UNIVERSITÉ DU QUÉBEC À MONTRÉAL

# SYNTHÈSE D'INHIBITEURS DE L'ADHÉSION DU FIMH DE E. COLI

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# THE SYNTHESIS OF E. COLI FIMH ADHESION INHIBITORS

MEMORY

PRESENTED

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TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetate |
| $Ac_2O$ | acetic anhydride |
| AcOH | acetic acid |
| b | broad |
| BOP | benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate |
| bs | broad singlet |
| tBu | tert-butyl |
| COSY | shift correlation spectroscopy |
| d | doublet |
| DCC | dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| dd | doublet of doublet |
| ddd | doublet of doublet of doublet |
| DEPT | distortionless enhanced polarization transfer |
| DIPEA | diisopropylethylamine |
| DMF | N,N-dimethylformamide |
| DMS | dimethylsufide |
| DMSO | dimethylsulfoxide |
| eq | equivalent(s) |
| $Et_3N$ | triethylamime |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| Grubbs (I) | benzylidine-bis(tricyclohexylphosphine) dichlororuthenium (IV) |

| | |
|---|---|
| Grubbs(II) | benzylidine [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (IV) |
| hr | hour(s) |
| Hz | Hertz |
| IR | infrared |
| Lit. | literature |
| m | multiplet |
| M | molar |
| $M^+$ | parent molecular ion |
| MeOH | methanol |
| Me | methyl |
| MHz | MegaHertz |
| min | minute(s) |
| mmol | millimole(s) |
| mol | mole(s) |
| mp | melting point |
| MS | mass spectrometry |
| MW | molecular weight |
| m/z | mass to charge ratio |
| NaOMe | sodium methoxide |
| NMR | nuclear magnetic resonance |
| ppm | parts per million |
| Rf | retention factor |
| rt | room temperature |
| s | singlet |
| SPR | surface plasmon resonance |

| | |
|---|---|
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |

# RÉSUMÉ

Dérivé des deux termes grecs « *anti* » et « *biotikos* », le terme antibiotique signifie « contre la vie ». Les antibiotiques attaquent et détruisent les bactéries vivantes et les empêchent de se multiplier dans l'organisme humain.

Depuis leur première utilisation, tout un arsenal d'antibiotiques a été développé pour le traitement de diverses infections chez l'humain. L'utilisation à profusion, et dans certains cas à outrance des antibiotiques pour le traitement des infections microbiennes, a permis à certaines souches bactériennes d'acquérir une résistance à ces médicaments. Dans cette optique une alternative aux antibiotiques s'impose de plus en plus.

La première étape de nombreuses infections bactériennes est la colonisation des surfaces épithéliale de l'hôte. L'adhésion est médiée par des structures présentes à la surface de la cellule bactérienne, appelées adhésines, qui interagissent avec des composants présents à la surface de la cellule hôte ou à hauteur de la matrice extra-cellulaire, appelés récepteurs. Les lectines sont les adhésines bactériennes les plus étudiées. De nature protéique, elles ont été classées en différents groupes sur la base de leurs propriétés d'hémagglutination, leurs ultrastructures et leurs spécificités de récepteurs. Les lectines du premier groupe sont responsables d'hémagglutination sensible au mannose et présentent une structure de nature fimbriaire (fimbriae de type 1, FimH). Les futures stratégies thérapeutiques résident probablement dans l'utilisation de diverses adhésines, comme cibles thérapeutiques ou comme porteur d'épitopes étrangers, afin de produire des anticorps contre différents facteurs de virulence.

Utilisant de nouvelles méthodes de *C*-glycosidations combinées à la 'click chemistry' une série de *C*-mannosides a été synthétisée. Le potentiel d'inhibition de l'adhésion du FimH de ses glycomimétiques apportera de précieuses informations dans le cadre d'une grande étude relation-structure-activité (QSAR).

Mots-clés : antibiotique, adhésion, lectine, FimH, *C*-glycosidation, click chemistry

# SUMMARY

Derived from the two Greek terms 'anti' and 'biotikos', the term antibiotic means 'against life'. Antibiotics attack, destroy bacteria, and prevent them from multiplying in the human organism.

Since their first use, a whole arsenal of antibiotics was developed for the treatment of various infections in humans. In certain cases, antibiotics were used in such an excess for microbial infection treatments that made possible for certain strains to acquire resistance to these drugs. An alternative to antibiotics is increasingly essential.

The first stage of many bacterial infections is the epithelial colonization on the host surfaces. Adhesion is mediated by structures present at the bacterial cell surfaces called adhesins, which interact with glycoproteins present at the surface of the host cells or on the extracellular matrix. Lectins are the most studied bacterial adhesins, classified in various groups on the basis of their property of hemagglutination, their ultrastructure, and their specific receptors. The lectins responsible for hemagglutination sensitive to mannose can be represented by a fimbriated structure (fimbriae of type 1, FimH). The future therapeutic strategies may lie in the use of various anti-adhesins, like therapeutic targets or foreign carriers of epitopes, capable of triggering antibodies against various factors of virulence.

Using new *C*-glycosidation methods combined with 'click chemistry', a series of *C*-mannosides was synthesized. The potential inhibition of FimH adhesion by these glycomimetics will bring valuable information for the basis of a major structure-activity relationship (QSAR).

Key words: antibiotic, adhesion, lectin, FimH, *C*-glycosidation, click chemistry

# INTRODUCTION

Since the rise of the earliest civilizations mankind has tried to treat bacterial infections with mixed success. Treatments have included use of moldy bread or garlic on wounds to prevent infections in ancient Egypt and China as well as bloodletting and herbal mixtures for treatment of plague in medieval Europe. Although Arabic physicians had knowledge about the benefits of clean environments and fresh air when treating patients as early as the 8th century, illnesses were commonly thought to be caused by evil spirits or imbalance of the four body fluids, blood, phlegm, black bile and yellow bile as stated by the Greek physician Hippocrates. It was not until the late 19th century, through the work of Pasteur and Koch among others, that infectious disease was found to be caused by microbes not visible to the eye. In the forthcoming years advances with vaccinations and chemical preparations led to treatment of bacterial infections like anthrax and syphilis. Eventually the broad-spectrum antibiotics Penicillin and Sulfa drugs were introduced through the efforts of Fleming, Florey, Chain, and Domagk in the mid 1930's. Since then, thousands of new antibacterial agents have been discovered and introduced, giving mankind the ability to battle any given bacterial infections and saving millions of lives each year. However, over- and under consumption of these drugs, in combination with the quick cell cycle of bacteria and their rapid ability to mutate, has led to bacterial strains resistant to many known antibiotics, making it crucial to find new therapies to prevent bacterial infections. [1]

# A Escherichia coli

***Escherichia coli***, usually abbreviated to ***E. coli***, (coli is Latin for "of the colon") discovered by Theodor Escherich, a German pediatrician and bacteriologist, is one of the main species of bacteria that live in the lower intestines of mammals, known as gut flora. Specimens have also been located on the edge of hot springs. According to the US Department of Health and Human Services Centers for Disease Control and Prevention, the *E. coli* strain O157:H7, one of hundreds of strains of the bacterium *E. coli*, causes illness in humans. Presence in surface water is a common indicator of fecal contamination. It belongs among the Enterobacteriaceae and is commonly used as a model organism for bacteria in general. One of the root words of the family's scientific name, "enteric", refers to the intestine, and is often used synonymously with "fecal"

The number of individual *E. coli* bacteria in the feces that a human excretes in one day averages between 100 billion and 10 trillion. All the different kinds of fecal *coli* bacteria, and all the very similar bacteria that live in the ground (in soil or decaying plants, of which the most common is *Enterobacter aerogenes*), are grouped together under the name *coliform* bacteria. Technically, the "coliform group" is defined as all the aerobic and facultative anaerobic, non-spore-forming, Gram-negative, rod-shaped bacteria that ferment lactose with the production of gas within 48 hours at 35 °C (95 °F). In the body, this gas is released as flatulence. *E. coli* cells are elongated, 1–2 $\mu$m in length and 0.1–0.5 $\mu$m in diameter.

*E. coli* can cause several intestinal and extra-intestinal infections such as urinary

tract infections or UTIs (meningitis, peritonitis, mastitis, septicemia and gram-negative pneumonia etc). [2]

UTIs are serious health problems being the second most common of all bacterial infections. UTIs account for approximately 15% of all antibiotic consumption at a cost of $2 billion each year in the US alone. Uropathogenic *Escherichia coli* (UPEC) is the most common cause of infections both in the urethra (urethritis) and the bladder (cystitis) in the lower urinary tract, as well as the more severe infections in the kidneys (pyelonephritis) that can develop if the infection is not treated in time.

One of the most important virulence factors in bacteria is their ability to adhere to cell tissues. Many Gram-negative bacteria depend on adhesive, supramolecular protein appendages that extend from the bacterial surface, so called pili, to recognize, attach to and invade host cells. Once inside an environment rich in nutrients they can start to replicate which in turn triggers the host's immune response and consequently causes an inflammation.

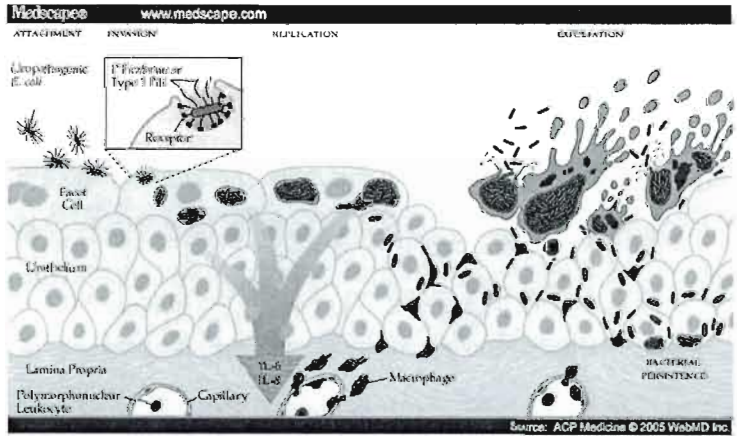



**Figure 1**. The pathogenic cascade in UTIs. Pili are required for the adherence (1) and invasion (2) of the host and have been proposed to be necessary for both biofilm formation in pods (3) and to trigger apoptosis (4). Recurrent infections may come from bacteria that have been in hibernation since a previous infection.

E. coli displays a variety of adhesins and adhesive organelles on their surfaces, one of the most important being type 1 pili. Adhesins at the tip of type 1 pili (FimH) constitute unique carbohydrate receptors and are responsible for the attachment to mannose residues on glycoproteins in the bladder.

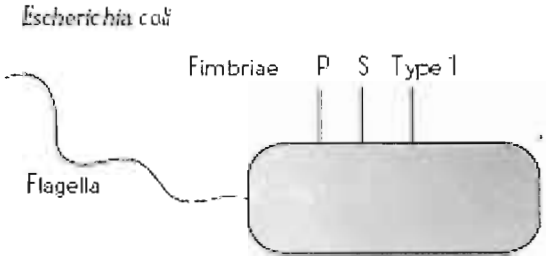



**Figure 2.** The pilis type of E. Coli

## B Targeting adherence as an antimicrobial chemotherapy

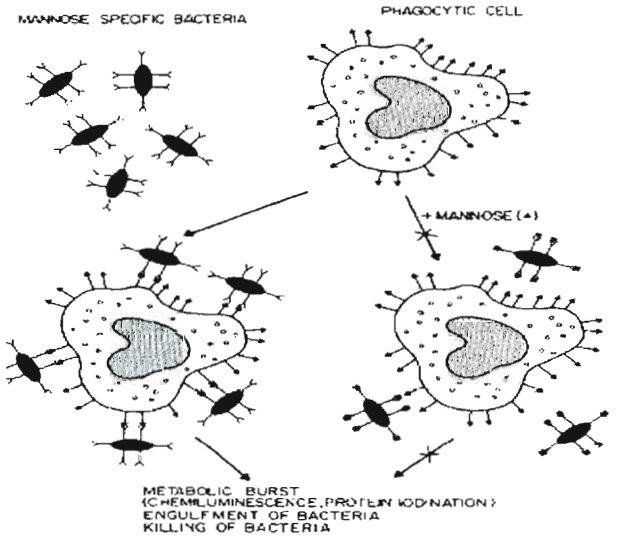



**Figure 3.** The mechanism of antimicrobial chemotherapy [3].

Targeting the bacteria's ability to adhere to host cells is a very attractive way to prevent and treat bacterial infections, offering many advantages over conventional antimicrobial treatments. The most commonly used antibiotics today are either bacteriocidic, i.e. they kill the bacteria by targeting for instance the synthesis of the bacterial cell wall (e.g. penicillin), or bacteriostatic, which means that they inhibit cell growth and replication by interrupting the bacterial metabolism such as biosynthesis of the vitamin folic acid (e.g. Sulfa drugs). Since both types of treatments result in that non-resistant bacteria do not multiply or are killed off they leave room for resistant strains to flourish, hence resulting in an evolutionary pressure on the bacteria that are beneficial for mutant strains that have gained resistance to the drugs.

However, if the bacterial pathogenicity is targeted, the microbe will only be disarmed, i.e. unable to cause an infection but otherwise thriving. This will ease the natural selection making it harder for resistant strains to emerge. Targeting highly conserved adherence mechanisms would also be advantageous since the preservation of those mechanisms alone indicates that viable mutations in these pathways are less likely to occur. Furthermore, given that the pilus assembly is highly conserved within different kinds of bacteria, it provides the opportunity to develop broad-spectrum chemotherapies.

## C The structure of FimH

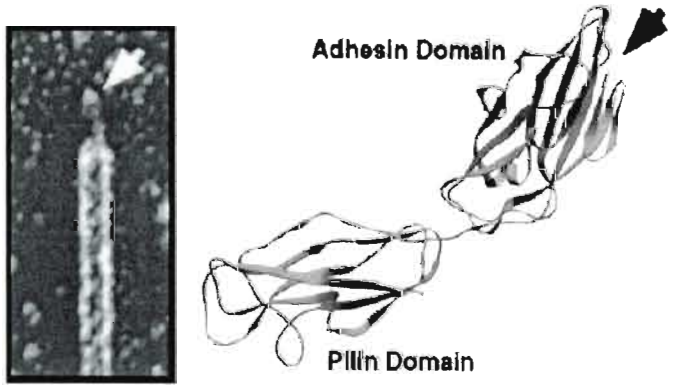



**Figure 4:** The crystalline structure of FimH. [4]

Gram-negative pathogens, *E. coli* can express a number of adhesive organelles assembled by several distinct pathways allowing them to target and colonize specific niches in the host. Type 1 fimbriae (*Fim*) is a well characterized adhesin of *E.coli.* Of the various E.Coli adhesins, type 1 pili, by far the most prevalent, bind to high-mannose glycoproteins. FimH is a two-domain adhesin protein at the end of the tip fibrillum, responsible for the mannose sensitive bacterial adhesion. The amino-terminal lectin domain (residues 1–158) is joined to the carboxy-terminal pilin domain (residues 159–279) that links the adhesin to the rest of the pilus. FimH mediated adhesion can be inhibited by D-mannose (Old,1972; Hung *et al.*, 2002) and a variety of natural and synthetic saccharides containing terminal mannose residues (Firon *et al.*, 1982; 1983; 1984; 1987; Neeser *et al.*,1986; Lindhorst *et al.*, 1998; Nagahori *et al.*, 2002). Blocking of the FimH–receptor interaction has been shown to prevent bacterial adhesion to the epithelium and thereby infections

(Langermann *et al.*, 1997; 2000; Thankavel *et al.*, 1997; Langermann and Ballou, 2003). [5]

By crystal structures of the FimH lectin domain of E. coli, one found butyl α-D-mannoside in the mannose binding site and furthermore simple alkyl mannosides bind with nanomolar affinities to FimH. This indicated that small-molecule inhibitors, targeting with high-affinity the FimH mannose binding site, may prevent infections by interfering with the attachment of E. coli to the cells

**Table 1.** Kd and calculated $\Delta G^0$ for a series of alkyl and aryl mannosides.

| Ligand | $K_d$ SPR (nM) | $\Delta G^\circ$ SPR (kcal mol$^{-1}$) | $K_d$ displace (nM) | $\Delta G^\circ$ displace (kcal mol$^{-1}$) |
|---|---|---|---|---|
| Mannose | $2.3 \times 10^3$ | −7.6 | $4.1 \times 10^3$ | −7.3 |
| Methyl$\alpha$man | $2.2 \times 10^3$ | −7.7 | $2.4 \times 10^3$ | −7.6 |
| Ethyl$\alpha$man | $1.2 \times 10^3$ | −8.1 | 730 | −8.3 |
| Propyl$\alpha$man | 300 | −8.9 | 400 | −8.7 |
| Butyl$\alpha$man | 151 | −9.3 | 150 | −9.3 |
| Pentyl$\alpha$man | 25 | −10.4 | 200 | −9.1 |
| Hexyl$\alpha$man | 10 | −10.9 | 100 | −9.5 |
| Heptyl$\alpha$man | 5 | −11.3 | 32 | −10.2 |
| Octyl$\alpha$man | 22 | −10.4 | 28 | −10.3 |
| PNP$\alpha$Man | 44 | −10.0 | 26 | −10.3 |
| MeUmb$\alpha$Man | 20 | −10.5 | 12 | −10.8 |

The SPR and displacement binding experiments define heptyl α-D-mannopyranoside as the best binder.

## D Mannose binding pocket

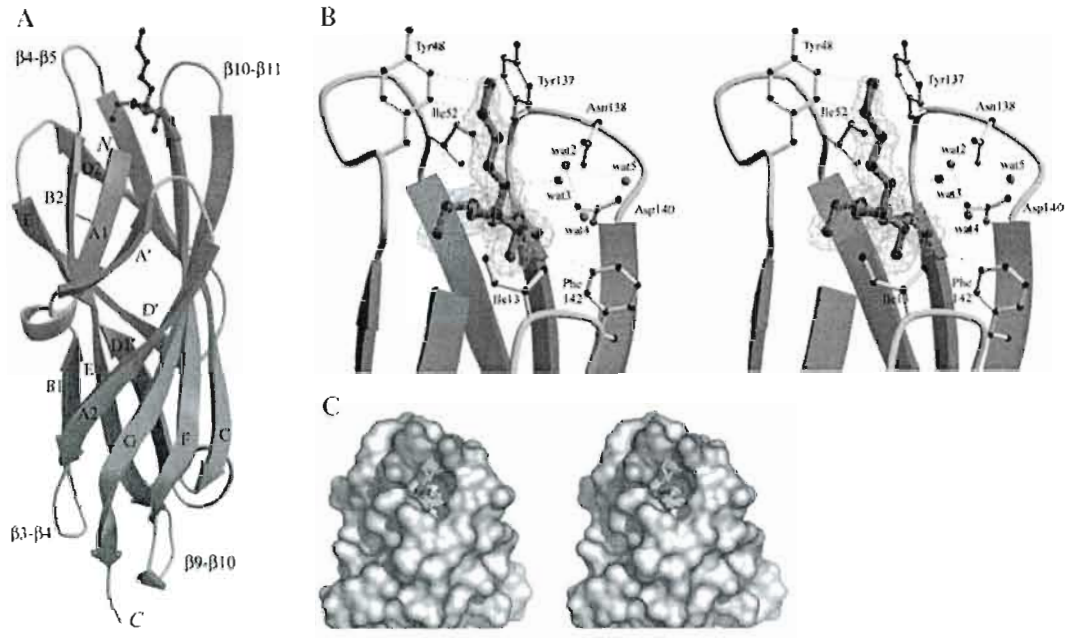



**Figure 5:** Stereo views of FimH.

A Three-dimensional structure of the FimH lectin domain is an elongated 11-stranded (-barrel with an immunoglobulin fold.

B Focus on the mannose-binding pocket, in the same orientation as (A), showing the hydrophobic contacts (within 4.6 Å, orange) with butyl a-D-mannoside and the water network (salmon pink) present at O1.

C Surface presentation (wheat yellow) of the different alkyl conformations of the butyl (-D-mannoside in the crystal structures of FimH truncates 1 and 2: FimHtr1 butyl group (cyan), FimHtr1 Tyr48 (marine blue), FimHtr2 butyl group and Tyr48 (salmon pink), Tyr137 (violet), Ile52 (pink).

As described previously (Hung et al., 2002), the mannose ring makes 10 direct hydrogen bonds to the side-chains of residues Asp54, Gln133, Asn135 and Asp140,

and to the main chain of Phe1 and Asp47, and indirect water-mediated hydrogen bonds via O2 to the side-chain of Glu133 and to the main chain oxygen of Phe1 and Gly14. The alpha-anomeric hydroxyl group O1 of mannose is involved in a hydrogen-bonding water network with the Asn138 and Asp140 side-chains, through a water molecule (wat 2, **Figure 5.** B) that is conserved between the two truncate structures. The positions of the other water molecules participating in this network depend on the crystal packing of FimHtr1 and FimHtr2.

## E Interactions of the butyl Aglycon with FimH

The butyl moiety of butyl α-D-mannopyranoside extends out of the mannose-binding pocket towards Tyr48 and Tyr137, making van der Waals contacts to both tyrosine rings and Ile52 (**Figure 5.** B and C). These residues are part of two loops (b4–b5 and b10–b11) that form the higher rear end of a hydrophobic collar around the binding site (**Figure 5.** A and B). In both subunits of the FimHtr2 (FimH truncate 2, from the E. coli K-12 laboratory strain MG1655) structure, the Tyr48 and Tyr137 side-chains are in the same, almost parallel, orientation as in the FimC:FimH structure, forming a gatelike structure at the back of the binding site (**Figure 5.** C). The closest hydrophobic interactions (3.1–3.6 Å) with the alkyl chain are made between Tyr48 and the two non-terminal atoms of the butyl group. In the FimHtr1 (FimH truncate 1, originating from the UPEC strain J96) structure, a crystal contact to Val155 of a neighbouring molecule prevents the parallel orientation of the Tyr48 ring, which instead is packed edge-to-face with Tyr137 (**Figure 5.** B). The repositioning of Tyr48 is accompanied by a change in the conformation of the butyl chain of the ligand, with the butyl chain in a more extended conformation than in the FimHtr2

structure, and with the four carbon atoms nearly in one plane (**Figure 5.** B and C). The new conformations of Tyr48 and the butyl moiety result in an almost parallel stacking of the aromatic ring of Tyr48 onto the butyl plane, with the closest hydrophobic interactions (3.7 Å) involving the two terminal carbon atoms of the butyl (**Figure 5.** B).

Surface plasmon resonance, as well as equilibrium binding, indicate that FimH binds butyl α-D-mannoside 15–30 times stronger than α-D-mannose. The importance of the added hydrophobic contacts is clearly demonstrated by the binding of alkyl mannosides (Table 1). The best binding alkyl mannosides bind a few hundred times stronger than mannose.

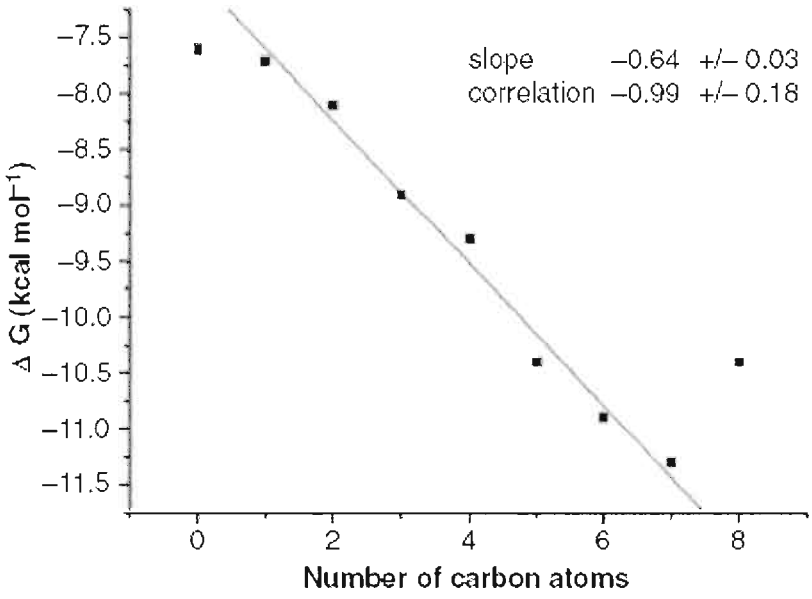



**Figure 6:** Linear free energy relationship for the alkyl chain on alkyl mannoside. A linear fit was made, using 1 up to 7 methyl groups, with the program MICROCAL ORIGIN 5.0.

Interestingly, the butyl moiety takes on significantly different conformations in FimHtr1 and FimHtr2 (**Figure 5.**C), indicating that intrinsic conformational flexibility in the aglycon is allowed. Indeed, in spite of the larger flexibility expected for longer alkyl mannosides, the binding energy increases linearly with increasing length of the alkyl chain between one and seven carbon atoms (**Figure 6**). The affinity reaches its maximum for mannoside with a seven-carbon alkyl, heptyl α-D-mannopyranoside and SPR measurements suggest that the affinity decreases from eight carbon atoms on. Evidently, the eighth carbon atom goes beyond the hydrophobic interaction surface and protein edge, which is penalized with a decrease in affinity. We propose that the affinity increase results from an increased interaction surface with the hydrophobic gateway. Alkyl aglycons fit well in the tyrosine gate and, as observed in the two crystal structures, in at least two different conformations that depend on the conformation of Tyr48. Nevertheless this flexibility may indicate that aglycons can interact rather non-specifically with the hydrophobic gateway, resulting in a 100- to 1000-fold increase in affinity.

## F C-Mannosides

All molecules we have discussed above are *O*-mannosides which, unfortunately, aren't stable *in vivo since*, they can be hydrolyzed by enzymes. Therefore, we have to synthesize another series of *C*-mannosides which are more stable *in vivo* than *O*-mannosides.

# G C-Glycosides

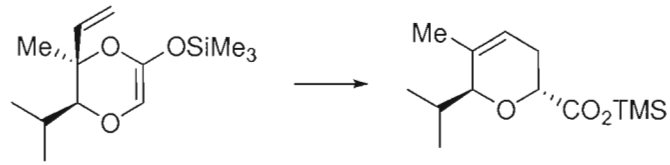
## I. INTRODUCTION

C-glycosides in which the glycosidic oxygen is replaced by a carbon atom, are an important branch of sugar chemistry. Many routes are available for their synthesis and a few are presented herein.

## II. CONCERTED REACTIONS

### II.1 Sigmatropic Rearrangements

**Scheme 1**



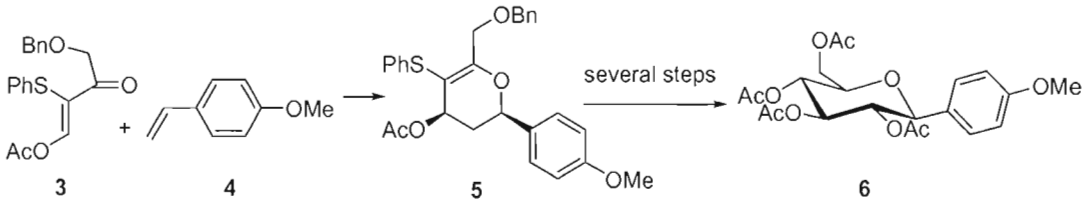

**1** **2**

Silyl enol ether **1** was converted to **2** by Claisen methodology to stereospecifically synthesize a C-glycoside (Scheme 1). [6]

### II.2 Cycloadditions

The Diels-Alder reaction, which is possibly the most important reaction in organic chemistry, has also found application in C-glycoside synthesis.

**Scheme 2**



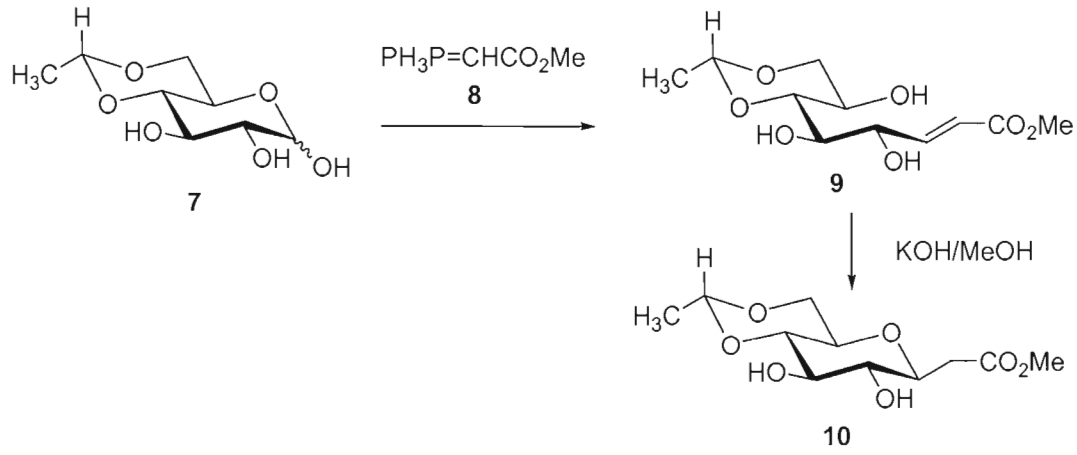

The cycloadduct **5** is formed in good yield by reaction of hetero diene **3** with the substituted styrene **4** and further steps gave the C-glycoside **6.** [7]

## III. WITTIG APPROACHES

The Wittig reaction has also been extensively applied to *C*-glycoside syhthesis. Ylides can react with lactols to yield open chain sugars which either *in situ* to produce a *C*-glycoside, or can be isolated and cyclized via other means Both Wittig like reactions on sugar lactones and reactions of anomeric phosphoranes with suitable carbonyl compounds have been used to construct exo-methylenic sugars.

**III.1** Reactions of Hemiacetals followed by ring Closure.

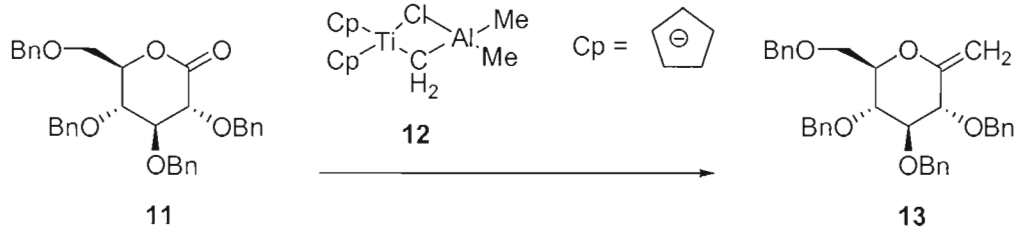
**Scheme 3**




Reaction of compound **7** with Wittig reagent **8** gave compound **9** in good yield. Addition of **9** to potassium hydroxide in methanol produced mainly the β-isomer **10.** [8]

**III.2** Reactions of Sugar Lactones

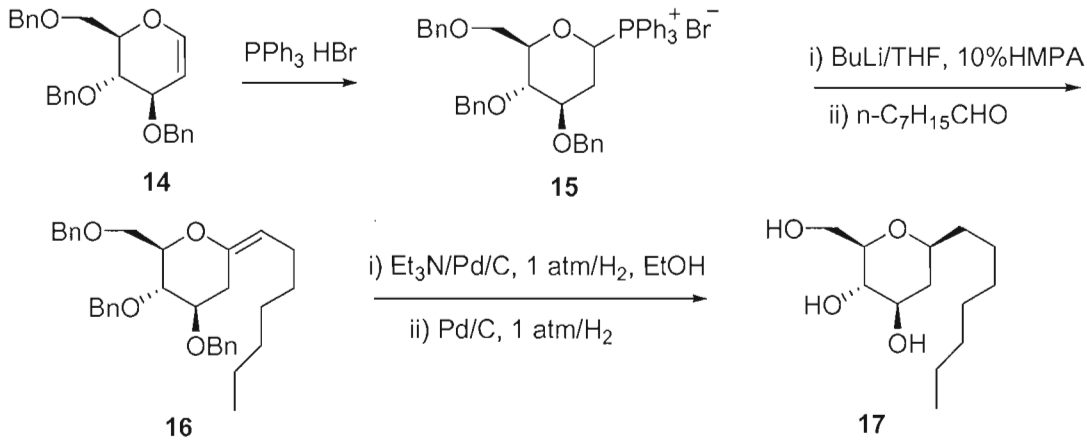
**Scheme 4**




Latone **11** is treated with Tebbe's reagent **12**, and the exo-methylenic sugar **13** is produced. [9]

### III.3 Reactions of Anomeric Phosphoranes

**Scheme 5**



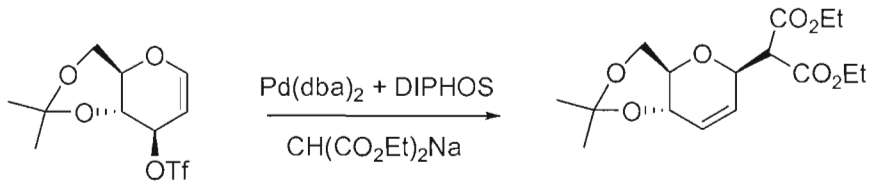

**14** **15** **16** **17**

The Wittig reagent was derived from the sugar itself, to give the phosphonium bromide **15**. This material was then deprotonated and treated with octanal to form the C-glycoside **16**. Reduction of the double bond followed by benzyl group removal afforded the 2-deoxy-C-glycoside**17.** [10]

## IV. PALLADIUM MEDIATED REACTIONS

### IV.1 π-Allyl Complexes

**Scheme 6**

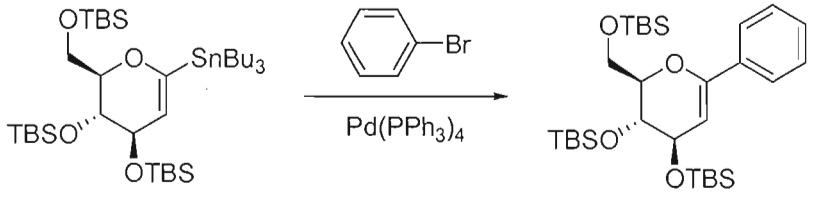



**18** **19**

The reaction of **18** with the enolate of malonic ester was carried out in THF in the presence of bis(dibenzylideneacetone)-Pd(O) and bis(diphenylphosphino)ethane and gave **19** in 56% yield. [11]

**IV.2** Stille Couplings

**Scheme 7**



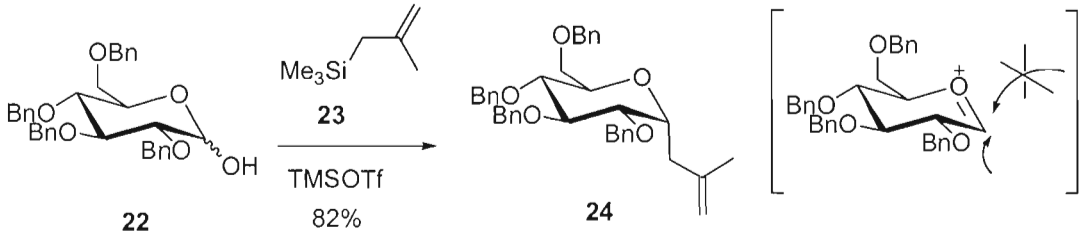

**20** **21**

Stannane **20** reacted with bromobenzene in THF in the presence of palladium catalyst to give **21** in 70% yield. [12]

## V. SUGAR ELECTROPHILES

**V.1** Lactols (Sakurai reaction)

**Scheme 8**

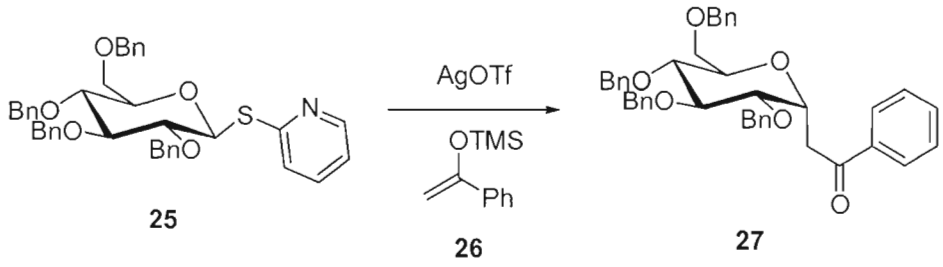



**22** **24**

The reaction of compound **22** with 2-methyltrimethylallylsilane **23** was carried out in the presence of the Lewis-acid, the main product, the α-isomer was formed in 82% yield. This facial preference is due to axial attack, under the influence of the anomeric effect, on the pyroxonium triflate. [13]

## V.2 Glycosides

**Scheme 9**

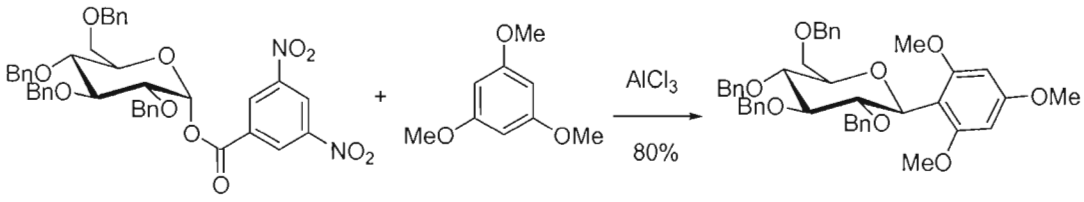



**25** **26** **27**

Treatment of the thiopyridyl glycoside **25** with silyl enol ether **26** in the presence of silver triflate produced the C-glycoside **27.** [14]

## V.3 Anomeric Esters

**Scheme 10**

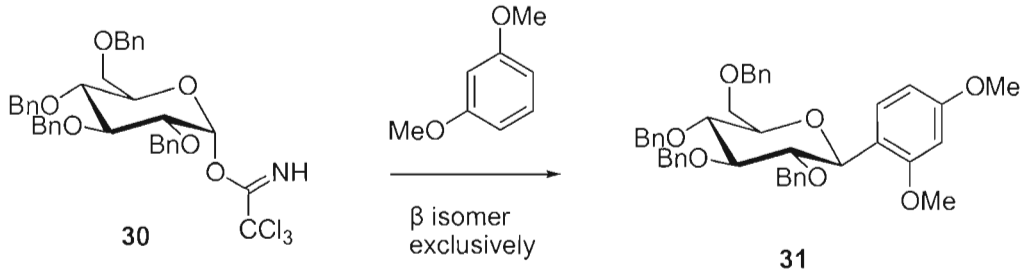



**28** **29**

Treatment of activated glucopyranosyl ester **28** with 1,3,5-trimethoxybenzene in the presence of aluminum trichloride gave the β-isomer **29** in 80% yield. This type of methodology provides access to oxygenated aryl C-glycosides. [15]

## V.4 Anomeric Imidates

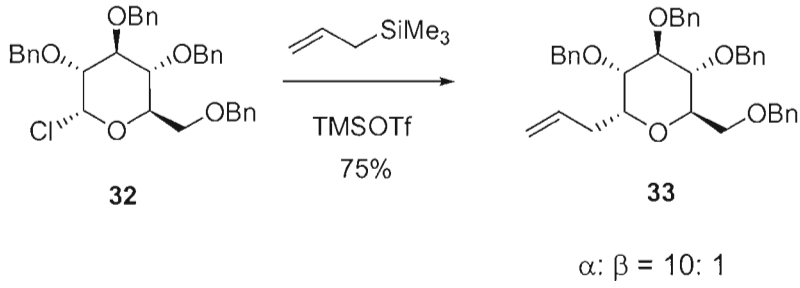
**Scheme 11**




Reaction of the glucosyl imidate **30** with 1,3-dimethoxybenzene in the presence of boron trifluoride etherate gave the β-isomer **31** exclusively. [16]

## V.5 Glycosyl Halides

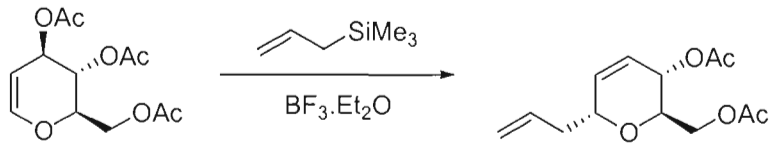
**Scheme 12**



The use of pyranosyl chlorides in Lewis-acid catalyzed allylations also provides good yields of α-C-glycosides. Treatment of compound **32** with trimethylallylsilane in the presence of trimethylsilyl triflate provides a 75% yield of both anomers, with the α-anomer **31** favored by a factor of 10:1. [17]

## V.6 Glycals

**Scheme 13**

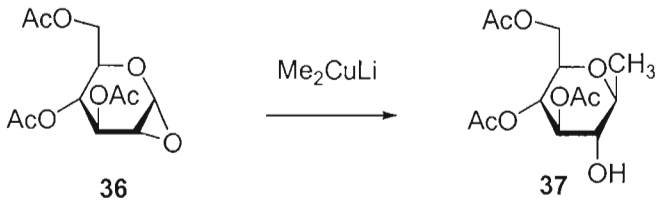



**34** **35**

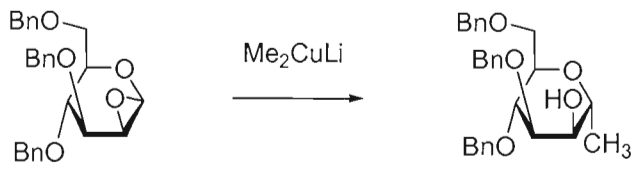
Allylation of **34** under standard conditions described above gave the expected product **35.** [18]

## V.7 Enitols & Anhydro Sugars

**Scheme 14**




**36** **37**

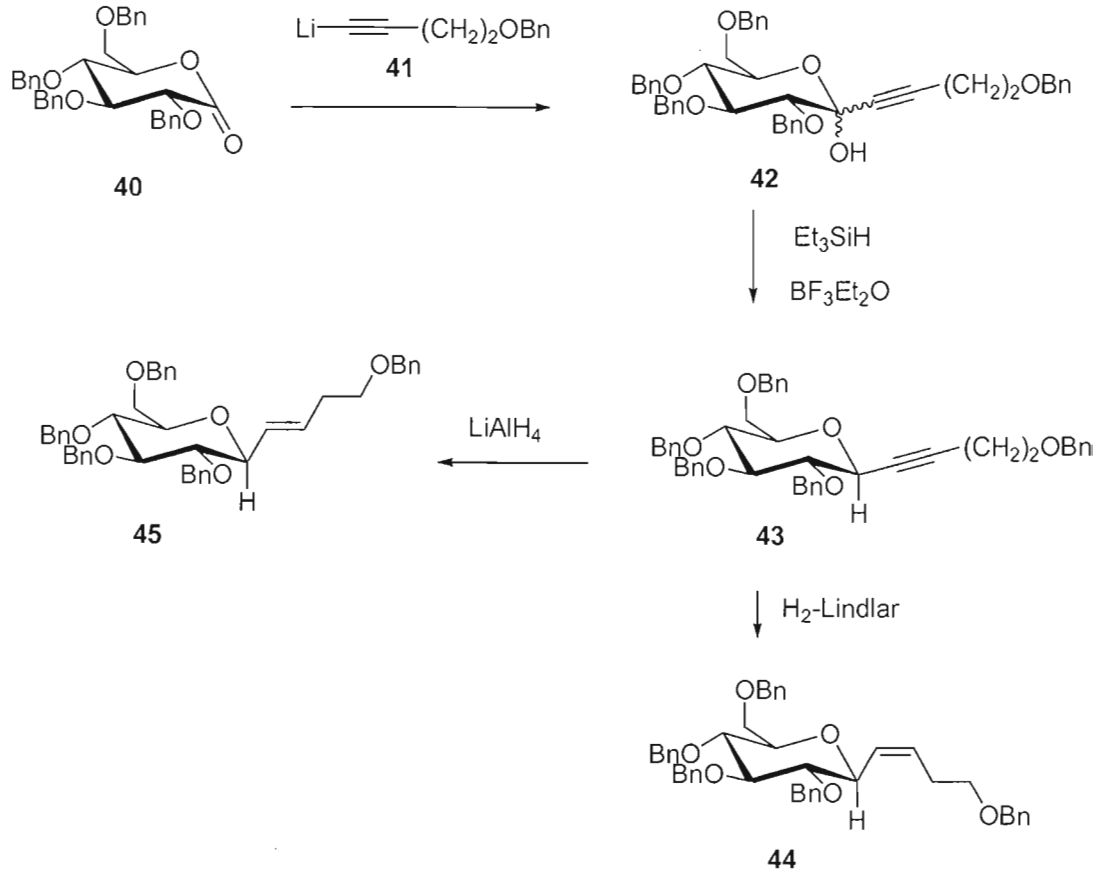



**38** **39**

1,2-Anhydro sugars can also serve as useful precursors to C-glycosides. Reaction of 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose **36** with lithium dimethylcuprate in diethyl ether provided **37**. The reaction proceeds by attack at C-1. Likewise in the *manno* series, reaction of **38** gave compound **39.** [19]

**V.8** Sugar Lactones (Kishi's reaction)

**Scheme 15**

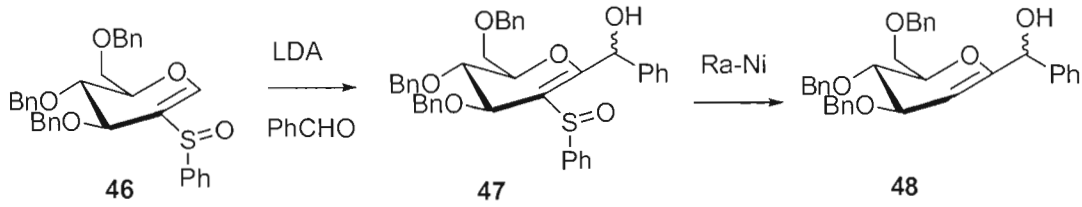


Addition of the lithium acetylide **41** to the protected gluconolactone **40** gave a mixture of epimers **42**. Stereoselective reduction with triethylsilane and boron trifluoride etherate then gave β-anomer **43** as the exclusive product. Then the triple bond can be manipulated to give either the Z-isomer **44** or the E-isomer **45.** [20]

## VI. NUCLEOPHILIC GLYCOSIDES

### VI.1 C-1-Lithio Derivatives

**Scheme 16**

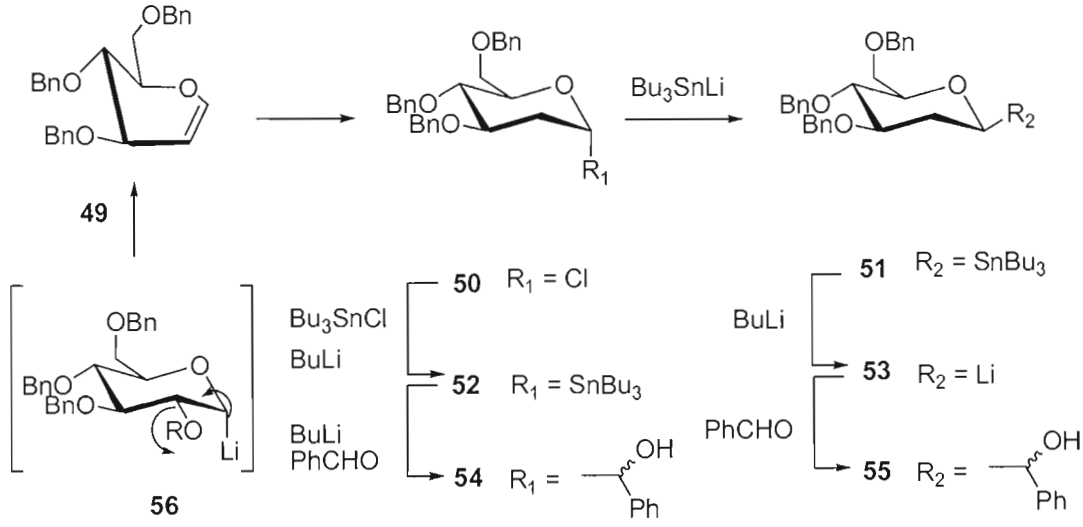



**46** **47** **48**

An unsatuated sulfoxide **46** which is deprotonated with LDA and subsequently treated with benzaldehyde afforded the C-glycoside **47**. The reaction of Raney nickel on **47** gave the desulfurized product **48.** [21]

