Fuctionalized Alkyl Quinolines: Synthesis and Characterization

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at George Mason University.

By

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DEDICATION

This thesis is dedicated to my parents, John and Barbara Dripps. Especially to my mother who has read so many drafts of my chemistry papers and even though she has no background in chemistry she has come so far to understanding what is being said.

ACKNOWLEDGEMENT

The author wishes to thank her advisor, Dr. Robert V. Honeychuck for his guidance throughout this research and for taking her on as an undergraduate and helping her get this far. Thanks for the advice on doctorial school and for our conversations. The author also wants to thank the Department of Chemistry and Biochemistry at George Mason University, especially to Mery Tucker for being there to talk to while reactions were running and being the post we can lean on when classes, research, and teaching became stressful. Also, to Dr. David Kort for being entertaining to go talk to when a break was needed and for being a sounding board when one was needed.

Dr. Paulette W. Royt of George Mason University's Department of Molecular and Microbiology that grew the researcher's group toward this topic of the biochemistry of *Pseudomonas aeruginosa*.

Finally, thanks to my parents, John N. Dripps and Barbara B. Dripps, for their money that paid all my years of tuition, housing, gas, insurance, food, and recreation, I love you guys and you made the college experience amazing. Thanks for your everlasting love and encouragement and for standing beside me with your support, even when you do not agree. Do not worry brother, I did not forget you. Thanks to my brother, J. David Dripps. For fighting with me, teasing me, and helping to make me the person I am today. One day you will do great things, and I will be there to support you. I love all of you and would not be writing this today without you!

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LIST OF ABBREVIATIONS

HAQ(s)	4-hydroxy-2-alkylquinoline(s)
HQNO	4-hydroxy-2-alkylquinoline N-oxide
PQS	Pseudomonas Quinolone Signal
n-BuLi	*n*-Butyllithium
THF	Tetrahydrofuran
NMR	Nuclear Magnetic Resonance
^{1}H	Proton
^{13}C	Carbon-13
CPD	Composite Pulse Decoupled
IR	Infrared Spectroscopy
DEPT	Distortionless Enhancement by Polarization Transfer
$CDCl_3$	Deuterated Chloroform
DMSO-d_6	Dimethylsulfoxide-d_6
Unisol	50:50 $CDCl_3$:DMSO-d_6
TLC	Thin Layer Chromatography

ABSTRACT

FUNCTIONALIZED ALKYL QUINOLINES: SYNTHESIS AND CHARACTERIZATION

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Thesis Director: Dr. Robert V. Honeychuck

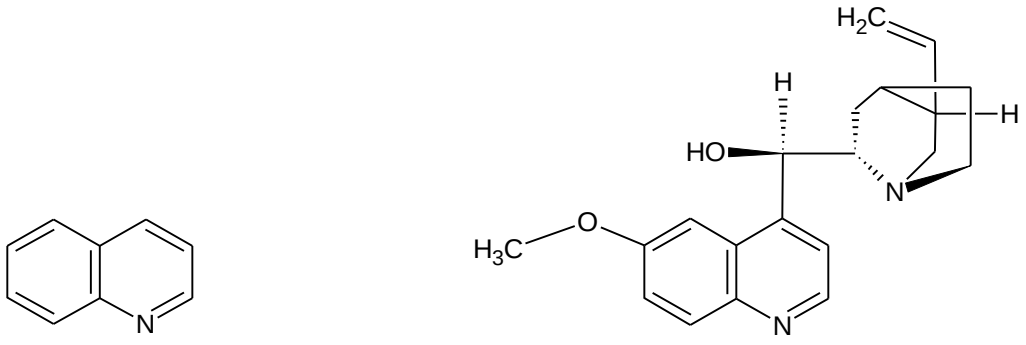
Novel syntheses using 4-methoxy-2-methylquinoline were attempted by using a strong base to remove the most acidic proton, one of the protons of the methyl in the 2-position, to generate a carbanion. Upon the introduction of a halide with an electrophile, the electrophile will attack the carbanion where the proton was removed in an SN2 reaction to make a new compound. The methods for how this type of reaction was tried were attempted temperatures and bases are described.

The DEPT-90 and 135 of 4-methoxy-2-methylquinoline were run, analyzed and the spectra are given. The DEPT spectra for this compound constitute a new contribution to the reference information for 4-methoxy-2-methylquinoline.

1. Background

1.1 Quinolines used in Pharmaceuticals

Quinolines **(1)** originate from quinine **(2)**, which can be extracted from *Cinchona* bark.[1] It is believed that plants have evolved to produce these chemicals to protect themselves from predators. Quinolines are commonly used today as pesticides, herbicides, pharmaceuticals (antimalaria drug), and preservatives. Originally extracted from coal tar in 1834 by Friedlieb Ferdinand Runge, quinolines have become important molecules in producing pharmaceuticals.[2] Both the synthetic and natural substituted quinolines are sought for use with pharmaceuticals, and used to achieve different uses such as a malaria drug.[2] Synthesis of quinolines, and their derivatives, have been of considerable interest to organic and medicinal chemists, because many natural drugs contain a heterocyclic core.[3] The major use of quinolines in medicine, is as a precursor to 8-hydroxyquinoline, an iron chelator.



(1) **(2)**

Figure 1: Quinoline **(1)** and Quinine **(2)**

The name "Pseudans" is often given to quinolines such as 4-hydroxy-2-alkylquinoline **(3)**, because they are found in bacteria of the genus Pseudomonas.[4] Pseudans have generated a considerable amount of medical interest. It is believed that these iron binding agents can conceivably be used in pharmaceuticals to reduce high levels of iron in the body. In particular, the pseudans with long chains may be attached in various regions of the body with high iron levels. This has led to our team to synthesizing pseudans with carbon chains of varying lengths at the 2-position.

1.2 4-Hydroxy-2-alkylquinoline (3)

The broad-host opportunistic pathogen, *Pseudomonas aerugino,* is a gram-negative bacterium. It is a major cause of debilitating bacterial infections in immune compromised and cystic fibrosis patients, and individuals with severe burns.[5] Bronchial infections due to *Pseudomonas aeruginosa,* lead to a deterioration in respiratory function and clinical conditions such as cystic fibrosis.[6] All of the clinical conditions lead to with

early mortality. The iron chelator of *Pseudomonas aeruginosa* has been extracted from the membranes of iron-rich cells, and the structures of the chelators have been determined to be 4-hydroxy-2-nonylquinoline and 4-hydroxy-2-heptylquinoline, HAQ **(3)**.[3] These HAQs belong to a family of antimicrobial *Pseudomonas aeruginosa* products.[3]

Wells was the first to describe HAQs in 1952, and included three bacteriostatic compounds containing either a C_7, C_9, or a monounsaturated C_9 side chain, at the 2 position (Figure 2).[6] Another series of HAQs, was subsequently discovered, that has an *N*-oxide group in place of the quinoline nitrogen, and the C_7 (HQNO, **4**) or a C_9 alkyl chain.[5] Large amounts of HAQs are produced in high iron environments, and their functions are not fully understood. This may be the result of sequestering excess iron, which is toxic to the bacterium. These HQNOs have antibiotic activity and have been shown to prevent growth of Gram-positive bacteria, and to be active against most strains of *Staphylococcus aureus* including those resistant to methicillin.[3,5] Gram-positive bacteria has a thinner cell wall with two distinct layers. One of those layers is an outer membrane. Gram-positive bacteria has typically does not have an outer membrane and contain large amounts of peptidoglycan.

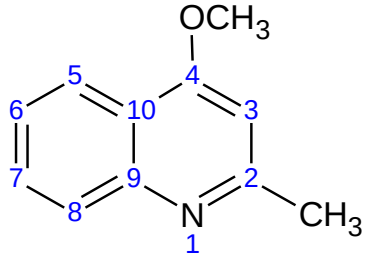
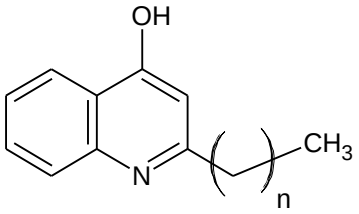
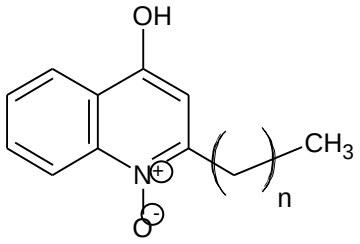


Figure 2: Quinoline Numbering System



n = 6

(3)



n = 6

(4)

Figure 3: 4-hydroxy-2-alkylquinoline **(3)**
and 2-heptyl-4-hydroxyquinoline *N*-oxide **(4)**

In nature, most bacteria live as a pseudo multicellular organism that coordinates its population behavior by small extracellular signal molecules.[7] Since intercellular communication leads to cooperative and coordinated bacterial behavior in a cell density-dependent manner, it is referred to as quorum sensing, the regulation of gene expression in response to fluctuations in cell-population density.[8,11] Quorum sensing bacteria produce and release chemical signal molecules called *autoinducers*, that increase in concentration as a function of cell density.[8] This regulation allows all the cells to behave as a community to achieve the best results.[9] Another HAQ, 3,4-dihydroxy-2-heptylquinoline, first identified in 1959, was later named the "Pseudomonas quinolone signal" (PQS), when it was recognized to participate in quorum sensing.[5] PQS is found in the lungs of cystic fibrosis patients, indicating that *Pseudomonas aeruginosa* uses quorum sensing in this type of infection.[5] A quorum sensing molecule associated with *Pseudomonas aeruginosa,* has been identified as a transcriptional regulator which is

required for the regulation of secreted compounds, including 3,4-dihydroxy-2-heptylquinoline.[10]

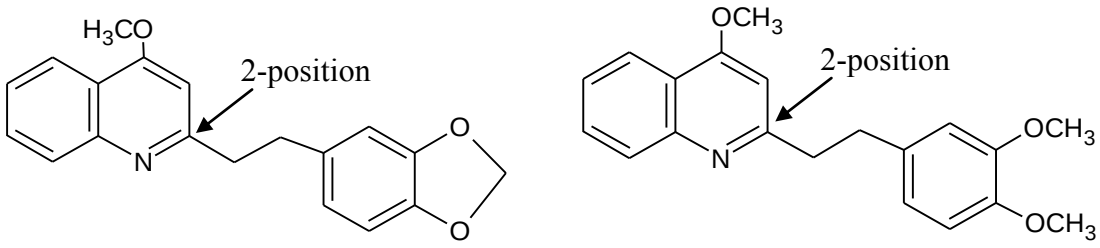
There is a growing concern that multiresistant pathogenic bacteria are emerging, and will gradually render antimicrobial treatment ineffective.[11] Therefore, an urgent need for new approaches to treat bacterial infections has emerged. Cell-to-cell signals have been recognized as promising targets for alternative therapeutic strategies, that decrease bacterial virulence, as significant amounts of signal molecules have been detected at sites of infection in vivo.[11]

1.3 4-Methoxyquinoline Substituted at the 2-Position

Only a few 2-alkyl and 2-aryl-4-methoxyquinolines are known to occur in nature.[18] A main compound in this research, 4-Methoxy-2-alkylquinolines, comes from the bark of a tree in the family *Rutaceae*, the same plant family as 4-hydroxy-2-alkylquinolines are found. About four alkaloids are found in the bark of trees in the family *Rutaceae*. One such tree, Angostura, is commonly used for extractions. The two most well known alkaloids extracted from the bark are cusparine (5), galipine (6).[15] The bark also contains an ethereal oil and a glucoside.

Angostura is a medical plant native to South America, and found in the most abundance in Venezuela. Discovered as a medicine by Johann Siegert in 1824, angostura bitters were originally used to cure fevers and internal stomach disorders.[13] Other names for the angostura tree are *Cusparia*, *Carony*, *Cusparia febrifuga*, or *Galipea cusparia.*[12] Cusparine **(5)** and galipine **(6)** (Figure 3) are the most abundant alkaloids discovered by

Korner and Bohringer, and are removed from the extract of the bark of the angostura tree.[12] Cusparine is the easiest of the alkaloids to isolate, and is used as a sympathomimetic and respiratory stimulant.[16] Cusparine and galipine, which are 4-methoxyquinolines with more complicated groups at the 2-position, have led researchers to look at 4-methoxyquinolines substituted at the 2-position for medicines, since cusparine and galipine are already being used.



(5) **(6)**

Figure 4: Cusparine **(5)** and Galipine **(6)**

1.3.1 Synthesis of 4-Methoxyquinoline Substituted at the 2-Position

There are several methods that can be used to create 4-methoxyquinolines.

