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I. A NEW SYNTHETIC APPROACH TO THE SYNTHESIS OF N-(PHOSPHONOACETYL)-L-ORNITHINE, II. THE INFLUENCE OF PYRIDINE ON THE OZONOLYSIS OF ALKENES

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I. A NEW SYNTHETIC APPROACH TO THE SYNTHESIS OF δ-N-(PHOSPHONOACETYL)-L-ORNITHINE

II. THE INFLUENCE OF PYRIDINE ON THE OZONOLYSIS OF ALKENES

by

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I. A NEW SYNTHETIC APPROACH TO THE SYNTHESIS OF δ-N-(PHOSPHONOACETYL)-L-ORNITHINE.

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Bradley M. Johnson, M.S.

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Part I.

The use of chemical inhibitors to manipulate the level of amino acids in cells has proven to be invaluable in the mechanistic study of gene expression in bacteria and fungi. Here we present a new approach to the synthesis of δ-N-(phosphonoacetyl)-L-ornithine (PALO), a potent ornithine transcarbamylase inhibitor, using a new amino acid protecting group, 9-borabicyclononane (9-BBN). Starting from commercially available reagents and utilizing mild reaction conditions, we were able to form PALO in fewer synthetic steps and in greater yields than previous attempts.

Part II.

Ozonolysis is widely used to transform alkenes into oxygen-rich functional groups (e.g.– alcohols, aldehydes, and acids). We were interested in the ability of Bronsted acids or bases to influence the reactivity of the carbonyl oxide intermediates in ozonolysis. Our preliminary investigations with a hydrogen-bonding urea and a Bronsted base demonstrated absolutely no influence on the

stereoselectivity of trapping of carbonyl oxides. However, we did observe that ozonolysis in the presence of pyridine greatly furnished significant amounts of aldehyde or ketone products at the expense of the expected ozonide. The enhanced formation of aldehydes or ketones was not observed for ozonolyses in the presence of an alcohol nucleophile, which resulted in the typical formation of hydroperoxyacetals.

There have been a number of anecdotal accounts describing the favorable influence of added pyridine on selective ozonolysis within polyunsaturated systems. We investigated the influence of pyridine and related molecules on the selectivity of ozonolysis for four dienes: citronellene, limonene, geranyl acetate, and 4-vinyl-1-cyclohexene. The presence of pyridine was found to always enhance the selectivity for oxidative cleavage of the more electron-rich alkene.

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A NEW SYNTHETIC APPROACH TO THE SYNTHESIS OF *δ*-*N*-(PHOSPHONOACETYL)-L-ORNITHINE

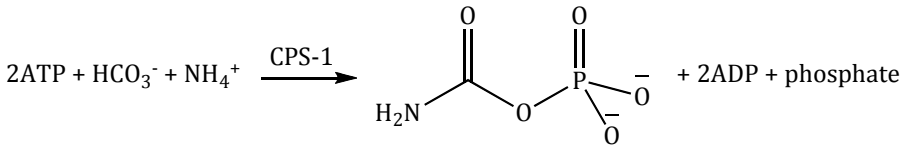
Bradley M. Johnson, M.S.

University of Nebraska, 2010

Adviser: Patrick H. Dussault

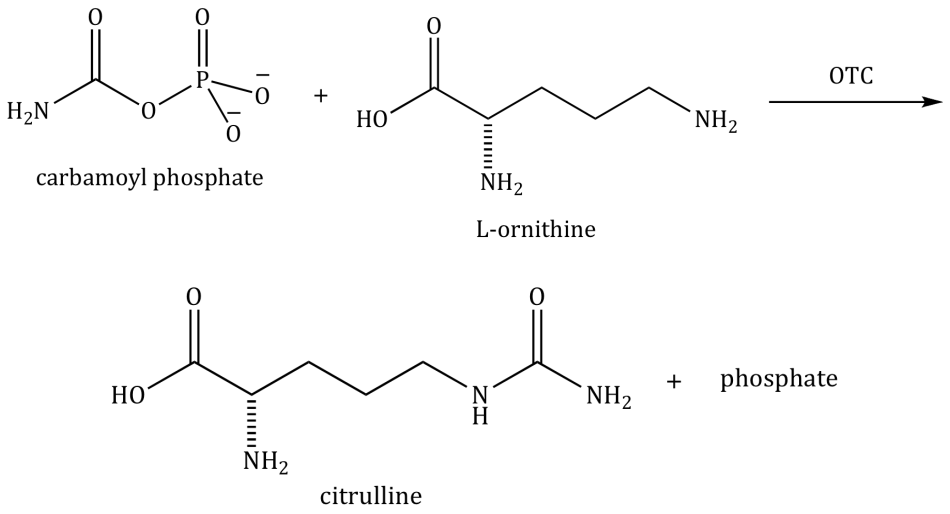
Introduction

Living organisms must eliminate excess nitrogen from the breakdown of amino acids; nitrogen is excreted as ammonia or it is converted into less toxic compounds such as uric acid or urea. Most terrestrial animals utilize a biological mechanism called the urea cycle, which takes place in the liver and converts ammonia into urea, which is than eliminated as urine by the kidneys. The urea cycle is shown in Eqs. 1.1 – 1.5:[1]

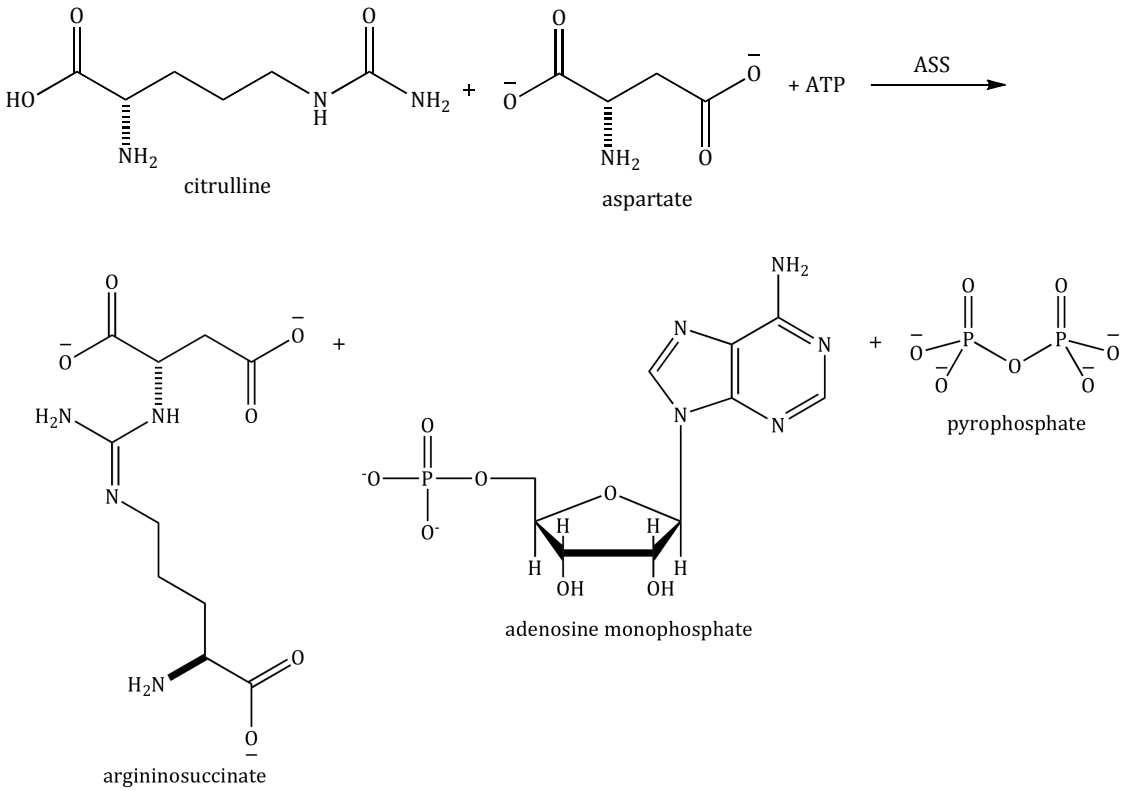


carbamoyl phosphate

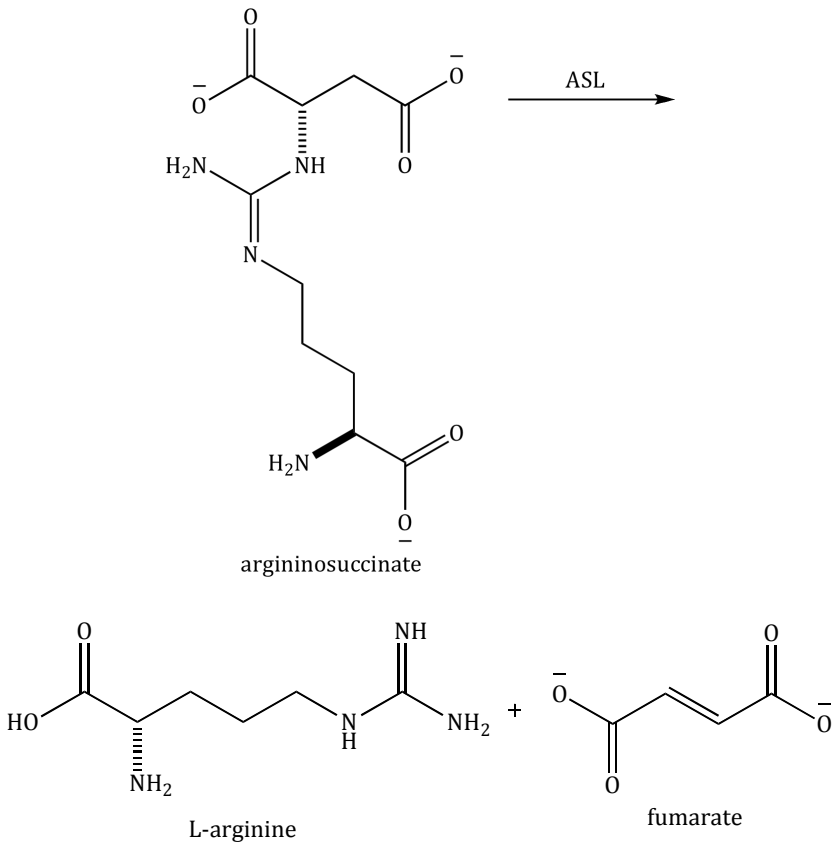
CPS-1 – carbamoyl phosphate synthetase (1.1)



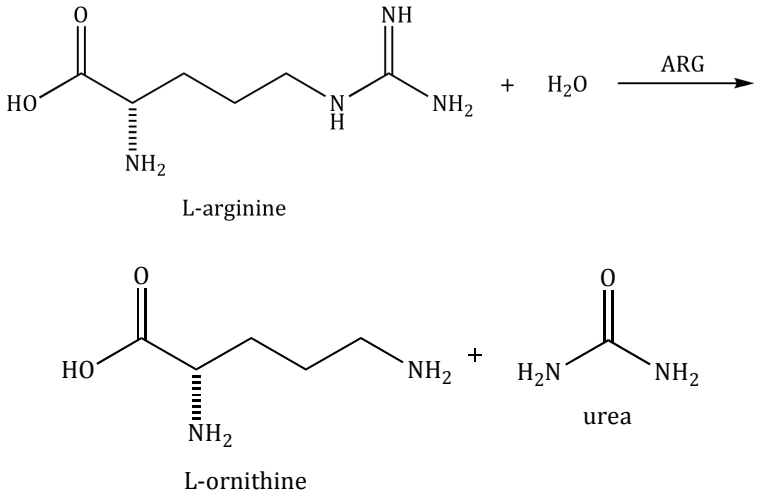
(1.2)



OTC – ornithine transcarbamylase **ASS** – argininosuccinate synthetase (1.3)



(1.4)

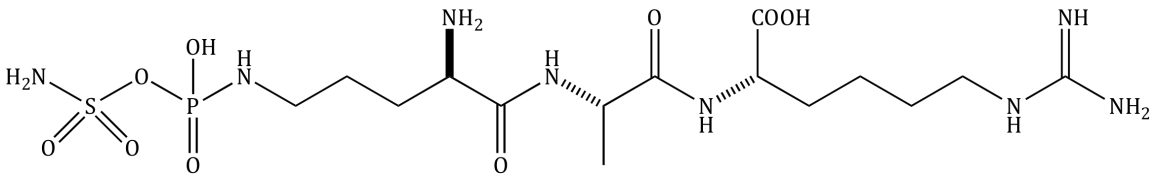


ASL – argininosuccinase **ARG** - arginase (1.5)

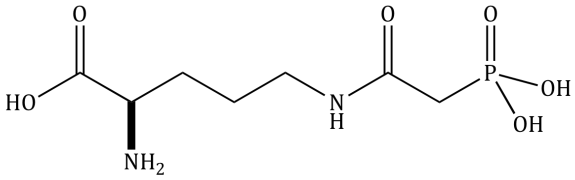
Steps 1.1 – 1.2 take place in the mitochondria, whereas steps 1.3 – 1.5 take place in the cytosol. Finally, the L-ornithine and urea formed in step 1.5 are recycled and excreted as waste, respectively. If this cycle cannot occur, the result is a build-up of ammonia in the blood, called hyperammonemia. When this occurs in newborns as a result of a deficiency in ornithine transcarbamylase activity, brain damage and death can result.[3]

Ornithine transcarbamoylase (OTCase, E.C. 2.1.3.3) catalyzes the reaction between carbamoyl phosphate and ornithine, forming citrulline and phosphate (See 1.2). A common disorder of inherited hyperammonemia is X-linked Ornithine Transcarbamylase Deficiency, which as mentioned earlier, can lead to death in a newborn by overwhelming the body's ability to manage excess ammonia in the bloodstream, especially around the brain. Ninety identified mutations in the ornithine transcarbamylase can lead to a decrease in enzymatic activity.[3]

Since enzymes bind more tightly to activated complexes than to the individual substrates (i.e.-carbamoyl phosphate and L-ornithine), chemical analogs of activated complexes should, in theory, inhibit enzymatic activity.[3]
In regards to ornithine transcarbamylase, several synthetic transition-state analogs have shown significant enzyme inhibition, including N-(N'-sulfodiaminophosphinyl)-L-ornithine, phaseolotoxin, and N-(phosphonoacetyl)-L-ornithine (PALO). The latter two examples have shown to be potent inhibitors of ornithine transcarbamylase, each having an inhibition constant (K_i) of approximately 2.5 μM at pH of 7.4. [4,5a]



phaseolotoxin



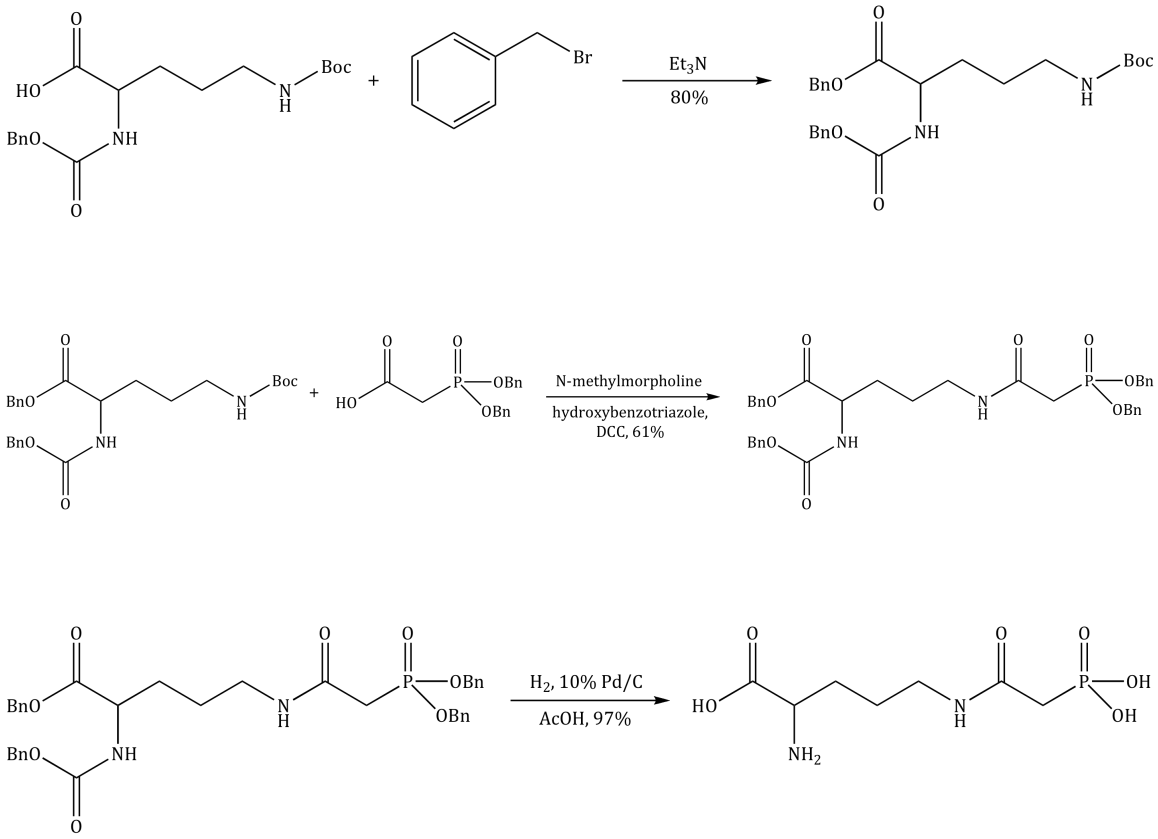
N-(phosphonoacetly)-L-ornithine

As part of collaboration with Dr. Audrey Atkin (School of Biological Sciences, University of Nebraska), PALO is being used in studies to understand the physiology of amino acid transcription in *Saccharomyces cerevisiae* cells. PALO was earlier shown to increase the transcription of the amino acid biosynthetic genes, *HIS3, TRP5, CPA,* and *CPA2* without affecting the growth rate of the aforementioned yeast strain.[5b] Dr. Atkin's research will focus on whether there is, in fact, an increase in transcription of these genes by using mRNA analysis with and without PALO present.

Results and Discussion

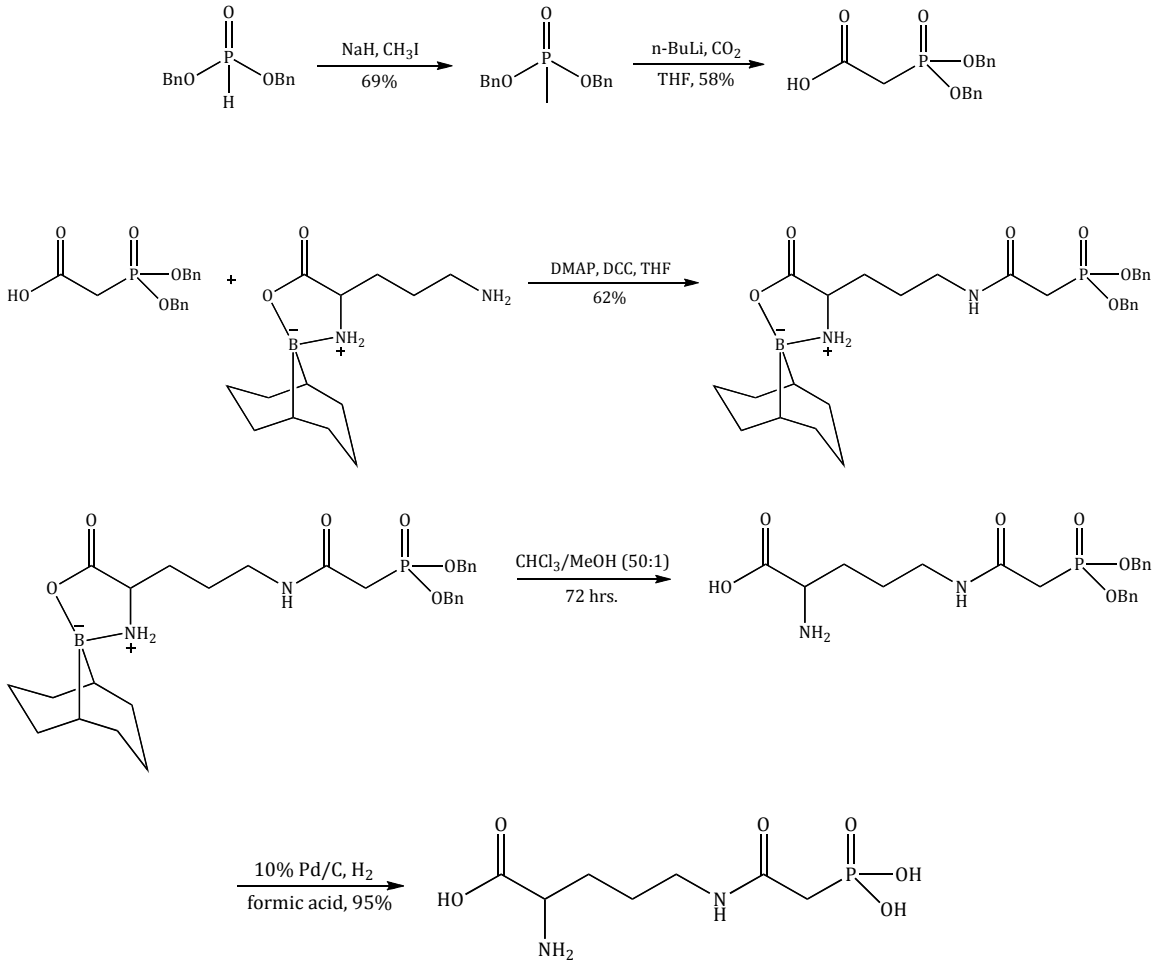
N-(phosphonoacetyl)-L-ornithine (PALO) has been synthesized by various methods and in yields ranging from 8-25%.[6-10] Since PALO is not a very complex molecule, the synthetic schemes are very similar; mainly differing only in the protecting groups used for the amino acid and the phosphonic acid moiety. The following synthetic scheme by Alewood[7] (Scheme 1), utilized separate protecting groups for each of the amine groups as well as the carboxyl group. However, as the protected L-ornithine starting material is no longer commercially available; it would have to be synthesized.

Scheme 1



The new synthesis presented here employs easily accessible reagents, good purity, and a novel “bidentate” protecting group for the amino acid to provide PALO in reasonable yield (Scheme 2).

Scheme 2

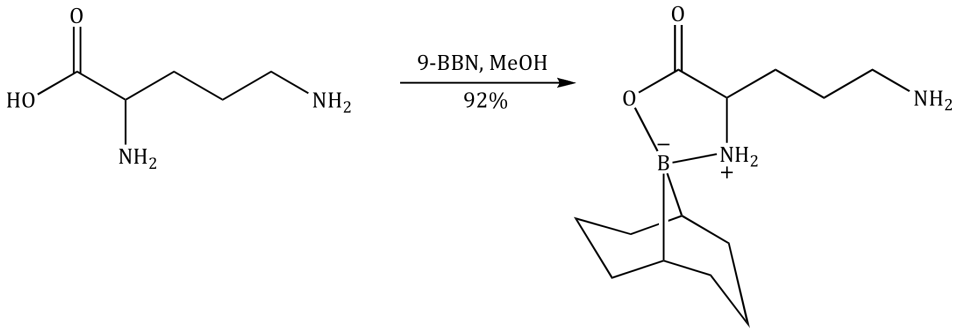


The protection schemes need to address the reactive amine and carboxylic acid groups on the L-ornithine and the phosphonate group. The protection of the latter as the dibenzyl phosphonate was achieved by use of dibenzyl phosphite as a

precursor. The L-ornithine portion required protection of the acid group and the α-amino group, either separately or simultaneously. A problem with protecting them separately for L-ornithine is the presence of the δ-amino group. Differentiation of the two amino groups during protection would be problematic, leading to a mixture of mono-protected and fully protected products. An attractive protecting method, which is presented here, is the simultaneous blocking of the acid and α-amino group while leaving the δ-amino group untouched. Several approaches to this two-fold protection have been reported, including copper chelation or reaction with various boron derivatives.[11]

The trialkyl boron, 9-borabicyclononane (9-BBN), used here, has been utilized for the complexation of amino acids through the electrophilic boron atom. This protection strategy has seen increased use because of the ease of protection/removal, the stability of the intermediate, and the increased solubility of the protected amino acids in organic solvents.[12] Scheme 3 shows the first step, where the α-amino acid of L-ornithine is selectively complexed with 9-BBN. A solution of L-ornithine in anhydrous methanol was reacted with a THF solution of 9-BBN for four hours at reflux and then allowed to cool. The solution was then concentrated and the resulting solid was purified by trituration with hot diethyl ether.

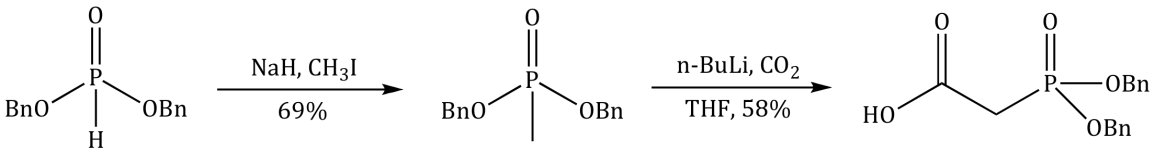
Scheme 3



The ornithine complex was used "as is" because of the difficulty of obtaining analytically pure 9-BBN-L-ornithine. The material was triturated several times with hot diethyl ether to remove excess 9-BBN. The ^{1}H NMR spectrum still showed slight impurities. However, the use of the crude reaction product was determined to not have an effect on the next step.

Synthesis of the other half of PALO started from dibenzyl phosphite, which was first methylated with iodomethane. The resulting methyl phosphate was then carboxylated to form dibenzylphosphonoacetic acid.

Scheme 4

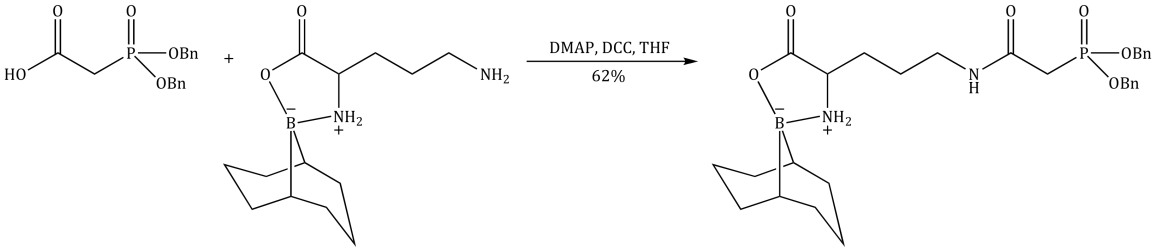


For the formation of dibenzyl methylphosphonate (Scheme 4), dibenzyl phosphite was deprotonated with sodium hydride and iodomethane was added to yield the intended product in 69% yield. The product was then deprotonated with n-

butyllithium and the resulting lithiophosphonate was added to a saturated solution of dry ice in diethyl ether. After purification, a colorless oil was isolated in 58% yield. This step was somewhat problematic because any excess n-butyllithium was trapped by CO_2 to form pentanoic acid as a side product, which required flash chromatography to remove. Use of only one equivalent of n-butyllithium avoided the formation of the carboxylic acid side product and allowed purification to be accomplished simply through an acid/base extraction. The use of anhydrous diethyl ether and fresh dry ice minimized the reformation of starting material by protonation, leading to higher product yields. In principal it would simpler to use the Arbuzov reaction with bromoacetic acid and tribenzyl phosphite to form the required phosphonoacetic acid in one step instead of two. However, the latter reagent is not available commercially and would need to be made from phosphorus trichloride and benzyl alcohol, the former being a controlled substance as well as toxic.

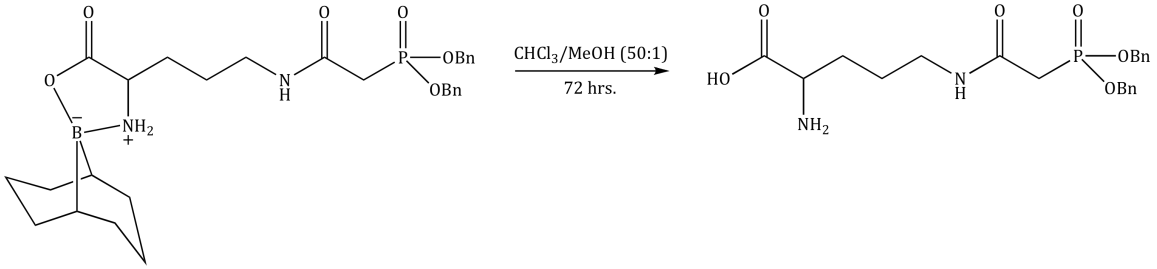
The coupling of 9-BBN-L-ornithine and dibenzylphosphonoacetic acid was accomplished using stoichiometric amounts of dimethylaminopyridine (DMAP) and the coupling agent, dicyclocarbodiimide (DCC). A benefit to using DCC as the coupling agent is that upon reaction completion, the byproduct dicyclohexylurea can often be filtered from the reaction solution leaving behind the coupled product in good yield (Scheme 5).

Scheme 5



Alternatively, the use of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) was explored because of the ability to wash out the water-soluble urea side product it forms during the extraction step. The yields obtained with the two coupling agents were comparable and DCC was primarily used.

Scheme 6



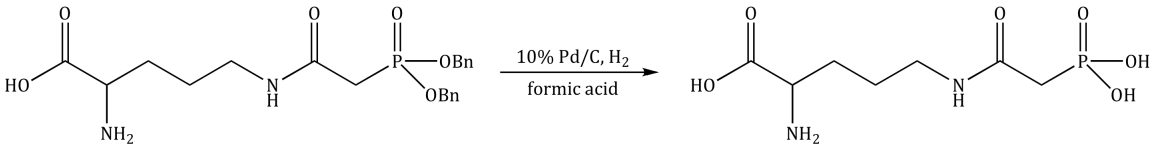
Once the coupled product was isolated and purified, the next step was to remove the 9-BBN protecting group, which proved to be surprisingly difficult. Literature reports suggested that the 9-BBN group can be easily removed from simpler frameworks by either aqueous HCl or ethylenediamine. However, for the

PALO precursor, attempted deprotection with either of these methods led to little or no deprotection.

Method	**Time (hrs)**	**% Yield (NMR)**
Refluxing MeOH	24	0
Aqueous HCl	1, 24	0, decomposition
$CHCl_3$/MeOH	72	80-90
ethylenediamine	1, 24	0, 10

Alternative deprotection schemes have been found to be fruitful for other boron analogs used for amino acid protection, including refluxing in anhydrous methanol or simply stirring the protected amino acid in a solution of methanol and chloroform.[13, 14] The former approach showed no formation of the deprotected product. However, stirring the fully protected compound in a 50:1 solution of chloroform and methanol for 3 days produced the deprotected amino acid in 90% yield (Scheme 6). Purification was accomplished by ion exchange using Dowex 50X2-200 cation resin and 1% ammonium hydroxide as the eluent. The resulting fractions were lyophilized, yielding a white solid. Hydrogenolysis, (Scheme 7) was then used to remove the benzyl protecting groups from the phosphonic acid moiety by using formic acid and 10% Pd/C under a balloon of hydrogen. After 24 hours, filtration of the solution and lyophilization, yielded a white solid in 95% yield.[15] The ^{1}H, ^{13}C, and ^{31}P NMR spectrum of the final product showed a pure compound with spectral properties consistent with previously reported syntheses.[7]

Scheme 7



Conclusion

The formation of PALO has been determined to be helpful in determining the enzyme reaction mechanism of X-linked Ornithine Transcarbamylase Deficiency, which often causes death in newborns by causing a high concentration of ammonia to be present in the brain. A synthetic approach, which forms PALO in few steps and with good yield using common reagents, could be very useful. In this study, we have demonstrated that the synthesis of PALO can be accomplished by using L-ornithine protected with a "bidentate" protecting group and coupling that to phosphonacetic acid, which upon complete deprotection resulted in an overall yield of 21%. As noted earlier, Dr. Atkin (School of Biological Sciences, University of Nebraska) has been attempting to utilize PALO in the study of amino acid transcription in *Saccharomyces cerevisiae* cells and while, at this point, her research has been unable to come to a conclusion our approach to an improved synthesis of PALO has allowed us develop methods which may be broadly applicable to terminally-functionalized ornithine and lysine derivatives.

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Experimental

All reagents and solvents were used as supplied commercially, except THF, which was distilled from Na/Ph_2CO, and methanol, which was distilled from Mg/I_2. ^1H, ^{13}C, and ^{31}P spectra were recorded on Bruker 300, 400, 500, and 600 MHz NMR spectrometers; individual peaks are reported as (multiplicity, number of hydrogens, coupling constant in Hz). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer as neat films or solids on a zinc selenide plate. Selected absorbances are reported in wavenumber (cm^{-1}). Thin layer chromatography (TLC) analyses were done on Analtech Uniplate Silica Gel GHLF (250 μm) and Analtech Uniplate reversed-phase HPTLC-RP18F (150μm) plates. Progress of reactions were monitored by TLC, using a vanillin indicator (3 g vanillin, 3 mL concentrated sulfuric acid, and 97 mL anhydrous ethanol), ninhydrin indicator (0.3 g ninhydrin, 100 mL n-butanol, and 3 mL glacial acetic acid), bromocresol green indicator (0.04 g bromocresol green, 100 mL ethanol, and 0.1 N NaOH until blue), and UV visualization using a hand-held shortwave UV light source (254 nm). Mass spectra were obtained at the Center for Mass Spectrometry, University of Nebraska-Lincoln.

Dibenzyl methylphosphonate [16]

(This compound was prepared using a modification of a reported procedure.)[16]

Into a nitrogen-flushed, oven-dried 100 mL flask equipped with a magnetic stir bar was added dry sodium hydride (95%) (0.625 g, 26 mmol, 1.3 eq.) and anhydrous THF (22 mL). This suspension was cooled to 0 °C and dibenzyl phosphite

(5.23 g, 20 mmol, 1 eq.) was added drop wise. The reaction was then allowed to stir for 1 hr (a large evolution of gas was noticed from the middle of the addition to the end and it was important that the flask size and venting was adequate enough to accommodate this) after which was added iodomethane (1.62 mL, 26 mmol, 1.3 eq.). The reaction was stirred for an additional 2 hr. at 0 °C and then quenched by the addition of water (30 mL) and diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic fractions were dried with anhydrous sodium sulfate. The residue obtained from filtration and concentration (4.7 g, containing benzyl alcohol and the product) was purified by flash chromatography (R_f = 0.34, 1:1 ethyl acetate/hexanes) to yield a colorless oil (3.83 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.36 (m, 10H), (5.08) (dd, 2H, $^{3}J_{HP}$ = 8.9, 11.8 Hz), 4.98 (dd, 2H, $^{3}J_{HP}$ = 8.3, 11.8 Hz), 1.49 (d, 3 H, $^{2}J_{H\text{-}P}$ = 17.7 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4 (d, $^{3}J_{CP}$ = 6.1 Hz), 128.6, 128.4, 127.9, 67.1 (d, $^{2}J_{CP}$ = 6.2 Hz), and 11.7 (d, $^{1}J_{CP}$ = 144 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 31.71 ppm; IR: 3033, 1497, 1455, 1416, 1310, 1239, 1214, 991, 915, 825, 728, 694 cm^{-1}. HRMS *m/z* calculated for $C_{15}H_{17}O_3P$ $(M+H)^+$: 277. 099358; found 277.10021 (3.1 ppm).

Dibenzylphosphonoacetic acid

(This compound was prepared using a modification of a reported procedure.)[17]

Into a -78 °C solution of dry THF (10 mL) in nitrogen-flushed, oven-dried 50 mL round bottom flask equipped with a magnetic stir bar was added n-butyllithium (4.2 mL of a nominally 2.5 M solution in hexanes, 10 mmol, 1 eq.). After the resulting

solution had stirred for 5 min at -78 °C, a solution of dibenzyl methyl phosphonate (2.76 g, 10 mmol, 1 eq.) dissolved in dry THF (2 mL) was added in a dropwise fashion. The resulting yellow/brown solution was allowed to stir at -78 °C for 30 min, and then poured directly into an Erlenmeyer flask containing dry ice-saturated diethyl ether (100 mL). An opaque white suspension resulted which was allowed to warm to room temperature while stirring (~ 2 hrs.), resulting in a clear and nearly colorless solution. The reaction was quenched with water (30 mL) and the organic layer was washed with saturated sodium bicarbonate (3 x 30 mL). The combined aqueous layers were washed with diethyl ether (2 x 20 mL) and then acidified to pH 1 with 6M hydrochloric acid. The acidified aqueous layer was saturated with sodium chloride and extracted with dichloromethane (3 x 20 mL). The combined dichloromethane layers were dried with anhydrous sodium sulfate and filtered. The residue obtained upon concentration (1.85 g, 58%) was sufficiently pure to be used directly. Further purification can be accomplished using flash chromatography (ethyl acetate, R_f = 0.70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (br, 1H), 7.29 – 7.34 (m, 10H), 5.12 (dd, 2H, J_{HP} = 9.1, 17.3 Hz), 5.08 (dd, 2H, J_{HP} = 9.1, 17.3 Hz), 3.04 (d, 2H, $^{2}J_{H\text{-}P}$ = 21.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (d, J_{CP} = 5.3 Hz), 135.7, 128.6, 128.1, 68.6 (d, J_{CP} = 6.3 Hz), and 34.5 (d, J_{CP} = 136 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 22.21 ppm; IR (film) v 3200-2500, 1720, 1210, 990, 730, 695 cm^{-1}; HRMS m/z calculated for $C_{16}H_{21}O_3P$ $(M+H)^+$: 321.08919; found: 321.08806 (3.5 ppm).

_N_-Borabicyclononane (9-BBN) protected L-ornithine

(This compound was prepared using a modification of a reported procedure.)[12]

To a nitrogen-flushed, oven-dried, one-necked 500 mL round bottom flask equipped with a magnetic stir bar and reflux condenser was added anhydrous methanol (150 mL) and 9-BBN (65 mL of a nominally 0.5 M solution in THF, 1.3 eq.). The stirring solution was flushed with nitrogen for 5 minutes and then L-ornithine hydrochloride (4.22 g, 25 mmol, 1 eq.) was added. The solution was refluxed for 4 h, and the colorless solution was then allowed to cool to room temperature. After stirring overnight, the colorless solution was concentrated by rotary evaporation. The residue was redissolved in hot THF (100 mL) and filtered. The yellow-brown oil obtained upon concentration of the filtrate was triturated with hot diethyl ether (50 mL x 4) and the residue dried under high vacuum for 1-1.5 hours. The resulting white powder (5.82 g, 92 %) was used without further purification. HRMS *m/z* calculated for $C_{13}H_{26}BN_2O_2$ (M^+): 253.20873; found: 253.20774 (3.9 ppm); $[\alpha]^{20}$: -5.2° (*c* 2.0, methanol).

9-BBN-protected L-ornithinyl dibenzyl phosphonoacetamide

In a nitrogen-flushed, oven-dried, 50 mL round bottom flask equipped with a magnetic stir bar was added dry THF (33 mL) and 9-BBN-protected L-ornithine (1.31 g, 5.2 mmol, 1.1 eq.). The mixture was allowed to stir until fully homogeneous and then dibenzylphosphonoacetic acid (1.50 g, 4.7 mmol, 1 eq.), dimethylamino pyridine (DMAP) (0.574 g, 4.7 mmol, 1 eq.), and dicyclocarbodiimide (DCC) (1.07 g,

5.2 mmol, 1.1 eq.) were added. The reaction was allowed to stir overnight at room temperature. The resulting suspension was concentrated by rotary evaporation and then re-suspended in ethyl acetate and filtered through a fritted glass filter funnel. The filtrate was sequentially washed with saturated sodium bicarbonate (2 x 15 mL), water (15 mL), 1 M HCl (2 x 15 mL), and water (15 mL). The organic layer was dried with anhydrous sodium sulfate and filtered. The residue obtained upon concentration was purified by flash chromatography (R_f = 0.40, 1% MeOH/ethyl acetate) to yield a white solid (1.61 g, 2.9 mmol, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.38 (m, 10H), 6.78 (t, 1H, J = 5.7 Hz), 5.31 (dd, 1H, J = 8.0 Hz, J = 11.6 Hz), 4.92 – 5.06 (m, 5H), 3.62 – 3.69 (m, 1H), 3.34 – 3.43 (m, 1H), 3.08 – 3.16 (m, 1H), 2.86 (d, 2H, J = 21.0 Hz), 1.41 – 2.10 (m, 16H), and 0.59 (d, 2H, J = 12.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 135.5, 128.8, 128.0, 68.3, 54.9, 38.9, 31.4, 28.0, 24.1 ppm; ^{31}P NMR (75.5 MHz, $CDCl_3$) δ 23.3 ppm; IR (solid) v 3292, 3174, 3108, 2923, 2877, 2838, 1692, 1664, 1240, 1214, 1008, 998, 724 cm^{-1}; HRMS m/z calculated for $C_{29}H_{40}BN_2O_6P$ (M^+): 555.27953; found: 555.27801 (2.7 ppm); $[\alpha]^{20}$: -13.4° (c 2.0, chloroform); MP = 125-129° C

L-Ornithinyl dibenzyl phosphonoacetamide

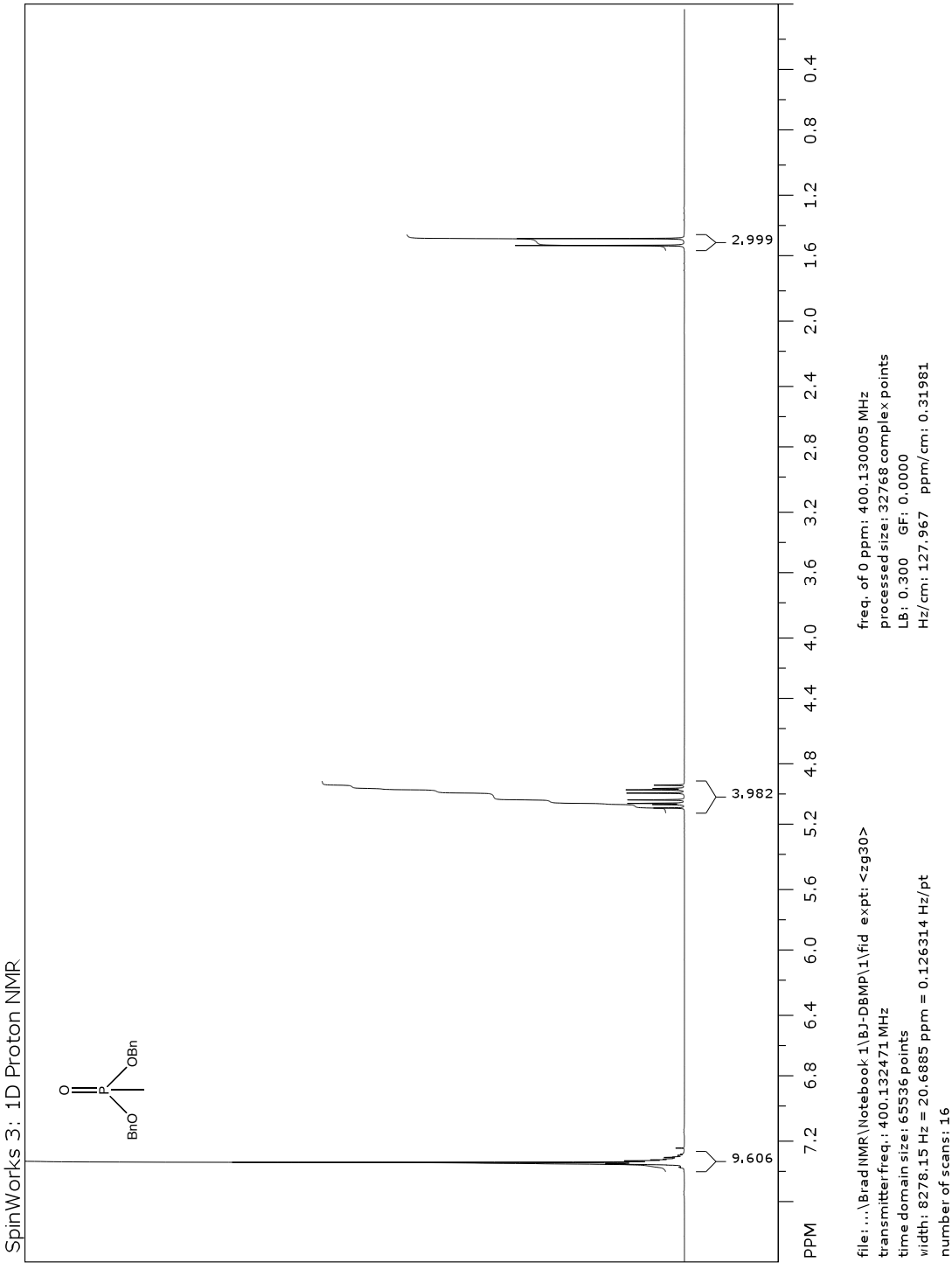
To a ~25 mL vial, equipped with a magnetic stir bar, was added 9-BBN L-ornithinyl dibenzyl phosphonoacetamide (120 mg, 0.22 mmol), methanol (200 µL), and chloroform (10 mL). The reaction was allowed to stir at room temperature for 72 hours and monitored by TLC (Product R_f = 0.50 on C18 RP-TLC plates 3:1 MeOH/H_2O, developed with ninhydrin). Once the reaction appeared to be complete,

the solution was concentrated to an oil, purified by ion exchange (~2 g. Dowex 50X2-200; column – 1.5 cm x 30 cm, pre-acidified with 2M HCl, eluting solvent: 1% NH_4OH), and lyophilized to yield a fluffy, white solid (85.6 mg, 0.20 mmol, 90%). ^1H NMR (400 MHz, MeOH) δ 7.39-7.32 (m, 10H), 5.09 (dd, 2H, J = 11.8, 11.4 Hz; ABX system involving 5.04 ppm), 5.04 (dd, 2H, J = 11.8, 11.4 Hz; ABX system involving 5.09 ppm), 3.53 (dd, 1H, J = 6.6, 6.6 Hz), 3.27 – 3.14 (m, 2H), 3.02 (d, 2H, J = 21.7 Hz), 1.93 – 1.75 (m, 2H), and 1.66 – 1.57 (m, 2H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 174.38, 137.74, 129.82, 129.78, 129.32, 69.70, 55.86, 40.35, 36.99, 35.49, 29.88, and 26.33 ppm; ^{31}P NMR (162 MHz, MeOD) δ 24.08 ppm; IR (solid) v 3350-3250, 3150-2800, 1630, 1550, 1230, 995, 900, 825, and 670 cm^{-1}; HRMS m/z calculated for $C_{21}H_{28}N_2O_6P$ $(M+H)^+$: 435.16850; found: 435.16846 (0.1 ppm); $[\alpha]^{20}$: +1.2° (c 2.1, methanol); MP = 167-170°C.