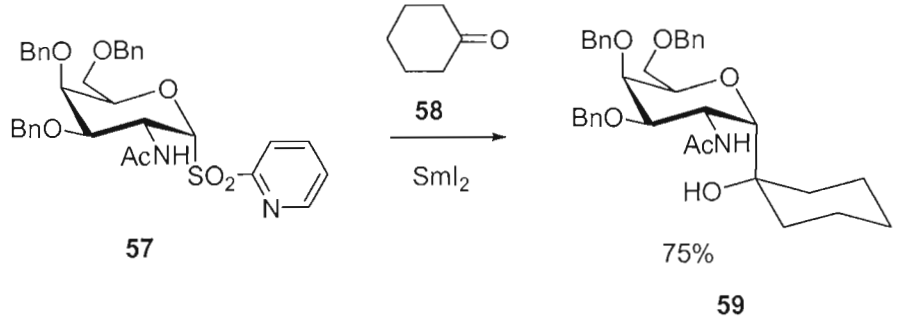
### VI.2 Anomeric Stannanes

**Scheme 17**



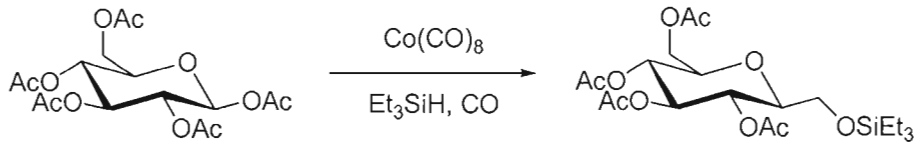

**49** can be converted either to the α- or β-tin glycosides. Treatment of **51** or **52** with n-butyllithium and reaction with an appropriate electrophile then yields **54** and **55**. It should be noted that both the α- and β-tin glycosides are available from the same readily available α-pyranosyl chloride. However, this method is restricted to 2-deoxyglycosides since an intermediate anion of structure **56** would undergo elimination as shown above. [22] However this can be avoided by the use of $SmI_2$, and glycosyl sulfones. [23]

**Scheme 18**



**VI.3** Anomeric Transition Metal Complexes

**Scheme 19**

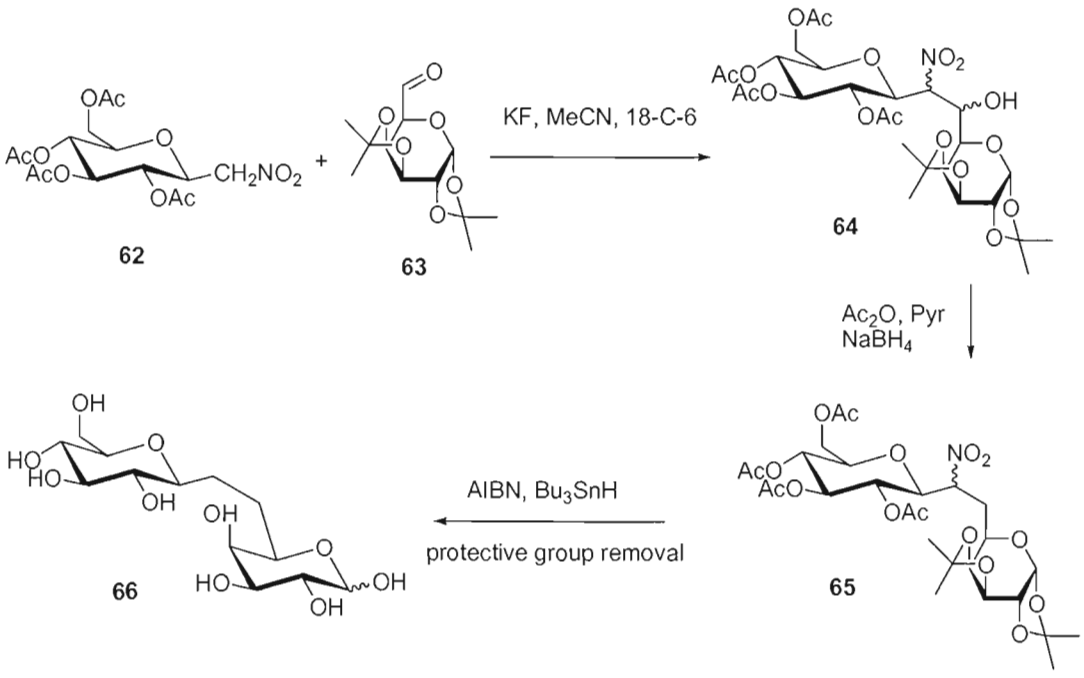



**60** **61**

A number of other transition metals have been used to construct C-glycosides, and Scheme 19 shows a simple method for generating a C-glycoside in a highly stereospecific manner. Reaction of 1,2,3,4,6-penta-O-acetyl-β-D-glucose **60** with $Co(CO)_8$ in the presence of triethylsilane and carbon monoxide gave the C-glycoside **61.** [24]

**VI.4** Nitro Compounds.

**Scheme 20**

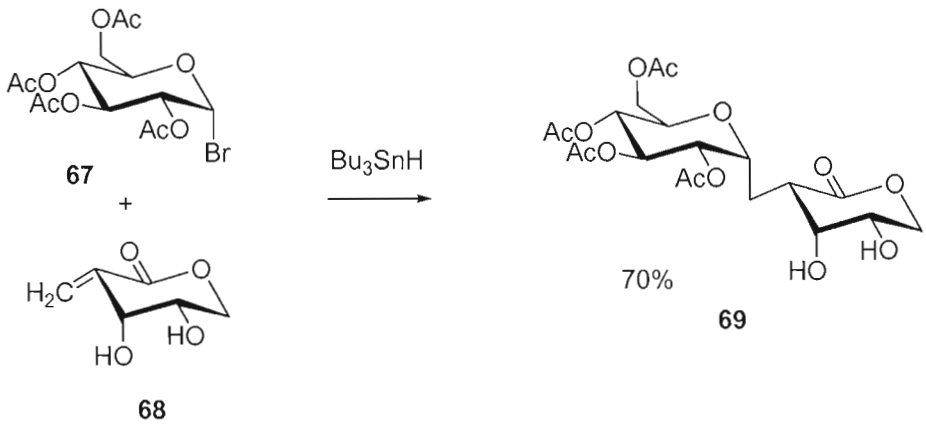



If the interglycosidic oxygen in a disaccharide is replaced by a methylene unit, one obtains a non-metabolizable *C*-disaccharide. Nitroaldol condensation of **62** with aldehyde **63** in acetonitrile, containing potassium fluoride and 18-Crown-6, afforded the aldol product **64**. Acetylation, elimination, and reduction of the double bond by the action of sodium borohydride furnished **65** as a mixture of epimers. Tin hydride reduction of the nitro group followed by deprotection gave the *C*-glycosides **66.** [25]

## VII. FREE RADICAL APPROACHES

### VII.1 Intermolecular Additions

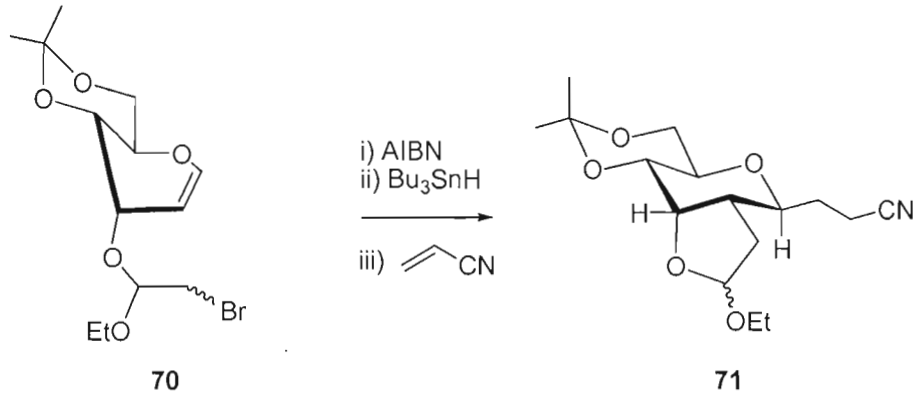
**Scheme 21**




Reaction of glucosyl bromides **67** with **68** and tributyltin hydride under photolytic conditions gave the *C*-glycosides **69.** [26]

**VII.2** Intramolecular Additions

**Scheme 22**




Reaction of **70** under free radical conditions with acrylonitrile afforded, in good

yield, compound **71.** [27]

## H Rational design

Rational design is the term used for a wide variety of different methods where structural knowledge of the drug target and/or a known ligand is used to virtually design compounds with a potentially better biological response.

## I Structure based design

A model of the drug target, derived either by X-ray crystallography, solution NMR spectroscopy or homology models made from a known protein of a similar class, is used as a template for the design of potential binders. By examination of the receptors, various molecular scaffolds can be appropriately substituted to directly exploit the structural characteristics of the receptor binding site. Hence, a good match with the receptor in regards to steric fit, complementary surfaces, hydrogen bonding, and so forth can be achieved. Suitable scaffolds can be obtained in different ways, often depending on the circumstances; modification of a known ligand, so called structure based ligand design, is an approach that has a high probability of success and is most often used when the structure for a ligand-receptor complex is known. If only the structure of the receptor is known, other approaches such as virtual screening, *i.e.* sampling of databases of molecular structures through the receptor, or *de novo* design, where the molecule is spawned from a seed structure within the active site, needs to be considered.

Structure based design has several weaknesses such as the difficulty to

correctly predict the affinity of the virtual complex and the fact that simplistic assumptions of the conformational change of both the ligand and the receptor upon binding often have to be made to speed up calculations. However, there are still several drugs on the market, such as HIV-potease inhibitors (e.g. Indinavir, Ritonivir) and the influenza drug Relenza, that authenticate the effectiveness of structure based design.

The aims of this thesis are the design, synthesis, and biological evaluations of compounds targeting adherence in *E. coli*, by inhibiting the binding of FimH pili to epithelial host cells. Efforts have been put into the synthesis of compounds targeting carbohydrate receptors for the type 1 pili adhesin FimH thereby attempting to prevent bacterial attachment to host epithelial cells.

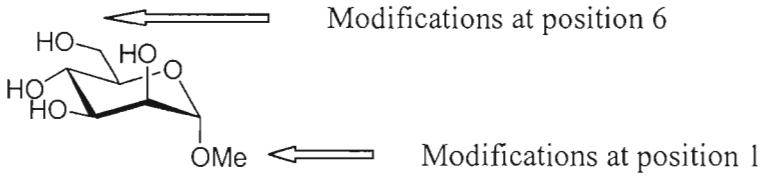
# SYNTHETIC STRATEGIES

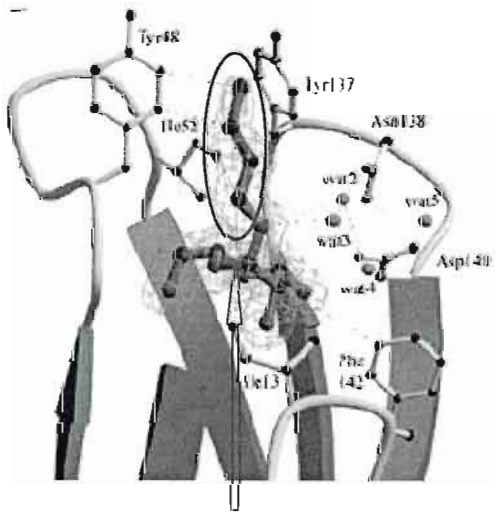
## Introduction

Taking into account the objectives defined previously, we undertook the synthesis of mannose derivatives, modified at position 1 and position 6 to increase their affinities within FimH-subunit binding site.

In literature, mannose derivatives modified at position 1 have been most successful, so we began to synthesize the derivatives modified at position 1.

**Scheme 23: synthetic strategies**



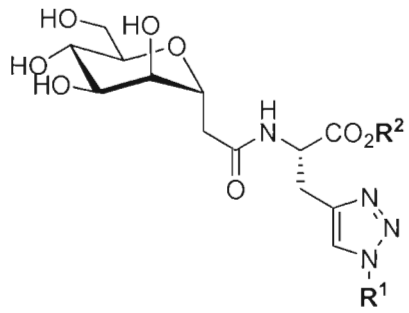

**Modifications at position 1**

**Figure 7:** Interaction between the mannoside's aglycon and of the FimH binding site.

In this figure, the butyl group at position 1 of mannose interacts with the hydrophobic gateway formed by Tyr48, Tyr137 and Ile52, so our purpose is to modify the group at position 1 to increase hydrophobic interaction (mainly π-π interactions) between the ligand and FimH.

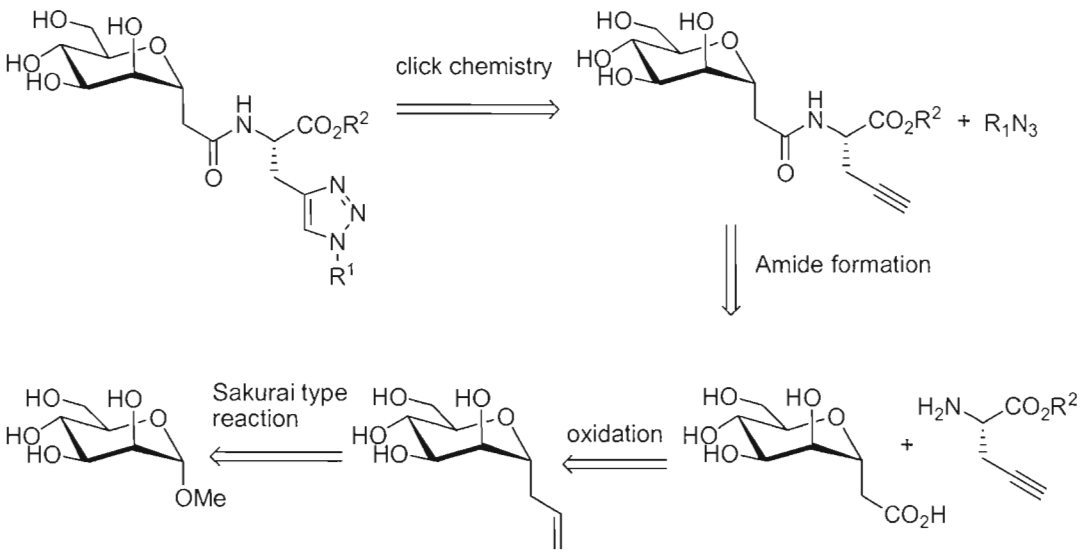
Because *O*-glycosides can be hydrolyzed by enzyme *in vivo*, we will synthesize another series of mannosides: the *C*-mannosides which are more stable *in vivo* than the *O*-glycosides. Since 'click chemistry' easily enables the synthesis of new pharmacophores, we combined these two methods to synthesize the following compounds .

**Scheme 24 : target compounds**




Retrosynthetic analysis of this compound is as follows:

**Scheme 25: retrosynthetic analysis of target compounds**



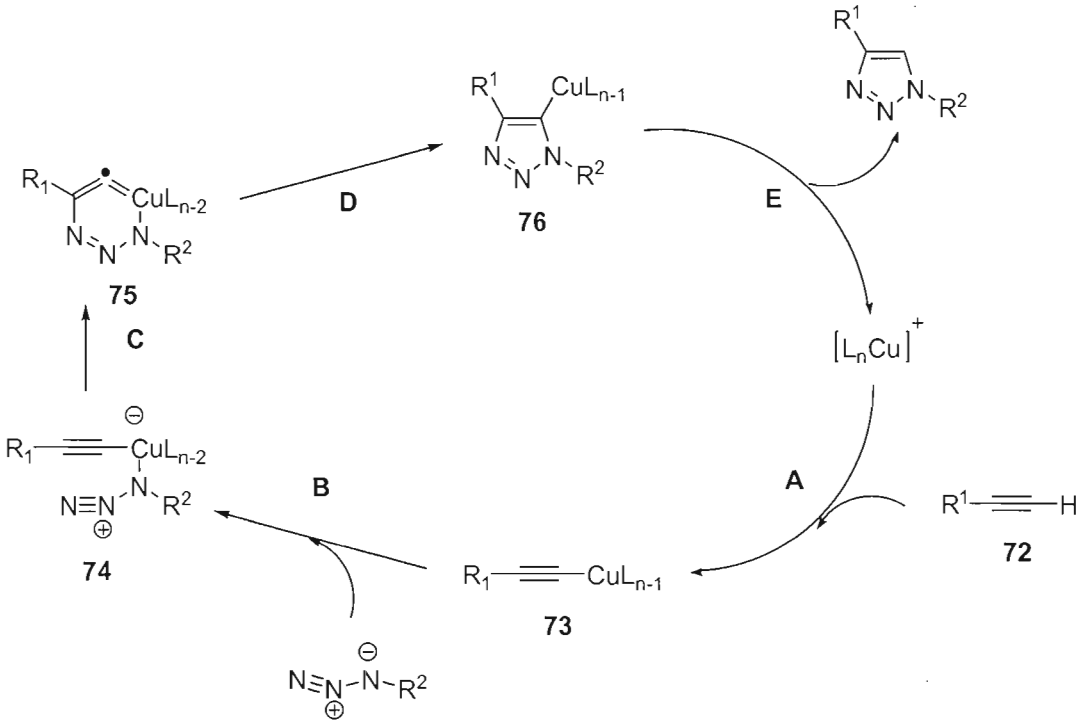

Initially, the cyclic triazoles can be formed by click chemistry; the target compounds can be broken up into two synthons: the azide and the alkyne derivatives. The alkyne compound, can be formed by propargylglycine and 2-(α-D-mannopyranosyl)ethanoic acid by amide formation reaction, The acid can be formed starting with methyl α-D-mannopyranoside via Sakurai standard reaction followed by oxidation reaction. Thus the target compound can be broken up into three synthons: **azide derivatives, propargylglycine and 2-(α-D-mannopyranosyl) ethanoic acid.**

1,2,3-Triazoles are attractive constructs, and because of their unique chemical properties and structure should find many applications in organic, orgametallic, and medicinal chemistry. Not present in natural products, they are remarkably stable to metabolic transformations, such as oxidation, reduction, and both basic and acidic hydrolysis. Furthermore, 1,2,3-triazole moieties are emerging as powerful pharmacophores in their own right. [28]

Several methods have been described for the synthesis of 1,2,3-triazoles. Among

them, the most important and useful one is the cycloaddition of azide with alkyne. Sharpless used Cu(I) salt as a catalyst to promote the reaction of azides with terminal alkynes to give, in high regioselectivity, the 1,4-substituted products. This kind of reaction is now called 'Click Chemistry'. [29]

**Scheme 26: Proposed Reaction Mechanism of click chemistry**




The first step in the mechanism of the 'Click Chemistry' is the conversion of the alkyne **72** to the copper acetylide **73**, the azide then replaces one of the ligands and binds to the copper atom via the nitrogen proximal to carbon, forming intermediate **74**. After that, the distal nitrogen of the azide in **74** attacks the C-2 carbon of the acetylide, forming the unusual six-membered copper (III) metallacycle **75**. From **75**, triazolyl-copper derivative **76** is formed by ring contraction. Proteolysis of **76** releases the triazole product, thereby completing the catalytic cycle. [30]

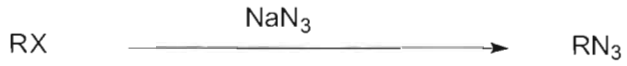
We then synthesized these three synthons respectively.

# Chapter 1 Synthesis of azide derivatives

Two methods are used for the efficient single step preparation of desired azides starting from halides or amines.

## 1.1 Starting from halides, azide derivatives can be synthesized by simple $S_N2$ reactions.

**Scheme 27: Preparation of azide derivative starting from halide**




Halides were treated with sodium azide in appropriate reaction, furnishing the corresponding azide derivatives. [31]

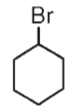
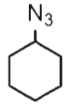
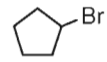
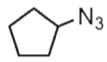
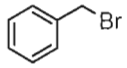
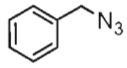
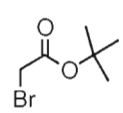
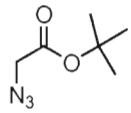
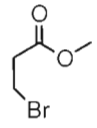
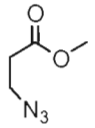
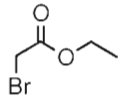
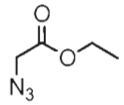
We have synthesized **a series of azide derivatives** from alkyl halides (See Table 2).

**Table 2:** Halides, corresponding azides, and reaction conditions.

| Halides | Azides | $NaN_3$ eq | Solvant | T (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| MeI | $MeN_3$ | 1.2 | $DMF/H_2O$ | 55 | 24 | 15 |
|  |  | 1.2 | $DMF/H_2O$ | 85 | 16 | 73 |
|  |  | 1.2 | $DMF/H_2O$ | 85 | 16 | 91 |
|  |  | 1.2 | $DMF/H_2O$ | 85 | 16 | 88 |
|  |  | 1.2 | $DMF/H_2O$ | 85 | 16 | 93 |
|  |  | 1.2 | $DMF/H_2O$ | 85 | 16 | 55 |

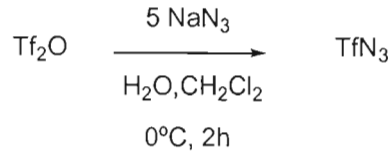
**Preparation other azides** cyclic alkyl halides, benzyl halide and ester halide, react with sodium azide catalyzed by PTC in appropriate conditions to provide the corresponding azides (Table 3)

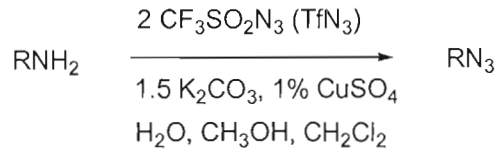
**Table 3**: Other halide, corresponding azides, and reaction conditions

| Halide | Azide | $NaN_3$ (eq) | Solvant | PTC | T (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
|  |  | 2 | $H_2O$ | $Bu_4NHBr$, 5% | 100 | 16 | 75 |
|  |  | 2 | $H_2O$ | $Bu_4NHBr$, 5% | 100 | 16 | 80 |
|  |  | 2 | $Et_2O/H_2O$ | $Bu_4NHSO_4$,10% | T.P. | 24 | Quant |
|  |  | 1.5 | $Et_2O/H_2O$ | $Bu_4NHSO_4$,10% | T.P. | 24 | 92 |
|  |  | 2 | $Et_2O/H_2O$ | $Bu_4NHSO_4$,10% | T.P. | 24 | 61 |
|  |  | 2 | $Et_2O/H_2O$ | $Bu_4NHSO_4$,10% | T.P. | 24 | Quant |

**1.2. Starting from amino acid, azides can be formed by diazotransfer reaction**

**Scheme 28: Preparation of azide derivative starting from amino acid**



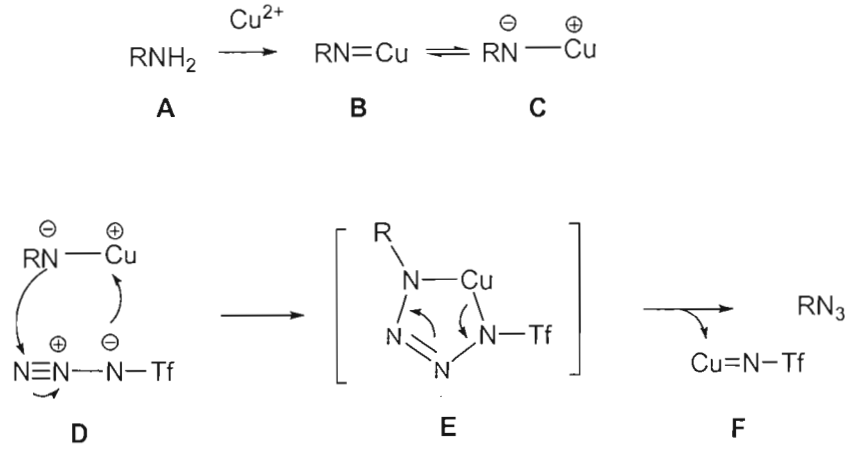



First, trifluoromethanesulfonic anhydride ($Tf_2O$) was reacted with a large excess of sodium azide in a mixed-solvent system. The crude trifluoromethanesulfonyl azide extract was then reacted with a series of amino acids, a reaction catalyzed by copper sulfate in another solvent mixture ($H_2O/CH_3OH$). The corresponding azides were obtained mostly in good yields. [32]

By this method, several amino acids and tyramine were transformed into the corresponding azides with various yields (see Table 4).

The mechanism of the diazotransfer reaction is currently unknow. Chi-Huey Wong [33] suggested a mechanism as shown in Scheme 29.

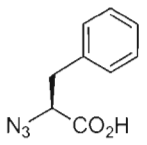
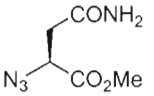
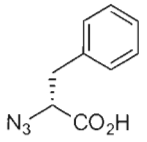
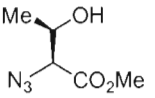
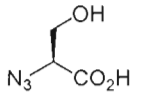
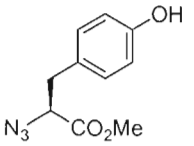
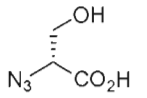
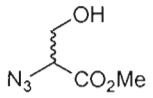
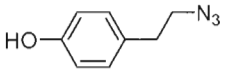
**Scheme 29: The mechanism of the diazotransfer reaction**




Amine A, complexation to the copper catalyst, under basic conditions, may provide C, nucleophilic attack by C on the highly electrophilic triflyl azide, might form the copper-stabilized mixed tetrazene E, possibly via a reverse [3 + 2] dipolar

cycloaddition, would product azide and zinc-triflyl imido complex F.

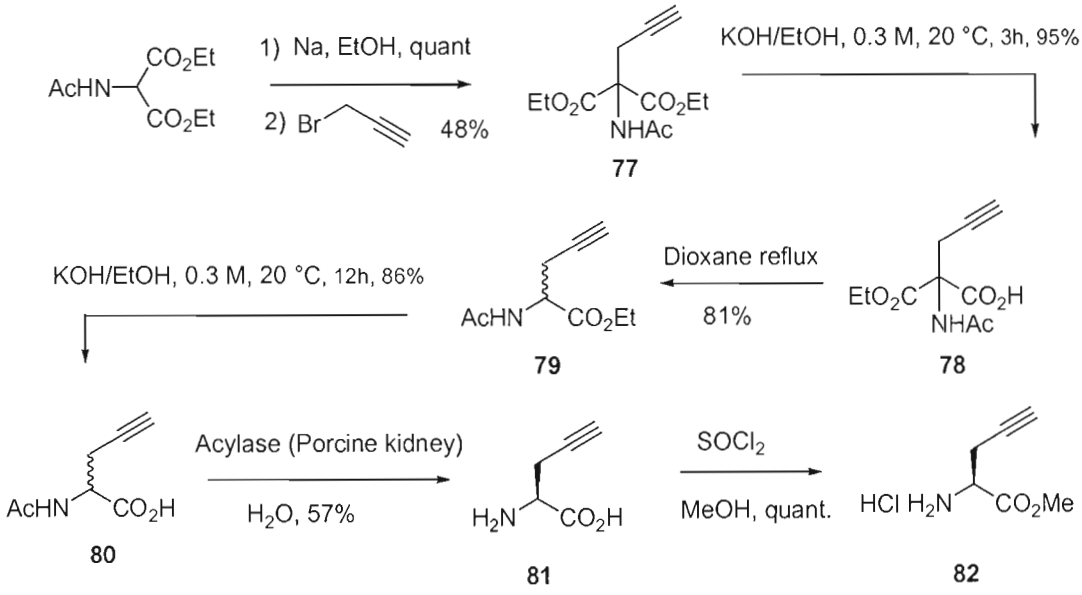
**Table 4:** Amino acids and their corresponding azides.

| Amino Acid | Azido Acid | Yield (%) | Amino Acid | Azido Acid | Yield (%) |
|---|---|---|---|---|---|
| L-Phe |  | 85 | L- Asn |  | 48 |
| D-Phe |  | 90 | L-Thr |  | 47 |
| L-Ser |  | 37 | L-Tyrosine |  | 76 |
| D-Ser |  | 66 | | | |
| D, L-Ser-Me |  | 86 | Tyramine |  | 87 |

# Chapter 2 Preparation of L-Propargylglycine methyl ester hydrochloride (L-Pra)

The titled compound was synthesized by a known method which is described below. [34]

**Scheme 30: L-Propargylglycine methyl ester hydrochloride (L-Pra)**




The first step in the synthesis of L-propargylglycine was the condensation of the sodium salt of diethyl α-acetamidomalonate and propargyl bromide to yield diethyl α-acetamido-α-propargylmalonate **77**. This was converted by the usual procedure via monoethyl α-acetamido-α-propargylmalonate **78** and ethyl D, L-N-acetyl-propargylglycinate **79** to D, L-N-acetyl-propargylglycine **80**. L-Propargylglycine **81** was obtained in good yield from **80** by stereospecific hydrolysis of the acetamide group with porcine kidney acetylase.

The enantiomeric purity of **81** was confirmed by optical rotation $[\alpha]^{20}_{D}$ -31.0 (c = 1, $H_2O$), lit: $[\alpha]^{20}_{D}$ -35.0 (c = 1, $H_2O$); melting point, 230 °C (decomp. beginning at 210 °C), lit 230 °C (decomp. beginning at 210 °C).

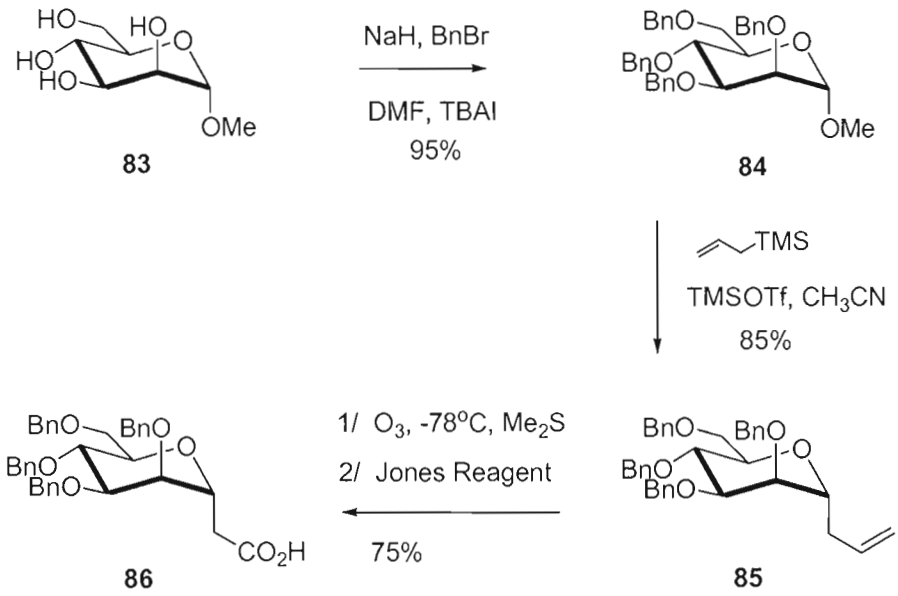
To further establish the enantiomeric purity of L-propargyl glycine obtained by enzymatic hydrolysis and to study the precision of hydrolysis carried out by porcine kidney acylase acylase, we have adopted a method to introduce another chiral centre and make the protons on L-propargyl glycine methyl ester diastereotopic which are non equivalant and than can be separated on $H^1$ NMR. In this experiment we chose Mosher acid chloride to make Mosher amide of L-propargyl glycine methyl ester and racemic propargyl glycine methyl ester and characterized by $H^1$NMR. NMR of Mosher amide of racemic propargyl glycine methyl ester has shown two sets of peaks corresponding to both the isomers of racemic propargyl glycine methyl ester at 1:1 ratio showing the presence of 1:1 mixture of both isomers, whereas in case of Mosher amide of L-propargyl glycine methyl ester there are only one set of peaks corresponding to L-propargyl glycine methyl ester indicating the presence of single isomer (see appendix 1).

Finally, **81** was esterified by methanol and thionyl chloride, to give L-Propargylglycine methyl ester hydrochloride **82**.

# Chapter 3 Preparation of 2-(tetra-O-acetyl-α-D-mannopyranosyl)ethanoic acid

The synthesis of the known titled compound is complex. First, 2-(tetra-*O*-benzyl-α-D-mannopyranosyl) ethanoic acid was synthesized using a published method.

**Scheme 31: 2-(tetra-*O*-benzyl-α-D-mannopyranosyl)ethanoic acid**

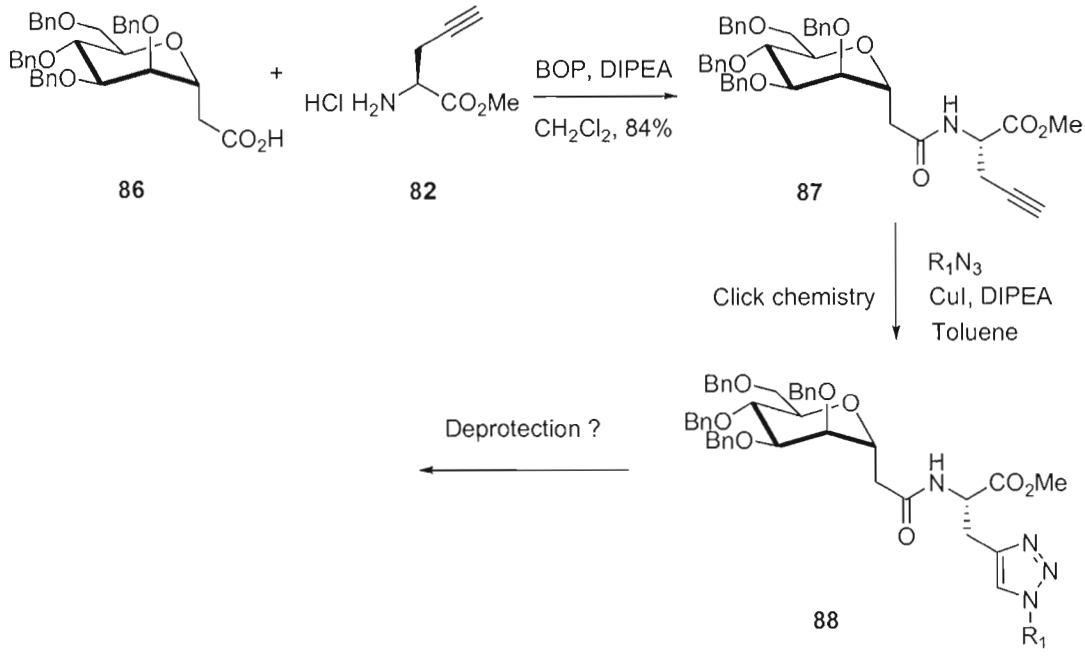



Methyl α-D-mannopyranoside **83** was protected by benzyl bromide,[35] to yield methyl 2, 3, 4, 6-tetra-*O*-benzyl-α-D-mannopyranoside **84**, which was then activated with TMSOTf and coupled to allyl trimethylsilane to provide 3-(tetra-*O*-benzyl-α-D-mannoppyranosyl)-1-propene **85.**[36] Compound **85** was oxidized by ozone and Jones reagent to afford 2-(tetra-*O*-benzyl-α-D-mannopyranosyl)ethanoic acid **86**.

By this method, we obtained the α-anomer exclusively; no trace of the β-isomer

were detected by NMR spectroscopy.

**Scheme 32: synthesis of target product**




Thus we have 2-(tetra-*O*-benzyl-α-D-Mannopyranosyl)ethanoic acid **86**, it reacted with L-propargylglycine methyl ester hydrochloride **82** catalyzed by BOP reagent. The obtained intermediary compound **87** was then reacted with a series of azides ($R_1N_3$) to obtain another series of compounds **88**.

Unfortunately, the deprotection of the benzyl group was found out to be somewhat difficult. We have tried following methods, but none of them gave a good result:

**A:** $H_2$, Pd $(OH)_2$/C, 20%, Ethanol, HCl, T.P.

Reduced with hydrogen, catalyzed with palladium hydroxide in ethanol with a little hydrochloric acid.

**B:** $H_2$, Pd $(OH)_2$/C, 20%, Hexane, EtOH, Reflux.

Reduced with hydrogen, catalyzed with palladium hydroxide in hexane and ethanol refluxed overnight;

**C:** HCOOH, Pd/C, 10%, MeOH, Reflux.

Reduced with formic acid, catalyzed with 10% palladium on carbon in methanol, refluxed overnight; [37]

**D:** $HCOONH_4$, Pd/C, 10%, MeOH, Reflux.

Reduced with ammonium formate, catalyzed with 10% palladium on carbon in methanol, refluxed overnight; [38]

**E:** $Li/NH_3$, THF, -78°C.

Reduced with lithium and liquid ammonia at -78 °C (Birch conditions)

**F:** $Br_2$, $CCl_4$, hv.

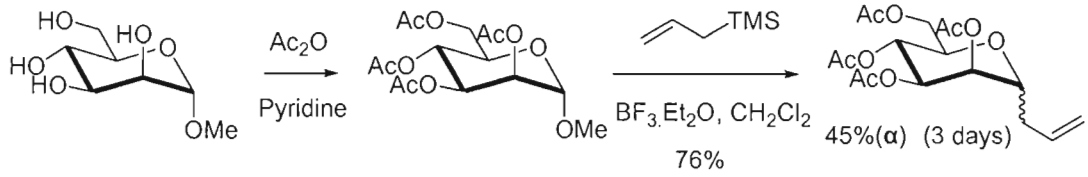
Reduced with bromide by radical reaction; [39]

**G:** EtSH, $BF_3$:$Et_2O$, R.T.

Reduced with thioethanol in presence of $BF_3$:$Et_2O$.

The reasons for failure remain unclear, so instead, we protected the sugar with acetic anhydride, because the acetate group could be easily deprotected under Zemplén conditions.

**Scheme 33: 3-(tetra-O-acetyl-α-D-mannoppyranosyl)-1-propene**



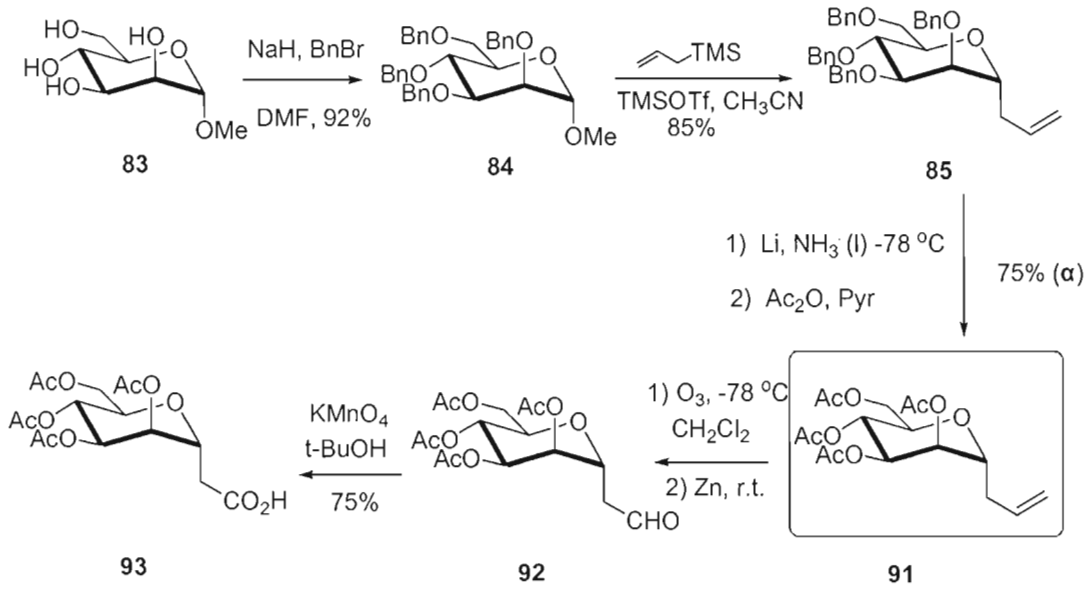

**83** **89** **90**

Methyl α-D-mannopyranoside **83** was protected with acetic anhydride in pyridine, a methyl tetra-*O*-acetyl-α-D-mannoppyranoside **89** was obtained with

excellent yield, which was then activated with $BF_3$:$Et_2O$ and coupled to allyl trimethylsilane to provide allyl mannoside **90.** [40]

At this point, we encountered another problem; the resulting product **90** was obtained as an inseparable mixture of anomers. Thus we had to combine these two above methods to synthesize the pure 2-(tetra-*O*-acetyl-α-D-mannopyranosyl) ethanoic acid α-anomer that was formed exclusively and was easily deprotected.

**Scheme 34: 2-(tetra-O-acetyl-α-D-mannopyranosyl)ethanoic acid**




Methyl α-D-mannopyranoside **83** was actived by sodium hydride and protected with bromobenzene to provide methyl 2,3,4,6-tetra-O-benzyl α-D-mannopyranoside **84**, which was activated with TMSOTf and coupled to allyl trimethylsilane to provide 3-(tetra-O-benzyl-α-D-mannopyranosyl)-1-propene **85**. Compound **85** was deprotected using Birch conditions and reprotected with acetic anhydride, to give 3-(tetra-O-acetyl-α-D-mannoppyranosyl)-1-propene **91**. The purity of compound **91** was confirmed by **$^1$H NMR** (the purity was above 98%). Compound **91** was then

ozonolysed and reduced using zinc to give the corresponding aldehyde: 2-(tetra-O-acetyl-α-D-mannopyranosyl) ethanal **92**. This was oxidized by potassium permanganate to give 2-(tetra-O-acetyl-α-D-mannopyranosyl) ethanoic acid **93** in good yield. [40]

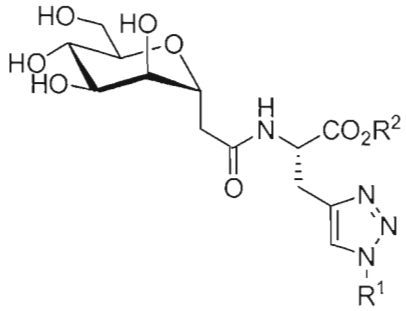
The three synthons were then used to prepare the final products.

# Chapter 4. Preparation of final products modified at position 1

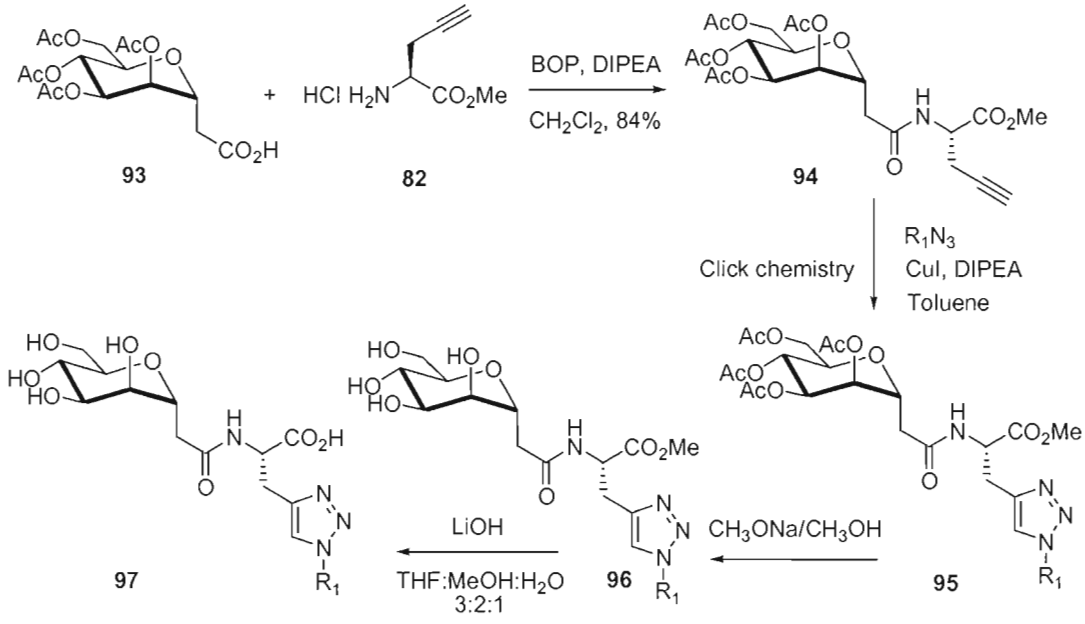
## 4.1 Synthesis of a series of products modified at position 1 — C-mannosides (series 1)

A series of C-mannosides were first prepared.

**Scheme 24: target compound of series 1**

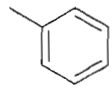
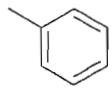
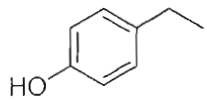
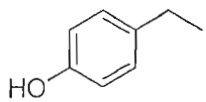
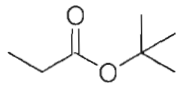
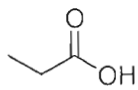
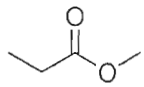
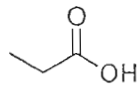
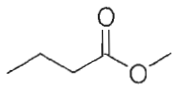
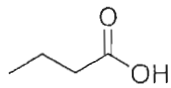
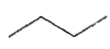
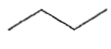
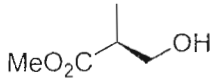


**Schema 35: synthesis of a series of products modified at position 1 (series 1)**



The acid **93** was combined with methyl L-propargylglycinate **82** in the presence of BOP to give **94**, which was then treated with a series of azides using click chemistry conditions to give a series of compounds **95**. They were de-*O*-acetylated by the standard Zemplén method (NaOMe, MeOH), to give another series of compounds **96**, which was further saponified by solution of lithium hydroxide (LiOH) in aq. THF, to give the first series **97** having a free acid. The following final products were obtained

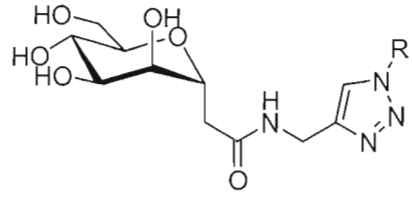
**Table 5**: Final products modified at position 1 (series 1) (following page).

| | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| 99 |  | Me | 81 |
| 100 |  | H | 94 |
| 102 |  | Me | 73 |
| 103 |  | H | 95 |
| 105 |  | Me | 43 |
| 106 |  | H | quant |
| 108 |  | Me | 31 |
| 109 |  | Me | 41 |
| 111 |  | Me | 88 |
| 112 |  | H | quant |
| 114 |  | Me | 74 |
| 115 |  | H | quant |
| 117 |  | Me | 75 |
| 118 |  | H | 91 |
| 119 |  | Me | 7 |

## 4.2 Syntheses of another series of products modified at position 1 — C-mannosides (series 2)

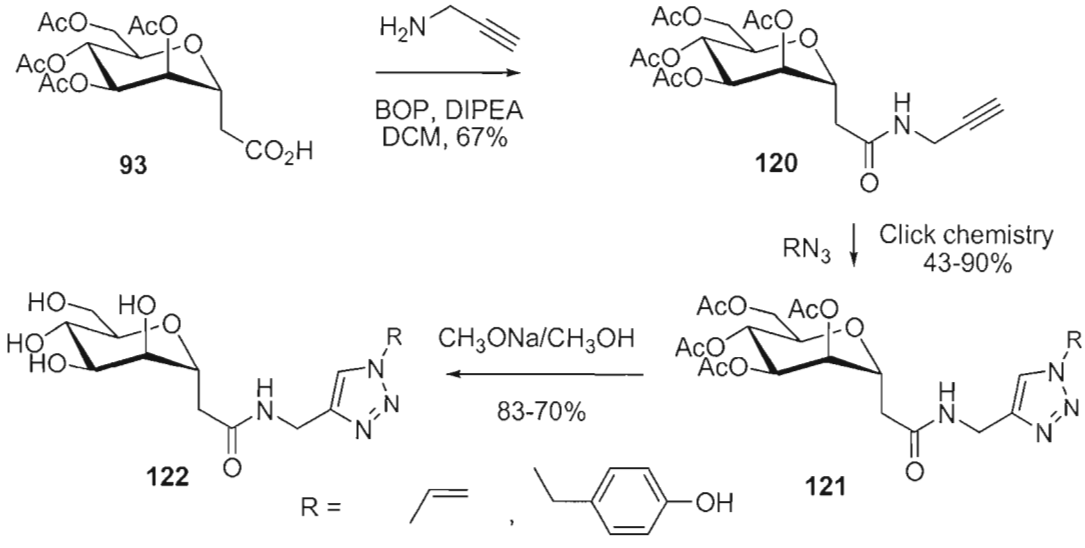
To determine better inhibitors, another series of compounds, modified at position 1 by replacing propargylglycine with propargylamine, were synthesized.

