ABSTRACT

Design and Synthesis of Novel β-Cyclodextrins and Their Application as Chiral Stationary Phases for Gas Chromatography

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Enantiomers can be directly separated only with use of systems containing a chiral selector. Cyclodextrins (CDs) and modified cyclodextrins have been used as chiral selectors for their ability to form host-guest complexes with various analytes. The scaffold of the CD allows for assembly of functional groups with controlled geometry. CDs can be readily modified through substitution of the hydroxyl groups, giving rise to derivatives with significantly different properties, especially increased solubility and controlling the hydrophobicity of the cavity. Even though CDs can be readily modified, the syntheses can be tedious and complicated with various protecting group strategies to control the reactivity of the various alcohols. The preparation of modified cyclodextrins for use as chiral stationary phases (CSP) for gas chromatography (GC) is the focal point of this research.

Our effort to identify useful new β-CD derivatives involved attempts to make bridged (annulated) derivatives, could increase the thermal stability of the derivatives, and change the length, width and polarity of the CD cavity. To date, there are no reports of annulated

CD derivatives in the chemical literature. In the process of evaluating a wide range of electrophiles that could accomplish annulation, several new β-CD derivatives, i.e., per(6-O-TBS-2,3-O-cyclodimethylsilyl)- β-CD, per(6-O-TBS-2,3-O-cyclodiphenylsilyl)- β-CD per(6-O-Pivaloyl-2,3-O-cyclodimethylsilyl)-β-CD, per(6-deoxy-2,3-O-methyl)- β-CD, and per(6-deoxy-2,3-O-allyl)- β-CD, were synthesized. Two of the new derivatives were evaluated as components of stationary phases for GC, per(6-O-TBS-2,3-O-cyclodimethylsilyl)- β-CD and per(6-deoxy-2,3-O-methyl)- β-CD. Overall, this work resulted in five new CD derivatives.

Design and Synthesis of Novel β-Cyclodextrins and Their Application as Chiral Stationary Phases for Gas Chromatography

by

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A Dissertation

Approved by the Department of Chemistry & Biochemistry

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Å angstroms

Ac acetyl

AIBN azobisisobutyronitrile

b.p. boiling point

t-Bu tertiary butyl

cat. catalytic

CD cyclodextrin

CSA camphor sulfonic acid

CSP chiral stationary phase

DMAP 4-dimethylaminopyridine

DMF *N*,*N*-dimethylformamide

DMSO dimethylsulfoxide

equiv equivalents

ESI electrospray ionization

Et ethyl

Et_2O diethyl ether

EtOAc ethyl acetate

g grams

GC gas chromatography

GC/MS gas chromatography/mass spectrometry

h hours

HPLC high performance liquid chromatography

I.D. internal diameter

KHMDS potassium hexamethyldisilazane

L liters

LC liquid chromatography

m meter

M molarity

MALDI matrix-assisted laser desorption/ionization

Me methyl

min minute

mL milliliter

mm millimeter

μm micrometer

m.p. melting point

MS mass spectrometry

MsCl methane sulfonylchloride

NMR nuclear magnetic resonance

Nu nucleophile

OAc acetate

OMe methoxy

Ph phenyl

Piv pivaloyl

ppm parts per million

psi pounds per square inch

pyr pyridine

sec second

TBAF tetrabutylammonium fluoride

TBS *tert*-butyldimethylsilyl

THF tetrahydrofuran

TLC thin layer chromatography

TMS trimethylsilyl

Tos tosyl

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I would not have survived graduate school and finished without the support of many. First, and foremost, I thank God for allowing me to live this incredible life. I would like to express extreme thanks to my advisor, Dr. Charles Garner, for his guidance, crazy enthusiasm and helpful suggestions with this research. Even when faced with back-to-back disappoints in the lab, his encouragement to try new reactions allowed me to go down paths I never thought possible. He made me enjoy carbohydrate chemistry when I thought he was insane. I am also thankful to the members of my committee, Drs. Bob Kane, Kevin Pinney, Kevin Chambliss, and Mark Taylor for their time and suggestions throughout this project.

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DEDICATION

My grandmother, Eloiyse Turner, your sticks of gum were always a welcome surprise

CHAPTER ONE

Introduction

Cyclodextrins

The first reported discovery of cyclodextrins (CDs) appeared in 1891, when Villiers[1] observed the formation of an unidentified crystalline substance during the fermentation of starch. The cyclic structure of the crystalline dextrin remained unknown until the late 1930's. Cyclodextrins have been extensively studied in the pharmaceutical, cosmetic, and food industries.[2] CDs structure demonstrates the ability to complex other molecules within their annuli, exhibiting size and chiral discrimination between guest molecules.[3] Smaller guest molecules can enter the cyclodextrin's cavity, forming inclusion complexes. This phenomenon is called *molecular recognition*, while the selectivity in the formation of complexes with enantiomeric species as guests is called *chiral recognition*.[4] Their inherent chirality has lead to their widespread use in chiral separation techniques; this aspect will be discussed further as it becomes increasingly important in chromatography.

Since its structural elucidation by Freudenberg and coworkers,[5] numerous studies have been dedicated to the fundamentals of cyclodextrin chemistry with a large emphasis on the molecules ability to exhibit host-guest inclusion complexes. These naturally occurring molecules play an important role in supramolecular chemistry for several reasons: (i) they are now produced by the thousands of tons per year, making their initially high prices drop to a level that has become acceptable for most industrial

purposes. (ii) Among all potential hosts, cyclodextrins seem to be the most important ones for host-guest interactions due to their inclusion-forming ability, (iii) the non-toxic effect of CDs can be exploited by selecting the appropriate CD or derivative and the appropriate mode of application. As a result, cyclodextrins can be consumed by humans as ingredients of drugs, foods, or cosmetics.[6] Moreover, the chemical modification of cyclodextrin has become a research area, advancing the utilization of this macromolecule in laboratory and industrial processes.

Cyclodextrin Structure and Properties

Naturally occurring cyclodextrins are homochiral cyclic oligosaccharides, the most common of which are composed of 6, 7, or 8 α-1, 4-linked D-glucopyranose units (often referred to as α-, β-, and γ-, respectively) (Figure 1.1).

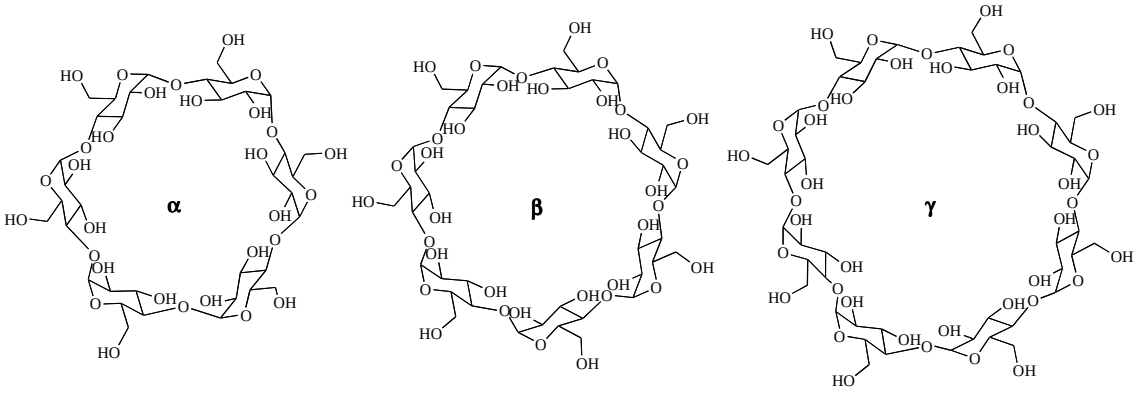


Figure 1.1Molecular structures of α-, β-, γ-cyclodextrins

They are produced, along with other oligosaccharides, through the degradation of starch by the enzyme CD glucosyltransferase.[3] As a consequence of its well known binding ability and availability,[7] β-cyclodextrin (also known as Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaglucan, and cycloheptaamylose, symbolized as β-CD) has

high commercial potential and is the key ingredient of this research. β-CD contains seven glucopyranose units that take the shape of a hollow truncated cone with secondary 2- and 3- OH groups on the hydrophilic wide ends and the primary 6-OH groups on the narrow ends, reminiscent of a lamp shade (Figure 1.2).

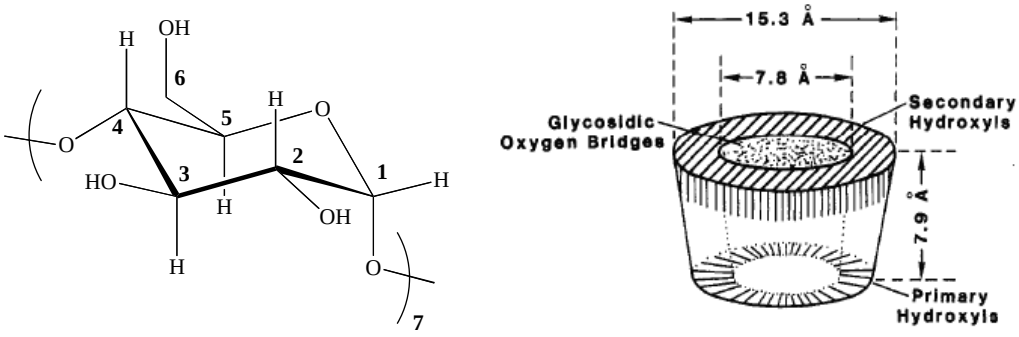


Figure 1.2 Structural Scheme of β-CD[8]

The hydrophobic annular interiors are lined with H(3), H(5) and H(6) hydrogens and O(4) ether oxygens. Crystallographic X-Ray studies show that each glucose unit adopts a $^4C_1$ chair conformation, also confirming its rigid structure. The C-2-OH group of one glycopyranoside unit can form a hydrogen bond with the C-3-OH group of the adjacent glucopyranose unit. In β-CD, a complete secondary belt is formed by these H bonds, which contributes to the more rigid structure[3,6] compared to α- and γ-CDs. This arrangement of hydrogen bonding can explain the observation that β-CD has the lowest solubility of all CDs.[9] The most important physical and chemical characteristics of the most common CDs can be compared in Table 1.1.[3] CDs were originally thought to have completely rigid structures; however, this has been shown to be inconsistent with the CDs ability to selectively complex guests of various shapes.[4] CD complexes are held together

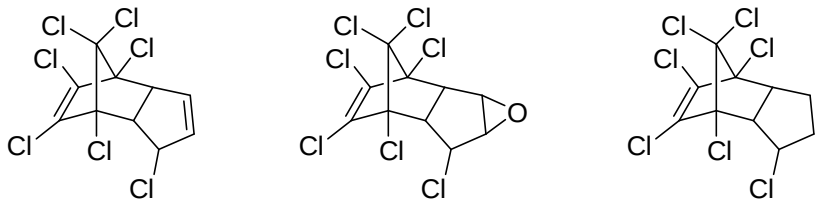
by weak intermolecular forces which somewhat limit the mobility of the CD, but does not render it completely rigid. A completely rigid structure is also inconsistent with the ease of formation of inclusion complexes of various shapes and sizes, since the above implies an efficient fit of the host and guest is required.[10]

Table 1.1Some characteristics of α, β, and γ-CD.[3]

CD	α-CD	β-CD	γ-CD
Number of glucopyranose units	6	7	8
Molecular weight (anhydrous)	972.85	1134.99	1297.14
Solubility per dm^3 H_2O at 298.2 K	14.5	1.85	23.2
Annular diameter measured from C(5) hydrogens, Å	4.7	6	7.5
Annular diameter measured from C(3) hydrogens, Å	5.2	6.4	8.3
Annular depth from primary to secondary hydroxyl groups, Å	7.9-8.0	7.9-8.0	7.9-8.0
Annular volume, $Å^3$	174	262	472
Partial molar volumes, cm^3 mol^{-1}	311.4	703.8	801.2
pKa O(2)H and O(3)H at 298.2 K	12.33	12.20	12.08

Other important properties of cyclodextrins include the following: (1) they are non-reducing sugars, (2) glucose is the only product of acid hydrolysis, (3) their molecular weights are always integral numbers of (162.1), the value of glucose, (4) they are non-toxic, and (5) they do not appreciably absorb UV or visible light.[3] As a result, the extensive investigation into the chemical modifications of cyclodextrins have been concerned primarily with (i) influencing their solubilities, (ii) host-guest interactions and complexation, (iii) enzyme modeling, and (iii) forming insoluble, immobilized CD-containing structures (for chromatographic purposes).[11]

Cyclodextrins find application as chiral selectors in gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis (CE).[12] Chromatography is one of the most important methods for direct studies of molecular and chiral recognition by CDs today. The amazing sensitivity of CDs to the shapes of guest molecules is illustrated by the significant differences in retention times of very similar compounds. For illustration, the separation of enantiomers of photo-heptachlor (**1.1),** photo-heptachlorepoxide (**1.2**), and photo-chlordane (**1.3**), polychlorinated pesticides on a CD GC column (CP-Chiralsil-Dex CB β-CD) was shown to exhibit large differences in retention times with baseline separation of the enantiomers (Figure 1.3).[13]



1.1 **1.2** **1.3**

Figure 1.3 Three polychlorinated pesticides separated on CD GC column

Cyclodextrin Complexes

The complexation of a guest by cyclodextrin involves the partial or complete desolvation of the guest as it enters the CD cavity, displacement of the water (or other solvent) from the cavity and adjustment of the guest to the thermodynamically most favorable orientation within the cavity.[3]

The majority of CD complexation studies have been carried out in aqueous solution and considerable attention has been focused on the hydration of the CD and the guest during the complexation process.[3] Cyclodextrins form complexes with differing

amounts of water, with β-CD holding approximately 7-8 molecules per water in its cavity. Even if CDs don't contain water or a guest, there is usually solvent occupying the space.[4] Hydrogen bonding stabilizes complexes along with conformational changes by either the guest or CD. Other effects demonstrated by complexation behavior include hydrophobic effects, release of high energy water from the CD cavity, relief of conformation strain in the uncomplexed CD, dipole-dipole interactions, and London dispersion forces.[3] The entry of a guest into the CD annulus expels some or all of the water, an important part of the complexation process. The enthalpy and entropy of complexation follows a trend where ΔHo is negative and ΔSo is negative, and as a consequence CD complexation is said to be enthalpy driven. The inherent chirality and shape of CDs provide opportunities for both chiral and size discrimination by complexation.

The cavity of β-CD and its derivatives is wide enough to accommodate adamantane.[14] Predominately, analytes such as adamantane enter the CD cavity through the secondary face first, shown by ^{1}H NMR studies, although examples of exceptions do exist.

Novel Modified β-CDs as Chiral Selectors in GC

Enantioseparations are generally carried out by chiral chromatography on a chiral stationary phase containing a resolving agent of high (but not necessarily complete) enantiomeric purity.[12] The use of cyclodextrins as chiral selectors in GC has provided a deeper understanding into the mechanisms of chiral recognition. In this report, we will introduce the progress we have made toward the development of unique modified β-CD derivatives. The majority of enantiomer separations have been carried out with use of β-

CD and its various derivatives due to its generally greater efficiency and commercial availability, and this is precisely the reason, along with cost, for its use in our research. Since cyclodextrins have been so widely applied in the separation sciences, the evolution of cyclodextrins and its derivatives has been intense over the last two decades, resulting in a number of different phases with different selectivities. For example, the Chiraldex series by Astec offers the widest variety of commercially available chiral GC columns, marketing eight different types of cyclodextrin derivatives, two of which are unique, patented GC phases (Table 1.2). In addition, these eight types of derivatization are available for all three of the common cyclodextrins (α, β and γ). One of the Astec phases (DM) corresponds to that offered by J&W as CycloSil-B.

Table 1. 2 Several Currently Available Cyclodextrin-based CSPs

Phase	Cyclodextrin
TA*	Trifluoroacetyl (2,6-di-O-pentyl-3-trifluoroacetyl)
DM	Dimethyl (2,3-dimethoxy-6-O-tert-butyldimethylsilyl)
DP	Dipropionyl (2,3-di-O-propionyl-6-O-tert-butyldimethylsilyl)
DA	Dialkyl (2,6-di-O-pentyl-3-methoxy)
PN	Propionyl (2,6-di-O-pentyl-3-propionyl)
BP	Butyryl (2,6-di-O-pentyl-3-butyryl)
PH*	S-Hydroxypropyl ((S)-2-hydroxy propyl methyl ether)
PM	Permethyl (2,3,6-tri-O-methyl)

* denotes patented

Our research into new synthetic derivatives of CDs has been motivated by the relatively low thermal stability of the current commercially available columns and especially by the fact that each CD derivative has different separation characteristics, i.e., there is no one best phase for all separations. This means that only a limited number of chiral separations can currently be performed on any single CD stationary phase,[9] supporting the continual need for improved chiral selectors. There is no universal chiral stationary phase available, nor can the separation of any given anaytes be predicted, thus the selectivity and efficiency are often determined by trial and error. Our objectives are to synthesize novel β-cyclodextrins that are significantly different structurally from what is currently used in existing CSPs and to test their performance as chiral selectors in enantioseparations by gas chromatography. To accomplish this, our derivatization efforts will be primarily focused on increasing the temperature stability, cavity width, length and polarity of the β-CD.

Cyclodextrin Derivatives

Although the chemical modification of the hydroxyl groups of CDs is a major area of interest, it is recognized as a rather demanding process. The only established approach to elaborate CDs is through reaction of their hydroxyl groups. In cyclodextrins, every glucopyranose unit has three free hydroxyl groups available for modification. For β-CD, this represents twenty-one modifiable hydroxyl groups, generating the potential for a complex mixture of fully substituted to partially substituted products. The secondary hydroxyl groups are the C(2)- and C(3) –groups, while the C(6)-OH hydroxyl group is primary as shown in Figure 1.2. The chemistry performed on cyclodextrins is largely influenced by the difference in reactivity of the three different hydroxyl groups on the

ends of the glycopyranoside residues. The reactivity decreases in the order of: 6-OH > 2-OH > 3OH. This trend can be attributed to the hydrogen bonding between the secondary hydroxyl groups and the regio- orientation of the hydroxyl group.

Purpose of Research

Modification generally involves the substitution of the hydrogen atom or the hydroxyl group by a wide variety of substituents, though reactions of this type generally result in a large number of positional isomers and a complex reaction mixture. It is often possible to control, to some degree, the regioselectivity of the reactions, to substitution of either one or a specific combination of hydroxyl groups. The regioselective protection of all the primary hydroxyl groups is difficult due to steric interactions that develop with increasing degree of substitution. Unlike the functionalization at the primary face of cyclodextrins, which has been extensively studied, the available chemistry for the functionalization of the secondary face is not as well developed. Considerable attention has been given to the chemical modification, as described above, of β-cyclodextrin in order to optimize its separation properties and is precisely the focus and goal of this research. We have pursued structurally unique *bridging groups* for the C(2) and C(3) oxygens. Annulations of this type have not yet been reported for cyclodextrin stationary phases, though annulations reactions have been reported for glucose derivatives.[15] We hoped that similar functionality could be realized on cyclodextrin and its derivatives.

In addition, replacement of the primary hydroxyl group with smaller groups was also considered when designing our chiral selectors. Contributions made by Baer et al. in the development of per(6-deoxy)-β- cyclodextrins[16] has provided a straightforward approach to the synthesis of cyclodextrins bearing smaller functional groups (i.e., methyl)

on the primary side. To our knowledge, derivatives of this type have not been explored for their ability to perform enantioseparations. We believe that β-cyclodextrin derivatives containing the described attributes could offer a potential change in the thermal stability and chiral recognition properties. The following pages will include details concerning the modification of βCD at the secondary hydroxyl face in order to extend the cavity of the CD and improve the properties beneficial in chromatographic enantiomeric discrimination (i.e. temperature range, binding/complexation properties, etc.). Also, modification of βCD at the primary hydroxyl face in order to increase the solubility of the CD is included. Finally, development of β-cyclodextrin coated capillary columns for gas chromatography is also reported.

CHAPTER TWO

Model Systems for the Annulation of β-cyclodextrin

Introduction

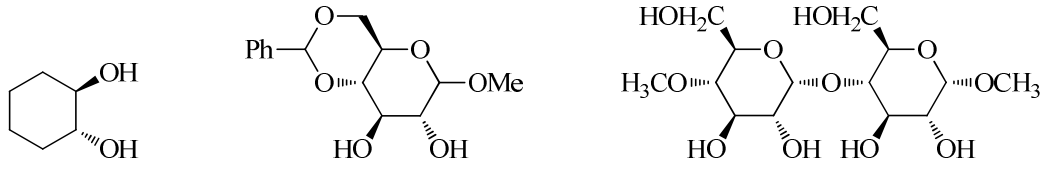
By modifying the hydroxyl groups in cyclodextrins (CDs) by chemical reactions, the CD derivatives with various degrees of substitution can become hosts for guest analytes. The selectivity can be of the hosts can be altered, but not necessarily in a predictable way. The properties of modified CDs differ from those of non-modified CDs. The selectivity of enantiomer separation can be improved by increasing solubility of the analytes, using the ability of CD derivatives to form secondary intermolecular attractions or controlling the degree of hydrophobicity of the CD cavity.[12] Two main factors considered when modifying CDs is the potential for complexation with reagents used in the reactions and the nucleophilicity of the primary and secondary hydroxyl groups. The primary hydroxyl groups, C(6)-OH, are the most basic and most nucleophilic, where as the secondary hydroxyl groups have lesser, but varied, reactivity. The C(2)-OH hydroxyl group is the most acidic and the C(3)-OH group is the most inaccessible. The diminished reactivity of the C(3)-OH group has been attributed to the hydrogen bonding capability with the C(2)-OH group on a neighboring glucose unit. The decreasing order of reactivity: C(6)-OH > C(2)-OH > C(3)-OH is well documented.[12]

Since no per-annulated CD derivatives are known in the literature, three different model systems (Figure 2.1) were envisioned to probe the reactivity and selectivity of the secondary hydroxyl groups. The model systems do not have the added complexity of the

macrocyclic nature of CDs. We speculate complexation of the reagents and electrophiles within the CD annulus may prove beneficial by increasing the initial reactivity of the CD and electrophile but could decrease the reactivity of the C(2)-hydroxyl groups overall through crowding. The model systems can circumvent this problem to test the annulation reactions.

Synthesis of trans-cyclohexandiol Derivatives

Trans-1,2-cyclohexanediol **(2.1)** was used to test the viability of annulating trans-secondary hydroxyl groups. With this model system, the secondary hydroxy groups have the same reactivity. The D-glucopyranoside derivative **2.2** was envisioned to probe the differing reactivities of the C(2)-OH and C(3)-OH under annulation conditions. 4-*O*-methyl methyl β-maltoside derivative **2.3** was designed to probe annulations across neighboring glucose moeties and if they would hinder our desired annulations. Studies were undertaken of reactions with electrophiles that could potentially form 5-, 6-, 7-, and 8-membered rings and to optimize potential reaction conditions for β-cyclodextrin.



2.1 **2.2** **2.3**

Figure 2.1 Model Systems 2.1-2.3

Five-membered Annulations of 2.1

The simplest annulation of a model system attempted was preparation of acetonide derivative **2.4**. The first method attempted was a kinetically controlled acetalation using 2-methoxypropene with catalytic PPTS in DMF.[17] The reaction was followed by GC/MS and the product's mass of 156.12 was detected, but the product could not be isolated by chromatography or distillation. Following the work of Becher and co-workers,[18] transacetalation was attempted with 2,2-dimethoxy propane and catalytic PPTS in DMF. The reaction was also followed by GC/MS and the desired mass was observed, but the product decomposed upon attempted distillation. We conclude that this derivative is thermally unstable.

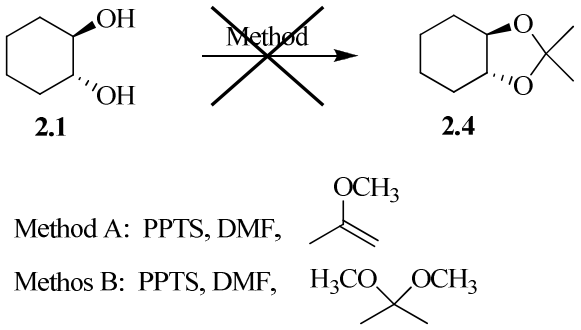
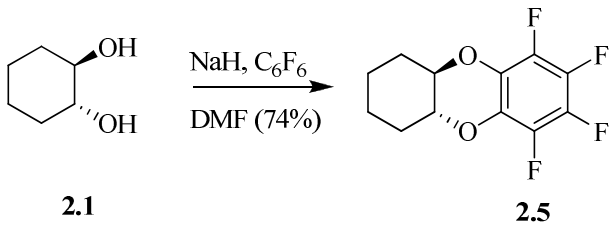


Figure 2.2 Attempted syntheses of acetonide 2.4

Six-membered Annulations of 2.1

The first six-membered annulation attempted with **2.1** used hexafluorobenzene, C_6F_6, as shown in Figure 2.3. The reaction was first performed by undergraduate Ellan Hays and later reproduced for characterization purposes. Optimal annulation for this novel compound was achieved by slow addition of C_6F_6 in DMF to a mixture of diol and NaH in DMF to produce the new fluorinated compound **2.5** in 74% yield after

recrystallization. This reaction is not a typical substitution reaction of an alkoxide on an electrophile, but instead a nuclophilic aromatic substitution reaction. This successful reaction on the model system **2.1** presents a unique pathway to new and novel annulated CD derivatives.



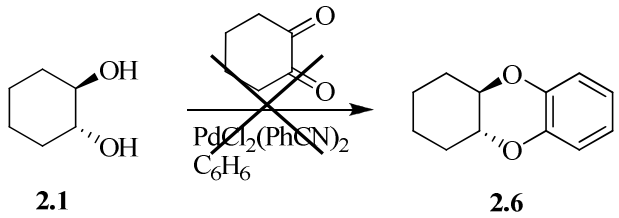
2.1 **2.5**

Figure 2.3 Formation of novel fluorinated derivative 2.5

Encouraged by the cyclization of **2.1** with C_6F_6, preparation of a known, non-fluorinated analog, 1,2,3,4,4a,10a-hexahydrooxanthrene **(2.6)** was attempted. Following the procedure of Mincione and co-workers, [19] **2.1** was reacted with excess $PdCl_2(PhCN)_2$ and 1,2-cyclohexanedione in refluxing benzene.

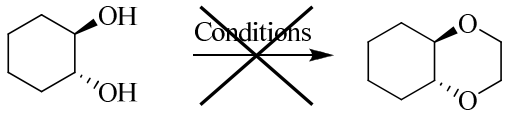
This annulation was not successful, as **2.6** was not detected by GC/MS and the resonances reported in the literature were not seen in the crude ^{1}H NMR. Since we did not examine this reaction further, it is not known if the complete aromatization of the ring was unsuccessful or if the $PdCl_2(PhCN)_2$ was of insufficient purity as to why the reaction did not proceed as reported.

A simpler diether analog **2.7** has been synthesized by Jensen and Neese[20] but the strongly acidic conditions and high temperatures used to synthesize the compound would not be adaptable for reactions with cyclodextrins. We attempted the synthesis of **2.7** by reacting 1,2-dibromoethane with **2.1** (Figure 4). Unfortunately, despite employing several



2.1 **2.6**

Figure 2.4 Synthesis of 1,2,3,4,4a,10a-hexahydrooxanthrene (2.6)[19]



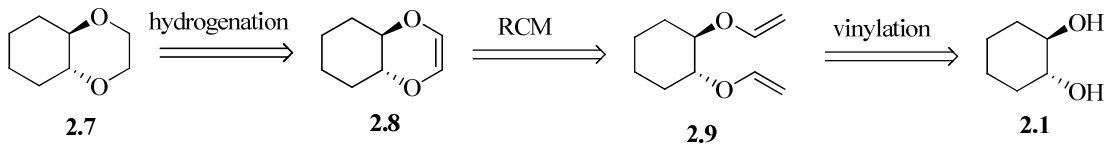
2.1 **2.7**

Figure 2.5 Attempted synthesis of diether analog 2.7

Table 2.1 Attempted conditions to form 2.7

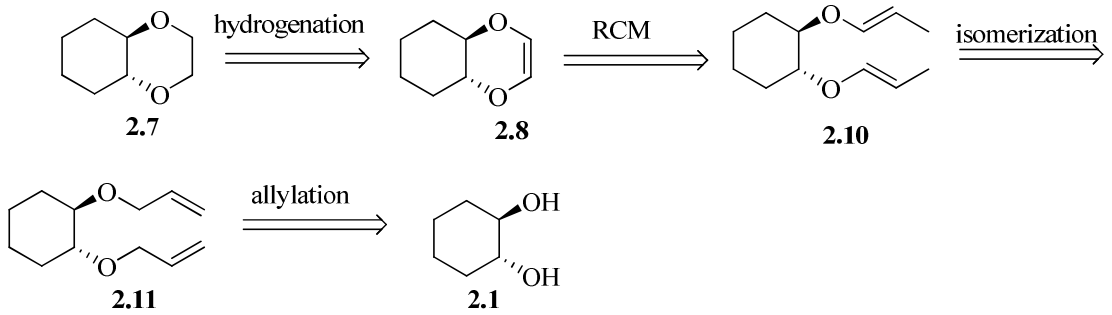
Base	**Electrophile**	**Solvent**	**Results**
NaH	$BrCH_2CH_2Br$ or ICH_2CH_2I	THF or DMF	inconclusive
KOtBu	$BrCH_2CH_2Br$	THF or DMF	inconclusive

solvent/base combinations (shown in Table 2.1), **2.7** was not detected by TLC, GC/MS, or ^{1}H NMR under any conditions. Another route to **2.7** was attempted as shown in Scheme 1. The diether **2.7** was envisioned to be possible from the hydrogenation of **2.8**, which could be made from the ring closing metathesis (RCM) of novel divinyl ether **2.9** with a Grubb's catalyst. Vinylation of **2.1** should afford divinyl ether **2.9**, not previously reported.



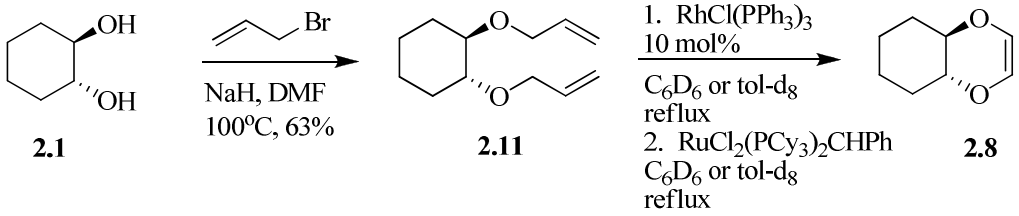
Scheme 2.1 Alternate proposed synthesis of 2.7

Following a similar procedure reported by Denmark and co-workers,[21] excess ethyl vinyl ether and **2.1** were refluxed overnight in the presence of $Hg(OAc)_2$. An alternate procedure by Gurjar,[22] using use $Hg(OCOCF_3)_2$, was also followed. Even though the product's mass of 168.12 was detected as a major peak by GC/MS, **2.9** was never successfully isolated by chromatography or distillation. Each time, **2.1** was recovered and it was assumed the vinyl ether was destroyed by slightly acidic conditions. A recent report of direct vinylation of glucose derivatives with acetylene at high pressures was reported by Trofimov and co-workers,[23] but the synthesis was not attempted because facilities for handling acetylene under high pressure were not available. Compound **2.7** was also envisioned to be possible from the literature reported trans-1,2-bis(allyloxy)cyclohexane (**2.11)**.[24] Isomerization of the allyl ethers, followed by *in situ* RCM should afford **2.8**.

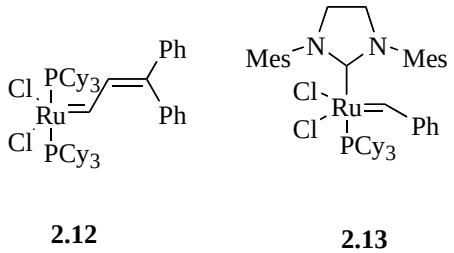


Scheme 2.2 Alternate proposed synthesis of 2.7 via 2.11

The diallyl ether **2.11** was synthesized in 63% yield as shown in Scheme 2.3. Following the allylation, Wilkinson's catalyst, [$RhCl(PPh_3)_3$], was used for the isomerization of the allyl ethers. The isomerization step was followed by ^1H NMR to note the disappearance of the terminal vinyl Hs and subsequent formation of allylic methyl groups (CH_3s). Compound **2.10** was never isolated, and Grubbs' 1st generation catalyst,[25] $RuCl_2(PCy_3)CHPh$ (5-20 mol%) was added to the reaction and allowed to reflux for 24 h. The reaction was monitored by ^1H NMR but the desired intermediate was never observed. Grubb's 2nd generation catalyst[26] **2.13** (Figure 2.6) as well as **2.12** have been shown to succeed in metathesis reactions of problematic electron-rich olefins but they were not tried on this model system due to availability.



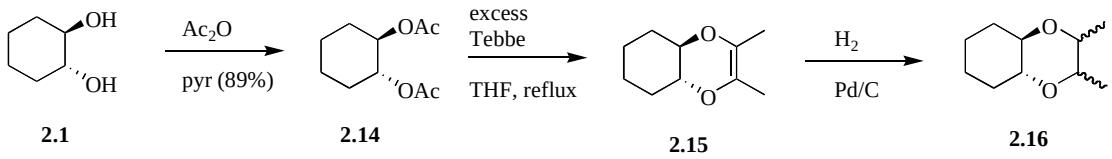
Scheme 2.3 Synthesis of diallyl ether **2.11** and attempted isomerization and RCM to produce **2.8**.



2.12 **2.13**

Figure 2. 6 Grubbs' 1st and 2nd generation catalysts used in RCM

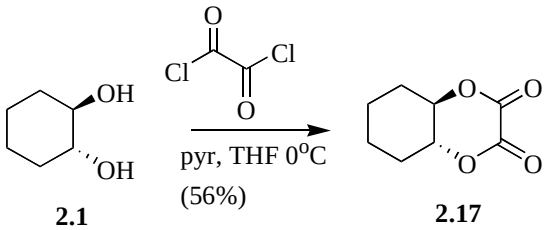
A compound similar to **2.8** was envisioned that would come from the olefination and RCM of *trans*-cyclohexane-1,2-diyl diacetate (**2.14)** with Tebbe reagent ($Cp_2TiCH_2ClAlMe_2$)[27] as seen in Scheme 2.4. The Tebbe reagent is well known to convert esters to enol ethers and with excess Tebbe reagent, the enols are known to undergo olefin metathesis reactions. The reaction was difficult to follow by ^{1}H NMR due to the overlapping resonances of the Tebbe reagent and solvent so the six-membered annulation analogs that entailed an RCM step were abandoned. Diacetate **2.14** was synthesized according to a modified literature procedure.[28] Pyridine was used as the scavenging base and solvent instead of Et_3N as reported by Lefevre and Reymond, since the CDs to be studied later have better solubility in pyridine.



2.1 **2.14** **2.15** **2.16**

Scheme 2.4 Proposed synthesis of 2.16

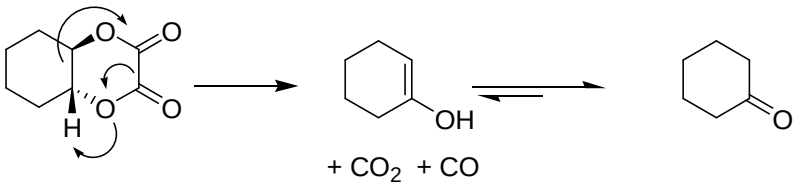
Following the literature precedent of Itaya and co-workers,[29] preparation of (4,8-*trans*)-hexahydro-1,4-benzodioxine-2,3-dione (**2.17)** was attempted. Unfortunately, the published procedure of reacting **2.1** with oxalyl chloride in Et_3N and THF did not give the desired product as **2.17** was not observed by ^{1}H NMR or GC/MS. However, we found success with the conditions shown in Figure 2.7.



2.1 **2.17**

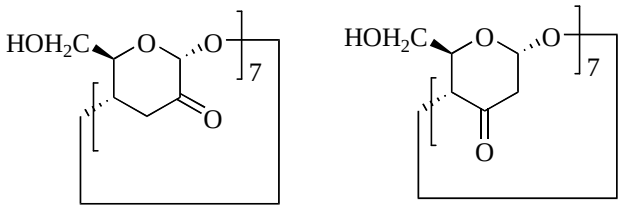
Figure 2.7 Synthesis of cyclic oxalate 2.17

The stability of the product was less than what was described by Itaya, and our product quickly decomposed after Kugelrohr distillation (225°C and 0.1 torr) upon standing at room temperature for 1-2 hours or after 1 day of being stored in the freezer. Recrystallization from hexanes-CH_2Cl_2 gave the same result. The question arose if decarboxylation of the oxalate was occurring to form the ketone (Scheme 2.5). If so, this would prove to give interesting and new CD derivatives, **2.18** or **2.19**, where the C(2)-OH or C(3)- OH hydroxyl groups would be removed and the other would be oxidized to the ketone (Figure 2.8).. These CDs have not been reported in the literature. Unfortunately, the mechanism of decomposition was not pursued.



2.17

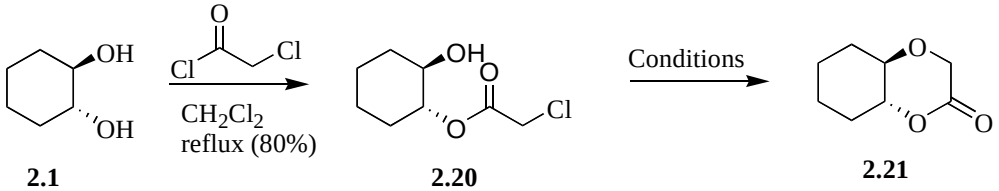
Scheme 2. 5 Proposed decomposition of 2.17



2.18 **2.19**

Figure 2.8 Unique CD derivatives 2.18 and 2.19

In a similar vein as **2.17**, monochloroacetate was used as an electrophile for six-membered ring formation. Instead of forming a symmetrical oxalate, the asymmetrical product might shown unique properties as a CD derivative. Following the modified procedure of Sakai,[30] new monochloroacetate **2.20** was produced from **2.1** in 80% yield (Scheme 2.6). Preparation of the novel cyclized **2.21** was attempted. Unfortunately, all combinations of solvent, base and temperature tried were unsuccessful in producing **2.21** (Table 2.2). The use of NaH in THF or DMF did not produce **2.21** but gave the reactant **2.20**. Similar results were observed with pyridine, a weaker base, in DMF. Hydrolysis of the ester was not observed at elevated temperatures under these conditions. Interestingly, the use of KH in DMF resulted in the formation of **2.1**, where hydrolysis of the ester was observed. The use of a larger base, KHMDS gave both the hydrolyzed **2.1** and reactant **2.20**.



2.1 **2.20** **2.21**

Scheme 2.6 Synthesis of 2.20 and attempted cyclization to produce 2.21

Table 2.2 Attempted reaction conditions for 2.21

Base	Solvent	Temperature	Compound*
NaH	DMF or THF	rt	2.20
pyr	DMF	rt or 80^{o}C	2.20
KH	DMF	rt	2.1
KHMDS	DMF or THF	rt or 80^{o}C	2.20 + 2.1

*Reaction results were determined by GC/MS

Seven-membered Annulation

We proposed a seven-membered ring annulation with **2.1** and 3-chloro-2-(chloromethyl)prop-1-ene (**2.22**) to form **2.23**. Not only would this produce a seven-membered ring, the electrophile is reactive to substitution at both allylic positions but not elimination. If elimination is occurring with dibromoethane (Scheme 2.5), **2.22** will not have the same problems. Multiple reaction conditions were attempted (Table 2.2) and the best conditions found for the cyclization were using an excess of NaH and slow addition of the electrophile via syringe pump to give **2.23** in 39% yield prior to chromatography, as shown in Figure 2.9.

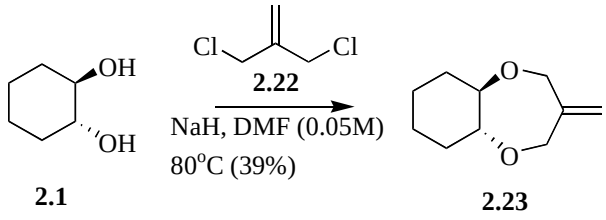


Figure 2. 9 Synthesis of novel compound 2.23 from 2.1 and 2.22

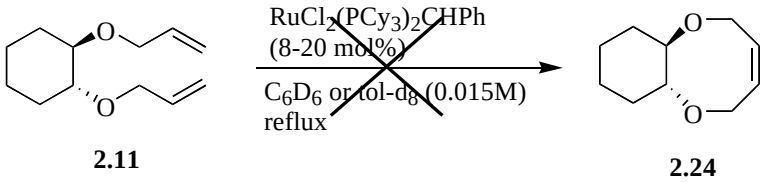
Table 2.3 Attempted reactions conditions to form 2.23

Base	Solvent	Temperature	Results*
NaH	DMF (0.04M)	rt	28% + sp
NaH	DMF (0.005 M)	rt (sonication)	14% +sp
NaH	DMF (0.2M)	80°C	43% + sp
NaH	DMF (0.002 M)	80°C	53% +sp
KH	DMF (0.005 M)	rt	8% + sp
NaH	THF (0.02 and 0.05 M)	rt	0% + 2.1
NaH	THF (0.02 and 0.05 M)	80°C	0% + 2.1
MeCN	THF (0.02 and 0.05 M)	rt	0% + 2.1
MeCN	THF (0.02 and 0.05 M)	80°C	0% + 2.1

*Reaction results were determined by GC/MS. rt = room temperature,
sp = side product unable to remove via distillation or column chromatography

Eight--membered Annulation

With compound **2.23** in hand, larger annulated systems were envisioned. RCM of diallyl ether **2.11** was attempted with Grubb's 1st generation catalyst, $RuCl_2(PCy_3)CHPh$, but the subsequent metathesis product **2.24** was not detected by ^1H NMR or GC/MS and detection of **2.11** was observed. Compound **2.24** is known in the literature but the researchers used the other 1st generation catalyst **2.12**.[25]



2.11 **2.24**

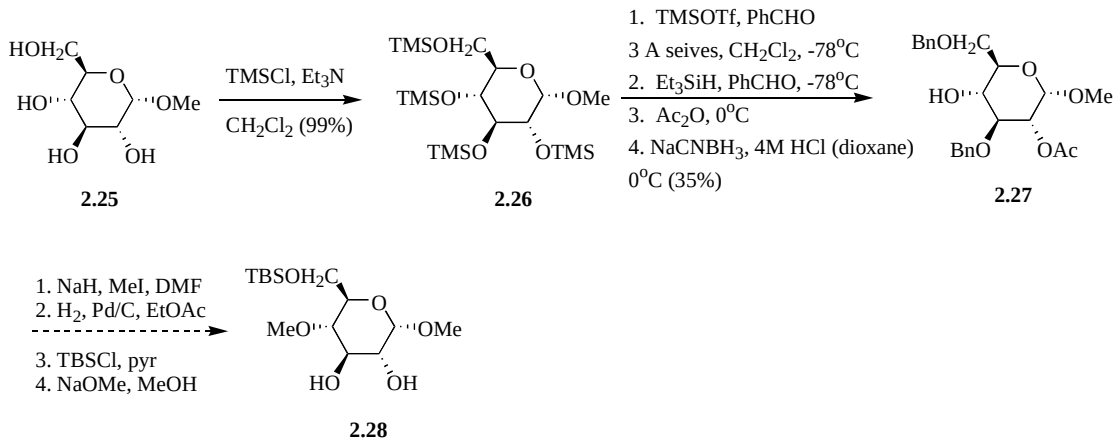
Figure 2. 10 Attempted synthesis of 2.24

Synthesis of Glucose Model System 2.2

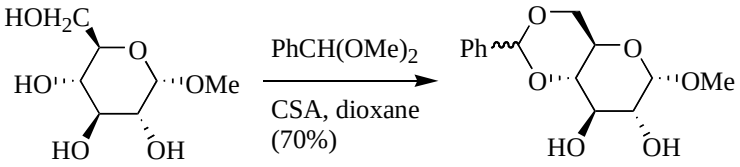
The use of **2.1** as a simple model system proved beneficial to determine that annulation of trans-diols was feasible in some cases, and allowed us to optimize reaction conditions somewhat. Glucose model system **2.2** could aid in determining if the difference in reactivity of the C(2)-OH and C(3)-OH hydroxyl groups would cause problems on CD derivatives.

Initially, compound **2.27** was envisioned as a precursor to glucose model system **2.28** to test the annulation of C(2)- and C(3)-OH hydroxyl groups (Scheme 2.6). Per-*O*-trimethylsilylation of methyl α-D-glucopyranoside (**2.25**) gave the corresponding 2,3,4,6-tetra-*O*-TMS ether **2.26** in 99% yield. Following the one-pot procedure reported by Wang,[31] **2.27** was synthesized from **2.26** in 35% yield. Due to time constraints, the synthesis of **2.28** was not completed.

The synthesis of **2.28** was envisioned to include a methylation of the C(4)-OH, followed by de-benzylation of C(3)- and C(6)-OH hydroxyl groups. Subsequent TBS protection of C(6)-OH and deacetylation of C(2)-OH should produce **2.28**.



Scheme 2.7 Synthesis of glucose model precursor **2.25** and proposed synthesis of **2.26**



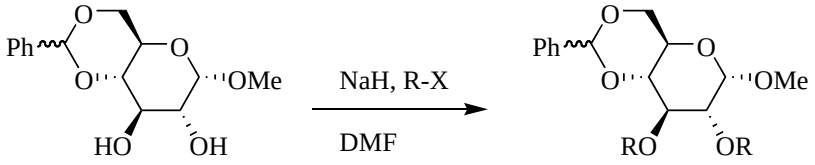
2.25 **2.2**

Figure 2. 11 Synthesis of glucose model 2.2

Glucose model **2.2** was synthesized from methyl α-D-glucopyranoside (**2.25**) instead in one step (70% yield) following the work of Kawada and Rosenau as shown in Figure 2.11.[32] The 4,6-O-benzylidene group on 2.2 is stable to basic conditions and therefore a desirable protecting group for C(6)-OH hydroxyl group. Many CD reactions are carried out under basic conditions instead of acidic conditions to prevent cleavage of the CD ring.[31]

Annulation Attempts with 2.2

Literature known compounds **2.29**[33] and **2.30**[34] were successfully synthesized (Figure 2.12) following traditional methylation and allylation conditions used on β-CDs, respectively.

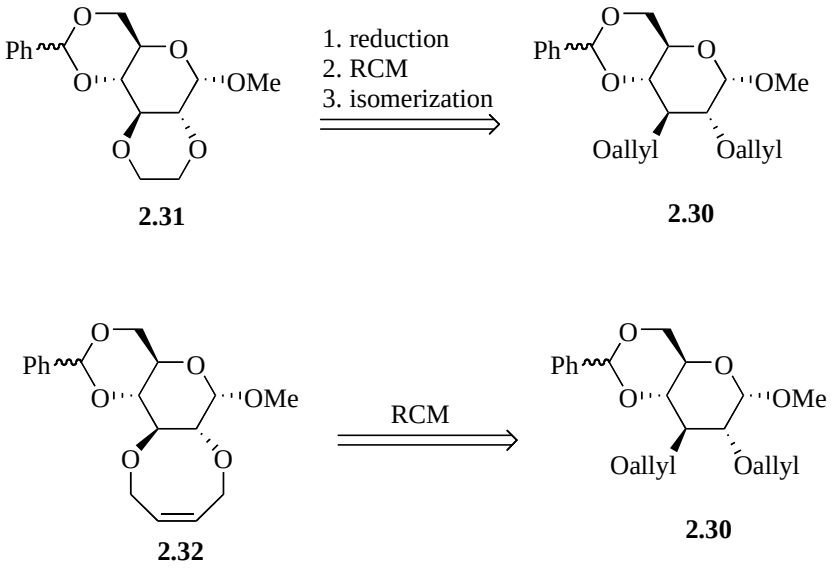


2.2

2.29 R = Me, X = I (30%)
2.30 R = allyl, X = Br (85%)

Figure 2.12 Synthesis of 2.29 and 2.30

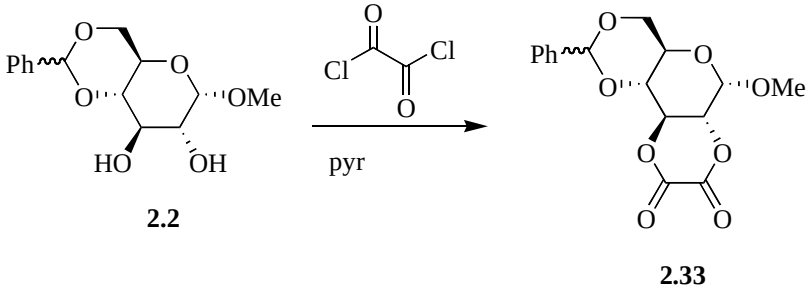
The formation of annulated compounds **2.31** and **2.32** (Figure 2.13) was envisioned to come from **2.30** and follow the previous conditions used with **2.7** and **2.24**, but the reactions were not attempted due to limited material and time constraints.