<u>*δ – N* – (phosphonoacetyl)-L-ornithine</u>

To a nitrogen-flushed 5 ml vial equipped with a magnetic stir bar and rubber septum was added L -ornithinyl dibenzyl phosphonacetamide (133 mg, 0.3 mmol, 1 eq.), formic acid (1.1 mL), and 10% palladium on charcoal (54 mg, 28 mol %). The mixture was stirred for 5 min while being flushed with nitrogen and then placed under a balloon filled with hydrogen. The head space was vented with a needle for ~ 1 min to replace nitrogen with hydrogen, and then the reaction was allowed to stir for 24 hours under a balloon of hydrogen. The solution was then filtered through a plug of Celite and then lyophilized, yielding a white solid (72 mg, 95 %). ^1H NMR (300 MHz, D_2O) δ 4.00 (t, 1H, J = 5.9 Hz), 3.26 (t, 2H, J = 5.9 Hz), 2.75 (d, 2H, $^2J_{H\text{-}P}$ =

20.4 Hz), 2.08 (m, 2H), 1.54 (m, 2H) ppm; ^{13}C NMR (75.5 MHz, D_2O) δ 172.69, 170.22, 53.10, 38.67, 38.42 (d, J = 122 Hz), 27.24, and 24.10 ppm; ^{31}P NMR (121.5 MHz, D_2O) δ 15.0 ppm; IR (solid) v 3600-2350, 1715, 1630, 1547, 1300, 1204, 1020, and 915; HRMS m/z calculated for $C_6H_{13}N_2O_6P$ $(M+H)^+$: 255.074600; found: 255.074685 (0.3 ppm); $[\alpha]^{20}$: +3.6° (c 1.0, water); MP- change observed at 70°C and TGA/TA showed no significant change in heat flow.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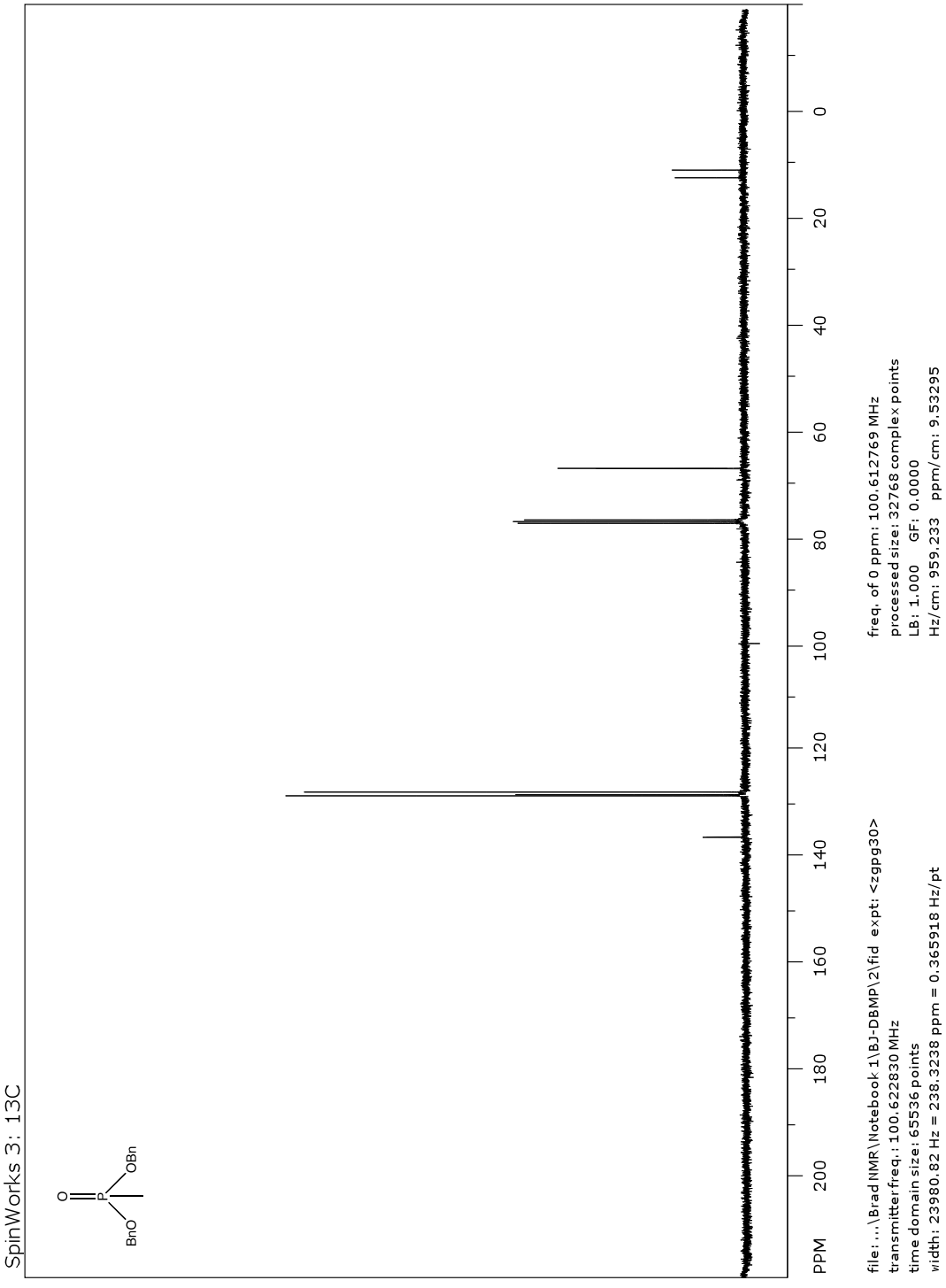
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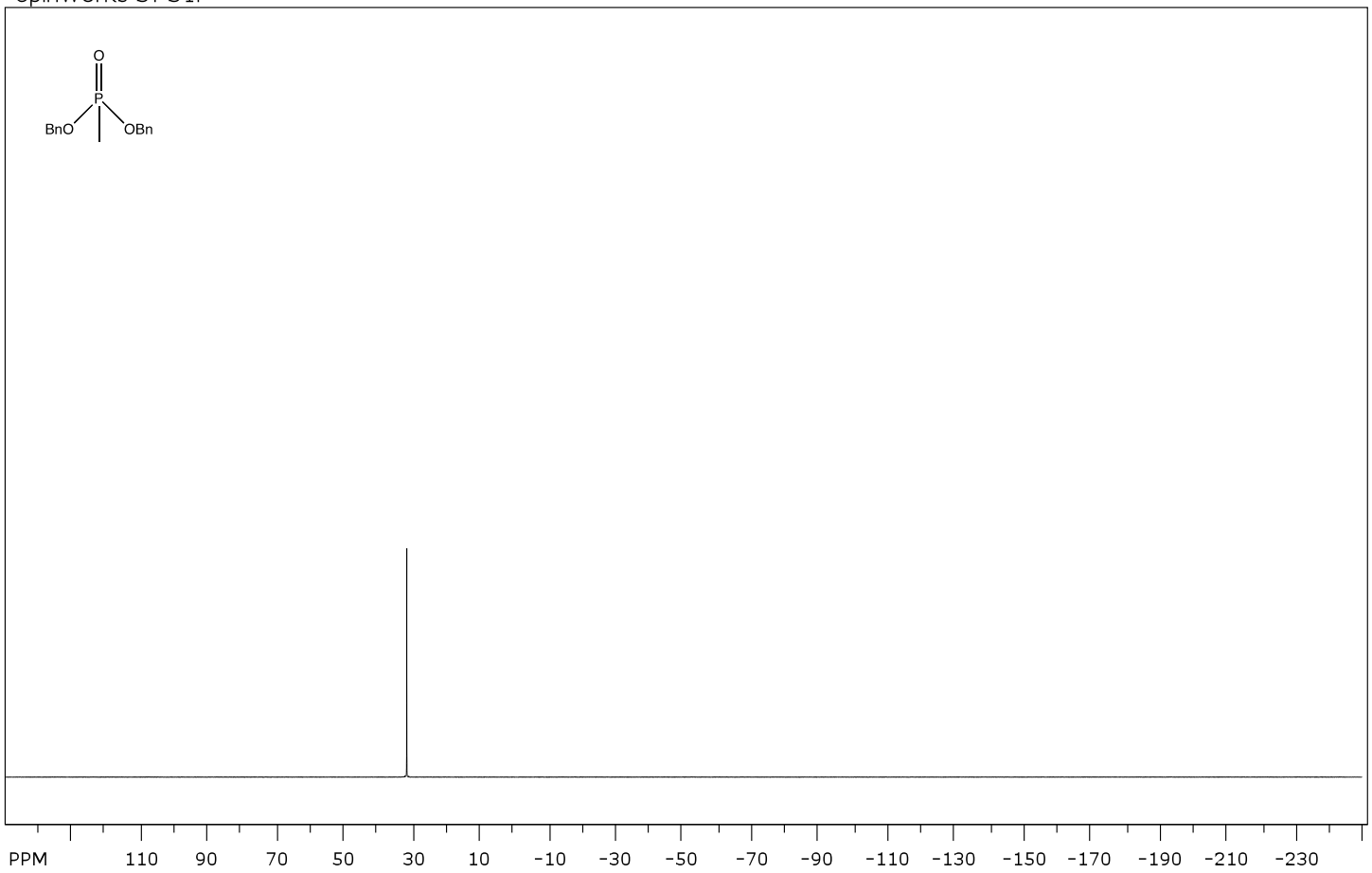

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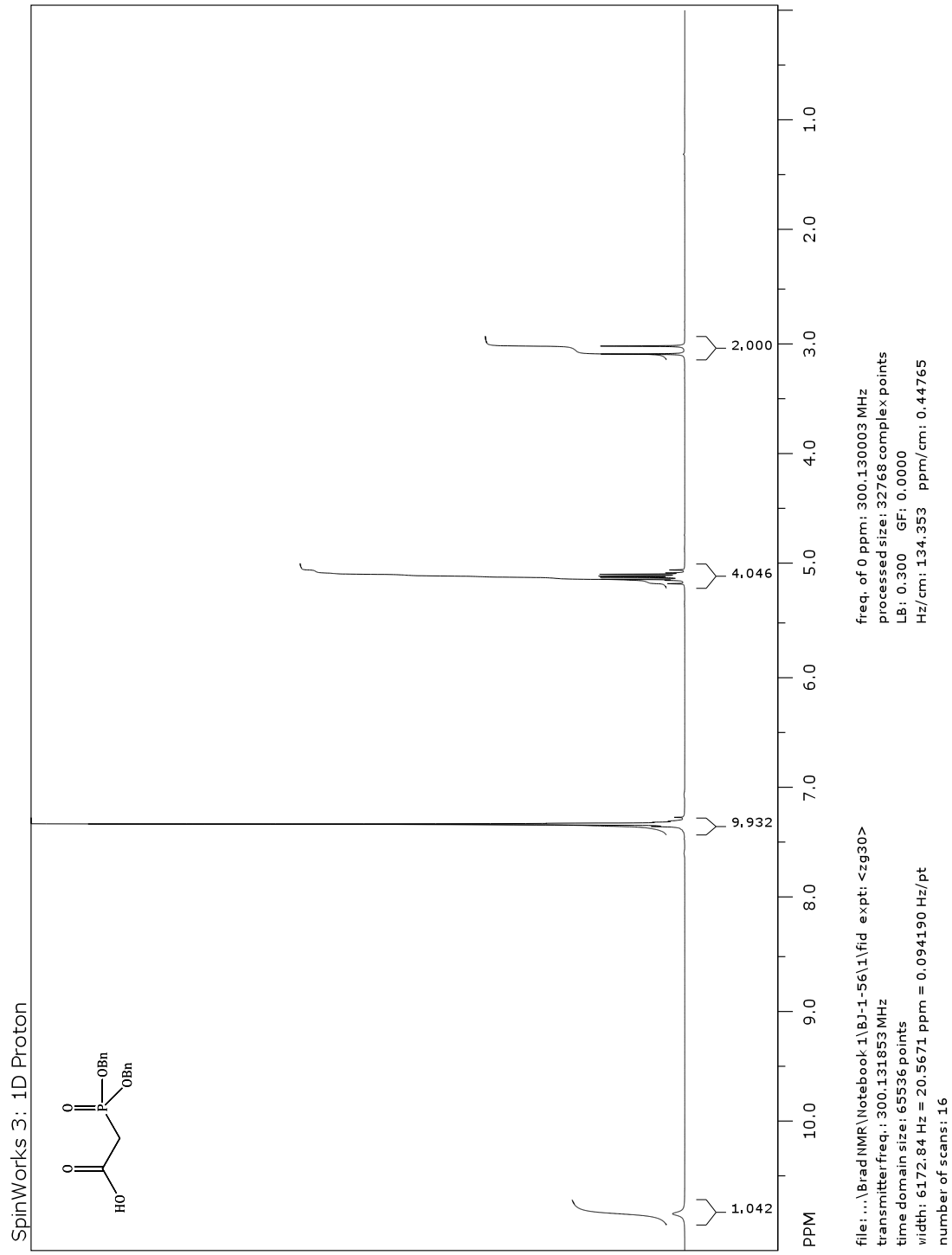
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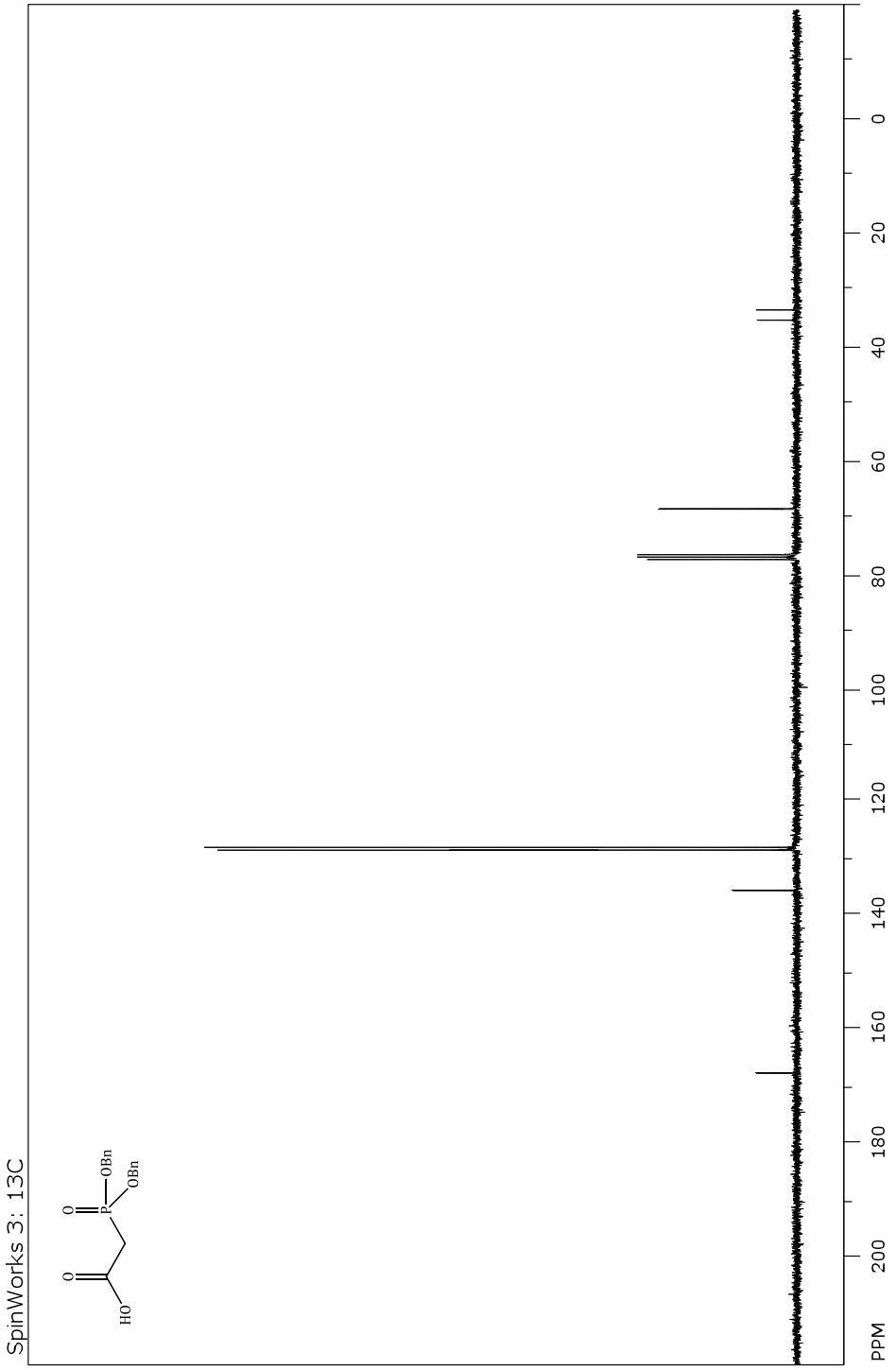
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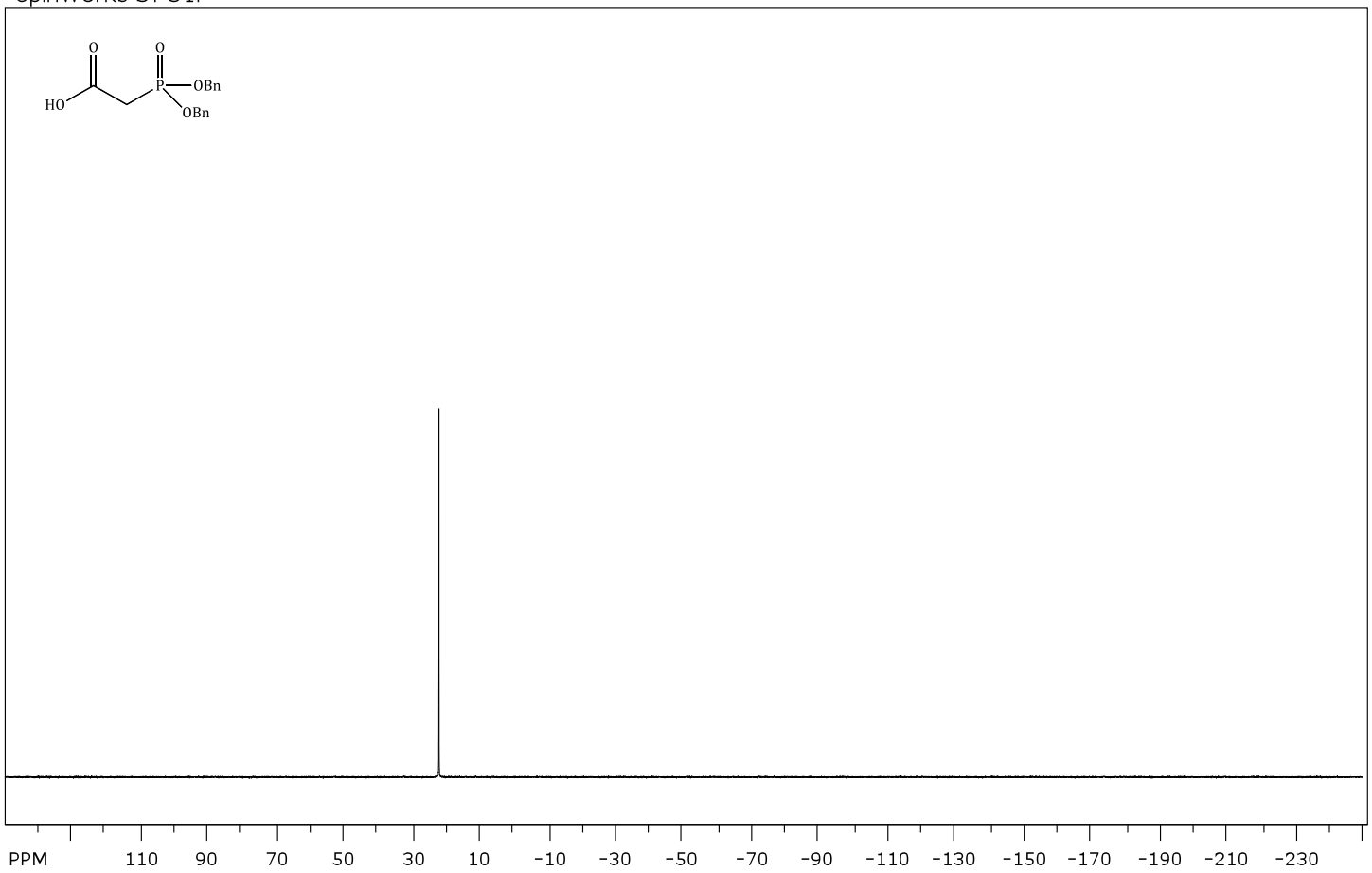

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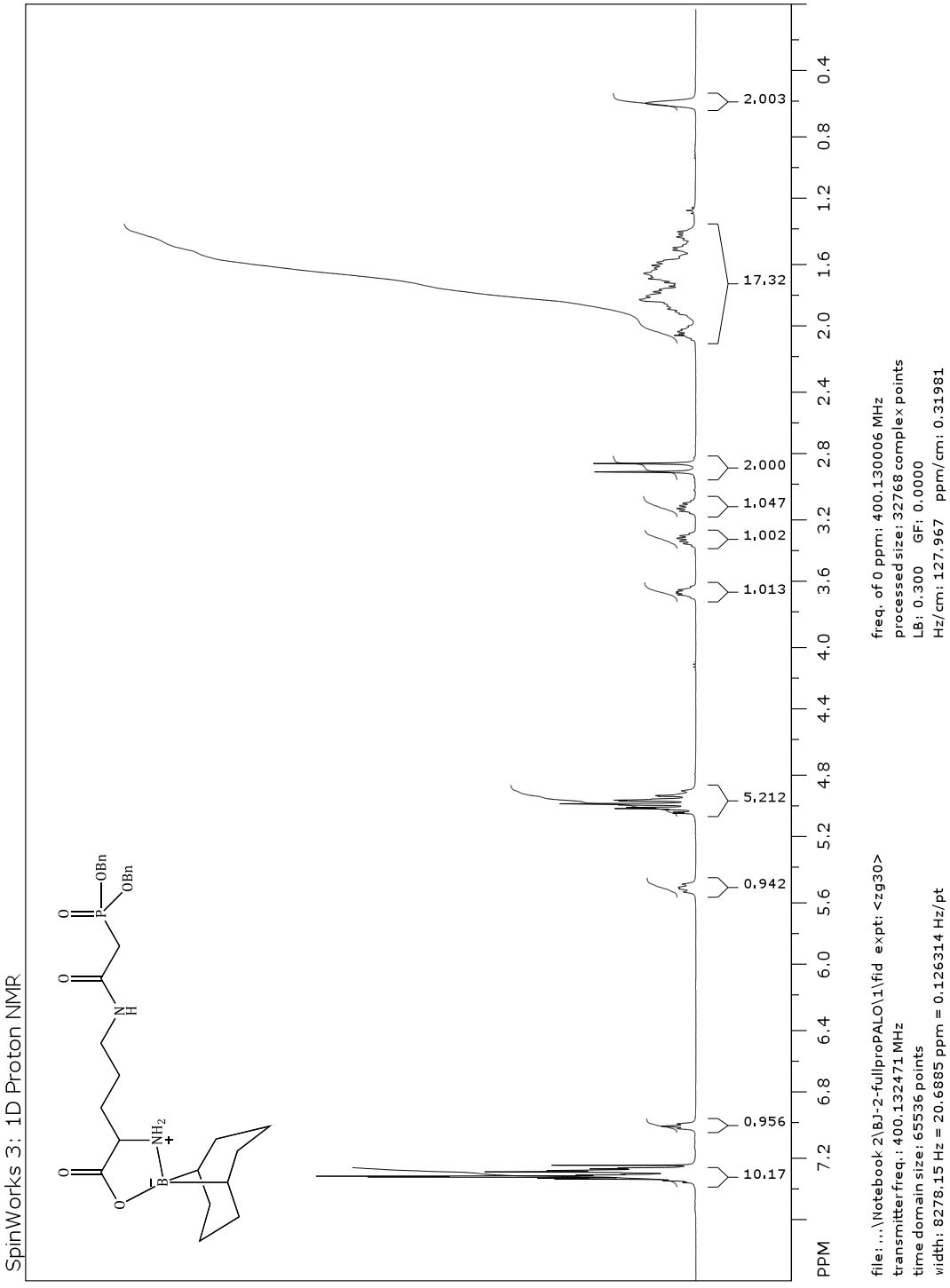
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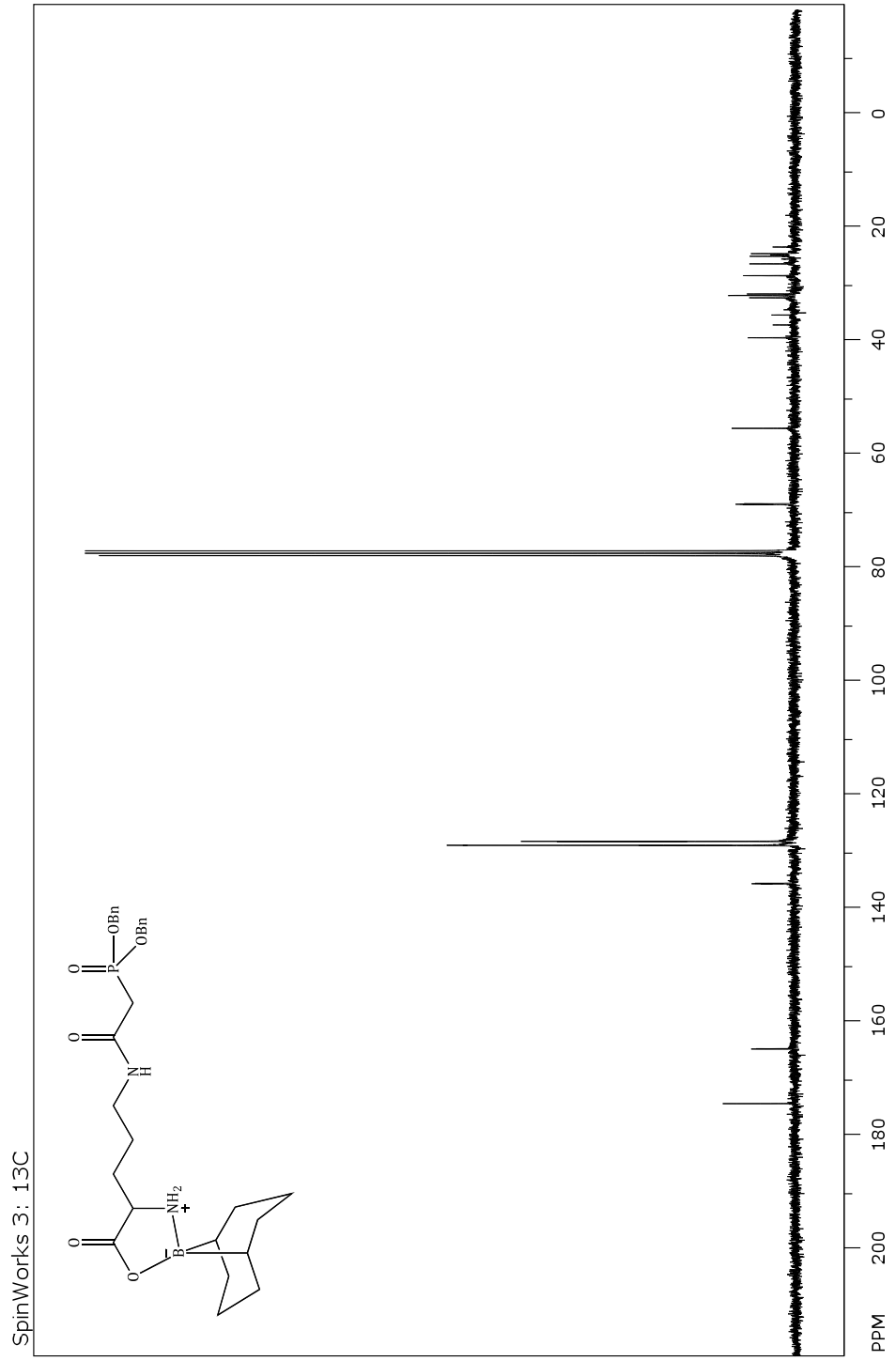
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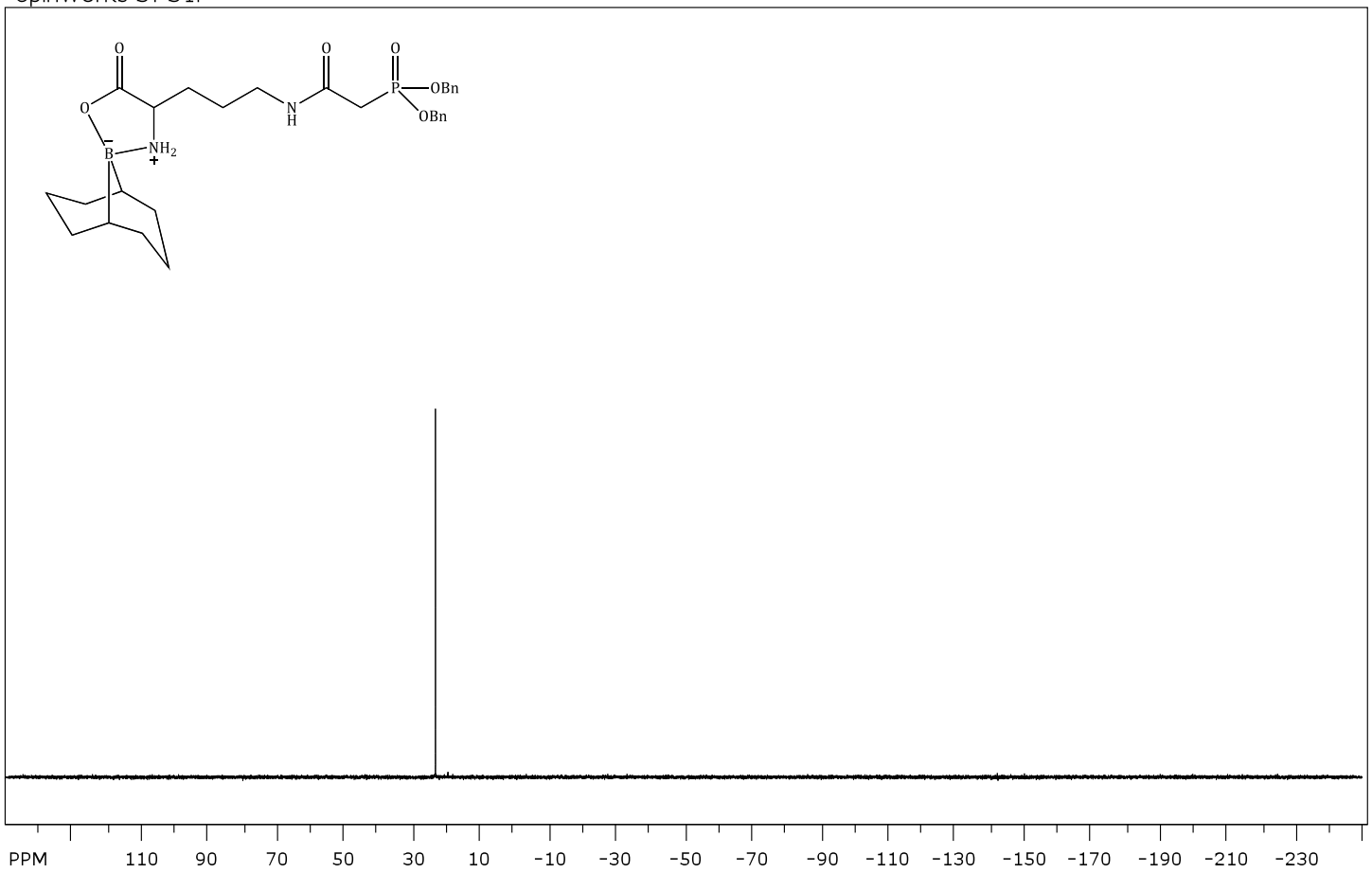

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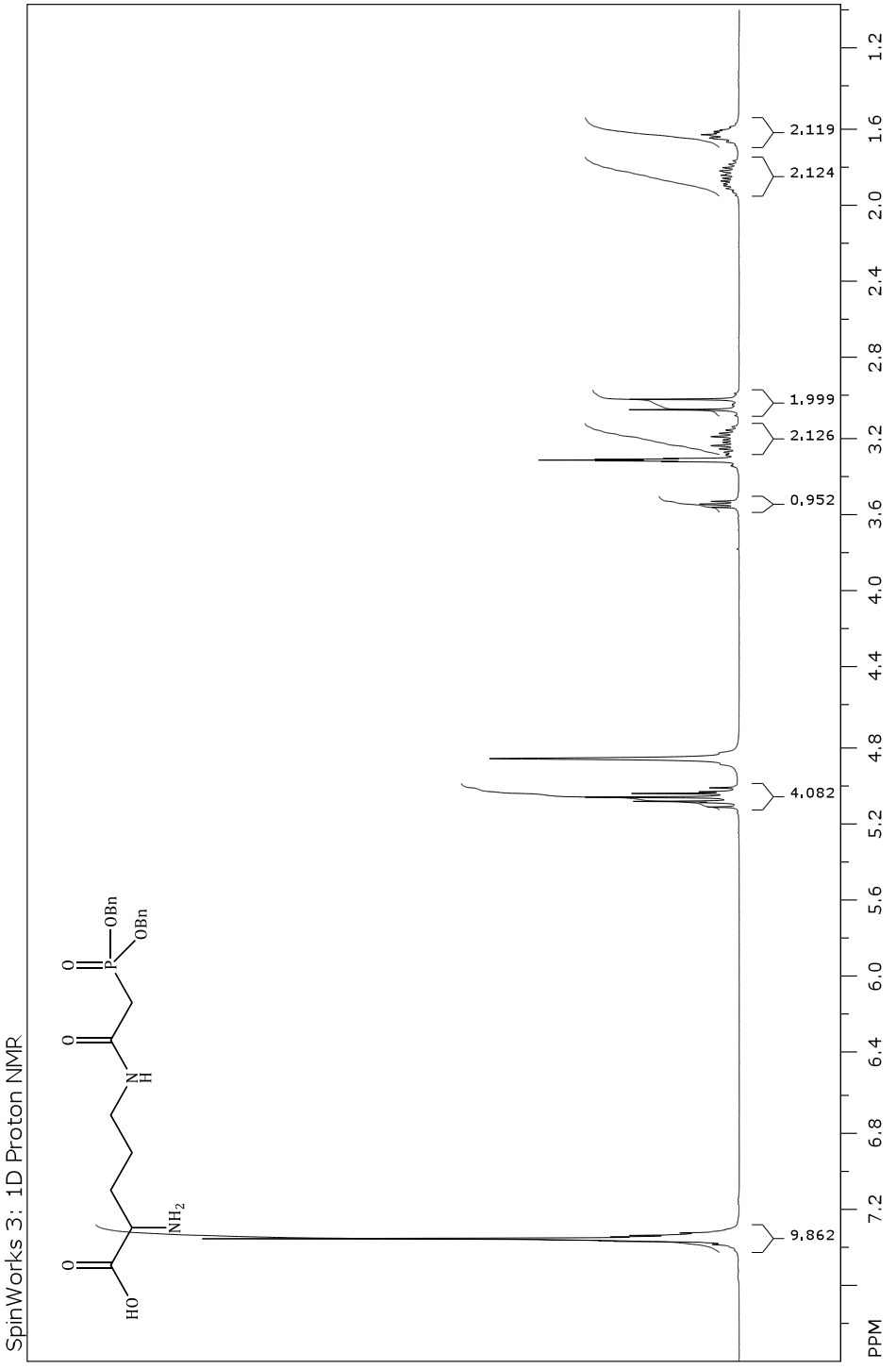
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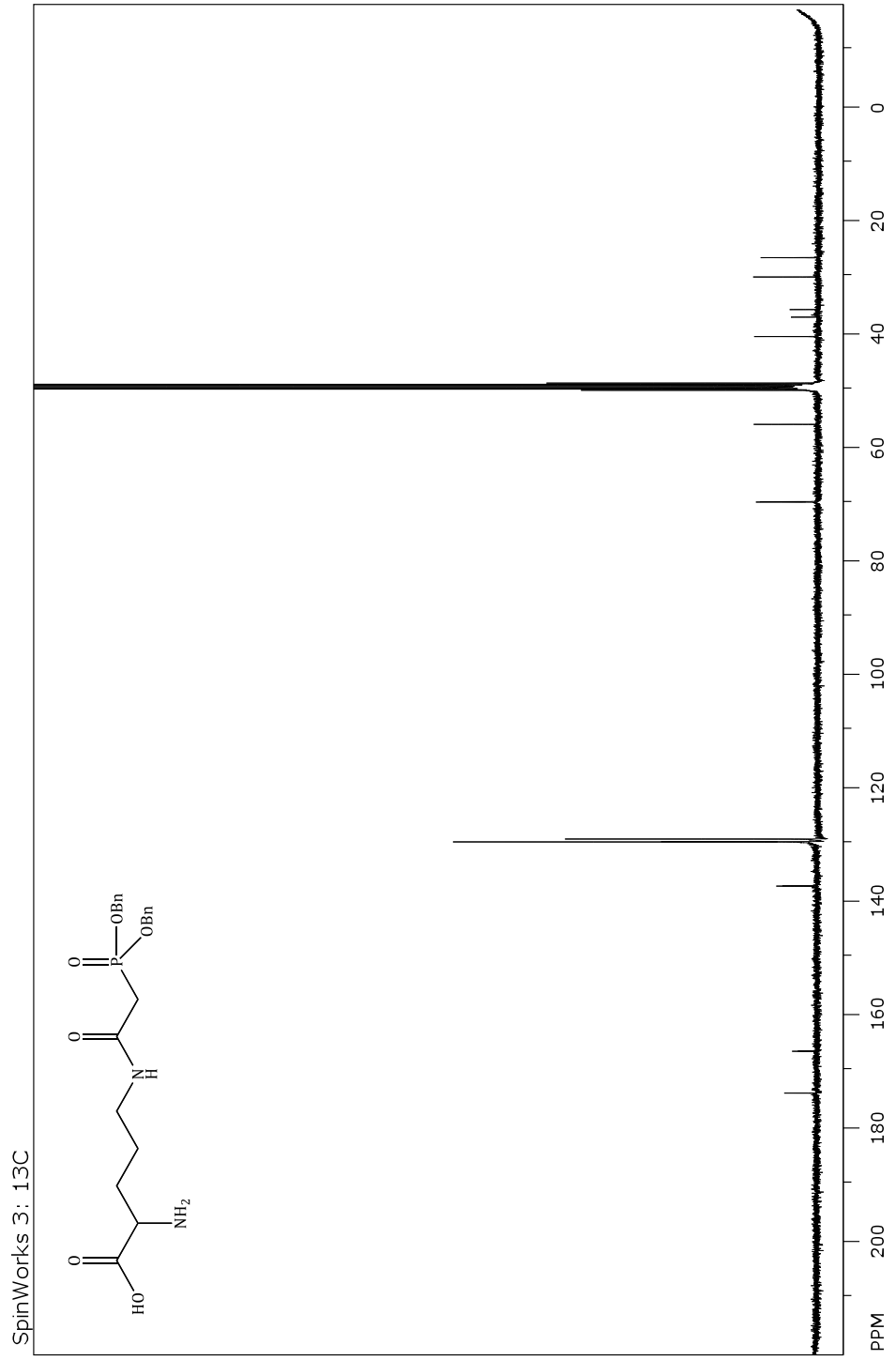
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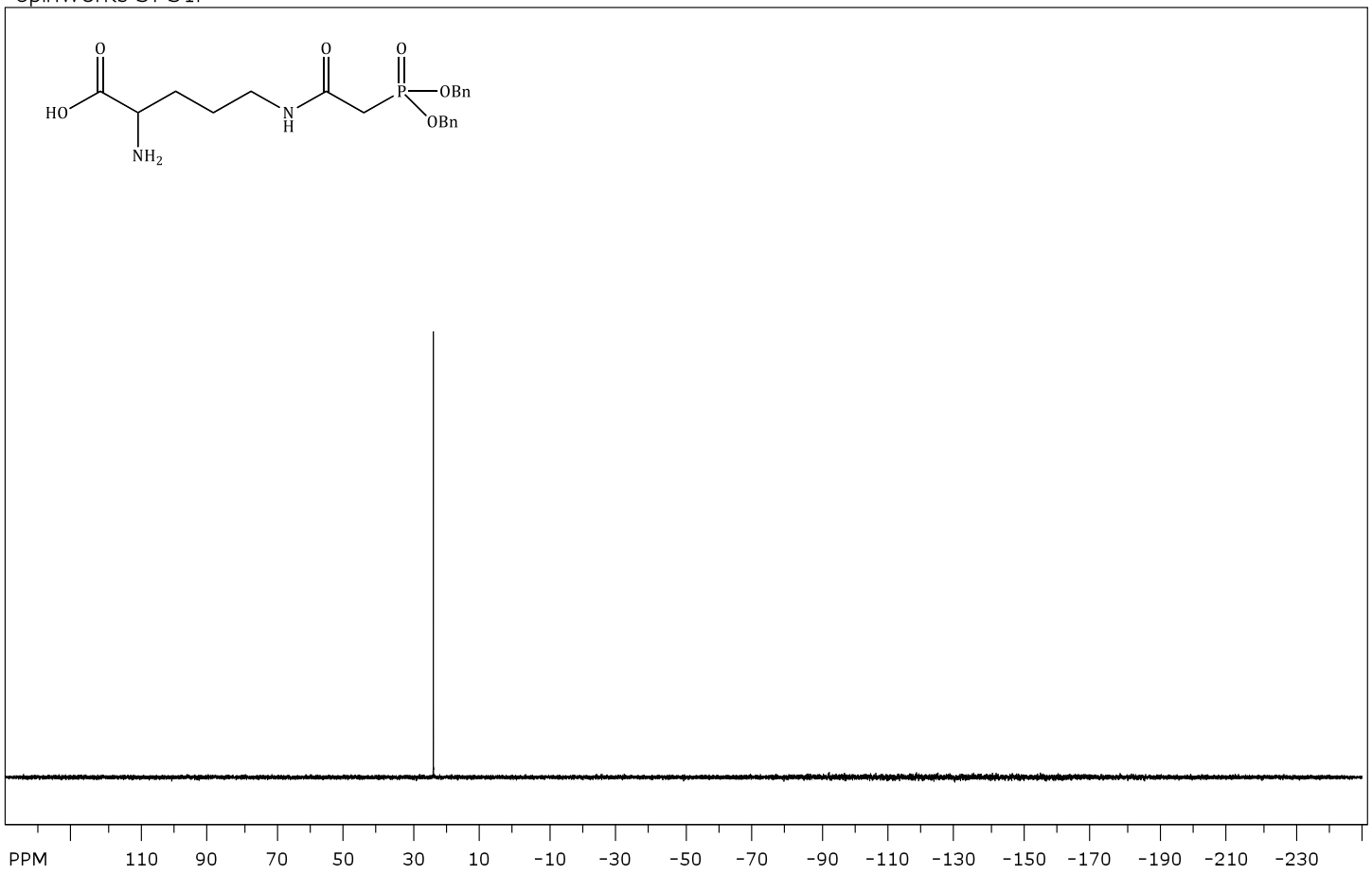

