THE USE OF $In(OTf)_3$ AS A LEWIS ACID IN CARBOHYDRATE CHEMISTRY, AND EXPLORATION IN SILICON TETHERED REACTIONS

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

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November 2008

DEDICATION

The thesis is dedicated to my wife Briana McLeod Wright Bizier. This thesis, and the work contained therein were only made possible by her love and support.

ACKNOWLEDGEMENTS

I would like to thank a number of people who contributed to this thesis in many ways. First, and foremost, is my wife Briana Bizier who gave me constant love, support and understanding through my time a Montana State University. I would like to thank my parents Michael and Evelyn Bizier, and my sisters Kathryn and Jen Bizier, all of whom have provided support through the entire process. I would also like to thank my wife's parents Laurel McLeod, James Allen, and Bruce and Sharon Wright and sister in-law Kelsey Wright for advice and support through difficult times.

Dr. Mary Cloninger, my advisor, has been of tremendous help through this process. I have enjoyed working with her, and sincerely appreciate her time, patience, knowledge and direction. I would also like to acknowledge two of my colleges: Jacob O'Dell, and Mark Wolfenden, these two individuals have contributed through numerous conversations and friendship in my time at Montana State University.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

LIST OF SCHEMES

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

LIST OF SCHEMES–CONTINUED

Scheme Page

ABSTRACT

The feasibility of using Indium (III) triflate as a Lewis Acid for a number of different carbohydrate reactions was explored. First, the use of $In(OTf)_3$ as a catalyst in the acylation of a number of carbohydrates was explored. The utility and compatibility of the $In(OTf)_3$ reaction conditions with a number of protecting groups on the sugars were examined by ^1H NMR analysis. In the second part of the carbohydrate methodology, the feasibility of using $In(OTf)_3$ to promote glycosylation reactions using a number of glycosyl donors was evaluated. These studies were conducted using ^1H NMR, ^{13}CNMR, and Micro-ToF mass spectrometry. In both cases, $In(OTf)_3$ was found to be a viable if highly acidic Lewis acid for these reactions.

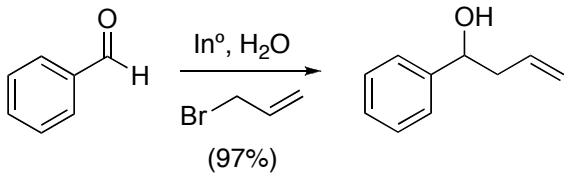
Silicon tether methodology was explored with the goal of obtaining 1,3 and 1,2-amino alcohols. The parameters for this reaction were explored after precursors and 1,3-amino alcohols were synthesized. These studies were conducted using ^1H NMR, ^{13}C NMR, IR spectroscopy, and Micro-ToF mass spectrometry. While some success was achieved, this route is unlikely to be widely adopted due to the multi-step syntheses that are required to obtain viable reaction precursors.

CHAPTER 1

INTRODUCTION TO THE USE OF INDIUM SALTS AS LEWIS ACIDS

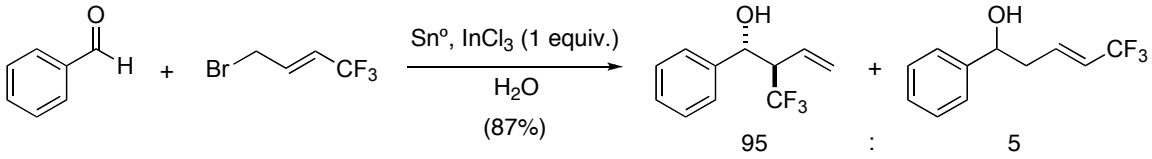
Traditionally, Lewis acids such as $AlCl_3$ and $TiCl_4$ have been used for the promotion of organic reactions. However, these Lewis acids are air and moisture sensitive and can only be used once. More air and moisture stable catalysts are slowly evolving.[1] Development of catalysts with improved properties including increased water tolerance, better reusability, and decreased environmental impact is also important.

Among the "new" Lewis acids that have been developed, indium complexes have captured significant attention for use in the laboratory. Indium as an organic reagent may be best known for its allylating properties. In 1991, Chan reported that stoichiometric amounts of indium metal could be used to affect the allylation of aldehydes and ketones with allyl halides in aqueous medium (Scheme 1),[2] achieving a Grignard-type reaction in the presence of water.

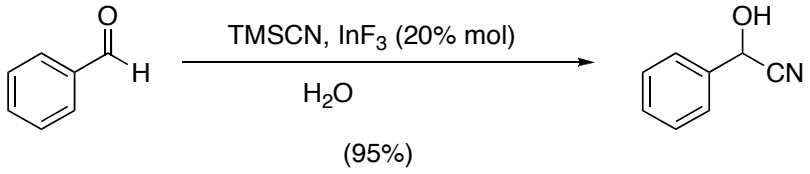


Scheme 1. Allylation of aldehydes mediated by Indium.

Use of indium salts to promote reactions to carbonyl compounds owes much of its development to Loh, who reported reactions such as the $InCl_3$ promoted addition of organic compounds in water (Scheme 2)[3] and the formation of cyanohydrins by treatment of aldehydes with TMSCN (Scheme 3).[4]

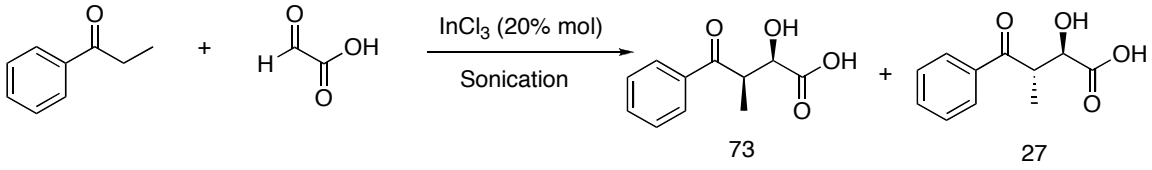


Scheme 2. $InCl_3$ promoted addition of organic compounds in water.

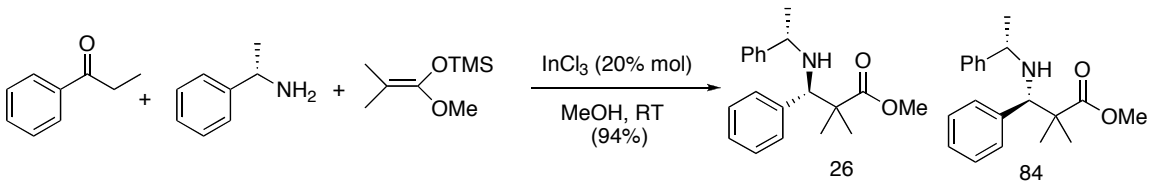


Scheme 3. $InCl_3$ formation of cyanohydrins by treatment of aldehydes with TMSCN.

Loh later reported that $InCl_3$ could be used as an effective catalyst for aldol reactions with glyoxylic acid (Scheme 4).[5] These reactions were conducted under solvent free conditions, using sonication to accelerate the reaction. Although yields were high, the *syn* to *anti* ratios were not particularly impressive. Employment of $InCl_3$ for Mannich type reactions was reported by Loh in 2002 (Scheme 5).[6]



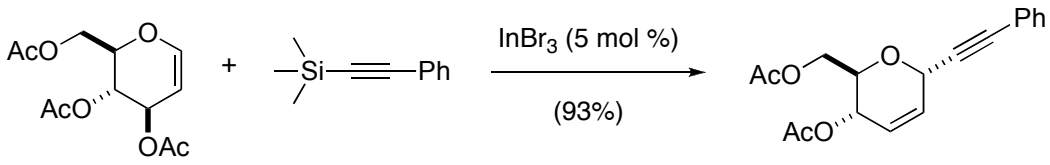
Scheme 4. $InCl_3$ as a catalyst for aldol reactions.



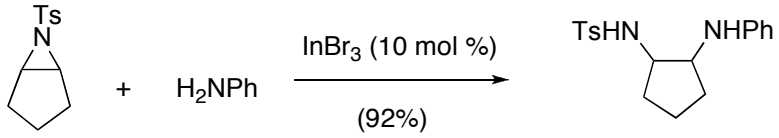
Scheme 5. Employment of $InCl_3$ for Mannich type reactions.

$InBr_3$ is a similar Lewis acid for the mediation of organic transformations. Like $InCl_3$, $InBr_3$ is a water stable, crystalline solid that is often considered to be a "green" alternative to many of the more popular Lewis acids.

Yadav and co-workers are among the primary researchers using $InBr_3$ and have developed a variety of $InBr_3$ mediated transformations. One of the first reactions published by this group was the $InBr_3$-promoted allylation of glycols to afford alkenyl glycosides (Scheme 6).[7] Aminolysis of aziridine molecules to give vicinal diamines was also reported by Yadav (Scheme 7),[8] as was a procedure for the use of $InBr_3$ with hexamethyldisilazide to protect alcohols.[9]

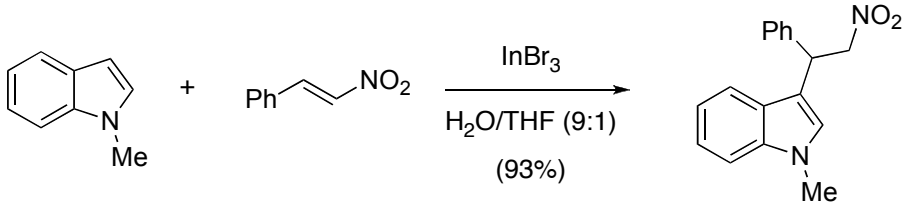


Scheme 6. $InBr_3$ promoted allylation of glycols.



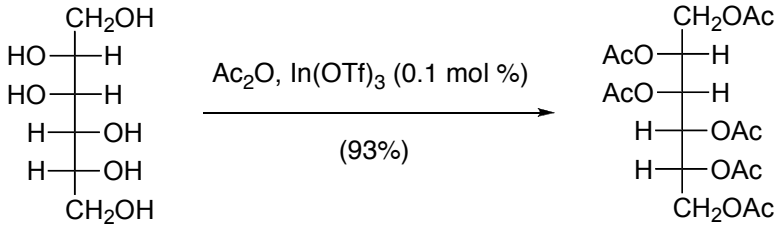
Scheme 7. Aminolysis of aziridine molecules to give vicinal diamines.

Banadini also used $InBr_3$ to successfully affect the Michael addition of nitroalkenes to indoles.[10] This reaction was particularly noteworthy because it was conducted in a 9:1 H_2O/THF solution (Scheme 8), while Yadav used only organic solvents for his reactions.

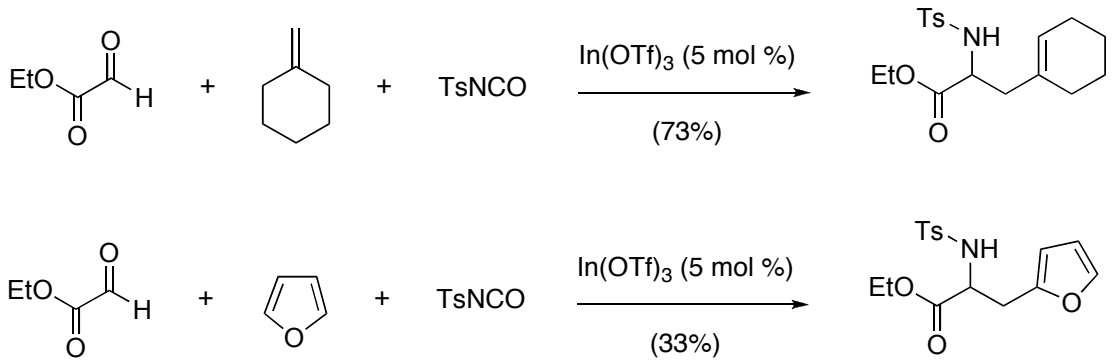


Scheme 8. Michael addition of nitroalkenes to indoles.

$In(OTf)_3$ was developed as a Lewis acid concurrently with both $InCl_3$ and $InBr_3$. For example, Frost used $In(OTf)_3$ to develop a number of reactions. Among the first of these was acylation of alcohols using a catalytic amount of $In(OTf)_3$ in CH_3CN (Scheme 9).[11] Frost also developed an $In(OTf)_3$ mediated method for Friedel-Crafts and ene reactions (Scheme 10).[12]

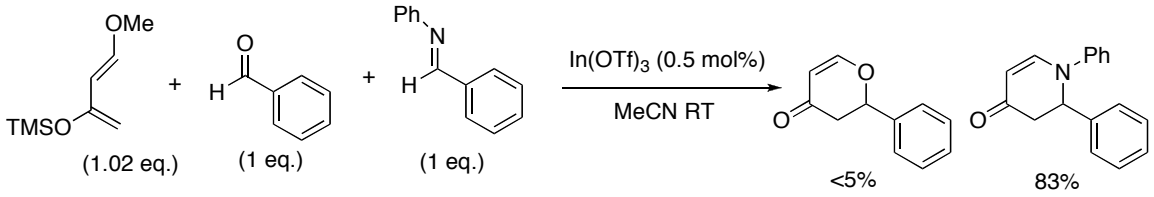


Scheme 9. Acylation of D-mannitol catalyzed by $In(OTf)_3$.



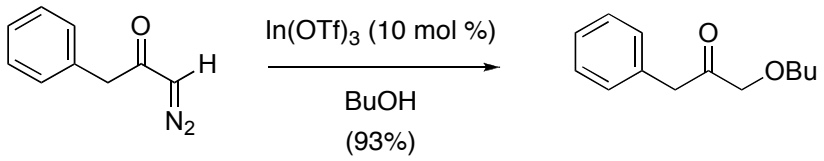
Scheme 10. $In(OTf)_3$ mediated Friedel-Crafts and ene reactions.

Frost also found that $In(OTf)_3$ was an effective catalyst for hetero Diels-Alder reactions (Scheme 11).[13] A significant finding in this study was that the catalyst promoted the cycloaddition of imines to the reactive diene over that of the parent aldehyde.



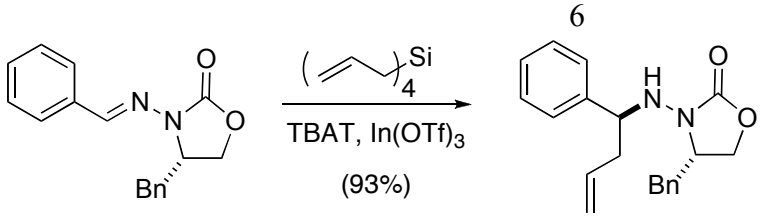
Scheme 11. $In(OTf)_3$ as a catalyst for hetero Diels-Alder reactions.

Muthusamy used $In(OTf)_3$ to successfully promote the insertion of alcohols into diazo compounds in 2002 (Scheme 12).[14] Since harsh Lewis acids are usually required for this type of reaction, Muthusamy's mild conditions allowed for the reaction to take place in the presence of a wider array of functional groups than was previously possible.



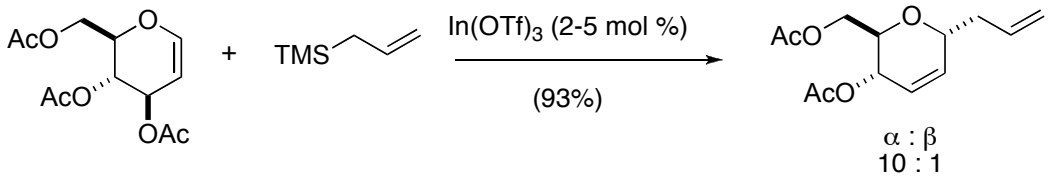
Scheme 12. $In(OTf)_3$ insertion of alcohols into diazo compounds.

Friestad accomplished the addition of allyltrimethylsilane to hydrazones (Scheme 13) with impressive enantioselectivity (dr 98:2) by using $In(OTf)_3$ as the Lewis acid catalyst, with fluoride to activate the allylsilane.[15]



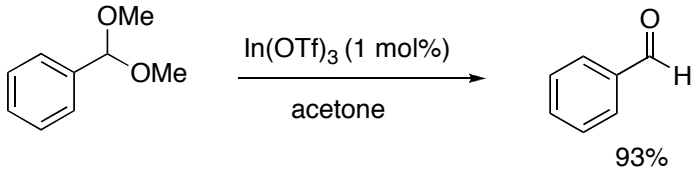
Scheme 13. $In(OTf)_3$ mediated addition of allyltrimethylsilane to hydrazones.

C-glycosylation was developed by Ghosh, who used $In(OTf)_3$ to effect addition of allyltrimethylsilane and trimethylsilyl cyanide to glycal derivates in high yields and with good anomeric selectivity (Scheme 14).[16]



Scheme 14. $In(OTf)_3$ catalyzed addition of allyltrimethylsilane to glycols.

Most recently, $In(OTf)_3$ has been used to deprotect acetals. Treatment of the acetal with a catalytic amount of $In(OTf)_3$ in acetone rapidly unmasks the acetal under mild conditions (Scheme 15).[17]



Scheme 15. $In(OTf)_3$ catalyzed cleavage of acetals.

In summary, while the full chemistry of indium salts is by no means understood, developments using indium salts have afforded important results as discussed above. The

main advantages of indium salts are that they are crystalline and water stable. How the different ligands affect the properties of the salt is not fully understood at this time.

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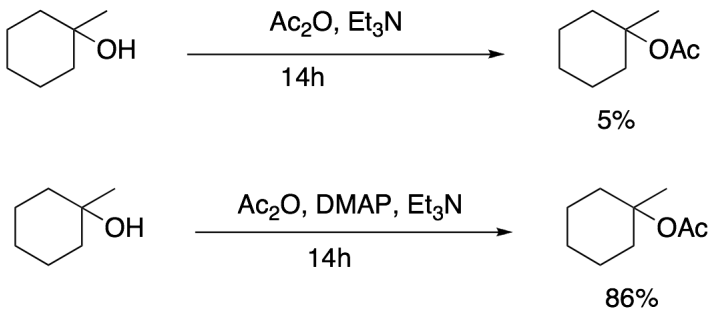
CHAPTER 2

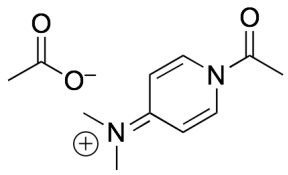
$In(OTf)_3$ CATALYZED ACYLATION OF CARBOHYDRATES

Introduction

Acylation is often performed to mask the acidic nature of the parent alcohol or amine. Verley and Bolsing reported early acylations using pyridine as the solvent in 1901.[1] This method, along with the use of triethylamine as an alternative solvent, remained the central method of acylation for organic chemists for almost 70 years. Acylation of sterically hindered alcohols remained a challenge until 1969, when Steglich and Holfe introduced *N,N*-dimethylaminopyridine (DMAP) as a co-catalyst.[2] Acylation reactions with DMAP proceeded up to 10,000- fold faster than when using pyridine alone (scheme 16),[3] and the active catalytic species is most likely the pyridinium **1** shown below. The increase in the rate of the reaction is due to the increased nucleophilicity of DMAP relative to pyridine. Excess base such as triethylamine or pyridine is added to prevent protonation of the DMAP, which would reduce the reaction rate.[4]



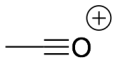
Scheme 16. Acylation of 1-methyl-cyclohexan-1-ol with and without DMAP.



1

Refluxing Ac_2O with sodium acetate has also been used to effect acylation, mainly on carbohydrate substrates.[5] Although the reaction conditions are somewhat harsh, as large amounts of acetic acid are produced, the protected β anomer is selectively obtained from molecules such as glucose due to neighboring group participation.

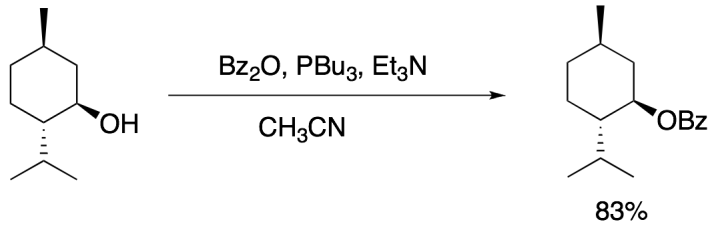
The use of $FeCl_3$ with acetic anhydride as the solvent was reported in1989 by Srivastava for the acylation of carbohydrates.[6] The primary acetylating agent in this reaction was reported to be the acylium ion **2.** This method produced excellent yields of the desired sugars but often required long reaction times (up to 38 hours). In addition, acetolysis of the anomeric position, which creates mixtures of α/β products especially with disaccharide substrates, was observed.



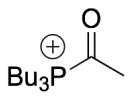
2

With the exception of the protocol using $FeCl_3$ as noted above, base catalyzed acylation of alcohols remained the primary method available until the early 1990s, when a number of new methods of acylation were introduced. In1993, Vedejs introduced tributylphosphine (PBu_3) as an active acylating agent (scheme 17).[4] While still technically a base, the almost neutral pKa of PBu_3 allowed for the acylation of compounds that were base sensitive. The active acetylating agent **3**, as ascertained from ^{31}P NMR experiments, is analogous to that of DMAP. Vedejs noted that PBu_3 is less expensive then DMAP and is also less toxic (750 mg/Kg, versus 56 mg/Kg, rat). In large

scale reactions, both cost and toxicity are important factors.[7] However, Vedejs also notes that the flammable nature of PBu_3 (flash point 37 °C) is a serious drawback to this methodology.

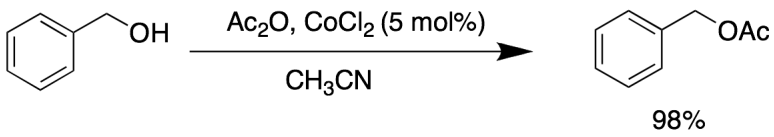


Scheme 17. Benzoylation of Menthol with Bz_2O and PBu_3.



3

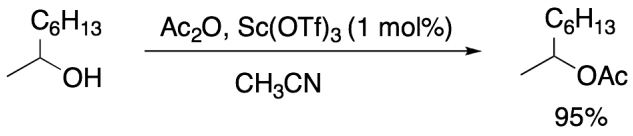
One of the first new "acid" catalyzed acylations of alcohols was performed by Iqbal in 1992,[8] when a catalytic amount of $CoCl_2$ (5 mol %) in CH_3CN was used to acylate primary alcohols in very good yields (>90%) at room temperature (scheme 18). Iqbal reported that secondary alcohols were also acylated in good yields, but the warming to 80 °C was required. The term "acid" catalyzed is used loosely here, since by-products from this reaction suggested that a radical mechanism was occurring and that the actual acylating agent was the acylium radical **4**. The reported goal for this reaction was the development of an acylation system in which elimination of β-hydroxyl carbonyl compounds does not occur, since this can be problematic with base catalyzed acylation methods.



Scheme 18. Acylation of benzyl alcohol catalyzed by $CoCl_2$.

4

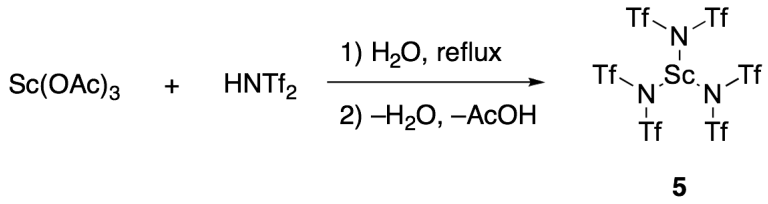
In 1995, Yamamoto introduced the Lewis acid $Sc(OTf)_3$ as a very effective acylation catalyst.[9] Yamamoto reported that, using only 1 mol % of $Sc(OTf)_3$ in CH_3CN, a broad spectrum of alcohols could be acylated in up to 95% yield (scheme 19). The temperature and time required for the reaction varied with the degree of steric hindrance of the substrate (tertiary alcohols usually required more time) and with the stability of the alcohols (allylic alcohols were acylated at low temperatures). The Yamamoto conditions afforded acetylation products at a rate approximately five times faster than the rate that was determined for reactions using DMAP.



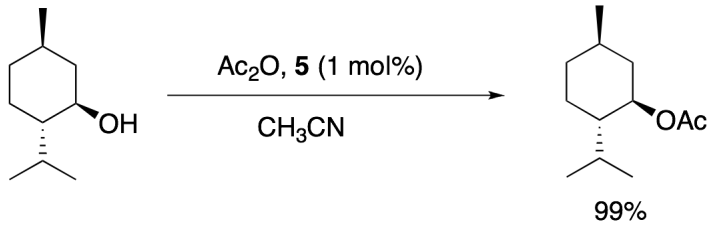
Scheme 19. Acylation of 2-octanol catalyzed by $Sc(OTf)_3$.

In 1996, Yamamoto improved this reaction by using scandium complex **5**,[10] which proved to be more active than $Sc(OTf)_3$. This was especially true for benzoylation reactions, which were slow with $Sc(OTf)_3$. However, catalyst **5** is not commercially

available and is synthesized by refluxing $Sc(OAc)_3$ with sulfonamide in water followed by drying *in vacuo* (scheme 20). An example of acylation using 5 is shown in scheme 21.



Scheme 20. Formation of scandium complex **5**.

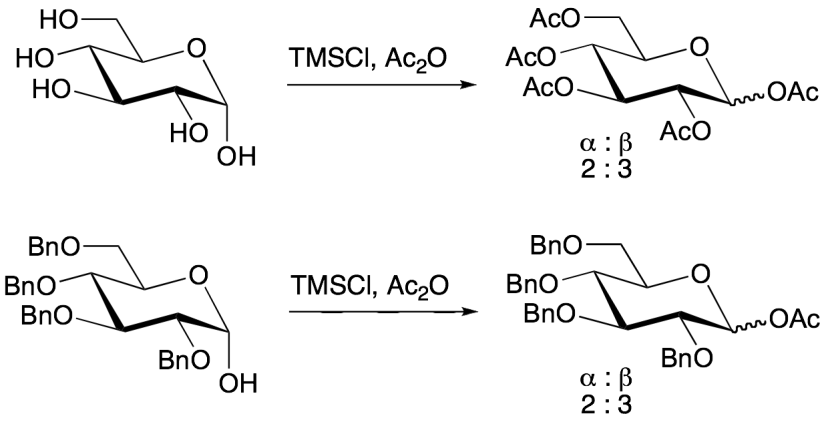


Scheme 21. Acylation of Menthol catalyzed by scandium complex **5**.

Vedejs published a second acylation procedure in 1996 in which 2 equiv. of $MgBr_2$ in anhydrous THF/CH_2Cl_2 were used along with a tertiary amine (triethylamine) to acylate tertiary alcohols (only tertiary alcohols were reported).[11] This method was particularly impressive because, in addition to acetic anhydride, acylating agents including benzoyl anhydride and pivaloyl anhydride could also be used.

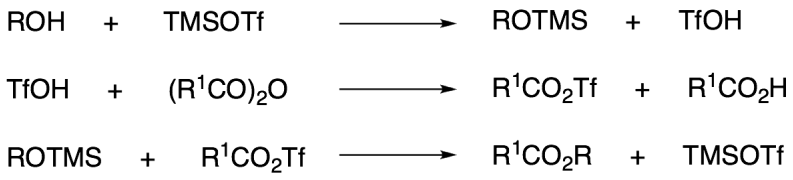
In 1997, a catalytic amount of TMSCl in CH_2Cl_2 or CH_3CN was used by Vankar to acylate a variety of alcohols.[12] Although TMSCl is readily available and is straightforward to use, competing elimination reactions were found to be problematic with both allylic and tertiary alcohols. This method was one of the first reports of the use

of acid catalyzed acylation procedures on carbohydrate substrates. Both glucose (in this case pure acetic anhydride was used as the solvent) and benzyl protected glucose could be acylated in good yields using this method (Scheme 22). However, a mixture of α/β ratios was obtained, probably due to the acidic nature of the reaction mixture, which likely facilitates the formation of the oxocarbenium ion.



Scheme 22. TMSCl catalyzed acylation of sugars.

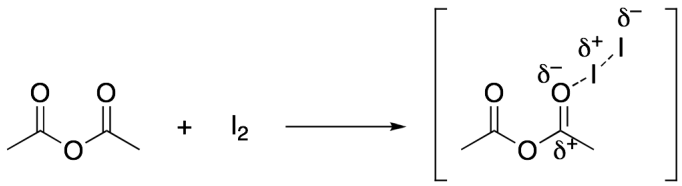
TMSOTf was used as a more powerful acylating agent by the Procopiou group in 1998.[3] A wide variety of functional groups were tolerated by this reagent system, which used TMSOTf (2-6 mol %) in either CH_2Cl_2 or CH_3CN, and the transformations occurred rapidly at 0-20 °C (5 minutes in most cases). A mechanism where the TMSOTf first reacts with the alcohol to generate TfOH was suggested (Scheme 23). The triflic acid then activates the anhydride by producing an acyl triflate, and the acyl triflate acylates the TMS-protected alcohol. Support for this mechanism includes an experiment where only triflic acid was added and no acylation occurred, indicating that the TMS portion of TMSOTf is vitally important.



Scheme 23. Mechanism of acylation of alcohols by TMSOTf .

A heterogeneous catalyst system was developed in 1998 by Logananthum, who used Montmorillonite K-10, a clay based solid catalyst, for the acylation of sugars.[13] While this catalyst was both easy to remove and environmentally friendly, α/β scrambling occurred during the reaction. Furanose formation when pyranosyl sugars were intended was also problematic.

The use of iodine as an acetylating reagent has been favorably reported in a number of cases. Kartha reported acylation of sugars using iodine in 1997.[14] The α/β ratios favored the α-product, with ranges varying from 4:1 for maltose to 25:1 for glucose. This reaction was very rapid; the products were formed in 10 minutes. Phukan reported an almost identical procedure for acylation in 2004. Although his examples included simpler alcohols, his results are noteworthy because of the short reaction time that was required for tertiary alcohols.[15] Iodine activation is shown in Scheme 24.

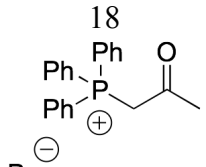


Scheme 24. Activation of Ac_2O by Iodine.

In 2003, Iadonisi used molecular sieves for the acylation of sugars.[16] This method seems underutilized since the reaction worked well and afforded products in yields of 80-90%. Many functional groups including isopropylidene, allyl and trityl groups were tolerated by the reaction conditions, and the reaction could be used to selectively protect the primary hydroxyl groups of sugars at room temperature. Full acylation of carbohydrates could be achieved at 80 °C. One important caveat, however, is that all sugars which were studied were previously protected at the anomeric position, so there is no data to suggest how this procedure would affect the α/β ratios at the anomeric positions.

In work by Misra, SiO_2 impregnated with $HClO_4$ was used to successfully acylate sugars.[17] The α/β ratios for reducing sugars were typically about 3:1 favoring the α product. While yields were very good, the major drawback of this procedure comes from the fact that dried $HClO_4$/silica gel is potentially explosive.

In 2005, Khan used the catalyst acetonytriphenylosphonium bromide (ATBP) (**6**) in Ac_2O to acylate a number of simple alcohols, amines, and thiols, as well as some partially protected carbohydrates.[18] This catalyst had the major advantage of being neutral, thus it could be used for base sensitive substrates. The reactions generally took 30-40 minutes; however, the more lipophilic the molecule, the faster the reaction went to completion (cholesterol was acylated in 3.5 minutes). Acylation of carbohydrates was accomplished using partially-protected derivatives, which were mostly benzoylated, indicating that more organic soluble substrates are required. The other drawback is that the precursor is not commercially available, although it is not difficult to make.[19]



6

$La(NO_3)•6H_2O$ was developed by the Venkateswarla group for the acylation of a large number of organic substrates using Ac_2O as the reagent and the solvent.[20] This catalyst was very mild, and acetylation of alcohols was accomplished without cleavage of a number of acid labile protecting groups such as THP, TBDMS, acetonides, and acetals.

One of the most impressive new catalysts for acetylation was introduced by Chakraborti in 2006.[21] He used $Mg(NTf)_2$ to catalyze acylation of alcohols under solvent free conditions. These reactions were rapid, efficient, and atom economical. Yields ranged from 75-100%, and this methodology could be used to introduce a number of different protecting groups such as pivaloyl and benzoyl groups. Although this method shows excellent promise, most of the substrates that were reported were very simple.

As previously mentioned, metal triflates are attractive candidates for the acylation of alcohols, with the first example using $Sc(OTf)_3$ coming from Yamamoto.[9] Metal triflates tend to be solids, and for the most part they are not moisture-sensitive. $Sc(OTf)_3$, $Cu(OTf)_2$,[22,23] $Bi(OTf)_3$,[24,25] $VO(OTf)_3$,[26] $Ce(OTf)_3$,[27] and $In(OTf)_3$[28] have all proven useful for the acylation of alcohols. Of these, $Bi(OTf)_3$ and $VO(OTf)_3$ have not been explored thoroughly for the acetylating of sugars.

Of the four remaining, $Cu(OTf)_3$ and $Ce(OTf)_3$ give α/β mixtures when acylation is attempted. $In(OTf)_3$, used by the Frost group, was only reported using D-mannitol, which is a non-reducing sugar, and it should be noted that CH_3CN (in which most sugars are not soluble) was used as a solvent. The most relevant example for our work comes

from the Hung group,[29] where 5 mol % of $Sc(OTf)_3$ was used to acetylate hexopyranoses in very good yields with apparently perfect anomeric selectivity.

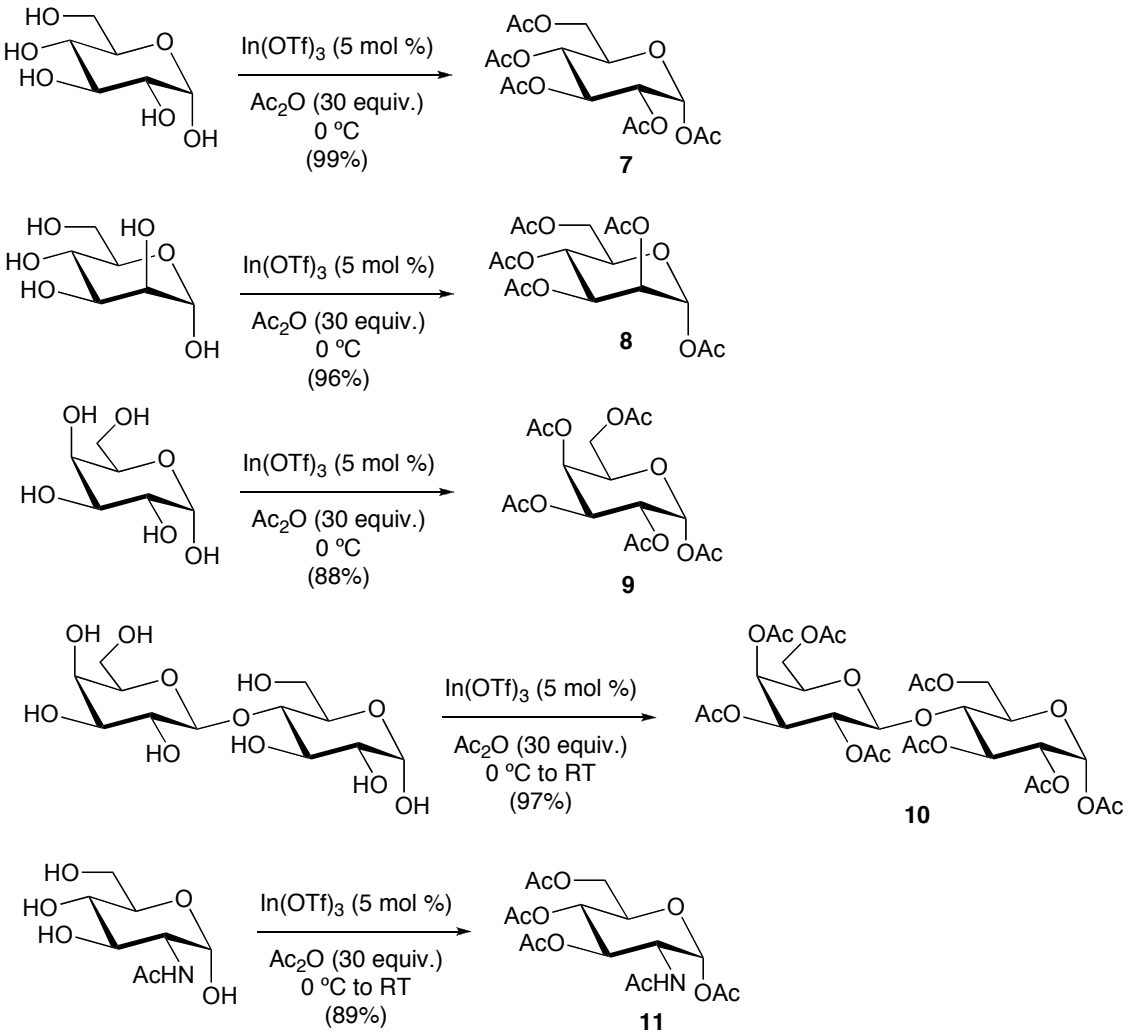
The preliminary results that have been reported from the Hung and Frost groups indicated that $In(OTf)_3$ could be developed as an attractive catalyst for the acylation of sugars. $In(OTf)_3$ mediated acetylation reactions for carbohydrate chemistry are desirable because $In(OTf)_3$ is relatively inexpensive, non-toxic, and air and moisture insensitive. Development of this reaction is described below.

Development of an $In(OTf)_3$ Mediated Acetylation Reaction for Carbohydrates

For initial exploration of the viability of the $In(OTf)_3$ mediated acetylation of carbohydrates, a stoichiometric amount of $In(OTf)_3$ was used with 100 equiv. of Ac_2O on mannoside. Under these forcing conditions, the acylation proceeded rapidly to afford acetylated mannose in just a few minutes. However, obvious drawbacks of using a stoichiometric amount of $In(OTf)_3$ included the costly nature of the reagent and the highly exothermic nature of the reaction, which increases the likelihood α/β scrambling. In addition, removal of the large excess of Ac_2O proved difficult.

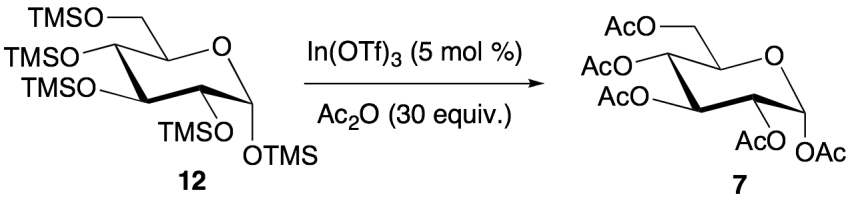
Reduction of the amount of metal triflate to 5 mol % of $In(OTf)_3$ and reduction of the amount of solvent to 30 equivalents of Ac_2O afforded the desired peracylated carbohydrate in high yield. The amount of Ac_2O was not further reduced because 30 equivalents afforded an easy to manipulate reaction mixture, and the excess Ac_2O was readily removed by hydrolysis. Addition of an EtOAc and 10% aqueous Na_2CO_3 solution to the crude reaction mixture in equal ratios, stirring for 1 hour, separation of the phases,

drying of the organic layer, and removal of the solvent provided the desired acetylated sugars in good yields. The carbohydrates that were evaluated are shown in Scheme 25. Due to the exothermic nature of the reaction, acylations with glucose, mannose, and galactose were conducted at 0 °C. However the low solubility of lactose and N-acetylglucosamine in Ac_2O required warming to room temperature for complete reaction to occur.



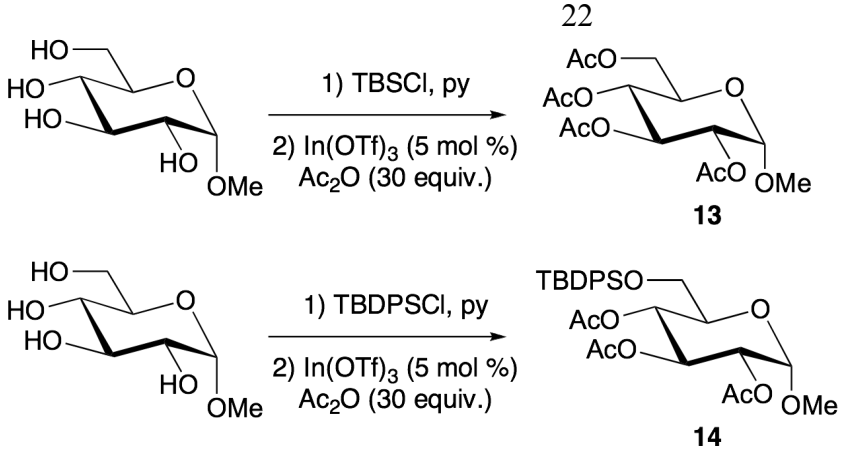
Scheme 25. Acylation of sugars catalyzed by $In(OTf)_3$.

The tolerance of silicon protecting groups under these reaction conditions was investigated. The fully trimethylsilylated (TMS) derivative of glucose **12** was synthesized using the Wells method[30] and was exposed to the acylating conditions. Only fully acetylated sugar **7** was obtained (Scheme 26), but this outcome was as expected due to the acid liability of TMS groups. In fact, these finding were consistent with previous reports that $Sc(OTf)_3$ catalyzed the exchange of silyl groups for acetyl groups.[31]



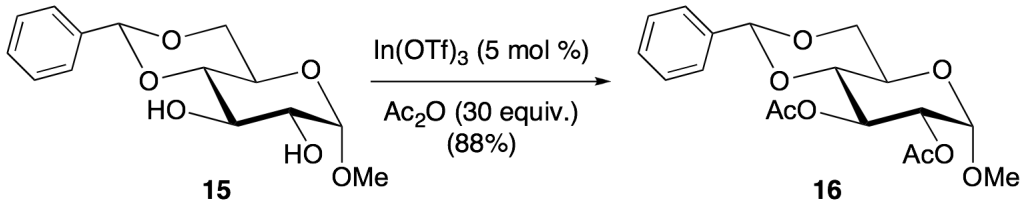
Scheme 26. Cleavage of TMS ethers by $In(OTf)_3$.

The incompatibility of the *tert*-butyldimethylsilyl (TBS) group with acylation was demonstrated by protection the six position of methyl glucopyranoside with TBSCl in pyridine followed by removal of the solvent and exposure to the acylation conditions. Again, the only product obtained was the fully acetylated sugar **13**. These findings were again consistent with the Whitefield group and their work with scandium(III)-catalyzed acetylations.[31] Only when we evaluated the robust *tert*-butyldiphenylsilyl TBDPS ether at the 6-postion did we find that the silyl group was not removed upon formation of **14** (Scheme 27).



Scheme 27. Cleavage of TBS ether and survival of TBDPS ether under acylation conditions.

The compatibility of the $In(OTf)_3$ mediated acetylation with a benzylidene acetal was evaluated. Construction of a 4,6-benzylidene acetal of O-methyl glucose **15** in the normal fashion and treatment with $In(OTf)_3/Ac_2O$ led to formation of the acetyl protected sugar **16** in good yield (88%, Scheme 28).[32] Thus, the reaction with $In(OTf)_3$ was again consistent with the Whitefield finding that $Sc(OTf)_3$ did not destroy isopropylidene groups.[31] With $In(OTf)_3$, side reactions such as Friedel-Crafts acylation chemistry were not observed.



Scheme 28. Survival of benzylidene acetals under acylation conditions.

The acylation of glucosamine could not be performed using $In(OTf)_3$ in Ac_2O. This is likely due the insolubility of glucosamine in Ac_2O; even upon sonication, no reaction was observed. DMF was also added as a cosolvent, but again no reaction occurred (although it should be noted that the sugar did not go into solution). Addition of water to the DMF mixture did not improve the solubility of glucosamine.

The Marko group analyzed the mechanism for the acylation of simpler alcohols and suggested that triflic acid played a significant role in the acylation.[33] Addition of the proton sponge 2,6-di-(*tert*-butyl)pyridine to an acylation reaction caused considerable inhibition of the process; only 12-15% of the desired acylation product was obtained.

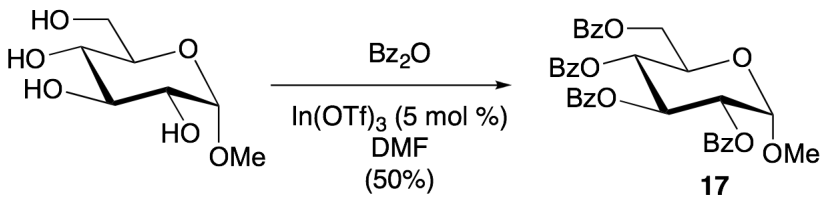
Two control experiments were performed to evaluate this $In(OTf)_3$ mediated acetylation reaction. First, 5 mol % of TfOH was added to a mixture of glucose in Ac_2O. Acylation proceeded quickly and very exothermically, producing the desired peracetylated sugar in 84% yield. Second, 2.2 equiv. of 2,6-di-(*tert*-butyl)pyridine were added to the reaction using glucose, and the reaction mixture was stirred overnight. Recovery of unreacted glucose and isolation of only 11% yield of the desired per-acylated sugar suggests that $In(OTf)_3$ either produces during the reaction or is contaminated by a small amount of TfOH, which performs the actual catalysis of the acylation. However, if the TfOH catalyzed pathway is eliminated, then the indium(III) does mediate acetylation, albeit inefficiently. Although this suggests that TfOH could be used directly to catalyze acetylation of carbohydrates, $In(OTf)_3$ is significantly milder and is less likely to cause substrate and/or product decomposition.

$InBr_3$ and $InCl_3$ were briefly evaluated to investigate the effect of different ligands coordinated to the indium on the reaction. While both catalysts did produce fully

acetylated products, in each case the yield was lower than the $In(OTf)_3$ catalyzed reaction (86% and 71%, respectively) and longer reaction times were required (6 and 12 hours, respectively). These findings again suggest that the protic acid in these Lewis acids is actually doing the catalysis, since the lower the pKa of the resultant acid, the faster and more productive the reaction was.

Benzoylation of carbohydrates using $In(OTf)_3$ was also evaluated. Since benzoyl anhydride is a solid (unlike Ac_2O), a solvent was needed. Based on prior art, reactions were studied in CH_3CN.[28] $In(OTf)_3$ (5-100 mol %) and 10 equiv. of Bz_2O in CH_3CN and reaction times of up to 48 hours were evaluated. In all cases, the sugars remained as a white solid at the bottom of the flask. Sonication, heating, and microwave irradiation methods did not allow for sufficient solvation for reaction to occur. Addition of water as a cosolvent in up to 50 mol % was also unsuccessful.

In DMF, upon treatment with 10 equiv. of benzoic anhydride with 5 mol % of $In(OTf)_3$, benzoylation was achieved to give **17** in 50% yield (Scheme 29). However, the workup of this reaction was much less pleasant than the acetylation reactions that were described above in acetic anhydride. Extraction and column chromatography were required to obtain the desired product. Thus, the $In(OTf)_3$ catalyzed acetylation of carbohydrates is not directly amendable to modification to perform benzoylation reactions.



Scheme 29. $In(OTf)_3$ catalyzed benzoylation of glucose in DMF.

Summary

Acylation is a ubiquitous procedure in organic chemistry, as the introduction of an acetyl group allows for the masking of the acidic nature of the parent alcohol. This is particularly important for carbohydrate substrates; the acylation of the carbohydrate is often the first step in multistep synthetic routes to complex oligosaccharides.

While the methods for the introduction of an acetyl group are varied, they are generally either acid or base catalyzed. Base catalysis is most common and often employs pyridine, a noxious and high boiling solvent. Methods for acid catalysis are much more varied. While a large number of acids are available for the acylation of simple alcohols, less practical solutions are available for carbohydrates. Many existing methods of acid catalyzed acylation lead to α/β mixtures. In some cases this may not be a problem. However, as will be discussed in the next chapter, there are often differences in the reactivity of α and β acetate-protected carbohydrates.

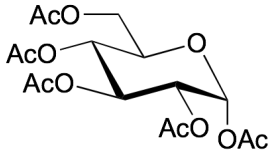
At present only two viable methods exist for the acid catalyzed acylation of sugars which give only one anomer: the use of $Sc(OTf)_3$, and our method utilizing $In(OTf)_3$. Both methods appear to have advantages. $Sc(OTf)_3$ uses far less Ac_2O than is used in $In(OTf)_3$ mediated reactions, suggesting that $Sc(OTf)_3$ is likely the more active catalyst. However, $Sc(OTf)_3$ is far more expensive than $In(OTf)_3$. Because Ac_2O is an inexpensive and readily available starting material, $In(OTf)_3$ is ultimately the more cost effective reagent for acetylation reactions. Although atom efficiency is reduced and waste production is increased, the main by-product is the sodium salt of acetic acid, which is

innocuous. These studies did not include an extensive investigation into the minimum amount of Ac_2O that would be sufficient for the $In(OTf)_3$ catalyzed acetylation reaction.

Both the $Sc(OTf)_3$ and $In(OTf)_3$ catalyzed acylation reactions are a significant advance compared to traditional methods using pyridine/DMAP as they are fast, purification is simple, and high yields of the desired products are obtained.

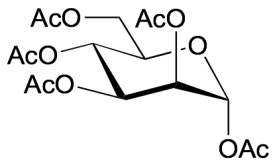
Experimental Methods

Indium triflate was purchased from Aldrich Chemical Co. and was used without additional purification. Acetic anhydride was purchased from Acros Chemical Co. and was used without additional purification. NMR spectra were recorded on a Bruker 500 MHz spectrometer.

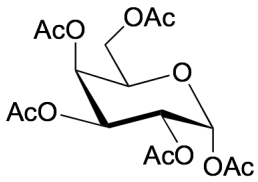


1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7) . To Ac_2O (3.3 mL, 30 equiv.) was added 200 mg (1.1 mmol) of α-D-glucose and the solution was cooled to 0 °C. $In(OTf)_3$ (30 mg, 53 μmol, 0.05 equiv.) was added, and the reaction was allowed to stir for 1 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 429 mg (99% yield) of product as a clear, colorless syrup. ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ 6.25 (d, J= 3.6 Hz, 1H), 5.39 (1H, t, J = 10 Hz, 1H), 5.02 (m, 2H), 4.20 (d, J = 9.0 Hz,

1H), 4.05 (m, 2H), 2.10 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H). These values agree with previously reported spectra.[34]

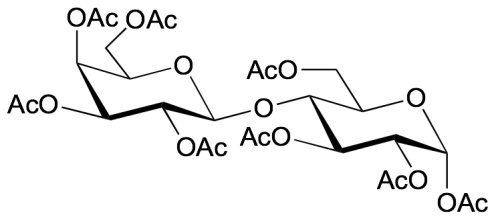


Preparation of 1,2,3,4,6-penta-O-acetyl-α-D-mannopyranoside (8). To Ac_2O (3.1 mL, 30 equiv.) was added 186 mg (1.03 mmol) of α-D-mannose, and the solution was cooled to 0 °C. $In(OTf)_3$ (29 mg, 51 μmol, 0.05 equiv.) was added, and the reaction was allowed to stir for 1 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 386 mg of product (96% yield). ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ 6.07 (d, J = 1.5 Hz, 1H), 5.33 (m, 2H), 5.25 (s, 1H), 4.27 (dd, J = 12.3, 4.9 Hz, 1H), 4.09 - 4.03 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H) 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H). These values agree with previously reported spectra.[34]



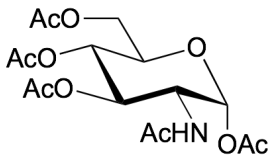
Preparation of 1,2,3,4,6-penta-O-acetyl-α-D-galactopyranoside (9). To Ac_2O (3.6 mL, 30 equiv.) was added 212 mg (1.17 mmol) of α-D-galactose, and the solution was cooled to 0 °C. $In(OTf)_3$ (32 mg, 56 μmol, 0.05 equiv.) was added, and the reaction was allowed

to stir for 1 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 404 mg of product (88% yield). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 6.33 (s, 1H), 5.45 (s, 1H), 5.29 (s, 2H), 4.30 (t, J = 6.6 Hz, 2H), 4.08-4.01 (m, 2H), 2.114 (s, 3H), 2.112 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H) These values agree with previously reported spectra.[34]

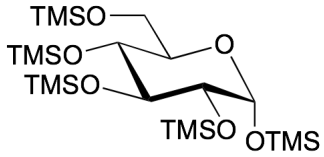


Preparation of 2,3,4,6-tetra-O-acetyl-β-galactopyranose [1→4] 1,2,3,6-tetra-O-acetyl-β-glucopyranose (10). To Ac_2O (7.9 mL, 30 equiv.) was added 1.0 g (2.76 mmol) of lactose, and the solution was cooled to 0 °C. $In(OTf)_3$ (79.5 mg, 141 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. EtOAc (100 mL) and 10% aqueous Na_2CO_3 solution (150 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with water (3 x 50 mL) and brine (3 x 50 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 1.88 g of product (97% yield). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 6.22 (d, J = 3.7 Hz, 1H), 5.43 (t, J = 10 Hz, 1H), 5.33 (d, J = 2.9 Hz, 1H), 5.12-5.07 (m, 1H), 4.99-4.94 (m, 2H), 4.46-4.41 (m, 2H), 4.09-4.04 (m, 3H), 3.98, (dd, J = 2.0, 2.0 Hz, 1H), 3.85 (t, J = 6.9 Hz, 1H), 3.80 (t, J = 10 Hz), 2.15 (s, 3H), 2.13 (s, 3H), 2,10

(s, 3H), 2.039 (s, 3H), 2.305 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H). These values agree with previously reported spectra.[35]

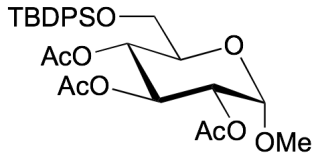


1,3,4,6-tetra-O-acetyl-2-N-acetyl-α-D-glucosamine (11). To Ac_2O (2.7 mL, 30 equiv.) was added 176 mg (0.90 mmol) of N-acetyl α-D-glucosamine, and the solution was cooled to 0 °C. $In(OTf)_3$ (30 mg, 55 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 287 mg of product (89% yield). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 6.09 (d, J = 3.5 Hz, 1H), 5.76 (d, J = 9.0 Hz, 1H), 5.17 (t, J = 9.5 Hz, 1H), 5.13 (t, J = 9.4 Hz, 1H) 4.42 (q, J = 3.5 Hz, 1H), 4.18 (dd, J = 12.4, 3.9, 1H), 4.01-3.93 (m, 2H) 2.12 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.86 (s, 3H). These values agree with previously reported spectra.[36]



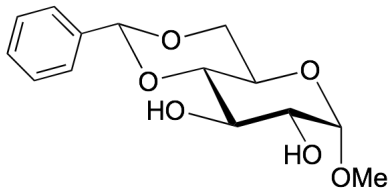
1,2,3,4,6-O-penta(trimethylsilyl)-α-D-glucose (12). To pyridine was added 0.456 (2.35 mmol) grams of O-methyl-glucose, and the solution was brought to 0°C. To this solution was added hexamethyldisilazide (3.2 ml 15.5mmol) and TMSCl (0.253 ml, 2.35 mmol),

and the resulting solution was allowed to stir for 15 min. The pyridine was removed under reduced pressure, and the mixture was taken up into ethyl acetate and washed with water x3, dried over $NaSO_4$ and the solvent was removed under reduced pressure to give 1.15g of product (91% yield. ^{1}H-NMR($CDCl_3$, 500 MHz, ppm) δ 4.98 (d, *J* = 3.0 Hz, 1H) 3.75-3.63 (m, 5H), 3.38 (t, *J*= 8.8 Hz, 1H), 3.32-3.30 (m, 1H) 0.15 (s, 9H), 0.10 (s, 9H), 0.08 (s, 9H) 0.03 (9H, s). These values agree with previously reported spectra.[30]

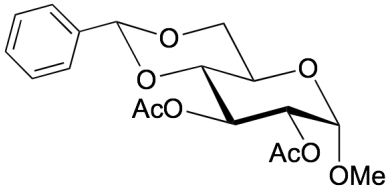


Preparation of 1-O-methyl-2,3,4-tri-O-acetyl-6-O-tertbutyldiphenylsilyl-α-D-glucopyranoside (14). To pyridine (16 mL) was added 1-O-methyl-α-D-glucopyranoside (345 mg, 1.61 mmol). The solution was cooled to 0 °C, tertbutyldiphenylsilyl chloride (443 mg, 1.61 mmol) was added, and the reaction was stirred for 3.5 h.[38] Pyridine was removed under reduced pressure. The resulting intermediate was cooled to 0°C, Ac_2O (5.3 mL, 30 equiv.) and $In(OTf)_3$ (49 mg, 88 μmol, 0.05 equiv.) were added, and the reaction was stirred for 1 h while warming to room temperature. EtOAc (20 mL) and 10% aq. Na_2CO_3 solution (20 mL) were added and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded crude product, which was chromatographed (9:1 hexane/EtOAc) to afford 853 mg of product (86% yield). ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm) δ 7.66 (t, J = 7.5 Hz, 4H), 7.2 (appt t, J = 7.5 Hz, 6H),

5.46 (t, J= 9.8 Hz, 1H), 5.08 (t, J =9.8 Hz, 1H), 4.95 (s, 1H), 4.88 (dd, J= 7.5, 3.1 Hz, 1H) 3.85 (m, 1H), 3.68 (m, 2H), 3.38 (s, 3H), 2.06 (s, 3H), 1.98 (s, 3H). 1.86 (s, 3H) 1.03 (s, 9H). These values agree with previously reported spectra.[37]



4,6-O-benzylidene-α-D-O methyl glucose (15). Methyl α-D-glucopyranoside (9.7 g, 50 mmol) and benzaldehyde (7.6 g, 50 mmol) were dissolved in 40 ml of dry DMF, and to this was added *p*-toluenesulfonic acid (25 mg, 0,14 mmol). The solution was stirred under reduced pressure at 60° C for 1 h. After this time, the DMF was removed under reduced pressure (rotovap), and a solution of $NaHCO_3$ (1 g in 50 ml of H_2O) was added, and the residue was heated to 100°C until the product was finely dispersed. The mixture was cooled to rt and the product was filtered off, washed with water, and dried under vacuum, to 11.5 g of product (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 (d, J=3.0 Hz, 2H), 7.34 (d, J=3.0 Hz, 3H), 5.49 (1H, s), 4.73 (d, J=3.7 Hz, 2H), 4.22 (dd, J = 9.8, 4.4 Hz, 1H) 3.88 (t, J=9.3 Hz, 1H), 3.79-3.70 (m, 2H) 3.67 (s, 1H), 3.44 (t, J = 9.3 Hz), 3.41 (3H, s), 3.13 (bs, 1H) 2.59 (bs, 1H). These values agree with previously reported spectra.[32]



4,6-O-benzylidene-2,3-O-diacetyl-1-O-methyl-α-D-glucopyranoside (16). To Ac_2O (3.3 mL, 30 equiv.) was added 200 mg (1.11 mmol) of 4,6-O-benzylidene-1-O-methyl-α-D-glucopyranoside, and the solution was cooled to 0 °C. $In(OTf)_3$ (30 mg, 55 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 228 mg of product as a syrup (88% yield). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.43 (d, J = 3.5 Hz, 2H), 7.34-7.33 (m, 3H), 5.56 (t, J = 9.7 Hz, 1H), 5.48 (s, 1H), 4.93-4.88 (m , 2H), 4.29 (dd, J=10.3, 4.8, 1H), 3.94-3.78 (m, 1H), 3.75 (t, J = 10.0 Hz, 3H), 3.63 (t, J = 10.0 Hz), 3.39 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H). These values agree with previously reported spectra.[38]

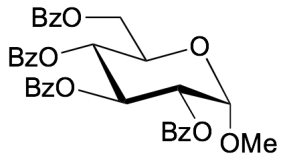
Protocol for TfOH Mediated Peracetylation Reaction to Form 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7). To Ac_2O (2.7 mL, 30 equiv.) was added 103 mg (0.50 mmol) of α-D-galactose, and the solution was cooled to 0 °C. TfOH (2 μl, 28 μmol, 0.05 equiv.) was added, and the reaction was allowed to stir for 10 min. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and

drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 187 mg of product as a syrup (84% yield, characterization data and reference are provided above).

Protocol for $In(OTf)_3$ Mediated Peracetylation Reactions with Proton Scavenger. Preparation of 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7). To Ac_2O (1.6 mL, 30 equiv.) was added 97 mg (0.53 mmol) of α-D-glucose and the solution was cooled to 0 °C. $In(OTf)_3$ (30 mg, 55 μmol, 0.05 equiv.) and 2,6-di-tert-butyl pyridine (0.226 mL, 1.06 mmol, 2.2 equiv.) were added, and the reaction was allowed to warm to room temperature while stirring for 24 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 23 mg of product (11% yield, characterization data and reference are provided above).

$InBr_3$ mediated preparation of 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7). To Ac_2O (3.5 mL, 30 equiv.) was added 213 mg (1.18 mmol) of α-D-glucose and the solution was cooled to 0 °C. $InBr_3$ (21 mg, 59 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 5 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 396 mg (86% yield) of product as a syrup. Characterization data and reference are provided above.

$InCl_3$ mediated preparation of 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7). To Ac_2O (3.1 mL, 30 equiv.) was added 196 mg (1.03 mmol) of α-D-glucose and the solution was cooled to 0 °C. $InCl_3$ (12 mg, 54 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 12 h. EtOAc (20 mL) and 10% aqueous Na_2CO_3 solution (20 mL) were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* afforded 301 mg (71% yield) of product as a syrup. Characterization data and reference are provided above.



1-O-methyl-2,3,4,6-penta-O-benzoyl-α-D-glucopyranoside (17). To DMF (9.0 mL) was added 173 mg (0.89 mmol) of 1-O-methyl-α-D-glucose and benzoyl anhydride (2.01 g, 8.9 mmol, 10 equiv.) and the solution was cooled to 0 °C. $In(OTf)_3$ (25 mg, 45 μmol, 0.05 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 12 h. The reaction was quenched with 20 mL H_2O and washed with EtOAc (10 mL x 3). The organic layer was isolated, washed with sat. aq. $NaHCO_3$ solution (2 x 10 mL), and drying over $MgSO_4$ followed by solvent removal *in vacuo* to afford 293 mg of product (50% yield). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.03 (d, J = 7.5 Hz, 2H), 7.97 (d, J =7.5 Hz, 2H) 7.93 (d, J= 7.5 Hz, 2H), 7.86 (d, J = 7.5 Hz, 2H) 7.55- 7.47 (m, 3H), 7.42- 7.27 (m, 7H), 7.26-7.25 (m, 2H), 6.18 (t, J = 9.9 Hz, 1H), 5.67 (t, J = 9.9 Hz,

1H), 5.30-5.23 (m, 2H), 4.61-4.58 (m, 1H), 4.49-4.40 (m, 2H), 3.41 (s, 3H). These values agree with previously reported spectra.[39]

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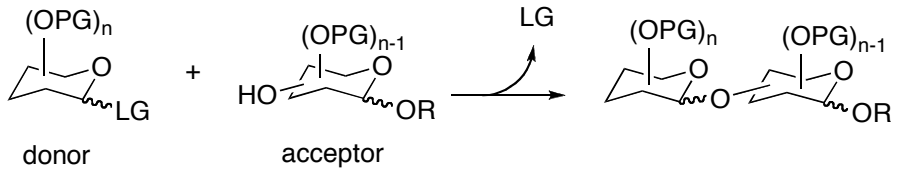
CHAPTER 3

$In(OTf)_3$ AS A PROMOTER FOR GLYCOSYLATION REACTIONS

Introduction

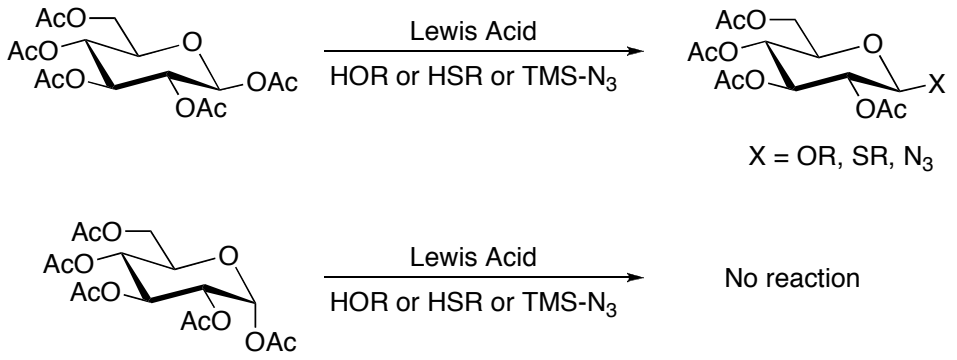
The formation of the glycoside bond lies at the heart of carbohydrate chemistry. A glycoside bond is the bond formed at the anomeric position of one carbohydrate and whatever it is attached to. Almost all natural products containing more than one saccharide contain a glycosidic bond, including glycoproteins (proteins that bear a carbohydrate linkage) and glycolipids (lipid molecules that contain one or more saccharide). Thus formation of the glycoside bond is of utmost importance to the carbohydrate chemist. Numerous ways of forming these bonds have been devised during the last century, and some of the most important methods are discussed below.

Most glycoside bond formation relies on the strategy outlined in Scheme 30. The glycosyl donor, or electrophile, contains a leaving group, and the other hydroxyl groups are masked by protecting groups. To this sugar is added a nucleophile (shown in Scheme 24 as another sugar). The donor is treated with a promoter (often a Lewis acid), creating an electrophilic species such as an oxocarbenium ion, and the acceptor then forms a bond at the anomeric position.



Scheme 30. Explanation of donor acceptor terminology.

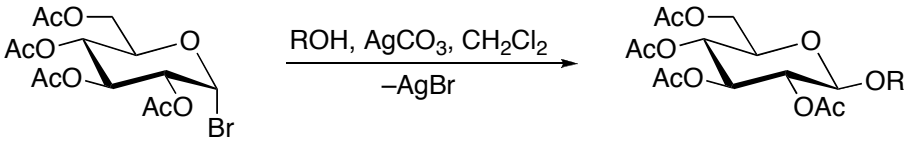
Perhaps the simplest of all the cases of O-glycosylation occurs with peracylated monosaccharide as shown in Scheme 31. These carbohydrates can be treated with a Lewis acid such as BF_3•OEt_2 and then with simple alcohols, thiols, and azides.[1,2,3] However, this method is not suitable for more complex oligosaccharides, most likely due to the harsh nature of the reaction conditions (these reactions are usually conducted overnight at room temperature). It is interesting to note that in the case of per-0-acylated-glucose, only the β anomer is reactive in most cases. This may be due to the stability afforded by the anomeric effect, i.e. the α-acetate is simply too stable to be a good leaving group. Unsurprisingly neighboring group participation results in formation of the β-product.



Scheme 31. Lewis acid mediated reaction of acyl protected sugars with nucleophiles.

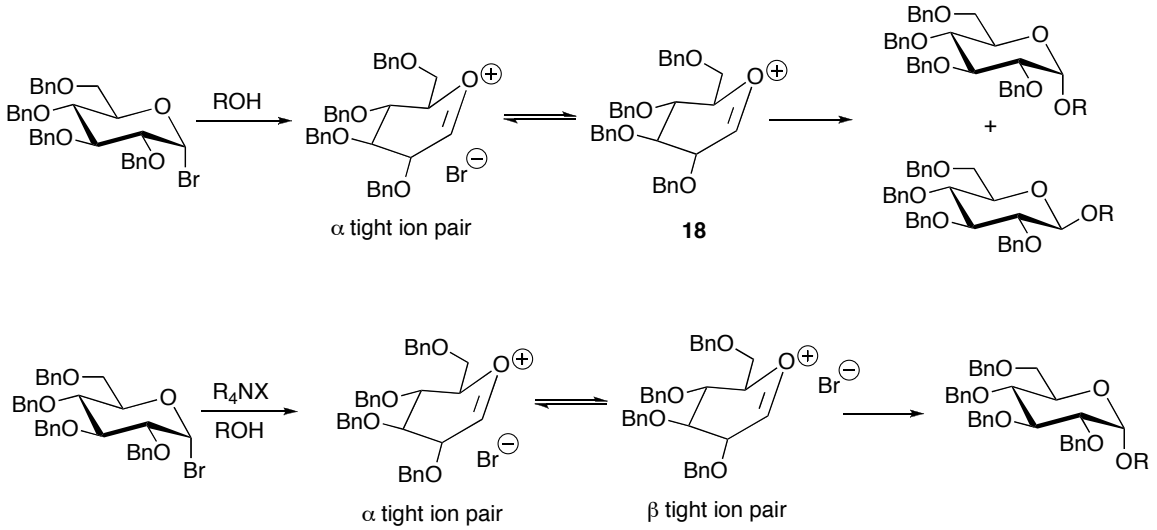
When using more complex acceptor molecules such as a saccharide, a number of different leaving groups have been utilized including glycosyl halides, trichloroacetimidates, thioglycosides, and n-pentenyl glycosides. Each method will be discussed in turn.

The oldest method for glycosylations is referred to as the Koenigs-Knorr method, developed by Wilhelm Koenigs and Edward Knorr. This reaction involves treating an anomeric halogen with a silver salt in the presence of an alcohol (Scheme 32).[4] The reaction proceeds by solvolysis of the halogen to give an oxocarbenium ion. Neighboring group participation then occurs as it did in the case of the acetate.



Scheme 32. Koenigs-Knorr reaction.

When there is a protecting group that does not allow for neighboring group participation on the C-2 position, stereoselective bond formation becomes more challenging. While the product that results from the reaction appears to be that which would arise from a standard S_n2 reaction, work by Lemieux provides evidence for a more complex mechanism (Scheme 33).[5] Lemieux noted that a mixture of anomers is formed when there is no neighboring group participation; however, isomerization of the alpha bromide to the beta bromide is unlikely due to the anomeric effect. Lemieux suggested that solvolysis of the bromide forms a tight ion pair in the alpha mode, and this pair further dissociates to give oxocarbenium ion **18**. Ion **18** then proceeds to afford both the *cis* and *trans* glycoside. In the presence of tetralkylammonium halide, the tight alpha ion pair can alternatively isomerize to give a tight ion pair in the β- configuration, affording the cis isomer.



Scheme 33. Formation of 1,2-*trans* and 1,2-*cis* glycosides in the presence of tetralkylammonium halides.

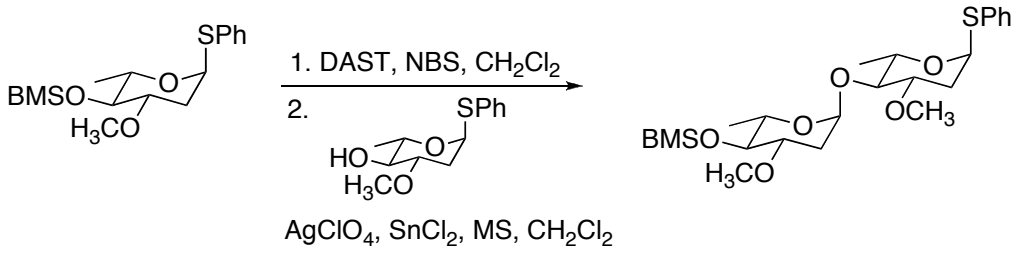
Since the pioneering work of the Koenigs-Knorr reaction, there have been many efforts to improve this reaction, such as utilizing a co-solvent to improve the formation of the oxocarbenium ion, using a desiccant such as powdered molecular sieves to absorb both water and acid,[6] adding iodine to improve solvolysis,[7] and distinguishing the roles of "promoter" versus "acid acceptor". To this end, metal salts such as mercury (II) bromide (promoter) /mercury (II) oxide (acid scavenger), have been utilized.[8] In addition, soluble promoters such as mercury cyanide and silver triflate are commonly used in the Koenings-Knorr method.[9]

For most of the Koenigs-Knorr reactions, bromide is the most used of the halide ions. The substrate containing the chloride is often too stable to be of much use, and the iodo sugar is too unstable. Logically, if the chlorosaccharide were too stable, then the fluorine would be "a rock." This was the case until 1980, when Mukaiyama introduced a

range of promoters that allowed glycosyl fluorides to act as reasonable donors (Figure 1).[10] Nicolaou contributed greatly to this area when he showed that a thioglycoside could be converted into a fluoride for use as a glycosyl donor (Scheme 34).[11]

Figure 1. Lewis Acids that Mukaiyama has introduced for the activation of glycosyl fluorides.

