# SYNTHESES OF ENEDIYNERIBOFURANOSIDES

By

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# ABSTRACT

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**Adviser: Professor Panayotis Meleties**

Enediynes are natural bacterial products isolated in the 1980s. They are characterized by nine- or 10-memberd rings containing two triple bonds separated by a double bond. These molecules have powerful antitumor activity. The enediyne moiety, which is often referred as "war head", undergoes Bergman cyclization to form a highly reactive 1,4-benzenoid diradical. These radicals cleave the DNA strand by hydrogen abstraction. Calicheamicin, esperamicin, dynemicin, and neocarzinostatin are some natural enediynes which are biologically active against Gram-positive and Gram-negative bacteria, Leukemia P388, Murine tumors P388, B16, Melanoma B16, and Tumor cells including L1210.

Despite of their biological activity, the usefulness of natural enediynes as therapeutic agents have been limited due to their poor selectivity for the cancer cells. The structural complexity of the natural compounds also makes their synthesis cumbersome. So the quest for developing synthetic analogs by incorporating enediyne functional group on various substrates has been developed. Carbohydrate based enediynes have rarely been reported as templates for enediyne molecules. Careful study of the structures and biological activity of natural enediynes reveals that the carbohydrate part of these molecules plays a crucial role in the selectivity. So the goal of this research attempt is to design unique reaction schemes to synthesis a new class of enediynes on carbohydrate substrate such as ribose which are expected to have better selectivity for the target cell.

**To**

**Dr. MARCIA KEIZS**

**The president of York College**

**&**

**Ms. ALICE POLIMINO**

**Senior Lab Technician, Chemistry Department**

**Bronx Community College**

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# CHAPTER I

# Structure and biological activity of natural and synthetic enediynes

# CHAPTER 1

## Structure and biological activity of natural and synthetic enediynes

### 1.1. Introduction

Natural products have always been used as valuable compounds in the medicinal field. Their complex molecular structures and their modes of action in exhibiting their biological activity aroused the interest of chemists to develop various synthetic procedures to prepare both natural and synthetic compounds. Among the vast number of natural products reported, enediynes, a class of bacterial products, received greater attention for their fascinating structures[1] and for their potential reactivity in cleaving DNA molecules.[2] These molecules are characterized by either nine- or ten-membered rings containing two triple bonds separated by a double bond.

Enediynes were isolated in the late 1980s.[1] They bind within the minor groove of the target cell's DNA, and initiate a cascade of reactions, leading to the cycloaromatization of the enediyne functional group to produce 1,4-benzenoid diradical.[1] These diradicals abstract hydrogen atoms from the sugar phosphate backbone of the adjacent DNA strands, causing the cleavage of DNA double helix.[3] Enediynes exhibit extraordinary activities against murine tumors and they are about 4000-fold more active than adriamycin, one of the most effective clinically used antitumor antibiotics.[4,5]

There are also some disadvantages associated with the natural enediynes. For example, the use natural enediynes as therapeutic agent is limited because of their poor selectivity for the cancer cells. Also their structural complexity makes their syntheses challenging. So, it is essential to design simple synthetic enediyne molecules with better selectivity for the cancer cells. It has been reported[3] that the carbohydrate part of the natural enediynes plays a crucial role in selectivity. So the goal of this research project is to design unique reaction schemes to synthesize simpler enediyne molecules based on a carbohydrate template. For this purpose, ribose is considered as a suitable substrate, because ribose and its derivatives have important role in biological processes. Ribose is also an important component of nucleic acids and C-nucleosides. These ribose based enediyne molecules are also water soluble, which influences the pharmacokintic properties such as circulation and elimination in the biological system.

## 1.2. Structural aspects of natural enediyne

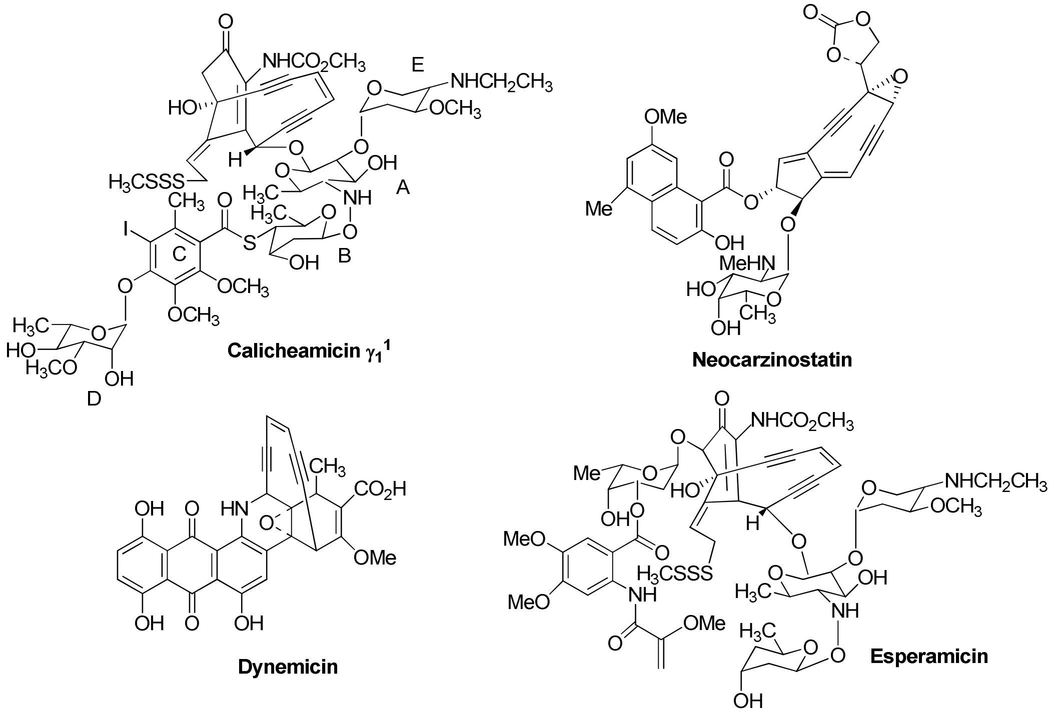


**Figure 1**. Natural enediyne anticancer antibiotics

Based on the molecular structure, natural enediyne molecules are classified into three major groups. Examples from each group include calicheamicins/esperamicins, dynemicins, and chromoproteins (Figure1).

### 1.2.1. Calicheamicin and Esperamicin

Calicheamicin $\gamma_1^1$ is the most important and prominent member of the calicheamicin family. It was isolated from *Micromonospora echinospora ssp calichensis*.[4] Calicheamicin binds to the minor groove of the double helical DNA, and displays high specificity for the sequences such as 5'-TCCT-3' and 5'-TTTT-3' via hydrophobic interactions.[3] Esperamicin, which has similar structural features as calicheamicin, was isolated from the cultures of *Actinomadura verrucosospora* and *Micromonospora echinospora*.[6] In both calicheamicin and esperamicin, the glycoside part is attached to a common aglycon frame work. The aglycon part consists of an allylic trisulfide group, acting as a trigger, and the enediyne part, which is responsible for the DNA cleavage.[7]

### 1.2.2. Dynemicin

Dynemicin, a violet color anticancer antibiotic, was extracted from the fermentation broth of *Micromonospora chersina*.[8] It exhibits promising *in vivo* antibacterial activity with low toxicity.[9] Dynemicin cleaves the double stranded DNA, creating both double and single strand cleavage. It also displays strong reactivity against Gram-positive bacteria.[8] Structurally, dynemicin is a novel fusion of anthraquinone and tetracyclo1,5-diyne-3-ene (Figure 1).

### 1.2.3. Neocarzinostatin

Neocarzinostatin (NCS), is isolated from the cultures of *Streptomycescarzinostaticus F-41*.[10] It is a chromoprotein molecule, formed from the noncovalent association of 1:1 mixture of a protein component (NCS apoprotein) and a chromophoric component (NCS chromophore). Biological activity resides on the chromophoric group and the protein part helps for the stabilization and mobility of the drug.[3] But recent studies reveal that the apoprotein is also contributing to the cytotoxicity through selective proteolytic activity.[3] Apoprotein component consists of 133 amino acid polypeptide chain based on the gene based sequence.[3] The chromophore has a polyeneyne skeleton. Structure of the chromophoric part of neocarzinostatin is shown in Figure 1.

Endiyne natural products have three common structural domains.**[11,12]**

They are:

a) The enediyne functional group, referred as a "warhead". Upon activation, this structural unit will undergo cycloaromatization to give reactive diradical.

b) A structural unit, acting as an intercalating vehicle, which delivers the enediyne molecule to the target DNA.

c) A "safety catch" that imposes a structural restraint, which upon suitable activation initiates a cascade of reactions, leading to the generation of benzenoid diradical.

For example, in calicheamicin, the oligosaccharide is the intercalating vehicle, the enamine double bond is the safety catch that unleashes the reactivity and the trisulfide unit is the trigger. In dynemicin, the anthraquinone is the delivery unit and the safety catch is the epoxide group.

### 1.3. Biological activity of natural enediyenes

Natural enediyne molecules have exhibited astonishing biological effect at very low concentrations (Table 1). Their antitumor activities range from the sensitive leukemia tumors to the resistant melanoma cell lines.[11] Calicheamicins are extremely active against Gram-positive and Gram-negative bacteria.[11] They exhibit extraordinary potency against murine tumors such as P338, L1210 leukemias, and solid neoplasms, such as colon 26 and B-16 melanoma.[11]

**Table 1**. Biological activity of the natural enediynes

| **Entry** | **Natural enediynes** | **Active against** | **Concentration** |
|---|---|---|---|
| 1 | Calicheamicin | Gram positive bacteria | less than 1 pgmL$^{-1}$ |
| | | Gram negative bacteria | |
| | | Murine tumors P388, L1210 | 0.15-5 µg/ kg |
| | | Melanoma B-16 | |
| 2 | Esperamicin | Murine tumors P388, B16 | 100 ng/kg |
| | | Melanoma B-16 | |
| 3 | Dynemicins | Leukemia P388 | <1 pg/mL |
| | | Melanoma B16 | |
| 4 | Neocarzinostatin | Gram positive bacteria | 0.1 µg/kg |
| | | Tumor cells including L1210 | |
| | | Burkitt lymphoma | |

Esperamicin exhibits powerful activity against a number of murine tumor models such as P388, B-16, and M5076.[3,11] Dynemicin shows high potency against a variety of cancer cell lines and significantly prolongs the life span of mice inoculated with P388 leukemia and B-16 melonoma cells.[11] Neocarzinostatin is the first enediyne molecule used in clinical studies for the treatment of leukemia, gastric carcinoma and pancreatic adenocarcinoma.[1]

In general enediyne antitumor activities are associated with the following four principal effects in cells.[1,13]

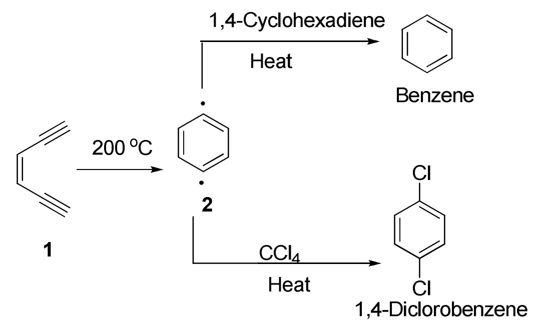
1. Mutagenicity.
2. Antimitotic activity associated with cell-cycle arrest.
3. Apoptosis induction.
4. Differential induction

## 1.4. Mechanistic aspects of DNA cleavage

The reactivity of enediynes is attributed to the presence of 3-ene-1,5-diyne functionality. Activation of the enediyne unit takes place only after the intercalation of the enediyne natural products, their analogs or their derivatives, within the minor groove of DNA. This initiates a cascade of reactions leading to the cycloaromatization giving 1,4-benzenoid diradicals. These radicals abstract hydrogen atoms from the ribose phosphate backbone of adjacent DNA strands, thus cleaving the double helix.[3]

### 1.4.1. Bergman cyclization

**Scheme 1**. Bergman cyclization



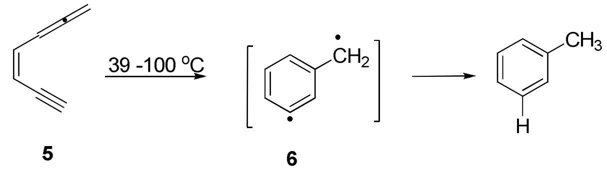
Biological activity of enediynes depends on a specific type of cyclization reaction. This cyclization, known as Bergman cyclization,[14,15] was reported in the early 1970s by Masamune and Bergman. Bergman observed that when heating the 3-ene-1,5-hexadiyne (**1**) to 200 °C in the gas phase, led to the formation of a very reactive 1,4-benzene diradical species **2** (Scheme 1). The diradical **2** abstracted hydrogen atoms from 1,4-cyclohexadiene, a hydrogen donar, yielded benzene.[11,15] When heated in the presence of $CCl_4$, 1,4-dichlorobenzene was formed, a product typical of a free radical reaction, suggesting a 1,4-benzyne diradical intermediate.

Nicolaou et al. have reported[11,12] that cyclic enediynes can undergo cycloaromatizartion reaction at a lower temperature than the acyclic enediynes. For example, the ten-membered cyclodecaenediyne **3**, underwent Bergman cyclization at 37 °C compared to the acyclic enediyne **1**, which underwent cyclization only at 200 °C. After the cyclization, enediyne **3** was converted to tetralin **4** in the presence of excess of 1,4-cyclohexadiene in benzene (Scheme 1).

### 1.4.2. Myers-Saito cyclization

Enediyne molecules with 10-membered enediyne rings, such as calicheamicins and dynemicins undergo cycloaromatization via Bergman cyclization. But compound *Z*-1,2,4-heptatrien-6-yne (**5**), a nine-membered enediyne, cyclized via a different type of mechanism (Myers-Saito).[11,16] In 1989, Myers et al. observed that compound **5** underwent cyclization via 3-didehydrotoluene diradical **6**, which upon hydrogen abstraction from suitable donor molecules, yielded toluene (Scheme 2). Natural enediynes with nine-membered rings, such as neocarzinostatin undergo Myers-Saito type of cyclization to generate active diradicals that cleave DNA strands in the course of exhibiting their biological activity.[11]

**Scheme 2**. Myers-Saito cyclization

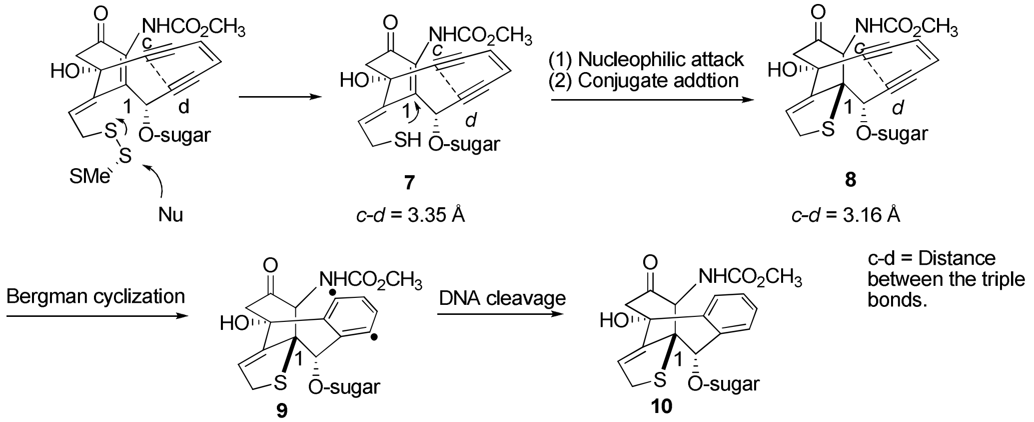


## 1.5. Mechanistic aspect of DNA cleavage by natural enediynes

### 1.5.1. DNA cleavage by calicheamicin and related compounds

Calicheamicins and esperamicins undergo nucleophilic attack at the central sulfur atom of the trisulfide group to form the thiol **7** (Scheme 3). This thiol or the corresponding thiolate ion can undergo conjugate addition to C-1 to form the dihydro intermediate **8**, which changes the hybridization at C-1 from $sp^2$ to $sp^3$.[11] This geometrical change from trigonal bridgehead to tetrahedral structure reduces the *c-d* distance between the triple bonds from 3.35 Å to 3.16 Å.

**Scheme 3**. Proposed mechanism of DNA cleavage by calicheamicin[11]

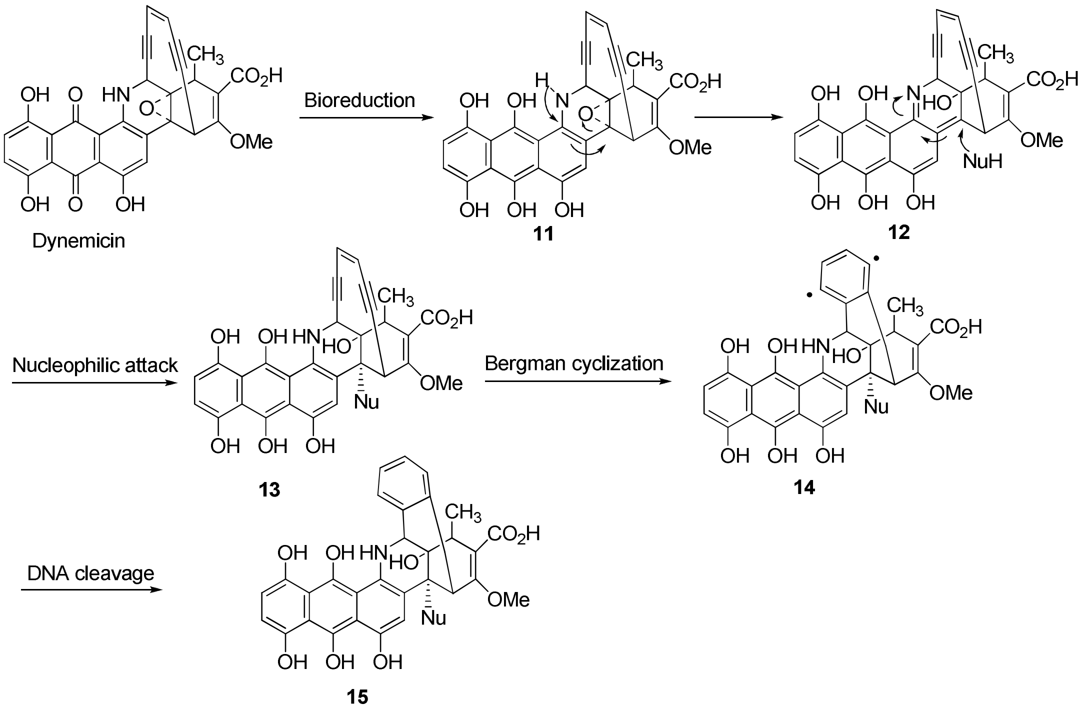


c-d = Distance between the triple bonds.

Reduction of this distance increases the strain in the 10-membered enediyne ring.[17] This strain is relieved by undergoing Bergman cyclization generating the benzenoid diradical **9**. The diradical then abstracts hydrogen atoms from the C-5 cytidine DNA position, leading to the cleavage of DNA[17,18] giving **10**.

## 1.5.2. DNA cleavage by dynemicin

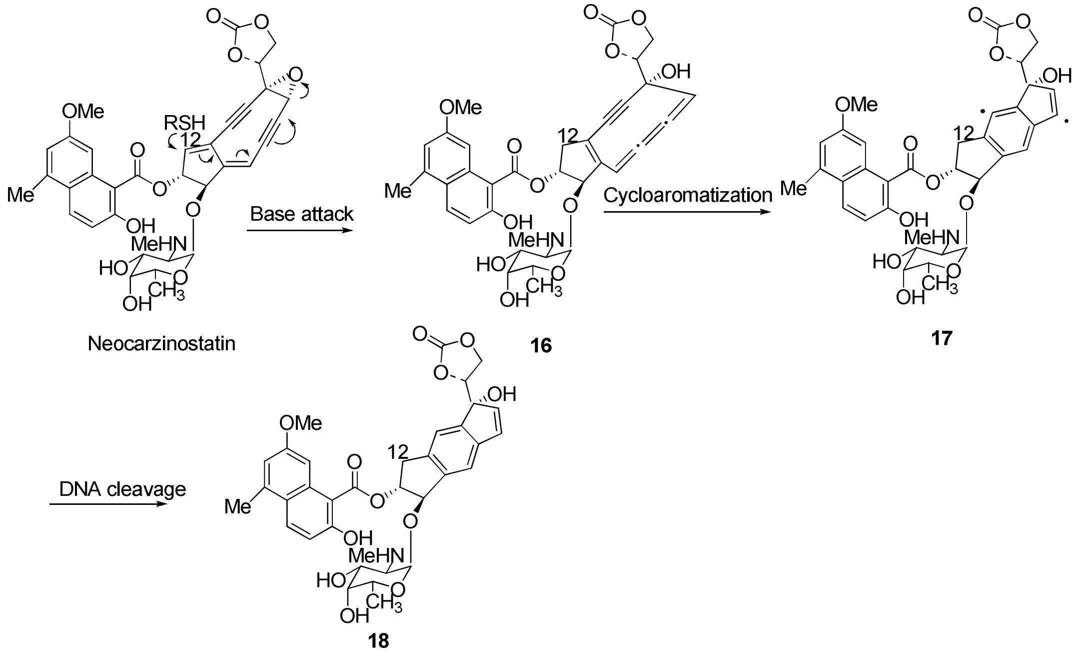
**Scheme 4**. Proposed mechanism of DNA cleavage by dynemicin[11]



In dynemicin, the quinone moiety undergoes bioreduction to give **11** (Scheme 4). Internal electronic rearrangement initiated by the amino group facilitates the epoxide ring opening, leading to the formation of the intermediate **12**.[3] Attack by nucleophiles, such as water or thiols present in the living cell systems converts **12** to **13**, which then undergoes Bergman cyclization to yield the diradical **14**. Hydrogen abstraction by the diradical **14** cleaves the DNA yielding **15**.[11]

### 1.5.3. DNA cleavage by neocarzinostatin

**Scheme 5**. Proposed mechanism of DNA cleavage by neocarzinostatin



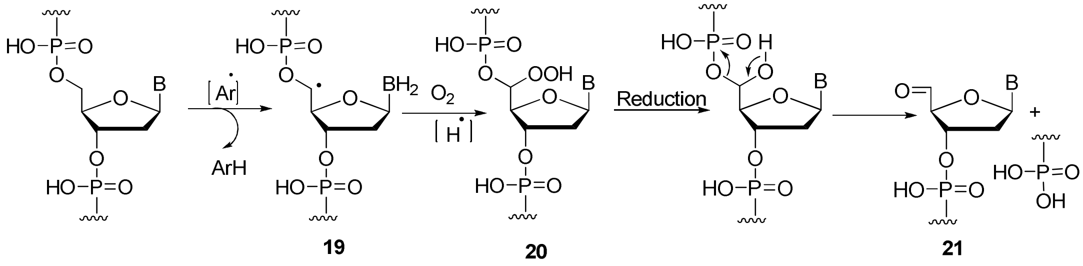
In the case of neocarzinostatin, nucleophilic attack by thiol at C-12 triggers a reaction cascade leading to the opening of the epoxide ring to form cumulene **16**. This intermediate is highly strained, and it immediately undergoes Myers-Saito cyclization reaction resulting in the formation of the diradical **17**. Hydrogen abstraction by the diradical **17** causes the DNA cleavage generating the final product **18** (Scheme 5).[3]

## 1.6. Mechanism of DNA cleavage by hydrogen abstraction

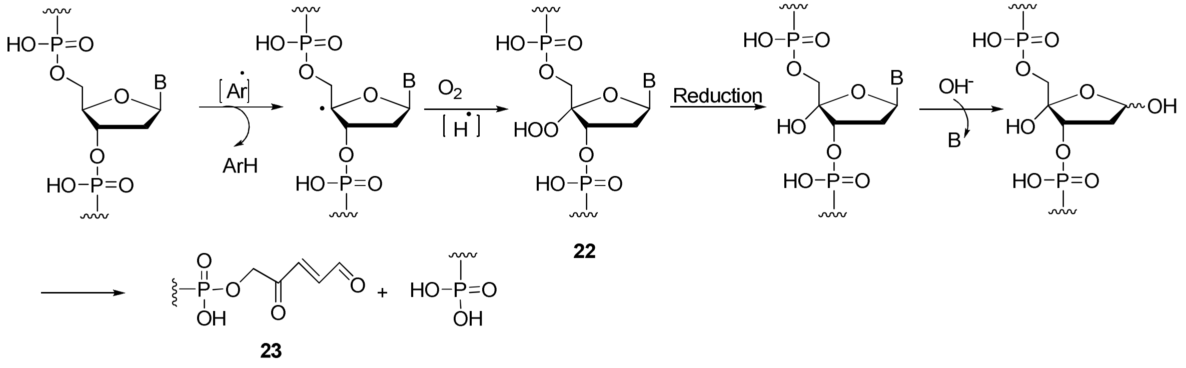
The reactive diradicals formed from the Bergman cyclization and from the Myers-Saito cyclization can cleave the DNA either in aerobic or in anaerobic conditions.

### 1.6.1. DNA Cleavage in aerobic condition

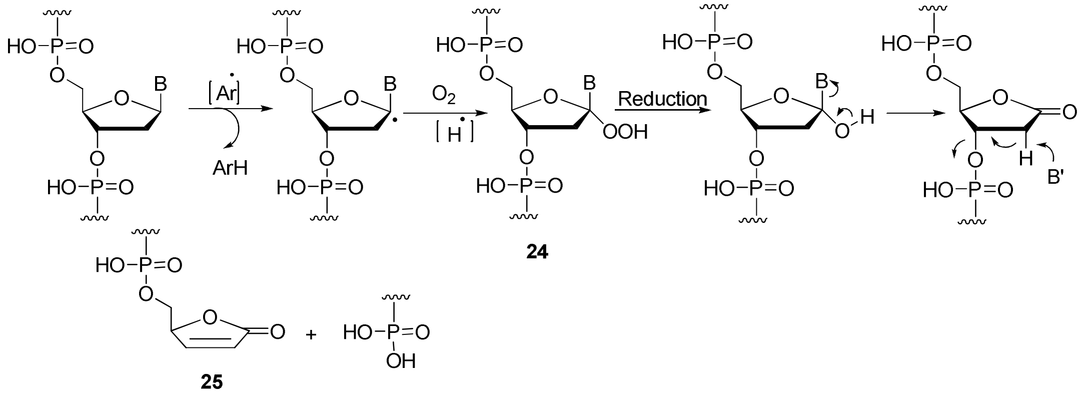
**Scheme 6**. C5' hydrogen atom abstraction



**Scheme 7**. C4' hydrogen atom abstraction



**Scheme 8.** C1' hydrogen atom abstraction

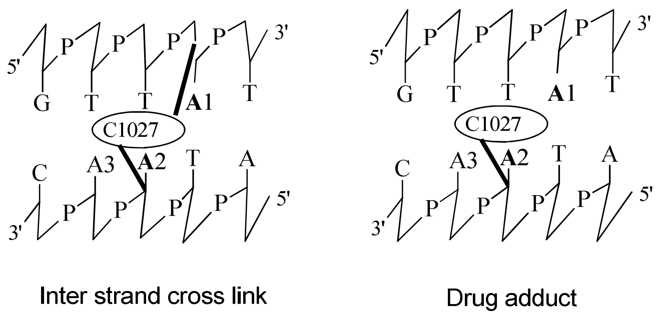


Under aerobic condition, hydrogen atoms is abstracted from C5′, C4′, and C1′ positions of the deoxyribose backbone of DNA molecule ( Scheme 6,7, and 8), causing the cleavage of DNA.[3,11] Abstraction of hydrogen from the C5′ position of the deoxyribose results in the formation of DNA radical **19**, which under aerobic condition reacts with oxygen to form peroxide intermediate **20**.[11] The peroxide intermediate eventually undergoes reduction leading to the cleavage of DNA forming C5′aldehyde of adenosine **21** and phosphate derivative (Scheme 6). DNA strand cleavage through C5′ hydrogen abstraction is the major pathway. Only less than 20% DNA strand cleavage is due to C4′ and C1′ hydrogen abstraction.[11]

Hydrogen atom abstraction from C4′ position is followed by the formation of peroxide **22** under aerobic condition. The peroxide eventually becomes dienone **23** and phosphate derivatives (Scheme 7). DNA cleavage initiated by C1' is a minor pathway. Under aerobic condition, the furanose radicals formed abstract hydrogen atom and generates the anomeric peroxide **24**, which finally yields enelactone **25** and phosphate derivative (Scheme 8).

### 1.6.2. DNA cleavge in anaerobic condition

DNA strand cleavage is also possible under anaerobic condition.[19] Under anaerobic condition, benzenoid diradicals are formed, but the lack of oxygen forces the radicals to form adducts and cross links the DNA strands. For example, when oxygen is depleted from the reaction, the enediyne antibiotic C1027 produces sequence-specific covalent DNA drug adducts and DNA interstrand cross links mediated by the drug (Figure 2). Interstrand cross-links by C1027 induce cytotoxicity in central regions of large tumors, where relatively anaerobic conditions prevail.[20]



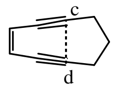
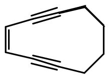
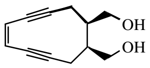
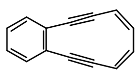
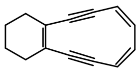
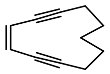
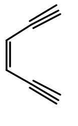
Inter strand cross link

Drug adduct

**Figure 2**. DNA damage by C1027 enediyne under anaerobic condition

## 1.7. Reactivity of enediynes

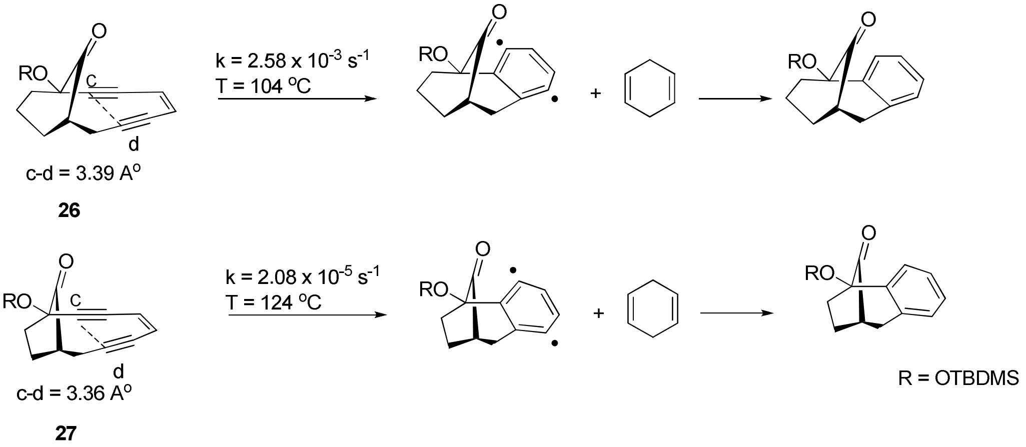
**Table 2.** Stability of enediynes[11]

| Entry | Compound | Ring size | *c-d* distance Å | Stability |
|---|---|---|---|---|
| 1 |  | 9 | 2.84 | Unknown |
| 2 |  | 10 | 3.25 | $t_{1/2}$ = 18 h at 37 °C |
| 3 |  | 10 | 3.20 | $t_{1/2}$ = 11.8 h at 37 °C |
| 4 |  | 10 | 3.01 | Cyclized at < 25 °C |
| 5 |  | 10 | 2.99 | Cyclized at < 25 °C |
| 6 |  | 11 | 3.61 | Stable at 25 °C |
| 7 |  |  | 4.12 | $t_{1/2}$ = 30 s at 200 °C |

As a general rule, the distance between the two remote acetylene carbons of the enediyne molecules (*c-d*), provides a useful guideline to determine the rate of cycloaromatization reaction. Molecular modeling studies on the natural products and their analogs suggest that the distance between the triple bonds is 3.4 Å -3.6 Å before the triggering event and 3.15 Å-3.20 Å after the triggering event.[1,11] The relationship between the distance of the triple bonds (*c-d* distance) and the stability of the several enediyne systems are given in Table 2.[11] The predicted distance for the cyclonanoenediyne (entry1) is 2.84 Å. This compound has not been isolated because it cyclizes spontaneously. Cyclodecaenediyne (entry 2), with a *c-d* distance of 3.25 Å, has a half life of 18 h at 37 °C.[21] The dihydroxy enediyne[22,23] (entry 3, 3.20 Å) undergoes cyclization with half life of 11.8 h at 37 °C. The substrate for the original Bergman cyclization (entry 7) needs to be heated to 200 °C because of the *c-d* distance of 4.12 Å.[14]

These correlations between the *c-d* bond distance and the rate of cycloaromatization was based on the study of simple cyclicenediynes. But for strained bicyclic enediyne systems, the difference in strain energy between the ground and the transition state is a key factor in the determination of the rate of Bergman cyclization.[24]

**Scheme 9**. Rate of cyclization of strained bicyclic enediynes[24]



Magnus and Schreiner had reported[24] that at 124 °C, compound **26**, a [7.3.1] bridgehead ketone enediyne, with *c-d* distance of 3.39 Å, cyclized 650 times faster than the compound **27**, a

[7.2.1] bridgehead ketone enediyne with the *c-d* distance of 3.36 Å (Scheme 9).[24] This is because, compound **26**, a six-membered cyclic ketone, undergoes conformational change from the boat to the chair form (confirmed by X-ray crystallography) while going from the ground state to the excited state and released 6.0 kcal of energy. But compound **27**, a five-membered cyclic ketone, suffers an increase of 1.5 kcal of energy as it moved from enediyne to diradical intermediate in the excited state.

## 1.8. Synthetic enediynes and their biological activity

### 1.8.1. Synthetic enediynes

Even though naturally occurring enediynes have enormous biological activities, their complex structures make them as a formidable targets for synthesis. In addition, they have poor selectivity for cancer cells and unfortunately, they cleave DNA of the healthy cells as well. Therefore, syntheses of simpler enediyne molecules with better reactivity and more selectivity have been considered.

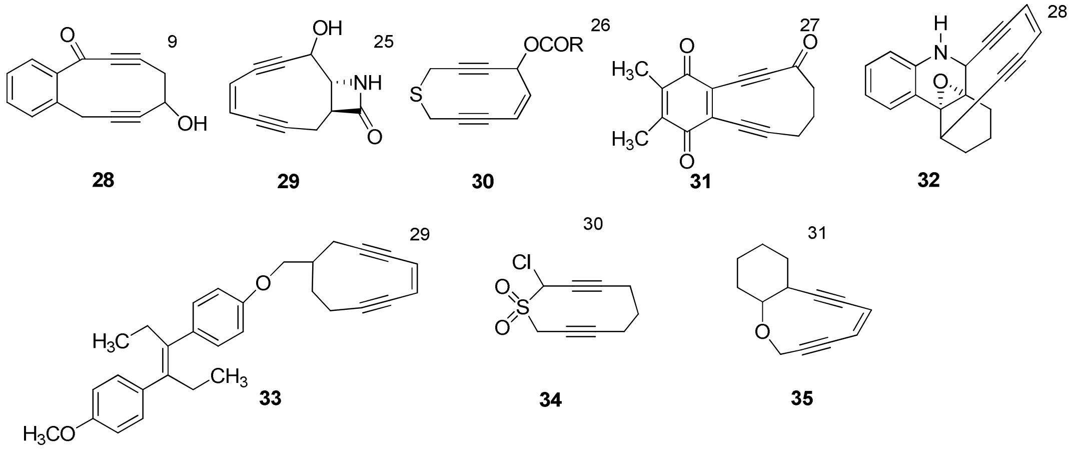


**Figure 3**. Examples of synthetic enediynes

It has been observed from the natural enediynes, that the reactivity of enediyne molecules are locked by some structural constraints.[11] Activation of these molecules will unlock the systems by removing the molecular constraint, leading to cycloaromatization. Based on this concept, many simple enediyne molecules were synthesized (Figure 3). These molecules were built with various reactive functional groups, which can act as triggers to induce cycloaromatization.

In designing the synthesis of synthetic enediynes, three major strategies have been adapted. The first one, as found in the natural enediyne is, building strained enediynes.[32] These enediynes will be activated by releasing the strain. In the second strategy, the stable enediyne can be activated by raising the energy of the ground state. Finally, the activation can be induced by introducing a π-bond in to a diyne system to make the enediyne molecule. The purpose of all these strategies is to overcome an activation barrier of 80-105 kJmol$^{-1}$ so that at physiological temperature a fast cyclization to the aromatic diradical can occur.

### 1.8.2. Biological activity of synthetic enediynes

**2. Table 3**. Biological activity of synthetic enediynes

| Entry | Designed Enediyne | Active against | Concentration |
|---|---|---|---|
| 1 | **28** | Murine bladder carcinoma MB49 | 3.4 μM |
| 2 | **30** | ΦX 174 DNA | 50 μM |
| 3 | **31** | Colon Carcinoma HT-29<br>Breast Carcinoma MCF-7 | 1 $10^{-4}$ –1 $10^{-5}$ M |
| 4 | **32** | Cancer cell lines including<br>Melanoma cells SK-Mel-28, M-14 | 1.6-2 $10^{-8}$ μmol |
| 5 | **33** | Breast cancer cells MCF-7 | 2.2 $10^{-5}$ M |
| 6 | **34** | Colon Carcinoma HT-29 | 1μM |

Most of these new classes of designed enediynes rely on their natural propensity for cyclization to exert their biological activites. Others include triggering units to bring the triple bonds closer to initiate cyclization. These synthetic enediynes are biologically active at lower concentrations ($IC_{50}$ $10^{-6}$-$10^{-14}$M) than the established antitumor drugs such as taxol (mitosis inhibitor, $IC_{50}$ $10^{-9}$ M) and Vinblastine (mitosis inhibitor, $IC_{50}$ $10^{-9}$ M).

# CHAPTER II

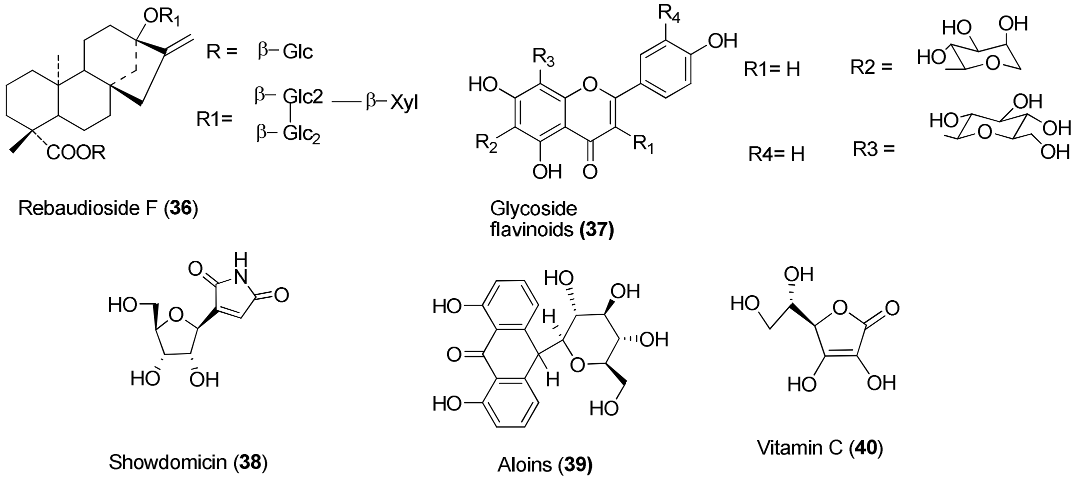
## Application of carbohydrates in everyday life

# CHAPTER II

## Application of carbohydrates in everyday life

### 2.1. Glycosides in nature

Carbohydrates are essential molecules for life and play major role in biological processes. Examples of some natural glycosides are shown in Figure 4. Rebaudioside F[33] **36**, glycoside flavonoids **37** extracted from green tea leaves,[34] showdomicin[35] **38**, aloins[36] 39, and Vitamin C **40** are some natural products that contain carbohydrates as part of their structures.



Rebaudioside F (**36**)

Glycoside flavinoids **(37)**

Showdomicin (**38**)

Aloins (**39**)

Vitamin C (**40**)

**Figure 4**. Examples of some natural glycosides

Rebaudioside **36**, extracted from the leaves of stevia is more than 200 times sweeter than sucrose. Showdomicin **38** is active against Gram-positive and Gram-negative bacteria and it is especially active against streptococcus hemolyticus and streptococcus pyogenes. Aloin **39** is responsible for the strong and sharp taste, and purgative principle of aloe. In addition to these, the other important glycoside molecules present in the biological system are glycoproteins and glycolipids. These compounds play crucial roles in life processes. For example, glycoprotein, a polypeptide, covalently bonded to carbohydrate moiety, is the basic constituent of the cell wall.[37] Glycolipids are molecules, where a lipid molecule is connected with carbohydrates. Glycolipids provide energy and serve as markers for cellular recognition.[38]

## 2.2. Glycosides in medicine

Many biologically active compounds are glycosides and in many cases their biological activity depend on the glycoside unit.[41] Carbohydrate based drugs have already been involved in making vaccines,[39] and drugs effective against HIV.[40] Since glycosides are hydrophilic in nature, they help to increases the solubility of the drugs to which they are attached. This solubility effect influences the pharmacokinetic properties of the drugs such as circulation, elimination, and the concentrations in the body fluids. Developments in glycobiology, a new field of science, which combines the knowledge of both carbohydrate biochemistry and molecular biology, are helpful in the syntheses of effective glycodrugs. Glycopeptide antibiotics, amino glycoside antibiotics, and enediyne antibiotics are some carbohydrate based drugs which have already been used in treatment of various diseases.

### 2.2.1. Glycopeptide antibiotics

Glycopeptides syntheses have been reported since the 1950s. They were originally isolated from plants and soil bacteria. These antibiotics have mono-, di-, and tetrasaccharides attached to a complex polypeptide aglycones**.** The Glycosidic residue plays an important role in their activity. Examples for the first-generation glycopeptide antibiotics are vancomycin, teicoplanin, and bleomycin.

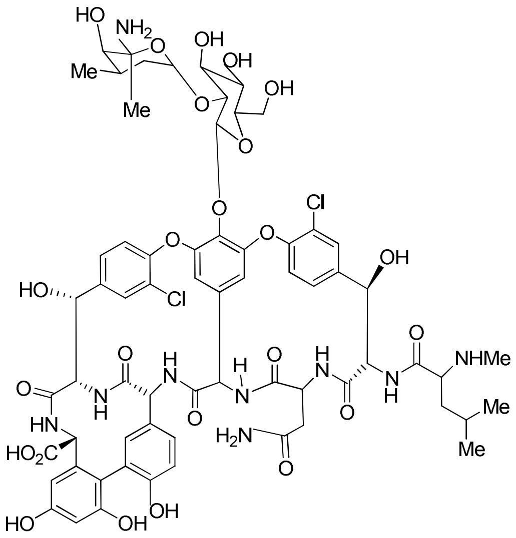


**Figure 5**. Vancomycin (glycopeptide antibiotic)

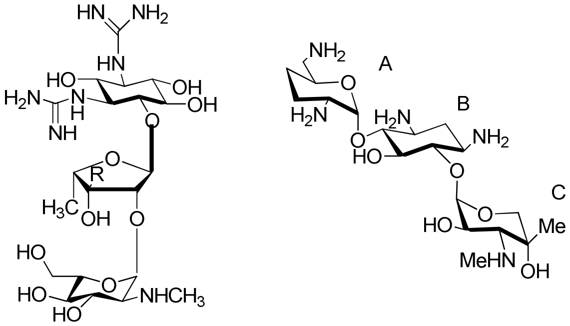
Vancomycin (Figure 5) is very effective against multiple resistant bacteria.[41] Bleomycin is clinically used against several types of cancers such as, malignant lymphomas, squamous cell carcinomas and testicular cancer.[42,43] These are crucial compounds to cure the multiple resistant bacterial infections and they have the ability to bind and to degrade DNA. Teicoplanin is used to cure serious infections caused by Gram-positive bacteria. It exhibits the biological activity by inhibiting the bacterial cell wall synthesis.

### 2.2.2. Aminoglycoside antibiotics

Aminoglycosides are molecules composed of sugar group and amino group. Amino glycosides are potent bactericidal antibiotics discovered in the 1940s. Examples of some important aminoglycosides include gentamycin, streptomycin, and dihydrostreptomycin (Figure 6).[41]Streptomycin is a protein synthesis inhibitor and leads to the death of the microbial cell.

It was the first antibiotic remedy for tuberculosis. These antibiotics interact with ribosomal RNA causing decrease in translational accuracy and inhibit translocation of the ribosome.[44]

Gentamycin binds to the major groove of the RNA. Ring A and B are responsible for specific RNA drug interaction.[41]



Streptomycin, R= CHO
Dihydrostreptomycin, R= $CH_2OH$

Gentamycin

**Figure 6.** Aminoglycoside Antibiotics

### 2.2.3. Enediyne antibiotics

Enediynes exhibit their antitumor activity by cleaving DNA strands. In these molecules, the carbohydrate part is responsible for target specificity. For example, in calicheamicin $\gamma_1^1$ (Scheme 1), the aryl carbohydrate tail helps the drug to target the minor groove.[3] Enediyne C-1027 shows potent cytotoxicity against KB carcinoma cells ($IC_{50}$ 0.1 ng/mL) *in vitro*[45] and a powerful antitumor activity toward tumor bearing mice *in vivo*.[46]

All these examples demonstrate the significant and vital roles that carbohydrates play in the development of drugs. Therefore, a vast amount of work has been dedicated in the pharmaceutical field in the syntheses of potential pharmacophores anchored on a carbohydrate scaffold.

# CHAPTER III

## Overview of reactions used in the syntheses of glycosides

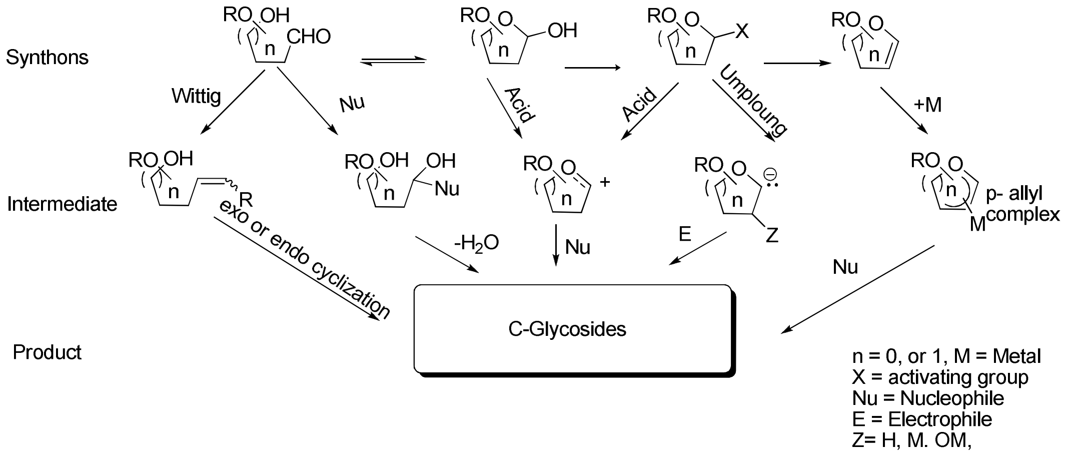
# CHAPTER III

## Overview of reactions used in the syntheses of glycosides

### 3.1. Common synthons and intermediates in the synthesis of C-glycosides

Syntheses of glycosides are very important because many physiologically active compounds have glycosides as part of their structures. For example, showdomicin,[35] streptomycin,[41] and vancomycin[41] are important glycoside antibiotics used in medicine. Usually, glycosides are formed by replacing anomeric oxygen by nitrogen (N-glycosides), by sulfur (thio glycosides), and by carbon (C-glycosides). Various synthetic strategies have been developed for the stereocontrolled formation of C-glycoside bonds. Introduction of anomeric C-glycoside bond is the first step in carbohydrate homologation reactions to synthesize very complex of biologically important macromolecules such as the marine natural product palytoxin[47] and spongistatin.[48]

**Scheme 10**. Common synthons and intermediates for glycosylation reactions[49]



The most common synthons and intermediates involved in the glycosylation reactions are shown in Scheme 10.[49] In general, the C-glycosylation reactions are carried out by nucleophilic addition to a carbohydrate electrophile. The most commonly employed carbon nucleophiles are silyl enolethers, alkenes, allylsilanes, allylstannanes, organometallic compounds such as organomagnesium (Grignard reagent), organolithium, and organocuprates. Examples of carbohydrate electrophiles are glycosyl halides, glycols, acetates, lactones, glycals, and anhydrous sugars (Figure 7).

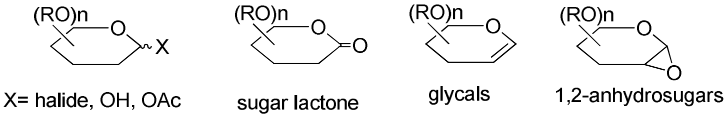
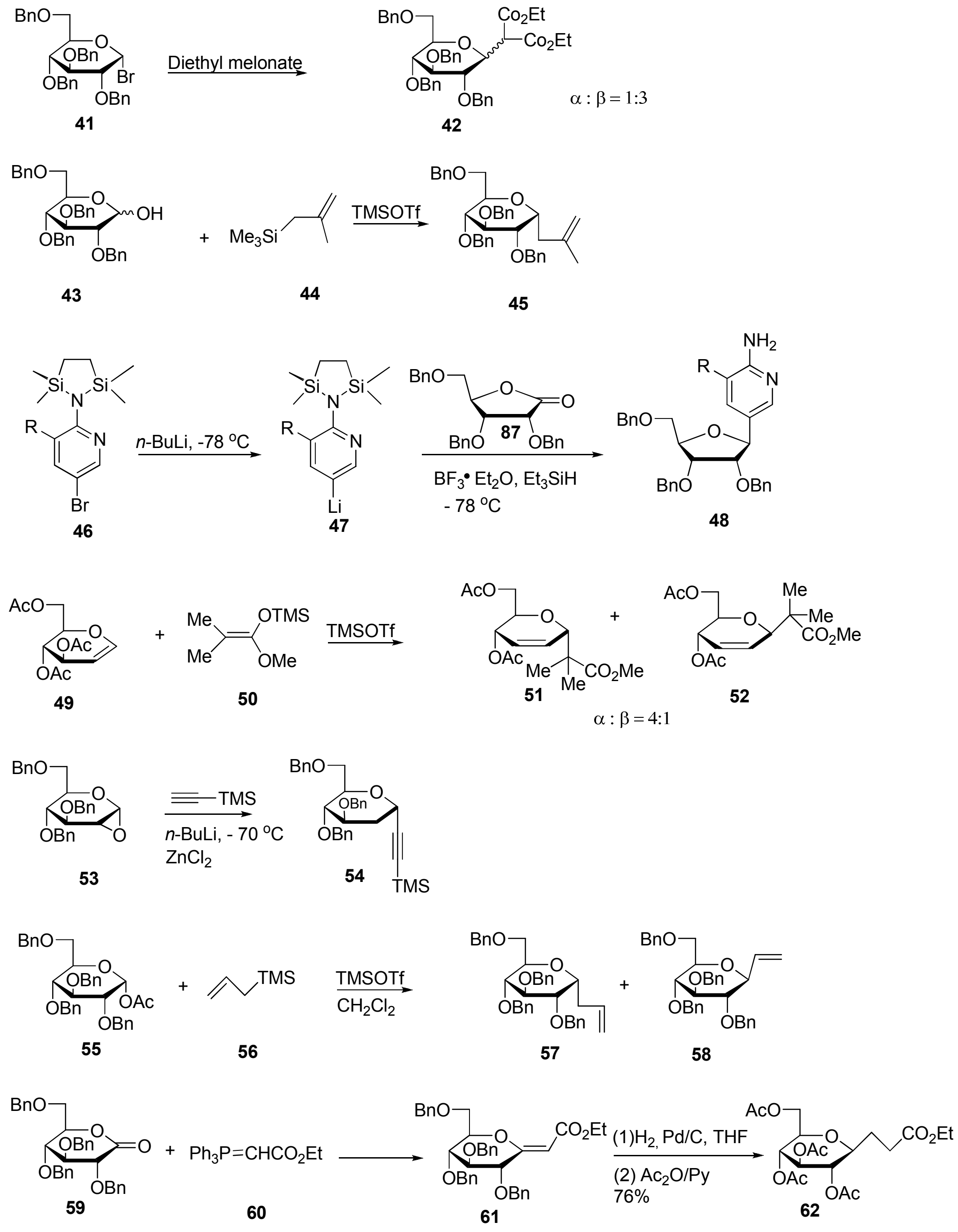


**Figure 7**. Examples of carbohydrate electrophiles

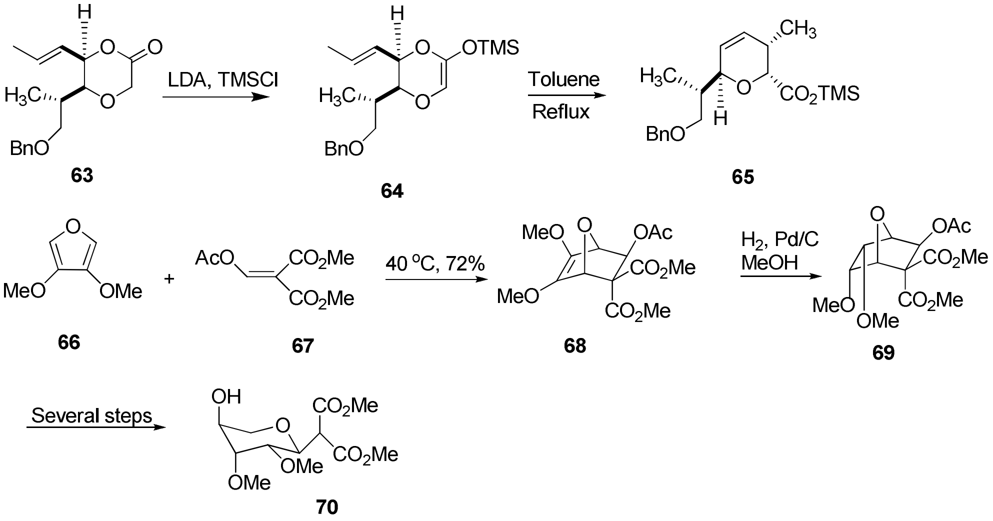
## 3.2. Examples of reported glycosylation reactions with various carbohydrate electrophiles

Typical examples of glycosylation reactions with different carbohydrate electrophiles and nucleophiles are shown in Scheme 11. For example, glycosyl bromide **41** reacts with sodium diethylmalonate via the $S_N2$ reaction yielding glycoside **42** with α:β ratio of 1:3.[50] Lactol **43**, a common carbohydrate electrophile, reacts with 2-methyltrimethylallylsilane **44** yielding glycoside **45** as the main product.[51] In general, nucleophilic attack on the lactone substrate forms hemiacetal intermediate, which is further reduced by Lewis acid and triethylsilane.[52] This reaction has greater stereocontrol and higher product yield. For example amino pyridine **46** can be lithiated to give **47**. The lithiated compound 47 can perform nucleophilic addition with lactone **87** to yield exclusively the β-isomer **48**.[53] Glycal **49** reacts with 1- methoxy-2-methyl-1-(trimethylsiloxy)-propene **50** gives the α and β glycosides **51**, **52** in a 4:1 ratio.[54]

**Scheme 11**. Glycosylation reactions using common carbohydrate electrophiles



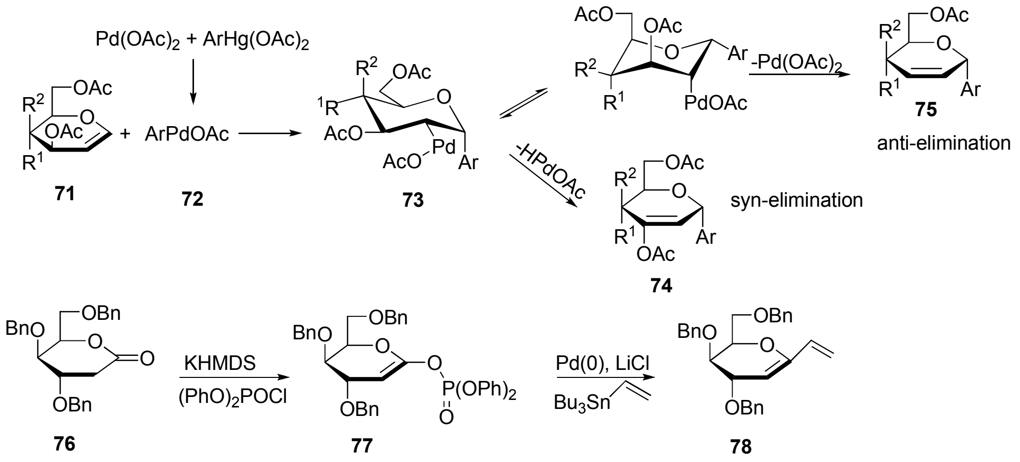
**Scheme 12**. Synthesis of glycosides using Claisen rearrangement and [4+2] cycloaddition



Suitably protected 1,2-anhydro carbohydrate derivatives are also widely used in C-glycosylation. Van Boom used the anhydro sugar **53** to get 51% of **54**.[55] C-glycosides are also synthesized using C-1 acetylated carbohydrates. The acetoxy glycoside **55** undergoes nucleophilic attack by the allyl silane **56** in the presence of Lewis acids. The reaction generated a mixture of C-glycosides **57** and **58**.[56] In the Wittig reaction, lactone **59** is reacted with two equivalents of **60** to yield **61** which upon reduction, debenzylation followed by acetylation gives glycoside **62** in 76% (Scheme 11).[57]

In addition to these reactions, other notable reactions for stereoselective synthesis of C-glycosides are the Claisen rearrangement[58] and cycloaddtion reactions[59] (Scheme 12). The enolether **64**, formed from the reaction of lactone **63**, when refluxed in toluene undergoes a Claisen rearrangement to give **65**. Diels Alder cycloaddition of the substituted furan **66** with enol acetate **67** produces the bicyclic compound **68**. Upon hydrogenation it is converted to **69**, which in turn is transformed to the glycoside **70**.

