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Investigation of the Tandem Alkylation-Cyclization of Endocyclic Enol Ethers for the Preparation of Unusual Oxygen Heterocycles

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Abstract

The purpose of this research is to study the alkylation and subsequent cyclization reaction of endocyclic enol ethers such as 2H-dihydropyran. This sequence is expected to yield oxygen heterocycles whose structures represent unique scaffolds with promising functionality.

A series of trichloroacetimidates were selected for the direct alkylation of 2H-dihydropyran. Following the alkylation, the addition of acid was expected to induce an intramolecular cyclization reaction that would yield the desired oxygen heterocycles. This stepwise scheme would then be converted into a tandem process in which the reaction would be expected to proceed in a single pot.

Studies showed that the alkylation step of the reaction was unreliable, often yielding an unexpected compound as the major product or leading to the formation of vast amounts of side products, and very little desired product. In future studies optimization of the alkylation step in regards to the selected trichloracetimidates could prove useful in achieving the formation of oxygen heterocycles as the end goal.

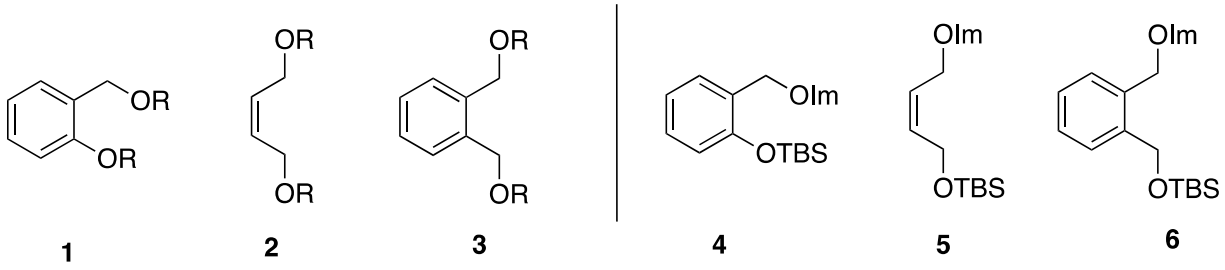
Executive Summary

Many biologically active substances are derived from natural products or synthetic compounds based on these natural products. These compounds and their structures exist in the known and synthetically accessible chemical space. As drug development continues, the value of biological targets that lie outside of this defined chemical space has become of interest. This new chemical space, the gaps between the known, is where new chemical structures synthesized through novel means exist. Using known molecules that exhibit activity, structurally relatable compounds that have yet to be synthesized and characterized can be explored. The molecular core, or scaffold, that originates a compound's activity is used to relate new compounds and aid in the creation of natural product like libraries that extend chemical knowledge into the unexplored, potentially bioactive space. In a perfect system, these new compounds are formed in reactions that require few steps and contain branching points to allow for the use of different sets of reagents that produce a higher diversity of products.

One such unexplored area of interest lies in the chemistry of 2H-dihydropyrans. The pyran skeleton is found in the substructures of many biologically active compounds, specifically those of oxygen heterocycles. The focus of this research to form these pyran-containing heterocycles through the tandem alkylation and intramolecular cycloaddition reaction of 2H-dihydropyran with a number of selected nucleophiles, a reaction type that has been unexplored for dihydropyrans. These reactions were first performed separately in order to ensure reactivity and formation of the alkylation product. The addition of acid to the alkylation product is expected to induce the intramolecular cyclization and formation of the desired carbon heterocycle.

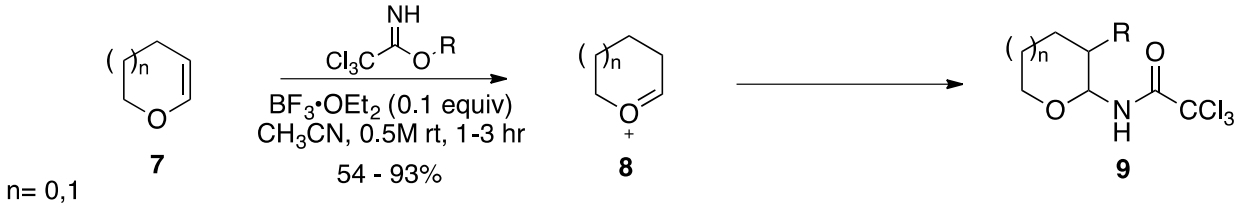
This reaction sequence was carried out first through the formation of the nucleophile, which begins with easily obtained electron rich benzylic and allylic systems. These alcohols are reacted with trichloroacetonitrile to form trichloroacetimidates that serve as the alkylating agents in the reaction with 2H-dihydropyran. The compounds used in this experiment required the addition of a protecting group (such as tert-butyldimethylsilyl) before the formation of the imidate. Some examples of starting materials and respective imidates are seen below (*Figure 1*).

Figure 1



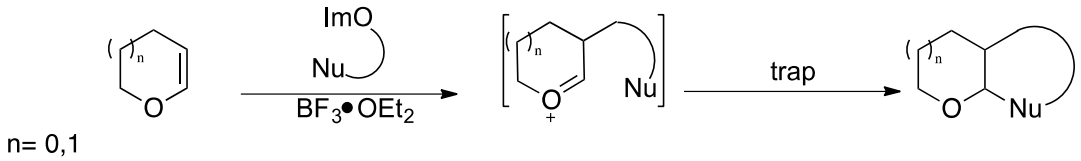
Once the imidate is formed, the alkylation reaction can be conducted. Past research in the Totah laboratory has shown the feasibility of direct alkylation of endocylic enol ethers such as 2H-dihydropyran. Treatment of endocylic ether **7** with trichloroacetimidates in the presence of Lewis acid BF_3•OEt_2 gave the mixed acetal **9** as the major product (*Scheme 1*). Formation of this compound results from initial alkylation to give the oxocarbenium ion **8** followed by addition of trichloroacetamide that is formed as a by-product in the alkylation reaction.

Scheme 1



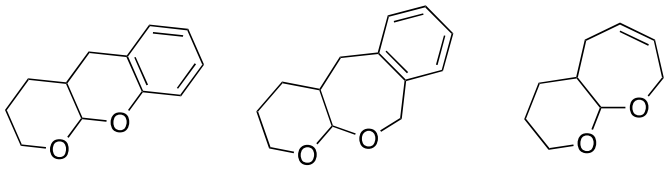
This chemistry is then extended to include the intramolecular trap of the intermediate oxocarbenium ion with a heteroatom or carbon nucleophile. The general framework of these reactions is shown below: (*Scheme 2*).

Scheme 2



This sequence is expected to produce ring systems of varying types, depending on the nucleophile used. In *Figure 2* **10**, **11**, and **12** are the corresponding expected products for imidates **4**, **5**, and **6** respectively. If the stepwise sequence is successful, the reactions should be easily converted into a tandem sequence that can be performed in a single-pot with the addition of acid to the reaction mixture after the alkylation process.

Figure 2



Overall, this project involves the synthesis of the imidates and evaluation of these compounds in both stepwise and one-pot tandem alkylation/nucleophile trap reaction sequences. This will result in the preparation of unusual new oxygen heterocycles through the exploration of a largely undocumented synthetic methodology in the hopes of uncovering new molecular scaffolds with promising functionality.

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Acknowledgements

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Chapter 1

Introduction

I. Structural Diversity and a New Chemical Space

Organic synthesis is often employed in the preparation of natural products and their analogs. It poses a way in which to prepare these compounds in larger quantities and facilitates the development of new molecules by providing a schematic for the design of products of interest. By forging ahead into new methods of synthesis, the understanding of chemical knowledge can be expanded into new possibilities.

Known compounds and their structures are said to occupy the known and synthetically accessible chemical space. In the interest of drug development and the creation of new leads, the value of biological targets that are identified to lie outside of this defined chemical space has become of increasing interest. The use of new synthetic methods can aid in the access and diversification of chemical structures. The “new chemical space”, the gaps between the known, is where new chemical structures synthesized through innovative means exist.[1]

In the early days, the discovery of new drugs and potential chemical structures was often by chance. These compounds formed the basis of the presently known chemical space. Through the use of current knowledge, more precise and rational studies can be conducted. This process begins through the identification of the gaps in the chemical space in order to create a guide.[2] By beginning with known molecules that possess a core or functional group that produces certain biological behavior, natural product-like libraries can be generated.[1] Exploring the new chemical space can lead to unusual molecular frameworks. Through the incorportation of key structural

elements of known compounds, these new molecules have a great potential to mimic the activity of biologically active substances, and may have improved potency or other beneficial properties.

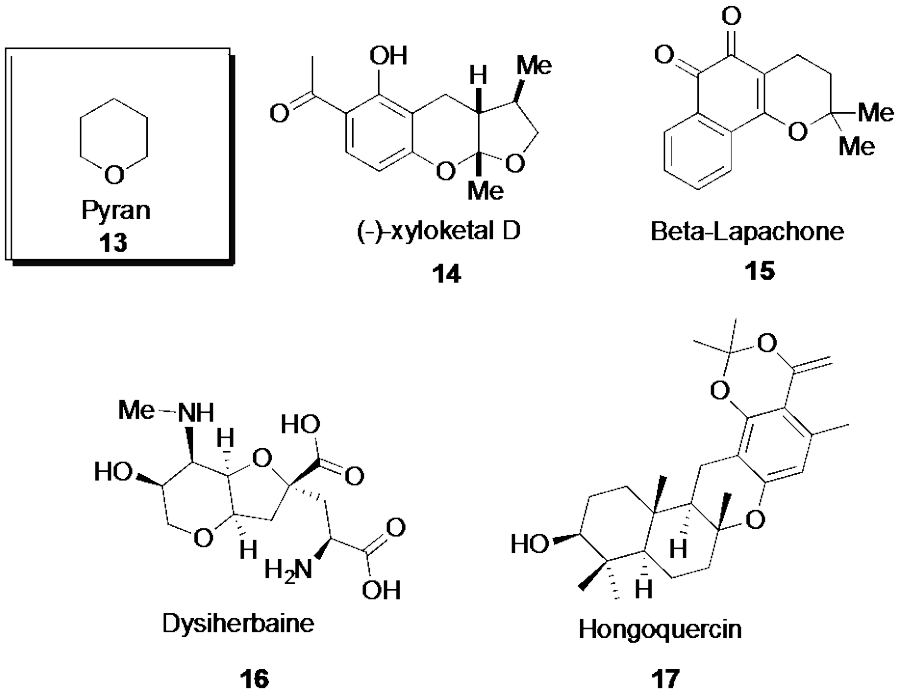
When new compounds are designed, it is beneficial if they are formed in sequences that require few steps and contain branching points to allow for the application of different sets of reagents that produce a higher diversity in the products. A linear multi-step process can take a considerable amount of time and has the potential to culminate in low yields. For this reason, when exploring new chemical space, the employment of different synthetic methodologies can be a key tactic.[2]

For example, one such method is the use of tandem reactions, where several steps can be performed at the same time in what is called a "one-pot" process. Each step of the reaction makes way for the next step by forming the needed reaction intermediates. These processes have the potential to greatly shorten procedures and provide synthetic routes with higher yields. When tandem reactions are employed in a clear and directed manner, new molecular scaffolds with promising functionality can be uncovered. These discoveries can help lead the way to new drug leads and other compounds with biologically relevant functions.

II. Pyran Derivatives as Targets for Oxygen Heterocycle Scaffolds

The chemistry of pyrans is an area of interest due to the occurrence of this basic pyran skeleton **13** found in the structures of naturally occurring, biologically active natural products.[3] Xyloketal D[4] **14**, Beta Lapachone[5] **15**, Dyhiserbaine[6] **16**, and Honqouercin[7] **17** are just a few examples of biologically active oxygen heterocycles.

Figure 3



Xyloketal D **14** is a fungal metabolite isolated from mangrove fungus obtained from the South China Sea.[4] β-Lapachone **15** is another natural product, and it is found in bark of the lapacho tree of South America. It has potential in the treatment of cancer, with a promising synergistic lethality with chemotherapy drug Taxol.[5] Dysiherbaine **16** is a selective agonist of non-NMDA type glutamate receptors, kainate receptors, that originates from the marine sponge *Dysidea herbacea*.[6] This biological activity is interesting as kainate receptors have yet to be fully understood due to the lack of compounds that interact with them. Lastly is Hongoquercin **17**, isolated from the extracts of an unidentified terrestrial fungus. This compound has shown antibiotic activity particularly against vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* bacteria.[7]

These are just a few examples of oxygen heterocycles. Compounds of this type are often seen to possess anti-tumor, antibiotic, or anti-fungal activity. It is for this reason that such oxygen heterocycles are a desirable scaffold to study in the development of the new chemical space.

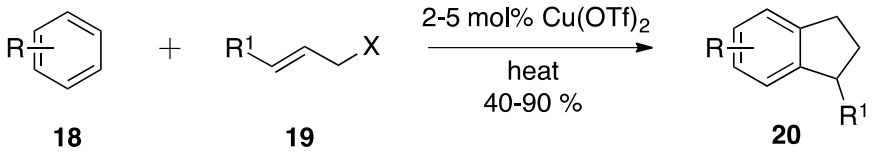
III. Tandem Reactions

Tandem reactions hold much promise in the synthesis of complex products as a number of reactions can be executed sequentially in a single pot. This process can effectively increase yield and lower the time needed to obtain a target molecule. Several successful examples of tandem reactions are shown below, enumerating the usefulness of such a strategy in the pursuit of natural product-like compounds with potential bioactivity.

a) Tandem Copper(II) Triflate Catalyzed Friedel-Crafts Alkylation and Intramolecular Cyclization

The Zhang group has developed a tandem one-pot synthesis of dihydroindenes.[8] Dihydroindenes are found in many biological active natural products, and although other syntheses exist, they are often multi-step processes that suffer from low yields.[8] Zhang describes a one pot synthesis of dihydroindenes from substituted benzenes and haloalkenes using copper(II) triflate to catalyze a tandem Friedel-Crafts alkylation/cyclization reaction (*Scheme 3*).

Scheme 3

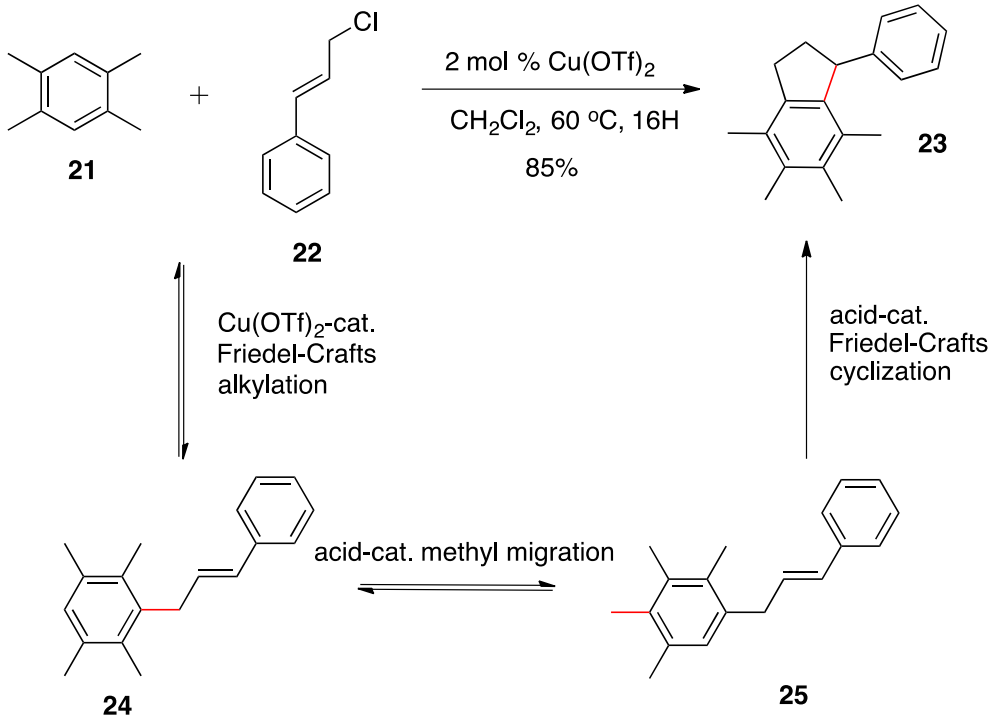


18 **19** **20**

This process was successfully conducted using a total of thirteen different arenes, consisting of different bis-, tris-, and tetrakis- methyl substitutions as well as two phenols and an ether. The yields varied from 40% to 90%, and the reactions proceeded under fairly mild conditions at temperatures of 100° C or less over 16 hours.

The tandem synthesis using a Friedel-Crafts cyclization used below (*Scheme 4*) is notable due to the formation of multiple carbon-carbon bonds in a single step. In this reaction sequence, alkylation of the tetrasubsitituted benzene **21** with an allylic halide was followed by an intramolecular cyclization to yield the desired dihydroindene skeleton.

Scheme 4



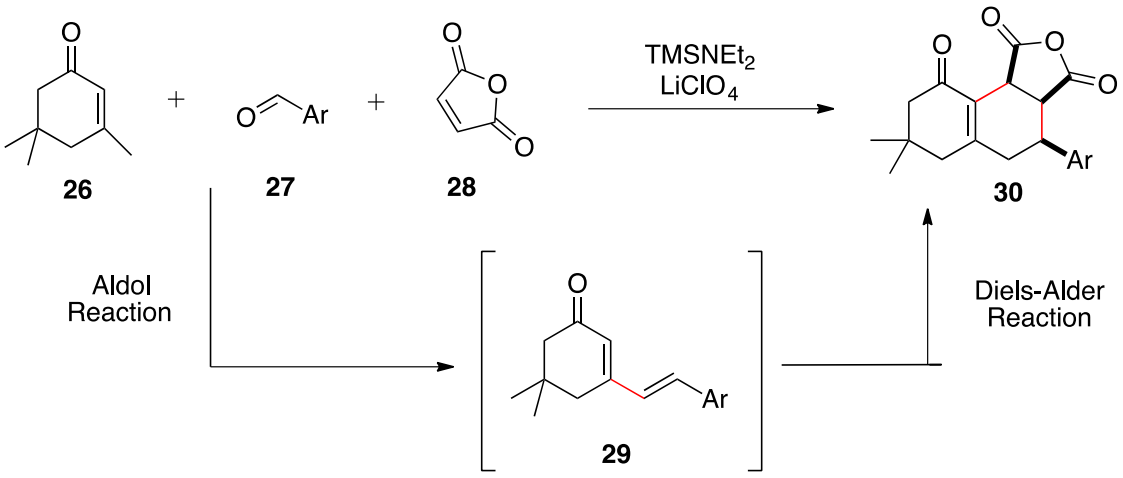
For example, as shown in *Scheme 4*, the alkylation occurs at the allylic position of the substituted benzene. A double methyl migration then occurs which is promoted by the Lewis acid catalyst $Cu(OTf)_2$. The acid then induces an intramolecular alkylation to form the final cyclized product.