1.3.1.1 Synthesis proposed by Clemo and Perkin

The quantitative formation of 4-methoxyquinoline from the chloro-derivative was proposed by Clemo and Perkin, and can be done by the reaction shown in Figure 4.[14] The toluenesulfonyl group is thought to migrate to the carbonyl oxygen atom with the

formation of a sulfonic ester, which then reacts with methyl-alcoholic potassium hydroxide.[14]

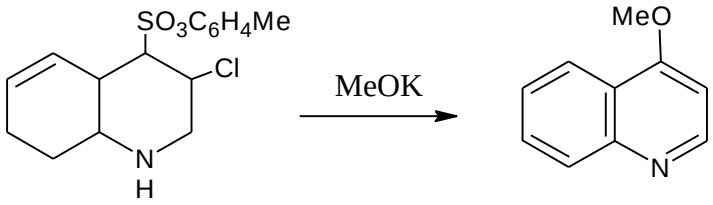


Figure 5: Synthesis Proposed by Clemo and Perkin

1.3.1.2 Friedlander Reaction

In the classic Friedlander quinoline synthesis, the reactant is an aromatic amine having a carbonyl in the *ortho*-position, and another carbonyl compound which contains at least two α-protons. The first step of the reaction is the formation of an enamine, this is followed by an aldol-type cyclization yielding the 2,3-disubstituted quinoline (Figure 5).[19]

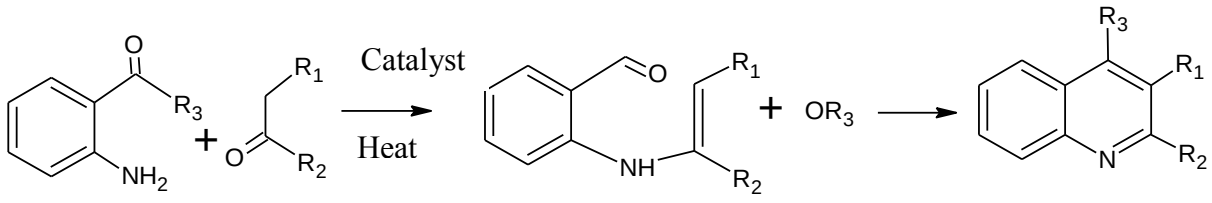


Figure 6: Friedlander Reaction

Two quinoline syntheses to the Friedlander reaction are the Pfitzinger reaction (Figure 6) and the Niementowski reaction, and can be considered as extensions of the Friedlander synthesis.[3,20] The Pfitzinger reaction uses an isatic acid, or isatin, and the Niementowski reaction uses an anthranilic acid for condensation.[20]

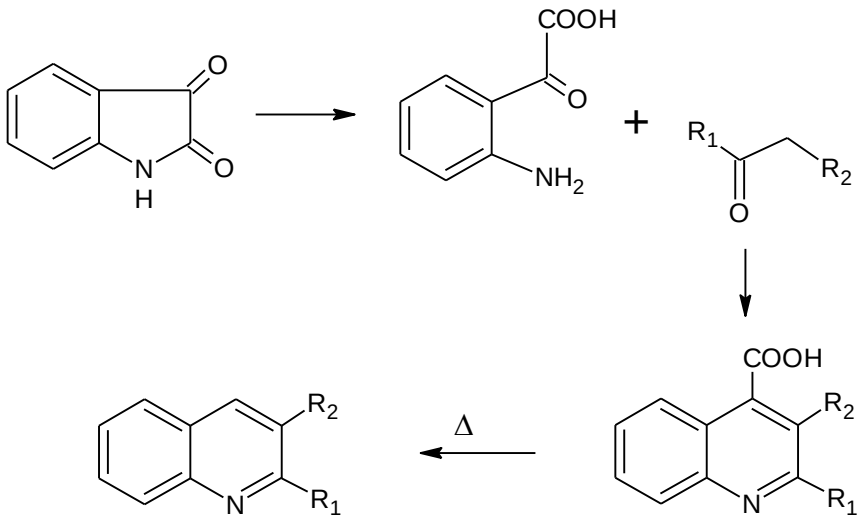


Figure 7: Pfitzinger Reaction

There is a simple and efficient method for the synthesis of 4-substituted quinolines. A one-pot reaction of anilines, with alkylvinylketones on the surface of silica gel with indium(III) chloride, under microwave irradiation for 5 minutes in the absence of any solvent (Figure 7).[3] A yield of 85% was reported.[3]

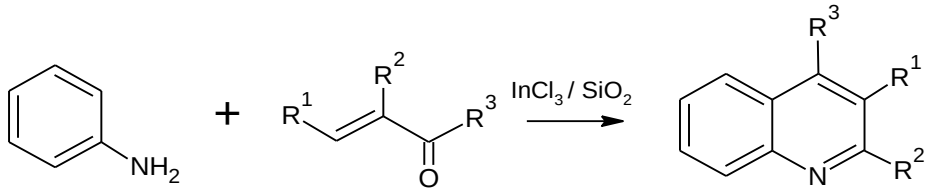


Figure 8: One-pot Synthesis for a 2-Substituted Quinoline

1.3.1.3 Combes Synthesis

The Combes quinoline synthesis forms quinolines by condensation of β-diketones with primary aryl amines, followed by acid-catalyzed ring closure of the intermediate Schiff base (Figure 8).[3]

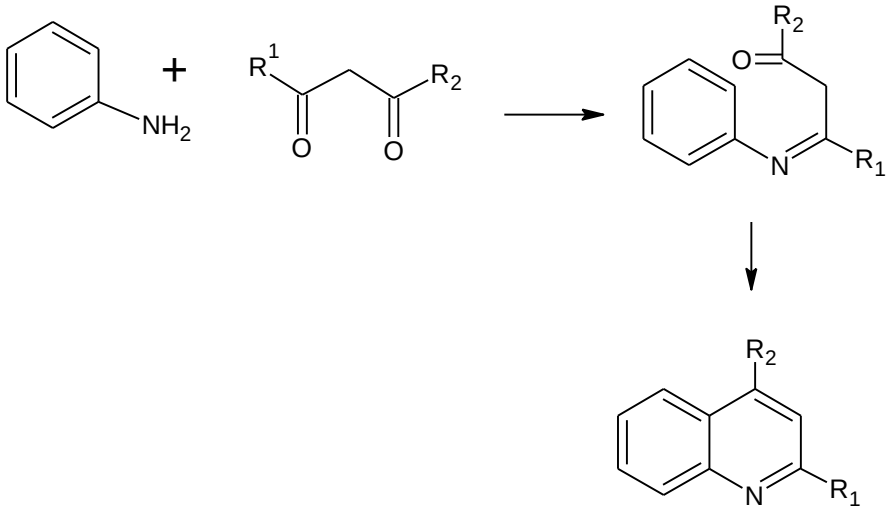


Figure 9: Combes Synthesis

1.3.1.4 Synthesis by Smith and Somanathan

Smith and Somanathan proposed a reaction (Figure 9) for 4-hydroxy-2-alkylquinoline. They started with a substituted β-ketoester, condensed with aniline, and followed by the cyclization of the formed Schiff's base.[18]

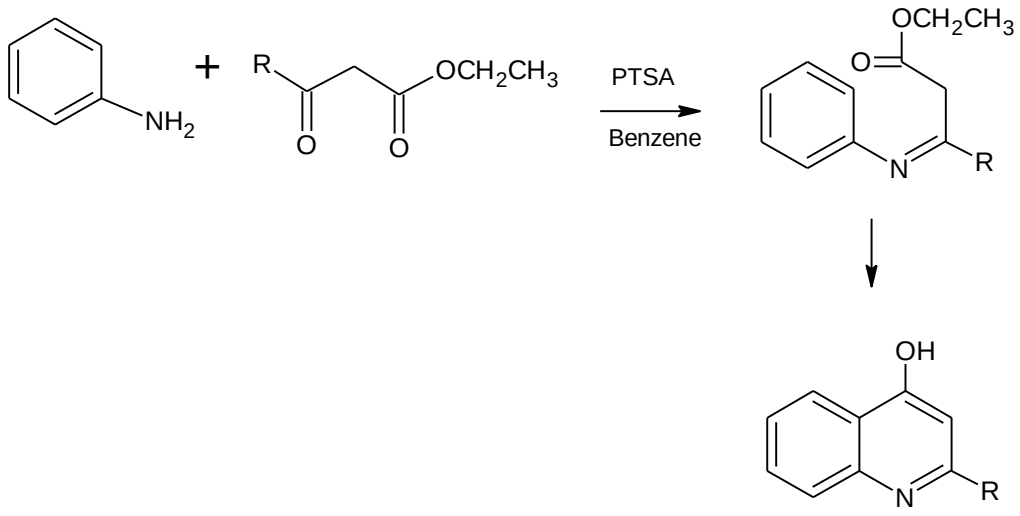
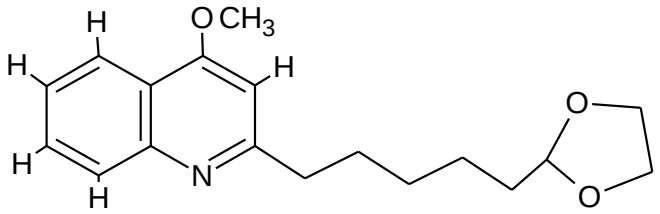


Figure 10: Synthesis by Smith and Somanathan

There are similarities between the synthesis proposed by Smith and Somanathan and the Combes Synthesis. However, the Combes Synthesis gives more freedom in the groups attached to the quinoline structure, and would allow a methoxy group to be attached in the 4-position on the quinoline instead of the hydroxyl group.

2. Objective

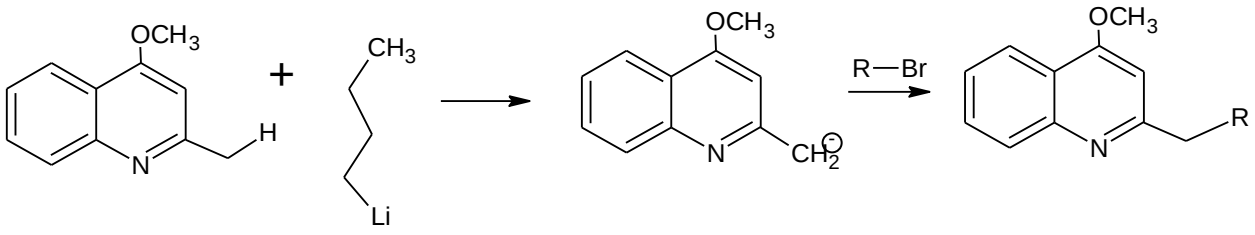
The purpose of this research was to functionalize 4-substituted quinolines at a position away from the quinoline ring system. This was done on a side chain at the 2-position. An S_N2 reaction was utilized to react a quinoline **(1)** anion with a bromoalkyldioxolane. The desired product was 2-[4-(1,3-dioxolan-2-yl)pentyl]-4-methoxyquinoline **(7)**.



(7)

Figure 11: 2-[4-(1,3-dioxolan-2-yl)pentyl]-4-methoxyquinoline **(7)**

It was proposed by Rogers that one might synthesize 4-methoxyquinolines substituted at the 2-position, by reacting 4-methoxy-2-methylquinoline **(8)** with a strong base such as *n*-butyllithium (Figure 11).[4] The base would remove one of the three equally acidic protons from the methyl group at the 2-position, generating a carbanion **(9)**.[4] Upon the introduction of a halide or some other electrophile, the carbanion would attack the electrophile, making a new 4-methoxyquinoline substituted at the 2-position.[4] This substitution allows for the attachment of the side chain to a solid structure, to later remove the ring system at the opposing end.



(8) **(9)**

Figure 12: Proposed Synthesis of 4-Methoxyquinolines
Substituted at the 2-Position

The ability of the human race to combat new strains of bacteria is constantly challenged. In order to provide an arsenal of molecules and/or materials to effectively fight resistant bacteria, new structures are constantly sought. Solid functional surfaces are becoming more important in the sensing field, as they can provide a method of determining of analytes, both in air and in human fluids. The molecules made will be attached to a solid surface to test the structures ability to repel or kill bacteria.

3. Discussion

3.1 Synthesis of 4-Methoxy-2-Methylquinoline at the 2-Position

Details of the performed reactions may be found in Section 5. The three protons on the methyl group are equally acidic and the most acidic protons of 4-methoxy-2-methylquinoline. The method of using a strong base, proposed by Rogers, was utilized in this research. Methylene chloride was used along with water in the workup to keep conditions basic.

3.1.1 Synthesis with *n*-Butyllithium

3.1.1.1 Synthesis with *n*-Butyllithium and Tetrahydrofuran at Constant Temperature

Glassware was cleaned and dried in an oven, then placed in a dessicator to cool to room temperature while remaining dry. *n*-BuLi and tetrahydrofuran are very sensitive to the water in the air. The reactions were run under nitrogen gas, and the reagents were injected via a syringe through rubber septa. The reagents were constantly mixed during the reaction by a magnetic stirring bar. The base was added to a stirring solution of 4-methoxy-2-methylquinoline **(8)** and THF. After stirring for ten minutes, 2-(4-bromobutyl)-1,3-dioxolane **(10)** was added and allowed to react for 1 to 2 hours. The reaction was quenched with water and methylene chloride. The organic layer was separated from the aqueous layer with a separtory funnel. Then the organic layer was dried over magnesium sulfate, filtered, and the solvent was removed (Figure 13).

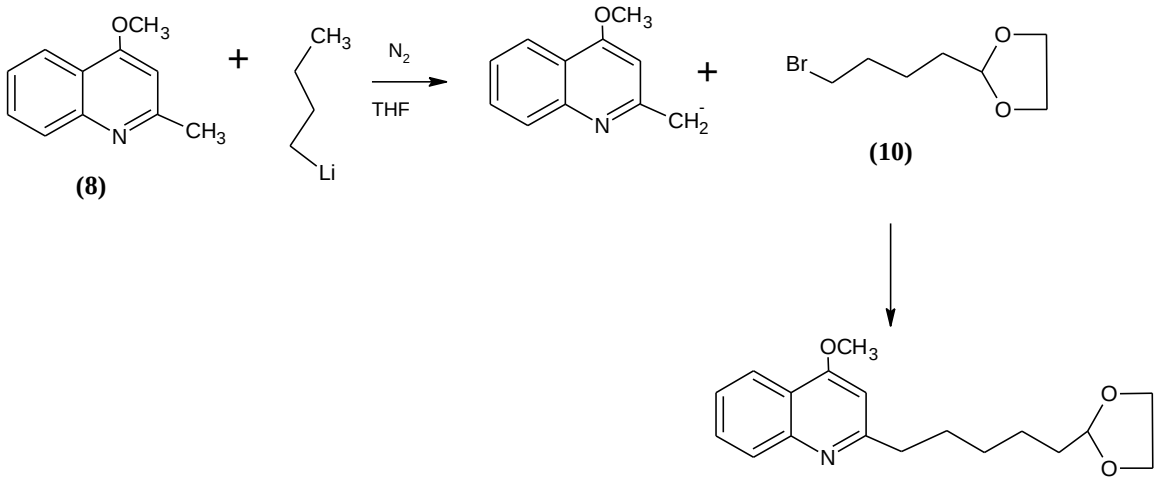


Figure 13: Synthesis with *n*-BuLi and THF

Once dry, the purification of the residue was attempted with a CombiFlash sg100. A 4g column of normal phase silica gel was used. The computer was set to control the solvent gradient by first starting with pure hexanes, and gradually adding pure ethyl acetate while slowly removing the hexanes, to end with pure ethyl acetate. This method of purification did not separate the multiple compounds in the residue.