2.31 **2.30** **2.32** **2.30**

Figure 2. 13 Proposed synthesis of 2.31 and 2.32 from 2.30

The mass of cyclic oxalate **2.33** (336.08) was detected by GC/MS as the major component of the reaction of **2.2** and oxalyl chloride but attempts to purify the crude reaction mixture by column chromatography were unsuccessful (Figure 2.14).



2.2 **2.33**

Figure 2.14 Attempted synthesis of 2.33

Compound **2.34** was not detected by GC/MS in the reaction of **2.2** with C_6F_6, but the mass of the mono-substituted compound **2.35** (448.09) was detected (Figure 2.15).

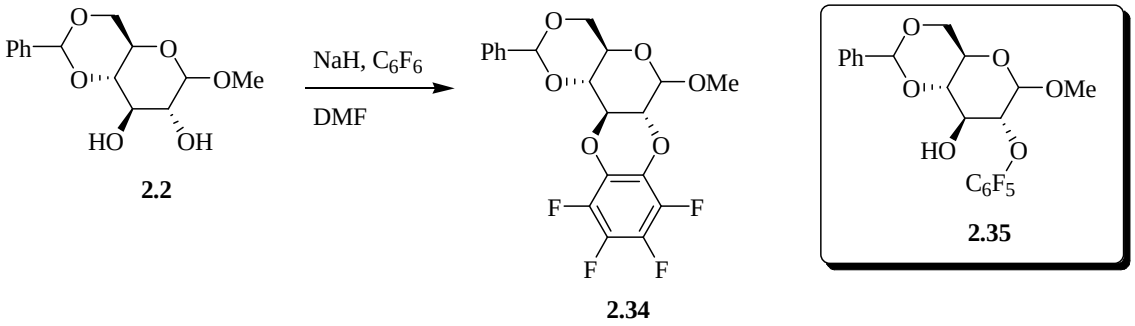


Figure 2.15 Attempted synthesis of 2.33

Similar results were also seen with the reaction of **2.2** with **2.22** to form **2.37**. Only the non-cyclized compound **2.38** was detected by GC/MS (Figure 2.16).

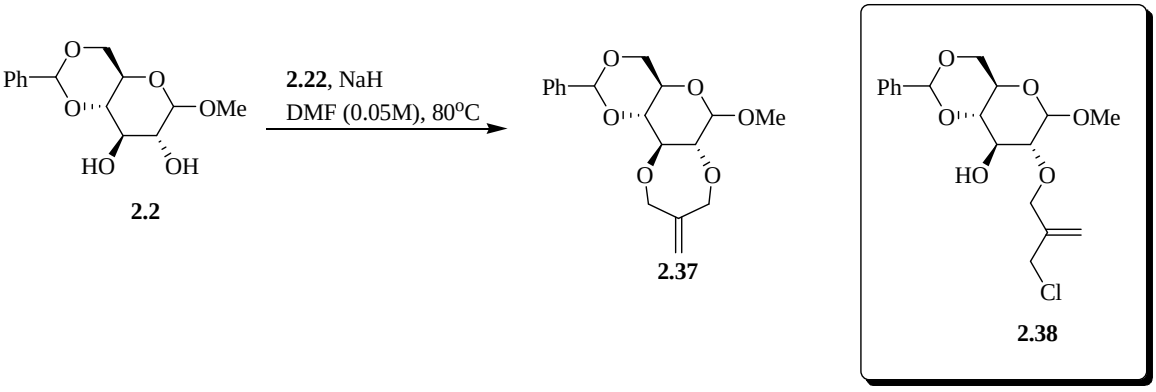


Figure 2.16 Attempted synthesis of 2.37

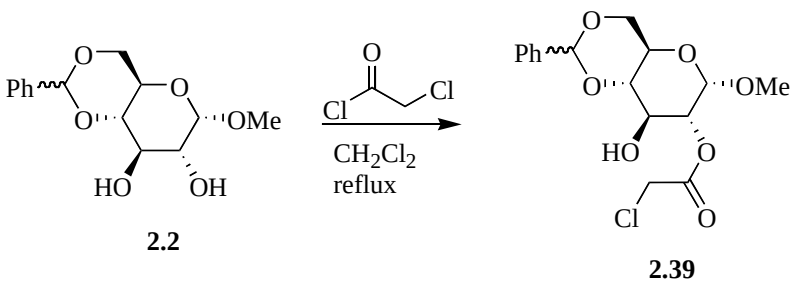


Figure 2.17 Attempted synthesis of 2.39

The reaction of **2.2** with chloroacetyl chloride did not yield compound **2.39**, and in this case even the mass of 358.08 for **2.39** was not detected by GC/MS (Figure 2.17). The incomplete cyclizations of **2.33**, **2.34** and **2.37** are most likely due to difference in reactivities of the C(2)- and C(3)-OH hydroxyl groups, with the C(2)-OH being the most reactive. The mono-substituted **2.35** and non-cyclized **2.38** were not isolated due to time constraints and further attempts to optimize the reaction conditions were not pursued.

Synthesis of 4-O-methyl methyl β-maltoside derivative 2.3

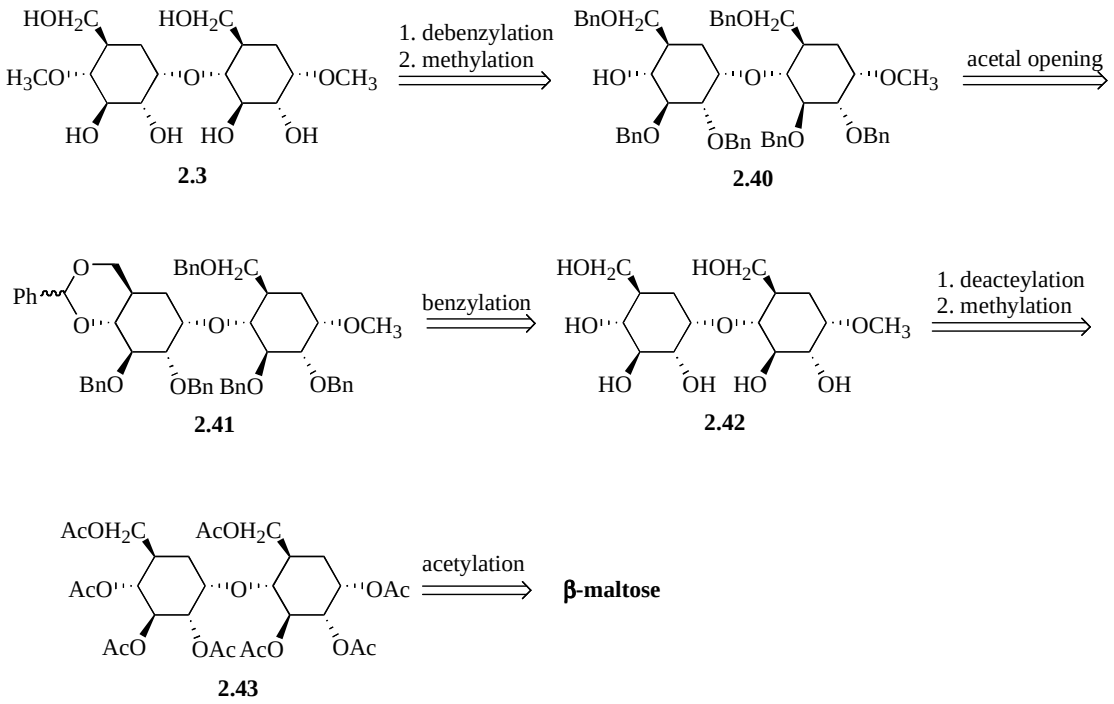
The purpose of synthesizing **2.3** was to probe the interactions of a neighboring C(2)-OH hydroxyl group on the C(3)-OH hydroxyl groups reactivity. It is well known that the diminished reactivity of the C(3)-OH group has been attributed to the hydrogen bonding capability with the C(2)-OH group on a neighboring glucose unit. The synthesis of **2.3** was envisioned to come from **2.40** after methylation of the C(4)-OH group and debenzylation of the remaining hydroxyl groups. Benzylation of methyl β-maltoside (**2.42**), followed by opening of the benzylidene acetal **2.41** should produce **2.40**. Methyl β-maltoside can be formed from the methylation and deacteylation of maltose octaacetate

(**2.43**). Maltose octaacetate can be synthesized from the acetylation of β-maltose as shown in Scheme 2.8.

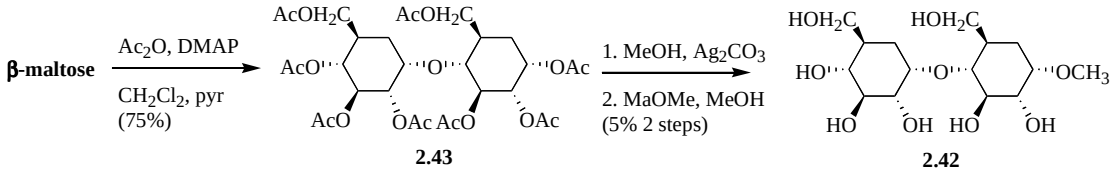
Beginning with β-maltose, maltose octaacetate (**2.43**) was synthesized in 75% (Scheme 2.9) following the reported procedure by Gosney.[35] Hodge reported the direct methylation of **2.43** with a mixture of $BF_3{\cdot}OEt_2$ and CH_2N_2,[36] but we chose to follow the procedure reported by Newth and co-workers to form methyl b-maltoside in 5% yield.[37] The low yield of **2.42** and the long synthesis to form **2.3** proved daunting and this model system was not pursued.

Conclusion

Two different model systems were used to probe the annulation reactions envisioned to make novel β-CD derivatives. Trans-1,2-cyclohexane diol (**2.1**) was used to successfully synthesize novel fluorinated derivative **2.5**, and certain other annulated derivatives. The reaction conditions that were optimized for **2.1** were used with model system **2.2**. Even though the annulated compounds were not synthesized, methylated and allylated compounds **2.29** and **2.30** were synthesized in modest yields. These results proved promising for β CD and the derivatives synthesized will be discussed in the following chapters.



Scheme 2.8 Proposed synthesis of 2.3



Scheme 2.9 Synthesis of methyl β-maltoside (2.42)

CHAPTER THREE

Preparation and Reactions of 6-OTBS and 6-OMe β-Cyclodextrins

Introduction

Since each CD has multiple sites for modification, reactions of the hydroxyl groups can occur to different degrees in different positions. A complex mixture of full and partially substituted products would create a myriad of problems with purification by either recrystallization or column chromatography, in addition to complicating analysis of the reaction mixture by common spectroscopic techniques. Controlled modification of CDs can be employed by exploiting the different reactivities of the hydroxyl groups (C(6)-OH > C(2)-OH > C(3)-OH). The C(6) carbon on the primary face is generally substituted with non-polar groups such as alkyl or silyl groups, and bulky groups are more selective for the C(6) hydroxyl (i.e., less C(2) alkylation occurs). It has been reported that varying the size of the substituent at the C(6) position can also affect the selectivity of the CD due to the different shapes created by the various substituents.[38] Kobor found that the shape differences of the (6-O-methoxy-2,3-dimethoxy)- and the (6-O-TBS-2,3-dimethoxy)-β-CD resulted in differences in their enantioselectivities.[39] In addition, large non-polar groups at C(6)-OH increased the solubility of CD derivatives while smaller groups increased the polarity of the derivatives. Protecting the primary face of CDs is important to focus derivatization only on the secondary face. Even more desirable is the masking of all the primary C(6)-OH hydroxyl groups at one time. This can be challenging, depending on the size of the protecting group. The use of excess p-

toluenesulphonyl chloride (TsCl) in pyridine can give the 6-O-per-tosylated β-CD and a mixture of incomplete tosylation of the secondary hydroxyl groups. The competing reaction at the secondary face can increase as the degree of substitution on the CD increases.[3] However, if the protecting group is too large, in the case of trityl chloride (TrCl), a mixture of di-, tri- and tetra-trityl derivatives are isolated but the per-trityl derivative is not detected in the mixture. Increasing the amount of trityl chloride only succeeds in alkylating the secondary face.[40] The use of bulky silyl ethers, such as *t*-butyldimethylsilyl (TBSCl) and triisopropylsilyl (TIPSCl), as masking groups has an added benefit of increasing the solubility in common organic solvents and silyl ethers are stable in neutral and basic conditions.[41]

The secondary hydroxyl groups are more acidic than the primary groups, with the C(2)-OH being the most acidic. The secondary hydroxyl groups are located on the wider end of the CD with the C(2)-OH pointing towards the cavity. Inclusion of reagents in the CD annulus, along with orientation of the reactive groups in the complex, can affect the regioselectivity of reactions on CDs.[4] Substituents on the secondary face of β–CD, such as alkyl and acyl groups, are typically introduced to alter the selectivity of the βCD. By adjusting the pH of the reaction, substitution at the C(2)-OH hydroxyl group can predominate over C(6)-OH substitution. Increasing the pH of the reaction from acidic or neutral conditions to a pH of 10 will selectively modify the secondary hydroxyl groups over the primary. This secondary face selectivity is evident in the reaction of β-CD with TBSCl in alkaline conditions to produce *3.1*.[42] By decreasing the pH and using pyridine as the base, primary silylation is achieved to produce 6-*O*-TBS-β-CD **3.2** (Figure 3.2).[41]

Strategies used to derivatize the secondary face tend to proceed through nucleophilic substitution reactions of tosyl and silyl ether intermediates.

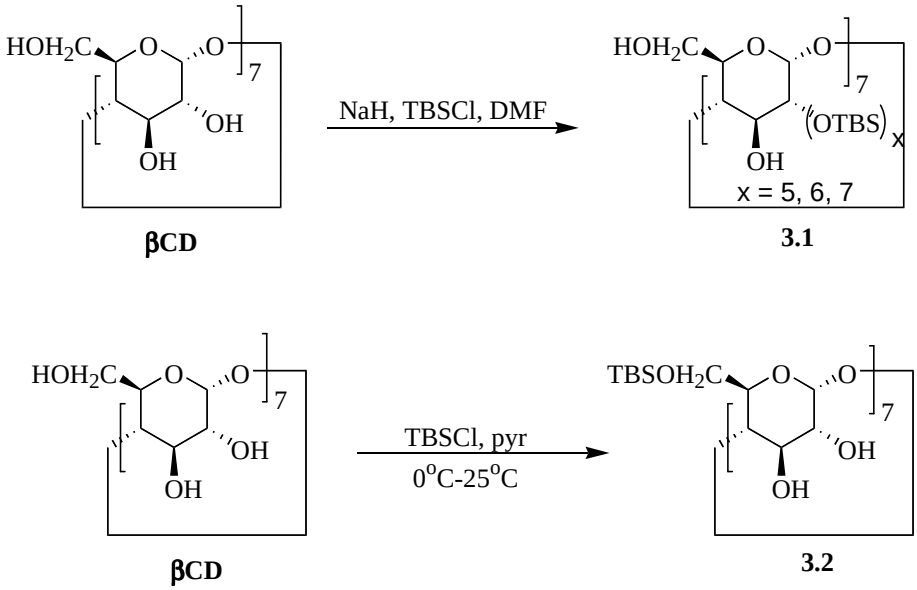


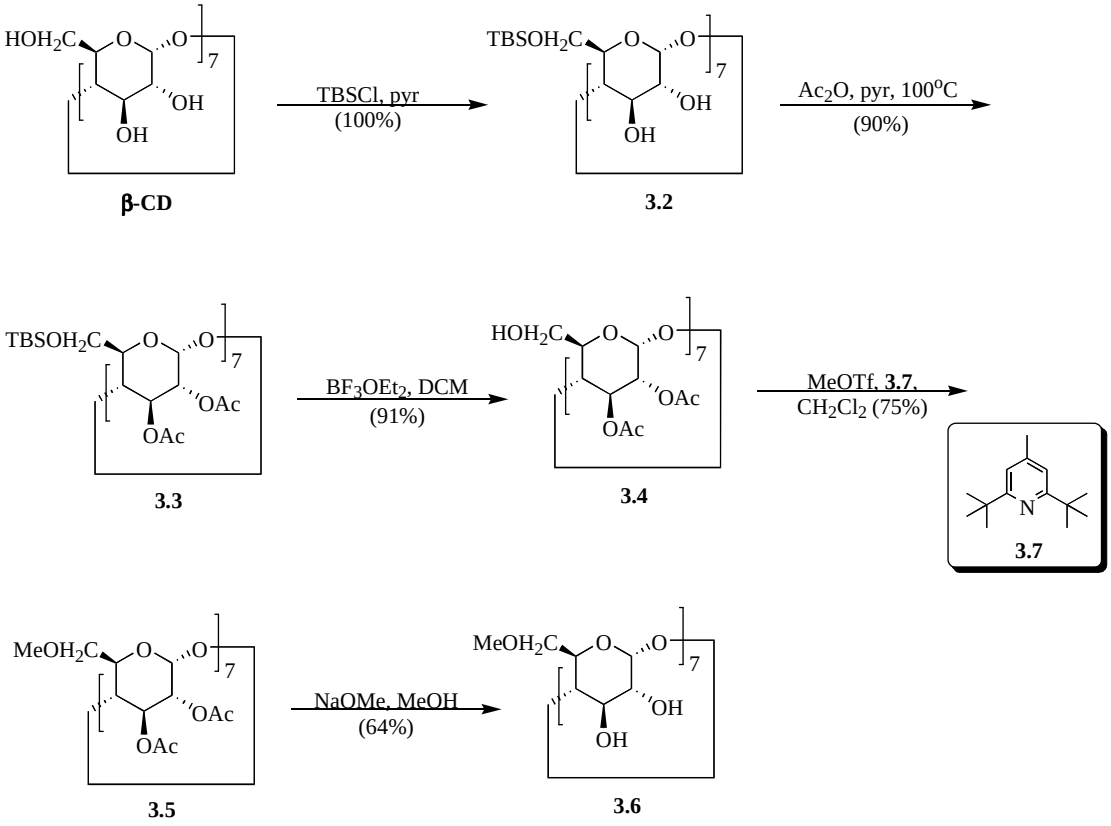
Figure 3.1 Attenuated protection of C(2)-OH v. C(6)-OH hydroxyl groups on β-CD[41,42]

Synthesis of 6-OTBS βCD 3.2 and 6-OMe βCD 3.6

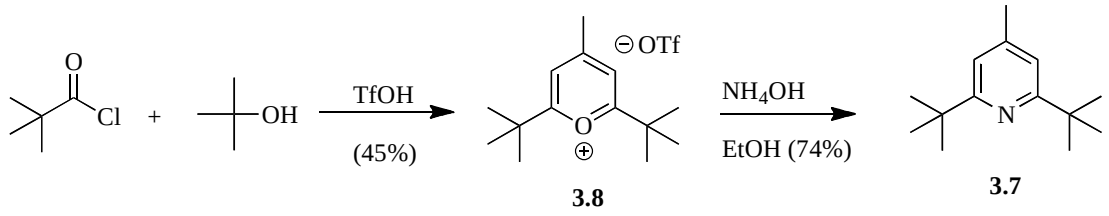
We chose to initially focus on protection of the C(6)-OH hydroxyl group with a non-reactive methyl substituent. Synthesis of known heptakis(6-*O*-methyl) cyclomaltoheptaose (6-OMe βCD, **3.7**) was undertaken as the precursor to novel β-CD derivatives, **3.9**-**3.12**. Following the procedure reported by Stoddart,[7] β-CD was reacted with TBSCl in anhydrous pyridine to produce 6-OTBS βCD **3.2** in 100% yield as shown in Scheme 3.1.

We improved upon the purification of **3.2** by eliminating column chromatography and triturating the crude product in EtOH. β–CD crystallized from the solution upon cooling and the resulting filtrate is decanted and evaporated to give pure **3.2**. Following

the work of Takeo,[43] subsequent acetylation of **3.2** gave known **3.3** (6- OTBS-2,3-OAc) in 90% yield. A one-pot synthesis was attempted as reported by Fugedi[41] but the purification proved daunting and the yield was significantly worse (45%) than the two-step procedure used. Desilylation of **3.3** with $BF_3 \cdot OEt_2$ afforded known **3.4** (6-OH-2,3-OAc) in 91% yield followed by methylation in a sealed tube to give known **3.5** (6-OMe-2,3-OAc) (75% yield). Due to the cost of the hindered pyridine base **3.7**, 2,6-lutidine and 2,4,6-collidine were tried but **3.5** was never attained. Considerable time was spent synthesizing **3.7** (Scheme 3.2) and attempts to recycle and reuse the base more than once proved unsuccessful.[44] Deacetylation of **3.5** under basic conditions produced **3.6** (64% yield) as a white solid.



Scheme 3.1 Synthesis of (6-OMe βCD, **3.6**)[7,41,43]



Scheme 3.2 Synthesis of hindered pyridine base **3.7**

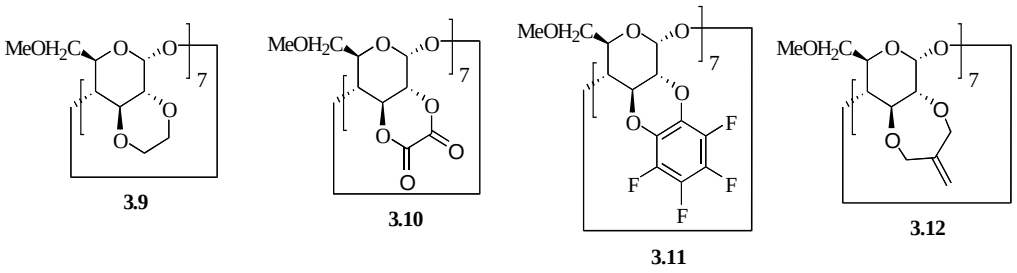


Figure 3.2 Proposed novel 6-OMe β-CD derivatives

It was found that **3.6** was completely soluble in H_2O or DMSO at room temperature but needed elevated temperatures for complete solubility in DMF, pyridine, DMF/pyridine mixture, or THF/pyridine mixture.

With 6-OMe β-CD in hand, the preparation of four different novel β-CD derivatives, **3.9**-**3.12**, was attempted (Figure 3.2). Even though the synthesis of **2.7** was unsuccessful, similar reaction conditions were used in an attempt to synthesize **3.9** (Figure 3.3 and Table 3.1).

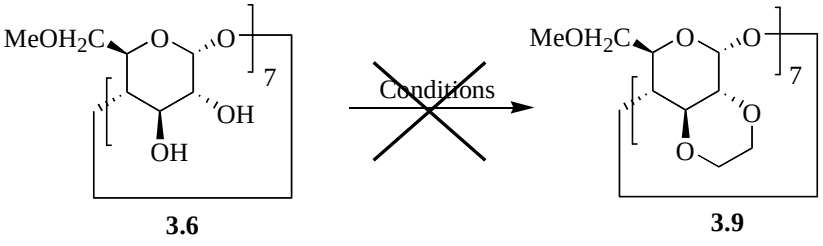


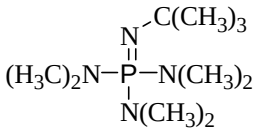
Figure 3.3 Attempted synthesis of **3.9**

Table 3.1 Reaction conditions for synthesis of **3.9**

Base	Electrophile	Solvent	Compound*
NaH	$BrCH_2CH_2Br$	THF or DMF	3.6
Pyridine	$BrCH_2CH_2Br$	DMF/pyr (1:1) or Pyridine	3.6
KHMDS (0.6M in toluene)	$BrCH_2CH_2Br$	THF or DMF	3.6
KOtBu	$BrCH_2CH_2Br$	THF or DMF	3.6
NaH	ICH_2CH_2I	THF or DMF	3.6
KOtBu	ICH_2CH_2I	THF or DMF	3.6
P_1-tBu	$BrCH_2CH_2Br$	THF or DMF	3.6
P_1-tBu	ICH_2CH_2I	THF or DMF	3.6

Results based on TLC and recovery of **3.6** after column chromatography purification

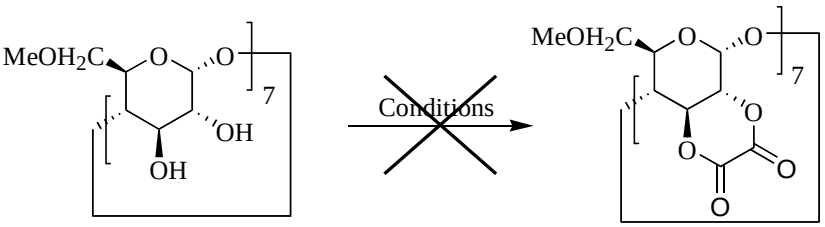
We believe that 1,2-dibromoethane and 1,2-diiodoethane were unsuccessful due to a competing elimination reaction of the electrophile and base. If the second halogen is eliminated after substitution on **3.6**, a labile vinyl ether substituent would be produced. If elimination of the electrophile occurs before substitution can occur, then only **3.6** would be seen by ^{1}H NMR. Monitoring the reactions by ^{1}H NMR proved challenging due to the asymmetrical nature of the spectra. It was assumed that a combination of incomplete alkylation and elimination were occurring. Another hurdle was the differing reactivities of the C(2)- and C(3)-OH groups. If alkylation at the C(2)-OH was successful, the much lower reactivity of the C(3)-OH may not react fast enough to compete with elimination of the electrophile. The use of a phosphazene base, P_1-*t*-Bu (Figure 3.4),[45] was also attempted in hopes that a stronger (pKa of conjugate acid ~25 in MeCN) and larger base would efficiently deprotonate the C(3)-OH and yield an especially reactive anion. This too did not yield the desired annulated **3.9**. Many alkylations were attempted using this base, with uniformly poor results.



P_1-*t*-Bu

Figure 3.4 Phosphazene base, P_1-*t*-Bu

Oxalyl chloride was successful with model system **2.1** to form **2.17** but did not give the desired results with **3.6** to produce **3.10** (Figure 3.5). All conditions tended to produce an insoluble solid that would not dissolve even upon heating (Table 3.2). The reactions were monitored by TLC and consistently showed inconclusive results with **3.6**. Less polar spots than **3.6** were observed on TLC and this was considered a criterion of success of some reaction occurring. Again, the sluggish reactivity of the C(3)-OH group was the main concern with the reaction.



3.6 **3.10**

Figure 3.5 Attempted synthesis of **3.10**

Table 3. 2 Reaction conditions for synthesis of **3.10**

Base	Electrophile	Solvent	Compound*
Pyr.	Oxalyl chloride	Pyr or DMF/pyr.	3.6
NaH	Oxalyl chloride	Pyr or DMF/pyr.	3.6

Results based on TLC and recovery of **3.6** after column chromatography purification

The optimal conditions (NaH, slow addition) found for fluorinated model compound **2.5** and 7-membered annulated compound **2.23** did not translate to success for the syntheses of **3.11** and **3.12**, respectively (Figure 3.6).

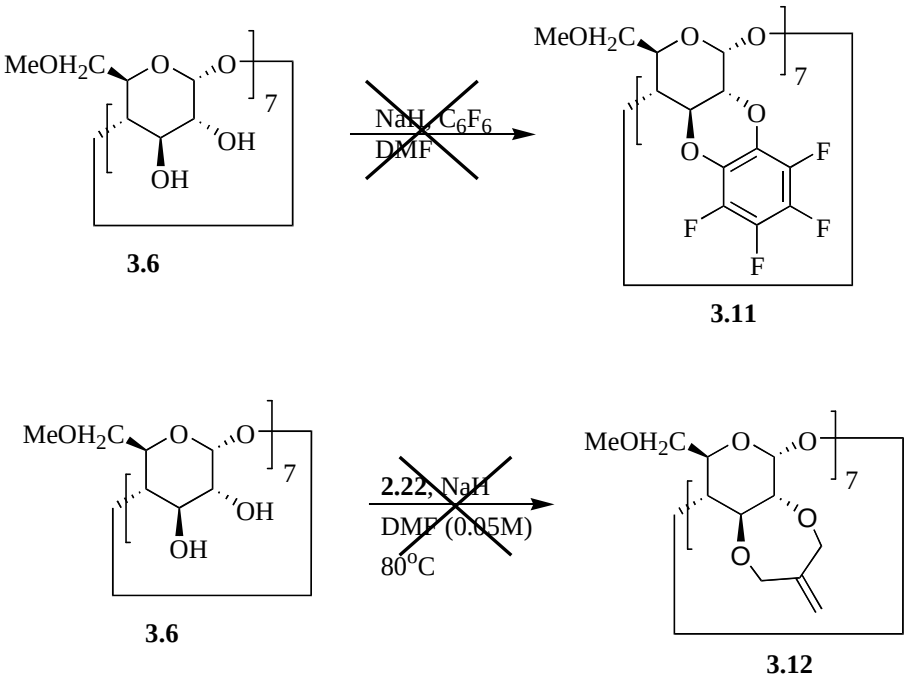


Figure 3. 6 Attempted synthesis of **3.11** and **3.12**

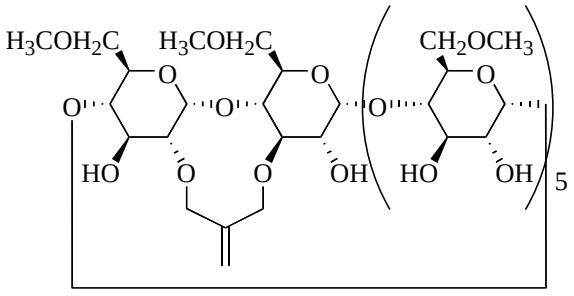


Figure 3.7 Annulation of adjacent glucose moieties in 6-OMe β-CD

Being a larger electrophile and forming a 7-membered ring instead of a 6-membered ring, the idea of **2.22** bridging two adjacent glucose moieties, to form a 10-membered ring, was considered as shown in Figure 3.7. Even though formation of the 10-membered ring is disfavored over the 7-membered ring, annulation of adjacent moieties has been reported in the reaction of 6-OPiv β–CD **3.13** with benzaldehyde dimethyl acetal (Figure 3.8).[46] Unfortunately, we were unable to detect any reaction of **2.22** with **3.6** by spectroscopic or spectrometric techniques.

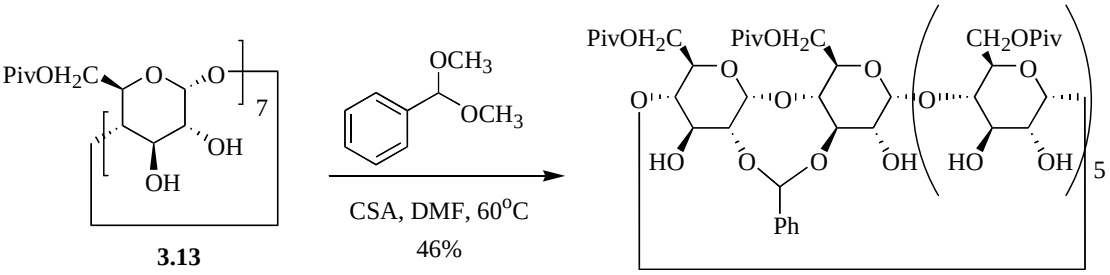


Figure 3. 8 Inter glycosidic benzylidene synthesis

Known derivative, per-methylated β–CD **3.14**,[47] was synthesized in 25% yield following procedure reported by Szejtli. The formation of **3.14** shows that alkylation can occur at the C(2)- and C(3)-OH groups, even in sparingly soluble conditions, with simple electrophiles like methyl iodide.

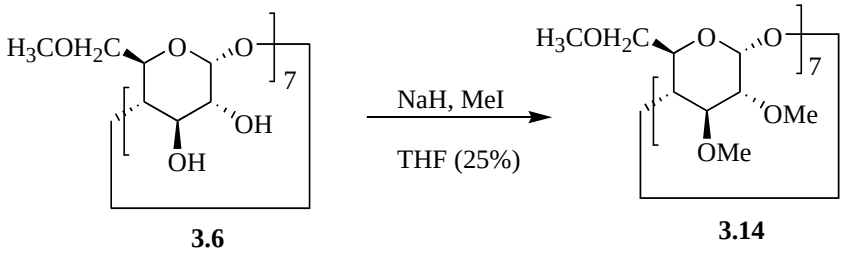


Figure 3.9 Synthesis of per-methylated βCD **3.14**

To bypass the decreased solubility of **3.14**, 6-OTBS βCD **3.2** was thought to be a worthwhile annulation precursor due to its increased solubility in a variety of solvents (hexanes to DMF). It was also made in one step from βCD, versus five steps for **3.6**. Synthesis of novel derivatives **3.15-3.18** were attempted from **3.2** as shown in Figure 3.10 and Table 3.3. Desilylation at the C(6)-OH group of **3.2** was observed by ^{1}H NMR when reacting with C_6F_6. This was seen as a positive sign that nucleophilic aromatic substitution was occurring and F^- was being formed in solution. Desilylation of silyl ethers is well known using F^- reagents.[48] Attempts to push the reaction to completion to form **3.17** (additional base, elevated temperatures, dilution) were unsuccessful and we were unable to determine the extent of aryl substitution by ^{1}H NMR and all attempts at purification of the reaction mixtures were unsuccessful.

Table 3. 3 Reaction conditions for the synthesis of **3.15-3.18**

Base	Electrophile	Solvent	Compound*
NaH	$BrCH_2CH_2Br$	THF or DMF (DMF/pyr)	**3.2** + non-polar compounds
KOtBu	$BrCH_2CH_2Br$	THF or DMF (DMF/pyr)	**3.2** + non-polar compounds
KHMDS (0.6M in toluene)	$BrCH_2CH_2Br$	THF or DMF (DMF/pyr)	**3.2** + non-polar compounds
Pyr	Oxalyl chloride	Pyr or DMF/pyr.	**3.2** + non-polar compounds
NaH	Oxalyl chloride	Pyr or DMF/pyr.	**3.2** + non-polar compounds
NaH	C_6F_6	THF or DMF or pyr.	Loss of TBS at C(6)-OH
NaH	**2.22**	DMF	**3.2** + non-polar compounds

Results based on TLC and recovery of **3.2** after column chromatography purification

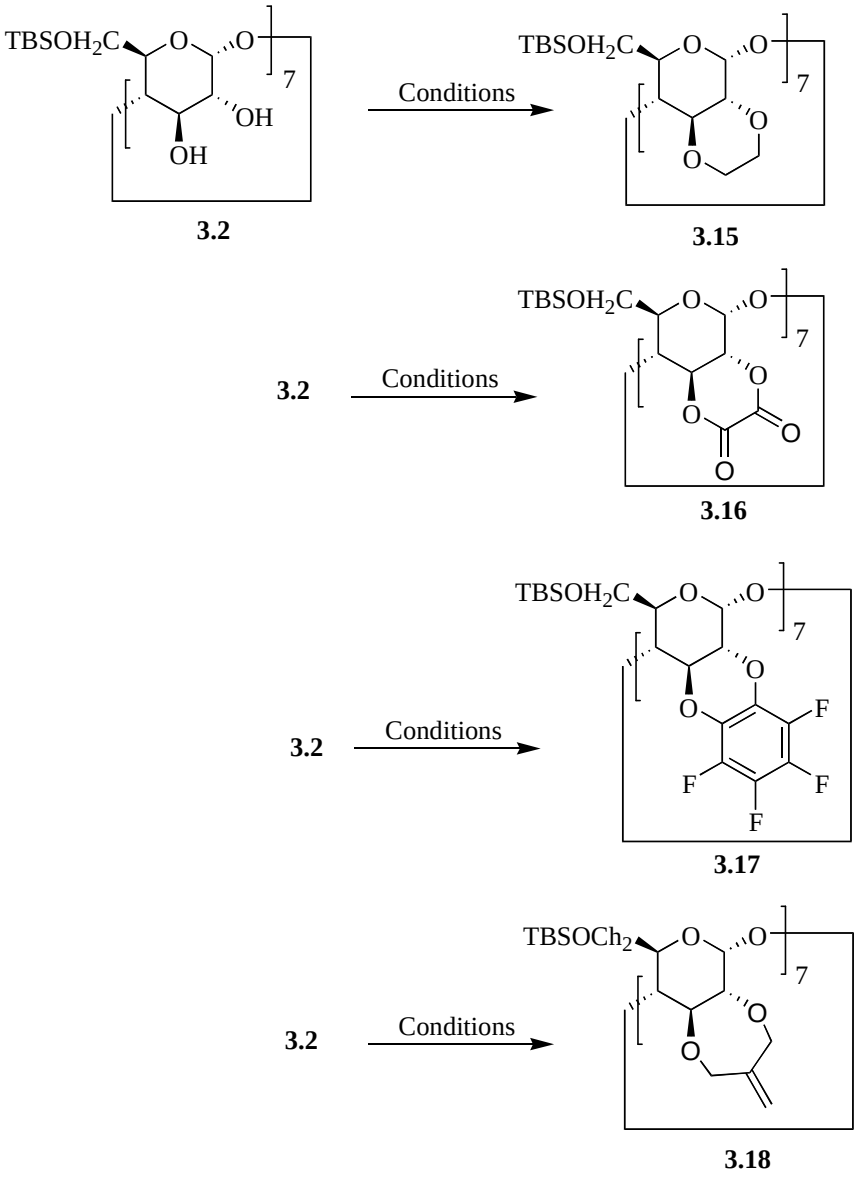


Figure 3.10 Attempted syntheses of **3.15-3.18**

To circumvent the slower reactivity of C(3)-OH, we sought to exploit the silyl migration seen by Stoddart and Konig.[49] It is well documented that under basic conditions, a C(2)-O-silyl functionality will migrate to the C(3)-O position. Two different intermediates, both bearing a pentacovalent silicon atom, have been proposed for the silyl migration (Figure 3.11).

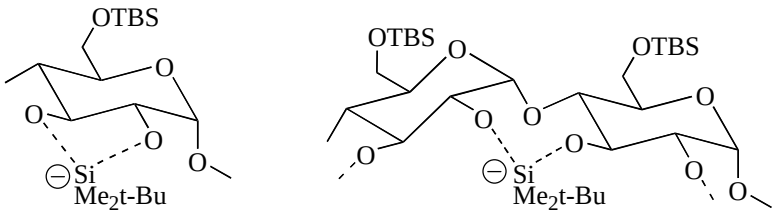


Figure 3.11 Proposed intermediates for silyl migration

Trimethylsilylation at C(2)-OH position of **3.2** to produce **3.19**[50] (54% yield) proved successful with the use of TMS-acetamide (TMA) in DMF (Figure 3.12). By adding DMAP to the reaction conditions used to produce **3.2** and increasing the temperature to 100^{o} C, (2,6-di-*O*-*t*-butyldimethylsilyl)-β-CD (**3.20**)[49a] was synthesized in 53% yield following the procedure reported by Stoddart (Figure 3.13).

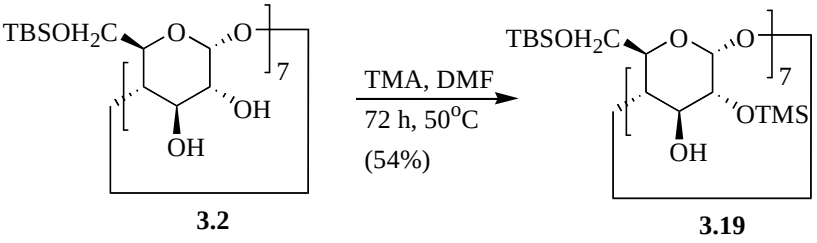


Figure 3. 12 Synthesis of (6-*O*-*t*-butyldimethylsilyl-2-*O*-trimethylsilyl)-β-CD (**3.19**)

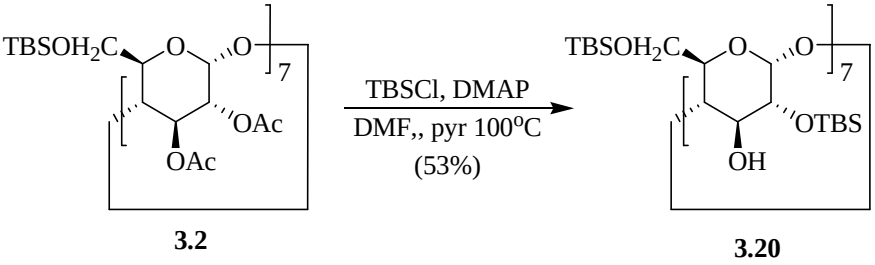


Figure 3.13 Synthesis of (2,6-di-O-t-butyldimethylsilyl)-β-CD (**3.20**)

Attempts to form (2,6-di-O-trimethylsilyl)-β-CD **(3.21)**[51] using TMS-imidazole or TMSCl proved unsuccessful (Figure 3.14). The lability of TMS ethers on β–CDs is known and the more TMS groups on a cyclodextrin, the more the molecule is prone to hydrolysis.

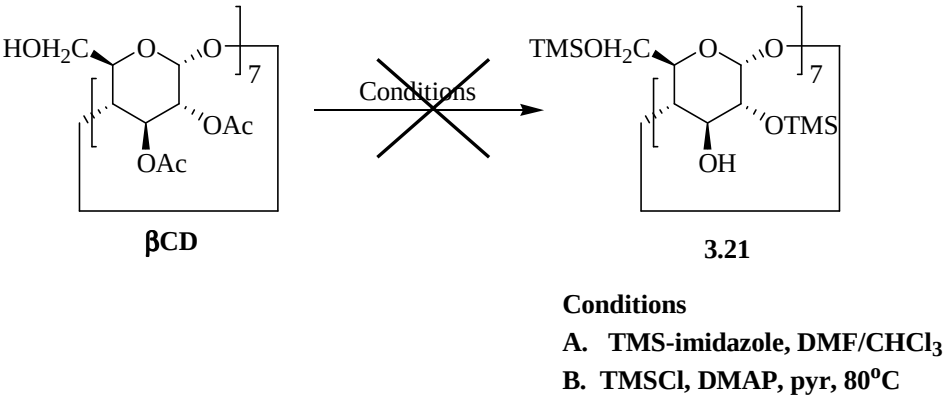


Figure 3.14 Attempted synthesis of 3.21

Attempted annulation of **3.19** and **3.20** with $BrCH_2CH_2Br$ under alkaline conditions and subsequent slow addition addition of TBAF did not yield **3.15** or the desilylated compound **3.20** (Figure 3.15).

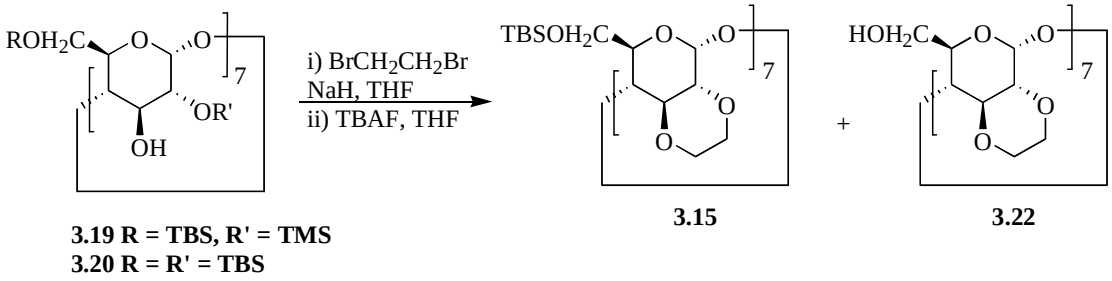
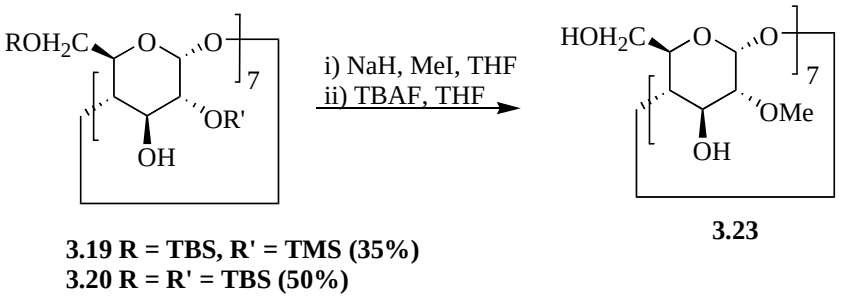


Figure 3.15 Attempted annulation of 3.19 and 3.20

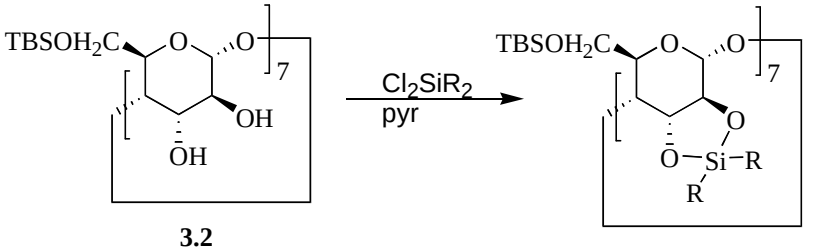


3.19 R = TBS, R' = TMS (35%)
3.20 R = R' = TBS (50%)

3.23

Figure 3.16 Synthesis of (2-O-methyl)-β-cyclodextrin (3.23)

Following the procedure reported by Stoddart,[49a] addition of NaH and methyl iodide in THF to **3.19** and **3.20** did yield **3.23** after desilylation with TBAF (Figure 3.16). Our first successful annulation on a CD derivative occurred by reacting **3.2** with $Cl_2Si(CH_3)_2$ in pyridine (Figure 3.17). Purification on deactivated silica gel gave **3.24** (20% yield). A similar derivative **3.25** was produced from the reaction of **3.2** with Cl_2SiPh_2 but the pure compound could not be isolated by recystallization or column chromatography. These new compounds proved that annulation on β–CD was possible and not completely elusive. Attempts to use **3.24** and **3.25** as precursors to **3.15** or **3.22** were unsuccessful along with methylation conditions to produce **3.23**.

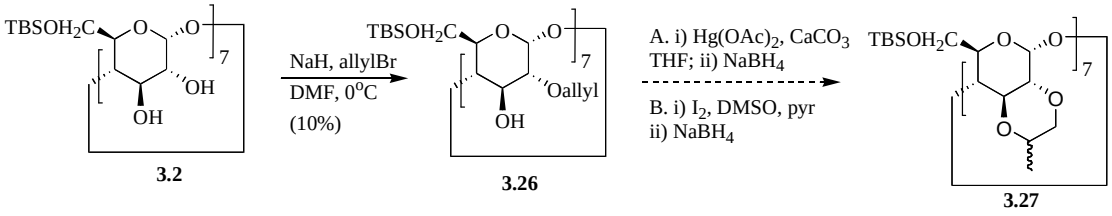


3.2

3.24 R = Me (20%)
3.25 R = Ph (crude)

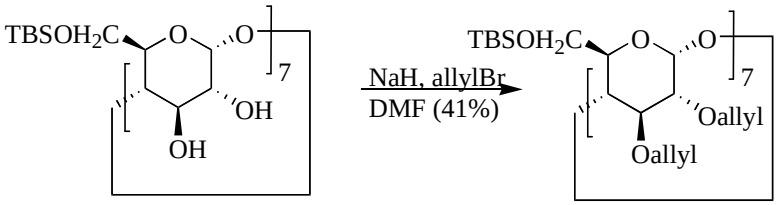
Figure 3.17 Synthesis of novel βCD derivatives **3.24** and **3.25**

A route to **3.27**, which is similar to attempted annulated derivative **3.15**, was envisioned by an iodination/cyclization[52] or a oxymercuration/demurcuration/ cyclization[53] reaction on (6-O-t-butyldimethylsilyl-2-O-allyl)-β-cyclodextrin (**3.26**)[54] as shown in Scheme 3.3. Selective allylation of **3.2** was achieved in 10% yield after tedious column chromatography. Even though oxidative conditions were found to attempt the cyclization of **3.27**, the reactions were never attempted due to time constraints and the promise of other cyclodextrin derivatives.