This one-pot tandem reaction used above is of significance as it results in the formation of the dihydroindene skeleton using a tandem alkylation with a methyl migration followed by an intramolecular cyclization under reasonably mild conditions. The same method can be used in the formation of indene skeletons or benzo-fused carbocycles.[8]

b) Direct Synthesis of Dehydrodecaline Derivatives Through Tandem Aldol Condensation and Diels-Alder Reactions

The Abaee group successfully prepared dehydrodecaline derivatives through a tandem aldol condensation and Diels-Alder sequence of cyclic ketone **26** with selected aromatic aldehydes **27** and maleic anhydride **28**.[9] This process results in the formation of several carbon-carbon bonds. (*Scheme 5*)

Scheme 5



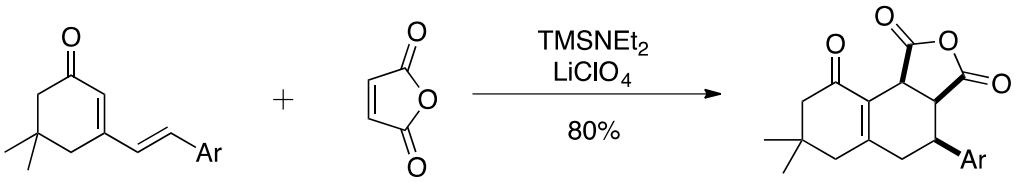
The first step in the sequence involves the aldol condensation reaction between ketone **26** and alydehyde **27** in the presence of $TMSNEt_2$ and $LiClO_4$ to create the intermediate diene **29** used in the Diels-Alder step. (*Scheme 6*)

Scheme 6

26 **27** **29**

This reaction is quite useful due to its ability to form conjugated diene products, and in this case the diene used in the Diels-Alder step of the reaction is produced.[9] The Diels-Alder reaction occurs when the dienophile **28** is then added to the reaction mixture, resulting in a cyclization that leads to formation of a six-membered ring. Diels-Alder reactions are useful as they not only form two carbon-carbon bonds and multi-membered rings, but also are predictable with the potential to form several stereocenters.[9]

Scheme 7



29 **28** **30**

The final product **30**, the *endo* Diels-Alder product, was exclusively formed in high yield within 120 minutes (*Scheme 7*). A selection of different aldehydes was used to show the versatility of the reaction through different substitutions of the aryl group. Yields ranged from 72% to 86% with reaction times of 60-120 minutes.

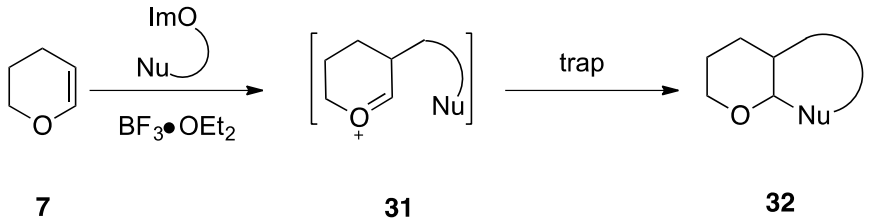
The procedures reported by the Abaee group present an efficient synthesis of dehydrodecalines with high yields and with no need for isolation of the intermediate diene. The reaction is predictable and results in the formation of three new carbon-carbon bonds as well as a six-membered ring in a one pot process.[9]

IV. Direct Alkylations of Dihydropyran

Tandem reactions have shown themselves to be successful in the rapid formation of complex molecular skeletons. The potential utility of the pyran scaffold combined with the efficiency of tandem reaction sequences presents an opportunity to form unusual oxygen heterocycles.

Through a tandem alkylation-cyclization sequence, the formation of unique pyran derivatives is possible. These products can be used as intermediates in natural product synthesis or for the synthesis of compounds that represent the new chemical space.

Scheme 8

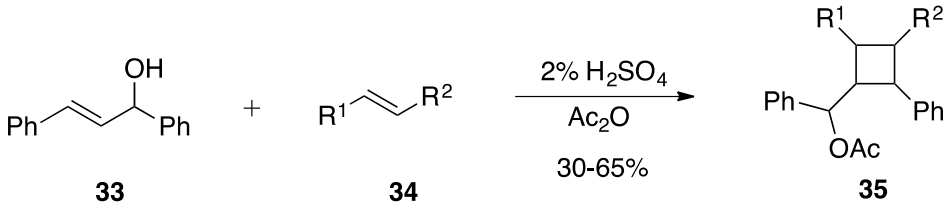


Alkylation of 2H-dihydropyran with a suitable functionalized imidate is expected to give a fused ring system after an intramolecular trap of the intermediate oxocarbenium ion **31** with an oxygen or carbon nucleophile (*Scheme 8*). For this sequence, further studies on the alkylation of 2H-dihyropyran and other endocyclic enol ethers was needed. Information on the direct alkylation of endocyclic enol ethers is scarce, though this reaction has been shown to be feasible. The Siedlecka and Zhu groups have reported single examples of a direct alkylation of dihydropyran.[10,11] The Totah group has recently studied the reaction in more detail.

a) Alkylation of 2H-Dihydropyran with a Diphenyl Allylic Alcohol

Some evidence for the direct alkylation of 2H-dihydropyran may be found in the existing literature. For example, while exploring a new method for the synthesis of cyclobutanes, the Siedlecka group observed the direct alkylation of a cyclic enol ether. The primary method of synthesis was the use of a cationic [2+2] cycloaddition reaction between an allyl cation and an electron rich double bond. This reaction led to the formation of cyclobutanes, which are a compound of significance found as the substructures in natural products.[10]

Scheme 9

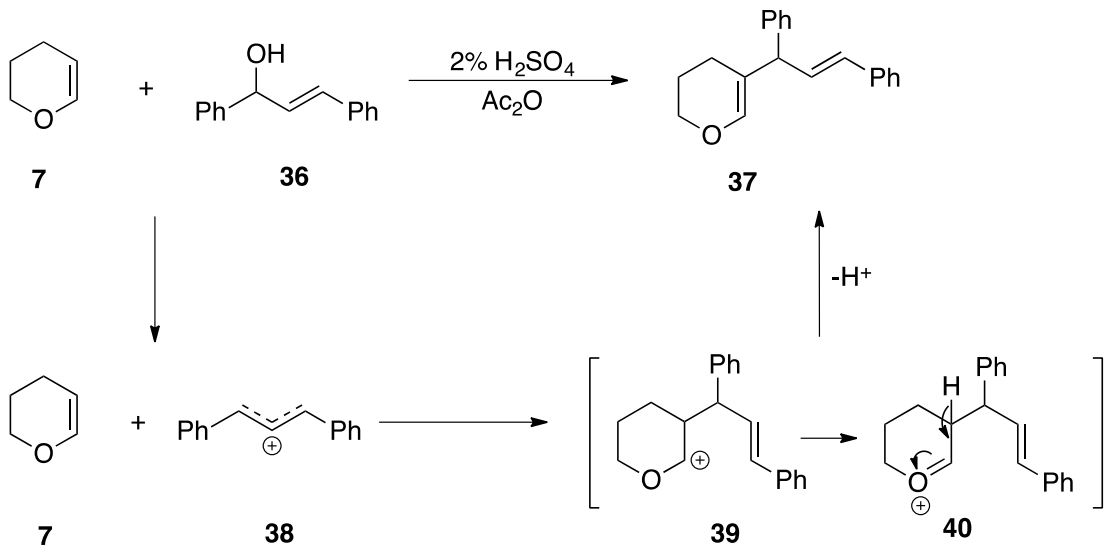


33 **34** **35**

The reaction was conducted several times, varying both R groups on alkene **34**. The R groups tested consisted of phenols, various allyl groups, and acetyl groups. These reactions resulted in the formation of cyclobutane products that were for the most part new compounds.[10] Yields ranged from 30% to 65% for the reactions.

In an attempt to identify the mechanism of the cyclobutane formation, 2H-dihydropyran and an allylic alcohol were subjected to the same reaction conditions (*Scheme 9*). 2H-dihydropyran was selected due to its usefulness as a carbocation trapping agent.[10] The result of the reaction was an alkylation of the dihydropyran with the carbocation from the allylic alcohol **33**. This reaction helped support the theory that an intermediate carbocation was generated during the cyclobutane formation.

Scheme 10



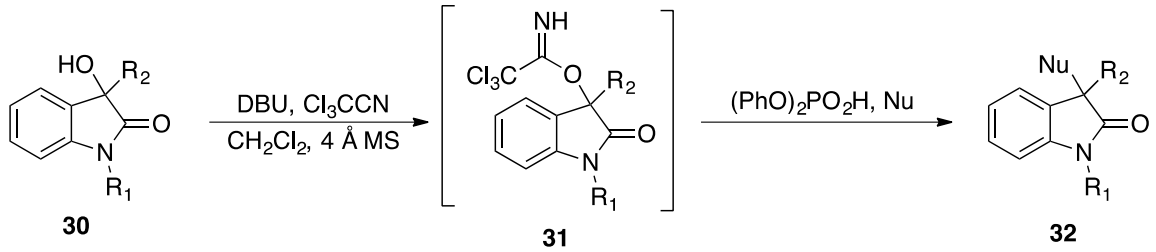
This example is one of few found for the direct alkylation of dihydropyran, and was not the primary goal of the research, but rather a side reaction carried out to gather more information about the process under study.

b) Alkylation of 2H-Dihydropyran Through The Use of Trichloroacetimidates to form 3-Hydroxy-oxindoles

A second example of the alkylation of 2H-dihydropyran was reported by the Zhu group as part of their efforts towards the preparation of 3,3-disubstituted oxindoles. Oxindole substructures are found in many biologically active natural products.[11] The researchers used a one-pot conversion of 3-hyroxyindole **30** to a trichloroacetimidate, and an acid-catalyzed substitution reaction to prepare 3,3-disubstituted oxindoles like **32** (*Scheme 11*). Trichloroacetimidates are excellent leaving groups, and in the presence of acid a carbocation can be formed for the addition to the oxygen of the imidate. The reaction was conducted in a solution

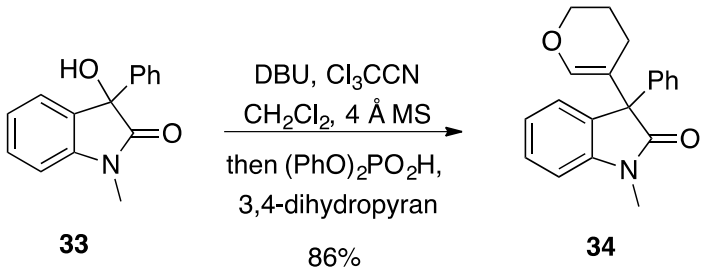
of dichloromethane with trichloroacetonitrile and catalytic 1,8-diazabicycloundec-7-ene (DBU) and allowed to stir at room temperature. Diphenylphosphoric acid and a selected nucleophile were then added to the reaction mixture to facilitate the nucleophilic displacement.

Scheme 11



The nucleophiles used in order to evaluate the scope of the tandem reaction included alcohols, phenols, thiols, amines, anilines, indoles, pyrroles, and an enol ether. 2H-dihydropyran was selected due to its reactivity as a nucleophile. The resulting alkylation of the oxindole with dihydropyran afforded an 86% yield. This reaction illustrated the effectiveness of trichloroacetimidates in the alkylation of 2H-dihydropyran.

Scheme 12

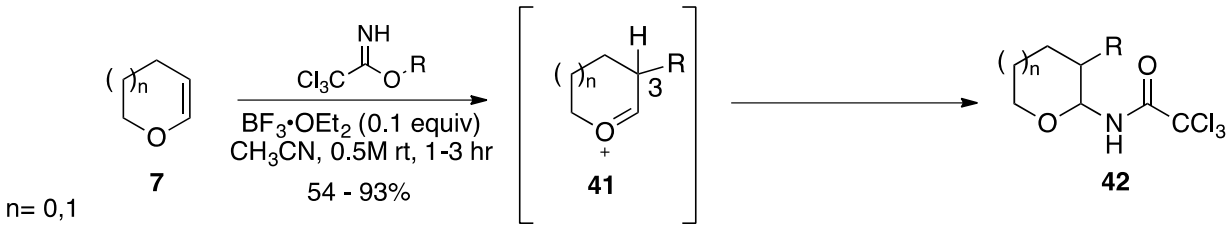


Although the main subunit of interest was the 3-hydroxyindole and the resulting 3,3-disubstituted oxindole, the reaction with dihydropyran is essentially an alkylation reaction. The experiment itself was not geared towards studying dihydropyran and its reactivity in alkylations, but nonetheless provides a relevant example.

c) Optimization Studies of the Alkylation of Endocyclic Enol Ethers with Trichloroacetimidates

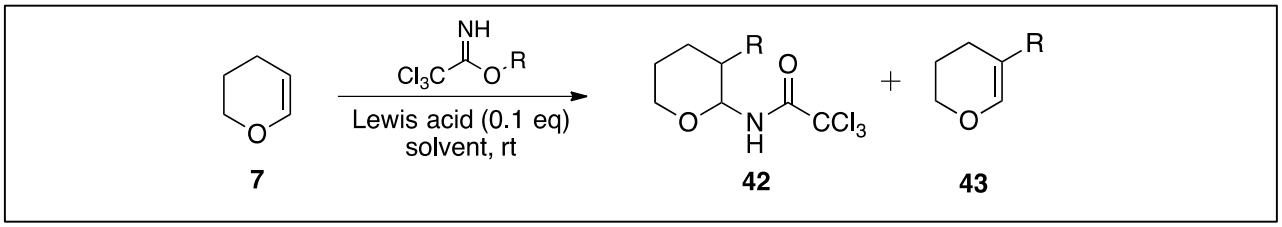
Past work in the Totah group has further shown that direct alkylation of endocylic enol ethers is feasible.[12] Treatment of endocylic ethers **1** with allylic and benzylic trichloroacetimidates in the presence of BF_3•OEt_2 gave the mixed acetal **42** as the major product (*Scheme 13*). Formation of this compound results from initial alkylation to give the oxocarbenium ion **41** followed by addition of trichloroacetamide that is formed as a by-product in the reaction. In this reaction, trichloroacetimidates are used as the alkylating agents.

Scheme 13



Direct alkylation of 2H-dihydropyran can result in both addition product **42** and elimination product **43**. It is hypothesized that after alkylation the trichloroacetamide attacks the oxonium ion intermediate to give addition product **42**. The trichloroacetamide is generated during formation of the electrophile, which is facilitated by a catalytic amount of BF_3•OEt_2. Alternatively, loss of a proton from C3 of intermediate **41**, results in the formation of the elimination product **43.** Through a series of optimization studies, conditions were identified to give addition product **42** in the highest yield, (*Table 1*).

