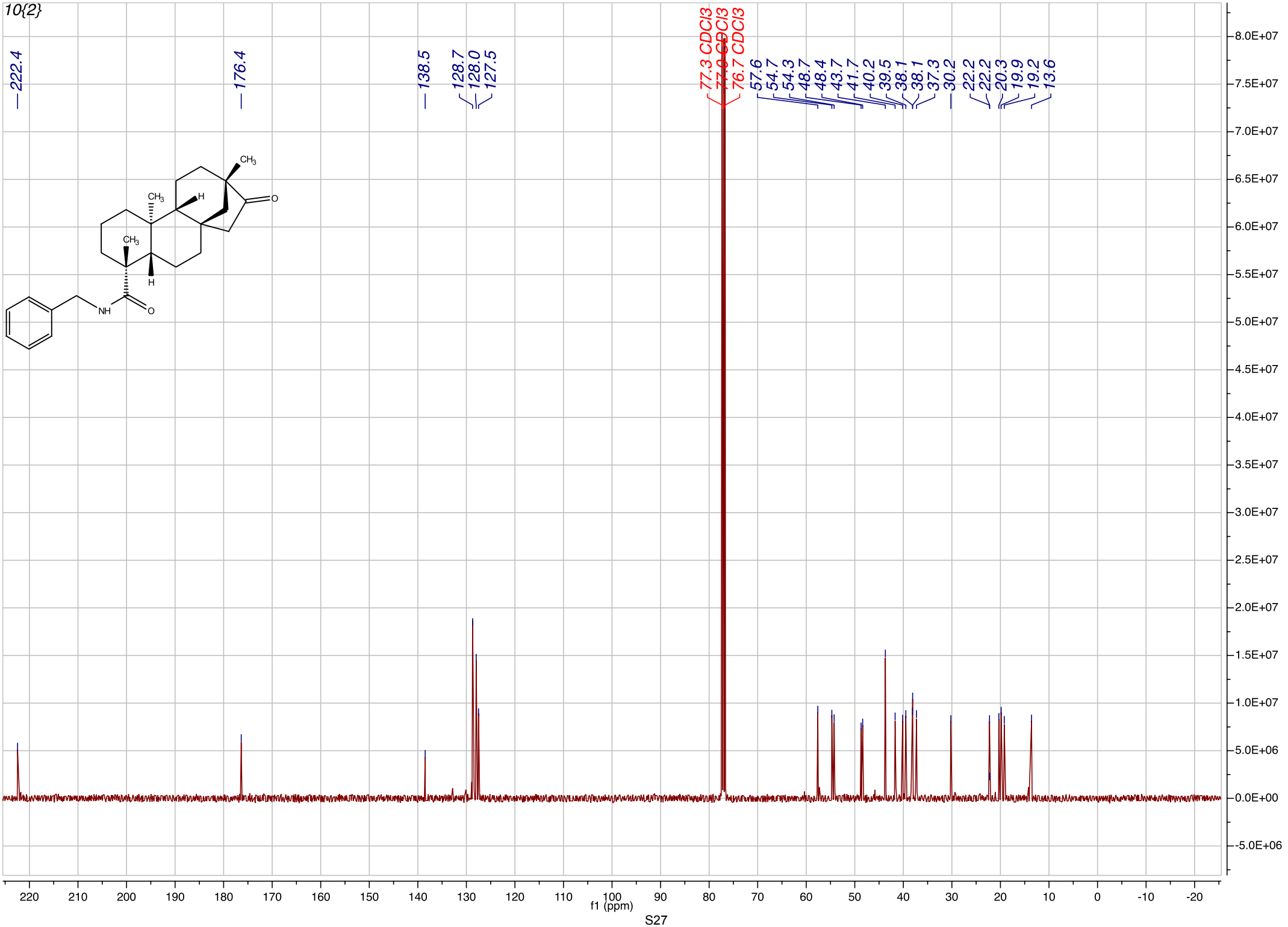
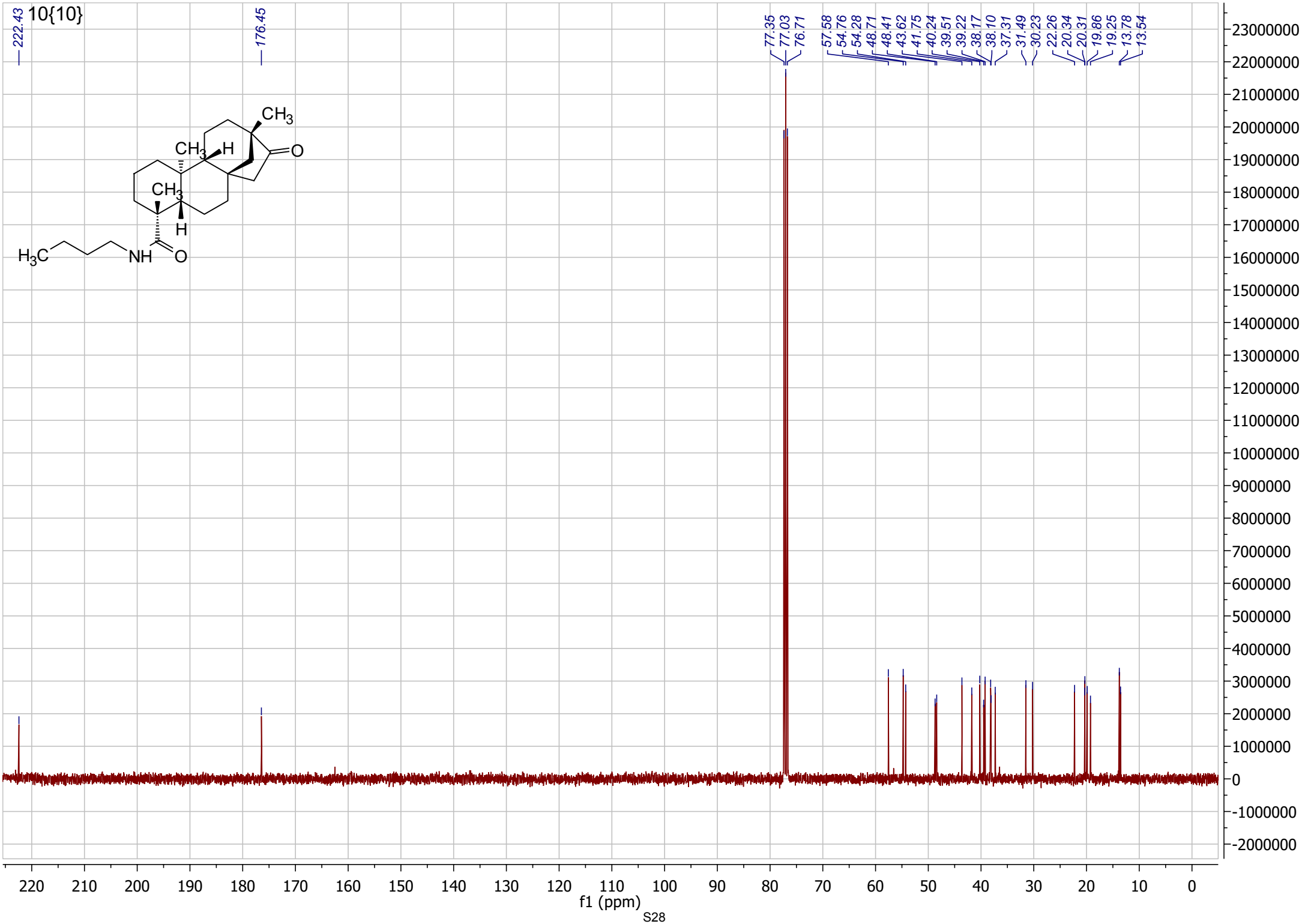
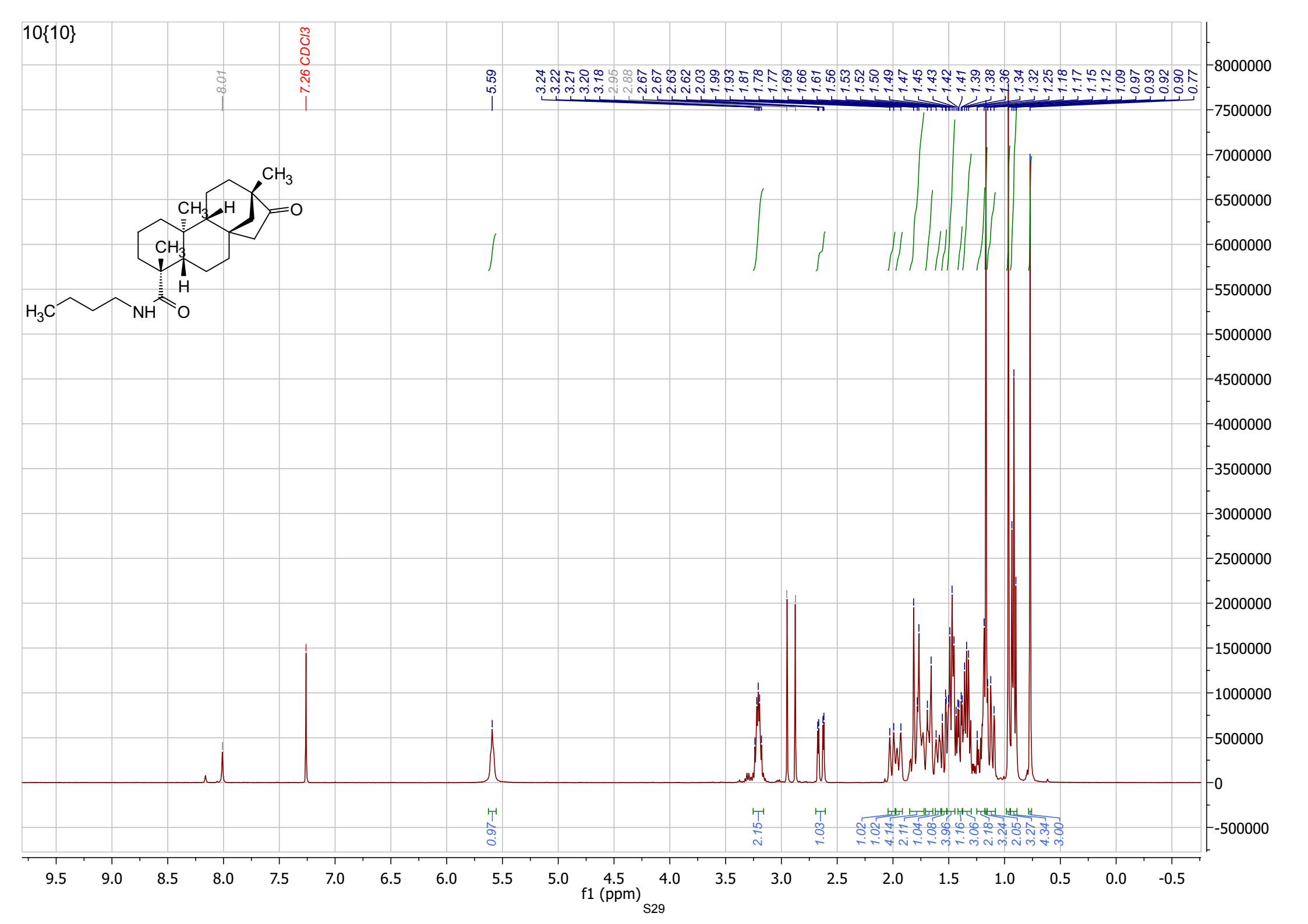
1.99 1.95 1.87 1.76 1.71 1.63 1.60 1.52 1.50 1.47 1.47 1.44 1.40 1.38 1.36 1.35 1.20 1.18 1.17 1.15 1.13 1.08 1.05 1.05 0.91 0.88 0.87 0.84 0.71 0.66 0.65
1.11 1.05 1.98 2.06 1.12 2.24 3.13 2.26 4.12 3.06 2.13 3.01 1.35 3.29 1.25 2.92 1.04
f1 (ppm)
S24

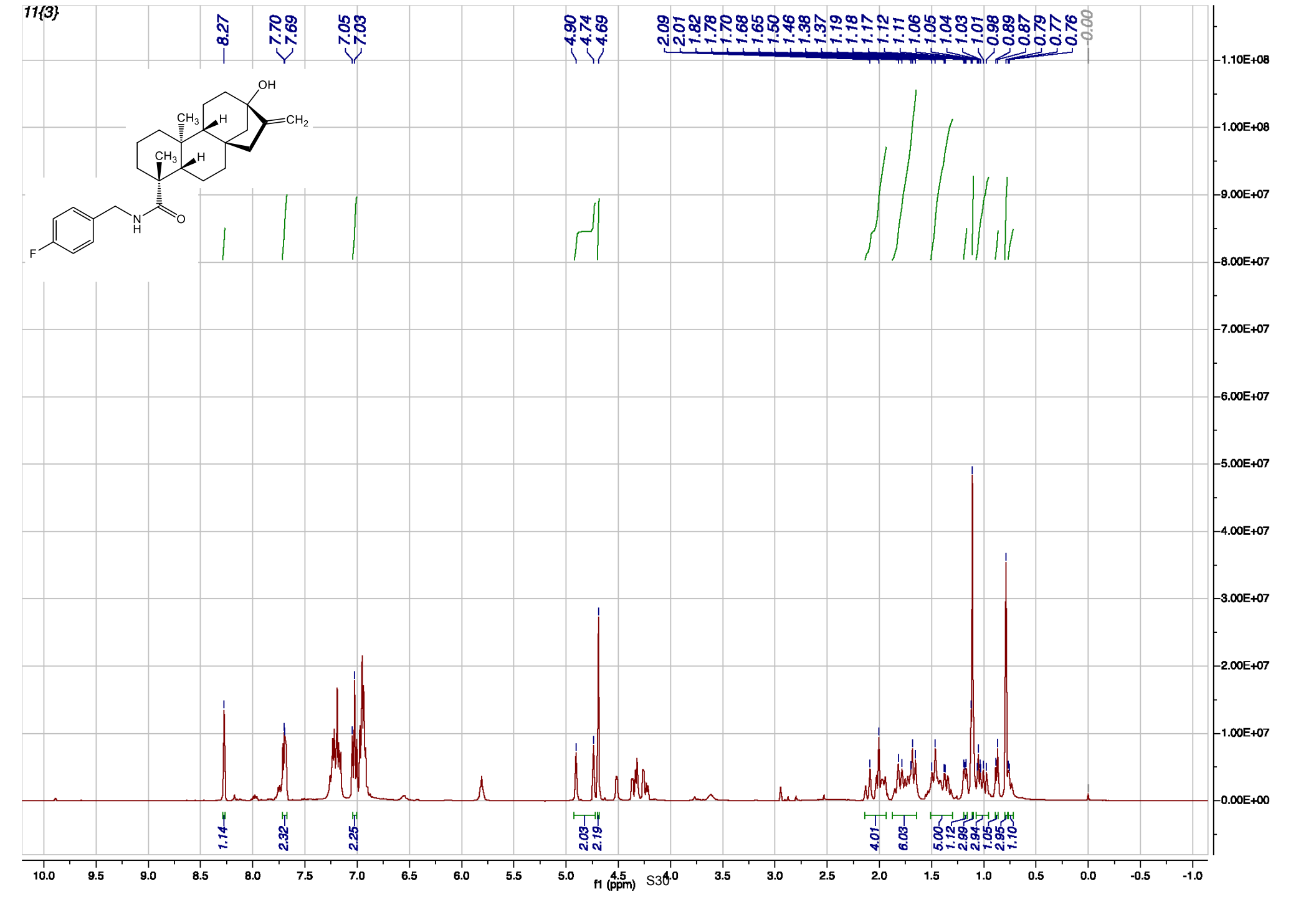

10{1}
222.6
176.4
134.4
116.6
77.4 CDCl3
77.0 CDCl3
76.7 CDCl3
57.5
57.2
54.7
54.2
48.7
48.4
43.7
41.9
41.7
40.2
39.5
38.1
37.3
30.2
22.2
20.3
19.9
19.2
13.6
CH3
H
O
CH3
CH3
H
H2C
NH
O
3.8E+07
3.6E+07
3.4E+07
3.2E+07
3.0E+07
2.8E+07
2.6E+07
2.4E+07
2.2E+07
2.0E+07
1.8E+07
1.6E+07
1.4E+07
1.2E+07
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
-2.0E+06
-4.0E+06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

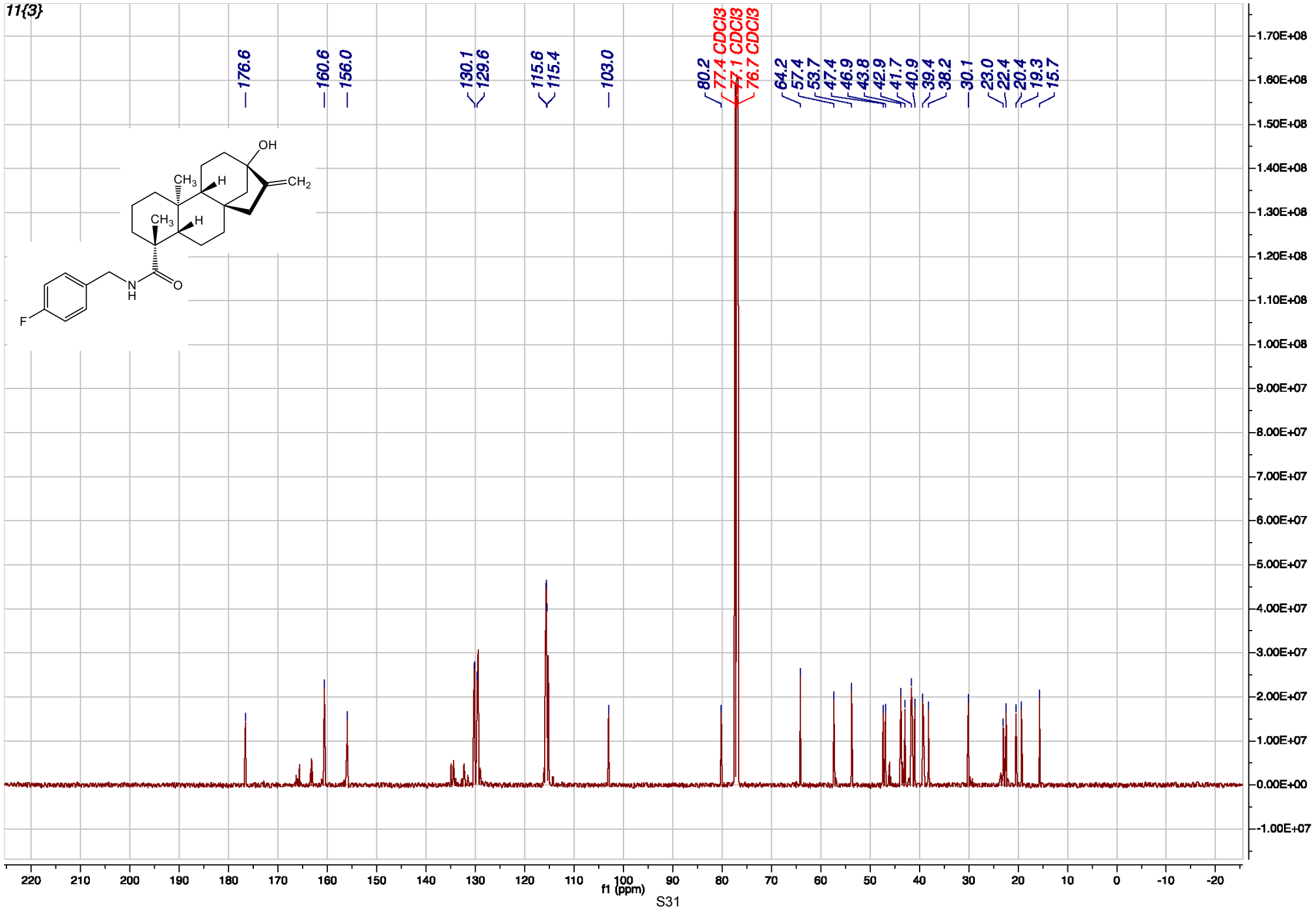

10{2}
7.34 7.32 7.31 7.28 7.27 7.25
5.86 4.41 4.39 2.65 2.64 2.60 2.59 2.03 2.01 1.92 1.80 1.78 1.77 1.75 1.71 1.68 1.68 1.67 1.65 1.64 1.61 1.58 1.55 1.54 1.52 1.52 1.48 1.47 1.46 1.45 1.44 1.42 1.41 1.40 1.38 1.37 1.35 1.33 1.27 1.25 1.23 1.21 1.19 1.18 1.16 1.14 1.11 1.11 0.96 0.92 0.91 0.86 0.74
CH3
H
CH3
CH3
O
H
NH
O
8.5E+07
8.0E+07
7.5E+07
7.0E+07
6.5E+07
6.0E+07
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
5.01
1.00
2.00
1.18
2.13
6.07
7.16
1.11
3.02
2.03
3.00
1.21
3.09
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)

