

Ring Closing Metathesis Reactions of α -Methylene- β -Lactams: Application to the Synthesis of a Simplified Phyllostictine Analogue with Herbicidal Activity

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Supplementary Information

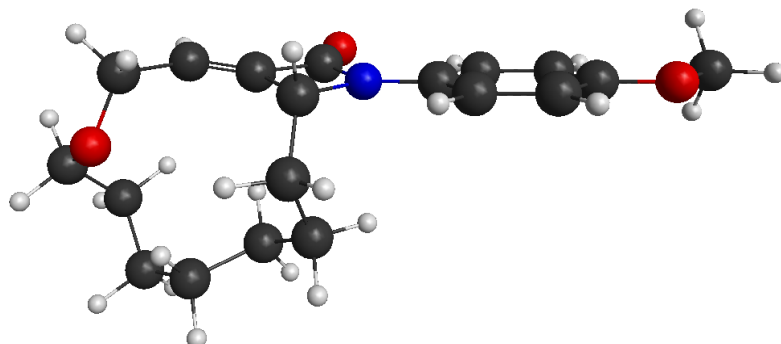
DFT Modelling of <i>E</i> - and <i>Z</i> - 19 , <i>E</i> - and <i>Z</i> - 21	2-7
Depiction of the X-ray crystal structure of <i>Z</i> - 21	8
HPLC traces showing equilibration of RCM products.....	9
Growth inhibition assay with <i>Chlamydomonas reinhardtii</i>	10
Copies of ¹ H and ¹³ C NMR spectra of 9-14a , 19-23	11-24
References.....	25

DFT Calculations

DFT calculations were performed using PCGAMESS/Firefly 8.0.1.¹ with Grimme's B3LYP-D3(BJ) functional² and the SVP basis set³ for geometry optimisations and zero-point energies (ZPE) calculations. Final energies were then calculated using the TZVP basis set.³

Structure	B3LYP-D3(BJ) / SVP energy (H)	B3LYP-D3(BJ) / SVP ZPE (H)	B3LYP-D3(BJ) / TZVP (H)	TZVP + ZPE (H)	Relative energy (kJ / mol)
<i>E</i> -19	-1018.85621	0.412343	-1019.947407	-1019.535064	0
<i>Z</i> -19	-1018.85474	0.412188	-1019.946925	-1019.534737	0.858

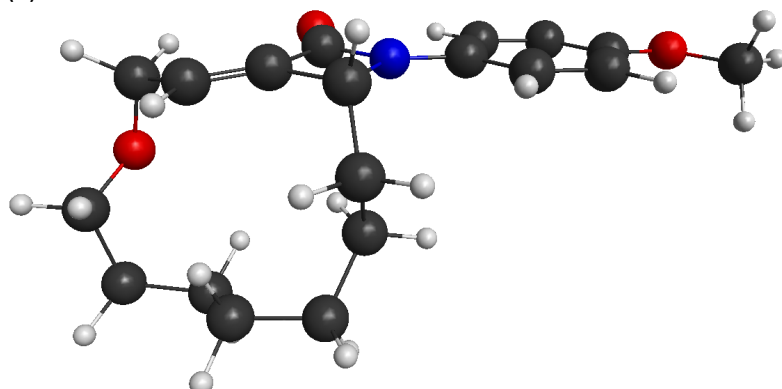
E-19



C	6.0	-2.6925890762	-4.0105155032	17.7334298408
O	8.0	-2.6797324983	-2.6117792185	17.5690143488
C	6.0	-1.9698525083	-2.0827322288	16.5379640165
C	6.0	-1.9815113502	-0.6827303719	16.4276197350
C	6.0	-1.2835753610	-0.0478276393	15.4064383256
C	6.0	-0.5559055287	-0.8010295888	14.4660478805
C	6.0	-0.5420645267	-2.2013600999	14.5754026706
C	6.0	-1.2429716417	-2.8360916814	15.6028636463
N	7.0	0.1548414176	-0.1670803108	13.4486756439
O	8.0	1.5057615826	-1.7194438569	12.2507516420
C	6.0	1.0894368216	-0.6170913467	12.5184354853
C	6.0	1.3245113963	0.7933840986	12.0595731153
C	6.0	0.2663704904	1.2633613433	13.0636068261
C	6.0	-1.0152568418	1.9364829079	12.5519071645
C	6.0	-1.9271172086	1.0727659177	11.6678784297
C	6.0	-1.4218014004	0.7984983553	10.2448937068
C	6.0	-1.4184546610	2.0383217452	9.3436265172
C	6.0	-0.6739289439	1.8378819043	8.0157418964
C	6.0	0.8482720756	1.6624970589	8.1290896117
C	6.0	1.6085199115	2.9080447162	8.5923389093
O	8.0	1.3366114373	3.3088845968	9.9268567403
C	6.0	2.2300232835	2.8432683243	10.9207109696
C	6.0	2.1621934679	1.3579180610	11.1901697893
H	1.0	-3.1303756185	-4.5235210228	16.8572586946
H	1.0	-3.3137854386	-4.2185126336	18.6154073614
H	1.0	-1.6776567091	-4.4139251258	17.9063539153
H	1.0	-2.5475563782	-0.1085500515	17.1639092471
H	1.0	-1.2984414594	1.0412210500	15.3415158741

H	1.0	0.0309862460	-2.7825483198	13.8526818188
H	1.0	-1.2120847210	-3.9240550394	15.6618748842
H	1.0	0.7010895176	1.8719158773	13.8784372706
H	1.0	-0.7111225233	2.8543552254	12.0226060640
H	1.0	-1.5951324107	2.2731284154	13.4269627158
H	1.0	-2.1152141668	0.1170832278	12.1840222923
H	1.0	-2.9076468999	1.5763402992	11.6030967348
H	1.0	-2.0570350939	0.0211531265	9.7849404632
H	1.0	-0.4120496967	0.3649556616	10.2906608319
H	1.0	-0.9648226116	2.8869214493	9.8749171901
H	1.0	-2.4645131979	2.3227522013	9.1308629218
H	1.0	-1.0913916088	0.9558034365	7.4973289487
H	1.0	-0.8763911218	2.7001081894	7.3546791860
H	1.0	1.0908272028	0.8130121883	8.7876290930
H	1.0	1.2484372676	1.3966381130	7.1341469508
H	1.0	2.6983541002	2.7554530478	8.4625995469
H	1.0	1.3238272942	3.7623195494	7.9526926159
H	1.0	1.9632622152	3.3981384954	11.8335277369
H	1.0	3.2694264169	3.1189476702	10.6528129215
H	1.0	2.8220590577	0.6895987854	10.6249278081

(Z)-19

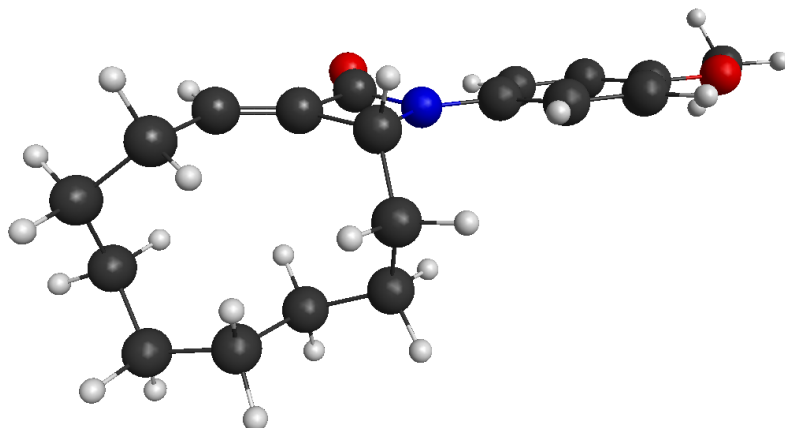


C	6.0	2.6875865884	12.5075656148	3.1861196413
O	8.0	1.4671040212	11.8799677414	3.4986523743
C	6.0	1.4222983454	10.5225523712	3.5414403710
C	6.0	2.5167657404	9.6817317973	3.2997211501
C	6.0	2.3598362173	8.2925632221	3.3683532140
C	6.0	1.1149977701	7.7266493607	3.6715532094
C	6.0	0.0151060565	8.5762369191	3.9193284079
C	6.0	0.1747326299	9.9525749780	3.8543863859
N	7.0	0.9560300942	6.3441682407	3.7284497422
O	8.0	-1.2690043841	5.7588523429	4.3496769356
C	6.0	-0.1317619293	5.5190853965	4.0161208307
C	6.0	0.7068403389	4.3063764903	3.7293486734
C	6.0	1.8889355188	5.2288601231	3.4324054623
C	6.0	2.4425563739	5.1284251239	2.0072041657
C	6.0	1.4288874655	5.4796424084	0.9043631554
C	6.0	1.5812404145	4.6309035821	-0.3672531101
C	6.0	1.0271166544	3.2037165128	-0.2291052434
C	6.0	-0.5045659044	3.1482117647	-0.1812834325

C	6.0	-1.0959183931	1.7621307827	0.1068599252
C	6.0	-0.8830468072	1.2986364121	1.5452558187
O	8.0	-1.4799468333	2.2431084707	2.4140883473
C	6.0	-0.8951444549	2.3862126577	3.6967666476
C	6.0	0.4827320735	2.9995846428	3.6000776363
H	1.0	3.0486076981	12.2262208244	2.1793093016
H	1.0	3.4754233388	12.2657332186	3.9236315653
H	1.0	2.5003622598	13.5899426935	3.2073348872
H	1.0	3.4982084598	10.0899281747	3.0584436547
H	1.0	3.2219495355	7.6498567637	3.1840478764
H	1.0	-0.9507327193	8.1332619020	4.1626312934
H	1.0	-0.6657089959	10.6234143092	4.0442652510
H	1.0	2.7053288612	5.1696578193	4.1746576036
H	1.0	2.7914636758	4.0867040143	1.8945071130
H	1.0	3.3454450641	5.7522844713	1.9034378781
H	1.0	0.4030414599	5.3624303988	1.2863677695
H	1.0	1.5264218564	6.5490566075	0.6584424957
H	1.0	2.6475758904	4.5909354210	-0.6534723875
H	1.0	1.0628201131	5.1322846537	-1.2031248007
H	1.0	1.3848849253	2.5871024661	-1.0727368722
H	1.0	1.4491973284	2.7374087816	0.6784506702
H	1.0	-0.8823353502	3.8329931663	0.5939110754
H	1.0	-0.9004803526	3.5177494780	-1.1431749348
H	1.0	-2.1816047998	1.7853006191	-0.0854903583
H	1.0	-0.6691511984	1.0042601202	-0.5746056478
H	1.0	-1.3339891084	0.2978358450	1.7021524692
H	1.0	0.1982477251	1.1950905486	1.7490970261
H	1.0	-0.8497162278	1.4113271952	4.2222355652
H	1.0	-1.5612238604	3.0573222348	4.2564257489
H	1.0	1.3204488247	2.3555123173	3.3082674481

Structure	B3LYP-D3(BJ) / SVP energy (H)	B3LYP-D3(BJ) / SVP ZPE (H)	B3LYP-D3(BJ) / TZVP (H)	TZVP + ZPE (H)	Relative energy (kJ / mol)
	-943.7053782	0.407759	-944.7085129	-944.3007539	0
<i>E</i> -21	-943.7077529	0.407512	-944.7100018	-944.3024898	-4.55672
<i>Z</i> -21					

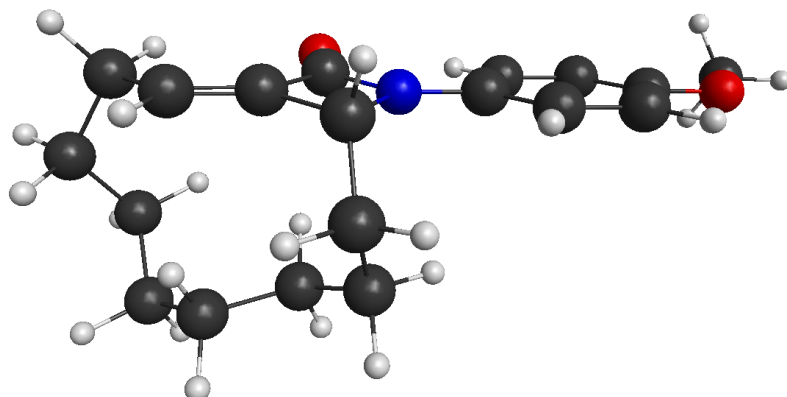
E-21



C	6.0	7.6297504951	0.5508387243	16.6125699799
O	8.0	7.6393236518	-0.2444175237	15.4506526667
C	6.0	8.3418214692	0.1868051647	14.3693854224
C	6.0	9.0747270198	1.3826979716	14.3187587676
C	6.0	9.7727165487	1.7351991470	13.1614731632
C	6.0	9.7477873462	0.9001167225	12.0320859147
C	6.0	9.0002489023	-0.2916944687	12.0821868932
C	6.0	8.3109820078	-0.6432157089	13.2375448129
N	7.0	10.4429921031	1.2597595614	10.8780162735
C	6.0	11.0074263341	2.4611099834	10.4477415841
O	8.0	11.1552794829	3.5286306309	10.9950636895
C	6.0	11.3210056881	1.8535524509	9.1138328492
C	6.0	10.6681801271	0.5469101519	9.5951981892
C	6.0	11.9043813339	2.3366491617	8.0159757770
C	6.0	12.2252776491	1.5836141855	6.7591026362
C	6.0	13.6518905409	1.8688006344	6.2389861187
C	6.0	14.8143990914	1.7329986459	7.2383688630
C	6.0	15.2872276321	0.3125052849	7.5849776119
C	6.0	14.3097862544	-0.5671514063	8.3747911356
C	6.0	13.9355498244	-0.0200040548	9.7573357798
C	6.0	12.7760907484	-0.7660708949	10.4327675818
C	6.0	11.4437640436	-0.7711354869	9.6717714265
H	1.0	7.1935894750	1.5493260813	16.4244071903
H	1.0	8.6452938096	0.6834272111	17.0296345681
H	1.0	7.0082273214	0.0236702059	17.3494189579
H	1.0	9.1134121078	2.0540679091	15.1767837182
H	1.0	10.3349375535	2.6680745217	13.1154786406
H	1.0	8.9496172217	-0.9445267830	11.2096907965
H	1.0	7.7302195867	-1.5664730627	13.2870761983
H	1.0	9.7107124269	0.3597767351	9.0725342896