*Table 1***.** Optimization of the addition product



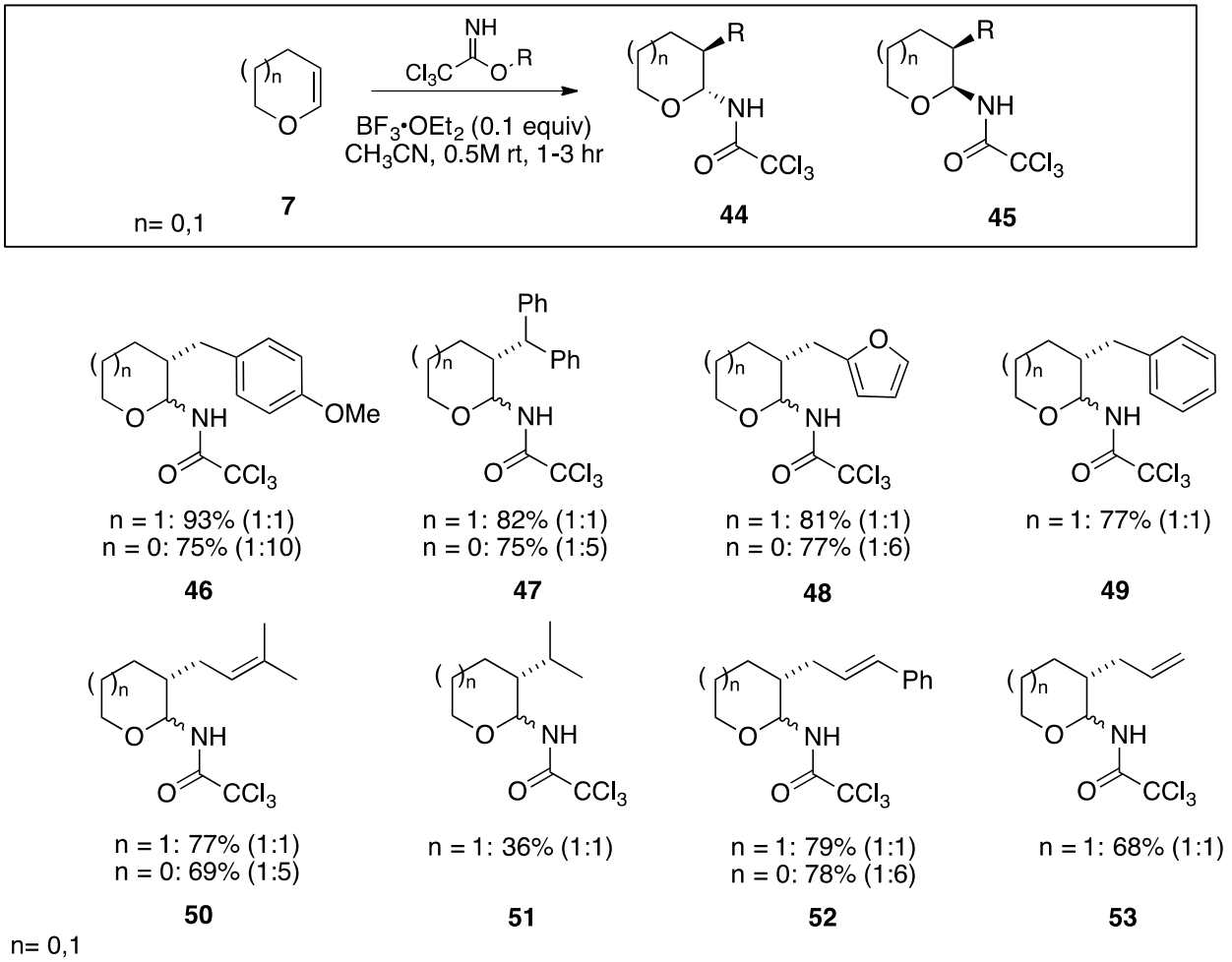
entry	R[a]	Lewis Acid	solvent	concentration	Ratio (42:43)	Yield 42
1	PMB	BF_3•OEt_2	benzene	0.5 M	5:1	75%
2	PMB	BF_3•OEt_2	EtOAc	0.5 M	4:1	27%
3	PMB	BF_3•OEt_2	THF	0.5 M	5:1	66%
4	PMB	BF_3•OEt_2	CH_2Cl_2	0.5 M	4:1	68%
5	PMB	BF_3•OEt_2	MeCN	0.5 M	1:0	86%
6	PMB	BF_3•OEt_2	MeCN	0.1 M	1:0	77%
7	DPM	$EtAlCl_2$	MeCN	0.5 M	10:1	71%
8	DPM	$TiCl_4$	MeCN	0.5 M	2:1	75%
9	DPM	$AlCl_3$	MeCN	0.5 M	--	--
10	DPM	$ZnCl_2$	MeCN	0.5 M	--	--
11	DPM	$MgBr_2$	MeCN	0.5 M	--	--

a. PMB: p-methoxy benzyl, DPM: diphenyl methyl

Several conditions were tested in order to ensure addition **42** formed in the highest yield, while reducing the formation of the elimination product **43**. The use of Lewis acids $AlCl_3$, $ZnCl_2$, and $MgBr_2$ in entries 9 through 11 resulted in no product, as none could be observed in the crude NMR. As seen in entries 7 and 8, $EtAlCl_2$ and $TiCl_4$ did provide the reaction products in fairly good yield, but the ratio between addition and elimination product were not as good as with BF_3•OEt_2. When a lower concentration reaction with BF_3•OEt_2 was used (entry 6) a lower yield was reported. Entry 5 shows that the 0.5 M reaction with BF_3•OEt_2 in acetonitrile gave the highest yields while solely providing the desired addition product **42**.

A variety of allylic and benzylic imidates reacted cleanly with both dihydropyran and dihydrofuran under the established conditions. Both *cis* and *trans* products were isolated from the reaction mixture in good to excellent yields (*Figure 4*).

Figure 4



Alkylation using 2H-dihyropyran resulted in equal ratios of *cis* to *trans* product, while dihydrofuran exhibited a higher selectivity favoring formation of the *trans* product. Generally a lower yield was seen with alkylations of dihyrofuran. Alkylations with 2H-dihyropyran were met with satisfactory yields of 68% to as high as 93%, with the exception of compound **51**. Compound **51** did however show the possibility of alkylation with aliphatic imidates, albeit with a reduced yield.

These studies show the feasibility of using the direct alkylation of an enol ether such as 2H-dihydropyran as part of a tandem reaction process. It is expected that with the use of selected imidates, a cyclization can be induced to occur following the alkylation of 2H-dihyropyran.

Chapter 2

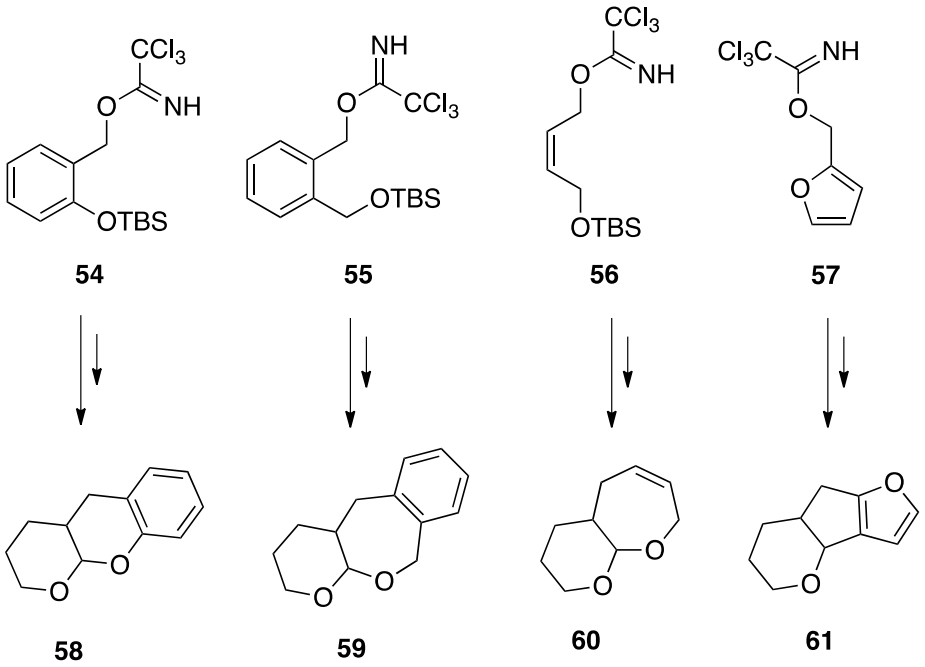
Results & Discussion

I. Tandem Alkylation and Intramolecular Cyclization of Endocyclic Enol Ethers

The direct alkylation of endocylic enol ethers such as 2H-dihydropyran has been shown to be feasible. It is the goal of this research to expand on this chemistry in order to define conditions that promote an intramolecular cyclization that can later be run in tandem with the alkylation. These steps will first be conducted separately, and upon successful completion are expected to be capable of conversion into a tandem sequence. The tandem alkylation and cyclization reactions will prepare oxygen heterocycles with the basic pyran skeleton that represent potentially useful structures. The alkylation reaction will utilize 2H-dihydropyran with a number of trichloroacetimidates, which will serve as the alkylating agents. This sequence is expected to produce ring systems of varying types, depending on the nucleophile used.

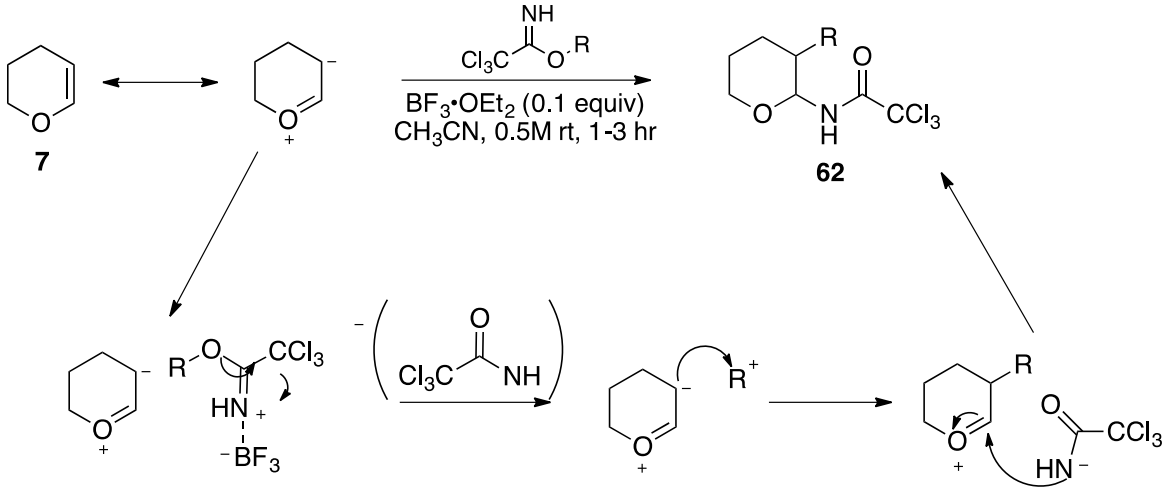
The compounds selected to serve as the trichloroacetimidates were chosen due to the possession of allylic and benzylic hydroxyl systems, some of which may be N and O heterocycles, and all of which contained additional functionality that could serve as the secondary nucleophile to trap the oxonium ion in the intramolecular cyclization. These potential substrates were compounds that could be produced in one to two steps from commercially available compounds, as before the imidate was prepared, often the compound required the protection of functional groups to maintain the chemoselectivity of the subsequent reactions. The following compounds were targeted to be prepared and alkylated in the scope of this study, with their expected final products:

Figure 5



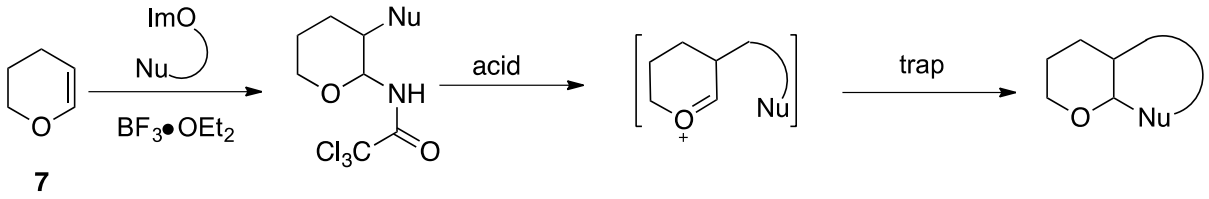
Imidates **54, 56,** and **57** were successfully prepared, but only imidates **54** and **56** were alkylated. Imidates were prepared using the reagent trichloroacetonitrile with catalytic 1,8-diazabicycloundec-7-ene in dry dichloromethane. This process proceeded with fairly good yields of about 84% to 90%. After the imidates were successfully prepared, the alkylation reaction could be conducted. The alkylation reaction is believed to proceed via an S_n1 mechanism:

Scheme 14



The reaction involves the direct alkylation of 2H-dihydropyran with catalytic BF_3•OEt_2. In the presence of BF_3•OEt_2, the trichloroacetimidate will fall apart, yielding the cationic R group and the trichloroacetamide anion. The 2H-dihydropyran then attacks the electrophilic R group. The trichloroacetamide anion then adds at the double bond of the oxonium ion that is formed by the resonance of 2H-dihydropyran, thereby resulting in alkylation product **62**. As seen in the examples conducted by the Totah group in the past, this reaction is expected to yield *cis* and *trans* forms of the product.

Scheme 15



7

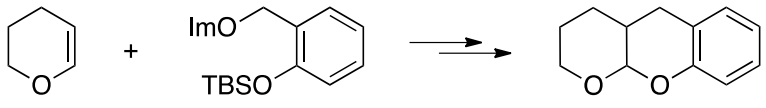
The next step in the process after the alkylation is the intramolecular nucleophilic trap by which a fused ring heterocycle will be formed. The addition of acid to the reaction mixture would induce the intramolecular trap. This is catalyzed by the loss of a protecting group from the electrophilic R group containing a secondary nucleophilic functionality, thereby allowing for an intramolecular nucleophilic trap.

The anticipated heterocycles formed by this process can potentially possess interesting functionality and represent structures unlike those found in nature. If the stepwise sequence is successful, alkylation followed by cyclization, the reactions should be capable of conversion into a tandem sequence that can be done in a single-pot.

II: Alkylation of dihydropyran with o-(t-butyldimethylsilyloxy)benzyl alcohol imidate with dihydropyran and attempted cyclization

The first system studied was the preparation of ketal **58** from 2H-dihydropyran **7** and o-(t-butyldimethylsilyloxy)benzyl alcohol imidate **54**, the selected trichloroacetimiade for this process (*Scheme 16*).

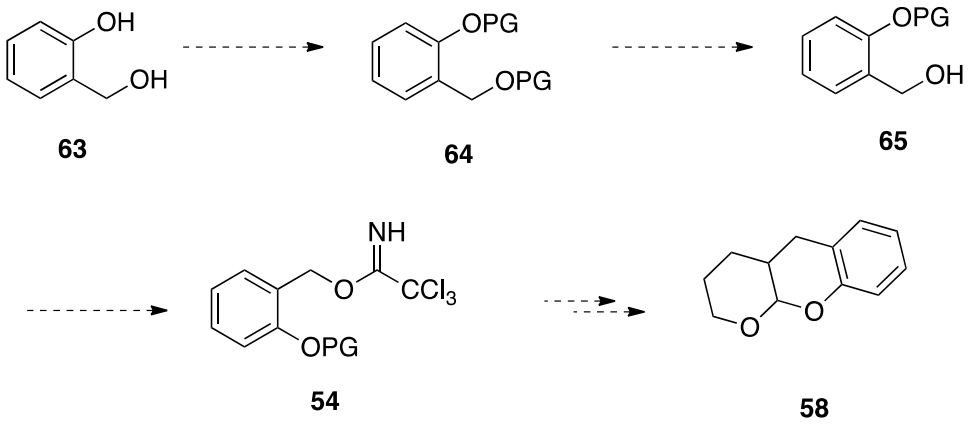
Scheme 16



7 **54** **58**

This process began through the preparation of imidate **4** from the commercially available compound 2-hydroxybenzyl alcohol **63**.

Scheme 17



63 **64** **65**

54 **58**

In order to product the desired imidate, the reactivity of the phenol needed to be masked through the selective incorporation of at protecting group at that position. This proved to be a difficult task as both alcohol groups were known to possess similar reactivity, thus requiring a complete protection followed by a selective deprotection of the primary alcohol. This reaction is known, and was then followed by the formation of imidate **54**. After this step an attempted

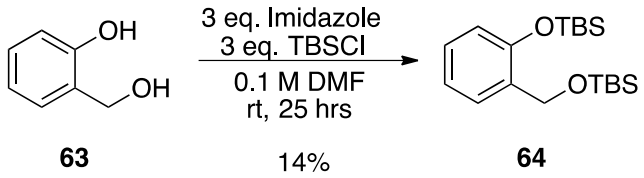
alkylation and cyclization were carried out with the anticipation that oxygen heterocycle **58** would be formed.

a) Protection and Selective Deprotection of 2-hydroxylbenzyl alcohol

Due to the expected similarity in reactivity between the phenol and the benzyl alcohol, the protection process for 2-hydroxybenzyl alcohol first required the complete protection of both alcohol groups followed by the selective deprotection of the phenol.

The first step, the protection of both alcohol groups, was attempted using two different methods. The first method involved the use of imidazole with tert-butyldimethylsilyl chloride in dimethylformamide at room temperature. Even after a reaction time of 25 hours, the reaction did not go to completion. After purification the reaction provided a relatively low yield of about 14% (*Scheme 18*). The tertbutyldimethylsilyl protecting group is sensitive to acid and was found to decay due to the acidity of silica when the compound was analyzed through TLC. The low yield may then be explained by the lack of the use of a basic compound in the eluent, such as triethylamine, during purification via flash chromatography. This would thereby reduce the yield of the desired product. It was ascertained that these conditions might not have been optimal for the protection of diol **63**, therefore necessitating the search for a different method of protection.

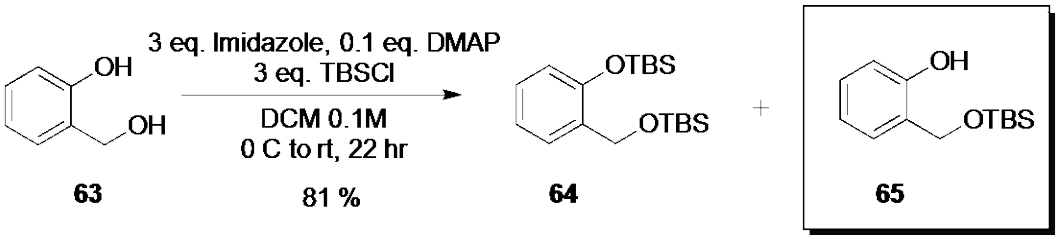
Scheme 18



The second method explored used catalytic dimethylaminopyridine with dichloromethane as the solvent. The reagents were added at 0°C and the reaction was allowed to slowly warm to room temperature. These reaction conditions and the addition of dimethylaminopyridine as a

catalyst proved to be superior to the previous method as this reaction had a notably higher yield of 81% (*Scheme 19*). In this case, the improved yield may also be due to the use of triethylamine during purification to ensure that the protecting groups did not fall off in the acidic environment of the silica gel in the flash chromatography column. Henceforth, every reaction purification involving a compound that had a protecting group was purified with 2%-5% triethylamine in the eluent.

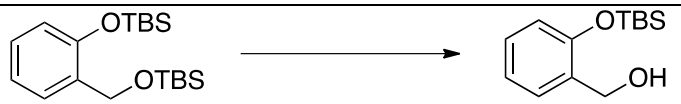
Scheme 19



Although the reaction yield was generally higher with this method, sometimes the reaction did not proceed to completion, and a monoprotected compound was also isolated. This was discovered to be the product with only the benzylic alcohol protected **65**.

A selective deprotection of the di-protected compound **64** was the next step. The selective deprotection reaction itself proved to be more difficult than expected.