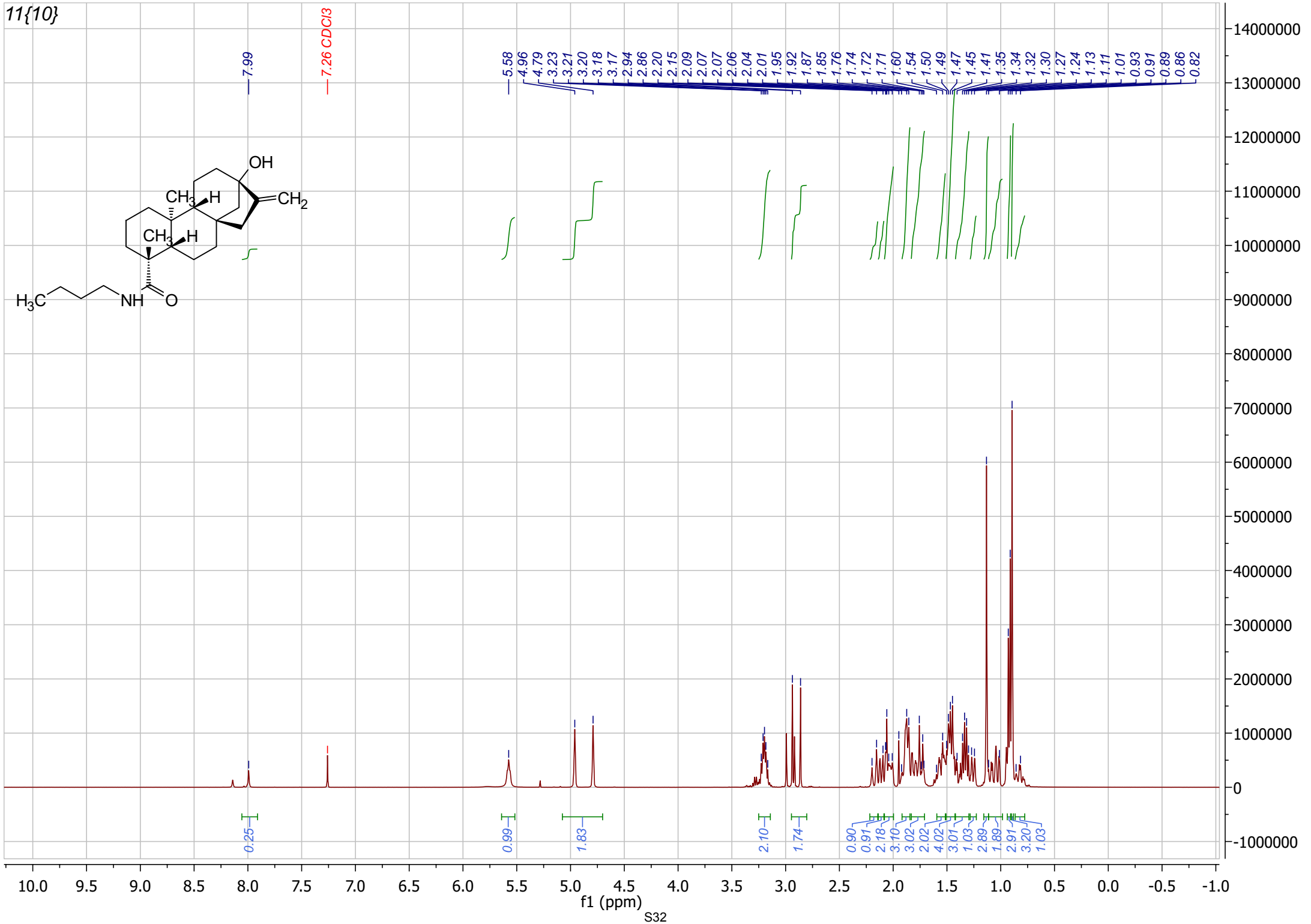

10{2}
222.4
176.4
138.5
128.7
128.0
127.5
77.3 CDCl3
77.0 CDCl3
76.7 CDCl3
57.6
54.7
54.3
48.7
48.4
43.7
41.7
40.2
39.5
38.1
38.1
37.3
30.2
22.2
22.2
20.3
19.9
19.2
13.6
CH3
CH3
CH3
H
H
O
NH
O
8.0E+07
7.5E+07
7.0E+07
6.5E+07
6.0E+07
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

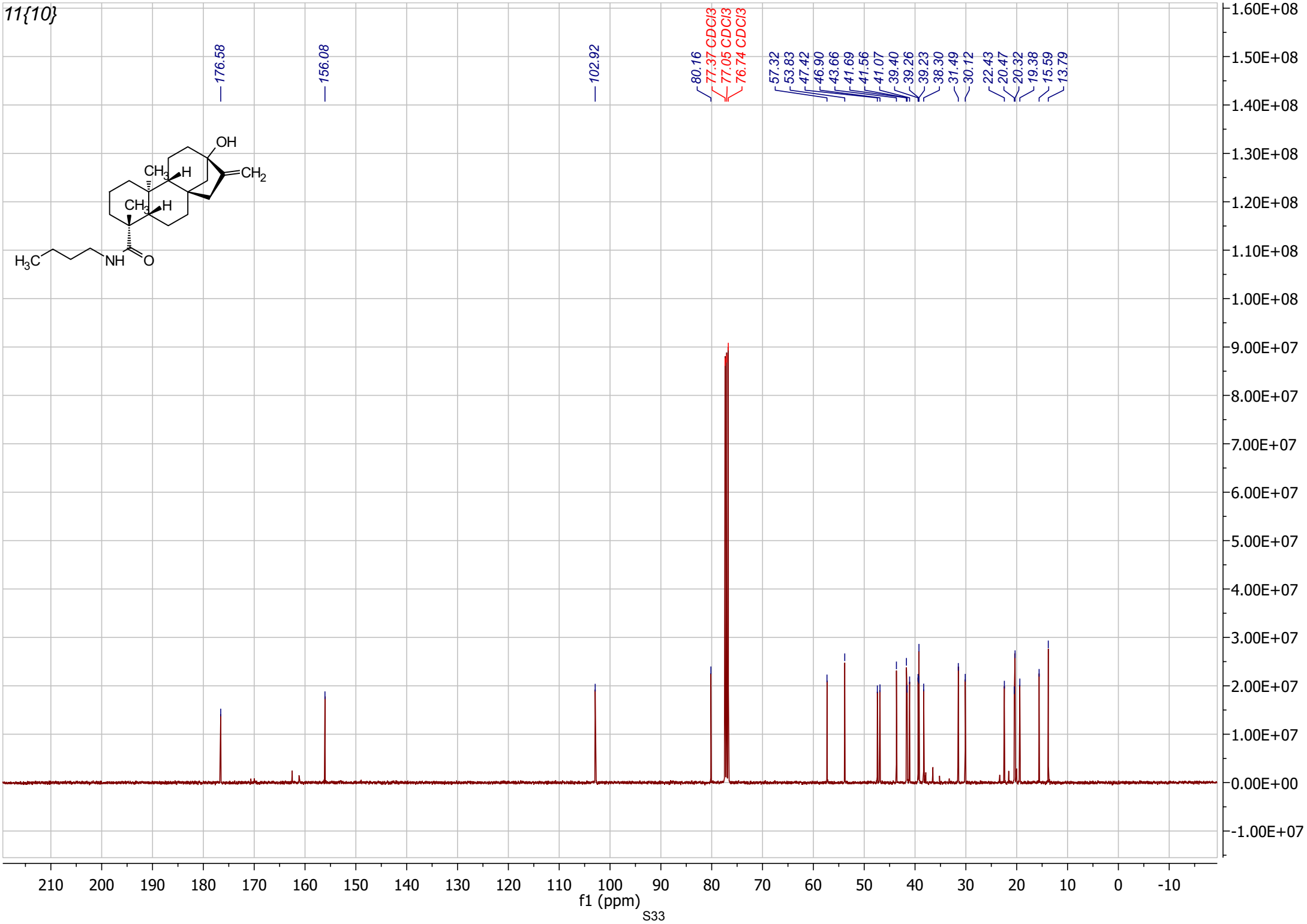

10{10}
222.43
176.45
77.35
77.03
76.71
57.58
54.76
54.28
48.71
48.41
43.62
41.75
40.24
39.51
39.22
38.17
38.10
37.31
31.49
30.23
22.26
20.34
20.31
19.86
19.25
13.78
13.54
CH3
CH3
H
CH3
H
O
H3C
NH
O
f1 (ppm)

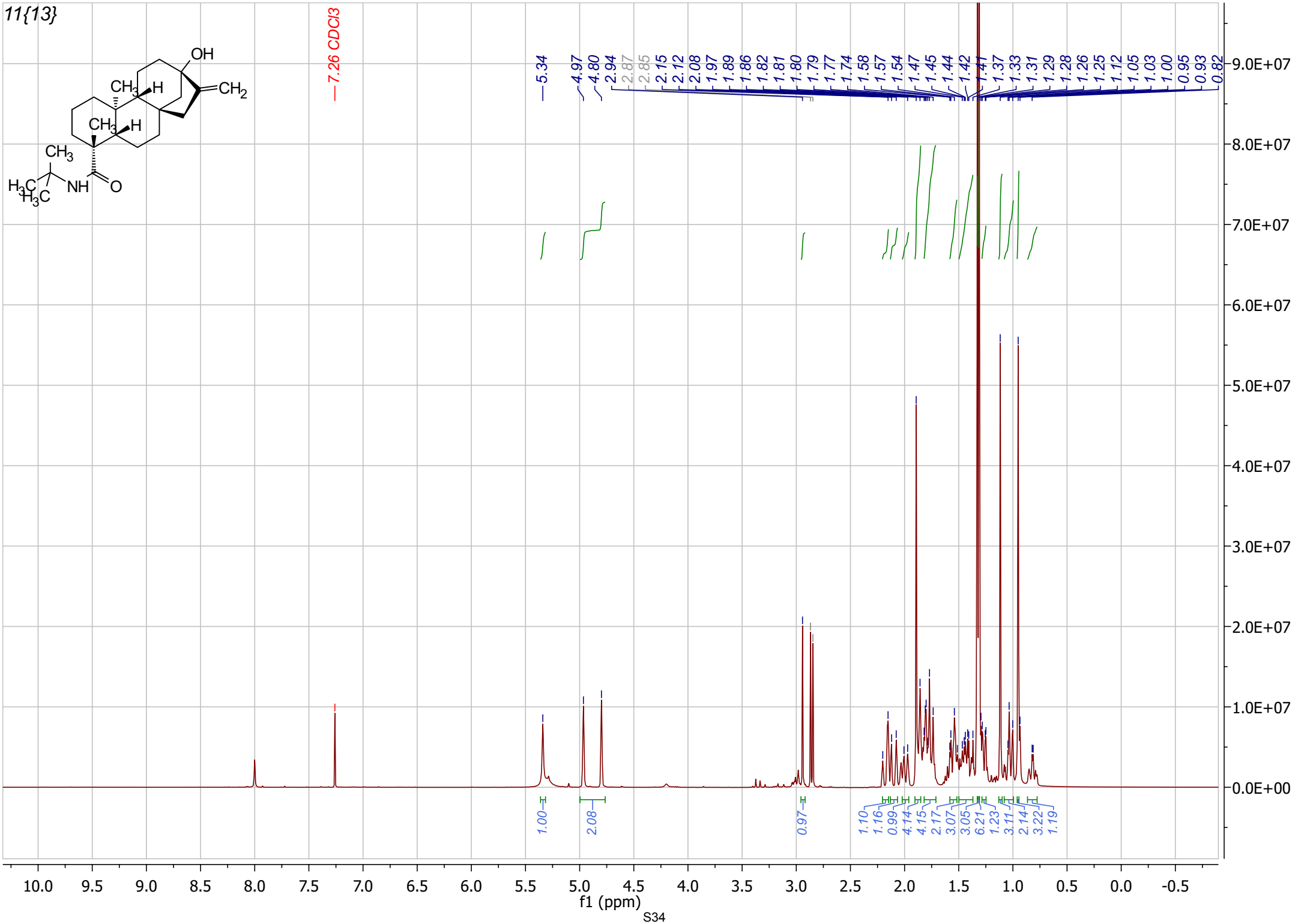

10{10}
8.01
7.26 CDCl3
5.59
3.24 3.22 3.21 3.20 3.18 2.95 2.88 2.67 2.67 2.63 2.62 2.03 1.99 1.93 1.81 1.78 1.77 1.69 1.66 1.61 1.56 1.53 1.52 1.50 1.49 1.47 1.45 1.43 1.42 1.41 1.39 1.38 1.36 1.34 1.32 1.25 1.18 1.17 1.15 1.12 1.09 0.97 0.93 0.92 0.90 0.77
CH3
CH3
H
O
CH3
H
H3C
NH
O
0.97
2.15
1.03
1.02 1.02 4.14 2.11 1.04 1.08 3.96 1.16 3.06 2.18 3.24 2.05 3.27 4.34 3.00
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
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)

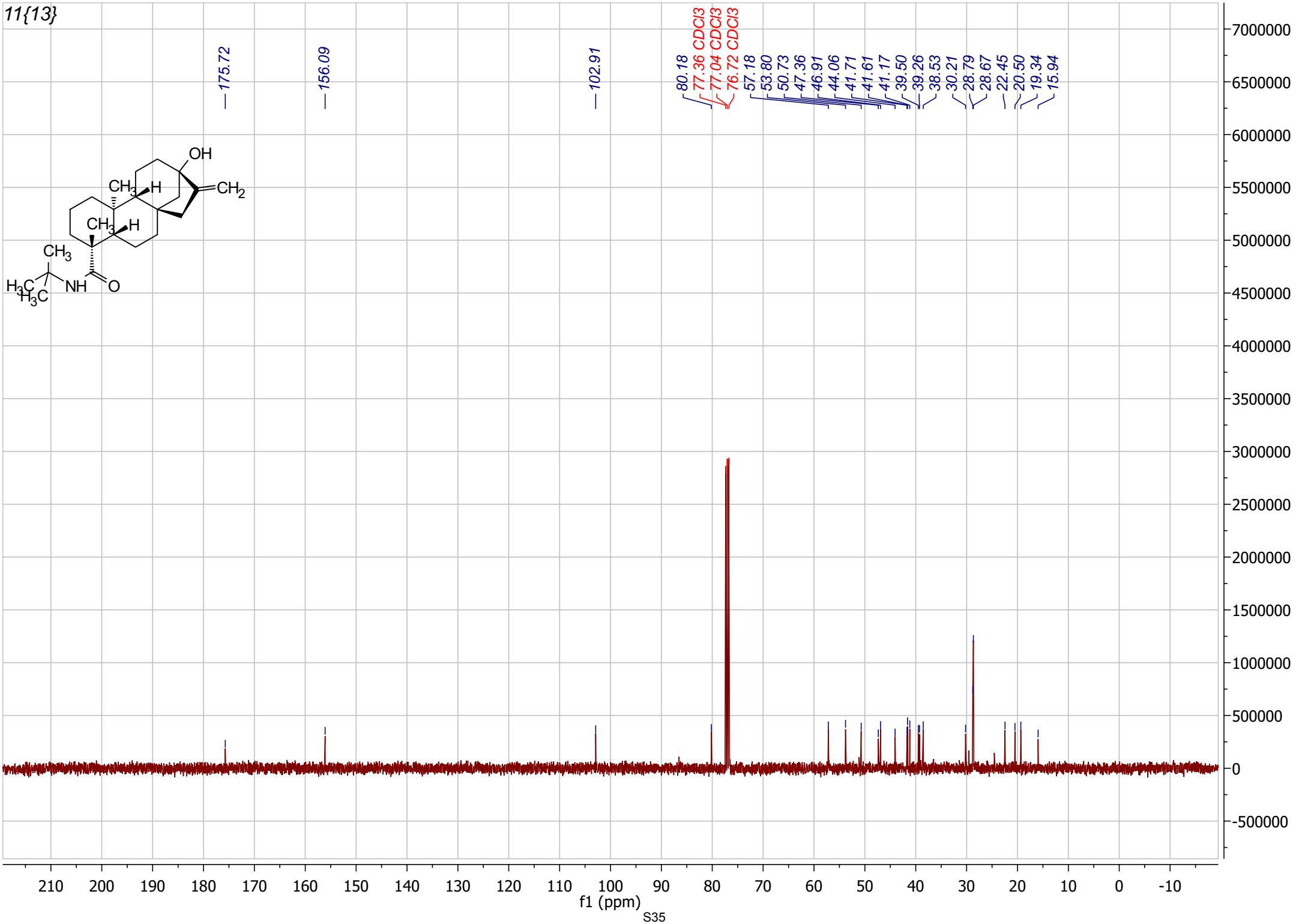

11{3}
8.27
7.70
7.69
7.05
7.03
4.90
4.74
4.69
2.09
2.01
1.82
1.78
1.70
1.68
1.65
1.50
1.46
1.38
1.37
1.19
1.18
1.17
1.12
1.11
1.06
1.05
1.04
1.03
1.01
0.98
0.89
0.87
0.79
0.77
0.76
0.00
OH
CH3
H
CH2
CH3
H
N
H
O
F
1.14
2.32
2.25
2.03
2.19
4.01
6.03
5.00
1.12
2.99
2.94
1.05
2.95
1.10
f1 (ppm)
S30

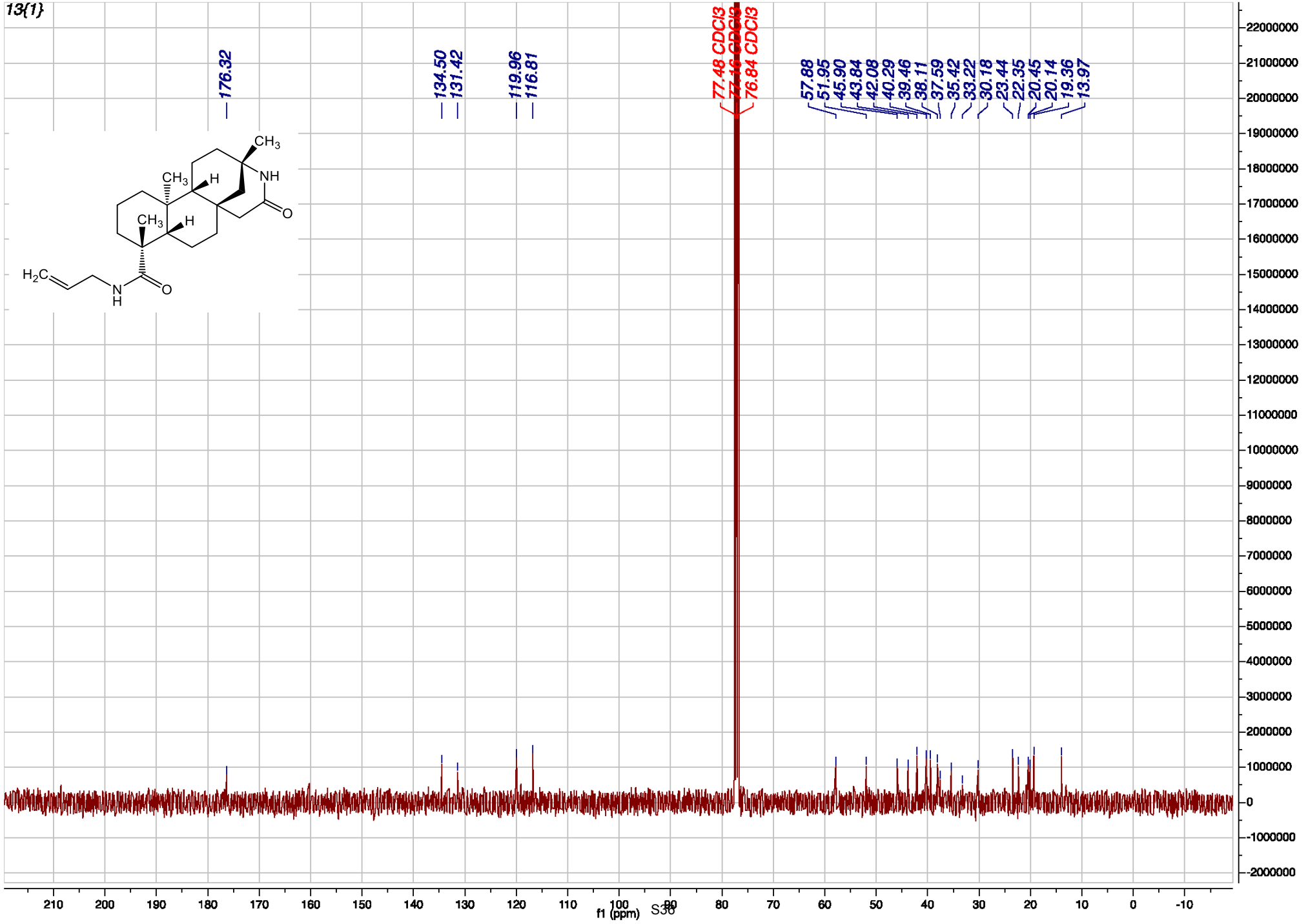

11{3}
176.6
160.6
156.0
130.1
129.6
115.6
115.4
103.0
80.2
77.4 CDCl3
77.1 CDCl3
76.7 CDCl3
64.2
57.4
53.7
47.4
46.9
43.8
42.9
41.7
40.9
39.4
38.2
30.1
23.0
22.4
20.4
19.3
15.7
OH
CH3
H
CH2
CH3
H
N
H
O
F
1.70E+08
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

