SYNTHESIS OF GLYCOSIDES, SACCHARIDES AND GLYCOCONJUGATES VIA ALKYNE ACTIVATION

Mr. SUDHIR KASHYAP

Dr. Srinivas Hotha

(RESEARCH SUPERVISOR)

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE – 411008 (INDIA)

[May 2008]

SYNTHESIS OF GLYCOSIDES, SACCHARIDES AND GLYCOCONJUGATES VIA ALKYNE ACTIVATION

A THESIS

SUBMITTED TO

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

Mr. SUDHIR KASHYAP

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE – 411008 (INDIA)

May 2008

Dedicated
To

My Parents, Brothers, Sister-in-law, Wife and Nephews

CERTIFICATE

This is to certify that the research work presented in thesis entitled "***Synthesis of glycosides, Saccharides and glycoconjugates via Alkyne Activation***" has been carried out under my supervision at National Chemical Laboratory, Pune and is a bonafide work of **Mr. Sudhir Kashyap.** This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008 **(Dr. Srinivas Hotha)**

May 2008 **Research Supervisor**

DECLARATION

I hereby declare that the research work presented in this thesis was carried out by me at National Chemical Laboratory, Pune under the supervision of **Dr. Srinivas Hotha**, Organic Chemistry Division, National Chemical Laboratory, Pune - 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
National Chemical Laboratory
Pune-411008
May 2008

(**Sudhir Kashyap**)

Acknowledgements

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence.

It is a pleasant feeling for me to have this opportunity to express my gratitude for all of them who have been accompanied and supported throughout the time I spent working for my doctoral studies.

It gives me immense pleasure to express my deep sense of gratitude to my supervisor and mentor ***Dr. Srinivas Hotha*** *for his excellent guidance, continuous encouragement, and generous support in achieving this entire endeavor. I am very much grateful to him for motivating me in carbohydrate (The Sweet Molecules of Life) chemistry and appreciate his able guidance, wholeheartedly. Working with him was really a great pleasure and fetched me a lot of learning experience. I do sincerely acknowledge the freedom rendered by him in the laboratory for the independent thinking, planning and execution of research. Although this eulogy is insufficient, I preserve an everlasting gratitude for him. Without his encouragement and constant guidance, I could not have finished my doctoral degree. He was always there to meet and talk about my ideas, to proofread and mark up my papers and chapters, and to ask me good questions to help me think through my problems.*

It would be very inappropriate of me not to make mention Dr. B. L. V. Prasad, Mr. I. Sivakumar, Dr. C. V. Ramana and Dr. H. V. Thulasiram who were always ready for their help, guidance and moral support.

I wholeheartedly thank and give acknowledgements to entire NMR and Elemental analysis group especially Dr. Rajmohan, Mr. Sathe and Mrs. Phalgune from NMR facility. I also thank Dr. M. J. Kulkarni and Mrs. Shantakumari for their timely help in mass spectroscopic analysis.

During the course of this work in NCL, I learnt that a journey is easier when we travel together. I would like to thank my labmates, Ashish (bheja fry), Girish, Susheel, Suresh (what is your problem), Rao (appa), Ashif (baal ud gaye), Suneel (ipod), Ram (sahi re), Sandesh, Mahesh, Abhijeet (sethji) and Shivaji (busy) for their kind help and support, invaluable discussions which we shared and maintaining a lively environment in the laboratory during every walk of life in the laboratory to achieve this goal.

I wholeheartedly thank my friends Ashwani pajji (with family), Sreedhar (chipli), Srikant (tiger), Kishore (bhaiya), Atul (chu…..), Patwa (ever ready), Sonar, Sush, Sammer ji, Dillu (ball nayi hai), Dr. Arif (capt.), Prasanna (Prof.), Swarup (most wanted), Rajendra (smarty), Kannan (bakwas), Ramanujan (ya..ya), Mishra (dekho bete), JP (chacha), Saurabh (champ), Ganya, Ramesh, Abhijeet (symond), Kamendra (nahi aa sakta), Nishant (wide nahi hai..), Abhilash (hadd hai), Malli, NCL sports community, GP Lab, KNG lab, MKG-Ramana lab, PKT lab, Pedireddi lab, Sanjayan lab, OCS-OCT and Biochem division ... for their unconditional support and continuous encouragement during my stay in NCL.

During this work I have collaborated with many colleagues for whom I have great regard, and I wish to extend my warmest thanks to all those who have helped me with my work. I also extend my thanks to my fellow colleagues in NCL, Satyendra, Raman, Pushpesh, Somesh, Rishi, Arshad, Ishwar, Anirban, Baagh, Amol, Mandeep, Ankush, Lakshi, Ajit, Nagraj, Sagar, Chetan, Sarvesh, Arun, Ambrish, Sanjay, Deepti, Amit (sasur) Sudharshan, and Pratap ... for their cheerful company and making my life in NCL very lively and enjoyable.

I would like to express my deep and sincere gratitude to my M.Sc. teachers, MDU, Rohtak, and my M. Sc. colleagues Rajeev, Suresh, Mukesh, Anil, Dinesh, DJ, Sanjay, Ajju, Krazy 4 (asha, babita, kavita, sonal), G2, and whole chemistry dept. ... for their understanding, encouraging and guidance during my Post graduation in MDU, Rohtak.

I am grateful to Council of Scientific and Industrial Research, Government of India, for awarding the junior and senior research fellowships and Dr. S. Sivaram, Director, National Chemical Laboratory to carry out my research works, extending all infrastructure facilities.

Last, but not least, I dedicate this achievement to my wife Amita who walked along with me, sharing every ups and downs. Finally, it has been a difficult task to capture and express my feelings for my family members. What I am and intend to be in the future is because of the good will and unstinted support of my grandmother, parents, elder brothers (Mukesh, Kuldeep, Sunil bhai), younger brothers (Situ, Sunny, Sonu, Chanchal, Bobby, Pankaj, Neeraj), my nephews (Nonny, Chiku (jannu beta), Kannu), niece (Isha, Lovely), and my bhabhis (Manju, Neeru, Renu) without knowing much what I am doing exactly, just wishing me all the time with no expectations. No words are enough to acknowledge them for their patience and sacrifice which were always remain a source of inspiration and will remain throughout my life. My success now and always will be dedicated to them.

"Chances favor the prepared mind."

Sudhir

Contents

General Remarks

- All the melting points were recorded on the Celsius scale using Buchi B 540 melting point apparatus and are uncorrected.
- ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV-50 MHz, AV-100 MHz, and DRX-125 MHz spectrometer.
- Mass spectra were recorded on Applied Biosystems API QSTAR Pulsar Mass Spectrometer (Electro spray ionization, direct infusion method, solvents used acetonitrile/methanol). EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Elemental analysis was carried out on Thermo Finnigan Flash EA 1112 series analyzer.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- UV/Visible spectra were recorded on Perkin Elmer Lambda 35 spectrophotometer.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Büchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography.
- Scheme, Figure and Compound numbers in abstract and individual chapters are different.

Abbreviations

Ac	Acetyl/Acetate	*J*	Coupling constant
Ac_2O	Acetic anhydride	M	Molar
ACN	Acetonitrile	mL	Milliliter
Ar	Aryl	mol	Mole
Boc	*tert*-butoxycarbonyl	mmol (mM)	Millimole
Bn	Benzyl	m.p.	Melting point
Bz	Benzoyl	MsCl	Methanesulphonyl chloride
CAN	Ceric ammonium nitrite	Na-Asc.	Sodium ascorbate
DCM	Dichloromethane	NIS	*N*-iodosuccinimide
DDQ	2,3-dichloro-5,6-dicynao *p*-benzoquinone	NMO	*N*-morphiline oxide
		-OMe	Methoxy
DIPEA	*N,N*-diisopropylethylamine	PTSA	*p*-toluene sulfonic acid
DMAP	4-(dimethylamino)pyridine	Ph	Phenyl
DMDO	2,2 Dimetyhldioxirane	Py	Pyridine
DMF	*N,N*-dimethylformamide	TBAF	Tetrabutylammonium fluoride
DMSO	Dimethyl sulfoxide	TBDPS	*tert*-butyldiphenylsilyl
Fmoc	9-Flourenylmethoxy Carbonyl	TBS	*tert*-butyldimethylsilyl
		TBTA	*tris*-(benzyltriazolylmethyl) amine
g	Gram		
h	Hour	TfOH	Triflic acid
HBTU	*O*-(1H-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl uron ium hexafluoro phosphate	TFA	Trifluoroacetic acid
		THF	Tetrahydrofuran
		TLC	Thin layer chromatography
HMDS	Hexamethyl disilazane	TMS	Trimethylsilyl
HoBt	1-Hydroxybenzotriazole hydrate	TMSCl	Trimethylsilyl chloride
		$TMSN_3$	Trimethylsilyl azide
Hz	Hertz	TEA	Triethyl amine
IDCP	Iodonium-dicollidine perchlorate	TsOH	*p*-toluene sulfonic acid
		TsCl	*p*-toluene sulfonic chloride
		Tr	Trityl

Abstract

Abstract

Thesis Organization

The thesis entitled "Synthesis of Glycosides, Saccharides and Glyconjugates *via* Alkyne Activation" is organized in three chapters.

The first chapter demonstrates the development of an efficient and flexible approach for the synthesis of unsaturated glycosides from glycals exploiting the alkynophilicity of gold catalysts whereas the second chapter highlights the anomeric alkyne activation for the synthesis of glycosides, thioglycosides, glycoconjugates and different glycosyl donors for the synthesis of higher saccharides. The third chapter describes "click" chemistry for the chemical ligation of oligosaccharides to oligosaccharides/peptides under neutral reaction conditions.

Chapter 1: Synthesis of Unsaturated Glycosides from Glycals

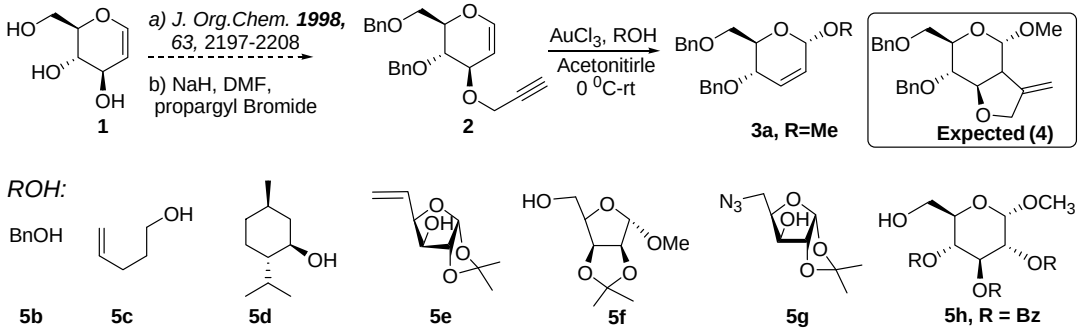
Section A. Stereoselective synthesis of 2,3-unsaturated *α*-glycopyranosides

The development of newer methods for stereoselective formation of *α*- or *β*-*O*-glycosides has been extensively investigated owing to the critical roles carbohydrates play in a variety of biological systems. It is well known that *endo*-glycals (1,2-unsaturated sugars) are utilized frequently for the synthesis of neoglycoconjugates and for chiron approach. Due to their enol ether structure, glycals demonstrate versatile reactivity and therefore are effectively exploited to synthesize various Lewis and blood group determinants, gangliosides, and tumor-associated antigens, as well as many bioactive natural products. Due to the synthetic versatility, 2,3-unsaturated glycosides have received wide attention in recent years particularly in the synthesis of several biologically active natural products and also as chiral synthons. Different in modality from the majority of glycosylations, the Ferrier reaction achieves glycosylation *via* S_N2' displacement of the *C*-3 substituent in a glycal to furnish 2,3-unsaturated glycosides,

As part of our ongoing research in carbohydrate chemistry and our continued interest in the development of novel methods for glycoconjugates, Au-mediated cyclizations were performed on 4,6-di-*O*-benzyl-3-*O*-propargyl glucal (**2**) to explore the utility of alkynophilic gold catalyst. We envisioned that the reaction of an acceptor such as methanol with an Au^{3+} coordinated enyne system of a glucal might be a good model substrate. In doing so, we might be able to check the effect of Au^{3+} on the enyne moiety to give the bicyclic product (**4**) or the allylic rearrangement product (**3a**) similar to Ferrier reaction (Scheme 1). Our study began with the conversion of easily accessible glucal (**1**) to 3-*O*-propargyl per benzylated glucal (**2**).

Upon treatment of **2** with a preformed solution of 5 mol% $AuCl_3$ in acetonitrile at room temperature in presence of methanol, the reaction proceeded smoothly to furnish the Ferrier-like product 2,3-unsaturated glucoside (**3a**) in good yield with high selectivity in favor of the *α*-anomer instead of the preconceived Au-mediated cyclization product (**4**) (Scheme 1). Having optimized conditions, the scope of this new observation was studied by the parallel synthesis of 2,3 unsaturated *α*-*O*-glucosides using a diverse range of aglycones comprising aromatic (**5b**), aliphatic (**5c**), acyclic (**5d**) and monosaccharidic alcohol (**5e-h**) to obtain 2,3-unsaturated glucosides (**3b-h**) was carried out (Scheme 1).

Scheme 1. *Au Catalyzed "Ferrier-like" Reaction*



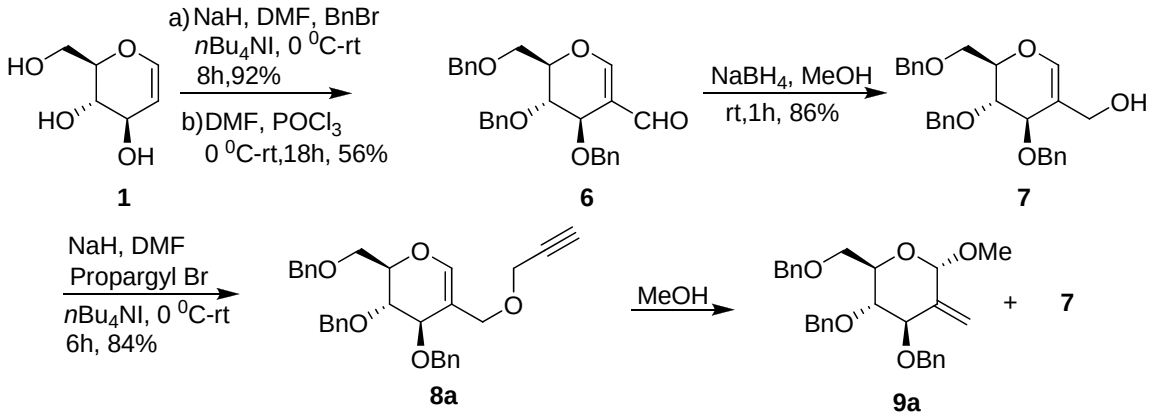
In summary, we identified that the 4,6-di-*O*-benzyl-3-*O*-propargyl glucal undergoes Ferrier-like reaction (S_N2' reaction) in the presence of catalytic amount of $AuCl_3$ to afford the synthesis of 2,3-unsaturated α-glucopyranosides in a stereoselective manner.

Section B. Synthesis of *C*-2 methylene glycosides from *C*-2 propargyloxy methyl glycals

The chemistry of unsaturated and branched chain sugars continues to receive wide attention owing to the importance of such compounds in the total synthesis of many natural products. The 2-*C*-methylene group is a key structural feature of molecules involved in the inactivation of the enzyme ribonucleotide diphosphate reductase, and furthermore, 2-*C*-methylene glycosides are precursors for the synthesis of *C*-disaccharides. However, only a few methods for the preparation of 2-*C*-substituted glycals have been reported, mostly involving several steps.

In continuation of our earlier results, the utility of alkynophilic Au^{3+} catalysts was studied for the synthesis of 2-*deoxy*-2-*C*-methylene glycosides using *C*-2 propargyloxy methyl glycals, which contain an enyne system very similar to 4,6-di-*O*-benzyl-3-*O*-propargyl glucal (**2**). Accordingly, per-*O*-benzylated *C*-2 propargyloxy methyl glycals (**8a-c**) were prepared following standard procedures. Glucal (**1**) was converted to per-*O*-benzyl glucal and subsequently converted to *C*-2 formyl glucal (**6**) using Vilsmeier-Haack reaction. Reduction of *C*-2 formyl glucal (**6**) with sodium borohydride in methanol afforded the corresponding *C*-2-

Scheme 2. *Synthesis of C-2 propargyloxymethyl per-O-benzyl glycal*



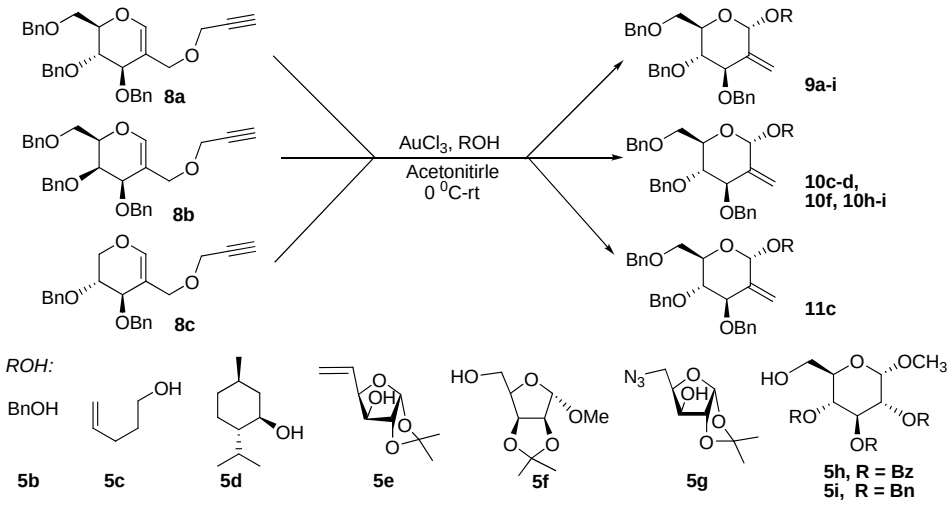
Entry	Catalyst	Solvent	Time	Temp	%**9a**	%**7**
1	$AuCl_3$, 5 mol%	CH_3CN	5 h	rt	63	0
2	$AuCl_3$, 5 mol%	CH_2Cl_2	5 h	rt	45	0
3	$Co_2(CO)_8$,1eq	CH_3CN	8 h	rt	0	25
4	$Co_2(CO)_8$,1eq	CH_3CN	8 h	60^{o}C	0	70
5	$PtCl_2$, 5 mol%	CH_3CN	6 h	rt	0	0
6	$RuCl_3$, 5 mol%	CH_3CN	4 h	rt	57	0
7	$Cu(OAc)_2$,10 mol%	CH_3CN	8 h	rt	0	0

hydroxymethyl glucal (**7**). Propargylation of primary hydroxyl group with NaH/propargylbromide/$nBu_4N^+I^-$ yielded the desired propargyl ether **8a** (Scheme 2).

Similarly substrates **8b** and **8c** were prepared starting from galactal and xylal. An acetonitrile solution of **6** was treated with 5 mol% of $AuCl_3$ solution in acetonitrile in presence of methanol at room temperature to furnish 2-*deoxy* glucoside **9a**. The reaction was also studied by using other alkyne activators, such as $Cu(OAc)_2$, $PtCl_2$, $Co_2(CO)_8$ and $RuCl_3$ under different conditions. It is significant to mention that $Cu(OAc)_2$, $PtCl_2$ and $Co_2(CO)_8$ did not afford the desired product (entry 3,4,5 and 7) whereas $Co_2(CO)_8$ activated the alkyne group but resulted in simple deprotection of propargyl moiety to give *C*-2 hydroxymethyl glucal (**11)** (Scheme 2, entry 3 & 4). $RuCl_3$ (5 mol%) in anhydrous acetonitrile gave desired *C*-2-methylene *α-O*-glucosides (**9a**) in satisfactory yield (Scheme 2, entry 6). Nevertheless, the $AuCl_3$ emerged as the best alkyne activator for the 2-*deoxy* glucoside synthesis (Scheme 2). Having optimized conditions in hand, the general applicability of this new methodology was explored and a parallel synthesis of 2-*C*-methylene glycosides using per-*O*-benzylated *C*-2 propargyloxy methyl glucal (**8a**), galactal (**8b**) and xylal (**8c**) and a diverse range of aglycones (**5b-i**) (Scheme 3) was carried out.

In summary, we identified again that the propargyloxy group behaves as a leaving group in the presence of catalytic amount of $AuCl_3$ in acetonitrile.

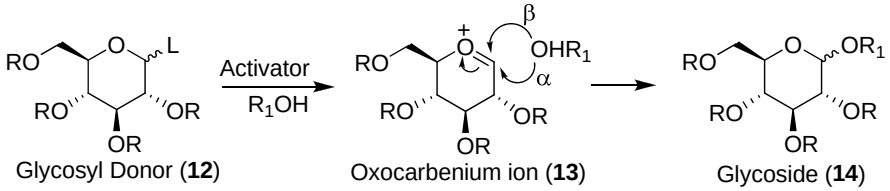
Scheme 3. *Au catalyzed Synthesis C-2 methylene glycosides*



Chapter 2: Alkyne activation for Glycoside and Saccharide syntheses

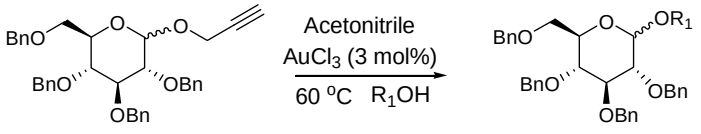
Many different theories have been advanced concerning the biological roles of the saccharides of individual classes of glycoconjugates. With the stimulant biological background, the *O*-glycosylation method which is a crucial synthetic organic methodology to attach a sugar to another sugar moiety or other molecules (aglycone) *via* the anomeric oxygen is again a more significant proposition. These facts have made the area of saccharide syntheses an ideal and challenging for the development of new synthetic methodologies. In general, a glycosylation reaction involves displacement of a leaving group (L) from anomeric carbon of a glycosyl donor (**12**) by an aglycone (R_1OH) frequently containing a lone hydroxyl group. Activators promote the easy formation of an oxocarbenium ion (**13**) which will then be attacked by the aglycone to form glycosides (**14**) (Scheme 4).

Scheme 4. *General Glycosylation Reaction*



Among the common glycosylation protocols, the stable thioglycosides and 4-*n*-penten-1-yl glycosides are widely used glycosyl donors for the synthesis of oligosaccharides and glycoconjugates. Aforementioned experiments in Chapter-I helped us to understand that propargyloxy group becomes a leaving under the influence of catalytic amount of Au(III) salts. In our synthetic endure, we thought of utilizing propargyl glycosides (**15a**) as stable glycosyl donors for the synthesis of glycosides (**16**) exploiting alkynophilicity of gold catalysts.

Scheme 5. *Novel Transglycosylation Protocol*



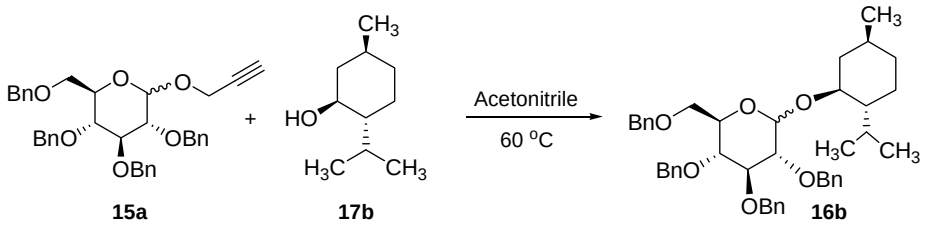
15a **16**

Aglycone (R_1OH)	*Time/Temp/Yield*	*R_1*
H_2O (**17a**)	12h/RT/70%	H (**16a**)
Menthol (**17b**)	6h/60°C/68%	Menthyl (**16b**)

To begin our investigation, propargyl 2,3,4,6-tetra-*O*-benzyl-α/*β*-glucoside (**15a**) was hydrolyzed with 5 mol% of $AuCl_3$ in acetonitrile at room temperature to yield corresponding per-*O*-benzylated lactol (**16a**). Encouraging results prompted us to swipe H_2O with menthol (**17b**) [an aglycone] in order to facilitate transglycosylation, an interesting landscape for the syntheses of disaccharides (Scheme 5).

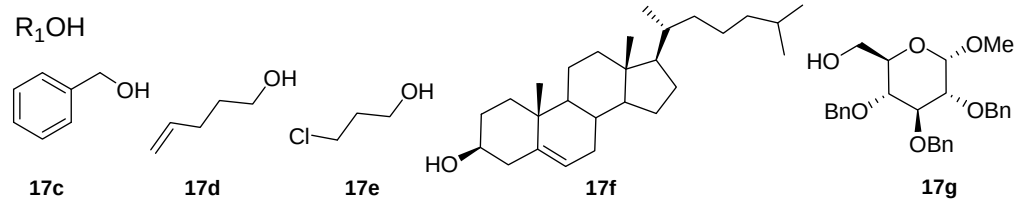
The transglycosylation protocol was also studied by using other alkyne activators, such as $Cu(OAc)_2$, $PtCl_2$, $Co_2(CO)_8$ and $RuCl_3$ under different conditions. It is significant to mention that $PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$, for the glycosylation reaction resulted in either the decomposition or isolation of the glycosyl donor (**15a**). Efforts to promote the transformation with other gold catalysts such as AuCl and Au_2O_3 were unsuccessful (Scheme 6, entry 1), whereas $HAuCl_4$ catalyzed glycosylation to give 30% of desired menthyl glucoside (**16b**) along with 45% of lactol (**16a**) (Scheme 6, entry 2).

Scheme 6. *Optimization of Transglycosylation Protocol*



15a **17b** **16b**

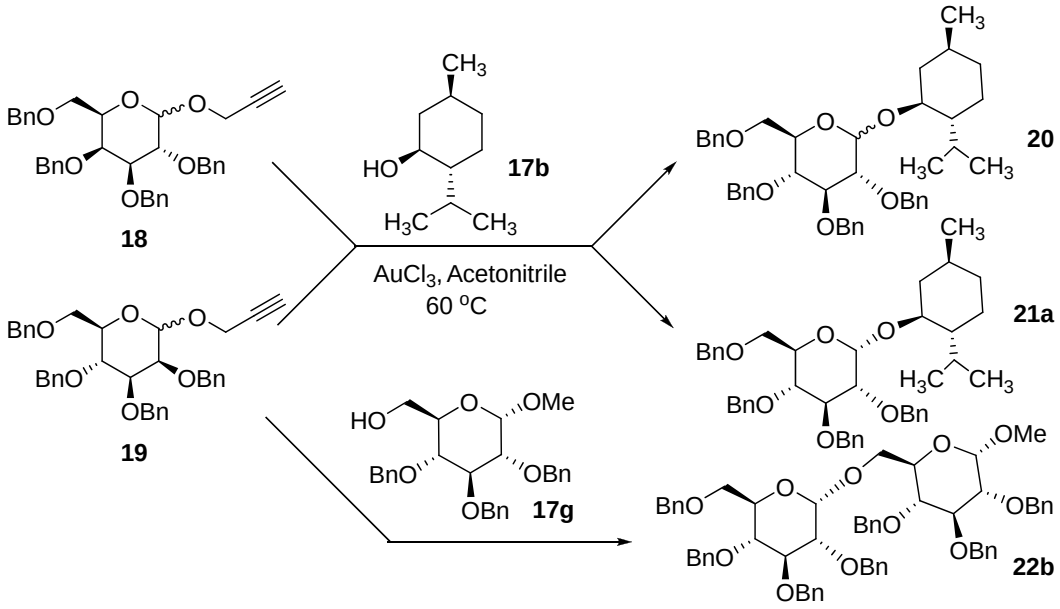
Entry	Conditions	Yield	Inference
1	Au_2O_3/AuCl	0 % No Reaction	Au (III) alone is not enough
2	$HAuCl_4$	45 % (**16a**) 30% (**16b**)	Au (III) and HCl are Required
3	$AuCl_3$ + Lewis Acid	0 % No Reaction	Au (III) and HCl are Required
4	$AuCl_3$ + Et_3N/DIPEA	0 % No Reaction	Presence of HCl in the Reaction
5	$AuCl_3$	60 °C/ 6 h	Au (III) activates alkyne
6	Et_2O.HCl / Dioxane.HCl	0 % No Reaction	HCl alone is not sufficient



17c **17d** **17e** **17f** **17g**

Furthermore, the optimization of yield by addition of Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $ZnCl_2$, $LiClO_4$ (entry 3) and organic bases such as triethyl amine and diiisoproyl ethyl amine along with $AuCl_3$ (Scheme 6, entry 4) were unsuccessful. Moreover, the glycosylation reaction does not proceed in dioxane.HCl or Et_2O.HCl alone (Scheme 6, entry 6). Nevertheless, the $AuCl_3$ emerged as the best alkyne activator for the transglycosylation reaction (Scheme 6, entry 5).

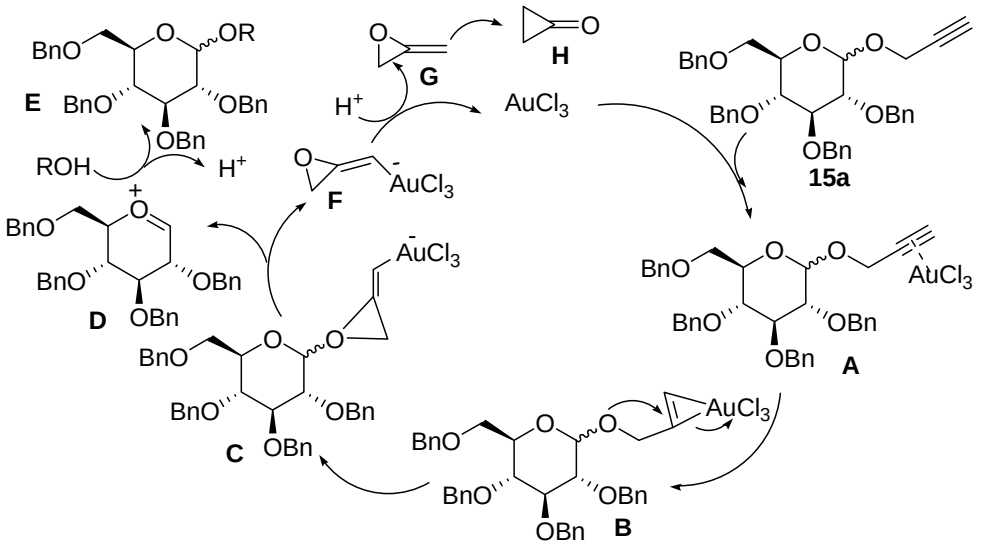
Scheme 7. *Synthesis of Glycosides-General Applicability*



Scope and generality of this new methodology was demonstrated by using a range of aglycones comprising alicyclic (**17b**), aromatic (**17c**), aliphatic (**17d, 17e**), steroidal (**17f**) and sugar alcohols (**17g**) (Scheme 7). In addition, the current methodology was extended to other propargyl glycoside donors such as propargyl galactoside (**18**) and mannoside (**19**) to obtain respective glycosides (**20, 21a, 22b**) in good yields. Alkyne activation by Au catalysts is highly competent and demonstrates a high degree of substrate compatibility. Mannosyl donor **19** reacted with **17b** and **17g** giving only 1,2-*trans*-mannosides (**21a** and **22b**), which can be endorsed to the steric crowding due to the axially disposed benzyl ether at *C*-2 position and anomeric effect (Scheme 7).

Though a detailed mechanism of the present transglycosylation protocol awaits further studies, a simple plausible pathway can be put forward (Scheme 8). Coordination of alkynophilic $AuCl_3$ to the glycosyl donor **15a** (complex **A**) would be followed by formation of the cyclopropyl gold carbene intermediate (**B**). As a result of increased electrophilicity, an intermediate of type **C** would be possible, which can lead to an oxocarbenium ion (**D**) with the expulsion of an alkenyl gold complex (**F**).

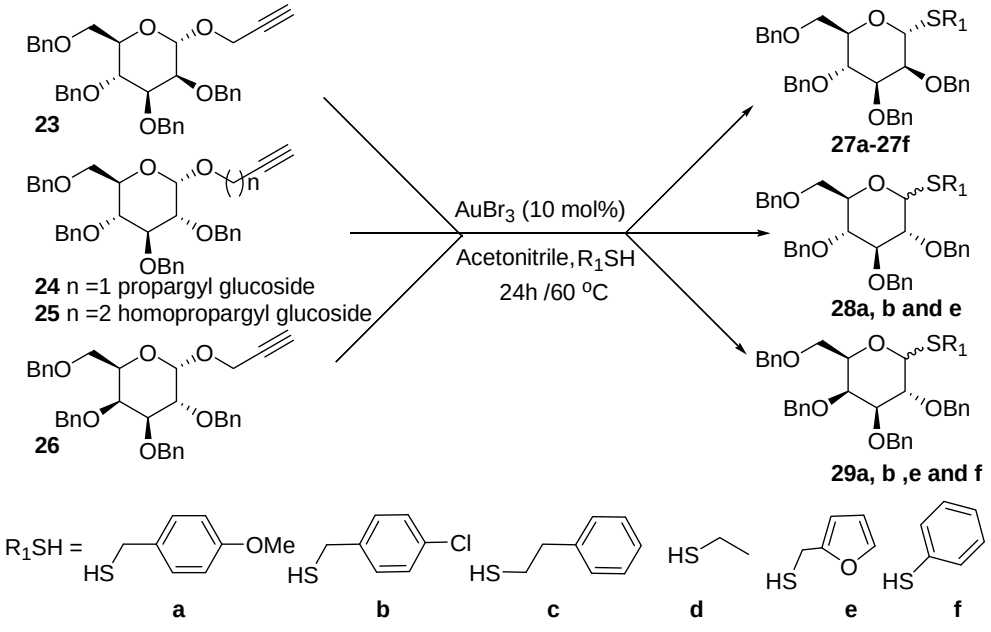
Scheme 8. *Tentative mechanism for Transglycosylation*



Acid-mediated protodemetalation of the methyleneoxirane-$AuCl_3$ complex (**F**) generates $AuCl_3$ and extrudes methyleneoxirane (**G**), which can further rearrange to cyclopropanone (**H**). Intermediate **D** can in turn be trapped by aglycones to yield observed glycosides (**E**).

In continuation of this study, we thought of extending the novel transglycosylation repertoire to the synthesis of thioglycosides as well. Thioglycosides are often the glycosyl donors of choice for the synthesis of oligosaccharides, especially in glycosidation of amino sugars. The oxidized form of thioglycosides such as glycosyl sulfoxides or sulfinil glycosides proved to be very adaptable and advantageous as glycosyl donors.

Scheme 9. *Au catalyzed Synthesis of Thioglycosides from Propargyl Glycosides*



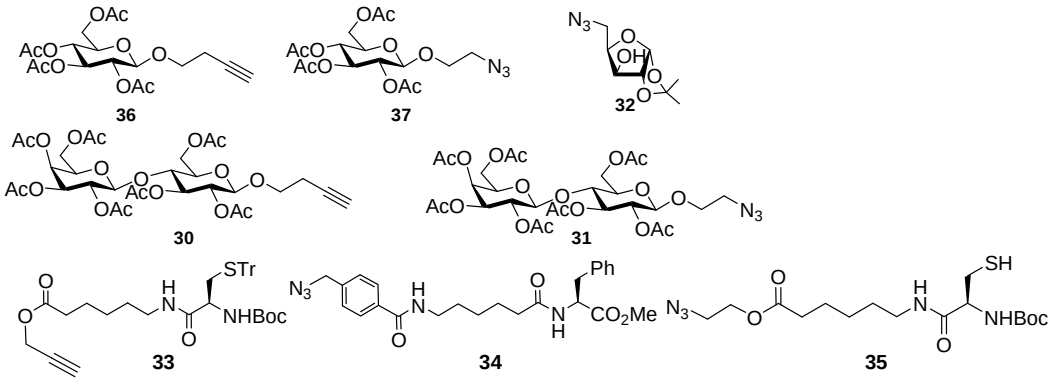
Initial experiments for thioglycosidation were performed with propargyl mannoside **23** as a glycosyl donor for anomeric activation and *p*-methoxybenzyl mercaptan (**a**) as a thiol acceptor at 60 ^{o}C for 24 h using 10 mol% of $AuBr_3$ to obtain 1,2-*trans*-thiomannoside (**27a**). The scope and general applicability of this protocol was extended for the preparation of thiomannosides (**27a-f)**, thioglucosides (**28a, b** and **e)** and thiogalactosides (**29a**, **b**, **e** and **f)** from respective propargyl glycosides (**24-26**) and in doing so we exploited various thiols comprising *p*-chlorobenzyl mercaptan (**b**), benzene ethanethiol (**c**), ethane thiol (**d**), furfuryl mercaptan (**e**), and thiophenol (**f**) (Scheme 9).

In conclusion, propargyl glycosides were identified as novel and stable glycosyl donors. Various aglycones were reacted with propargyl glycosides, resulting in the formation of an α/*β*-mixture of glycosides and disaccharides in good yields. We have also successfully synthesized thioglycosides from propargyl glycosides.

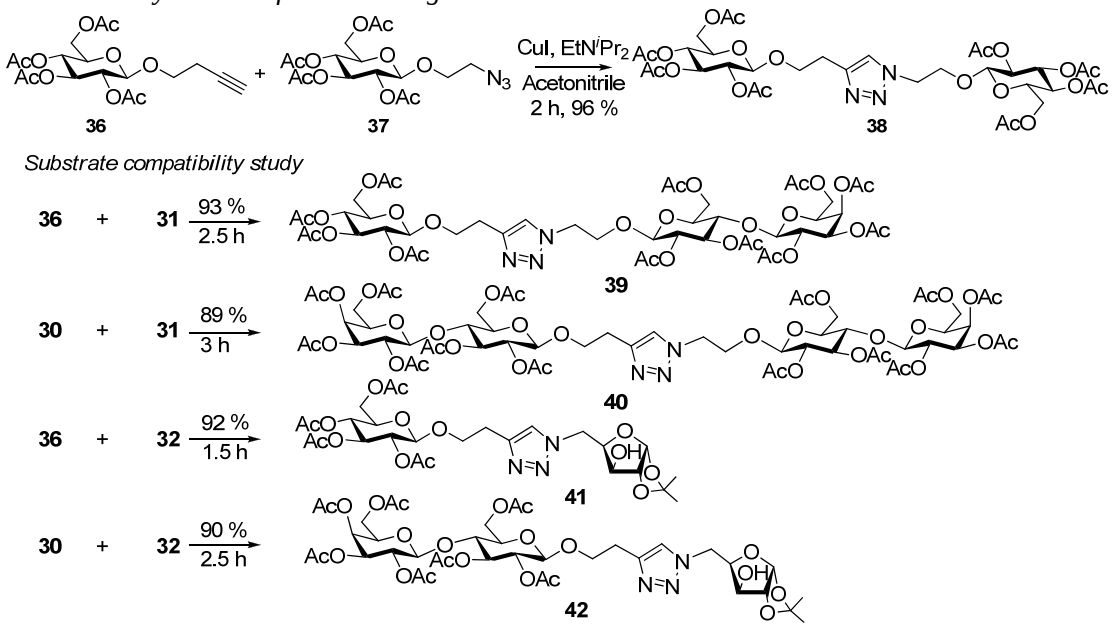
Chapter 3: Synthesis of *Pseudo*-Oligosaccharides and Amino Acid Glycoconjugates

Carbohydrates play a central role in the metabolism, cell-cell interaction and in many important biological activities, offering a host of attractive drug discovery opportunities. Despite this great potential, drug discovery based on sugars are generally slow, costly, and hindered by complex syntheses. Therefore, a set of criteria defining reliable reactions known as "click" chemistry, in particular, the copper(I)-catalyzed ligation of azides and alkynes, promises to simplify and accelerate the discovery of high affinity carbohydrate mimetics. The process utilizes several appropriate building blocks to provide variety of useful chemical substances such as mimics of pharmacophores, drugs, natural products, etc. Incorporation of amino acids in synthetic study of biologically useful molecules can enhance the target protein binding of that molecule so as to elicit the biological activity. It is anticipated that homo- and hetero- dimeric glycoconjugates will be excellent probes and could act as potent reversible cross-linking reagents.

Figure 1. *Building Blocks for the Synthesis of Glycoconjugates*

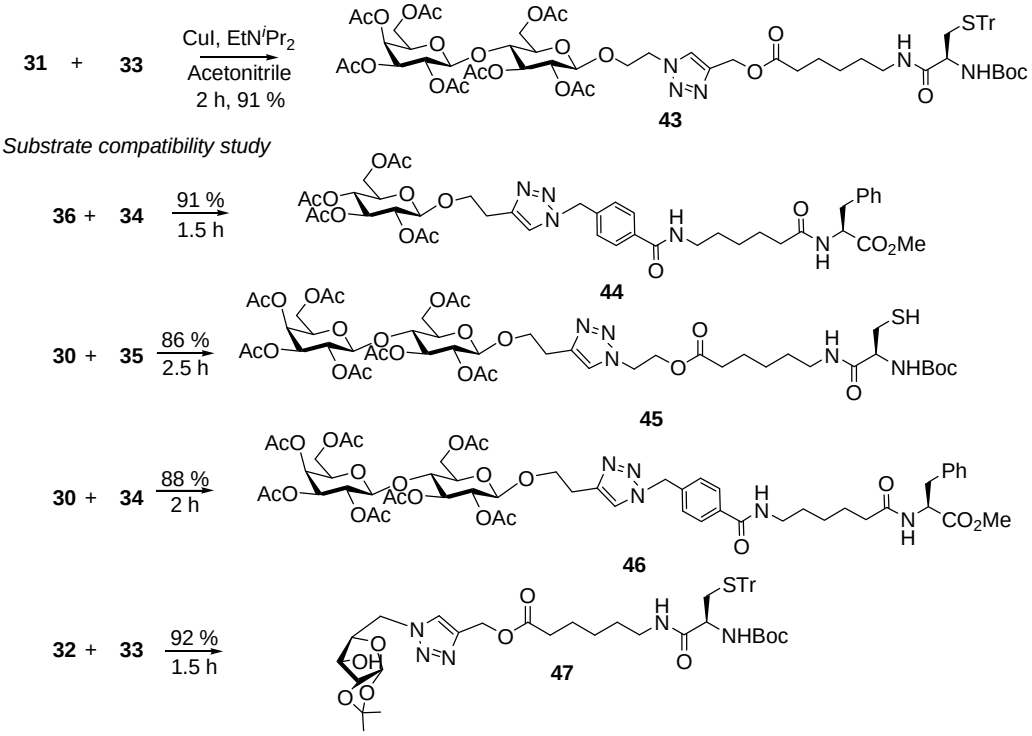


Scheme 10. *Synthesis of Pseudo-Oligosaccharides*



In our synthetic efforts, we planned to utilize the copper mediated azide alkyne cycloaddition (CuAAC) between sugar and peptide derived terminal alkyne and azide for chemical ligation of carbohydrates to carbohydrates/peptides to make *pseudo*-oligosaccharides and amino acid glycoconjugates. Accordingly, carbohydrate derived alkynes (**30**, **36**), azides (**31**, **32** and **37**) and amino acid derived alkyne (**33**) and azides (**34**, **35**) for CuAAC were synthesized using standard reaction conditions.

Scheme 11. *Synthesis of Amino Acid Glycoconjugates*



The crucial 1,3-dipolar cycloaddition reaction was performed in an acetonitrile solution of **36** and **37** with stoichiometric amount of CuI in presence of *N,N*-diisopropylethylamine to afford highly regioselective 1,4-disubstituted 1,2,3-triazole containing *pseudo*-oligosaccharide (**38**) in excellent yield.

Having identified a practical procedure for the chemical ligation of oligosaccharides, an initial substrate compatibility study was performed to conjugate *gluco*-, *lacto*- and *xylo*-derived alkynes (**30, 36**) and azides (**31, 32** and **37**) to form 1,2,3-triazole conjugated oligosaccharides (**39-42**) (Scheme 10). Furthermore, we have synthesized alkynyl (**33**) and azide (**34** and **35**) containing amino acids using the traditional *t*-Boc chemistry and used in the ligation to other carbohydrate derived alkynes/azides in different combination for the synthesis of various amino acid glycoconjugates (**43-47**) (Scheme 11).

In conclusion, we have designed a competent and practical procedure for the ligation of oligosaccharides to oligosaccharides/peptides and should potentially give rise to a large number of *pseudo*-oligosaccharides and amino acid glycoconjugates.

Note: Compound numbers in abstract are different from those in the thesis.

Chapter 1

Synthesis of Unsaturated Glycosides from Glycals

Chapter 1: Introduction

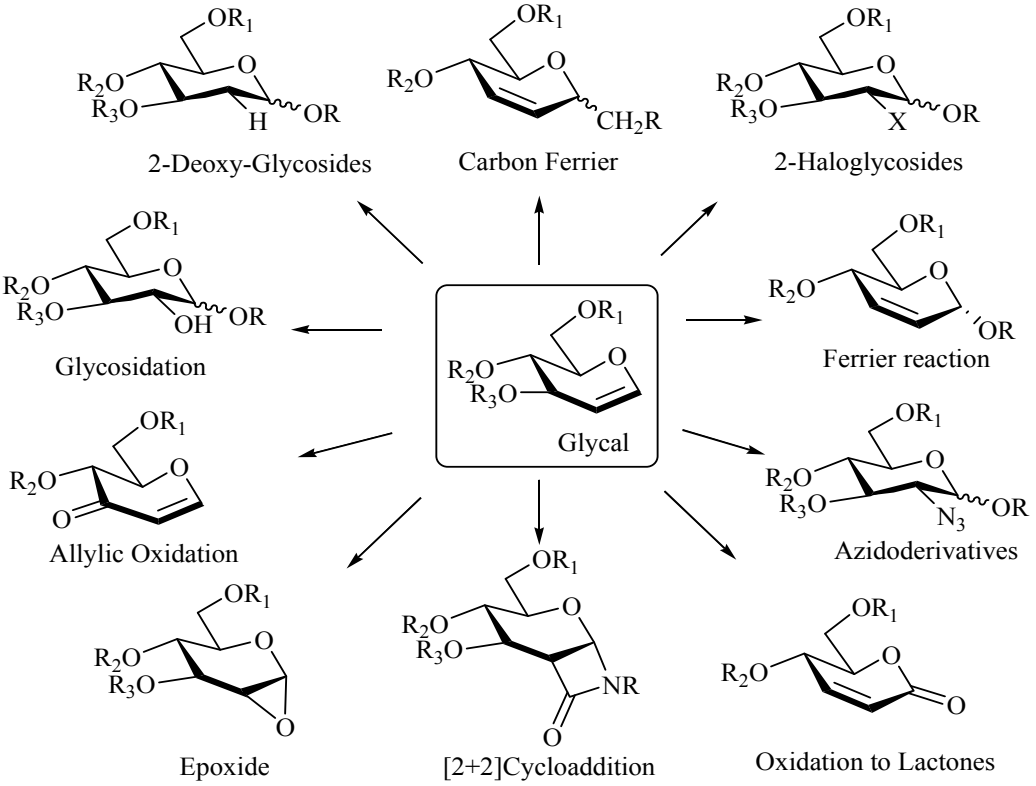
The synthesis of carbohydrate-based structures is emerging as a major frontier area for organic chemistry. In addition to their well-appreciated roles in supporting structural matrices, in energy storage, and as biosynthetic starting materials, carbohydrates are cast in a variety of interesting settings as glycoconjugates, for example as antibiotics, antitumor agents, and cardiotonic glycosides. The gangliosides are being increasingly implicated as tumor antigens and cellular differentiation markers. Several naturally occurring glycosidase inhibitors have recently been shown to possess various interesting biological activities, e.g., some have been reported to alter the infection of the causative agent of AIDS, the human immunodeficiency virus (HIV), possibly by perturbing the gp120 linked glycan structure.[1] The potential of these glucosidase inhibitors as anti-HIV therapeutic agents warrant further investigation especially since these glucosidase inhibitors show little toxicity *in vitro* and *in vivo*.[2] The importance of the carbohydrate domains in glycoproteins and glycolipids as elements in cell surface recognition is manifested by their role in cellular adhesion[3a,b] and as determinants in blood group typing.[3c] Another incentive for focusing on carbohydrates is their usefulness as enantiomerically pure starting materials for the synthesis of various natural products and other types of target molecules.[3d]

Glycosidic bond formation is must to incorporate appropriate glycoforms into various biomolecules. The development of newer methods for stereoselective formation of α- or β-*O*-glycosides has been extensively investigated owing to the critical roles carbohydrates play in a variety of biological systems.[4] To date many efforts have focused on developing new methods and reagents for the generation of isolated glycosyl donors which subsequently undergo glycosidic bond formation with nucleophilic glycosyl acceptors.[5] Despite their potential applications to complex carbohydrate synthesis, each of these methods relies on the nature of the substrates to stereoselectively control the formation of glycosidic bonds.

Glycals are interesting, inexpensive starting materials and utilized as versatile building blocks in glycosylations and for the synthesis of neoglycoconjugates and for Chiron approach. Fisher and Zach[6a] in 1913 reported the classical preparation of glycals, 1,2-unsaturated derivatives of pentaoses or hexaoses, from 1-halogeno sugars by reductive elimination with zinc. Due to their enol ether structure, glycals demonstrate versatile reactivity and therefore can be effectively utilized to synthesize various monosaccharide derivatives[6b] through hydration,[7] hydrogenation,[7] epoxidation,[8] or allylation[9] (Figure 1). Glycals have been starting materials in complex synthesis, including that of brevitoxin,[10] tetrahydropyranoid antibiotics,[11]

C-glycosides,[12] and okadaic acid.[13] Not surprisingly, glycals are also subjects of considerable interest in combinatorial chemistry and, as chiral building blocks, have been precursors for a broad variety of optical active products and for oligosaccharide synthesis.[14] An elegant 'glycal assembly strategy' for the formation of oligosaccharides, via reaction of 1,2-anhydro sugars (glycosyl donors) with glycals (glycosyl acceptors) has been described in detail. Following coupling, epoxidation of the glycal converts it to a glycosyl acceptor and allows reaction with a second glycal equivalent to continue the sequence.[14,15]

Figure 1: Some reactions starting from glycals

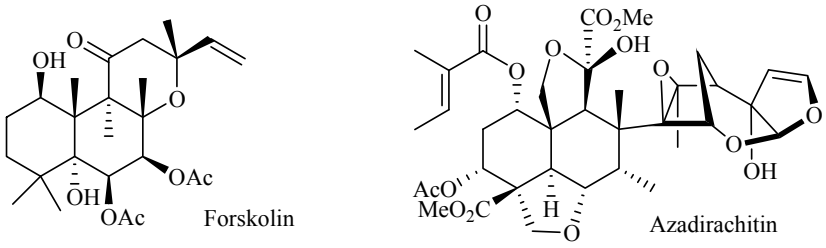


It is well known that glycals (1,2-unsaturated sugars) are utilized as flexible building blocks in chemical glycosylations such as the Ferrier reaction and Danishefsky's glycal assembly procedure. Both methods have been developed as effective methods to synthesize various glycoconjugates, including Lewis and blood group determinants, gangliosides, and tumor-associated antigens,[15] as well as many bioactive natural products (e.g., Forskolin[16a] and Azadirachitin,[16b-e] Figure 2).

Mobilization of glycals both as glycosyl donors and glycosyl acceptors led to the strategy of glycal assembly. Several new glycosylation techniques were developed to provide practical underpinning for this logic of glycal assembly. Glycal based paradigms have been shown to be nicely adaptable to solid phase supported synthesis. Moreover, glycal assembly,

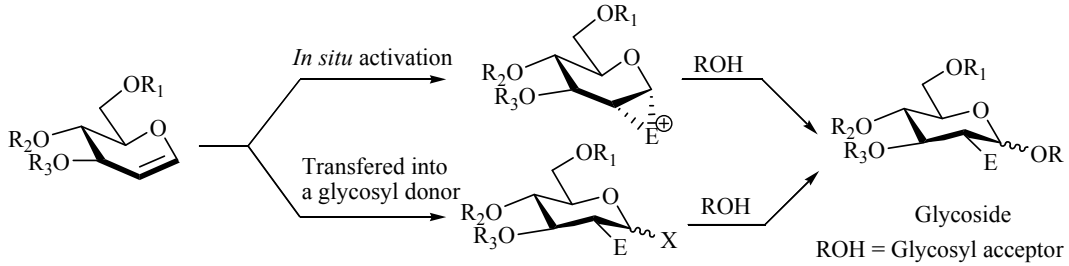
both in solution and on solid phases has been used to gain relatively concise and efficient entry to a variety of biologically interesting and potentially valuable constructs. Some of these syntheses, particularly in the field of tumor antigens, have led to novel compounds which are in the final stages of preclinical assessment.[14]

Figure 2



Glycals in oligosaccharide synthesis were first used by Lemieux[17] in 1960s, by Thiem[18] in 1980s and since then, by Danishefsky and co-workers.[14a] The component that contributes the anomeric carbon of the resultant glycoside is described as the glycosyl donor (Scheme 1). The donor reacts with a glycosyl acceptor to establish a glycoside. In the overwhelming majority of glycosylation reactions, the acceptor is a nucleophile that furnishes the oxygen of the resultant glycoside by replacement of a leaving group at the anomeric carbon of the electrophilic glycosyl donor. However, the novel glycosylations of Schmidt,[19a] David[19b] and Lubeneau[19c] and Kahne[19d] attest to the need to decouple the terms "glycosyl donor" and "glycosyl acceptor" from mechanistic descriptors such as "nucleophile" and "electrophile". It is also well to distinguish two modalities by which glycals can be used as glycosyl donors in two modalities.

Scheme 1

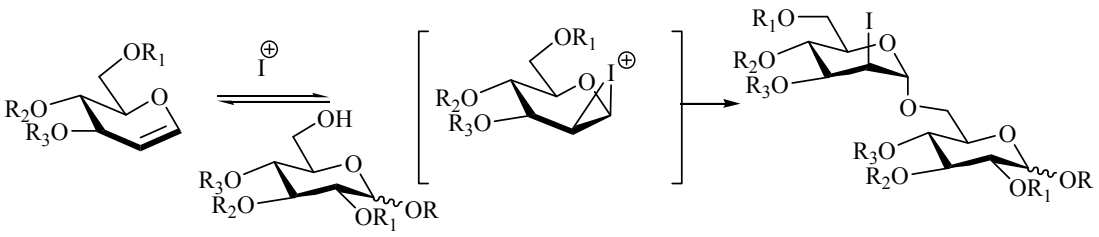


In the 1st motif, *in situ* activation makes the glycal act as glycosyl donor by forming a non isolable intermediate. In the 2nd motif, the glycal is first converted into an isolable or at least identifiable glycosyl donor through different types of reactions (epoxidation,[20] azidonitration[19e] or sulfonamide glycosylation,[19g] Scheme 1). In essence, the glycal is precursor of a structurally defined glycosyl donor. Moreover, glycals could serve both as glycosyl donors and as glycosyl acceptors in a broad range of couplings, a reiterative strategy

for the syntheses of complex glycoconjugates, including oligosaccharides, could be contemplated. A potentially important advantage of glycal-based glycosylations was to be the simplification of achieving differentiated hydroxyl protection and presentation.

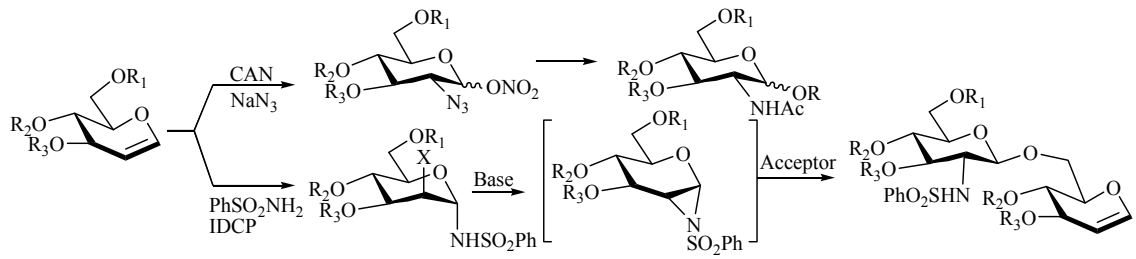
On the other hand, Lemieux[17] and Thiem[18] established a halonium-mediated iodoglycosylation reaction of a glycal to suitable acceptors. These particular reactions had the tendency to give a *trans*-diaxial addition and provide a crucial route to α-linked disaccharides having an axial 2-iodo function at the non-reducing end. In iodoglycosylation, the glycal linkage is attacked by an "I' equivalent" reagent, for example N-iodosuccinimide or *sym*-collidine iodinium perchlorate. In the ordinary case, the presumed substoichiometric intermediate arising from the attack of I^+ on the glycal is attacked by coexisting non-glycal acceptor. Halo-glycosylation has been mainly applied to the synthesis of 2-deoxy sugars owing to the difficulty in effecting nucleophilic displacement of the iodine in such systems (Scheme 2).

Scheme 2



Two methods for introducing nitrogen at *C*-2 via a glycal had been studied earlier by Lemieux. An important first advance employed nitrosochlorination[19f] of glycals. Because the displacement of an axial iodine atom has proven to be very difficult, aza-glycosylation of glycals has been investigated with the idea of preparing glycosides of 2-acylaminosugars. Azidonitration with CAN/NaN_3 was constituted an important advance and the conversion of the nitro-azido compounds into oligosaccharides has not been fully optimized with regards to the yield and stereoselectivity (Scheme 3).[19e]

Scheme 3

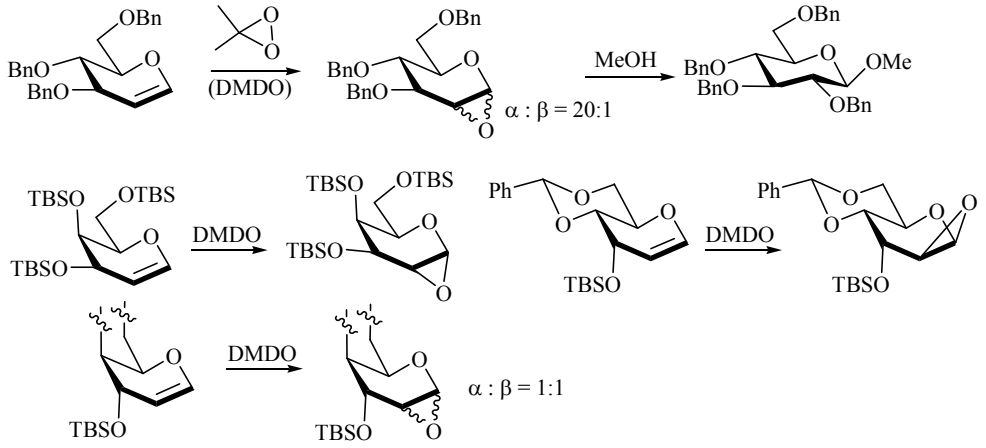


Other procedures, such as iodo-sulfonamidoglycosylation[19g] developed by David Griffith have been used with more success for the synthesis of 2-acylamino oligosaccharides.

This method implies a *trans*-diaxial addition of an *N*-halobenzene sulfonamide to a glycal followed by a base treatment that gives an intermediate that reacts with a wide range of acceptors. For instance, another glycal with suitably substituted hydroxy group can undergo sulphoamidoglycosylation reaction to furnish glycosides of *α*-benzenesulfonyl glucosamine derivative (Scheme 3).

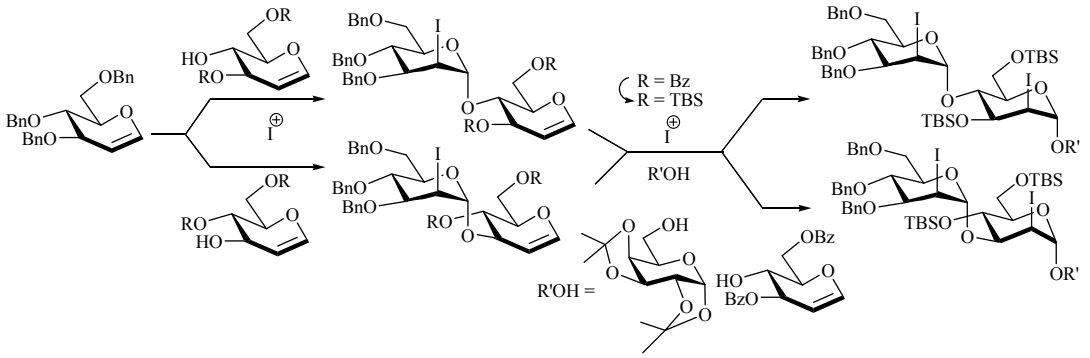
Once the glycal is converted into the 1,2-oxirane, it may react with several acceptors leading to disaccharides. This method has been the most widely used for the rapid assembly of oligosaccharides and is appropriate for the solid-phase synthesis. With regards to 1,2-anhydro sugars, the method was able to be applied when it was discovered that glycals react smoothly with 2,2-dimethyldioxirane (DMDO) prepared as a solution in dichloromethane, giving 1,2-anhydro sugars in good yields.[20] The stereoselectivity of the epoxidation highly depends on the type of protecting groups and on the steric hindrance of the substituents.[20a] The 3,4,6-tri-*O*-benzyl-D-glucal reacted smoothly with DMDO to afford the epoxide in near quantitative yield. Solvolysis of per-*O*-benzylated glucal with neat methanol gave the corresponding methyl glucoside with a stereoselectivity of 20:1 in favour of the *α*-isomer. However, with resident acetyl protecting groups, the stereoselectivity of the epoxidation is much reduced. Steric hindrance also has an influence. In the event, glycal bearing axial 3-TBS or acetals protecting groups also give high stereoselective epoxidations. Reaction of TBS-protected galactal gives stereoselectively the *α*-epoxide, while the presence of an axial substituent at *C*-3 on the glycal promotes a quite selective epoxidation from its *β*-face. On the other hand, the gulal configurated glycal with hindering substituents on both faces of the double bond gave a 1:1 mixture of epoxides (Scheme 4).[20a]

Scheme 4



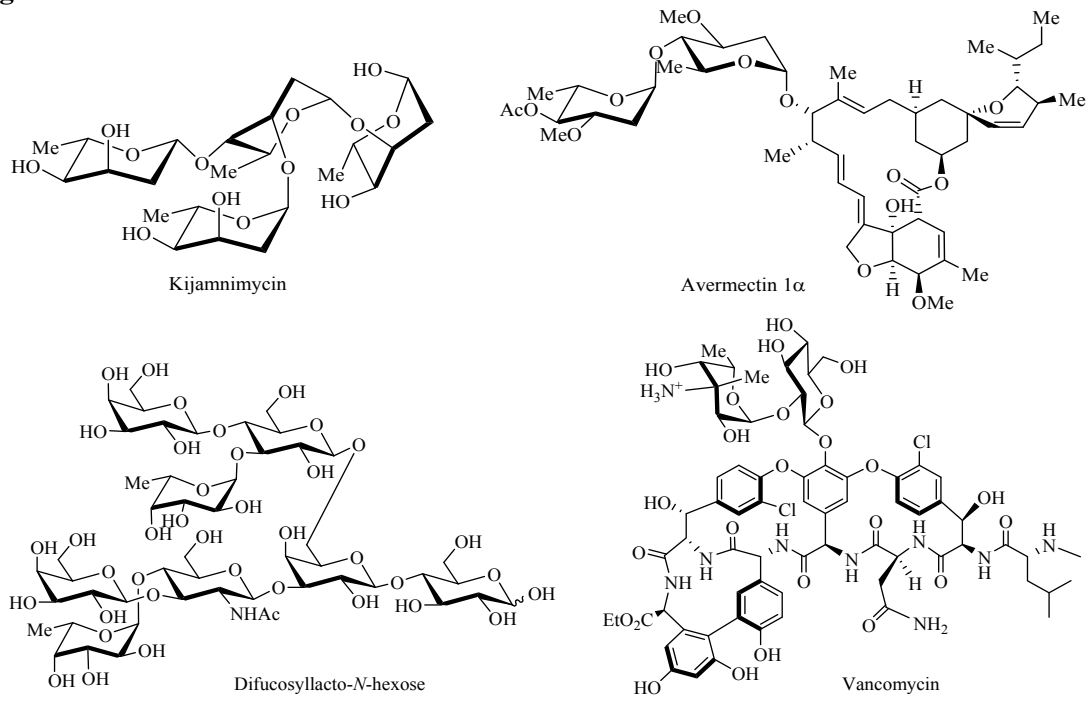
Protecting groups influence the reactivity of glycals as donors.[21a,b] The armed-disarmed concept that prevails in pentenyl glycosides and thioglycosides is also applied here.[21c,d] When a benzylated glycal is made to react with benzoylated glycal no self-condensation is observed and only one product is obtained derived from the more reactive glycal acting as donor (Scheme 5).

Scheme 5



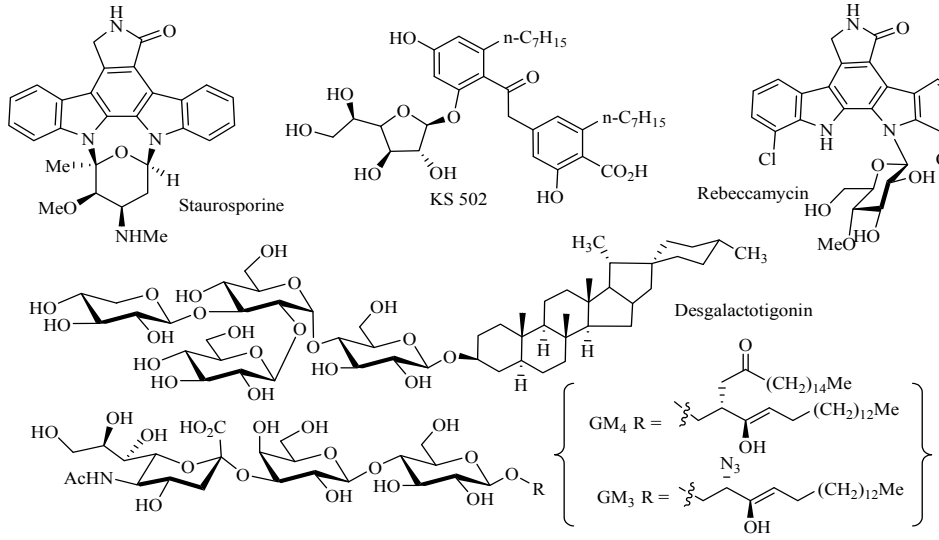
Halo-glycosylation has been mainly applied to the synthesis of 2-deoxy sugars due to the inconveniences that the substitution of an iodine atom from the *C*-2 position generally offers. NIS promoted glycosylation of glycals followed by reduction with H_2/Pd or any other reducing agent and manipulation of protecting groups furnished the desired Kijanimycin.[22a] A similar approach has been applied for the synthesis of Avermectine[22b] and in the total synthesis Difucosyllacto-*N*-hexaose,[22c] a tumor-Related Antigens N3 which is isolated from human milk and its composition depends on the blood type of the lactating mother (Figure 3).[H-J]

Figure 3



On the other hand, possibility of utilizing glycal epoxide method has been explored in the synthesis of carbohydrate containing bioactive natural products such as potent antibiotic vancomycin,[23a] calmodulin-dependent phosphodiesterase inhibitor KS 502,[23b] protein kinase-C inhibitor staurosporine,[23c,d,e] antitumor agent rebeccamycin,[23f] gangliosides GM_3[23g] , GM_4[23h] and branched oligosaccharide fragment of desgalactotigonin,[23i,j] a complex saponin, (Figure 4). The strategy consists on the preparation of a glycal epoxide that reacts as donor with a glycosyl acceptor leading to a *C*(1)-*O*-sugar, with one hydroxyl group at *C*-2.

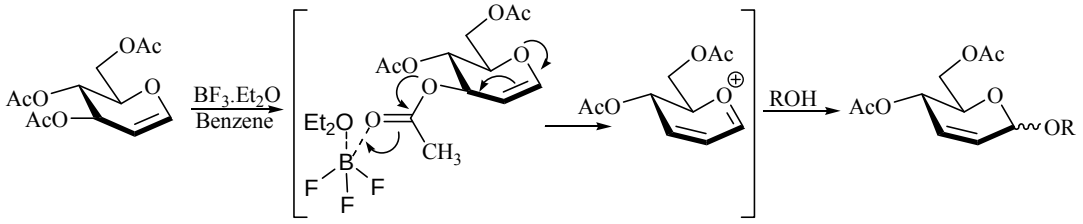
Figure 4



Ferrier Reaction:

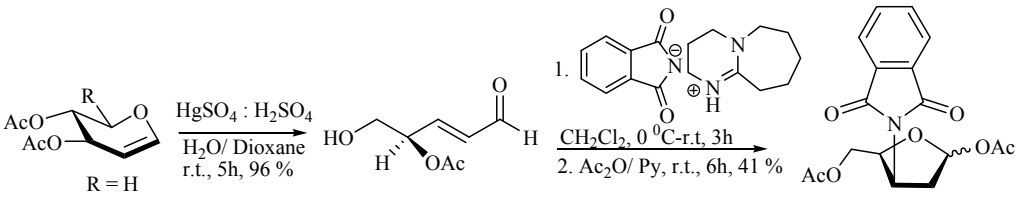
The Lewis acid-catalyzed rearrangement of glycals in the presence of alcohols is an excellent method for the preparation of 2,3-unsaturated glycosides and this process is known as the Ferrier reaction.[24] The reaction, as originally stated by Ferrier, involves an intermediate cyclic allylic oxocarbenium ion to which the nucleophile adds preferentially in the quasi-axial orientation. The most commonly employed Lewis acid to effect this transformation is boron trifluoride etherate (BF_3**.**Et_2O). Since its discovery in 1969, Ferrier's rearrangement has gained a great significance in the area of carbohydrate chemistry. The unsaturated glycosides obtained initially through this reaction play an important role in the transformation of these compounds into other interesting carbohydrates.

Scheme 6



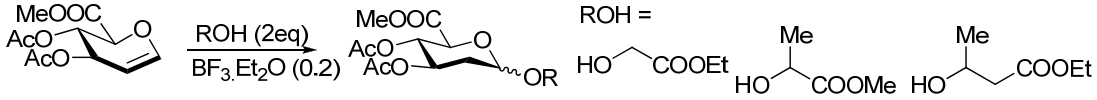
For example, the double bond formed between *C*-2 and *C*-3 atoms by the reaction of tri-*O*-acetyl-D-glucal and *N*-hydroxymethylphthalimide could easily be converted to *N*-phthaloylmethyl *α*-D-mannopyranoside. These products and other unsaturated *N*-phthaloylmethyl glycosides have been found to reduce plasma cholesterol and triglyceride levels significantly in mice. A similar reaction to Ferrier reaction, which substitutes the alcohol with *m*-chlorperbenzoic acid leads to 2,3-unsaturated lactones.[24a] While the treatment of glycals with mercury sulfate/sulphuric acid leads to acyclic *β*-unsaturated aldehydes which can further be used in the synthesis of L-3'-Amino-2',3'-dideoxyuridines. This reaction can be performed in good yield on many glycals (Scheme 7).[24d]

Scheme 7



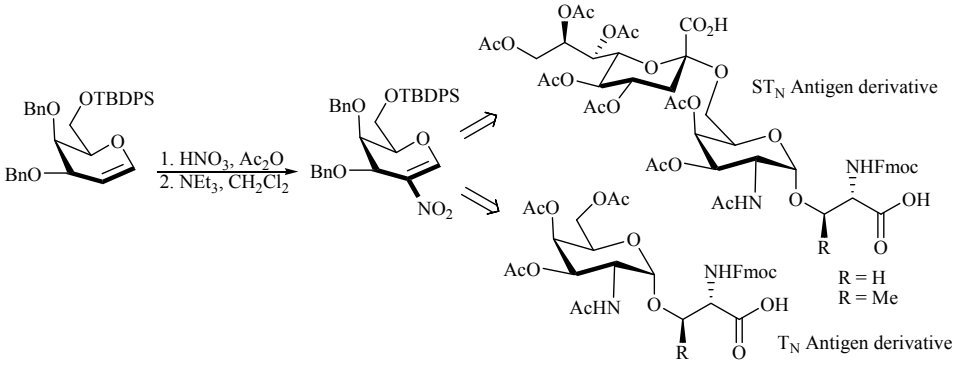
E. Wieczorek and J. Thiem described methyl 3,4-di-*O*-acetyl-D-glucuronal under Ferrier conditions and with various hydroxy acid esters as aglycone did not led to 2,3-unsaturated glycosides via typical allylic rearrangement but rather to novel class of 1,3-disubstituted derivatives (Scheme 8).[25d]

Scheme 8



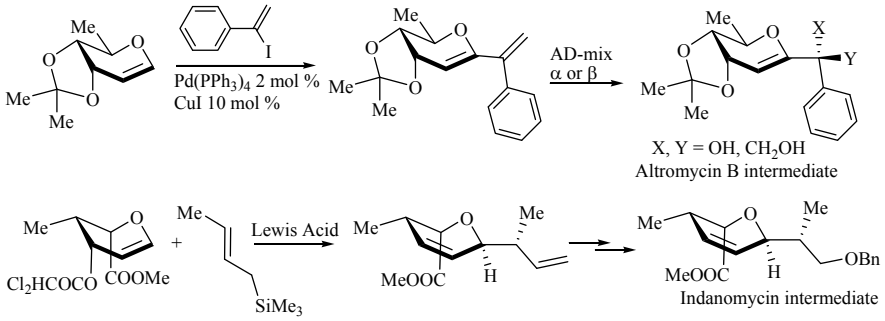
Schmidt *et al.,* recently demonstrated the synthesis of T_N, ST_N antigens and other glycopeptides achieved by using Michael addition to 2-nitrogalactal. Nitroglycal concatenation has been applied reiteratively and combined with either anomeric leaving group based glycosylations or the glycal assembly method demonstrating its versatility to access highly stereoselective 3-*O*- and 6-*O*-branched mucin structures (Scheme 9).[25a-c]

Scheme 9



Several *C*-glycosides are potent antitumor, antiviral, antibacterial or antibiotic agents.[26] Another class of *C*-glycosides, *C*-disaccharides, are non-metabolizable analogs of *O*-disaccharides and are used for enzyme receptor site studies.[27] The utility of glycals as precursors was also shown in the synthesis of ionophores, leukotriens or *C*-glycosides,[26,27] which in turn were frequently used as chiral starting materials to access natural products such as Altromycin B.[28a] A key reaction developed can be regarded as a Lewis acid promoted "carbon-Ferrier" process. Thus reactions of allyltrimethylsilane with activated glucal or galactal derivatives afforded *C*-glycosides bearing axial ally1 functions. The nucleophilic tendencies of such silanes toward Lewis acid activated electrophilic centers have been broadly demonstrated in the regio- and stereoselective synthesis of *C*1-branched glycosides for the syntheses of indanomycin,[28b] zinophorin,[28c] and avermectin A[28d,e] (Scheme 10).

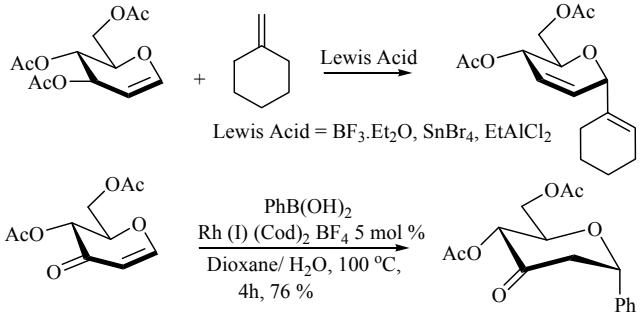
Scheme 10



On the other hand, Jean Herscovici and co-workers showed that the treatment of per-*O*-acetylated glycals with olefins in the presence of Lewis acids gave 2,3-unsaturated *C*-glycosides in good to excellent yields. The reaction was completely regioselective and showed a high degree of stereoselectivity leading mostly to the *α*-isomer. Generally the addition gave the *C*-glycoside with an unsaturated aglycone (Scheme 11).[29a]

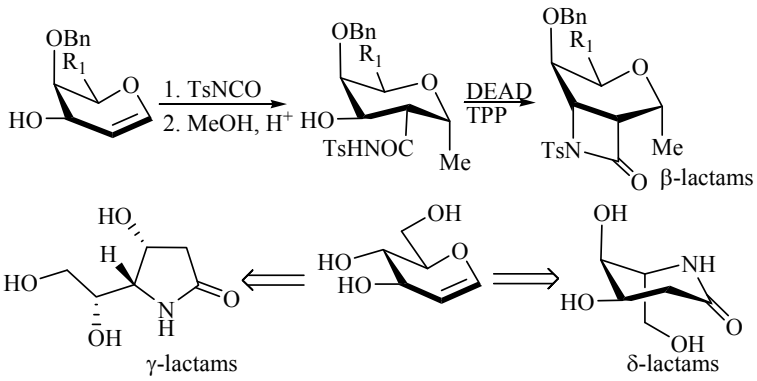
Shawn P. Maddaford *et al.* developed a new method for the formation of *C*-glycosides employing a cationic rhodium (I)-catalyzed 1,4-addition of arylboronic acids to enones derived from glycals. The reaction is stereoselective for the *α*-anomer and is highly dependent on the nature of the rhodium catalyst (Scheme 11).[29b]

Scheme 11



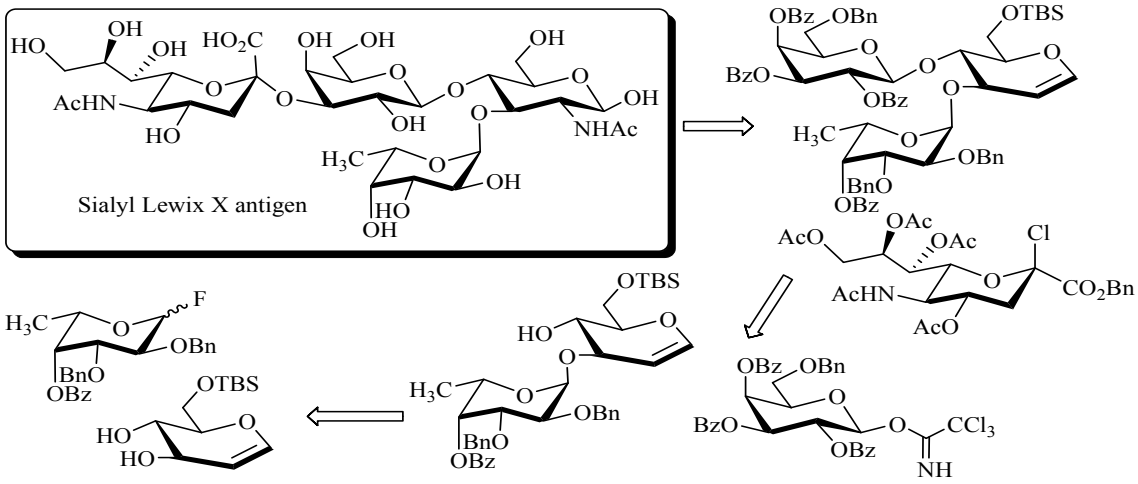
Glycals are very significant starting materials for stereoselective preparation of important aza sugars and oxetanes or *β*-lactams building blocks needed in glycoconjugate synthesis (Scheme 12).[30a] Since the hemiaminal moiety in azasugars is reported to undergo easy dehydration, and the lack of hydroxyl at *C*-2 to lower inhibition, recent work showed that more stable *δ*-lactams can act as nonbasic glycosidase inhibitors. The syntheses of all eight stereoisomers of D-glyconic-*δ*-lactams and *γ*-lactams have been accomplished mainly from carbohydrates such as glycals or other naturally occurring compounds, and their glycosidase inhibitory properties have been evaluated.[30b,c]

Scheme 12



A very rare Sialyl-Lewis X glycal, which was developed in Danishefsky's group, is a moderate inhibitor of *α*-1,3-fucosyltransferase and has been successfully utilized for completing the total synthesis of sialyl-Lewis X antigen.[31a] Further, glycals could be also used in chemoenzymatic synthesis of oligosaccharides and rare sugars. Recently glycal derivatives were studied as glycosidase and glycosyl transferase inhibitors and have been used as antigens to raise antibodies (Figure 5).[31b]

Figure 5

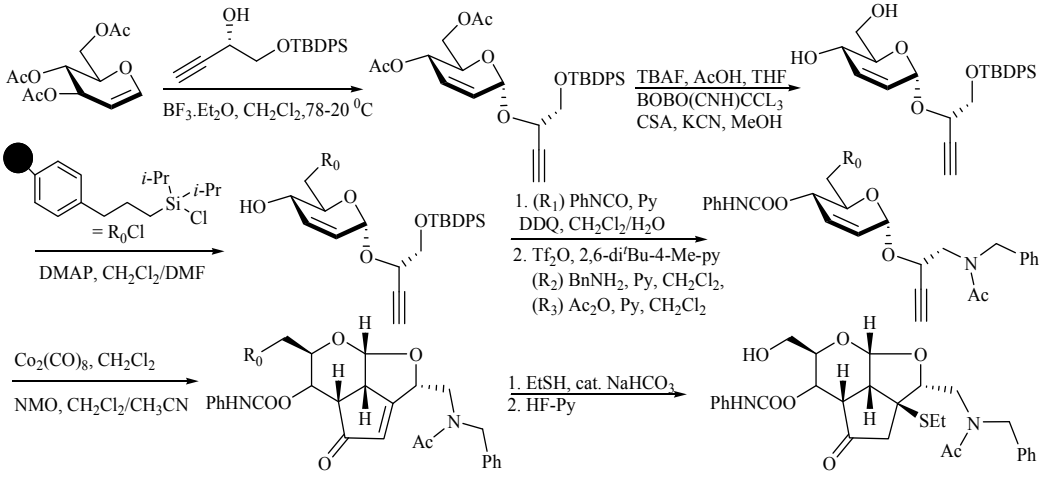


Glycal and Diversity Oriented Synthesis:

Organic synthesis, especially *diversity-oriented synthesis*, would play a vital role in drug discovery in the future. The term "*diversity-oriented synthesis*" (DOS)[32a,b] was coined by Stuart Schreiber and is aimed at building natural product-like, complex architectures in a high-throughput manner. This was attributed to the growing need for having a rapid access to diverse natural product-like skeletons that could be further utilized in the library generation. Unlike traditional combinatorial approaches that were focused on the library generation of aromatic and heterocyclic products, building three-dimensional structural complexity by exploring stereo- and enantioselective reactions on solid phase is one of the thrust areas in DOS. In general, the libraries generated by DOS are utilized as small-molecule chemical probes for understanding cellular processes and are not biased to a given biological target.