H	1.0	12.2121071091	3.3900558035	8.0575996880
H	1.0	12.0576153997	0.5082476904	6.9142556573
H	1.0	11.5159346113	1.8887984139	5.9666835288
H	1.0	13.6591065674	2.9066167857	5.8620199039
H	1.0	13.8430810452	1.2290753769	5.3593730518
H	1.0	15.6778410067	2.2667651011	6.8062359980
H	1.0	14.5679201927	2.2848248599	8.1612995398
H	1.0	15.5547727869	-0.2073314940	6.6472234956
H	1.0	16.2269807700	0.3982995886	8.1598528236
H	1.0	13.4032746203	-0.7221121395	7.7710375313
H	1.0	14.7514845735	-1.5726609506	8.4949403963
H	1.0	13.6840212819	1.0465348025	9.6838048261
H	1.0	14.8212863789	-0.0735742691	10.4146967644
H	1.0	12.6088253434	-0.3465716526	11.4390561850
H	1.0	13.0717529327	-1.8184277265	10.5901541038
H	1.0	11.5844599595	-1.1285064098	8.6386510587
H	1.0	10.7808406244	-1.5153344751	10.1420589520

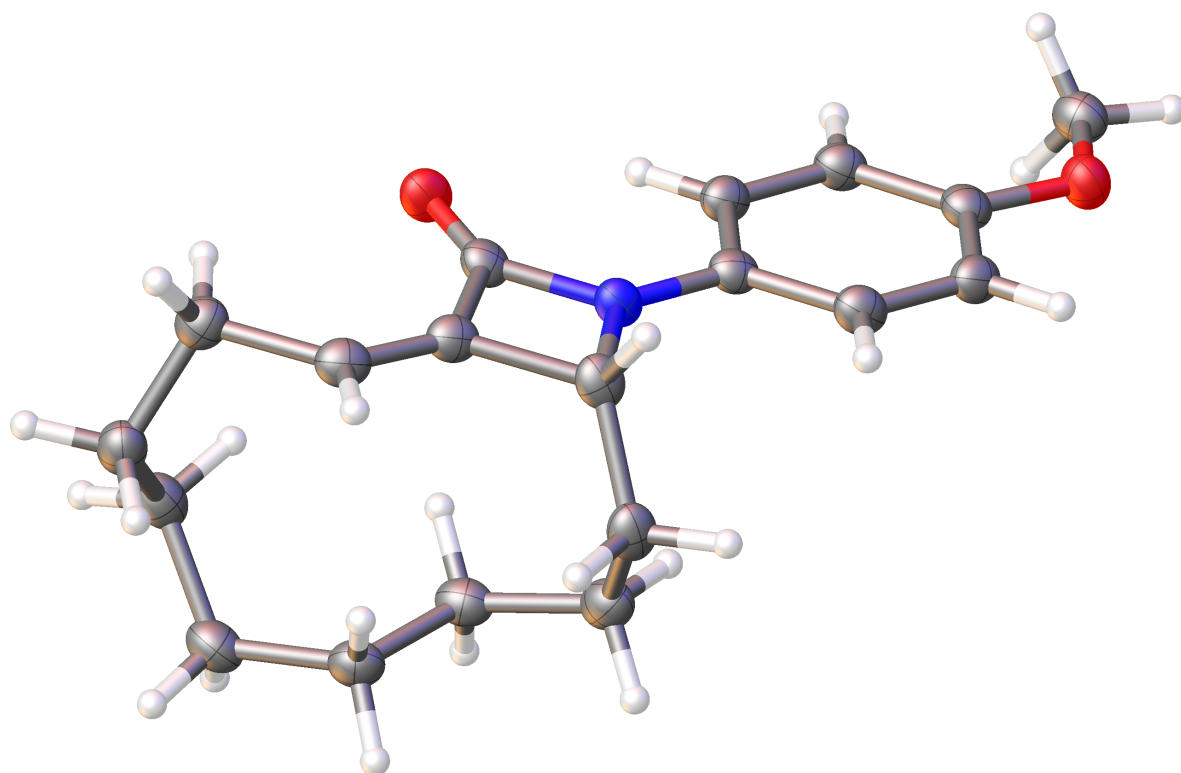
Z-21



C	6.0	8.8050300562	1.7036515617	17.1505730903
O	8.0	9.3319729355	0.5435798357	16.5512013566
C	6.0	9.6310324992	0.5709589338	15.2253170478
C	6.0	9.4635290051	1.6885402625	14.3928940674
C	6.0	9.8021119940	1.6187106073	13.0396359473
C	6.0	10.3110109809	0.4282729241	12.4950555906
C	6.0	10.4738362352	-0.6920594630	13.3313560579
C	6.0	10.1402207744	-0.6183517729	14.6789744941
N	7.0	10.6442235474	0.3544641367	11.1444699103
C	6.0	10.4865883980	1.2300938146	10.0707317260
O	8.0	10.0413503799	2.3545388506	9.9999146075
C	6.0	11.1044532386	0.2253428312	9.1461083056
C	6.0	11.2811357201	-0.7173086863	10.3374746880
C	6.0	11.4310325275	0.1953661589	7.8542729325
C	6.0	11.2596669379	1.3406231010	6.9016253646
C	6.0	12.6079107491	1.9788447787	6.5007875272
C	6.0	13.3093467636	2.7821039586	7.6237189884
C	6.0	14.6335031708	2.1932718213	8.1416655273
C	6.0	14.5162589700	0.9357778259	9.0148838751
C	6.0	13.8726609021	1.2111899278	10.3762754883
C	6.0	13.6256339635	-0.0190498255	11.2605562919

C	6.0	12.7121538265	-1.1255157088	10.7109793586
H	1.0	7.8465347206	2.0060191668	16.6894063332
H	1.0	9.5084514681	2.5547849193	17.0903267418
H	1.0	8.6306795607	1.4603543241	18.2077320288
H	1.0	9.0686133320	2.6261492751	14.7844378092
H	1.0	9.6705101280	2.4833342337	12.3889545859
H	1.0	10.8598304683	-1.6272439262	12.9224124086
H	1.0	10.2627607869	-1.4808048243	15.3372814355
H	1.0	10.6393631157	-1.6153120025	10.2764967911
H	1.0	11.9223813443	-0.7055570383	7.4625255248
H	1.0	10.6070706890	2.1038379442	7.3530144285
H	1.0	10.7583662497	0.9736610912	5.9884852692
H	1.0	12.4157246728	2.6424827832	5.6418884180
H	1.0	13.2830099423	1.1913902812	6.1183233273
H	1.0	13.5231523297	3.7956167650	7.2471591391
H	1.0	12.6075548474	2.9286108529	8.4617095457
H	1.0	15.2851580846	1.9769521445	7.2761416389
H	1.0	15.1585680461	2.9712759959	8.7244579932
H	1.0	13.9475216685	0.1641531526	8.4723983826
H	1.0	15.5236435324	0.5104419995	9.1721834513
H	1.0	12.9331692530	1.7638233254	10.2348774943
H	1.0	14.5277475735	1.9032298084	10.9350215763
H	1.0	13.2134956007	0.3230478872	12.2243826169
H	1.0	14.5970755783	-0.4874417067	11.4991016775
H	1.0	13.1543866244	-1.5878690265	9.8110802822
H	1.0	12.6694898069	-1.9328572997	11.4611058565

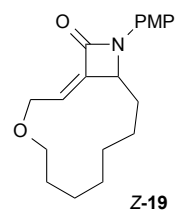
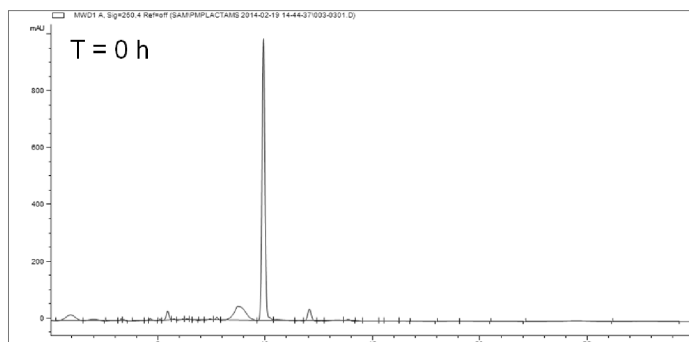
X-ray crystal structure of Z-21:



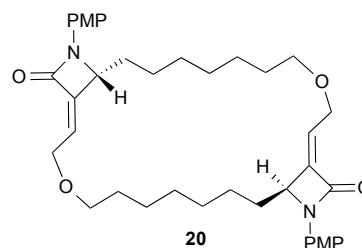
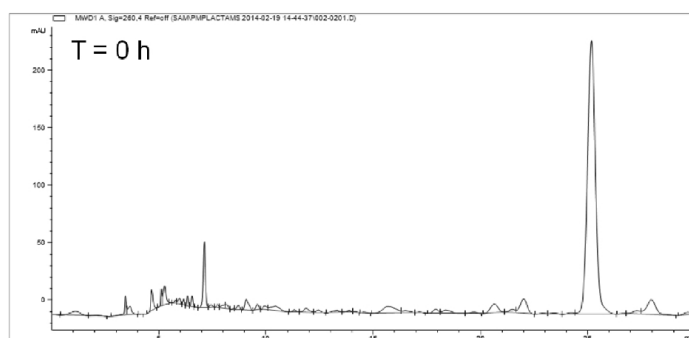
Deposited as CCDC 1048608

HPLC traces showing equilibration of RCM products

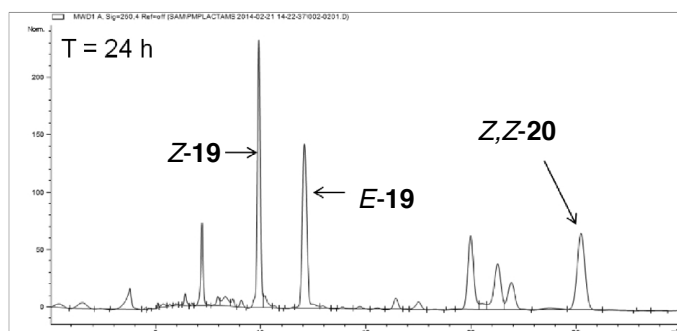
Purified **Z-19**:



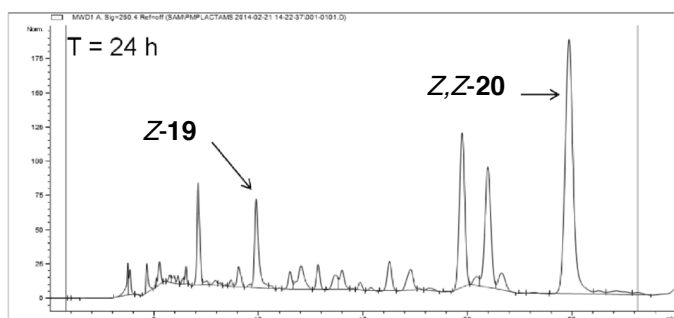
Purified **Z,Z-20**:



After resubjection of **Z-19** to RCM conditions [**16** (10 mol%) in CH_2Cl_2 (2 mM) for 24 h]:



After resubjection of **Z-21** to RCM conditions [**16** (10 mol%) in CH_2Cl_2 (2 mM) for 24 h]:



HPLC conditions (Agilent Prep C-18 scalar column, 0.5 mL/min, 10% H_2O in MeCN, $\lambda = 260$ nm).

Growth inhibition assay with *Chlamydomonas reinhardtii*

Cell culture conditions

Herbicidal activity of Z-**23** was assessed by means of a growth inhibition assay with *Chlamydomonas reinhardtii* based on the method of Lagator *et al.*⁴ Stock *Chlamydomonas* cultures were maintained in Bold's medium (BM)⁵ in disposable borosilicate 25 x 125 mm glass tubes and shaken in an orbital incubator at 180 rpm, 28°C under constant illumination (light intensity of 130 $\mu\text{mol m}^{-2} \text{s}^{-1}$).

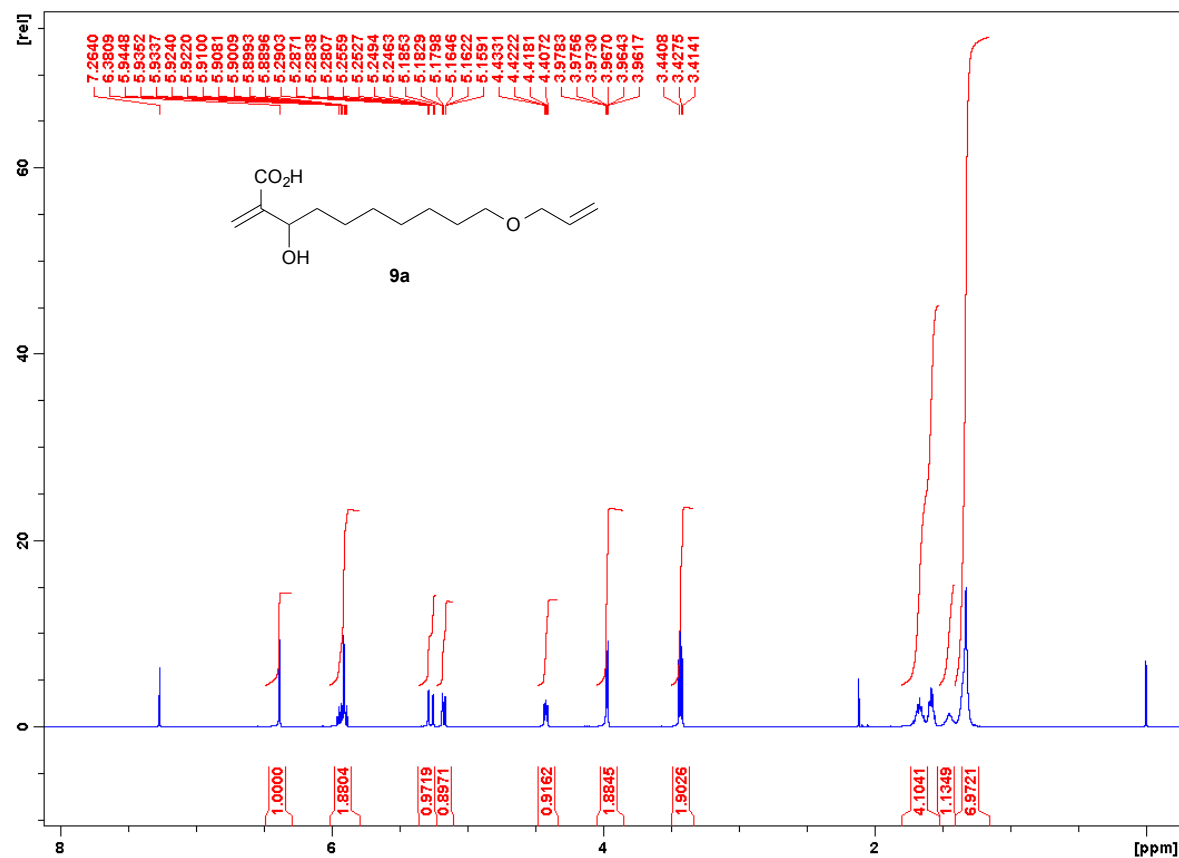
Assay system

The activity of Z-**23** was compared to that of the commercial herbicide glyphosate. The cell culture conditions were as described above with a total assay volume of 5 ml and a starting population of 100,000 cells. Tubes were prepared containing BM plus test compound (Z-**23** or glyphosate) at final concentrations of 10 and 50 μM with DMSO at 0.5% v/v. Four replicate tubes were prepared for each treatment with eight replicates for controls (BM plus DMSO at 0.5% v/v only).