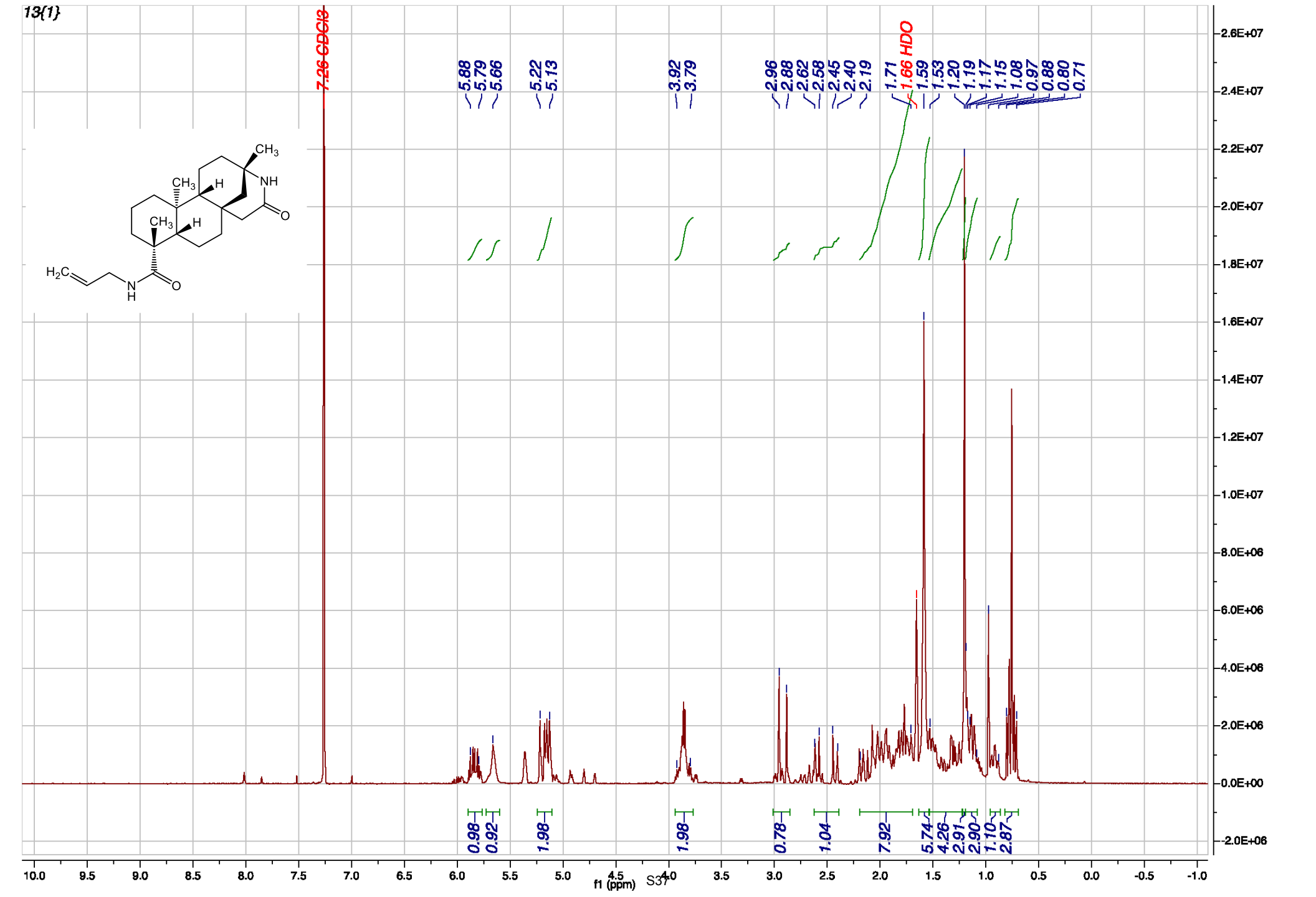

11{10}
7.99
7.26 CDCl3
5.58
4.96
4.79
3.23
3.21
3.20
3.18
3.17
2.94
2.86
2.20
2.15
2.09
2.07
2.07
2.06
2.04
2.01
1.95
1.92
1.87
1.85
1.76
1.74
1.72
1.71
1.60
1.54
1.50
1.49
1.47
1.45
1.41
1.35
1.34
1.32
1.30
1.27
1.24
1.13
1.11
1.01
0.93
0.91
0.89
0.86
0.82
OH
CH3
H
CH2
CH3
H
H3C
NH
O
0.25
0.99
1.83
2.10
1.74
0.90
0.91
2.18
3.10
3.02
2.02
4.02
3.01
1.03
2.89
1.89
2.91
3.20
1.03
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
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)

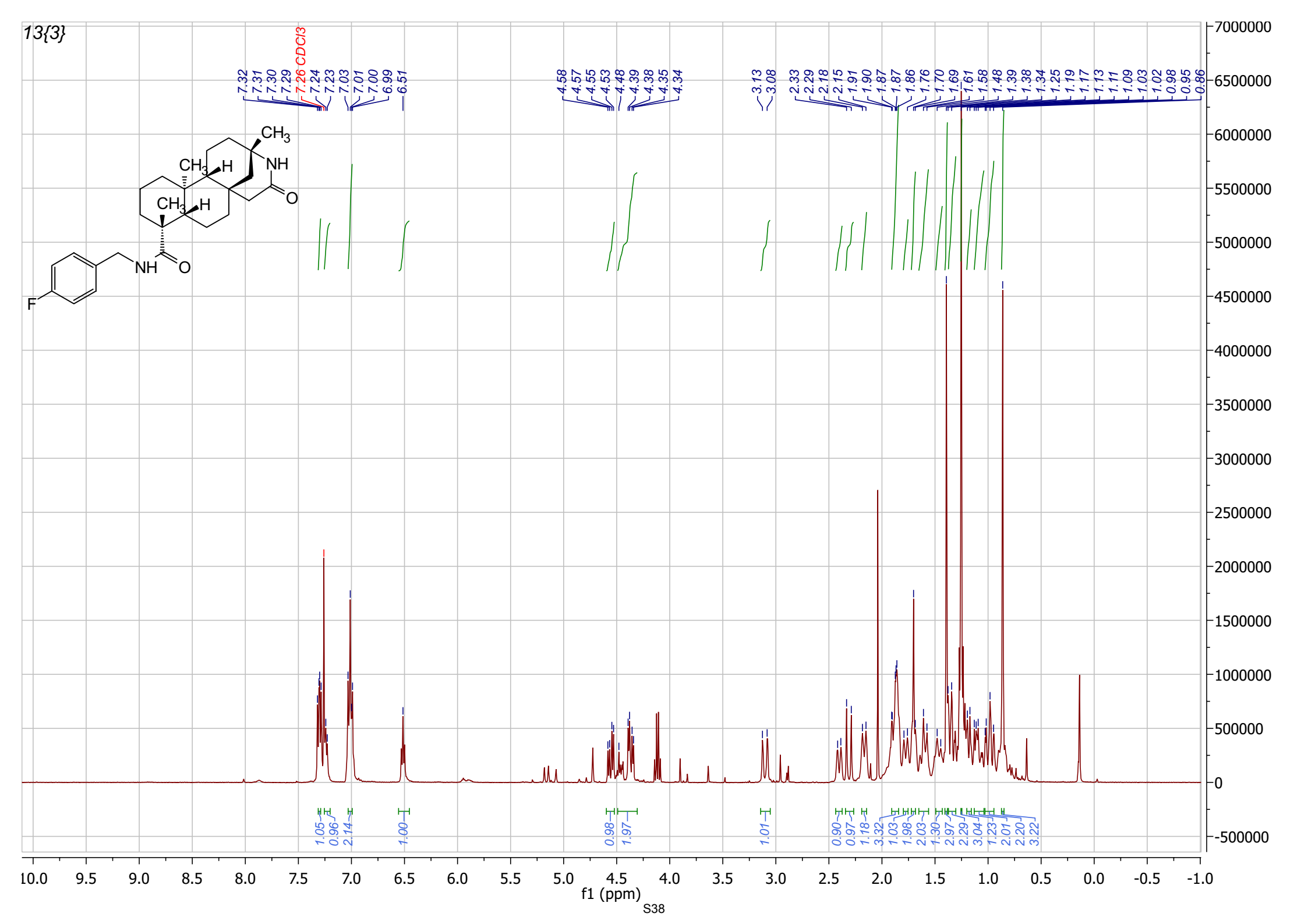

11{10}
176.58
156.08
102.92
80.16
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
57.32
53.83
47.42
46.90
43.66
41.69
41.56
41.07
39.40
39.26
39.23
38.30
31.49
30.12
22.43
20.47
20.32
19.38
15.59
13.79
OH
CH3
H
CH2
CH3
H
H3C
NH
O
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

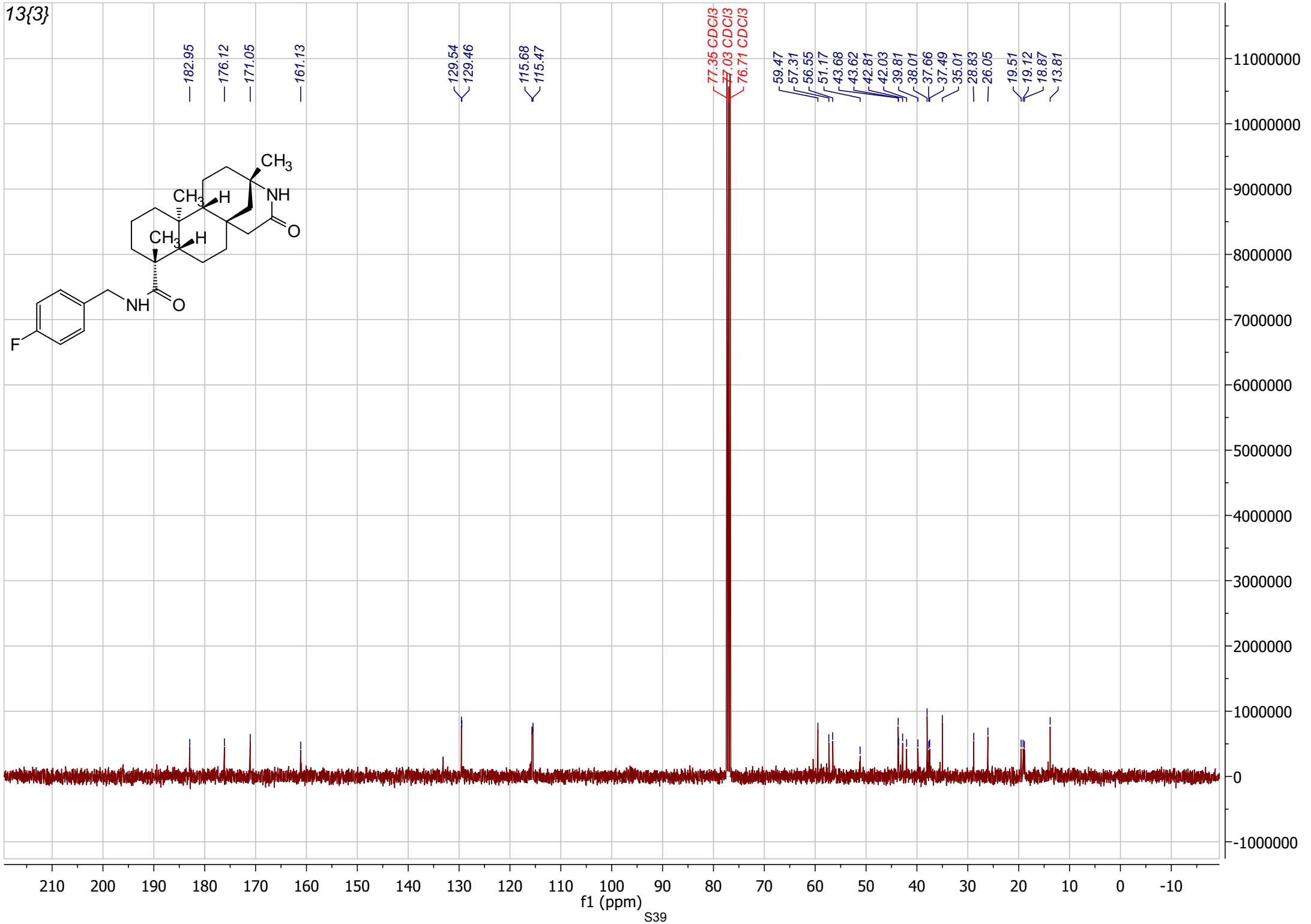

11{13}
OH
CH3
H
CH2
CH3
H
CH3
H3C
H3C
NH
O
7.26 CDCl3
5.34
4.97
4.80
2.94
2.87
2.85
2.15
2.12
2.08
1.97
1.89
1.86
1.82
1.81
1.80
1.79
1.77
1.74
1.58
1.57
1.54
1.47
1.45
1.44
1.42
1.41
1.37
1.33
1.31
1.29
1.28
1.26
1.25
1.12
1.05
1.03
1.00
0.95
0.93
0.82
1.00
2.08
0.97
1.10
1.16
0.99
4.14
4.15
2.17
3.07
3.05
6.21
1.23
3.11
2.14
3.22
1.19
9.0E+07
8.0E+07
7.0E+07
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+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
f1 (ppm)

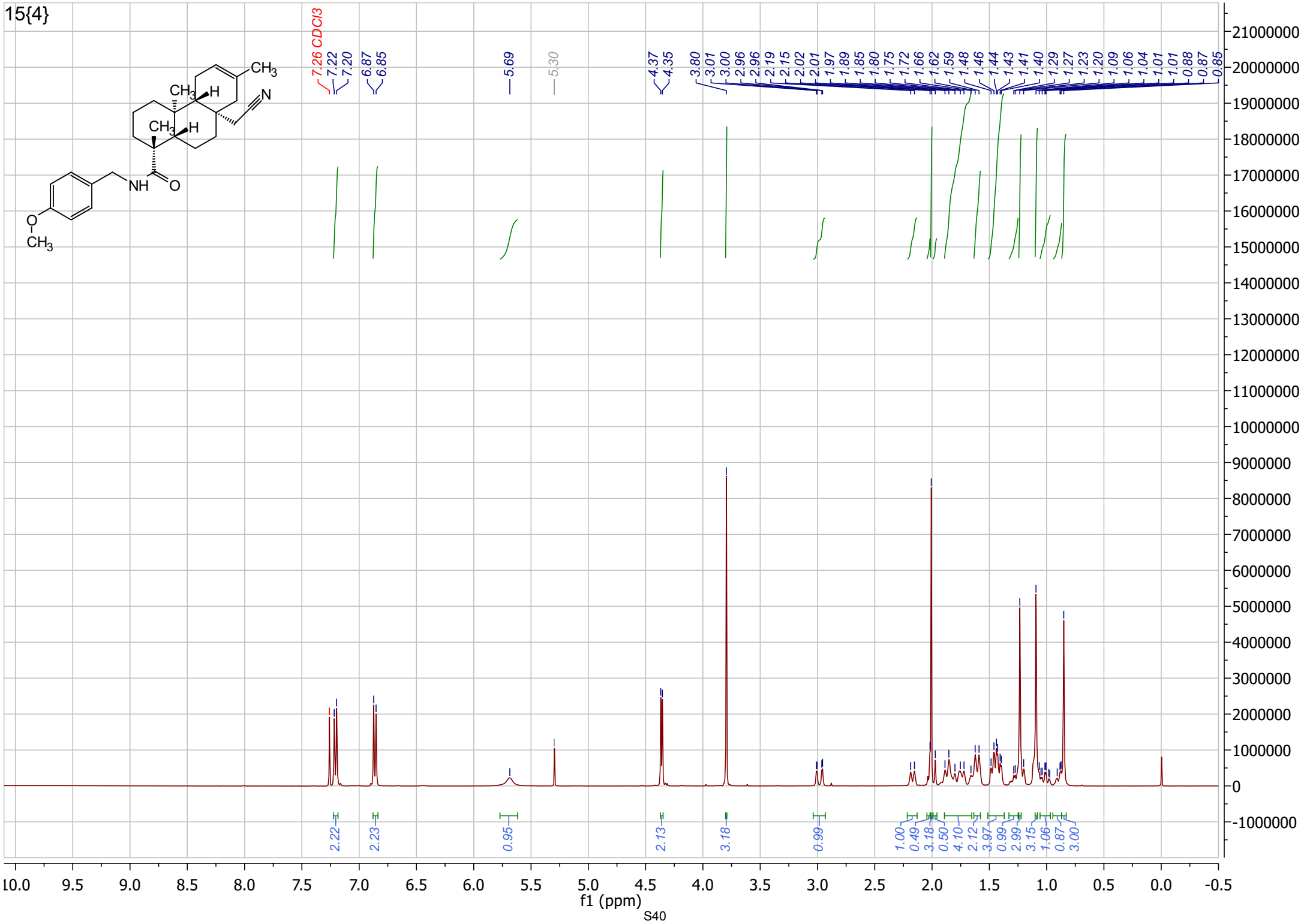

11{13}
175.72
156.09
102.91
80.18
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
57.18
53.80
50.73
47.36
46.91
44.06
41.71
41.61
41.17
39.50
39.26
38.53
30.21
28.79
28.67
22.45
20.50
19.34
15.94
OH
CH3
H
CH2
CH3
H
CH3
H3C
H3C
NH
O
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