**Scheme 13**. Synthesis of glycosides using the Heck and the Stille coupling reactions



Palladium catalyzed reactions such as Heck reaction[60] and Stille reactions[61] are also used in glycoside synthesis (Scheme 13). Glycal **71** undergoes Heck coupling reaction when treated with arylpalladium acetate **72** giving **73**, which are converted two different glycosides **74** and **75**. [49] Lactone **76** is converted to enol phosphate **77**, which under standard Stille reaction gives **78**.[49] C-glycosylation is also possible under radical reaction using glycosyl bromides, tributyltin hydride and AIBN, with conjugated electron deficient alkenes.[62]

# CHAPTER IV

# Synthetic approaches to make enediyne ribofuranosides

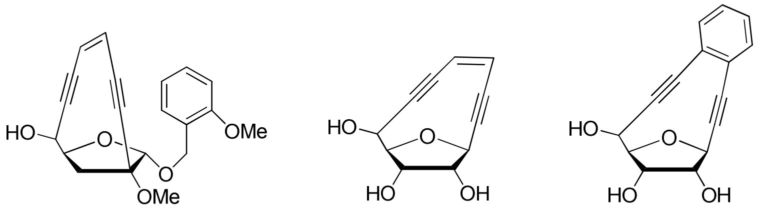
# CHAPTER IV

## Synthetic approaches to make enediyneribofuranosides

### 4.1. Enediyne furanosides.

Natural enediynes are extremely active, but they are nonselective and they are highly toxic[3] to healthy cells. More over, the structural complexity of natural enediynes makes their syntheses nontrivial. The syntheses of natural enediyne products were reported by Nicolaou et al.[11] The multistep step syntheses reported provided incentives to prepare more accessible simpler analogs using shorter synthetic routes. Synthetic enediyne molecules with better control over selectivity, yet with simpler molecular architectures have been reported (Figure 3).[9,25-31] In these examples, the enediyne functionality was either part of a ten-membered ring without any substitution or the enediyne functional group was built on substrates, such as a β-lactam **29**, and benzoquinone **31** etc. Carbohydrate substrates have rarely been reported as templates to synthesize enediyne molecules. Brandstetter and Maier reported the synthesis of oxabicyclo [7.2.1] enediyne on D-xylose substrate **79** (Figure 8).[32] The bicyclic system **79** is stable, and it underwent Bergman cyclization at 80 °C in the presence of 1,4-cyclohexadiene. Enediynes constructed between the anomeric and terminal carbon of the furanose ring have not yet been reported. Therefore, the main goal of this dissertation is to study, and to develop synthetic procedures to prepare a new class of enediyne ribofuranoside molecules such as **80** and **81** (Figure 8).

## 4.2. Goal of the research project-Synthesis of enediyne ribofuranosides



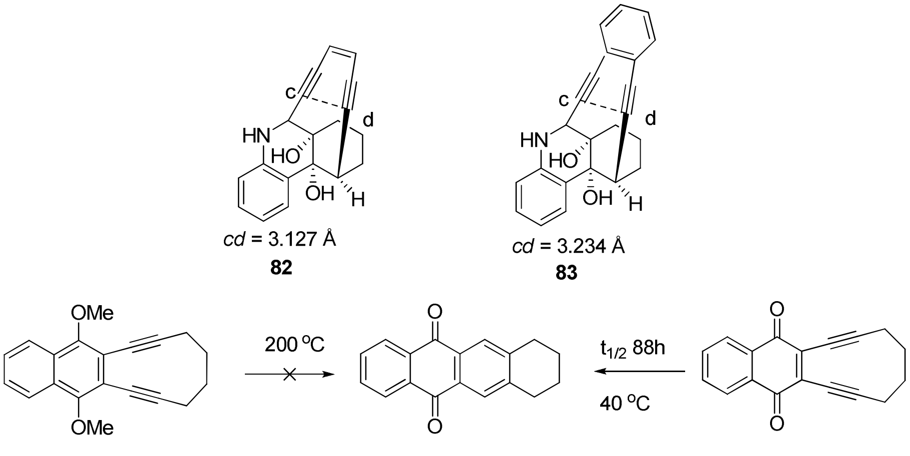
**79** **80** **81**

**Figure 8**. Carbohydrate based enediynes

Compound **80** is the simpler representative of this new class of cyclic enediyne molecules. It can become the model template to study other ribofuranoside enediyne analogs such as **81**. Proposed enediynes **80** and **81** are soluble in water, which influence the pharmacokinetic properties of the drugs such as circulation and elimination. Modifications in **80** can be achieved either by introducing substituent on the enediyne chromophore or by introducing different functional groups in the place of hydroxyl groups. These modifications may help to control the reactivity and selectivity of the enediyne derivatives.

For example, by fusing a benzene ring on enediyne **80**, derivative **81** can be envisioned with properties and reactivity different from **80**. Introducing the hydrophobic benzene ring may increase the interactions of the enediyne substrate with the minor DNA groove. A stronger interaction with DNA may reflect a higher percentage of DNA cleavage. Compound **81** is expected to be more stable than **80** with reduced rate of Bergman cyclization, because it has been reported[63] that fusion of aromatic rings with the enediyne chromophore increases the distance between the remote acetylene bonds. For example, the distance between the triple bonds (*cd*) is increased from 3.127 Å to 3.234 Å when going from the simple enediyne **82** to enediyne **83**, in which there is a conjugation of benzene ring on enediyne chromophore.

**Scheme 14.** Bergman cyclization in benzene conjugated enediynes



84 85 86

Elementary MM2 calculations gave an estimated *c-d* bond distance value of 3.285Å for the simple enediyne **80** and 3.369 Å for the benzene conjugated enediyne **81**, which is in supportive of the reported values.[63] Many examples have also been been cited[27,64] idicating the reduced reactivity of enediynes having benzene conjugated with the enediyne chromophore. For example, when benzene becomes the part of the enediyne chromophore as in **84** (Scheme 14), it strongly inhibits the Bergman cyclization. In fact, compound **84** did not undergo Bergman cyclization at various temperatures even after heating up to 200 °C.

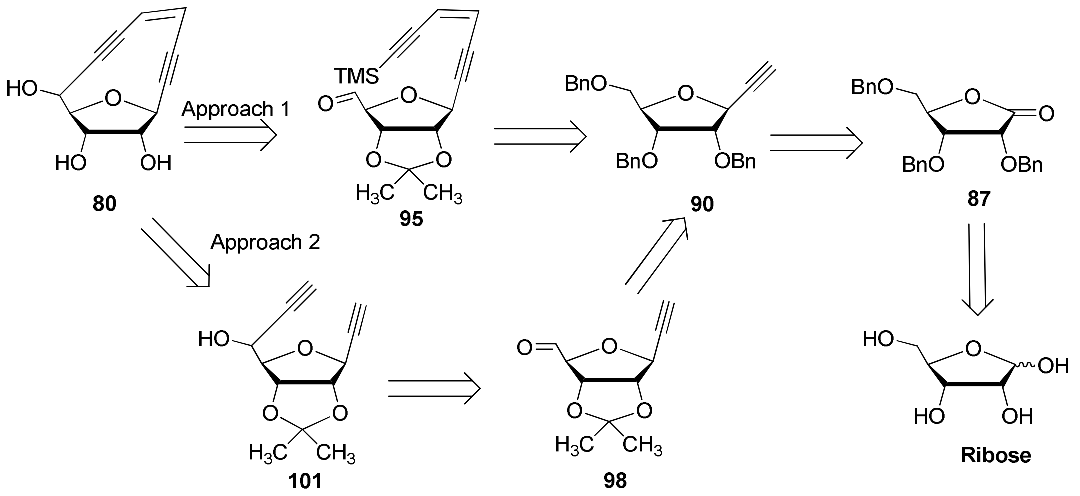
### 4.3. Synthetic plan

Carbohydrates are convenient chiral molecules available in cyclic and acyclic forms employed extensively as stereogenic precursors in the synthesis of natural products.[65,66] The most commonly employed carbohydrate precursors are D-glucose, D-arabinose and D-ribose. For the present research effort, D-ribose was chosen as the starting material because it is found in the living cells as part of the cellular macromolecules such as RNA and the DNA. Ribose is also not cost prohibititive and is readily available. The enediynes **80** and **81** will be constructed between the anomeric and terminal C-5′ carbon of ribose in a stereoselective manner to yield the β-isomer specifically.

### 4.3.1. Retrosynthetic plan for the synthesis of cyclic enediyne 80

Two different retrosynthetic approaches are considered to prepare **80** from ribose (Scheme 15). In approach 1, cyclicenediyne **80** will be formed from enediyne **95**, in which the enediyne moiety will be introduced at the anomeric carbon. Intramolecular ring-closing of enediyne **95** will provide the cyclicenediyne **80**. In approach 2, a dialkyne **101** will be made by introducing the ethyne functional group both at anomeric carbon and at C-5'position. The diyne **101** will be coupled with *Z*-1,2-dichloroethene to give **80**. Different synthetic schemes have been proposed for approaches 1 and 2 in schemes 16 and 17 reapectively.

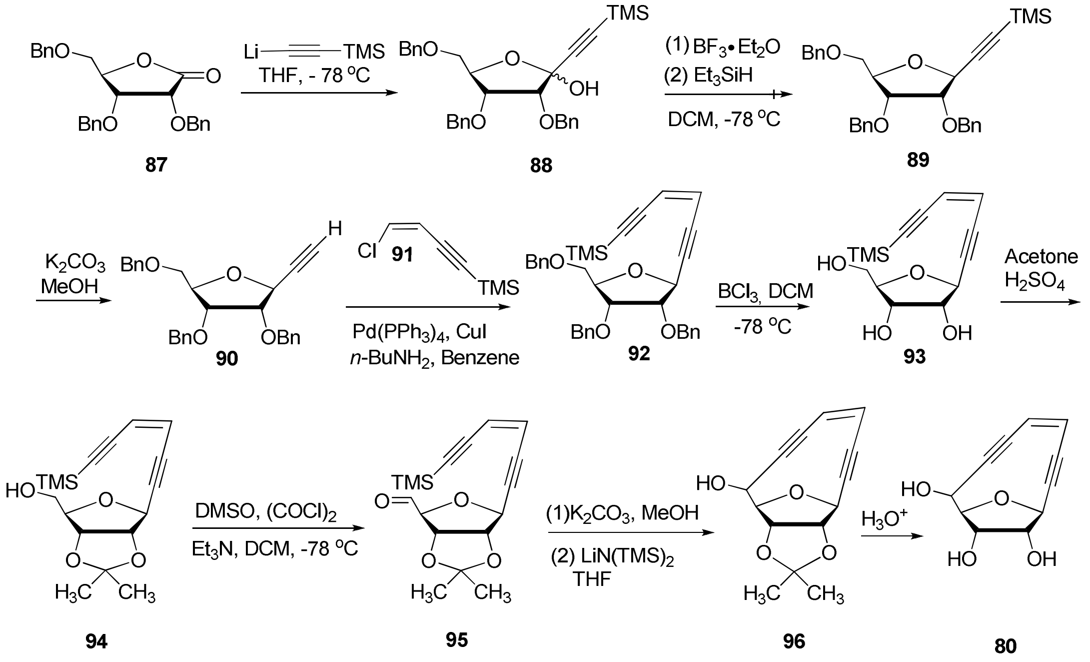
**Scheme 15**. Retrosynthetic approache to synthesize cyclic enediyne **80**



### 4.3.2. Proposed synthetic plan for approach 1

In synthetic approach 1, compound 2,3,5-tri-*O*-benzyl-D-ribonolactone (**87**), will be reacted with lithium trimethylsilyl acetylene[32] at -78 °C to yield the hemiacetal **88**. Reduction of **88** with $BF_3{\cdot}Et_2O$ and $Et_3SiH$ will give **89**.

**Scheme 16**. Proposed synthetic plan to synthesize enediyne **80** by approach 1

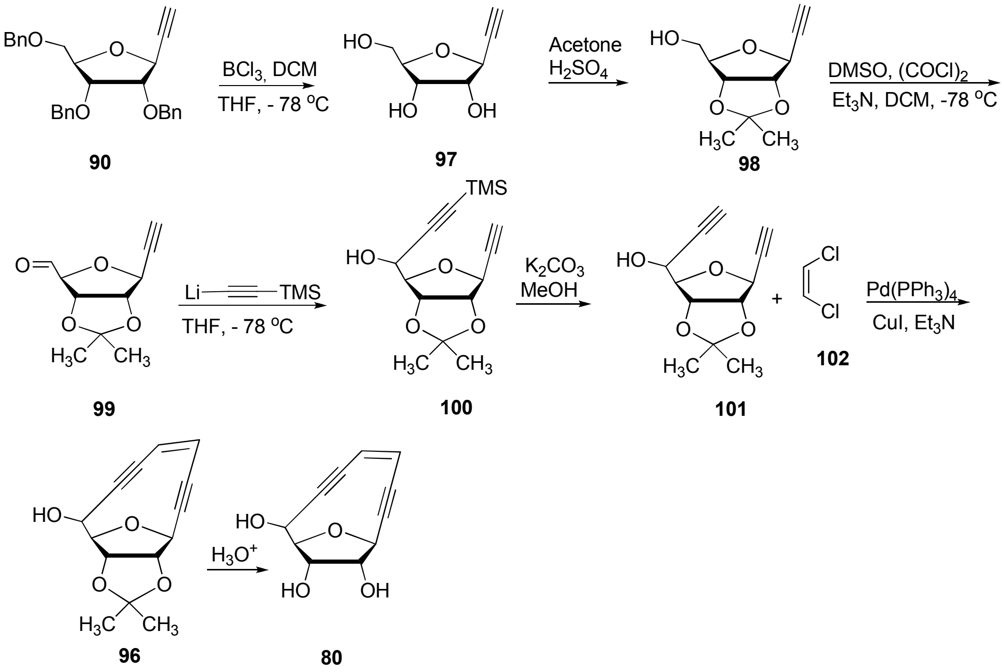


Desilylation of **89** with anhydrous $K_2CO_3$ and methanol will give **90**. Compound **90** can be coupled with *Z*-1-chloro-4-trimethylsilyl-1-buten-3-yne[67] **91** to produce the enediyne **92**. Debenzylation of **92** using $BCl_3$ in methylene chloride at -78 °C will yield the triol **93**, which will be treated with acetone and $H_2SO_4$ to provide the isopropylidene derivative **94**.[68] Compound **94** can be converted to **95** by Swern oxidation to give the aldehyde **95**. Desilylation of compound **95** using $K_2CO_3$ and methanol followed by treating with lithium acetylide will produce **96**. Deprotection of the isopropylidene group by acid hydrolysis should furnish the compound **80**.

### 4.3.3. Proposed synthetic plan for approach 2

In approach 2, compound **90** will be debenzylated[69] using $BCl_3$ in methylene chloride to yield the triol **97**. The isopropylidene derivative **98** can be prepared by treating the triol **97** with acetone and $H_2SO_4$. Oxidation of **98** will yield the aldehyde **99**, which will be treated with lithium trimethylsilyl acetylene to produce **100**.

**Scheme 17.** Proposed synthetic plan to synthesize enediyne **80** by approach 2



Desilylation of **100** using $K_2CO_3$ and methanol will provide the diyne **101**, which will be cyclized with commercially available *Z*-1,2-dichloroethene **102** to yield the cyclized product **96**, which upon acid hydrolysis will provide the cyclic enediyne **80**.

# CHAPTER V

## Synthesis of appropriately protected ribose derivatives

# CHAPTER V

## Synthesis of appropriately protected ribose derivatives

### 5.1. Protection of carbohydrates

The stereocontrolled addition of acetylene at the anomeric position requires proper protection of the ribose. So the first step in the research is to protect the hydroxyl groups of ribose, which will enable the stereocontrolled synthesis of ethynylriboglycosides. In general, synthetic approaches using carbohydrate substrates are hampered by challenges associated with:

a) The regioselective protection of polyhydroxyl groups.

b) Stereoselective assembly of glycoside linkages.

Protection of one or more of the hydroxyl groups is often the first step performed on any unprotected carbohydrate starting material. The choice of the protecting group is critical because, it should be stable under the reaction conditions and it should be easily removed once it has fulfilled its protecting role. Since ribose is a polyhydroxy compound, it is necessary to protect the hydroxyl groups that are not participating in the reaction, in order to ensure appropriate chemoselectivity. Common protecting groups for the hydroxyl groups are silyl ethers such as trimethylsilyl ether (TMS),[70] *tert*-butyldimethylsilyl ether (TBDMS),[71]and triphenylsilyl ethers(TPS),[72] alkoxyalkyl ethers such as methoxymethyl ether (MOM),[73] and benzyloxymethyl ether (BOM).[74] Hydroxyl groups can also be protected as alkyl ethers such as methyl,[75] allyl,[76] and also as ester groups.[77,78] Most silyl protecting groups are readily removed under acidic conditions, by Lewis acids such as $BF_3$. Hydroxyl groups can also be protected as benzyl ethers, which are generally insensitive to acidic conditions, and they are compatible with organometallic reagents.[79,80]

## 5.2. Synthesis of protected ribose derivatives

Commercially available D-ribose was protected to yield three different substrates. They are:

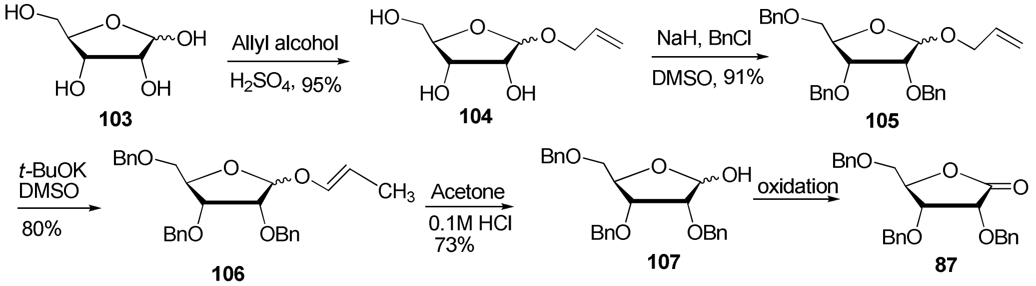
a) 2,3,5-Tri-*O*-benzyl-D-ribonolactone (**87)** (Scheme 18)

b) 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (**110)** (Scheme 19)

c. 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone (**113)** (Scheme 20)

### 5.2.1. Synthesis of 2,3,5-tri-*O*-benzyl-D-ribonolactone (87)

**Scheme 18**. Synthesis of 2,3,5-tri-*O*-benzyl-D-ribonolactone



Ribose **103** was converted to 1-*O*-allyl-α,β-D-ribofuranoside (**104**) by treating it with allyl alcohol and catalytic amount of sulfuric acid in 95% yield.[81] Treatment of **104** with sodium hydride and benzyl chloride in anhydrous DMSO produced 2,3,5-tri-*O*-benzyl-1-*O*-allyl-α,β-D-ribofuranoside (**105**).[81] Isomerization of **105** with potassium *tert*-butoxide in DMSO gave 1-*O*-propenyl-2,3,5-tri-*O*-benzyl-α,β-D-ribofuranoside (**106**).[81,82] Hydrolysis of **106** with a solution of acetone and 0.1 M HCl yielded the 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (**107**). Oxidation of **107** produced 2,3,5-tri-*O*-benzyl-D-ribonolactone (**87**).

Four different oxidation methods have been attempted:

a) DMSO and acetic anhydride.[83]

b) Pd and bromobenzene.[84]

c) $Br_2$ and $NaHCO_3$.[85]

d) $KMnO_4$ and acetone.[68]

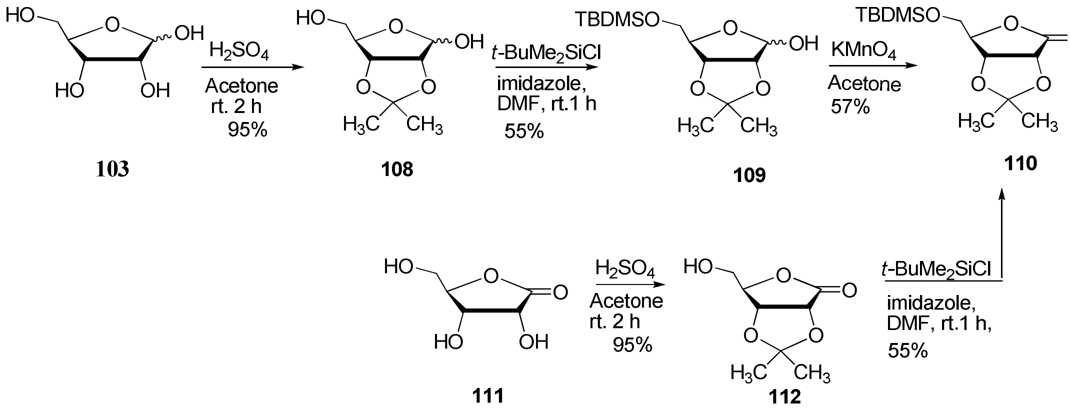
Oxidation by acetic anhydride and DMSO was carried out by dissolving 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (**107)** in DMSO and acetic anhydride. The mixture was stirred overnight at room temperature under a nitrogen atmosphere. After work up, analysis of the crude product showed the expected lactone **87**, contaminated with many by products rendering purification difficult.

In the Pd-catalyzed oxidation method, a solution of palladium acetate and triphenylphosphine in distilled THF was treated with 2,3,5-tri-*O*-benzyl-D-ribonofuranose (**107**), $K_2CO_3$ and bromobenzene. The mixture was stirred vigorously under reflux for 6 h and then worked up. The expected product **87** was not obtained here, instead the starting material **107** was recovered.

In oxidation by bromine method, the product **87** was obtained in 40% yield. Even though this reaction worked, it is advantageous to avoid the use of bromine. So an alternative method was tried using $KMnO_4$ as the oxidizing agent. In this method 2,3,5-tri-*O*- benzyl-α,β-D-ribofuranose (**107**) was dissolved in acetone and to this solution $KMnO_4$ was added. Stirring was continued at room temperature for 2 h. After the workup, the yield of the product **87** was found to be 60%. This could be readily purified using petroleum ether/ethyl acetate (3/1). However, when the compound was purified using silica column the yield was considerably reduced. This may be due to its instability on silica gel. The yield of the pure compound after purification was about 30%. This method is simple and gave better results compared to the other oxidation methods attempted.

### 5.2.2. Synthesis of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (110)[68]

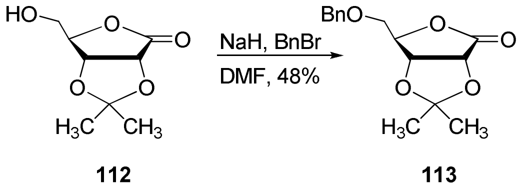
**Scheme 19.** Synthesis of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D- ribonolactone



Ribose **103** was treated with acetone and catalytic amount of sulfuric acid to yield 2,3-*O*-isopropylidene-α,β-D-ribonofuranose (**108**) in 95% yield. Reaction of **108** with TBDMSCl and imidazole yielded 5-*O*-*tert*-butyldimethylsilyl-2,3- *O*-isopropylidene-α,β-D-ribofuranose (**109**). Lactol **109** was oxidised using $KMnO_4$ gave the ribonolactone **110** (Scheme 19). Compound **110** can also be prepared from the commercialy available ribonolactone **111** (Scheme 19). Ribonolactone was converted to the isopropylidene deivative **112** using acetone and catalytic amount of $H_2SO_4$. Protection of **112** with TBDMSCl yielded **110** in 55% yield.

### 5.2.3. Synthesis of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone (113) [86a,b]

**Scheme 20.** Synthesis of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone



In this method, sodium hydride (60% in mineral oil) and benzyl bromide was added to a mixture of 2,3-*O*-isopropylidene-D-ribonolactone (**112**) in DMF at 0 $^{o}$C. The mixture was stirred for 30 min. The reaction was further stirred for 16 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 0.1 M HCl. After the work up, the crude mixture was chromatographed using hexane/ethyl acetate (3/2) to give pure 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone ( **113**) in 48% yield.

# CHAPTER VI

# Synthesis of ethynylribofuranosides

# CHAPTER VI

## Synthesis of ethynylribofuranosides

### 6.1. Carbohydrate electrophiles used in this research

To achieve the synthesis of the simple enediyne molecule **80**, it is important to make β-ethynylribosides first (Scheme 15). Therefore, nucleophilic addition of trimethylsilyl acetylene was performed on three different ribose derivatives. Examples of some carbohydrate electrophiles are shown in the Scheme 11. For the research purpose, the following ribose based elctrophiles were considered:

(1) Lactones.

(2) Lactols.

(3) Anomeric acetates.

### 6.2. Ethynylation using ribonolactones

**Stereochemical outcome of nucleophilic addition to five-membered lactones**

Lactones are commonly used to introduce carbon-carbon bond at the anomeric center. So the ethynylation reaction was attempted first on ribonolactone derivatives. For five-membered lactones, the stereochemical analysis of the nucleophilc addition products is complicated compared to the same type of reaction in the six-membered lactones. The most stable conformation of six-membered ring is the chair form. During conformational inversion, the substituents that are axial in one chair conformation become equatorial in another chair conformation. Depending on each group position, there is substantial energy difference between the two conformers, facilitating the understanding of the observed stereoselectivity. In contrast, the furanose ring, being more flexible than six-membered ring, undergoes dynamic conformational changes[88] between the envelope and half chair forms (Figure 9).[87]

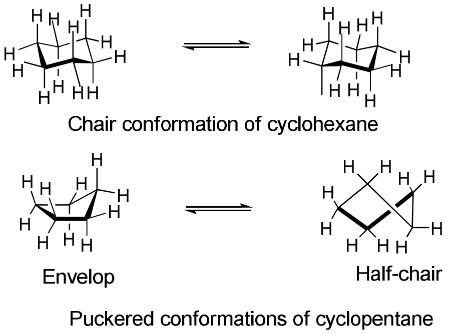


**Figure 9**. Conformations of cyclohexane and cyclopentane rings[87]

This rapid interconversion and greater tendency to pucker make the anomeric effect less pronounced in five-membered rings compared to the six-membered rings. In addition, the spin-spin coupling constant between the anomeric proton and the adjacent proton at C-2′ is not consistently diagnostic in the determination of stereochemistry at the anomeric carbon of five-membered rings. In such cases, analyzing and understanding the stereochemical outcome of the reactions are challenging.

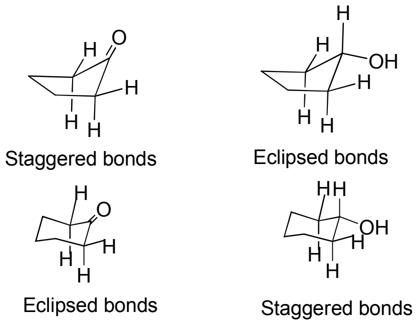
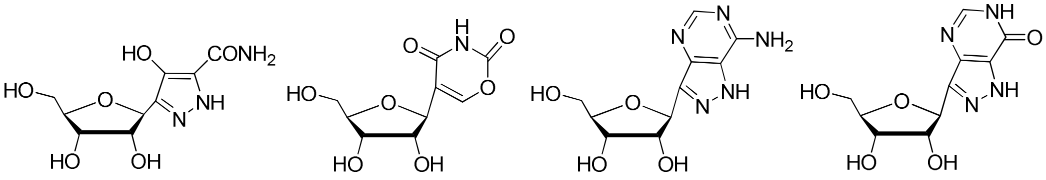


**Figure 10**. Impact of torsional strain on reactivity[90]

In cyclic systems, torsional strain plays a major role in the relative ease of converting carbon atoms in a ring from sp$^3$ to sp$^2$ or vice versa. In six-membered rings, the conversion from sp$^2$ carbon to sp$^3$ carbon is more feasible than the corresponding change in the five-membered rings. For example, cyclohexanone is reduced by sodium borohydride 23 times faster than cyclopentanone.[89] This is because converting an $sp^2$ carbon atom to an $sp^3$ carbon atom in six-membered rings leads to a completely staggered chair arrangement. But the same reaction in a five-membered rings increases the number of eclipsing interactions (Figure 10).[87] This steric demand on reaction of cyclopentanone results in low reactivity. Investigating and developing reactions and protocols, which lead to the stereoselective synthesis of β-carboribofuranosides will also facilitate and contribute to the preparation of many naturally occurring biologically active β-ribofuranosides[91-94] (Figure 11).



Pyrazofurine Oxazinomycin Formycin Formycin B

**Figure 11**. Examples of natural β-ribofuranosides

One of the most useful methods to synthesize anomeric acetynyl derivatives is the nucleophilic addition of trimethylsilyl acetylene to the lactone electrophile followed by the reduction of the hemiacetal formed during the reaction.[95,32] The yield and the stereoselectivity of the product formed during the reduction depend upon on the nature of the protecting groups. Protecting groups which are acid sensitive will be cleaved under acidic conditions resulting in the lower product yields.

If the lactones enolize readily, such as β and γ lactones, strongly basic nucleophiles will enolize the lactones and will minimize the nucleophilc addition product.[96] Organocerium reagents have recently been reported[97] to react with such ketones to give mainly the nucleophilic addition products because they are less basic than the organomagnesium and the organolithium reagents.[97] Trivalent cerium is also strongly oxophilic.[97]

In this research project, syntheses of ethynylribosides were explored on three differently protected ribonolactone substrates:

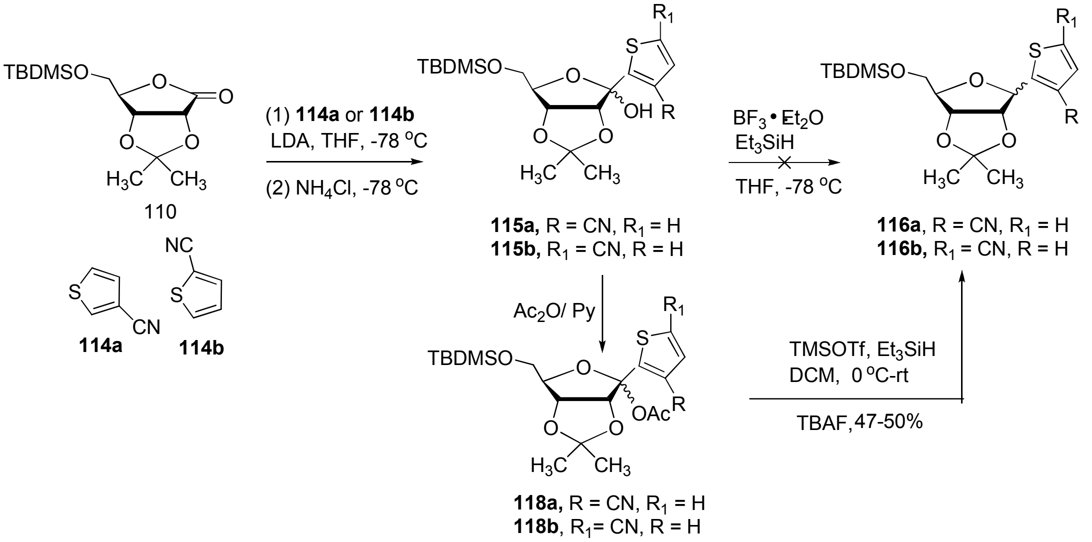
(a) 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropyledine-D-ribonolactone (**110**).

(b) 5-*O*-benzyl-2,3-*O* isopropylidene-D- ribonolactone (**113**).

(c) 2,3,5-Tri-*O*-benzyl-D-ribonolactone (**87**).

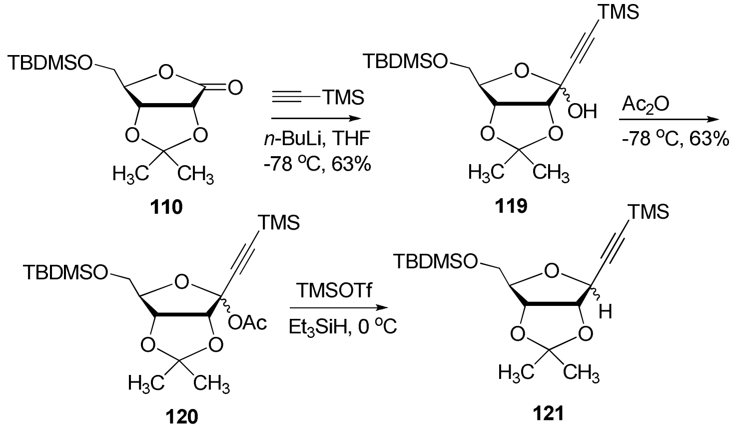
### 6.2.1. Ethynylation using 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (110)

**Scheme 21**. Synthesis of C-nucleoside **116a** and **116b**[98]



The synthetic protocol to prepare 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-trimethylsilylethynylriboside **121** (Scheme 22) from **110** was based on the work attempted by Batoux et al. (Scheme 21).[98] In the syntheses of the C-nucleosides **116a**, and **116b**, lactone **110** was treated with the lithiated thiophenes **114a** and **114b** for 30 min at -78 °C. The reaction mixture was then quenched with saturated $NH_4Cl$ to yield the hemiacetals **115a** and **115b**. Attempt to reduce **115a** and **115b** using $BF_3 \cdot Et_2O$ and triethylsilane to yield **116a** and **116b** was not successful. Unsuccessful deoxygenation reactions of this type have been reported earlier.[99] In an alternative procedure, Townsend et al. converted the hemiacetals **115a** and **115b** to acetates **118a** and **118b** by *in situ* addition of acetic anhydride at -70 °C.[98] Reduction of the acetate derivatives with trimethylsilyltriflate (TMSOTf) and $Et_3SiH$ in methylene chloride yielded α/β mixture of **116a** and **116b** in 1.4/1 ratio.

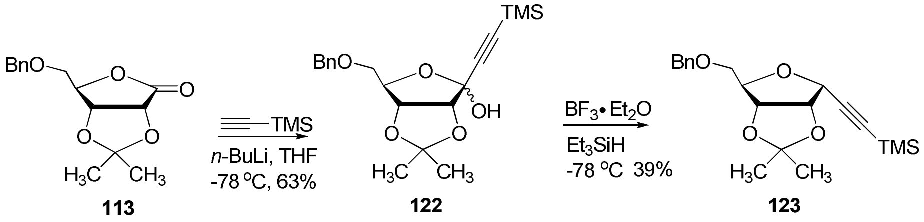
**Scheme 22**. Synthesis of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-trimethylsilylethynylriboside



Therefore, lactone **110** was treated with lithium trimethylsilyl acetylene in THF at -78 °C for 30 min. The intermediate hemiacetal **119** was then converted to the acetoxy derivative **120**. Deacetylation of **120** with TMSOTf and $Et_3SiH$ in dichloromethane at 0 °C yielded **121** (Scheme 22). Isolation and purification of **121** was difficult due to the formation of many side products formed. In addition, extensive desilylation and cleavage of isopropylidene protecting groups were observed which reduced the overall yield of the product.

### 6.2.2. Ethynylation using 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone

**Scheme 23**. Synthesis of 5-*O*-benzyl-2,3-*O*-isopropylidene-1-trimethylsilylethynylriboside



Due to the desilylation observed in the synthesis of **121** from lactone **110**, the TBDMS group in **110** was replaced by a benzyl group to get **113** in order to eliminate the cleavage of TBDMS group in the reduction step. Therefore, the utility of benzyl lactone derivative **113** was explored next (Scheme 23). Trimethylsilyl acetylene was added to **113** at -78 °C to yield the hemiacetal derivative **122**. When deoxygenation was performed on **122** using 14 equivalents of $BF_3$· $Et_2O$ and 7 equivalents of $Et_3SiH$, white crystals of **123** were obtained in 20% yield. Cleavage of the isopropylidene group under the Lewis acid may account for the lower product yield. The reaction yield was improved to 39% when the amount of the $BF_3$·$Et_2O$ and $Et_3SiH$ was reduced to 7 and 3.5 equivalents respectively

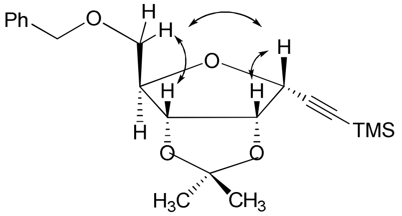


**Figure 12**. Sterochemical assignment of 5-*O*-benzyl-2,3-*O*-isopropylidene -1-trimethylsilylethynylriboside **123**

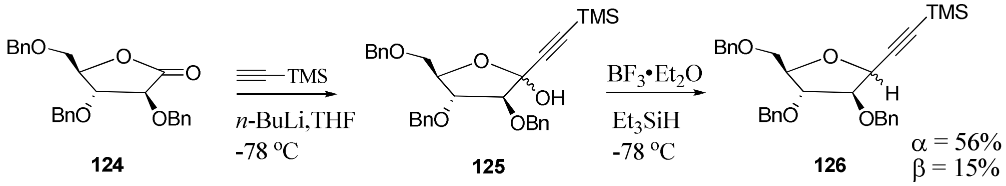
NOE analysis of **123** confirmed that it is a α-isomer. NOE data of **123** showed interactions between H-1' and H-5' or H-5″ protons and between H-1' and H-2' protons. No nOe interaction was seen between H-1' and H-4' protons, which would be normally be present for a β-isomer (Figure 12).

### 6.2.3. Ethynylation using 2,3,5-tri-*O*-benzyl-D-ribonolactone

Nucleophilic addition on the ribonolactone **113**, produced the α-**123** instead of the expected β-**123**. So in the next attempt, benzylprotected lactone **87** was used. Nucleophilic addition to lactone **87** was reported by different research groups during the syntheses of β-C-nucleosides. For example, ribonolactone **87** was the substrate used by Jasenka et al. for the synthesis of 5-(β-D-ribofuranosyl)-pyridine-2-one.[52] Krohn was able to synthesize β-benzamide ribose[69] using lactone **87**. Therefore, 2,3,5-tri-*O*-benzyl-D-ribonolactone (**87**) was reacted with lithium trimethylsilyl acetylene. The molar ratio of trimethylsilyl acetylene and lactone **87** were critical here. First, the reaction was attempted using 2:1 molar ratio of trimethylsilyl acetylene and the lactone **87** at -78 °C in THF. No product was isolated here. So the reaction was repeated with 1:1 molar ratio of trimethylsilyl acetylene and lactone **87.** This condition produced an inseparable mixture of the starting material and the product **88**.

Ribonolactone **87** is, of course, a γ-lactone. Therefore, cerium trimethylsilyl acetylide was used next to prevent any competing enolization reaction that might have taken place during nuclophilic addition. Cerium trimethylsilyl acetylide was synthesized by transmetallation reaction between the lithium trimethylsilyl acetylide and $CeCl_3$.[96,97] The anhydrous $CeCl_3$ obtained after heating the commercially available $CeCl_3 \cdot 7H_2O$ under *vacuum* about 140 °C was mixed with lithium trimethylsilyl acetylene in THF and cooled to -78 °C to get cerium trimethylsilyl acetylide. The lactone **87** in THF was then added to it with stirring and the reaction mixture was stirred for 4 h at - 78 °C. After the workup, a brownish viscous residue was obtained, which contained none of the desired product **89**. The reaction did not go as expected, probably because $CeCl_3.7H_2O$ was not effectively dried.

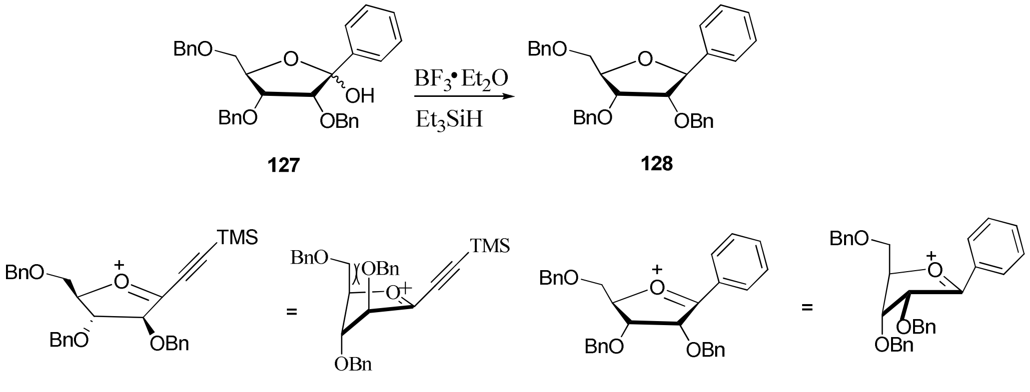
**Scheme 24**. Synthesis of 2,3,5-tri-*O*-benzyl-1-trimethylsilylacetylidearabinoside[95]



Finally the method adapted by Wightman et al. in the synthesis of 2,3,5-tri-*O*-benzyl-1-trimethylsilylethynylarabinoside **126** was considered[95] (Scheme 24). Treatment of 2,3,5-tri-*O*-benzylarabinolactone (**124**) and trimethylsilyl acetylene in 1: 1.5 ratio gave a mixture of disastereoisomer lactols **125**. Reduction of lactol **125** with $BF_3$·$Et_2O$ and triethylsilane gave **126** in a 56/15 ratio of α/β isomer. Deoxygenation of hemiacetals under acidic conditions are likely to procced through oxocarbenium intermediates.[100] Therefore, it is expected that reduction of **125** to **126** will proceed via the oxocarbenium ion intermediate**129** (Scheme 25).

It had been reported [101,102] that in five- and six-membered oxocarbenium ions, addition of hydride ion takes place predominantly cis to the alkoxy group present at C-3□ position. Therefore, the ethynylarabinoside **126** formed from the oxocarbenium ion **129** is expected to have β-stereochemistry, due to 1,3-cis hydride addition. Instead, the α-**129** was the major product. It has also been reported[101] that the 1,3-cis hydride addition is enhanced if the two benzyloxy groups at C-2 and C-3 positions are cis to each other (Scheme 25). For example, in the deoxygenation of the acetal **127**, where the OBn groups at C-2 and C-3 are cis to each other, 1,3-cis hydride addition yielded exclusively the β-**128**.[101]

**Scheme 25**. α-hydride attack (1,3-cis addition) in oxocarbenium ions



127 128

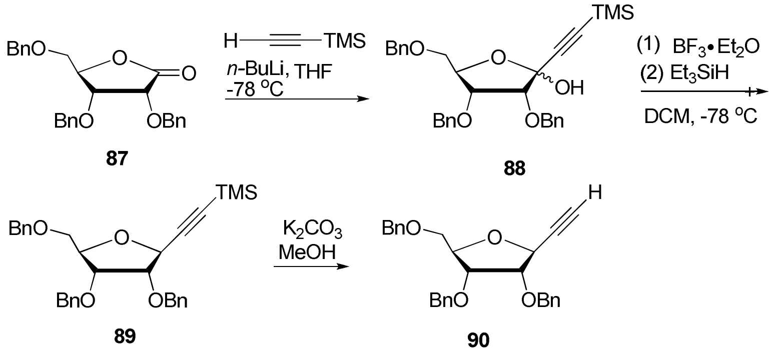
129 129a 130 130a

If we compare the ground state conformations of the oxocarbenium ions **129a** and **130a**, formed from the lactols **125** and **127**, respectively (Scheme 25), oxocarbenium ion **129a**, in which the C-2 and C-3 benzyloxy groups are trans to each other, is destabilized by steric interaction developed from the unfavorable pseudoaxial C-2β -OBn group. This accounts for the lower yield and poor selectivity for β-isomer (15%).[101] This steric interaction is absent in **130a** where C-2 and C-3 benzyloxy groups are cis to each other enhancing 1,3-cis addition giving exclusively β-**128**.

Therefore lactone **87**, with cis orientation of the C-2 and C-3 benzyloxy groups, is expected to proceed through carbenium ion **130**, giving the β-isomer of **90** (Scheme 26). Ribonolactone **87** was treated with trimethylsilyl acetylene (1:1.5 molar equiv) in freshly distilled THF at -78 °C for 2 h. The reaction mixture was quenched with ammonium chloride, and after the work up, the yield of the crude lactol **88** was 84%. Infrared spectrum of the crude product indicated partial desilylation of the product. Compound **88** was reduced using BF$_3$·Et$_2$O and triethylsilane at -78 °C for 1 h. Analysis of the NMR and NOE spectra supported the β-stereochemistry of the product **89**. No α- isomer was isolated in this reaction. Compound

**89** was desilylated using anhydrous $K_2CO_3$ and methanol to yield ethynylriboside **90** quantitatively.

**Scheme 26**. Synthesis of 2,3,5-tri-*O*-benzyl-1-ethynylriboside (**90**)



### 6.2.3a. Stereochemical analysis of 2,3,5-tri-*O*-benzyl-1-trimethysilylylethynylriboside 89

The NOE spectrum of **89** showed weak interaction between H-1' and H-4' indicating their position on the same ring face. There was no nOe interaction between H-1' and H-5' or H-5'' protons. Because of the overlapping of H-1' and the benzylic protons at C-2' and C-3', it was not clear whether any nOe exists between the H-1' to H-2'. The expected nOe interaction between the benzylic protons between at C-2' position and H-1' could not be discovered clearly due to signal overlap of H-1' and the benzylic protons. None of the benzyl protons is singlet, they are all AB quartet. The presence of weak nOe interaction between H-1' and H-4' is in supportive of the β-stereochemistry at C-1' position of the compound **89**. This is further confirmed by comparing the nOe data of compound α-**123**, which was synthesized ealier in this research. In compound **123**, nOe interactions between H-1' and H-2' and between H-1' and H-5', H-5'' are observed, but there is no nOe interaction between H-1' and H-4'.

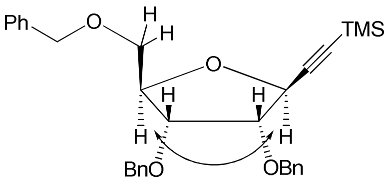


**Figure 13**. Stereochemical assignment of compound **89**

Similar spectroscopic analysis and observations were reported for ribosides **131**, **132** and **133**, and **134** (figure 14).[103,104] The β-stereochemistry of compounds **131** and **132** was clearly supported by the nOe between H-1' and H-4'.[103,104] The corresponding α-anomers **133** and **134** showed no nOe between H-1' and H-4', but they do show nOe between H-1' and H-2'.[103,104]

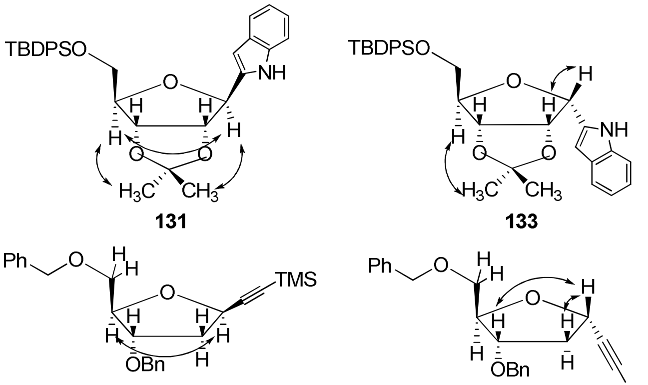

**131**
**133**
**132**
**134**

**Figure 14**. nOe interaction of reported riboglycosides

The establishment of the β-anomeric stereochemistry of compound **89** was further supported by comparing the H-1' chemical shift values of similar compounds. Figure 15 depicts the structures of α and β furanosides of related compounds. H-1' chemical shift values of compounds **135**, **136**, **137**, and **138** are given in Table 4. The chemical shift of H-1 protons of β-anomers **135** and **136** appear slightly smaller (δ = 4.80-4.99 ppm) than those α- anomers **137** and **138** (δ = 5.0–5.01 ppm).[105,106] The chemical shift for the H-1' in compound **89** is 4.78 ppm, which is within the range for products with β-anomeric stereochemistry.

**Figure 15**. H-1' Chemical shift values of reported riboglycosides

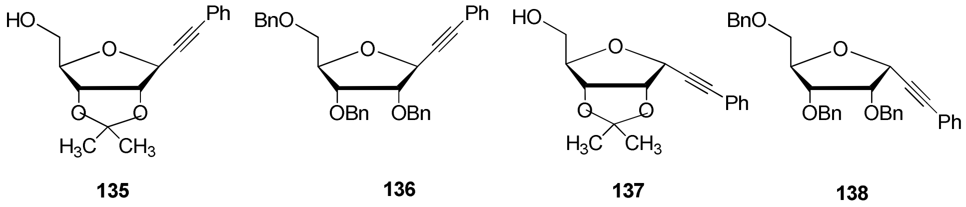


**Table 4**. H-1' Chemical shift valves of reported compounds and **89**

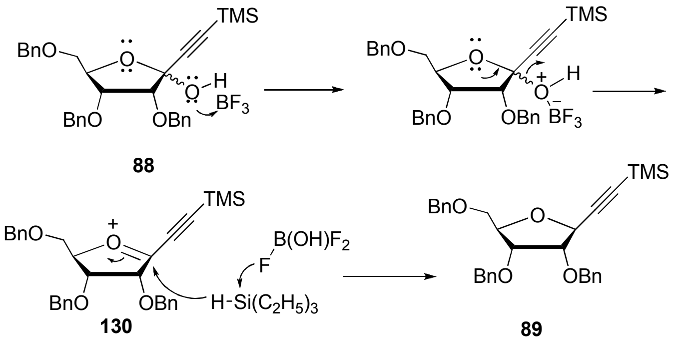
| Compound | H-1' in ppm |
|---|---|
| **135** (β) | 4.80-4.99 |
| **136** (β) | 4.89 |
| **137** (α) | 5.01 |
| **138** (α) | ~ 5.0 |
| **89** (β) | 4.78 |

### 6.3. Mechanism of Hydride addition to the oxocarbenium ion

The Lewis acid promoted reduction of lactol involves the formation of oxocarbenium ion intermediate.[100] Suggested mechanism for the formation of **89** from **88** is given in Scheme 27. Deoxygenation of the lactol **88** using $BF_3$ will procced via the formation oxocarbenium ion **130**.[100] Addition of hydride ion to **130** will takes place in a 1,3-cis fashion (α-face) to give **89** exclusively with β stereoselectivity.