Thin layer chromatography was used to separate the residue with a solvent of 80% methylene chloride and 20% hexanes. The residue was allowed to run up the silica plates of 0.1 mm depth to reveal the separation of the compounds within the residue. The plates were looked at under low wavelength ultraviolet light to show the separated compounds. Each compound was removed from the plates via scrapings and kept separate. Then the compounds were removed from the silica by filtration and methylene chloride. The methylene chloride was allowed to evaporate, leaving just the compound. The various attempts of this reaction with the controlable variables are listed in Table 1.

Table 1: Comparison of *n*-BuLi Syntheses

Temperature of Reaction	Reaction Time	Amounts:			
		2-(4-bromobutyl) -1,3-dioxolane	THF	4-methoxy-2-methylquinoline	*n*-BuLi
-78°C	1 hr	0.065 g	5 mL	0.050 g	0.11 mL
	2 hr	0.065 g	5 mL	0.050 g	0.10 mL
0°C	1 hr	0.065 g	5 mL	0.050 g	0.10 mL
	2 hr	0.065 g	5 mL	0.050 g	0.12 mL
20°C	1 hr	0.065 g	5 mL	0.050 g	0.11 mL
	2 hr	0.066 g	5 mL	0.050 g	0.10 mL

The NMR spectra of the six residues formed were run and, all showed peaks that were consistent with the peaks found on the NMR spectra of 4-methoxy-2-methylquinoline and 2-(4-bromobutyl)-1,3-dioxolane. By comparing the NMR spectra of the residues to the NMR spectra of the two starting compounds, it can be the residues from these reactions were the two original starting compounds.

3.1.1.2 Synthesis with *n*-Butyllithium and Toluene

THF was not used in this experiment instead toluene was used in an attempt to protect the methoxy group. The *n*-BuLi could have been attacking the methoxy group leading to a substitution at the 4-position on the quinoline ring, which would have explained why the desired product was not achieved. Toluene was used to prevent an S_N2 reaction with the methoxy group because toluene is less polar than THF. A reaction

at the 4-position with THF was not the case, because even with toluene the methyl group was not attacked.

Glassware was cleaned and dried in an oven, then placed in a dessicator to cool to room temperature while remaining dry. The reactions were run under nitrogen gas, and the reagents were injected via a syringe through rubber septa. The reagents were constantly mixed during the reaction by a magnetic stirring bar. *n*-BuLi was added to the 4-methoxy-2-methylquinoline that already contained toluene. After stirring for ten minutes and allowing the reaction to cool down to -78°C, 2-(4-bromobutyl)-1,3-dioxolane was added and allowed to react for 30 minutes. The mixture was then allowed to warm to room temperature. The reaction was quenched with water and methylene chloride. The organic layer was separated from the aqueous layer with a separtory funnel. Then the organic layer was dried over magnesium sulfate, filtered, and the solvent was removed (Figure 14).

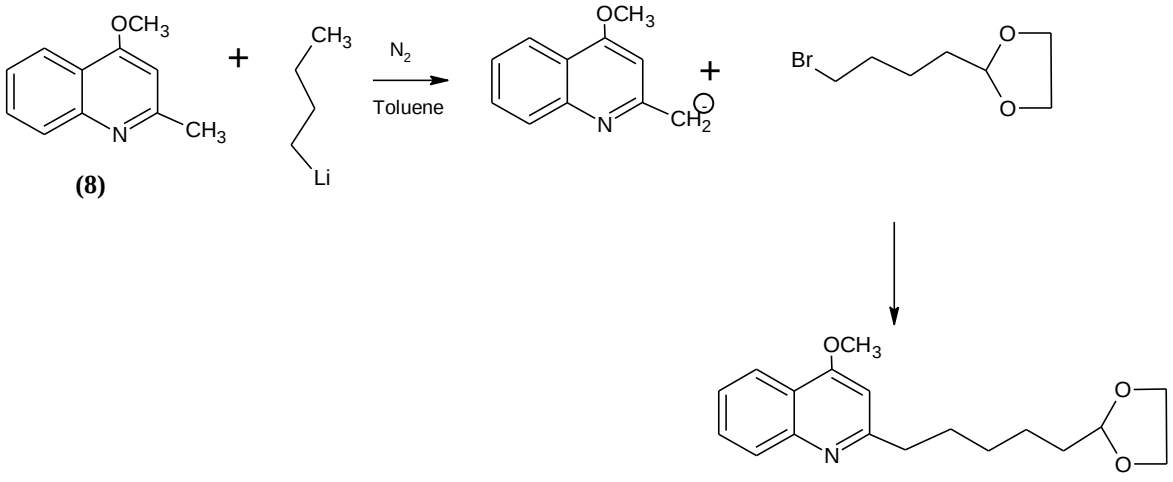


Figure 14: Synthesis with *n*-BuLi and Toluene

Thin layer chromatography was used to separate the residue with a solvent of 99% methylene chloride and 1% triethylamine. The purpose of the triethylamine was

prevention of any acidic conditions due to the silica gel. The residue was allowed to run up the silica plates of 0.1 mm depth to reveal the separation of the compounds within the residue. The plates were looked at under low wavelength ultraviolet light, to show the separated compounds. Each compound was removed from the plates via scrapings and kept separate. The compounds were removed from the silica gel by suction filtration using methylene chloride. The methylene chloride was allowed to evaporate, leaving just the compound. To run the NMR for this reaction with toluene, the residue was dissolved in Unisol (essentially 50:50 $CDCl_3$:DMSO-d_6) instead of $CDCl_3$ because the residue would not dissolve in $CDCl_3$.

3.1.1.3 Synthesis with *n*-Butyllithium and Tetrahydrofuran at Variable Temperature

Glassware was cleaned and dried in an oven, then placed in a dessicator to cool to room temperature while remaining dry. The reactions were run under nitrogen gas, and the reagents were injected via a syringe through rubber septa. The reagents were constantly mixed during the reaction by a magnetic stirring bar. A 50 mL round bottom, THF, and 4-methoxy-2-methylquinoline **(8)** were cooled to -78°C before the reaction was started. The *n*-BuLi was added to the 4-methoxy-2-methylquinoline **(8)** that already contained THF. After stirring for 2 hours, the solution was allowed to warm to room temperature and 2-(4-bromobutyl)-1,3-dioxolane **(10)** was added and allowed to react for 30 minutes. The reaction was quenched with water and methylene chloride. The organic layer was separated from the aqueous layer with a separtory funnel. Then the organic

layer was dried over magnesium sulfate, filtered, and the solvent was removed (Figure 15).

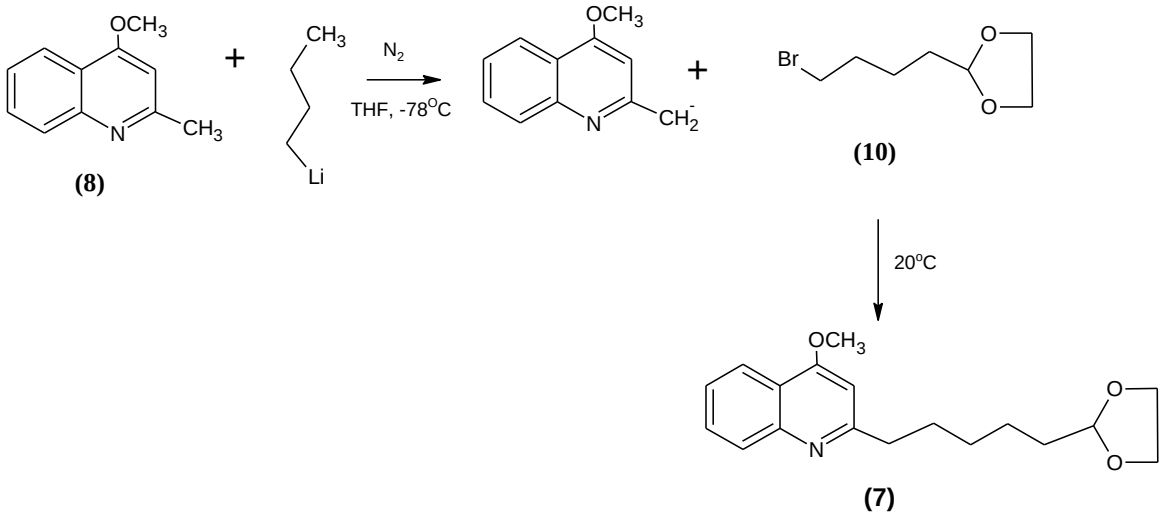


Figure 15: Synthesis with *n*-BuLi and THF – Variable Temperature

Thin layer chromatography was used to separate the residue with a solvent of 60% hexanes and 40% acetone. The residue was allowed to run up the silica plates of 0.1 mm depth, to reveal the separation of the compounds within the residue. The plates were observed under low wavelength ultraviolet light to show the separated compounds. Each compound was removed from the plates via scrapings and kept separate. The compounds were removed from the silica by filtration and methylene chloride. The methylene chloride was allowed to evaporate, leaving just the separated compound. This reaction had varying temperatures but still following the basic S_N2 reaction with *n*-BuLi and THF. However, it still failed to produce the desired product for this research.

3.1.2 Silver Oxide as the Base

Werner created o-methylated 4-hydroxy-2-methylquinoline using Ag_2O and MeI in DMF.[4,21] Ag_2O is commonly used with DMF, and acetonitrile as solvents because these solvents increase the transesterfication when making a silver halide. In this experiment acetonitrile was used (Figure 16). This method is easier to do with the acetonitrile than with the DMF, as in Werner's reaction, because the acetonitrile is easier to remove during distillation even though there are other solvents that can be used.[4] After the silver iodide is removed by filtration, the reaction vessel may be left in a fume hood overnight to allow the acetonitrile to evaporate.[4] The 2-[4-(1,3-dioxolan-2-yl)butyl]-4-methoxyquinoline **(7)** may then be extracted from the residue.[4] Boiling hexanes were poured over the residue to ause crystallization of the residue as the hexanes cooled and evaporated. The majority of the hexanes were decanted off.[4] The hexanes were allowed to evaporate in a fume hood and should result in pure crystals (Figure 16).[4]

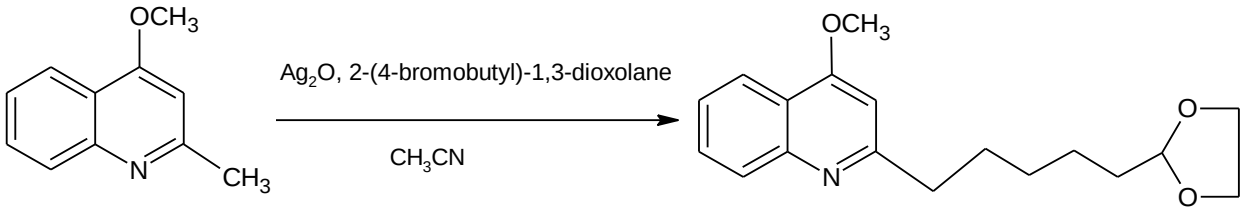
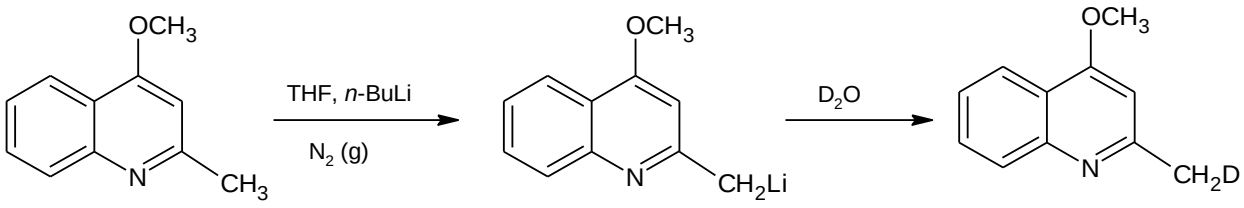


Figure 16: Attachment of 2-(4-bromobutyl)-1,3-dioxolane to 4-methoxy-2-methylquinoline by Silver Oxide in Acetonitrile

Silver iodide is extremely sensitive to light, and should be stored in a manner to protect it.[4] It is common to cover the reaction vessel to reduce the amount of light accessing the silver iodide and the other reagents. For this experiment, the reaction vessel was covered with aluminum foil until the reaction was completed.

3.1.3 Synthesis of Deuterated 4-Methoxy-2-Methylquinoline

Glassware was cleaned and dried in an oven, then placed in a dessicator to cool to room temperature while remaining dry. The reactions were run under nitrogen gas, and the reagents were injected via a syringe through rubber septa. The reagents were constantly mixed during the reaction by a magnetic stirring bar. *n*-BuLi was added to the 4-methoxy-2-methylquinoline **(8)** that already contained THF. After stirring for an hour, deuterium oxide was added and allowed to react for 10 minutes. The reaction was quenched with water and methylene chloride. The organic layer was separated from the aqueous layer with a separtory funnel. Then the organic was dried over magnesium sulfate. The water was removed by a Pasteur pipette and the desired residue was decanted the magnesium sulfate. The methylene chloride evaporated, and the residue was removed using an oil vacuum pump (Figure 17).



(8) **(11)**

Figure 17: Synthesis of Deuterated-4-Methoxy-2-Methylquinoline **(11)**

The residue was recrystallized from methylene chloride and hexanes. The residue was first dissolved in methylene chloride, and a layer of hexanes was pipetted on top of the methylene chloride with a Pasteur pipette, without disturbing the surface of the methylene chloride. The hexanes is added to the methylene chloride in this manner to allow the hexanes to slowly diffuse into the methylene chloride causing a slow crystallization that results in better quality crystals. The methylene chloride:hexanes ratio was 3:1 for this recrystallization. The reaction vessel was then placed in the freezer for 18 hours. The crystals were filtered, and evaporated using rotary evaporator and followed by an oil vacuum pump.