$SnCl_2$, $AgClO_4$,	Et_2OBF_3
$SnCl_2$, $TrClO_4$	SiF_4
Cp_2MCl_2 (M=Ti, Zr, Hf)	TiF_4
$AgClO_4$	Me_3SiOTf
Me_2GaCl	Tf_2O
$La(ClO_4)_3.nH_2O$	$Yb(OTf)_3$
$TrB(C_6F_5)_4$	

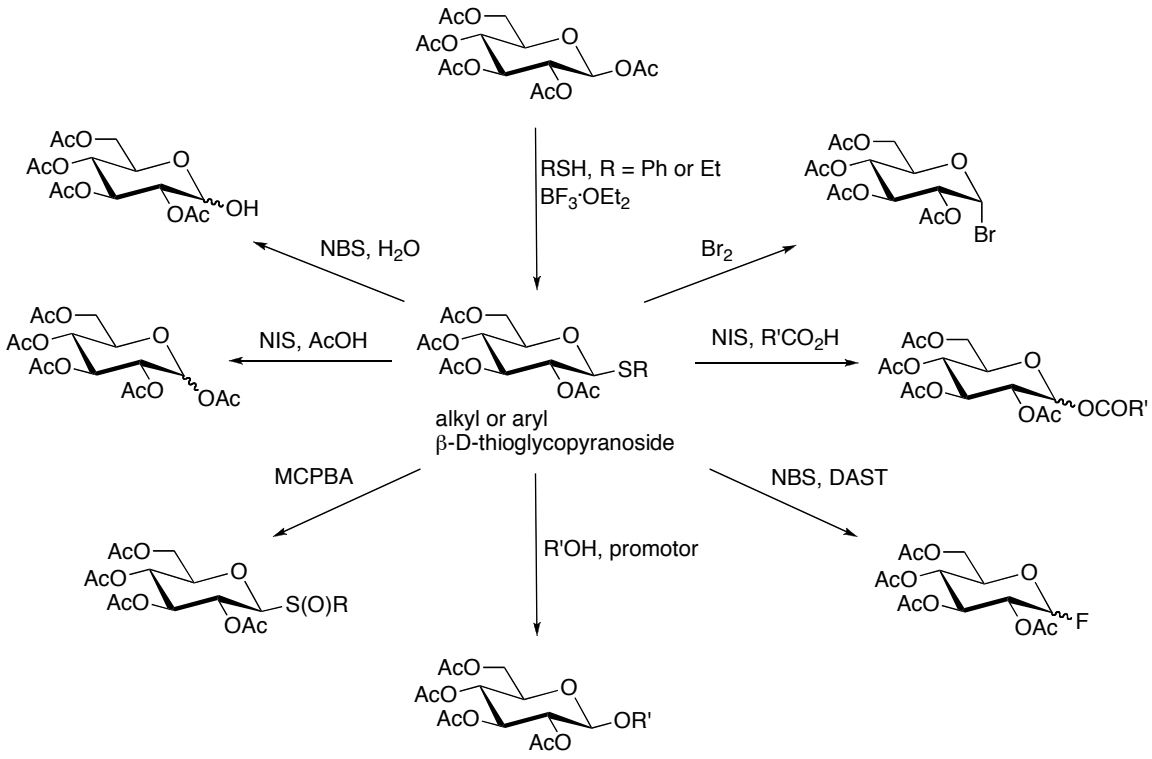


Scheme 34. Use of DAST for activation of thioglycosides.

Glycosyl fluorides can be used for the synthesis of both 1,2-*cis* and 1,2-*trans* glycosides. As expected, donors that bear an ester at the C-2 position generally follow the principles of the Koenigs–Knorr reaction: anomeric assistance leads to formation of *trans*

glycosides in the case of the glucosides. When there is a non-participating group at the C-2 position of a beta-substituted glycosyl fluoride, the alpha isomer is the major product.[10]

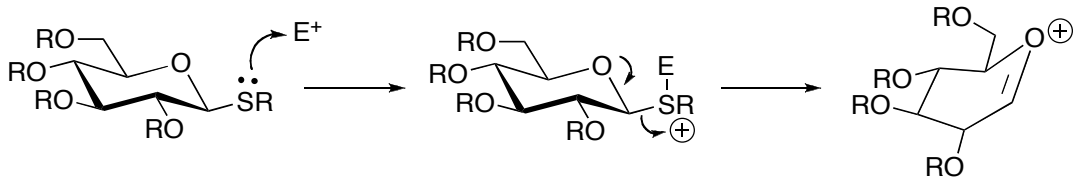
In addition to anomeric halides, thioglycosides are important glycosyl donors. Preparation of these donors is most often achieved by treatment of acetylated hexopyranoses with a thiol in the presence of $BF_3 \bullet Et_2O$. The major product is the *trans* product. A number of simple manipulations can be performed using thioglycosides, as shown in Scheme 35.



Scheme 35. Reactions of thioglycosides.

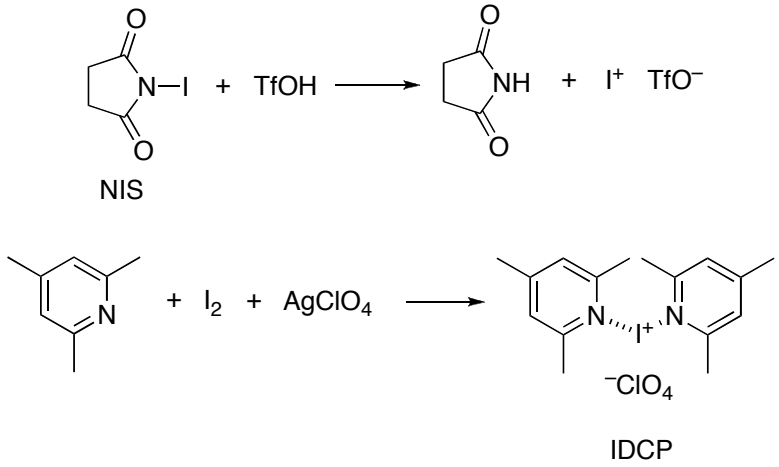
The activation of a thioglycoside for the addition of an alcohol or glycosyl acceptor can be achieved using a wide range of electrophilic promoters. These promoters

create an intermediate sulfonium ion, which upon leaving creates an oxocarbenium ion suitable for glycosylation (Scheme 36).



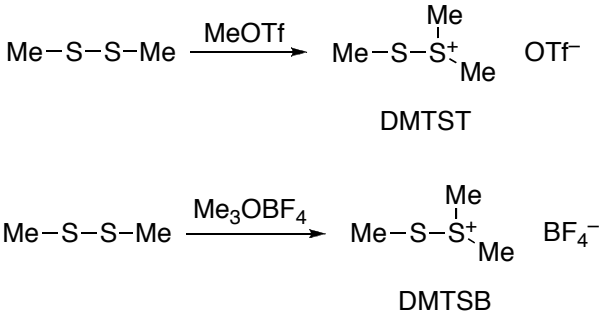
Scheme 36. Mechanism of thioglycoside activation.

One common method of activation is to use an electrophilic source of iodine, which then creates the sulfur iodonium ion. Two common sources of electrophilic iodine for these reactions are NIS/TfOH and ICDP.[12,13,14] In the former, NIS (N-iodosuccinimide) reacts as shown in Scheme 37 to give I+. ICDP, or iodonium dicollidine perchlorate, is formed by treating iodine with collidine in the presence of silver perchlorate.



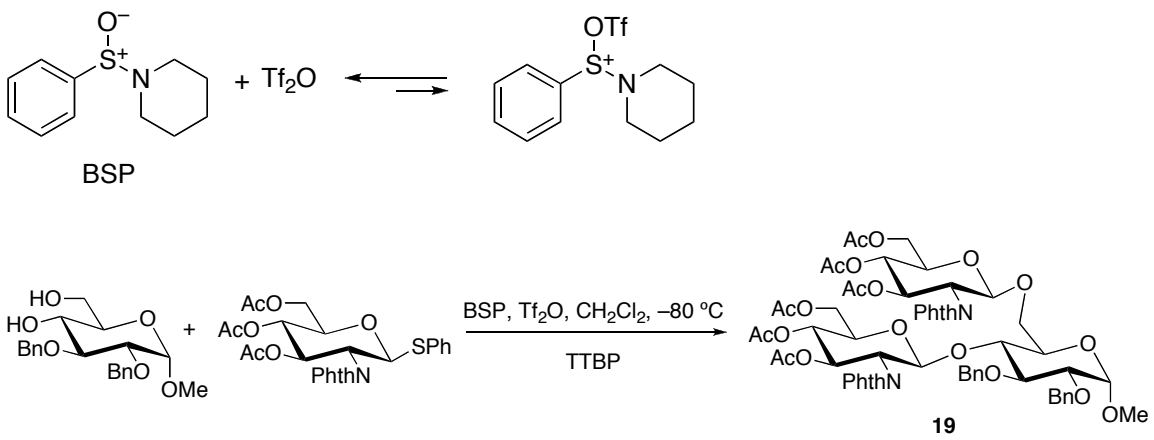
Scheme 37. Formation of ICDP.

Alkylating agents can also be used to form the intermediate sulfonium ion. To this end, MeOTf was one of the first methylating agents described.[14] However, this reagent had several drawbacks: it was volatile, extremely toxic, and, in the case of slow reacting glycosyl donors, methylation of the acceptor at the unmasked alcohol was a significant problem. For these reasons, other thiophilic promoters have been developed. Among the most commonly employed are dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSB).[15,16,17] DMTST is created by adding methyl triflate to dimethylsulfide, while DMTSB is produced by adding trimethyloxonium tetrafluoroborate to dimethyl sulfide. It should be noted that DMTSB is a salt that is easier to handle (Scheme 38).



Scheme 38. Formation of DMTST and DMTSB.

Phenylselenyl triflate (PhSeOTf) has also been employed to activate thioglycosides.[18] An outgrowth of this method has led to the development of the 1-phenylsulfinyl piperidine/triflic anhydride (BSP-Tf_2O) system. This combination of reagents forms a powerful electrophilic salt that activates thioglycosides. Crich used this set of reagents along with the acid scavenger 2,4,6-tri-*tert*butylpyridine (TTBP) to synthesize the tri-saccharide **19** in 85% yield (Scheme 39).

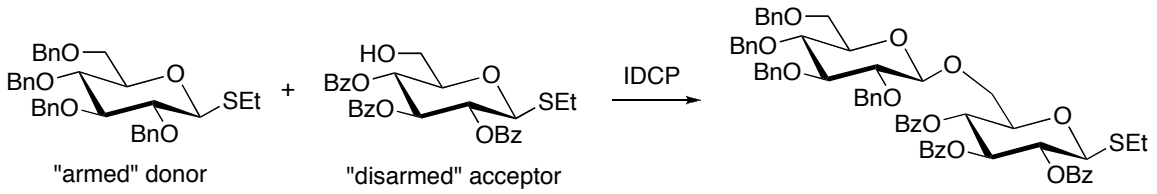


Scheme 39. Formation and use of BSP Tf_2O system for glycosylation.

The α/β selectivity of thioglycoside donors with either O or N acyl groups at the C-2 position leads to the expected neighboring group participation that generally directs addition. However, when there is a non-participating group at C-2, the α/β ratios are substrate specific and can be influenced by the choice of solvent and promoter.

One interesting concept that can be demonstrated with thioglycosides (and with all glycoside donors) is that of armed/disarmed systems, which was first noticed by Paulsen[19] and further elaborated by Fraser-Reid for use with n-pentenyl glycosides.[20] The protecting groups on the sugar influence the reactivity of donor/acceptor pairing. In their work it was shown that benzyl groups activate, or "arm," a glycoside to be a good donor. Conversely, acyl groups serve to deactivate, or "disarm," sugars, and subsequently make them less reactive donors. The following example demonstrates this effect. If the armed/disarmed concept were not in play, then one would expect to find a mixture of products where **20** coupled with itself, as well as with the donor. However, the donor and

acceptor pairing leads to one major product in 84% yield with 7:1 α/β selectivity (Scheme 40).



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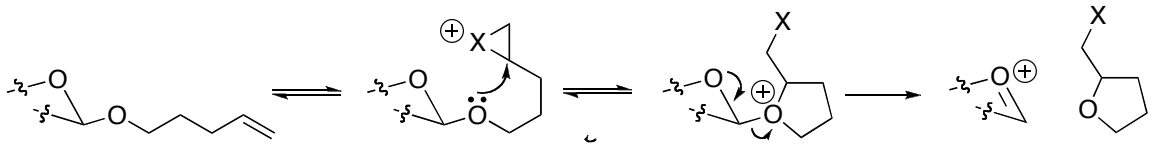
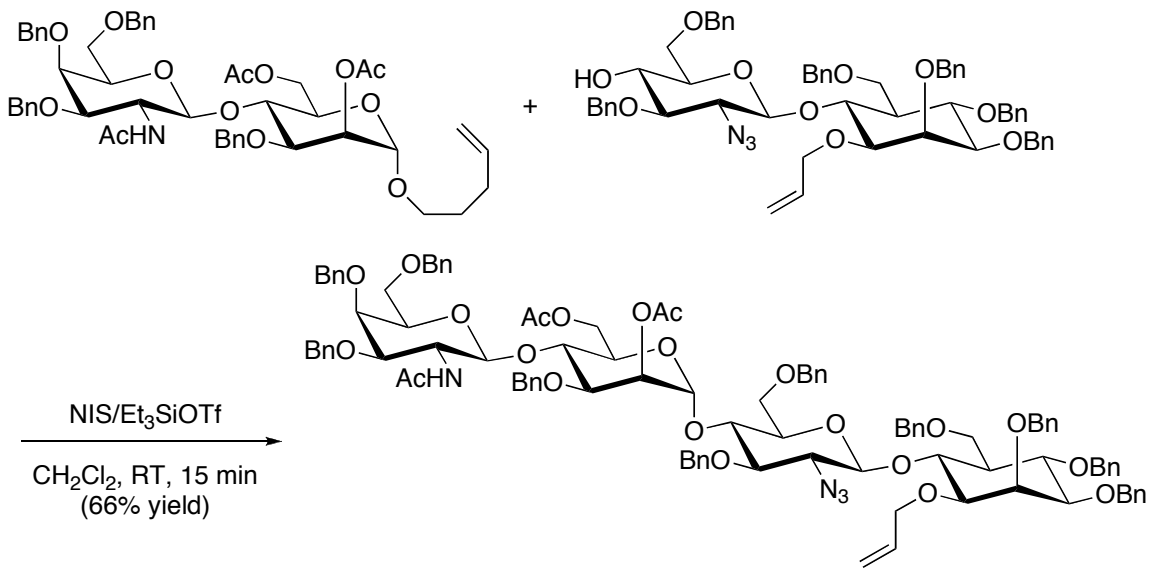
Scheme 40. "Armed and Disarmed" concept for glycoside bond formation.

Fraser-Reid introduced n-pentenyl glycosides as a donor system that is complementary to the methods described above, owing to the fact that they are unreactive to most conditions except hydrogenation. Their method of action lies in an ingenious reaction pathway. When they are introduced to an electrophilic halonium ion, a cyclic halonium ion intermediate is formed. This intermediate is then opened by the lone pair of electrons on the carbohydrate oxygen at the anomeric position. This new oxonium intermediate is cleaved to give 2-halomethyltetrahydrofuran (Scheme 41).



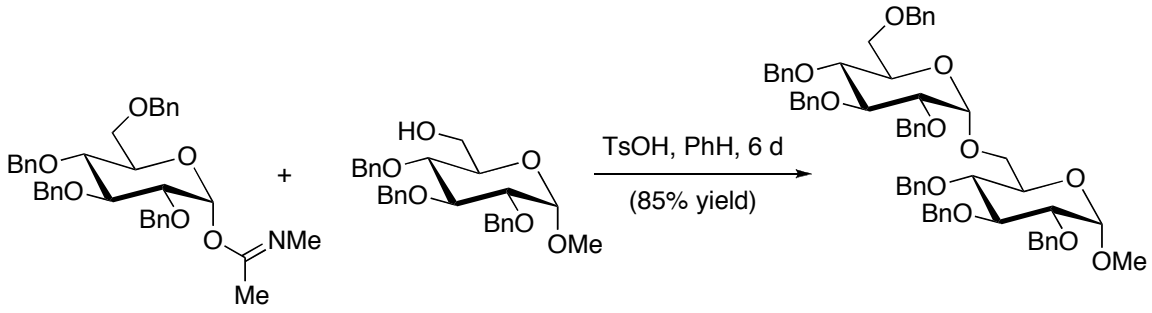
Scheme 41. Mechanism for activation of n-pentenyl glycosides.

While many sources of electrophilic halide have been used for this reaction, the best results are obtained with NIS/triethylsilyl triflate (TESOTf). Fraser-Reid put this combination to use in the impressive synthesis of the pseudo-tetrasaccharide shown in Scheme 42.[21]



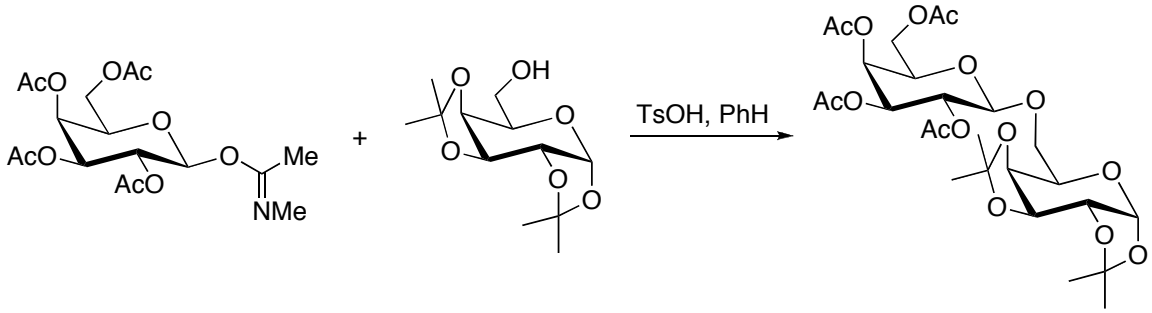
Scheme 42. Use of n-pentenyl glycosides for formation of a complex pseudo-tetrasaccharide.

The last major category of glycosyl donors is that of the imidates. The pioneering work in this area can be traced back to the work of Nef in 1895.[22] However, the use of imidates in carbohydrate chemistry was not developed until 1976, when Sinay reported the reaction of methyl imidates with alcohols, catalyzed by p-TSOH.[23] The imidates were synthesized by treating anomeric bromides with methyl acetimide in the presence of Ag_2O, molecular sieves, and Hunig's base. One could then use imidates as donors in anhydrous benzene to make disaccharides. The reaction was typically very slow (6 days), but did give impressive yields (85%) of the desired *trans* carbohydrates. (Scheme 43).



Scheme 43. Reaction of methyl imidates catalyzed by p-TsOH.

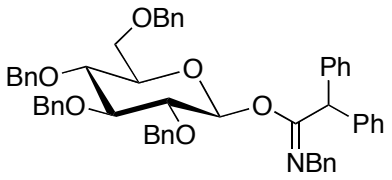
The use of methyl imidates with acylated sugars was not practically applicable.[24] Upon treatment with acid, acyl protected sugars gave mainly the orthoester (Scheme 44). The other major disadvantage of this method is that the imidates are derived from halo sugars. Thus they do not bypass the drawbacks of the Koenigs-Knorr method, as anomeric halides are inherently unstable and prone to hydrolysis.



Scheme 44. Orthoester formation from methyl imidates.

The major advancement in this area of chemistry was reported by Schmidt. While his first attempts at this involved benzyl imidates such as **21**,[25] his real contribution was the discovery of trichloroacetimidates such as **22**.[25,26] The new trichloroacetimidates had many advantages: they could be made from anomerically deprotected sugars that were easier to make than halosugars, they reacted quickly and efficiently with a number of

Lewis acids which could then be fine-tuned to give the desired product, and one could make the α or β product depending on the reactions conditions used to make the imidate.



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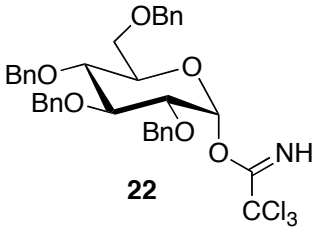
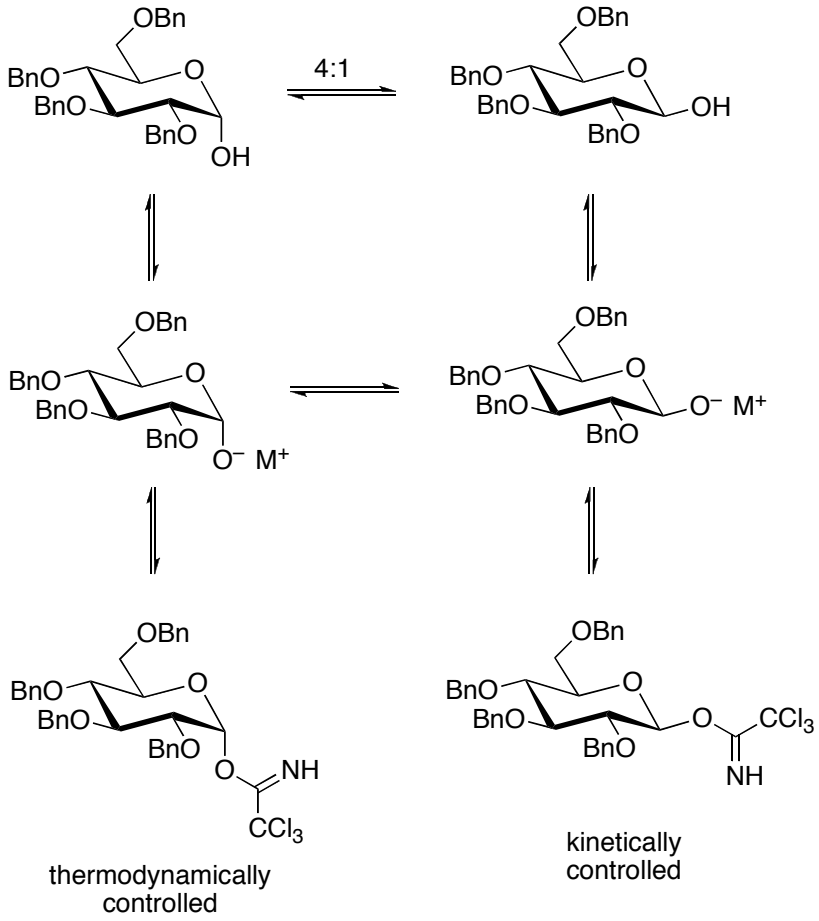


22

The method for formation of trichloroacetimidates involved using NaH and an anomerically deprotected sugar, followed by treatment with trichloroacetonitrile.[25,26] Schmidt recognized that one could make either the α or β product depending on the reaction time (Scheme 45). He rationalized this finding by invoking a kinetic/ thermodynamic argument. His explanation goes as follows: an α sugar in solution exists in a 4:1 mixture with the β sugar. Once treated with base, both sugars are deprotonated, and then are in equilibrium with one another. The more nucleophilic β-sugar first reacts with trichloroacetonitrile to form the β trichloroacetimidate. However, this product is in equilibrium with the deprotonated sugar. When the α-deprotonated sugar reacts with trichloroacetonitrile, it forms a more stable product due to the anomeric effect, and it does not react in a reverse fashion. Thus, eventually the α product is formed as the major product. If the reaction is stopped at an earlier period, one can isolate more of the β product. Also, when a weaker base such as potassium carbonate is used, there is no retro reaction by the β-trichloroacetimidate, and one isolates this product as the major component.

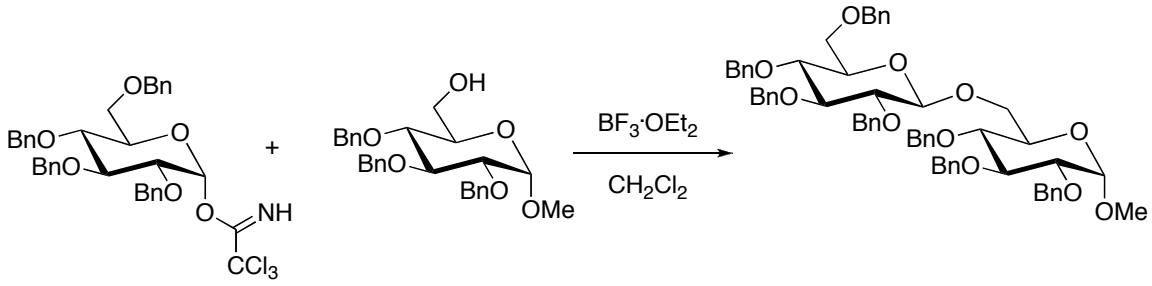


Scheme 45. Mechanism of formation of both α and β trichloroacetimidates.

Once the trichloroacetimidate is formed, a number of manipulations can be performed. The halide or azide can be synthesized by treatment of the trichloroacetimidate with a mineral acid. Simple alcohols can also be added by treatment with a Lewis acid.[14] However, the real utility of these imidates lies in oligosaccharide synthesis.

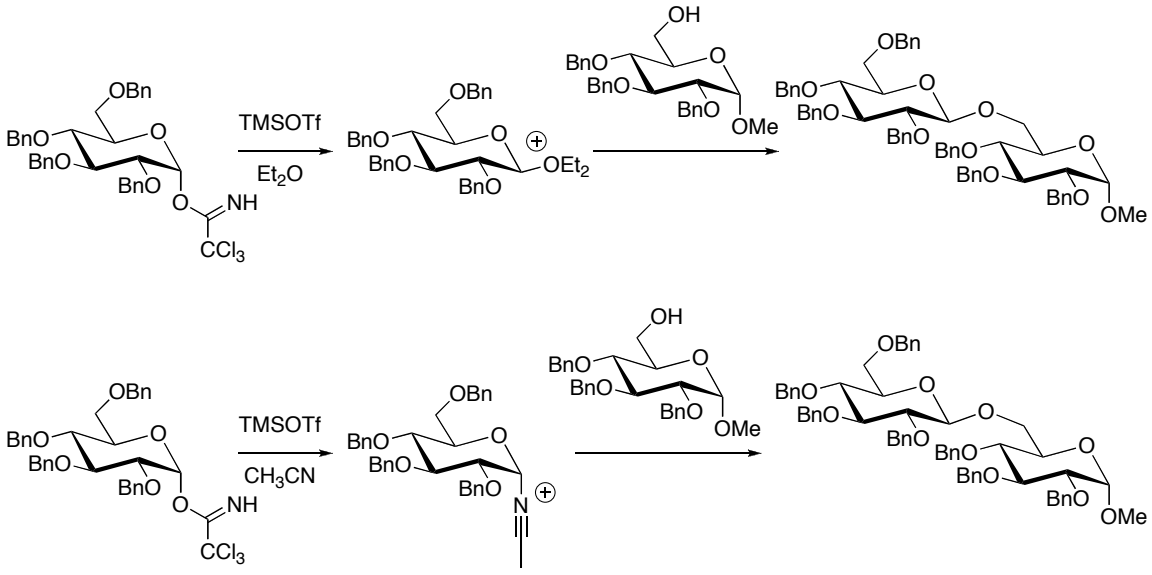
The stereochemical outcome of the formation of the trichloroacetimidates is important for this reason: when a mild Lewis acid such as BF_3•OEt_2 is used with activated donors, inversion of the stereochemistry is generally observed (Scheme 46).[14]

This process is generally thought of as an Sn2 type process. When a more powerful Lewis acid is used such as TMSOTf with an alpha trichloroacetimidate, the outcome generally depends on the solvent.



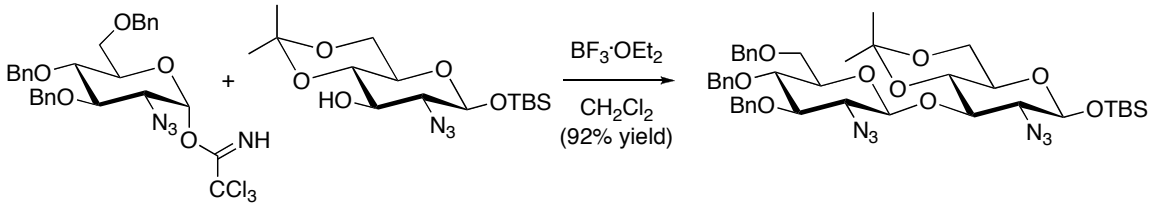
Scheme 46. BF_3•Et_2O mediated reaction of tetra-benzyl glucose trichloroacetimidate.

When the stronger Lewis acid TMSOTf is used to activate a trichloroacetimidate without a participating neighboring group, the choice of solvent plays a key role. In a non-coordinating solvent such as dichloromethane the stable α-D-glycoside is formed.[14] In ethereal solvents the α-anomer is formed, which is reported to be enhanced by the formation of an intermediate β-D-oxonium ion (Scheme 47). When acetonitrile is used as the solvent at low temperatures, an α-nitrilium ion is thought to be formed due to steric interactions with the benzyl group, and nitrilium ion formation leads to formation of the β-glycoside.[14]



Scheme 47. Solvent effects on trichloroacetimidate glycosylations.

The power of these trichloroacetimidates has been demonstrated by Schmidt in a number of difficult carbohydrate syntheses. A good example is the synthesis of the chitin building block, which arises from repeating units of glucosamine (Scheme 48). Schmidt was able to make the key glycoside linkage in 92% yield using BF_3•OEt_2 as a promoter.[27]

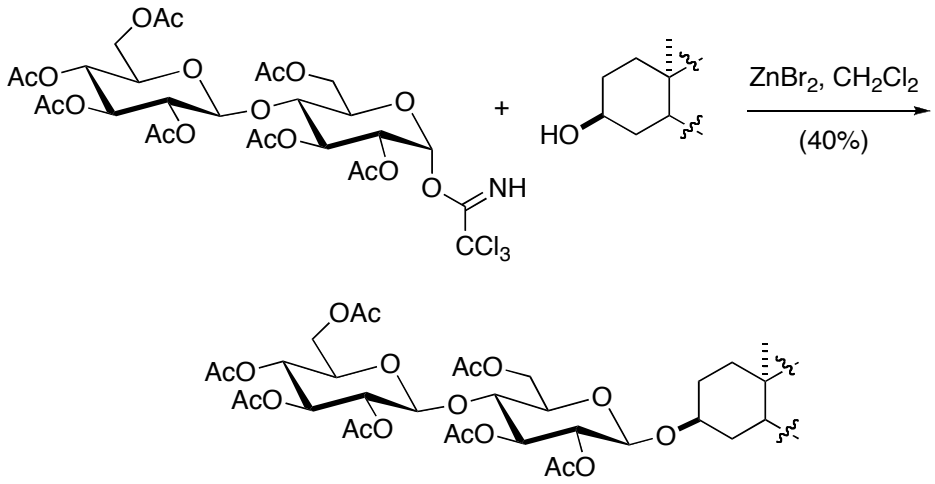


Scheme 48. Synthesis of Chitin building block.

While BF_3•OEt_2 and TMSOTf are most commonly used as promoters in the trichloroacetimidate method, many other Lewis acids have been used with varying degrees of success. There are two main reasons for the investigation of other Lewis acids.

First, many glycosylation reactions require “fine tuning”, as acceptors and donors have different electronic and steric demands. Second, both BF_3•OEt_2 and TMSOTf are water sensitive, often contain varying amounts of protic acid, and often need to be distilled before use. These factors make their application challenging for large scale synthesis.

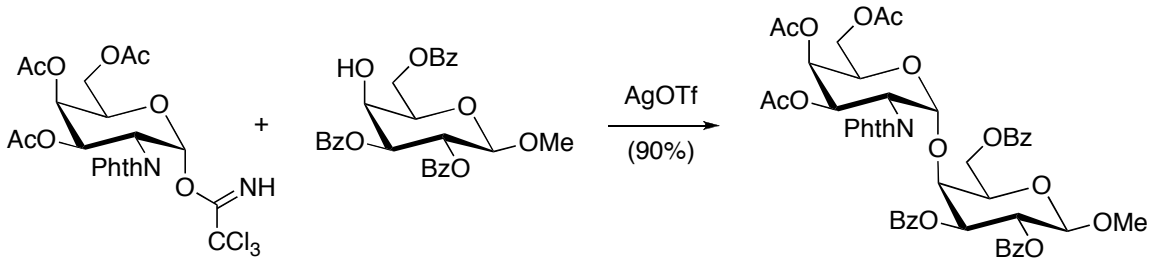
Zinc bromide was found to be a superior promoter compared to BF_3•OEt_2 in the addition of steroidal units to cellobiose donors in work done by Urban (Scheme 49).[28] He found that BF_3•OEt_2 promoted mainly acetate exchange to the acceptor, while $ZnBr_2$ over a prolonged time was much better at promoting addition.



Scheme 49. Activation of trichloroacetimidates by $ZnBr_2$.

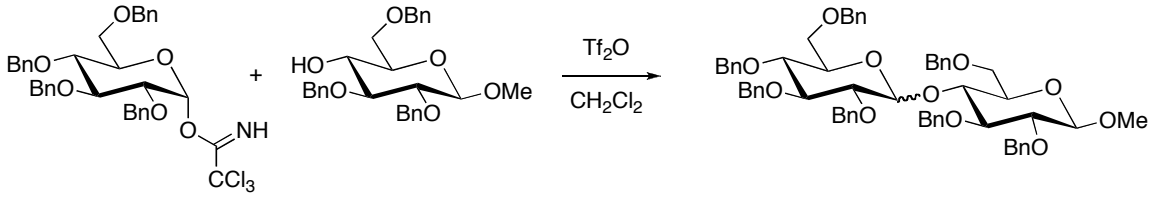
The Whitefield group examined AgOTf as a promoter for glycosylation reactions.[29] Again, the driving force behind this investigation was problems with the transfer of acyl groups (benzoyl in this case) when attempting couplings of galactose and galactosamine. The authors surmised that the higher affinity of Ag(I) for nitrogen than that of BF_3OEt_2 would lead to the Lewis acid attacking the trichloroacetimidate rather than the acyl groups. These experiments were very successful, in that the yields of

glycosylation were increased from 40% with BF_3•OEt_2 to 90% with Ag(OTf) (Scheme 50).



Scheme 50. Activation of trichloroacetimidates by AgOTf.

Triflic anhydride has been shown to be a powerful promoter for the addition reaction of trichloroacetimidates.[30] The Wessal group found that addition of the unreactive donor 2,3,6-tri-O-benzyl-α-D-glucopyranoside reacted with 2,3,4,6-tetra-O-benzyl-glucopyranotrichloroacetimdate in an astonishing 94% yield (Scheme 51). However, the α/β ratios that were obtained were not much better than 1:1 using both the α and β trichloroacetimidates.



Scheme 51. Activation of trichloroacetimidates by Tf_2O.

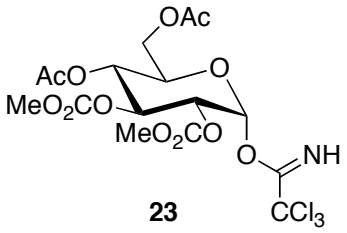
Lubineau explored the use of LiOTf as an effective catalyst for the activation of trichloroacetimidates.[31] He found that as little as 0.05 equivalents of the salt could promote the addition of a number of alcohols and glucose derivatives in good yield to 2,3,4,6-tetra-O-benzyl-α-glucopyranotrichloroacetimidate. The reaction was best carried

out in CH_2Cl_2 and gave predominately inversion of stereochemistry, yielding mostly the β- product. One of the main advantages of this reaction is that the conditions are essentially neutral, so interactions with acid sensitive protecting groups could be minimized.

A very innovative use of trichloroacetimidates as donors was put forth by the Mukhopdhya group in 2005.[32] They used $HClO_4$ immobilized on silica gel as a promoter in their reactions, and they obtained good yields in the 70-80% range using acetyl-protected sugars as donors. This reaction was especially interesting because it was conducted on a column. The first phase of the column contained the promoter, followed by a section of column that held normal silica gel for separation. However, this method suffers from two drawbacks: the reaction medium is very acidic, so not all functional groups can tolerate these conditions, and, as stated in the acylation chapter, dried $HClO_4$/silica is potentially explosive.

In the body of work most closely related to the experiments described here, Iadonisi was responsible for the development of a number of new promoters for glycosylation using trichloroacetimidates, namely $Sm(OTf)_3$, $Yb(OTf)_3$, I_2/Et_3SiH, and acid washed molecular sieves. His work commenced with that of $Sm(OTf)_3$, a commercially available salt that is water stable. His first experiments proceeded with armed donors, and while the yields were good, he found that the α/β ratios of his products were not satisfactory.[33] He then turned to the use of $Yb(OTf)_3$ as a cheaper and more powerful catalyst, as it produced good yields of disaccharides using disarmed donors.[34] One interesting aspect to this chemistry is that the typical acetate protected sugars predominately produced the ortho ester products. To combat this problem Iadonisi

used 2-O-alkoxycarbonylatyed glycosyltrichloroacetimidate **23** as the donor. He later found that the rate and the yield of this reaction could be enhanced by the addition of acid washed molecular sieves.[35]



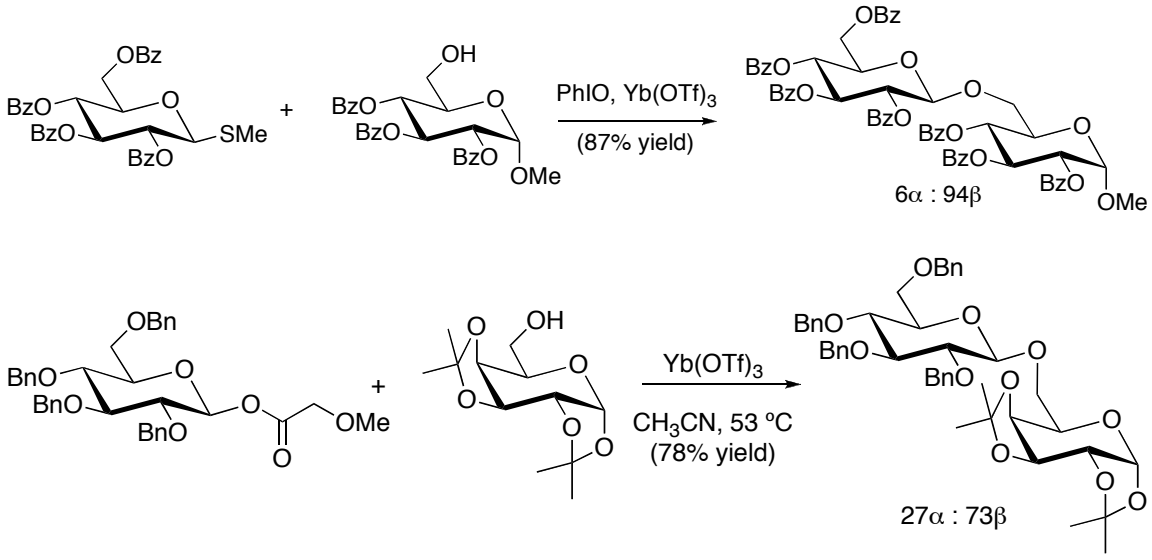
23

Iadonisi also found that the combination of iodine and triethylsilane could effectively promote the addition of the previously mentioned 2-O-alkoxycarbonylated glycosyltrichloroacetimidate to donors.[36] He speculated that these reaction conditions were generating a small of amount of HI, which was then mediating the promotion. Again, as in the case of $Yb(OTf)_3$, the reaction proceeded faster and produced better yields if acid washed molecular sieves were added. Finally, Iadonisi examined the role of the acid washed molecular sieves themselves and found that they did indeed promote addition, however in a very slow manner (24 h).[35]

While many of the developments discussed above are significant advancements toward the synthesis of sugars, each method provides its own unique drawbacks: anomeric halides are unstable and often require heavy metal salts to activate; trichloroacetimidates require moisture and air sensitive Lewis acids for activation; anomeric sulfides often require elaborate activation and fine tuning for their reaction optimization; and n-pentenyl glycosides require strong oxidants. In fact, the overall truth of the matter is that the creation of new methods that can be used to activate sugars at the anomeric position represents an advancement for carbohydrate chemistry.

Development of $In(OTf)_3$ as a Lewis acid for glycosylation reactions

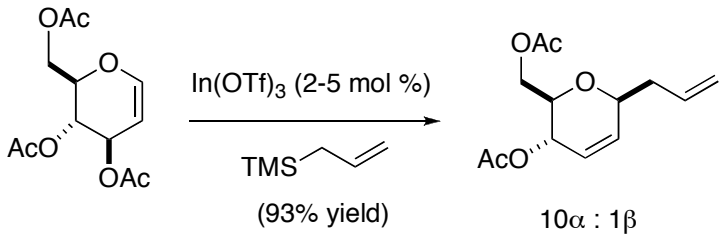
Due to recent success with $In(OTf)_3$ for the acylation of sugars (see chapter 2), the usefulness of indium triflate for the activation of sugars at the anomeric position was explored. As noted above, the use of the metal triflates such $Yb(OTf)_3$ was investigated by Iadonisi. Fukase also used $Yb(OTf)_3$ in conjunction with PhIO on anomeric sulfides to mediate addition, although $Yb(OTf)_3$ was not found to be the optimum Lewis acid in this case.[37] Inanaga used a range of rare earth metals to catalyze glycosylation of 1-methoxy sugars, with $Yb(OTf)_3$ being the most efficient (Scheme 52).[38]



Scheme 52. $Yb(OTf)_3$ mediated glycosylations.

To our knowledge, $In(OTf)_3$ has never been used as a Lewis acid to mediate O-glycosylation of any donors. There is one case of C-glyscosylation reported by Ghosh, in which $In(OTf)_3$ was used to affect addition of allyltrimethylsilane and trimethylsilyl

cyanide to glycal derivates in high yields and good anomeric selectivity (Scheme 53).[39] For this affect, it was unclear which potential leaving groups would be applicable to this activation, what the stereochemical outcome of the reaction might be, what conditions such as solvent and temperature should be used, and what the actual catalyst (protic or Lewis acid) should be. As discussed in the previous chapter, a small amount of triflic acid was probably the main catalyst for acetylation reactions.

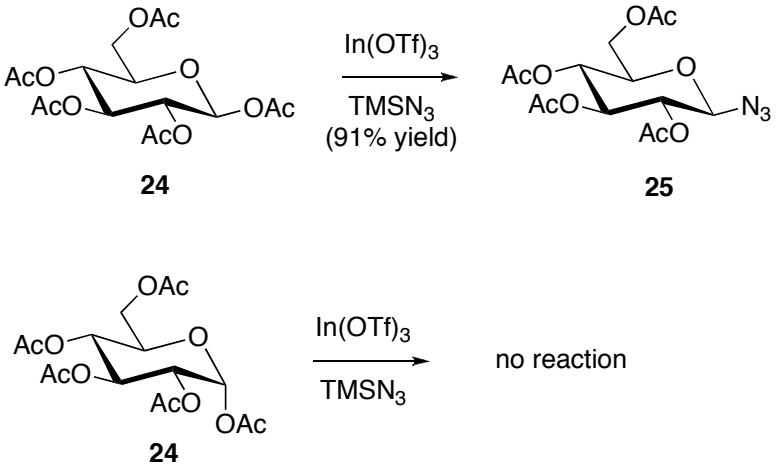


Scheme 53. $In(OTf)_3$ catalyzed allylation of glycols.

The use of indium(III) based Lewis acids, however, opens a slightly larger range of prior examples. Gosh's first foray into the use of indium(III) as a Lewis acid began with $InCl_3$ to mediate the reaction shown in Scheme 53, but the yields and reaction rates were lower and slower, respectively.[40]

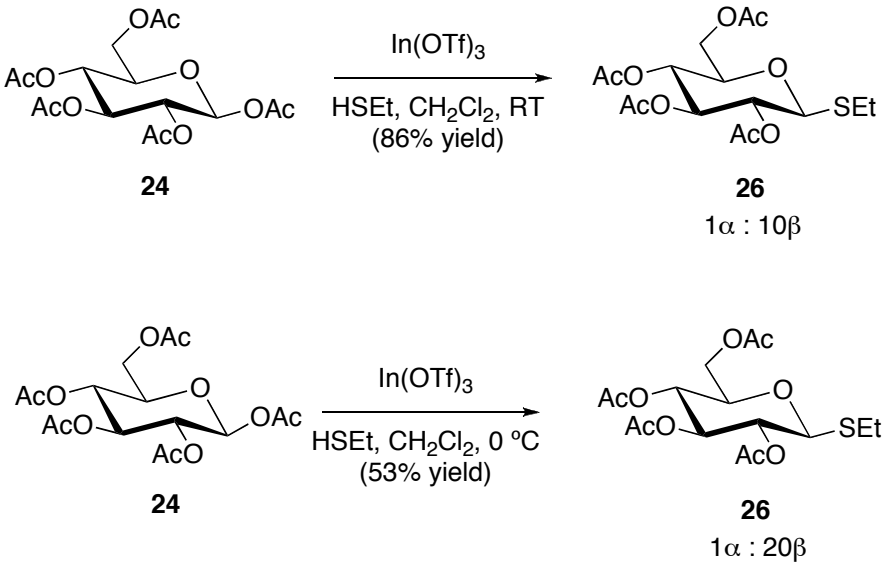
To begin this work, reactions using peracetylated glucose were explored. The reaction was performed with $TMSN_3$ and 1 equivalent of $In(OTf)_3$. This reaction was previously shown to be catalyzed by 1 equivalent of $BF_3 \bullet Et_2O$. It was also known that other rare earth metals could be used to catalyze this reaction. [41] The desired azide was isolated in 91% yield from the beta acetate. When the reaction was conducted with the alpha acetate, no reaction was observed (Scheme 54). This second result was not entirely

unexpected, since alpha acetates are known to be unreactive toward activation and subsequent displacement at the anomeric position.



Scheme 54. Formation of tetra-acetyl glucose azide by $In(OTf)_3$.

The second reaction that was investigated was the displacement of the beta acetate of glucose by ethanethiol. This reaction is also usually catalyzed by $BF_3 \bullet OEt_2$. Again, after treatment with one equivalent of $In(OTf)_3$ and reaction overnight at rt, the desired anomeric sulfide was formed in 86% yield. It is important to note that 5-10% of the starting material is the undesired, unreactive alpha product. However, the product was formed in a 1:10 α/β mixture (inseparable). To eliminate this problem, the experiment was conducted at lower temperatures, but only a 53% yield of the desired product was obtained. Formation of the desired beta isomer, however, was obtained, and product ratios of up to 20:1 were observed (Scheme 55).

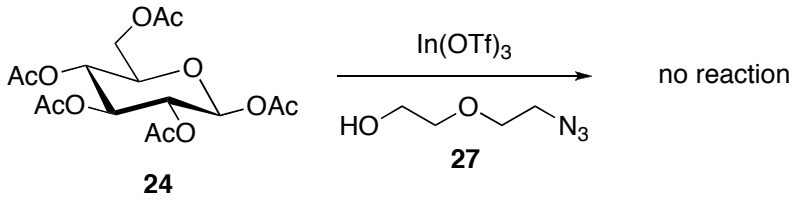


Scheme 55. Formation of thioglycosides by $In(OTf)_3$.

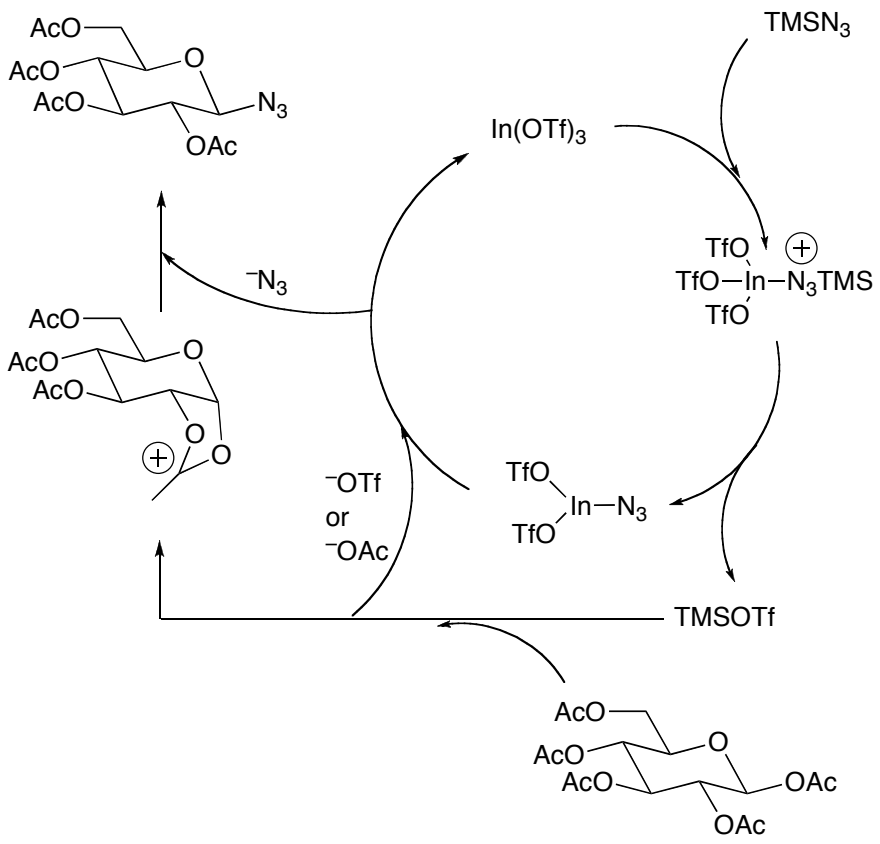
At this point, catalytic variants of the $In(OTf)_3$ mediated glycosylation reaction were evaluated. After trials using 20 mol %, 10 mol % and 1 mol % of $In(OTf)_3$, it was determined that the reaction could be carried out with as little as 1 mol % catalyst loading to give a 91% yield of the desired sulfide in a 10:1 beta to alpha ratio. Although only mixtures at the anomeric position were obtained, when anomeric sulfides are used for glycosylation reactions the stereochemistry at the anomeric site is unimportant since an intermediate oxocarbenium ion is formed. Thus, the desired product was formed in high yields using a catalytic amount of a crystalline Lewis acid, which appears to be tolerant of advantageous water (no air sensitive techniques were employed in this reaction). $In(OTf)_3$ is approximately five times more expensive than $BF_3 \bullet OEt_2$, but since it was used in such a small amount, the preparation reported here is actually cost efficient. It is also important to note that $In(OTf)_3$ was purchased and used without purification, while distillation of $BF_3 \bullet OEt_2$ from CaH_2 is required for glycosylation reactions.

Addition of alcohols to carbohydrates with an acetate at the anomeric position was next evaluated. This is again a reaction that is typically performed using BF_3•OEt_2. Addition of alcohol **27** to the beta acetate of glucose was evaluated for a number of reasons. The first is that that this alcohol was likely to have less water in it than some of the simpler alcohols, such as methanol or ethanol. The second is that this alcohol is routinely used in the synthesis of glycodendrimers, so some samples were readily available for NMR comparison and others were needed for other projects.

Upon treatment of acetate **24** with one equivalent of alcohol **27** and one equivalent of $In(OTf)_3$, no reaction was observed (Scheme 56). This suggests that the mechanism of this reaction involves triflic acid or, in the case of azide, TMSOTf. The formation of the latter is not a far speculation, as it has been noted in the past that TMSCl and rare earth metals provide TMSOTf *in situ*.[41] A process where the azide attacks the $In(OTf)_3$ and eliminates TMSOTf can be envisioned. Once this happens, TMSOTf activates the acetate for dissociation, creating the typical oxocarbenium ion. This is then followed by displacement of azide by either the triflate or the resulting acetate, and the powerful nucleophile intercepts the oxocarbenium ion to form the desired acetate (Scheme 57).



Scheme 56. Lack of reaction of β-pentaacetate of glucose with alcohol.

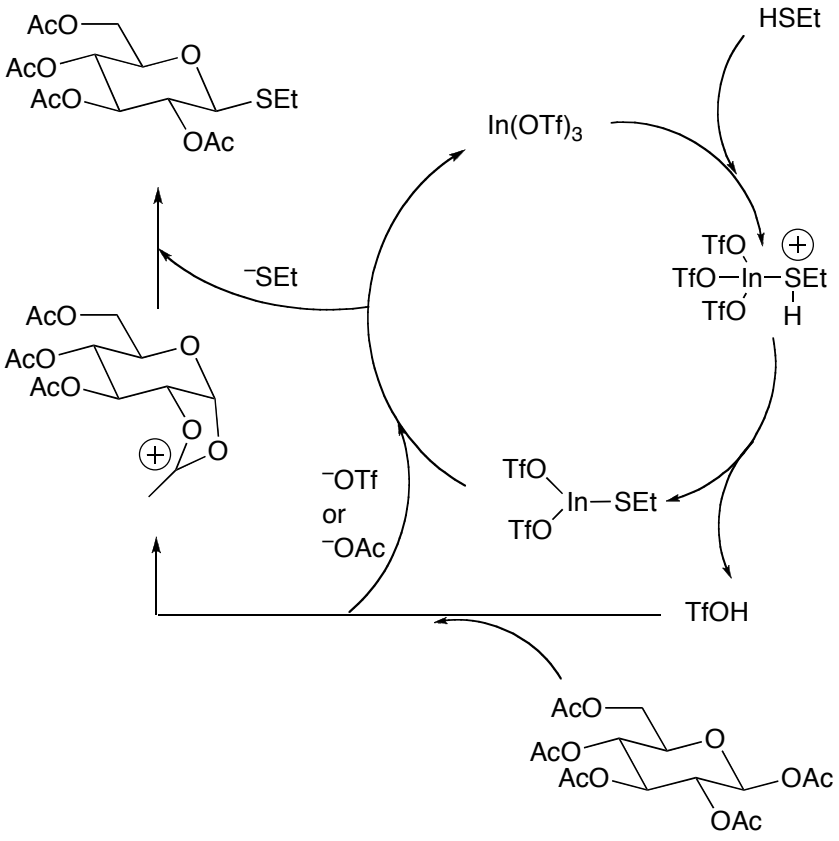


Scheme 57. Possible mechanism for anomeric azide formation.

While the above scenario is quite reasonable for the azide, it is not clear why the sulfide reacts and the alcohol does not. Certainly the sulfide is a much better nucleophile than the alcohol (as was the azide). However, if the reaction were simply an S_n2 process, then the beta azide and the beta sulfide would not be formed.

Two possible reasons for the non-reactivity of the alcohol are as follows. First, the pKa of the thiol is approximately 9, but the pKa of the alcohol is about 16. This difference in basicity may allow for a small amount of triflic acid to form in the case of the sulfide, while equilibrium of the alcohol might be such that no triflic acid can form with the alcohol.

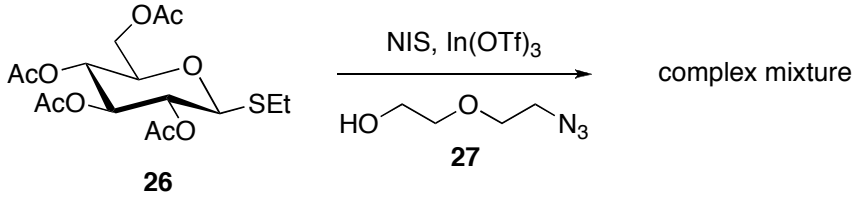
The second possible reason why alcohol and thiol nucleophiles behave so differently in this reaction may lie in the nature of the nucleophiles. The first step of the reaction may require the incipient nucleophile to add to $In(OTf)_3$, and then subsequently eliminate triflic acid. The triflic acid could be the main Lewis acid for activation of the anomeric acetate (Scheme 58). Certainly, the nucleophilic capacity of the thiol over the alcohol could be the main reason for the change in reactivity. However, a hard soft acid-base argument can also be invoked. Indium is rather far down the periodic table, and thus indium (III) is a relatively soft Lewis acid in comparison to the more commonly used BF_3•OEt_2. This softness would more correctly pair with the thiol than the alcohol, making this proposed mechanism more plausible for the thiol.



Scheme 58. Possible mechanism for thioglycoside formation.

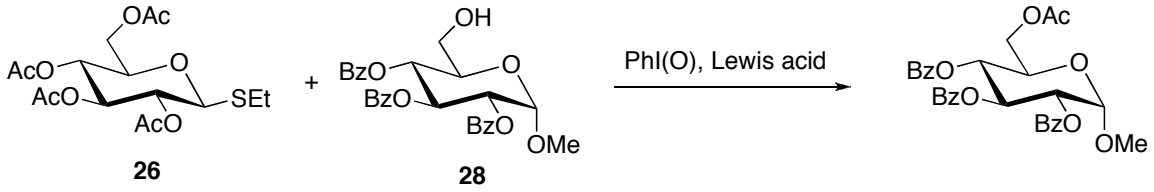
$In(OTf)_3$ mediated reactions with anomeric sulfides were evaluated since the triflate ligand might act as a coactivating agent for the release of the sulfur iodonium species created in the reaction mixture. Again, this line of inquiry was spurred by Fukase's work, where $Yb(OTf)_3$ was used successfully to induce the addition of sugars to sulfides.

The previously synthesized glycoside 2,3,4,6-terta-O-acetyl-β-D- ethyl thioglucopyranoside (**24**) (Scheme 59) was combined with 1 equiv. of alcohol **27**, 5 equiv. of NIS, and 1 equiv. of $In(OTf)_3$. Almost instantly, the solution turned bright red. After quenching, many undesirable products were obtained. There are two likely reasons why this reaction failed to proceed as planned. Fukase used a rather exotic source of electrophilic iodine, a source which may be more compatible with rare earth metals than NIS.[37] Fukase also noted that benzoyl protected sugars were the only ones to react in the appropriate manner. When the acceptor **28** was used, the only discernable product that was formed arose from the transfer of the acetate (Scheme 60). Thus the acetylated substrate may not have been appropriate. Further development of an $In(OTf)_3$ mediated glycosylation reaction with thioglycosides was not pursued, as activation of trichloroacetimidate substrates was more successful (see below).



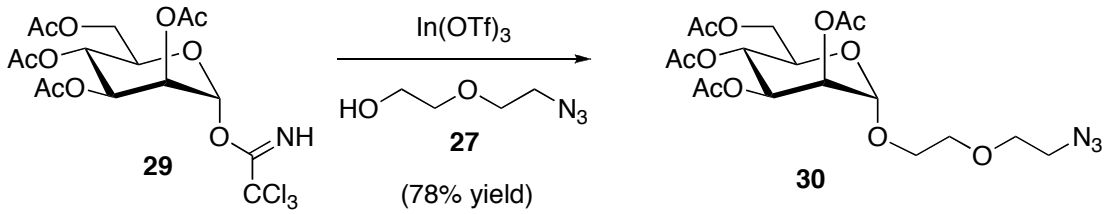
26 **27**

Scheme 59. Reaction of thioglucoside with NIS and $In(OTf)_3$.



Scheme 60. Acetate transfer with thioglucose.

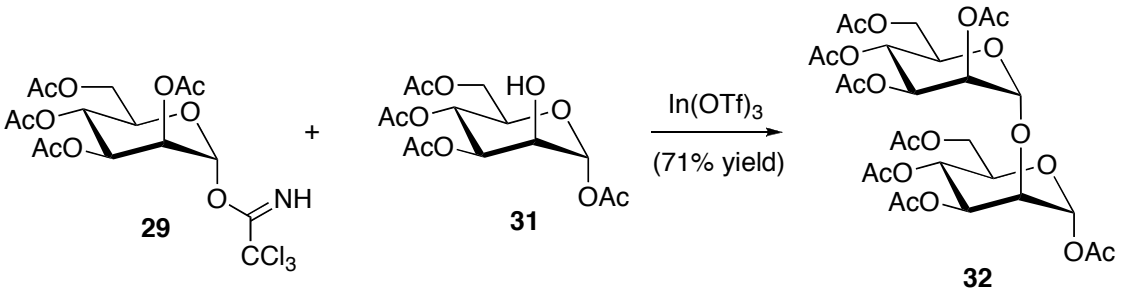
Evaluation of trichloroacetimidate substrates in $In(OTf)_3$ mediated glycosylations first began with 2,3,4,6-tetra-O-acetyl-α-D-mannosyl trichloroacetimidate **29**. In the standard fashion, 1 equiv. of $In(OTf)_3$ and one equiv. of alcohol **27** were used for the addition. This reaction was conducted at room temperature for 3 h in dichloromethane as per the procedure for activation using BF_3•OEt_2. After quenching and isolation, the desired product was formed in 78% yield (Scheme 61). Although complete consumption of the starting material was observed, some breakdown of the substrate (rather than complete transformation to product) occurred.



Scheme 61. Activation of mannose trichloroacetimidate by $In(OTf)_3$.

Since the parameter that is most likely to influence the yield of this reaction temperature, the reaction was performed at -50 °C and at -78° C. Even at -78 ºC, the reaction proceeded rapidly (30 min) to provide the desired product in 81% yield.

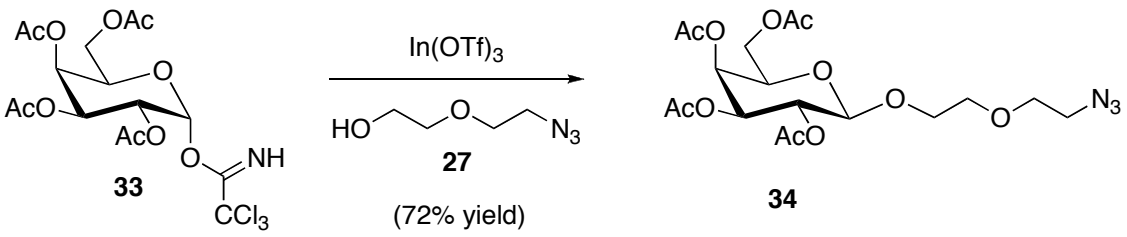
Addition of a second sugar to the trichloroacetimidate **29** was also explored. Carbohydrate **31** was used as the acceptor (Scheme 62). Disaccharide **32** is biologically relevant in both antifungal studies and in HIV.[42] Upon treatment of the trichloroacetimidate **29** with 1 equiv. of $In(OTf)_3$ and 1 equiv. of the acceptor **31**, coupling was observed in a 71% yield to afford **32**.



Scheme 62. Formation of 1,2-dimannose mediated by $In(OTf)_3$.

After the preliminary investigation depicted in Scheme 56, evaluations of which sugars could be coupled, of the α/β ratio for products, of whether a catalytic amount of $In(OTf)_3$ could be used, and of the reaction mechanism were performed.

Addition of alcohol **27** to the trichloroacetimidate of galactose **33** with 1 equiv. of $In(OTf)_3$ at -78° C in dichloromethane afforded product **34** in 72% yield. It should be noted that only the beta product was formed, as is expected with neighboring group participation (Scheme 63).



Scheme 63. Activation of galactose trichloroacetimidate by $In(OTf)_3$.

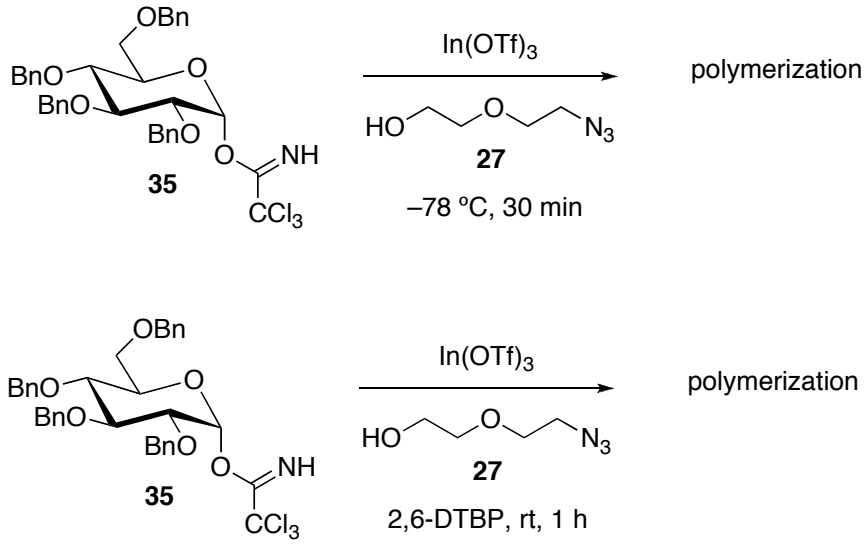
Reactions with lower catalyst loadings were also evaluated. Unfortunately, reactions with 10 mol % and 20 mol % catalyst loading did not progress to completion. Addition of incremental amounts of $In(OTf)_3$ increased the amount of product, but a full equivalent of the catalyst was required for complete conversion. Increased temperatures were used in an effort to improve turnover, but at room temperature the solution turned red and the substrate decomposed. The red color is suggestive of triflic acid formation, as this is the same color as TMSOTf that has degraded.

Since triflic acid is probably a by-product formed during reactions at higher temperatures, triflic acid could be the activator. However, addition 2,6 di*tert*butylpyridine to the reaction mixture as an acid scavenger did not inhibit product formation. Both TLC and ^1H NMR analysis indicated that the substrate was consumed and that product formation occurred. This indicates that indium triflate is activating the reaction, not triflic acid. Experiments conducted using $InBr_3$ and $InCl_3$ in stoichiometric amounts showed that both Lewis acids facilitate the reaction, however the reaction rates were significantly slower. One possible explanation for the observed rate change is that a mechanism occurs where the displacement of a ligand precedes activation.[43] Because the triflate is not a very strongly coordinating ligand, it would be more easily displaced, followed by the bromide and then the chloride ion. These results are also consistent with the non-catalytic nature of the reaction. If the resulting amide coordinates to the ligand, it might poison the catalyst and stop the reaction.

For substrates bearing protecting groups that preclude neighboring group participation, an evaluation of the product stereochemistry should provide insight

regarding the reaction mechanism. If inversion of stereochemistry at the anomeric position is observed in a non-coordinating solvent such as dichloromethane, then the mode of action of $In(OTf)_3$ resembles that of BF_3•OEt_2. Conversely, if a mixture of the anomers is obtained, then the mode of action of $In(OTf)_3$ is more like that of the stronger Lewis acid TMSOTf.

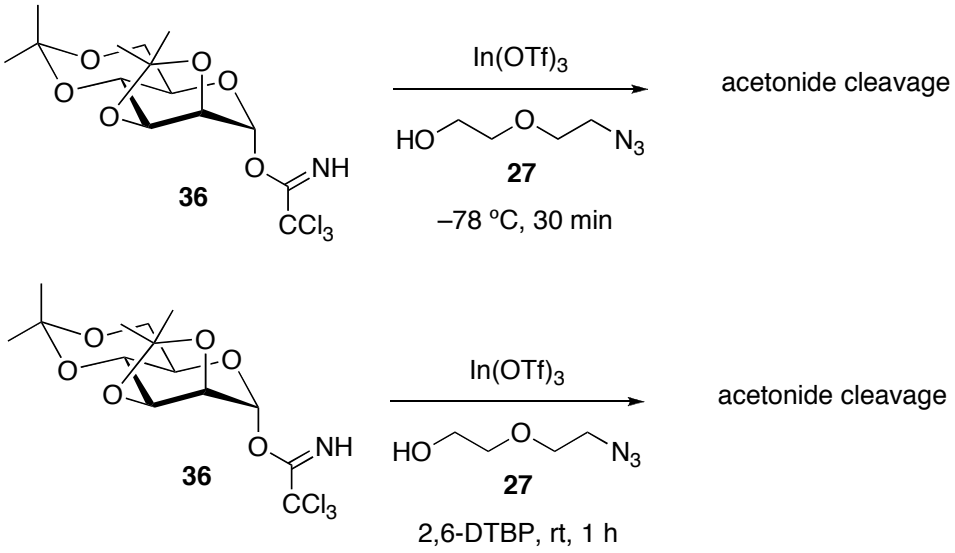
Upon treatment of the benzylated glucose trichloroacetimidate **35** with $In(OTf)_3$ in CH_2Cl_2, polymerization of the material was the only major product. This experiment was repeated with 2,6-DTBP to scavenge acid, but again polymerized material was obtained. $In(OTf)_3$ is has previously been employed for Friedel-Crafts reactions, and thus this initiator may be facilitating reactions on the benzyl rings (Scheme 64).[44]



Scheme 64. Reaction of tetra-benzylated glucose trichloroacetimidates with $In(OTf)_3$.

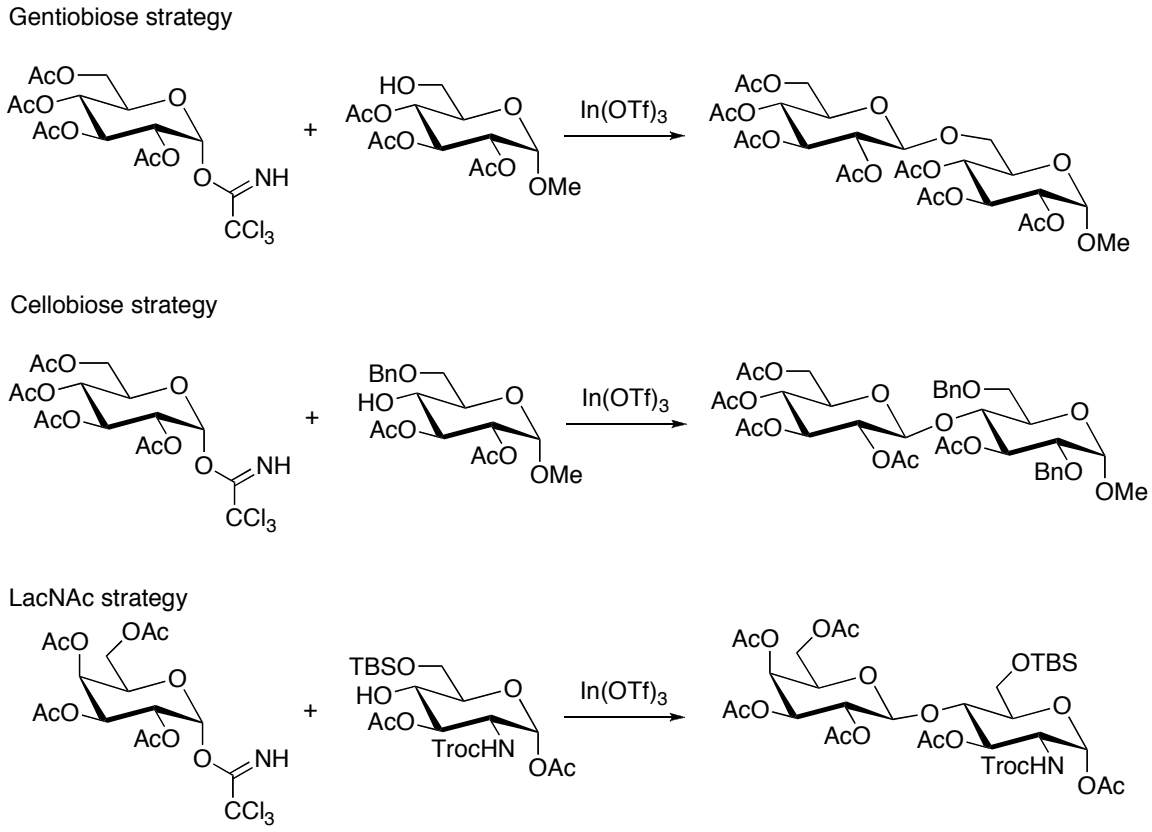
For the diisopropylidene protected mannose trichloroacetimidate **36** both with and without an acid scavenger, the reaction did not progress in a straightforward manner, as ^{1}H NMR results indicated that the isopropylidene groups were cleaved (Scheme 65). The

results with benzylated and ketal protected carbohydrates suggest that that $In(OTf)_3$ is best suited for reactions with inactivated trichloroacetimidates.



Scheme 65. Reaction of acetal protected mannose with $In(OTf)_3$.