Extensive studies on the strereoselectivity of hydride addition to six-membered oxocarbenium ions were reported by Woerpel et al. According to their observations stereoselectivity of the six-membered oxocarbenium ions depends upon both the electronic and stereoelectronic effects.[107,108] For five-membered rings, due to their rapid conformational changes,[109] it is very difficult to develop a stereochemical model to understand the stereochemistry of the products formed.

**Scheme 27**. Proposed mechanism of reduction of cyclic acetal in acidic medium



Since five- and six-membered ring oxocarbenium ions have parallel selectivity patterns, conformational analysis of hetero-substituted six membered ring oxocarbenium ions helps to understand the behavior of the five-membered ring analogs.[107,110] Studies indicated that the alkoxy group present only at C-3'position has greater influence in directing the incoming hydride nucleophile.[101] The substituents at C-2' and C-4' are not critical for stereoselectivity. Woerpel et al. have also reported that alkoxy groups tend to occupy pseudoaxial position in the oxocarbenium ions and alkyl substituent will occupy pseudoequtorial position.[108]

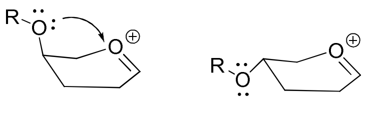
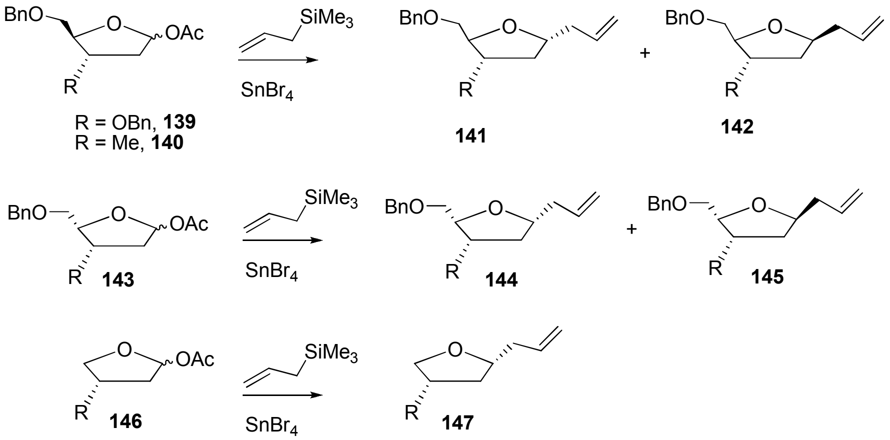


**Figure 16**. Through-space electronic stabilization by axial alkoxy group[111]

The pseuodoaxial position of the alkoxy group helps to maximize the attrative electrostatic interactions between the alkoxy group and the carbon cation in the oxocarbenium ion. Computational studies reveal that in six-membered oxocarbenium ions, pseudoaxial arrangement of alkoxy group promotes effective through-space electrostatic stabilization of the carbocation by developing an electrostatic attraction (Figure16).[111] *Ab initio* calculations of model molecules fully support this conclusions.[111] This through space electrostatic interaction, which stabilizes the oxocarbenium ion is possible only when the alkoxy group is in pseudoaxial position.

It has been observed that electronegative substituents such as alkoxy groups at C-3' often undergoes reactions with opposite diastereoselectivity compared to the C-3' alkyl substituted oxocarbenium ion. This conformational preference is supported by experimental studies with six-membered ring oxocarbenium ions[107, 108] and with ribose derived oxocarbenium ions[101] (Scheme 28). For example, the oxocarbenium ion formed from **139** will direct the incoming nucleophile cis to the alkoxy group (OBn) at C-3' to give more than 99% of α product **141**. At the same time in compound **140**, due to the presence of an alkyl group at C-3', the nucleophile will add anti to the methyl group to give more of β anomer **142** (Table 5)

**Scheme 28**. 1,3-cis selectivity of 3-alkoxy furanosides[101]



The difference in stereoselectivity observed between the alkyl and the alkoxy group is independent of the relative positions of substituents at C-3'and C-4' positions. For example in compounds **139** and **143** the relative stereochemistry of the subsituents at C-3′ and C-4′ are different, yet the stereochemical outcome of the product **144** and **145** are similar ratio as observed for compounds **139** and **140**. Also the 1,3-cis stereo selectivity is independent of the size of the protecting group at C-3′.

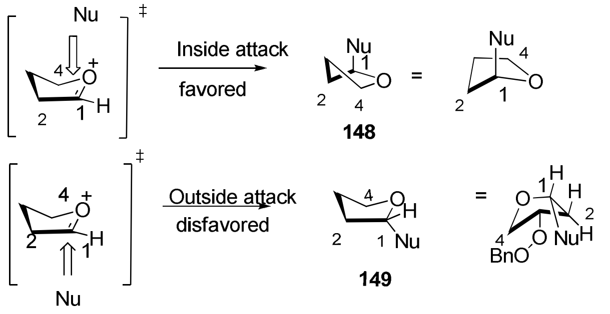
**Table 5**. Stereoselectivity of C-3alkyl and alkoxy groups in furanosides[101]

| Compound | 1,3-cis (α) % | 1,3- trans (β)% |
|---|---|---|
| **141** (R = OBn) | > 99 | 1 |
| **142** (R = Me) | 5 | 95 |
| **144** (R = OBn) | 88 | 12 |
| **145** (R = Me) | 7 | 93 |
| **147** ( R = OBn) | 94 | 6 |
| (R = t- BuMe$_2$SiO) | 94 | 6 |
| ( R= MeOCH$_2$O) | 94 | 6 |

For example, the stereoselectivity of the compound **147** formed from **146** is not affected by the size of the R groups such as benzyl, TBDMS, and MOM present at the C-3' position. The reactions of alkyl substituted cations appears to be dominated by steric effect and alkoxy substitution is dominated by electronic effects.[107]This explains the opposite stereoselectivity in the addition of nucleophiles to alkoxy- and alkyl- substituted oxocarbenium ions.

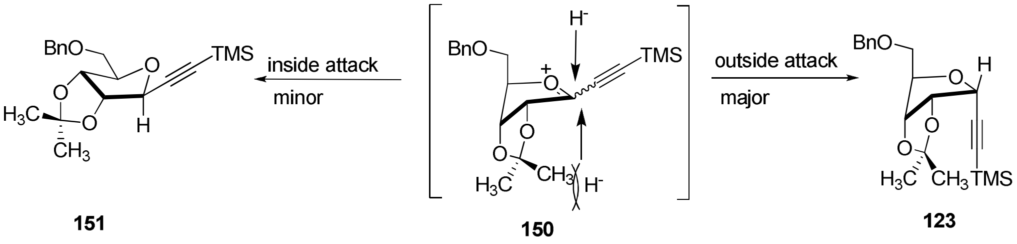
The preferred conformation of a five-membered ring oxocarbenium ions is much like an envelope conformation, where the C=O$^+$ resides in the planar part of the envelope.[110] The nucleophile can approach the envelope either from “inside” or from “outside” to give two possible products (Scheme 29).

**Scheme 29**. Stereoelectronic preference for the addition of nucleophiles to five-membered oxocarbonium ion[110]



Attack from inside results in all staggered conformer **148**, but attack from outside results in the conformer **149** that suffers from eclipsing interactions between the C-1′ and C-2′ substituents. So inside attack is preferable to give β product.

**Scheme 30**. Approach of hydride ion in isopropylidene protected the oxocabenium ion



Based on the above experimental data and explanations offered, it is reasonable to conclude that the oxocarbenium ion **130** (Scheme 25), with cis orientation of benzyloxy groups at C-2′ and C-3′, undergoes only 1,3-cis hydride addition giving **89** exclusively with β-stereochemistry. No α-isomer was detected. In the case of isopropylidene protected oxocarbenium ion **150**, hydride ion is added via 1,3-anti fashion to produce α-**123** as a major product (Scheme 30). The possible explanation is that oxocarbenium ion **150** suffers from significant steric interactions from one of the alkyl groups of the cyclic ketal moiety (Scheme 30). This can lead to the "outside attack" as a major pathway giving a greater proportion of α poroduct **123**.[112] No β-**123** was isolated. It was also reported that isopropylidene ring imposes conformational rigidity on the oxocarbenium ion intermediate contributing to the poor β stereoselectivity.[80]

# CHAPTER VII

## Synthesis of ethynylriboside using lactols sand ribosylacetate

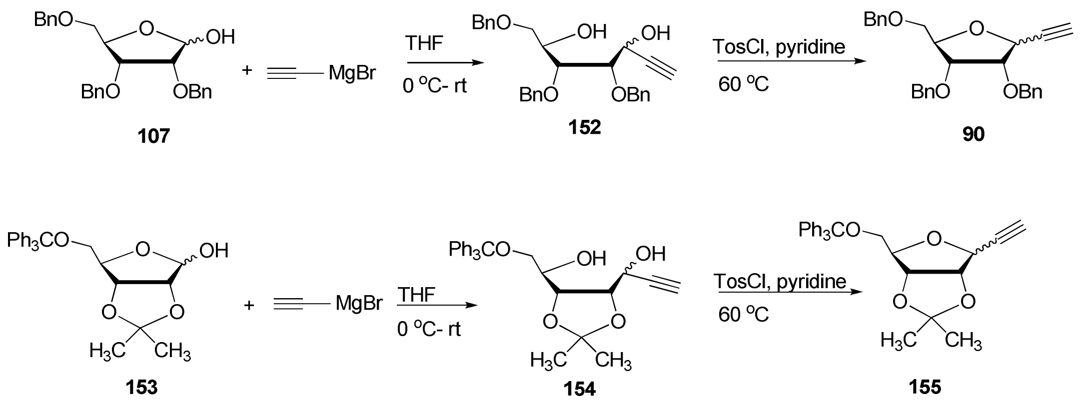
# CHAPTER VII

## Synthesis of ethynylribosides using lactols and ribosylacetate

### 7.1. Synthesis of ethynylribosides using lactols

It is well established that hemiacetals are in equilibrium with their carbonyl tautomers. Therefore, they can undergo nucleophilc addition with the organometallic reagents yielding diols. Under certain reaction conditions,[113] these diols will undergo intramolecular dehydration giving glycoside derivatives. This protocol was used by Buchanan et al. in the synthesis of ethynylribofuranosides **90** and **155** from the corresponding hemiacetals **107** and **153** (Scheme 31).[113,114]

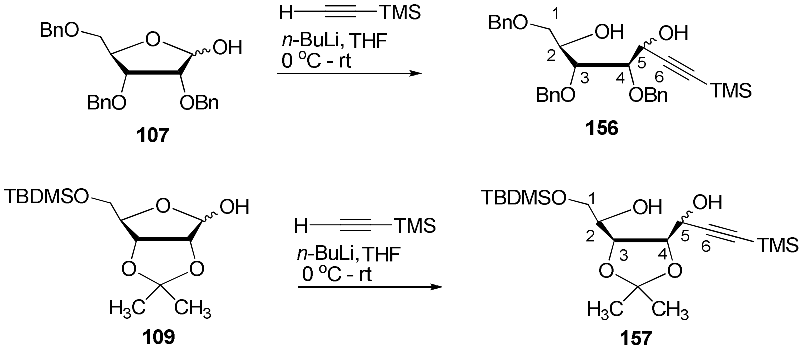
**Scheme 31**. C-ethynylation using ribonolactols[113,114]



In their work, 2,3,5-tri-*O*-benzyl-D-ribofuranose **107** was treated with excess of Grignard reagent to form a mixture of diols **152**. Refluxing the diol mixture **152** with pyridine and p-toluenesulfonylchloride (TosCl) at 60 °C yielded a mixture of α/β isomers of the cyclized glycoside **90**.[113] The α-anomer was the minor product (13%) and the β-anomer was the major product (52%). In the same way, hemiacetal **153** was converted to a mixture of diols **154** by treating with EtMgBr. Refluxing **154** with tosyl chloride (TosCl) and pyridine gave a mixture of the glycoside **155** with 90% α-selectivity.

### 7.1.1. Ring opening reactions of lactols 107 and 109

**Scheme 32**. Ring opening of the lactols **107** and **109** using lithium trimethylsilyl acetylene

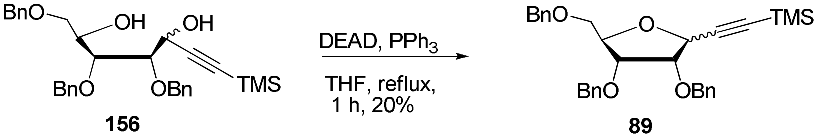


Since synthesis of ethynylribofuranoside **121** from the nucleophilic addition of lithium trimethylsilyl acetylene to the ribonolactone **110** (Scheme 22) was not successful, Buchanan's procedure was used next in an attempt to get the ethynylribofuranosides **121** from lactol **109**. Lactol **107** was also used for the comparative study of stereoselectivity. In two separate reactions, lactols **107** and **109** were treated with trimethylsilyl acetylene and *n*-butyl lithium in THF at 0 °C (Scheme 32). Diols 1,3,4-tri-*O*-benzyl-7-(trimethylsilyl)-6-yne-2,5-diol (**156**) and 1-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-7-(trimethylsilyl)-6-yne-2,5-diol (**157**) formed respectively, from **107** and **109** were isolated and were subjected to cyclization condition.

### 7.1.2. Ring-closing reactions of diols 156 and 157

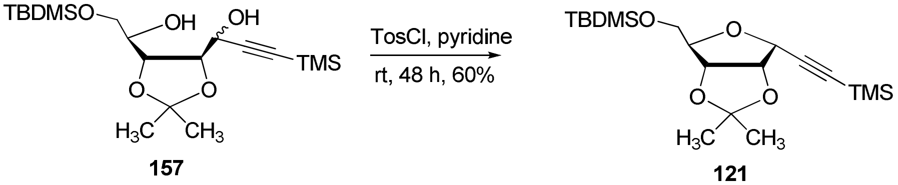
Cyclization of diol **156** was done using Mitsunobu reaction condition,[104] as well as refluxing it with TosCl in pyridine[113] (Scheme 33). Refluxing the diol **156** with TosCl and pyridine did not give any product **89**. Krohn et al. also reported[69] that Buchanan's method of ring-closing of diol **156** by refuxing with pyridine and TosCl was in effective.

**Scheme 33**. Cyclization of diol **156**



Cyclization of the diol **156** using Mitsunobu procedure yielded yellow color syrup. Comparison of TLC, and NMR analysis of the yellow syrup indicated that the compound isolated here was same as 89, which was originally obtained by the nucleophilic addition of lithium trimethylsilyl acetylide to the lactone **87** (Scheme 26). But the yield was very low (5-8%), and the purification was difficult.

**Scheme 34**. Cyclization of diol **157**



Cyclization of the diol **157** by Mitsunobu reaction condition yielded very small amounts of **121** (< 10%) and it was very difficult to purify. However boiling a solution **157** with tosyl chloride in pyridine gave **121** in 30% yield. A higher yield (60%) of **121** was obtained when the reaction was performed at room temperature for 48 h (Scheme 34). Ethynylriboside **121** was isolated and purified by column chromatography using hexane/ethyl acetate (16/1) to yield white crystals of **121**. MNR analysis confirmed α stereochemistry of **121** (Figure 17).

### 7.1.3. Stereochemical assignment for 121

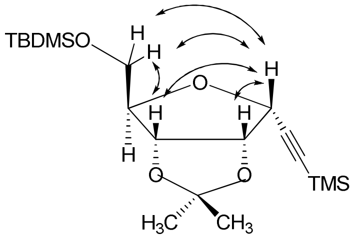
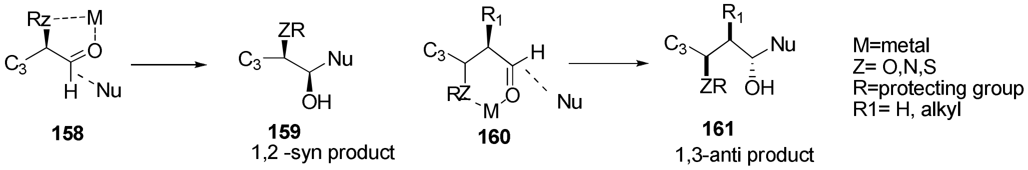


**Figure 17**. Sterochemical assignment for **121**

The NOE spectra of **121** showed strong interactions between H-1' and H- 5’, H-5□ protons, and between the H-1' and H-2' as well as between H-1' and H-3' protons support the α-stereochemistry of **121** (Figure 17). No nOe interaction was observed between H-1' and H-4 '. This assignment is consistent with the compound α-**123**, which was synthesized earlier in this research and also in agreement with the reported values of some known ribonylglycosides shown in Figure 14.

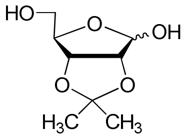
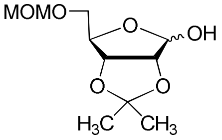
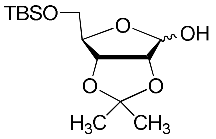
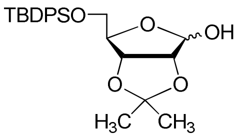
### 7.1.4. Mechanism of ring opening and ring-closing reactions

**Scheme 35**. Stereochemical outcome of addition of nucleophiles to aldehydes[115]



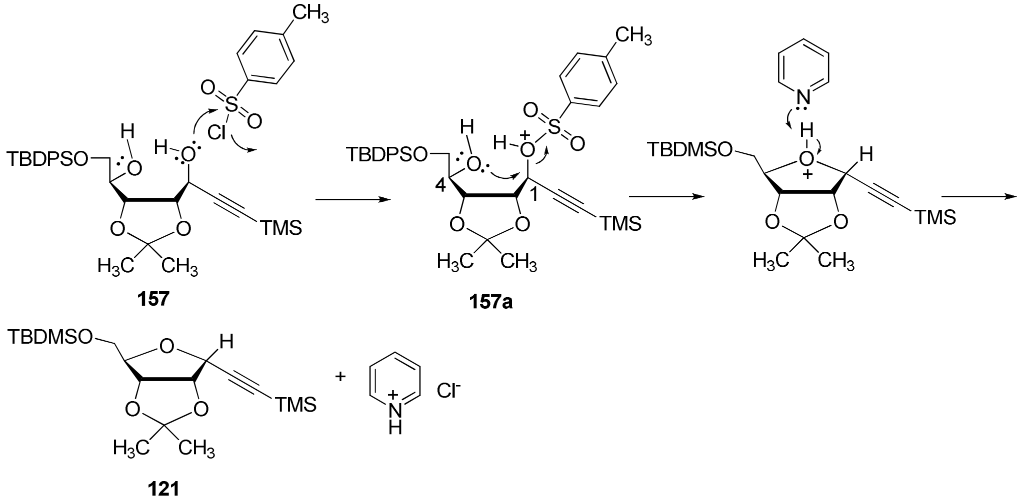
During the ethynylation of the furanosyl hemiacetals, the stereoselectivity of the diols formed depends on the substituent at the C-2□ and C-3□ positions.[115] When a heteroatom (O, N, and S) is present at the C-2□ or C-3□ position of the aldehyde1,2-chelation favors 1,2-syn approach of the nucleophile and 1,3-chelation favors the 1,3-anti approach of the nucleophile.[115] For example, when using the organomagnesium reagents, magnesium can chelate with the carbonyl oxygen producing 1,2-syn product **159**, via 1,2-chelation from aldehyde **158**, and 1,3-anti product **161** via 1,3- chelation from aldehyde **160** (Scheme 35).

**Table 6**. Stereochemical outcome of diols formed from ribonolactols[117-119]

| Substrate | Nucleophile | 1,2-cis | 1,2-trans | Reference |
|---|---|---|---|---|
|  | Li—≡—nBu | 25 | 75 | 91 |
|  | Li—≡ | 5 | 95 | 92 |
|  | Li—≡ | 0 | 100 | 93 |
|  | Li—≡—nBu | 25 | 75 | 91 |

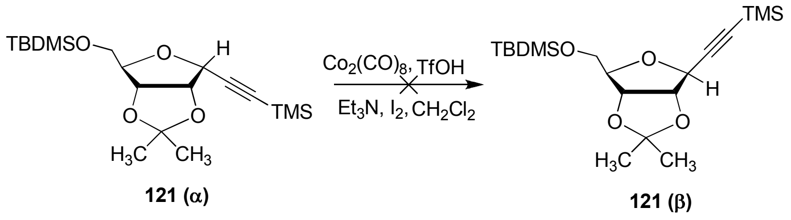
Due to the poor chelating ability of lithium,[116] the nucleophile using lithiated nucleophiles can attack from either side of the aldehyde. In such cases, the stereochemistry of the product is predicted by the traditional Felkin-Anh rule. Ring opening of ribose hemiacetals with lithium acetylide nucleophiles mainly results in the formation of 1,2-trans diols (Table 6).[117-119] These experimental results indicate that diol **157** formed from the hemiacetal **109** should also have 1,2-anti stereochemistry. Formation of 1,2-anti product plays a major role in determining the stereochemical outcome of ring-closing of the diols. Diol **157** upon treatment with tosylchloride and pyridine at room temperature undergoes cyclization via the $S_N2$ mechanism to yield the α-**121** as the major product. The suggested cyclization mechanism is shown in Scheme 36. Followed by the formation of the C-1 sulfonate ester **157a**, nucleophilic attack of the C-4 hydroxyl group at C-1 replaces the sulfonate group and closes the ribose ring

**Scheme 36**. Proposed mechanism of diol cyclization using tosylchloride and pyridine



### 7.1.5. Epimerization of α-alkynyl 121 to β-alkynyl 121

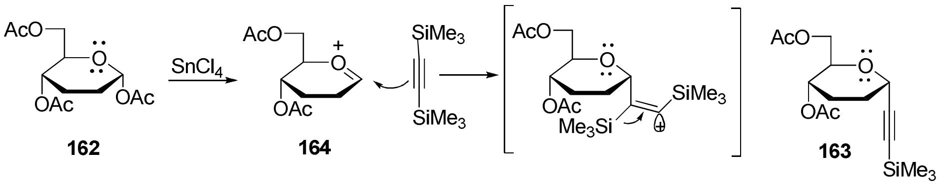
**Scheme 37**. Possible epimerization of α-alkyne to β-alkyne



The preparation of the β- **121** can be the result of the α-**121** epimerization. Therefore α-anomer **121** was treated with dicobalt octacarbonyl and 0.2 equivalent of triflic acid in methylene chloride, Nicholas reaction (Scheme 37).[104] The reaction mixture was stirred for 5 h and quenched with $Et_3N$ followed by the addition of $I_2$. After the workup, the crude product obtained was very polar, difficult to separate. It could be due of the cleavage of isopropylidene group under acidic conditions. The product was not purified.

## 7.2. Glycosylation using glycosyl acetate

**Scheme 38**. Synthesis of ethynylglycosides from glycosyl acetate[121]



Carbohydrate acetates have been used as electrophilic substrates for the synthesis of C-glycosides.[120] Reaction of trimethylsilyl acetylene derivatives with acetoxy glycosides, in the presence of Lewis acid such as $SnCl_4$ has been employed to prepare the corresponding C-glycosides.[121] For example, C-glycosylation of 2,3-dideoxyglucose derivative **162** using di(trimethylsilyl) acetylene yielded the α-anomer **163** (Scheme 38). Reaction of the acetate derivative **162** with the Lewis acid ($SnCl_4$) generated an oxocarbenium ion **164**. Nucleophilic attack of ditrimethylsilylacetylene on oxocarbenium ion **164** yielded α-glycoside **163**.

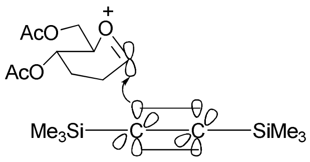
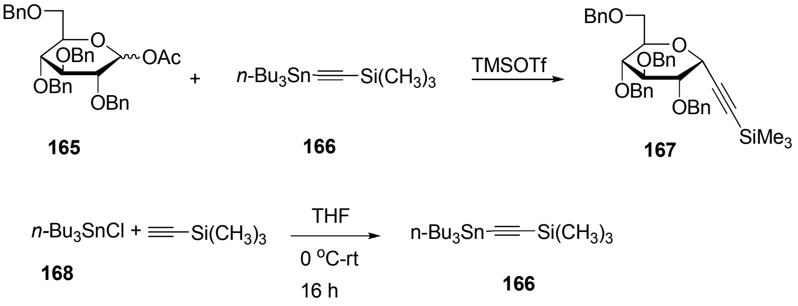


**Figure 18**. Stereoelectronic effect to form α-product

Silylacetylene approachs the α-face of the oxocarbenium ion **164** due to interaction between the two p-electrons of the oxocarbenium ion and the p-orbitals of the silyl acetylene (Figure 18) can explain the stereoseletivity.[121] Isobe and co-workers[122,123] and Dondoni et al.[120] used tributylstannyl(trimethylsilyl) acetylide **166** as the nucleophile of preference for the synthesisof ethynylglycoside**167** from carbohydrate acetate **165** (Scheme 39).

**Scheme 39**. Ethynylation of carbohydrate acetates using tributylstannyl-(trimethylsilyl) acetylide[124]

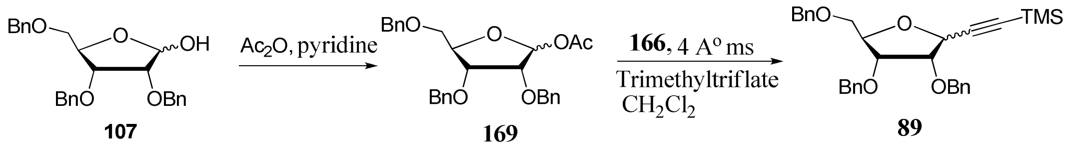


**165** **166** **167** **168** **166**

Tributylstannyl(trimethylsilyl) acetylene **166** was prepared from chlorotributylstannane **168** and lithiumtrimethylsilyl acetylide (Scheme 39).[124] To a solution of lithium trimethylsilyl acetylide at 0 °C, chlorotributylstannane **168** in THF was added dropwise. The reaction mixture was stirred 16 h at room temperature. The crude product was distilled under reduced pressure to give the product **166** (Scheme 39). Isolation of pure **166** was difficult because of contamination by tin compounds.

### 7.2.3. Synthesis of 89 using 1-acetylribofuranoside 169

**Scheme 40**. Synthesis **89** from 2,3,5-tri-*O*-benzylribosyl-1-aceate **169**



**107** **169** **89**

Stannane derivative **166** was used next for the synthesis of **89** from 2,3,5-tri-*O*-benzylribosyl-1-aceate **169**, Compound **169** was treated with tributylstannyl (trimethylsilyl) acetylene **166** to yield **89**. Spectroscopic analysis of the crude product confirmed the formation of **89** (Scheme 40). But the purification was challenging.

# CHAPTER VIII

## Syntheses of the enediyneribofuranosides using Sonogashira coupling reaction

# CHAPTER VIII

## Syntheses of the enediyneribofuranosides using Sonogashira coupling reactions

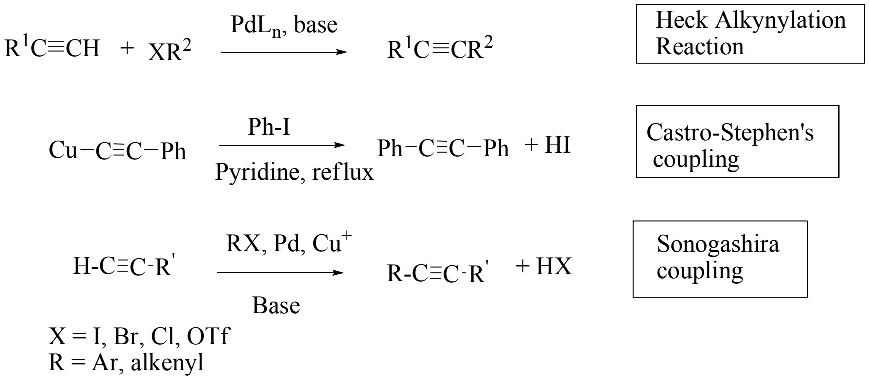
### 8.2. Palladium catalyzed coupling reactions

Transition-metal catalyzed cross-coupling reactions, especially with palladium has became a powerful tool to construct C-C[125-128] and C-N bonds.[129] Pd-catalyzed cross-coupling reactions are used to construct bonds between C(sp$^2$) and C(sp) to yield eneynes and enediynes. In spite of the well established success of these reactions, Palladium catalysts suffer from drawbacks, such as their sensitivity to oxygen and water. So reactions using Pd(0) catalysts need to be carried out under inert condition.

### 8.2.1. Sonogashira Coupling

Pd-catalyzed cross-coupling reaction between aryl and alkenyl halides or triflates with terminal alkynes is one of the most important methods available for the syntheses of aryl alkynes,[130] conjugated eneynes,[131] and enediynes.[132] The coupling between alkenyl halides with terminal acetylene was reported earlier by Heck using palladium catalyst.[133] Later on, Castro-Stephens coupling was introduced to carry out such cross-coupling reactionss.[134] In Castro-Stephens coupling reaction, palladium catalyst was not used; instead, preformed copper acetylide was used to couple with phenyl or vinyl halides. In 1973, Sonogashira introduced a modified form of cross coupling reaction using both the aspects of the Heck and the Castro couplings. In the Sonogashira coupling reaction, a palladium catalyst, copper (I) salt as a cocatalyst, and a base is used (Scheme 41).

**Scheme 41**. Sonogashira reaction (Hybrid of Heck and Castro Reactions)



This reaction was first reported by Sonogashira and Hagihara in 1973.[135] There are many drawbacks that lead to poor yield in the Castro-Stephens reaction. The reaction is carried out under harsh conditions, such as refluxing in pyridine or DMF. Addition of preformed copper acetylide leads to poor yields due to homocoupling.[136] After the discovery of Pd-catalyzed cross-coupling reaction to build the conjugated eneynes and enediynes, Sonogashira reaction became a most popular procedure for ethynylation of aryl or alkenyl halides.

### 8.2.2. Limitations of Sonogashira coupling

Even though Sonogashira coupling was used successfully to make conjugated eneynes and enediynes, it has some drawbacks which are responsible for the low yield of the reaction. The major problems in this reaction are:

(a) Limited availability of the $sp^2$ electrophiles.

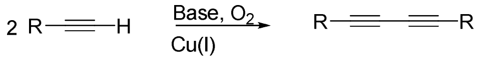
(b) Homocoupling between the terminal alkynes.

### Reactivity of the vinyl and aryl substrates

Sonogashira reaction is applicable only to very few $sp^2$ electrophilic substrates. The order of reactivity of the organic electrophiles is vinyl iodide ≥ vinyl triflate > vinyl bromide > vinyl chloride > ArI > Aryl triflate ≥ aryl bromide >>> aryl chloride.[142] The coupling becomes very challenging for the unactivated aryl halides especially for chlorides and bromides.

### Homocoupling (Glaser coupling)

**Scheme 42**. Glaser coupling

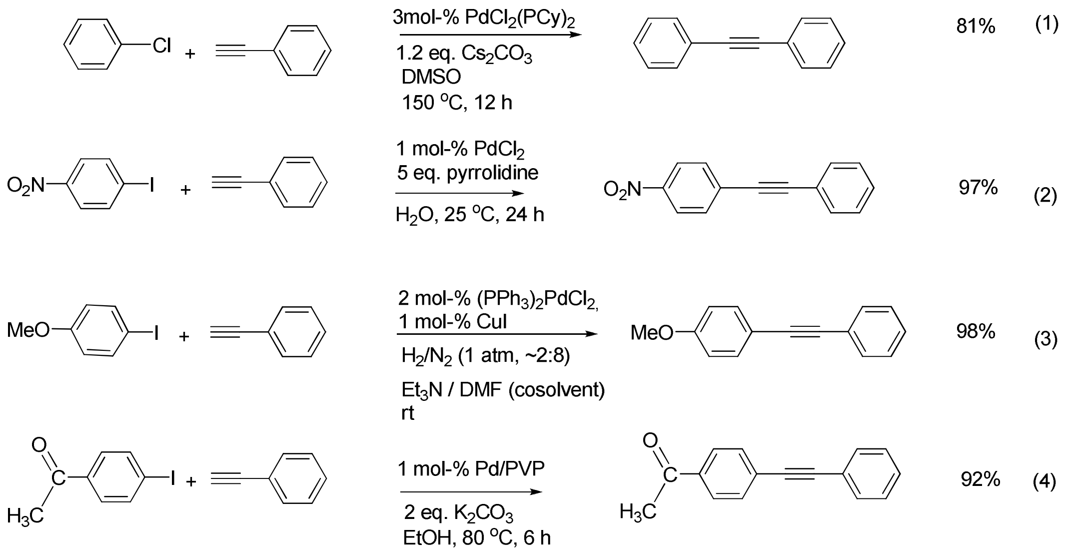


Addition of copper salts as cocatalysts generate homocoupled products of the terminal alkynes. This is similar to Glaser coupling to produce symmetrical acetylenes (Scheme 42). These kinds of acetylene homocoupling reactions are generally useful when symmetrical acetylenes are the desired products, but when targeting cross-coupled products, this reaction presents a major drawback. This is because, the terminal acetylenes are either very expensive or require multistep syntheses.

Therefore, Sonogashira protocols were repeatedly modified to reduce the homocoupling reactions to increase the yields of the cross-coupled products. The modified Sonogashira coupling procedures include copper free coupling (eq. 1),[137] running reaction under aerobic condition (eq. 2),[138] under inert condition (eq. 3),[139] and using nanosized Pd metal (eq. 4) (Scheme 43).[140] Recent developments in Sonogashira reaction is coupling between primary alkyl iodides and alkynes.[141]

Another significant problem is the product purification. This process is cumbersome and some products need strict exclusion of oxygen during purifications. Apart from the above mentioned drawbacks, the other factors that limit the application of these coupling reactions are high cost of the palladium catalysts and life time of the catalysts. These catalysts are very sensitive to air and needs proper storage. Nevertheless, this is one of the best reactions for the cross-coupling between C($sp^2$) and C(sp) species to give eneynes and enediynes.

**Scheme 43**. Modified Sonogashira coupling



## 8.3. Mechanistic aspects of Sonogashira coupling

The copper co-catalyzed Sonogashira coupling is believed to take place through two independent cycles (Scheme 44).[143]

The proposed mechanism consisted of three major steps:

a) Oxidative addition.

b) Transmetallation.

c) Reductive elimination.

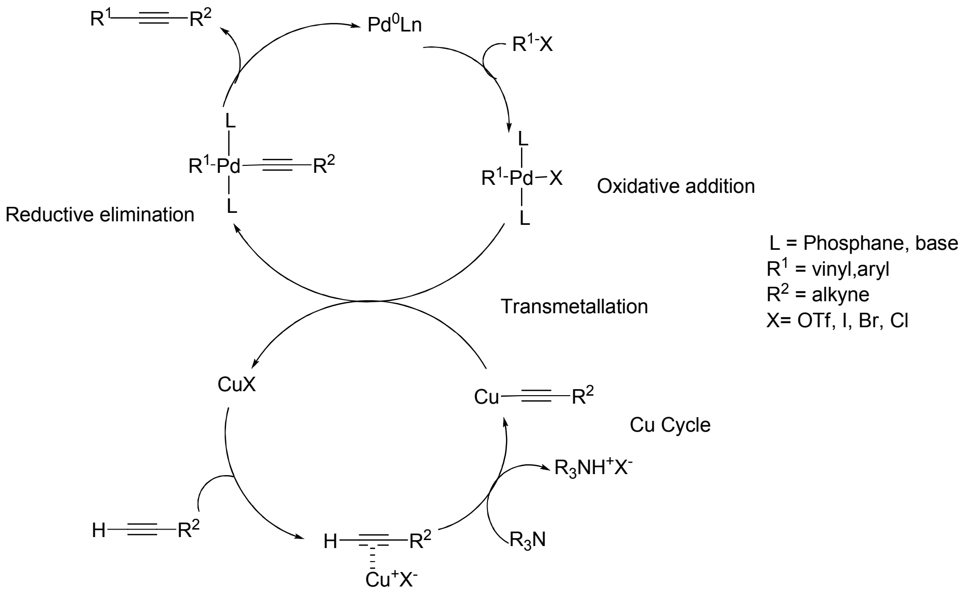
### Oxidative addition

Oxidative addition reaction (Scheme 44) involves the insertion of a low oxidation state Pd metal with empty coordination site in to a covalent bond ($R^1$-X). In doing so the metal is oxidized, typically by 2e-. Transfer of the two electrons from the metal breaks the covalent bond ($R^1$-X) forming two new anionic groups. At least one of these new anionic ($R^1$) group ends up bonded to the metal center. In the Sonogashira coupling $R^1$ could be the vinyl, aryl, and X could be iodides, triflates, bromides, and chlorides. The catalyst is usually a 14 electron $Pd^0$ $L_2$ species which can also be formed by the reduction of various Pd (II) complexes with electron donor ligands such as phosphines and amines. The oxidative addition of $R^1X$ to the palladium catalyst is easier if X is a good leaving group, such as -OTf and iodide. Oxidative addition is typically a fast reaction.

### Transmetallation

This step is also called the Cu-cycle in the Sonogashira reaction. The transmetallation of the copper acetylide to Pd is believed to be the rate-determining step. This step is poorly understood. In this step, the amine base is used to abstract hydrogen atom from the acetylene to form copper acetylide.

**Scheme 44.** Mechanism of Sonogashira coupling[143]



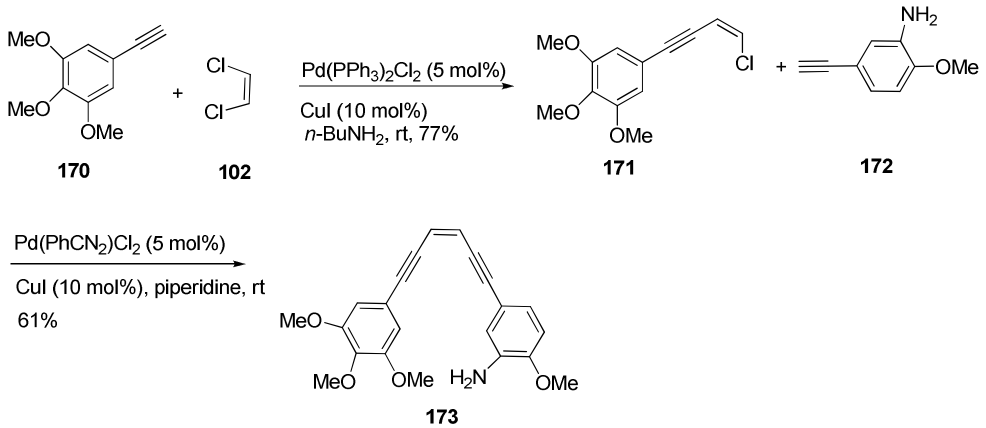
### Reductive elimination

Reductive elimination is reverse of oxidative addition and involves the elimination of a molecule from a transition metal complex. In this process the metal center is reduced by two electrons. This step generates the desired coupled eneyne product with the regeneration of the Pd(0) complex.

## 8.4. Synthesis of eneynes and enediynes (Application of Sonogashira coupling)

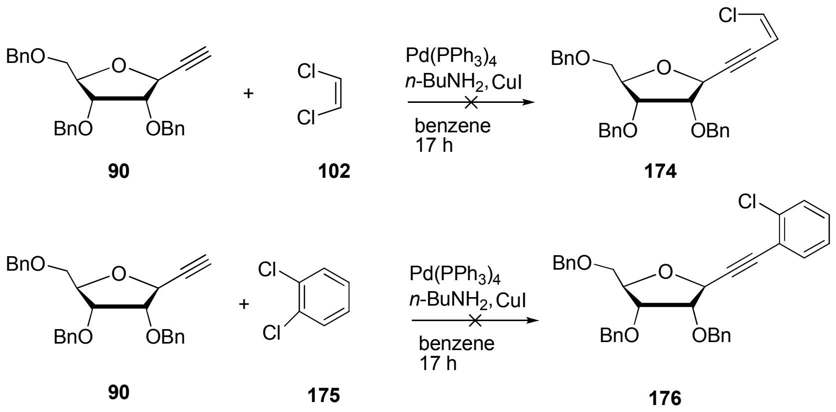
Sonogashira coupling was found useful in the synthesis of various natural products[144] and in the construction of complex unsaturated framework of eneynes[145] and enediyne antibiotics.[146] For example, the Sonogashira coupling was useful in the synthesis of enediyne analog **173** of the cytotoxic natural stilbene combretastatin (Scheme 45).[147] Here trimethoxy aryl alkyne **170** was cross-coupled with *Z*-1,2-dichloroethene **102** to give the enyne **171** which was further coupled with **172** to give the enediyne **173**.[147]

**Scheme 45**. Synthesis of enediynes using Sonogashira coupling



## 8.5. Synthesis of enediyne ribofuranosides

**Scheme 46**. Synthesis of eneynes derivatives from ribofuranoside **90**

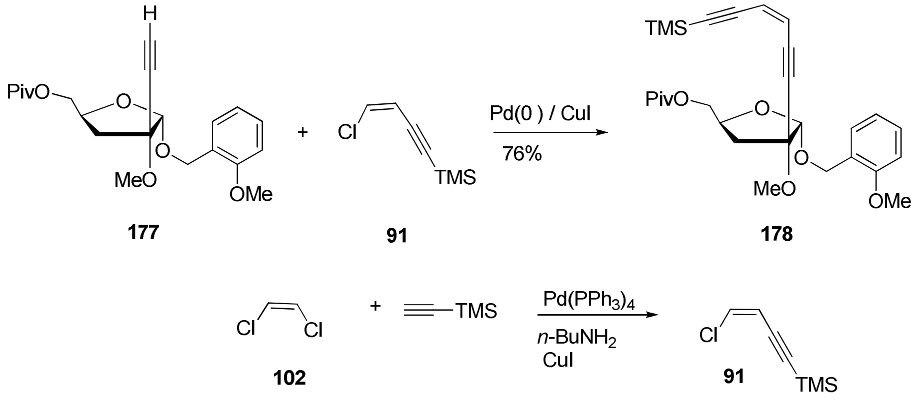


Since the Sonogashira reaction was successfully used to construct both natural and synthetic enediynes, cross-coupling reactions were attempted using **90** with *Z*-1,2-dichloroethene **102** and with 1,2-dichlorobenzene **175** to synthesize the eneynes **174** and **176** respectively (Scheme 46). These reactions were carried out using Pd(PPh$_3$)$_4$, Et$_3$N, and CuI in benzene. In both cases desired products **174** and **176** were not obtained. The reason could be the low reactivity of the vinyl and aryl chlorides.[143] Heating the reaction might have helped to activate the halides. The product was a black tar like substance difficult to identify.

### 8.5.1. Synthesis of 2,3,5-tri-*O*-benzyl-β-1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) riboside 92

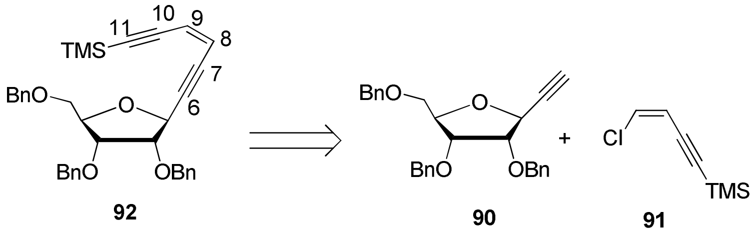
Brandstetter and Maier synthesized enediyne **178** (Scheme 47) in 76% yield by coupling *Z*-1,2-chloro-4-trimethylsilylbut-1-en-3-yne (**91**) with the alkyne **177**.[32] This reaction can be used as a model to build the enediyne moiety on the ribose substrate **90**. The retrosynthetic approach for the synthesis of **92** is shown in Scheme 48.

**Scheme 47**. Synthesis of the oxabicyclo [7.2.1] enediyne on D-xylose[32]



In order to synthesis **92**, chloroeneyne **91** should be prepared first using *Z*-1,2-dichloroethene (**102**) (Scheme 47). Compound **91** was synthesized by adding a solution of *Z*-1,2-dichloroethene (**102**) in benzene to a mixture of Pd(PPh$_3$)$_4$, *n*-BuNH$_2$ and trimethylsilyl acetylene. After 10 min CuI was introduced and the reaction was continued for 5 h. The crude product was purified by flash chromatography using pentane.

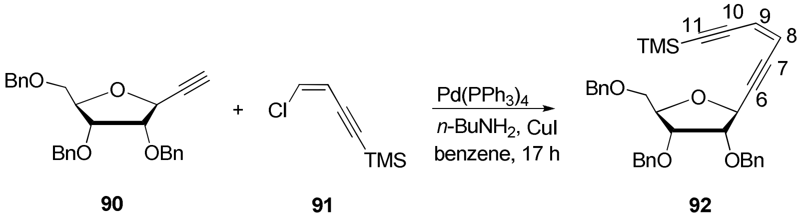
**Scheme 48**. Retrosynthetic approach to synthesis enediyne **92** from the alkyne **90**



## Synthesis of (2,3,5-tri-*O*-benzyl-β-1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) ribofuranoside (92)

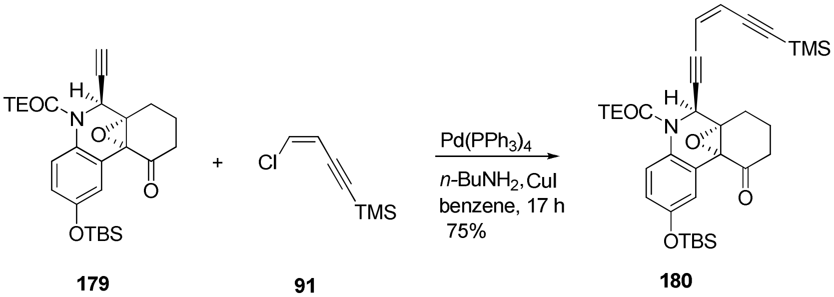
To the solution of alkyne **90** in freshly distilled benzene was successively added 91, *n*-BuNH$_2$, CuI (0.1equiv), and Pd (PPh$_3$)$_4$ (0.03 equiv) (Scheme 49). The resulting mixture was stirred for 17 h under argon.

**Scheme 49**. Synthesis of **92**



Analysis of the product showed that the desired product **92** was not obtained. It was a black substance which was difficult to purify. The reasons for the failure of the reaction might be the nature of the solvent, reaction conditions and the stochiometric amount of the reactants used. The solvent benzene was freshly distilled but it was not degassed. This could have affected the reactivity of Pd($PPh_3$)$_4$, because Pd catalyst is air sensitive. The molar ratios of the reagents used in this reaction are comparatively lower than the method used by Danishefsky group in building the enediyne **180** (Scheme 50).[148]

**Scheme 50**. Synthesis of enediyne **180**[148]



So the reaction procedure was modified using the procedure of Danishefsky group.[148] To the solution of Pd($PPh_3$)$_4$ (0.05 equiv) in dry degassed benzene, *n*-$BuNH_2$ (4 equiv) was then added followed by the addition of chloroeneyne **91** (3.25 equiv). A solution of acetylene **90** (1.5 mmol) in dry benzene was then added followed by the addition of CuI (0.2 equiv) (Scheme 49). The solution was stirred at 25 °C for overnight. The yield of the crude before purification was more than the theoretical yield, this may be due to the presence of triphenylphosphene. The crude was purified using petroleum ether/ethyl acetate (4/1). The yield after purification was 42%. By repeating the reaction under controlled air free conditions, homocoupling was reduced considerably and the product yield was increased to 60%. The simple enediyne unit on the ribose substrate therefore was constructed successfully. The next goal of the research was to synthesize the benzene conjugated enediyne **182**, which should be cyclized to get the next target enediyne **81**.

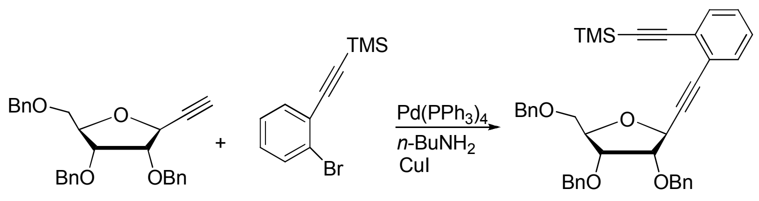
### 8.5.2. Synthesis of benzene conjugated enediyne 182

To achieve the synthesis of next target enediyne **81**, the alkyne **90** was used. To couple with **90** to give the enediyne **182,** a suitable aryl halide is necessary. It had already been established that 1,2-dichloro benzene **175** failed to undergo cross-coupling reaction (Scheme 46). Therefore commercially available bromo benzene derivative **181** was considered next to couple with the alkyne **90**.

#### Synthesis of benzeneconjugated endiyne 182 using 2-bromo(phenylethyne)-trimethylsilane 181

To a solution of **90** in dry degassed benzene was added triethylamine and the resulting mixture was stirred for 10 min at 25 $^{o}$C followed by the addition of $Pd(PPh_3)_4$ and 2-(bromophenylehyne)-trimethylsilane **181** (Scheme 51). NMR analysis indicated the formation of the compound **182**, but the yield of the crude was less than 10%. Purification was very challenging. According to published literature,[149] a high yield (99%) was reported for coupling of substituted bromobenzene with terminal alkynes using the catalyst $Pd(PPh_3)_2Cl_2$ in THF solvent. So coupling between **90** and **181** was attempted using $Pd(PPh_3)_2Cl_2$ in THF (Scheme 52). No desired product was isolated here.

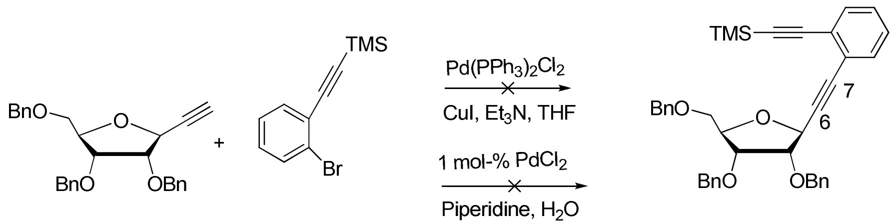
**Scheme 51.** 2,3,5-Tri-*O*-benzyl-6,7-yne-(1-phenyltrimethylsilylacetylide)ribofuraniside **182**



**90** **181** **182**

Copper-free, aerobic Sonogashira coupling reactions were also reported[150] to decrease the formation of homocoupled products and to increase the yield of cross-coupled products. So coupling between **90** and **181** was done under copper free aerobic condition, but desired product **182** was not obtained here (Scheme 52).

**Scheme 52**. Synthetic approach of **182** using different reaction Sonogashira conditions

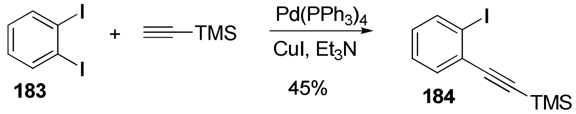


**90** **181** **182**

## Synthesis of (2-iodophenylethynyl)-trimethylsilane

All the attempts to synthesize the benzene conjugated enediyne **182** either gave very low yield (Scheme 51), or no yield (Scheme 52). So the next attempt was choosing a iodobenzene derivative **184** to couple with **90.** Compound **184** was synthesized by treating 1,2-diiodobenzene **183** with $Pd(PPh_3)_4$, CuI, trimethylsilyl acetylene in dry and degassed benzene. Triethylamine was used as a base. The reaction went smoothly and yielded 1.2 g of **184** (Scheme 53).

**Scheme 53**. Synthesis of (2-iodophenylethynyl)-trimethylsilane

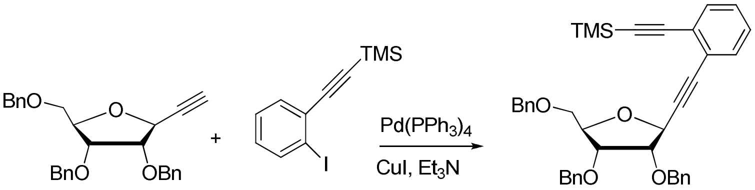


**183** **184**

### Synthesis of benzene conjugated enediyne 182 using 2-iodo(phenylethyne)-trimethylsilane 184

Synthesis of compound **182** was attempted using **90** and the aryl iodide **184**. To the solution of $Pd(PPh_3)_4$, **184** and $Et_3N$ in dry degassed benzene was added a solution of **90** and cuprous iodide in dry degassed benzene. The resulting mixture was stirred at 40 °C for 2 h (Scheme 54). The crude was purified using diethyl ether/petroleum ether (33/67). NMR spectrum of the product confirmed the formation of desired product **182**. The construction of simple as well as benzene conjugated enediynes on ribose backbone was completed successfully. These enediynes have a β- configuration.