A proton NMR spectrum of the crystals dissolved in $CDCl_3$ was run and compared to the proton spectrum of 4-methoxy-2-methylquinoline. For the deuterated compound, the triplet peak for the deuterated methyl should have all three peaks at the same height. The proton-deuterium coupling constant should be in the 2.2-3.0 Hz range.[22, 30] The proton NMR for the residue formed, showed a singlet, indicating

a nondeuterated methyl group. Since the peak that should have been a triplet was a singlet, the same as the methyl peak in 4-methoxy-2-methylquinoline, this deuterium reaction did not proceed as predicted.

3.2 Additional Spectra Performed

The CPD is the composite-pulse decoupling ^{13}C NMR spectrum run on 4-methoxy-2-methylquinoline. DEPT 90 and 135 are a form of a ^{13}C NMR spectrum that completely eliminates ^{1}H-^{13}C coupling by irradiating the entire proton chemical shift range.[22] The DEPT sequence is the preferred procedure for determining the number of protons directly attached to the individual ^{13}C nucleus (Table 2).[22]

Table 2: Assignments from CPD & DEPT-90 and -135

Assignments from CPD & DEPT			
CPD	DEPT 90	DEPT 135	Assignment
up	null	up	1°
up	null	down	2°
up	up	up	3°
up	null	null	4°

The DEPT-90 and DEPT-135 of 4-methoxy-2-methylquinoline were run during the period of this research. A DEPT-90 uses a pulse sequence that produces a carbon spectrum showing only tertiary carbons. However, the DEPT-135 exhibits positive primary and tertiary carbon peaks and negative secondary carbon peaks. Quaternary carbons are not detected in any DEPT sequence.[22] By comparing the ^{13}C NMR spectrum to the DEPT-90 and DEPT-135, the eleven carbons that make up 4-methoxy-2-methylquinoline are shown with three separate spectra. This gives further evidence for the 4-methoxy-2-methylquinoline structure synthesized by Rogers. The ^{1}H NMR, CPD ^{13}C NMR, and IR run for this experiment were identical to those run by Rogers.[4]

4. Conclusion

While many different reactions were performed, with many and varied conditions, none of them produced the desired product, 2-[4-(1,3)-dioxolan-2-yl)butyl]-4-methoxyquinoline **(7)**. This is likely due to the relative acidities of the proton on the methyl group in the 2-position of the 4-methoxy-2-methylquinoline. In other words, the *n*-butyl anion may not be a stronger base than carbanion **(9)**.

It has been shown that the reaction of *n*-BuLi with 4-methoxy-2-methylquinoline **(8)** followed by 2-(4-bromobutyl)-1,3-dioxolane **(10)** does not yield 2-[4-(1,3)-dioxolan-2-yl)butyl]-4-methoxyquinoline **(7).** However, since this experiment was run at different temperatures (Table 1) with a consistent reaction, the conclusion can be drawn that this reaction is not temperature dependent.

Since a proton on the methyl group in the 2-position on 4-methoxy-2-methylquinoline did not remove from main structure during the synthesis with *n*-BuLi and neither toluene nor THF, the lithiation did not succeed at -78°C. Since the lithiation did not work there was no possibility for the *n*-BuLi synthesis to work successfully. The DEPT-90 and DEPT-135 spectra constitute a new addition to the 4-methoxy-2-methylquinoline literature.

5. Experimental

All IR spectra were taken using a Perkin Elmer Paragon 1000 Spectrometer, an FTIR.

1H and 13C NMR spectra were collected using a Bruker DPX-300 and the solvent used was either CDCl3 or Unisol (50:50 CDCl3:DMSO-d6). DEPT-90 and DEPT-135 spectra were obtained on the same instrument with CDCl3 as the solvent.

The spectra of all the desired products in this thesis were identical to those of the starting materials. The spectrum of 4-methoxy-2-methylquinoline **(8)** was run by Rogers.[4] The spectrum of 2-(4-bromobutyl)-1,3-dioxolane **(10)**, found in the Appendix, was identical to the literature spectrum.[29]

Synthesis with *n*-Butyllithium and Tetrahydrofuran at 0°C, 20°C, and -78°C (Section 3.1.1.1) In a 100 mL round-bottom flask with a side arm place a magnetic stirring bar and tetrahydrofuran (THF, 5 mL) was added to dissolve 4-methoxy-2-methylquinoline **(8)** (0.050 g, 0.314 mmol). In either a 0^{o}C ice/water bath or at -78^{o}C the round bottom was placed in a mixture of dry ice and isopropyl alcohol. Each opening of the round-bottom was covered with a septum. An inlet and outlet needle was inserted into the side arm to provide an inert atmosphere of nitrogen gas in the flask, while the n-butylithium (0.138 mL, 2.5 M in hexanes, 0.346 mmol), at room temperature, was injected through the main opening with a syringe through the septum. The magnetic stirring bar remained constant throughout the experiment.

In a separate beaker, 2-(4-bromobutyl)-1,3-dioxolane **(10)** (0.065 g, 0.314 mmol, at room temperature, and tetrahydrofuran (5.10 mL) were combined to make a different solution. This mixture was then syringed into the one necked round-bottom flask and was allowed to react for approximately 20 minutes.

The reaction was quenched by turning off the nitrogen gas and the magnetic stirring bar, removing the needles and septa, and adding distilled water (5 mL) and methylene chloride (5 mL). The solution was then transferred into a separatory funnel. Water (5 mL) was added with shaking until the separate layers were visible. The organic layer was drained. The aqueous layer was extracted two more times with methylene chloride (3 mL). The combined organic layers were dried with magnesium sulfate and the magnesium sulfate was removed from the product by gravity filtration. Methylene chloride was used to wash the flask of the product and drying agent.

For this experiment the separation techniques employed to isolate and separate the product were a rotary evaporator, an oil vacuum pump, and flash chromatograph. The filtered product was placed on a rotary evaporator, removing any remaining solvents. The round-bottom was set to rotate and placed in a 65°C water bath while on the rotary evaporator. Next, the product was evacuated by an oil vacuum pump for 15 to 20 minutes. The flash chromatograph was used to separate the remaining compounds from one another. The instrument was used with a gradient of hexanes and ethyl acetate. The product was mixed with approximately 20 drops of ethyl acetate before being inserted directly onto a 4g silica flash column with solvents of hexanes and ethyl acetate. This enabled the separation of the compounds. The separated compounds were placed

again onto the rotary evaporator with the same conditions and allowed to run for approximately 20 to 25 minutes. The product was pulled on by a trapped oil vacuum pump until the ethyl acetate and hexanes evaporated. ^{1}H NMR of the 0°C reaction product ($CDCl_3$), Figure 22, δ 0.072 (s, silicone grease), 0.880 (d, unknown compound), 1.128 (s, unknown compound), 1.918 (s, unknown compound), 2.171 (s, unknown compound), 2.709 (s, 3H, CH_3), 4.034 (s, 3H, OCH_3), 6.634 (s, 1H, OCH_3C**CH**C CH_3 of 4-methoxy-2-methylquinoline), 7.440 (t, J=8 Hz, 1H, aromatic), 7.636 (t, J=8 Hz, 1H, aromatic), 7.968 (d, J=8 Hz, 1H, aromatic), 8.153 (d, J=8 Hz, 1H, aromatic). ^{1}H NMR of the 20°C reaction product ($CDCl_3$), Figure 23, δ 0.91 (s, unknown compound), 1.25 (s, unknown compound), 1.58 (t, J=10 Hz, 2H, CH_2 in the chain of 2-(4-bromobutyl)-1,3-dioxolane), 1.67 (t, J=8 Hz, 2H, CH_2 in the chain of 2-(4-bromobutyl)-1,3-dioxolane), 1.89 (m, 2H, J=9 Hz, CH_2 in the chain of 2-(4-bromobutyl)-1,3-dioxolane), 3.42 (t, 2H, J=9 Hz, Br**CH$_2$**CH_2), 2.68 (s, 3H, CH_3 of 4-methoxy-2-methylquinoline), 3.83 (t, 2H, J=3 Hz, CH_2 in the ring of 2-(4-bromobutyl)-1,3-dioxolane), 3.97 (t, 2H, J=6 Hz, CH_2 in the ring of 2-(4-bromobutyl)-1,3-dioxolane), 3.98 (s, 3H, OCH_3 of 4-methoxy-2-methylquinoline), 4.85 (t, 1H, J=3 Hz, CH_2**CH**O_2 of 2-(4-bromobutyl)-1,3-dioxolane), 6.59 (s, 1H, OCH_3C**CH**C CH_3 of 4-methoxy-2-methylquinoline), 7.44 (t, J=8Hz, 1H, aromatic of **(8)**), 7.64 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.96 (d, J=8 Hz, 1H, aromatic of **(8)**), 8.13 (d, J=8 Hz, 1H, aromatic of **(8)**). ^{1}H NMR of the -78°C reaction product ($CDCl_3$), Figure 24, δ 0.1 (s, silicone grease), 0.927 (s, unknown compound), 1.594 (t, J=10 Hz, 2H, CH_2 in ring of 2-(4-bromobutyl)-1,3-dioxolane), 1.673 (t, J=8 Hz, 2H, CH_2 in ring of 2-(4-bromobutyl)-1,3-dioxolane), 1.908 (m, 2H, J=9 Hz, CH_2 in the chain of 2-

(4-bromobutyl)-1,3-dioxolane), 3.431 (t, 2H, J=9 Hz, Br**CH$_2$**CH$_2$), 4.027 (s, 3H, OCH$_3$ of 4-methoxy-2-methylquinoline), 4.871 (t, 1H, J=3 Hz, CH$_2$**CH**O$_2$ of 2-(4-bromobutyl)-1,3-dioxolane), 6.618 (d, J=25 Hz, 1H, aromatic of **(8)**), 7.278 (s, 1H, aromatic of **(8)**), 7.989 (d, J=92 Hz, 1H, aromatic of **(8)**), 8.148 (d, J=66 Hz, 1H, aromatic of **(8)**).

Synthesis with *n*-Butyllithium and Toluene (Section 3.1.1.2) In a 100 mL round-bottom flask with side arm place a magnetic stirring bar and 4-methoxy-2-methylquinoline **(8)** (0.050 g, 0.314 mmol) was dissolved in toluene (5 mL). The solution was cooled to 0°C. Room temperature, *n*-butyllithium in hexanes (0.138 mL, 2.5 M, 0.346 mmol) was injected and reacted for 45 minutes. The solution had a distinct color change, giving a final gold colored solution. THF (5.10 mL) was used to pre-dissolve 2-(4-bromobutyl)-1,3-dioxolane **(10)** (0.065 g, 0.314 mmol) and injected into the round-bottom to complete the S_N2 reaction. The product was pulled on by a rotary evaporator (40°C) and a trapped oil vacuum pump. ^{1}H NMR (Unisol), Figure 25, 2.69 (s, 3H, CH$_3$ of **(8)**), 3.20 (s, unknown compound), 4.06 (s, 3H, OCH$_3$ of **(8)**), 6.66 (s, 1H, OCH$_3$C**CH**C CH$_3$ of **(8)**), 7.44 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.65 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.74 (s, chloroform), 7.89 (d, J=8 Hz, 1H, aromatic of **(8)**), 8.14 (d, J=8 Hz, 1H, aromatic of **(8)**).

Synthesis with *n*-Butyllithium and Tetrahydrofuran at -78°C Warming to Room Temperature (Section 3.1.1.3) In a 100 mL round-bottom flask with a side arm place a magnetic stirring bar, then take the round bottom and place it in a dry ice bath (-78°C), THF (5 mL) was added to dissolve 4-methoxy-2-methylquinoline **(8)** (0.050 g, 0.314 mmol). Both openings of the round-bottom were covered with septa. An inlet and outlet needle was inserted into the side arm to provide an inert atmosphere of nitrogen gas in the flask, while the n-butylithium (0.138 mL, 2.5 M in hexanes, 0.346 mmol), at room temperature, was injected through the main opening with a syringe through the septum. The magnetic stirring bar remained constant throughout the experiment, and the mixture reacted for one hour.

In a separate beaker, 2-(4-bromobutyl)-1,3-dioxolane **(10)** (0.065 g, 0.314 mmol), at room temperature, and THF (5.10 mL) were combined as a different solution. The THF and 4-methoxy-2-methylquinoline **(8)** solution was removed from the dry ice bath and allowed to come to room temperature. The 2-(4-bromobutyl)-1,3-dioxolane **(10)** and THF mixture was then syringed into the one necked round-bottom flask and was allowed to react, remaining within the nitrogen environment.

The reaction was quenched by turning off the nitrogen gas and the magnetic stirring bar, removing the needles and septa, and adding distilled water (5 mL) and methylene chloride (5 mL). The solution was then transferred into a separatory funnel. The solution was then transferred into a separatory funnel. Water (5 mL) was added with shaking until the separate layers were visible. The organic layer was drained. The aqueous layer was extracted two more times with methylene chloride (3 mL). The

combined organic layers were dried with magnesium sulfate and the magnesium sulfate was removed from the product by gravity filtration. Methylene chloride was used to wash the flask of the product and drying agent. A rotary evaporator and an oil vacuum pump were used to isolate and separate any solvents from the product. The product was then run on an NMR with $CDCl_3$ as the solvent. The NMR spectrum showed multiple compounds in the sample. To separate the compounds, thin layer chromatography was used with a solvent of 99% methylene chloride and 1% triethylamine. Three products were obtained by using scrapings from the TLC plates. The residues were removed from the silica gel by gravity filtration with methylene chloride as the solvent. The methylene chloride was allowed to evaporate. ^{1}H NMR ($CDCl_3$), Figure 26, 2.714 (s, 3H, CH_3 of **(8)**), 4.028 (s, 3H, OCH_3), 6.625 (s, 1H, OCH_3C**CH**C CH_3 of **(8)**), 7.243 (s, unknown compound), 7.435 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.656 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.966 (d, J=8 Hz, 1H, aromatic of **(8)**), 8.137 (d, J=8 Hz, 1H, aromatic of **(8)**).