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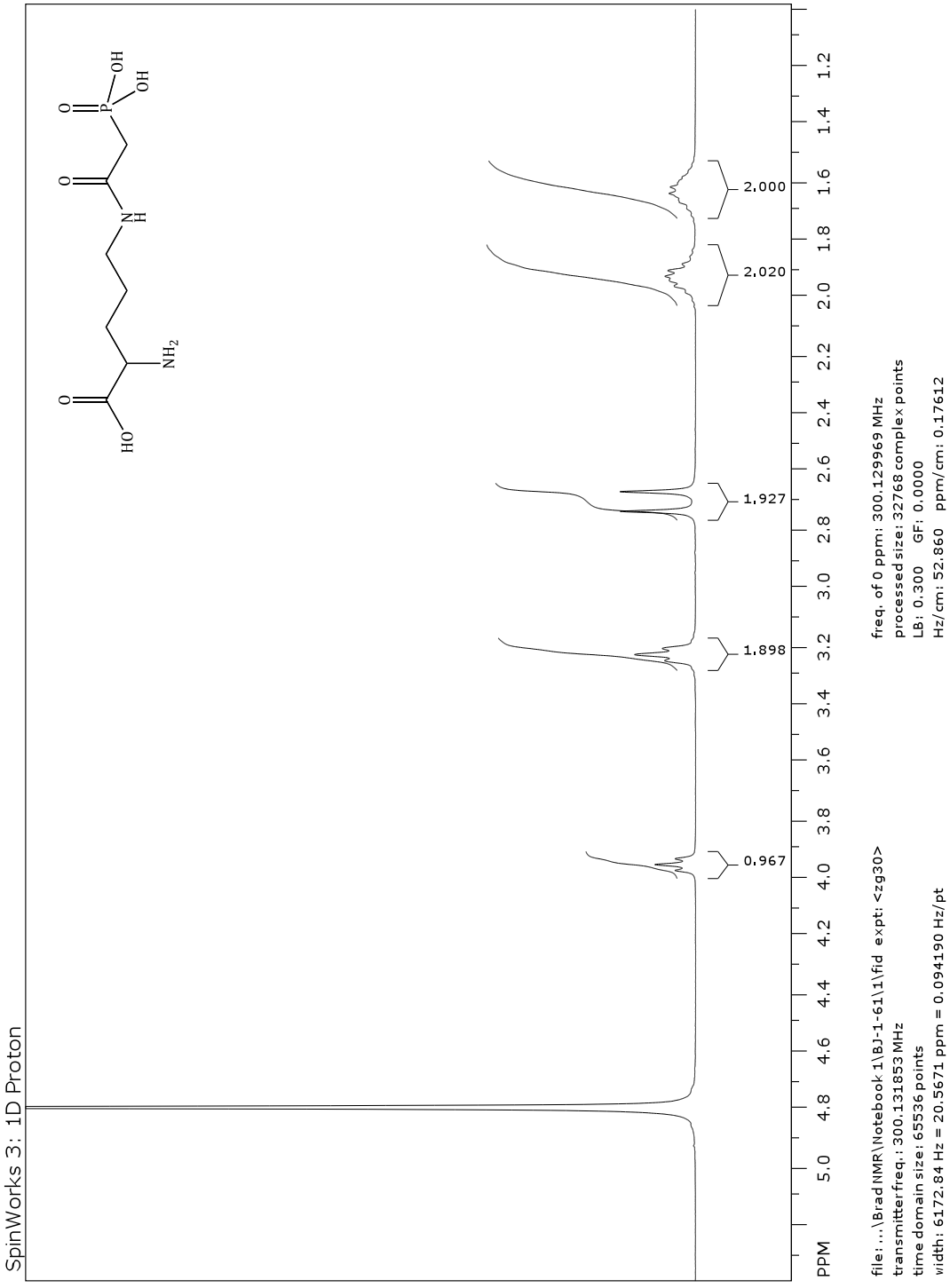
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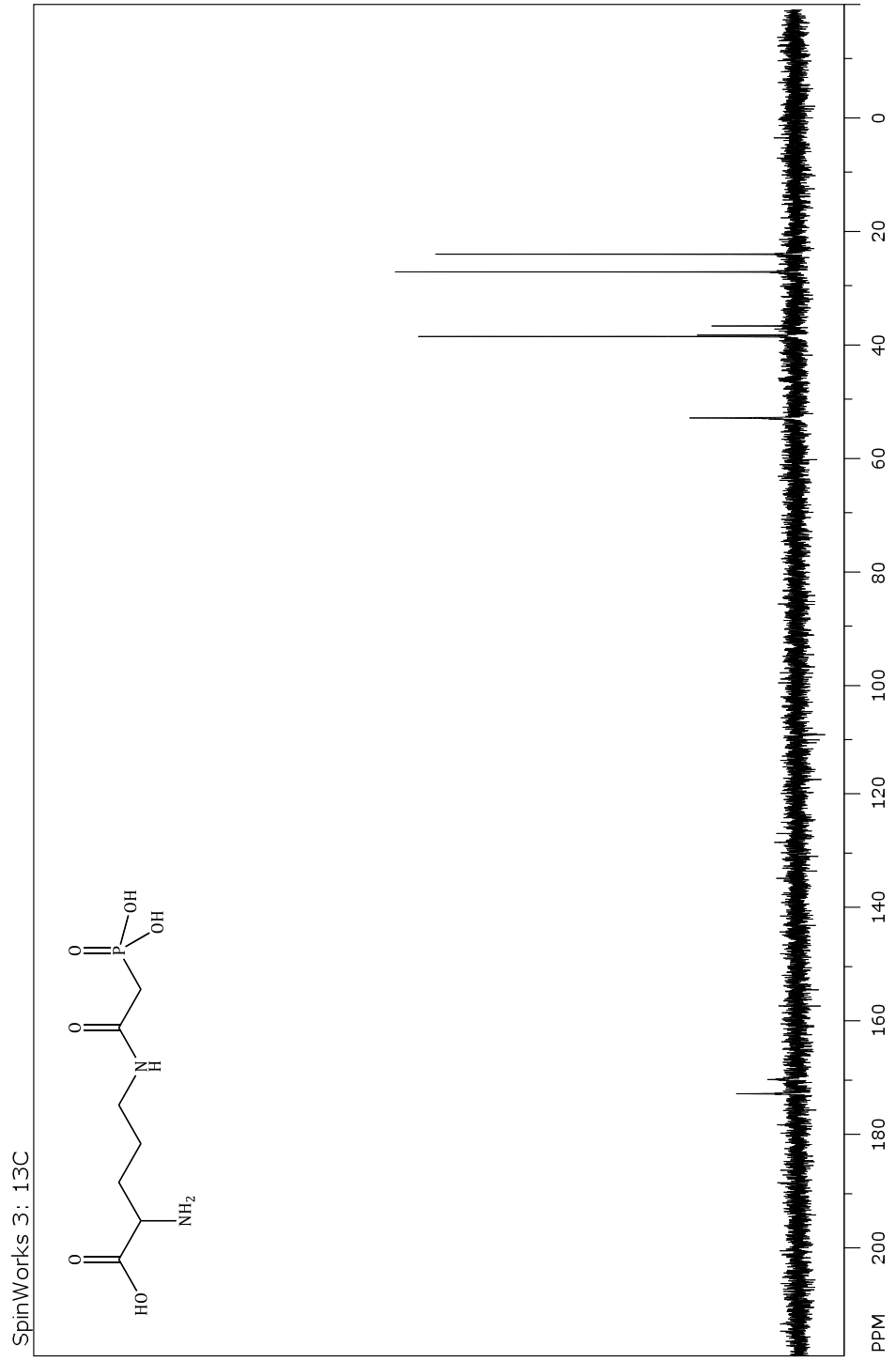
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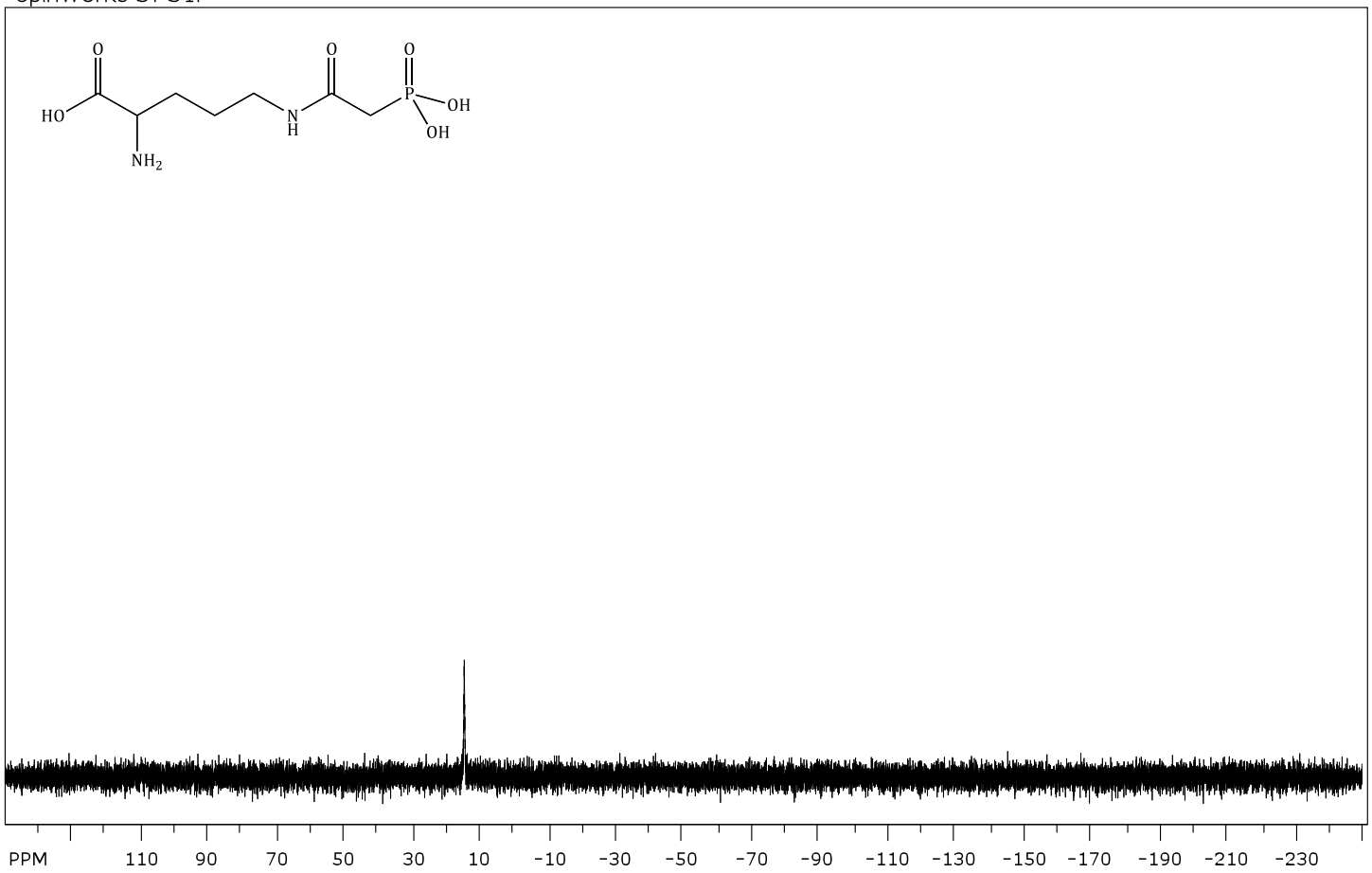
SpinWorks 3: 31P



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Hz/cm: 1946.472 ppm/cm: 16.02183

THE INFLUENCE OF PYRIDINE ON THE OZONOLYSIS OF ALKENES

Bradley M. Johnson, M.S.

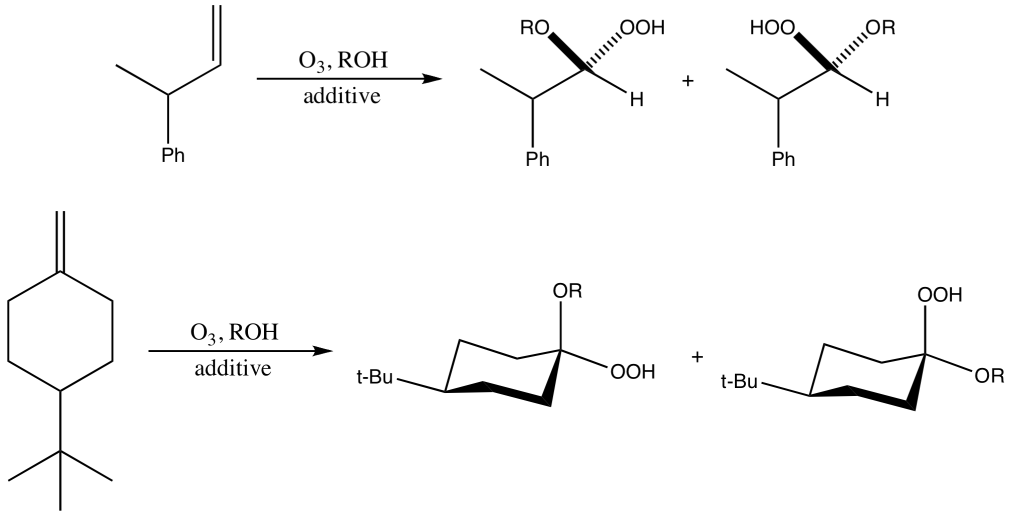
University of Nebraska, 2010

Adviser: Patrick H. Dussault

Introduction

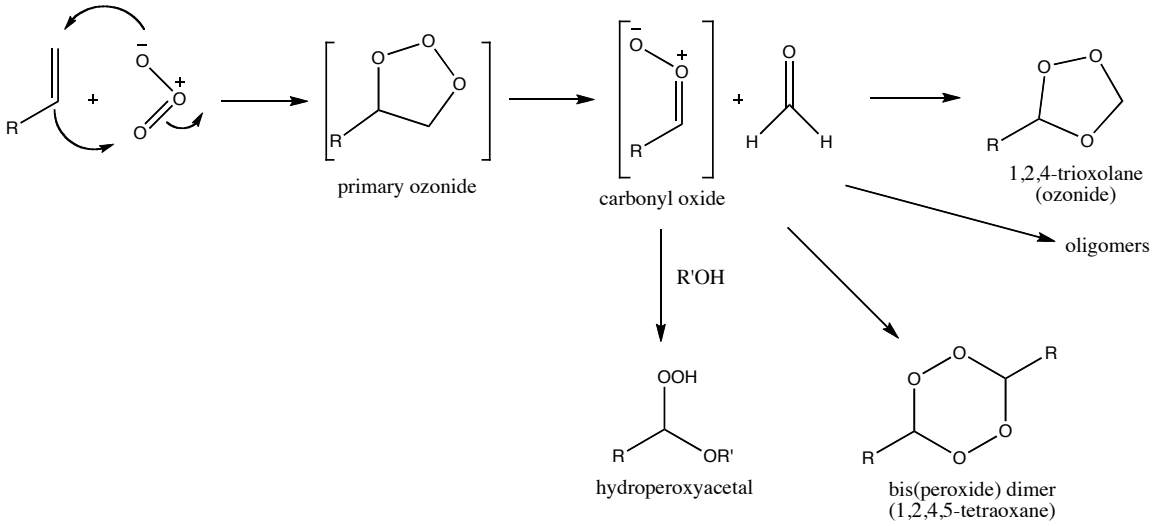
The transformation of alkenes into other functional groups is an important part of organic synthesis. One of the most important transformations of alkenes is oxidative cleavage to form carbonyl groups. Oxidative cleavage by high-valent metal oxides such as $KMnO_4$, RuO_4, or $OsO_4/NaIO_4$ results in the direct formation of aldehydes, ketones, or carboxylic acids. An alternative method for cleavage of alkenes is based upon reaction with ozone to generate isolable ozonide or hydroperoxyacetal intermediates. These peroxides are sometimes of synthetic interest themselves, but are more commonly subjected to reduction or fragmentation to generate carbonyl or carboxyl products. The focus of this thesis is the influence of pyridine and other additives on the formation of the peroxide intermediates in ozonolysis (Scheme 1).

Scheme 1



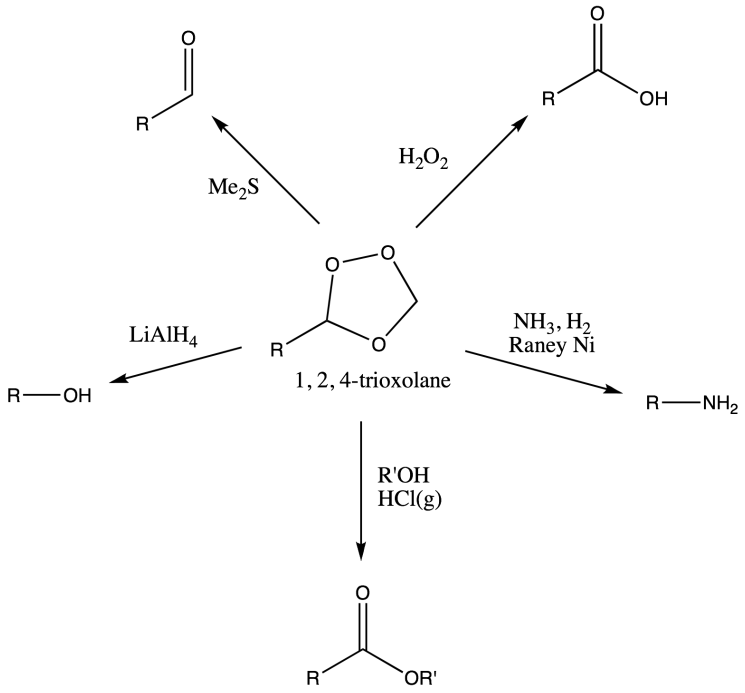
The ozonolysis of alkenes proceeds through several steps (Scheme 2). Reaction with ozone converts alkenes into a primary ozonide, which immediately rearranges into a 1,2,4-trioxolane.[1] The intermediate species that form following the formation of the primary ozonide is a molecule of carbonyl oxide and aldehyde or ketone, depending on whether the alkene is internal or terminal. Carbonyl oxides, highly reactive species that are not observed in solution chemistry, can undergo several different reactions. This reactive intermediate can be "trapped" by various nucleophiles such as an unhindered alcohol to yield a hydroperoxyacetal. Alternatively, the carbonyl oxide can undergo cycloaddition with the aldehyde or ketone byproduct to form a 1,2,4-trioxolane (ozonide) or react with another carbonyl oxide species forming a 1,2,4,5-tetraoxane. The formation of oligomers is also possible but typically a minor reaction pathway in the presence of a nucleophile or a reactive carbonyl dipolarophile.

Scheme 2



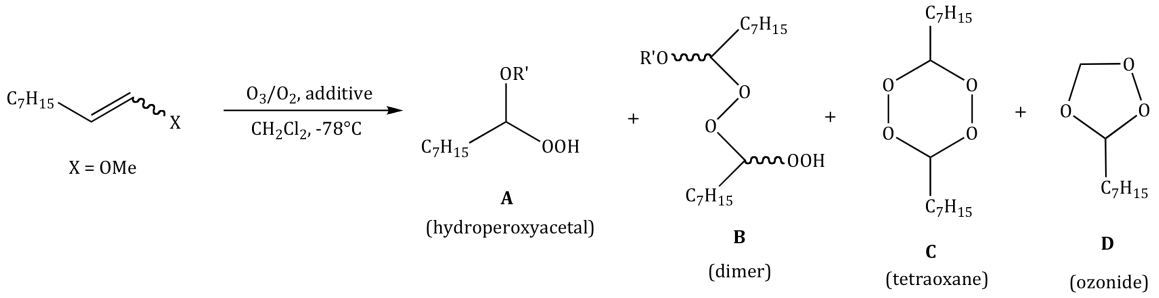
The 1,2,4-trioxolane and hydroperoxyacetal byproducts of ozonolysis can easily be transformed into several different functional groups depending on work-up conditions (Scheme 3). For example, workup procedures for ozonides (trioxolanes) involve reduction with a reagent such as PPh_3, Me_2S, or Zn/AcOH, whereas common workup procedures for hydroperoxyacetals include reaction with PPh_3 or Me_2S to generate an aldehyde or ketone.

Scheme 3



The ability to control the reactivity of carbonyl oxides is a little studied field with only a few examples of mechanistic approaches. Recent efforts in our group have investigated the possibility of altering the distribution of products from alkene ozonolysis by directing the reactivity of the intermediate carbonyl oxide towards a particular outcome. An example of this approach is illustrated in Scheme 4. This approach utilized alkoxide- or phenoxide-bearing Lewis acids to transfer a nucleophile to a carbonyl oxide, presumably via a metal-coordinated intermediate, forming a hydroperoxyacetal.[4]

Scheme 4



		yields (%)[a]			
additive	R'	A	B	C	D
none				4	
MeOH	Me	75	8		
$(MeO)_3B$	Me	25	39		
i-PrOH	*i*-Pr	68	11		
$(i\text{-PrO})_3B$	*i*-Pr	trace	trace		
$(i\text{-PrO})_3Al$	*i*-Pr	8	18		
$(i\text{-PrO})_3Ti$	*i*-Pr	20	27		
PhOH	Ph	12	20	8	
$(PhO)_3B$	Ph	11	39	7	

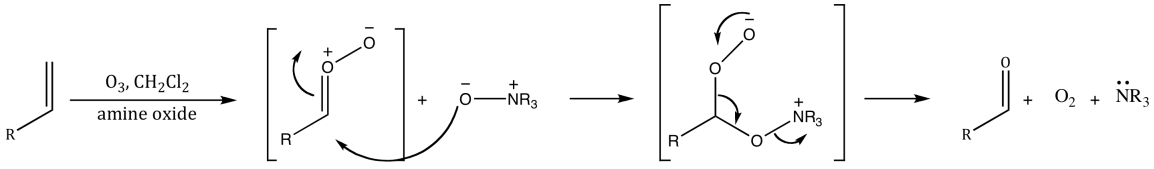
[a] Isolated yields.

When less bulky nucleophiles such as methanol or 2-propanol were ozonized with 1-methoxy-1-nonene, a large amount of hydroperoxyacetal was isolated, whereas the use of methyl- and isopropyl-bearing Lewis acids showed a higher amount of dimeric hydroperoxyacetal formation. However, when ozonizing 1-decene in the presence of nucleophiles of increasing bulk such as 2-propanol and phenol, the formation of hydroperoxyacetal was small with dimeric hydroperoxyacetal and 1,2,4-trioxolane being formed in much greater amounts. When titanium isopropoxide and triphenyl borate, respectively, were added to the reaction, the formation of hydroperoxyacetal was the primary species isolated. This

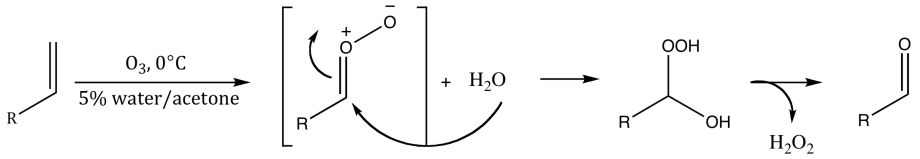
suggested that the Lewis acid complexation was followed by an intramolecular transfer of the ligand to the carbonyl oxide.

Other work in our lab has investigated methods for capturing the carbonyl oxide intermediates to directly form carbonyl products, avoiding the need to isolate and separately decompose the potentially hazardous peroxide intermediates. Examples of this approach are shown in Scheme 5 and 6.[2,3]

Scheme 5



Scheme 6

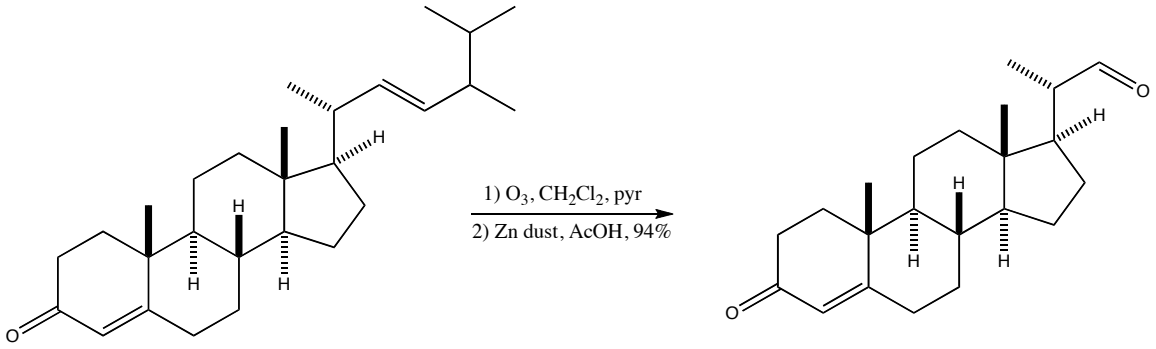


Pyridine:

Pyridine is unusual as a Lewis and Bronsted base in that it is not readily oxidized by ozone. An aromatic Lewis base, pyridine has been used on multiple occasions as an additive to influence the outcome of alkene ozonolysis. Several examples of the application of pyridine are illustrated below. The first example is highly representative of this class of reactions (Scheme 7). Pyridine was found to influence the ozonolysis reaction of 4,22-stigmastadien-3-one by selectively

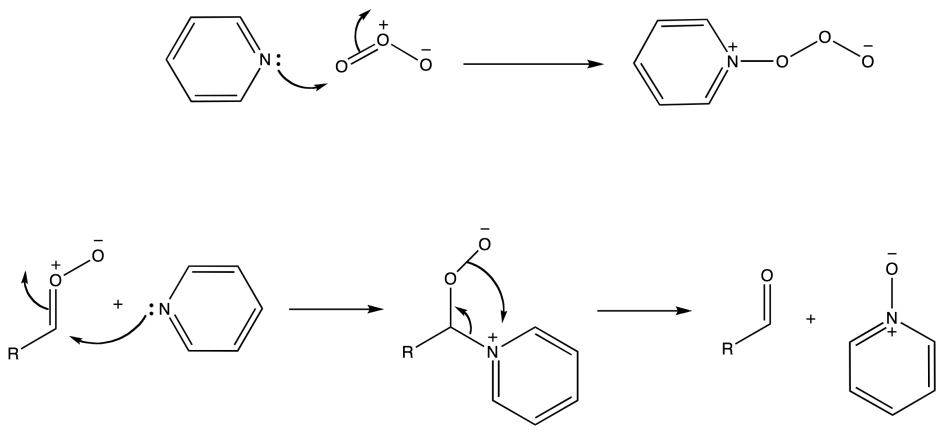
cleaving the least substituted alkene and forming the resulting aldehyde in high yield upon reduction.[7] In the absence of pyridine, infrared studies by Slomp showed that the trisubstituted enone was being attacked by ozone as well, leading to a mixture of cleavage products.

Scheme 7



The authors postulated that the pyridine was acting as a nucleophile and either reacting with ozone to form a pyridine-ozone adduct which went on to react with the carbonyl oxide or by attacking the electrophilic carbon of the carbonyl oxide directly and, following rearrangement, forming aldehyde and pyridine N-oxide (Scheme 8).

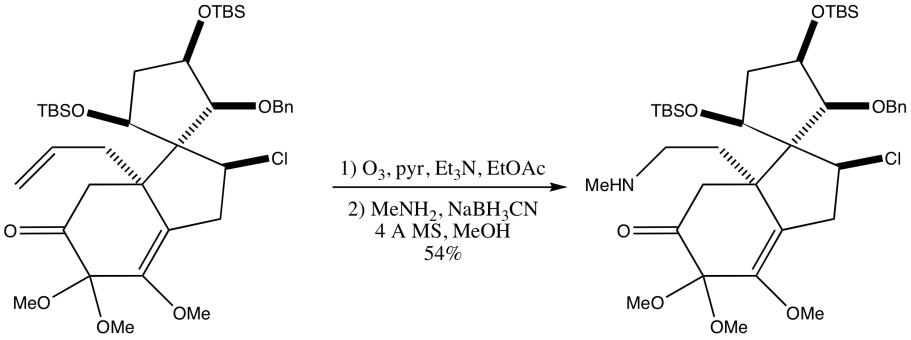
Scheme 8



However, the intermediate pyridine N-oxide has since been ruled out as an active contributor in the reaction.[8] Griesbaum ozonized tetramethylethylene in the presence of stoichiometric amounts of pyridine and monitored the reaction by NMR spectroscopy. He concluded that at no time during the reaction was pyridine N-oxide formed nor was a significant amount of the pyridine consumed. From the earlier mentioned postulate, the other mechanism is the formation of a pyridine-ozone adduct which apparently decreases the reactivity of ozone. Regardless of the exact mechanism, Slomp's discovery of selective ozonolysis has been utilized in several natural product syntheses where selective ozonolysis was necessary.[9]

For example, during the synthesis of (-)-acutumine (Scheme 9), Castle's group utilized pyridine to selectively cleave the least substituted alkene by having pyridine present during ozonolysis. When ozonolysis was conducted without the presence of pyridine, a lower yield of aldehyde was formed as well as a significant production of side products from the reaction with the electron-rich methyl enol ether.

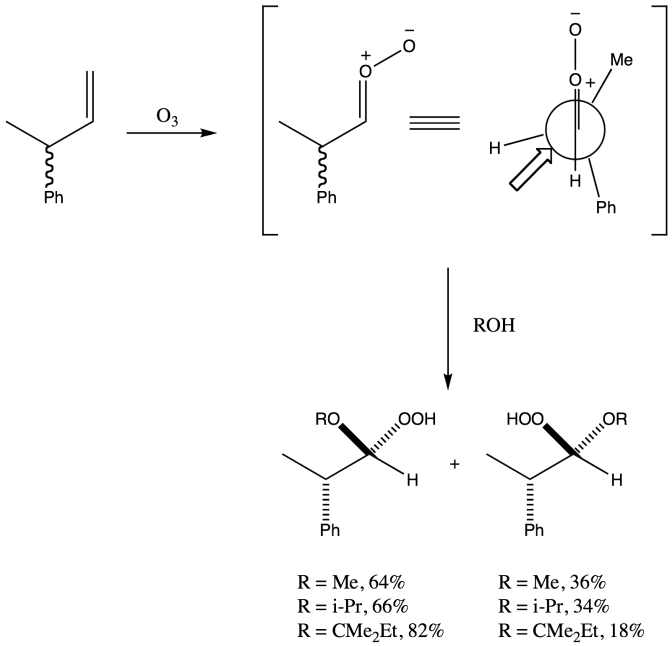
Scheme 9



Methods for assessing carbonyl oxide reactivity:

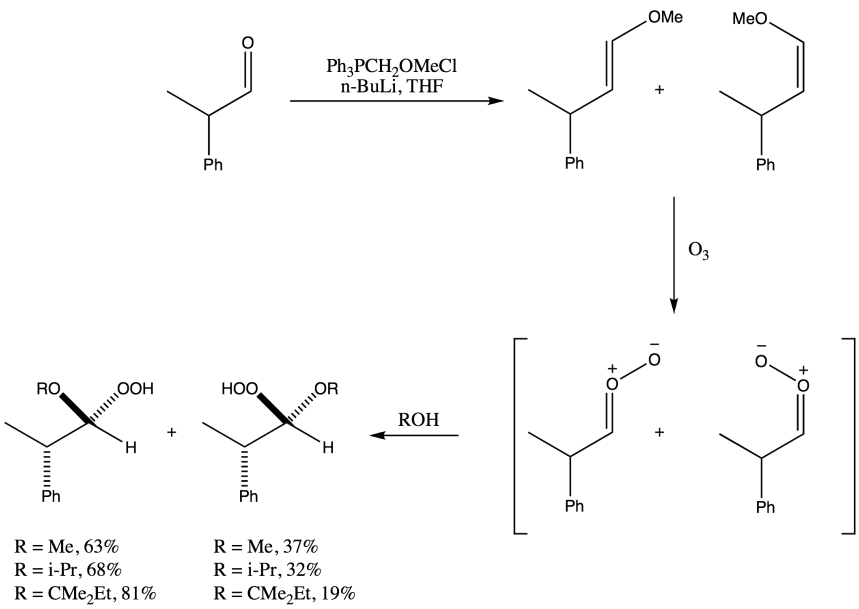
Another examination of carbonyl oxide chemistry looked at the diastereoselectivity of nucleophilic additions to chiral carbonyl oxides and whether they followed the same rules as aldehyde addition (Scheme 10).[5] This approach relied solely on the carbonyl oxides that were generated during ozonolysis of a chiral alkene such as 3-phenyl-1-butene. When various protic nucleophiles were present during ozonolysis, addition to the carbonyl oxide were found to proceed with Felkin-Ahn-type selectivity with the nucleophile approaching opposite the largest group (i.e.-phenyl) on the α-carbon. This analysis presumes that the conformational preferences of the carbonyl oxides are similar to those of aldehydes and ketones.

Scheme 10



Enol ethers are particularly useful since they can direct regioselection of carbonyl oxide formation where (E) and (Z) enol ethers preferentially form *syn* and *anti* carbonyl oxides, respectively.[6] However, when the reaction was conducted on 1-methoxy-3-phenyl-1-butene, the same Felkin-Ahn-type selectivity resulted, showing no relation to the geometry of the carbonyl oxide and the conformational preference of nucleophilic attack (Scheme 11).

Scheme 11



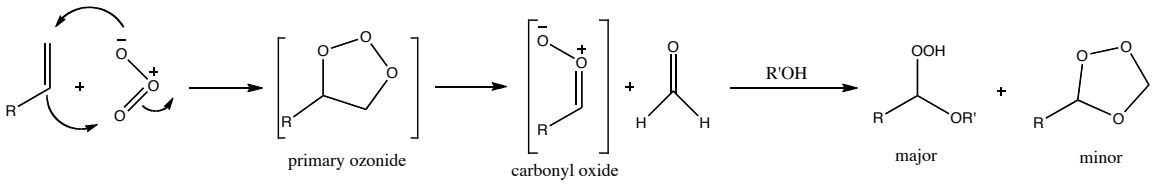
After reading that pyridine has an apparent role in selective oxidative cleavage with ozone, as well as our research into carbonyl oxide chemistry, we became interested in whether pyridine would have an influence on the distribution of products in a typical alkene ozonolysis. Our goal was to determine if any stereochemical influence could be observed by using pyridine as an additive. In addition, we wanted to see how alkene selectivity can be influenced by pyridine during ozonolysis. We focused primarily on two reagents, one that is chiral and one that is a cyclohexyl derivative with a bulky substituent. The former will be used to observe if Felkin-Ahn predictions hold true as in nucleophilic addition to aldehydes, whereas the latter will focus on whether pyridine has an effect on equatorial/axial attack of the nucleophile. Either approach may be able to determine what role pyridine has on the reaction, if any, and whether it is "complexing" with the carbonyl oxide leading to selective nucleophilic addition. Lastly, using dienes, we

will explore whether the addition of pyridine to the ozonolysis reaction will have any effect on alkene cleavage selectivity.

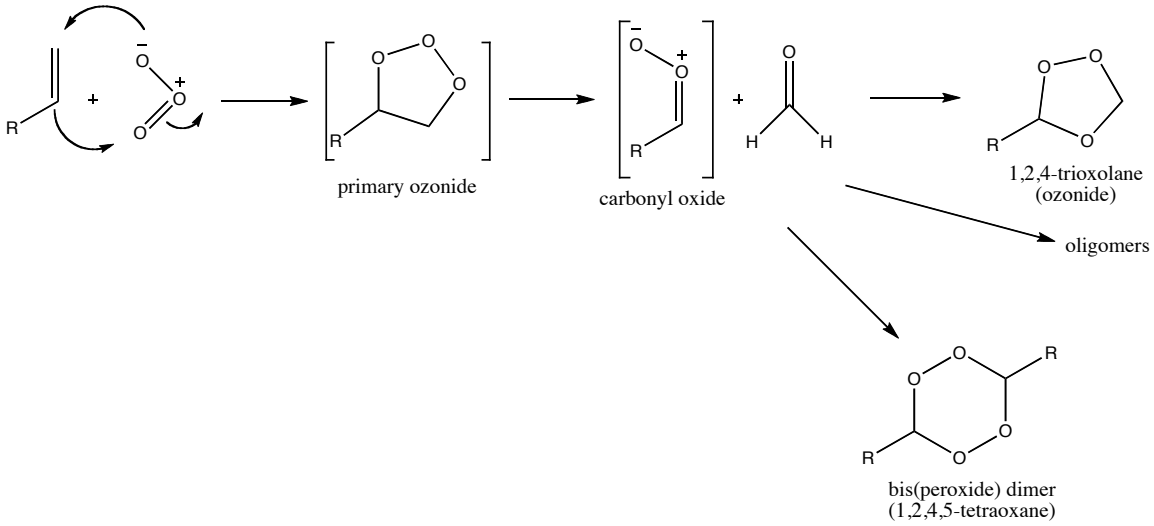
Results and Discussion

As described earlier, our group has been interested in the question of whether the outcome of an ozonolysis reaction can be controlled by the interaction of additives with the intermediate carbonyl oxide. In this section, we will describe our investigations into the influence of weak organic bases and hydrogen-bonding additives on the distribution of products from typical alkene ozonolyses.

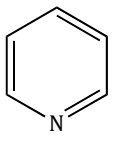
Ozonolysis in the presence of a nucleophile:



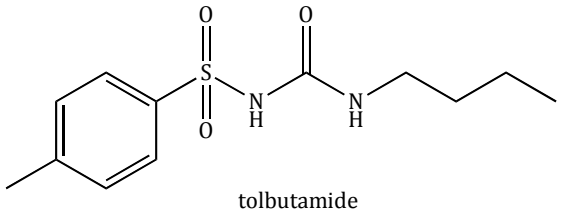
Ozonolysis in the absence of a nucleophile:



Several substrates were ozonized in the presence or absence of pyridine with and without an external nucleophile present, and the products analyzed both in terms of yield and relative distribution. A similar set of experiments was conducted using the commercially available hydrogen-bonding organocatalyst,[10] tolbutamide. Because the nature of the products varied significantly depending on substrate, the experiments were divided by substrate class.



pyridine



tolbutamide

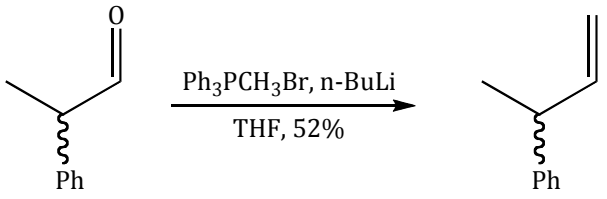
Ozonolysis in the presence of a nucleophile-

The largest set of experiments involved investigation into the influence of basic or hydrogen-bonding additives on the products derived from ozonolysis of alkenes in the presence of a nucleophilic trap. As stated earlier, the presence of a nucleophile in excess during ozonolysis primarily forms the respective hydroperoxyacetal.

3-phenyl-1-butene

This substrate, which is easily prepared by methylenation of commercially available 2-phenylpropionaldehyde, undergoes ozonolysis to form a carbonyl oxide adjacent to a chiral center. Earlier work from our lab had established that the addition of alcohol nucleophiles to this carbonyl oxide occurred with the same sense of stereochemistry as for Felkin-Ahn addition of organometallics to chiral aldehydes and ketones (Scheme 10).[5] Our hope was that the diastereoselectivity of addition would be sensitive to the presence of additives, providing an indicator of the ability to influence the reactivity of carbonyl oxides.

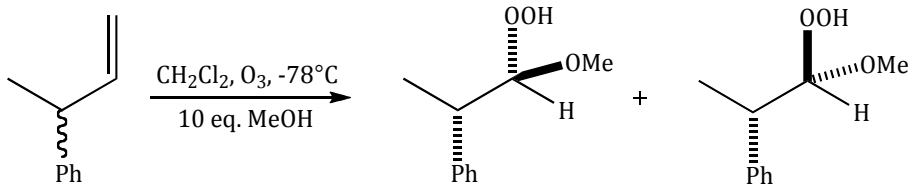
The substrate was formed by a Wittig reaction between methyltriphenylphosphonium bromide and 2-phenylpropionaldehyde using n-butyllithium as the base.



The reaction was monitored by TLC and quenched as soon as the starting material was consumed, as allowing the reaction to stir longer resulted in isomerization to the more substituted, conjugated alkene. Following purification by flash chromatography, the product was analyzed by ^{1}H and ^{13}C NMR as well as GC/MS, which demonstrated that the desired terminal alkene was formed with greater than 95% selectivity relative to the internal alkene regioisomers.

The methanolic ozonolysis of 3-phenyl-1-butene (10 mol equivalents of anhydrous methanol in anhydrous dichloromethane as solvent) was compared in the presence or absence of 1 mol equivalent of anhydrous pyridine (Scheme 12).