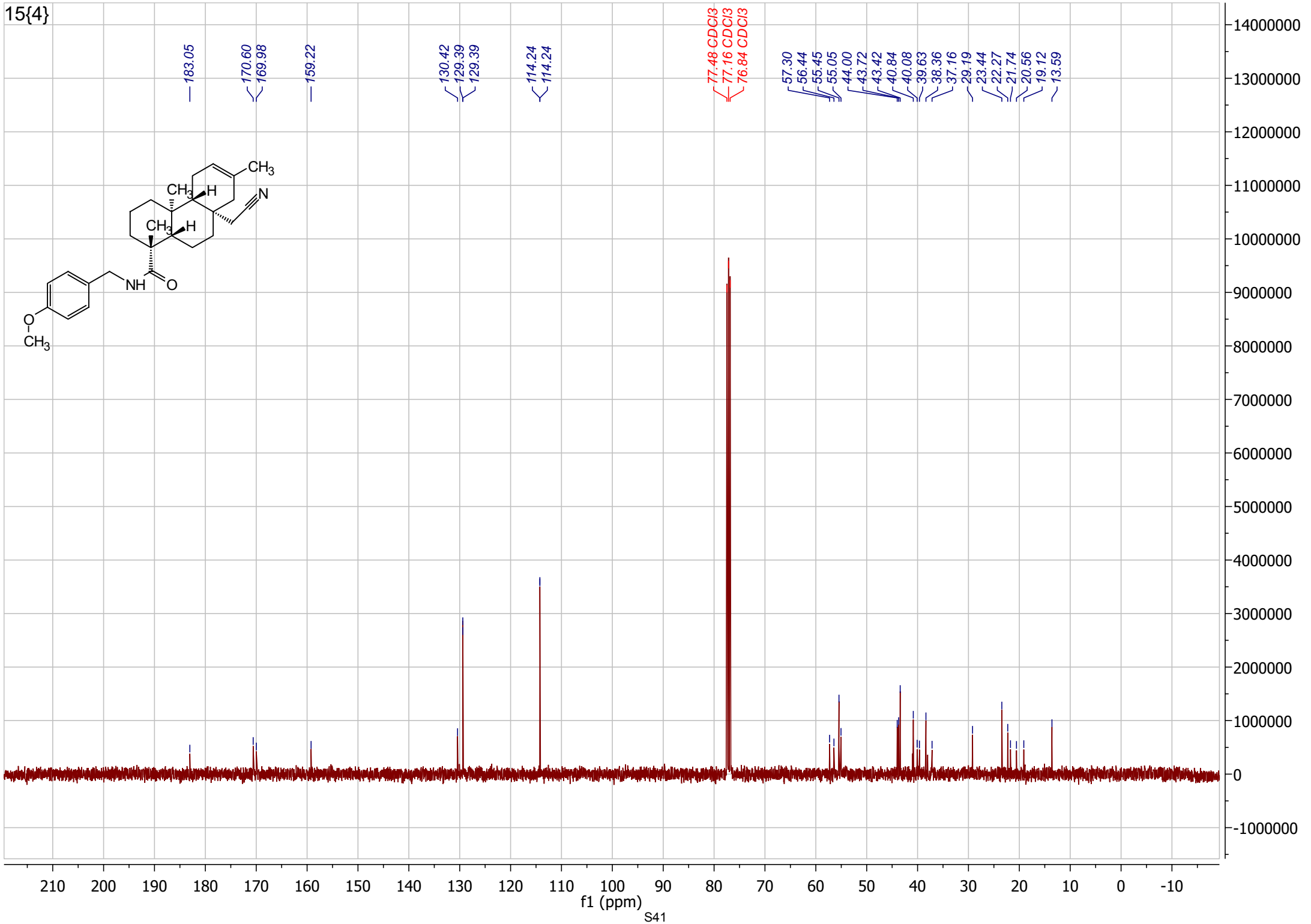

13(1)
176.32
134.50
131.42
119.96
116.81
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
57.88
51.95
45.90
43.84
42.08
40.29
39.46
38.11
37.59
35.42
33.22
30.18
23.44
22.35
20.45
20.14
19.36
13.97
CH3
CH3
CH3
H
H
NH
O
H2C
N
H
O
f1 (ppm)

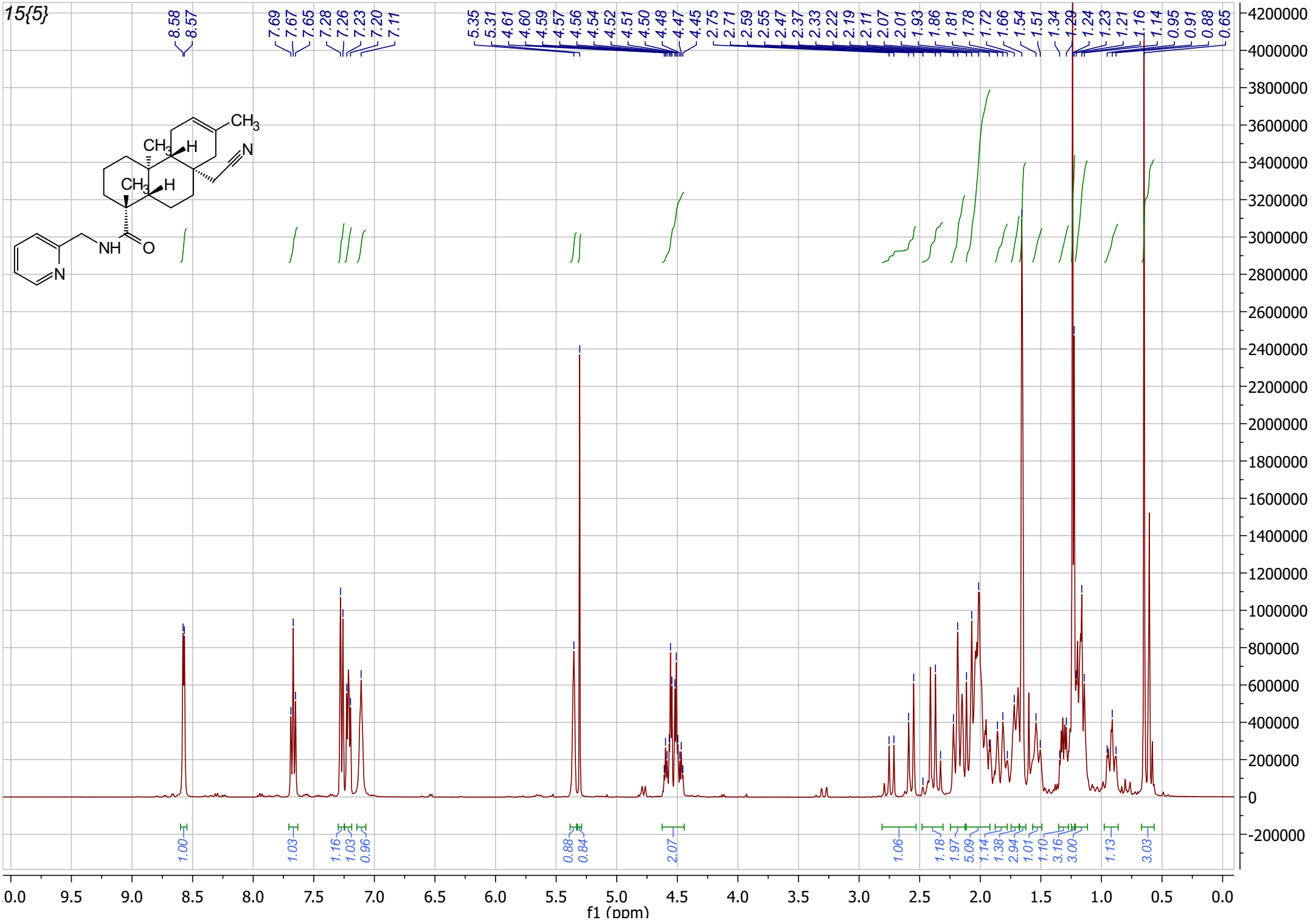

13(1)
7.26 CDCl3
5.88
5.79
5.66
5.22
5.13
3.92
3.79
2.96
2.88
2.62
2.58
2.45
2.40
2.19
1.71
1.66 HDO
1.59
1.53
1.20
1.19
1.17
1.15
1.08
0.97
0.88
0.80
0.71
CH3
H
NH
O
CH3
H
H2C
N
H
O
0.98
0.92
1.98
1.98
0.78
1.04
7.92
5.74
4.26
2.91
2.90
1.10
2.87
f1 (ppm)
S37


13{3}
7.32
7.31
7.30
7.29
7.26 CDCl3
7.24
7.23
7.03
7.01
7.00
6.99
6.51
4.58
4.57
4.55
4.53
4.48
4.39
4.38
4.35
4.34
3.13
3.08
2.33
2.29
2.18
2.15
1.91
1.90
1.87
1.87
1.86
1.76
1.70
1.69
1.61
1.58
1.48
1.39
1.38
1.34
1.25
1.19
1.17
1.13
1.11
1.09
1.03
1.02
0.98
0.95
0.86
CH3
NH
CH3
H
CH3
H
O
NH
O
F
1.05
0.96
2.14
1.00
0.98
1.97
1.01
0.90
0.97
1.18
3.32
1.03
1.98
2.03
1.30
2.97
2.29
3.04
1.23
2.01
2.20
3.22
f1 (ppm)
S38

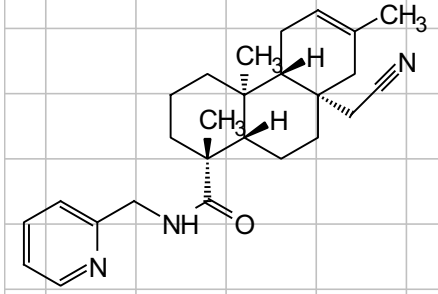

13{3}
182.95
176.12
171.05
161.13
129.54
129.46
115.68
115.47
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
59.47
57.31
56.55
51.17
43.68
43.62
42.81
42.03
39.81
38.01
37.66
37.49
35.01
28.83
26.05
19.51
19.12
18.87
13.81
CH3
NH
O
CH3
H
CH3
H
NH
O
F
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


15{4}
7.26 CDCl3
7.22
7.20
6.87
6.85
5.69
5.30
4.37
4.35
3.80
3.01
3.00
2.96
2.96
2.19
2.15
2.02
2.01
1.97
1.89
1.85
1.80
1.75
1.72
1.66
1.62
1.59
1.48
1.46
1.44
1.43
1.41
1.40
1.29
1.27
1.23
1.20
1.09
1.06
1.04
1.01
1.01
0.88
0.87
0.85
CH3
H
CH3
H
N
NH
O
O
CH3
2.22
2.23
0.95
2.13
3.18
0.99
1.00
0.49
3.18
0.50
4.10
2.12
3.97
0.99
2.99
3.15
1.06
0.87
3.00
f1 (ppm)
S40


15{4}
183.05
170.60
169.98
159.22
130.42
129.39
129.39
114.24
114.24
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
57.30
56.44
55.45
55.05
44.00
43.72
43.42
40.84
40.08
39.63
38.36
37.16
29.19
23.44
22.27
21.74
20.56
19.12
13.59
CH3
CH3
H
N
CH3
H
NH
O
O
CH3
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


15{5}
8.58
8.57
7.69
7.67
7.65
7.28
7.26
7.23
7.20
7.11
5.35
5.31
4.61
4.60
4.59
4.57
4.56
4.54
4.52
4.51
4.50
4.48
4.47
4.45
2.75
2.71
2.59
2.55
2.47
2.37
2.33
2.22
2.19
2.11
2.07
2.01
1.93
1.86
1.81
1.78
1.72
1.66
1.54
1.51
1.34
1.29
1.24
1.23
1.21
1.16
1.14
0.95
0.91
0.88
0.65
CH3
CH3
H
CH3
H
N
NH
O
N
1.00
1.03
1.16
1.03
0.96
0.88
0.84
2.07
1.06
1.18
1.97
5.09
1.14
1.38
2.94
1.01
1.10
3.16
3.00
1.13
3.03
f1 (ppm)

15{5}

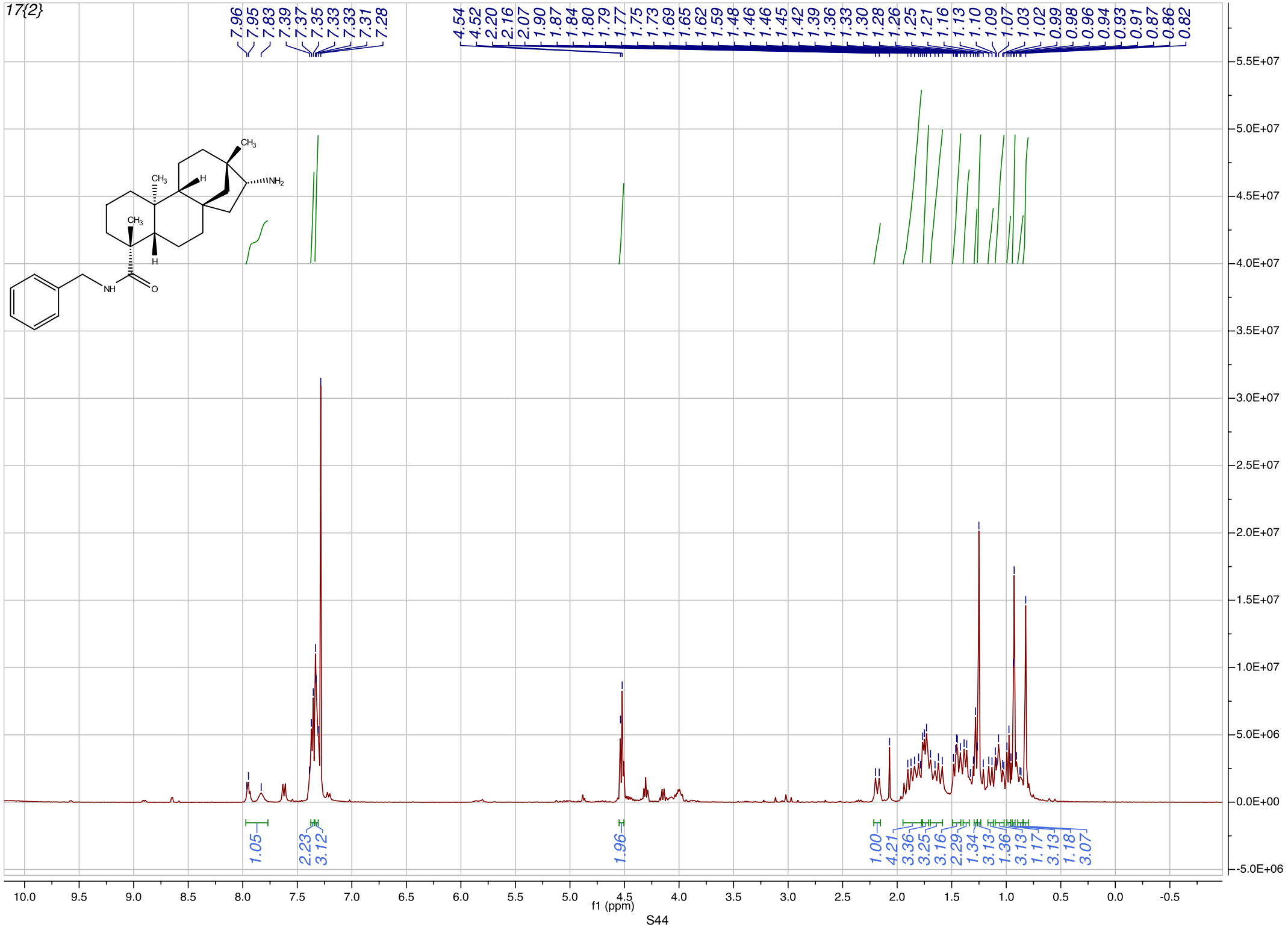


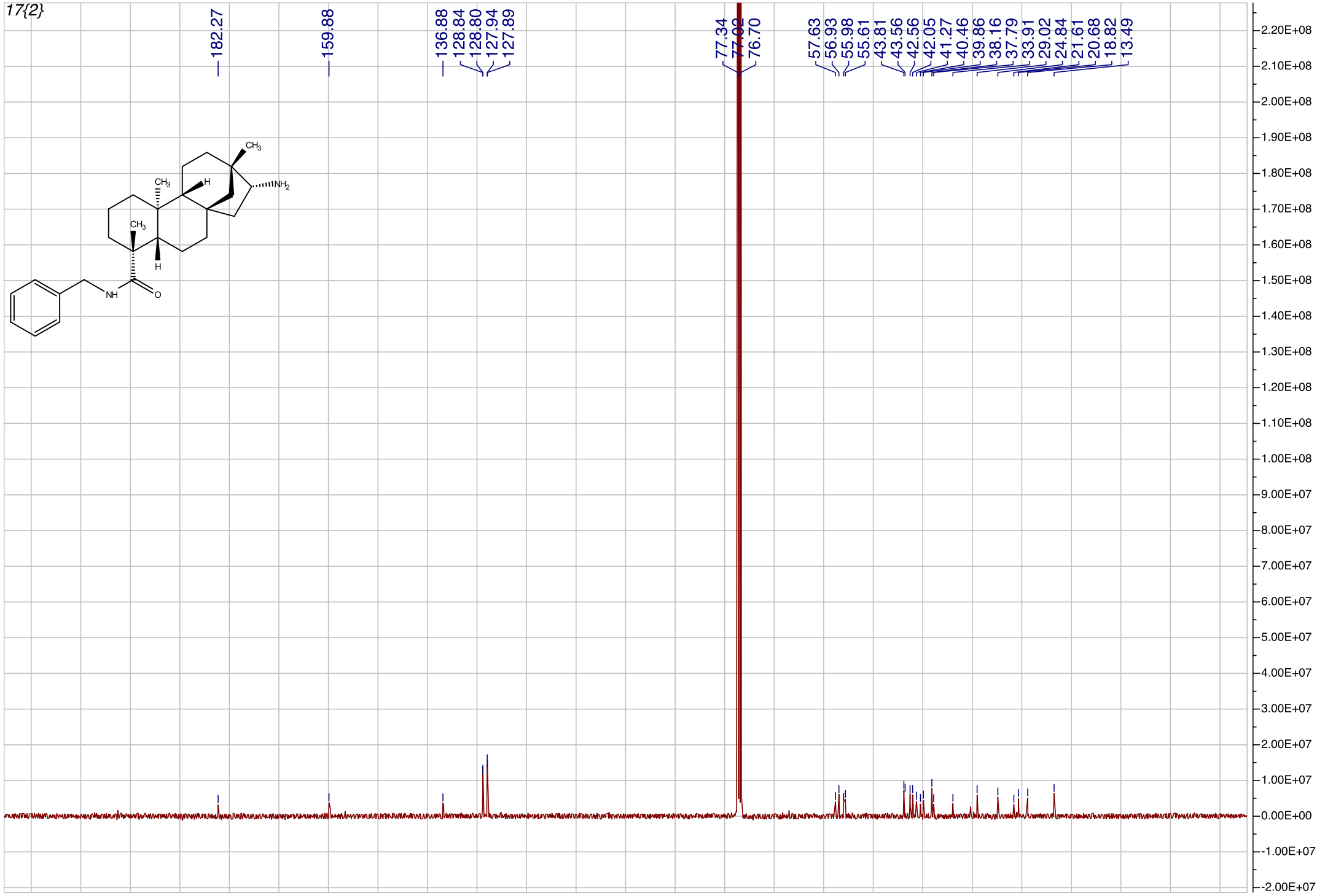
176.58
156.39
149.00
136.73
131.15
122.35
122.31
119.86
119.00
77.40 CDCl3
77.08 CDCl3
76.76 CDCl3
57.74
51.74
45.67
44.37
43.72
40.17
39.37
37.94
37.44
35.29
29.90
23.31
22.17
20.18
19.90
19.12
13.51

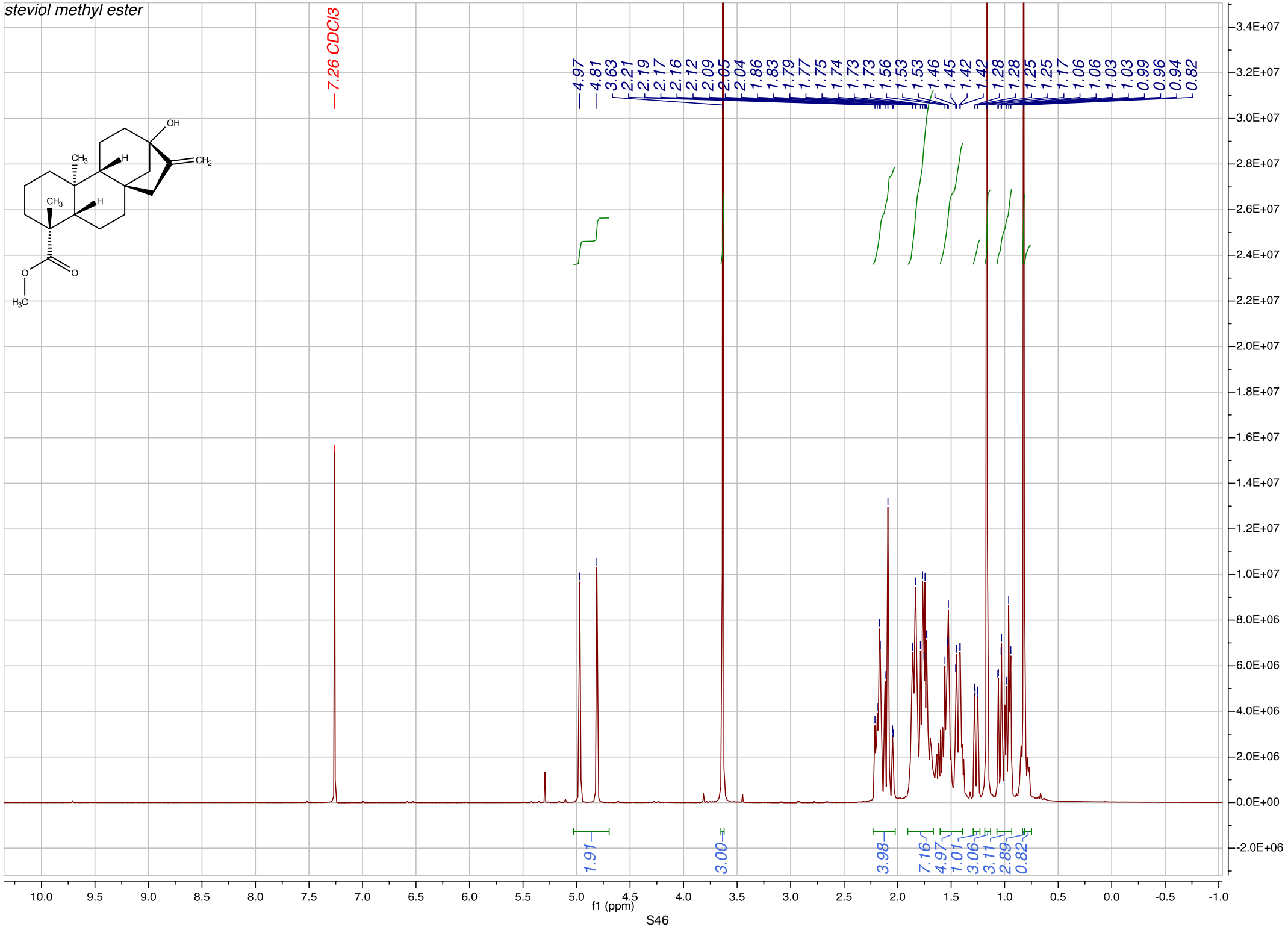
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