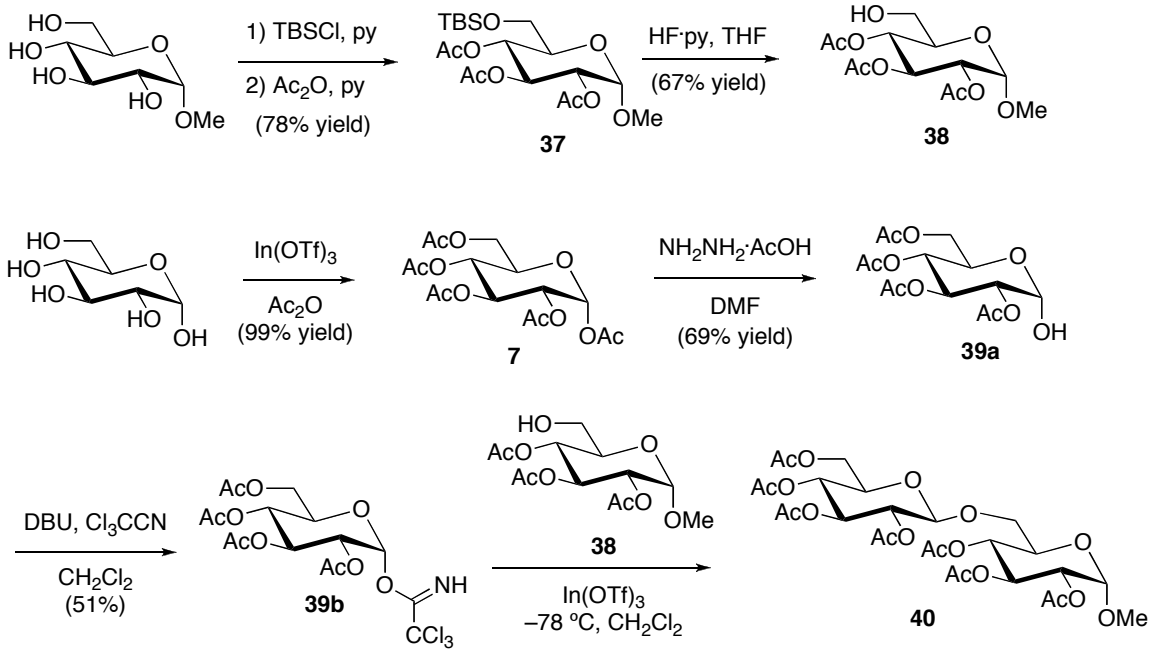
To probe the scope of the $In(OTf)_3$ mediated glycosylation reaction, three target disaccharides were chosen. O-methyl gentiobiose, O-methyl cellobiose, and N-acetyl lactosamine (LacNAc) are shown in Scheme 66. Gentiobiose is 1-6-β-diglucose, and the C6 hydroxyl group is a rather good nucleophile. Cellobiose is 1-4-β-diglucose, which has a more challenging coupling. Lastly, N-acetyl lactosamine is a biologically relevant molecule that is challenging to make and rather expensive ($1,000/gram). Thus, a successful synthesis of LacNAc is a significant contribution to carbohydrate chemistry.



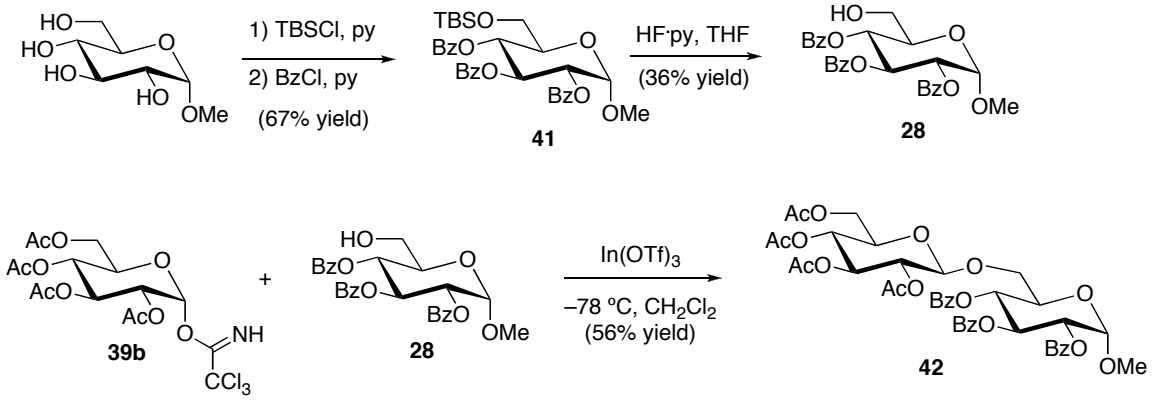
Scheme 66. Strategy for formation of gentiobiose, celliobiose, and LacNAc.

To make gentiobiose, the primary alcohol of O-methyl glucose was protected by treating the glycoside with TBSCl in pyridine at 0°C for three hours. Addition of acetic anhydride and stirring overnight afforded **37** in 78% yield for the two reaction sequence. The TBS group was cleaved by treatment with HF•py to give the 6-deprotected sugar **38** in good yield. The trichloroacetimidate **39b** was synthesized using standard procedures, and the glycosylation was performed at -78°C for 30 min to give the desired product **40** (Scheme 67). However, separation of the starting alcohol from reaction mixture was difficult. With benzoyl-protected acceptor **28**, the reaction proceeded well and the

product purification was much easier. Thus, the synthesis of the protected form of O-methyl gentiobiose **42** was completed (Scheme 68).

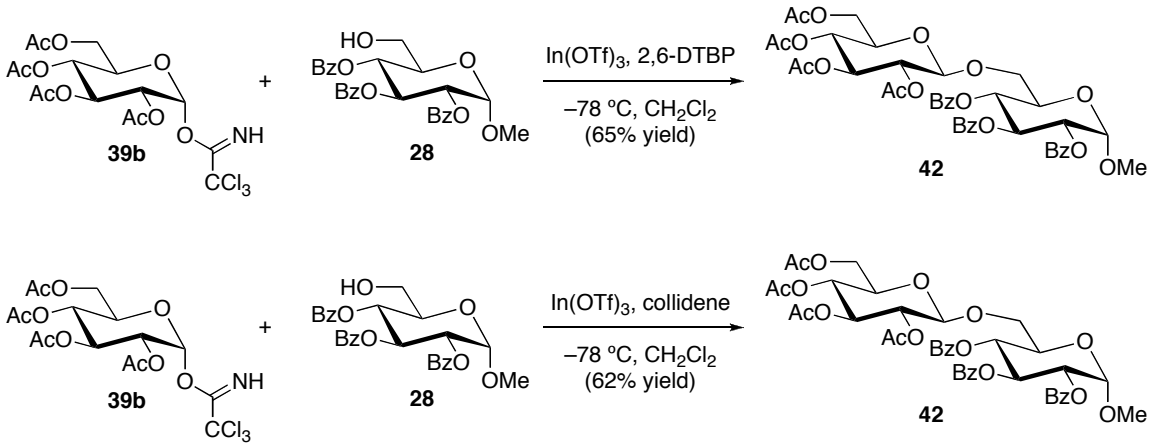


Scheme 67. Acetylated O-methyl gentiobiose formation.



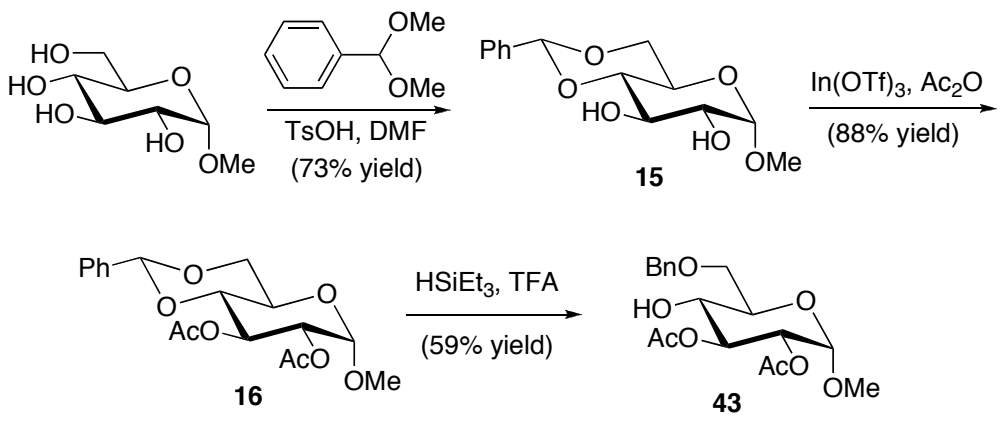
Scheme 68. Synthesis of O-methyl gentiobiose derivative.

With 2,6-DTBP, a Bronstead acid scavenger present in the reaction, product formation was slow at -78°C. However, warming the reaction to room temperature and stirring for 1 h produced the desired product in 65% yield. While this suggests that the reaction is catalyzed by both TfOH and In (III), the addition of 2,6-DTBP is undesirable since it is very expensive base. Collidine containing reactions, however, progressed smoothly and gave the desired product in 62% yield (Scheme 69).



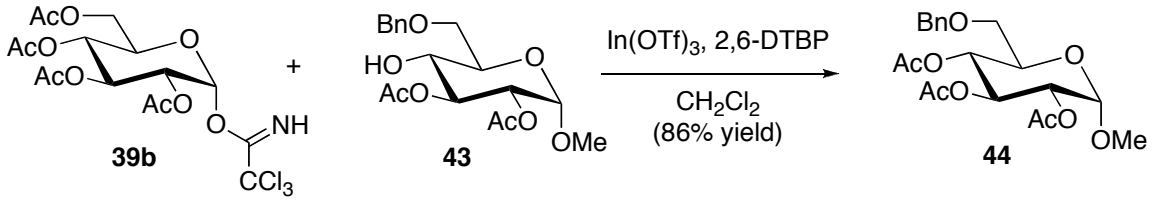
Scheme 69. Synthesis of O-methyl gentiobiose derivative with proton scavengers.

The synthesis of cellobiose was less successful, since the acceptor **43** (4-deprotected glucose) is not very reactive.[28] The acceptor was synthesized by protecting the 4 and 6 position of O-methyl glucose as the benzylidene acetal **15** and then acylating the remaining hydroxyl groups using the $In(OTf)_3$ protocol described in Chapter 2 to give the diacetate **16**. The benzylidene acetal was successfully migrated to the 6 position to become a benzyl group with triethylsilane and TFA to afford **43** (Scheme 70).[45]



Scheme 70. Synthesis of celliobiose acceptor.

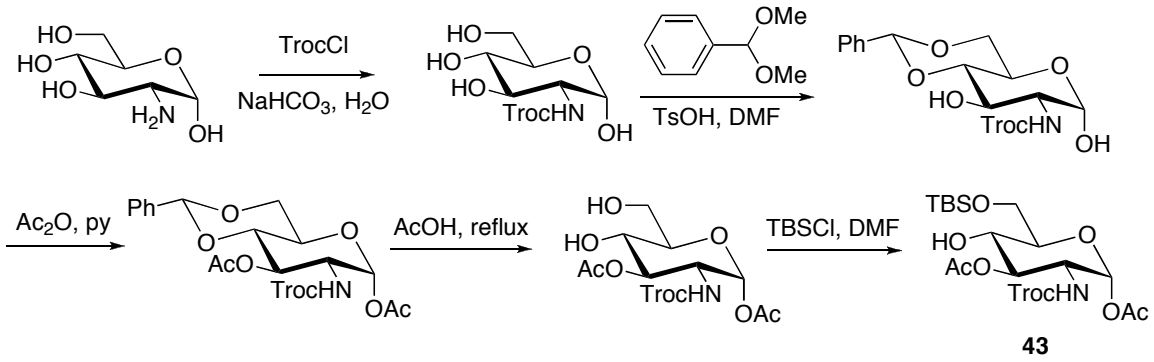
Upon coupling, two distinct outcomes were observed. First, when the glycosylation was attempted at -78°C with $In(OTf)_3$ alone, the trichloroacetimidate decomposed and the acceptor was recovered. When the reaction was attempted in the presence of base (2,6-DTBP), the only product recovered was fully acetylated **44** (Scheme 71). The poor nucleophilicity of **43** is likely responsible for the observed outcome.[28]



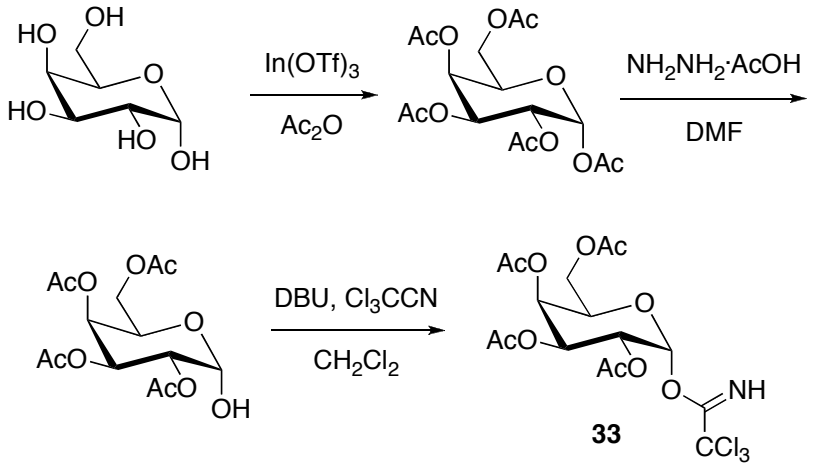
Scheme 71. Acyl transfer side reaction in the synthesis of celliobiose.

TMSOTf mediated glycosylations for the formation of lacNAc afford product with variable yields, indicating that a successful $In(OTf)_3$ mediated glycosylation for this reaction would provide an attractive alternative synthesis.

The glucosamine acceptor synthesized by colleague Mark Wolfenden as follows: protection of the amine as the Troc ester, protection of the 4 and 6 positions as the benzylidene acetal, acylation of the 2-position using Ac_2O in py, and cleavage of the benzylidene acetal in refluxing AcOH. The 6-position was protected as the TBS ether in DMF to afford **45** (Scheme 72). The galactose trichloroacetimidate (**33)** donor was obtained via our standard procedures (Scheme 73).

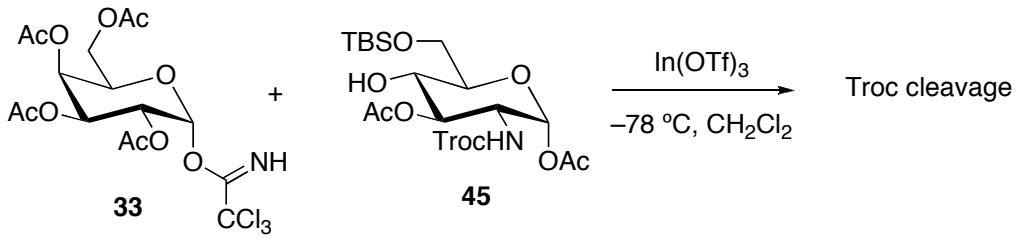


Scheme 72. Synthesis of LacNAc acceptor.



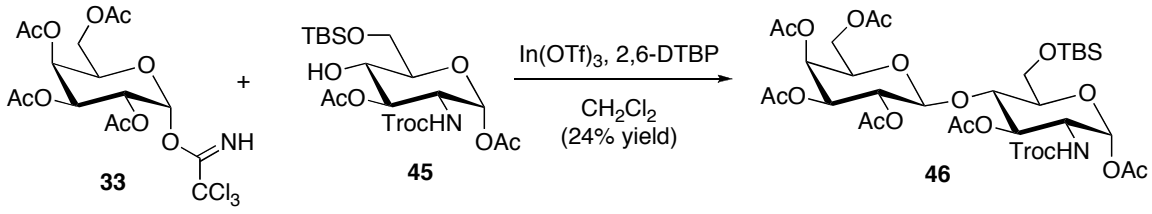
Scheme 73. Synthesis of galactose trichloroacetimidate.

The coupling of these two molecules did not proceed well. Upon treatment with $In(OTf)_3$ at -78°C for 30 min, a very polar compound was formed. NMR analysis indicated that the Troc group was cleaved in this reaction (Scheme 74). Surprisingly, the TBS portion of the molecule appeared to be intact. This was unexpected, the TBS group was expected to be the most labile portion of the acceptor due to its low stability in acid.



Scheme 74. Troc cleavage of LacNAc precursor.

With this surprising result in mind, the coupling was explored using $In(OTf)_3$ and base (2,6-DTBP) at rt for 1 h. LacNAc **46** was formed, but only in 11% yield. The reaction was repeated, and the low yield was reproducible (Scheme 75). Purification of this product was also very challenging, and Troc protecting group cleavage seemed to be a major problem. There is some evidence in the ligature that suggests that indium salts react with chlorides in a manner similar to silver salts,[46] and this side reaction may be the underlying cause of the low reaction yield.



Scheme 75. Synthesis of LacNAc.

Summary

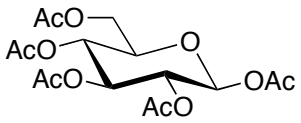
The findings reported here indicate that a new Lewis acid, $In(OTf)_3$, should prove useful for carbohydrate synthesis. $In(OTf)_3$ is a commercially available, water stable, crystalline salt, and the activity of $In(OTf)_3$ is well showcased in the activation of the relatively unreactive acetate protected carbohydrates. Both azides and thioglycosides can be formed using catalytic amounts of $In(OTf)_3$, providing a new and useful route to these molecules.

For glycosylation, $In(OTf)_3$ also proves useful. Two different sets of conditions can be used to effect glycosylation. The first utilizes low temperature and $In(OTf)_3$ alone, while the second involves a room temperature reaction and addition of a base such as 2,6-DTBP or collidine. The success with both of these reaction conditions provides for a more useful system, as the acid stability of both the donor and acceptor is important. This method unfortunately seems to be only applicable to deactivated donors, as both the activated donors that were surveyed degraded in the presence of highly active $In(OTf)_3$. However, as suggested by the name, deactivated donors are often more challenging to couple using glycosylation chemistry. Thus, the $In(OTf)_3$, system works well in difficult cases.

Limitations for $In(OTf)_3$ include the lability of common protecting groups. Protecting groups including Troc, isopropylidene, and benzyl groups could not withstand the presence of $In(OTf)_3$. Contamination by TfOH may be an issue, or the highly reactive nature of $In(OTf)_3$ itself may be the problem.

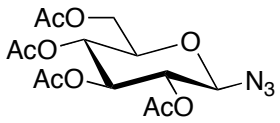
In summary, a new Lewis acid mediated for glycosylation reaction has been developed. The Lewis acid, $In(OTf)_3$, is easy to use since it is both water stable and crystalline. Reactions only require 30 min to 1 h, and disarmed glycosyl donors are activated when very nucleophilic donors such as primary alcohols are used. This $In(OTf)_3$ mediated glycosylation procedure coupled to the acetylation reaction described in Chapter 2 provides a new and innovative methodology for carbohydrate synthesis.

Experimental Methods

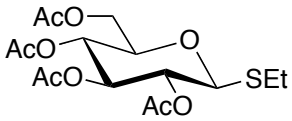


1,2,3,4,6-penta-O-acetyl-β-D-glucopyranoside (24): Anhydrous sodium acetate 2.5 g (0.03 mmol) in 30 ml (0.32 mmol) of acetic anhydride was heated to reflux. The heat was then removed and anhydrous D-glucose (5 g, 0.03 mmol) was added in portions so that the reaction mixture continued to reflux. After the glucose was added, the reaction mixture was heated under reflux for 30 min. The reaction was cooled, and the solvent was removed under reduced pressure. The mixture was then dissolved in 100 mL of EtOAc and washed twice with sat aq. $NaHCO_3$ (40 mL) and once with water (40 mL). The EtOAc layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting white solid was recrystallized from ethanol to give 7.3 g (63%) of a colorless solid. Approximately 90% desired β-anomer, 10 % α-anomer. ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, major isomer reported) δ 5.64 (1H, d, J=8.3 Hz), 5.18 (1H, t, J=9.5 Hz), 5.07-5.03 (2H, m), 4.23-4.20 (1H, m), 4.04-4.01 (1H, m), 3.79-3.76 (1H, m),

2.03 (3H, s), 2.00 (3H, s), 1.95 (6H, s), 1.93 (3H, s). These values agreed with previously reported spectra.[41]

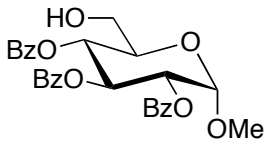


2,3,4,6-*O*-acetyl-β-D-glucopyranosyl azide (25). 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranoside **24** (123 mg, 0.31 mmol) was dissolved in 3 mL of CH_2Cl_2, and to this solution was added (36 μL, 0.31 mmol) of azidotrimethylsilane, followed by $In(OTf)_3$ (177 mg, 0.31 mmol). The reaction was allowed to stir overnight at rt. The solvent was removed and the mixture was subjected to column chromatography (6:4 hexane/EtOAc) to give 105 mg of product (91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (1H, t, J=4.6 Hz), 5.07 (1H, t, J=9.5 Hz), 4.92 (1H, t, J = 9 Hz), 4.61 (1H, d, J=8.5 Hz), 4.25-4.24 (1H, m) 4.14-4.11 (1H, m), 3.77-3.75 (1H, m) 2.10 (3H, s), 2.06 (3H s), 1.99 (3H, s), 1.97 (3H, s). These results agreed with previously published data.[41]



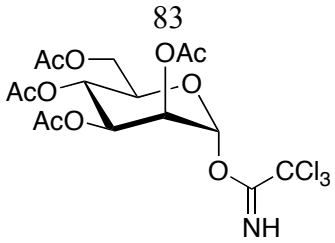
2,3,4,6-tetra-*O*-acetyl-β-D-ethylthioglucopyranoside (26): 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranoside **24** (788 mg, 2.0 mmol) was dissolved in 10 mL of CH_2Cl_2. To this solution was added (92 μL, 2.0 mmol) of ethanethiol and $In(OTf)_3$ (11 mg, 20 μmol), and the reaction was stirred overnight. The solvent was removed and the resultant yellow oil was subjected to column chromatography (7:3 hexane/EtOAc) to afford 729 mg (91% yield) of a clear oil. NMR revealed that there was approximately 9% alpha product in the

reaction mixture (values for the major isomer follow). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (1H, t, J= 9.3 Hz), 4.99-4.91 (2H, m) 4.40 (1H, d, J=10 Hz), 4.13-4.12 (1H, m) 4.00 (1H, appt d, J = 12.2 Hz), 3.64-3.61 (1H, m), 2.59 (2H, appt. sept, J=7.4 Hz), 1.95 (3H, s), 1.92 (3H, s), 1.90 (3H, s), 1.88 (3H, s), 1.16 (3H, t, J = 7.4 Hz).[47]

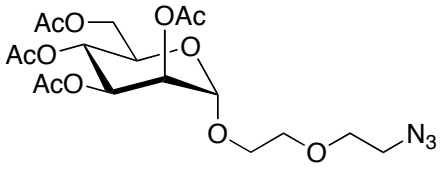


2,3,4-*O*-benzoyl-α-D-*O*-methyl glucoside (28). 2,3,4-*O*-benzoyl-6-*tert*-butyldimethylsilyl-α-D-*O*-methyl glucoside (4.21 g, 6.79 mmol) was dissolved in THF (70 mL), and to this solution was added 22 mL of a 30% solution of HF/pyridine. The solution was allowed to stir for 1 h at rt. A saturated solution of copper sulfate was added. The mixture was extracted with EtOAc, and the organic layer was collected, dried over $MgSO_4$, and concentrated. The oil was subjected to column chromatography (6:4 hexane/EtOAc) to afford 1.27 g (37% yield) of product in approximately 90% purity (values for the major isomer follow). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.95 (4H, m), 7.87 (2H, d, J=7.2 Hz), 7.51 (2H, q, J=10.0 Hz), 7.75-7.25 (7H, m), 6.22 (1H, t, J=9.7 Hz), 5.48 (1H, t, J=10.1 Hz), 5.28-5.25 (2H, m), 4.03 (1H, d, J=7.1 Hz) 3.83-3.81 (2H, m), 3.79-3.70 (1H, m) 3.45 (3H, s), 2.73 (1H, t, J = 7.1 Hz), 1.24 (1H, t, J=7.1 Hz).[48]

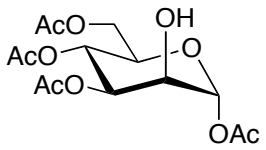
83



2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl trichloroacetimidate (29). A solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranoside (4.01 g, 10.6 mmol), hydrazine acetate (1.27 g,13.8 mmol), and DMF (15 mL) were stirred at 55°C for 30 min. EtOAc (100 mL) was added and the organic layer was washed with water (50 mL). The aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined and washed with water (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The EtOAc layer was dried over $MgSO_4$ and concentrated under reduced pressure to leave to afford 2.44 g, (69% yield) of product as highly viscous oil. This product was used without further purification.^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, appt dd, *J*=10.1, 3.3 Hz), 5.58-5.18 (3H, m), 4.23-4.18 (2H, m) 4.12-4.09 (1H, m), 3.80 (1H, bs), 2.12 (3H, s), 2.07, (3H, s), 2.01 (3H, s), 1.96 (3H, s). These values corresponded with previously published data.[49] DBU (0.10 ml 0.688mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (2.31 g, 6.88 mmol) and trichloroacetonitrile (3.5 mL) in CH_2Cl_2 (2.47 mL, 24.1 mmol) at 0°C. After 3 hours, the solvent was removed *in vacuo* and the residue was filtered through a plug of silica (6:4 hexane/EtOAc). The solution was concentrated to leave a yellow oil which was purified on silica gel (6:4 hexane/EtOAc) to afford 2.41 g (71% yield) of product.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, s), 6.22 (1H, s), 5.41 (1H, s) 5.36-5.31 (2H, m), 4.23-4.08 (3H, m) 2.14 (3H, s), 2.02 (3H, s), 2.01 (3H,s), 1.95 (3H, s). These values correspond to previously published data.[49]

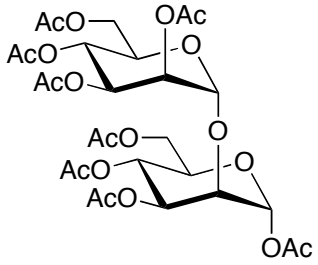


1-*O*-(5-azido-3-oxapentyl)-2,3,4,6-tetra-*O*-α-D-mannopyranoside (30). 2,3,4,6- tetra-*O*-acetyl-α-D-mannosyl trichloroacetimidate **29** (89 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (1.2 mL) and cooled to –78°C. To this solution was added alcohol **27** (23 mg, 0.18 mmol) and $In(OTf)_3$ (101 mg, 0.18 mmol), and the reaction was stirred for 30 min. The reaction was quenched with solid $NaHCO_3$ and filtered. The solvent was removed and the mixture was chromatographed (4:6 hexane/EtOAc) to afford 70 mg of product **30** (78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36-5.34 (1H, m), 5.29-5.26 (2H, m) 4.86 (1H, s) 4.29-4.25 (1H, m), 4.10-4.05 (2H, m) 3.83-3.80 (m, 1H), 3.68-3.64 (m, 5H), 3.38-3.26 (m, 2H), 2.13 (3H, s), 2.08 (3H, s), 2.02 (3H, s), 1.97 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 169.9, 169.9, 169.7, 97.7, 70.1, 70.0, 69.4, 69.0, 68.4, 67.2, 66.0, 62.4, 50.6, 20.9, 20.8, 20.7, 20.6 ppm; IR ($CDCl_3$) 2938, 2113, 1754 cm^{-1} HRMS (micro –TOF) 500.1304 g/mol (calculated M+K=500.1277 g/mol for $C_{18}H_{27}O_{11}N_3K$).



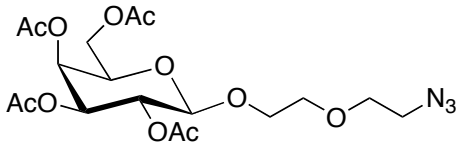
1,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (31). Compound **31** was prepared according to published literature methods.[52] A 70% solution of perchloric acid in water (12 drops) was added to a solution of a α-D-mannose (10 mg, 60 μmol) in acetic

anhydride (75 mL). While this yellow solution was stirred, α-D-mannose (18.48 g, 103 mmol) was slowly added, with cooling in an ice bath as necessary to maintain the temperature below 45 °C. The dark brown solution was stirred at 30 °C for 30 minutes and then at 0 °C for 1 h. Phosphorous tri-bromide (13 mL, 37 g, 140 mmol) was added, followed by H_2O (7 mL). This orange solution was stirred for 75 minutes at 30 °C followed by the addition of an 80% solution of sodium acetate (75 mL) with cooling as necessary to maintain the temperature below 45 °C. Stirring continued for an additional 25 min. The product was extracted with chloroform (3 x 75 mL) and washed with sat. aq. $NaHCO_3$ solution (2 x 75 mL) and water (2 x 75 mL) and then dried over $MgSO_4$. The chloroform was removed *in vacuo*, leaving an orange oil. Addition of cold ether (500 mL) led to the formation of a white solid which was filtered and dried to give 4.11 g (11.8 mmol, 11.5 % yield) of product ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (1H, s), 5.37 (1H, t, J=9.9 Hz), 5.01 (1H, dd, J=9.8, 2.9 Hz), 4.30-4.27 (1H, m), 4.17 (1H d, J = 2.9 Hz), 4.10-4.08 (1H, m), 3.77-3.74 (1H, m), 2.30 (1H,bs), 2.16 (3H, s), 2.10 (3H, s), 2.07 (3H,s), 2.03 (3H, s) ppm. These results agreed with previously published data.[50]



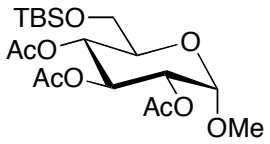
1,3,4,6-tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-α-D-mannopyranose (32). 1,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **31** (0.24 g, 0.68 mmol) was added to 2,3,4,6- tetra-*O*-acetyl-α-D-mannosyl trichloroacetimidate **29** (0.34

g, 0.68 mmol), and the mixture was dissolved in 6 mL of CH_2Cl_2 and cooled to -78° C. To this was added 4 Å mol sieves and $In(OTf)_3$ (0.38 g, 0.69 mmol), and the reaction was monitored by TLC (3:7 hexane/EtOAc). After 30 min the reaction was quenched with sat. aq. $NaHCO_3$ solution, and was allowed to warm to rt. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The solvent was removed under reduced pressure to give an oil which was subjected to column chromatography (3:7 hexane/EtOAc), and which yielded 71% of product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (1H, s), 5.45-5.42 (1H, m), 5.33-5.25 (3H, m), 5.10 (1H, dd, J=9.7, 2.7 Hz), 4.95 (1H, s) 4.37 (1H, d, J = 10.1 Hz) 4.31 (1H, d, J= 4.2 Hz), 4.27-4.21 (1H, m), 4.19-4.10 (2H, m) 4.00-3.97 (1H, m), 3.75-3.73 (1H, m), 2.104 (3H, s), 2.098 (3H, s), 2.07 (3H, s), 2.04 (3H, s), 2.03 (3H, s), 1.987 (3H, s), 1.986 (3H, s), 1.96 (3H, s). These values coincided with previously published values. [51]

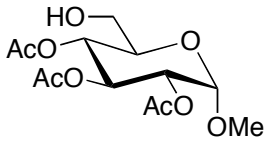


1-*O*-(5-azido-3-oxapentyl)-2,3,4,6-tetra-*O*-β-D-galactopyranoside (34). 2,3,4,6- tetra-*O*-acetyl-α-D-galactosyl trichloroacetimidate (58 mg, 0.12 mmol) was dissolved in dry CH_2Cl_2 (1.2 mL) and cooled to –78 °C. To this solution was added alcohol **27** (15 mg, 0.12 mmol) and $In(OTf)_3$ (66 mg, 0.12 mmol), and the reaction was stirred for 30 min. The reaction was quenched with solid $NaHCO_3$ and filtered. The solvent was removed and the mixture was chromatographed (4:6 hexane/EtOAc) to give 39 mg of product **41** (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, d, *J*=2.8 Hz), 5.21-5.18 (1H, m)

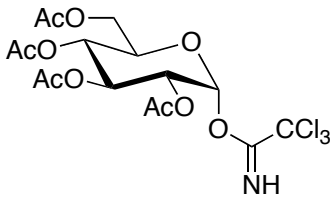
5.02-4.99 (1H, m) 4.55 (1H, d, J=8.9 Hz), 4.15-4.12 (2H, m), 3.96-3.89 (1H. m), 3.76-3.74 (1H, m), 3.65-3.64 (m, 4H), 3.36-3.34 (2H, m), 2.13 (3H,s), 2.05 (3H,s), 2.03 (3H, s), 1.96 (3H, s). ^{13}C NMR ($CDCl_3$, 125Mz) δ 174.4, 172.0, 170.7, 169.7, 90.1, 77.7, 70.1, 69.4, 69.0, 68.5, 67.7, 66.0, 62.4, 50.6, 20.9, 20.8, 20.7, 20.6. IR ($CDCl_3$) 2948, 2113, 1754 cm^{-1}. HRMS (micro –TOF) 500.1212 g/mol (calculated M+K=500.1277 g/mol for $C_{18}H_{27}O_{11}N_3K$).



2,3,4-*O*-acetyl-6-*tert*butyldimethylsilyl-α-D-*O*-methyl glucose (37). To a solution of *O*-methyl-α-glucose (0.783 g, 4.03 mmol) in pyridine (40 mL) was added *tert*butyldimethylsilyl chloride (0.604 g, 4.03 mmol) at 0 °C. The solution was allowed to stir for 3 h, after which Ac_2O (1.35 mL, 13.2 mmol) and DMAP (0.147 g, 1.2 mmol) were added. The solution was allowed to stir overnight, the pyridine was removed under reduced pressure, and 50 mL of EtOAc was added. The EtOAc layer was washed with water (3 x 20 mL), dried over $NaSO_4$, and filtered. The solvent was removed under reduced pressure. Column chromatography (7:3 hexanes/EtOAc) afforded 1.33 g (76% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (1H, t, J=9.8 Hz), 4.98 (1H, t, J=9.8 Hz), 4.85 (1H, s) 4.87 (1H, m) 3.82 (1H, dd, J=6.6, 3.7 Hz), 3.37 (2H, d,= 2.9 Hz), 3.37 (3H, s), 2.05 (3H, s), 2.00 (3H, s), 1.98 (3H, s), 0.867 (9H, s), 0.025 (6H, s). These values agreed with previously published data.[52]

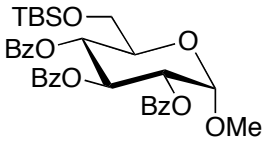


2,3,4-*O*-acetyl-α-D-*O*-methyl glucose (38). 2,3,4-*O*-acetyl-6-*tert*butyldimethylsilyl-α-D-*O*-methyl glucose **37** (0.981 g, 2.26 mmol) was dissolved in THF (20 mL), and to this solution was added 0.745 mL of a 30% solution of HF/pyridine. The solution was allowed to stir for 1 h at rt. A saturated solution of copper sulfate was added. The mixture was extracted with EtOAc, and the organic layer was collected and dried over $MgSO_4$ before being concentrated and subjected to column chromatography (5:5 hexane/EtOAc) to afford 0.441 g (61% yield) of product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (1H, t, J=9.9 Hz), 4.88-4.81 (2H, m), 4.47-4.44 (1H, m) 4.28-4.25 (1H, m), 3.80, (2H, dd, J = 9.9, 2.6 Hz), 3.54 (1H, t, J = 9.1 Hz), 3.37 (3H, s), 2.99 (1H, d, J= 2.6 Hz), 2.11 (3H, s), 2.08 (3H, s), 2.06 (3H, s).[52]



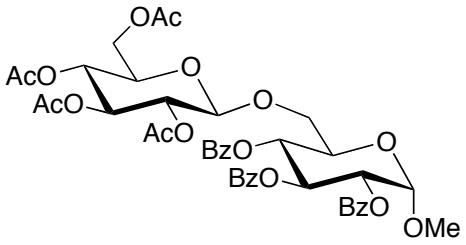
2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (39b). A solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranoside (3.67 g, 9.41 mmol), hydrazine acetate (1.12 g, 12.2 mmol), and DMF (10 mL) were stirred at 55 °C for 30 min. EtOAc (100 mL) was added and the organic layer was washed with water. The aqueous layer was then extracted with EtOAc (50 mL). The organic layers were combined and washed with water (2 x 50 mL), sat. aq. $NaHCO_3$ solution (2 x 50 mL), and brine (2 x 50 mL). The

EtOAc was dried over $MgSO_4$ and was concentrated under reduced pressure to afford 2.9 g (88% yield) of product as a highly viscous oil. This product was used without further purification.[1]H NMR (300 MHz, $CDCl_3$) δ 5.42 (1H t, J=4.5 Hz) 5.33 (1H, s), 4.56 (1H, q, J=10.1) 4.76 (1H, dd, J=10.1, 4.5 Hz), 4.69 (1H, s), 4.14 (1H, m) 4.00 (1H), 1.98 (3H, s), 1.96 (3H, s), 1.92 (3H, s) 1.90 (3H, s).[49] DBU (46 μmmol, 0.31 mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (2.14 g, 6.1 mmol), and trichloroacetonitrile (3 mL, 21 mmol) in CH_2Cl_2 (60 mL) at 0°C. After 3 hours, the solvent was removed *in vacuo* and the residue was filtered through a plug of silica (6:4 hexane/EtOAc). The solution was concentrated to leave a yellow oil that was purified on silica gel (6:4 hexanes/EtOAc) to afford 1.22 g (41% yield) of product. [1]H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, s), 6.22 (1H, s), 5.41 (1H, s) 5.36-5.31 (2H, m), 4.23-4.09 (3H, m) 2.14 (3H, s), 2.04 (3H, s), 2.01 (3H,s), 1.94 (3H, s). These values corresponded with previously published data.[49]



2,3,4-*O*-benzoyl-6-*tert*butyldimethylsilyl-α-D-*O*-methyl glucose (41). To a solution of *O*-methyl-α-glucose (3.63 g, 18.7 mmol) in pyridine (50 mL) was added *tert*butyldimethylsilyl chloride (2.80 g, 18.7 mmol), at 0 °C. The solution was allowed to stir for 3 h and benzoyl chloride (7.19 mL, 61.7 mmol) and DMAP (0.684 g, 5.6 mmol) were added. The solution was allowed to stir overnight. The pyridine was removed under reduced pressure and 50 mL of EtOAc was added to the reaction. The EtOAc was washed with water (3 x 10 mL) dried over $NaSO_4$, filtered, and the solvent was removed under

reduced pressure. Column chromatography (8:2 hexane/EtOAc) afforded 7.76 g (67% yield) of product, which contained a by-product in addition to the main product (values for the majors product follow, except for the aromatic region where all peaks are reported). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (2H, d, J=7.6 Hz), 8.02-7.93 (5H, m), 7.86 (2H, d, J=7.6 Hz), 7.43 (1H, t, J=7.2 Hz), 7.5 (1H, m), 7.44-7.26 (10H, m) 6.14 (1H, t, J=9.6 Hz) 5.52 (1H, t, J= 9.8 Hz), 5.39-5.37 (2H, m) 4.10 (1H, d, J = 9.5) 3.81-3.79 (2H, m), 3.42 (3H, s), 0.87 (9H, s), 0.02 (6H, s). These values corresponded with known literature values.[48]



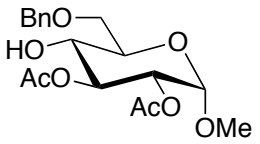
2,3,4,6-tetra-*O*-acetyl-β-glucopyranose [1→4] 2,3,4-tri-*O*-benzoyl-1-*O*-methyl- β-glucopyranose (42). 2,3,4-O-benzoyl-α-D-O-methyl glucose (0.13 g, 0.25 mmol) was added to 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (0.122 g, 0.25 mmol), and the mixture was dissolved in 3 mL of CH_2Cl_2 and cooled to -78 °C. To this was added $In(OTf)_3$ (0.14 g, 0.25 mmol) After 30 min the reaction was quenched with sat. aq. $NaHCO_3$ solution (1 mL) and allowed to warm to room temp. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL) . The solvent was removed under reduced pressure to give an oil, which was subjected to column chromatography (4:6 hexane/EtOAc) to afford 114 mg of product (56% yield). The product appeared to be a mixture of anomers in a 9:1 ratio plus a small amount of

contaminant; values are given for the major isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.91 (4H, m), 7.82 (2H, d, J=7.7 Hz), 7.51-7.40 (2H, m), 7.38-7.24 (7H, m), 6.11 (1H, t, J=9.5 Hz), 5.39 (1H, t, J=10.0 Hz), 5.21-5.17 (3H, m), 5.06-5.00 (3H, m), 4.55 (1H, d, J=8 Hz), 4.25-4.20 (3H, m), 4.05-4.01 (2H, m), 3.70-3.66 (2H, m), 3.42 (3H, s), 2.07 (6H, s) 2.02 (9H, s).. HRMS (micro –TOF) 859.2418 g/mol (calculated M+Na=859.2467 g/mol for $C_{42}H_{44}O_{18}Na$).

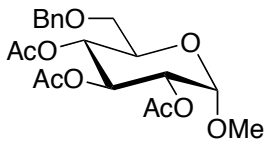
Alternative procedure for 2,3,4,6-tetra-O-acetyl-β-glucopyranose [1→4] 2,3,4-tri-*O*-benzoyl-1-*O*-methyl- β-glucopyranose (42). 2,3,4-*O*-benzoyl-α-D-*O*-methyl glucose (0.056 g, 0.11 mmol) was added to 2,3,4,6- tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (0.054 g, 0.11 mmol), and the mixture was dissolved in 3 mL of CH_2Cl_2. Once the components were dissolved 2,6-DTBP was added (0.045 mL, 0.24 mmol). To this was added $In(OTf)_3$ (0.061 g, 0.11 mmol), and the reaction was allowed to stir at rt for 1 h. The reaction was quenched with an aq. sat. solution of $NaHCO_3$ (1 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure to give an oil, which was subjected to column chromatography (4:6 hexane/EtOAc) to afford 162 mg of product (62% yield). Characterization data provided above.

Alternative procedure for 2,3,4,6-tetra-*O*-acetyl-β-glucopyranose [1→4] 2,3,4-tri-*O*-benzoyl-1-*O*-methyl- β-glucopyranose (42). 2,3,4-*O*-benzoyl-α-D-*O*-methyl glucose (0.17 g, 0.33 mmol) was added to 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (0.164 g, 0.33 mmol), and the mixture was dissolved in 3 mL of

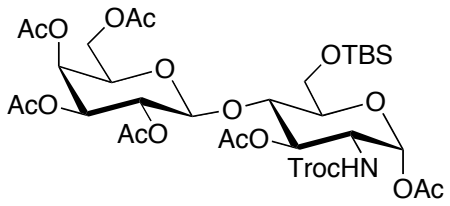
CH_2Cl_2. Collidine was added (0.112 mL, 0.72 mmol). To this was added $In(OTf)_3$ (0.185 g, 0.33 mmol), and the reaction was allowed to stir at rt for 1 h. The reaction was quenched with aq. sat. $NaHCO_3$ solution (1 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The solvent was removed under reduced pressure to give an oil that was subjected to column chromatography (4:6 hexane/EtOAc) to afford 162 mg of product (62% yield). Characterization data provided above.



2,3-*O*-acetyl-6-*O*-benzyl-α-D-*O*-methyl glucose (43). 2,3-*O*-acetyl-4,6-*O*-benzylidene-α-D-*O*-methyl glucose (3.52 g, 12.4 mmol) was dissolved in CH_2Cl_2 (124 mL) and cooled to 0 °C. To this solution was added 5 equiv. of triethylsilane (6.9 mL, 62 mmol) and trifluoroacetic acid (7 mL, 62 mmol). The reaction was warmed to rt and allowed to stir for 3 h. The reaction was quenched with an aq. sat. solution of $NaHCO_3$ (30 mL). The two layers were separated and the organic layer was washed with water (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (8:2 hexane/EtOAc) afforded 1.86 g (53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m), 5.28 (1H, t, J=9.7 Hz), 4.88-4.83 (m, 2H), 4.57 (2H, q, J=8.1 Hz), 3.79-3.70 (4H, m) , 3.37 (3H, s), 2.87 (1H, bs), 2.07 (3H, s) 2.05 (3H, s).[28]



2,3,4-tri-*O*-acetyl-6-*O*-benzyl-*O*-methyl glucose (44). 2,3-*O*-acetyl-6-*O*-benzyl-α-D-*O*-methyl glucose (73 mg, 0.19 mmol) was added to 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (93 mg, 0.19 mmol) and the mixture was dissolved in 2 mL of C. To this was added $In(OTf)_3$ (0.14 g, 0.25 mmol). Once the components were dissolved, 2,6-DTBP was added (0.045 mL, 0.24 mmol). To this was added $In(OTf)_3$ (0.061 g, 0.11 mmol), and the reaction was allowed to stir at rt for 1 h. The reaction was quenched with an aq. sat. solution of $NaHCO_3$ (1 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The solvent was removed under reduced pressure to give an oil that was subjected to column chromatography (4:6 hexane/EtOAc) to afford 64 mg of product (86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.24 (5H, m), 5.44, (1H, t, J=10.4 Hz), 5.11 (1H, t, J=10.2 Hz), 4.94-4.87 (2H, m) , 4.57 (1H, d, J=12 Hz), 4.48 (1H, d, J=12 Hz), 3.92-3.90 (1H, m), 3.51 (2H, m), 3.39 (3H, s), 2.05 (3H, s), 1.98 (3H, s), 1.88 (3H, s).[53]



1,3,2',3',4'6'-hexa-*O*-acetyl-6-TBS-2-*N*-Troc-lactosamine (46). 73 mg (0.13 mmol) of 1,3-*O*-acetyl-6-TBS-*N*-Troc-glucosamine and 78 mg (0.15 mmol) of 2,3,4,6-peracetyl-1-trichloroacetimidategalactopyranoside were combined in 2 mL dry CH_2Cl_2. Once the

compounds had dissolved, 2,6-DTBP was added (63 μL, 33 mmol), followed by $In(OTf)_3$ (73 mg, 0.13 mmol) and the reaction was allowed to stir for 1 h. The CH_2Cl_2 was removed under reduced pressure and the residue was subjected to silica gel column chromatography (7:3 toluene/EtOAc) to afford 27 mg of product (24% yield). The product was obtained in 80% purity (values for the major isomer follow). ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (1H, d, J =3.1 Hz,), 5.35 (1H, s), 5.17 (2H, m), 5.06 (1H, d, J = 8.0 Hz), 4.90 (1H, dd, J = 10.2, 3.3 Hz), 4.76 (1H, d, J = 12.1 Hz,), 4.68 (1H, d, J = 8.0 Hz,), 4.63 (1H, d, J = 12.1 Hz,), 4.10 (2H, m), 4.00 (2H, appt. t, J = 9.5 Hz), 3.81 (3H, m), 3.63 (1H, d, J = 9.7 Hz), 2.04 (3H, s), 2.02 (3H, s), 2.06 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.96 (3H, s), 0.90 (9H, s), 0.07 (6H, d, J = 1.4 Hz). HRMS (Micro-TOF) 906.1738 g/mol (calculated M+Na=906.1797 for $C_{33}H_{50}Cl_3NO_4$ + Na).

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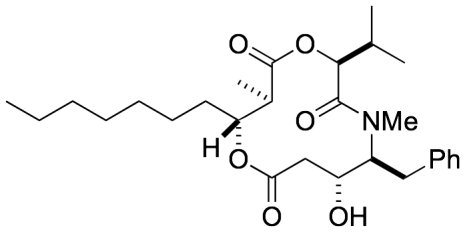
CHAPTER 4

DEVELOPMENT OF SILICON TETHERED REACTIONS

Introduction

Vicinal amino alcohols are common structural motifs in naturally occurring compounds. The structural characteristics of both the amine and the alcohol functionalities can vary extensively. Either or both can be acylated, alkylated, or part of a ring system. A recent review on amino alcohols illustrates the structural diversity of amino alcohols by grouping them into several different categories including peptide based, lipid-like, cyclic, amino sugars, and chiral auxiliaries.[1] Peptide based amino alcohols have the vicinal amino alcohol incorporated with one or more peptides. Hapalosin **47**, a member of this category, is noted for its ability to hinder the growth of multi-drug resistant cancer cells by inhibiting the protein necessary for the expulsion of other cytotoxic drugs.[2-6]

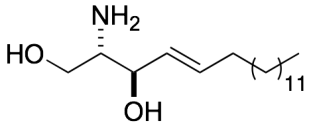


Hapalosin

47

Lipid-like molecules are composed of three basic parts: the amino alcohol, a polar head group, and a long hydrocarbon chain. Perhaps the most synthesized natural product

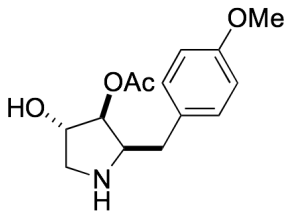
in this group is D-erythro-Sphingosine **48**, which has been shown to be important in cell signaling.[7]



Sphingosine

48

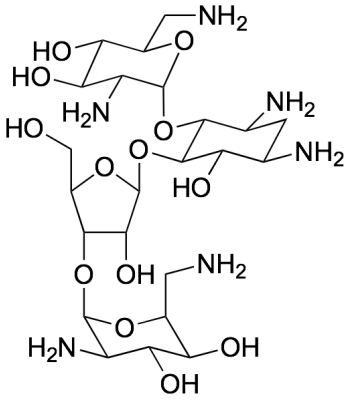
The cyclic amino alcohols comprise the third class of molecules bearing the amino alcohol functionality. In Anisomycin **49** the amine is part of a ring and the beta hydroxyl group is acetylated.[8,9] Anisomycin has been shown to be a potent inhibitor of protein biosynthesis and may be useful as an anti-cancer agent.[10,11]



Anisomycin

49

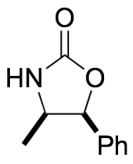
The amino sugars constitute a fourth class of molecules containing the vicinal amino alcohol moiety, where one or more amino groups replace the hydroxyls on the sugar. Neomycin B **50** is an example from a large class of aminogylcoside antibiotics, which has found use as an antibiotic agent against both gram-positive and gram-negative bacteria.[12]



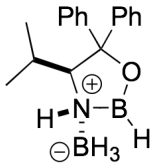
Neomycin B

50

A class of non-naturally occurring but highly useful amino alcohols is those that are used to form chiral auxiliaries. Oxazolidinone **51**, which is used as an agent for stereospecific aldol-condensations[13] and the chiral reducing agent **52** illustrate the broad applications of these amino alcohols.[14]



51

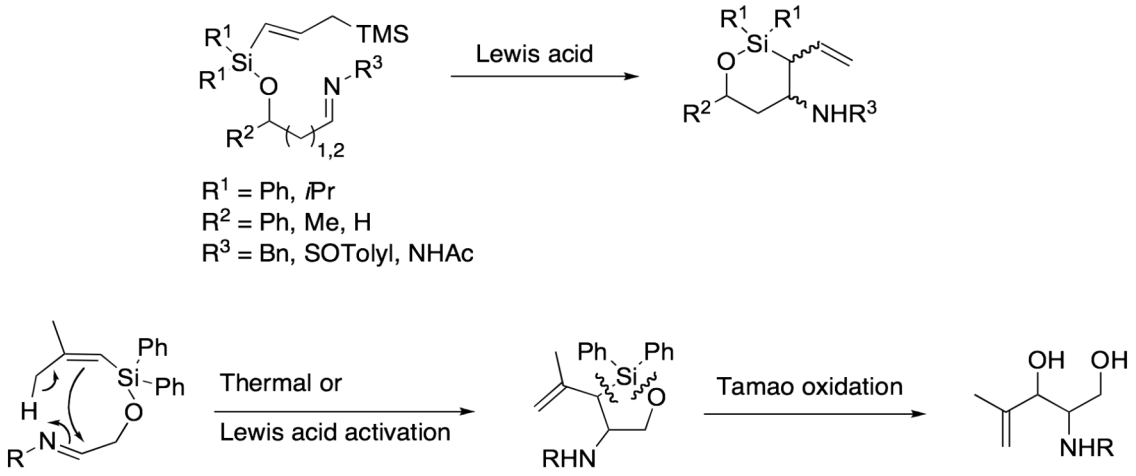


52

Many synthetic strategies have proven effective for the synthesis of molecules containing the 1,2-amino alcohol moiety. Methods include the Sharpless asymmetric amino hydroxylation, the Henry reaction, opening of epoxides with nitrogen nucleophiles, and addition of nucleophilic carbons to amino aldehydes. These methods are summarized below.

The goal of this project was to use a silicon tethered allylation or ene rearrangement to produce 1,2-amino alcohols (Scheme 76). The synthesis of the appropriate tethering system and the evaluation of various Lewis acids as catalysts for the

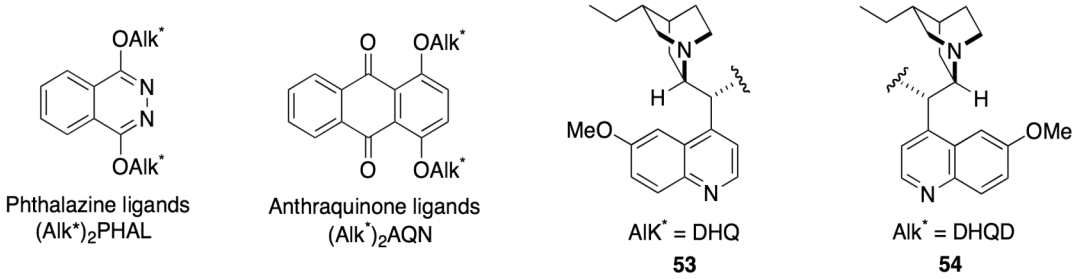
desired transformations was performed. Successful reactions were performed with a very electrophilic nitrogen source in combination with a relatively new Lewis acid, $In(OTf)_3$, that has found utility in a number of carbohydrate reactions.



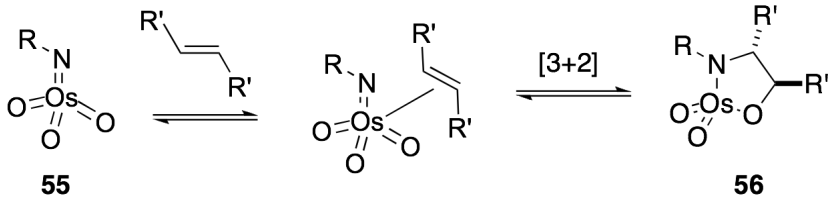
Scheme 76. Allylation and ene strategies for formation of amino alcohols.

The Sharpless Asymmetric Aminohydroxylation

The Sharpless asymmetric aminohydroxylation (AA), first reported in 1996, is perhaps the most straightforward way to synthesize the 1.2-amino alcohol functionality.[15] AA allows for the catalytic and enantioselective introduction of the alcohol and a protected amine in one step starting from a simple alkene precursor. The catalyst is a *Chinchona* alkaloid derived ligand (**53,54)** and osmium species $K_2OsO_2(OH)_4$, along with a nitrogen source (typically a tosyl amine, carbamate or amide) which also serves as the oxidant.



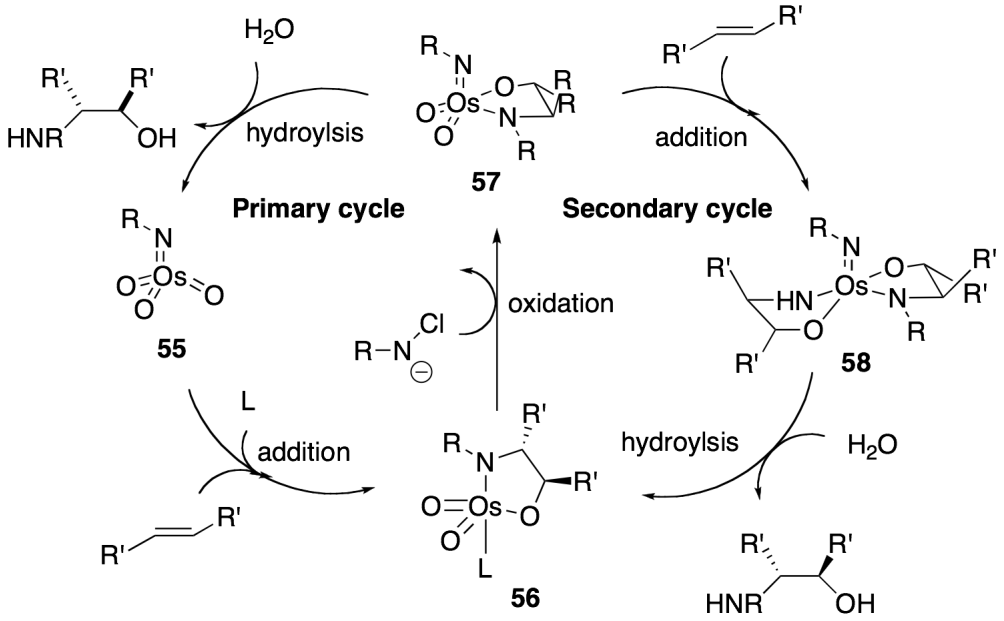
The reaction mechanism put forth by Sharpless involves a [3+2] reaction with imidotrioxoosmium species **55,** which undergoes ligand association, followed by bond cyclization to give the osmium azaglycolate product **56.**[16] Disassociation leads to the desired amino alcohol (Scheme 77). This mechanism uses an electronic argument to justify the preference for the addition of nitrogen to the β-position of alkenes in the absence of an electron withdrawing substituent.



Scheme 77. Osmium azaglycolate product **56**.

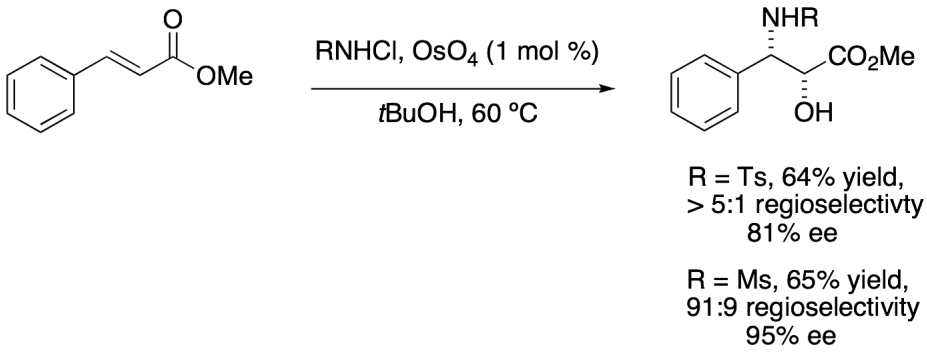
Sharpless proposes that there are two cycles in this reaction that account for selectivity of the reaction (Scheme 78).[17] The primary cycle starts with the imidotrioxoosmium species **55**, the ligand addition and the alkene addition happen concurrently to form **56.** Intermediate **56** is subsequently oxidized by th**e** nitrogen species present in the reaction mixture to form azaglycolate complex **57**. In the primary cycle this complex undergoes hydrolysis to regenerate **55** along with the resultant amino alcohol. In the secondary pathway, **57** reacts with another alkene to form azaglycolate species **58**

which, upon hydrolysis, reforms **56** and produces the new amino alcohol. It should be noted that the primary cycle produces higher selectivity than the secondary cycle does.



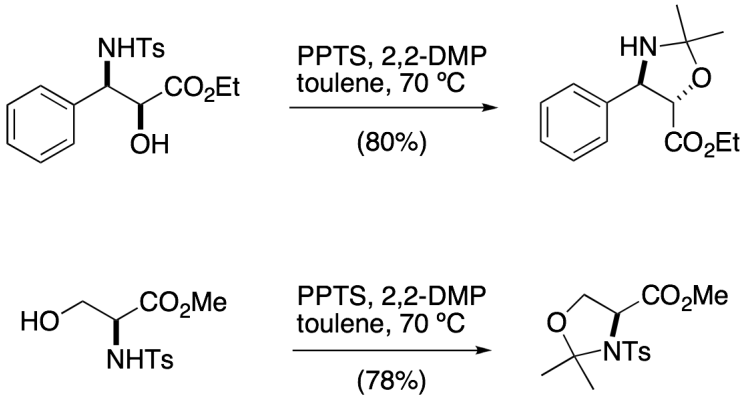
Scheme 78. Sharpless asymmetric amino hydroxylation reaction mechanism.

The source of nitrogen for the Sharpless AA includes three main classes: sulfonamides, carbamates and amides, which are all converted to their respective alkali salts before addition.[18] The sulfonamide variant was the first to be introduced, owing to the fact that it was used in a catalytic but non-asymmetric variation of the AA. Chloramine-T [TsN(Na)Cl] is the most commonly used of the sulfonamide nitrogen sources due to its commercial availability.[19,20,21] Chloramine-M is the next most common sulfonamide used, although it must be prepared *in situ*. However, higher yields and better regioselectivities are generally observed with Chloramine-M than with the sulfonamide Chloroamine-T. An example of this trend is illustrated in Scheme 79, which shows products derived from methyl cinnamate.



Scheme 79. Use of Chloramine-T and Chloramine-M in the Sharpless AA reaction.

The harsh conditions needed to remove a sulfonamide group present a major drawback of this reaction variant. One development that addresses this problem was presented by Chandrasekhar, [22] who found that treatment of Sharpless (AA) products that had an adjacent ester with PPTS and 2,2-DMP in toluene at 70 °C formed the oxazolidine and removed the tosyl group. Unfortunately this reaction was not suitable for all complex substrates (Scheme 80).

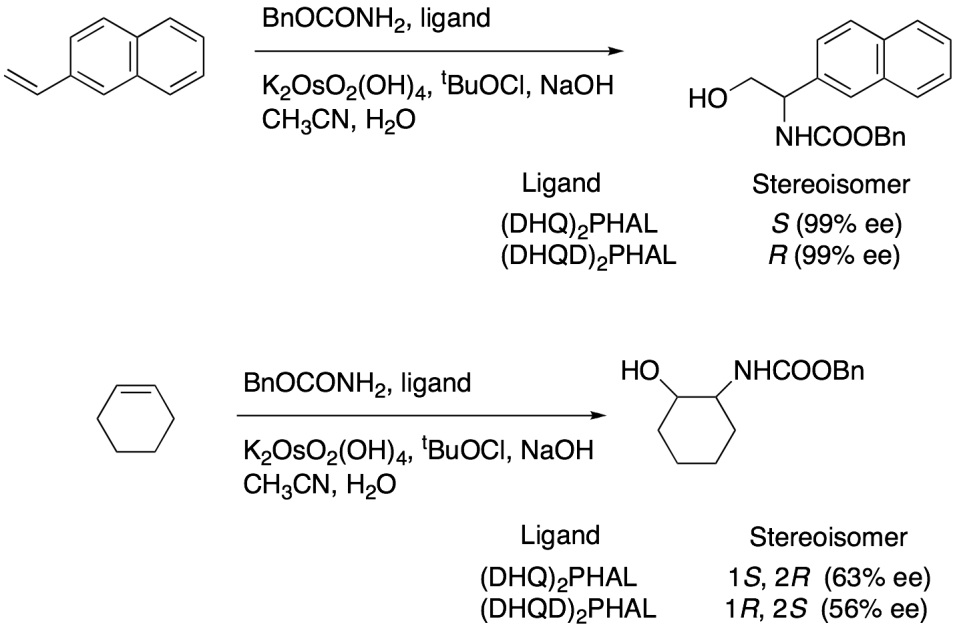


Scheme 80. Tosyl group cleavage of Sharpless AA products.

The development of carbamates as nitrogen sources was a significant advance in the scope of the Sharpless AA.[23] Styrenes and terminal alkenes could be functionalized with this new nitrogen source, instead of just the α,β-unsaturated esters, phosphonates, and amides which could be functionalized by the sulfonamide based AA. The ease of removal of carbamate protecting groups also made this development significant. All of the commercially available carbamates can be used successfully for this reaction in most cases, although purification including the separation of the starting carbamate from the product is often difficult.

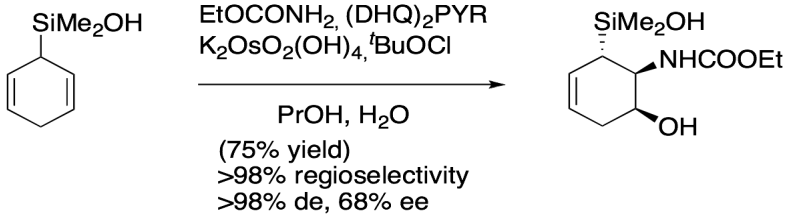
The most recent advance in the Sharpless AA has involved using amides as the nitrogen source. The scope of this reaction is similar to that of the carbamate-derived reaction. One great advantage of this form of the reaction is that only one equivalent of the N-haloamide is required, making isolation of the resultant products much simpler. While Hoffmann rearrangement of N-chlorocarbamides is a problem, this can be overcome by use of the lithium salt of N-bromocarbamides, which suppress the rearrangements at temperatures below 4 °C.

The enantioselectivity obtained in the Sharpless AA is highly substrate specific, as shown in Scheme 81.[23] In the case of the 2-vinylnaphthalene, very high enantioselectivity was achieved. However, when cyclohexene was subjected to the same conditions, a significantly lower ee was obtained. In general, substrates that work well for the closely related asymmetric dihydroxylation also work well for the AA.



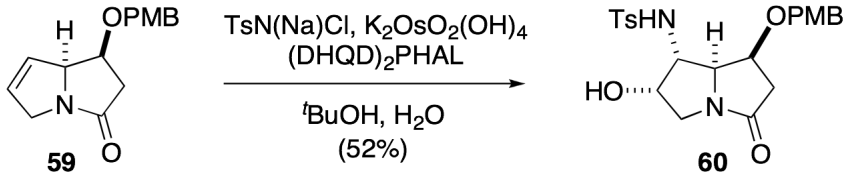
Scheme 81. Example of enantioselectivity in a Sharpless AA reaction.

When considering an asymmetric reaction, the question of diastereoselectivity quickly comes into play, as well as how stereocenters effect the reaction. This issue is addressed by the Sharpless' kinetic resolution procedure. One recent desymmetrization of silyl cyclohexadienes by Landais provides a striking example.[24] The bulky nature of the silyl group induced *anti* addition to the alkene, and regioselectivity was also outstanding (Scheme 82).



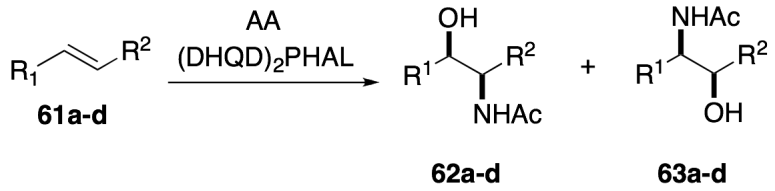
Scheme 82. Desymmetrization of silyl cyclohexadienes by Sharpless AA.

Good diastereoselectivity was also achieved in the synthesis of (+)-loline by White.[25] Treatment of **59** with the correct catalyst loading allowed for the formation of **60** in 52% yield (Scheme 83). However, it should be noted that diol formation and regioselective control were significant problems in this reaction.



Scheme 83. Synthesis of (+)-loline.

As suggested earlier, regioselectivity is perhaps the biggest issue with the Sharpless AA reaction. When there is little to no polarization of the alkene, the nitrogen typically adds to the less hindered side.[26] However, this pattern is by no means absolute, as is demonstrated in Scheme 84.

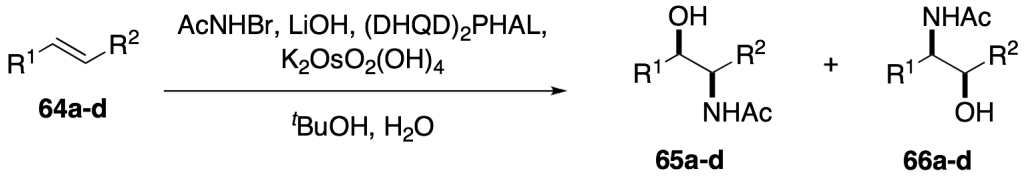


Substrate	R^1	R^2	**62:63**
61a	$TBDPSOCH_2CH_2$	H	>20:1
61b	*p*-MeO-$C_6H_4OCH_2CH_2$	H	1.2:1
61c	$TBDPSOCH_2CH_2$	Et	2.0>1
61d	*p*-MeO-$C_6H_4OCH_2CH_2$	Et	1:3.5

Scheme 84. Example of regioselectivity in the Sharpless AA.

Alkene polarization appears to have some affect on the Sharpless AA, and α,β-unsaturated esters almost always give the β-amino adduct.[27] A suggestion in favor of this

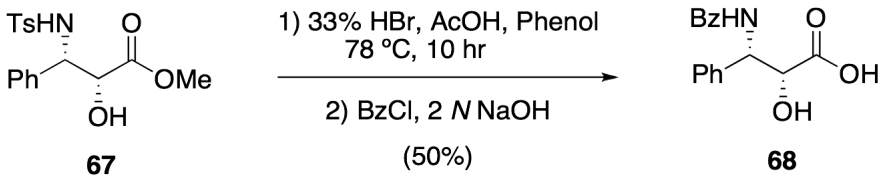
observation lies in the greater nucleophilicity of the Os=NR bond than of the Os=O bond, favoring nitrogen addition to the more electrophilic carbon. There is also some evidence that aromatic groups on one side of the alkene promote addition to the corresponding side as shown in Scheme 85.



Substrate	R^1	R^2	**65:66**
64a	$TBDPSOCH_2$	CH_2-O-2-naphthoyl	>20:1
64b	$TBDPSOCH_2$	CO_2-CH_2-(2-naphthyl)	17:1
64c	*p*-methoxybenzoyl-OCH_2	CO_2Et	1:>20
64d	Ph	CO_2Et	1:>20

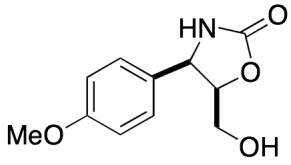
Scheme 85. Effect of aromatic groups on Sharpless AA.

The regioselectivity afforded by use of the Sharpless AA when a methyl cinnamate ester was the substrate allowed for one of the first synthetic uses of the Sharpless AA.[27] Compound **67** could be isolated in high purity from direct crystallization of the reaction mixture. Two manipulations of the protecting groups yielded **68,** which is the C-13 side chain of Taxol (Scheme 86).

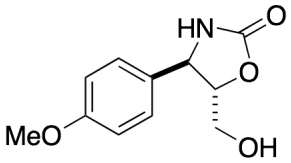


Scheme 86. Synthesis of C-13 side chain of Taxol.

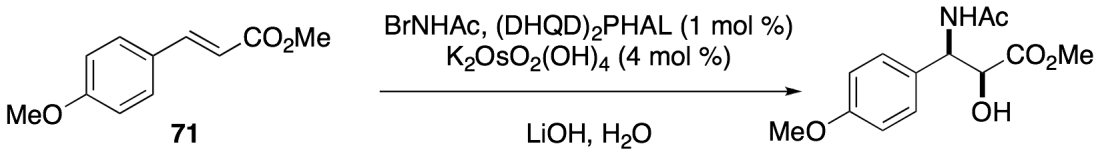
Saicic used this methodology to introduce key functionality into (–)-Cytoxazone **69** and its epimer **70**.[28] The Sharpless AA reaction with *p*-methoxy cinnamate afforded **71** smoothly in 72% yield (Scheme 87). Once this backbone was in place, the cyclic carbamate formation and reduction were accomplished in a straightforward manner.



69 (-) Cytoxazone

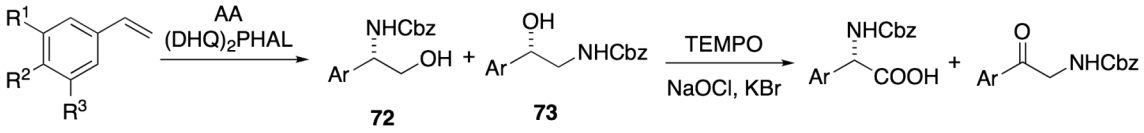


70 (+)-*epi*-Cytoxazone



Scheme 87. Synthesis of precursor of (-)-Cytoxazone by Sharpless AA.

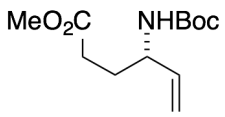
Aryl glycines have been obtained using the Sharpless AA. Good regioselectivity was achieved (~80%) when the reaction was carried out on a number of styrenes (Scheme 88).[29] Oxidation with TEMPO produced the protected amino acid analogs in high ees (90%), and thus made isolation of the desired products much easier.



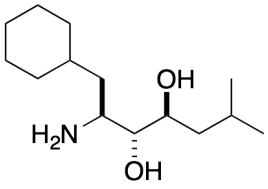
R^1	R^2	R^3	**72:73**
H	OBn	H	88:12
H	OAc	H	50:50
OBn	OMe	OBn	88:12
H	Cl	H	86:14

Scheme 88. Formation of aryl glycines by Sharpless AA.