**Scheme 54. Synthesis of benzene conjugated enediyne 182 using 184**

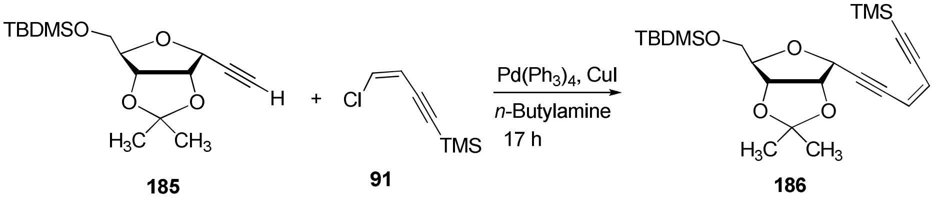


**90** **184** **182**

### 8.5.3. Synthesis of 2,3-*O*-isopropyledine-5-OTBDMS -1-(6,7,10,11-diyne-8,9-ene) riboside 186

Sonogashira coupling was also attempted using **185,** which has α-stereochemistry (Scheme 55), with **91** to get the enediyne **186**. Compound **185** was obtained by desilylation of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-trimethylsilylethynylribofuranoside (**121**) using anhydrous $K_2CO_3$ and methanol. Compound **185** was coupled with **91** using the similar procedure used to synthesize **92**. The product **186** was purified using petroleum ether/ethyl acetate ( 6/1) giving **186** in 42% yield.

**Scheme 55.** Synthesis of enediyne **186**



# CHAPTER IX

# Intramolecular ring-closure of enediynes

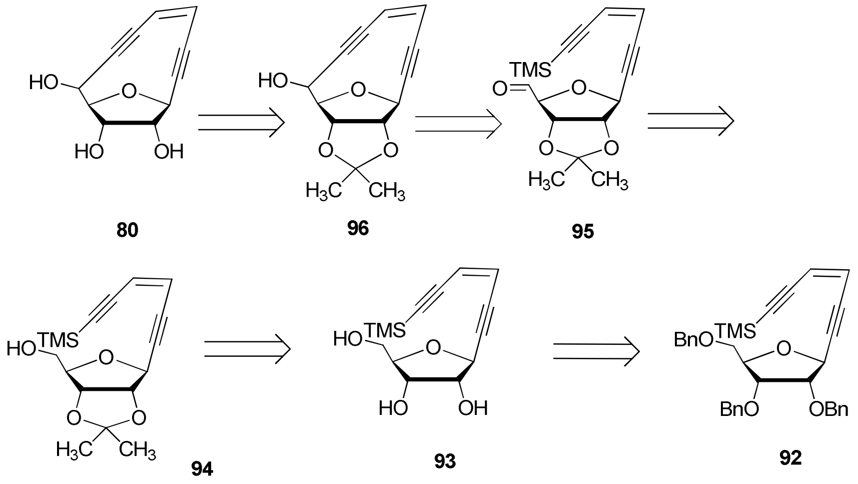
# CHAPTER IX

## Intramolecular ring-closing of enediynes

### 9.1. Synthesis of cyclic enediyne 80

Retrosynthetic approach to synthesize compound **80** is explained in Scheme 56. In order to achieve the synthesis of the cyclic enediyne **80**, the enediyne **92** will be debenzylated to get **93**, which will be further protected as **94**. Compound **94** will be oxidized to **95**, which then will be subjected to intramolecular-coupling conditions to produce **96**. Upon acid hydrolysis **96** will provide the cyclic enediyne **80**.

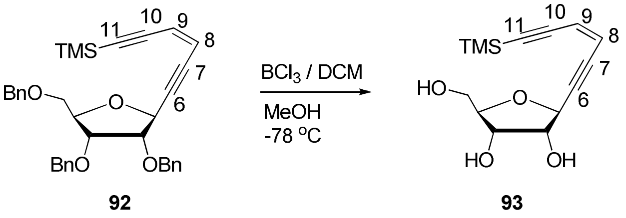
**Scheme 56**. Retrosynthetic approach to synthesis cyclic enediyne **80** from **92**



### 9.1.1. Synthesis of 1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) ribofuranoside 93

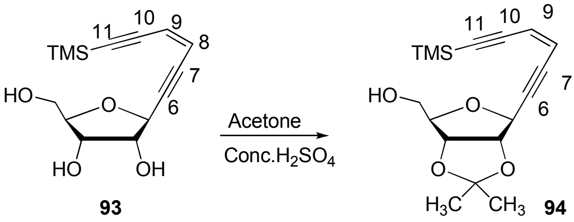
Usually the debenzylation is done by catalytic hydrogenation,[151] reductive cleavage with sodium and ethanol,[152] or with liquid ammonia.[153] These procedures are unsuitable for the enediyne **92**. Hydrogenation will convert the enediyne unsaturated unit to a saturated compound. Therefore, Lewis acids such as $BCl_3$ or $BBr_3$ in methylene chloride[154,155,69] was used for the debenenzylation reaction (Scheme 57). A solution of $BCl_3$ (1M in methylene chloride) was added to a solution of enediyneglycoside **92** in dichloromethane at -78 °C. After 30 min the reaction was quenched with methanol. The yield of the isolated crude triol **93** was 92%. Analysis of NMR and IR spectra of the crude confirmed the product **93**. The IR spectrum exhibited the broad peak around 3500 $cm^{-1}$ corresponding to the hydroxyl absorptions.

**Scheme 57**. Synthesis of 1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) riboside



### 9.1.2. Synthesis of 2,3-*O*-isopropylidene-1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) ribofuranoside 94

**Scheme 58**. Synthesis of 2,3-*O*-isopropylidene-1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) riboside



Catalytic amount of concentrated $H_2SO_4$ was added to a solution of **93** in acetone. The solution was stirred for 1.5 h. The pH of the solution was adjusted to 7 using $Ca(OH)_2$. The resulting slurry was filtered through Celite and the filtrate was concentrated (Scheme 58). The yield was 95%.

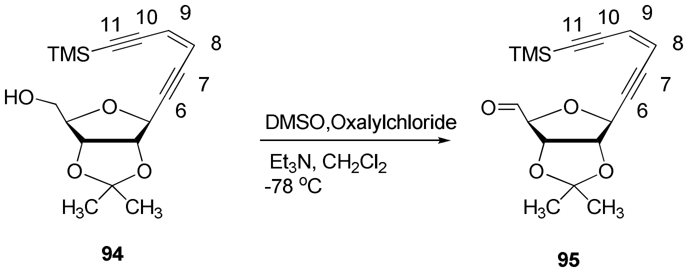
## 9.2. Oxidation of 2,3- *O*-isopropylidene-1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl) ribofuranoside 94

Oxidation of alcohols to the corresponding carbonyl compounds is frequently used in organic syntheses.[156] There have been various mild oxidation methods available for the controlled oxidation of primary alcohols to corresponding aldehydes.[157,158] Oxidation of alcohols using metals such as Pd is also commonly employed.[159] Activated DMSO-mediated oxidations are widely used especially in carbohydrate field for the conversion of the primary alcohol to aldehyde without overoxidation to carboxylic acids. For example, acetic anhydride activated DMSO oxidation procedure is used in number of carbohydrate alcohols.[160] But activation of DMSO by oxalyl chloride at low temperature in methylene chloride, named as Swern oxidation serves as a better procedure for oxidation of diverse alcohols such as heteroaromatic, heterocyclic, small rings, allylic and in carbohydrates based alcohols.[161]

### 9.2.1. Swern oxidation of enediyne alcohol 94

In the synthesis of reported[32] xylose based enediyne **79**, Swern oxidation method was used to oxidize the C5′ primary hydroxyl group to aldehyde without further oxidation to carboxylic acid. Therefore, oxidation of enediyne alcohol **94** was attempted using similar reaction conditions (Scheme 59). In this procedure, to a cooled (-78 °C) solution of oxalyl chloride in dry dichloromethane was added DMSO under argon. After 15 min the solution of alcohol **94** in $CH_2Cl_2$ was added and stirred for 1 h at -78 °C. $Et_3N$ was then added and the mixture was allowed to warm to room temperature. Analysis of NMR spectrum of the product **95** showed a broad peak around 9.6 ppm corresponding to the aldehyde proton. Purification of this product was very difficult due to the unstable nature of **95**. The reaction was repeated several times, but the yields were very poor and purification was challenging.

**Scheme 59**. Synthesis of 5-al-2,3-*O*-isopropylidene-1-(6,7,10,1-diyne-8,9-ene-11-trimethylsilyl) ribofuranoside **95**

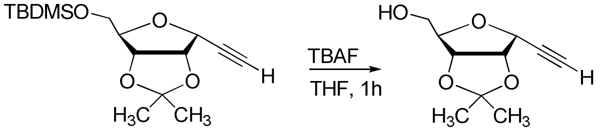


### 9.2.2. Oxidation of alcohol 187 using TEMPO oxidation methods

Since the aldehyde **95** formed by Swern oxidation of **94** could not be isolated, other mild oxidation methods have been tried. Oxidation of alcohols by oxoammonium salts such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) have been reported by Golubev.[162] This procedure have been widely used for the successful conversion of primary and secondary alcohols to corresponding aldehydes and ketones.[163, 164] This method is commonly used for the oxidation of aromatic, cyclic, acyclic, allylic alcohols, especially for the oxidation of C5′ hydroxy groups in furanosides.[165,166]

Due to the multistep syntheses involved to synthesize enediyne alcohol **94**, TEMPO oxidation was not attempted using this alcohol. Instead, alcohol 1**87**, one of the compound synthesized in this research was used to carry out a pilot TEMPO oxidation. Alcohol **187** could be obtained by the desilylation of the alkyne **185** using tetrabutylammonium fluoride (TBAF) (Scheme 60).[167] Compound **187** was purified using methylene chloride/methanol (95 /5) in 78% yield.

**Scheme 60**. Synthesis of 5-hydorxy-2,3-*O*-isopropylidene-D-ribofuranosyl-1-ethyne



**185** **187**

Oxidation of 5-hydroxy-2,3-*O*-isopropylidene-D-ribofuranosyl-1-ethyne **187** was carried out by two different TEMPO oxidation procedures:.

(a) TEMPO and [bis (acetoxy)-iodo] benzene (BAIB) as co-oxidant.[165]

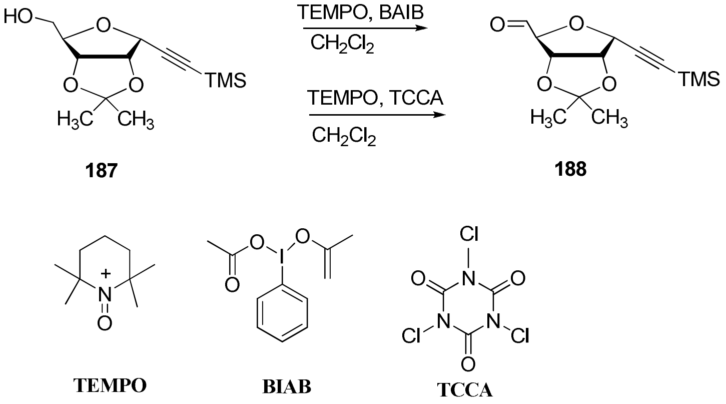
(b) TEMPO and trichloroisocyanuric acid (TCCA) as co-oxidant.[168]

Oxidation of primary alcohols using TEMPO and BAIB is very mild and under this experimental condition, the primary alcohols are oxidized to aldehydes without overoxidation to carboxylic acids. Catalytic amount of TEMPO was added in one portion to a solution of **187** and bis-acetoxy iodobenzene (BAIB) in methylene chloride. The reaction was stirred for 24 h (Scheme 61).[165] IR analysis of the light yellow syrup indicated a carbonyl signal at 1724 $cm^{-1}$ indicating the possible oxidation of **187** to compound **188**, but nmr interpretation was not clear.

In the oxidation procedure involving TEMPO and TCCA, a catalytic amount of TEMPO was added in one portion to the solution of **187** and trichloroisocyanuric acid (TCCA) in methylene chloride.[168] The reaction was stirred for 3 h at room temperature under dry conditions (Scheme 61). NMR analysis of the crude product **188** indicated a weak broad signal at around 9.8 ppm indicating the presence of aldehyde group. Isolation of the pure aldehyde **188** was not successful.

Since both the TEMPO oxidation methods were not giving reliable results, these methods were not tried on the enediyne alcohol **94**. Out of these oxidation methods tried, experimental results indicated that Swern oxidation procedure is a better method to oxidize the enediyne alcohol **94**.

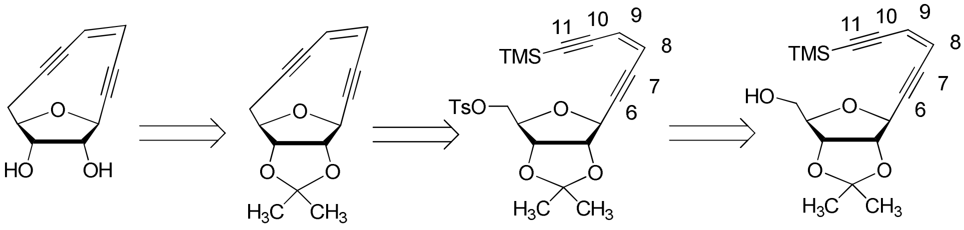
**Scheme 61.** TEMPO oxidation of **187** using BAIB and TCCA



## 9.3. Alternative plan for *in situ* intramolecular cyclization

Due to the problems associated with the oxidation of alcohol **94**, an alternative approach was considered to synthesize the cyclic enediyne **191** from the enediyne alcohol **94** by avaoiding the oxidation step. The retrosynthetic approach to synthesis compound **191** was shown in Scheme 62.

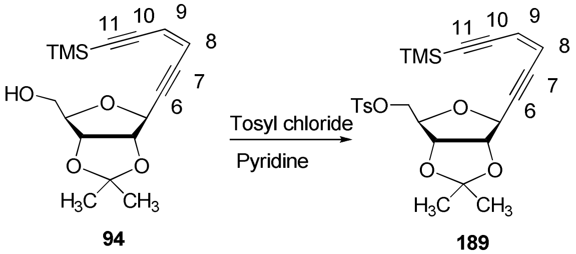
**Scheme 62**. Retrosynthetic approch to synthesis **191**



In this alternate plan, the primary alchol group in compound **94** will be protected with a good leaving group, such as tosyl group to make compound **189**.[169] The tosylated compound **189** will be treated with CsF[170,171] for the *insitu* desilylation at C-11 position to get terminal alkyne, which in turn can intramolecularly replace the tosyl group at C5′position to close the enediyne ring giving **190**. Upon acid hydrolysis compound **190** will be converted to **191**.

This procedure will not only helps to avoid the oxidation step, but also avoids the additional step involved in the desilylation at C-11 position to get the terminal alkyne substrate. To the ice cold solution of alcohol **94** in methylene chloride triethylamine was added. Tosyl chloride was added to this solution over 2 h period. Nmr analysis of the crude confirmed the successful formation of **189**, but purification was challanging. This reaction should be repeated and better purification methods should be developed for the future wok.

**Scheme 63**. Synthesis of 5-*O*-tosyl-2,3-*O*-isopropylidene1-(6,7,10,11-diyne-8,9-ene) ribofuranoside



**94** **189**

Out of these different oxidation procedures attempted, spectral analysis indicated that Swern oxidation method may be a better choice. For future work effort should be made to optimize the reaction conditions of Swern oxidation protocol.

# CHAPTER X

## CONCLUSIONS

# CHAPTER X

# CONCLUSIONS

The main goal of this research project was to investigate the syntheses of a new class of enediyneribofuranosides. Simple enediyne molecules **92**, **182** and **186** were synthesized along with othe key riboside derivatives **90**, **121**, and **123**.

The following objectives were successfully accomplished:

(a) Synthesis of protected riboside derivatives.

(b) Synthesis of α and β ethynyl ribosides from the nucleophilic addition reactions using trimethylsilyl acetylene and carbohydrate electrophiles such as lactones, lactols and ribonyl acetate.

(c) Synthesis of enediynes **92**, **182** and **186** by the successful application of the Sonogashira cross-coupling reactions.

(d) Attempt to carry out intramolecular cyclization reaction.

(e) Isolation, purification and stereochemical analysis of the key riboside intermediates such as **90**, **121** and **123**.

(a) Commercially available ribose was protected to give three different ribonolactone derivatives such as 2,3,5-tri-*O*-benzyl-D-ribonolactone (**87**), 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (**110**), and 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone (**113**). Synthesis of benzyl protected ribonolactone **87** was a multistep process with lower yield. The other two isopropylidene protected lactones **110** and **113** were synthesized with better yields compared to **87**.

(b) Three different carbohydrate electrophiles such as lactones, lactols and anomeric acetate of ribose derivatives were used to synthesize the ethynylribosides.

At first, trimethylsilyl acetylene was added to ribonolactone electrophilic substrates, such as **87**, **110** and **113**. Nucleophilic addition in all these three substrates gave the corresponding lactols. The lactols were reduced using Lewis acids such as $BF_{3,}$ TMSOTf using triethylsilane. The reduction of acetyl derivative **119** formed from the lactone **110** suffered from deprotection of the protecting groups resulting in very low yield. At the same time lactone **113** gave α-ethynylriboside **123** in 39% yield. Nucleophilic addition of trimethylsilyl acetylene on benzyl protected lactone **87** exclusively yielded β-ethnynylriboside **89**. From the experimental results, it was concluded that for the nucleophilic addition to ribonolactone derivatives by organometallic reagents, compound **87**, the benzyl protected lactone, served as a suitable substrate. This was in agreement with the published reports.[52,69] Lactone **110** did not serve as a good substrate to get ethynylribosides due to the deprotection of the silyl and the isopropylidene protecting groups. Deprotection of these groups made the reaction products very polar, which complicated the purification process. Lactone **113** produced only α-ethynylriboside. In lactone **113**, the rigidity of the isopyopylidene protecting group did not favor of the formation of the β-glycoside,[80] and only α-**123** was isolated.

In the second approach, trimethylsilyl acetylene was added to the benzyl protected lactol **107** and isopropylidene protected lactol **109** to get the correponding diols **156** and **157**. These diols were subjected to ring-closure using both Mitsunobu reaction and pyridine and tosyl chloride. Lactol **156**, under refluxing conditions, using pyridine and tosyl chloride did not give any cyclized product **89**, which is in agreement with the published reports.[69] But **157** was cyclized under Mitsunobu reaction conditions to give **89** in low yield. When treated with pyridine and tosyl chloride for 48 h at room temperature, diol **157** underwent cyclization to give α-ethynylriboside **121** in 60% yield.

In the third approach, tributylstannyl (trimethylsilyl) acetylide **166** was treated with 2,3,5-tri-*O*-benzylribosyl-1-acetate **169** to get the ethynylriboside **89**. NMR analysis indicated the formation of the product **89**, but purification was not successful.

(c) Sonogashira coupling reaction was used for the syntheses β-**92**, β-**182** and α-**186** enediynes successfully. The yields of the reactions were considerably increased by performing the reactions under controlled conditions. For example, homocoupling byproducts were considerably reduced by running the reactions under strict air free conditions. It was concluded from the experimental results that aryl chloride was unreactive in Sonogashira coupling, but aryl iodide was very reactive and gave the desired cross-coupled product **182**. Aryl bromides are less reactive than aryl iodides. Two different palladium catalysts $PdCl_2$ and $Pd(PPh_3)_4$ were used for the Sonogashira coupling procedures, but $Pd(PPh_3)_4$ successfully used to synthesize enediynes **92**, **182**, and **186**.

(d) Intramolecular cyclization of the enediyne **92** to get the bicyclic product **80** involved several steps such as deprotection of benzyl group to get **93**, protection of C-2'and C-3' hydroxyl groups as isopropylidene derivative to get **94**, and oxidation of the primary alcohol group at C-5′ position to aldehyde **95**. Compounds **93** and **94** were succesfully made. Oxidation of the enediyne alcohol to aldehyde **95** was attempted via Swern oxidation. NMR analysis was supportive of the aldehyde **95**, but isolation of the aldehyde was very difficult. A pilot oxidation was done on alcohol **187** using TEMPO oxidation using different co-coxidants such as, BAIB and TCCA to get the aldehyde **188**. In these cases also the isolation of the products were challenging, but the NMR analysis was in supportive of the aldehyde **188**.

Since the desired aldehyde **95**, which is a crucial substrate for intramolecular ring-closing was difficult to isolate. An alternate ring-closing method was attempted by converting the C-5′ primary alcohol of substrate **94** to a tosylate **189**, so that *in situ* desilylation using CsF could produce the desired alkyne, by an intramolecular displacement of the tosyl leaving group and close the enediyne ring. The tosylated product **189** was synthesized and purification of this product is in progress.

(e) In the process of making the main enediyne compounds, many synthetically important key riboside derivatives, such as **89**, **121**, and **123** were isolated, purified and characterized. These intermediates can serve as key starting materials to synthesize other biologically active natural products. Stereochemistry of these key intermediates was also supported by NOE analysis. It was concluded that compounds **121** and **123** have α-stereochemistry and compound **89**

has β-stereochemistry.

In conclusion, the research project resulted in:

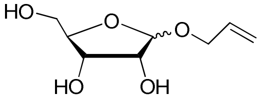
1. The successful synthesis of enediyneribofuranosides with α and β-stereochemistry and synthetically important riboside intermediates. Since asymmetric synthesis is widely used as crucial step in organic chemistry, the riboside intermediates may serve as valuable chiral templates for the stereochemical syntheses of β-C-glycoside derivatives. These intermediates can further be modified and eventually used in the syntheses of other desired biologically active carbohydrate based substrates, such as β-nucleosides.

2. The successful synthesis of β-enediynes **92**, **182** and the α-enediyne **186** has been accomplished. Even though intramolecular-cyclization reaction remains to be explored, these enediynes with their own characteristic functionality and reactivity will be the valuable substrates for studieson the Bergman cyclization and for *in vivo* DNA cleavge studies.

3. Modifications of the hydroxyl functional groups and substitution on the enediyne part of the final products **92**, **182**, and **186** can open new avenues for the possible syntheses of variety of new compounds with different biological selectivity and activity.

# EXPERIMENTAL PROCEDURES

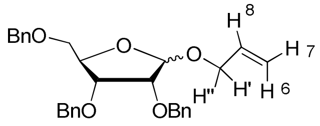
## 1-*O*-allyl–α, β-D-ribofuranoside (104)



**104**

Concentrated sulfuric acid (0.52 mL) was added dropwise to a vigorously stirred ice-cold suspension of finely powdered D-ribose (5.0 g, 0.033 mol) and granulated calcium sulfate (2.5 g) in allyl alcohol (70 mL, 1.03 mol). The reaction was stirred for 6 h at room temperature. The mixture was filtered through Celite, washed with fresh dry allyl alcohol (50 mL). The filtrate was passed through a column of Amberlite IR-410-ion exchange resin packed with dry allyl alcohol. The combined elutes and washings were concentrated in *vacuo* and the residue was dried overnight using phosphorous pentoxide. The product was pale yellow syrup (6 g, 95% yield). The crude product was purified using column chromatography, $R_f$ 0.62, 0.50 (petroleum ether/1-propanol 9/2). $^{13}$C (125 MHz, $DMSO_6$): α-anomer δ 135.7 (=CH), 117.1 (=$CH_2$), 101.8 (C1), 85.6 (C4), 71.9 (C2), 70.0 (C-3), 68.5 (allyl-O-$CH_2$), 62.3 (C5), β-anomer: δ 135.5 (=CH), 117.2 (=$CH_2$), 106.8 (C1), 84.1 (C4), 74.9 (C2), 71.7 (C3), 68.0 (allylO-$CH_2$), 63.9 (C5).

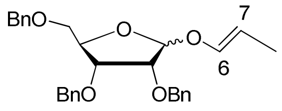
## 2,3,5-Tri-*O*-benzyl-1-*O*-allyl-α-β-D-ribofuranoside (105)



**105**

A solution of 1-*O*-allyl-α,β-D-ribofuranoside **104** (3 g, 15.77 mmol) in dry DMSO (9 mL) was added dropwise to a vigorously stirred ice-cold suspension of 95% sodium hydride (1.77 g, 70 mmol) in DMSO (12 mL) under nitrogen. The mixture was stirred for 1 h at 25 °C. Dry benzyl chloride (8.0 mL, 70 mmol) was then added dropwise, and the solution was stirred overnight at 25 °C. Methanol (3 mL) was added to this solution to destroy the excess sodium hydride and the mixture was diluted with water (100 mL), and extracted with ether (3 x 30 mL). The combined extracts were washed with water (3 x 30 mL), dried ($MgSO_4$), and concentrated in *vacuo* to yield 2,3,5-tri-*O*-benzyl-1-*O*-allyl-α-β-D-ribofuranoside (**105**) as a pale yellow syrup ( 6.4 g, 91% yield). $R_f$ 0.67 (petroleum ether/ethyl acetate, 3/1). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.25-7.56 (phenyl protons), 5.91 (m, 1H, H8), 5.29 (dd, $J_{6,8}$ = 17.0 Hz, $J_{6,7}$ = 1.5 Hz, 1H, H6), 5.22 (d, $J_{7,8}$ = 5.5 Hz, 1H, H7), 5.17 ( s, 1H, H1), 4.76 (d, $J_{AB}$ = 12.2 Hz, 1H, $OCH_2Ph$), 4.71 (d, $J_{AB}$ = 12.2 Hz, 1H, $OCH_2Ph$), 4.66 (d, $J_{AB}$ = 10.0 Hz, 1H, $OCH_2Ph$), 4.65 (d, $J_{AB}$ = 10.0 Hz, 1H, $OCH_2Ph$), 4.62 (d, $J_{AB}$ =12.2 Hz, 1H, $OCH_2Ph$), 4.55 (d, $J_{AB}$ =12.2 Hz, 1H, $OCH_2Ph$), 4.46 (dt, 2H, H□, H□), 4.27 ( q, $J_{4,3}$ = 4.8 Hz, $J_{4,5}$ = 4.0 Hz, 1H, H4), 4.17 (q, $J_{2,1}$ = 4.4 Hz, $J_{2,3}$ = 4.8 Hz, 1H, H2 ), 4.01 (q, $J_{3,2}$ = 4.8 Hz, $J_{3,4}$ = 6.3 Hz, 1H, H3), 3.72 (app.q, $J_{4,5b}$ = 4.0 Hz, $J_{5a,5b}$ = 10.7 Hz, 1H, H5b), 3.62 (app.q, $J_{4,5a}$ = 5.8.0 Hz, $J_{5a,5b}$ = 10.7 Hz, 1H, H5a). $^{13}$C (125 MHz, $CDCl_3$): δ 138.5, 138.1, 134.4 (3C), 127.7−128.6 (phenyl C),117.5 ($CH_2$=),104.7 (C1), 80.7 (C2), 80.0 (C3), 78.8 (C4), 73.4, 72.7, 72.5 ($CH_2$ Ph), 71.6 (C-5), 68.5 (allyl $OCH_2$).

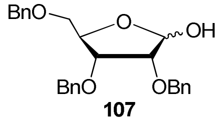
### Prop-1-*O*-enyl- 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranoside (106)



**106**

A solution of 2,3,5-tri-*O*-benzyl-1-*O*-allyl-α-β-D-ribofuranoside **105** (1 g, 2.17 mmol) in dry DMF (10 mL) was heated with potassium *t*-butoxide (1.26 g, 11.23 mmol) for 1 h at 95-100 °C. It was cooled and diluted with water (10 mL), extracted with ether (3 x 30 mL). The combined ether extracts were washed with saturated NaCl, dried ($MgSO_4$) and concentrated in *vacuo* to yield **106** ( 0.80 g, 80%). $R_f$ 0.53 (petroleum ether/ethylacetate, 5/1). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.28-7.40 ( phenyl protons), 5.23 (d, $J_{6,7}$ = 4.2 Hz, 1H, H6), 6.10 (d, $J_{H7,CH3}$ = 6.0 Hz, 1H, H7), 4.67 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.65 (s, 1H, H1), 4.53-4.59 (m, 3H, $OCH_2Ph$), 4.49 (d,1H, $J_{AB}$ = 12.0 Hz, $OCH_2Ph$), 4.47 (d,1H, $J_{AB}$ = 12.0 Hz, $OCH_2Ph$), 4.09 (app.q, 1H, H4), 3.97-4.00 (m, 2H, H-2, H-3), 3.60 (app.q, $J_{5b,4}$ = 6.0 Hz, $J_{5a,5b}$ = 12.0 Hz, 1H, H5b), 3.51 (app.q, $J_{4, 5a}$ = 6.0 Hz, $J_{5a, 5b}$ =12.0 Hz, 1H, H5a), 0.15 (d, $J_{CH3,H7}$ = 6.6 Hz, $CH_3$). $^{13}$C (75 MHz, $CDCl_3$): δ 142.3 (=CH), 138.2- 138.7 (3C), 127.9-128.8 (Phenyl carbons), 105.6 (OCH), 103.8 (C1), 81.6 (C2), 79.9 (C3), 78.9 (C4), 73.5, 72.9 , 72.7 ($CH_2Ph$), 71.4 (C5), 9.9 ($CH_3$),

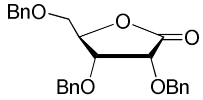
### 2,3,5-Tri-*O*-benzyl-α,β-D-ribofuranoside 107



**107**

To a solution of **106** (2.55 g, 5.54 mmol) in acetone (200 mL) was added 0.1 M HCl (22.3 mL). The solution was refluxed for an hour and neutralized with concentrated ammonia, and evaporated. The residue was diluted with methylene chloride (300 mL), washed with water (3 x 200 mL), and dried with $MgSO_4$. Yield was 1.7 g (73%).

### 2,3,5-Tri-*O*-benzyl-D-ribonolactone (87)



**87**

Four methods were attempted to oxidize **107** to get 2,3,5-tri-*O*- benzyl-D-ribonolactone **87**.

a) Oxidation using DMSO and acetic anhydride.

b) Pd catalyst oxidation using bromobenzene.

c) Oxidation using $Br_2$ and $NaHCO_3$.

d) Oxidation using $KMnO_4$ and acetone.

#### a. Oxidation using DMSO and acetic anhydride

Compound 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose **(107)** (0.93 g, 2.21 mmol) was treated with DMSO (24 mL) and acetic anhydride (12 mL). The mixture was stirred overnight under nitrogen at room temperature. The resulting mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was washed several times with water to remove the acetic anhydride and dried ($Na_2SO_4$). The crude product **87** was contaminated with lot of byproducts and was difficult to separate.

#### b. Palladium catalyzed oxidation

A mixture of palladium acetate (5.6 mg, 0.025 mmol) and $PPh_3$ (13.1 mg, 0.38 mmol) in dry THF (20 mL) was stirred under nitrogen for 2 min. To this solution, compound **107** (1.05 g, 2.5 mmol), $K_2CO_3$ (0.69 mg, 0.005 mmol) and bromobenzene (0.56 mL, 5.3 mmol) were added. The mixture was stirred vigorously under reflux for 6 h, cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried using $MgSO_4$, evaporated under diminished pressure at 70 °C to remove the excess PhBr. The expected product **87** was not obtained, but the starting material was recovered.

### c. Oxidation using $Br_2$ and $NaHCO_3$

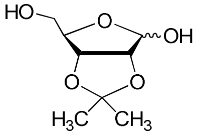
To a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose **(107)** (2 g, 4.76 mmol) in butanol (50 mL) and water (5 mL) was added $NaHCO_3$ (0.79 g, 9.4 mmol). The solution was stirred for 15 min at room temperature. The reaction flask was then immersed in an ice water bath. Bromine (0.26 mL, 5 mmol) was then added and the orange color solution obtained was stirred for additional 50 min under dark condition. Sodium bisulfite was added to completely discharge the orange color. The clear solution was evaporated (60 $^{o}$C -70 $^{o}$C) to get wet slurry, which was dissolved in ether (50 mL), washed with water (3 x10 mL) and dried ($MgSO_4$) to get the product 87 ( 1.1g, 55%).

### d. Oxidation using $KMnO_4$ and acetone

To a vigorously stirred solution of 2,3,5-tri-*O*- benzyl-α,β-D-ribofuranose **(107)** (0.2 g, 0.48 mmol) in reagent acetone (5 mL), $KMnO_4$ (0.114 g, 0.72 mmol) was added in portions over 1 h period. The temperature of the mixture was maintained between 25 $^{o}$C-45 $^{o}$C. Stirring was continued at room temperature for 2 h. The mixture was then filtered through Celite and the crude solid obtained was washed with fresh acetone. The combined filtrates were evaporated to yield a residue which was redissolved in ether and washed with water. After drying with anhydrous $MgSO_4$ the solvent was evaporated to yield the lactone **87** (0.12 g, 60%). $R_f$ 0.46, (petroleum ether/ethyl acetate, 3/1). The yield of the pure compound after column was about 25% to 30%. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.18-7.40 (phenyl groups), 4.97 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.77 ( d, $J_{AB}$ = 12.5 Hz, 1H, $OCH_2Ph$), 4.72 (d, $J_{AB}$ =12.0 Hz, 1H, $OCH_2Ph$), 4.57 ( d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$), 4.51 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.42-4.45(m, 4H, H2, H4, $CH_2$ of $CH_2Ph$), 4.13 (q, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 1.5 Hz, 1H, H3), 3.68 (app.q, $J_{4,5b}$ = 2.5

Hz, $J_{5a,5b}$ = 11.0 Hz, 1H, H5b,), 3.57 (app.q, $J_{4, 5a}$ = 2.5 Hz, $J_{5a, 5b}$ 10.5 Hz, 1H, H5a). $^{13}$C (125 MHz, $CDCl_3$): δ 173.9 (Carbonyl), 137.4, 137.3, 137.1 (3C), 127.8-128.7 (Ph), 81.9, 75.6, 73.9 (C2, C3, C4), 73.8, 72.9, 72.6 ( $CH_2Ph$), 68.9 (C5).

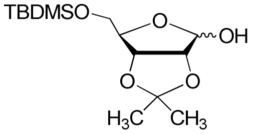
### 2,3-*O*-isopropylidene-α,β-D-ribonofuranose ( 108)



**108**

Conc.$H_2SO_4$ (0.13 mL) was added to a slurry of ribose (4 .9 g, 0.033 mol) in dry acetone (50 mL) at room temperature. A clear solution was obtained within 5 min. Stirring was continued for an hour. The pH of the solution was adjusted to 7 using calcium hydroxide. The resulting slurry was filtererd through a Celite and the clear filtrate was evaporated in *vacuo*, to get a light yellow viscous oil of **108** (5.9 g , 95%). $^1$H NMR (300 MHz, $CDCl_3$): δ 5.35 (s,1H, H1), 4.77 (d, $J_{2,3}$ = 5.7 Hz, 1H, H2), 4.53 (d, $J_{3,2}$ = 5.7 Hz, 1H, H3), 4.33 ( b,1H, H4), 3.66 (m, 2H, H5a, H5b), 1.43, 1.27 (2s, 6H, $C(CH_3)_2$). $^{13}$C (125MHz, $CDCl_3$): δ 112.4 (C), 102.9 (C1), 87.8, 86.9 (C2, C3), 81.8 (C4), 63.6 (C5), 24.9, 26.5 ($(CH_3)_2$).

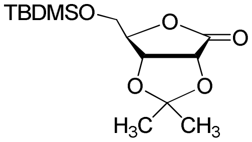
### 5-*O*-*tert*-butyldimethylsilyl-2,3 *O*-isopropylidene-α,β-D-ribofuranose (109)



**109**

To a solution of 2,3-*O*-isopropylidene-α,β-D-ribonofuranose (**108**) (3 g, 15.8 mmol) and imidazole (3 g, 44.06 mmol) in dry DMF (6 mL) was added *t*-$BuMe_2SiCl$ (2.61 g, 17.3 mmol) in one portion. The solution was stirred at 25 °C for 2 h. It was diluted with water (25 mL), extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with water (2 x 15 mL) and dried ($MgSO_4$). The solvent was evaporated to yield the product **109** (2.64 g, 55%). $R_f$ 0.64 ( hexane/ethyl acetate, 4/1). $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.30 (d, $J_{OH,1}$ = 11.5 Hz,1H, OH ), 4.78 (d, $J_{1,OH}$ = 11.5 Hz, 1H, H1), 4.71(d, $J_{2,3}$ = 5.0 Hz, 1H, H2), 4.51(d, $J_{3,2}$ = 5.0 Hz, 1H, H3), 4.35 (m, 1H, H4), 3.73-3.77 (m, 2H, H5a, H5b), 1.33, 1.49 (2s, 6H, $(CH_3)_2$), 0.93 (s, 9H, $Si(CH_3)_3$), 0.15, 0.14 (2s, 6H, $(CH_3)_2Si$ ). $^{13}C$ (125 MHz, $CDCl_3$): δ 112.2 (C $(CH_3)_3$), 103.6 (C1), 87.8, 87.2 (C2, C3), 82.0 (C4), 65.0 (C5), 25.9 (C $(CH_3)_3$), 26.7, 25.1 (OC $(CH_3)_2$), 18.5 (C $(CH_3)_3$), -5.4 (Si $(CH_3)_2$).

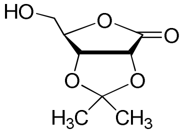
**5-*O*-*tert*-butyl dimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (110)**



**110**

To a vigoursly stirred solution of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose (**109**) (4.95 g, 16.3mmol ) in reagent acetone (50 mL), $KMnO_4$ ( 3.90 g, 24.68 mmol ) was added in portions over one hour period at a temperature between 25 °C -45 °C. Stirring was continued for another 2 h. The mixture was filtered using Celite and was washed with acetone (20 mL). The combined washings were evaporated to give the residue which was dissloved in ether (95 mL), washed with water (3 x 20 mL) and dried with $MgSO_4$. The solvent was evaporated to yield white crystals of **110** (2.8 g, 57%). $R_f$ 0.50 (hexane/ethyl acetate, 4/1). $^1H$ NMR (500 MHz, $CDCl_3$): δ 4.84, 4.78 (2d, $J$ = 5.7 Hz, 5.4 Hz, 2H, H2, H3), 4.62(m, 1H, H4), 3.91 (app. q, $J_{5b,a}$ = 11.4 Hz, $J_{5b,4}$ = 2.1 Hz, 1H, H5b), 3.82 (app. q, $J_{5a,b}$ = 11.4 Hz, $J_{5a,4}$ = 1.5 Hz, 1H, H5a), 1.48, 1.40 (2s, 6H, $C(CH_3)_2$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.08, 0.07 (2s, 6H, $(CH_3)_2Si$). $^{13}C$ (125 MHz, $CDCl_3$): δ 174.4 (C=O), 113.1 ($C(CH_3)_2$), 82.4 (C2), 78.6, 75.9 (C3, C4), 63.1 (C5), 25.9 (C $(CH_3)_3$), 27.0, 25.7 ($OC(CH_3)_2$), 18.4 (C $(CH_3)_3$), -5.4, -5.6 ($(CH_3)_2Si$).

**2,3-*O*-isopropylidene-D-ribonolactone 112**



**112**

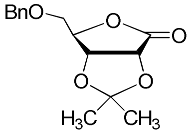
D-(+)-Ribonic- γ- ribonolactone (9 g , 0.033 mol) was dissolved in dry acetone (50 mL). To this solution catalytic amount of con.$H_2SO_4$ (0.13 mL) was added and stirred. A clear solution was obtained within 5 min. Stirring was continued for 1 h and the pH of the solution was adjusted to 7 using calcium hydroxide. The resulting slurry was filtererd through Celite and the clear filtrate was evaporated in *vacuo* to give a white solid (5.9 g, 95 %). $R_f$ 0.65 (hexane/ ethyl acetate/isopropanol, 3/1.5/0.5). $^1$H NMR (300 MHz, $CDCl_3$): δ 4.86 (q, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 2.1 Hz, 1H, H3), 4.65 (m, 1H, H4), 4.02 (d, $J_{5a,5b}$ = 12.0 Hz, 1H, H5a), 3.83 (app.q, $J_{4,5b}$ = 3.5 Hz, $J_{5a,5b}$ = 12.0 Hz, 1H, H5b), 2.98 (1H, H2), 1.39, 1.48 (2s, 6H, $(CH_3)_2Si$ ). $^{13}$C (125 MHz, $CDCl_3$): δ 175.5 (C=O), 113.3 (C1), 83.2, 78.6, 76.0 (C2, C4, C3), 62.1 (C5), 25.7, 26.9 ($OC(CH_3)_2$).

**Synthesis of 5-*O*-tert-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone 110 using 112**

To a solution of 2,3-*O*-isopropylidene-D-ribonolactone **112** (5g, 026 mol) in anhydrous DMF (20 mL) was added *t*- $BuMe_2SiCl$ (5 g, 0.033 mol). The mixture was stirred for one hour and was subsequently poured in to 200 mL of $H_2O$. The mixture was stirred for 30 min. The crysalline product was washed with water (2 x 50 mL). The solid product was redissolved in

$CH_2Cl_2$ and dried ($MgSO_4$). The solvent was evaporated under pressure to give the product **110** (4.62 g, 55%)

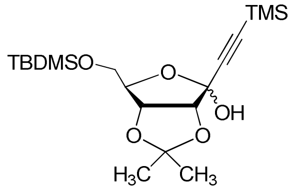
### 5-*O*-benzyl-2, 3-*O*-isopropylidene-D-ribonolactone (113)



**113**

To a solution of sodium hydride (60% in mineral oil) (0.196 g) in DMF (5 mL) was added a solution of 2,3-*O*-isopropylidene-D-ribonolactone **112** (1.4 g, 7.44 mmol) in DMF (15 mL) at 0 $^{o}$C. The mixture was stirred for 30 min. Benzyl bromide (1.12 mL, 9.4 mmol) was added slowly under the same temperature. The reaction was stirred overnight 16 h at room temperature. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with 0.1N HCl (3 x 20 mL). The organic layer was washed with saturated sodium bicarbonate (3 x 20 mL), then with brine (2 x 15 mL). The organic layer was dried using anhydrous magnesium sulfate and concentrated to give an oily mixture of **113** (0.99 g, 48%). $R_f$ 0.69 (hexane/ethyl acetate, 3/2). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.13-7.27 (phenyl), 4.69 (d, $J_{2,3}$ = 5.0 Hz, 1H, H2), 4.62 (d, $J_{3,2}$ = 5.0 Hz, 1H, H3), 4.56 (m, 1H, H4), 4.38, 4.47 (app.q, $J_{A,B}$ = 12.0 Hz, 2H, $OCH_2Ph$,), 3.63 (app. q, $J_{4,5b}$ = 2.0 Hz, $J_{5a,5b}$ = 10.5 Hz, 1H, H5b), 3.59 (app. q, $J_{4,5b}$ = 1.5 Hz, $J_{5a,5b}$ = 10.0 Hz, 1H, H5a), 1.37, 1.27 (2s, 6H, $C(CH_3)_2$). $^{13}$C (125 MHz, $CDCl_3$): δ 174.7 (CO), 137.2 (C), 127.8-128.8 (phenyl), 113.3 ($\underline{C}$ $(CH_3)_2$), 81.3, 78.5, 75.8 (C2, C3, C4), 74.1 ($CH_2Ph$), 69.2 (C5), 25.8, 27.0 (C $(CH_3)_2$).

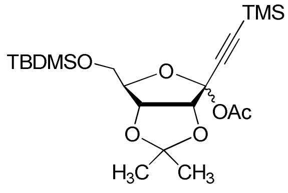
### 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-hydroxyl-1-trimethylsilylethynylriboside 119



**119**

A solution of trimethylsilyl acetylene (3 mL, 21.1 mmol) in dry THF (50 mL) was cooled to -78 $^{o}$C. Butyl lithium (1.6 M in hexane, 13.2 mL, 21.1 mmol) was then added and the mixture was stirred for 30 min. A solution of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone **110** (4.26 g, 14.1 mmol) in dry THF (50 mL) was added and the mixture was stirred for 30 min at -78 $^{o}$C. The reaction was quenched with saturated solution of $NH_4Cl$ (30 mL) and extracted with ether (2 x 50 mL). The organic layer was washed with a saturated solution of $NaHCO_3$, with water, dried with $MgSO_4$ and concentrated to get **119** (4.22 g, 75%). $R_f$ 0.6 (petroleum ether/ethyl acetate, 7/1). $^1$H ppm ($CDCl_3$, 500MHz): δ 5.33 (s,1H, OH), 4.78 (d, $J_{2,3}$ = 6.0 Hz, 1H, H2), 4.53 (d, $J_{3,2}$ = 5.5 Hz, 1H, H3), 4.39 (b, 1H, H4), 3.78 (app. q, $J_{4,5b}$ = 2.5 Hz, $J_{5b,5a}$ = 11.5 Hz, 1H, H5b), 3.74 (app.q, $J_{4,5a}$ = 2.0 Hz, $J_{5a,5b}$ =11.0 Hz, 1H, H5a), 1.54, 1.36 (2s, 6H, $C(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 9H, $Si(CH_3)_3$), 0.13 (d, 6H, $Si\text{-}(CH_3)_2$). C$^{13}$ ($CDCl_3$,125MHz): δ 113.3 ($O_2CCH_3)_2$), 101.9 (C1), 100.0 (C ≡), 91.4 (C≡), 89.0 (C3), 86.4 (C4), 82.3 (C2), 64.7 (C5), 29.9 (C $(CH_3)_3$), 26.8 ($C(CH_3)_2$), 25.8 ((C $(CH_3)_2$), 18.4 (C $(CH_3)_3$), -0.1 (Si $(CH_3)_3$), -5.5 (Si $(CH_3)_2$).

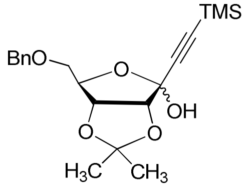
**1-*O*-acetyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-(trimethylsilylacetylene)-D - ribofuranoside 120**



**120**

A solution of trimethylsilyl acetylene (3 mL, 21.1 mmol) dry THF (50 mL) was cooled to -78 °C. Butyl lithium (1.6 M in hexane, 13.2 mL, 21.1 mmol) was then added and the mixture was stirred for 30 min. To this, a solution of **110** (4.26 g, 14.1 mmol) in dry THF (50 mL) was added and the mixture was stirred for 30 min at -78 °C and warmed to -70 ° C to -60 ° C. Acetic anhydride ( 7.1 mL, 75 mmol) was added and stirring was continued for another 30 min at -60 °C. The reaction mixture was quenched with saturated solution of $NH_4Cl$ (20 mL). The organic layer was washed with saturated solution of $NaHCO_{3,}$ with water and the combined organic layer was extracted with ether, dried using $MgSO_4$ and concentrated to get the product as a light yellow oil (5.3 g, 85%). $R_f$ 0.54 (hexane/ethyl acetate, 7/1). Only one isomer was detected. $^1$H ppm ($CDCl_3$,500MHz): δ 4.79 (d, $J_{2,3}$ = 6.2 Hz, 1H, H2), 4.73 (dd, $J_{3,2}$ = 6.2 Hz, $J$ = 1.46 Hz, 1H, H3), 4.20 (m, 1H, H4), 3.68-3.73 (b, 2H, H5a, H5b), 2.03 (s, 3H, $OCCH_3$), 1.31, 1.50(2s, 6H, $C(C\underline{H_3})_2$), 0.82(s, 9H, $C(C\underline{H_3})_3$), 0.08 (s, 9H, $Si(C\underline{H_3})_3$), 0.002 (s, 6H, $Si(CH_3)_2$). $C^{13}$($CDCl_3$,125MHz): δ 167.7( $OCCH_3$ ), 115.1 ($O_2C(CH_3)_2$), 100.1 (C≡), 98.5 (C≡), 91.5 (C1), 87.8 (C2), 84.4 (C3), 81.0( C4), 62.7 (C5), 26.3, 26.1 ( $C(CH_3)_3$), 21.9 ($C(CH_3)_3$), 18.4 ($OCCH_3$), -0.1 ( $Si(CH_3)_3$), -5.3 ($Si(CH_3)_2$.

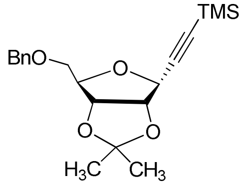
**5-*O*-benzyl-2,3-*O*,*O*-isopropylidene-1-hydroxy-1-trimethylsilylacetylide 122**



**122**

To a solution of trimethylsilyl acetylene (5.3 mL, 37.50 mmol) in 90 mL of dry THF (90 mL) cooled at -78 °C was added *n*-butyl lithium (1.6 M in hexane, 23.4 mL, 37.50 mmol). The mixture was stirred for 30 min. A solution of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone **113** (6.95 g, 24.9 mmol) in THF (90 mL) was added to this reaction mixture and it was was stirred at -78 °C for 30 min. The reaction mixture was quenched with ammonium chloride (100 mL) and extracted with ether. The combined organic layers were washed with sodium bicarbonate solution (3 x100 mL), water (3 x100 mL), brine and dried using anhydrous $Na_2SO_4$ to get the product **122** (7.19 g, 76.5%). $R_f$ 0.67 (hexane/ethyl acetate, 4/1). $^1$H ppm ($CDCl_3$,500MHz): δ 7.25-7.32 (m, 5H, phenyl), 4.97 (s, 1H, OH), 4.76 ( d, $J_{2,3}$ = 6.0 Hz, 1H, H2), 4.57 (d, $J_{AB}$ = 11.0 Hz,1H, $OCH_2Ph$), 4.50 (d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$), 4.48 (d, $J_{3,2}$ = 5.0 Hz, 1H, H3), 3.62 (app. q, $J_{5b,5a,}$ = 10.0 Hz, $J_{4,5b}$ = 2.5 Hz, 1H, H5b), 4.39 (b, 1H, H4), 3.56 (app. q, $J_{4,5a}$ = 2.5 Hz , $J_{5a,5b}$ = 10.5 Hz, 1H, H5a), 1.35, 1.54 (2s, 6H, $C(CH_3)_2$), 0.20 (s, 9H, Si $(CH_3)_3$), $C^{13}$ ($CDCl_3$, 125MHz): δ 136.2 (C), 128.3-129.0 (Phenyl), 113.4 ($C(CH_3)_2$, 102.2 (C-1), 100.0 (C≡C-TMS), 91.5 (≡C-TMS), 88.8 (C2), 84.9 (C3), 82.7 (C4), 74.3 ($CH_2Ph$), 71.1 (C-5), 26.9, 25.8 (C(CH3)$_2$), -0.6 (Si $(CH_3)_3$).

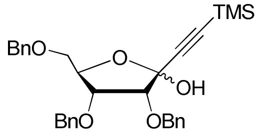
### 5-*O*-benzyl-2,3-*O*-isopropylidene-1-trimethylsilylacetylide 123



**123**

A solution of 5-*O*-benzyl-2,3-*O*-isopropylidene-1-hydroxy-1-trimethylsilylacetylide **122** (1.38 g, 3.67 mmoL) in dichloromethane (92 mL) was cooled to -78 °C. To this solution, $BF_3 \cdot Et_2O$ (6.4 mL, 51.2 mmol) was added followed by the addition of triethylsilane (4.1 mL, 23.8 mmol,). The solution was stirred for 1 h. The mixture was neutralized with $NaHCO_3$ solution (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, reduced under *vacuo* to get **123** (0.33 g, 25%). $R_f$ 0.37 (hexane/ethyl acetate, 6/1). $[\alpha]_D^{24}$ -14.45 ($c$ = 0.011, $CH_2Cl_2$). $^1H$ ppm ($CDCl_3$, 500 MHz): δ 7.28-7.17 (m, 5H, Ph), 4.72 (t, $J_{2,1} = 4.5$ Hz, $J_{2,3} = 6.0$ Hz, 1H, H2), 4.68 (d, $J_{3,2} = 5.6$ Hz, 1H, H3), 4.44, 4.52 (app.q, $J_{AB} = 11.7$ Hz, 2H, $CH_2Ph$), 4.18 (m, 1H, H4), 3.54 (app. q, $J_{5Hb,5Ha} = 10.2$ Hz, $J_{5Hb.\ H4} = 3.0$ Hz, 1H, H5b), 3. 46 (app. q, $J_{5Ha,5Hb} = 10.5$ Hz, $J_{H5a,\ H4} = 3.0$ Hz, 1H, H5a), 1.28,1.49 (2s, 6H, $(OCH3)_2$), 0.12 (s, 9H, $Si(CH3)_3$). $C^{13}$($CDCl_3$, 125MHz): δ 137.9 (C), 127.6-128.7 (phenyl carbons), 113.5 ($O_2C(CH_3)_2$), 99.9 (≡C-TMS), 93.6 (C≡C-TMS), 83.5 (C1), 82.7 ( C2), 82.2 (C3), 74.6 (C4), 73.9 (-O-$CH_2$-Ph), 72.2 (C5), 25.8, 26.7 (2s, 6H, $C(CH_3)_2$), 0.1($C-(CH_3)_2$).

### 2,3,5-Tri-*O*-benzyl-α-β-1-hydroxyl-1-trimethylsilylethynylriboside 88



**88**

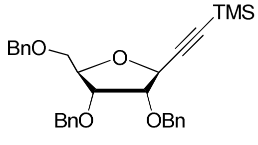
#### (a) Using cerium trimethylacetylide

Anhydrous cerium chloride (1.97 g, 7.99 mmol) was dissolved in dry THF (25 mL). The solution was stirred under argon and the stirring was continued for 2 h at room temperature. The resultant suspension was cooled to -78 °C. A solution of lithiumtrimethylsilyl acetylene was prepared by dissolving trimethylsilyl acetylene (1.1 mL, 7.89 mmol) and *n*-BuLi (4.9 mL, 7.89 mmol) in THF (10 mL) at -78 °C and it was added to the cerium chloride suspension with constant stirring at -78 °C. The resultant solution was stirred for additional 30 min. A solution of 2,3,5-tri-*O*-benzyl-D-ribonolactone **87** (2.2 g, 5.46 mmol) in dry THF (10 mL) was added dropwise and was stirred for another 2 h, at -78 °C. It was then diluted with 0.1M HCl (15 mL) and extracted with ether (3 x 15 mL). The combined organic extracts were dried with $Na_2SO_4$ and concentrated. The desired product was not obtained.