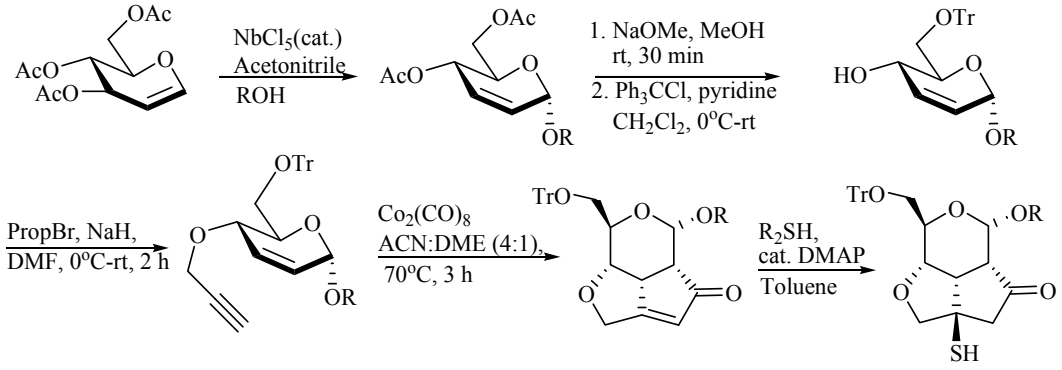
Schreiber *et al.*[32c] developed an efficient, stereoselective synthesis of tricyclic compounds by exploring Ferrier and Pauson-Khand[32d-f] reactions on a glycal template. This methodology was further utilized in developing a stereoselective synthesis of a library of 2500 compounds. Solid-phase synthesis was performed on 500–600 μm polystyrene alkylsilyl-derivatized macrobeads.[32g] Ferrier reaction of 3,4,6-tri-*O*-acetyl-glucal with (*S*)-1-TBDPS-3-buytyn-2-ol gave the *pseudo*-glucal as an *α*-anomer. The first solid-phase diversity step (R_1) is the functionalization of the 4-hydroxy group of the *pseudo*-glucal. Phenylisocyanate reacted quantitatively to afford the carbamate. Deprotection of the BOB group resulted in the alcohol, which was the second diversity position after triflation followed by S_N2 reaction with primary amine. Reaction of the resulting secondary amine with different acylation agent resulted in the third diversity point. Pauson–Khand reaction on resulted in tricyclic *α,β*-unsaturated ketone, which was further subjected to a hetero-Michael reaction to result in the fourth diversity (Scheme 13).

Scheme 13



Similarly, Hotha *et al*.[32h] reported a diversity oriented synthesis using glycals as the starting template to enable oxygen-rich stereochemically pure scaffolds. The unsaturated bond as well the poly-hydroxyl functionality coupled with the inherent chirality of the glycals can be easily exploited to generate structurally diverse libraries in short steps. They introduce a three level of diversity into our libraries using the range of complexity generating reactions like Ferrier, Pauson-Khand and Michael Addition reactions (Scheme 14).

Scheme 14



*****

Chapter 1: Present Work

Section A. Stereoselective Synthesis of 2,3-unsaturated *α*-glycopyranosides

Unsaturated carbohydrates are a versatile class of compounds for use in synthesis, and have so far been prepared mainly by direct elimination reactions applied to suitable saturated carbohydrate derivatives.[24] Efficient and selective construction of glycosidic linkages continues to be important due to the critical roles played by various glycoconjugates in nature. Different in modality from the majority of chemical glycosylations, the Ferrier reaction achieves glycosylation via displacement of the *C*-3 substituent in a glycal system to furnish 2,3-unsaturated glycosides.[24] 2,3-Unsaturated glycosides have received wide attention in recent years particularly in the synthesis of several biologically active natural products,[33] glycopeptides,[34] natural product-like compounds,[32a] modified carbohydrate derivatives,[35] nucleosides and oligosaccharides[36] and also as chiral synthons. The 2,3-olefinic group in the pyran rings can be diversified by a number of complexity generating reactions such as asymmetric dihydroxylation, amino hydroxylation, hydrogenation and epoxidation in order to achieve structural diversity.[37] Due to the synthetic versatility of the 2,3-unsaturated glycoside, this method has proven useful for a wide range of applications. The exceptional synthetic value of the Ferrier process, however, has been translated significantly to carbohydrate chemistry, despite the original conception of the reaction for direct *O*-glycosylation.[38]

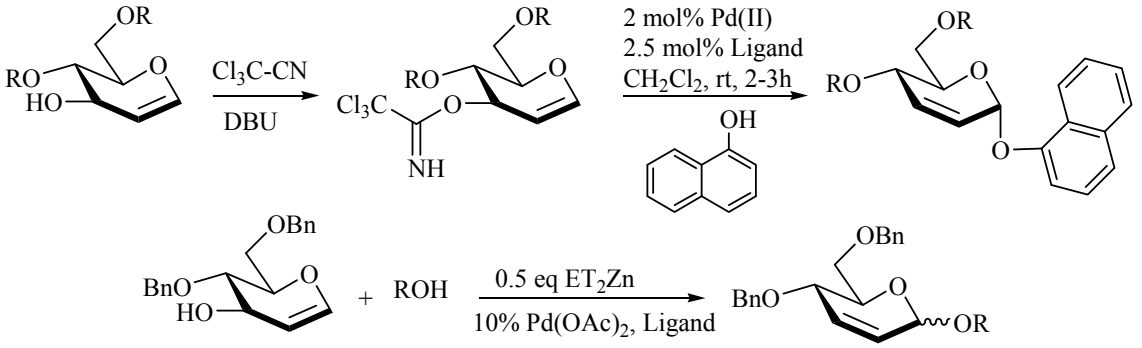
Ferrier reaction[24a] has evolved many folds since its discovery in 1964, a variety of Lewis acids have been employed to effect this transformation include $InCl_3$,[39a] Montmorillonite K10, [39b] $SnCl_4$,[39c] $BiCl_3$,[39d] $FeCl_3$,[39e] $Sc(OTf)_3$,[39f] $ZnCl_4$,[39g] $LiBF_4$,[39h] $Dy(OTf)_3$[39i] and $ZrCl_4$.[39j] In addition to these Lewis acids, oxidizing agents such as 2,3-dicholoro-5,6-dicyano-*p*-benzoquinone (DDQ),[40a] *N*-iodosuccinimide (NIS),[40b] iodine, iodonium dicollidine perchlorate (IDCP),[40c] ceric ammonium nitrate[40d] and $HClO_4$ impregnated on silica gel[40e] produce the desired 2,3-unsaturated glycopyranosides. The requirement of an acid catalyst to bring about the Ferrier rearrangement precludes its applicability to substrates that are sensitive to acidic conditions. This has led to the development of essentially non-acidic alternative method *viz*., iodonium reagents (NIS or iodonium dicollidinium perchlorate as promoter) by Fraser-Reid.[41a] Furthermore, Toshima *et al.*[41b,c] reported a novel method for the glycosidation of glycals under neutral conditions by using a catalytic amount of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to furnish 2,3-unsaturated glycosides in high yields. Mereyala *et al.*[41d] described a general and efficient route to 1,6-anhydro-2,3-dideoxy-*β*-D-*erythro*-hex-2-enopyranoses *via*

intramolecular Ferrier rearrangement catalyzed by $BF_3.Et_2O$. Toshima *et al.*[42] came out with a practical method for the glycosidation of glycals using montmorillonite K-10 (a clay catalyst), an environmentally acceptable, inexpensive catalyst, and this method was successfully extended for the synthesis of 2,3-unsaturated galactosides under microwave irradiation conditions.[43a] However, $LiBF_4$ in CH_3CN (LTAN) was found to be an useful alternative catalyst to $SnCl_4$,[43b,c] providing a practical method for the synthesis of 2,3-unsaturated alkyl glycosides, particularly for 2,3-unsaturated galactopyranosides in good yields.[44]

Indium(III) chloride ($InCl_3$) is a relatively strong Lewis acid and used as a catalyst for a wide variety of organic reactions.[45] However, Indium trichloride has hardly been used in the carbohydrate field. K. K. Balasubramanian and co-worker found an interesting application for $InCl_3$ as an efficient and versatile catalyst for the expeditious synthesis of alkyl and aryl 2,3-unsaturated glycopyranosides *via* Ferrier rearrangement.[46] Recently a few reports have appeared on the $InCl_3$ catalyzed, microwave assisted Ferrier rearrangement of glycals leading to 2,3-unsaturated *O*- and *C*-glycosides in good to excellent yields.[47]

The use of glycal derivatives as glycosyl donors has been utilized in allylpalladium strategies for the stereoselective synthesis of 2,3-unsaturated *O*-glycosides. However, because of the poor reactivity of the glycal donors as well as the alcohol nucleophiles, these groups utilized the more activated pyranone donors.[48] Lee and co-workers,[37] who recognized the challenge in this approach, utilized Zn(II) ion to activate both the alcohol acceptors for the nucleophilic addition and the glycal donors for the ionization. In contrast to the Lewis acid mediated Ferrier rearrangement, the anomeric stereochemistry of this reaction is controlled by the employed ligands (Scheme 15).

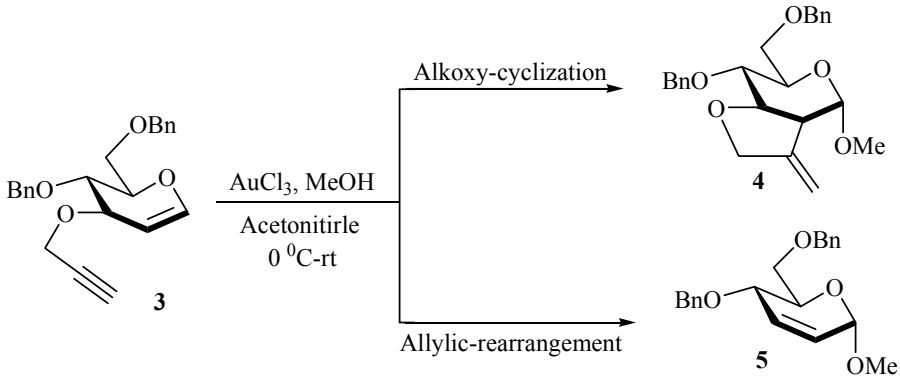
Scheme 15



Recently, Zhang and Kozmin reported[49] a novel alkoxy-cyclization catalyzed by Au(III) and we thought of extending this repertoire to carbohydrate scaffolds. Accordingly, we thought of performing Au-mediated cyclization on 4,6-di-*O*-benzyl-3-*O*-propargyl glucal (**3**) to explore the utility of alkynophilic gold catalyst. We envisioned that the reaction of an

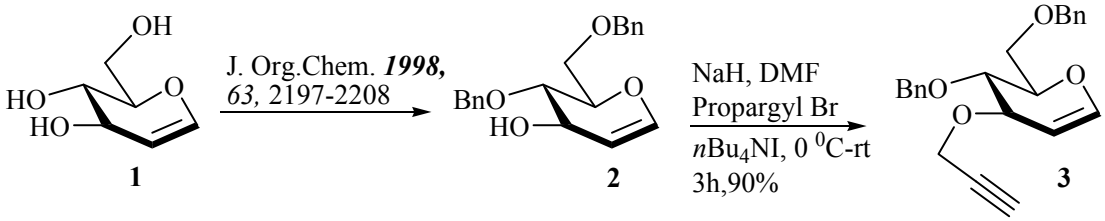
acceptor such as methanol with an Au^{3+} coordinated enyne system of a glucal might be a good model substrate. In doing so, we might be able to check the effect of Au^{3+} on the enyne moiety to give the bicyclic product (**4**) or the allylic rearrangement product (**5**) similar to Ferrier reaction (Scheme 16).[61a]

Scheme 16



To begin our investigation, the easily accessible glucal **1** was converted to 4,6-di-*O*-benzyl glucal **2** which was then transformed to the corresponding 3-*O*-propargyl derivative **3** using NaH/propargyl bromide/*n*-Bu_4NI in 90% yield, which serve as a novel substrate for Gold(III) catalyzed reaction (Scheme 17).

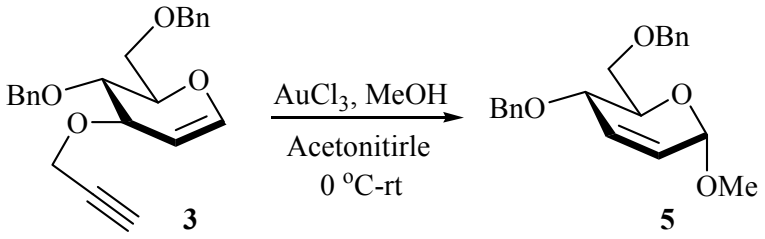
Scheme 17



The ^1H NMR spectrum of enyne **3** showed the acetylenic methine proton at δ 2.42 ppm as a triplet with coupling constant of J = 2.41 Hz and aromatic protons corresponding to benzyl group were identified at δ 7.21-7.35 ppm as multiplet along with all other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum of **3** showed the presence of propargyl methylene (-CH_2-) resonances at δ 55.7 ppm and the olefinic anomeric carbon was noticed at δ 144.9 ppm whilst the *C*-2 olefinic proton was observed at δ 99.3 ppm along with all other signals in accordance with the assigned structure. However, the DEPT spectrum of **3** unambiguously confirmed the presence of four inversely intense methylene (-CH_2-) groups by showing the resonances at δ 55.7, 68.3, 73.5, 73.5 ppm. In addition to this, compound **3** gave satisfactory elemental analysis and mass spectral analysis [mol wt calcd 364.43, Found 387.69 (M^+ + 23 for Na)]. Moreover, IR spectrum of **3** showed the acetylenic -CH transmittance at 3305.76 cm^{-1}.

After successful preparation of 4,6-di-*O*-benzyl-3-*O*-propargyl glucal (**3**), we utilized compound **3** as a novel substrate for Ferrier-like reaction in the stereoselective synthesis of 2,3-unsaturated *α*-*O*-glycosides (**5**), exploiting the alkynophilicity of gold catalysts. Subsequently, upon treatment of **3** with a preformed solution of 3 mol% $AuCl_3$ in acetonitrile at room temperature in presence of an aglycone such as methanol (**a**), the reaction proceeded smoothly to furnish the methyl 4,6-di-*O*-benzyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosides (**5**) in 38% yield with high selectivity in favor of the *α*-anomer along with 50% recovery of the starting material **3** without any evidence of bicyclic product (**4**). Our efforts to increase the yield and completion of reaction by changing of the temperature, solvents, and addition of 4 Å molecular sieves powder were unsuccessful. However, when the reaction was carried out in presence of 5 mol % of $AuCl_3$ under an argon atmosphere at 0 ^oC to room temperature for 15 h, the overall yield of the reaction was enhanced to 67% (Scheme 18).

Scheme 18

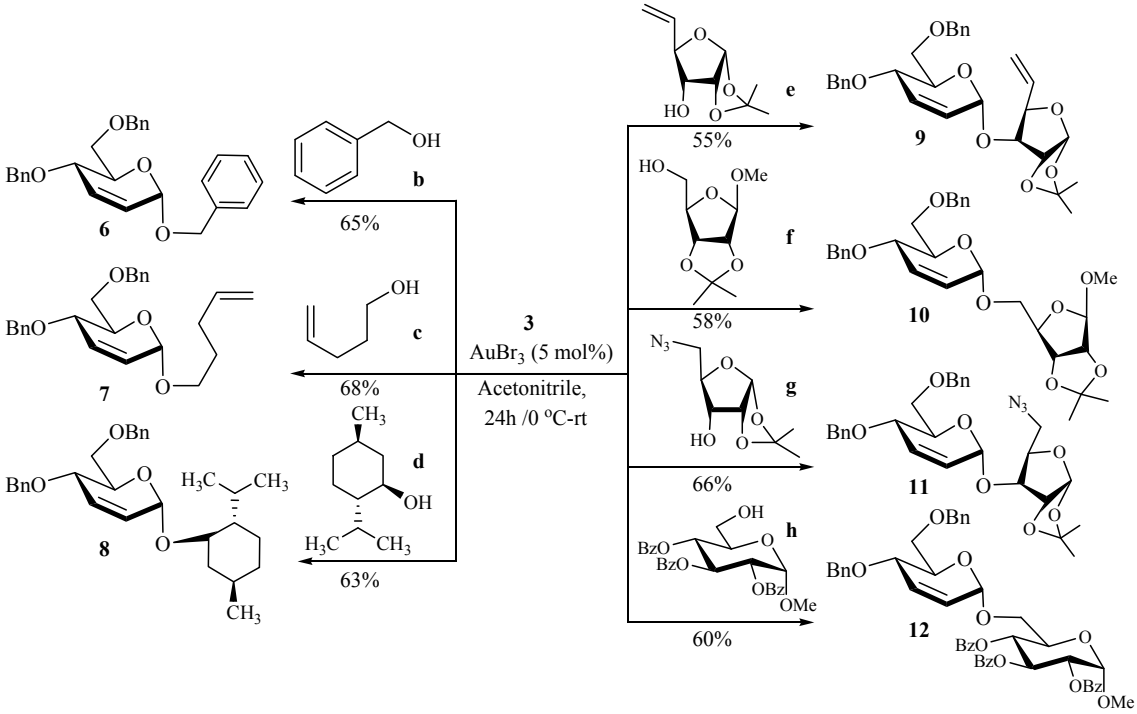


In the ^1H NMR spectrum of the product **5** in the Au-mediated reaction, resonances due to the olefin moiety were observed between δ 5.62 and 6.10 ppm and the methoxy group was identified at δ 3.44 ppm as a sharp singlet integrating for three protons along with all other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum showed the presence of -OMe resonances at δ 55.8 ppm whilst the olefinic carbons were at δ 126.5 and 130.8 ppm and at the same time, the anomeric carbon were evident at δ 95.7 ppm along with all other resonances in complete agreement with the assigned structure. However, the DEPT NMR spectrum of compound **5** revealed the presence of three inversely intense methylene ($-CH_2-$) groups by showing the resonances at δ 68.9, 71.0, 7345 ppm and there was no methylene group in the olefinic region which confirmed that the resultant product was the 2,3-unsaturated methyl *α*-*O*-glucoside (**5**). In addition, compound **5** was confirmed by elemental and mass spectral analysis.

To assess the feasibility of this novel Au^{3+} catalyzed Ferrier-like reaction in the context of 2,3-unsaturated *α*-*O*-glycosides synthesis, we performed parallel synthesis using a diverse range of aglycones comprising aromatic (**b**), aliphatic (**c**), alicyclic (**d**) and monosaccharidic alcohols (**e-h**). Thus, the enyne **5** was treated with various aglycones (**b-h**) in presence of 5

mol % of $AuCl_3$ in acetonitrile under inert atmosphere to afford aromatic **6**, aliphatic **7**, alicyclic **8** and monosaccharidic (**9-12**) unsaturated glucosides. It is worth mentioning here that all the Au^{3+} catalyzed Ferrier-like reactions resulted in the formation of respective 2,3-unsaturated *α*-*O*-glucosides (**8-11**) in stereoselective manner with good yield (Scheme 19). It should be noted that the current methodology tolerates various functional groups such as olefin (**c,e**), isopropylidene (**e-g**), azide **g** and esters **h**.

Scheme 19

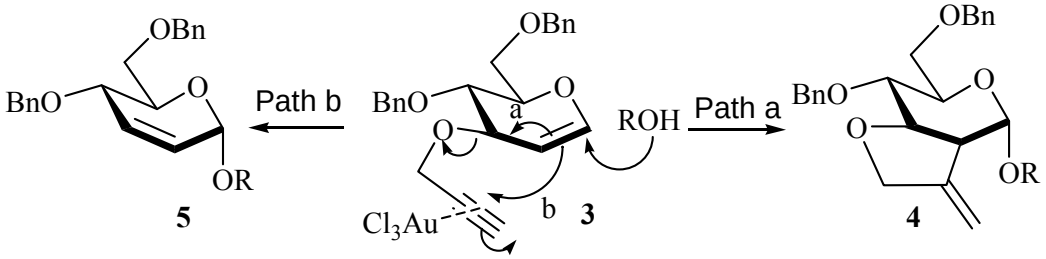


For example, structure of menthyl 4,6-di-*O*-benzyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranosides (**8**) was confirmed by ^1H, ^{13}C, DEPT NMR spectrum and elemental analysis. In the ^1H NMR spectrum of compound **8**, resonances corresponding to propargyl and acetylenic proton were disappeared and new proton resonances attributed to menthol moiety were apparent in the aliphatic region and resonances due to the olefin moiety were observed between δ 5.75 and 6.09 ppm whilst anomeric proton was observed at δ 5.09 ppm along with other proton resonances in complete agreement with the assigned structure. In the ^{13}C NMR spectrum of compound **8**, anomeric carbon was noticed at δ 96.3 ppm whilst the olefinic carbons were observed at δ 126.8 and 130.2 ppm along with all other resonances in complete agreement with the assigned structure. In addition, the DEPT spectrum unambiguously confirmed the presence of six -CH_2- (inversely intense) group by showing the resonances at δ 23.2, 34.3, 43.1, 69.0, 70.0, 73.4 ppm. Furthermore, structure of menthyl 2,3-unsaturated *α*-*O*-glucosides (**8**) was confirmed by means of elemental analysis as well.

In the ^{1}H NMR spectrum of disaccharide **12,** characteristic resonances of methoxy group were identified at δ 3.45 ppm as a singlet integrating for three protons and at the same time aromatic protons equivalent to two benzyl and four benzoyl groups were identified around δ 7.26-7.99 ppm as multiplets integrating for twenty-five protons along with all other proton resonances in the complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum of disaccharide **12** showed characteristic resonances corresponding to methoxy group at δ 55.6 ppm and the two anomeric carbons were evident at δ 94.8 and 97.1 ppm whilst the olefinic carbons were observed at δ 126.0 and 131.3 ppm and at the same time three carbonyl groups were characterized at δ 165.0, 165.8 and 165.8 ppm with remaining signals in accordance with the assigned structure. Moreover, the DEPT spectrum of compound **12** confirmed the presence of four -CH_2 groups (negative intensity) and eight quarternary carbons as compared with ^{13}C NMR spectrum. Similarly, structures of all other 2,3-unsaturated glucosides were confirmed by ^{1}H, ^{13}C, DEPT NMR spectral and elemental analysis.

Though a detailed mechanism of the Au-mediated Ferrier like reaction awaits further studies, a proposed mechanism for Au(III)-catalyzed formation of *α-O*-glycosides is outlined in Figure 6. Alkynophilic Au^{3+} chemoselectively coordinated with the enyne system of a glucal. Due to increase electrophilicity, Au^{3+} activated triple bond makes the propargyl moiety a leaving group thereby leading to a Ferrier-like reaction (Figure 6, path **a**) instead of trapping the Au-alkyne complex via an alkoxycyclization (Figure 6, path **b**).

Figure 6



Section B. Synthesis of *C*-2 methylene glycosides from *C*-2 propargyloxy methyl glycals

C-Branched sugars in natural antibiotics, bacterial polysaccharides and macrolides are often associated with specific biological functions.[50] Unnatural *C*-2 branched sugars also serve as metabolic substrates, e.g., Bertozzi et al. tested *C*-2 acetonylsugars, derived from 2-iodosugars, as mimics of *N*-2 acetylsugars for cell surface engineering[51] and Hindsgaul et al. prepared a *C*-2 acetamide sugar from a 2,3-epoxide as an inhibitor of the biosynthesis of lipid A.[52] Most *C*-2 branched sugars are synthesized from glycals through 1,2-cyclopropanation followed by selective ring opening via solvolysis,[53,54] which often provides an anomeric mixture of glycosides with *α*-glycosides being favored due to the anomeric effect because of the involvement of an oxocarbenium-like intermediate. A recent ring-opening of sugar cyclopropane carboxylates mediated by NIS provided 1,2-*trans C*-2 branched glycosides.[55]

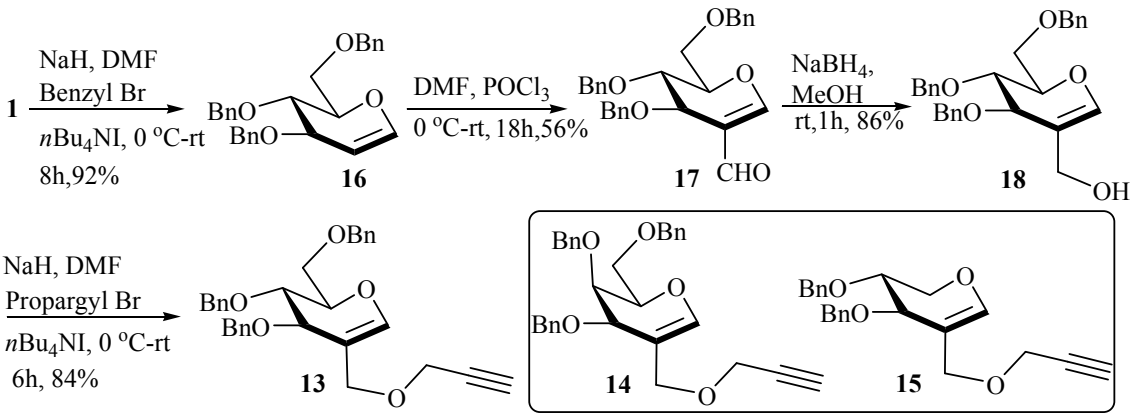
The chemistry of unsaturated and branched chain sugars continues to receive wide attention owing to the importance of such compounds in the total synthesis of many natural products.[56] 2-Deoxy-*C*-2-substituted carbohydrates belong to an important class of branched chain deoxy sugars and unsaturated nucleosides.[57] Particularly, the *C*-2 methylene group is a key structural feature of molecules involved in the mechanism based inactivation of ribonucleotide diphosphate reductase and *C*-2 methylene glycosides are precursors for the synthesis of *C*-disaccharides. For example, Matsuda et al. identified that the *C*-2' methylene group of *C*-2' methylene nucleosides is essential for the inactivation of the ribonucleotide phosphate reductase enzyme which is involved in tumour progression.[58]

Most often approach is toward the synthesis of *C*-2 methylene glycosides involves S_N2' addition of an alcohol on *C*-2-acetoxymethyl glycals in the presence of a Lewis acid, the process known as modified Ferrier reaction.[59] Booma and Balasubramanian reported the first approach for the synthesis of *C*-2 methylene glycosides from *C*-2-acetoxymethylene glycal based on a Ferrier reaction using $BF_3.Et_2O$ as a Lewis acid catalyst.[59a] A subsequent study employed Nafion-H,[59b] Montmorillonite K-10 or $Pd(PPh_3)_4$ to effect similar transformations to obtain *C*-2 methylene glycosides. More recently, Ghosh et al.[59c] reported the $InCl_3$-mediated preparation of these compounds. Our programme to synthesize diverse molecular architectures from carbohydrate precursors led us to synthesize *C*-2 methylene glycosides to exploit their salient features for the development of a diversity oriented synthesis pathway.

In continuation of our earlier results,[61a] the utility of alkynophilic Au^{3+} catalysts was studied for the synthesis of 2-*deoxy*-*C*-2 methylene glycosides using *C*-2 propargyloxy methyl glycals,[62b] which contain an enyne system very similar to 4,6-di-*O*-benzyl-3-*O*-propargyl glucal (**3**). Accordingly, per-O-benzylated *C*-2 propargyloxy methyl glycals (**13-15**) were

prepared following standard procedures. Glucal (**1**) was converted to per-*O*-benzyl glucal and subsequently converted to *C*-2 formyl glucal (**16**) using Vilsmeier-Haack reaction. Reduction of *C*-2 formyl glucal (**17**) with sodium borohydride in methanol afforded the corresponding *C*-2-hydroxymethylglucal (**18**).[59a,60a] Propargylation of primary hydroxyl group with NaH/propargylbromide/$nBu_4N^+I^-$ yielded the desired propargyl ether (1,5-Anhydro-3,4,6-tri-*O*-benzyl-1,2-di-*deoxy*-2-propargyloxymethyl-D-*arabino*-hex-1-enitol) **13**. Similarly compounds **14** and **15** were prepared starting from galactal and xylal (Scheme 20).

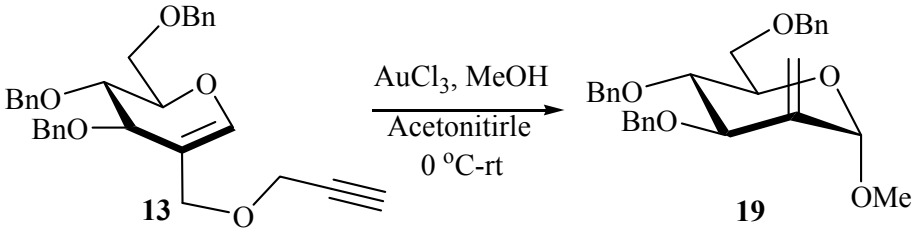
Scheme 20



In the ^{1}H NMR spectrum of enyne **13**, resonances corresponding to the acetylenic methine proton was characterized at δ 2.38 ppm as a triplet with coupling constant of J = 2.34 Hz and characteristic resonances due to propargylic -CH_2 group were identified at δ 4.08 as a triplet (J = 2.36 Hz) integrating for two protons and at the same time, anomeric carbon was evident at δ 6.51 ppm as a singlet whilst aromatic protons corresponding to benzyl group were identified at δ 7.22-7.37 ppm as multiplet along with all other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum of compound **13** showed the presence of propargyl methylene (-CH_2-) resonances at δ 55.6 ppm whilst the anomeric and *C*-2 olefinic carbon were noticed at δ 144.3 and δ 108.6 ppm respectively. However, the DEPT spectrum of enyne **13** unambiguously confirmed the presence of six inversely phased signals attributable to methylene (-CH_2-) groups by showing the resonances at δ 55.6, 66.9, 68.0, 72.7, 72.8, 73.2 ppm. In addition to this, compound **13** gave satisfactory elemental analysis and mass spectral analysis [mol wt calcd 484.58, Found 507.04 (M^+ + 23 for Na)]. Moreover, IR spectrum of compound **13** revealed the presence of characteristics transmittance due to acetylenic -CH at 3286.48 cm^{-1}. Similarly, structures of **14** and **15** were confirmed by ^{1}H, ^{13}C, DEPT NMR spectrum and elemental analysis.

Initial experiments for $AuCl_3$-mediated S_N2' reaction were performed with 3,4,6 tri-*O*-benzyl-*C*-2 propargyloxymethyl glucal as a novel substrate for Au-mediated Ferrier-like reaction and methanol as the glycosyl acceptor. Accordingly, an acetonitrile solution of enyne **13** was treated with 5 mol% of $AuCl_3$ solution in acetonitrile in presence of methanol at 0 ^oC to room temperature to furnish the Methyl 2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside (**19**) in 63% yield supporting further the behaviour of the propargyloxy group in the presence of $AuCl_3$ (Scheme 21).

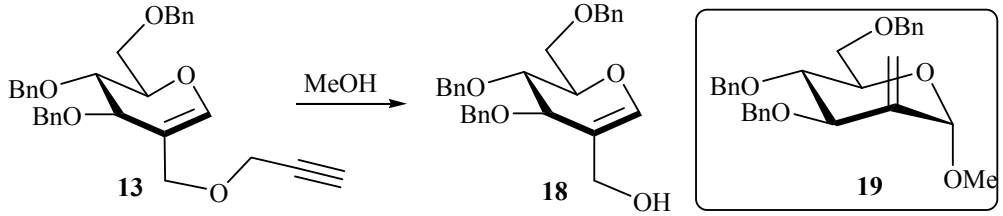
Scheme 21



The ^1H NMR spectrum of *C*-2 methylene glucoside **19** revealed the absence of an acetylenic methine proton at δ 2.38 ppm and the presence of proton resonances characteristic with an exomethylene group around δ 5.15-5.31 ppm whilst characteristic resonances of methoxy group were identified at δ 3.38 ppm as a singlet integrating for three protons along with other proton resonances in complete agreement with the assigned structure. The ^{13}C NMR spectrum of compound **19** also confirmed the presence of an olefin by showing the resonances at δ 110.7 and 142.4 ppm and characteristic resonances corresponding to methoxy group at δ 54.5 ppm and at the same time, the anomeric carbon was identified at δ 102.4 ppm confirming the product as an *α*-*O*-glucoside. Furthermore, the DEPT spectrum of compound **19** confirmed the presence of five -CH_2 groups (negative intensity) at δ 68.8, 73.4, 73.4, 74.9, 110.7 ppm. In addition to this, compound **13** gave satisfactory elemental analysis and mass spectral analysis [mol wt calcd 460.56, Found 483.04 (M^+ + 23 for Na)] and the overall spectroscopic data were in agreement with that reported by Booma *et al.*[59a]

Optimization studies were carried out by using other alkyne activators, such as $Cu(OAc)_2$, $PtCl_2$, $Co_2(CO)_8$ and $RuCl_3$ under different conditions. Initial optimization of novel Au-mediated S_N2' reaction was performed with the *C*-2 propargyloxy methyl glucal (**13**) in presence of methanol employing a variety of reagents and temperature conditions in different solvents under inert atmosphere of argon. Efforts to promote the reaction with $Cu(OAc)_2$, $PtCl_2$ and $Co_2(CO)_8$ did not afford the 2-*deoxy*-2-*C*-methylene glucoside **19** (entry 3,4,5 and 7) whereas $Co_2(CO)_8$ activated the alkyne group but resulted in simple deprotection of propargyl moiety to give *C*-2 hydroxymethyl glucal (**18**) (Scheme 22 entry 3 & 4).

Scheme 22



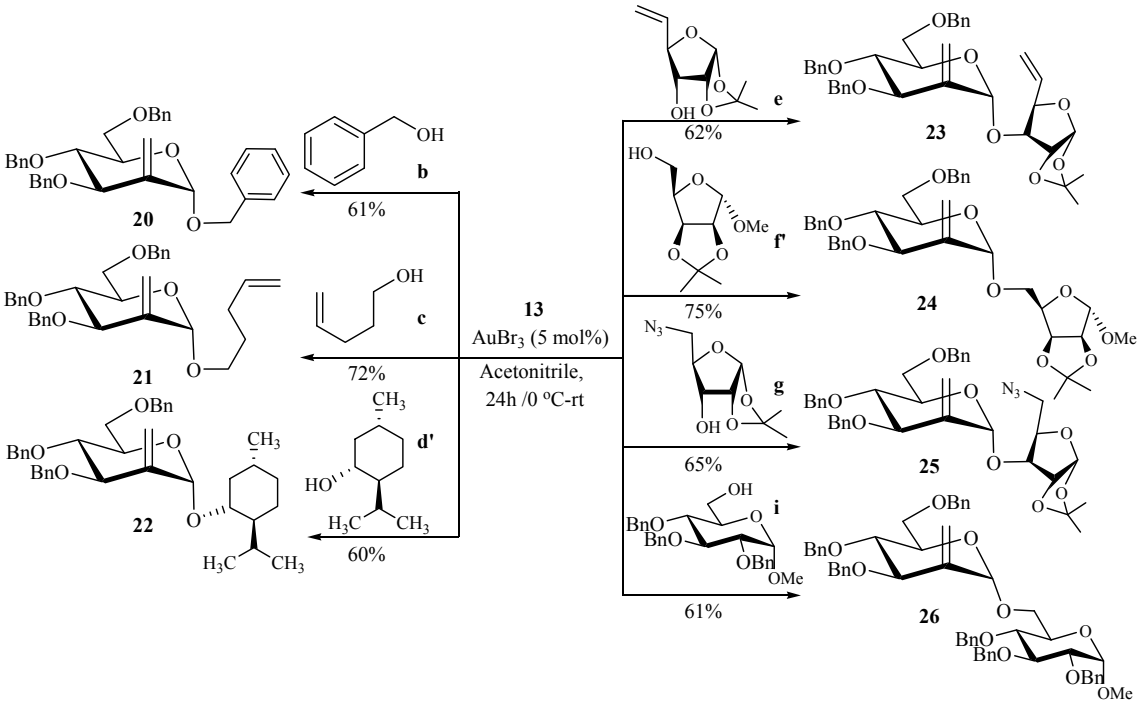
Entry	*Catalyst*	*Solvent*	*Time*	*Temp*	*% **18***	*% **19***
1	$AuCl_3$, 5 mol%	CH_3CN	5 h	rt	0	63
2	$AuCl_3$, 5 mol%	CH_2Cl_2	5 h	rt	0	45
3	$Co_2(CO)_8$,1eq	CH_3CN	8 h	rt	25	0
4	$Co_2(CO)_8$,1eq	CH_3CN	8 h	60^oC	70	0
5	$PtCl_2$, 5 mol%	CH_3CN	6 h	rt	0	0
6	$RuCl_3$, 5 mol%	CH_3CN	4 h	rt	0	57
7	$Cu(OAc)_2$,10 mol%	CH_3CN	8 h	rt	0	0

It is significant to mention that, $RuCl_3$ (5 mol %) in anhydrous acetonitrile gave desired *C*-2-methylene product **19** in acceptable yield (Scheme 22, entry 6). Nevertheless, the $AuCl_3$ emerged as the best alkyne activator for the synthesis of 2-*deoxy*-2-*C*-methylene glucoside (Scheme 22).

Having optimized conditions in hand, the feasibility and general applicability of this new methodology was explored and a parallel synthesis of *C*-2 methylene glycosides using enyne **13** and a diverse range of aglycones comprising aromatic (**b**), aliphatic (**c**), alicyclic (**d'**) and monosaccharidic alcohol (**e-i**). Accordingly, the reaction was carried out with preformed acetonitrile solution of **13** and aglycones (**b-i**) prepared *vide supra* in the presence of 5 mol % of $AuCl_3$ in acetonitrile under inert atmosphere at room temperature resulted in the formation of respective 2-*deoxy*-2-*C*-methylene glucoside (**20-26**) in good yields with high selectivity in favor of the *α*-anomer (Scheme 23).

The ^{1}H NMR spectrum of disaccharide **24** revealed the presence of the -OMe group at δ 3.31 ppm as a singlet integrating for three protons whilst characteristic resonances due to an exomethylene group were observed around δ 5.16-5.32 ppm and at the same time, two sharp singlets corresponding to isopropylidene moiety were noticed at δ 1.30 and 1.42 ppm along with all other proton resonances in complete agreement with the assigned structure. In the ^{13}C NMR spectrum of compound **24**, two anomeric carbons were evident at δ 101.4 and 107.1 ppm whilst characteristic resonances corresponding to methoxy group at δ 54.5 ppm and at the same time, structure of **24** was confirmed by the presence of an olefin showing resonances at δ 110.7 and 142.3 ppm along with all the other resonances were in complete agreement with the assigned structure.

Scheme 23

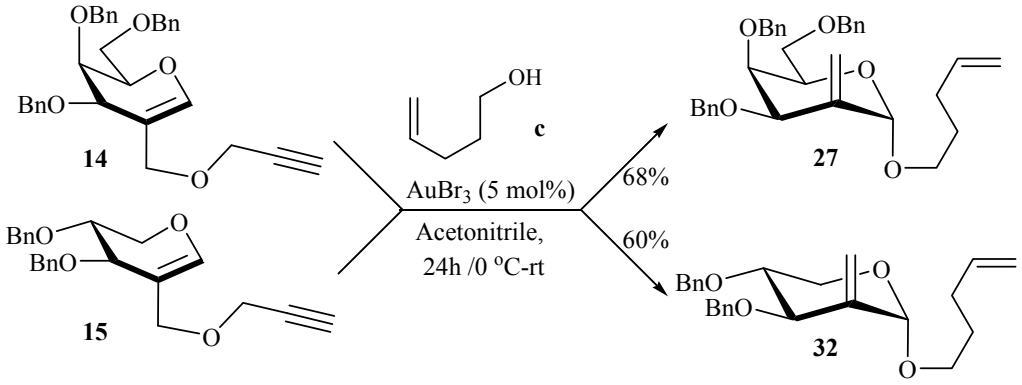


Furthermore, the DEPT NMR spectrum of **24** unambiguously confirmed the presence of six -CH_2- groups (inversely intense) and five quarternary carbons (absent in the DEPT spectrum when compared with ^{13}C NMR). In addition to this, compound **24** was further confirmed by MALDI-TOF spectrum which shows relative intense peak at 656.85 (M^+ + 23; Calcd for $C_{37}H_{44}O_9$: 632.74) and gave satisfactory elemental data. Similarly, structure of all other *C*-methylene glycoside products were confirmed by ^{1}H, ^{13}C, DEPT NMR, mass spectral and elemental analysis data.

In addition, we thought of extending this protocol for the per-*O*-benzylated *C*-2-propargyloxymethyl galactal **14** and per-*O*-benzylated *C*-2-propargyloxymethyl xylal **15**. Accordingly, compounds **14** and **15** were reacted with a wide range of aglycones to give the corresponding 2-*deoxy*-2-*C*-methylene galactosides (**27-31**) and xylosides (**32**) in a stereoselective manner. For example, galactal and xylal derived enynes (**14** and **15**) reacted with pentenyl alcohol to give *C*-2 methylene-containing pentenyl galactoside **27** and *C*-2 methylene-bearing pentenyl xylopyranoside **32** in 68% and 60% yields, respectively (Scheme 24).

The ^{1}H NMR spectrum of **27** revealed the absence of an acetylenic methine proton at δ 2.33 ppm and the presence of proton resonances characteristic with exomethylene group and terminal methylene group of pentenyl moiety around δ 5.03-5.92 ppm along with other proton resonances in complete agreement with the assigned structure.

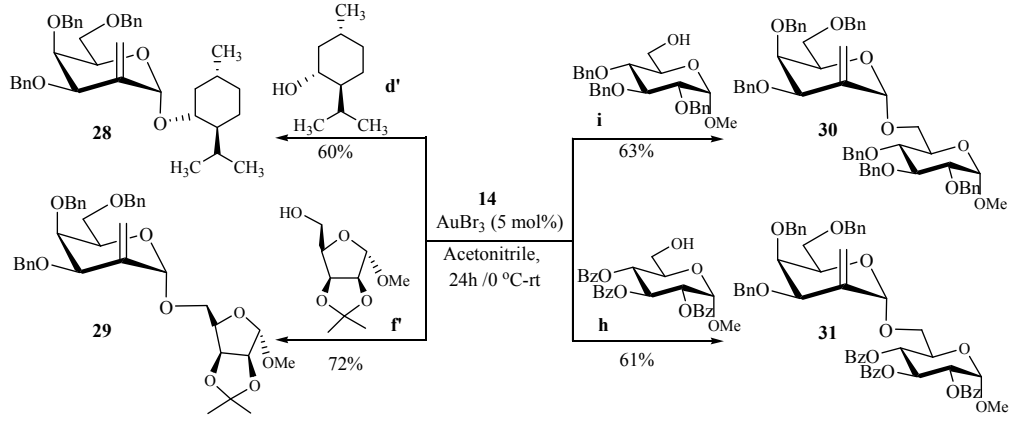
Scheme 24



The ^{13}C NMR spectrum of compound **27** also confirmed the presence of two olefinic methylene groups by showing the resonances at δ 111.3 and 114.8 ppm whilst the anomeric carbon was identified at δ 101.5 ppm along with other resonances in complete agreement with the assigned structure confirming the product as *C*-2 methylene-*α*-*O*-galactoside. Furthermore, the DEPT spectrum of compound **27** confirmed the presence of nine -CH_2 groups (negative intensity) at δ 28.7, 30.2, 66.7, 69.3, 71.5, 73.4, 74.0, 11.3, 114.8 ppm and six quarternary carbons at δ 114.8, 138.0, 138.1, 138.4, 138.6, 141.0 ppm. In addition to this, compound **27** gave satisfactory elemental analysis and mass spectral analysis [mol wt calcd 514.65, Found 537.46 (M^+ + 23 for Na)].

Likewise, alicyclic and sugar-derived aglycones also reacted with enyne **14** under aforementioned Au-mediated reaction conditions to give corresponding 2-*deoxy*-2-*C*-methylene galactosides (**28-31**) in good yield. It is worth mentioning here that *C*-2-propargyloxymethyl galactal **14** reacts with all nucleophilic acceptors in the Au^{3+} catalyzed reaction, giving respective 2-*deoxy*-2-*C*-methylene *α*-*O*-galactosides (**28-31**) in good yields (Scheme 25).

Scheme 25



The structure of Menthyl 2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside (**28)** was confirmed by ^{1}H, ^{13}C, DEPT NMR and Mass spectra. In the ^{1}H NMR spectrum of compound **28**, resonances corresponding to propargyl and acetylenic proton were absent and new resonances attributed to menthol moiety were apparent in aliphatic region at δ 0.76 ppm (d, 3H, *J* = 6.87 Hz), 0.83 ppm (d, 3H, *J* = 6.51 Hz), 0.89 ppm (d, 3H, *J* = 6.93 Hz) whilst characteristic resonances due to an exomethylene group was observed around δ 5.18-5.38 ppm along with all other resonances in accordance to assigned structure. The ^{13}C NMR spectrum of compound **28** also confirmed the presence of an olefin showing resonances at δ 110.2 and 141.3 ppm and at the same time, the anomeric carbon was identified at δ 103.3 ppm confirming the product as 2-*deoxy*-2-*C*-methylene *α*-galactoside, along with other resonance in the complete agreement with the assigned structure. Furthermore, the DEPT NMR spectrum of compound **28** unambiguously confirmed the presence of eight inversely intense -CH_2- groups by showing the resonances at δ 23.3, 29.7, 34.4, 42.8, 69.5, 71.5, 73.4, 74.0, 110.3 ppm and four quarternary carbons (absent in the DEPT spectrum when compared with ^{13}C NMR). In addition to this, compound **28** was further confirmed by MALDI-TOF spectrum which shows relatively intense peak at 607.30 (M^+ + 23; Calcd for $C_{38}H_{48}O_5$: 584.78) and gave satisfactory elemental data. Similarly, structure of all other 2-*deoxy*-2-*C*-methylene galactoside products (**29-31**) were confirmed by ^{1}H, ^{13}C, DEPT NMR, mass spectral and elemental analysis data.

In summary, we have identified that the alkynophilicity of Au(III) promotes a Ferrier-like reaction when suitably substituted glycal (enyne feature contained within the glycal structure) was treated with $AuCl_3$ in the presence of acetonitrile.[61] The utility of the methodology was established using a diverse range of aglycones and enable the stereoselective synthesis 2,3-unsaturated *α*-glucopyranosides and *C*-2-methylene *α*-*O*-glycopyranosides via S_N2' reaction onto 3-*O*-propargyl glucal and *C*-2 propargyloxymethyl glycal respectively. The current methodology is highly stereoselective, moisture tolerant, catalytic and high yielding. The main advantage of this methodology is its extensive applicability and flexibility and in addition to this, current methodology tolerates the diverse functional groups such as isopropylidene, olefin, ester and azide as well.

*****

Chapter 1: Experimental Section

General experimental procedure for *O*-benzylation:

To a solution of glycal (1 equiv) in anhydrous *N,N*-dimethylformamide (10 mL) at 0 ^{o}C was added sodium hydride (3.2 equiv) and stirred at room temperature for 30 min. The resulting dark brown solution was cooled to 0 ^{o}C and was added *n*-$Bu_4N^+I^-$ followed by dropwise addition of benzyl bromide (3.6 equiv) under nitrogen atmosphere, stirred at room temperature for 15 h. At the end of the reaction (judged by TLC), excess of NaH was quenched by the addition of 10 mL methanol. The reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (3 x 20 mL), combined organic layers were dried over anhydrous sodium sulphate, concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography to give corresponding per-*O*-benzylated glycal.

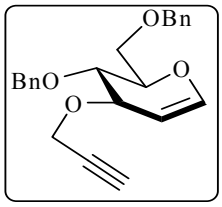
General experimental procedures for *O*-propargylation:

To an ice-cooled solution of the per-*O*-benzylated *C*-2-hydroxymethyl glycal (1 mmol) in anhydrous DMF (5 mL) was added sodium hydride (1.5 equiv, 60% oil suspension) and stirred for 1 h at room temperature. Propargyl bromide (1.5 equiv) was introduced dropwise to the reaction mixture at 0 °C and stirred at room temperature for 1 h. At the end of the reaction (judged by TLC), resulting suspension was quenched with saturated ammonium chloride and extracted with ethyl acetate (3 x 20 mL), combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and concentrated *in vacuo* to give the crude *O*-propargyl derivative which was purified by silica gel column chromatography using ethyl acetate and light petroleum (60-80 °C) to give corresponding per-*O*-benzylated-*C*-2 propargyloxy methyl glycal.

General procedure for $AuCl_3$ mediated Ferrier like reaction:

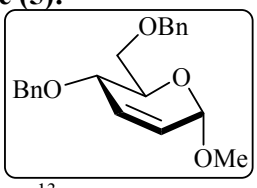
To a solution of Ferrier substrate or enyne (1.0 equiv) in anhydrous acetonitrile (5 mL) were added aglycone (1.2 equiv) and $AuCl_3$ (5 mol % in acetonitrile) at 0 ^{o}C and the resulting mixture stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the crude residue was redissolved in ethyl acetate and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography using light petroleum (60–80 ^{o}C) and ethyl acetate to afford the 2,3-unsaturated or exomethylene *α*-*O*-glycosides in good yields.

4,6-di-*O*-benzyl-3-*O*-Propargyl *α*-D-glucal (3):



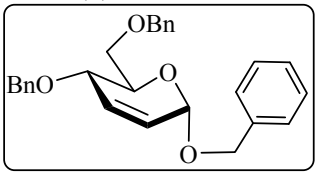
$[\alpha]_D^{25}$ = +42.39 (*c*, 1.00, $CHCl_3$); IR ($CHCl_3$): 3305.76 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 2.42 (t, 1H, *J* = 2.40 Hz), 3.75-3.84 (m, 3H), 4.01-4.10 (m, 1H), 4.19-4.21 (m, 2H), 4.27-4.32 (m, 1H), 4.57 (d, 1H, *J* = 1.88 Hz), 4.58-4.65 (m, 2H), 4.82-4.88 (m, 2H), 6.42 (dd, 1H, *J* = 1.27, 6.20 Hz), 7.21-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 55.7, 68.3, 73.4, 73.5, 74.1, 74.4, 75.3, 76.6, 79.9, 99.3, 127.6-128.3, 137.9, 138.1, 144.9; CHNS Anal. Calcd for $C_{37}H_{38}O_6$: C, 75.80; H, 6.64; O, 17.56; Found: C, 75.44; H, 6.88; MALDI-TOF: mol wt calcd for $C_{23}H_{24}O_4$: 364.43; Found 387.54 (M^+ + 23 for Na).

Methyl 4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside (5):



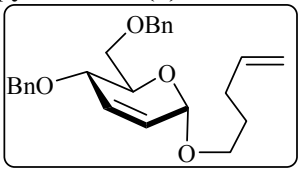
$[\alpha]_D^{25}$ = +77.43 (*c*, 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 200.13 MHz): δ 3.44 (s, 3H), 3.73 (d, 2H, *J* = 3.10 Hz), 3.89-3.97 (m, 1H), 4.15-4.21 (m, 1H), 4.41-4.69 (m, 4H), 4.91 (d, 1H, *J* = 2.11 Hz), 5.77 (ddd, 1H, *J* = 1.95, 2.66 Hz), 6.07 (dt, 1H, *J* = 1.38, 10.37 Hz), 7.22-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 55.8, 68.9, 69.2, 70.4, 71.0, 73.4, 95.7, 126.5, 127.6-128.4, 130.8, 138.1, 138.2; CHNS Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11; O, 18.80; Found: C, 74.36; H, 7.48; MALDI-TOF: mol wt calcd for $C_{21}H_{24}O_4$: 340.41; Found 363.78 (M^+ + 23 for Na).

Benzyl 4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside (6):



$[\alpha]_D^{25}$ = +52.92 (*c*, 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 200.13 MHz): δ 3.63 (dd, 1H, *J* = 2.10, 10.57 Hz), 3.73 (dd, 1H, *J* = 3.40, 10.66 Hz), 3.97-4.04 (m, 1H), 4.16-4.23 (m, 1H), 4.41-4.68 (m, 5H), 4.81 (d, 1H, *J* = 11.74 Hz), 5.12 (s, 1H), 5.80 (ddd, 1H, *J* = 1.89, 2.65 Hz), 6.08 (dt, 1H, *J* = 1.36, 10.34 Hz), 7.24-7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 68.9, 69.4, 70.0, 70.4, 71.0, 73.4, 93.9, 126.6, 127.6-128.4, 130.8, 138.1, 138.1, 138.2; CHNS Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78; O, 15.37; Found: C, 77.34; H, 6.37; MALDI-TOF: mol wt calcd for $C_{27}H_{28}O_4$: 416.51; Found 439.27 (M^+ + 23 for Na).

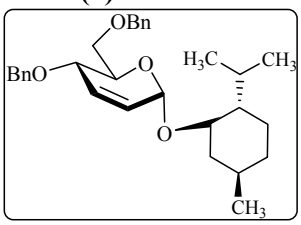
4-Pent-1-enyl 4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside (7):



$[\alpha]_D^{25}$ = +57.89 (*c*, 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.59-1.76 (m, 2H), 2.05-2.17 (m, 2H), 3.44-3.55 (m, 1H), 3.67-3.86 (m, 3H), 3.92-3.99 (m, 1H), 4.14-4.21 (m, 1H), 4.40-4.68 (m, 4H), 4.90-5.05 (m, 3H), 5.70-5.90 (m, 2H), 6.08 (dt, 1H, *J* = 1.37, 10.35 Hz), 7.21-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 29.0, 30.3, 67.9, 69.0, 69.2, 70.4, 71.0, 73.4, 94.6, 114.7,

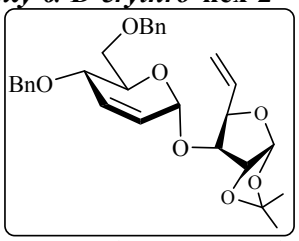
126.7, 127.6-128.4, 130.5, 138.1, 138.2, 138.2; CHNS Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66; O, 16.22; Found: C, 75.20; H, 7.43; Calcd mass for $C_{25}H_{30}O_4$: 394.50; Found 417.62 (M^+ + 23 for Na).

Menthyl 4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside (8):



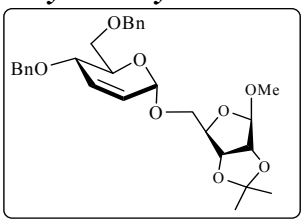
$[\alpha]_D^{25}$ = +27.44 (*c*, 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.77 (d, 3H, *J* = 6.92 Hz), 0.82 (d, 3H, *J* = 6.56 Hz), 0.89 (d, 3H, *J* = 7.01 Hz), 0.98-1.09 (m, 2H), 1.28-1.43 (m, 3H), 1.62-1.65 (m, 2H), 2.02-2.25 (m, 2H), 3.42 (td, 1H, *J* = 4.59, 10.59 Hz), 3.67-3.74 (m, 2H), 3.98-4.06 (m, 1H), 4.13-4.19 (m, 1H), 4.39-4.70 (m, 4H), 5.09 (d, 1H, *J* = 2.02 Hz), 5.81 (ddd, 1H, *J* = 1.89, 2.64 Hz), 6.06 (dt, 1H, *J* = 1.30, 10.21 Hz), 7.20-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 16.3, 21.2, 22.2, 23.2, 25.6, 31.7, 34.3, 43.4, 48.9, 68.9, 69.0, 70.5, 70.9, 73.4, 80.3, 96.3, 126.8, 127.6-128.3, 130.2, 138.2, 138.2; CHNS Anal. Calculated for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68; O, 13.77; Found: C, 77.87; H, 8.93; Calcd mass for $C_{30}H_{40}O_4$: 464.64; Found 487.47 (M^+ + 23 for Na).

1,2-*O*-isopropylidene-5,6-di-*deoxy*-3-*O*-(4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside)-*α*-D-*xylo*-hex-5-enofuranose (9):



$[\alpha]_D^{25}$ = +47.69 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.22 (s, 3H), 1.50 (s, 3H), 3.45 (d, 1H, *J* = 5.56 Hz), 3.63-3.78 (m, 2H), 3.90-4.00 (m, 1H), 4.04-4.11 (m, 1H), 4.20 (d, 1H, *J* = 2.92 Hz), 4.39-4.69 (m, 4H), 4.78 (d, 1H, *J* = 3.64 Hz), 5.04 (d, 1H, *J* = 2.14 Hz), 5.25-5.48 (m, 2H), 5.72 (ddd, 1H, *J* = 1.85, 2.66 Hz), 5.82-5.99 (m, 2H), 6.07 (dt, 1H, *J* = 1.19, 10.20 Hz), 7.21-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 26.1, 26.8, 69.2, 69.7, 70.4, 71.0, 73.5, 81.2, 82.9, 84.2, 95.6, 104.8, 111.5, 119.3, 125.8, 127.6-128.4, 130.7, 132.2, 137.9, 138.1; CHNS Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43; H, 6.93; O, 22.64; Found: C, 70.78; H, 6.72; Calcd mass for $C_{29}H_{34}O_7$: 494.58; Found 517.96 (M^+ + 23 for Na).

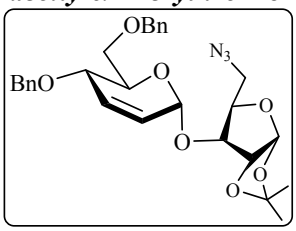
Methyl 2,3-*O*-isopropylidene-5-*O*-(4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside)-*β*-D-ribofuranoside (10):



$[\alpha]_D^{25}$ = +22.08 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.30 (s, 3H), 1.46 (s, 3H), 3.29 (s, 3H), 3.31-3.32 (m, 1H), 3.44-3.54 (m, 2H), 3.72-3.86 (m, 2H), 3.89-3.97 (m, 1H), 4.17-4.24 (m, 1H), 4.34-4.40 (m, 1H), 4.46-4.71 (m, 5H), 4.95 (s, 1H), 5.04 (d, 1H, *J* = 2.03 Hz), 5.72 (ddd, 1H, *J* = 2.01, 2.64 Hz), 6.06 (dt, 1H, *J* = 1.24, 10.19 Hz), 7.21-7.36 (m, 10H); ^{13}C NMR

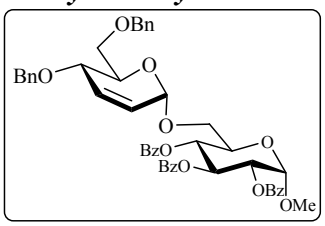
($CDCl_3$, 50.32 MHz): δ 25.0, 26.5, 54.8, 68.7, 69.4, 69.5, 70.2, 71.2, 73.4, 82.2, 85.2, 85.3, 95.4, 109.3, 112.3, 126.2, 127.6-128.5, 130.8, 138.0, 138.2; CHNS Anal. Calculated for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08; O, 24.97; Found: C, 68.23; H, 7.25; Calcd mass for $C_{29}H_{36}O_8$: 512.59; Found 535.75 (M^+ + 23 for Na).

1,2-*O*-isopropylidene-5-*deoxy*-5-azido-3-*O*-(4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside)-*α*-D-xylofuranose (11):



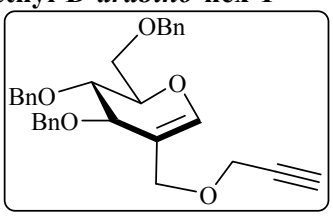
$[\alpha]_D^{25}$ = +34.54 (*c*, 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.15 (s, 3H), 1.47 (s, 3H), 3.44-3.76 (m, 4H), 3.99 (d, 1H, *J* = 2.15 Hz), 4.18 (d, 1H, *J* = 3.03 Hz), 4.21-4.37 (m, 1H), 4.40-4.65 (m, 5H), 4.98 (d, 1H, *J* = 3.62 Hz), 5.11 (d, 1H, *J* = 2.03 Hz), 5.75 (dd, 1H, *J* = 2.32, 10.26 Hz), 5.84 (d, 1H, *J* = 3.53 Hz), 6.09 (d, 1H, *J* = 10.18 Hz), 7.21-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 26.0, 26.8, 49.0, 69.3, 69.9, 70.4, 71.1, 73.5, 78.3, 82.2, 83.4, 96.4, 105.0, 111.8, 125.9, 127.7-128.4, 130.8, 137.7, 138.0; CHNS Anal. Calculated for $C_{28}H_{33}N_3O_7$: C, 64.23; H, 6.35; N, 8.03; O, 21.39; Found: C, 64.47; H, 6.45; N, 7.98; Calcd mass for $C_{28}H_{33}N_3O_7$: 523.58; Found 546.23 (M^+ + 23 for Na).

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(4,6-di-*O*-benzyl-2,3-di-*deoxy*-*α*-D-*erythro*-hex-2-enopyranoside)-*α*-D-glucopyranoside (12):



$[\alpha]_D^{25}$ = +75.58 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 3.45 (s, 3H), 3.47-3.51 (m, 1H), 3.60 (dd, 1H, *J* = 3.44, 10.66 Hz), 3.70 (dd, 1H, *J* = 4.11, 10.86 Hz), 3.90 (d, 1H, *J* = 8.87 Hz), 4.03 (dd, 1H, *J* = 4.14, 10.86 Hz), 4.18-4.26 (m, 2H), 4.23 (d, 1H, *J* = 12.15 Hz), 4.42-4.60 (m, 3H), 5.03 (s, 1H), 5.23 (s, 1H), 5.22-5.27 (m, 1H), 5.60-5.72 (m, 2H), 6.03 (d, 1H, *J* = 10.37 Hz), 6.11(t, 1H, *J* = 9.62 Hz), 7.26-7.99 (m, 25H); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 55.6, 66.4, 68.4, 68.5, 69.2, 69.5, 70.1, 70.7, 70.9, 72.2, 73.3, 94.8, 97.1, 126.0, 127.5-130.0, 131.3, 133.0, 133.2, 133.3, 138.1, 138.3, 165.0, 165.8, 165.8; CHNS Anal. Calculated for $C_{48}H_{46}O_{12}$: C, 70.75; H, 5.69; O, 23.56; Found: C, 70.81; H, 5.83; Calcd mass for $C_{48}H_{46}O_{12}$: 814.87; Found 837.93 (M^+ + 23 for Na).

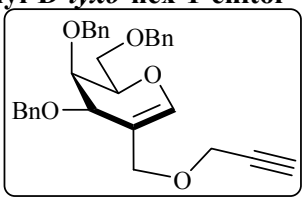
1,5-Anhydro-3,4,6-tri-*O*-benzyl-1,2-di-*deoxy*-2-propargyloxymethyl-D-*arabino*-hex-1-enitol (13):



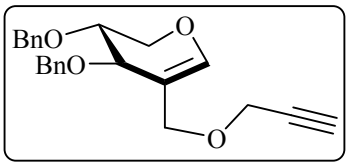
$[\alpha]_D^{25}$ = +69.20 (*c*, 2.00, $CHCl_3$); IR ($CHCl_3$): 3286.48, 2864.09, 1666.38, 1454.23, 1070.42 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.38 (t, 1H, *J* = 2.39 Hz), 3.74 (dt, 2H, *J* = 3.77, 5.22 Hz), 3.86 (d, 1H, *J* = 11.36 Hz), 3.90 (dd, 1H, *J* =

5.22, 6.54 Hz), 4.08 (t, 2H, *J* = 2.39 Hz), 4.14–4.32 (m, 3H), 4.53 (s, 2H), 4.64 (s, 2H), 4.67 (ABq, 2H, *J* = 11.68 Hz), 6.51 (s, 1H), 7.22–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): 55.6, 66.9, 67.9, 72.6, 72.8, 73.2, 73.5, 73.9, 74.3, 76.4, 79.7, 108.6, 127.4–128.3, 137.7, 137.8, 138.2, 144.3; CHNS Anal. Calculated for $C_{31}H_{32}O_5$: C, 76.84; H, 6.66; O, 16.51; Found: C, 76.99; H, 6.82; Calcd mass for $C_{31}H_{32}O_5$: 484.58; Found, 507.05 (M^+ + 23 for Na).

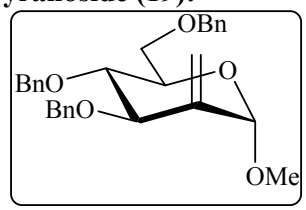
1,5-Anhydro-3,4,6-tri-*O*-benzyl-1,2-di-*deoxy*-2-propargyloxymethyl-D-*lyxo*-hex-1-enitol (14): $[\alpha]_D^{25}$ = +39.01 (*c*, 1.10, $CHCl_3$); IR ($CHCl_3$): 3292.48, 2863.23, 1667.32 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.33 (t, 1H, *J* = 2.32 Hz), 3.64-3.79 (m, 3H), 3.92 (t, 1H, *J* = 3.35 Hz), 3.97 (d, 2H, *J* = 2.16 Hz), 4.42-4.33 (m, 3H), 4.42 (d, 2H, *J* = 10.62 Hz), 4.50-4.65 (m, 2H), 4.75 (d, 2H, *J* = 11.97 Hz), 6.39 (s, 1H), 7.25-7.33 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): 55.9, 67.1, 67.8, 70.8, 72.0, 72.8, 73.0, 73.2, 74.2, 75.4, 79.7, 109.0, 127.2–128.0, 137.7, 137.9, 138.4, 143.4; CHNS Anal. Calculated for $C_{31}H_{32}O_5$: C, 76.84; H, 6.66; O, 16.51; Found: C, 76.62; H, 6.80; Calcd mass for $C_{31}H_{32}O_5$: 484.58; Found, 507.17 (M^+ + 23 for Na).



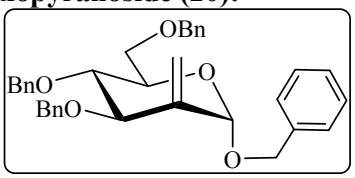
1,5-anhydro-2-*deoxy*-3,4-di-*O*-(benzyl)-2-propargyloxy-methyl-α-D-*threo*-pent-1-enitol (15): $[\alpha]_D^{25}$ = -4.12 (*c*, 1.00, $CHCl_3$); IR ($CHCl_3$): 3287.84, 2893.32 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.40 (t, 1H, *J* = 2.39 Hz), 3.64–3.68 (m, 1H), 3.89 (d, 1H, *J* = 11.60 Hz), 3.91 (dd, 1H, *J* = 1.65, 12.11 Hz), 4.06 (t, 2H, *J* = 2.08 Hz), 4.13–4.22 (m, 3H), 4.58 (d, 4H, *J* = 4.09 Hz), 6.62 (s, 1H), 7.25–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): 55.4, 63.7, 67.8, 69.2, 71.0, 71.5, 72.0, 74.2, 79.9, 107.5, 127.7–128.5, 137.8, 138.2, 146.3; CHNS Anal. Calculated for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64; O, 17.56; Found: C, 75.63; H, 6.79; Calcd mass for $C_{23}H_{24}O_4$: 364.43; Found, 387.70 (M^+ + 23 for Na).



Methyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-α-D-*xylo*-hexopyranoside (19): $[\alpha]_D^{25}$ = +28.85 (*c*, 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.38 (s, 3H), 3.61 (t, 1H, *J* = 9.42 Hz), 3.70–3.75 (m, 2H), 3.92 (m, 1H), 4.40–4.90 (m, 7H), 5.06 (s, 1H), 5.16 (dd, 1H, *J* = 1.25, 2.00 Hz), 5.30 (dd, 1H, *J* = 1.25, 2.00 Hz), 7.10–7.42 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): 54.4, 68.8, 71.5, 73.4, 73.4, 74.9, 80.0, 81.2, 102.4, 110.7, 127.5–128.4, 138.1, 138.2, 138.3, 142.4; CHNS Anal. Calculated for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00; O, 17.37; Found: C, 75.48; H, 6.87; Calcd mass for $C_{29}H_{32}O_5$: 460.56; Found 483.06 (M^+ + 23 for Na).

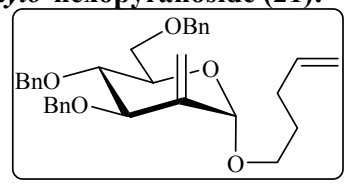


Benzyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside (20):



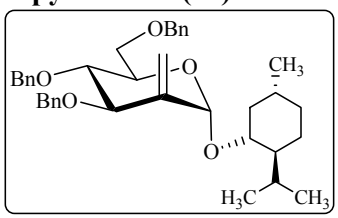
$[\alpha]_D^{25}$ = +37.97 (*c*, 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.58-3.68 (m, 2H), 3.73 (dd, 1H, *J* = 3.94, 10.58 Hz), 4.00 (ddd, 1H, *J* = 2.10, 3.75 Hz), 4.44-4.61 (m, 5H), 4.66-4.80 (m, 3H), 4.87 (d, 1H, *J* = 10.68 Hz), 5.13 (dd, 1H, *J* = 1.31, 1.99 Hz), 5.26 (s, 1H), 5.30 (dd, 1H, J = 1.31, 1.99 Hz), 7.08–7.43 (m, 20H); ^{13}C NMR (CDCl3, 50.32 MHz): 68.8, 68.9, 71.8, 73.4, 73.5, 75.0, 80.1, 81.3, 100.8, 110.8, 127.4–128.4, 137.5, 138.2, 138.3, 138.4, 142.3; CHNS Anal. Calculated for $C_{35}H_{36}O_5$: C, 78.33; H, 6.76; O, 14.91; Found: C, 78.28; H, 6.81; Calcd mass for $C_{35}H_{36}O_5$: 536.66; Found 559.04 (M^+ + 23 for Na).

4-Pent-1-enyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside (21):



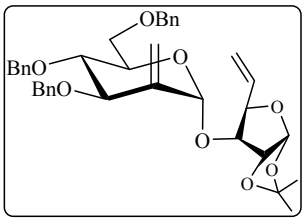
$[\alpha]_D^{25}$ = +34.26 (*c*, 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.60-1.76 (m, 2H), 2.06-2.17 (m, 2H), 3.39-3.80 (m, 5H), 3.95 (ddd, 1H, *J* = 2.01, 3.67 Hz), 4.41-4.68 (m, 3H), 4.74 (d, 2H, *J* = 4.13 Hz), 4.81-5.07 (m, 4H), 5.14 (s, 2H), 5.29 (t, 1H, *J* = 1.26 Hz), 5.74-5.98 (m, 1H), 7.13-7.41 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 28.7, 30.3, 66.6, 68.8, 71.6, 73.4, 73.4, 74.9, 80.1, 81.2, 101.4, 110.3, 114.8, 127.5-128.4, 138.0, 138.1, 138.3, 138.3, 142.6; CHNS Anal. Calculated for $C_{33}H_{38}O_5$: C, 77.01; H, 7.44; O, 15.54; Found: C, 76.87; H, 7.58; Calcd mass for $C_{33}H_{38}O_5$: 514.65; Found 537.39 (M^+ + 23 for Na).

Menthyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside (22):



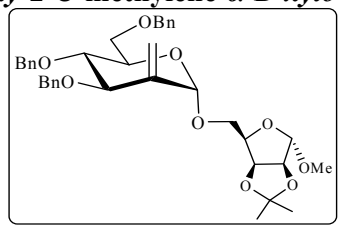
$[\alpha]_D^{25}$ = +17.62 (*c*, 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.77 (d, 3H, *J* = 6.91 Hz), 0.85 (d, 3H, *J* = 6.64 Hz), 0.89 (d, 3H, *J* = 7.05 Hz), 0.95-1.26 (m, 4H), 1.57-1.65 (m, 3H), 1.98-2.18 (m, 2H), 3.38 (td, 1H, *J* = 4.41, 10.59 Hz), 3.54-3.70 (m, 2H), 3.77 (dd, 1H, *J* = 4.02, 10.51 Hz), 4.11 (dd, 1H, *J* = 2.01, 3.63 Hz), 4.40 (t, 1H, *J* = 1.81 Hz), 4.45 (d, 1H, *J* = 1.26 Hz), 4.50 (d, 1H, *J* = 2.90 Hz), 4.65 (d, 1H, *J* = 12.10 Hz), 4.74 (d, 2H, *J* = 3.48 Hz), 4.87 (d, 1H, *J* = 10.69 Hz), 5.03 (t, 1H, *J* = 1.68 Hz), 5.20 (s, 1H), 5.21 (s, 1H), 7.12-7.42 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 16.4, 21.0, 22.2, 23.4, 25.8, 31.7, 34.3, 43.0, 48.7, 69.0, 71.6, 73.4, 73.4, 74.9, 80.2, 80.5, 81.3, 103.3, 109.1, 127.5-128.4, 138.2, 138.4, 138.4, 142.9; CHNS Anal. Calculated for $C_{38}H_{48}O_5$: C, 78.05; H, 8.27; O, 13.68; Found: C, 78.21; H, 8.42; Calcd mass for $C_{38}H_{48}O_5$: 584.78; Found 607.63 (M^+ + 23 for Na).

1,2-*O*-isopropylidene 5,6-di-*deoxy*-3-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside)-*α*-D-xylo-hex-5-enofuranose (23):



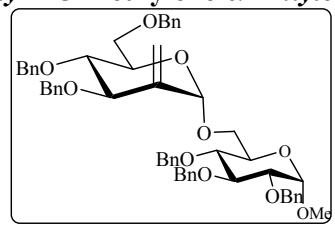
$[\alpha]_D^{25}$ = +17.06 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.50 (s, 3H), 1.56 (s, 3H), 3.55-3.62 (m, 1H), 3.70 (dd, 1H, *J* = 1.92, 10.41 Hz), 3.74 (dd, 1H, *J* = 3.93, 10.68 Hz), 3.93-3.97 (m, 1H), 4.10-4.16 (m, 1H), 4.19 (d, 1H, *J* = 2.62 Hz), 4.31-4.38 (m, 1H), 4.46-4.53 (m, 2H), 4.59-4.76 (m, 4H), 4.85 (d, 1H, *J* = 10.75 Hz), 5.10 (s, 1H), 5.21 (s, 1H), 5.27-5.32 (m, 2H), 5.44 (dd, 1H, *J* = 17.37 Hz), 5.78-5.93 (m, 2H), 7.14-7.39 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 26.1, 26.8, 68.9, 72.4, 73.4, 73.5, 75.0, 79.8, 80.8, 81.4, 81.6, 84.0, 101.9, 104.8, 113.3, 111.62, 119.7, 127.5-128.5, 132.2, 138.0, 138.1, 138.2, 141.4; CHNS Anal. Calculated for $C_{37}H_{42}O_8$: C, 72.29; H, 6.89; O, 20.82; Found: C, 72.43; H, 6.97; Calcd mass for $C_{37}H_{42}O_8$: 614.72; Found 637.03 (M^+ + 23 for Na).

Methyl 2,3-*O*-isopropylidene-5-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside)-*α*-D-lyxofuranoside (24):



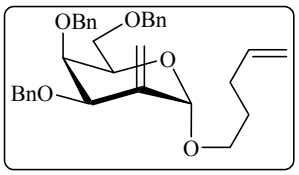
$[\alpha]_D^{25}$ = +37.24 (*c*, 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 Hz): δ 1.30, 1.42 (2s, 6H), 3.31 (s, 3H), 3.48–3.91 (m, 5H), 4.08 (m, 2H), 4.41–4.92 (m, 10H), 5.16 (dd, 1H, *J* = 1.26, 1.87 Hz), 5.23 (s, 1H), 5.30 (dd, 1H, *J* = 1.26, 1.87 Hz), 7.12–7.42 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 25.0, 26.1, 54.6, 64.8, 68.7, 71.6, 73.3, 73.4, 74.9, 78.1, 79.7, 80.0, 81.1, 84.9, 101.4, 107.1, 110.7, 112.5, 127.5–128.4, 138.1, 138.2, 138.4, 142.3; CHNS Anal. Calculated for $C_{37}H_{44}O_9$: C, 70.23; H, 7.01; O, 22.76; Found: C, 70.41; H, 6.97; Calcd mass for $C_{37}H_{44}O_9$: 632.74; Found, 655.84 (M^+ + 23 for Na).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*xylo*-hexopyranoside)-*α*-D-glucopyranoside (26):



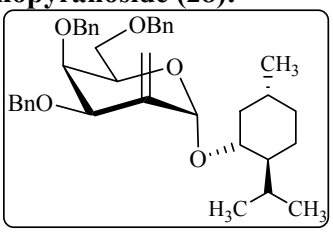
$[\alpha]_D^{25}$ = +36.09 (*c*, 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.34 (s, 3H), 3.45-4.10 (m, 10H), 4.35-5.02 (m, 14H), 5.11 (s, 1H), 5.21 (s, 1H), 5.24-5.27 (m, 1H), 7.19-7.34 (m, 30H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 55.0, 65.6, 68.6, 69.8, 71.6, 73.2, 73.3, 73.3, 73.5, 74.8, 75.7, 77.8, 79.9, 80.0, 80.8, 82.1, 97.8, 101.5, 110.7, 126.9-129.5, 138.1, 138.1, 138.2, 138.3, 138.4, 138.6, 142.1; CHNS Anal. Calculated for $C_{56}H_{60}O_{18}$: C, 75.31; H, 6.77; O, 17.92; Found: C, 75.49; H, 6.92; Calcd mass for $C_{56}H_{60}O_{10}$: 893.07; Found 916.58 (M^+ + 23 for Na).

4-Pent-1-enyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside (27):



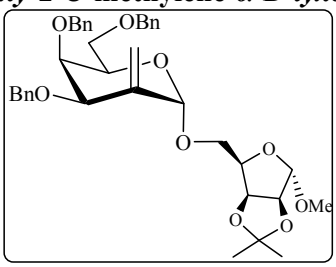
$[\alpha]_D^{25}$ = -2.23 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.59-1.75 (m, 2H), 2.04-2.14 (m, 2H), 3.37-3.85 (m, 5H), 3.98 (d, 1H, *J* = 2.34 Hz), 4.10 (t, 1H, *J* = 6.45 Hz), 4.36-4.75 (m, 4H), 4.87-5.06 (m, 4H), 5.18 (s, 1H), 5.24 (s, 1H), 5.40 (t, 1H, *J* = 1.32 Hz), 5.70-5.91 (m, 1H), 7.21-7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 28.7, 30.3, 66.7, 69.3, 70.6, 71.6, 73.4, 74.0, 75.4, 78.1, 101.5, 111.3, 114.8, 127.1-128.5, 138.0, 138.1, 138.4, 138.6, 141.0; CHNS Anal. Calculated for $C_{33}H_{38}O_5$: C, 77.01; H, 7.44; O, 15.54; Found: C, 77.20; H, 7.52; Calcd mass for $C_{33}H_{38}O_5$: 514.65; Found 537.46 (M^+ + 23 for Na).