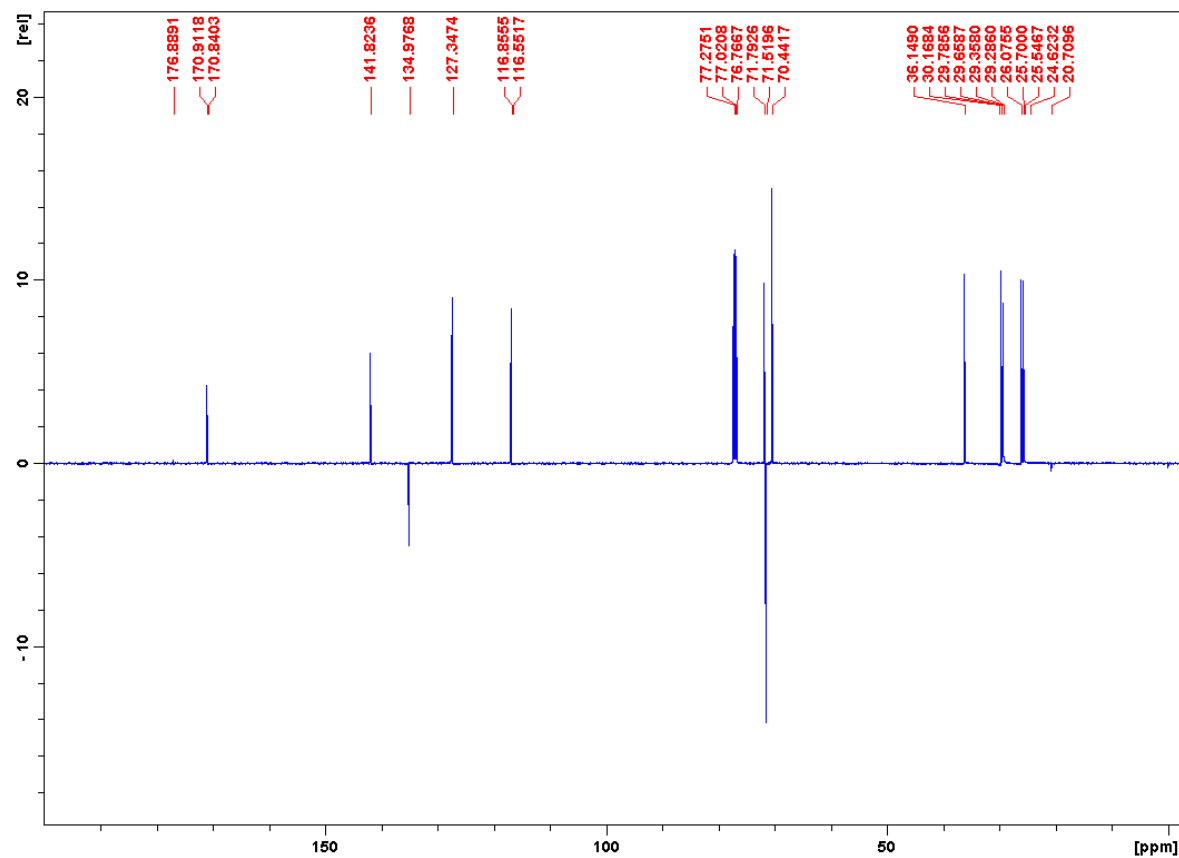
After 7 days' incubation three aliquots of 200 μl from each tube were transferred into BD Falcon flat bottomed, 96 well plates and OD₇₅₀ was measured on a Labtech LT4000 bench-top spectrophotometer. Growth inhibition was calculated as percentage decrease in OD₇₅₀ relative to untreated tubes.