**Scheme 36: target compounds of series 2**



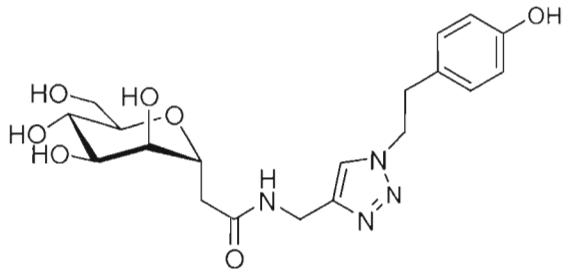
By retrosynthesis analysis, this compound can be decomposed in three parts: **azide, propargylamine, and the sugar acid**. The synthesis of the azide and the acid are described above, propargylamine is a commercial product, so the three synthons could be combined together.

**Scheme 37: syntheses of another series of products modified at position 1 (series 2)**

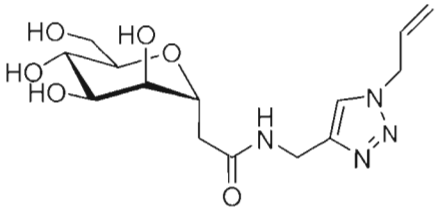


The acid **93** was treated with propargylamine in the presence of BOP to provid propargyl amide **120**, which was reacted with a series of azides using click chemistry conditions to give a series of compounds **121**, After de-*O*-acetylation, a series of compounds **122** was obtained. So we got following two products:

**Scheme 38: final product of series 2**



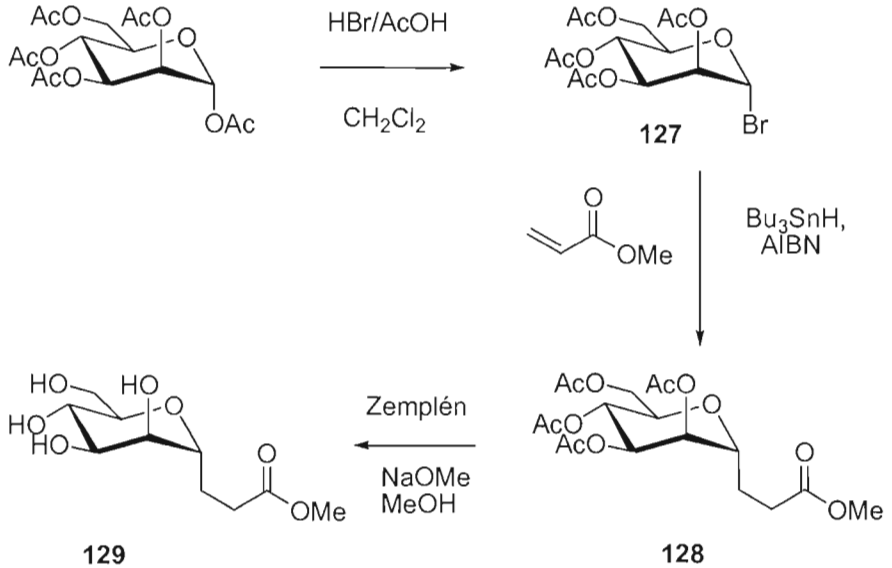
**124**



**126**

## 4.3 Synthesis of mannoside modified at position 1 with elongated carbon chain

**Sheme 39: synthesis of methyl 3-(α-D-mannopyranosyl)propanoate 129**

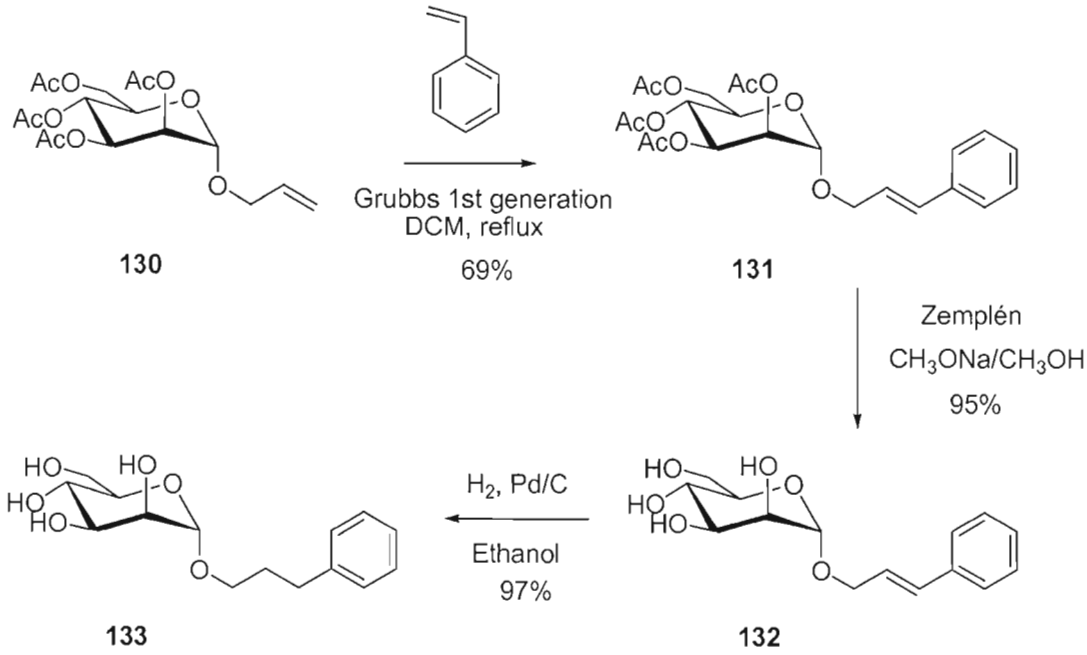


2, 3, 4, 6-Tetra-O-acetyl-α-D-mannopyranosyl bromide **127** was prepared by the usual method and then treated with methyl acrylate under radical conditions to give methyl 3-(2', 3', 4', 6'-tetra-O-acetyl-α-D-mannopyranosyl)propanoate **128**, which was de-*O*-acetylated by the standard Zemplén method to give the final product methyl 3-(α-D-mannopyranosyl)propanoate **129.** [41]

## 4.4 Synthesis of a series of products modified at position 1 (O-mannosides)

To determine the best inhibitor of FimH, we have synthesized the following O-mannosides using cross metathese:

**Scheme 40: synthesis of *O*-mannoside derivatives modified at position 1**



Allyl 2, 3, 4, 6-tetra-*O*-acetyl-α-D-mannopyranoside **130** was treated with styrene by cross metathese catalyst (Grubbs first generation), to give 3'-phenylallyl 2, 3, 4, 6-tetra-*O*-acetyl-α-D-mannopyranoside **131**. After de-O-acetylation by the standard Zemplén method, 3'-phenylallyl α-D-mannopyranoside **132** was obtained. This compound was reduced by hydrogen catalyzed by palladium and 3'-phenylpropyl α-D-mannopyranoside **133** was obtained in very good yield (97%).

## Chapter 5 Synthesis of mannoside derivatives modified at position 6

To determine potentially better inhibitors, several other mannoside derivatives modified at position 6 were synthesized

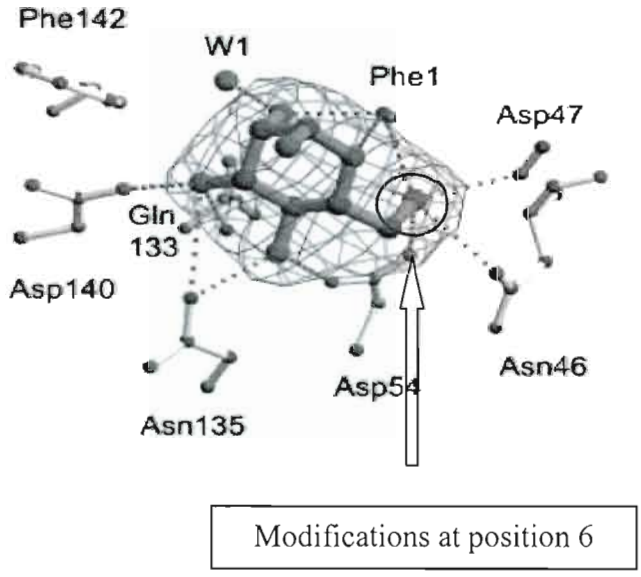
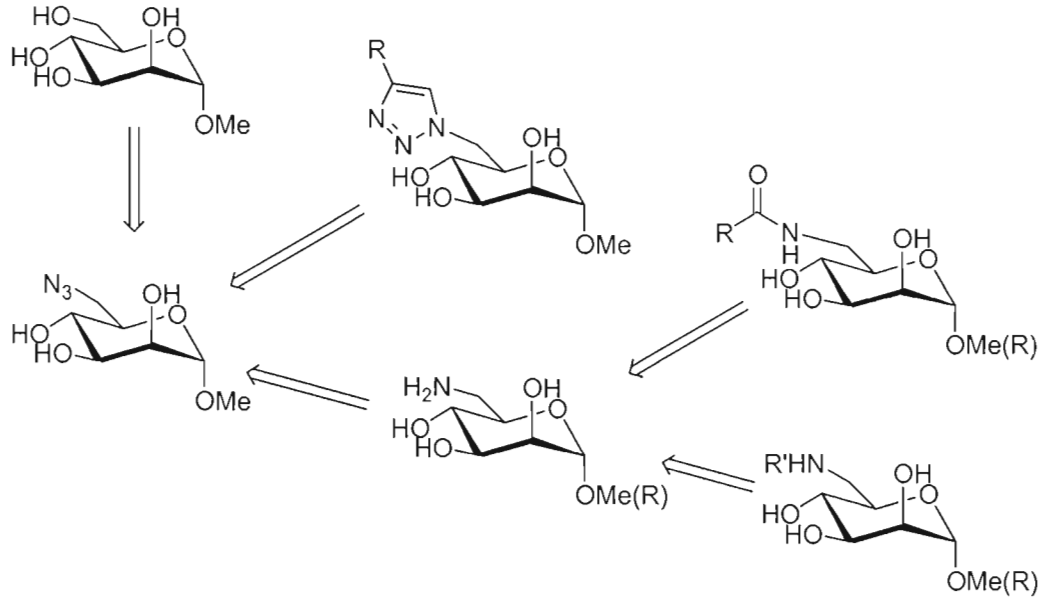



**Figure 8:** Interaction between the groups at position 6 of mannoside and aminoazid residues of FimH

In this figure, oxygen at position 6 forms several hydrogen bridges with acidic FimH residues; therefore, we decided to replace the oxygen atom with other groups to increase potential binding interactions between them.

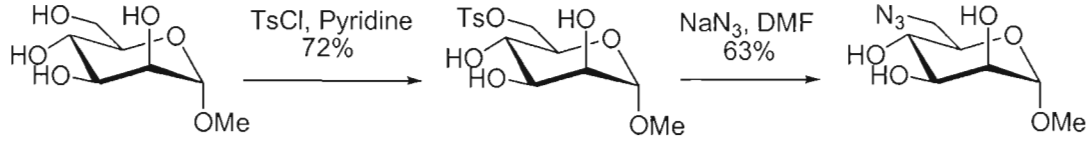
**Scheme 41: retrosynthetic analysis of α-D-mannopyranoside derivatives at position 6**



First, the hydroxyl group at position 6 of methyl α-D-mannopyranoside was transformed into an azide which was then converted to a triazole by click chemistry or reduced to an amine, and the amine can be further transformed into an amide or a secondany amine

## 5.1 Preparation of azide at position 6

**Scheme 42: methyl 6-azido-6-deoxy-α-D-mannopyranoside**

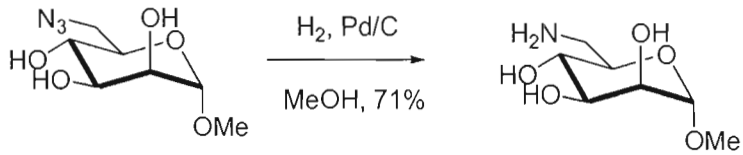



**83** **134** **135**

Methyl α-D-mannopyranoside **83** was actived by TsCl in pyridine.[42] The resulting 6-O-tosylate was then displaced by $NaN_3$ in DMF to provide the known methyl 6-azido-6-deoxy-α-D-mannopyranoside **135** in good yield.

## 5.2 Preparation of amine at position 6

**Scheme 43: synthesis of methyl 6-amino-6-deoxy-α-D-mannopyranoside**

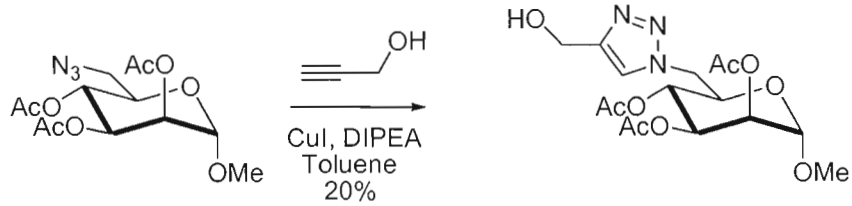



**135** **136**

Methyl 6-azido-6-deoxy-α-D-mannopyranoside **135** was reduced by hydrogenation in the presence of 10% palladium on carbon (Pd/C) in methanol, to afford known methyl 6-amin-6-deoxy-α-D-mannopyranoside **136** with good yield.

## 5.3 Preparation of triazole at position 6

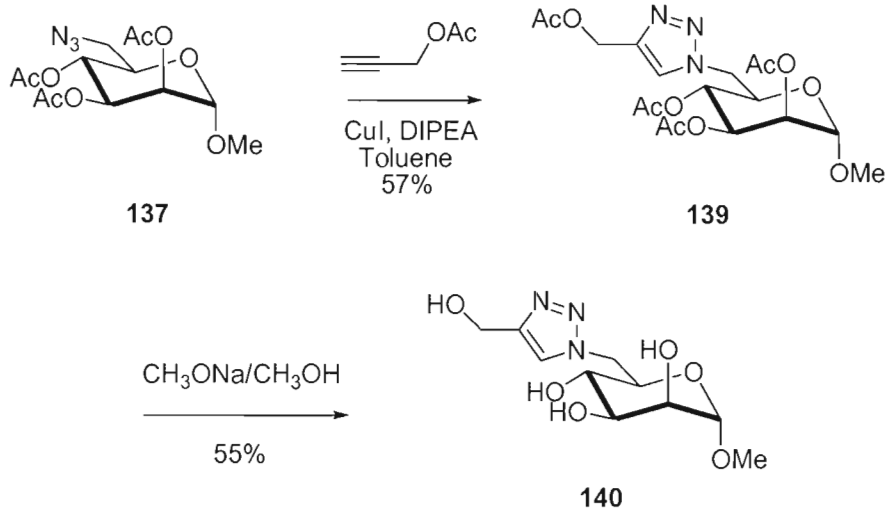
**Scheme 44: synthesis of triazole 138**




**137** **138**

Methyl 2, 3, 4-*O*-triacetyl-6-azido-6-deoxy-α-D-mannopyranoside **137** was treated with propargyl alcohol under click chemistry conditions (catalyzed by CuI), to give the corresponding triazole **138** in low yield (20%). To increase the yield, we changed the strategy; we used propargyl acetate instead of propargyl alcohol. The reaction is as follow:

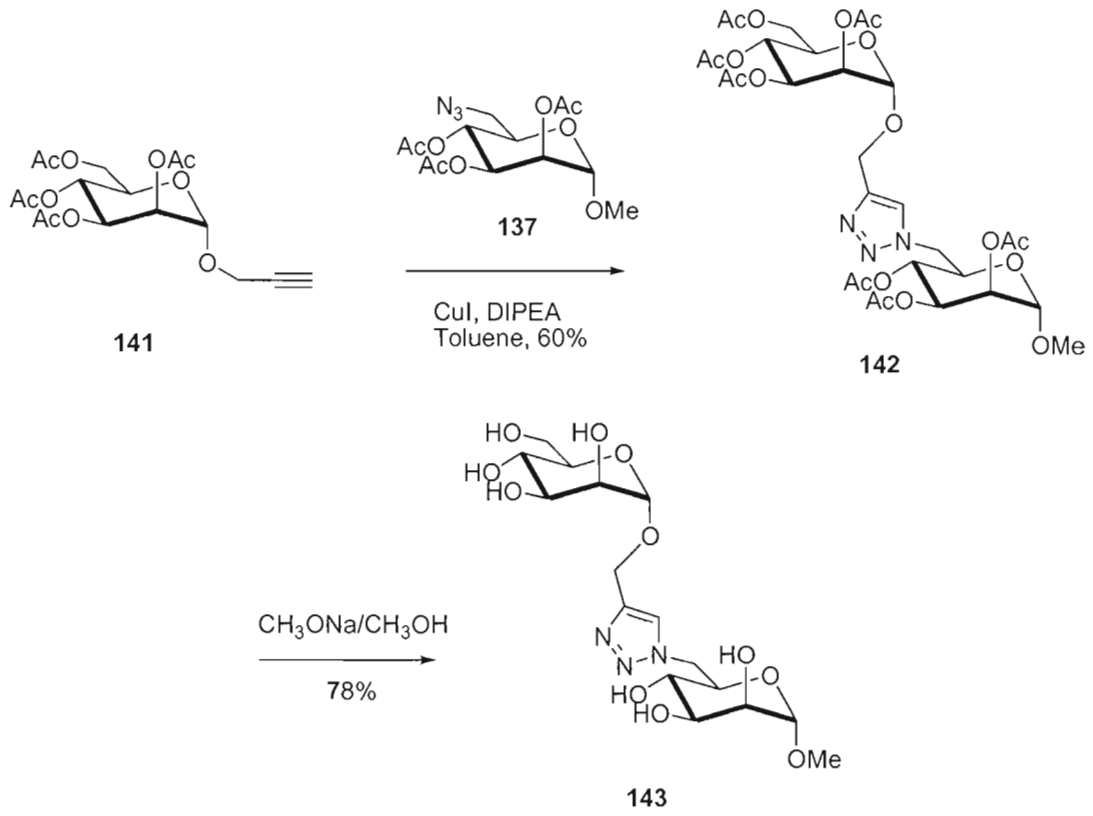
**Scheme 45: synthesis of 140**




Propargyl acetate reacted with methyl 2,3,4-tri-*O*-triacetyl-6-azido-6-deoxy-α-D-mannopyranoside **137** under the same click chemistry conditions (catalyzed by CuI), to give the corresponding triazole **139** with increased yield (57%). After de-*O*-acetylation, the final product **140** was obtained in a moderate yield.

Finally, we synthesized other triazoles:

**Scheme 46: synthesis of 143**




Methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-mannopyranoside **137** reacted with propargyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **141** under click chemistry conditions to give the corresponding triazole **142** in 60% yield. After de-*O*-acetylation, the final product **143** was obtained with 78% yield.

# BIOLOGICAL TEST

The relative binding ability of the mannosides was evaluated by surface plasmon resonance (SPR) measurements on a Biacore3000™. The affinity of the lectin domain of isolated FimH of *E. coli* toward our mannosides was obtained by competition between an immobilized anti-FimH antibody (1C10) and free mannosides (**Table 6**).

## Surface Plasmon Resonance measurements on a Biacore3000™

### Expression and Purification

Bacteria were grown in minimal medium containing 40 μg/ml of all the amino acids, 0.4% glucose, 2 μg/ml biotine, 2 μg/ml thiamine, 2 mM $MgCl_2$ and 25 μg/ml kanamycine at 37 °C. At $OD_{600nm}$ = 0.6 the C43 (DE3) cells were induced with 1 mM IPTG. After over night incubation at 37 °C, cells were collected and the periplasmic content was extracted. The lectin domain of FimH was purified by dialysing for 4 h at 4 °C against 20 mM Na formate, pH 4, and loading it onto a Mono S column (Pharmacia). The protein was eluted with 20 mM Na formate, 1 M NaCl pH4. Fractions containing FimH lectin domain were pooled and dialysed overnight at 4°C against 20 mM Hepes, 150 mM NaCl pH 8.

### Immobilization of Fab fragments of the monoclonal antibody 1C10

Affinity measurements using SPR was performed basically as described in materials and methods in Bouckaert *et al.* (2005). All SPR measurements were performed on a Biacore3000.™ A monoclonal antibody 1C10 against the mannose-binding pocket of FimH was produced by a mouse hybridoma cell line at Medimmune and its Fab fragments were purified. We used these Fab fragments to determine the solution affinity of the lectin domain of FimH for different mannose derivatives. The surface of flow cell 2 (Fc2) was activated with 35 μl of EDC/NHS

[mixture of EDC (200 mM) and NHS (50 mM)]. 1C10 Fabs dissolved at 100 μg/ml in 10 mM sodium acetate buffer pH 5 was subsequently covalently coupled as ligands onto a CM5 biosensor chip (*BIAapplications Handbook*, Biacore AB, Uppsala, Sweden) at 530 RU (resonance units = pg ligand per $mm^2$) in Fc2 via free amine groups. The excess of succinimide esters on the surface of the chip were deactivated by the injection of 35 μl of 1 M ethanolamine at pH 8.5. Fc1 was activated and deactivated the same way as Fc2, but without Fab immobilisation, and was used as the reference cell.

**Determination of the affinity of FimH for the immobilized Fab fragments**

The kinetic constants for binding of the lectin domain of FimH to the immobilized 1C10 antibody were measured by flowing a two-fold serial dilution of FimH, ranging from 2000 nM down to 1.95 nM in running buffer [20 mM Hepes pH 7.4, 150 mM NaCl, 0.005% surfactant P20 and 3 mM EDTA], sequentially over Fc1 and Fc2, at 298 K. The evolution of the optical signal from Fc2 minus Fc1, measured in Rus, was followed in time. The flow rate was 20 μl per min, the association time 4.5 minutes. The dissociation was allowed to proceed for 25 minutes, by injecting only running buffer, to completely dissociate FimH from the 1C10 antibody before starting another binding cycle. Zero concentration data was obtained by injecting only running buffer over the sensor chip. The binding of FimH to 1C10 was evaluated using the BIAevaluation software version 4.1. A Langmuir binding isotherm with a 1:1 stoichiometry was fitted simultaneously to the association and dissociation phases, to obtain in global reaction rate constants $k_a$ and $k_d$ and the maximum analyte binding response $R_{max}$.

**Affinity measurements and fittings**

The affinity of the lectin domain of FimH for different mannose derivatives was obtained by competition between antibody and sugar for the FimH lectin domain. Each mannose derivative was diluted at least 11 times in a two-fold serial dilution. To each of the sugar

concentrations, including a zero concentration, a concentration of the lectin domain of FimH was added that was close to the dissociation constant at equilibrium $K_d$ of the FimH-antibody interaction, calculated from the foregoing experiment. Analyses of all binding cycles were again performed using the BIAevaluation software version 4.1. The concentrations of FimH lectin domain free from sugar and thus able to interact with the immobilised 1C10 antibody were obtained by fitting a Langmuir binding isotherm with 1:1 stoichiometry to the data, using the global parameters $k_a$, $k_d$ and $R_{max}$ from the former experiment. These FimH concentrations were plotted as a function of the sugar concentrations. Fitting using the solution affinity interaction model $(B-A-K_d)/2+(0.25*(A+B+K_d)^2-A*B)^{0.5}$, where A is the sugar concentration, B is the initial fixed concentration of the lectin domain of FimH added to each sugar concentration delivered $K_d$, the dissociation constant at equilibrium or the affinity of FimH for the sugar.

# CONCLUSIONS AND PERSPECTIVE

After biological testing, the following results were obtained:

**Table 6:** The results of biological test (in structure)

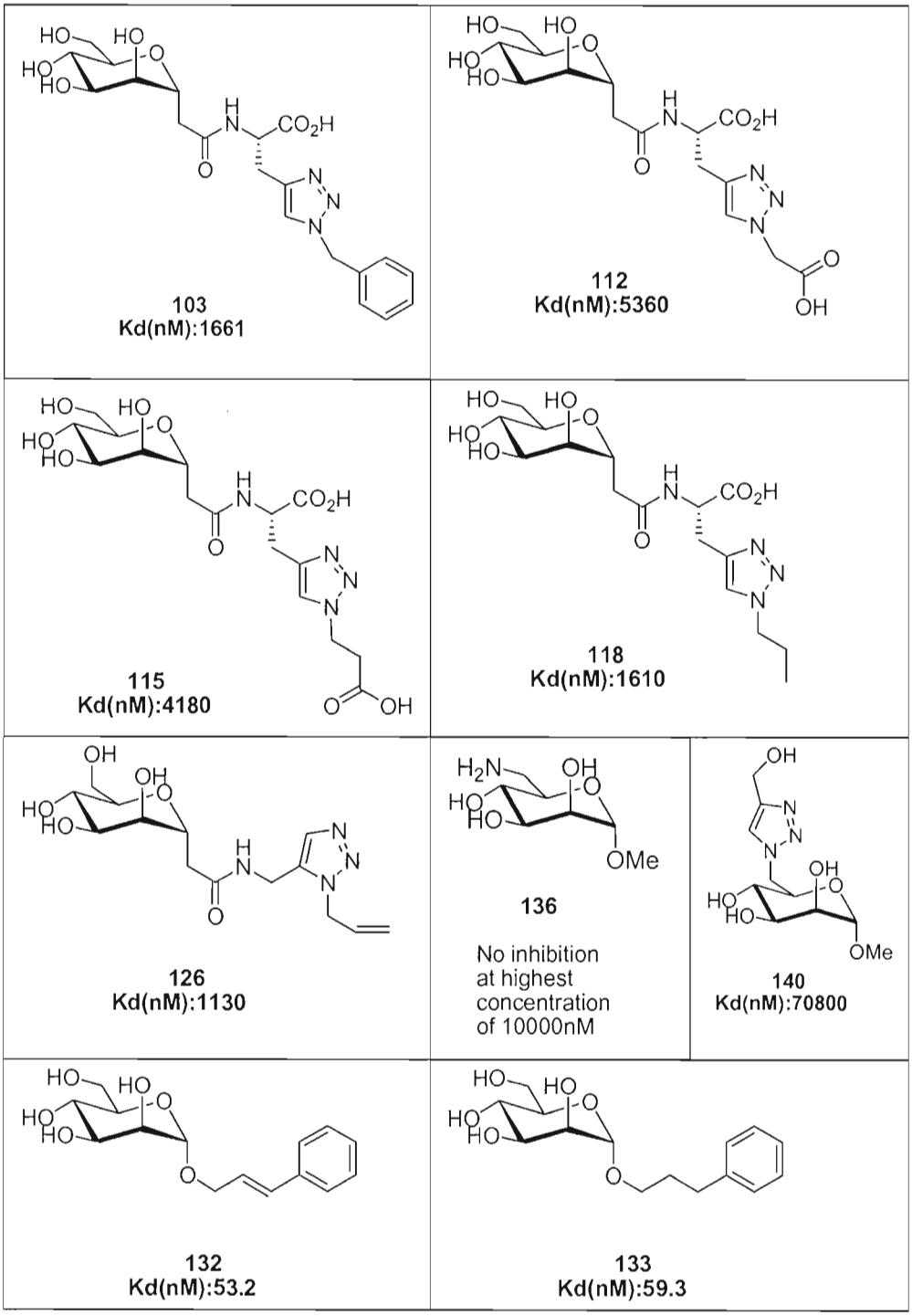
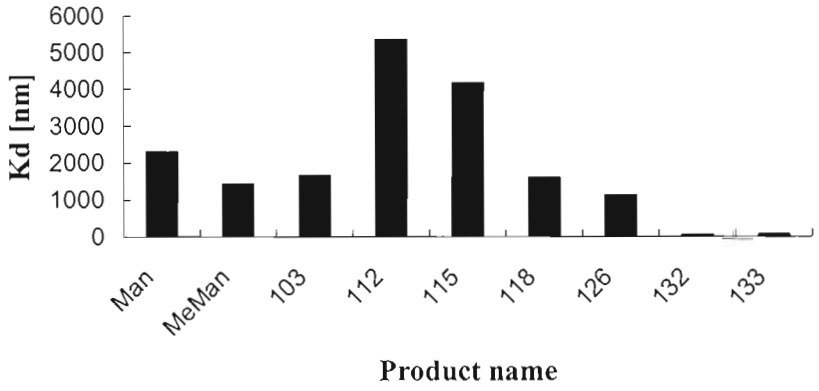


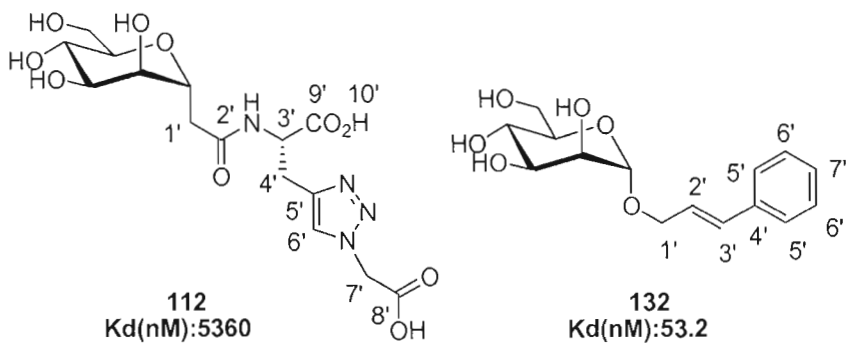
**Table 7:** The results of biological test (in table)

| Product name | Kd [nM] |
|---|---|
| Man | 2300 |
| MeMan | 1430 |
| **103** | 1661 |
| **112** | 5360 |
| **115** | 4180 |
| **118** | 1610 |
| **126** | 1130 |
| **132** | 53.2 |
| **133** | 59.3 |
| **136** | No activity |
| **140** | 70800 |

**Graphic 1:** The results of biological test



**Scheme 46: The less active product 112 and the most active produt 132**




**112**
**Kd(nM):5360**

**132**
**Kd(nM):53.2**

**112** has two terminal hydrophilic groups and no hydrophobic groups, it has less activity. **132** has one hydrophobic group, it hasn't any terminal hydrophilic groups (except the sugar part), it has the most activity,

From the above results, one can get following conclusions:

**A:** The compounds modified at position 6 (compounds **136** and **140**) are far less active than the compounds modified at position 1 (anomeric position);

**B:** All *C*-mannosides are less active than *O*-mannosides;

**C:** For *C*-mannosides modified at the anomeric position, **126** is less complex than **103**, **112, 115**, **118** and it is more active than them;

**D:** For compounds **103**, **112, 115**, **118**, they can be divided in two groups: **103** and **118** have one terminal free acid group and one hydrophobic group respectively, and **112** and **115** have two terminal acid groups. **103** and **118** are more active than **112** and **115**;

**E:** For **103** and **118**, the **103** has one terminal aromatic group, **118** has one terminal aliphatic group, and their activity are nearly the same;

**F:** **132** and **133** are *O*-mannosides, their activities are nearly the same, there into **132** is an unsaturated derivative and **133** is a saturated derivative, **132** is slightly more active than **133**.

For future work, one should synthesize mannosides inhibitor according to following principles:

**A.** Modifiy at the anomeric position;

**B.** If possible, synthesize *O*-mannopyranoside;

**C.** If *C*-mannopyranoside must be synthesized, molecule structure similar to **126** is the priority choice;

**D.** Increase the number of terminal hydrophobic groups and reduce the number of terminal hydrophilic groups.

# CLAIMS

The first step of looking for a medication is decision of therapeutic target. The works of professor Henri De Greve tell us that FimH adhesin located at the tips of type 1 pili are important virulence factors for the establishment of *Escherichia coli* urinary tract infections (UTIs) which is the most common cause of infections both in the urethra (urethritis) and the bladder (cystitis) in the lower urinary tract, as well as the more severe infections in the kidneys (pyelonephritis) that can develop if the infection is not treated in time. Blocking of bacterial adhesion is able to prevent infection. Professor Henri De Greve and co-workers provided for the first time, binding data of the molecular events underlying type 1 fimbrial adherence, by crystallographic analyses of the FimH receptor binding domains, and affinity measurements with mannose, and a series of alkyl and aryl mannosides.

Butyl α-D-mannopyranoside, bound in the crystal structures, exhibits a significantly better affinity for FimH (Kd = 0.15 mM) than mannose (Kd = 2.3 mM). Exploration of the binding affinities of α-D-mannopyranoside with longer alkyl tails revealed affinities up to 5 nM. In the chemical part, we have synthesized several series of mannopyrannosides modified at either the anomeric position or position 6 using 'Click Chemistry', Cross metathese, Sakurai type reaction, Diazotransfer reaction and Radical reaction. For mannopyranosides modified at the anomeric position, we have synthesized two series of compounds; *O*-mannopyranoside and *C*-mannopyranoside to compare their affinity.

The relative binding ability of the mannopyranosides was evaluated by surface plasmon resonance (SPR) measurements. The results of biological testing told us that:

A. Mannopyranosides modified at position 6 are far less active than mannopyranosides modified at the anomeric position;

B. All *O*-mannopyranosides are more active than *C*-mannopyranosides;

C. Mannopyranosides which have terminal hydrophobic groups are more active than mannopyranosides which have terminal hydrophilic groups.

D. Mannopyranosides which have unsaturated groups have nearly the same activity as mannopyranosides which have saturated groups.

The result of present work has been published in 3 journals. See page 131.

# EXPERIMENTAL PART

## General methods:

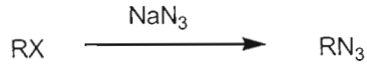
Flash chromatography was performed using Merck silica gel 60 (0.04020.063 mm, 2302400 mesh). TLC was performed on Kieselgel 60 F254 plates from Merck. Detection was carried out under UV light or by spraying with 20% ethanolic sulfuric acid or ammonium molybdate solution [50 g $(NH_4)_6Mo_7O_{24}.4H_2O$, 12.2 g $Ce(SO_4)_2$, 200 ml concentrated $H_2SO_4$, 1.8 L distilled water] followed by heating. Tetrahydrofuran was distilled on sodium prior to use.

Infrared spectra were recorded on a Perkin-Elmer 1600 (KBr) FTIR instrument. NMR spectra were measured with a Varian 300 (300 MHz for $^1H$ and 75 MHz for $^{13}C$ NMR) spectrometer. Chemical shifts are in ppm, relative to internal TMS ($\delta$ = 0.00 for $^1H$ and $^{13}C$ NMR) or solvent peaks, which were calibrated as follows: $CDCl_3$ ($\delta$ = 7.27 for $^1H$ and $\delta$ = 77.0 for $^{13}C$ NMR), [d4] methanol ($\delta$ = 3.30 for $^1H$ and $\delta$ = 49.0 for $^{13}C$ NMR). Where necessary, DEPT, APT, and two-dimensional $^1H$-$^1H$ COSY experiments were performed for complete signal assignments. Optical rotation values were obtained using a JASCO P-1000 Polarimeter (Na-D line, 589 nm, cell length 5 cm). ESI-MS analyses were carried out on a MICROMASS Quattro LC instrument at the University of Montreal.

## I Preparation of azides

The structures of all azides were confirmed by IR and displayed a strong, sharp band between 2100-2095 $cm^{-1}$ for the azide stretching band and these were used without further purification except were indicated.

**I.1** Preparation of azides from halides




**Methyl Azide**


Methyl iodide (0.62 ml, 10 mmol) was heated at 55 °C overnight in 6.2 ml DMF containing 1.5 ml of water and sodium azide (0.77 g, 11.8 mmol). The product was distilled out of the reaction mixture to give 88 mg of methyl azide [31]. (in toluene)

Yield: 15%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.01 (3 H, s, $CH_3$)

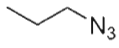
**Ethyl azide**


Ethyl bromide (0.75 ml, 10 mmol) was refluxed overnight in 6.2 ml DMF containing 1.54 ml of water and sodium azide (0.77 g, 11.8 mmol). The product was distilled out of the reaction mixture and dried over sodium sulfate to give 520 mg of ethyl azide. [31]

Yield: 73%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.45-3.35 (2 H, q, $J$ = 7.40 Hz, $CH_2$), 1.30-1.24 (3 H, t, $J$ = 7.28 Hz, $CH_3$)

**Propyl Azide**




Same procedure as for the preparation of ethyl azide.

Yield: 91%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.29-3.21 (2 H, t, $J$ = 6.87 Hz, $CH_2N_3$), 1.70-1.58 (2 H, m, $CH_3C\underline{H}_2$), 1.04-0.95 (3 H, t, $J$ = 7.29 Hz, $CH_3$).

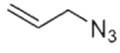
**Isopropyl Azide**


Same procedure as for the preparation of ethyl azide.

Yield: 88%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.69-3.56 (1 H, m, CH), 1.27-1.22 (6 H, d, $J$ = 6.32 Hz, 2 x $CH_3$).

**Allyl Azide**



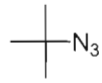

Same procedure as for the preparation of ethyl azide.

Yield: 93%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 5.97-5.81 (1 H, m, $CH_2$=C$\underline{H}$), 5.38-5.28 (2 H, m,

$C\underline{H_2}$=CH), 3.82-3.75 (2 H, d, $J$ = 6.04 Hz, $C\underline{H_2}N_3$)

**Tert-butyl azide**

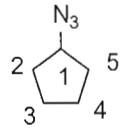



Same procedure as for the preparation of ethyl azide.

Yield: 93%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 1.28 (9 H, s, 3 x $CH_3$).

**Cyclopentyl azide**



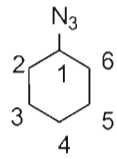

Cyclopentane bromide (1.07 ml, 10 mmol) was refluxed overnight in 4 ml of water containing $Bu_4NBr$ (0.326 g, 1.0 mmol) and sodium azide (1.307 g, 20 mmol). The product was extracted with $Et_2O$, dried over sodium sulfate; solvent was evaporated under reduced pressure slowly to give 4.86 g of cyclopentyl azide.

Yield: 80%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.99-3.90 (1 H, m, CH), 1.85-1.50 (8 H, m, 4 x $CH_2$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 62.7 (C-1), 31.8 (C-2, C-5), 23.2 (C-3, C-4).

**Cyclohexyl azide**



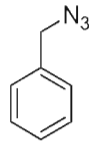

Same procedure as for the preparation of cyclopentyl azide.

Yield: 75%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 1.60-1.40 (11 H, m).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 59.8 (C-1), 31.5 (C-2, C-6), 25.2 (C-4), 24.1 (C-3, C-5).

**Benzyl azide**

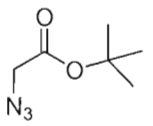



Benzyl bromide (1.19 ml, 10 mmol) was dissolved in water (4 ml) and $Et_2O$ (4 ml), sodium azide (1.3 g, 20 mmol) and $Bu_4NHSO_4$ (0.34 g, 1.0 mmol) were added successively, the mixture was stirred at room temperature for one day. The two phases were then separated, and the aqueous phase was extracted with $Et_2O$, while the combined organic phases were dried over sodium sulfate and evaporated under reduced pressure to afford 1.428 g of product.

Yield: quantitative.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.46-7.30 (5 H, m, $H_{aromatique}$), 4.38 (2 H, s, $CH_2$).

**Tert-butyl 2-azidoacetate**

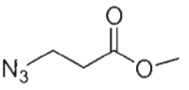


Same procedure as for the preparation of benzyl azide.

Yield: 92%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.78 (2 H, s, $CH_2$), 1.51 (9 H, s, 3 x $CH_3$).

**Methyl 3-azidopropionate**



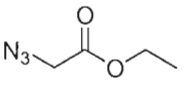
Same procedure as for the preparation of benzyl azide.

Yield: 61%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.73 (3 H, s, $CH_3$), 3.61-3.56 (2 H, t, $J$ = 6.32 Hz, $COCH_2$), 2.61-2.57 (2 H, t, $J$ = 6.32 Hz, $CH_2N_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.3 (C=O), 51.9 ($CH_3$), 46.7 ($CH_2N_3$), 33.7 ($\underline{C}H_2CO$).

**Ethyl 2-azidoacetate**



Same procedure as for the preparation of benzyl azide.

Yield: quantitative.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 4.31-4.23 (2 H, q, $J$ = 7.14 Hz, $C\underline{H}_2CH_3$), 3.87 (2

H, s, $CH_2N_3$), 1.34-1.30 (3 H, t, $J$ = 7.14 Hz, $CH_2\underline{C}H_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 168.3 (C=O), 61.8 ($\underline{C}H_2CH_3$), 50.3 ($CH_2N_3$), 14.1 ($CH_2\underline{C}H_3$).

**I.2** From amines and amino acids

First, the triflyl azide reagent was prepared by the following method ($TfN_3$)

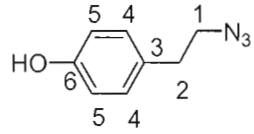
$$Tf_2O \xrightarrow[H_2O,CH_2Cl_2]{5NaN_3} TfN_3$$
$$0°C,\ 2h$$

Sodium azide (1.78 g, 27.38 mmol) was dissolved in distilled water (4.5 ml) with DCM (7.5 ml) and cooled on an ice bath. $Tf_2O$ (0.93 ml, 5.53 mmol) was added slowly over 5 min with stirring was continued for 2 hrs. The mixture was then placed in a separatory funnel and the organic phase removed. The aqueous phase was extracted with DCM (2 x 3.75 ml). The organic fractions were pooled and washed once with saturated sodium sulfate (5 ml) and used without further purification. [32]

The following azides were then prepared by the diazotransfert reaction using the crude triflyl azide. [32]

$$RNH_2 \xrightarrow[1.5\ K_2CO_3,\ 1\%\ CuSO_4]{2\ CF_3SO_2N_3\ (TfN_3)} RN_3$$
$$H_2O,\ CH_3OH,\ CH_2Cl_2$$

**Azido tyramine**



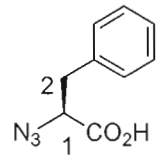

Tyramine (138 mg, 1.0 mmol) was combined with $K_2CO_3$ (207 mg, 1.5 mmol), $CuSO_4.5H_2O$ (2.5 mg, 0.01 mmol), distilled water (3.2 ml) and $CH_3OH$ (6.5 ml). $TfN_3$ (6.7 ml, 1.85 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was then separated, and the aqueous portion was extracted with DCM, while the combined organic portions were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 20%) to afford azido tyramine (142 mg). [32]

Yield: 87%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.07-7.04 (2 H, dd, *J* = 2.22, 6.32 Hz, H-4), 6.77-6.74 (2 H, dd, *J* = 2.22, 6.32 Hz, H-5), 3.45-3.40 (2 H, t, *J* = 7.14 Hz, H-2), 2.82-2.76 (2 H, t, *J* = 7.14 Hz, H-1).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 154.0 (C-6), 130.0 (C-3), 129.8(2 x C-4), 115.4 (2 x C-5), 52.4 (C-1), 34.1 (C-2).

**Azido-L-phenylalanine**



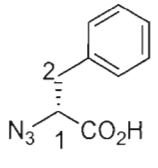

L-phenylalanine (166 mg, 1.0 mmol) was combined with $K_2CO_3$ (207 mg, 1.5 mmol), $CuSO_4.5H_2O$ (2.5 mg, 0.01 mmol), distilled water (3.2 ml) and $CH_3OH$ (6.5 ml). $TfN_3$ (6.7 ml, 1.85 mmol) was added and the mixture was stirred

at room temperature overnight. The organic solvents were then removed under reduced pressure and aqueous slurry was diluted with water (18 ml). This was acidified to pH 6 with concentrated HCl, diluted with phosphate buffer (18 ml, pH 6.2) and extracted with EtOAc (4 x 12 ml). The aqueous phase was then acidified to pH 2 with concentrated HCl, extracted with EtOAc (3 x 12 ml), dried with sodium sulfate and evaporated to dryness (171 mg),

Yield: 85%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.40-7.20 (5 H, m, $H_{aromatic}$), 4.19-4.10 (1 H, dd, $J$ = 5.09, 8.93 Hz, Ha-2), 3.27-3.20 (1 H, dd, $J$ = 4.95, 14.01 Hz, H-1), 3.04-2.98 (1 H, dd, $J$ = 8.79, 14.01 Hz, Hb-2).

**Azido-D-phenylalanine**

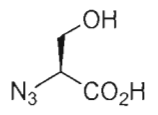



Same procedure as for preparation of Azido-L-phenylalanine.

Yield: 90%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.38-7.20 (5 H, m, $H_{aromatic}$), 4.15-4.07 (1 H, dd, $J$ = 9.07, 14.01 Hz, Ha-2), 3.25-3.15 (1 H, dd, $J$ = 4.94, 14.01 Hz, H-1), 3.04-2.95 (1 H, dd, $J$ = 4.94, 8.79 Hz, Hb-2).

**Azido-L-serine**

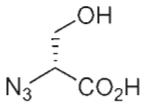


Same procedure as for the preparation of azido-L-phenylalanine.

Yield: 37%.

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 4.02-3.97 (1 H, t, $J$ = 4.4 Hz, CH), 3.80-3.77 (2 H, d, $J$ = 4.39 Hz, $CH_2$).

**Azido-D-serine**

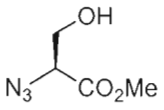



Same procedure as for preparation of azido-L-phenylalanine.

Yield: 66%.

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 4.03-3.96 (1 H, t, $J$ = 4.12 Hz, CH), 3.90-3.86 (2 H, d, $J$ = 4.4 Hz, $CH_2$).

**Azido-methyl L-serine**



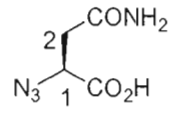

Methyl L-serine (156 mg, 1.0 mmol) was combined with $K_2CO_3$ (207 mg, 1.5 mmol), $CuSO_4.5H_2O$ (2.5 mg, 0.01 mmol), distilled water (3.2 ml) and $CH_3OH$ (6.5 ml). $TfN_3$ (7.2 ml, 2.0 mmol) was added and the mixture was stirred at room temperature overnight. Two phases were then separated and the aqueous portion was extracted with DCM (3 x 10 ml), while the combined organic portions were dried with sodium sulfate and purified by flash chromatography on silica gel

(EtOAc/Hexane = 50%) to afford Azido-methyl L-serine (124 mg).

Yield: 86%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 4.06-4.09 (1 H, t, *J* = 4.72 Hz, CH), 3.88-3.90 (2 H, d, *J* = 4.67 Hz, $CH_2$), 3.80 (3 H, s, $CH_3$).

**Azido-L-Asparagine**

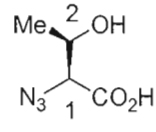



Same procedure as for the preparation of Azido-L-phenylalanine.

Yield: 48%.

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 4.43-4.37 (1 H, dd, *J* = 4.67, 8.51 Hz, H-1), 2.78-2.72 (1 H, dd, *J* = 4.67, 15.66 Hz, Ha-2), 2.62-2.55 (1 H, dd, *J* = 8.51, 15.66 Hz, Hb-2).

**Azido-L-Threonine**



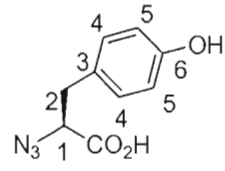

Same procedure as for the preparation of Azido-L-phenylalanine.

Yield: 47%.

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 4.42-4.38 (1 H, m, H-2), 3.95-3.92 (1 H, d, *J* = 2.74 Hz, H-1), 1.40-1.38 (3 H, d, *J* = 6.60 Hz, $CH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 173.0 (C=O), 68.6 (C-1), 66.7 (C-2), 19.6 ($CH_3$).

**Azido-L-Tyrosine**




Same procedure for the preparation of azido-L-phenylalanine.

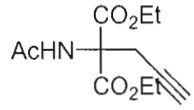
Yield: 47%.

**$^1$H NMR (300 MHz, DMSO):** δ 7.05-7.00 (2 H, d, *J* = 8.52 Hz, H-4), 6.69-6.65 (2 H, d, *J* = 8.51 Hz, H-5), 4.10-4.01 (1 H, dd, *J* = 4.67, 9.06 Hz, H-1), 3.00-2.95 (1 H, dd, *J* = 4.81, 14.14 Hz, Ha-2), 2.80-2.74 (1 H, dd, *J* = 8.93, 14.14 Hz, Hb-2),

**$^{13}$C NMR (75 MHz, DMSO):** δ 171.8 (C=O), 156.1 (C-6), 130.1 (C-3), 127.2 (C-4), 115.1 (C-5), 63.4 (C-1), 36.2 (C-2).