Menthyl 3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside (28):



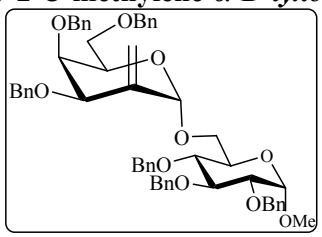
$[\alpha]_D^{25}$ = +0.02 (*c*, 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 0.76 (d, 3H, *J* = 6.82 Hz), 0.83 (d, 3H, *J* = 6.30 Hz), 0.89 (d, 3H, *J* = 6.83 Hz), 0.91-1.02 (m, 2H), 1.16-1.37 (m, 2H), 1.57-1.64 (m, 3H), 2.03-2.12 (m, 2H), 3.36 (td, 1H, *J* = 4.29, 10.59 Hz), 3.52-3.58 (m, 2H), 3.99 (d, 1H, *J* = 2.15 Hz), 4.25 (t, 1H, *J* = 6.36 Hz), 4.39-4.49 (m, 3H), 4.63 (d, 1H, *J* = 8.38 Hz), 4.65 (d, 1H, *J* = 8.38 Hz), 4.69 (d, 1H, *J* = 12.07 Hz), 4.90 (d, 1H, *J* = 12.07 Hz), 5.15 (t, 1H, *J* = 1.75 Hz), 5.25 (s, 1H), 5.34 (dd, 1H, *J* = 1.46, 1.95 Hz), 7.21-7.39 (m, 15H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 16.3, 21.1, 22.2, 23.3, 25.7, 31.7, 34.4, 42.8, 48.8, 69.5, 70.7, 71.5, 73.4, 74.0, 75.5, 78.3, 79.9, 103.3, 110.2, 127.1-128.4, 138.2, 138.5, 138.8, 141.3; CHNS Anal. Calculated for $C_{38}H_{48}O_5$: C, 78.05; H, 8.27; O, 13.68; Found: C, 78.21; H, 8.47; Calcd mass for $C_{38}H_{48}O_5$: 584.78; Found 607.30 (M^+ + 23 for Na).

Methyl 2,3-*O*-isopropylidene-5-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside)-*α*-D-lyxofuranoside (29):



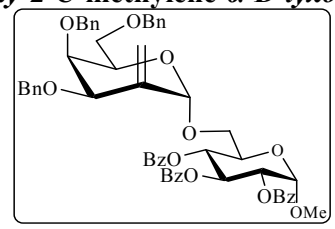
$[\alpha]_D^{25}$ = -6.01 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.13 Hz): δ 1.32, 1.48 (2s, 6H), 3.27 (s, 3H), 3.43 (t, 1H, *J* = 9.56 Hz), 3.55 (d, 2H, *J* = 6.40 Hz), 3.70-3.78 (m, 2H), 3.99 (d, 1H, *J* = 2.03 Hz), 4.12 (t, 1H, *J* = 6.35 Hz), 4.33 (dd, 1H, *J* = 5.44, 9.08 Hz), 4.38-4.51 (m, 3H), 4.57 (d, 1H, *J* = 5.89 Hz), 4.61-4.71 (m, 3H), 4.89 (d, 1H, *J* = 12.02 Hz), 4.95 (s, 1H), 5.19 (s, 1H), 5.24 (s, 1H), 5.41 (s, 1H), 7.21–7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 25.0, 26.4, 54.9, 68.4, 69.1, 70.8, 71.6, 73.4, 74.1, 75.3, 78.0, 82.2, 85.0, 85.2, 102.1, 109.3, 111.7, 112.3, 127.1–128.4, 138.0, 138.3, 138.6, 140.6; CHNS Anal. Calculated for $C_{37}H_{44}O_9$: C, 70.23; H, 7.01; O, 22.76; Found: C, 70.04; H, 6.84; Calcd mass for $C_{37}H_{44}O_9$: 632.74; Found, 655.08 (M^+ + 23 for Na).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside)-*α*-D-glucopyranoside (30):



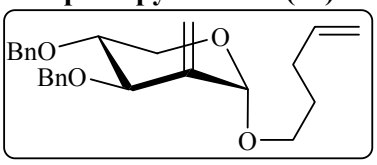
$[\alpha]_D^{25}$ = +32.10 (*c*, 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.30 (s, 3H), 3.44-3.53 (m, 4H), 3.67-3.82 (m, 3H), 3.92-3.12 (m, 3H), 4.35 (d, 2H, *J* = 4.73 Hz), 4.49-5.00 (m, 12H), 5.21 (s, 1H), 5.24 (s, 1H), 5.37 (s, 1H), 7.18-7.35 (m, 30H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 55.0, 65.9, 69.1, 69.8, 70.7, 71.3, 73.3, 73.3, 74.0, 74.9, 75.8, 75.3, 75.8, 77.5, 78.0, 82.0, 97.7, 101.7, 111.4, 127.1-128.4, 138.0, 138.1, 138.2, 138.2, 138.6, 138.6, 140.6; CHNS Anal. Calculated for $C_{56}H_{60}O_{10}$: C, 75.31; H, 6.77; O, 17.92; Found: C, 75.45; H, 6.62; Calcd mass for $C_{56}H_{60}O_{10}$: 893.07; Found 916.87 (M^+ + 23 for Na).

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*deoxy*-2-*C*-methylene-*α*-D-*lyxo*-hexopyranoside)-*α*-D-glucopyranoside (31):



$[\alpha]_D^{25}$ = +33.42 (*c*, 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 3.37 (s, 3H), 3.35-3.42 (m, 2H), 3.64 (dd, 1H, *J* = 2.44, 11.00 Hz), 3.90 (dd, 1H, *J* = 5.15, 11.24 Hz), 3.93 (d, 1H, *J* = 2.00 Hz), 4.05 (t, 1H, *J* = 6.48 Hz), 4.21-4.24 (m, 1H), 4.24 (d, 1H, *J* = 11.72 Hz), 4.31 (d, 1H, *J* = 12.00 Hz), 4.43 (d, 1H, *J* = 2.23 Hz), 4.59-4.62 (m, 2H), 4.67 (d, 1H, *J* = 12.01 Hz), 4.87 (d, 1H, *J* = 11.72 Hz), 5.19 (d, 1H, *J* = 3.72 Hz), 5.21 (s, 1H), 5.24-5.29 (m, 2H), 5.38 (t, 1H, *J* = 1.72 Hz), 5.60 (t, 1H, *J* = 9.91 Hz), 6.12 (d, 1H, *J* = 9.78 Hz), 7.18-7.99 (m, 30H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 55.4, 65.7, 68.2, 69.1, 69.5, 70.6, 70.7, 71.5, 72.0, 73.1, 74.0, 75.4, 77.8, 96.9, 101.6, 111.9, 127.2-129.9, 133.0, 133.3, 133.3, 138.1, 138.5, 138.6, 140.4, 165.3, 165.8, 165.8; CHNS Anal. Calculated for $C_{56}H_{54}O_{13}$: C, 71.93; H, 5.82; O, 22.24; Found: C, 71.79; H, 5.68; Calcd mass for $C_{56}H_{54}O_{13}$: 935.02; Found 958.20 (M^+ + 23 for Na).

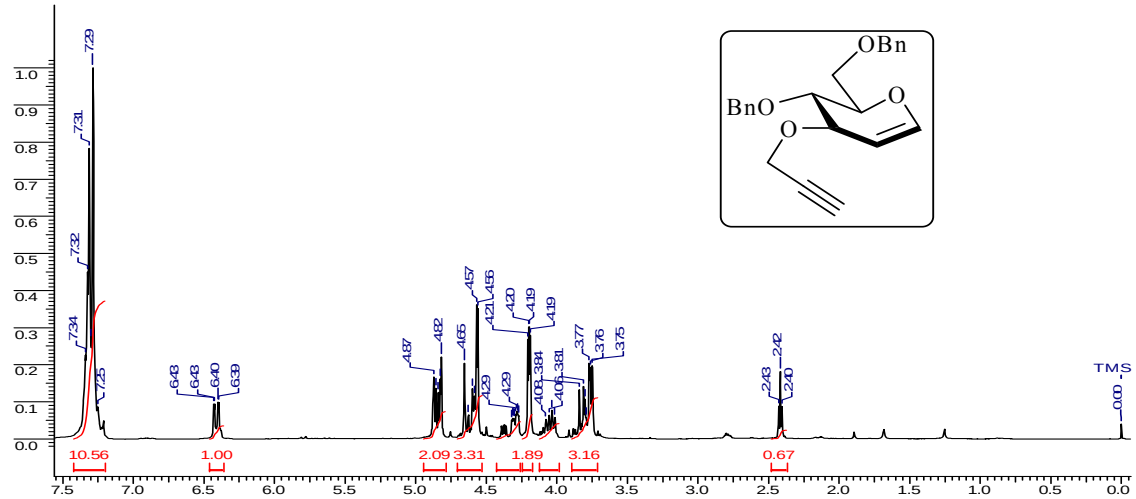
4-Pent-1-enyl 2-*deoxy*-2-*C*-methylene-3,4-di-*O*-benzyl-*α*-D-*threo*-pentopyranoside (32):



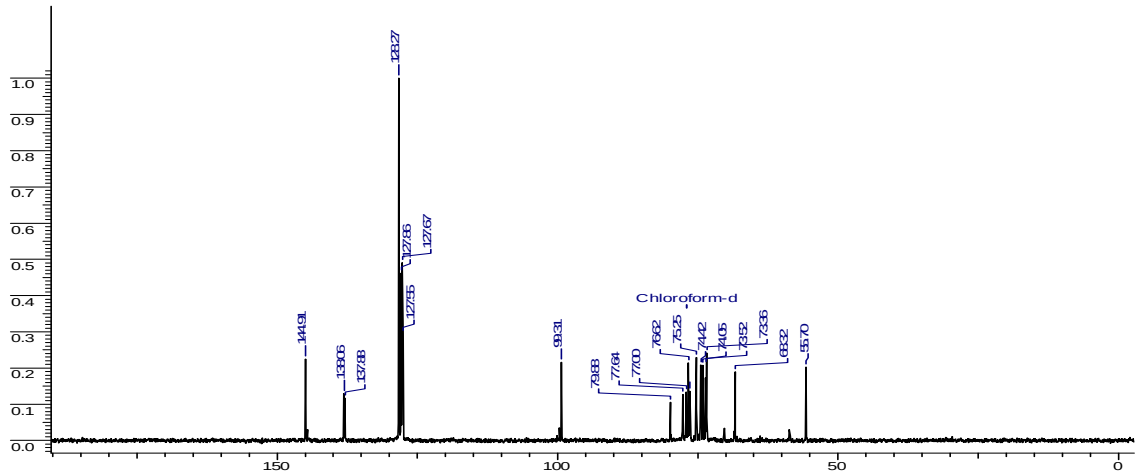
$[\alpha]_D^{25}$ = +83.06 (*c*, 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.62-1.76 (m, 2H), 2.07-2.18 (m, 2H), 3.30-3.55 (m, 2H), 3.73-4.15 (m, 6H), 4.59-4.61 (m, 2H), 4.91-5.00 (m, 3H), 5.06 (d, 1H, *J* = 1.46 Hz), 5.72-6.02 (m, 2H), 7.26-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 28.9, 30.3, 61.3, 67.7, 67.8, 69.9, 70.1, 70.6, 93.9, 114.7, 114.9, 122.1, 127.6-128.4, 138.1, 138.2, 138.7; CHNS Anal. Calculated for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66; O, 16.22; Found: C, 76.37; H, 7.80; Calcd mass for $C_{25}H_{30}O_4$: 394.50; Found 417.81 (M^+ + 23 for Na).

*****

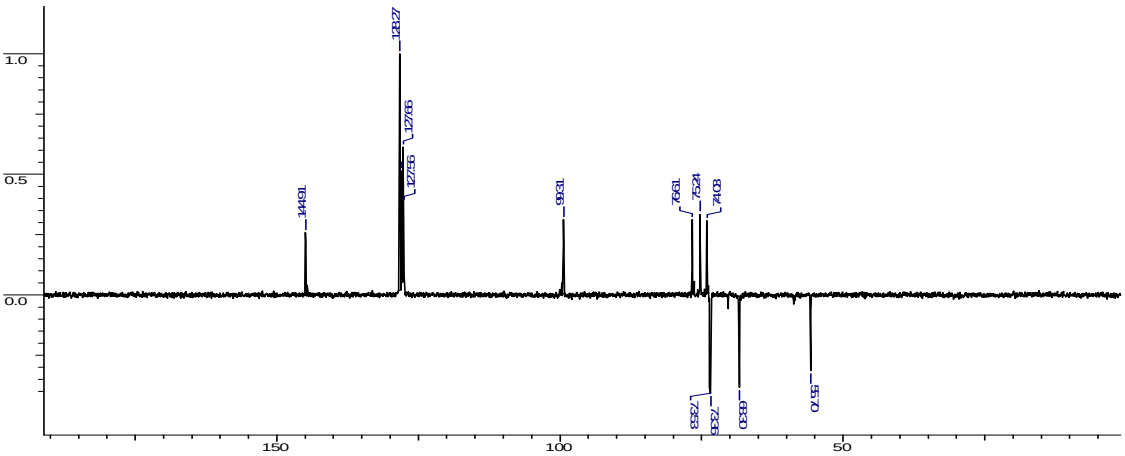
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **3**



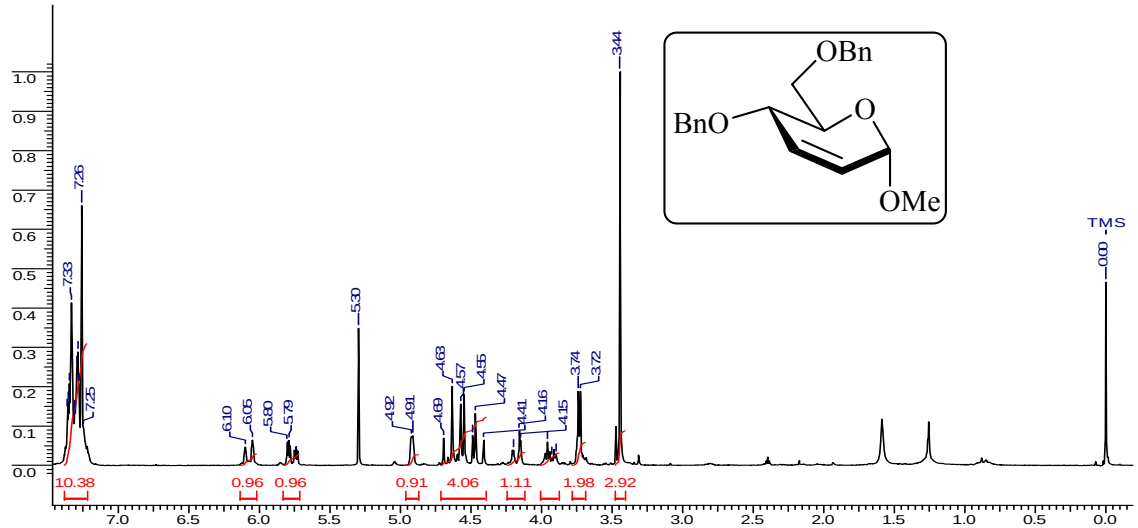
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **3**



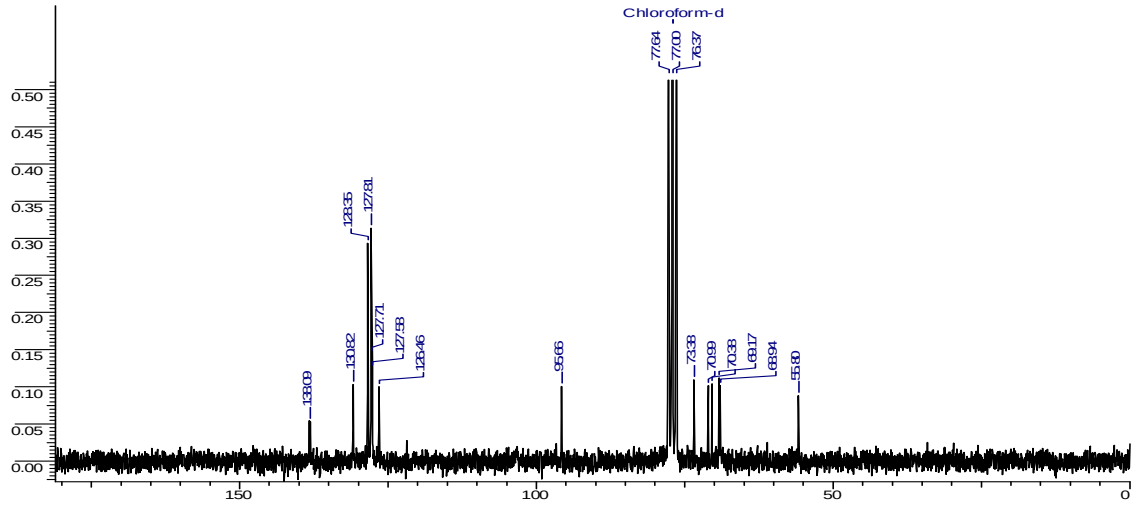
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **3**



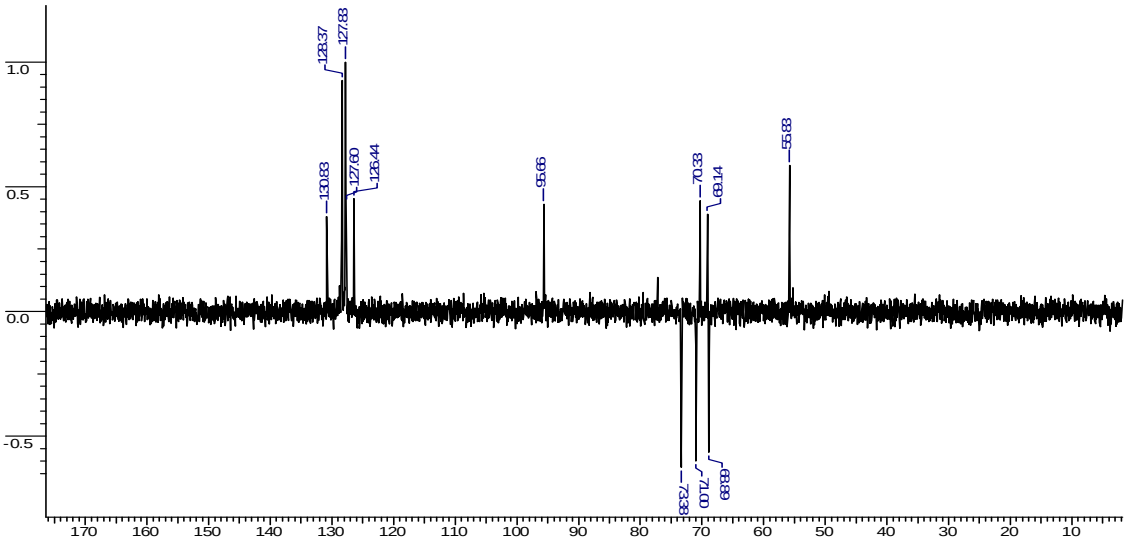
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **5**



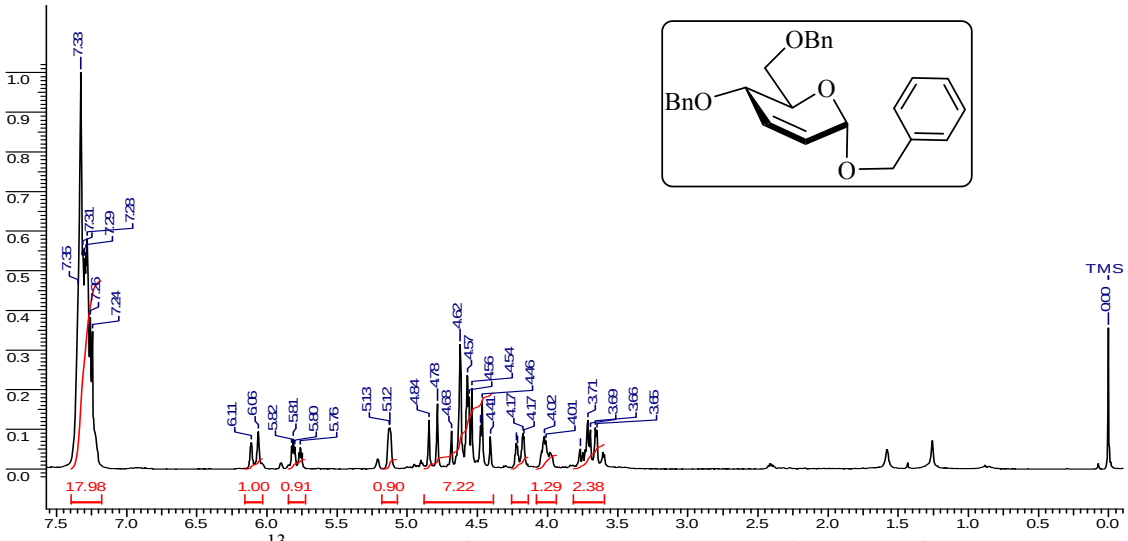
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **5**



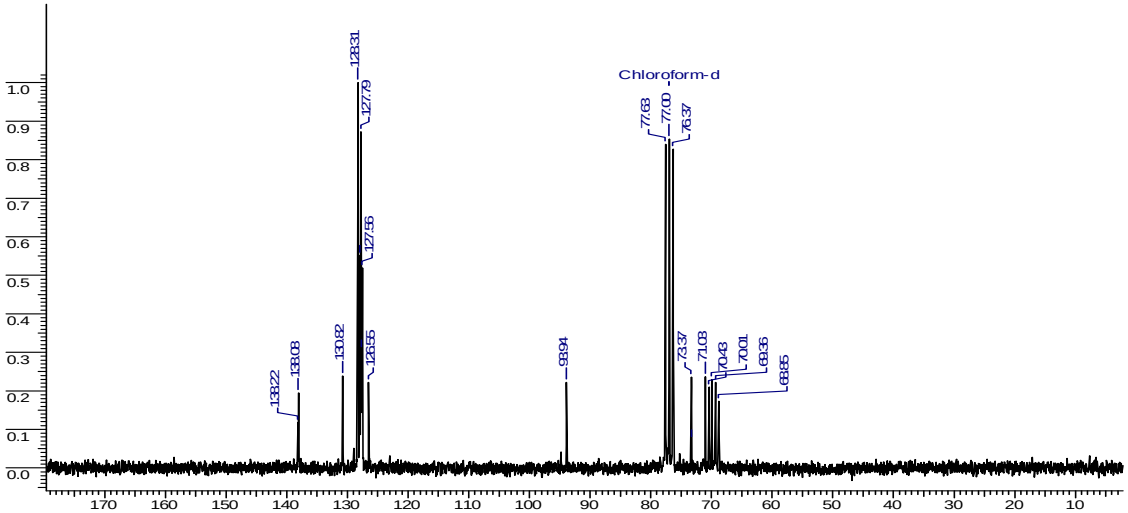
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **5**



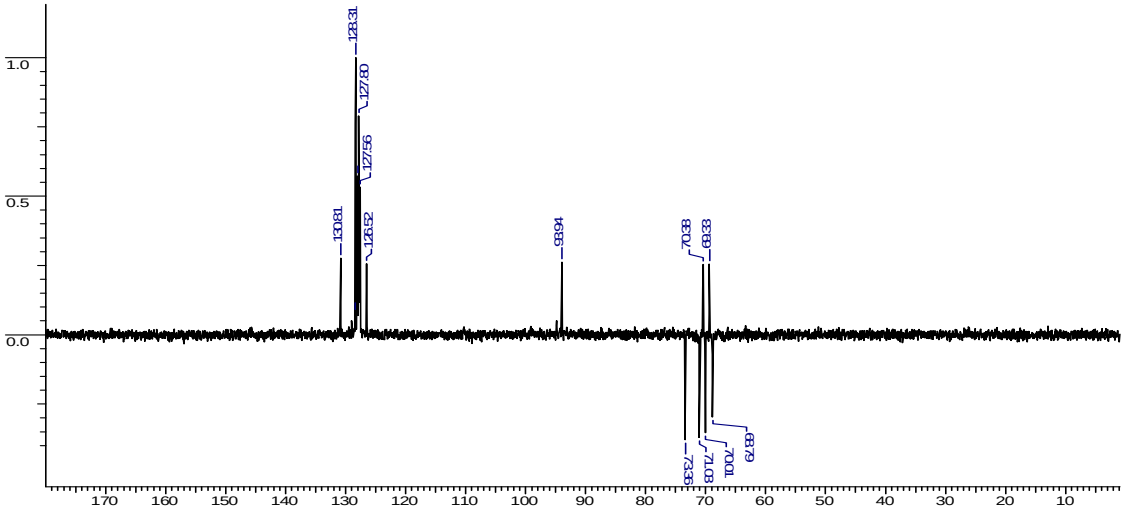
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **6**



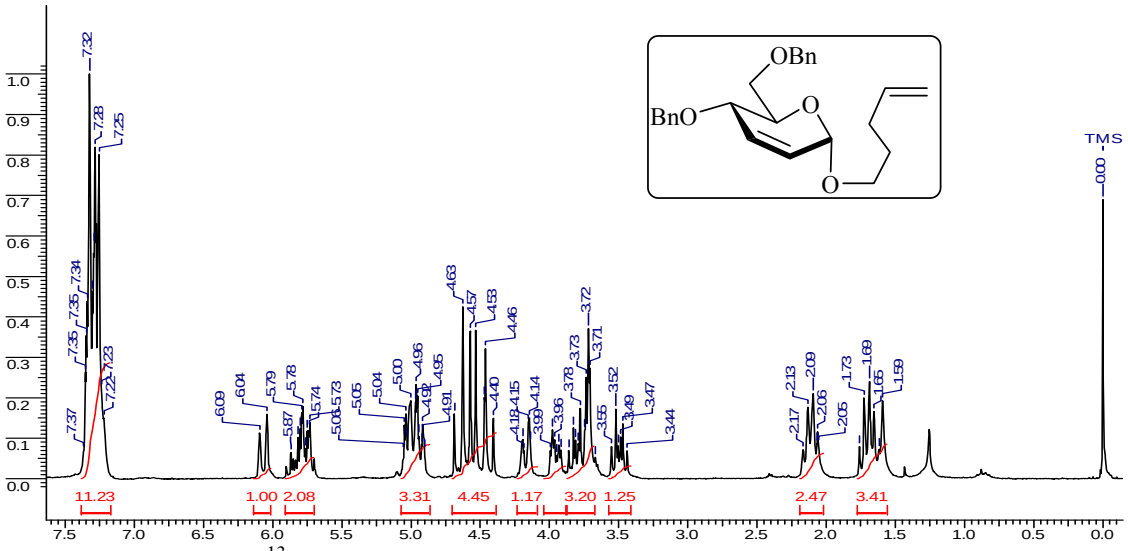
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **6**



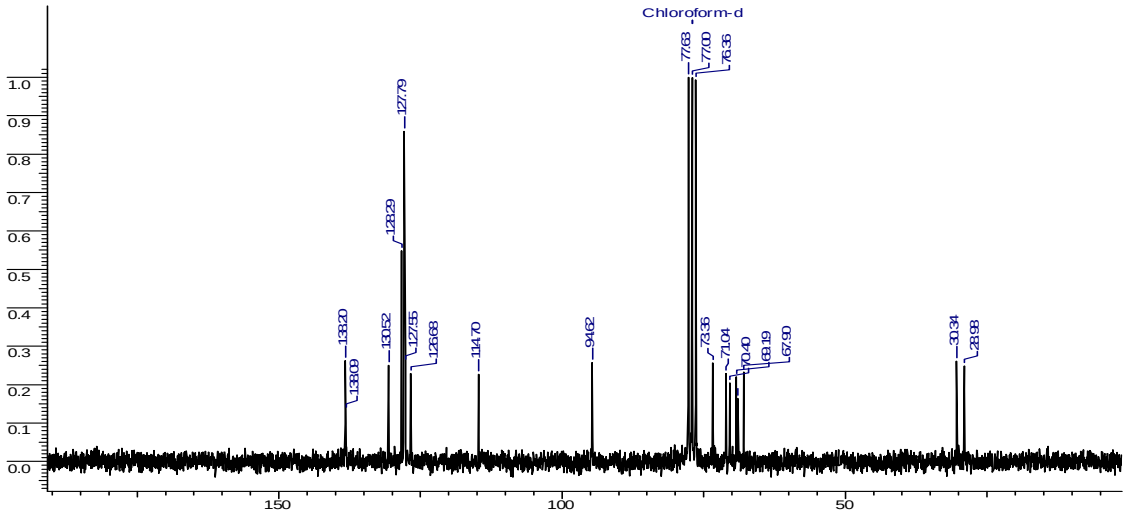
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **6**



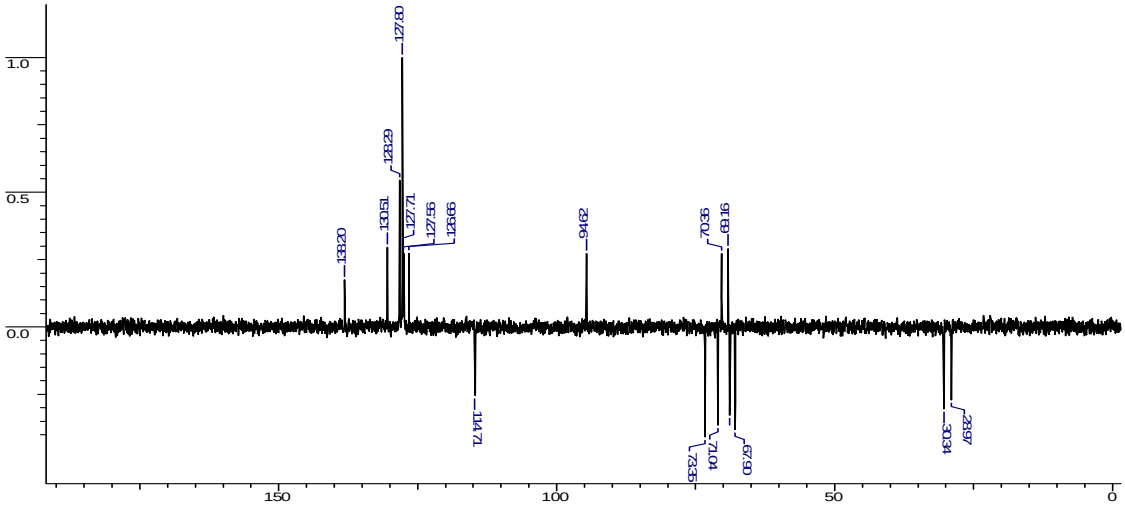
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **7**



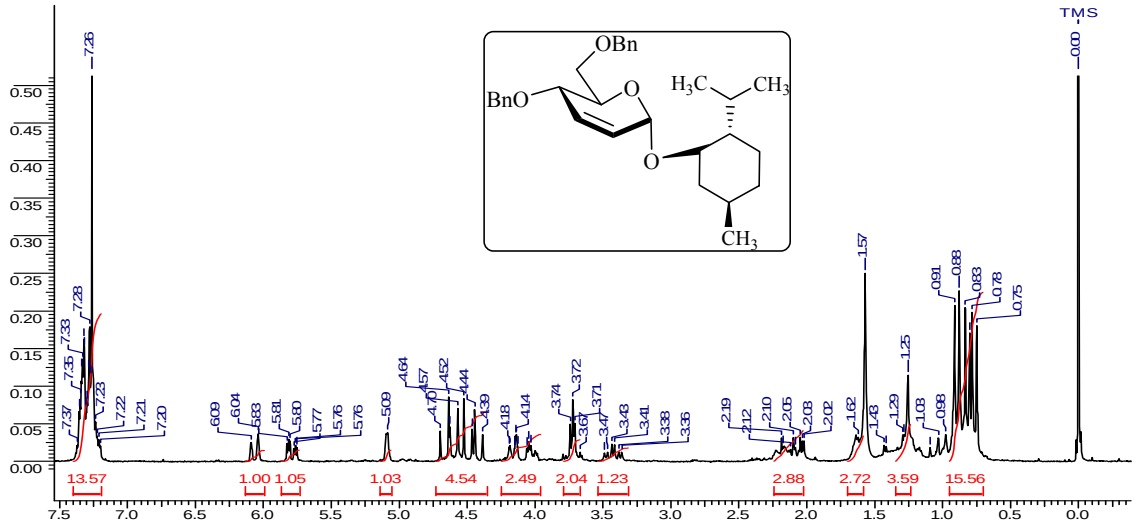
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7**



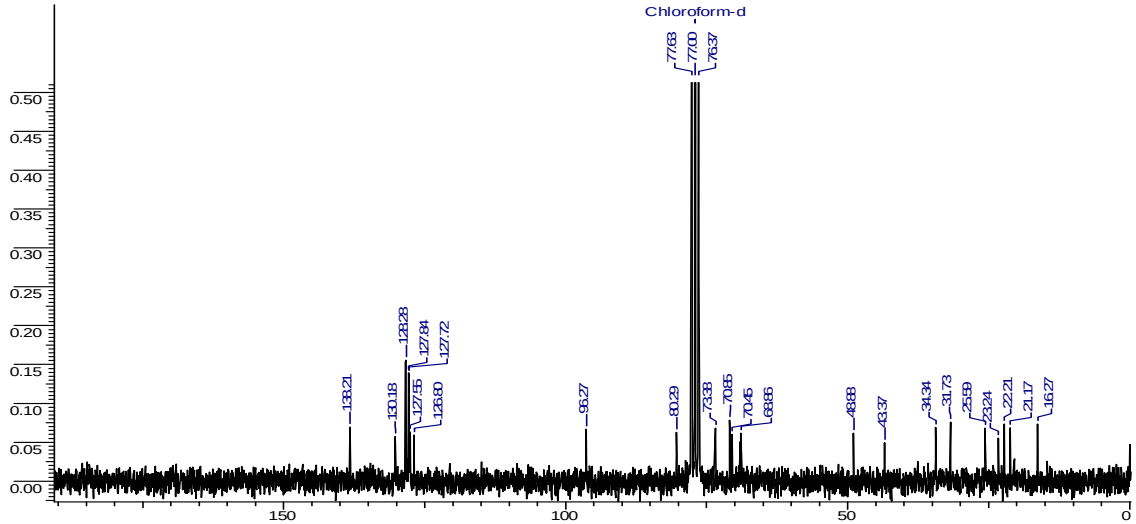
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7**



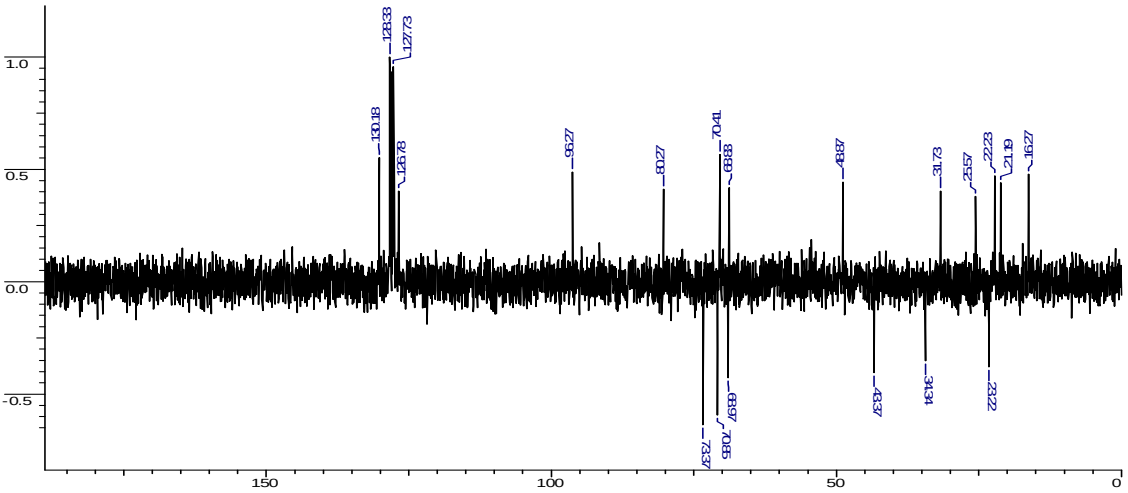
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **8**



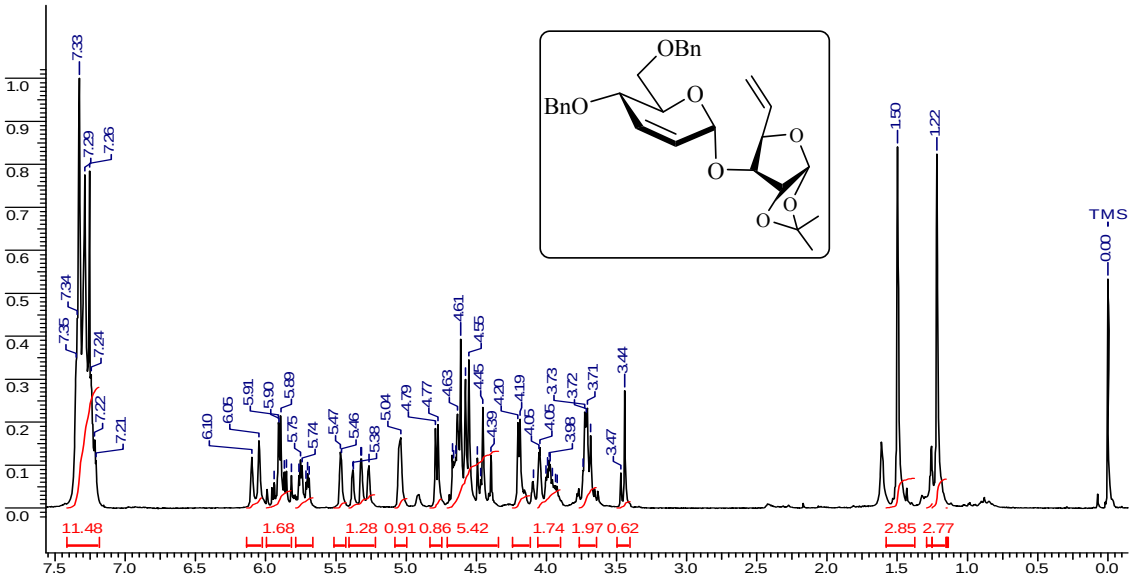
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **8**



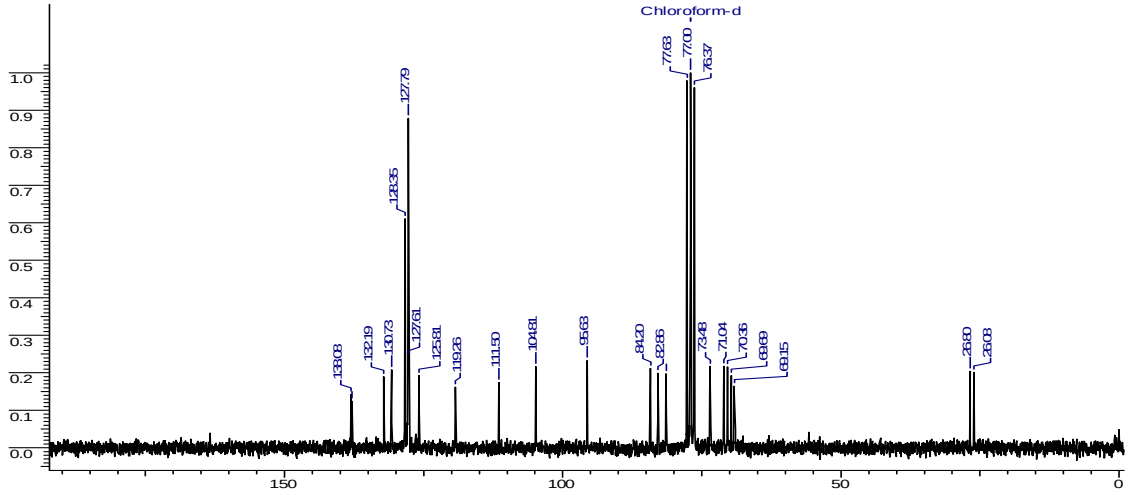
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **8**



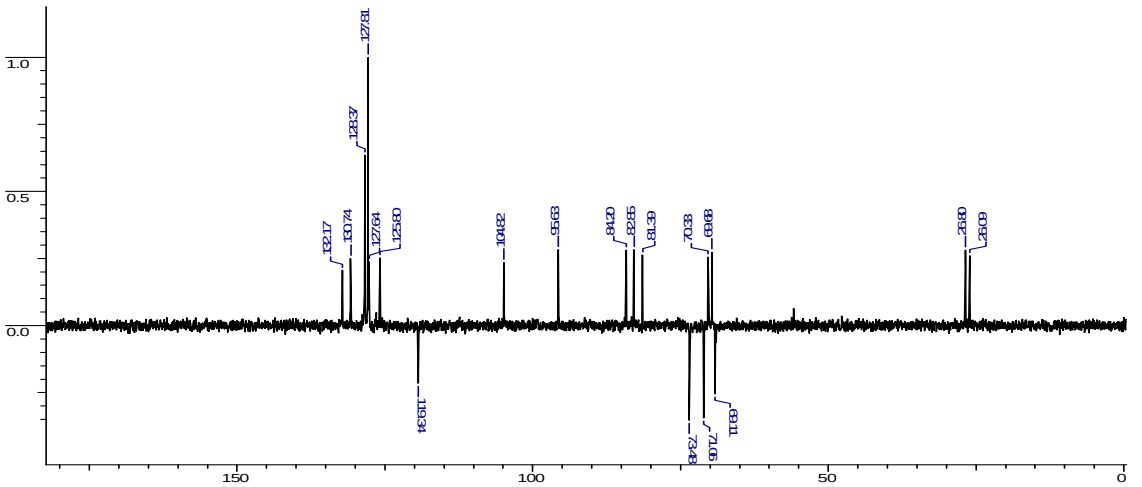
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **9**



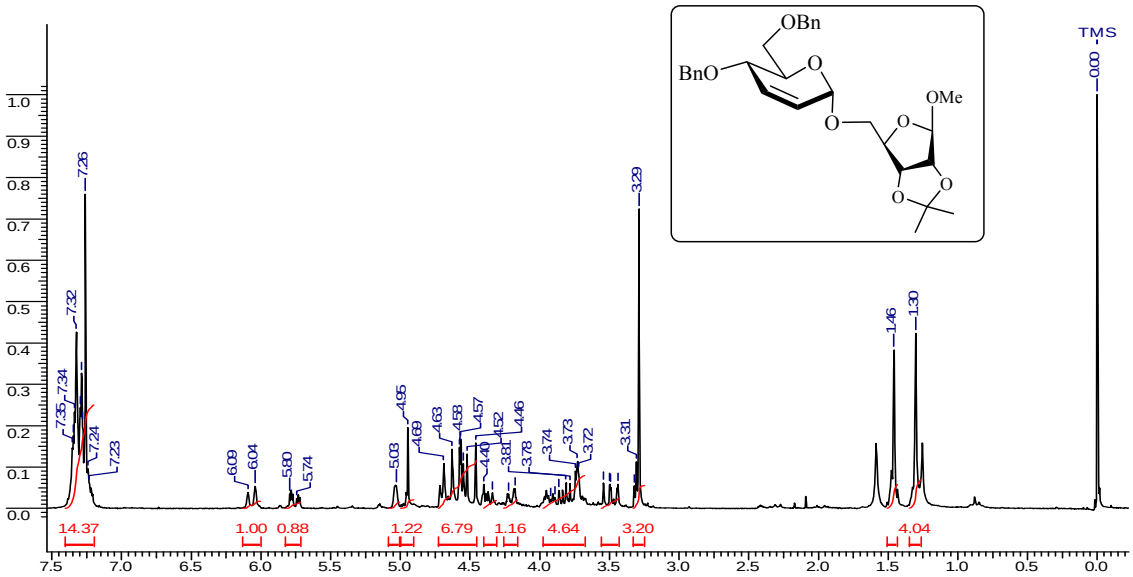
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



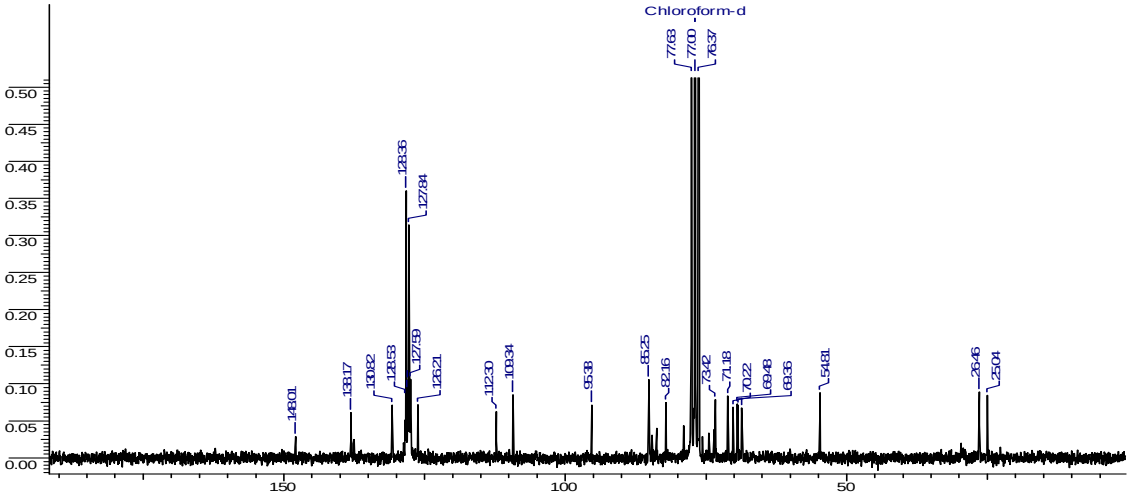
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



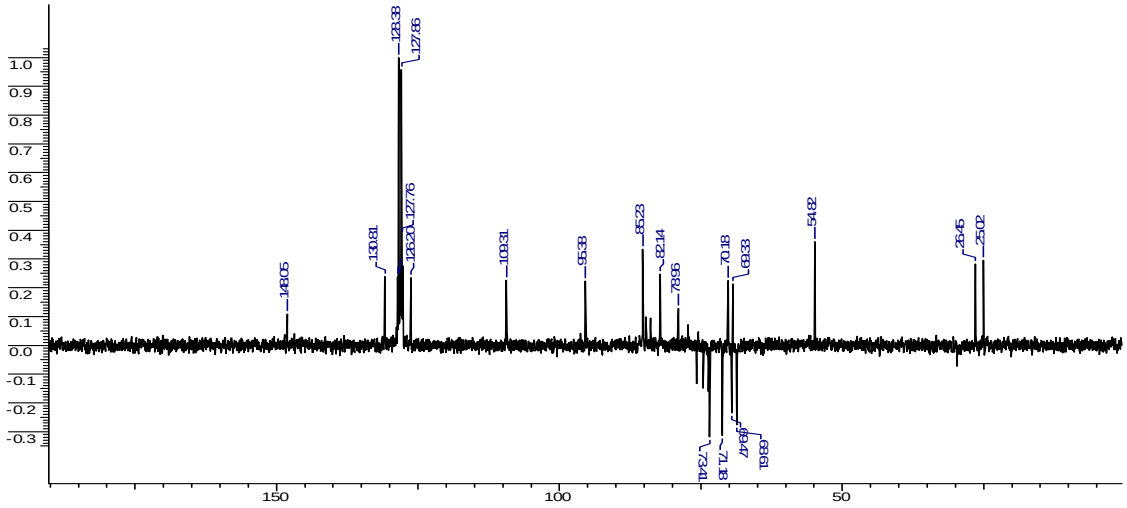
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **10**



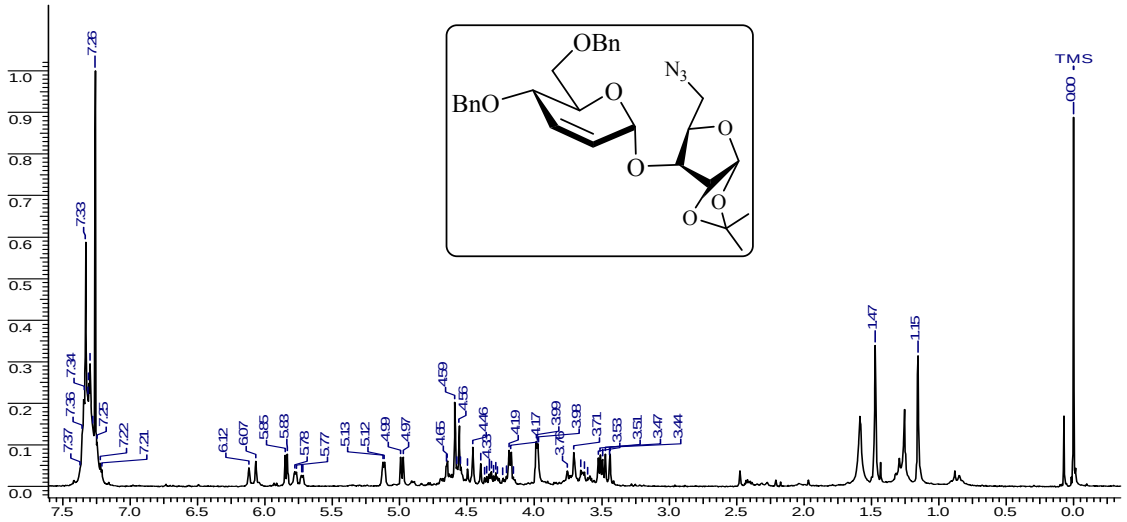
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **10**



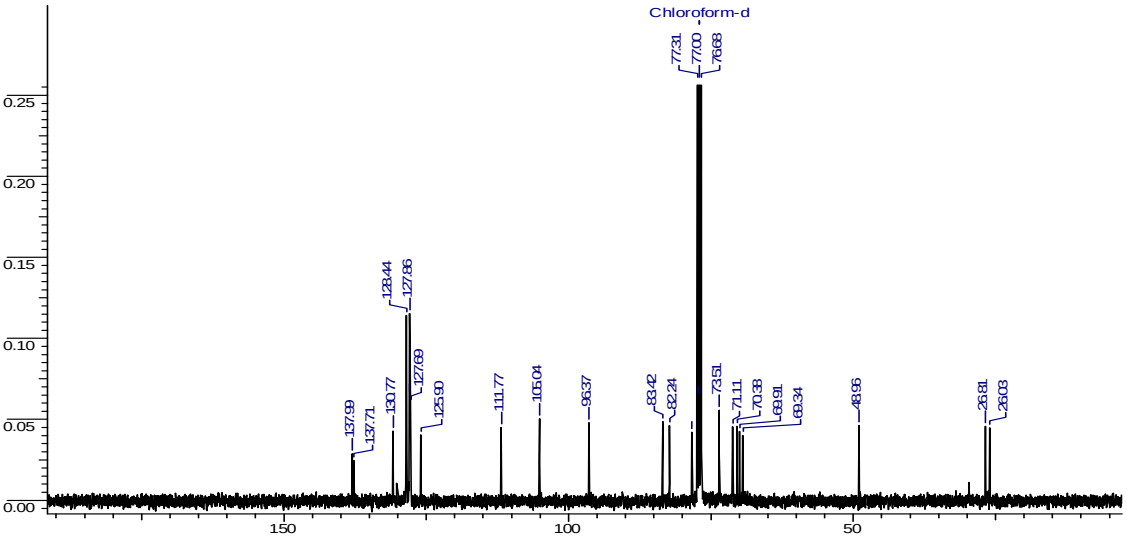
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **10**



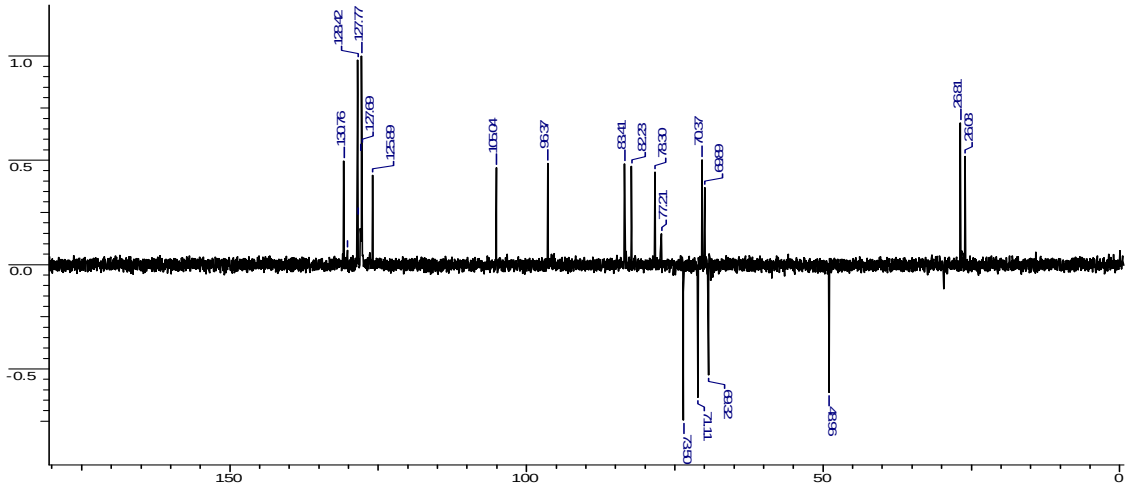
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **11**



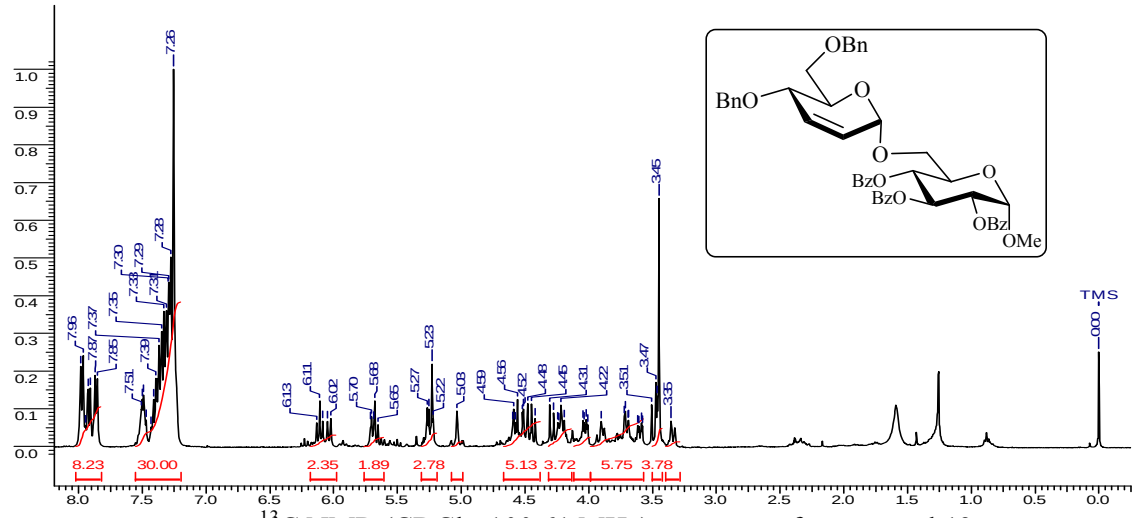
^{13}C NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11**



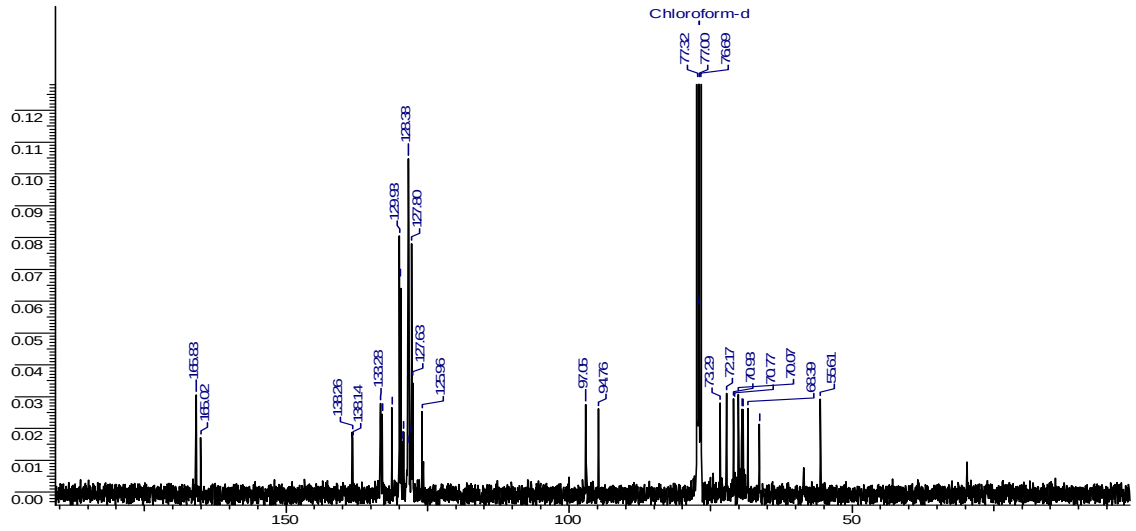
DEPT NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11**



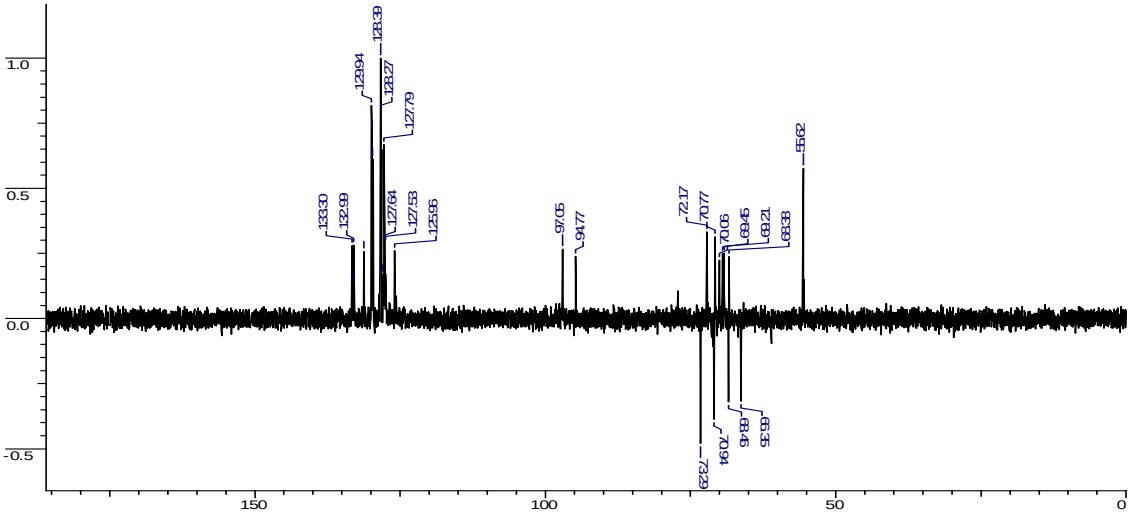
^{1}H NMR ($CDCl_3$, 400.13 MHz) spectrum of compound **12**



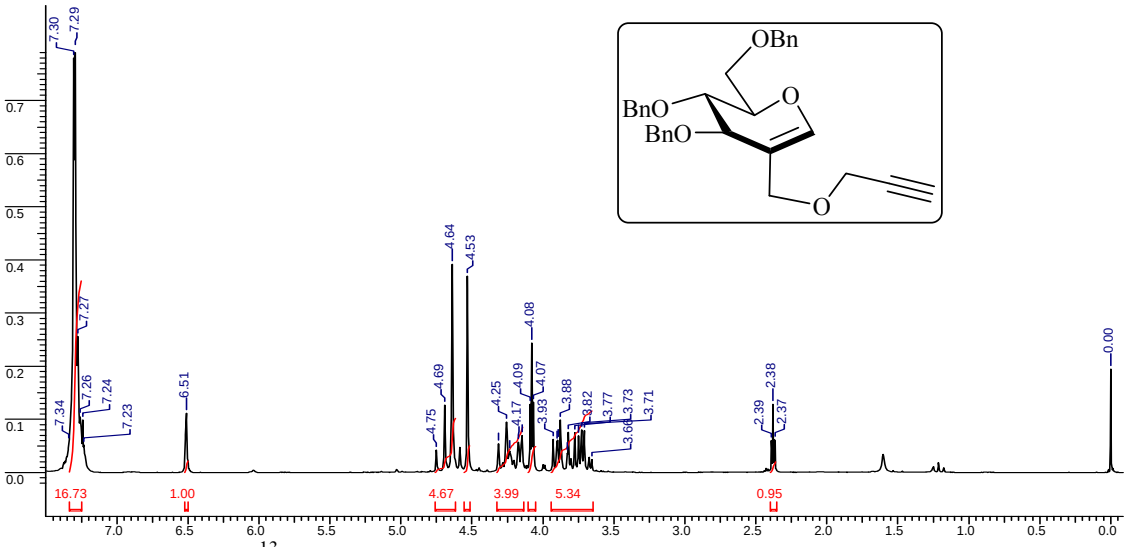
^{13}C NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **12**



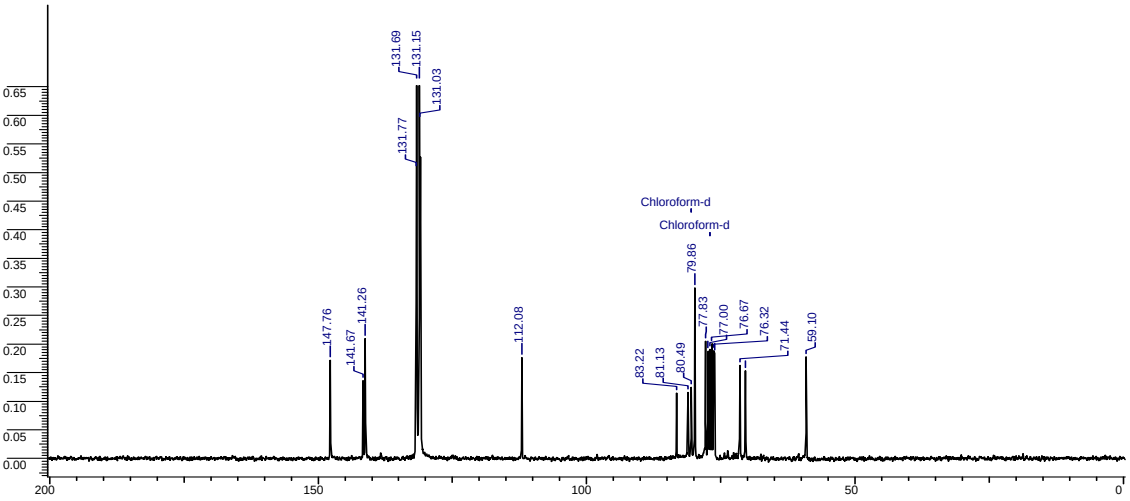
DEPT NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **12**



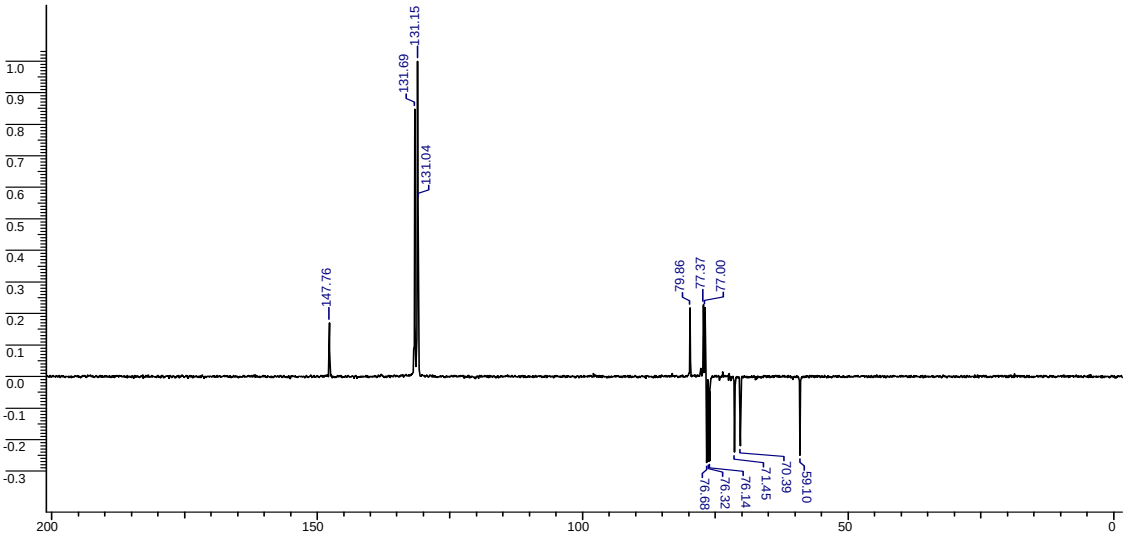
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **13**



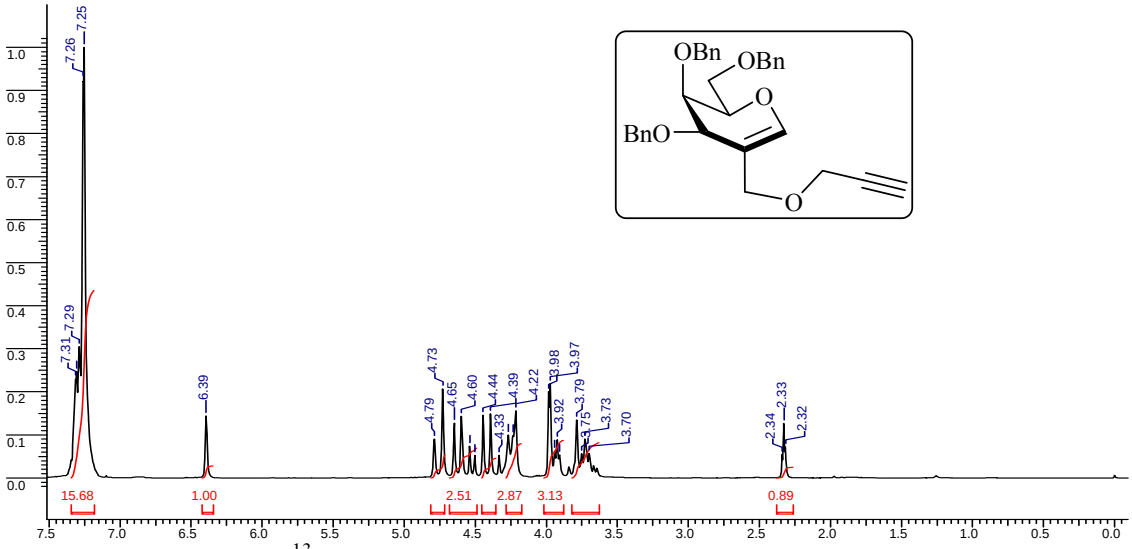
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **13**



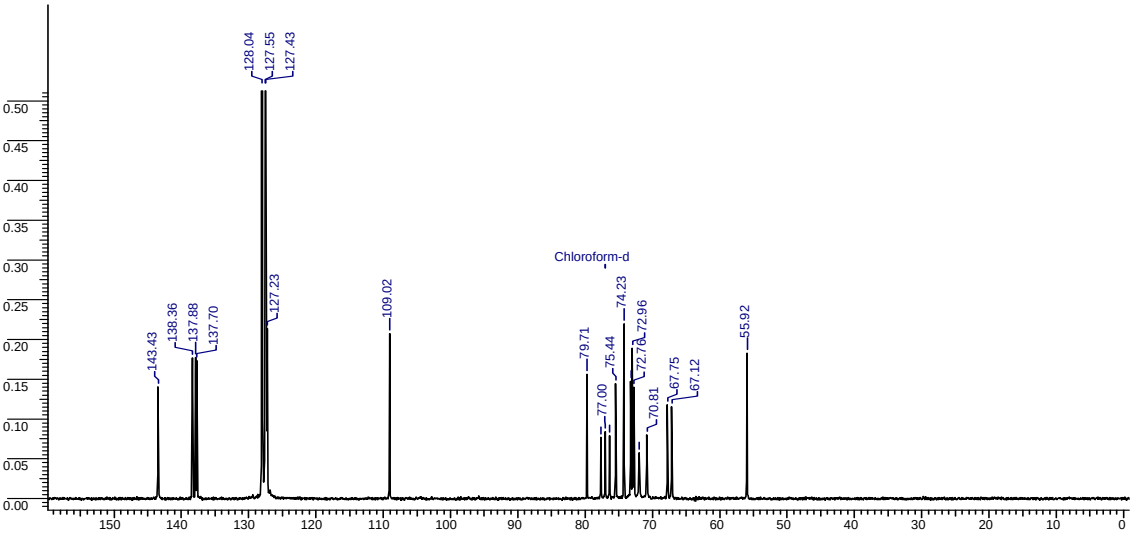
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **13**



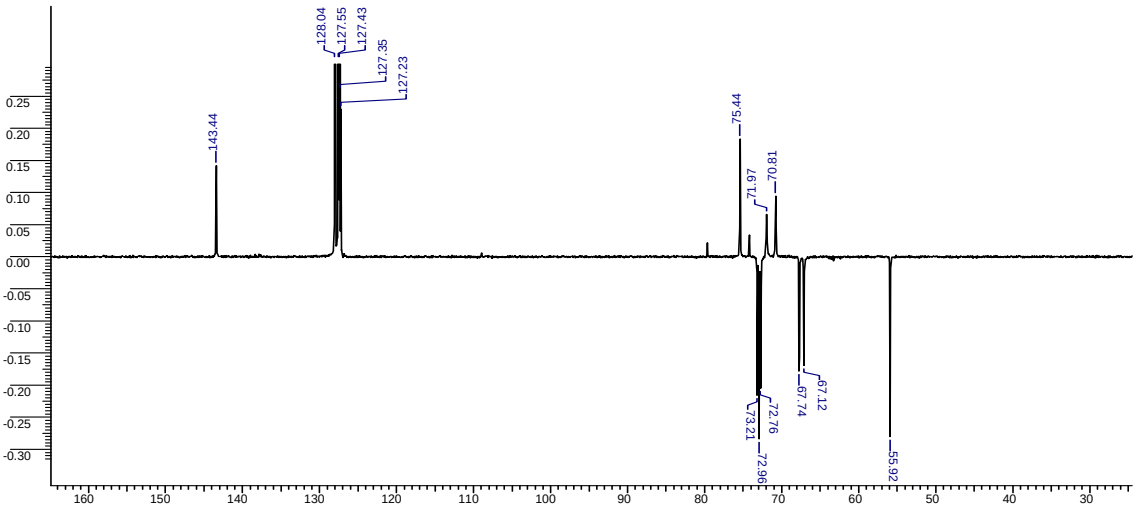
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **14**



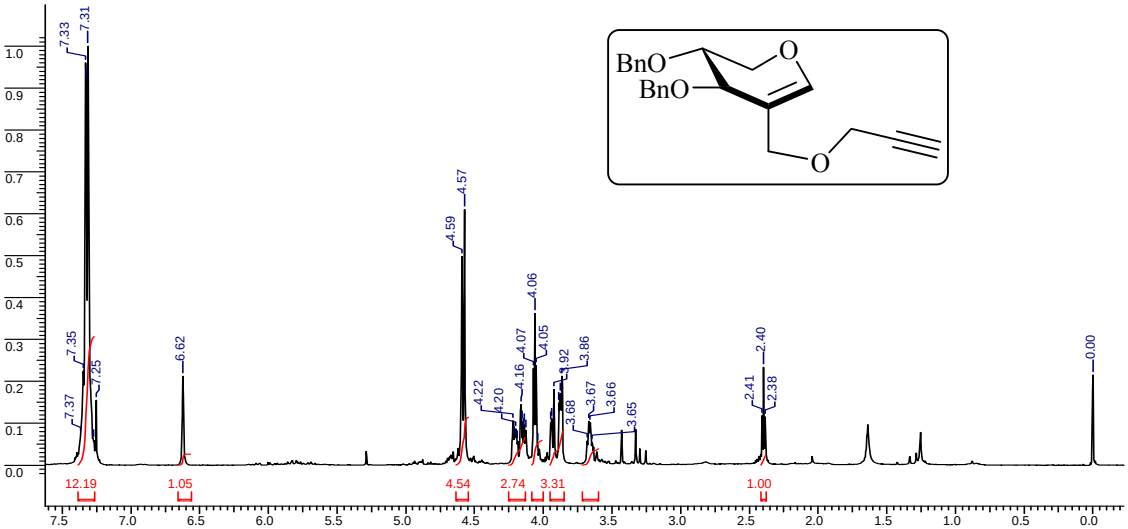
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



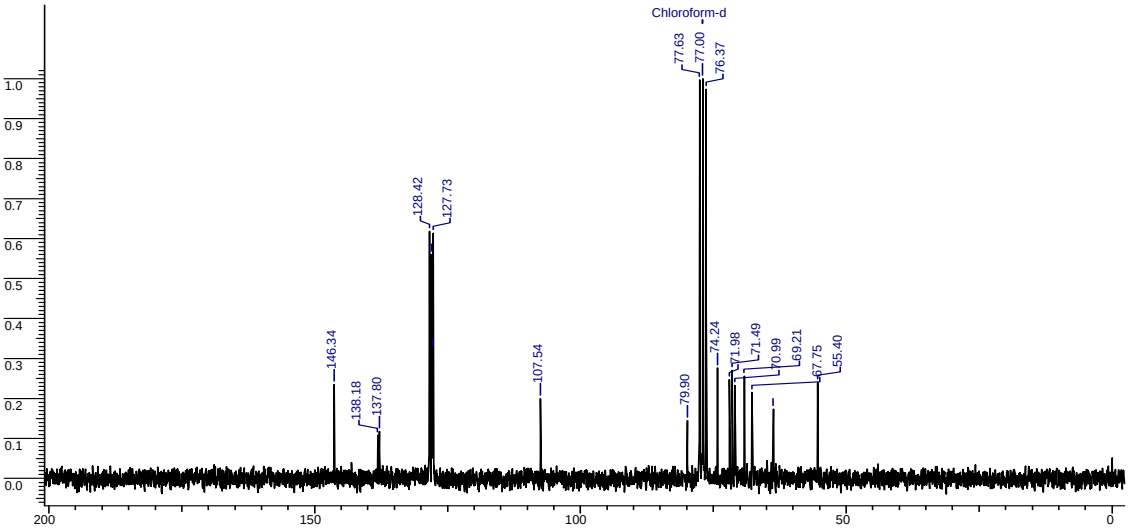
Dept NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



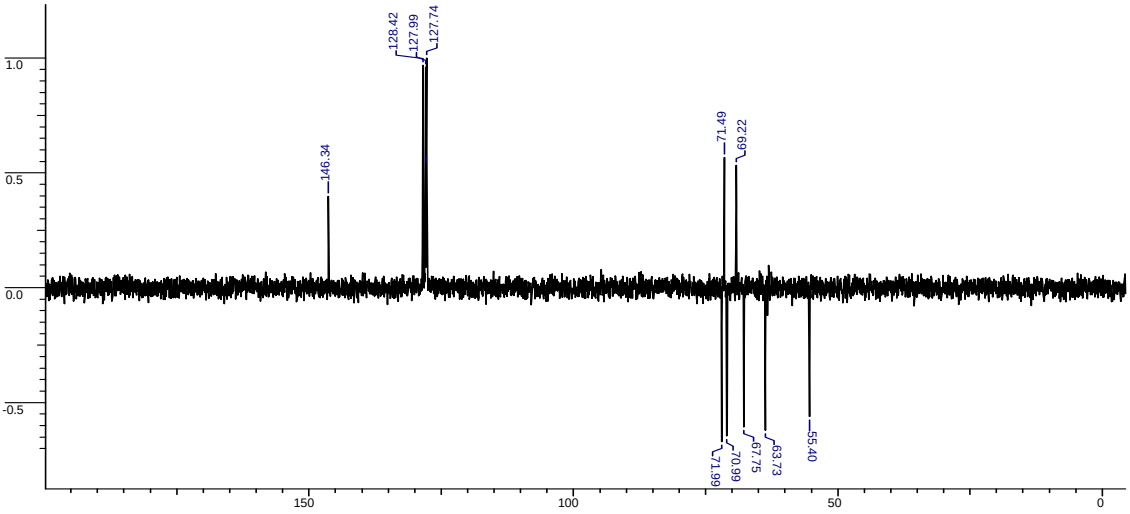
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **15**



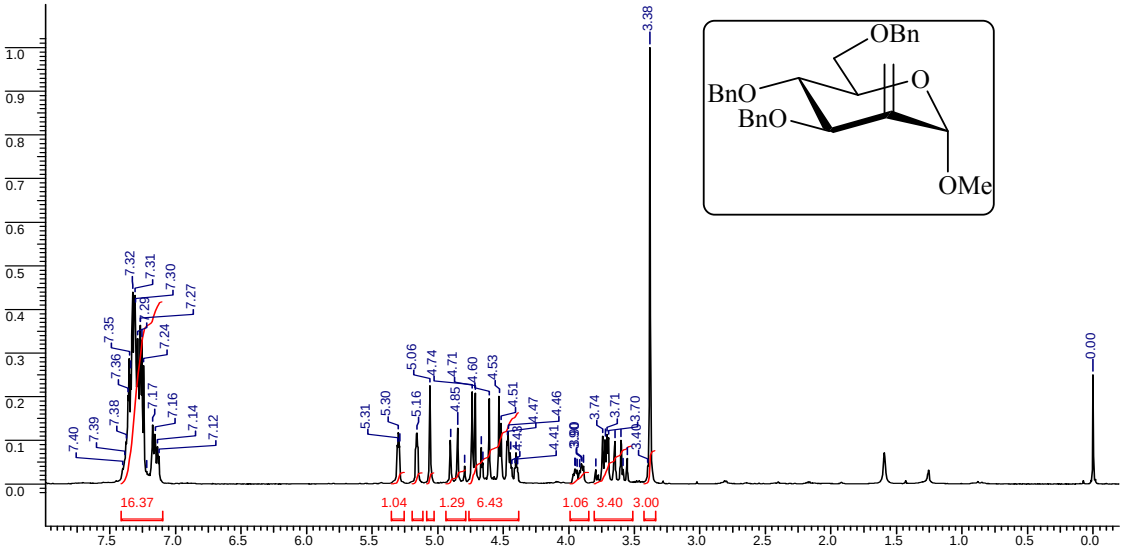
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



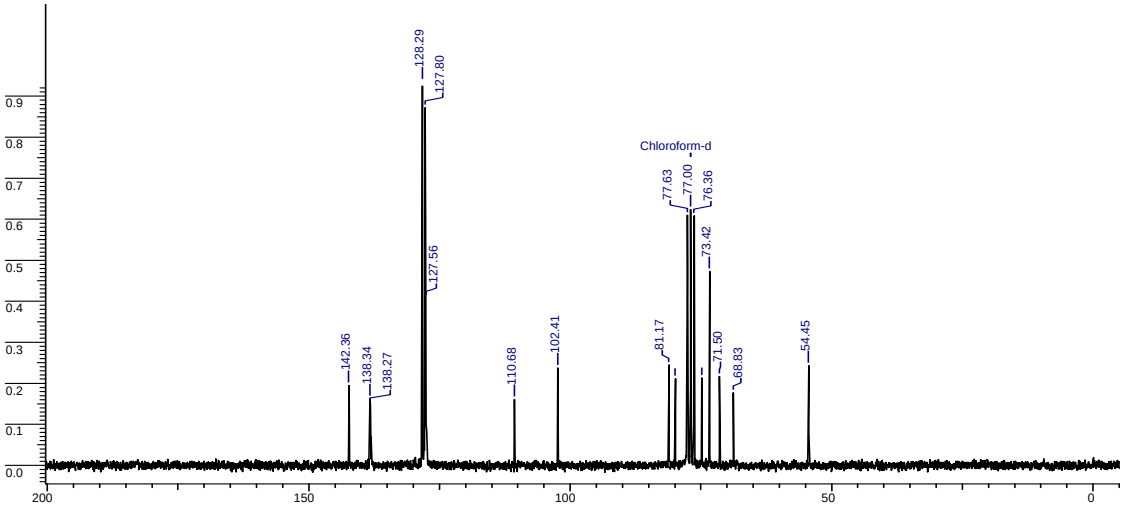
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