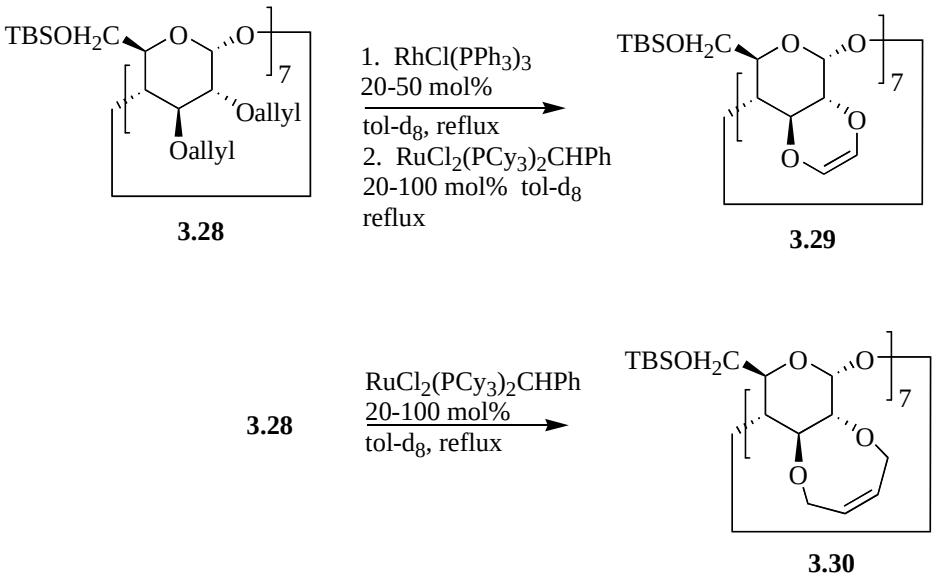
Scheme 3.3 Synthesis of (6-O-t-butyldimethylsilyl-2-O-allyl)-β-cyclodextrin (**3.26**)

Per-allylation of **3.2** to yield **3.28**[55] (41% yield) was achieved with excess NaH and allylbromide in DMF (Figure 3.18). Similar to the model compound **2.11**, isomerization and RCM to form **3.29** was attempted unsuccessfully. RCM was also attempted on **3.28** with Grubb's 1st generation catalyst, $RuCl_2(PCy_3)_2CHPh$ to form **3.40**, but the reaction was inconclusive. Attempts to follow the isomerization of **3.29** and RCM reactions for **3.29** and **3.40** were difficult due to overlapping resonances in the alkenyl region of the ^1H NMR.



3.2 **3.28**

Figure 3. 18 Formation of diallyl CD derivative **3.28**



3.28 **3.29** **3.30**

Figure 3. 19 Attempted formation of **3.29** and **3.30** from **3.28**

Conclusion

Improved reaction conditions to prepare the previously-reported (6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin (**3.2**) were established. The reaction conditions circumvented a tedious purification and increased the yield significantly. Simultaneously, other efforts to develop a more effective route to modified cyclodextrins were proving to be more successful than those using 6-OTBS and 6-OMe CD derivatives and will be discussed in the following chapter. In addition, two new cyclodextrin derivatives, **3.24**

and **3.25**, were successfully synthesized from (2,3-di-*O*-allyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin (**3.28**). Unfortunately, the annulation reactions only proved successful when a five-membered ring incorporating a silyl group was employed. Attempts to generate five-, six-, seven-, and eight-membered rings incorporating carbon atoms were inconclusive or unsuccessful. It is possible that electrophilic carbons do not lead to successful annulations with CD based on these attempts. The potential for inter-glycosidic annulation cannot be ruled out and possibly annulation across the CD with the larger electrophiles. Without the access to analytical instrumentation, such as HPLC, ESI MS and MALDI MS, the complex reaction mixtures were chllenging to analyze by ^{1}H NMR.

CHAPTER FOUR

Preparation and Reactions of 6-OPiv and 6-deoxy β-Cyclodextrins

Introduction

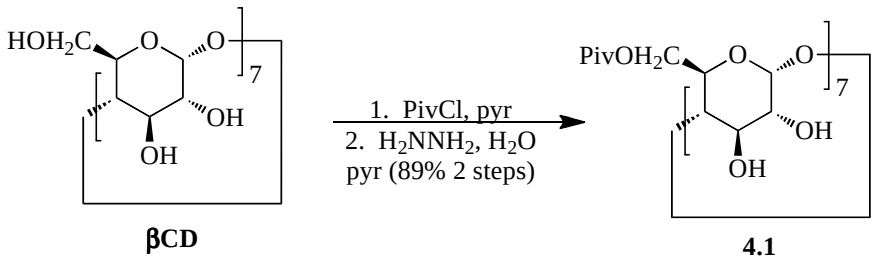
A rarely-used protecting group for the C(6)-OH hydroxyl groups of β-CD was studied to explore the effect of size and shape differences on the reactivity of the secondary face and selectivity for enantiomeric separation of guest analytes. The pivaloyl ester is a large protecting group that offers good stability in a wide range of reaction conditions. Pivaloyl esters are stable to hydrolysis in solution ranging in pH 1-12 and high temperatures (above 100^{o}C). This stability is attributed to the hindered nature of the t-butyl group blocking the electrophilic carbon of the carbonyl to attack.[48] This protecting group is envisioned to keep the primary face of β–CD derivatives blocked, in the same manner as 6-OTBS CD derivatives. The problems associated with desilyation of **3.2** in the presence of C_6F_6, or any naked F^- ion, and base are avoided with the ester. The per(6-OPiv)-β-CD derivatives were also expected to have increased solubility over the per(6-OMe)-β-CD derivatives previously reported.

To explore the effect of small unreactive group on the primary face of β-CD, per(6-deoxy)-β-CD was synthesized. As modified cyclodextrins, these are of interest for several reasons. First, there is no group at the C(6)-position that can deprotect and thus complicate synthetic efforts at the C(2)-OH and C(3)-OH positions. Second, deoxygenation at C(6) would be expected to change the polarity and perhaps inclusion complex-forming characteristics. The placement of a small group at the primary face

might potentially create a larger opening and increased access to the smaller end of the cavity.

Synthesis of per(6-OPiv)-β-CD and Derivatives

Following the procedures of Sakairi,[56] the known per(6-O-pivaloyl)-β-CD (**4.1**) was prepared from β-CD in two steps in 89% yield (Scheme 4.1). This involved the initial esterification of dried β-CD with pivaloyl chloride in pyridine at room temperature and then increasing the temperature to 60 ^{o}C overnight followed by excess hydrazine hydrate[57] in pyridine at room temperature for 24 h. The reaction mixture was used without purification from the first to the second step. It was assumed that all C(2)- and C(6)-OH hydroxyl groups were pivaloated, but in actuality there was a complex mixture of esterification at the C(2)-OH hydroxyl groups.

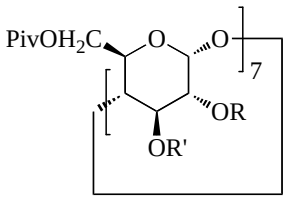


βCD **4.1**

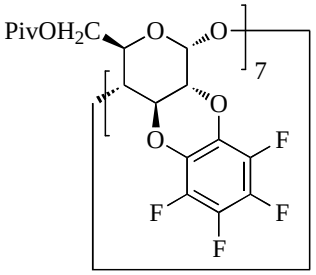
Figure 4.1 Synthesis of per(6-*O*-pivaloyl)-β-CD (**4.1**)[56]

This derivative was soluble in H_2O, methanol, DMSO, DMF, THF, ethyl acetate, methylene chloride and slighty soluble in hot hexanes. The expanded solubility over per(6-*O*-methyl)-β-CD was advantageous and allowed the exploration of various substitution reaction conditions to produce novel CD derivatives.

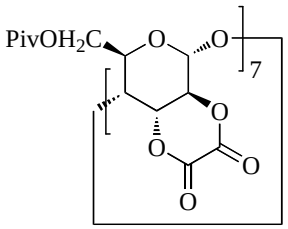
Similar to per(6-OTBS)-β-CD and per(6-O-methyl)-β-CD, the preparation of the following compounds were attempted with **4.1** (Figure 4.2). All the proposed compounds would be new and novel β-CD derivatives except **4.2**. Acetylation of **4.1** with acetic anhydride in pyridine at 100°C to produce the known per(2,3,-di-*O*-acetyl-6-*O*-pivaloyl)-β-CD (**4.2**) was not successful as previously reported with **3.2** and **3.6**. Loss of the pivaloyl group at the C(6)-position was observed under these reaction conditions. This hydrolysis was uncharacteristic for pivalate esters and it is postulated that a complex with the cavity of **4.1** is formed with the reagents to promote the unwanted hydrolysis. Compound **4.2** was successfully synthesized from the reaction of known **3.6** with pivaloyl chloride in pyridine over 3 days (75% yield) as shown in Figure 4.3.[57]



4.2 R = R' = Ac
4.3 R = R' = Me
4.4 R = R' = allyl
4.5 R = allyl, R' = H
4.6 R = R' = TMS
4.7 R = TMS, R' = H



4.8



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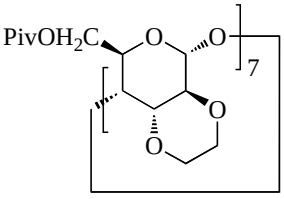

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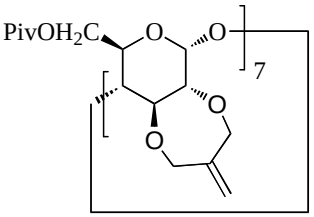
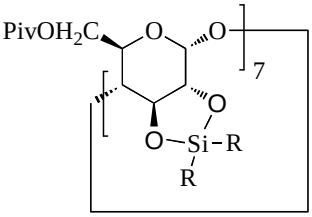
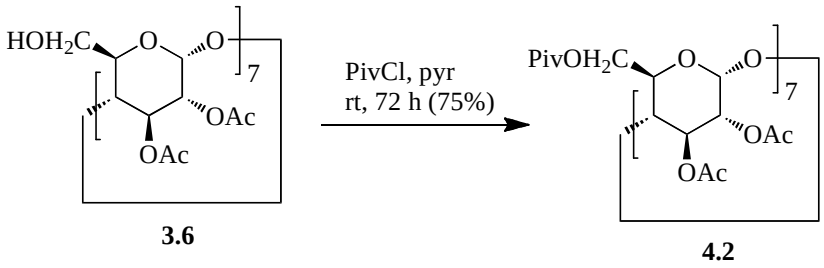


4.11



4.12 R = Me
4.13 R = Ph

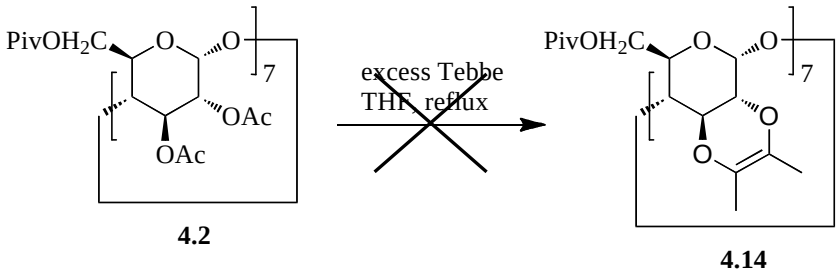
Figure 4. 2 Proposed 6-OPiv β-CD derivatives **4.2-4.10**



3.6 **4.2**

Figure 4. 3 Synthesis of per(2,3,-di-*O*-acetyl-6-*O*-pivaloyl)-β-CD (**4.2**)[57]

Olefination of **4.2** was attempted with freshly prepared Tebbe reagent[58] in refluxing THF in an attempt to produce annulated **4.14** (Figure 4.4). Similar to model compound **2.15**, the reaction was difficult to follow by ^{1}H NMR. The dual role of the tebbe reagent as an olefination reagent and metathesis reagent could complicate the reaction analysis. We were unable to determine if olefination had occurred at all 14 secondary esters. A possible explanation for the difficulty with this reaction is improper orientation of the reagent and the acetate groups on the secondary face. Complexation of the Tebbe reagent within the CD annulus could potentially hinder the olefination process.

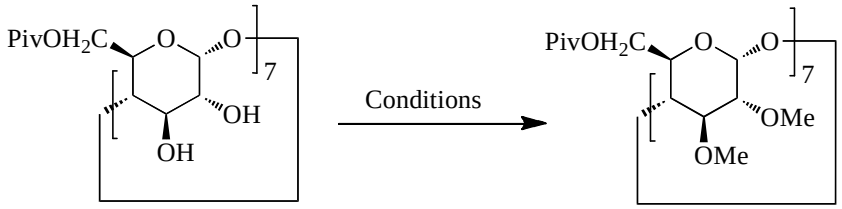


4.2 **4.14**

Figure 4. 4 Preparation of attempted **4.11**

Methylation of **4.1** to produce novel per(2,3-di-*O*-methyl-6-*O*-pivaloyl)-β-CD (**4.3**) also proved problematic. It was assumed the pivaloyl groups would be stable to basic conditions, but we observed a range of incomplete hydrolysis to complete

hydrolysis of the pivalate esters at the C(6)-position with all bases tried (Figure 4.5, Table 4.1). This was a surprise and it is postulated that complexation of the bases within the CD cavity can promote conditions to hydrolyze pivalate esters on CDs.



4.1 **4.3**

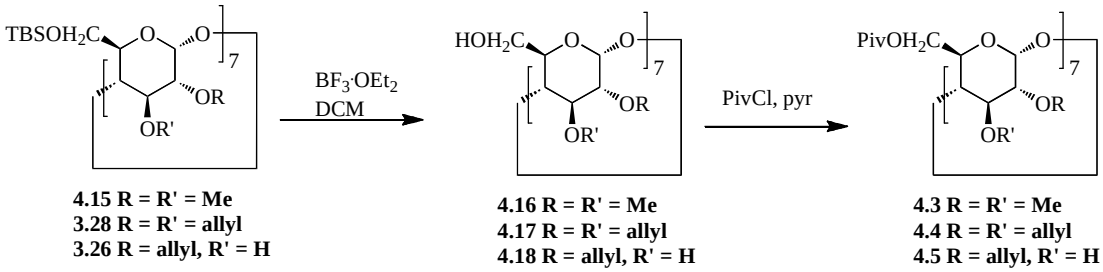
Figure 4.5 Attempted preparation of **4.3**

Table 4.1 Reactions conditions for the synthesis of 4.3

Base	Solvent	Temperature
NaH	DMF, THF, or MeCN	rt and reflux
LiH	DMF, THF	rt and reflux
KHMDS (0.6M in toluene)	DMF, THF, MeCN	rt and reflux
P_1-t-Bu	DMF, THF	rt and reflux

Following the same procedures to synthesize the known 6-OTBS allyl derivatives **3.24** and **3.26**,[54,55] allylation of **4.1** to produce novel **4.4** and **4.5** was also complicated by pivalate hydolysis. An alternate route to **4.3** was proposed to bypass loss of the esters at the C(6)-position, as shown in Scheme 4.1. Beginning with the known per(2,3-*O*-dimethyl-6-*O*-t-butyldimethylsilyl)-β-CD (**4.15**), desilylation with $BF_3{\cdot}OEt_2$ in methylene chloride should produce known (2,3-di-*O*-methyl)-β-CD (**4.16**).[43] Formation of the pivalate esters with pivaloyl chloride in pyridine should yield **4.3**. Even though the desilylation reaction for **4.15** is known in the literature and proceeds in high yield, we did

not pursue this method to form **4.16**. Out attention turned to the more complex annulated derivatives **4.8**-**4.13**. Similar routes were proposed to synthesize **4.4** and **4.5** by starting with the respective 6-TBS derivatives, **3.28** and **3.26** (Scheme 4). The desilylation of **3.28** has been reported by Baer,[55] but the desilylation of **3.26** would be a new reaction.



4.15 R = R' = Me
3.28 R = R' = allyl
3.26 R = allyl, R' = H

4.16 R = R' = Me
4.17 R = R' = allyl
4.18 R = allyl, R' = H

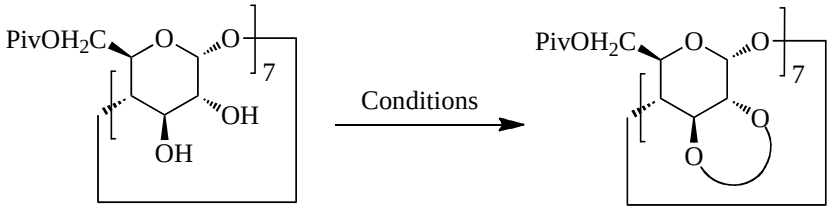
4.3 R = R' = Me
4.4 R = R' = allyl
4.5 R = allyl, R' = H

Scheme 4.1 Alternate routes to **4.3**-**4.5**

Direct annulation of **4.1** was attempted with the different electropiles shown in Figure 4.6 and Table 4.2. Reacting **4.1** with C_6F_6 and various bases in differing solvents did not yield annulated derivative **4.8**. We did see significant hydrolysis at the C(6)-position based on ^{1}H NMR analysis, but we were unable to purify the complex reaction to determine the level of hydrolysis or if mono-substitution of the electrophile occurred to produce **4.19** (Figure 4.7). Due to the large molecular weight of the desired per-annulated derivative (2744 g/mol) or per-substituted derivative (2884 g/mol), we were unable to analyze the reaction mixture by GC/MS or ESI MS. It is suggested that complexation of the electrophile within the cavity of **4.1** may hinder the reaction and slow down the substitution at the C(2)-OH position.

Formation of oxalate derivative **4.9** also proved difficult to achieve. Hydrolysis of the pivalate ester was observed by ^{1}H NMR of the complex reaction mixture, and we were unable to verify if any substitution occurred at C(2)-OH hydroxyl group. Similar

disappointing results were also observed with $BrCH_2CH_2Br$ and ICH_2CH_2I to form **4.10**, and with **2.22** to form the seven-membered annulation derivative **4.11**. Different additives were introduced to the reactions of **2.22** with **4.1** to gauge the effect of blocking the cavity of the CD to prevent complexation of the electrophile. It is well documented that inclusion complexes are formed between βCD and dimethyl



4.1 **4.8-4.13**

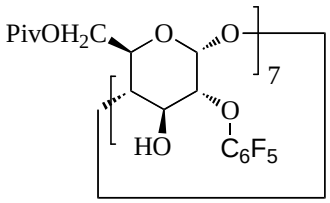
Figure 4.6 Attempted synthesis of annulated derivatives **4.8**-**4.13**

Table 4.2 Conditions for the attempted synthesis of **4.8**-**4.13**

Electrophile	Base	Solvent	Temperature	Results
C_6F_6	NaH	DMF or THF	rt and 60°C	inconclusive
C_6F_6	KHMDS	DMF	60°C	inconclusive
C_6F_6	P1-t-Bu	DMF	60°C	inconclusive
$(ClCO)_2$	Pyr	pyr or DMF/pyr	rt and 60°C	inconclusive
$BrCH_2CH_2Br$	NaH	DMF or THF	rt and 60°C	inconclusive
$BrCH_2CH_2Br$	KHMDS	DMF	60°C	inconclusive
$BrCH_2CH_2Br$	P1-t-Bu	DMF	60°C	inconclusive
ICH_2CH_2I	P1-t-Bu	DMF	60°C	inconclusive
2.22	NaH	DMF* or THF*	rt and 60°C	inconclusive
2.22	KHMDS	DMF*	60°C	inconclusive
2.22	P1-t-Bu	DMF*	60°C	inconclusive
$SiCl_2Me_2$	Pyr	Pyr	rt	**4.12** (16%)
$SiCl_2Ph_2$	Pyr	Pyr	rt	inconclusive

* Additives- xylenes, butyl benzene, and toluene were introduced in separate reactions

naphthalene derivatives,[4] adamantane,[59] and 4-nitrophenol.[3] We introduced xylenes, butyl benzene and toluene to the reaction mixture before addition of the electrophile to attempts to block the CD cavity. These additives did not improve the reaction mixtures. Success was observed with the formation of new βCD derivative **4.12**. Reacting **4.1** with $SiCl_2Me_2$ in pyridine at room temperature gave the silyl annulated derivative **4.12** in 16% yield (Figure 4.8). It was observed that either slow addition of dichlorodimethylsilane or adding the electrophile to the reaction all at once did not have an effect on the yield.

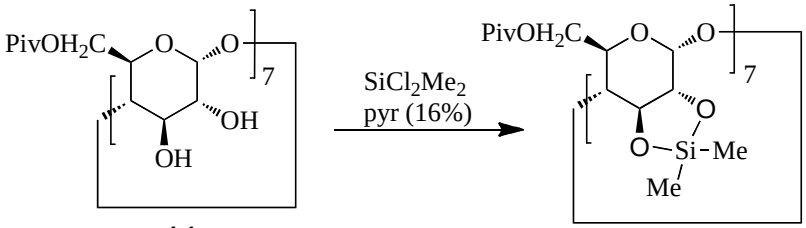


4.17

Figure 4.7 Mono-substituted derivative **4.17**

Compound **4.12** was soluble in methylene chloride and could be purified by column chromatography in the presence of 1% Et_3N. However, even with the added triethylamine, a significant amount of product was lost during column chromatography, presumably due to the cleaving of the silyl group by the acidic silica gel, resulting in a lower isolated yield. Attempts to isolate the larger diphenylsilyl annulated derivative **4.13** from the reaction mixture were unsuccessful. The ^1H NMR of the crude product looked promising, but we were unable to obtain a pure sample after column chromatography. It is speculated that pyridine was trapped in the cavity. Attempts to remove the solvent at high temperature and reduced pressure resulted in decomposition of the compound.

The success of the preparation of new β–CD derivative **4.12** shows that annulation of the secondary hydroxyls is feasible with at least some electrophiles. The role of the solvent, base and electrophile are extrememly important in the success of the reaction.



4.1 **4.12**

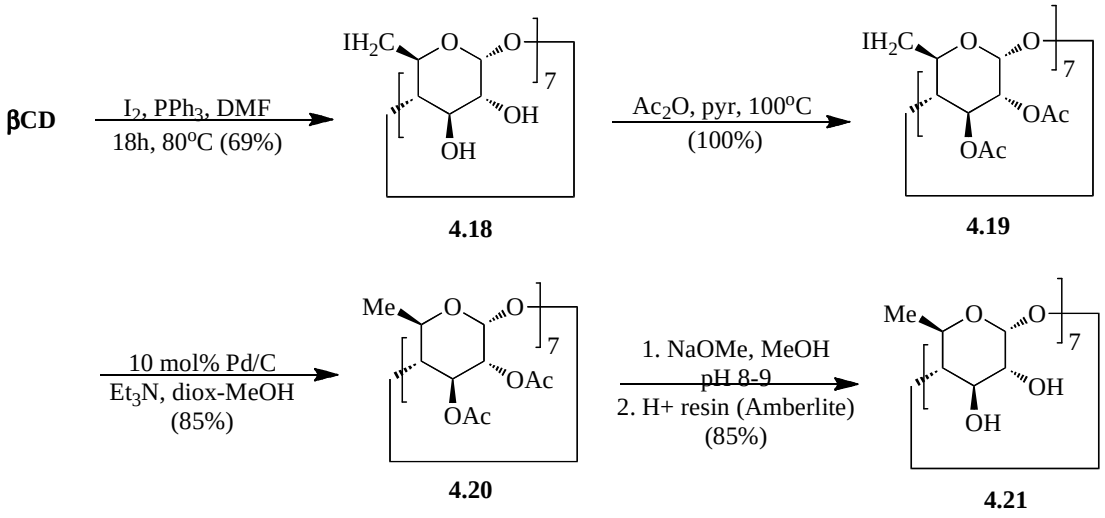
Figure 4.8 Synthesis of new silyl annulated CD derivative **4.12**

Synthesis of per(6-OPiv)-β-CD and Derivatives

Synthesis of per(6-deoxy)-β-CD and corresponding derivatives were proposed to explore the effect of small group on the primary face of β-CD. The elimination of functionality the C(6)-position should permit harsh condition, if necessary, to annulate the secondary face. In addition, the very small groups at C(6) are expected to create a larger opening and increased access to the smaller end of the cavity.

Using the improved preparation by Baer,[16] the known (6-deoxy) compound **4.21** was obtained in four steps in 48% overall yield (Scheme 4.2). This involved the initial halogenation of the C(6)-position by the addition of β-CD to a mixture of iodine with PPh_3 in DMF at 80 ^oC for 18h to give the known (6-deoxy-6-iodo)-β-CD (**4.18**) in 69% yield. Compound **4.18** was then conventionally acetylated over 48 h to give the known diacetylated derivative **4.19** quantitatively. Reductive dehalogenation in the presence of 10 mol% Pd/C and triethylamine gave known per(2,3-di-O-acetyl-6-deoxy)-β-CD (**4.20)**

in 85% yield.[43] The known **4.20** was deacetylated to give the desired (6-deoxy)-β-CD (**4.21**).[16] In attempt to maximize yield and efficiency, a modified preparation for the deacetylation was developed that did not require exposure to water and the subsequent difficulty in extracting the product in pure form. A solution of **4.21** was dissolved in dry methanol and was made alkaline with ~4M NaOMe in methanol (pH 8-9) to afford the poly-sodium salt of **4.21**. After distillation of the methanol (which ensures complete deacetylation), the polyanion was protonated by passing the solution through Dowex 50-W 8x (H+) cation-exchange resin, and evaporated to give the sodium-free (6-deoxy)-β-CD (**4.21**) in good yield (85%). This derivative was soluble in H_2O, methanol and DMSO, but not in ethyl acetate, methylene chloride, or hexanes.

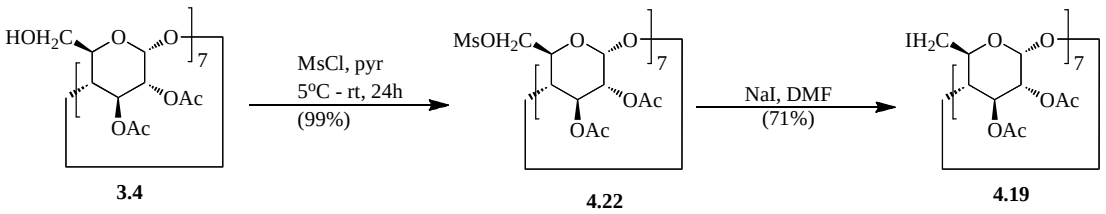


4.18 **4.19** **4.20** **4.21**

Scheme 4.2 Synthesis of known (6-deoxy)-β-CD (**4.21**)[16]

Compound **4.19** was also synthesized in two steps from per(2,3-di-*O*-acetyl)-β-CD (**3.4**) in 71% yield (Scheme 4.3). Mesylation of the primary hydroxyl groups with in pyridine at 5°C and warming to room temperature overnight produced known compound

4.22 in 99% yield.[16] Iodination with sodium iodide in DMF gave the desired compound **4.19** in 71% yield after chromatography.[43] The reduction of **4.19** was accomplished using three different methods (Table 4.3). The first method was a direct reductive halogenation with $NaBH_4$ in DMF to produce known **4.20** in 65%.[60] This method was low-yielding and involved a complicated workup. Compound **4.20** was extremely soluble in H_2O and care was taken to limit the amount of water used in the workup, but this did not completely remove the boronate salts produced in the reaction. After column chromatography, the salts were passed through acid resin give pure **4.20**. The second method used tributyltin hydride with catalytic AIBN in refluxing toluene to produce **4.20** in 80% yield.



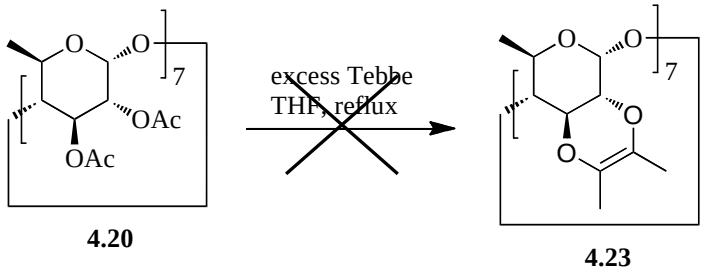
Scheme 4. 3 Synthesis of **4.19**

Table 4. 3 Conditions to synthesize per(2,3-di-O-acetyl-6-deoxy)-β-CD (**4.20**)

Conditions	Yield
$NaBH_4$, DMF	65%
Bu_3SnH, AIBN, toluene, reflux	80%
H_2, Pd/C, Et_3N, dioxane:MeOH (2:1)	85%

This reduction was complete in 45 min, but also contained a tedious purification step. The final method was an overnight reductive dehalogenation of **4.19** in a 2:1 mixture of 1,4-dioxane:methanol in a hydrogen atmosphere in the presence of 10 mol %

Pd/C and triethylamine to give **4.20** in 85% yield.[43] With the hydrogenation conditions, the workup involved filtration through a Celite pad followed by a short column. Attempts to replace Et_3N with pyridine or other nitrogenous bases affected the yield, and deviating from the 2:1 solvent mixture also proved detrimental to the yield of **4.20**. As in previous attempts with model compound **2.14** and pivalylated **3.2**, per(2,3-di-O-acetyl-6-deoxy)-β-CD (**4.20**) was subjected to olefination conditions to synthesize the novel annulated derivative **4.23** (Figure 4.9). Similar inconclusive results were obtained with **4.20** and the explanations remain the same. With a larger opening at the primary face, the Tebbe reagent may have greater access to the cavity and allow for improper orientation of the reagent and the acetate groups on the secondary face and hinder reactivity.



4.20 **4.23**

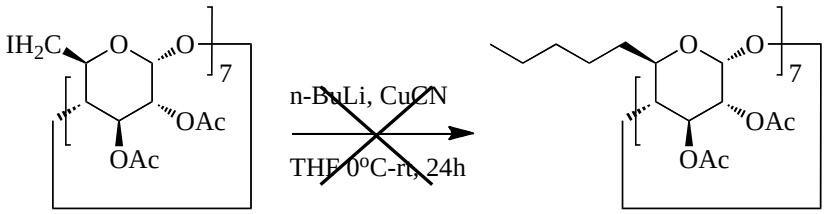
Figure 4. 9 Attempted preparation of **2.43**

Attempts to optimize the formation of **4.21** by direct reductive dehalogenation of **4.18** and bypassing the acetylation/deacetylation steps were deemed unsuccessful in the isolation of the desired compound. The three successful methods used to form **4.20** not feasible with the deprotected secondary hydroxyl groups. The increased solubility of (6-deoxy)-β-CD over the acetylated analogs proved detrimental during work-up. Increasing

the reaction amounts, reaction time and passing the crude reaction mixtures through acid resin did not aid in successfully producing **4.21**.

The synthesis of (6-deoxy)-β-CD also prompted an investigation into the synthesis of 6-deoxy compounds bearing an alkyl group. Mentioned earlier, large non-polar groups at the C(6)-position would have the main advantage of increasing the solubility, a common problem encountered working with the relatively polar (6-deoxy) CD derivatives. Also, information might be gained about how the shape and selectivity of the modified cyclodextrin changes as the size of the group changes. In the process of preparing **4.21**, we realized that organocuprates might effectively be used for the alkylation of the previously prepared (6-iodo-2,3-diacetoxy)-β-CD (**4.19**).

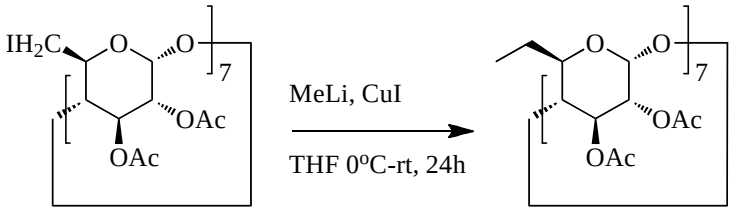
Cuprates react well with primary iodides are stable toward ester functionalities, making **4.19** an attractive substrate. To our knowledge, the reaction of CDs with cuprates has not been studied and no examples could be found in the literature. Therefore, initial attempts to alkylate **4.19** were based on the general protocol typically employed in organocopper reactions.[61] The addition of n-BuLi and CuCN to a solution of **4.19** in THF at 0 ^{o}C did not provide the alkylated product, (6-deoxy-6-butyl-2,3-diacetoxy)-β-CD (**4.24**) as shown in Figure 4.10.



4.19 **4.24**

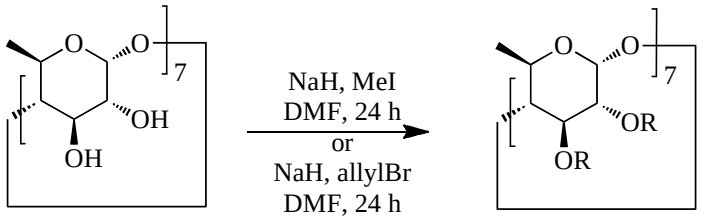
Figure 4.10 Attempted preparation of **4.24**

Sheree Allen, a member of our group, was able to synthesize (6-deoxy-6-methyl-2,3-diacetoxy)-β-CD (**4.25)** using MeLi and CuI in THF in 36% yield (Figure 4.10).[62] We did not investigate why the methylated compound was successful but the butylated compound was not isolated. The use of CuCN over CuI is should be advantageous since CuCN is not hygroscopic or light sensitive and does not require purification before use. It is speculated that the butyl group might be too large for to effectively substitute at all seven iodides on the primary face of the CD and the reaction mixture may have contained partially butylated CDs. Alternatively, the less-stable butylcuprate may have tended to decompose rather than react efficiently. Derivatives **4.23** and **4.25** could (in theory) be deacetylated under the conditions described above to yield the corresponding hydroxyl compounds; however, we have not yet carried these materials on to new derivatives.



4.19 **4.25**

Figure 4. 11 Synthesis of **4.25** by Sheree Allen



4.21

4.26 R = Me (85%)
4.27 R = allyl (25%)

Figure 4.12 Synthesis of new derivatives **4.26** and **4.27**

New derivatives **4.26** and **4.27** were not annulated derivatives but they do add to the knowledge of CD reactivity (Figure 4.12). Reacting **4.21** with methyl iodide in the presence of sodium hydride in DMF overnight produced per(2,3-di-*O*-methyl-6-deoxy)-β-CD (**4.26)** in 85% yield. This new derivative is unique in that both ends of the CD are open and accessible by virtue of the very small 6-methyl (i.e., 6-deoxy) functionality. Replacing methyl iodide with allyl bromide, new derivative per(2,3-di-*O*-allyl-6-deoxy)-β-CD (**4.27)** was produced in 25% yield. This new derivative is also unique in that the primary face is more open than the secondary face.

Conclusion

New CD derivatives, pivalylated dimethyl silyl annulated derivative **4.12** and non-annulated **4.26** and **4.27**, were synthesized. In additon to the formation of new silyl annulated CD derivatives **3.24** and **3.25,** the testing of these compounds as CSPs was made possible by an agreement with Agilent Technologies, Inc., to prepare coated capillary columns.[62] The performance of each stationary phase could then be tested chromatographically to determine their ability to perform enantioseparations. These results will be discussed in greater detail in Chapter 5.

CHAPTER FIVE

Chromatographic Testing of Unique Chiral Stationary Phases: Collaboration with Agilent Technologies

Chiral Stationary Phases Developed for Gas Chromatography

Capillary GC columns containing chiral stationary phases (CSPs) incorporating the chiral selectors developed in our group were collaboratively provided by Agilent Technologies, a leading company in the development and manufacturing of capillary columns. The efficiency of these CSPs can be determined by evaluating their ability to perform enantiomer separations against a selected set of analytes. The information gathered can be used to gain insight about the inclusion characteristics and selectivity of each new CSP. The compiled results can also be used to make clear comparisons to current, commercially available CSPs.

New Chiral Stationary Phases

Since each chiral selector is functionally different, we hypothesized that each CSP may display selectivity towards particular analytes. The cyclodextrin structures of the chiral stationary phases that were tested are shown in Figure 5.1. The CSPs labeled **BU1** and **BU2** come from compounds **4.26** and **3.24**, respectively. The other CSPs, **BU3-BU7**, come from compounds that were synthesized by Sheree Allen[62] and will not be discussed here. New CD derivatives **3.25**, **4.12** and **4.27** were not evaluated as CSPs, but may be tested at a later date.

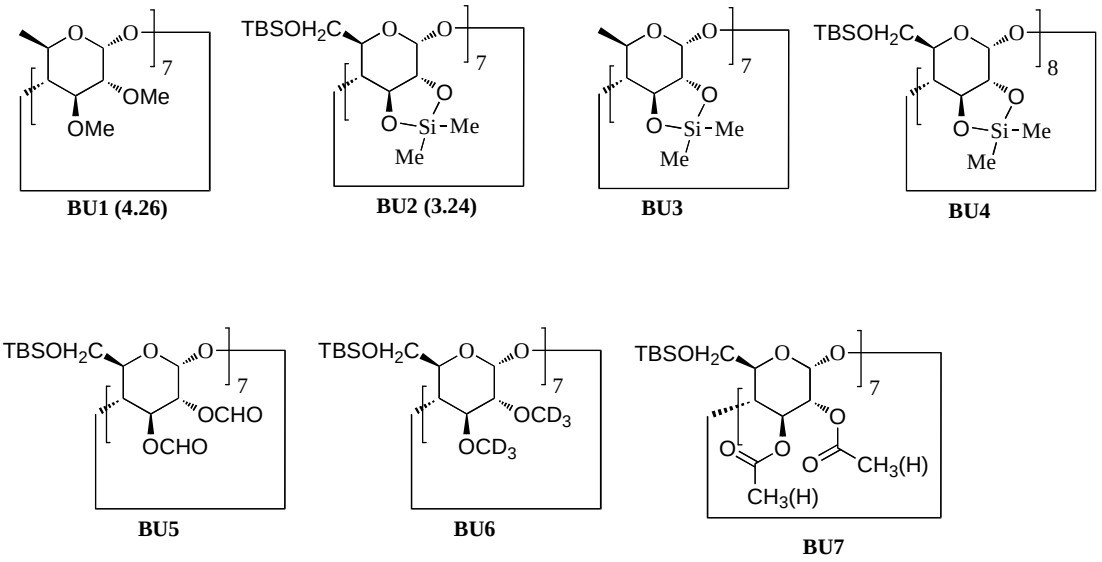


Figure 5.1 Structures of new CD based CSPs for GC

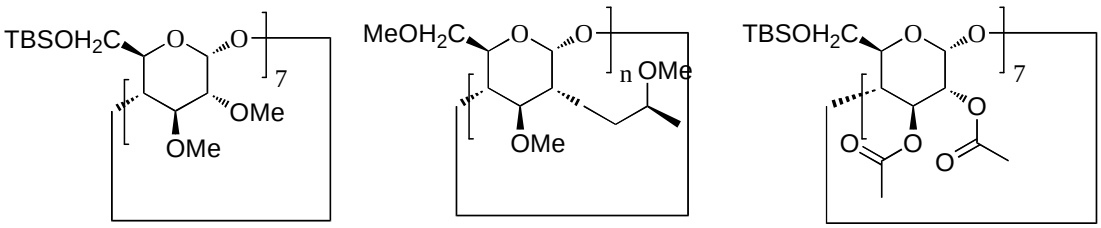
The majority of these phases contain functionality that is significantly different from what is currently used in existing CSPs. As in **BU1** and **BU3**, we varied the size of the group at the 6-position. For **BU1** this allows for both ends of the cavity to be fully accessible by virtue of the 6-deoxy functionality. It was unknown whether the small methyl group would be advantageous, since studies have pointed to the 6-*tert*-butyldimethylsilyl group as being preferred.[63] To our knowledge, the 6-deoxy phases represent the first of their kind to be tested in gas chromatography.

BU2-4 are unique derivatives bearing an annulating group bridging the C(2) and C(3) positions. These groups serve to extend the cavity, alter the polarity and possibly improve the thermostability. To our knowledge, no annulated cyclodextrins have been reported in literature, and our initial expectation was that such functionality will impose a greater degree of enantioselectivity by virtue of the increased organization of the cavity.

The size of the CD is also important. Thus, **BU 4**, the γ-CD analog of **BU 2**, was developed,. This phase should allow us to draw conclusions about how the size of the CD effects the separation. In addition, if the bridging silyl group "chokes" the cavity in **BU 2** by virtue of the methyl groups that are directed inwards, then perhaps the analytes would interact more freely with the larger γ-CD cavity size.

Commercially Available Chiral Stationary Phases

In order to fully assess the applicability of our CSPs for enantioseparations in GC, the results were compared with those from the chromatographic testing to commercially available columns. Four such phases are shown in Figure 5.2. These phases were thought to represent some of the most efficient CD phases currently available.



CycloSil B (J&W)

Chiraldex PH
A-PH n = 6
B-PH n = 7
(Supelco/Astec)

Rt-βDex$_{sa}$
Restec

Figure 5.2 Commercially available CD-based CSPs

Approximately 30 different analytes were chosen based on marginal separability on commercially available phases and availability. The Advanced Separation Technologies (Astec) catalog gives information on the separation of nearly 400 chiral compounds.[64] Although approximately 13 phases are referred to at various places, the

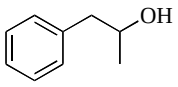
separation for any given compound is generally given on only one stationary phase, implying that the phase listed is the best phase for the separation of a given compound.

The separations are characterized by their α values,separation factor, which is the ratio of the retention times of each enantiomer after correcting for column dead volume. Analytes were selected that exhibited an α value of 1.02 or less (i.e., no more than a 2% difference in retention times) and that could be purchased or easily made in racemic (50:50) form. (An α value of 1.00 means no separation was observed). Given that Astec offers nearly every commercially available chiral phase, if a new stationary phase we make exhibits better α values than those reported, we can tentatively conclude that we have a stationary phase better than any that are commercially available, at least with respect to analytes that are marginal on Astec columns. In a few cases, analytes were chosen based on their use in the Garner group. The set of analytes selected for enantioseparation testing are shown in Figure 5.3 Several of these compounds had to be synthesized before testing could begin; this was generally accomplished following literature preparations and was done by Dr. Charles Garner or Sheree Allen.[62]

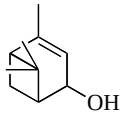
GC Parameters and Pertinent Information[62]

Column testing was conducted by Sheree Allen on a Hewlett Packard 5890 series II GC with aflame ionization detector. Injection volumes were maintained at 1⁄2 μL with a split ratio of >100:1. The stationary phase compositions and specifications can be found in Appendix B:Tables (5.1 and 5.2). All columns tested were of the same dimensions, 30 m X 0.25 mm I.D. Each column was operated under hydrogen carrier gas with a linear velocity of 40 cm/sec, determined using methane at 80 ^{o}C. For each analyte, the initial temperature and ramp rate was determined such that a retention

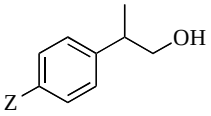
Alcohols



5.1

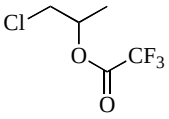


5.2 cis



5.3 Z = H
5.4 Z= Me
5.5 Z = OMe
5.6 Z = Cl

Alcohol Derivatives



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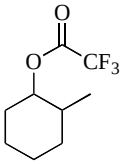
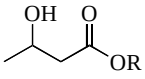
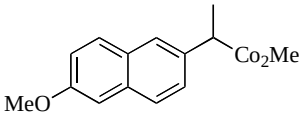


5.8

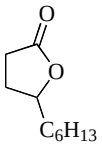


5.9 R = Me
5.10 R = Et
5.11 R = *i*-Pr
5.12 R = *t*-Bu

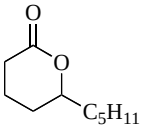
Esters & Lactones



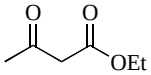
5.13



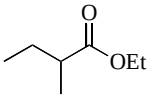
5.14



5.15



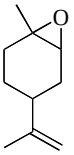
5.16



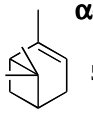
5.17

Epoxides

5.18 R = C_8
5.19 R = C_{10}
5.20 R = C_{12}
5.21 R = $CH_2OC_6H_5$



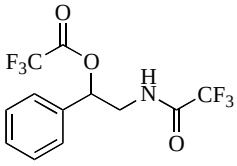
cis & trans 5.22



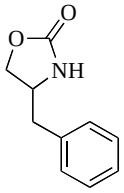
α-pinene

5.23

Amino Alcohol Derivatives

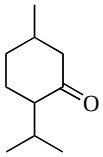


5.24



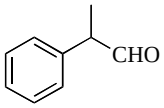
5.25

Ketones



5.26

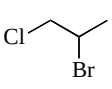
Aldehydes

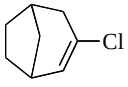


5.27

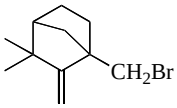
Halides

5.28





5.29



5.30

Figure 5. 3 Structures and types of selected analytes

time of 8-15 min was observed. In Appendix B: Table 5.1, the ability of each column to separate enantiomers was evaluated and recorded in the form of α, k' (capacity factor_, and R_s values. Those analytes showing any separation, that is, having an α value ≥1.000 and a resolution value > 0.5, were recorded. In all cases where enantiomer separation was observed, a theoretical plate calculation (*N*) was included. For each column tested, column efficiency (*N*) was also determined using dodecane, with an initial temperature and rate such that a retention time of 8-15 min was obtained.

The samples were prepared by dissolving 1 mg of the racemic analyte in 1 mL of 2,2-dimethylbutane, except in the case of the naphthalene analyte and the two amino acid derivatives, which required distilled methylene chloride. We found 2,2-dimethylbutane to be an optimal solvent due to the fact that it gives a single, fast-eluting and sharp solvent peak. This could be attributed to its low boiling point (50 ^{o}C) and possibly steric hindrance, preventing inclusion into the cyclodextrin cavity. In contrast, hexanes gave multiple solvent peaks spread over a range of up to 1.6 minutes, depending on choice of initial column temperature.

Comparison and Chromatographic Testing of Commercially Available Phases

J & W CycloSil B. CycloSil-B contains 30% (2,3-*O*-dimethyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin dissolved in OV-1701. Given that the **BU1** and CycloSil-B differ only in functionalization at the 6-position, where CycloSil-B contains a larger *tert*-butyldimethylsilyl group and **BU1** incorporates a small methyl group, we felt that a direct comparison would address the structural value of these size differences. To summarize, **BU1** separated 35% of the analytes we used, giving an average α of 1.01 ± 0.004, and an average R_s of 0.9 ± 0.4 for compounds that exhibited any separation.

Comparatively, CycloSil B separated 60% of the analytes, giving an average α of 1.010 ± 0.004, and an average R_s of 1.6 ± 0.7. Overall, this phase separated a broad range of analytes. Of the analytes separated, most were baseline resolved; however, on a few occasions the separations were marginal.

CycloSil B gave better separations for all the analytes compared to all the BU phases. Based on these observations, it would seem reasonable to conclude that the larger *tert*- butyldimethylsilyl group is advantageous at the 6 position.

New Chiral Stationary Phases

BU 1-2. **BU 1** separated 35% of the analytes we used, giving an average α of 1.010 ± 0.004, and an average R_s of 1.6 ± 0.7. Based on the values provided by Agilent, it also offers the higher maximum allowable temperature (see Appendix B: Tables 5.1 and 5.2) compared to the other columns tested. This phase often showed the best selectivity for alcohols, lactones, and esters. In some cases **BU 1** showed better selectivity than the PH phases; however, the Rt-βDEXsa remained superior in most cases. In the cases where **BU 1** was superior to the PH phases, the majority of the analytes contained more polar functional groups. In two cases, 2-ethylbutyric acid ethyl ester (**5.17**) and trifluoroaetic acid, 1,-phenyl-2-(2,2,2-trifluoroacetylamino)-ethyl ester (**5.24**), **BU 1** showed better resolution compared to all the commercially available columns tested.

Unfortunately, no separations were observed for the **BU 2** chiral selector; however, all of the analytes showed some retention in this phase. Of the select analytes, only α -pinene exhibited some separation ($\alpha = 1.01$, $R_s = 0.741$). It was our expectation that **BU 2**, which is the first derivative tested containing an annulation between the C(2) and C(3) oxygens, would show improved results compared to currently available phases;

however, this was not the case. A plausible explanation for the lack of selectivity might be due to the annulated silyl group blocking the cavity.

Overall, the Restek Rt-β-DEXsa phase gave better separations for the selected analytes compared to the other commercially available columns and **BU 1-2**. The Supleco/Astec PH phases were less efficient in that for A-PH and B-PH combined, only in seven cases (or 11% of analytes) were the separations baseline resolved. **BU 1** was comparable to the PH phases and in many cases gave better separation.
The commercially available CycloSil B and the Restek Rt-bDEXsa proved to be superior phases during testing. The Restek phase separated slightly more of the selected analytes than the CycloSil B phase. The **BU 2** phase behaved poorly compared to **BU 1**. These results are further illustrated in Tables 5.1 and 5.2 which show a comparison of resolution and selectivity (R_s and α, resp.) for two of the analytes (**5.1**) and (**5.23**), each having different functionality, against all of the commercial columns tested and **BU 1-2**.