Synthesis with Diethyl Ether [4] In a clean, dry 50 mL round-bottom flask place a magnetic stirring bar and add 4-methoxy-2-methylquinoline **(8)** (0.565 g). Seal the flask with a rubber septum. A vacuum was pulled on the flask for 5 minutes, and then it was filled with nitrogen gas. This was repeated; then the vacuum was pulled on the flask, and 12 mL of dry diethyl ether was moved by suction into the flask through a cannula. The nitrogen flow was started, the flask was suspended in an ice bath, and the ether was stirred. A solution of *n*-BuLi in hexanes (1.35 mL, 2.5 M) was injected via a syringe. After one hour, 2-(4-bromobutyl)-1,3-dioxolane **(10)** (0.409 g) was injected into the flask, and the ice bath was removed. Stirring was continued for 4 hours. Workup was

commenced by washing the ether solution with two 25 mL portions of water. The washing revealed two distinct layers that were separated and allowed to evaporate. ^{1}H NMR ($CDCl_3$), Figure 27, 2.75 (s, 3H, CH_3 of **(8)**), 4.06 (s, 3H, OCH_3), 6.65 (s, 1H, OCH_3C**CH**C CH_3 of **(8)**), 7.26 (s, unknown compound), 7.47 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.69 (t, J=8 Hz, 1H, aromatic of **(8)**), 8.04 (d, J=8 Hz, 1H, aromatic of **(8)**), 8.14 (d, J=8 Hz, 1H, aromatic of **(8)**).

Synthesis of Deuterated-4-Methoxy-2-Methylquinoline (Section 3.1.3) In a 500 mL round-bottom flask with a side arm place a magnetic stirring bar, and add THF (25 mL) to dissolve 4-methoxy-2-methylquinoline **(8)** (0.251 g, 0.157 mmol). Both openings, of the round-bottom, were covered with septa. A nitrogen gas needle was inserted into the side arm for pressure, while the n-BuLi (0.15 mL, 2.5 M in hexanes, 0.157 mmol), at room temperature, was injected through the main opening. The solution was allowed to react for 1 hour and the magnetic stirring bar remained constant throughout the experiment.

One ampule (1g) of deuterium oxide was syringed into the round-bottom flask and was allowed to react for approximately 10 minutes. The liquid from the solution was allowed to evaporate, and the residue was pulled on by an oil vacuum pump for 10 minutes.

The residue was put into an Erlenmeyer flask and transferred with methylene chloride. Water (5 mL) was added to the dissolved residue, shaken, and pipetted off with a Pasteur pipette. Magnesium sulfate was added to the solution, and the solution was decanted away from the magnesium sulfate. Methylene chloride (15 mL) was added and

hexanes (5 mL) were pipetted onto the methylene chloride without disrupting the surface of the solution. The solution was then place in a freezer for 18 hours.

The flask was removed from the freezer and the residue was filtered by vacuum filtration. The flask and the residue were washed with methylene chloride. ^{1}H NMR ($CDCl_3$), Figure 28, 2.679 (s, 3H, CH_3 of **(8)**), 3.964 (s, 3H, OCH_3 of **(8)**), 6.567 (s, 1H, OCH_3C**CH**CCH_3 of **(8)**), 7.283 (s, unknown compound), 7.415 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.641 (t, J=8 Hz, 1H, aromatic of **(8)**), 7.916 (d, J=8 Hz, 1H, aromatic of **(8)**), 8.114 (d, J=8 Hz, 1H, aromatic of **(8)**).

DEPT 90 and DEPT 135 (Sections 3.2) The DEPT 90 and 135 were run at 75 MHz using $CDCl_3$. The peaks at 162, 160, 148, and 119 ppm in the CPD ^{13}C NMR are quaternary carbons. Peaks at 129, 128, 124, and 121 ppm are most likely tertiary carbons in the non-nitrogen containing ring. The three remaining peaks at 100, 55, and 25 ppm correspond to the methoxy, methyl, and C3 (Figure 2) in the nitrogen ring. The DEPT-90 and DEPT-135 spectra exhibited no negative peaks (Figure 29 and 30).