# II L-Propargylglycine methyl ester hydrochloride

## II-1 Diethyl α-acetamido-α-propargylmalonate 77



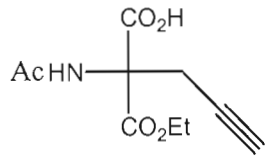

Sodium (1.68 g, 40 mmol) was dissolved in 40 ml of abs. ethanol under nitrogen. To this clear solution, 13.88 g (64 mmol) of diethyl α-acetamidomalonate, dissolved in 80 ml of abs. ethanol, was added dropwise. The temperature was raised to 60°C. After 6 h, the solvent was evaporated and the oily residue was treated with dry acetonitrile, and a solid was obtained. The solid residue (64 mmol) was dissolved in 60 ml of DMF and treated with 8.69 g (71 mmol) of propargyl bromide (stirring at 80 °C under $N_2$). The temperature was raised to 120°C and stirring continued for 3 h. After cooling, the precipitated NaBr was removed by filtration, the solvent evaporated, and the residue dissolved in water and ether. The organic phase was washed twice time with water, dried, and evaporated. The residue crystallized from isopropyl alcohol/petroleum ether to give **77** (7.79 g). [34]

Yield: 48%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 6.95 (1 H, s, NH), 4.30 (4 H, q, $J$ = 7.14 Hz, $OCH_2$), 3.28 (2 H, d, $J$ = 2.47 Hz, $C\underline{H}_2CCH$), 2.07 (3 H, s, $CH_3CO$), 1.98 (1 H, t, $J$ = 2.47 Hz, $CH_2CC\underline{H}$), 1.27 (6 H, t, $J$ = 7.14 Hz, $OCH_2C\underline{H}_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 169.2, 166.6, 78.2, 71.3, 65.2, 62.9, 23.8, 22.9, 13.9.

## II.2 Monoethyl α-acetamido-α-propargylmalonate 78

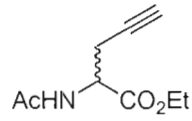



A solution of KOH (2.24 g, 40 mmol) in 5.5 ml of water and 84.5 ml of ethanol was slowly added to a solution of diethyl α-acetamido-α-propargylmalonate (6.8 g, 26.6 mmol) in 44 ml of ethanol. The resulting solution, 0.3 M with respect to KOH, was kept for 3 h at 20°C. Excess alkali was neutralized with 6.7 ml 2 N HCl; after 15 h at 4°C KCl was removed by filtration and the filtrate evaporated. The residue was dissolved in 83.4 ml of water at 0°C, acidified to pH 2 with 2 N HCl, and the precipitate gathered, washed, and dried to give product **78** (5.14 g). [34]

Yield: 85%

**$^1$H NMR (300 MHz, $CD_3COCD_3$ ):** δ 7.68 (1 H, s, NH), 4.22 (2 H, q, $J$ =7.14 Hz, $OOC\underline{H}_2CH_3$), 3.23 (2 H, s, $C\underline{H}_2CCH$), 2.47 (1 H, s, CCH), 2.06 (3 H, s, $COCH_3$), 1.22 (3 H, t, $J$ =7.14 Hz, $OOCH_2C\underline{H}_3$).

### II.3 Ethyl D, L-N-acetyl-propargylglycinate 79




The solution of monoethyl α-acetamido-α-propargylmalonate (4.72 g, 20. 8 mmol) in 49 ml of dioxane was boiled for 24 h (bath temp. 130°C). The solvent was evaporated and the residue was purified by flash chromatography on silica gel

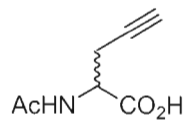
(MeOH/$CH_2Cl_2$ = 5%) to afford ethyl D, L-N-acetyl-propargylglycinate 3.11 g. [34]

Yield: 81%

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 6.33 (1 H, bs, NH), 4.73 (1 H, m, NHC<u>H</u>), 4.25 (2 H, m, $J$ = 7.15 Hz, C<u>H</u>$_2$CH$_3$), 2.79 (2 H, m, $J$ = 2,61 Hz, C<u>H</u>$_2$CCH), 2.07 (3 H, s, $COCH_3$), 2.03 (1 H, t, $J$ = 2,61 Hz, CCH), 1.31 (3 H, t, $J$ = 7.15 Hz, $CH_2C\underline{H}_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$)**: δ 170.3, 169.7, 78.5, 71.5, 62.0, 50.6, 23.2, 22.5, 14.1.

## II.4 (D, L)-N-Acetyl-propargylglycine 80

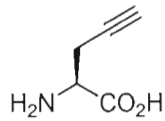



Ethyl D, L-N-acetyl-propargylglycinate (0.312 g, 1.7 mmol) was dissolved in 3 ml of ethanol and hydrolyzed for 15 h at 20°C with 0.112 g (2 mmol) of KOH in 0.25 ml of water and 2.5 ml of ethanol. The ethanol was then evaporated, and the residue acidified to pH 2 with 1 N HCl. The product was extracted with ethyl acetate and dried by vacuum pump. 0.209 g of D, L-N-Acetyl-propargylglycine was obtained. [34]

Yield: 86%

**$^1$H NMR (300 MHz, DMSO):** δ 8.28 (1 H, bs, NH), 4.30 (1 H, m, NHC<u>H</u>), 2.88 (1 H, t, $J$ = 2.75 Hz, CCH), 2.55 (2 H, m, C<u>H</u>$_2$CCH), 1.81 (3H, s, $CH_3CO$).

## II.5 L-Propargylglycine 81



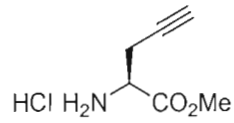
D, L-N-Acetyl-propargylglycine (0.204 g, 1.31 mmol) was dissolved in water (13 ml). After adjustment of the pH to 7.5 with ammonia, 1 mg of porcine renal acylase I (Sigma-Aldrich) and 1.56 mg $CoSO_4.7H_2O$ were added. After 15 h at 37°C more acylase (1 mg) was added, and the hydrolysis was continued for 4 h. The reaction was stopped, and the acylase denatured by the addition of 0.1 ml of trifluoroacetic acid and heating at 50°C for 10 min. The solution was cleared with charcoal, and its pH was adjusted to 7 with ammonia. Most of the solvent was evaporated, the residue treated with 42 mg of precipitate was obtained. [34]

Yield: 57%

$[\alpha]^{20}_D$ -31.0; Literature: $[\alpha]^{20}_D$ -35.0.

**$^1$H NMR (300 MHz, $D_2O$):** δ 3.76 (1 H, t, *J* = 5.36 Hz, $NH_2C\underline{H}$), 2.71 (2 H, bs, $C\underline{H}_2CCH$), 2.38 (1H, s, CCH).

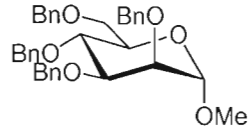
### II-6 L-Propargylglycine methyl ester hydrochloride 82



L-propargylglycine (0.182 g, 1.61 mmol) was stirred in MeOH (4 ml), $SOCl_2$ (0.2 ml, 2.7 mmol) was added, the mixture was stirred for several hours at room temperature then concentrated under reduced pressure to give methyl-L-propargyl glycinate which was used as a crude product without further purification.

## III Preparation of 2-(tetra-*O*-acetyl-α-D-mannopyranosyl) ethanoic acid and intermediary product **94**

### III.1 Methyl 2, 3, 4, 6-tetra-*O*-benzyl-α-D-mannopyranoside 84



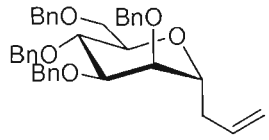

NaH (8.25 g, 200 mmol) in 50 ml DMF was stirred at 0 °C. Methyl α-D-mannopyranoside (5.01 g, 25.8 mmol) in 60 ml DMF was added by nozzle. After 2 h TBAI (0.949 g, 2.58 mmol) and BnBr (23.7 ml, 200 mmol) were added and the mixture was stirred overnight. Excess NaH was decomposed with MeOH (10 ml) and water (350 ml), and the mixture was extracted with EtOAc, washed with water, dried with $NaSO_4$ and concentrated under reduced pressure. The residue was eluted from a column of silica gel with EtOAc/Hexane (15%) to give **84** (11.50g) as a colorless oil. Spectroscopie data corresponded well with those of the literature. [35]

Yield: 80%

Rf: 0.50 (Hexane : EtOAc 7 : 3)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.40 (20 H, m, 4 x $C_6H_5$), 5.00 (1 H, m, H-1), 4.90-4.58 (8 H, m, 4 x $PhCH_2$), 4.05 (1 H, m), 3.98 (1 H, m), 3.85 (4 H, m), 3.41 (3 H, s, $CH_3$).

### III.2 3-(Tetra-*O*-benzyl-α-D-mannoppyranosyl)-1-propene 85



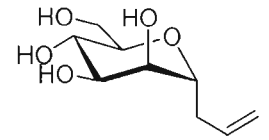

Compound **84** (9.3 g, 16.8 mmol) in $CH_3CN$ (25 ml) was stirred at 0 °C, TMSAllyl (7.2 ml, 45 mmol) was added, after 15 minute TMSOTf (3.9 ml, 20.2 mmol) was added dropwise, the reaction was stirred at 0 °C for 4 h and at room temperature for 20 h. Saturated $NaHCO_3$ solution (140 ml) was then added with stirring for 1 h. The mixture was extracted with $CH_2Cl_2$, washed with a solution of brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was eluted from a column of silica gel with EtOAc/Hexane (15%) to give **85** (7.509 g) as colorless oil. [36]

Yield: 79 %

Rf: 0.65 (Hexane: EtOAc 7: 3)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.38-7.20 (20 H, m, 4 x $C_6H_5$), 5.80-5.70 (1 H, m, C<u>H</u>=CHH), 5.02 (1 H, m, CH=C<u>H</u>H), 5.00 (1 H, m, CH=CH<u>H</u>), 4.60-4.50 (8 H, m, 4 x $PhCH_2$), 4.06 (1 H, m, H-1), 3.88-3.70 (5 H, m), 3.61 (1 H, dd, $J$ = 3.02, 4.67 Hz), 2.35 (2 H, m,C<u>H</u>$_2$CH).

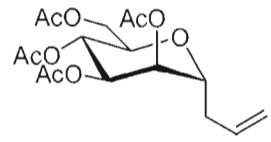
### III.3 3-(α-D-Mannopyranosyl)-1-propene 85a




To a solution of **85** (7.922 g, 14.0 mmol) in THF cooled to -78 °C was added lithium 1.0 g (144 mmol) and $NH_3$ (liquid) was condensed until the solution had a persistent blue color (about 4 h). The reaction mixture was stirred for an

additional 2 h and then quenched with ethanol. The reaction turned a pale yellow and was allowed to warm to room temperature and was stirred overnight to allow time for the ammonia to evaporate. The remaining solution was concentrated under reduced pressure to dryness.

### III.4 3-(Tetra-*O*-acetyl-α-D-mannoppyranosyl)-1-propene 91




The dried **85a** was dissolved in acetic anhydride (200 ml) and pyridine (200 ml), and catalytic DMAP (about 1 g) was added. The mixture was stirred over night, after which the solvent was evaporated with toluene. The crude product was extracted with $CH_2Cl_2$, washed with brine solution (saturated) and dried with $Na_2SO_4$. The residue was eluted from a column of silica gel with EtOAc/Hexane (15%) to give **91** (2.74 g, 7.36 mmol). [40]

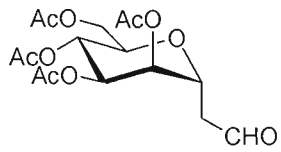
Yield: 53%

Rf: 0.16 (Ethyl acetate: hexane 3: 7)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 5.84-5.75 (1 H, m, C<u>H</u>=$CH_2$), 5.28-5.24 (1 H, dd, *J* = 3.30, 8.79 Hz, H-3), 5.22-5.12 (4 H, m, CH=C<u>H</u>$_2$), 4.35-4.29 (1 H, dd, *J* = 6.32, 12.09 Hz), 4.10 (1 H, dd, *J* = 2.75, 12.09 Hz), 4.07-4.01 (1 H, m), 3.92-3.86 (1 H, m), 2.59-2.38 (2 H, m, C<u>H</u>$_2$CH), 2.12-2.02 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.1, 170.6, 170.3, 170.1 (O<u>C</u>O$CH_3$), 132.9 (<u>C</u>H=$CH_2$), 118.7 (CH=<u>C</u>H$_2$), 74.5, 71.0, 70.4, 69.1, 67.3, 62.8, 33.9 (<u>C</u>H$_2$CH), 21.3, 21.1, 21.1 (OCO<u>C</u>H$_3$).

### III.5 2-(Tetra-*O*-acetyl-α-D-mannopyranosyl)ethanal 92




Compound **91** (2.74 g, 7.36 mmol) was dissolved in dichlomethane [40] (50 ml), the solution was cooled to -78 °C and ozone was bubbled through the solution until a blue color was obtained (about 2-3 h). Nitrogen gas was then bubbled through the solution until it became colorless. Acetic acid (6.5 ml) was added to the solution at -78 °C and zinc dust (6.5 g) was slowly added to the vigorously stirred solution. This was allowed to come to room temperature and left stirring for the week end.

The mixture was filtered over Celite and concentrated and purified by flash column chromatography using EtOAc/Hexane (50%) affording the purified compound as a colorless oil (1.31 g). [40]

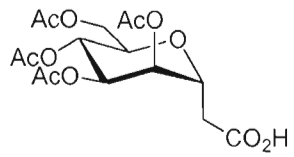
Yield: 48 %

Rf: 0.22 (Ethyl acetate : hexan 1 : 1)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.73-9.71 (1 H, dd, *J* = 1.37, 3.02 Hz, CHO), 5.27-5.24 (1 H, dd, *J* = 3.30, 6.87Hz), 5.12-5.05 (2 H, m), 4.64-4.53 (2 H, m), 4.10-4.05 (1 H, dd, *J* = 3.57, 12.09 Hz), 3.99-3.93 (1 H, m, H-1), 2.83-2.74 (1 H, ddd, *J* = 3.02, 9.34, 16.48 Hz, C<u>H</u>HCHO), 2.69-2.62 (1 H, ddd, *J* = 1.37, 4.40, 16.48 Hz, CH<u>H</u>CHO), 2.13-2.09 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 198.7 (<u>C</u>HO), 171.1, 170.2, 169.9 (O<u>C</u>$OCH_3$), 72.7, 69.6, 68.1, 67.8, 67.5, 61.5, 44.3 (<u>C</u>$H_2$CHO), 21.1, 21.1, 21.1, 21.1 (4 x $OCO\underline{C}H_3$).

### III.6 2-(Tetra-*O*-acetyl-α-D-mannopyranosyl) ethanoic acid 93



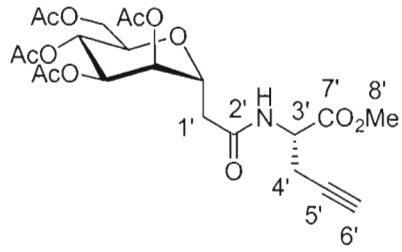

Compound **92** (1.310 g, 3.50 mmol) was dissolved in tert-butanol [40] (18 ml), $KH_2PO_4$ (1.25 M, 6.14 ml) was added and the solution was vigorously stirred. $KMnO_4$ (1.0 M, 7.3 ml) was added and vigorously stirred for 10 minute. $Na_2SO_3$ solution (saturated) was then added drop wise to neutralize the $KMnO_4$. The precipitated $MnO_2$ was filtered, washed with 95% EtOH and the filtrate was concentrated under reduced pressure. $CHCl_3$ (33 ml) and saturated NaCl (13 ml) were added to the concentrated solution and the pH was adjusted to 3.0 with 1.0 N aqueous HCl solution. The acid was taken up in $CHCl_3$ and the aqueous layer was extracted with $CHCl_3$ (33 ml x 2). The combined organic extract was dried over $Na_2SO_4$ and concentrated to afford **93** (1.282 g); it was used directly without further purification.

Yield: 94%

Rf: 0.41 (Methanol: dichloromethane 1: 9)

**$^1$H NMR (300 MHz, $CHCl_3$):** δ 10.12-10.18 (1 H, bs, $CO_2H$), 5.17 (1 H, bs), 5.07 (2 H, bs), 4.35 (2 H, bs), 4.09 (1 H, bs), 3.92 (1 H, bs), 2.63 (2 H, bs, $C\underline{H}_2CO_2H$).

### III.7 N-(Methyl propargyl-L-glycine)-1'-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)acetamide 94




To solution of 2-(tetra-O-acetyl-α-D-mannopyranosyl) ethanoic acid **93** (0.785 g, 2.01 mmol) in DCM (20 ml), L-methylpropargylglycine hydrochloride (0.403 g, 2.46 mml) and BOP( 1.08 g, 2.44 mmol) were added successively, then under nitrogen DIPEA (1.15 ml, 6.58 mmol) was added. The reaction was stirred overnight at room temperature. The mixture was then evaporated under reduced pressure, the residue was washed with 1 M $KHSO_4$, 1 M NaOH, and brine, dried with $Na_2SO_4$, and purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$ = 5%) to afford **94** (0.84 g) as a syrup.

Yield : 84%

Rf: 0.27 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_D$ = +22.7 (*c* = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 6.90-6.87 (1 H, d, *J* = 7.97 Hz, NH), 5.30-5.28 (1 H, dd, *J* = 3.30, 6.60 Hz), 5.16-5.10 (2 H, m), 4.78-4.72 (1 H, dt, *J* = 7.69, 4.95 Hz,H-3'), 4.49-4.40 (2 H, m), 4.30-4.24 (1 H, dd, *J* = 4.81, 11.95 Hz), 4.07-4.04 (1 H, dd, *J* = 5.08, 11.90 Hz), 3.79 (3 H, s, $OCH_3$), 2.80-2.78 (2 H, m, H-4'), 2.69-2.61 (1 H, dd, *J* = 8.79, 15.38 Hz, Ha-1'), 2.60-2.54 (1 H, dd, *J* = 4.40, 15.38 Hz, Hb-1'), 2.11-2.08 (12 H, m, $OCOCH_3$), 2.07 (1 H, s, H-6').

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.0, 170.2, 169.9, 169.9, 169.0 ($O\underline{C}OCH_3$, C-2', C-7'), 78.8 (C-5'), 72.5, 72.2, 69.5, 69.3, 68.1, 67.8, 61.8 (C-6'), 53.1 (C-3'), 51.1 (C-8'), 37.4 (C-1'), 22.6 (C-4'), 21.2, 21.1, 21.0 ($OCO\underline{C}H_3$).

# IV Synthesis of α-D-mannopyranoside derivatives modified at position 1 — series 1 of C-mannosides

**General procedure of click chemistry**

To solution of alcyne derivative (1 eq) in toluene, azido derivative (1.2- 2 eq), and CuI (1% molar) were added, and under nitrogen, DIPEA (1.2-1.5 eq) was added, the mixture was stirred overnight at room temperature. The mixture was then evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$ = 5%) to afford products as oil.

**Standard Zemplén deacetylation procedure**

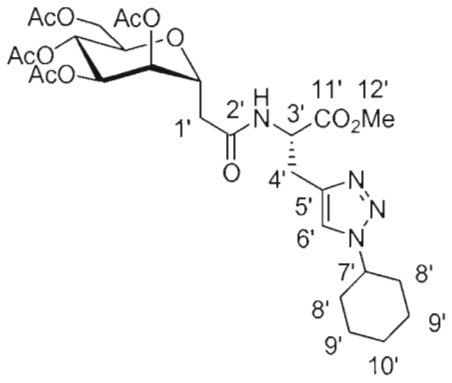
The sugars were dissolved in methanol followed by the addition of a 1 M solution of sodium methoxide in methanol (0.5 – 1.0 eq). The reaction mixtures were stirred overnight at room temperature and neutralized with Amberlite resin IR-120 ($H^+$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$ = 15%) or lyophilized to afford sugars as a solid.

**Standard saponification procedure with LiOH solution (1M, THF: MeOH: $H_2O$ = 3: 2: 1)**

The sugars were dissolved in LiOH solution, the mixture was stirred at room temperature until the reaction was finished as checked by TLC. Amberlite resin IR-120 ($H^+$) was then added to adjust the pH to 7, filtered with filter paper, and washed with MeOH. The filtrate was evaporated under reduced pressure and the residues were lyophilized to afford sugars as solids.

## IV.1 Synthesis of compound 100

### IV.1.0 Synthesis of compound 98




Synthesis of compound **98** was accomplished by following the 'General procedure of click chemistry' described above using cyclohexyl azide and compound **94**.

Yield: 94%

Rf: 0.24 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_{D}$ +21.2 ($c$ = 1, $CHCl_3$)

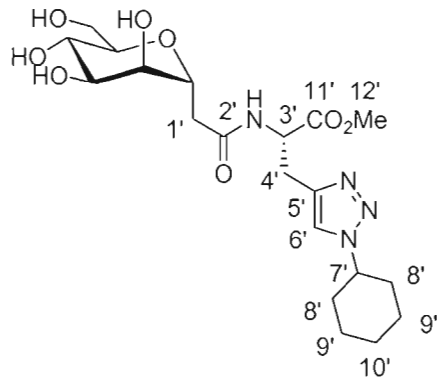
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.38 (1 H, s, H-6'), 7.14-7.12 (1 H, d, $J$ = 7.69 Hz, NH), 5.28-5.24 (1 H, dd, $J$ = 3.30, 7.14 Hz), 5.17-5.13 (2 H, m), 4.92-4.86 (1 H, dd, $J$ = 5.22, 12.91 Hz, H-3'), 4.45-4.35 (2 H, m), 4.20-4.16 (1 H, dd, $J$ = 4.40, 11.82 Hz), 4.05-4.00 (1 H, dd, $J$ = 5.91, 10.58 Hz), 3.72 (3 H, s, H-12'), 3.27-3.24 (2 H, t, $J$ = 5.22 Hz, H-4'), 2.68-2.60 (1 H, dd, $J$ = 8.79, 15.11 Hz, Ha-1'), 2.58-2.51 (1 H, dd, $J$ = 4.67, 15.11 Hz, Hb-1'), 2.19-2.16 (2 H, m), 2.09-2.05 (12 H, m, $OCOCH_3$), 1.97-1.90 (2 H, m), 1.78-1.66 (3 H, m), 1.54-1.43 (2 H, m), 1.33-1.25 (1 H, m).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.6, 170.9, 170.1, 170.0, 169.8, 169.0 ($O\underline{C}OCH_3$, C-2', C-11'), 142.5 (C-5'), 120.1 (C-6'), 71.9 (C-1), 70.6 (C-5), 69.6

(C-2), 68.5 (C-3), 67.4 (C-4), 62.0 (C-6), 60.3 (C-7'), 52.7 (C-3'), 52.2 (C-12'), 37.0 (C-1'), 33.6 (C-8'), 27.9 (C-10'), 25.3 (C-9'), 21.0, 21.0, 20.9 (4 x $OCO\underline{C}H_3$).

**MS (ESI):** 625.5 $[M+H]^+$, calcd. 625.27 for $C_{28}H_{40}N_4O_{12} + H^+$

### IV.1.1 Synthesis of compound 99




Deprotection of acetylated **98** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 81%

Rf: 0.53 (Methanol: dichloromethane 2: 8)

$[\alpha]^{20}_D$ +20 ($c$ = 1, $CH_3OH$)

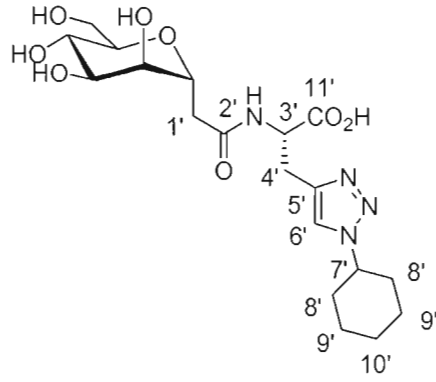
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.80 (1 H, s, H-6'), 4.69-4.65 (1 H, dd, $J$ = 5.36, 7.83 Hz, H-3'), 4.44-4.36 (1 H, m), 4.23-4.17 (1 H, m, H-1), 3.85-3.79 (1 H, dd, $J$ = 6.59, 11.81 Hz), 3.67-3.63 (6 H, H-12' and 3 H of sugar), 3.57-3.53 (1 H, m), 3.24-3.17 (1 H, dd, $J$ = 5.22, 14.83 Hz, Ha-4'), 3.13-3.05 (1 H, dd, $J$ = 8.10, 14.83 Hz, Hb-4'), 2.64-2.56 (1 H, dd, $J$ = 9.20, 15.11 Hz, Ha-1'), 2.50-2.44 (1 H, dd, $J$ = 4.94, 15.11 Hz, Hb-1'), 2.11-2.06 (2 H, m), 1.88-1.83 (2 H, m), 1.79-1.68 (3 H, m), 1.53-1.43 (2 H, m), 1.39-1.24 (2 H, m).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 174.0 (C-2'), 173.7 (C-11'), 144.2 (C-5'), 123.4

(C-6'), 78.3 (C-5), 74.7 (C-1), 73.2 (C-3), 72.4 (C-2), 70.4 (C-4), 63.1 (C-6), 62.3 (C-7'), 54.6 (C-3'), 53.8 (C-12'), 38.1 (C-1'), 35.2 C-8'), 29.3 (C-4'), 27.0 (C-10').

**MS (ESI):** 457.4 $[M+H]^+$, calcd. 457.23 for $C_{20}H_{32}N_4O_8 + H^+$

### IV.1.2. Synthesis of compound 100




Hydrolysis of the methyl ester function of **99** was accomplished following the 'Standard saponification procedure with a solution of LiOH described above.

Yield: 94%

$[\alpha]^{20}_D$ +38.5 ($c$ = 1, $CH_3OH$)

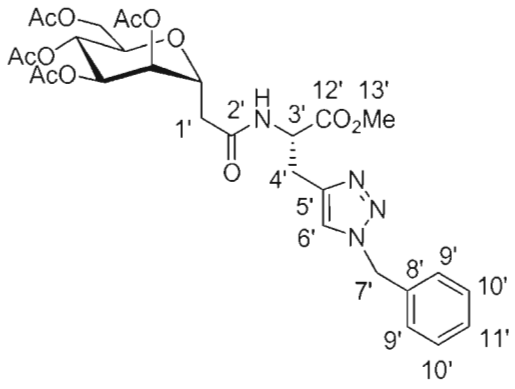
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.80 (1 H, s, H-6'), 7.72 (1 H, s, NH), 4.65 (1 H, m, H-3'), 4.48 (1 H, b), 4.38 (1 H, m), 4.20 (1 H, m), 3.80 (1 H, m), 3.60 (3 H, m), 3.20 (1 H, m, Ha-4'), 3.10 (1 H, m, Hb-4'), 2.60 (1 H, m, Ha-1'), 2.45 (1 H, m, Hb-1'), 2.10 (2 H, m), 1.78 (5 H, m), 1.42 (2 H, m), 1.25 (1 H, m).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 174.1, 173.7, 173.3 (C=O), 142.8 (C-5'), 123.5 (C-6'), 78.4 (C-5), 74.9 (C-1), 73.2 (C-3), 72.6 (C-2), 70.3 (C-4), 63.1 (C-6), 62.3 (C-7'), 54.6 (C-3'), 53.8, 38.0 (C-1'), 35.3 (C-8'), 30.5 (C-4'), 29.3 (C-10'), 27.0 (C-9').

**MS (ESI):** 443.4 $[M+H]^+$, calcd. 443.22 for $C_{19}H_{30}N_4O_8 + H^+$

## IV.2 Synthesis of compound 103

### IV.2.0 Synthesis of compound 101




Synthesis of compound **101** was accomplished by following the 'General procedure of click chemistry' described above using benzyl azide and compound **94**.

Yield: 95%

Rf: 0.18 (Methanol: dichloromethane 2: 8)

$[\alpha]^{20}_{D}$ +22.9 ($c$ = 1, $CHCl_3$)

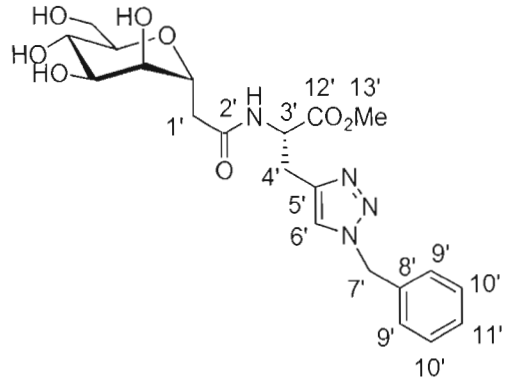
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.32 (1 H, s, H-6'), 7.31-7.28 (2 H, m, H-10'), 7.21-7.28 (3 H, m, H-9', H-11'), 5.45 (2 H, s, H-7'), 5.23-5.20 (1 H, dd, $J$ =3.16, 7.56 Hz, H-3'), 5.13-5.09 (2 H, m), 4.83-4.81 (1 H, m), 4.38 (1 H, m), 4.28 (1 H, m), 4.18-4.13 (1 H, m), 3.97-3.95 (1 H, m), 3.62 (3 H, s, H-13'), 3.19-3.18 (2 H, d, $J$ = 4.67 Hz, H-4'), 2.64-2.56 (1 H, dd, $J$ =8.65, 15.25 Hz, Ha-1'), 2.54-2.47 (1 H, dd, $J$ = 4.94, 15.11 Hz, Hb-1'), 2.04-1.99 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.6 (C-2'), 170.9 (C-12'), 170.2, 170.0, 169.8, 168.9 ($O\underline{C}OCH_3$), 143.4 (C-5'), 135.1 (C-8'), 129.3 (C-9'), 129.0 (C-10'), 128.2 (C-11'), 123.0 (C-6'), 72.0 (C-1), 70.5 (C-5), 69.5 (C-2), 68.5 (C-3), 67.4 (C-4),

62.0 (C-6), 54.2 (C-7'), 52.7 (C-3'), 52.1 (C-13'), 36.9 (C-1'), 28.0 (C-4'), 21.1, 21.0, 20.9 ($OCO\underline{C}H_3$).

**MS (ESI):** 633.4 $[M+H]^+$, calcd. 633.24 for $C_{29}H_{36}N4O_{12} + H^+$

### IV.2.1 Synthesis of compound 102




Deprotection of acetylated **101** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 73%

Rf: 0.40 (Methanol: dichloromethane 2: 8)

$[\alpha]^{20}_D$ +22.2 ($c$ = 1, $CH_3OH$)

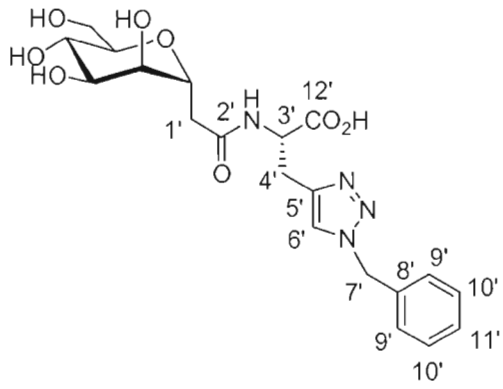
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.75 (1 H, s, H-6'), 7.35-7.23 (5 H, m, H-9', H-10', H-11'), 5.51 (2 H, s, H-7'), 4.69-4.65 (1 H, dd, $J$ = 5.49, 8.24 Hz, H-3'), 4.19 (1 H, m, H-1), 3.84-3.77 (1 H, dd, $J$ = 6.87, 11.81 Hz ), 3.68-3.63 (4 H, m ), 3.61 (3 H, s, H-13'), 3.54-3.49 (1 H, m), 3.23-3.17 (1 H, dd, $J$ = 5.22, 14.83 Hz, Ha-4'), 3.11-3.03 (1 H, dd, $J$ = 8.24, 14.83 Hz, Hb-4'), 2.59-2.51 (1 H, dd, $J$ = 9.34, 14.83 Hz, Ha-1'), 2.44-2.37 (1 H, dd, $J$ = 4.95, 14.83 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 174.0 (C-2'), 173.7 (C-12'), 145.5 (C-5'), 137.7 (C-8'),130.9 (C-9'), 130.4 (C-10'), 129.9 (C-11'), 125.5 (C-6'), 78.3 (C-5), 74.9 (C-1), 73.2 (C-3), 72.5 (C-2), 70.3 (C-4), 63.1 (C-6), 55.7 (C-7'), 54.5 (C-3'),

53.8 (C-13'), 38.0 (C-1'), 29.3 (C-4').

**MS (ESI):** 465.4 $[M+H]^+$, calcd. 465.20 for $C_{21}H_{28}N_4O_8 + H^+$

### IV.2.2. Synthesis of compound 103




Hydrolysis of the methyl ester function of **102** was accomplished following the 'Standard saponification procedure with a solution of LiOH as described above.

Yield: 95%

Rf: 0.2 (Methanol: dichloromethane 1: 1)

$[\alpha]^{20}_D$ +51.3 ($c$ = 1, $CH_3OH$)

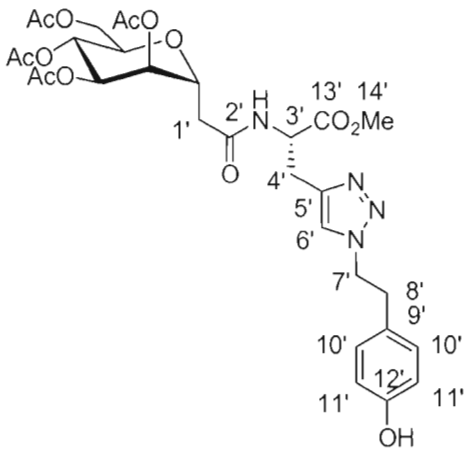
**$^1$H NMR (300 MHz, $CD_3OD$ + $D_2O$):** δ 7.66 (1 H, s, H-6'), 7.24-7.19 (3 H, m, H-9', H-11'), 7.14-7.11 (2 H, m, H-10'), 5.39 (2 H, s, H-7'), 4.52 (1 H, l, H-3'), 4.09-4.08 (1 H, m), 3.63-3.49 (5 H, m), 3.36 (1 H, s), 3.13-3.10 (1 H, m, Ha-4'), 2.99-2.92 (1 H, Hb-4'), 2.55-2.47 (1 H, m, Ha-1'), 2.25-2.17 (1 H, m, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$ + $D_2O$):** δ 174.5 (C-12'), 173.8 (C-1'), 145.5 (C-5'), 137.1 (C-8'), 130.9 (C-9'), 130.4 (C-10'), 129.8 (C-11'), 125.7 (C-6'), 77.0 (C-5), 76.1 (C-1), 72.8 (C-3), 72.7 (C-2), 69.4 (C-4), 62.8 (C-6), 55.7 (C-7'), 49.8 (C-3'), 37.3 (C-1'), 29.1 (C-4').

**MS (ESI):** 451.4 $[M+H]^+$, calcd. 451.19 for $C_{20}H_{26}N_4O_8 + H^+$

## IV.3. Synthesis of compound 106

### IV.3.0 Synthesis of compound 104




Synthesis of compound **104** was accomplished by following the 'General procedure of click chemistry' described above using azido tyramine acetate and compound **94**.

Yield: 59%

Rf: 0.28 (Methanol: dichloromethane 5: 95)

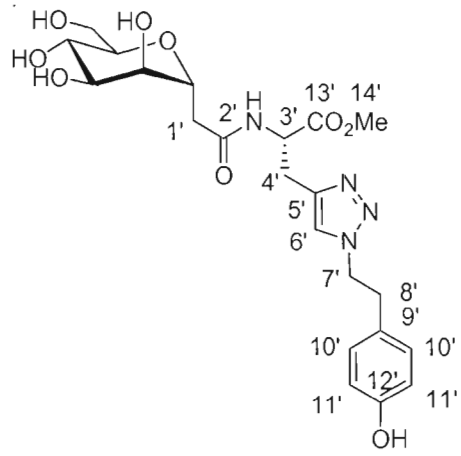
$[\alpha]^{20}_{D}$ +6.8 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.07 (1 H, s, H-6'), 6.87-6.74 (4 H, m, H-10', H-11'), 5.24-5.07 (2 H, m), 4.81-4.75 (1 H, dd, $J$ = 5.22 Hz, 7.42 Hz, H-3'), 4.62-4.51 (1 H, m), 4.48-4.30 (3 H, m), 4.20-4.15 (1 H, dd, $J$ = 3.85, 12.36 Hz), 4.02-3.97 (1 H, dd, $J$ = 5.91, 9.75 Hz), 3.47 (1 H, s), 3.71 (3 H, s, H-14'), 3.46 (1H, s), 3.20-3.18 (2 H, d, $J$ = 5.22 Hz, H-4'), 3.09-3.05 (2 H, t, $J$ = 6.46 Hz, H-8'), 2.66-2.61 (1 H, dd, $J$ = 8.79, 15.11 Hz, Ha-1'), 2.46-2.40 (1 H, dd, $J$ = 5.08, 15.25 Hz, Hb-1'), 2.09-2.03 (12 H, m , $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.5, 171.3, 170.5, 170.4, 170.0, 169.0 ($O\underline{C}OCH_3$, C-2', C-13'), 155.9 (C-12'), 142.2 (C-5'), 130.3 (C-9'), 128.6 (C-10'), 123.5 (C-6'), 116.0 (C-11'), 71.9 (C-1), 71.0 (C-5), 69.7 (C-2), 68.8 (C-3), 67.3 (C-4), 62.3 (C-6), 53.0 (C-3'), 52.3 (C-14'), 36.6 (C-8'), 36.1 (C-1'), 27.9 (C-4'), 21.2, 21.1, 21.0 ($OCO\underline{C}H_3$).

**MS (ESI):** 663.4 $[M+H]^+$, calcd.663.25 for $C_{30}H_{38}N_4O_{13} + H^+$

### IV.3.1 Synthesis of compound 105




Deprotection of acetylated **104** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 43%

Rf: 0.28 (Methanol: dichloromethane2: 8)

$[\alpha]^{20}_D$ +15.2 ($c$ = 1, $CH_3OH$)

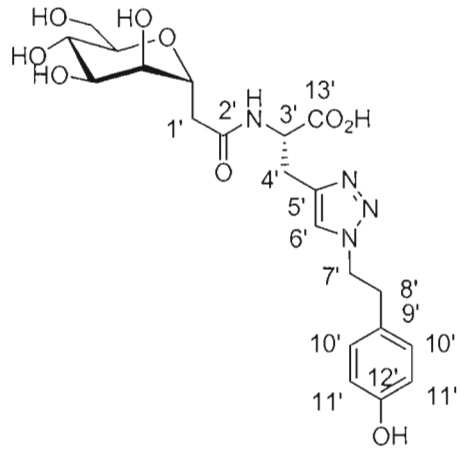
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.55 (1 H, s, H-6'), 6.89-6.87 (2 H, d, $J$ = 8.52 Hz, H-10'), 6.66-6.63 (2 H, d, $J$ = 8.52 Hz, H-11'), 4.66-4.62 (1 H, m, H-3'), 4.51-4.48 (2 H, t, $J$ = 7.01 Hz, H-7'), 4.21-4.18 (1 H, m, H-1), 3.85-3.79 (1 H, dd, $J$ = 6.87, 11.81 Hz), 3.69-3.61 (8 H, m, H-14', H-4', 3xHsucre), 3.56-3.52 (1 H,

m), 3.21-3.14 (1 H, dd, $J$ = 5.49, 15.11 Hz ), 3.01-3.06 (2 H, t, $J$ = 7.28 Hz, H-8'), 2.62-2.54 (1 H, dd, $J$ = 9.34, 14.83 Hz, Ha-1'), 2.49-2.43 (1 H, dd, $J$ = 4.94, 14.83 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 174.0, 176.6 (C=O), 158.1 (C-12'), 144.6 (C-5'), 131.6 (C-9'), 130.2 (C-10'), 125.6 (C-6'), 117.2 (C-11'), 78.3 (C-5), 74.8 (C-1), 73.2 (C-3), 72.4 (C-2), 70.4 (C-4), 63.1 (C-6), 54.5 (C-3'), 53.8 (C-14'), 38.1 (C-1'), 37.5 (C-8'), 29.2 (C-4').

**MS (ESI):** 495.4 $[M+H]^+$, calcd.495.21 for $C_{22}H_{30}N_4O9 + H^+$

### IV.3.2 Synthesis of compound 106




Hydrolysis of the methyl ester function of **105** was accomplished following the 'Standard saponification procedure with a solution of LiOH as described above.

Yield: quantitative

Rf: 0.08 (Methanol: dichloromethane2: 8)

$[\alpha]^{20}_D$ +23.5 ($c$ = 1, $H_2O$)

**$^1$H NMR (300 MHz, $CD_3OD$ + $D_2O$):** δ 7.59 (1 H, s, H-6'), 6.81-6.78 (2 H, d, $J$

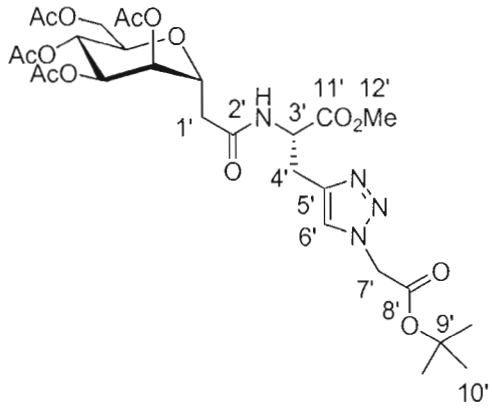
= 8.21 Hz, H-10'), 6.53-6.51 (2 H, d, *J* = 8.21 Hz, H-11'), 4.50-4.46 (3 H, m, H-7', H-3'), 4.21 (1 H, l, H-1), 3.81-3.68 (4 H, m, H-7', 2 x Hsucre), 3.66-3.61 (1 H, m), 3.55-3.50 (1 H, m), 3.27-3.20 (1 H, dd, *J* = 4.12, 14.83 Hz ), 3.08-3.03 (1 H, m), 3.00-2.95 (2 H, t, *J* = 9.34 Hz, H-8'), 2.69-2.62 ( 1H, dd, *J* = 9.34, 14.83 Hz, Ha-1'), 2.46-2.39 (1 H, dd, *J* = 4.94, 14.83 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$ + $D_2O$):** δ 178.3 (C-13'), 173.4 (C-2'), 166.9 (C-12'), 145.7 (C-5'), 131.3 (C-6'), 125.5 (C-9'), 124.5 (C-10'), 120.6 (C-11'), 77.5 (C-5), 75.7 (C-1), 72.9 (C-3), 72.1 (C-2), 69.9 (C-4), 63.0 (C-6), 56.6 (C-7'), 54.1 (C-3'), 37.8 (C-1'), 37.5 (C-8'), 30.2 (C-4').

**MS (ESI):** 481.4 $[M+H]^+$, calcd.481.20 for $C_{21}H_{28}N_4O_9 + H^+$

### IV.4 Synthesis of compound 108 and compound 109

#### IV.4.0 Synthesis of compound 107




Synthesis of compound **107** was accomplished by following the 'General procedure of click chemistry' described above using tert-butyl 2-azido acetate and compound **94**.

Yield: 99%

Rf: 0.25 (Methanol: dichloromethane 5: 95)

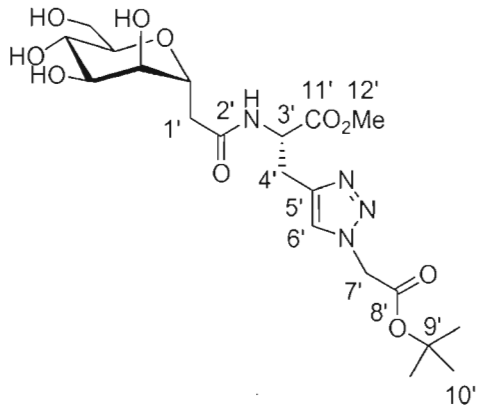
$[\alpha]^{20}_{D}$ +26.9 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.51 (1 H, s, H-6'), 7.14-7.11 (1 H, d, $J$ = 7.69 Hz, NH), 5.22-5.19 (1 H, dd, $J$ = 3.16, 7.55 Hz), 5.13-5.09 (2 H, m), 5.01 (2 H, s, H-7'), 4.90-4.86 (1 H, dd, $J$ = 5.22, 12.91 Hz, H-3'), 4.39-4.30 (2 H, m), 4.29-4.11 (1 H, dd, $J$ = 3.98, 11.95 Hz), 3.98-3.93 (1 H, dd, $J$ = 6.04, 10.16 Hz), 3.70 (3 H, s, H-12'), 3.27-3.25 (2 H, d, , $J$ = 5.22 Hz, H-4'), 2.65-2.51 (2 H, m, H-1'), 2.05-2.01 (12 H, m, $OCOCH_3$), 1.44 (9 H, s, H-10').

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.6 (C-2'), 170.9 (C-11'), 170.1, 170.0, 169.8, 168.9 ($O\underline{C}OCH_3$), 169.7 (C-8'), 143.2 (C-5'), 124.0 (C-6'), 83.9 (C-9'), 72.1 (C-1), 70.4 (C-5), 69.4 (C-2), 68.4 (C-3), 67.3 (C-4), 61.9 (C-6), 52.9 (C-7'), 52.0 (C-3'), 51.7 (C-12'), 36.9 (C-1'), 28.2 (C-4'), 28.0 (C-10'), 21.1, 21.0, 20.9 ($OCO\underline{C}H_3$).

**MS (ESI):** 657.4 $[M+H]^+$, calcd. 657.26 for $C_{28}H_{40}N_4O_{14} + H^+$

**IV.4.1a Synthesis of compound 108**




Deprotection of acetylated **107** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 31%

Rf: 0.30 (Methanol: dichloromethane 2:8)

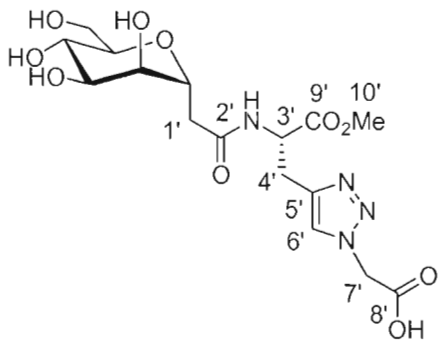
$[\alpha]^{20}_D$ +13.1 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.87 (1 H, s, H-6'), 5.31 (2 H, s, H-7'), 4.75 (1 H, b, H-3'), 4.24 (1 H, m, H-1), 3.78 (3 H, s, H-12'), 3.72 (3 H, m), 3.68 (2 H, m), 3.56 (1 H, b), 3.25 (1 H, m, Ha-4'), 3.18 (1 H, m, Hb-4'), 2.64 (1 H, dd, $J$ = 9.34, 14.83 Hz, Ha-1'), 2.51 (1 H, dd, $J$ = 4.95, 14.83 Hz, Hb-1'), 1.28 (9 H, s, H-10').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 173.4 (C-2'), 173.4 (C-11'), 169.6 (C-8'), 77.9 (C-5), 74.8 (C-1), 73.0 (C-3), 72.3 (C-2), 70.0 (C-4), 62.8 (C-6), 54.1 (C-3'), 53.9 (C-12'), 53.5 (C-7'), 37.7 (C-1'), 31.3 (C-4'), 29.0 (C-10').

**MS (ESI):** 489.5 $[M+H]^+$, calcd.489.22 for $C_{20}H_{32}N_4O_{10} + H^+$

### IV.4.1b Synthesis of compound 109




Deprotection of acetylated **107** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 41%

Rf: 0.19 (Methanol: dichloromethane 1:1)

$[\alpha]^{20}_D$ +30.5 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $D_2O$):** δ 7.69 (1 H, s, H-6'), 4.89 (2 H, s, H-7'), 4.21-4.16 (1

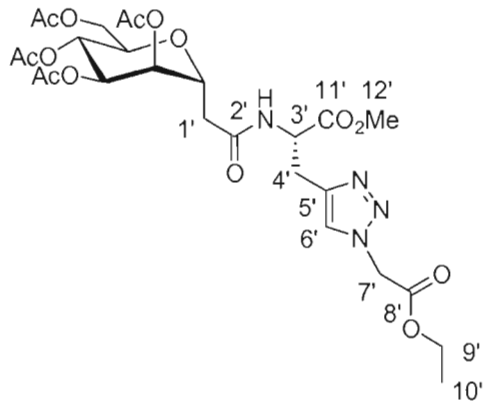
H, m, H-1), 3.74-3.69 (2 H, m), 3.64-3.53 (6 H, m, OMe), 3.45-3.41 (1 H, m), 3.22-3.12 (2 H, m, H-4'), 2.70-2.62 (1 H, dd, $J$ = 9.75, 14.97 Hz, Ha-1'), 2.45-2.39 (1 H, dd, $J$ = 5.08, 14.97 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $D_2O$):** δ 173.4 (C-8'), 172.9 (C-2'), 172.6 (C-9'), 125.5 (C-6'), 80.1 (C-5), 75.0 (C-1), 70.8 (C-3), 70.6 (C-2), 67.1 (C-4), 61.0 (C-6), 53.2 (C-7'), 52.7 (C-3'), 52.6 (C-10'), 35.1 (C-1'), 26.9 (C-4').