We conclude that (a) bridging 2,3-*O*-dimethylsilyl group of BU 2 block the larger opening too much to allow analytes access; (b) 6-*O*-TBS groups are superior to the 6-deoxy derivative both in terms of performance and in terms of solubility in the siloxane matrix; (c) assuming solubility issues were not responsible for the observed behavior, the 6-deoxy derivative does not allow analytes access to the smaller end of the cavity or such access is ineffectual in enantiomer discrimination.

Table 5.1 Separation factor, α, values for analytes **5.1** and **5.23** for columns tested

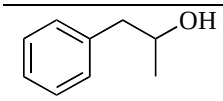
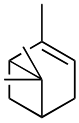
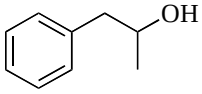
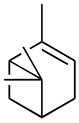
	CycloSil B	**Chiraldex A-PH**	**Chiraldex B-PH**	**Restek Rt-βDEXsa**	**BU1**	**BU2**
Compound			**α**			
	1.014	1.003	-	1.008	1.007	-
	1.020	-	1.017	-	1.019	1.014

Table 5.2 Resolution, R_s, values for analytes **5.1** and **5.23** for columns tested

	CycloSil B	**Chiraldex A-PH**	**Chiraldex B-PH**	**Restek Rt-βDEXsa**	**BU1**	**BU2**
Compound			**R_s**			
	2.413	0.465	-	2.063	1.140	-
	1.740	-	0.528	-	1.257	0.672

CHAPTER SIX

Experimental

General Section

All reactions which required the use of air or water sensitive reagents were carried out in flame-or oven-dried glassware under nitrogen atmosphere, unless otherwise stated. Cannulas and metal luer needles were oven-dried and stored in the oven prior to use and disposable needles were dried with a stream of dry air and stored at room temperature prior to use. Methanol (MeOH), ethanol (EtOH), acetone, diethyl ether (Et_2O), and *N*,*N*-dimethylformamide (DMF) were obtained from Aldrich Chemical Company, VWR, Acros Chemical, or Fischer Scientific and used as obtained. Hexanes, ethyl acetate (EtOAc), and methylene chloride (CH_2Cl_2), were obtained from these same sources and distilled prior to use. Solvents that required special drying such as pyridine and tetrahydrofuran (THF) were distilled from calcium hydride and potassium, respectively. Unless otherwise stated, all reactions were monitored by either thin layer chromatography (TLC), or nuclear magnetic resonance (NMR) and in some cases electron-ionization mass spectrometry (ESI-MS). Chiral gas chromatography was carried out on a Hewlett Packard 5890 series II GC with a flame ionization detector. Gas chromatography/mass spectroscopy was carried out on either a Hewlett Packard GCD 1800a with electron impact ionization or a Thermo GC/MS with electron impact ionization. ^{1}H and ^{13}C NMR spectra were obtained using a Varian Innova 500 MHz NMR operating at 500 MHz for proton and 125 MHz for carbon, or a Brüker Advance

300 MHz NMR operating at 300 MHz for proton and 75 MHz for carbon. Chemical shifts are expressed in ppm, and peaks are reported as singlets (s), doublets (d), triplets (t), quartets (q), pentets (pent), multiplets (m), or any combination of these with coupling constants (*J*) reported in Hz. All carbon spectra are proton-decoupled. Slow additions were accomplished using a KdS 100 digital syringe pump. Concentration *in vacuo* was accomplished using a rotory evaporator followed by house vacuum (between 5 and 25 torr) and further concentrated by use of a mechanical pump (~ 0.1 torr) if necessary. Unless otherwise stated, isolated yields are reported. All aqueous solutions were prepared using deionized (DI) water. All commercially available chemicals were obtained from Aldrich, Acros, VWR, Fischer, and TCI and were used as obtained without further purification, unless otherwise stated. Analytes and electrophiles were obtained from similar commercial sources as stated above and used as obtained unless otherwise noted.

Drying of β-cyclodextrin and derivatives was accomplished by subjecting the commercially available material to an Abderhalden drying pistol under reduced pressure with refluxing toluene in the presence of P_2O_5.

Preparation of Compounds

Annulated hexafluorobenzene (**2.5**). To an oven-dried flask, NaH (271 mg, 4.7 equiv., 60% in oil) was added and the system purged with N_2. *trans*-Cyclohexanediol (256 mg, 2.4 mmol) and DMF (75 mL) were added to the reaction vessel with stirring. Hexafluorobenzene (0.3 mL, 2.6 mmol) in DMF (25 mL) was added to the stirred solution via a digital syringe pump set at a rate of 2.0 mL/h. After 24 h, the resulting mixture was cooled to 0^oC and quenched with MeOH. The solvent mixture was removed

under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (2 x 5mL), brine (5 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation. Recystallization in EtOAc/Hexanes afforded **2.5** as a white powder (467 mg, 74%), mp = 97-98^oC. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74 (br, 2H), 2.32 (d, *J* = 11.8 Hz, 2H), 1.88 (dd, *J* = 5.07, 1.38, 2H), 1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 77.0, 29.4, 23.4; ^{19}F NMR ($CDCl_3$, 282 MHz): -154.6, -169.8. MS: 262 [M]+, 81.

Trans-1,2-bis(allyloxy)cyclohexane (**2.11**).[24] To an oven-dried flask, *trans*-cyclohexanediol (3.0 g, 25.8 mmol) and allylbromide (4.95 mL, 56.8 mmol), in dry DMF (100 mL) were stirred at 0^oC, and NaH (1.5 g, 60.3 mmol, 60% in oil) was added in small portions. Vigorous foaming occurred. The mixture was then stirred for 3 h at 0^oC and then allowed to warm to rt overnight. The reaction mixture was cooled and pured into ice-water, extracted with Et_2O (2 x 50mL), then dried over $MgSO_4$ and concentrated. Distillation gave the diallyl ether as a clear oil (1.9 g, 63%), bp 140-145^oC at 38 mmHg. Characterization data matches literature values. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.94 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 2H), 5.27 (dd, *J* = 17.2, 1.8 Hz, 2H), 5.13 (dd, *J* = 10.4, 1.8, 2H), 4.12 (d, *J* = 5.5 Hz, 4H), 3.25 (m, 2H), 1.95 (m, 2H), 1.65 (m, 2H), 1.25 (m, 2H), 0.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 135.7, 116.1, 80.9, 70.9, 30.3, 23.5.

Trans-hexahydro-1,4-benzodioxin-2,3-dione (**2.17**). A solution of oxalyl chloride (0.16 mL, 1.9 mmol) in THF (7 mL) was added dropwise to a solution of *trans*-cyclohexanediol (200 mg, 1.72 mmol) and pyridine (0.68 mL) in THF (34 mL) over 1h at 0^oC under N_2. The mixture was allowed to stir for an additional 2h at 0^oC and then concentrated under reduced pressure. The residue was partitioned between EtOAc (50

mL) and H_2O (20 mL). The organic phase was separated, washed with 5% citric acid (aq.) and satd. Na_2CO_3 (aq), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from (2:1) hexanes:CH_2Cl_2 to afford **2.17** (164 mg, 56%). Characterization data matches literature values. mp 160-163 ^oC. ^{13}C NMR ($CDCl_3$, 300 MHz): δ 153.8, 80.2, 29.4, 22.8. After 1-2d at rt, the compound decomposed to a yellow solid.

Trans-1,2-bis(acetoxy)cyclohexane (**2.14**).[28] To a solution of trans-cyclohexanediol (10 g, 86 mmol) in dry pyridine (140 mL) was added Ac_2O (32 mL, 338 mmol). The reaction was allowed to stir at room temperature overnight under N_2. The reaction was quenched with MeOH and distilled under vacuum to gve a yellow syrupy oil **2.14** (15.34 g, 89%). Characterization data matches literature values. ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (m, 2H), 2.02 (m, 2H), 2.00 (s, 6H), 1.70 (m, 2H), 1.30-1.38 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.0, 73.9, 30, 23.6, 21.0.

Trans-chloroacetoxycyclohexanol (**2.20**). To a solution of trans-cyclohexanediol (5 g, 43 mmol) in CH_2Cl_2 (100 mL) was added chloroacetyl chloride (3.7 mL, 47 mmol) via syringe pump (rate 0.5 mL/h). After stirring at room temperature under N_2 overnight, the reaction mixture was refluxed for 4h. The reaction was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (75:25 Hexanes:EtOAc) gave **2.20** (6.63g, 80%), ^1H NMR (300 MHz, $CDCl_3$): δ 4.65 (m, 1H), 4.08 (s, 2H), 3.59 (m, 1H), 2.06 (m, 3H), 1.72 (m, 3H), 1.33 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.6, 80.4, 75.7, 72.7, 41.3, 33.3, 30.0, 24.0.

Seven-membered annulation (**2.23**). To an oven-dried flask, NaH (400 mg, 8.6 equiv., 60% in oil) was added and the system purged with N_2. *trans*-Cyclohexane diol (1 g, 0.52 mmol) and DMF (40 mL) were added to the reaction vessel with stirring. **2.22** (0.5 mL, 4.108 mmol) in DMF (5 mL) was added to the stirred solution via a digital syringe pump set at a rate of 1 mL/h. After additon, the reaction was warmed to 80^{o}C for 4 h and then cooled to room temperature and allowed to stir under N_2 overnight. The resulting mixture was cooled to 0^{o}C and quenched with MeOH. The solvent mixture was removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (2 x 5mL), brine (5 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation. Chromatography (50:50 Hexanes:EtOAc) gave **2.23** (564 mg, 39%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.89 (s, 2H), 4.40 (d, J = 8.4, 2H), 4.29 (d, J = 9, 2H), 3.10 (m, 2H), 1.94 (m, 2H), 1.68 (m, 2H), 1.19-1.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 148.9, 109.9, 86.3, 73.3, 31.7, 24.2.

Per(6-O-tert-butyldimethylsilyl-2,3-dihydroxy)-β-*cyclodextrin* (**3.2**): Per(6-*O*-TBS-2,3-*O*-dihyroxy)-β-CD was synthesized according to the method of Stoddart[7] and is prepared as follows: Dry β-CD (**1**) (9.04 g, 7.96 mmol) was dissolved under vigorous stirring in dry pyridine (100 mL). The solution was cooled in an ice bath to 0 ^{o}C, producing a thick gel. A solution of TBSCl (14.5 g, 96.2 mmol) in dry pyridine (100 mL) was then added dropwise via an addition funnel to the cooled reaction vessel over 3.5 h. During this time the gel liquified. Cooling was continued for an additional 3 h before the solution was allowed to warm to room temperature. After 18 h, the solvent was removed under reduced pressure to give a brown solid, which was taken up in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with $KHSO_4$ (100 mL, 1 M) to remove

any residual pyridine, followed by saturated aqueous NaCl solution. The CH_2Cl_2 was separated, dried with anhydrous Na_2SO_4, and evaporated to dryness. The crude mixture was dissolved in hot EtOH and upon standing, β-CD precipitated. The filtrate was decanted and evaporated to dryness to afford **3.2** (15.41 g, 100%) as a white solid. Characterization data matches literature values. m.p. 299-302^{o}C (dec.)R_f 0.24 (MeOH/CH_2Cl_2, 10:90); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 7H), 5.26 (s, 7H), 4.88 (d, *J* = 3 Hz, 7H), 4.03 (dd, *J* = 9.5, 9.5 Hz, 7H), 3.89 (dd, *J* = 11, 2 Hz, 7H), 3.70 (bd, *J* = 11 Hz, 7H), 3.65 (dd, *J* = 9.5, 3 Hz, 7H), 3.59 (bs, 7H), 3.55 (dd, *J* = 9.5, 9.5 Hz, 7H), 0.86 (s, 63H), 0.04 (s, 21H), 0.03 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 102.1 (C-1), 81.8 (C- 4), 73.7, 73.4, 72.6 (C-2,3,5), 61.7 (C-6), 25.9, 18.3, -5,1, -5.2.

Per(2,3-di-O-acetyl-6-O-tert-butyldimethylsilyl)-β-cyclodextrin (**3.3**): **3.3** was synthesized according to the method of Takeo[43] and is prepared as follows: A solution of **3.2** (3.55 g, 1.83 mmol) in Ac_2O (30 mL) and pyridine (40 mL) was stirred for 4 h at 100^{o}C and then concentrated. The last traces of solvent were removed by coevaporation with toluene. Column chromatography of the brown residue (Hexanes/EtOAc, 25:75 to 100% EtOAc) gave **3.3** as a pale yellow solid (4.17 g, 1.65 mmol). Characterization data matches literature values. R_f (Hexanes/EtOAc, 25:75) 0.34. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.34 (dd, *J* = 9.9 Hz, 8.6, 7H), 5.23 (d, *J* = 3.6, 7H), 4.76 (dd, *J* = 10 Hz, 3.6 Hz, 7H), 4.03 (d, *J* = 10.9Hz, 7H), 3.86 (bs, 14H), 3.71 (d, *J* = 11.6 Hz, 7H), 2.06 (s, 21H), 2.05 (s, 21H), 0.89 (s, 63H), 0.06 (s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 170.5, 169.3, 96.5, 75.25, 71.9, 71.5, 71.25, 61.9, 25.9(21C), 20.9, 20.7, 18.3, -4.9, -5.2.

Per(2,3-di-O-acetyl)-β-*cyclodextrin* (**3.4**): **3.4** was synthesized according to the method of Takeo[43] and is prepared as follows: To a solution of **3.3** (3.37 g, 1.34 mmol) in CH_2Cl_2 (40 mL) was added 47% $BF_3.OEt_2$ (3.4 mL). The mixture was stirred for 6 h at room temperature, diluted with CH_2Cl_2, and poured into ice-water. The organic layer was separated, washed successively with H_2O, satd. $NaHCO_3$, and H_2O, dried over $MgSO_4$ and concentrated in vacuo. Column chromatography of the residue (Hexanes/EtOAc, 25:75 to 100% EtOAc) gave **3.4** as a white solid (2.09 g, 1.22 mmol). Characterization data matches literature values. m.p. 185-188^oC. R_f (EtOAc/MeOH, 90:10) 0.065. ^1H NMR (300 MHz, DMSO-d_6) : δ 5.25 (dd, *J* = 10.2 Hz, 8.1 Hz, 7H), 5.08 (d, *J* = 3.5 Hz, 7H), 4.77 (bs, 7H), 4.59 (dd, *J* = 10.3 Hz, 3.5 Hz, 7H), 3.8 (bs, 21H), 3.61 (d, *J* = 11 Hz, 7H), 2.01 (s, 21H), 1.99 (s, 21H); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 170.1, 169.2, 95.9, 75.1, 71.9, 70.6, 70.3, 59.5, 20.5 (14C).

Per(2,3-di-O-acetyl-6-O-methyl)-β-*cyclodextrin* (**3.5**): **3.5** was synthesized according to the method of Takeo[43] and is prepared as follows: A mixture of **3.4** (0.4 g, 0.24 mmol), MeOTf (0.9 mL, 8.22 mmol), and **3.7** (2.36 (11.49 mmol) in CH_2Cl_2 (11 mL) was heated in a sealed tube for 3 h at 80^oC and then cooled. MeOH (6 mL) was added, and the mixture was kept for 30 min at room temperature and then concentrated in vacuo. A solution of the residue in $CHCl_3$ was washed successively with H_2O, cold 5% HCl, satd. $NaHCO_3$, and H_2O, dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (100% EtOAc) of the green mixture afforded **3.5** (0.32 g, 0.17 mmol) as a white solid. Characterization data matches literature values. m.p. 132-139oC. Rf 0.286. ^1H NMR (300 MHz, $CDCl_3$) : δ 5.33 (t, *J* = 9.6 Hz, 7H), 5.12 (d, *J* = 3.7 Hz, 7H), 4.79 (dd, *J* = 9.8, 3.6 Hz, 7H), 4.00 (m, 7H), 3.91-3.80 (m, 14H), 3.53 (d, *J* = 10.4 Hz,

7H), 3.38 (s, 21H), 2.06 (s, 21H), 2.03 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 170.6, 169.4, 96.4, 75.7, 71.2, 70.9, 70.8, 70.5, 59.1, 20.8, 20.7.

Per(6-O-methyl)-β-*cyclodextrin* (**3.6**): **3.6** was synthesized according to the method of Takeo[43] and is prepared as follows: A solution of **3.5** (0.23 g, 0.128 mmol) in methanol (10 mL) was treated with 4 M NaOMe (0.01 mL) and kept for 1 h at room temperature. Water (10 mL) was added, and the solution was neutralized with Dowex 50-W 8x cation-exchange resin (H+), filtered and concentrated. Trituration in a small amount of methanol afforded **3.6** (99 mg, 0.08 mmol) as a white powder. Characterization data matches literature values. m.p. 303-310^{o}C (dec). ^{1}H NMR (300 MHz, D_2O) : δ 5.06 (d, *J* = 3.1 Hz, 7H), 4.05-3.92 (m, 14H), 3.76 (bs, 14H), 3.68-3.52 (m, 14H), 3.36 (s, 21H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 102.3, 82.3, 73.0, 72.3, 70.9, 70.3, 58.1.

*2,6-di-t-butyl-4-methylpyrilum Triflate (**3.8**):* **3.8** was synthesized according to the method of Stang[44] and is prepared as follows: Into a 100 mL three-neck round bottom flask, equipped with a dry ice condenser capped with a drying tube, N_2 inlet, constant-pressure addition funnel, and a magnetic stirrer was added pivaloyl chloride (8.24 mL, 66.96 mmol) and t-butanol (1.6 mL, 27.68 mmol). After the apparatus was flushed with a slow stream of N_2, the dry ice condenser was charged with dry ice/iPrOH and the reaction ixture was heated to 85^{o}C by means of an oil bath; then TfOH (2.9 mL, 11.39 mmol) was added over a period of 15 min. After addition was completed the mixture was tirred for an additional 10 min at 85^{o}C, then the light brown mixture was cooled in an ice bath and poured into 100 mL of cold Et_2O. The light tan precipitae was collected by filtration and

air dried to give **3.8** (4.4 g, 12.45 mmol) that was used without further purification in the next step. Characterization data matches literature values. m.p. 168-171^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.78 (s, 2H), 2.86 (s, 3H), 1.53 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ186.0, 176.6, 120.4, 38.9, 28.1, 24.8.

*2,6-di-t-butyl-4-methylpyridine (**3.7**):* **3.7** was synthesized according to the method of Stang[44] and is prepared as follows: To a 250 mL round bottom flask containing 25 mL of conc. NH_4OH cooled to -60^{o}C was added in one portion with stirring a slurry of **3.8** (2.6 g, 7.3 mmol) in 50 mL of 95% EtOH also cooled to -60^{o}C. The yellow reaction mixture was held at -60^{o}C for 30 min, then maintained at -40^{o}C for 2 h, during which time the slurry dissolved; the reaction mixture was then allowed to slowly warm up to room temperature. The reaction mixture was poured into 130mL of 2% NaOH solution and the resulting emulsion was extracted with 4 x 25 mL pentane. The combined organic extracts were washed with 10 mL satd. NaCl and the pentane was removed in vacuo. The light yellow residue was chromatographed on activated alumina (100% pentane) to yield 1.33 g (74%) of **3.7** as a light yellow oil. Characterization data matches literature values. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5 (s, 2H), 2.66 (s, 3H), 1.57 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 147.8, 116.2, 35.4, 30.0, 21.4.

Per(6-O-tert-butyldimethylsilyl-2-O-trimethylsilyl)-β-*cyclodextrin* (**3.19**): **3.19** was synthesized according to the method of Bukowska[50] and is prepared as follows: A mixture of **3.2** (1.2 g, 0.62 mmol), N-TMS-acetamide (1.0 g, 7.59 mmol) and DMF (5 mL) was stirred for 72 h at 50^{o}C. The mixture was cooled to room temperature and the solvent was removed by Kughelrohr distillation. Hexanes were added to the resulting

solid and the precipitated acetamide was removed by filtration. The hexanes solution was evaporated to produce a yellow-brown sticky solid which was dissolved in CH_2Cl_2. MeOH was added to precipitate **3.19** as a white solid (0.82 g, 54%). An impurity was noticed as TBSOH which was not removed. Characterization data matches literature values. m.p. 281-285^oC. R_f (100% Hexanes) 0.354. ^1H NMR (300 MHz, $CDCl_3$): δ 4.93 (s, 7H), 4.43 (s, 7H), 3.93 (dd, *J* = 11.3 Hz, 2.7 Hz, 7H), 3.83 (t, *J* = 9.3 Hz, 7H), 3.42-3.65 (m, 28H), 0.89 (s, 63H). 0.18 (s, 63H), 0.08 (s, 21H), 0.01 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.5, 82.0, 74.96, 72.1, 71.9, 61.9, 25.9, 18.9, .19, -4.5, -5.3.

Per(2,6-di-O-tert-butyldimethylsilyl)-β-*cyclodextrin* (**3.20**): **3.20** was synthesized according to the method of Stoddart[49a] and is prepared as follows: TBSCl (1.64 g, 10.85 mmol) and DMAP (20 mg) were added to a solution of **3.2** (2 g, 1.03 mmol) in dry DMF (10 mL) and dry pyridine (6 mL) under N_2. The resulting mixture was heated to 100^oC for 18 h. After cooling the solvents were removed under high vacuum. The resulting solid was partitioned between water (25 mL) and CH_2Cl_2 (30 mL). The organic layer was retained and washed successively with $KHSO_4$ (0.5 M, 25 mL) and H_2O (25 mL). After drying ($MgSO_4$), the solvent was removed in vacuo to afford crude **3.20**. Column chromatography (100% CH_2Cl_2) gave **3.20** as a white solid (1.5 g, 53%). Characterization data matches literature values. m.p. 286^oC (dec). ^1H NMR (300 MHz, $CDCl_3$): δ 4.87 (s, 7H), 4.36 (s, 7H), 3.88-3.99 (m, 14H), 3.45-3.68 (m, 28H), 0.89 (s, 63H), 0.85 (d, 63H), 0.13 (s, 21H), 0.12 (s, 21H), 0.0 (s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.6, 82.0, 47.9, 73.4, 72.1, 61.9, 26.3, 25.7, 18.9, 18.3, -4.44, -4.64, -5.27, -5.37.

Per(6-O-tert-butyldimethylsilyl-2,3-di-O-cyclodimethysilyl)-β-*cyclodextrin* (**3.24**): To an oven-dried flask, dry **3.2** (500 mg, 0.26 mmol) was dissolved in anhydrous pyridine (15 mL) to which dichlorodimethylsilane (0.25 mL, 2.07 mmol) was added via a digital syringe pump set at a rate of 0.05 mL/h. The reaction was quenched with H_2O (5 mL) and the product was extracted with CH_2Cl_2, dried, concentrated under reduced pressure to give **3.24** (120 mg, 20%) after column chromatography (EtOAc/ hexanes, 20:80). m.p. 280-285^oC dec.). R_f 0.78. ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (bs, 7H), 4.04 (m, 7H), 3.77-3.82 (m, 21H), 3.54 (s, 2H), 0.88 (s, 63H), 0.35 (s, 21H), 0.11 (s, 21H) 0.06 (s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 103.6, 82.2, 84.8, 72.3, 61.6, 25.9, 18.4, 0.5, -0.1, -4.6.

Per(6-O-tert-butyldimethylsilyl-2,3-di-O-cyclodiphenylsilyl)-β-*cyclodextrin* (**3.25**): **3.25** was synthesized following an analogous procedure as previously described for **3.24**. To an oven-dried flask, dry **3.2** (500 mg, 0.26 mmol) was dissolved in anhydrous pyridine (15 mL) to which dichlorodiphenyllsilane (0.43 mL, 2.07 mmol) was added via a digital syringe pump set at a rate of 0.05 mL/h. The reaction was quenched with H_2O (5 mL) and the product was extracted with CH_2Cl_2, dried, concentrated under reduced pressure to give **3.24** as a crude mixture. Attempts to purify via recrystallization or column chromatography did not yield pure compound. R_f 0.88 (EtOAc/Hexanes, 20:80)

Per(6-O-tert-butyldimethylsilyl-2-O-allyl)-β-*cyclodextrin* (**3.26**): **3.26** was synthesized according to the method of Stoddart[54] and is prepared as follows: A solution of **3.2** (2.5 g, 1.29 mmol) in DMF (100 mL) under an atmosphere of N_2 was cooled to 0 °C, and NaH powder (60% in oil, 0.4 g, 10.2 mmol) was added portionwise. The reaction

was allowed to stir at 0 °C for 1.5 h and then overnight at room temperature. The reaction vessel was cooled to 0 °C, and allyl bromide (0.82 mL, 9.5 mmol) was added dropwise. The reaction was then allowed to stir at 0 °C for 1 h and finally overnight at room temperature. The reaction was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (125 mL) and washed with brine (100 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford a white foam. Purification by column chromatography (5% EtOAc/hexane to 20% EtOAc/hexanes) afforded pure **3.26** as a white foam (0.3 g, 19%). Characterization data matches literature values. R_f (Hexanes/EtOAc, 80:20) 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88-5.95 (ddt, *J* = 13 Hz, 6.5 Hz, 1.5 Hz, 7H), 5.72 (dd, *J* = 17 Hz, 1.5 Hz, 7H), 5.18 (d, *J* = 10.5, 7H), 4.87 (s, 14H), 4.45 (dd, *J* = 12.5 Hz, 5.5 Hz, 7H), 4.20 (dd, *J* = 12.5 Hz, 6.5 Hz, 7H), 3.62 (d, *J* = 10.5 Hz, 7H), 3.54 (d, *J* = 9.5 Hz, 7H), 3.47 (t, *J* = 9 Hz, 7H), 3.28 (dd, *J* = 10 Hz, 4 Hz, 7H), 3.88-3.95 (m, 14H), 0.85 (s, 63H), 0.01 (s, 42H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 118.5, 101.5, 82.4, 79.8, 73.5, 71.9, 62.0, 26.2, 18.5, -4.8, -4.9.

Per(6-O-tert-butyldimethylsilyl-2,3-di-O-allyl)-β-*cyclodextrin* (**3.28**): **3.28** was synthesized according to the method of Stoddart[54] and is prepared as follows: To a chilled (0oC) solution of **3.2** (2.3 g, 1.2 mmol) in dry DMF (100 mL) was added NaH (60% in oil, 2.5 g) and the mixture was stirred under N2 for 2 h at 0oC and overnight at room termperature. Allyl bromide (13 mL) was then added, and stirring continued for 2 d. The excess NaH was decomposed by addition of MeOH (5 mL) and the mixture was concentrated to dryness in vacuo. A solution of the residue was dissolved in CHCl3 (100 mL) and washed successively with H2O, aq. NaHCO3, H2O, then dried (MgSO4) and concentrated in vacuo. Column chromatography (100% Hexanes to Hexanes/EtOAc

80:20) gave **3.28** as a glassy foam (1.25 g, 41%). Characterization data matches literature values. R_f (Hexans/EtOAc, 80:20) 0.710. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (ddt, *J* = 17 Hz, 10.5 Hz, 5.5 Hz, 7H), 5.90 (ddt, *J* = 17 Hz, 10.5 Hz, 5.5 Hz, 7H), 5.18-5.29 (m, 21H), 5.07-5.21 (m, 14H), 4.5 (dd, *J* = 12 Hz, 6 Hz, 7H), 4.25 (dd, *J* = 12 Hz, 6 Hz, 7H), 4.16-4.19 (m, 21H), 3.81 (t, *J* = 9 Hz, 7H), 3.72 (t, J = 9.5 Hz, 7H), 3.65 (d, *J* = 11 Hz, 7H), 3.54 (d, *J* = 9.5 Hz, 7H), 3.21 (dd, *J* = 10 Hz, 3.5 Hz, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4, 135.4, 116.6, 115.9, 98.3, 80.2, 79.4, 77.9, 74.7, 72.2, 72.1, 62.3, 25.9, 18.3, -4.8, -5.2.

Per(6-O-pivaloyl)-β-cyclodextrin (**4.1**): **4.1** was synthesized according to the of method of Sakairi[56] and is prepared as follows: To a solution of β-CD (3.0 g, 2.64 mmol) in dry pyridine (60 mL) was added pivaloyl chloride (3.0 mL, 24.05 mmol) dropwise at room temperature and then slowly warmed to 60^{o}C overnight. MeOH (10 mL) was added to react with any left over PivCl and the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) poured into ice-water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined and washed with 5% HCl (50 mL), aq. $NaHCO_3$ (50 mL), and H_2O (50 mL). The mixture was dried over $MgSO_4$ and concentrated. The crude mixture was assumed to be **4.1** and a mixture (2,6-di-O-pivaloyl-β-CD and was used without purification in the next step. To the crude mixture in pyridine (60 mL) was added hydrazine hydrate (1.63 mL, 15 equiv.) and allowed to stir at room temperature for 16 h. The reaction was followed by TLC (90:10 CH_2Cl_2/MeOH) until completion. Acetone was added the reaction and the solvent was removed in vacuo. Column chromatography of the mixture (90:10 CH_2Cl_2/MeOH) gave **4.1** as a pale brown solid (4.05 g, 89%).

Characterization data matches literature values. R_f (5:1 $CHCl_3$/MeOH) 0.25. m.p. 235-240°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.83 (d, *J* = 6.5 Hz, 7H), 5.74 (s, 7H), 4.79 (s, 1H), 4.21 (d, *J* = 12 Hz, 7H), 4.02 (d, *J* = 10 Hz, 7H), 3.84 (d, *J* = 9 Hz, 7H)), 3.63 (t, *J* = 9 Hz, 7H), 3.45-3.30 (m, 14H), 1.10 (s, 63H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.8, 102.1, 81.6, 72.7, 72.0, 69.0, 62.7, 38.1, 26.7.

Per(2,3-di-O-acetyl-6-O-pivaloyl)-β-cyclodextrin (**4.2**): **4.2** was synthesized according to the of method of Santoyo-Gonzalez[57] and is prepared as follows: To a solution of **3.4** (0.75 g, 0.44 mmol) in dry pyridine (15 mL) was added PivCl (3.0 mL, 24.05 mmol). The mixture was kept at room temperature for 72 h and then poured into ice water (100 mL), extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined and washed with 5% HCl (50 mL), aq. $NaHCO_3$ (50 mL), and H_2O (50 mL). The mixture was dried over $MgSO_4$ and concentrated. Column chromatography (Hexanes/EtOAc 50:50 to 100% EtOAc) gave **4.2** as a pale yellow solid (0.75 g, 75%). Characterization data matches literature values. R_f (100% EtOAc) 0.75. m.p. 150-154°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (t, *J* = 8.5 Hz, 7H), 5.07 (d, *J* = 3.5 Hz, 7H), 4.74 (dd, *J* = 9.5 Hz, 5 Hz, 7H), 4.50 (d, *J* = 11.5 Hz, 7H), 4.21 (dd, *J* = 13 Hz, 3.5 Hz, 7H), 4.10 (d, *J* = 9.5 Hz, 7H), 3.77 (t, *J* = 9 Hz, 7H), 2.06 (s, 21H), 2.04 (s, 21H), 1.23 (s, 63H); ^{13}C NMR (125 MHz, DCl_3): δ 177.5, 171.0, 169.6, 97.0, 76.6, 71.2, 71.1, 70.1, 62.4, 39.1, 27.4, 21.1, 21.0.

Per(6-O-pivaloyl-2,3-di-O-cyclodimethysilyl)-β-*cyclodextrin* (**4.12**): Annulation of **4.12** (0.5 g, 0.29 mmol) was synthesized in an analogous manner as **3.24**. Column chromatography (CH_2Cl /MeOH (90:10) gave **4.12** (98 mg, 16%). R_f 0.67. ^{1}H NMR

(500 MHz, $CDCl_3$): δ 4.82 (d, *J* = 3.5 Hz, 7H), 4.43 (d, *J* = 11.5 Hz, 7H), 4.04 (m, 14H), 3.91 (d, *J* = 10 Hz, 7H), 3.80 (dd, *J* = 9.5 Hz, 3.5 Hz, 7H), 3.37 (t, *J* = 9.5 Hz, 7H), 1.21 (s, 63H), 0.35 (s, 21H), 0.17 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 103.6, 82.9, 75.9, 74.9, 69.8, 62.4, 38.8, 27.2, 0.6, -0.5.

Per(6-iodo-2,3-dihydroxy)-β-*cyclodextrin* (**4.18**): Per(6-deoxy)-β-CD was synthesized according to the method of Baer[16] and is prepared as follows: To a stirred solution of dessicator-dried PPh_3 (21 g) in dry DMF (80 mL) was added I_2 (20.5 g) in small portions, followed after 30 min by dry β-CD (**1**) (4.32 g, 3.8 mmol). The mixture was stirred for 18 h at 80^{o}C under nitrogen atmosphere, and then concentrated at reduced pressure to half its volume, cooled to 5^{o}C, made alkaline with NaOMe in MeOH (~4 M) to pH 9-10, and kept at room temperature for 30 min. The solution was then poured into vigorously stirred ice-water (1.5 L), and the beige-colored precipitate was collected by filtration. The product was washed well with water, dried in the air, and suspended in CH_2Cl_2 (1 L). After thorough agitation of the suspension the undissolved material was filtered off, washed several times with CH_2Cl_2, dissolved in DMF (100 mL), and precipitated by pouring the solution into stirred ice-water. The dried product was freed from some remnant, discoloring impurity by trituration with a small amount of MeOH, to give colorless (**15**) (5.03 g, 69%). Characterization data matches literature values. R_f 0.4 (EtOAc/Hexanes, ^{1}H NMR (500 MHz, DMSO-d_6): δ6.03 (d, *J* = 6.5 Hz, 7H), 5.95 (s, 7H), 4.99 (d, *J* = 3 Hz, 7H), 3.80 (d, *J* = 10Hz, 7H), 3.64 (t, *J* = 9.5, 7H), 3.59 (t, *J* = 9.5 Hz, 7H), 3.44 (t, *J* = 10.5 Hz, 7H), 3.27-3.39 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ102.0(C-1), 85.8 (C-4), 72.1, 71.8, 70.9 (C-2,3,5), 9.4 (C-6).

Per(6-iodo-2,3-diacetoxy)-β-cyclodextrin (**4.19**): (a) **4.19** was synthesized according to the method of Baer[16] and is prepared as follows: A solution of **4.18** (2.0 g) in Ac_2O (15 mL) and pyridine (10 mL) containing a catalytic amount of DMAP was kept for 48 h at room temperature. The mixture was quenched by the slow addition of MeOH (30 mL), and co-evaporation of the solvent with additional MeOH and several portions of toluene. The crude product was purified by column chromatography to give **4.19** (2.6 g, 100%). R_f 0.4 (EtOAc/Hexanes, 1:1).

(b) **4.19** was synthesized according to the method of Takeo[43] and is prepared as follows: A solution of **4.22** (0.48 g, 2.1 mmol) in DMF (10 mL) was stirred with NaI (0.6 g, 4 mmol) for 3 h at 100°C. The mixture was concentrated and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was separted, washed with H_2O, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (EtOAc/Hexanes, 50:50) gave **4.19** (0.37 g, 71%). Characterization data matches literature values. m.p. 172-177°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.30 (dd, *J* = 10, 9.5 Hz, 7H, H-3), 5.17 (d, *J* = 4 Hz, 7H, H- 1), 4.80 (dd, *J* = 10, 9.5 Hz, 7H, H-2), 3.56- 3.79 (complex m, 28H, H-4,5,6,6'), 2.06 (s, 21H), 2.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.2 (2 CO), 96.4 (C-1), 80.4, (C- 4),70.3, 70.1, 70.0, (C-2,3,5), 20.7, 20.6 (2 $COCH_3$), 7.8 (C-6).

Per(6-deoxy-2,3-diacetoxy)-β-*cyclodextrin* (**4.20**): *(a)* **4.20** was synthesized according to the method of Takeo[43] and is prepared as follows: A solution of **4.19** (0.28 g) in 2:1 1,4-dioxane-MeOH (15 mL) containing Et_3N (0.2 mL) was hydrogenated in the presence of 10% Pd/C (0.35 g) at atmospheric pressure overnight at room temperature, then filtered through a Celite pad, and concentrated in vacuo. A solution of the residue in $CHCl_3$ was washed successively with H_2O, cold 5% HCl, aq. $NaHCO_3$ and H_2O. The

organic layer was dried ($MgSO_4$) and concentrated. Column chromatography (CH_2Cl_2/MeOH 95:5) gave **4.20** (0.15 g, 85 %).

(b) **4.20** was synthesized according to the method of Takeo[43] and is prepared as follows: NaBH4 (212 mg, 5.6 mmol) was added in DMF (60 mL) in one portion and the temperature ws raided to 70oC. After the hydride had dissolved, **2.19** (2 g, 0.8 mmol) in DMF (20 mL) was slowly added and stirred for 2 h at 70^{o}C under N_2. The reaction was concentrated in vacuo and the resulting solid was poured into 2% HOAc (200 mL) with a trace of MeOH. The solution was extracted with CHCl3 (3 x 70 mL), and the organic layer was washed with ice water until neutralized, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (Hexanes/EtOAc 25:75) gave **4.20** (65%).

(c) **4.20** was synthesized according to the method of Baer[16] and is prepared as follows: A solution of **4.19** (2.29 g), Bu_3SnH (6 mL), and a catalytic amount of AIBN in toluene (100 mL) was refluxed for 45 min under nitrogen atmosphere. The solvent was evaporated, and the residue, dissolved in CH_2Cl_2 (100 mL), washed with H_2O (2 x 60 mL). The dried (Na_2SO_4) organic phase was concentrated and the product purified by column chromatography to give **4.20** (1.18 g, 80 % yield). R_f 0.10 (ether, 200mL, followed by EtOAc/Hexanes, 3:1). Characterization data matches literature values. m.p. 194-197^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.265 (t, *J* = 8.5 Hz, H-3), 4.98 (d, *J* = 4 Hz, H-1), 4.76 (dd, *J* = 10, 4 Hz, H-2), 4.05 (m, H-5), 3.33(t, *J* = 9 Hz, H-4), 2.06, 2.04(2 s, 6H, 2 OAc), 1.37 (d, *J* = 6 Hz, 3H, CH3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 169.4(2 CO), 96.5 (C-1), 82.5 (C-4), 71.2, 71.1 (C-2,3), 67.2 (C-5), 20.8 (2 $COCH_3$), and 17.9 (C-6).

Per(6-deoxy)-β-*cyclodextrin* (**4.21**): *From* **4.20** Baer[16] reported subjecting a solution of **4.20** in dry MeOH to a solution of NaOMe until alkaline and then passing the solution through Amberlite IR- 120 (H+) cation-exchange resin, and evaporated to give sodium-free **4.21**. Our modified method is described as follows: To an oven-dried flask with stir bar **4.20** (3.52 g, 2.18 mmol) was added anhydrous MeOH (50 mL). Followed by a 10% excess of NaOMe (7.7 mL, 33.6 mmol, 15.4 equiv.) (25 wt% solution in MeOH, ~4.36 M), a white precipitate formed immediately. The flask was equipped with a distillation head and heated to slowly distill away the MeOH until a thick slurry remained. After cooling to room temperature, MeOH (40 mL) was added to make a stirable suspension. Then Dowex 50-W 8x cation-exchange resin (H+) (10.5 g) was added to the reaction vessel. Between 0.5-1.5 h, the solution became slightly cloudy yellow, indicating neutral or slightly acidic pH. The cloudy solution was filtered through Hirsch funnel with no filter paper, and evaporated to dryness to obtain **4.21** (1.9 g, 85% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.7 (d, J = 6.5 Hz, 2-OH), 5.60 (s, 3-OH), 4.80 (s, H-1), 3.71 b(s, H-5), 3.56 (bs, H-3), 3.32 (d, J = 9.5 Hz, H-2), 3.01 (bs, H-4), and 1.20 (d, J = 5.5 Hz, 3H, CH3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 102.1(C-1), 87.8 (C-4), 72.9 (C-3), 72.4 (C-2), 66.4 (C-5) and 17.1 (C-6).

Per(2,3-diacetoxy-6-O-methylsulfonyl))-β-*cyclodextrin* (**4.22**): **4.22** was synthesized according to the of method of Baer[16] and is prepared as follows: MsCl (1 mL) was added ropwise, at 0oC, to a solution of **3.4** (0.5 g, 0.27 mmol) in dry pyridine (15 mL). The mixture was kept for 2 h at 0^{o}C and 20 h at room temperature. Water (1 mL) was added and after 15 min the mixture was poured into ice-water. The precipitate was washed with H_2O, dissolved in $CHCl_3$ (50 mL), and then washed with 5% HCl (100

mL), aq. $NaHCO_3$ (100 mL) and H_2O. The solution was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (EtOAc/Hexanes, 20:1) gave **4.22** (0.71 g, 99%) as a crystalline solid. Characterization data matches literature values. R_f ($CHCl_3$/MeOH, 90:10) 0.4. m.p. 165-167°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (dd, *J* = 9.5, 8.0 Hz, 7H), 5.14 (d, *J* = 4.0 Hz, 7H), 4.80 (dd, *J* = 10.0, 3.5 Hz, 7H), 4.63 (d, *J* = 10.5 Hz, 7H), 4.56 (dd, *J* = 12.0, 3.5 Hz, 7H), 4.17 (d, *J* = 10.0 Hz, 7H), 3.79 (t, *J* = 8.5 Hz, 7H), 3.1 (s, 21H), 2.07 (s, 21H), 2.05 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.3, 96.8, 76.1, 70.2, 70.1, 69.5, 68.4, 20.7 (2C).

Per(6-deoxy-2,3-dimethoxy)-β-*cyclodextrin* (**4.26**): To an oven-dried flask NaH (20 equiv.), and **4.21** (540 mg, 0.53 mmol) was reacted in DMF (40 mL). MeI (0.65 mL, 20 equiv.) is added to the reaction mixture and then it is allowed to stir overnight. The reaction mixture is quenched slowly with MeOH and H_2O (5 mL) is added, after which it is concentrated to dryness. The solid is dissolved in EtOAc and washed with H_2O, dried, and concentrated to give **4.26** (541 mg, 85%), R_f 0.25 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (d, *J* = 3.5, H-1), 3.81 (dd, *J* = 9.5 Hz, 6 Hz, H-5), 3.60 (s, CH3), 3.47 (s, CH3), 3.43 (t, *J* = 9 Hz, H-3), 3.10-3.15 (m, H-2, H-4), 1.32 (d, *J* = 6.5 Hz, CH3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 98.7 (C-1), 86.8 (C-4), 82.3 (C-2), 81.8 (C-3), 67.0 (C-5), 61.4, 58.6 (2 x CH3) and 18.1 (C-6).

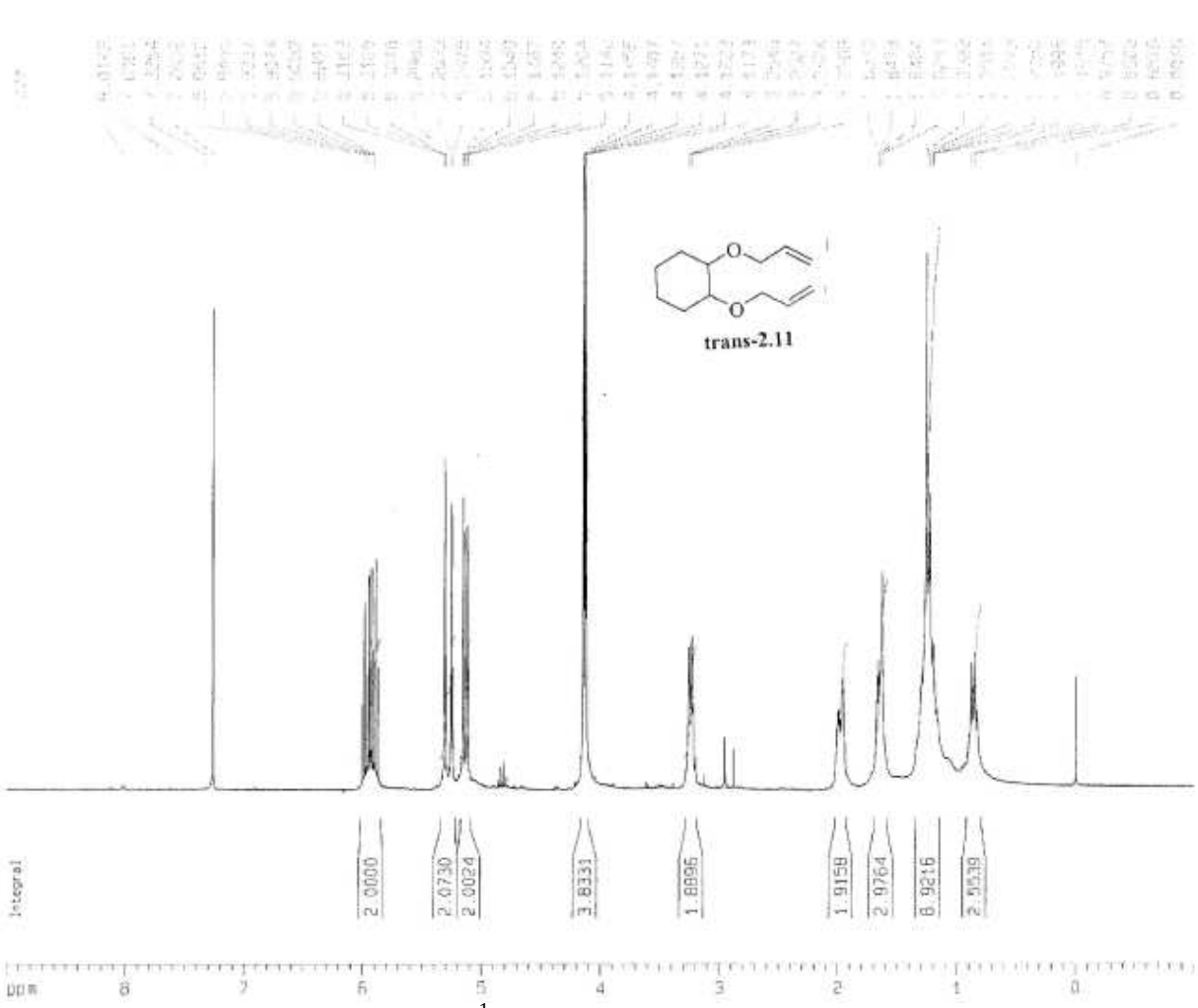
Per(6-deoxy-2,3-di-O-allyl)-β-*cyclodextrin* (**4.27**): To an oven-dried flask NaH (0.275, 6.84 mmol), and **4.21** (100 mg, 0.1 mmol) was reacted in DMF (40 mL). MeI (0.6 mL, 6.84 mmol) is added to the reaction mixture and then it is allowed to stir overnight. The reaction mixture is quenched slowly with MeOH and H_2O (5 mL) is

added, after which it is concentrated to dryness. The solid is dissolved in EtOAc and washed with H_2O, dried, and concentrated to give **4.2** (38 mg, 25%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (ddt, *J* = 17 Hz, 10.5 Hz, 5.5 Hz, 7H), 5.89 (ddt, *J* = 17 Hz, 10.5 Hz, 5.5 Hz, 7H), 2.54 (m, 14H), 5.11 (m, 14H), 5.00 (d, *J* = 3.5 Hz, 7H), 4.47 (dd, *J* = 12 Hz, 5 Hz, 7H), 4.24 (dd, *J* = 12 Hz, 6 Hz, 7H), 4.14 (m, 14H), 3.83 (dd, *J* = 10.5 Hz, 6 Hz, 7H), 3.66 (t, *J* = 9.5 Hz, 7H), 3.33 (dd, *J* = 9.5 Hz, 3.5 Hz, 7H), 3.23 (t, *J* = 9 Hz, 7H), 1.32 (d, *J* = 6.5 Hz, CH3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4, 135.4, 116.8, 115.7, 98.5, 82.6, 79.9, 79.4, 74.4, 72.3, 67.2, 18.3.