Table 3. Selective deprotection reactions of di-protected 2-hydroxylbenzyl alcohol



64 **66**

Entry	Scale (g)	Reagents	Solvent	Temperature	Time	Yield
1	0.1	0.1 eq PPTS	0.1 M EtOH	50°C	60	N/R
2	0.1	cat. PMA/SiO_2	0.1 M THF	rt	30	N/R
3	0.1	0.1 eq PPTS	0.1 M EtOH	50°C	60	78%
4	0.5	0.1 eq PPTS	0.1 M EtOH	50°C	60	27%
5	0.75	0.1 eq PPTS	0.1 M EtOH	50°C	60	33%
6	0.5	0.1 eq PPTS	0.1 M EtOH	50°C	90	89%
7	2.00	0.1 eq PPTS	0.1 M EtOH	50°C	72	96%

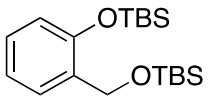
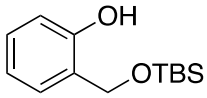
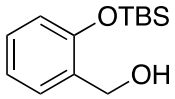
As seen above, this reaction was run several times. The first attempt at using pyridinium p-toluene sulfonate (PPTS) at 50°C resulted in no reaction taking place after being allowed to run for an hour. It is unknown as to why this reaction did not proceed. It may have been due to the presence of not enough pyridinium p-toluene sulfonate to cause the reaction, or the reaction failing to reach a temperature of 50°C. An improperly calibrated balance and a faulty thermometer could cause these problems. In subsequent entries following the first attempt, a different thermometer and re-calibrated balance were used.

A new method was discovered for the selective deprotection, requiring the preparation of a PMA/SiO_2 catalyst from $H_3PMo_{12}O_{40}\bullet 24H_2O$ and SiO_2 in methanol. The catalyst was prepared by slowly adding silica to a mixture of PMA in methanol. The solution was allowed to stir for 36 hours, at which point the methanol was removed *in vacuo*. The reaction did not

proceed with the use of the prepared catalyst, and it is hypothesized that the catalyst was improperly prepared and therefore did not function as expected.

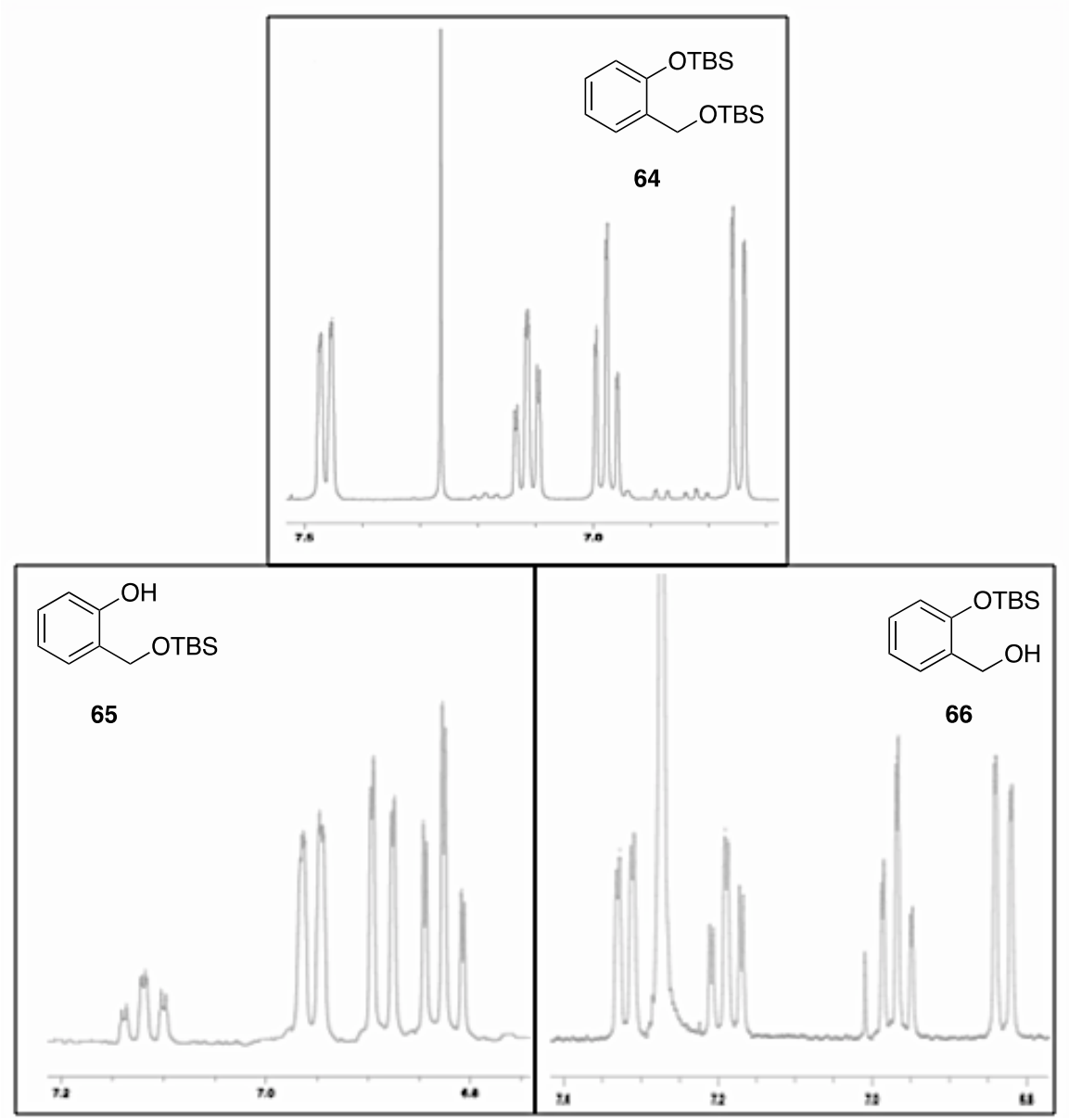
At this point, the first method was attempted a second time. This time a yield of 78% resulted (entry 3). The reaction evidently contained enough reagents and was run at a temperature allowing for the selective deprotection during this attempt. This same reaction was run several more times. Over the course of these reactions, several points were discovered. Firstly, with the exception of entry 4, it seems the larger the scale of the reaction, the higher the yield. This is seen most distinctly between entries 3, 6, and 7 where the yield gradually increased all the way to an impressive 96% yield at a reaction scale of 2.0 grams. Better yields were also observed when the reaction was allowed to run longer than reported by the literature, a trend seen in entries 6 and 7. Another important feature of this reaction was that it needed to be worked up and purified the same day. If the reaction mixture was stored overnight, even at -20°C, the product would decompose into the original diol **63**. This problem accounts for the low yields in entries 4 and 5.

*Table 4***.** Literature reported values of chemical shifts for **64**[13], **65**[14], and **66**[13].

Functional Group	 **64**		 **65**		 **66**	
	Chemical Shifts (δ) and Multiplicity					
OH			8.03	singlet	2.19	singlet
Aromatic	7.43	doublet	7.12	triplet	7.31	doublet
	7.07	triplet	6.91	doublet	7.18	triplet
	6.94	triplet	6.84	doublet	6.96	triplet
	6.71	doublet	6.78	triplet	6.82	doublet
CH_2	4.73	singlet	4.87	singlet	4.68	singlet
tBu	0.97	singlet	0.90	singlet	1.02	singlet
	0.92	singlet				
SiMe	0.18	singlet	0.11	singlet	0.26	singlet
	0.07	singlet				

Another problem encountered throughout the protection and selective deprotection process was due to the similarity in ^{1}H NMR peaks and chemical shifts of the fully protected **64** and the two-monoprotected products **65**, **66** (*Table 4*). Verification using published data was used to ascertain the identity of the individual isomers. All three compounds featured two doublets and two triplets in the aromatic region, with each set of peaks representing a single aromatic proton. While the order of these peaks and their chemical shifts differed slightly, they possessed a similar pattern of peaks and were not possible to identify by inspection. Research into the spectral data of these compounds proved challenging as it was difficult to find reliable sources. *Figure 6* shows the aromatic peaks for diprotected product **64** and the primary alcohol protected product **65** as well as the aromatic peaks for compound **66**.

Figure 6: Aromatic peaks from ^{1}H NMR of protection reaction products.



Upon acquiring the spectral data for all three compounds, a study of the ^{1}H NMR products from *Scheme 19* showed that product **65** was indeed the side product. Unfortunately, the desired product with only the phenol protected **65**, did not appear in the protection reaction as a secondary product. This suggests that the primary alcohol was protected first in the reaction and attempting to use an excess of di-protected **65** with tert-butyldimethylsilyl chloride in order to promote monoprotection would probably yield product **65** instead of the desired product **66.**

To identify between products, the multiplicity and chemical shifts of the aromatic peaks were the identifying features. Di-protected diol **64** and the product with protection of only the primary alcohol **65** featured very similar chemical shifts, but the multiplicities of their aromatic peaks were different. It was also helpful to note that all peaks for product **65** occurred upfield to the solvent peak (deuterated chloroform) at δ 7.27 ppm.

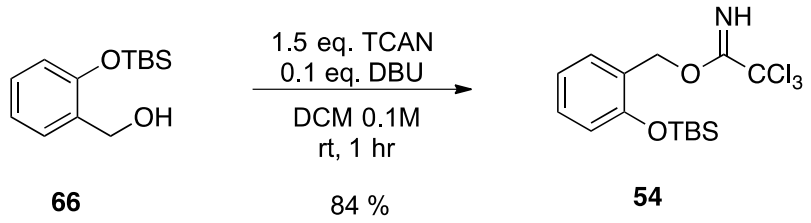
The selective deprotection step presented the real challenge in identifying products. This reaction further required careful analysis of the ^{1}H NMR. Starting material **64** not only had the same order of multiplicity of aromatic peaks as product **66**, but the locations of the chemical shifts for these peaks were also close. The differentiation between these two compounds was more easily made through comparison of TLC R_f values due to the higher polarity of the unprotected alcohol in compound **66** giving it a lower R_f value than di protected **64**. The protected primary alcohol **65** and the protected phenol **66** were more easily differentiated once information on their spectra was obtained from the literature. Although their peaks possess similar chemical shifts, compound **66** has a doublet downfield of the solvent peak, followed by two triplets upfield from the solvent peak and a doublet, while compound **66** had a triplet two doublets and a triplet upfield to the solvent peak.

Through several attempts a successful method for the protection and selective deprotection of 2-hydroxybenzyl alcohol **63** was perfected. This method of deprotection enabled the formation of larger amounts of material in preparation for the synthesis of the imidate.

b) Imidate formation from 2-tert-butyldimethylsilyloxyphenylmethanol

The formation of the imidate on the primary alcohol of monoprotected compound **66** was fairly straightforward.

Scheme 20



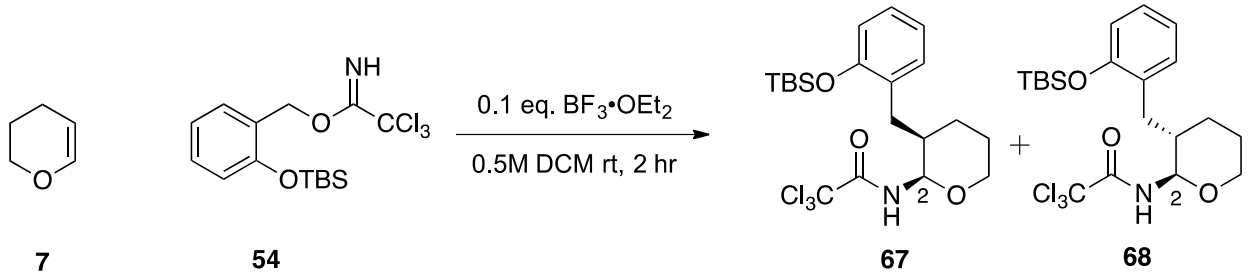
66 84 % **54**

Using trichloroacetonitrile with catalytic 1,8-diazabicycloundec-7-ene in dry dichloromethane, the trichloroacetimidate was formed with a high yield of 84%.[15] The same reaction was run two more times with yields of 42% and 64%. Upon concentration of the reaction mixture the product was purified by column chromatography. As in previous reactions, the use of triethylamine was added to the elution solvent to counteract the acidity of the silica.

c) Alkylation using the imidate formed from 2-hydroxylbenzyl alcohol

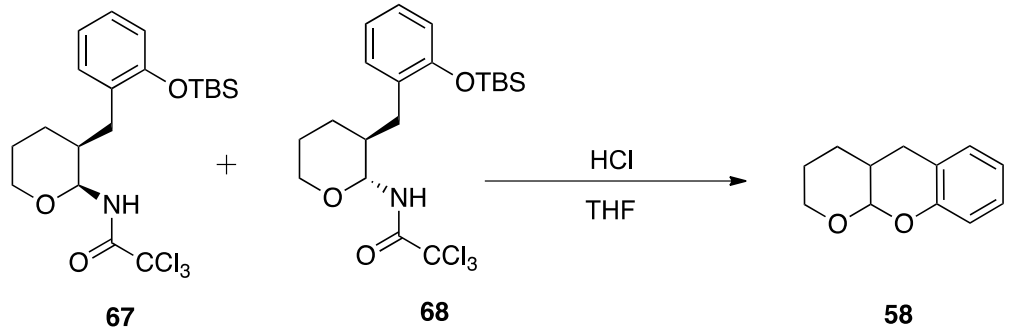
The next step was then the alkylation of the prepared imidate **54**. The reaction was run with one equivalent of 2H-dihydropyran in dichloromethane followed by catalytic BF_3•OEt_2, at which point the reaction was left to run for two hours under an argon atmosphere. The first attempt yielded the *cis* product **67** and *trans* product **68** according the ^{1}H NMR of the crude reaction. Alkylation products are defined by two peaks in the NMR spectra, one triplet representing the *trans* product, and a doublet of doublets that defines the *cis* product. These peaks stem from the proton on the C2 of both products.

Scheme 21



The crude product was dissolved in tetrahydrofuran with 10% hydrochloric acid in order to see if the cyclization could be induced. The attempt at cyclization was inconclusive, as the TLC plate did not seem to change greatly over the course of several hours due to the presence of a vast multitude of side product. The reaction was halted and an ^{1}H NMR was obtained. This spectrum showed that the peaks denoting products **67** and **68** had disappeared; but that the presence of side product and contaminants was so high, very little could be observed. *Scheme 21* shows the desired products of the alkylation and the subsequent cyclization. It would seem that the impurities present from using the crude alkylation product in this reaction made it difficult to identify cyclization product **58**.

Scheme 22



The alkylation was later attempted again. It was done one the same scale as the previous alkylation (200 mg) and produced similar results. The alkylation was successful according to the ^{1}H NMR, but there was a large presence of side product. Attempts at purification yielded some

product, but it could not be separated from the unknown side products of the reaction. Fractions from the column of the crude reaction were taken with the expectation that further purification via column chromatography could yield the desired products. These fractions still could not be separated from impurities.

A third and final attempt was made at alkylating with compound **54**. This was done on a larger scale of 0.50 grams. The alkylation yet again appeared to be successful, but with a myriad of side products. Following column chromatography, *trans* product seemed to prevail in the column fractions. A single fraction believed to contain a large amount of *trans* product **68** was taken and treated with tetra-n-butylammonium fluoride. This was done in the hope of removing the protecting group on the phenol, thereby making the product more polar in order to make separation from the non-polar side products easier. Treatment with tetra-n-butylammonium fluoride proved to be inconclusive as such a small amount of product was left over at this point that further analysis was difficult, and the desired product was not able to be isolated from the reaction mixture.

Another fraction from the column purification was taken and purified via preparatory TLC. Even with this method, a pure sample remained elusive, with only 4 milligrams to work with after purification. The ^{1}H NMR did show a slightly purer *trans* product, but even this was still mired with too many impurities. Even with such attempts at purification, it became apparent that the large volumes of side product rendered the reaction inefficient with low yields of desired product.

Additionally, it seems the *cis* product **67** seemed to disappear over time with each further attempt at purification. It is interesting to note that the reaction mixture showed an approximately 1:2 ratio of *cis* to *trans* products. As the *cis* isomer was minor alkylation product, it was

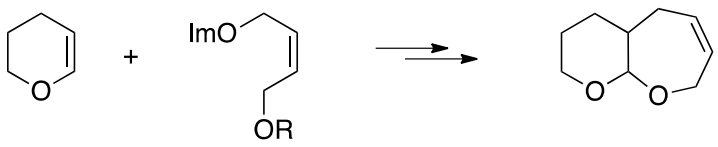
considered that equilibration of the *cis* and *trans* isomers might have occurred on the columns. Such equilibration is not normally observed in these products, although at least one of the products isolated previously by the Totah group underwent this process.[12]

At this point, attempts to prepare the cyclization product **58** were abandoned due to the large amount of impurities formed in this alkylation reaction and the inability to isolate pure materials in large enough quantities to carry forward.

III. Attempted alkylation/cyclization using the imidate derived from cis-2-butene-1,4-diol

The synthesis of the seven membered ketal **12** from 2H-dihydropyran **7** and the imidate **72** derived from cis-2-butene-1,4-diol (*Scheme 23*).