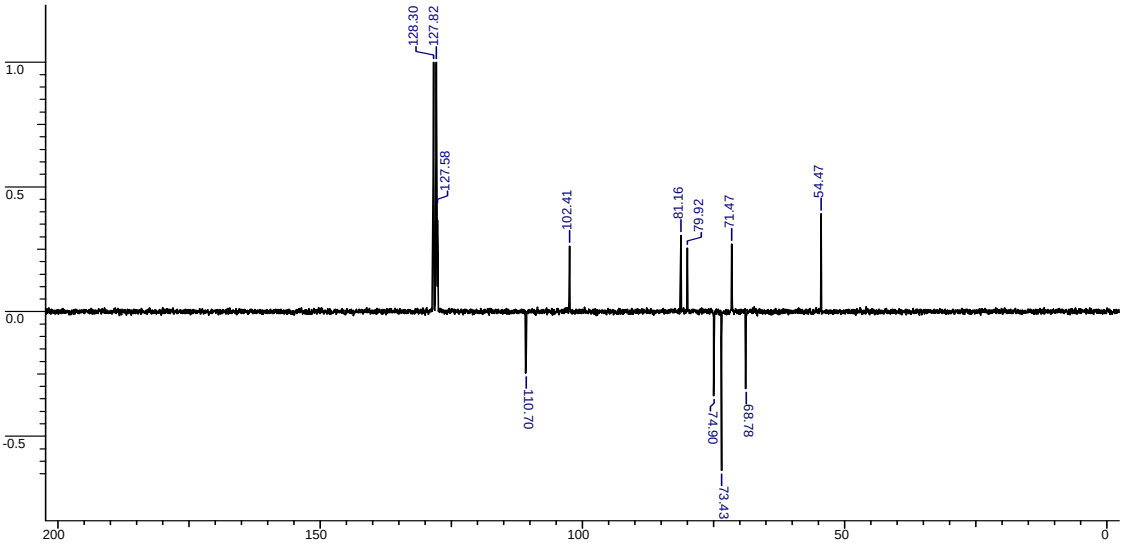
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **19**



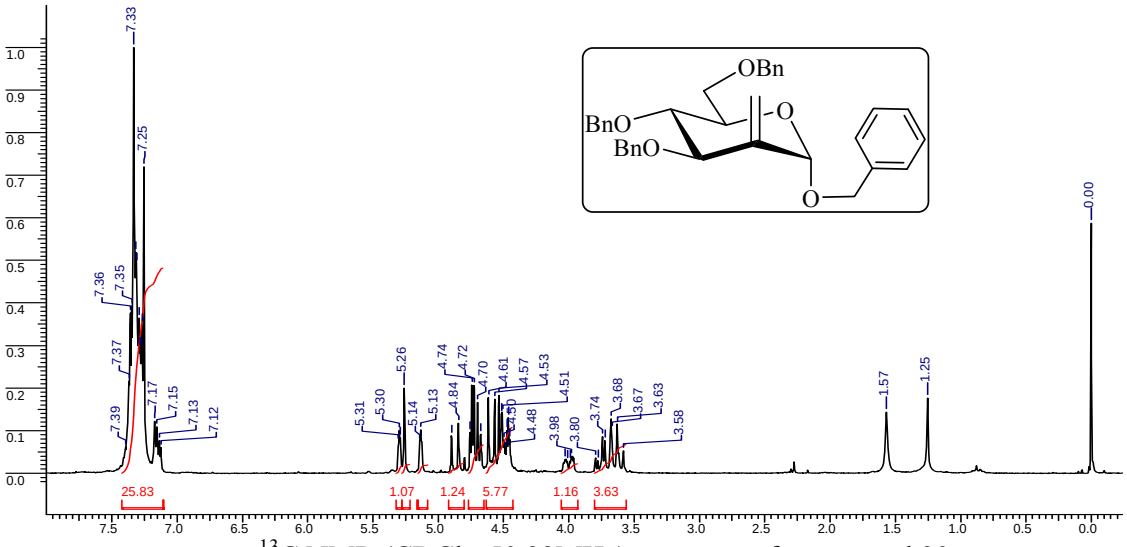
^{13}C NMR ($CDCl_3$, 50.32MHz) spectrum of compound **19**



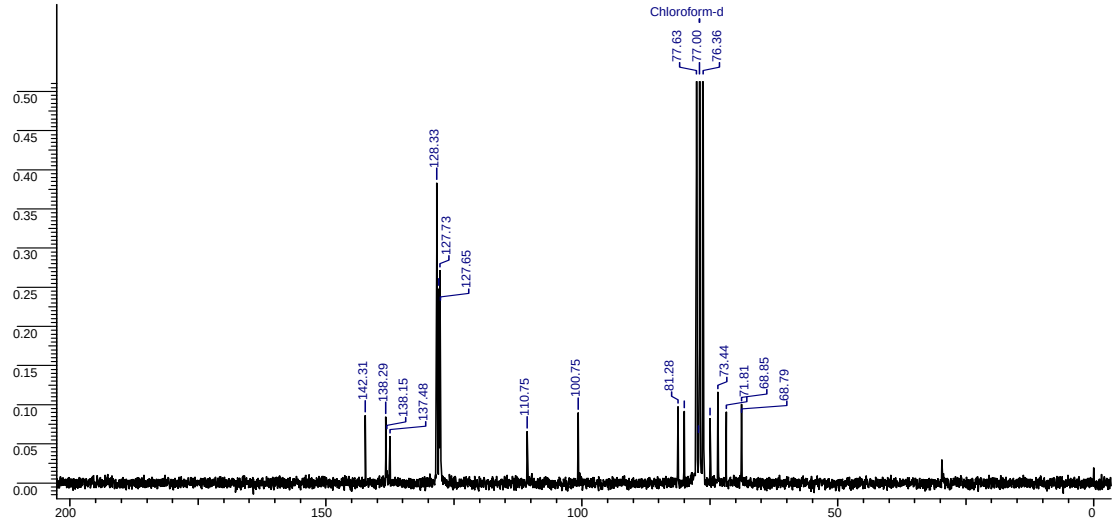
DEPT NMR ($CDCl_3$, 50.32MHz) spectrum of compound **19**



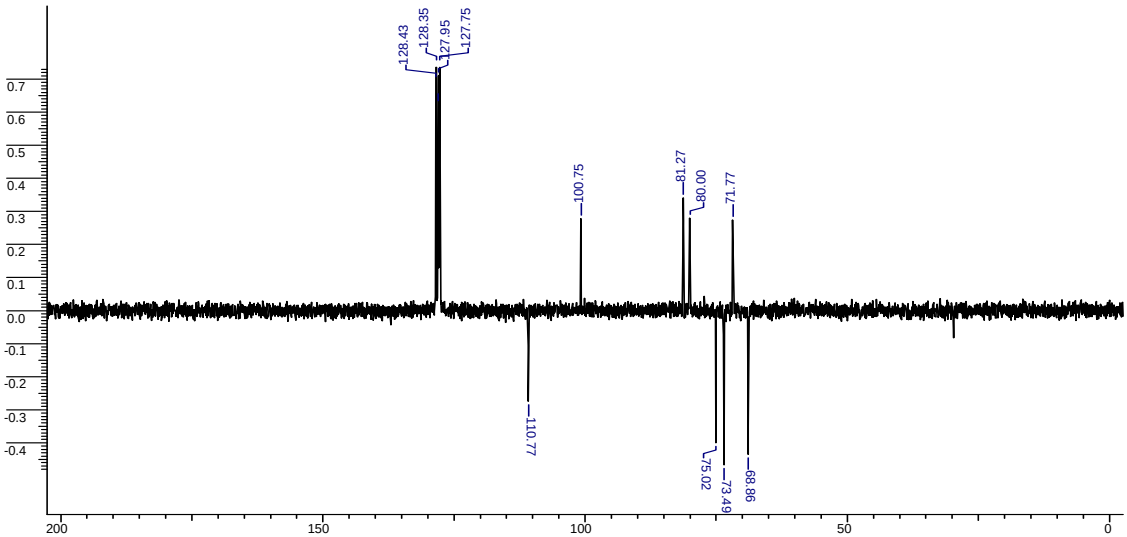
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **20**



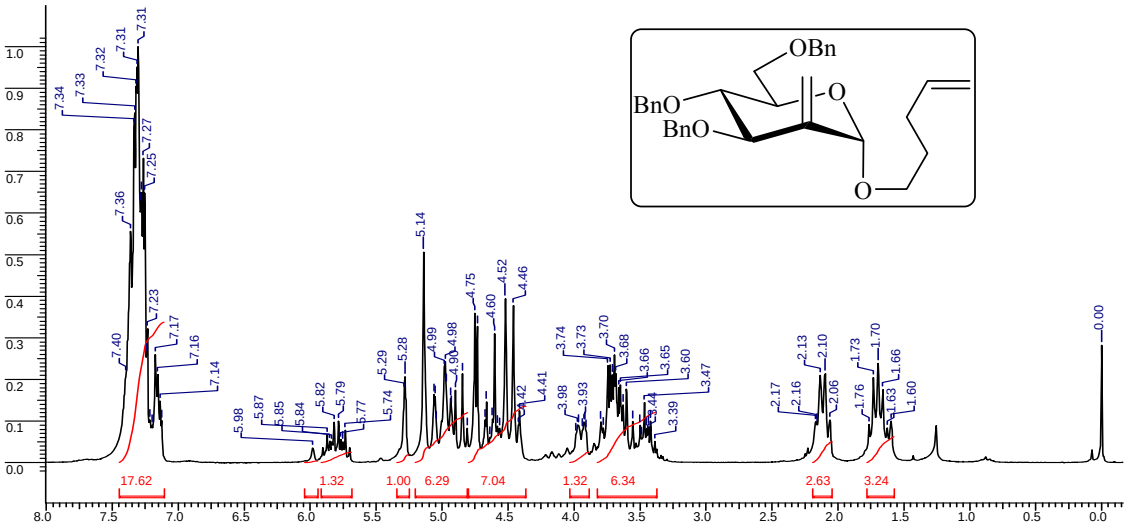
^{13}C NMR ($CDCl_3$, 50.32MHz) spectrum of compound **20**



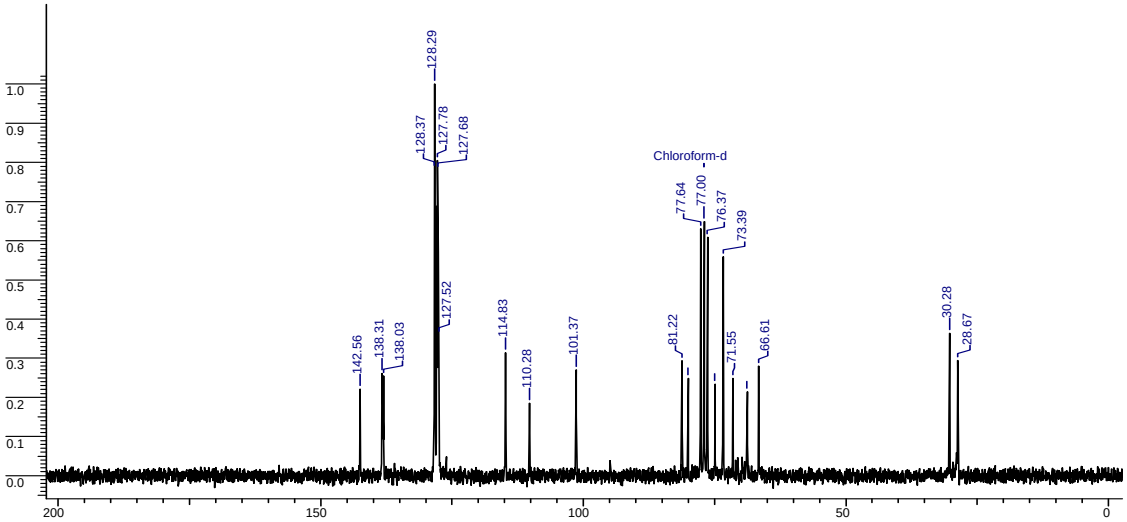
DEPT NMR ($CDCl_3$, 50.32MHz) spectrum of compound **20**



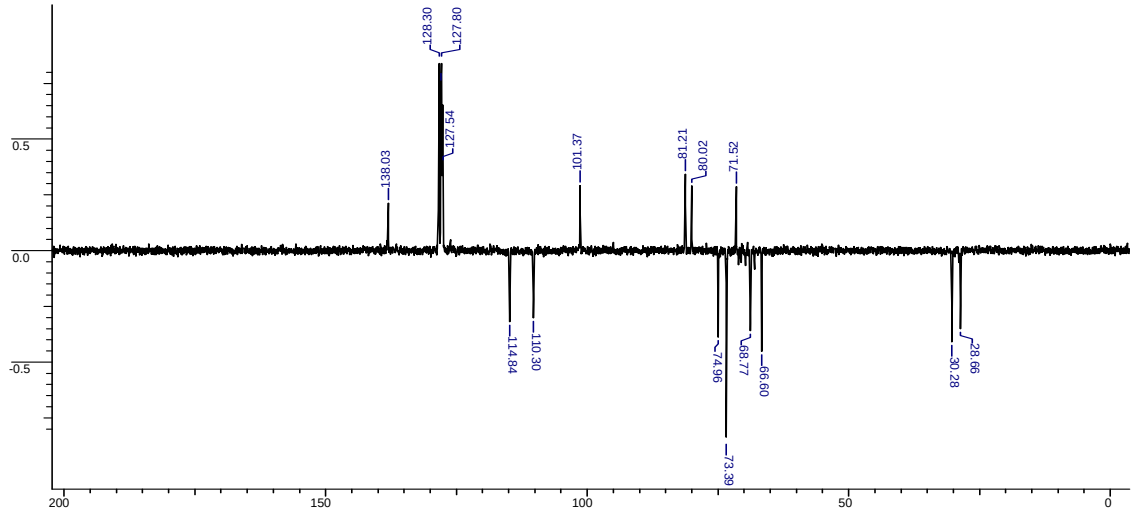
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **21**



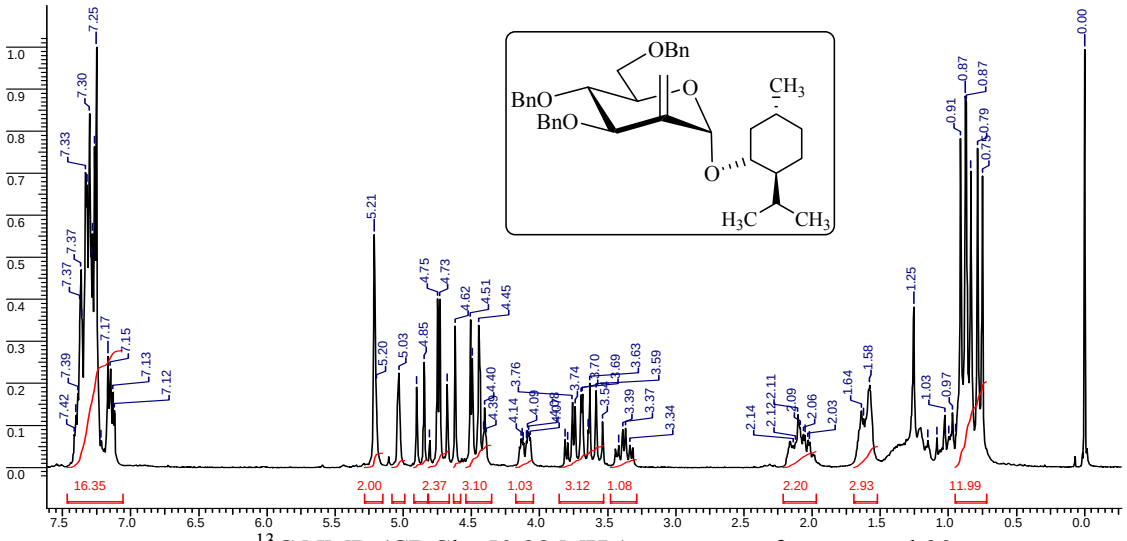
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **21**



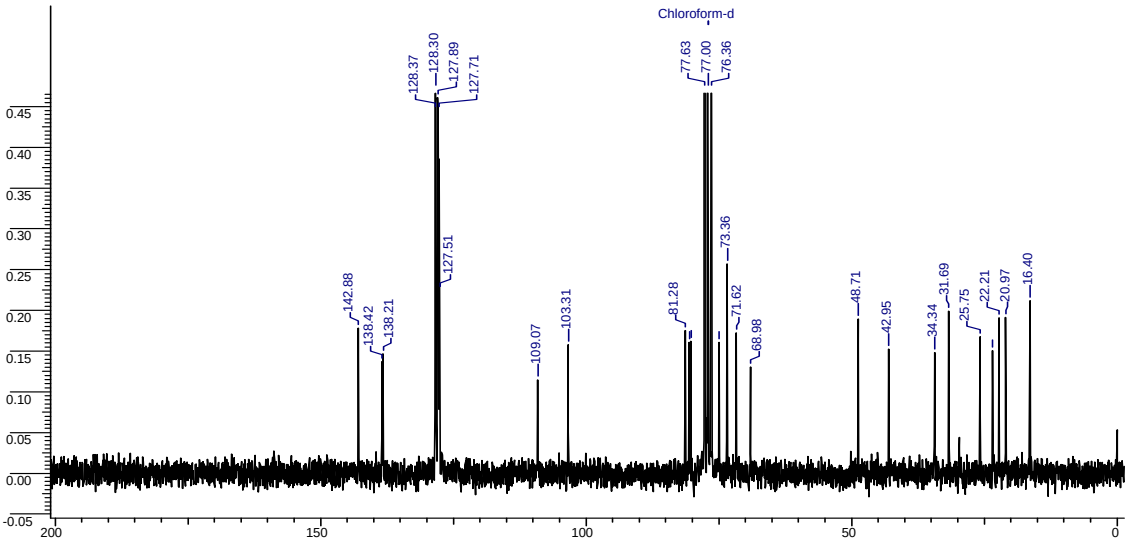
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **21**



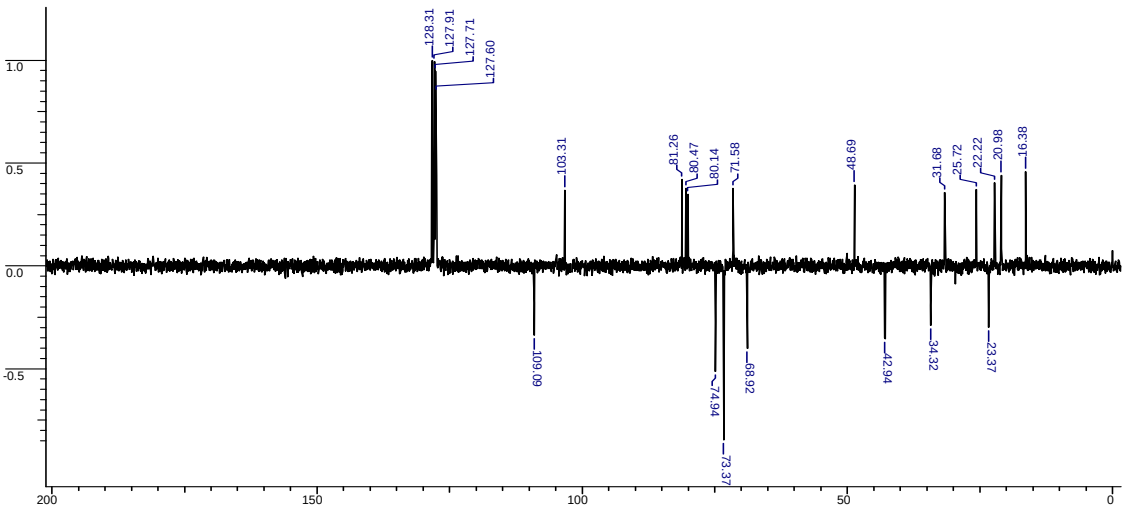
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **22**



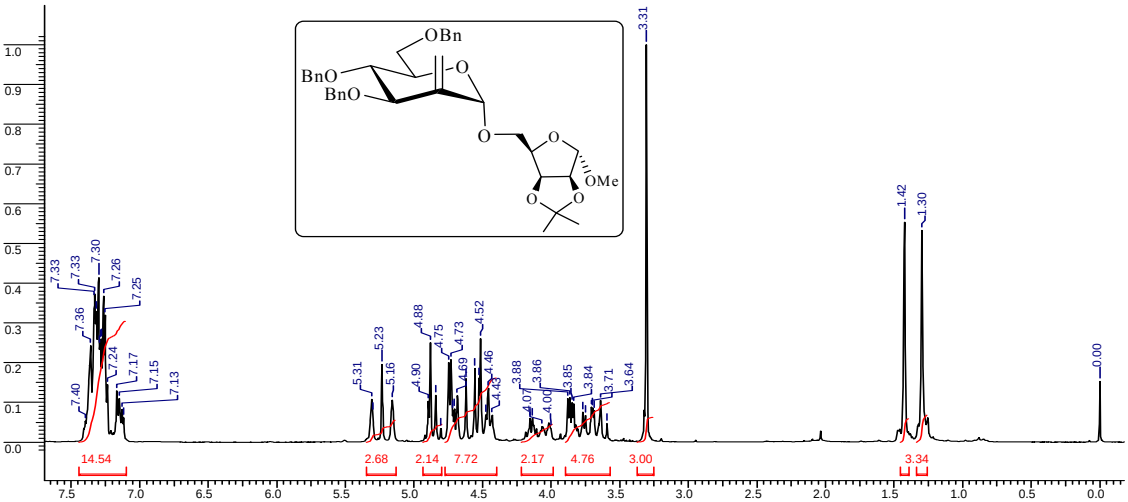
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **22**



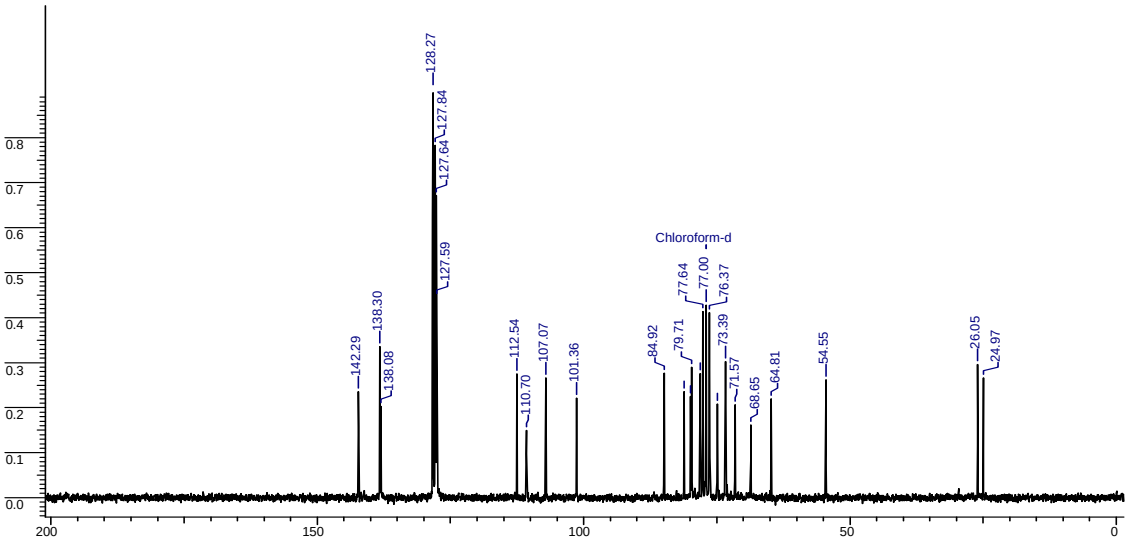
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **22**



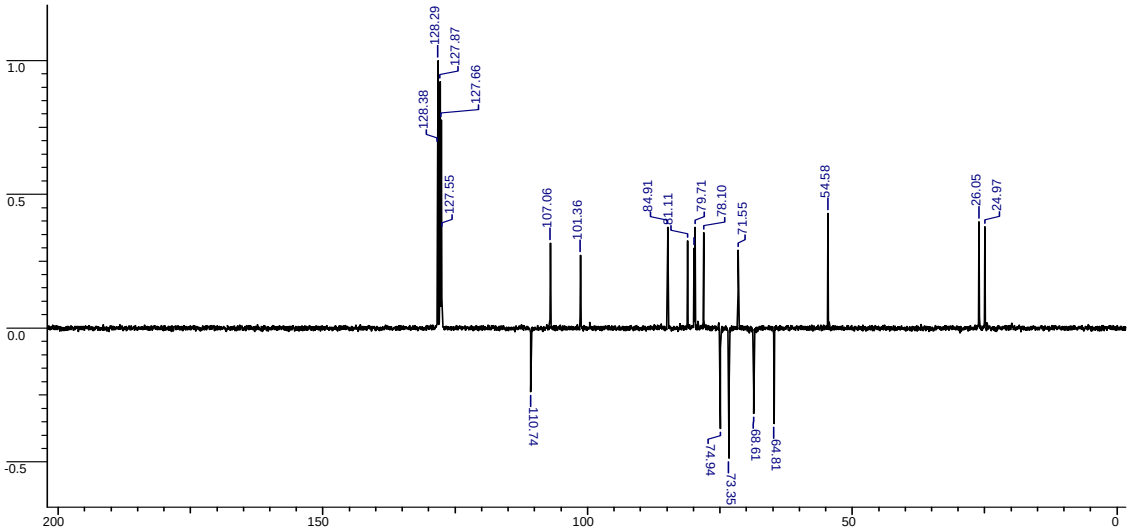
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **24**



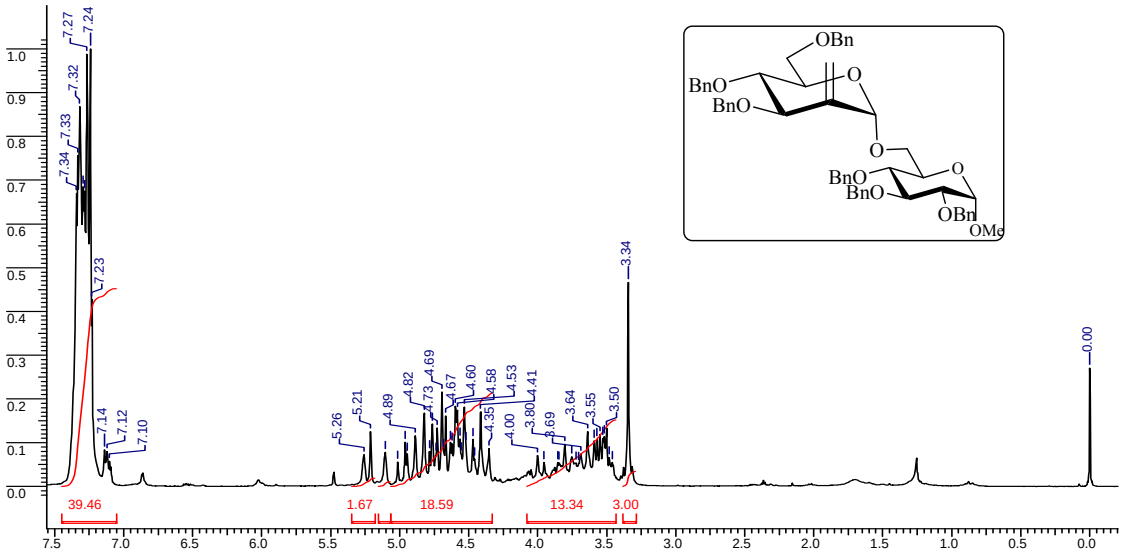
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **24**



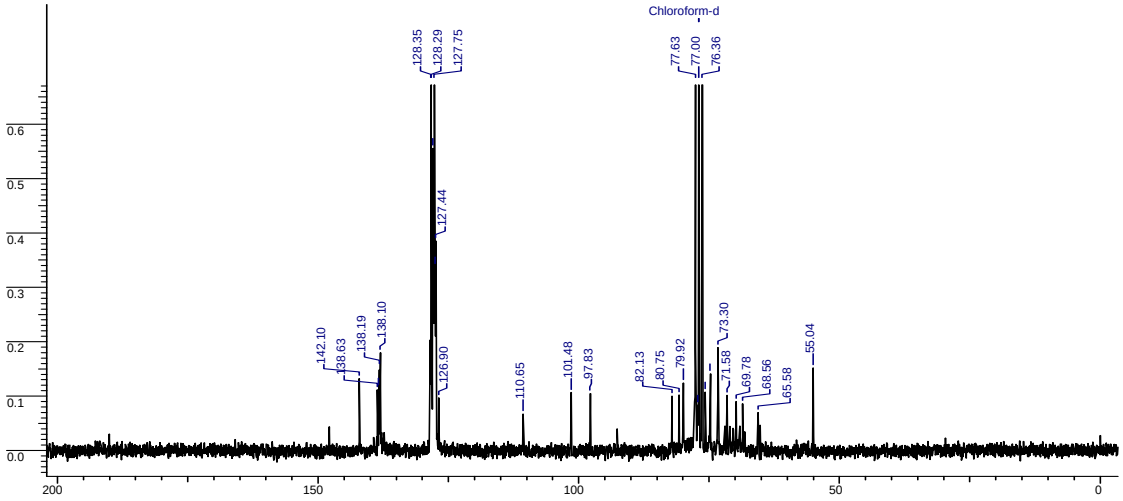
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **24**



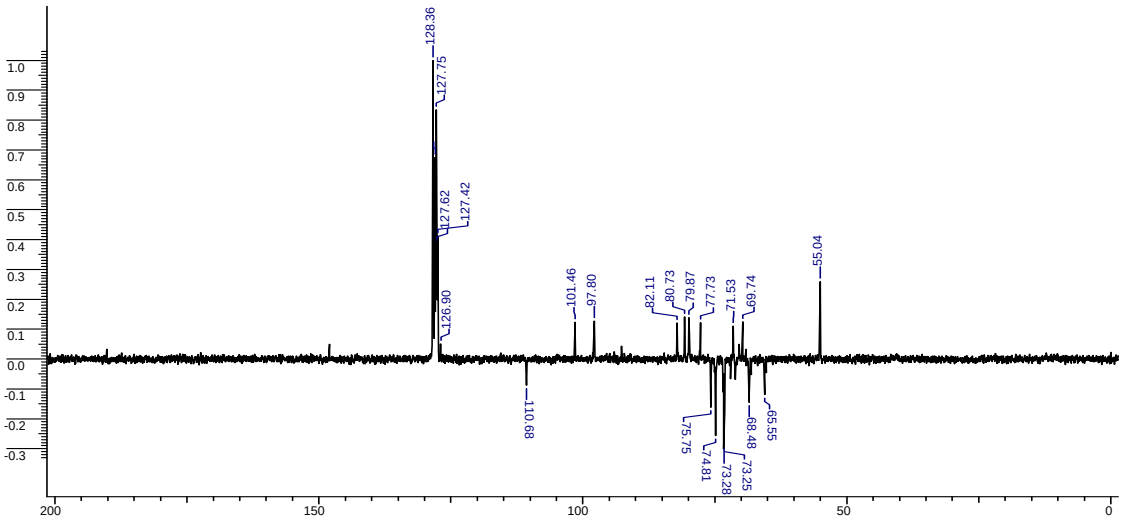
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **26**



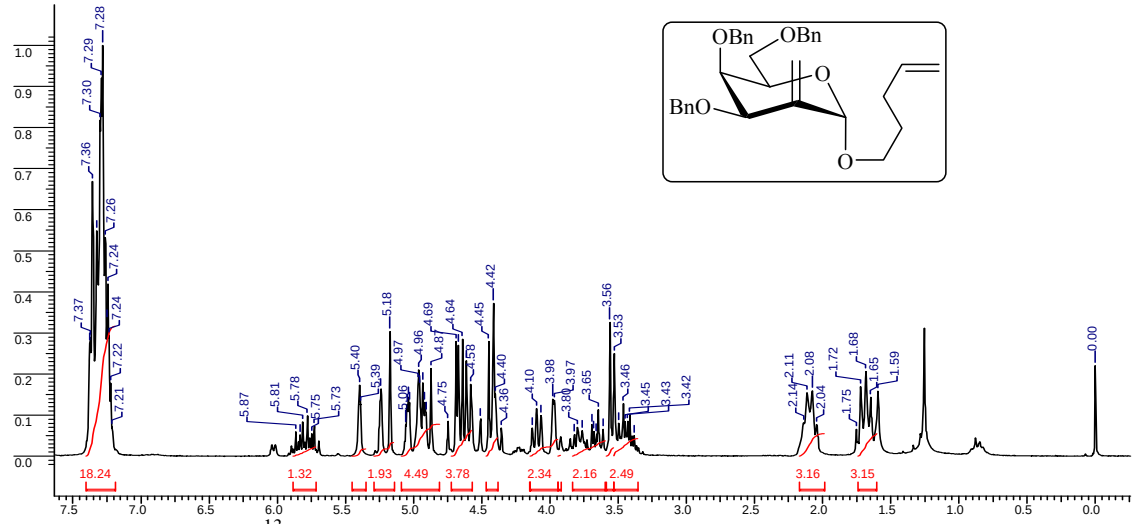
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **26**



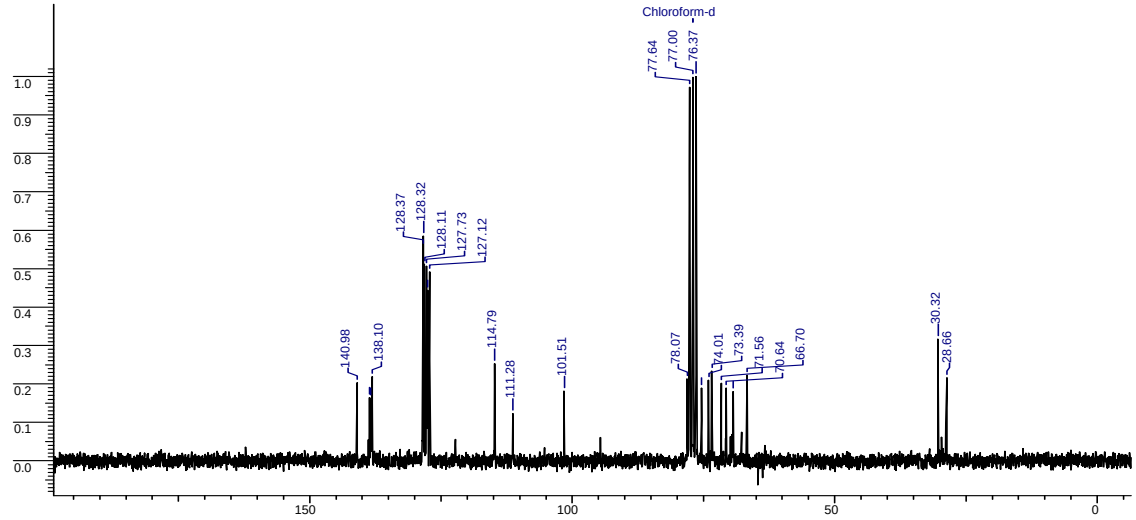
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **26**



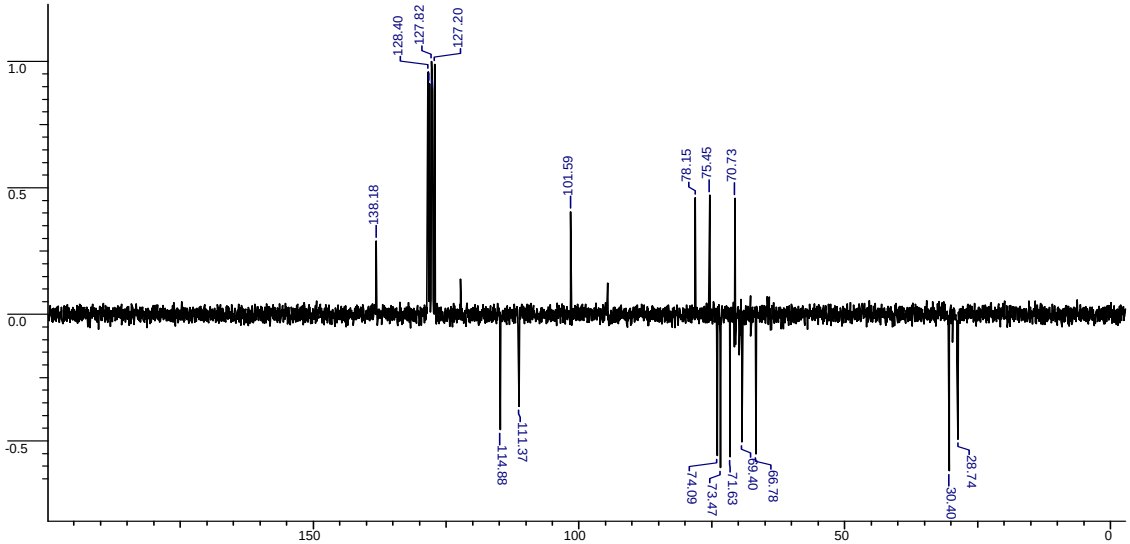
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **27**



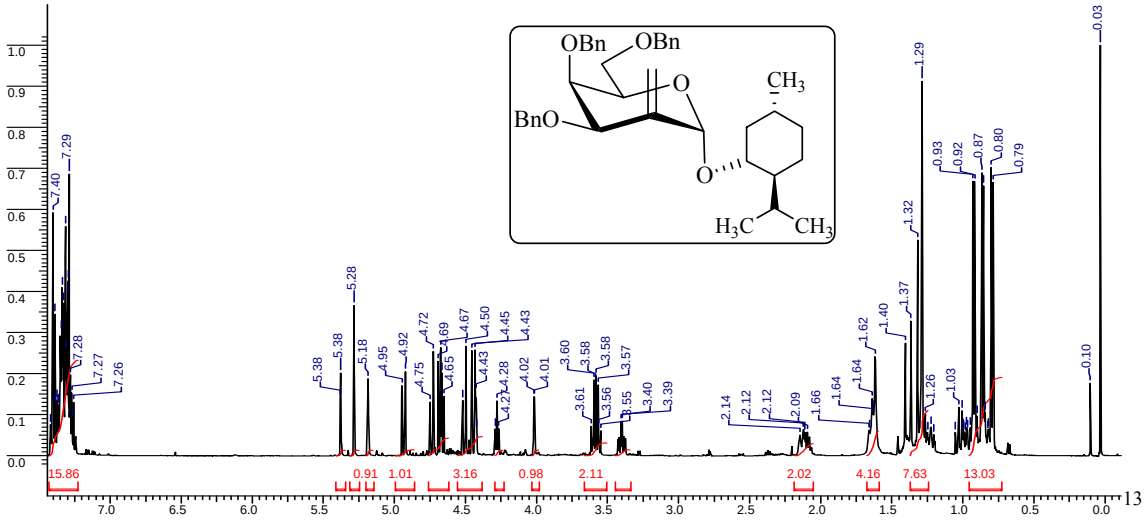
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **27**



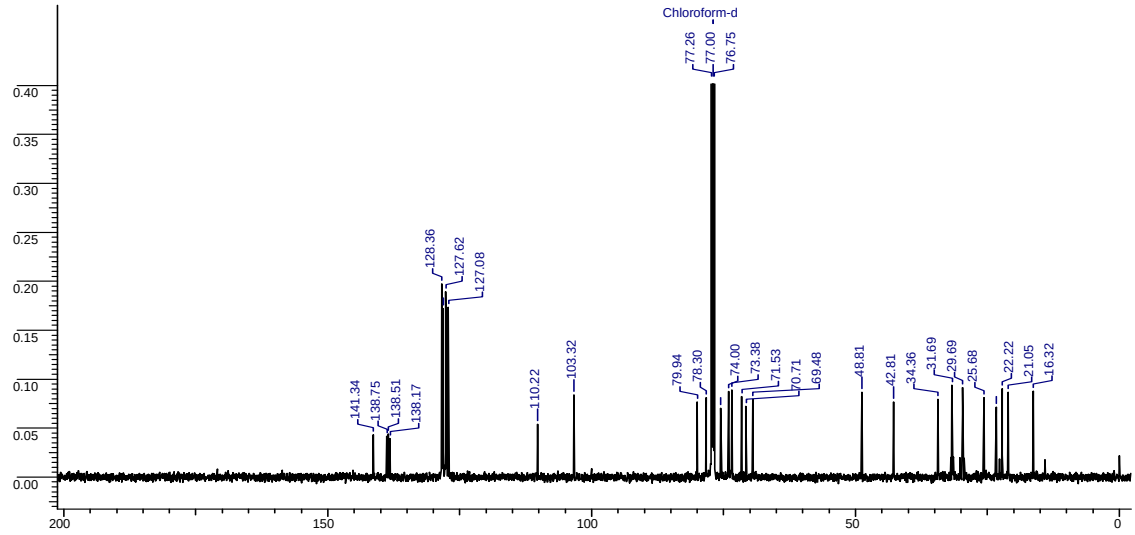
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **27**



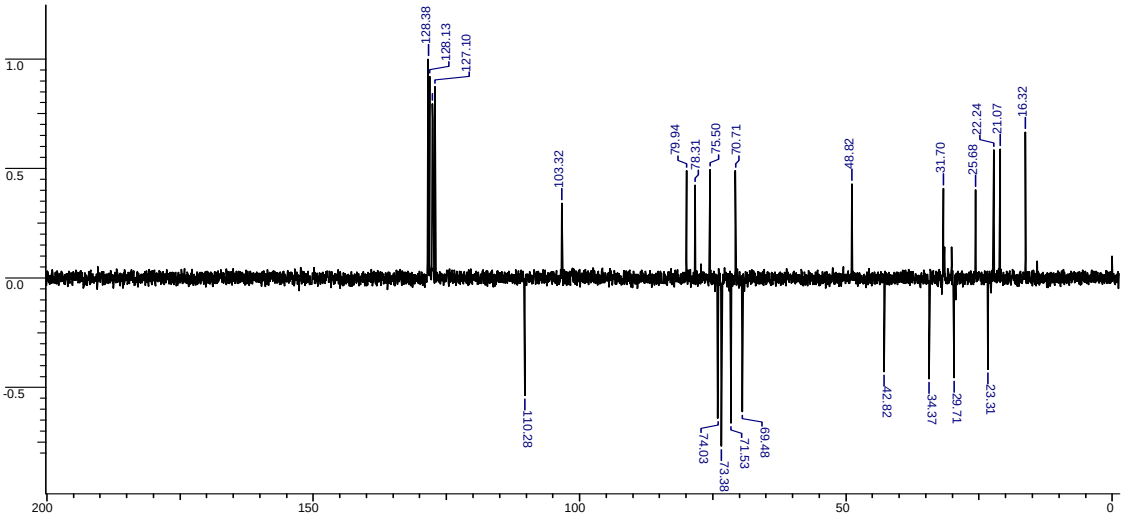
^{1}H NMR ($CDCl_3$, 500.13 MHz) spectrum of compound **28**



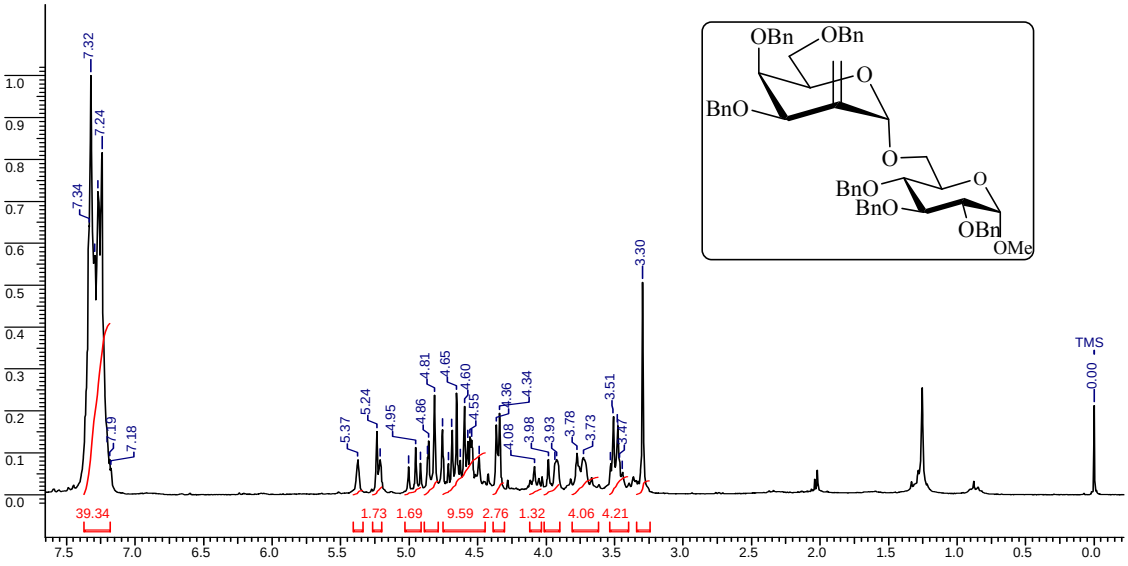
C NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **28**



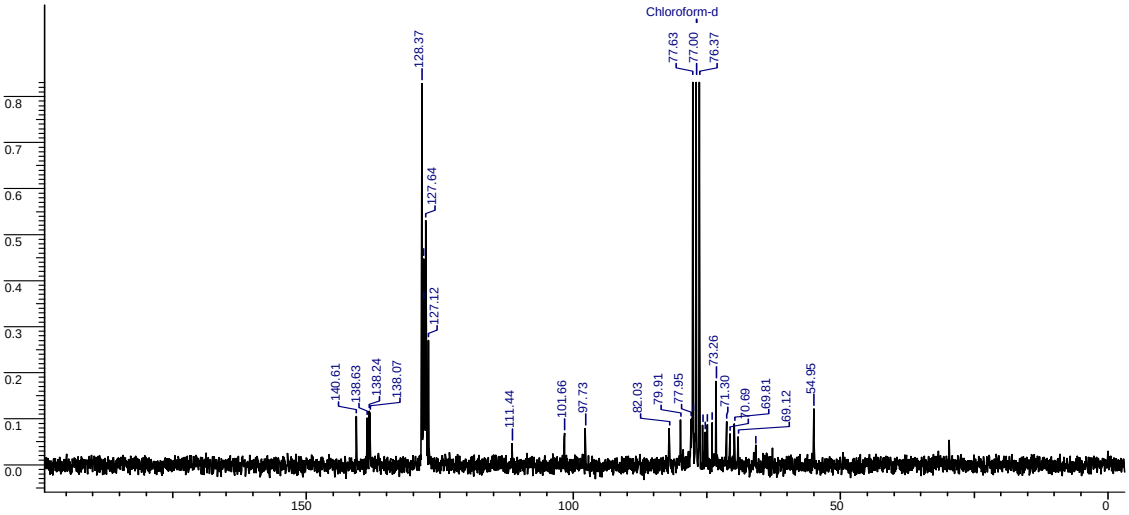
DEPT NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **28**



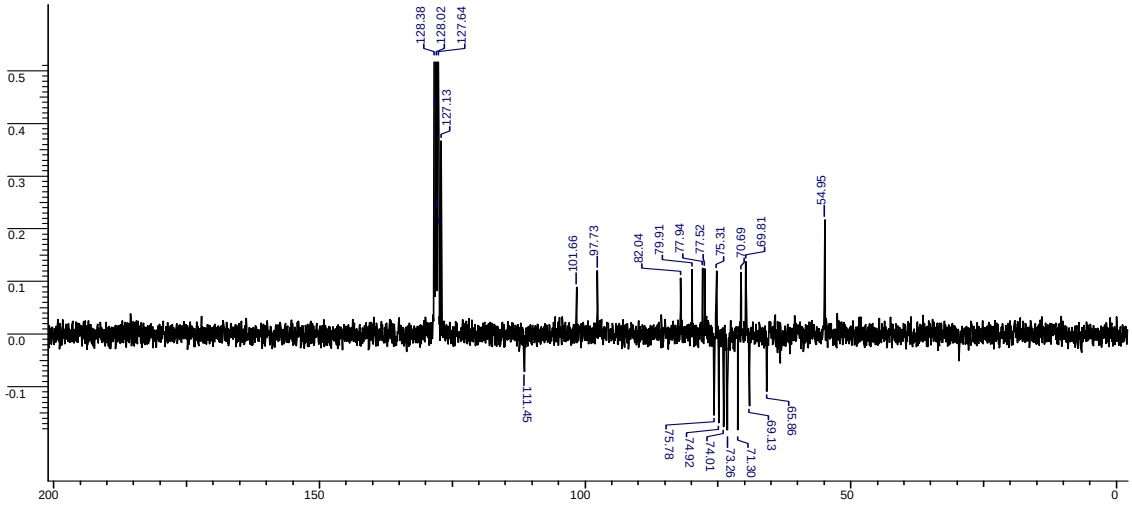
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **30**



^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **30**



DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **30**



Chapter 1: References

1. (a) Gruters, R. A.; Neetjes, J. J.; Tersmett, M.; Geode, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (b) Klatzmann, D.; Champagne, E. Chamaret, S.; Gruest, J.; Guetard, D.; Hercend, T.; Gluckman, J. C.; Montagnier, *Nature* **1984**, *312*, 767.
2. (a) Fuhrmann, U.; Bause, E.; Ploegh, H. L. *Biochim. Biophys. Acta* **1985**, *825*, 95. (b) Joubert, P. H.; Bam, W. J.; Manyane, M. *Eur. J. Clin. Pharmacol.* **1986**, *30*, 253. (c) Shack, C.; Roggla, G.; Luger, A,; Schernthan, G. *Eur. J. Clin. Pharmacol.* **1986**, *30*, 417.
3. (a) Varki, A. *Proc. Null Acad. Soc. USA* **1994**, *PI*, 7390. (b) Levy, D. E.; Tang, P. C.; Musser, J. H. In *Annuul Reports in Medicinul Chemistry* (Ed.: W. *K.* Hagmann). Academic Press, Sdn Diego. **1994**, p 215.171. (c) Lowe, J. B. In *The Moleculur Basis of Blood Diseuses* (Eds.: G. Stamatoyannopoulos. A. W. Nienhuis. P. W. Majerus. H. Varmus). Saunders. Phllddelphia, **1987**, Chapter 8, p. 293. (d) Hannessian, S. *Tom/ Synthesis of Natural Products The Chiron Approuch.* Pergamon, **1983**.
4. (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683-720. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357-2364. (c) Helenius, A.; Aebi, M. *Science* **2001**, *291*, 2364-2369. (d) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576-1624.
5. (a) Sinary, P. *Pure. Appl. Chem.* **1991**, *63*, 519-528. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-1531. (c) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21-123. (d) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095-1121. (e) Davis, B. G. *J. Chem. Soc.; Perkin Trans. 1* **2000**, 2137-2160.
6. (a) Fischer, E.; Zach, K. *Chem. Zentralblatt* **1913**, *I*, 1968. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1965**, *20*, 67-137; **1969**, *24*, 199.
7. Helferich, B. *Adv. Car. Chem.* **1952**, *7*, 209-245.
8. Charette, A. B.; Marcoux, J.-F.; Cote, B. *Tetrahedron Lett.* **1991**, *32*, 7215-7218. (b) Crich, D.; Lim, L. B. L. *Tetrahedron Lett.* **1994**, *35*, 2565-2568. (c) Sanders, W. J.; Kiessling, L. L. *Tetrahedron Lett.* **1994**, *35*, 7335-7338. (d) Rao, M. V.; Nagarajan, M. *J. Org. Chem.* **1998**, 53, 1184-1196. (e) Fu, Y.-L.; Bobek, M. *J. Org. Chem.* **1980**, *45*, 3836-3840.
9. Danishefsky, S.; Kerwin, J. F. *J. Org. Chem*. **1982**, *47*, 3803-3805.
10. Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc. Chem. Commun.* **1985**, 1359-1362.

11. Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082-2089.
12. (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Elsevier: Tarrytown, NY, **1995**. (b) Farr, R. N.; Daves, G. D. *J. Carbohydr. Chem.* **1990**, *9*, 653-660. (c) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193-199. (d) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433-1445. (e) Daves, G. D. *Acc. Chem. Res.* **1990**, *23*, 201-206. (e) Daves, G. D. *Carbohydrates-Synthetic Methods and Applications in Medicinal Chemistry;* Ogura, H., Hasegawa, A., Suami, T., Eds.; VCH: New York, **1992**, pp 49-65.
13. Ichikawa, Y.; Isobe, M.; Goto, *T. Tetrahedron Lett*. **1987**, *43*, 4749-4758.
14. (a) Danishefsky, S. J.; Biodenau, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (b) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Aldrichim. Acta* **1997**, *30*, 75-92. (c) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685.
15. (a) Williams, L. J.; Garbaccio, R. M.; Danishefsky, S. J. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, **2000**; Vol. 1, pp 61-92. (b) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685. (c) Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 786. (d) Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126. (e) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064. (f) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. (g) Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. C* **1966**, 441. (h) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.
16. (a) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065. (b) Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268. (c) Henry, K. J.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128. (d) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250. (e) For a detailed review, please see: Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57.
17. (a) Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473. (b) Lemieux. R. U.; Morgan, A. R. *ibid.* **1965**, *43*, 2190.
18. (a) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**. 696. (b) Thiem, J.; Karl, H.; *Tetrahedron Lett.* **1978**, *19*, 4999. (c) Thiem. J.; Ossowowski, P. J. *Carbohydr. Chern.* **1984**, *3*, 287. (d) Thiem, J.; Prahst, A.; Wendt, T. *Liebigs Ann. Chem.* **1986**, 1044. (e) Thiem, J.; Klaffke, W. *J Org. Chem.* **1989**, *54*, 2006. (f) Thiem, J. *ACS Symp. Ser.* 1989, 396, Kap. **8.**
19. (a) Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem., Inl. Ed. EngI.* **1986**, *25*, 212. (b) David, S.; Lubinedu, A.; Vate1e. J.-M. *J. Chem. Soc. Chem. Cummun.* **1978**, 535.

(c) Vasella, A. *Pure Appl. Chem.* **1991**, *63*. 507. (d) Kahne. D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110,* 8716. (e) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. (f) Lemieux, R. U.; Nagdbhushan, T. L. *Can. J. Chem.* **1968**, *46*. 401. (g) Griffth. D. A.; Danishefsky, *S.* J. *J. Am. Chem. Soc.* **1990**, *112,* 5811.

20. (a) Danishefsky, S. J.; Halcomb, R. I. *J. Am. Chem. Soc.* **1989***, 111*, 6661. (b) Murray, R. W.; Jeyaraman, R. *J Org. Chem.* **1985**, *50,* 2847.
21. (a) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* **1990***, 112*, 8895. (b) Paulsen, H. *Angew. Chem., Inl. Ed. EngI.* **1982**, *94*, 184;. **1982**, *21,* 155. (c) Mootoo, D. R.; Kondradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110,* 5583.
22. (a) Thiem. J.; Köpper, S. *Tetrahedron* **1990**, *46*, 113. (b) Danishefshy S. J.; Selnick, H. G. ; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109,* 8119. (c) Kim, H. M.; Kim, I. J.; Danishefshy S. J. *J. Am. Chem. Soc.* **2001**, *123,* 35-48.
23. (a) Dushin. R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3472. (b) Dushin. R.; Danishefshy S. J. *J. Am. Chem. Soc.* **1991**, *113.* 655. (c) Link. J. T.; Gallant, M.; Huber, S.; Danishefshy S. J. *J. Am. Chem. Soc.* **1993**, *115,* 3782. (d) Link. J. T.; Raghavan, S.; Danishefshy S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552. (e) Link. J. T.; Raghavan, S.; Gallant, M.; Danishefshy S. J.; Chou, T. C.; Ballas. M. *ibid.* **1996**, *118,* 2825. (f) Gallant, M.; Link. J. T.; Danishefshy S. J. *J Org. Chem.* **1993**, *58,* 343. (g) Liu, K. K-C.; Danishefshy S. J. *J. Am. Chem. Soc.* **1993**, *115.* 4933. (h) Gervay, J.; Peterson, J. M.; Oriyama, T. Danishefshy S. J. *J Org. Chem.* **1993**, *58,* 5465. (i) Randolph, J. T.; Danishefshy, S. J. *J. Am. Chem. Soc.* **1993**, *115,* 8473. (J) Randolph, J. T.; Danishefshy S. J. *J. Am. Chem. Soc.* **1995**, *117,* 5693.
24. (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570-574. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 581-586. (c) Hotha, S.; Tripathi, A. *Tetrahedron Lett.* **2005**, *46*, 4555-4558, and references cited therein. (d) Wengel, J.; Lau, J.; Pedersen, E. B. *Synthesis* **1989**, 829.
25. (a) Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2654. (b) Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167. (c) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609. (d) E. Wieczorek, J. Thiem, *Synlett*, **1997**, 467
26. (a) Postema, H. H. *C-Glycosides Synthesis*, CRC Press, London, **1995**. (b) Hanessian, S.; Pernet, A. G. *Adv. Car. Chem. Biochem*. **1976**, *33*, 111-188. (c) Hacksell, U.; Daves, G.

D. *Prog. Med. Chem.* **1985**, *22*, 1-65. 67. (d) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 2175-2178.

27. (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1-56. (b) Armstrong, R. W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 915-922. (c) Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc. Chem. Commun.* **1989**, 642-643. (d) Dyer, U. C.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 3383-3384. (e) Martin, O. R.; Lai, W. *J. Org. Chem.* **1990**, *55*, 5188-5190.
28. (a) Koo, B.; McDonald, F. E. *Org. Lett.* **2005**, *17*, 3621-3624. (b) Danishefsky, S. J.; DeNinno. S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (c) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110,* 4368. (d) Danishefsky, S. J.; Armistead, D. M.; Wincott. F. E.; Selnick. H. G.; Hungate. R. *J. Am. Chem. Soc.* **1989**, *111,* 2967, *ibid.* **1987**, *109*, 8117. (e) Danishefsky, S. J.; Selnick. H. G.; Armistead, D. M.; Wincott. F. E. *ibid.* **1987**, 109, 8119.
29. (a) Herscovici, J.; Muleka, K.; Boumalza, L. I.; Antonakis, K. *J. Chem. Soc. Perkin. Trans. I* **1990**, 1995. (b) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *16*, 2571
30. (a) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, 57, 1244. (b) Squarcia, A.; Vivolo, F.; Weinig, H-G.; Passacantilli. P.; Piancatelli, G. *Tetrahedron Lett.* **2002**, *43*, 4653–4655.
31. (a) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Oriyama, T.; Griffith, D. A. *J. Am. Chem Soc.* **1992**, *114*, 8329. (b) Yu, J. *J. Bioorg. Med. Chem.* **1998**, *6*, 1145.
32. (a) Schreiber. S. L.; *Science* **2000**, *287*, 1964-1969. (b) Burke M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed*. **2004**, *43*, 46-58. (c) Kubota, H.; Lim, J.; Depew, K. M.; Schreiber, S. L. *Chem. Biol.* **2002**, *9*, 265-276. (d) Geis O.; Schmalz. H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911–914. (e) Brummond K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283. (f) Fletcher A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657-1668. (g) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312–318. (h) Hotha, S.; Tripathi, A. *J. Comb. Chem*. **2005**, *7*, 968-976.
33. (a) Domon, D.; Fujiwara, K.; Ohtaniuchi, Y.; Takezawa, A.; Takeda, S.; Kawasaki, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett*. **2005**, *46*, 8279-8283. (b) Reddy, B. G.; Vankar, Y. D. *Tetrahedron Lett*. **2003**, *44*, 4765-4767. (c) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549-5552. (d) Patterson, L.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727-5730.

34. (a) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 45-55. (b) Dorgan, B. J.; Jackson, R. F. W. *Synlett* **1996**, 859-861.
35. Schmidt, R. R.; Angerbauer, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 783-784.
36. (a) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res*. **1979**, *72*, 272-275. (b) Borrachero-Moya, P.; Cabrera-Escribano, F.; Go´mez-Guille´n, M.; Peredes-Leon, M. R. *Carbohydr. Res.* **1998**, *308*, 181-190. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380-1419. (d) Bussolo, V. D.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515-13516.
37. Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336-1337.
38. (a) Fraser-Reid, B. *Acc. Chem. Res*. **1975**, *8*, 192; **1985**, *18*, 347; **1996**, *29*, 57. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycoside*; Pergamon Press: Tarrytown, NY, 1995. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995. (d) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron* **1996**, *52*, 6397.
39. (a) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271-1274. (b) Shanmugasundaram, B.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.* **2002**, *43*, 6795-6798. (c) Grynkiewiez, G.; Priebe, W.; Zamojski, A. *Carbohydr. Res.* **1979**, *68*, 33-41. (d) Swami, N. R.; Venkateswarlu, A. *Synthesis* **2002**, 598-600. (e) Masson, C.; Soto, J.; Bessodes, M. *Synlett* **2000**, 1281-1282. (f) Yadav, J. S.; Reddy, B. V. S.; Murthy, C. V. S. R.; Kumar, G. M. *Synlett* **2000**, 1450-1451. (g) Bettadaih, B. K.; Srinivas, P. *Tetrahedron Lett.* **2003**, *44*, 7257-7259. (h) Babu, B. S.; Balasubramanian, K. K. *Synth. Commun.* **1998**, *29*, 4299-4305. (i) Yadav, J. S.; Reddy, B. V. S.; Reddy, J. S. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390-2394. (j) Smitha, G.; Reddy, C. S. *Synthesis* **2004**, 834–836.
40. (a) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M.; Konoshita, M. *J. Chem. Soc., Chem. Commun.* **1993**, 704-706. (b) Fraser-Reid, B.; Madsen, R. *J. Org. Chem.* **1995**, *60*, 3851-3858. (c) Koreeda, M.; Houston, T. A.; Shull, B. K.; Klemke, E.; Tuinman, R. J. *Synlett* **1995**, 90-92. (d) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1992**, 94-95. (e) Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *New J. Chem.* **2001**, *25*, 538-540. (f) Agarwal, A.; Rani, S.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 6137-6140. (g) Suzuki, K.; Hashimoto, T.; Maeta, H.; Matsumoto, T. *Synlett* **1992**, 125-128.
41. (a) Lopez, J. C.; Gomez, A. M.; Valverde, S.; Fraser-Reid, B. *J. Org. Chem*., **1995**, *60*, 3851. (b) Toshima, K.; Tatsuta, K. *Chem. Rev*., **1993**, *93*, 1503. (c) Toshima, K; Ishizuka, T; Matsuo, G; Nakata, M; Kinoshito, M. *J.Chem.Soc., Chem.Commun*. **1993**, 704. (d) Mereyala, H. B.; Venkataramanaiah, K. C. *J. Chem. Res (S)*. **1991**, 197.

42. (a) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. S*ynlett*, **1995**, 306. (b) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *J. Chem. Soc., Chem. Commun*., **1995,** 306. (c) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *J. Chem. Soc., Chem. Commun*., **1996**, 1379.
43. (a) Bhagavathy, S.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.,* **2002**, *43*, 6795. (b) Ferrier, R.J. *Topics in Current Chemistry*, **2001,** *215*, 153. (c) Boga, S. B.; Balasubramanian, K. K. *Carbohydrate Lett*. **1999**, *3*(5), 339.
44. (a) Boga, S. B.; Balasubramanian, K. K. ''Lithium tetrafluoroborate catalyzed Ferrier rearrangement of tri-*O*-acetyl-D-galactal-Facile synthesis of alky 2,3-unsaturated glycopyranosides'' *215th American Chemical Society meeting*, Dallas, USA, March 29 to April 2, **1998**. (b) Boga, S. B.; Balasubramanian, K. K. *Syn. Commun.* **1999**, *29*, 4299. (c) Boga, S. B.; Balasubramanian, K. K. *Tetrahedron Lett.* **1999,** *40*, 5777. (d) Boga, S. B.; Balasubramanian, K. K. ''Lithium tetrafluoroborate in organic synthesis-Some recent developments'' *Acros Organics Acta* **1999**, *7*, 1.
45. (a) Li, C. J.; Chan, T-H. *Tetrahedron* **1999**, *55*, 11149. (b) Babu, G.; Perumal, P. T. *Aldrichima Acta.* **2000**, *33*, 16. (c) Ghosh, R. *Indian. J. Chem*, **2001**, *40B*, 550.
46. (a) Boga, S. B.; Balasubramanian, K. K. ''Synthesis of alkyl and aryl 2,3-unsaturated glucopyranosides-Catalyzed by indium trichloride'' *218th American Chemical Society meeting*, New Orleans, USA, August 22-26, **1999**. (b) Boga, S. B.; Balasubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271.
47. (a) Yadav, J. S.; Reddy, B. V. S.; Raman, J. V.; Niranjan, N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett*. **2002**, *43*, 2095. (b) Das, S. K.; Reddy, K. A.; Roy, J. S*ynlett*., **2003**, *11*, 1607 and references cited there in. (c) Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K. V. L. N.; Sacwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003,** *44*, 4507.
48. Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. Org. Lett. **2007**, *9*, 3173-3176.
49. Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962-6963.
50. (a) Chapleur, Y.; Chetien, F. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, **1997**; pp 207-262. (b) Yoshima, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69-134. (c) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1987**, *48*, 279-318. (d) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28,* 413-453.
51. Hang, H. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 1242-1243.
52. (a) Jackman, J. E.; Fierke, C. A.; Tumey, L. N.; Pirrung, M.; Uchiyama, T.; Tahir, S. H.; Hindsgaul, O.; Raetz, C. R. H. *J. Biol. Chem*. **2000**, *275*, 11002-11009. (b) Li, X.; Uchiyama, T.; Raetz, C. R. H.; Hindgaul, O. *Org. Lett*. **2003**, *5*, 539-541.

53. For reviews, see: (a) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev*. **2000**, *29*, 165-174. (b) Lebel, H.; Marcoux, J.-F.; Malinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151-1196. (d) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919-7946. (e) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198.

54. For solvolysis conditions, see: (a) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.* **1996**, *291*, 205-208. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094-2096. (c) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295-1297. (d) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533-2536. (e) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem*. **1997**, *62*, 7694-7703. (f) Ramana, C. V.; Nagarajan, M. *Synlett* **1997**, 763-764. (g) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000-8003. (h) Beyer, J.; Skaanderup, P. R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575-9583. (i) Beyer, J.; Madsen, R. *J. Am. Chem. Soc*. **1998**, *120*, 12137-12138.

55. Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran *Org. Lett.* **2004**, *6*, 1777-1779.

56. (a) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1970**, *48*, 3253-3257. (b) Bischofberger, K.; Brink, A. J.; de Villiers, O. G.; Hall, R. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1472-1476. (c) Herscovici, J.; Egron, J. M.; Antonakis, K. *Carbohydr. Res.* **1985**, *142*, 324–328. (d) Sugimura, H.; Osumi, K.; Koyama, T. *Chem. Lett.* **1991**, 1379-1382. (e) Takenuki, K.; Matsuda, A.; Ueda, T.; Sasaki, T.; Fujii, A.; Yamagami, K. *J. Med. Chem.* **1988**, *31*, 1063-1064. (f) Ueda, T.; Matsuda, A.; Yoshimura, Y.; Takenuki, K. *Nucleosides Nucleotides Nucleic Acids* **1989**, *8*, 743-752. (g)Samano, V.; Robis, M. J. *Synthesis* **1991**, 283-288. (h) Ali, M. H.; Collins, P. M.; Overend, W. G. *Carbohydr. Res.* **1990**, *205*, 428-434.

57. For 2-deoxy-2-C-substituted carbohydrates and 2'C-methylene nucleosides refer: Sugimura, (a) H.; Osumi, K.; Koyama, T. *Chem. Lett.* **1991**, 1379-1382. (b) Herscovici, J.; Egron, J.M.; Antonakis, K. *Carbohydr. Res.* **1985**, *142,* 324-328. (c) Bischofberger, K.; Brink, A.J.; de Villiers, O.G.; Hall, R.H.; Jordaan, *A. J. Chem. Soc., Perkin Trans 1* **1977**, 1472-1476. (d) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1970**, *48,* 3253-3257. (e) Samano, V.; Robins, M. J. *Synthesis* **1991**, 283-288. (f) All, M.H.; Collins, P.M.; Overend, W.G. *Carbohydr. Res.* **1990**, *205,*428-434.

58. (a) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.: Ueda, *T. J. Med. Chem.* **1991**, *34,* 812-819. (b) Baker, C.H.; Banzon, J.; Bollinger, J.M.; Stubbe, J.; Samano, V.; Robins, M.J.; Lippert, B.; Jarvi, E.; Resvick, R. *Chemtracts-Organic Chemistry* **1991**, *4*, 426-429.

59. (a) Booma, C.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1993**, 1394-1395. (b) Gupta, A.; Vankar, Y. D. *Tetrahedron* **2000**, *56*, 8525-8531. (c) Ghosh, R.; Chakraborty, A.; Maiti, D. K.; Puranik, V. G. *Tetrahedron Lett*. **2005**, *46*, 8047-8051. (d) Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1993**, *34*, 6757-6760. (e) Wolf, J.; Monneret, C.; Pontikis, R.; Florent, J.-C. *Eur. J. Org. Chem.* **1998**, 2417–2423. (f) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron* **1995**, *51*, 255–272.

60. (a) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett*. **1991**, *32*, 3875–3878. For a review on C-2 formyl glycals, see: (b) Ramesh, N. G.; Balasubramanian, K. K. *Eur. J. Org. Chem*. **2003**, 4477–4487.

61. (a) Kashyap, S.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 2021-2023. (b) Kashyap, S.; Vidadala, S. R.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 8960-8962.

******

Chapter 2

Alkyne activation for glycoside and saccharide syntheses

Chapter 2: Introduction

The area of organic chemistry that deals with the study, preparation and biological role of carbohydrates, from monosaccharides to complex saccharides and their analogues, is called Glycobiology. Advances in glycobiology established the role played by oligosaccharides and glycoconjugates in various biological processes.[1] Complex carbohydrates are distributed in numerous biological systems, play significant roles in a diverse set of processes, including viral and bacterial infection, tumor metastasis, angiogenesis, inflammation, immunological response, signal transduction, and cell–cell communication.[2] A major problem to advance in glycobiology is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in micro-heterogeneous forms, which complicate their isolation and characterization.[3] Furthermore, the development of routine procedures for the chemical synthesis of oligonucleotide fragments (DNA and RNA) as well as peptide and lipid-bound glycoconjugates has altered the face of modern biology. The important role of carbohydrates in Biology and Biomedicine has been a major incentive for devising new methods for the chemical and enzymatic synthesis of this class of molecules. The increased appreciation of the role of carbohydrates in the biological and pharmaceutical sciences resulted in a revival of interest in carbohydrate chemistry. All these facts have made the area of saccharide synthesis an ideal and challenging area for the development and testing of new synthetic methodologies. For the synthesis of these potent sugars, the development of novel and efficient methodologies to construct the glycosidic bond has gained an immense attention in carbohydrate chemistry.

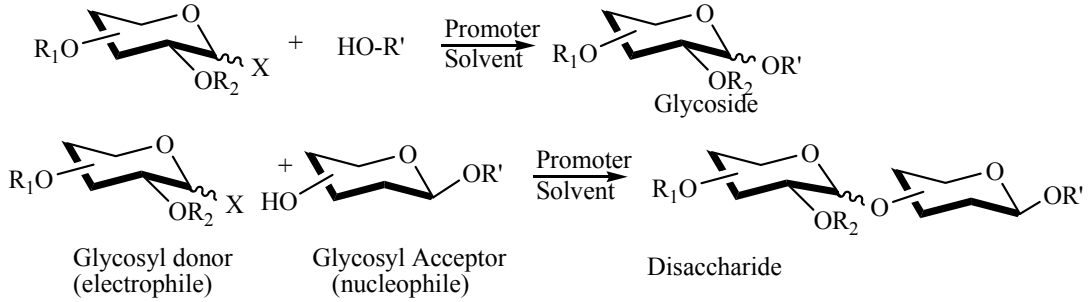
Glycosidic bond formation:

Synthetic manipulation of anomeric center of glycosyl donor is significantly important, since it plays a key role in the syntheses of oligosaccharides and higher saccharides. The chemical synthesis of oligosaccharides is much more complicated than the synthesis of other biopolymers such as peptides and nucleic acids. The difficulties in the preparation of complex oligosaccharides are a result of a greater number of possibilities for the combination of monomeric units to form oligosaccharides. In addition the glycosidic linkages have to be introduced stereospecifically.

The chemical synthesis of glycosides involves nucleophilic displacement of a leaving group (X) from anomeric carbon of a sugar moiety, a fully protected saccharide, by an aglycones (R'OH, Figure 1) frequently containing only one hydroxyl group.[4] The sugar that "gives" the glycosyl moiety, is called the *glycosyl donor*, and the alcohol that receives it, is

known as *glycosyl acceptor*. The reaction generally is performed in the presence of an activator called "promoter". Generally promoters such as Lewis acids assist the departure of leaving group and promote the easy formation of an oxocarbenium ion which will then be attacked by the aglycone to form glycosides.[4,5] Promoters are often used in catalytic amounts, although in some instances they are used stoichiometrically. In some cases, other additives such as molecular sieves or any base that may act as acid scavenger are used.

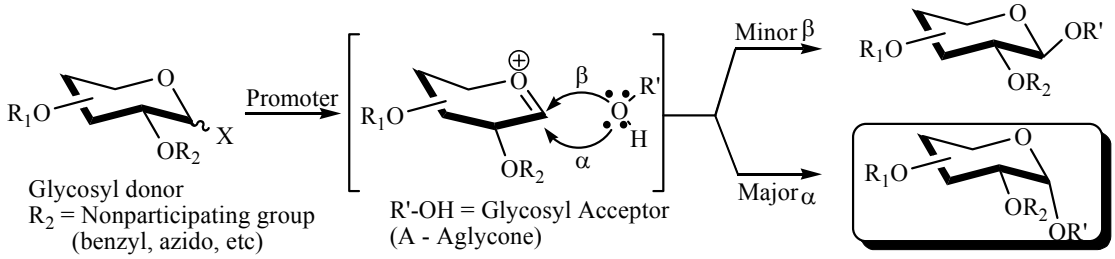
Figure 1



General Mechanism for Glycosidation:

In a disaccharide synthesis, two polyfunctional sugar components must be linked. Regioselectivity is generally achieved when the glycosylating component (glycosyl donor) possesses selectively protected hydroxyl groups and an activating group at the anomeric carbon atom and when the sugar component with the free hydroxyl group (glycosyl acceptor) possesses protecting groups at all other hydroxyl functions.[6] Thus, complicated protecting strategies and suitable procedures for activation at the anomeric carbon atom are required. In addition, glycosylation step must occurs diastereoselectively with respect to the formation of an α or β linkage.

Figure 2

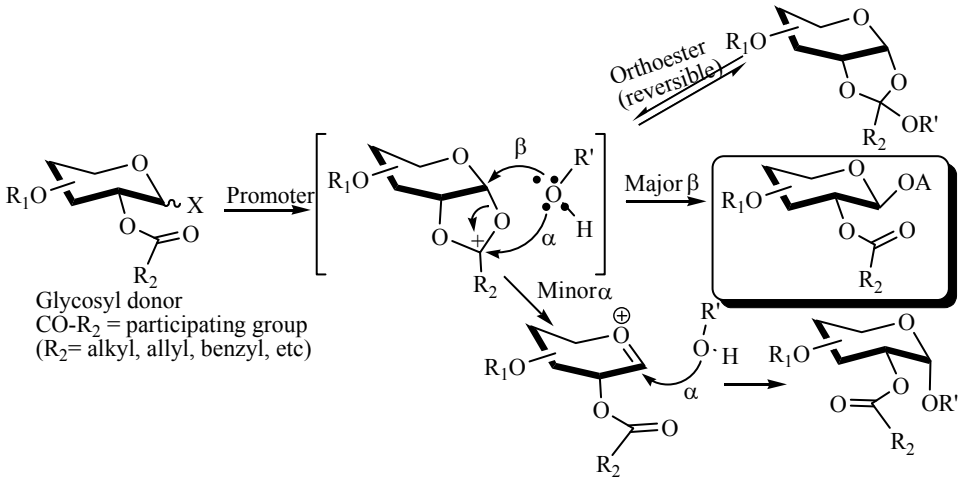


In general, the glycosidation proceeds via a simple mechanism. There are some exceptions such as *in situ* anomerization,[7] intramolecular aglycone delivery and the use of additives such as acetonitrile, which appears to react at the anomeric center itself. In the case of glycosyl donors having substituents such as ethers etc., at *C*-2, initial formation of

oxocarbenium ion followed by attack of an alcohol from both faces resulting in the formation of 1, 2- *cis* and 1, 2-*trans* isomers (Figure 2).

While in case of orthoester glycosyl donors or glycosyl donors having substituent such as esters etc., at *C*-2, initial formation of oxocarbenium ion and then, this will be in equilibrium with the stable dioxolenium (acyloxonium) ion which was formed by neighbouring group participation of 2-*O*-acyl or 2-*O*-benzoyl group that allows a unidirectional attack of an aglycone resulting in the formation of 1, 2-*trans* isomer (Figure 3).

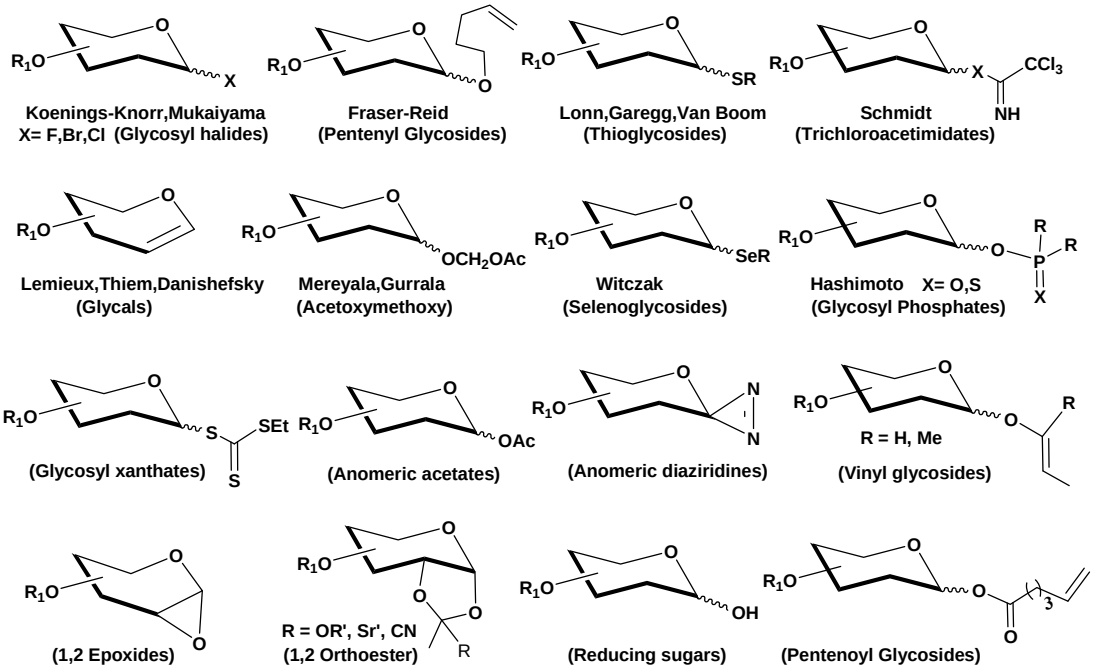
Figure 3



General Glycosyl Donors used for Saccharide Synthesis:

The preparation of oligosaccharides of a particular size is only possible when a synthetic strategy is highly convergent. In such a glycosylation strategy, most of the synthesis effort is directed towards the preparation of the monomeric glycosyl donors and acceptors. Most of the efforts have focused on the invention of new glycosyl donors. There are numerous glycosylation methods involving different glycosyl donors.[8] Glycosyl trichloroacetimidates,[8a] thioglycosides,[8b-c] glycosyl halides,[8d] 4-*n*-penten-1-yl glycosides,[8e] glycosyl sulfoxides,[8f] glycals,[8g] selenoglycosides,[8h] glycosyl phosphates,[8i] phosphites,[8j] and 2-(hydroxycarbonyl) benzyl glycosides[8k] are most widely used glycosyl donors for the synthesis of oligosaccharides and glycoconjugates. Among these common protocols, the stable thioglycosides and 4-*n*-penten-1-yl glycosides serve not only as anomeric-protected sugars for manipulation of functional groups at various positions, but also as glycosyl donors for further coupling with various alcohols in the presence of activators. The name of the glycosylation method generally reflects the functionality of the glycosyl donor except for the Fischer glycosylation that uses reducing sugars and the Köening-Knorr procedures that use glycosyl halides as donors.

Structure of glycosyl donors:



Factors affecting the glycosylation:

The success of coupling reaction between two sugars and α/β ratio mainly depend on

- Reactivities of glycosyl donor and glycosyl acceptor
- Orientation of substituent R: equatorial vs. axial
- Substituent R: participating vs. non-participating
- Configuration, substituent, steric and electronic effect in donors and acceptor (e.g. D-glucopyranosyl and D-galactopyranosyl donors with identical substituent sometimes give different α/β ratio with the same alcohol acceptor.
- Preferred selectivity of the reaction towards the α- and β- anomeric form
- Type of leaving group (X)
- Type of promoter, Solvent, Temperature and Pressure

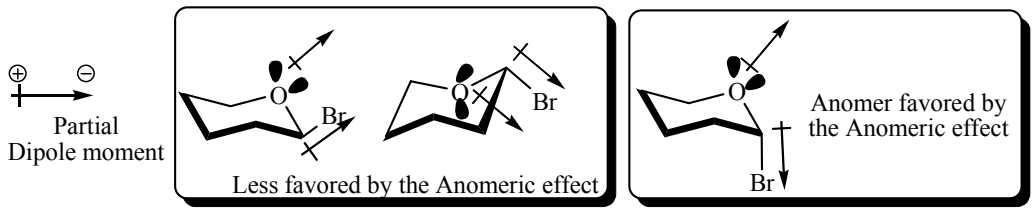
Anomeric effect:[9]

The equatorially substituents of a pyranose chair ring are most energetically favored as compared to their axial counterparts because of steric reasons. However, in D-pyranosides and especially carbohydrates derivative with electronegative group at anomeric center, an axial position is often more stable than that would be predicted from the steric interaction with adjacent substituent. The unusual preference of sterically unfavored axial position over the equatorial position at anomeric center has been termed as 'anomeric effect'. The anomeric effect is different for each case and is strongly influenced by the substituent at *C*-2 position. When this is equatorial, as in glucose and galactose, the anomeric effect is weakened, and is

enhanced in *C*-2 axial substituent in mannose. Moreover, the nature of anomeric group is of crucial influence for the anomeric effect, as it is proportional to the electronegativity of the anomerically bound atom. Solvents also influence the anomeric effect, such that increased polarity of the solvent used decreases the anomeric effect on the equilibrium of the two alternative conformers in solution.