**MS (ESI):** 433.5 $[M+H]^+$, calcd.433.16 for $C_{16}H_{24}N_4O_{10} + H^+$

## IV.5 Synthesis of compound 112

### IV.5.0 Synthesis of compound 110




Synthesis of compound **110** was accomplished by following the 'General procedure of click chemistry' described above using ethyl 2-azido acetate and compound **94**.

Yield: 77%

Rf: 0.19 (Methanol: dichloromethane 5:95)

$[\alpha]^{20}_D$ +31.3 ($c$ = 1, $CHCl_3$)

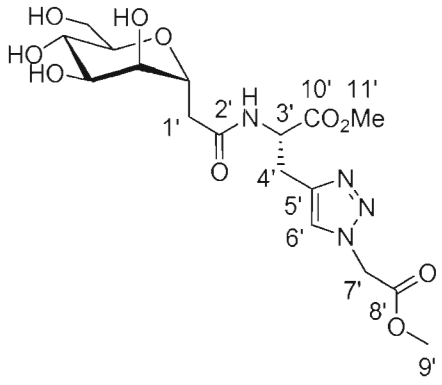
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.54 (1 H, s, H-6'), 7.20-7.15 (1 H, t, $J$ = 6.87 Hz,

NH), 5.21-5.18 (1 H, dd, $J$ = 3.17, 7.56 Hz), 5.13-5.09 (4 H, m, H-7'), 4.87-4.85 (1 H, d, $J$ = 6.87 Hz, H-3'), 4.37-4.27 (2 H, m, H-1), 4.23-4.16 (2 H, q, $J$ = 7.14 Hz H-9'), 4.14-4.09 (1 H, dd, $J$ = 2.89, 11.95 Hz), 3.97-3.94 (1 H, dd, $J$ = 6.04, 9.89 Hz), 3.69 (3 H, s, H-12'), 3.26 (2 H, s, H-4'), 2.62-2.57 (2 H, m, H-1'), 2.04-1.99 (12 H, m, $OCOCH_3$), 1.27-1.22 (3 H, t, $J$ = 7.14 Hz, H-10').

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.6 (C-2'), 170.9 (C-11'), 170.2, 170.1, 169.8, 169.0 ($O\underline{C}OCH_3$), 166.7 (C-8'), 143.2 (C-5'), 124.2 (C-6'), 71.9 (C-1), 70.7 (C-5), 69.4 (C-2), 68.5 (C-3), 67.2 (C-4), 62.5 (C-6), 62.0 (C-9'), 52.9 (3'), 52.0 (12'), 51.0 (C-7'), 36.7 (C-1'), 27.9 (C-4'), 21.1, 21.0, 20.9 ($OCO\underline{C}H_3$), 14.3 (C-10').

**MS (ESI):** 629.4 $[M+H]^+$, calcd.629.23 for $C_{26}H_{36}N_4O_{14} + H^+$

### IV.5.1 Synthesise of compound 111




Deprotection of acetylated **110** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 88%

Rf: 0.28 (Methanol: dichloromethane 20:80)

$[\alpha]^{20}_D$ +23.4 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.87 (1 H, s, H-6'), 5.32 (2 H, s, H-7'), 4.78-4.73 (1 H, dd, $J$ = 5.22, 7.97 Hz, H-3'), 4.27-4.21 (1 H, m, H-1), 3.86-3.80

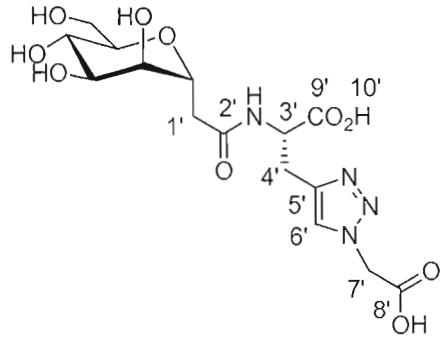
(1 H, m), 3.78 (3 H, s, $CH_3$), 3.72 (3 H, s, $CH_3$), 3.68-3.64 (4 H, m), 3.58-3.54 (1 H, m), 3.31-3.25 (1 H, dd,

$J$ = 5.22, 15.11 Hz, Ha-4'), 3.20-3.13 (1 H, dd, $J$ = 8.24, 15.11 Hz, Hb-4'), 2.70-2.61 (1 H, dd, $J$ = 9.20, 14.97 Hz, Ha-1'), 2.55-2.48 (1 H, dd, $J$ = 5.08, 14.97 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 173.9 (C-2'), 173.7 (C-10'), 169.9 (C-8'), 145.3 (C-5'), 127.0 (C-6'), 78.1 (C-5), 75.1 (C-1), 73.2 (C-3), 72.5 (C-2), 70.2 (C-4), 63.1 (C-6), 54.4 (C-3'), 54.2 (C-11'), 53.8 (C-9'), 52.4 (C-7'), 38.0 (C-1'), 29.2 (C-4').

**MS (ESI):** 447.4 $[M+H]^+$, calcd.447.18 for $C_{17}H_{26}N_4O_{10} + H^+$

### IV.5.2 Synthesis of compound 112




Hydrolysis of the methyl ester function of **111** was accomplished following the 'Standard saponification procedure with a solution of LiOH as described above.

Yield: 99%

Rf: 0.18 (Methanol: dichloromethane 20:80)

$[\alpha]^{20}_D$ +33.5 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.77 (1 H, s, H-6'), 4.77 (1 H, s, H-3'), 4.25 (1

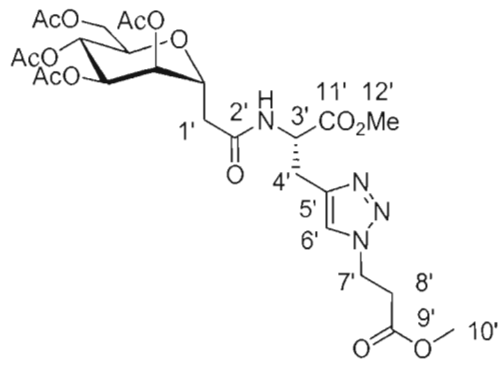
H, s, b, H-1), 3.84-3.79 (1 H, m), 3.74 (2 H, s, H-7'), 3.72-3.60 (4 H, m), 3.57-3.55 (1 H, m), 3.22 (2 H, bs, H-4'), 2.68-2.60 (1 H, dd, $J$ = 8.65, 14.70 Hz, Ha-1'), 2.58-2.51 (1 H, dd, $J$ = 5.63, 14.70 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 174.0 (C-9'), 173.8 (C-8'), 173.5 (C-2'), 127.0 (C-6'), 78.0 (C-5), 75.4 (C-1), 73.1 (C-3), 72.6 (C-2), 70.2 (C-4), 63.1 (C-6), 54.3 (C-3'), 53.8 (C-7'), 37.9 (C-1'), 29.2 (C-4').

**MS (ESI):** 419.6 $[M+H]^+$, calcd.419.14 for $C_{15}H_{22}N_4O_{10} + H^+$

## IV.6 Synthesis of compound 115

### IV.6.0 Synthesis of compound 113




Synthesis of compound **113** was accomplished by following the 'General procedure of click chemistry' described above using methyl 3-azido propionate and compound **94**.

Yield: 92%

Rf: 0.20 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_D$ +24.0 ($c$ = 1, $CHCl_3$)

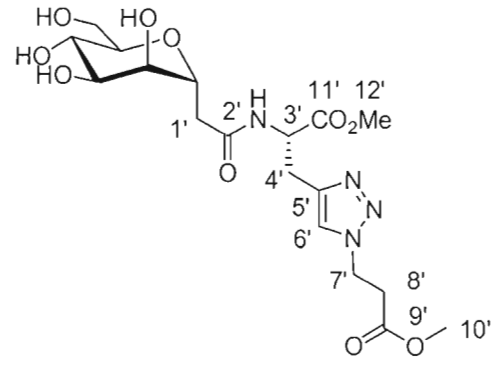
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.46 (1 H, s, H-6'), 7.16-7.13 (1 H, d, $J$ = 7.69 Hz, NH), 5.20-5.16 (1 H, dd, $J$ = 3.30, 7.69 Hz, Ha-6), 5.09-5.07 (2 H, Hb-6, H-2),

4.84-4.77 (1 H, dd, $J$ = 5.22, 12.91 Hz, H-3'), 4.57-4.52 (2 H, t, $J$ = 6.46 Hz, H-8'), 4.38-4.32 (1 H, m, H-1), 4.29-4.23 (1 H, dd, $J$ = 5.76, 12.09 Hz, H-4), 4.14-4.09 (1 H, dd, $J$ = 3.98, 12.45 Hz, H-5), 3.97-3.92 (1 H, dd, $J$ = 5.91, 10.30 Hz, H-3), 3.65 (3 H, s, $CH_3$), 3.62 (3 H, s, $CH_3$), 3.19-3.17 (2 H, d, $J$ = 5.22 Hz, H-4'), 2.90-2.86 (2 H, t, $J$ = 6.46 Hz, H-8'), 2.65-2.57 (1 H, dd, $J$ = 8.52, 15.11 Hz, Ha-1'), 2.55-2.48 (1 H, dd, $J$ = 5.22, 15.11 Hz, Hb-1'), 2.02-1.97 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.5, 171.1, 170.9, 170.1, 170.0, 169.8, 168.9 ($O\underline{C}OCH_3$, C-2', C-9', C-11'), 142.8 (C-5'), 123.4 (C-6'), 71.9 (C-1), 70.7 (C-5), 69.5 (C-2), 68.5 (C-4), 67.3 (C-3), 62.0 (C-6), 52.7 (C-3'), 52.3 (C-12'), 52.0 (C-10'), 45.7 (C-7'), 36.8 (C-1'), 34.5 (C-4'), 27.8 (C-8'), 21.0, 21.0, 20.9, 20.9 ($OCO\underline{C}H_3$).

**MS (ESI):** 629.4 $[M+H]^+$, calcd.629.23 for $C_{26}H_{36}N_4O_{14} + H^+$

### IV.6.1 Synthesis of compound 114




Deprotection of acetylated **113** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 74%

Rf: 0.25 (Methanol: dichloromethane 20: 80)

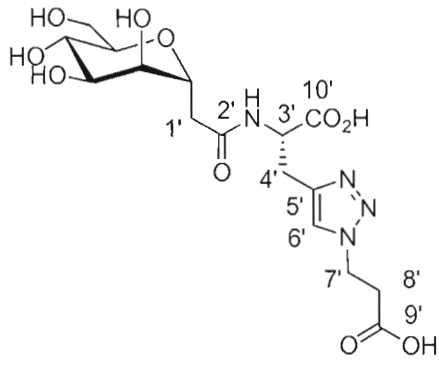
$[\alpha]^{20}_{D}$ +20.8 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.83 (1 H, s, H-6'), 4.75-4.70 (1 H, dd, $J$ = 5.22, 7.97 Hz, H-3'), 4.66-4.62 (2 H, t, $J$ = 6.59 Hz, H-7'), 4.25-4.21 (1 H, m, H-1), 3.87-3.81 (1 H, dd, $J$ = 6.59, 11.81 Hz), 3.71 (3 H, s, $CH_3$), 3.67 (3 H, s, $CH_3$), 3.71-3.67 (4 H, m), 3.60-3.55 (1 H, m), 3.21-3.28 (1 H, dd, $J$ = 5.22, 15.11 Hz, Ha-4'), 3.16-3.08 (1 H, dd, $J$ = 8.24, 14.83 Hz, Hb-4'), 2.00-1.96 (2 H, t, $J$ = 6.59 Hz, H-8'), 2.69-2.61 (1 H, dd, $J$ = 9.07, 14.83 Hz, Ha-1'), 2.55-2.49 (1 H, dd, $J$ = 5.08, 14.83 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 173.1, 172.8, 172.6 (C=O), 144.0 (C-5'), 125.1 (C-6'), 77.4 (C-5), 74.1 (C-1), 72.4 (C-3), 71.7 (C-2), 69.5 (C-4), 62.2 (C-6), 53.6 (C-3'), 53.0 (C-12'), 52.5 (C-10'), 46.9 (C-7'), 37.2 (C-1'), 35.1 (C-4'), 28.4 (C-8').

**MS (ESI):** 461.4 $[M+H]^+$, calcd.461.19 for $C_{18}H_{28}N_4O_{10} + H^+$

### IV.6.2 Synthesis of compound 115




Hydrolysis of the methyl ester function of **114** was accomplished following the 'Standard saponification procedure with a solution of LiOH as described above.

Yield: quantitative

$[\alpha]^{20}_D$ + 41.1 (c = 1, $CH_3OH$)

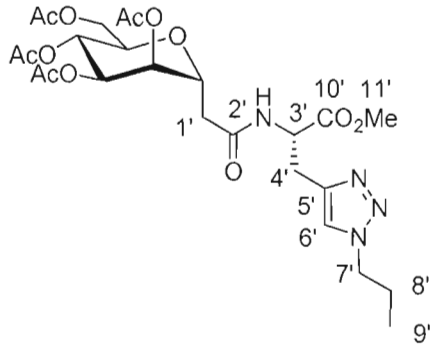
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.83 (1 H, l, H-6'), 4.64-4.60 (2 H, t, *J* =6.40 Hz, H-7'), 4.24 (1 H, b, H-3'), 3.81 (1 H, b), 3.72-3.49 (6 H, m), 3.57 (1 H, m), 3.13 (1 H, b, Ha-4'), 3.00-2.95 (2 H, t, *J* = 7.09 Hz, H-8'), 2.82 (1 H, b, Hb-4'), 2.69-2.61 (1 H, m, Ha-1'), 2.55-2.48 (1 H, m, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 172.5, 172.0, 171.5 (C=O), 123.8 (C-6'), 76.3 (C-5), 73.0 (C-1), 71.1 (C-3), 70.6 (C-2), 68.4 (C-4), 61.1 (C-6), 51.3 (C-3'), 45.7 (C-7'), 36.1 (C-1'), 33.9 (C-8'), 28.2 (C-4').

**MS (ESI):** 433.5 $[M+H]^+$, calcd.433.16 for $C_{16}H_{24}N_4O_{10} + H^+$

## IV.7 Synthesis of compound 118

### IV.7.0 Synthesis of compound 116




Synthesis of compound **116** was accomplished by following the 'General procedure of click chemistry' described above using propyl azide and compound **94**.

Yield: 80%

Rf: 0.30 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_D$ +27.8 (*c* = 1, $CHCl_3$)

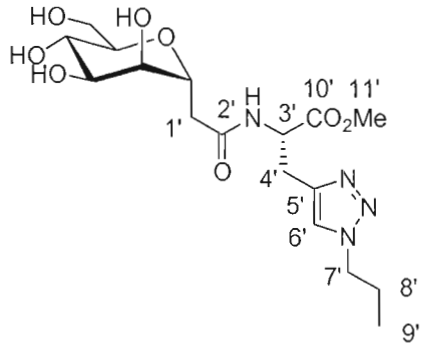
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.35 (1 H, s, H-6'), 7.22-7.20 (1 H, d, *J* = 6.32

Hz, NH), 5.20-5.17 (1 H, m, H-3), 5.11-5.06 (2 H, m, H-2, H-4), 4.83-4.80 (1 H, m, H-3'), 4.36-4.34 (1 H, m, H-1), 4.27-4.19 (3 H, m, Ha-6, H-7'), 4.14-4.10 (1 H, m, Hb-6), 3.96-3.94 (1 H, m, H-5), 3.63 (3 H, s, H-11'), 3.18 (2 H, b, H-4'), 2.65-2.57 (1 H, dd, $J$ = 8.71, 15.11 Hz, Ha-1'), 2.54-2.47 (1 H, dd, $J$ = 4.81, 15.11 Hz, Hb-1'), 2.02-1.96 (12 H, m,$OCOCH_3$), 1.88-1.80 (2 H, m, H-8'), 0.88-0.81 (3 H, m, H-9').

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.2, 170.4, 169.7, 169.5, 169.3, 168.5 ($O\underline{C}OCH_3$, C-2', C10'), 142.4 (C-5'), 121.9 (C-6'), 71.5 (C-1), 70.2 (C-5), 69.1 (C-2), 68.0 (C-4), 66.9 (C-3), 61.5 (C-6), 52.3 (C-7'), 51.6 (C-3'), 51.6 (C-11'), 36.5 (C-1'), 27.5 (C-4'), 23.4 (C-8'), 20.6, 20.5, 20.5, 20.5 ($OCO\underline{C}H_3$), 10.7 (C-9').

**MS (ESI):** 585.4 $[M+H]^+$, calcd.585.24 for $C_{25}H_{36}N_4O_{12} + H^+$

### IV.7.1 Synthesis of compound 117




Deprotection of acetylated **116** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 75%

Rf: 0.30 (Methanol: dichloromethane 2: 8)

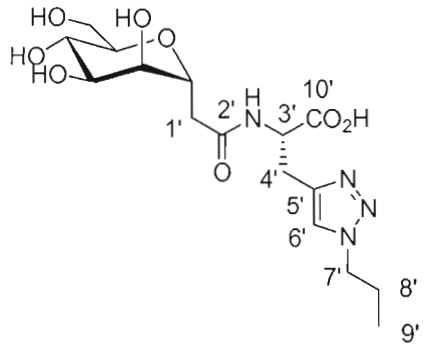
$[\alpha]^{20}_D$ +26.8 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.81 (1 H, s, H-6'), 4.87 (s, OH), 4.74-4.70 (1 H, dd, *J* = 5.36, 7.83 Hz, H-3'), 4.35-4.31 (2 H, t, *J* = 6.87 Hz, H-7'), 4.26-4.23 (1 H, m, H-1), 3.88-3.82 (1 H, dd, *J* = 6.59, 11.8 1Hz), 3.71 (7 H, b, H-11', 4 x Hsucre), 3.58 (1 H, l), 3.29-3.22 (1 H, dd, *J* = 5.22, 14.56 Hz, Ha-4'), 3.18-3.10 (1 H, dd, *J* = 8.24, 15.11 Hz, Hb-4'), 2.69-2.61 (1 H, dd, *J* = 9.48, 14.70 Hz, Ha-1'), 2.54-2.48 (1 H, dd, *J* = 4.81, 14.97 Hz, Hb-1'), 1.93-1.86 (2 H, q, *J* = 7.14 Hz, H-8'), 0.92-0.87 (3 H, t, *J* = 7.42 Hz, H-9').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 173.2, 172.9 (C-2', C-10'), 144.1 (C-5'), 124.6 (C-6'), 77.4 (C-5), 74.1 (C-1), 72.4 (C-3), 71.6 (C-2), 69.4 (C-4), 62.2 (C-6), 53.7 (C-7'), 53.0 (C-3'), 52.9 (C-11'), 37.2 (C-1'), 28.4 (C-4'), 24.6 (C-8'), 11.2 (C-9').

**MS (ESI):** 417.4 $[M+H]^+$, calcd.417.20 for $C_{17}H_{28}N_4O_8 + H^+$

### IV.7.2 Synthesis of compound 118




Hydrolysis of the methyl ester function of **117** was accomplished following the 'Standard saponification procedure with a solution of LiOH as described above.

Yield: 91%

Rf: 0.18 (Methanol: dichloromethane 2: 8)

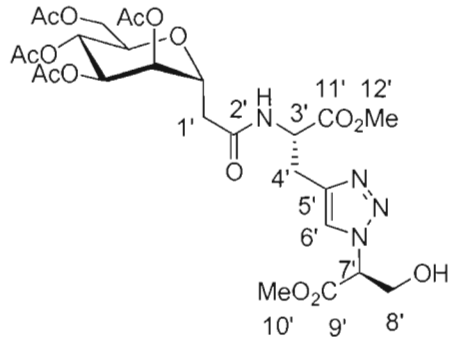
$[\alpha]^{20}_D$ +53.6 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.78 (1 H, bs, H-6'), 4.56 (1H, bs), 4.33-4.28 (2 H, t, $J$ = 7.01 Hz, H-7'), 4.24 (1 H, b), 3.91-3.80 (1 H, b), 3.71-3.64 (5 H, b), 3.31-3.29 (1 H, b, Ha-4'), 3.12 (1 H, b, Hb-4'), 2.65-2.60 (1 H, m, Ha-1'), 2.52-2.47 (1 H, m, Hb-1'), 1.89 (2 H, q, $J$ = 6.93 Hz, H-8'), 0.91 (3 H, t, $J$ = 6.93 Hz, H-9').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 172.6 (C=O), 124.5 (C-6'), 77.6 (C-5), 74.0 (C-1), 72.3 (C-3), 71.7 (C-2), 69.6 (C-4), 62.3 (C-6), 52.9 (C-3'), 37.5 (C-1'), 29.6 (C-4'), 24.6 (C-8'), 11.3 (C-9').

**MS (ESI):** 403.4 $[M+H]^+$, calcd.403.19 for $C_{16}H_{26}N_4O_8 + H^+$

## IV.8 Synthesis of compound 119




Synthesis of compound **119** was accomplished by following the 'General procedure of click chemistry' described above using azido-methyl L-serine and compound **94**.

Yield: 7%

Rf: 0.19 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_D$ +23.6 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.94 (1 H, s, H-6'), 7.06-7.03 (1 H, d, $J$ = 7.69

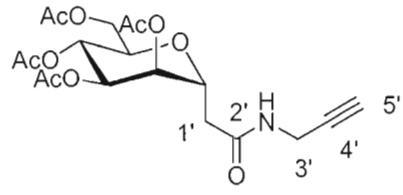
Hz, NH), 6.52 (1 H, s), 6.47 (1 H, s), 5.29-5.29 (1 H, m, H-3), 5.16-5.11 (2 H, m), 4.96-4.90 (1 H, m, H-3'), 4.45-4.39 (1 H, m, H-1), 4.40-4.34 (1 H, dd, $J$ = 6.32, 12.09 Hz, Ha-6), 4.25-4.19 (1 H, dd, $J$ = 4.40, 12.09 Hz, Hb-6), 4.05-3.99 (1 H, m, H-5), 3.92 (3H, s, $CH_3$), 3.76 (3 H, s, $CH_3$), 3.34-3.33 (2 H, d, $J$ = 5.22 Hz, H-4'), 2.69-2.61 (1 H, dd, $J$ = 8.79, 15.38 Hz, Ha-1), 2.60-2.53 (1 H, dd, $J$ = 4.95, 15.38 Hz, Hb-1), 2.09-2.07 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.6, 171.1, 170.3, 170.1, 170.0, 169.1 ($O\underline{C}OCH_3$, C-2', C-9', C-11'), 142.9 (C-5'), 134.0 (C-6'), 72.4 (C-1), 70.1 (C-5), 69.5 (C-2), 68.4 (C-3), 67.7 (C-6), 62.0 (C-4), 53.6 (C-10'), 53.1 (C-3'), 52.2 (C-8'), 52.2 (C-12'), 37.3 (C-1'), 30.1 (C-4'), 27.9, 21.2 ($OCO\underline{C}H_3$), 21.1 ($OCO\underline{C}H_3$), 21.1 ($OCO\underline{C}H_3$).

**MS (ESI):** 646.4 $[M+H]^+$, calcd.645.23 for $C_{26}H_{36}N_4O_{15} + H^+$

## V. Synthesis of α-D-mannopyranosides derivatives modified at anomeric position — series 2 of C-mannosides

### V.0 Synthesis of *N*-propargyl 1'-(2, 3, 4, 6-tetra-*O*-acetyl-α-D-manno pyranosyl)ethanamide 120




To solution of **94** (0.314 g, 0.804 mmol) in DCM (7 ml), propargylamine (0.055 ml, 0.80 mmlo) and BOP( 0.437 g, 1.23 mmol) were added successively, then under nitrogen DIPEA (0.45 ml, 3.2 mmol) was added, the reaction was

stirred overnight at room temperature. The mixture was then evaporated under reduced pressure, the residue was washed with 1 M $KHSO_4$, 1 M NaOH, and brine, dried over $Na_2SO_4$, and purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1.6%) to afford **120** (0.229 g) as a syrup.

Yield: 67 %

Rf: 0.15 (Methanol: dichloromethane 1: 19)

$[\alpha]^{20}_D$ +13.1 ($c$ = 1, $CHCl_3$)

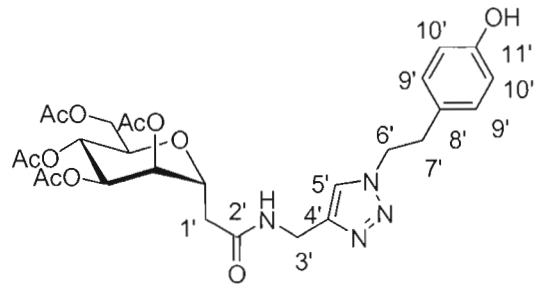
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 6.70 (1 H, NH), 5.27-5.21 (1 H, dd, J = 3.29, 6,59 Hz), 5.08-5.02 (2 H, m), 4.43-4.34 (2 H, m), 4.20-4.15 (1 H, dd, $J$ = 3.57, 12.09 Hz ), 4.05-3.99 (3 H, m, 2 x H-3'), 2.64-2.56 (1 H, dd, $J$ = 9.61, 15.38 Hz, Ha-1' ), 2.53-2.46 (1 H, dd, $J$ = 4.12, 15.38 Hz, Hb-1' ), 2.24-2.22 (1 H, t, $J$ = 2.47 Hz, H-5' ), 2.08-2.04 (12 H, m, 4 x $OCO\underline{C}H_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.5, 169.7, 169.5, 169.4, 168.6 ($O\underline{C}OCH_3$, C=O), 79.4(C-4'), 72.1 (C-1), 71.6 (C-5), 69.0 (C-2), 67.6 (C-3), 67.4 (C-4), 61.4 (C-6), 36.7 (C-1'), 29.0 (C-3')

**MS (ESI):** 428.4 $[M+H]^+$, calcd. 428.16 for $C_{19}H_{25}N_1O_{10} + H^+$

## V.1 Synthesis of compound 124

### V.1.1 Synthesis of compound 123




Synthesis of compound **123** was accomplished by following the 'General

procedure of click chemistry' described above using azido tyramine and **120**.

Yield: 90 %

Rf: 0.12 (Methanol: dichloromethane 1: 19)

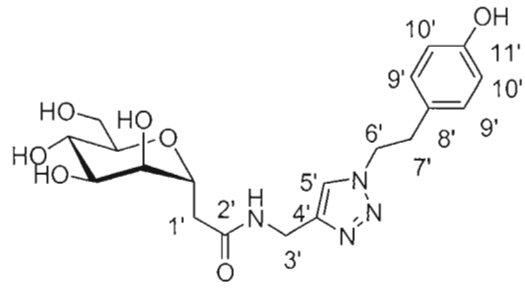
$[\alpha]^{20}_{D}$ +9.78 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 8.10 ( 1 H, bs, OH), 7.80 (1 H, bs, NH), 7.38 (1 H, s, H-5'), 6.87-6.84 (2 H, d, $J$ = 8.52 Hz, H-9'), 6.73-6.71 (2 H, d, $J$ = 8.24 Hz, H-10'), 5.27-5.23 (1 H, dd, $J$ =3.30 Hz, 8.24 Hz), 5.16-5.11 (2 H, m), 4.53-4.34 (5 H, m, H-3', H-6'), 4.32-4.26 (1 H, m), 4.12-4.07 (1 H, dd, $J$ = 3.02 Hz, 12.09 Hz), 4.03-3.99 (1 H, m), 3.05-3.01 (2 H, t, $J$ = 7.01 Hz, H-7'), 2.76-2.68 (1 H, dd, $J$ = 9.89 Hz, 14.83Hz, Ha-1'), 2.57-2.50 (1 H, dd, $J$ = 4.54 Hz, 14.83 Hz, Hb-1'), 2.06-2.00 (12 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.7, 170.1, 169.8, 169.5, 169.3 ($O\underline{C}OCH_3$, C=O), 155.6 (C-11'), 144.2 (C-4'), 129.6 (C-8'), 127.8 (C-5'), 123.1 (C-9'), 115.6 (C-10'), 71.4 (C-1), 70.8 (C-5), 69.5 (C-2), 68.3 (C-4), 67.0 (C-3), 61.8 (C-6), 51.8(C-6'), 36.3 (C-3'), 35.6 (C-7'), 34.6 (C-1'), 20.7 ($OCO\underline{C}H_3$), 20.6 ($OCO\underline{C}H_3$).

**MS (ESI):** 591.4 $[M+H]^+$, calcd. 591.23 for $C_{27}H_{34}N_4O_{11} + H^+$

### V.1.2 Synthesis of compound 124




Deprotection of acetylated **123** was accomplished following the 'Standard

Zemplén deacetylation procedure' described above.

Yield: 70 %

Rf: 0.10 (Methanol: dichloromethane 20: 80)

$[\alpha]^{20}_{D}$ +17.9 ($c$ = 1, $CH_3OH$)

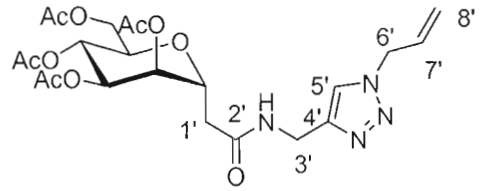
**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.64 (1 H, s, H-5'), 6.89-6.87 (2 H, d, $J$ = 8.52 Hz, H-9'), 6.64-6.61 (2 H, d, $J$ = 8.52 Hz, H-10'), 4.51-4.46 (2 H, t, $J$ = 7.14 Hz, H-6'), 4.36-4.35 (2 H, d, $J$ = 7.02 Hz, H-3'), 4.27-4.22 (1 H, m, H-1), 3.85-3.78 (1 H, dd, $J$ =7.14 Hz, 11.81Hz), 3.68-3.59 (4 H, m,), 3.56-3.52 (1 H, m), 3.05-3.00 (2 H, t, $J$ = 7.14 Hz, H-7'), 2.61-2.53 (1 H, dd, $J$ = 9.48 Hz, 14.83 Hz, Ha-1'), 2.50-2.44 (1 H, dd, $J$ = 4.81 Hz, 14.83Hz, Hb-1')

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ: 173.3 (C=O), 157.7 (C-11'), 146.1 (C-4'), 130.8 (C-8'), 129.1 (C-5'), 124.5 (C-9'), 116.6 (C-10'), 77.6 (C-5), 73.8 (C-1), 72.4 (C-3), 71.7 (C-2), 69.7 (C-4), 62.2 (C-6), 53.0 (C-6'), 37.5 (C-3'), 36.7 (C-1'), 35.7 (C-7').

**MS (ESI):** 423.4 $[M+H]^+$, calcd. 423.19 for $C_{19}H_{26}N_4O_7 + H^+$

## V.2 Synthesis of compound 126

### V.2.1 Synthesis of compound 125




Synthesis of compound **125** was accomplished by following the 'General procedure of click chemistry' described above using allyl azide and compound **120**.

Yield: 43%

Rf: 0.24 (Methanol: dichloromethane 5: 95)

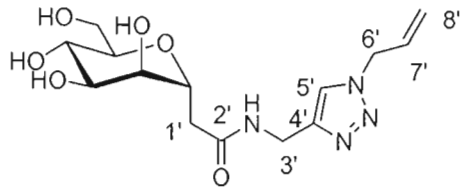
$[\alpha]^{20}_{D}$ +12.9 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.59 (1 H, s, H-5'), 7.42 (1 H, s, NH), 6.04-5.95 (1 H, m, H-7'), 5.36-5.24 (3 H, m, H-8'), 5.13-5.09 (2 H, m), 4.96-5.94 (2 H, d, $J$ = 6.32 Hz, H-6'), 4.50-4.32 (4 H, m, H-3'), 4.17-4.11 (1 H, dd, $J$ = 2.23 Hz, 3.71 Hz), 4.05-4.00 (1 H, m), 2.71-2.63 (1 H, dd, $J$ = 9.16 Hz, 15.11Hz, Ha-1), 2.58-2.52 (1 H, dd, $J$ = 4.40 Hz, 15.11Hz, Hb-1),2.07-2.04 (12 H, 4 x s, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ:170.6 (C-2'), 169.8, 169.6, 169.5, 168.9 ($OCOCH_3$), 144.9 (C-4'), 131.1 (C-7'), 122.4 (C-5'), 120.4 (C-8'), 71.8 (C-1), 70.0 (C-5), 69.2 (C-2), 68.0 (C-4), 67.3 (C-3), 61.6 (C-6), 52.7 (C-6'), 36.8 (C-3'), 34.8 (C-1'), 20.8, 20.7, 20.7 ($CH_3$).

**MS (ESI):** 511.4 $[M+H]^+$, calcd. 511.21 for $C_{22}H_{30}N_4O_{10}$ + $H^+$

### V.2.2 Synthesis of compound 126




Deprotection of acetylated **125** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 83 %

Rf: 0.13 (Methanol: dichloromethane 20: 80)

$[\alpha]^{20}_{D}$ +23.5 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.87 (1 H, s, H-5'), 6.12-5.99 (1 H, m, H-7'), 5.32-5.21 (2 H, m), 5.00-4.98 (2 H, d, $J$ = 5.77 Hz), 4.46-4.44 (2 H, d, $J$ = 6.32 Hz,

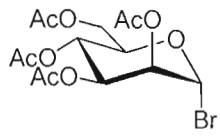
H-6'), 4.30-4.27 (1 H, m), 3.87-3.81 (1 H, m), 3.73-3.64 (4 H, m), 3.59-3.57 (1 H, b), 2.67-2.2.59 (1 H, dd, *J* = 9.61Hz, 14.83Hz, Ha-1'), 2.56-2.49 (1 H, dd, *J* = 4.81Hz, 14.97 Hz, Hb-1').

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 173.3 (C-2'), 146.5 (C-4'), 133.2 (C-7'), 124.3 (C-5'), 119.9 (C-8'), 77.6 (C-5), 73.9 (C-1), 72.4 (C-3), 71.7 (C-2), 69.6 (C-4), 62.2 (C-6), 53.6 (C-6'), 37.5 (C-3'), 35.8 (C-1').

**MS (ESI):** 343.4 $[M+H]^+$, calcd. 343.16 for $C_{14}H_{22}N_4O_6 + H^+$

## VI Synthesis of α-D-mannopyranoside derivatives modified at position 1 with elongated carbon chain

### VI.1 2, 3, 4, 6-tetra -*O*-acetyl-α-D-mannopyranosyl bromide 127



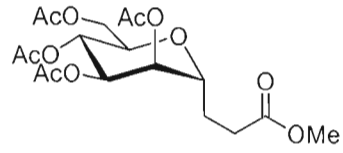

Mannose pentaacetate (5.0 g, 12.81 mmol) was dissolved in dichloromethane (80 ml) and HBr/AcOH (33%) was added. The reaction mixture was stirred at room temperature for 2 h, and $NaHCO_3$ was added to quench the reaction. The mixture was washed with $NaHCO_3$ and water. The organic layer was dried over $Na_2SO_4$, filtered and concentrated to give **127** (3.967 g, 9.65 mmol). The crude product was used directly without further purification.

Yield: 75.3 %

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 6.26-6.25 (1 H, d, *J* = 1.10 Hz, H-1), 5.67-5.62 (1 H, dd, *J* = 3.30, 10.16 Hz, H-3), 5.40-5.38 (1 H, dd, *J* = 1.37, 3.30 Hz, H-2), 5.35-5.28 (1 H, t, *J* = 10.16 Hz, H-4), 4.30-4.25 (1 H, dd, J = 4.67, 12.36 Hz,

Ha-6), 4.19-4.14 (1 H, m, H-5), 4.10-4.05 (1 H, dd, $J$ = 1.92, 12.36 Hz, Hb-6).

**VI.2 Methyl 3-(O-tetraacetyl α-D-mannopyranosyl)propanoate 128**




A solution of 2, 3, 4, 6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide **127** (2.914 g, 7.09 mmol) and methyl acrylate (1.15 ml, 33.39 mmol) in degassed toluene was stirred at 85 °C and a solution of $Bu_3SnH$ (2.1 ml, 7.9 mmol) and AIBN (24 mg, 0.426 mmol) in toluene was added dropwise over 30 min. Then the stirring was continued for 0.5 h at 85 °C and the residue was dried under high vacuum. The residual syrup was dissolved in $CH_3CN$, washed with hexane, and concentrated and purified by flash column chromatography using EtOAc/Toluene (20%), obtained product 1.986 g. [41]

Yield: 67 %

Rf: 0.50 (EtOAc: Toluene 5: 95)

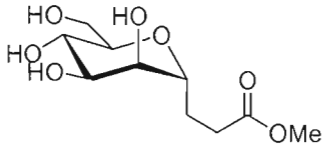
$[\alpha]^{20}_D$ +8.04 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 5.26-5.22 (1 H, dd, $J$ = 3.30, 8.52 Hz, H-3), 5.20-5.17 (1 H, d, $J$ = 7.69 Hz, H-2), 5.15-5.13 (1 H, t, $J$ = 3.30 Hz, H-4), 4.40 (1 H, dd, $J$ = 6.59, 12.36 Hz, Ha-6), 4.07-4.02 (1 H, dd, $J$ = 3.02, 12.09 Hz, Hb-6), 4.01-3.95 (1 H, m, H-5), 3.90-3.85 (1 H, m, H-1), 3.68 (3 H, s, $OCH_3$), 2.46-2.40 (2 H, m, $CH_2C\underline{H}_2CO$), 2.11-2.02 (12 H, 4 x s, 4 x $CH_3$), 1.86-1.96 (2 H, m, $C\underline{H}_2CH_2CO$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 173.0 ($\underline{C}O_2CH_3$), 170.6, 170.1, 169.8, 169.6 (4 x $CH_3\underline{C}O$), 73.5 (C-1), 70.7 (C-5), 70.3 (C-2), 68.7 (C-3), 66.9 (C-4), 62.1 (C-6), 51.8 ($CO_2\underline{C}H_3$), 29.7 ($CH_2\underline{C}H_2C{=}O$), 23.9 ($\underline{C}H_2CH_2C{=}O$), 20.9, 20.7, 20.7, 20.6

(4 x $\underline{C}H_3CO$).

### VI.3 Methyl 3-(α-D-mannopyranosyl) propanoate 129




The Methyl 3-(α-D-mannopyranosyl) propanoate **128** (138 mg, 0.33 mmol) was dissolved in methanol (3 ml) followed by the addition of a 1 M solution of sodium methoxide in methanol (0.33 ml). The reaction mixture was stirred overnight at room temperature and neutralized with Amberlite IR-120 ($H^+$) resin, filtered and evaporated under reduced pressure. The residue was lyophilized to afford **129** (79 mg) as a solid. [41]

Yield: 96%

Rf: 0.05 (Methanol: EtOAc 10: 90)

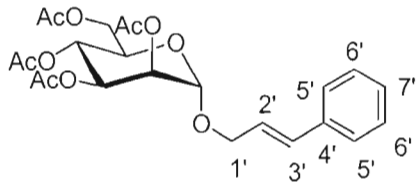
$[\alpha]^{20}_D$ +20.8 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $D_2O$):** δ 3.75 (2 H, bs, $H_{sugar}$), 3.65 (2 H, bs, $H_{sugar}$), 3.57 (4 H, s, $CH_3$ and $H_{sugar}$), 3.50 (1 H, bs, $H_{sugar}$), 3.46 (1 H, bs, $H_{sugar}$), 2.36 (2 H, bs, $CH_2C\underline{H}_2CO$), 1.98 (1 H, bs, $C\underline{H}_2CH_2CO$), 1.69 (1 H, bs, $C\underline{H}_2CH_2CO$).

**$^{13}$C NMR (75 MHz, $D_2O$):** δ 176.5 (C=O), 77.7 (C-1), 73.8 (C-5), 71.5 (C-3), 70.9 (C-2), 67.4 (C-4), 61.3 (C-6), 52.4 ($CH_3$), 30.3 ($CH_2\underline{C}H_2CO$), 23.0 ($\underline{C}H_2CH_2CO$).

# VII Synthesis of manopyranoside derivatives modified at position 1 (O-mannoside)

## VII.1 Synthesis of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl -3'-phenyl -3'-propylene ether 131




To solution of allyl2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **130** (258 mg, 0.664 mmol) in DCM (6 ml), styrene (0.152 ml, 1.328 mmol) and Grubbs catalyst (first generation, 23 mg, 0.028 mmol) were added, and the mixture was refluxed overnight. The solvent was then evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (DCM/Hexane = 70%) to afford **131** (214 mg) as an oil.

Yield: 69 %

Rf: 0.81 (Methanol: dichloromethane 5: 95)

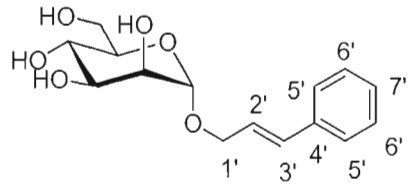
$[\alpha]^{20}_{D}$ +57.5 (*c* = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.42-7.32 (5 H, m, $H_{aromomatic}$), 6.66-6.61 (1 H, d, *J* = 15.66 Hz, H-3'), 6.31-6.22 (1 H, m, H-2'), 5.43-5.38 (1 H, dd, *J* = 3.44, 10.03 Hz), 5.36-5.28 (2 H, m), 4.943-4.937 (1 H, d, *J* = 1.65 Hz, H-1), 4.39-4.27 (2 H, m, H-1'), 4.24-4.20 (1 H, dd, *J* = 6.87, 12.64 Hz), 4.15-4.10 (1 H, dd, *J* = 2.47, 12.36 Hz), 4.09-4.04 (1 H, m), 2.16-2.00 (12 H, 4 x s, 4 x $OCOCH_3$)

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.6, 169.9, 169.8, 169.7 ($O\underline{C}OCH_3$), 136.1 (C-4'), 134.0 (C-3'), 128.6 (C-6'), 128.0 (C-7'), 126.5 (C-5'), 123.8 (C-2'), 96.4

(C-1), 69.6 (C-2), 69.1 (C-5), 68.5 (C-4), 68.3 (C-3), 66.1 (C-6), 62.4 (C-1'), 20.8, 20.7, 20.6 ($OCO\underline{C}H_3$).

### VII.2 Synthesis of α-D-mannopyranosyl 3'-phenyl-3'-propylene ether 132




Deprotection of acetylated **131** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 95 %

Rf: 0.05 (Methanol: dichloromethane 5: 95)

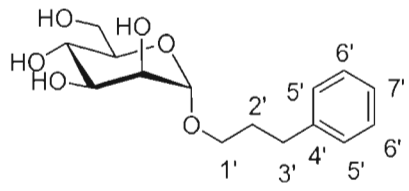
$[\alpha]^{20}_D$ +80.2 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.41-7.38 (2 H, m, $H_{aromatic}$), 7.31-7.21 (3 H, m, $H_{aromatic}$), 6.66-6.61 (1 H, d, $J$ = 15.93 Hz, H-3'), 6.37-6.28 (1 H, td, $J$ = 6.04, 15.93 Hz, H-2'), 4.86 (1 H, H-1), 4.39-4.32 (1 H, ddd, $J$ = 1.37, 5.49, 12.91 Hz, Ha-1'), 4.20-4.13 (1 H, ddd, $J$ = 1.37, 6.53, 12.91 Hz, Hb-1'), 3.88-3.81 (2 H, m), 3.77-3.70 (2 H, m), 3.66-3.60 (2 H, m).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 138.1 (C-4'), 133.9 (C-3'), 129.6 (C-6'), 128.7 (C-7'), 127.5 (C-5'), 126.3 (C-2'), 100.7 (C-1), 74.7 (C-5), 72.6 (C-2), 72.2 (C-3), 68.6 (C-4), 62.9 (C-6).

**MS (ESI):** 319.1 $[M+Na]^+$, calcd. 319.11 for $C_{19}H_{26}N_4O_7 + Na^+$

### VII.3 Synthesis of α-D-mannopyranosyl 3'-phenyl-3'-propane ether 133




To solution of **132** (37 mg, 0.125mmol) in ethanol (3 ml) Pd/C catalyst (10%) was added, and the mixture was stirred at room temperature overnight. Pd/C was then filtered over Celite, the filtrate was evaporated under reduced pressure, and the residue was lyophilized to afford **133** (36 mg) as a white solid.

Yield: 97 %

Rf: 0.50 (Methanol: dichloromethane 15: 85)

$[\alpha]^{20}_{D}$ +46.4 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.27-7.14 (5 H, m), 4.723-4.718 (1 H, d, $J$ = 1.73 Hz, H-1), 3.81-3.59 (6 H, m, Ha-1', 5 x $H_{sugar}$), 3.55-3.52 (1 H, m), 3.44-3.36 (1 H, m, Hb-1'), 2.71-2.65 (2 H, m, H-3'), 1.93-1.86 (2 H, m, H-2').

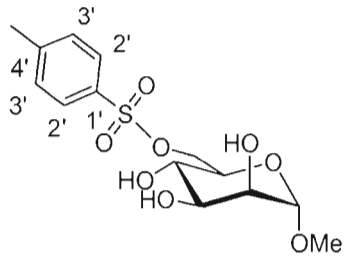
**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 143.1 (C-4'), 129.4 (C-6'), 129.4 (C-5'), 126.8 (C-7'), 101.6 (C-1), 74.6 (C-5), 72.7 (C-2), 72.2 (C-3), 68.6 (C-4), 67.8 (C-6), 62.8 (C-1'), 33.4 (C-3'), 32.4 (C-2').

**MS (ESI):** 321.1 $[M+Na]^+$, calcd. 321.13 for $C_{19}H_{26}N_4O_7 + Na^+$

# VIII Synthesis of α-D-manopyranoside derivatives modified at position 6

## VIII.1 Methyl 6-azido-6-deoxy-α-D-mannopyranoside 135

### VIII.1.1 Methyl 6-*O*-toluenesulfonyl-α-D-mannopyranoside 134




Methyl α, D-mannopyranoside (5.00g, 25.7 mmol) was dissolved in pyridine (75 ml) and the solution was cooled to 0 °C, after which toluenesulfonyl chloride (6g, 31.5 mmol) was added in portions. The reaction was stirred at room temperature and the reaction was monitored by TLC. The pyridine was then co-evaporated with toluene under reduced pressure. The residue was purified by flash column chromatography using Methanol/DCM (3.5%) and afforded the purified compound as colorless syrup [42] (6.835 g, 19.6 mmol).

Yield: 93.1%

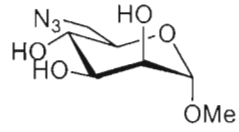
Rf: 0.22 (Methanol: dichloromethane 1: 9)

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 7.80 (2 H, d, *J* = 7.8 Hz), 7.33 (2 H, d, *J* = 7.8 Hz), 4.67 (1 H, s), 4.32 (2 H, m), 3.91 (1 H, m), 3.73 (2 H, m), 3.29 (3 H, s, $OCH_3$), 2.43 (3 H, s, $CH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 145.2 (C-4'), 132.8 (C-1'), 130.2 (C-3'), 128.3 (C-2'), 101.2 (C-1), 71.9 (C-2, C-5), 70.7 (C-3), 70.3 (C-4), 70.1 (C-6), 55.2

($OCH_3$), 21.9 ($CH_3$).

### VIII.1.2 Methyl 6-azido-6-deoxy-α-D-mannopyranoside 135




Compound **134** (1.005 g, 2.88 mmol) was dissolved in 15 ml of dry DMF, and the solution was heated to 60 °C. Sodium azide (2.06 g, 31.73 mmol) was then added in portions. When TLC indicated that all of the starting material had disappeared, the white precipitate was removed by vacuum filtration and the solvent was evaporated under vacuum. Column chromatography purification of the crude product provided **135** (0.4 g) as a colorless syrup. [42]

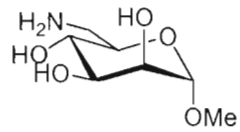
Yield: 63%

Rf: 0.31 (Methanol: dichloromethane 4%)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 4.64 (1 H, d, *J* = 1.5 Hz, H-1), 3.80 (1 H, dd, *J* = 3.0, 1.5 Hz, H-2), 3.65-3.60 (2 H, m, H-3 and H-5), 3.58 (1 H, t, *J* = 9.1 Hz, H-4), 3.48 (1 H, dd, *J* = 2.5, 13.2 Hz, Ha-6), 3.43 (1 H, dd, *J* = 7.1, 13.2 Hz, Hb-6).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 101.0 (C-1), 71.4 (C-2), 71.2 (C-3), 70.7 (C-4), 68.2 (C-5), 55.2 ($OCH_3$), 51.3 (C-6).