APPENDIX

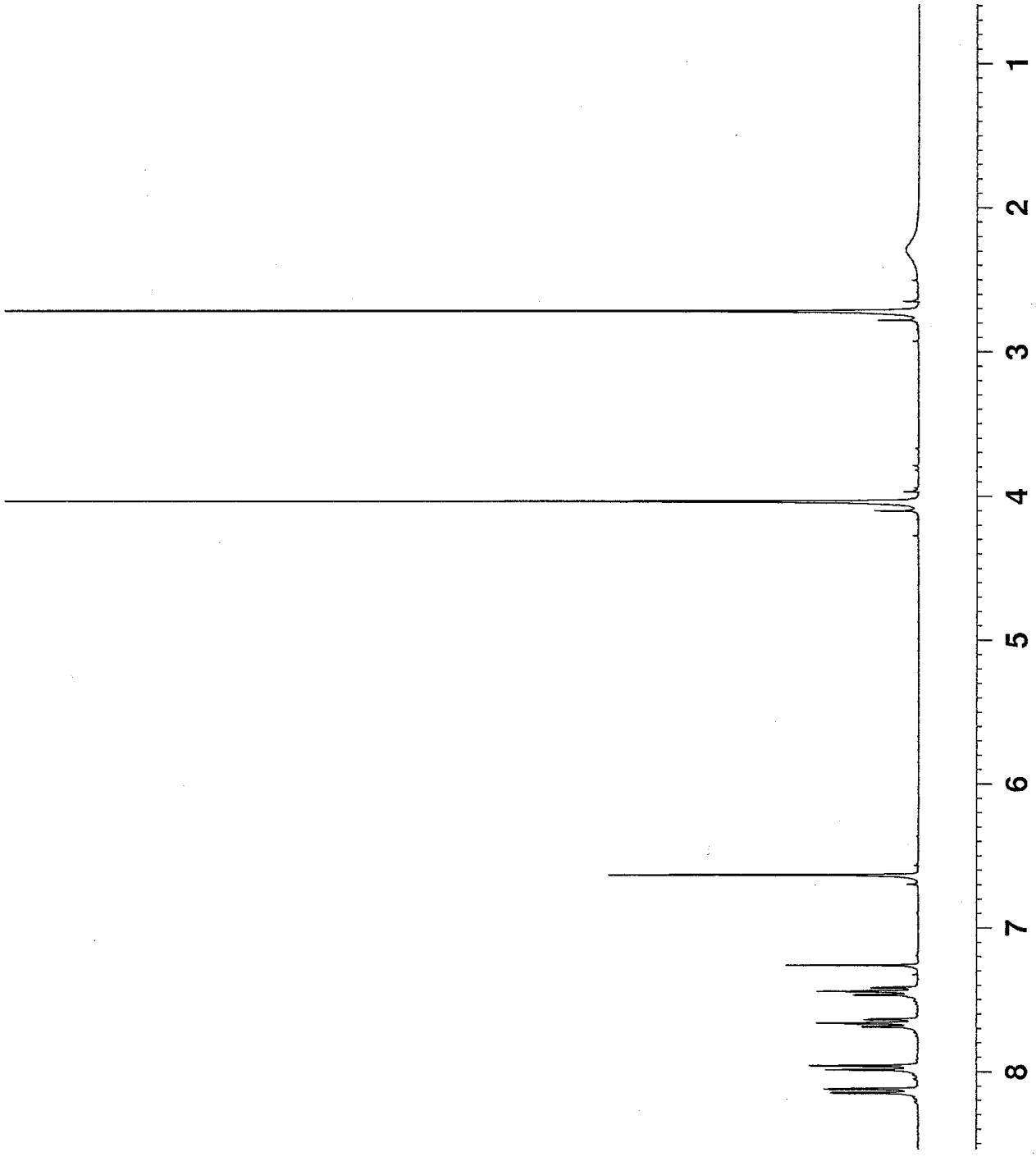


Figure 18: ^{1}H NMR of 4-methoxy-2-methylquinoline

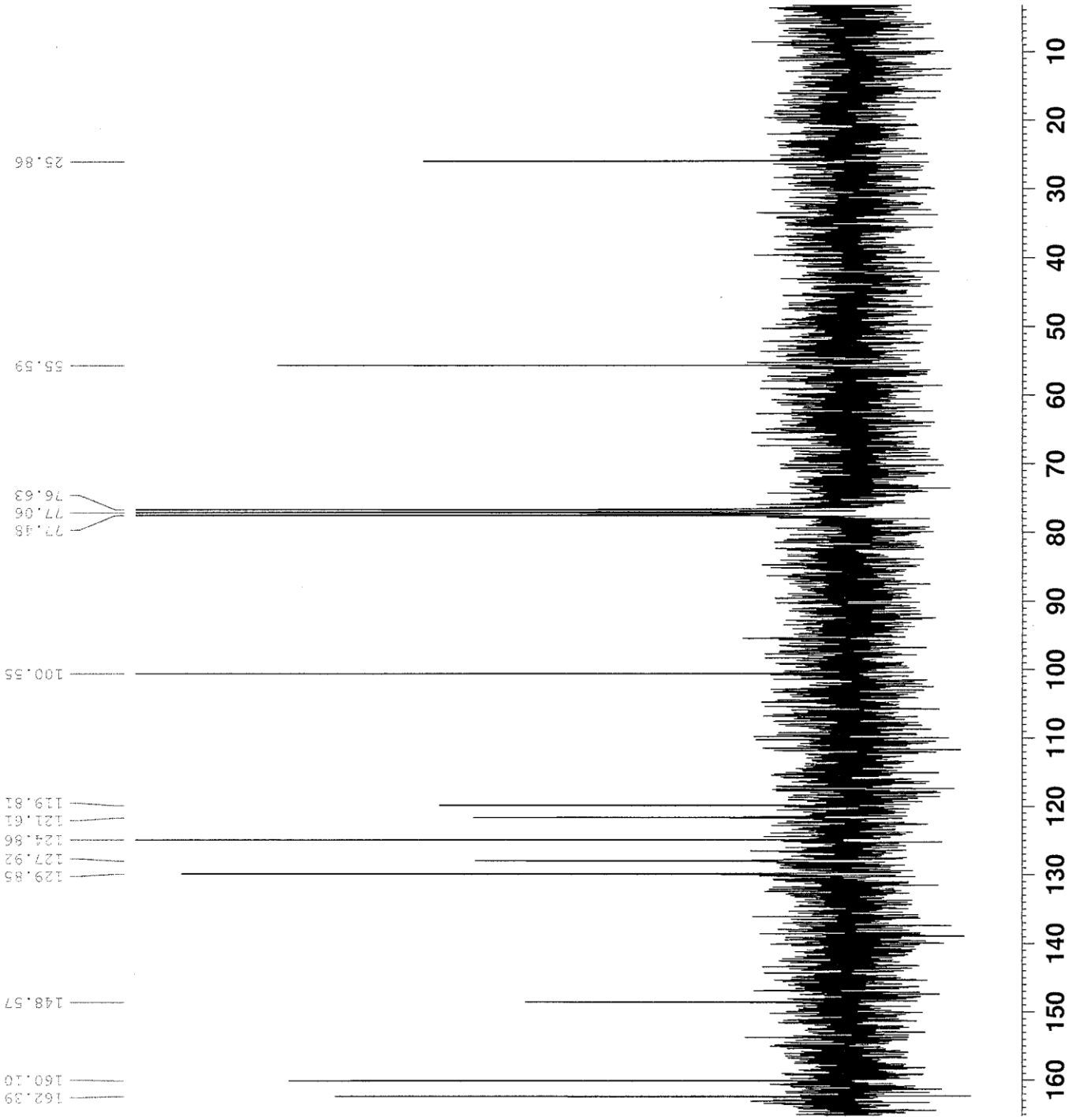


Figure 19: ^{13}C NMR of 4-methoxy-2-methylquinoline

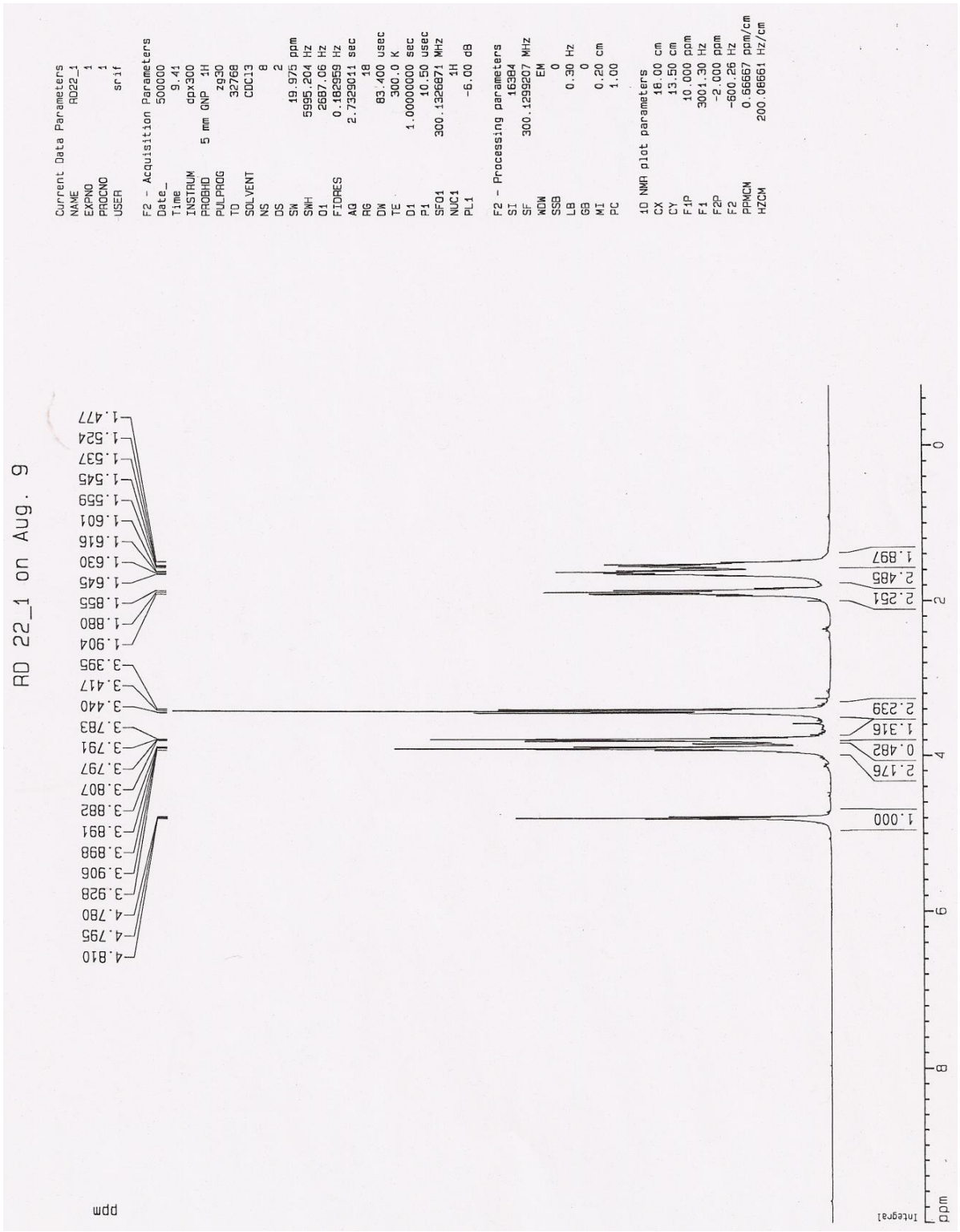


Figure 20: ^{1}H NMR of 2-(4-bromobutyl)-1,3-dioxolane

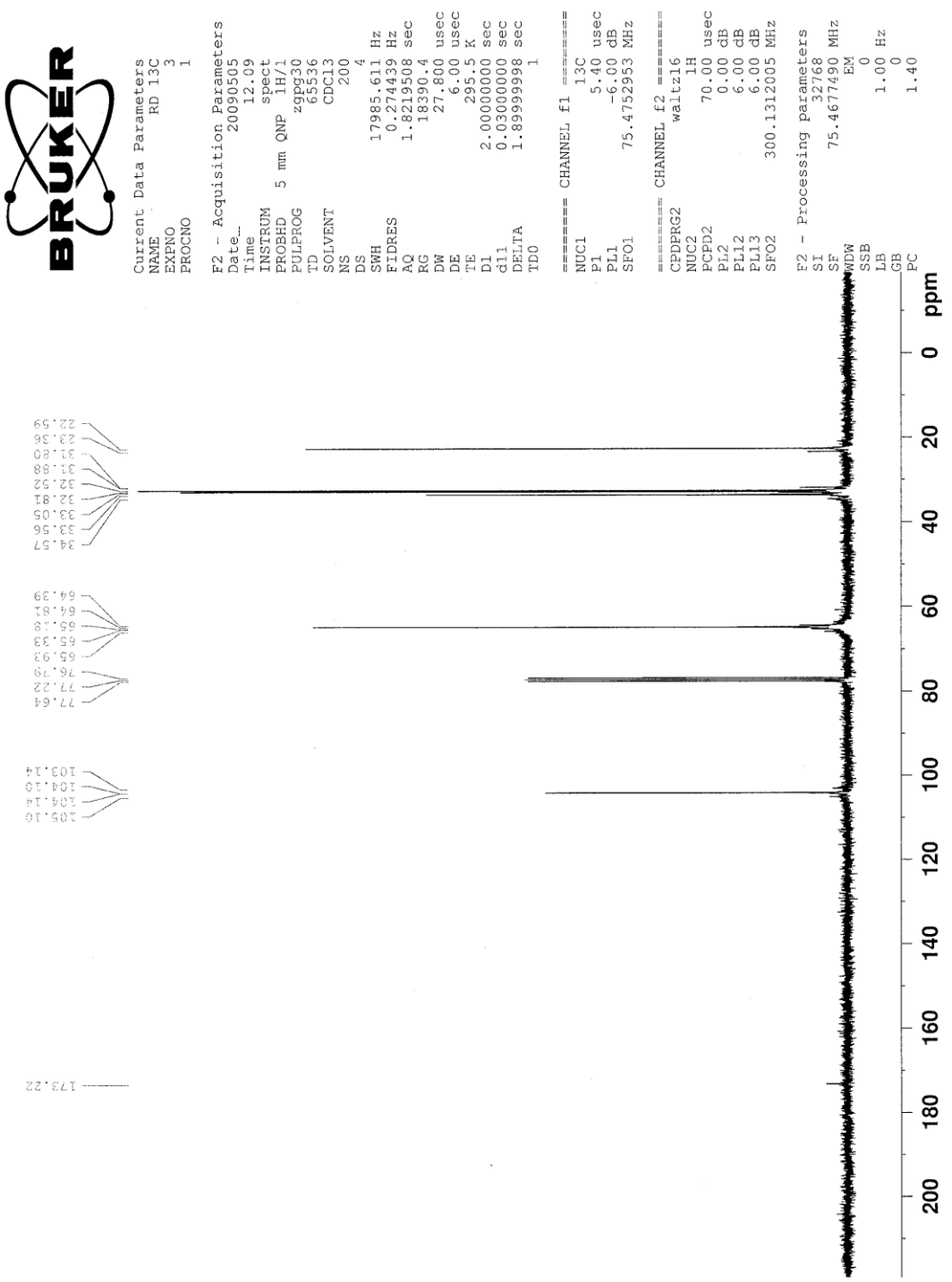


Figure 21: ^{13}C NMR of 2-(4-bromobutyl)-1,3-dioxolane

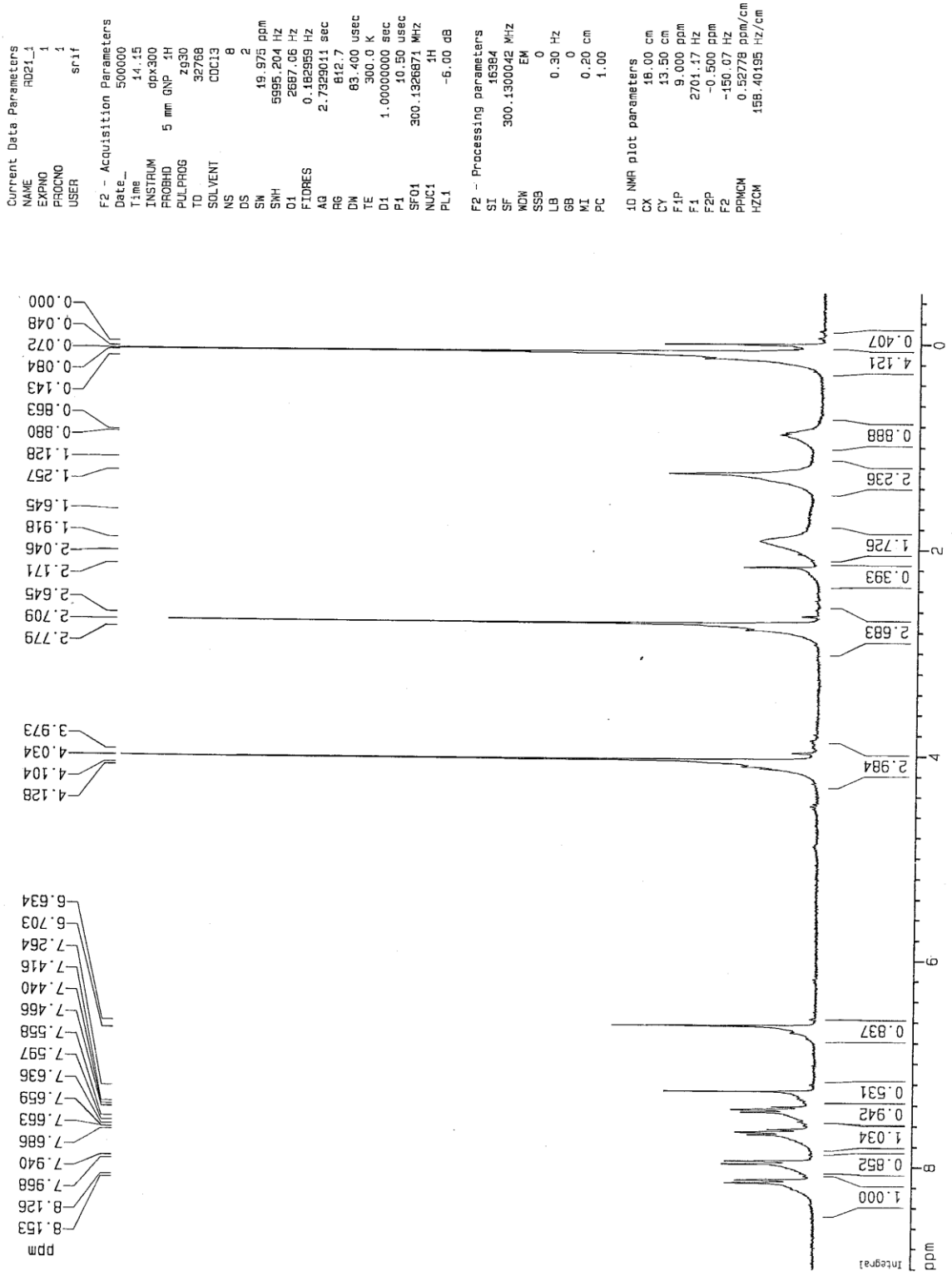


Figure 22: ^{1}H NMR of the product of a reaction with *n*-BuLi and THF at 0°C

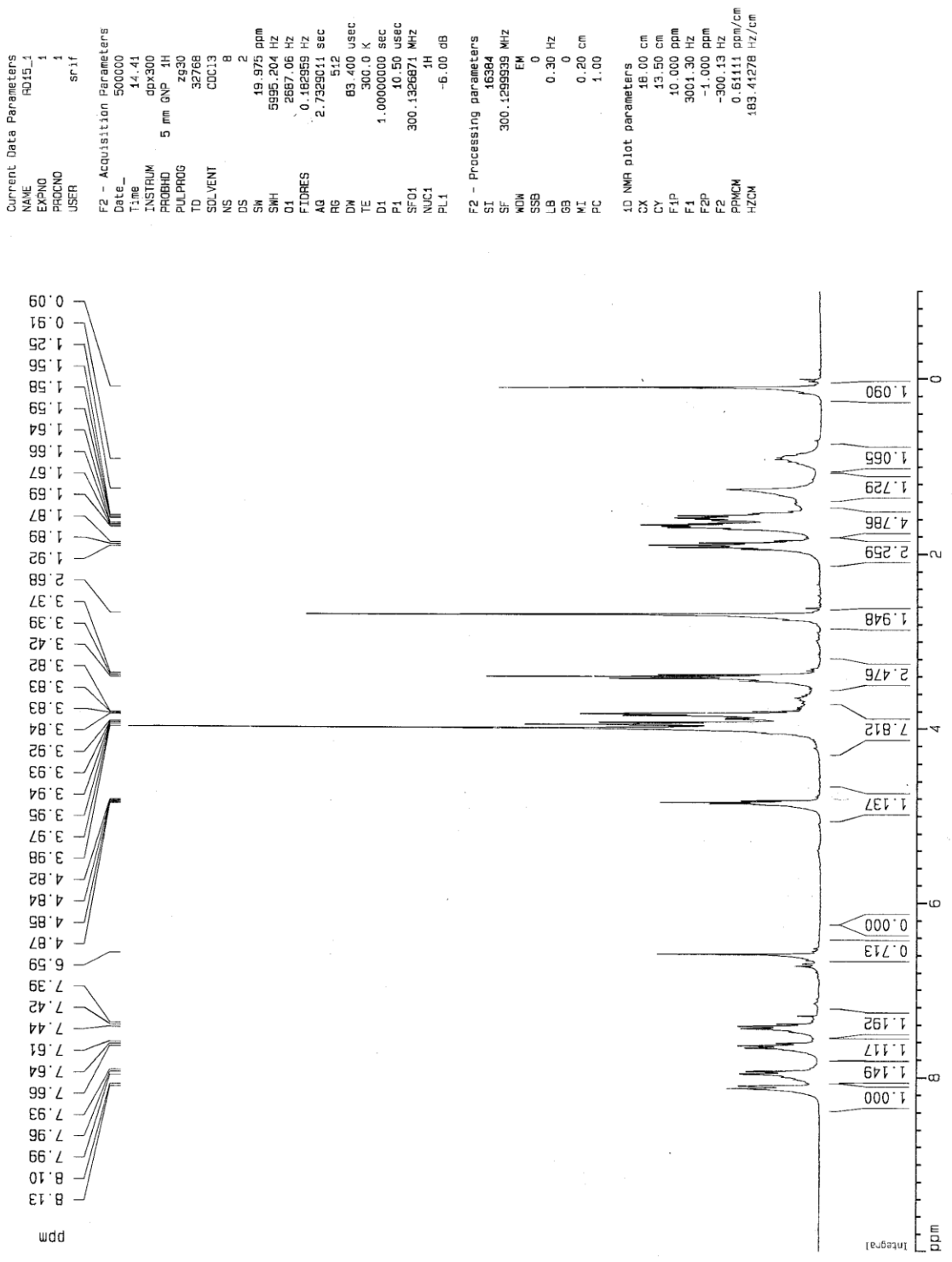