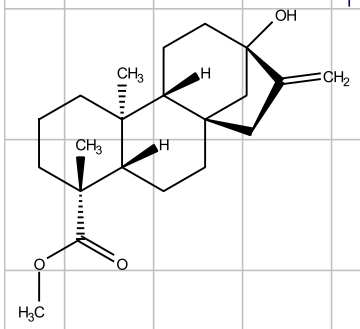
f1 (ppm)


17{2}
7.96 7.95 7.83 7.39 7.37 7.35 7.33 7.33 7.31 7.28
4.54 4.52 2.20 2.16 2.07 1.90 1.87 1.84 1.80 1.79 1.77 1.75 1.73 1.69 1.65 1.62 1.59 1.48 1.46 1.46 1.45 1.42 1.39 1.36 1.33 1.30 1.28 1.26 1.25 1.21 1.16 1.13 1.10 1.09 1.07 1.03 1.02 0.99 0.98 0.96 0.94 0.93 0.91 0.87 0.86 0.82
CH3
NH2
H
CH3
CH3
H
NH
O
1.05
2.23
3.12
1.96
1.00
4.21
3.36
3.25
3.16
2.29
1.34
3.13
1.36
3.13
1.17
3.13
1.18
3.07
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
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)


17{2}
182.27
159.88
136.88
128.84
128.80
127.94
127.89
77.34
77.02
76.70
57.63
56.93
55.98
55.61
43.81
43.56
42.56
42.05
41.27
40.46
39.86
38.16
37.79
33.91
29.02
24.84
21.61
20.68
18.82
13.49
CH3
CH3
CH3
H
H
NH2
NH
O
2.20E+08
2.10E+08
2.00E+08
1.90E+08
1.80E+08
1.70E+08
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
-2.00E+07
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

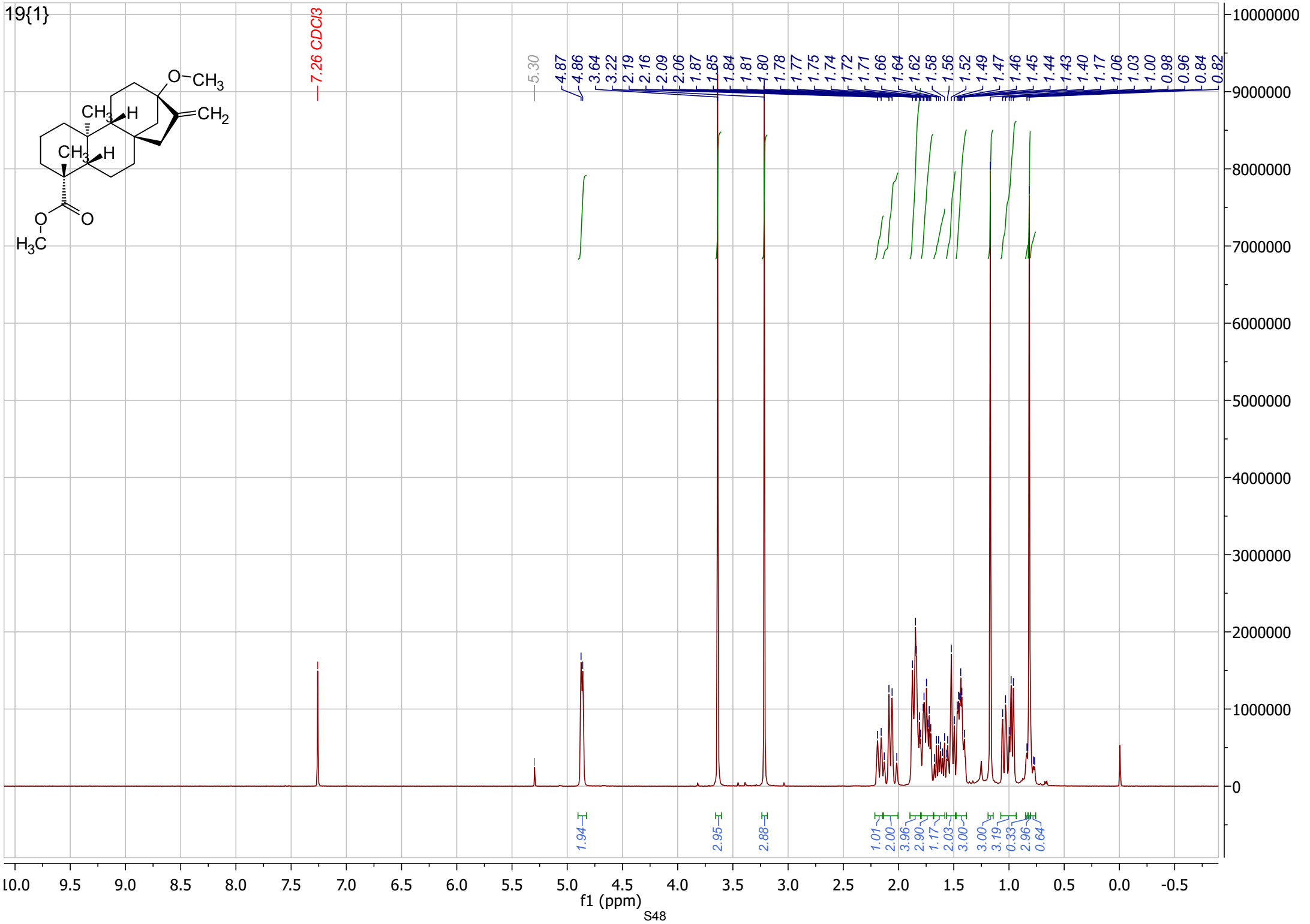

steviol methyl ester
7.26 CDCl3
4.97
4.81
3.63
2.21
2.19
2.17
2.16
2.12
2.09
2.05
2.04
1.86
1.83
1.79
1.77
1.75
1.74
1.73
1.73
1.56
1.53
1.53
1.46
1.45
1.42
1.42
1.28
1.25
1.25
1.17
1.06
1.06
1.03
1.03
0.99
0.96
0.94
0.82
OH
CH3
H
CH2
CH3
H
O
O
H3C
1.91
3.00
3.98
7.16
4.97
1.01
3.06
3.11
2.89
0.82
f1 (ppm)

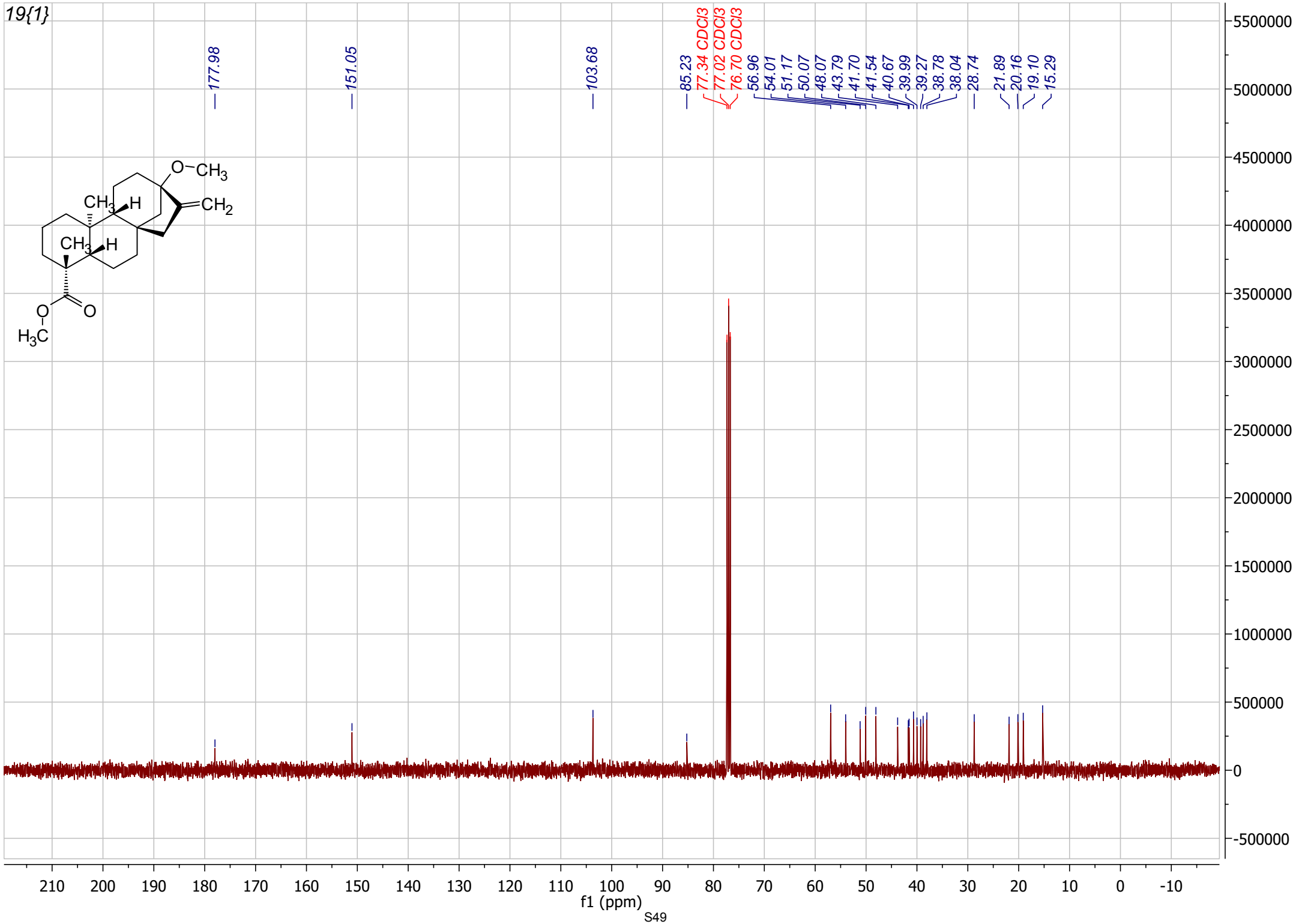
steviol methyl ester



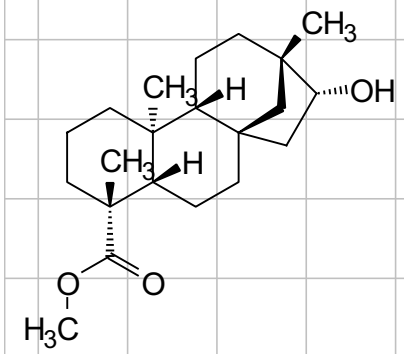
178.01
156.03
102.93
80.25
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
56.91
53.76
51.17
47.41
46.93
43.77
41.62
41.31
40.67
39.43
39.22
38.01
28.70
21.86
20.40
19.07
15.29

f1 (ppm)


19{1}
7.26 CDCl3
5.30
4.87
4.86
3.64
3.22
2.19
2.16
2.09
2.06
1.87
1.85
1.84
1.81
1.80
1.78
1.77
1.75
1.74
1.72
1.71
1.66
1.64
1.62
1.58
1.56
1.52
1.49
1.47
1.46
1.45
1.44
1.43
1.40
1.17
1.06
1.03
1.00
0.98
0.96
0.84
0.82
1.94
2.95
2.88
1.01
2.00
3.96
2.90
1.17
2.03
3.00
3.00
3.19
0.33
2.96
0.64
f1 (ppm)


19{1}
177.98
151.05
103.68
85.23
77.34 CDCl3
77.02 CDCl3
76.70 CDCl3
56.96
54.01
51.17
50.07
48.07
43.79
41.70
41.54
40.67
39.99
39.27
38.78
38.04
28.74
21.89
20.16
19.10
15.29
O–CH3
CH3
H
CH2
CH3
H
O
O
H3C
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

reduced isosteviol methyl ester



7.11 CDCl3

3.67 3.65 3.64 3.63 3.42 1.97 1.94 1.73 1.66 1.60 1.59 1.58 1.57 1.56 1.54 1.52 1.51 1.48 1.43 1.39 1.38 1.37 1.29 1.28 1.21 1.18 1.15 1.14 1.11 1.08 1.07 1.01 0.98 0.96 0.83 0.82 0.80 0.75 0.70 0.67 0.66 0.64 0.63 0.52

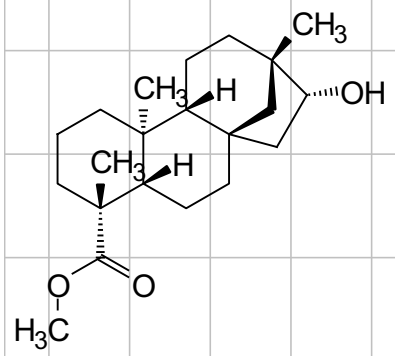
1.00 2.90 0.99 0.95 5.95 3.92 4.03 2.96 3.95 3.12 0.90 2.90

1.60E+08 1.50E+08 1.40E+08 1.30E+08 1.20E+08 1.10E+08 1.00E+08 9.00E+07 8.00E+07 7.00E+07 6.00E+07 5.00E+07 4.00E+07 3.00E+07 2.00E+07 1.00E+07 0.00E+00 -1.00E+07

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)

reduced isosteviol methyl ester



178.1

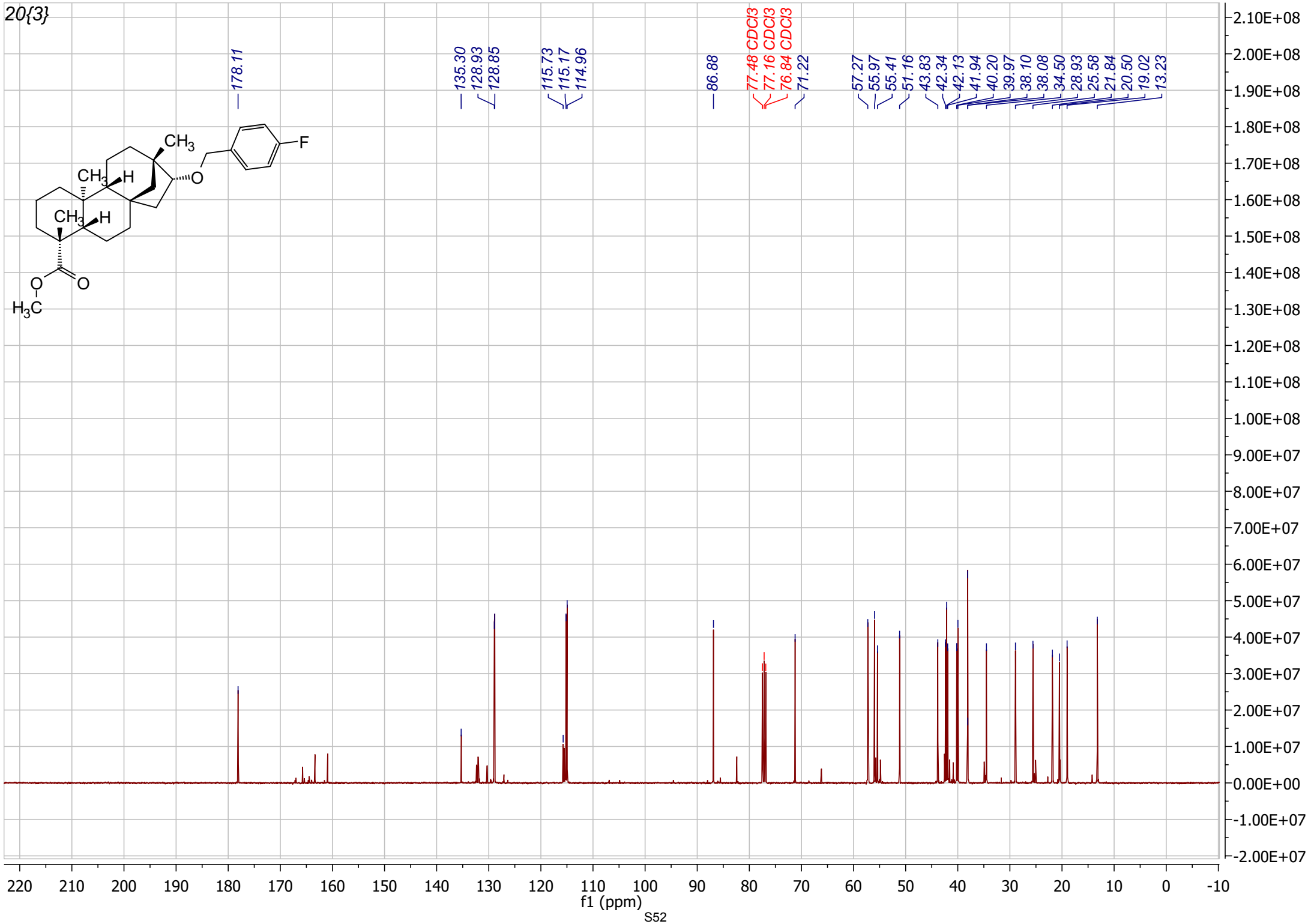
80.4
77.4 CDCl3
77.1 CDCl3
76.8 CDCl3

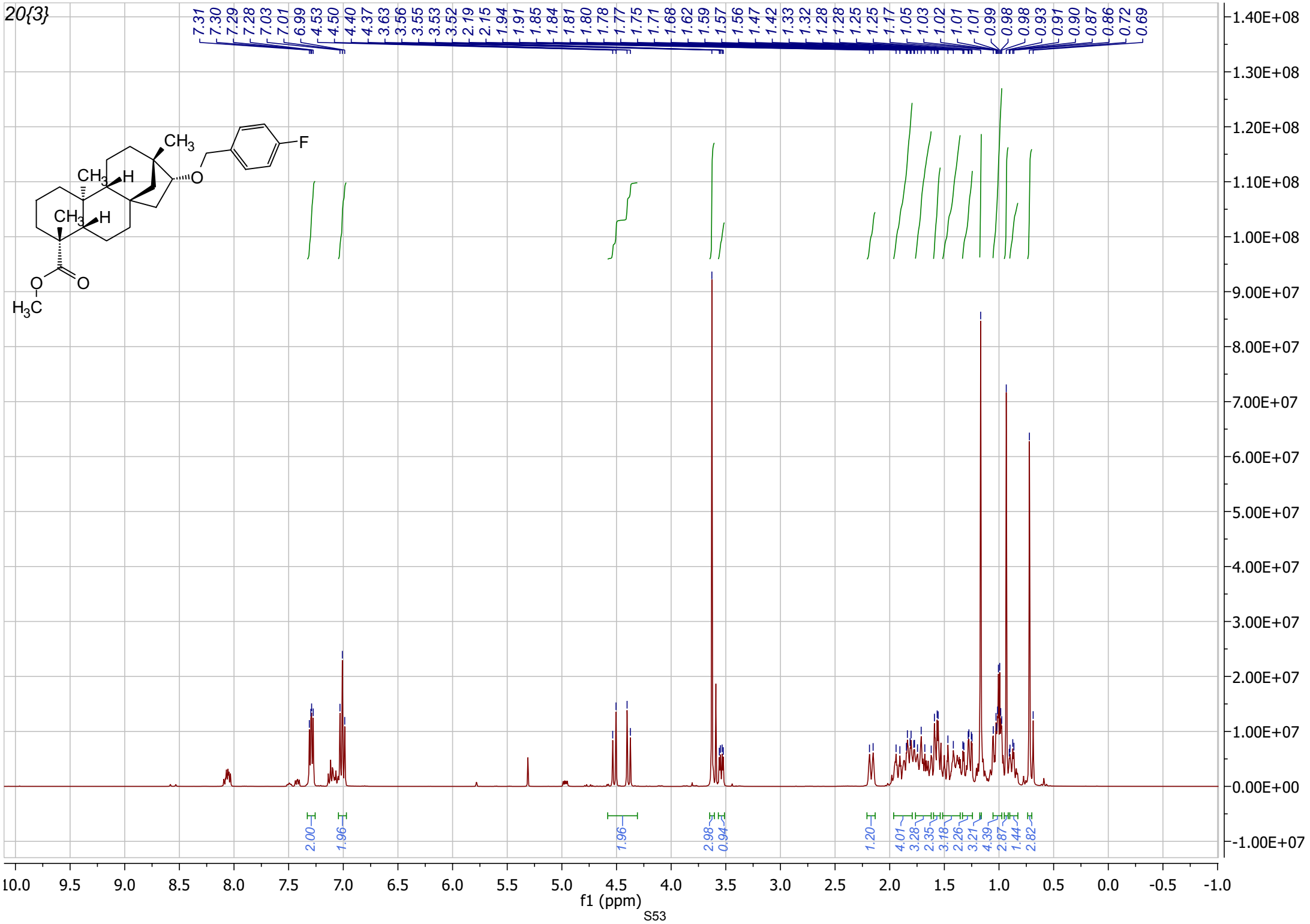
57.1
55.8
55.2
51.1
43.7
42.8
42.0
42.0
41.7
39.9
38.0
38.0
33.7
28.9
24.9
21.7
20.4
18.9
13.1