### VIII.2 Methyl 6-amino-6-deoxy-α-D-mannopyranoside 136



The compound **135** (0.40 g, 1.82 mmol) was dissolved in 35 ml of methanol, to which was added Pd/C as catalyst. The reaction was stirred at room temperature for 17 h under a hydrogen atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated to a very small volume. Flash column chromatography of the residue with $CH_2Cl_2/CH_3OH$ (2:1 to 1:1) as eluting solvent provided f (250 mg, 1.29 mmol) as a colorless solid. [42]

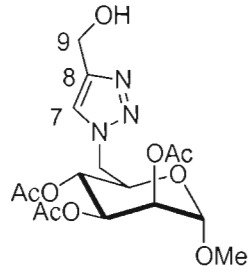
Yield: 70.6%

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 4.47 (1 H, s, H-1), 3.57 (1 H, m, H-2), 3.40 (1 H, dd, *J* = 3.3, 9.3 Hz, H-3), 3.33 (1 H, t, *J* = 9.3 Hz, H-4), 3.23 (1 H, s, $OCH_3$), 3.16 (1 H, dt, *J* = 3.3, 7.4 Hz, H-5), 2.81 (1 H, dd, *J* = 3.0, 13.2 Hz, Ha-6), 2.58 (1 H, dd, *J* = 7.1, 13.2 Hz, Hb-6).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 101.1 (C-1), 73.8 (C-2), 70.9 (C-3), 70.2 (C-4), 68.5 (C-5), 53.9 ($OCH_3$), 43.3 (C-6).

## VIII.3 Synthesis of triazoles at position 6

### VIII.3.1 Synthesis of compound 138




Synthesis of compound **138** was accomplished by following the 'General procedure of click chemistry' described above using methyl 6-azido-6-deoxy-2, 3, 4-tri-*O*-acetyl α-D-mannopyranoside and propargyl alcohol.

Yield: 20%

Rf: 0.34 (Methanol: dichloromethane 1: 9)

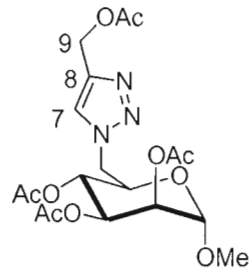
$[\alpha]^{20}_{D}$ +29.1 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.72 (1 H, s, H-7'), 5.34-5.30 (1 H, dd, $J$ = 2.93, 10.03 Hz, H-3), 5.23-5.21 (1 H, dd, $J$ = 1.79, 3.44 Hz, H-2), 5.16-5.09 (1 H, t, $J$ = 10.03 Hz, H-4), 4.79 (2 H, s, H-9), 4.643-4.637 (1 H, d, $J$ =1.65 Hz, Ha-6), 4.63-4.57 (1 H, dd, $J$ = 2.47, 14.29 Hz, H-1), 4.44-4.36 (1 H, dd, $J$ = 8.65, 14.15 Hz, Hb-6), 4.18-4.10 (1 H, td, $J$ = 2.47, 10.16 Hz, H-5), 3.11 (3 H, s, $CH_3$), 2.14 (3 H, s, $OCOCH_3$), 2.11 (3 H, s, $OCOCH_3$), 1.99 (3 H, s, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.1, 169.9, 169.7 ($O\underline{C}OCH_3$), 147.7 (C-8), 123.3 (C-7), 98.4 (C-1), 69.3 (C-2), 69.1 (C-4), 68.7 (C-3), 67.3 (C-5), 56.3 (C-9), 55.3 (C-6), 50.9 ($OCH_3$), 20.8, 20.7, 20.6 ($OCO\underline{C}H_3$).

**MS (ESI):** 402.4 $[M+H]^+$, calcd.402.15 for $C_{16}H_{23}N_3O_9 + H^+$

### VIII.3.2 Synthesis of compound 139




Synthesis of compound 139 was accomplished by following the 'General procedure of click chemistry' described above using methyl 6-deoxy-6-azido-2, 3, 4-tri-*O*-acetyl α-D-mannopyranoside and acetyl propargyl alcohol.

Yield: 43%

Rf: 0.49 (Methanol: dichloromethane 5: 95)

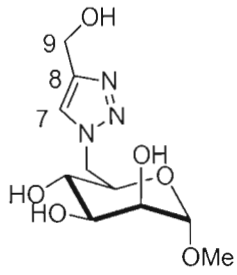
$[\alpha]^{20}_{D}$ +23.4 ($c$ = 1, $CHCl_3$)

**$^1$H NMR (300 MHz, $CDCl_3$):** δ7.76 (1 H, s, H-7), 5.30-5.25 (1 H, m, H-3), 5.18 (1 H, m, H-2), 5.19-5.12 (2 H, m, H-9), 5.10-5.06 (1 H, dd, *J* = 1.92, 9.89 Hz, H-4), 4.61 (1 H, s, H-1), 4.61-4.55 (1 H, m, Ha-6), 4.40-4.32 (1 H, dd, *J* = 8.79, 14.29 Hz, Hb-6), 4.11-4.05 (1 H, td, *J* = 9.89, 1.92 Hz, H-5), 3.05 (3 H, s, $CH_3$), 2.10 (3 H, s, $OCOCH_3$), 2.07 (3 H, s, $OCOCH_3$), 2.00 (3 H, s, $OCOCH_3$), 1.95 (3 H, s, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.9, 170.3, 170.0, 169.9 ($OCOCH_3$), 143.0 (C-8), 125.2 (C-7), 98.6 (C-1), 69.5 (C-2), 69.2 (C-4), 68.8 (C-3), 67.5 (C-5), 57.7 (C-9), 55.4 (C-6), 51.2 ($OCH_3$), 21.0 (($OCOCH_3$), 20.9 (($OCOCH_3$), 20.8 ($OCOCH_3$).

**MS (ESI):** 444.4 $[M+H]^+$, calcd. 444.16 for $C_{18}H_{25}N_3O_{10} + H^+$

### VIII.3.3 Synthesis of compound 140




Deprotection of acetylated **139** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 55%

Rf: 0.26 (Methanol: dichloromethane 2: 8)

$[\alpha]^{20}_D$ +63.5 (*c* = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 7.96 (1 H, s, H-7), 4.87-4.82 (1 H, dd, *J* = 2.20, 14.29 Hz ), 4.66 (2 H, s, H-9), 4.57 (1 H, s), 4.52-4.47 (1 H, dd, *J* = 8.51, 14.01 Hz), 3.82-3.76 (2 H, m, H-1, Ha-6), 3.68-3.64 (1 H, dd, *J* = 3.30, 9.34 Hz, Hb-6),

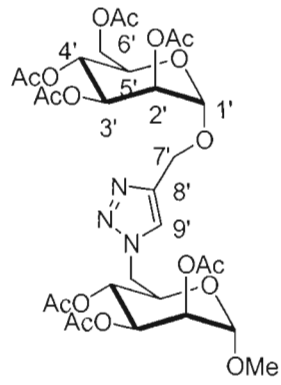
3.64-3.47 (1 H, t, $J$ = 9.48 Hz, H-5), 3.07 (3 H, s, $CH_3$).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 148.9 (C-8), 125.5 (C-7), 102.8 (C-1), 72.8 (C-2), 72.4 (C-3), 71.9 (C-4), 69.7 (C-5), 56.4 (C-9), 55.2 (C-6), 52.5 ($OCH_3$).

**MS (ESI):** 276.4 $[M+H]^+$, calcd. 276.12 for $C_{10}H_{17}N_3O_6 + H^+$

## VIII.4 Synthesis of other triazoles at position 6

### VIII.4.1 Synthesis of compound 142




Synthesis of compound **142** was accomplished by following the 'General procedure of click chemistry' described above using methyl 6-deoxy-6-azido-2, 3, 4-tri-*O*-acetyl-α-D-mannopyranoside and propargyl 2', 3', 4', 6'-tetra-*O*-acetyl-α-D-mannopyranoside.

Yield: 60 %

Rf: 0.46 (Methanol: dichloromethane 5: 95)

$[\alpha]^{20}_D$ +49.0 ($c$ = 1, $CHCl_3$)

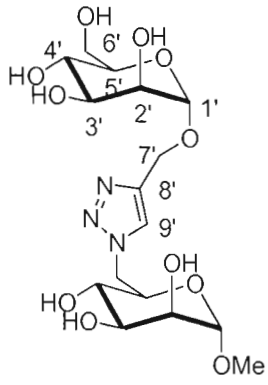
**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.71 (1 H, s, H-9'), 5.28-5.21 (3 H, m), 5.17-5.06 (3 H, m), 4.88 (1 H, s), 4.81-4.77 (1 H, d, $J$ =12.09 Hz), 4.64-4.54 (3 H, m), 4.39-4.31 (1 H, m), 4.26-4.20 (1 H, dd, $J$ = 4.95, 12.09 Hz), 4.12-3.99 (3 H, m),

3.02 (3 H, s, $CH_3$), 2.10-2.05 (12 H, m, $OCOCH_3$), 1.97-1.91 (9 H, m, $OCOCH_3$).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 170.4, 170.0, 169.8, 169.7, 169.5, 169.5 ($O\underline{C}OCH_3$), 143.3 (C-8'), 124.3 (C-9'), 98.2 (C-1), 96.6 (C-1'), 69.1 (C-2'), 68.9 (C-4), 68.8 (C-2), 68.5 (C-5'), 68.5 (C-4'), 67.3 (C-3), 65.8 (C-3'), 62.2 (C-6', C-5), 60.7 (C-7'), 55.0 (C-6), 50.9 ($OCH_3$), 20.6, 20.6, 20.5, 20.4 ($OCO\underline{C}H_3$).

**MS (ESI):** 732.4 $[M+H]^+$, calcd.732.25 for $C_{30}H_{41}N_4O_{18} + H^+$

### VIII.4.2 Synthesis of compound 143




Deprotection of acetylated **142** was accomplished following the 'Standard Zemplén deacetylation procedure' described above.

Yield: 78%

Rf: 0.56 (Methanol: dichloromethane 1: 1)

$[\alpha]^{20}_D$ +93.6 ($c$ = 1, $CH_3OH$)

**$^1$H NMR (300 MHz, $CD_3OD$):** δ 8.09 (1 H, s, H-9'), 4.84-4.77 (2 H, m), 4.67-4.48 (3 H, m), 3.88-3.47 (11 H, m), 3.07 (3 H, s, $CH_3$).

**$^{13}$C NMR (75 MHz, $CD_3OD$):** δ 145.0 (C-8'), 126.9 (C-9'), 102.8 (C-1), 100.5 (C-1'), 75.0 (C-5'), 72.8 (C-2'), 72.5 (C-2), 72.4 (C-3'), 72.0 (C-3), 71.9 (C-4), 69.6 (C-4'), 68.6 (C-5), 63.0 (C-6'), 60.4 (C-7'), 55.2 (C-6), 52.6 ($OCH_3$).

**MS (ESI):** 438.4 $[M+H]^+$, calcd.438.18 for $C_{16}H_{27}N_3O_{11} + H^+$

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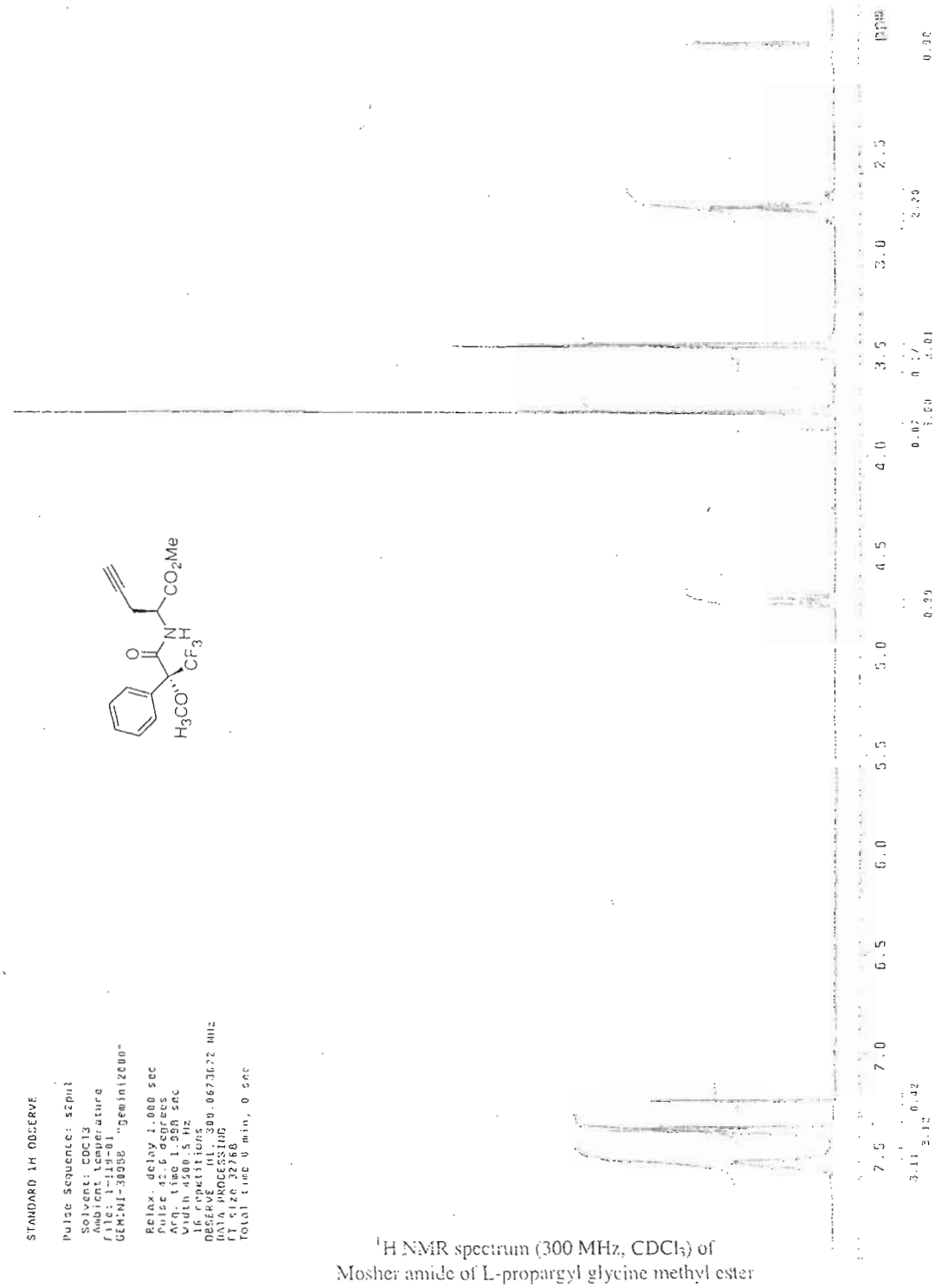
# LIST OF PUBLICATIONS

1. Tri- and hexavalent mannoside clusters as potential inhibitors of type 1 fimbriated bacteria using pentaerythritol and triazole linkages. Mohamed Touaibia, Tze Chieh Shiao, Alex Papadopoulos, Jonathan Vaucher, **Qingan Wang,** Karima Benhamioud and René Roy. *Chem. Comm.* (**2007**) 380-382.

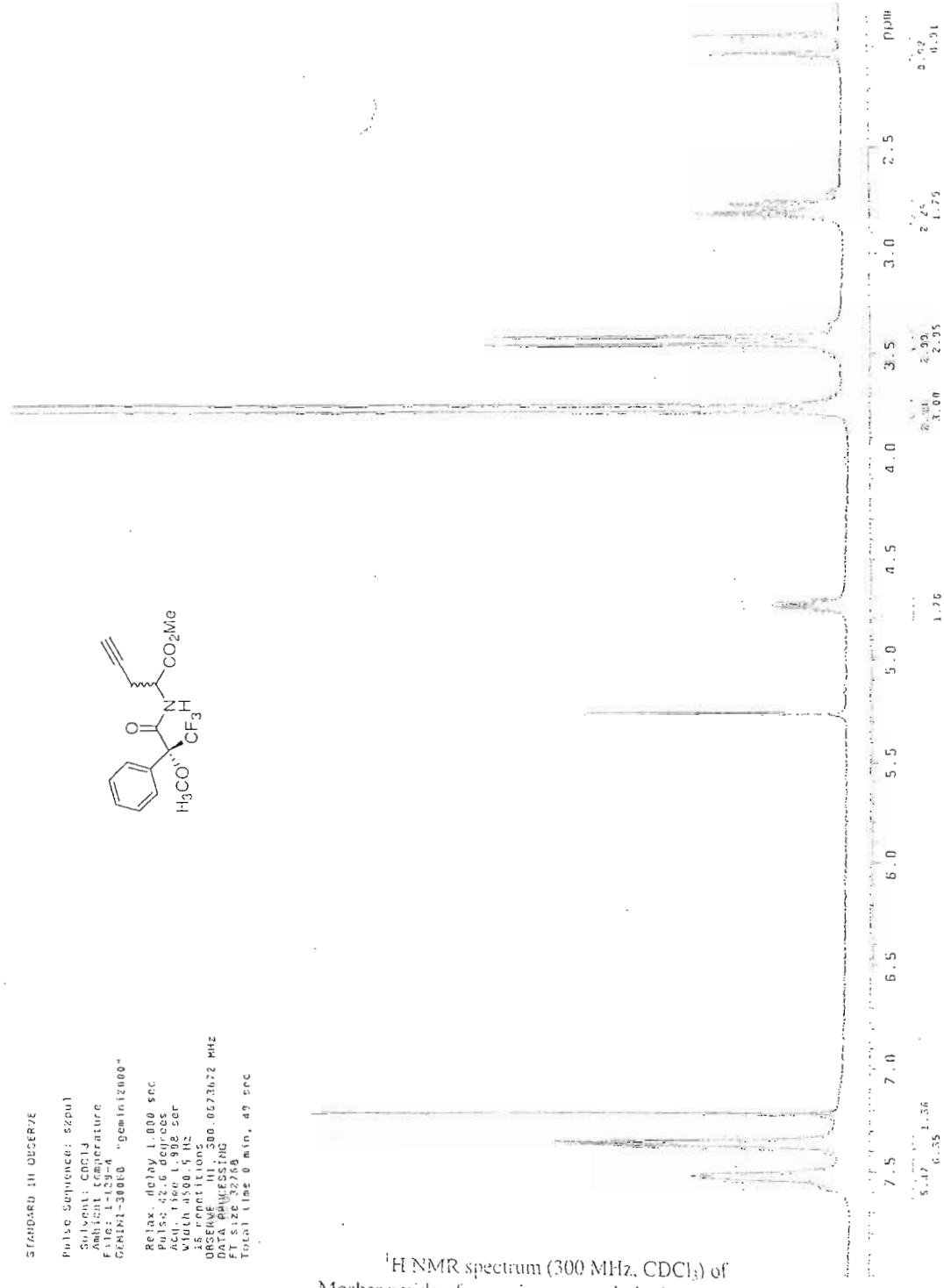
2. Mannosylated G(0) Dendrimers with Nanomolar Affinities to *Escherichia coli* FimH. Mohamed Touaibia, Adinda Wellens, Tze Chieh Shiao, Qingan Wang, Suzanne Sirois, Julie Bouckaert, and René Roy *ChemMedChem*. **2007**, 2, 1190-1201.

3. Design and synthesis of novel Mannosides as *E.coli* ligands. *J. Med. Chem.* (in preparation).

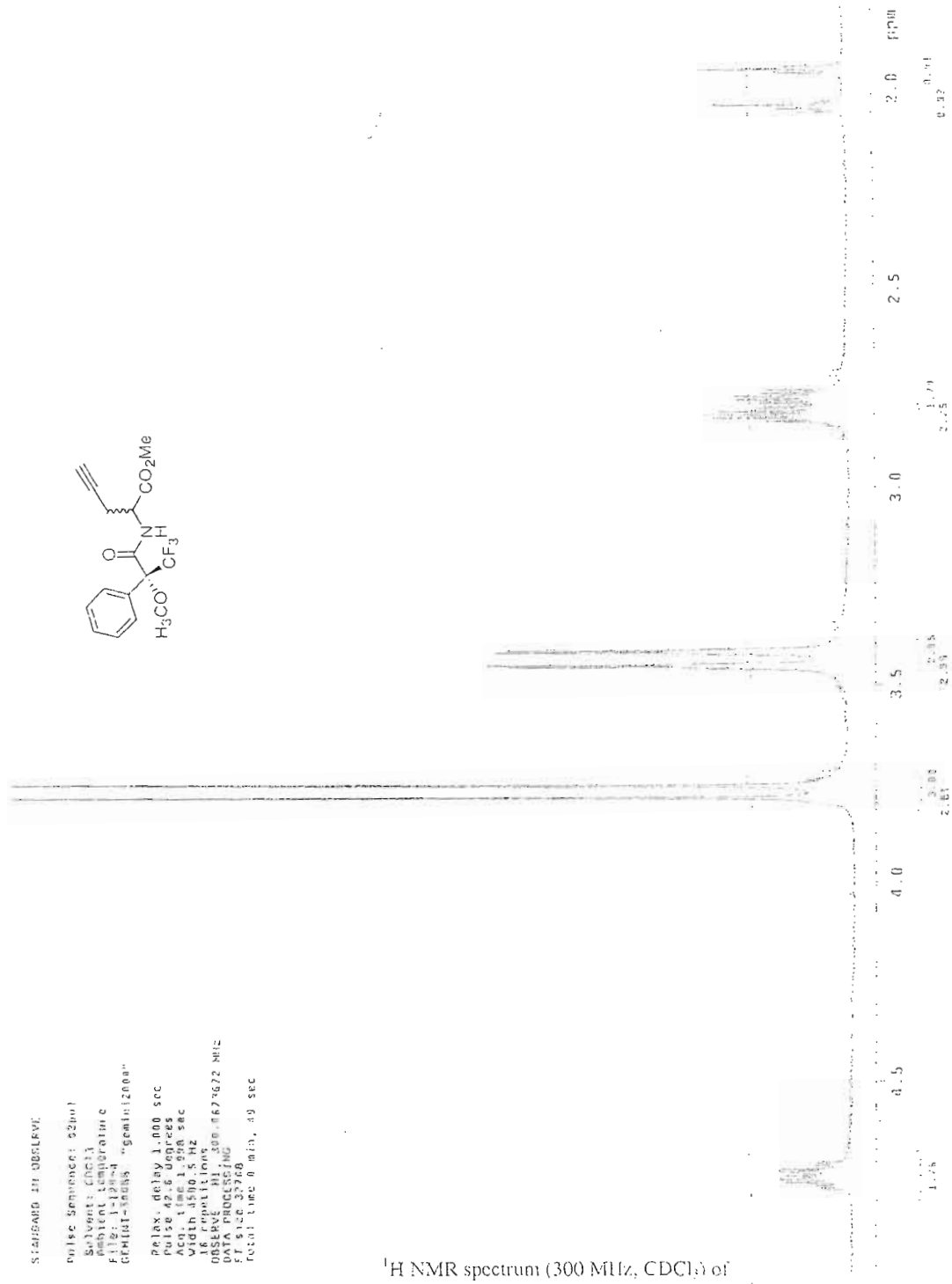



$^1$H NMR spectrum (300 MHz, $CDCl_3$) of
Mosher amide of L-propargyl glycine methyl ester

$^1$H NMR spectrum (300 MHz, $CDCl_3$) of
Mosher amide of L-propargyl glycine methyl ester




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of
Mosher amide of racemic propargyl glycine methyl ester




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of
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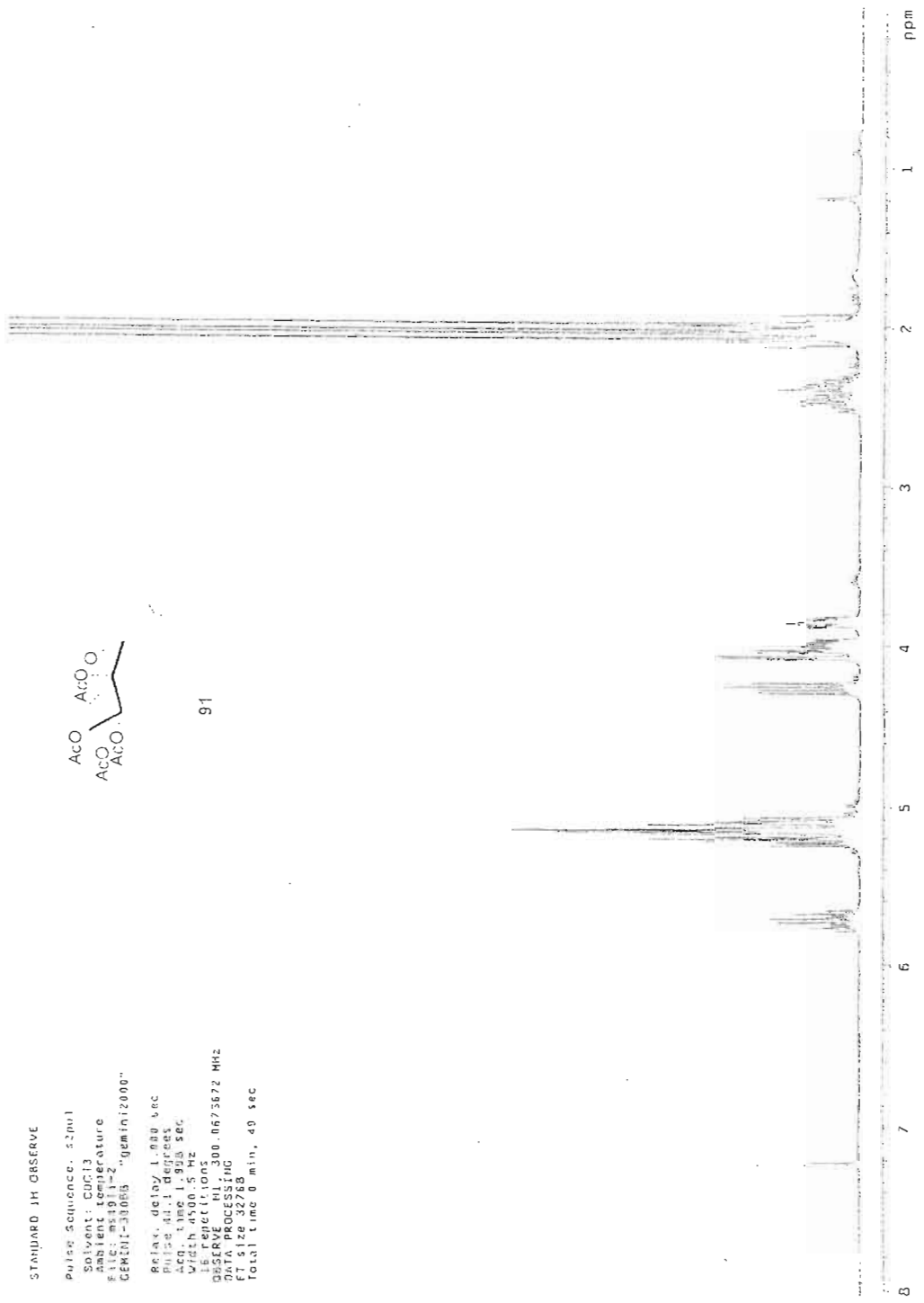
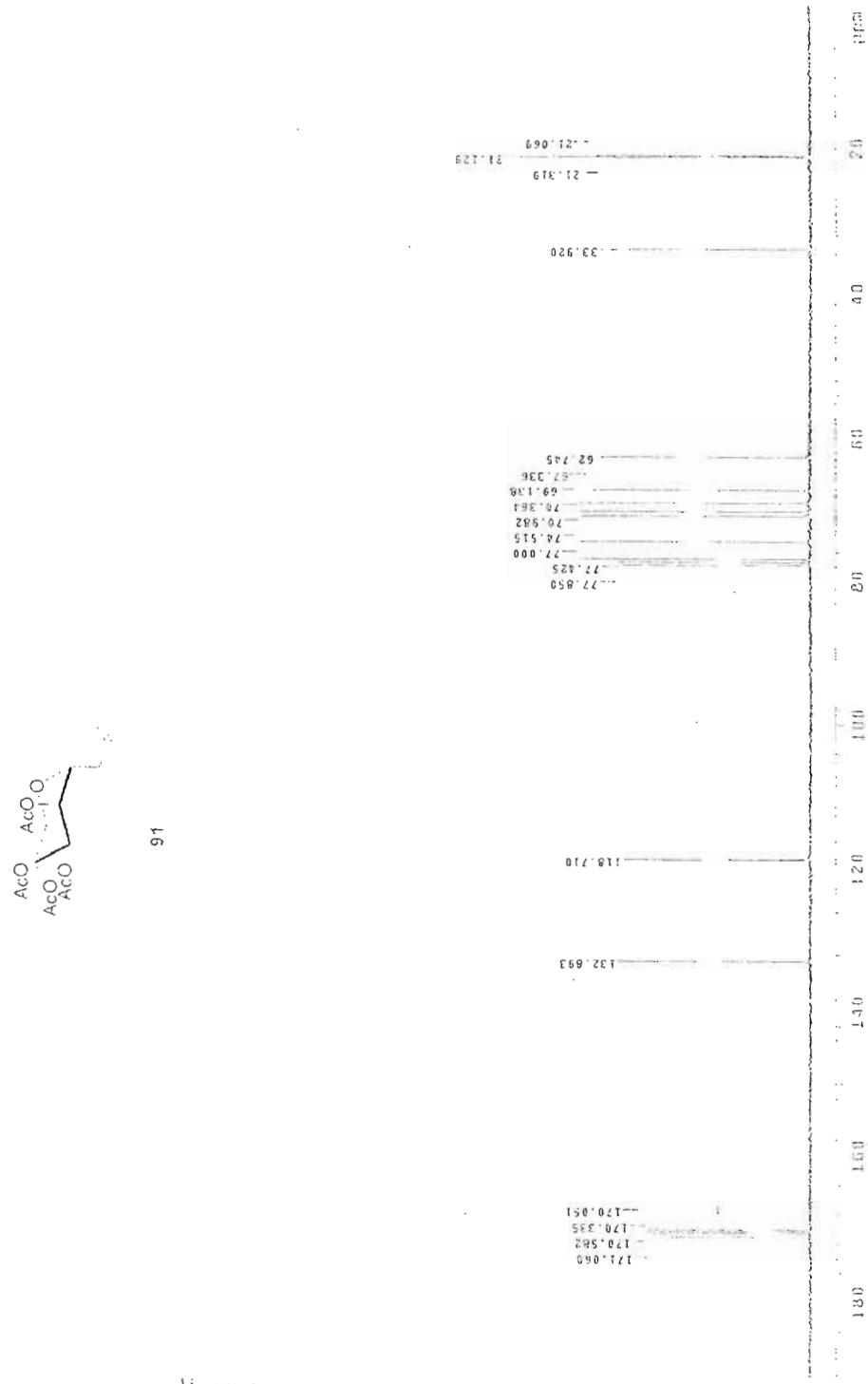
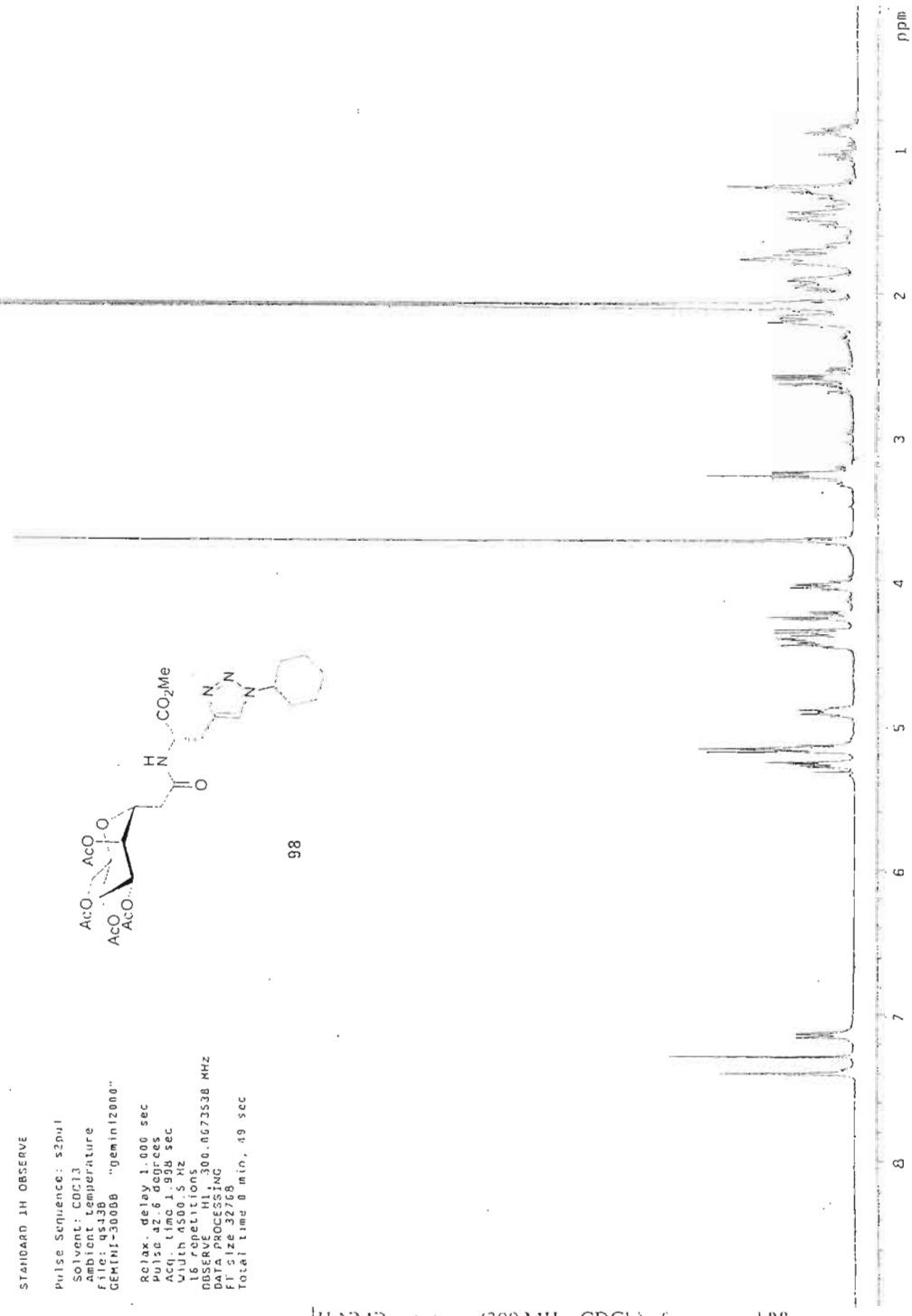