#### (b) Using lithium trimethysilylacetylide

A solution of trimethylsilyl acetylene (1.17 mL, 8.3 mmol) in of dry THF (30 mL) was cooled to -78 ºC. *n*-Butyl lithium (1.6 M in hexane, 5.2 mL, 8.3 mmol,) was added to it and the mixture was stirred for 30 min. A solution of 2,3,5-tri-*O*-benzyl-D-ribonolactone (**87**) (2.23 g, 5.54 mmol) in dry THF (30 mL) was added to it , and the mixture was stirred at -78 ºC for a another 2 h. The reaction mixture was quenched with ammonium chloride (30 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with sodium bicarbonate, water, and brine. It was dried using $Na_2SO_4$ and concentrated to get **88** (2.32 g, 84%). NMR and IR spectra are in supportive of the partial desilylation of the product.

**2,3,5-Tri-*O*-benzyl-α-β-1-trimethylsilylethynylriboside (89)**

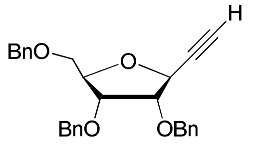


**89**

Solution of **88** (3.02 g, 5.85 mmoL) in dichloromethane (150 mL) was cooled to -78 °C. To this solution, $BF_3 \cdot Et_2O$ (10.57 mL, 84.56 mmol) was added followed by the addition of triethylsilane (6.64 mL, 38.54 mmol). The solution was stirred for 1 h. The mixture was neutralized with a saturated solution of $NaHCO_3$ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried using $MgSO_4$ and evaporated to get **89** (2.03 g, 70%). The crude was purified using silica gel. Two products were isolated with $R_f$ 0.49 corresponding to **89** and $R_f$ 0.55 corresponding to the desilylated product (petroleum ether/ethyl acetate, 4/1). $[\alpha]_D^{24}$ -10.75 (*c*= 0.072,$CH_2Cl_2$), $^1$H NMR (500 MHz, CDCl3): δ 7.04-7.22 (phenylgroups), 4.82 (d, $J_{AB}$ = 12.0 Hz,1H, $OCH_2Ph$), 4.78 (s,1H, H1), 4.76 (d, $J_{AB}$ = 12.5 Hz,1H,$OCH_2Ph$), 4.73 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.69 (d, $J_{AB}$ = 12.0 Hz, $OCH_2Ph$, 1H)**,** 4.62 (d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$), 4.61(d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.29 (q, $J_{4,5}$ = 4.4 Hz, $J_{4,3}$ = 4.4 Hz, 1H, H4 ), 4.14 (t, $J_{2,3}$ = 4.8 Hz, 1H, H2), 4.12 (t, $J_{3,2}$ = 4.8 Hz, 1H, H3), 3.71 (app. q, $J_{5b,4}$ = 4.9 Hz, $J_{5a,5b}$ = 11.2 Hz,1H, H5b), 3.68 (app.q, $J_{5a,4}$ = 4.4 Hz, $J_{5a,5b}$ = 11.2 Hz, 1H, H5a), 0.29 (s, 9H, $Si(CH_3)_3$), $^{13}$C (125 MHz, $CDCl_3$) : δ 137.6, 137.8, 138.2 (C), 127.9-128.7 (aromatic), 103.1 (≡C-TMS), 91.7 (C≡C-TMS), 81.8 (C2), 81.5 (C4), 77.9 (C3), 72.2, 73.4 ($CH_2$), 72.1

(C1), 71.3 ($CH_2$), 70.0 (C-5), 0.2 (C-TMS), HRMS (ESI) for $C_{31}H_{36}O_4Si$ $(M+NH_4)^+$, calcd 518.2721, found 518.2727.

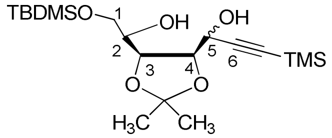
**2,3,5-Tri-*O*-benzyl-β-D-1-ethynylribiside 90**



**90**

A solution of **89** (1.63 g, 3.26 mmol) and anhydrous $K_2CO_3$ (0.018 g, 0.13 mmol) in methanol (25 mL) was stirred for 5 h. The solvent was evaporated under reduced pressure and the residue was mixed with sodium bicarbonate (25 mL) and extracted with DCM (3 x 15 mL). It was dried ($MgSO_4$), concentrated to get the alkyne **90** (1.25 g, 91%). $R_f$ 0.55 (petroleum ether/ethyl aceta, 4/1). $[\alpha]_D^{24}$ +7.08 ($c$ = 0.38, $CH_2Cl_2$), $^1$H NMR (500 MHz, CDCl3): δ 7.37-7.49 (m, 15H, Ar-H), 4.75 (s, 1H, H1), 4.82 (d, $J_{AB}$ = 11.71 Hz, 2H,2$OCH_2$Ph), 4.71 (d, $J_{AB}$ = 12.09 Hz, 2H, 2$OCH_2$), 4.63 (d, $J_{AB}$ =12.09 Hz, 2H, 2$OCH_2$ ), 4.32 (app.q. $J_{4,5}$ = 4.0 Hz, $J_{4,3}$ = 4.0 Hz, . 1H, H-4), 4.15 (t, 1H, H2, $J_{2,3}$ = 5.0 Hz), 4.13 (t, $J_{3,2}$ = 5.5 Hz, 1H,H3), 3.70 (app.q, $J_{5b,4}$ = 4.0 Hz, $J_{5a,5b}$ = 10.98 Hz, 1H, H5b,), 3.67 (app.q, $J_{5a,4}$ = 4.7 Hz, $J_{5a,5b}$ = 10.99 Hz, 1H, H5a), 2.64 (d, $J_{1,1'}$ = 2.0 Hz, 1H, acetylene). $^{13}$C (125 MHz, $CDCl_3$): δ 137.4, 137.6, 138.1 (C), 127.3-128.4 (aromatic), 81.8 (C≡), 81.5 (≡ C), 81.4 (C2), 77.8 (C4), 75.0 (C3), 72.2, 73.3 ($CH_2$), 72.1 (C1), 70.7 ($CH_2$), 69.9 (C5). HRMS (ESI) for $C_{28}H_{28}O_4$ $[M+NH_4]^+$ calcd 446.2326, measured 446.2333.

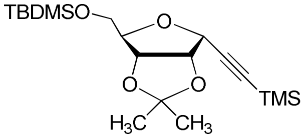
**1-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-7-(trimethylsilyl)-6-yne-2,5-diol 157**



**157**

To a solution of trimethylsilyl acetylene (2.28 mL, 16.1mmol) in THF (20 mL) was added 1.6 M butyllithium in hexane (8.3 mL ,13.2 mmol) at 0 °C. After stirring the mixture for 30 min a solution of **109** (2 g, 6.57 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at 0 °C for additional 30 min. and warmed up to room temperature. It was stirred for another 3 h period. The reaction mixture was then quenched by adding saturated $NH_4Cl$ (30 mL), diluted with ether (50 mL), washed with $NH_4Cl$ (2 x 25 mL), brine (2 x 25 mL), dried ($MgSO_4$) and evaporated to get **157** (1.48 g, 56%). $R_f$ 0.58 (hexane/ethyl acetate, 4/1). $^1$H NMR (300MHz, $CDCl_3$): δ 4.64 (dd, $J_{5,4}$ = 4.2Hz, $J_{5,OH}$ = 9.3 Hz,1H, H5), 4.33 (dd, $J_{4,3}$ = 6.3 Hz, $J_{4,5}$ = 4.2 Hz, 1H, H4), 4.16 (dd, $J_{3,4}$ = 6.3 Hz $J_{3,2}$ = 9.0 Hz, 1H, H3), 3.98 (d, $J_{OH,5}$, = 9.31H, OH), 3.84 (app.q, $J_{1ba}$ = 10.2 Hz, $J_{1,2}$ = 3.0 Hz, 1H, H1$_b$), 3.66 (app. q, $J_{1ab}$ = 10.2Hz, $J_{1,2}$ = 5.7 Hz,1H, H1$_a$), 3.12 (d, $J$ = 7.2 Hz, 1H, OH), 1.49 (s, 3H, $O_2C(CH_3)_2$), 1.34 (s, 3H, $O_2C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.16 (s, 9H, $Si(CH_3)_3$), 0.083 (s, 6H, $Si(CH_3)_2$). $^{13}$C NMR (75MHz, $CDCl_3$): δ 109.4 ($O_2C(CH_3)_2$), 104.4 (C≡CTMS), 90.7 (C≡CTMS), 80.2 ( C2), 76.5 ( C3), 69.3 ( C4), 64.4 (C5), 62.0 (C1), 27.8 ($O_2C(CH_3)_2$), 26.0 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), 25.6 ($O_2C(CH_3)_2$), 0.001( $Si(CH_3)_3$), -5.22 ($Si(CH_3)_2$).

### **5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-trimethylsilylethynyl riboside 121**



**121**

#### **a) Using 1-*O*-acetyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-(trimethylsilylacetylene)-D-riboside 120**

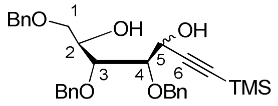
To a solution of **120** (0.57 g, 1.29 mmol, 1 equiv) in of dry dichloromethane (10 mL) with molecular sieves was added triethylsilane (0.79 ml, 6.45 mmol, 5equiv) and freshly distilled TMSOTf (0.54 ml, 2.98 mmol, 2.5 equiv) at 0 $^{o}$C. The reaction mixture was stirred under nitrogen atmosphere. The reaction was warmed up to room temperature and stirred for 30 min. It was then quenched with $NH_4Cl$ (20 mL), diluted with DCM, washed with water (2 x 5 mL), dried (anhydrous $MgSO_4$) and evaporated. NMR analysis confirmed formation of the produt **121**, but it was contaminted with many by-products and the purification was difficult.

#### **(b) 5-*O*-tert-butyldimethylsilyl-2,3-*O*-isopropylidene-1-trimethylsilylethynyl riboside 121 from ring-closing of 157.**

A solution of alkynyl diols **157** (0.69 g, 1.71 mmol) in dry pyridine (37 mL) was stirred at room temperature. Tosyl chloride (2.29 g, 12.01 mmol) was then added in one portion and the mixture was stirred for 48 h. The reaction mixture was then diluted with 5 mL of water and evaporated. The residue was triturated with hot ether and evaporated to give oily syrup **121**, which was purified to get clear crystals (0.4 g, 61%). $R_f$ 0.51(petroleum/ethyl acetate, 16/1). $[\alpha]_D^{24}$ -23.72 ($c$ = 0.0383, $CH_2Cl_2$), $^1$H NMR (500 MHz $CDCl_3$): δ 4.85 (d, $J_{1,2}$ = 5.0 Hz,1H, H-1), 4.78 (d, $J_{3,2}$ = 5.5Hz, 1H, H-3), 4.72 (, t, $J_{2,1}$=5.0 Hz, $J_{2,3}$ = 5.5 Hz, 1H H-2), 4.17 (m, 1H, H-4), 3.75 (app. q, $J_{5b,5a}$ = 10.5 Hz, $J_{5b,4}$ = 2.0 Hz, 1H, H-$5_b$), 3.67 (app.q, $J_{5a,5b}$=10.5 Hz, $J_{5a,4}$ = 2.0

Hz, 1H, $H5_a$), 1.54 (s, 3H, $O_2C(C\underline{H}_3)_2$), 1.36 (s, 3H, $O_2C(CH_3)_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.17 (s, 9H, $Si(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$). $^{13}$CNMR (125MHz $CDCl_3$): δ 113.2 ($O_2C(CH_3)_2$), 100.2 (C≡CTMS), 93.3 (C≡CTMS), 84.2( C4), 83.4 (C3), 82.44 (C2), 74.7 (C1), 65.62 (C5), 26.6 ($O_2C(CH_3)_2$), 26.0 ( $SiC(CH_3)_3$), 25.7 ( $O_2C(CH_3)_2$), 18.3 ( $SiC(CH_3)_3$), 0.05 ($Si(CH_3)_3$), -5.51 ($Si(CH_3)_2$) .

**1, 3, 4-Tri-*O*-benzyl-7-(trimethylsilyl)-6-yne-2, 5-diol 156**



**156**

To a solution of trimethylsilyl acetylene (0.83 mL, 5.95 mmol,) in THF (8 mL) was added 1.6M butyllithium in hexane (4.76 mmol, 3 mL) at 0 °C. After stirring the mixture was 45 min a solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose **107** (1 g, 2.37 mmol) in THF (8 mL) was added dropwise at the same temperature. The reaction mixture was stirred at 0 °C for additional 30 min and warmed up to room temperature. It was stirred for another 5 h period. The reaction mixture was then quenched by adding saturated aqueous $NH_4Cl$ solution (3 mL), diluted with ether (50 mL), washed with $NH_4Cl$ (2 x 25 mL), brine (2 x 25 mL), dried ($MgSO_4$) and evaporated. The crude was used for the further ring-closing reaction.

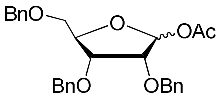
**2,3,5-Tri-*O*-benzyl-α-β -1-trimethylsilylethynylriboside 89 from 156 using Mitsunobu condition**

A solution of alkynyl diols **156** (0.9 g, 1.74 mmol) and triphenylphosphine (1.19 g, 4.5 equiv) in freshly distilled THF (18 mL) was refluxed. To this solution was added 40% diethylazodicarboxylate (DEAD) (1.73 mL, 4.3 mmol) in toluene and refluxing was continued for an additional hour and the reaction mixture was evaporated to give a thick dark brown oil, which was chromatographed to get **89** (5-10% yield)

### Synthesis of tributylstannyl(trimethylsilyl) acetylide (166)

To an ice cold solution of lithium trimethylsilylacetylene (4.2 mL, 30 mmol), a solution of chlorotributylstannane (10.2 g, 7.8 mL, 30.1mmol) in THF (5 mL) was added dropwise. The mixture was stirred overnight at room temperature. The mixture was then diluted with $CH_2Cl_2$ (100 mL), washed with water (3 x 15 mL), saturated NaCl (3 x 10 mL), and dried using $CaSO_4$. The residue was distilled under reduced pressure to give the product **166**. The crude was not separated in to very high purity, but the expected product was separated with some impurity and used for the next step.

### 2, 3, 5-Tri-*O*-benzyl-1-acetyl-α,β-D-ribofuranoside 169



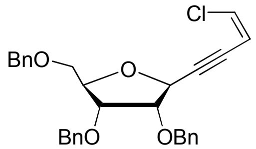
**169**

2,3,5-Tri-*O*-benzylribofuranose **107** (2 g, 4.75 mmol) was added to a ice cold mixture of acetic anhydride (2.3 mL, 24.3 mmol) and pyridine (10 mL). The reaction mixture was stirred overnight. It was diluted with ether (50 mL), washed with water (3 x 15 mL), 2% $CuSO_4$ (3 x 20 mL) and finally with water. The solution was dried using $MgSO_4$ to get **169** ( 2 g, 90%)

### 2, 3, 5-Tri-*O*-benzyl-1- trimethylsilylethynylriboside 89 from 169

A solution of **169** (1 g, 2.16 mmol), tributylstannyl(trimethysilyl)acetylide (1.67 g, 4.31mmol), and actvated 4A powdered molecular sieves (1.0 g), in anhydrous $CH_2Cl_2$ (7 mL) was stirred at room temperature for 15 min and TMSOTf (0.61 mL, 3.37 mmol) was added dropwiswe. The dark brown mixture was stirred at room temperature for additional 1.5 h, diluted with $Et_3N$ (1 mL) and $CH_2Cl_2$ (30 mL), filtered through Celite and concentrated. Nmr analysis showed that the product **89** was formed but it was very difficult to separate.

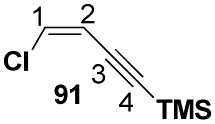
### 2,3,5-Tri-*O*-benzyl-β-1-(6,7-yne-8,9-ene-chloro)-D-ribofuranose 174



**174**

To a solution of $Pd(PPh_3)_4$ (0.025 g, 0.0216 mmol) in dry benzene (5 mL) and *n*-$BuNH_2$ (0.19 mL, 1.92 mmol) was added *Z* -1,2-dichloroethene (0.18 mL, 2.38 mmol). To this, a solution of **90** (0.2 g, 0.47 mmol) in benzene (1.7 mL) was added, followed by the addition of CuI (0.018 g, 0.094 mmol). The solution was stirred at 25 °C overnight. It was then poured in to a saturated solution of $NaHCO_3$ and was extracted with DCM. The organic layer was dried using $Na_2SO_4$ and concentrated. Desired product **174** was not obtained.

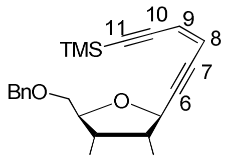
### (*Z*)-1-Chloro-4-trimethylsilylbut-1-en-3-yne 91



**91**

To a solution of *Z*-1,2-dichloroethene **102** (5.8 g, 60 mmol) in dry, degassed benzene (40 mL) was rapidly added in to a solution of $Pd(PPh_3)_4$ (1.73 g, 1.5 mmol), *n*-$BuNH_2$ (6 mL, 60 mmol) and trimethylsilylacetylene (4.2 mL, 30 mmol) in benzene. After 10 min cuprous iodide (0.57 g, 3 mmol) was introduced. The reaction was cooled in a water bath. After 5 h the mixture was hydrolysed with saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated. The major part of the triphenylphosphine was precipitated with a minimum volume of ether/pentane (50/50). The crude product was purified with flash chromatography using pentane giving the product **91** (4.4 g, 49%). $R_f$ 0.57 ( pentane). $^1$H NMR (500 MHz, CDCl3): δ 6.39(d, $J_{1,2}$ =7.3 Hz, 1H, H1), 5.88 (d, $J_{2,\,1}$ = 7.8 Hz, 1H, H2), 0.22 (s, 9H, TMS). $^{13}$C (125 MHz, $CDCl_3$): δ 129.4(C1), 111.3 (C2), 103.9 (C≡), 98.3 (C≡), -0.06 (C-TMS).

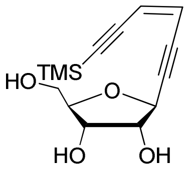
**2,3,5-Tri-*O*-benzyl-β-1-(6,7,10,11-diyne-8, 9-ene-11-trimethylsilyl) ribofuranoside 92**



**92**

In a recovery flask was placed Pd $(PPh_3)_4$ (0.23 g, 0.199 mmol) in dry degassed benzene (70 mL). To this solution *n*.$BuNH_2$ (1.75 mL, 17.7 mmol) was added followed by the addition of chloroeneyne **91** (2.2 g, 14 mmol) in benzene . A solution of acetylene, **90** (1.85 g, 4.32 mmol) in dry benzene (70 mL) was then added to the solution followed by the addition of CuI (0.165 g, 0.87 mmol) and the stirring was continued overnight at room temperature . The solution was then poured in to saturated solution of $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (2 x 50 mL) and the organic layer was dried ($Na_2SO_4$) and concentrated. The yield before purification was more than the theoretical yield. Yield after purification was 1g (60%). $R_f$ 0.7 (petroleum ether/ ethyl acetate, 4/1). $[\alpha]_D^{24}$ +23.54 (*c* = 0.0114,$CH_2Cl_2$). $^1$H NMR (500 MHz, CDCl3): δ 7.27-7.42 (m, 15H, Ar-H), 5.88 (d, *J* =11.0 Hz, 1H, olefin protons ), 5.84 (dd, *J* = 11.0 Hz, 1.5 Hz, olefin proton), 4.91 ( dd, $J_{1,2}$ = 4.4 Hz, $J_{1,\ \mathrm{olefin}}$ = 1.5 Hz, 1H, H1), 4.78 (d, $J_{AB}$ = 11.5 HZ , 1H, $OCH_2Ph$), 4.70 (d, $J_{AB}$ = 12.5 Hz, 1H,$OCH_2Ph$), 4.66 (d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$ ), 4.62 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.55 (d, 2H, $OC\underline{H_2}Ph$), 4.26 (app q, $J_{4,5}$ = 4.0 Hz, $J_{4,3}$ = 4.5 Hz , 1H, H4), 4.13 (t, , $J_{3,4}$ = 5.0 Hz, 1H, H2), 4.08 (t, $J_{3,2}$ = 5.0 Hz, 1H, H3), 3.65 (app.q, $J_{5b,4}$ = 3.9 Hz, $J_{5a,5b}$ = 10.7 Hz, 1H, H5b), 3.62 (app.q, $J_{5a,4}$ = 4.4 Hz, $J_{5a,\ 5b}$ = 10.7 Hz, 1H, H5a), 0.21 (s, 9H, Si (CH$_3$)$_3$). $^{13}$C (125 MHz, CDCl$_3$): δ 138.1, 137.7, 137.5 (3C), 127.4-128.3(aromatic), 119.7-120.0 (olefin carbons), 103.1 (C≡), 101.8(C≡), 94.6(C≡), 83.8 (C≡), - 81.9 (C2), 81.3 (C4), 78.2 (C3), 72.2-73.3 (3CH$_2$), 71.6 (C1), 70.1 (C5), 0.1(CTMS), HRMS (ESI) for $C_{35}H_{38}O_4Si$ $[M+NH_4]^+$ calcd 568.2877, measured, 568.2881.

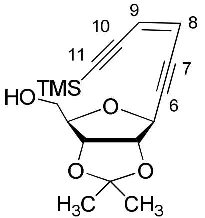
**1-(6,7,10,11-diyne-8,9-ene-11-trimethylsilyl)ribofuranose 93**



**93**

To a solution of **92** (0.15 g, 0.27 mmol) in methylene chloride (8 mL) was added dropwise 1M BCl$_3$ in methylene chloride (2.04 mL) at -78 $^o$C for 30 min. Methanol (0.17 mL) was added to quench the reaction and the reaction was warmed up to 3 h at room temperature. The reaction mixture was evaporated and chromatographed, first by using a mixture of hexane/ethyl acetate (4/1), and then with ethyl acetate/hexane (3/1) followed by ethyl acetate/hexane (9/1), ethyl acetate, and finally with ethylacetate/methylalcohol (9/1). The yield of the reaction was 0.07 g, 92%. IR spectrum showed the presence of broad peak around 3500cm$^{-1}$for the –OH group and NMR analysis showed the removal of the benzyl groups.

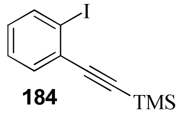
**2,3-*O*-isopropylidene-1-(6,7,10,11-diyne-8, 9-ene-11-trimethylsilyl) riboside 94**



**94**

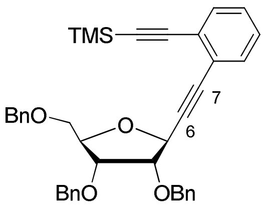
The solution of **93** (0.23 g, 0.82 mmol) in acetone (7.0 mL) and concentrated $H_2SO_4$ (45 μL) was added and the solution was stirred for 1hr and 30 min. The pH of the solution was adjusted for 7 using $Ca(OH)_2$. The resulting slurry was filtered through Celite and the filtrate was evaporated. $R_f$ 0.45 (ethyl acetate/hexane, 6/1). Yield was 0.24 g, 92%. $[\alpha]_D^{24}$ = +2.35 (*c* = 0.0022, in $CH_2Cl_2$). $^1$H NMR (500 MHz, CDCl3): δ 5.89 (d, *J* = 11.0 Hz, 1H, olefin), 5.83 (dd, *J*=10.5 Hz, 1.5 Hz, 1H, olefin), 4.91 (t. $J_{1,2}$ = 2.2 Hz, $J_{1,olefin}$ = 1.5 Hz, 1H, H1), 4.86 (t, $J_{3,2}$ = 6.4 Hz, $J_{3,4}$ = 2.5 Hz, 1H, H3), 4.25 (t, $J_{2,3}$ = 3.0 Hz, $J_{2,1}$= 2.0Hz, 1H, H2), 4.23 (t, $J_{3,2}$ = 3.0 Hz, $J_{4,3}$ = 2.0 Hz, 1H, H3), 3.77 (d, $J_{5,4}$ = 5.0 Hz, 2H, H5a,5b), 2.08(b, 1H, OH), 1.34, 1.53 (2s, 6H, $(CH_3)_2Si$), 0.23 (s, 9H, Si $(CH_3)_3$). $^{13}$C (125 MHz, $CDCl_3$): δ 154.3 (C), 120.8, 118.9 (olefin C), 113.4 (C≡), 101.3 (C≡), 94.1(C≡), 86.6 (C≡), 86.3 (C2), 84.0 (C4), 82.1 (C3), 75.3 (C1), 62.7 (C5), 26.7, 25.0 ($C(\underline{C}H_3)_2$), -0.3 (C TMS), HRMS (ESI) calcd for $C_{17}H_{24}O_4Si$ $[M+NH_4]^+$ 343.1336, Found, 343.1342.

### 2-Iodo (phenylethyne) trimethylsilane 123 using 1,2-diiodobenzene 184


**184**

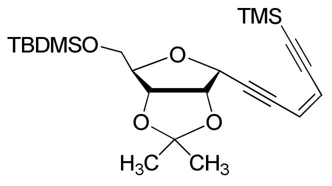
A solution of rimethylsilyl acetylene (7.43 mmol, 1.048 mL), triethylamine (1.55 mL, 11.1 mmol), and 1,2-diiodobenzene (3 g, 1.19 mL, 9 mmol) in dry, degassed benzene (15 mL) was cooled in an ice water bath (0 $^{o}$C). Pd(PPh$_3$)$_4$ (0.0861 g, 0.074 mmol) and CuI (0.2257 g, 1.19 mmol,) were added to it and the resulting solution was stirred at 25 $^{o}$C for 2 h. The reaction mixture was diluted with ether (50 mL), washed with NH$_4$Cl (2 x 30 mL), sodium bicarbonate (2 x 30 mL), and dried (MgSO$_4$). The filtrate was evaporated and the yield after purification was 1.2g (45%). *R$_f$* 0.36 (petroleum ether). $^{1}$H NMR (500 MHz, CDCl3): δ 7.84 ( dd, *J* = 8.0 Hz, 1.0 Hz, 1H,), 7.48 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.28 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.99 (dt, J= 7.8, 1.4, 1H), 0.27 (s, 9H, (Si(CH$_3$)$_3$). $^{13}$C (125 MHz, CDCl$_3$): δ 0.06 (Si($\underline{C}$H$_3$)$_3$), 98.99 (C≡), 101.50 (C≡), 106.75, 127.89, 129.75, 132.92, 138.88 (C)

### Benzene conjugated enediyne 182 using 184


**182**

To a solution of **90** (0.5 g, 1.16 mmol) with cuprous iodide (0.045 g, 0.23 mmol) in dry degassed benzene (15 mL) was added triethylamine (0.25 mL, 1.81mmol). The resulting mixture was stirred for 10 min at 25 $^{o}$C followed by the addition of a solution of Pd(PPh$_3$)$_4$ (0.067 g, 0.057 mmol) and **184** (0.32 g, 1.05 mmol) in dry degassed benzene. The resulting mixture was stirred at 40 $^{o}$C for 2 h. It was then quenched with saturated NH$_4$Cl solution (25 mL), saturated $NaHCO_3$ (25 mL) and extracted with ethylether (2 x 25 mL). The combined organic layers were dried ($NaSO_4$), and evaporated to get **182** (0.52 g, 74%). $R_f$ 0.55 (diethyl ether/petroleum ether, 33/67). $[\alpha]_D^{24} = -6.03$ ($c$ = 0.023, in $CH_2Cl_2$): $^1$H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, 1H, Ar),7.47 ( 2H, Ar), 7.27-7.43 (m,16H, Ar-H), 5.05 (d, $J_{1,2}$ = 4.6 Hz, 1H, H1), 4.87 (d, $J_{AB}$ = 12.0 Hz, 1H, $OCH_2Ph$), 4.79 (d, $J_{AB}$ = 12.0 Hz, 1H,$OCH_2Ph$), 4.74 (d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$), 4.68 (d, $J_{AB}$ =12.5 Hz, 1H, $OCH_2Ph$)**,** 4.62 (d, $J_{AB}$ = 11.5 Hz, 1H, $OCH_2Ph$), 4.61 (d, $J_{AB}$ =12.0 Hz, 1H, $OCH_2Ph$), 4.37 (app.q, $J_{4,5}$ = 4.8 Hz, $J_{4,3}$ = 4.8 Hz, 1H, H4), 4.28 (t, $J_{3,2}$ = 5.2 Hz, $J_{2,1}$ = 4.6 Hz, 1H, H2), 4.21 (t, $J_{3,4}$ = 4.8, $J_{3,2}$ = 5.4 Hz, 1H, H3), 3.75 (app.q, $J_{5b,4}$ = 4.1Hz, $J_{5a,5b}$ =11.0 Hz, 1H, H5b), 3.71 (app.q, $J_{5a,4}$ = 4.8 Hz, $J_{5a, 5b}$ = 11.0 Hz, 1H, H5a), 0.32 (s, 9H, Si $(CH_3)_3$). $^{13}$C (125 MHz, $CDCl_3$): δ 138.5, 138.1, 137.9 (3C), 127.4-128.3 (aromatic), 132.6.4, 132.5,125.8, 125.4 (aromatic), 103.6 (C≡), 98.8 (C≡), 90.8 (C≡), 85.5 (C≡)**,** 82.3 (C2), 81.6 (C4), 78.6 (C3), 72.6, 72.6, 73.7 (3$CH_2$), 72.0 (C1), 70.4 (C5), 0.3 (C (C-TMS), HRMS (ESI) calcd for $C_{39}H_{40}O_4Si$ $[M+NH_4]^+$ 618.3034, Found, 618.3048.

**2, 3-*O*-isopropyledine-5-OTBDMS -1-(6,7,10,11-diyne-8,9-ene) ribofuranoside**

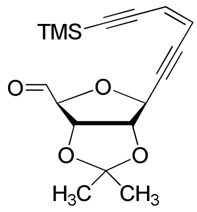


**186**

In a recovery flask was placed Pd $(PPh_3)_4$ (0.173 g , 0.162 mmol) in dry degassed benzene (17 mL). *n*.Bu$NH_2$ (1.3 mL, 13.1 mmol) was then added followed by chloroeneyne (1.6 mL, 10.5 mmol). A solution of **121** (1.01 g, 3.23 mmol) in 53 mL of dry benzene was then added followed by the addition of CuI (0.12 g, 0.654 mmol). The solution was stirred at 25 °C overnight. The solution was then poured in to a saturated $NaHCO_3$ (50 mL), extracted with

$CH_2Cl_2$ (2 x 50 mL). The organic layer was separated, dried ($Na_2SO_4$), and concentrated to get the prodct **186** (1g, 42% ). $[\alpha]_D^{24}$ = -2.96 (*c* = 0.037, in $CH_2Cl_2$). $^1H$ ppm ($CDCl_3$, 500MHz): $\delta$ 0.05 (s, 6H, $(CH_3)_2Si$ ), 0.20 (s, 9H, $Si(CH_3)_3$), 0.88 (s, 9H, $Si(CH_3)_3$ , 1.38, 1.57 (2s, 6H, $(CH_3)_2Si$), 3.71(app. q, $J_{5a,4}$ = 2.9 Hz, $J_{5a,\ 5b}$ = 11.2 Hz, 1H, H5a), 3.79 (app.q, $J_{5b,4}$ = 2.9 Hz, $J_{5a,5b}$ =11.2 Hz, 1H, H5b), 4.17 (b, 1H, H4), 4.78 (dd, $J_{2,1}$= 4.5Hz, $J_{2,3}$ = 6.0Hz, 1H, H2), 4.84(t, $J_{3,2}$=5.9 Hz, $J_{3,4}$= 1.2 Hz, 1H, H3), 5.09 (dd, $J_{1,2}$= 4.8 Hz, $J_{1,1'}$= 1.9 Hz, 1H, H1), 5.83 (d, 1H, H2', $J_{2',\ 1'}$= 10.7 Hz), 5.91 (dd, 1H, H-1', $J_{1',\ 2'}$=10.7 Hz, $J_{1',1}$= 1.9 Hz, olefin protons ). $^{13}C$($CDCl_3$, 125MHz): $\delta$ -5.5,-5.3 ($Si(CH_3)_2$), 0.2 ( $Si(CH_3)_3$), 18.2 ($C(CH_3)_3$), 26.0 ( $C(CH_3)_3$), 25.6, 26.7 ($O_2C(CH_3)_2$), 65.7 (C5), 74.6 (C1), 82.8( C3), 83.2 (C4), 84.4 (C2), 85.1 (C≡), 92.1(C≡), 102.1 (C≡), 113.3(C≡), 120.1, 120.4(olefin C), 154.7 ($OCCH_3$). HRMS (ESI) calculated for $C_{23}H_{38}O_4Si_2$ $[M+NH_4]^+$ 452.2647, Found, 452.2667.

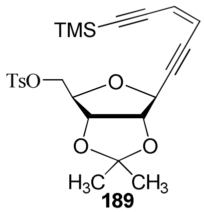
**2,3- *O*-isopropylidene-5-al-1-(6,7,10,11-diyne-8,9-ene) riboside 95**



**95**

To a cooled (-78 °C) solution of oxalyl chloride (0.0341mL, 0.362 mmol) in dry dichloromethane (0.5 mL) was added DMSO (0.05 mL, 0.724 mmol) under argon. After 15 min the solution of alcohol 94 (0.03 g, 0.121 mmol) in $CH_2Cl_2$ (0.086 mL) was added and stirred for 1 h at -78 °C. $Et_3N$ (0.22 mL, 1.57 mmol) was added and the mixture was allowed to warm to room temperature. It was washed with saturated solution of sodium carbonate, dried with $MgSO_4$ and evaporated. NMR spectra of the crude product showed a broad peak around 9.8 ppm, but a pure compound **95** was not obtained.

### 2,3-*O*-isopropylidene-5-*O*-tosyl-1-(6,7,10,11-diyne-8,9-ene) ribosode 189



**189**

To the ice cold solution of alcohol (0.14g, 0.4368mmol) with methylene chloride (6mL) triethhylamine 0.876mmol, 0.123mL) was added. Tosyl chloride ( 0.876mmol, 0.166g) was added to this solution over 2hrs. The reaction mixture was warmed up to 2 hours to room temperature,evaporated to dryness and titurated with boiling ether, evaporated. The tlc was done using hexnae/ Ethylacetate 3:1. The compound was purified using preperatory tlc for further analysis.

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 Ambient temperature
Operator: meleties
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INOVA-500  "capella500"

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 Width 25000.0 Hz
 432 repetitions
OBSERVE  C13, 125.6680118 MHz
DECOUPLE  H1, 499.7755824 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec
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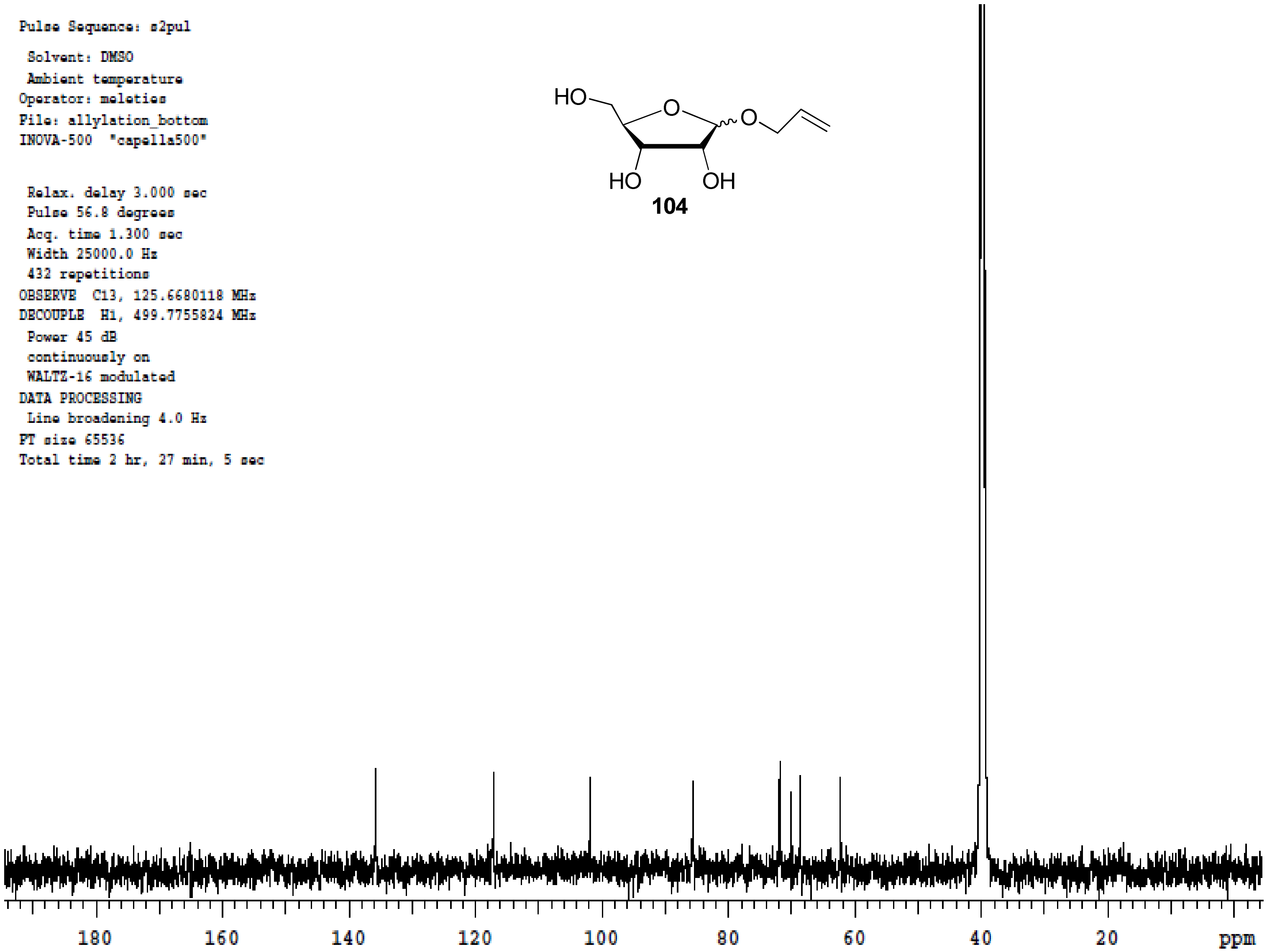
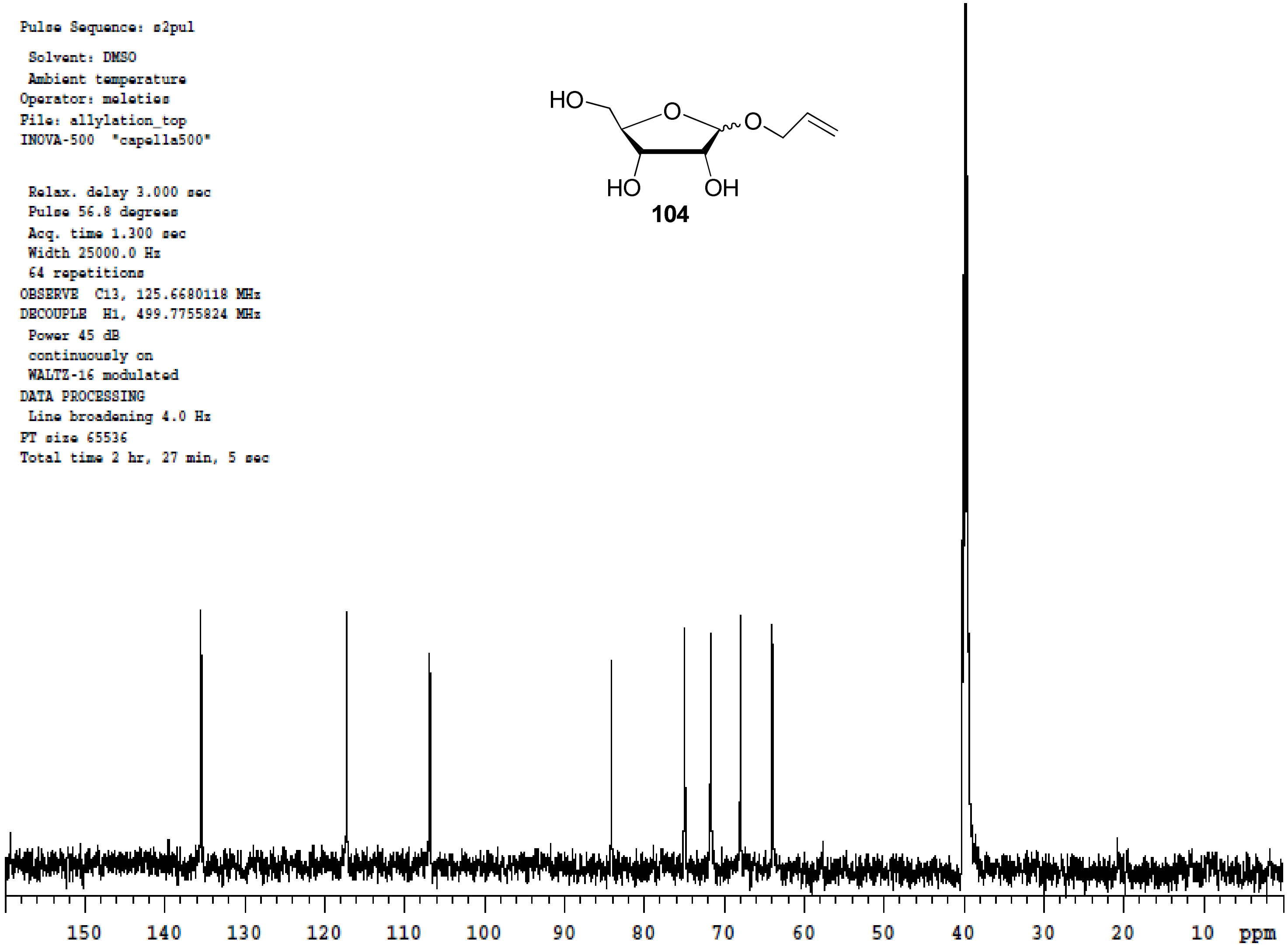
**104**





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Ambient temperature
Operator: meleties
File: allylation_top
INOVA-500 "capella500"

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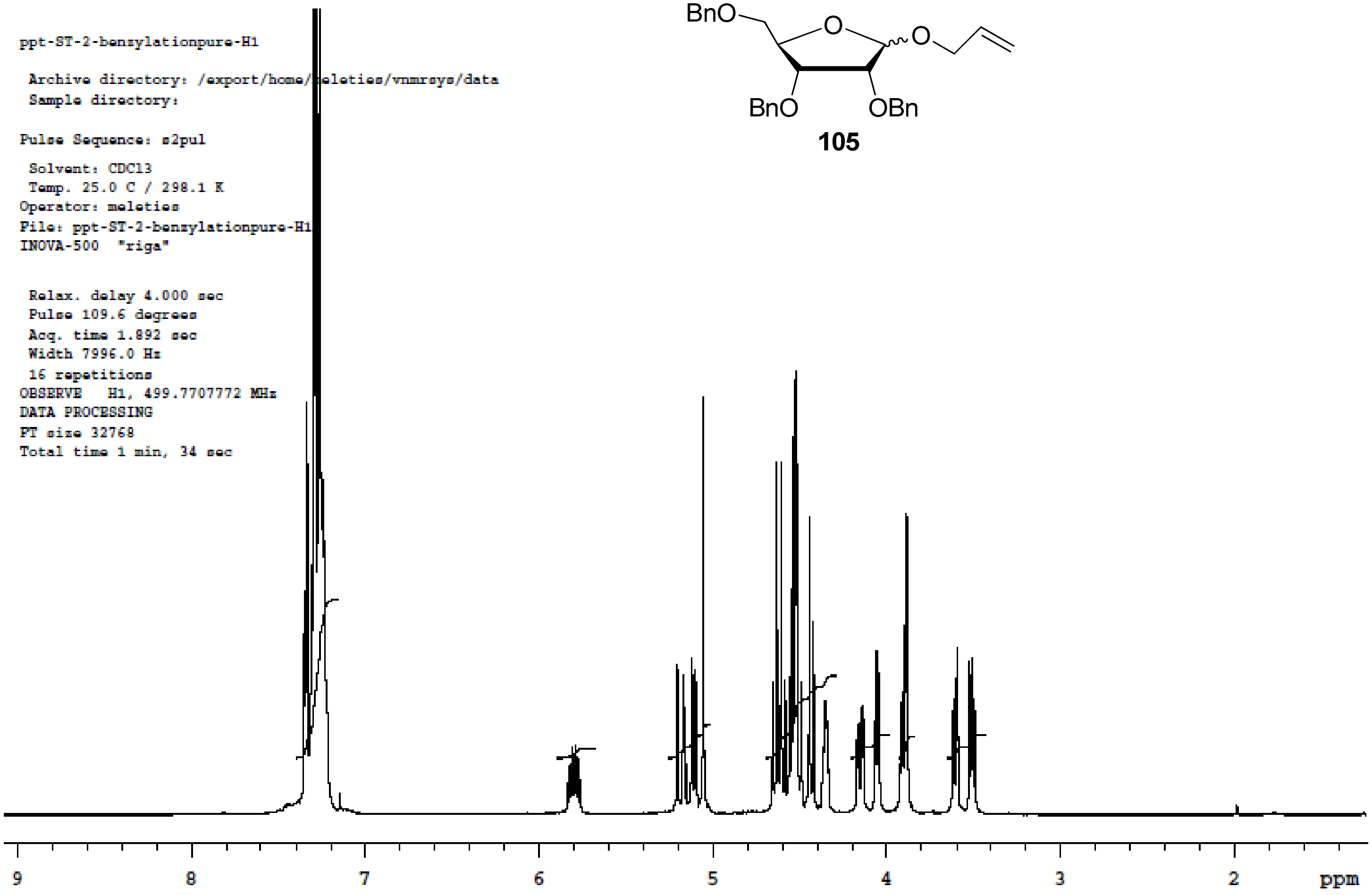
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 125.6680118 MHz
DECOUPLE H1, 499.7755824 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 2 hr, 27 min, 5 sec

**104**



**105**

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 Sample directory:

Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: ppt-ST-2-benzylationpure-H1
INOVA-500  "riga"

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DATA PROCESSING
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Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: Therese-PPT-ST2-021309-pure-13C
INOVA-500  "riga"

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 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 80 repetitions
OBSERVE  C13, 125.6674251 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
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FT size 131072
Total time 56 min, 28 sec
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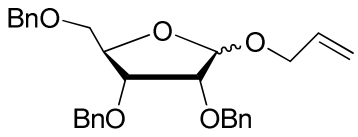
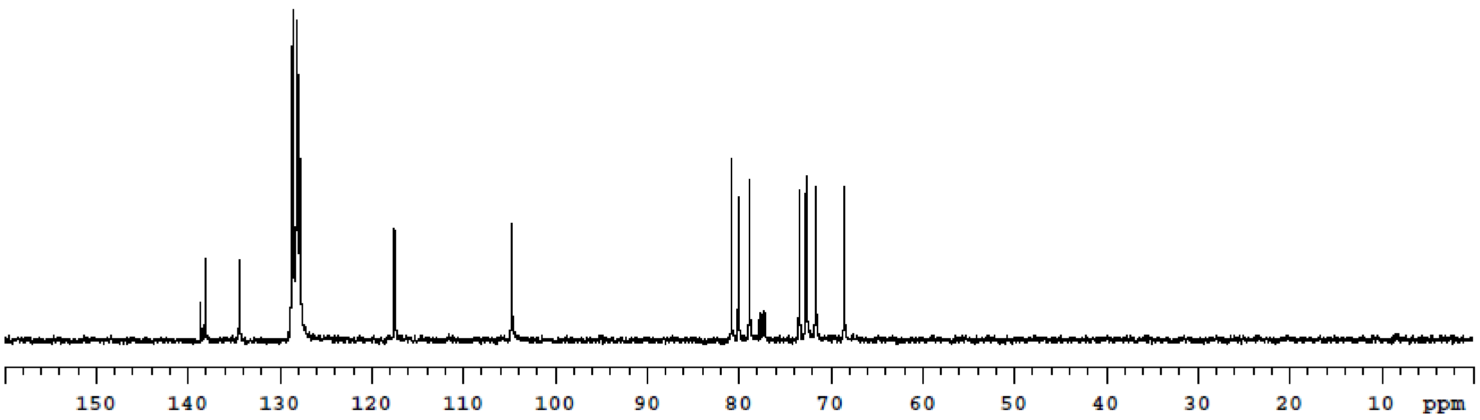
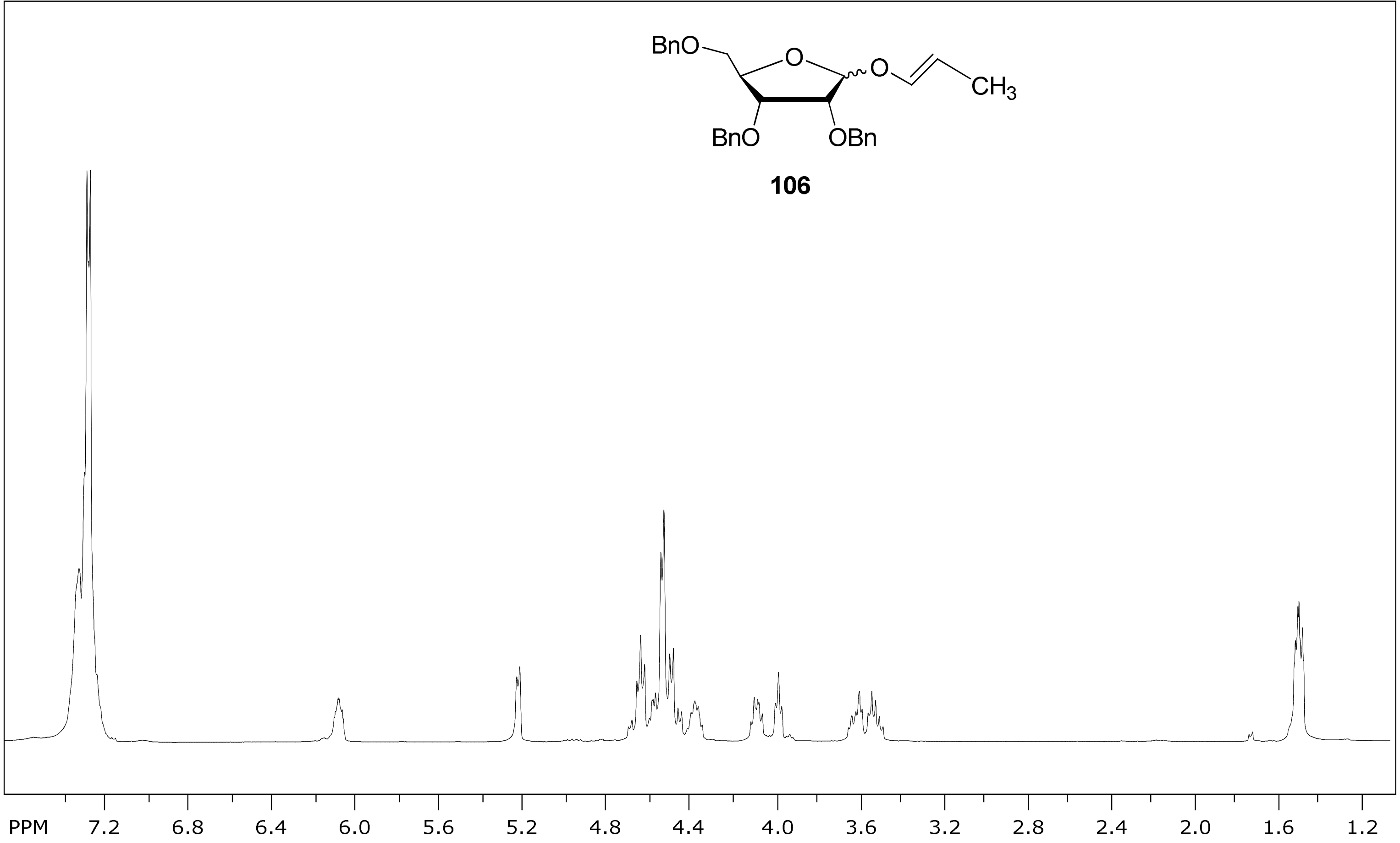