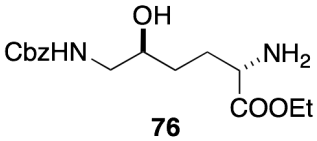
As suggested by the schemes, the Sharpless AA is a powerful tool for the formation of many amino acid products. This reaction has also been used to synthesize the protected form of the anticonvulsive reagent Vigabatrin **74**,[30] the backbone of the aspartic protease inhibitor **75**,[31] and the hydroxylysine derivative **76**.[32]



74

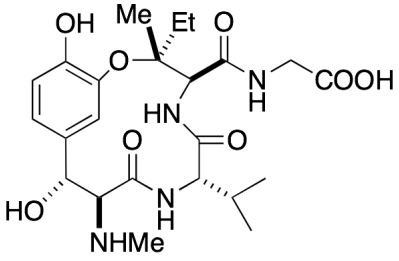


75



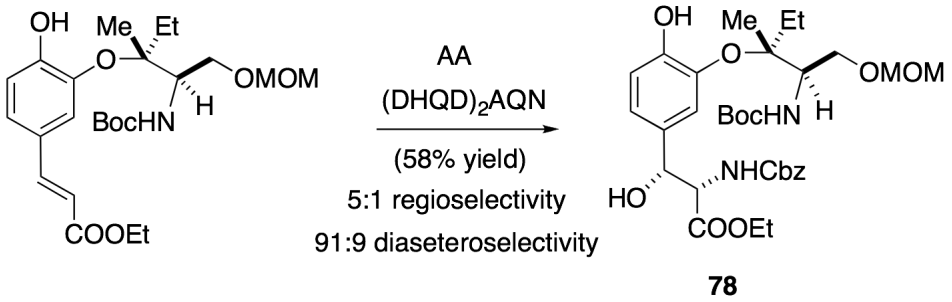
76

One interesting and powerful aspect of the Sharpless AA is that reverse regioselectivity can often be achieved by changing the aromatic spacer of the *Chinchona* alkaloid ligands from a phthalazine unit to an anthraquinone unit.[33] This aspect was put to use in one of the most complex examples of AA to date by Cao *et al*. In their synthesis of Ustiloxin D (**77**), anthraquinone ligands were used to form key intermediate **78** (Scheme 89).



Ustiloxin D

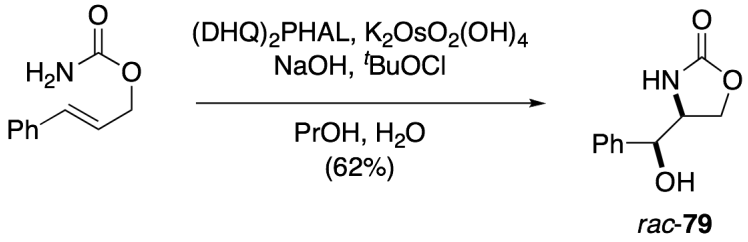
77



78

Scheme 89. Formation of Ustiloxin D precursor by Sharpless AA.

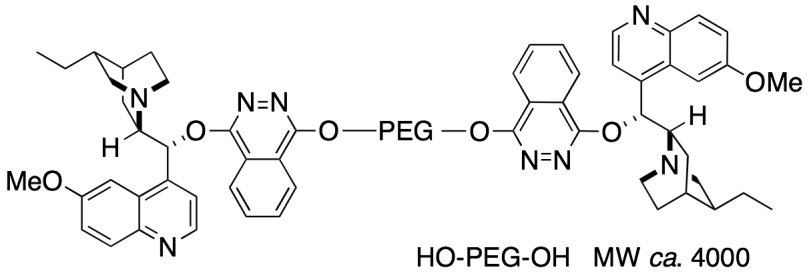
Regioselectivity was also addressed by Donohoe, who used a tethered carbamate system in the Sharpless AA for allylic alcohol substrates.[34] The oxazolidinone **79** was formed regioselectively; however, no enantioselectivity was observed (Scheme 90).



rac-**79**

Scheme 90. Regioselectivity of Sharpless AA with a tethered carbamate.

The cost associated with osmium tetraoxide and the *Chinchona* alkaloids is one drawback to the Sharpless AA. To address this problem, many groups have explored the possibility of recycling the reaction components. One interesting example in this area can be found in the work of Xu and Lin.[35] The *Chinchona* alkaloids were bound to a large PEG tether to produce the immobilized ligand **80,** which was effective in catalyzing the reaction and was also easily recoverable through filtration.



80

The Sharpless AA is an efficient and powerful tool for the formation of vicinal amino alcohols. It allows for the installation of both the oxygen and the nitrogen in one efficient step from a simple substrate (an alkene). While this a very elegant method for the formation of vicinal amino alcohols, it does have limitations. Regioselectivity is modest in cases where electronics do not direct the addition, and the reaction components are costly (*Chinchona* alkaloids), and hazardous (osmium).

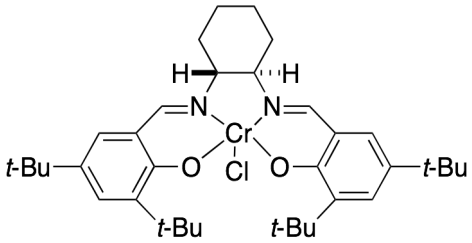
Stereoselective Opening of Epoxides

The opening of epoxides with a nitrogen nucleophile is perhaps the most common way to generate the 1,2-amino alcohol functionality. In simple cases the reaction follows the rules that govern S_n2 reactions, usually forming products where the alcohol and nitrogen are situated in an *anti* arrangement. Typically, due to the "hard" nature of the epoxide, an azide is the nucleophile of choice to introduce nitrogen.

While there are many useful ways to stereospecifically introduce an epoxide into a molecule (Sharpless asymmetric epoxidation and the Jacobsen epoxidation procedures are among the best), the regiospecific opening of an epoxide becomes a problem when the two electrophilic sites are not differentiated by sterics or electronics. To address this

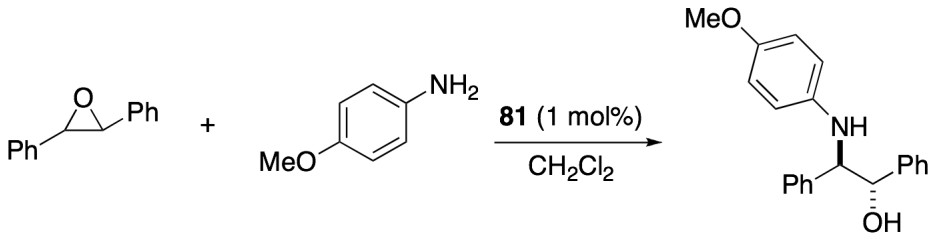
problem, a number of catalysts have been developed. The work in this area has focused mainly on the desymmetrization of meso epoxides to produce asymmetric compounds. These catalysts generally fall into three categories, namely (salen)Cr(III) complexes, triisopropanolamine Zr complexes, and complexes involving the lanthanide metal group.

Perhaps the most famous of the chromium catalysts was developed by Jacobsen.[36] Catalyst **81** was found to effectively promote the addition of $TMSN_3$ to a variety of cyclic meso epoxides in yields of 80-90% and ee's of 88-95%. The catalyst was also found to be effective in solventless conditions, and fully recyclable.



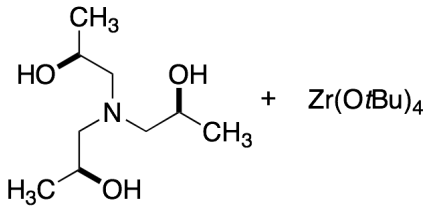
81

Bartoli later showed that Jacobsen's catalyst was effective in promoting the addition of electron rich anilines (*para* or *ortho* methoxy substituted) to epoxides.[37] While the yields and ees of this reaction were outstanding (up to 99% in both cases), the effectiveness of this method was limited to the opening of aromatic epoxides, where the addition of the nitrogen occurred regiospecifically at the benzyllic position (Scheme 91).



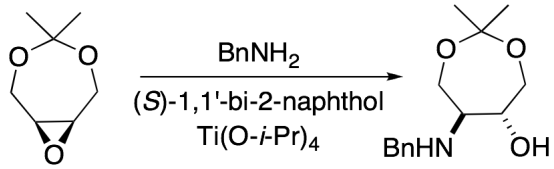
Scheme 91. Opening of meso aromatic epoxide by an analine derivative using chromium complex **81**.

The zirconium complexes, such as **82** that was developed by Finn**,** are generated by the addition of triisopropanolamine to a zirconium alkoxide.[38] The complexes promote the addition of $TMSN_3$ in yields and enantioselectivities which are comparable to the chromium salen complexes developed by Jacobsen.



82

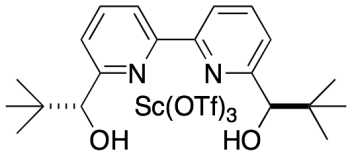
In 1999, Inaba developed a bi-naphthol titanium complex to promote the addition of amines to epoxides (Scheme 92).[39] This catalyst system is of particular interest due to its ability to promote asymmetric addition of a range of different primary amines. However, the main drawback is that useful conversion of the epoxide to the amine was only successful when the epoxide contained a cyclic ketal group.



Scheme 92. Opening of a meso epoxide by benzyl amine catalyzed by Zirconium complex **82.**

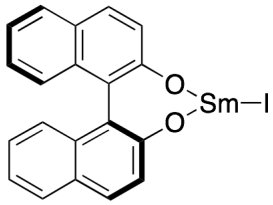
In 2004, Schneider reported a complex **83** based upon scandium, and this complex was effective for both the addition of alcohols and amines to *meso*-epoxides.[40] Reaction

yields with this complex were very good when the epoxide contained aromatic substituents. However, if the epoxide only had alkyl groups, the reaction yield dropped to about 50%.



83

The samarium binaphtholate complex **84** was shown by Collin to catalyze the addition of aromatic amines to meso epoxides in up to 93% ee.[41] A number of different anilines were found to be effective nucleophiles for use with this reagent, but benzyl amine afforded product in low yield and low enantioselectivity. This may be due to catalyst deactivation by the more nucleophilic benzyl amine.

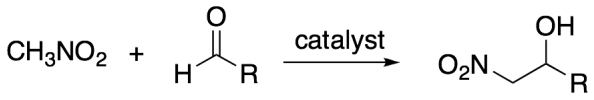


84

The opening of epoxides will most likely always remain an important method of constructing β-amino alcohols thanks to the large number of excellent ways to make epoxides stereospecifically. However, as with almost all nucleophilic additions to epoxides, regiospecificity is a problem when introducing the nitrogen nucleophile. The catalysts discussed above represent an advance toward solving this problem. While significant progress has been made, there still remains work to be done to produce more general catalysts.

Henry Reaction

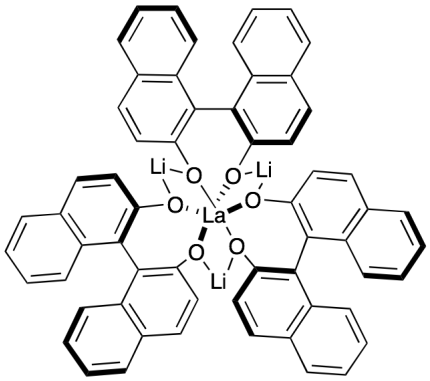
The Henry reaction, or nitro aldol reaction, has been known for a long time.[42] The Henry reaction involves the reaction of nitro-alkane (enolate or enol equivalent) and a carbonyl compound in the presence of an acidic or basic catalyst, resulting in the formation of a nitroalcohol (Scheme 93). While an amino alcohol is not formed directly from the reaction, the ease of the reduction of nitro groups to amines makes this reaction a powerful tool in formation of amino alcohols.



Scheme 93. Henry Reaction.

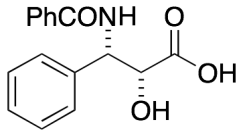
Since the Henry reaction has been known for some time, it is inevitable that there has been a large amount of work in the area.[43] While examples of the non-stereospecific reaction are ubiquitous, the asymmetric version of the reaction has only recently begun to emerge,[44] and that version will be the focus of this discussion.

Shibasaki developed the first major advance in the catalytic Henry reaction in 1992.[45] He found that the Lanthium complex **85** efficiently promoted the addition of nitromethane to both aromatic and aliphatic aldehydes, obtaining ees up to 95%. The *syn/anti* ratio was also quite impressive, with formation of up to 89% of the *syn* diastereomer. (Control of the *syn/anti* ratios had long been a problem for this reaction.)

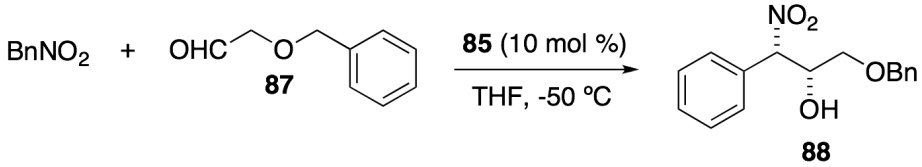


85

The usefulness of catalyst **85** was shown in 2004 by Burua et al[46] in the short and efficient synthesis of the side chain of taxol **86.** The key C-C bond forming event was accomplished by the reaction of phenylnitromethane with aldehyde **87** in the presence of 10 mol % of catalyst to arrive at nitro alcohol **88** in 80% overall yield (Scheme 94). Standard manipulations yielded **86** in four steps.



86

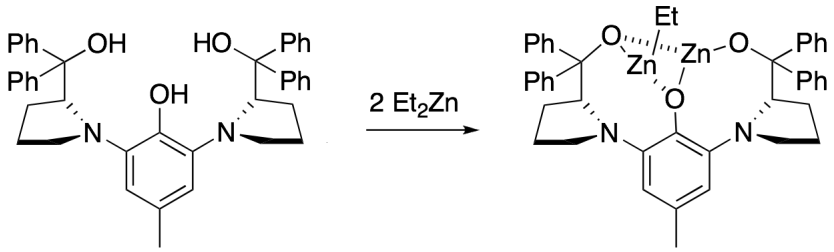


88

Scheme 94. Use of Lanthium complex **85** to catalyze the Henry Reaction to form the side chain of Taxol.

The binuclear Zn catalyst **90** was later developed by Trost.[47] The catalyst is produced by treating phenol **89** with two equivalents of $ZnEt_2$ to produce **90** (Scheme 95).

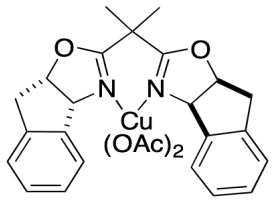
This catalyst promoted reactions between both aromatic and aliphatic aldehydes and nitromethane. Like Shibasaki's reaction, THF was found to be the solvent of choice. The use of this catalyst generally afforded products in 60-70% yields with ee values in the range of 80-90%.



89 **90**

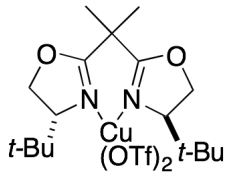
Scheme 95. Formation of Zinc catalyst **90.**

In 2003, Evans showed that copper bisoxazoline catalysts were also efficient promoters of the Henry reaction.[48] Of the different catalysts screened, **91** was the most efficient promoter of the reaction. The effectiveness of the catalysis was however limited to the addition of nitromethane to both aromatic and aliphatic aldehydes. The yield and ee values for products formed using this catalyst were generally both above 90%.

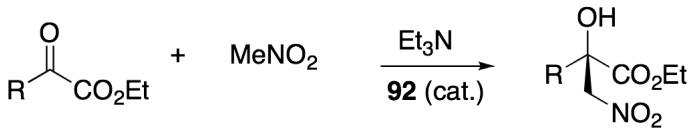


91

The examples discussed above present additions of nitroalkanes to aldehydes. In general, the Henry reaction of ketones is a slow and reversible process, but an exception can be found in work of Xu.[49] Xu found that in presence of Et_3N the copper bisoxazoline **92** efficiently promoted the addition of nitromethane to α-ketoesters (Scheme 96).



92



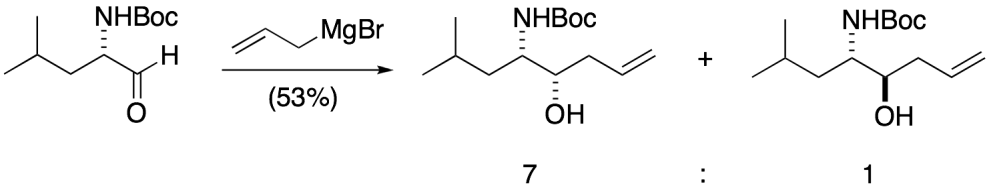
Scheme 96. Addition of nitromethane to α-ketoesters catalyzed by copper catalyst **91.**

In recent work by Choudary, nanocrystalline MgO was successfully used as a catalyst for the Henry reaction.[50] When these nanocrystals were used in conjunction with a chiral auxiliary such as (*S*)-(-)-binol, or (1*R*,2*R*)-(-)-diaminocyclohexane, high yields (90%) and ees up to 90% were observed for the reaction of nitromethane with benzaldehyde. This catalyst system also successfully promoted the addition of nitromethane to alpha keto esters, the same substrates used by Jorgenson. This system represents one of first effective and recyclable heterogeneous catalyst systems that is effective for the Henry reaction.

While the Henry reaction has long been familiar, only recently have there been advances that have allowed for the reaction to be performed asymmetrically. While large strides have been made by some of the most talented chemists of this period, there still remain some challenges to be overcome. Currently, catalytic systems are limited mostly to reactions of simple nitroalkanes and simple aldehydes. This hurdle currently prevents the Henry reaction from providing a major contribution to the synthesis of amino alcohols.

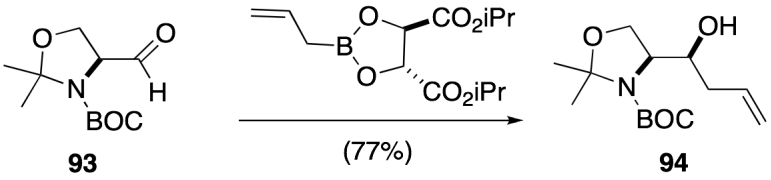
Addition of a Nucleophile to an α-Amino Carbonyl

Perhaps the simplest way to make amino alcohols is by the addition of an organometallic reagent to an α-amino carbonyl. While straightforward, this approach is often plagued with problems such as the stability of the amino carbonyl and low diastereoselectivity. For example, the addition of allyl magnesium bromide to the valine derivative proceeds in only 53% yield in a 7:1 *syn*:*anti* ratio (Scheme 97).[51]



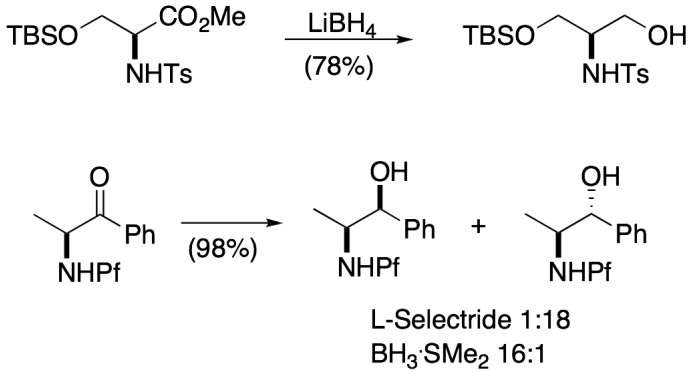
Scheme 97. Addition of allylmagnesium bromide to a valine derivative.

Success in this area has been achieved by using different protecting groups for the amino aldehydes. Garner's aldehyde **93** is a common example of a protected amino aldehyde. Allyl boron reagents can successfully add to **93**, giving **94** as the *syn* product in 77% yield (Scheme 98).[52]



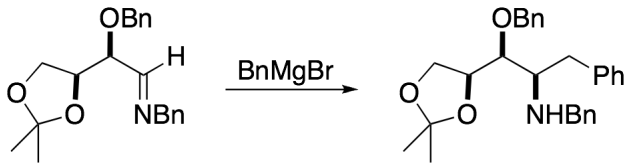
Scheme 98. Reaction of Garner's aldehyde with an allyl boron reagent.

The reduction of α-amino carbonyl compounds is a well-used route to vicinal amino alcohols. While the reduction of esters or aldehydes proceeds in the usual manner, no new stereochemistry is created, of course. Examples of this reaction are shown below. In the first, a protected serinate is reduced by $LiBH_4$ leading to the resultant amino alcohol in 77% yield. In the second example L-Selectride gives the *syn* diastereomer in 98% and 1:18 diastereoselectivity, while reduction with BH_3•SMe_2 gives the anti diastereomer in 98% and 1:16 selectivity (Scheme 99).[53,54]



Scheme 99. Reduction of 2-amino-carbonyl compounds.

The corresponding reactions between a protected α-hydroxyimine and a nucleophile are not as well represented due to the relative instability of the imines. One example in which a protected α-hydroxyimine is used directly is shown in Scheme 100. Giving the *syn* isomer as the major product, yields for similar substrates range from 37-78%.[55]



Scheme 100. Addition of benzylmagnesium bromide to alpha-hydroxyimine.

Formation of amino alcohols via addition of nucleophiles to aldehydes or imines, is a path that often requires optimization for each specific case. The numerous protecting groups that have to be employed for addition to happen in the desired manner make this method of synthesizing vicinal amino alcohols challenging.

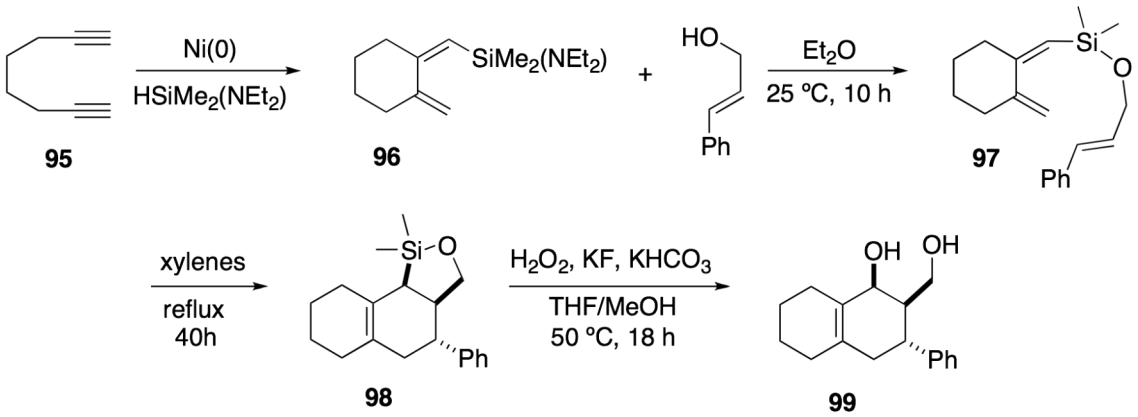
Silicon Tether

It has long been known that intramolecular reactions hold many advantages over their intermolecular counterparts. The lessened entropic demands of the intramolecular reaction often lead to faster rates of reaction and milder conditions. This is often coupled with improved regio and stereospecificity. To take advantage of these factors, synthetic chemists have devised a number of tethering systems to temporarily link two molecules together, perform a chemical manipulation and then remove the undesired linker. The ideal tether would be easily introduced, impart the desired chemical behavior to the system as a whole, and be removed easily both chemically from the reactants and physically from the reaction mixture.

The strategy of using silicon as a temporary tethering system was first developed by Tamao in the early 1990s.[56] Silicon has many of the desired properties to be an ideal tether. There are a variety of different difunctional silicon species that are widely

available and can be easily attached to either an alcohol or a carbon. With wide array of available silicon-containing reagents, one can impart large steric bulk to part of the molecule by using a bulky tether such as a diisopropyl tether or use the electronics of silicon to direct nucleophilicity. Removal of the silicon tether can be achieved specifically by use of the fluoride anion or the Tamao oxidation.[57] Physical removal of the tether is often straightforward due to the nonpolar nature of most silicon compounds, and column chromatography is often a simple matter.

Tamao's first utilization of the silicon tether to control the regio and stereo selectivity of the Diels-Alder reaction is shown in Scheme 101.[56] The actual tether was introduced by nickel catalyzed hydrosilation of diyne **95** to form the vinyl silane **96**. Treatment of **96** with cinnamyl alcohol gave the Diels-Alder precursor **97**, which upon heating in refluxing xylene gave the cycloadduct **98**. Treatment with Tamao's oxidizing conditions yielded the diol **99** in 75% overall yield from **96.**

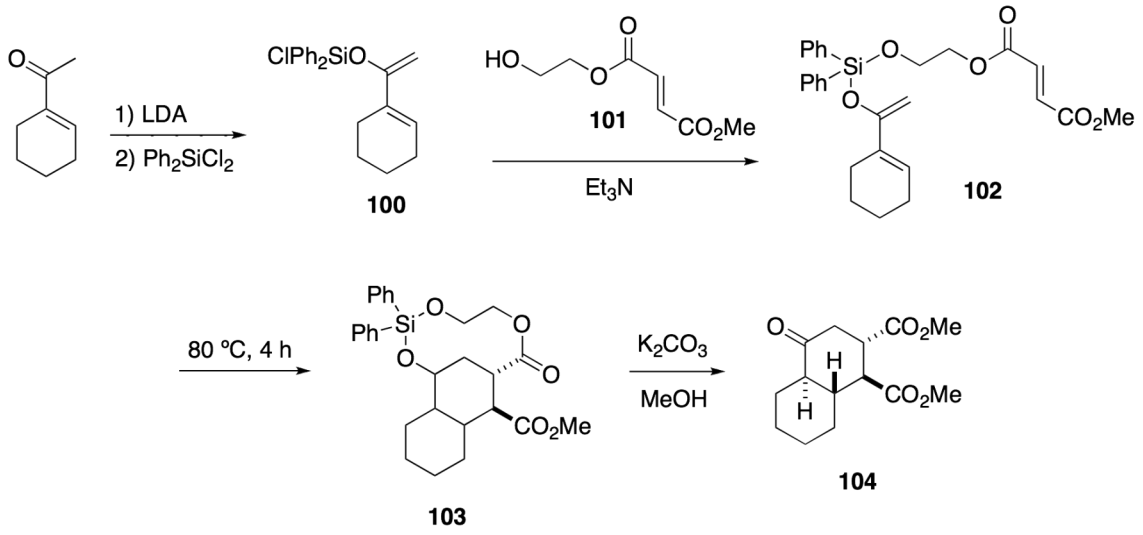


95 **96** **97** **98** **99**

Scheme 101. Silicon tethered Diels-Alder reaction performed by Tamao.

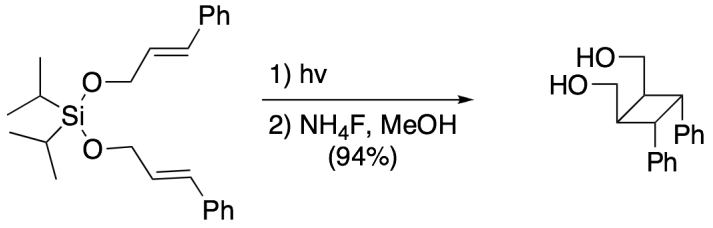
Shea and co-workers used the temporary silicon tether strategy to control regioselectivity of a Diels-Alder reaction (Scheme 102).[58] The enolate of 1-

acetylcyclohexene was treated with dichlorodiphenylsilane to produce **100**. This intermediate was then treated with alcohol **101** to produce triene **102.** Cyclization was affected under relatively mild conditions to afford **103**, which could then be hydrolytically cleaved to give decalone **104** as a single isomer**.** It should be noted that this reaction gives an inseparable mixture of isomers if performed in a bimolecular fashion.



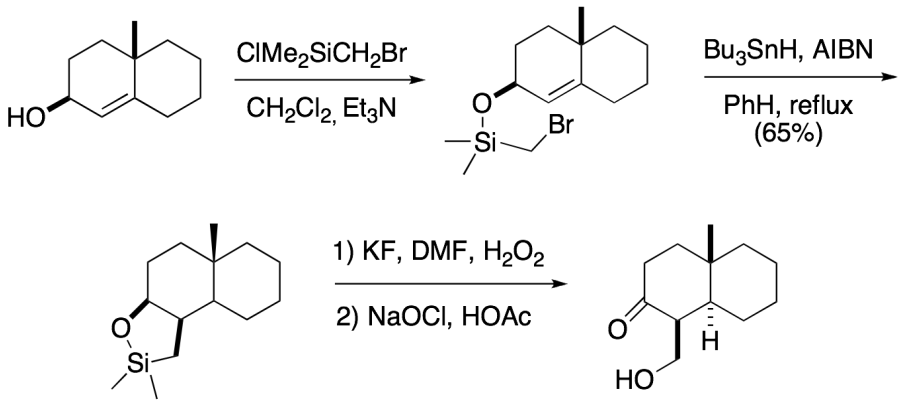
Scheme 102. Silicon tethered Diels-Alder reaction preformed by Shea.

The use of the silicon tether has also proven effective for [2+2] cycloaddition reactions. In work done by Flemming and Ward, cinnamyloxysilylacetal was synthesized and subjected to irradiation, providing access to a number of cyclobutane molecules (Scheme 103).[59] This example demonstrates the power of the silicon tether, as untethered substrates did not react under the same conditions.



Scheme 103. Silicon tethered [2+2] cycloaddition.

The silicon tether has been used extensively for radical cyclizations. In examples developed by Stork and others, an allylic alcohol can be functionalized using commercially available (bromomethyl)dimethylchlorosilane and subjected to standard radical cyclization procedures (Bu_3SnH, AIBN, refluxing benzene) to stereoselectively append a carbanol unit (Scheme 104).[60]

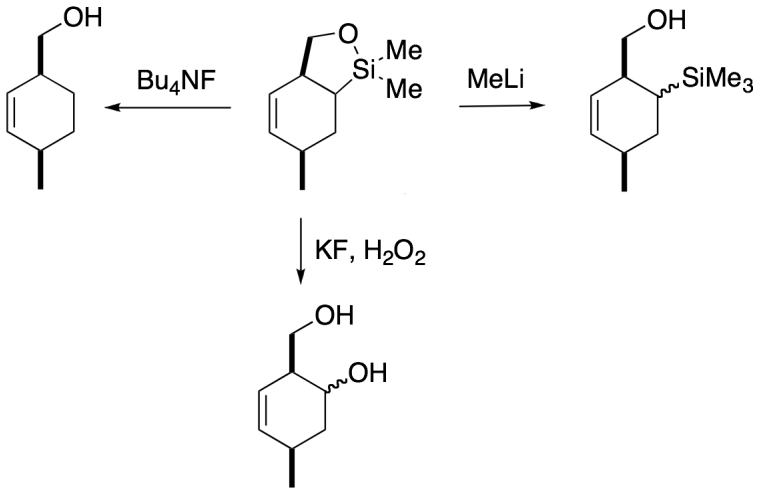


Scheme 104. Silicon tethered radical cyclization.

One of the salient points to be addressed when using silicon tether methodology is which tether to use. The work described in this thesis is revealing on this point, but a deeper evaluation of prior literature was necessary to fully understand why different tethers are used under different circumstances.

Perhaps the most commonly used of all the tethers is the dimethylsilyl tether. This tether has many advantages. First and foremost, it is the least expensive of the difunctional silicon reagents. Second, the protocol for attaching this tether to alcohols is relatively simple. The first alcohol is treated with excess dimethyldichlorosilane, and then the unreacted starting material is removed at reduced pressure. The second alcohol is added to achieve the desired transformation.

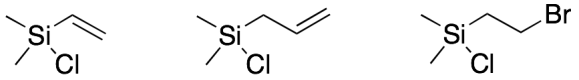
A third advantage of the dimethylsilyl tether series is the transformations that can be performed once the tether is formed. As seen in Scheme 105, protodesilation using the Tamao oxidation is facile, as is treatment with methyllithium to achieve the resulting silane.[61]



Scheme 105. Cleavage of dimethylsilyl tethers with fluoride and methyl lithium.

One major drawback of using the dimethylsilyl tether is that once the desired transformation is accomplished, the resulting silacycle is prone to hydrolysis.[61] Often, the Tamao oxidation must be accomplished *in situ*, which can lead to lower yields.

Another advantage of the dimethylsilyl tethers is that the vinyl, allyl, and β-bromo species **105, 106**, **107** are all commercially available. The first two are often used for Diels-Alder reactions, while the third is used largely for radical cyclizations.



105 **106** **107**

The diethylsilyl tether is not often used for cyclization reactions, but it does enforce a more sterically hindered reaction, which can be advantageous if isolation of the silacycle is desired.

The second most common tether is the diphenylsilyl tether, whose use has a number of advantages. The diphenylsilyl linkers afford a much more stable cycle, which can make isolation of the resultant product more straightforward. The diphenylsilyl tethers are also chromophoric, which can facilitate column chromatography. The steric hindrance of the tether seems to be about the same for diphenyl and diethyl species (considering cone angles). One other advantage of the diphenylchlorosilane is its ability to trap enolates, which are then often used for Diels-Alder reactions. Like the dimethylsilyl tether, the vinyl and allyl substituted the diphenylsilyl reagents are commercially available.

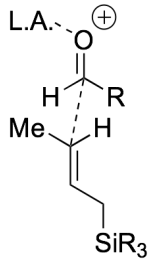
If additional steric hindrance is necessary, the diisopropylsilyl tether is commonly used. This species has the advantage of making stable di-alcohol linkers, which can be purified by column chromatography.

The dibutylsilyl tethers provide the greatest amount of steric hindrance in the linker. While the resultant products of addiction are very stable, there are a number of

disadvantages to this tethering system. First is that it is difficult to make a carbon silicon bond through an organometallic addition. To make an oxygen linkage, the mono triflate is required, and this adds an extra step to the synthesis. If there is a carbon present in the silacycle that is formed in the reaction, then Tamao oxidation can unfortunately be very difficult.

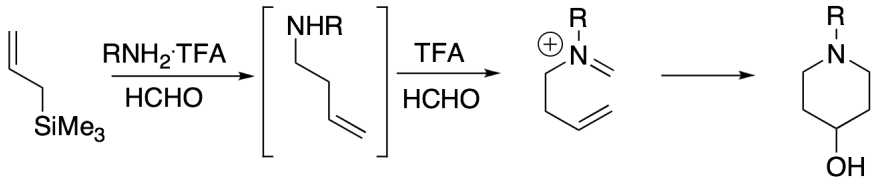
Allylsilane Transfers

The Lewis acid catalyzed addition of allylsilanes to aldehydes is well documented. The stereochemistry of this reaction and its utility have been extensively explored by Panek and others.[63] The reaction proceeds by addition of the nucleophilic allylsilane, which adds to the activated aldehyde in an open transition state as shown below. Desilation quickly occurs if the substituents on the silicon are small, such as in the case of the trimethylsilyl group. However, if the groups surrounding the silicon are sufficiently large, desilation does not occur and the 1,3-silanyl alcohol is observed.



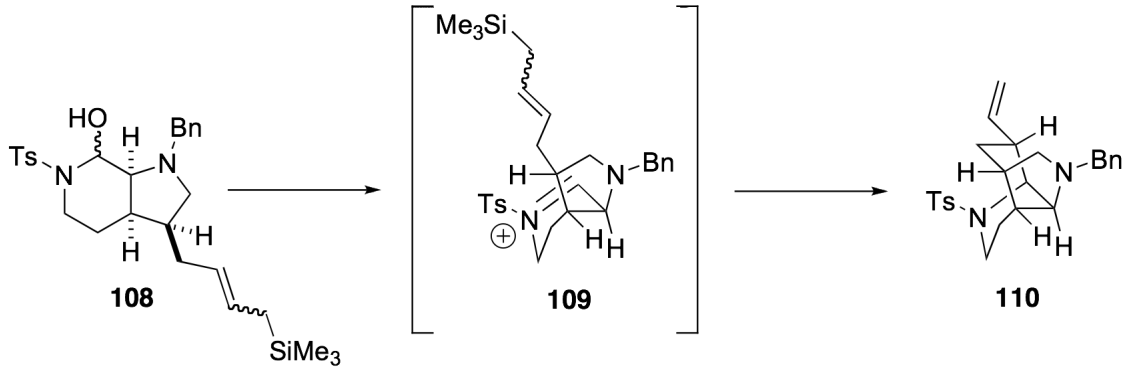
The addition of allylsilanes to imines or iminium ions has been met with limited success. This is due to the low reactivity of the allylsilane as well as the propensity of the imine to undergo tautomerization to the enamine. Several methods have circumnavigated this problem. The first and most simple method is to generate an iminium, which does not undergo tautomerization. This can be accomplished quite nicely by condensing an amine

with paraformaldehyde. Grieco used this strategy to form a tethered silane to create piperidines (Scheme 106).[64] The utility of this reaction was remarkable because the transformation was achieved in water.



Scheme 106. Allylation of an iminium ion, in water by allyltrimethylsilane, performed by Grieco.

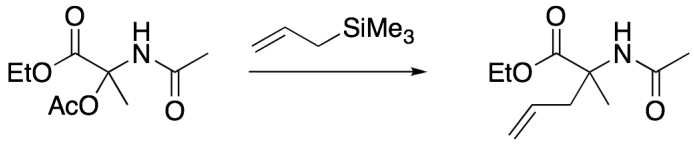
Other ways of circumnavigating this problem include the use of an electron withdrawing substituent such as a tosyl or acyl group on the imine or iminium ion. Weinreb used $FeCl_3$ to active the aminal **108** to give tosyl iminium **109**, which cyclized to give the core structure of Sarain A **110** as shown in Scheme 107.[65]



Scheme 107. Formation of core structure of Sarain A.

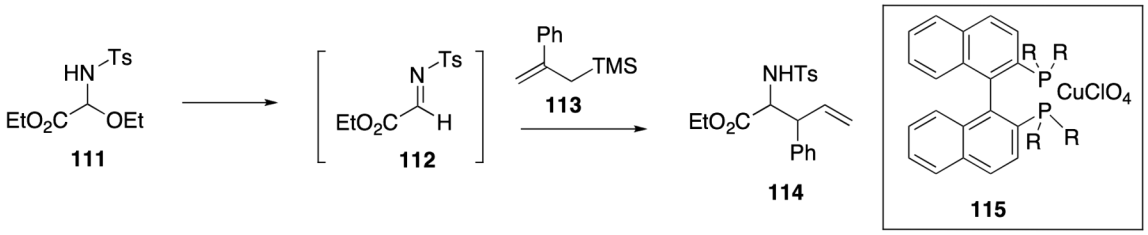
Use of the acyl group to activate the iminium ion to achieve addition of the allylsilane is more common. One example of this can be found in work by Speckamp, in

which an iminium ion was generated by the addition of TMSOTf to an acyl amide. The addition of several allylsilane derivatives was achieved (Scheme 108).[66] This strategy was used to generate a number of unnatural amino acids.



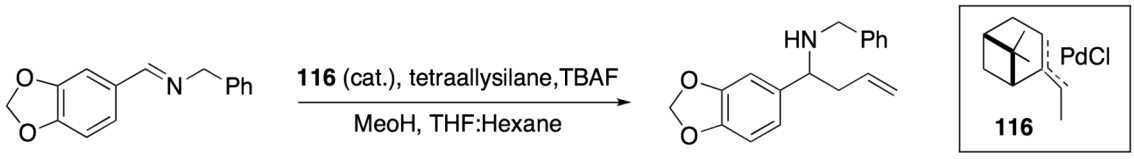
Scheme 108. Addition of allyltrimethylsilane to form unnatural amino acids.

In 1999, Lectka published an allylation reaction where **111** was subjected to elimination of the alcohol to give imine **112**, which underwent enantioselective addition of allylsilane **113** to afford amino acid derivative **114** (Scheme 109).[67] This reaction was catalyzed by the chiral copper catalyst **115.**



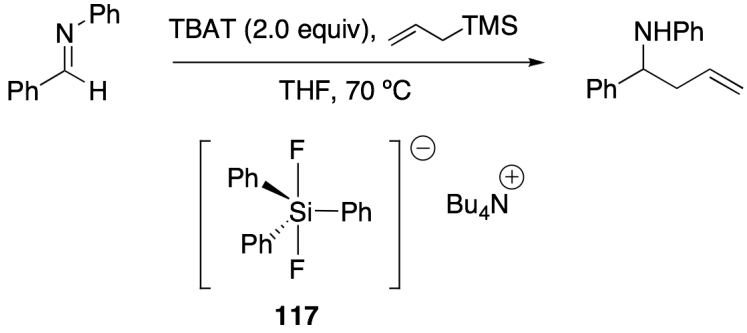
Scheme 109. Enantioselective addition of allylsilane 113 to amino acid derivative 114 catalyzed by chiral copper catalyst 115.

In 2004, Yamamoto published the allylation of simple amines without an electron withdrawing drawing group using tetraallylsilane, a rare feat.[68] The reaction (Scheme 110) was catalyzed by palladium complex **116** and gave yields of up to 96%. It should however be noted that the allyl imines contained no α-hydrogens.



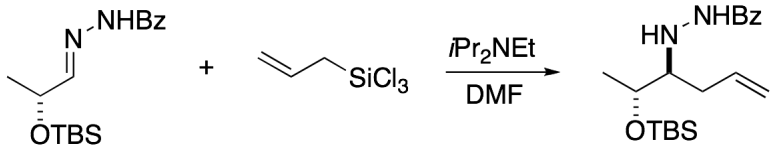
Scheme 110. Allylation of simple imines by palladium complex **116**.

Addition of allyltrimethylsilane to an imine without electron withdrawing groups was also accomplished in work by DeShong (Scheme 111)[69] using tetrabutylammonium triphenyldifluorosilicate **117** as a fluoride source to cause elimination of the silicon group, effectively creating an allyl anion equivalent. Again, it should be noted that no examples of this reaction contained imines with an α-hydrogen.



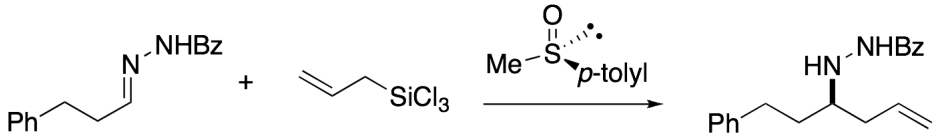
Scheme 111. Addition of allyltrimethylsilane to an imine promoted by TBAT.

The third way around the tautomerization problem is through the use of a hydrazone. Kobayashi was one of the first to utilize this solution (Scheme 112).[70] In Kobayashi's work, allyltrichlorosilane was added efficiently to benzoylhydrazones in the presence of DMF. This reaction is quite notable because crotylsilanes could be used as well as hydrazones bearing an acidic α-proton.



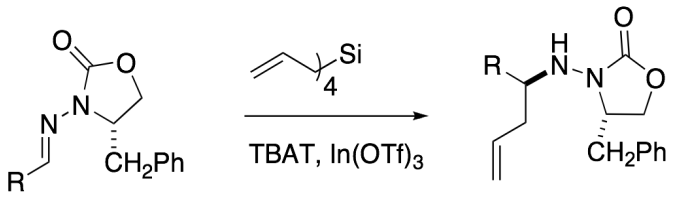
Scheme 112. Allylation of benzoylhydrazone by allyltrichlorosilane.

In 2003, Kobayashi reported an asymmetric version of this reaction, using chiral sulfoxides as neutral coordinate-organocatalysts for this reaction (Scheme 113).[71] Once again crotylsilanes could be used for the reaction, with ees up to 93%.



Scheme 113. Asymmetic allylation of benzoylhydrazone by allyltrichlorosilane mediated by a chiral sulfoxide.

Two other asymmetric versions of this reaction have been put forth by Friestad and Leighton. Friestad used chiral hydrazone **118** and achieved impressive entantioselectivity though the use of $In(OTf)_3$ as a Lewis acid catalyst and fluoride to activate the allylsilane (Scheme 114)[72].

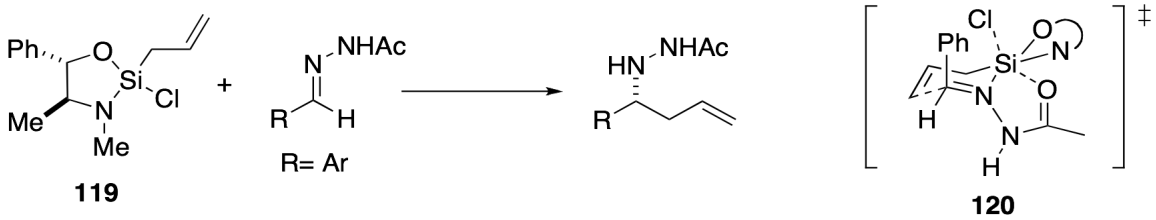


118

R= alkyl or Ar

Scheme 114. . $In(OTf)_3$ as a Lewis acid to promote the allylation of chiral hydrazones.

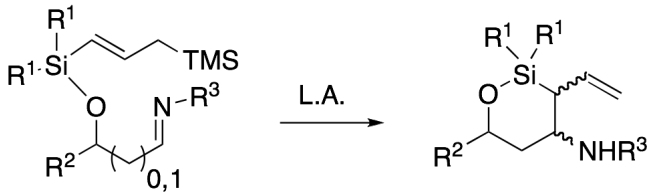
The work by Leighton uses a different approach whereby the hydrazone is achiral and the silane, which is delivering the allyl group, is chiral **119** (Scheme 115).[73] Activation of the hydrazone was accomplished though the Lewis acidic nature of the strained silicon, which is in a five membered ring and is flanked by two electron withdrawing groups. The transition state for this reaction (**120)** involves a hexacoordinate silicate species.



Scheme 115. Use of strained silacycle to effect allylation of hydrazones.

Development of Silicon-Tethered Allylating Agents

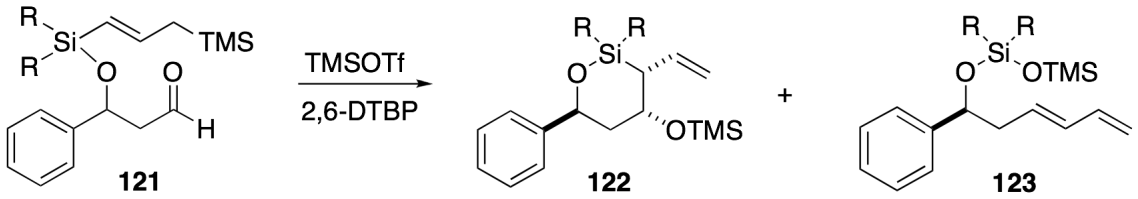
Tethering the allylsilane to the imine should increase the likelihood of allyl transfer and reduce the likelihood of enamine formation (Scheme 110). This transformation would provide a new route to 1,3-amino alcohols upon Tamao oxidation of the silacycle. The formation of 1,2-amino alcohols by using a substrate with a carbon linker containing one less carbon was also envisioned (Scheme 116).



R_1=Ph, ^{i}Pr
R_2=Ph, Me, H
R_3=Bn, SOTolyl, NHAc

Scheme 116. Silicon tethered strategy for formation of 1,3-imino alcohols.

This strategy was inspired by Cox, who used the tethering system shown with compound **121** to successfully initiate cyclization by activation with TMSOTf in the presence of 2,6-di-*tert*-butylpyridine to give silacycle **122** (Scheme 117).[74] This cyclization gave good yields; however, one problem that was noted was the formation of diene **123**. Presumably formation of **123** was due to a cascade where the initial cyclization was followed by a second addition to the resultant allylsilane. This side reaction was suppressed by increasing the steric bulk of the silicon substituents present in the tether from dimethyl to diethyl groups.



Scheme 117. Silacycle formation achieved by Cox.

This work was further developed by Cox to include the allylation of carbohydrates for the formation of beta-substituted mannose derivatives (Scheme 112).[75] The side reaction that is shown in Scheme 118 was also observed with the diethylsilyl-

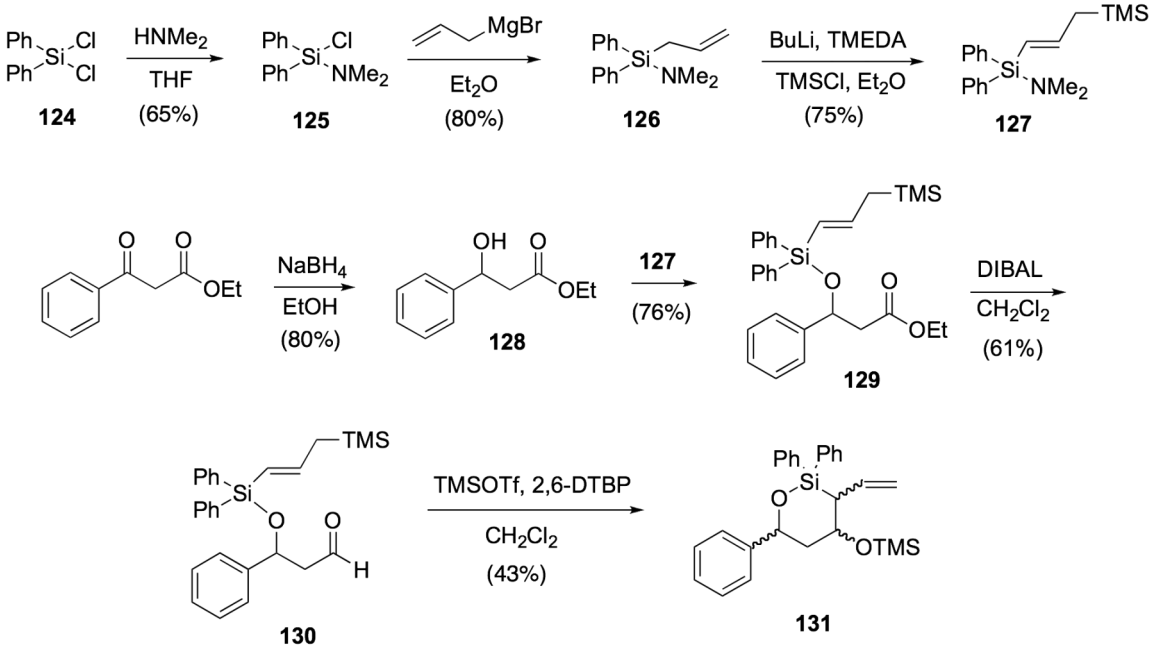
tethered carbohydrates, motivating Cox to switch to the bulkier diisopropylsilane linker. With the diisopropylsilane, diene formation was suppressed.

Scheme 118. Silicon tethered formation of beta-substituted mannose derivatives.

With Cox's observations in mind, the degree to which the silyl substituents influence the reactivity of the substrate was explored. The diphenylsilane should increase the steric hindrance to the tether and improve the cyclization. To test this hypothesis, diphenylsilane **130** was synthesized, and the cyclization of this compound was evaluated (Scheme 119).

Starting with dichlorodiphenylsilane **124**, one of the chlorides was displaced by dimethylamine to give chlorodimethylaminodiphenylsilane **125**. The chloride was displaced by an allyl group by refluxing **125** with allylmagnesium bromide to give allylsilane **126**. Lithiation with butyllithium in the presence of TMEDA followed by quenching with TMSCl gave the allylvinylsilane **127**. A neat mixture of alcohol **128** and **127** was warmed to 40 °C and stirred overnight to afford **129.** The resulting ester **129** was then reduced with DIBAL to give aldehyde **130**. Treatment with TMSOTf in the presence of 2,6-DTBP provided the desired silacycle **131**, albeit in low yield (Scheme 113). However, as in Cox's work, the product included an inseparable biproduct. This

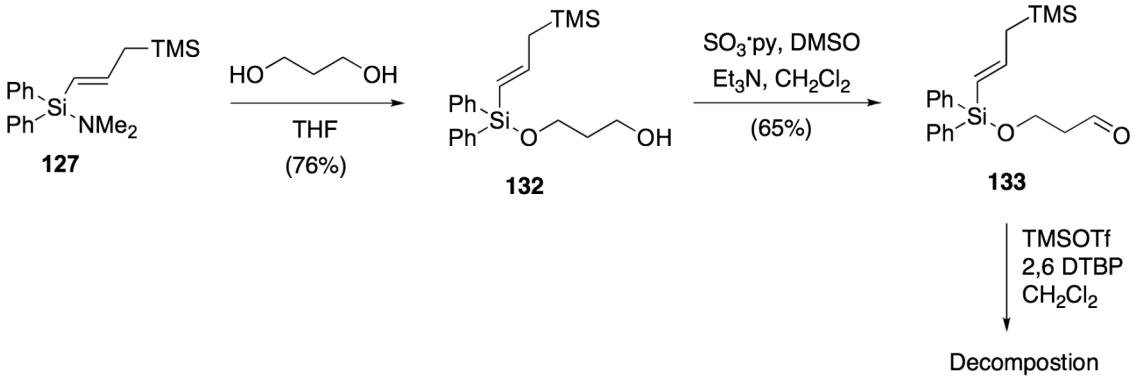
biproduct was assumed to be diene **131a**. At this point it was clear that the diphenylsilane tether was appropriate for cyclization. Stereochemical aspects of this reaction are discussed for the diisopropylsilane below (which could be isolated and characterized in pure form).



Scheme 119. Synthesis of Silacycle **131**.

Next, the importance of the phenyl group alpha to the siloxy position was investigated. Cox noted that cyclization was not possible with his substrates if there was only a methyl group at this position, suggesting that perhaps steric hindrance around the silyl group was necessary for this transformation. The new tether was formed by mixing the allylvinylsilane **127** with 1,3-propanediol to give alcohol **132** (Scheme 120). The alcohol was oxidized to the corresponding aldehyde using SO_3•py to afford aldehyde **133**. However, upon treatment with TMSOTf and 2,6-DTBP, decomposition of the

starting material was observed. This result suggested that the steric environment around silicon is vitally important for this reaction.



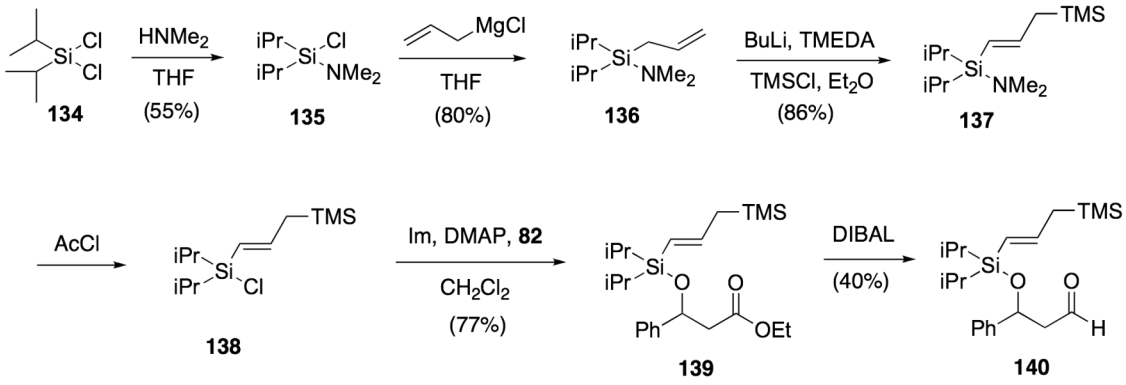
Scheme 120. Decomposition of **133** by TMSOTf.

These results and Cox's observation about diene formation indicate that the steric crowding around the silicon center is an important factor for cyclization. Although the initial goal was to achieve a reaction with no substituent alpha to the siloxy group, the results discussed above indicate that beta-elimination may prevent generalization of this reaction.

The diisopropylsilane was explored as a substrate that might bear sufficient bulk to cyclize readily, even when a less electron withdrawing system such as an imine was present. Construction of the tether system is shown in Scheme 121 and was successful as before with two notable changes compared to synthesis of compound **129**. Addition of the allyl group to chlorodiisopropylaminosilane could only be accomplished with allyl magnesium chloride in THF. Allylmagnesium bromide in Et_2O induced only minor addition of the allyl group. Since allylmagnesium bromide in Et_2O exists as an aggregate

while the corresponding chloride in THF is thought to be a monomer, the sterically hindered silane was apparently added more readily to the monomer.[76]

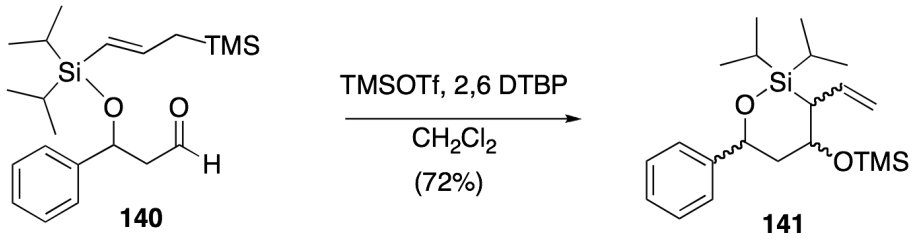
The second alteration was that the aminoallylsilane had to be further activated to allow for the addition of the alcohol. To accomplish this, aminoallylsilane **137** was treated with AcCl for 24 hours in CH_2Cl_2, to from the corresponding chloride. The alcohol was introduced with the assistance of imidazole and DMAP. The reduction of ester **139** to aldehyde **140** occurred without incident, albeit in low yield.



Scheme 121. Synthesis of aldehyde **140**.

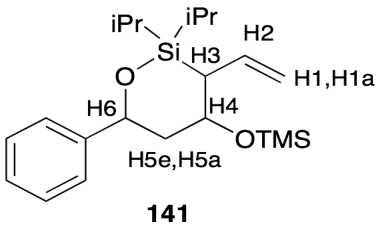
Exposure of aldehyde **140** to TMSOTf in the presence of 2,6-DTBP produced the desired silacycle **141** (Scheme 122). The stereochemical outcome of this reaction was determined from NoE studies. Irradiation of proton H4 (labels shown below) at 4.2 ppm induced the 7.4% NoE effect in proton H3 at 2.1 ppm. This indicates that protons H4 and H3 are located on the same side of the ring. A 4.7% NoE effect between H4 and H5e, which is the equatorial hydrogen of the methylene group, was also observed. The stereochemistry of the H6 proton was determined by its coupling constant with H5a, J = 10.5 Hz, which is strongly indicative of an axial orientation for the H6 proton. The

stereochemistry of the molecule is shown on 141 below. The stereochemistry of **131** could not be determined because of contamination by **131a**.

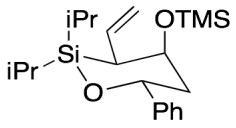


140 **141**

Scheme 122. Formation of silacycle **141**.

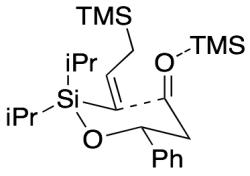


141



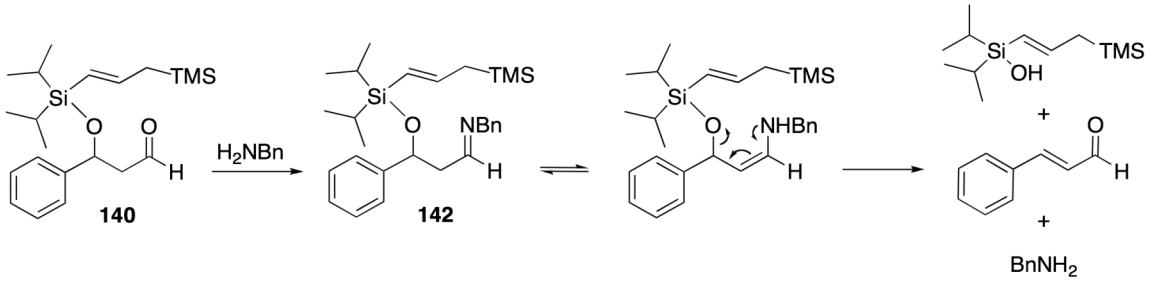
141

The orientation of the molecule suggests that this reaction may proceed through the chair transition state shown below. While this transition state does place the aldehyde in an axial position, this the orbital overlap from this conformer is better for bond formation than the orbital overlap would be if the aldehyde were placed equatorially.



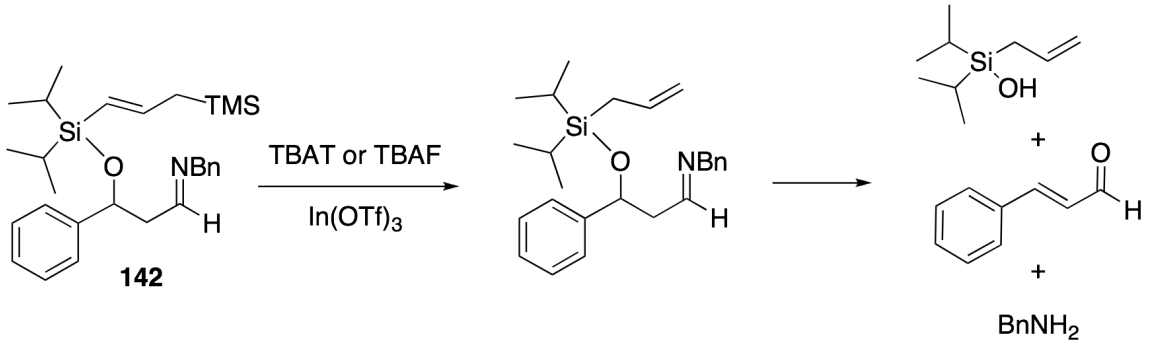
141

After formation of **141**, the formation of the benzyl imine **142** was evaluated with the goal of increasing the steric hindrance of the silicon group to induce the desired transformation. However, the only discernable reaction was beta elimination, which gave the silanol, benzyl imine and cinnamaldehyde (Scheme 123).



Scheme 123. β-Elimination of benzyl imine **142**.

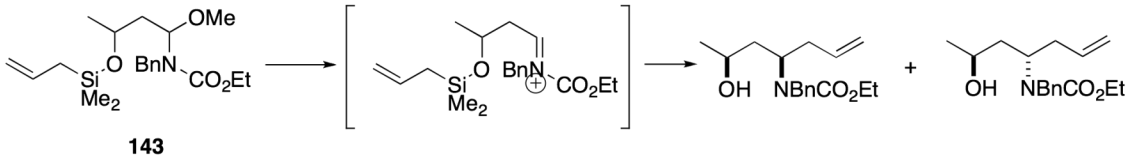
Initiation of the cyclization from the benzyl imine **142** by treatment with $In(OTf)_3$ in presence of both TBAF and TBAT was also explored (*vies a vie* and Friestad).[72] These experiments only led to the formation of the allylsilane, presumably by protodesilation followed by beta elimination (Scheme 124).



Scheme 124. Desilation and **117** β-elimination of benzyl imine **142** by TBAT and $In(OTf)_3$.

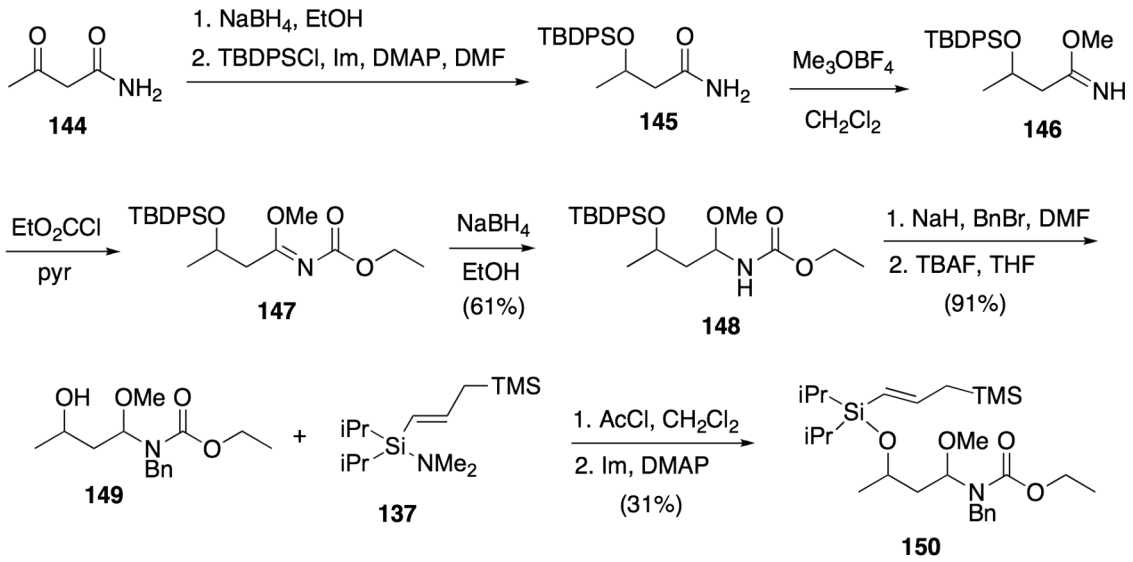
Based on these results, and the knowledge from the ene cyclization attempts (see below), beta elimination is clearly a formidable problem for this methodology. Since Hioki used allylsilane **143** to successfully transfer an allyl group to the acyl iminium ion created by α- degradation of an aminal (Scheme 125),[77] a more electrophilic nitrogen

species was envisioned as one possible way to induce the system to favor cyclization over beta elimination.



Scheme 125. Silicon tethered allylation performed by Hioki.

Acetoacetamide **144** reduced with $NaBH_4$ and protected as the TBDPS silyl ether 1**45**. The amide was then treated with Me_3OBF_4 to give the imidate **146**, reacted with ethyl chloroforomate to give the acyl imidate **147**, and reduced with $NaBH_4$ to give the aminal **148**. Benzylation followed by deprotection gave alcohol **149**. The allylvinylsilane **137** was added to **149** after activation with AcCl, and the reaction mixture was stirred in the presence of DMAP and imidazole to provide **150** (Scheme 126).



Scheme 126. Synthesis of aminal **150**.

With **150** in hand, screening of Lewis acids for cyclization could begin. The Lewis acids which were initially examined were BF•Et_2O, $TiCl_4$, $SnCl_4$, TMSOTf, and $In(OTf)_3$.The first four are the Lewis acids that Hioki reported for allylation reactions, and $In(OTf)_3$ was screened based on Friestad's work with acyl hydrazones.

All of the reactions were conducted in deuterated solvent so that they could be followed by ^1H NMR. TMSOTf was found only to promote desilation. This was not entirely surprising since TfOH is a known contaminant that often plagues this Lewis acid. BF•Et_2O, $TiCl_4$ and $In(OTf)_3$ appeared to promote changes in the aromatic region, suggesting that perhaps some type of Friedel-Crafts reaction was occurring. Only $SnCl_4$ appeared to afford more significant transformations. After optimization it was found that the desired silacycle **151** could be formed in 67% yield (Scheme 127).

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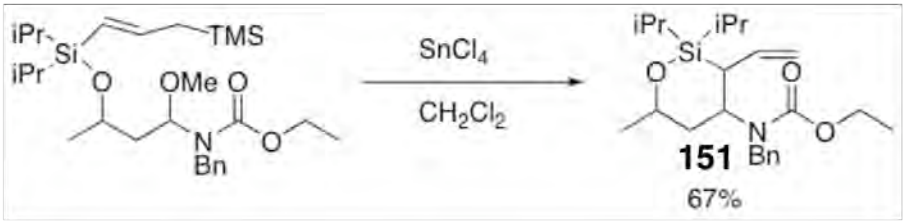
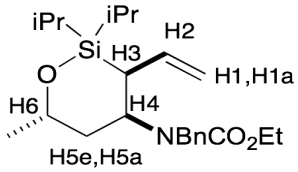


Scheme 127. Formation of silacycle **151**.

The stereochemical outcome of the reaction was similar to that of compound **141**. A 7.0% NoE effect was observed between protons H3 and H4 of **151** (see labels below), indicating that the protons were on the same side of the ring, as was the case for **141**. The coupling constant between H6 and H5a is 10.0 Hz, which suggests that these proton are

in the axial position, placing the methyl group equatorial and corresponding to the structure that was previously determined for **141**.



151

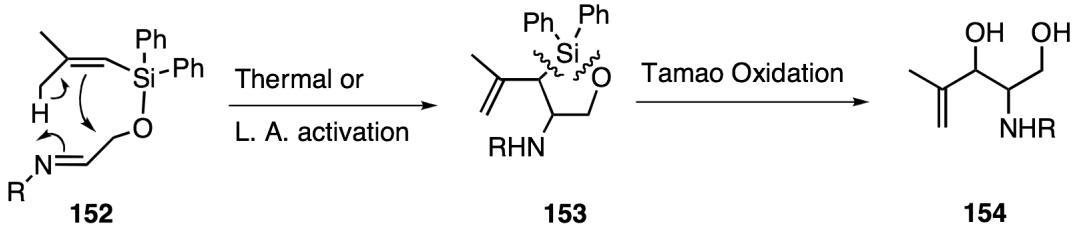
Although the desired transformation occurred, the problems inherent in this approach are numerous. First, the route to rearrangement precursors is now quite circuitous, and the nitrogen quadrant of this molecule is difficult and tedious to make. Extensive experimentation would be necessary to obtain variants of **150**. Second, dichlorodiisopropylsilane is expensive.

In summary, silicon tethers can be effective used as allylating reagents to add to nitrogen sources. Ultimately, this chemistry could be used to synthesize vicinal amino alcohols. However, the nitrogen species must be very electrophilic and the reported substrates were difficult to make. The problems that are faced by most additions of nucleophiles to imines, namely tautomerization to the enamine and further reaction from there, still apply even for the intramolecular variant described here.

Development of a Silicon-Tethered Ene Reaction

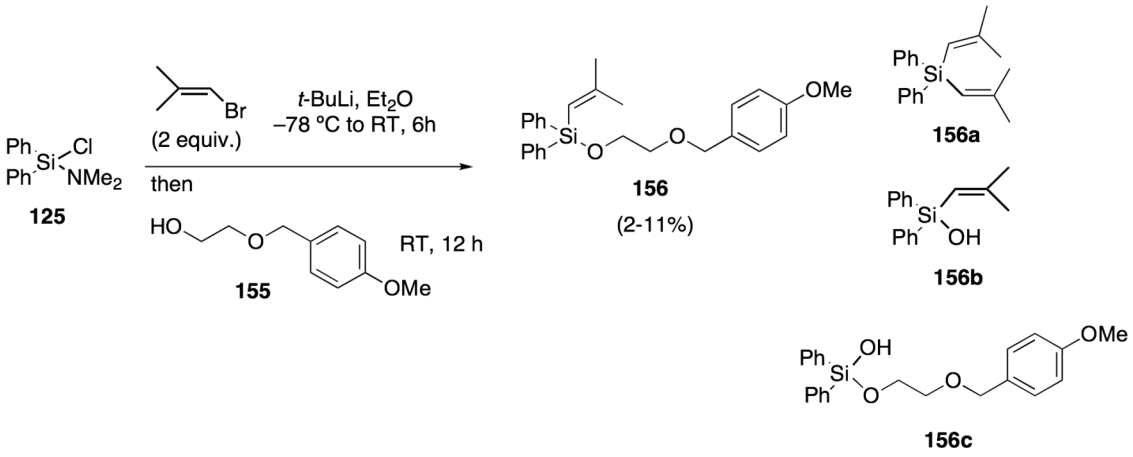
Development of an ene reaction that could afford amino alcohol precursors was also explored. The envisioned synthesis utilizes a silicon tether to bind an alkene bearing allylic hydrogens to an α-hydroxyimine as shown in compound **152** that, upon either thermal or Lewis acid activation, would afford the desired oxasilacycle **153** (Scheme

128). Tamao oxidation of **153** would furnish the desired 1,2-amino alcohol **154**. This methodology benefits from the inherent flexibility of the tethering system. Both the ene portion and the α-hydroxyimine portion of the tether can be modified independently to provide elaborated amino alcohols.



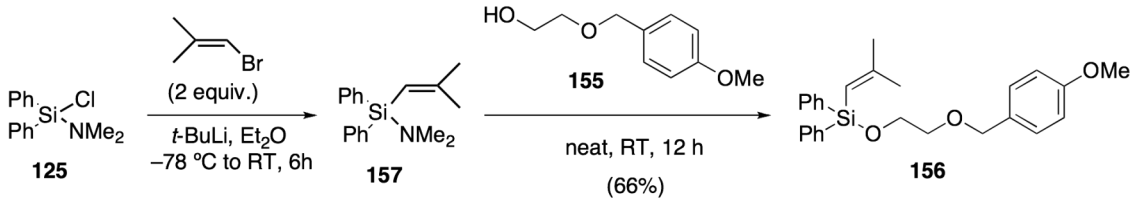
Scheme 128. Ene strategy for formation of 1,2-amino alcohols.

Based on precedent by Stork using the dimethylsilane tether, tether formation was first explored in a one-pot reaction (Scheme 129).[78] Although small amounts of the desired product **156** were formed (2-11%), the main products were bis-isopropenylsilane **156a**, silanol **156b**, and silanol **156c**.



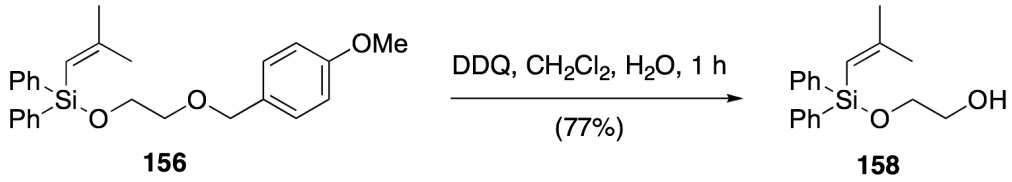
Scheme 129. Formation of **156** and bi-products.