Scheme 12



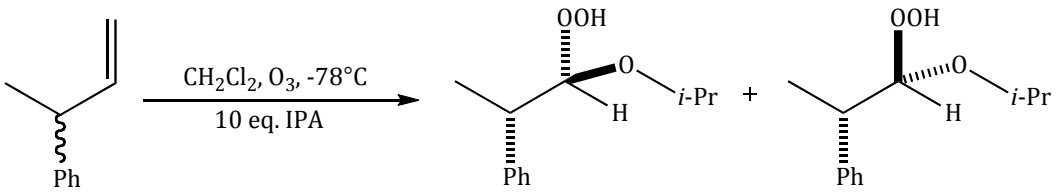
w/ pyridine: 42%, (70:30)
w/o pyridine: 57%, (70:30)

The purified products were analyzed by NMR and it was found that without pyridine present, the hydroperoxyacetal was formed in 57% yield with an isomeric ratio of 70:30. This ratio was determined by analyzing the ^{1}H NMR and integrating the methoxyl (singlet) signals at 3.4 and 3.6 ppm, respectively. This ratio is in agreement with that reported previously,[5] where the nucleophile adds opposite to the large group (phenyl) in the preferred Felkin-Ahn conformer. In the case where pyridine was present during ozonolysis, the results show a decrease in overall yield

of isolated product and a similar isomeric ratio. In addition, we consistently noticed that the ozonolyses conducted in the presence of pyridine became brown/yellow in color. This was not observed in typical ozonolyses, which remain colorless. Control reactions involving ozonolysis of pyridine in dichloromethane remain colorless, and the pyridine is not oxidized (NMR) by ozone at reaction times relevant to these studies. Also, a control experiment was conducted in order to determine if the resulting hydroperoxyacetal was reacting with pyridine.[18] Analysis by ^{1}H NMR of a stirred solution of hydroperoxyacetal with 1 mol equivalent pyridine or imidazole in deuterated chloroform showed no observable level of decomposition at reaction times relevant to these studies.

In order to investigate whether or not the size of the nucleophile would have an effect, anhydrous isopropanol (10 eq.) was used in a similar fashion as methanol (Scheme 13).

Scheme 13



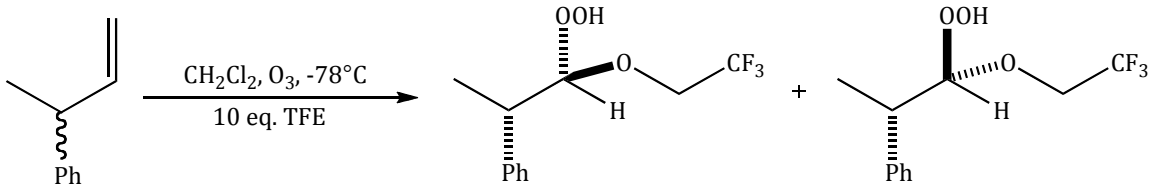
w/ pyridine: 44%, (80:20)
w/o pyridine: 59%, (80:20)

When pyridine was absent, the respective hydroperoxyacetal was formed in 59% yield with an isomeric ratio of 80:20. However, with pyridine present, the yield

decreased to 44%, although the ratio of isomers remained unchanged. This ratio was determined by integration of the isopropoxyl (heptet) signals at 3.8 and 4.0 ppm in the ^{1}H NMR spectrum, respectively. Similar to the methanol trials described above, the sense of stereoselection continued to follow the Felkin-Ahn model.[5]

We also investigated the influence of pyridine on the stereoselectivity of addition of trifluoroethanol, a sterically unhindered but electron-poor alcohol known to be a weak nucleophile towards carbonyl oxides.[12] Again, under identical reaction conditions as with isopropanol and methanol, 3-phenyl-2-butene was ozonized with 10 eq. of trifluoroethanol (Scheme 14).

Scheme 14



w/ pyridine: 14%, (60:40)
w/o pyridine: 16%, (60:40)

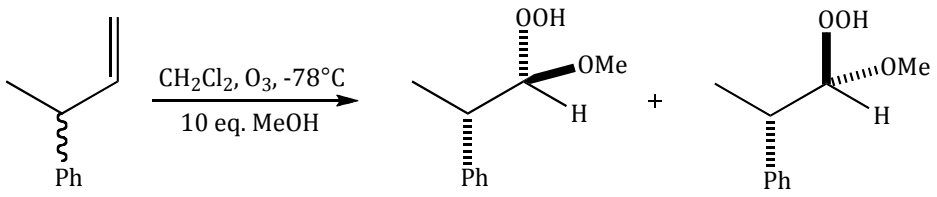
The yields of hydroperoxyacetal addition products were greatly reduced relative to reactions with methanol or isopropanol. The diastereoselectivity was less than the reactions with the other alcohols, although the same diastereoselectivity was observed in the presence or absence of pyridine. Isomeric ratio was determined by the relative integration of the doublets for the acetal CH in the two diastereomers at 5.00 and 5.03 ppm in the ^{1}H NMR spectrum. The ratio could also be determined by

the relative integration of the signal for the CF_3 group (triplet) at -74.7 and -74.4 ppm in the ^{19}F NMR spectrum. Both gave comparable integration values, so either can be used independently to determine isomeric ratio, with the ^{19}F spectrum giving more reliable results with a crude sample. Of note is the change of isomeric ratio; these results seem to follow a mix of factors relating primarily to nucleophilicity and steric bulk. It is known that trifluoroethanol is weakly nucleophilic and quite polar, whereas isopropanol and methanol differ in steric bulk, however are similar in polarity.[13, 15] It has also been shown that nucleophilic addition to carbonyl oxides with trifluoroethanol forms significantly different products than that of either methanol or isopropanol, mainly because of the significant difference in nucleophilicities.[15] This difference would likely explain the low overall yield of hydroperoxyacetal formation when trifluoroethanol is used as a carbonyl oxide trap. Therefore, we believe that the stereoselectivity of trifluoroethanol addition results from its poor nucleophilicity, whereas the stereoselectivity of addition of methanol and isopropanol is based on both differences in nucleophilicity and sterics.

Overall, the only influence of pyridine on the nucleophilic addition of alcohols to a chiral carbonyl oxide appeared to be a reduction in the yield of the isolated hydroperoxyacetal. We thought to try imidazole, a similar heterocyclic base that was more basic and more nucleophilic. Because the ozonolysis reaction with methanol was done many times before and its behavior and purification were well known we decided to conduct this reaction with and without imidazole present. In control reactions, imidazole was found to undergo limited decomposition upon ozonolysis in deuterated chloroform (NMR monitoring). We therefore investigated the

influence of imidazole at 1 and 2 equivalents stoichiometry in order to compensate for partial destruction during the experiments; this decomposition was not noted with pyridine under identical conditions so no change in molar equivalents was necessary. As noted earlier, control experiments with imidazole showed no observable decomposition of hydroperoxyacetals under reaction times relevant to this study.

Scheme 15

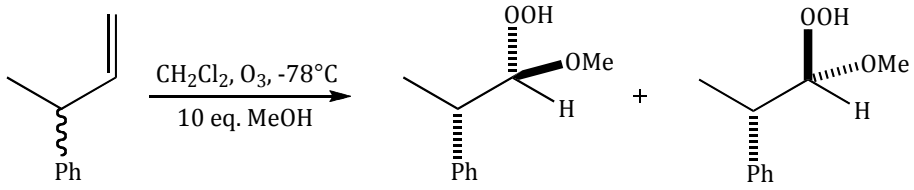


w/ imidazole: 43%, (70:30)
w/o imidazole: 53%, (70:30)

As noted in Scheme 15, when imidazole was absent, the hydroperoxyacetal was isolated in 53% yield. When imidazole was present the yield dropped to 43%. The isomeric ratio was identical to that observed in the presence of pyridine (70:30). This experiment showed that, in this case, no change was observed when compared to similar experiments using pyridine.

Two other experiments were conducted with 3-phenyl-1-butene. In one, we used 1 eq. tolbutamide to see whether this hydrogen-bonding additive would have any effect on the nucleophilic addition of methanol to a carbonyl oxide (Scheme 16).

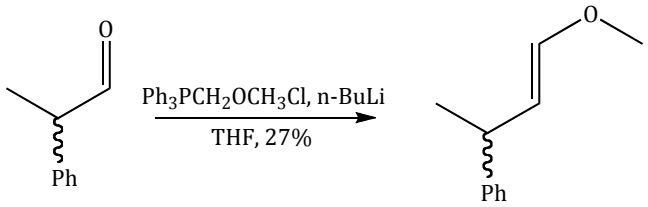
Scheme 16



w/ tolbutamide: 48%, (70:30)
w/o tolbutamide: 57%, (70:30)

The results showed that a 48% yield of hydroperoxyacetal was isolated by column chromatography with the same 70:30 isomeric ratio as observed in the absence of the additive (57% yield, 70:30).

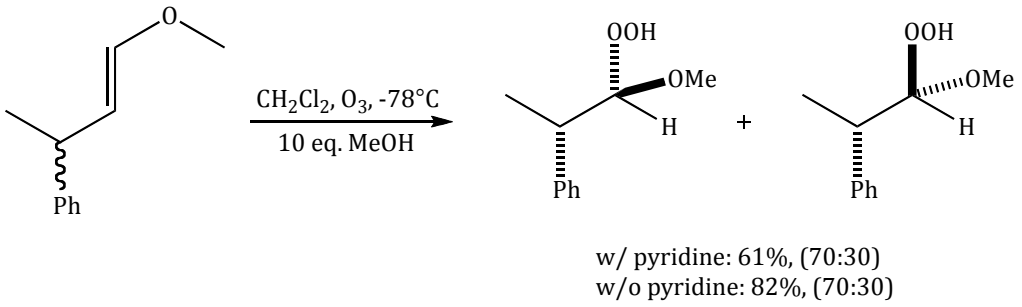
A second series of experiments employed the enol ether, 1-methoxy-3-phenyl-1-butene as the substrate. Ozonolysis of enol ethers is known to occur with high selectivity for generation of the carbonyl oxide on the non-oxygen bearing carbon of the alkene. Moreover, the ester byproducts derived from ozonolysis of enol ethers are poor dipolarophiles, and ozonides are rarely observed as products in these reactions.[13] The formation of 1-methoxy-3-phenyl-1-butene was basically the same as for 3-phenyl-1-butene, except that methoxymethyltriphenylphosphonium chloride was used as the Wittig salt.



The reaction was stirred at room temperature for 1 hour after the addition of the aldehyde then quenched with deionized water. The organic layer was dried with sodium sulfate, filtered through a cotton plug, concentrated and purified by flash chromatography using silica gel deactivated with 2% v/v triethylamine in hexanes to yield a 1:1 mixture of E/Z isomers as a colorless oil in fair yield.

As with the other experiments, 10 eq. anhydrous methanol was used with and without added anhydrous pyridine (Scheme 17).

Scheme 17



w/ pyridine: 61%, (70:30)
w/o pyridine: 82%, (70:30)

The trial without pyridine yielded 82% of the appropriate hydroperoxyacetal, whereas with pyridine added, the yield dropped to 61%. Between the two experiments the isomeric ratio was 70:30, the same as when the terminal alkene, 3-phenyl-1-butene was used under similar reaction conditions. The increase in yield for isolated hydroperoxyacetal is almost certainly due to the enhanced regioselectivity for carbonyl oxide formation in the enol ether system. As noted earlier (Scheme 2), ozonolysis of alkenes initially generate a primary ozonide (1,2,3-trioxolane) that can undergo cycloreversion to give two different carbonyl oxides. In

the case of a terminal alkene such as 3-phenyl-1-butene, cycloreversion of the primary ozonide[13] mainly forms the aldehyde O-oxide plus formaldehyde but also gives on the order of 20% of the formaldehyde O-oxide plus aldehyde. Thus, the maximum possible yield of the hydroperoxyacetal derived from the aldehyde O-oxide is on the order of 80%. In contrast, ozonolysis of enol ethers proceeds with very high selectivity of formation of the carbonyl oxide plus a formate ester; as a result, the yield of products derived from trapping of the aldehyde O-oxide is somewhat higher. In the end, the addition of pyridine and tolbutamide had no positive effect on the ozonolysis reaction with either 3-phenyl-1-butene or its respective enol ether, 1-methoxy-3-phenyl-1-butene.

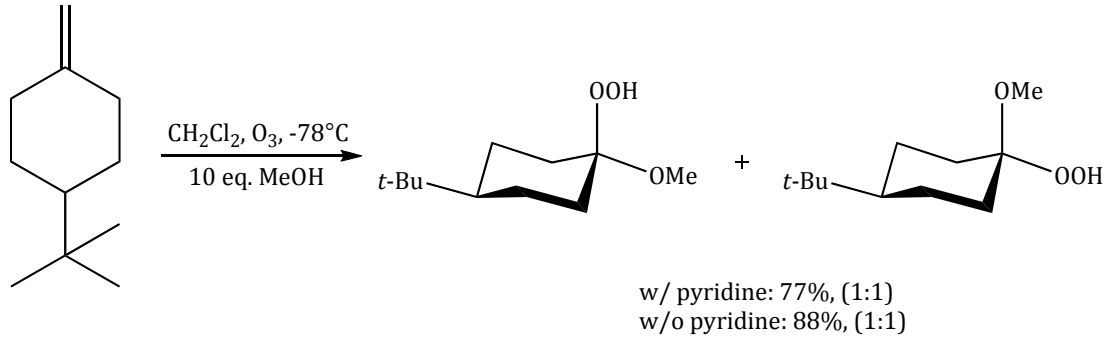
1-(t-butyl)-4-methylenecyclohexane

Following the trials using 3-phenyl-1-butene, a chiral alkene, and noticing that pyridine showed only a noticeable decrease in isolated yields with the majority of nucleophiles tested, we decided to try a different substrate. We next investigated reactions of a 1,1-disubstituted alkene. 1-(*t*-Butyl)-4-methylenecyclohexane was chosen as a substrate. Simple cyclohexanes overwhelmingly favor a conformation (ΔG° = 4.9 kcal/mol)[14] placing the *t*-butyl substituent in an equatorial position. As a result, addition of an alcohol or a carbonyl to the axial and equatorial faces of the carbonyl oxide would result in diastereomeric hydroperoxyacetal or ozonide products, providing a potential tool for investigating the influence of basic or hydrogen-bonding additives.

The synthesis of 1-(*t*-butyl)-4-methylenecyclohexane was done in a similar fashion as the formation of 3-phenyl-1-butene. Starting with *t*-butylcyclohexanone, we were able to form the methylene group by using methyltriphenylphosphonium bromide as the Wittig salt and n-butyllithium as the base. Following the dropwise addition of the ketone, the solution was allowed to warm to room temperature and stirred for 16 hours. Upon warming, the solution became transparent and dark red, which changed to a yellow-orange colored solution with noticeable precipitate as triphenylphosphine was being formed. Unlike the synthesis of 3-phenyl-1-butene, isomerization of 1-(*t*-butyl)-4-methylenecyclohexane was not a noticeable problem for the time allotted. Both ^{1}H NMR and GC/MS showed exclusive formation of the desired product in good yield.

We again turned to anhydrous methanol as our first nucleophile. Both experiments with and without 1 eq. anhydrous pyridine were conducted (Scheme 18).

Scheme 18



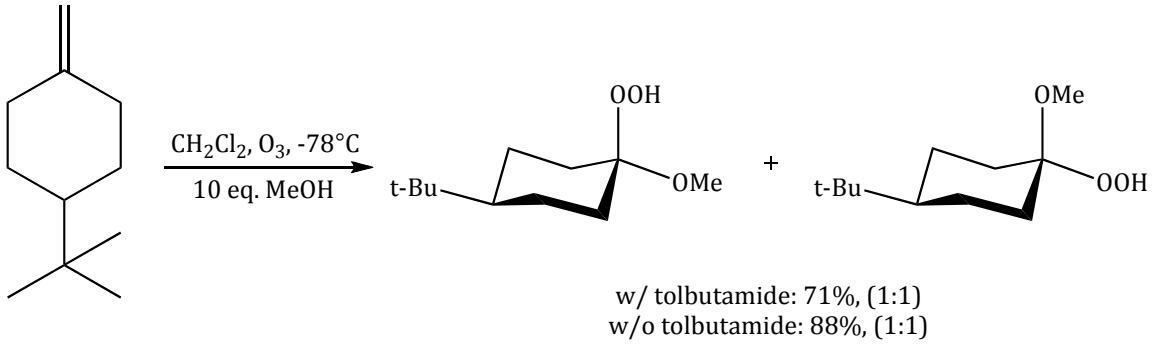
Ozonolysis with alkene and 10 eq. anhydrous methanol was found to yield 88% of the hydroperoxyacetal after flash chromatography, whereas with pyridine absent, the yield dropped to 77%. Upon ^{1}H NMR analysis, it was determined that there was a 1:1 ratio of equatorial/axial isomers under both conditions. This was accomplished by integrating the two isomeric methoxyl signals (singlet) at 3.31 and 3.27 ppm, respectively. These isolated yields are quite larger than when using 3-phenyl-1-butene under identical conditions because of the preference of ozonolysis reactions forming the more substituted carbonyl oxide. This allows for an increase in the carbonyl oxide of interest. The ability to assign an exact identity to this mix of diastereomers (axial vs. equatorial) is a challenge because of the remoteness of the methoxyl protons to the *t*-butyl protons, which are the only protons that could be realistically used to assign stereochemistry. To the best of our knowledge, no such assignment has been made experimentally with this or any similar system (4-*t*-butyl substituent).

To see if any difference could be noticed in the overall product formation with and without pyridine we decided to conduct an experiment identical to those above but using deuterated chloroform in place of dichloromethane so that a spectra of the crude reaction mixture could be directly acquired. When pyridine was present, there was a noticeably cleaner spectrum than without pyridine, meaning fewer signals of unidentified side products, especially in the methoxy region (3.2 – 3.4 ppm). Also of note is the observation of a decrease in both methanol consumption and trioxolane formation when pyridine was present. The former

point could explain the consistently lower yield of isolated hydroperoxyacetal when pyridine was present in the reaction.

As with 3-phenyl-1-butene, an experiment using 1 eq. of the hydrogen-bonding organocatalyst, tolbutamide, was conducted to see if there was, in fact, hydrogen-bonding occurring with the carbonyl oxide intermediate and whether or not this bulky additive would have any effect on the nucleophilic addition of methanol (Scheme 18).

Scheme 18



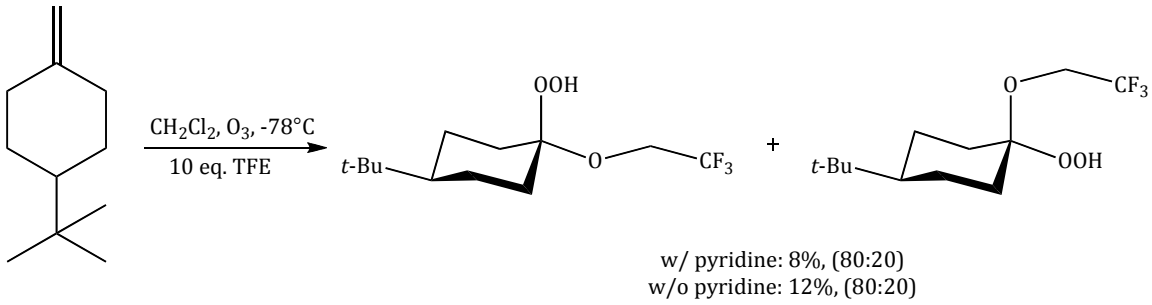
w/ tolbutamide: 71%, (1:1)
w/o tolbutamide: 88%, (1:1)

This experiment showed no change in isomeric ratio but did show a reduction in isolated yield (71%) when compared to that without any additive (88%). Apparently, the hydrogen-bonding catalyst is not having any directing effect, but what is surprising is that we see a noticeable decrease in isolated yield. This is counterintuitive because if the organocatalyst were hydrogen-bonding to the carbonyl oxide than there should be an increase in reactivity at the electrophilic site

of the carbonyl oxide, in turn leading to an increase in nucleophilic trapping (i.e.-yield).

We also compared the reaction of the cyclohexanone O-oxide with the weak nucleophile, trifluoroethanol in the presence and absence of pyridine (Scheme 19).

Scheme 19



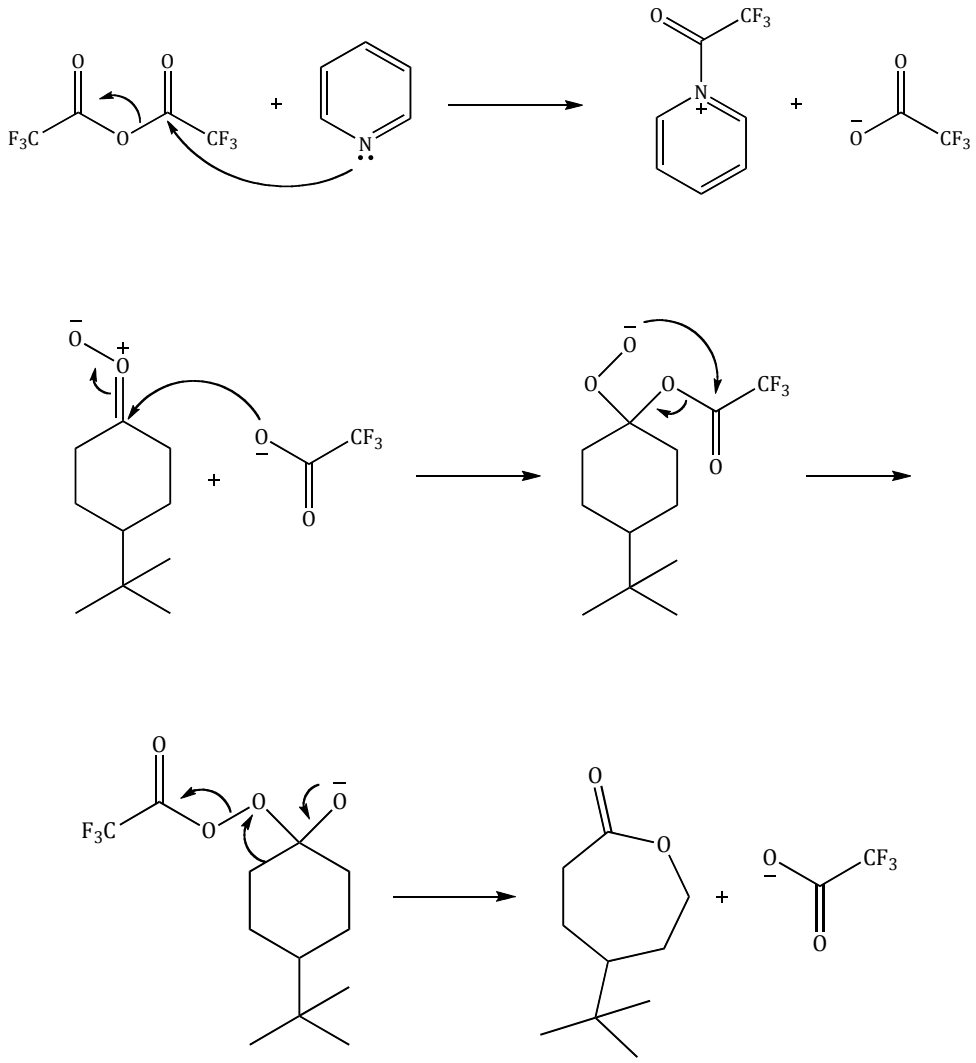
w/ pyridine: 8%, (80:20)
w/o pyridine: 12%, (80:20)

The yield of addition products was low even in the absence of pyridine, and slightly lower in the absence of pyridine. Although a similar trend has been described for other substrate/alcohol combinations, it is dangerous to read too much into the difference here given the poor overall yields. One thing of note is the change of isomeric ratio. As noted earlier, there are significant differences between trifluoroethanol and methanol, both in steric bulk and polarity (nucleophilicity). The isomeric ratio can possibly be attributed to the increase in steric bulk of trifluoroethanol when compared to that of methanol. As noted earlier, when trifluoroethanol is used as a carbonyl oxide trap, it forms a significant amount of side products that are not present with other alcohols.[15] This is hypothesized to

result from the weak nucleophilicity of trifluoroethanol and would explain the low yield of isolated hydroperoxyacetal.

Lastly, experiments where trifluoroacetic anhydride was added to reactions with and without pyridine was done to see if pyridine was complexing with the carbonyl oxide and making the terminal oxygen more nucleophilic. In this case, only reactions run in deuterated chloroform were performed so as to be able to immediately analyze them by ^{1}H NMR. It was observed in these crude spectra that no noticeable amount of peroxyester was formed. However, we observed ketone, trioxolane (ozonide), and, in the case where pyridine was present, a small amount of 7-membered lactone (observed by NMR but not isolated). The formation of this Baeyer-Villiger oxidation product (Scheme 20) was interesting, as a noticeable amount of activity (i.e.- heat and gas) was noted as soon as trifluoroacetic anhydride was added to the alkene/pyridine solution prior to reaction, indicating something different was happening from the reaction without pyridine. The presence of this product in the crude spectra was the only noticeable difference between the two experiments and isolation of any of the products was not conducted, as their concentrations were very low.

Proposed Baeyer-Villager mechanism (Scheme 20):

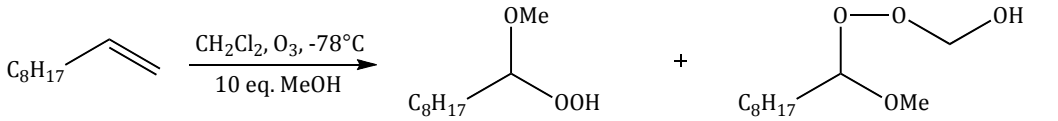


The above product was identified by the signals of the two protons α to the ester oxygen (ddd and dd) at 4.31 and 4.14 ppm, respectively, in the ^{1}H NMR spectrum.[16]

1-decene

The final set of results discussed reflects some of the first trials conducted in our lab. 1-Decene proved an unusual substrate compared with those discussed previously in that pyridine had a pronounced effect on the product distribution. When 1-decene was ozonized in the presence of 10 eq. of anhydrous methanol, a mixture of peroxyacetal products was isolated in 75% yield. The spectrum of this mixture showed the presence of both 1-methoxy-1-hydroperoxyacetal and a derived hemiacetal, (1-methoxynonylperoxy)methanol, resulting from acetalization with formaldehyde (Scheme 21).[13] The two products ran close to one another on TLC and we were not able to effectively separate them using either flash chromatography or HPLC.

Scheme 21



1-methoxy-1-hydroperoxyacetal (1-methoxynonylperoxy)methanol

w/ pyridine: 51%, (34:66)
w/o pyridine: 75%, (90:10)

1-Methoxy-1-hydroperoxyacetal was the predominant species observed under the conditions where pyridine was absent, however, when pyridine was present the ratio changed from 90% hydroperoxyacetal to 34%. A possible explanation for this is that pyridine is activating the nucleophilic peroxide group.

This would more easily allow the nucleophilic peroxide tail to add to the formaldehyde, resulting in the increase of hemiacetal formation.[13] To rule out the possibility that the formation of (1-methoxynonylperoxy)methanol resulted from the presence of impurities in the reagents, the reaction was repeated in the presence of several different sources of methanol, decene, and pyridine. However, similar results were obtained in all cases.

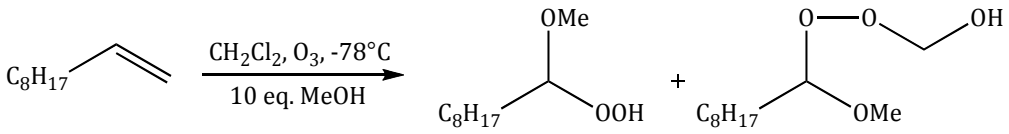
The quantification of the two species was accomplished by integration of either the methoxyl signals (singlet) at 3.52 (hydroperoxyacetal) and 3.50 (hemiacetal) ppm or the chiral hydrogen signals (triplet) at 4.83 (hydroperoxyacetal) and 4.74 (hemiacetal) ppm in the ^{1}H NMR spectrum. The presence of the hemiacetal was determined by the signal of the acetal CH_2 (singlet) at 5.30 ppm.

One experiment we used to try and determine if formaldehyde was, in fact, being activated by pyridine was by mixing isolated hydroperoxyacetal and formalin (37% w/w solution of formaldehyde) with and without pyridine in tetrahydrofuran. Under these conditions, we observed (TLC) the consumption of the hydroperoxyacetal and the formation of the hemiacetal only when pyridine was present. This phenomenon was only observed with this substrate; other substrates could have also formed such species but their concentrations were too low to isolate.

As with 3-phenyl-1-butene, imidazole was used to determine if a stronger nucleophile and base would have any noticeable change in product distribution. When 1-decene was ozonized in the presence of both 1 eq. and 2 eq. imidazole with

10 eq. anhydrous methanol the product distribution was determined to be the same as without imidazole present (90:10) in 62% yield (Scheme 22). It is curious that the more basic imidazole did not promote the hemiacetal formation observed for pyridine.

Scheme 22

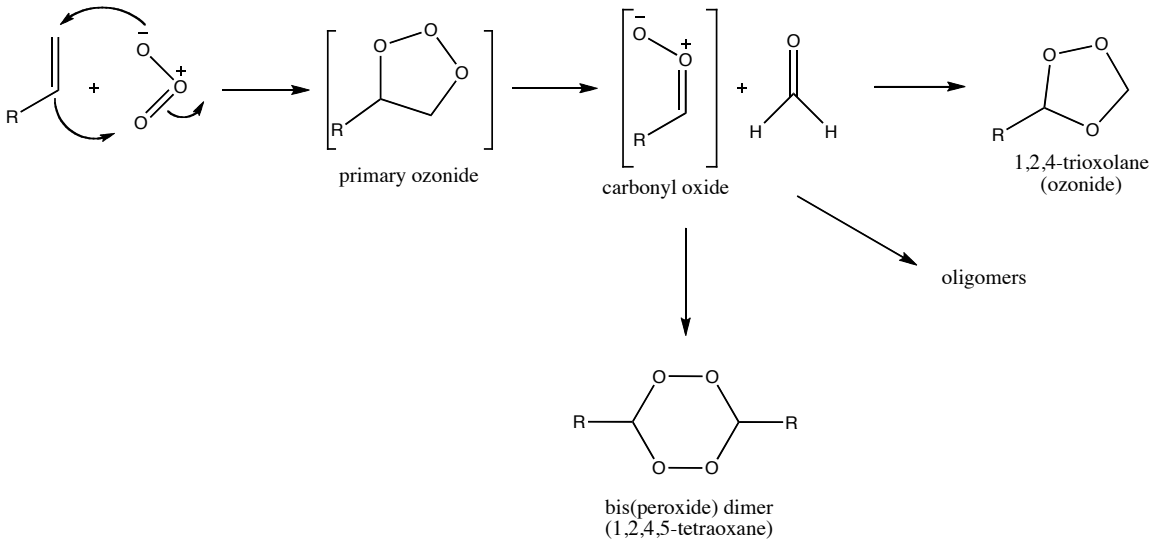


w/ imidazole: 62%, (90:10)
w/o imidazole: 75%, (90:10)

Effect on Ozonide Formation: Ozonolysis in the absence of a nucleophile

The carbonyl oxide formed from ozonolysis of an alkene in the absence of a nucleophile will either undergo cycloaddition with the cogenerated carbonyl or else undergo some form of dimerization or oligomerization(Scheme 23).[13, 17]

Scheme 23



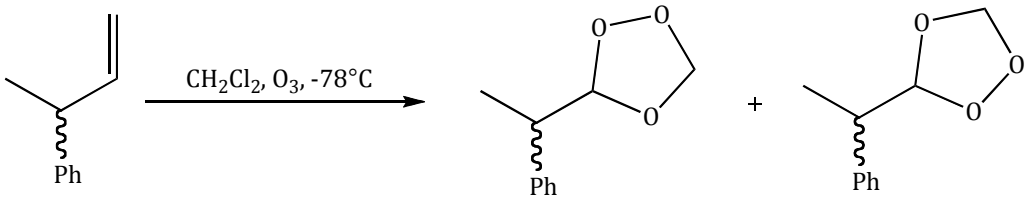
It is possible that pyridine may have an effect on ozonide formation because where the carbonyl oxide was primarily serving the role of electrophile when a large amount of nucleophile was present, in this case, there is a stoichiometric amount of cogenerated carbonyl present, theroetically making any influence from a pyridine/carbonyl oxide complex more apparent.

3-phenyl-1-butene

Using 3-phenyl-1-butene as a substrate, we were able to screen for any change in ozonide yield or sterochemistry. The experiment was simply the ozonolysis of 3-phenyl-1-butene in anhydrous dichloromethane with and without 1 eq. pyridine present. When pyridine was absent from the reaction, 1,2,4-trioxolane (ozonide) was isolated in 61% yield with an isomeric ratio of 60:40. This ratio was

determined by integration of the chiral hydrogen signals (doublet) of the isomers at 5.30 and 5.28 ppm, respectively, in the ^{1}H NMR spectrum.

Scheme 24



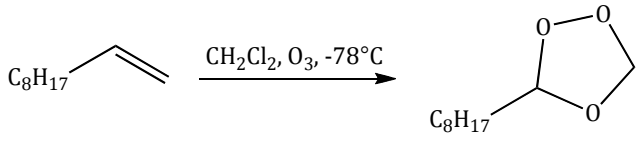
When 3-phenyl-1-butene was ozonized with pyridine there was a significant decrease in ozonide formation (14%), accompanied by the formation of a significant amount of aldehyde (30% as opposed to trace without pyridine). However the isomeric ratio of the ozonide stayed the same (60:40) as without pyridine. It was determined that an increase of polar side products was formed in the reaction. These products were tentatively determined to be oligomeric products of unknown identity. One possible explanation is that, in the absence of an external nucleophile, pyridine is complexing with the formed formaldehyde but the expected products from such complexation are not observed. However, if pyridine was significantly activating the formaldehyde formed during the reaction, it could be hypothesized that oligomeric products are using the resulting formaldehyde as the primary monomer. An overall reduction from 100 mol% to 50 mol% of added pyridine resulted in similar product distribution and ratios, however, when it was dropped to 10 mol%, a significant amount of ozonide was formed, demonstrating that the role

of pyridine is either not catalytic or that the catalysis involves a relatively slow step that does not permit rapid turnover at low loading. We also tried imidazole under identical conditions as with pyridine and found that aldehyde and ozonide were produced in similar amounts. We were initially concerned that the observation of increased products (aldehydes and ketones) in the presence of pyridine or imidazole might result from base-promoted fragmentation of ozonides.[18] However, subjecting isolated ozonide to stoichiometric amounts of either pyridine or imidazole in dichloromethane solution for a period of time (20 min) greater than our typical reaction times revealed (TLC) no decomposition.

1-decene

As before, we used 1-decene because of its predictable behavior under ozonolysis and because it was readily available, making it a prime test substrate. Reactions where 1 eq. anhydrous pyridine was and was not added were conducted to see if pyridine had any role in product distribution (Scheme 25).

Scheme 25



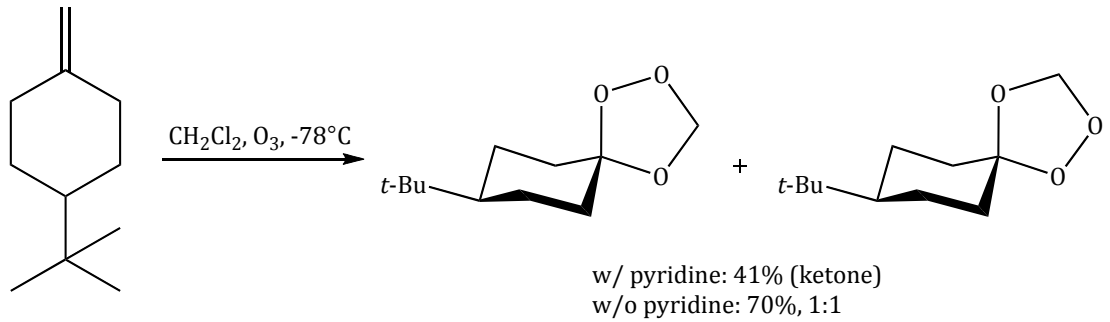
The reaction without pyridine produced a 73% yield of ozonide, where as when pyridine was added the amount of ozonide formed dropped to 16%. The latter

experiment was also interesting because decanal was formed in 25% yield, whereas only a trace amount was detected when pyridine was absent from the reaction.

1-(t-butyl)-4-methylenecyclohexane

The aprotic ozonolysis of this 1,1-disubstituted alkene was investigated in the presence or absence of pyridine. The bulky *t*-butyl substituent, while having little or no direct interaction with the carbonyl oxide center, serves to hold the cyclohexane ring in one chair conformation. As a result, selective dipolar addition to the axial and equatorial faces of the carbonyl oxide will result in the formation of two different ozonides. However, upon testing, the reaction with no pyridine added, formed a 70% yield of ozonide with a 1:1 isomeric ratio where the peroxy portion was either equatorial or axial (Scheme 26).

Scheme 26

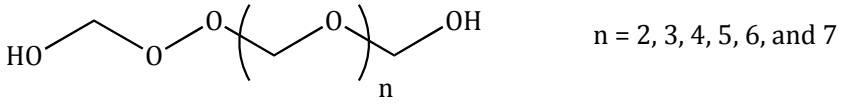


w/ pyridine: 41% (ketone)
w/o pyridine: 70%, 1:1

When the same reaction was conducted with 1 eq. anhydrous pyridine added, a significant amount of ketone was formed (41%) with virtually no ozonide

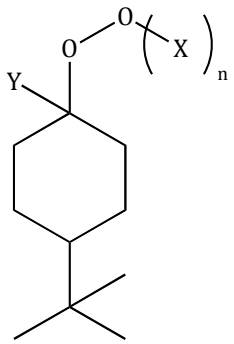
formation. Upon further analysis, it was found that, just as with 3-phenyl-1-butene, a significant amount of polar material was produced. This polar compound/s was isolated by column chromatography with 30% methanol/ethyl acetate and concentrated to a yellow, amorphous solid. ^{1}H NMR analysis showed very broad, indistinguishable peaks with some impurities present. Using low-resolution mass spectrometry (electrospray ionization), the impure sample showed oligomers made up of formaldehyde monomers with mass values (mass + Na) of 154, 184, 214, 244, 273, and 303 amu (Scheme 27).

Scheme 27



One other observation is that the protons of the *t*-butyl group were very apparent on the ^{1}H NMR spectrum, making it evident that this oligomer included the *t*-butyl cyclohexyl moiety (Scheme 28). At this time, we are uncertain the identity of X and Y, as a determination of the molecular weight of the oligomer using GPC (gel permeation chromatography) or vapor pressure osmometry was not possible due to technical difficulties.

Scheme 28



Since it was observed that the *t*-butylcyclohexyl moiety was assumedly being incorporated into an oligomeric product, we decided to determine how much. First, we tried to isolate the fraction that yielded the yellow, amorphous solid and reduce it in order to determine how much ketone could be isolated from this fraction and then add that mass to the previously isolated ketone formed during the ozonolysis reaction. The isolated yellow fraction was reacted with 5 eq. powdered zinc (based on starting material stoichiometry) in 5 mL glacial acetic acid. This solution was stirred until TLC showed consumption of starting material. Reduction of 255 mg of the oligomeric residue furnished 66 mg of isolated ketone. This amounted to ~21% of the theoretical formation of ketone (~43% theoretical yield), assuming all of the *t*-butylcyclohexyl moiety was either converted directly to ketone upon ozonolysis or trapped in this oligomeric product. The total isolated amount of ketone was ~64% of theoretical yield or 196 mg on a 2 mmol scale.

In order to rule out potential loss of material during a series of sequential purifications and reductions, we also investigated the direct reduction (Zn, as above) of the crude products derived from ozonolysis in the presence of pyridine.

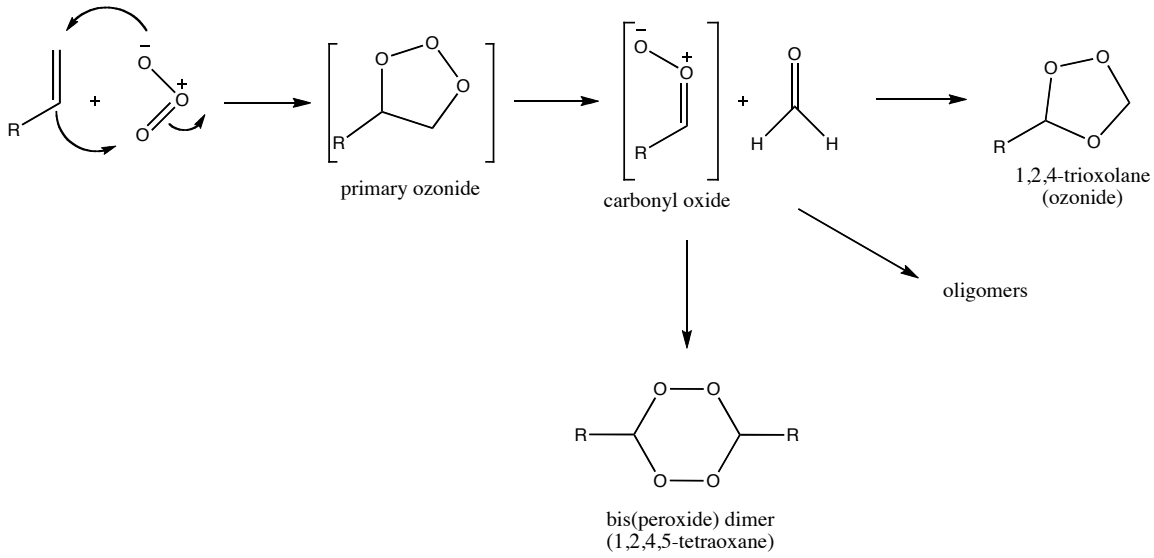
Following reduction, the residue was purified by flash column chromatography (10% ethyl acetate/hexanes) to yield 78% (241 mg) of the theoretical amount of ketone on a 2 mmol scale. We are uncertain as to the fate of the remaining percentage of the original ketone product.

Influence of pyridine on the selectivity of diene ozonolysis:

Beginning as far back as the 1950's, a series of papers reported anecdotal examples of the favorable influence of pyridine on the selectivity of ozonolytic cleavage within diene substrates.[7-9] To the best of our knowledge, no one has directly analyzed this selectivity in diene compounds with various combinations of alkene reactivities. As described below, this effect was quantitatively investigated for reactions of four different dienes, with each experiment run at least in duplicate.

Whereas the research described in previous sections of this thesis explored the potential influence of pyridine and other additives on the reactivity of ozonolysis-derived carbonyl oxides, the last major step in alkene ozonolysis, the ability of pyridine to enhance the chemoselectivity for ozonolysis of dienes suggests a significant influence on the initial dipolar cycloaddition with ozone, the first step in alkene ozonolysis (Scheme 29). This implication has been noted by several authors.[7-9] Our work verified the influence of pyridine on chemoselectivity and quantified this selectivity within several different classes of dienes. However, as will be discussed later, our results also clearly demonstrate that pyridine is simultaneously exerting a significant influence on the nature of products derived from these ozonolysis reactions.

Scheme 29

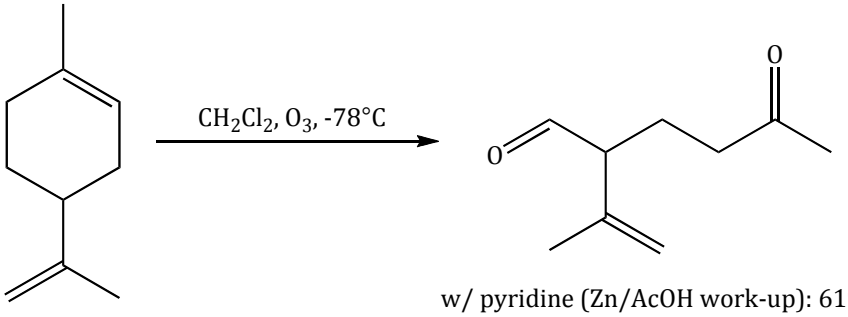


(R)-(+)-limonene

Our first substrate, limonene, includes both trisubstituted and 1,1-disubstituted alkenes. Limonene is commercially available and was anticipated to form carbonyl products of limited volatility, facilitating quantitative analysis. The first reaction involved using 1 eq. anhydrous pyridine, limonene, and anhydrous dichloromethane. Our previous experiments with simple alkenes had identified appropriate flow (O_2) and voltage settings on our ozonizer that would allow effective delivery of 1 mmol ozone/minute. We used this calibration to react the diene, limonene, with one molar equivalent of ozone. Following ozonolysis, the reaction was washed with 1M hydrochloric acid to remove pyridine, then deionized water, and, finally, brine. The organic layer was then dried with anhydrous sodium sulfate, filtered through a cotton plug, and concentrated to yield a colorless oil. (The acid wash was only done with the reactions where pyridine was present in order to remove the pyridine from the mixture. However, upon realizing that reduction was

not necessary for these reactions, the wash was omitted and the reaction was concentrated and then purified as is.) The oil was then reduced with zinc powder in glacial acetic acid (AcOH/Zn) to yield, in this case, the keto-aldehyde product in 61% yield (Scheme 30).