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

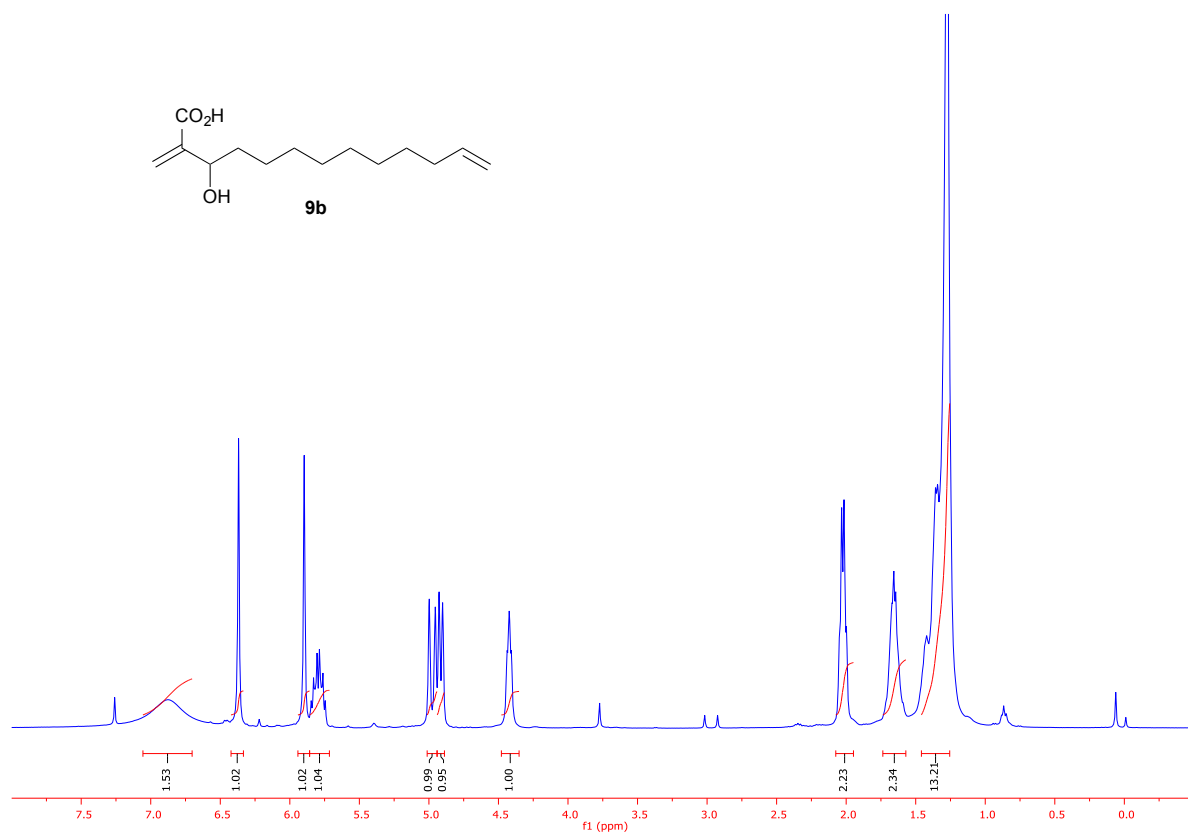
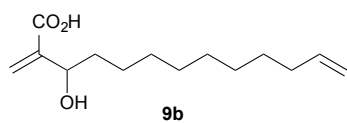
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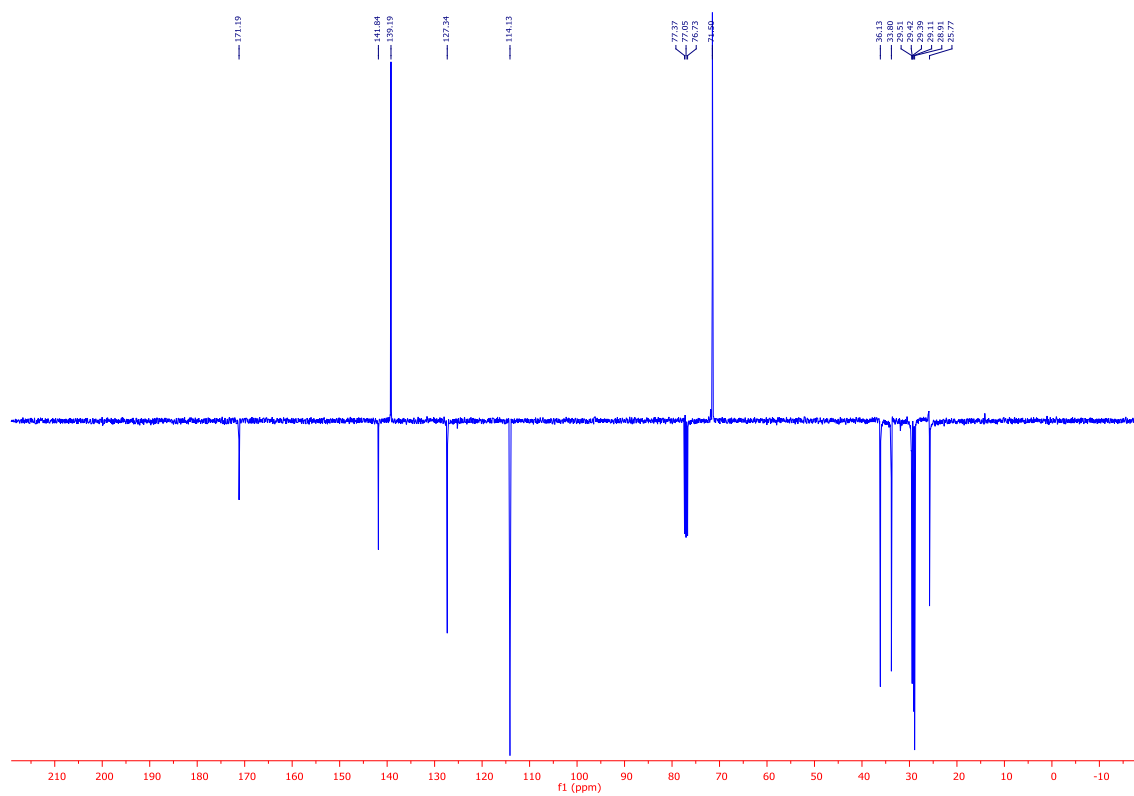
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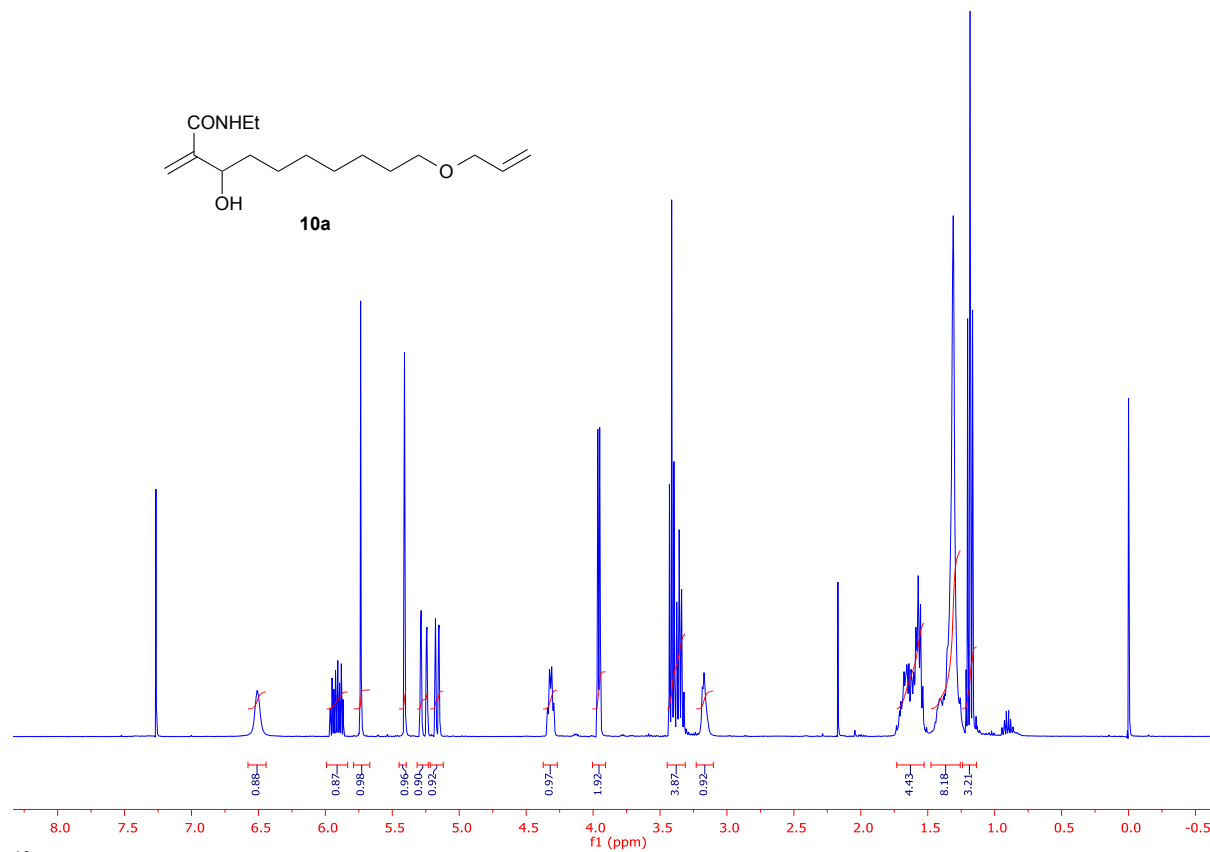
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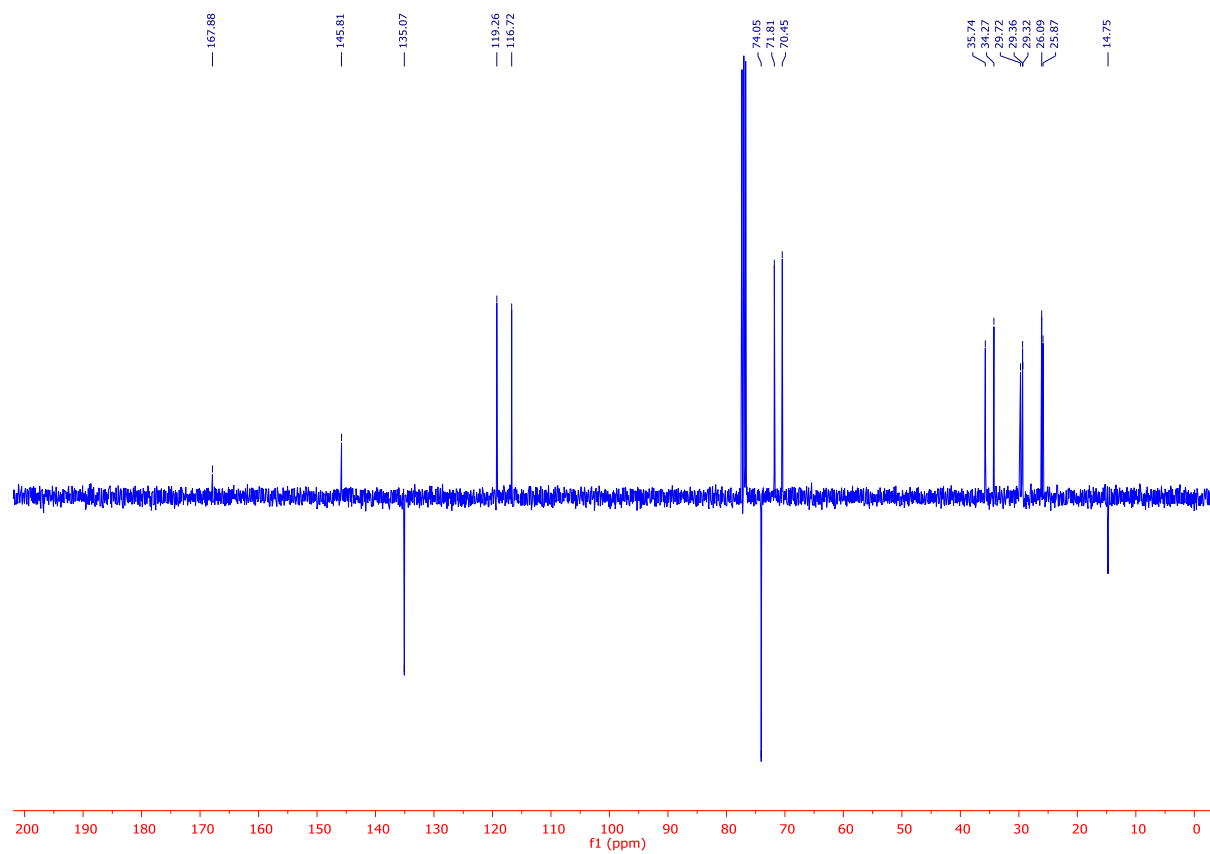
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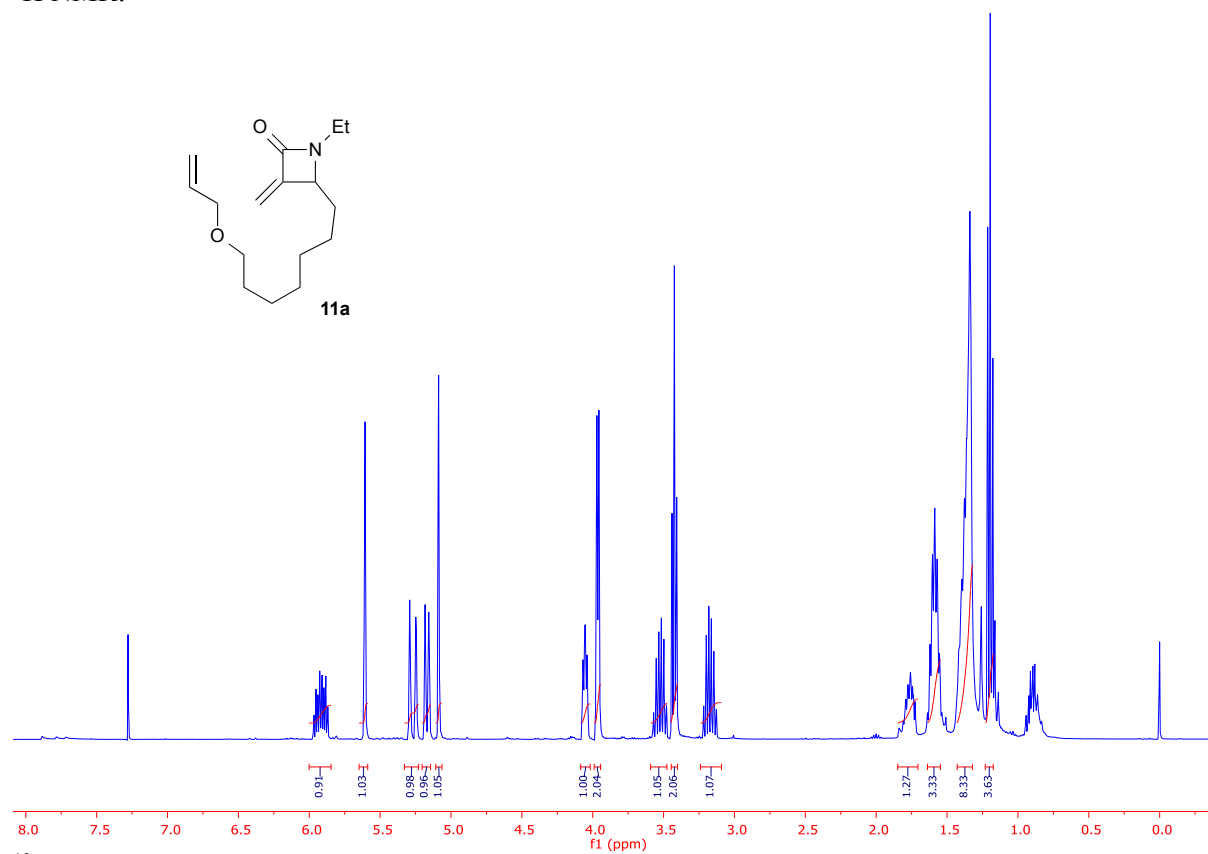