Reaction of dimethylaminodiphenylchlorosilane with 1-lithio-2-methylpropene allowed for isolation of product **157**. Subsequent addition of the neat alcohol **155** provided **156** in good yield (66%) (Scheme 130).



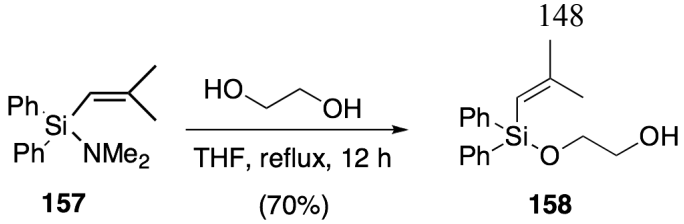
Scheme 130. Formation of **156** in a higher yielding reaction.

Removal of the *p*-methoxybenzyl protecting group was accomplished by treatment with DDQ (Scheme 131). Separation of **158** from the *p*-methoxybenzaldehyde byproduct by column chromatography followed by Kugelrohr distillation provided the alcohol in good yield on small scale.



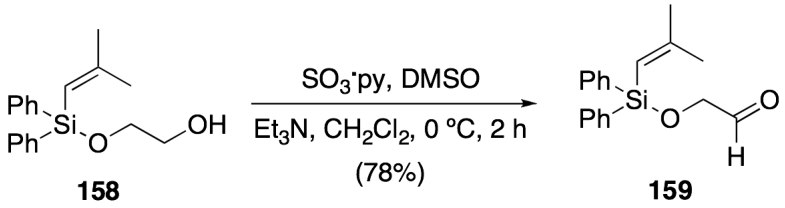
Scheme 131. Oxidative removal of PMB protecting group from **156**.

In an improved synthesis of **158**, the intermediate **157** was synthesized as shown in Scheme 122 and added to a 1:1 mixture of THF and ethylene glycol and refluxed for 12 hours to provide **158** in 70% yield after purification (Scheme 132). This new method was far superior, as the yield of **158** increased and the protection/deprotection steps were eliminated.



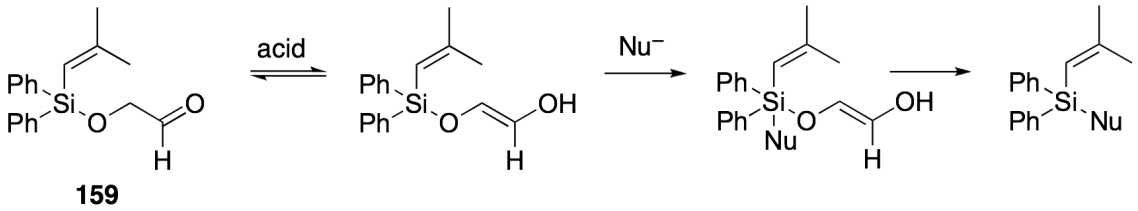
Scheme 132. Direct route to **158**.

Oxidation of **158** using TPAP/NMO, $Pd(OAc)_2/O_2$, and Swern conditions were inefficient. Fortunately, SO_3-pyridine, DMSO, and Et_3N led to complete consumption of the alcohol, and the resultant aldehyde **159** was isolated in good yield (78%) after column chromatography (Scheme 133).[79]



Scheme 133. Oxidation of **158** to aldehyde **159** using SO_3•py.

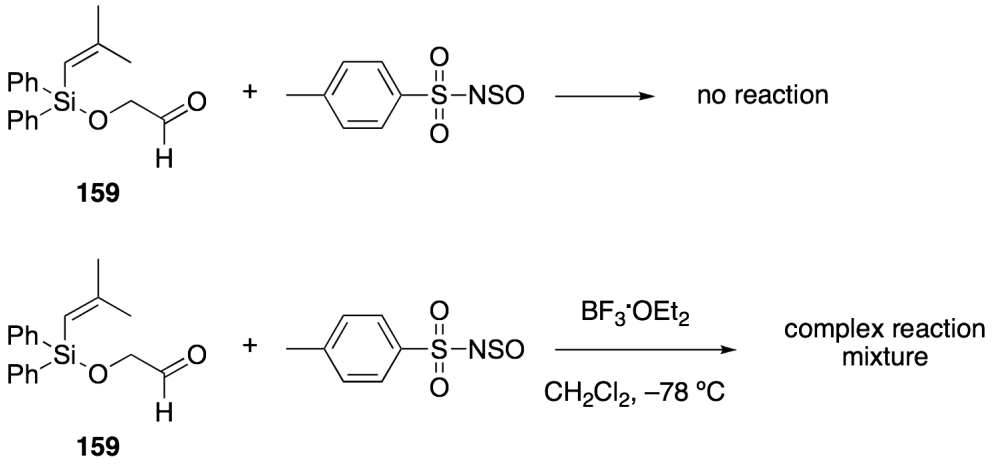
Using TPAP/NMO and Swern oxidation conditions, cleavage of the silicon oxygen bond was the primary outcome. This cleavage occurred readily with scaffolds that were developed to study the ene reaction: exposure of these compounds to acidic conditions caused cleavage of the silicon oxygen bond. Tautomerization of the aldehyde to the enol presumably occurs followed by nucleophilic cleavage of the silicon oxygen bond (Scheme 134).



159

Scheme 134. Decomposition of **159** by acid.

Although Weinreb reports the formation of tosyl imines via a [2+2] addition at room temperature using sulfinyl–tosyl imine,[80] no change in substrate was detected by NMR when these reaction conditions were employed with this substrate. *In situ* imine formation with subsequent cyclization using BF_3•Et_2O was briefly explored,[81] but even at low temperatures (-78 ºC), a complex mixture of products was formed (Scheme 135).



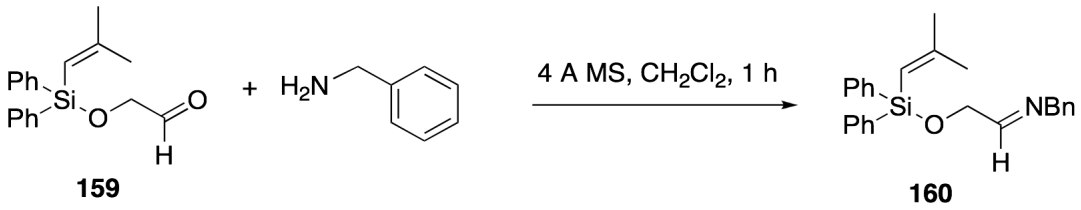
159

159

Scheme 135. Failed formation of tosyl imine.

Formation of the benzyl imine derivative **160** was significantly more straightforward. Addition of one equivalent of benzyl amine in CH_2Cl_2 in the presence of molecular sieves afforded product **160** (Scheme 136), as indicated by both NMR and

direct probe mass spectroscopic analysis. Attempts to isolate the imine, however, unsurprisingly led to decomposition into a mixture consisting of the silanol **156b,** benzyl amine, a small amount of aldehyde, and a polar, polymeric material that was not identified.



Scheme 136. Formation of benzyl imine **160**.

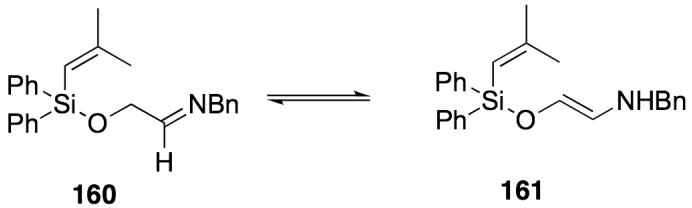
Formation of **160** was also evaluated in other deuterated solvents to test their viability as solvents for this reaction. The benzyl amine was formed in benzene and toluene, as well as in methylene chloride.

In situ formation of **160** followed by treatment with various Lewis acids to effect the cyclization was evaluated. BF_3•OEt_2, TMSOTf, $AlMe_2Cl$, $AlMeCl_2$ $ZnBr_2$, $Yb(OTf)_3$, 5M $LiClO_4$ in ether,[82] and thermal conditions (toluene, sealed tube, 150° C, 6 hr) resulted in no reaction. Treatment of the imine with the $TiCl_4$ and $SnCl_4$ led to very complex reaction mixtures. While not all compounds were identified, most were derived from cleavage of the silicon oxygen bond. A list of the conditions used for the benzyl imine cyclization can be found in Table 1.

Table 1. List of conditions evaluated for cyclization of **160**.

Lewis Acid	Equivalents	Solvent	Time	Temp	Product/outcome
BF_3OEt_2	1	CH_2Cl_2	12 h	RT	Si-O cleavage
$SnCl_4$	1	CH_2Cl_2	12h	RT	complex mixture
$SnCl_4$	0.1	CH_2Cl_2	4h	RT	complex mixture
$SnCl_4$	2	CH_2Cl_2	12h	-78 °C	complex mixture
$SnCl_4$	10	CH_2Cl_2	2h	-78 °C	complex mixture
$SnCl_4$	1	Benzene	12h	RT	complex mixture
$SnCl_4$	1	Toluene	12h	-78 °C	complex mixture
$SnCl_4$	1	CH_3NO_2	3h	0 °C	complex mixture
TMSOTf	1	Benzene	6h	RT	complex mixture
TMSOTf	1	TMSOTf	12h	-78 °C	Si-O cleavage
$Yb(OTf)_3$	1	Benzene	12h	RT	Si-O cleavage
$AlMe_2Cl$	1	CH_2Cl_2	12h	-78 °C to RT	Si-O cleavage
$AlMeCl_2$	1	CH_2Cl_2	12h	-78 °C to RT	Si-O cleavage
5 M $LiCO_4$ in Ether			72h	RT	Si-O cleavage
Thermal		Toluene	6h	150 °C	Si-O cleavage
$ZnBr_2$	1	CH_2Cl_2	8h	RT	Si-O cleavage
$TiCl_4$	1	CH_2Cl_2	12h	-78 °C to RT	complex mixture

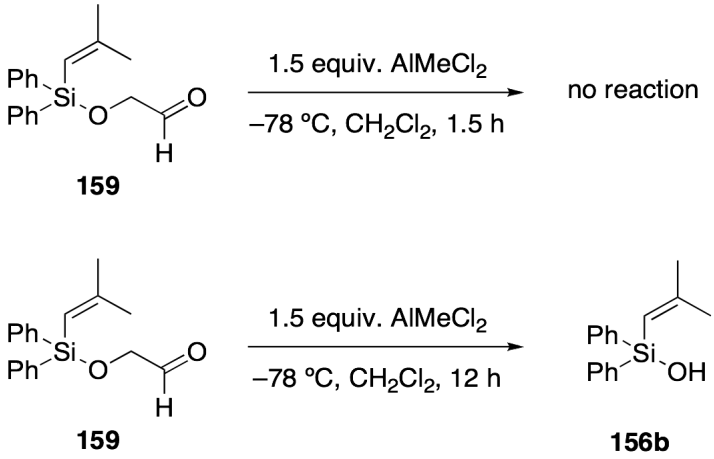
Both Nakagawa and Leighton reported that benzyl imines often fail to react in Lewis acid catalyzed ene reactions and allylation reactions.[83,84] While the reason for this is not entirely clear, tautomerization to the enamine **161** may be a significant problem (Scheme 137). With this in mind, an imine with a less electron donating substituent than a benzyl group was synthesized and studied as discussed below.



160 **161**

Scheme 137. Tautomerization of **160** to enamine **161**.

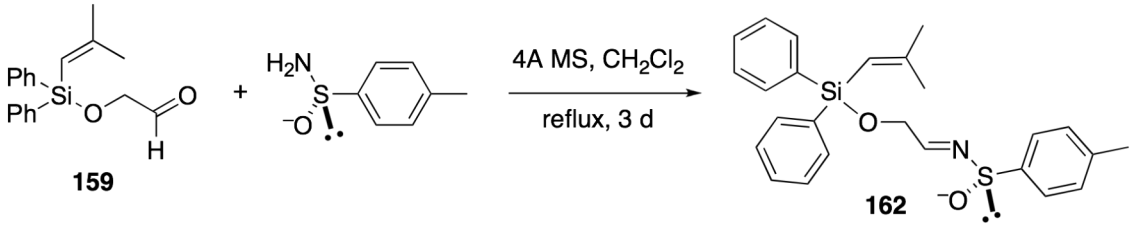
Cyclization of the aldehyde **159** was also studied to gain a better understanding of the substrate. Subjecting **159** to the conditions published by Robertson (1.5 equiv. $AlCl_2Me$ for 1.5 h) produced no change in the starting material.[85] However, treatment of the aldehyde with the same conditions for an extended period of time led to cleavage of the silicon oxygen bond to produce silanol **156b.** Exposure of the aldehyde to 5M $LiClO_4$ in ether[82] for 3 hours produced no change in the aldehyde as well (Scheme 138).



Scheme 138. Reaction of aldehyde **159** with $AlMeCl_2$.

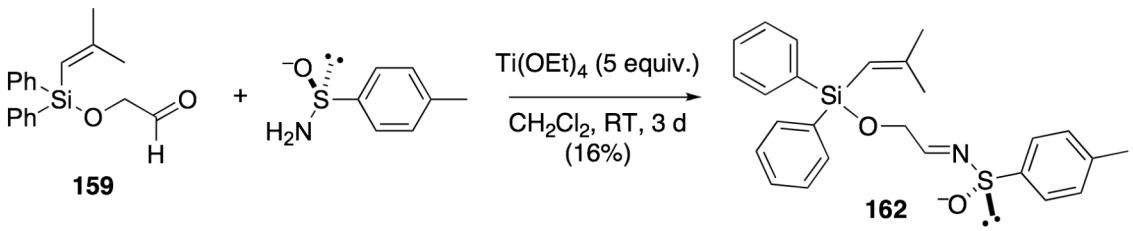
Two routes toward the synthesis of the Davis chiral sulfinimine were evaluated.[86] The first involved refluxing a mixture of the aldehyde and the sulfinyl tosyl amine and activated molecular sieves in a solution of dichloromethane for several days. TLC analysis of that reaction mixture indicated that degradation of the starting material into silanol **156b** became a significant problem at long reaction times. Purification by column chromatography yielded a mixture of imine **162** and aldehyde **159**. Kugelrohr distillation

that was intended to remove unreacted aldehyde from the reaction mixture led to decomposition of **162** at 70 °C (Scheme 139).



Scheme 139. Formation of sulfynyl imine **162** using molecular sieves.

Synthesis of **162** by treatment of **159** with 5 equivalents of $Ti(OEt)_4$ in CH_2Cl_2 at room temp, as per the Davis protocol for the synthesis of α-*tert*-butyldimethylsiloxy sulfinimines,[87] led to a poor yield (16%) of the desired product (Scheme 140). At this point, however, enough **162** was available to test the reactivity of this substrate. Initial investigations with 1 equivalent of $SnCl_4$ again led to a complex mixture of products. This mixture was similar to that formed by the benzyl imine under the same conditions. Again, it appeared that cleavage of the silicon oxygen bond was a dominant method of reaction.



Scheme 140. Formation of sulfynyl imine **162** by $Ti(OEt)_4$.

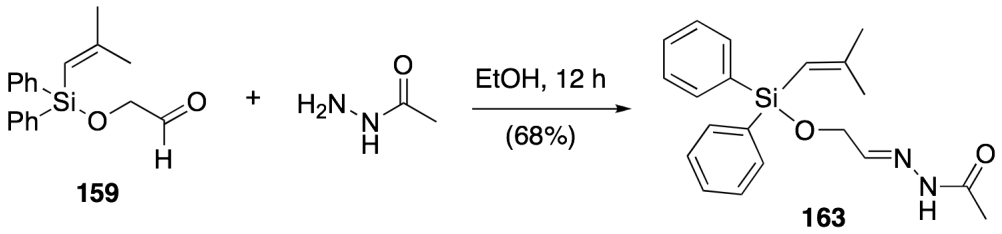
Subjection of **162** to conditions used by Saito in a similar reaction as well as to thermal conditions led a to complex mixture of products in which the sulfinyl portion of

the molecule had apparently undergone some type of rearrangement, while the vinylsilane and the tether portion remained intact. These two findings, coupled with the lengthy time needed to optimize the formation of this particular imine, led us to explore alternative options.

Table 2. List of conditions evaluated for cyclization of **162**.

Lewis Acid	Equivalents	Solvent	Time	Temp	Product/outcome
$SnCl_4$	1.0	CH_2Cl_2	3h	0 °C	complex mixture
$TMSCl/Et_3N$	1.5/2	CH_3CN	24h	0 °C to RT	complex mixture
5M $LiClO_4$ in Ether			76h	RT	no reaction
Thermal		Toluene	6h	150 °C	complex mixture
$Yb(OTf)_3$	1.0	CH_2Cl_2	12 h	RT	Si-O cleavage

Based on Leighton's reports of the addition of allyl silanes to acyl hydrazones, this imine derivative is less likely to undergo tautomerization problems than benzyl imine. Following the procedure by Leighton, acyl hydrazide and aldehyde **159** were combined in ethanol and stirred for 12 hours, resulting in 68% of the acylhydrazone **163** after column chromatography (Scheme 141).[73]



Scheme 141. Formation of acyl hydrazone **163**.

Preliminary results with the acyl hydrazone derivative **163** with several Lewis acids were not very promising. With the Lewis acids $TiCl_4$, $Yb(OTf)_3$, $SnBr_4$, and $AlMe_2Cl$, the dominant products were cleavage of the silicon oxygen bond or derivatives thereof.

Table 3. List of conditions evaluated for cyclization of **163.**

Lewis Acid	Equivalents	Solvent	Time	Temp	Product/outcome
$SnBr_4$/2,6-DTBP	1.0/1.2	CH_2Cl_2	4 h	-78 °C	no reaction
$SnBr_4$/2,6-DTBP	1.2	CH_2Cl_2	15 h	0 °C to RT	complex mixture/ Si-O cleavage
5M $LiClO_4$ in ether			24 h	RT	some Si-O cleavage
$TiCl_4$/2,6DTBP	1.0/1.2	CH_2Cl_2	3 h	-78 °C	complex mixture/ Si-O cleavage
$Yb(OTf)_3$	1.0	CH_2Cl_2	12 h	RT	Si-O cleavage

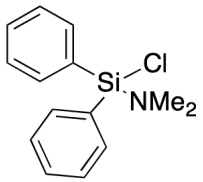
In conclusion, ene cyclization using the substrates reported here were unsuccessful for a number of reasons. First the silicon oxygen bond was not stable enough for the desired reaction to occur, primarily because of tautomerization of the imines to enamines. However, difficulties with ene cyclization were also encountered with substrate that should not have tautomerized as readily, including the sulfinyl imine and the acyl hydrazone. These results indicate that silicon rather than the imine carbon was actually the most electrophilic part of the molecule.

Summary

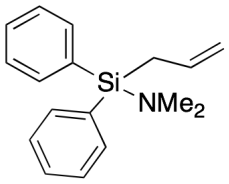
The development of a silicon tethered allyl transfer or ene reaction to create amino alcohols was met with a number of challenges. Cleavage of the silicon oxygen bond was often a problem, mainly because of tautomerization of the imine to the enamine. To counter this problem in the allylation reaction, a bis electrophilic nitrogen species was developed that eventually led to cyclization. However, the route to the requisite substrate was circuitous. Steric hindrance around the silicon center was also an important factor in inducing cyclization to occur.

Ene cyclization reactions were met with the same hurdles that plagued the allylation chemistry (tautomerization, followed by silicon oxygen bond cleavage). In this series of reactions, none of the desired amino alcohol precursors were obtained.

The substrates described in this chapter did not have the correct electronics for the desired allylation and ene reactions to take place readily. However some guiding principles were elucidated: steric crowding around the silicon center is important, as is a very electrophilic iminium species.

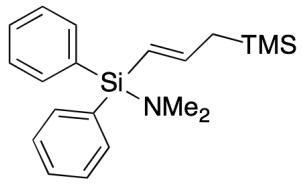


Cholorodimethylaminodiphenylsilane (125). Following the procedure by Washburne,[88] 20 mL of anhydrous ether was added to a flame dried flask cooled under a stream of argon, and cooled to -50° C (temperature monitored internally). The ether was charged with 2 mL (9.4 mmol) of dichlorodiphenylsilane. Dimethylamine (2 M in THF, 10 mL, 10 mmol, 2 equiv.) was added drop-wise by syringe, keeping the temperature below –46° C. Once the addition was complete the white precipitate was filtered off, and the solvent was removed by distillation. Kugelrohr distillation provided a clear oil, which was noted to smoke upon exposure to air (1.55 g, 65% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (4H, s), 7.53 (6H, s) 2.82 (6H, s). Characterization data was in agreement with published data.[88]



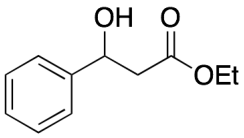
Allyldimethyldiphenylsilane (126). Chlorodimethylaminosilane (0.31 g, 1.22 mmol) was added to 6 mL of allylmagnesium bromide (1M in THF, 6 mL, 6.1 mmol,) and heated overnight. The THF was removed *in vacuo*, and the resulting slurry was dissolved in hexane and filtered though celite and subjected to Kugelrohr distillation (150 °C, 3mm) to produce 0.26 g of a colorless oil. (80% yield). IR (Neat) cm^{-1}: 3078 (C-H),

1957 (N-Me) 1601 (C=C Ar). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69-7.60 (4H, m) 7.42 (6H, s), 5.99-5.87 (1H, m), 5.06-4.94 (2H, m), 2.66 (6H, s,), 2.08 (2H, d, J= 8.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.3, 135.1, 130.1, 127.8, 125.1, 114.8, 39.1, 20.1.

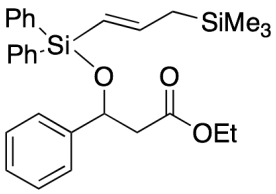


1-trimethylsilyl-2-en-dimethylaminodiphenylsilane (127). A flask was charged with 10 mL of ether and to this was added allyldimethylaminosilane (0.25 g, 0.95 mmol), TMEDA (0.14 mL, 0.95 mmol, 1 equiv.) and n-butyllithium (2.5 M in hexane 0.42 mL, 1.0 mmol, 1.1 equiv.). The reaction was allowed to stir for 3 h. TMSCl (0.12 mL, 0.9 equiv.) was added, the reaction was stirred 6 h. Ether was removed via rotary evaporator, and the mixture was dissolved in hexane and filtered through celite to provide yellowish oil which was then subjected to Kugelrohr distillation (170 °C, 3mm) to provide 0.24 g of a yellow oil in approximately 80% purity (75 % yield). IR (Neat) cm^{-1}: 2954 (C-H), 1759 (N-Me) 1600 (C=C Ar), 1427. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (4H, s), 7.34 (6H, s), 6.15-6.09 (1H, m), 5.76 (1H, t, *J*= 6.8 Hz), 2.25 (6H, s), 1.75 (2H, d, *J*=6.8 Hz) 0.01 (9H s).

159

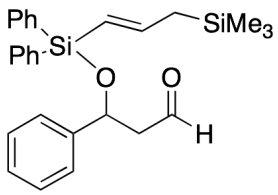


4-hydroxyethylbenzoacetate (128). Benzoyl acetate (0. 50 g, 2.6 mmol) was dissolved in 26 mL of ethanol. To the solution was added $NaBH_4$ (0.10 g, 2.8 mmol 1.1 equiv.) and allowed to stir for 1 h. At the end of this period 10 mL of saturated sodium bicarbonate was added and the ethanol was removed via rotary evaporator. The mixture was dissolved in EtOAc (100 mL) and washed with water (3 x 50 mL). The organic layer was brought to dryness and the resulting mixture was subjected to flash chromatography (8:2 hexane/EtOAc) to give 0.42 g of a yellowish oil (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.21, (5 H, m), 5.05 (1H, d, *J*= 7.3 Hz), 4.08 (2H, q, *J*= 7.1 Hz), 3.77 (1H, s), 2.71-2.67 (1H, m), 2.61-2.58 (1H, m), 1.18 (3H, t, *J*= 7.1 Hz). Characterization data was in agreement with published data.[74]



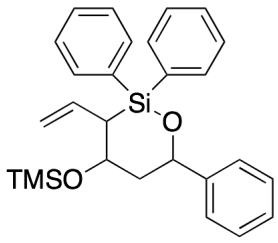
8-trimethylsilyl-5,5-diphenyl-5-silyl-3-phenyl-4-oxy-6-oct-en-ethyl-oate (129). 1-trimethylsilyl-2-en-dimethylaminodiphenylsilane (0.26 g, 0.75 mmol) was mixed with alcohol **128** (0.15 g, 0.77 mmol) and the mixture was heated overnight at 40 °C. The mixture was subjected to column chromatography (8:2 hexane/EtOAc) to afford 0.27 g of a clear oil (76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59-7.23 (15H, m), 6.10 (1H, dt, *J*=18.5, 7.9 Hz), 5.60 (1H, d, *J*=18.5 Hz), 5.30 (1H, t, *J*= 5.1 Hz), 3.94 (2H t, *J*=7.1 Hz),

2.91 (1H, ABX J = 14.8, 5.1 Hz), 2.74 (1H, ABX, J= 14.8, 5.1 Hz), 1.65 (2H, d, *J*=7.9 Hz) 1.27 (3H, q, *J*=7.1 Hz) -0.05 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 151.6, 143.3, 142.7, 137.1, 135.2, 135.0, 134.6, 129.7, 127.5, 121.3, 72.8, 70.3, 60.9, 43.5, 29.1 -1.78. HRMS calc. for $C_{29}H_{36}O_3Si_2$ +Na=511.2095, found=511.2011.

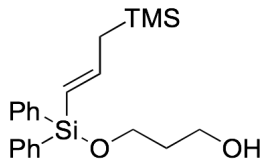


8-trimethylsilyl-5,5-diisphenyl-5-silyl-3-phenyl-4-oxy-6-octenal (130). The ester **129** (0.22 g, 0.45 mmol) was dissolved in CH_2Cl_2 (4.5 mL) and DIBAL (0.48 mL, 0.495 mmol) was added via syringe at -78° C. The reaction was stirred for 30 min, at which point a saturated solution of sodium tartrate was added and stirred for 1 h. The solution was diluted with CH_2Cl_2 (10 mL) and the reaction was washed twice with water. After the solvent was removed, the product was subjected to flash chromatography (5:5 pet ether/CH_2Cl_2) to give the aldehyde (0.122 g) as a clear oil in 61% yield, and approximately 80% purity. IR (Neat) cm^{-1}: 2943 (C-H), 2938, 1765 (C=O), 1600 (C=C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (1H, s), 7.51-7.23 (15H, m), 6.10 (1H, dt, *J*=18, 5.2 Hz), 5.59 (1H, d, *J*= 18 Hz), 5.29 (1H, m), 2.92 (1H, ABX J = 14.4, 5.0 Hz), 2.70 (1H, ABX = 14.4, 5.0 Hz), 1.65 (2H, d, *J*= 5.2 Hz), -0.01 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.7, 151.5, 135.0, 134.6, 129.8, 129.6, 128.2,127.5 126.1, 120.1, 70.8, 54.0, 17.9, 12.66, -1.88. HRMS calc. for $C_{27}H_{32}O_2Si_2$ +Na=467.1883, found=467.1963.

161

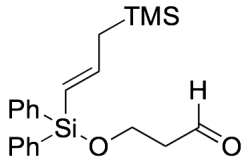


Silacycle (131). Aldehyde **130** (41 mg, 92 μmmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to -78 °C. To this solution was added 2,6-DTBP (38 μL, 203 μmol) , and TMSOTf, (20 μL, 92 μmol) and the reaction was stirred for 24 h. The reaction was diluted with CH_2Cl_2 and quenched with sat. aq. $NaHCO_3$ solution. The resulting oil was subjected to column chromatography (9:1, hexane/ ethyl acetate) to give 18 mg of the desired silacycle and a byproduct which is most likely diene **123**. Only NMR values for the silacycle are reported. (43% yield). IR (Neat) cm^{-1}: 3076, 2965, 2926, 2876, 2853, 1626. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.02 (15H, m), 6.04 (1H, app dt, *J*= 17.1, 10.2), 5.76 (1H, dt, *J*= 16.91, 10.1 Hz), 5.97 (1H d *J*=9.8 Hz), 5.48 (1H, d, *J*= 9.3 H), 4.99-4.84 (5H, m), 2.52-2.505 (1H, m), 2.14-2.09 (3H, m), 2.06-2.038 (3H, m), 1.86 (1H, s), 1.21 (3H, s), 0.81-0.71 (1H, s), 0.10 (1H, s), 0.00 (9H, m). LTC Electrospray: calc $C_{27}H_{32}O_2Si_2$ + Na+=467.1839, found= 467.1846.



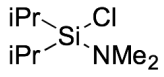
8-trimethylsilyl-5,5-diisphenyl-5-silyl-4-oxy-6-octenol (132). Allyl silane **127** (389 mg, 1.14 mmol) was added to a 1:1 mixture of THF (11 mL) and 1,3 propane diol (11 mL), and allowed to stir overnight. The THF was removed under reduced pressure and the

mixture was dissolved in EtOAc (25 mL) and washed with water (3 x 10 mL) dried over $MgSO_4$. The EtOAc was removed under reduced pressure. The resulting oil was subjected to column chromatography (8:2 hexane/EtOAc) to give 322 mg of alcohol **132** (76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59-7.57 (4H, m), 7.40-7.20 (6H, m), 6.27 (1H, dt, *J*= 18.5, Hz), 5.73 (1H, d, *J*= 18.5 Hz), 3.19 (2H, t, *J*= 5.7 Hz), 3.79 (2H, d, *J*= 5.6 Hz), 2.21 (1H, bs), 1.83-1.74 (4H, m), 0.01 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.5, 135.2, 134.9, 129.2 127.85, 120.54, 62,59, 61.821, 34.35, 29.28, -1.83. HRMS calc. for $C_{21}H_{30}O_2Si_2$ +Na= 393.1677, found 393.1879.

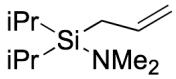


8-trimethylsilyl-5,5-diisphenyl-5-silyl-4-oxy-6-octenal (133). Alcohol **132** (73.4 mg, 0.248 mmol) was dissolved in 3 mL of a DMSO/CH_2Cl_2 (1:5) solution, and cooled to 0 ºC. To this solution was added SO_3•Py (78.9 mg, 0.496 mmol) and Et_3N (0.14 mL, 1.12 mmol).[33] After 2 h, CH_2Cl_2 (10 mL) was added, and the solution was washed with H_2O (3 x 5 mL). The organic phase was collected and dried over Na_2SO_4, and the solvent was removed at reduced pressure. Chromatography (8:2 hexane/EtOAc) afforded **133** as a clear oil. (47 mg, 65% yield). Bp. 120 °C, 3 mm Hg. IR (Neat) cm^{-1}: 2943 (C-H), 2940, 1762 (C=O), 1627. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.80 (1H, s), 7.62-7.59 (4H, m), 7.40-7.39 (6H, m), 6.29 (1 H, dt, *J* = 18.5, 7.9 Hz), 5.73 (1H, d, *J*= 18.5 Hz), 4.12 (2H, t, *J*= 6.0 Hz), 2.66 (2H, t, *J*= 6.0 Hz), 1.80 (2H, d, *J*= 7.9 Hz), 0.001 (9H, s). ^{13}C NMR

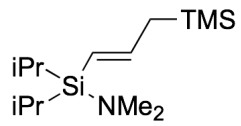
($CDCl_3$, 125 MHz) δ 201.8, 152.01, 134.96, 134.9, 129.90, 127.8, 120.47, 57.79, 46.42, 29.31, -1.83. HRMS calc. for $C_{21}H_{28}O_2Si_2$ +Na= 391.1520, found 391.1868.



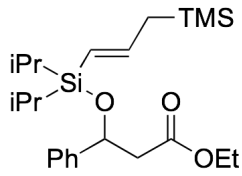
Chlorodimethylaminodiisopropylsilane (135). Ether (10 mL) was charged with dichlorodiisopropylsilane (1 mL, 5.5 mmol), and to this solution was added dimethyl amine (2 M in THF, 5.5 mL, 11.0 mmol). The reaction was allowed to stir for 30 min, and was filtered through an airless frit. The ether was removed and the resulting oil was subjected to Kugelrohr distillation give a clear oil (0.582 g, 55% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.53 (6H, s), 1.22 (2H, q, *J*=7.5 Hz), 1.07 (12H, d, *J*=7.5 Hz). Characterization data was in agreement with published data.[88]



Allyldiisopropylaminosilane (136). Chlorodimethylaminodiisopropylsilane (0.813 g, 4.2 mmol) was added directly to a solution of allylmagnesium chloride (2M in THF, 5.5 mL, 11 mmol) in a sealed tube, and the reaction was heated for 6 h. THF was removed via rotary evaporator, and the resulting solid was stirred with hexane. The hexane suspension was filtered though celite. After removal of the hexane, the resulting oil was subjected to Kugelrohr distillation to give 0.66 g of a clear oil (80% yield) . ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90-5.81 (2H, m), 4.90 (1H, d, *J*= 16.9 Hz), 4.80 (1H, d, *J*= 9.0 Hz), 2.51 (6H, s), 1.67 (2H, d, *J*= 9.0 Hz), 1.08-1.00 (14H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.6, 113.1, 39.3, 18.4, 17.9, 12.6.

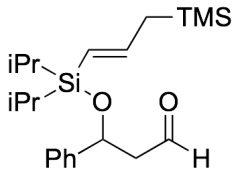


1-trimethylsilyl-2-en-dimethylaminodiisopropylsilane (137). To a solution of ether was added allyldimethylaminosilane (0.26 g, 1.3 mmol), TMEDA (0.20 g, 1.3 mmol), and n-butyl lithium (2.5 M in hexane, 0.74 mL, 1.4 mmol). The resulting solution was allowed to stir at room temperature for 3 h, and the reaction was quenched with TMSCl (0.15 mmol, 1.3 mmol), creating a blue solution. After 6 h, the ether was removed and the resulting mixture was filtered through celite. The hexane was removed via rotary evaporator, and the resulting yellowish oil was subjected to Kugelrohr distillation (120 °C, 3 mm Hg) to give 0.29 g of a clear oil (86% yield) in approximately 80% purity. IR (Neat) cm^{-1}: 2656 (C-H), 2372 (N-Me) 1600 (C=C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.07 (1H, dt, *J*= 18.5, 7.9 Hz), 5.21 (1H, d, *J*= 18.5 Hz), 2.52 (6H, s), 1.66 (2H, d, *J*= 7.9 Hz), 1.04-0.91 (12H, m), 0.01 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.8, 121.5, 57.5, 45.70, 39.42, 17,8, -1.97.



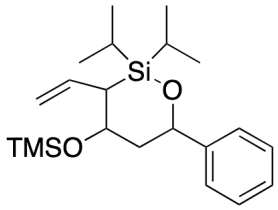
8-trimethylsilyl-5,5-diispropyll-5-silyl-3-phenyl-4-oxy-6-oct-en-ethyl-oate (139). Allylvinylsilane (0.28 g, 1.04 mmol) was dissolved in CH_2Cl_2 (10 mL) and to this was added AcCl (81 μL, 1.04 mmol), and the reaction was stirred for 24 h. To the solution were added alcohol **128** (0.201 g, 1.04 mmol), imidazole (0.155 g, 2.08 mmol) and

DMAP (0.126g, 1.04 mmol), and the reaction was stirred for 48 h. The solvent was removed via rotary evaporator, and the resulting mixture was dissolved in EtOAc (20 mL), washed twice with water (2 x 10 mL) and once with brine (10 mL), and dried over $MgSO_4$. The EtOAc was removed and the oil was subjected to flash chromatography (8:2 hexane/EtOAc) to provide 0.310 g of a clear oil (77% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.21 (5H, m), 6.10 (1H, dt, *J*= 18.5, 7.9 Hz), 5.24-5.19, (2H, m), 4.06 (2H, q, *J*= 3.7 Hz), 2.77 (1H, ABX, J = 14.6, 5.1 Hz), 2.55 (1H, ABX, J= 14.6, 5.1 Hz), 1.61 (2H d, *J*=7.9 Hz), 1.17 (7H, s), 0.84 (4H, s), 0.80 (3H,s), 0.01 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 147.9, 128.2, 127.4, 127.1, 126.1, 126.02, 113.2, 60.3, 46.0, 29.1, 12.7, 12.6, -1.89. HRMS calc. for $C_{23}H_{40}O_3Si_2$ +Na= 443.2408, found 443.2503.

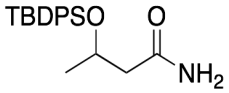


8-trimethylsilyl-5,5-diispropyll-5-silyl-3-phenyl-4-oxy-6-octenal (140). Ester **139** (0.30 g, 0.71 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled to -78° C. To this was added DIBAL (1 M solution in hexane, 0.781 mL, 78 mmol), and the reaction was stirred for 1 h. The reaction was quenched with a saturated solution of sodium potassium tartrate. The reaction was then diluted with CH_2Cl_2 (10 mL) and the organic layer was collected. The solvent was removed via rotary evaporator and the resulting oil was subjected to flash chromatography (6:4 pet. ether/ CH_2Cl_2) to provide 106 mg of aldehyde (40% yield). IR (Neat) cm^{-1}: 2943 (C-H), 2938, 1765 (C=O), 1607. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (1H, t, J = 2.6 Hz), 7.34-7.23 (5H, m), 6.11 (1H, dt, *J*= 18.5,

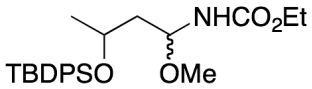
7.9 Hz), 5.26-5.20 (2H, m), 2.79 (1H, ABX, J =14.2, 5.1 Hz), 2.56 (1H, ABX, J =14.2, 5.1 Hz), 1.63 (2H, d, *J*= 7.9 Hz), 0.97 (7H, s), 0.88 (4H, s), 0.81 (3H, s), -0.24 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.6, 148.7, 135.1, 129.1, 128.7, 127.5, 126.1, 120.1, 70.8, 54.0, 17.9, 12.66, -1.88. HRMS calc. for $C_{21}H_{36}O_2Si_2$ +Na= 399.2146, found=399.2391.



Silacycle (141). The aldehyde **140** (88 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2.3 mL) and cooled to -78 °C. To this solution was added 2,6-DTBP (0.63 mL, 0.32 mmol 1.2 equiv.) and TMSOTf (51 μL, 0.23mmol), and the reaction was allowed to stir for 24 h. The reaction was quenched with water (1 mL). The organic layer was removed and brought to dryness, and the resulting oil was subjected to column chromatography (9:1 hexane/EtOAc) to give 63.6 mg of the desired as a colorless oil (72% yield).. ^{1}H NMR ($CDCl_3$, 500 MHz, non-removable solvent impurities skew the integrations between 0.5 and 2.0 ppm) δ 7.34-7.18 (5H, m), 5.98 (1H, dt, *J*= 17.2, 10.2 Hz), 5.23 (1H, d, *J* = 10.2 Hz), 4.98-4.87 (2H, m), 4.23 (1H, s), 2.04 (1H, dd, J =10.3, 2.8 Hz), 1.85 (1H, dd, J = 10.3, 2.1 Hz), 1.21 (2H, m), 1.14 (1H, m), 1.14-0.80 (16H, m), 0.15 (6H, s), -8.9 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.0, 129.8, 126.3, 127.5, 125.4, 113.8, 73.4, 69.1, 43.1, 37.5, 17.9, 12.6, 0.10. Micro-TOF calc. for $C_{21}H_{36}O_2Si_2$ +Na= 399.2146, found=399.2261.

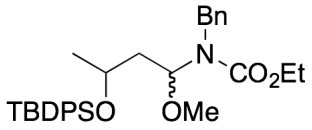


3-*tert*butyldiphenyloxybuterate (145). To a solution of acetoacetamide (10 g, 99 mmol) in MeOH (500 mL) was added $NaBH_4$ (3.6 g, 198 mmol, 2 equiv.), and the reaction was stirred at room temp for 2 h. The methanol was removed under reduced pressure, and the resulting solid was dissolved in CH_3CN and washed with brine. The CH_3CN was removed under reduced pressure and the solid was dissolved in DMF (200 mL). To this was added TBDPSCl (27.9 g, 108 mmol 1.1 equiv.) and imidazole (12.6 g, 217 mmol), which was allowed to stir for 12 h. The solution was diluted with EtOAc (200 mL) and washed with H_2O (2 x 100 mL) and once with brine (100 mL). The EtOAc was removed under reduced pressure, and the resulting oil was subjected to chromatography (4:6 hexane/EtOAc) to give a 16.1 g of a white solid (50% yield and approximately 85% purity, values for the major product are reported). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.64 (4H m), 7.45-7.23 (6H, m), 6.28 (1H, bs), 5.34 (1H, bs), 4.12 (1H, appt sex, J=7.8 Hz), 2.61 (1H, ABX, J=14.8, 4.9 Hz), 2.53 (1H, ABX, J = 14.8, 4.8 Hz), 1.23 (3H, d, J=7.8 Hz), 1.01 (9H, s). Characterization data was in agreement with published data.[77]



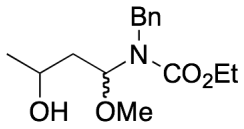
Aminal 148. A mixture of amide **145** (3.75g, 11.0 mmol) and Me_3OBF_4 (2.00g, 13.5 mmol) in CH_2Cl_2 (100 mL) was stirred for 6 h. The reaction mixture was then slowly transferred into a vigorously stirred sat. aq. $NaHCO_3$ solution (250 mL) by cannula. The

mixture was extracted with CH_2Cl_2 (3 x100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to furnish the crude product (4.08 g). To a mixture of the crude product and DMAP was added ethyl chloroformate (1.37 mL, 14.3 mmol) in pyridine (40 mL) at 0 °C . After the reaction mixture was stirred at rt for 1 h, 259 mL of water was added, which was extracted with hexane (1 x 250 mL, 2 x 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to furnish the crude product (4.95 g). To a solution of the imidate was added portionwise $NaBH_4$ (4.19 g, 111 mmol) in MeOH (150 mL). After stirring for 30 min, the mixture was extracted with hexane (150 mL) and water (250 mL). The aqueous layer was extracted with hexane (2 x 50 mL) again. The combined organic layers were dried over sodium sulfate and concentrated to furnish the crude product, which was purified by flash chromatography (9:1 hexane/EtOAc) to give the product (2.90 g, 6.75 mmol) as a colorless oil (61 % yield, diastereomers are present). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.66 (4H m), 7.41-7.34 (6H, m), 5.59 (0.5H, brd, *J*=9.4 Hz), 5.01-4.96, (1H, m), 4.70 (0.5H, brd,, *J*=9.4 Hz), 4.14-4.11 (2H, m), 3.94 (1H, q, J = 6 Hz), 3.31 (1.5 H, s), 3.15 (1.5 H, s), 1.91 (1H, m), 1.70 (2H, m), 1.23 (3H, t, J= 3.8 Hz), 1.04 (9H, d, J = 8.5 Hz), 1.00 (3H, d, *J*= 3.8 Hz). Characterization data was in agreement with published data.[77]

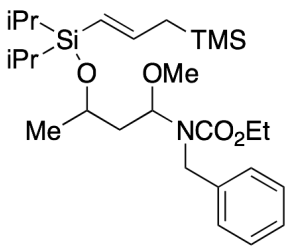


Aminal 149a. To a solution of the aminal **148** (1.5g, 3.5 mmol) in DMF (10 mL) was added NaH (0.83g 35 mmol) and benzyl bromide (3.1 mL, 17.5mmol) . This solution was stirred at O° C for 30 min, at which time the reaction was quenched with iPrOH (10 mL).

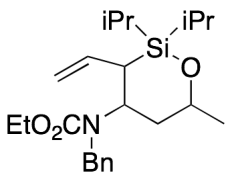
The reaction was then extracted with hexane (3x 50 ML) and the organic layer was dried over Na_cSO_4. The resulting product was subjected to flash chromatography (5:5 pet ether/ CH_2Cl_2) to give 0.89 grams of product as a colorless oil (46% yield, diastereomers and rotamers are present).^{1}H NMR (300MHz, $CDCl_3$) δ 7.70-7.65 (5H m), 7.42-7.35 (10H, m), 5.62-5.29 (1H, m), 4.24-4.12 (4H, m), 3.27 (3H, s), 1.75-1.27 (2H, m), 1.12-0.87 (15 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 139.2, 136.9 135.8, 128.2, 127.63, 127.5, 127.4, 126,6, 84,6, 66.7, 61.6, 43.3, 31.1, 27.0, 24.2, 20.2 12.4. HRMS calc. for $C_{31}H_{41}NO_4Si_1$ +Na= 542.2697, found 542.3017.



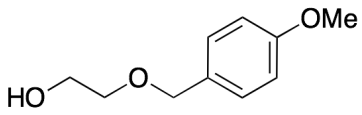
Aminal 149. To a solution of aminal **149a** (0.32 g, 0.76 mmol), was added n-Bu_4NF in THF (1 M solution in THF, 2.3 mL, 2.3 mmol) at room temperature. After stirring for 24 h the mixture was poured in saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (20 mL). The organic layers were dried over Na_2SO_4 and concentrated to furnish the crude product, which was purified by flash chromatography (3:1 hexane/EtOAc) to give 194 mg of product as a colorless oil that is a mixture of diastereomers (91% yield). IR (Neat) cm^{-1}: 3320 (OH), 2970, 1700. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (5H, m), 5.55-5.52 (1H, m), 4.49-4.46 (1H, m), 4.49-4.18 (3H, m), 3.74 (1H, s), 3.40 (1H, s), 3.23-3.20 (3H, s), 1.69-1.63 (1H, m), 1.54-1.53 (1H, m), 1.28-1.21 (2H, m), 1.00 (3H, d, J= 6 Hz), 1.22 (3H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 128.45, 128.25, 127.0, 126.6, 87.4, 64.4, 61.8, 54.1, 43.91, 22.8, 20.1, 14.5. HRMS calc. for $C_{15}H_{23}NO_4$ +Na= 304.1519, found=304.1718.



Aminal 150. Allyl vinyl silane **137** (170 mg, 0.64 mmol) was dissolved in CH_2Cl_2 (6 mL) and to this was added AcCl (49 μL, 0.64 mmol), and the reaction was stirred for 24 h. At the end of this time alcohol **149** (180 mg, 0.64 mmol) was added with imidazole (95 mg, 1.4 mmol), and DMAP (78 mg, 0.64mmol) and the reaction was allowed to stir for 48 h. The solvent was removed *in vacuo*, and the resulting mixture was dissolved in EtOAc (20 mL), washed with water (2 x 10 mL) and with brine (10 mL), and dried over $MgSO_4$. The EtOAc was removed and the oil was subjected to flash chromatography (9:1 hexane/EtOAc) to give 100 mg of a clear oil that was a mixture of rotamers and diastereomers (31% yield). ^{1}H NMR (500 MHz, $CDCl_3$) non-removable solvent impurities skew the integrations between 1.06 and 0.83 ppm) δ 7.27-7.20 (5H, m), 6.17 (1H, dt, J= 18.5, 3.5 Hz), 5.62-5.31 (1H, br m), 5.36 (1H, d, J=18.5 Hz), 4.98 (1H, d, J = 10 Hz), 4.30 (0.5 H, d J = 5.8 Hz), 4.23-4.13 (3.5H, m), 3.99 (1H, s), 3.16-3.14 (3H, m), 1.67 (2H, d, J=3.5 Hz), 1.56 (2H, d J=7.7 Hz), 1.06-0.83 (22H, m), -0.03 (9H, m) ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 131.2, 127.6, 127.1, 126.8, 121.1, 120.3, 85.17, 65.7, 61.6, 55.1, 43.6, 29.0, 17.5, 15.2, 14.7, 12.5, 12.5, 1.8. HRMS calc. for $C_{27}H_{49}NO_4$ + Na= 530.3092, found 530.3167.

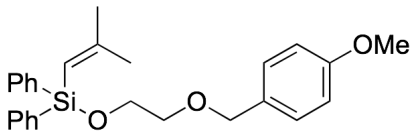


Silacycle 151. Aminal **150** (26 mg, 51 μmol) was dissolved in 2 mL CH_2Cl_2. To this solution was added $SnCl_4$ (6 μl, 51μmol). The solution was allowed to stir for 1 h, at the end of this period the reaction diluted with CH_2Cl_2 (10 mL) and quenched with aq sat $NaHCO_3$. The mixture was then washed twice with H_2O, and the organic layer was collected, and dried over Na_2SO_4, and concentrated. The residue was subject to column cromatrogphy (9:1 hex/EtOAc), to give a 13 mg of a colorless oil, in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) non-removable solvent impurities skew the integrations between 1.0 and 0.09 ppm) δ 7.27-7.24 (5H, m), 6.30 (1H, dt, J = 18.5, 6.7 Hz), 6.06 (1H, m), 5.70 (1H, q, J = 7.4 Hz), 5.10 (1H, d, J = 16.7 Hz), 4.97 (1H, d, J= 10.1 Hz), 4.05 (2H, q, J = 6.1 Hz), 2.25 (2H, m), 1.11-0.09 (30H, m). Micro-TOF Calc for $C_{23}H_{37}NO_3Si$+ H+=404.2615, found 404.2653, Micro-TOF Calc for $C_{23}H_{37}NO_3Si$+ Na+=426.2435, 426.2473.



1-Hydroxy [(4-methoxybenzyl) oxy)] ethane (155). Ethylene glycol (1.55 g, 24.9 mmol) and dibutyltin oxide (6.50 g, 26.1 mmol, 1.05 equiv.) were added to 100 mL of benzene. The mixture was refluxed overnight with a Dean-Stark apparatus. In a separate flask containing 100 mL of anhydrous ether, paramethoxybenzyl alcohol (5.51 g, 39.9 moles, 1.59 equiv.) was dissolved, and cooled to 0° C. To this solution was added HBr

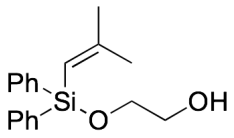
(50 mL, 48% aq. solution, 15.9 equiv.) and ether (50 mL), and the reaction was stirred for 1 h. After 1 h, the organic and aqueous layers were separated, the aqueous layer was washed with ether (50 mL), and the organic layers were combined. The ether was washed with a saturated solution of NaBr, and dried over K_2CO_3. The solvent was removed under reduced pressure, and the resultant oil was added to the ethylene glycol/dibutyltin oxide reaction along with $(Bu)_4NI$ (6.90 g, 18.7 mmol, 0.75 equiv.). The mixture was refluxed overnight to produce a yellow solution. The solvent was removed from the reaction, and the yellow oil was subjected to flash chromatography (2:1 hexane/EtOAc) to yield a yellow oil (4.0 g, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (2H, d, J=8 Hz), 6.82 (2H, d, J=8 Hz), 4.44 (2H, s), 3.78 (3H, s), 3.68 (2H, dt, J=5.2, 4.2 Hz), 3.58 (2H, t, 4.2 Hz), 2.63 (1H, d, J=5.2 Hz). Characterization data was in agreement with published data.[89]



6-methyl-3-oxy-1-paramethoxybenzyl-4,4-diphenyl-4 silyl- 5-en-1-ol (156).

Anhydrous ether (10 mL) was added to a flame dried round bottomed flask via cannula. The ether was placed under a continuous stream of argon and cooled to –78 °C. The flask was charged with *t*-butyl lithium (2.61 mL, 1.5 mL in pentane, 0.39 mmol, 2 equiv.) and 1-bromo-2-methyl-propene (1.81 mL, 1.98 mmol, 1 equiv.), and stirred for 30 min. Chlorodimethylaminodiphenylsilane (0.502 g, 1.98 mmol, 1 equiv.) was added, and the reaction was allowed to warm to room temp over a 6 h period. The ether was removed under reduced pressure and the yellow oil was dissolved in hexane and filtered though

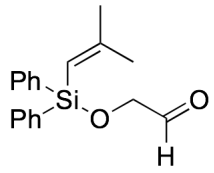
celite. The hexane was removed under reduced pressure to give a colorless liquid. To this liquid was added 1-hydroxy[(4-methoxybenzyl)oxy)]ethane (0.541 g, 2.97 mmol, 1.5 equiv.) and anhydrous ether (5 mL), and the mixture was allowed to stir for 12 h. The solvent was removed under reduced pressure and the resultant oil was chromatographed (8:2 hexane/EtOAc) to yield a colorless oil (0.546 g, 66% yield). Bp. 180 °C, 3 mm Hg. IR (Neat) cm^{-1}: 2915 (Si-Ph), 1245 (O-CH_3), 1132 (Si-O-C-H). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66-7.62 (4H, m), 7.41-7.33 (6H, m), 7.20 (2H, d, J=6.4 Hz), 6.84 (2H, d, J=6.4 Hz), 5.60 (1H, s), 4.46 (2H, s), 3.87 (2H, t, J=5.3 Hz), 3.78 (3H, s), 3.58 (2H, t, J=5.3 Hz), 1.95 (3H, s), 1.76 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 158.1,136.1, 134.8, 130.6, 129.6, 129.2, 127.7, 118.0, 113.8, 72.7, 71.0, 62.8, 55.3, 29.6, 24.2.



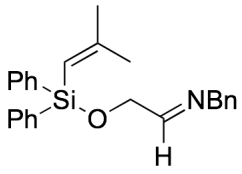
6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-1-ol (158). To a solution of CH_2Cl_2 (10 mL) and H_2O (2 mL) was added **156** (0.912 g, 2.18 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.544 g, 2.6 mmol, 1.2 equiv.). The mixture was stirred 1 h and CH_2Cl_2, (15 mL) was added. The reaction mixture was washed with sodium bicarbonate (3 x 10 mL). The organic layer was collected and dried over $MgSO_4$. Removal of the solvent at reduced pressure and chromatography on SiO_2 (8:2 hexane/EtOAc) provided a mixture of the product and paramethoxybenzaldyde. The mixture was then subjected to Kugelrohr distillation, which afforded pure alcohol as a colorless oil (0.497 g, 77% yield). Bp. 145° C, 3 mm Hg. IR (Neat) cm^{-1}: 3421 (OH), 1613.5 (C=C Ar), 1428 (C-H),

1115 (Si-O-C-H), 1048 (s, C-O). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.61 (4H, m), 7.42-7.34 (6H, m), 5.62 (1H, s), 3.80 (2H, t, J=4.2 Hz), 3.67 (2H, t, J=4.2 Hz), 2.08 (1H, bs), 1.97 (3H, s), 1.77 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 136.1, 134.7, 129.8, 127.9, 117.5, 64.5, 63.7, 29.5, 24.3. HRMS calc. for $C_{18}H_{20}O_2Si_1$= 298.1389; found 298.1392.

Alternative route to alcohol (158). Anhydrous ether (10 mL) was added to a flame dried round bottomed flask via cannula. The ether was placed under a continuous stream of argon and cooled to –78° C. The flask was charged with *t*-butyl lithium (3.09 mL, 1.5 mL in pentane, 4.64 mmol) and 1-bromo-2-methyl-propene (0.233 mL, 2.32 mmol), and stirred for 30 min. Chlorodimethylaminodiphenylsilane (0.608 g, 2.32 mmol) was added, and the reaction was allowed to warm to room temp over a 6 h period. The ether was removed under reduced pressure and the yellow oil was dissolved in hexane and filtered though celite. The hexane was removed under reduced pressure to give a colorless liquid. The aminosilane was dissolved in THF (5 mL) and was slowly added via syringe pump to a 1:1 solution of THF (10 mL) and 1,2-propanediol (10 mL), and allowed to stir at room temperature for 12 h. The THF was removed under reduced pressure. EtOAc (20 mL) was added, and the solution was washed with water (3 x 10 mL) and dried over $MgSO_4$. The resulting oil was subjected to column chromatography (8:2 hexane/EtOAc) to yield a clear oil (0.484 g, 70% yield).

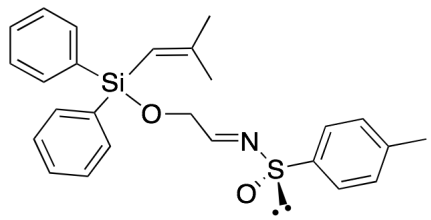


6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-enal (159). Alcohol **158** (73.4 mg, 0.248 mmol) was dissolved in 3 mL of a DMSO/CH_2Cl_2 (1:5) solution, and cooled to 0 ºC. To this solution was added SO_3•py (78.9 mg, 0.496 mmol) and Et_3N (0.137 mL, 1.12 mmol, 4.5 equiv.).[33] After 2 h, CH_2Cl_2 (10 mL) was added, and the solution was washed with H_2O (3 x 5 mL). The organic phase was collected and dried over Na_2SO_4, and the solvent was removed at reduced pressure. Chromatography (8:2 hexane/EtOAc) yielded **159** as a clear oil, in approximately 90 % purity (47 mg, 65% yield) Bp. 120 °C, 3 mm Hg. Accurate mass: Found 296.1228, $C_{18}H_{20}O_2Si_1$ (calculated 296.1232). IR (Neat) cm^{-1}: 2719 (Aldehydic C-H), 1735 (C=O), 1613 (C=C, Ar), 1109 (Si-O-C-H). ^1H NMR ($CDCl_3$ 300 MHz) δ 9.34 (1H, s), 7.71-7.63 (4H, m), 7.18-7.00 (6H, m), 5.59 (1H, s), 3.86 (2H, s), 1.75 (3H, s), 1.67 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.0, 159.5, 135.5, 134.8, 129.7, 127.9, 116.8, 69.4, 29.6, 24.3. HRMS calc. for $C_{18}H_{20}O_2Si$= 296.1233; found= 296.1228.

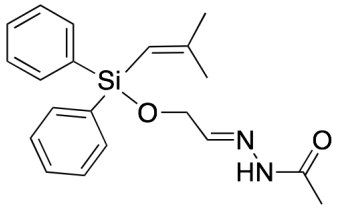


6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-*N*-benzyl imine (160). The aldehyde 1**59** (11 mg, 37 μmol) was dissolved in 0.8 mL of $CDCl_3$. To this solution was added benzyl amine (3.9 μL, 37 μmol), and 4 Å MS. The solution was allowed to stand for 1 h, and

NMR spectra were taken. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (1H, s), 7.65-7.14 (15 H, m), 5.63 (1H, s), 4.56 (1H, s), 4.42 (1H, s), 3.85 (2H, s), 1.97 (3H, s), 1.70 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 158.0, 140.1, 137.9, 137.5, 134.9, 134.5, 129.7, 129.6, 128.7, 111.8, 69.4, 46.3, 29.6, 24.3.



(*R*)-6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-*N*-*N*-sulfinyl tosyl imine (162). In a flame dried flask was added 1.5 mL of CH_2Cl_c, aldehyde ***** (92 mg, 0.31 mmol) and the (*R*)-(-)-*p*- toluenesulfinamide (104 mg, 0.62 mmol, 1.1). To this was then added titanium tetraethoxide (0.353 mL, 1.55 mmol). The reaction was stirred at room temp for 3 h. At completion the reaction was brought to -78° *C* and quenched with water. The organic layer was separated and the solvent removed *in vacuo*. The mixture was then taken up in ethyl acetate and filtered through celite. The ethyl acetate was removed *invaquo* and the mixture was chromatographed (7:3 hexane ethyl acetate) to afford the product. (20 mg, 16% yield). IR (Neat) cm^{-1}: 2679 (imine C-H), 1695 (C=N), 1613 (C=C, Ar), 1109 (Si-O-C-H). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (1H, t, J = 3.1 Hz), 7.59-7.24 (14H, m), 5.54 (1H, s), 4.5 (2H, d, J = 3.1 Hz), 2.40 (3H, s), 1.92 (3H, s), 1.70 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 159.5, 141.1, 140.1, 137.1, 135.5, 134.8, 129.7, 127.9, 126.1, 116.8, 69.4, 40.1, 29.6, 24.3. HRMS calc. for $C_{18}H_{20}O_2Si_1$= 448.1767; found= 448. 2634.



6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-*N*-acyl hydrazone (163). The aldehyde (39 mg, 0.13 mmol) was dissolved in ethanol (2 mL) and to this was added acyl hydrazine (10 mg, 0.14 mmol, 1.1 equiv.). The reaction was stirred for 6 h at rt. The ethanol was removed and the mixture was subjected to flash chromatography (1:1 hexane/EtOAc) to give the acyl hydrazone (31 mg, 68% yield). IR (Neat) cm^{-1}: 2850 (imine C-H), 1677 (C=N), 1613 (C=C, Ar), 1109 (Si-O-C-H). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.42 (1H, s), 7.62-7.60 (4H, m), 7.32-7.24 (6H, m), 7.13 (1H, t, J = 4.8 Hz), 5.59 (1H, s), 4.34 (2H, d, J = 4.8 Hz), 2.23 (3H, s), 1.93 (3H, s), 1.78 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 171.1, 152.5, 135.5, 134.8, 129.7, 127.9, 116.8, 69.4, 40.37 29.6, 24.3. HRMS calc. for $C_{18}H_{20}O_2Si_1$ +Na= 375.1505; found= 375.2617.

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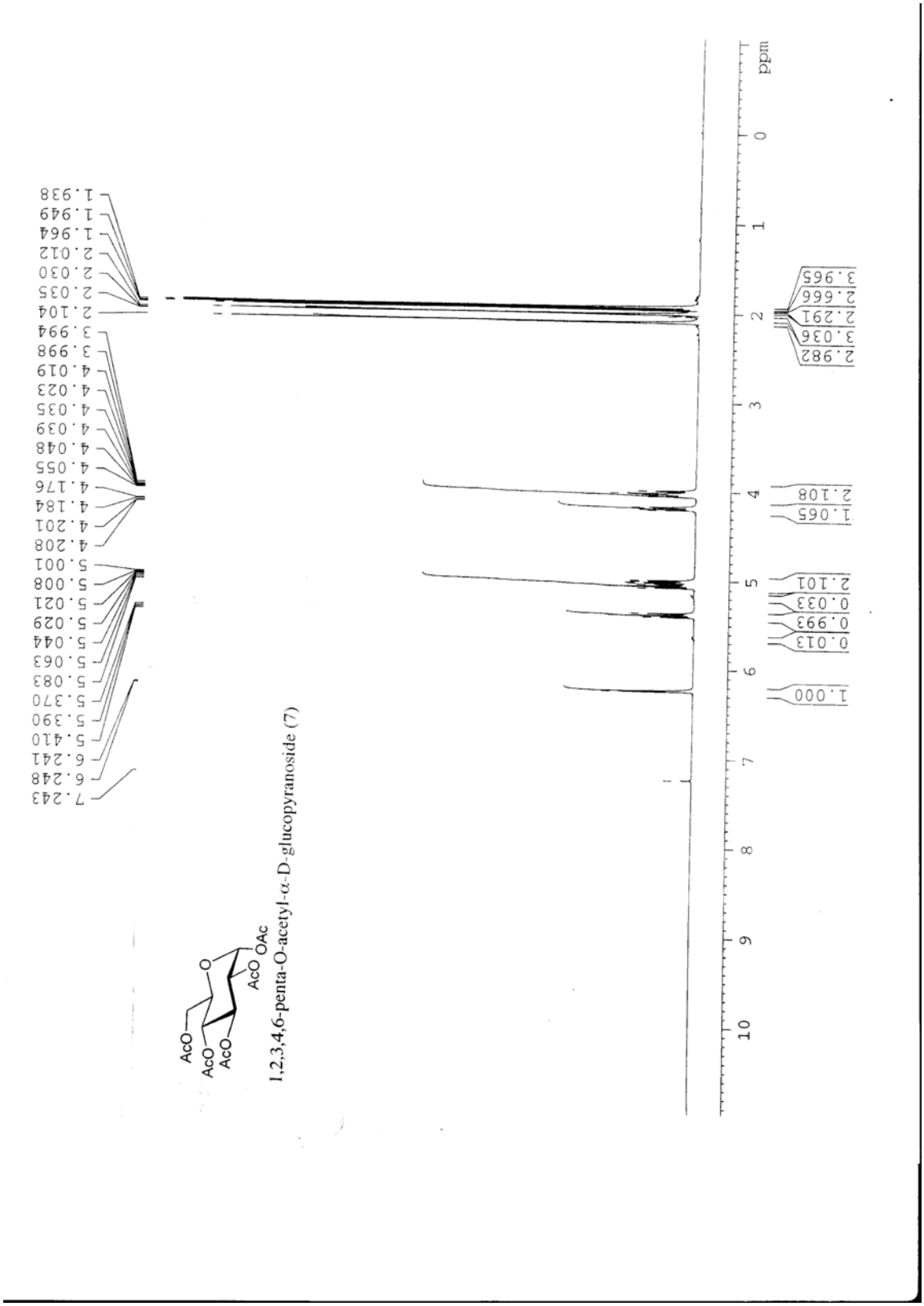
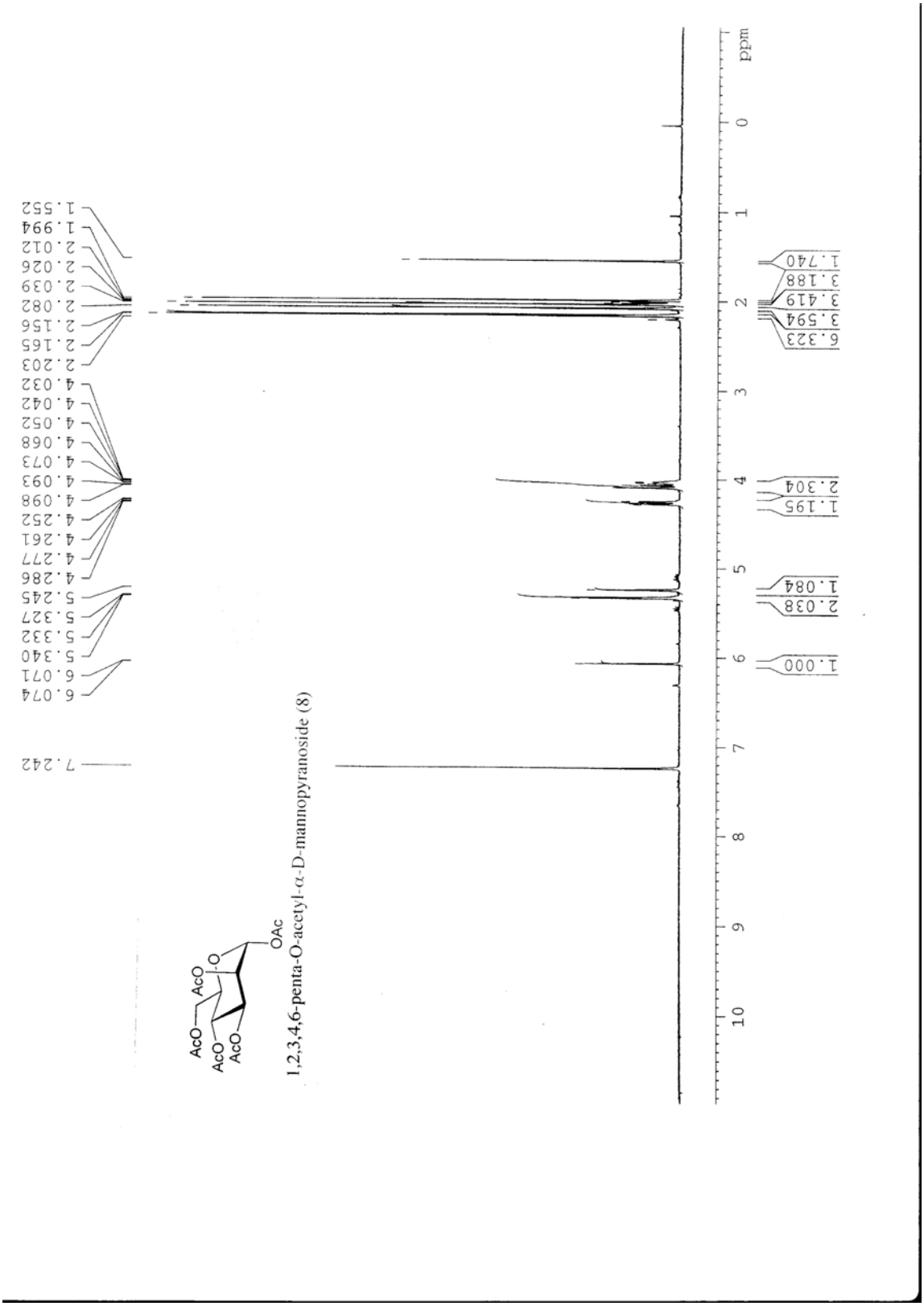
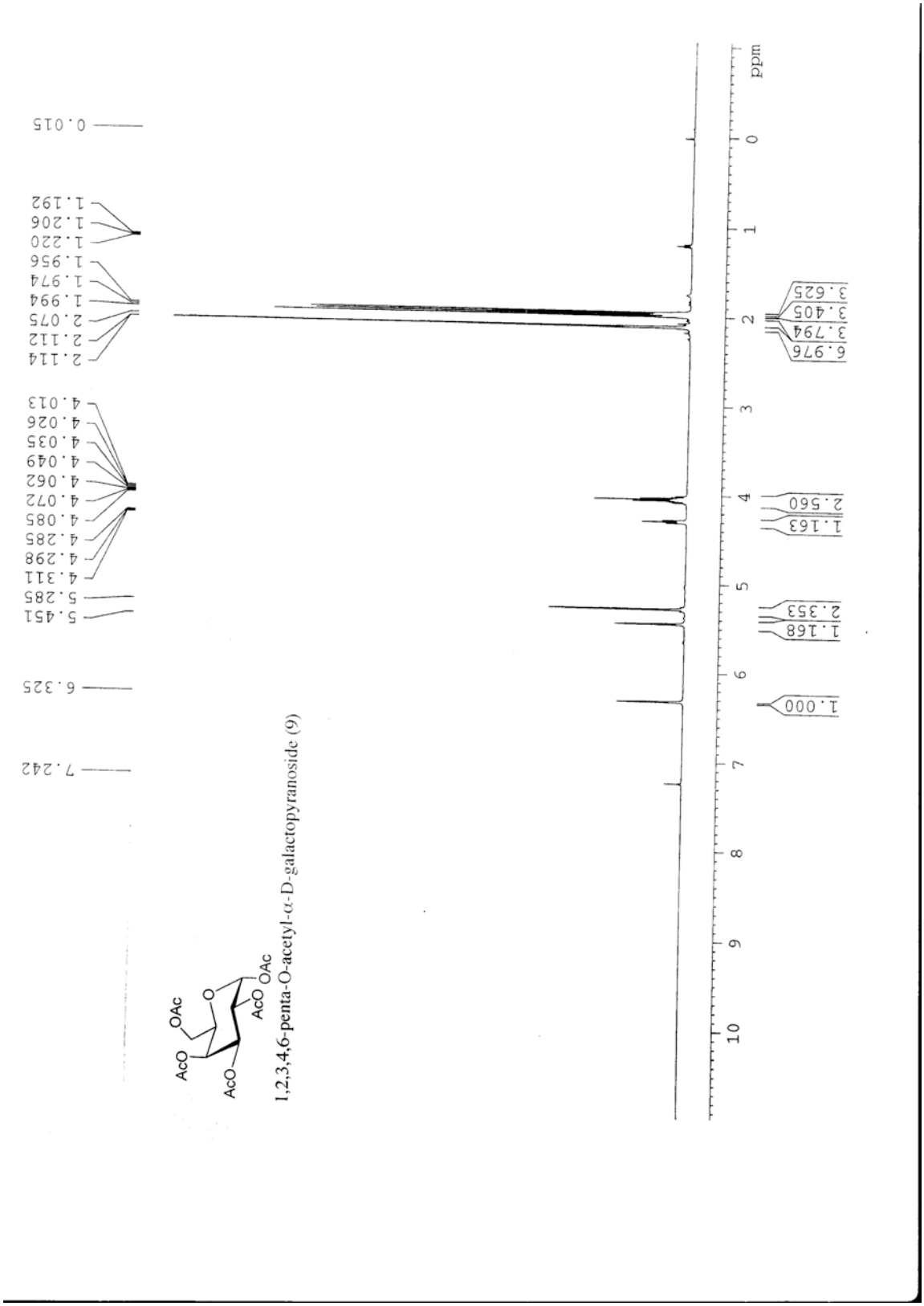
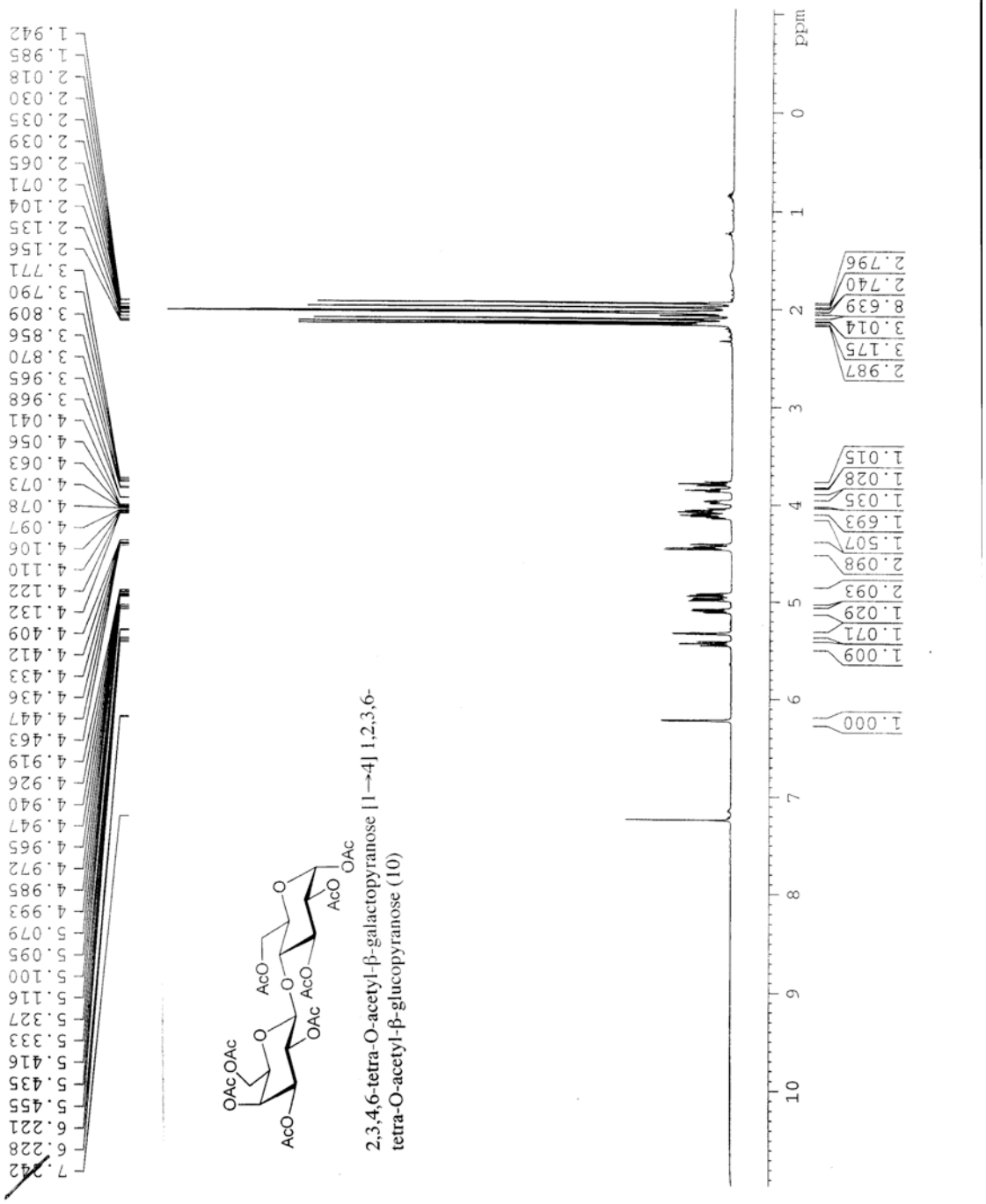
APPENDIX A