**105**



SpinWorks 3: isomerisation_new



**106**

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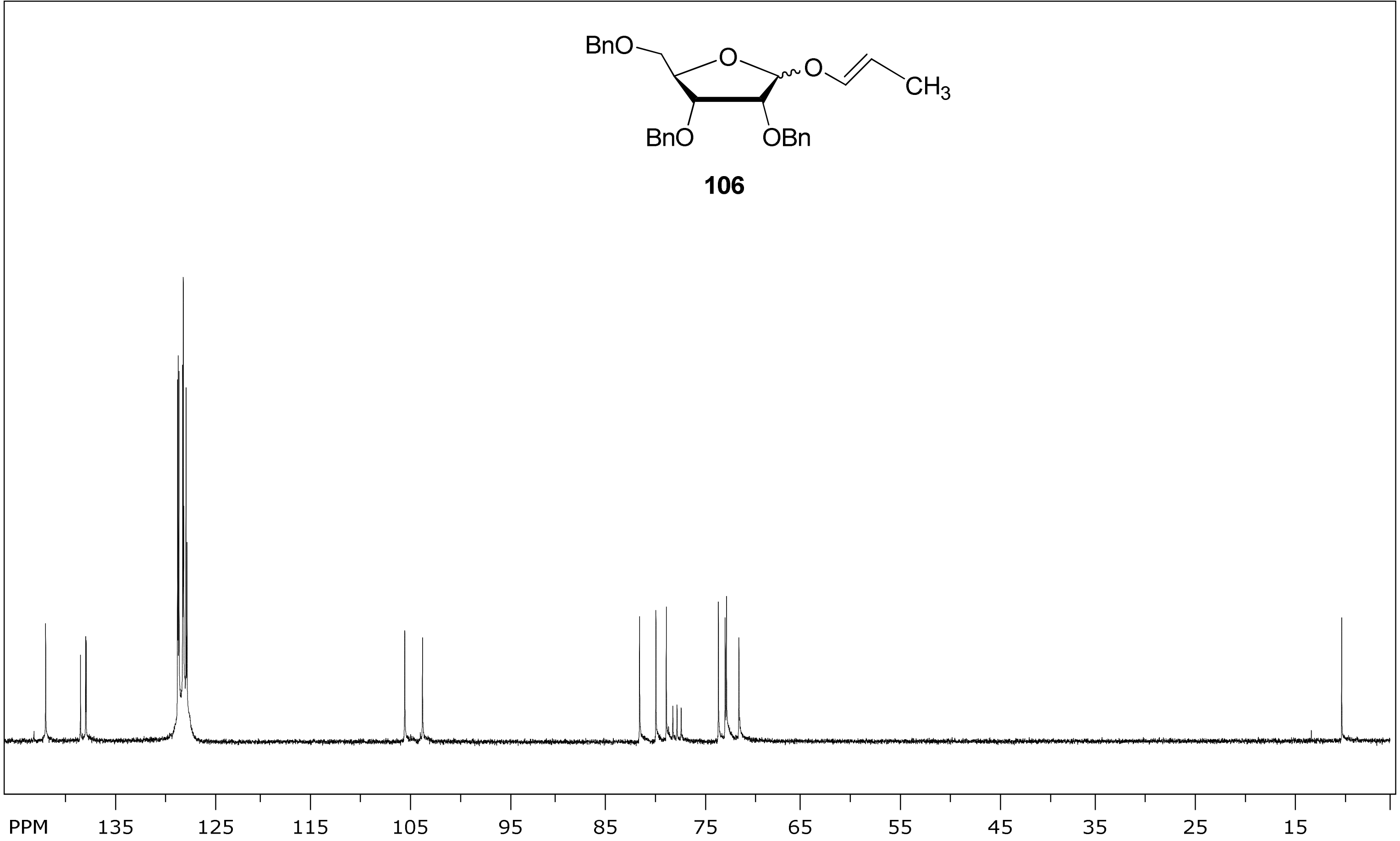
number of scans: 32

freq. of 0 ppm: 300.067400 MHz
processed size: 32768 complex points
LB: -1.000    GF: 0.0000
Hz/cm: 79.739    ppm/cm: 0.26574

SpinWorks 3: isomerisation_c13



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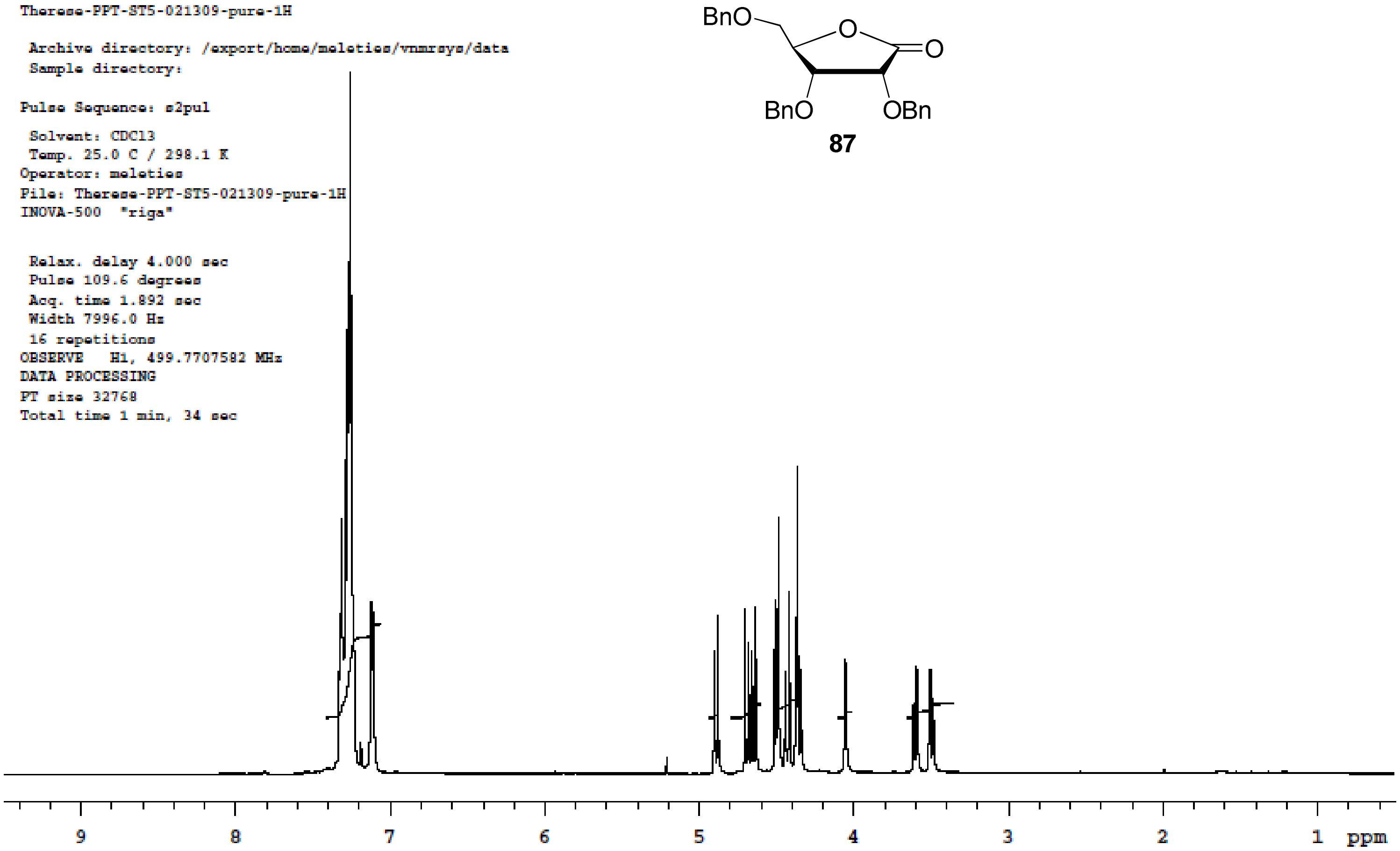

87

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Therese-PPT-ST5-021309-pure-1H

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 Sample directory:

Pulse Sequence: s2pul

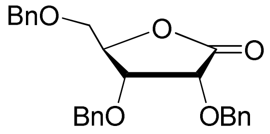
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: Therese-PPT-ST5-021309-pure-1H
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 109.6 degrees
 Acq. time 1.892 sec
 Width 7996.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707582 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 34 sec
```

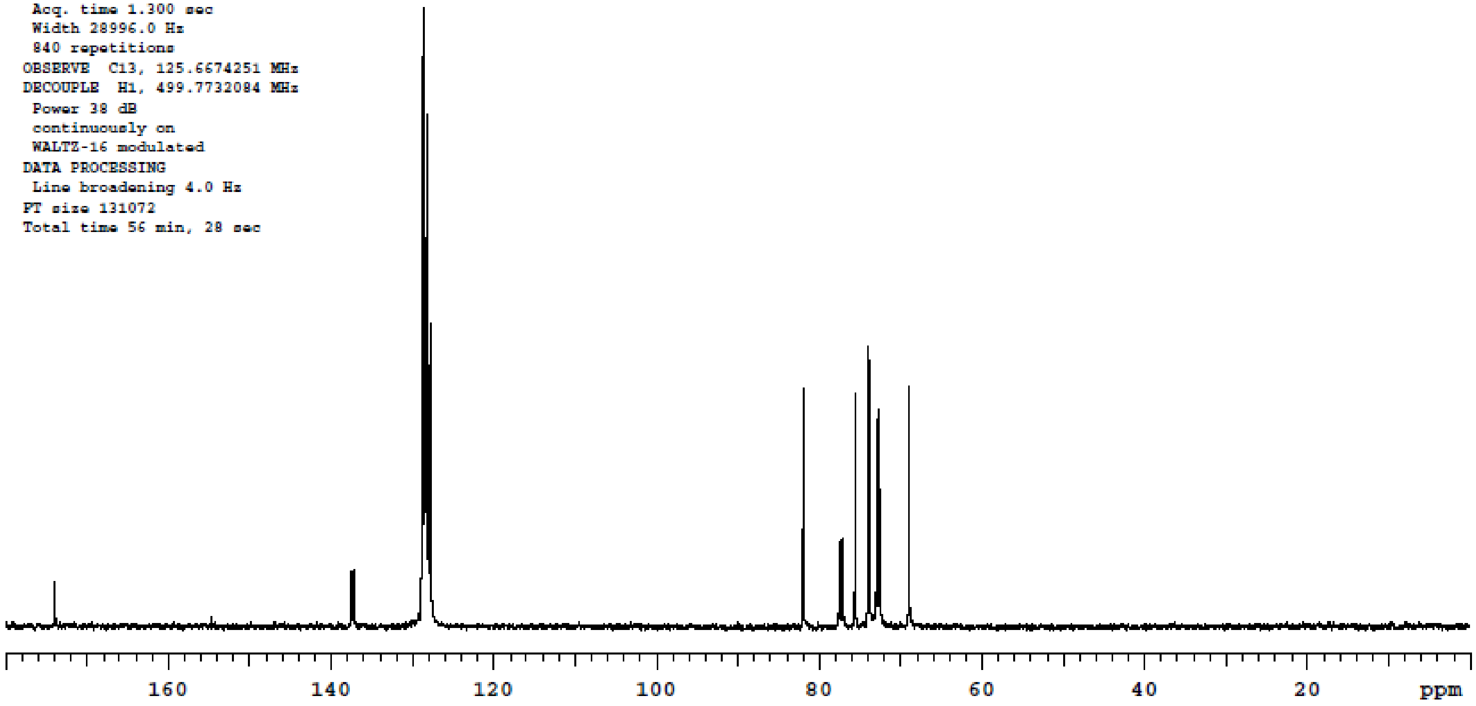
```
Therese-PPT-ST5-021309-pure-13C

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: Therese-PPT-ST5-021309-pure-13C
INOVA-500  "riga"

 Relax. delay 2.000 sec
 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 840 repetitions
OBSERVE  C13, 125.6674251 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 56 min, 28 sec
```



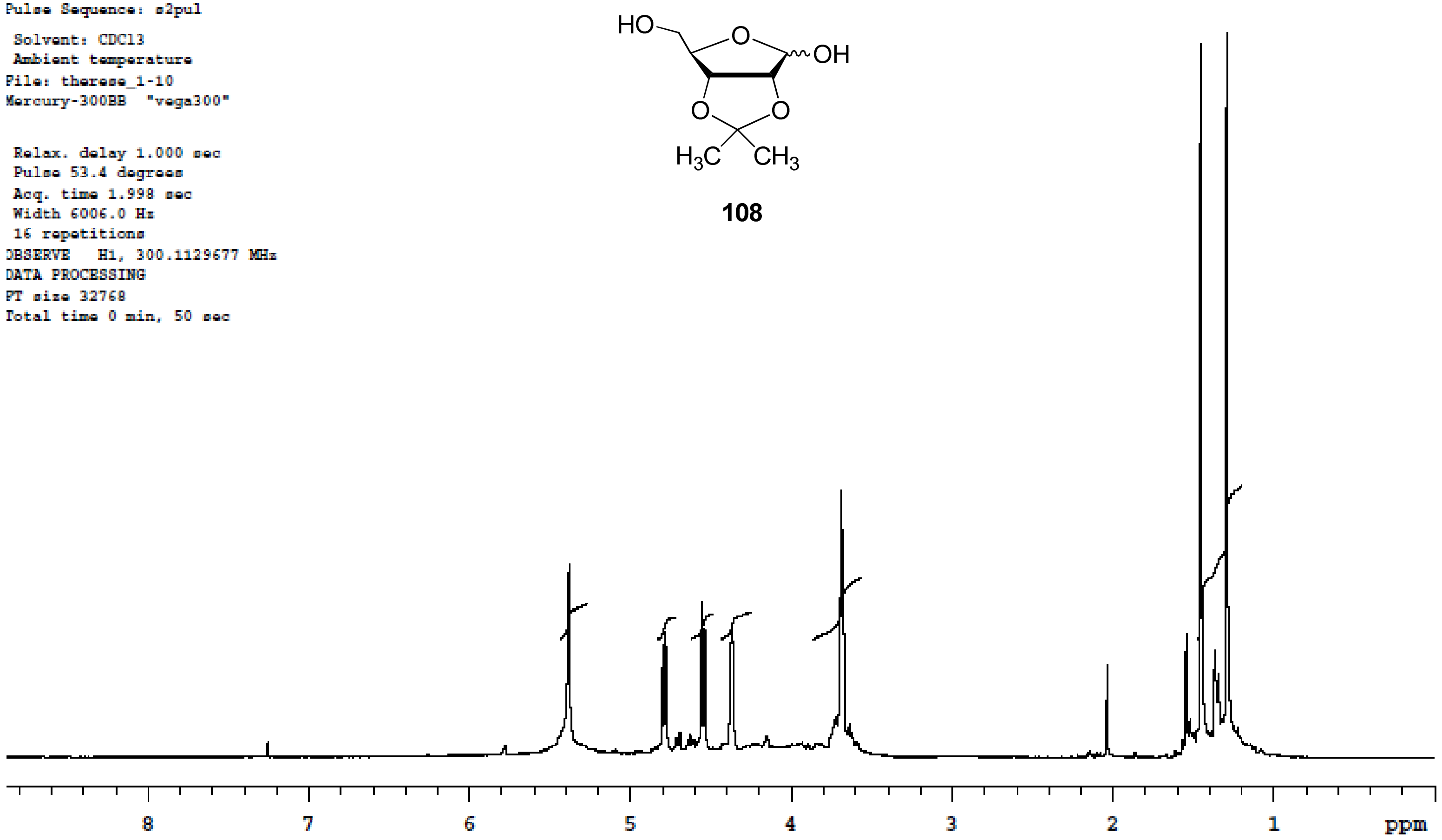
**87**



STANDARD 1H OBSERVE

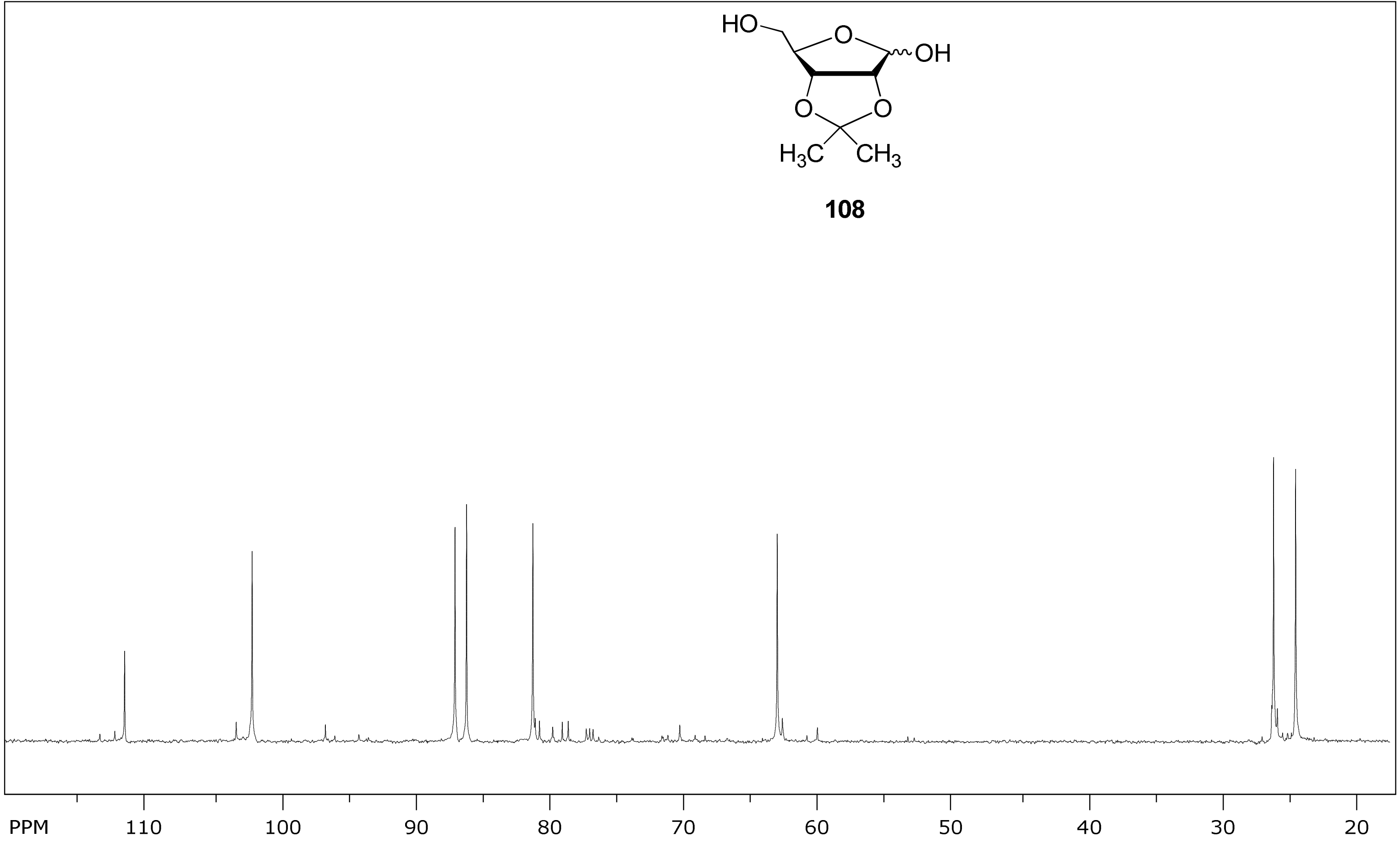
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: therese_1-10
Mercury-300BB "vega300"

Relax. delay 1.000 sec
Pulse 53.4 degrees
Acq. time 1.998 sec
Width 6006.0 Hz
16 repetitions
OBSERVE H1, 300.1129677 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 50 sec

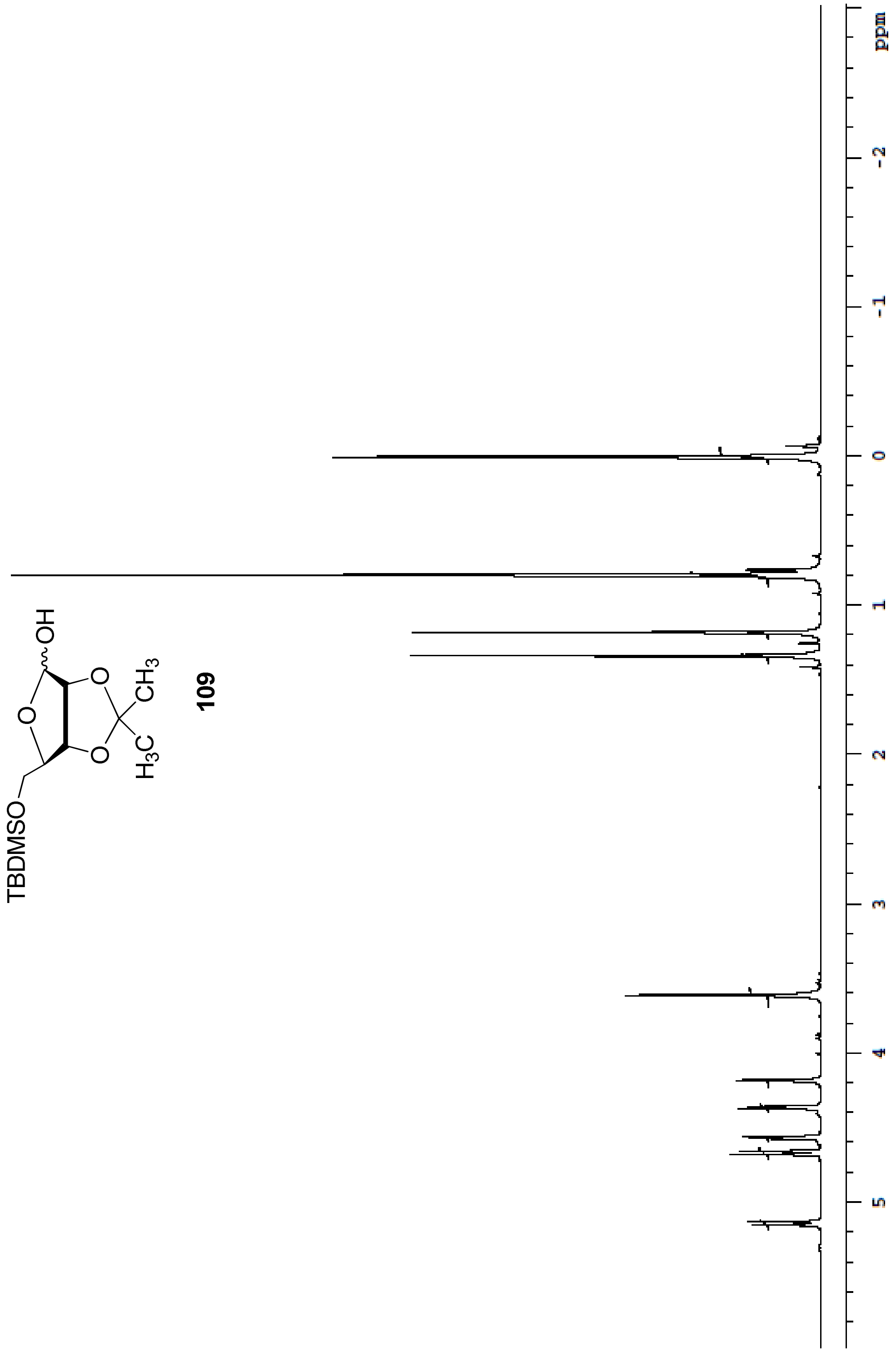


**108**

SpinWorks 3: PPT-ST19-isopropylidine-13C



```
file: ...PT-ST19-isopropylidine-13C.fid\fid  block# 1  expt: "s2pul"      freq. of 0 ppm: 125.667469 MHz
transmitter freq.: 125.679355 MHz                                         processed size: 131072 complex points
time domain size: 75418 points                                            LB: 4.000    GF: 0.0000
width: 28996.01 Hz = 230.7142 ppm = 0.384471 Hz/pt                        Hz/cm: 520.049    ppm/cm: 4.13790
number of scans: 48
```



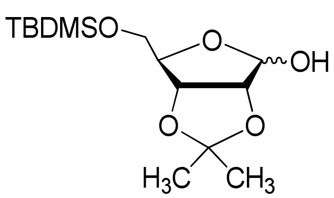
**109**

```
PPT-ST20-isopropylidine_TBDMS-13C

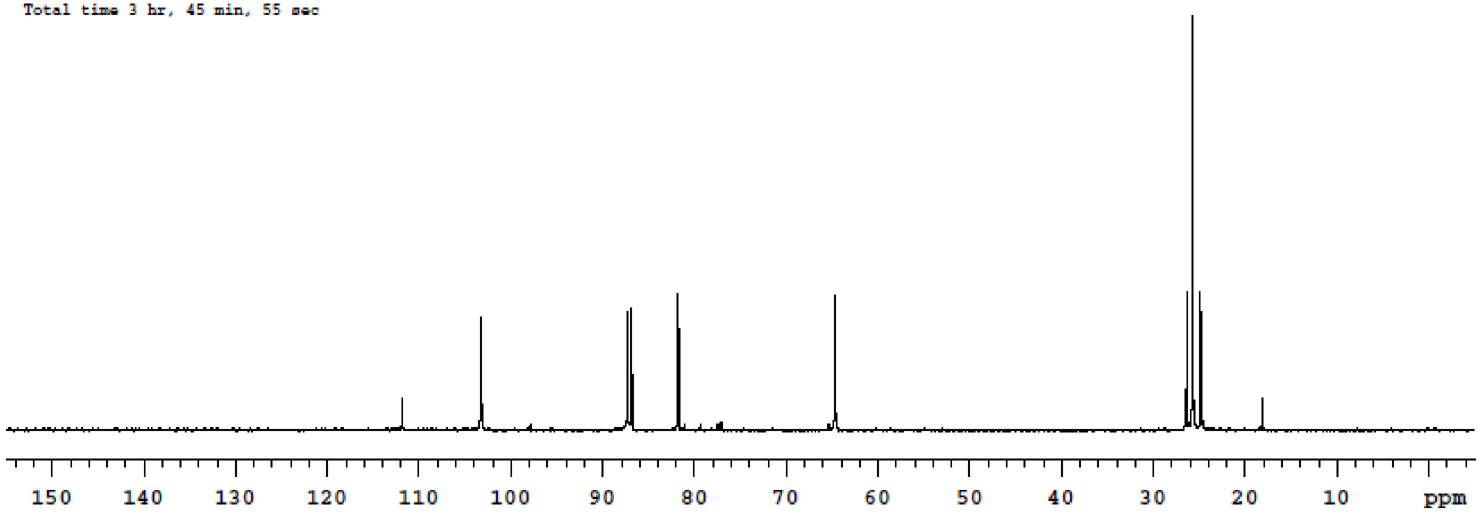
Pulse Sequence: s2pul

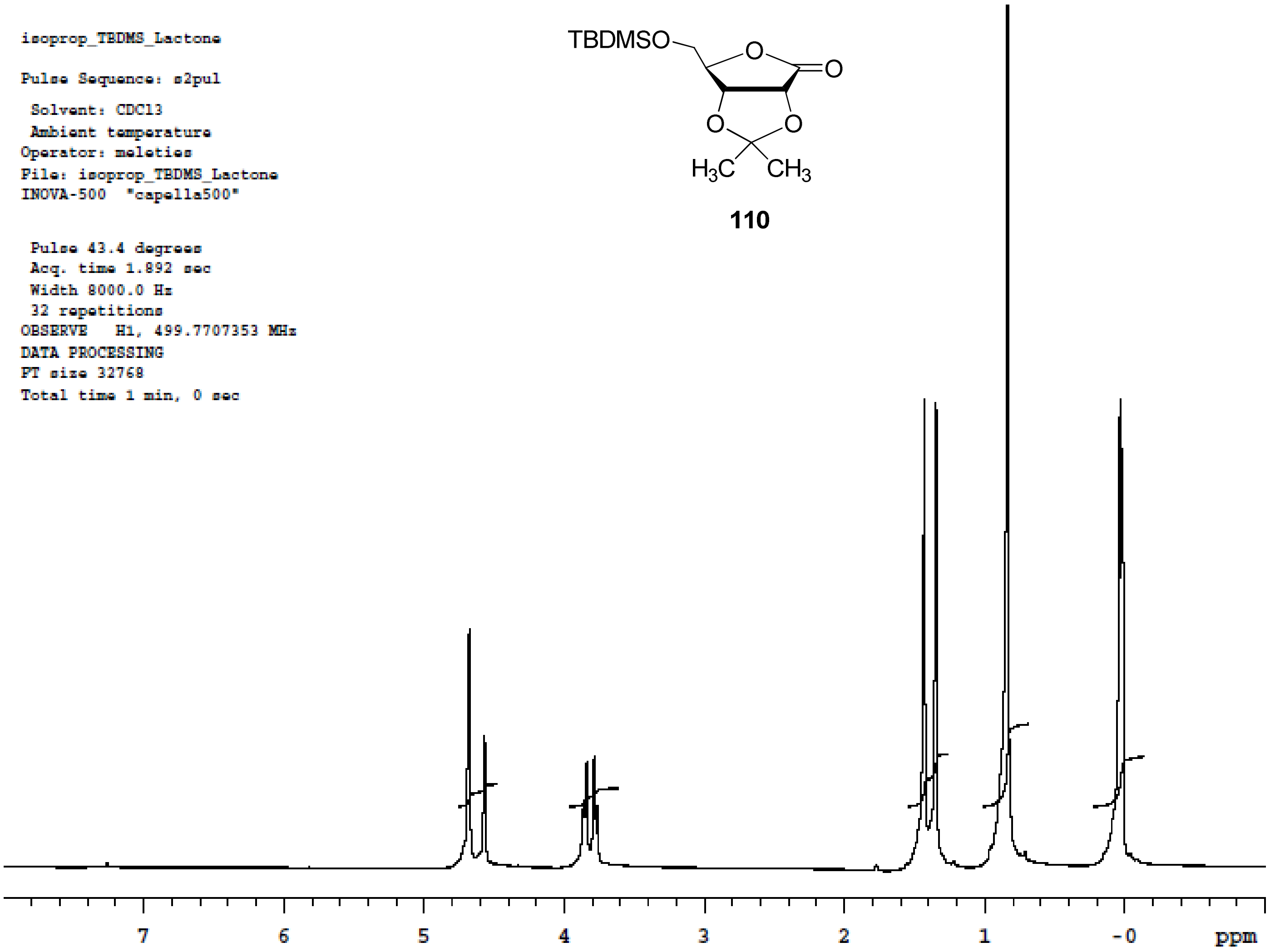
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: PPT-ST20-isopropylidine_TBDMS-13C
INOVA-500  "riga"

 Relax. delay 2.000 sec
 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 56 repetitions
OBSERVE  C13, 125.6674433 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 3 hr, 45 min, 55 sec
```



**109**





```
isoprop_TBDMS_Lactone

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: isoprop_TBDMS_Lactone
INOVA-500  "capella500"

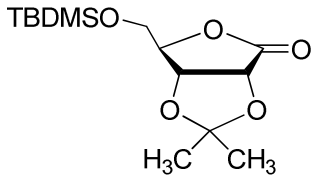
 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707353 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
```

**110**

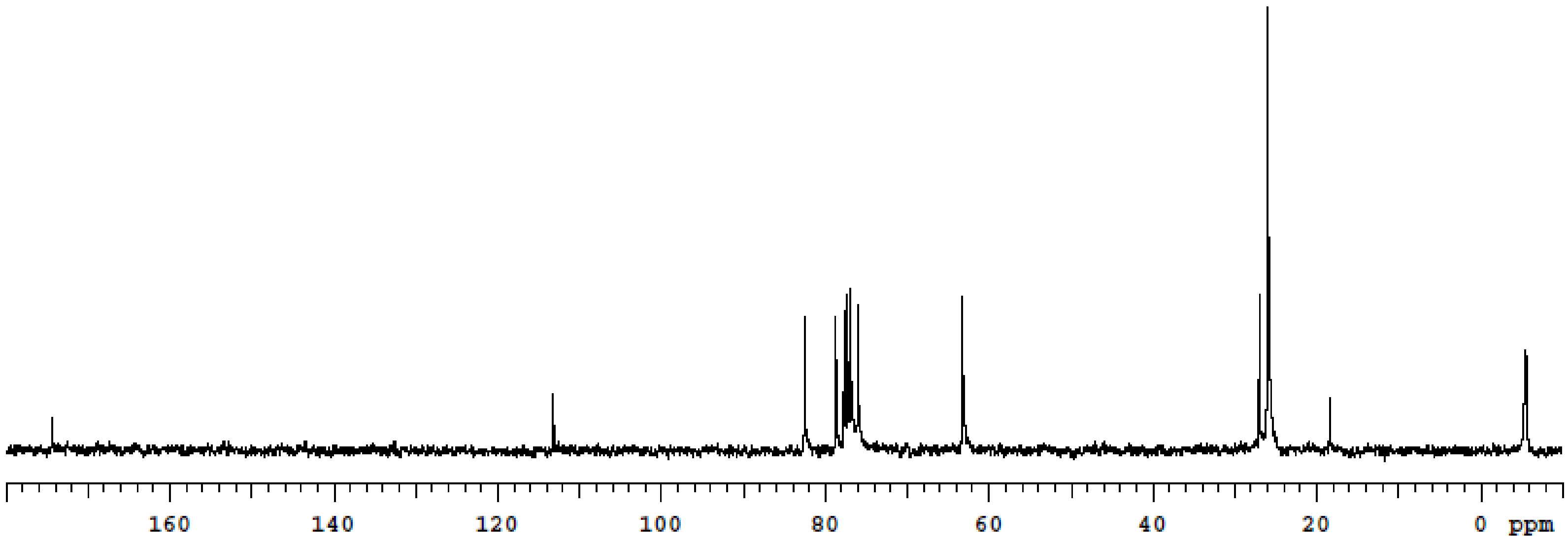
```
isoprop_Tbdmslactone

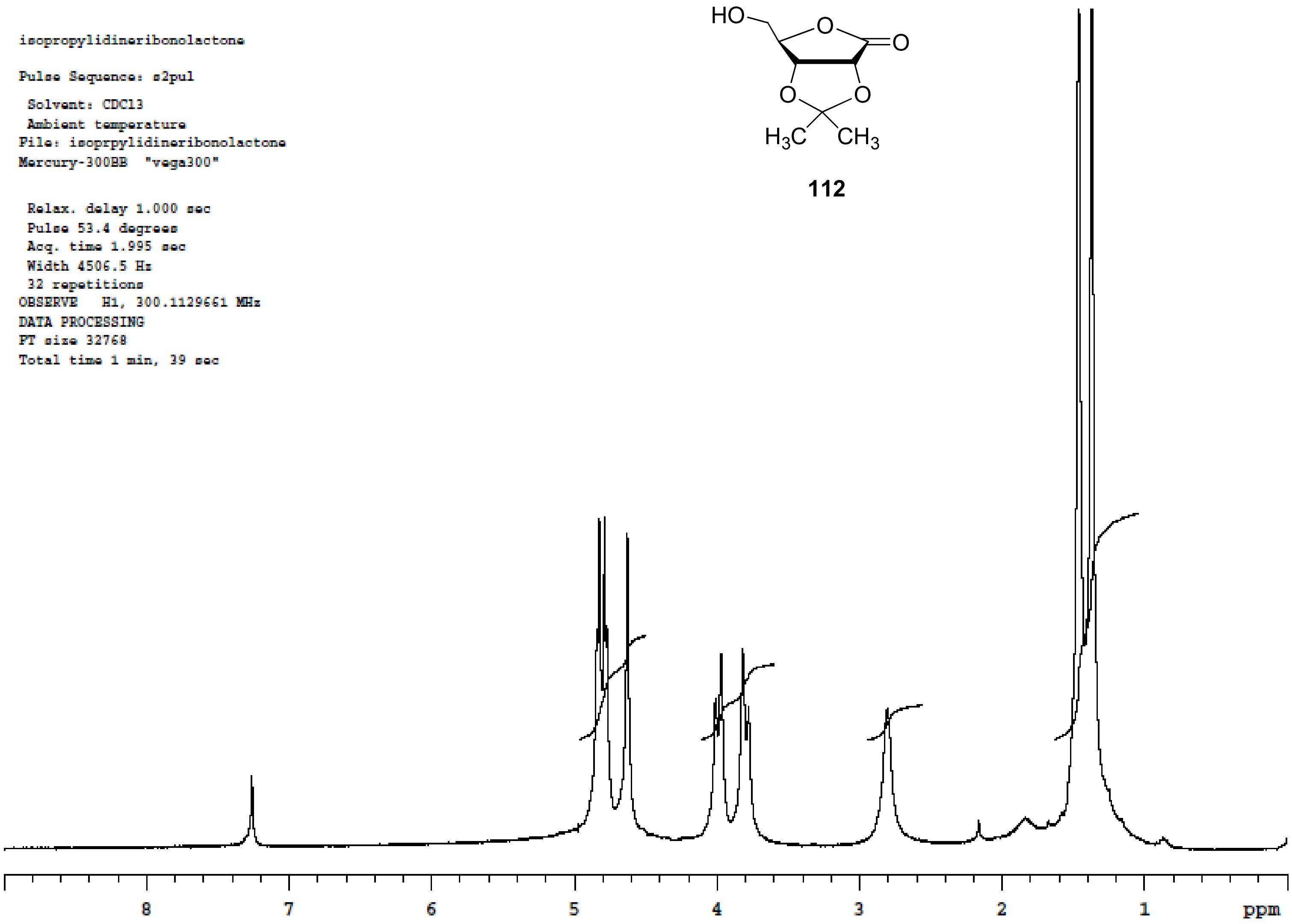
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
File: isoprop_TBDMSLACTONE_C13
Mercury-300BB  "vega300"

 Pulse 43.8 degrees
 Acq. time 1.815 sec
 Width 18761.7 Hz
 2048 repetitions
OBSERVE  C13,  75.4634477 MHz
DECOUPLE  H1, 300.1144582 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 1 hr, 12 min, 5 sec
```



**110**





```
isopropylidineribonolactone

Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
File: isoprpylidineribonolactone
Mercury-300BB  "vega300"

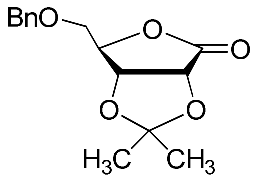
 Relax. delay 1.000 sec
 Pulse 53.4 degrees
 Acq. time 1.995 sec
 Width 4506.5 Hz
 32 repetitions
OBSERVE   H1, 300.1129661 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec
```

**112**

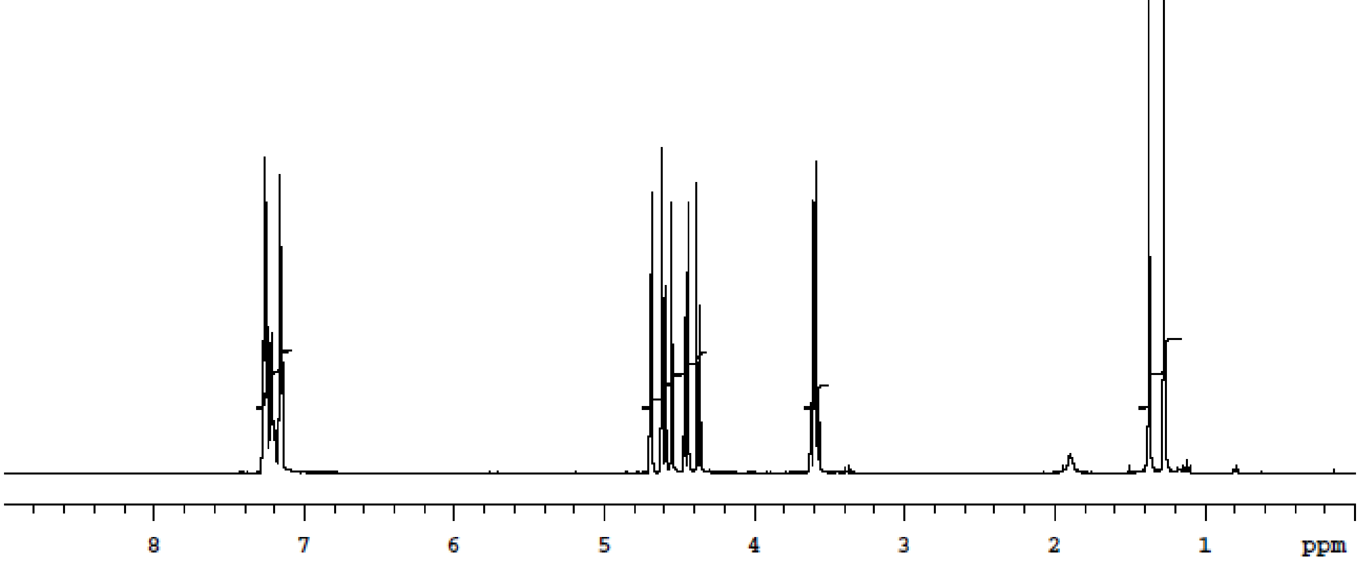
```
ST-isoprop_OBnlactone

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: ST-isoprop_OBnlactone
INOVA-500  "riga"

 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707651 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
```



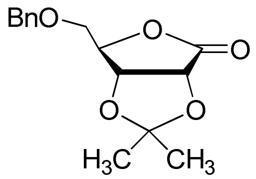
**113**



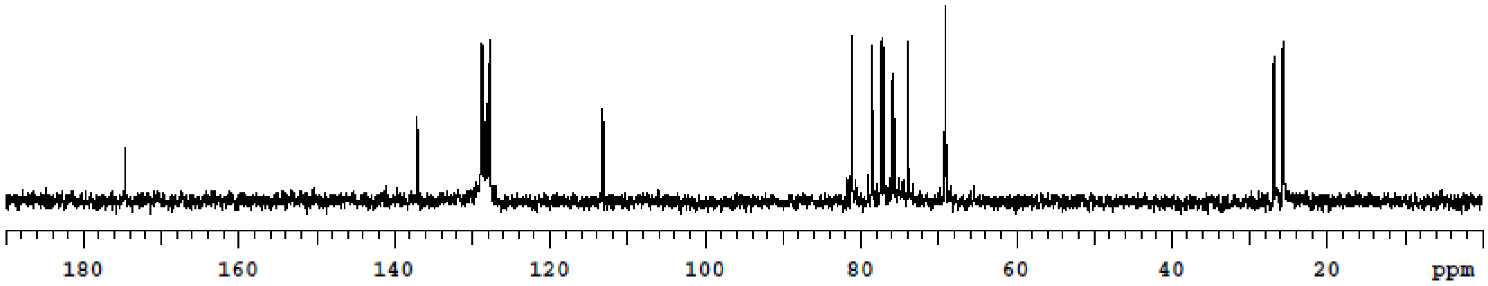
```
ST-isoprop_OBnlactoneC13

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: ST-isoprop_OBnlactoneC13
INOVA-500  "riga"

 Pulse 56.8 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 256 repetitions
OBSERVE  C13, 125.6674377 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 30 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 65536
Total time 22 min, 20 sec
```



**113**

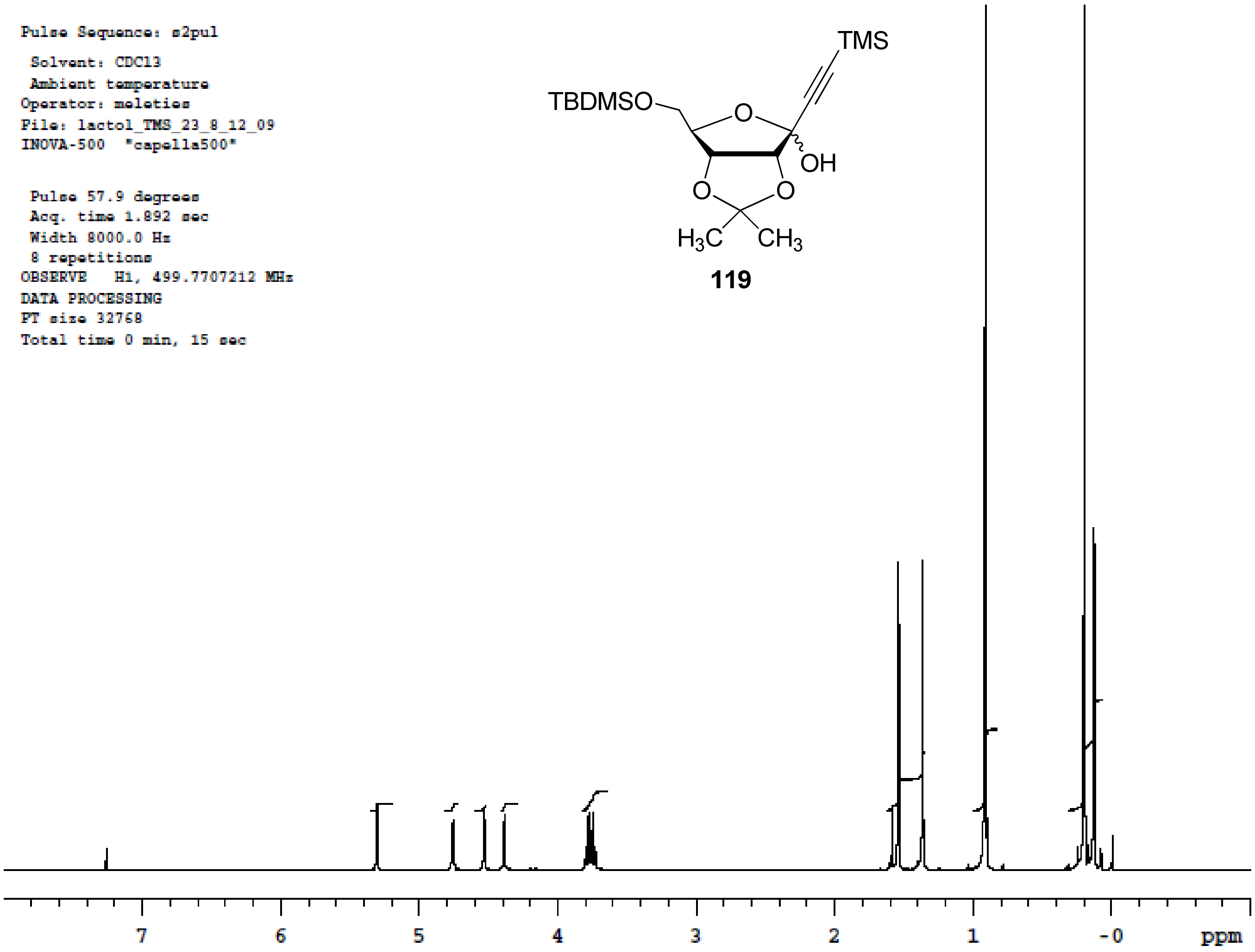


Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: meleties
File: lactol_TMS_23_8_12_09
INOVA-500 "capella500"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec

**119**

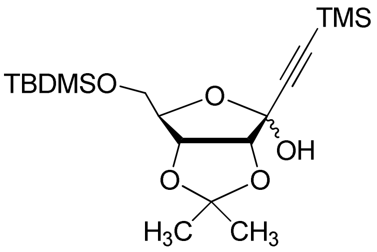


Chris-TMS-lactol-23-C13

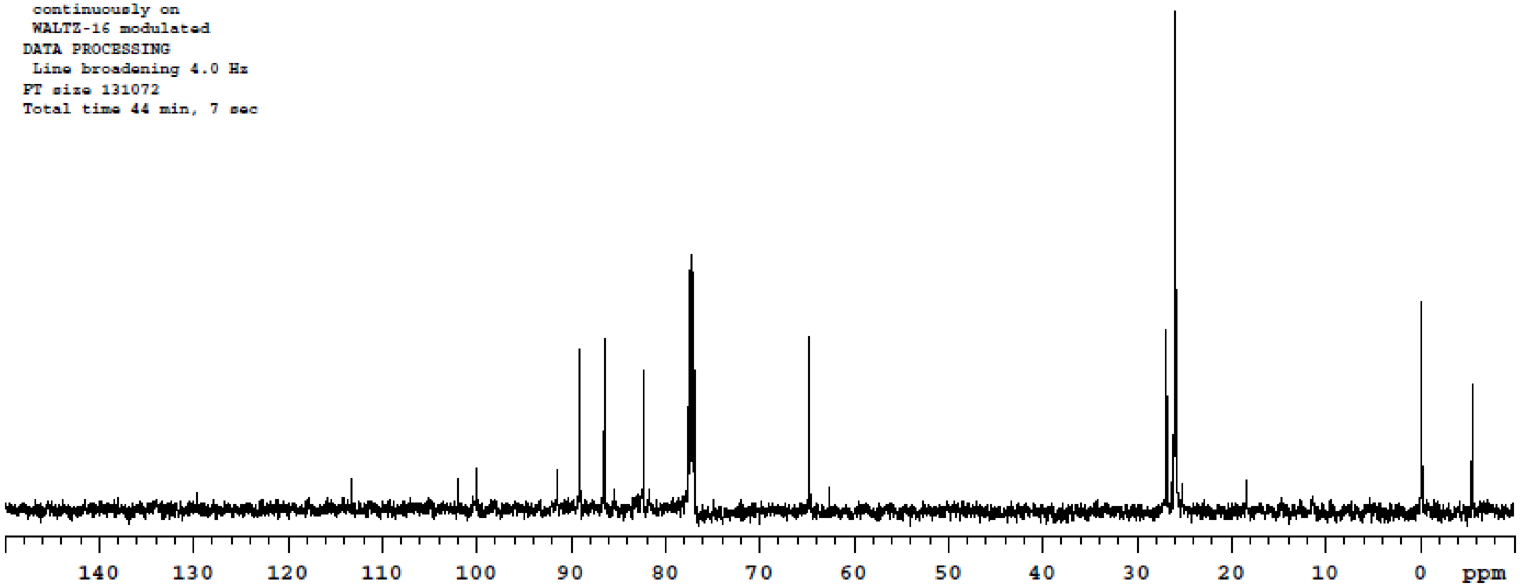
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: meleties
File: Chris-TMS-lactol-23-C13
INOVA-500 "riga"

Relax. delay 2.000 sec
Pulse 104.3 degrees
Acq. time 1.300 sec
Width 28996.0 Hz
736 repetitions
OBSERVE C13, 125.6674247 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 131072
Total time 44 min, 7 sec



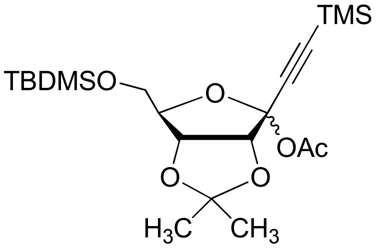
**119**



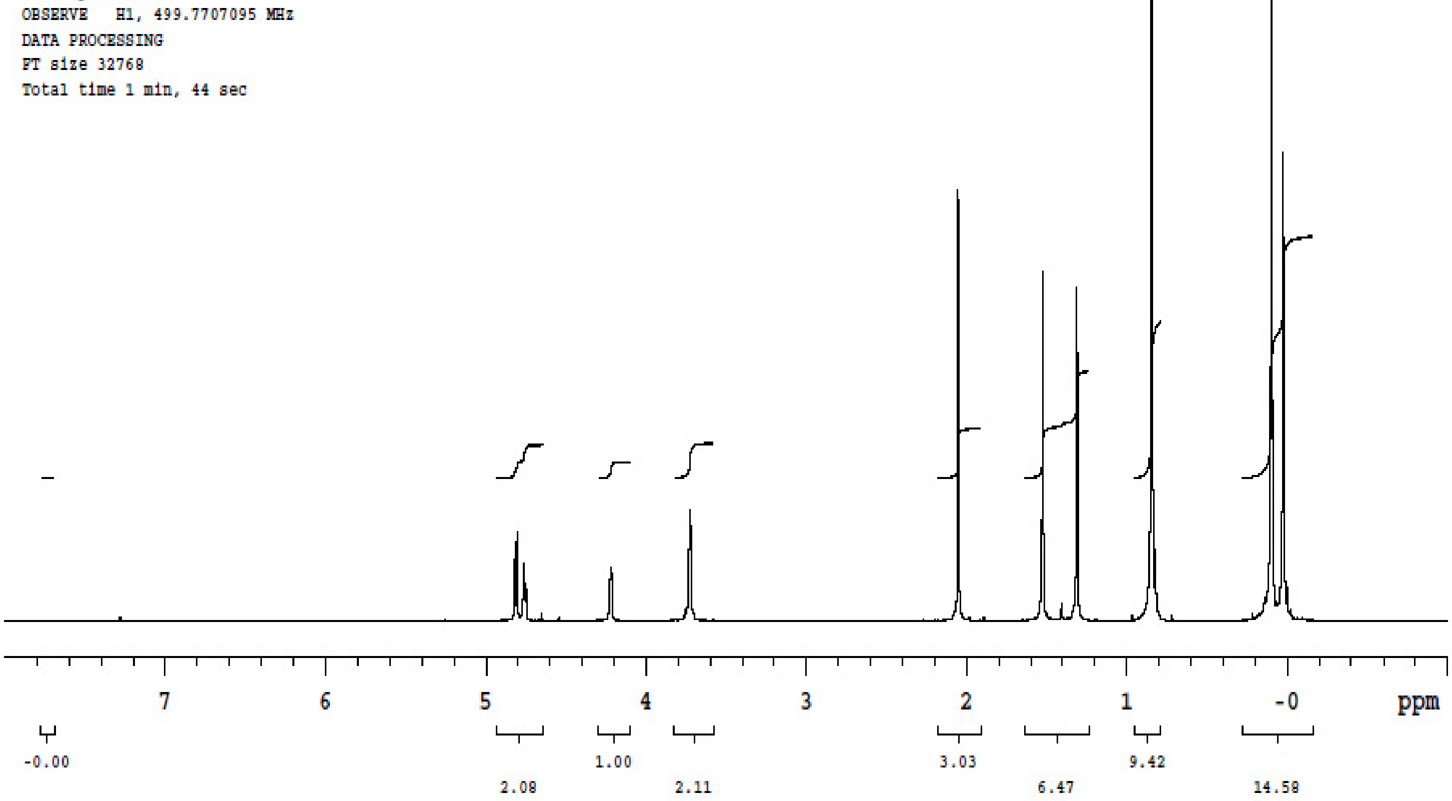
```
Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: TS_prop-acetate-1H-r
INOVA-500  "capella500"