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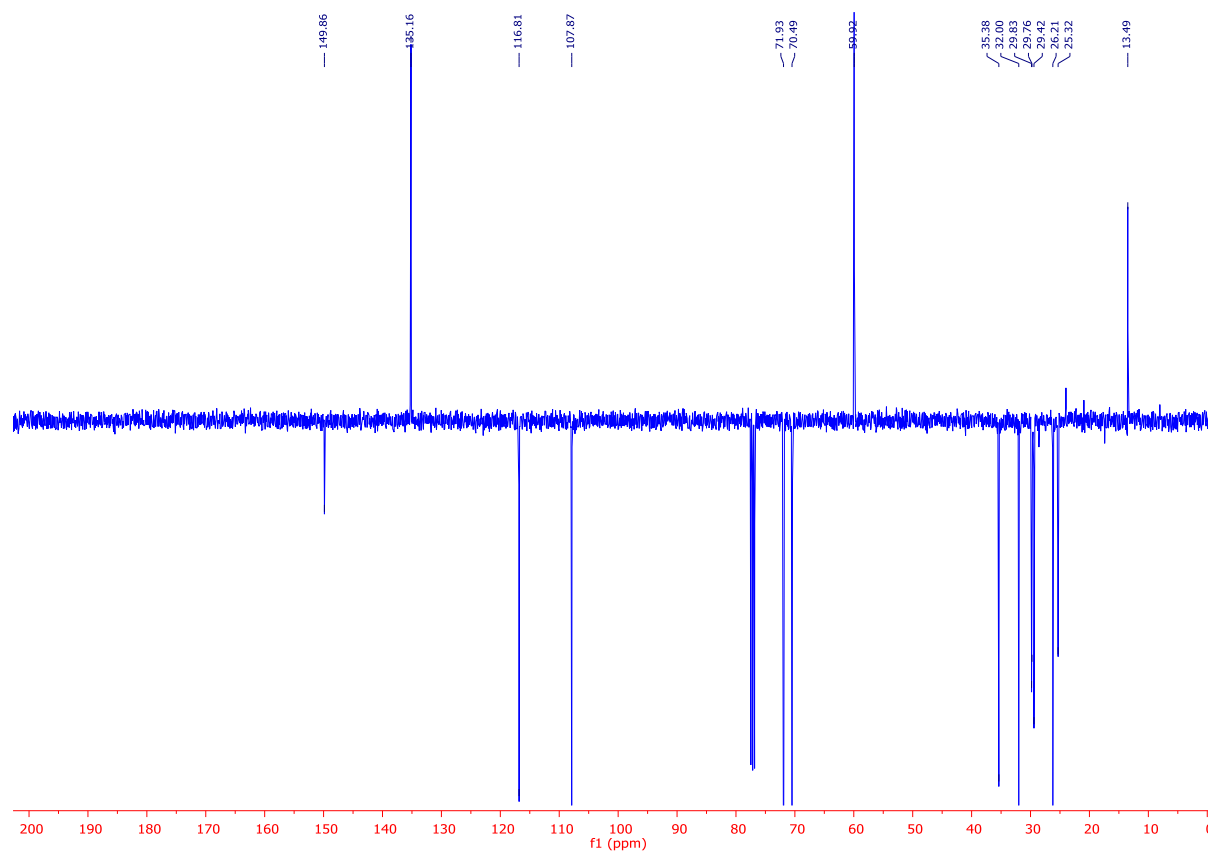
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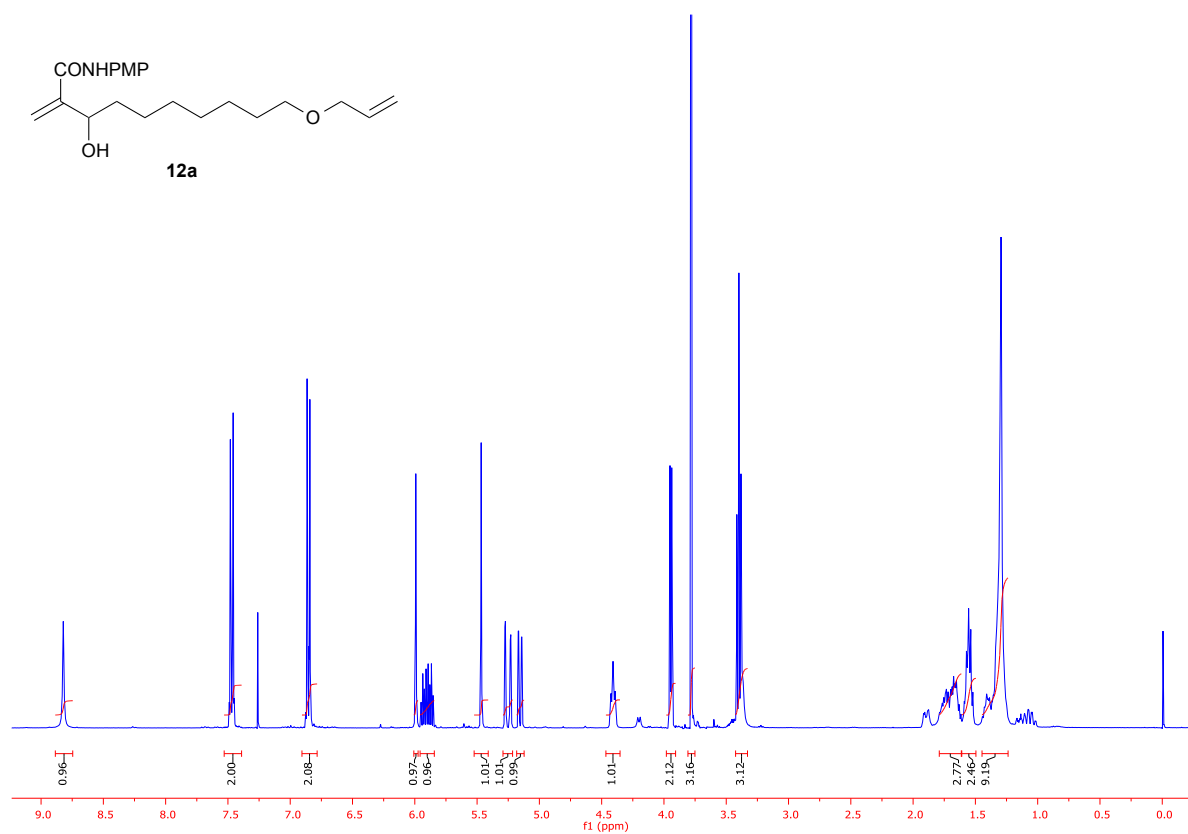
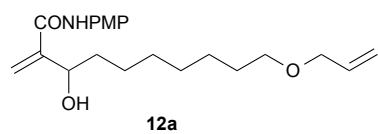
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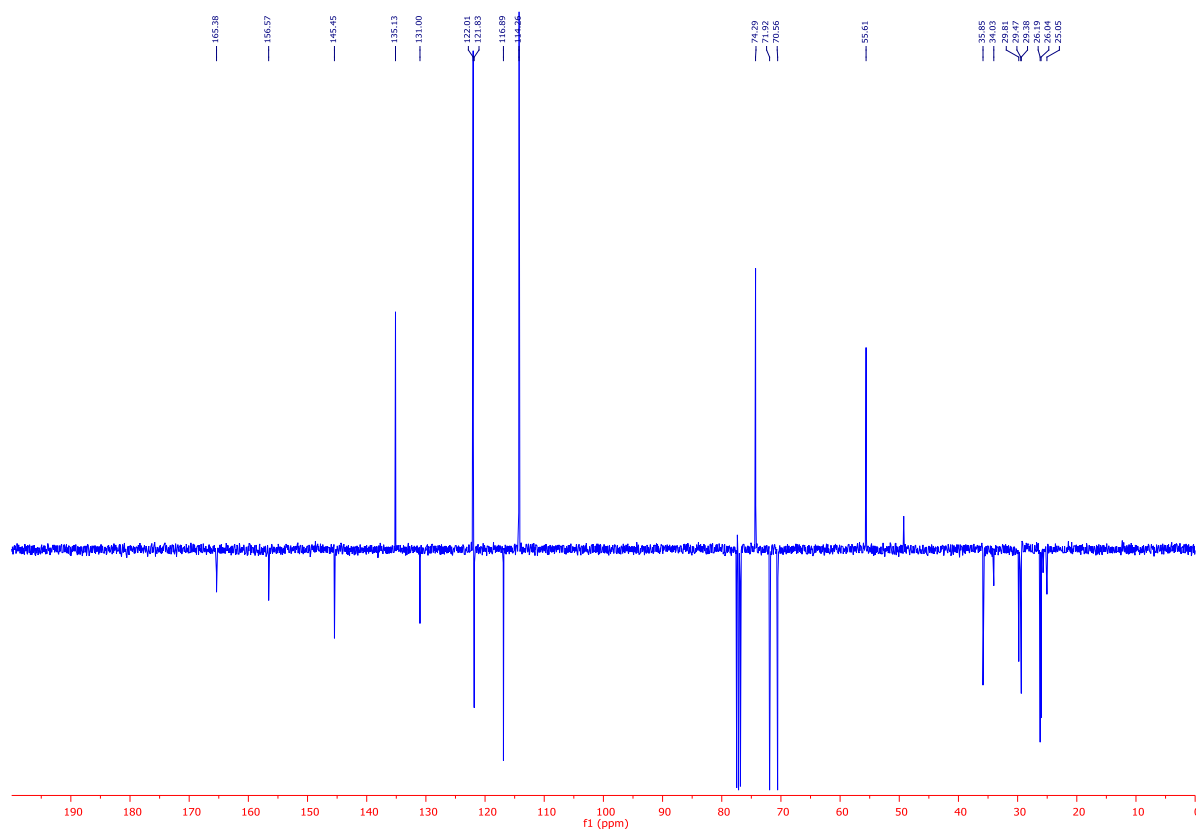
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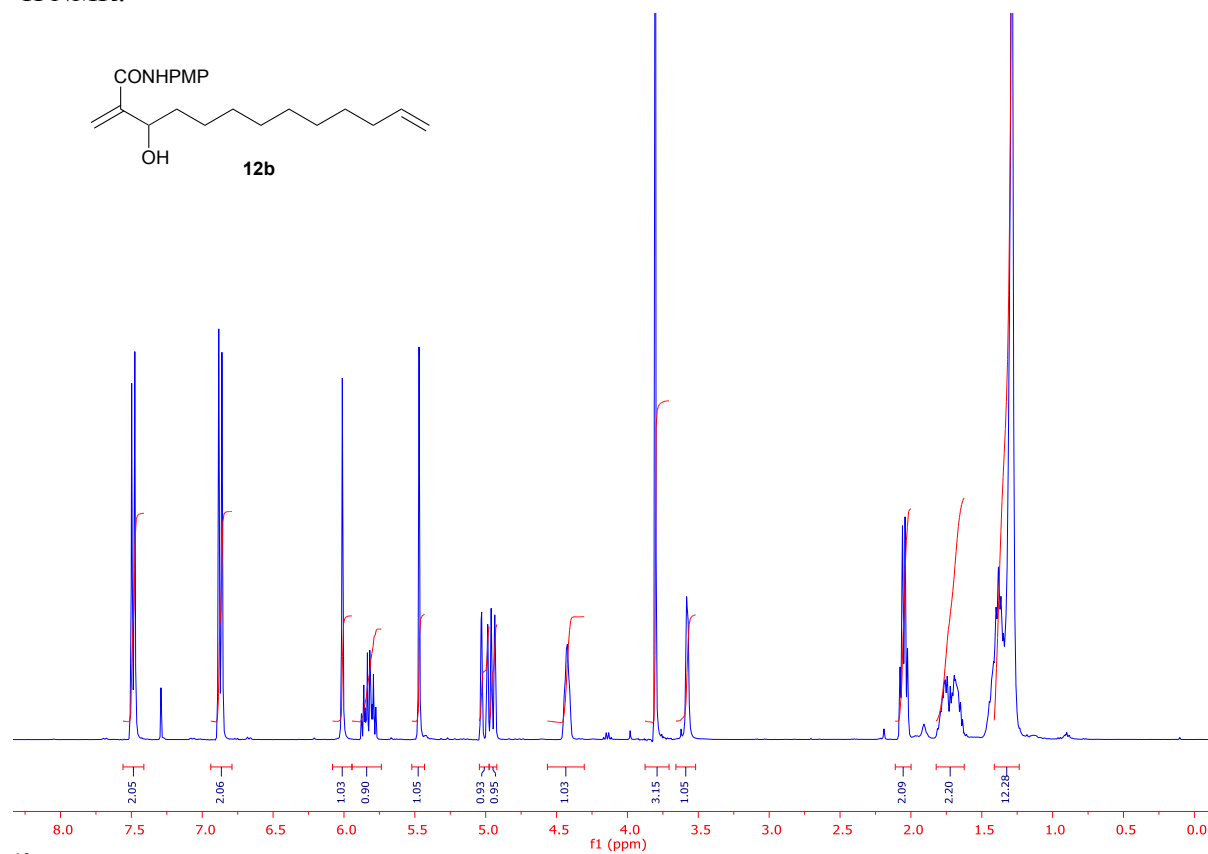
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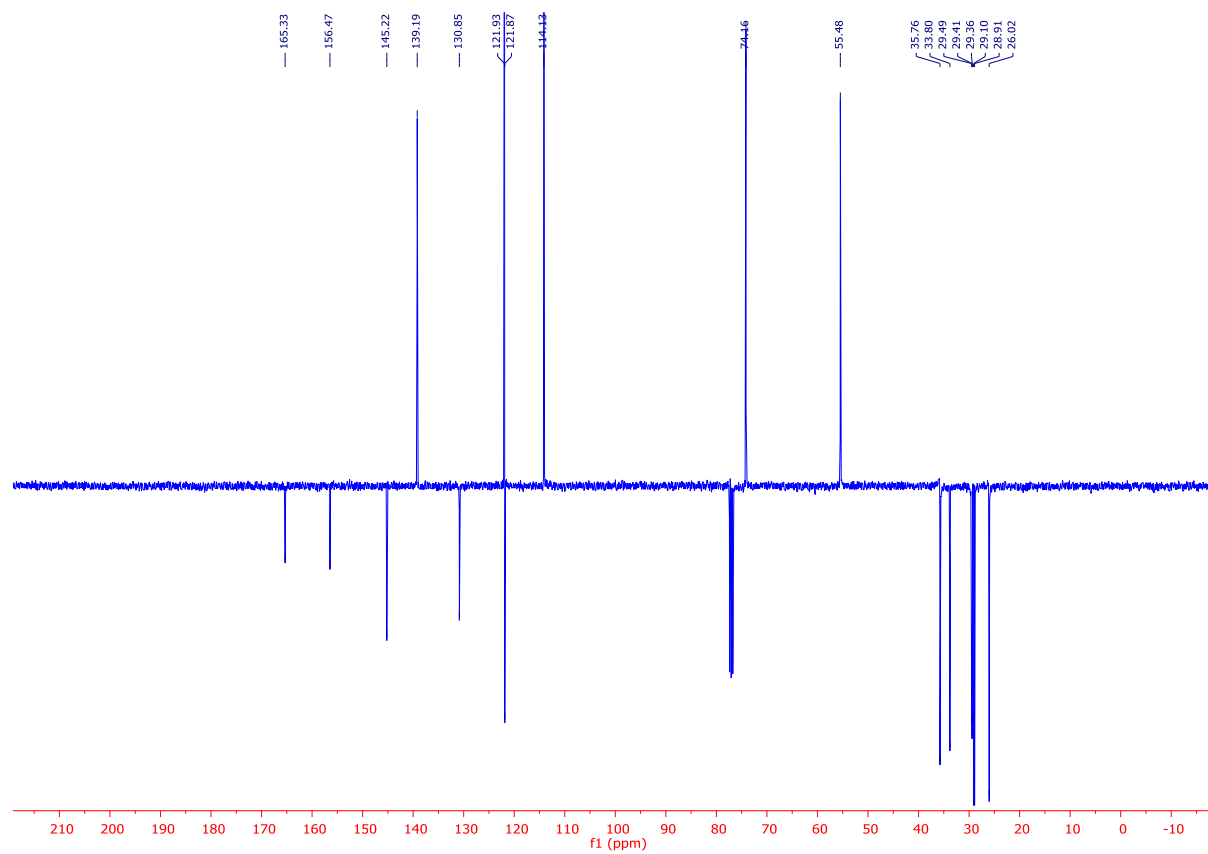