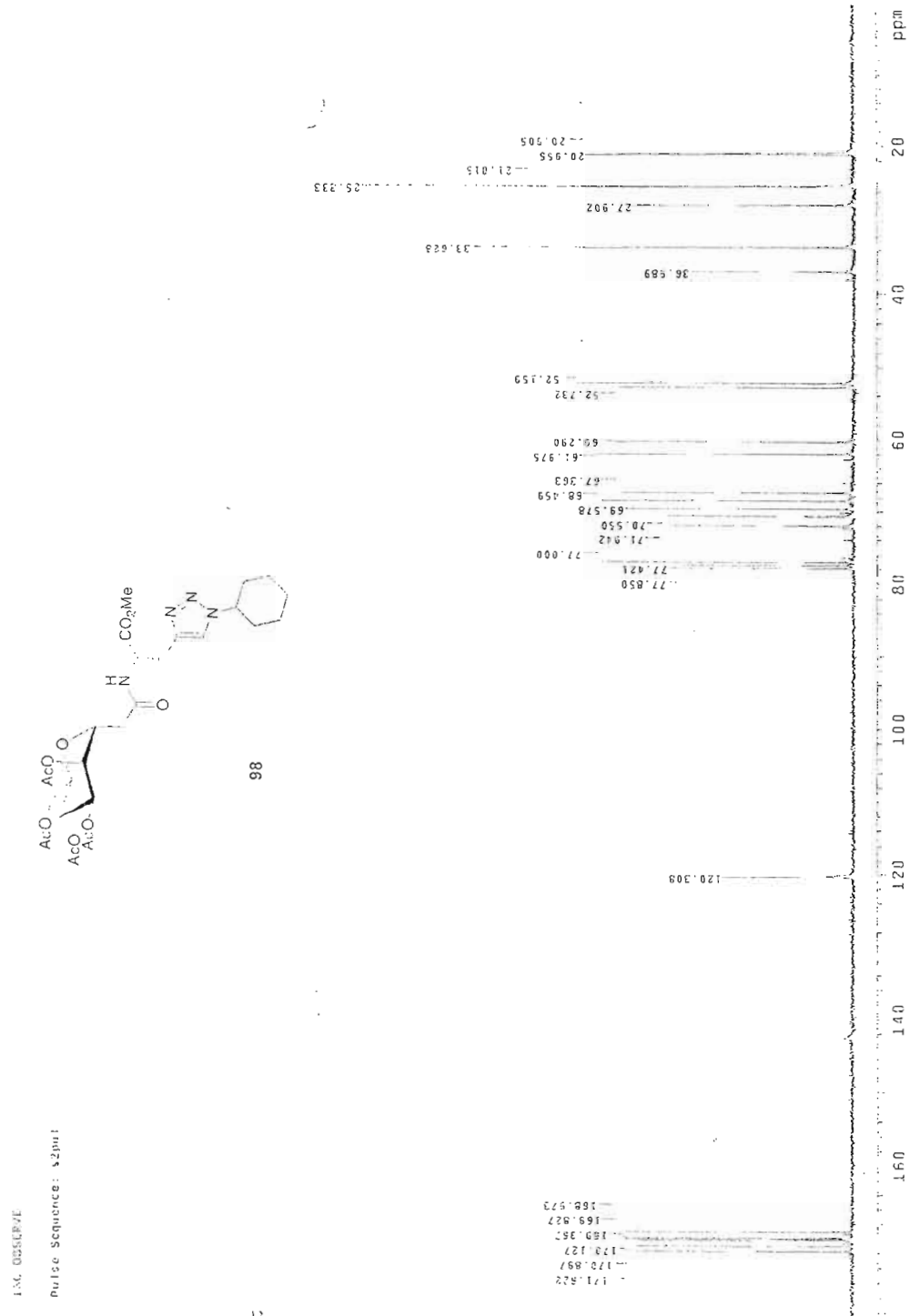

$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **91**



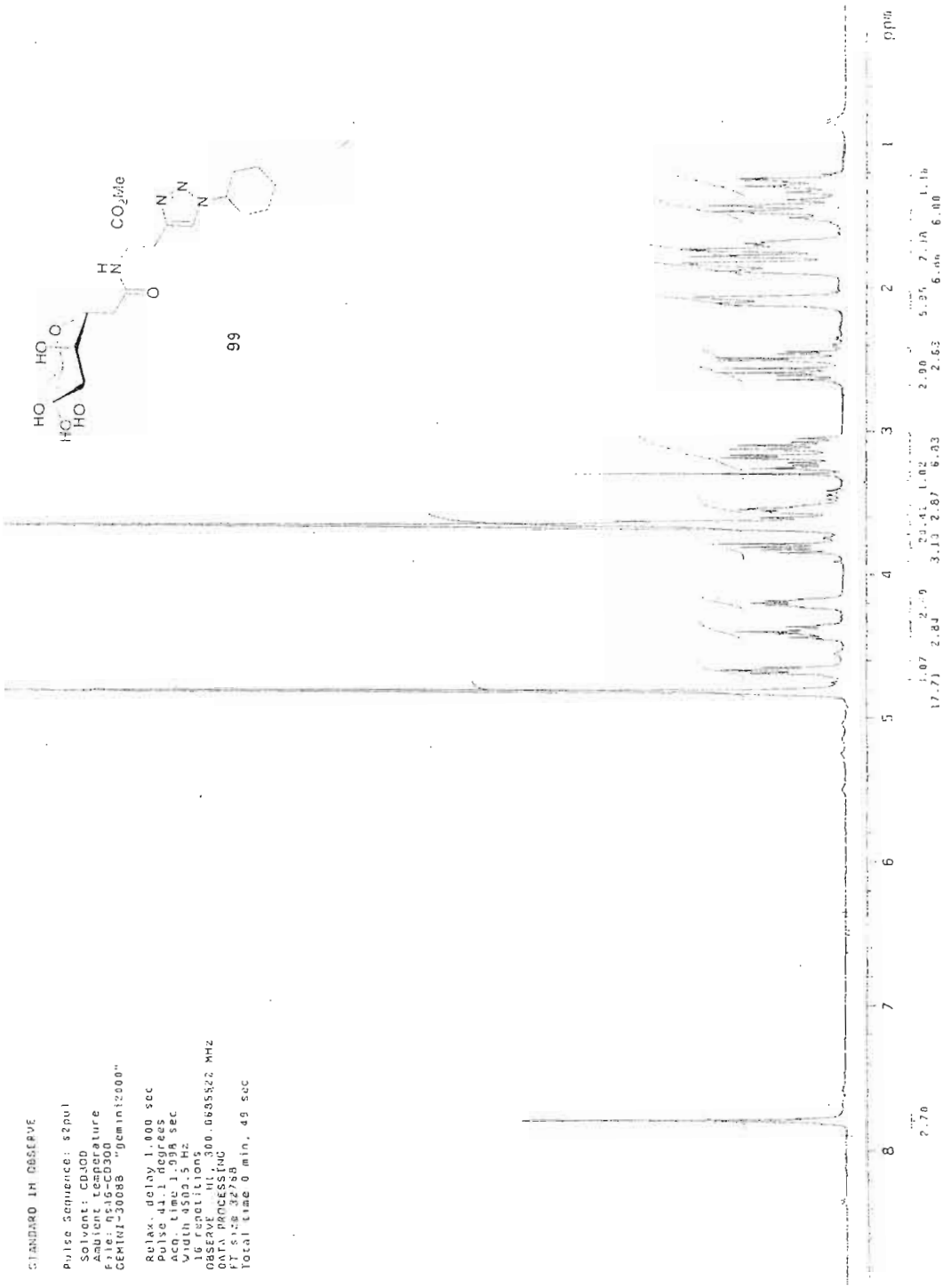

$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound **91**



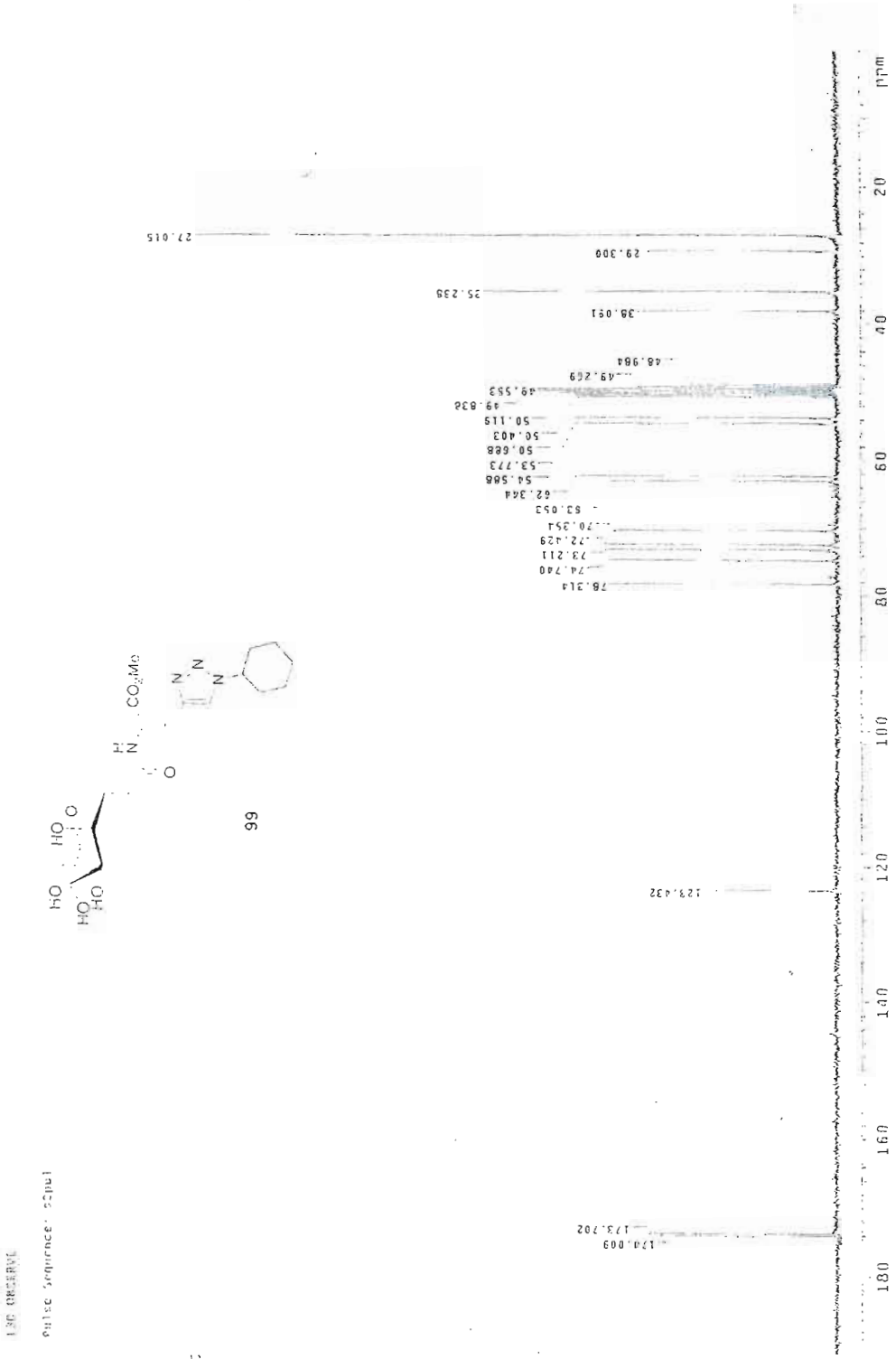

$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **98**



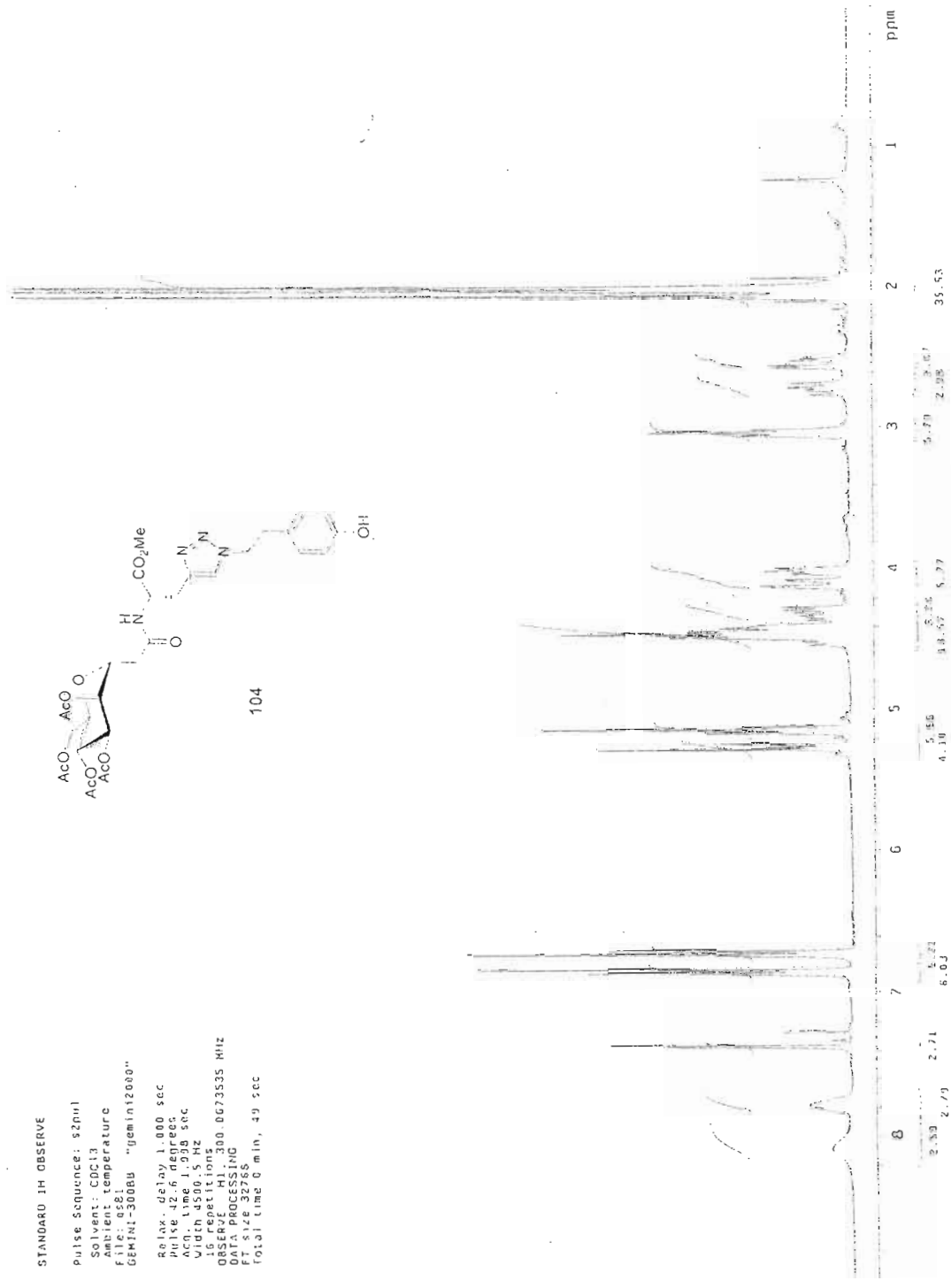

$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound **98**



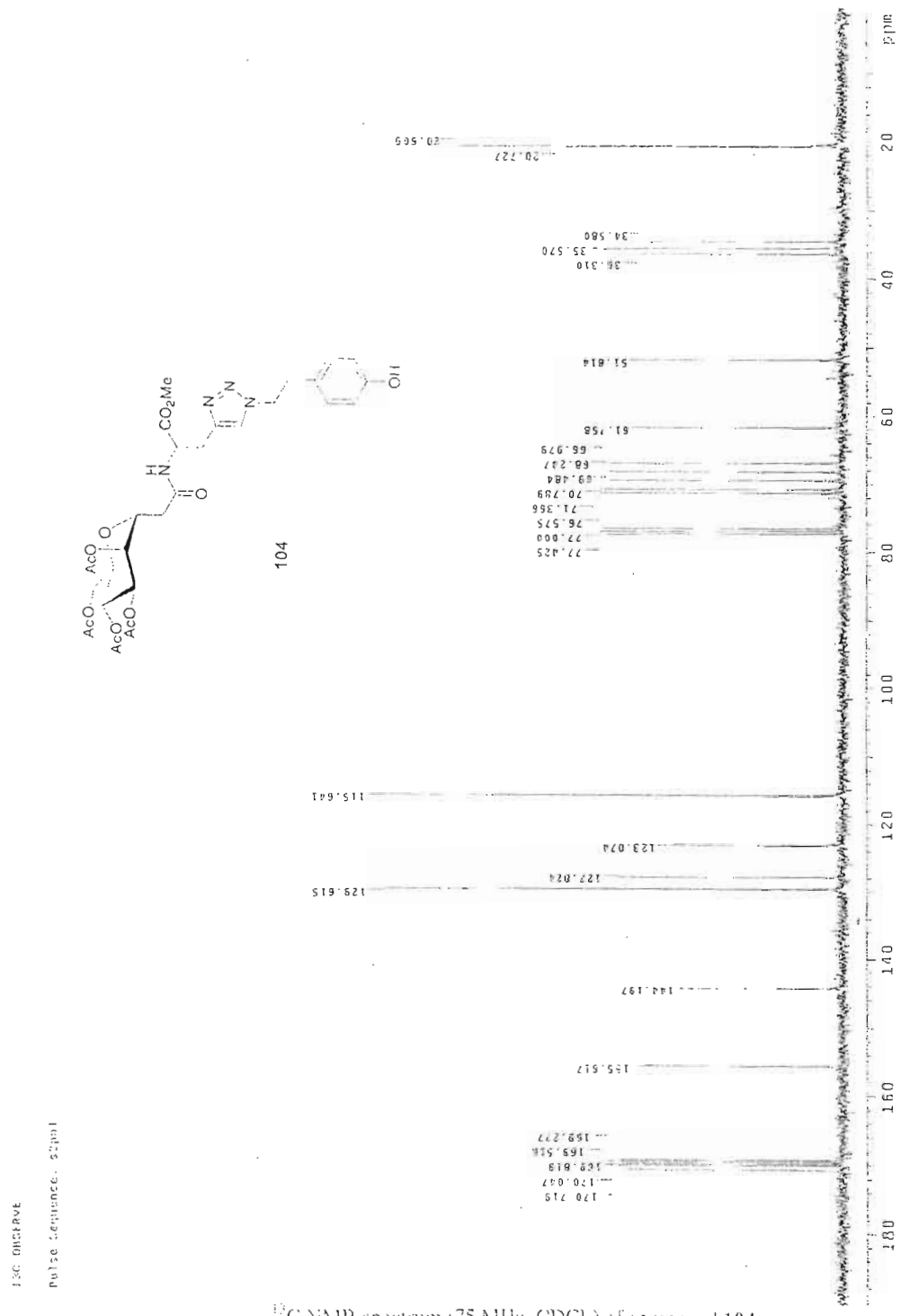

$^1$H NMR spectrum (300 MHz, $CD_3OD$) of compound **99**



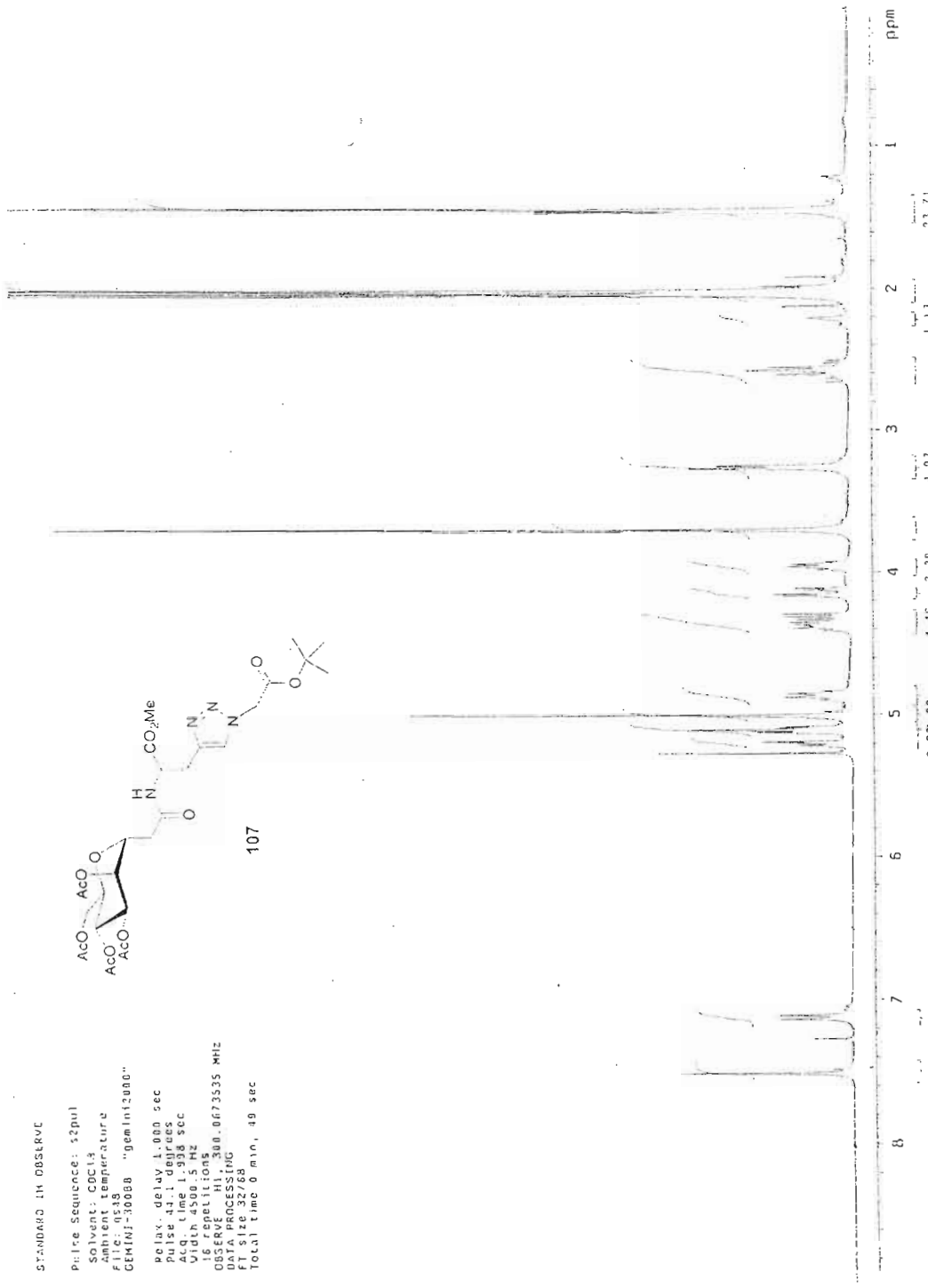

$^{13}$C NMR spectrum (75 MHz, $CD_3OD$) of compound **99**




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **104**




$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound 104

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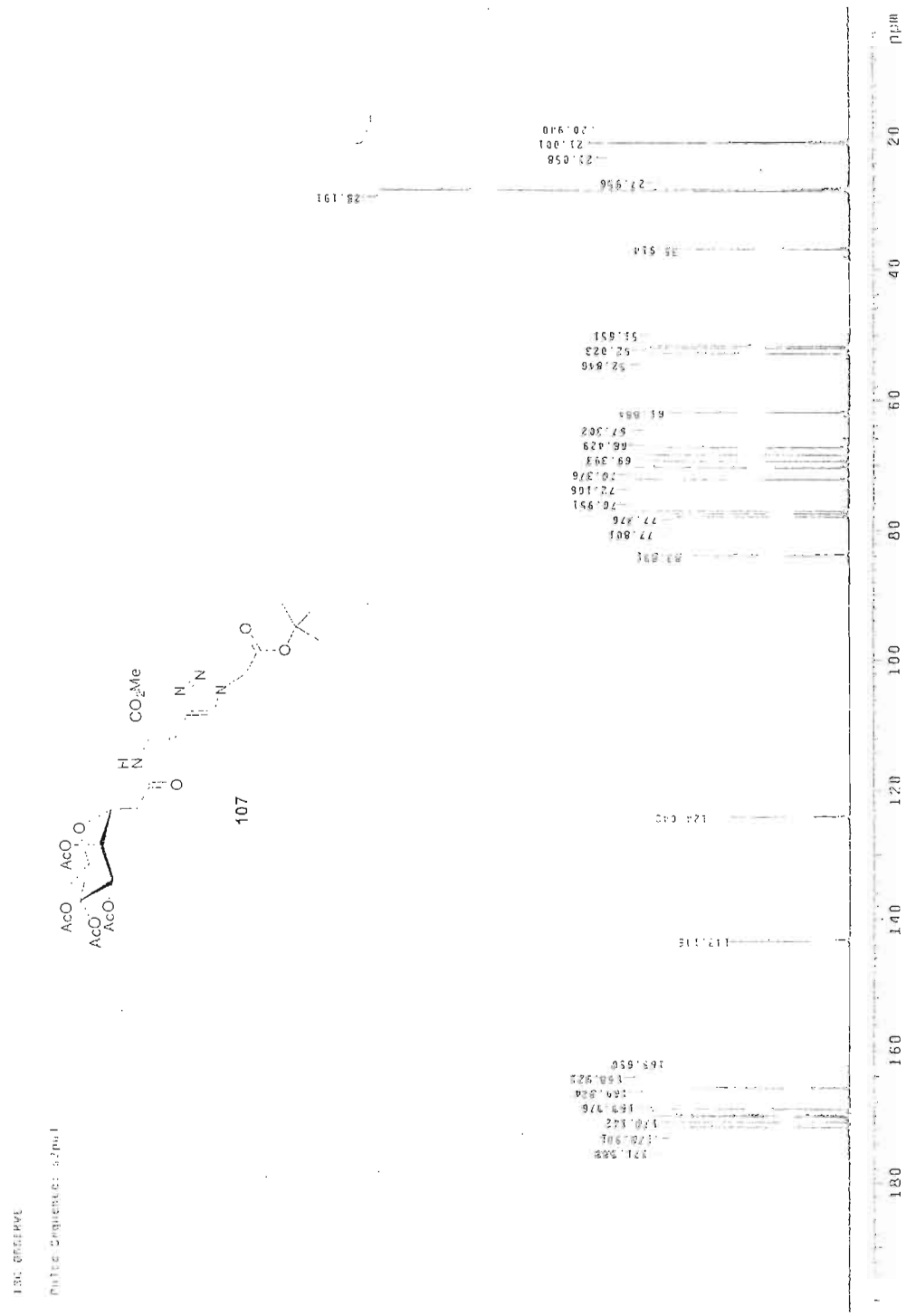
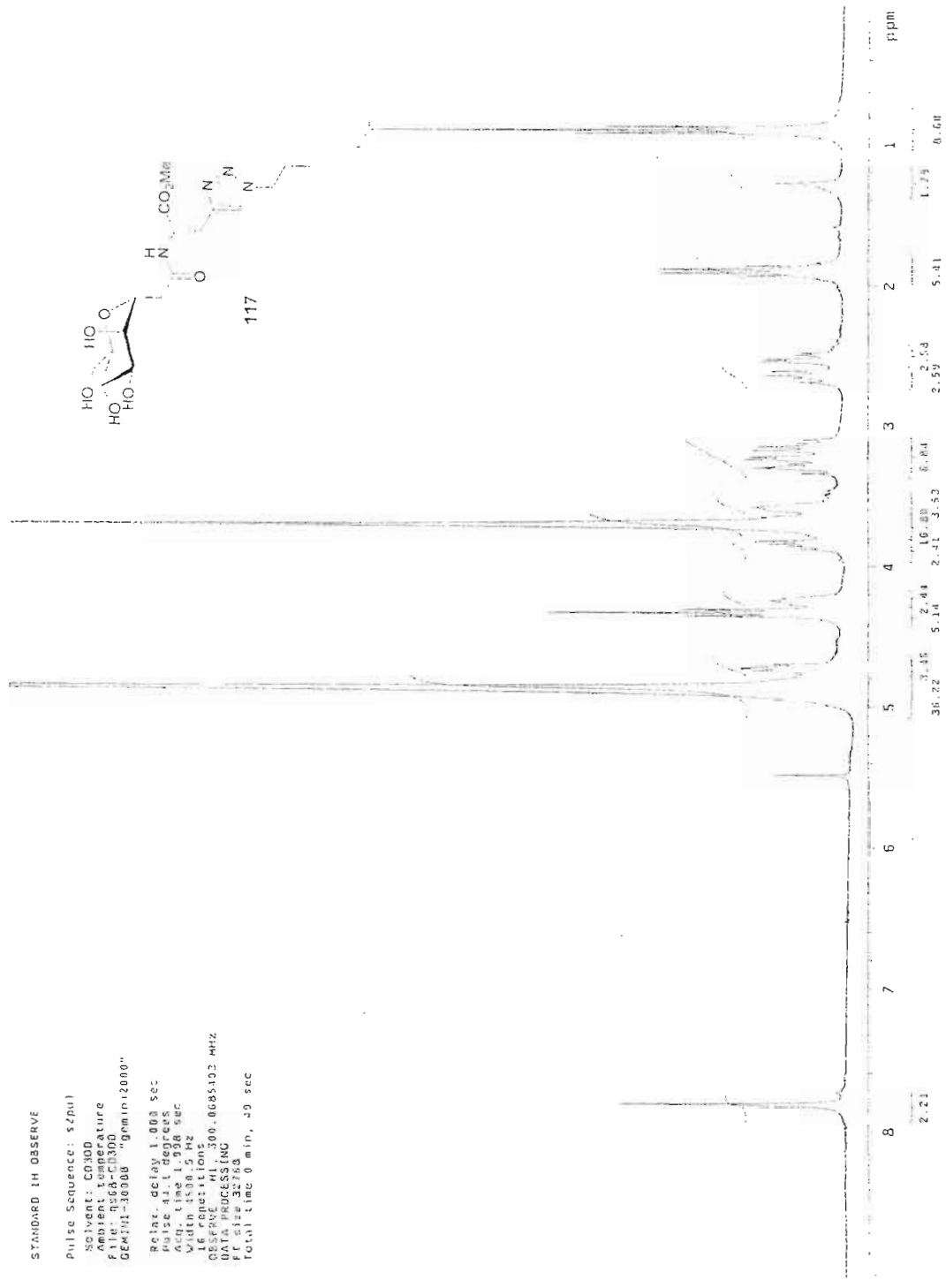



$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound 107

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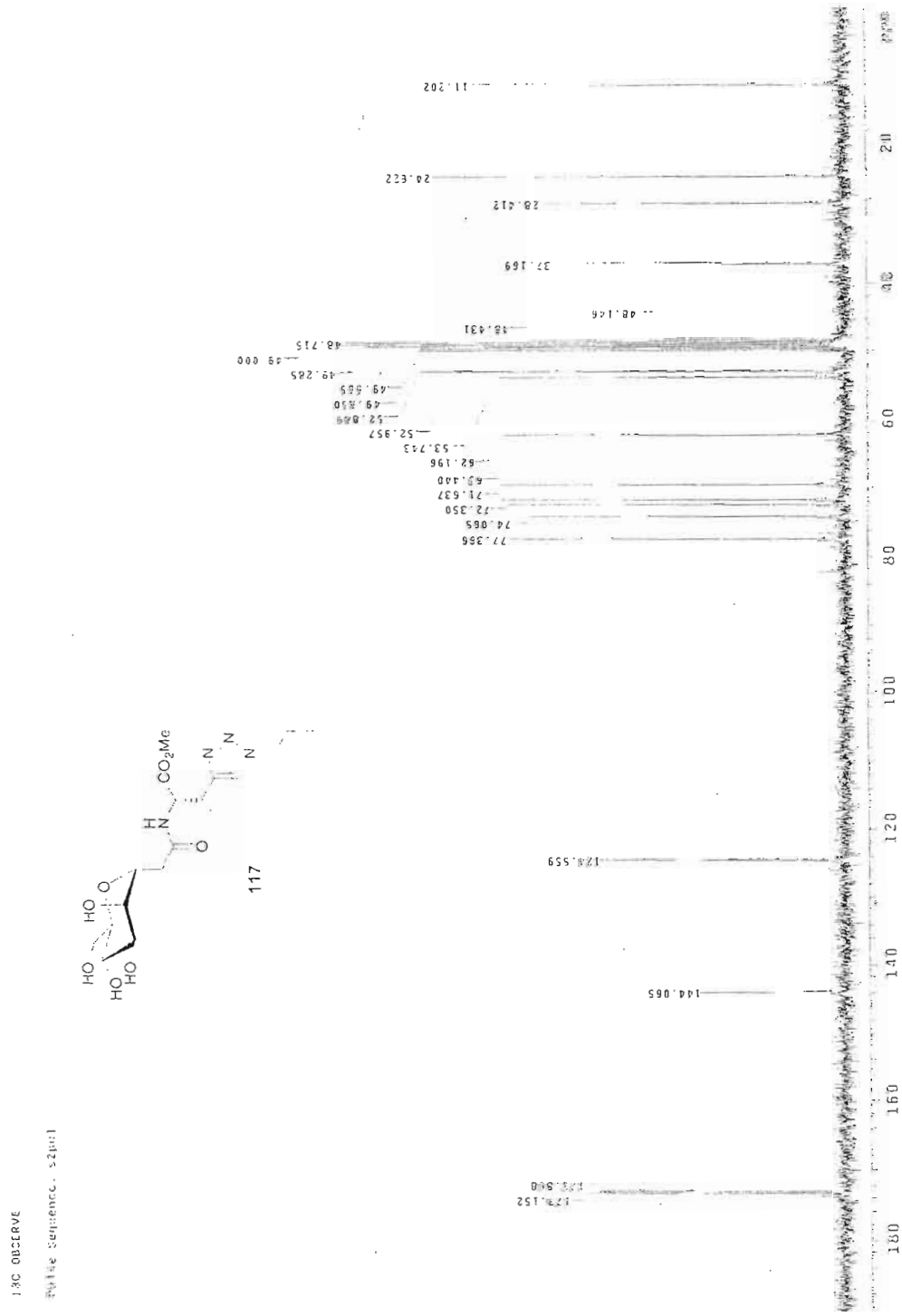


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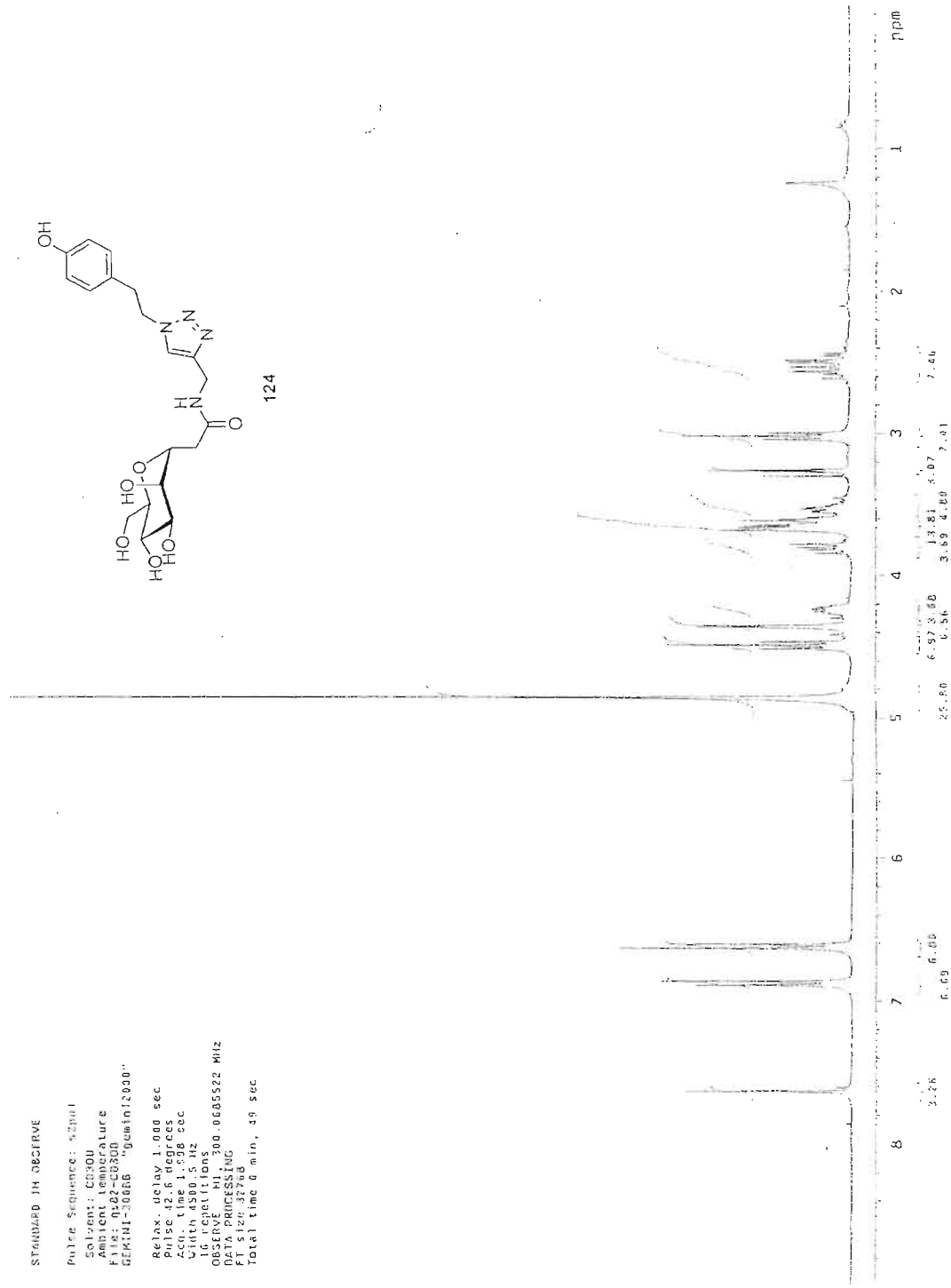


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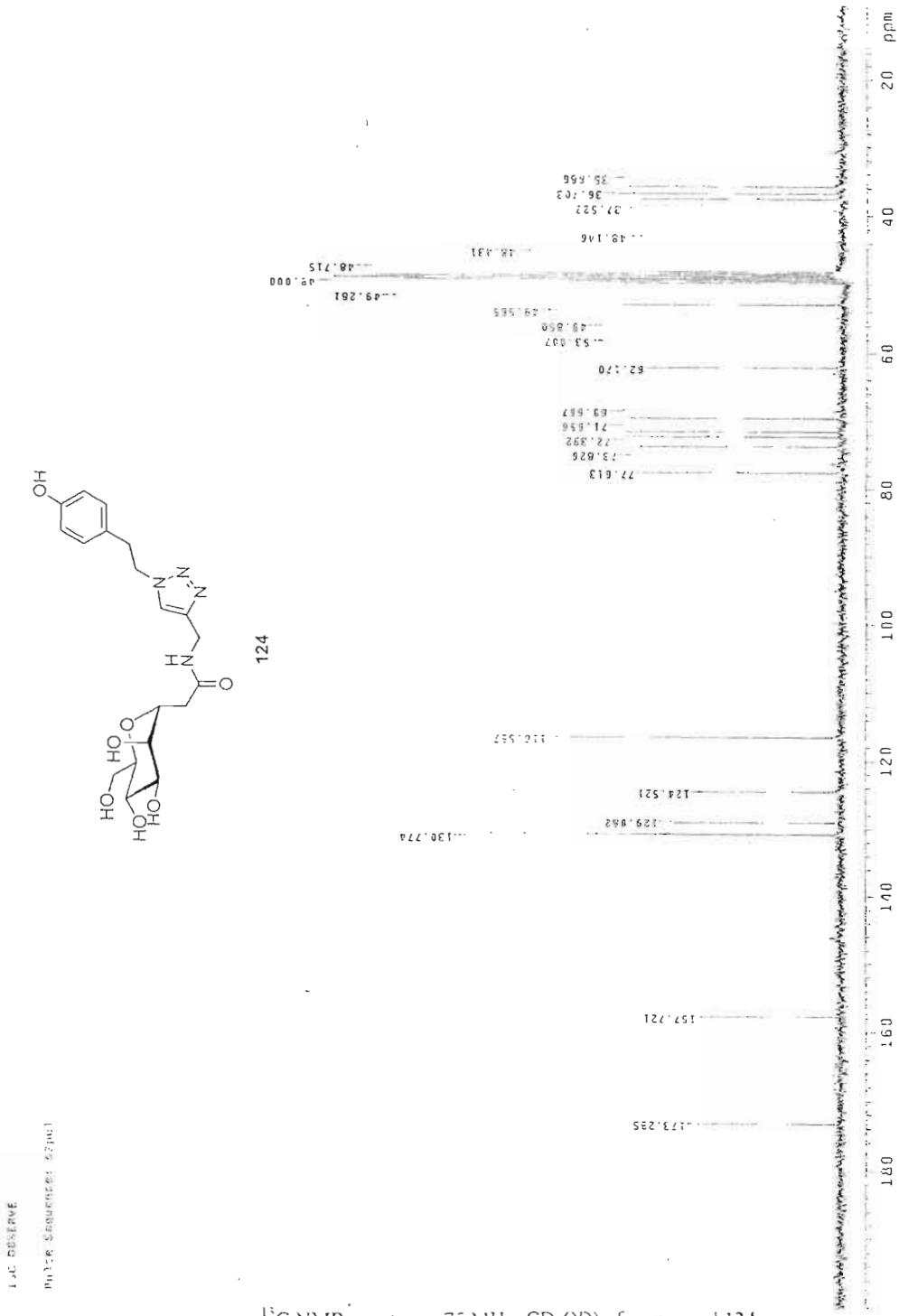
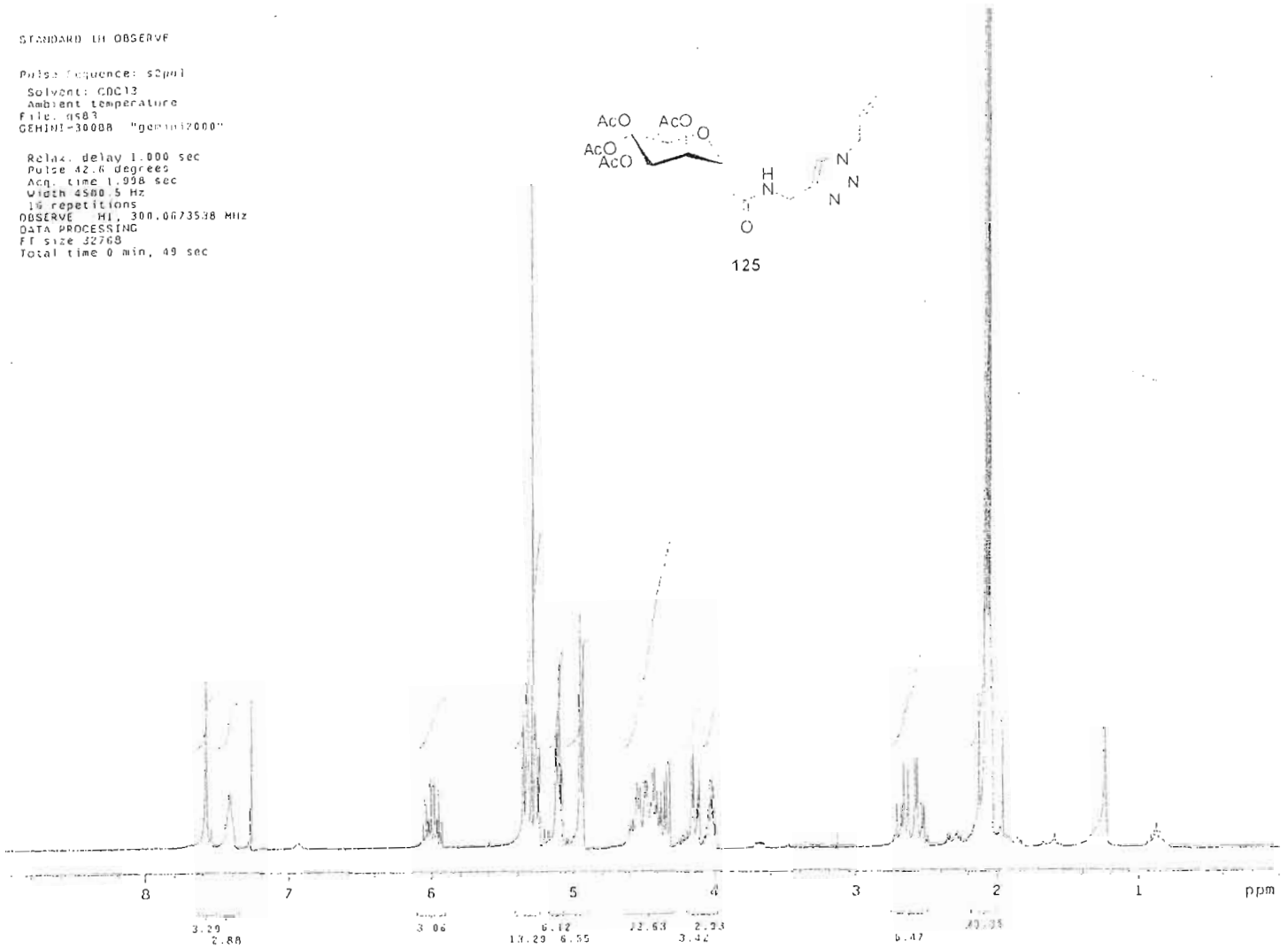
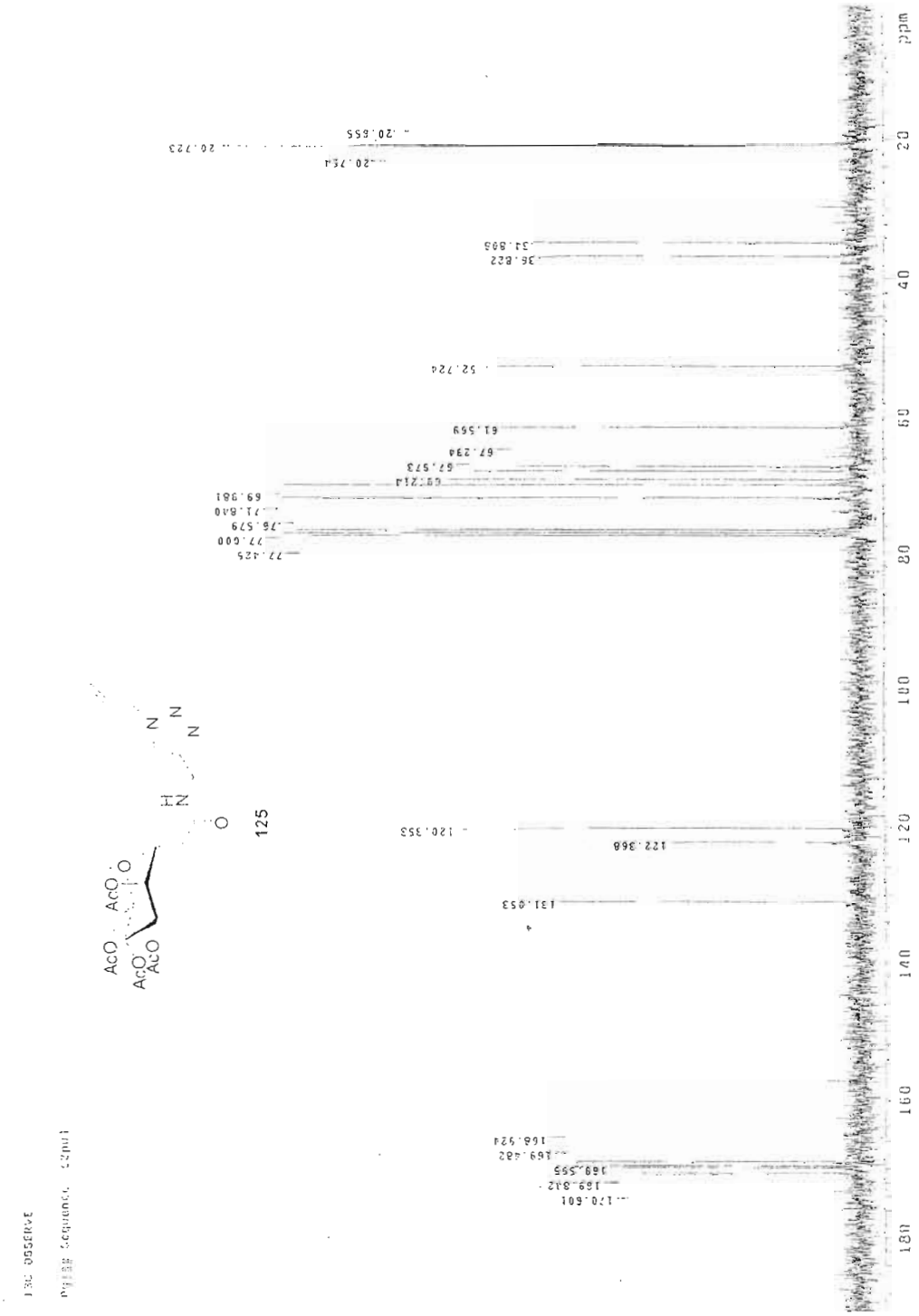



$^{13}C$ NMR spectrum (75 MHz, $CD_3OD$) of compound **124**




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **125**

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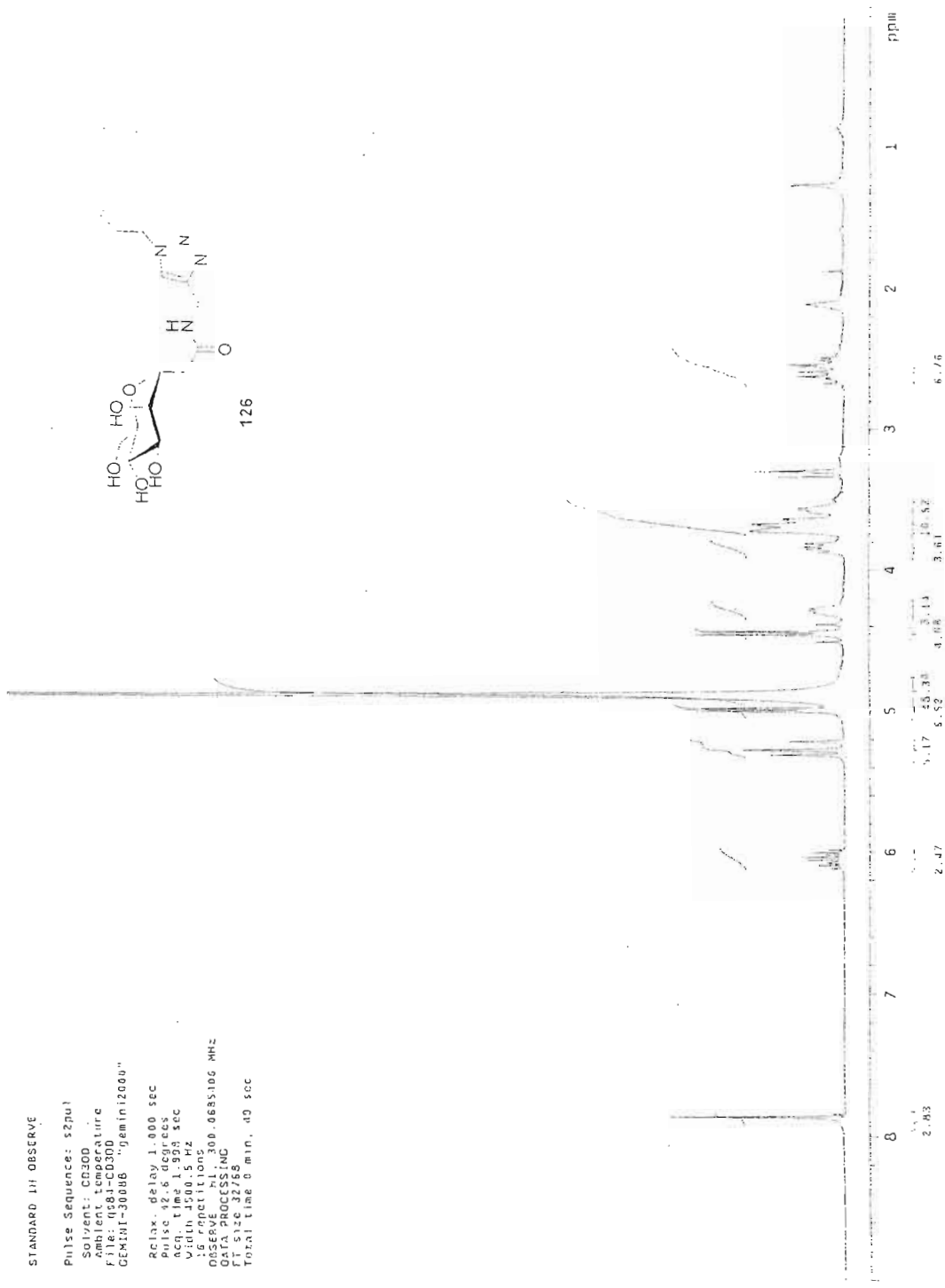
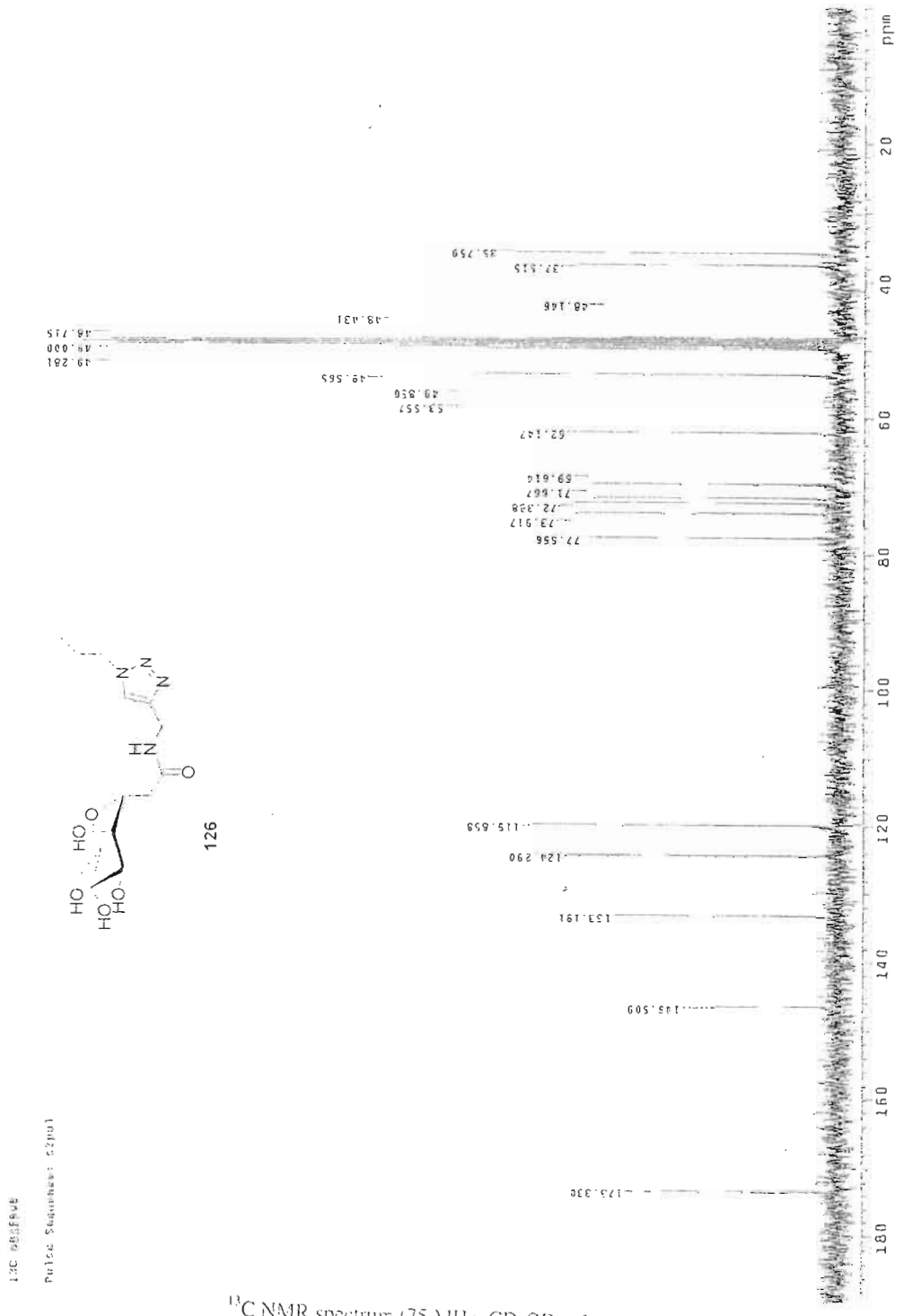
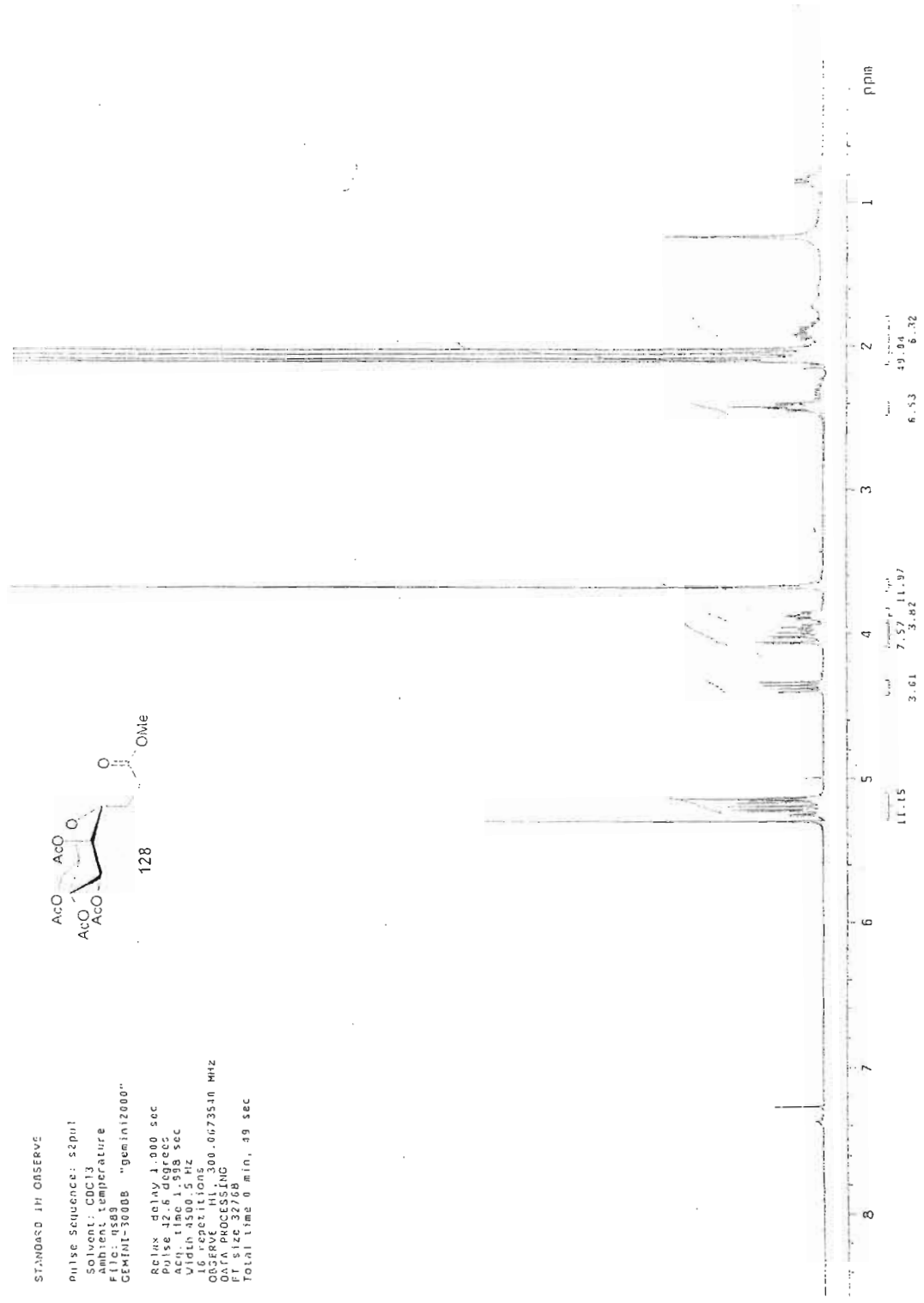