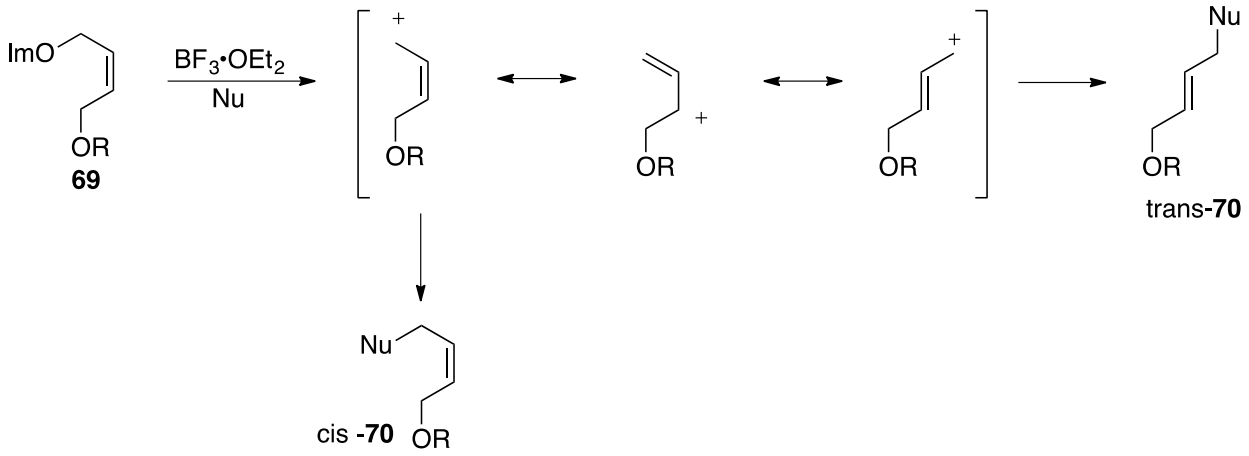
Scheme 23



7 **69** **12**

Protection of an alcohol group was again required, but in this case both alcohols of the starting material are identical. The protection is expected to be controlled by reaction stoichiometry. The imidate would then be formed on the remaining unprotected alcohol group.

Scheme 24

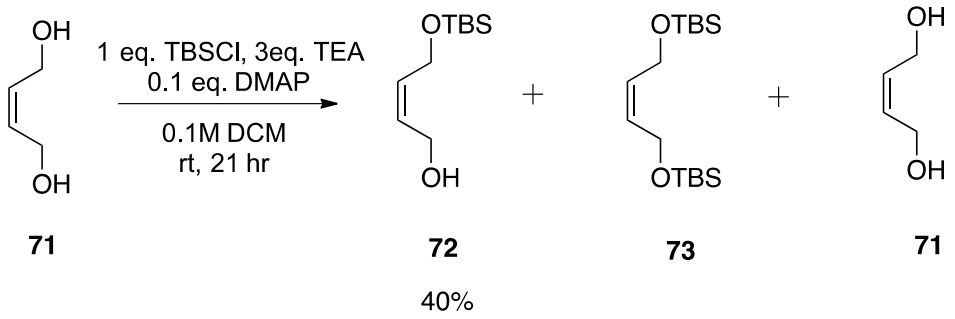


After the formation of the imidate **69**, cyclization would take place. In this case, it would be of interest to see if the alkylation/cyclization could be achieved without isomerization of the double bond to the *trans* isomer **70** (*Scheme 24*). This is of interest because only the *cis* isomer would be expected to undergo cyclization.

a) Mono-protection of cis-2-butene-1,4-diol

Cis-2-butene-1,4-diol required the selective addition of a protecting group. This compound possesses two identical hydroxyl groups, one of which would be protected, while the other would be the site of imidate formation. Because both alcohols are feature the same reactivity, use of an excess of the alcohol **71** to tert-butyldimethylsilyl chloride should give a high yield in the monoprotected product.[16]

Scheme 25



71 **72** **73** **71**

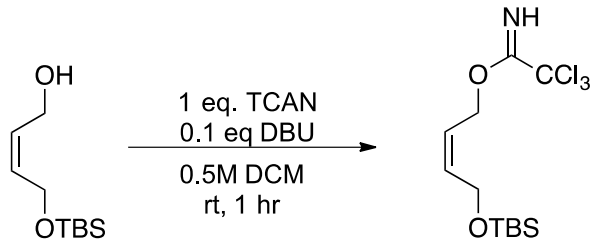
40%

Inadvertently, this reaction was performed using a 1:1 ratio of diol **71** to tert-butyldimethylsilyl chloride. Such a reaction generally leads to a 2:1:1 ratio of the mono-protected diol **72**, the di-protected diol **73**, and starting material **69**- a statistical product mixture (*Scheme 25*). The desired product was purified via flash chromatography using 3% triethylamine in order to ensure the protecting group was not lost. The yield of desired product **72** was 44%, but given the ratio of expected products, the yield of the desired product was 88% of its full potential.

b) Formation of the imidate from mono-protected cis-2-butene-1,4-diol

After the successful protection of one hydroxyl group on diol **71**, preparation of the imidate was next. Thus, the monosubstituted diol **74** was treated with trichloroacetonitrile and 1,8-diazabicycloundec-7-ene to give the desired product; imidate **75** with a 90% yield.

Scheme 26



72 **74**

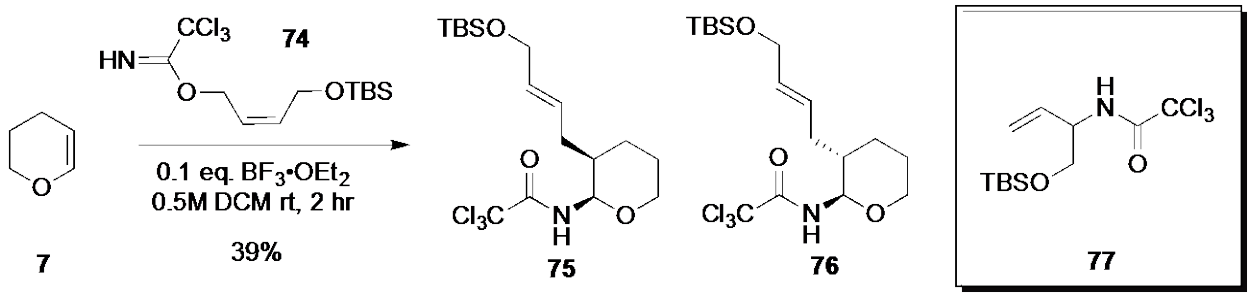
This same reaction was run twice more with yields of 54% and 69%. These lower yields are hypothesized to be due to the lack of triethylamine during purification. When 3% triethylamine was used during flash chromatography, the best yield of the desired product was achieved. Successful formation of imidate **74** allowed for the next step, the alkylation reaction.

c) Attempted alkylation with imidate 74

The alkylation of 2H-dihydropyran **7** with imidate **74** was carried out under standard conditions using a 1:1 ratio of 2H-dihydropyran to imidate and catalytic BF_3•OEt_2. While running the reaction and following by TLC, many apparent products appeared in the reaction lane of the plate as early as thirty minutes into the reaction. After running for two hours, the spot on the plate even with the starting material did not seem to fade. This reaction was more difficult to follow than the previous imidate **54** and its expected products because they exhibited UV activity on the TLC plate, while imidate **74** was not UV active.

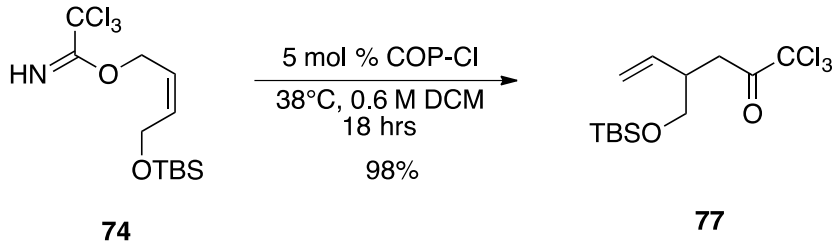
It was assumed that the reaction did not run to completion, at which point the reaction was halted and a crude ^{1}H NMR was taken. The NMR did not show the presence of alkylation products, as no peaks denoting the C2 proton of *cis* **75** and *trans* **76** alkylation products was observed. There were also no peaks associated with the starting material, **74** or 2H-dihydropyran **7**. Instead, an unknown alkene was isolated as the major product after purification using silica gel chromatography. Further analysis using the purified compound and ^{1}H NMR, DEPT-135 and ^{13}C analysis, identified compound **77**, the result of an Overman rearrangement, as the major product.

Scheme 27



The reaction was run a second time to verify that amide **77** formation took place instead of the alkylation. The same result was observed with this reaction. Amide **77** formed by an Overman rearrangement of the imidate **74**. The reaction of **74** to form **77** has been documented by the Overman group.[17] An Overman rearrangement is similar to a Claisen rearrangement and proceeds with allylic trichloroacetimidates (*Scheme 28*). The general reaction is shown below:

Scheme 28

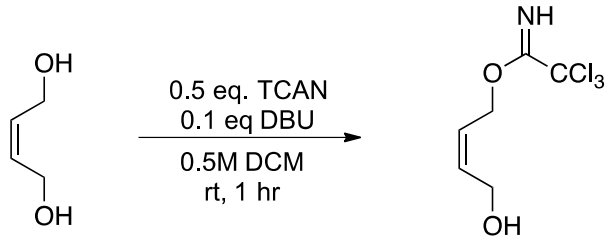


Through the use of a palladium-based catalyst (COP-Cl), the reaction was run by Overman at 38°C for 18 hours. They reported a 98% yield, displaying the effectiveness of the reaction. Preparation of compound **75** has also been reported by Richards using a palladium catalyst.[18] In this case it was concluded that the desired alkylation of **72** did not occur, and that BF_3•OEt_2 was capable of catalyzing the Overman rearrangement which took place faster than the alkylation reaction.

d) Formation of the mono-imidate of cis-2-butene-1,4-diol and alkylation

In order to test if an imidate with a reactive unprotected group would be able to alkylate, the mono-imidate of cis-2-butene-1,4-diol was prepared and used in the alkylation reaction. The mono-imidate was formed under the usual conditions except that an excess of diol **71** was used (diol:tricholoracetonitrile, 2:1). Imidate **80** was formed with an 85% yield.

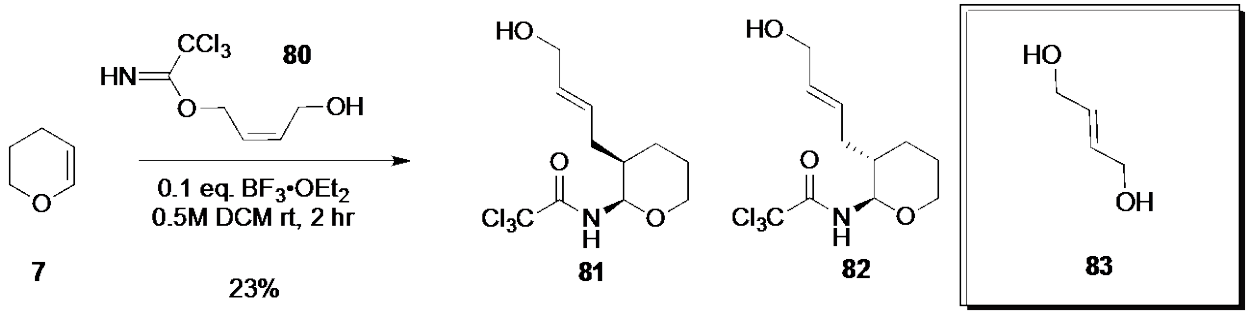
Scheme 29



71 **80**

After imidate **80** was successfully purified, the alkylation reaction was attempted. Unfortunately, none of the expected peaks for alkylation products **81** and **82** were observed by ^{1}H NMR. In this case, the major product of this reaction was tentatively identified as *trans*-2-butene-1,4-diol **83**.

Scheme 30



7 23% **81** **82** **83**

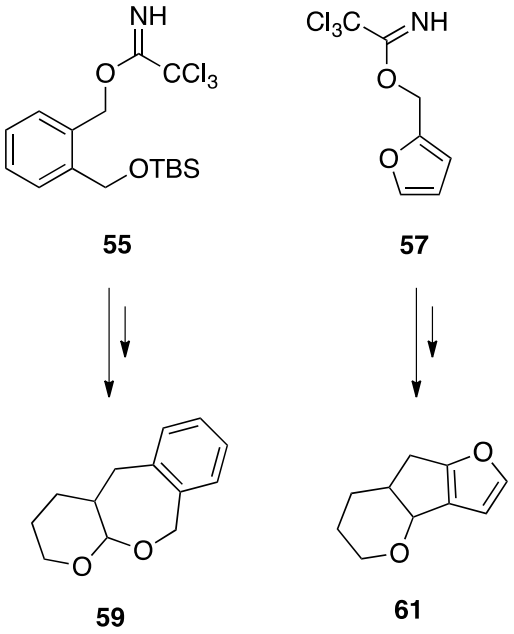
The alkylation of both protected **74** and unprotected **80** imidates of cis-2-butene-1,4-diol were unsuccessful. Instead, Overman rearrangent and isomerization of the double bond were

observed preferentially. Based on the results it became evident that the imidates of diol **71** did not function as a useful reagent for the alkylation of 2H-dihydropyran **7**.

IV. Sythesis of additional imidates

Several additional imidates including **55** and **57** were identified for use in the tandem alkylation/cyclization sequence to yield ketal **59** and **61** respectively.

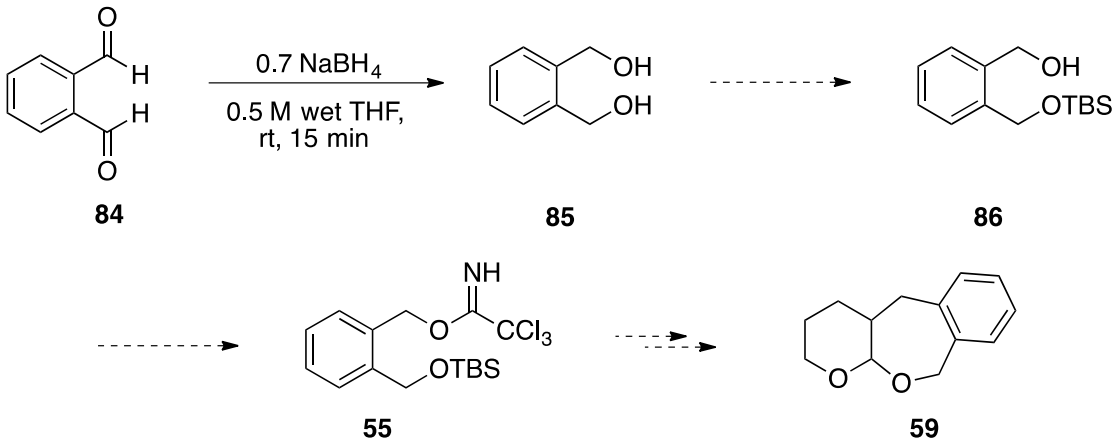
Figure 7



a) Progress toward the pthalyl alcohol imidate

Synthesis of imidate **55** was anticipated from o-pthalaldehyde **84** in four steps that would give the cyclization product **59**. These steps would consist of reduction of the aldehydes, followed by selective protection, imidate formation, and finally attempts at alkylation and cyclization. The steps in this process are seen in *Scheme 31*.

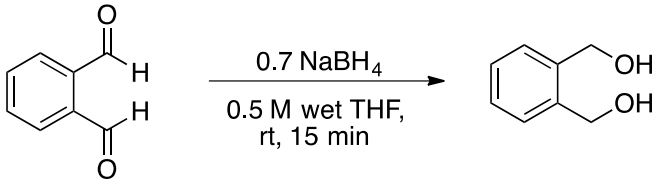
Scheme 31



84 **85** **86** **55** **59**

The first step was the formation of diol **82** from o-Pthalaldehyde **84** with sodium borohydride. This reagent is generally considered to be milder than other reducing reagents, such as lithium aluminum hydride.

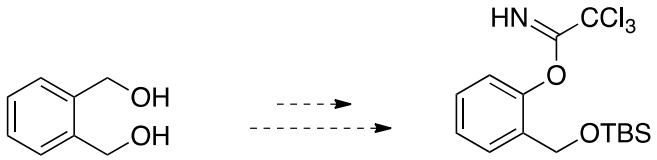
Scheme 32



84 **85**

Following the addition of compound **81** into the reaction solvent, sodium borohydride was slowly added at room temperate and the reaction was allowed to stir for 15 minutes, longer than the 4 minutes reported by the literature.[19] Due to the presence of water in the THF, monitoring the reaction via TLC in order to ensure reaction completion proved to be difficult. The water was however required as the literature reported significantly improved yields upon the use of a wet THF instead of dry THF as the reaction solvent.[15] Upon purification via column chromatography, the reaction afforded a yield of 58%.

Scheme 33



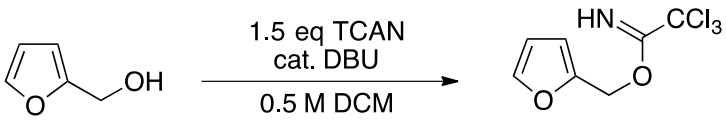
85 **55**

The next steps in this sequence are the mono protection of diol **82**, followed by formation of the imidate **55**. This process is expected to yield imidate **55** to that can be used in the alkylation and cyclization reactions to give ketal **59**. In future experiments the synthesis of imidate **55** will be completed and the alkylation with 2H-dihydropyran **7** will be carried out.

b) Synthesis of furfuryl alcohol imidate 88

The imidate of furfuryl alcohol **57** was another compound formed with the desire to perform an alkylation with 2H-dihydropyran **7.** Alkylation of imidate **57** followed by cyclization is expected to give the oxygen heterocycle **61.** The cyclization is expected to occur by a Friedel-Crafts reaction of the furan ring of furfuryl alcohol **87** and the oxonium ion intermediate of 2H-dihydropyran formed upon alkylation.

Scheme 34



87 **57**

The desired imidate **57** was prepared using the same reaction conditions as in previous imidate reactions, affording an 83% yield. This yield is consistent with that of the past imidate reactions and shows the reliability of these reaction conditions. Imidate **57** is highly reactive and efforts in the Totah lab have shown it can be used to alkylate with 2H-dihydropyran, but results

in a difficult purification, with many impurities formed during the alkylation reaction.[12] For this reason, the alkylation and cyclization sequence was not explored for imidate **57**.

VI. Conclusion and Future Work

The purpose of this series of reactions was to use a selected set of imidates to conduct a tandem alkylation/cyclization reaction with 2H-dihydropyran. The steps of the tandem reaction were first separated and conducted in several steps. The end results were expected to be a series of unique oxygen heterocycles, which not only represent unusual molecular scaffolds, but whose structures are similar to that of some biologically active natural products.