The anomeric effect can be explained on the basis of intramolecular electrostatic interaction of two dipoles next to the anomeric center. Anomeric configurations, where the two nearly perpendicular dipoles partially neutralize each other (an energetically more stable arrangement, as in axial substituent) are favored over the diastereomers where the anomeric configuration leads to intramolecular addition of the two parallel dipoles (an energetically unfavorable arrangement, as in equatorial substituent) (Figure 4).

Figure 4

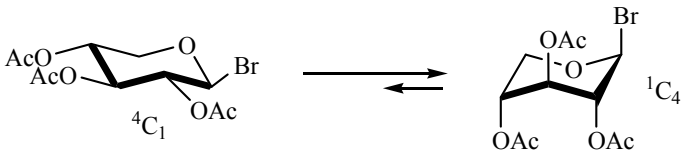


If two hetero atom bound to a tetrahedral center, essential group for the anomeric effect

C-X-C-Y Where X = N, O, S And Y = Br, Cl, F, O, S, N

In the absence of other effects, the existence of this dipole should favor the conformation with an axial orientation for electronegative groups. This may even lead to the conformational changes as *β*-xylopyranosyl bromide which prefer the sterically unfavored $^{1}C_{4}$ conformation due to the strongly anomeric effect of the bromo atom (Figure 5).

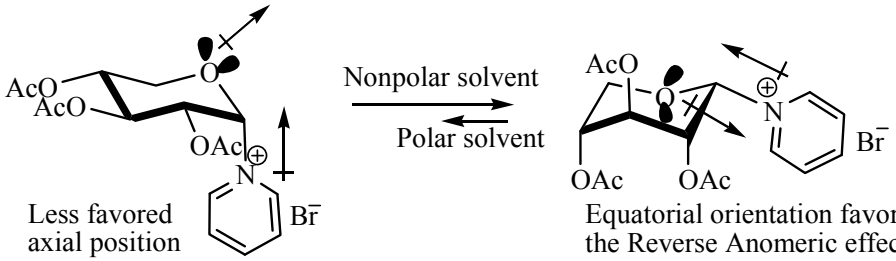
Figure 5



Reverse anomeric effect:[10]

If the substituent at anomeric center is clearly electropositive compared to the anomeric carbon, such as positively charged nitrogen atom or alkoxycarbonyl, the same electrostatic consideration lead to the stabilization of anomer with equatorially positioned anomeric group. This has been termed as 'reverse anomeric effect'. It is assisted by the fact that equatorial ring position is energetically more favored due to steric reasons alone, especially in the case of large substituent like pyridinium group (Figure 6).

Figure 6

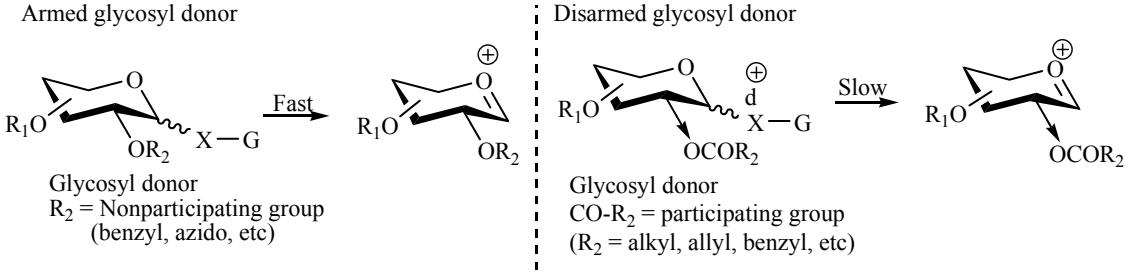


The reason for the existence reverse anomeric effect is probably primarily is a dipole-dipole interaction. Since these two dipoles are oriented in opposite direction, the most stable arrangement (an energetically favourable arrangement, as in equatorial substituent) for them is to be parallel to each other. An anomeric pyridinium group leads to a reverse dipole at the anomeric carbon and consequently a 'reverse anomeric effect' is observed.

Armed/Disarmed effects: Reactivities of glycosyl donors

The reactivity of glycosyl donors mostly depends on the choice of the protecting groups that are attached to it especially at *C*-2. Glycosyl donors are then classified into two main groups: armed donors with an ether group on *C*-2, and disarmed donors with esters, amides on *C*-2. A general rationalization for armed and disarmed effects first recognized in *n*-pentenyl glycosides[11] but recently this concept has been extended to a variety of glycosyl donors.[12] It is very difficult to predict which glycosyl donors will be the most suitable in glycosylation reaction to solve a problem in an oligosaccharide synthesis. However, there are some factors influencing the reactivity of glycosyl donors that should be taken into account and that can be further used in the optimization of an oligosaccharide synthesis. Generally armed donors are more reactive than disarmed donors as reaction of a glycosyl donor with an appropriate leaving group gives a positively charged intermediate (oxocarbenium ion), which is less favorable when there is electron-withdrawing group (for example -OCOR, as in a disarmed donor) than when there is an adjacent alkoxy group (as in the armed counterpart). These observations suggested that the glycosyl donor could be 'armed' or 'disarmed' by the type of protection group placed on the *C*-2 hydroxyl group (Figure 7).

Figure 7



A novel glycosyl donor must have the following characteristics.

Accessibility, Easier preparation, Stability toward environmental conditions, High stability toward protecting group manipulation and Requires mild activation conditions.

Reactivity of Glycosyl Acceptors:

With respect to the reactivity of the glycosyl acceptors,

- The nucleophilicity of the hydroxyl groups in partially protected carbohydrates affect the reactivity. Generally *primary* hydroxyl groups are more reactive than *secondary* hydroxyl groups in glycosylation.
- The spatial orientation of the hydroxyl groups also affects the reactivity of glycosyl acceptor. Generally, *equatorial* hydroxyl groups are more reactive than *axia*l hydroxyl groups.
- The presence of electron-withdrawing groups and bulky substituents in glycosyl acceptors also decrease the reactivity of an acceptor.

When all hydroxyl groups attached to *C*-2, *C*-3, *C*-4 and *C*-6 in an aldo-hexopyanoside have an equatorial orientation, the general orders of reactivity in forming glycosidic linkages are: 6-OH >> 3-OH >>2-OH >>4-OH.

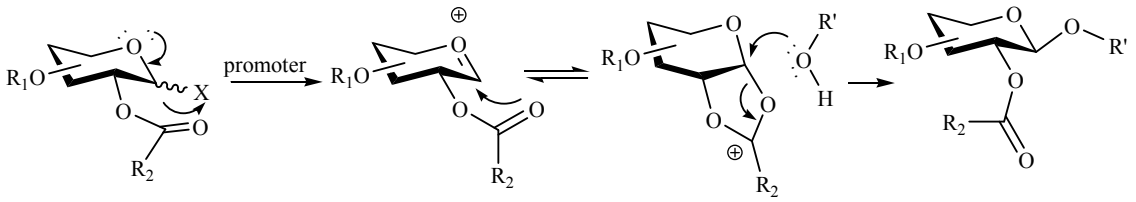
Anomeric Selectivity for 1,2-*cis* and 1,2-*trans* linkage:

Due to the multi-step character of typical synthetic schemes, the isolation of oligosaccharides and their derivatives by formation of a mixture of two stereoisomers that differ in the configuration of the anomeric centre is difficult. If these anomers are not separated after each glycosylation, complex mixtures of products cannot be used for biological studies. Routine oligosaccharide synthesis will only be possible when robust stereoselective glycosylation become available. The most reliable methods for stereoselective glycosidic bond formations are:

Neighbouring group Participation of the 2-*O*-acyl functionality:

In these reactions, a promoter activates an anomeric leaving group resulting in its departure and the formation of an oxocarbenium ion. The involvement of ester group at *C*-2 position in a glycosidation reaction leads to an acyloxonium (dioxolenium) ion intermediate which is formed from the oxocarbenium ion produced initially. Then, this is in equilibrium with a stable acyloxonium ion intermediate which was formed by neighbouring group participation of the *C*-2-*O*-acyl protecting group. Hence an aglycone can attack the anomeric centre of acyloxonium ion from only one face providing a 1, 2-*trans*-glycosides. Thus, in the case of glucosyl-type donors, β-linked products will be formed, while mannosyl type-donors will give α-glycosides (Figure 8).

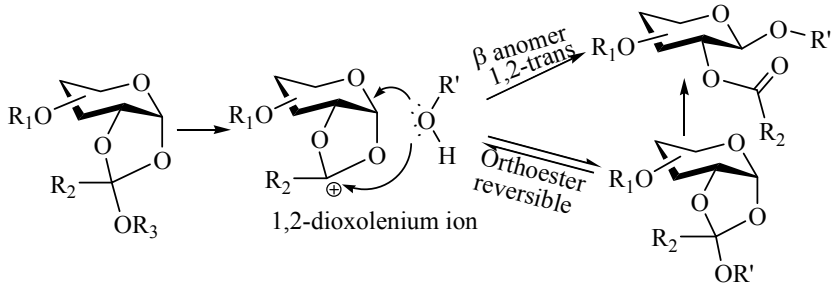
Figure 8



Ortho-ester strategy:

Nucleophilic attack of an aglycone at the dioxolane ring carbon of the oxocarbenium ion leads to the formation of orthoester, which might eventually be isomerized to respective glycoside. The formation of orthoesters can become more facile under the neutral or basic conditions. In case of axial *C*-2-*O*-acyl group (as in mannose) the intermediate acetoxonium ion is favored due to the 'reverse anomeric effect', and consequently orthoester formation may be predominant. Using benzoate or pivaloates group at *C*-2 position strongly reduces the formation of orthoester as compared to acetyl group. Thus, glycosidations proceed in a straightforward manner when 1,2-*trans* glycosides are the target molecules and *C*-2 neighboring groups are involved. The involvement of ester group at *C*-2 position in a glycosidation reaction leads to acyloxonium (dioxolenium) ion intermediate and furnish 1,2-*trans* isomer via direct glycosylation of an alcohol at anomeric carbon or through two-stage glycosylation in which the formation of intermediate orthoester followed by its isomerization leads to the formation of 1,2-*trans* isomer (Figure 9).

Figure 9

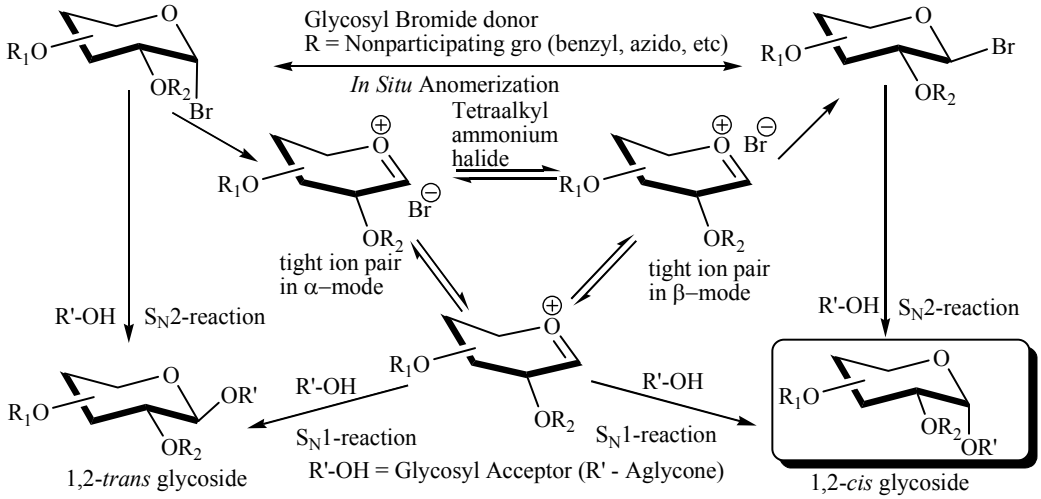


This is the case for β-glucosides, β-galactosides, and α-mannosides. On the other hand, introduction of 1,2-*cis*-glycosidic linkages, such as α-glucosides and α-galactosides is problematic and requires glycosyl donors with a non-assisting functionality like ethers at *C*-2. Thus, the synthesis of 1,2-*cis*-glycosidic bond formation is extremely difficult and especially the synthesis of β-mannosides is a particularly well known problem.

1,2-*cis*-glycosidation:[7]

1,2-*cis*-glycosidations are much more difficult than that the synthesis of 1,2-*trans*-glycosides. For example, the S_N2 reaction at anomeric center of a β-glycosyl bromide (non assisting substituent at *C*-2) would furnish α-glucosides and α-galactosides. However, this is not possible because β-glycosyl halides are greatly destabilized by 'anomeric effect'. Moreover, the α-glycosyl bromide reacts with the bromide anion of tetraalkyl ammonium bromide and produced highly reactive β-glycosyl bromide which reacts much faster than its α-analog to give large proportion of α-glycosides in a kinetically-controlled reaction. This process has been called *in situ* anomerization and works well for galactose and fucose as donors but less effective for glucose and β-mannosides cannot be obtained at all by this approach. Moreover, the proportion of α-glycosides is decreased with lower reactivity of donor and acceptor hydroxyl group (Figure 10).

Figure 10

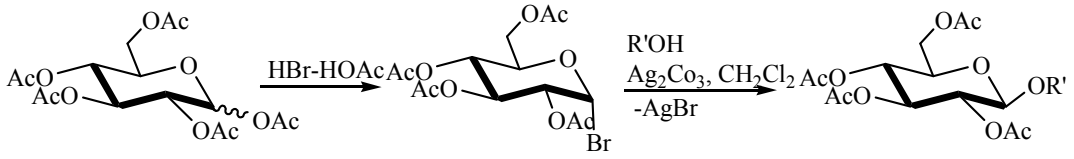


Some selected procedures for glycosylation reactions in oligosaccharide synthesis:

Köenings-Knorr and related methods:[13]

The oldest and still the most widely used method for the stereospecific synthesis of 1,2-*trans* glycosides is the Köenings-Knorr reaction. The Köenings-Knorr method uses glycosyl bromides and chlorides as glycosyl donors in the glycosylation reaction. Insoluble promoters such as Ag_2O and Ag_2CO_3 were initially used. Soluble catalysts including $HgBr_2$ and $Hg(CN)_2$[13b] (Helferich-Weiss, 1956) and AgOTf (Hanessian-Banoub, 1977),[13a] were exploited as promoters. Sometimes, tetramethyl urea along with promoter is necessary to increase the yield of glycosylated products in glycosylations. With participating groups at *C*-2 position the Köenings-Knorr reaction normally leads exclusively to 1,2-*trans* glycosides (Scheme 1).

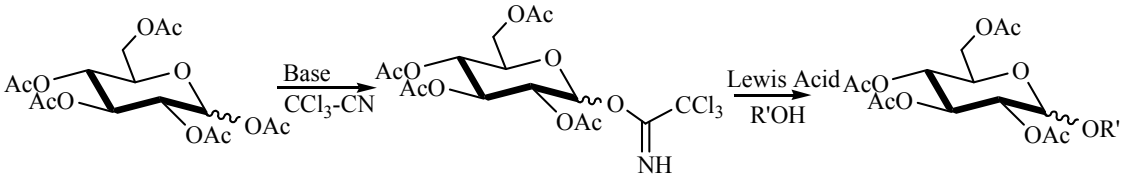
Scheme 1



Trichloroacetimidates method:[14]

In glycosyl trichloroacetimidates, the anomeric oxygen atom of hemiacetalic sugars has been derivatized into a good leaving group. This makes glycosyl trichloroacetimidates good glycosyl donors which can be activated by Lewis acid catalyst such as $BF_3.Et_2O$ or TMSOTf. *β*-glycosyl trichloroacetimidates are more stable than the respective glycosyl halides and can be synthesized directly from 2,3,4,6 -*O*-protected reducing sugar. Base treatment leads to anomeric oxyanion, which adds across the C≡N bond of trichloroacetonitrile to yield the desired glycosyl trichloroacetimidates (Scheme 2).

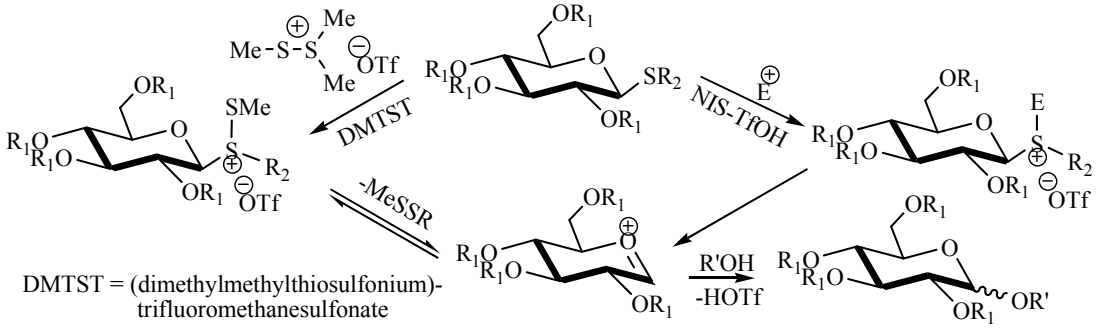
Scheme 2



Thioglycosides:

Thioglycosides are quite often the glycosyl donors[15,27] of choice for the synthesis of oligosaccharides, especially in glycosidation of amino sugar. In this method, an electrophile or a thiophilic reagent activates the thioglycoside by producing intermediate sulfonium ions, which then give rise to glycosylating carbocationic intermediates that react with the glycosyl acceptor giving the glycoside. The promoters for these reactions are iodinium dicollidine triflate, DMTST, MeOTf and NIS-TfOH (Scheme 3).[15,27]

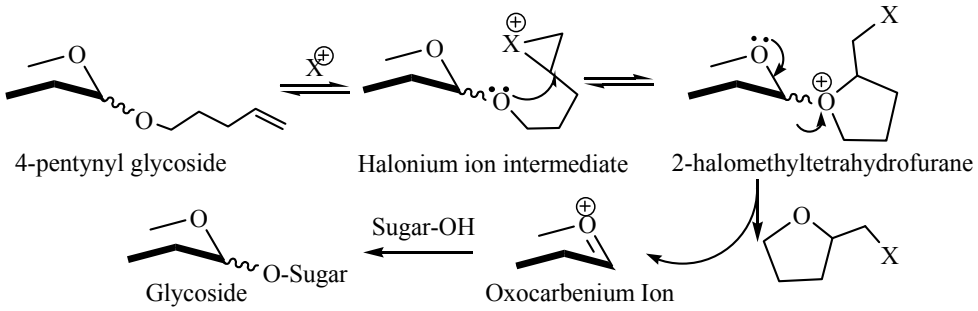
Scheme 3



4-Pent-1-enyl glycoside and 4-Pent-1-enyl-1,2-orthoester method:

4-Pentenyl glycosides are the stable under most conditions except those of hydrogenation. Interestingly, they can be regarded as masked glycosyl donors as they can be activated under very sophisticated condition introduced by Fraser-Reid.[11] Activation of the leaving group is based on an electrophilic addition of halonium ion leads to the formation of a cyclic halonium ion intermediate when reacted with the pentenyl double bond of the glycosyl donor. This intermediate then rearranges to a second intermediate containing a leaving group 2-halomethyltetrahydrofurane. Therefore, an intramolecular displacement by the ring oxygen and simultaneous expulsion of this leaving group results in the formation of an oxonium species which was then trapped by a glycosyl acceptor to form desired glycoside. The promoter of choice is any source of halonium ion, NBS or NIS alone or activated by Lewis acid, NIS/Et_3SiOTf, NIS/TfOH and NIS/Yb $(OTf)_3$ (Figure 11).[16]

Figure 11



*****

Chapter 2: Present Work

Many different theories for glycosylation methods have been advanced concerning the broad and diverse nature of the glycosyl donors. With the stimulant biological background, the *O*-glycosylation method, which is a crucial synthetic organic methodology to attach sugar to the other sugar moieties or other molecules (aglycone), is again becoming more and more important. Since the major historical advance of the Köenings-Knorr method in 1901, considerable attention has been directed toward the efficiency of the *O*-glycosylation method. From a synthetic standpoint, the efficiency of the *O*-glycosylation reaction generally demands high yielding, regioselectivity and stereoselectivity. Regioselectivity is generally achieved when the glycosylating component (glycosyl donor) possesses selectively protected hydroxyl groups and an activating group at the anomeric carbon atom and when the sugar component with the free hydroxyl group (glycosyl acceptor) possesses protecting groups at all other hydroxyl functions. Thus, complicated protecting strategies and suitable procedures for activation at the anomeric carbon atom are required. The stereoselective introduction of the glycosidic linkage is one of the most challenging aspects in oligosaccharide synthesis. The nature of the protecting group at *C*-2 of the glycosyl donor is a major determinant of the anomeric selectivity. A protecting group at *C*-2 which can perform neighbouring group participation during glycosylation will give 1,2-*trans* glycosidic linkages. On the other hand, when a non-assisting functionality is present at *C*-2 then the reaction conditions (e.g. solvent, temperature, and promoter) will determine the anomeric selectivity. Moreover, the constitution of the glycosyl donor and acceptor *(e.g.* type of saccharide, leaving group at the anomeric centre, protection and substitution pattern) have a major effect on the α:β selectivity.

In spite of the development of efficient variants, however, severe, partly inherent disadvantages of the known glycosylation methods for the synthesis of oligosaccharides could not be overcome. To date, there are no general applicable methods or strategies for oligosaccharide synthesis and consequently the preparation of these saccharide molecules is very time consuming. These disadvantages include the following:

- The glycosyl halides exhibit low thermal stability and can often be generated only in situ and at lower temperatures and are highly sensitive to hydrolysis, thus necessitating the use of compounds that are frequently sterically nonhomogeneous and sometimes even impure.

- Always requires combination of reagents. When using halosuccinimides alone, the reaction was very slow. In these cases, chances of the decomposition of glycosyl donor increases.
- Use of expensive heavy-metal salts, especially in large scale reactions, is often dangerous (toxicity of mercury salts, explosions with silver perchlorate; these risks can be reduced sometimes by using catalytic amounts).
- In most of existing glycosylation methods, relatively harsh conditions are needed for the generation of the intermediate oxocarbenium ion.
- Promoters were used in either stoichiometric or excess quantities.
- Due to the instability of glycosyl donors, non-stoichiometric quantity was observed in the ratio related to the donor: acceptor equivalents.

Due to some basic disadvantages in existing glycosylation methods and the synthetic challenges in oligosaccharide syntheses, most of the synthetic effort is directed towards the preparation of the monomeric glycosyl donors and acceptors. Most of the efforts have focused on the discovery of new glycosyl donors. A new saccharide synthesis must meet the following requirements:

1) The first step must involve a sterically uniform activation of the anomeric center resulting in the formation of a stable glycosyl donor having either an α- and/or β-configuration.
2) The second step should involve a catalytic activation of anomeric center, followed by irreversible glycosyl transfer to the acceptor and furnish desired glycoside in high chemical yield.

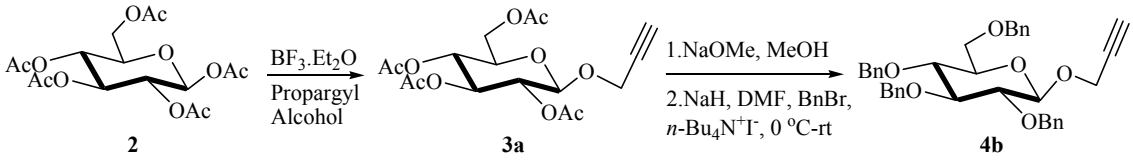
Thus the area of saccharide syntheses has been very challenging and lots of attention paid to this area for the designing and development of new glycosylation methodologies. The development and optimization of new glycosylation methodologies are of utmost importance in sugar chemistry. Our approach to this challenge grew out of the serendipitous discovery of propargyloxy group as a leaving group in the presence alkynophilic gold catalyst.[17,18b-c] The recent studies in our lab as delineated in chapter 1 have made us understand that the Propargyl glycosides could serve as stable glycosyl donors exploiting the gold catalysis. If successful then several advantages can be attributed to the propargyl glycosides.

In this premise, we envisaged that transition metal mediated activation of propargyl glycosides would be advantageous as propargyl glycosides can be (i) synthesized from aldoses by modified Fisher glycosidation, (ii) stable to diverse chemical manipulations, (iii) directly used for saccharide coupling, and (iv) chemoselectively activated. As part of our ongoing

research in carbohydrate chemistry and our continued interest in development of novel methods for glycoconjugates and saccharide syntheses,[17,18] utility of propargyl glycosides for anomeric activation and glycoside synthesis has been explored. To begin our investigation, our approach required propargyl glycosides precursor for the transglycosylation reaction.

Accordingly, commercially available stable penta-*O*-acetyl-*β*-D-glucopyranoside (**2**) has been reported to react with alcohol (3-5 mole equivalents) in the presence of Lewis acid catalyst such as $SnCl_4$,[19a] $BF_3.Et_2O$ (2-10 mole equivalents)[19b] and catalytic *p*-toluenesulfonic acid[19c] to form corresponding propargyl 2,3,4,6 tetra-*O*-acetyl-*β*-D-glucopyranoside (**3a**). The strategy involved preparation of propargyl 2,3,4,6 tetra-*O*-acetyl-*β*-D-glucopyranoside (**3a**) first and functional group transformation of **3a** through a two-step deacetylation (NaOMe, MeOH) and per-*O*-benzylation (NaH, BnBr) to furnish corresponding per-*O*-benzylated derivative (**4b**). Thus, penta acetate **2** was reacted with propargyl alcohol (1.2 mole equivalents) and $BF_3.Et_2O$ (1.5 mole equivalents) in dry dichloromethane at room temperature for 2 h to afford (**3a**) in very poor yield as compared to reported procedure (Scheme 4).[19b] In our experience, these reactions using **2** and propargyl alcohol are very much dependent upon time, temperature and concentration of the substrate and invariably lead to the formation of anomeric mixture in inconsistent yields and we could not easily optimise these conditions to obtain desired product in good yields. Hence, we have altered the procedure for preparing the propargyl glycosides.

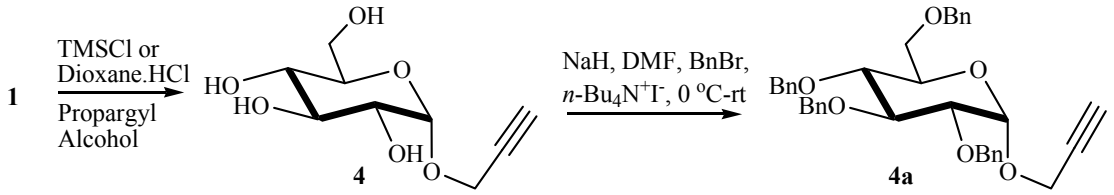
Scheme 4



Fisher glycosidation has been used for the anomeric protection of monosaccharides. The reaction is carried out in the presence of an acid catalyst in alcohols under reflux condition, certain amount of by-products are generally formed owing to the polymerization of the propargyl alcohol. Therefore, in a modified procedure, 10 equivalents of TMSCl reported to effectively promote the Fisher glycosidation under mild conditions.[20] At the early stage of reaction, *β*-anomers were preferentially formed. Three days were required for sufficient anomerization from *β*-anomers to *α*-anomers and *α*-glycoside **4** was obtained with high selectivity which was subsequently converted to per-*O*-benzylated derivative (**4a**) using aforementioned benzylation procedure (Scheme 5). The ^{1}H NMR spectrum of **4a** showed the acetylenic methine proton at δ 2.42 ppm as a triplet with coupling constant of J = 2.45 Hz and

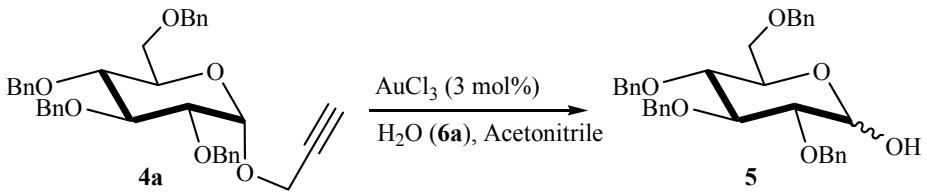
at the same time, aromatic protons corresponding to benzyl group were identified at δ 7.10-7.40 ppm as multiplet along with other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum of **4a** showed the presence of propargyl methylene (-CH_2-) resonances at δ 54.3 ppm and the anomeric carbon was noticed at δ 95.2 ppm along with all other signals accordance with assigned structure. In addition to this, compound **4a** gave satisfactory elemental analysis and mass spectral analysis [mol wt calcd 578.69, found 601.43 (M^+ + 23 for Na)].

Scheme 5



After successful preparation of propargyl glycosides, we utilized propargyl glycosides (**4a**) as glycosyl donors for synthesis of glycosides (**5**), exploiting the alkynophilicity of gold catalysts. Aforementioned observations in Chapter-I helped us to understand that propargyloxy group becomes a leaving under the influence of catalytic amount of Au^{3+} salts. To begin our investigation, **4a** was treated with water and 3 mol% of $AuCl_3$ in acetonitrile at room temperature for 12 h to observe complete hydrolysis of **4a** to corresponding 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**) in 70% yield (Scheme 6). The ^1H NMR spectrum of compound **5** showed the absence of acetylenic methine proton at δ 2.42 ppm along with the presence of other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR and DEPT spectrum unambiguously confirmed the presence of all other resonances in accordance with the assigned structure and showed the absence of propargyl -CH_2- resonances at δ 54.3 ppm. In addition, the product (**5**) was confirmed by means of mass spectral and elemental analysis.

Scheme 6

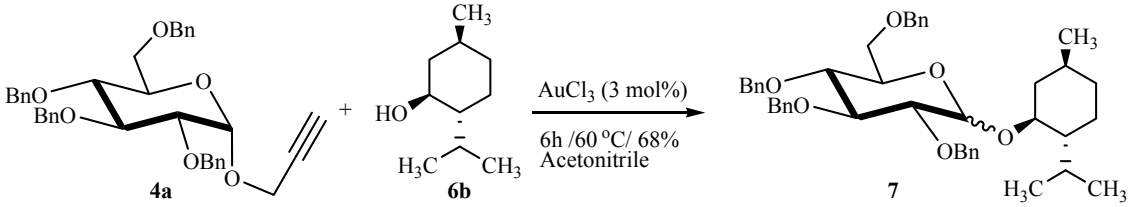


The present study clearly demonstrated the promising reactivity of Au^{3+} catalyst for activation of propargyl glycosyl donor, which should find utility in saccharide synthesis. Encouraging results prompted us to swipe H_2O (**6a**) with menthol (**6b**) [an aglycone] in order to facilitate transglycosylation reaction, an interesting landscape for the syntheses of

disaccharides (Scheme 7). Initial experiments for transglycosylation were performed with **4a** as a glycosyl donor and menthol (**6b**) as the glycosyl acceptor. Upon treatment of preformed acetonitrile solution of **4a** and **6b** with 3 mol% of $AuCl_3$ under inert atmosphere, menthyl glucoside (**7**) formation was observed, though the reaction was not completed even after 24 h. However, the percentage of conversion of **4a** to product **7** increased with incremental rise in the temperature, and complete conversion of **4a** was observed at 60 °C in 6 h to obtain a 1:1 α/*β* -mixture of menthyl glucosides (**7**), which were separated by silica gel column chromatography in 68% overall yield (Scheme 7).

The structure of menthyl glucoside was confirmed by ^{1}H, ^{13}C, DEPT NMR and Mass spectrum. In the ^{1}H NMR of *α* and *β* menthyl glucosides, resonances corresponding to propargyl and acetylenic proton were vanished and new resonances attributed to menthol moiety were apparent in aliphatic region along with all other resonances in accordance to the assigned structure. In the ^{13}C NMR spectrum, anomeric carbon was noticed at δ 98.6 ppm for *α*-menthyl and at δ 100.8 ppm for *β*-menthyl glucoside whilst all the other resonances were in complete agreement with assigned structure. However, the DEPT spectrum unambiguously confirmed the presence of eight -CH_2- group by showing the resonances at δ 22.9, 34.2, 43.0, 68.6, 73.2, 73.4, 75.1, 75.5 ppm for *α*-menthyl and at δ 23.2, 34.4, 40.9, 69.3, 73.6, 74.8, 75.0, 75.6 ppm for *β*-menthyl glucoside. In addition structure of *α* and *β* menthyl glucosides were confirmed by means of mass spectral [MALDI-TOF spectrum shows relative intense peak at 701.24 and 701.47 for *α* and *β* menthyl glucosides respectively (M^+ + 23); Calcd for $C_{44}H_{54}O_6$: 678.90] and elemental analysis as well.

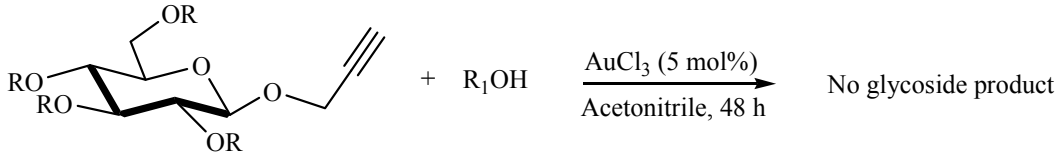
Scheme 7



In order to check the effect of *α/β*- anomers on the course of propargyl mediated transglycosylation reaction, in a control experiment, 1:1 α/*β*- mixture of **4a** and **4b** were reacted with menthol (**6b**). As anticipated, the α/*β* ratio of the transglycosylation product **7** was found to be independent of the α/*β* (at anomeric *C*-1) of donor thereby giving us a hint for the formation of oxocarbenium ion intermediate. Furthermore, glycosylation reaction between per-*O*-acetylated (**3a**) or per-*O*-benzoylated (**3b**) propargyl glucosides and **6b** did not furnish transglycosylated products at all. In doing so, preformed acetonitrile solution of **3a** or **3b** and

6b was treated with 5 mol% of $AuCl_3$ in acetonitrile under inert atmosphere at room temperature for 48 h, even the increase in temperature up to 60 ^oC failed to produce corresponding menthyl glycoside. These observations suggested that like *n*-pentenyl glycosides, propargyl glycosyl donors also could be "armed" or "disarmed" depending on the type of substituent placed at the *C*-2 position. Armed/disarmed effects were also evident in hydrolysis of glycosyl donor (**3a** or **3b**) using 3-5 mol% of $AuCl_3$ in acetonitrile at room temperature for 48 h (Scheme 8).

Scheme 8

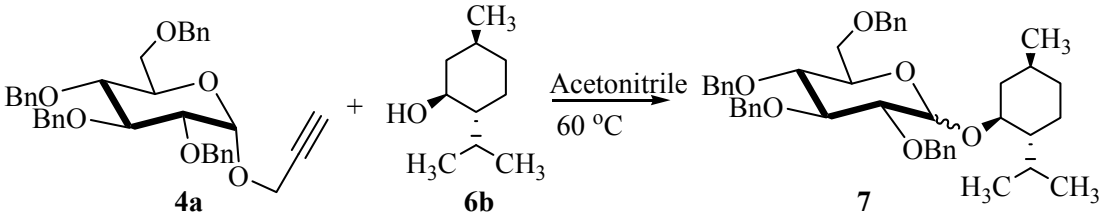


3a, R=AC
3b, R=Bz

$R_1OH = H_2O$ (**6a**),
Menthol (**6b**)

Initial optimization of transglycosylation protocol for coupling of **4a** and **6b** employing a variety of reagent combinations and temperature conditions in acetonitrile solvent is summarized in scheme 9. Our efforts to increase the yield by changing of the temperature, solvents, and addition of 4 Å molecular sieves powder were unsuccessful. The transglycosylation protocol was also studied by using other alkyne activators, such as $Cu(OAc)_2$, $PtCl_2$, $Co_2(CO)_8$ and $RuCl_3$ under different conditions. It is significant to mention that $PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$, for the glycosylation reaction resulted in either the decomposition or isolation of the **4a**.

Scheme 9



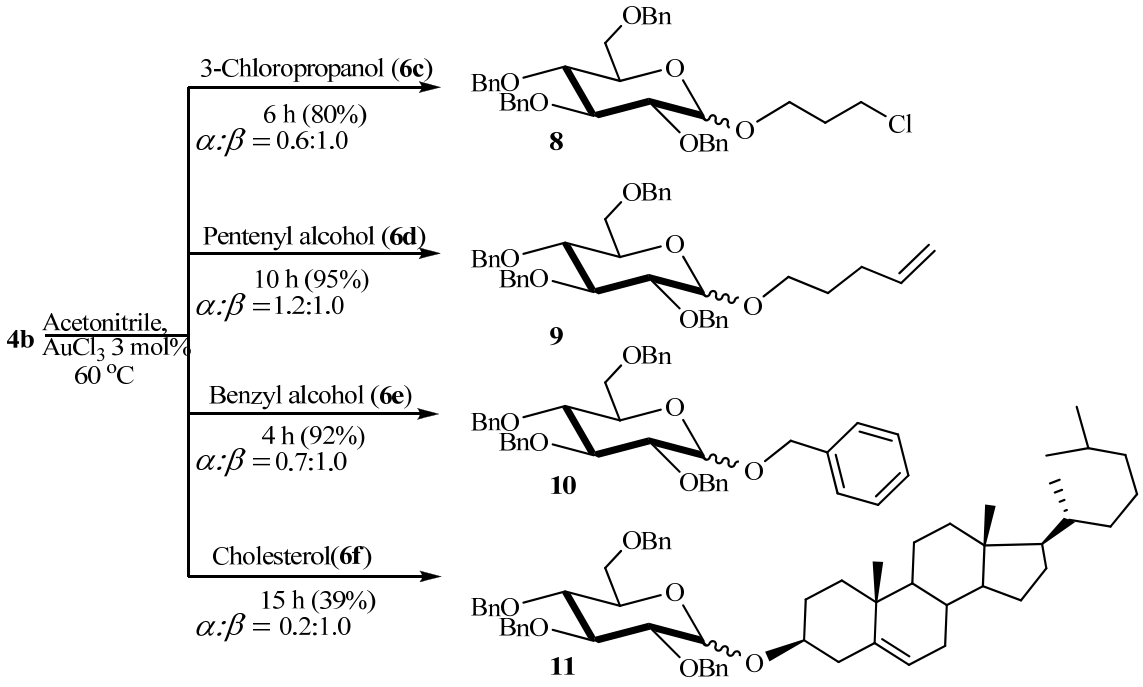
4a **6b** **7**

Entry	*Conditions*	*Yield*	*Inference*
1	Au_2O_3/AuCl	0 % No Reaction	Au (III) alone is not enough
2	$HAuCl_4$	45 % (**5**), 30% (**7**)	Au (III) and HCl are Required
3	$AuCl_3$ + Lewis Acid	0 % No Reaction	Au (III) and HCl are Required
4	$AuCl_3$ + Et_3N/DIPEA	0 % No Reaction	Presence of HCl in the Reaction
5	$AuCl_3$	60 ^oC/ 6 h	Au (III) activates alkyne
6	Et_2O.HCl / Dioxane.HCl	0 % No Reaction	HCl alone is not sufficient

Efforts to promote the transformation with other gold catalysts such as AuCl and Au_2O_3 were unsuccessful (Scheme 9, entry 1) whereas $HAuCl_4$ catalyzed glycosylation to give 30% of desired menthyl glucoside (**7**) along with 45% of lactol (**5**) (Scheme 9, entry 2). Furthermore, the optimization of yield by addition of Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $ZnCl_2$, $LiClO_4$ (entry 3) and organic bases such as triethyl amine and diiisoproyl ethyl amine along with $AuCl_3$ (Scheme 9, entry 4) were unsuccessful. Moreover, the glycosylation reaction does not proceed in dioxane.HCl or Et_2O.HCl alone (Scheme 9, entry 6). Nevertheless, the $AuCl_3$ emerged as the best alkyne activator for the transglycosylation reaction (Scheme 6, entry 5).

After successful optimization of the new protocol, the efficiency of transglycosylation reaction using a range of aglycones comprising alicyclic (**6b**), aliphatic (**6c, 6d**), aromatic (6**e**), steroidal (**6f**) and sugar alcohols (**6g**) was studied (Scheme 10). Accordingly, transglycosylation reaction was performed using **4a** and aglycones (**6c-6f**) in presence of 3 mol% of $AuCl_3$ in acetonitrile under inert atmosphere at 60 ^oC for given time period. It is worth mentioning here that all the transglycosylation reactions resulted in the formation of respective glycosides (**8-11**) in specified *α/β* ratio with excellent yield, except with cholesterol as glycosyl accepter (Scheme 10). The low yield in the case of **11** was attributed to the poor solubility of cholesterol in acetonitrile. Both distereomers were easily separated by silica gel column chromatography and identified by ^1H, ^{13}C, DEPT NMR spectroscopic studies.

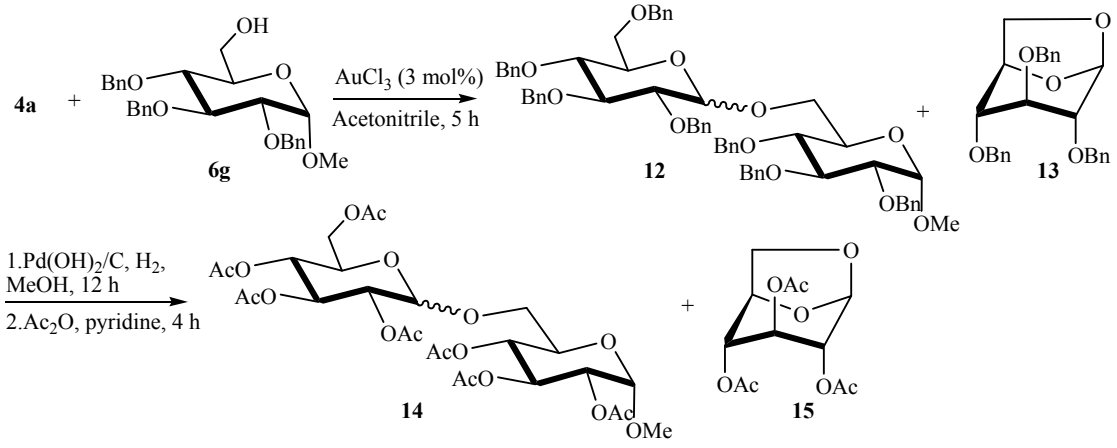
Scheme 10



In the ^{1}H NMR spectrum of α and β cholesteryl glucosides (**11**), resonances corresponding to propargyl and acetylenic proton were vanished and new resonances attributed to cholesterol moiety were apparent in aliphatic region along with all other resonances in accordance to assigned structure. The ^{13}C NMR spectrum of product (**11**) showed characteristic anomeric carbon at δ 94.7 ppm for α and at δ 102.2 ppm for β-cholesteryl glucoside whilst all the other resonances were in complete agreement with the assigned structure. The DEPT NMR spectrum unambiguously proved the presence of sixteen $-CH_2-$ group (inversely intense) by showing the resonances at δ 21.1, 23.8, 24.3, 27.5, 28.2, 32.0, 36.2, 37.1, 39.5, 39.8, 39.9, 68.6, 73.1, 73.4, 75.1, 75.7 ppm for α-cholesteryl and at δ 21.1, 23.8, 24.3, 28.2, 30.0, 32.0, 36.2, 37.3, 39.1, 39.5, 39.8, 69.2, 73.4, 74.9, 75.0, 75.7 ppm for β-cholesteryl glucoside. In addition to this, compound **11** gave satisfactory elemental analysis and mass spectral data [mol wt calcd for $C_{61}H_{80}O_6$: 909.28, found 931.13 (M^+ + 23 for Na)]. Similarly, structure of all other glycosides and α/β ratio were confirmed by ^{1}H, ^{13}C, DEPT NMR, mass spectral and elemental analysis data.

These results guided us to explore the potential of propargyl glycosides as glycosyl donor for disaccharide synthesis. To test this hypothesis, coupling of **4a** with known D-glucopyranosyl 6-OH (**6g**) in presence of 3 mol% of $AuCl_3$ in acetonitrile under inert atmosphere at 60 ^{o}C for 5 h furnished the 0.7:1.0 α/β mixture of desired disaccharide [Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-glucopyranosyl)-α-D-glucopyranoside **12**] in 74% yield along with 38 % of 1,6 anhydro 2,3,4 tri-*O*-benzyl-α-D-glucopyranoside (**13**) as side product. The desired disaccharide (**12**) was separated from side product **13** through a two-stepped debenzylation [$Pd(OH)_2/C$, H_2, MeOH, 12 h] followed by acetylation (Ac_2O, pyridine, 4 h) (Scheme 11). The α/β ratio was obtained from ^{1}H and ^{13}C NMR spectral analysis.

Scheme 11

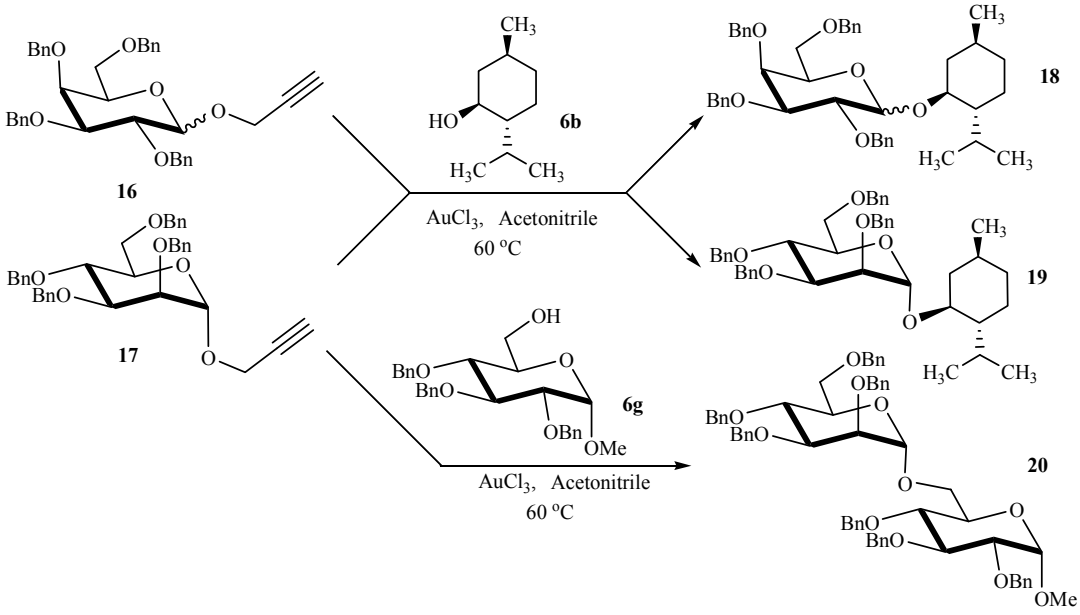


In the ^{1}H NMR spectrum of *α*/*β* mixture of disaccharide (**14**), resonances corresponding acetylenic methine proton at δ 2.42 ppm as a triplet was vanished and at the same time methoxy groups corresponding to aglycone (**6g**) were identified at δ 3.39 and 3.44 ppm as singlets and resonances of acetyl groups were observed at δ 2.00-2.11 ppm along with all other requisite resonances in accordance with the assigned structure. Furthermore, the ^{13}C NMR spectrum of product **14** showed the presence of -OMe resonances at δ 55.2 and 55.3 ppm and the anomeric carbons were evident at δ 95.6, 96.4 and 100.9 ppm whilst a bunch of acetate ester carbonyls were noticed at δ 169.2 to 170.6 ppm (absent in the DEPT spectrum when compared with ^{13}C NMR) along with all other resonances in accordance with the assigned structure of **14**. Moreover, the DEPT NMR spectrum of disaccharide **14** unambiguously confirmed the presence of four -CH_2- groups (inversely intense) by showing the resonances at δ 61.8, 61.8, 66.3, 68.1 ppm. In addition to this, compound **14** gave satisfactory elemental analysis and MALDI-TOF: mol wt calcd 650.58, found 673.05 (M^+ + 23 for Na). The side product was recognized as 1,6 anhydro 2,3,4 tri-*O*-acetyl glucopyranoside (**15**) and structure of compound **15** was unambiguously determined in comparison with the literature reports[21a] and through analysis of ^{1}H, ^{13}C, DEPT NMR, Mass spectra and elemental data though we could not rationalize the formation of **15**.

In continuation, in order to elucidate the applicability of propargyl glycosides, the current methodology was extended to other propargyl glycosyl donors. Accordingly, propargyl galactoside (**16**) and mannoside (**17**) were prepared *via* aforementioned modified Fisher glycosidation reaction (TMSCl and propargyl alcohol)[20] from respective monosaccharides in straight forward manner. Resultant propargyl tetraols derived from galactose and mannose were subjected to per-*O*-benzylation using BnBr and NaH in anhydrous DMF in order to get respective propargyl per-*O*-benzylated glycosides as glycosyl donors. The structure of **16** and mannoside **17** were confirmed by ^{1}H, ^{13}C, DEPT NMR and Mass spectral analysis. Propargyl activation by Au catalysts is highly competent and demonstrates a high degree of substrate compatibility. For the next step of reactivity evaluation, we determined that galactosyl donor **16** can be glycosylated with menthol (**6b)** as glycosyl acceptor in the presence of 3 mol% of $AuCl_3$ in acetonitrile under inert atmosphere at 60 ^{o}C for 5 h. Thus, the reaction proceeded effortlessly and afforded the corresponding *α*/*β* mixture (0.5:1.0) of menthyl galactoside (**18**) in an acceptable 73% yield (Scheme 12). The structure of **18** and *α*/*β* ratio was unambiguously recognized by means of ^{1}H, ^{13}C, DEPT NMR, Mass spectral and elemental analysis.

On the other hand, upon treatment of mannosyl donor **17** with a preformed solution of 5 mol% $AuCl_3$ in acetonitrile at room temperature in presence of **6b** and **6g**, the reaction proceeded smoothly to furnish the 1,2-*trans*-mannosides (**19** and **20**) respectively in satisfactory yield (Scheme 12). Highly stereoselective formation of 1,1'-*α,α'*-linked mannosides (**19** and **20**) is noteworthy which can be endorsed to the steric crowding due to the axially disposed benzyl ether at *C*-2 and anomeric effect (Scheme 12). Configuration of compounds **19** and **20** were unambiguously determined through data comparison with the literature reports and *via* analyses of ^1H, ^{13}C, DEPT NMR, Mass spectral and elemental data. For example, the ^1H NMR spectrum of menthyl mannoside **19** was very similar to menthyl glucoside (**7**) and showed the absence of propargyl and acetylenic protons and at the same time, new resonances due to menthol moiety were apparent in aliphatic region at δ 0.62, 0.65, 0.80, 0.81, 0.83, 0.84 ppm along with all other resonances in accordance with the assigned structure. In ^{13}C NMR spectrum, anomeric carbon was evident at δ 99.8 ppm whilst all the other resonances were in complete agreement with assigned structure. However, the DEPT spectrum unambiguously confirmed the presence of eight -CH_2- (negative intensity) group by showing the resonances at δ 23.2, 34.2, 42.8, 69.5, 72.2, 72.4, 73.3, 75.1 ppm. In addition to this, compound **19** was further confirmed by MALDI-TOF: mol wt calcd 678.9, found 701.02 (M^+ + 23 for Na) and gave satisfactory elemental data.

Scheme 12

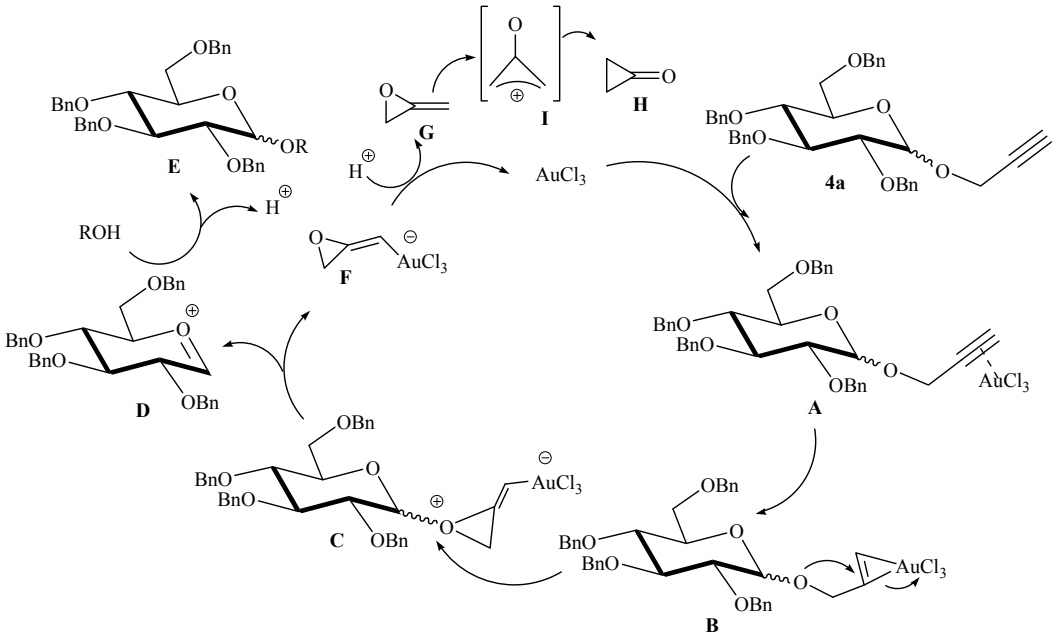


In the ^1H NMR spectrum of disaccharide **20**, characteristic resonances of methoxy group were identified at δ 3.30 ppm as a singlet integrating for three protons and at the same time, aromatic protons equivalent to seven benzyl groups were identified around δ 7.10-7.40

ppm as a multiplet integrating for thirty-five protons along with other proton resonances in complete agreement with the assigned structure. Furthermore, the ^{13}C NMR spectrum of **20** showed the characteristic resonances corresponding to methoxy group at δ 55.1 ppm and the anomeric carbons were evident at δ 92.2 and 97.8 ppm along with all other signals in accordance with the assigned structure. In the DEPT spectrum, nine methylene groups (negative intensity) were noticed at δ 65.8, 69.1, 72.0, 72.4, 73.2, 73.2, 74.9, 75.0, 75.8 ppm. In addition to this, compound **20** gave satisfactory elemental analysis and MALDI-TOF spectrum shows relative intense peak at 1008.97 (M^+ + 23 for Na), mol wt calcd for $C_{62}H_{66}O_{11}$; 986.18).[21b-c]

Though a detailed mechanism of the present protocol based on various Literature reports[22] was put forwarded as schematic illustration (Figure 12). Coordination of alkynophilic $AuCl_3$ to the glycosyl donor **4a** (complex **A**) would be followed by the formation of the cyclopropyl gold carbene intermediate (**B**).[22c] As a result of the increased electrophilicity, an intermediate of type **C** would be possible, which can further lead to an oxocarbenium ion (**D**) with the expulsion of an alkenyl gold complex (**F**). Acid-mediated protodemetalation of the methyleneoxirane-$AuCl_3$ complex (**F**) generates $AuCl_3$ and extrudes methyleneoxirane or allene oxide (**G**) and electrocyclic ring opening in highly strained methyleneoxirane (**G**) leading to its tautomer, cyclopropanone (**H**). Conversion of **G** to **H** was studied intensively for over two decades following Hoffmann's extended-Huckel-theory calculations suggested the oxyallyl intermediate (**I**) by Mclafferty.[22a]

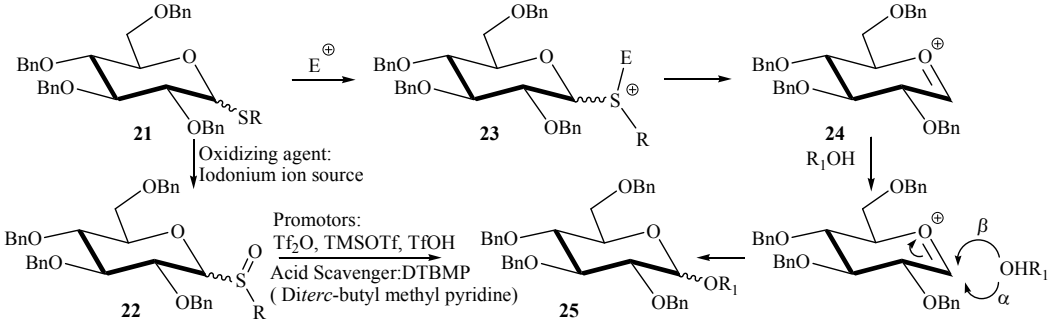
Figure 12



Synthesis of Thioglycoside from Propargyl glycosides:

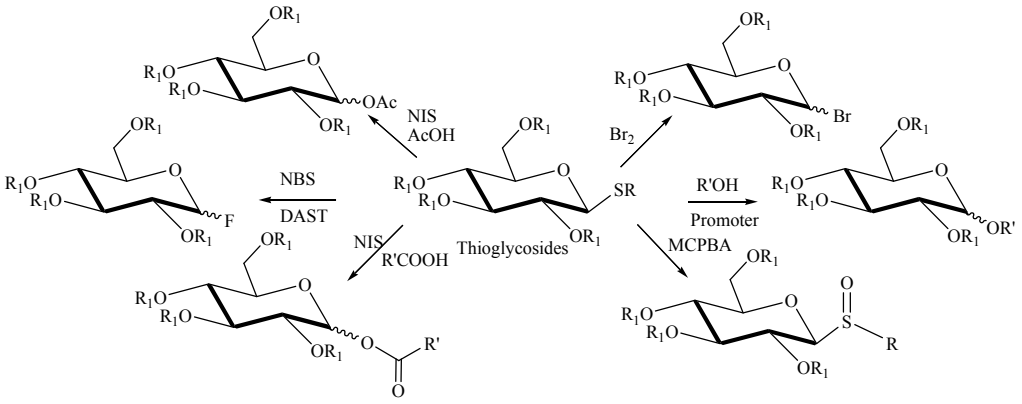
Over the time, several glycosyl donors have reported which are unique and the glycobiology explored those for the synthesis of neoglycoconjugates and oligosaccharides. Among the various glycosyl donors, the oxidized form of thioglycosides (**21**) such as glycosyl sulfoxides or sulfinil glycosides (**22**) proved to be very adaptable and advantageous[23] glycosyl donors in which group having sulphur are used in place of exocyclic hemiacetal oxygen for anomeric activation. Due to the high stability of thioglycoside functionality to enzymatic cleavage and most of the protecting group transformations, thioalkyl and thioaryl-glycosides are considered as a promising substrate for the synthesis of carbohydrate based therapeutics,[23,24] and found enormous applications in the development of synthetic carbohydrate chemistry[25] especially in glycosidation of amino sugars. The sulfur atom in thioglycoside is a soft nucleophile and can be easily activated by thiophilic promoter such as DMTST or NIS/catalytic TfOH (a source of I^+ commonly used in *S*-alkyl/aryl glycosides activation), to generate an intermediate sulfonium ion (**23**), as a result of increased electrophilicity on sulfur atom, a glycosylating carbocationic intermediate (**24**) would form which can be trapped by aglycone to furnish glycoside (**25**) (Scheme 13).[23-25]

Scheme 13



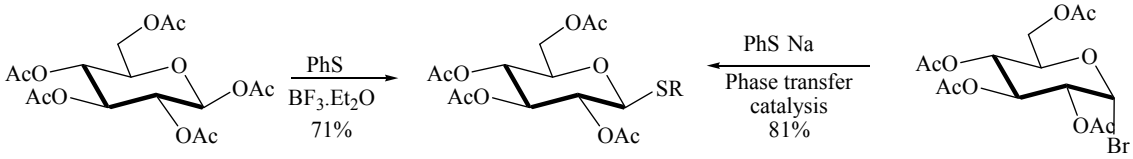
Thioglycosides are stable in the absence of thiophilic promoters and interconvertable in a number of useful ways. They can be converted to all other glycosyl donors directly or by two-step procedure. The synthetic potential of thioglycosides is further extended by the fact that donor activity of benzylated thioglycosides is higher (as in "armed" glycosyl donor) than that of the acetylated or benzoylated analogs (as in "disarmed" glycosyl donor) allowing the chemoselective cross-coupling glycosylations. Importantly, as a result of the stability of the thioglycoside function, this class of compounds can serve not only as glycosyl donors but also as glycosyl acceptors. This feature, combined with the tunable reactivity of thioglycosides, could be taken into an advantage for the development of various synthetic strategies for higher oligosaccharides and today they are the most frequently used type of compounds in oligosaccharide syntheses (Scheme 14).

Scheme 14



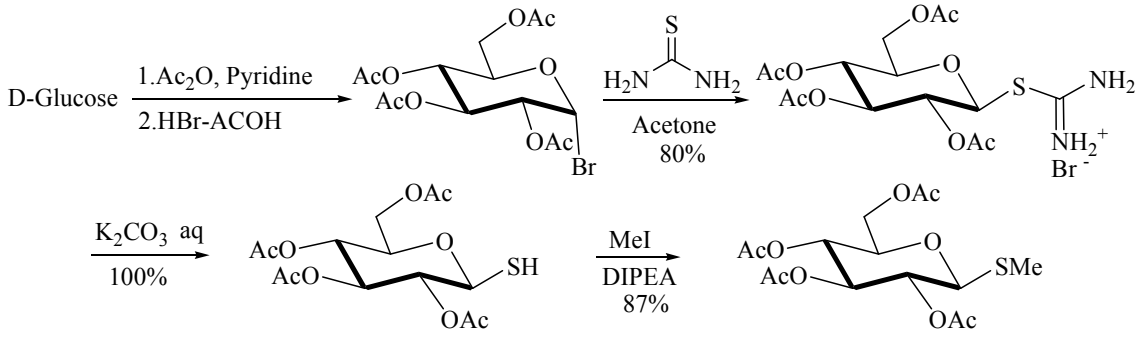
The most often employed approaches toward the synthesis of thioglycosides are the treatment of per-*O*-acetylated sugars with malodorous and toxic alkyl/aryl thiols or expensive alkyl/aryl thiotrimethylsilanes in the presence of a Lewis acid.[26] Alternatively, thioglycosides can also be prepared in one-pot manner from unprotected reducing sugars using S-glycosyl isothiouronium salts.[26f-g] Conventionally, synthesis of thioglycosides involves Lewis acid promoted displacement at anomeric center with *S*-nucleophile from sugar derivative. In general, fully protected acetylated haxopyranoses reacts with thiols such as thiophenol or thioethanol in the presence of Lewis acids such as $BF_3.Et_2O$ to give predominantly 1,2 *trans*-products.[27a] Whereas glycosyl bromide and glycosyl trichloroacetimidates does not servive deacetylation, acetylated thioglycosides can be deacetylated without degradation, so that protecting group manipulation is possible. In contrast, base-promoted method involves phase transfer catalyzed nucleophilic substitution at anomeric center of glycosyl halide with S-nucleophile[27b] (Scheme 15).

Scheme 15



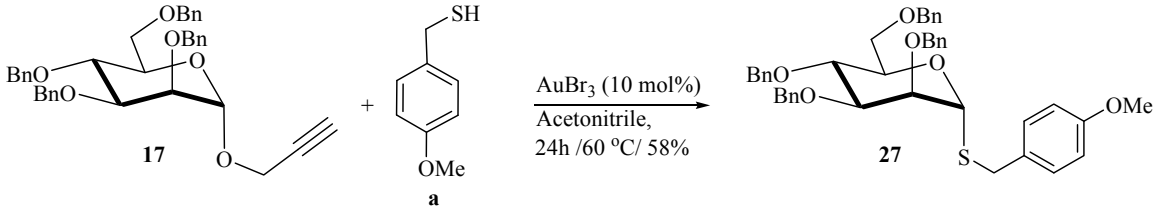
In practice, an interesting alternative for the preparation of per-*O*-acetylated thioglycosides from unprotected reducing sugars involves at least four steps consisting of (1) acetylation using excess acetic anhydride and pyridine or pyridine derivatives as solvent and activator despite their known toxicity and unpleasant odor, (2) bromination using HBr-AcOH, and (3) treatment of acetobromo sugar with thiourea which gives rise to an intermediate *pseudo*thiuronium salt that can be hydrolyzed with aqueous potassium carbonate to furnish acetylated 1-thioglycopyranose followed by (4) in *situ S*-alkylation of *S*-thioglycopyranose with alkyl halide, which require intermediate isolation and purification through conventional workup, causing the synthetic sequence to be tedious (Scheme 16).[27c]

Scheme 16



In continuation of novel transglycosylation study delineated above, we thought of extending the repertoire to the synthesis of thioglycosides as well. Thereby the novelty and versatility of propargyl glycosides would therefore be enhanced, and a novel thioglycosidation protocol could be developed. Accordingly, propargyl glycosides **4a, 16, 17** and homopropargyl glucoside (**26**)[19d] were prepared according to standard procedure and used as model substrate in this study. Initial experiments for thioglycosidation were performed with propargyl mannoside **17** as a glycosyl donor for anomeric activation and 4-methoxybenzyl mercaptan **(a)** as a thiol acceptor. An acetonitrile solution of **17** and **a** was treated with 5 mol% of $AuBr_3$ in acetonitrile at 60 ^oC for 16 h under inert atmosphere. However, the reaction was not completed as judged by TLC, and complete conversion of **17** was observed at 60 ^oC in 24 h using 10 mol% of $AuBr_3$ to obtain stereoselective 1,2-*trans*-thiomannoside (**27**) in 58% yield (Scheme 17).

Scheme 17

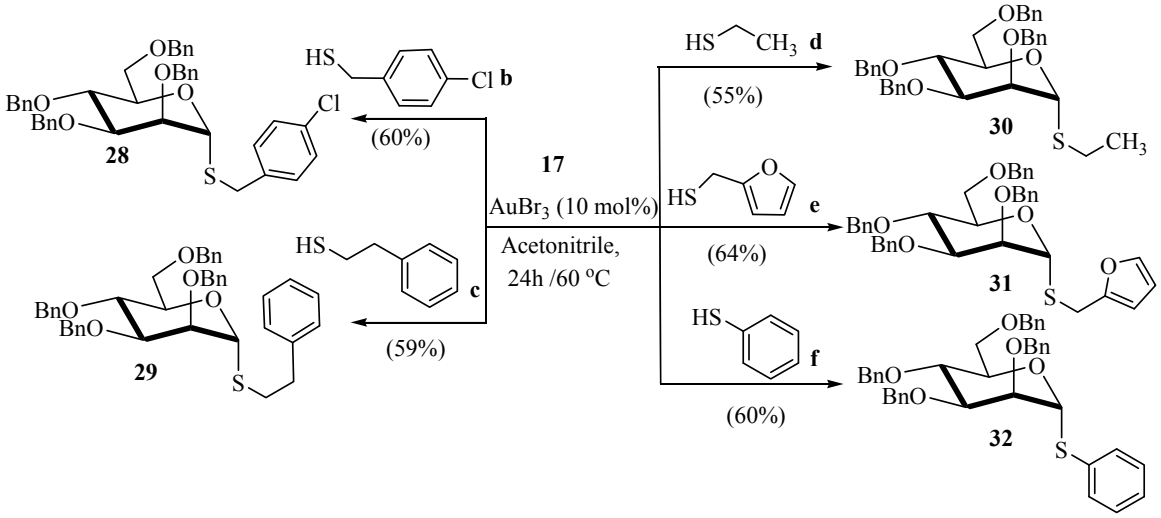


The ^1H NMR spectrum of thiomannoside **27** showed the absence of acetylenic methine proton at δ 2.39 ppm and at the same time distinguishable resonances of methoxy group corresponding to 4-methoxybenzyl mercaptan (**a**) were identified at δ 3.78 ppm as a singlet integrating for three protons along with all other resonances in accordance with the assigned structure. Furthermore, the ^{13}C NMR spectrum of thiomannoside **27** showed the presence of -OMe resonances at δ 55.23 ppm and the anomeric carbon was evident at δ 80.59 ppm confirming it as 1,2-*trans*-thiomannosides. Moreover, the characteristic resonances corresponding to *ortho, meta* and quarternary *para* aromatic carbons of *p*-methoxybenzyl mercaptan moiety were observed at δ 130.1, 113.9 and 158.6 ppm respectively along with all

other resonances according to the assigned structure. However, the DEPT NMR spectrum of thiomannoside **27** unambiguously confirmed the presence of characteristic -SCH_2 by showing the resonances at δ 34.07 ppm and five methylenes (negative intensity) corresponding to benzyl groups at δ 69.1, 71.7, 71.9, 73.3, 75.1 ppm along with all other resonances. In addition to this, compound **27** gave satisfactory mass analysis and MALDI-TOF spectrum showing relative intense peak at 699.77 (M^+ + 23; Calcd for $C_{42}H_{44}O_6S$: 676.86). Stereoselective formation of 1,2-*trans*-thiomannosides can be attributed to the steric crowding due to the axially predisposed benzyl ether at *C*-2 as well as the anomeric effect.

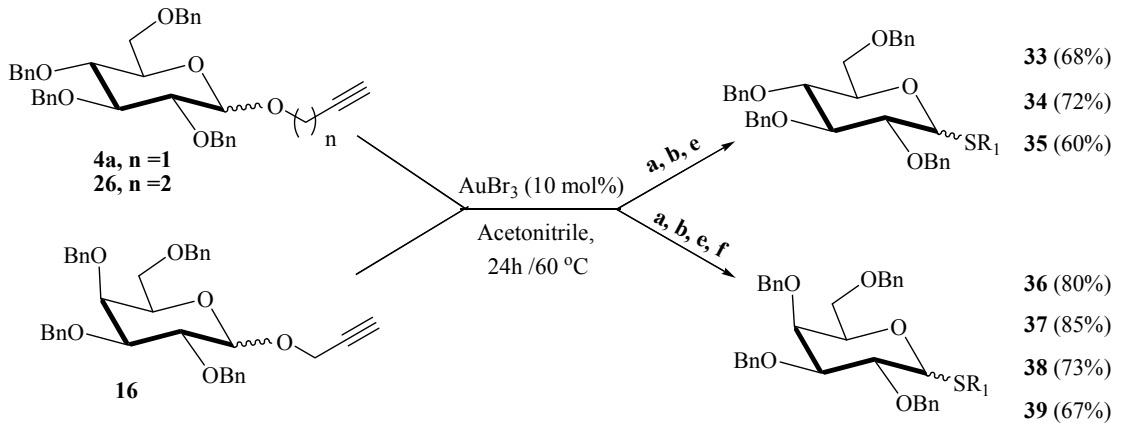
The scope and general applicability of this protocol was established by means of various thiols comprising 4-chlorobenzyl mercaptan (**b**), benzene ethanethiol (**c**), ethane thiol (**d**), furfuryl mercaptan (**e**) and thiophenol (**f**). It is worth mentioning here that propargyl mannopyranoside (**17**) acted as a glycosyl donor in all the reactions, giving 1,2-*trans*-thiomannosides in good yields (Scheme 18).

Scheme 18



Furthermore, the current methodology was extended to other propargyl glycoside donors like propargyl glucoside (**4a**), homopropargyl glucoside (**26**) and propargyl galactoside (**16**) to obtain respective thioglycosides ranging from 60% to 85% yields (Scheme 19). Accordingly, per-*O*- benzylated donors **4a, 26** and **16** were treated with thiol acceptors (**a-f**) under aforementioned standard procedure in order to obtain an *α*/*β*-mixture of thioglycosides (**33-39**). The *α:β* ratio was obtained from ^1H, ^{13}C NMR analysis and column purification and yields are unoptimized. The ^1H NMR spectrum of *α*/*β*-mixture of compound **33** shows the absence of acetylenic -CH at δ 2.39 ppm and at the same time, distinguishing resonances of methoxy group were identified at δ 3.77 and 3.80 ppm as a singlet integrating for three protons each along with all other resonances in accordance with the assigned structure.

Scheme 19



In addition, the ^{13}C NMR spectrum of thioglucoside **33** showed the resonances of *p*-OMe group (corresponding to thiol accepter **a)** at δ 55.2 and 55.3 ppm and the anomeric carbons were evident at δ 83.0 and 86.6 ppm. Moreover, the characteristic resonances corresponding to *ortho* and *meta* aromatic carbons of *p*-methoxybenzyl mercaptan were observed at δ 130.2, 130.3 ppm and δ 113.8, 113.9 ppm respectively whilst, quarternary *para* positioned carbon of thiol moiety were identified at δ 158.5 and 158.6 ppm. The DEPT NMR spectrum of thioglucoside **33** unambiguously confirmed the presence of characteristic -SCH_2 by showing the resonances at δ 32.7 and 33.7 ppm (negative intensity) along with all other resonances. In addition to this, compound **33** was confirmed by MALDI-TOF spectrum, showing relatively intense peak at 699.80 (Calcd for $C_{42}H_{44}O_6S$, M + 23: 676.86). It is worth mentioning here that all thioglycosidation reactions resulted in the formation of respective glycosides (**33-39**) in specified *α/β* ratio with excellent yield. The structure of all other thioglycoside products and *α/β* ratio were established by ^1H, ^{13}C, DEPT NMR and mass spectral analysis.

In conclusion, propargyl glycosides were identified as novel and stable glycosyl donors. Various aglycones comprising aromatic, alicyclic, steroidal, aliphatic, carbohydrate derived alcohols and thiols were reacted with propargyl glycosides to give corresponding *O*-glycoside and *S*-glycoside.[17] The current protocol is highly competent and demonstrates a standard set of conditions. The main advantage of this method is its flexibility and wide scope which enables the activation of propargyloxy group of propargyl glycosides in presence of variety of acceptors, resulting in the formation of 1,2-*trans*-mannosides, *α,β*-mixture of galactosides and glucosides. In addition, this protocol is catalytic, mild, has negligible effect of moisture and high yielding.

*****

Chapter 2: Experimental Section

General experimental Procedure for Fisher glycosidation:

The typical procedure for Fisher glycosidation at room temperature used 10 equivalent of TMSCl. To a suspension of sugar (10 gm, 0.06 mol) in propargyl alcohol (30 mL, 0.50 mol) was added chlorotrimethylsilane (75.6 mL, 0.60 mol). The mixture was stirred at room temperature for 3 days and the resulting brownish solution was neutralized with excess triethylamine and concentrated *in vacuo*. Resulting reddish brown residue was co-evaporated with toluene (3 x 500 mL), dried under reduced pressure for 2 h and directly used in the next step.

General experimental Procedure for *O*-alkylation:

To a solution of propargyl glycosides (13g, 0.06 mol) prepared *vide supra* in anhydrous *N,N*-dimethylformamide (100 mL) at 0 ^{o}C was added sodium hydride (7.9g, 0.33 mol) and stirred at room temperature for 30 min. The resulting dark brown solution was cooled to 0 ^{o}C and was added *n*-$Bu_4N^+I^-$ followed by dropwise addition of benzyl bromide (33.5 mL, 0.28 mol) under nitrogen atmosphere, stirred at room temperature for 15 h. At the end of the reaction (judged by TLC), excess NaH was quenched by the addition of 20 mL methanol. The reaction mixture was diluted with 100 mL of water, extracted with ethyl acetate (3 x 100 mL), combined organic layers were dried over anhydrous sodium sulphate, concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography to give propargyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-glycosides.

General procedure for transglycosylation:

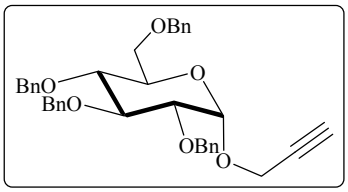
3 mol% of $AuCl_3$ in acetonitrile was added to a solution of glycosyl donor (1.0 equiv) and aglycone (1.2 equiv) and heated to 60 °C for 24h. At the end of the reaction (TLC monitored), the reaction mixture was concentrated in *vacuo* to obtain transglycoside product which was then purified by silica gel column chromatography using ethyl acetate –petroleum ether as mobile phase.

General procedure for $AuBr_3$ mediated thioglycosidation:

10 mol% of $AuBr_3$ in acetonitrile was added to a solution of glycosyl donor (1.0 equiv) and thiol-aglycone (1.2 equiv) and heated to 60 °C for 24h. After the completion of reaction (judged by TLC), the reaction mixture was diluted with 50 mL of water, extracted with ethyl acetate (3 x 20 mL) and combined organic layers were dried over anhydrous sodium sulphate

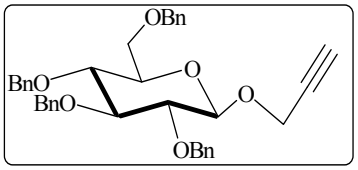
and concentrated in *vacuo* to obtain a crude residue of thioglycoside which was purified by silica gel column chromatography using ethyl acetate –petroleum ether as mobile phase.

Propargyl 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranoside (4a):



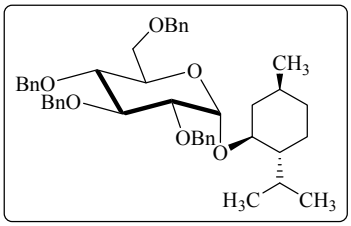
$[\alpha]_D^{25}$ = +31.93 (*c*, 0.95, $CHCl_3$); IR ($CHCl_3$): 3460.06, 2987.53, 2937.28, 2104.19 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 2.42 (t, 1H, *J* = 2.45 Hz), 3.57-3.62 (m, 1H), 3.64 (d, 1H, *J* = 1.52 Hz), 3.72 (d, 2H, *J* = 11.62 Hz), 3.99 (t, 1H, *J* = 9.22 Hz), 4.25 (d, 2H, *J* = 2.40 Hz) , 4.43 (d, 1H, *J* = 4.80 Hz), 4.48 (d, 1H, *J* = 3.41 Hz), 4.56 (s, 1H), 4.64 (d, 1H, *J* = 6.57 Hz), 4.72 (d, 2H, *J* = 2.78 ZH), 4.81 (q, 2H, *J* = 5.43 Hz), 4.99 (d, 1H, *J* = 10.87 Hz), 5.08 (d, 1H, *J* = 3.67 Hz), 7.10-7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 54.4, 68.3, 70.9, 72.9, 73.4, 74.7, 75.0, 75.7, 77.4, 78.9, 79.3, 82.9, 95.2, 127.5-128.3, 137.8, 137.9, 138.1, 138.7; CHNS Anal. Calcd for $C_{37}H_{38}O_6$: C, 76.79; H, 6.62; O, 16.59; Found: C, 76.84; H, 6.73; MALDI-TOF: mol wt calcd for $C_{37}H_{38}O_6$: 578.69; Found 601.43 (M^+ + 23 for Na).

Propargyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (4b):



$[\alpha]_D^{25}$ = +19.87 (*c*, 1.00, $CHCl_3$); IR (cm^{-1}): 3304.79, 3031.27, 3012.11, 2922.17, 2867.82, 1497.18; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 2.42 (t, 1H, *J* = 2.40), 3.44-3.57 (m, 2H), 3.61-3.73 (m, 4H), 4.43 (t, 2H, *J* = 2.59), 4.50 (s, 1H), 4.55-4.66 (m, 4H), 4.73 (d, 1H, *J* = 6.31), 4.79 (d, 1H, *J* = 1.77), 4.90-5.00 (m, 2H), 7.10-7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 54.4, 68.8, 73.5, 74.7, 74.8, 74.9, 75.0, 75.7, 77.6, 79.0, 82.0, 84.6, 101.4, 127.5-128.4, 138.1, 138.1, 138.4, 138.6; CHNS Anal. Calculated for $C_{37}H_{38}O_6$: C, 76.79; H, 6.62; O, 16.59; Found: C, 76.91; H, 6.74. Calcd mass for $C_{37}H_{38}O_6$: 578.69; Found 601.79 (M^+ + 23 for Na).