Scheme 30



w/ pyridine (Zn/AcOH work-up): 61%
w/ pyridine (no reductive work-up): 64%
w/o pyridine (Zn/AcOH work-up): 43%

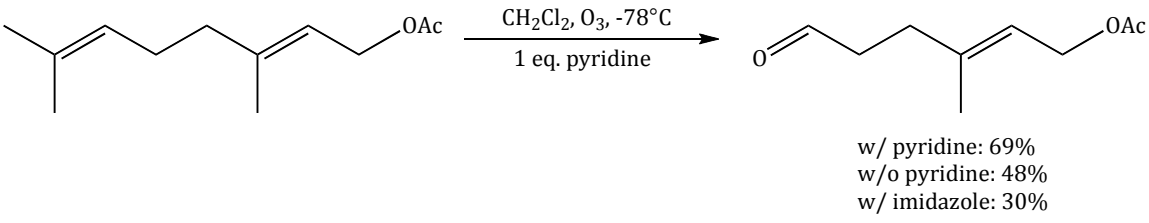
The reaction without pyridine furnished a number of products. Following a necessary reduction of the crude reaction mixture with Zn/AcOH, we isolated the keto-aldehyde shown above. The two results show a rather significant change in not only side product formation, but also overall yield of product. One significant observation was that the reaction with pyridine present required no reduction (64% yield). TLC analysis before and after reduction showed no observable change in product distribution and, upon further investigation, purification of the reaction with and without reduction yielded nearly identical yields. The keto-aldehyde product showed that ozone was selectively cleaving the trisubstituted alkene, which

is more electron-rich but also more hindered than the 1,1-disubstituted alkene.[20] We did not attempt to quantify products derived from cleavage of the 1,1-disubstituted alkene, or from cleavage of both alkenes.

Geranyl acetate

This substrate offered the chance to compare ozonolysis of trisubstituted alkenes which are electronically differentiated by the presence of an allylic oxygen. In addition, many of the expected cleavage products derived from geranyl acetate were expected to be of lower volatility, making them easily isolable. As was observed with limonene, reaction with and without pyridine showed a significant change in product yield, with the most reactive alkene being cleaved almost exclusively. Reactions were conducted as for limonene, with a reductive work-up (Zn/AcOH) performed only for the reactions in the absence of pyridine. Reactions involving pyridine again appeared to directly form the aldehyde product and were directly subjected to chromatography and analysis.

Scheme 31

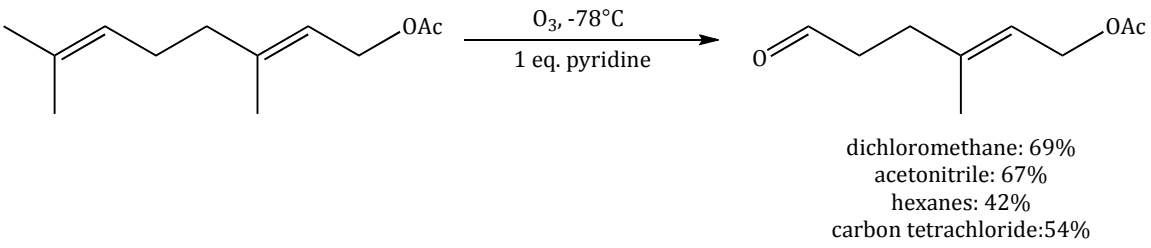


w/ pyridine: 69%
w/o pyridine: 48%
w/ imidazole: 30%

Ozonolysis in the presence of pyridine selectively furnished the aldehyde product derived from cleavage of the 6,7-alkene (Scheme 31); this aldehyde was isolated in 69% yield without any reductive work-up. In contrast, ozonolysis in the absence of pyridine followed by reductive work-up furnished the same aldehyde in 48% yield. We wondered if the increased basicity and nucleophilicity of imidazole would have any effect on the reaction. Repeating the ozonolysis in the presence of imidazole resulted in the apparent formation (TLC) of numerous products, and the isolation of the same aldehyde in poor yield. The very different outcomes observed for the reactions in the presence of pyridine (pK$_a$ of the protonated base is 5.25)[11] vs. the more basic imidazole (pK$_a$ of the protonated base is 6.95)[19] led us to investigate the less basic 2-chloropyridine (pK$_a$ of the protonated base is 0.49).[11] Reaction with 1 eq. 2-chloropyridine showed the same product distribution as when no additive was present. No yield was determined with this substrate.

To observe if there may be a change in product yield or distribution in varying solvents, we decided to test the reaction with 1 eq. anhydrous pyridine in anhydrous hexanes, anhydrous acetonitrile, and carbon tetrachloride (Scheme 32).

Scheme 32

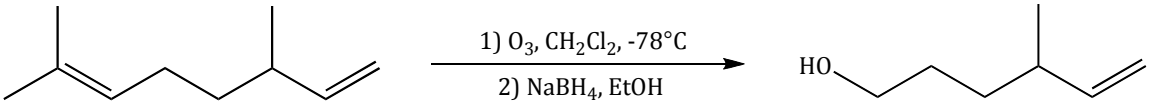


As noted above, the yields were greatest with more polar solvents and significantly less with non-polar solvents. One significant observation is the formation of a black residue upon ozonolysis of geranyl acetate with pyridine in both hexanes and carbon tetrachloride. This did not happen when pyridine was omitted from the reaction or when ozonolysis proceeded under polar conditions. It is possible that the decrease in yield is related to the formation of this residue. Whether it is consuming the starting material or not allowing pyridine to interact as readily with the substrate is unknown. However, it is obvious that the best yields occurred in either dichloromethane or acetonitrile, but the latter has a tendency to bring water into the reaction if it is not purified prior to use and this can cause side reactions.[2]

(-)-β-citronellene

Citronellene was an attractive substrate in that it is commercially available and that it allows determination of selectivity for cleavage of trisubstituted vs. monosubstituted alkenes. However, our investigations were initially complicated by the challenge in quantifying the relatively volatile aldehyde, 4-methyl-5-hexenal produced as the major product. The solution to this problem was to reduce the products of ozonolysis with sodium borohydride, a reducing agent capable not only of reducing ozonides, but also reducing any aldehydes or ketones to the corresponding alcohols (Scheme 33).[21]

Scheme 33



w/ pyridine: 67%
w/o pyridine: 42%

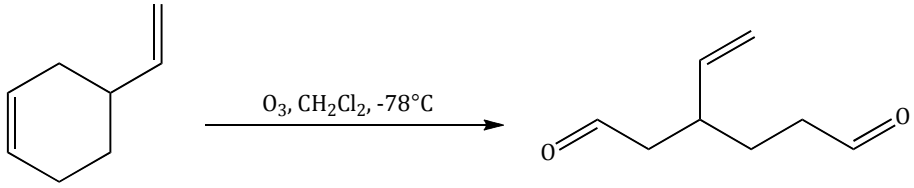
Both reactions were concentrated following ozonolysis and then reduction was done by diluting the residue with anhydrous ethanol, adding 4 eq. sodium borohydride, and adding a minimal amount of tetrahydrofuran to aid in dissolution of the reducing agent. This was stirred at room temperature until TLC analysis showed (~45 min.) complete consumption of aldehyde/ozonide. This was then quenched with deionized water and the organic layer was washed with brine, dried with anhydrous sodium sulfate, filtered through a plug of cotton, and concentrated. Flash chromatography yielded 67% with pyridine and 42% without pyridine. As with the previous examples, selective cleavage occurred on the most substituted alkene and the presence of pyridine increased the overall yield.

4-vinyl-1-cyclohexene

The final substrate tested was 4-vinyl-1-cyclohexene, which would allow comparison of selectivity for ozonolysis of disubstituted and monosubstituted alkenes. The anticipated major product, a di-aldehyde derived from cleavage of the ring alkene, was not anticipated to be particularly very volatile. However, ozonolysis in the absence of pyridine, followed by reductive work-up with Zn/AcOH as before,

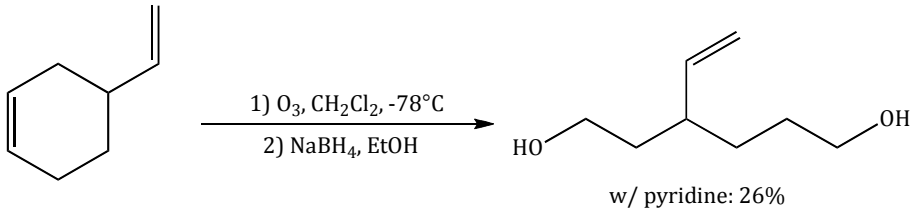
furnished a very low yield of product. The corresponding reaction with pyridine, which did not require a reductive work-up, provided an improved yield, but still nowhere near the types of yields observed with the other three substrates. These reduced yields are unlikely to reflect product volatility, as the use of a sodium borohydride work-up furnished the corresponding diols in very similar yield (Scheme 34, 35).

Scheme 34



w/ pyridine: 24%
w/o pyridine: 12%

Scheme 35



w/ pyridine: 26%
w/o pyridine: 12%

It is unknown as to why there was such a decreased amount of product isolated as TLC analysis of both reactions showed no other significant products formed prior to purification.

Conclusion

Ozonolysis has been used for over a century to transform alkenes into several different functional groups. In 1958, it was noticed that the addition of pyridine to the ozonolysis reaction had an effect on product distribution. The idea was that it formed a complex with ozone, allowing it to be a more selective reactant.[7,22]

Our hypothesis was that pyridine might be having a role on first and last steps of ozonolysis, primary ozonide formation and ozonolysis-derived carbonyl oxides, respectively. We decided to screen reactions that formed ozonides and hydroperoxyacetals using various nucleophiles. Unfortunately, pyridine showed no positive effect during the formation of hydroperoxyacetals. However, there was a noticeable effect when pyridine was present in reactions forming ozonides. It was noticed that ozonide formation was greatly reduced and aldehyde/ketone formation was increased. We are uncertain as to the reason behind this phenomenon, but it can be noted that when pyridine was present, a significant amount of polar species were formed that seem to be oligomers. Using the limited tools that we had available, it was determined that the oligomers were made up of a significant amount of starting material and formaldehyde.

Realizing that pyridine may not be interacting with the carbonyl oxide intermediate, at least not with a nucleophile present; we decided to analyze what effect the addition of pyridine would have on the selectivity of alkene ozonolysis. Using 4 different diene substrates, we determined that pyridine does have a significant affect on which alkene gets cleaved. Although this has been previously

noted anecdotally by several authors, our work has verified and quantified this effect in several diene systems: trisubstituted vs. 1,1-disubstituted alkenes; a trisubstituted allyl alcohol derivative vs. a trisubstituted alkene; trisubstituted and monosubstituted alkenes; and disubstituted vs. monosubstituted alkenes. However, our work uncovered an effect that has not been previously discussed; the ability of pyridine to somehow promote the direct formation of aldehydes and ketones in the ozonolysis reaction, avoiding the need for post-ozonolysis reduction. Based upon our survey of four different dienes, this reaction appears to be general. Pyridine is probably not the reducing agent because previous attempts to reduce ozonides in the presence of pyridine showed little to no change.

Our work has quantified the influence of pyridine on the chemoselectivity of diene ozonolysis, providing a basis for the more systematic application of this methodology as a tool for enhancing the application of alkene ozonolysis. In the course of this research, we discovered a new reaction, the *in-situ* generation of carbonyl products upon ozonolysis of alkenes in the presence of pyridine. This reaction, which allows the direct formation of carbonyl products without the need for any form of reduction or work-up, holds obvious synthetic potential. It is our hope that continued research can be pursued to determine the as yet unexplained mechanism of this reaction.

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Experimental

All reagents and solvents were used as supplied commercially, except THF, which was distilled from Na/Ph_2CO, and dichloromethane, which was distilled from CaH_2. ^1H, and ^{13}C spectra were recorded on Bruker 300, 400, 500, and 600 MHz NMR spectrometers; individual peaks are reported as (multiplicity, number of hydrogens, coupling constant in Hz). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer as neat films or solids on a zinc selenide plate. Selected absorbances are reported in wavenumber (cm^{-1}). Melting points were determined using a Mel-Temp brand melting point apparatus and glass capillary tube. Ozonolysis was performed using an Osmonics ozonizer with an oxygen flow of 2.4 L/min and an amperage setting of 0.75 amperes to deliver approximately 1 mmol/min ozone. Thin layer chromatography (TLC) analyses were done on Analtech Uniplate Silica Gel GHLF (250 μm) plates. Progress of reactions were monitored by TLC, using a vanillin indicator (3 g vanillin, 3 mL concentrated sulfuric acid, and 97 mL anhydrous ethanol), potassium permanganate indicator (0.316 g potassium permanganate, 100 mL water), peroxide indicator (2.4 g N,N-dimethyl-p-phenylenediamine dihydrochloride, 2 mL glacial acetic acid, 40 mL deionized water, and 200 mL methanol), and UV visualization using a hand-held shortwave UV light source (254 nm). Mass spectra were obtained at the Center for Mass Spectrometry, University of Nebraska-Lincoln.

1-(*t*-Butyl)-4-methylenecyclohexane

To a dried 250 mL RB flask equipped with a stir bar was added methyltriphenylphosphonium bromide (11.40 g, 32 mmol, 1.6 eq.) in anhydrous THF (45 mL). The resulting solution was allowed to stir at -78°C for approximately 5 minutes after which n-butyllithium (2.5 M, 12 mL, 30 mmol, 1.5 eq.) was added. The yellow solution was allowed to stir for 1 hour at -78°C and then *t*-butylcyclohexanone (3.08 g, 20 mmol, 1 eq.) was added as a solution with THF (10 mL) dropwise. The resulting solution was allowed to stir for an additional 30 minutes at -78°C and then allowed to warm to room temperature where the soluton was allowed to stir until TLC showed complete consumption of the ketone. At this time the reaction was quenched with water (25 mL) and the aqueous layer extracted with diethyl ether. The combined organic fractions where dried with anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The resulting oil was purified by flash chromatography ($R_f \sim 0.93$, pentane) to yield a colorless liquid (2.38 g, 78%, 99.5% GC/MS). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (t, 2H, J = 1.6 Hz), 2.34 (m, 2H), 2.00-1.85 (m, 4H), 1.15-1.00 (m, 3H), 0.86 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.28, 100.20, 48.09, 35.52, 32.65, 29.17, and 27.86 ppm; IR (film) v 3071, 2940-2838, 1651, 1446, 1365, 1240, 1220, and 885 cm^{-1}; HRCI-MS *m/z* calculated for $C_{11}H_{21}$ $(M+H)^+$: 153.1643; found 153.1645, (1.1 ppm).

8-*t*-Butyl-1,2,4-trioxaspiro[4.5]decane

In a dried, 25 mL RB was added methylene *t*-butylcyclohexane (0.304 g, 2 mmol) and anhydrous dichloromethane (10mL). The solution was cooled to -78°C and ozonized by a similar procedure as for 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The solution was then allowed to warm to room temperature and then concentrated. The residue was purifed by flash chromatography (2.5% ethyl acetate/hexanes, $R_f \sim 0.40$) to yield a colorless oil (0.280 g, 70%), which consisted of a 1:1 mixture of steroisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (s, 2H), 5.12 (s, 2H), 2.00-1.75 (m, 7H), 1.70-1.55 (m, 4H), 1.40-1.20 (m, 5H), 1.10-1.00 (m, 2H), 0.89 (s, 9H), and 0.87 (s, 9H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) δ 109.2, 109.1, 94.0, 93.9, 47.1, 46.9, 34.2, 33.9, 32.5, 27.8, and 24.9 ppm; IR (film) *v* 2952, 2871, 1366, 1193, 1123, 1095, 1058, 976, 950, 901, and 734 cm^{-1}; HRCI-MS *m/z* calculated for $C_{11}H_{21}O_3$ $(M+H)^+$: 201.1491; found: 201.1489 (0.8 ppm).

4-*t*-Butyl-1-hydroperoxy-1-(2,2,2-trifluoroethoxy)cyclohexane

To a dried, large vial was added methylene *t*-butylcyclohexane (0.152 g, 1 mmol, 1 eq.), 2,2,2-trifluorethanol (1.00 g, 730 μL, 10 mmol, 10 eq.), and anhydrous dichloromethane (5 mL). The solution was cooled to -78°C and ozonized by a similar procedure as for 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by column chromatography (2% ethyl acetate/hexanes, $R_f = 0.35$) to yield a colorless oil (0.032 g, 12%), which consisted of a 60:40 mixture of stereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 3.91 (app sextet, 2H, J = 8.7 Hz), 2.26 – 2.16 (m, 2H), 2.15 – 2.06 (m, 2H), 1.78 – 1.66 (m, 2H), 1.54 – 1.37 (m, 2H), 1.31 – 1.14 (m,

2H), 1.11 – 0.99 (m, 1H), and 0.87 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.6, 59.6, 59.2, 47.5, 47.4, 32.5, 31.8, 31.4, 27.8, 27.7, 23.8, and 23.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.9 (t, 3F, J = 8.7 Hz) and -74.1 (t, 3F, J = 8.7 Hz) ppm; IR (film) v 3415, 2953, 2870, 1284, 1156, 1104, 977, and 908 cm^{-1}; ESI-MS m/z calculated for $C_{12}H_{21}F_3O_3$ ($M+Na^+$): 293.1340; found 293.1348, (2 ppm).

4-*t*-Butyl-1-hydroperoxy-1-methoxycyclohexane

To a dried 50 mL RB flask was added anhydrous methanol (1.44 g, 45 mmol, 15 eq.), methylene *t*-butylcyclohexane (0.152 g, 3 mmol, 1 eq.) and anhydrous dichloromethane (15 mL). This was cooled to -78°C and then ozone was bubbled through until a blue color persisted. The solution was flushed with O_2 to dissipate the blue color and then concentrated behind a shield. The residue was purified by flash chromatography (14% ethyl acetate/hexanes, peroxide dip) to yield a white solid oil (0.534 g, 88%). NMR chromatography showed a ~1:1 mixture of diastereomers: mp = 55-58° C; R_f = 0.20 (10% ethyl acetate/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 2.20 (m, 1H), 2.10 (m, 1H), 1.66 (br t, 2H, J = 12.3 Hz), 1.35 (dddd, 2H, J = 4.1, 10.2, 13.9, 17.6 Hz), 1.25-1.12 (m, 2H), 1.01 (tq, 1H, J = 3.0, 12.1 Hz), and 0.84 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 105.7, 105.5, 48.7, 48.4, 47.8, 47.6, 32.5, 31.7, 31.1, 27.8, 23.8, and 23.6 ppm; IR (solid) v 3398, 3286, 2949, 2865, 1367, 1192, 1084, 1044, 1029, and 903 cm^{-1}; ESI-MS m/z calculated for $C_{11}H_{22}O_3Na$ ($M+Na^+$): 225.1467; found 225.1461, (3 ppm).

3-Phenyl-1-butene

To a dried 100 mL RB flask equipped with a stir bar was added methyltriphenylphosphonium bromide (10.72 g, 30 mmol, 1.5 eq.) and anhydrous THF (45mL). This was allowed to stir at -78°C for approximately 5 minutes after which n-butyllithium (2.5 M, 12 mL, 30 mmol, 1.5 eq.) was added. The yellow solution was then allowed to warm to 0°C and stirred for 1 hour. After this, the solution was cooled to -78°C and 2-phenylpropionaldehyde (2.68 g, 20 mmol, 1 eq.) in THF (15 mL) was added dropwise. After addition the solution was again warmed to 0°C and allowed to stir until TLC (1% ethyl acetate/hexane) showed total consumption of the aldehyde (~ 2.5 hours). At this time, the solution was quenched with water (15 mL) and the aqueous fraction was extracted with diethyl ether. The combined organic fractions were filtered through a sintered filter funnel with silica gel to remove triphenylphosphine oxide. This was washed with diethyl ether and the filtrate was dried with anhydrous sodium sulfate, filtered, and concentrated. The resulting oil was run on a flash column (hexane, R_f ~0.70) to yield a colorless liquid (1.52 g, 52%, 97% GC/MS): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.05 (ddd, 1H, J = 6.5, 10.4, 16.9 Hz), 5.10 (dt, 1H, J = 17.1, 1.6 Hz), 5.09 (dt, 1H, J = 10.3, 1.5 Hz), 3.52 (pent, 1H, J = 6.8 Hz), 1.42 (d, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.59, 143.29, 128.43, 127.26, 126.14, 113.12, 43.21, and 20.76 ppm; IR (film) v 3062-2872, 1637, 1601, 1492, 1451, 910, 755, 697, and 675 cm^{-1}; HRCI-MS m/z calculated for $C_{10}H_{12}$ (M^+): 132.0939; found: 132.0938 (0.8 ppm).

3-(1-Phenylethyl)-1,2,4-trioxolane

A solution of 3-phenyl-1-butene (0.132 g, 1 mmol) in anhydrous dichloromethane (5 mL) in a large, dried vial was ozonized by a similar procedure as for 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by flash chromatography (1:1 hexanes/dichloromethane) and concentrated to yield a colorless oil (0.110 g, 61%): $R_f \sim 0.80$ (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 5.30 (d, 1H, J = 5.3 Hz), 5.28 (d, 1H, J = 4.9 Hz), 5.27 (s, 1H), 5.21 (s, 1H), 5.08 (s, 1H), 5.05 (s, 1H), 3.21-3.15 (m, 1H), 1.46 (d, 3H, J = 7.1 Hz), and 1.44 (d, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 128.5, 128.1, 127.2, 106.0, 94.5, 94.3, 42.2, 41.6, 15.8, and 15.4 ppm; IR (film) v 3030, 2977, 2885, 1495, 1453, 1384, 1133, 1074, 1057, 965, 760, and 697 cm^{-1}; ESI-MS *m/z* calculated for $C_{10}H_{12}O_3Na$ ($M+Na^+$): 203.0684; found: 203.0691, (3 ppm).

1-Hydroperoxy-1-methoxy-2-phenylpropane

In a dried, large vial was added 1-methoxy-3-phenyl-1-butene (0.162 g, 1 mmol, 1 eq.), anhydrous methanol (0.320 g, 10 mmol, 10 eq.), and anhydrous dichloromethane (5 mL). This was cooled to -78°C and ozonized by the procedure used for 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by flash chromatography (20% ethyl acetate/hexanes, R_f = 0.53) to yield (0.150 g, 82%) a 70:30 ratio of hydroperoxyacetals: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.26 (s, 1H), 7.31 (m, 5H), 4.83 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.9 Hz), 3.58 (s, 3H), 3.41 (s, 3H), 3.19 (m, 1H), 1.37 (d, 3H, J = 7.0 Hz), and 1.35 (d, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.4, 128.0, 126.7, 112.0, 57.5, 42.2, 42.0,

and 17.1 ppm; IR (film) *v* 3346, 2936, 2838, 1495, 1453, 1145, 1078, 967, 760, and 698 cm^{-1}; ESI-MS: *m/z* calculated for $C_{10}H_{14}O_3$ ($M+Na^+$): 205.0835; found: 205.0841, (1 ppm).

1-Hydroperoxy-1-(2,2,2-trifluoroethoxy)-2-phenylpropane

In a dried, large vial was added 3-phenyl-1-butene (0.132 g, 1 mmol), 2,2,2-trifluoroethanol (1.00 g, 10 mmol), and anhydrous dichloromethane (5 mL). This was cooled to -78°C and then ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield a 65:35 mixture of hydroperoxyacetals (0.040 g, 16%): R_f = 0.30 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.14 (s, 1H), 7.40-7.25 (m, 5H), 5.03 (d, 1H, *J* = 7.0 Hz), 5.00 (d, 1H, *J* = 6.4 Hz), 4.23 (dq, 1H, A of AB, *J* = 12.6 and 8.8 Hz), 4.08 (dq, 1H, A of AB, *J* = 12.8 and 8.5 Hz), 4.07 (dq, 1H, B of AB, *J* = 12.6 and 8.8 Hz), 3.90 (dq, 1H, B of AB, *J* = 12.8 and 8.5 Hz), 3.20 (app pent, 1H, *J* = 6.9 Hz), 3.19 (app pent, 1H, *J* = 7.1 Hz), 1.40 (d, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 140.9, 128.6, 128.4, 128.2, 127.9, 127.1, 111.4, 67.3, 67.0, 42.4, 42.1, 16.9, and 16.3 ppm; ^{19}F NMR (375 MHz, $CDCl_3$) δ -74.4 (t, 3F, *J* = 8.6 Hz) and -74.7 (t, 3F, *J* = 8.6 Hz) ppm; IR (film) *v* 3427, 2942, 1454, 1278, 1154, 1108, 985, 963, 762, 700, and 678 cm^{-1}; ESI-MS: *m/z* calculated for $C_{11}H_{13}O_3F_3$ ($M+Na^+$): 273.0714; found: 273.0727, (4.7 ppm).

1-Hydroperoxy-1-isopropoxy-2-phenylpropane

In a dried 50 mL RB flask was added 3-phenyl-1-butene (0.264 g, 2 mmol), anhydrous isopropanol (1.20 g, 1.5 mL, 10 eq.), and anhydrous dichloromethane (10 mL). This was cooled to -78°C and then ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by flash chromatography (5% ethyl acetate/hexanes) to yield a 78:22 mixture of hydroperoxyacetals (0.428 g, 75%): R_f = 0.25 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (broad s, 1H), 8.01 (broad s, 1H), 7.37-7.22 (m, 7H), 4.95 (d, 1H, *J* = 6.8 Hz), 4.86 (d, 1H, *J* = 7.2 Hz), 4.00 (heptet, 1H, *J* = 6.1 Hz), 3.78 (heptet, 1H, *J* = 6.1 Hz), 3.20 (pentet, 1H, *J* = 7.2 Hz), 3.17 (pentet, 1H, *J* = 7.2 Hz), 1.38 (d, 3H, *J* = 7.2 Hz), 1.36 (d, 1H, *J* = 7.2 Hz), 1.32 (d, 1H, *J* = 6.1 Hz), 1.21 (d, 3H, *J* = 6.3 Hz), 1.16 (d, 1H, *J* = 6.3 Hz), 0.81 (d, 3H, *J* = 6.2 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.4, 126.7, 109.6, 109.3, 72.4, 72.2, 42.8, 42.3, 23.2, 22.2, 21.8, 17.0, 16.8 ppm; IR (film) *v* 3347, 2972, 1454, 1380, 1128, 1070, 978, 760, 698 cm^{-1}; ESI-MS: *m/z* calculated for $C_{12}H_{18}O_3Na$ ($M+Na^+$): 233.1154; found: 233.1150, (2 ppm).

1-Methoxy-3-phenyl-1-butene

In a dried, 250 mL RB flask with stir bar was added methoxymethyl triphenylphosphonium chloride (15.43 g, 45 mmol, 1.5 eq.) and THF (80 mL). The slurry was cooled to -78°C and then n-butyllithium (2.5M, 18 mL, 45 mmol, 1.5 eq.) was added. The yellow solution was allowed to warm to 0°C and stirred for 1 hour, forming a dark, transparent solution. The solution was, again, cooled to

-78°C and 2-phenylpropionaldehyde (4.02 g, 30 mmol, 1 eq.) was added in THF (20 mL) dropwise. Following addition, the solution was warmed to room temperature and allowed to stir until TLC (10% ethyl acetate/hexanes) showed complete consumption of aldehyde (~ 1 hour). The reaction was then quenched with water and the aqueous layer was extracted with diethyl ether. The combined organic fractions were dried and filtered through a fritted funnel packed with silica gel. The filter media was washed with diethyl ether and the filtrate was concentrated under vacuum. The residue was then purified using silica gel deactivated with 2% triethylamine/hexanes in a flash column to yield a colorless oil (1.30 g, 27%) as a 1:1 mixture of (E) and (Z) enol ethers: R_f = 0.85 (hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.22 (m, 10H), 6.41 (d, 1H, *J* = 12.6 Hz), 5.95 (d, 1H, *J* = 6 Hz), 5.01 (dd, 1H, *J* = 7.6, 12.7 Hz), 4.60 (dd, 1H, *J* = 6.4, 9.3 Hz), 4.02 (dq, 1H, *J* = 7.1, 9.5 Hz), 3.66 (s, 3H), 3.58 (s, 3H), 3.48 (app pent, 1H, *J* = 7.2 Hz), 1.43 (d, 3H, *J* = 6.9 Hz), and 1.40 (d, 3H, *J* = 6.9 Hz) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.3, 147.2, 147.0, 145.3, 128.5, 127.1, 127.0, 126.2, 126.0, 112.5, 108.9, 59.8, 56.1, 38.6, 34.52, 22.8, and 22.5 ppm; IR (film) *v* 3030-2870, 1652, 1451, 1251, 1206, 1158, 1098, 937, 742, and 697 cm^{-1}; HRCI MS: *m/z* calculated for $C_{11}H_{15}O$ ($M+H^+$): 163.1123; found: 163.1126, (1.9 ppm).

3-Octyl-1,2,4-trioxolane

In a dried 50 mL RB flask was added decene (0.421 g, 3 mmol, 1 eq.) and anhydrous dichloromethane (15 mL). This was brought to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The

residue was purified by flash chromatography (2.5% ethyl acetate/hexanes, peroxide dip) to yield a colorless oil (0.413 g, 73%): R_f = 0.55 (5% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.13 (t, 1H, J = 5 Hz), 5.03 (s, 1H), 1.75-1.70 (m, 2H), 1.48-1.40 (m, 2H), 1.35-1.22 (m, 12H), and 0.88 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.1, 94.2, 32.0, 31.3, 29.6, 29.3, 24.0, 22.8, and 14.3 ppm; IR (film) ν 2954, 2925, 2856, 1466, 1379, 1105, 1054, 974, and 723 cm^{-1}; HRFAB MS: *m/z* calculated for $C_{10}H_{21}O_3$ ($M+H^+$): 189.1491; found 189.1486, (2.4 ppm).

1-Hydroperoxy-1-methoxynonane

In a dried 50 mL RB flask was added decene (0.421 g, 3 mmol, 1 eq.), anhydrous methanol (0.961 g, 30 mmol, 10 eq.) and anhydrous dichloromethane (15 mL). This was cooled to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The residue was purified by flash chromatography (10% ethyl acetate/hexanes, R_f = 0.22) to yield a colorless oil (0.428 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 4.75 (t, 1H, J = 5.9 Hz), 3.51 (s, 3H), 1.80-1.60 (m, 2H), 1.42-1.20 (m, 14H), and 0.88 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 100.2, 56.0, 32.0, 31.5, 29.6, 24.8, 22.8, and 14.3 ppm; IR (film) ν 3354, 2923, 2854, 1465, 1378, 1103, 1070, and 968 cm^{-1}; ESI-MS: *m/z* calculated for $C_{10}H_{22}O_3$ ($M+Na^+$): 213.1461; found: 213.1467, (3 ppm).

4-Methyl-3-(3-oxobutyl)-4-pentenal

In a dried, 25 mL RB flask was added (R)-(+)-limonene (0.272 g, 2 mmol, 1 eq.), anhydrous pyridine (0.158 g, 0.16 mL, 2 mmol, 1 eq.), and anhydrous dichloromethane (10 mL). This was cooled to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The solution was then washed with 1 M HCl (10 mL x 1), deionized water (10 mL x 1), and brine (10 mL x 1). The organic fraction was dried with sodium sulfate, filtered, and concentrated to yield a yellow-brown residue. The residue was then purified by flash chromatography (R_f = 0.41, 25% ethyl acetate/hexanes) to yield a colorless liquid (0.204 g, 61%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, 1H, J = 2.2 Hz), 4.83 (m, 1H,), 4.77 (m, 1H), 2.66 (m, 1H), 2.45 (ddd, 2H, J = 2.5, 5.0, 7.2 Hz), 2.39 (t, 2H, J = 7.4 Hz), 2.13 (s, 3H), and 1.63 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 202.0, 145.2, 113.5, 47.6, 41.1, 41.0, 30.3, 26.6, and 18.6 ppm; IR (film) v 2922, 2853, 1714, 1645, 1366, 1161, 896, and 732 cm^{-1}; ESI-MS: *m/z* calculated for $C_{10}H_{16}O_2$ ($M+Na^+$): 191.1048; found: 191.1043, (2.6 ppm).

(E)-3-Methyl-6-oxohex-2-enyl acetate

In a dried, 25 mL RB flask was added geranyl acetate (0.392 g, 2 mmol, 1 eq.), anhydrous pyridine (0.158 g, 0.16 mL, 2 mmol, 1 eq.), and anhydrous dichloromethane (10 mL). This was cooled to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The solution was then washed with 1 M HCl (10 mL x 1), deionized water (10 mL x 1), and brine (10 mL x 1). The organic fraction was dried with sodium sulfate, filtered, and

concentrated to yield a yellow-brown residue. The residue was then purified by flash chromatography (R_f = 0.33, 20% ethyl acetate/hexanes) to yield a colorless liquid (0.235 g, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, 1H, *J* = 1.6 Hz), 5.31 (t, 1H, *J* = 7.0 Hz), 4.53 (d, 2H, *J* = 7.4 Hz), 2.54 (t, 2H, *J* = 7.6 Hz), 2.33 (t, 2H, *J* = 7.4 Hz), 2.00 (s, 3H), and 1.68 (s, 3H) ppm; ^{13}C NMR (125 Hz, $CDCl_3$) δ 201.8, 171.1, 140.1, 119.4, 61.2, 41.8, 31.5, 21.1, and 16.7 ppm; IR (film) *v* 2923, 2853, 1721, 1367, 1228, 1022, and 953 cm^{-1}; ESI-MS: *m/z* calculated for $C_9H_{14}O_3$ ($M+Na^+$): 193.0841; found: 193.0842, (0.5 ppm).

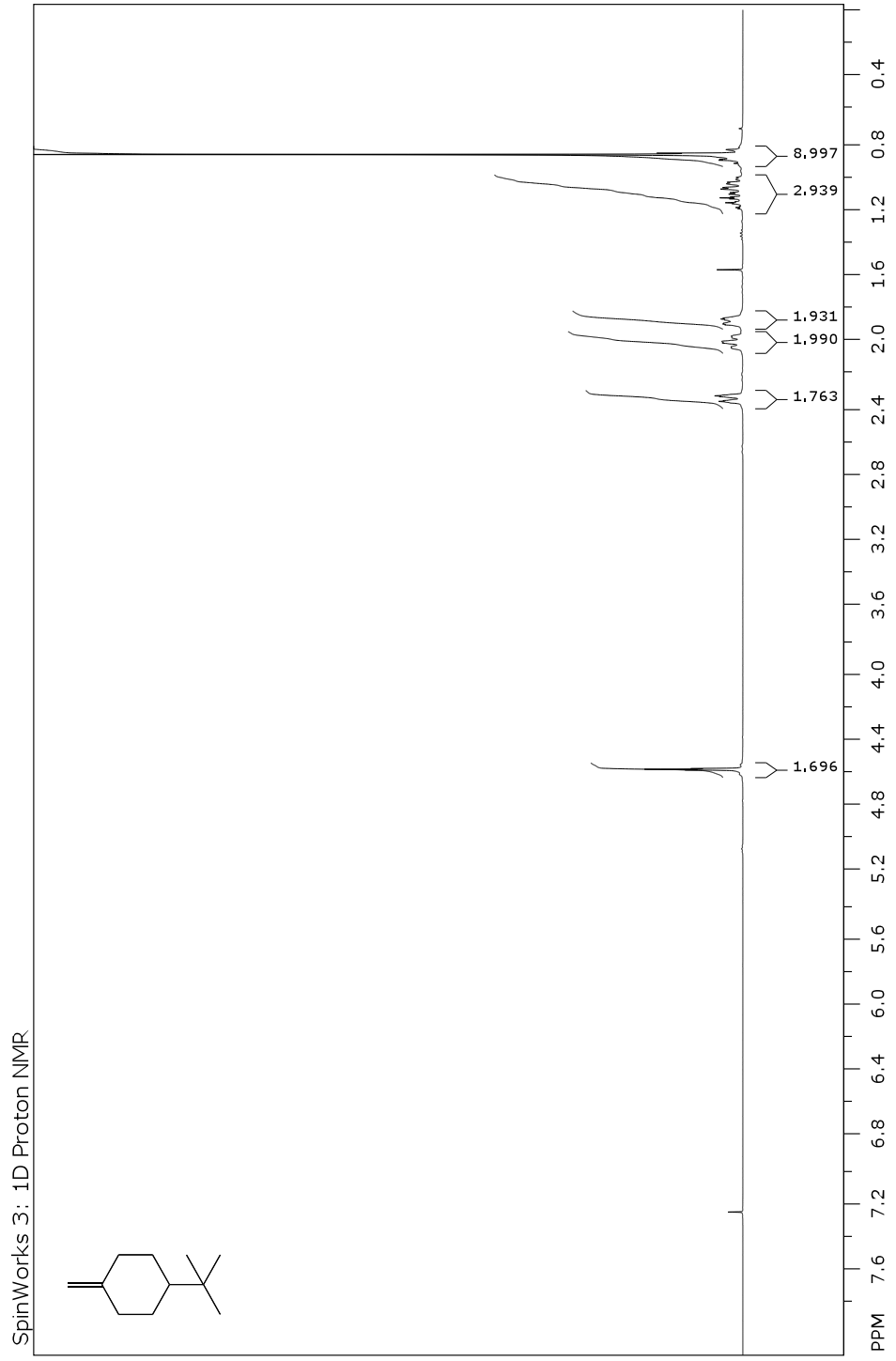
4-Methyl-5-hexen-1-ol

In a dried, 25 mL RB flask was added citronellene (0.276 g, 2 mmol, 1 eq.), anhydrous pyridine (0.158 g, 0.16 mL, 2 mmol, 1 eq.), and anhydrous dichloromethane (10 mL). This was cooled to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. To this solution was added sodium borohydride (303 mg, 4 eq., 8 mmol), anhydrous ethanol (10 mL), and THF (~ 5 mL) to aid in dissolution of borohydride. This was stirred at room temperature for ~ 45 min. At this time the reaction was quenched with water (10 mL) and the organic layer was washed with brine, dried with anhydrous sodium sulfate, and concentrated to a colorless residue. This was purified by column chromatography (7:3 pentane/diethyl ether) to yield a colorless liquid (0.154 g, 67%): R_f = 0.53 (6:4 pentane/diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, 1H, *J* = 7.6, 10.3, 17.4 Hz), 4.94 (m, 2H), 3.61 (t, 2H, *J* = 6.6 Hz), 2.13 (app heptet, 1H, *J* = 6.8 Hz), 1.90 (br s, 1H), 1.57 (m, 2H), 1.36 (m, 2H), and 1.00 (d, 3H, *J* = 6.8 Hz)

ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 112.9, 63.3, 37.8, 32.8, 30.7, 20.5, and 20.4 ppm; IR (film) *v* 3332, 2933, 2868, 1640, 1454, 1419, 1374, 1056, 994, and 908 cm^{-1}; HRCI MS: *m/z* calculated for $C_7H_{15}O$ ($M+H^+$): 115.1123; found: 115.1121, (1.7 ppm).