Though the tandem alkylation/cyclization sequence has yet to be demonstrated, through this research some highly functionalized imidates were prepared and characterized, and their reactivity in the alkylation reactions with dihydropyran was evaluated. These imidates were prepared cleanly with good yields of 83% to as high as 90%.

The imidate of 2-hydroxybenzyl alcohol required several steps to prepare in order to reach protection of the desired alcohol group, the phenol. Once formed, imidate **54** was found to be a new compound that had not been synthesized before. Although the alkylation reaction in this case proved extremely difficult to purify, an efficient synthesis of imidate **54** was developed which could be used in further studies. The issue of complications cause by side reactions, making the alkylation difficult to purify, was similarly experienced with the furfuryl alcohol imidate **57**.

Attempted alkylation of imidates derived from cis-2-butene-1,4-diol was also found to be problematic. In these cases, Overman rearrangement and double bond isomerization in the imidate was faster than alkylation.

Results of the alkylations were therefore inconclusive as the desired product was either formed in too low of a yield and was difficult to purify, or did not form at all. In the future, looking at modified reaction conditions through the use of different Lewis acids, lower reaction temperatures, and different solvents could help fix these problems. These changes could aid in the optimization of the use of these imidates in the alkylation reactions. It may also prove useful to explore the use of other, more stable, protecting groups to mask reactivity of the secondary nucleophile in the imidates.

The imidates formed did not work in the desired way or were not able to be tested, however, they pose reactive structures that have the potential to be used in further reactions. Although more work is needed to reach the goals of this study, oxygen heterocycles remain an interesting molecular framework.

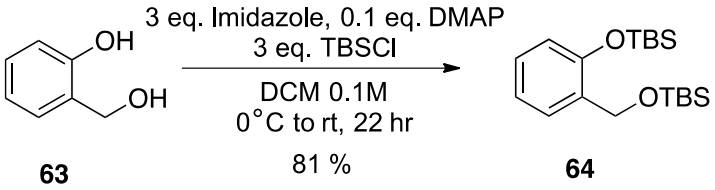
Chapter 3

Experimental

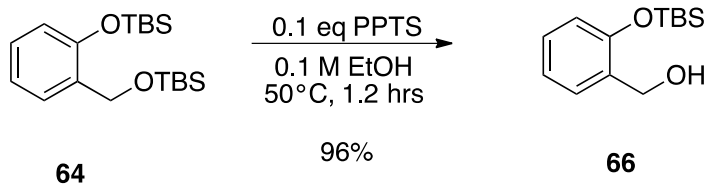
General Methods:

All air sensitive reactions were performed in oven dried glassware under an argon atmosphere. Dichloromethane was dried over calcium hydride and distilled prior to use. Tetrahydrofuran was dried over potassium hydroxide and distilled prior to use. All reagents were reagent grade and purified when necessary. Analytical thin layer chromatography was performed on EM silica gel 60 F_{254} glass plates (0.25 mm). Column chromatography was conducted with SilicaFlash P60 silica gel (40-63 μm) from SiliCycle, Inc. ^{1}H NMR spectra were acquired using the 400 MHz Bruker Ascend™ spectrometer. Chemical shifts are reported in ppm, using deuterated chloroform solvent peaks (δ 7.27 ppm) as the internal standard. ^{13}C NMR and DEPT were recorded using the Bruker 400 MHz Bruker Ascend™ spectrometer. IR Spectra were acquired through the use of the Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental analyses were performed using the Costech elemental combustion system.

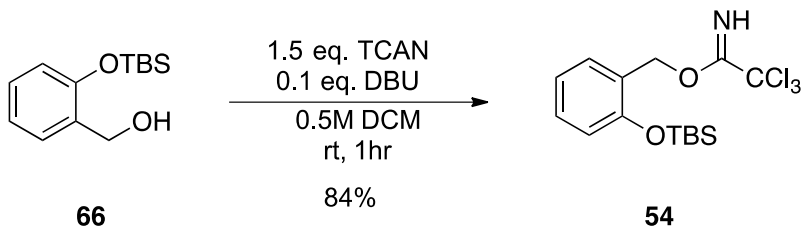
Experimental Procedures:



TBDMS Ether 64: 2-hydroxybenzyl alcohol (1.00 g, 8.1 mmol), imidazole (1.65 g, 24.3 mmol), and DMAP (0.10 g, 0.82 mmol) were dissolved in DCM (81 mL) at 0°C. TBSCl (2.56 g, 24.2 mmol) was then added and the reaction mixture was allowed to slowly return to room temperature. Stirring was continued for 22 hours. The Reaction mixutre was diluted with ether (100 mL) and washed in $NaHCO_3$ (100 mL x 2), followed by distilled water (100 mL x 3), and brine (100 mL x 2). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction was purified via flash chromatography using 20:1 hexanes to ethyl acetate and 3% triethylamine. TLC: R_f = 0.81 (hexanes:EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (1H, d, *J* = 8.4 Hz), 7.11 (1H, t, *J* = 15.6 Hz), 6.97 (1H, t, 15.2 Hz), 6.74 (1H, d, *J* = 8.0 Hz).

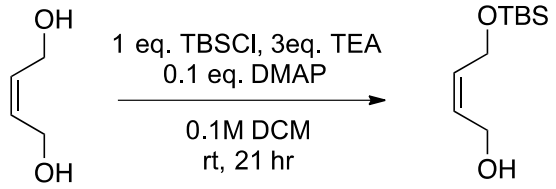


Protected Phenol 66: PPTS (0.143 g, 0.57 mmol) and TBDMS ether **64** (2.0 g, 5.67 mmol) were combined in ethanol (56.7 mL) and stirred at 50°C for 72 minutes. The reaction was then concentrated *in vacuo* and purified via flash chromatography using 15:1 hexanes to ethyl acetate and 3% triethylamine. TLC: R_f = 0.43 (hexanes:EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (1H, d, *J* = 7.2 Hz), 7.19 (1H, t, *J* = 7.0 Hz), 6.97 (1H, t, *J* = 7.1 Hz), 4.69 (2H, d, *J* = 6.4 Hz), 1.04 (9H, s), 0.28 (6H, s)



66 **54**

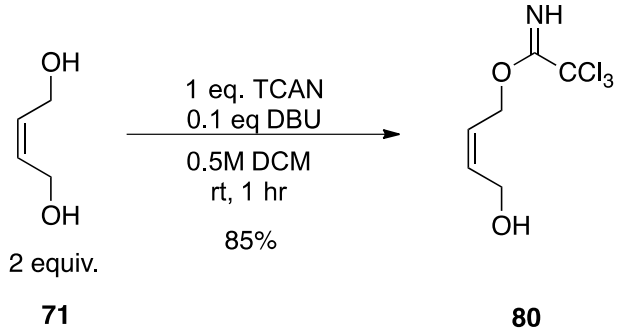
Imidate 55: Imidate **55** (0.246 g, 1.03 mmol) was combined with TCAN (0.15 mL, 1.55 mmol) followed by DBU (0.016 mL, 0.011 mmol) in DCM (12.1 mL) at room temperature and stirred for one hour. The reaction was concentrated *in vacuo* and purified via flash chromatography using a silica plug with 15:1 hexanes to ethyl acetate, and 5% triethylamine. TLC: R_f = 0.30 (hexanes:EtOAc, 10:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (1H, s), 7.44 (1H, d, *J* = 6.0 Hz), 7.23 (1H, t, *J* = 15.6 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 5.4 (2H, s), 1.02 (9H, s), 0.26 (6H, s) Anal. Calcd for $C_{15}H_{22}Cl_3NO_2Si$: C, 47.07%; H, 5.79%; N, 3.66%. Found: C, 47.40%; H, 5.73%; N, 3.63%.



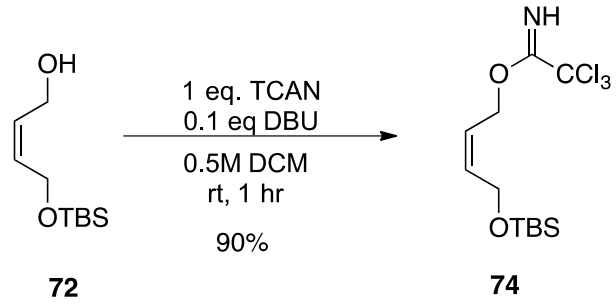
71 **72**

Silyl Ether 72: Cis-2-butene-1,4-diol **71** (1.0g, 11.3 mmol) was reacted with TBSCl (1.20g, 11.3 mmol), triethylamine (3.45g, 34 mmol), and DMAP (0.14g, 1.13 mmol) in DCM (113 mL). The reaction was allowed to stir at room temperature for 21 hours. The reaction was diluted with ether (200 mL) then washed with $NaHCO_3$ (100mL x 2), followed by distilled water (100 mL x 3), and brine (100 mL x 2) were then used. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified via flash chromatography using 4:1 hexanes to ethyl acetate. TLC: R_f = 0.39 (hexanes:EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400

MHz): δ 5.7 (2H, m), 4.21 (2H, dd, *J* = 21.2 Hz, 9.5 Hz), 2.51 (2H, q, *J* = 13.6 Hz), 0.91 (9H, s), 0.09 (6H, s).

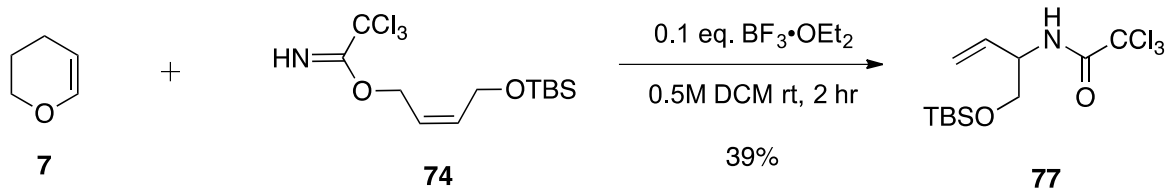


Imidate 79: Cis-2-butene-1,4-diol **71** (0.5 g, 5.7 mmol) was combined with TCAN (0.41 g, 2.8 mmol) and DBU (0.086 g, 0.57 mmol) in DCM (1.1 mL) and allowed to stir at room temperature for 1 hour. The reaction was concentrated *in vacuo* and purified via flash chromatography using 2:1 hexanes to ethyl acetate until the first spot came out, at which point the column was switched to 1:1 hexanes to ethyl acetate. TLC: R_f = 0.60 (hexanes:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (1H, s), 5.95 (1H, m), 5.74 (1H, m), 5.00 (2H, d, *J* = 7.2 Hz), 4.30 (2H, d, *J* = 6.0 Hz), 3.11 (1H, s).



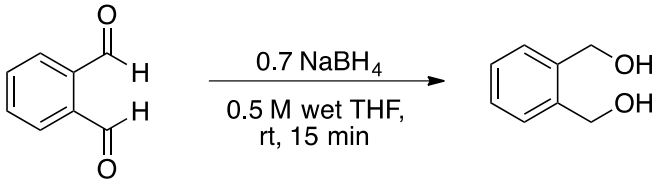
Imidate 74: Silyl ether **72** (0.46 g, 2.27 mmol) was combined with TCAN (0.49 g, 3.41 mmol) and DBU (0.035 g, 0.23 mmol) in DCM (1.1 mL) and allowed to stir at room temperature for 1 hour. The reaction was concentrated *in vacuo* and purified via flash chromatography using 10:1 hexanes to ethyl acetate, 3% triethylamine. TLC: R_f = 0.68 (hexanes:EtOAc, 5:1). ^{1}H NMR

($CDCl_3$, 400 MHz): δ 5.79 (1H, m), 5.71 (1H, m), 4.87 (2H, d, *J* = 6.0 Hz), 4.33 (2H, d, *J* = 5.5 Hz), (9H, s), (6H, s).



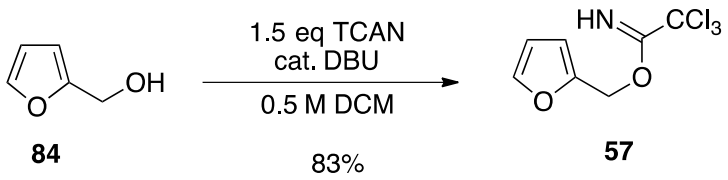
7 **74** **77**

Overman Product 77: Imidate **74** (0.64 g, 1.85 mmol) was added with 2,3-dihydropyran **7** (--, 1.85 mmol) and BF_3•OEt_2 (0.026 g, 0.185 mmol) in DCM (3.7 mL) and stirred for 2 hours at room temperature. The reaction was concentrated *in vacuo* and purified via flash chromatography using 20:1 hexanes to ethyl acetate. TLC: R_f = 0.69 (hexanes:EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97 (1H, s), 5.91-5.82 (1H, m), 5.51 (1H, m), 5.22 (2H, m), 0.85 (9H, s), 0.12 (6H, s).



81 58% **82**

Phythalyl Alcohol 82: o-Pthalaldehyde **81** (0.5g, 3.73 mmol) was combined with sodium borohydride (0.0995 g, 2.61 mmol) in wet THF (37.3 mL) and stirred for 15 minutes. Distilled water (15 mL) was added and stirring continued for another 15 minutes. The reaction mixture was extracted with CH_2Cl_2 (40 mL x 3), dried over $NaSO_4$, and filtered. The organic layer was concentrated *in vacuo* and purified via flash chromatography using 1:1 hexanes to ethyl acetate. TLC: R_f = 0.30 (hexanes:EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (4H, m), 4.73 (4H, s), 2.73 (2H, s).



84 83% **57**

Imidate 57: Furfuryl alcohol **84** (0.5 g, 5.10 mmol) was combined with TCAN (0.734 g, 5.1 mmol) and catalytic DBU (0.077 g, 0.51 mmol) in DCM (10.2 mL) and allowed to stir for 1 hour. The reaction was concentrated *in vacuo* and purified via flash chromatography using 5:1 hexanes to ethyl acetate. TLC: R_f = 0.64 (hexanes:EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (1H, s), 7.46 (1H, dd, *J* = 2.8 Hz, 0.8 Hz), 6.49 (1H, d, *J* = 3.2), 6.39 (1H, dd, *J* = 5.2 Hz, 2.0 Hz), 5.29 (1H, s).