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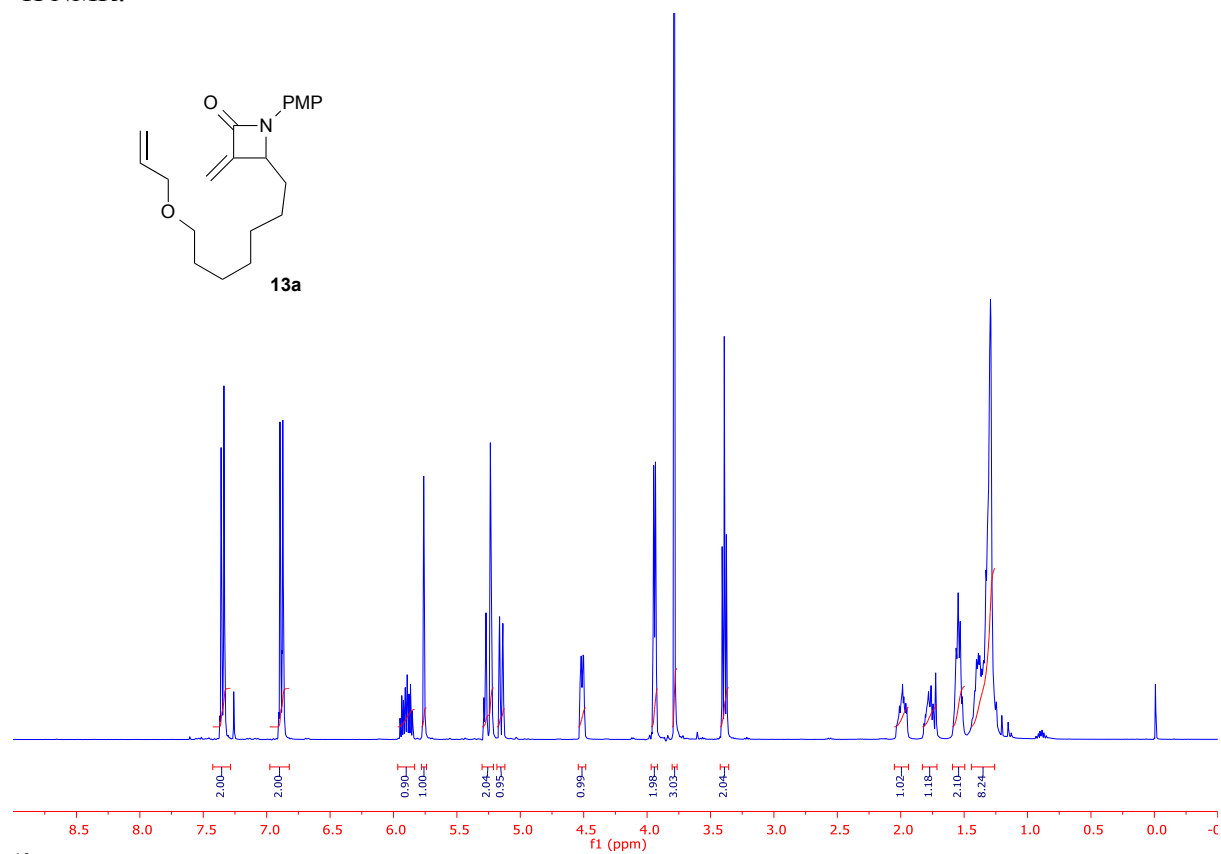
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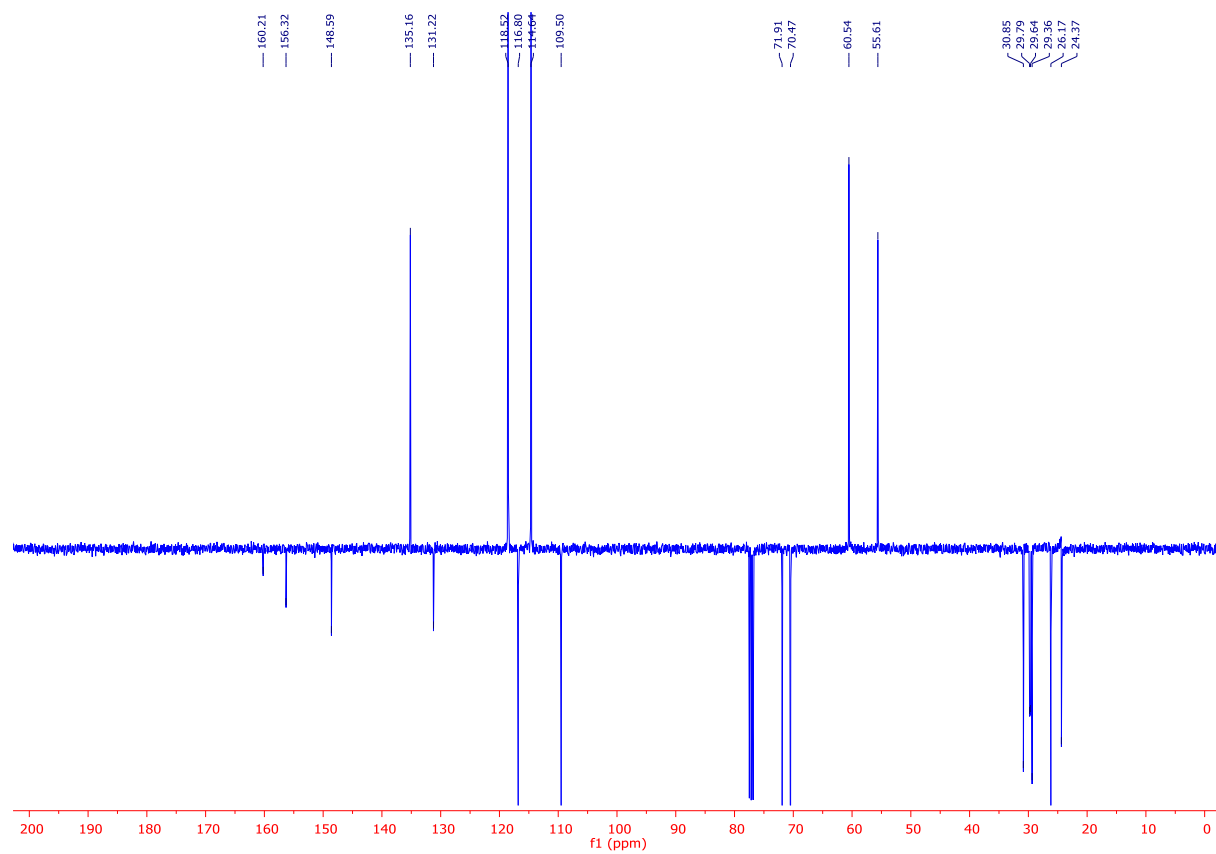
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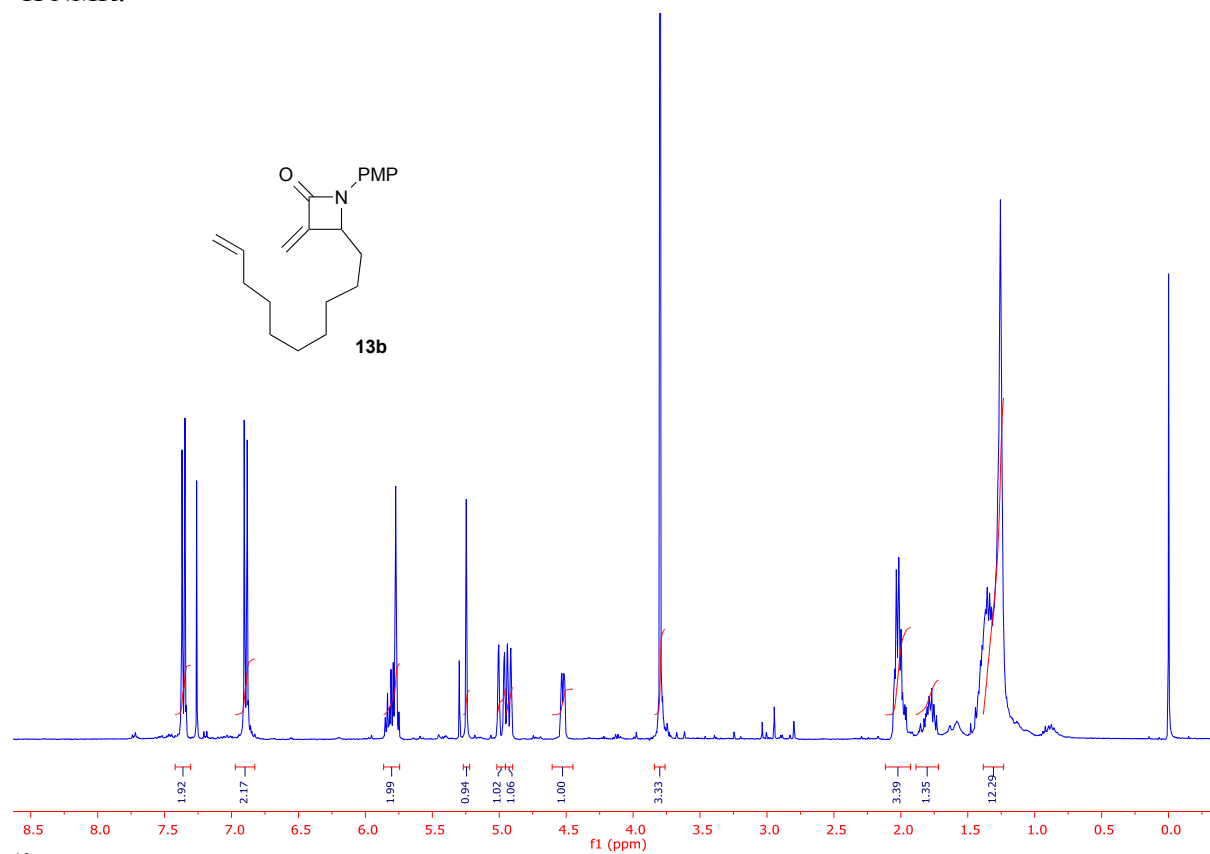
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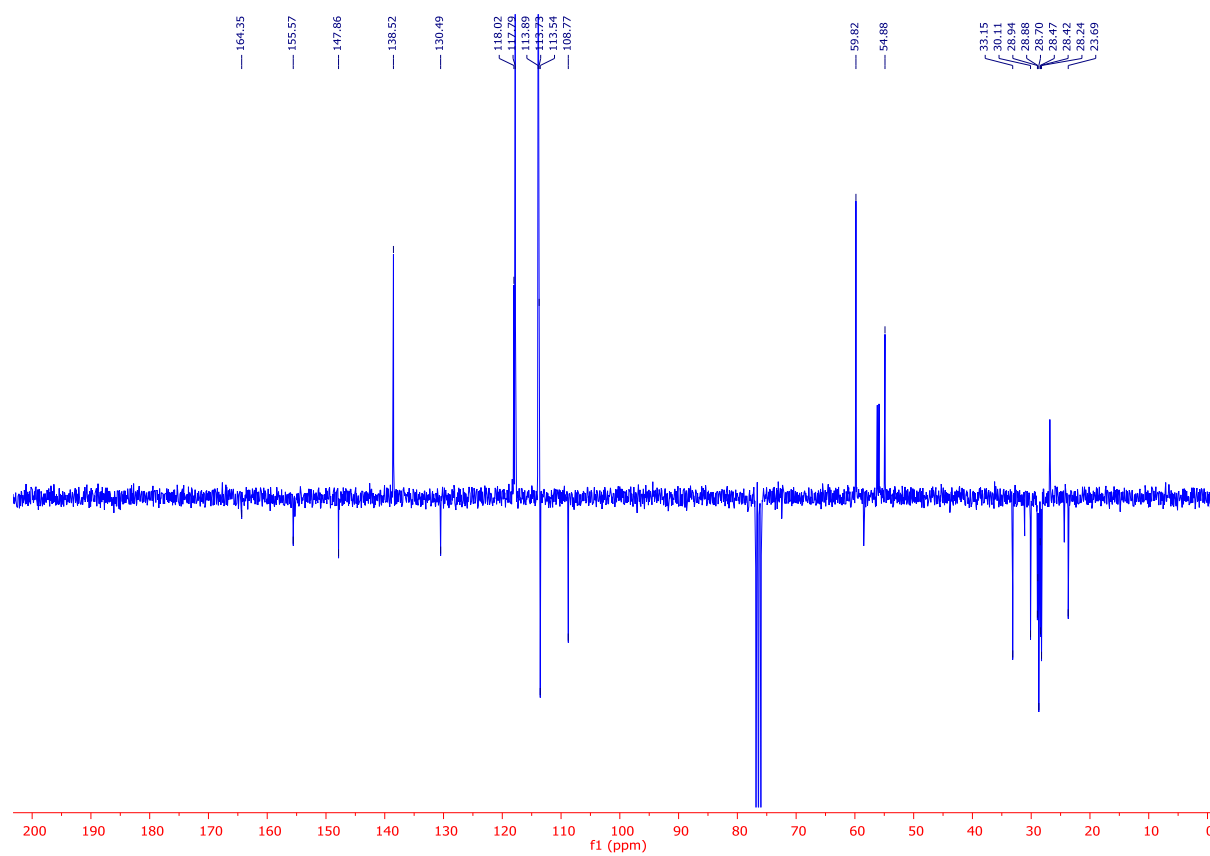
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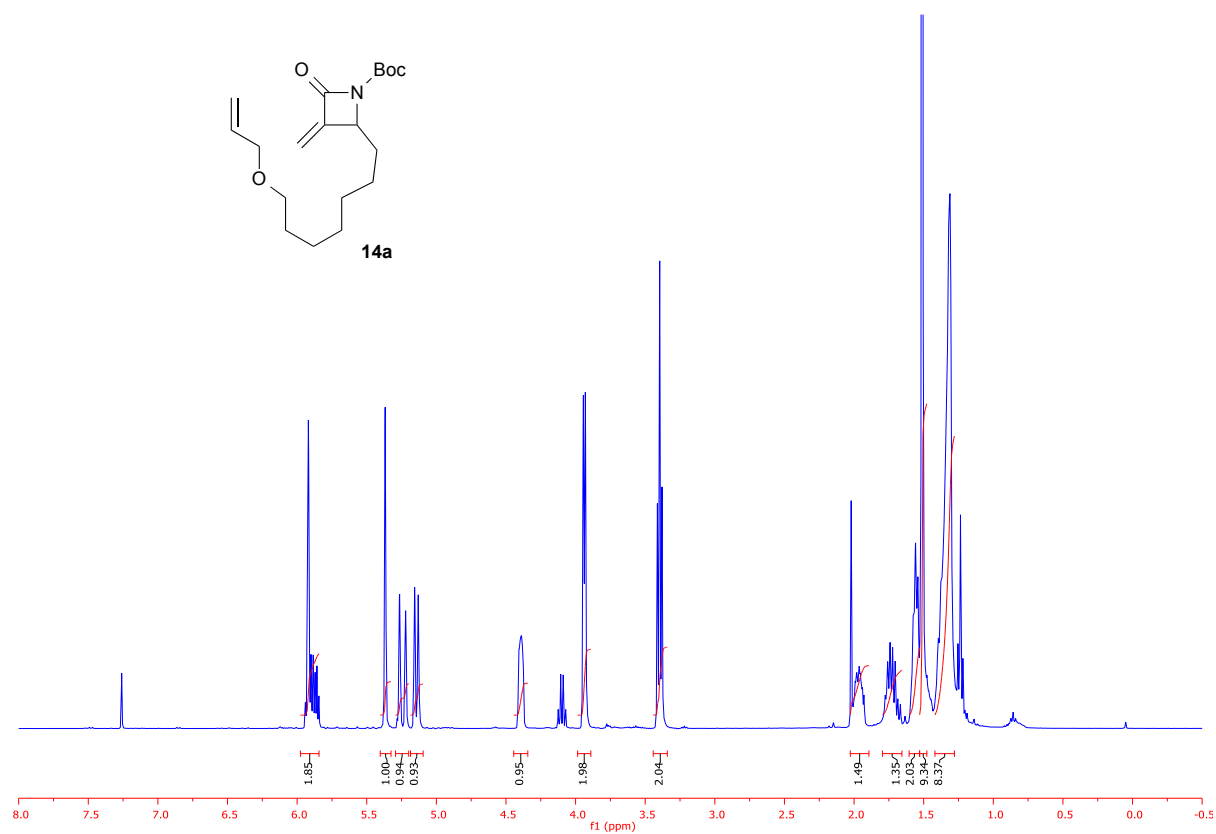
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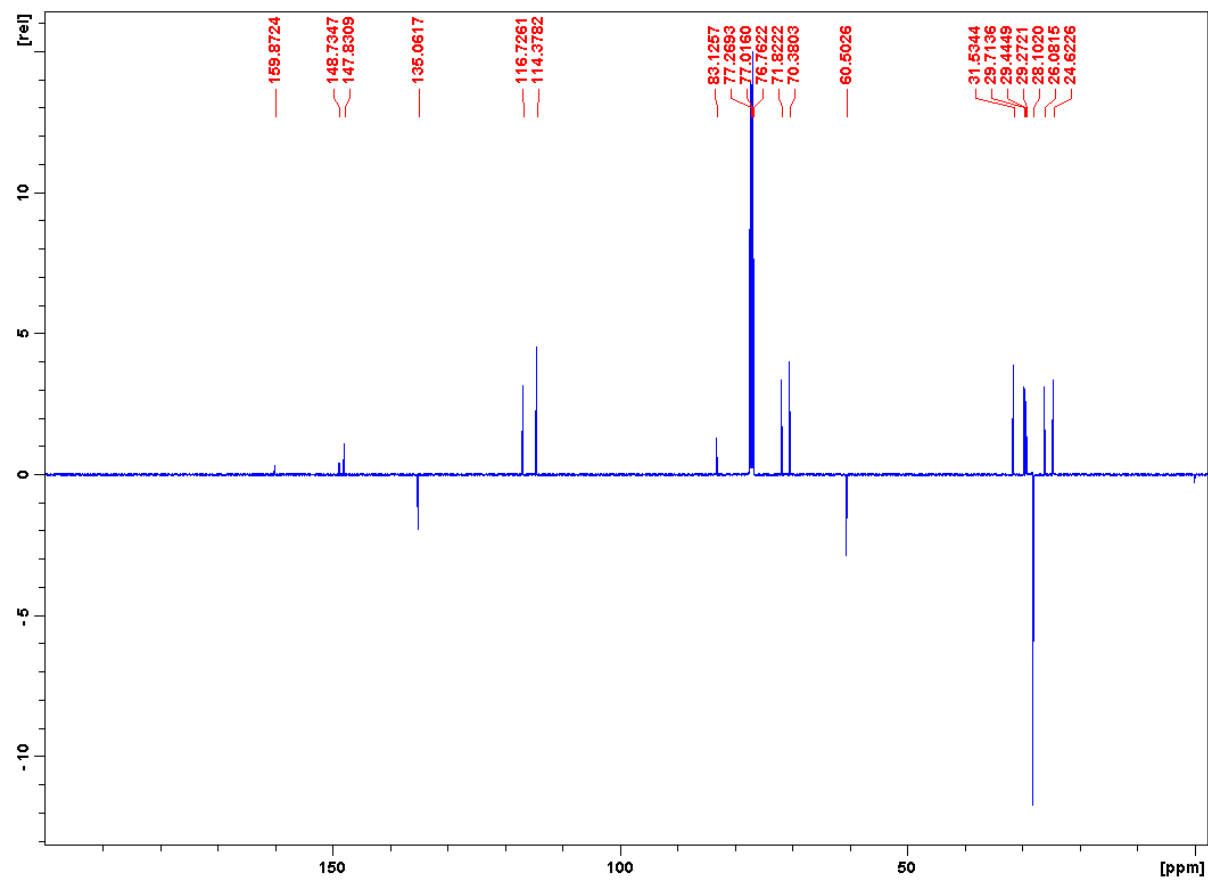