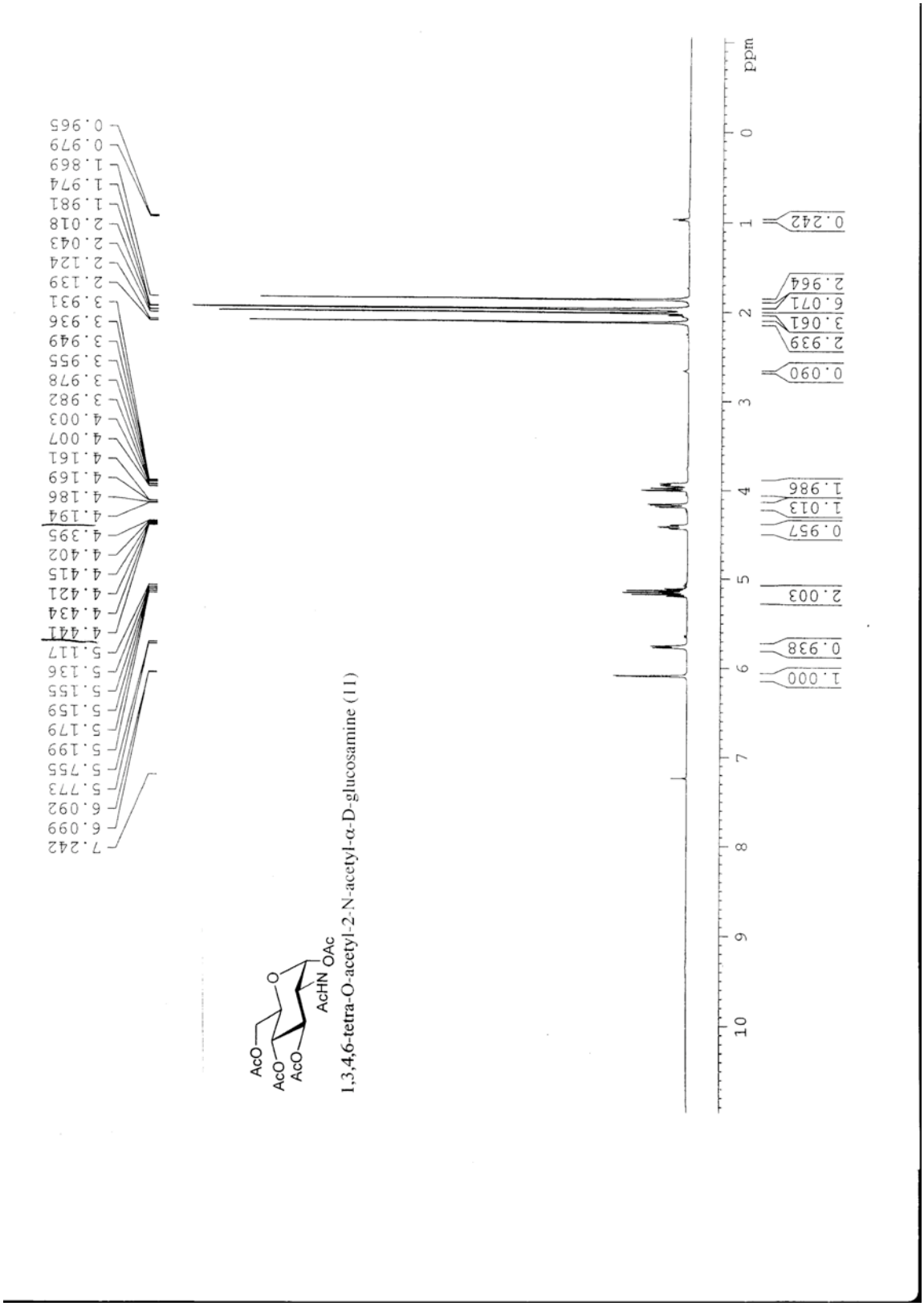
CHARACTERIZATION SPECTRA

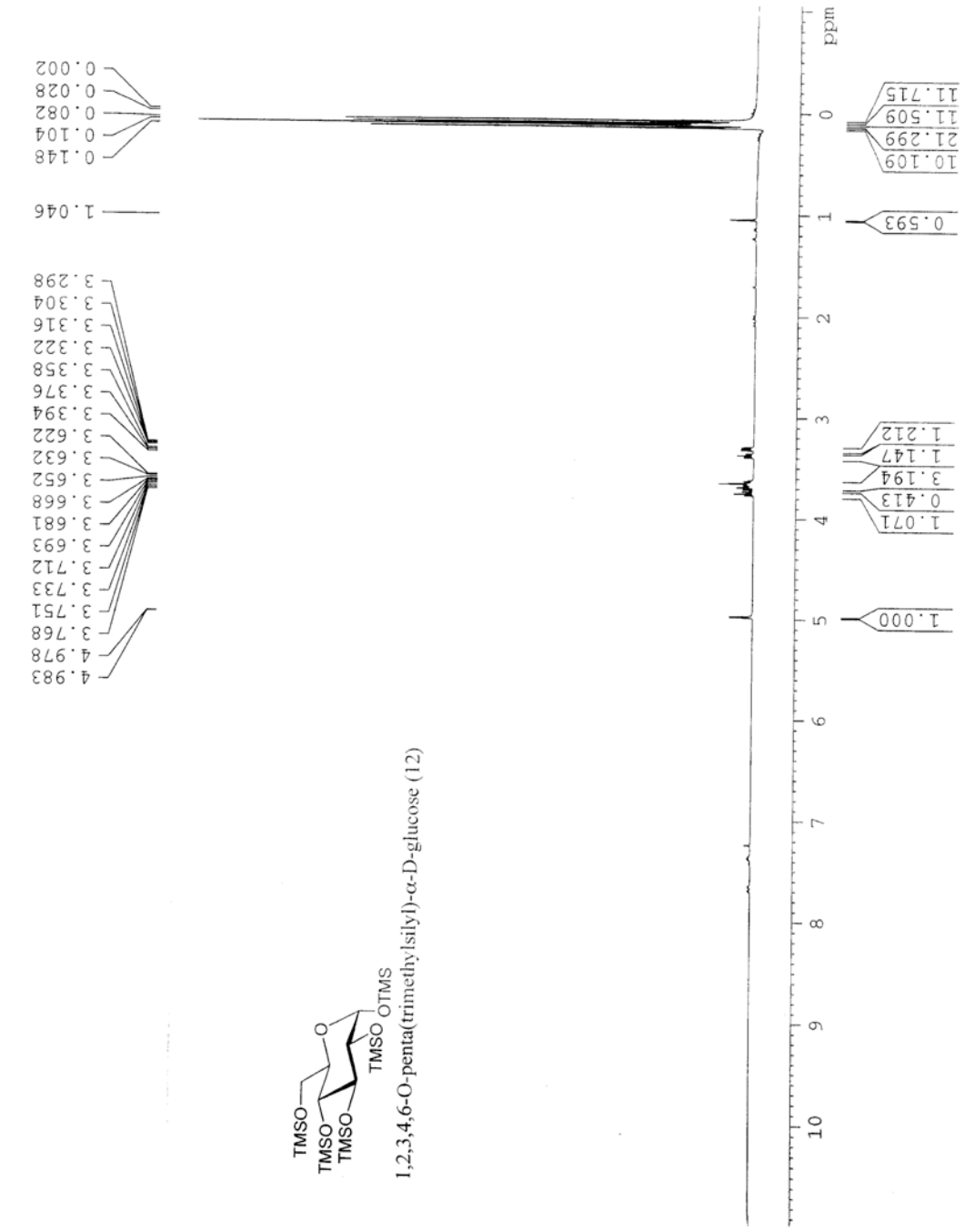

1,2,3,4,6-penta-O-acetyl-α-D-glucopyranoside (7)
AcO
AcO
AcO
AcO
OAc
O
ppm
1.000
0.013
0.993
0.033
2.101
1.065
2.108
2.982
3.036
2.291
2.666
3.965
7.243
6.248
6.241
5.410
5.390
5.370
5.083
5.063
5.044
5.029
5.021
5.008
5.001
4.208
4.201
4.184
4.176
4.055
4.048
4.039
4.035
4.023
4.019
3.998
3.994
2.104
2.035
2.030
2.012
1.964
1.949
1.938

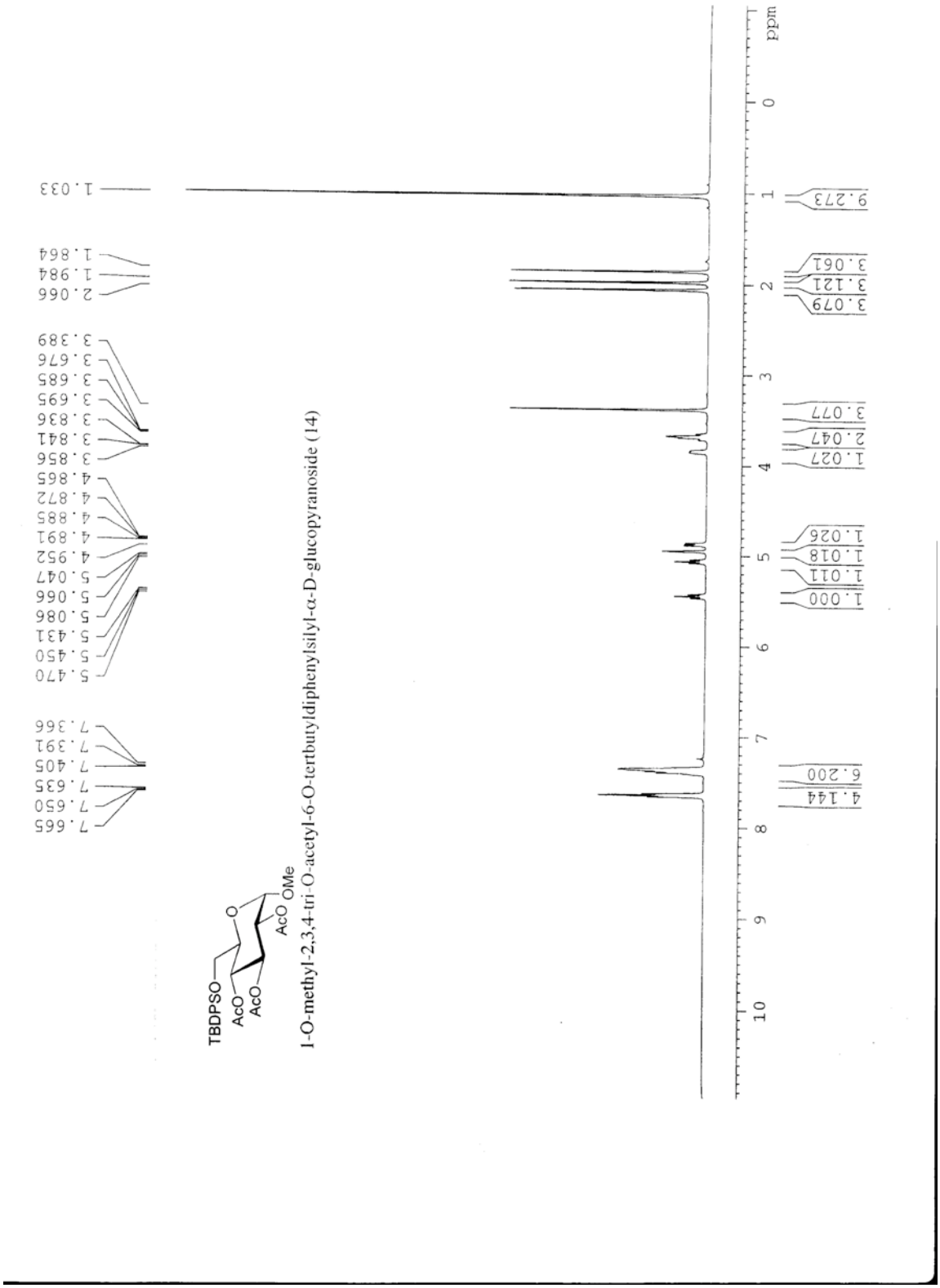

1,2,3,4,6-penta-O-acetyl-α-D-mannopyranoside (8)
AcO
AcO
AcO
AcO
OAc
O
ppm
0
1
2
3
4
5
6
7
8
9
10
1.000
2.038
1.084
1.195
2.304
6.323
3.594
3.419
3.188
1.740
7.242
6.074
6.071
5.340
5.332
5.327
5.245
4.286
4.277
4.261
4.252
4.098
4.093
4.073
4.068
4.052
4.042
4.032
2.203
2.165
2.156
2.082
2.039
2.026
2.012
1.994
1.552

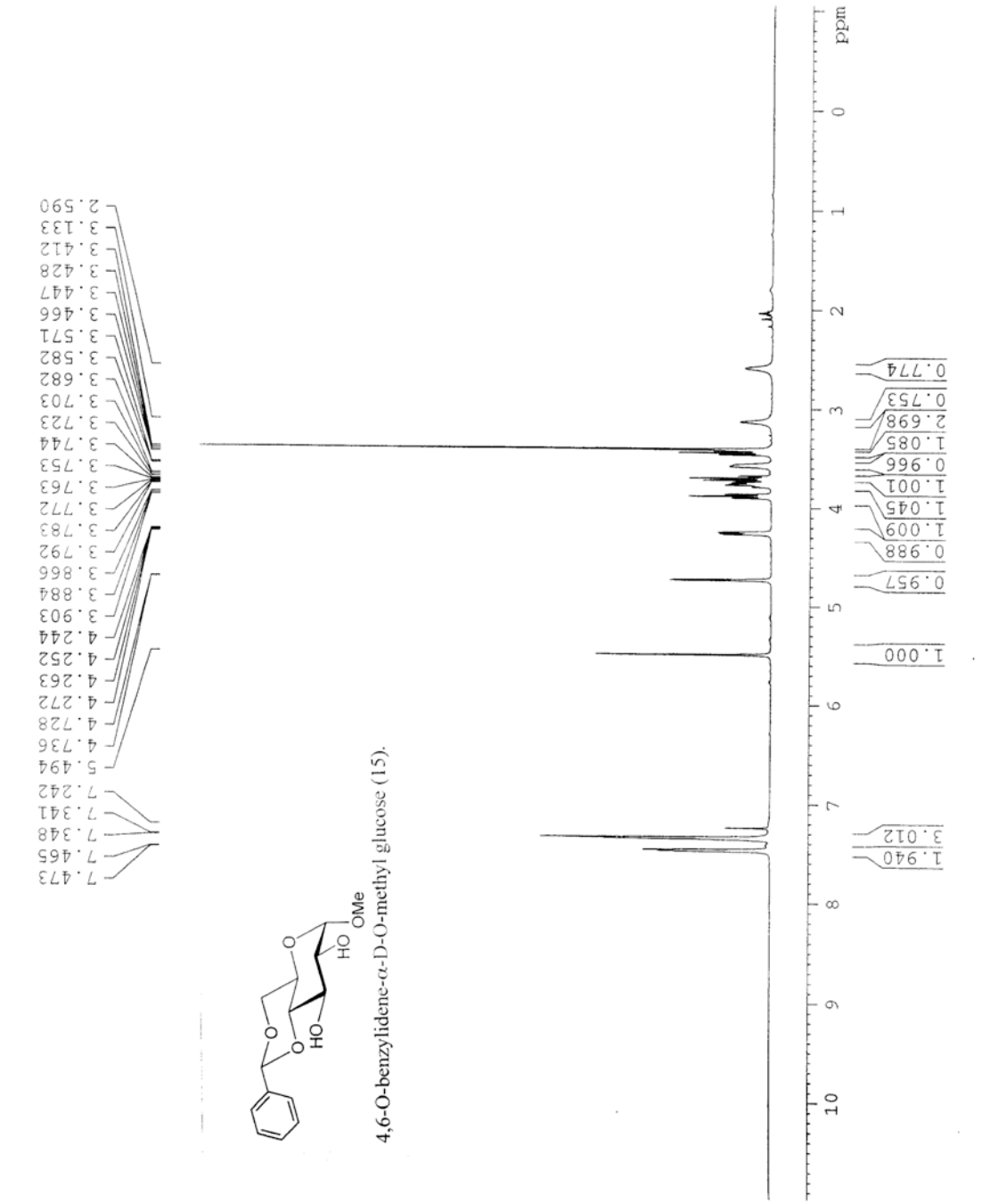

1,2,3,4,6-penta-O-acetyl-α-D-galactopyranoside (9)
AcO
OAc
AcO
OAc
AcO
OAc
ppm
0.015
1.192
1.206
1.220
1.956
1.974
1.994
2.075
2.112
2.114
4.013
4.026
4.035
4.049
4.062
4.072
4.085
4.285
4.298
4.311
5.285
5.451
6.325
7.242
1.000
1.168
2.353
1.163
2.560
3.625
3.405
3.794
6.976


7.242
6.228
6.221
5.455
5.435
5.416
5.333
5.327
5.116
5.100
5.095
5.079
4.993
4.985
4.972
4.965
4.947
4.940
4.926
4.919
4.463
4.447
4.436
4.433
4.412
4.409
4.132
4.122
4.110
4.106
4.097
4.078
4.073
4.063
4.056
4.041
3.968
3.965
3.870
3.856
3.809
3.790
3.771
2.156
2.135
2.104
2.071
2.065
2.039
2.035
2.030
2.018
1.985
1.942
OAc OAc
AcO
AcO
AcO
OAc
AcO
OAc
2,3,4,6-tetra-O-acetyl-β-galactopyranose [1→4] 1,2,3,6-tetra-O-acetyl-β-glucopyranose (10)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.009
1.071
1.029
2.093
2.098
1.507
1.693
1.035
1.028
1.015
2.987
3.175
3.014
8.639
2.740
2.796

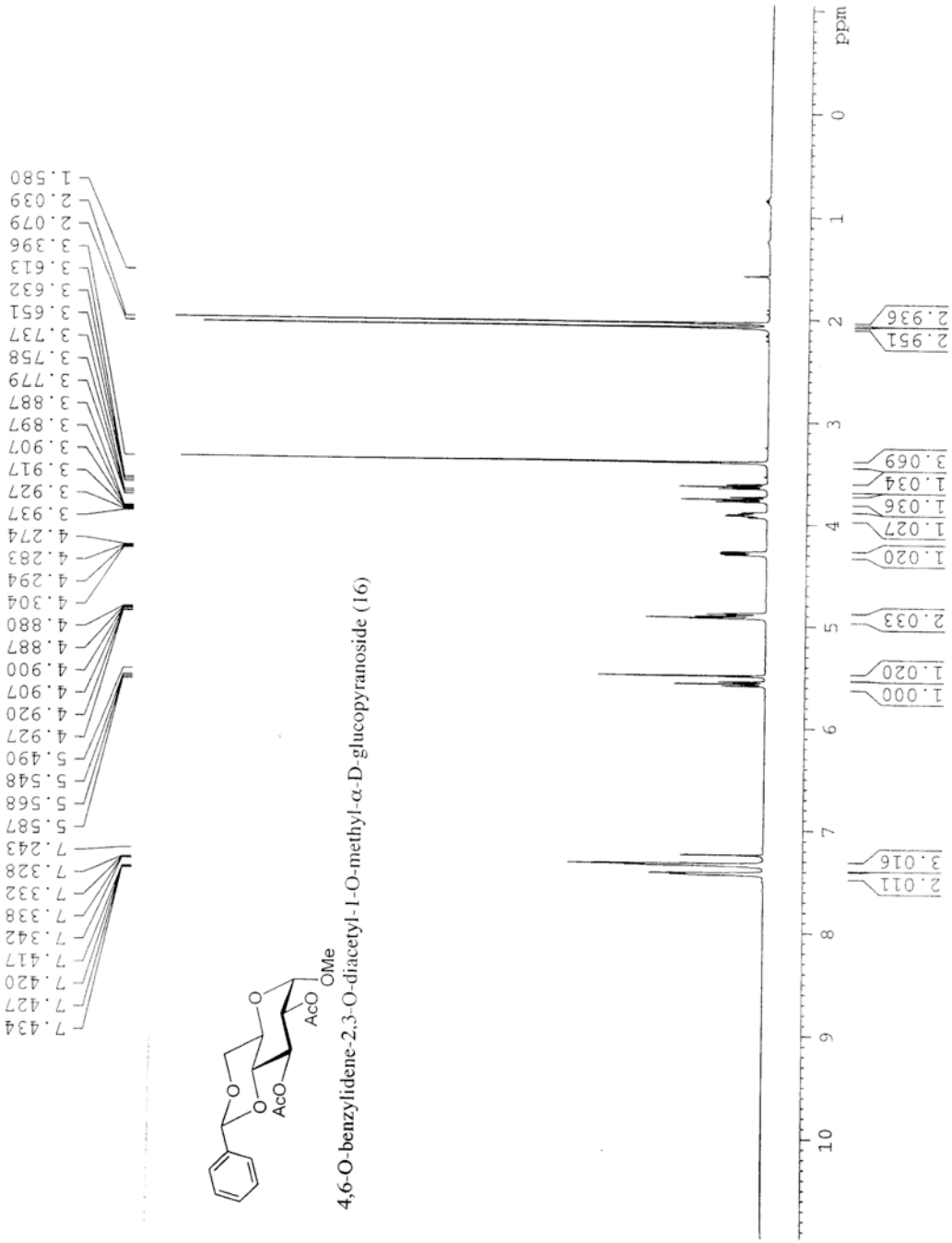

1,3,4,6-tetra-O-acetyl-2-N-acetyl-α-D-glucosamine (11)
AcO
AcO
AcO
AcHN
OAc
O
ppm
0 1 2 3 4 5 6 7 8 9 10
0.242
2.964
6.071
3.061
2.939
0.090
1.986
1.013
0.957
2.003
0.938
1.000
7.242
6.099
6.092
5.773
5.755
5.199
5.179
5.159
5.155
5.136
5.117
4.441
4.434
4.421
4.415
4.402
4.395
4.194
4.186
4.169
4.161
4.007
4.003
3.982
3.978
3.955
3.949
3.936
3.931
2.139
2.124
2.043
2.018
1.981
1.974
1.869
0.979
0.965

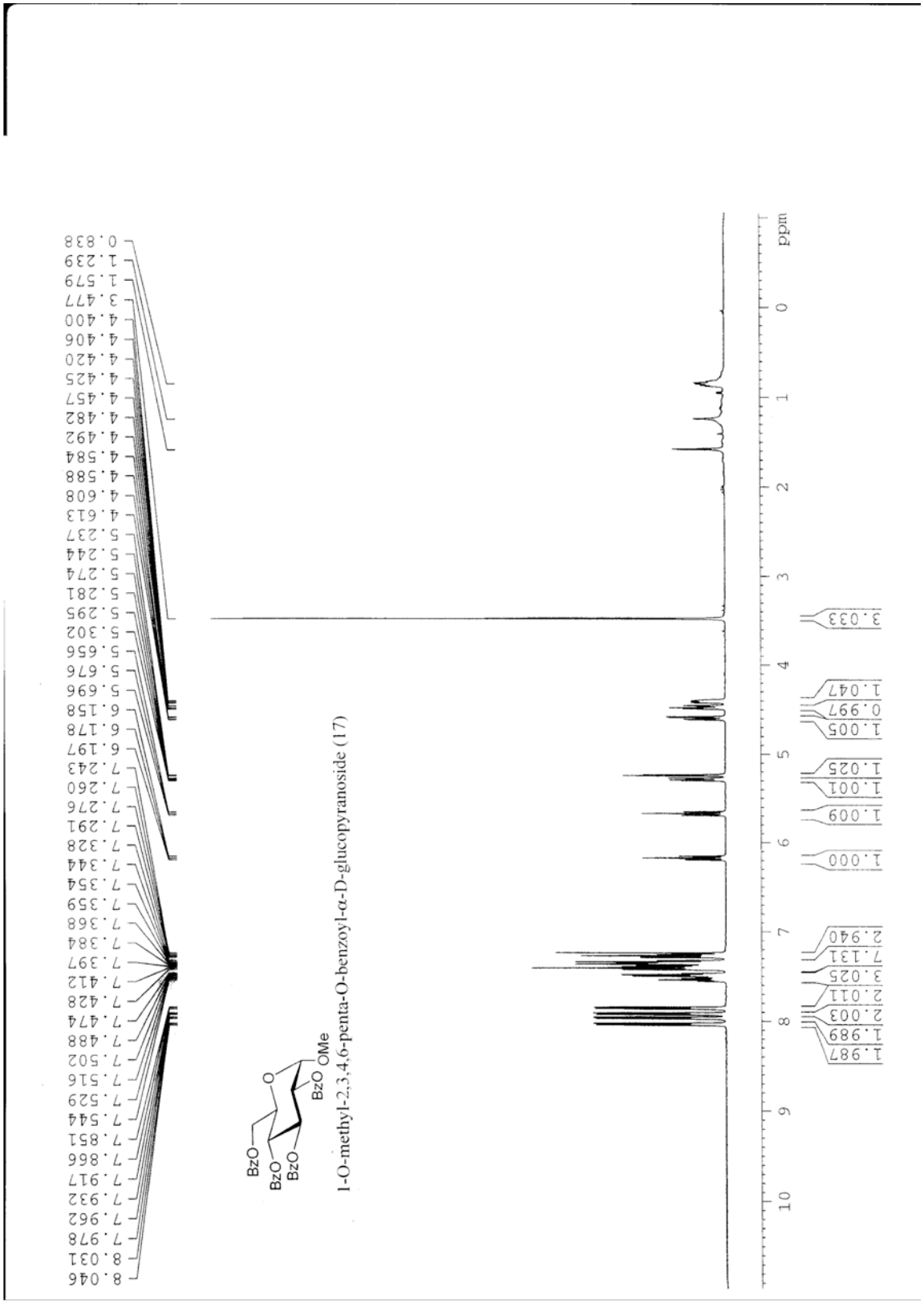

TMSO
TMSO
TMSO
TMSO
OTMS
O
1,2,3,4,6-O-penta(trimethylsilyl)-α-D-glucose (12)
ppm
0.002
0.028
0.082
0.104
0.148
1.046
3.298
3.304
3.316
3.322
3.358
3.376
3.394
3.622
3.632
3.652
3.668
3.681
3.693
3.712
3.733
3.751
3.768
4.978
4.983
10.109
21.299
11.509
11.715
0.593
1.000
1.071
0.413
3.194
1.147
1.212

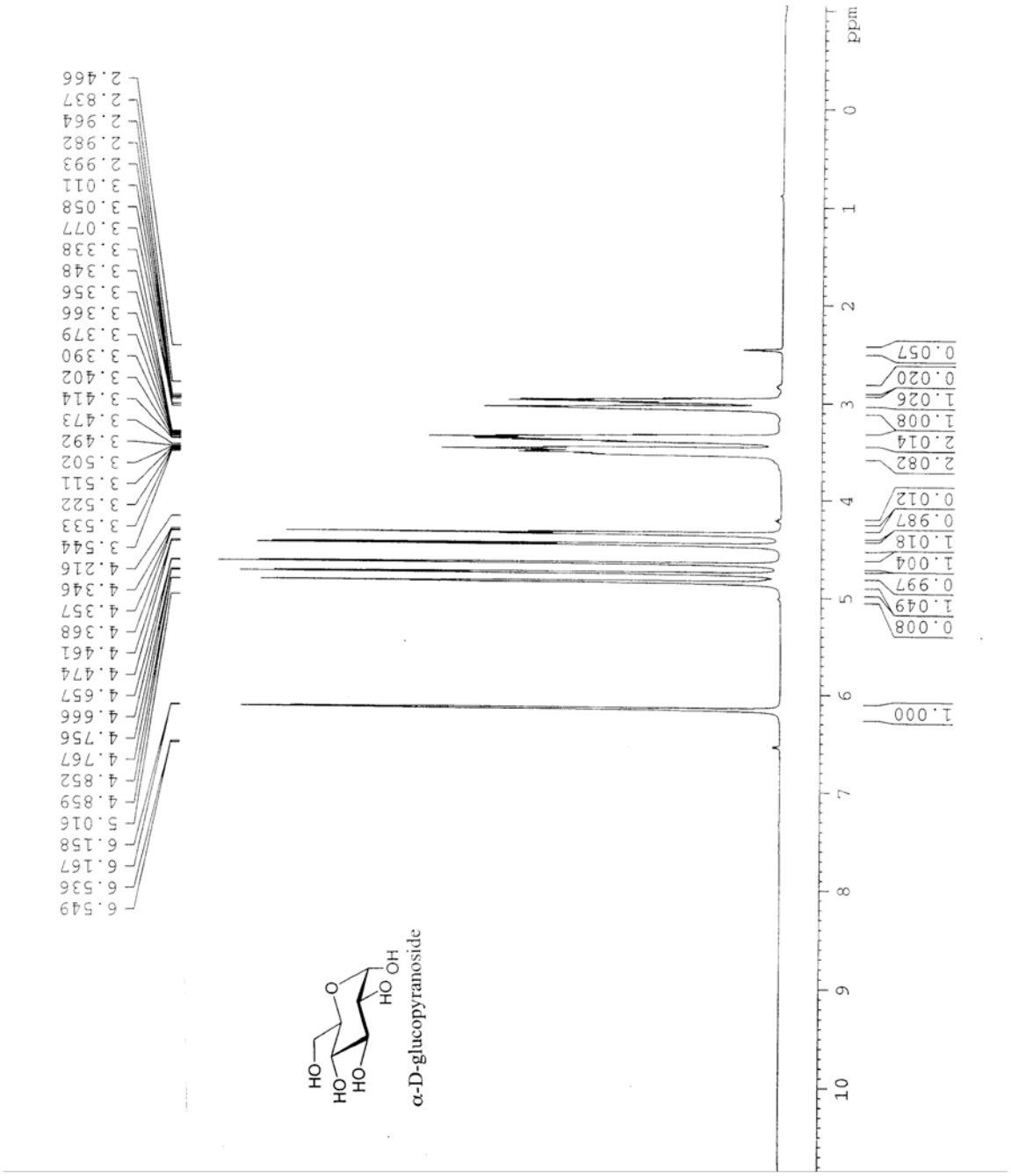

1-O-methyl-2,3,4-tri-O-acetyl-6-O-tertbutyldiphenylsilyl-α-D-glucopyranoside (14)
TBDPSO
AcO
AcO
AcO
OMe
O
ppm
1.033
1.864
1.984
2.066
3.389
3.676
3.685
3.695
3.836
3.841
3.856
4.865
4.872
4.885
4.891
4.952
5.047
5.066
5.086
5.431
5.450
5.470
7.366
7.391
7.405
7.635
7.650
7.665
9.273
3.061
3.121
3.079
3.077
2.047
1.027
1.026
1.018
1.011
1.000
6.200
4.144

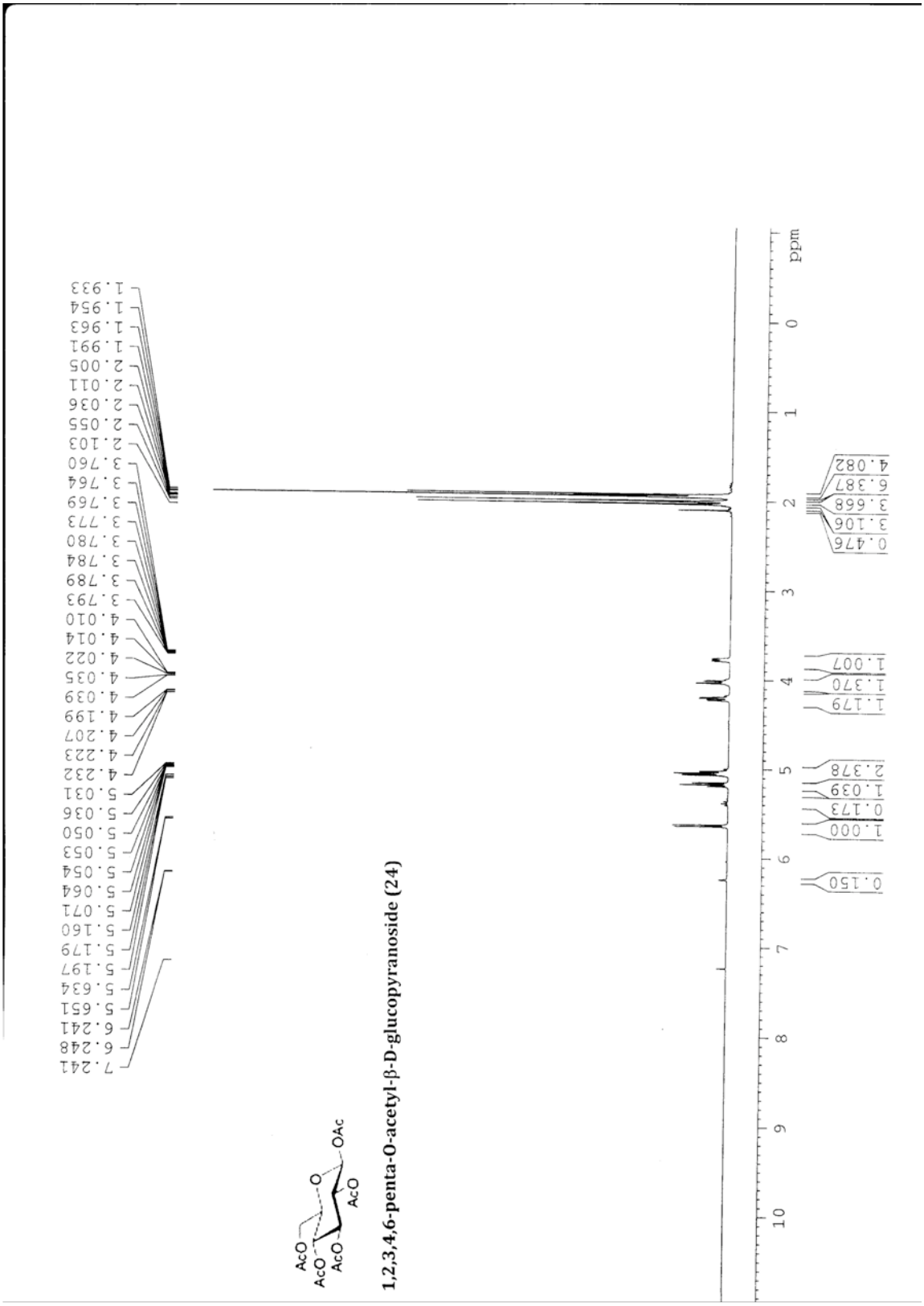


4,6-O-benzylidene-α-D-O-methyl glucose (15).


4,6-O-benzylidene-2,3-O-diacetyl-1-O-methyl-α-D-glucopyranoside (16)
AcO
AcO
OMe
ppm
1.580
2.039
2.079
3.396
3.613
3.632
3.651
3.737
3.758
3.779
3.887
3.897
3.907
3.917
3.927
3.937
4.274
4.283
4.294
4.304
4.880
4.887
4.900
4.907
4.920
4.927
5.490
5.548
5.568
5.587
7.243
7.328
7.332
7.338
7.342
7.417
7.420
7.427
7.434
2.011
3.016
1.000
1.020
2.033
1.020
1.027
1.036
1.034
3.069
2.951
2.936


1-O-methyl-2,3,4,6-penta-O-benzoyl-α-D-glucopyranoside (17)
BzO
BzO
BzO
BzO
OMe
ppm
1.987
1.989
2.003
2.011
3.025
7.131
2.940
1.000
1.009
1.001
1.025
1.005
0.997
1.047
3.033


ppm
0 1 2 3 4 5 6 7 8 9 10
1.000
0.008
1.049
0.997
1.004
1.018
0.987
0.012
2.082
2.014
1.008
1.026
0.020
0.057
6.549
6.536
6.167
6.158
5.016
4.859
4.852
4.767
4.756
4.666
4.657
4.474
4.461
4.368
4.357
4.346
4.216
3.544
3.533
3.522
3.511
3.502
3.492
3.473
3.414
3.402
3.390
3.379
3.366
3.356
3.348
3.338
3.077
3.058
3.011
2.993
2.982
2.964
2.837
2.466
HO
HO
HO
O
HO
OH
α-D-glucopyranoside


1,2,3,4,6-penta-O-acetyl-β-D-glucopyranoside (24)
AcO
AcO
AcO
AcO
OAc
O
ppm
0.150
1.000
0.173
1.039
2.378
1.179
1.370
1.007
0.476
3.106
3.668
6.387
4.082
7.241
6.248
6.241
5.651
5.634
5.197
5.179
5.160
5.071
5.064
5.054
5.053
5.050
5.036
5.031
4.232
4.223
4.207
4.199
4.039
4.035
4.022
4.014
4.010
3.793
3.789
3.784
3.780
3.773
3.769
3.764
3.760
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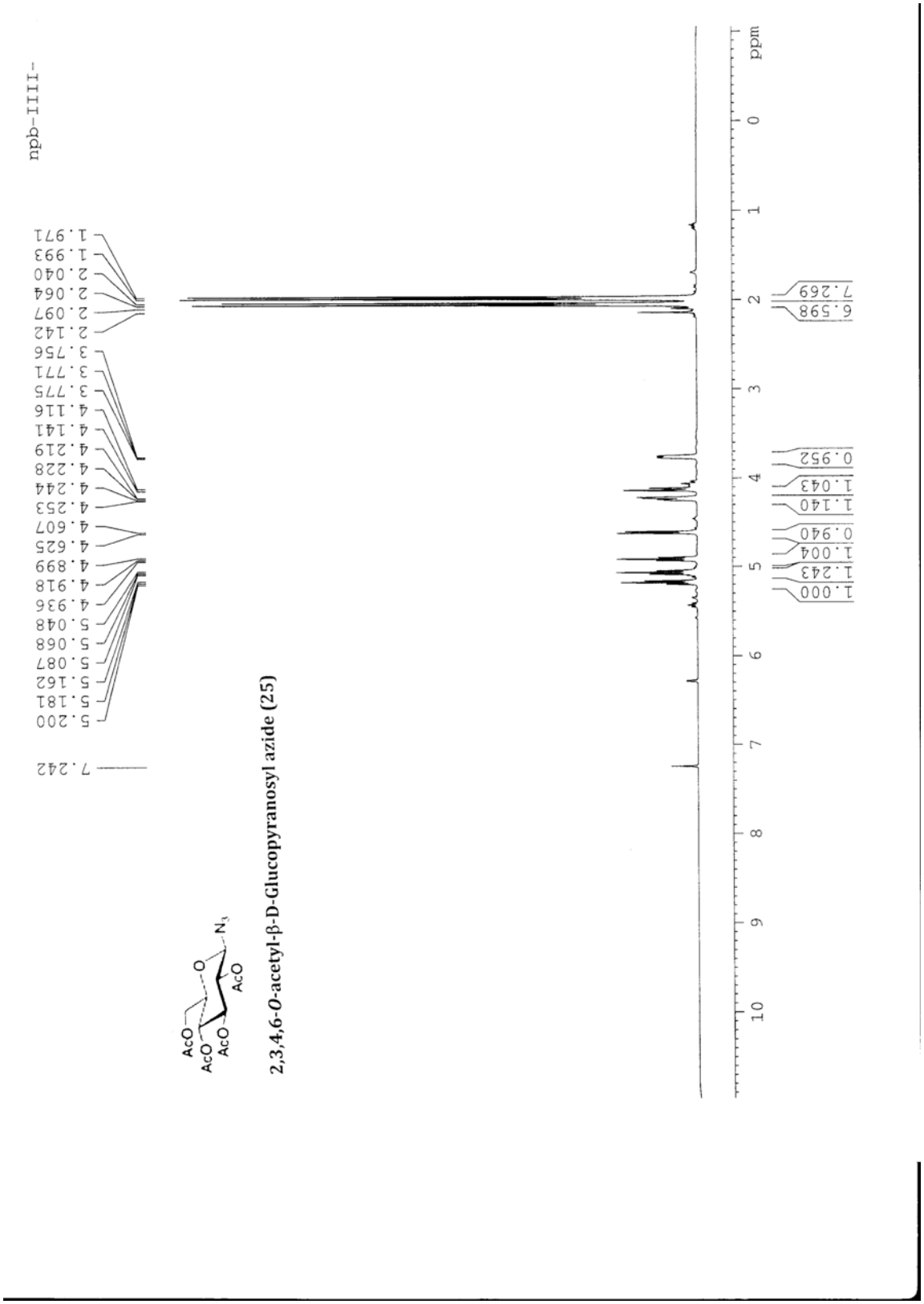
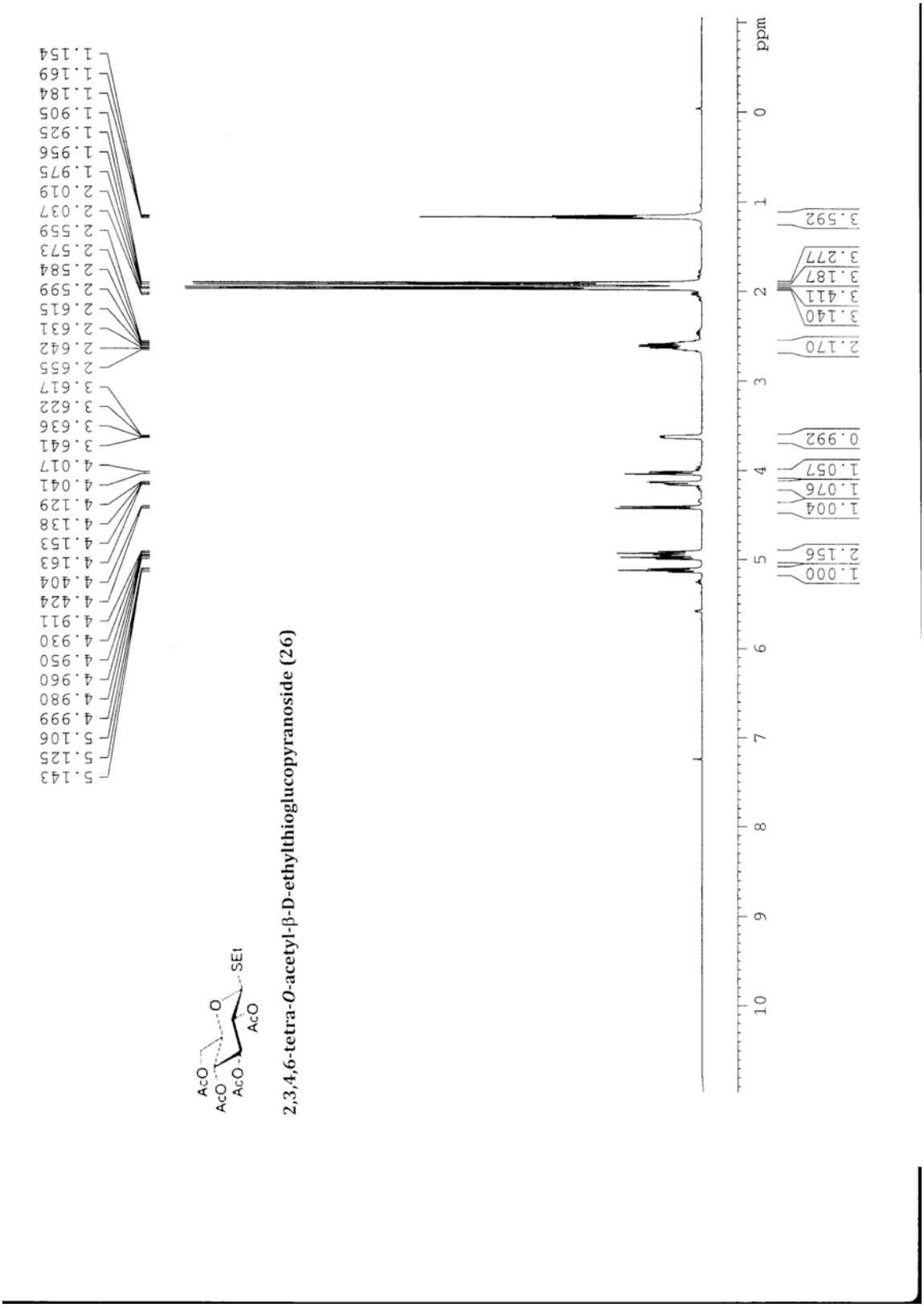
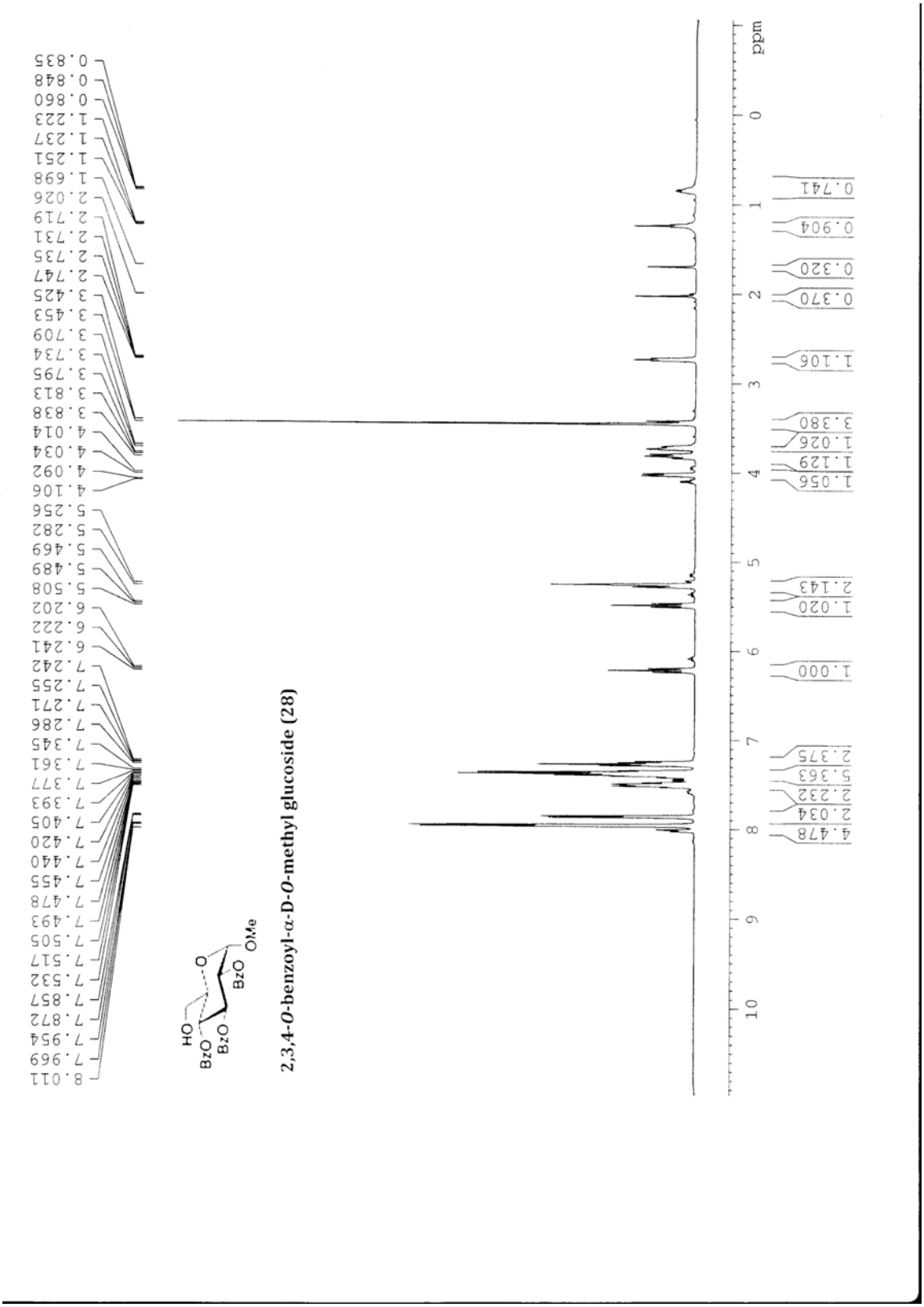
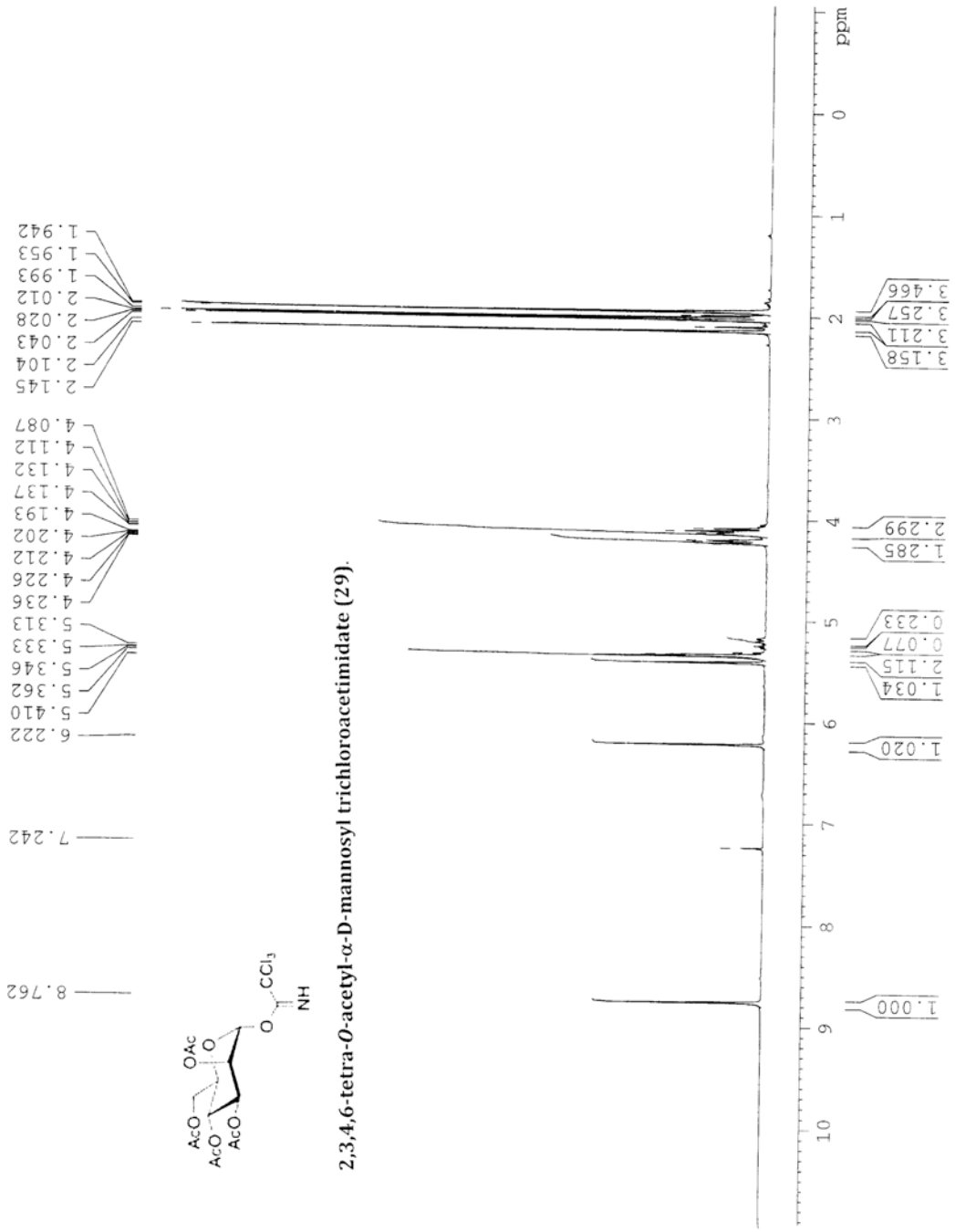
2.055
2.036
2.011
2.005
1.991
1.963
1.954
1.933

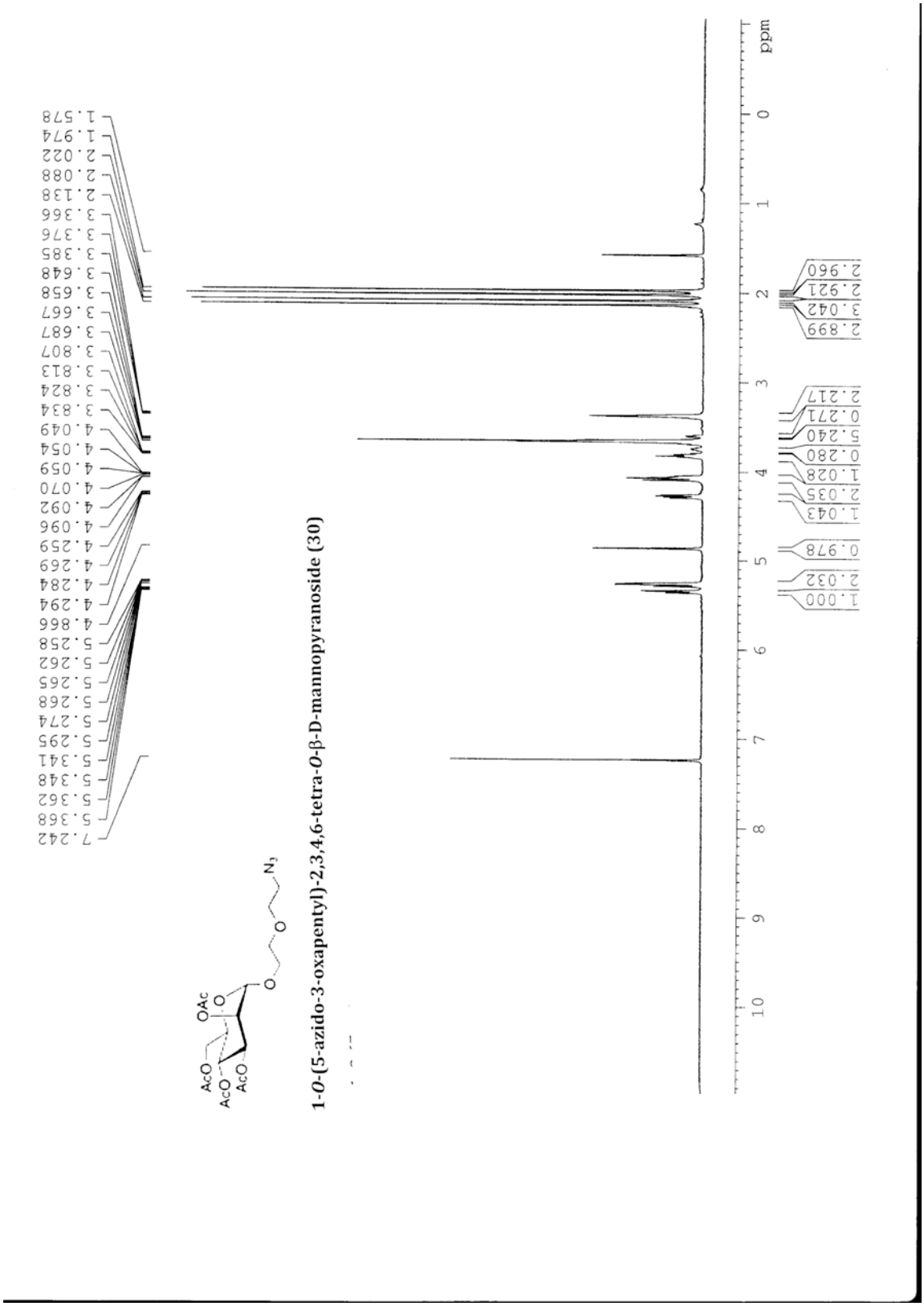

npb-IIII-
7.242
5.200
5.181
5.162
5.087
5.068
5.048
4.936
4.918
4.899
4.625
4.607
4.253
4.244
4.228
4.219
4.141
4.116
3.775
3.771
3.756
2.142
2.097
2.064
2.040
1.993
1.971
AcO
AcO
AcO
O
AcO
N3
2,3,4,6-O-acetyl-β-D-Glucopyranosyl azide (25)
1.000
1.243
1.004
0.940
1.140
1.043
0.952
7.269
6.598
ppm

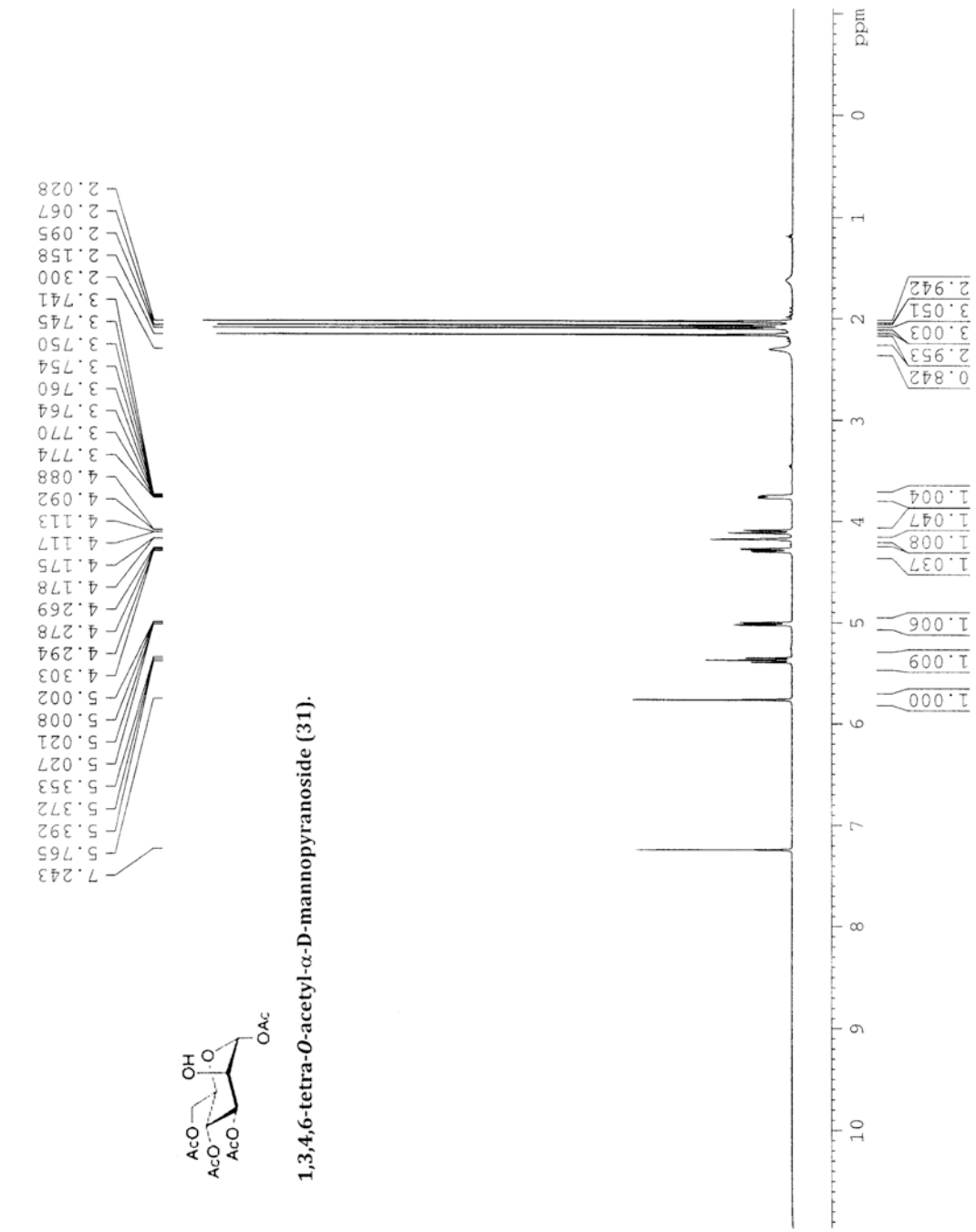

5.143
5.125
5.106
4.999
4.980
4.960
4.950
4.930
4.911
4.424
4.404
4.163
4.153
4.138
4.129
4.041
4.017
3.641
3.636
3.622
3.617
2.655
2.642
2.631
2.615
2.599
2.584
2.573
2.559
2.037
2.019
1.975
1.956
1.925
1.905
1.184
1.169
1.154
AcO
AcO
AcO
O
AcO
SEt
2,3,4,6-tetra-O-acetyl-β-D-ethylthioglucopyranoside (26)
1.000
2.156
1.004
1.076
1.057
0.992
2.170
3.140
3.411
3.187
3.277
3.592
ppm


2,3,4-O-benzoyl-α-D-O-methyl glucoside (28)
HO
BzO
BzO
O
OMe
ppm
0.741
0.904
0.320
0.370
1.106
3.380
1.026
1.129
1.056
1.020
2.143
1.000
4.478
2.034
2.232
5.363
2.375
8.011
7.969
7.954
7.872
7.857
7.532
7.517
7.505
7.493
7.478
7.455
7.440
7.420
7.405
7.393
7.377
7.361
7.345
7.286
7.271
7.255
7.242
6.241
6.222
6.202
5.508
5.489
5.469
5.282
5.256
4.106
4.092
4.034
4.014
3.838
3.813
3.795
3.734
3.709
3.453
3.425
2.747
2.735
2.731
2.719
2.026
1.698
1.251
1.237
1.223
0.860
0.848
0.835

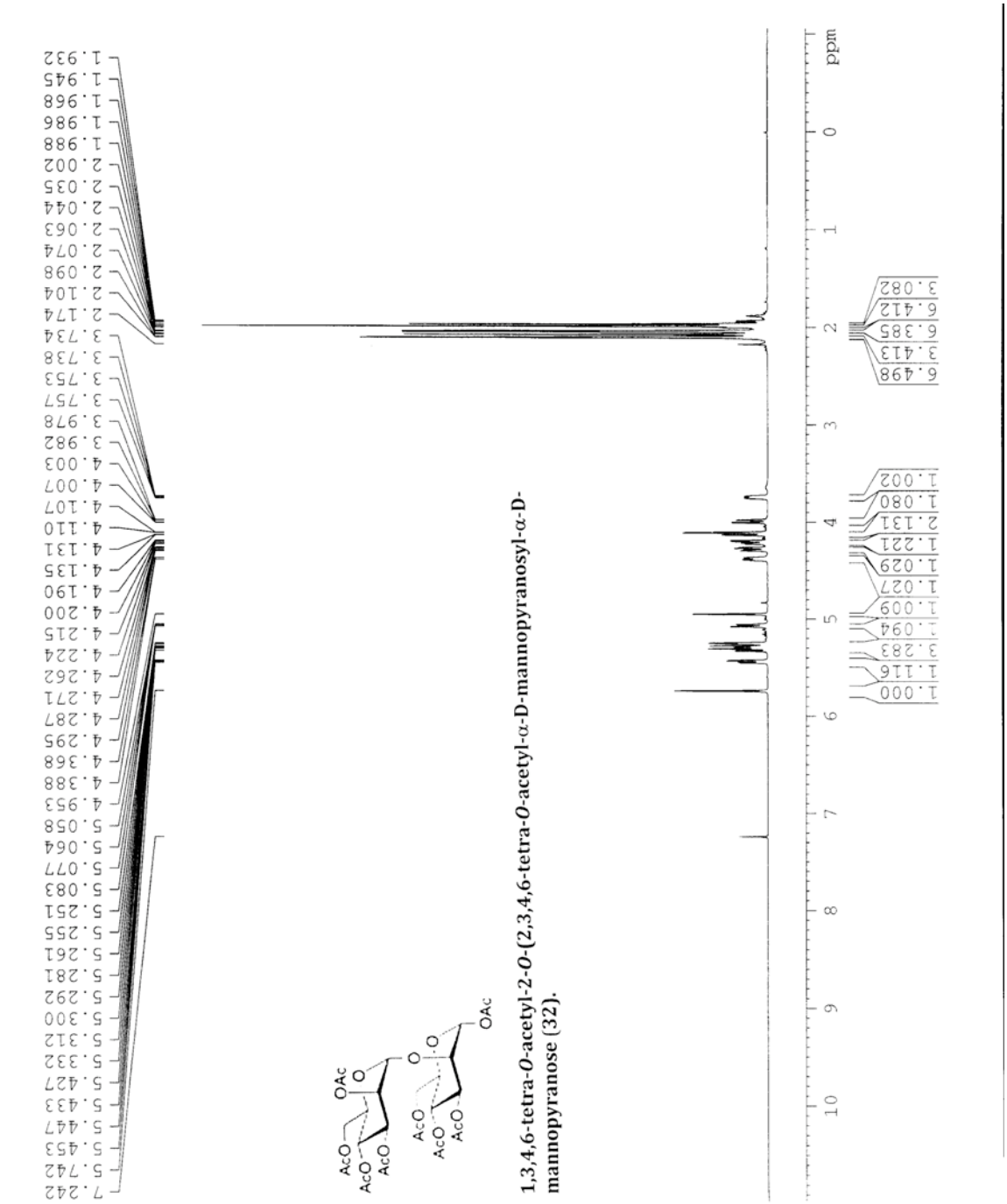


2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl trichloroacetimidate (29).

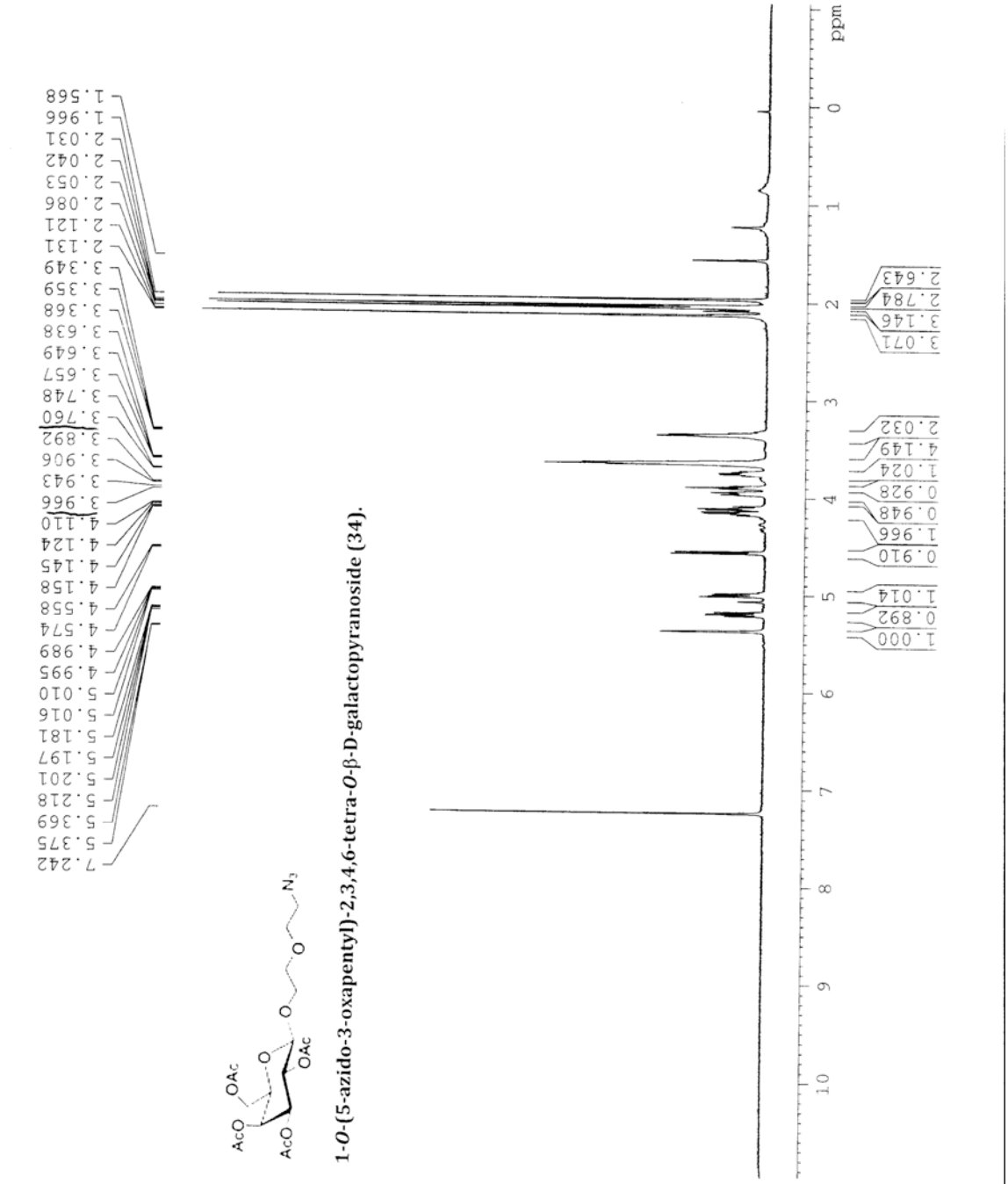

1-O-(5-azido-3-oxapentyl)-2,3,4,6-tetra-O-β-D-mannopyranoside (30)
ppm
7.242
5.368
5.362
5.348
5.341
5.295
5.274
5.268
5.265
5.262
5.258
4.866
4.294
4.284
4.269
4.259
4.096
4.092
4.070
4.059
4.054
4.049
3.834
3.824
3.813
3.807
3.687
3.667
3.658
3.648
3.385
3.376
3.366
2.138
2.088
2.022
1.974
1.578
1.000
2.032
0.978
1.043
2.035
1.028
0.280
5.240
0.271
2.217
2.899
3.042
2.921
2.960



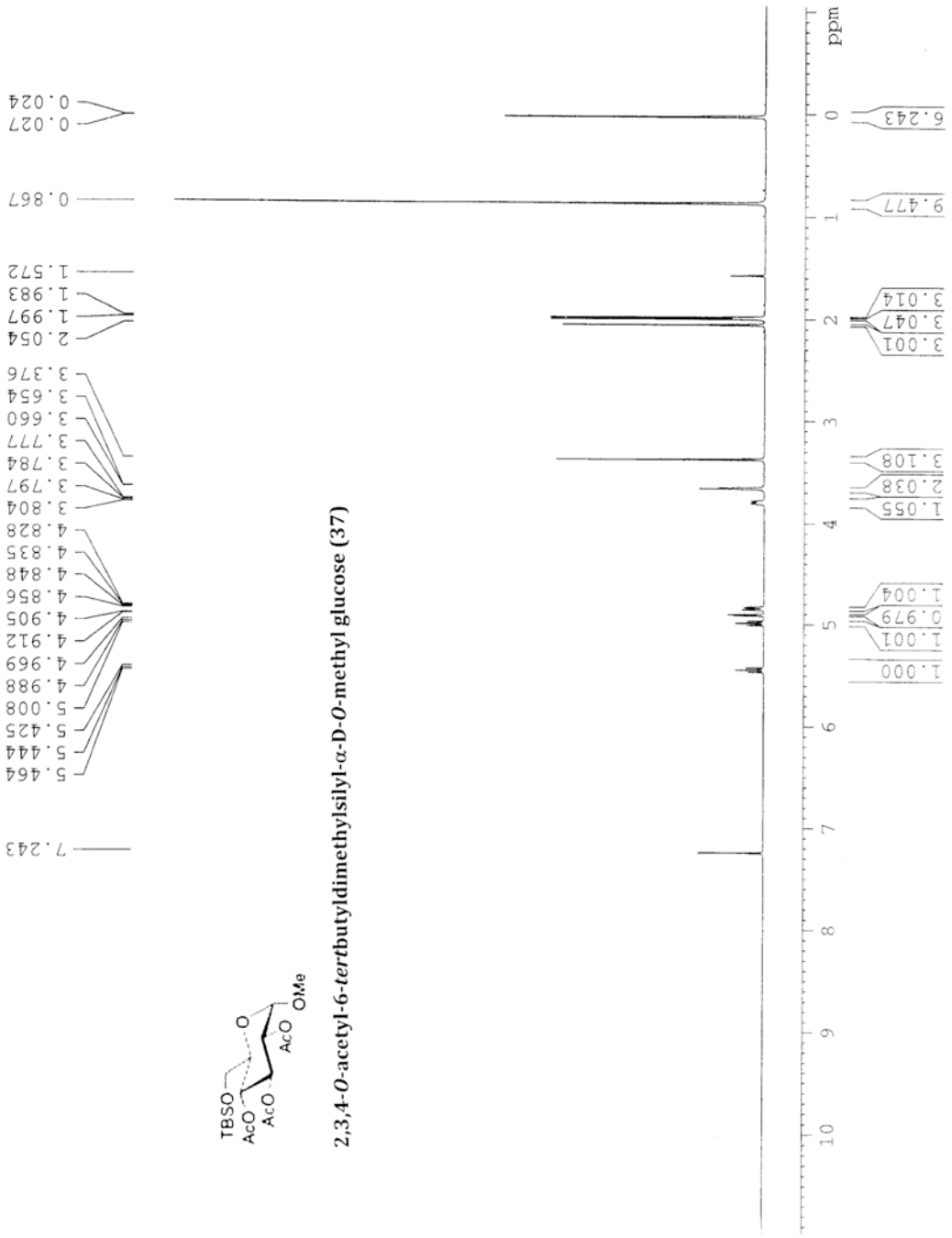
1,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (31).