APPENDICES

APPENDIX A

Selected NMR Spectra

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PROCNO                  1

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NS                     16
DS                      2
SWH              6172.838 Hz
FIDRES           0.094190 Hz
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RG                  161.3
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DE                  6.00 usec
TE                   0.0 K
D1               1.00000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

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PL1                 -2.20 dB
SFO1           300.1318534 MHz

F2 - Processing parameters
SI                     32768
SF             300.1300060 MHz
WDW                       no
SSB                        0
LB                    0.00 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                    20.00 cm
CY                    12.50 cm
F1P                   9.000 ppm
F1                 2701.17 Hz
F2P                  -1.000 ppm
F2                 -300.13 Hz
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HZCM             150.06500 Hz/cm
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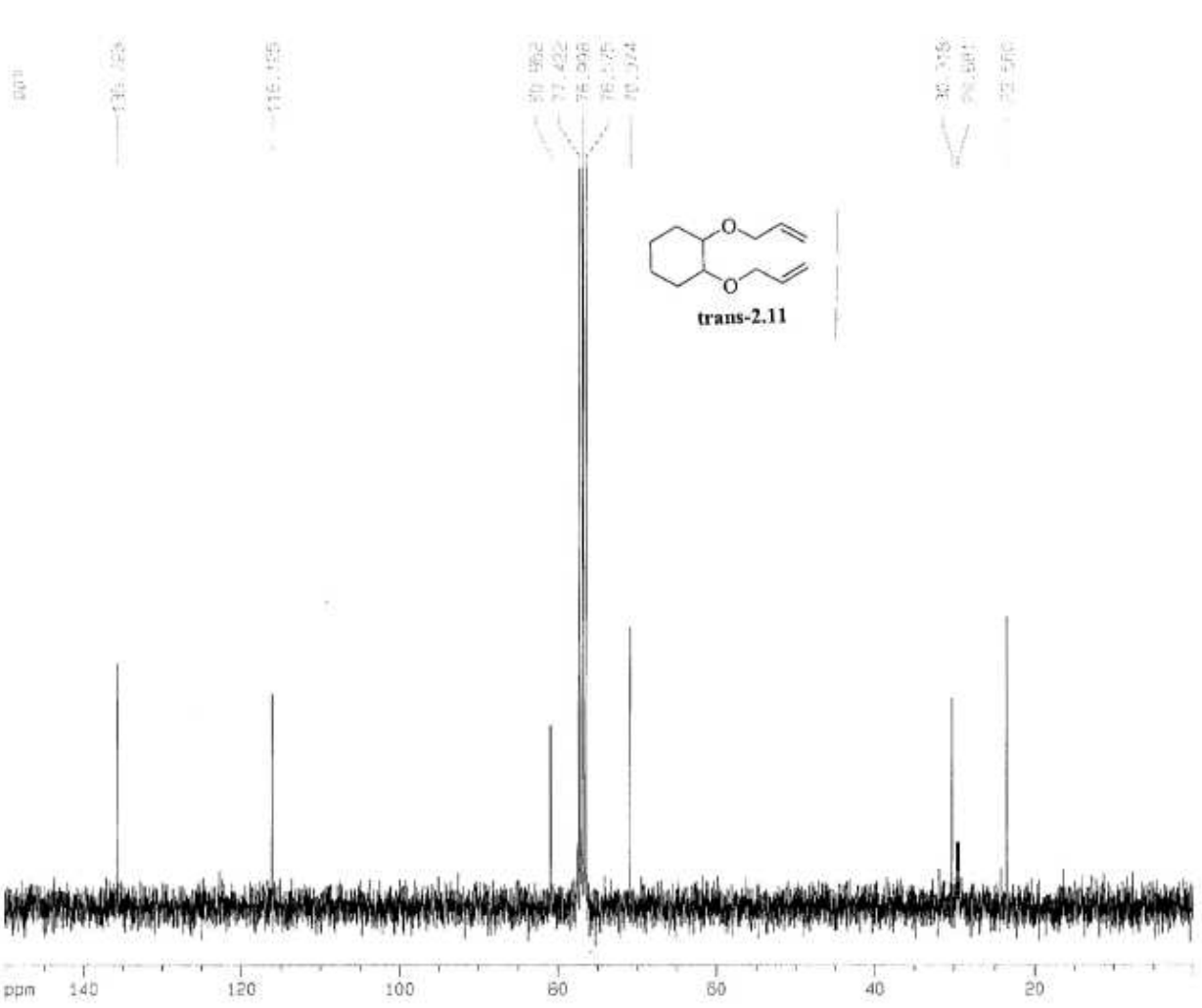
A.2.1. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**2.11**)

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TD                65536
SOLVENT             CDCl3
NS                     92
DS                      4
SWH           17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8219508 sec
RG                5160.6
DW               27.800 usec
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TE                 0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                   10.00 usec
PL1                  -0.20 dB
SF01          75.4752853 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                  -1.00 dB
PL12                 19.00 dB
PL13                 20.00 dB
SF02          300.1312005 MHz

F2 - Processing parameters
SI                     32768
SF            75.4577504 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                   20.00 cm
CY                    5.00 cm
F1P                150.000 ppm
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F2P                 -0.000 ppm
F2                  -0.00 Hz
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HZCM             566.00812 Hz/cm
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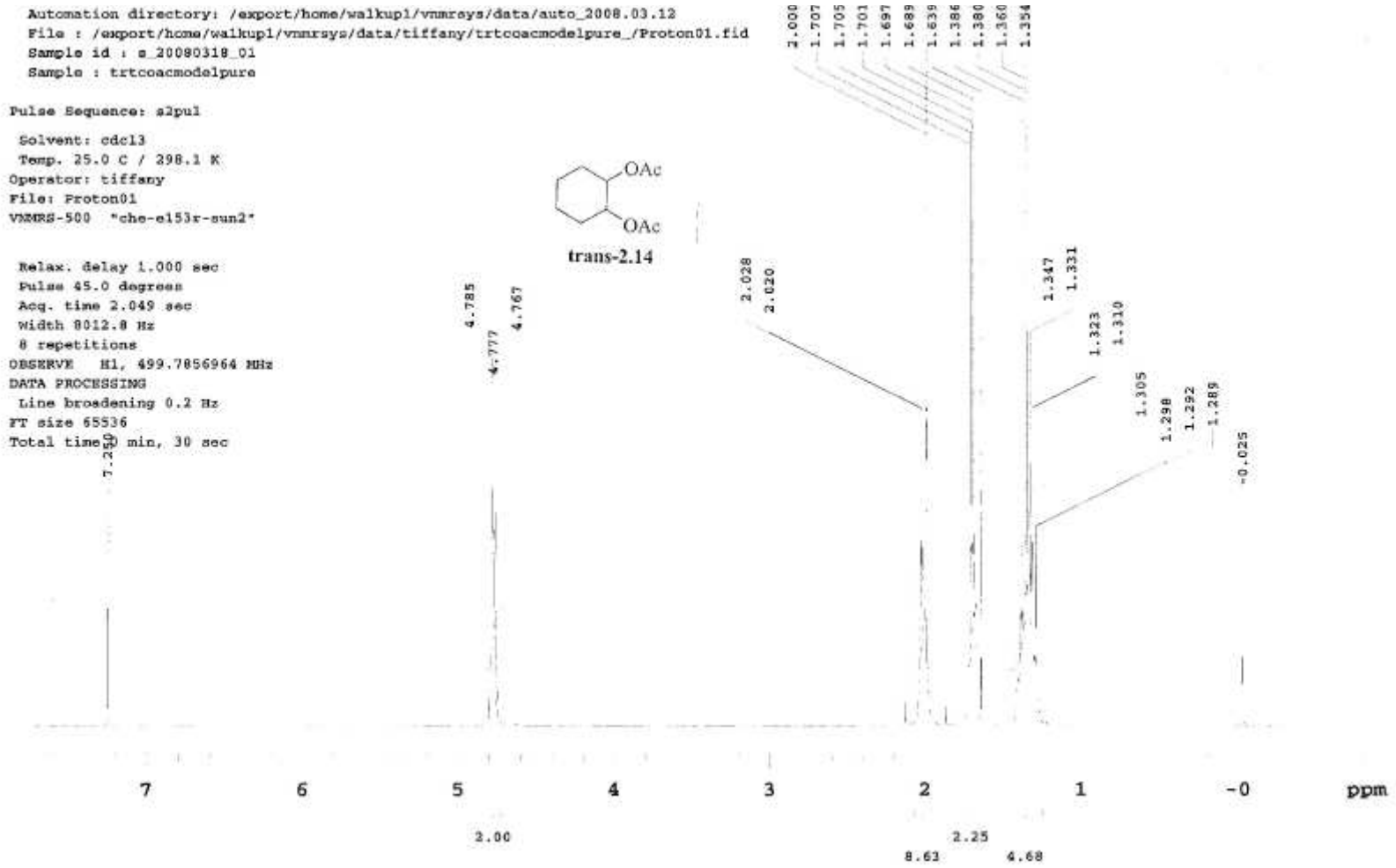
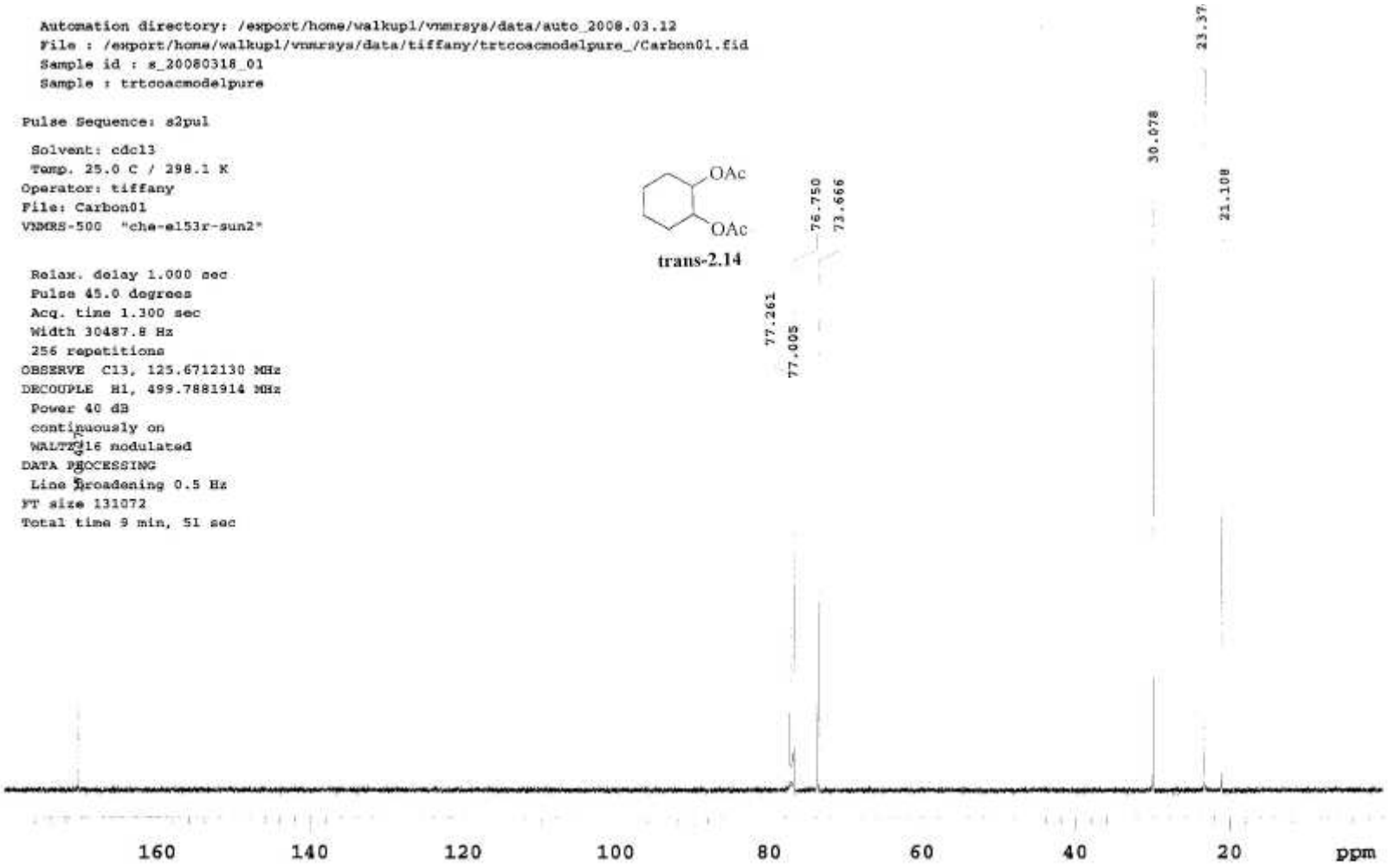
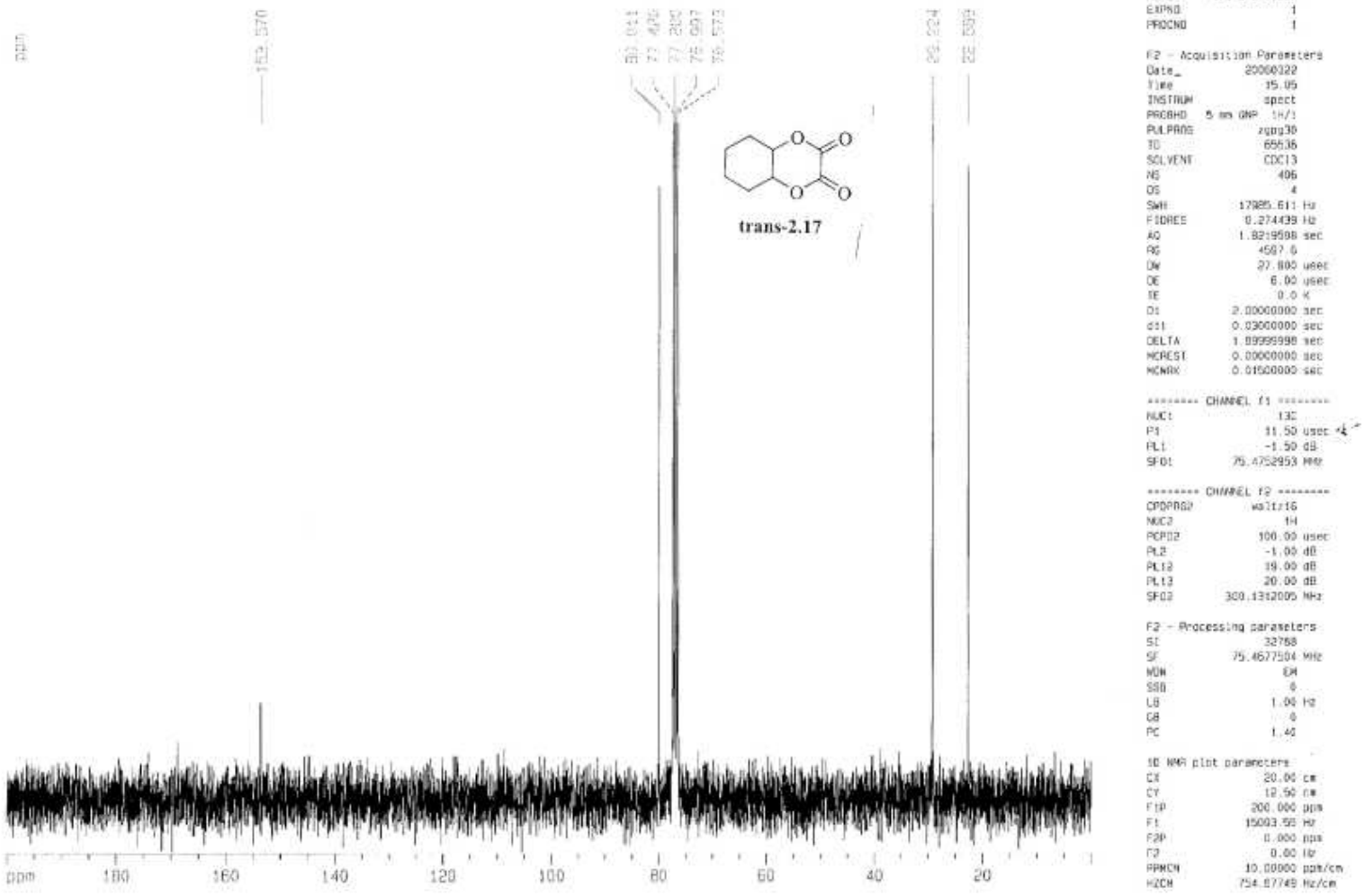
A.2.2. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**2.11**)



A.2.3. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**2.14**)



A.2.4. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**2.14**)

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MCWRK        0.01500000 sec

======== CHANNEL f1 ========
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P1               11.50 usec
PL1              -1.50 dB
SFO1         75.4752953 MHz

======== CHANNEL f2 ========
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PCPD2           100.00 usec
PL2              -1.00 dB
PL12             19.00 dB
PL13             20.00 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
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1D NMR plot parameters
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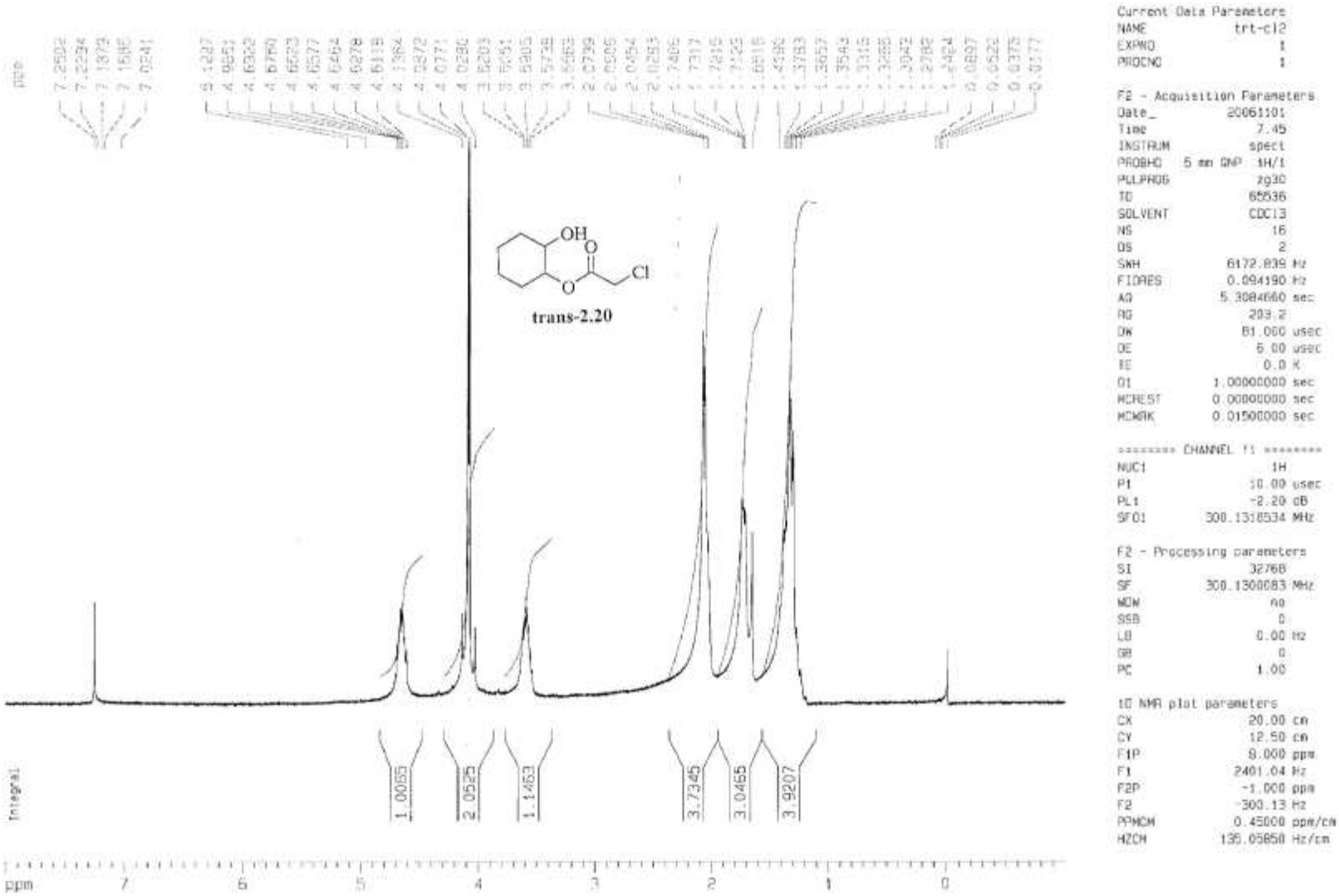
A.2.5. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**2.17**)

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PROCNO                     1

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TD                     65536
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DS                          2
SWH                 6172.839 Hz
FIDRES              0.094190 Hz
AQ                  5.3084660 sec
RG                      203.2
DW                     81.000 usec
DE                      6.00 usec
TE                       0.0 K
D1                  1.00000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      10.00 usec
PL1                     -2.20 dB
SFO1             300.1318534 MHz

F2 - Processing parameters
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SF               300.1300083 MHz
WDW                           no
SSB                            0
LB                      0.00 Hz
GB                             0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
CY                     12.50 cm
F1P                     8.000 ppm
F1                   2401.04 Hz
F2P                    -1.000 ppm
F2                    -300.13 Hz
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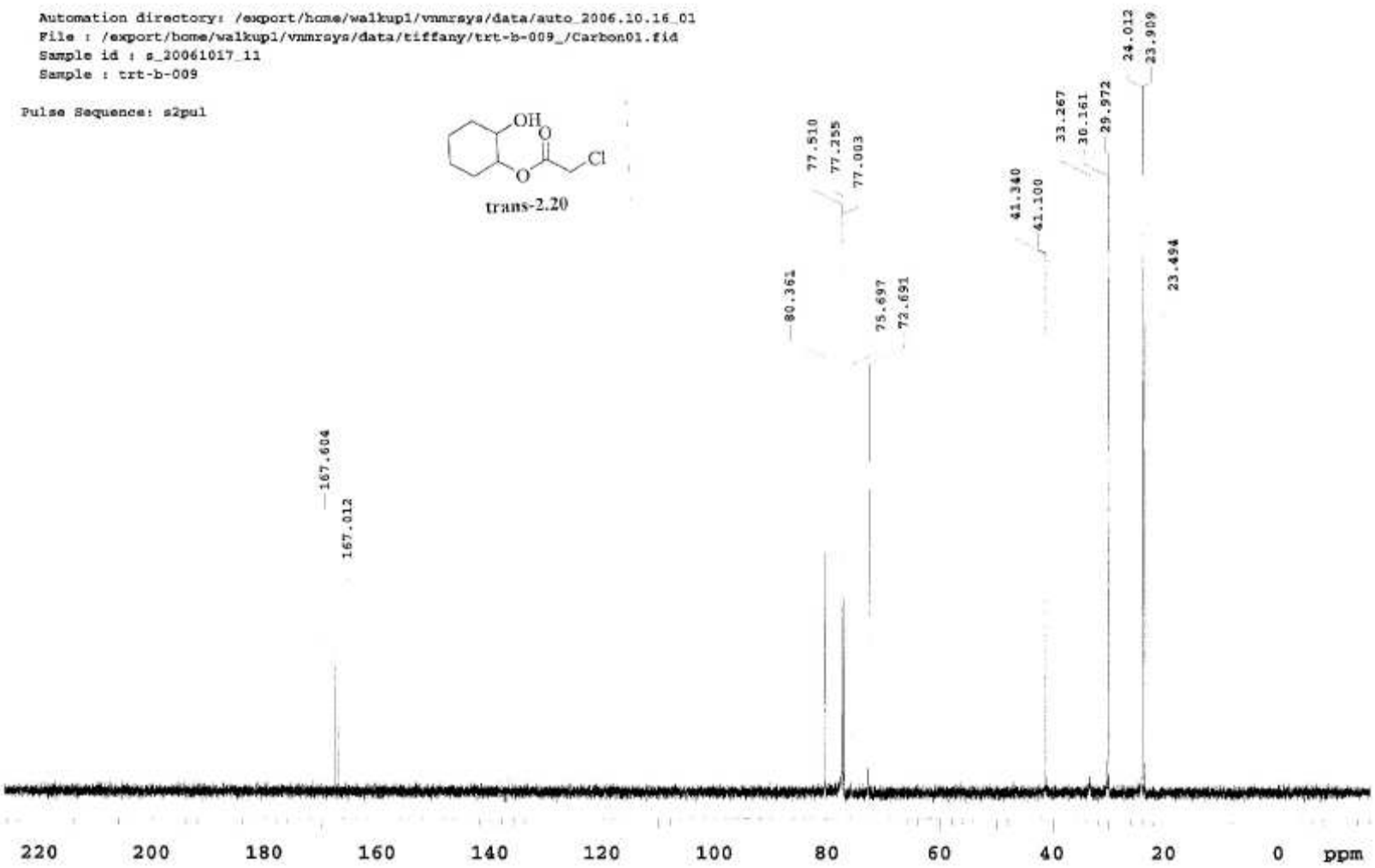
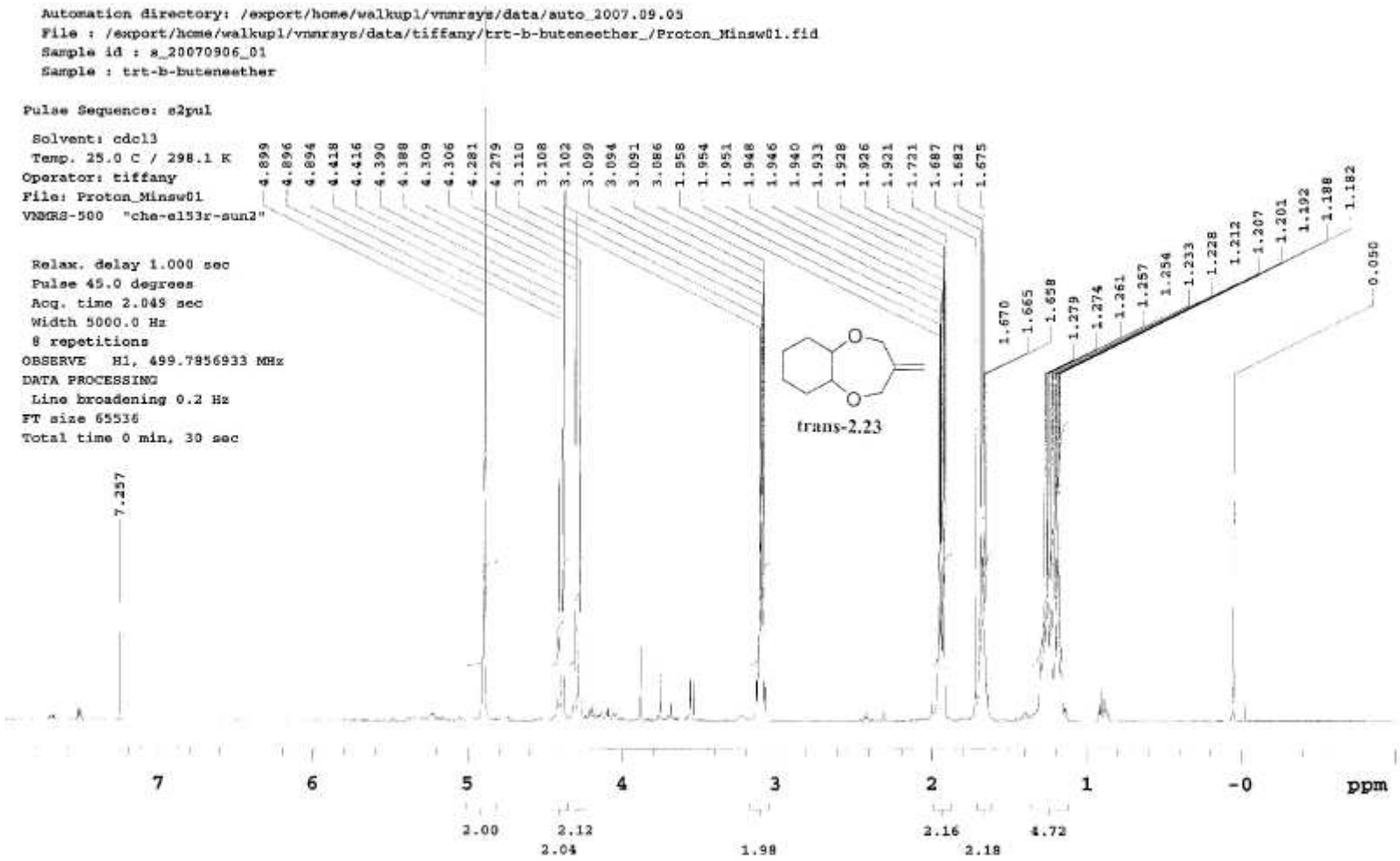
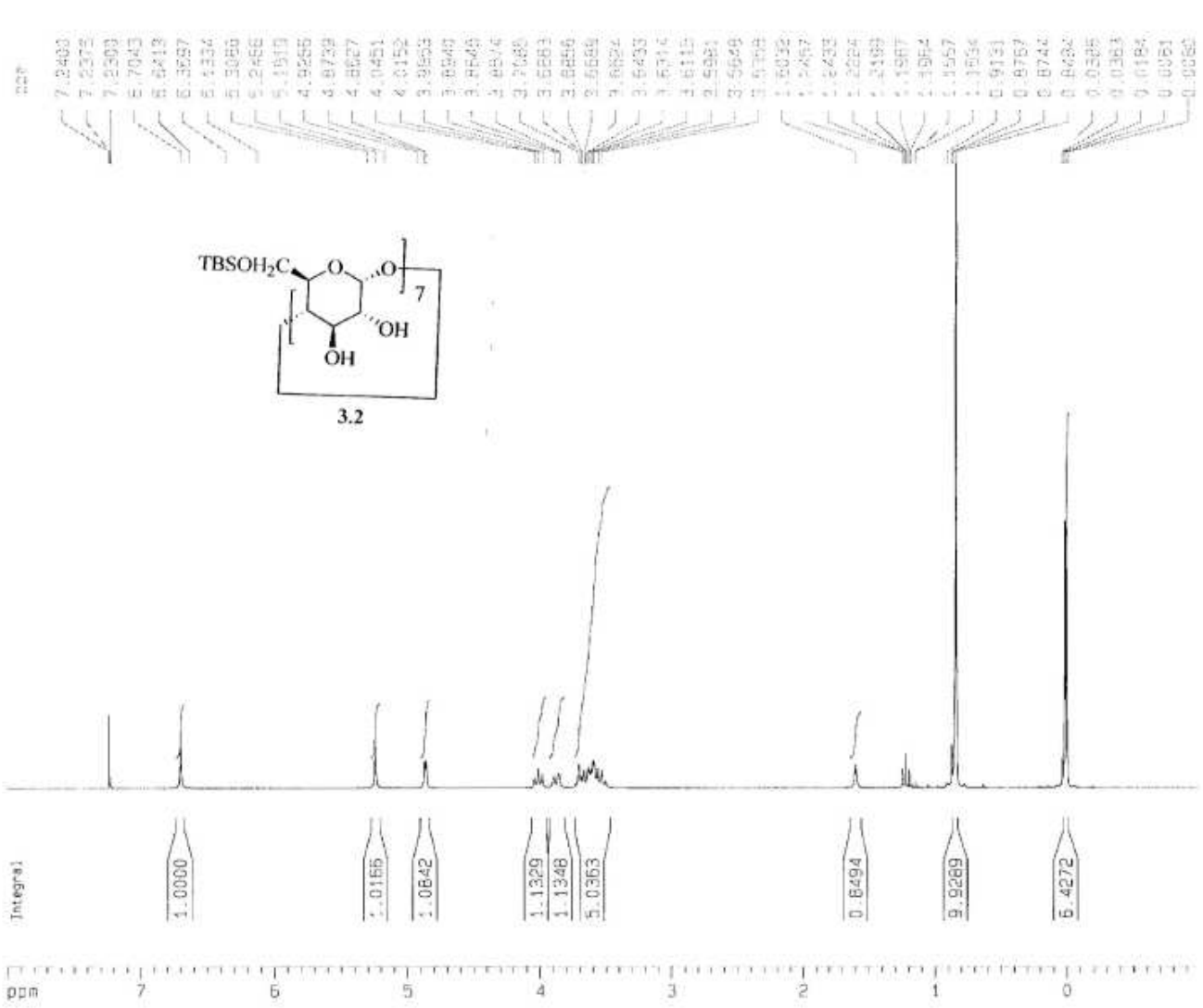
A.2.6. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**2.20**)



A.2.7. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**2.20**)



A.2.8. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**2.23**)

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NS                   16
DS                    2
SWH           6172.839 Hz
FIDRES        0.094190 Hz
AQ            5.3084660 sec
RG              228.1
DW             81.000 usec
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TE               0.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
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PL1             -2.20 dB
SFO1        300.1318534 MHz

F2 - Processing parameters
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WDW                  no
SSB                   0
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GB                    0
PC                 1.00

1D NMR plot parameters
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CY              12.50 cm
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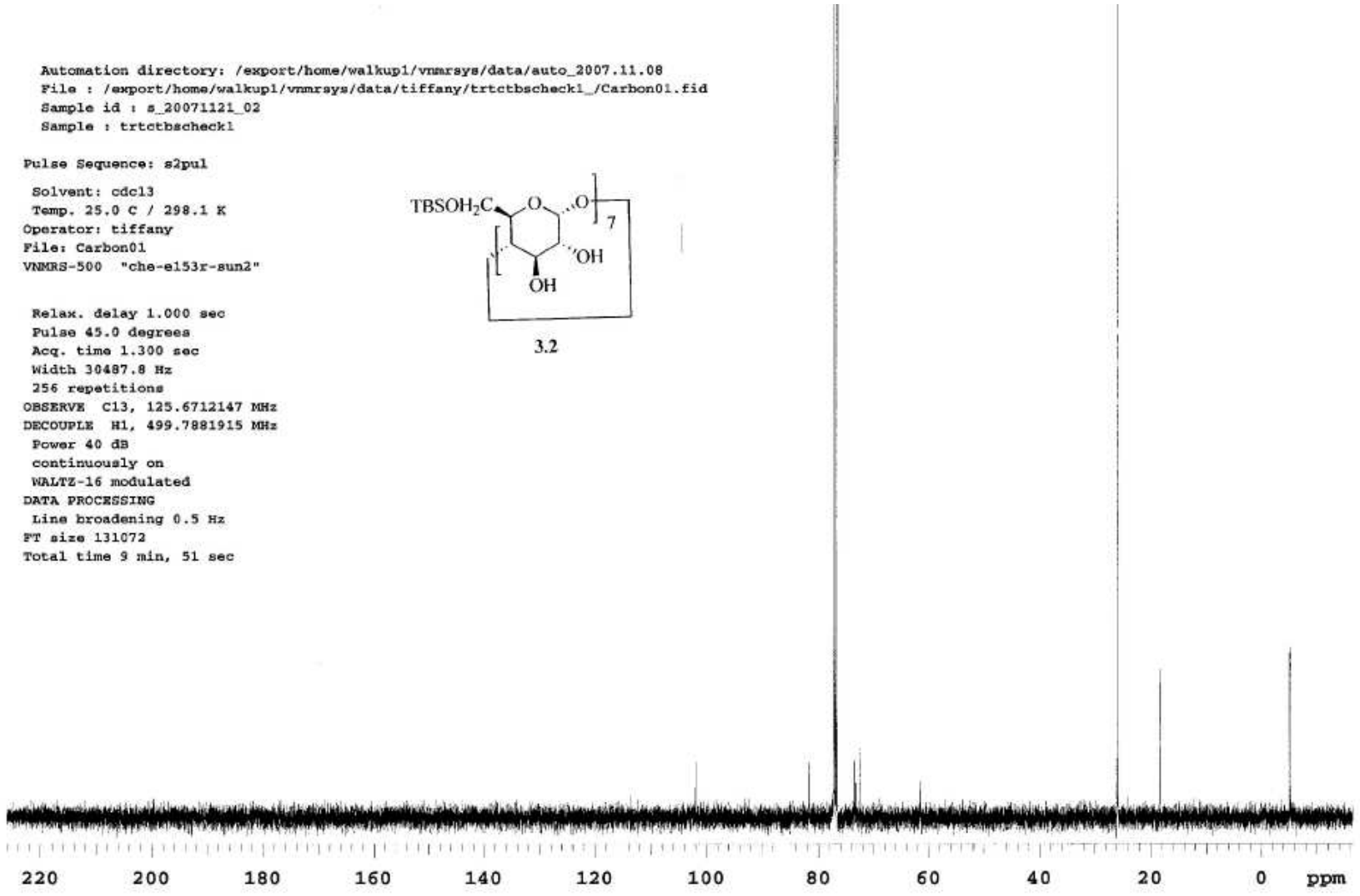
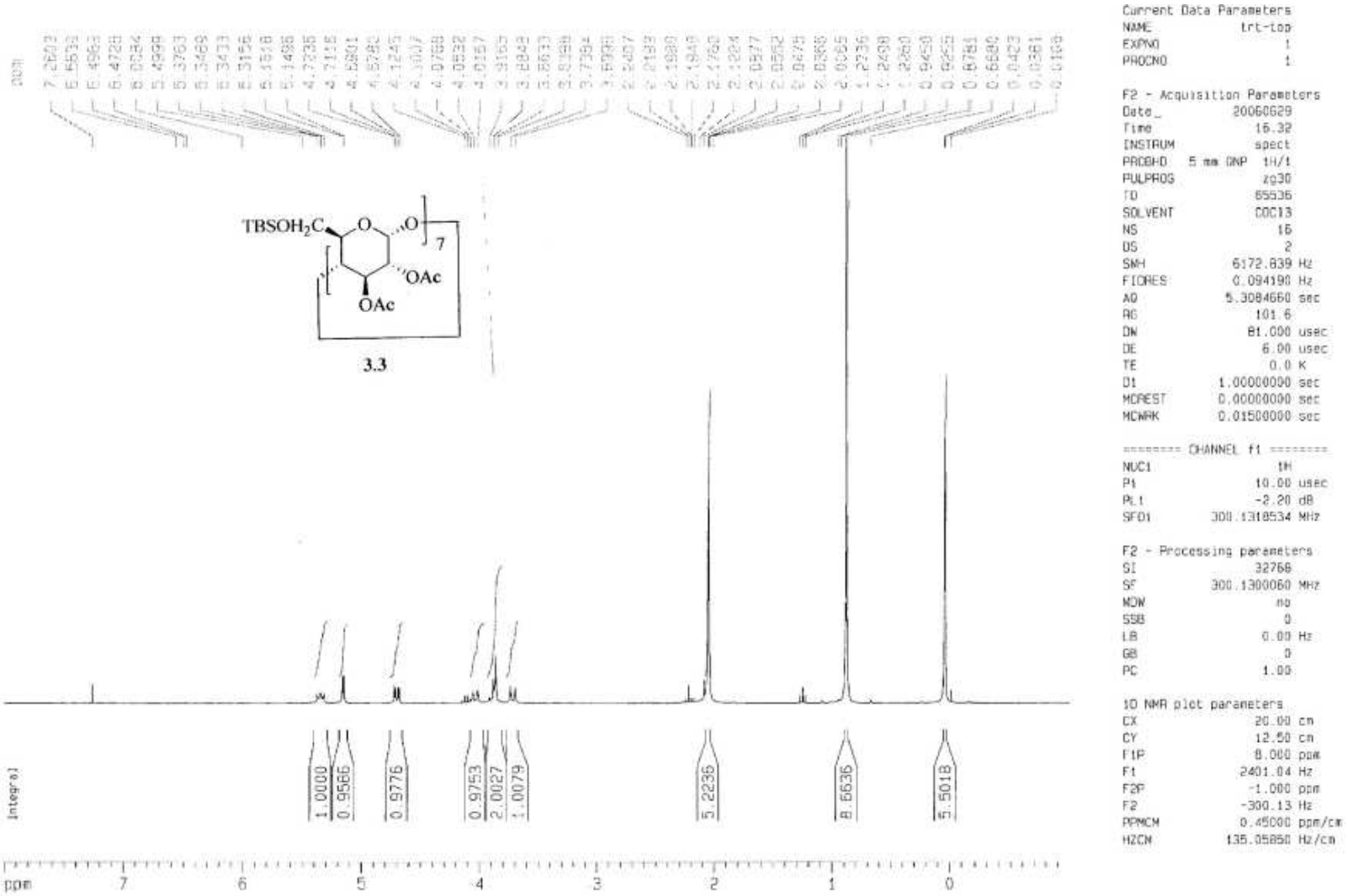
A.3.1. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.2**)



A.3.2. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.2**)

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F2 - Acquisition Parameters
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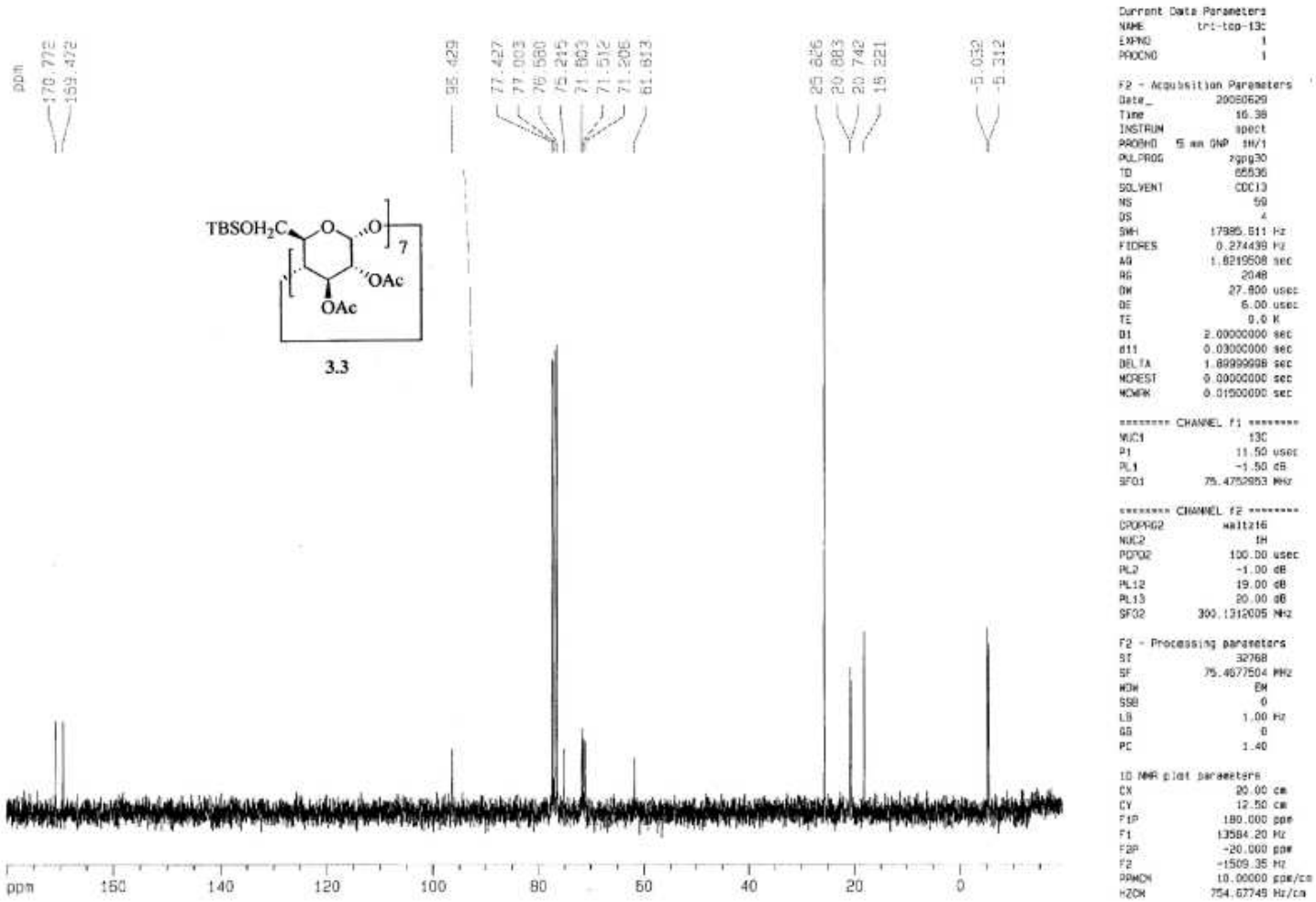
Time                    16.32
INSTRUM                 spect
PROBHD     5 mm DNP  1H/1
PULPROG                 zg30
TD                     65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                6172.839 Hz
FIDRES             0.094190 Hz
AQ                 5.3084660 sec
RG                     101.6
DW                    81.000 usec
DE                     6.00 usec
TE                      0.0 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      10.00 usec
PL1                     -2.20 dB
SFO1             300.1318534 MHz

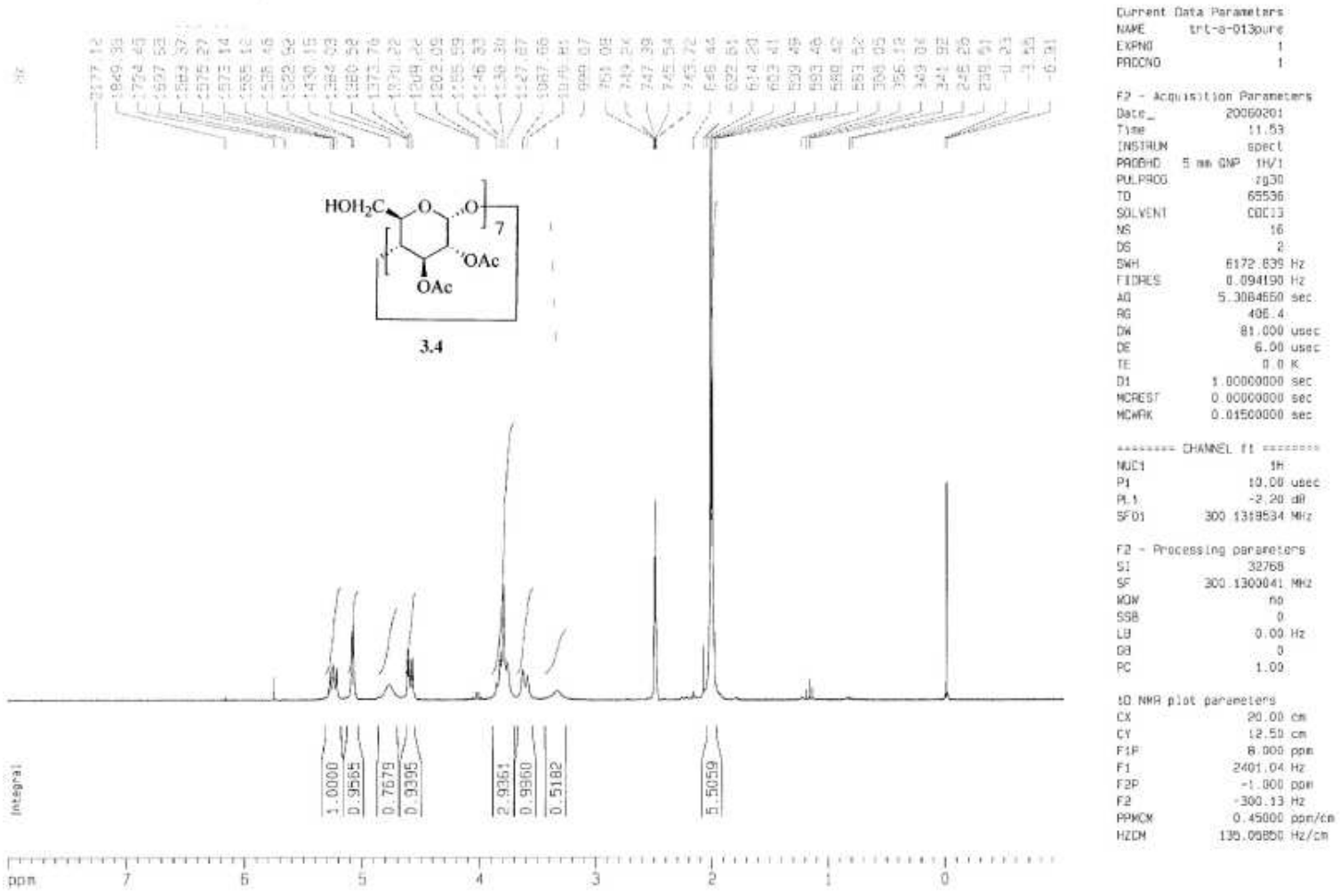
F2 - Processing parameters
SI                       32768
SF               300.1300060 MHz
WDW                         no
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.00

1D NMR plot parameters
CX                       20.00 cm
CY                       12.50 cm
F1P                       8.000 ppm
F1                     2401.04 Hz
F2P                      -1.000 ppm
F2                     -300.13 Hz
PPMCM                  0.45000 ppm/cm
HZCM                 135.05850 Hz/cm
```

A.3.3. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.3**)



A.3.4. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.3**)




```
Current Data Parameters
NAME        trt-a-013pure
EXPNO                   1
PROCNO                  1