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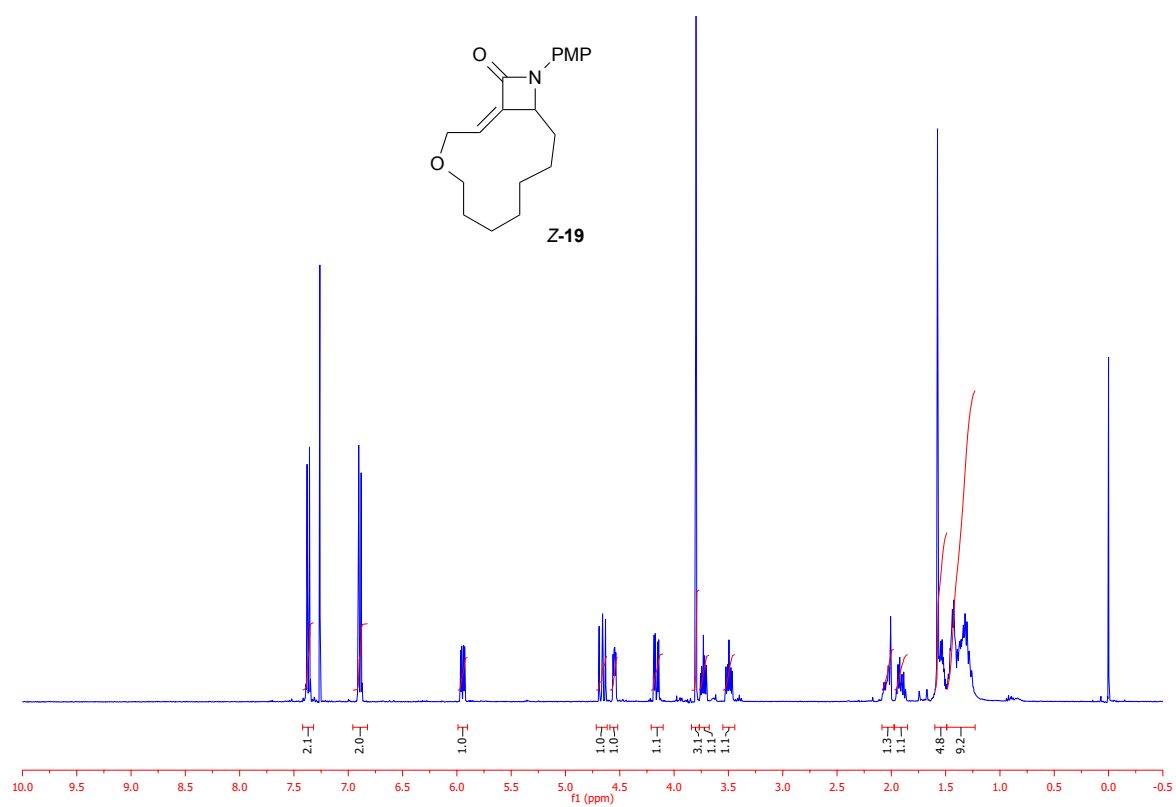
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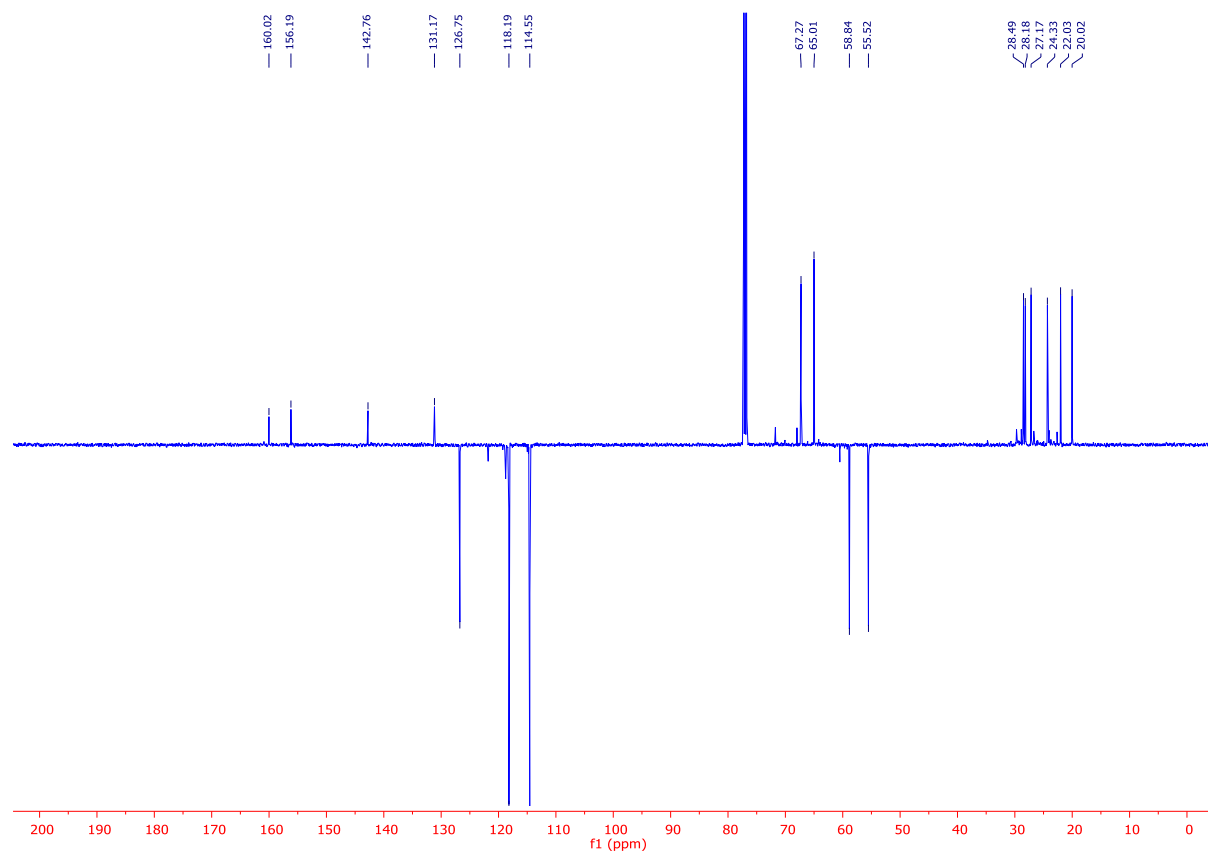
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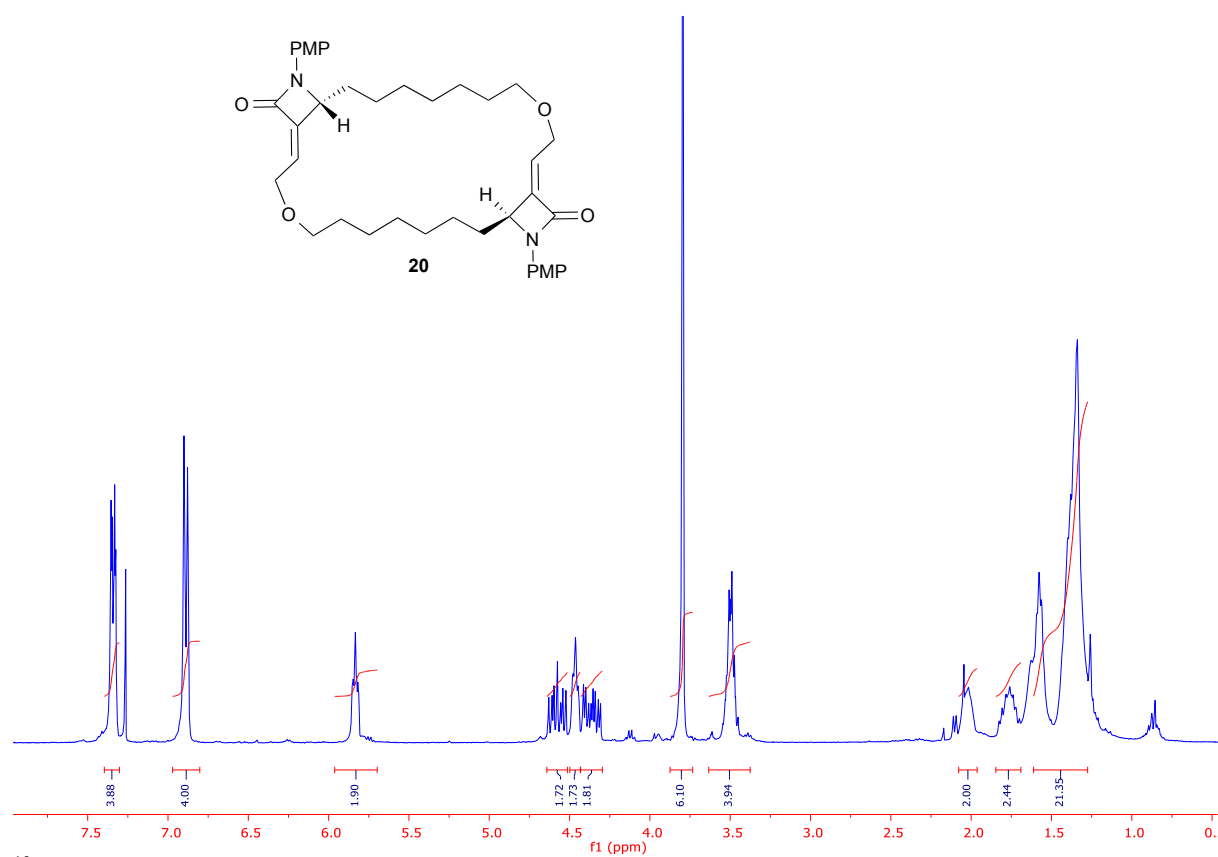
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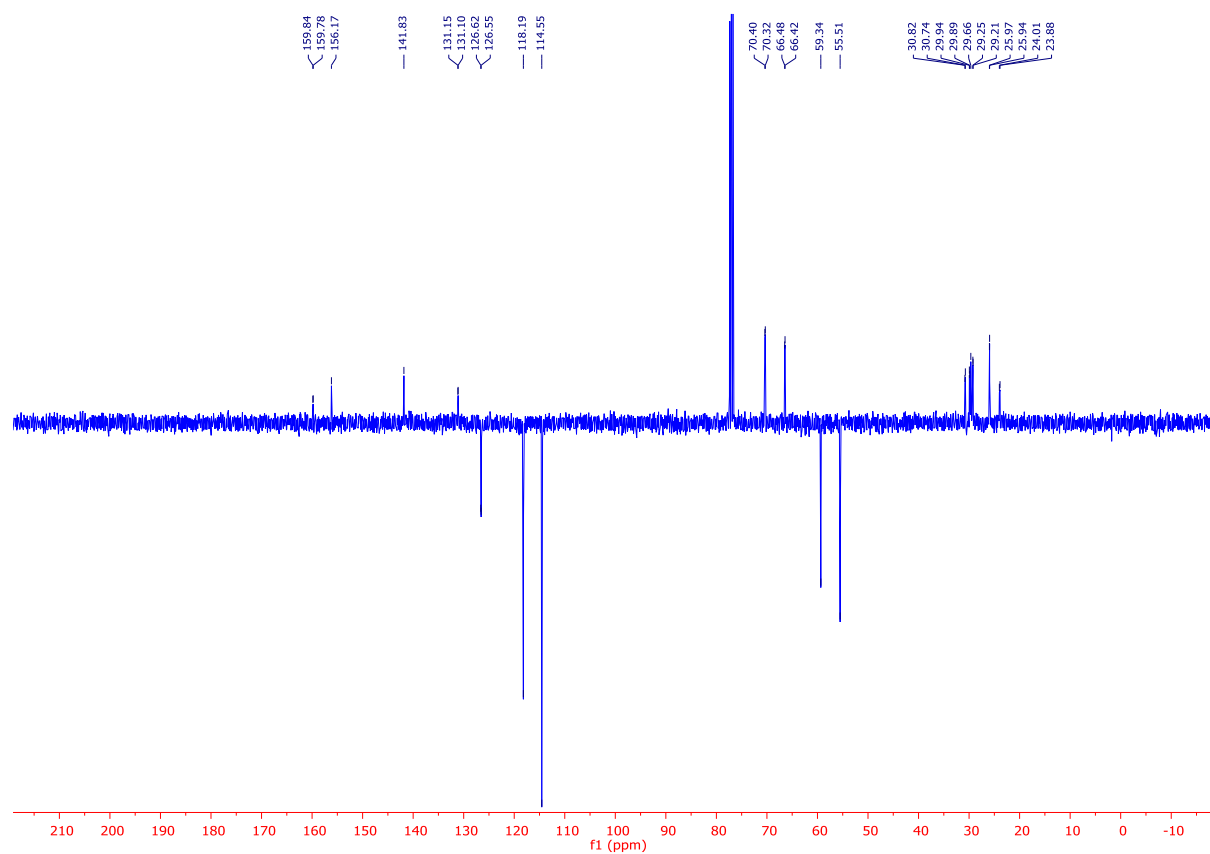
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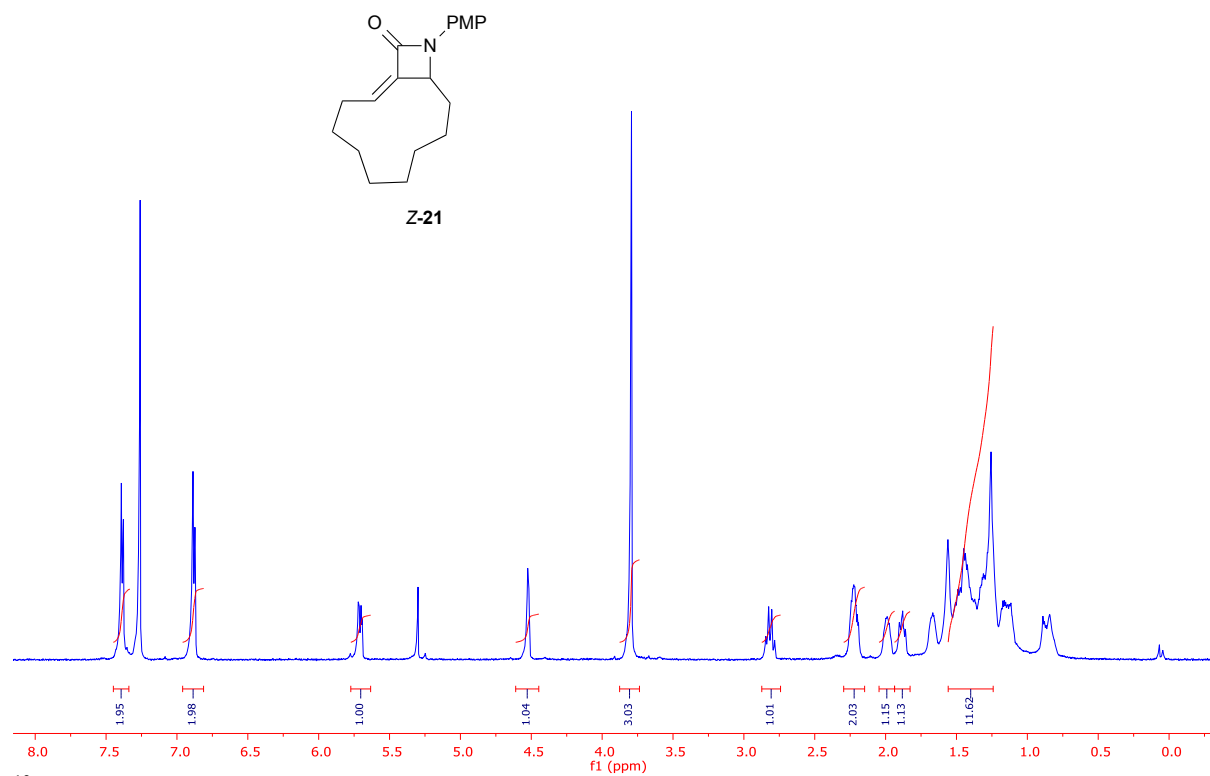
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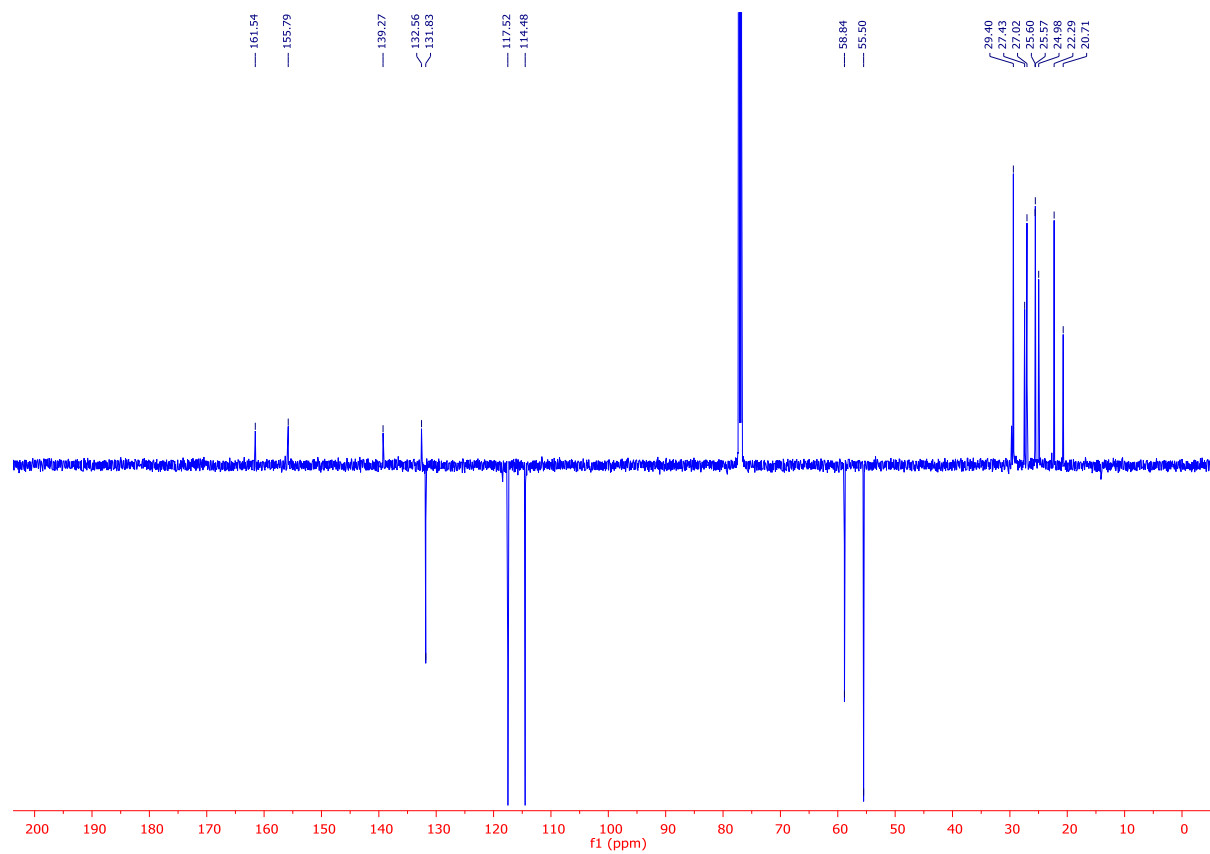