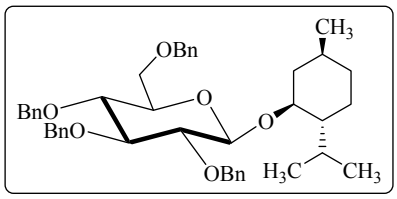
Menthyl 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranoside (7 α):



$[\alpha]_D^{25}$ = +25.43 (*c*, 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 200.13 MHz): δ 0.70 (d, 3H, *J* = 6.93), 0.81 (d, 3H, *J* = 0.89 Hz), 0.86 (s, 3H), 0.91 (d, 1H, *J* = 2.15 Hz), 1.03 (q, 2H, *J* = 11.50 Hz), 1.24-1.34 (m, 2H), 1.60 (dd, 2H, *J* = 2.41, 2.64 Hz), 2.07-2.17 (m, 1H), 2.41 (dq, 1H, *J* = 2.28 Hz), 3.35 (td, 1H, *J* = 4.33, 10.47 Hz), 3.51-3.68 (m, 3H), 3.75 (dd, 1H, *J* = 3.69, 10.50 Hz), 3.93-4.06 (m, 2H), 4.43 (d, 1H, *J* = 1.40 Hz), 4.49 (d, 1H, *J* = 2.99 Hz), 4.61 (s, 1H), 4.67-4.69 (m, 2H), 4.80 (d, 1H, *J* = 3.64 Hz), 4.85 (d, 1H, *J* = 4.03 Hz), 4.95 (s, 1H), 5.02 (d, 1H, *J* = 4.04 Hz), 7.10-7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 16.0, 21.1, 22.3, 22.9, 24.6, 31.7, 34.2, 43.0, 48.7, 68.7, 70.3, 73.2, 73.4, 75.0, 75.5,

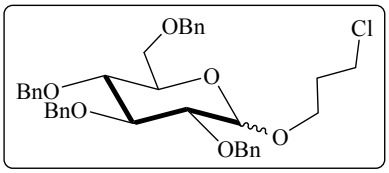
78.1, 80.5, 81.0, 82.0, 98.6, 127.5-128.3, 138.1, 138.3, 138.4, 138.9; CHNS Anal. Calculated for $C_{44}H_{54}O_6$: C, 77.84; H, 8.02; O, 14.14; Found: C, 77.97; H, 8.44; Calcd mass for $C_{44}H_{54}O_6$: 678.90; Found 701.24 (M^+ + 23 for Na).

Menthyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (7 β):



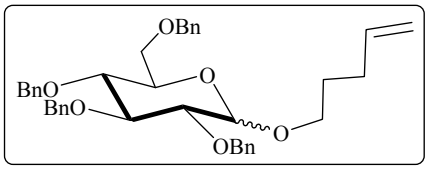
$[\alpha]_D^{25}$ = -18.38 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.83 (d, 3H, *J* = 6.81 Hz), 0.89 (d, 3H, *J* = 4.04 Hz), 0.92 (d, 3H, *J* = 4.51 Hz), 0.98 (d, 1H, *J* = 2.34 Hz), 1.06 (dd, 1H, *J* = 4.45, 12.86 Hz), 1.26-1.33 (m, 2H), 1.62-1.69 (m, 2H), 2.08-2.18 (m, 1H), 2.34 (dq, 1H, *J* = 2.44 Hz), 3.31-3.45 (m, 3H), 3.49-3.56 (m, 1H), 3.59-3.64 (m, 2H), 3.69 (d, 2H, *J* = 3.24 Hz), 4.47 (d, 1H, *J* = 7.71 Hz), 4.55-4.60 (m, 3H), 4.68 (d, 1H, *J* = 11.00 Hz), 4.80 (ABq, 2H, *J* = 6.68 Hz), 4.91 (d, 1H, *J* = 4.82 Hz), 4.97 (d, 1H, *J* = 4.70 Hz), 7.16-7.38 (m, 20H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 15.9, 21.1, 22.2, 23.2, 25.1, 31.4, 34.4, 41.0, 48.1, 69.3, 73.7, 74.8, 74.8, 75.0, 75.6, 77.7, 78.0, 82.2, 85.0, 100.8, 127.5-128.4, 138.2, 138.4, 138.6, 138.8; CHNS Anal. Calculated for $C_{44}H_{54}O_6$: C, 77.84; H, 8.02; O, 14.14; Found: C, 77.66; H, 8.27; Calcd mass for $C_{44}H_{54}O_6$: 678.90; Found 701.47 (M^+ + 23 for Na).

3-chloropropyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-D-glucopyranoside (8):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.97-2.20 (m, 4H), 3.40-3.55 (m, 3H), 3.58-3.73 (m, 12H), 3.76 (t, 1H, *J* = 2.48 Hz), 3.79-3.88 (m, 1H), 3.93(d, 1H, *J* = 9.28 Hz), 4.00-4.11 (m, 1H), 4.40 (d, 1H, *J* = 7.68 Hz), 4.43 (s, 1H), 4.49 (s, 2H), 4.55-4.66 (m, 3H), 4.65-4.69 (m, 2H), 4.75-4.85 (m, 6H), 4.88 (d, 2H, *J* = 4.61 Hz), 4.94 (d, 1H, *J* = 4.77 Hz), 4.99 (d, 1H, *J* = 10.99 Hz), 7.10-7.34 (m, 40H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.3, 32.8, 41.7, 41.8, 64.4, 66.3, 68.4, 68.8, 70.1, 73.2, 73.5, 73.5, 74.8, 74.9, 75.0, 75.1, 75.7, 75.7, 77.2, 77.8, 80.1, 82.0, 82.3, 84.7, 97.2, 103.7, 127.5-128.5, 137.9, 138.0, 138.1, 138.2, 138.2, 138.3, 138.5, 138.8; CHNS Anal. Calculated for $C_{37}H_{41}ClO_6$: C, 72.01; H, 6.70; Cl, 5.74; O, 16.59; Found: C, 72.24; H, 6.87; Cl, 5.79; Calcd mass for $C_{37}H_{41}ClO_6$: 617.17; Found 639.36 (M^+ + 23 for Na).

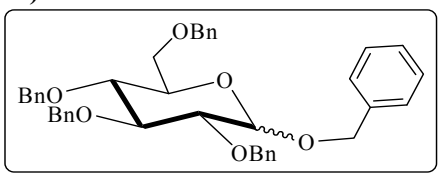
4-Pent-1-enyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-D-glucopyranoside (9):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.75 (m, 4H, *J* = 6.55 Hz), 2.15 (m, 4H, *J* = 7.30 Hz), 3.37-3.42 (m, 1H), 3.45 (s, 1H), 3.48 (d, 1H, *J* = 2.05 Hz), 3.53 (d, 1H, *J* = 2.23 Hz), 3.57-3.78 (m, 9H), 3.09 (t, 2H, *J* = 8.38 Hz), 4.39 (d, 1H, *J* = 7.72 Hz), 4.43 (d, 1H, *J* =

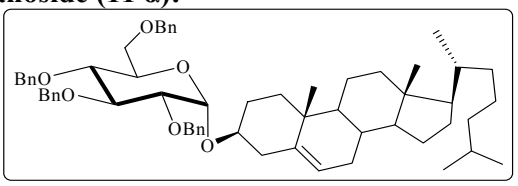
1.11 Hz), 4.49 (s, 2H), 4.55-4.61 (m, 4H), 4.67 (t, 2H, *J* = 5.70 Hz), 4.76 (s, 2H), 4.80 (d, 2H, *J* = 4.15 Hz), 4.85 (d, 2H, *J* = 2.80 Hz), 4.91-5.02 (m, 6H), 5.06 (s, 1H), 5.71-5.93 (m, 2H), 7.10-7.34 (m, 40H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 28.5, 29.0, 30.2, 30.2, 67.5, 68.5, 68.9, 69.3, 70.1, 73.1, 73.4, 73.4, 74.8, 74.8, 75.0, 75.1, 75.6, 75.6, 77.7, 77.9, 80.1, 82.1, 82.2, 84.7, 96.9, 103.6, 114.8, 114.9, 127.5-128.3, 137.9, 138.0, 138.0, 138.1, 138.2, 138.2, 138.3, 138.4, 138.6, 138.9; CHNS Anal. Calculated for $C_{39}H_{44}O_6$: C, 76.95; H, 7.29; O, 16.59; Found: C, 76.71; H, 7.52; Calcd mass for $C_{39}H_{44}O_6$: 608.76; Found 631.62 (M^+ + 23 for Na).

Benzyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-D-glucopyranoside (10):



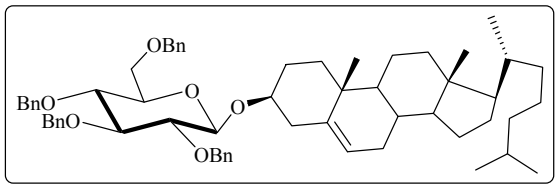
^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.49-3.83 (m, 11H), 4.05 (t, 1H, *J* = 9.18 Hz), 4.43 (d, 1H, *J* = 1.81 Hz), 4.49 (d, 2H, *J* = 0.89 Hz), 4.52 (d, 1H, *J* = 3.67 Hz), 4.56-4.58 (m, 3H), 4.61 (s, 1H), 4.64-4.67 (m, 2H), 4.70 (s, 1H), 4.72 (d, 1H, *J* = 3.22 Hz), 4.75 (s, 1H), 4.81 (s, 2H), 4.85 (d, 2H, *J* = 2.28 Hz), 4.90 (s, 1H), 4.94 (d, 2H, *J* = 3.91 Hz), 4.98 (d, 1H, *J* = 2.03 Hz), 5.02 (d, 1H, *J* = 3.66 Hz), 7.10-7.42 (m, 50H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 68.4, 68.9, 69.1, 70.3, 71.1, 73.0, 73.4, 73.4, 74.8, 74.9, 74.9, 75.0, 75.7, 75.7, 77.7, 77.9, 79.9, 82.1, 82.3, 84.7, 95.6, 102.6, 127.5-128.4, 137.2, 137.5, 137.9, 138.1, 138.2, 138.2, 138.3, 138.4, 138.6, 138.9; CHNS Anal. Calculated for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71; O, 15.22; Found: C, 78.42; H, 6.55; Calcd mass for $C_{41}H_{42}O_6$: 630.77; Found 653.19 (M^+ + 23 for Na). Calcd mass for $C_{41}H_{42}O_6$: 630.77; Found 653.19 (M^+ + 23 for Na).

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranoside (11 α):



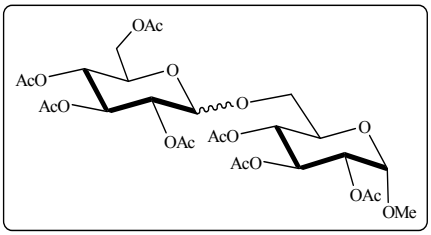
$[\alpha]_D^{25}$ = +11.11 (*c*, 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.68 (s, 3H), 0.87 (d, 9H, *J* = 6.59 Hz), 0.93 (d, 6H, *J* = 6.37 Hz), 1.01 (s, 3H), 1.12 (s, 3H), 1.26-1.28 (m, 8H), 1.46-1.68 (m, 6H), 1.87 (d, 2H, *J* = 10.51 Hz), 2.01 (d, 2H, *J* = 8.46 Hz), 2.27-2.35 (m, 1H), 3.41-3.73 (m, 4H), 3.84-3.92 (m, 1H), 3.99 (d, 1H, *J* = 9.53 Hz), 4.42 (d, 1H, *J* = 3.69 Hz), 4.48 (d, 1H, *J* = 1.96 Hz), 4.59 (s, 1H), 4.63 (d, 1H, *J* = 6.24 Hz), 4.71 (d, 1H, *J* = 13.09 Hz), 4.82 (dd, 2H, *J* = 3.53, 10.77 Hz), 4.93 (d, 1H, *J* = 3.46 Hz), 5.01 (d, 1H, *J* = 10.69 Hz), 5.21-5.37 (m, 2H), 7.11-7.33 (m, 20H); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 11.9, 18.7, 19.4, 21.1, 22.6, 22.8, 23.8, 24.3, 27.2, 27.5, 28.0, 28.2, 31.9, 31.9, 35.8, 36.2, 36.8, 37.1, 39.5, 39.8, 39.9, 42.3, 50.1, 56.2, 56.8, 68.6, 70.1, 73.4, 75.1, 75.7, 77.2, 77.9, 80.0, 82.1, 94.7, 121.7, 127.5-128.4, 138.0, 138.3, 138.3, 139,0, 140.9; CHNS Anal. Calculated for $C_{61}H_{80}O_8$: C, 80.57; H, 8.87; O, 10.56; Found: C, 80.73; H, 8.64; Calcd mass for $C_{61}H_{80}O_6$: 909.28; Found 931.13 (M^+ + 23 for Na).

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (11 β):



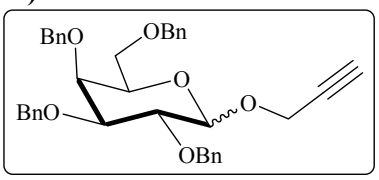
$[\alpha]_D^{25}$ = -32.87 (*c*, 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.68 (s, 3H), 0.87 (d, 9H, *J* = 6.40 Hz), 0.92 (d, 6H, *J* = 6.33 Hz), 1.03 (s, 3H), 1.12 (s, 3H), 1.26-1.30 (m, 8H), 1.48-1.58 (m, 6H), 1.83-2.04 (m, 2H), 2.27-2.35 (m, 3H), 3.40-3.76 (m, 5H), 3.89-4.18 (m, 2H), 4.44-4.52 (m, 2H), 4.56 (s, 1H), 4.58 (s, 1H), 4.64-4.74 (m, 2H), 4.80 (d, 1H, *J* = 1.86 Hz), 4.87 (d, 1H, *J* = 10.48 Hz), 4.97 (d, 1H, *J* = 10.70 Hz), 5.35 (s, 1H), 7.15-7.35 (m, 20H); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 11.9, 18.7, 19.4, 21.1, 22.6, 22.8, 23.8, 24.3, 28.0, 28.2, 30.0, 31.9, 32.0, 35.8, 36.2, 36.8, 37.3, 39.1, 39.5, 39.8, 42.3, 50.2, 56.2, 56.8, 69.2, 73.4, 74.8, 74.9, 75.0, 75.7, 78.0, 79.7, 82.4, 84.9, 102.2, 121.9, 127.5-128.4, 138.2, 138.3, 138.6, 138.7, 140.9; CHNS Anal. Calculated for $C_{61}H_{80}O_6$: C, 80.57; H, 8.87; O, 10.56; Found: C, 80.33; H, 8.51; Calcd mass for $C_{61}H_{80}O_6$: 909.28; Found 931.67 (M^+ + 23 for Na).

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-*α/β*-glucopyranosyl)-*α*-D-glucopyranoside (14):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.00 (s, 6H), 2.01 (s, 6H), 2.02 (s, 6H), 2.03 (s, 6H), 2.05 (s, 6H), 2.07 (s, 6H), 2.09 (s, 6H), 3.39 (s, 3H), 3.44 (s, 3H), 3.50-3.59 (m, 2H), 3.66-3.78 (m, 2H), 3.92 (dd, 2H, *J* = 2.06, 11.15 Hz), 3.96-4.01 (m, 1H), 4.07-4.22 (m, 3H), 4.28 (dd, 2H, *J* = 4.45, 12.41 Hz), 4.56 (d, 2H, *J* = 7.71 Hz), 4.82 (d, 2H, *J* = 3.64 Hz), 4.85-4.88 (m, 1H), 4.91 (s, 2H), 4.93 (s, 1H), 4.95-5.26 (m, 7H), 5.41-5.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 20.5, 20.5, 20.6, 55.2, 55.3, 61.8, 61.8, 66.3, 67.4, 68.0, 68.1, 68.3, 68.4, 69.0, 69.2, 69.9, 70.1, 70.1, 70.7, 70.8, 70.8, 71.0, 71.9, 72.6, 77.2, 95.6, 96.4, 96.4, 100.9, 169.2, 169.3, 169.5, 169.5, 169.6, 169.6, 169.9, 169.9, 170.0, 170.0, 170.1, 170.1, 170.6, 170.6; CHNS Anal. Calculated for $C_{27}H_{38}O_{18}$: C, 49.85; H, 5.89; O, 44.27; Found: C, 49.72; H, 5.99; Calcd mass for $C_{27}H_{38}O_{18}$: 650.58; Found 673.05 (M^+ + 23 for Na).

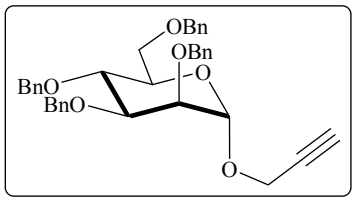
Propargyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-D-galactopyranoside (16):



IR (cm^{-1}): 3302.97, 3035.29, 3014.21, 2926.14, 2871.82, 1498.19; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.39 (t, 1H, *J* = 2.35 Hz), 2.43 (t, 1H, *J* = 2.41 Hz), 3.31-3.58 (m, 4H), 3.78-3.92 (m, 3H), 3.95 (s, 2H), 3.98-4.03 (m, 1H), 4.05-4.13 (m, 2H), 4.21 (d, 1H, *J* = 2.40 Hz), 4.26 (d, 2H, *J* = 2.27 Hz), 4.36 (d, 1H, *J* = 1.77 Hz), 4.40-4.43 (m, 3H), 4.47 (d, 1H, *J* = 3.54

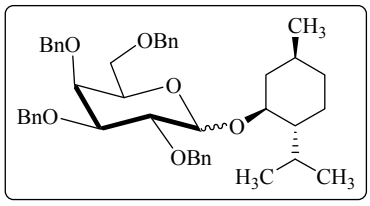
Hz), 4.49 (d, 1H, *J* = 1.62 Hz), 4.45 (dd, 2H, *J* = 2.07, 4.47 Hz), 4.59-4.72 (m, 3H), 4.75 (d, 2H, *J* = 2.19 Hz), 4.80 (d, 2H, *J* = 13.11 Hz), 4.90 (d, 1H, *J* = 4.01 Hz), 4.95 (d, 1H, *J* = 11.54 Hz), 5.12 (d, 1H, *J* = 3.63 Hz), 5.32 (d, 1H, *J* = 4.29 Hz), 7.25-7.41 (m, 40H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 54.5, 55.7, 64.2, 68.7, 69.6, 69.8, 71.4, 71.5, 72.4, 73.1, 73.4, 73.5, 74.5, 74.6, 74.8, 75.1, 76.1, 78.9, 79.1, 79.3, 79.8, 79.8, 81.4, 82.5, 95.8, 97.2, 127.4-128.5, 137.5, 137.6, 137.8, 138.0, 138.4, 138.6, 138.7, 138.9; CHNS Anal. Calculated for $C_{37}H_{38}O_6$: C, 76.79; H, 6.62; O, 16.59; Found: C, 76.67; H, 6.79; Calcd mass for $C_{37}H_{38}O_6$: 578.69; Found 601.67 (M^+ + 23 for Na).

Propargyl 2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranoside (17):



$[\alpha]_D^{25}$ = +38.76 (*c*, 1.1, $CHCl_3$); IR ($CHCl_3$): 3464.05, 2991.35, 2939.23, 2106.17 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.39 (t, 1H, *J* = 2.42 Hz), 2.69-3.80 (m, 3H), 3.83 (dd, 1H, *J* = 1.91, 2.85 Hz), 3.92 (d, 1H, *J* = 3.02 Hz), 4.20 (d, 2H, *J* = 2.41 Hz), 4.48 (d, 1H, *J* = 6.30 Hz) , 4.54 (d, 2H, *J* = 7.84 Hz), 4.60 (s, 2H), 4.64 (s, 1H), 4.74 (s, 2H), 4.88 (d, 1H, *J* = 10.77), 5.08 (d, 1H, *J* = 1.77), 7.13-7.41 (m, 20H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 54.1, 69.1, 72.1, 72.2, 72.6, 73.4, 74.4, 74.6, 74.7, 75.1, 78.9, 80.0, 96.4, 127.5-128.3, 138.2, 138.3, 138.4, 138.4; CHNS Anal. Calcd for $C_{37}H_{38}O_6$: C, 76.79; H, 6.62; O, 16.59; Found: C, 76.91; H, 6.75; MALDI-TOF: mol wt calcd for $C_{37}H_{38}O_6$: 578.69; Found 601.25 (M^+ + 23 for Na).

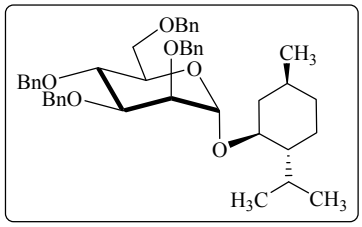
Menthyl 2,3,4,6-tetra-*O*-benzyl-*α/β*-D-galactopyranoside (18):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.87-0.92 (m, 18H), 1.03 (d, 2H, *J* = 11.09 Hz), 1.22-1.34 (m, 4H), 1.58-1.67 (m, 4H), 2.01-2.13 (m, 4H), 2.15-2.77 (m, 2H), 2.31-2.49 (m, 2H), 3.30 (dd, 1H, *J* = 4.31, 10.42 Hz), 3.37-3.41 (m, 1H), 3.46 (d, 1H, *J* = 4.64 Hz), 3.49-3.57 (m, 2H), 3.62-3.83 (m, 3H), 3.90 (dd, 1H, *J* = 2.57, 15.21 Hz), 3.99-4.06 (m, 3H), 4.12 (d, 1H, *J* = 7.35 Hz), 4.27 (d, 2H, *J* = 11.71 Hz), 4.39 (d, 1H, *J* = 3.38 Hz), 4.42-4.46 (m, 2H), 4.50 (s, 3H), 4.55 (d, 2H, *J* = 2.40 Hz), 4.62 (dd, 1H, *J* = 1.74, 6.86 Hz), 4.70 (d, 1H, *J* = 2.32 Hz), 4.74 (s, 2H), 4.76-4.80 (m, 2H), 4.91 (d, 1H, *J* = 4.00 Hz), 4.97 (d, 1H, *J* = 4.77 Hz), 5.02 (d, 1H, *J* = 3.23 Hz), 7.17-7.40 (m, 40H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 15.6, 16.0, 21.0, 21.1, 22.2, 22.4, 23.0, 23.1, 24.9, 25.1, 34.3, 34.5, 39.7, 39.7, 41.2, 42.9, 47.7, 48.8, 69.2, 69.3, 71.8, 71.8, 72.0, 72.6, 73.3, 74.4, 73.5, 73.6, 74.4, 74.7, 75.1, 76.1, 78.3, 79.2, 80.2,, 81.0, 82.7, 89.0, 99.3, 102.3, 127.3-128.4, 137.8, 138.0, 138.1, 138.3, 138.5, 138.7, 138.8, 138.9; CHNS Anal. Calculated for $C_{44}H_{54}O_6$: C, 77.84; H,

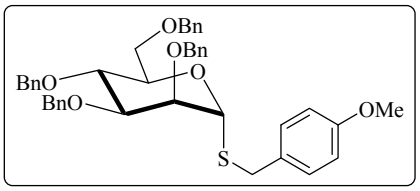
8.02; O, 14.14; Found: C, 77.61; H, 7.78; Calcd mass for $C_{44}H_{54}O_6$: 678.90; Found 701.10 (M^+ + 23 for Na).

Menthyl 2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranoside (19):



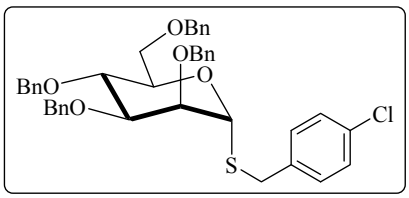
$[\alpha]_D^{25}$ = +12.19 (*c*, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 0.64 (d, 3H, *J* = 6.99), 0.80 (d, 3H, *J* = 1.37 Hz), 0.84 (d, 3H, *J* = 1.87 Hz), 0.87-0.95 (m, 2H), 1.25-1.43 (m, 2H), 1.52-1.85 (m, 4H), 2.14 (d, 1H, *J* = 11.90 Hz), 3.25 (td, 1H, *J* = 4.29, 10.58 Hz), 3.66-3.97 (m, 6H), 4.48 (d, 1H, *J* = 4.56 Hz), 4.54 (d, 2H, *J* = 6.03 Hz), 4.62-4.64 (m, 2H), 4.70 (d, 2H, *J* = 2.79 Hz), 4.97 (s, 1H), 4.92 (s, 1H), 7.15-7.38 (m, 20H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 16.3, 21.0, 22.1, 23.2, 25.7, 31.6, 34.2, 42.8, 48.6, 69.5, 71.8, 72.2, 72.4, 73.3, 74.4, 75.1, 75.2, 80.1, 81.1, 99.8, 127.4-128.3, 138.2, 138.5, 138.5, 138.6; CHNS Anal. Calculated for $C_{44}H_{54}O_6$: C, 77.84; H, 8.02; O, 14.14; Found: C, 77.99; H, 8.26. Calcd mass for $C_{44}H_{54}O_6$: 678.90; Found 701.02 (M^+ + 23 for Na).

***p*-Methoxybenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (27):**



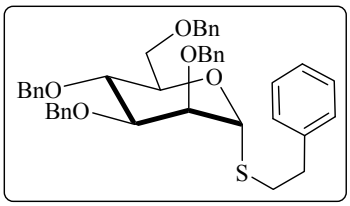
$[\alpha]_D^{25}$ = +35.55 (*c*, 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.52-3.77 (m, 5H), 3.78 (s, 3H), 3.84 (d, 1H, *J* = 2.65 Hz), 4.02 (t, 1H, *J* = 9.35 Hz), 4.10-4.20 (m, 1H), 4.48-4.56 (m, 4H), 4.60 (s, 1H), 4.65 (t, 1H, *J* = 2.95 Hz), 4.73 (d, 1H, *J* = 5.30 Hz), 4.88 (d, 1H, *J* = 10.87 Hz), 5.27 (s, 1H), 6.82 (d, 2H, *J* = 8.72 Hz), 7.10-7.38 (m, 22H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 34.1, 55.2, 69.1, 71.7, 71.9, 72.2, 73.3, 75.0, 75.1, 75.8, 80.4, 80.6, 113.9, 127.4-128.3, 129.7, 130.1, 137.9, 138.1, 138.3, 138.5, 158.6; Calcd mass for $C_{42}H_{44}O_6S$: 676.86; Found 699.77 (M^+ + 23 for Na).

***p*-Chlorobenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (28)**:



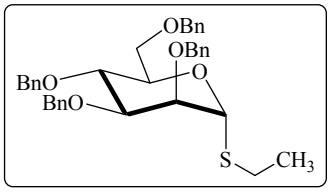
$[\alpha]_D^{25}$ = +40.00 (*c,* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.58-3.72 (m, 4H), 3.74-3.84 (m, 2H), 4.02 (d, 1H, *J* = 8.46 Hz), 4.48 (d, 1H, *J* = 1.64 Hz), 4.53 (s, 2H), 4.54 (s, 1H), 4.59 (d, 2H, *J* = 4.92 Hz), 4.63 (s, 1H), 4.66-4.75 (m, 1H), 4.88 (d, 1H, *J* = 10.74 Hz), 5.18 (d, 1H, *J* = 1.27 Hz), 7.15-7.39 (m, 24H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 33.9, 69.0, 71.9, 72.0, 72.2, 73.3, 74.9, 75.1, 75.8, 80.3, 80.7, 127.5-128.3, 128.6, 130.3, 132.8, 136.3, 137.8, 138.1, 138.2, 138.3; Calcd mass for $C_{41}H_{41}ClO_5S$: 681.28; Found 704.69 (M^+ + 23 for Na).

Ethylbenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside(29):



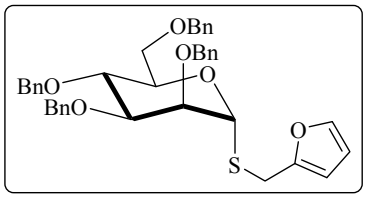
$[\alpha]_D^{25}$ = +22.72 (*c,* 1.10,$CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.74-2.91 (m, 4H), 3.67-3.85 (m, 4H), 3.97-4.17 (m, 2H), 4.47-4.73 (m, 7H), 4.87 (d, 1H, *J* = 10.74 Hz), 5.36 (s, 1H), 7.13-7.38 (m, 25H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.5, 36.3, 69.1, 71.9, 72.0, 72.0, 73.3, 75.0, 75.1, 76.2, 80.3, 82.3, 126.3, 127.4-128.5, 138.1, 138.2, 138.3, 138.4, 140.2; Calcd mass for $C_{42}H_{44}O_5S$: 660.86; Found 683.80 (M^+ + 23 for Na).

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (30):



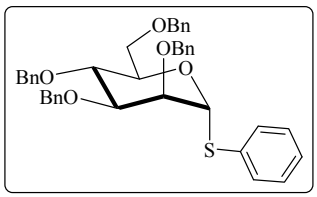
$[\alpha]_D^{25}$ = +12.50 (*c,* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.20-2.28 (m, 3H), 2.59 (t, 2H, *J* = 7.09 Hz), 3.67-3.86 (m, 4H), 3.98-4.17 (m, 2H), 4.50 (d, 2H, *J* = 11.88 Hz), 4.57 (s, 2H), 4.60-4.64 (m, 1H), 4.70 (d, 2H, *J* = 4.57 Hz), 4.88 (d, 1H, *J* = 10.87 Hz), 5.40 (d, 1H, *J* = 1.50 Hz), 7.14-7.41(m, 20H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 14.9, 25.3, 69.1, 71.9, 72.0, 72.0, 73.3, 75.0, 75.1, 76.3, 80.3, 81.8, 127.4-128.3, 138.1, 138.2, 138.3, 138.5; Calcd mass for $C_{36}H_{40}O_5S$: 584.76; Found 607.88 (M^+ + 23 for Na).

2-Furfuryl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (31):



$[\alpha]_D^{25}$ = +32.00 (*c,* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.62-4.26 (m, 7H), 4.48-4.74 (m, 6H), 4.85-4.98 (m, 2H), 5.39 (s, 1H), 6.16 (d, 1H, *J* = 2.93 Hz), 6.28 (dd, 1H, *J* = 1.89, 3.16 Hz), 7.14-7.33(m, 22H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 26.7, 69.3, 71.8, 71.9, 72.4, 73.3, 74.9, 75.1, 75.8, 81.1, 81.3, 107.9, 110.4, 127.4-128.3, 137.9, 138.1, 138.4, 138.4, 142.3, 150.8; Calcd mass for $C_{39}H_{40}O_5S$: 636.80; Found 659.71 (M^+ + 23 for Na).

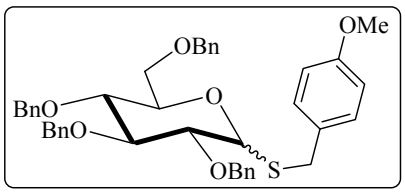
Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (32):



$[\alpha]_D^{25}$ = +10.00 (*c,* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.74 (dd, 1H, *J* = 1.95, 10.80 Hz), 3.77-3.89 (m, 2H), 4.00 (dd, 1H, *J* = 1.71, 2.97 Hz), 4.07 (t, 1H, *J* = 4.47 Hz), 4.29 (qd, 2H, *J* = 1.85 Hz, *J* = 4.69 Hz), 4.47 (d, 1H, *J* = 10.08 Hz), 4.53 (d, 1H, *J* = 8.98 Hz), 4.60 (s, 2H), 4.67 (dd, 2H, *J* = 4.70, 11.88 Hz), 4.91 (d, 1H, *J* = 10.77 Hz), 5.61 (d, 1H, *J* = 1.46 Hz), 7.17-7.47 (m, 25H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 69.1, 71.8, 72.0, 72.7,

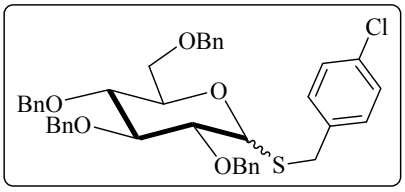
73.2, 74.9, 75.2, 76.1, 80.1, 85.7, 127.4-128.4, 129.0, 129.0, 131.6, 131.6, 134.3, 137.8, 138.1, 138.3, 138.4; Calcd mass for $C_{40}H_{40}O_5S$: 632.81; Found 653.70 (M^+ + 23 for Na).

***p*-Methoxybenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α/β*-D-glucopyranoside (33)**:



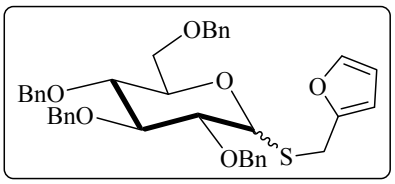
^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.54-3.79 (m, 12H), 3.77 (s, 3H), 3.78 (s, 3H), 3.86 (d, 1H, *J* = 3.16 Hz), 3.95 (s, 1H), 4.24 (d, 2H, *J* = 9.47 Hz), 4.44 (s,1H), 4.46-4.57 (m, 5H), 4.59 (s, 2H), 4.61 (s,1H), 4.65-4.67 (m, 1H), 4.71 (d, 1H, *J* = 3.28 Hz), 4.75-4.81 (m, 3H), 4.85 (t, 2H, *J* = 2.84Hz) 4.93 (d, 1H, *J* = 10.86 Hz), 5.20 (d, 1H, *J* = 5.05), 6.80 (d, 2H, *J* = 8.85 Hz), 6.83 (d, 2H, *J* = 8.71 Hz), 7.11-7.38 (m, 44H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.7, 33.7, 55.2, 55.3, 68.5, 69.1, 70.7, 71.8, 73.4, 73.4, 75.0, 75.0, 75.3, 75.7, 75.7, 77.4, 78.0, 78.9, 79.0, 81.6, 81.9, 82.8, 83.0, 86.6, 113.8, 113.9, 127.5-128.4, 129.4, 129.9, 130.2, 130.3, 137.6, 137.9, 138.0 138.1, 138.2, 138.4, 138.5, 138.6, 158.5, 158.6; Calcd mass for $C_{42}H_{44}O_6S$: 676.86; Found 699.80 (M^+ + 23 for Na).

***p*-Chlorobenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α/β*-D-glucopyranoide (34)**:



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.49-3.50 (m, 1H), 3.54-3.57 (m, 2H), 3.59 (d, 1H, *J* = 3.24 Hz), 3.62 (s, 1H), 3.65 (s, 2H), 3.69-3.72 (m, 1H), 3.75 (d, 1H, *J* = 3.86 Hz), 3.79 (d, 1H, *J* = 2.11 Hz), 3.83 (d, 1H, *J* = 2.89 Hz), 3.94-4.24 (m, 3H), 4.43 (s, 1H), 4.50 (s, 4H), 4.56-4.59 (m, 3H), 4.65 (d, 1H, *J* = 4.70 Hz), 4.71-4.75 (m, 2H), 4.78 (d, 2H, *J* = 2.80 Hz), 4.81 (d, 2H, *J* = 2.37 Hz), 4.85 (s, 2H), 4.90 (s, 1H), 4.96 (d, 1H, *J* = 2.41 Hz), 5.13 (d, 1H, *J* = 5.07 Hz), 7.11-7.36 (m, 48H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.5, 33.6, 68.4, 69.1, 70.7, 70.7, 72.2, 73.4, 73.4, 75.0, 75.1, 75.4, 75.7, 75.7, 77.4, 77.9, 78.9, 82.0, 82.7, 83.0, 86.6, 127.6-128.6, 128.6, 130.4, 130.5, 132.7, 132.8, 136.2, 136.4, 137.5, 137.7, 137.8, 138.0, 138.1, 138.2, 138.3, 138.6; Calcd mass for $C_{41}H_{41}ClO_5S$: 681.28; Found 704.79 (M^+ + 23 for Na).

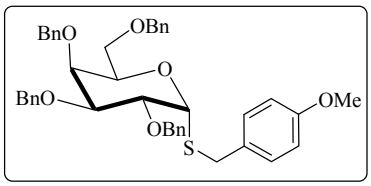
2-Furfuryl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α/β*-D-glucopyranoside (35):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.57-3.66 (m, 5H), 3.69-3.77 (m, 3H), 3.76-3.85 (m, 4H), 4.00 (d, 1H, *J* = 9.64 Hz), 4.19-4.20 (m,2H), 4.44 (s, 2H), 4.49 (s, 1H), 4.50 (s, 1H), 4.55-4.62 (m, 3H), 4.64-4.66 (m, 1H), 4.72 (s, 1H), 4.76 (d, 1H, *J* = 4.18 Hz), 4.81 (s, 2H), 4.84-4.86 (m, 2H), 4.87 (d, 1H, *J* = 1.63 Hz), 4.90 (d, 1H, *J* = 1.37 Hz), 4.96 (d, 1H, *J* = 1.75 Hz), 5.42 (d, 1H, *J* = 4.33 Hz), 5.62-5.63 (m, 1H), 6.02 (d, 1H,

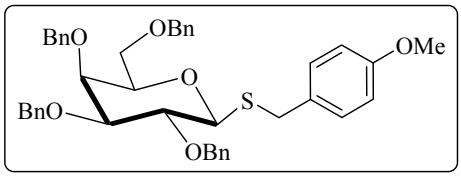
J = 1.80 Hz), 6.21 (t, 1H, *J* = 3.78 Hz), 6.27 (dd, 1H, *J* = 1.90, 3.27 Hz), 6.30 (dd, 1H, *J* = 1.85, 3.21 Hz), 7.11-7.36 (m, 44H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 25.5, 26.3, 68.3, 68.4, 70.6, 70.7, 70.8, 71.8, 73.3, 73.4, 75.0, 75.1, 75.7, 77.5, 77.9, 79.0, 79.6, 81.9, 82.6, 82.7, 86.6, 95.8, 107.7, 107.7, 110.4, 110.4, 125.5-128.4, 137.6, 137.8, 137.8, 138.0, 138.1, 138.2, 138.6, 138.7, 142.1, 142.1, 151.2, 151.2; Calcd mass for $C_{39}H_{40}O_5S$: 636.80; Found 659.89 (M^+ + 23 for Na).

***p*-Methoxybenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-galactopyranoside (36 *α*):**



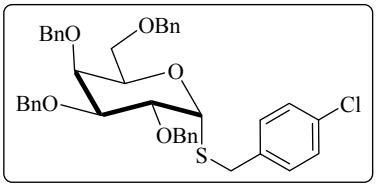
$[\alpha]_D^{25}$ = +55.95 (*c,* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.46-3.54 (m, 2H), 3.60 (d, 1H, *J* = 4.16 Hz), 3.63 (d, 1H, *J* = 4.41 Hz), 3.76 (s, 3H), 3.78-3.79 (m, 1H), 3.86 (d, 2H, *J* = 9.20 Hz), 3.92 (d, 1H, *J* = 2.27 Hz), 4.24 (d, 1H, *J* = 9.63 Hz), 4.46 (d, 2H, *J* = 3.68 Hz), 4.60 (d, 1H, *J* = 11.61 Hz), 4.69 (s, 2H), 4.74 (d, 2H, *J* = 3.54 Hz), 4.94 (d, 1H, *J* = 11.61 Hz), 6.74 (d, 1H, *J* = 1.99 Hz), 6.78 (d, 1H, *J* = 2.19 Hz), 7.21-7.33 (m, 22H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.3, 55.2, 69.2, 69.8, 71.9, 73.3, 73.4, 74.7, 74.9, 75.8, 79.7, 81.9, 113.7, 113.8, 127.4-128.3, 129.9, 130.0, 130.2, 138.0, 138.0, 138.5, 138.7, 158.5; Calcd mass for $C_{42}H_{44}O_6S$: 676.86; Found 699.92 (M^+ + 23 for Na).

***p*-Methoxybenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-galactopyranoside (36 *β*):**



$[\alpha]_D^{25}$ = -19.29 (*c,* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.52 (d, 1H, *J* = 6.30 Hz), 3.64 (d, 1H, *J* = 9.19 Hz), 3.70 (m, 1H), 3.75 (s, 1H), 3.77 (s, 3H), 3.78 (s, 1H), 3.83-3.92 (m, 1H), 4.21 (dd, 1H, *J* = 5.63, 9.80 Hz), 4.28-4.39 (m, 2H), 4.40 (d, 1H, *J* = 1.13 Hz), 4.45 (d, 1H, *J* = 4.52 Hz), 4.53 (d, 1H, *J* = 3.40 Hz), 4.62 (d, 1H, *J* = 9.77 Hz), 4.70 (d, 1H, *J* = 2.50 Hz), 4.82 (d, 1H, *J* = 11.82 Hz), 4.91 (d, 1H, *J* = 11.43 Hz), 5.25 (d, 1H, *J* = 5.67 Hz), 6.78 (d, 1H, *J* = 1.80 Hz), 6.81 (d, 1H, *J* = 2.08 Hz), 7.21-7.36 (m, 22H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 33.4, 55.2, 68.9, 72.8, 73.5, 73.7, 74.5, 75.6, 77.2, 78.3, 83.5, 84.0, 113.8, 127.5-128.4, 129.8, 130.2, 137.8, 138.2, 138.3, 138.6, 158.5; Calcd mass for $C_{42}H_{44}O_6S$: 676.86; Found 699.57 (M^+ + 23 for Na).

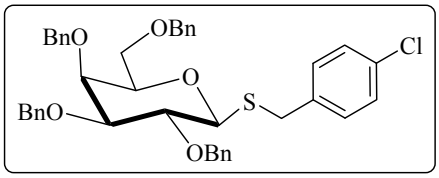
***p*-Chlorobenzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*α*-D-galactopyranoside (37 *α*):**



$[\alpha]_D^{25}$ = +84.93 (*c,* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.46 (d, 2H, *J* = 6.42 Hz), 3.59 (d, 1H, *J* = 4.88 Hz), 3.66 (d, 1H, *J* = 3.40 Hz), 3.72-3.75 (m, 1H), 3.79-3.81 (m,

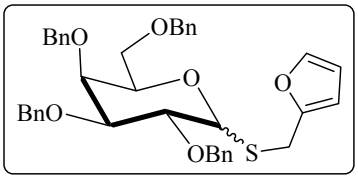
1H), 3.87-3.91 (m, 1H), 4.17-4.41 (m, 3H), 4.43 (d, 2H, *J* = 3.55 Hz), 4.52 (s, 2H), 4.74 (ABq, 2H, *J* = 11.85 Hz), 4.92 (d, 1H, *J* = 11.51 Hz), 7.22-7.35 (m, 24H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.1, 69.2, 69.9, 72.3, 73.4, 73.4, 74.7, 74.8, 75.8, 79.6, 81.9, 127.4-128.5, 130.5, 132.5, 136.7, 136.7, 137.9, 138.4, 138.6; Calcd mass for $C_{41}H_{41}O_5S$: 681.28; Found 704.77 (M^+ + 23 for Na).

_p_-Chlorobenzyl 2,3,4,6-tetra-_O_-benzyl-1-thio-_β_-D-galactopyranoside (37 _β_):



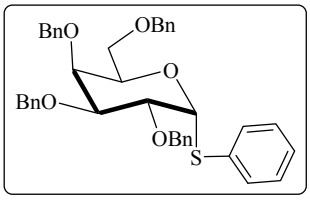
$[\alpha]_D^{25}$ = -19.56 (*c,* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.43-3.51 (m, 2H), 3.54-3.62 (m, 2H), 3.74-3.83 (m, 2H), 3.88 (s, 1H), 3.80-3.95 (m, 1H), 4.21 (d, 1H, *J* = 9.61 Hz), 4.45 (d, 2H, *J* = 3.42 Hz), 4.60 (d, 1H, *J* = 11.45 Hz), 4.69 (s, 2H), 4.73 (s, 2H), 4.94 (d, 1H, *J* = 11.45 Hz), 7.14-7.38 (m, 24H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 32.2, 68.9, 72.7, 73.5, 73.6, 74.5, 75.6, 77.2, 78.1, 83.3, 84.0, 127.5-128.5, 130.5, 132.6, 136.6, 137.7, 138.1, 138.2, 138.5; Calcd mass for $C_{41}H_{41}O_5S$: 681.28; Found 704.07 (M^+ + 23 for Na).

2-Furfuryl 2,3,4,6-tetra-_O_-benzyl-1-thio-_α_-D-galactopyranoside (38):



^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.50-3.62 (m, 5H), 3.66 (s, 1H), 3.68-3.75 (m, 1H), 3.78-3.82 (m, 2H), 3.85-3.87 (m, 1H), 3.91-3.96 (m, 3H), 4.01-4.09 (m, 1H), 4.14-4.38 (m, 4H), 4.41-4.45 (m, 3H), 4.48-4.65 (m, 4H), 4.70 (s, 2H), 4.74 (d, 1H, *J* = 2.52 Hz), 4.79 (s, 1H), 4.91 (d, 1H, *J* = 2.65 Hz), 4.97 (d, 1H, *J* = 2.90 Hz), 5.46 (d, 1H, *J* = 5.56), 6.15 (d, 2H, *J* = 3.25 Hz), 6.23 (dd, 1H, *J* = 1.89, 3.16 Hz), 6.28 (dd, 1H, *J* = 1.76, 3.15 Hz), 7.12-7.35 (m, 44H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 25.1, 25.6, 68.7, 69.0, 70.0, 72.0, 72.7, 73.3, 73.4, 73.5, 73.6, 74.5, 74.7, 74.9, 75.6, 75.8, 77.2, 78.1, 79.6, 82.7, 83.7, 84.0, 107.7, 107.8, 110.3, 110.4, 127.4-128.4, 137.8, 138.0, 138.0, 138.1, 138.3, 138.5, 138.6, 138.7, 142.0, 142.0, 151.2, 151.3; Calcd mass for $C_{39}H_{40}O_6S$: 636.80; Found 659.96 (M^+ + 23 for Na).

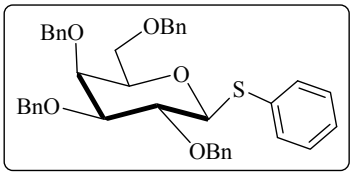
Phenyl 2,3,4,6-tetra-_O_-benzyl-1-thio-_α_-D-galactopyranoside (39 _α_):



$[\alpha]_D^{25}$ = +9.15 (*c,* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.57-3.68 (m, 4H), 3.91 (d, 1H, *J* = 9.47 Hz), 3.98 (d, 1H, *J* = 2.27 Hz), 4.44 (d, 2H, *J* = 3.41 Hz), 4.56-4.70 (m, 3H), 4.72 (s, 2H), 4.76 (d, 1H, *J* = 3.41 Hz), 4.97 (d, 1H, *J* = 11.50 Hz), 7.15-7.59 (m, 25H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 68.7, 72.7, 73.5, 73.5, 74.4, 75.6, 77.2, 84.1, 87.7,

127.0, 127.4-128.4, 128.8, 131.4, 134.1, 137.9, 138.2, 138.2, 138.7; Calcd mass for $C_{40}H_{40}O_5S$: 632.81; Found 655.03 (M^+ + 23 for Na).

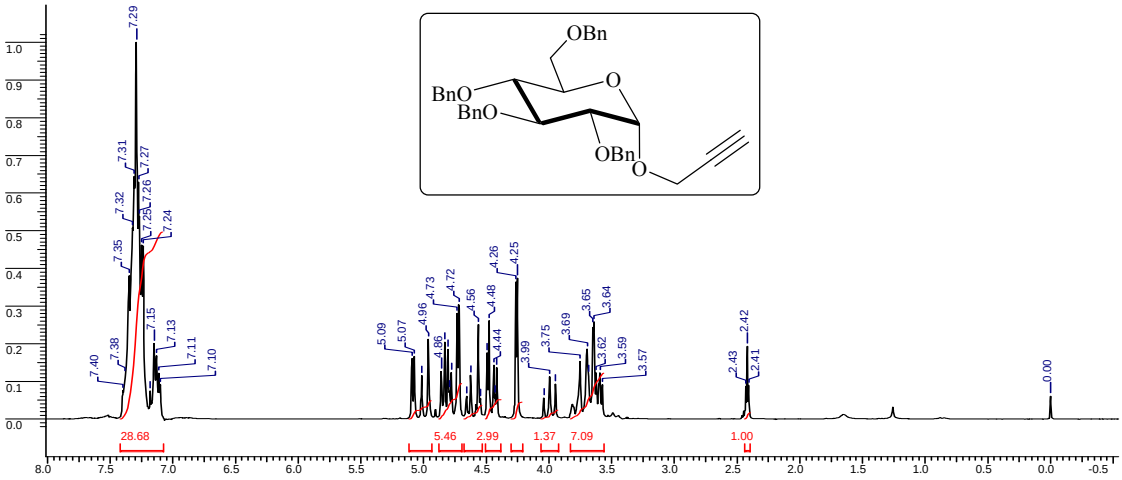
Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-galactopyranoside (39 *β*):



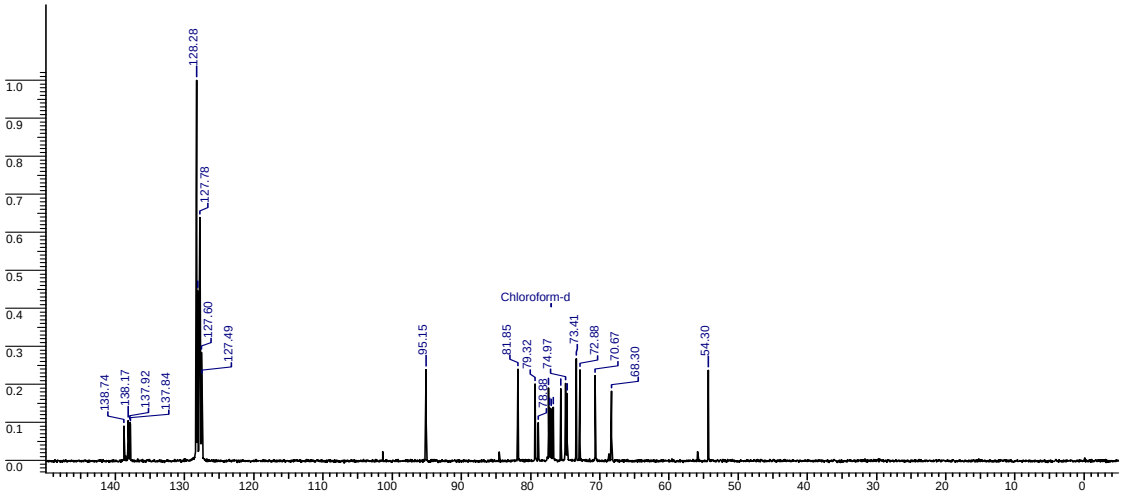
$[\alpha]_D^{25}$ = +89.70 (*c,* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.52 (d, 1H, *J* = 4.45), 3.54 (1H, *J* = 4.20 Hz), 3.82 (dd, 1H, *J* = 2.85, 10.05 Hz), 4.00 (d, 1H, *J* = 1.77 Hz), 4.33-4.50 (m, 4H), 4.59 (d, 1H, *J* = 11.51 Hz), 4.67-4.77 (m, 3H), 4.82-4.99 (m, 2H), 5.72 (d, 1H, *J* = 5.43 Hz), 7.19-7.51 (m, 25H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 68.8, 70.3, 72.6, 73.3, 73.4, 74.8, 75.0, 79.4, 87.5, 126.9, 127.5-128.3, 128.8, 131.6, 134.6, 137.9, 138.0, 138.5, 138.6; Calcd mass for $C_{40}H_{40}O_5S$: 632.81; Found 656.05 (M^+ + 23 for Na).

*****

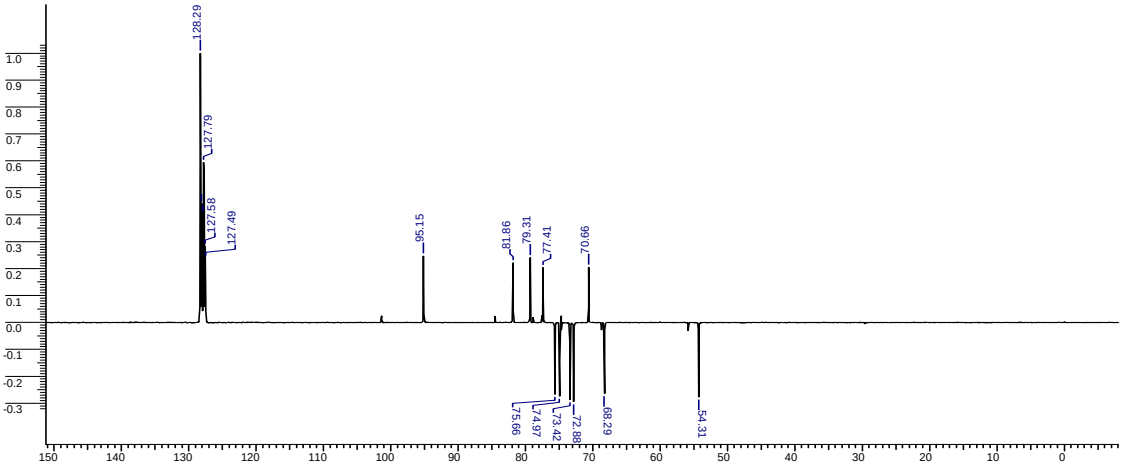
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **4a**



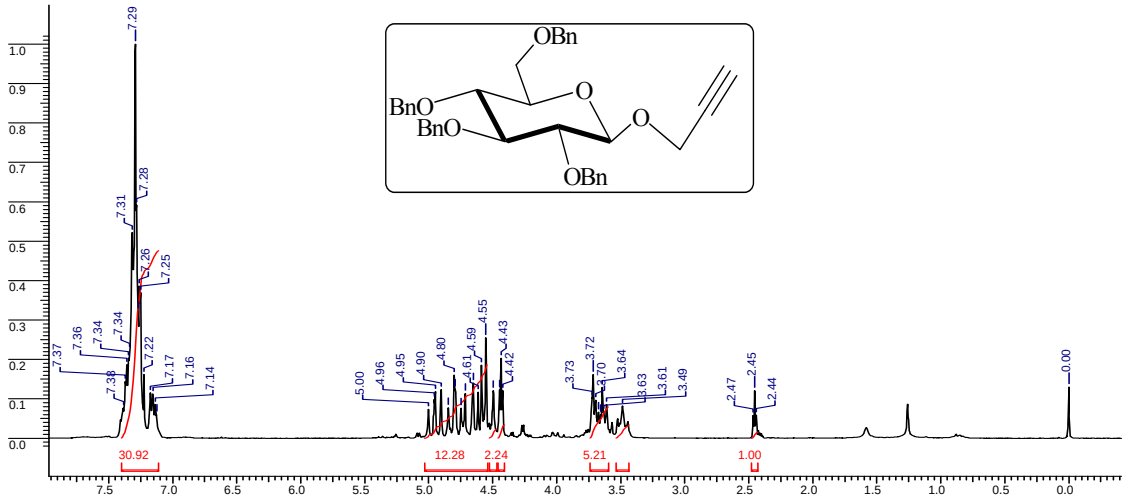
^{13}C NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **4a**



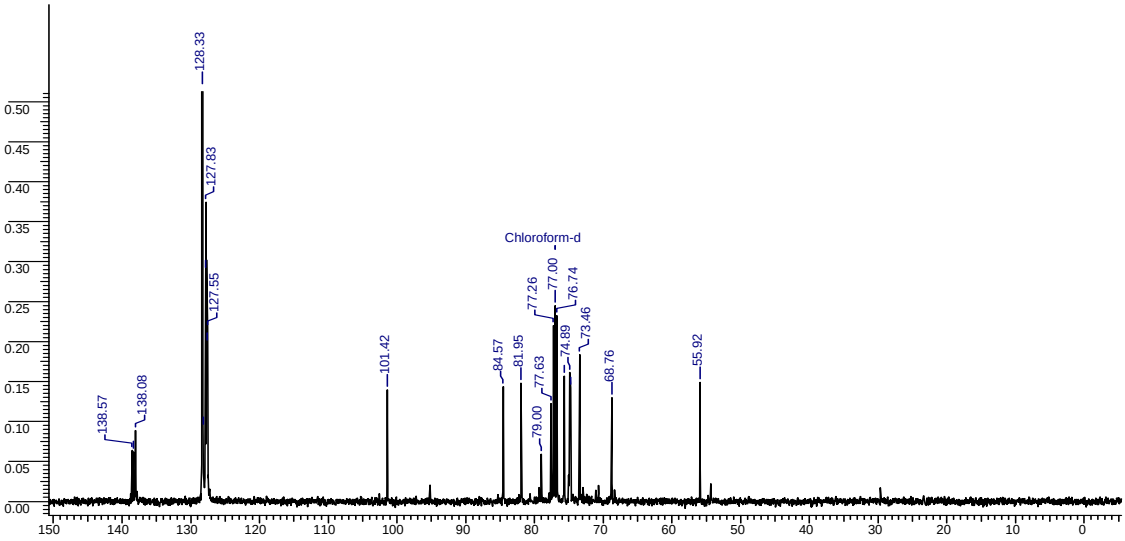
DEPT NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **4a**



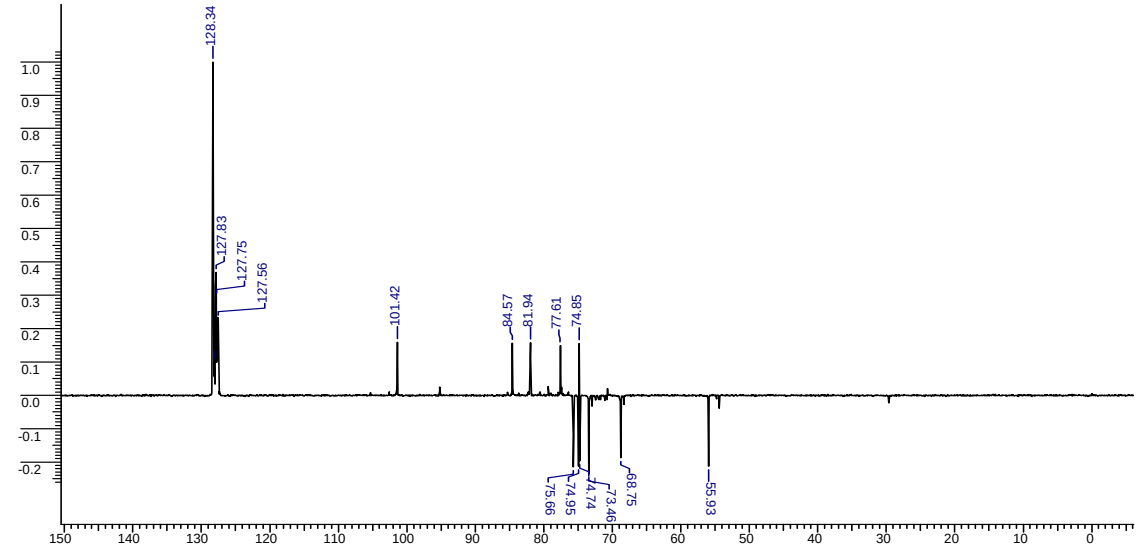
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **4b**



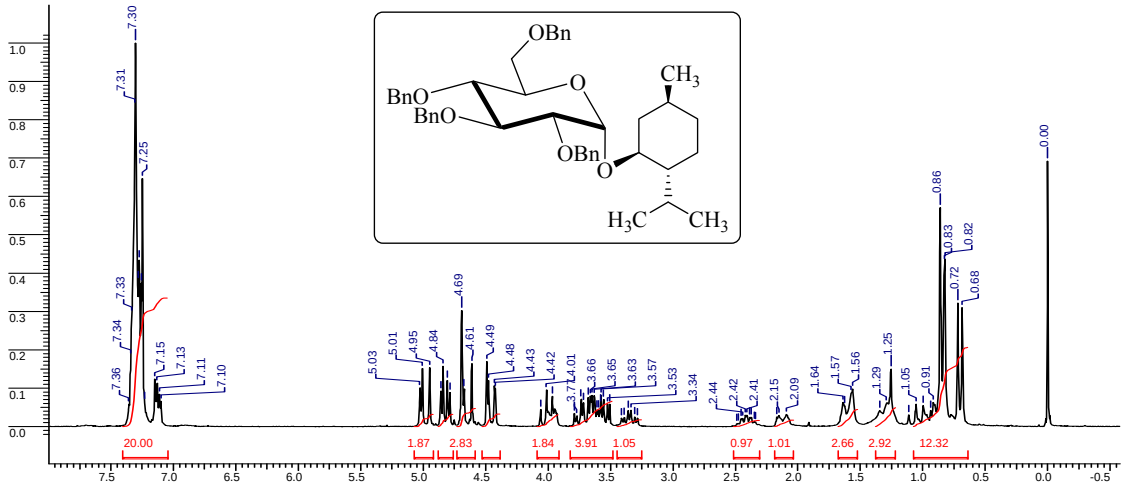
^{13}C NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **4b**



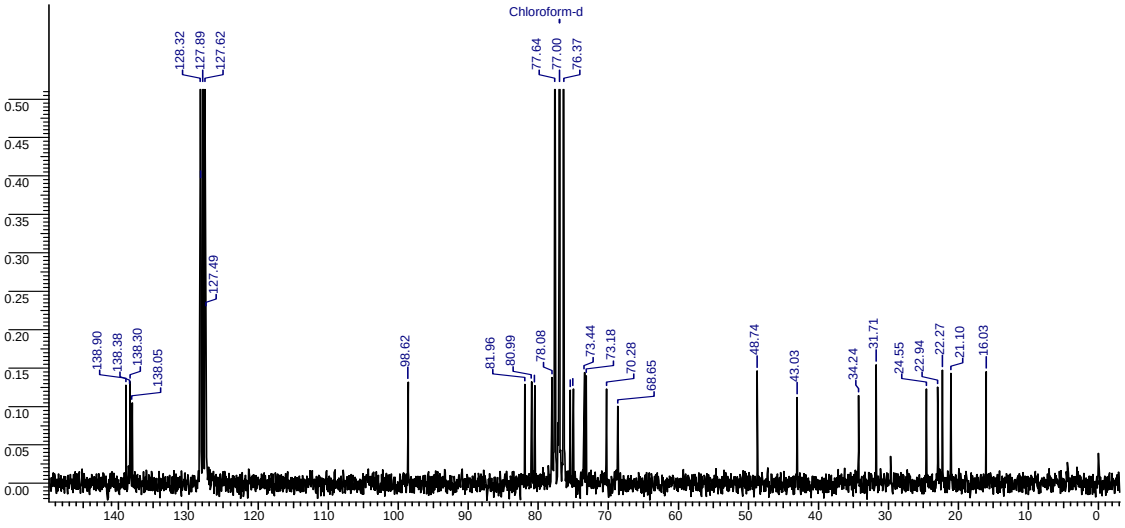
DEPT NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **4b**



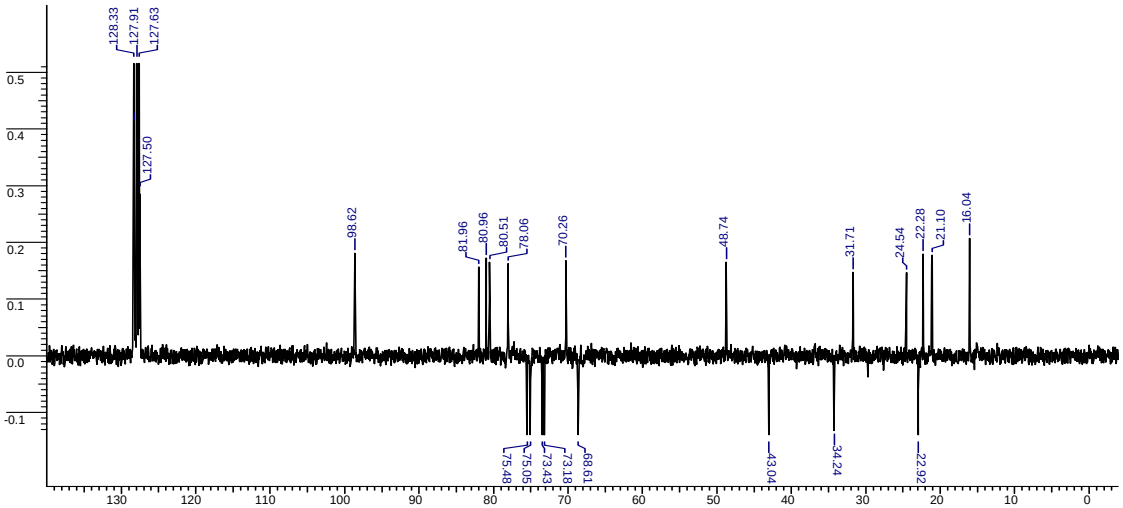
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **7(*α*)**



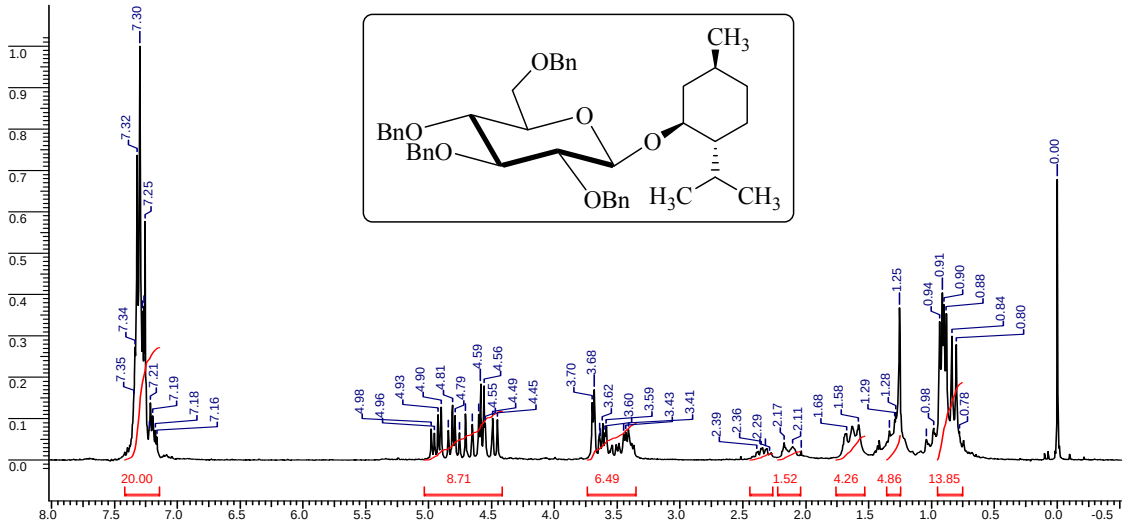
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7(*α*)**



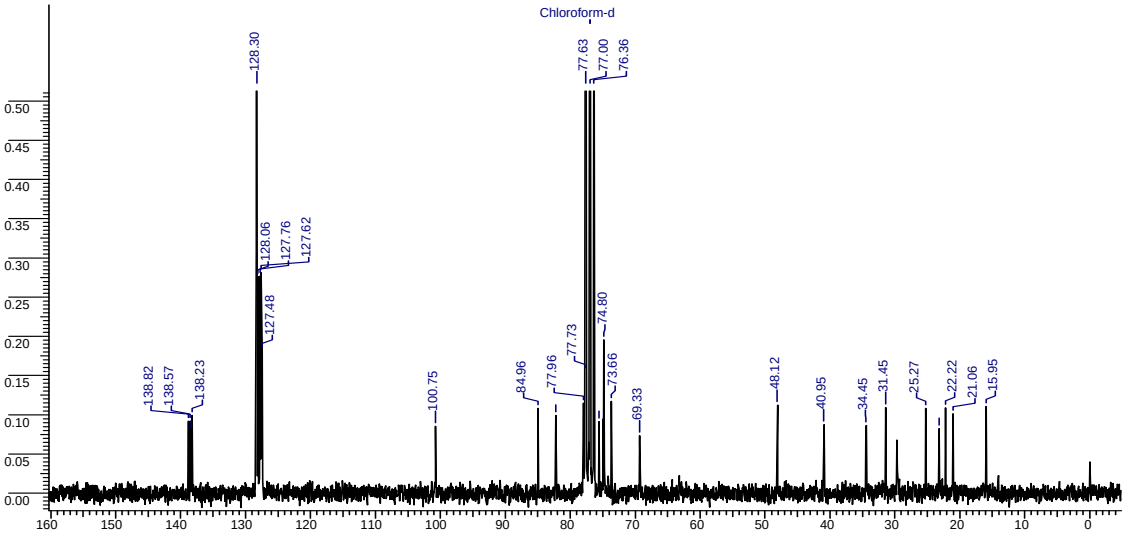
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7(*α*)**



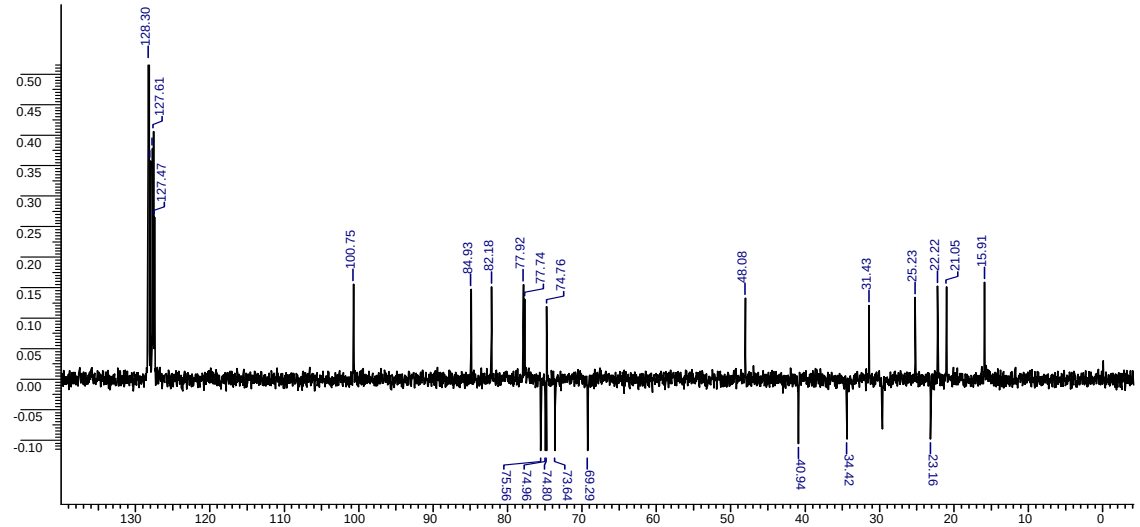
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **7(*β*)**



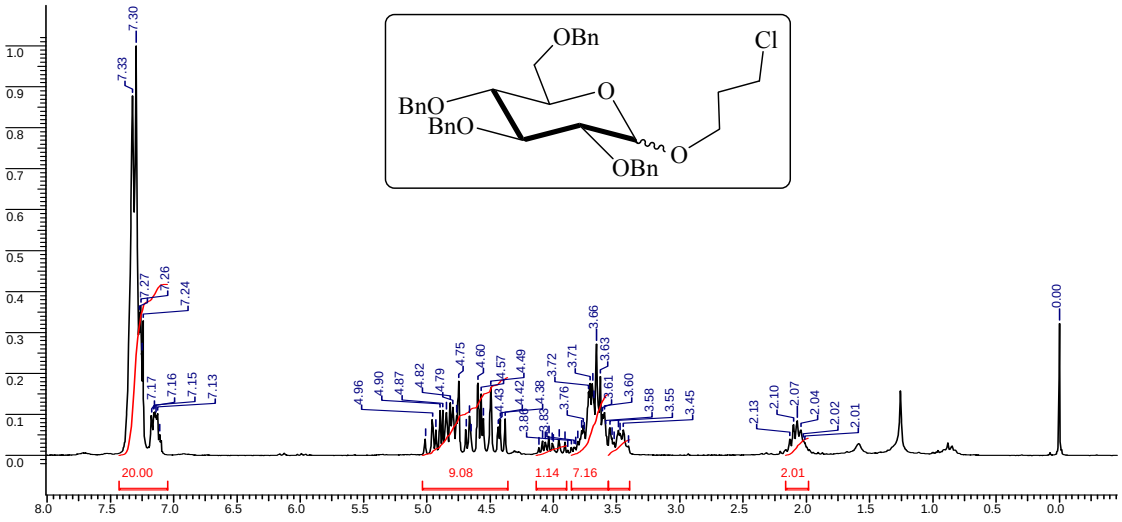
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7(*β*)**



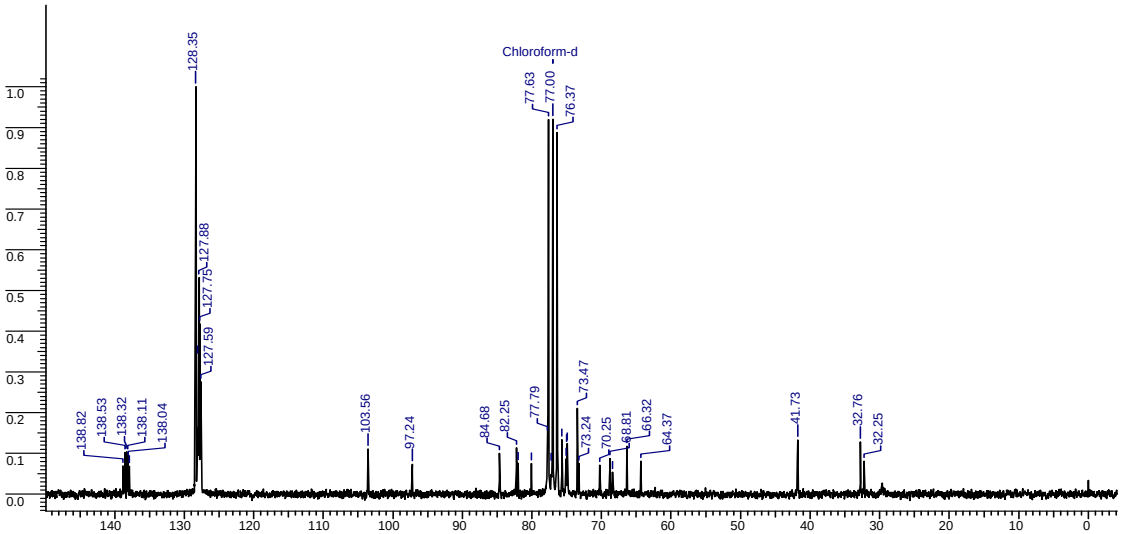
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7(*β*)**



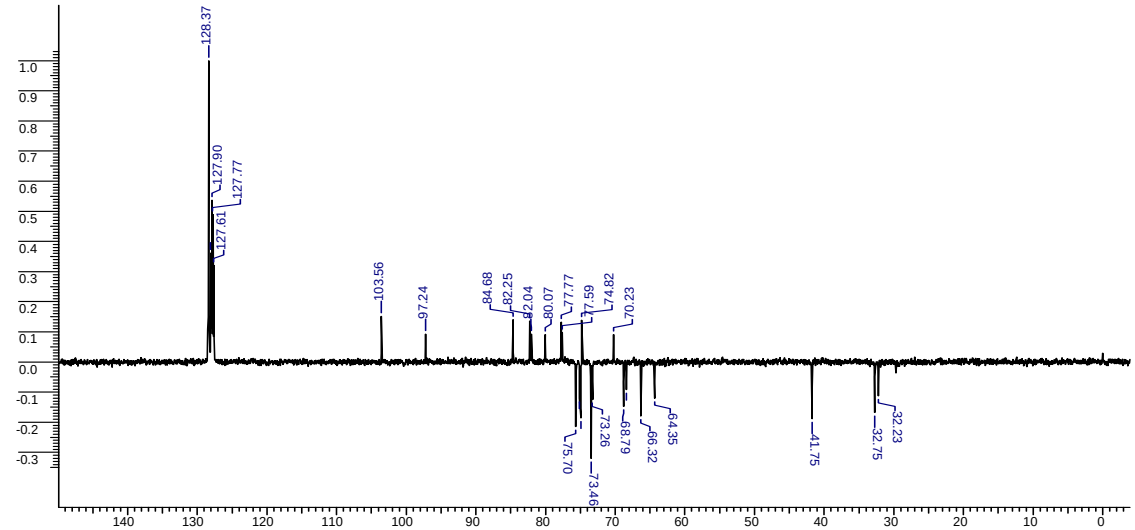
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **8**



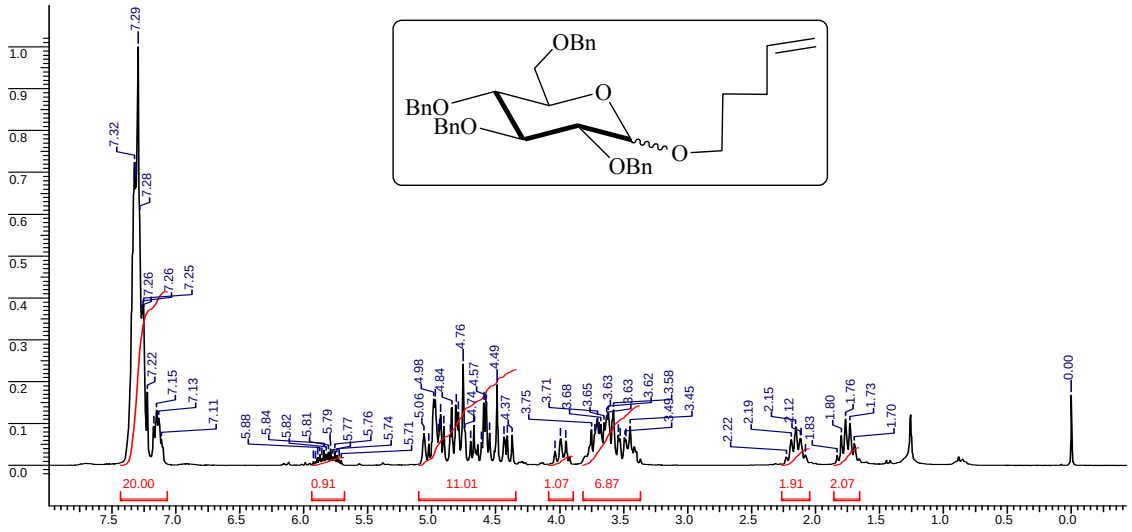
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **8**



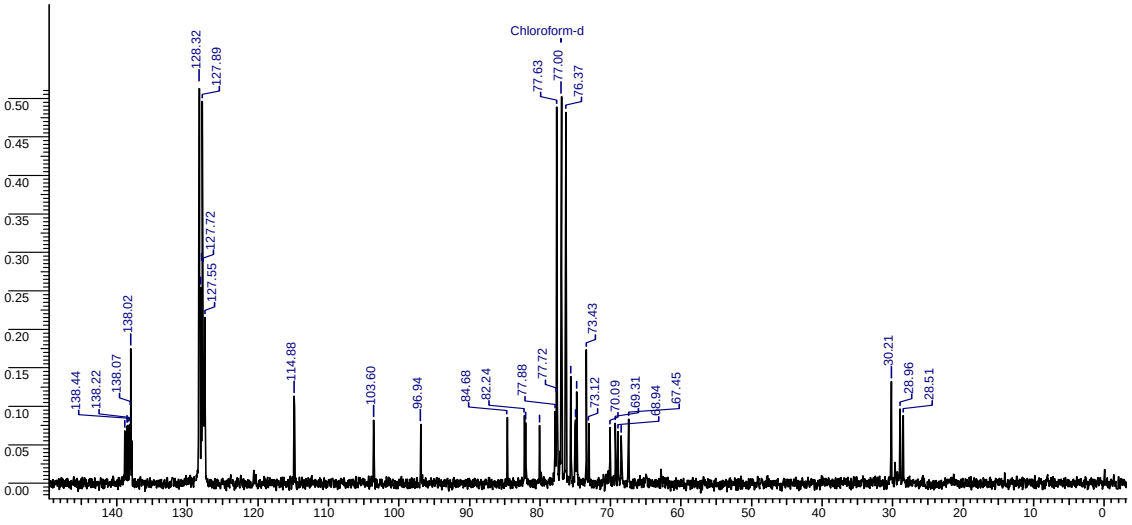
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **8**



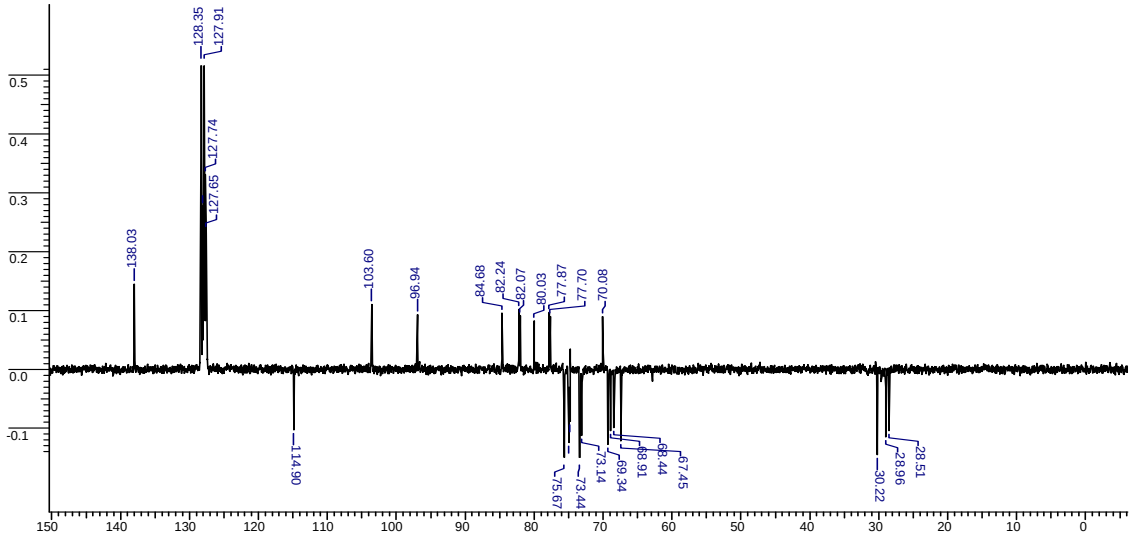
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **9**