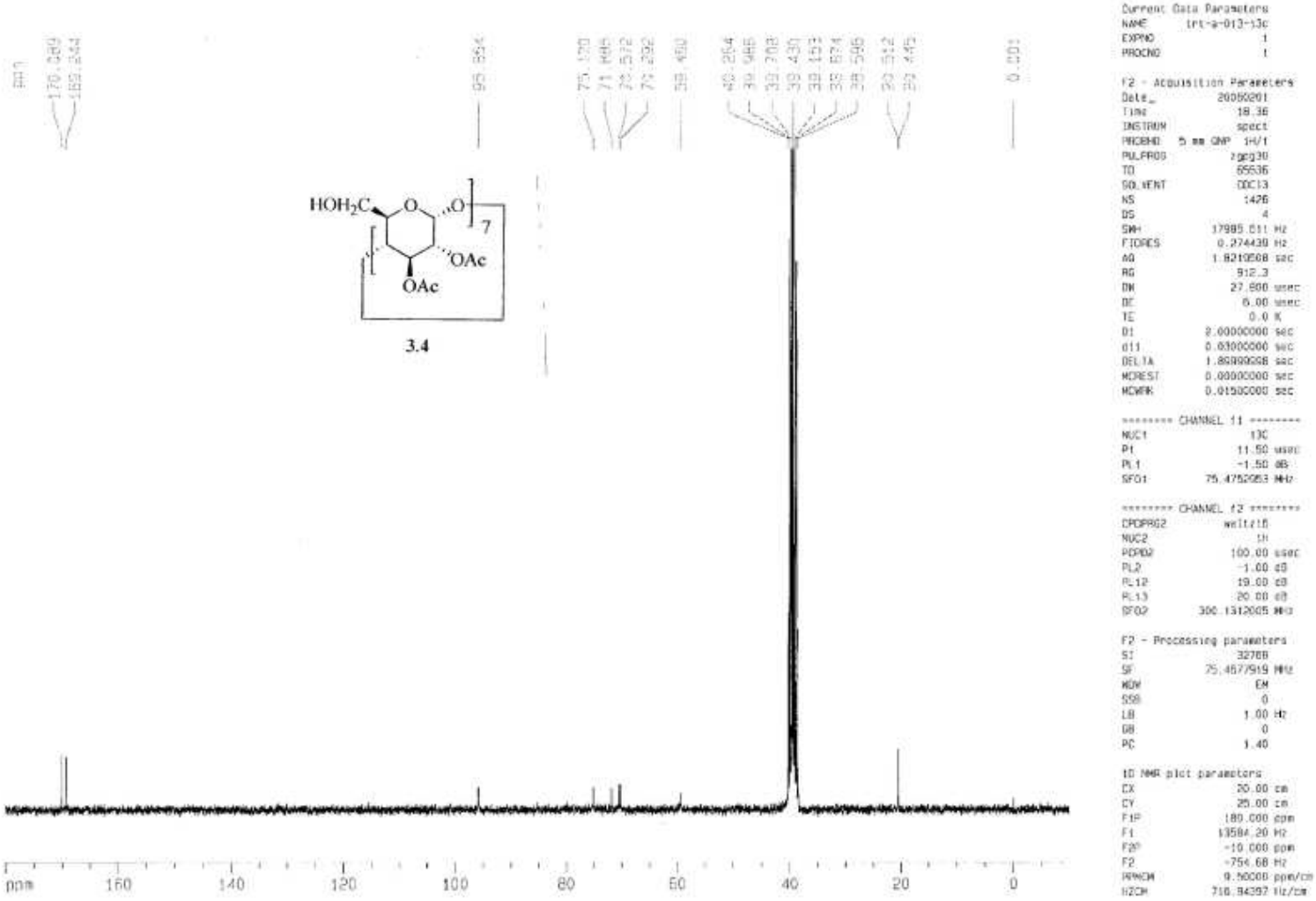
F2 - Acquisition Parameters
Date_            20060201
Time                11.53
INSTRUM             spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6172.839 Hz
FIDRES           0.094190 Hz
AQ               5.3084660 sec
RG                  406.4
DW                 81.000 usec
DE                  6.00 usec
TE                   0.0 K
D1               1.00000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                 -2.20 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                     32768
SF            300.1300041 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  12.50 cm
F1P                 8.000 ppm
F1                 2401.04 Hz
F2P                -1.000 ppm
F2                 -300.13 Hz
PPMCM              0.45000 ppm/cm
HZCM             135.06850 Hz/cm
```

A.3.5. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.4**)

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Current Data Parameters
NAME        krt-a-013-13c
EXPNO               1
PROCNO              1

F2 - Acquisition Parameters
Date_         20050201
Time              18.36
INSTRUM           spect
PROBHD  5 mm QNP 1H/1
PULPROG          zgpg30
TD               65536
SOLVENT          CDCl3
NS                1426
DS                   4
SWH          17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8210560 sec
RG              512.3
DW             27.800 usec
DE              6.00 usec
TE               0.0 K
D1            2.00000000 sec
D11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1               13C
P1                11.50 usec
PL1               -1.50 dB
SFO1         75.4752053 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2            100.00 usec
PL2               -1.00 dB
PL12              19.00 dB
PL13              20.00 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                32768
SF          75.4677919 MHz
WDW               EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40

1D NMR plot parameters
CX               20.00 cm
CY               25.00 cm
F1P             180.000 ppm
F1              13584.20 Hz
F2P             -10.000 ppm
F2              -754.68 Hz
PPMCM            9.50000 ppm/cm
HZCM           716.94397 Hz/cm
```
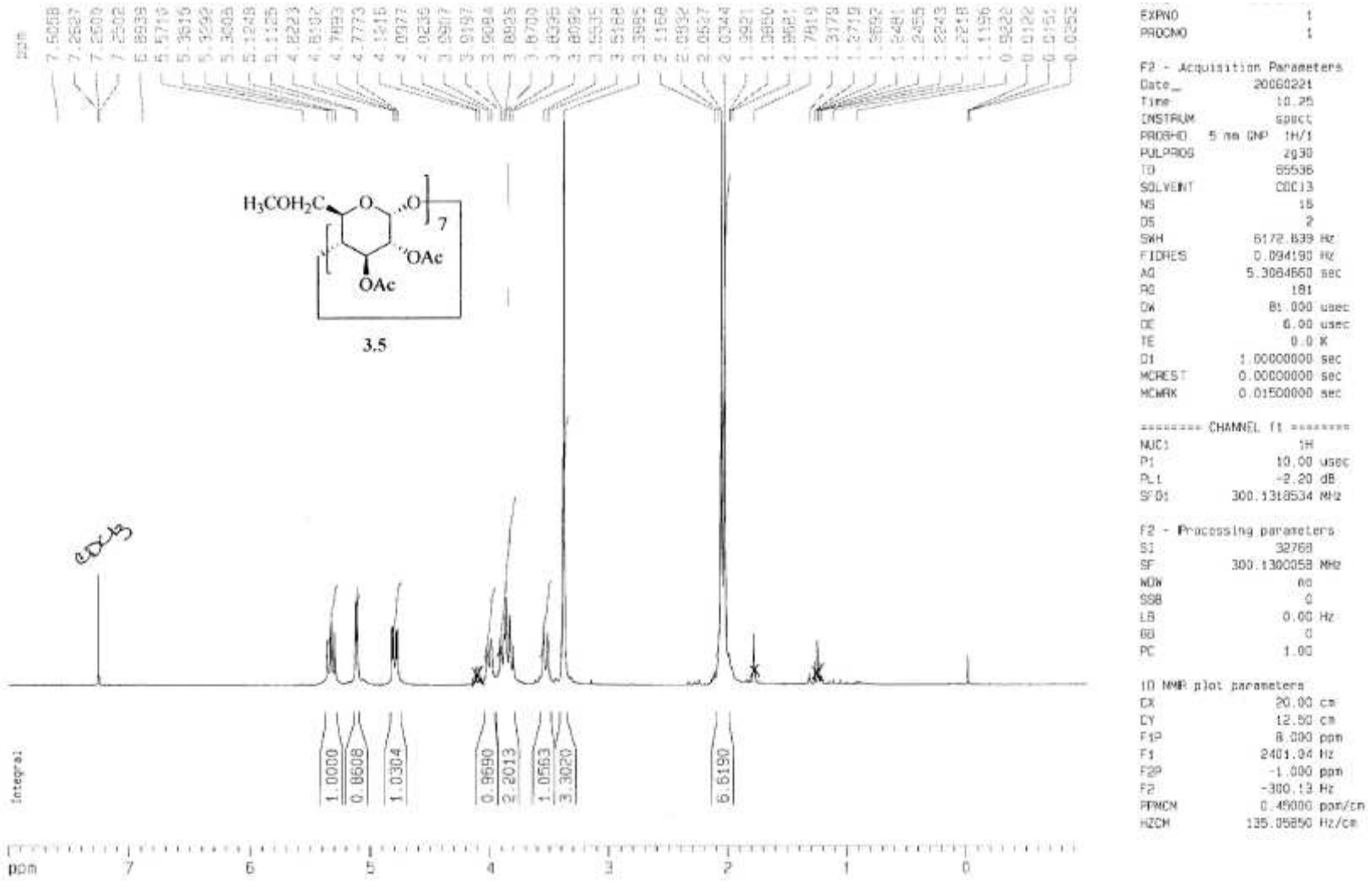
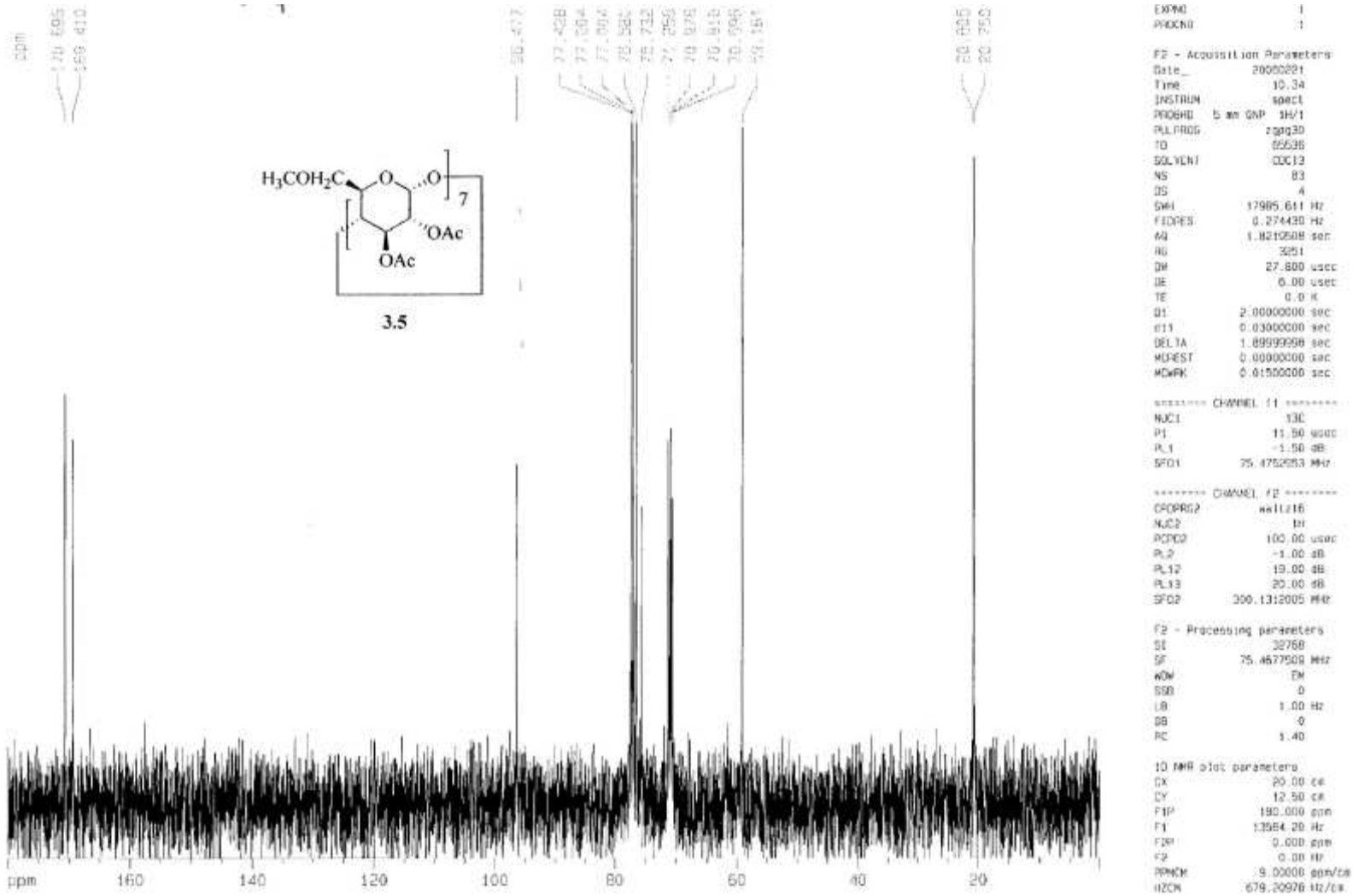
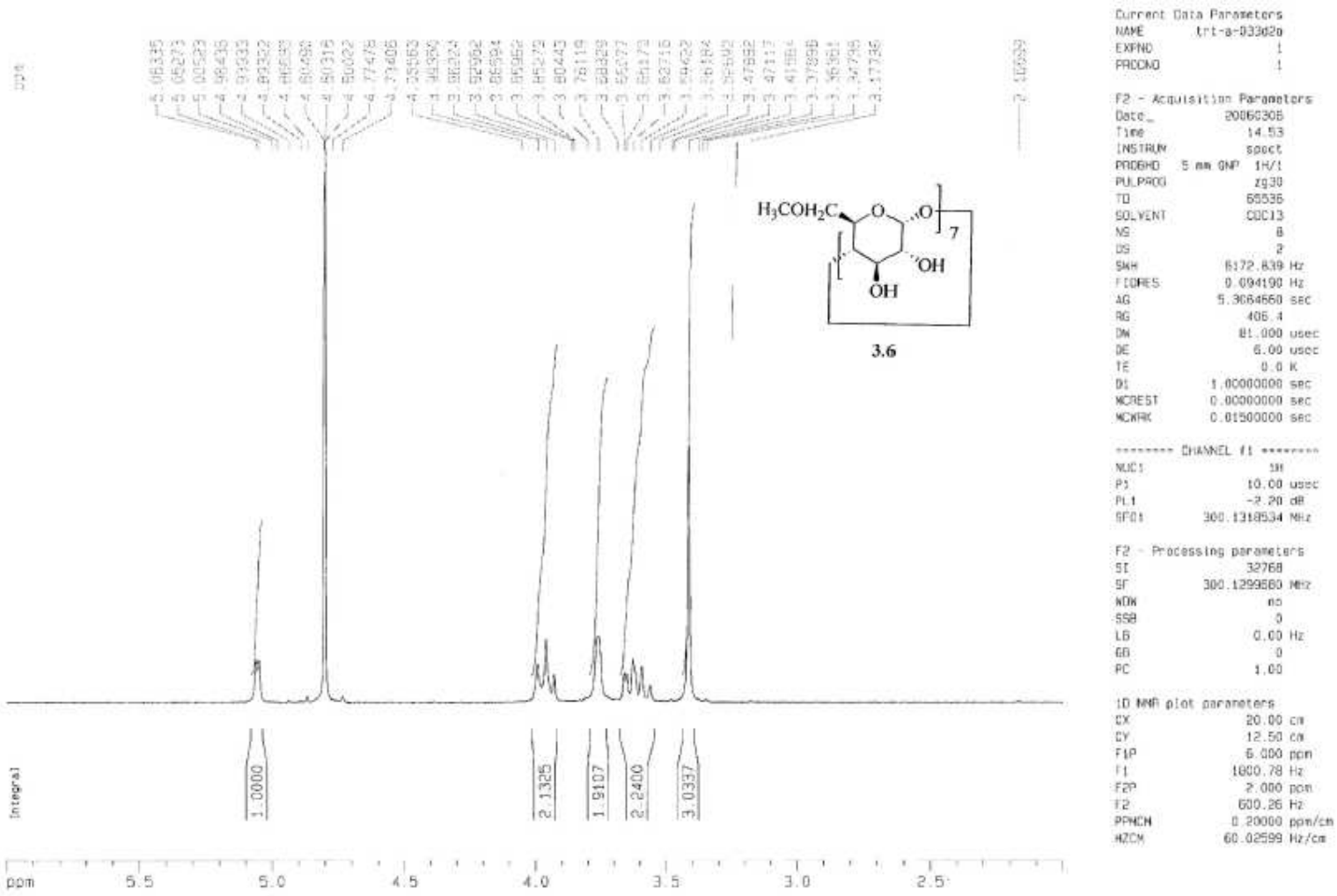

A.3.6. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.4**)



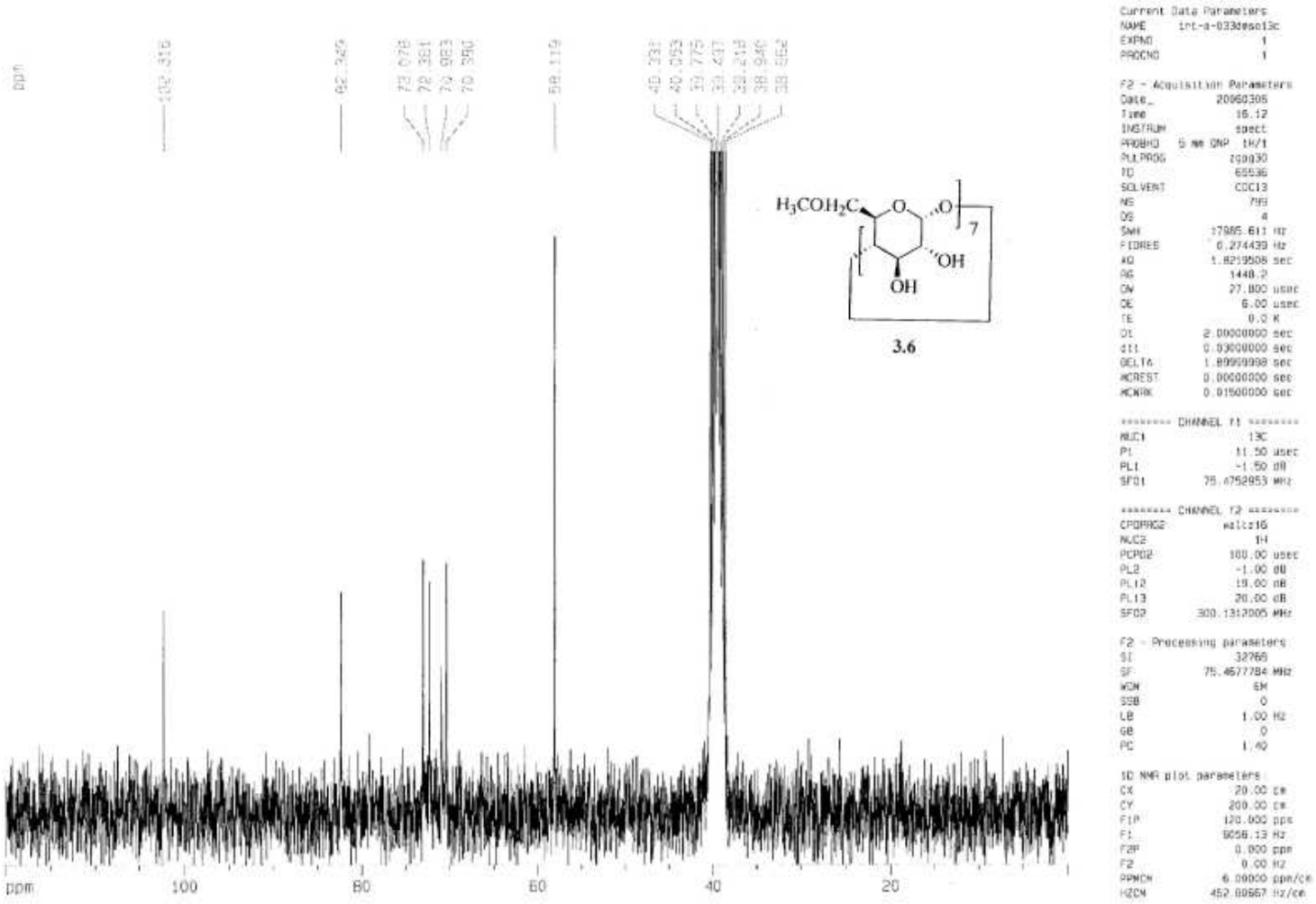
A.3.7. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.5**)



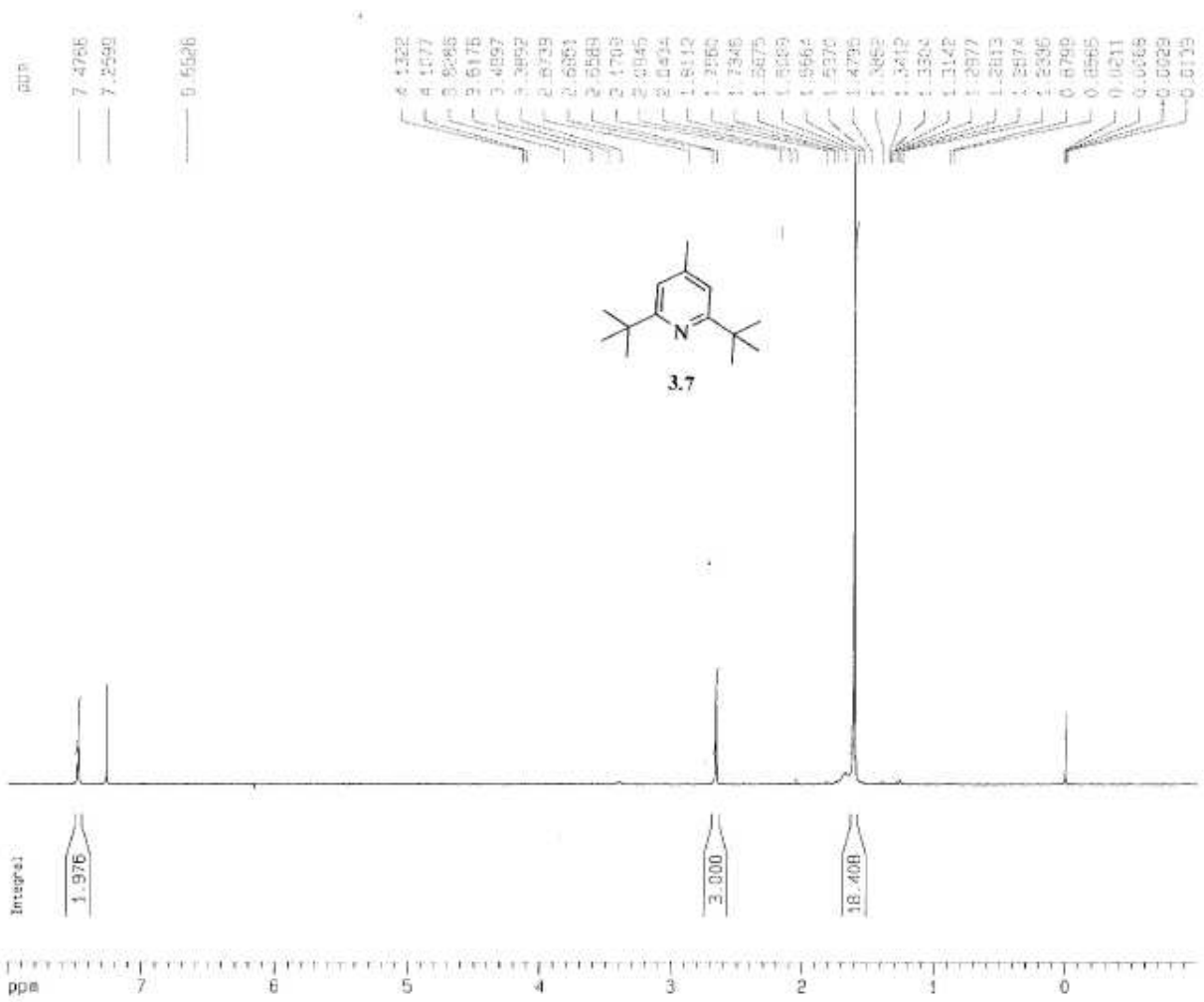
A.3.8. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.5**)



A.3.9. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.6**)

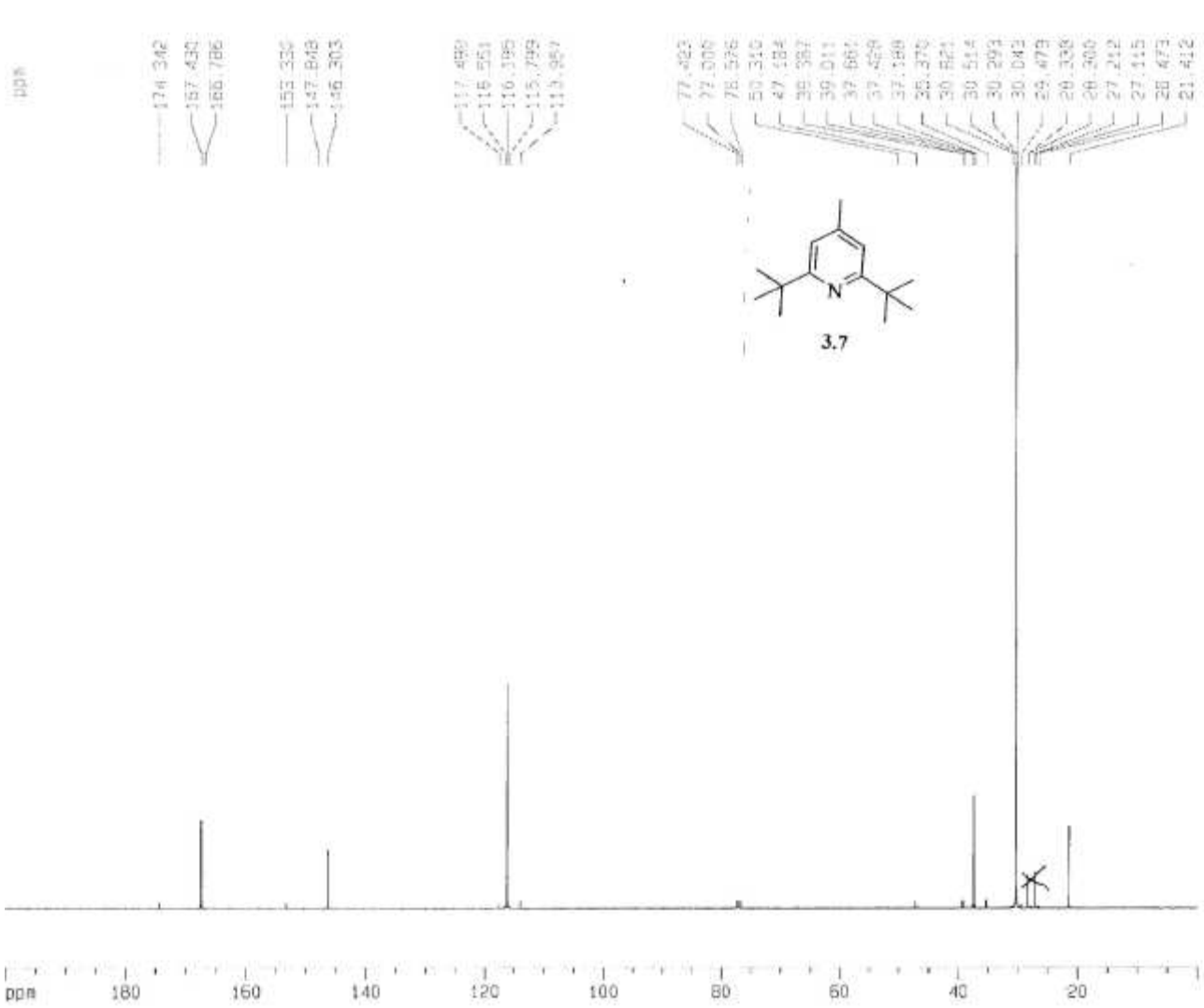


A.3.10. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.6**)



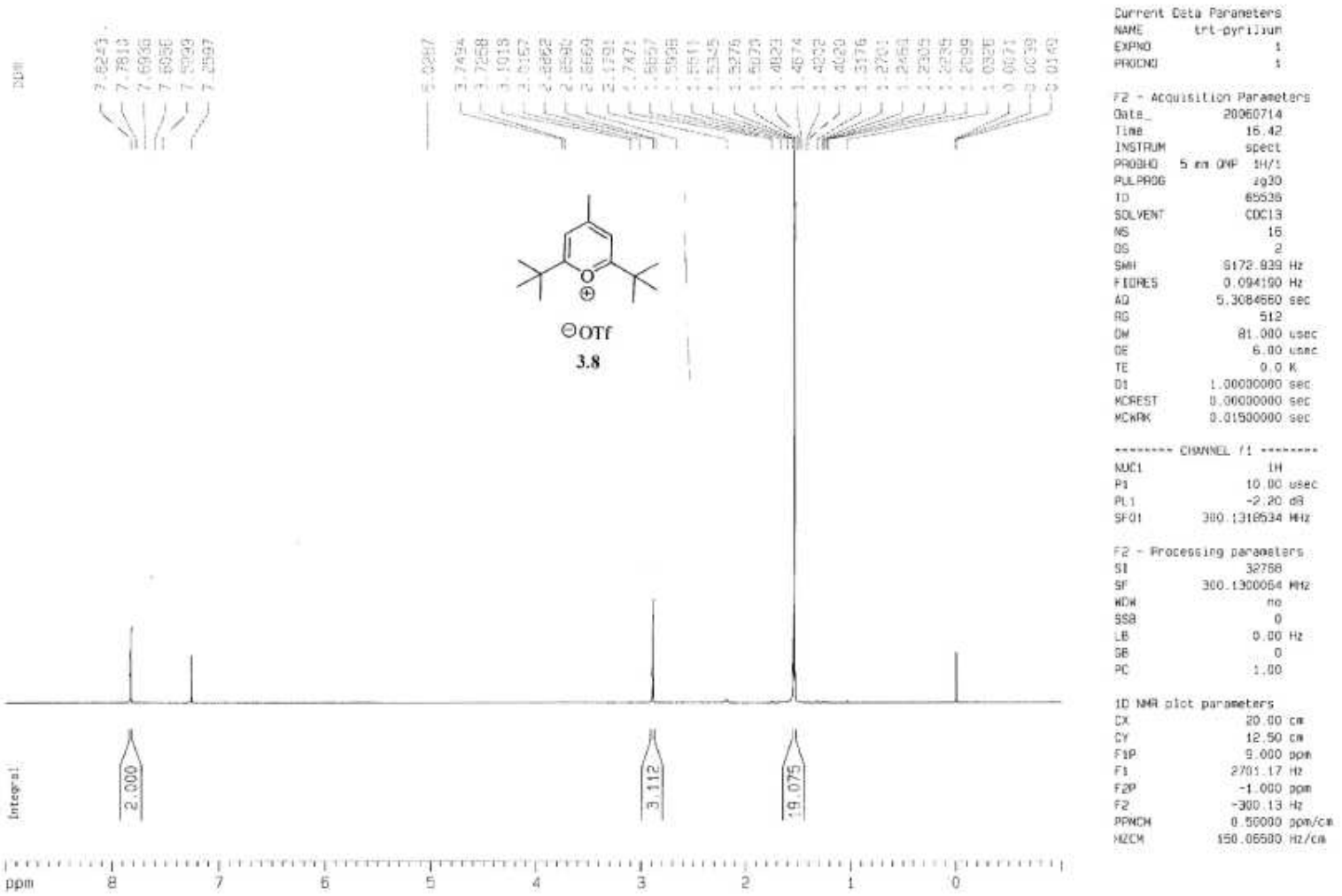

```
Current Data Parameters
NAME      trt-a-t-2-cdcl3
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20060803
Time              17.31
INSTRUM           spect
PROBHD   5 mm QNP 1H/1
PULPROG           zg30
TD               65536
SOLVENT           CDCl3
NS                  16
DS                   2
SWH            6172.839 Hz
FIDRES         0.094180 Hz
AQ             5.3084680 sec
RG               456.1
DW              81.000 usec
DE               6.00 usec
TE                0.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1               -2.20 dB
SFO1        300.1318534 MHz

F2 - Processing parameters
SI                32768
SF          300.1300064 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
CY                12.50 cm
F1P               8.000 ppm
F1                2401.04 Hz
F2P              -1.000 ppm
F2               -300.13 Hz
PPMCM             0.45000 ppm/cm
HZCM            135.05850 Hz/cm
```

A.311. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.7**)



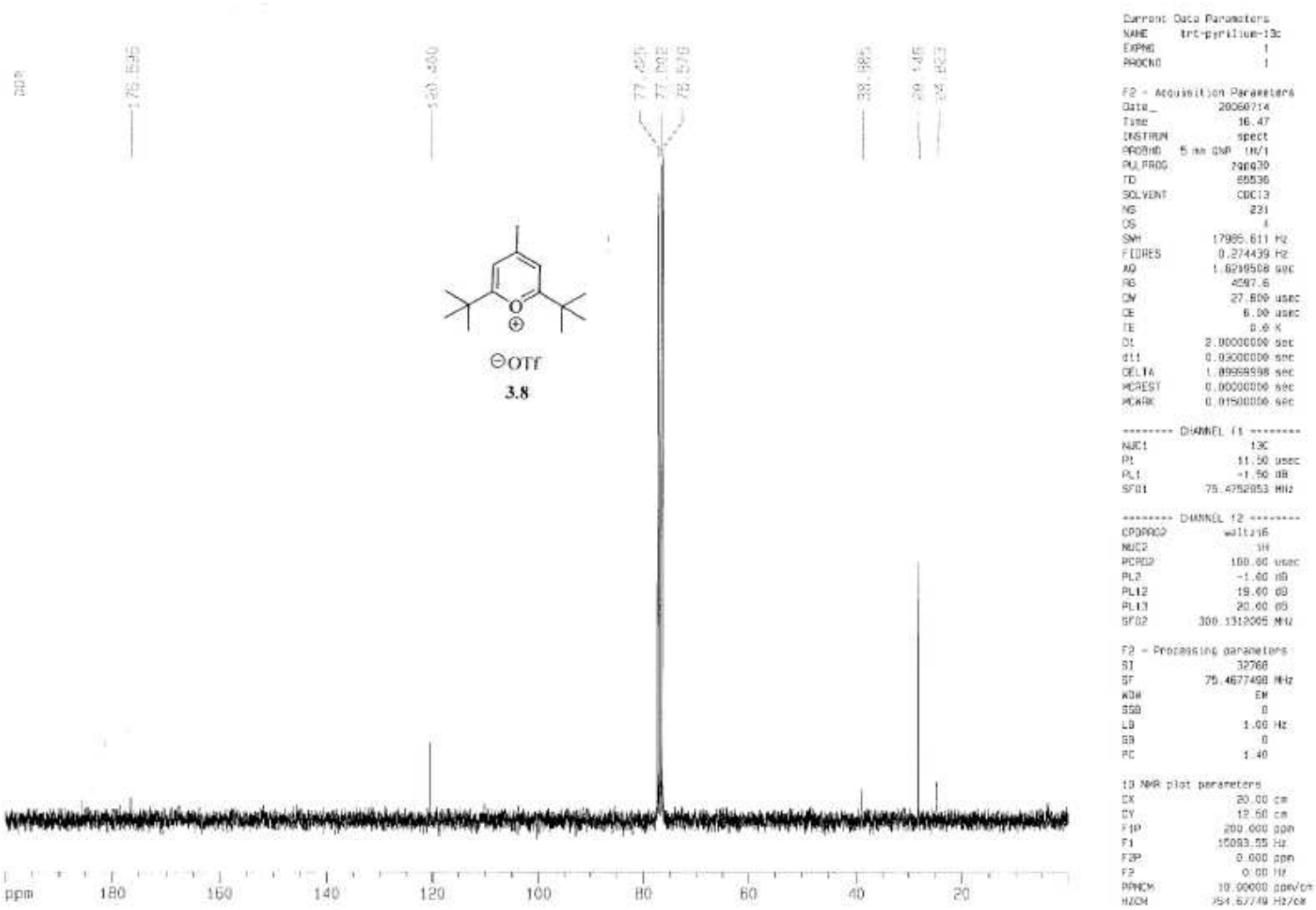

```
Current Data Parameters
NAME        trt-a-pyridine-13c
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20060719
Time                   9.44
INSTRUM                spect
PROBHD   5 mm QNP  1H/1
PULPROG                zgpg30
TD                      65536
SOLVENT                CDCl3
NS                         90
DS                          4
SWH               17985.611 Hz
FIDRES             0.274439 Hz
AQ                 1.8219508 sec
RG                    3649.1
DW                   27.800 usec
DE                    6.00 usec
TE                     0.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                      11.50 usec
PL1                     -1.50 dB
SF01              75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                  100.00 usec
PL2                     -1.00 dB
PL12                    19.00 dB
PL13                    20.00 dB
SF02             300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                75.4677641 MHz
WDW                           EM
SSB                            0
LB                      1.00 Hz
GB                             0
PC                          1.40

1D NMR plot parameters
CX                     20.00 cm
CY                     12.50 cm
F1P                  200.000 ppm
F1                  15093.55 Hz
F2P                    0.000 ppm
F2                     0.00 Hz
PPMCM                10.00000 ppm/cm
HZCM                754.67767 Hz/cm
```

A.3.12. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.7**)



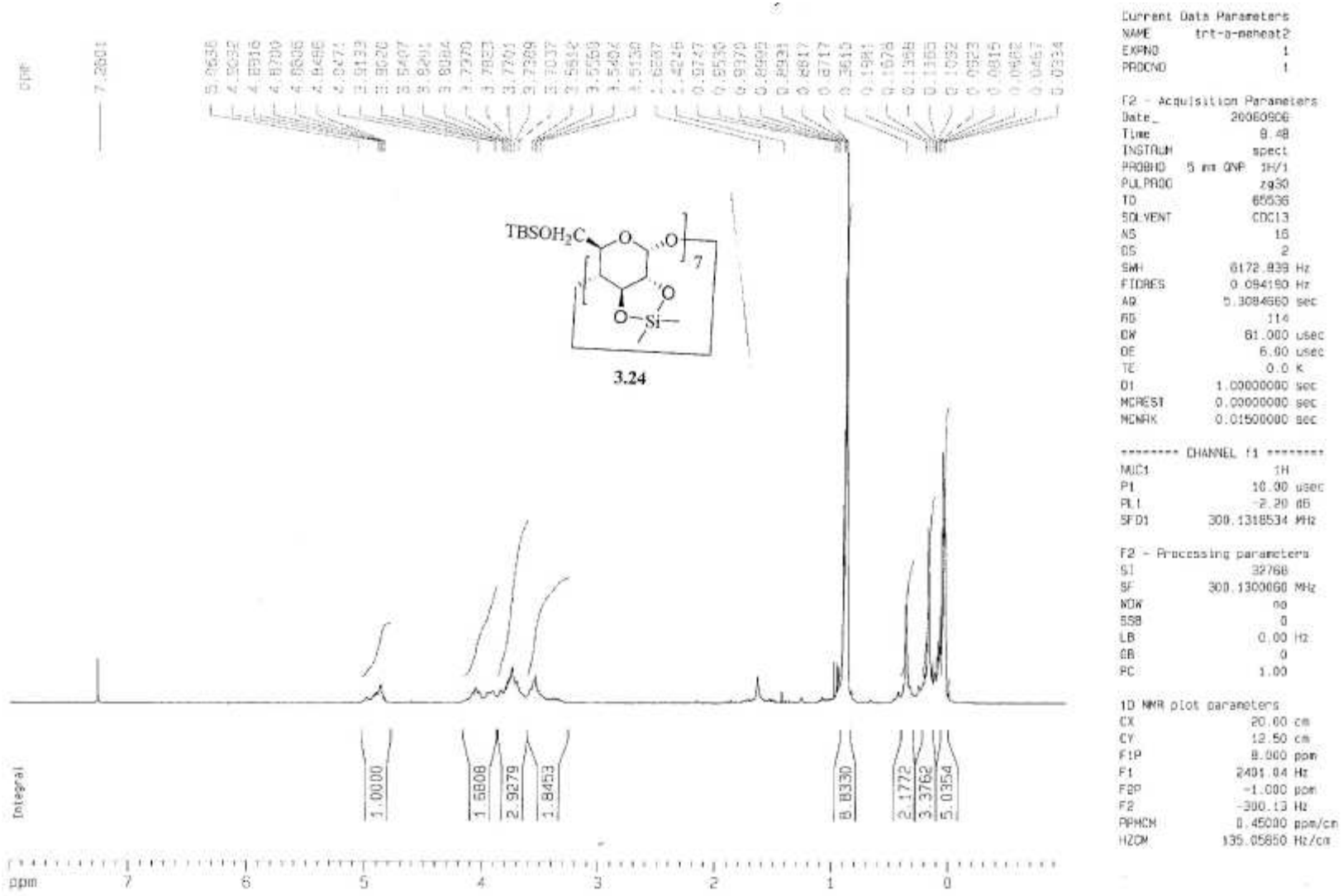

```
Current Data Parameters
NAME        trt-pyrilium
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20060714
Time               16.42
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG            zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           6172.839 Hz
FIDRES        0.094190 Hz
AQ            5.3084660 sec
RG                   512
DW              81.000 usec
DE               6.00 usec
TE                0.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

-------- CHANNEL f1 --------
NUC1                1H
P1                10.00 usec
PL1              -2.20 dB
SFO1        300.1318534 MHz

F2 - Processing parameters
SI                 32768
SF          300.1300064 MHz
WDW                   no
SSB                    0
LB                0.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                20.00 cm
CY                12.50 cm
F1P               9.000 ppm
F1              2701.17 Hz
F2P              -1.000 ppm
F2              -300.13 Hz
PPMCM             0.50000 ppm/cm
HZCM            150.06580 Hz/cm
```

A.3.13. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.8**)



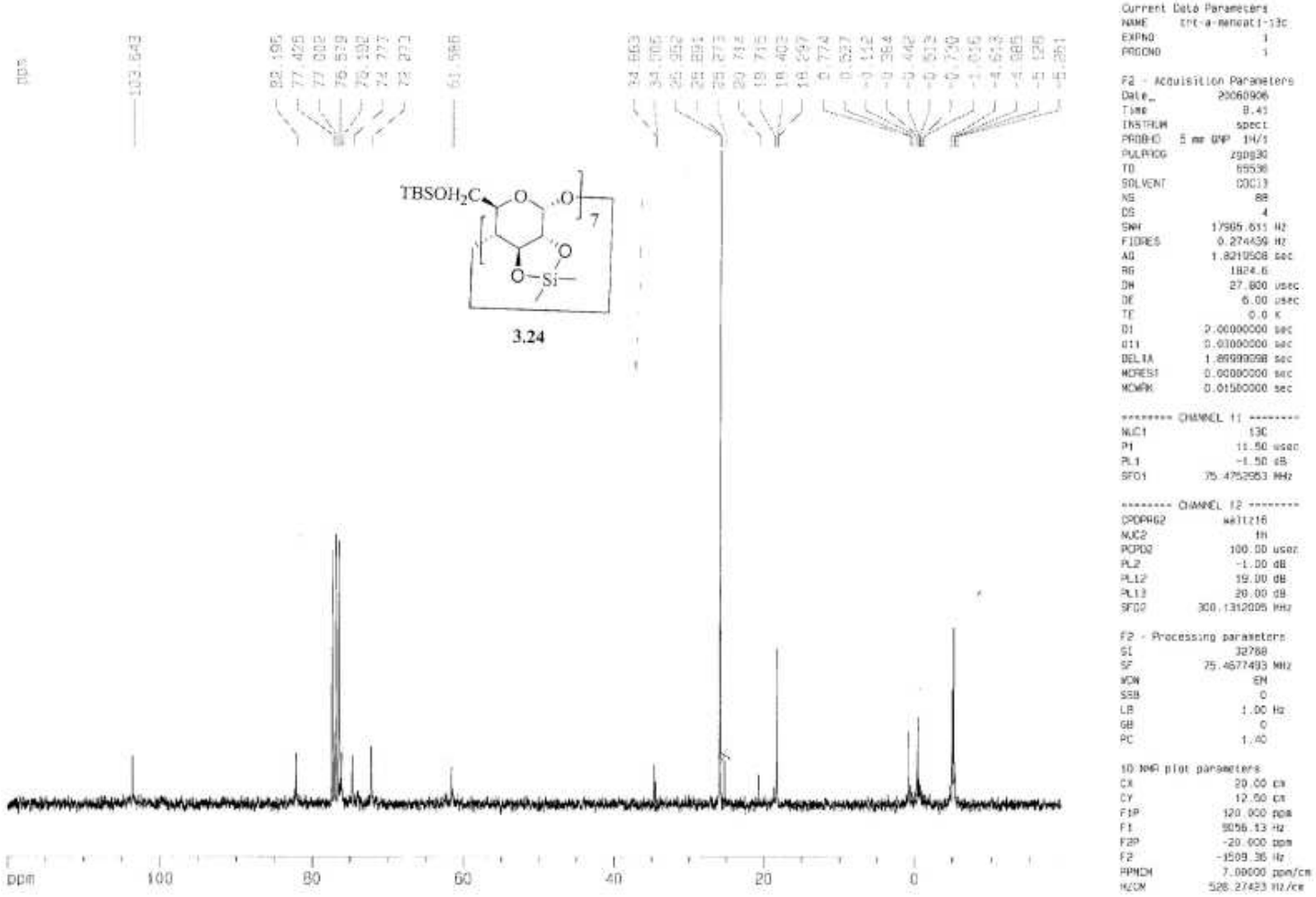

```
Current Data Parameters
NAME      trt-pyrilium-13c
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20060714
Time               16.47
INSTRUM             spect
PROBHD   5 mm QNP  1H/1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  231
DS                    4
SWH           17985.611 Hz
FIDRES        0.274439 Hz
AQ            1.8218508 sec
RG                4597.6
DW               27.800 usec
DE                6.00 usec
TE                 0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

-------- CHANNEL f1 --------
NUC1                  13C
P1                 11.50 usec
PL1                -1.50 dB
SF01          75.4752053 MHz

-------- CHANNEL f2 --------
CPDPRG2           waltz16
NUC2                   1H
PCPD2             100.00 usec
PL2                -1.00 dB
PL12               19.60 dB
PL13               20.00 dB
SF02         300.1312005 MHz

F2 - Processing parameters
SI                 32768
SF            75.4677498 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
CY                 12.50 cm
F1P              200.000 ppm
F1               15083.55 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM             10.00000 ppm/cm
HZCM           754.67749 Hz/cm
```

A.3.14. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.8**)