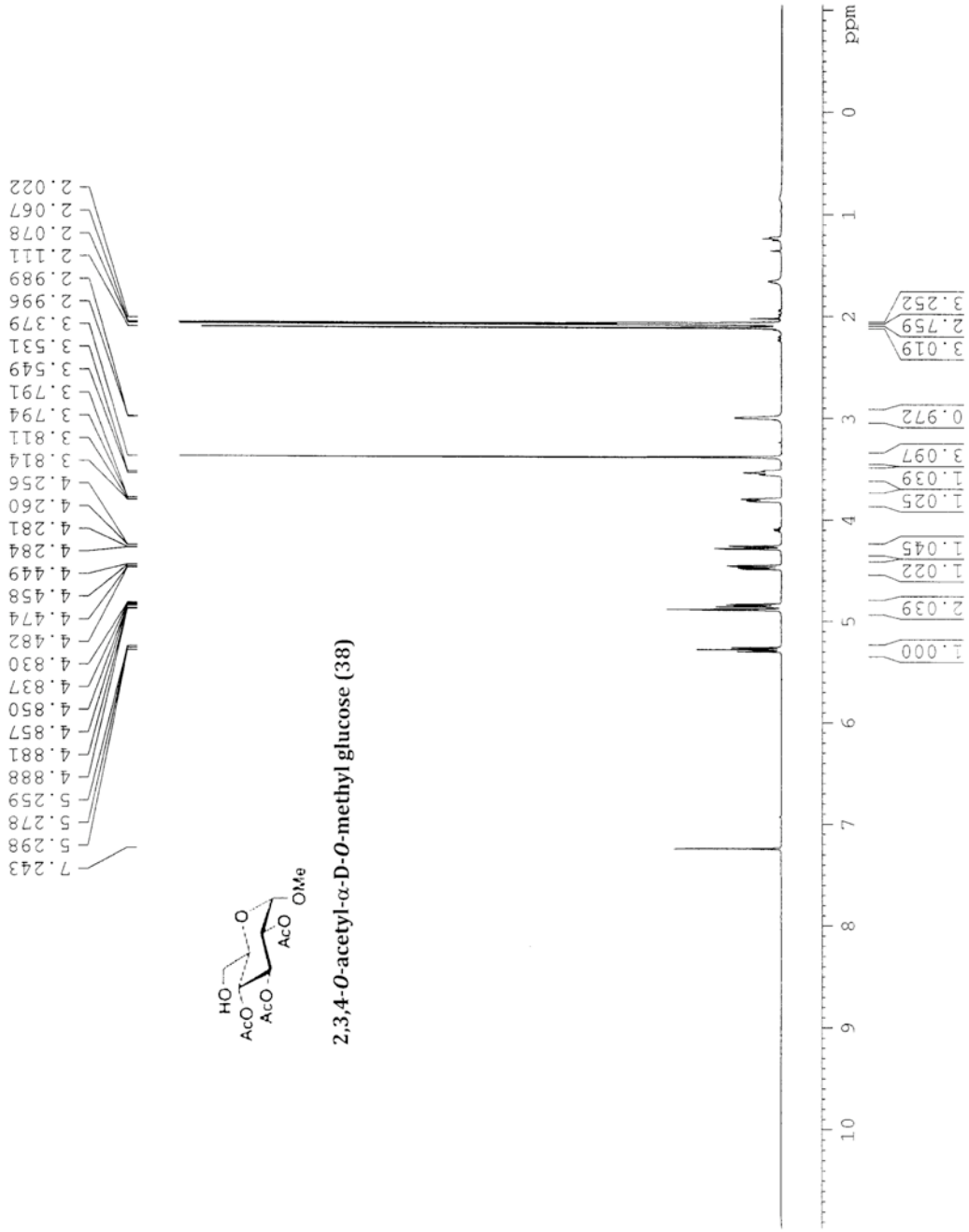
1,3,4,6-tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-α-D-mannopyranose (32).

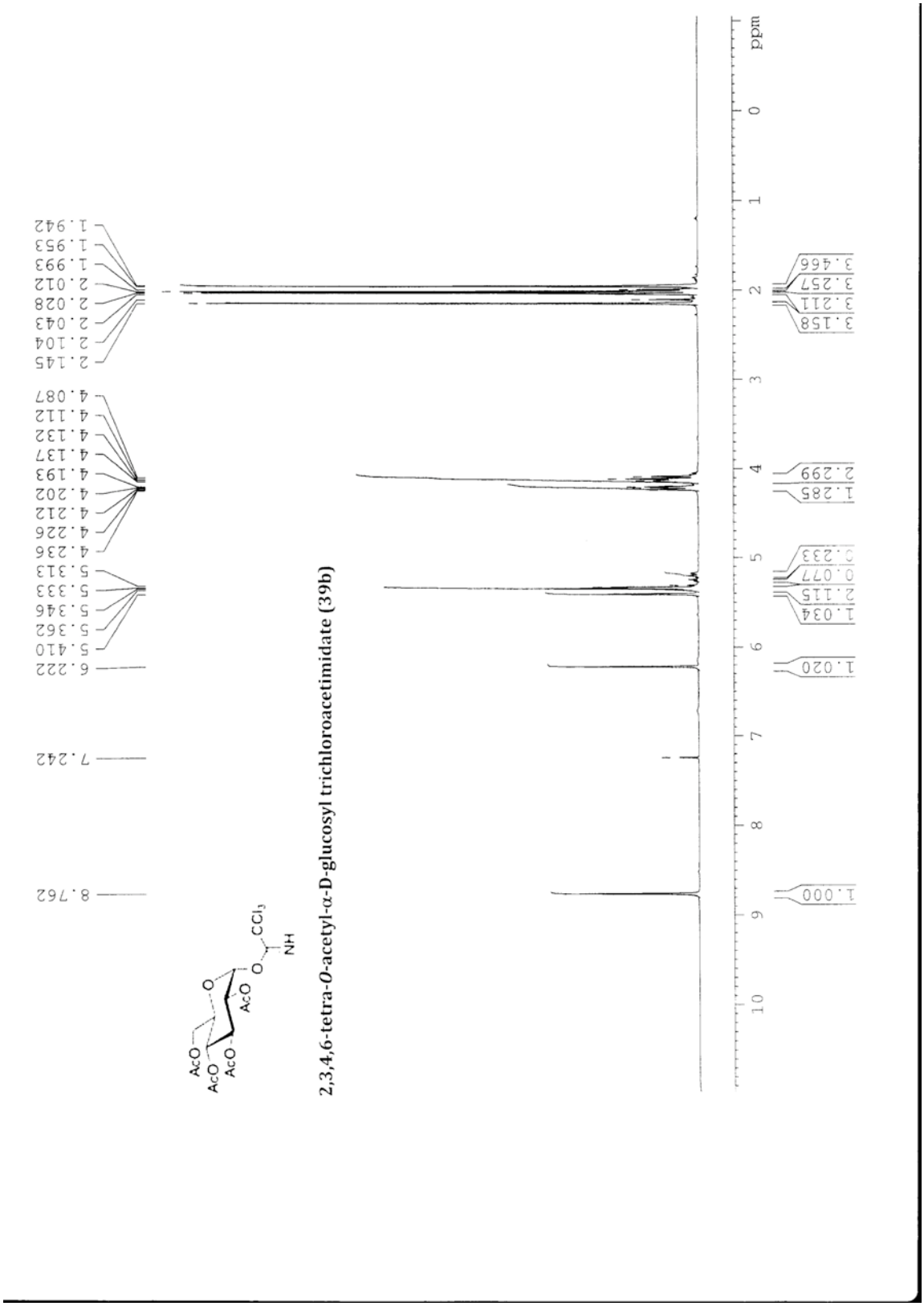


1-*O*-(5-azido-3-oxapentyl)-2,3,4,6-tetra-*O*-β-D-galactopyranoside (34).

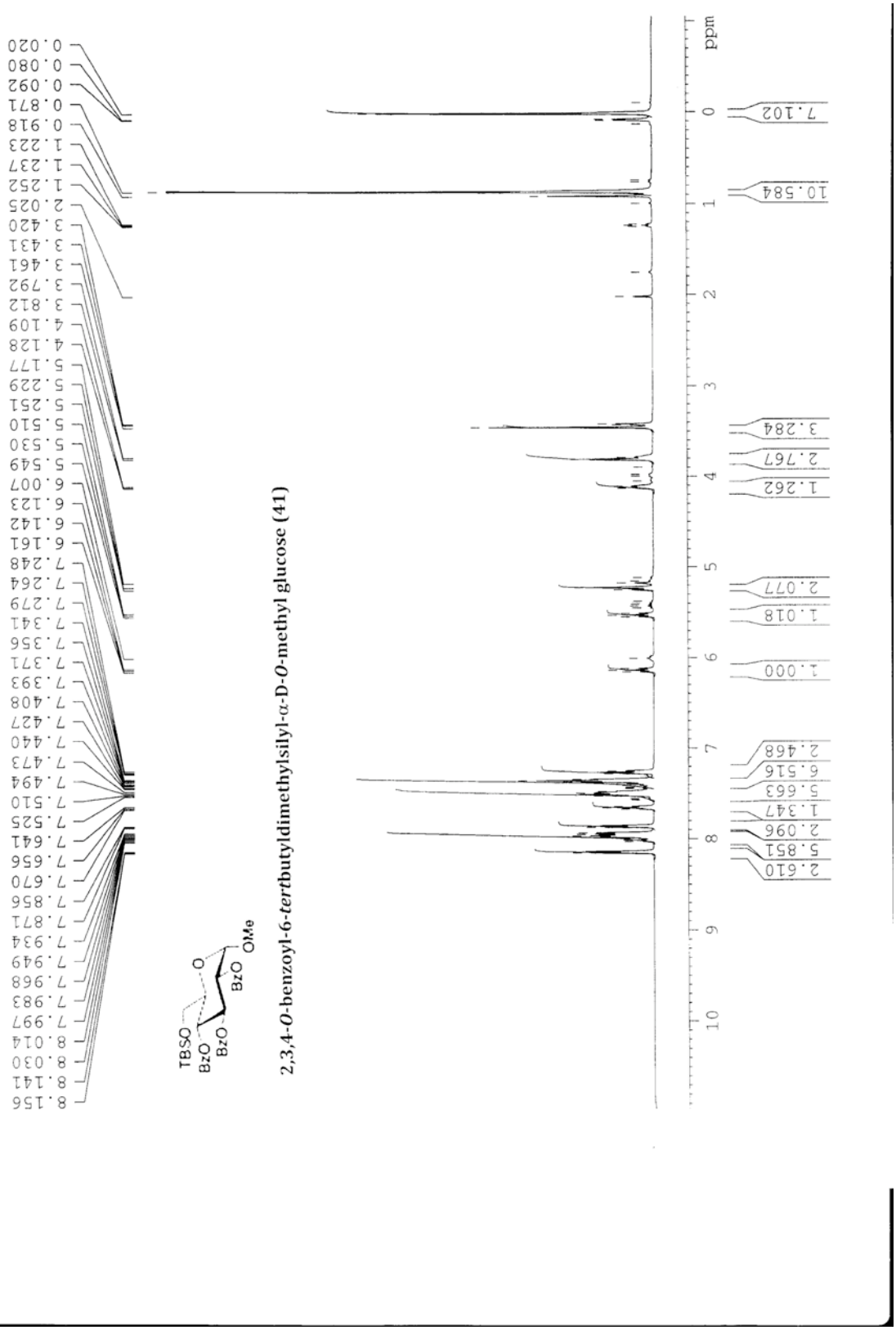


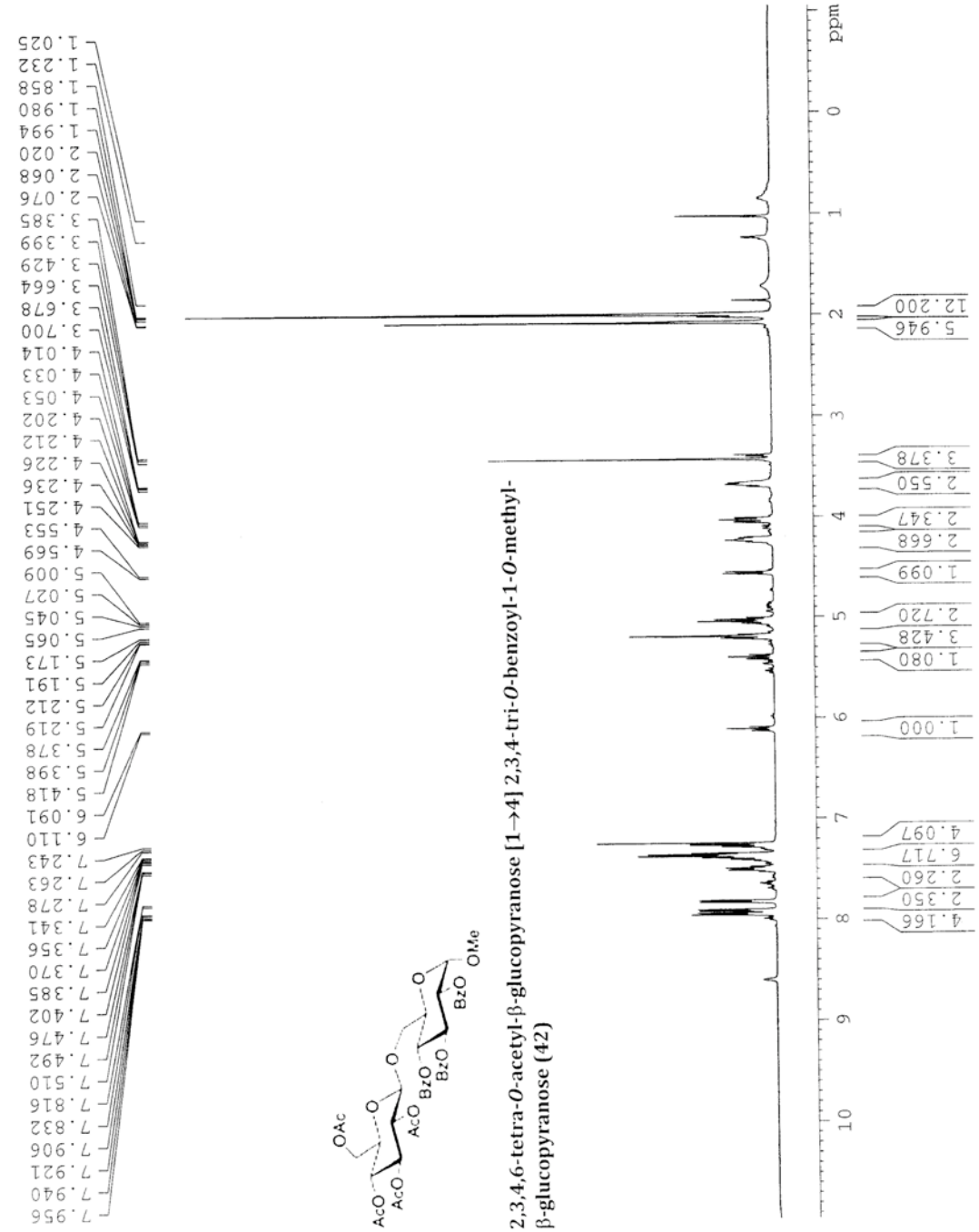
2,3,4-*O*-acetyl-6-*tert*butyldimethylsilyl-α-D-*O*-methyl glucose (37)


2,3,4-O-acetyl-α-D-O-methyl glucose (38)
HO
AcO
AcO
AcO
OMe
ppm
1.000
2.039
1.022
1.045
1.025
1.039
3.097
0.972
3.019
2.759
3.252
7.243
5.298
5.278
5.259
4.888
4.881
4.857
4.850
4.837
4.830
4.482
4.474
4.458
4.449
4.284
4.281
4.260
4.256
3.814
3.811
3.794
3.791
3.549
3.531
3.379
2.996
2.989
2.111
2.078
2.067
2.022



2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl trichloroacetimidate (39b)


2,3,4-O-benzoyl-6-tertbutyldimethylsilyl-α-D-O-methyl glucose (41)
TBSO
BzO
BzO
O
BzO
OMe
ppm
0.020
0.080
0.092
0.871
0.918
1.223
1.237
1.252
2.025
3.420
3.431
3.461
3.792
3.812
4.109
4.128
5.177
5.229
5.251
5.510
5.530
5.549
6.007
6.123
6.142
6.161
7.248
7.264
7.279
7.341
7.356
7.371
7.393
7.408
7.427
7.440
7.473
7.494
7.510
7.525
7.641
7.656
7.670
7.856
7.871
7.934
7.949
7.968
7.983
7.997
8.014
8.030
8.141
8.156
7.102
10.584
3.284
2.767
1.262
2.077
1.018
1.000
2.468
6.516
5.663
1.347
2.096
5.851
2.610



2,3,4,6-tetra-*O*-acetyl-β-glucopyranose [1→4] 2,3,4-tri-*O*-benzoyl-1-*O*-methyl-β-glucopyranose (42)

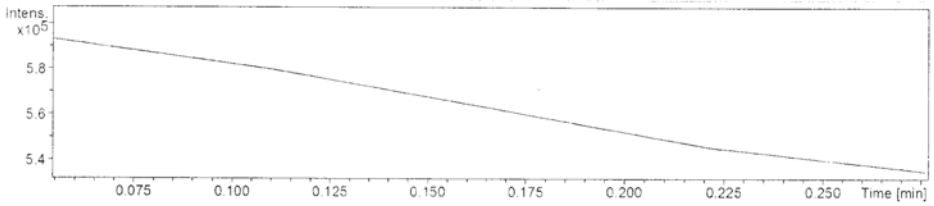
MSU MS Lab - Mass List Report

Analysis Info

Analysis Name	Y:\Facility\BizierN_080912_IIII_1.d	Acquisition Date	9/12/2008 15:47:41
Method	Phil_Facility_pos_wider_mid_high_080908.m	Operator	Phil
Sample Name	Bizier IIII-1	Instrument	micrOTOF 64
Comment	Sample labelled "npb-IIII-1" formula C24H44O18, Expected m/z: protonated form = 621.2600, Na adduct = 643.2420, K adduct = 659.2159. Mass of interest not found. This sample is badly contaminated with compounds at 249.15 and 475.33 m/z. If you can figure out what these are it would help, because these are persistant and have contaminated the instrument recently and took a long time to get rid of these contaminants.		

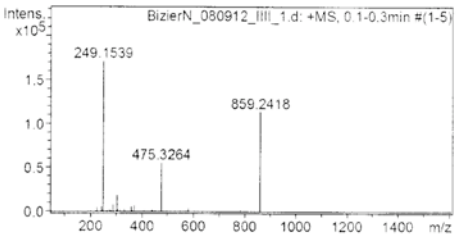
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Corrector Fill	68 V
Scan Range	n/a	Capillary Exit	105.0 V	Set Pulsar Pull	420 V
Scan Begin	50 m/z	Hexapole RF	115.0 V	Set Pulsar Push	420 V
Scan End	1600 m/z	Skimmer 1	40.0 V	Set Reflector	1180 V
		Hexapole 1	21.2 V	Set Flight Tube	9000 V
				Set Detector TOF	2200 V

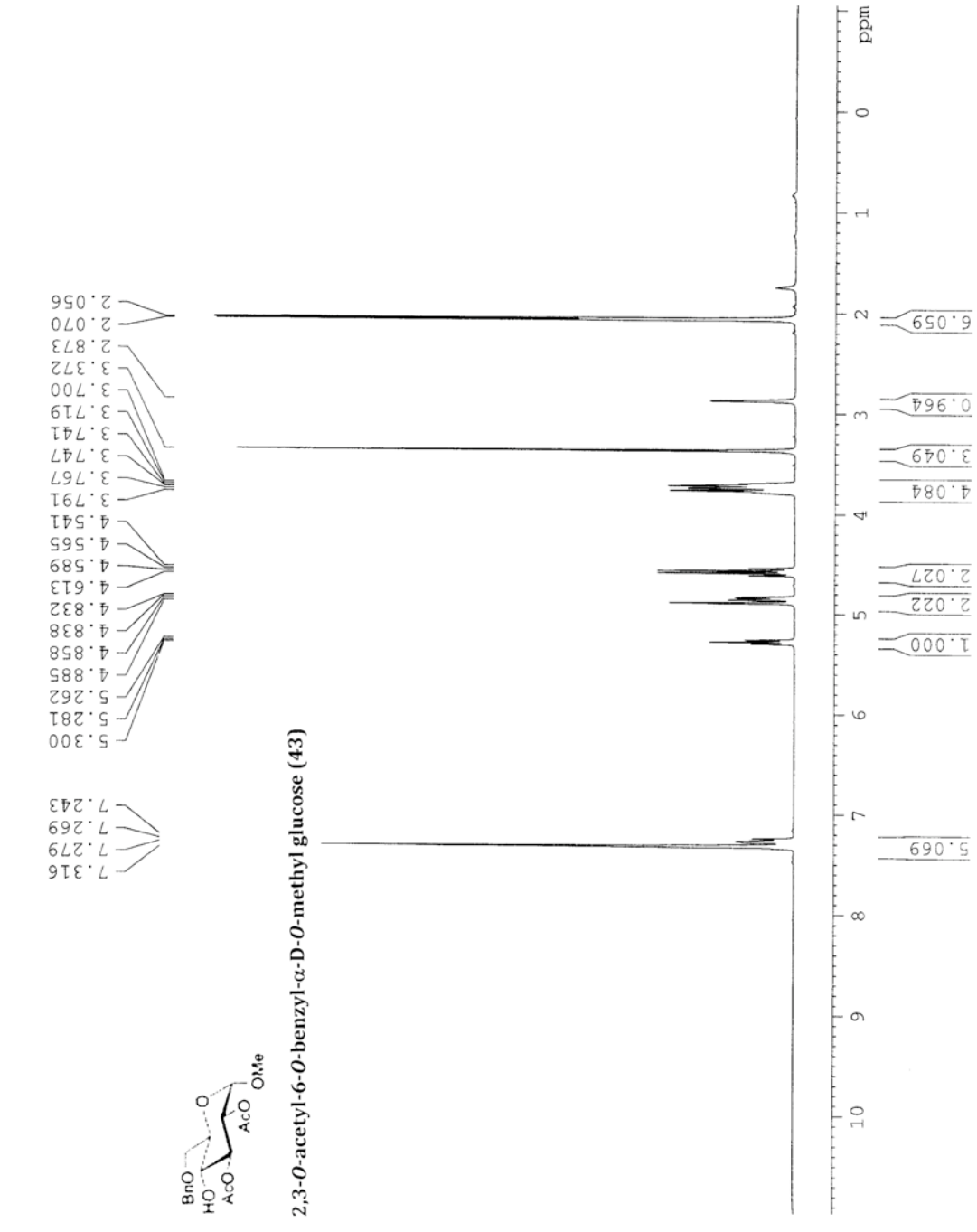


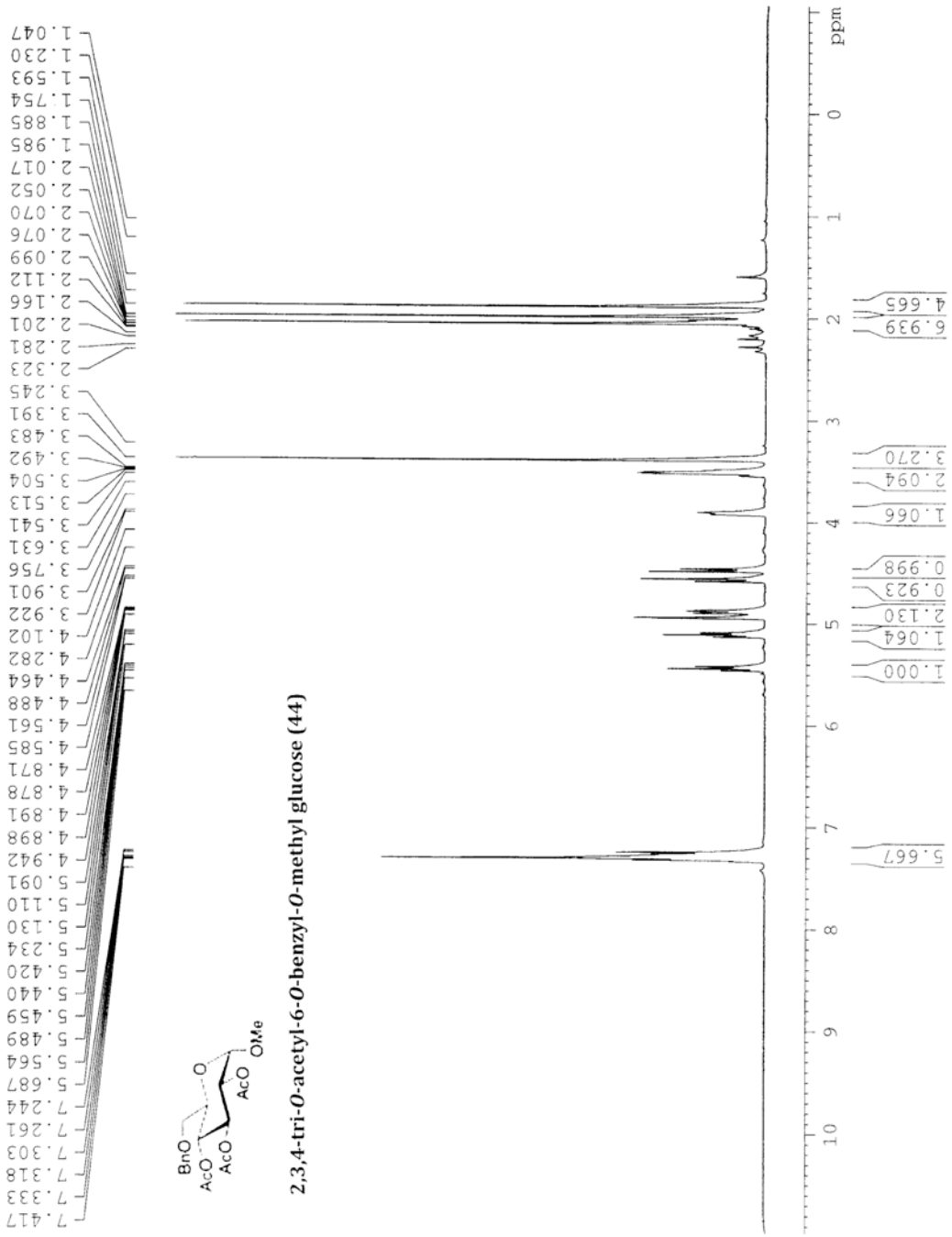
#	RT [min]	Area
n.a.	0.2	n.a.

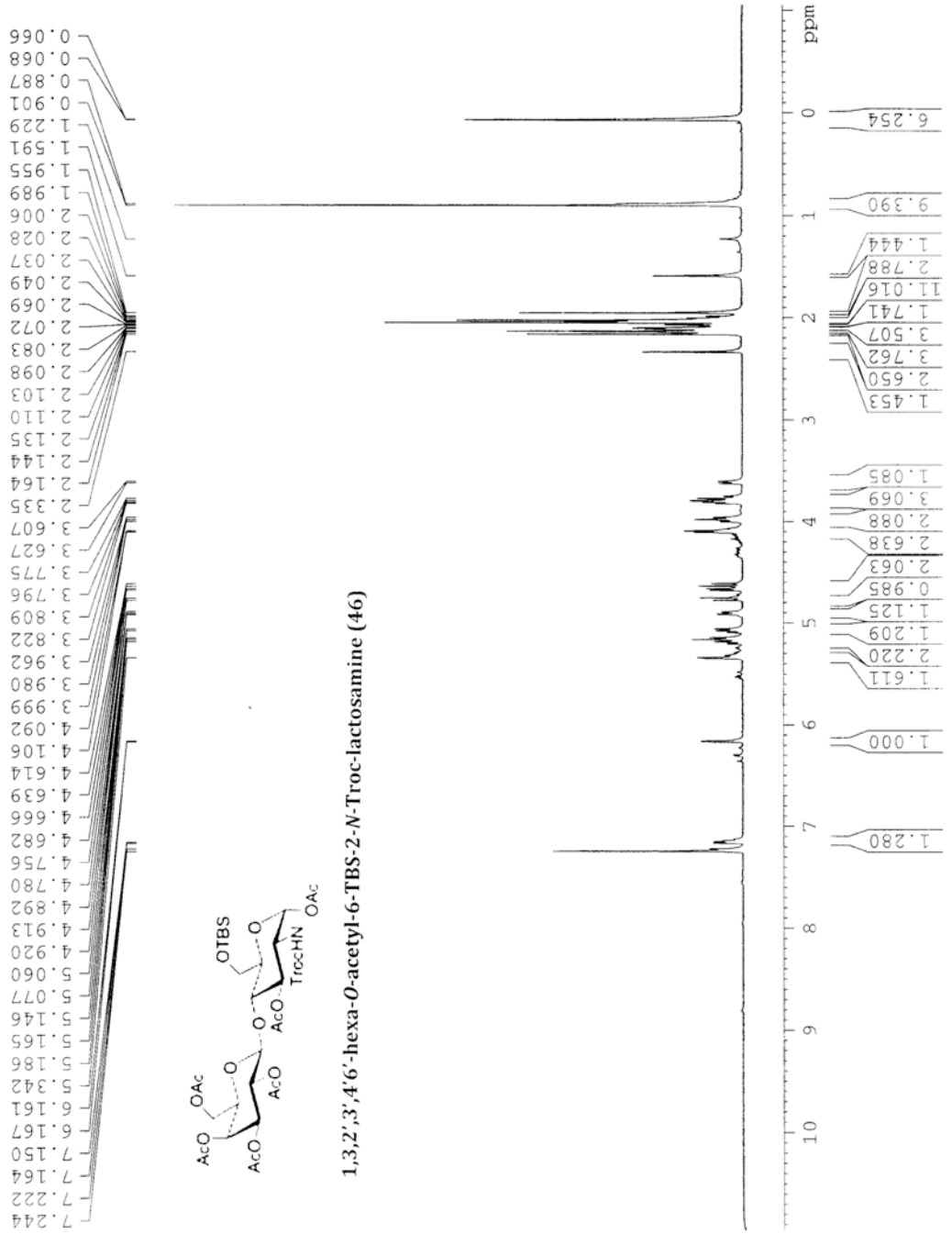
+MS, 0.1-0.3min #(1-5)

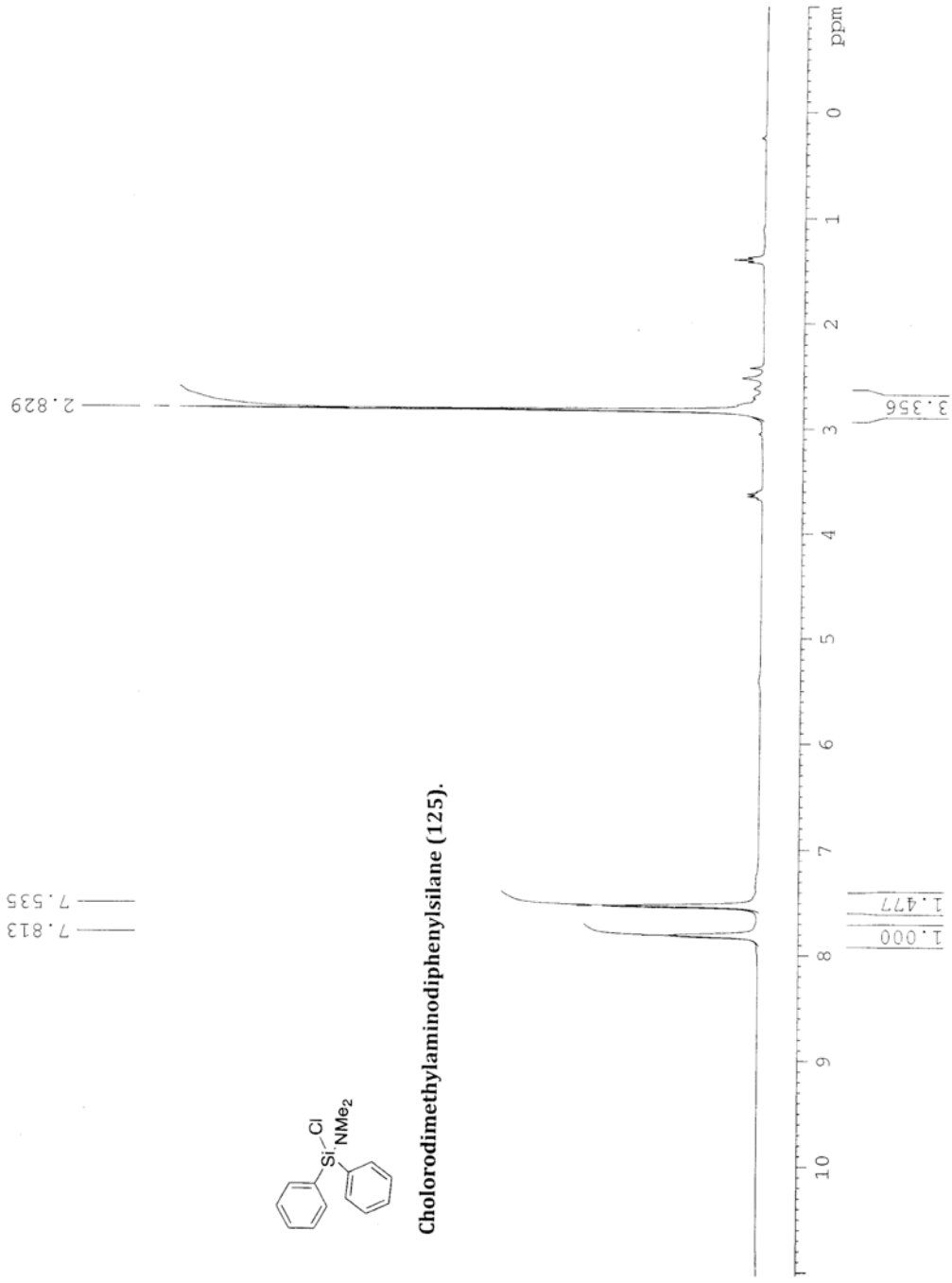


#	m/z	I
1	244.2596	5628
2	249.1539	170508
3	250.1583	9988
4	288.2878	7398
5	304.2648	18155
6	371.0966	6852
7	475.3264	54899
8	476.3301	6433
9	859.2418	113037
10	860.2454	25454

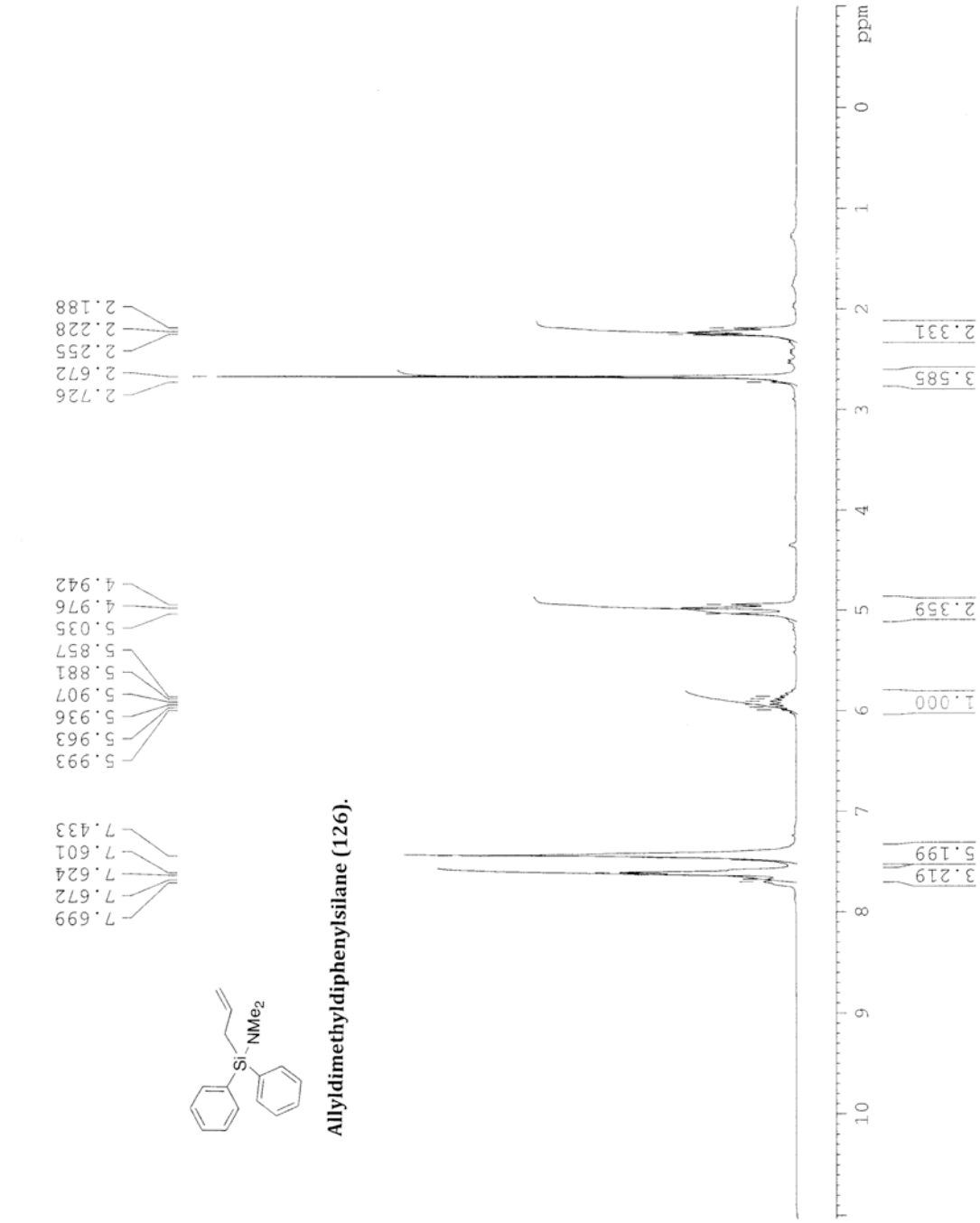

2,3-O-acetyl-6-O-benzyl-α-D-O-methyl glucose (43)
BnO
HO
AcO
AcO
O
OMe
7.316
7.279
7.269
7.243
5.300
5.281
5.262
4.885
4.858
4.838
4.832
4.613
4.589
4.565
4.541
3.791
3.767
3.747
3.741
3.719
3.700
3.372
2.873
2.070
2.056
ppm
5.069
1.000
2.022
2.027
4.084
3.049
0.964
6.059


1.047
1.230
1.593
1.754
1.885
1.985
2.017
2.052
2.070
2.076
2.099
2.112
2.166
2.201
2.281
2.323
3.245
3.391
3.483
3.492
3.504
3.513
3.541
3.631
3.756
3.901
3.922
4.102
4.282
4.464
4.488
4.561
4.585
4.871
4.878
4.891
4.898
4.942
5.091
5.110
5.130
5.234
5.420
5.440
5.459
5.489
5.564
5.687
7.244
7.261
7.303
7.318
7.333
7.417
BnO
AcO
AcO
O
AcO
OMe
2,3,4-tri-O-acetyl-6-O-benzyl-O-methyl glucose (44)
ppm
10
9
8
7
6
5
4
3
2
1
0
5.667
1.000
1.064
2.130
0.923
0.998
1.066
2.094
3.270
6.939
4.665

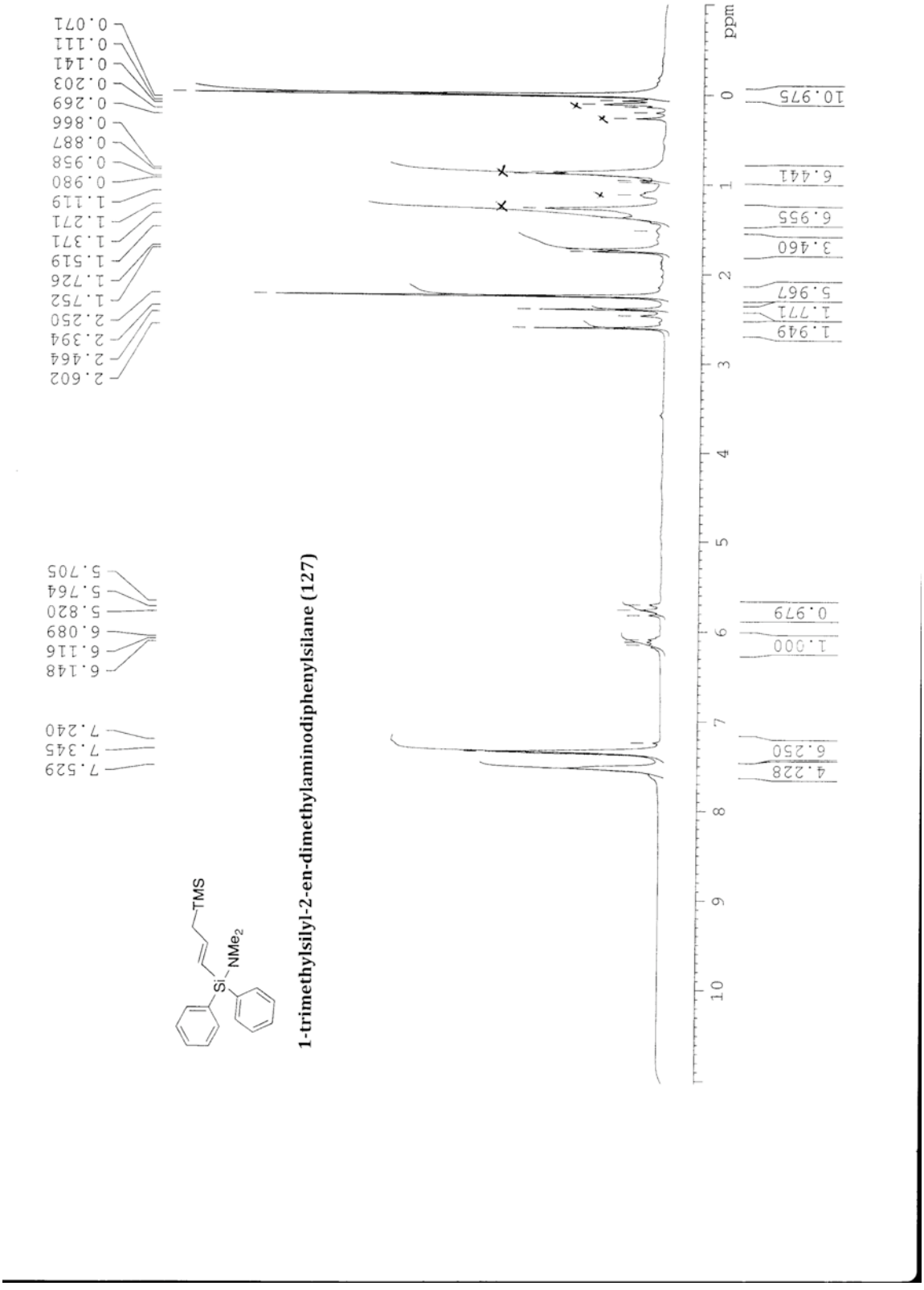

1,3,2',3',4'6'-hexa-O-acetyl-6-TBS-2-N-Troc-lactosamine (46)
OTBS
TrocHN
AcO
OAc
ppm
6.254
9.390
1.444
2.788
11.016
1.741
3.507
3.762
2.650
1.453
1.085
3.069
2.088
2.638
2.063
0.985
1.125
1.209
2.220
1.611
1.000
1.280

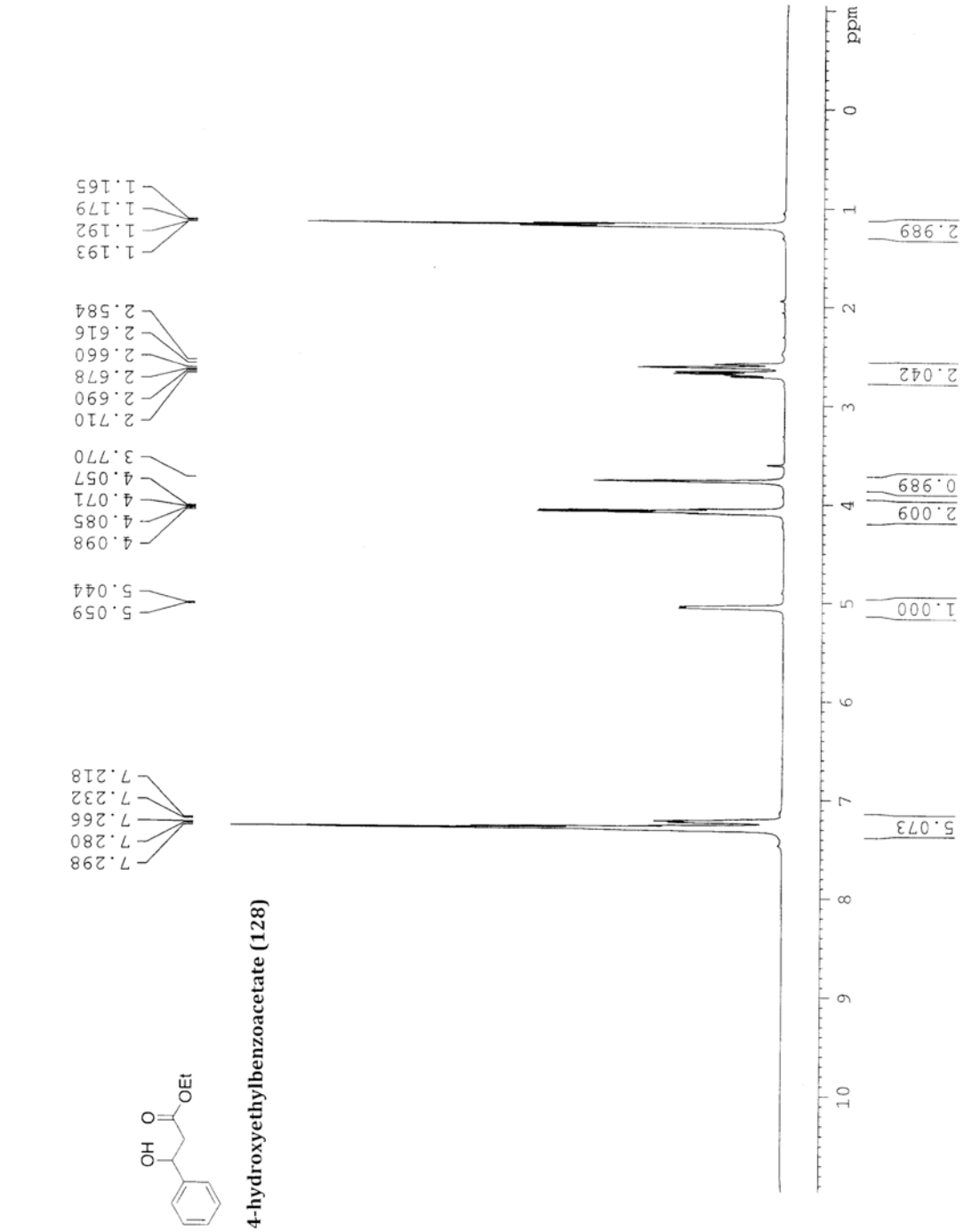


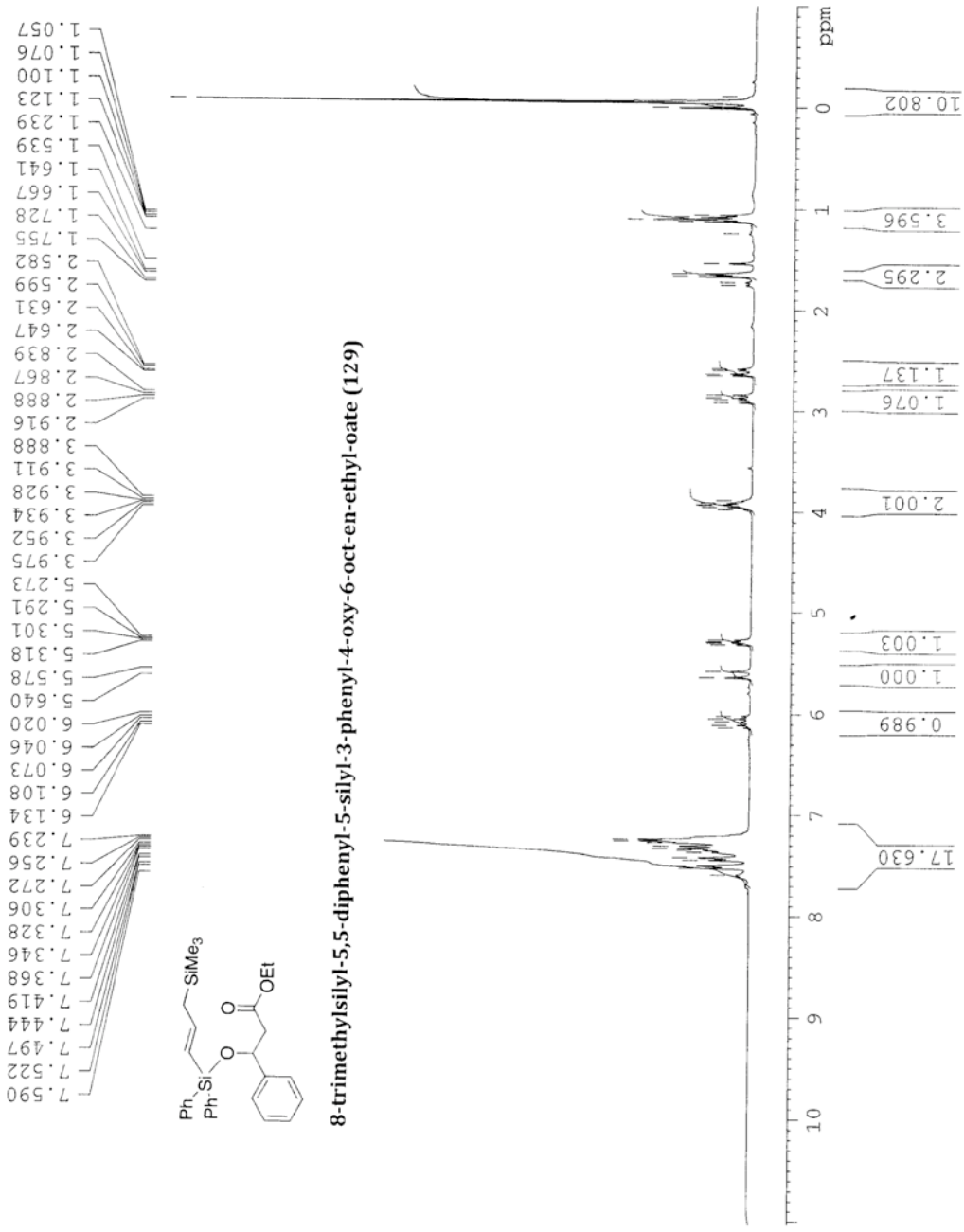
Cholorodimethylaminodiphenylsilane (125).



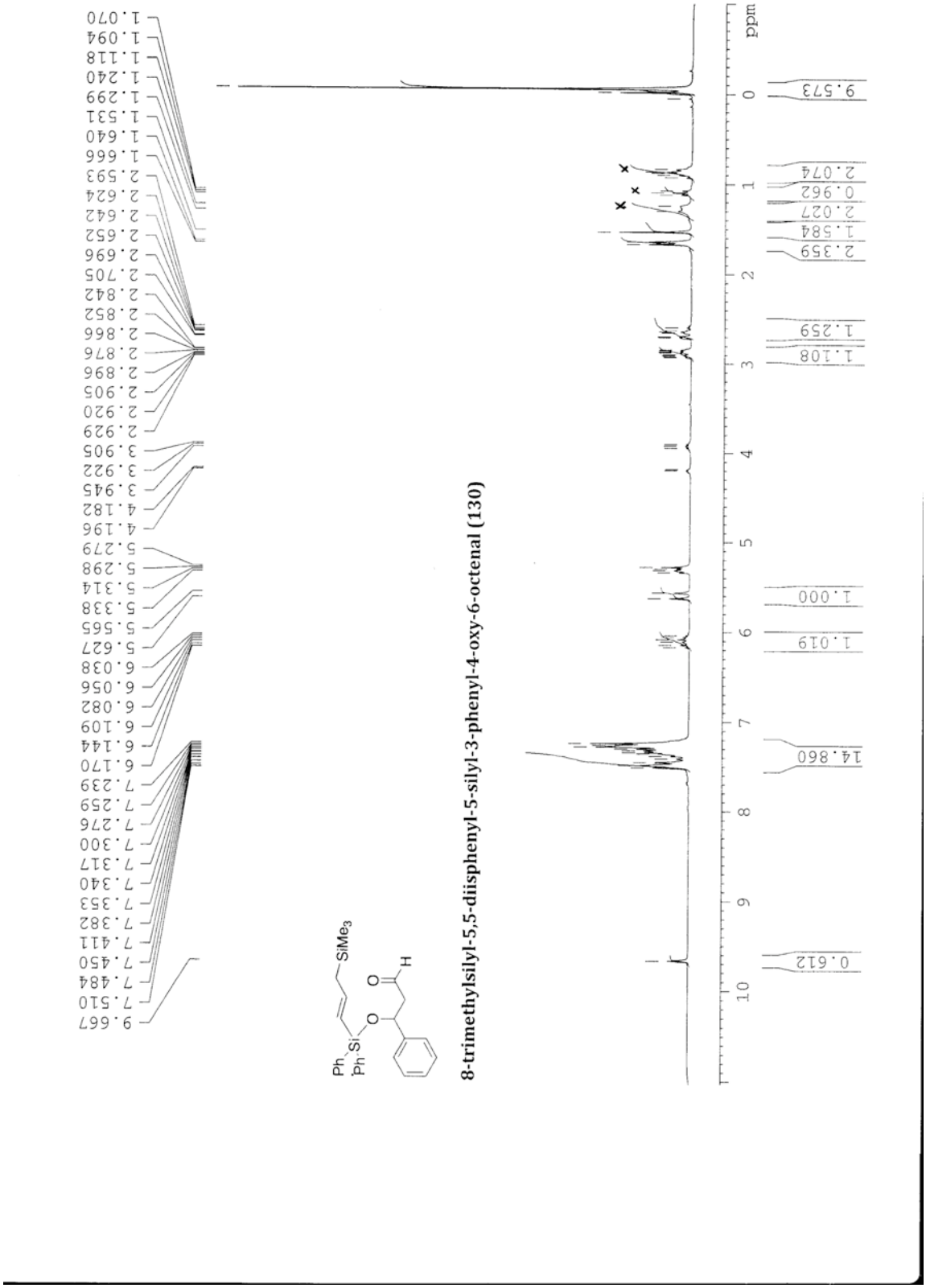
Allyldimethyldiphenylsilane (126).

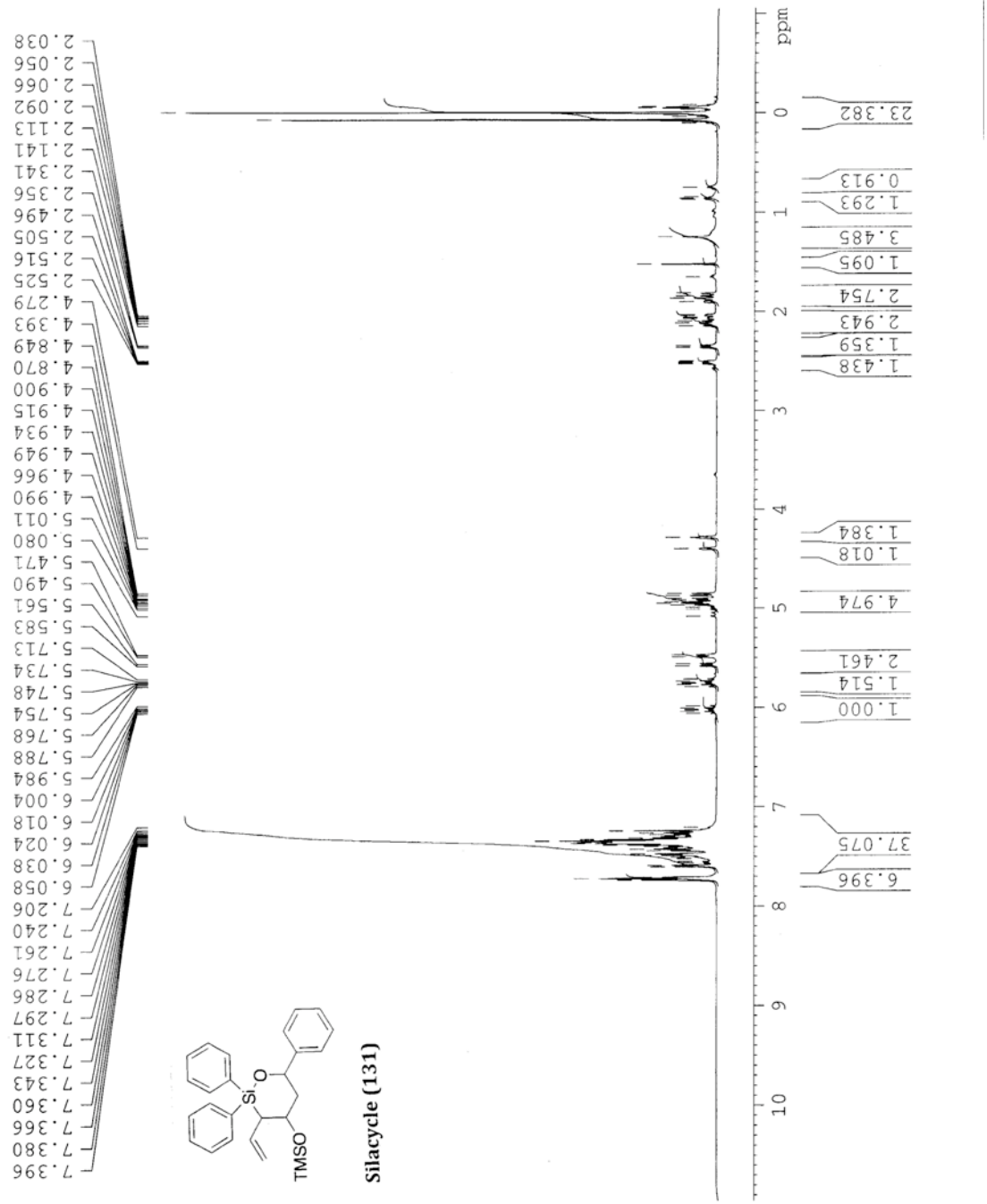

TMS
NMe2
Si
1-trimethylsilyl-2-en-dimethylaminodiphenylsilane (127)
ppm

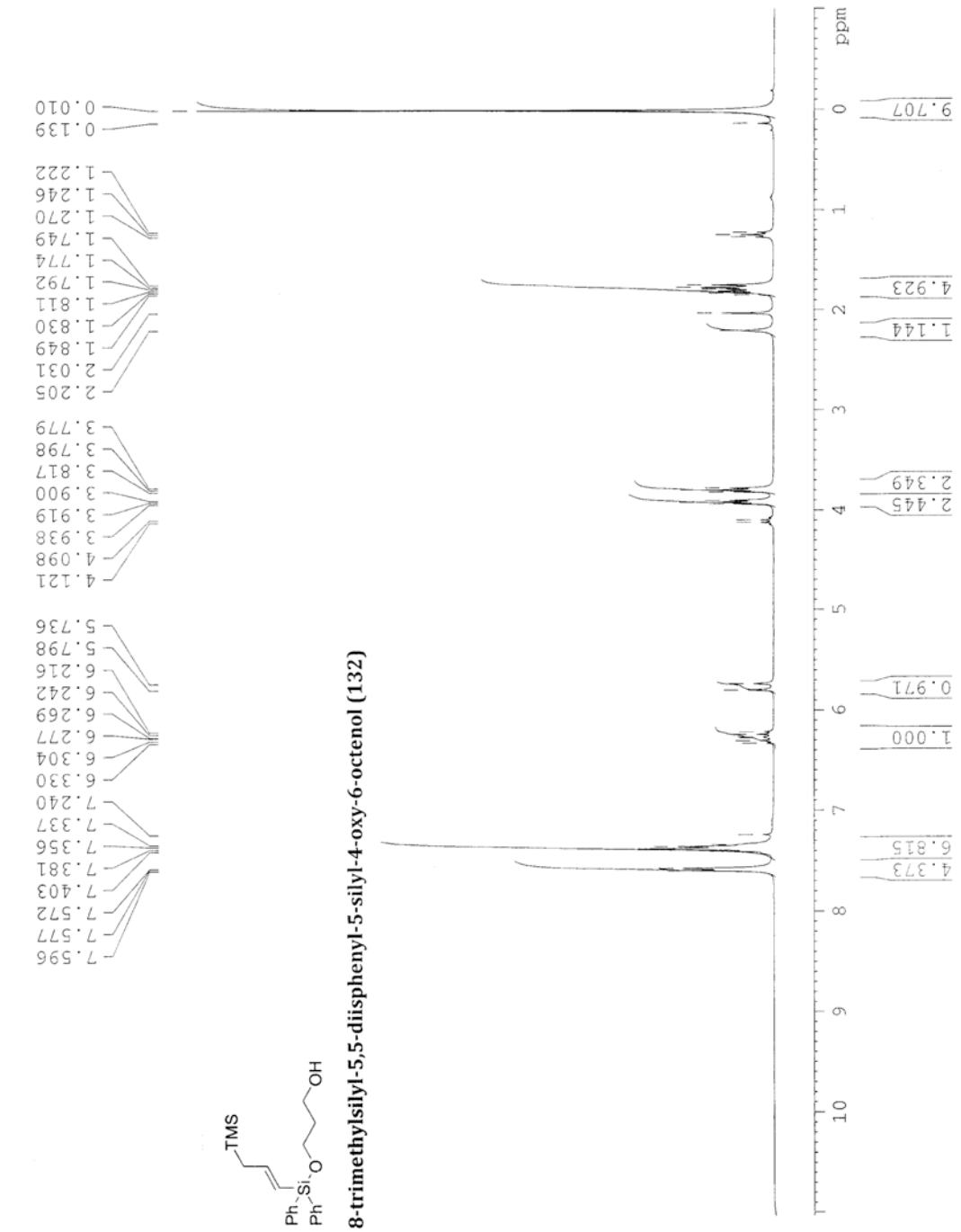

4-hydroxyethylbenzoacetate (128)
OH
O
OEt
7.298
7.280
7.266
7.232
7.218
5.059
5.044
4.098
4.085
4.071
4.057
3.770
2.710
2.690
2.678
2.660
2.616
2.584
1.193
1.192
1.179
1.165
ppm
5.073
1.000
2.009
0.989
2.042
2.989

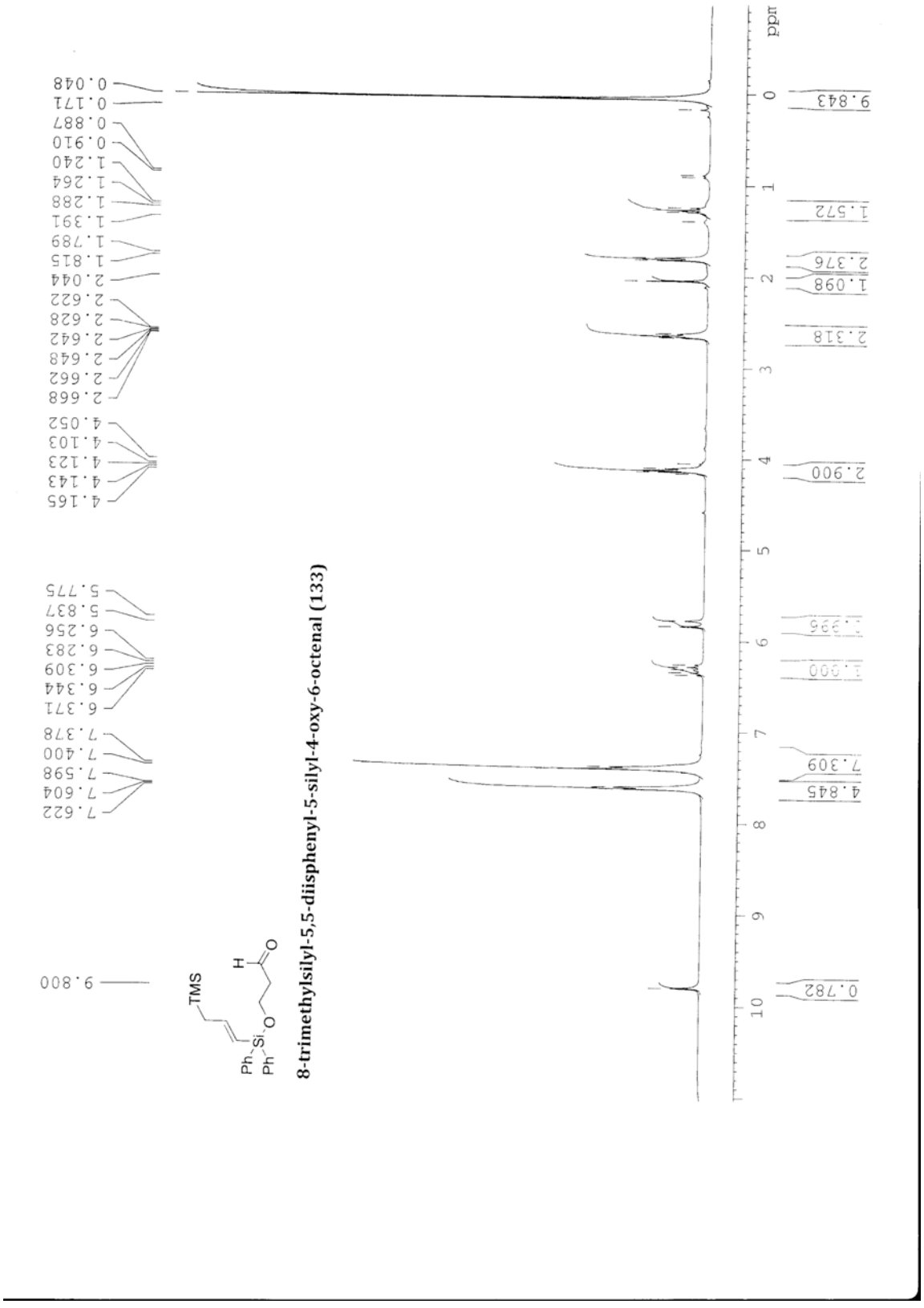


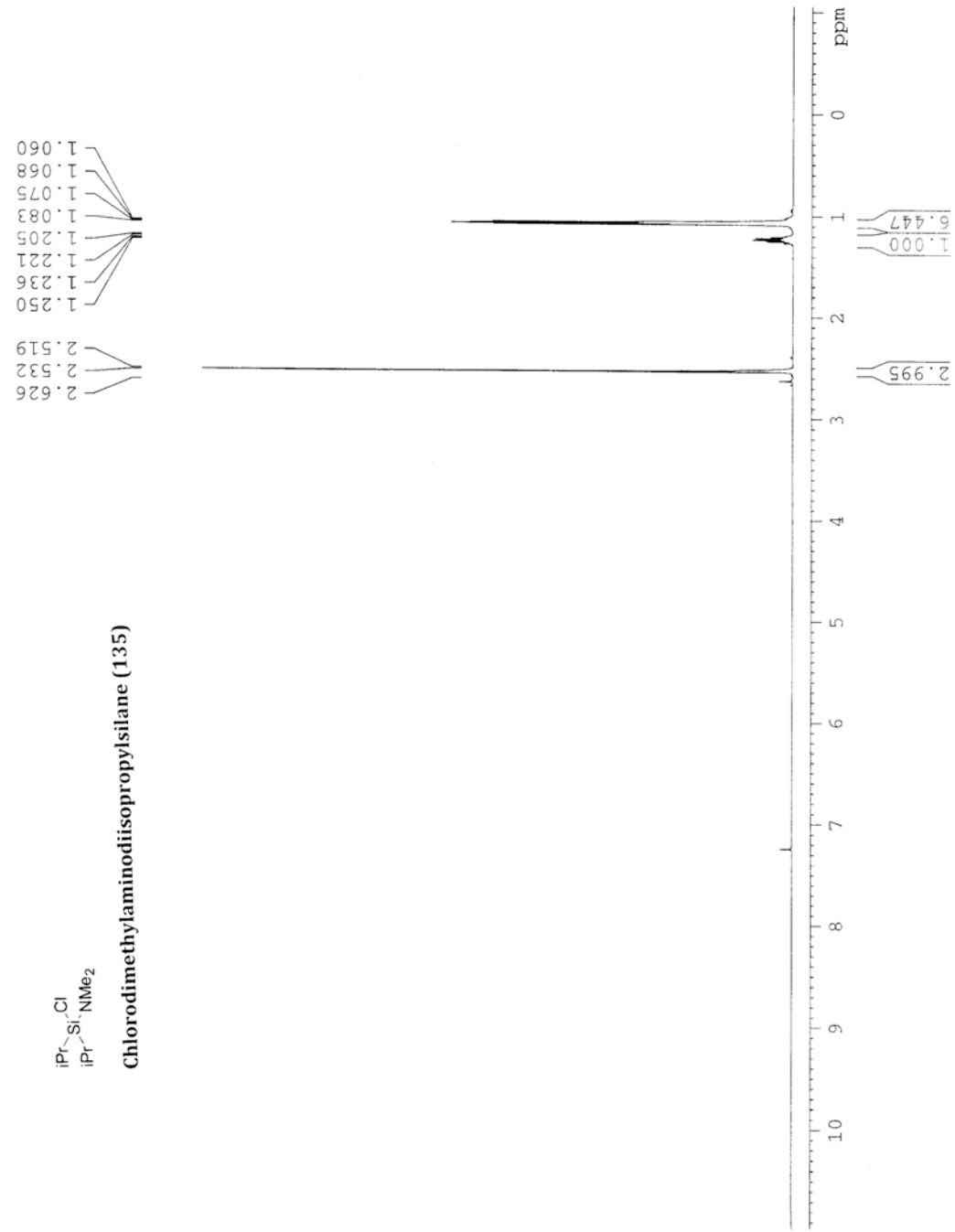
8-trimethylsilyl-5,5-diphenyl-5-silyl-3-phenyl-4-oxy-6-oct-en-ethyl-oate (129)