3-Vinylhexanedial

In a dried, 25 mL RB flask was added 4-vinyl-1-cyclohexene (0.216 g, 2 mmol, 1 eq.), anhydrous pyridine (0.158 g, 0.16 mL, 2 mmol, 1 eq.), and anhydrous dichloromethane (10 mL). This was cooled to -78°C and ozonized by the same procedure as 4-*t*-butyl-1-hydroperoxy-1-methoxycyclohexane. The solution was then washed with 1 M HCl (10 mL x 1), deionized water (10 mL x 1), and brine (10 mL x 1). The organic fraction was dried with sodium sulfate, filtered, and concentrated to yield a yellow-brown residue. The residue was then purified by flash chromatography (R_f = 0.40, 30% ethyl acetate/hexanes) to yield a colorless liquid (0.066 g, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 1.3 Hz), 9.72 (t, 1H, *J* = 2.0 Hz), 5.58 (ddd, 1H, *J* = 8.5, 10.4, 16.9 Hz), 5.08 (m, 2H), 2.64 (m, 1H), 2.47 (m, 4H), 1.82 (m, 1H), and 1.62 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 201.6, 139.8, 117.0, 48.8, 41.6, 38.0, and 26.7 ppm; IR (film) *v* 2924, 2828, 2727, 1717, 1410, 1391, 999, and 920 cm^{-1}; HRCI MS: *m/z* calculated for $C_8H_{13}O_2$ ($M+H^+$): 141.0916; found: 141.0917, (1.0 ppm).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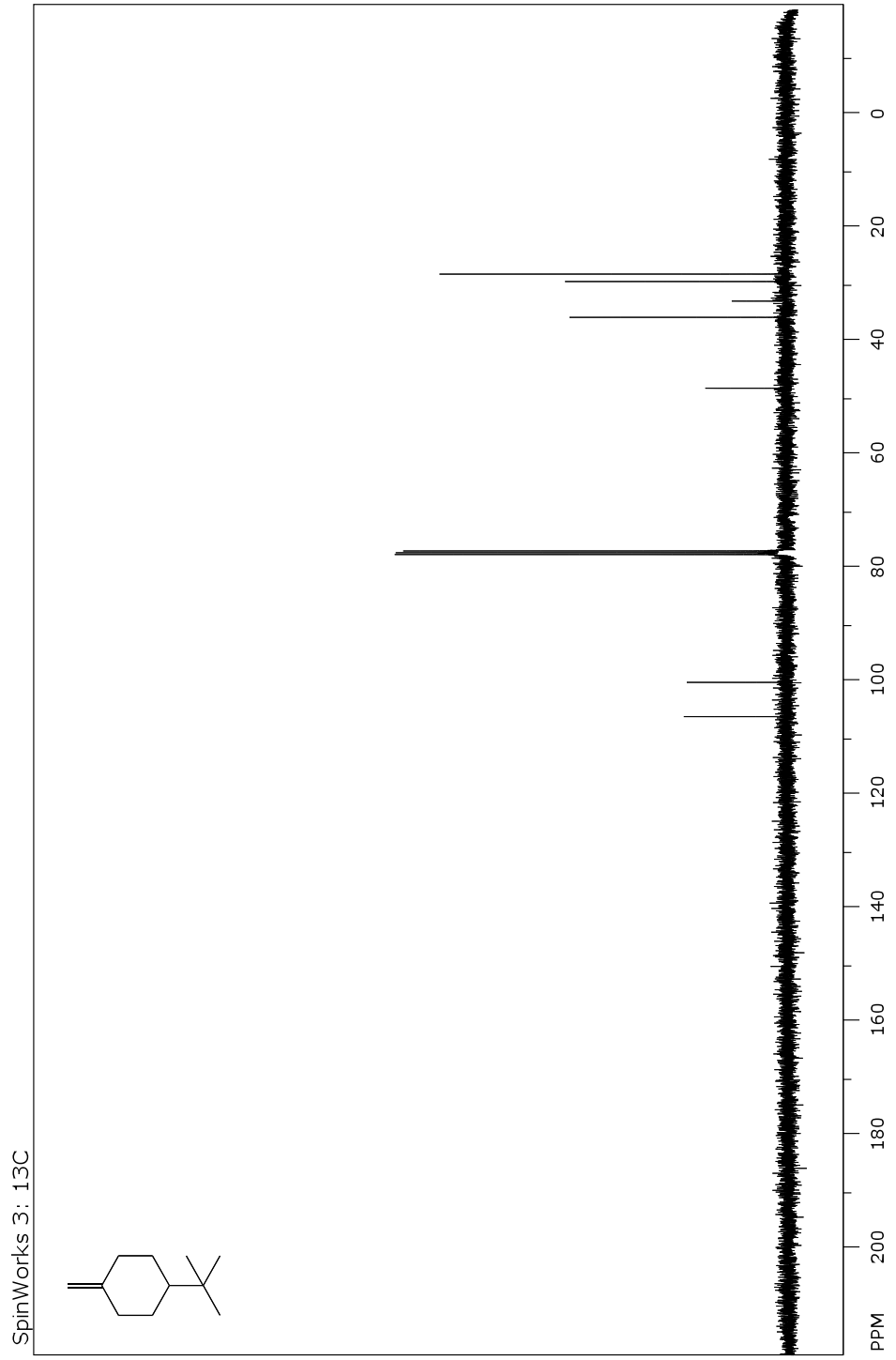
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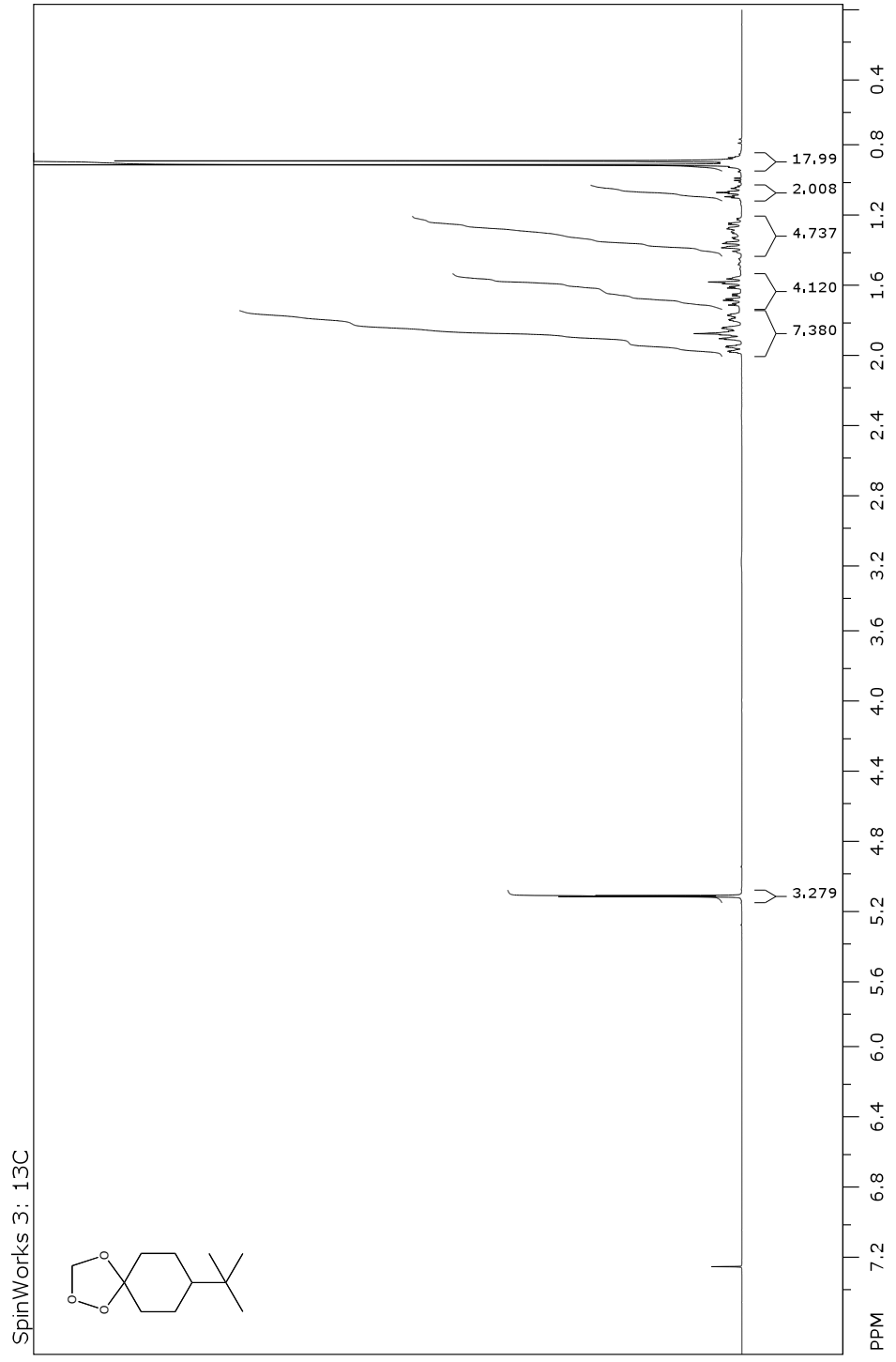
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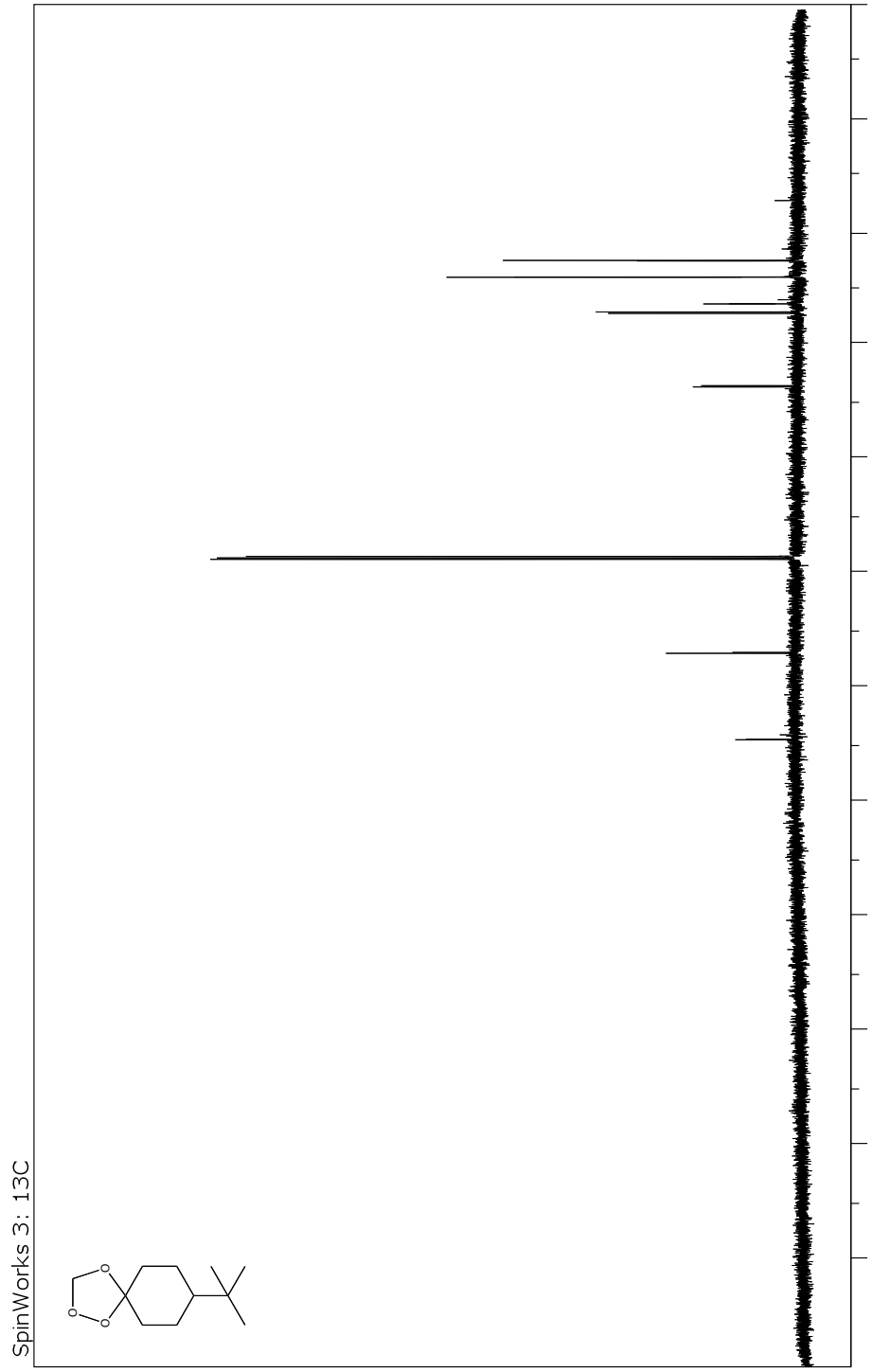
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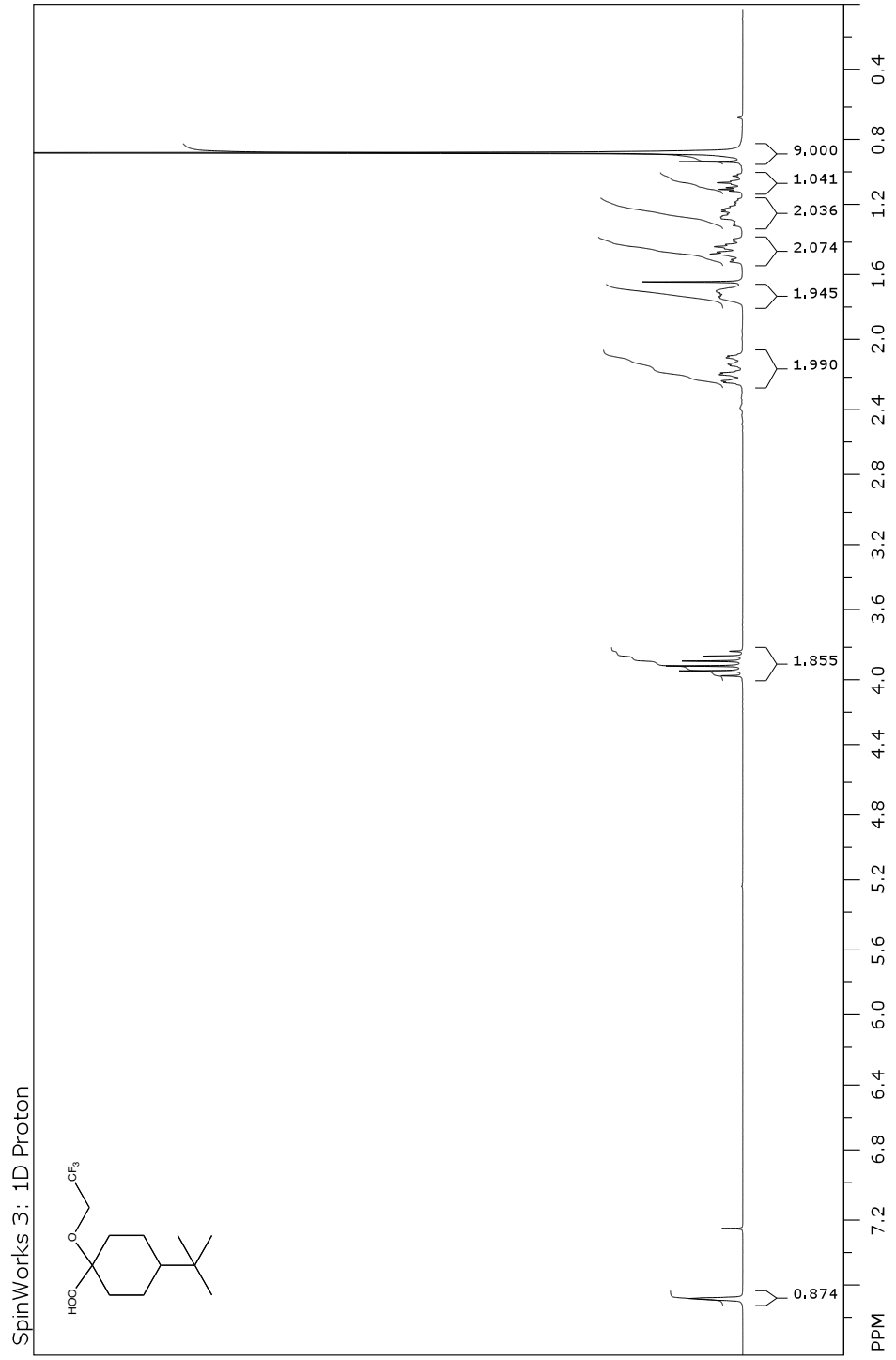
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6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
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1.2
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0.4
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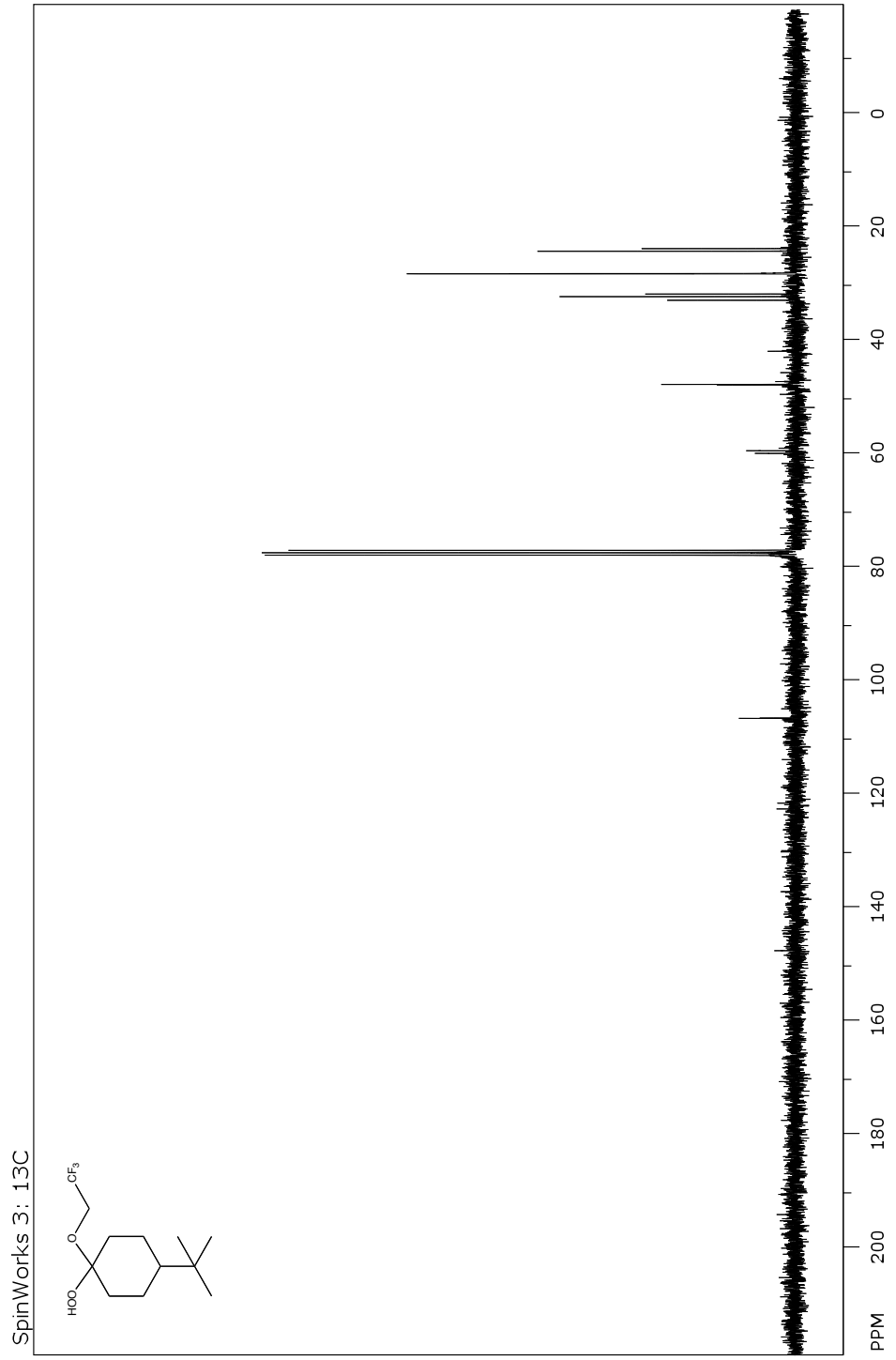
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CF3
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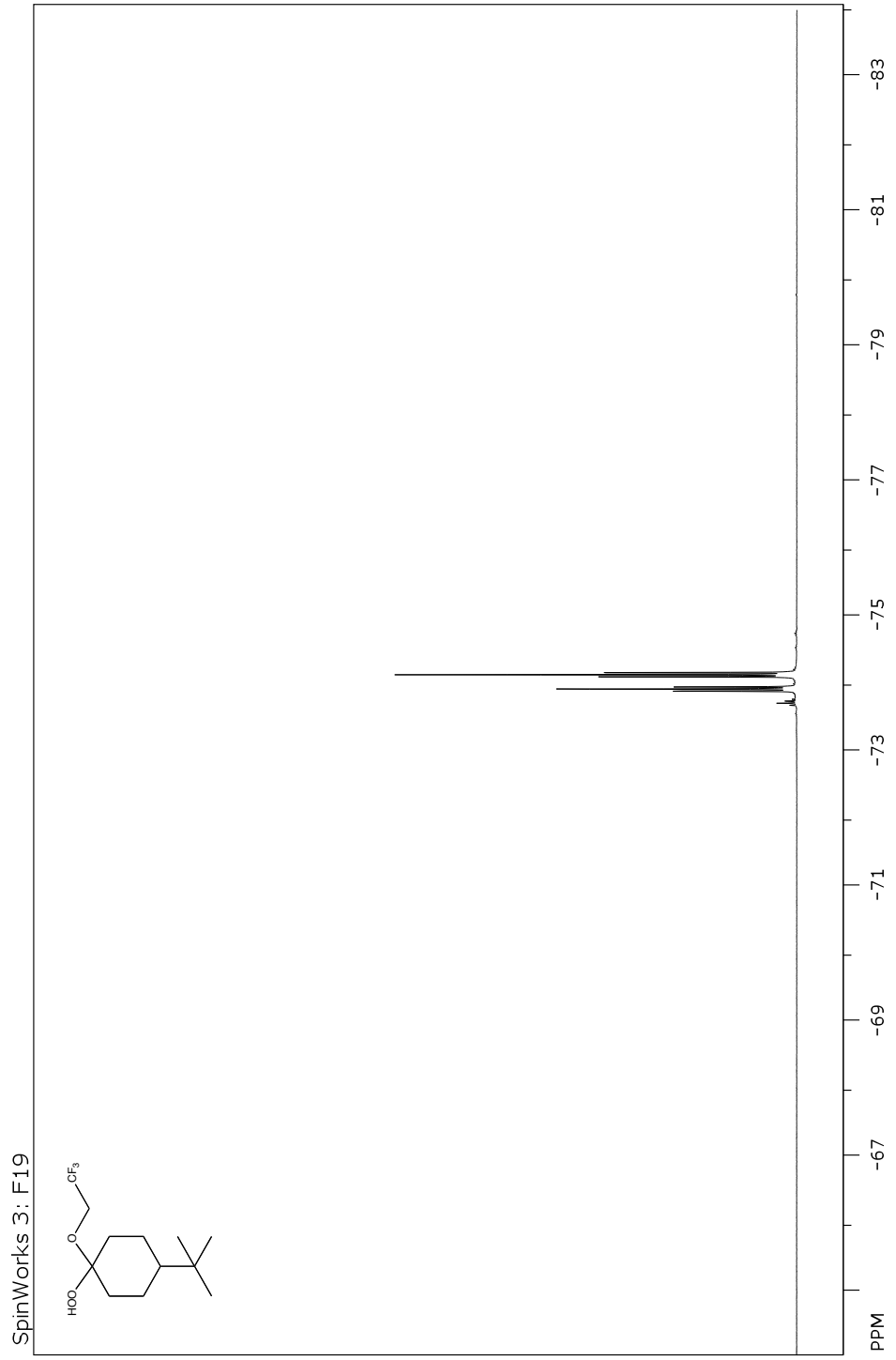
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-77
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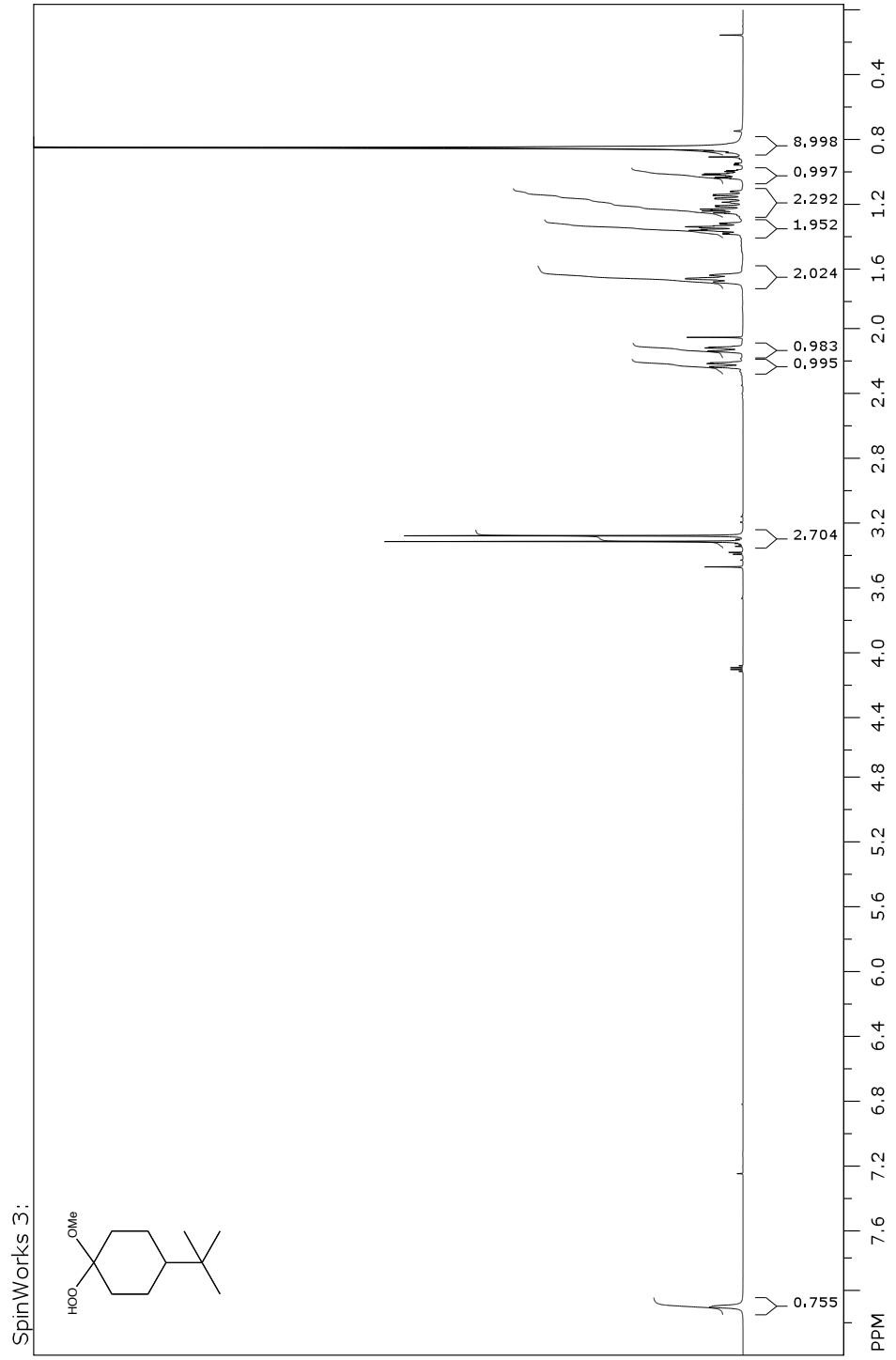
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7.2
6.8
6.4
6.0
5.6
5.2
4.8
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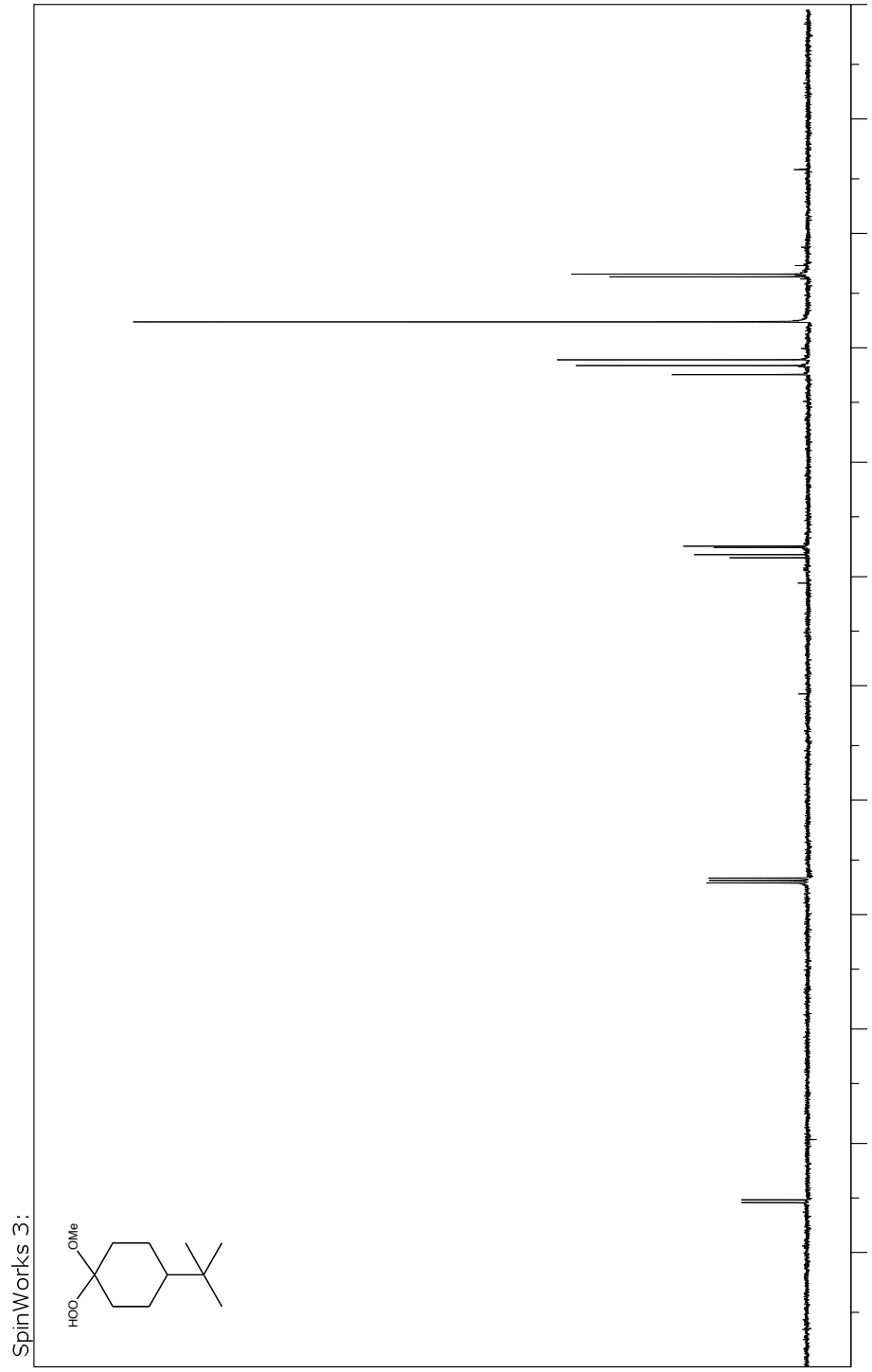
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PPM
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10
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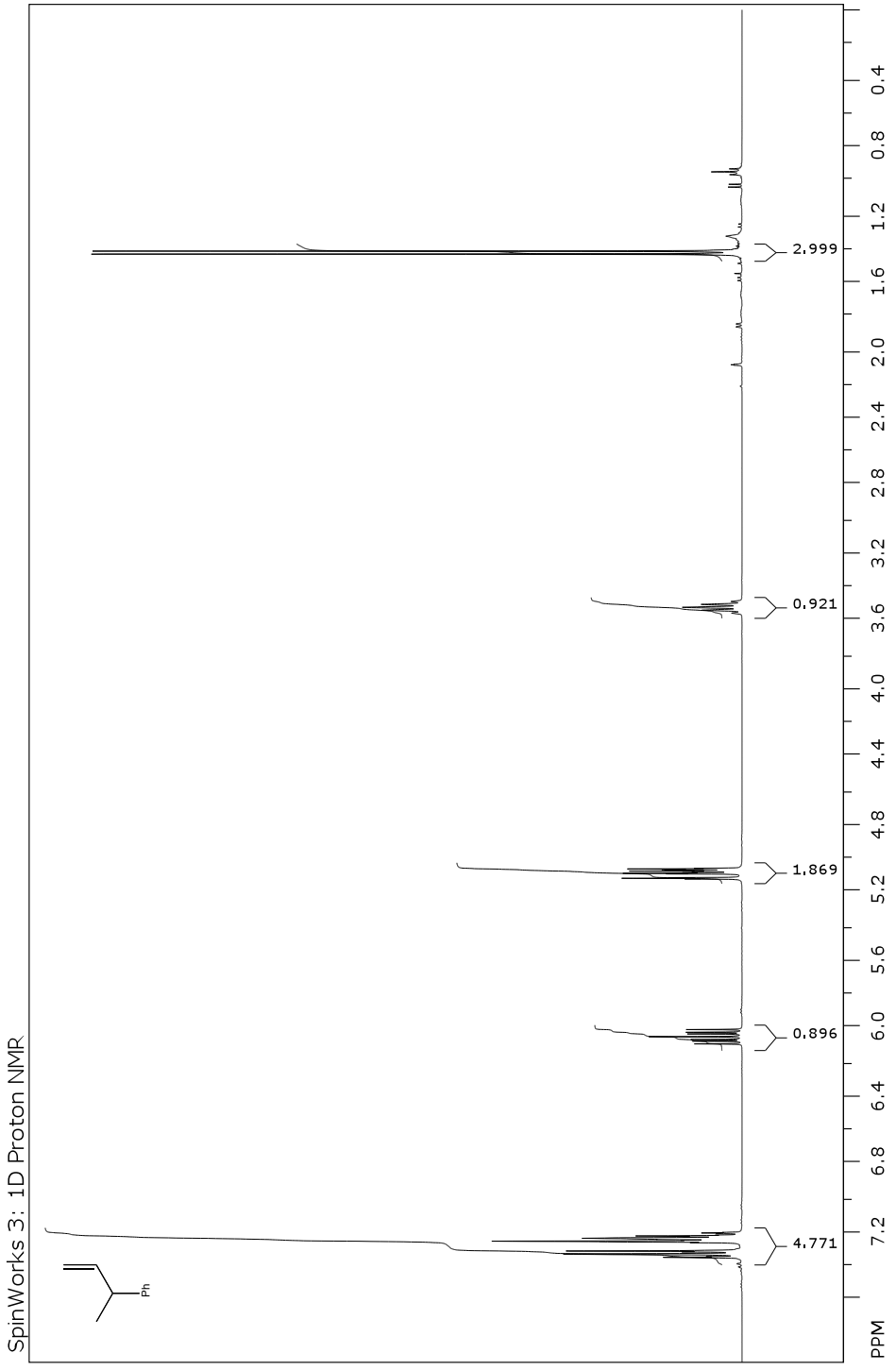
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5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
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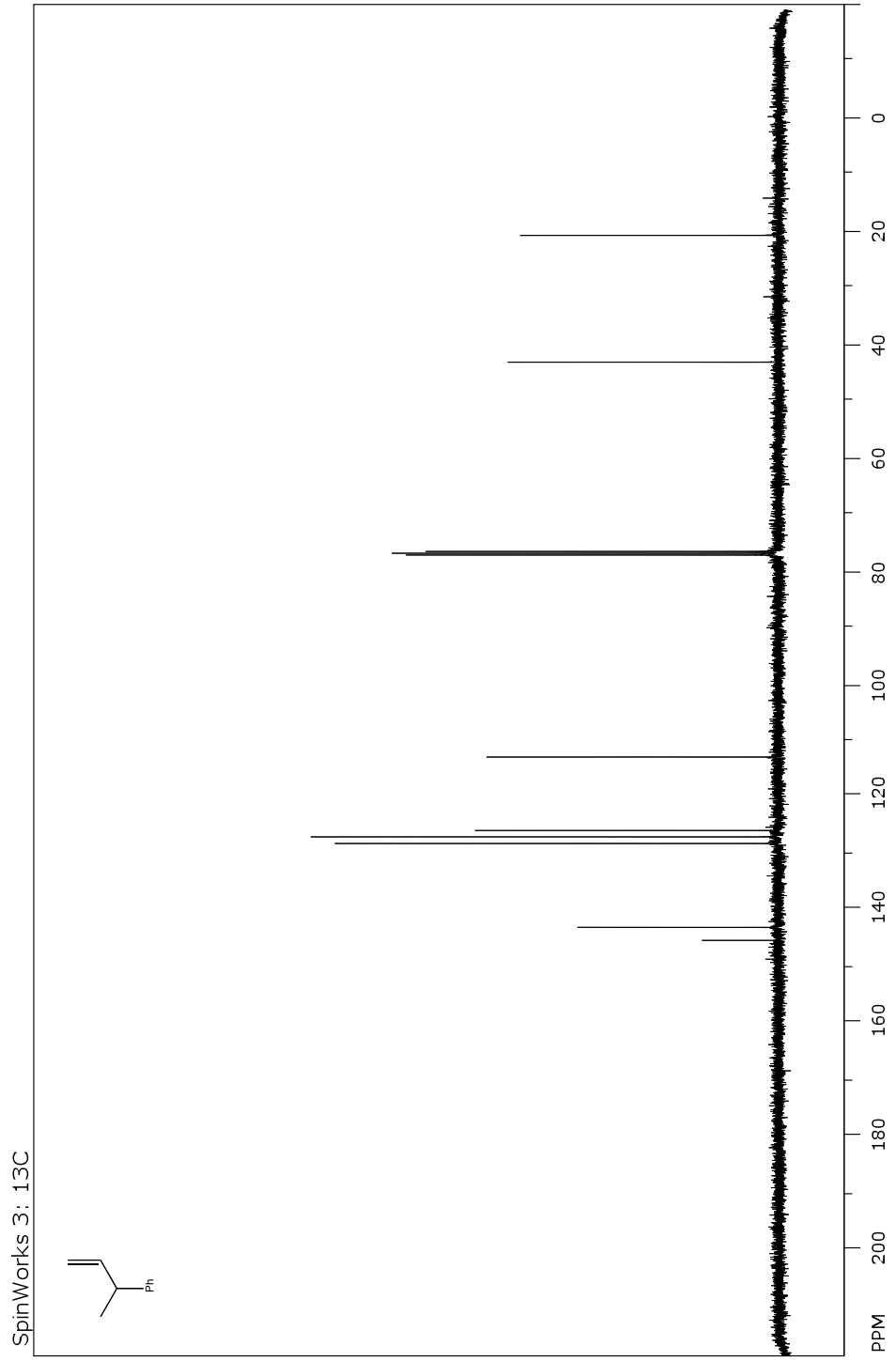
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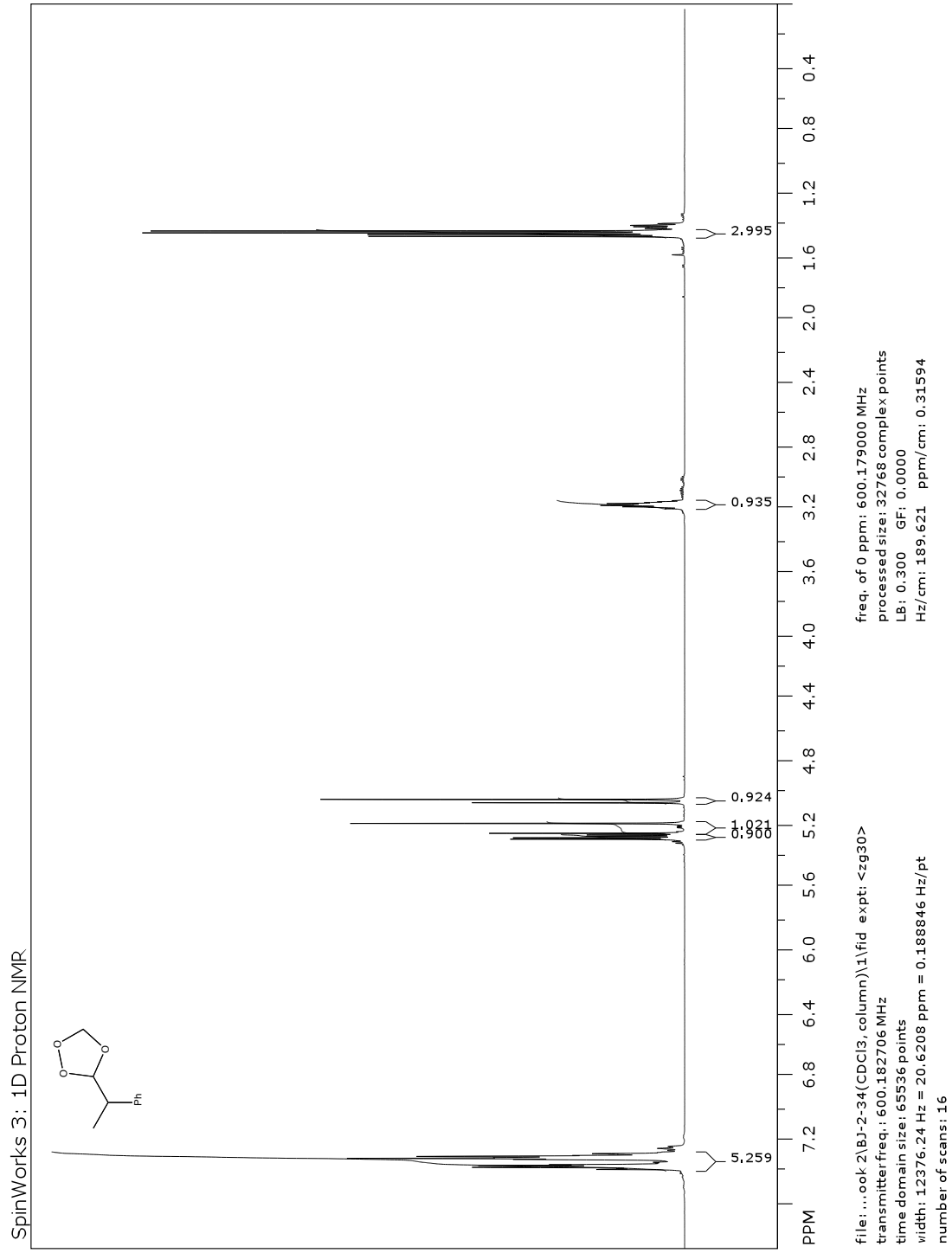
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6.0
5.6
5.2
4.8
4.4
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3.6
3.2
2.8
2.4
2.0
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0.4
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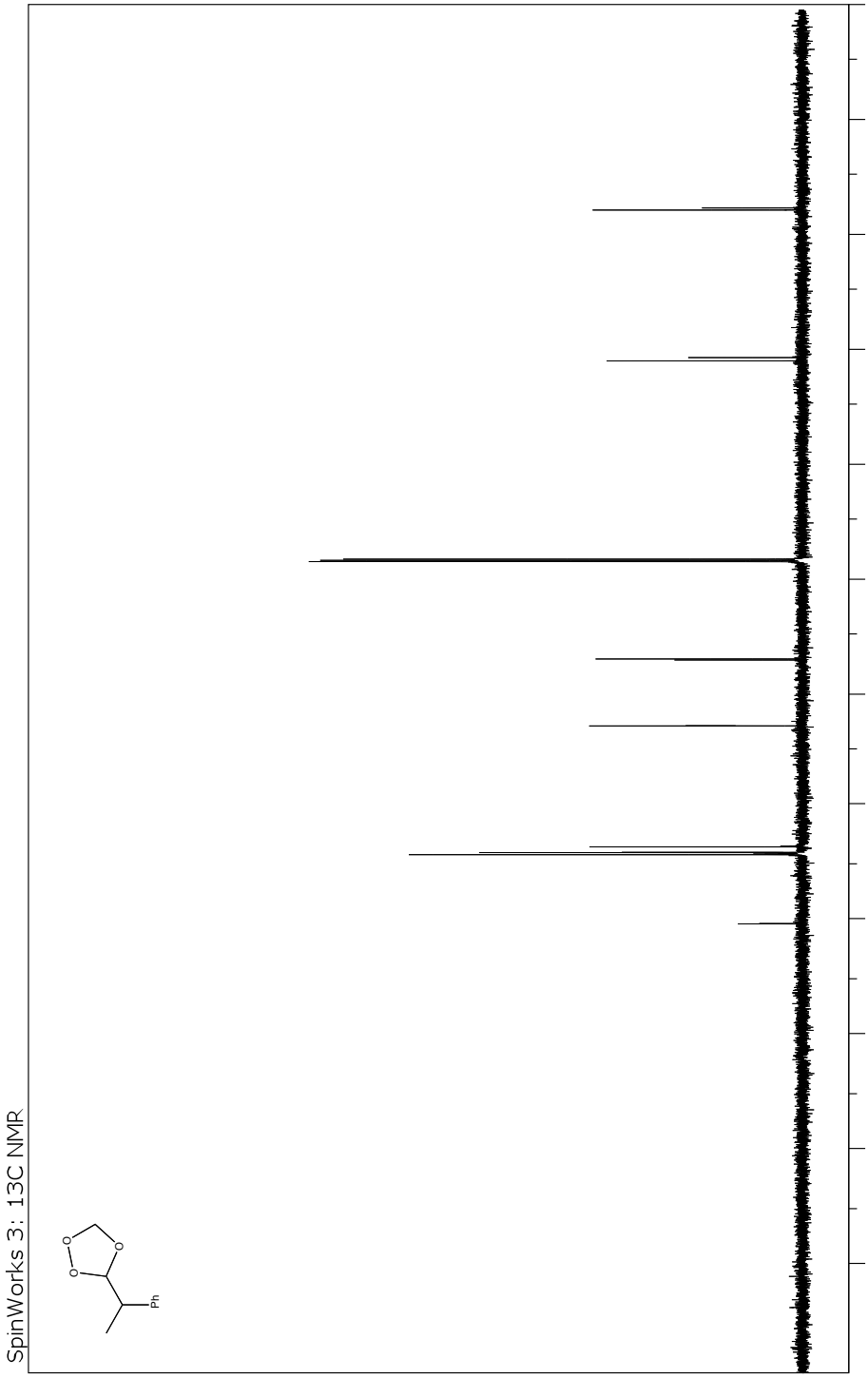
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PPM
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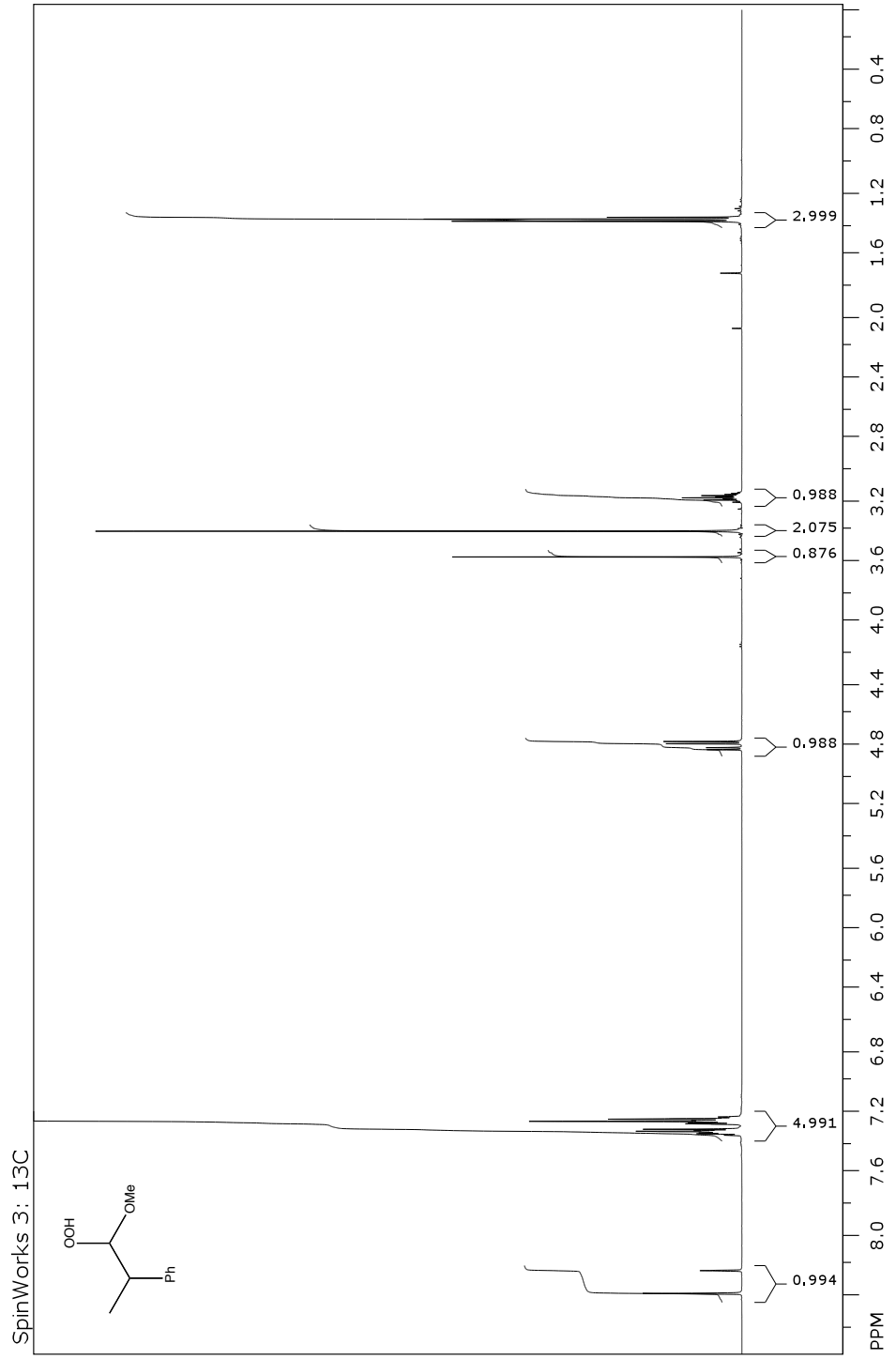
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PPM
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5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
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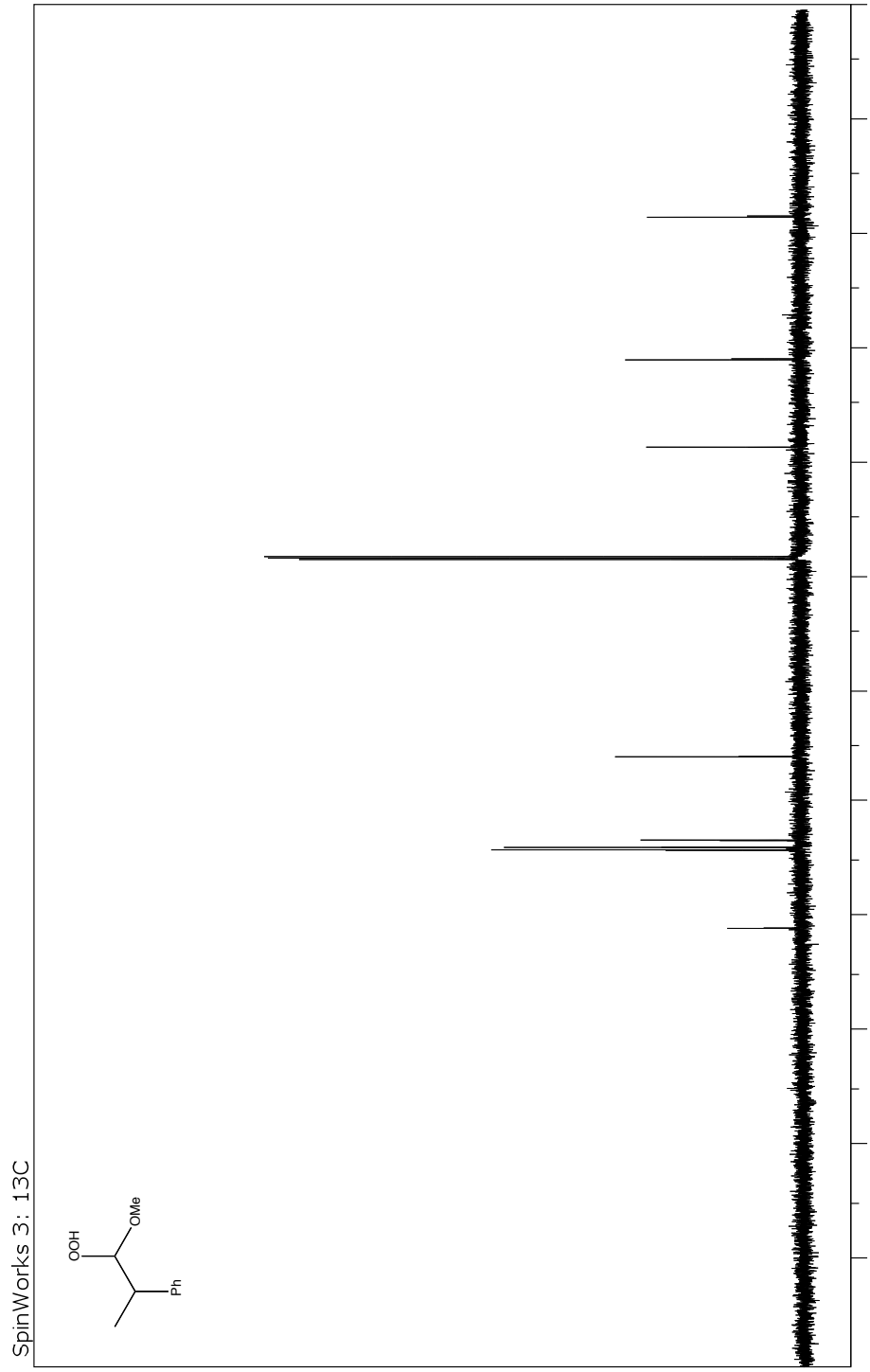
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PPM
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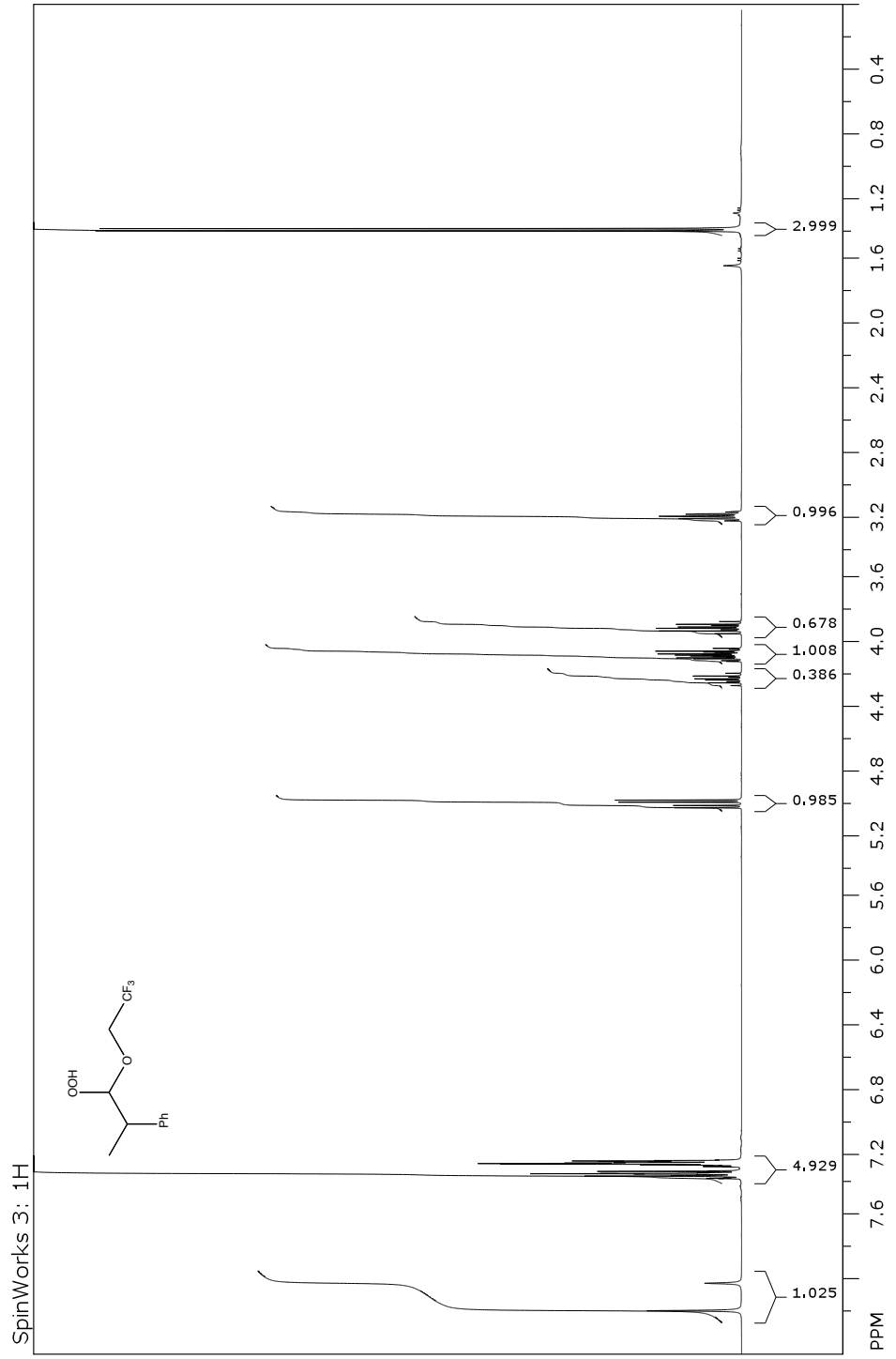
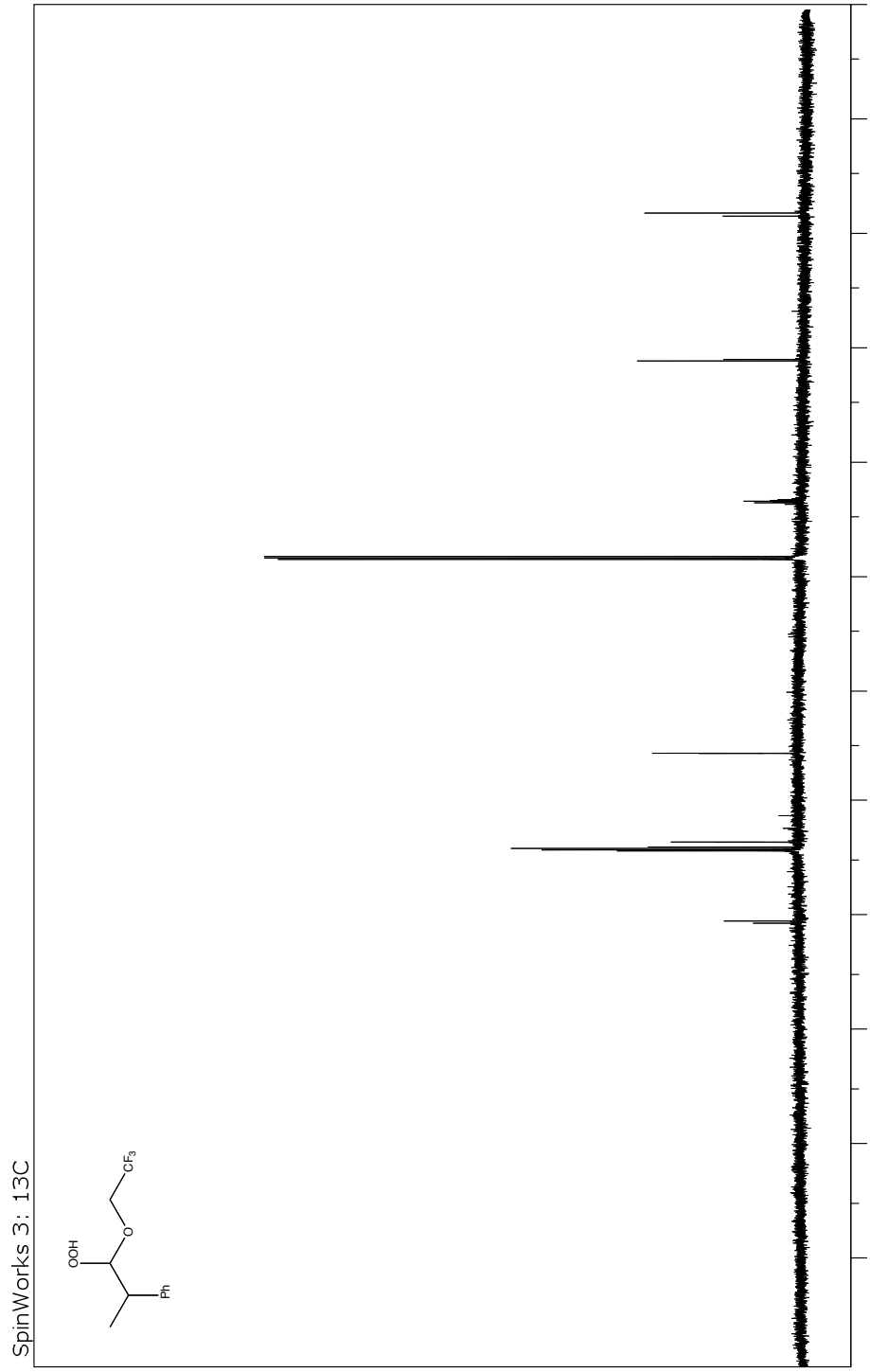
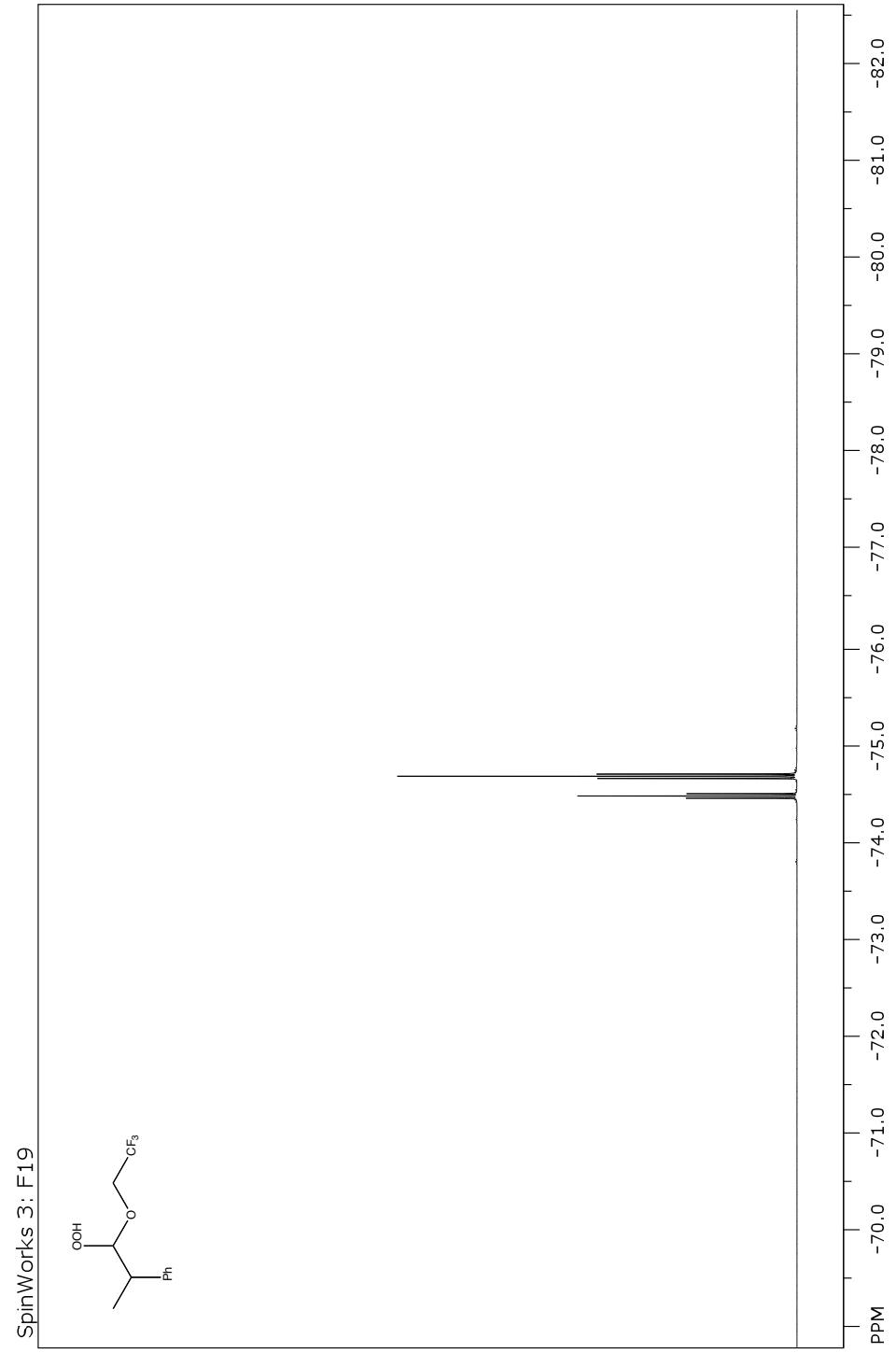
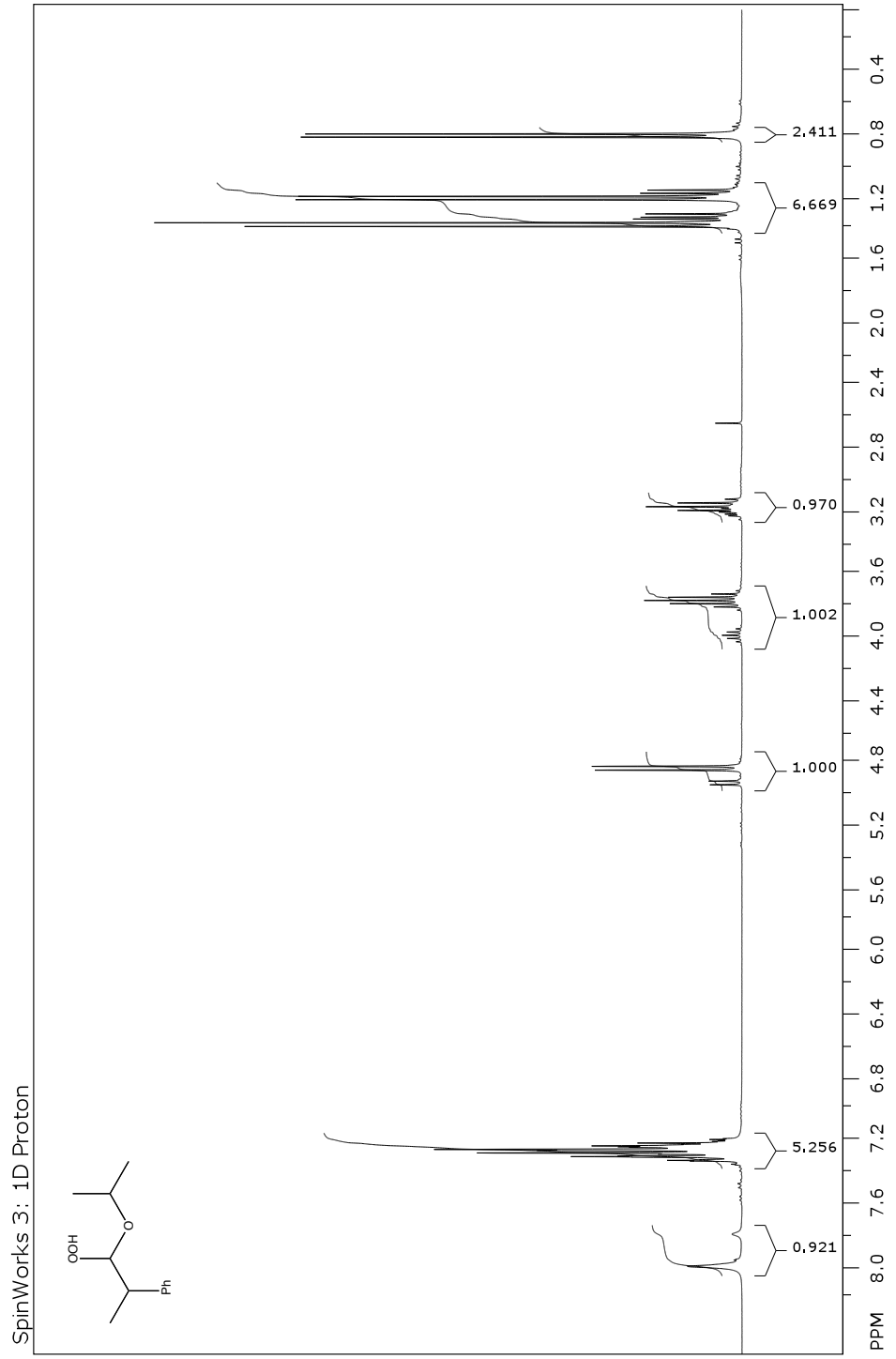
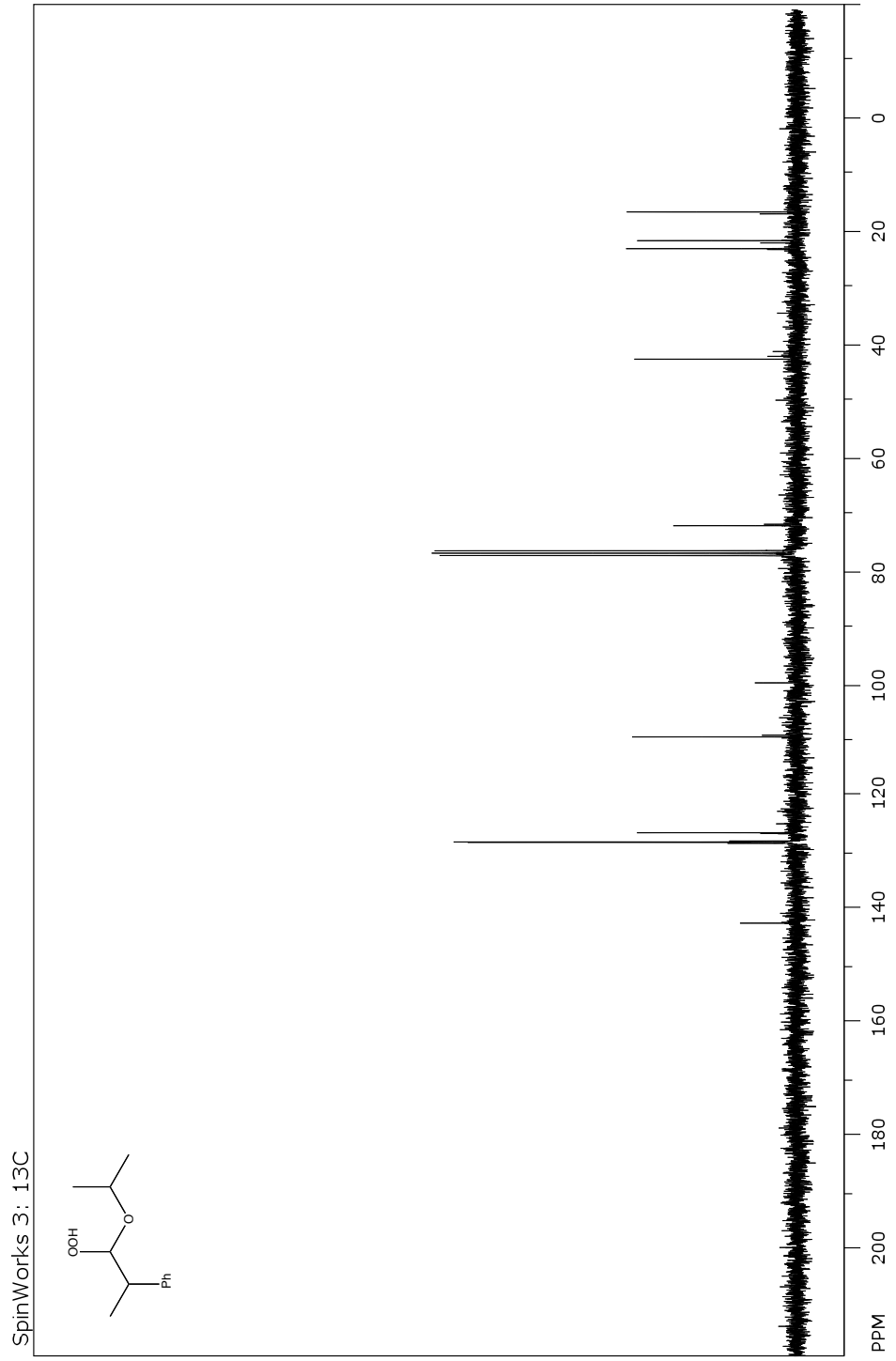
0
file: ...rad NMR\Notebook 2\BJ-2-40.2\2\fid expt: <zgpg30>
transmitter freq.: 125.770364 MHz
time domain size: 65536 points
width: 30030.03 Hz = 238.7687 ppm = 0.458222 Hz/pt
number of scans: 18
freq. of 0 ppm: 125.757789 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 1201.201 ppm/cm: 9.55075