 Relax. delay 4.000 sec
 Pulse 90.0 degrees
 Acq. time 2.502 sec
 Width 5998.8 Hz
 16 repetitions
OBSERVE   H1, 499.7707095 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 44 sec
```



**120**

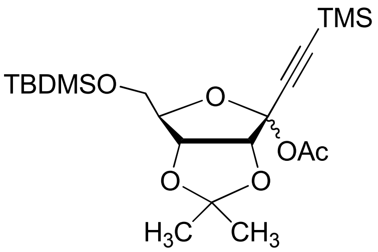


13C OBSERVE

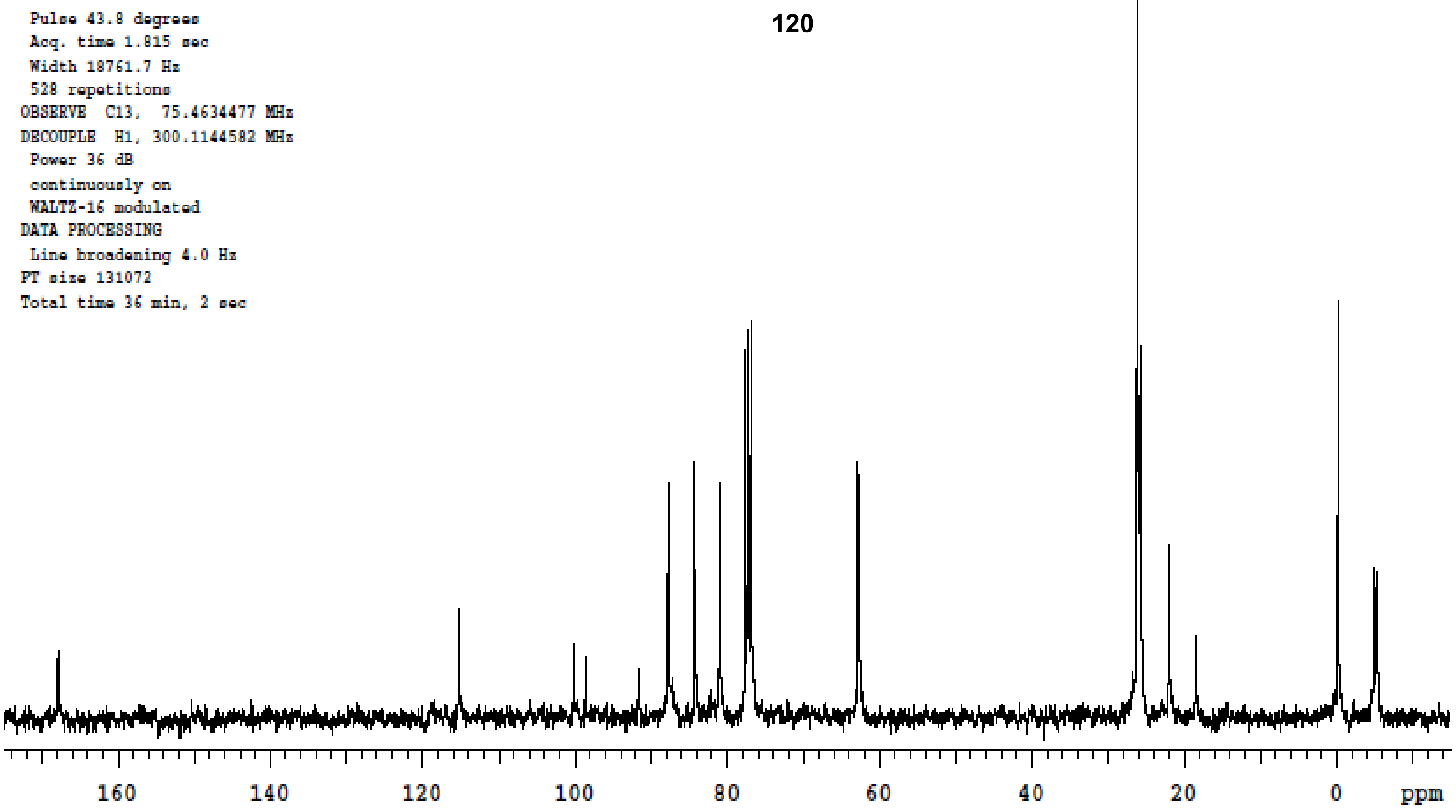
Pulse Sequence: s2pul

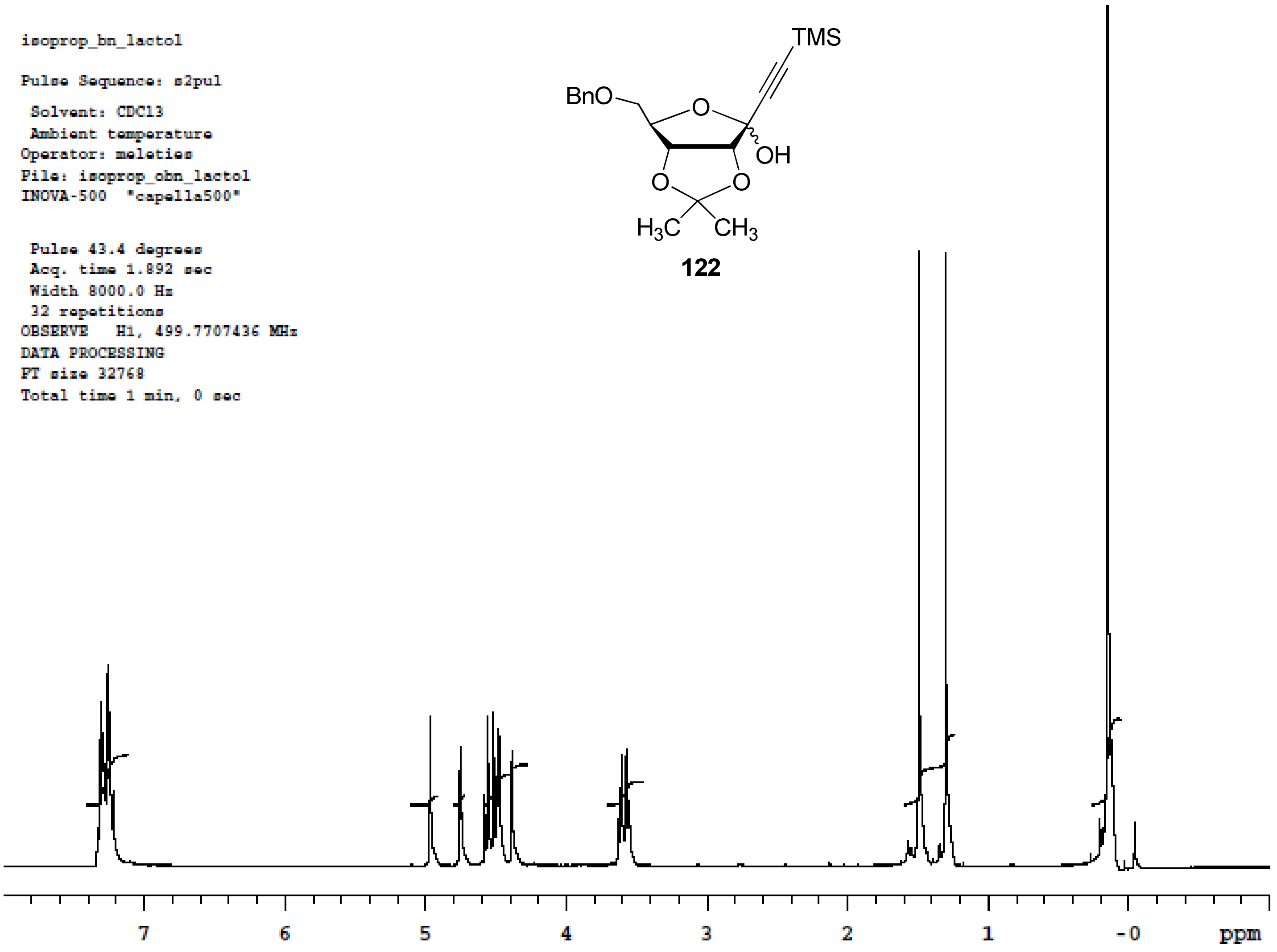
Solvent: CDCl3
Ambient temperature
File: therese_1-60C
Mercury-300BB "vega300"

Pulse 43.8 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
528 repetitions
OBSERVE C13, 75.4634477 MHz
DECOUPLE H1, 300.1144582 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 131072
Total time 36 min, 2 sec



**120**





isoprop_bn_lactol

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: meleties
File: isoprop_obn_lactol
INOVA-500 "capella500"

Pulse 43.4 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7707436 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec

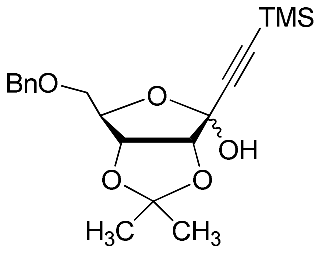
**122**

```
isoprop_obn_tmslactol

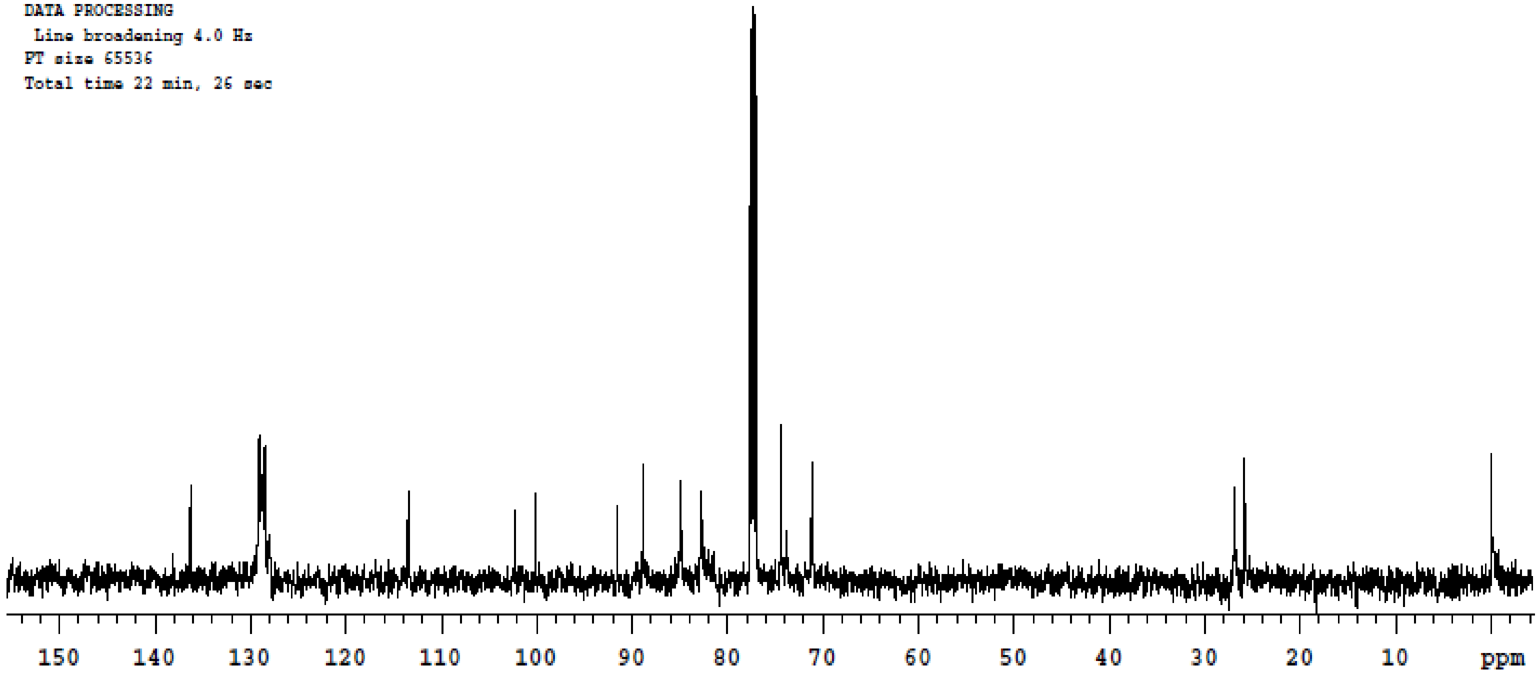
Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: isoprop_obn_tmslactol
INOVA-500  "capella500"


 Pulse 56.8 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 896 repetitions
OBSERVE  C13, 125.6674149 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 30 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 65536
Total time 22 min, 26 sec
```



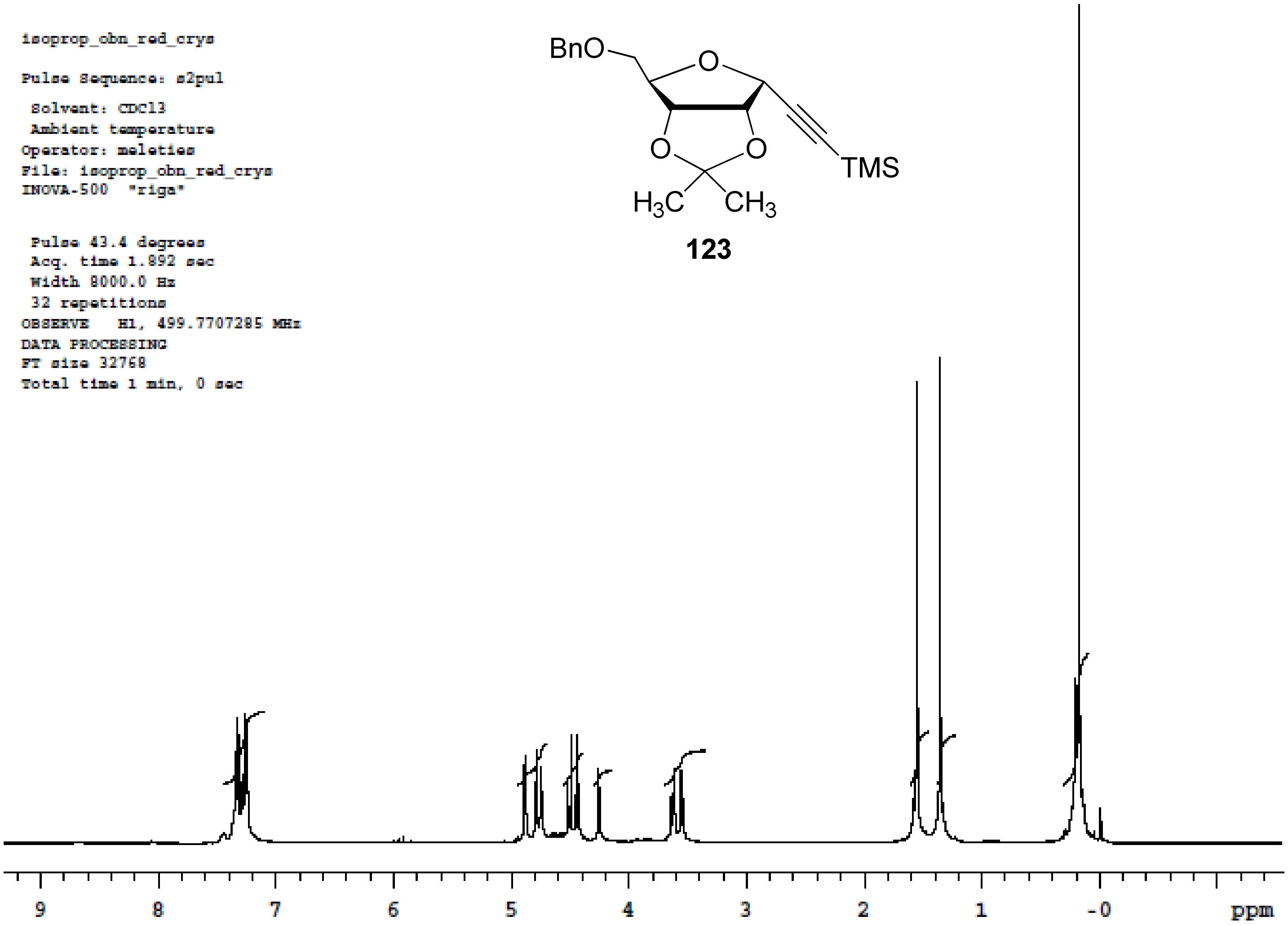
**122**



```
isoprop_obn_red_crys

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: isoprop_obn_red_crys
INOVA-500  "riga"

 Pulse 43.4 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 32 repetitions
OBSERVE   H1, 499.7707285 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
```

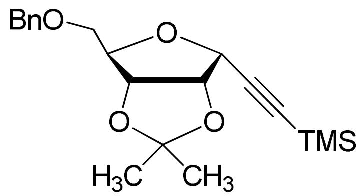


**123**

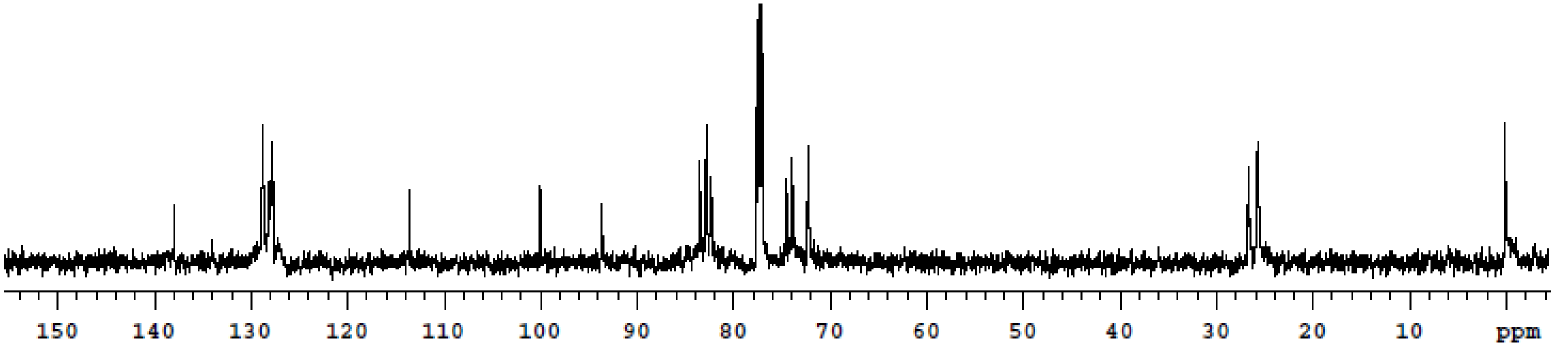
```
isoprop_obn_red_crys

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: isoprop_obn_red_crys_c13
INOVA-500  "capella500"

 Pulse 56.8 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 832 repetitions
OBSERVE  C13, 125.6674149 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 30 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 65536
Total time 44 min, 41 sec
```



**123**



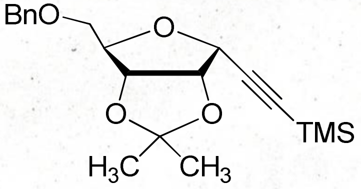
```
PPT-chris-isoprop-reduction-NOESY-081210

 File: PPT-chris-isoprop-reduction-NOESY-081210

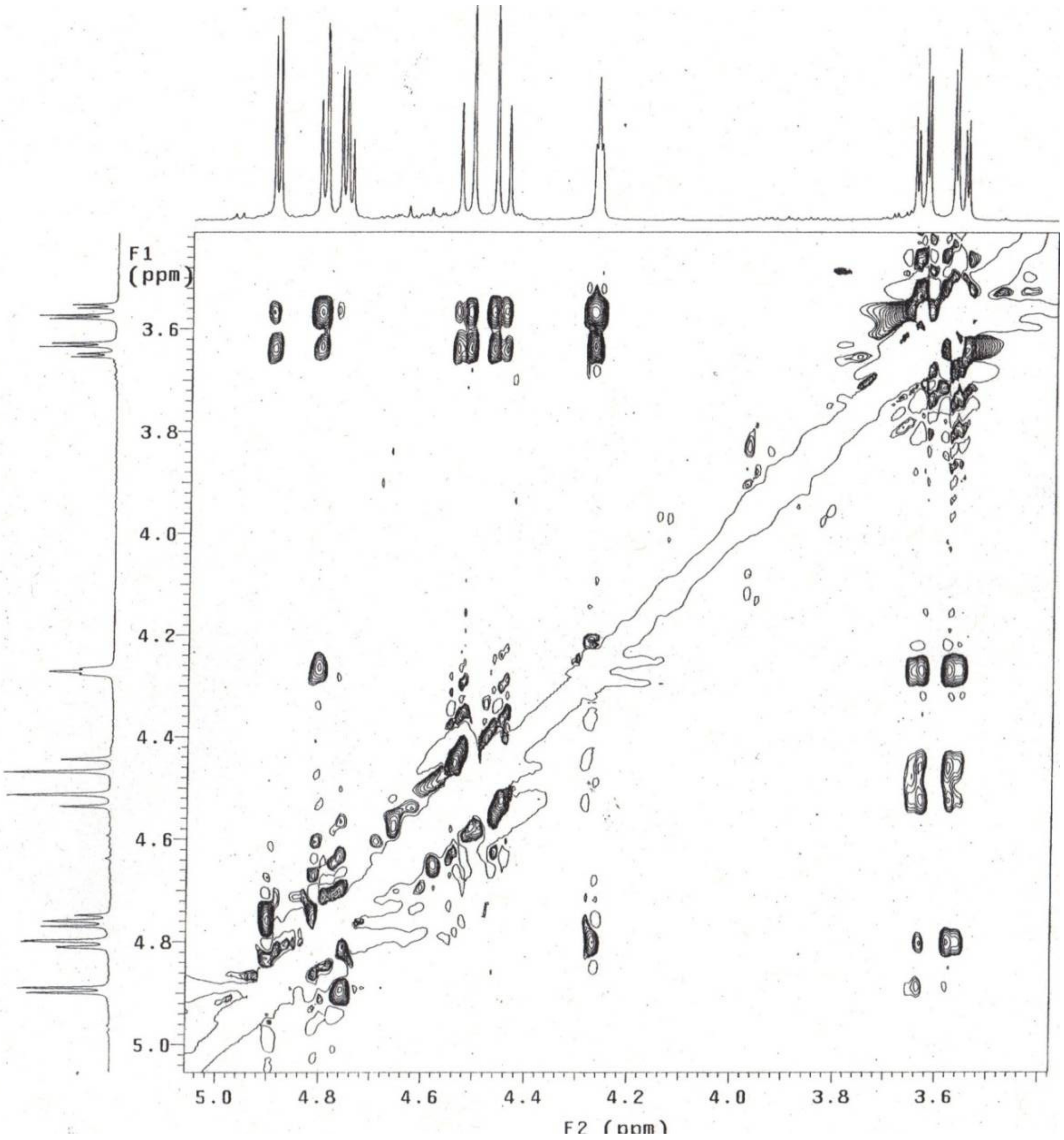
Pulse Sequence: NOESY

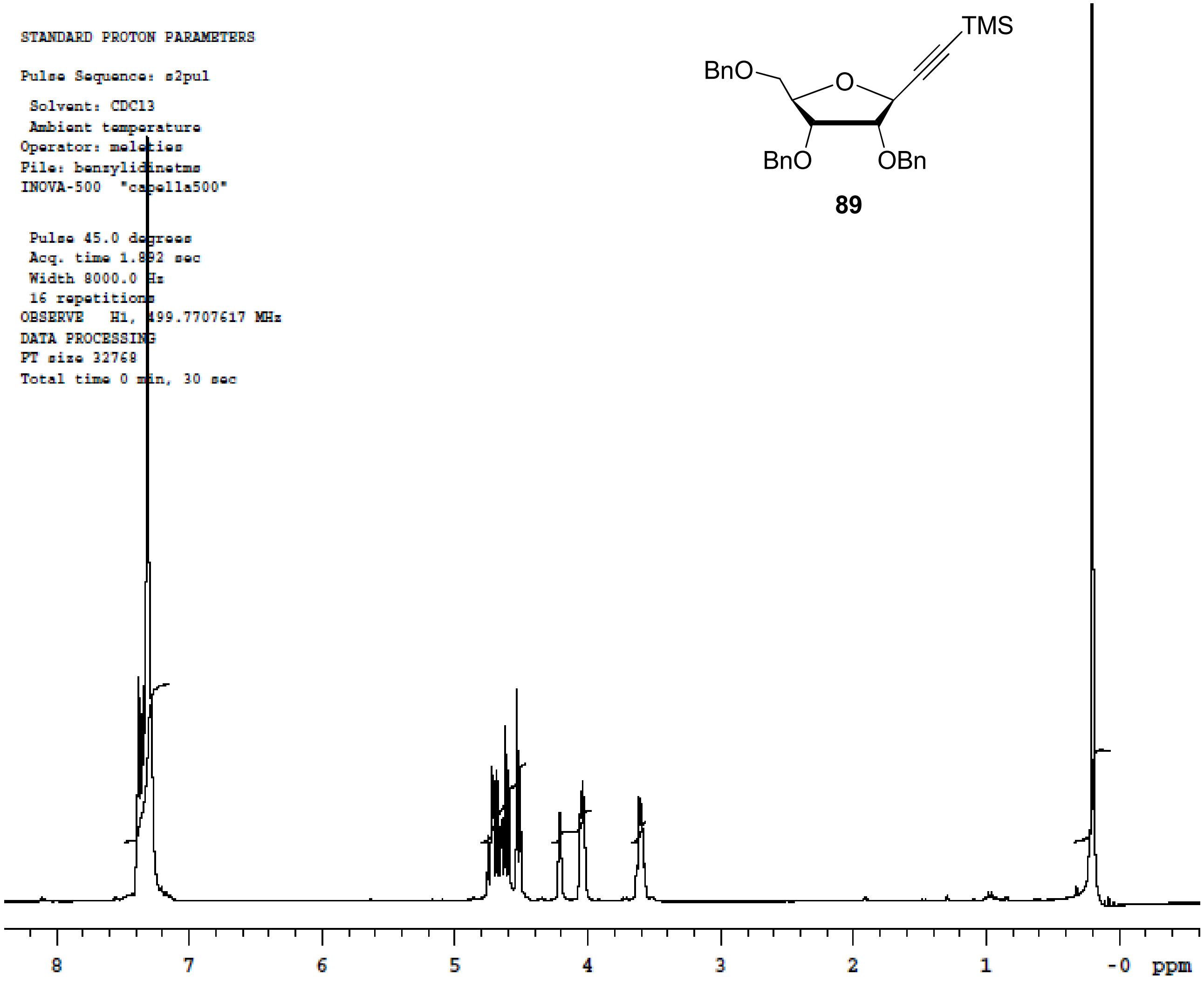
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: PPT-chris-isoprop-reduction-NOESY-081210
INOVA-500  "capella500"

 Relax. delay 1.200 sec
 Mixing 0.400 sec
 Acq. time 0.128 sec
 Width     6464.1 Hz
 2D Width 6464.1 Hz
 4 repetitions
 2 x 256 increments
OBSERVE   H1, 499.7707184 MHz
DATA PROCESSING
 Sq. sine bell 0.128 sec
  Shifted by -0.128 sec
F1 DATA PROCESSING
 Sq. sine bell 0.100 sec
  Shifted by -0.100 sec
FT size 4096 x 4096
Total time 1 hr, 43 sec
```



**123**





```
STANDARD PROTON PARAMETERS

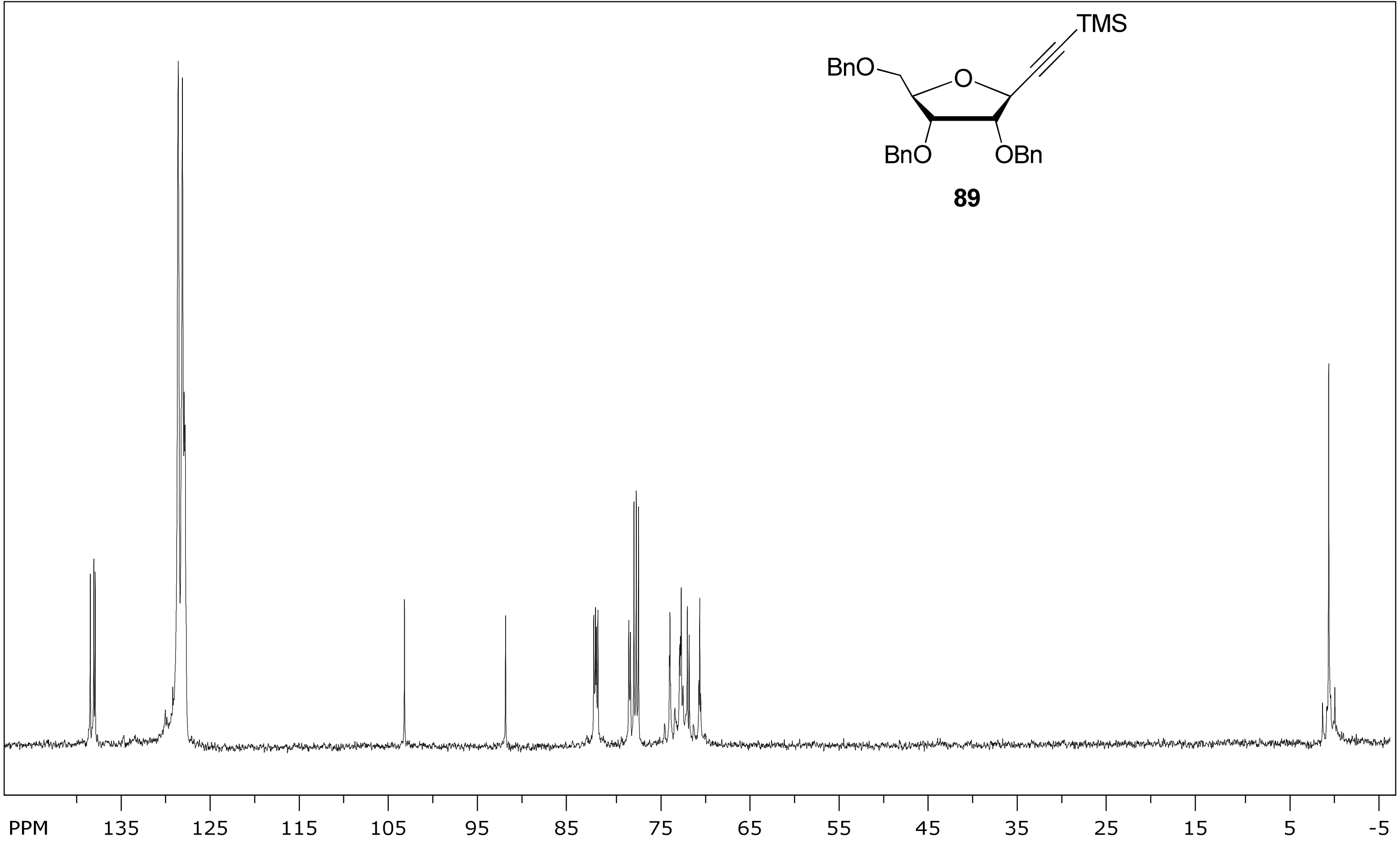
Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: benzylidinetms
INOVA-500  "capella500"

 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707617 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 30 sec
```

**89**

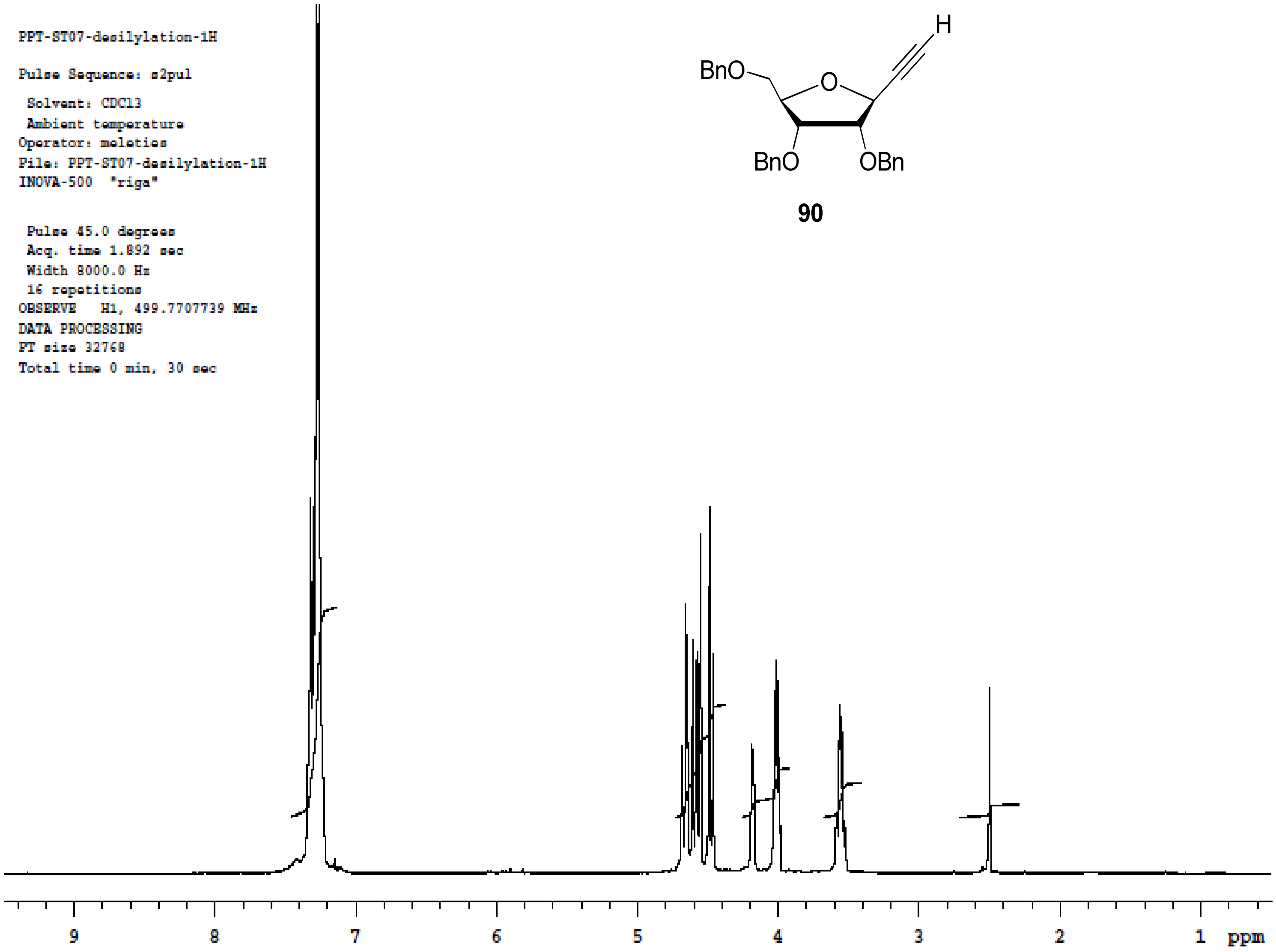
SpinWorks 3: TS_TMS-reduction-13C



**89**

file: ...samir\TS_TMS-reduction-13C.fid\fid  block# 1  expt: "s2pul"
transmitter freq.: 125.679355 MHz
time domain size: 78020 points
width: 29996.25 Hz = 238.6729 ppm = 0.384469 Hz/pt
number of scans: 32

freq. of 0 ppm: 125.667415 MHz
processed size: 131072 complex points
LB: 4.000    GF: 0.0000
Hz/cm: 778.501    ppm/cm: 6.19434



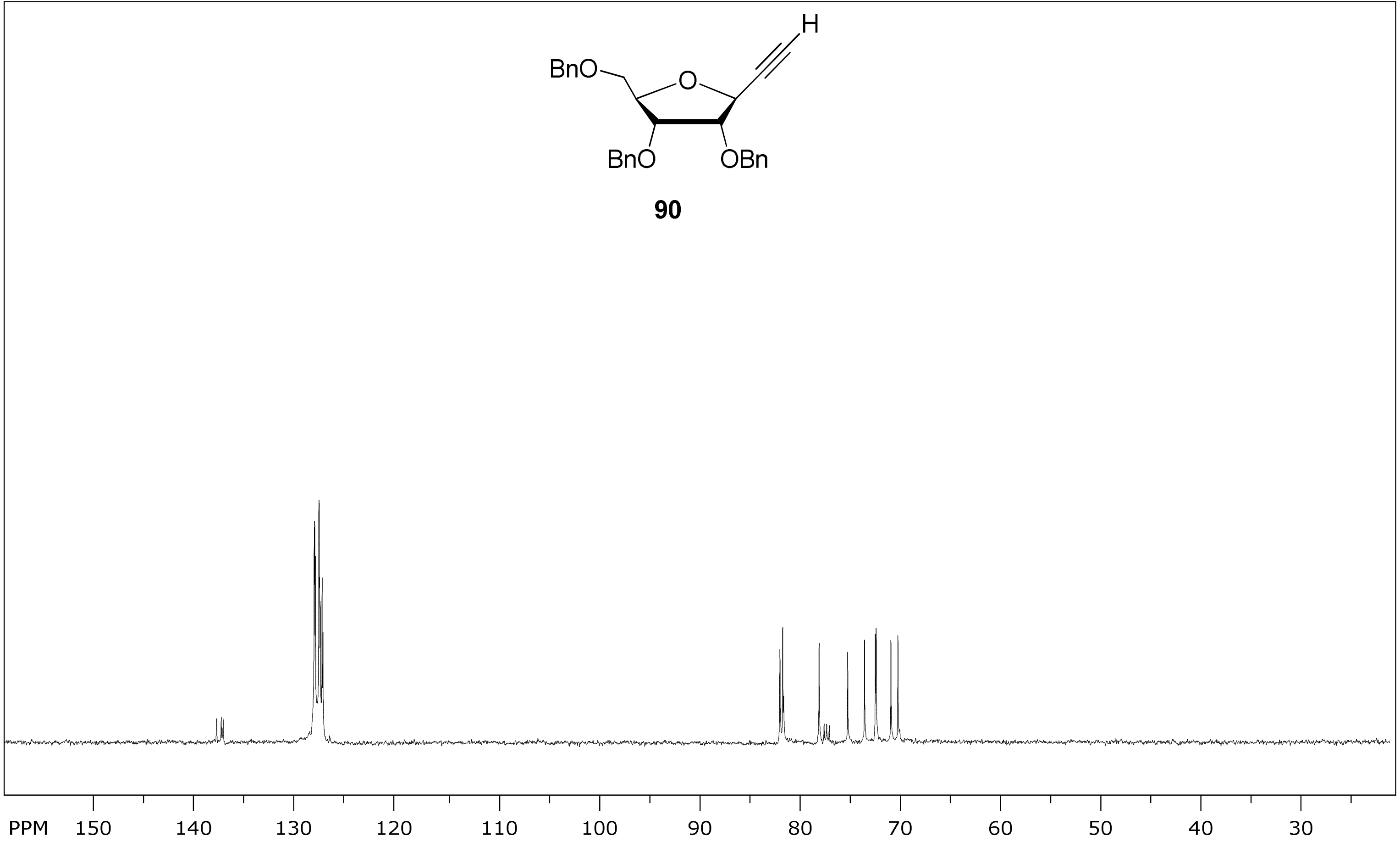
**90**

```
PPT-ST07-desilylation-1H

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: PPT-ST07-desilylation-1H
INOVA-500  "riga"

 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707739 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 30 sec
```

SpinWorks 3: PPT-ST07-desilylation-13C



**90**

file: ...\PPT-ST07-desilylation-13C.fid\fid block# 1 expt: "s2pul"
transmitter freq.: 125.679355 MHz
time domain size: 75418 points
width: 28996.01 Hz = 230.7142 ppm = 0.384471 Hz/pt
number of scans: 48

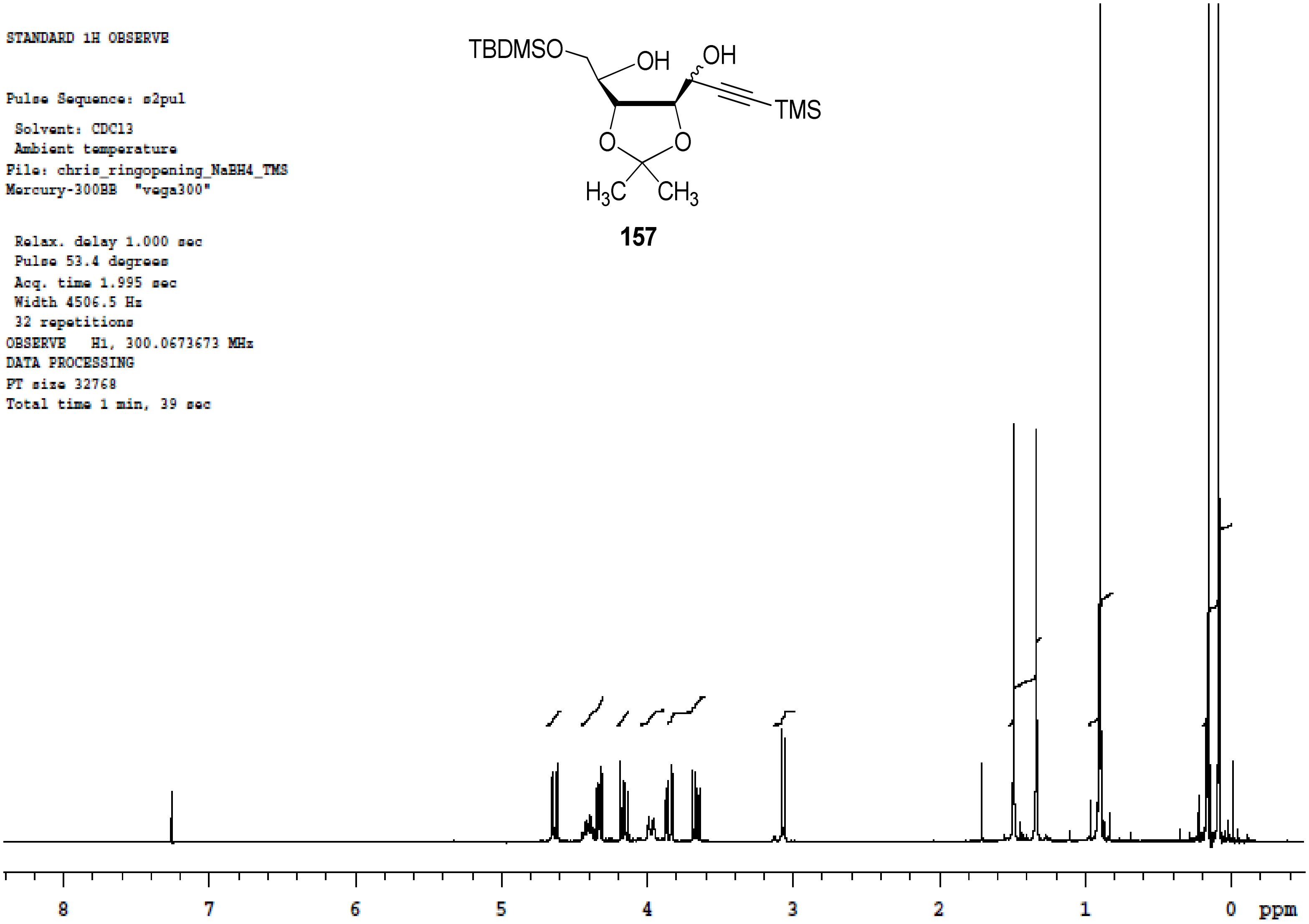
freq. of 0 ppm: 125.667469 MHz
processed size: 131072 complex points
LB: 4.000 GF: 0.0000
Hz/cm: 696.604 ppm/cm: 5.54270

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: chris_ringopening_NaBH4_TMS
Mercury-300BB "vega300"

Relax. delay 1.000 sec
Pulse 53.4 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
32 repetitions
OBSERVE H1, 300.0673673 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



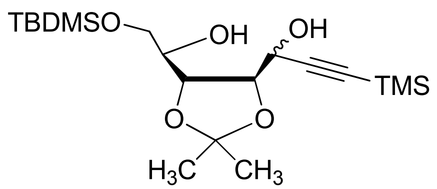
**157**

```
ringopening_c13_isopropylidene_tbdms_tms_acetylene

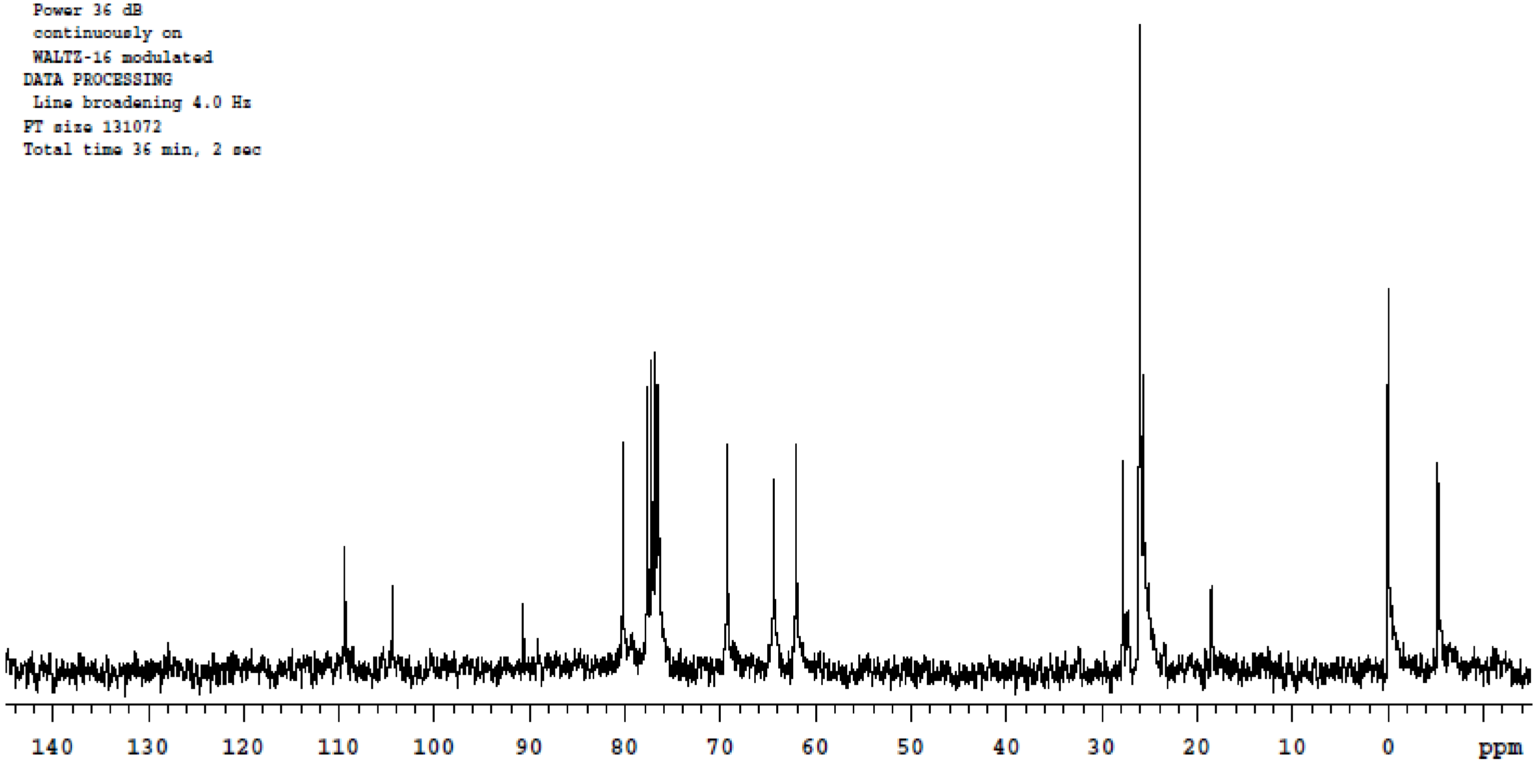
Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
File: ring_opening_c13_isopropylidene
Mercury-300BB  "vega300"

 Pulse 43.8 degrees
 Acq. time 1.815 sec
 Width 18761.7 Hz
 448 repetitions
OBSERVE  C13,  75.4634477 MHz
DECOUPLE  H1, 300.1144582 MHz
 Power 36 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 36 min, 2 sec
```



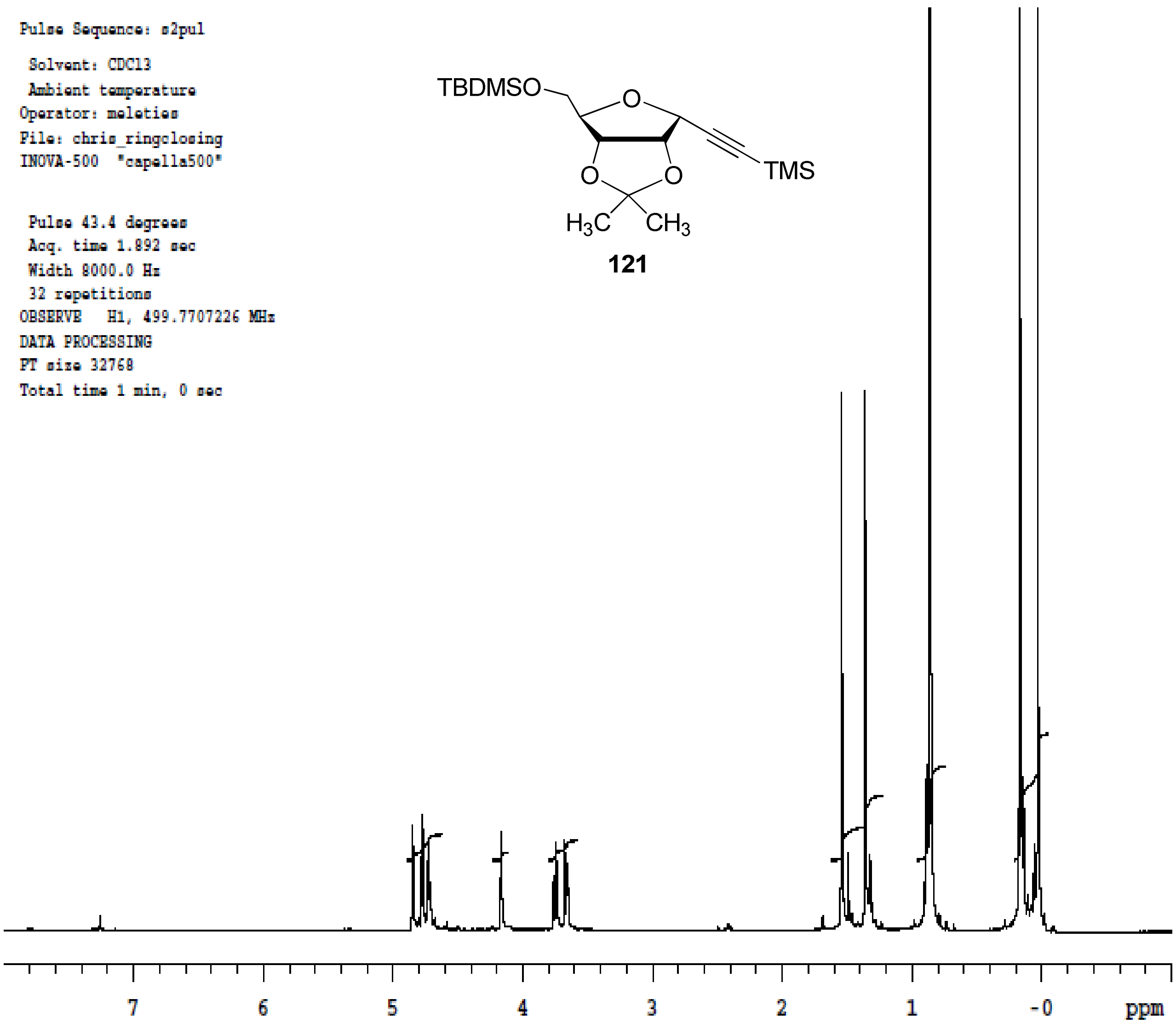
**157**

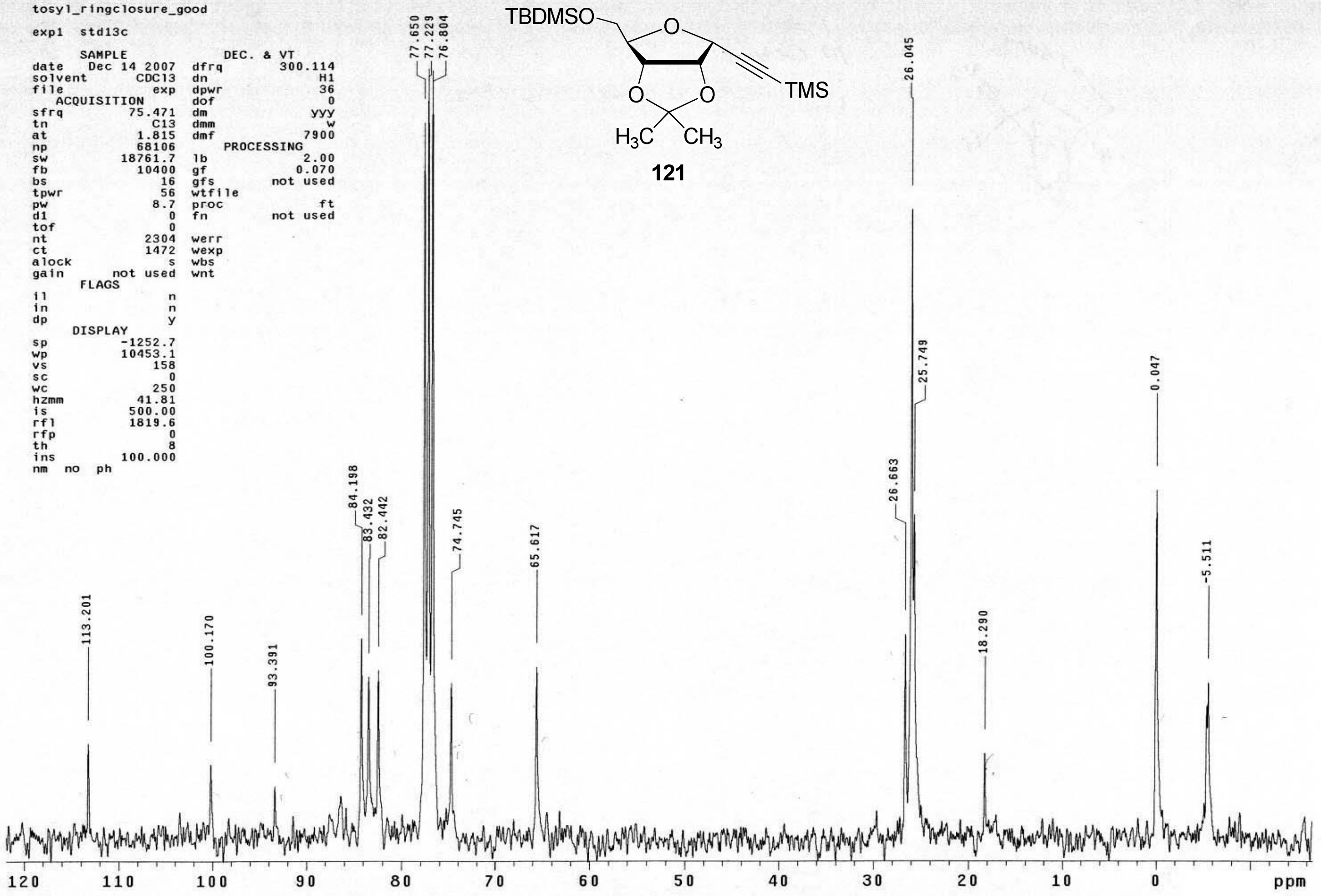


Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: meleties
File: chris_ringclosing
INOVA-500 "capella500"

Pulse 43.4 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7707226 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec





**121**