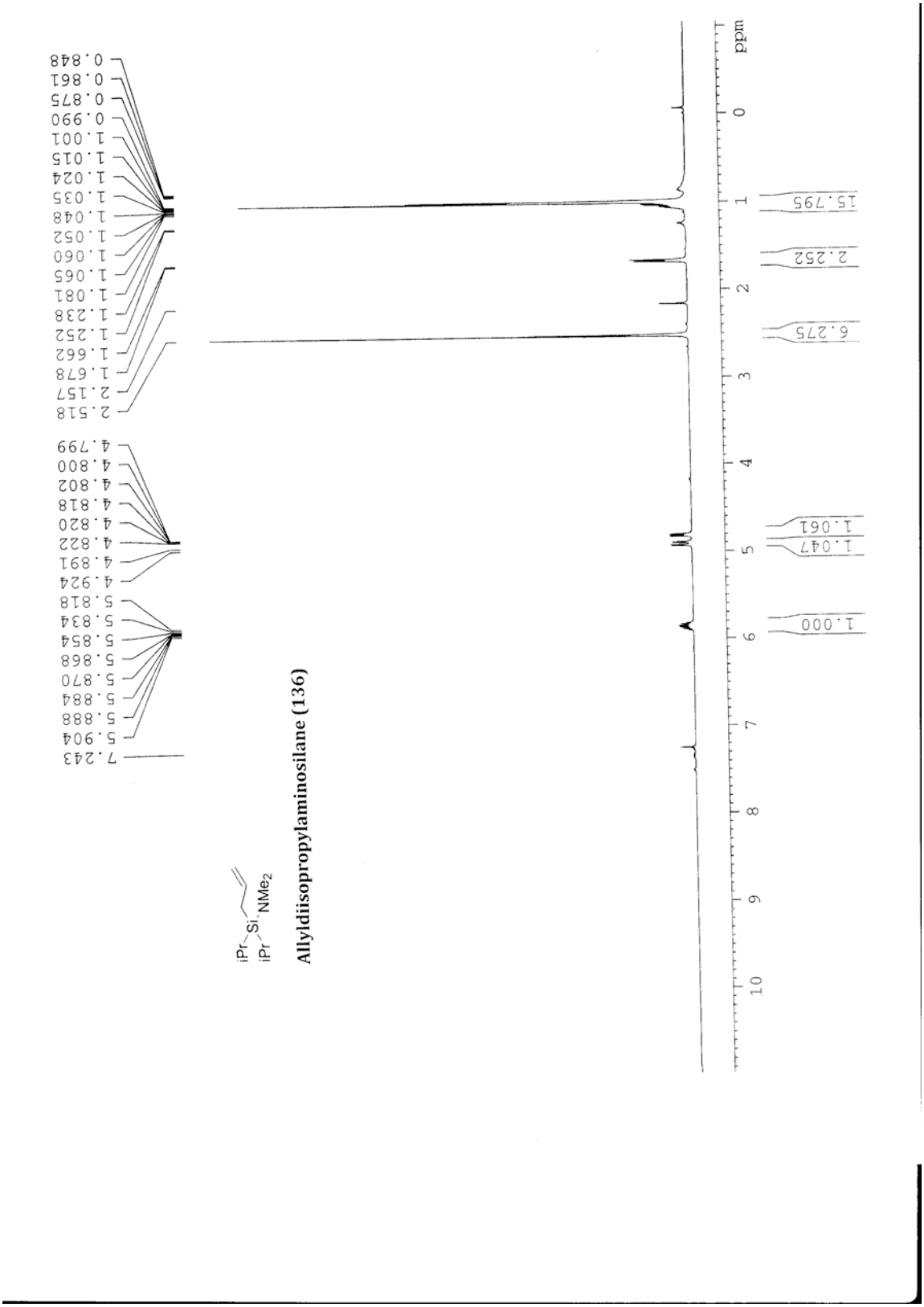

9.667
7.510
7.484
7.450
7.411
7.382
7.353
7.340
7.317
7.300
7.276
7.259
7.239
6.170
6.144
6.109
6.082
6.056
6.038
5.627
5.565
5.338
5.314
5.298
5.279
4.196
4.182
3.945
3.922
3.905
2.929
2.920
2.905
2.896
2.876
2.866
2.852
2.842
2.705
2.696
2.652
2.642
2.624
2.593
1.666
1.640
1.531
1.299
1.240
1.118
1.094
1.070
SiMe3
Ph
Ph
Si
O
O
H
8-trimethylsilyl-5,5-diisphenyl-5-silyl-3-phenyl-4-oxy-6-octenal (130)
ppm
10
9
8
7
6
5
4
3
2
1
0
0.612
14.860
1.019
1.000
1.108
1.259
2.359
1.584
2.027
0.962
2.074
9.573

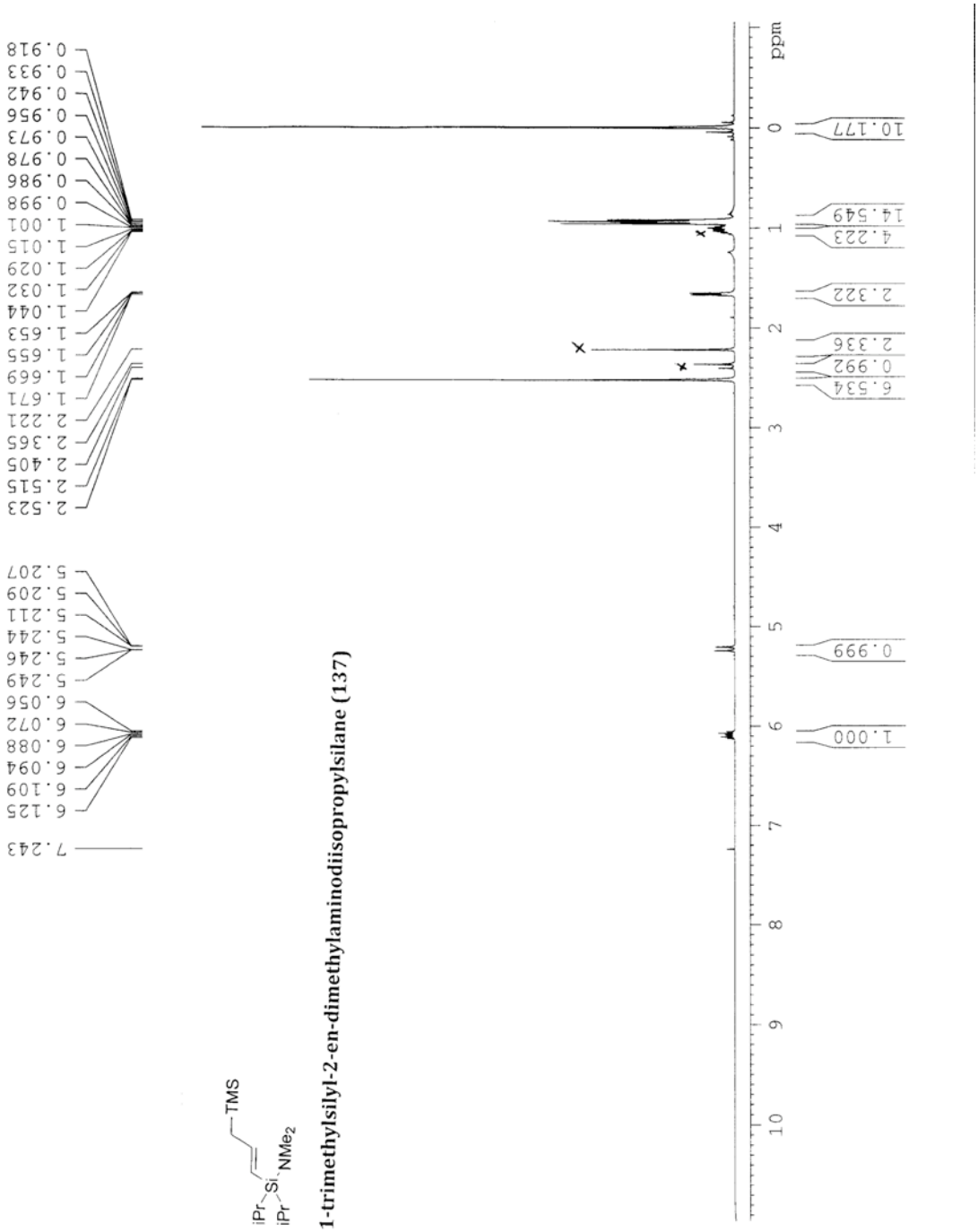

Silacycle (131)
TMSO
Si
O
ppm
23.382
0.913
1.293
3.485
1.095
2.754
2.943
1.359
1.438
1.384
1.018
4.974
2.461
1.514
1.000
37.075
6.396

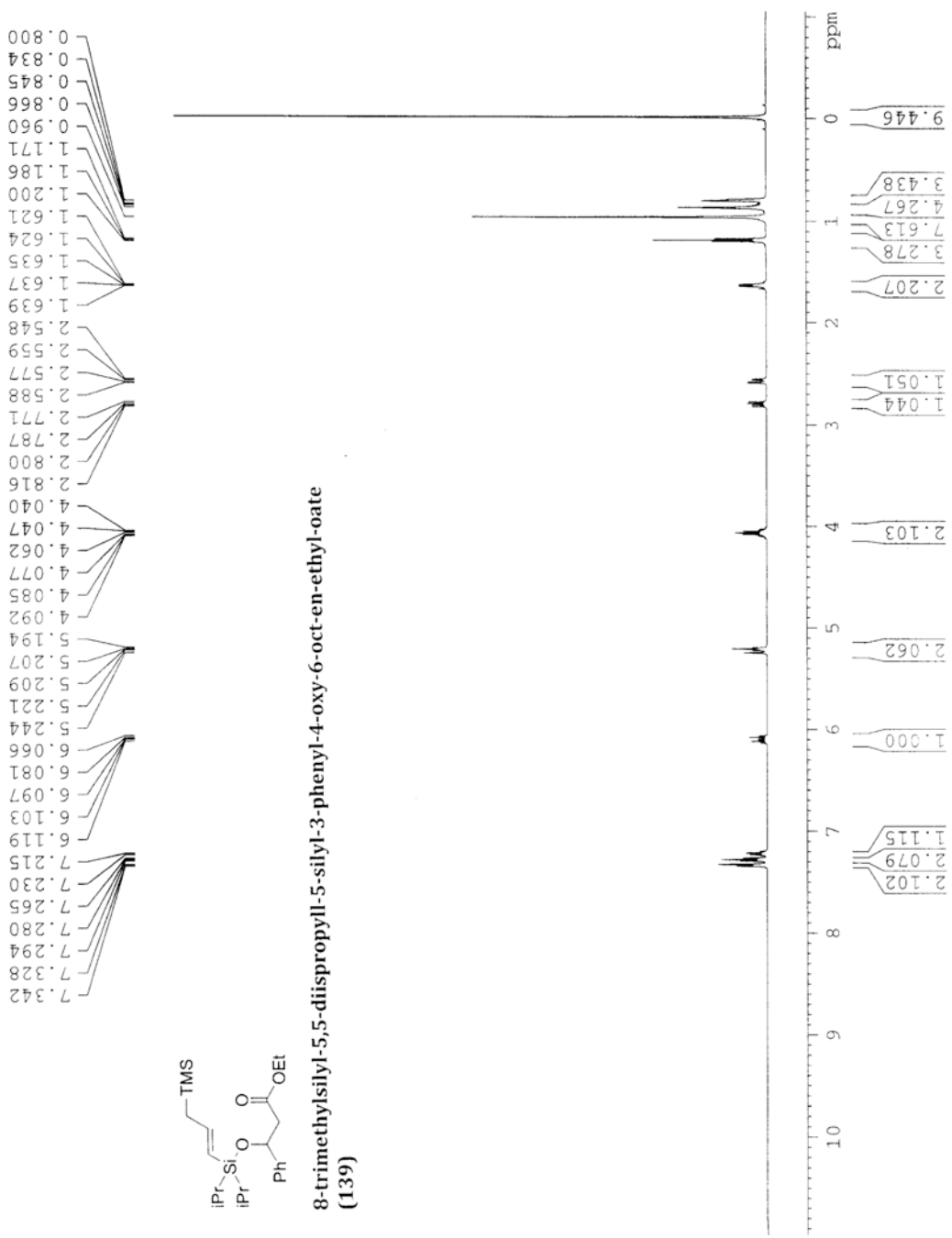

TMS
Ph
Si
Ph
O
OH
8-trimethylsilyl-5,5-diisphenyl-5-silyl-4-oxy-6-octenol (132)
ppm
9.707
4.923
1.144
2.445
2.349
0.971
1.000
6.815
4.373
0.010
0.139
1.222
1.246
1.270
1.749
1.774
1.792
1.811
1.830
1.849
2.031
2.205
3.779
3.798
3.817
3.900
3.919
3.938
4.098
4.121
5.736
5.798
6.216
6.242
6.269
6.277
6.304
6.330
7.240
7.337
7.356
7.381
7.403
7.572
7.577
7.596


9.800
7.622
7.604
7.598
7.400
7.378
6.371
6.344
6.309
6.283
6.256
5.837
5.775
4.165
4.143
4.123
4.103
4.052
2.668
2.662
2.648
2.642
2.628
2.622
2.044
1.815
1.789
1.391
1.288
1.264
1.240
0.910
0.887
0.171
0.048
TMS
Ph
Si
Ph
O
O
H
8-trimethylsilyl-5,5-diisphenyl-5-silyl-4-oxy-6-octenal (133)
ppm
0.782
4.845
7.309
1.000
1.395
2.900
2.318
1.098
2.376
1.572
9.843

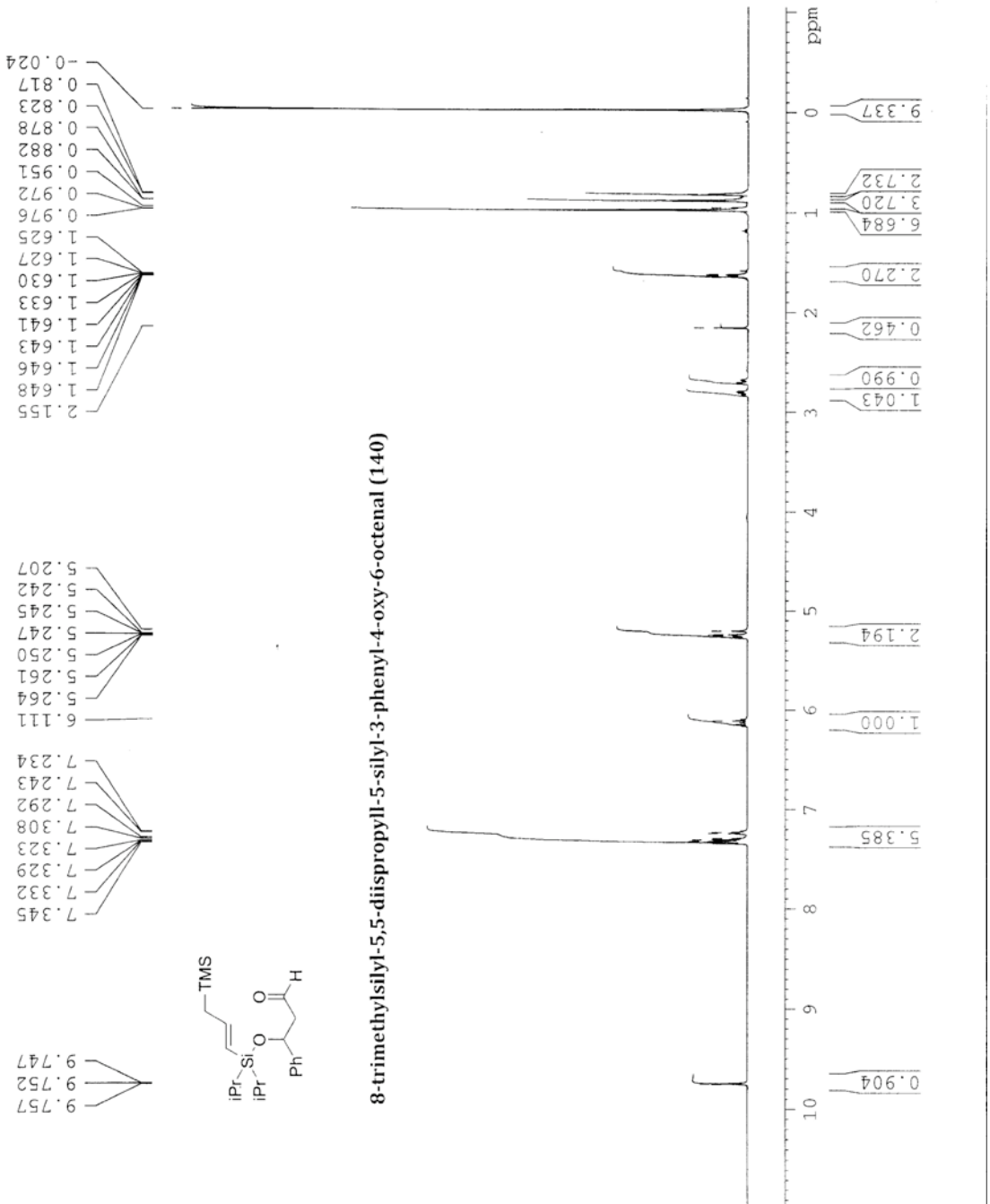

iPr
Si
Cl
iPr
NMe2
Chlorodimethylaminodiisopropylsilane (135)
2.626
2.532
2.519
1.250
1.236
1.221
1.205
1.083
1.075
1.068
1.060
2.995
1.000
6.447
ppm
0
1
2
3
4
5
6
7
8
9
10

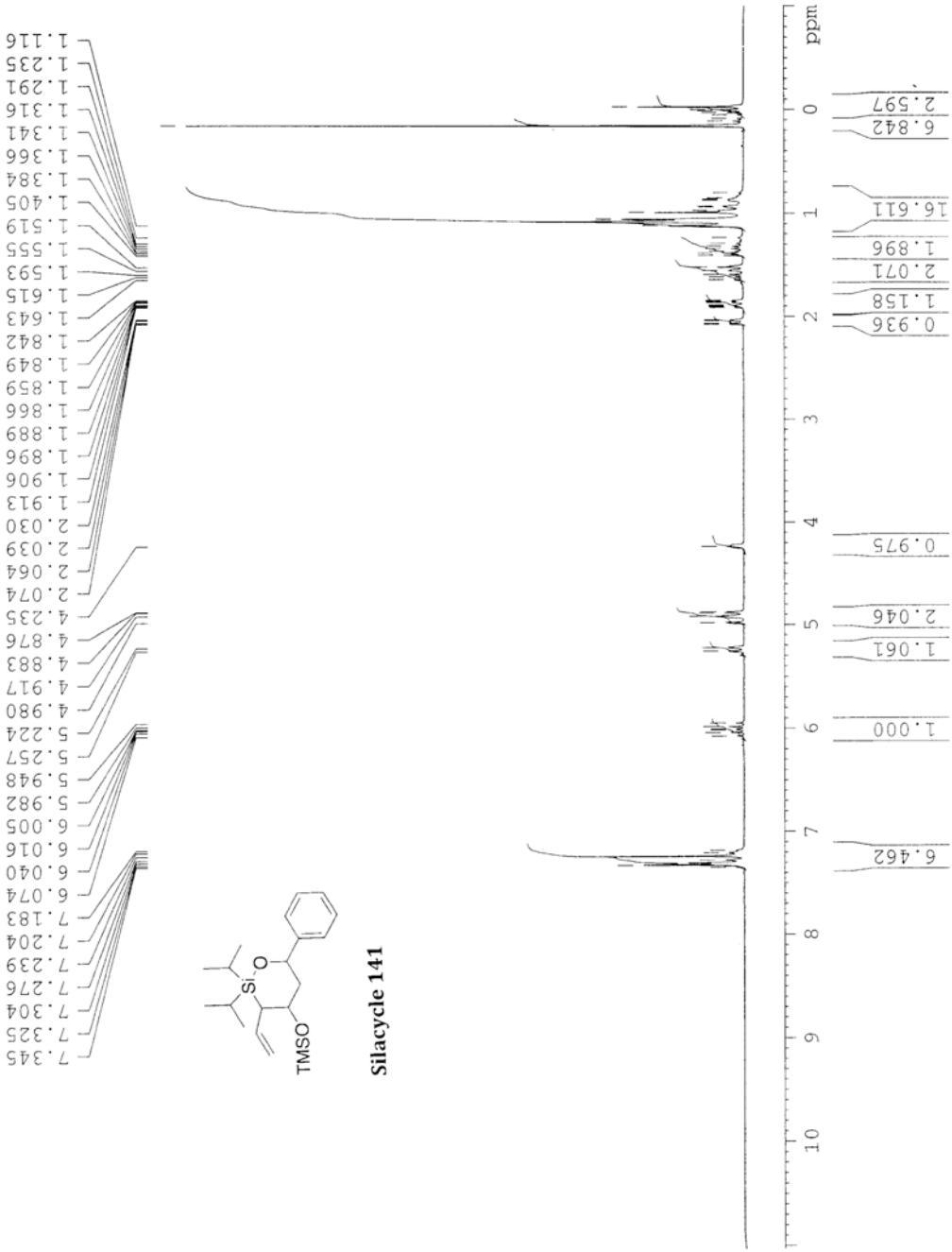

0.848
0.861
0.875
0.990
1.001
1.015
1.024
1.035
1.048
1.052
1.060
1.065
1.081
1.238
1.252
1.662
1.678
2.157
2.518
4.799
4.800
4.802
4.818
4.820
4.822
4.891
4.924
5.818
5.834
5.854
5.868
5.870
5.884
5.888
5.904
7.243
iPr
iPr
Si
NMe2
Allyldiisopropylaminosilane (136)
ppm
0
1
2
3
4
5
6
7
8
9
10
15.795
2.252
6.275
1.061
1.047
1.000


0.918
0.933
0.942
0.956
0.973
0.978
0.986
0.998
1.001
1.015
1.029
1.032
1.044
1.653
1.655
1.669
1.671
2.221
2.365
2.405
2.515
2.523
5.207
5.209
5.211
5.244
5.246
5.249
6.056
6.072
6.088
6.094
6.109
6.125
7.243
TMS
iPr
Si
iPr
NMe2
1-trimethylsilyl-2-en-dimethylaminodiisopropylsilane (137)
ppm
10.177
14.549
4.223
2.322
2.336
0.992
6.534
0.999
1.000

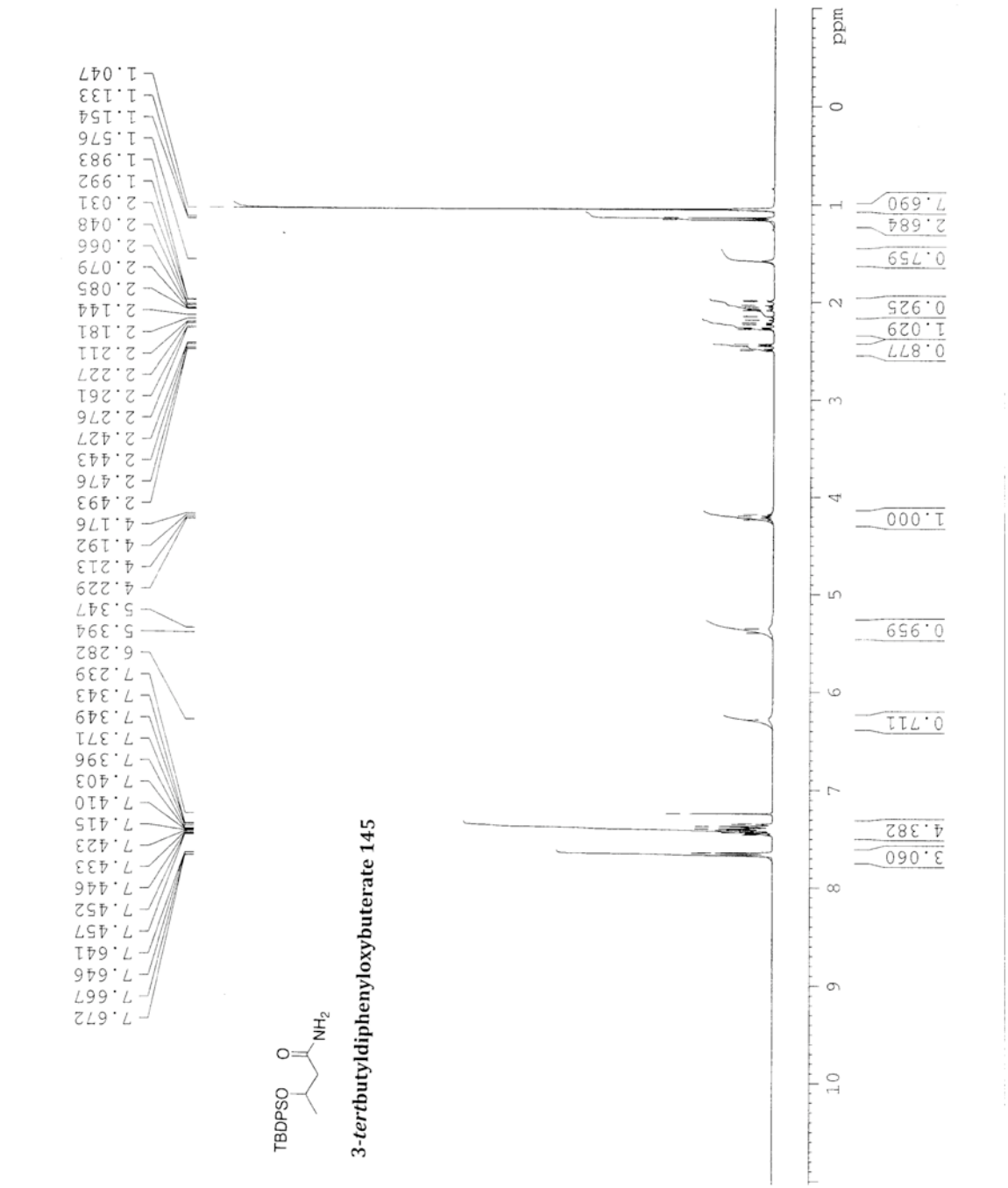


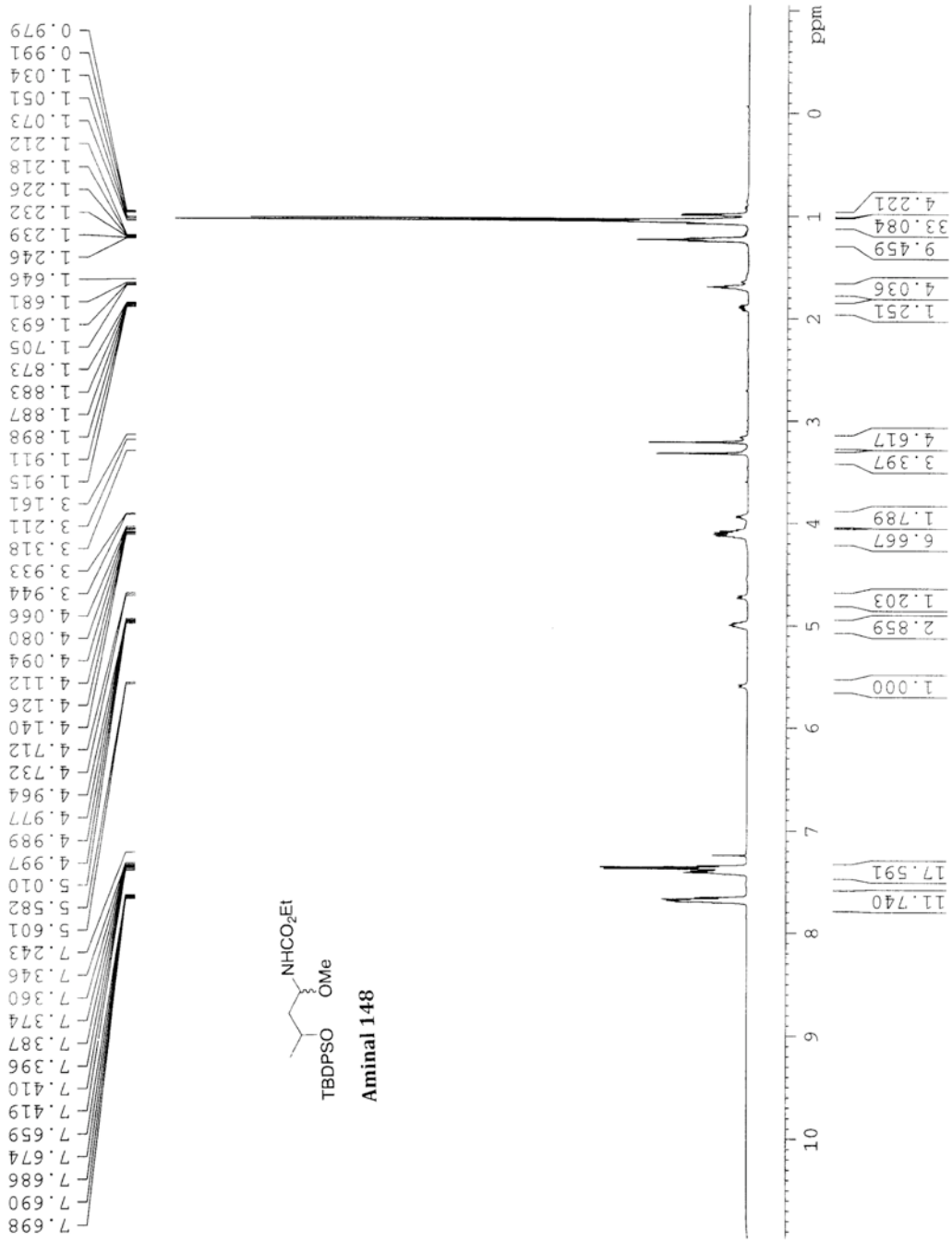
8-trimethylsilyl-5,5-diispropyll-5-silyl-3-phenyl-4-oxy-6-oct-en-ethyl-oate (139)

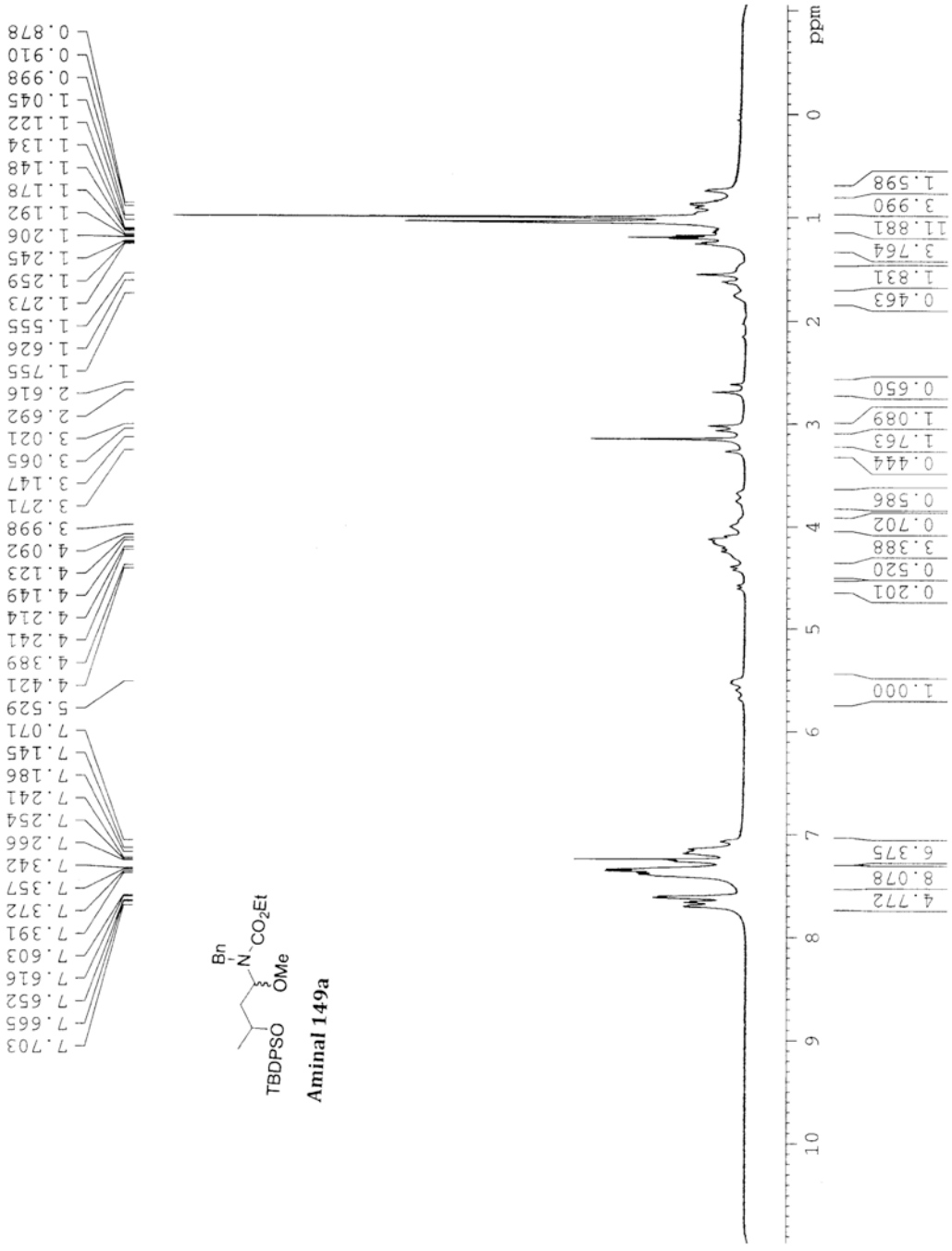

8-trimethylsilyl-5,5-diispropyll-5-silyl-3-phenyl-4-oxy-6-octenal (140)
TMS
iPr
Si
iPr
O
O
H
Ph
ppm
9.337
2.732
3.720
6.684
2.270
0.462
0.990
1.043
2.194
1.000
5.385
0.904
9.757
9.752
9.747
7.345
7.332
7.329
7.323
7.308
7.292
7.243
7.234
6.111
5.264
5.261
5.250
5.247
5.245
5.242
5.207
2.155
1.648
1.646
1.643
1.641
1.633
1.630
1.627
1.625
0.976
0.972
0.951
0.882
0.878
0.823
0.817
-0.024

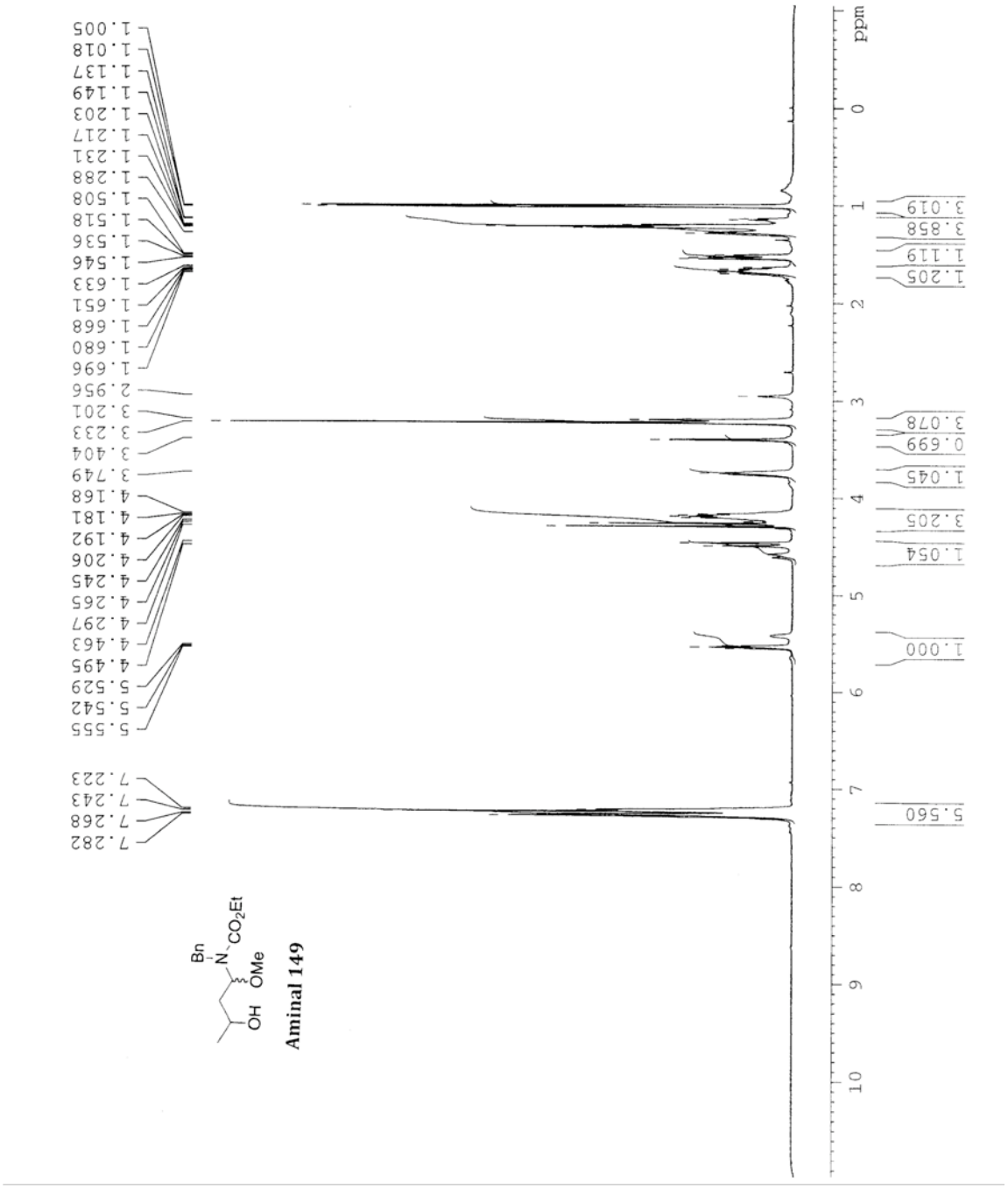


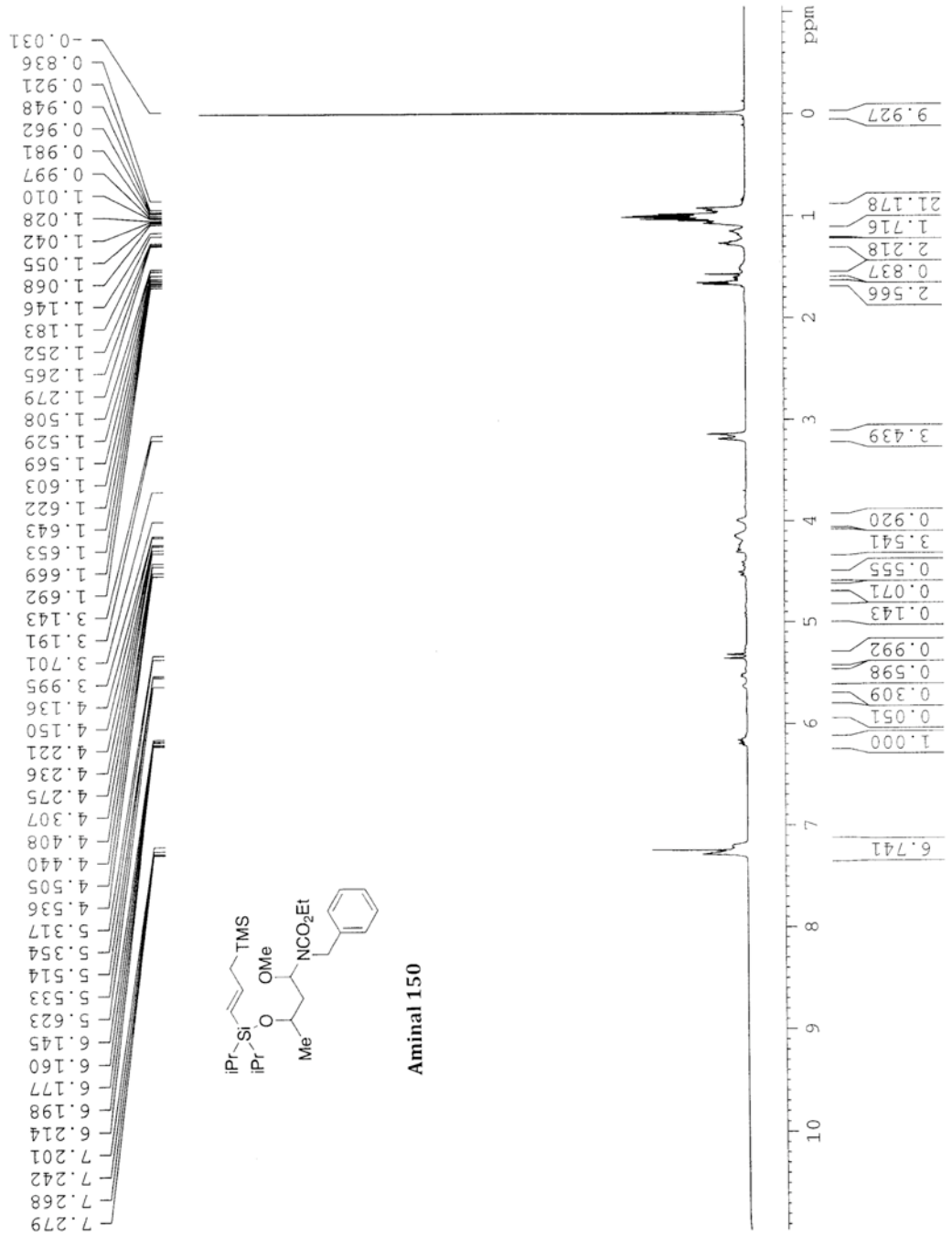
Silacycle 141


TBDPSO
O
NH2
3-tertbutyldiphenyloxybuterate 145
ppm
0 1 2 3 4 5 6 7 8 9 10
7.690
2.684
0.759
0.925
1.029
0.877
1.000
0.959
0.711
4.382
3.060
7.672
7.667
7.646
7.641
7.457
7.452
7.446
7.433
7.423
7.415
7.410
7.403
7.396
7.371
7.349
7.343
7.239
6.282
5.394
5.347
4.229
4.213
4.192
4.176
2.493
2.476
2.443
2.427
2.276
2.261
2.227
2.211
2.181
2.144
2.085
2.079
2.066
2.048
2.031
1.992
1.983
1.576
1.154
1.133
1.047

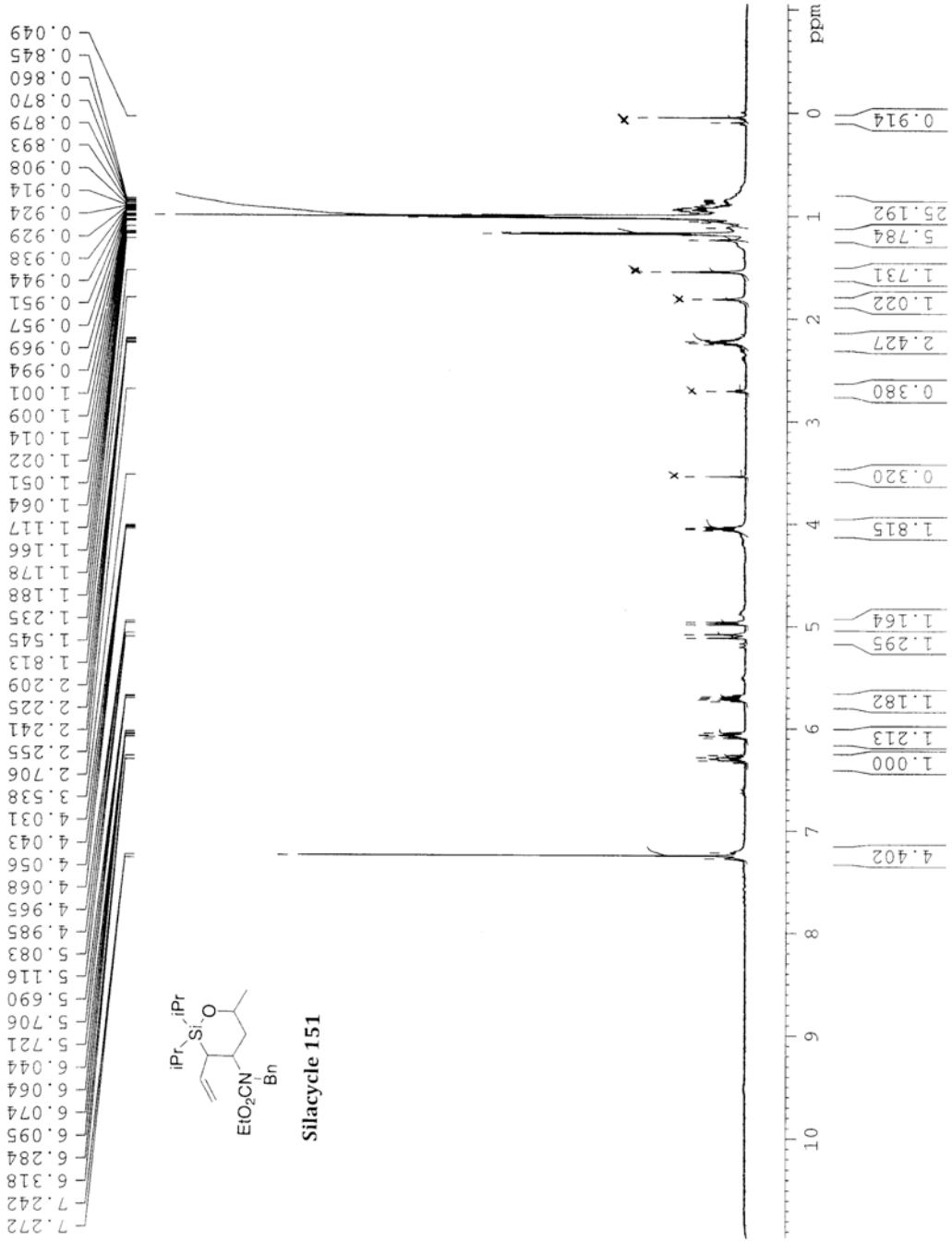

NHCO2Et
OMe
TBDPSO
Aminal 148
ppm
11.740
17.591
1.000
2.859
1.203
6.667
1.789
3.397
4.617
1.251
4.036
9.459
33.084
4.221

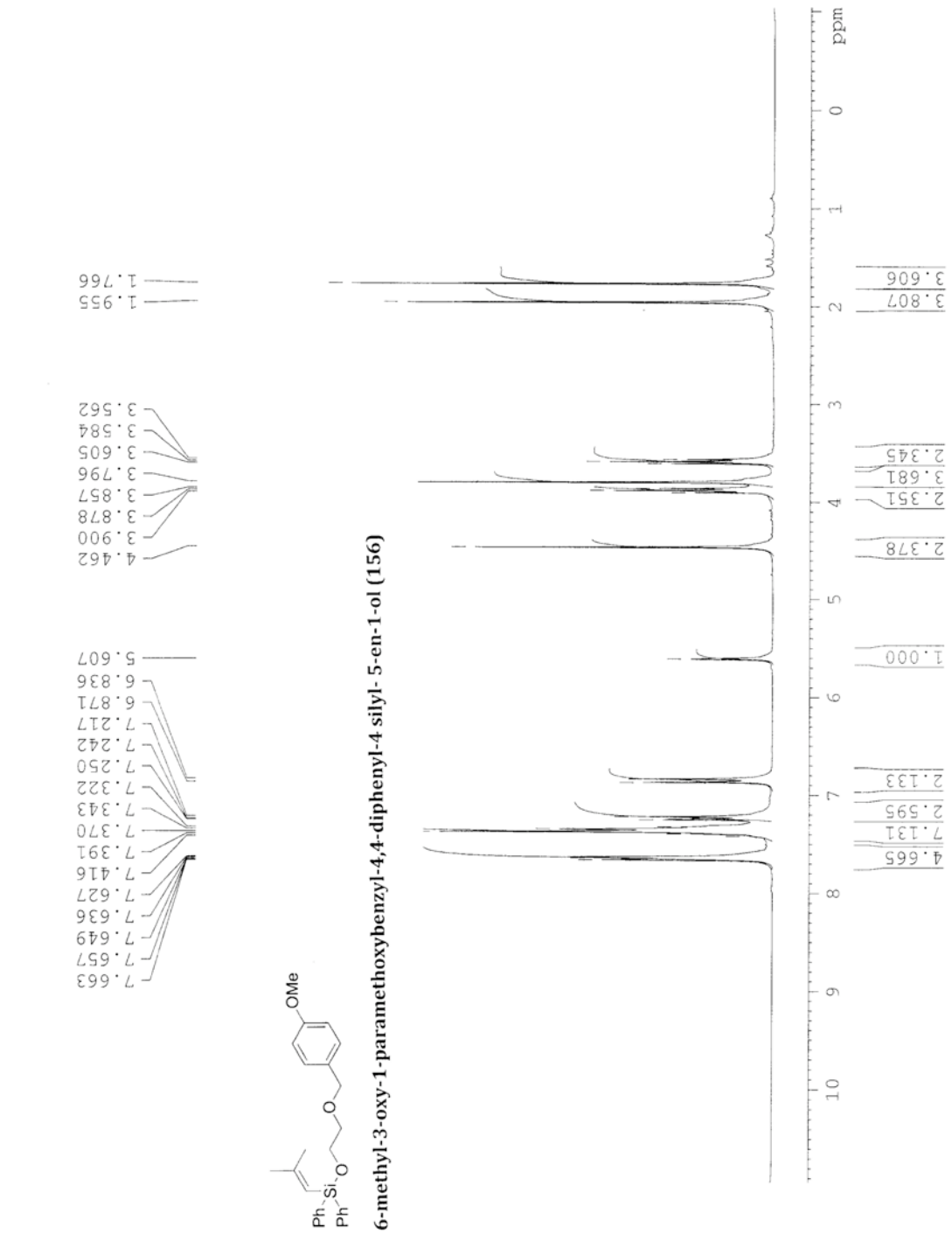

Bn
N
CO2Et
OMe
TBDPSO
Aminal 149a
ppm


Aminal 149
Bn
N
CO2Et
OMe
OH
ppm
7.282
7.268
7.243
7.223
5.555
5.542
5.529
4.495
4.463
4.297
4.265
4.245
4.206
4.192
4.181
4.168
3.749
3.404
3.233
3.201
2.956
1.696
1.680
1.668
1.651
1.633
1.546
1.536
1.518
1.508
1.288
1.231
1.217
1.203
1.149
1.137
1.018
1.005
5.560
1.000
1.054
3.205
1.045
0.699
3.078
1.205
1.119
3.858
3.019

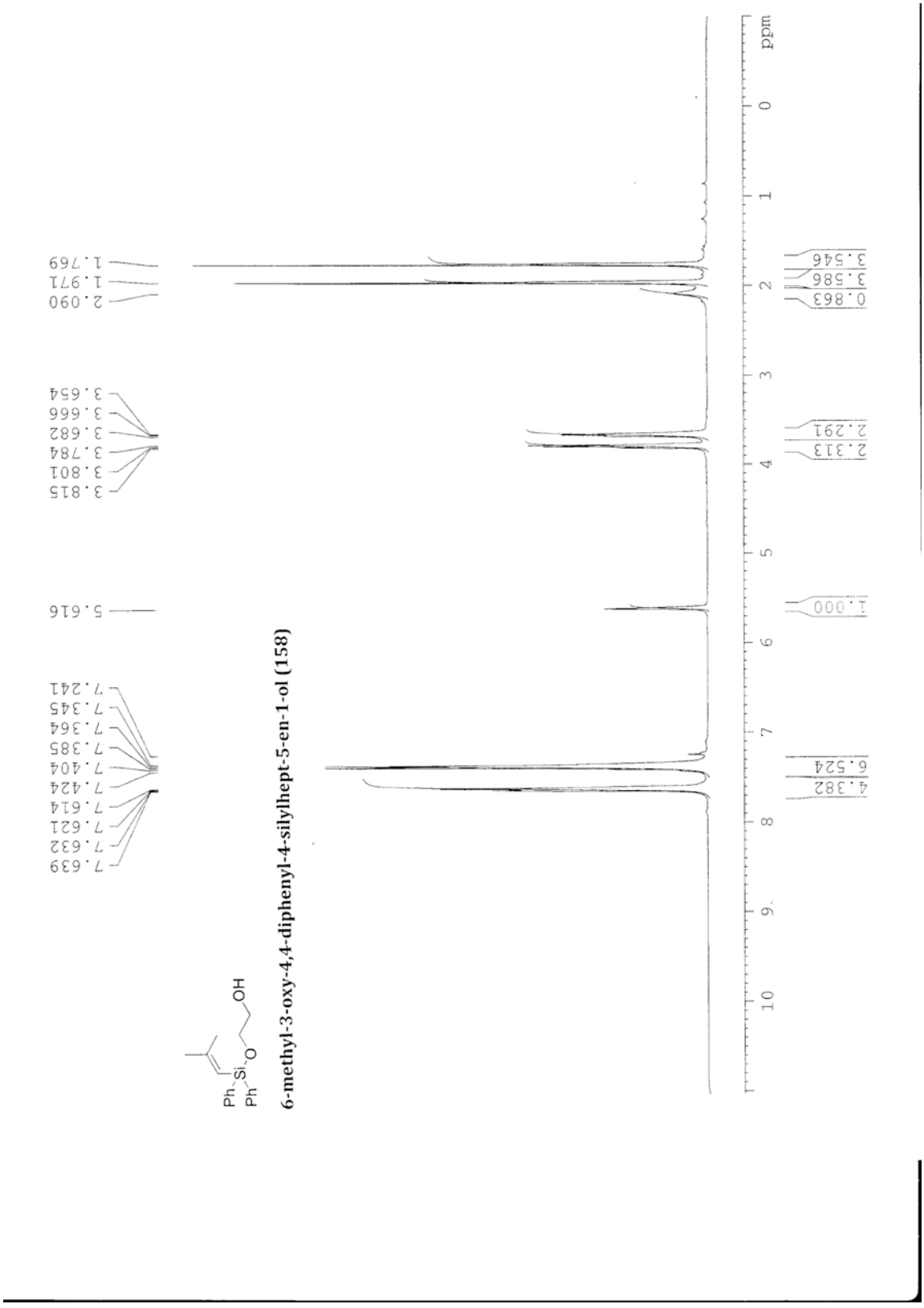

ppm
9.927
21.178
1.716
2.218
0.837
2.566
3.439
0.920
3.541
0.555
0.071
0.143
0.992
0.598
0.309
0.051
1.000
6.741
-0.031
0.836
0.921
0.948
0.962
0.981
0.997
1.010
1.028
1.042
1.055
1.068
1.146
1.183
1.252
1.265
1.279
1.508
1.529
1.569
1.603
1.622
1.643
1.653
1.669
1.692
3.143
3.191
3.701
3.995
4.136
4.150
4.221
4.236
4.275
4.307
4.408
4.440
4.505
4.536
5.317
5.354
5.514
5.533
5.623
6.145
6.160
6.177
6.198
6.214
7.201
7.242
7.268
7.279
TMS
OMe
NCO2Et
iPr
Si
iPr
O
Me

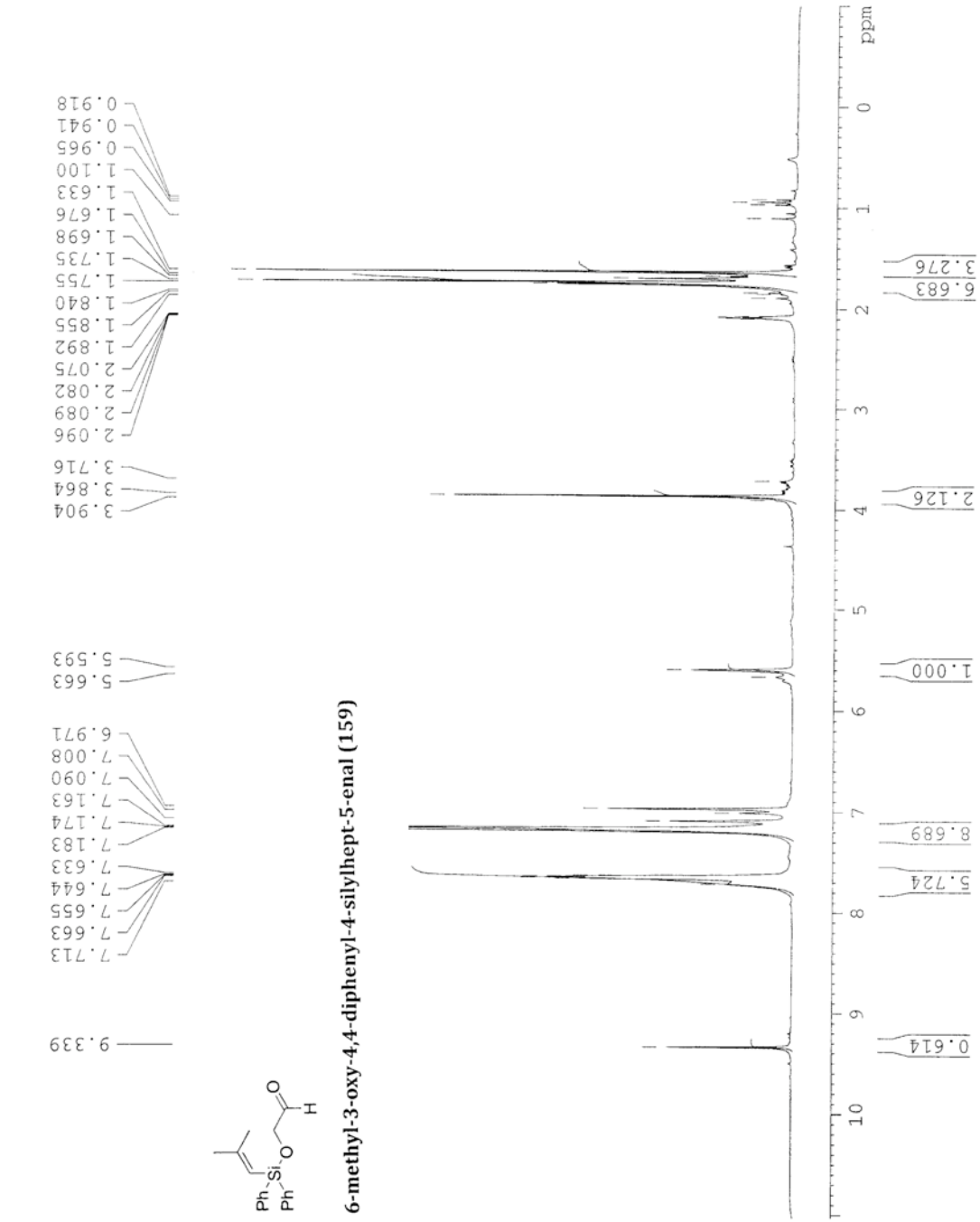
Aminal 150


ppm
0.914
25.192
5.784
1.731
1.022
2.427
0.380
0.320
1.815
1.164
1.295
1.182
1.213
1.000
4.402
Silacycle 151

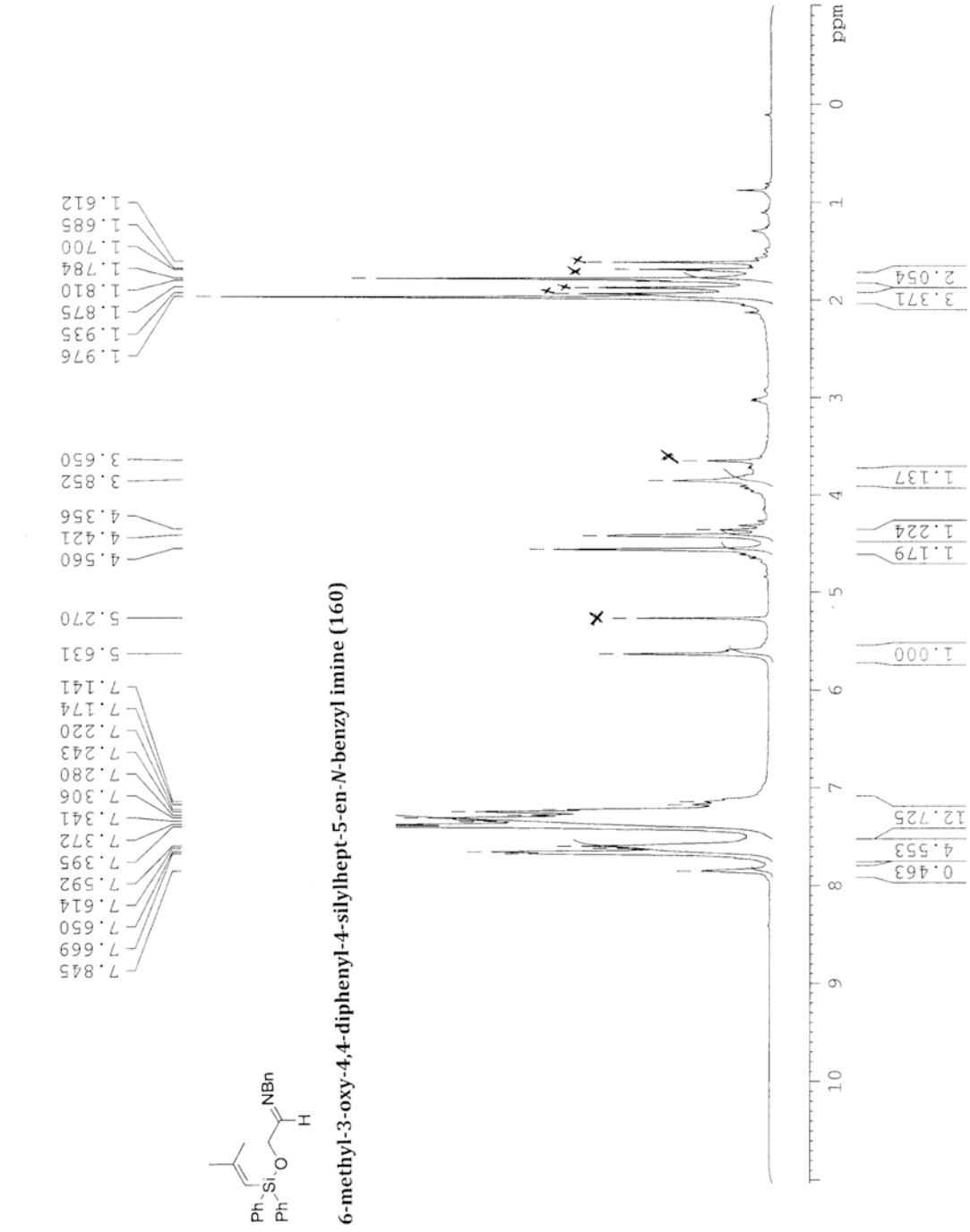


6-methyl-3-oxy-1-paramethoxybenzyl-4,4-diphenyl-4 silyl- 5-en-1-ol (156)

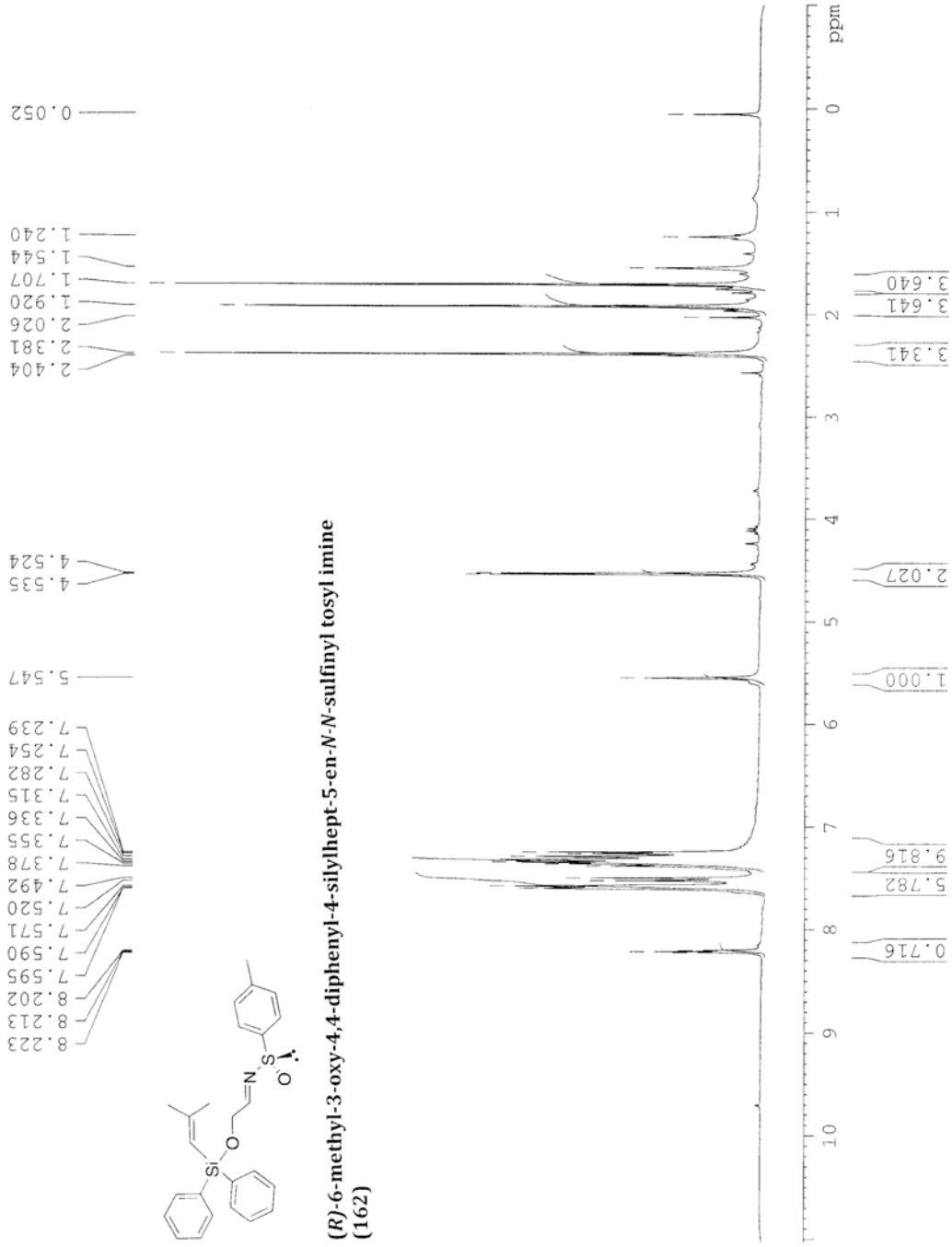

6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-1-ol (158)
Ph
Si
Ph
O
OH
7.639
7.632
7.621
7.614
7.424
7.404
7.385
7.364
7.345
7.241
5.616
3.815
3.801
3.784
3.682
3.666
3.654
2.090
1.971
1.769
4.382
6.524
1.000
2.313
2.291
0.863
3.586
3.546
ppm



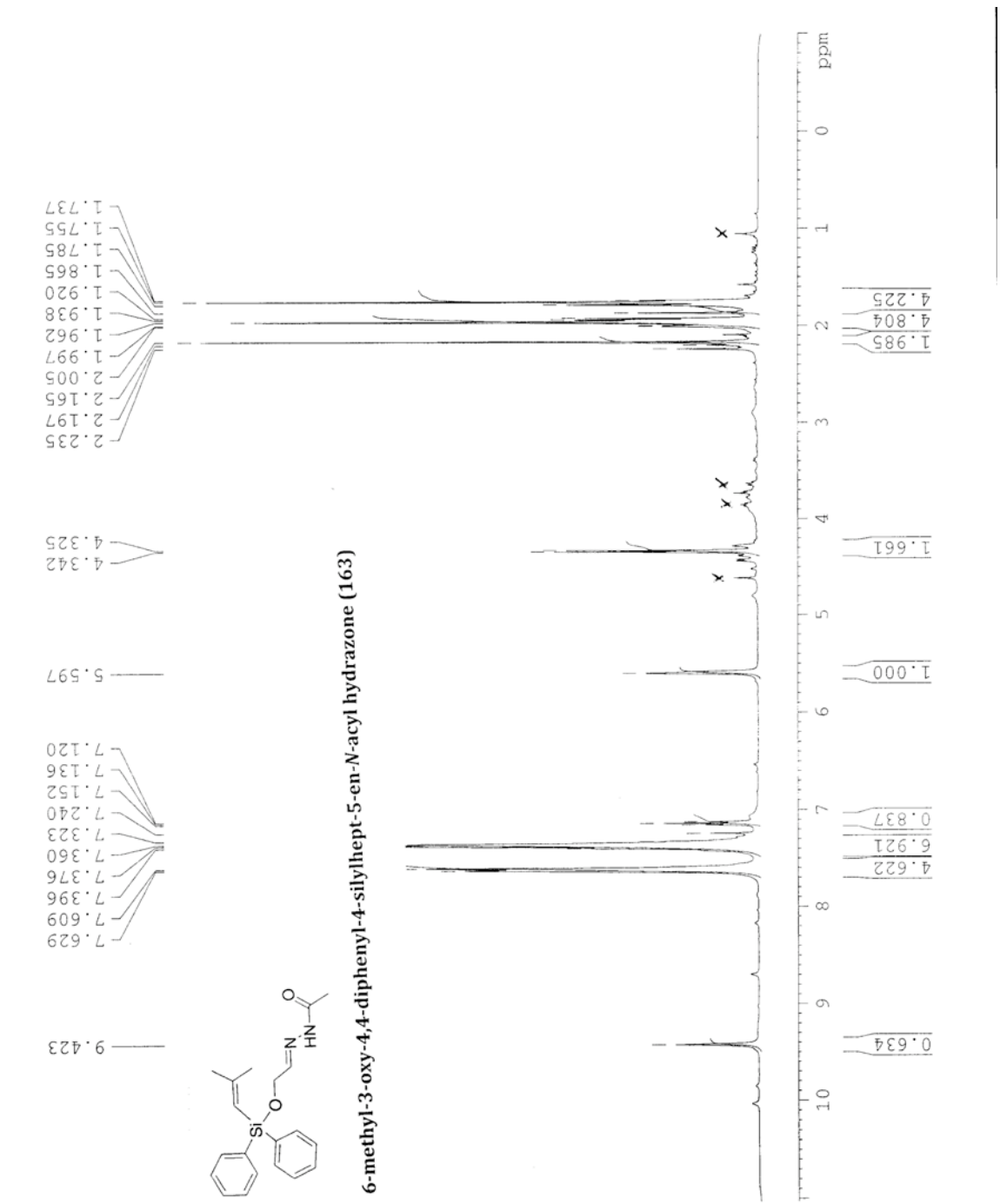
6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-enal (159)



6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-*N*-benzyl imine (160)



(*R*)-6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-*N*-*N*-sulfinyl tosyl imine (162)


9.423
7.629
7.609
7.396
7.376
7.360
7.323
7.240
7.152
7.136
7.120
5.597
4.342
4.325
2.235
2.197
2.165
2.005
1.997
1.962
1.938
1.920
1.865
1.785
1.755
1.737
0.634
1.661
1.000
0.837
6.921
4.622
1.985
4.804
4.225
ppm
6-methyl-3-oxy-4,4-diphenyl-4-silylhept-5-en-N-acyl hydrazone (163)