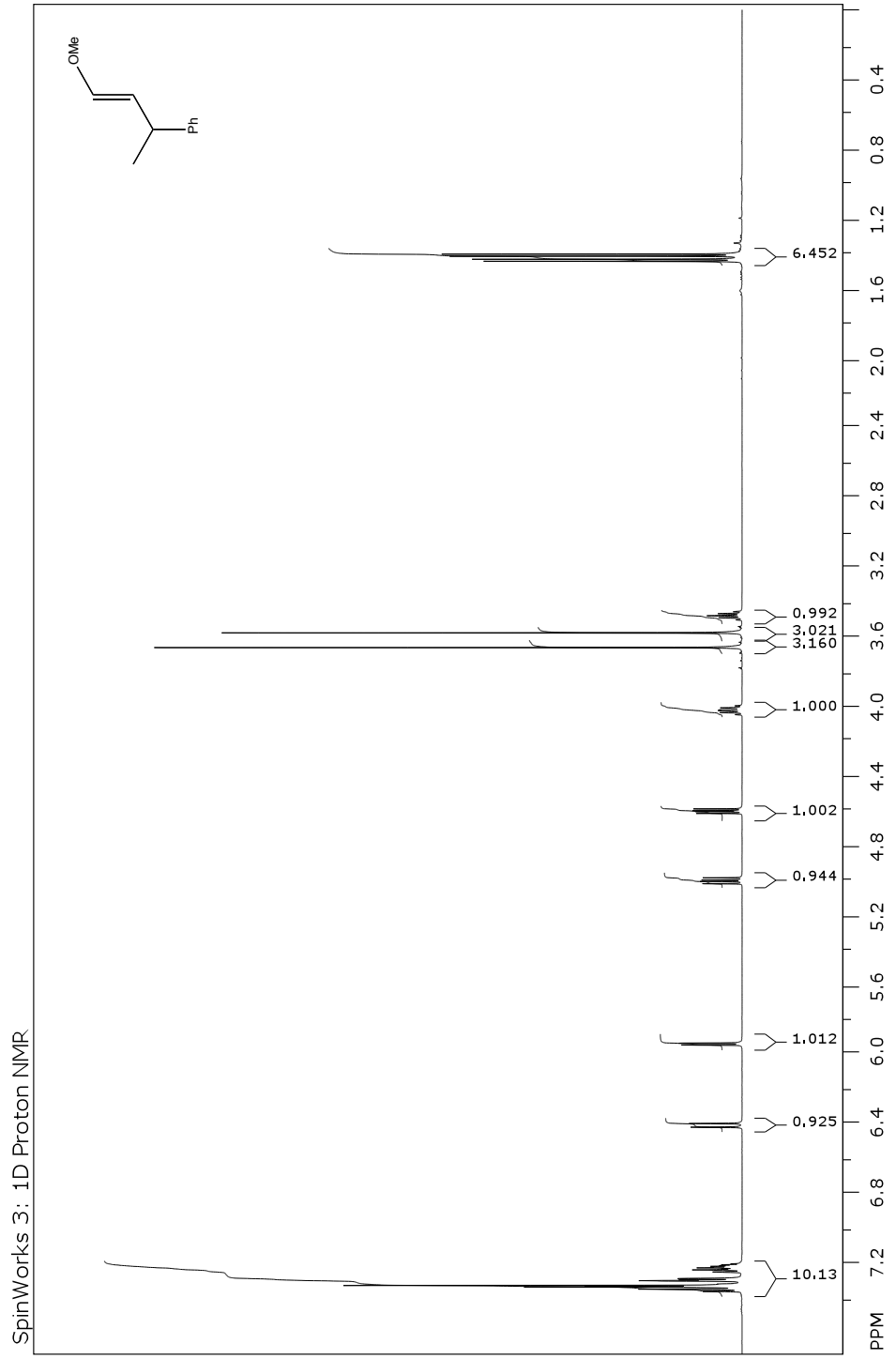

SpinWorks 3: 1H
OOH
O
CF3
Ph
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
1.025
4.929
0.985
0.386
1.008
0.678
0.996
2.999
file:...MR\Notebook 2\BJ-2-81(HPLC2)\1\fid expt: <zg30>
transmitter freq.: 500.133089 MHz
time domain size: 65536 points
width: 10330.58 Hz = 20.6557 ppm = 0.157632 Hz/pt
number of scans: 16
freq. of 0 ppm: 500.130000 MHz
processed size: 65536 complex points
LB: 0.000 GF: 0.0000
Hz/cm: 169.609 ppm/cm: 0.33913

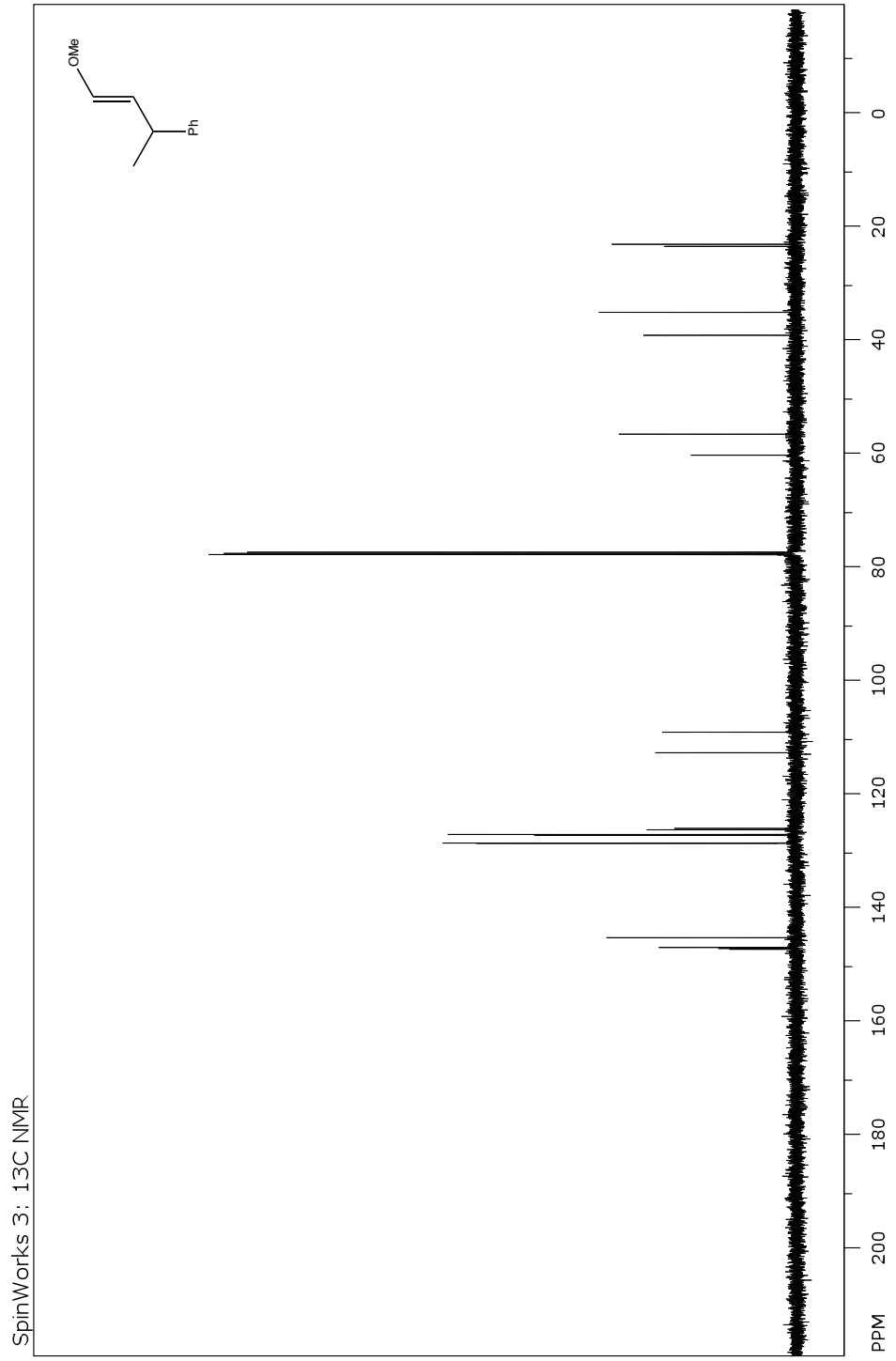

SpinWorks 3: 13C
OOH
O
CF3
Ph
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...NMR\Notebook 2\BJ-2-81(HPLC)\2\fid expt: <zgpg30>
transmitter freq.: 125.770364 MHz
time domain size: 65536 points
width: 30030.03 Hz = 238.7687 ppm = 0.458222 Hz/pt
number of scans: 100
freq. of 0 ppm: 125.757789 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 1201.201 ppm/cm: 9.55075

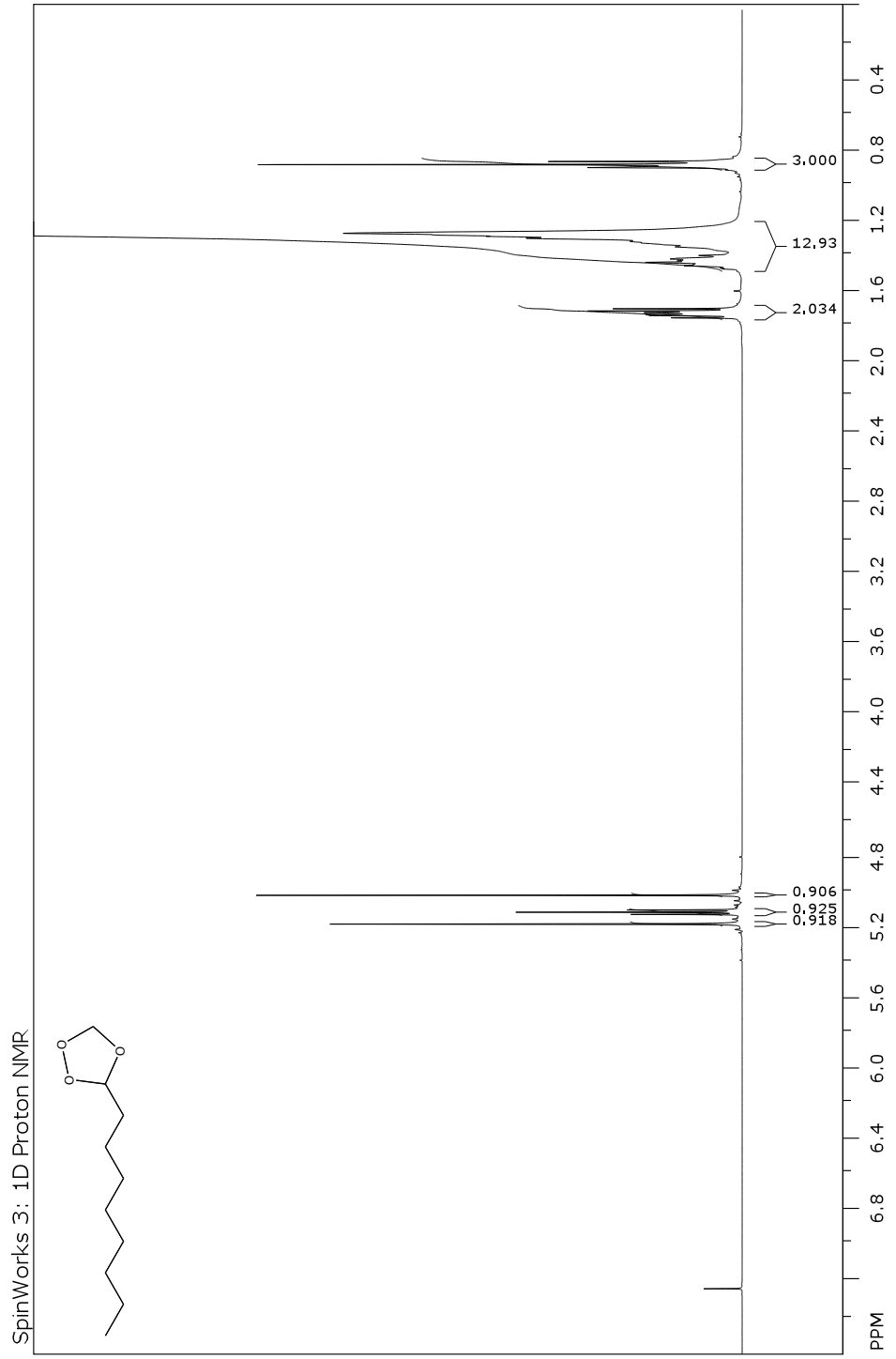

SpinWorks 3: F19
OOH
O
CF3
Ph
PPM
-70.0
-71.0
-72.0
-73.0
-74.0
-75.0
-76.0
-77.0
-78.0
-79.0
-80.0
-81.0
-82.0
file: ...Notebook 2\BJ-2-81(decouple)\4\fid expt: <zgflqn>
transmitter freq.: 376.460716 MHz
time domain size: 131072 points
width: 75187.97 Hz = 199.7233 ppm = 0.573639 Hz/pt
number of scans: 16
freq. of 0 ppm: 376.498354 MHz
processed size: 131072 complex points
LB: 0.000 GF: 0.0000
Hz/cm: 208.748 ppm/cm: 0.55450

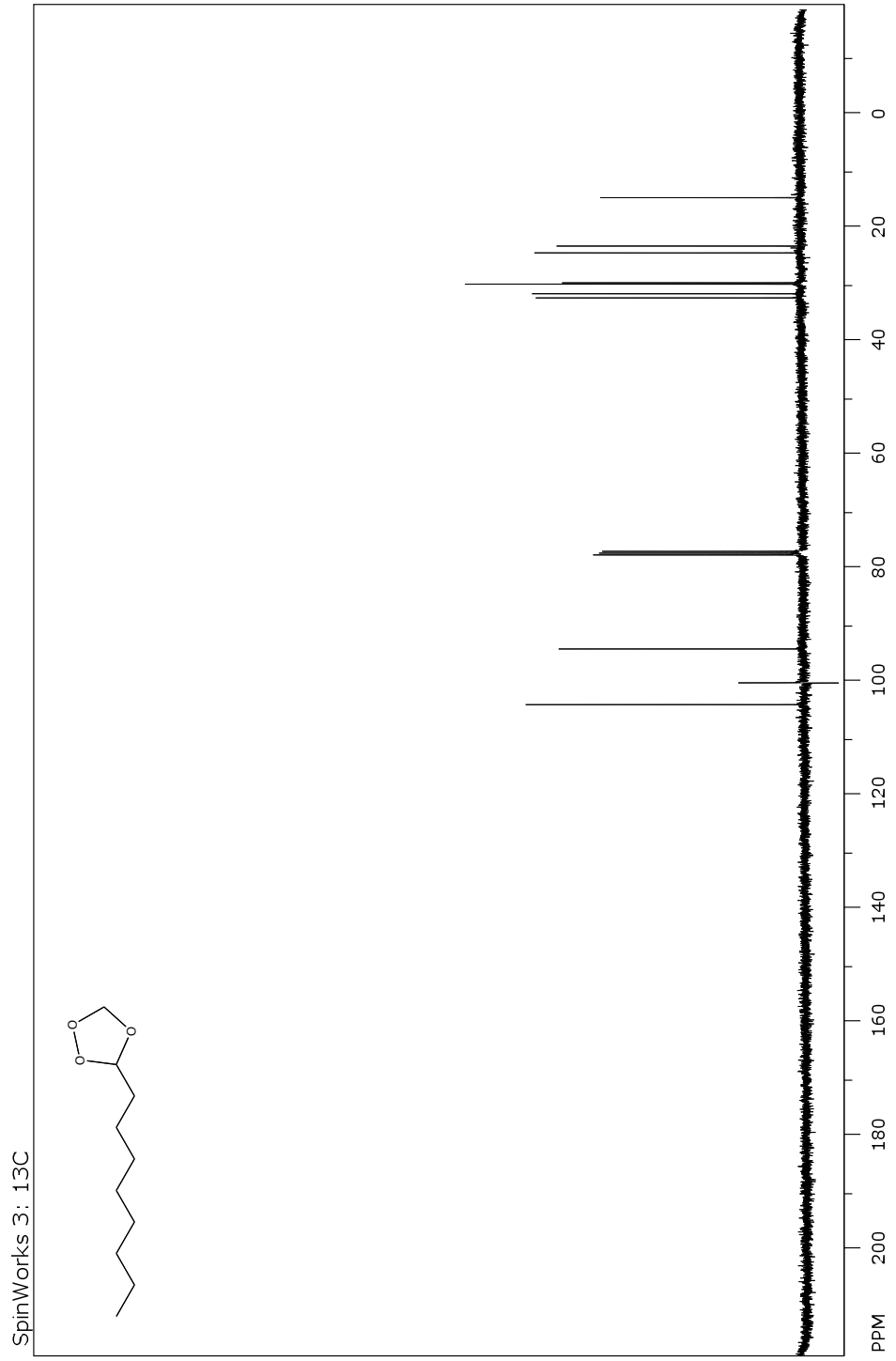

SpinWorks 3: 1D Proton
OOH
O
Ph
0.921
5.256
1.000
1.002
0.970
6.669
2.411
PPM 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4
file:...\Brad NMR\Notebook 2\BJ-2-64\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.5671 ppm = 0.094190 Hz/pt
number of scans: 16
freq. of 0 ppm: 300.130000 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 103.039 ppm/cm: 0.34331