```
tosyl_ringclosure_good

exp1  std13c

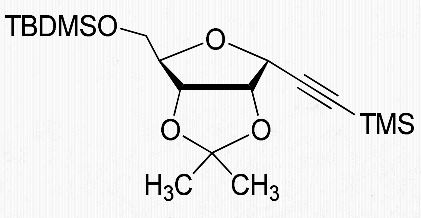
      SAMPLE                DEC. & VT
date   Dec 14 2007   dfrq        300.114
solvent      CDCl3   dn               H1
file           exp   dpwr             36
   ACQUISITION       dof               0
sfrq        75.471   dm              yyy
tn             C13   dmm               w
at           1.815   dmf            7900
np           68106        PROCESSING
sw         18761.7   lb             2.00
fb           10400   gf            0.070
bs              16   gfs        not used
tpwr            56   wtfile
pw             8.7   proc             ft
d1               0   fn         not used
tof              0
nt            2304   werr
ct            1472   wexp
alock            s   wbs
gain      not used   wnt
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp         -1252.7
wp         10453.1
vs             158
sc               0
wc             250
hzmm         41.81
is          500.00
rfl         1819.6
rfp              0
th               8
ins        100.000
nm  no  ph
```

```
Chris-bcc-TMSACtylene_crystal-012109-NOESY

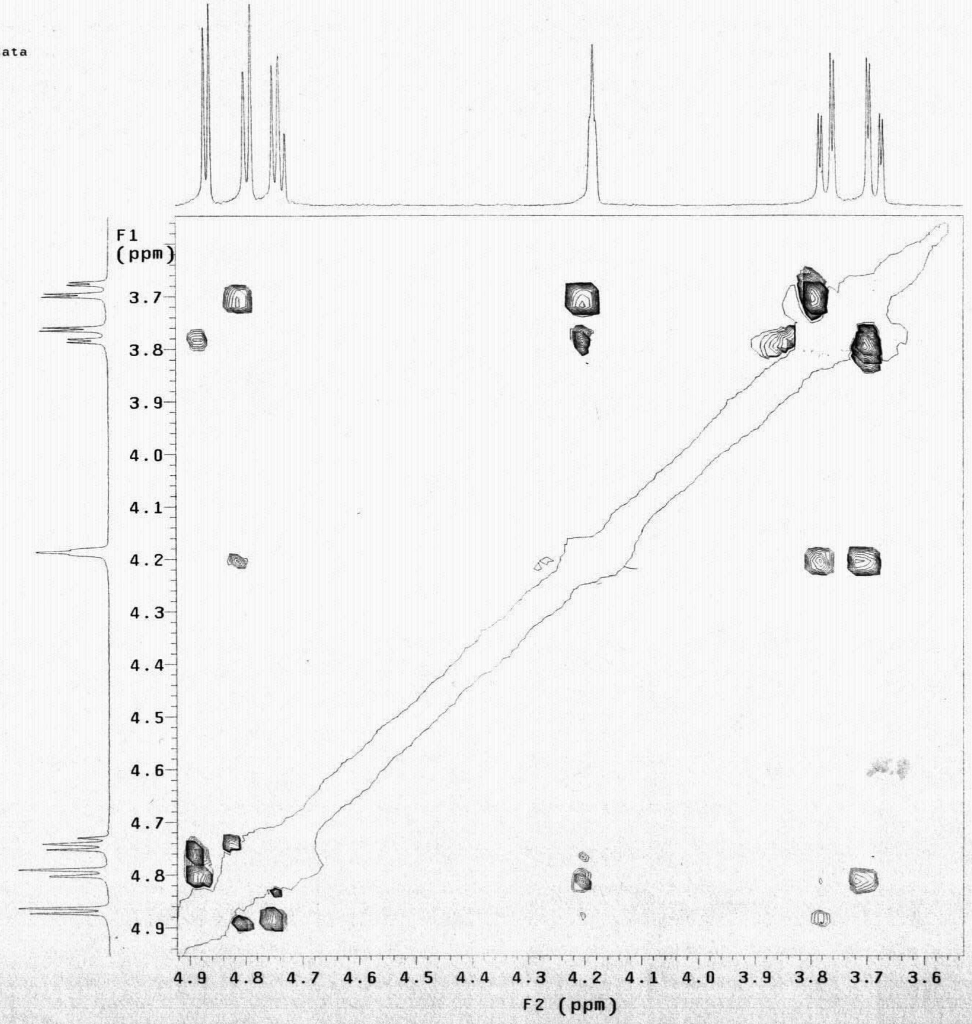
 Archive directory: /export/home/meleties/vnmrsys/data
 File: PROTON

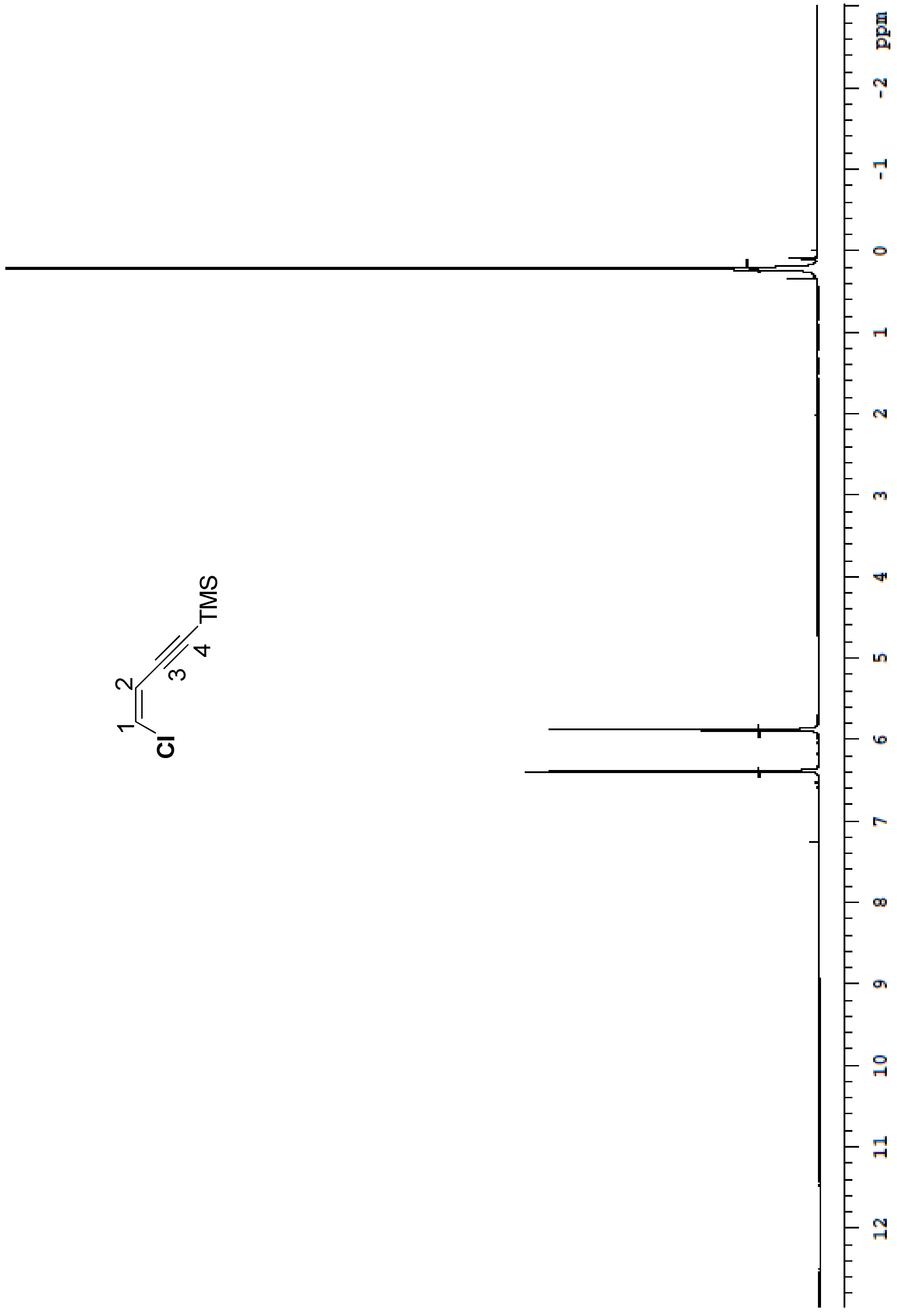
Pulse Sequence: NOESY
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
INOVA-500  "capella500"

 Relax. delay 1.000 sec
 Mixing 0.800 sec
 Acq. time 0.128 sec
 Width     7996.0 Hz
 2D Width 7996.0 Hz
 8 repetitions
 2 x 160 increments
OBSERVE   H1, 499.7707095 MHz
DATA PROCESSING
 Gauss apodization 0.059 sec
F1 DATA PROCESSING
 Gauss apodization 0.023 sec
FT size 2048 x 2048
Total time 1 hr, 24 min, 28 sec
```

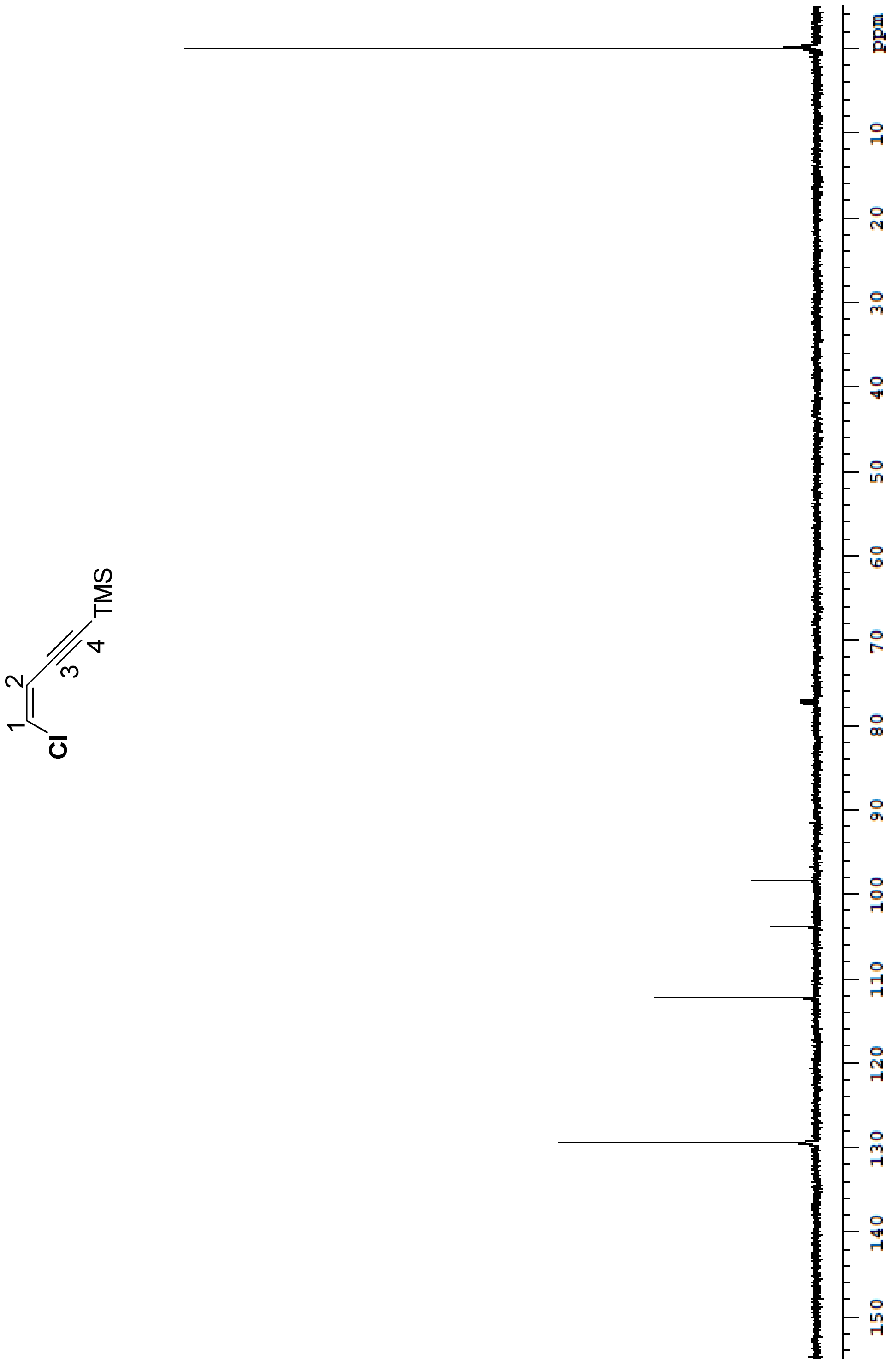


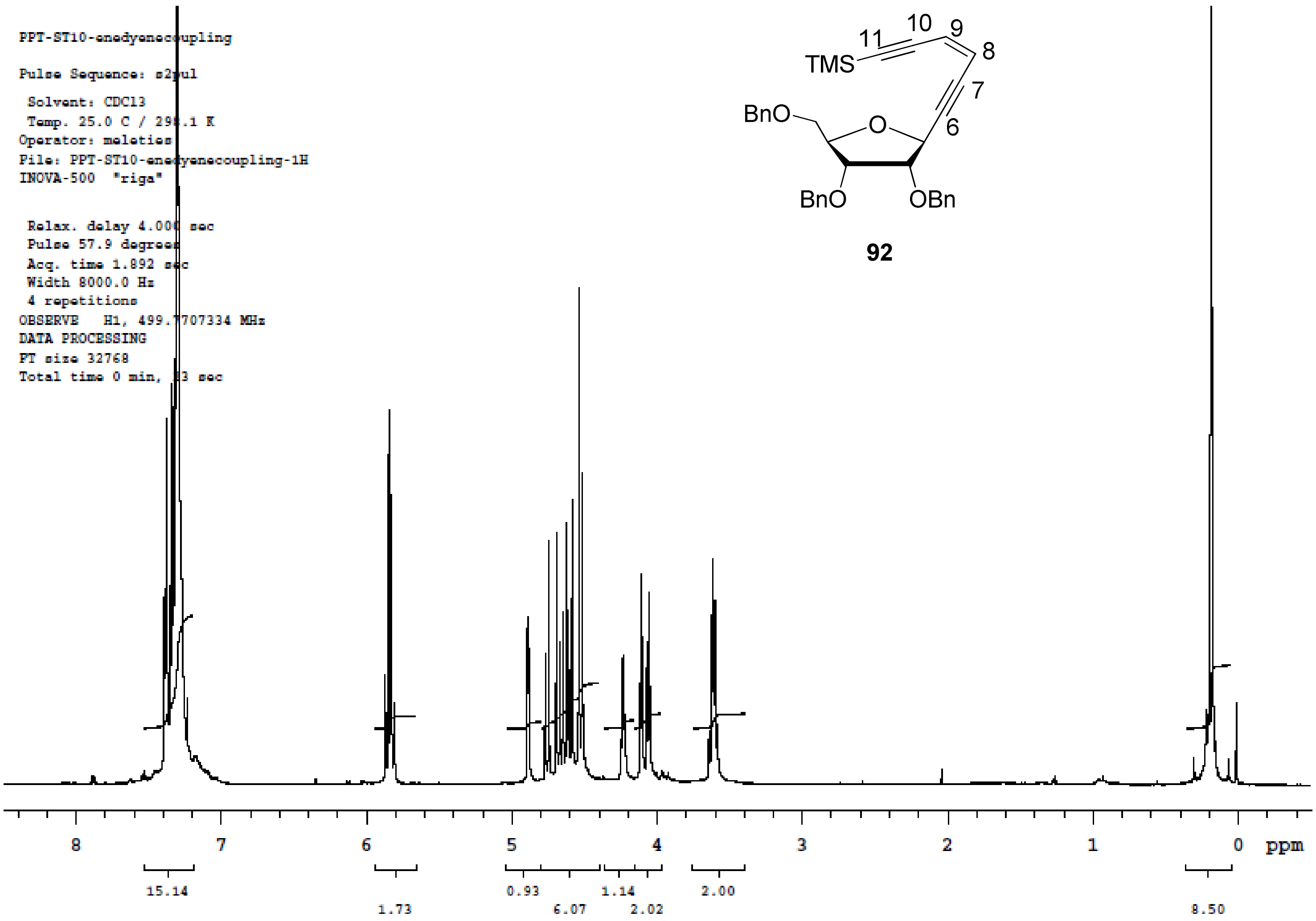
**121**





Cl
1
2
3
4
TMS
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm


Cl
1
2
3
4
TMS
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

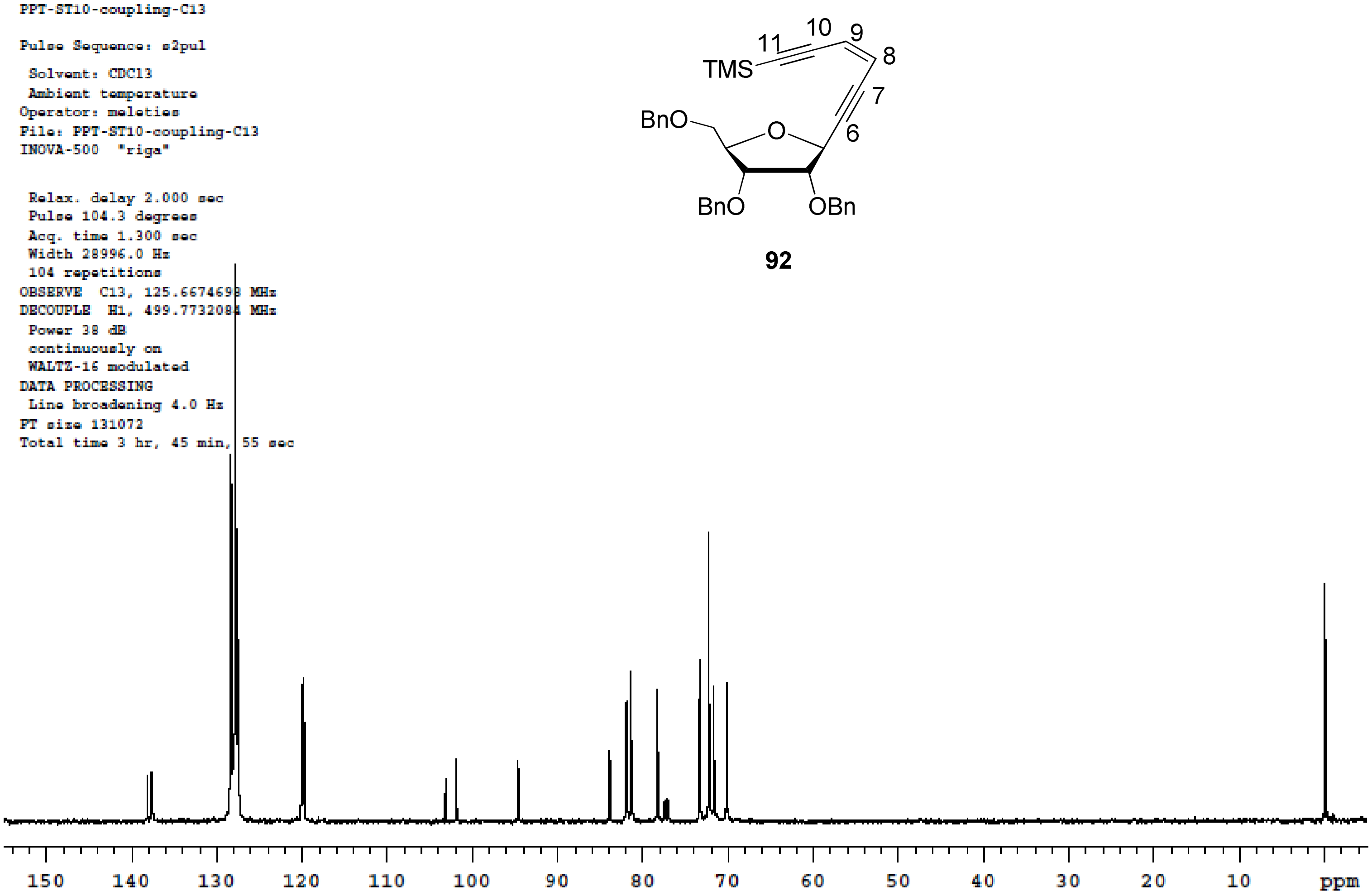


**92**

```
PPT-ST10-enedyenecoupling

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: PPT-ST10-enedyenecoupling-1H
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 57.9 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 4 repetitions
OBSERVE   H1, 499.7707334 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 23 sec
```



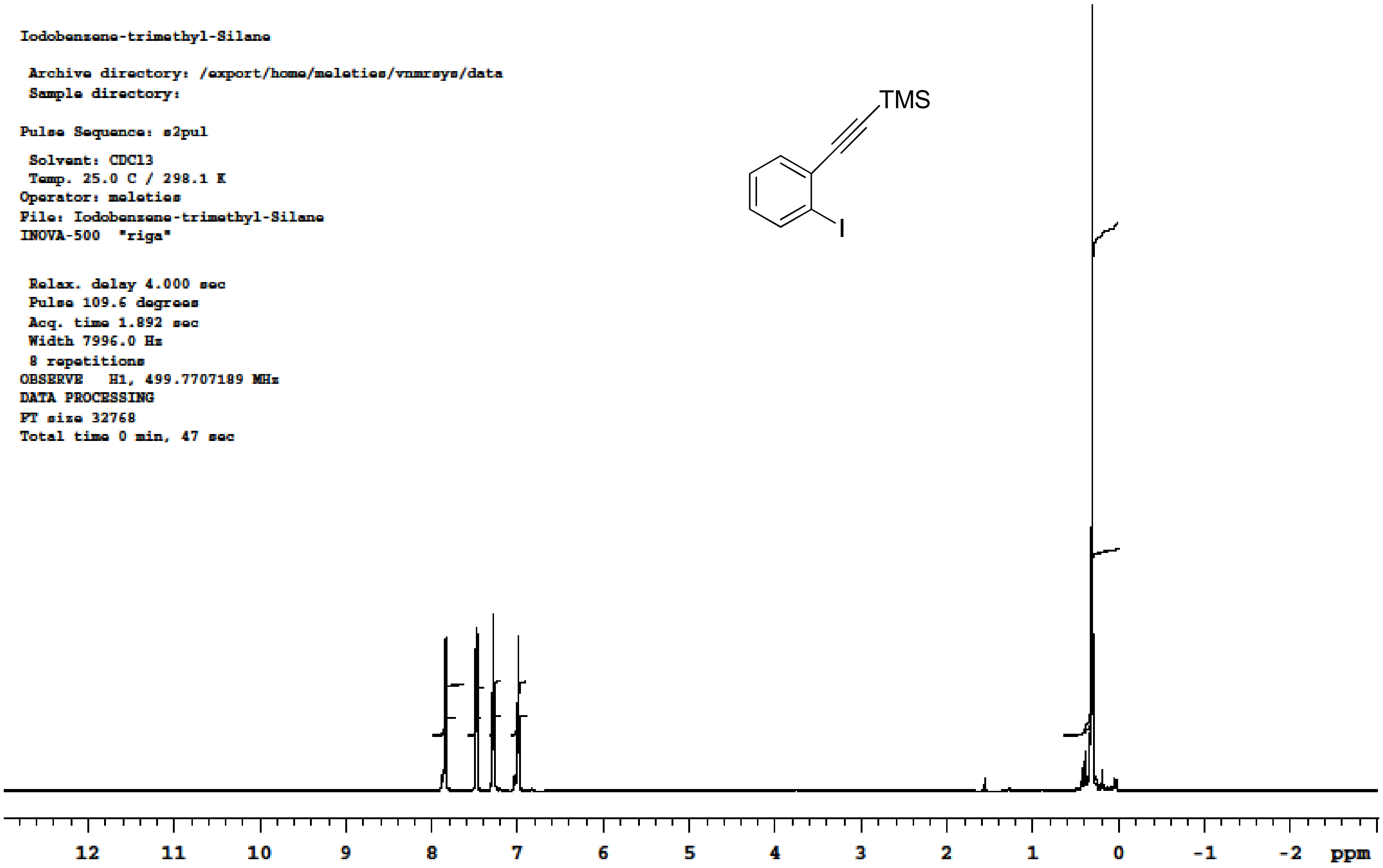
**92**

PPT-ST10-coupling-C13

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
Operator: meleties
File: PPT-ST10-coupling-C13
INOVA-500 "riga"

Relax. delay 2.000 sec
Pulse 104.3 degrees
Acq. time 1.300 sec
Width 28996.0 Hz
104 repetitions
OBSERVE C13, 125.6674698 MHz
DECOUPLE H1, 499.7732084 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 131072
Total time 3 hr, 45 min, 55 sec



```
Iodobenzene-trimethyl-Silane

 Archive directory: /export/home/meleties/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul

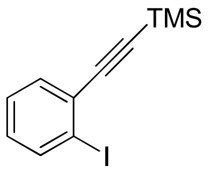
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: Iodobenzene-trimethyl-Silane
INOVA-500  "riga"

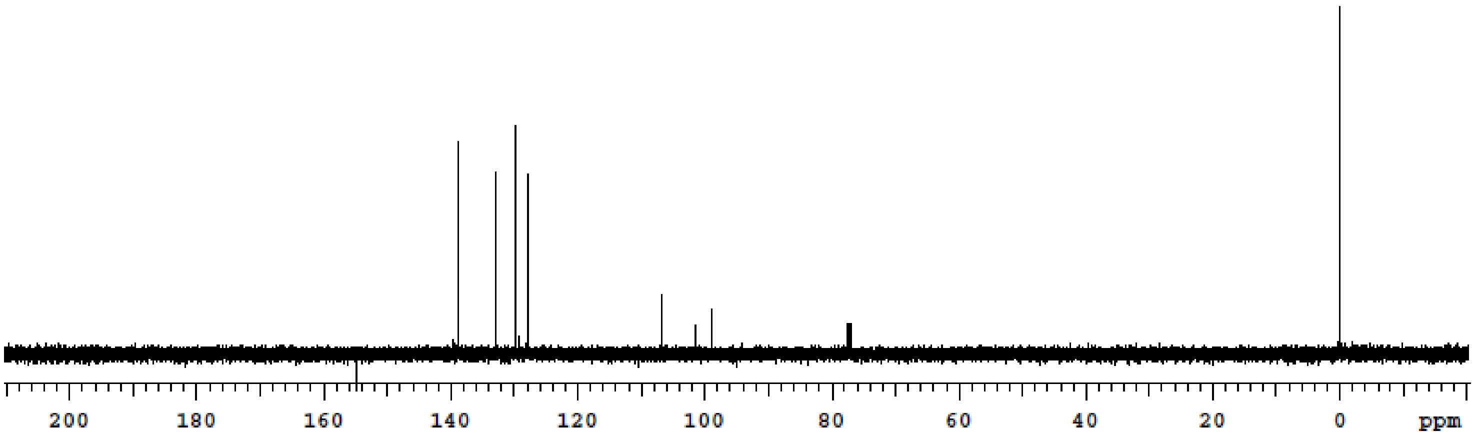
 Relax. delay 4.000 sec
 Pulse 109.6 degrees
 Acq. time 1.892 sec
 Width 7996.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707189 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 47 sec
```

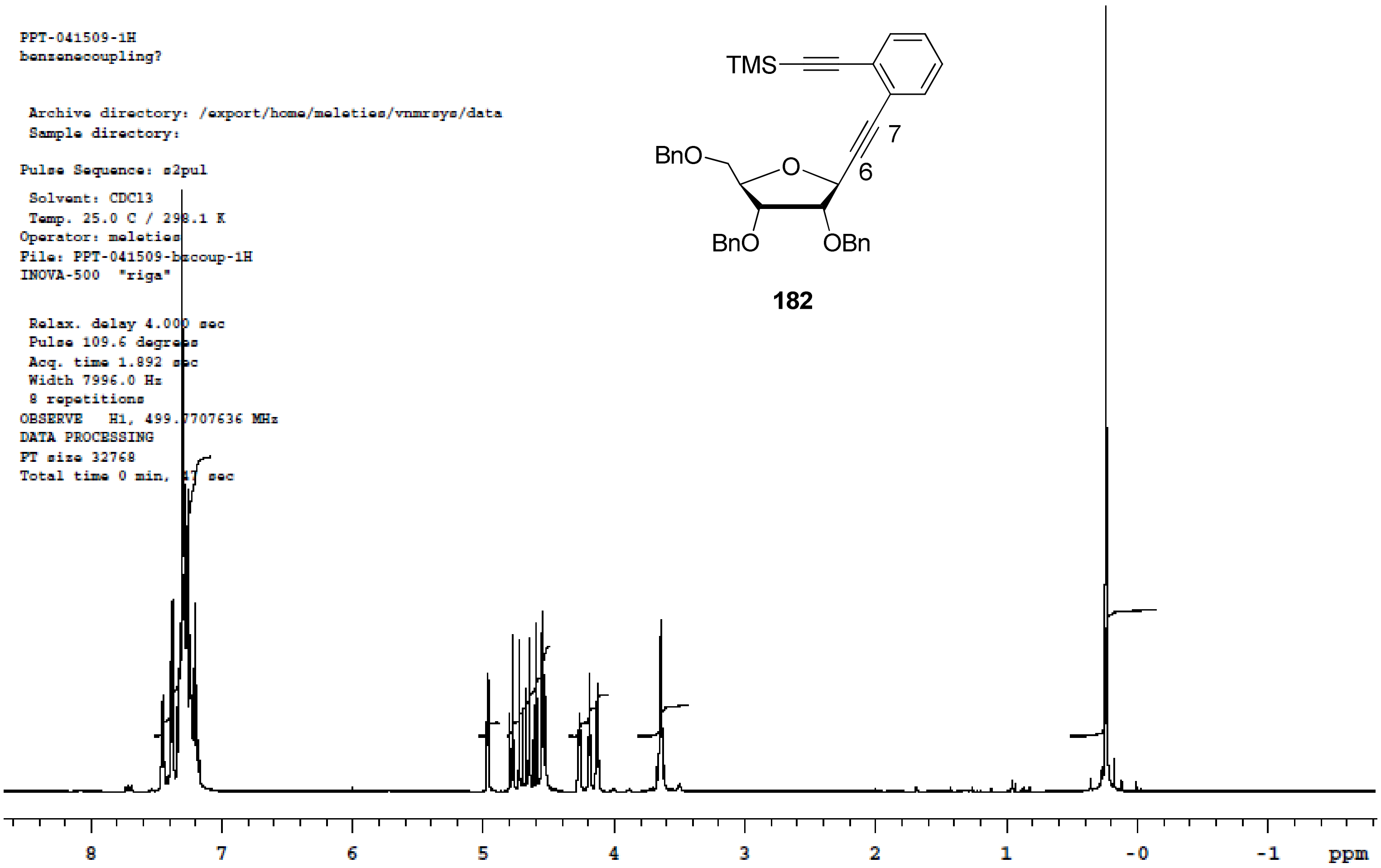
```
Iodobenzene-trimethyl-Silane-C13

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: Iodobenzene-trimethyl-Silane-C13
INOVA-500  "riga"

 Relax. delay 2.000 sec
 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 112 repetitions
OBSERVE  C13, 125.6674234 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
FT size 131072
Total time 14 min, 7 sec
```







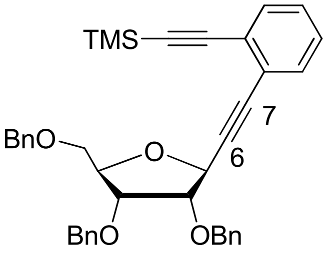
```
PPT-041509-1H
benzenecoupling?

 Archive directory: /export/home/meleties/vnmrsys/data
 Sample directory:

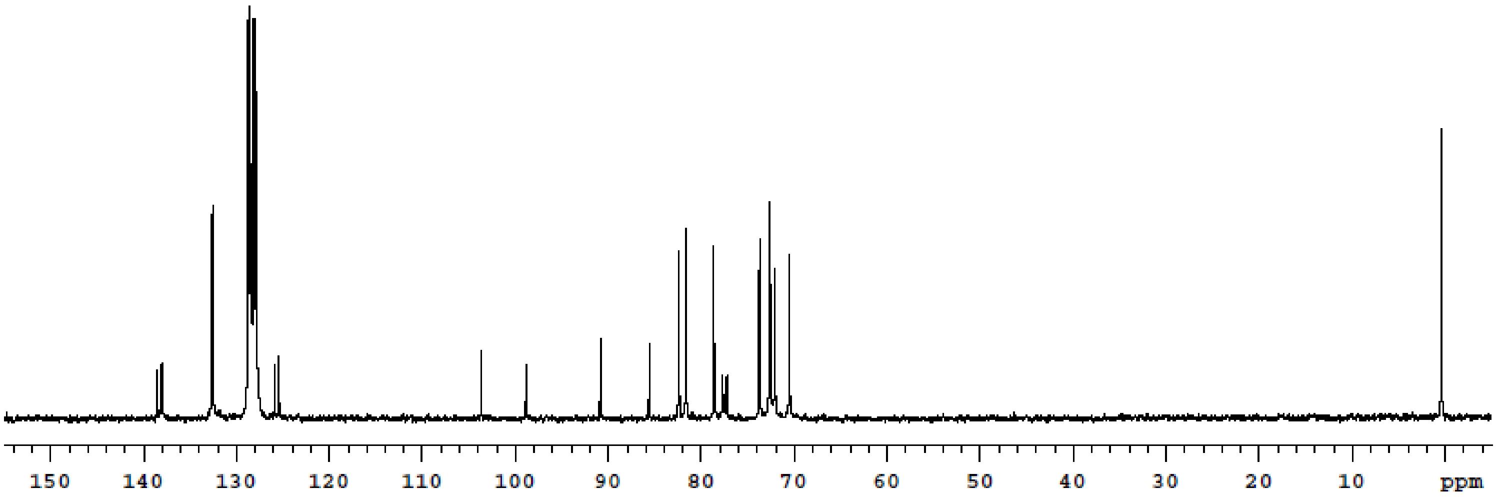
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: PPT-041509-bzcoup-1H
INOVA-500  "riga"

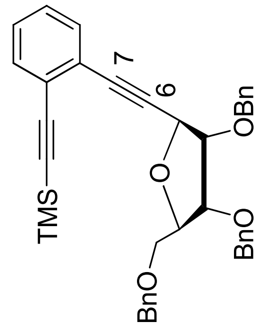
 Relax. delay 4.000 sec
 Pulse 109.6 degrees
 Acq. time 1.892 sec
 Width 7996.0 Hz
 8 repetitions
OBSERVE   H1, 499.7707636 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 47 sec
```

**182**

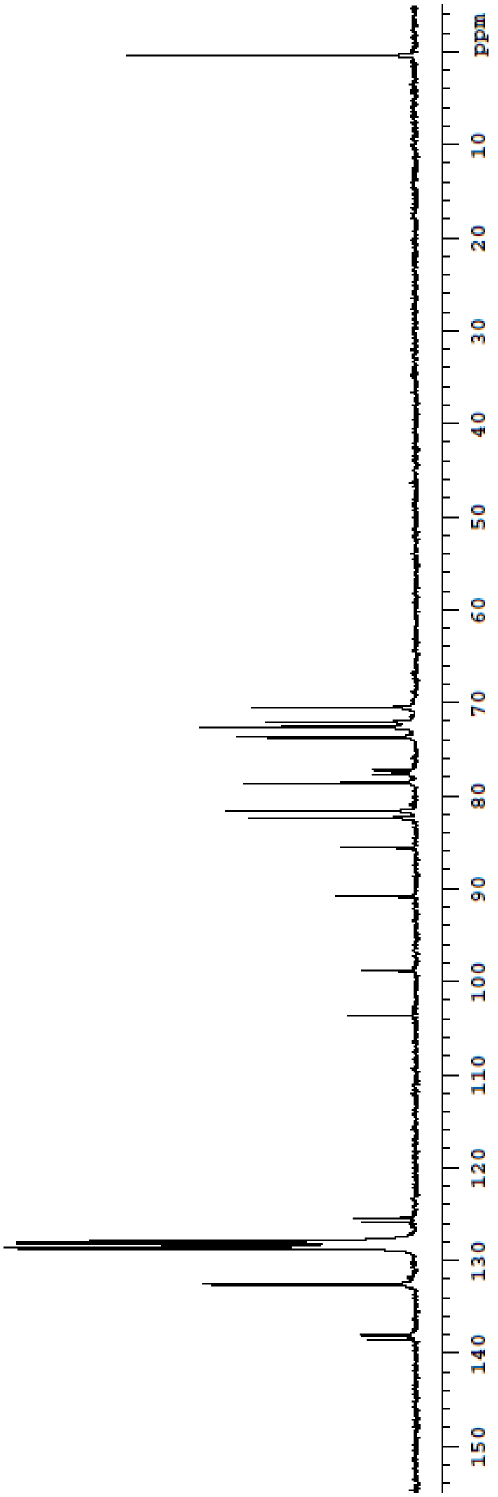

TMS
7
6
BnO
O
BnO
OBn

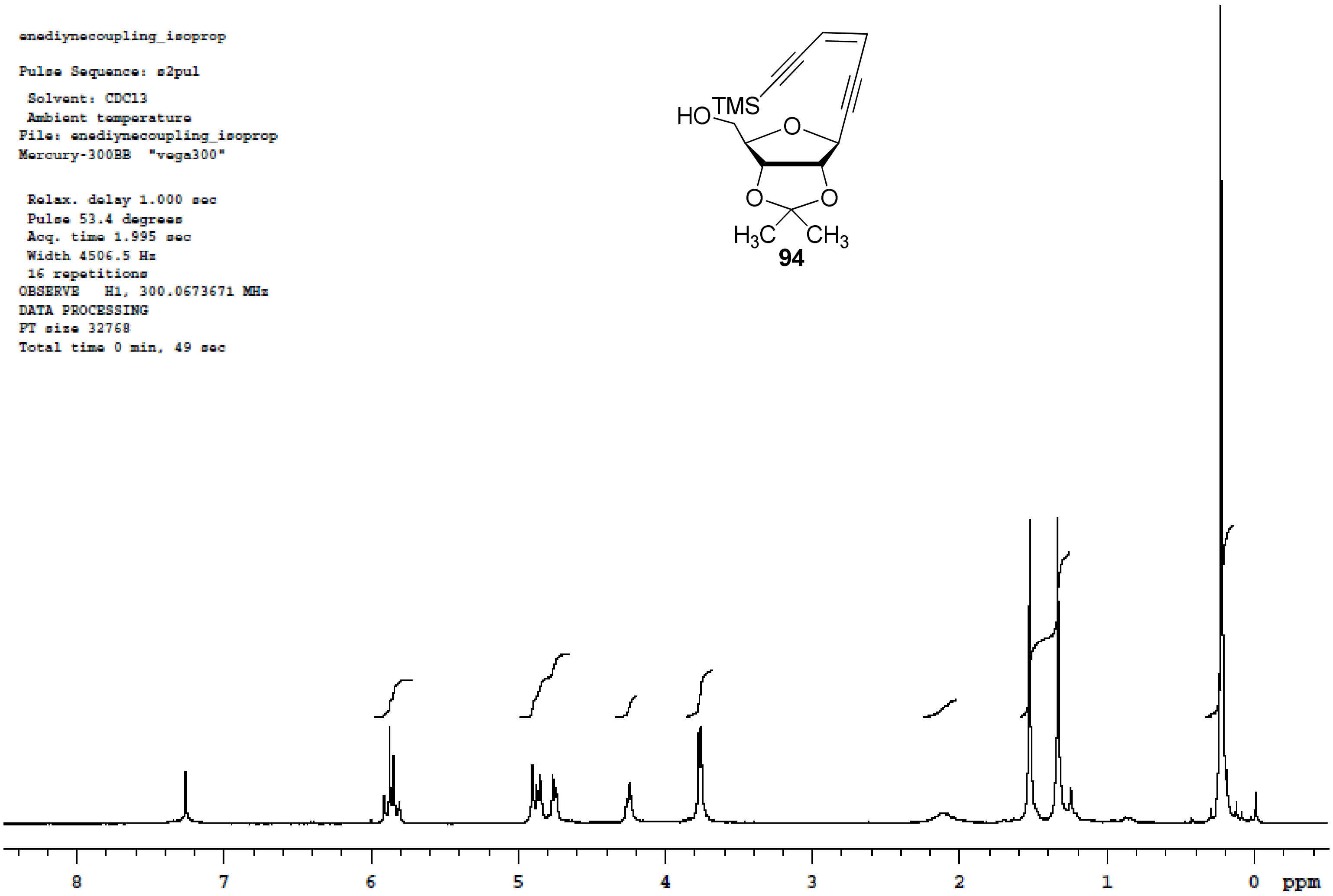
**182**


150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


TMS
7
6
O
OBn
BnO
BnO

**182**


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150



```
enediynecoupling_isoprop

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
File: enediynecoupling_isoprop
Mercury-300BB  "vega300"

 Relax. delay 1.000 sec
 Pulse 53.4 degrees
 Acq. time 1.995 sec
 Width 4506.5 Hz
 16 repetitions
OBSERVE   H1, 300.0673671 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
```

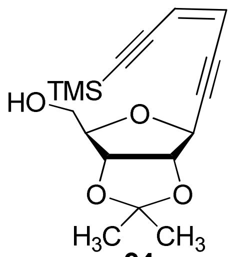
**94**

```
PPT-ST16_coupling-isopropylidin-13C

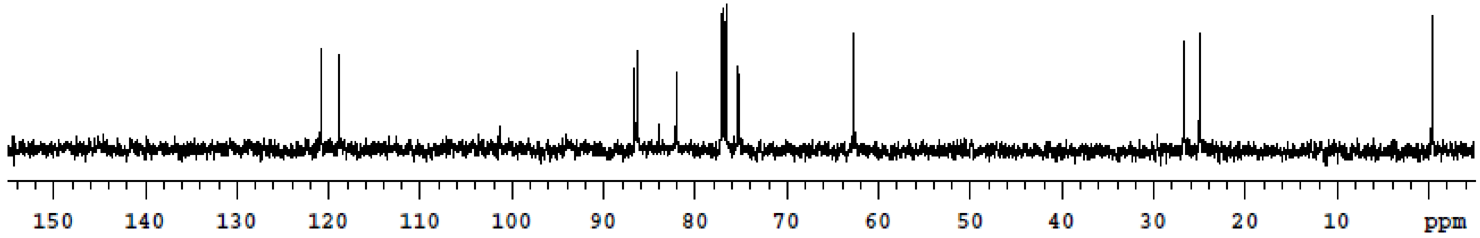
Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: PPT-ST16_coupling-isopropylidin-C13
INOVA-500  "riga"

 Relax. delay 2.000 sec
 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 312 repetitions
OBSERVE  C13, 125.6674640 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 3 hr, 45 min, 55 sec
```



**94**



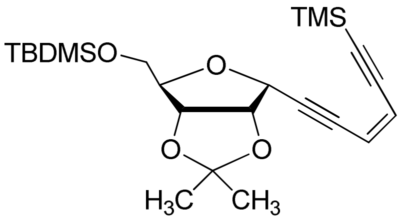
```
PPT-Isopropylidine-coupling-TBDMS-1H

 Archive directory: /export/home/meleties/vnmrsys/data
 Sample directory:

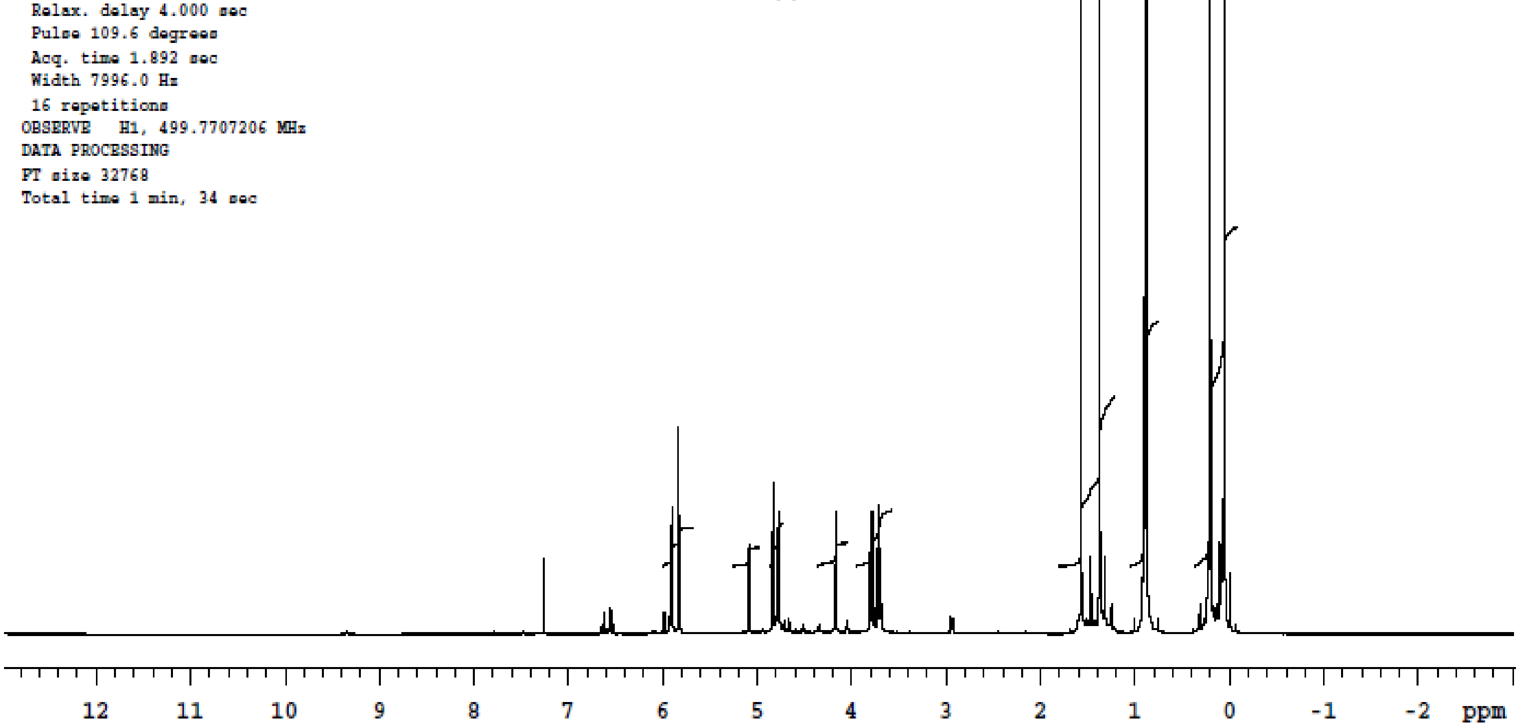
Pulse Sequence: s2pul

 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
Operator: meleties
File: PPT-Isopropylidine-coupling-TBDMS-1H
INOVA-500  "riga"

 Relax. delay 4.000 sec
 Pulse 109.6 degrees
 Acq. time 1.892 sec
 Width 7996.0 Hz
 16 repetitions
OBSERVE   H1, 499.7707206 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 34 sec
```



**186**

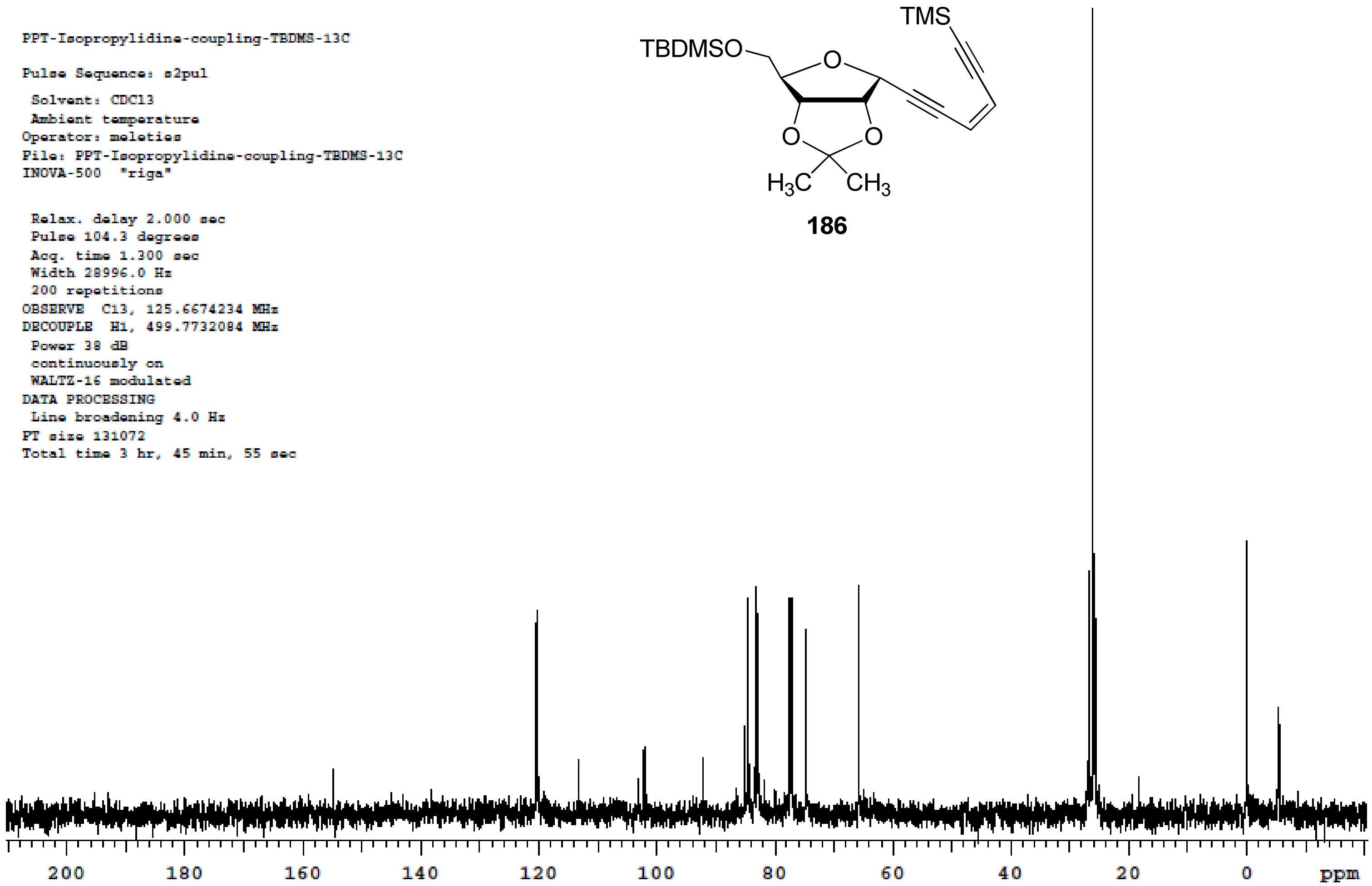


```
PPT-Isopropylidine-coupling-TBDMS-13C

Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
Operator: meleties
File: PPT-Isopropylidine-coupling-TBDMS-13C
INOVA-500  "riga"

 Relax. delay 2.000 sec
 Pulse 104.3 degrees
 Acq. time 1.300 sec
 Width 28996.0 Hz
 200 repetitions
OBSERVE  C13, 125.6674234 MHz
DECOUPLE  H1, 499.7732084 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 4.0 Hz
FT size 131072
Total time 3 hr, 45 min, 55 sec
```



**186**

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# LIST OF ABBREVIATION

| | |
|---|---|
| AIBN | Azobisisobutyronitrile |
| BAIB | [bis (acetoxy)-iodo] benzene (BAIB) |
| BnCl | Benzylchloride |
| BOM | Benzyloxymethyl |
| BuLi | Butyl lithium |
| t-BuOK | Potassium *tert*-butoxide |
| DCM | Dichloromethane |
| DMSO | Dimethylsulfoxide |
| DMF | Dimethylformamide |
| DNA | Deoxyribonuclic acid |
| Et | Ethyl |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| LDA | Lithium diisopropylamide |
| MeOH | Methyl alcohol |
| MOM | Methoxymethyl |
| Nu | Nucleophile |
| OAc | Acetae |
| Ph | Phenyl |
| Py | Pyridine |
| RNA | Ribonuclic acid |
| TBAF | Tetra-*n*-butylammonium fluoride |

| | |
|---|---|
| TBDMS | t-butyldimrthylsilyl |
| TEMPO | 2,2,6,6-tetramethylpiperidine-1-oxyl |
| THF | Tetrahydofuran |
| TMSCl | Trimethylsilyl chloride |
| TMSOTf | Trimethylsilyl Trifluoromethanesulfonate |
| Tos | p-toluenesulfonyl |
| TPS | Triphenylsilyl |
| TCCA | Trichloroisocyanuric acid |