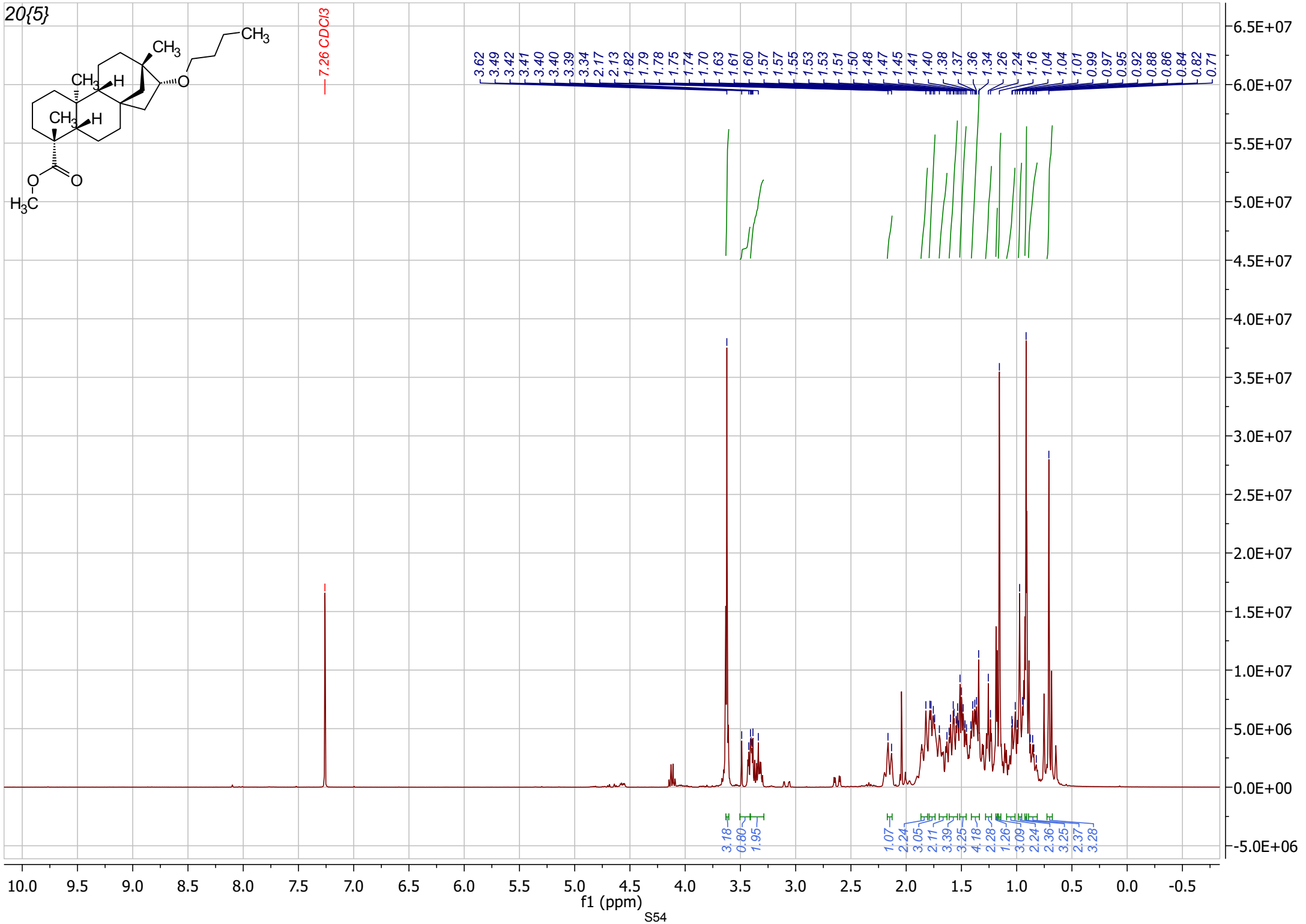
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07

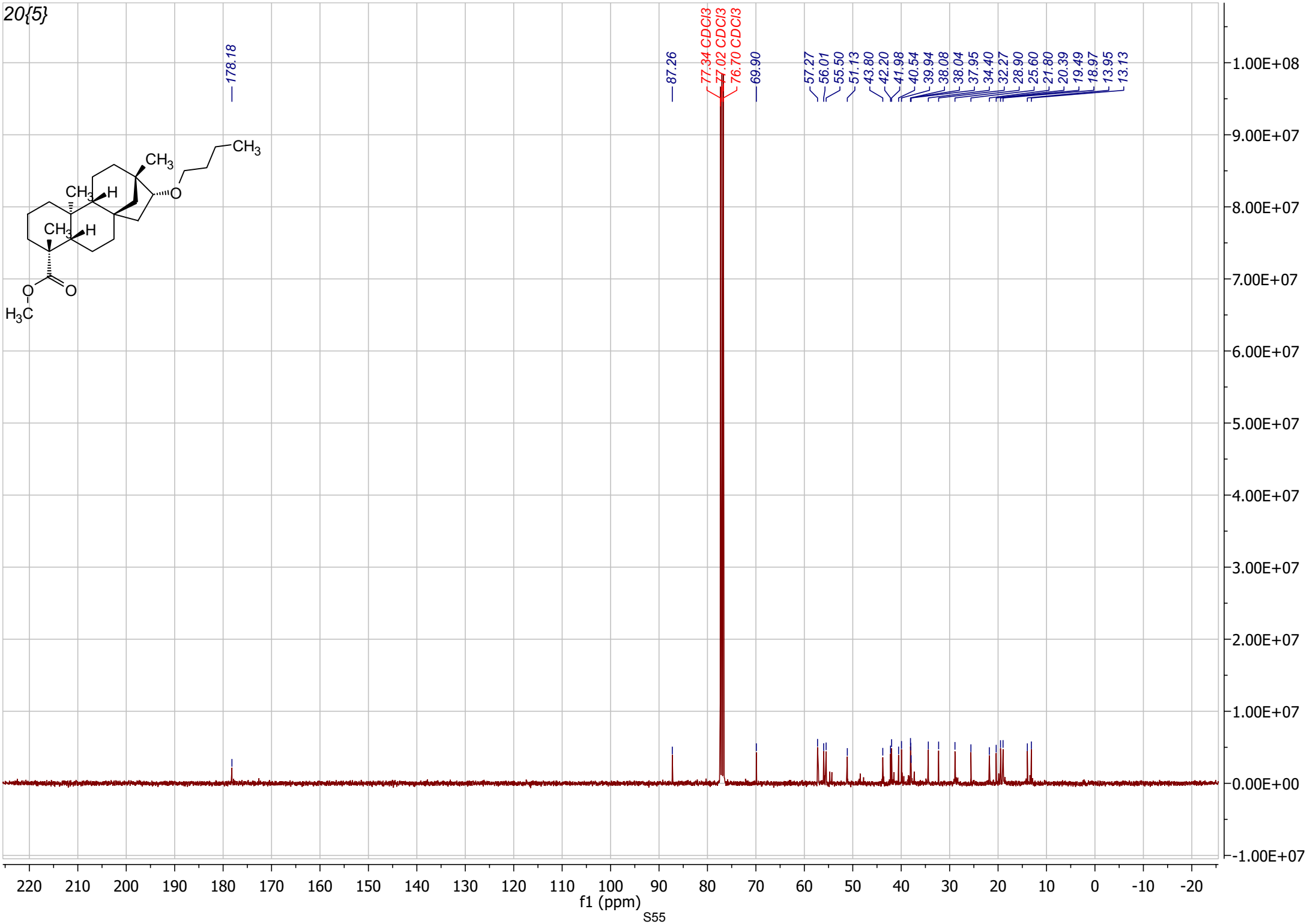
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

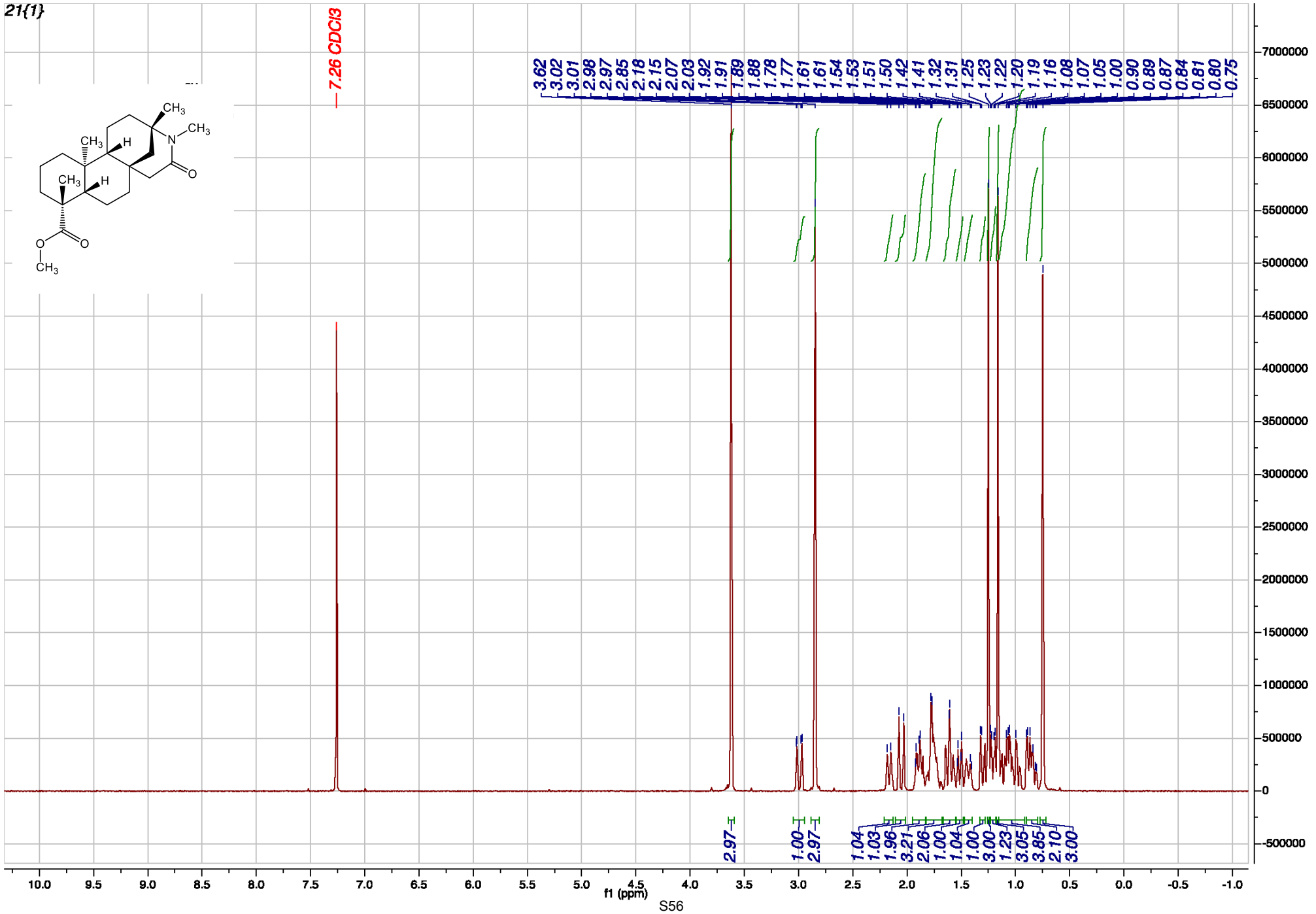
f1 (ppm)

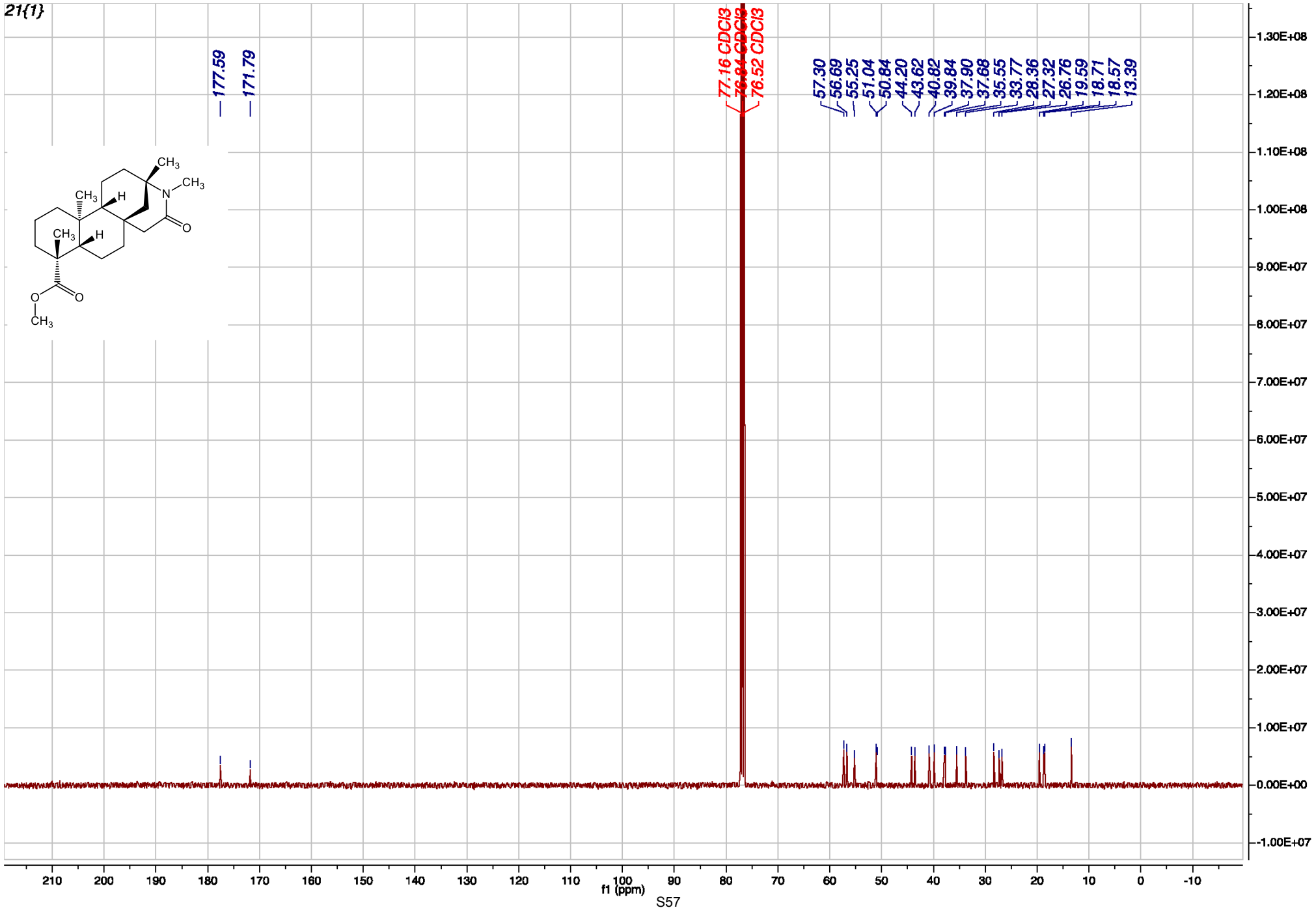

20{3}
178.11
135.30
128.93
128.85
115.73
115.17
114.96
86.88
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.22
57.27
55.97
55.41
51.16
43.83
42.34
42.13
41.94
40.20
39.97
38.10
38.08
34.50
28.93
25.58
21.84
20.50
19.02
13.23
CH3
F
CH3
H
O
CH3
H
O
O
H3C
2.10E+08
2.00E+08
1.90E+08
1.80E+08
1.70E+08
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
-2.00E+07
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

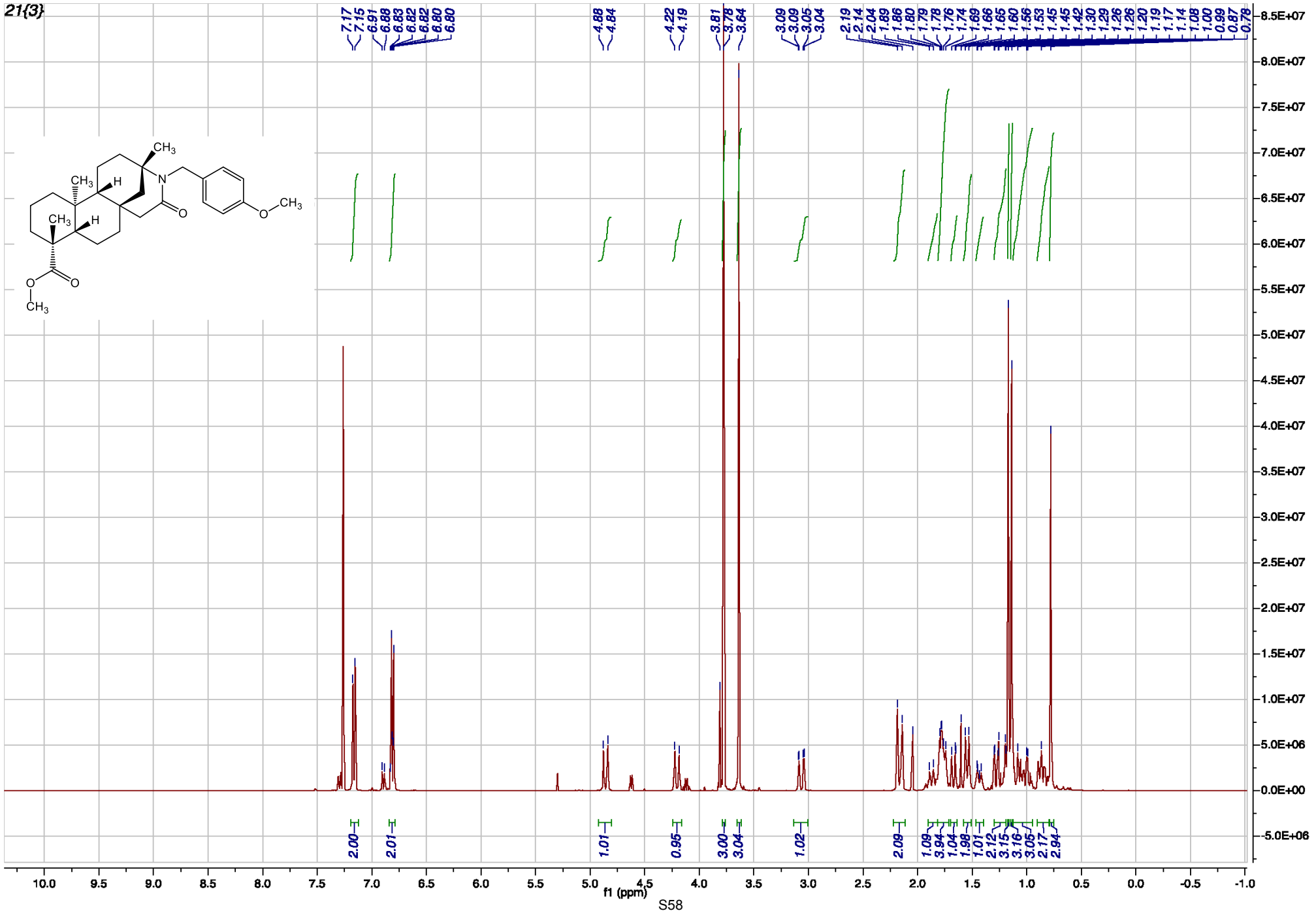

20{3}
7.31 7.30 7.29 7.28 7.03 7.01 6.99 4.53 4.50 4.40 4.37 3.63 3.56 3.55 3.53 3.52 2.19 2.15 1.94 1.91 1.85 1.84 1.81 1.80 1.78 1.77 1.75 1.71 1.68 1.62 1.59 1.57 1.56 1.47 1.42 1.33 1.32 1.28 1.28 1.25 1.25 1.17 1.05 1.03 1.02 1.01 1.01 0.99 0.98 0.98 0.93 0.91 0.90 0.87 0.86 0.72 0.69
CH3
F
CH3
H
O
CH3
H
O
O
H3C
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
2.00 1.96 1.96 2.98 0.94 1.20 4.01 3.28 2.35 3.18 2.26 3.21 4.39 2.87 1.44 2.82
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)