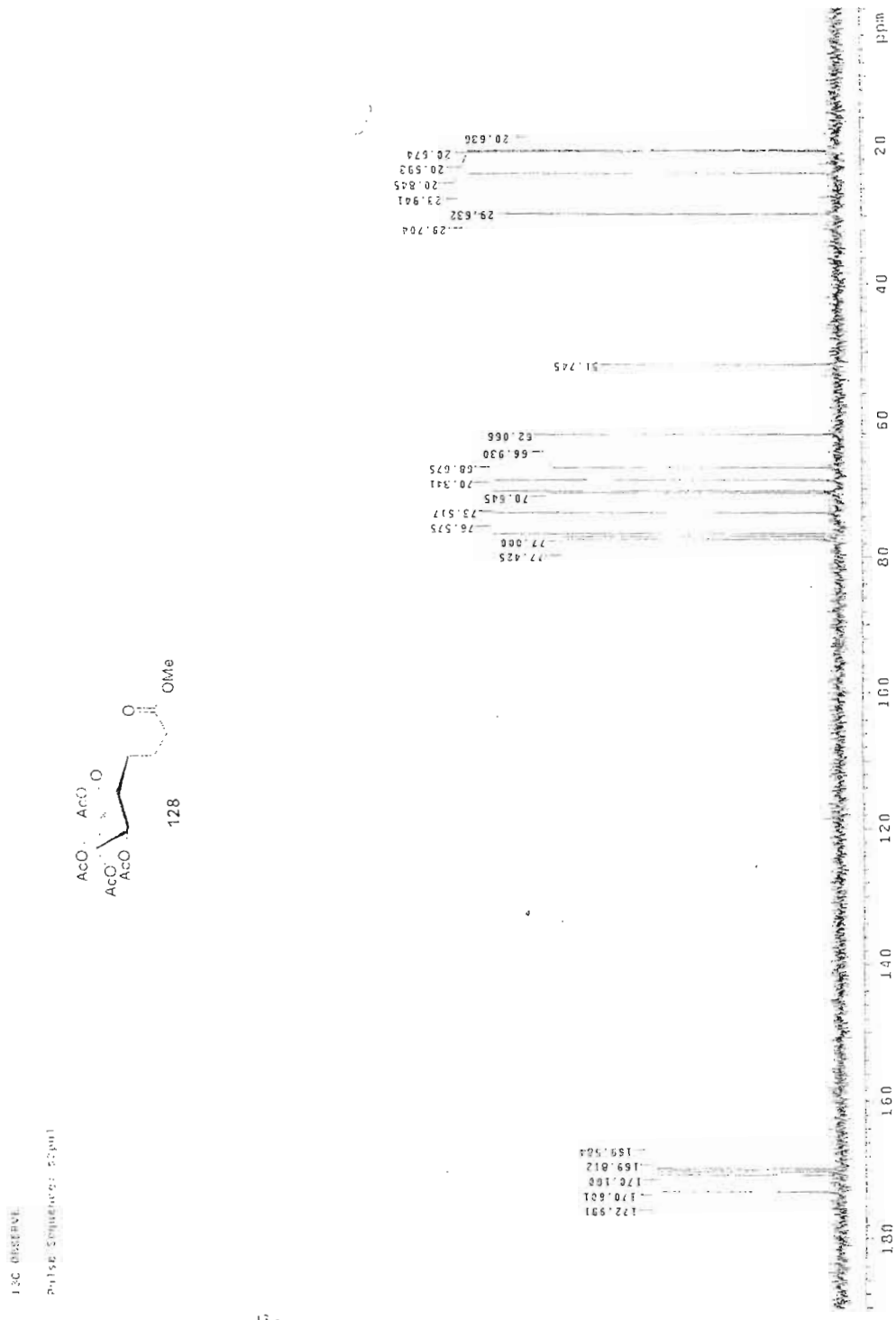

$^1$H NMR spectrum (300 MHz, $CD_3OD$) of compound **126**



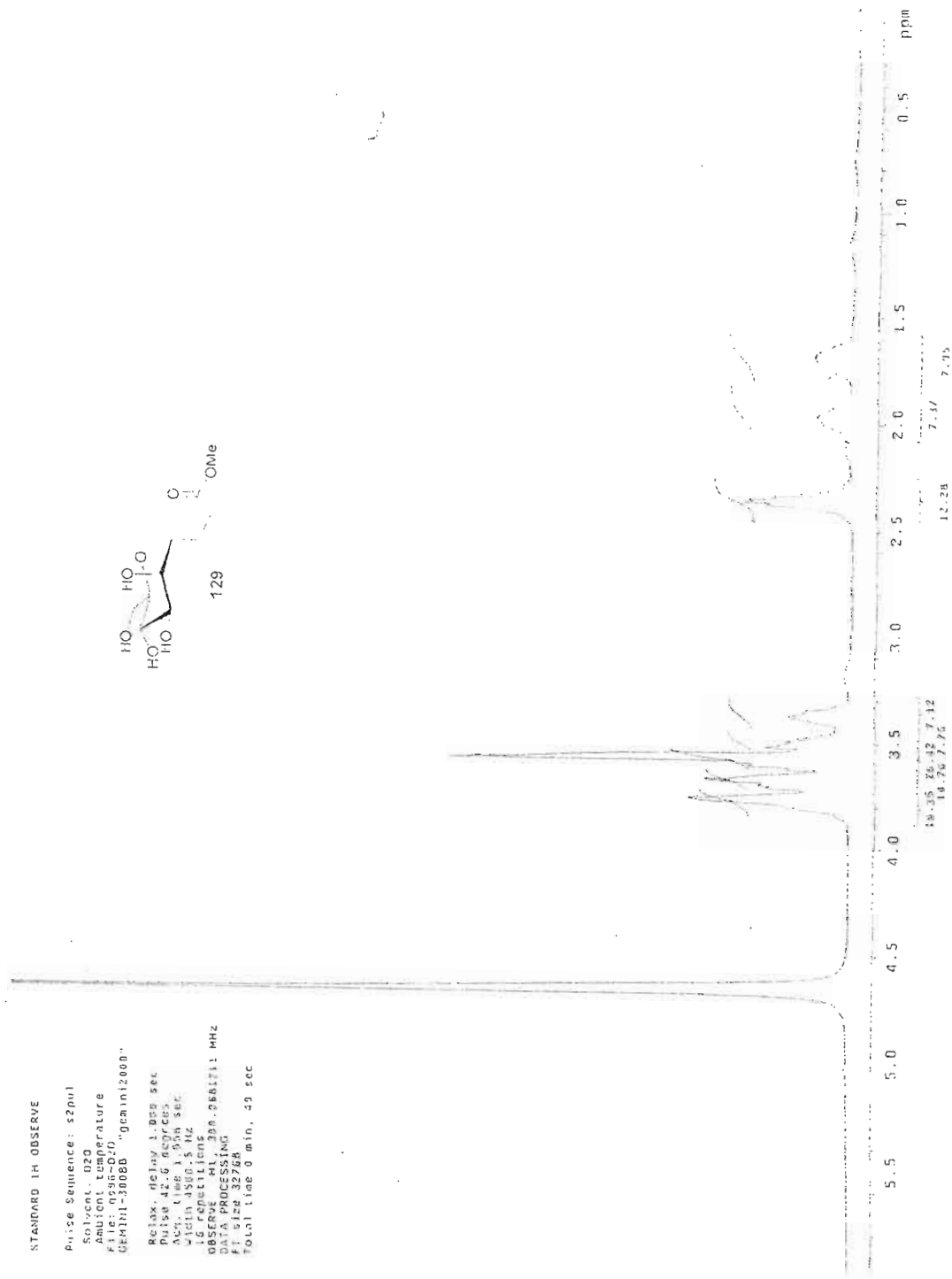

$^{13}C$ NMR spectrum (75 MHz, $CD_3OD$) of compound **126**




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **128**




$^{13}C$ NMR spectrum (75 MHz, $CDCl_3$) of compound 128

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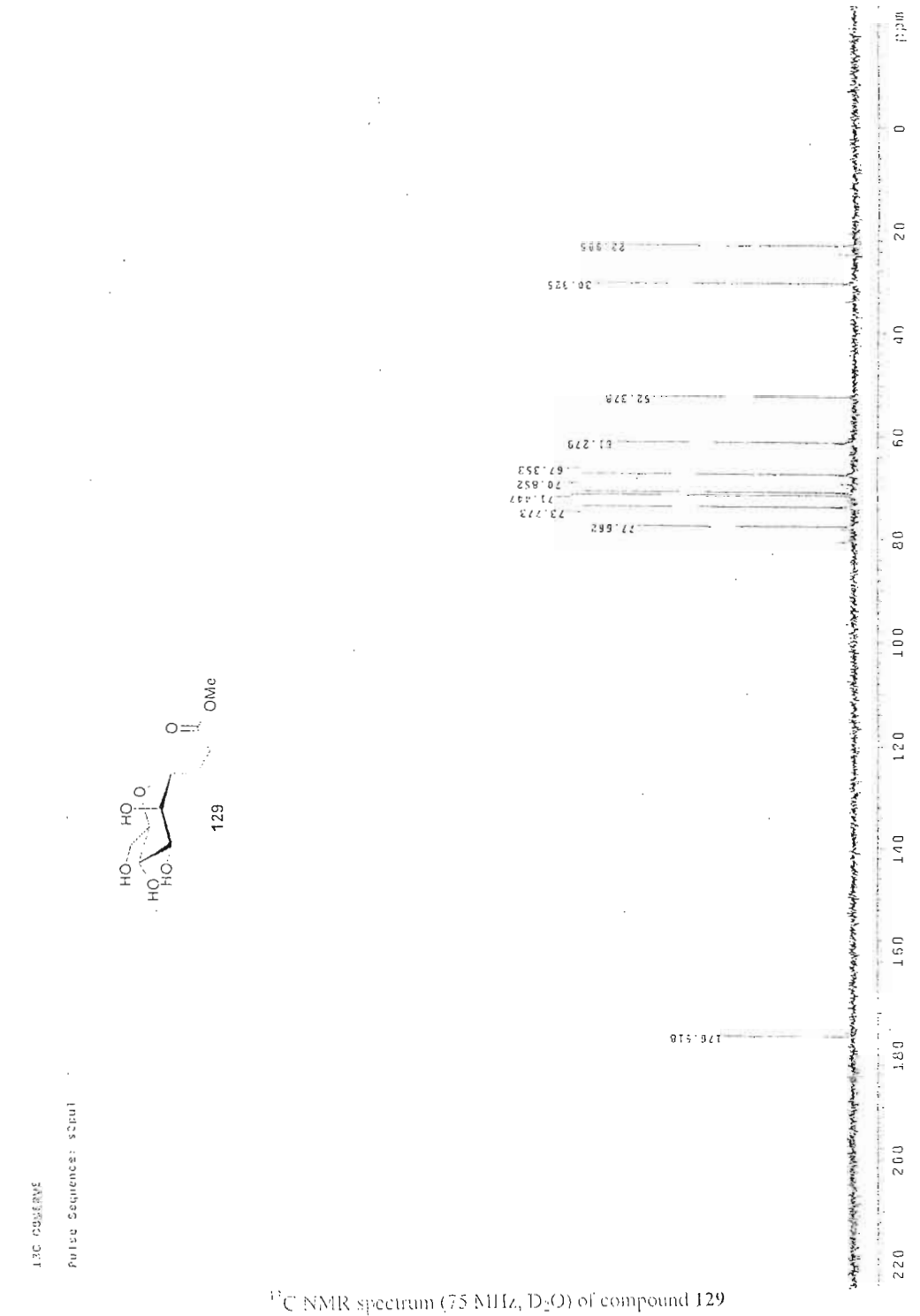


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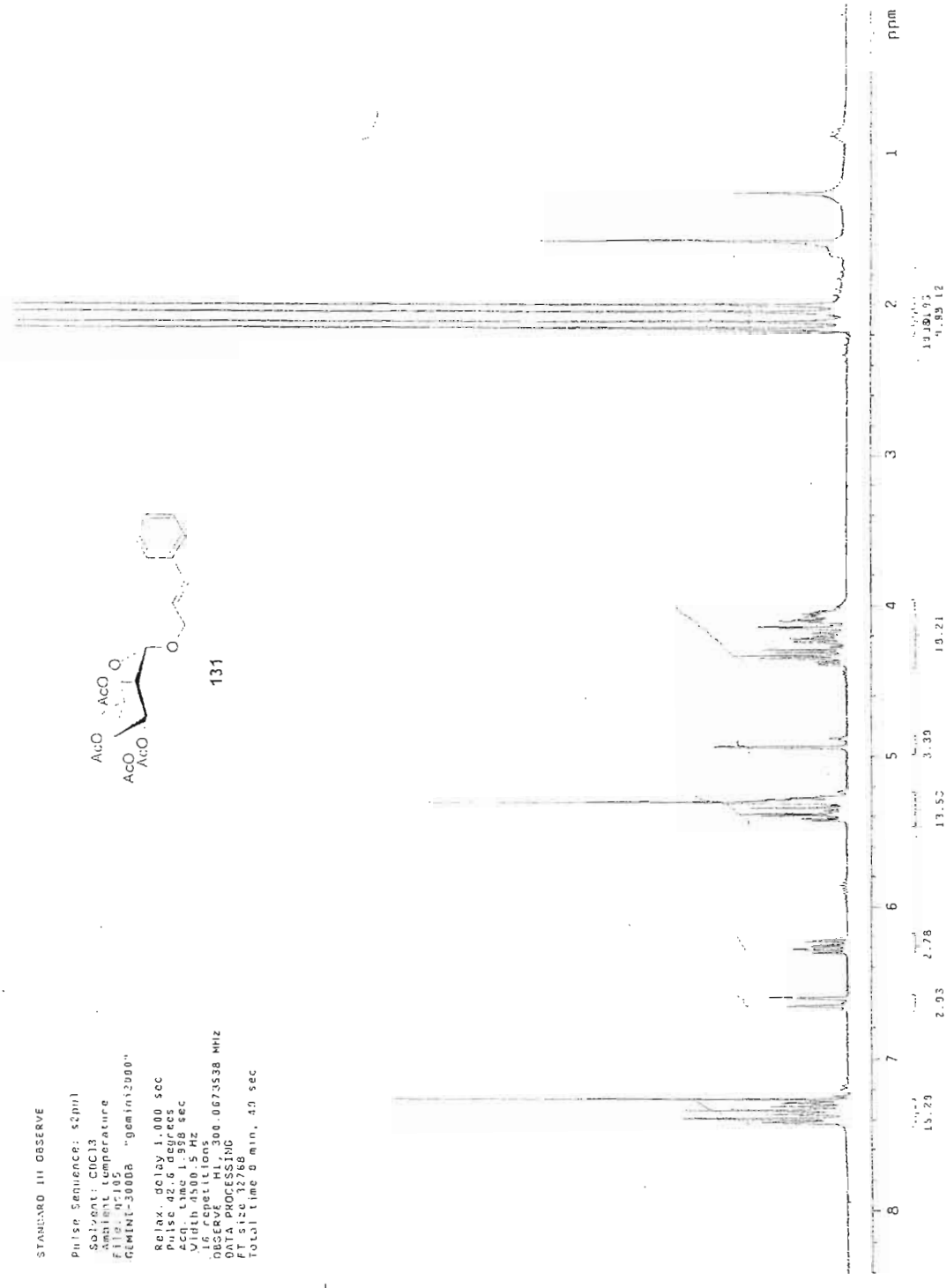


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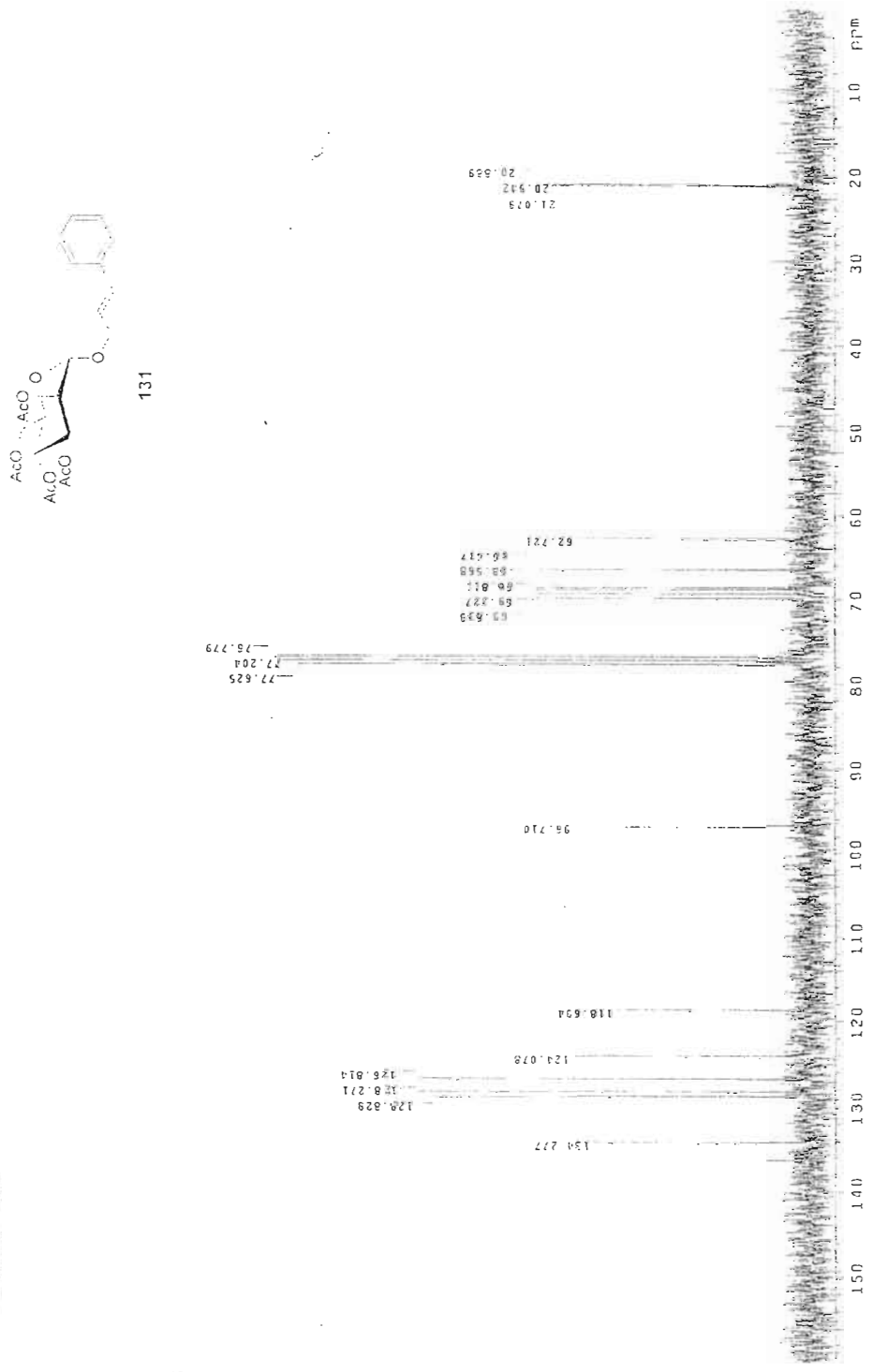
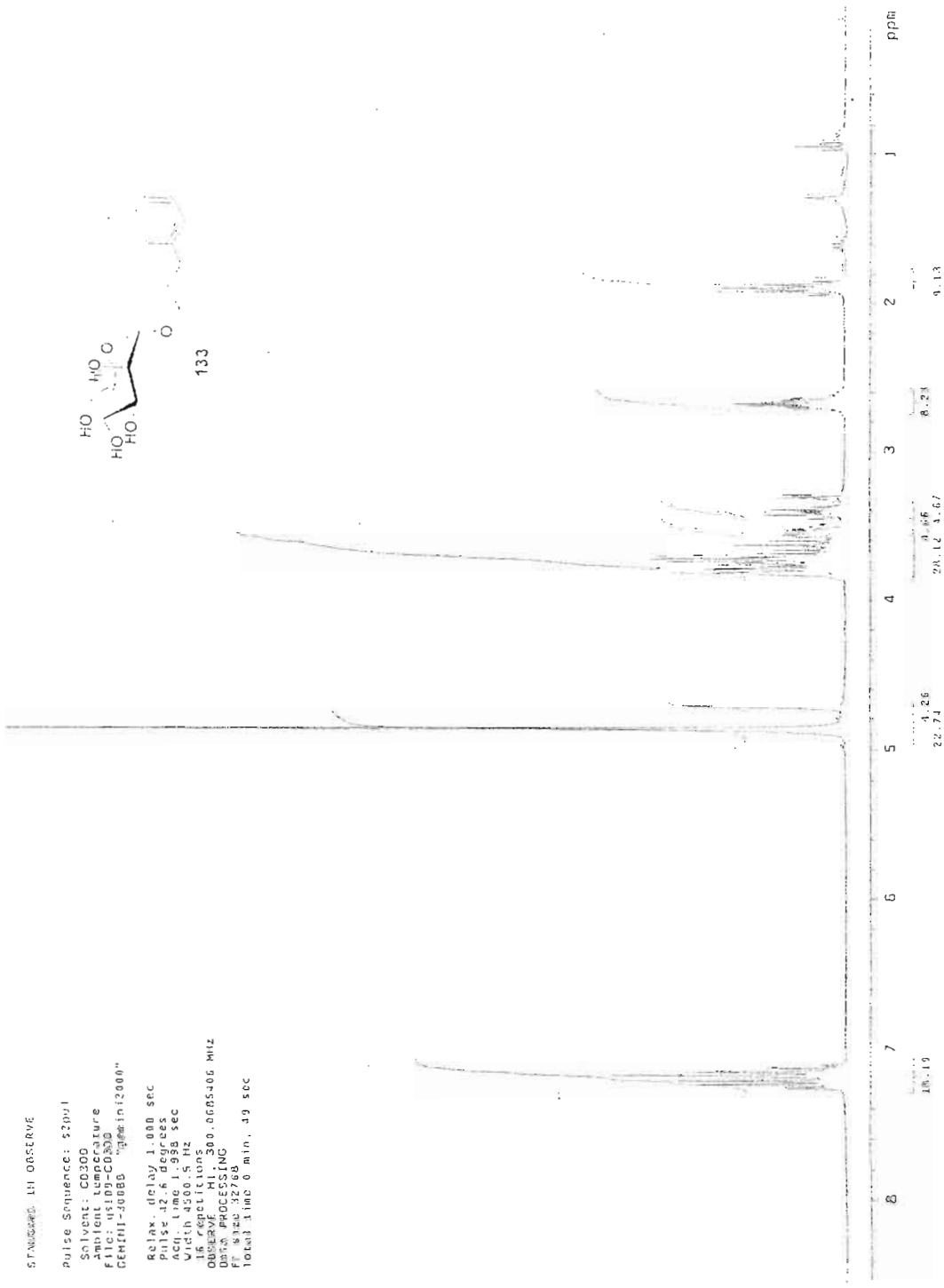
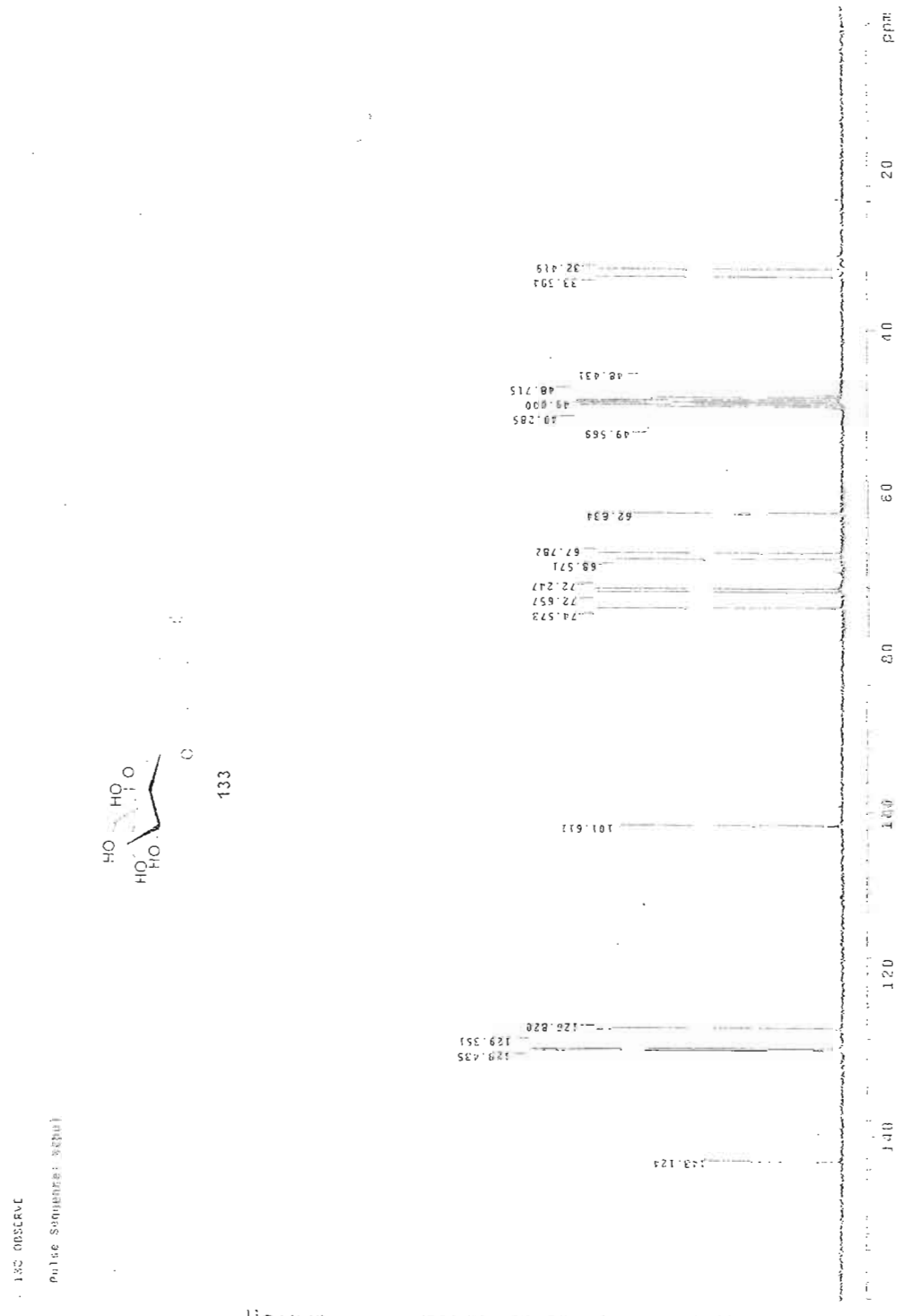


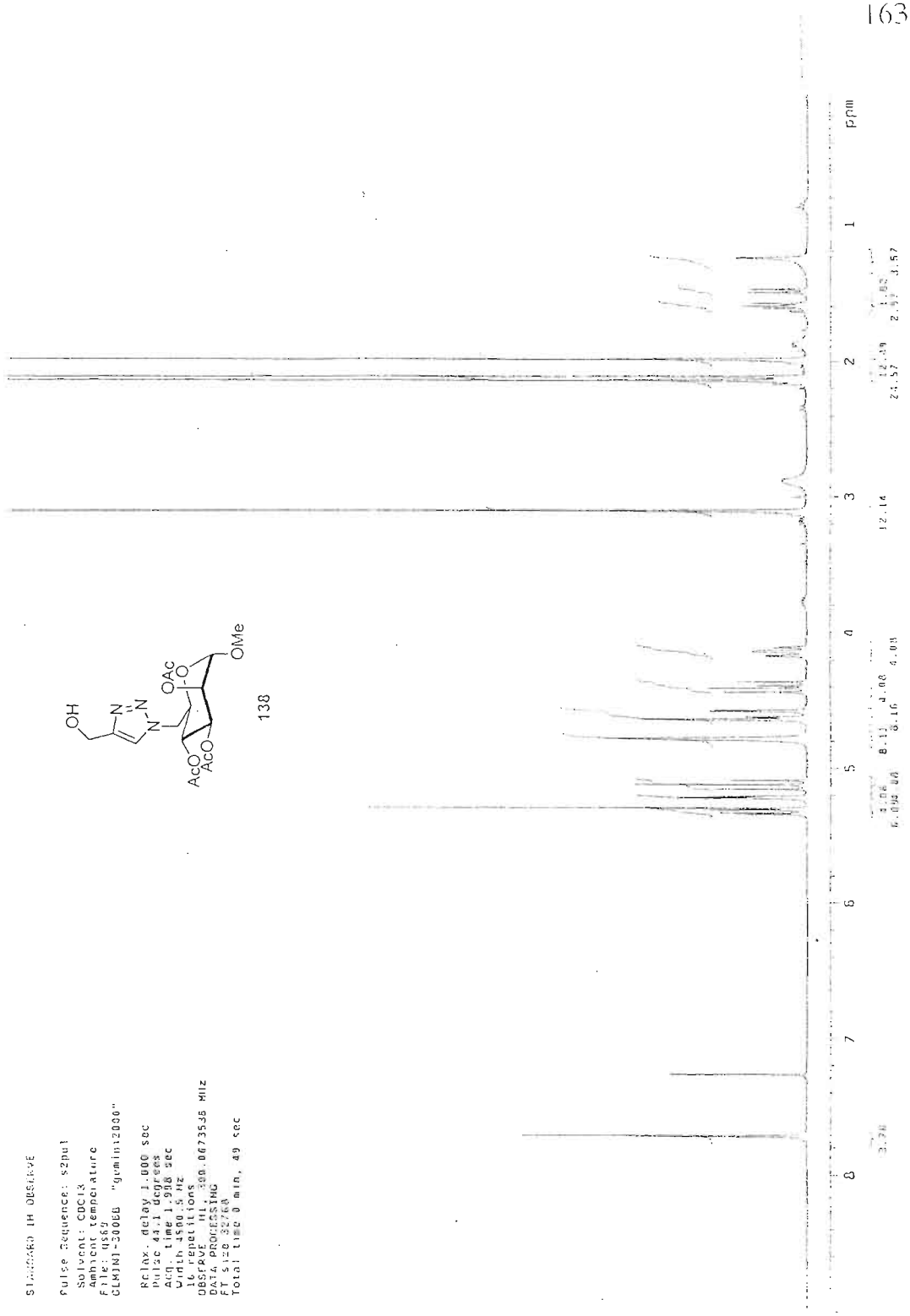

$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound 131



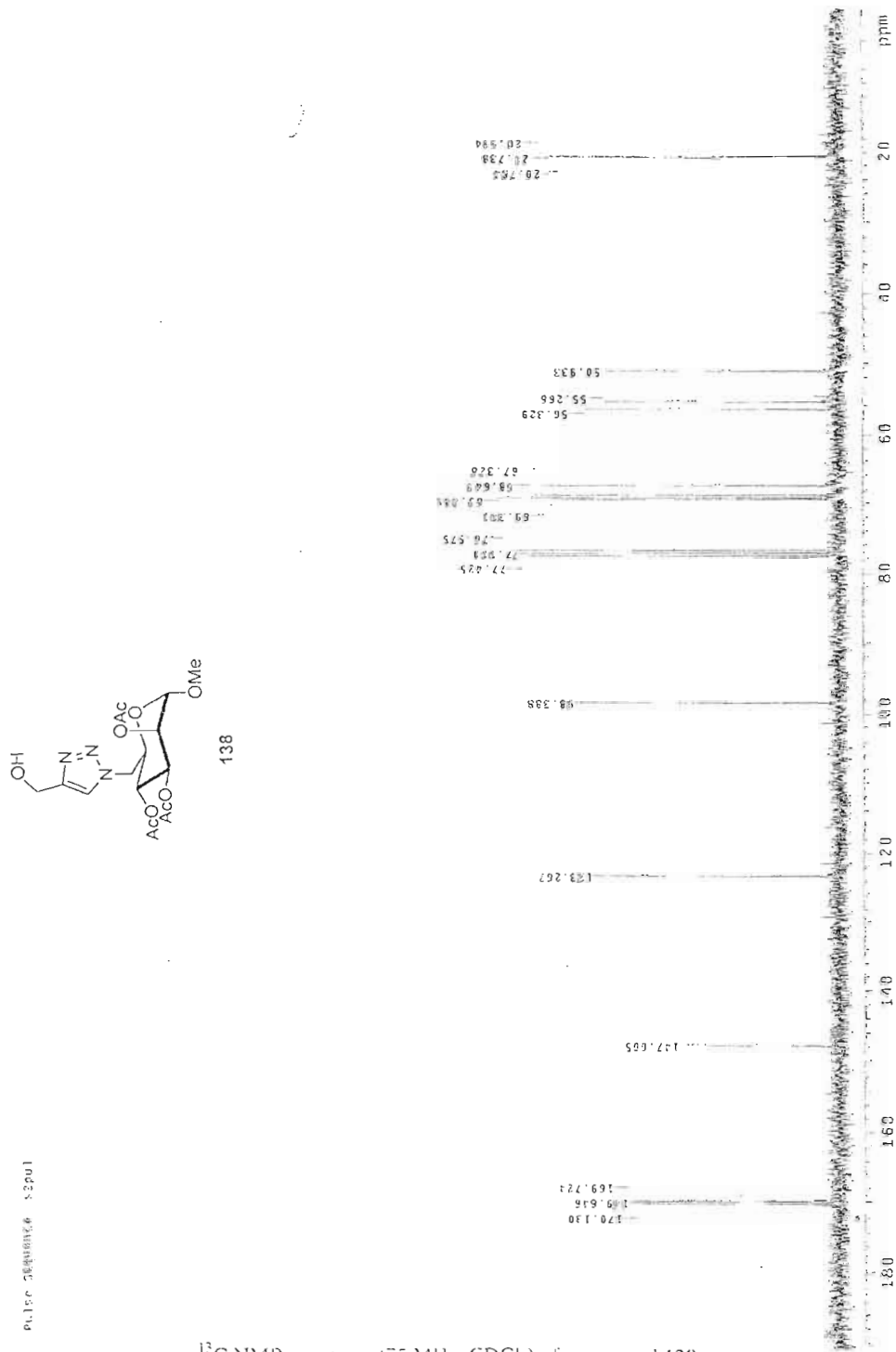

$^1$H NMR spectrum (300 MHz, $CD_3OD$) of compound **133**



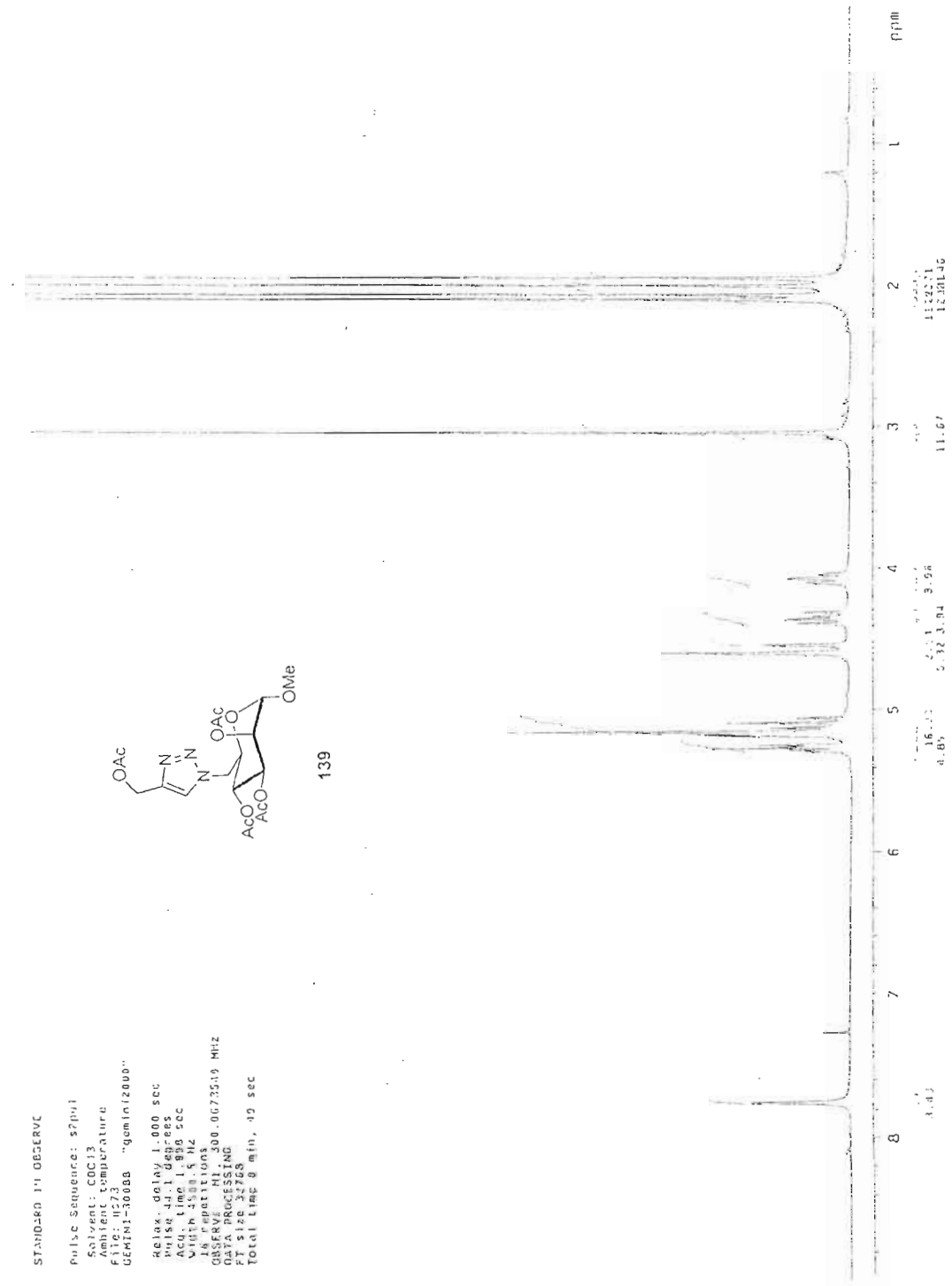

$^{13}$C NMR spectrum (75 MHz, $CD_3OD$) of compound **133**




$^1$H NMR spectrum (300 MHz, $CDCl_3$) of compound **138**




$^{13}$C NMR spectrum (75 MHz, $CDCl_3$) of compound **138**

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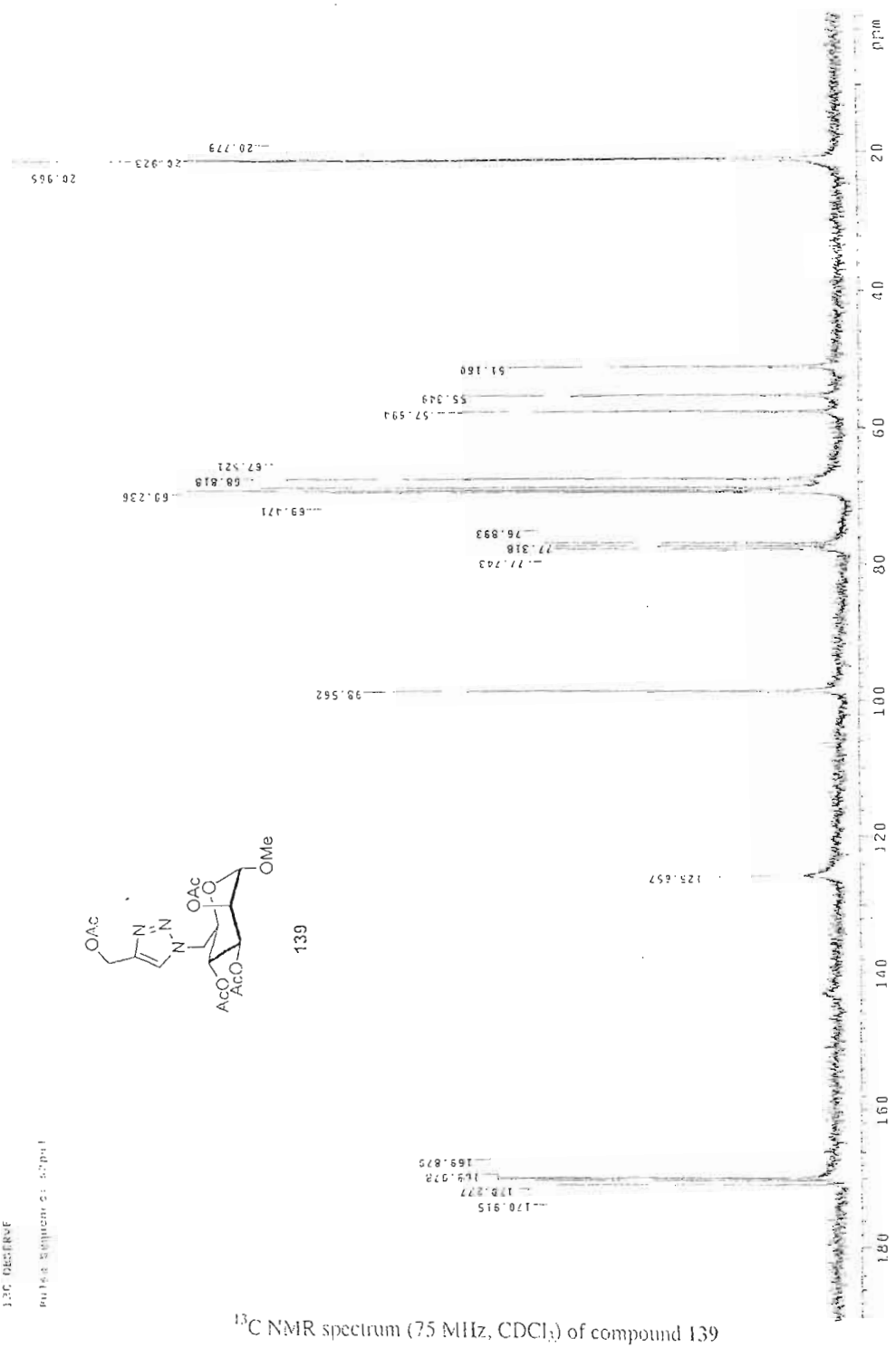


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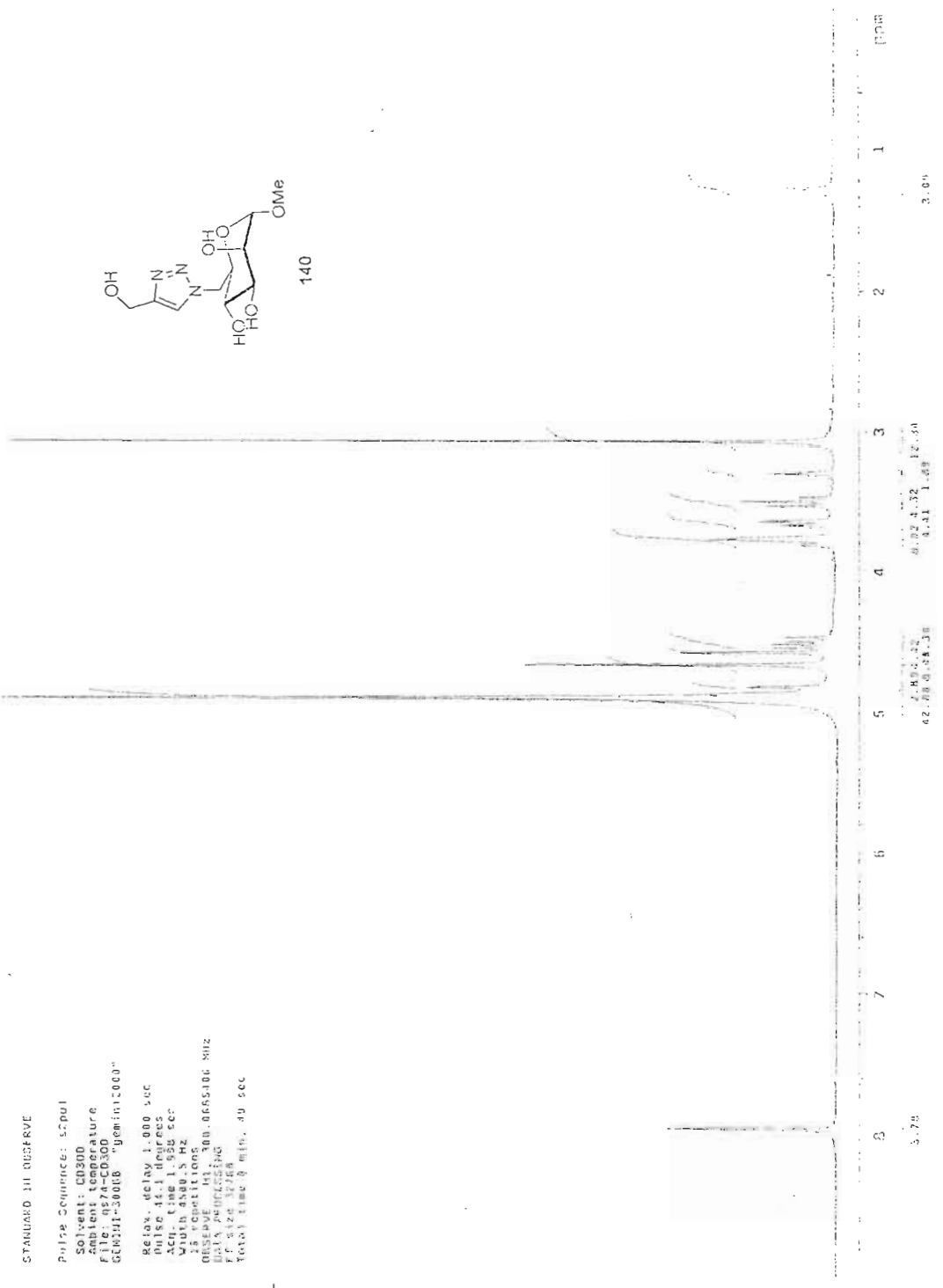


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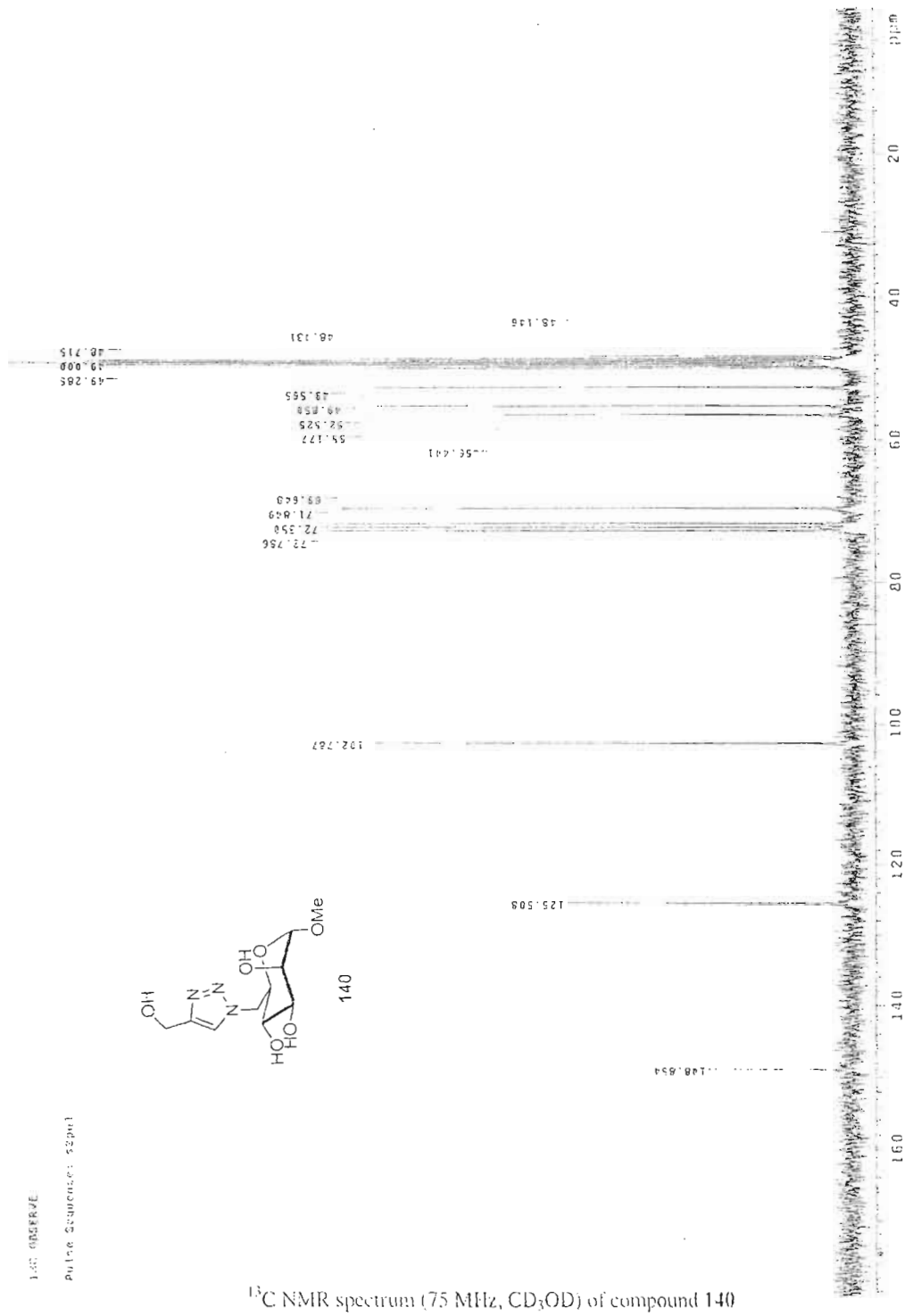


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