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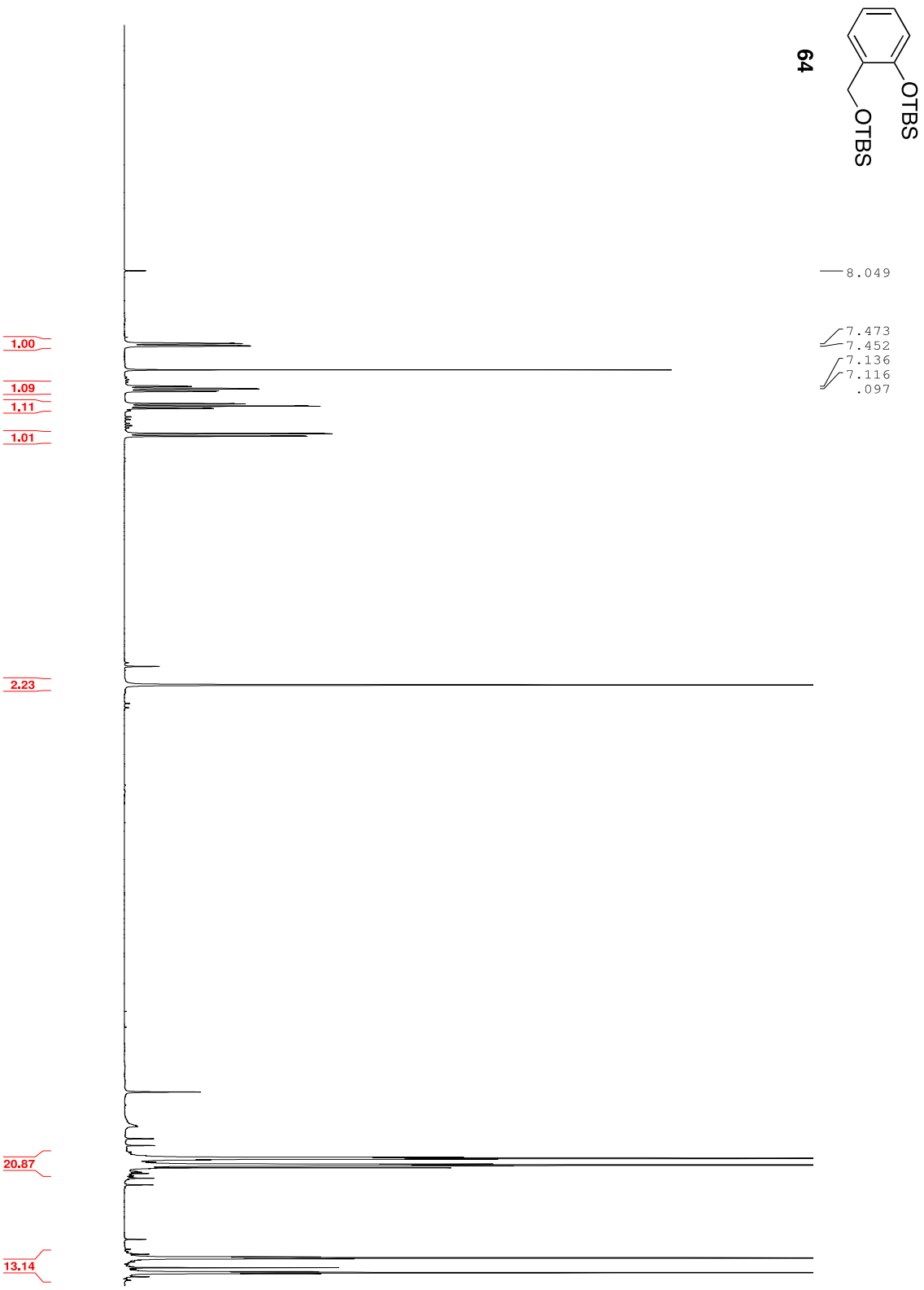
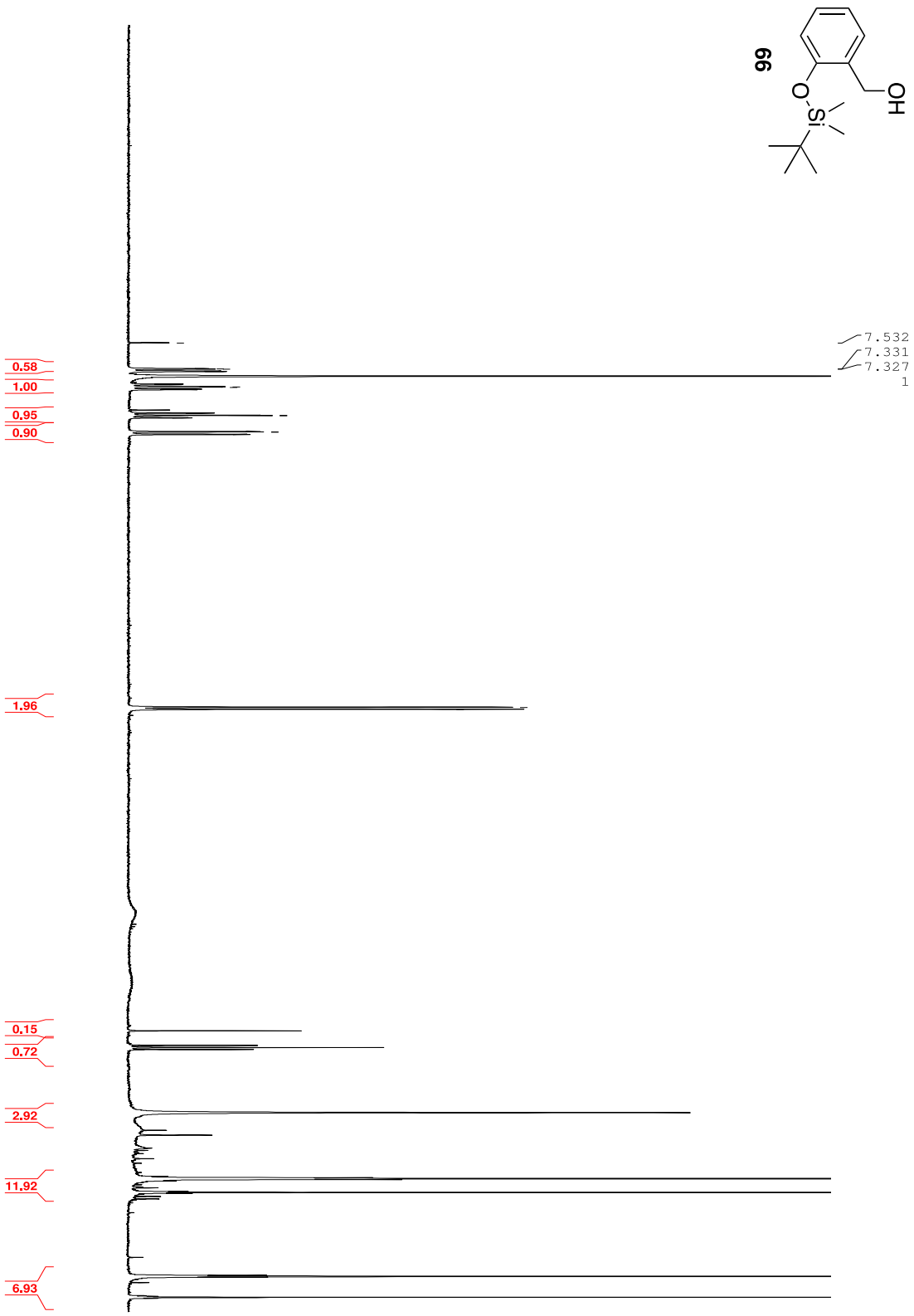
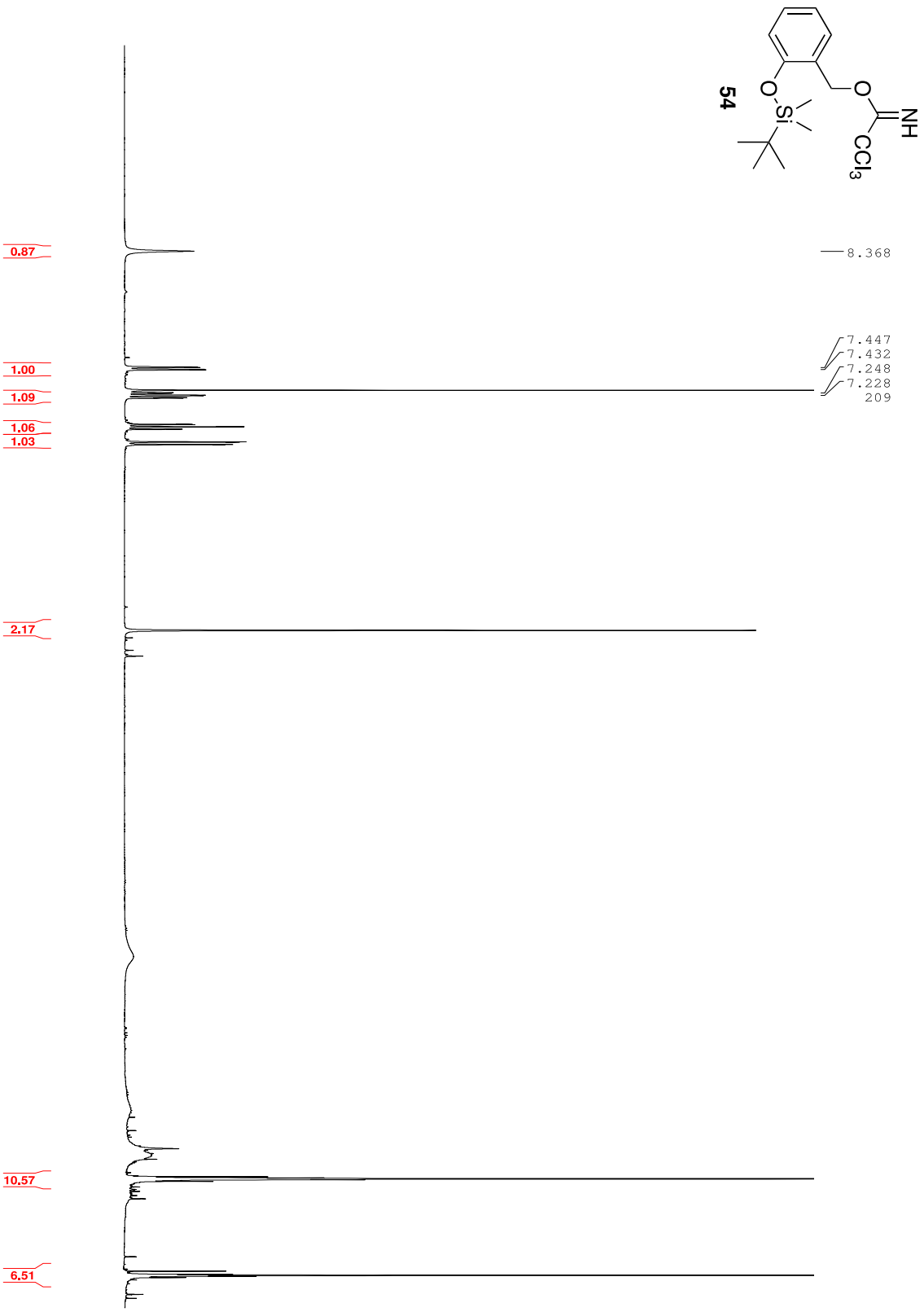
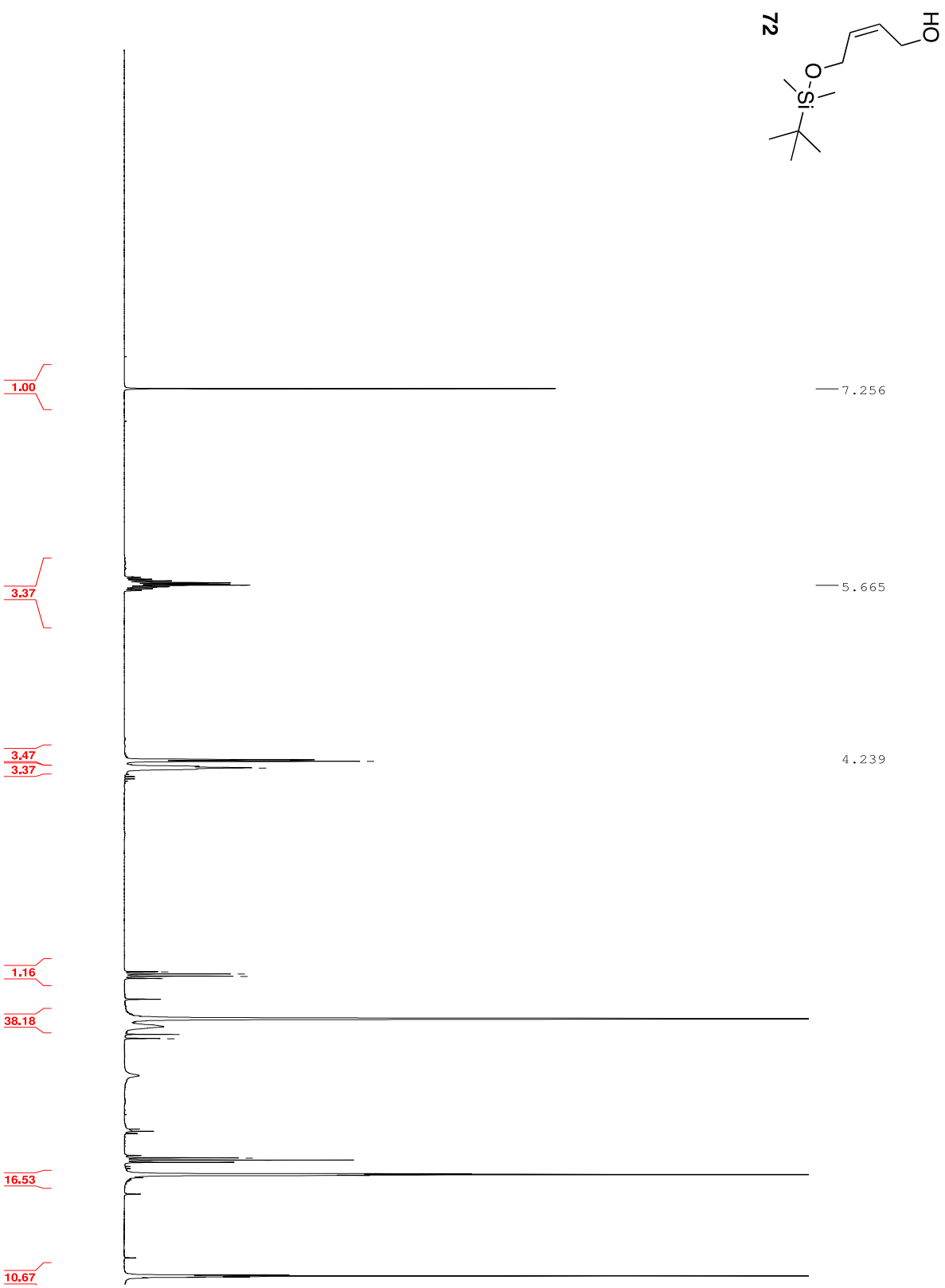
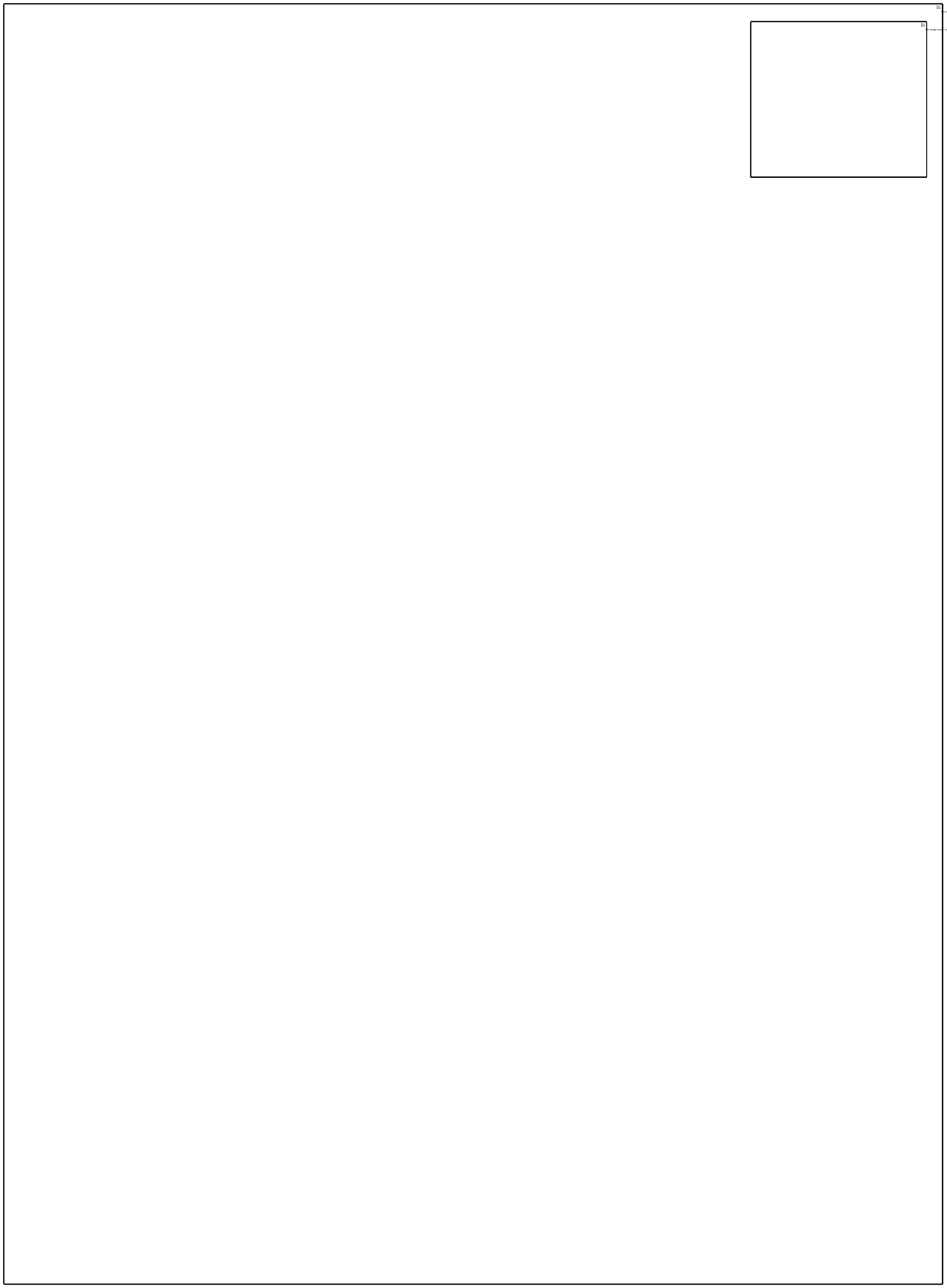
Appendix:

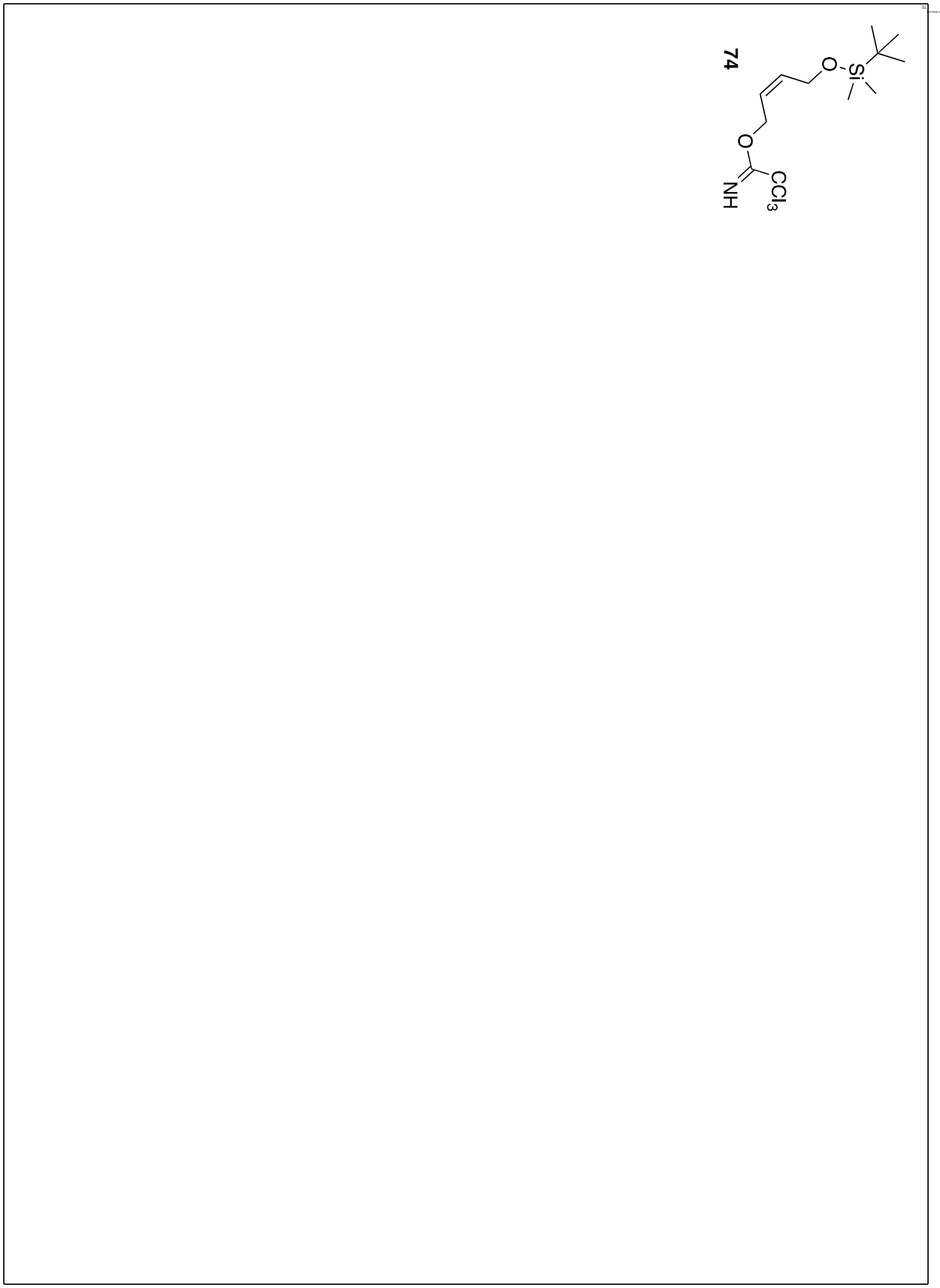

64
OTBS
OTBS
8.049
7.473
7.452
7.136
7.116
.097
1.00
1.09
1.11
1.01
2.23
20.87
13.14

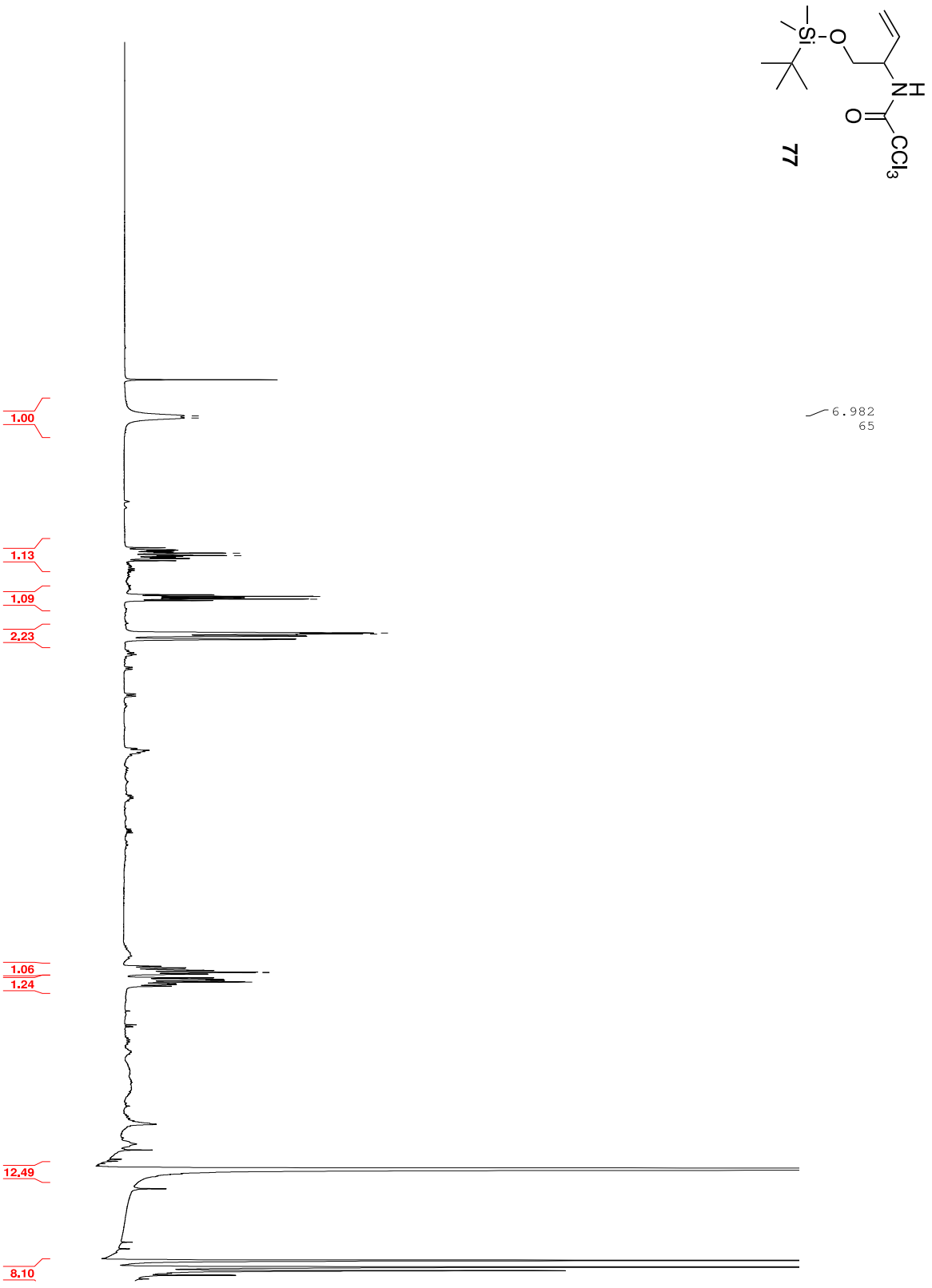

69
O
Si
OH
7.532
7.331
7.327
1
0.58
1.00
0.95
0.90
1.96
0.15
0.72
2.92
11.92
6.93

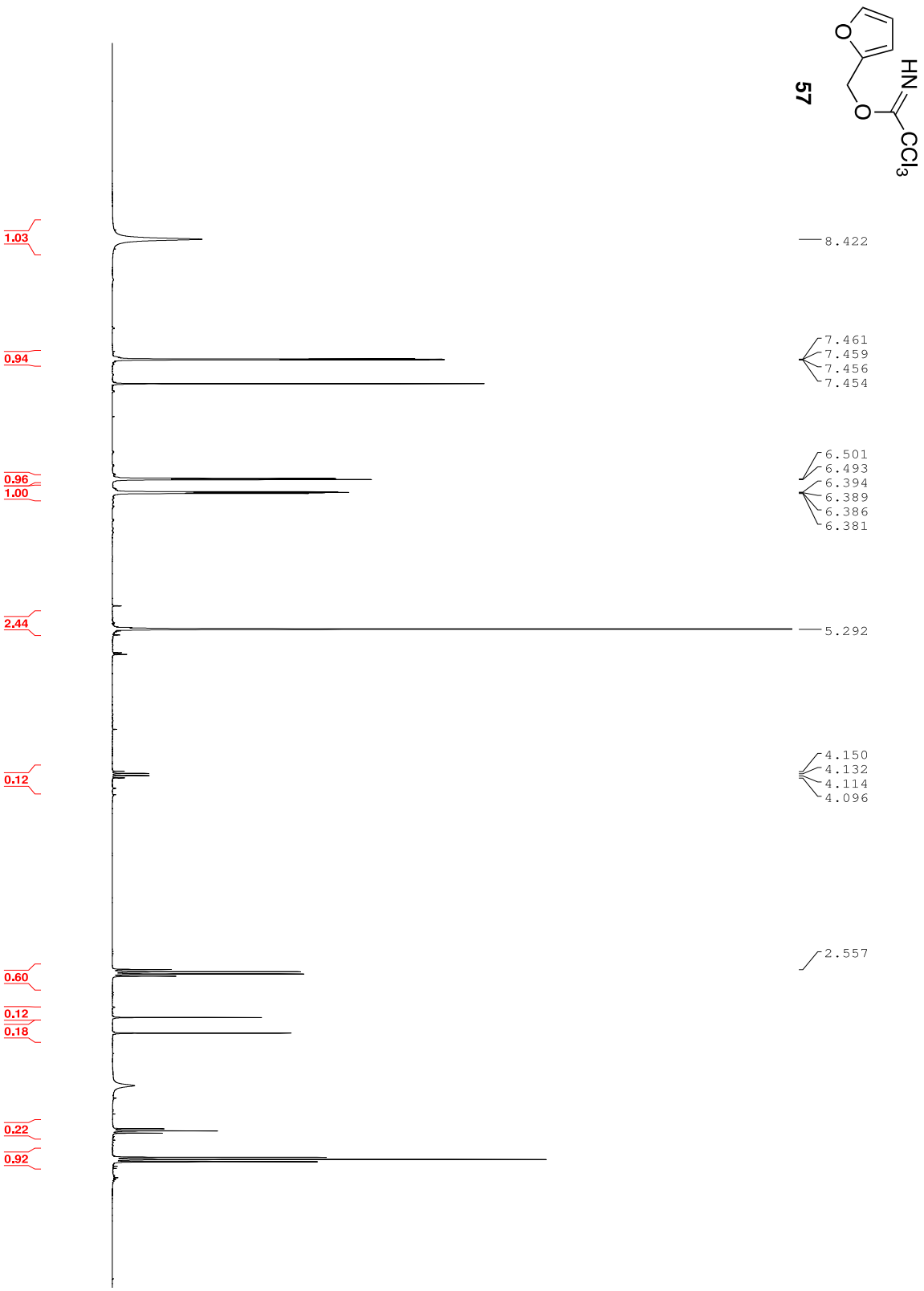

54
O
Si
O
NH
CCl3
8.368
7.447
7.432
7.248
7.228
209
0.87
1.00
1.09
1.06
1.03
2.17
10.57
6.51

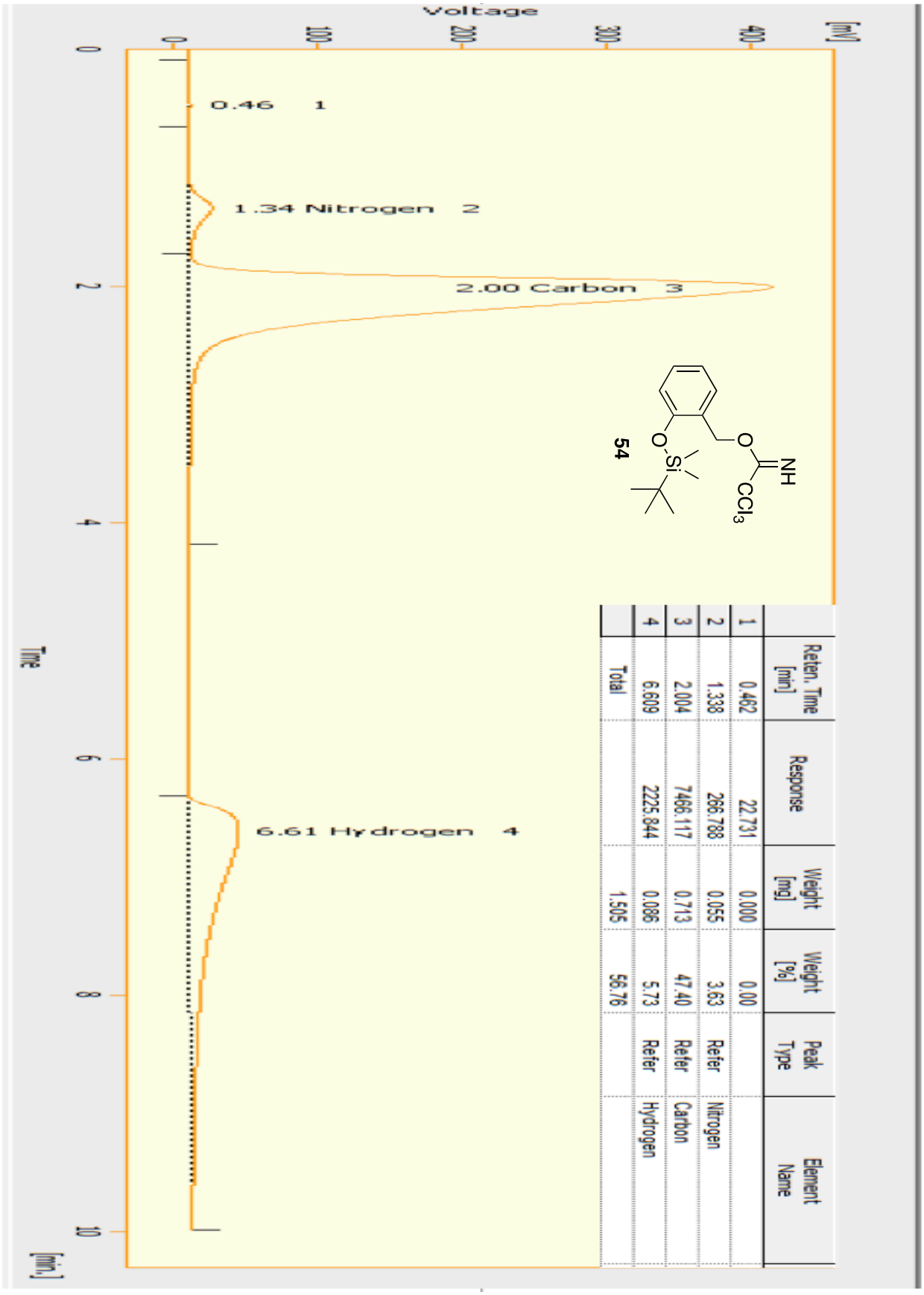

72
HO
O
Si
1.00
7.256
3.37
5.665
3.47
3.37
4.239
1.16
38.18
16.53
10.67



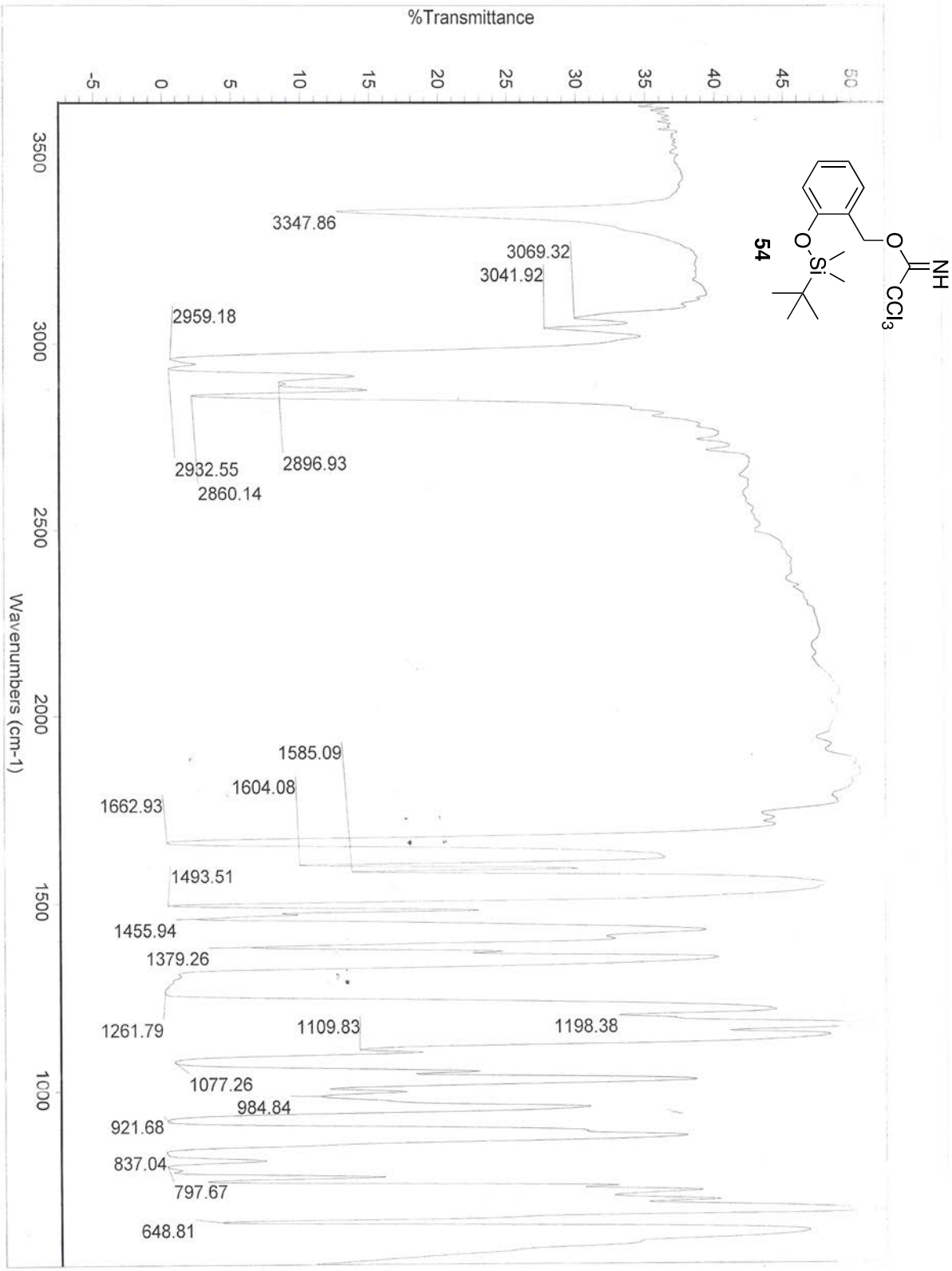

74
O
Si
O
NH
CCl3


77
6.982
65
1.00
1.13
1.09
2.23
1.06
1.24
12.49
8.10


57
HN
CCl3
8.422
7.461
7.459
7.456
7.454
6.501
6.493
6.394
6.389
6.386
6.381
5.292
4.150
4.132
4.114
4.096
2.557
1.03
0.94
0.96
1.00
2.44
0.12
0.60
0.12
0.18
0.22
0.92



	Reten. Time [min]	Response	Weight [mg]	Weight [%]	Peak Type	Element Name
1	0.462	22.731	0.000	0.00		
2	1.338	266.788	0.055	3.63	Refer	Nitrogen
3	2.004	7466.117	0.713	47.40	Refer	Carbon
4	6.609	2225.844	0.086	5.73	Refer	Hydrogen
	Total		1.505	56.76		


%Transmittance
-5
0
5
10
15
20
25
30
35
40
45
50
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
3347.86
3069.32
3041.92
2959.18
2932.55
2896.93
2860.14
1585.09
1604.08
1662.93
1493.51
1455.94
1379.26
1261.79
1109.83
1198.38
1077.26
984.84
921.68
837.04
797.67
648.81
54
O
Si
O
NH
CCl3