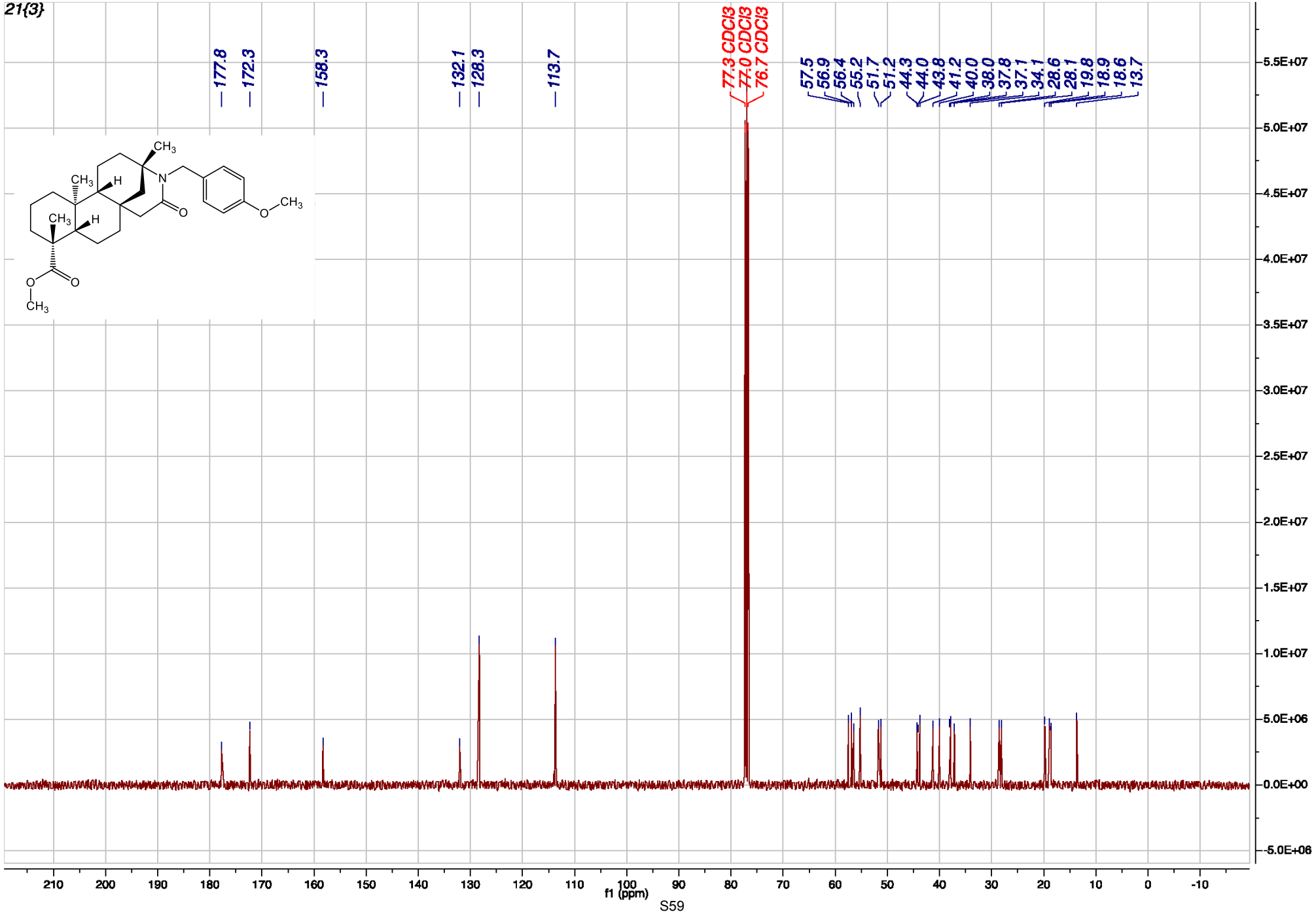

20{5}
7.26 CDCl3
3.62 3.49 3.42 3.41 3.40 3.40 3.39 3.34 2.17 2.13 1.82 1.79 1.78 1.75 1.74 1.70 1.63 1.61 1.60 1.57 1.57 1.55 1.53 1.53 1.51 1.50 1.48 1.47 1.45 1.41 1.40 1.38 1.37 1.36 1.34 1.26 1.24 1.16 1.04 1.04 1.01 0.99 0.97 0.95 0.92 0.88 0.86 0.84 0.82 0.71
3.18 0.80 1.95
1.07 2.24 3.05 2.11 3.39 3.25 4.18 2.28 1.26 3.09 2.24 2.36 3.25 2.37 3.28
6.5E+07 6.0E+07 5.5E+07 5.0E+07 4.5E+07 4.0E+07 3.5E+07 3.0E+07 2.5E+07 2.0E+07 1.5E+07 1.0E+07 5.0E+06 0.0E+00 -5.0E+06
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)


20{5}
178.18
87.26
77.34 CDCl3
77.02 CDCl3
76.70 CDCl3
69.90
57.27
56.01
55.50
51.13
43.80
42.20
41.98
40.54
39.94
38.08
38.04
37.95
34.40
32.27
28.90
25.60
21.80
20.39
19.49
18.97
13.95
13.13
CH3
CH3
CH3
H
CH3
H
O
O
O
H3C
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


21{1}
7.26 CDCl3
3.62 3.02 3.01 2.98 2.97 2.85 2.18 2.15 2.07 2.03 1.92 1.91 1.89 1.88 1.78 1.77 1.61 1.61 1.54 1.53 1.51 1.50 1.42 1.41 1.32 1.31 1.25 1.23 1.22 1.20 1.19 1.16 1.08 1.07 1.05 1.00 0.90 0.89 0.87 0.84 0.81 0.80 0.75
2.97 1.00 2.97 1.04 1.03 1.96 3.21 2.06 1.00 1.04 1.00 3.00 1.23 3.05 3.85 2.10 3.00
f1 (ppm)


21{1}
177.59
171.79
77.16 CDCl3
76.84 CDCl3
76.52 CDCl3
57.30
56.69
55.25
51.04
50.84
44.20
43.62
40.82
39.84
37.90
37.68
35.55
33.77
28.36
27.32
26.76
19.59
18.71
18.57
13.39
CH3
CH3
CH3
H
H
N
O
O
O
CH3
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


21(3)
7.17
7.15
6.91
6.88
6.83
6.82
6.82
6.80
6.80
4.88
4.84
4.22
4.19
3.81
3.78
3.64
3.09
3.09
3.05
3.04
2.19
2.14
2.04
1.89
1.86
1.80
1.79
1.78
1.76
1.74
1.69
1.66
1.65
1.60
1.56
1.53
1.45
1.45
1.42
1.30
1.29
1.26
1.26
1.20
1.19
1.17
1.14
1.08
1.00
0.99
0.87
0.78
CH3
CH3
H
N
O
O
CH3
CH3
H
O
O
O
CH3
2.00
2.01
1.01
0.95
3.00
3.04
1.02
2.09
1.09
3.94
1.04
1.98
1.01
2.12
3.15
3.16
3.05
2.17
2.94
f1 (ppm)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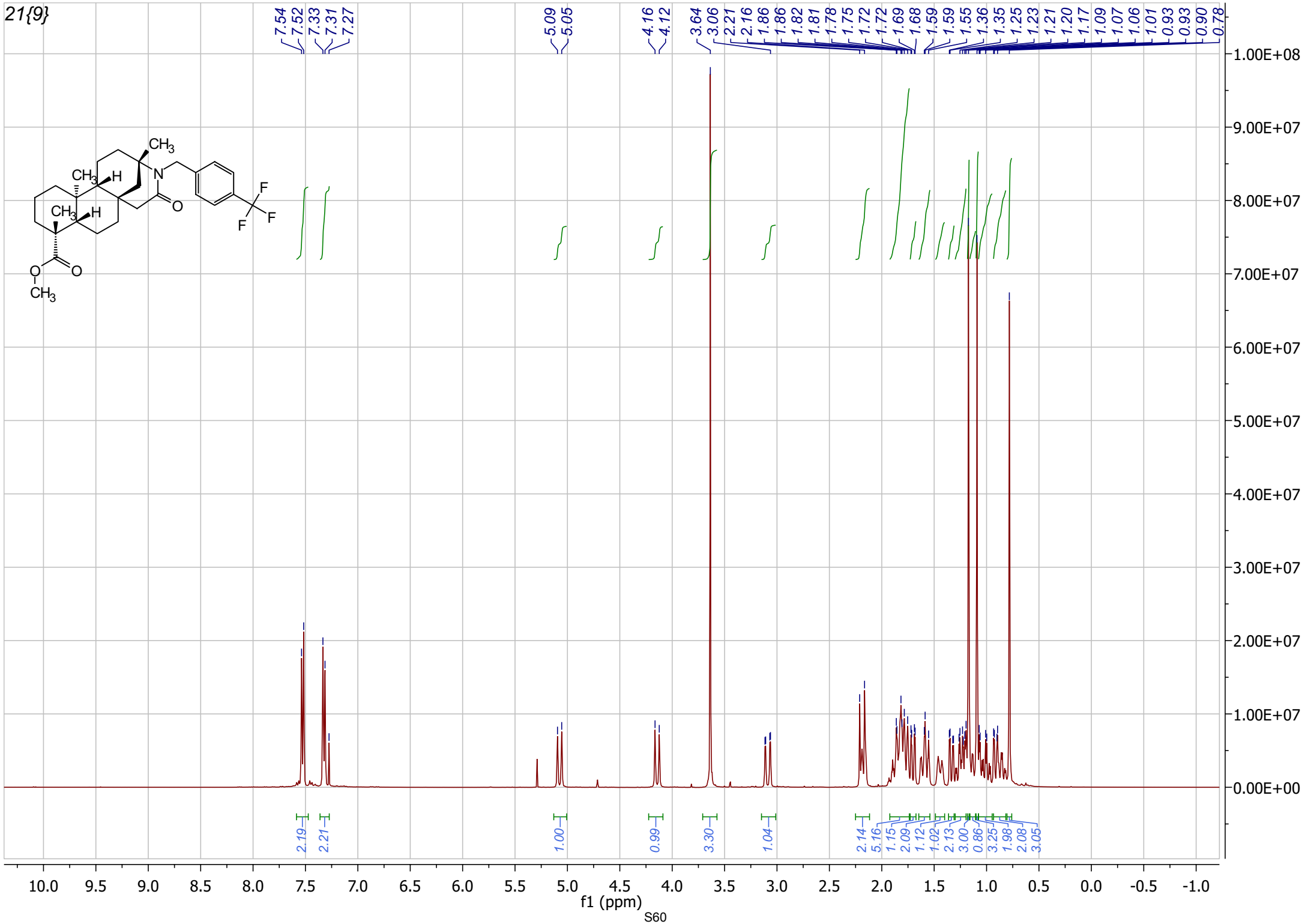
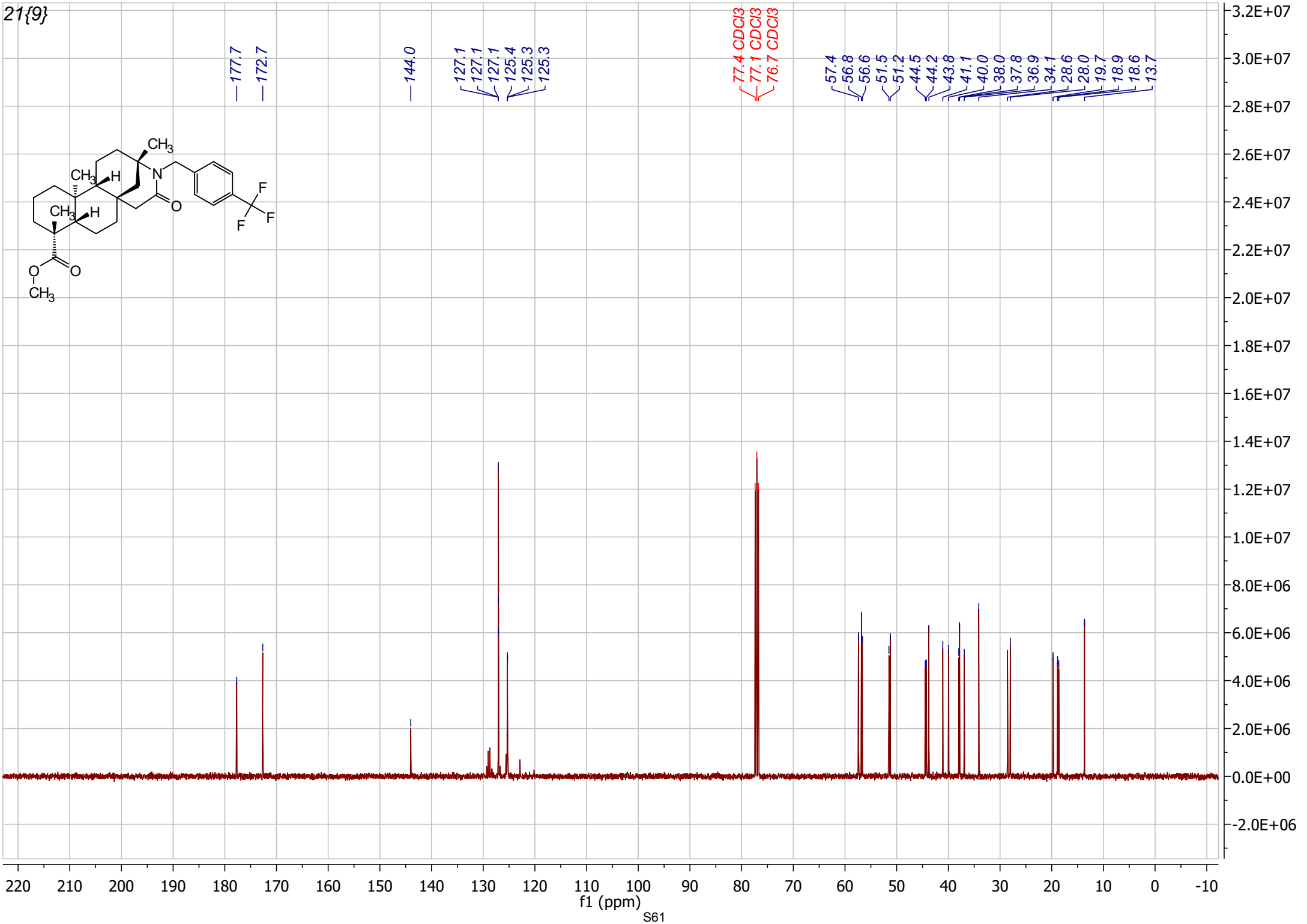
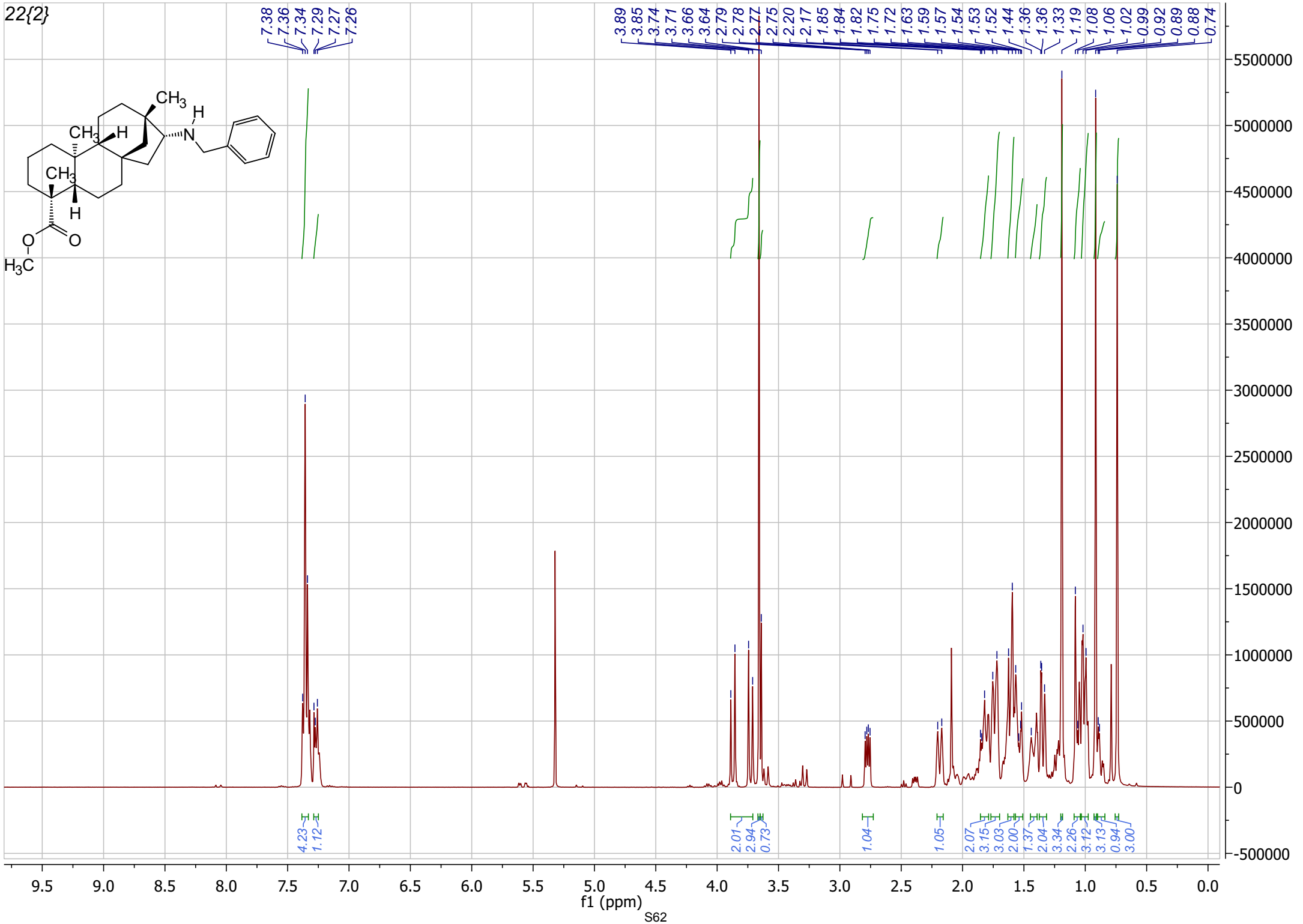
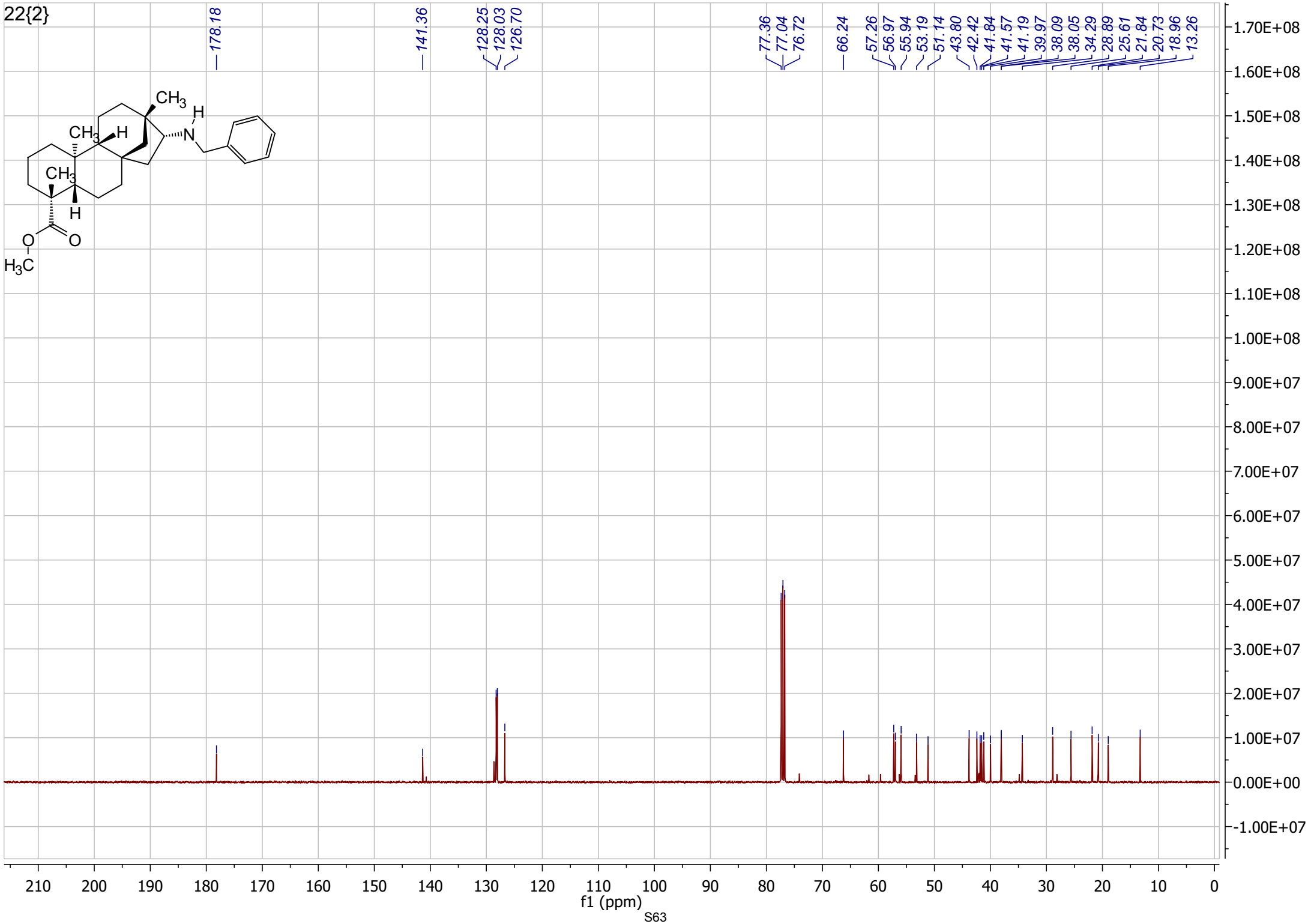
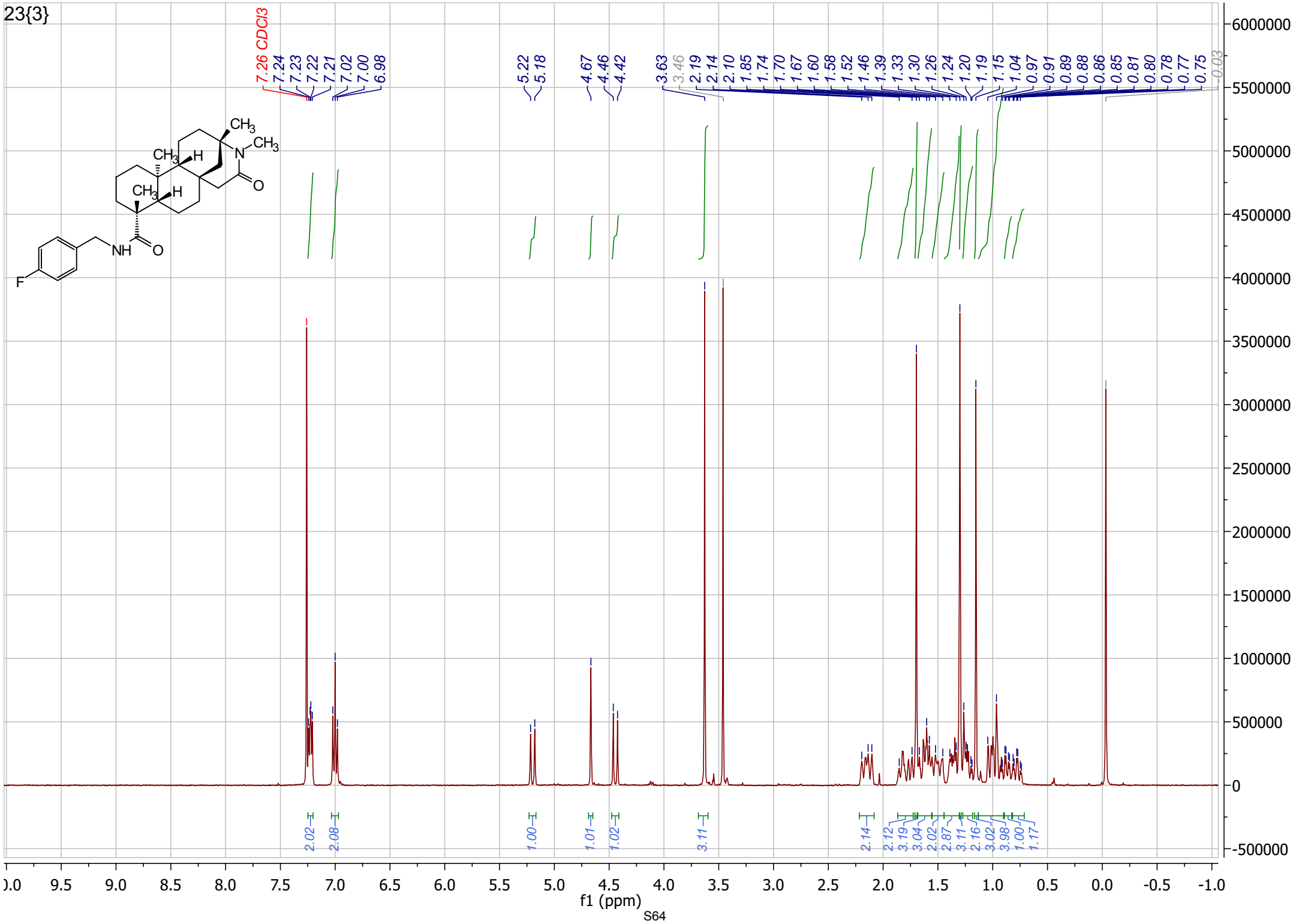
177.8
172.3
158.3
132.1
128.3
113.7
77.3 CDCl3
77.0 CDCl3
76.7 CDCl3
57.5
56.9
56.4
55.2
51.7
51.2
44.3
44.0
43.8
41.2
40.0
38.0
37.8
37.1
34.1
28.6
28.1
19.8
18.9
18.6
13.7
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