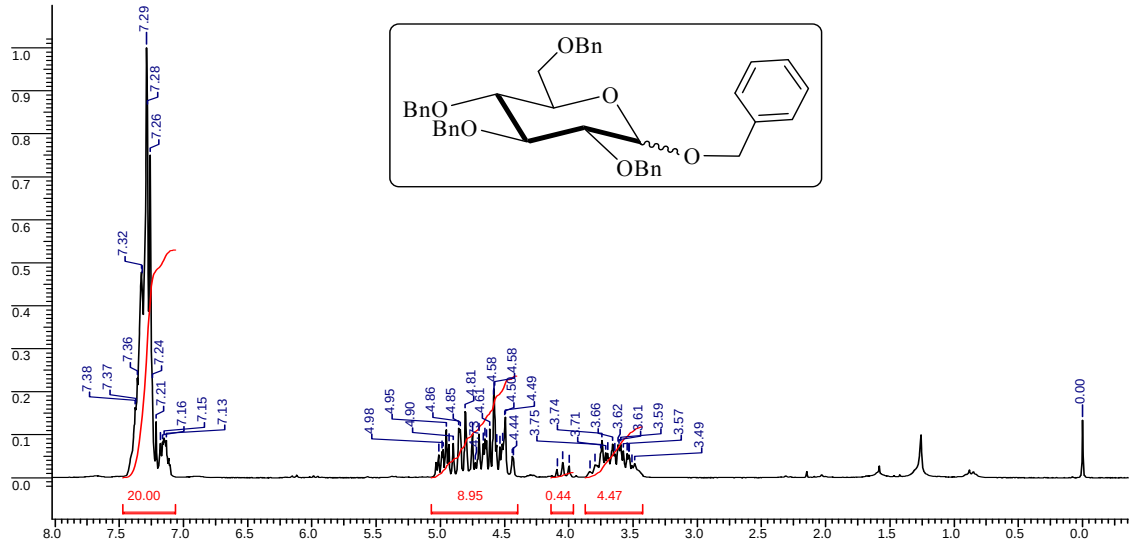
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



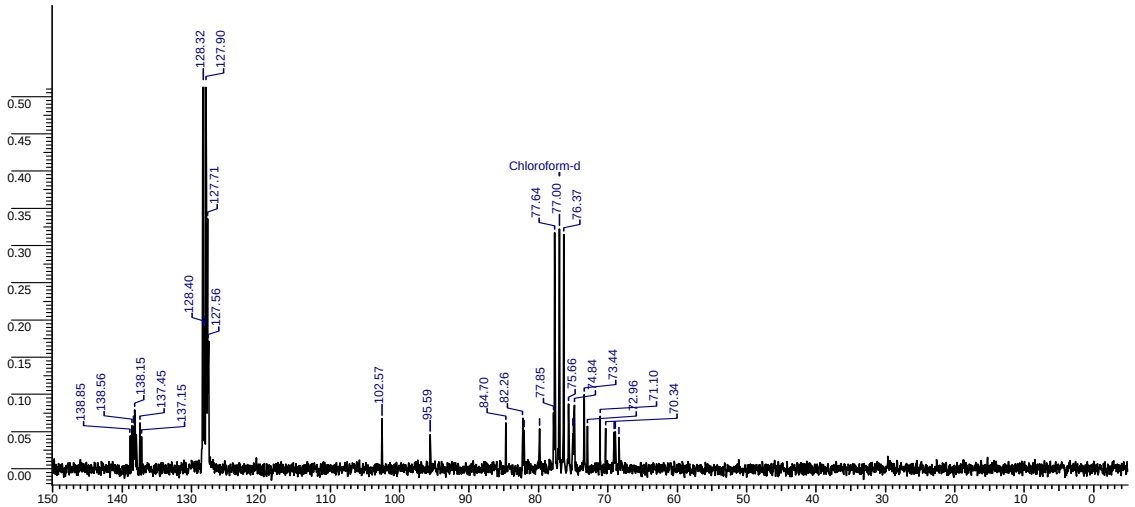
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



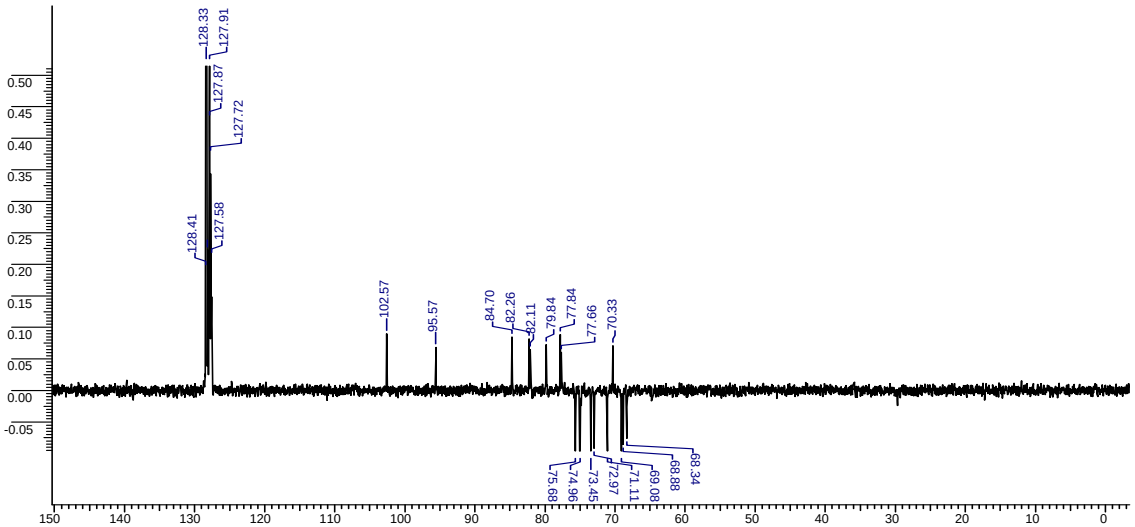
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **10**



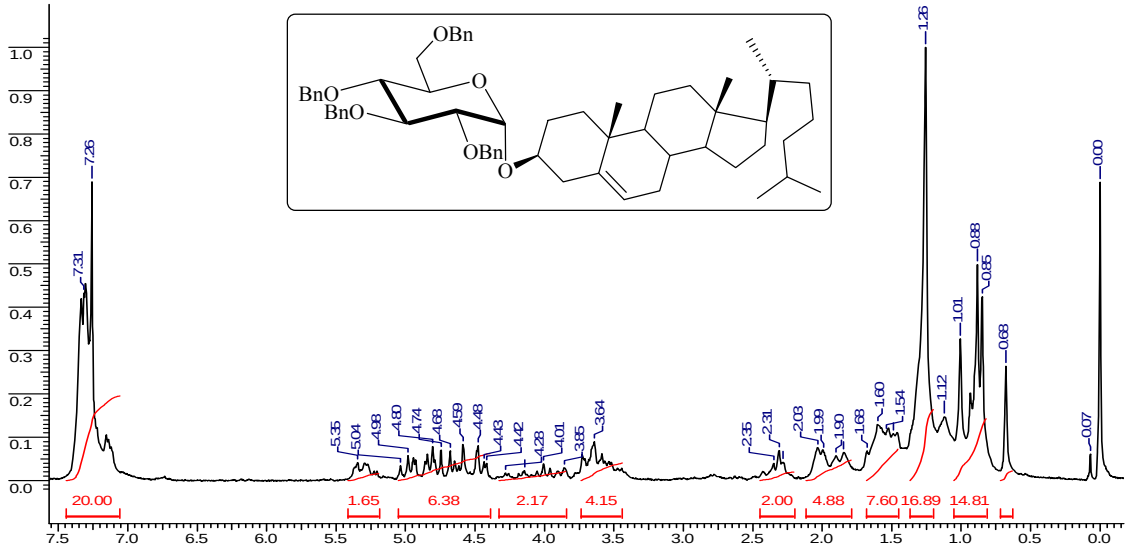
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **10**



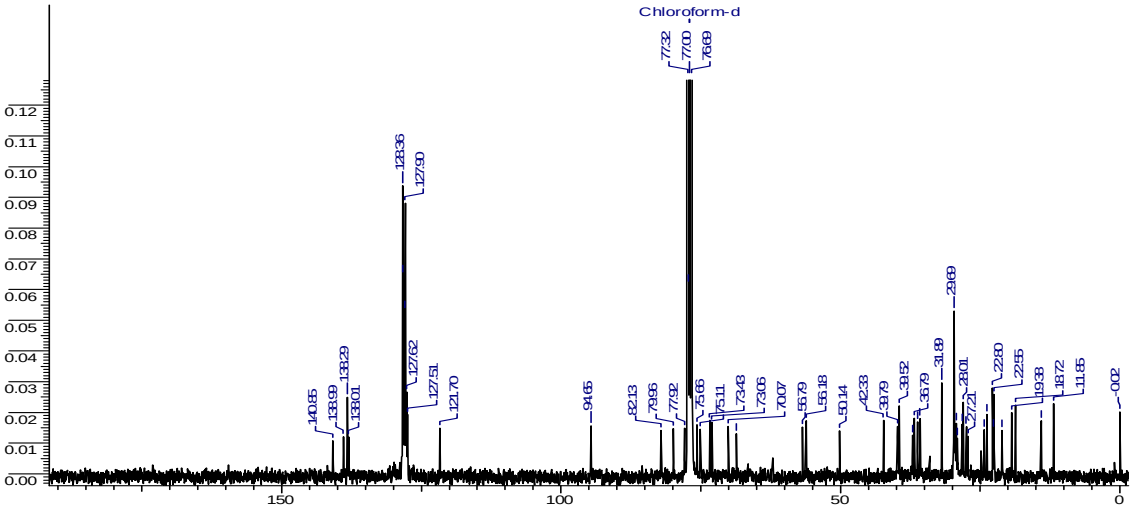
DEPT NMR ($CDCl_3$, 50.32 MHz spectrum of compound **10**



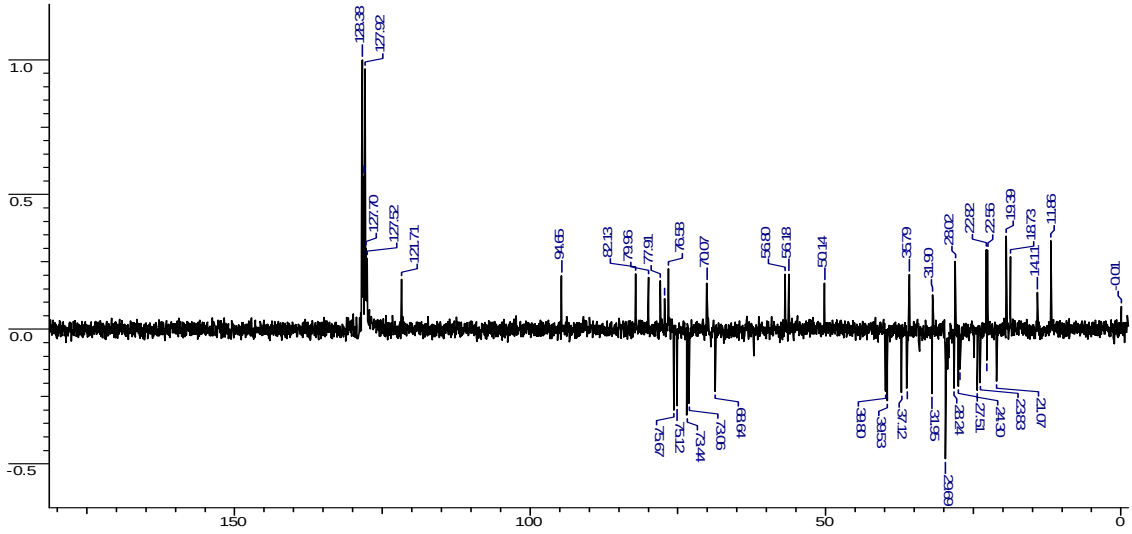
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **11 (*α*)**



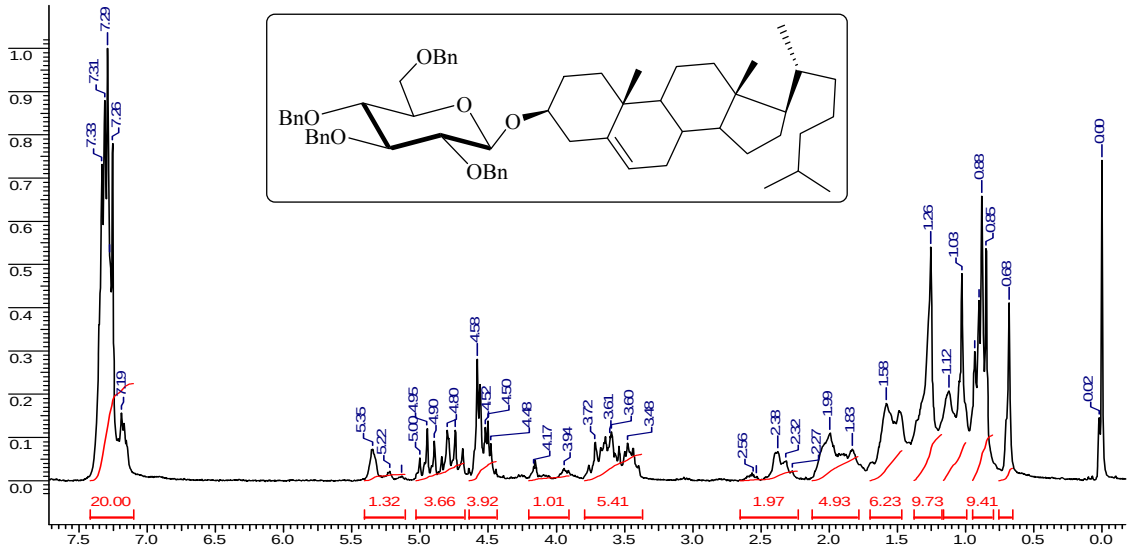
^{13}C NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11 (*α*)**



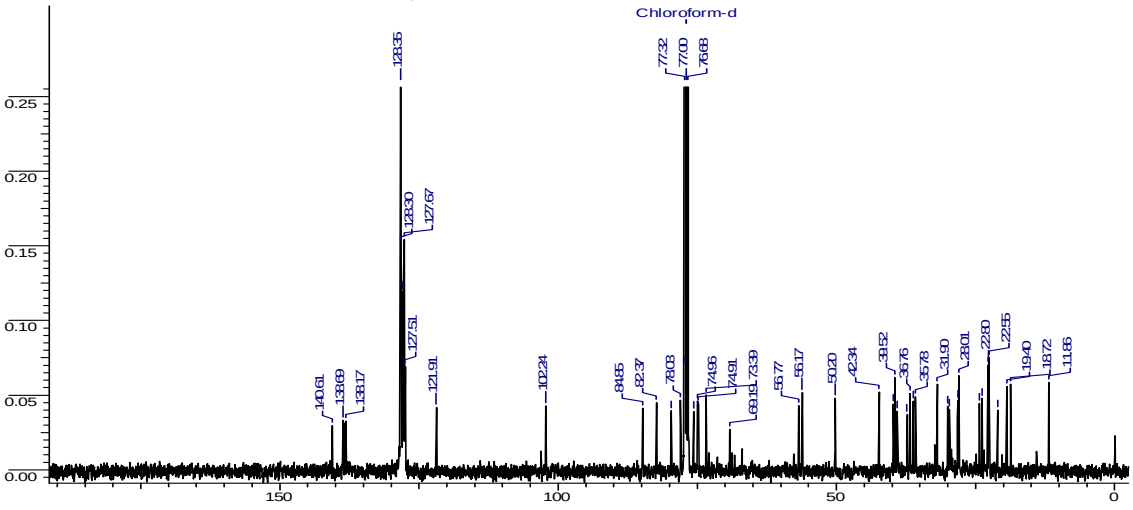
DEPT NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11 (*α*)**



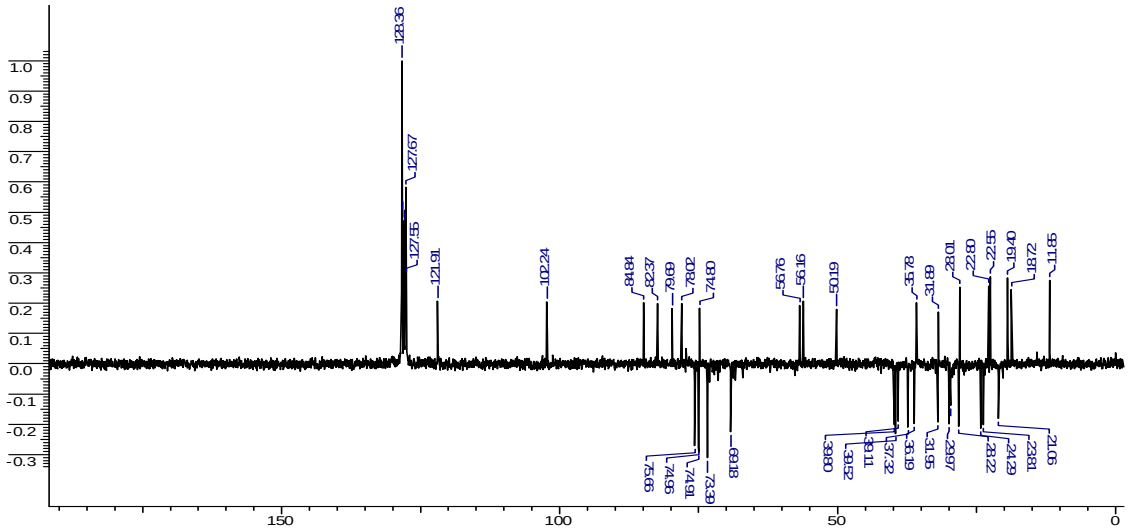
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **11 (*β*)**



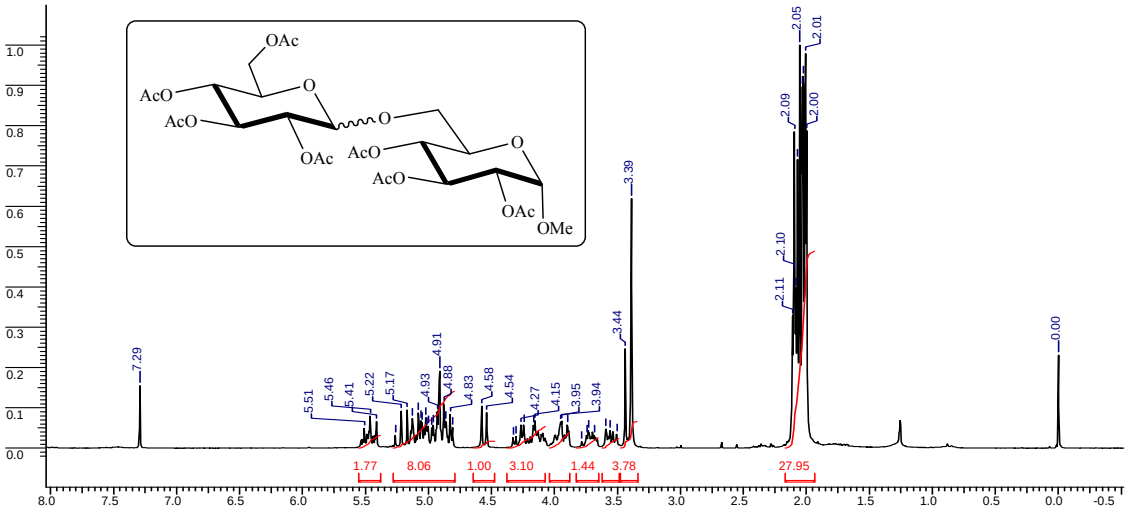
^{13}C NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11 (*β*)**



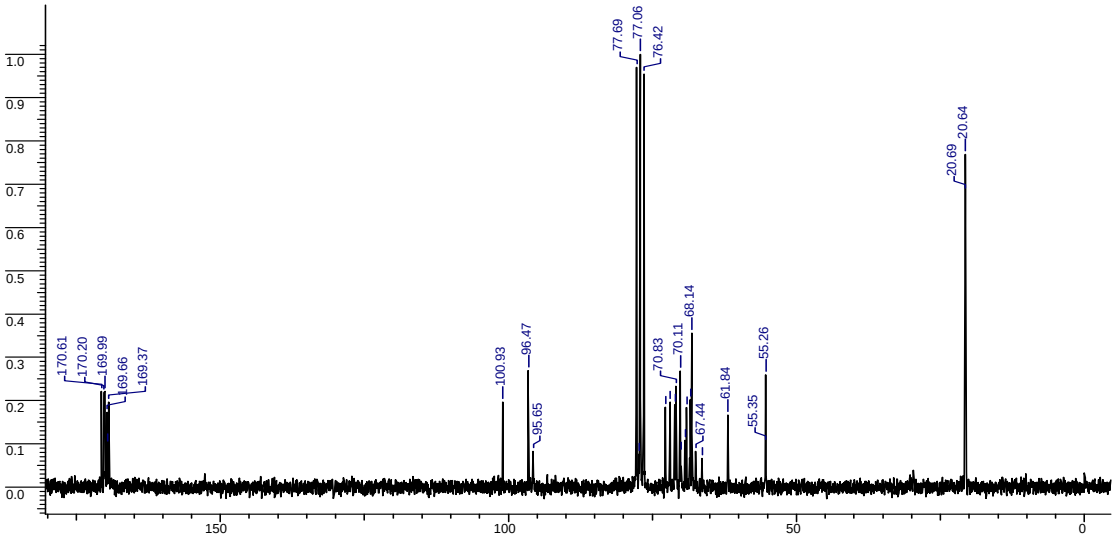
DEPT NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **11 (*β*)**



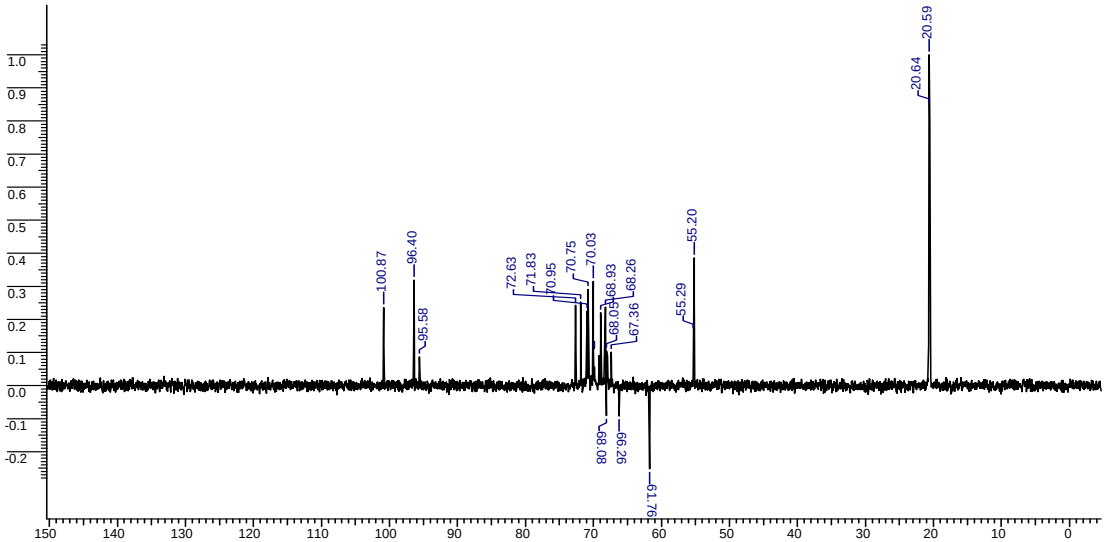
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **14**



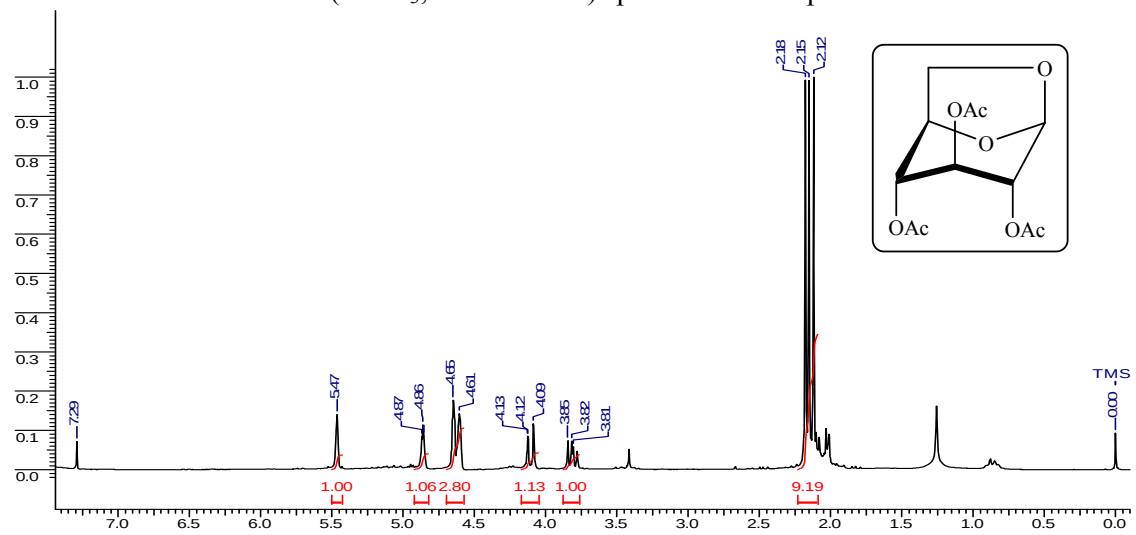
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



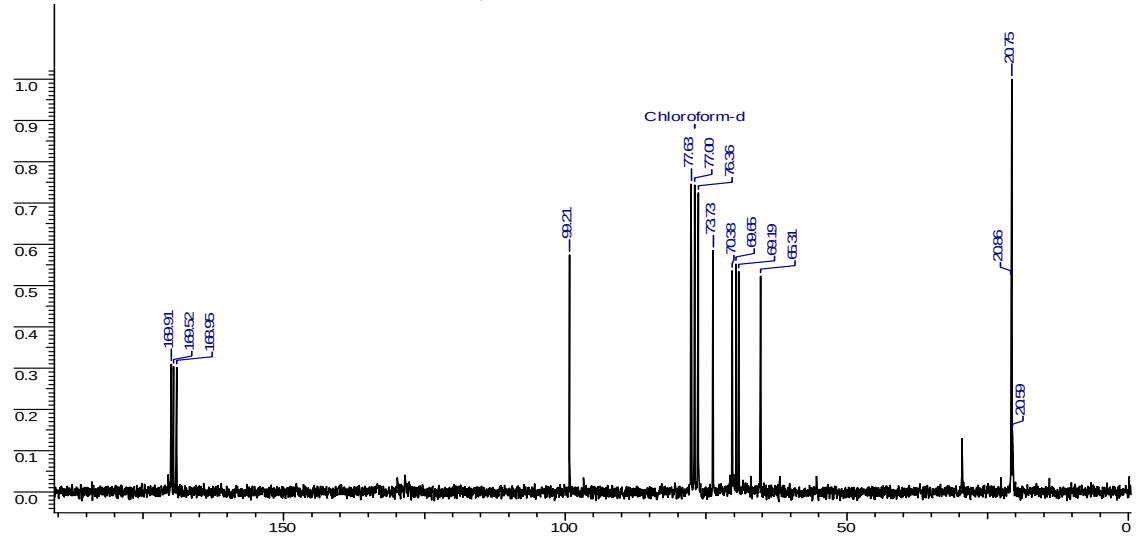
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



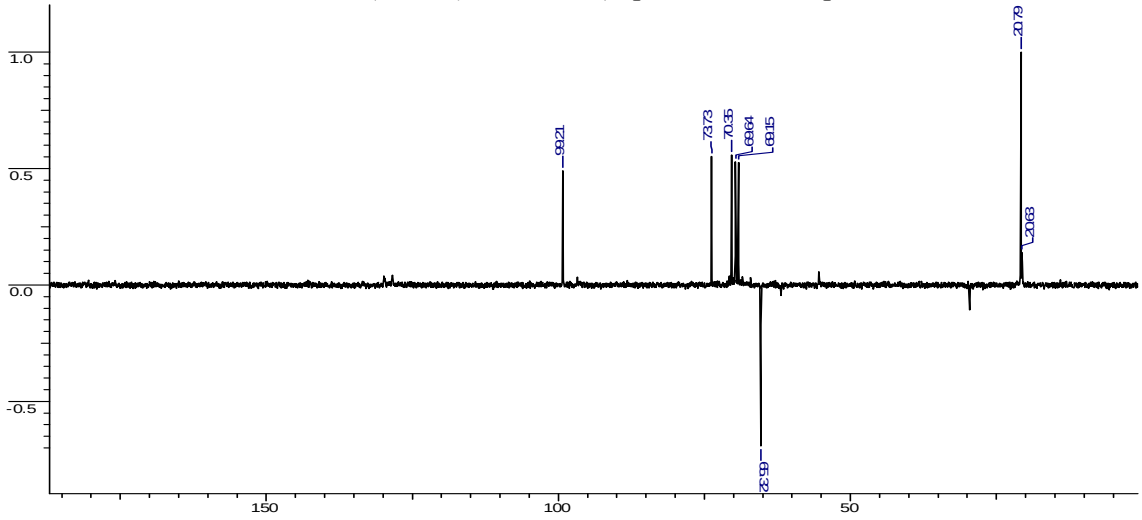
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **15**



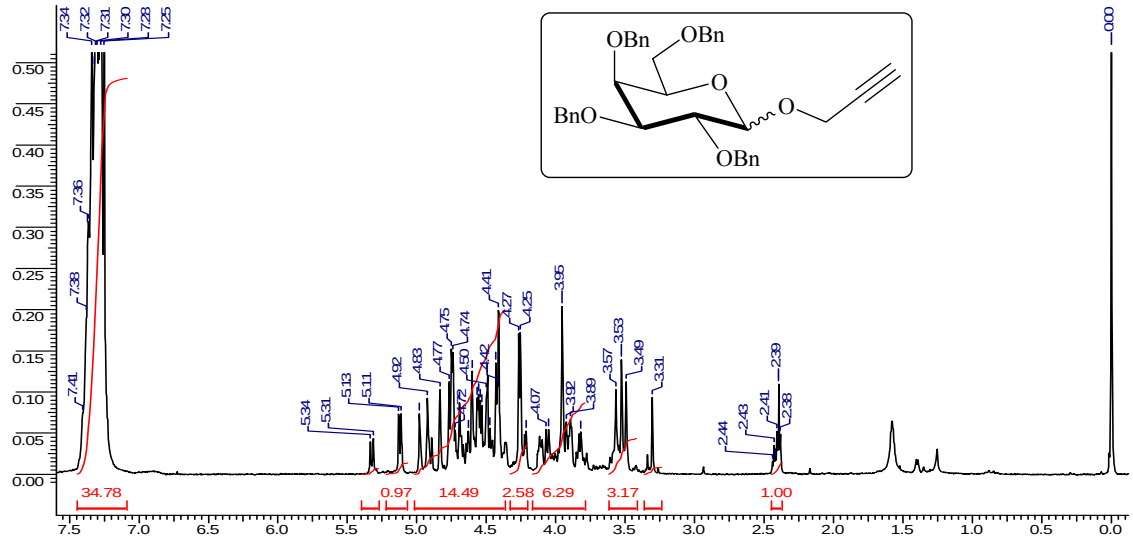
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



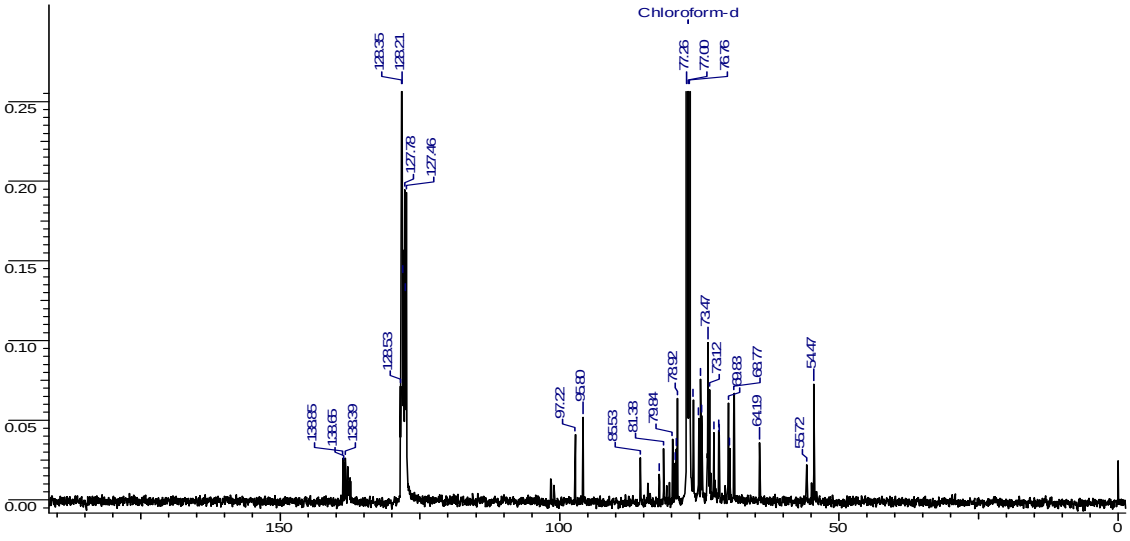
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



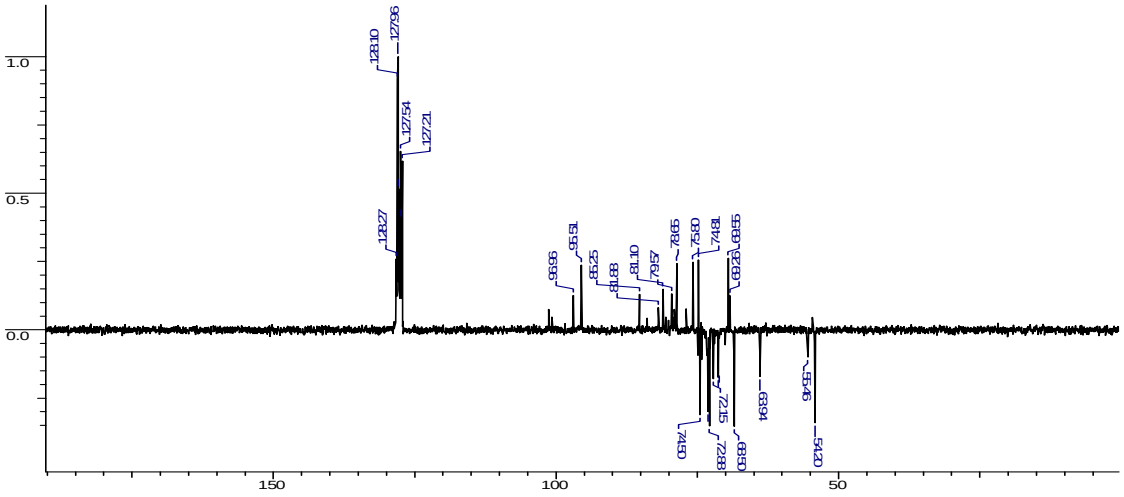
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **16**



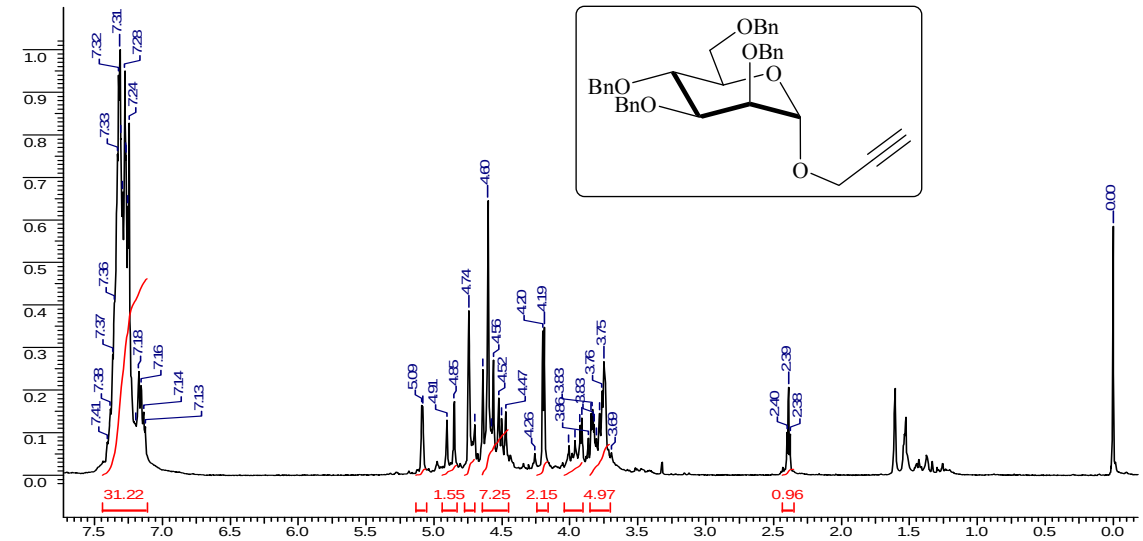
^{13}C NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **16**



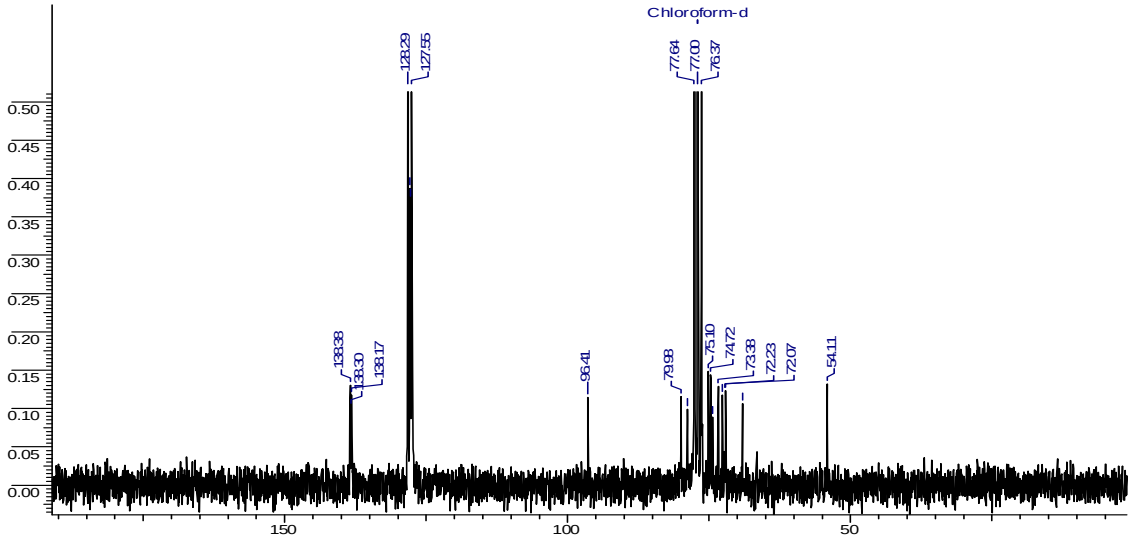
DEPT NMR ($CDCl_3$, 125.76 MHz) spectrum of compound **16**



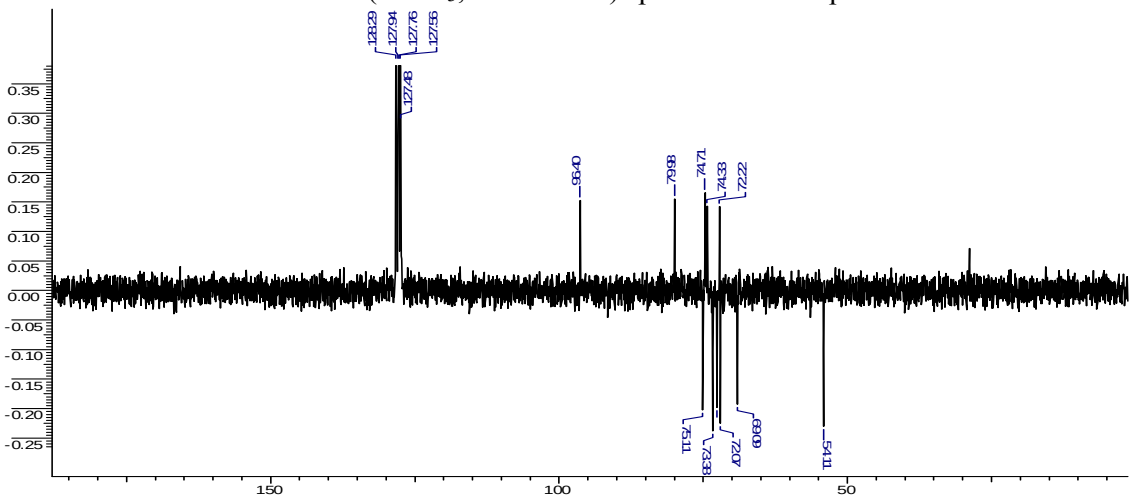
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **17**



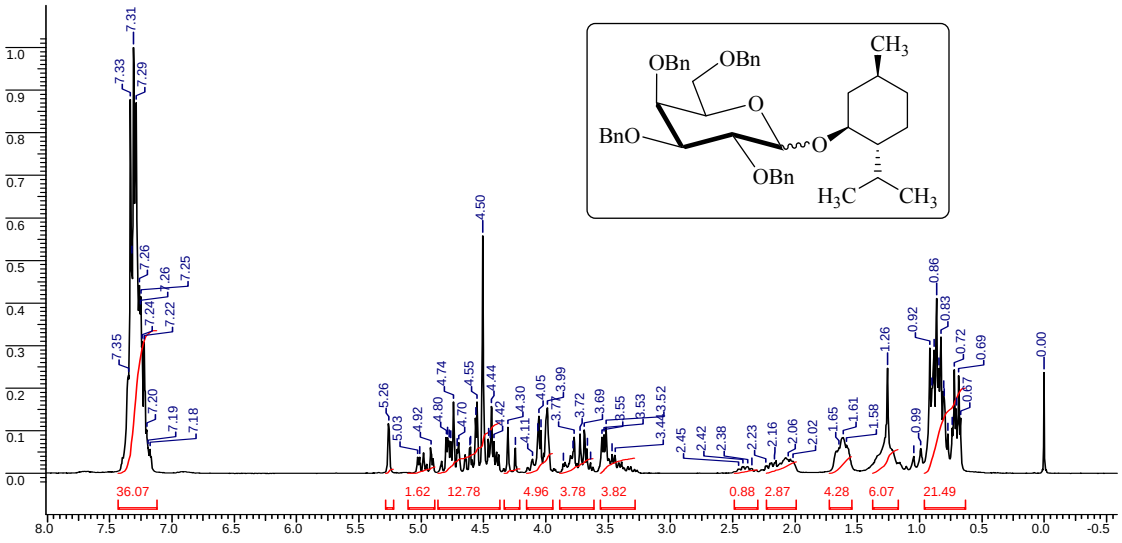
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **17**



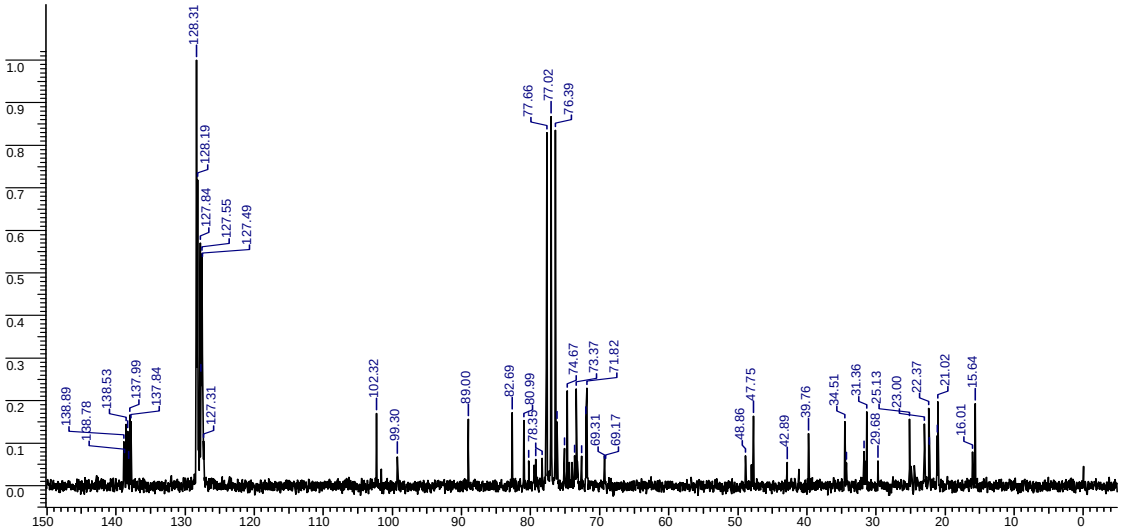
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **17**



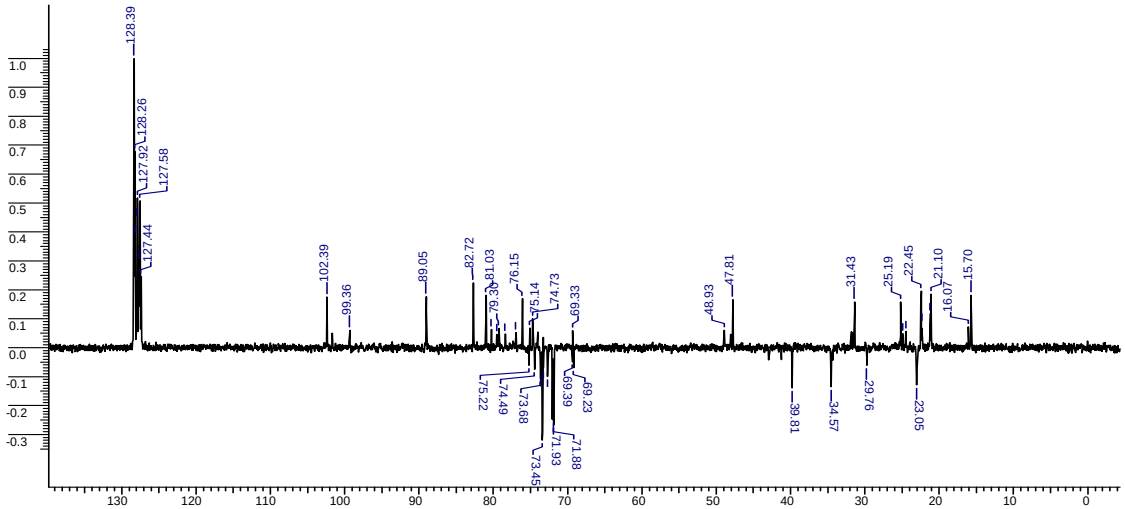
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **18**



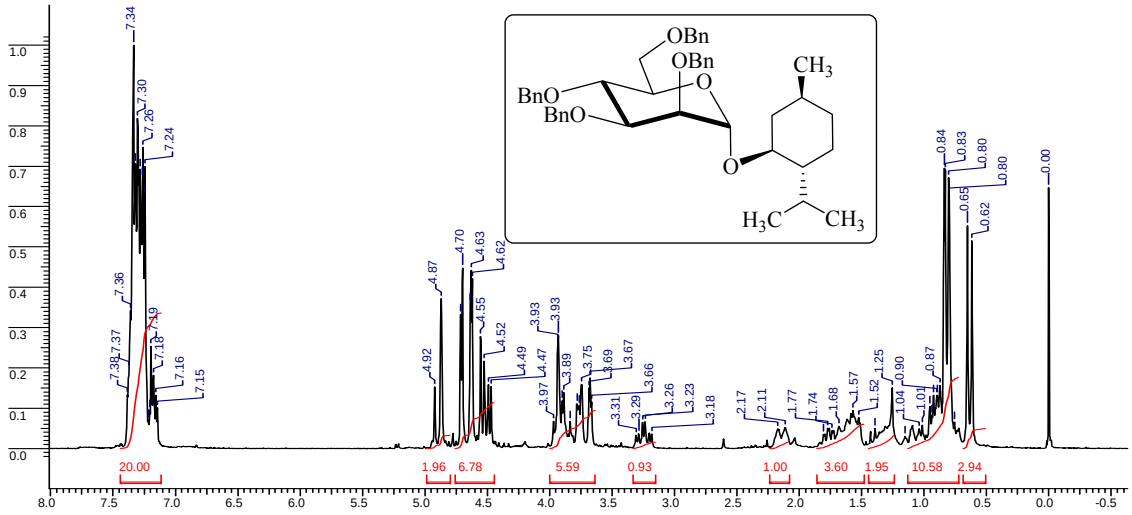
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **18**



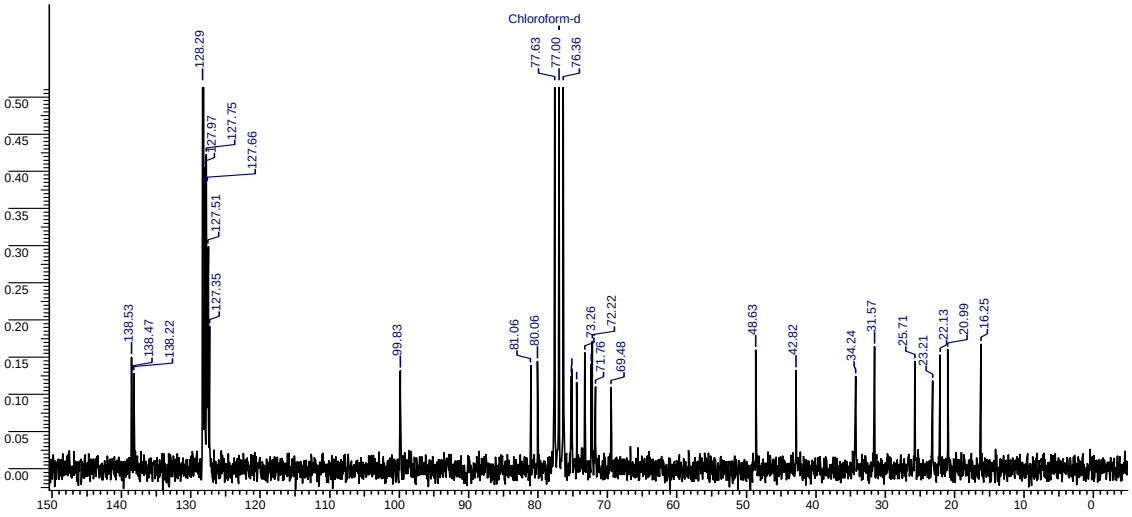
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **18**



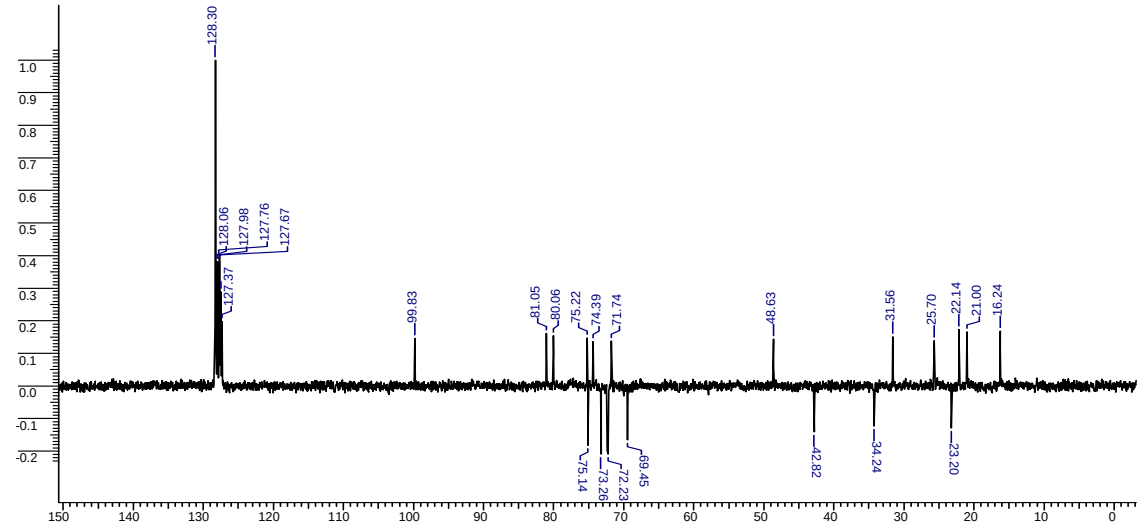
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **19**



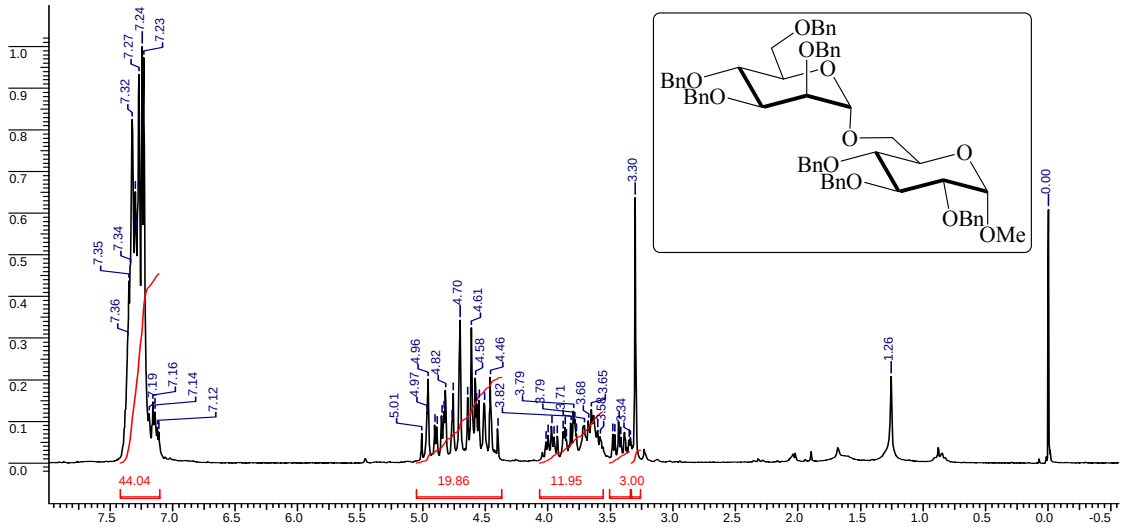
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **19**



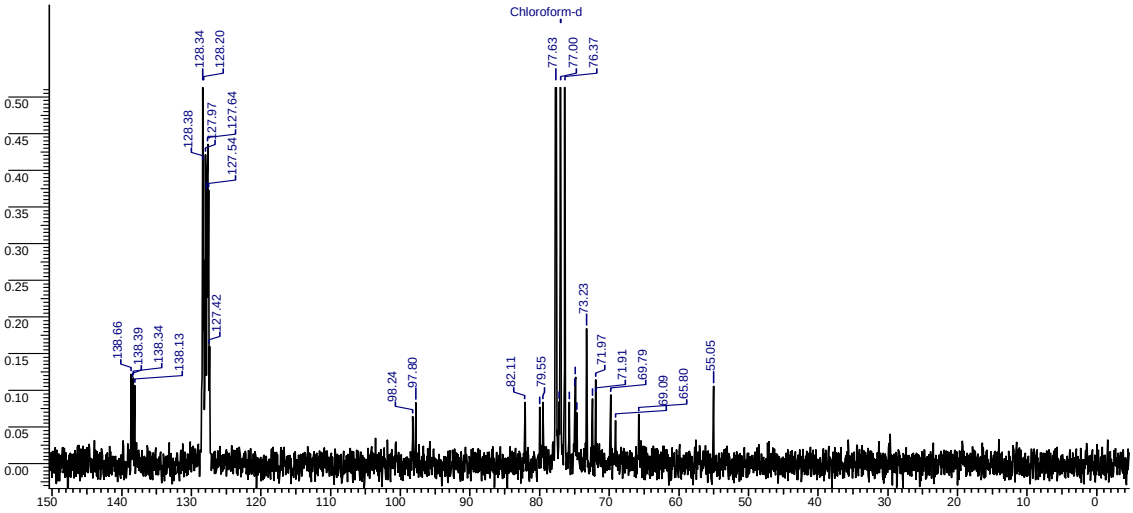
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **19**



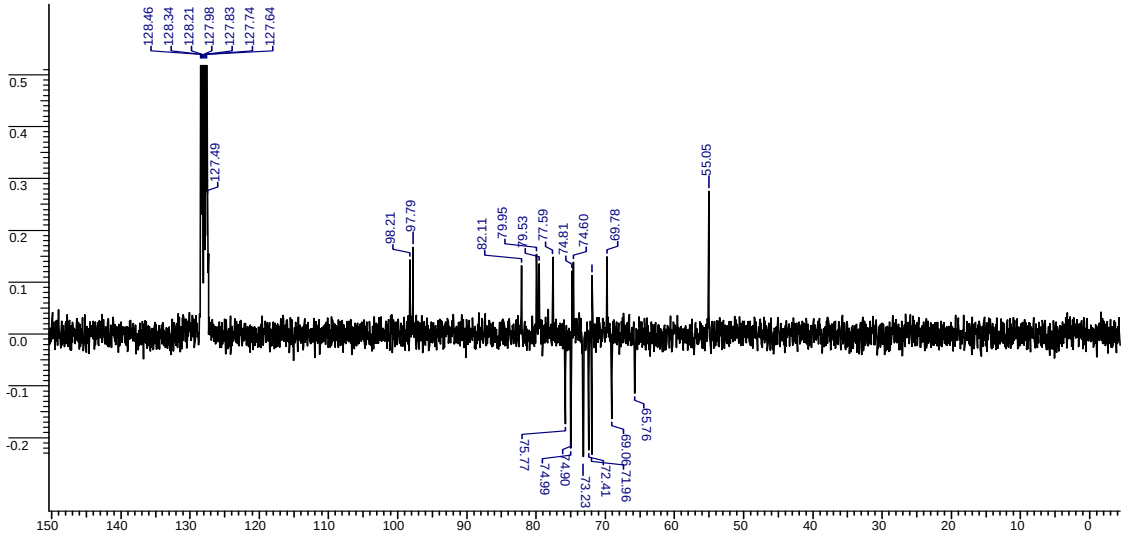
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **20**



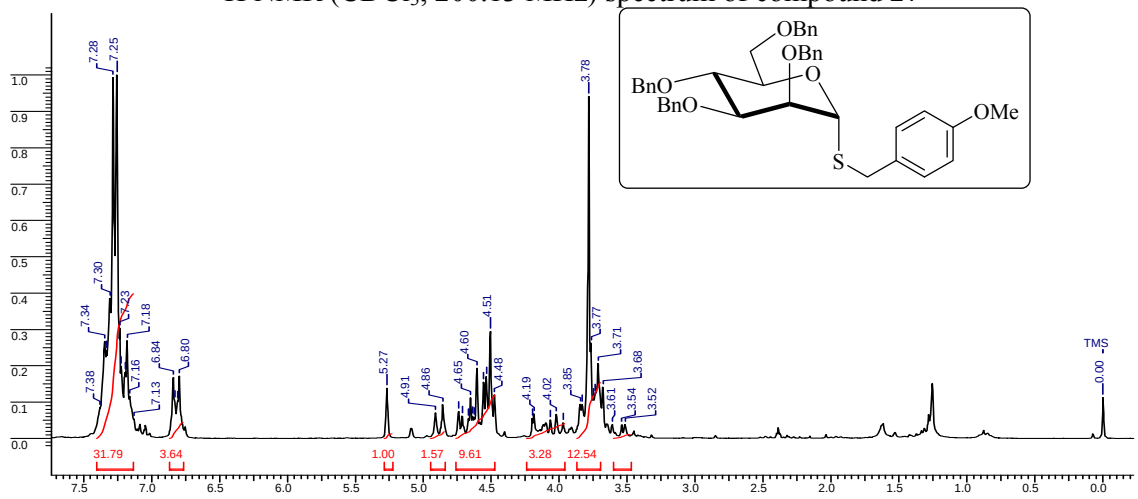
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **20**



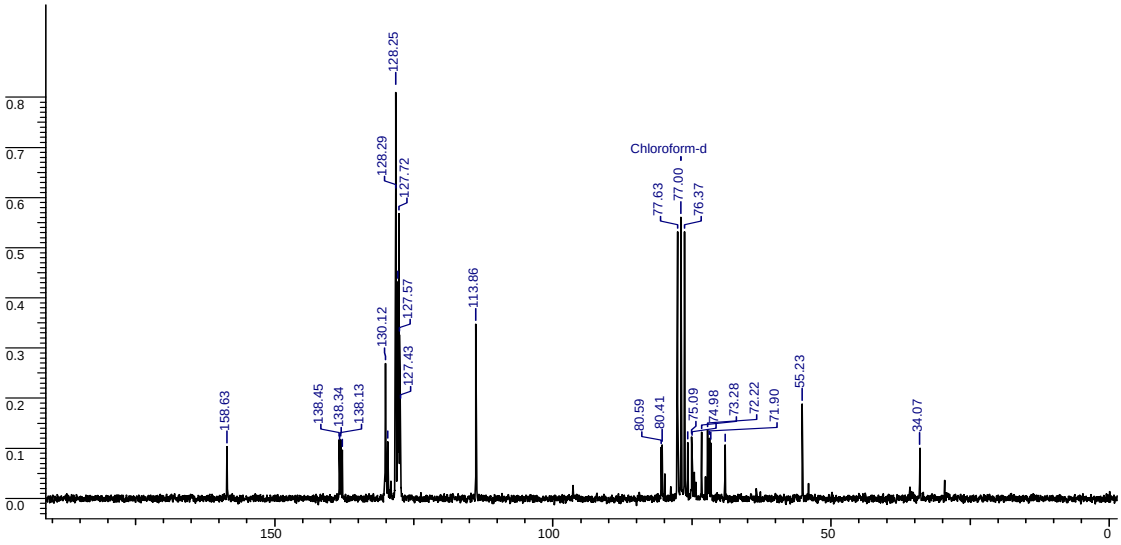
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **20**



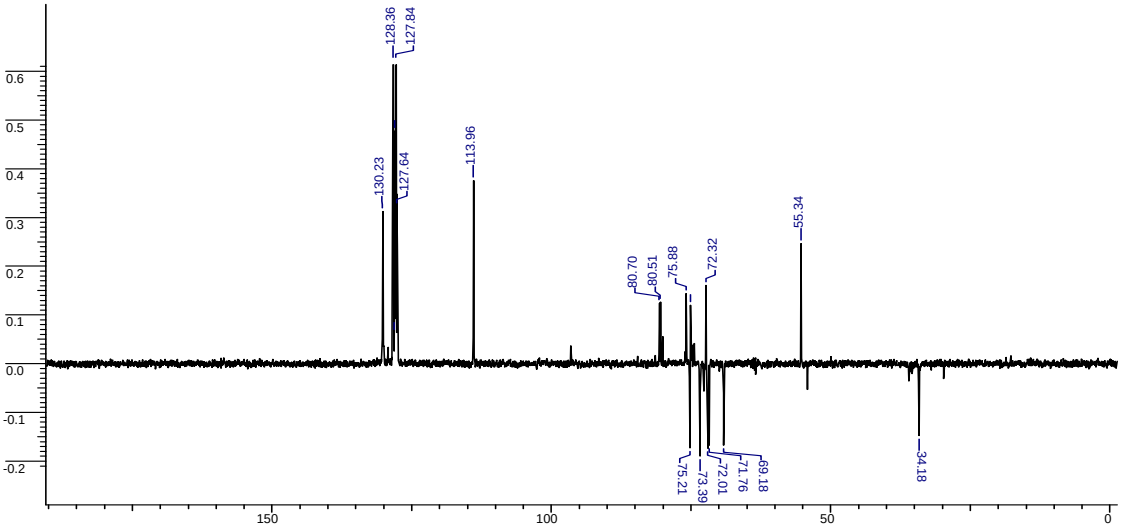
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **27**



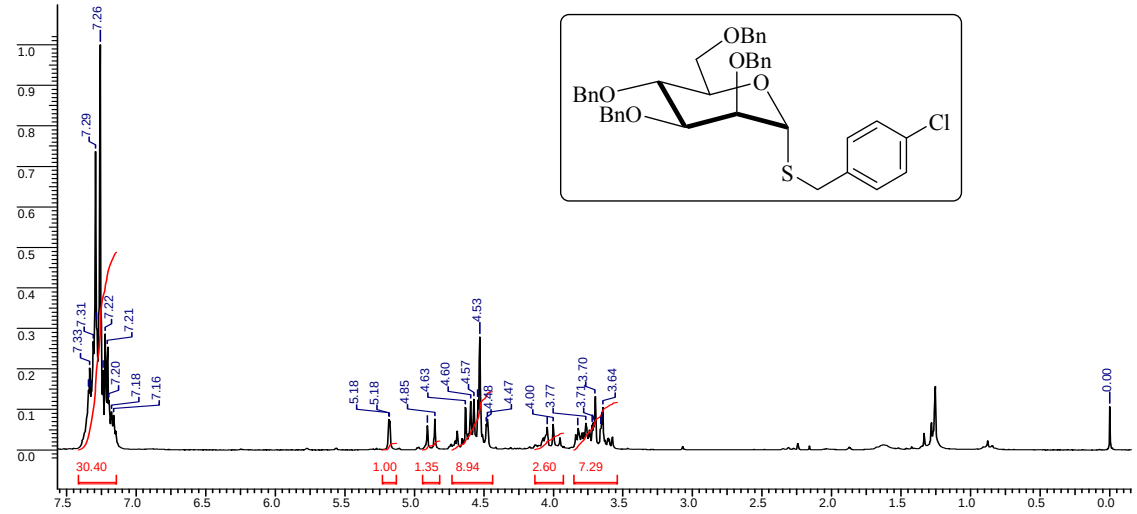
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **27**



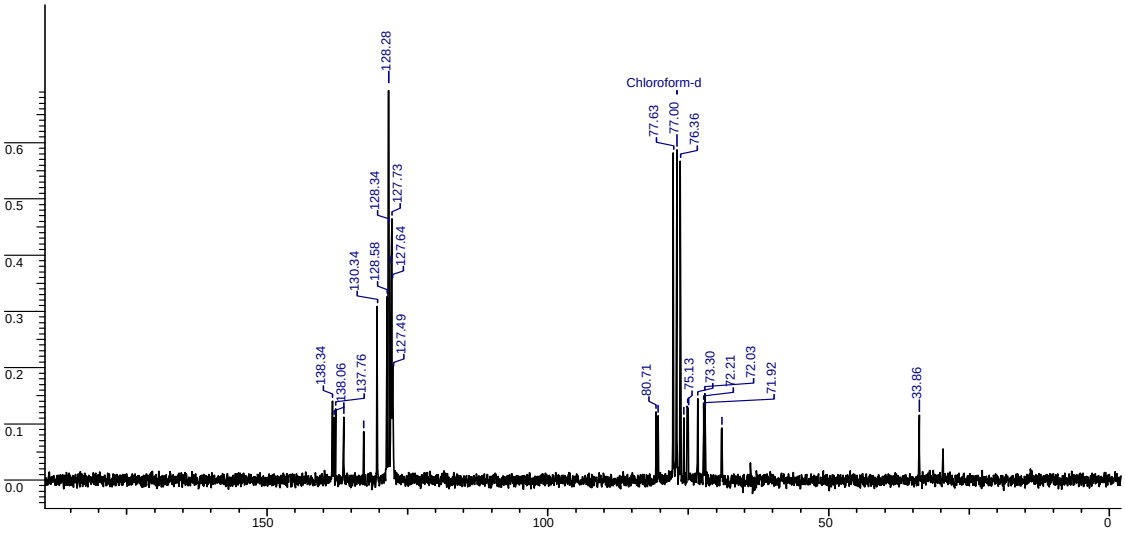
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **27**



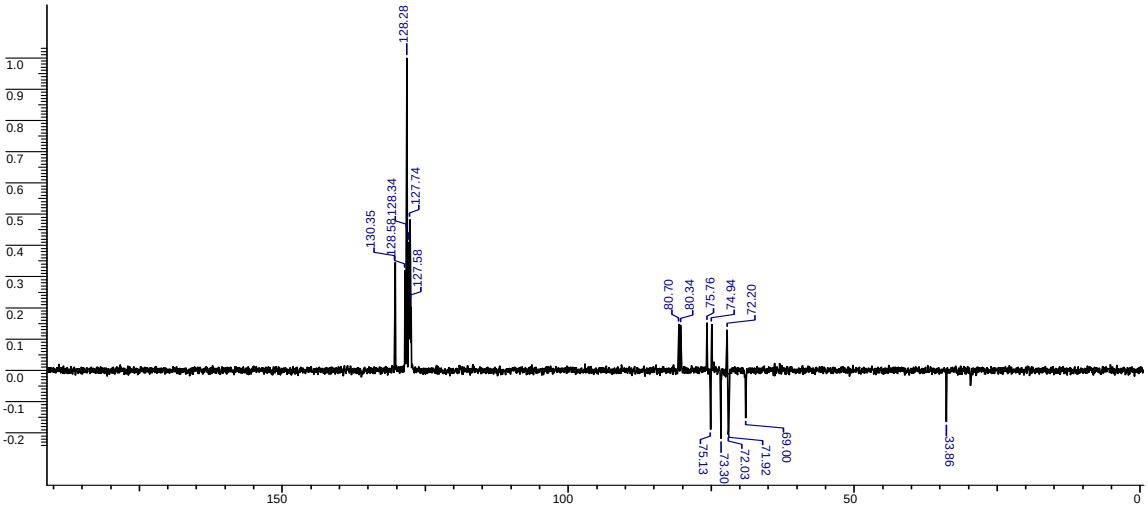
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **28**



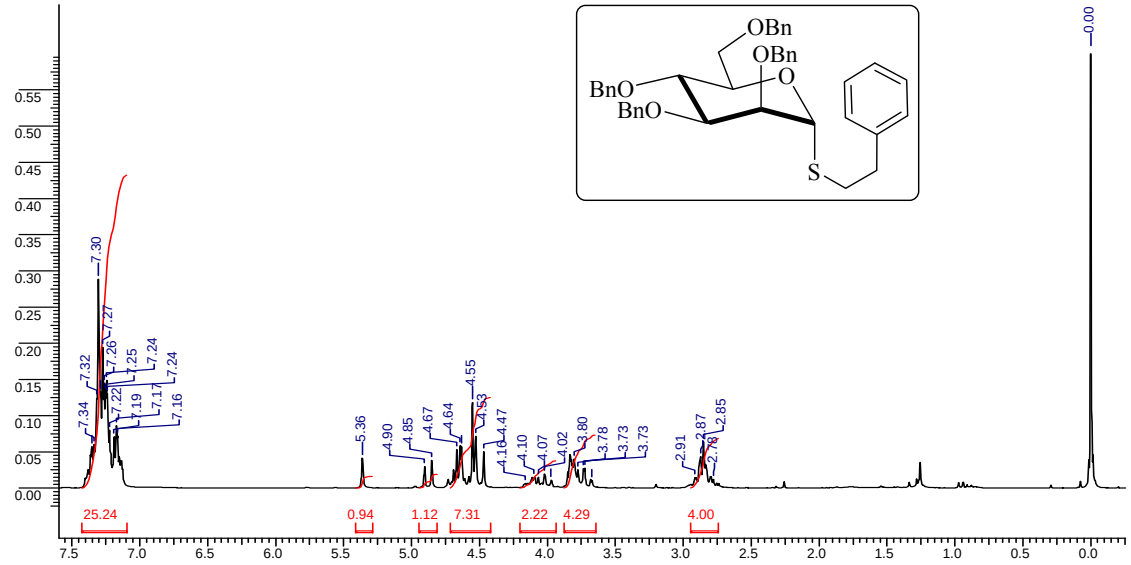
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **28**



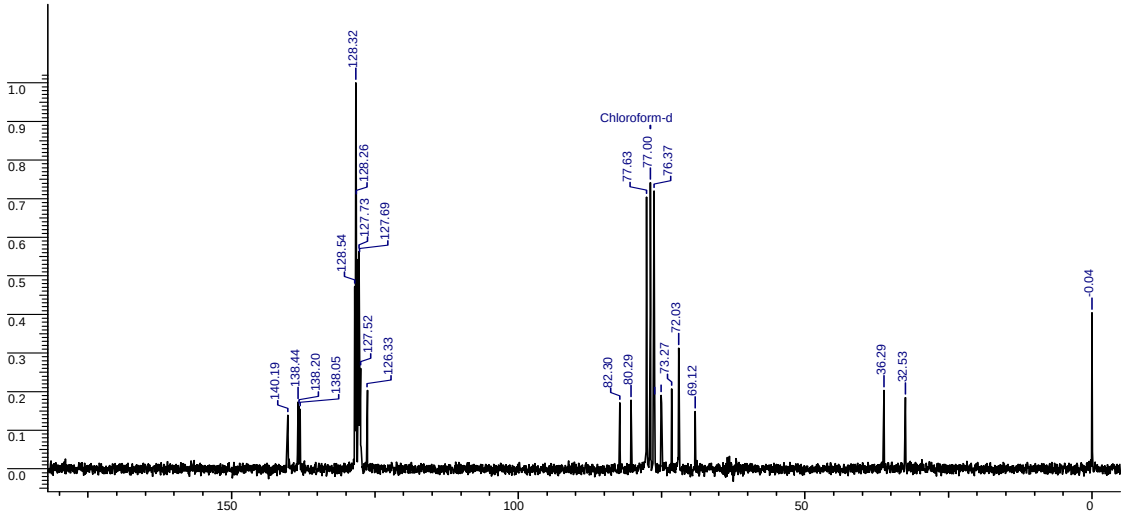
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **28**



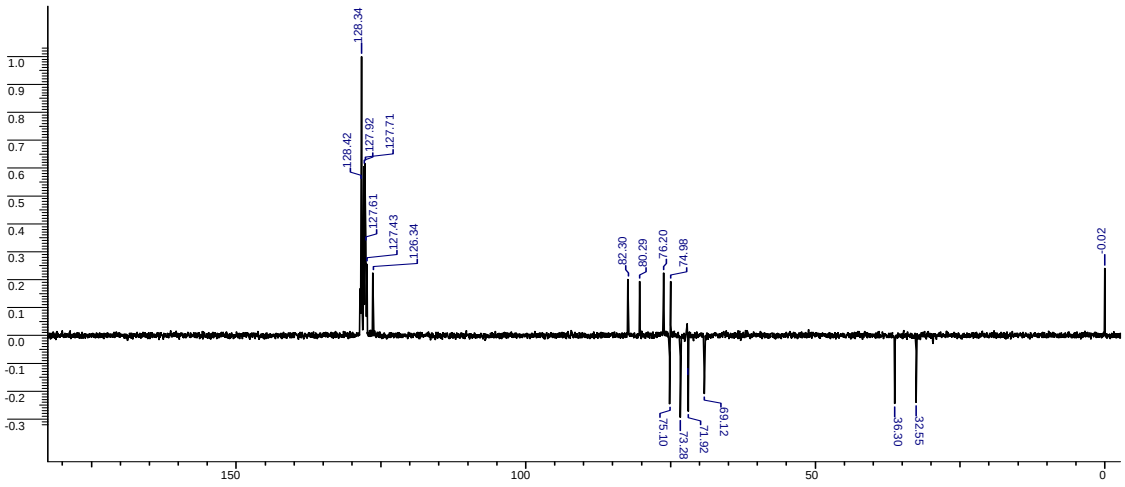
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **29**



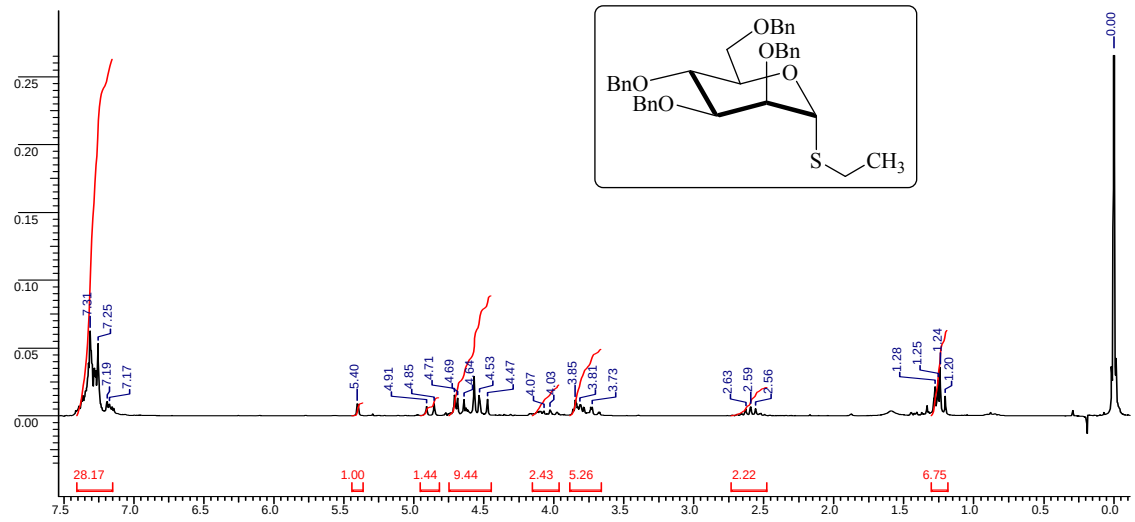
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **29**



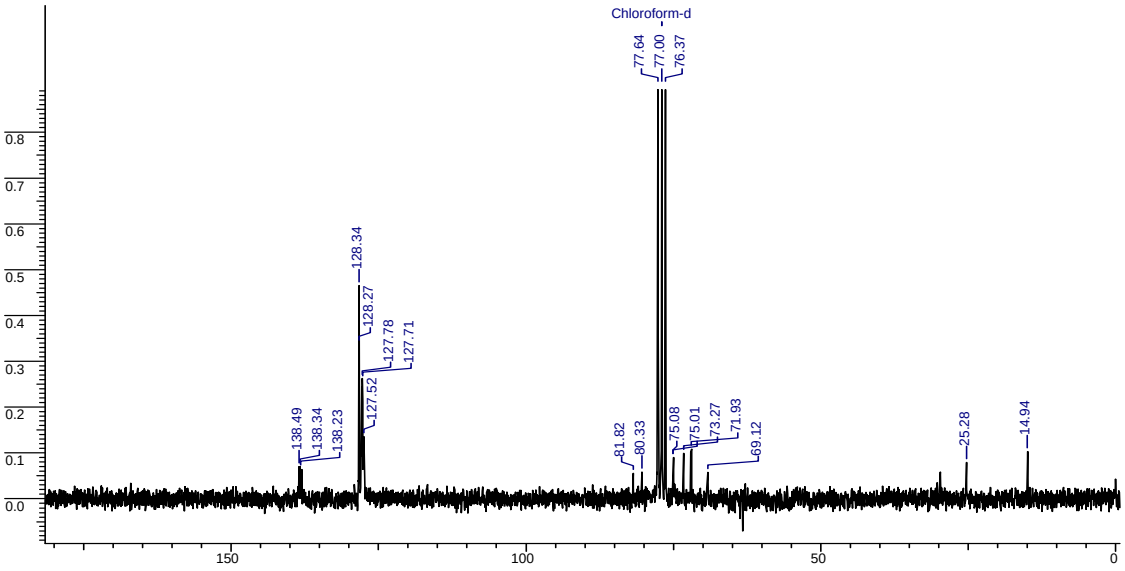
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **29**