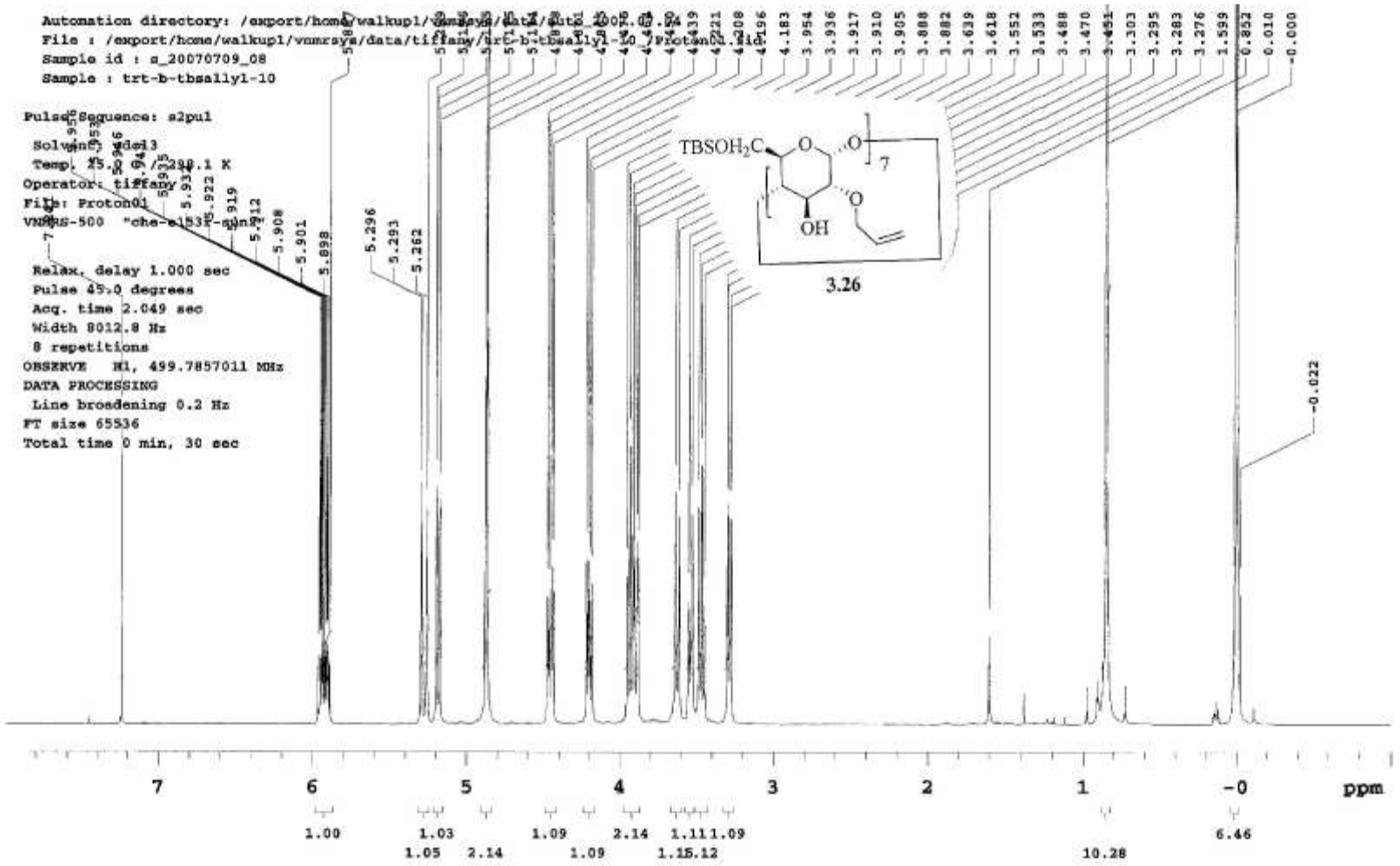



```
Current Data Parameters
NAME        trt-a-meheat2
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20060906
Time                 8.48
INSTRUM             spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH              6172.839 Hz
FIDRES           0.094150 Hz
AQ               5.3084660 sec
RG                   114
DW                81.000 usec
DE                 6.00 usec
TE                  0.0 K
D1               1.00000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                 -2.20 dB
SFO1         300.1318534 MHz

F2 - Processing parameters
SI                  32768
SF           300.1300060 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  12.50 cm
F1P                 8.000 ppm
F1                2401.04 Hz
F2P                -1.000 ppm
F2                 -300.13 Hz
PPMCM             0.45000 ppm/cm
HZCM            135.05850 Hz/cm
```

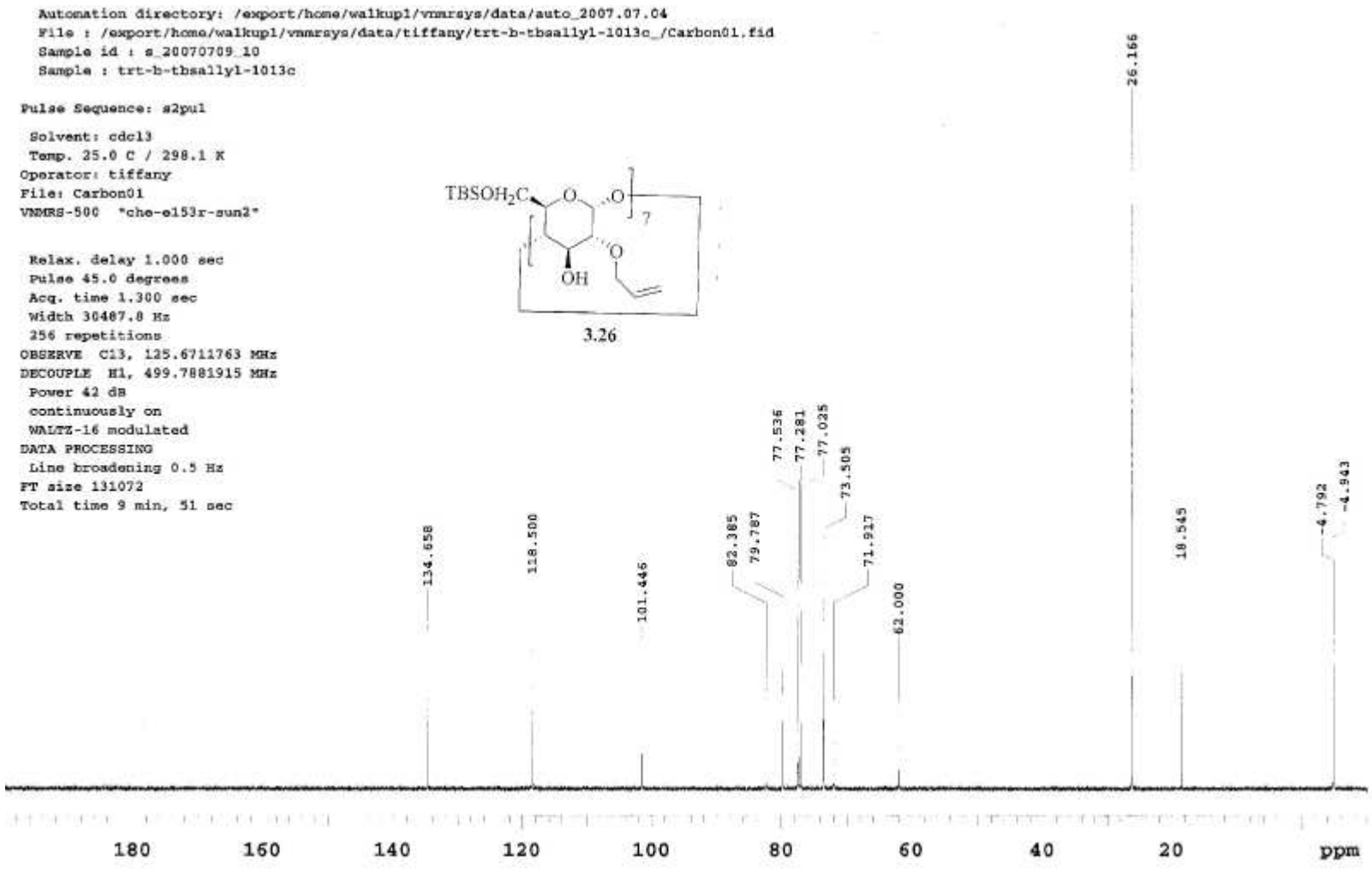
A.3.15. ^{1}H NMR ($CDCl_3$, 300 MHz) of Compound (**3.24**)



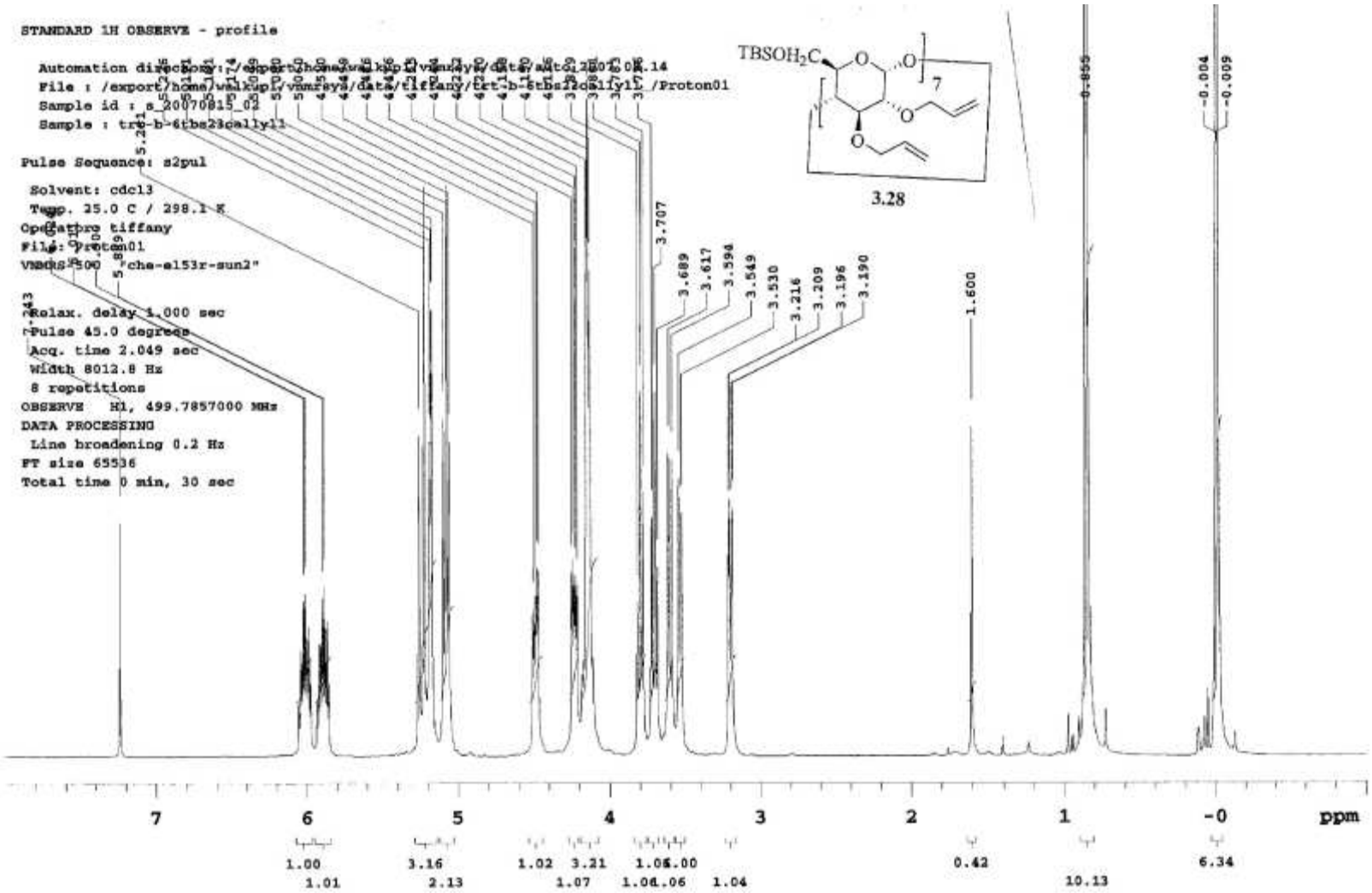
A.3.16. ^{1}C NMR ($CDCl_3$, 75 MHz) of Compound (**3.24**)



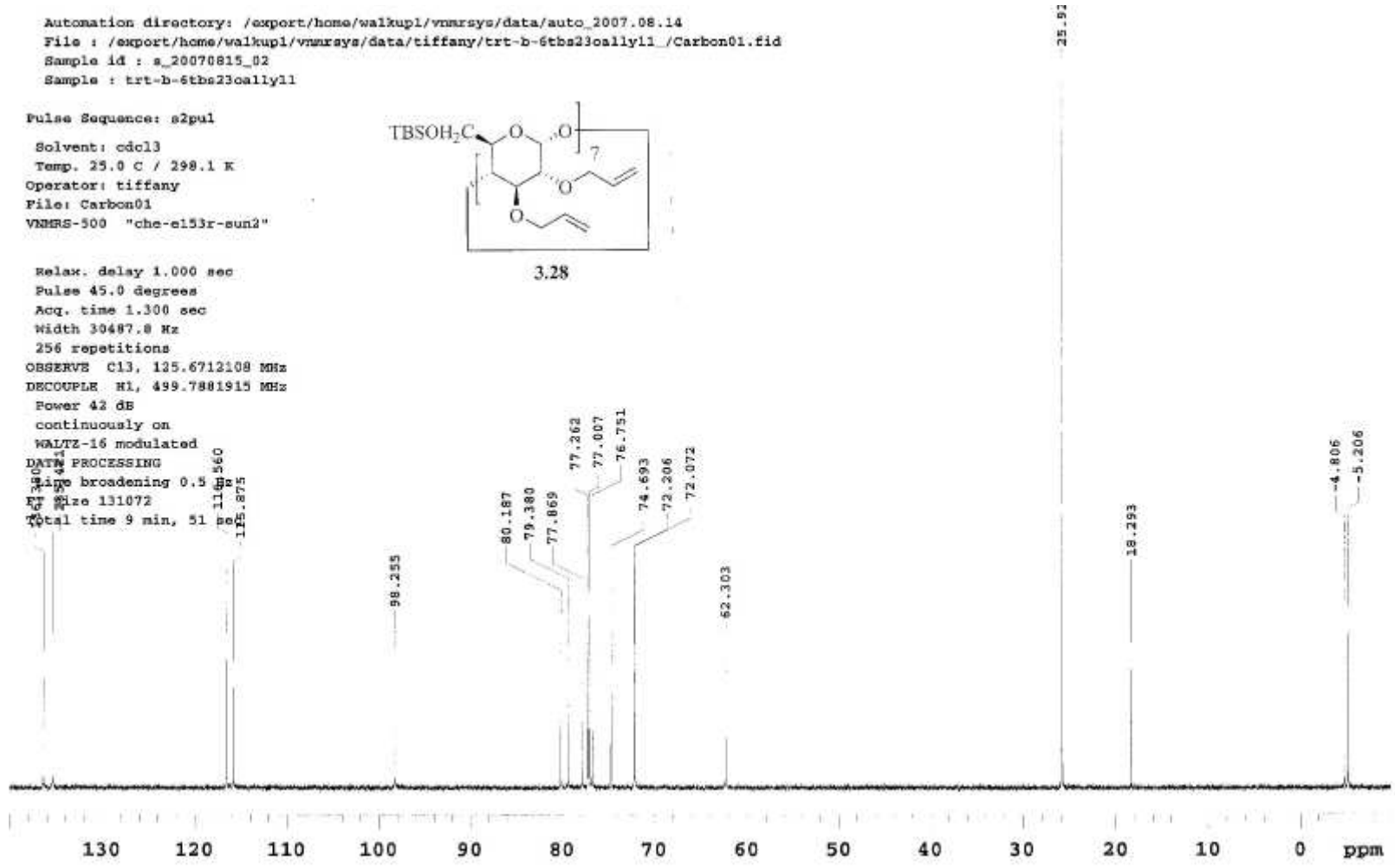
A.3.17. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**3.26**)



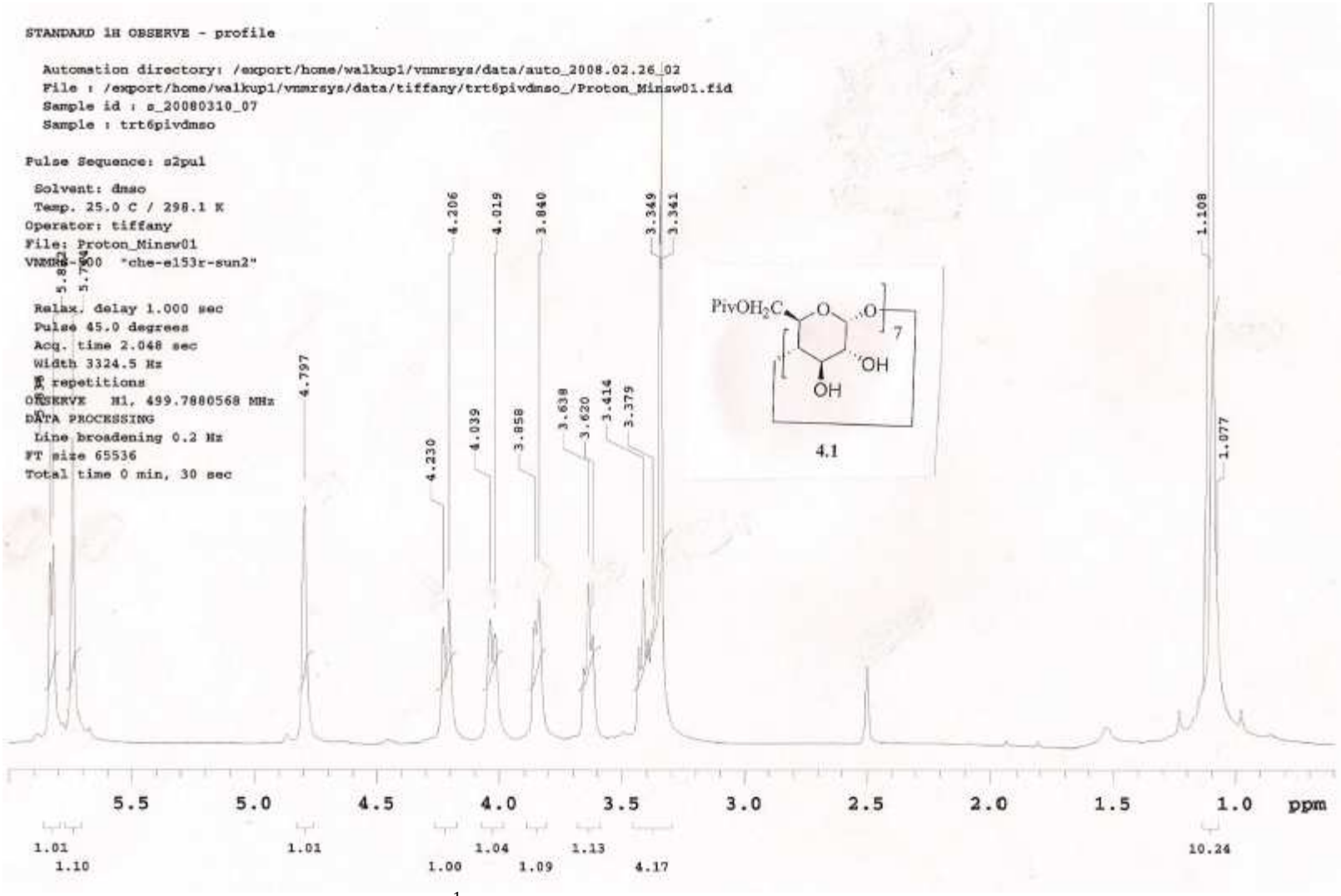
A.3.18. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**3.26**)



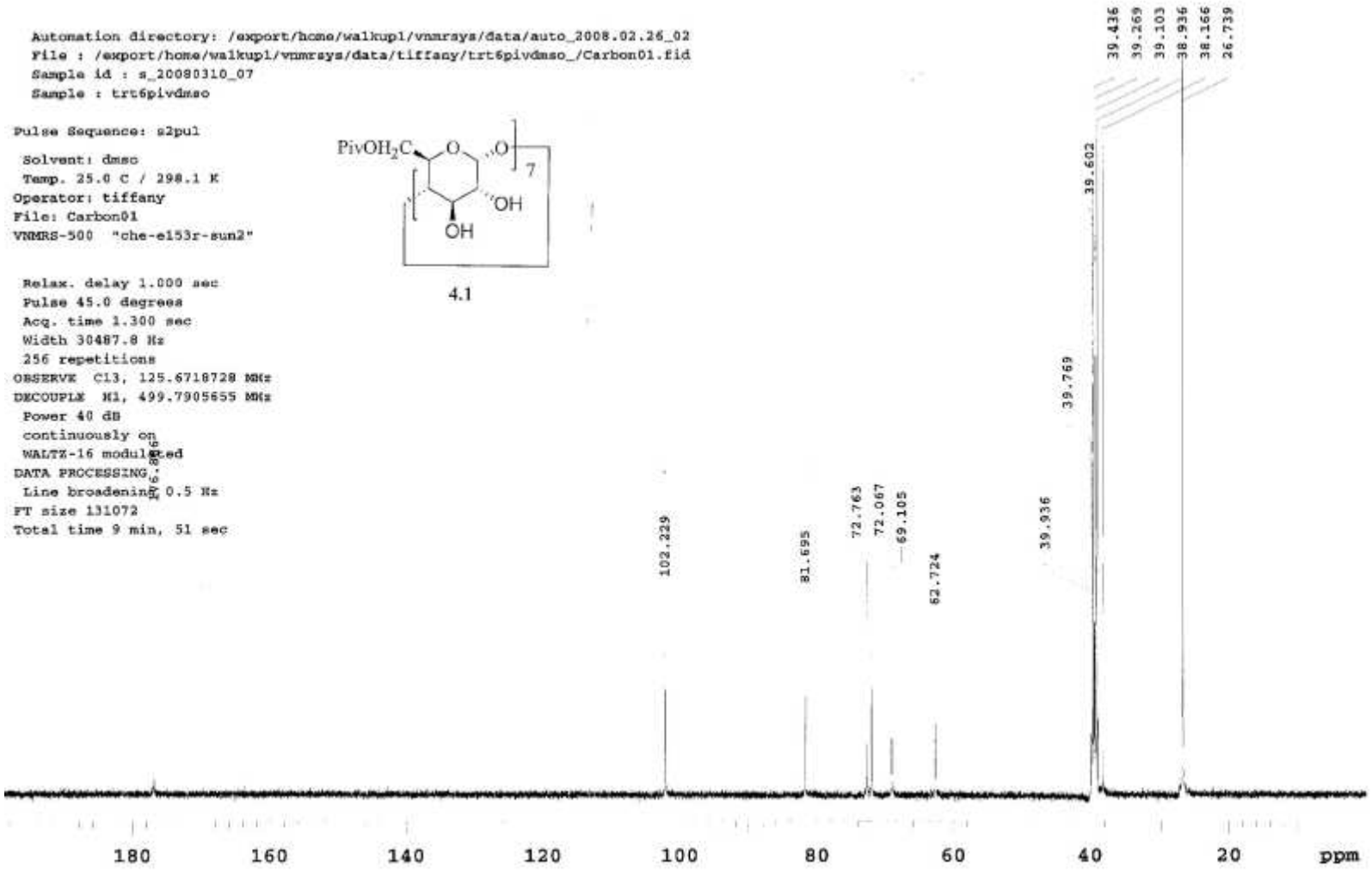
A.3.19. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**3.28**)



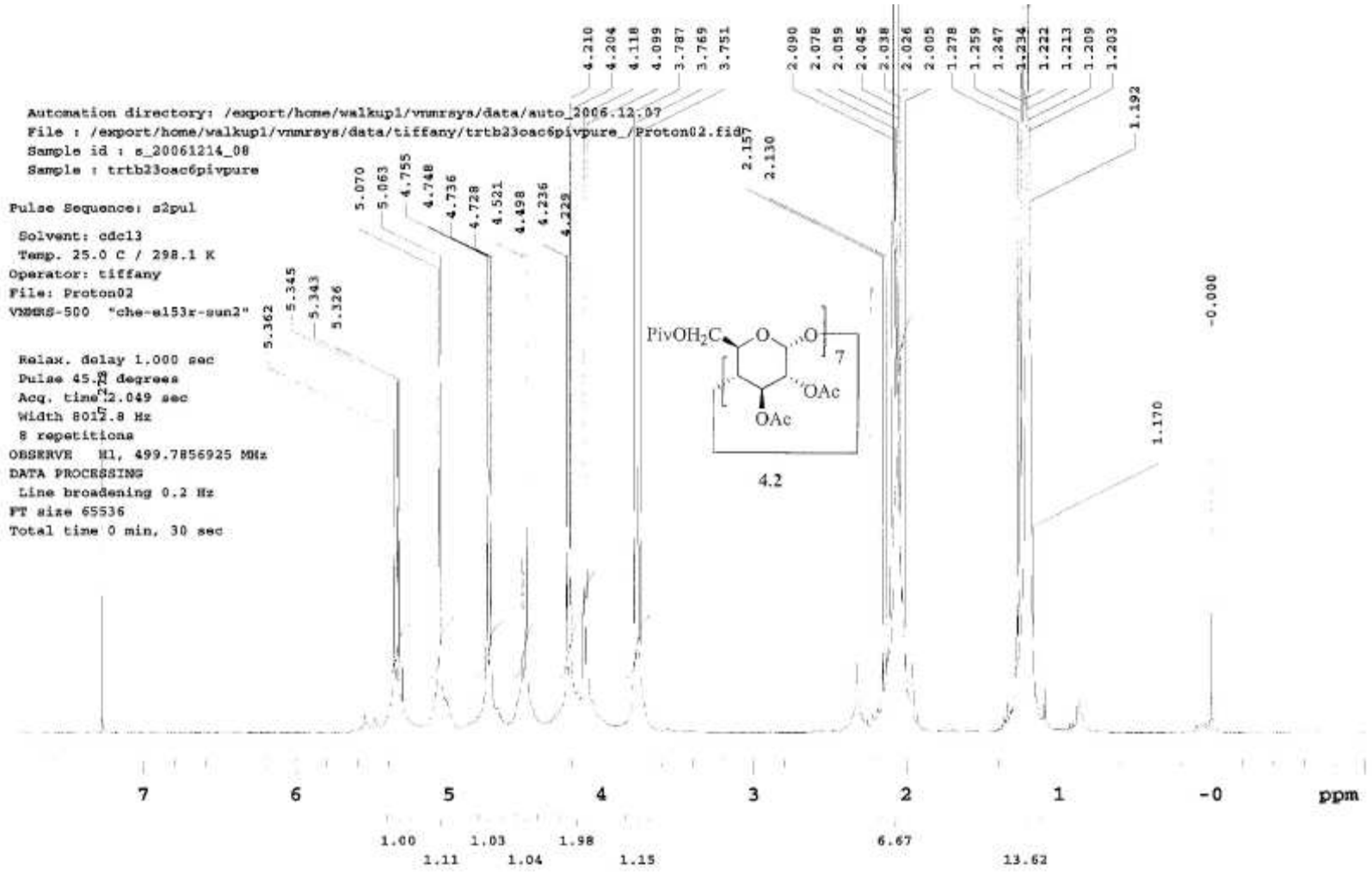
A.3.20. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**3.28**)



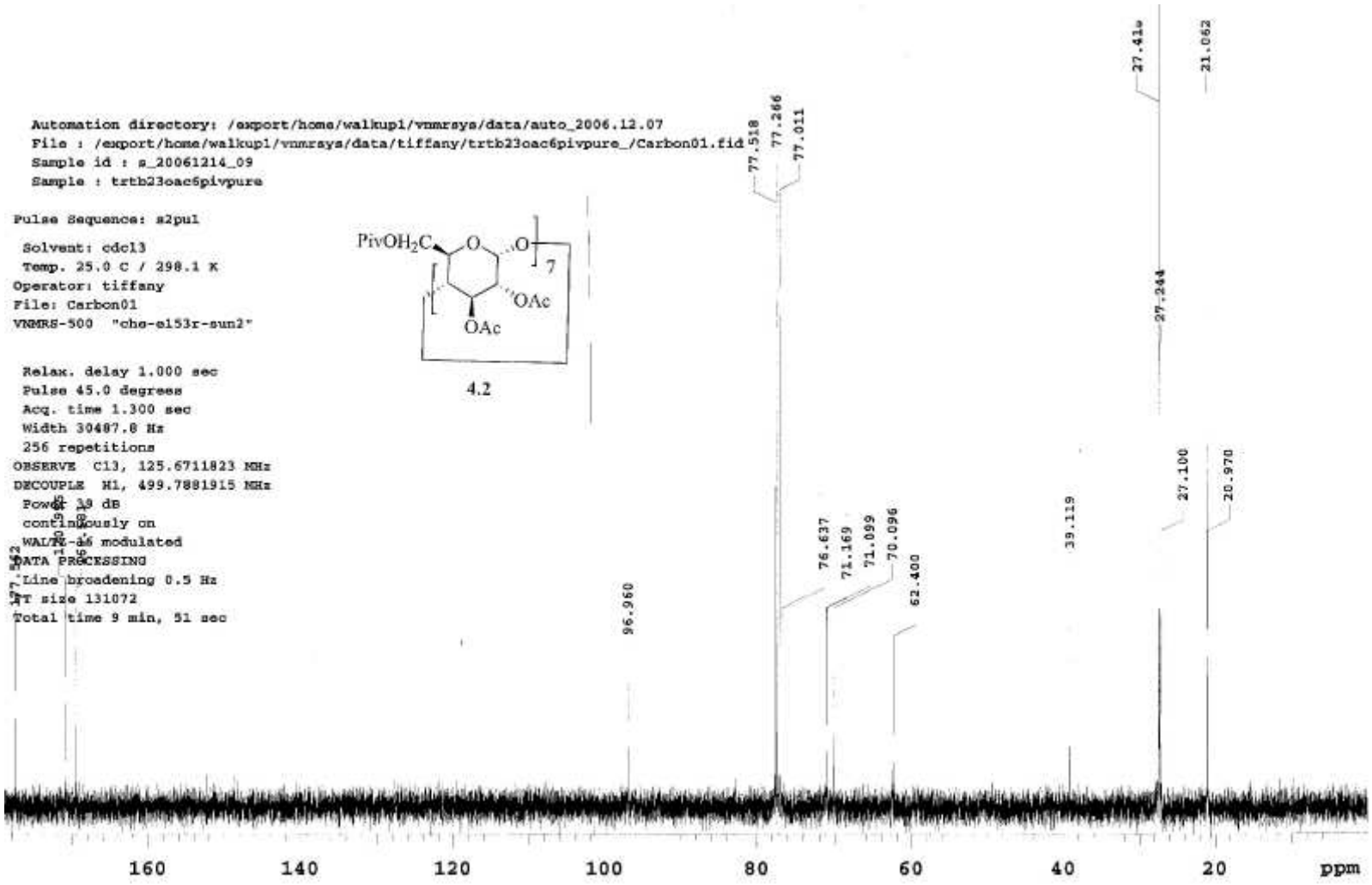
A.4.1. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.1**)



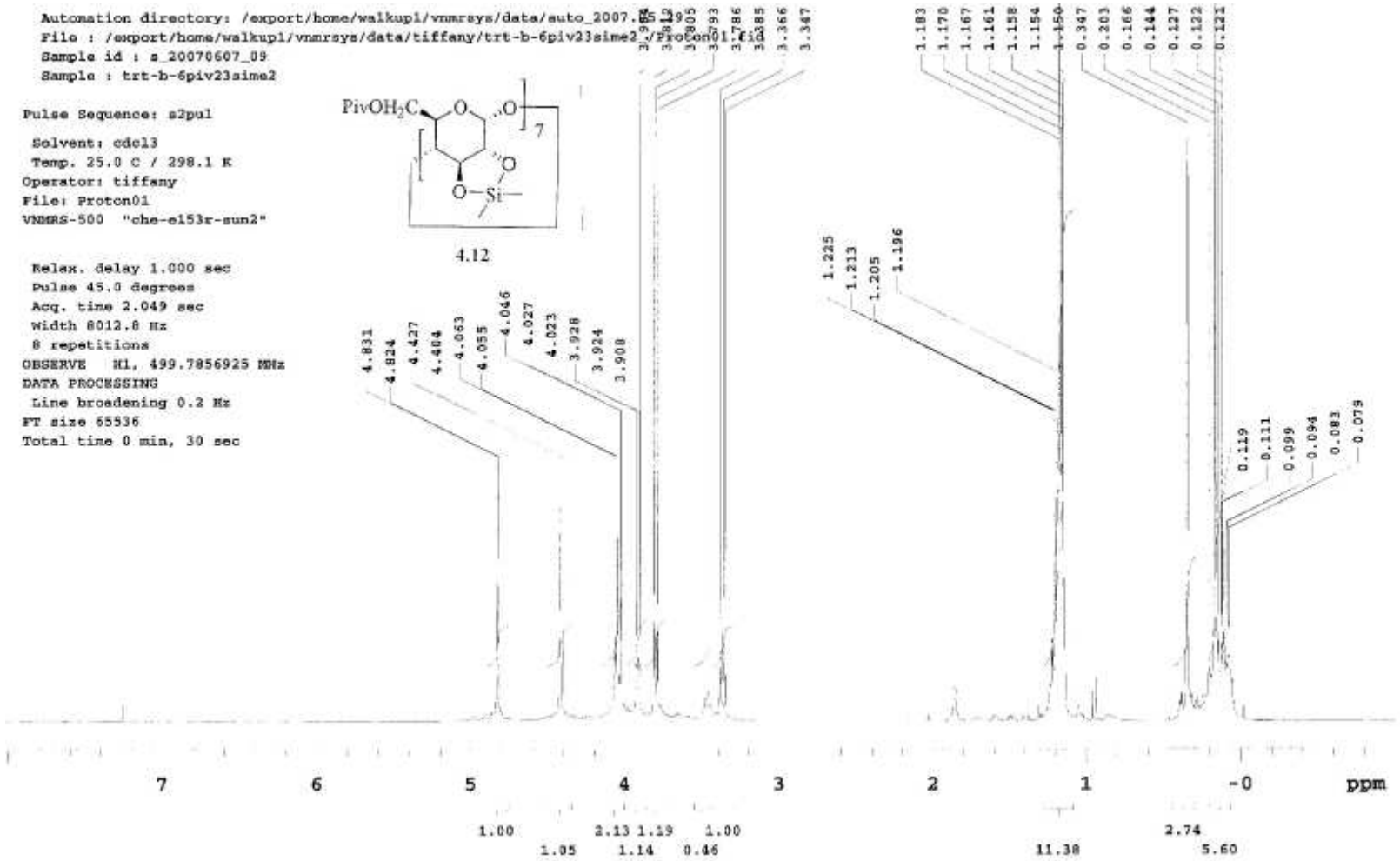
A.4.2. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.1**)



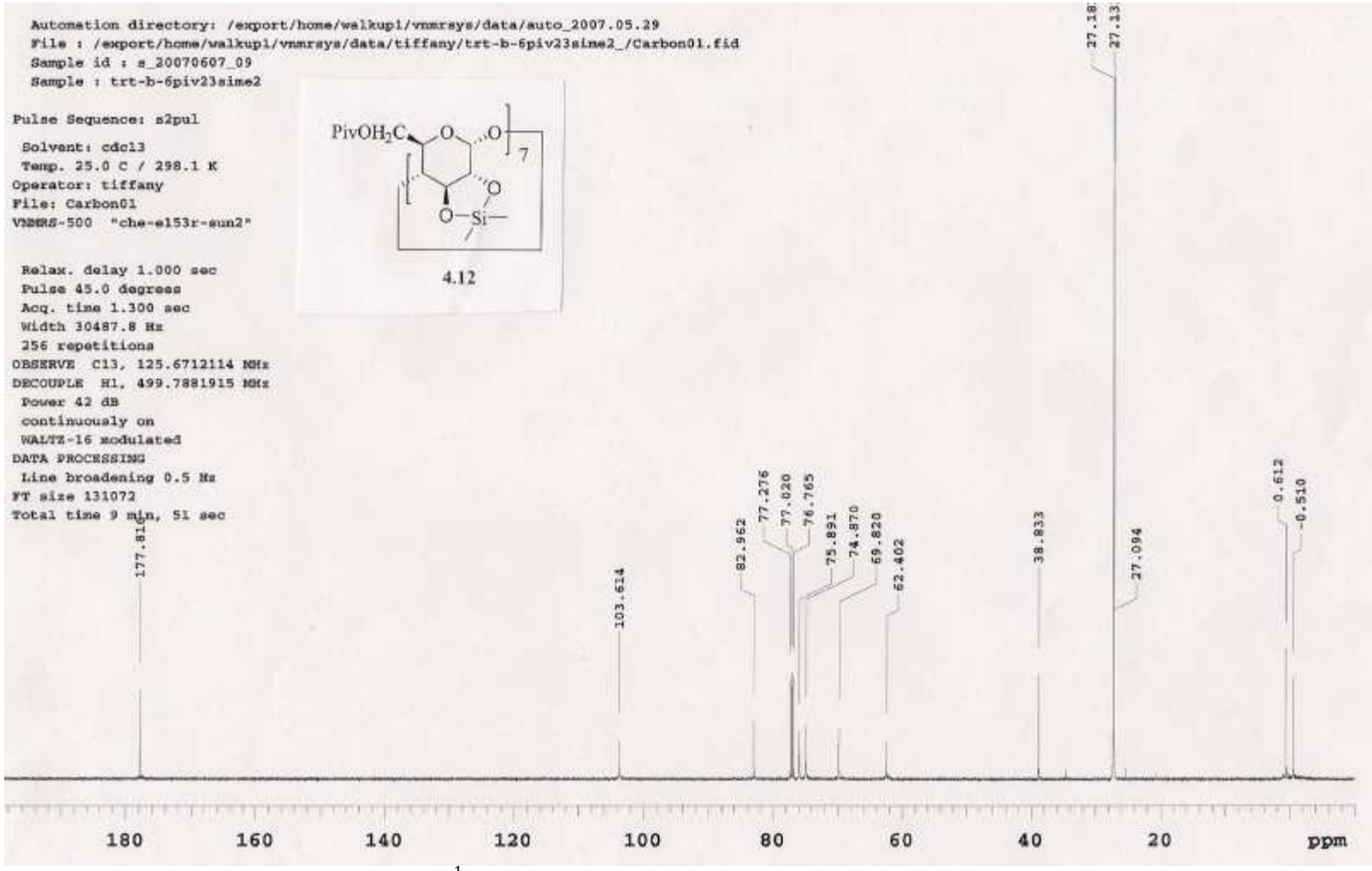
A.4.3. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.2**)



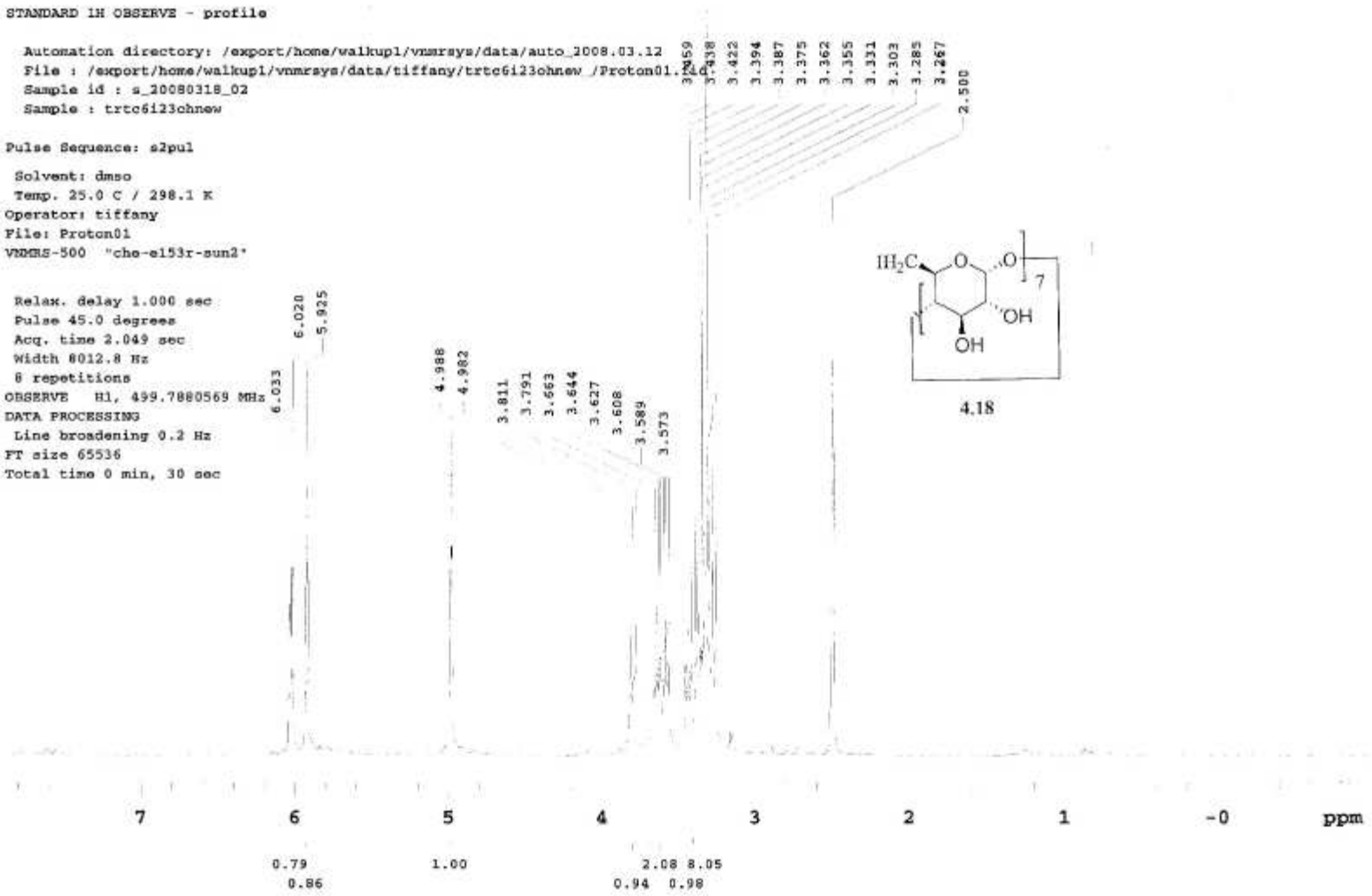
A.4.4. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.2**)



A.4.5. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.12**)

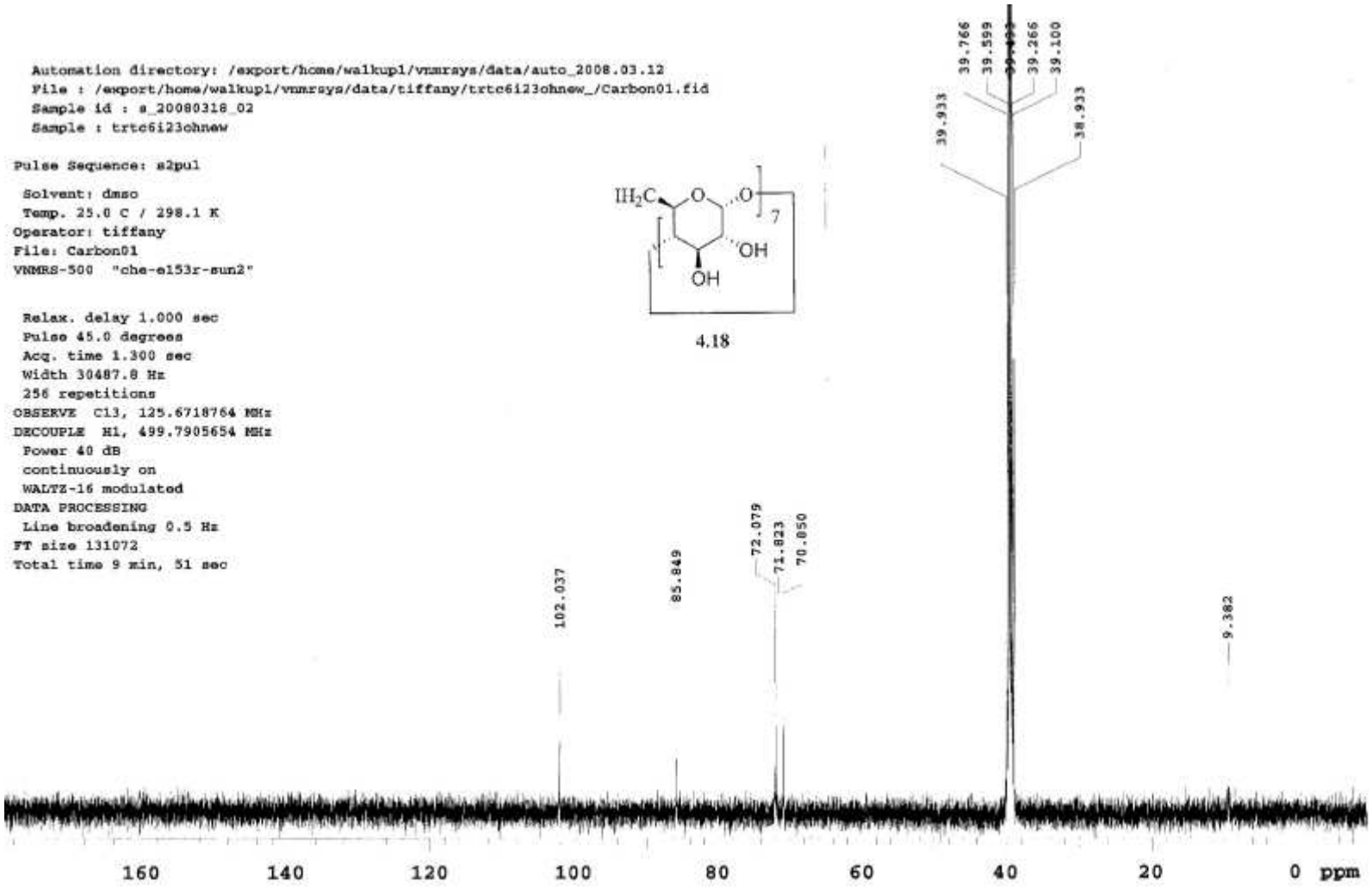


A.4.6. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.12**)

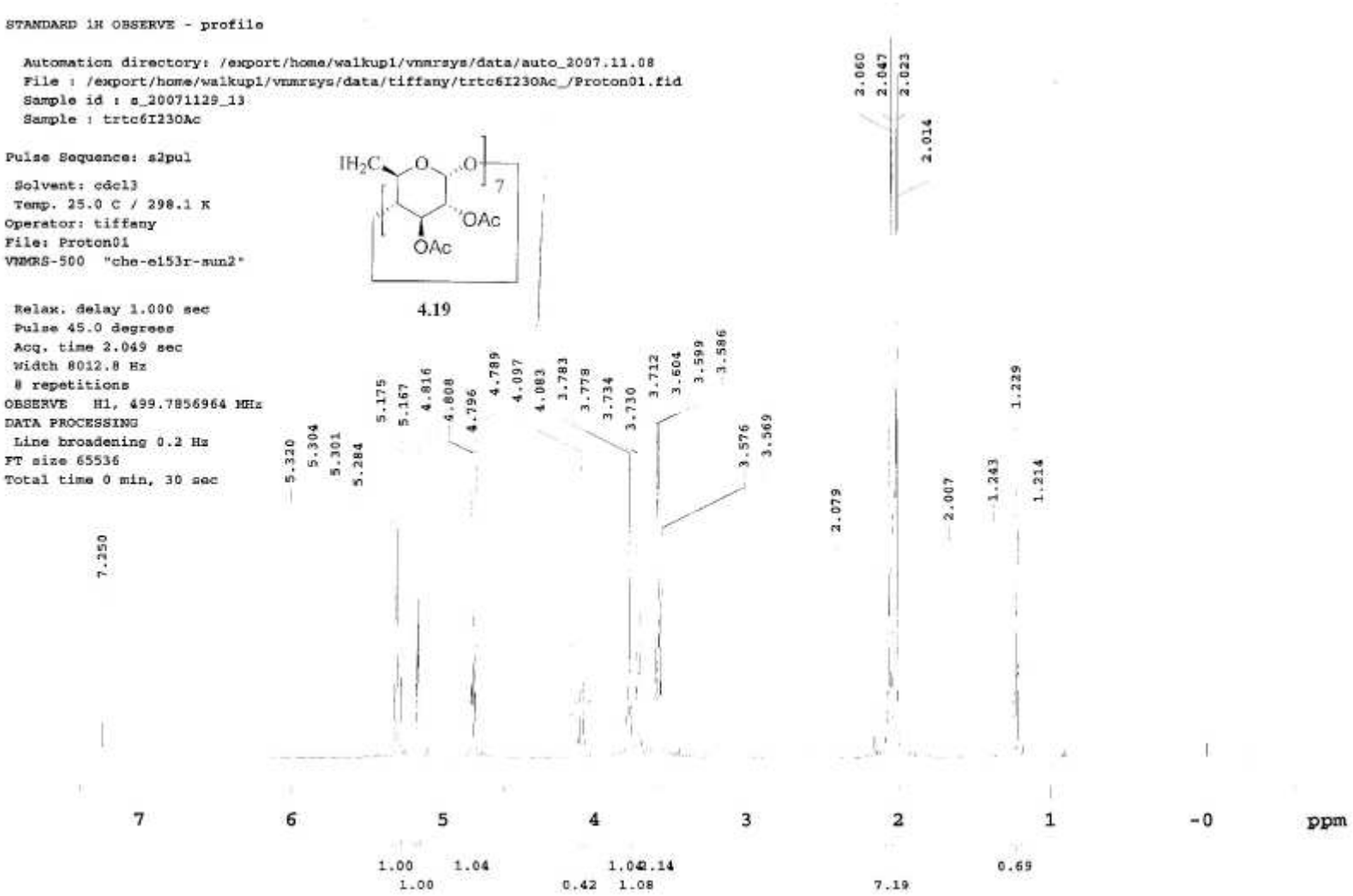


4.18

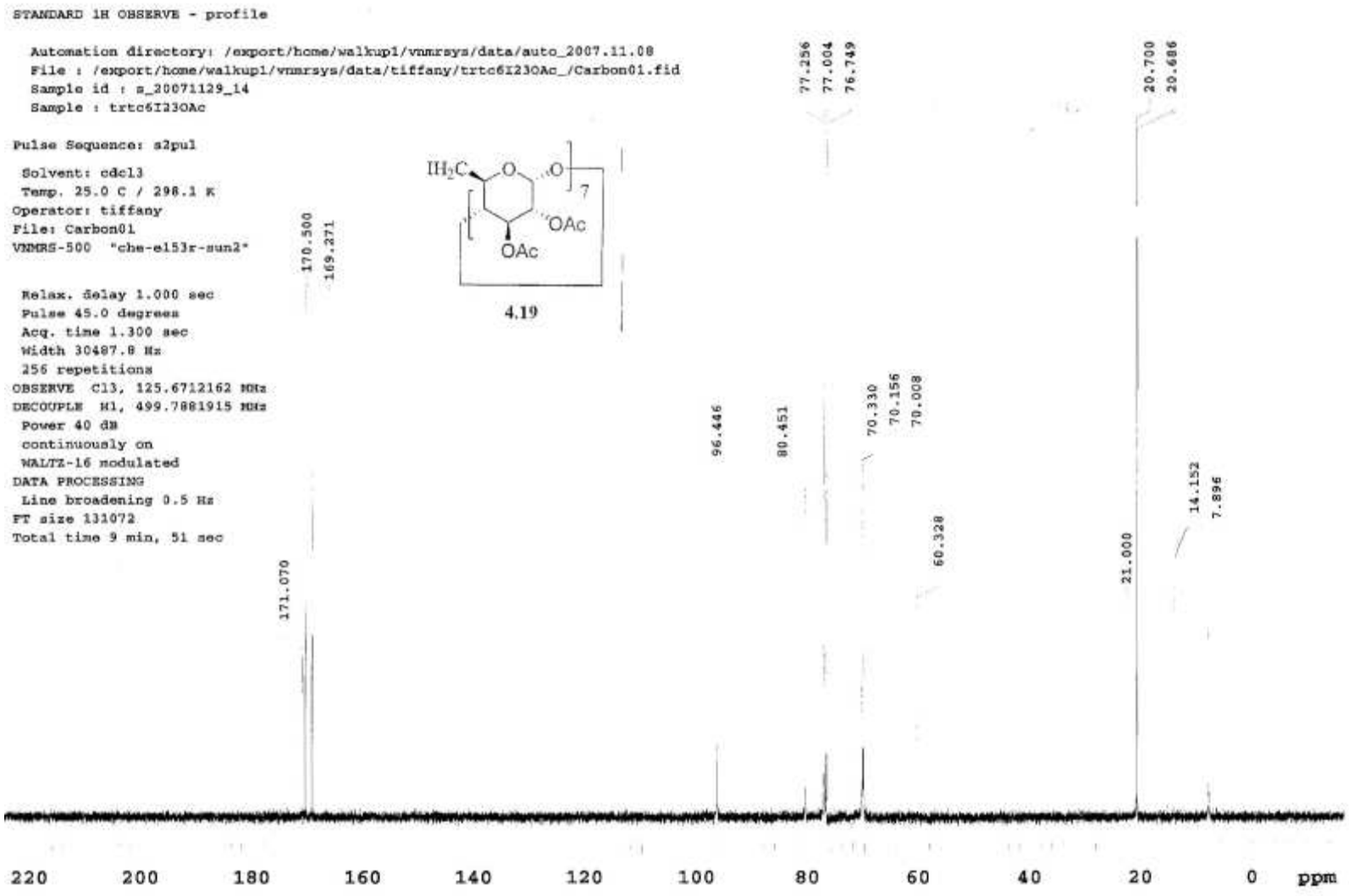
A.4.7. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.18**)