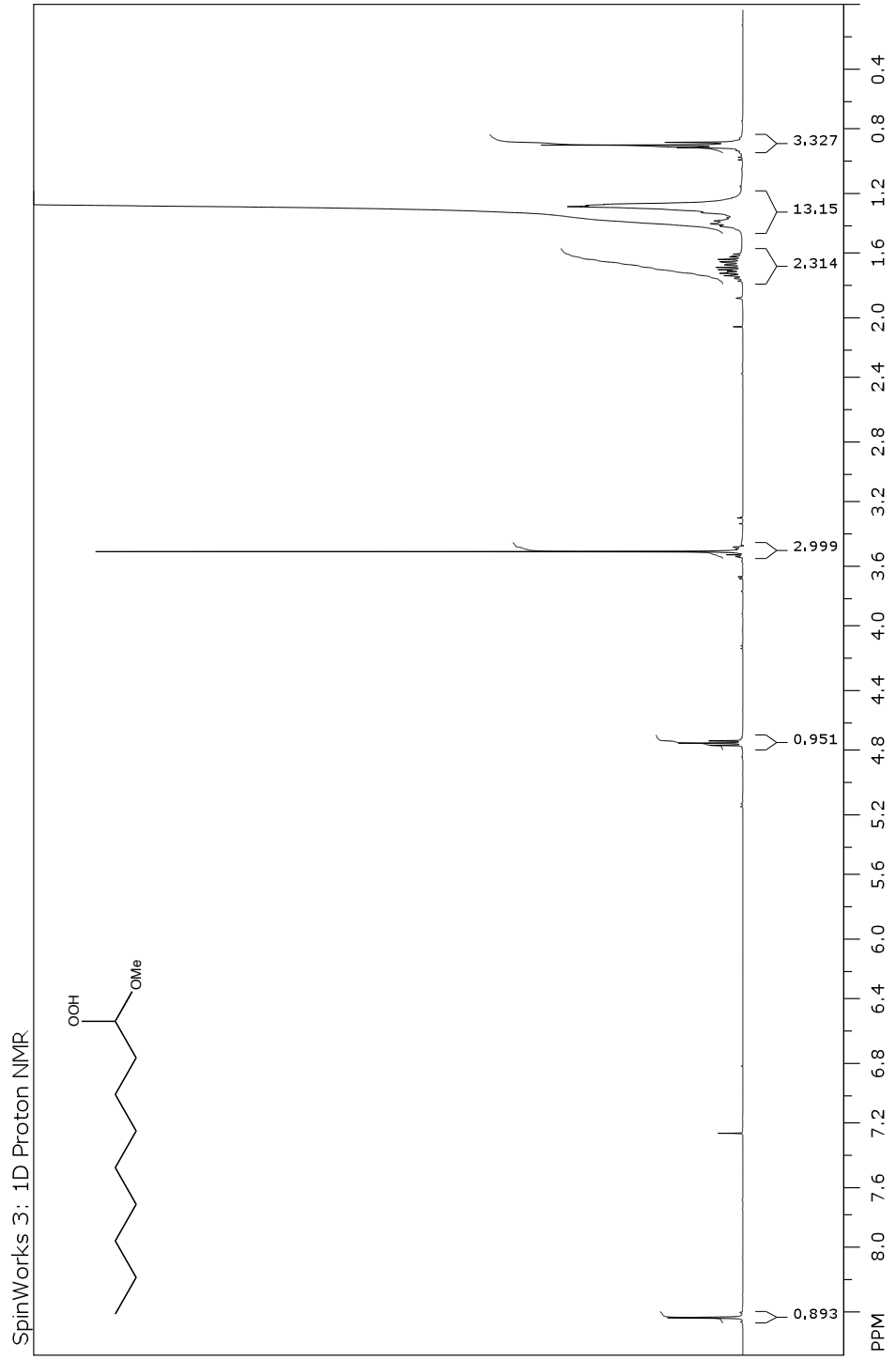

SpinWorks 3: 13C
OOH
O
Ph
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...\Brad NMR\Notebook 2\BJ-2-64\2\fid expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 32768 points
width: 17985.61 Hz = 238.2980 ppm = 0.548877 Hz/pt
number of scans: 67
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 719.424 ppm/cm: 9.53192

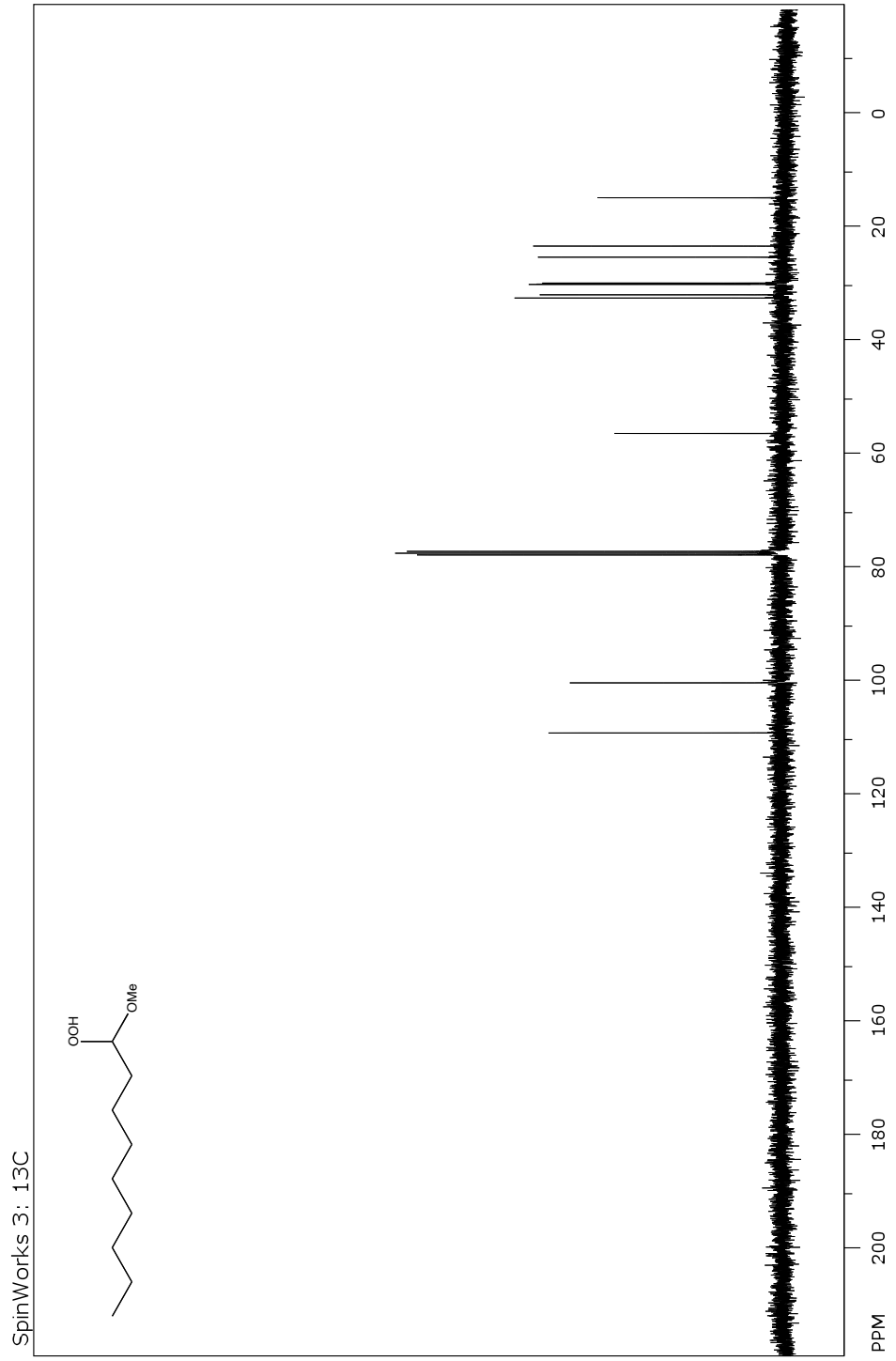

SpinWorks 3: 1D Proton NMR
OMe
Ph
6.452
0.992
3.021
3.160
1.000
1.002
0.944
1.012
0.925
10.13
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
file:...tebook 2\BJ-2-37(lower spot)\1\fid expt: <zg30>
transmitter freq.: 600.182706 MHz
time domain size: 65536 points
width: 12376.24 Hz = 20.6208 ppm = 0.188846 Hz/pt
number of scans: 16
freq. of 0 ppm: 600.179000 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 186.227 ppm/cm: 0.31028

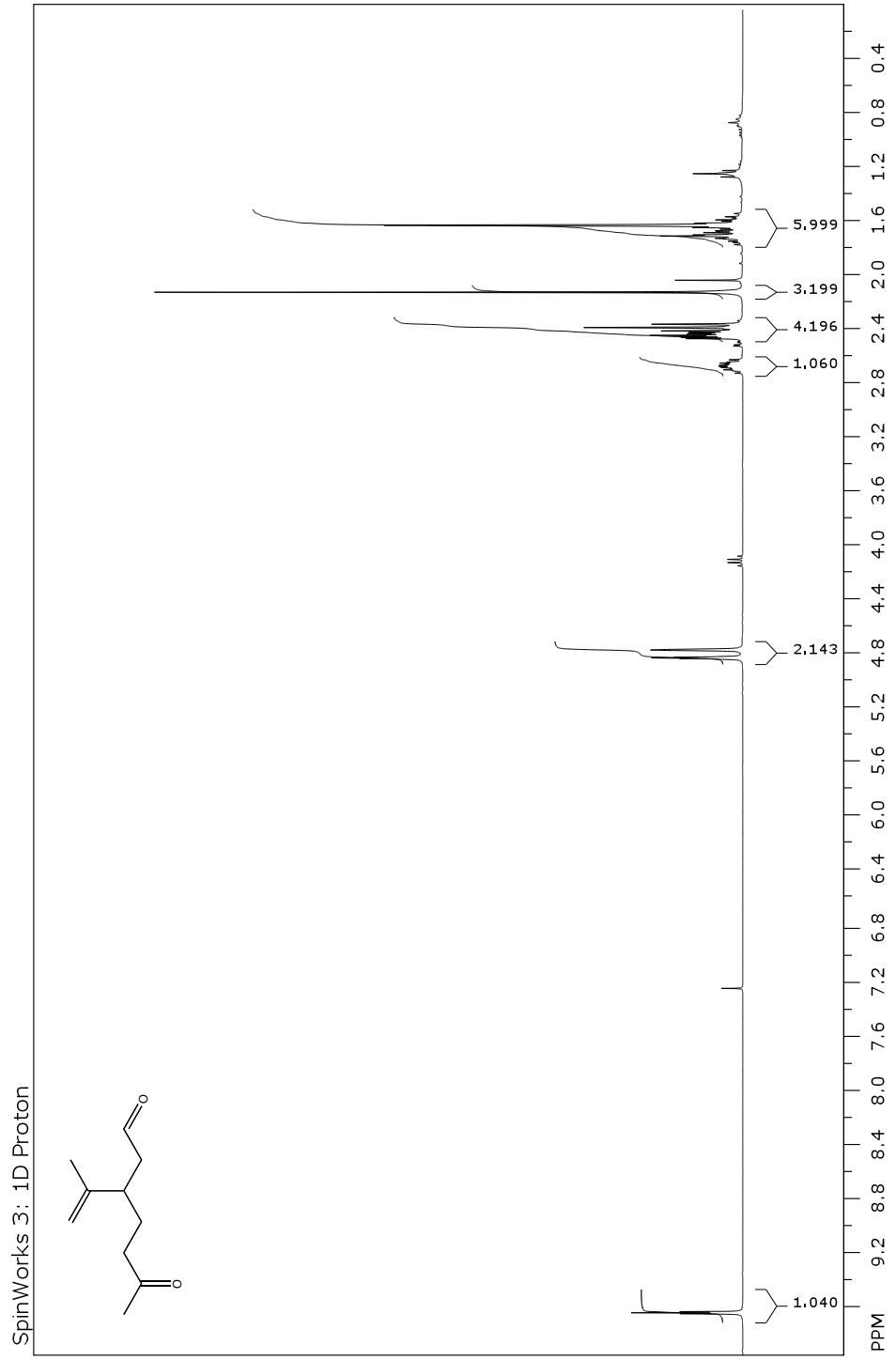

SpinWorks 3: 13C NMR
OMe
Ph
PPM
200
180
160
140
120
100
80
60
40
20
0
file:...tebook 2\BJ-2-37(lower spot)\2\fid expt: <zgpg30>
transmitter freq.: 150.930221 MHz
time domain size: 65536 points
width: 35971.22 Hz = 238.3302 ppm = 0.548877 Hz/pt
number of scans: 40
freq. of 0 ppm: 150.915108 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 1438.849 ppm/cm: 9.53321

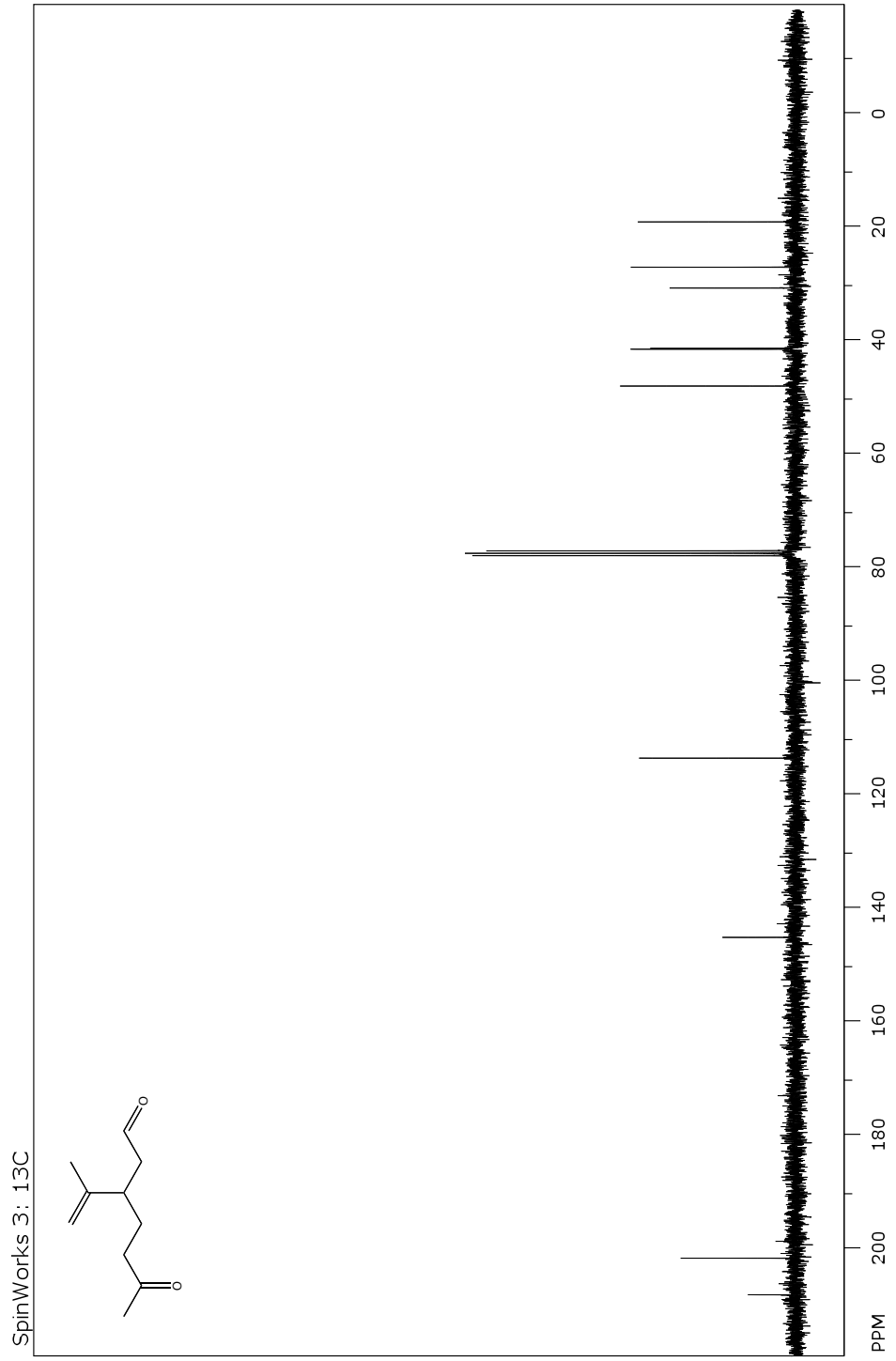

SpinWorks 3: 1D Proton NMR
PPM
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
3.000
12.93
2.034
0.906
0.925
0.918
file:...R\Notebook 2\BJ-2-17(column)\1\fid expt: <zg30>
transmitter freq.: 400.132471 MHz
time domain size: 65536 points
width: 8278.15 Hz = 20.6885 ppm = 0.126314 Hz/pt
number of scans: 16
freq. of 0 ppm: 400.130005 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 122.292 ppm/cm: 0.30563

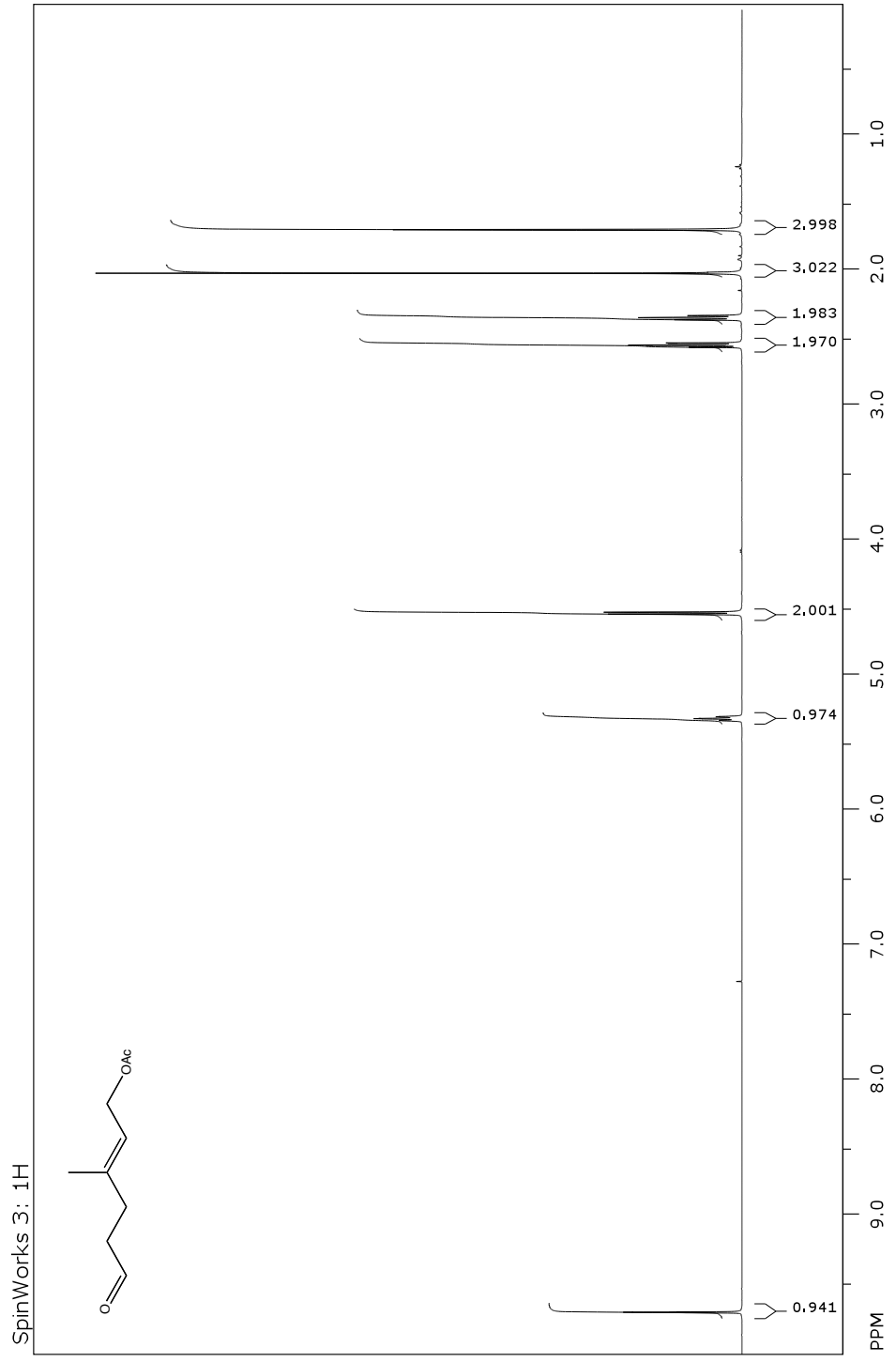

SpinWorks 3: 13C
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...R\Notebook 2\BJ-2-17(column)\2\fid expt: <zgpg30>
transmitter freq.: 100.622830 MHz
time domain size: 65536 points
width: 23980.82 Hz = 238.3238 ppm = 0.365918 Hz/pt
number of scans: 33
freq. of 0 ppm: 100.612748 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 959.233 ppm/cm: 9.53295

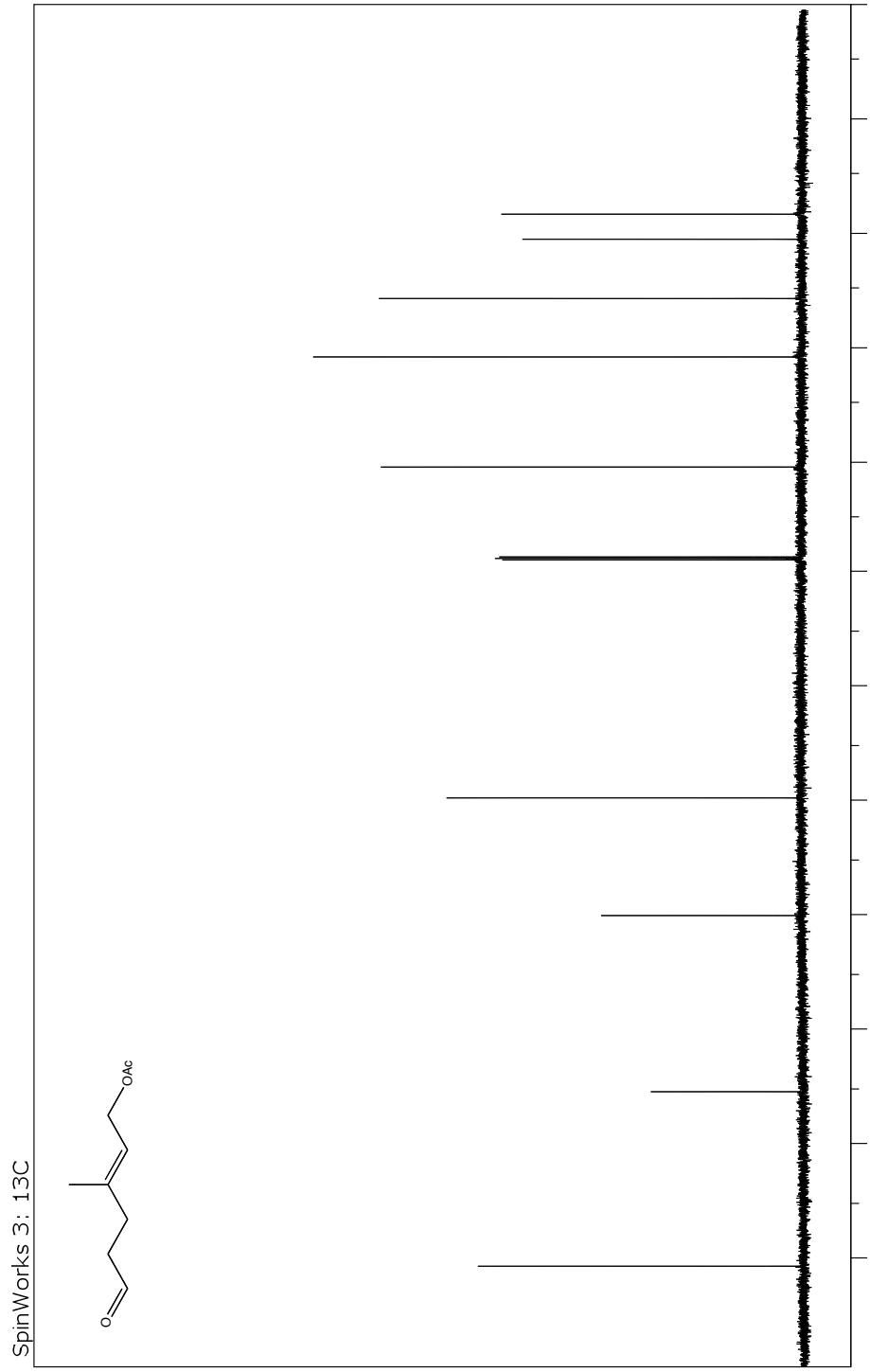

SpinWorks 3: 1D Proton NMR
OOH
OMe
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.893
0.951
2.999
2.314
13.15
3.327
file:...\Brad NMR\Notebook 2\BJ-2-19\1\fid expt: <zg30>
transmitter freq.: 400.132471 MHz
time domain size: 65536 points
width: 8278.15 Hz = 20.6885 ppm = 0.126314 Hz/pt
number of scans: 16
freq. of 0 ppm: 400.130005 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 139.317 ppm/cm: 0.34818

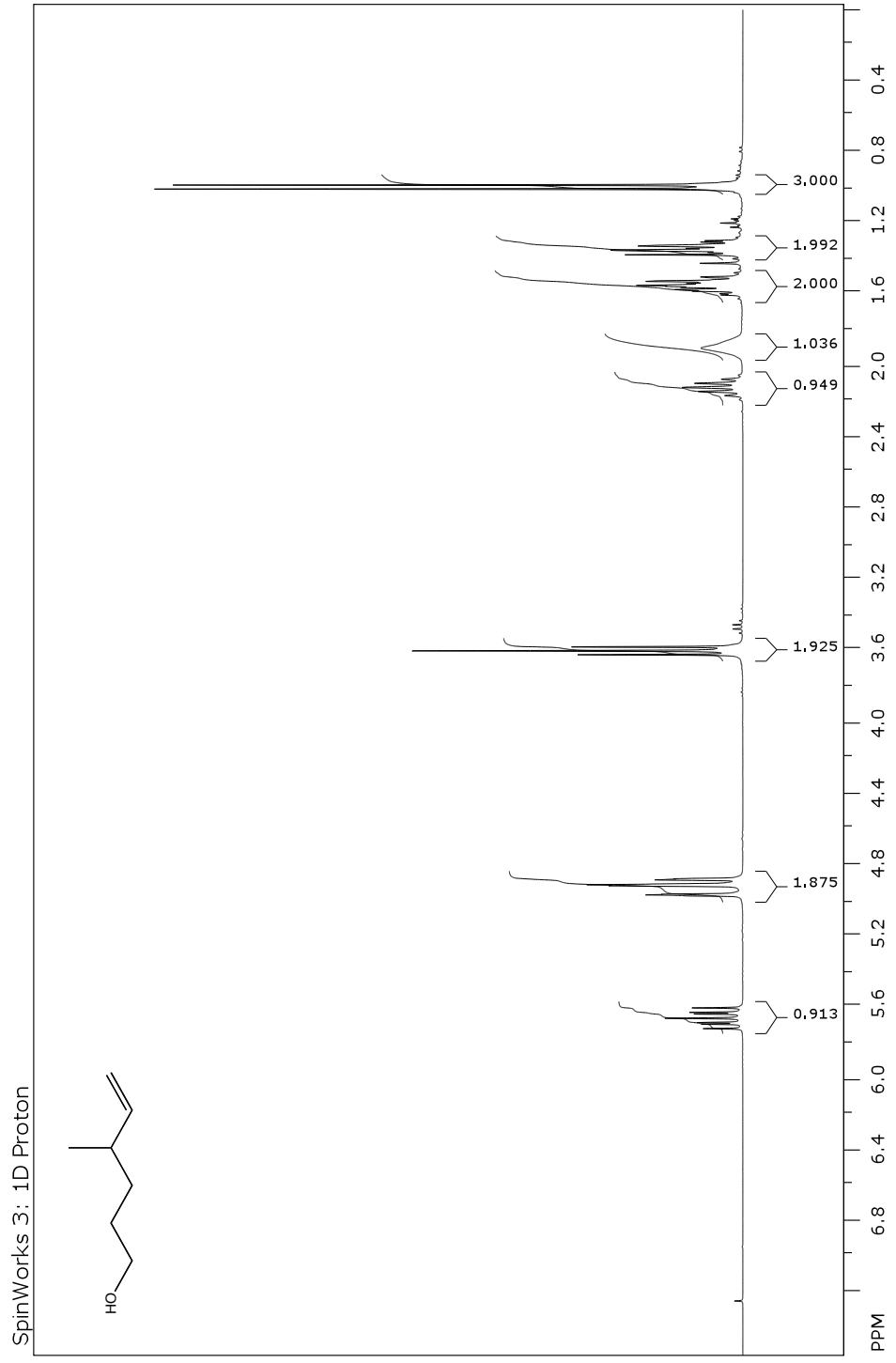

SpinWorks 3: 13C
OOH
OMe
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...\Brad NMR\Notebook 2\BJ-2-19\2\fid expt: <zgpg30>
transmitter freq.: 100.622830 MHz
time domain size: 65536 points
width: 23980.82 Hz = 238.3238 ppm = 0.365918 Hz/pt
number of scans: 29
freq. of 0 ppm: 100.612749 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 959.233 ppm/cm: 9.53295

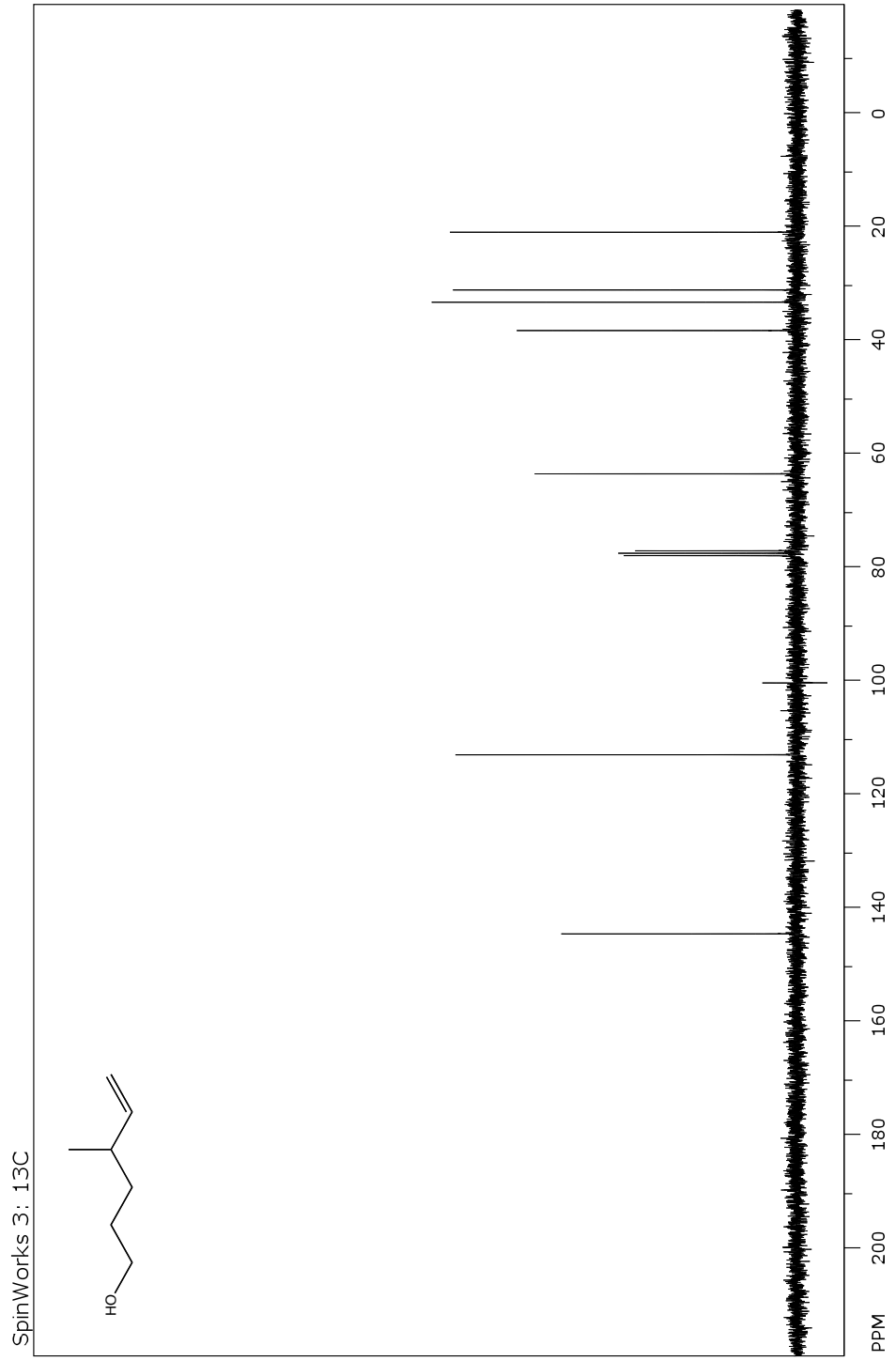

SpinWorks 3: 1D Proton
PPM
9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4
1.040
2.143
1.060
4.196
3.199
5.999
file:...tebook 2\BJ-2-88(blue-green)\1\fid expt:<zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.5671 ppm = 0.094190 Hz/pt
number of scans: 16
freq. of 0 ppm: 300.130003 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 119.331 ppm/cm: 0.39760

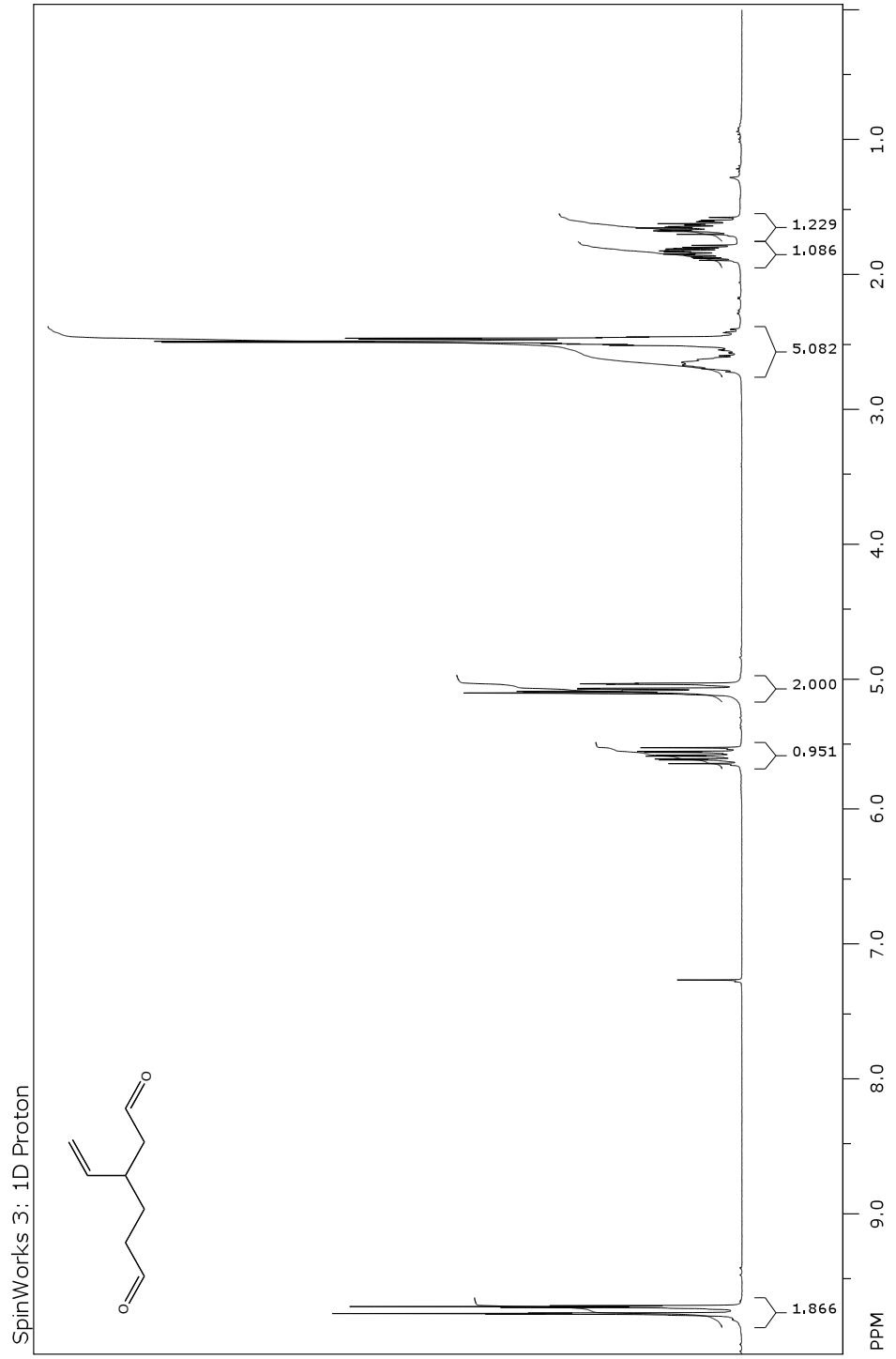

SpinWorks 3: 13C
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...tebook 2\BJ-2-88(blue-green)\2\fid expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 32768 points
width: 17985.61 Hz = 238.2980 ppm = 0.548877 Hz/pt
number of scans: 57
freq. of 0 ppm: 75.467735 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 719.424 ppm/cm: 9.53192

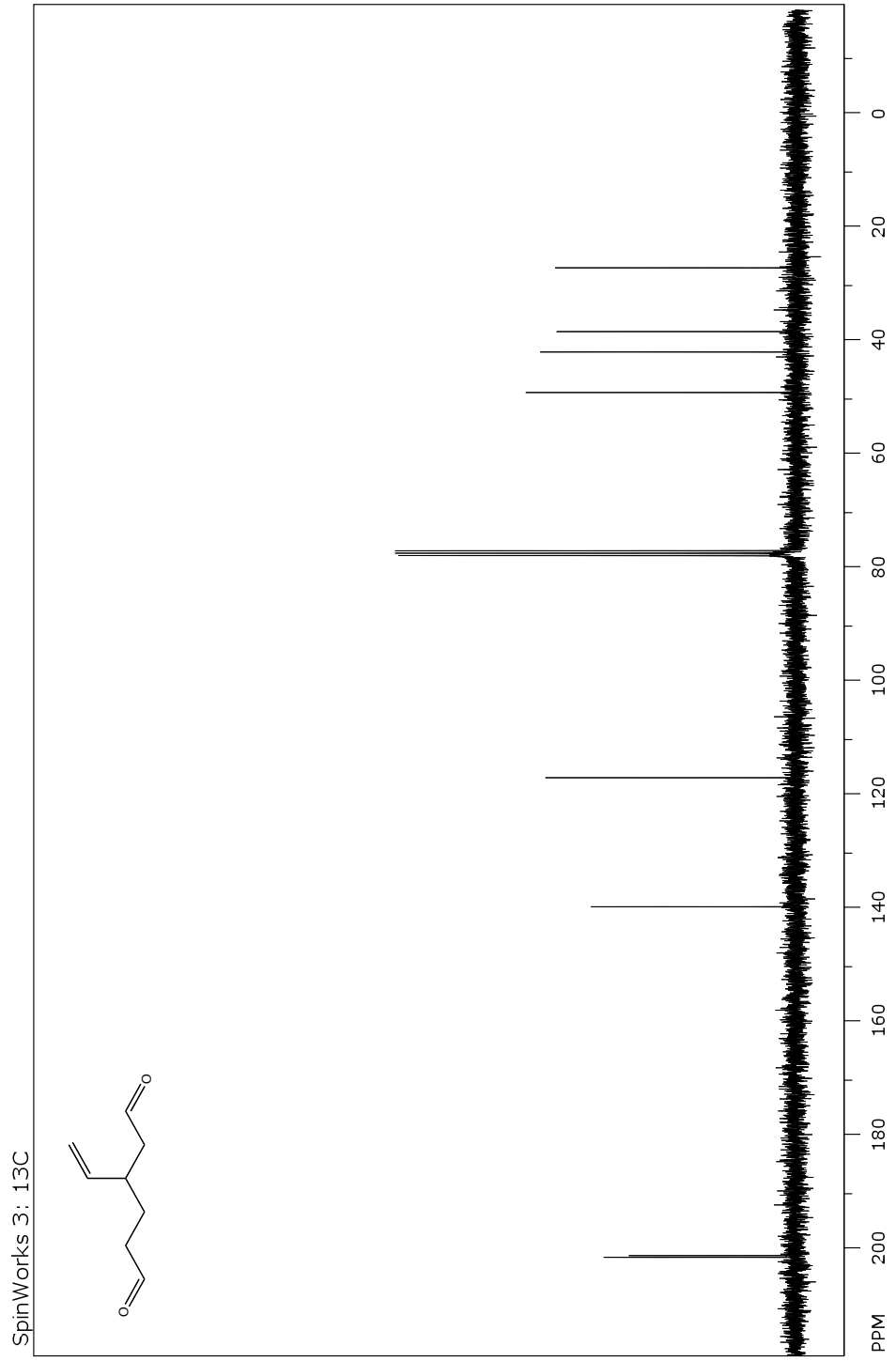

SpinWorks 3: 1H
OAc
O
2.998
3.022
1.983
1.970
2.001
0.974
0.941
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
file: ...p\Brad NMR\Notebook 3\BJ-3-2\1\fid expt: <zg30>
transmitter freq.: 500.133089 MHz
time domain size: 65536 points
width: 10330.58 Hz = 20.6557 ppm = 0.157632 Hz/pt
number of scans: 16
freq. of 0 ppm: 500.130008 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 200.061 ppm/cm: 0.40002


SpinWorks 3: 13C
OAc
O
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...p\Brad NMR\Notebook 3\BJ-3-2\2\fid expt: <zgpg30>
transmitter freq.: 125.770364 MHz
time domain size: 65536 points
width: 30030.03 Hz = 238.7687 ppm = 0.458222 Hz/pt
number of scans: 26
freq. of 0 ppm: 125.757774 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 1201.201 ppm/cm: 9.55075


SpinWorks 3: 1D Proton
HO
PPM
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.913
1.875
1.925
0.949
1.036
2.000
1.992
3.000
file:...Brad NMR\Notebook 3\BJ-3-17B\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 32768 points
width: 5995.20 Hz = 19.9752 ppm = 0.182959 Hz/pt
number of scans: 16
freq. of 0 ppm: 300.130003 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 91.033 ppm/cm: 0.30331


SpinWorks 3: 13C
HO
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...Brad NMR\Notebook 3\BJ-3-17B\2\fid expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 32768 points
width: 17985.61 Hz = 238.2980 ppm = 0.548877 Hz/pt
number of scans: 19
freq. of 0 ppm: 75.467734 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 719.424 ppm/cm: 9.53192


SpinWorks 3: 1D Proton
O
O
1.866
0.951
2.000
5.082
1.086
1.229
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
file: ...\Brad NMR\Notebook 3\BJ-3-18\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 32768 points
width: 5995.20 Hz = 19.9752 ppm = 0.182959 Hz/pt
number of scans: 16
freq. of 0 ppm: 300.130003 MHz
processed size: 32768 complex points
LB: 0.300 GF: 0.0000
Hz/cm: 121.034 ppm/cm: 0.40327


SpinWorks 3: 13C
O
O
PPM
200
180
160
140
120
100
80
60
40
20
0
file: ...\Brad NMR\Notebook 3\BJ-3-18\2\fid expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 32768 points
width: 17985.61 Hz = 238.2980 ppm = 0.548877 Hz/pt
number of scans: 92
freq. of 0 ppm: 75.467734 MHz
processed size: 32768 complex points
LB: 1.000 GF: 0.0000
Hz/cm: 719.424 ppm/cm: 9.53192