Figure 23: ^{1}H NMR of the product of a reaction with *n*-BuLi and THF at 20°C

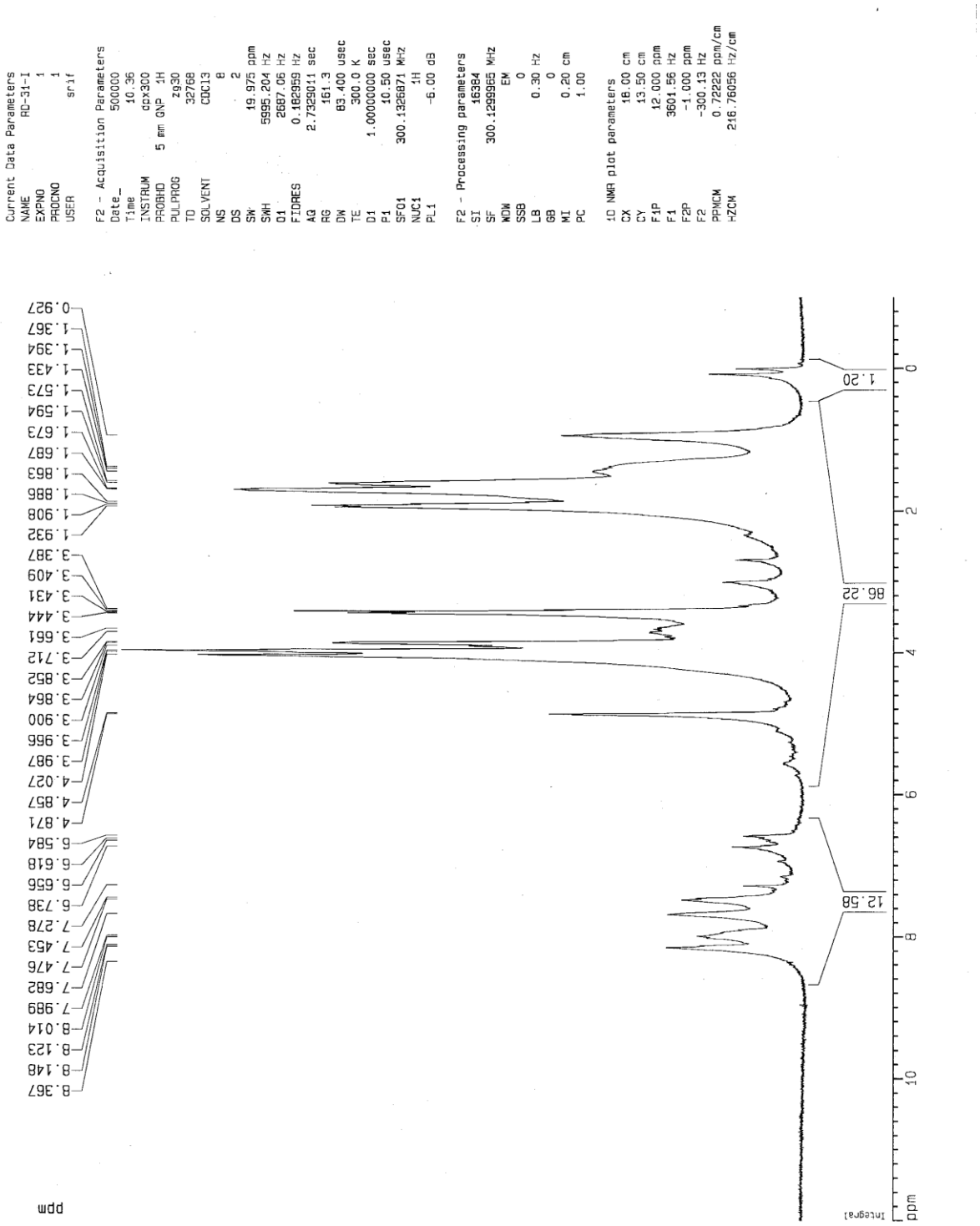


Figure 24: ^{1}H NMR of the product of a reaction with *n*-BuLi and THF at -78°C

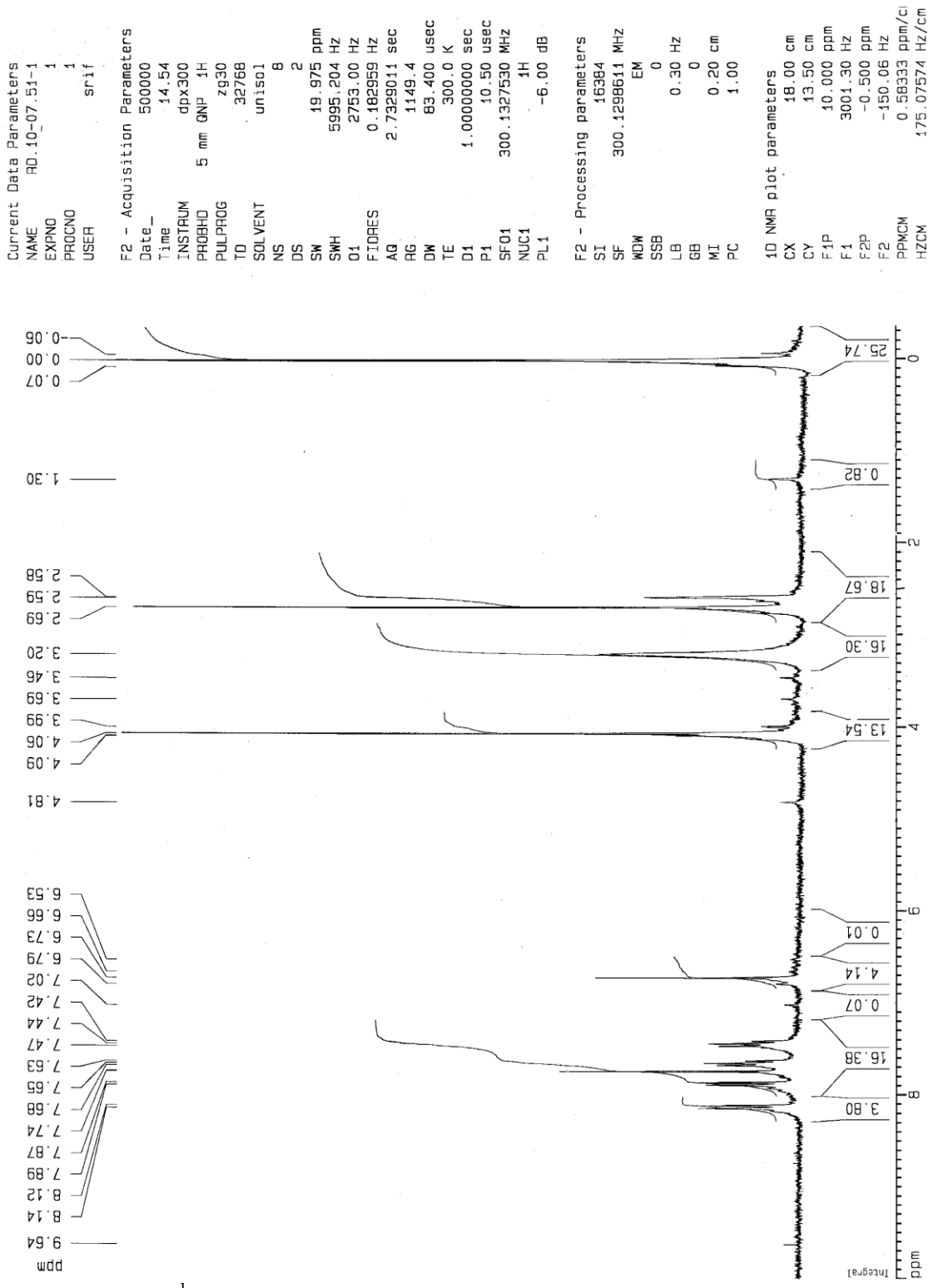


Figure 25: ^{1}H NMR of the product of a reaction with *n*-BuLi and Toluene

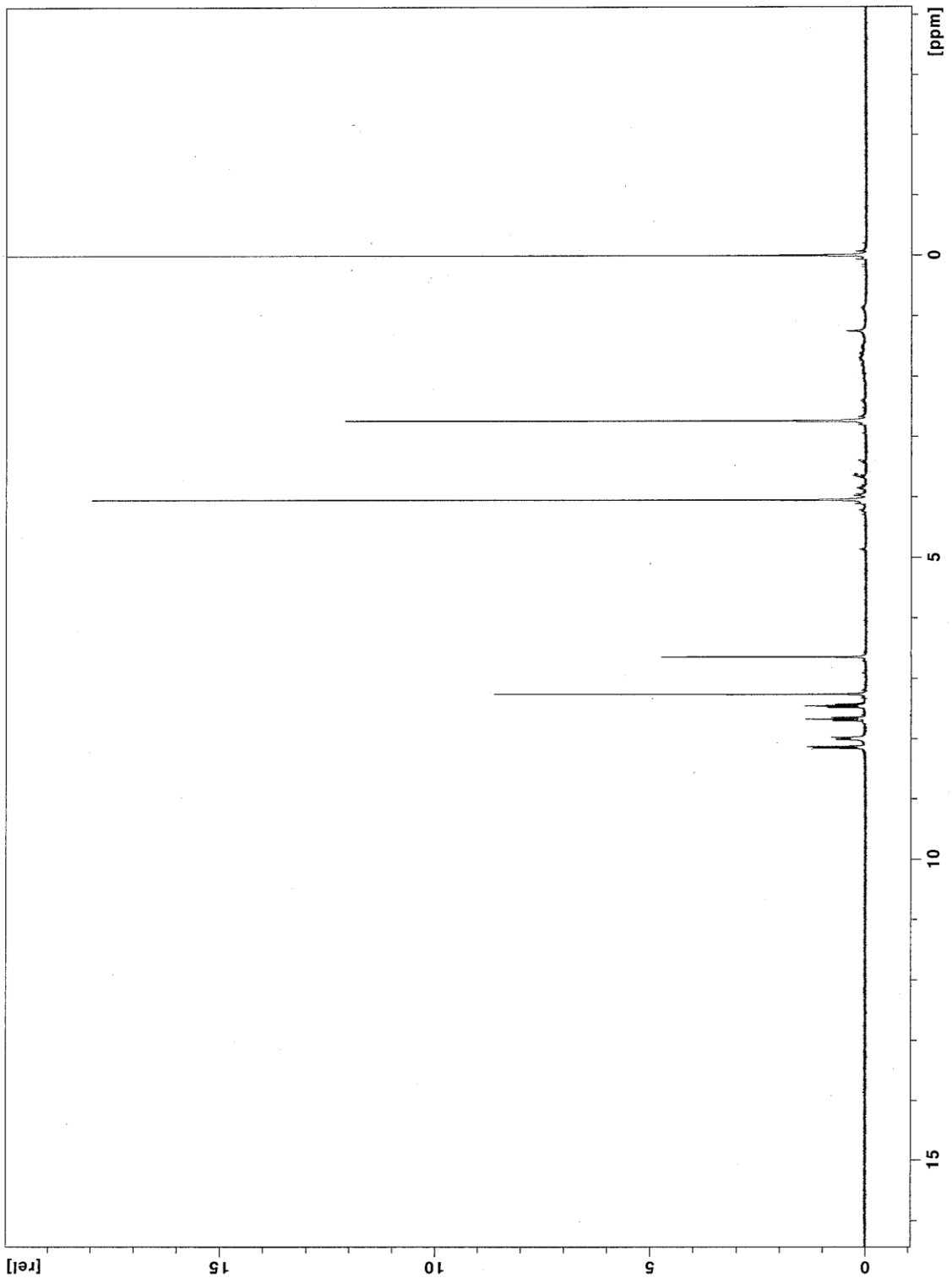


Figure 26: ^{1}H NMR of the product of a reaction with *n*-BuLi and THF at varying temperatures

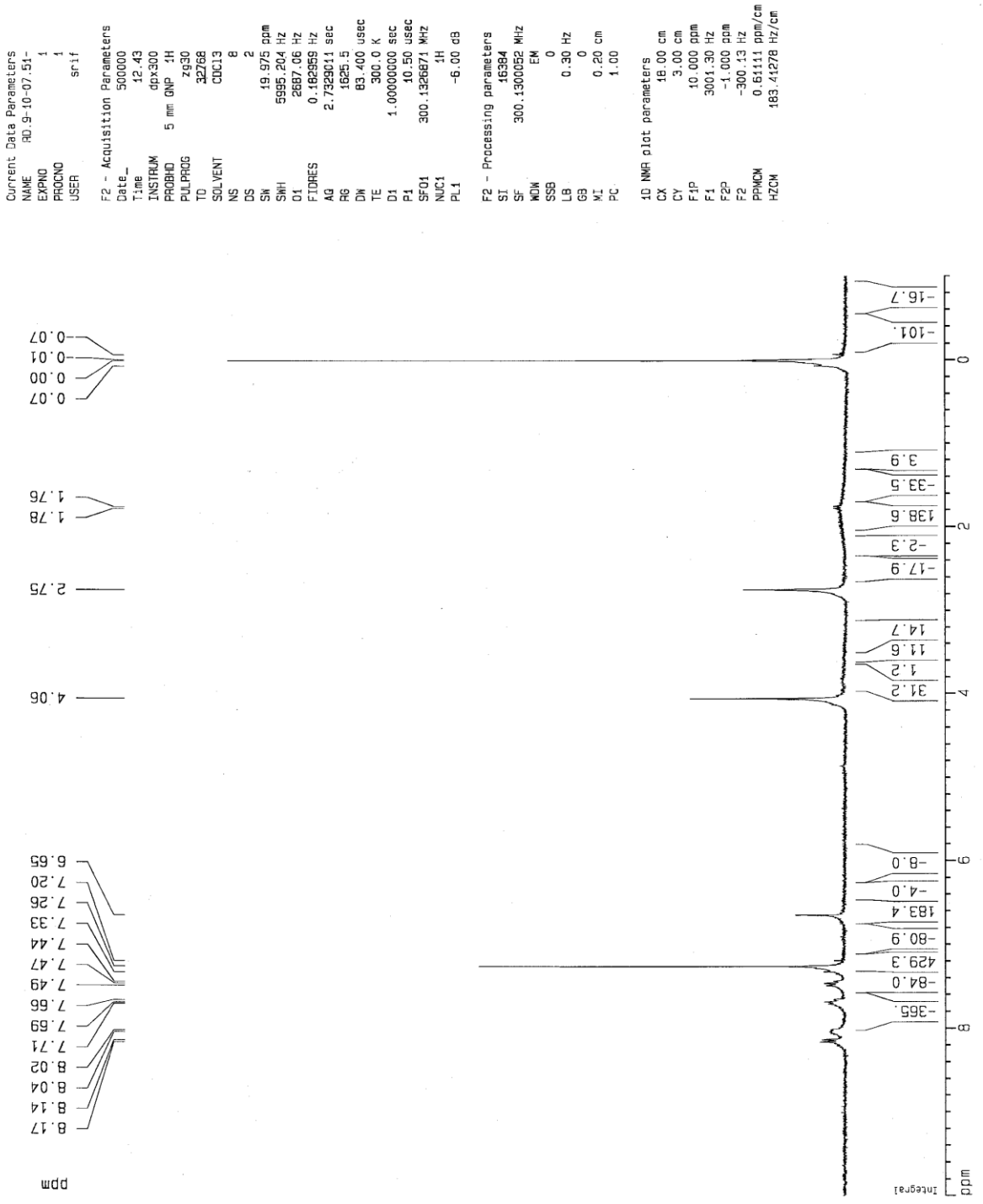


Figure 27: ^{1}H NMR of the product of the reaction with silver oxide as the base