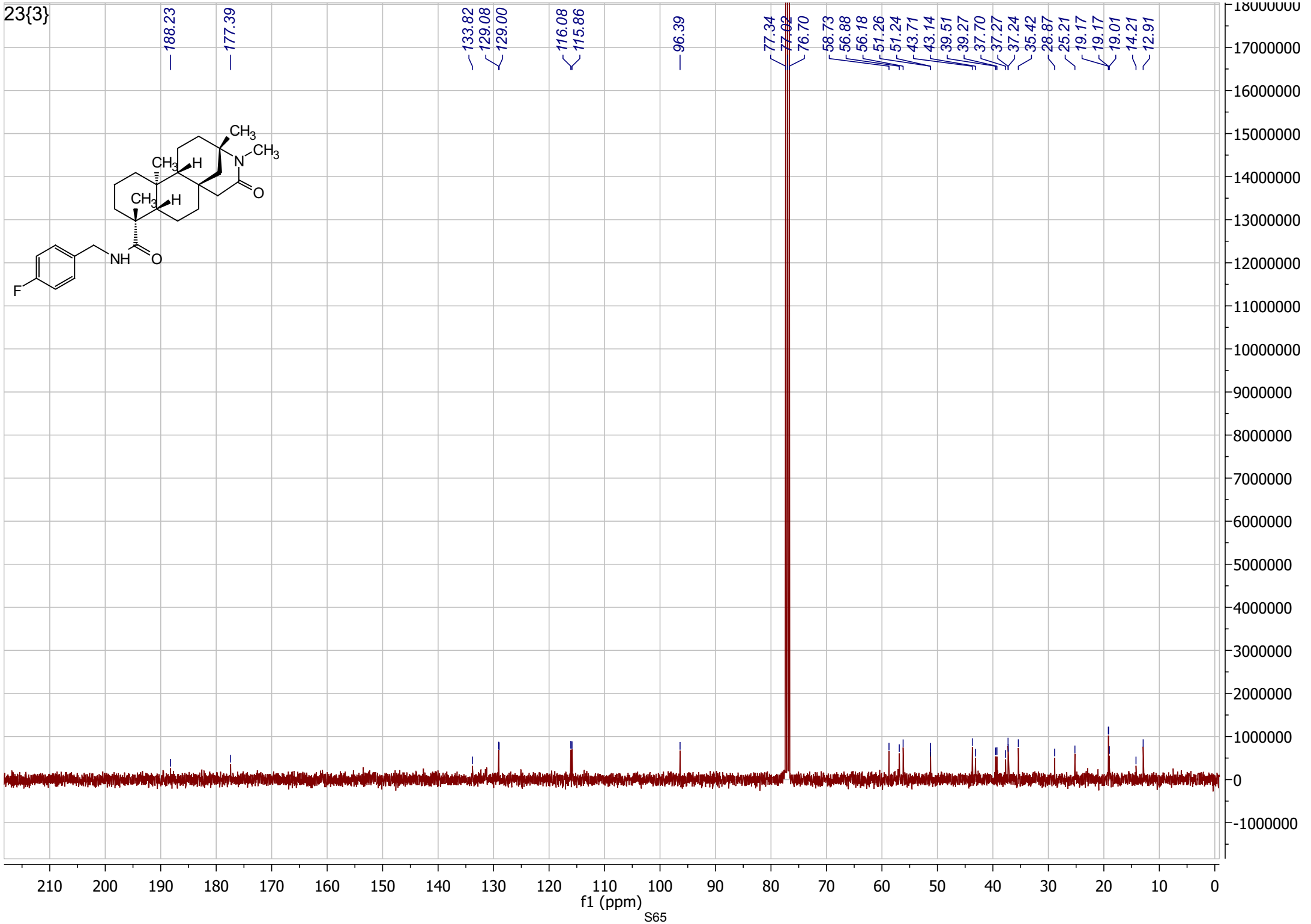

21{9}
7.54
7.52
7.33
7.31
7.27
5.09
5.05
4.16
4.12
3.64
3.06
2.21
2.16
1.86
1.86
1.82
1.81
1.78
1.75
1.72
1.72
1.69
1.68
1.59
1.59
1.55
1.36
1.35
1.25
1.23
1.21
1.20
1.17
1.09
1.07
1.06
1.01
0.93
0.93
0.90
0.78
CH3
CH3
H
N
O
CH3
H
F
F
F
O
O
CH3
2.19
2.21
1.00
0.99
3.30
1.04
2.14
5.16
1.15
2.09
1.12
1.02
2.13
3.00
0.86
3.25
1.98
2.08
3.05
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+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)

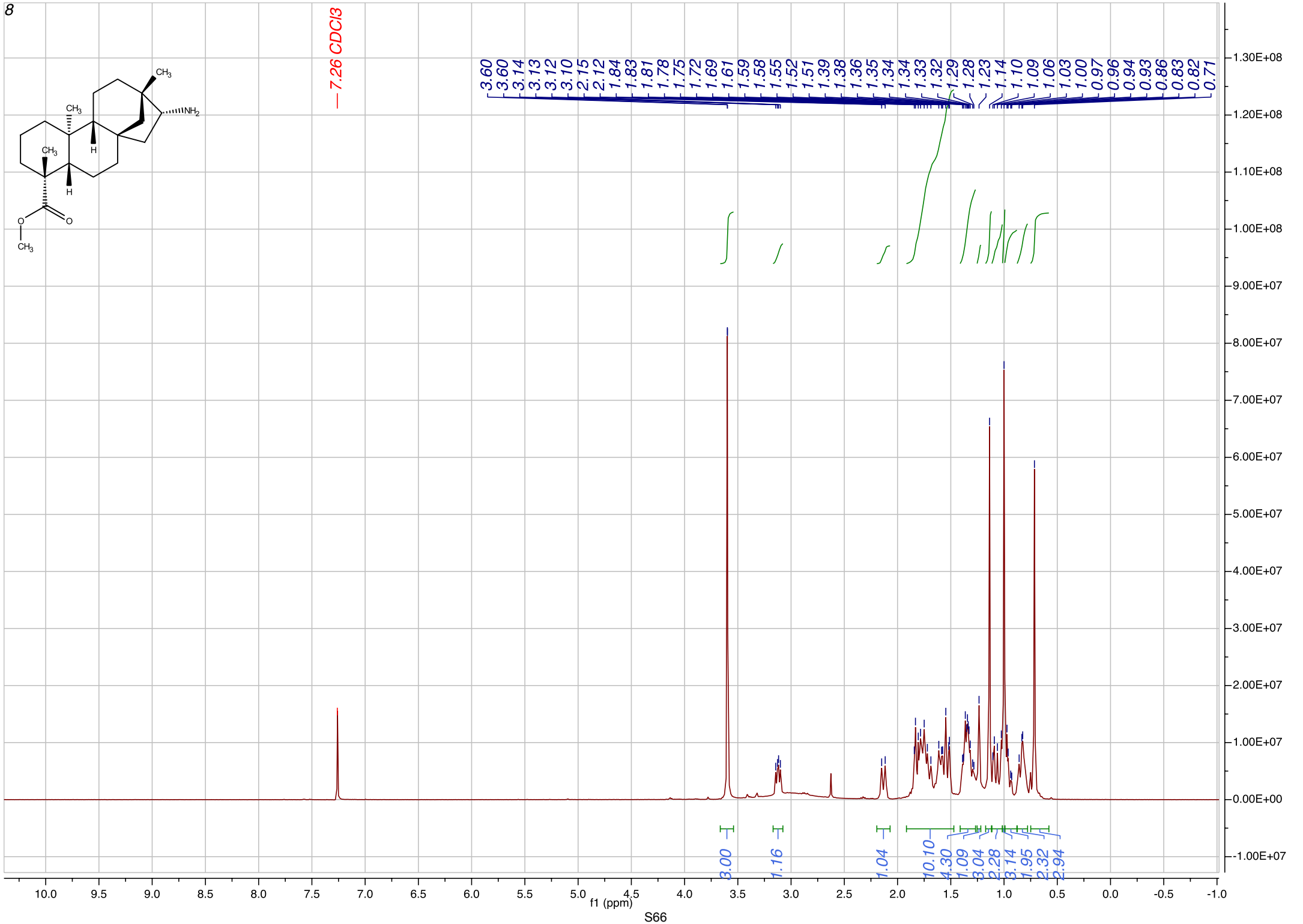

21{9}
177.7
172.7
144.0
127.1
127.1
127.1
125.4
125.3
125.3
77.4 CDCl3
77.1 CDCl3
76.7 CDCl3
57.4
56.8
56.6
51.5
51.2
44.5
44.2
43.8
41.1
40.0
38.0
37.8
36.9
34.1
28.6
28.0
19.7
18.9
18.6
13.7
CH3
CH3
H
N
O
CH3
H
F
F
F
O
O
O
CH3
3.2E+07
3.0E+07
2.8E+07
2.6E+07
2.4E+07
2.2E+07
2.0E+07
1.8E+07
1.6E+07
1.4E+07
1.2E+07
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
-2.0E+06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


22{2}
7.38
7.36
7.34
7.29
7.27
7.26
3.89
3.85
3.74
3.71
3.66
3.64
2.79
2.78
2.77
2.75
2.20
2.17
1.85
1.84
1.82
1.75
1.72
1.63
1.59
1.57
1.54
1.53
1.52
1.44
1.36
1.36
1.33
1.19
1.08
1.06
1.02
0.99
0.92
0.89
0.88
0.74
CH3
H
N
CH3
H
CH3
H
O
O
H3C
4.23
1.12
2.01
2.94
0.73
1.04
1.05
2.07
3.15
3.03
2.00
1.37
2.04
3.34
2.26
3.12
3.13
0.94
3.00
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
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)

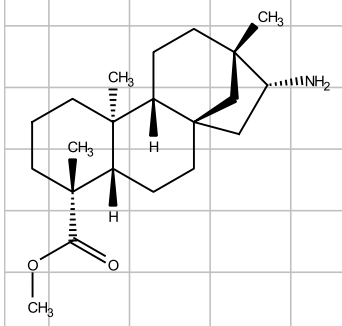

22{2}
178.18
141.36
128.25
128.03
126.70
77.36
77.04
76.72
66.24
57.26
56.97
55.94
53.19
51.14
43.80
42.42
41.84
41.57
41.19
39.97
38.09
38.05
34.29
28.89
25.61
21.84
20.73
18.96
13.26
CH3
H
N
CH3
H
CH3
H
O
O
H3C
1.70E+08
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


23{3}
7.26 CDCl3
7.24
7.23
7.22
7.21
7.02
7.00
6.98
5.22
5.18
4.67
4.46
4.42
3.63
3.46
2.19
2.14
2.10
1.85
1.74
1.70
1.67
1.60
1.58
1.52
1.46
1.39
1.33
1.30
1.26
1.24
1.20
1.19
1.15
1.04
0.97
0.91
0.89
0.88
0.86
0.85
0.81
0.80
0.78
0.77
0.75
0.03
CH3
CH3
H
N
CH3
CH3
H
O
NH
O
F
2.02
2.08
1.00
1.01
1.02
3.11
2.14
2.12
3.19
3.04
2.02
2.87
3.11
2.16
3.02
3.98
1.00
1.17
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
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)


23{3}
188.23
177.39
133.82
129.08
129.00
116.08
115.86
96.39
77.34
77.02
76.70
58.73
56.88
56.18
51.26
51.24
43.71
43.14
39.51
39.27
37.70
37.27
37.24
35.42
28.87
25.21
19.17
19.17
19.01
14.21
12.91
CH3
CH3
N
CH3
H
CH3
H
O
NH
O
F
18000000
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8
7.26 CDCl3
3.60
3.60
3.14
3.13
3.12
3.10
2.15
2.12
1.84
1.83
1.81
1.78
1.75
1.72
1.69
1.61
1.59
1.58
1.55
1.52
1.51
1.39
1.38
1.36
1.35
1.34
1.34
1.33
1.32
1.29
1.28
1.23
1.14
1.10
1.09
1.06
1.03
1.00
0.97
0.96
0.94
0.93
0.86
0.83
0.82
0.71
CH3
CH3
NH2
CH3
H
H
O
O
O
CH3
3.00
1.16
1.04
10.10
4.30
1.09
3.04
2.28
3.14
1.95
2.32
2.94
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
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)

8



178.1

77.0
76.7

59.6
57.0
56.0
55.6
51.1
43.7
42.4
41.2
41.1
39.7
39.0
38.0
38.0
33.0
28.8
24.6
21.6
20.2
18.8
12.9

f1 (ppm)