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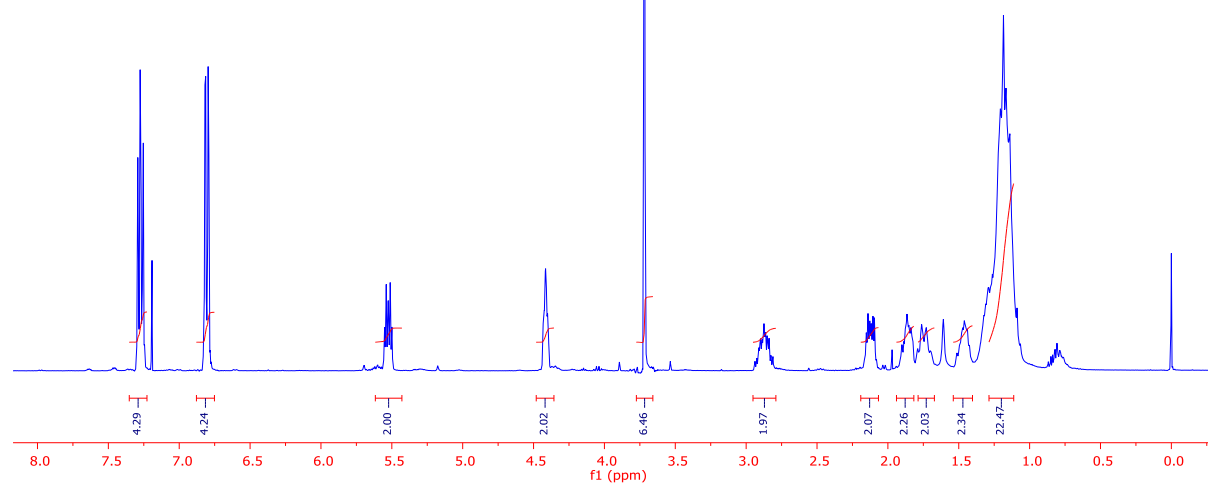
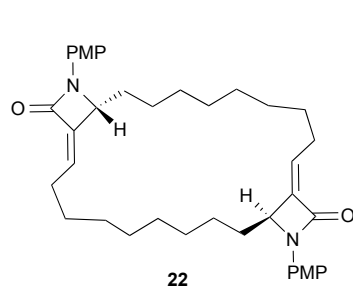
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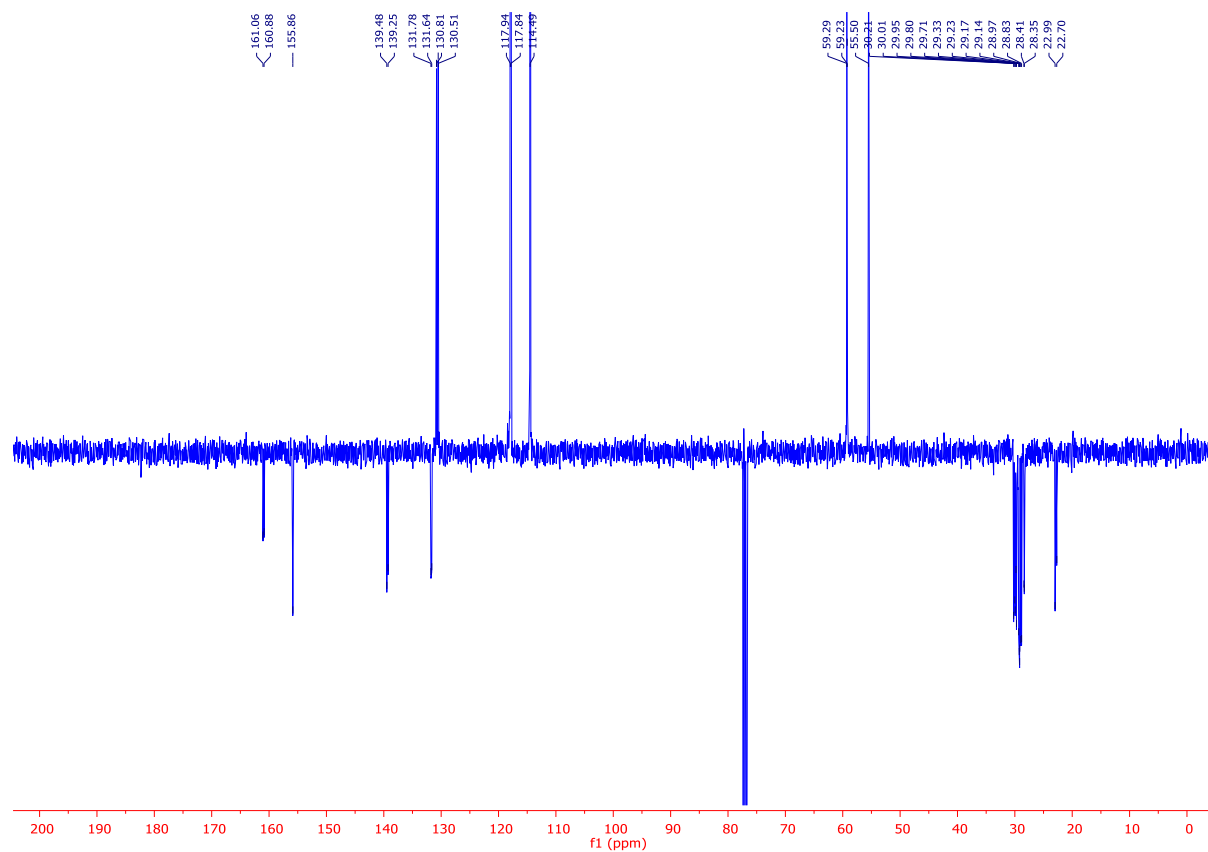
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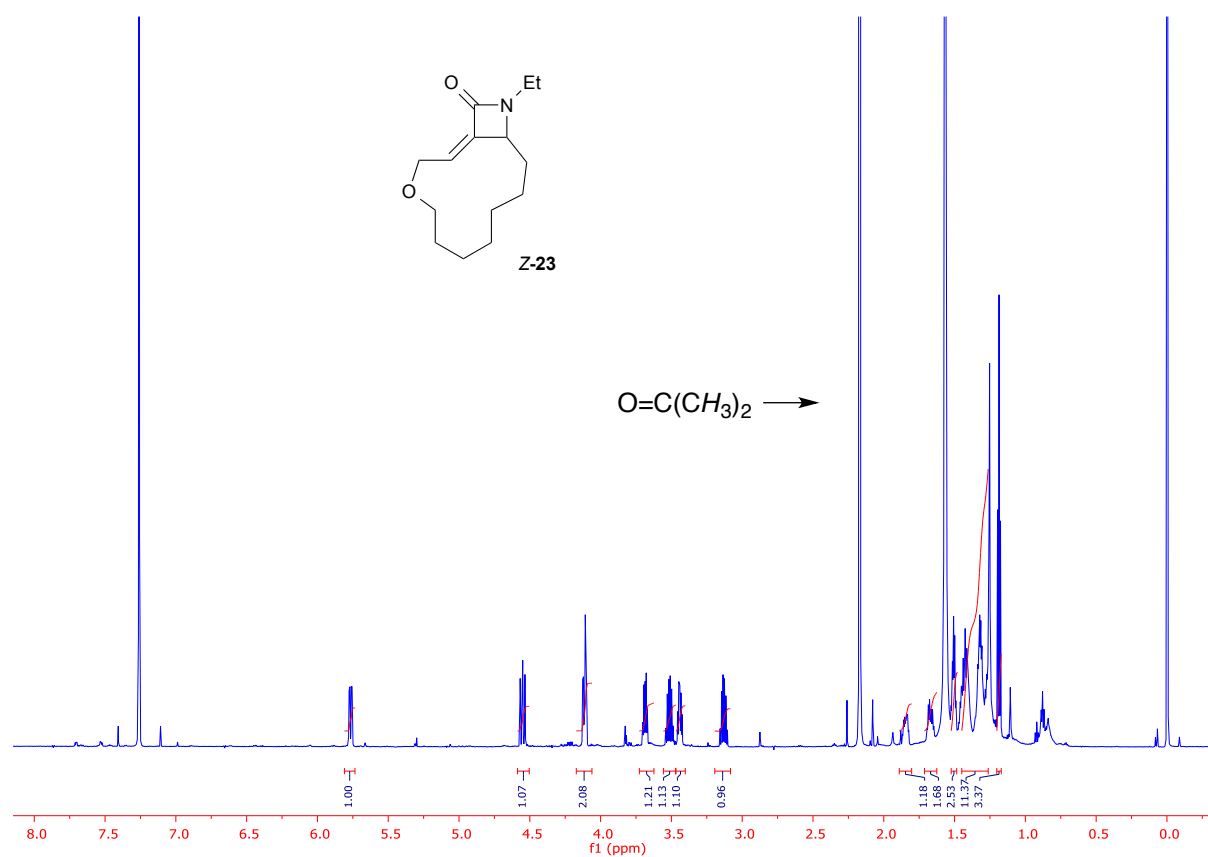
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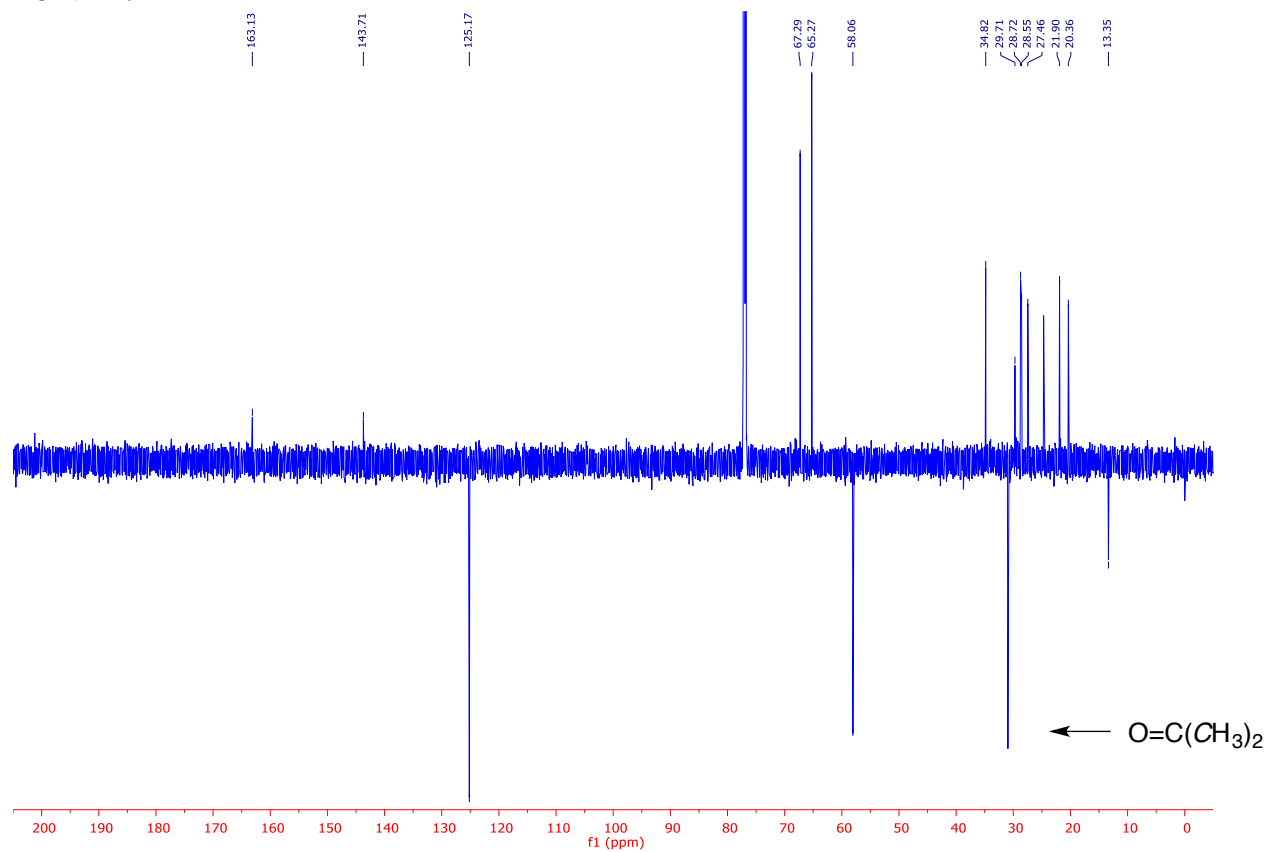
^{13}C NMR:



^1H NMR:



^{13}C NMR:



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