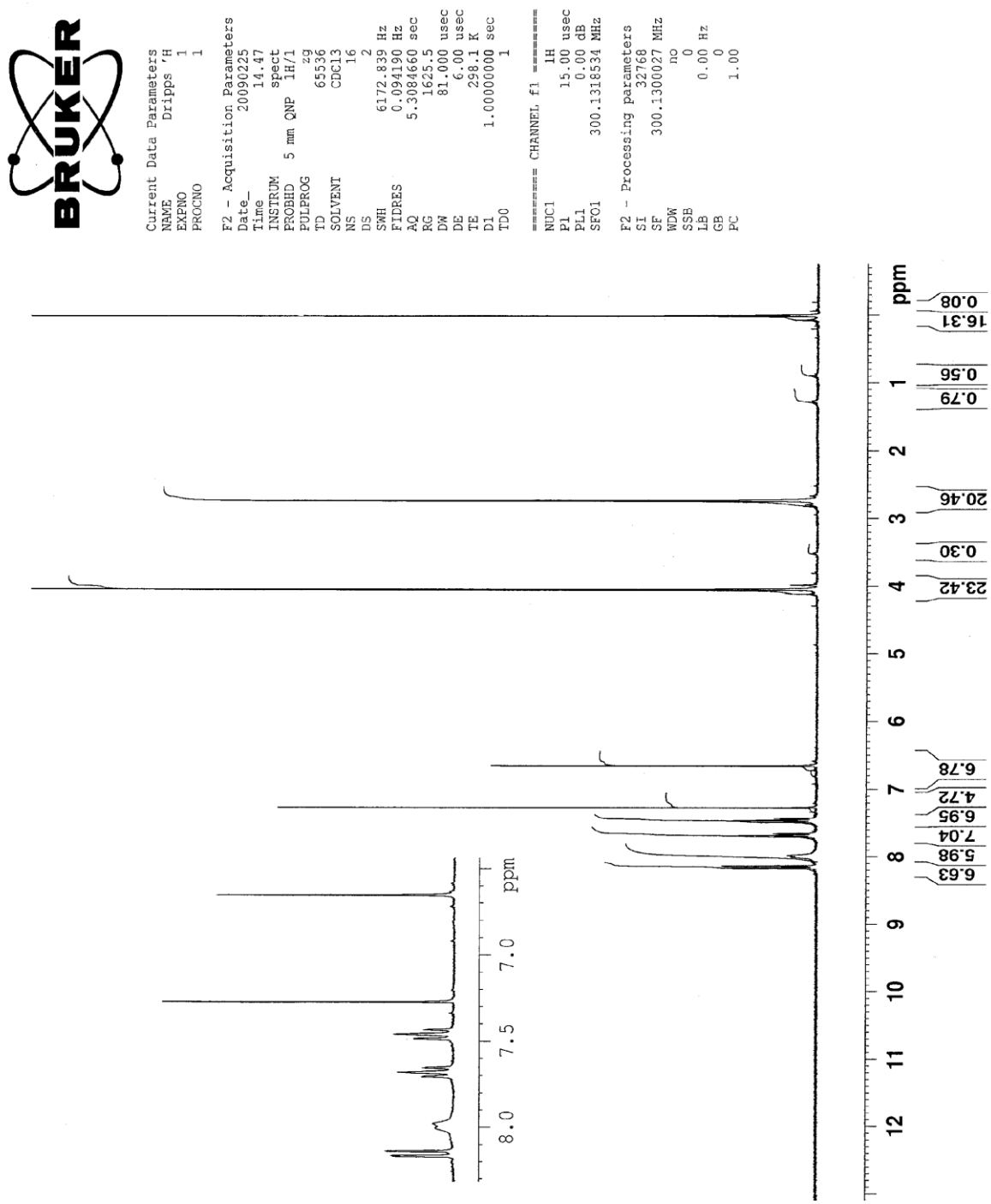


Figure 28: Attempted synthesis of deuterated 4-methoxy-2-methylquinoline: ^{1}H NMR

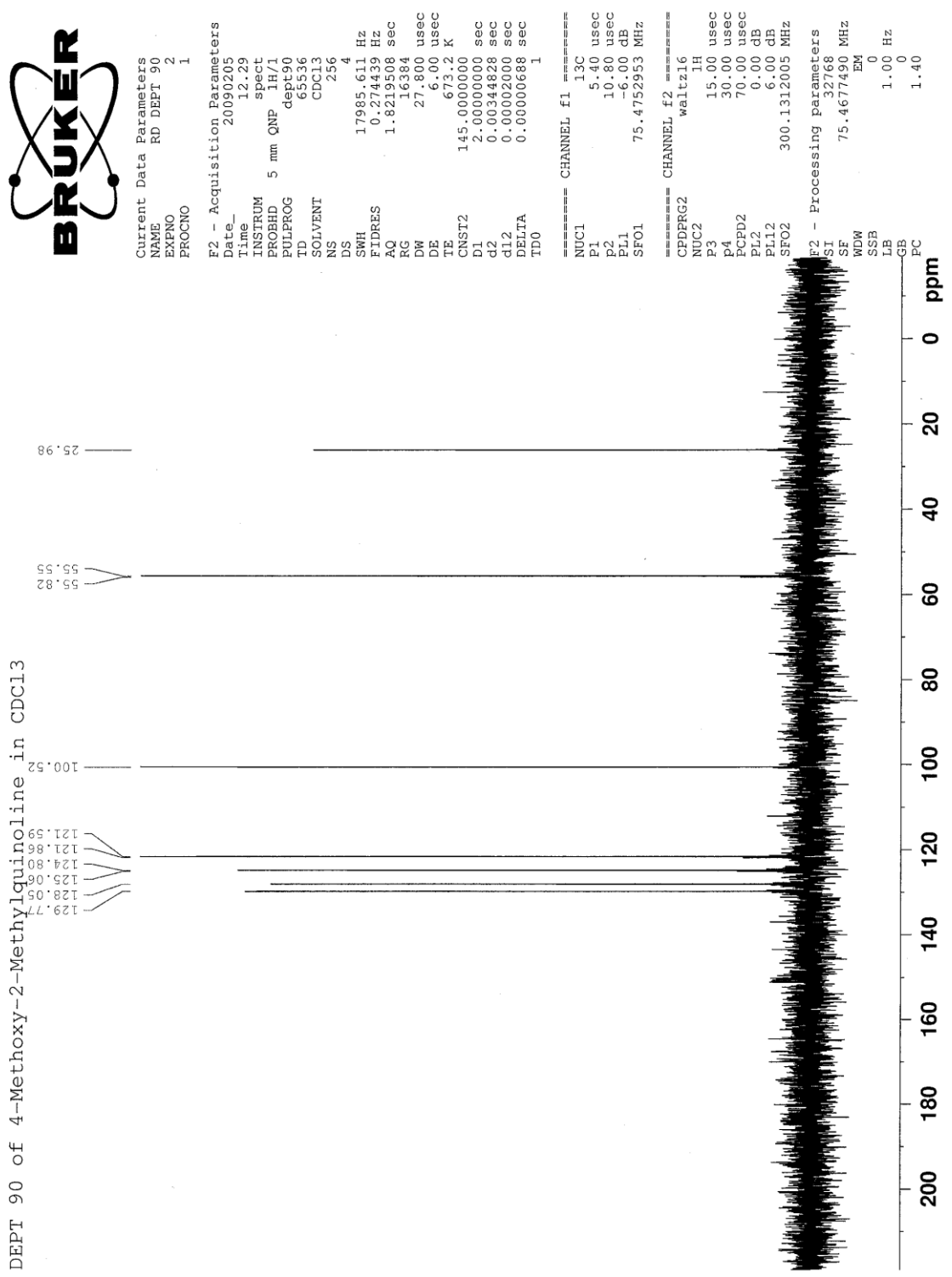


Figure 29: DEPT-90 of 4-methoxy-2-methylquinoline

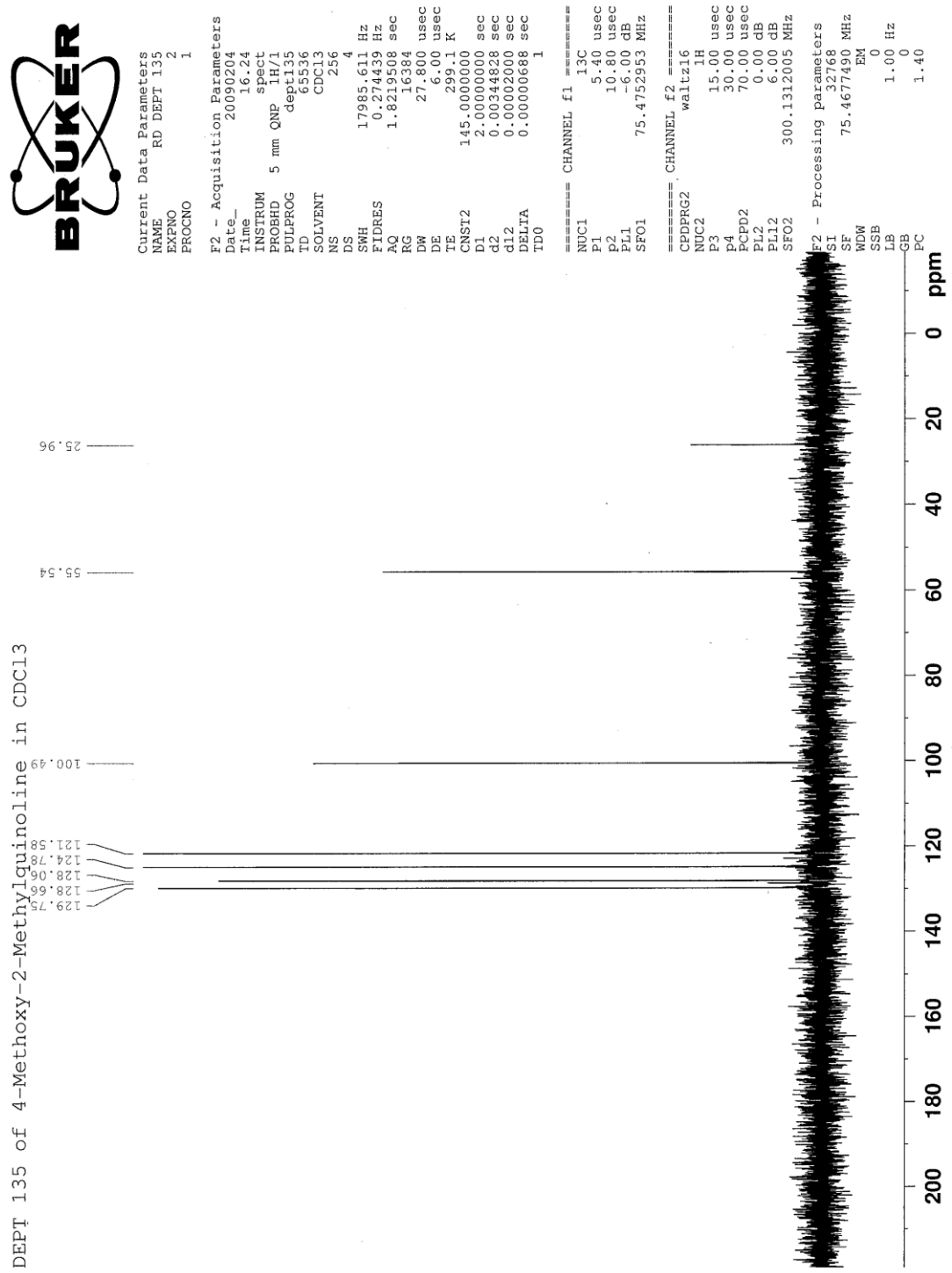


Figure 30: DEPT-135 of 4-methoxy-2-methylquinoline

WORK CITED

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CURRICULUM VITAE

I, Rachel Dripps, have a Bachelor of Science in chemistry from George Mason University and continued on to receive my Master's of Science there as well. My parents have been very supportive and loving. I have an older brother who brings comic relief to everyday activities. After my Master's degree, I am continuing on to get my PhD in chemistry from the University of Florida.