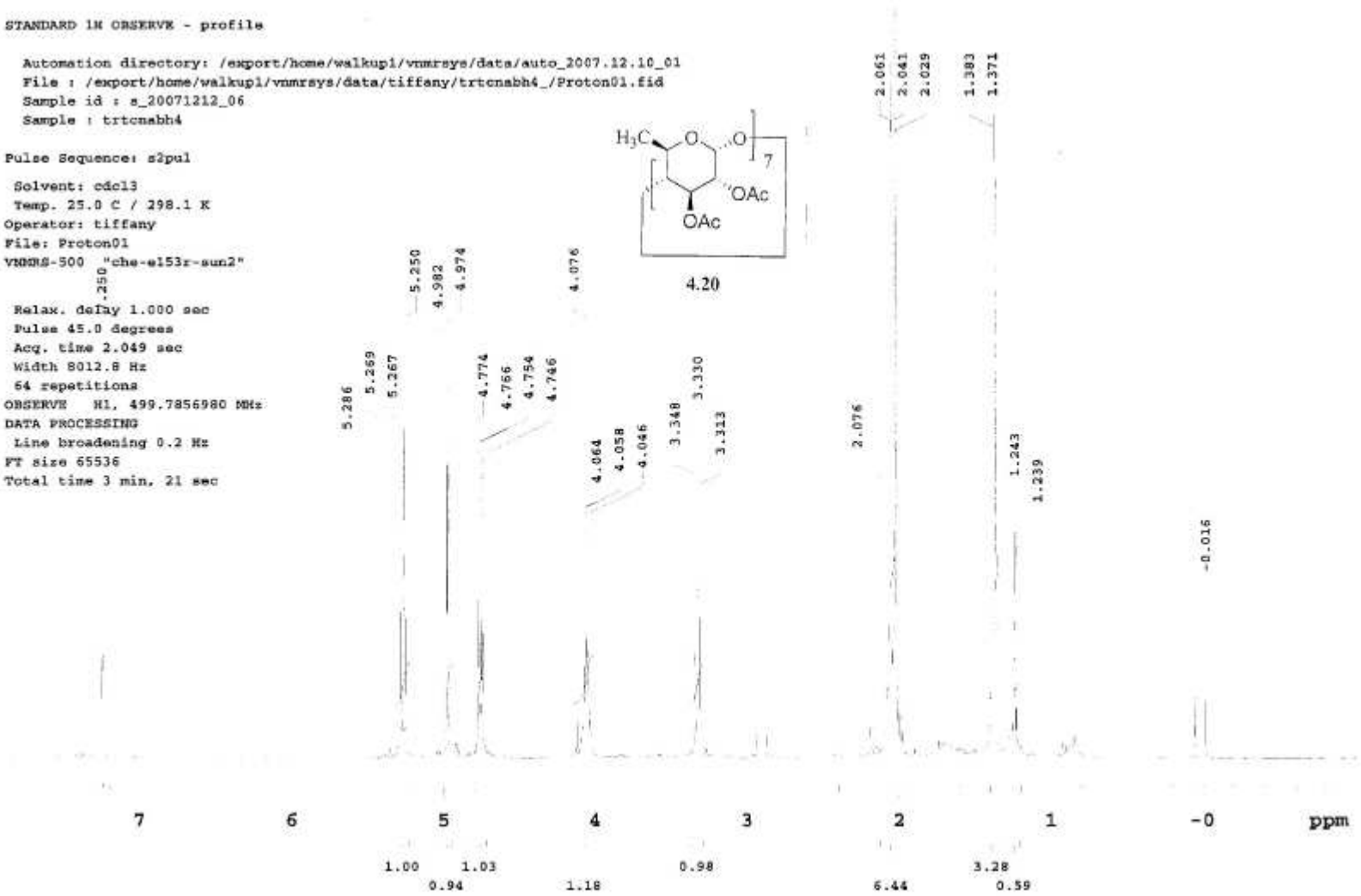
A.4.8. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.18**)



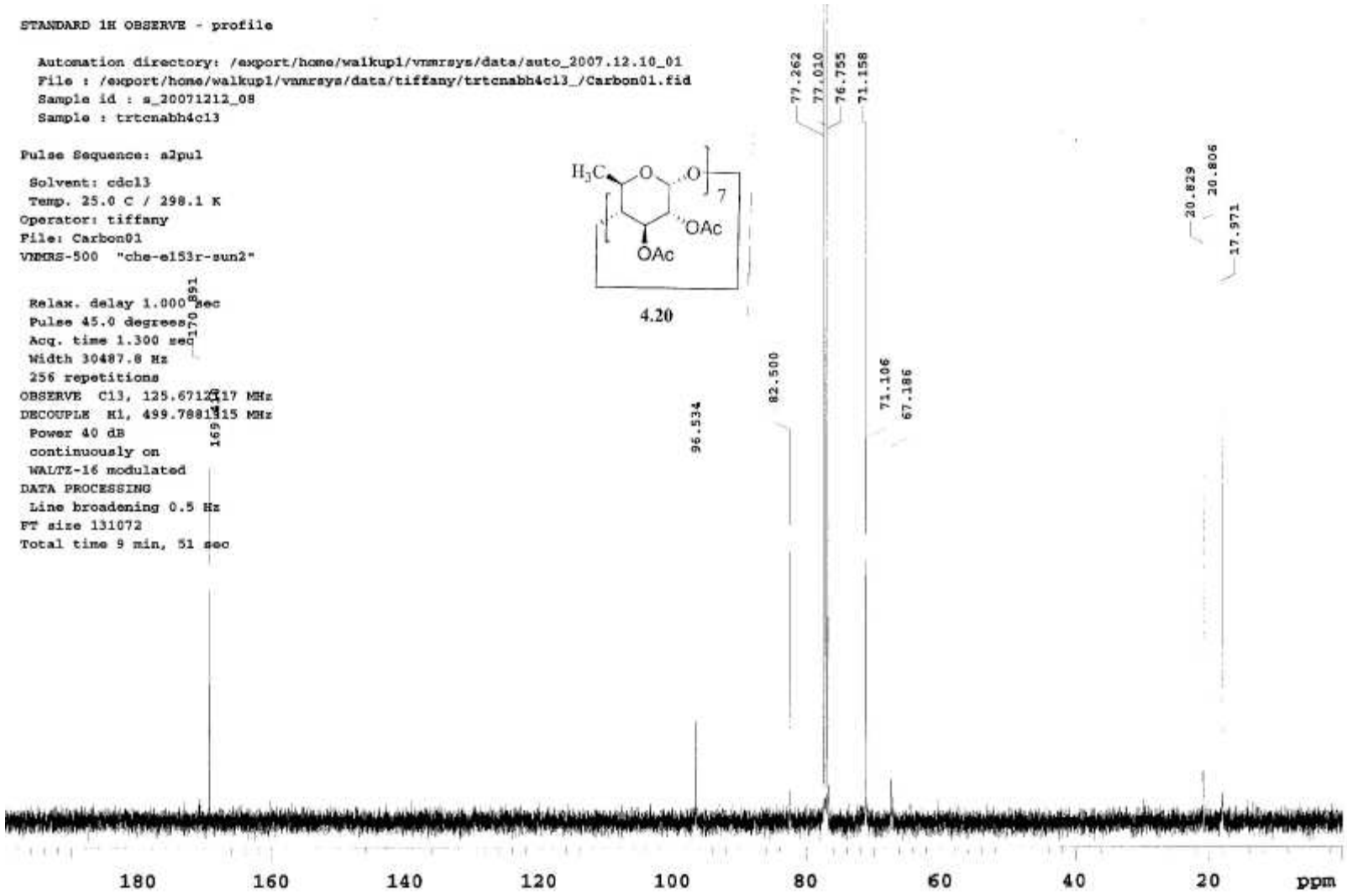
A.4.9. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.19**)



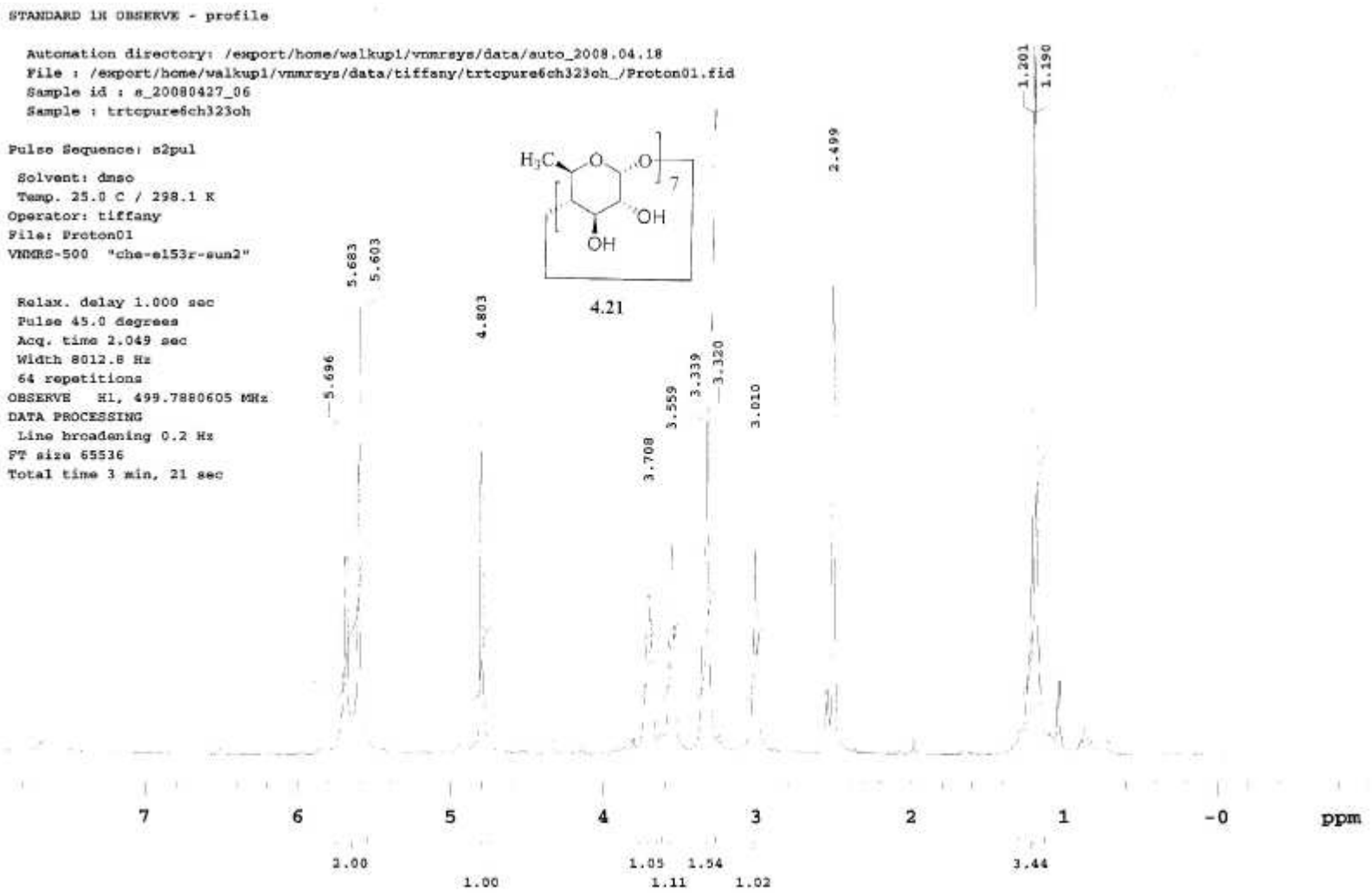
A.4.10. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.19**)



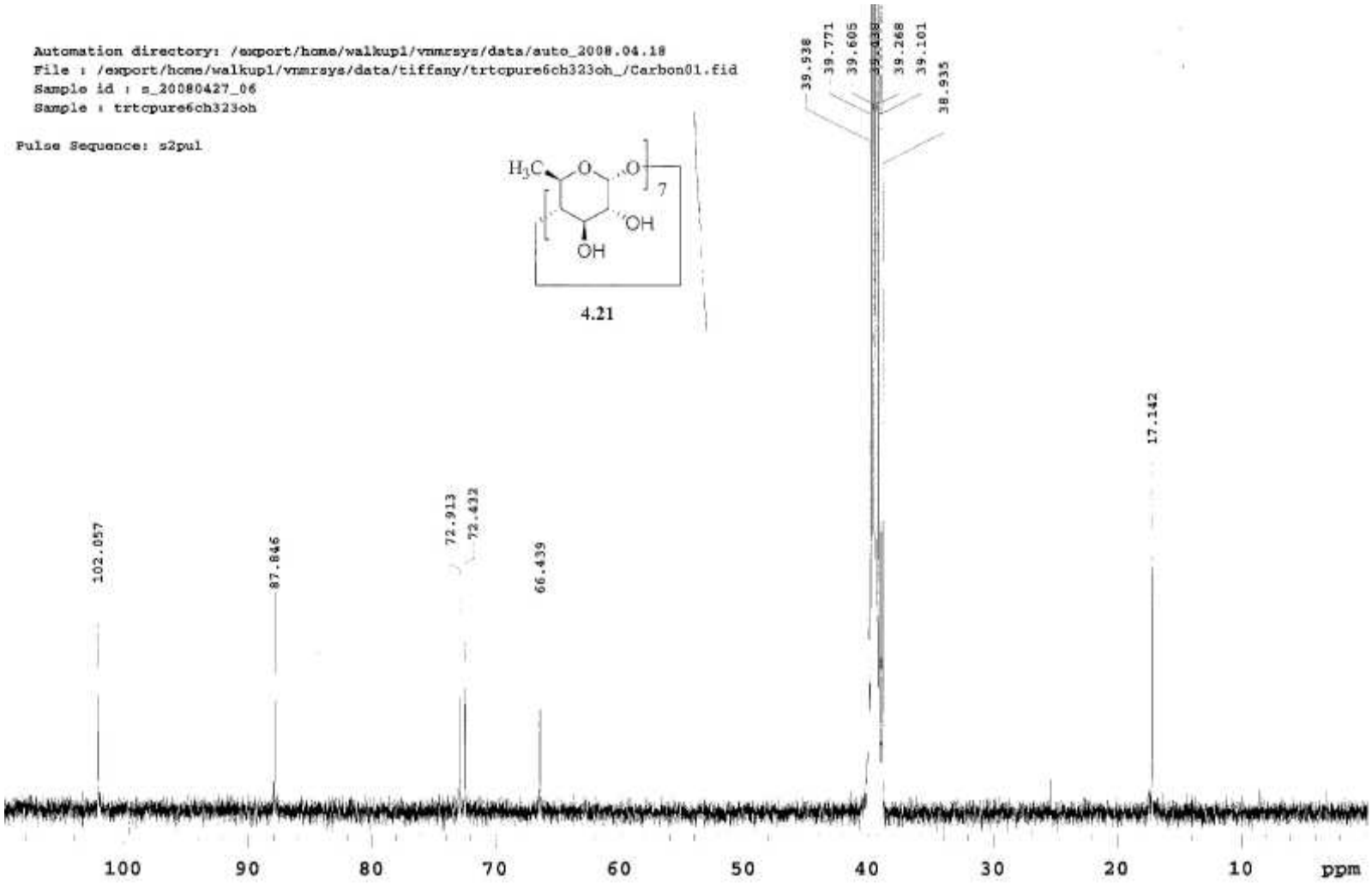
A.4.11. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.20**)



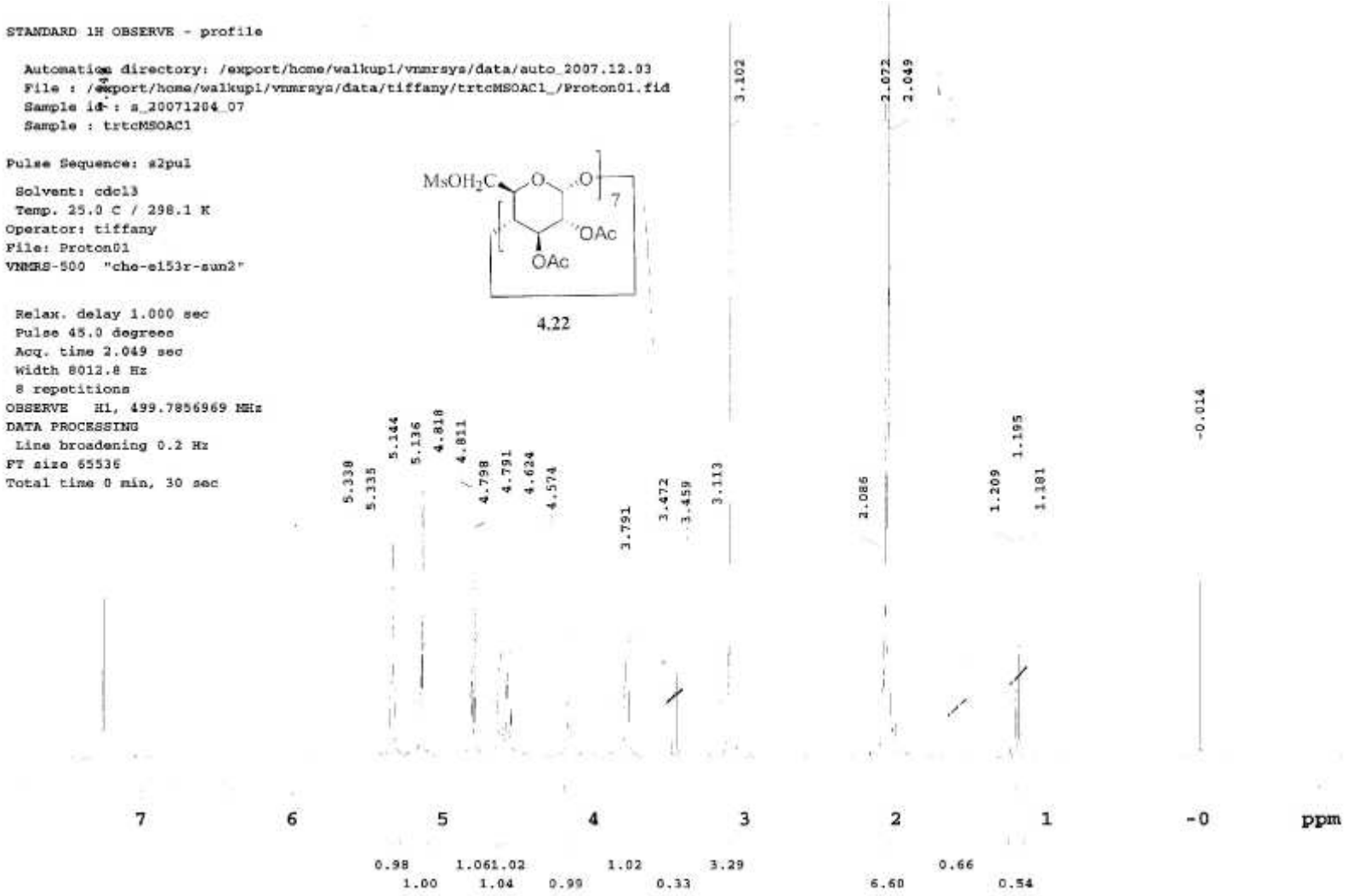
A.4.12. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.20**)



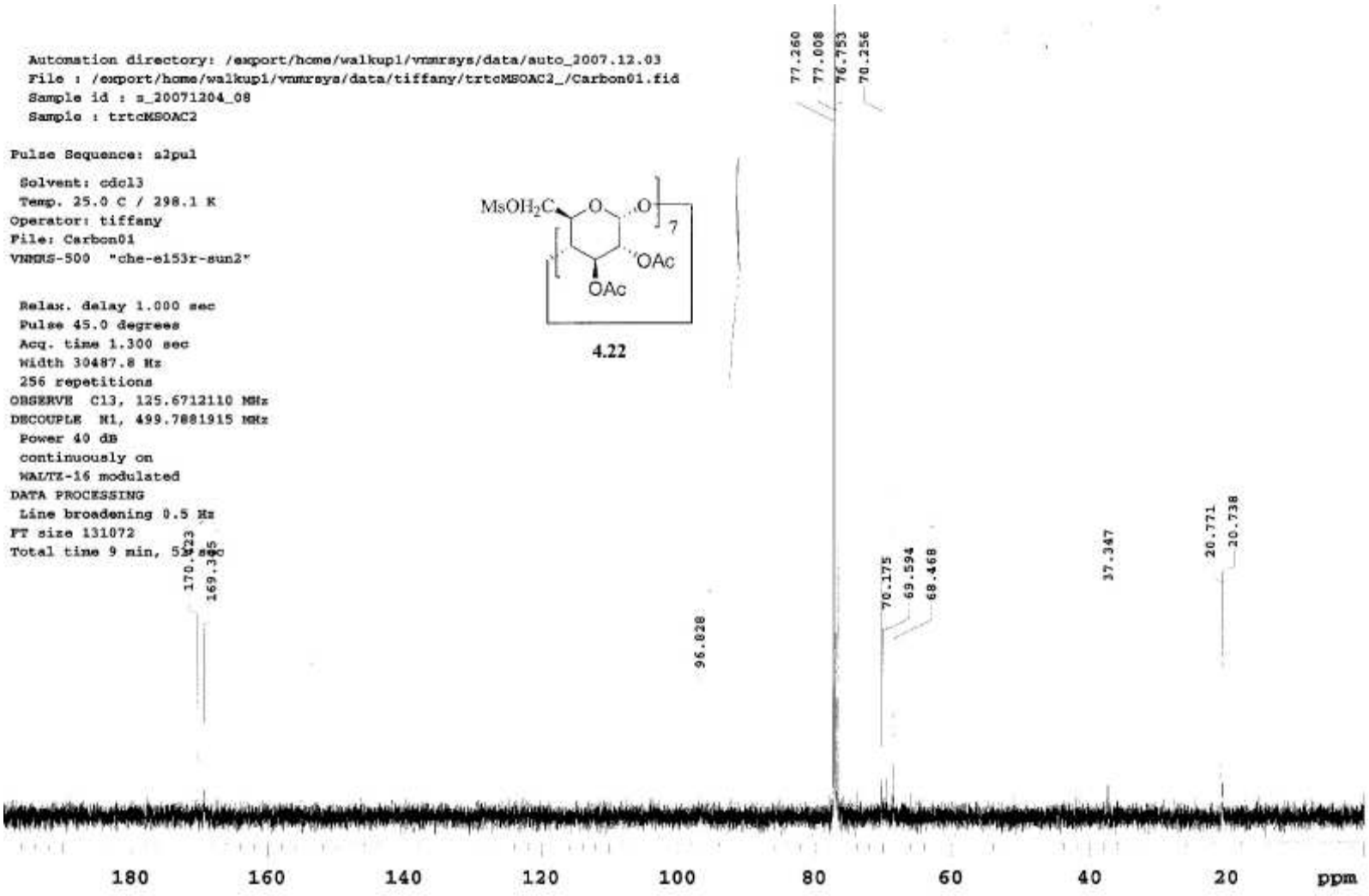
A.4.13. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.21**)



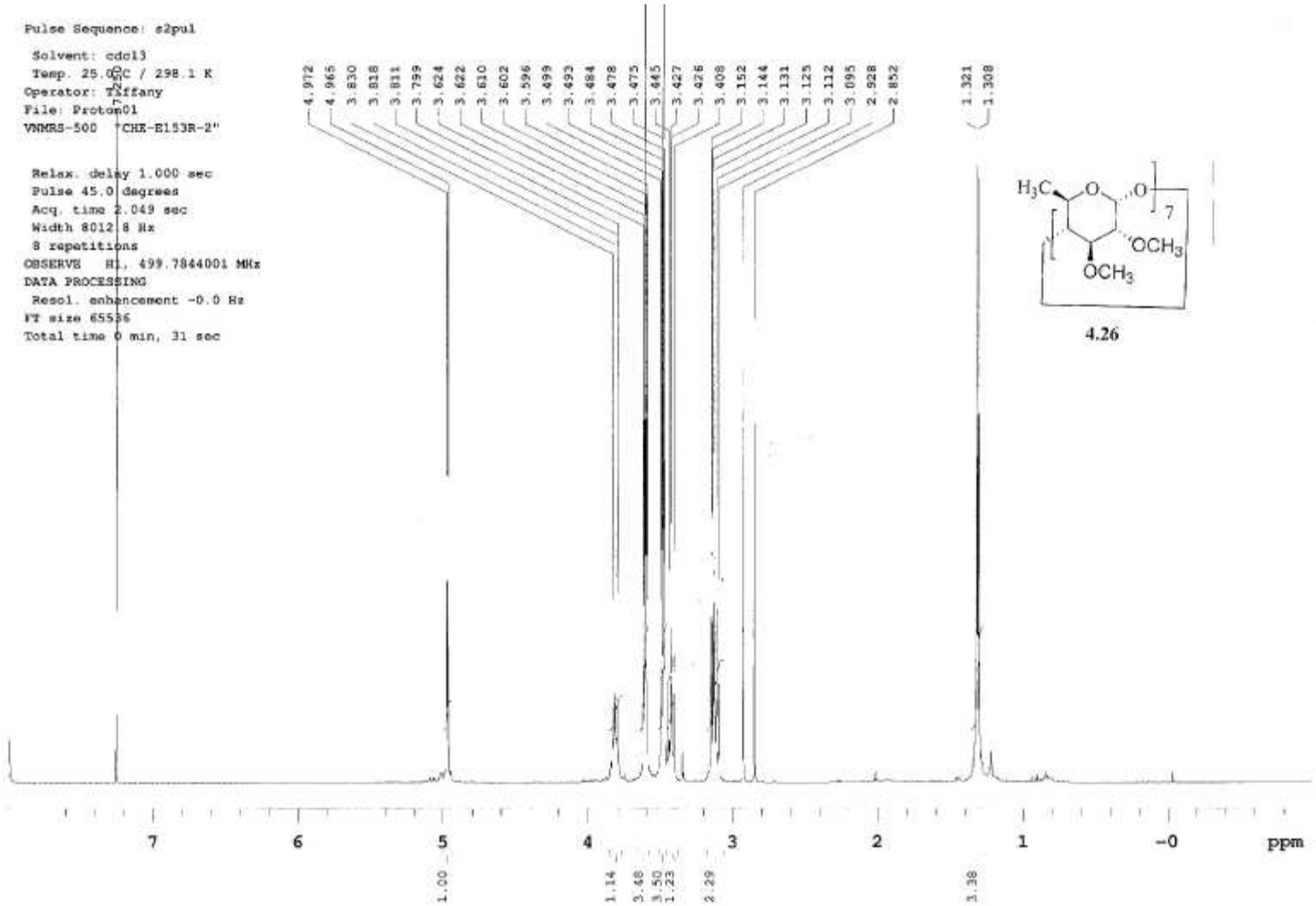
A.4.14. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.21**)



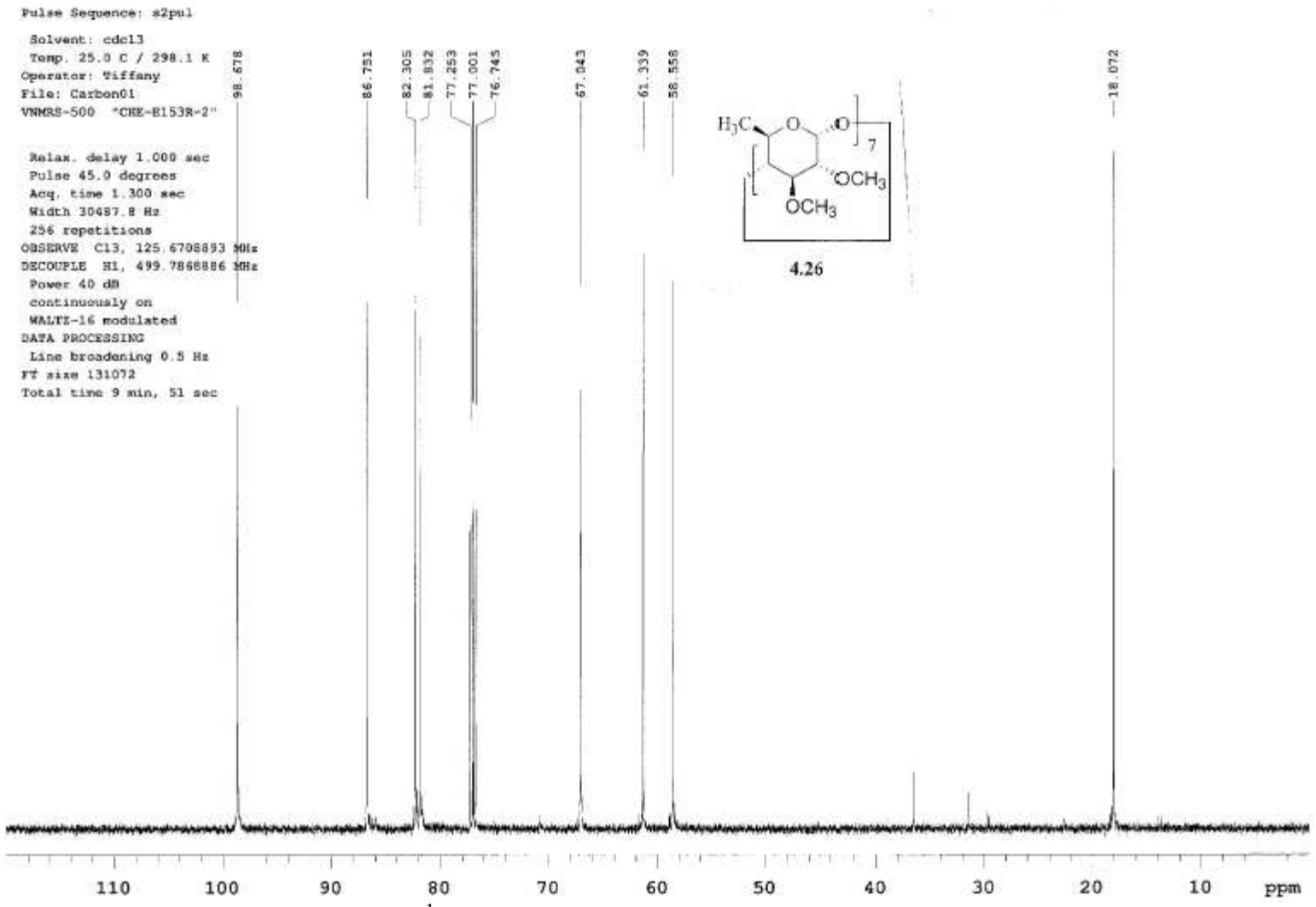
A.4.15. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.22**)



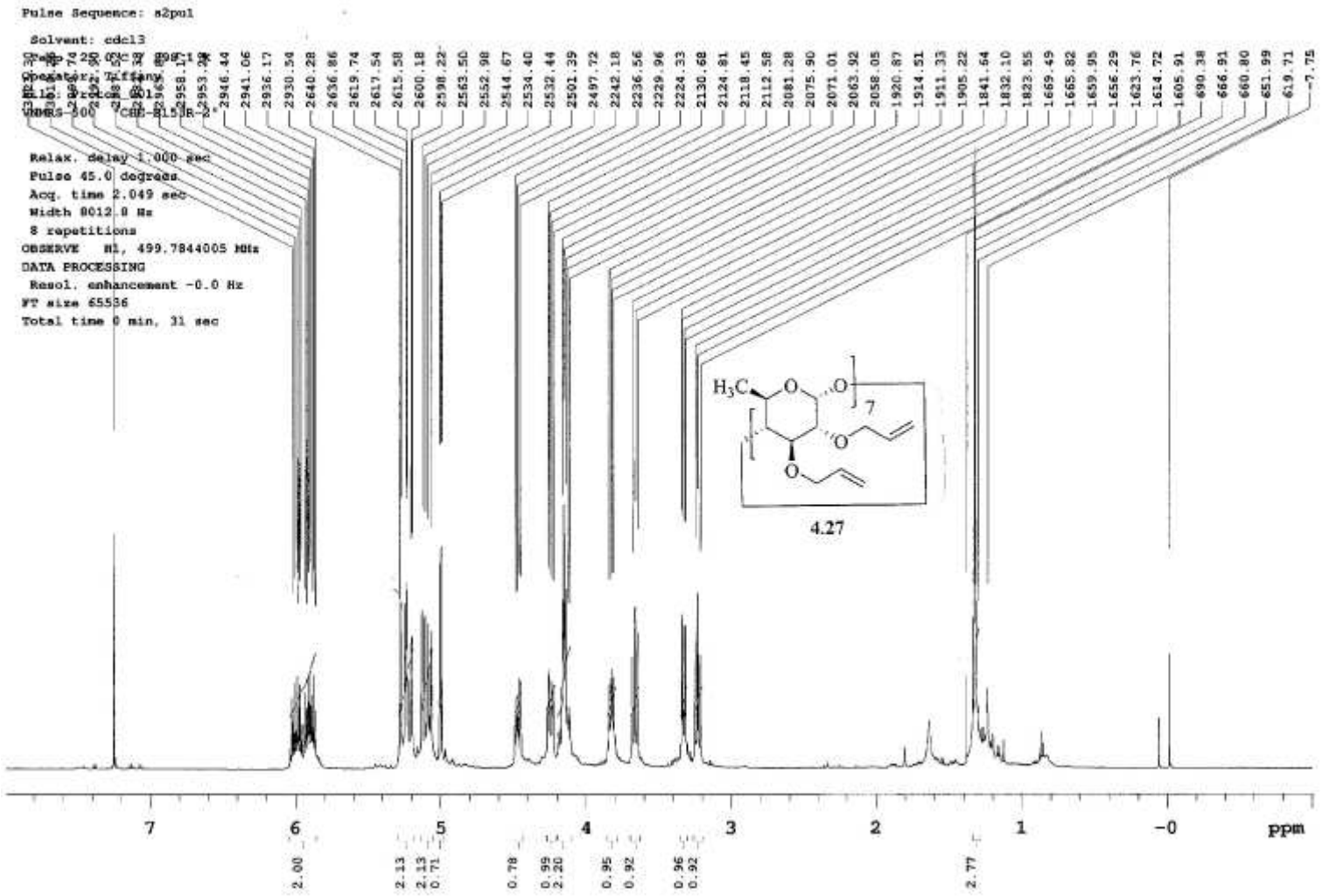
A.4.16. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.22**)



A.4.17. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.26**)

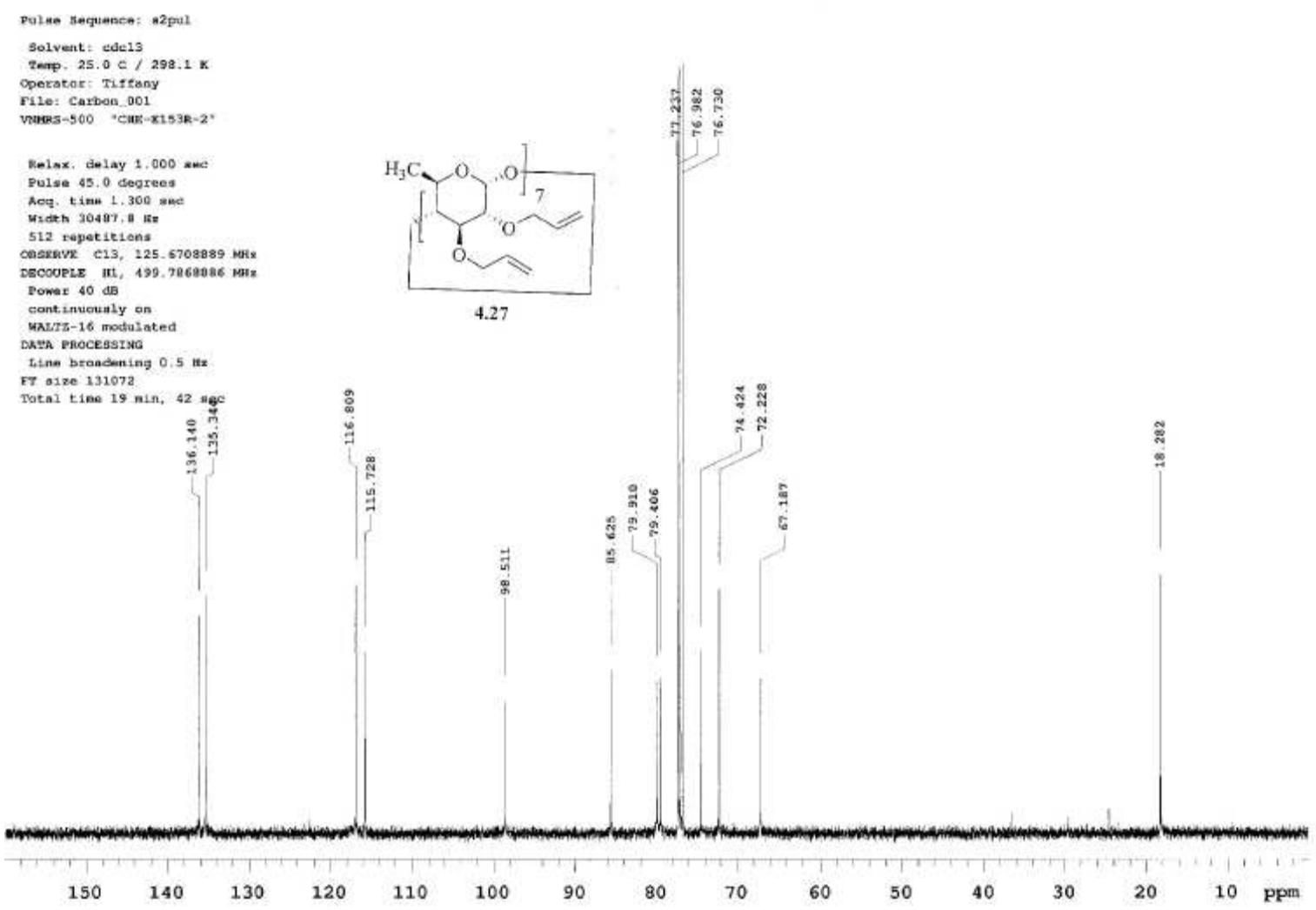


A.4.18. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.26**)



4.27

A.4.19. ^{1}H NMR ($CDCl_3$, 500 MHz) of Compound (**4.27**)



A.4.20. ^{1}C NMR ($CDCl_3$, 125 MHz) of Compound (**4.27**)

APPENDIX B

Tables of Data

Table B.5.1 Column Parameters of BU 1[62]

CD	T°C MAX		SPLIT RATIO	CARRIER GAS	HEAD PRESSURE	*N*
	Isothermal	Programmed				(dodecane)
2,3-O-dimethoxy-6-deoxy	230	250	>100:1	Hydrogen	23 psi	300,000

Table B.5.2 Column Parameters of BU 2[62]

CD	T°C MAX		SPLIT RATIO	CARRIER GAS	HEAD PRESSURE	*N*
	Isothermal	Programmed				(dodecane)
2,3-cyclodimethyl-6-*O*-*t*-butyldimethylsilyl	230	250	>100:1	Hydrogen	11.3 psi	000,000

Table B.5.3. Enantioseparation Data of CSPs[62]

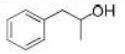
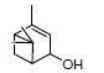
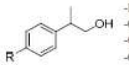
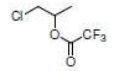
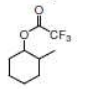
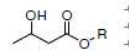
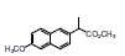
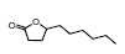
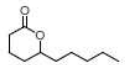
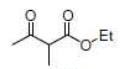
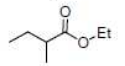
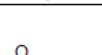
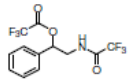
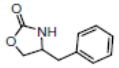
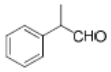
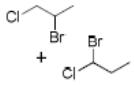
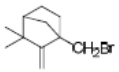
Structure	R=	T°C	J&W CycloSil B			Chiraldex A-PH			Chiraldex B-PH			Restek βDEXsa			BU 1			BU 2			BU 3			BU 4			BU 5			BU 6			BU 7		
			k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s
		80→160 @ 5°C/min	9.55	1.014	2.413	8.97	1.003	0.465	-	-	-	10.40	1.008	2.063	7.87	1.007	1.140	-	-	-	-	-	-	-	-	-	-	-	-	7.74	1.010	1.436	-	-	-
		80→120 @ 2°C/min	-	-	-	-	-	-	7.55	1.032	4.219	-	-	-	13.53	1.007	1.463	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.92	0.970	1.092
	-H		5.09	1.016	1.756	-	-	-	-	-	-	5.38	1.028	4.089	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.824	1.011	0.913	-	-	-
	-CH_3	120→200 @ 5°C/min	6.40	1.012	1.595	-	-	-	-	-	-	6.83	1.018	3.283	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.034	1.008	0.842	-	-	-
	-OCH_3		9.31	1.007	0.902	-	-	-	-	-	-	8.37	1.025	3.985	7.97	-	1.181	-	-	-	-	-	-	-	-	-	-	-	7.680	1.006	0.830	6.68	0.92	0.86
	-Cl		9.41	1.011	1.514	-	-	-	-	-	-	8.67	1.043	6.806	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.902	1.004	0.546	-	-	-
		80→120 @ 2°C/min	-	-	-	-	-	-	-	-	-	5.90	1.021	1.760	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	cis/trans	80→120 @ 2°C/min	6.42	1.046	3.652	-	-	-	-	-	-	3.71	1.013	0.715	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.896	1.024	1.267	-	-	-
			6.74	1.036	2.853							4.43	1.028	1.552															2.975	1.018	1.033	4.381	0.992	0.925
	-CH_3	60→120 @ 2°C/min	8.74	1.024	2.025	-	-	-	-	-	-	25.11	1.028	4.38	6.24	1.011	1.217	-	-	-	-	-	-	-	-	-	-	-	5.897	1.024	1.669	-	-	-
	-CH_2CH_3		11.42	1.027	3.168	10.49	1.005	0.680	-	-	-	25.95	1.045	6.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8.711	1.019	1.838	-	-	-
	-$CH(CH_3)_2$		12.61	1.046	5.751	10.88	1.008	0.982	-	-	-	26.71	1.011	1.80	10.12	1.014	1.957	-	-	-	-	-	-	-	-	-	-	-	9.872	1.034	3.573	-	-	-
		150→200x 10 @ 5°C/min	18.20	1.01	0.83	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		100→195 @ 5°C/min	12.77	1.009	1.974	-	-	-	11.82	1.002	0.759	12.55	1.029	4.561	10.12	1.014	1.957	-	-	-	-	-	-	-	-	-	-	-	8.82	1.005	0.646	-	-	-
		120→195 @ 5°C/min	10.04	1.002	0.334	9.17	1.003	0.861	-	-	-	9.64	1.033	4.526	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		90→120 @ 2°C/min	-	-	-	-	-	-	-	-	-	9.26	1.029	3.572	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		60→100 @ 2°C/min	3.58	1.050	3.025	-	-	-	-	-	-	3.87	1.020	1.062	2.97	1.013	1.077	-	-	-	-	-	-	-	-	-	-	-	2.89	1.027	1.526	-	-	-

Table B.5.4. Enantioseparation Data of CSPs[62]

Structure	R=	T°C	J&W CycloSil B			Chiraldex A-PH			Chiraldex B-PH			Restek βDEXsa			BU 1			BU 2			BU 3			BU 4			BU 5			BU 6			BU 7		
			k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s	k'	α	R_s
	$-C_8$		-	-	-	4.61	1.010	1.134	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	$-C_{10}$	100→195	-	-	-	7.73	1.006	1.407	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	$-C_{12}$	@ 5°C/min	-	-	-	11.04	1.003	0.989	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	$-CH_2OC_6H_5$		-	-	-	3.85	1.008	1.042	-	-	-	10.23	1.030	4.223	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		80→180 @ 5°C/min	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		60→120 @ 5°C/min	4.75	1.02	1.74	-	-	-	2.02	1.017	0.528	-	-	-	3.67	1.019	1.257	2.12	1.014	0.672	-	-	-	-	-	-	-	-	-	3.55	1.017	1.279	-	-	-
		120→200x 5 @ 5°C/min	13.61	1.03	4.72	8.25	1.006	1.886	-	-	-	29.66	1.011	2.676	9.79	1.012	3.289	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8.11	0.896	1.240
		150→220x 10 @ 5°C/min	16.91	1.008	0.852	-	-	-	9.07	1.024	2.983	8.35	1.047	2.021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	14.93	0.852	1.103
		80→190 @ 5°C/min	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		80→190 @ 5°C/min	7.86	1.005	0.607	5.78	1.008	1.170	-	-	-	11.51	1.014	3.015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.17	1.023	2.801	5.51	0.981	1.997
		60→100 @ 2°C/min	-	-	-	-	-	-	-	-	-	10.54	1.045	3.75	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			3.79	1.017	0.953							13.00	1.037	3.61																				
		100→190 @ 5°C/min	-	-	-	2.40	1.019	1.514	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		80→190 @ 5°C/min	17.46	1.010	2.376	16.35	1.006	2.220	16.19	1.010	4.271	10.82	1.010	1.852	14.39	1.007	2.369	-	-	-	-	-	-	-	-	-	-	-	-	13.56	1.004	0.687	-	-	-

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