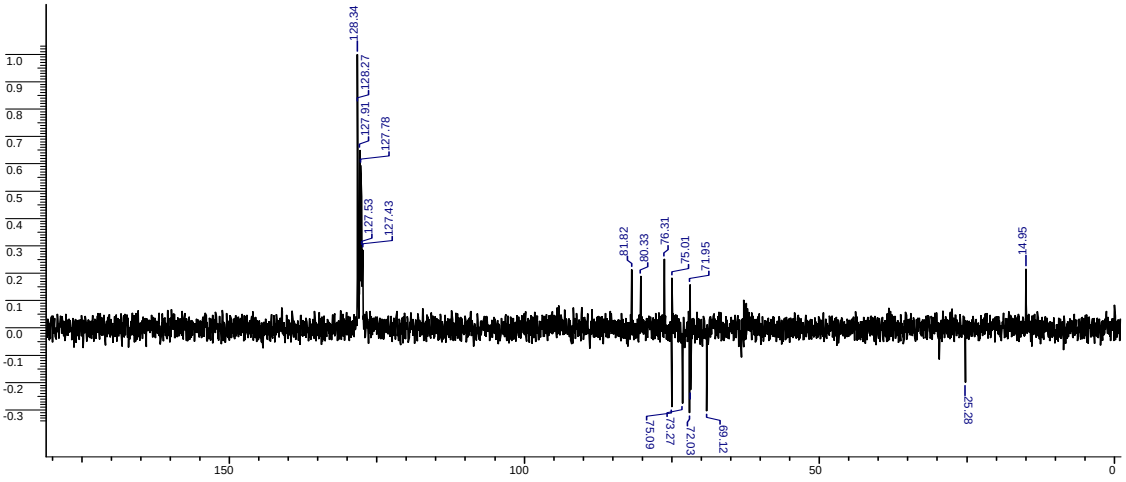
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **30**



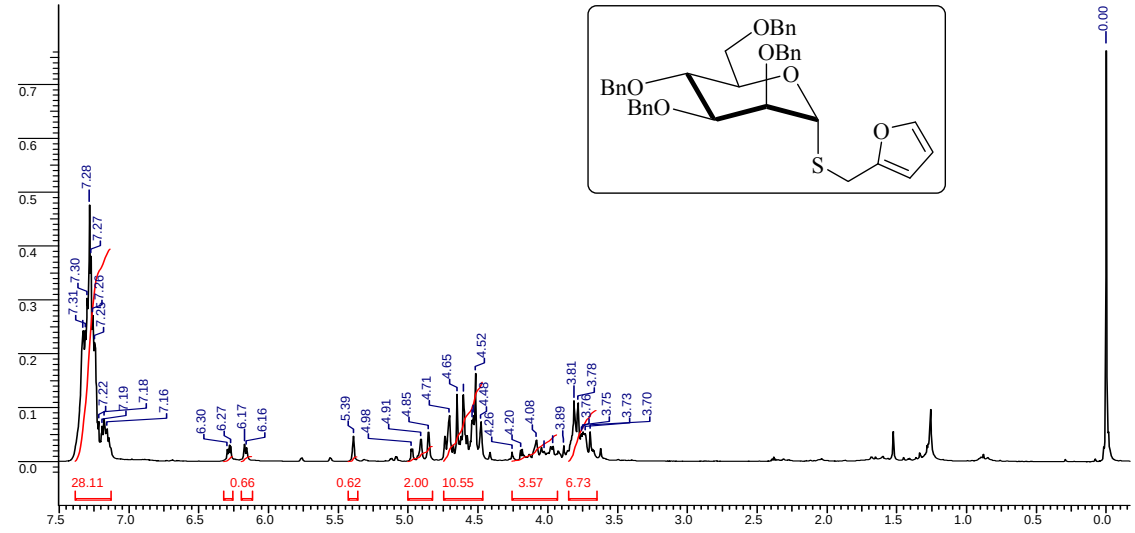
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **30**



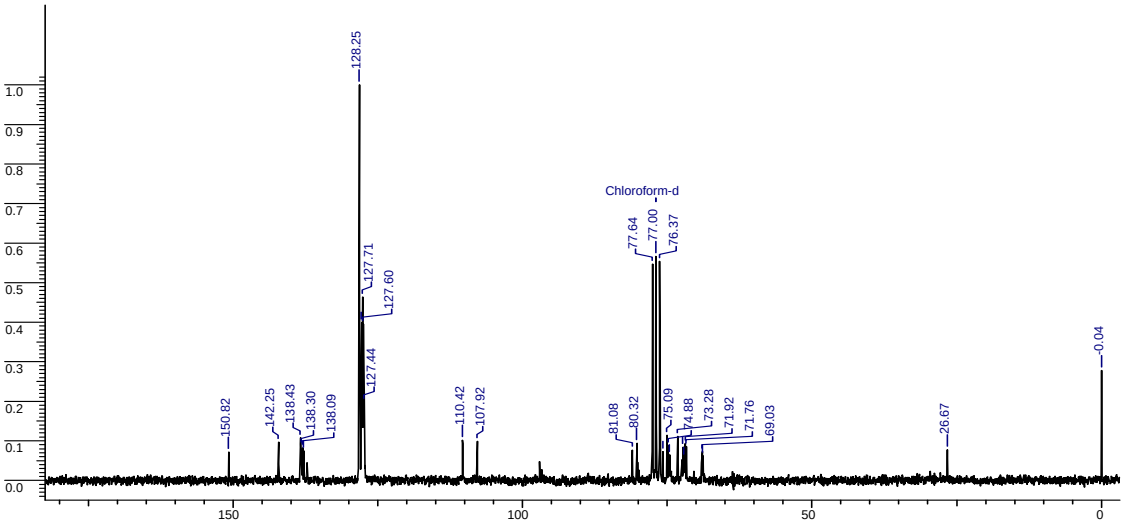
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **30**



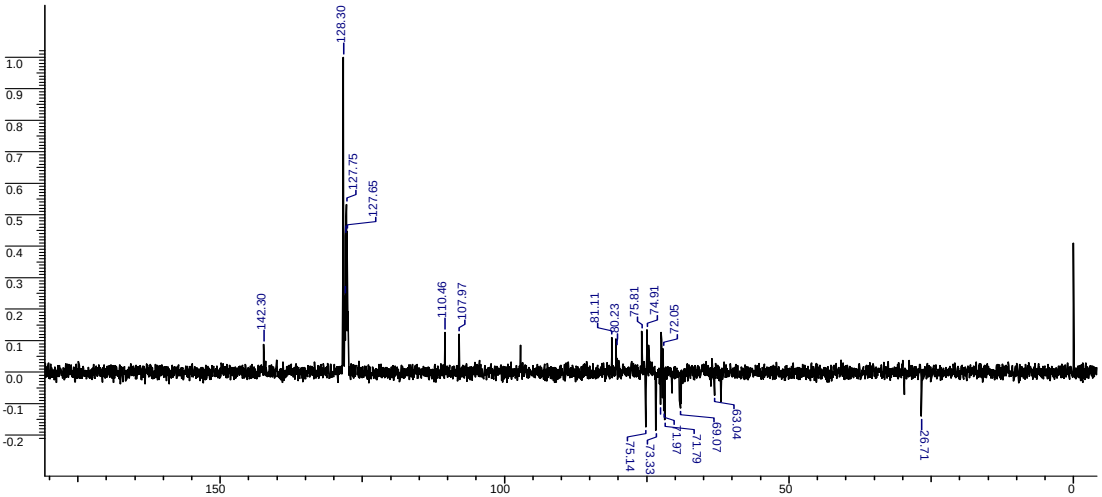
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **31**



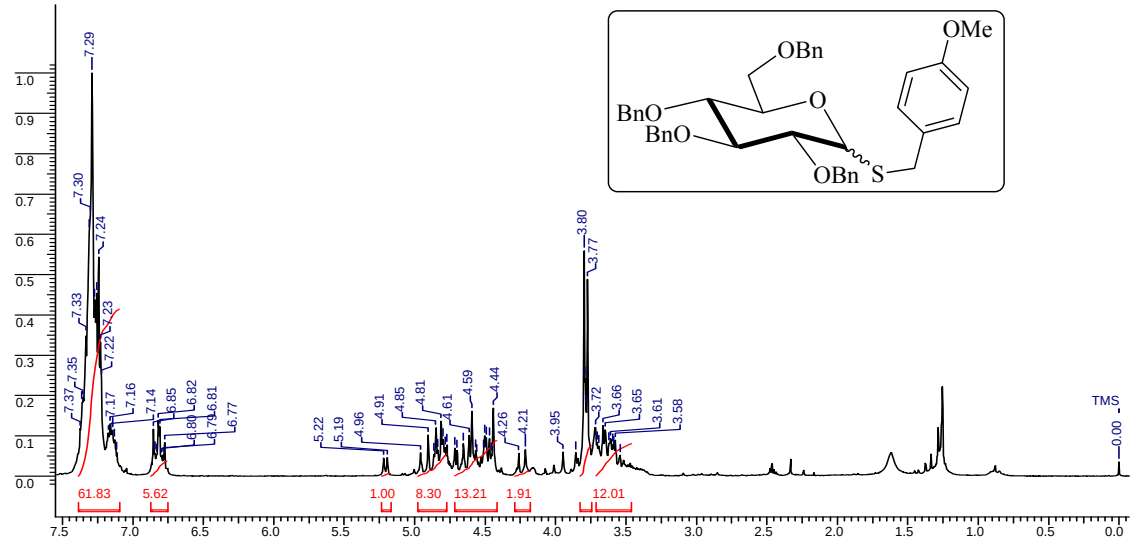
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **31**



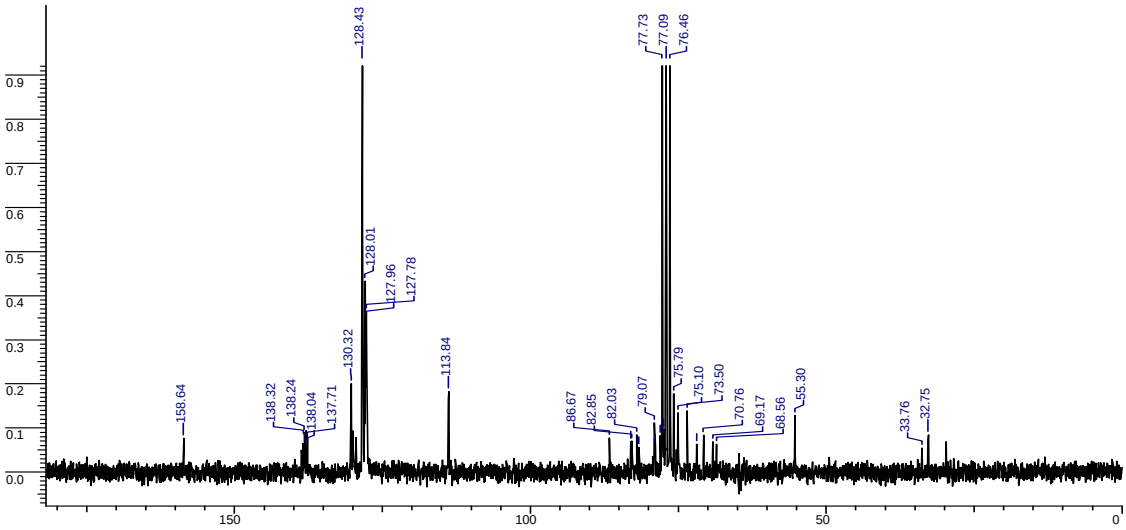
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **31**



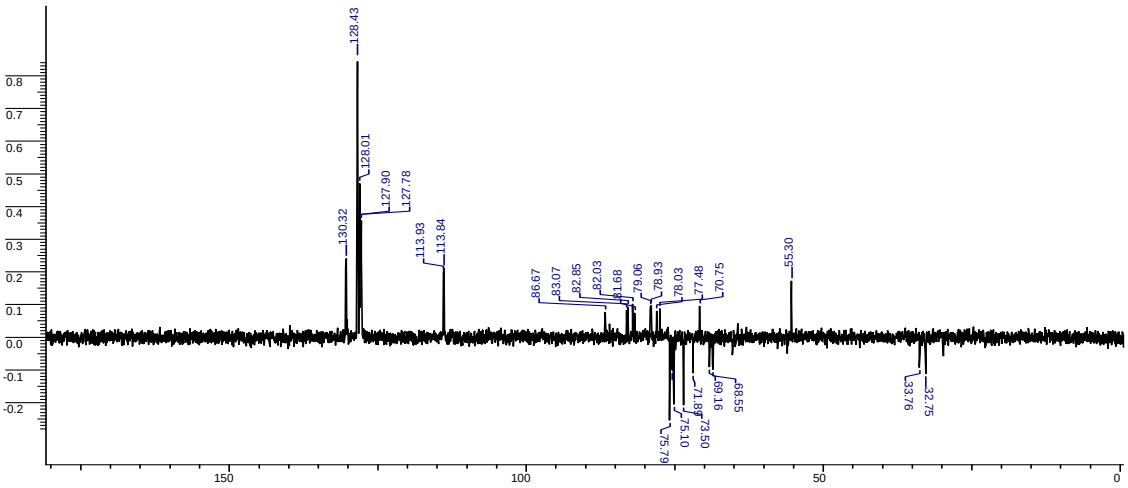
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **33**



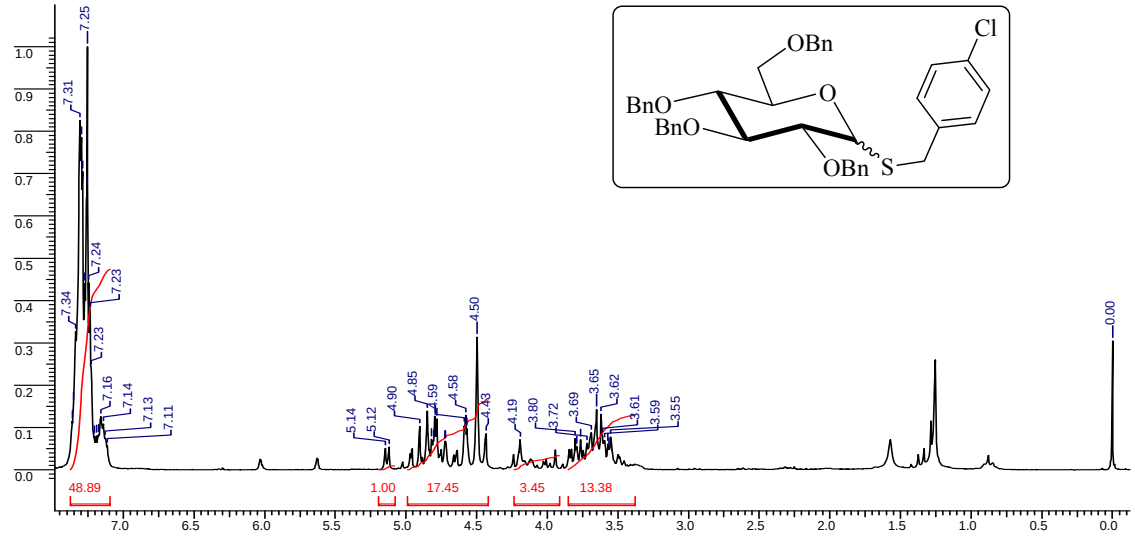
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **33**



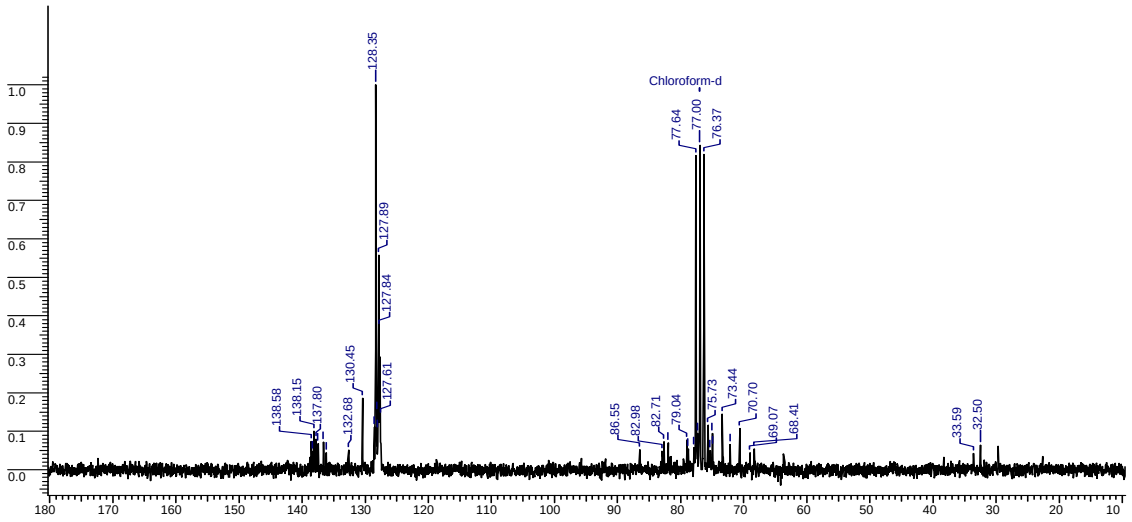
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **33**



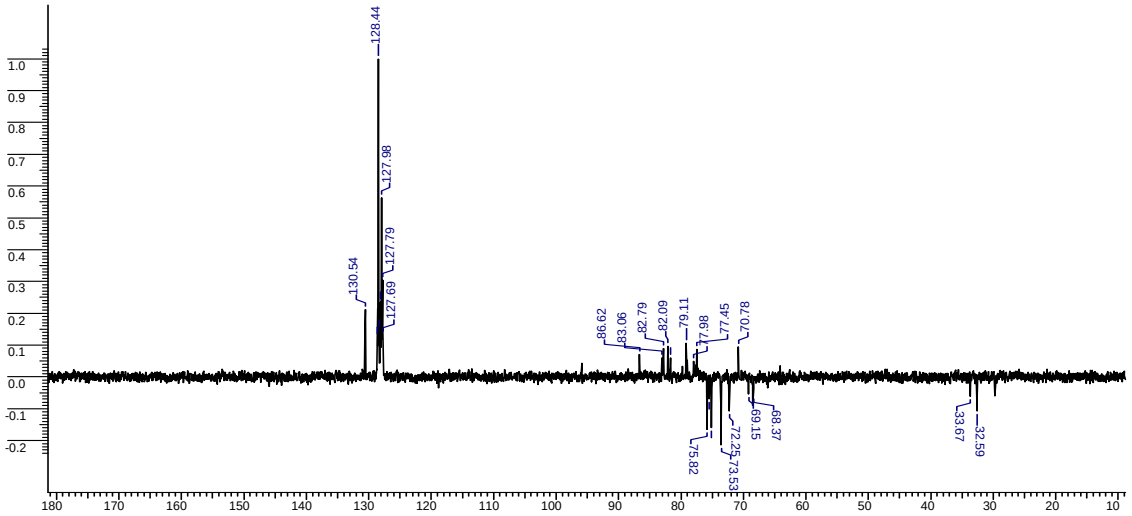
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **34**



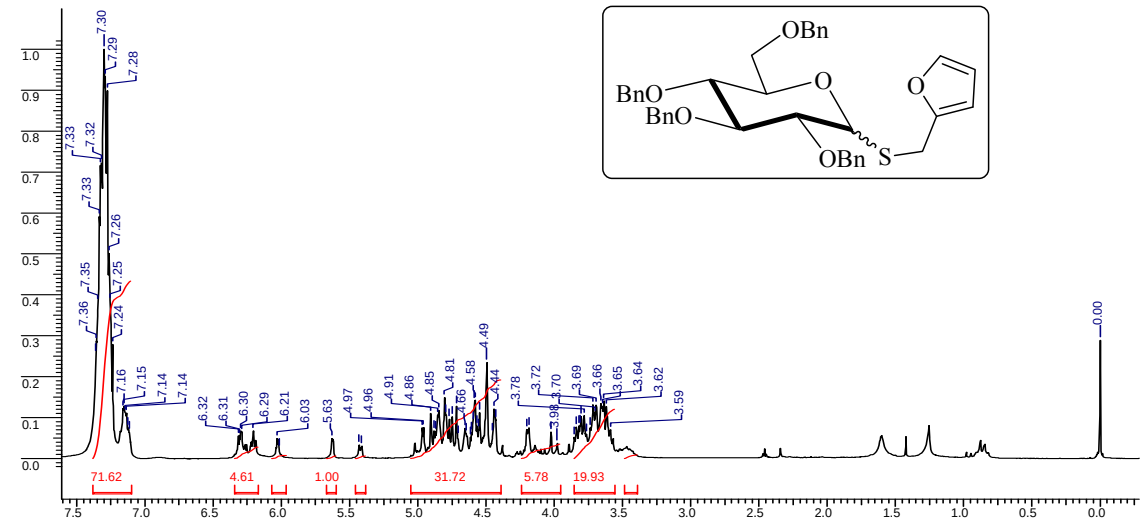
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **34**



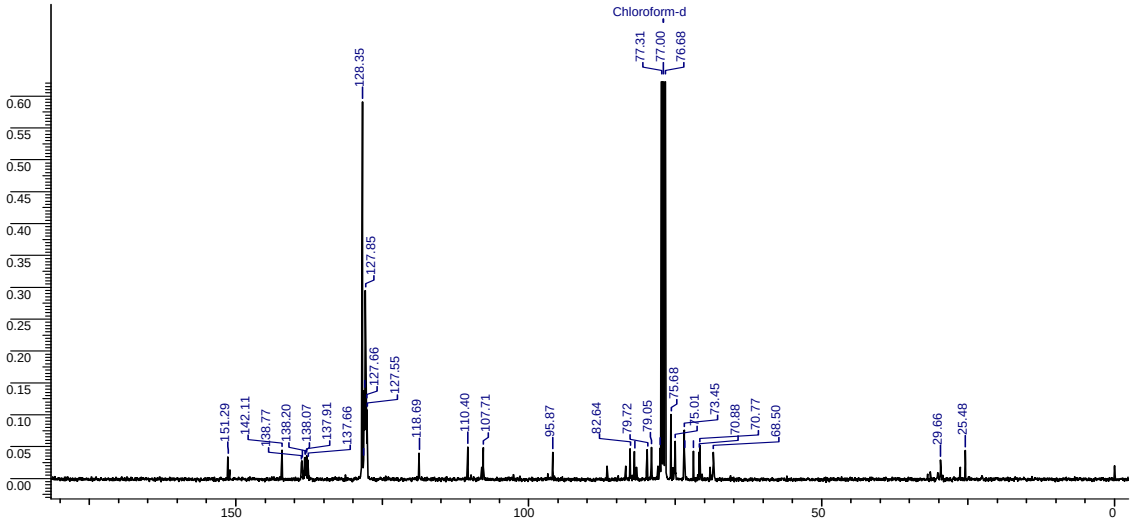
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **34**



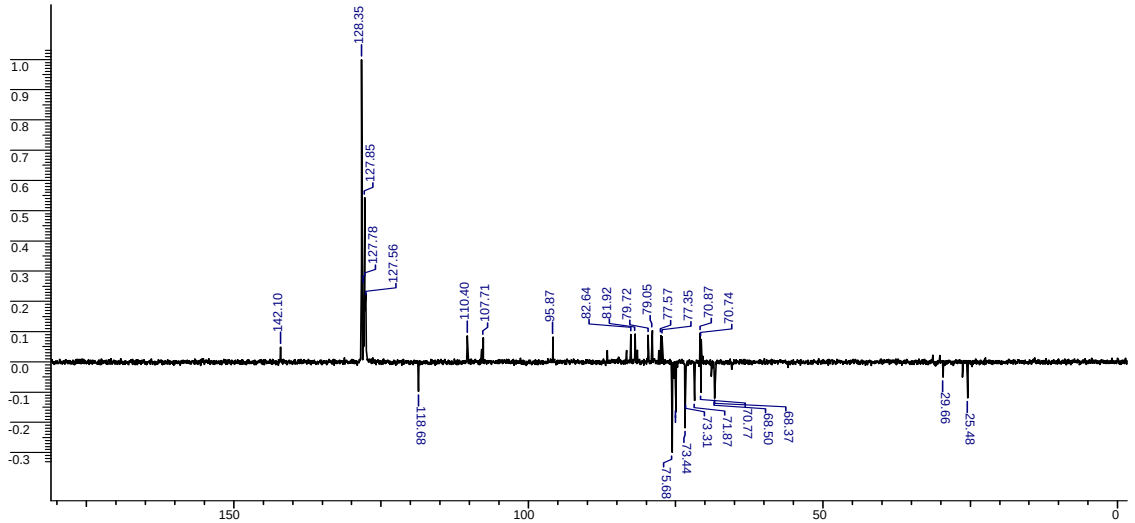
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **35**



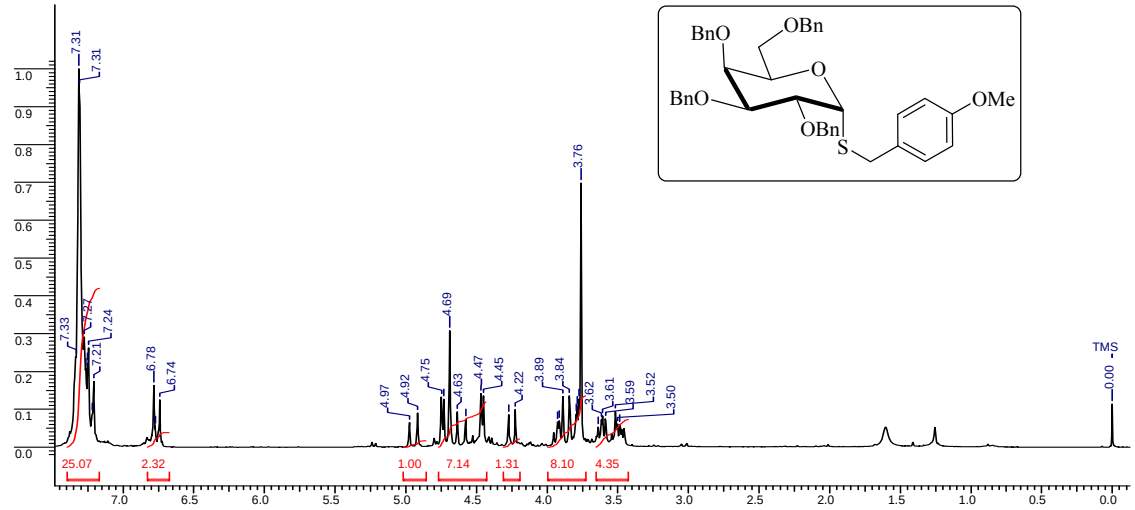
^{13}C NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **35**



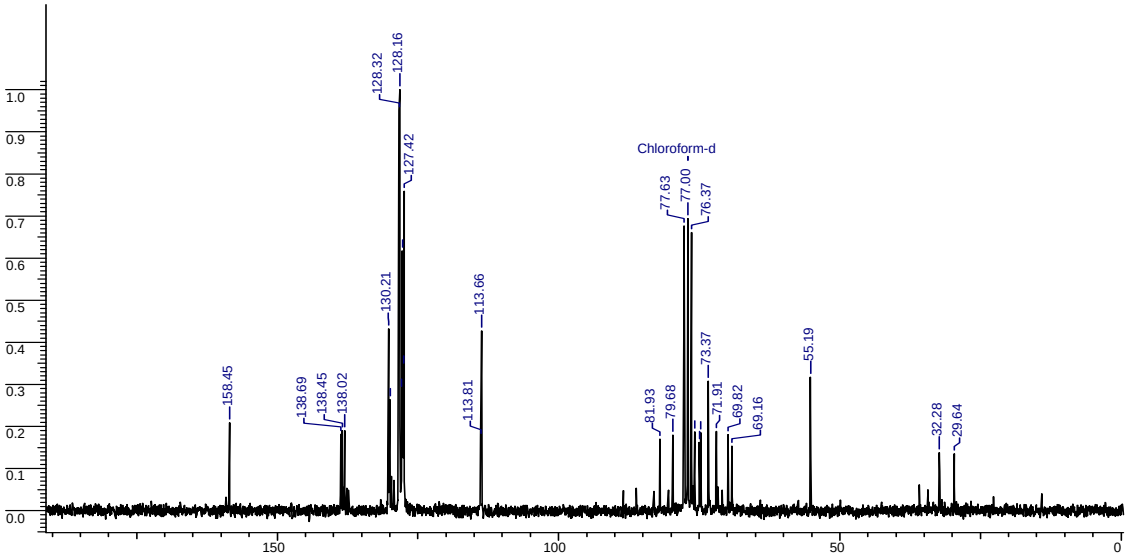
DEPT NMR ($CDCl_3$, 100.61 MHz) spectrum of compound **35**



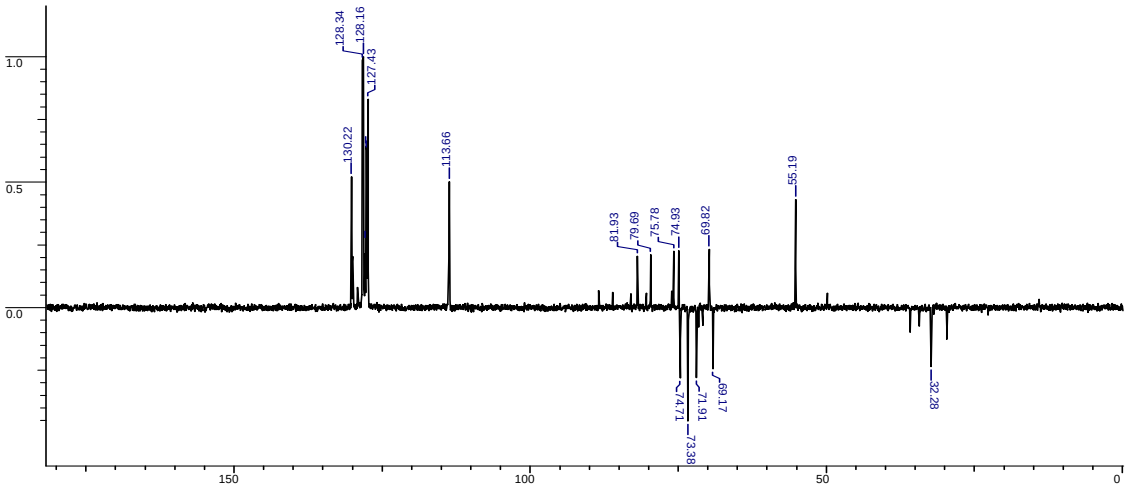
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **36 (*α*)**



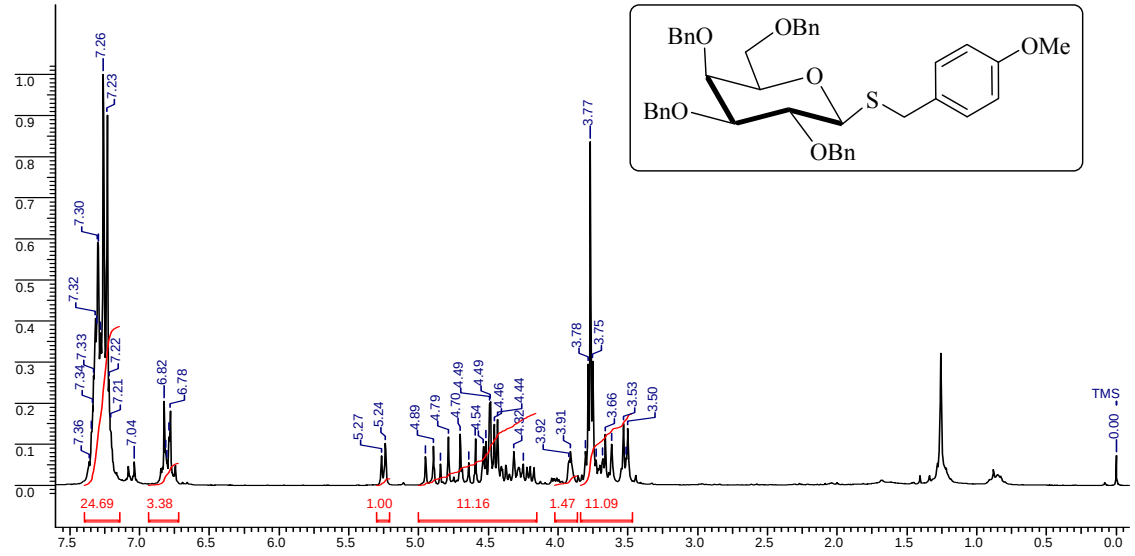
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36 (*α*)**



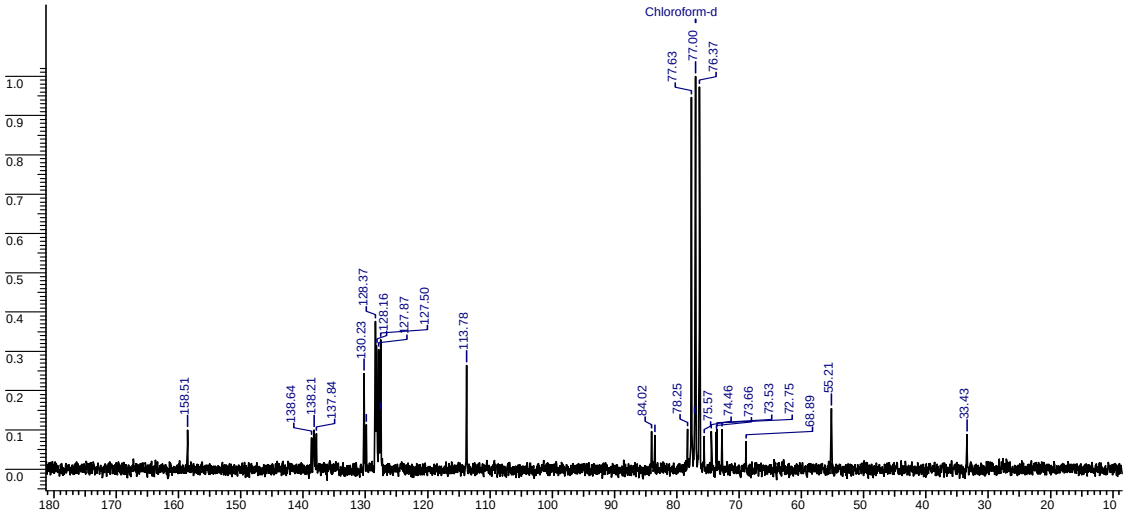
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36 (*α*)**



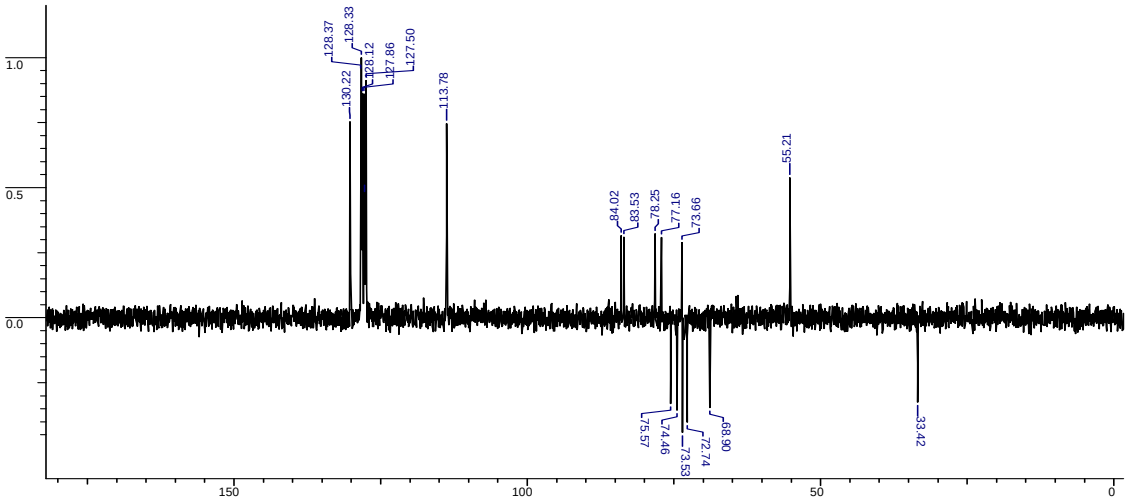
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **36 (*β*)**



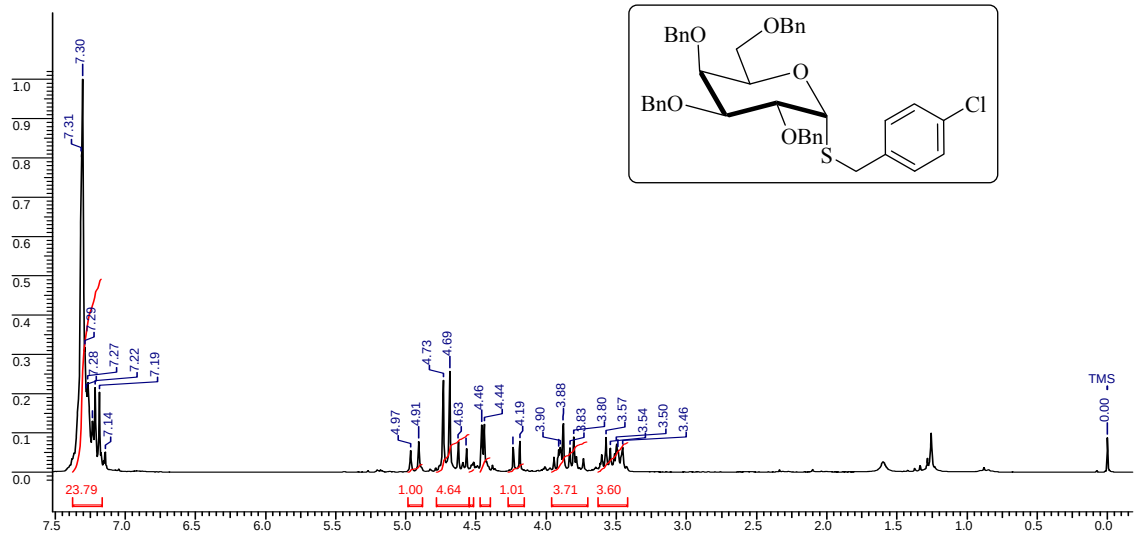
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36 (*β*)**



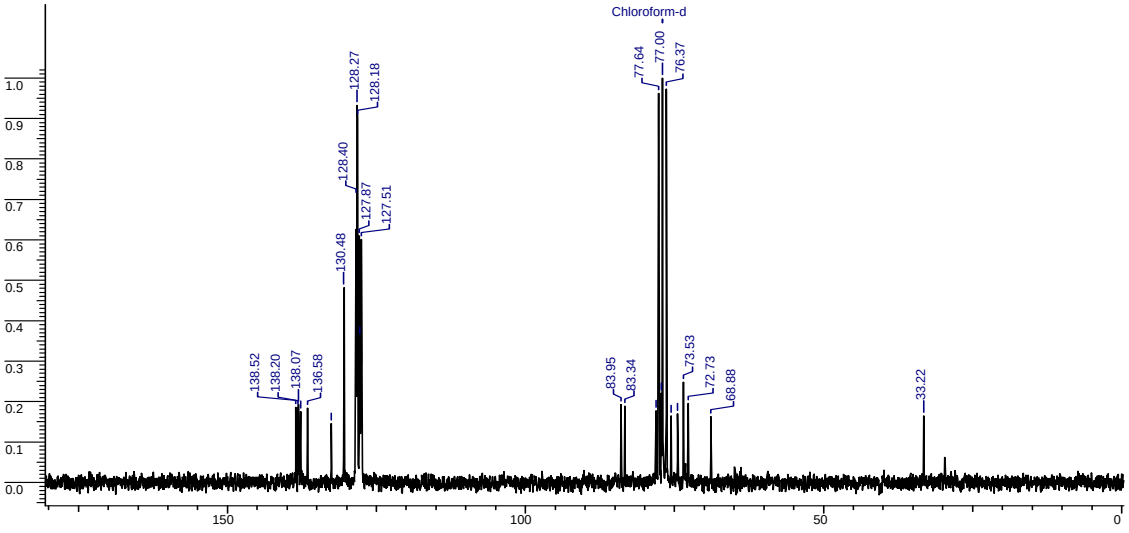
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36 (*β*)**



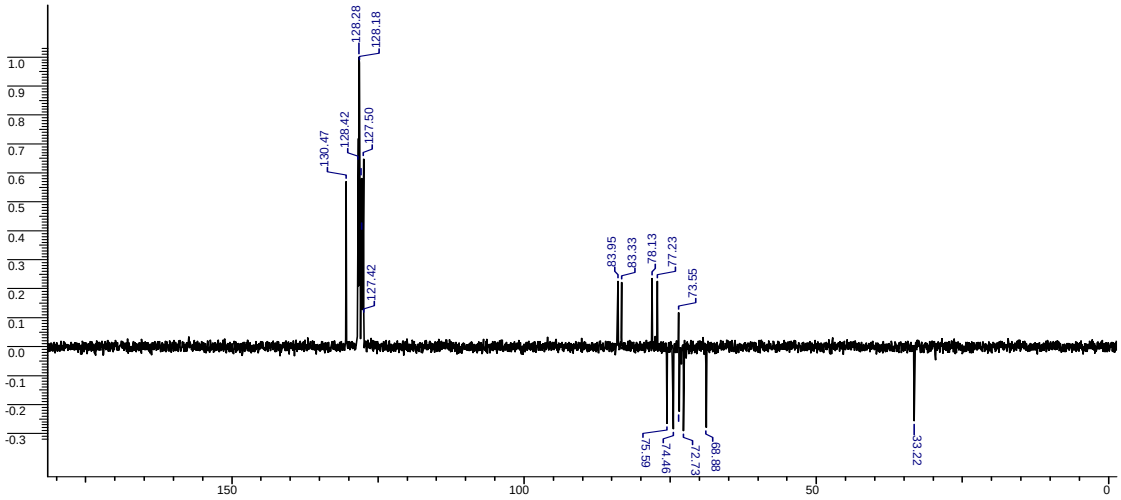
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **37 (*α*)**



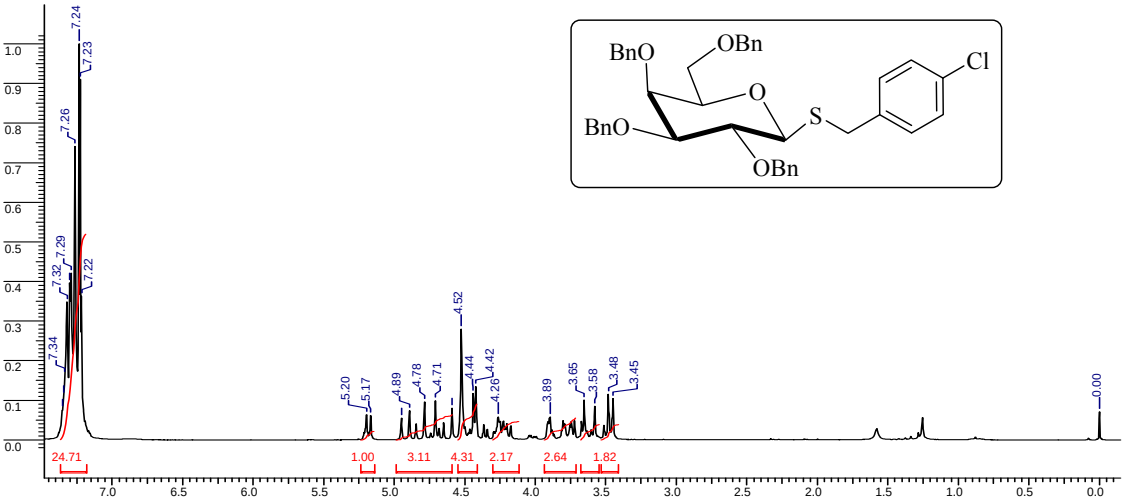
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37 (*α*)**



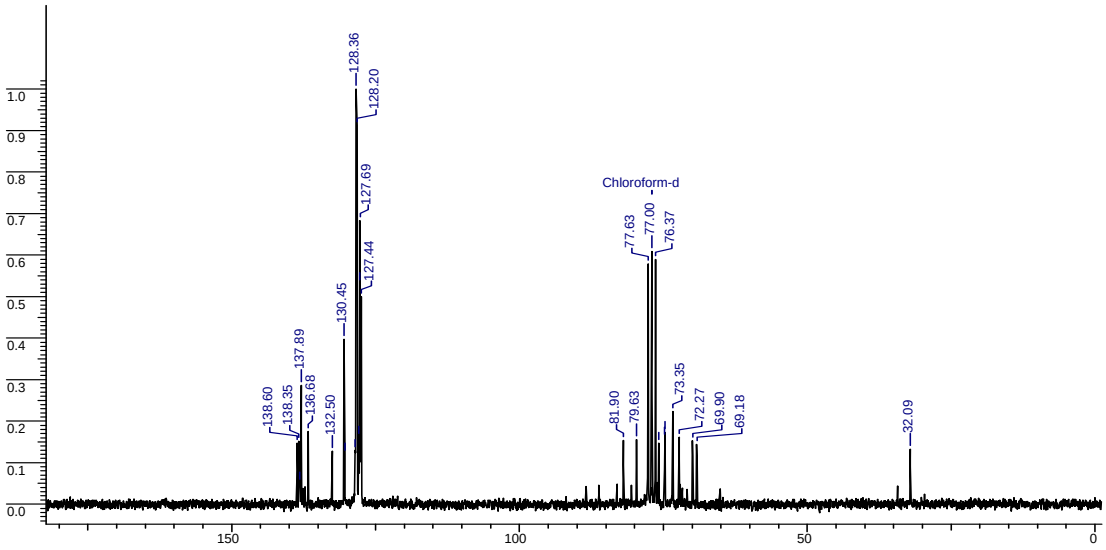
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37 (*α*)**



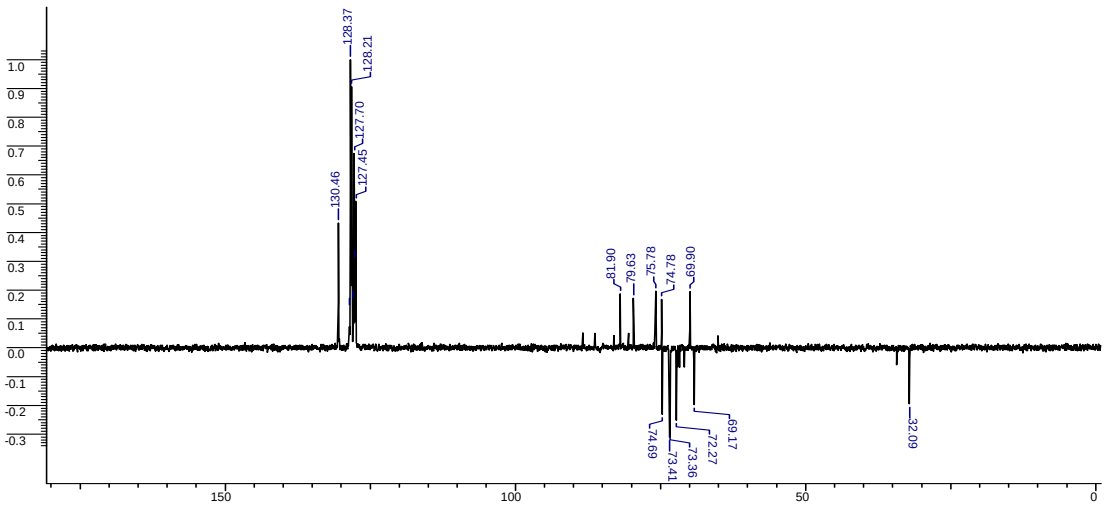
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **37 (*β*)**



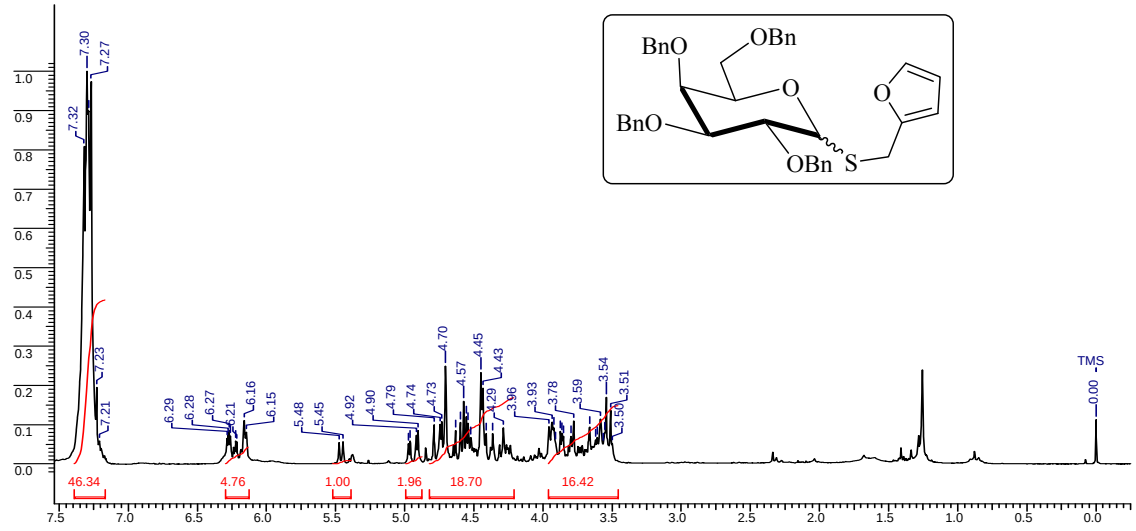
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37 (*β*)**



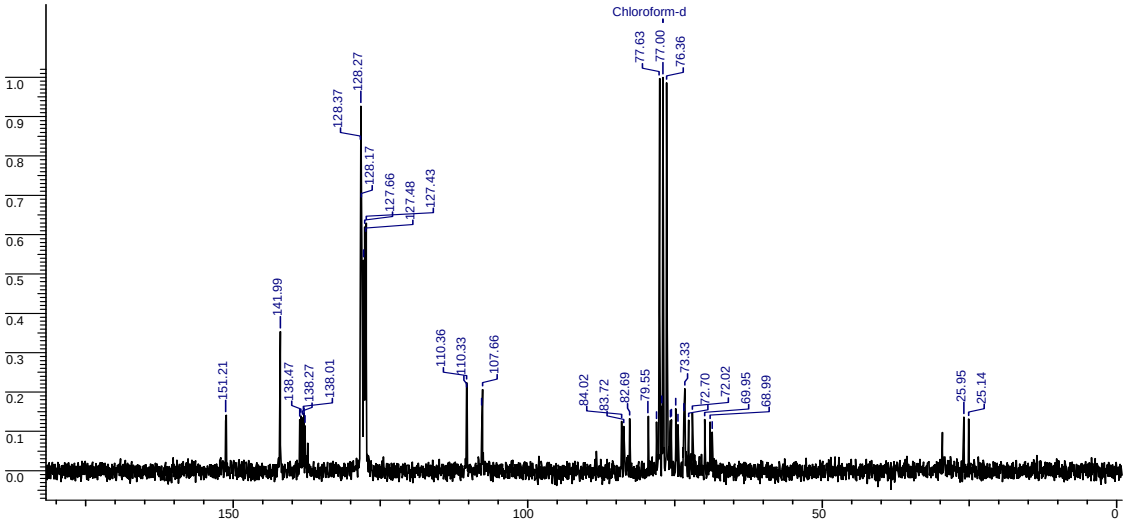
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37 (*β*)**



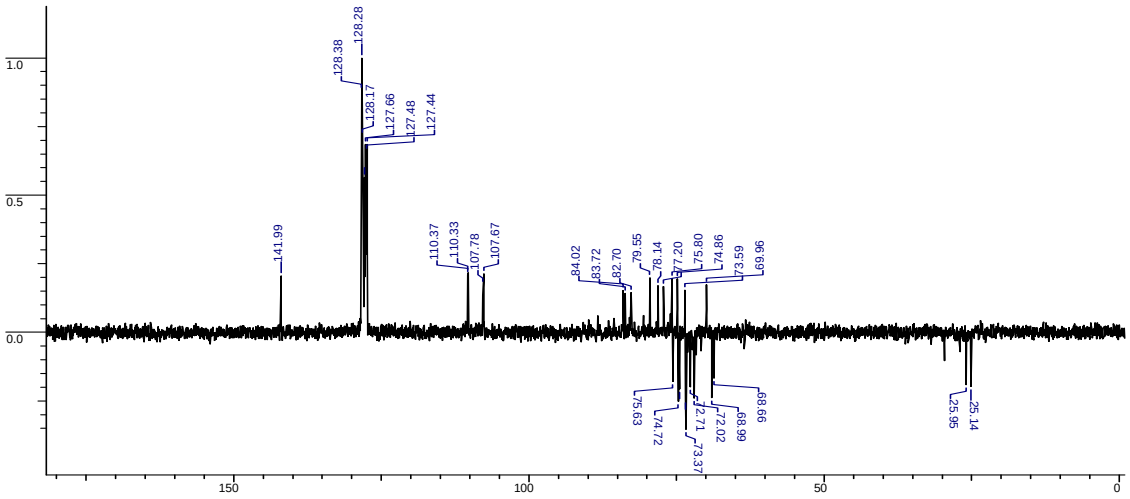
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **38**



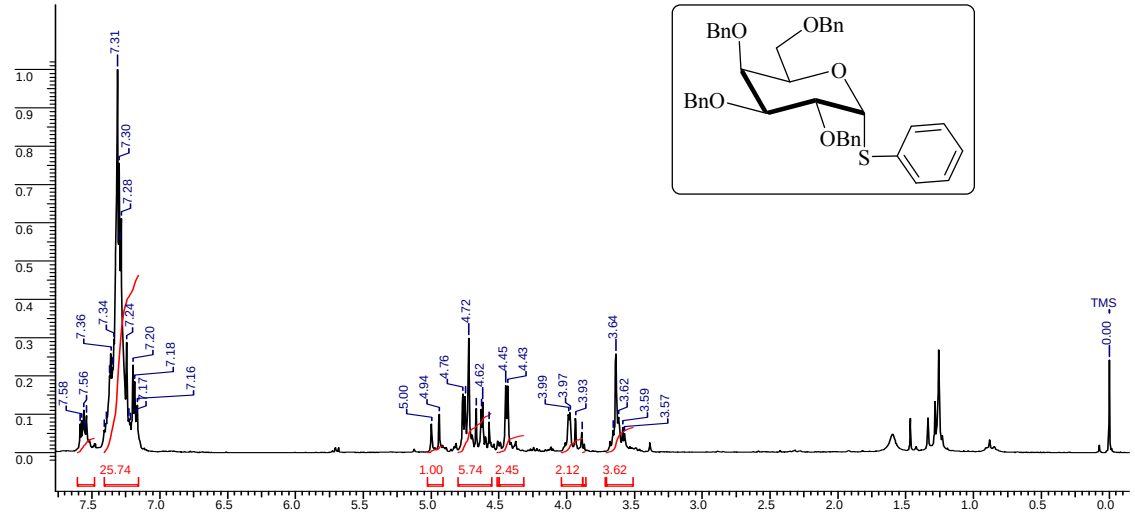
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **38**



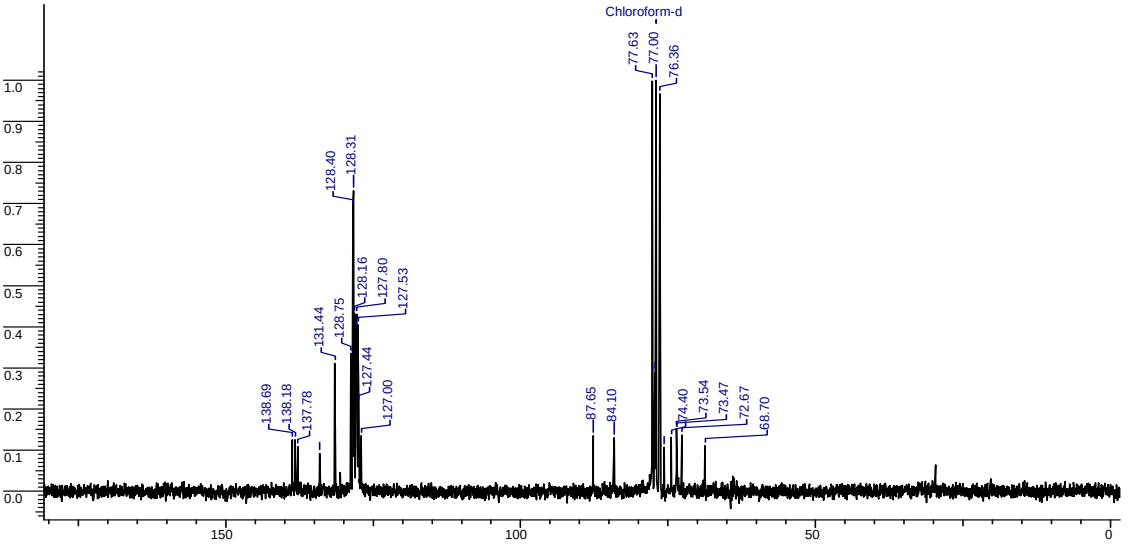
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **38**



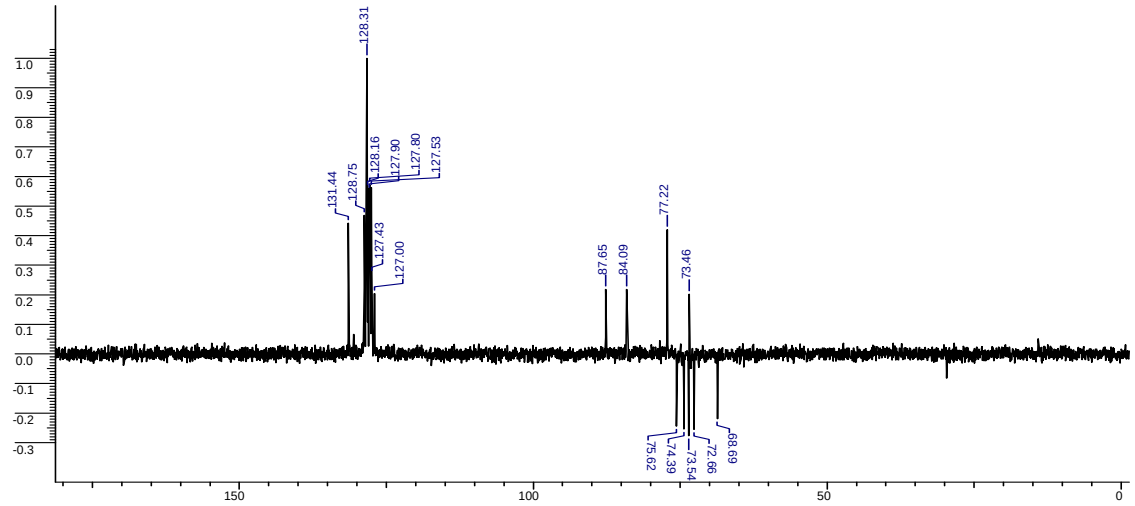
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **39 (*α*)**



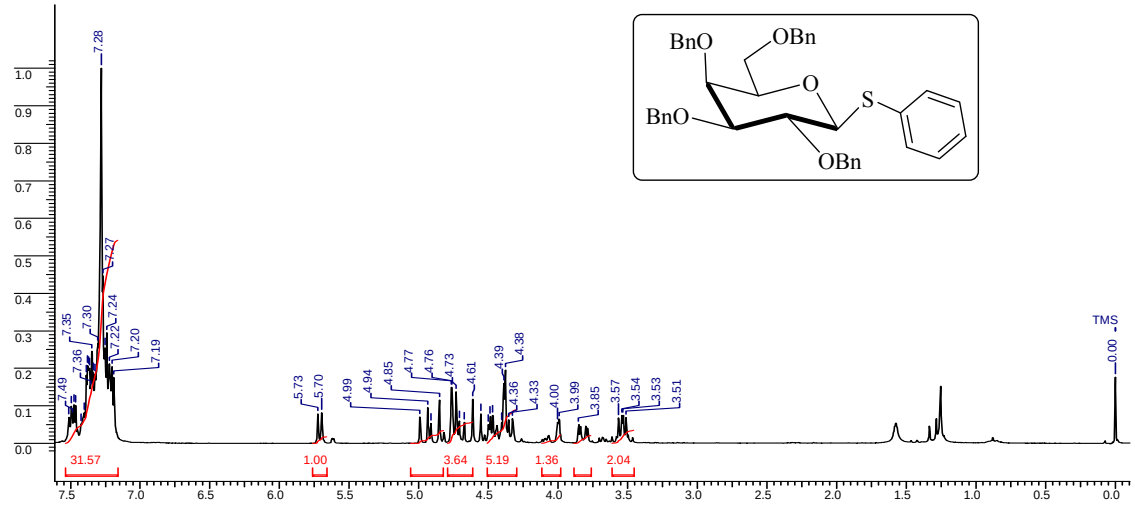
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **39 (*α*)**



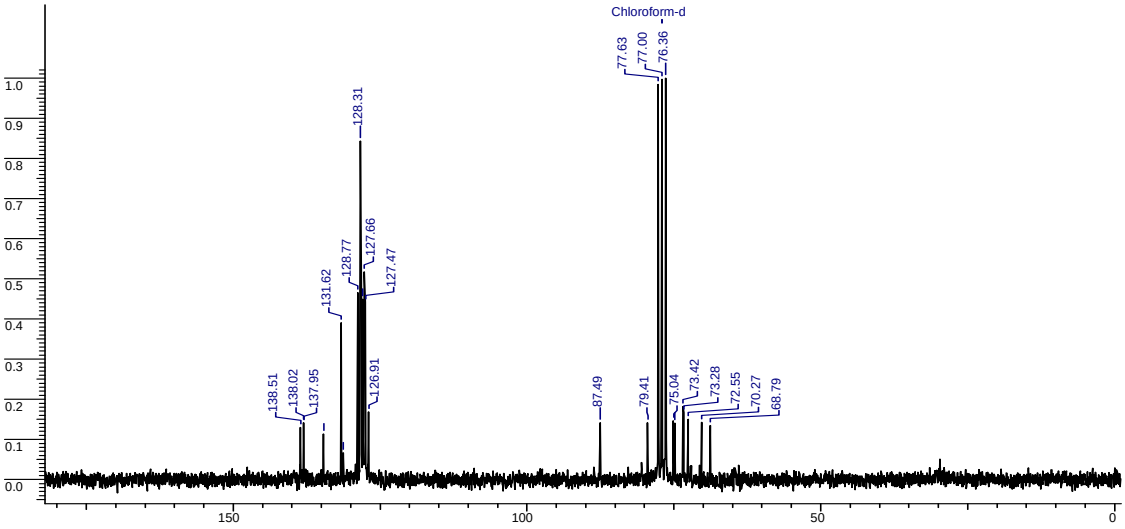
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **39 (*α*)**



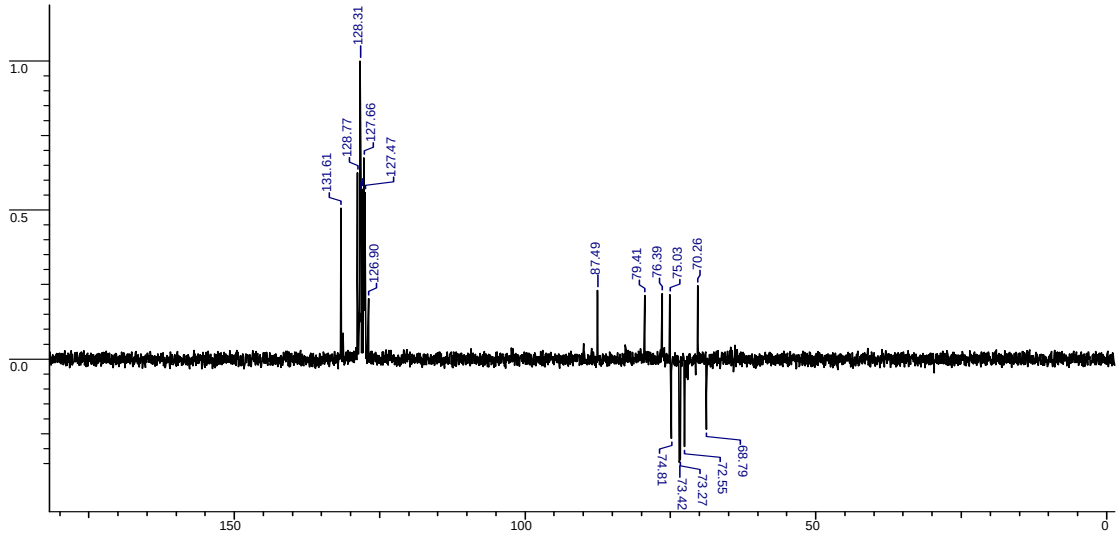
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **39 (*β*)**



^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **39 (*β*)**



DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **39 (*β*)**



Chapter 2: References

1. (a) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370. (b) McAuliffe, J. C.; Hindsgaul, O. *Front. Mol. Biol.* **2000**, *30*, 249. (c) Varki, A. *Glycobiology* **1993**, *3*, 97.
2. (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (b) *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, **1999**. (c) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357. (d) Ritchie, G. E.; Moffatt, B. E.; Sim, R. B.; Morgan, B. P.; Dwek, R. A.; Rudd, P. M. *Chem. Rev.* **2002**, *102*, 305.
3. (a) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465. (b) Ragupathi, G.; Koide, F.; Livingston, P. O.; Cho, Y. S.; Endo, A.; Wan, Q.; Spassova, M. K.; Keding, S. J.; Allen, J.; Ouerfelli, O.; Wilson, R. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 2715. (c) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 35. (d) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766
4. (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93,* 1503. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* 1986, *25*, 212. (c) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
5. (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823. (b) Schmidt, R. R. *Pure Appl. Chem.,* **1989**, *61*, 1257. (c) Sinay, P. *Pure Appl. Chem.,* **1991**, *63*, 519. (d) Nicolaou, K. C.; Caulfield, T. J.; Croneberg, R. D. *Pure Appl. Chem.* **1991**, *63*, 555. (e) Vasella, A. *Pure Appl. Chem.* **1991**, *63*, 507. (f) Fraser-Reid, B.; Udodong, U.; Wu, E. Z.; Ottoson, H.; Merritt, J. R.; Rao, S.; Roberts, C.; Madsen, R. *Synlett*, **1992**, *12*, 927.
6. For non-conventional glycosidic bond synthesis see for example: (a) Schmidt, R. R.; Reichrath, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 466. (b) Paquet, F.; Sinay, P. *J. Am. Chem. Soc.* **1984**, *106*, 8313. (c) Briner, K.; Vasella, A. *Helv. Chim. Acta.* **1989**, *72*, 1371. (d) Barrett, A. G. M.; Bezuidenhout, B. C. B.; Gasiecki, A. F.; Russell, A. R. *J. Am. Chem. Soc.* **1989**, *11*, 1392. (e) Crich D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun,* **1988**, 1461.
7. (a) Lemieux, R. U.; Haymi, J. I. *Can. J. Chem.* **1965**, *43,* 2162. (b) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* 1975, 97, 4056. (c) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61. (d) Barresi, F.; Hindsgaul, O.

"Glycosylation methods in oligosaccharide synthesis" Modern Synthetic Methods, **1995**, *7*, 281-330.

8. (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. (c) Demchenko, A. V.; Pornsuriyasak, P.; Meo, C. D.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069. (d) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799. (e) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662. (f) Kahne, D.; Walker, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (g) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380. (h) Witczak, Z. J.; Czernecki, S. *Adv. Carbohydr. Chem*. *Biochem*. **1998**, *53*, 143. (i) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem*. *Commun*. **1989**, 685. (j) Zhang, Z. Y.; Wong, C.-H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, **2000**; Vol. 1, pp 117-134. (k) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. (l) Kim, J. H.; Yang, H.; Boons, G.-J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947. (m) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem.* Soc. **2001**, *123*, 8477.
9. (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, *3*, 431. (b) Eliel, E. L.; Juaristi, E.; *ACS Symp. Ser.* **1979**, *87,* 95. (c) Kirby, A. J. *Anomeric Effect and Related Stereoelectronic Eflects at Oxygen,* Springer, Berlin **1983**, p. 10. (d) Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1979***,* 847. Dekongchampa, P. *Stereoelectronic Effects* in *Organic Chemistry,* Pergmon Press, Oxford, **1983**. (e) Schmidt, R. R.; Michel, J.; Roos, M. *Liebrgs Ann. Chem*. **1984**, 1343.
10. (a) Schmidt, R. R.; Riicker, E. *Tetrahedron Lett.* **1980**, *21,* 1421. (b) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.***1965**, *43,* 2205.
11. (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (b) Lu, J.; Jayaprakash, K. N.; Schlueter, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **2004***, 126,* 7540. (c) Roberts, C.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995***, 117*, 1546. (d) Christopher, S. B.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996,** *61,* 1609. (e) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem*. **1990**, *55*, 6068.
12. (a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990***, 31*, 275. (b) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* **1990***, 112*, 8895. (c) Zuurmond, H. M.; Veeneman, G. H.; van der Marel, G. A. and van Boom, J. H. *Tetrahedron Lett.* **1992***, 33*, 2063. (d) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989***, 111,* 6656. (e) Ley, S. V.;

Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997***, 3,* 431-440.

13. (a) H.; Banoub, J. *Methods in Carbohydr. Chem*. *Vol. 8*, Whistler, R. L.; BeMiller, J. N. Eds. Academic Press, New York, **1980**, 247. (b) Betaneli, V.; Ovchinnikov, M. V.; Backinowsky, Kotchekov, N. K., *Carbohydr. Res*. **1980**, *84,* 211.
14. (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Schmidt, R. *Angew. Chem. Int. Ed. Engl.* **1986***, 25*, 212. (c) W. Klotz, R. R. Schmidt, *J. Carbohydr. Chem.* **1994**, *13*, 1093. (d) Rembold, H.; Schmidt, R. R. *Carbohydr. Res.* **1993***, 246*, 137-159. (e) Robina, I.; López-Barba, E; Fuentes, J. *Tetrahedron* **1996**, *52*, 10771-10784.
15. (a) Galonić, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000. (b) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896.
16. (a) Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett,* **2002,** *43*, 6953. (b) Macha, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345.
17. (a) Hotha, S; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128,* 9620. (b) Sureshkumar, G.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 6564.
18. (a) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364 and 852. (b) Kashyap, S.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 2021-2023. (c) Kashyap, S.; Vidadala, S. R.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 8960-8962.
19. (a) Pathak, A. K.; Yahya A.; El-Kattan, Bansal, N.; Maddry, J. A; Reynolds, R. C. *Tetrahedron Lett.* **1998**, *39*, 1497. (b) Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351. (c) Tietze, L. F. ; Liigers, M. *Justus Liebigs Ann. Chem.* 261-265 (1990). (d) Tietze, L. F.; Bothe, U. *Chem. Eur. j.* **1998**, 4, 1179.
20. Izumi, M.; Koichi Fukase, K.; Kusumoto, S. *Biosci. Biotechnol, Bichem.* **2002**, *66*, 211.
21. (a) Cerny, M; Stanek, J. *Adv. Carbohydr. Chem*. *Biochem*. **1977**, *34*, 23. (b) Toshima, K.; Nagai, H.; Kasumi, K.; Kawahara, K.; Matsumura, S. *Tetrahedron* **2004**, *60*, 5331. (c) Lee, J. C.; Pan, G. R.; Kulkarni, S. S.; Luo, S.-Y.; Liao, C.-C.; Hung, S.-C. *Tetrahedron Lett*. **2006**, *47*, 1621. (d), Maeta H., Matsumoto, T.; Suzuki, K.; *Carbohydr. Res.* **1993**, *249*, 49.
22. (a) Turecek, F.; Drinkwater, D. E.; McLafferty, F. W. *J. Am. Chem. Soc.* **1991**, *113*, 950. (b) Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2994. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem*. *Soc*. **2005**, *127*, 6962.

23. (a) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97. (b) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52,* 179.

24. (a) Parsiegla, G.; Reverbel-Leroy, C.; Tardif, C.; Belaich, J. P.; Driguez, H.; Haser, R. *Biochemistry* **2000**, *39,* 1123. (b) Sulzenbacher, G.; Driguez, H.; Henrissat, B.; Schülein, M.; Davies, G. J. *Biochemistry* **1996**, *35,* 15280. (c) Czjzek, M.; Cicek, M.; Zamboni, V.; Burmeister, W .P.; Bevan, D. R.; Henrissat, B.; Esen, A. *Biochem. J.* **2001**, *354*, 37. (d) Comber, R. N.; Friedrich, J. D.; Dunshee, D. A.; Petty, S. L.; Secrist III, J. A. *Carbohydr. Res*. **1994**, *262*, 245. (e) Kiefel, M. J.; Beisner, B.; Bennett, S.; Holmes, I. D.; von Itzstein, M. *J. Med. Chem.* **1996**, *39,* 1314-1320.

25. (a) Eisele, T.; Toepfer, A.; Kretzschmar, G.; Schmidt, R. R. *Tetrahedron Lett.* **1996**, *37,* 1389. (c) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51,* 4923. (e) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 115. (g) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239. (h) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (i) Fügedi, P. 11th European Carbohydrate Symposium, Lisbon, Portugal **2001**; Abstract OC 31. (j) Fügedi, P.; Tatai, J. *Org. lett.* **2007**, *9*, 4647.

26. (a) Pozsgay, V.; Jennings, H. J. *Tetrahedron Lett.* **1987**, *28*, 1375. (b) Nambiar, S.; Daeuble, J. F.; Doyle, R. J.; Taylor, K. G. *Tetrahedron Lett.* **1989**, *30*, 2179. (c) Olsson, L.; Kelberlau, S.; Jia, Z. J.; Bert, F.-R. *Carbohydr. Res.* **1998**, *314*, 273. (d) Matsuit, H.; Furukawa, J.; Awano, T.; Nishi, N.; Sakairi, N. *Chem. Lett.* **2000**, 326. (e) Tai, C.-A.; Kulkarni, S. S.; Hung, S.-C. *J. Org. Chem.* **2003**, *68*, 8719. (f) Agnihotri, G.; Tiwari, P.; Misra, A. K. *Carbohydr. Res.* **2005**, *340*, 1393. (g) Tiwari, P.; Agnihotri, G.; Misra, A. K. *J. Carbohydr. Chem.* **2005**, *24*, 723.

27. (a) Ferrier, R.; Furneaux, R. *Methods in Carbohydr. Chem.* **1980***, 8*, 251. (b) Tropper, F.; Andersson, F.; Grandmaitre, C.; Roy, R. *Synthesis* **1991**, 734. (c) Horton, D. *Methods in Carbohydr. Chem.* **1963***, 2*, 433.

*****

Chapter 3

Synthesis of *Pseudo*-Oligosaccharides and Amino Acid Glycoconjugates

Chapter 3: Introduction

Secondary metabolites produced in the nature contain diverse architectures with complex structure. These compounds often possess important biological activities that make them potential therapeutic agents.[1] However, drug discovery based on these natural products is generally slow, costly, and hindered by complex syntheses. One of the most efficient ways to identify small molecule inhibitors is by the nature dictated process wherein several plants were screened (against a target protein) based on the pre-knowledge obtained from ayurvedic medical practitioners or general folk. The process of taking the molecule from identification to the market is a laborious process as the structure of the molecule has to be established beyond doubts and later a synthetic strategy for the molecule must emerge. Major concerns of the pharmaceutical industries are firstly, the availability of structural and skeletal analogues of the lead molecule(s) and the scale-up of the compound for evaluating its toxicology, bio-availability etc. Some of the lacunae can be addressed if the organic synthesis platform is more modular and easily scalable.[2]

Therefore, a set of criteria defining reliable reactions known as "click" chemistry was proposed by Sharpless and coworkers in order to accelerate the synthesis of drug-like molecules. "Click Chemistry" is a modern concept in synthetic chemistry that facilitates the construction of newer chemical substances, whose primary focus is to generate substances by joining small units together with heteroatom links (*C-X-C*).[2] The goal of such an endeavor is to develop an expanding set of powerful, selective, and modular 'blocks' that work reliably in both small- and large-scale applications. They laid a few stringent rules that a process must meet in order to become eligible to be considered as a click reaction. The approach makes use of a few near perfect chemical reactions i.e., the most facile and selective chemical transformations for the synthesis of designed molecules. The resultant molecules have a high built energy content that makes the chemical reaction spontaneous and irreversible, therefore highly stable product. The strategy is useful for the exploration of the novel molecules in lead discovery. Lead optimization is also faster through analog library generation by using "Click Chemistry". The process utilizes several appropriate building blocks to provide variety of useful chemical substances such as mimics of pharmacophores, drugs, natural products, etc.[1-3]

Click chemistry enables a modular approach to generate novel pharmacophores utilizing a collection of reliable chemical reactions. Scope of a click reaction must be modular, wide with stereoselectively high yield, both in small and large scale, without producing any offensive byproducts that can be removed by non-chromatographic methods. It must be easy

to perform, insensitive to oxygen or water, utilize only readily available reagents, the use of benign solvents or easily removed solvent or no solvent and have a thermodynamic driving force of at least 20 kcal mol^{-1}. The reaction workup and product isolation must be simple by using non-chromatographic methods, such as crystallization or distillation and product must be stable under physiological conditions.[2]

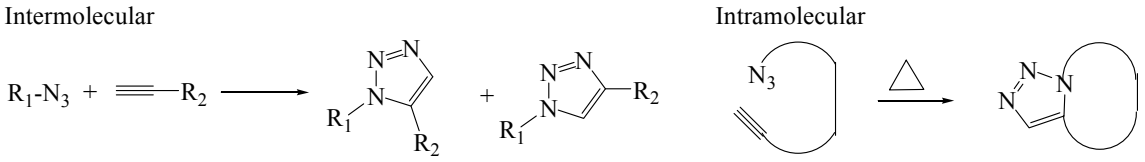
"Click Chemistry" uses carbon-heteroatom bond forming reactions from carbon-carbon multiple bonds. Olefins and acetylenes are regarded as the best and most energetic building blocks. Kolb and co-workers[2] framed some reliable processes for the synthesis of building blocks and compound libraries. The most common examples include the reactions such as,

- Cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions[4] but also the Diels-Alder family of transformation;[5a-c]
- Nucleophilic substitution chemistry, particularly ring-opening reaction of strained heterocyclic electrophiles such as epoxide, aziridines, aziridinium ions, and episulfonium ions;[2b]
- Carbonyl chemistry of the "non-aldol" type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones and amides; and
- Additions to carbon-carbon multiple bonds, especially oxidative cases such as epoxidation,[6a] dihydroxylation,[6b] aziridination[6c] and sulfenyl halide addition[6d] but also Michael additions of Nu-H reactants.

1,3-Dipolar Cycloaddition Reaction:

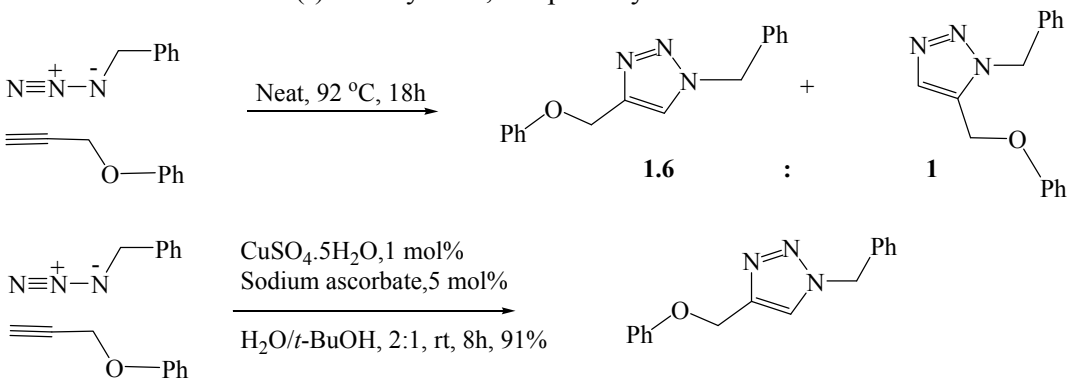
Of particular interest is the Huisgen [3 + 2] cycloaddition between a terminal alkyne and an azide to generate substituted 1,2,3-triazoles.[7a] This reaction has been termed the "cream of the crop" of click reactions[2a] and has found application in various facets of drug discovery.[2c] Among many reactions that became eligible, the best and well documented reaction in the click chemistry realms is the Huisgen's 1,3-dipolar cycloaddition of an alkyne and azide that results in the formation of a 1,2,3-triazole moiety (Figure 1).[7] Though Huisgen reaction was discovered fifty years ago, this reaction did not receive the desired attention probably due to the safety concerns w.r.t. the use of azides. However with the advent of modern methods, organic azides can be introduced easily, they are robust to variety of reaction conditions, they can be converted easily to aliphatic amine and they are stable to dimerization. Another important aspect of Huisgen's reaction is that complex structures can be easily assembled using this approach by zipping an azide and acetylene under neutral conditions. The recent literature is filled with many successful applications of click chemistry towards the chemical ligation of biomolecules in order to probe function of the synthesized material.[8]

Figure 1: Huisgen [3+2] Cycloaddition



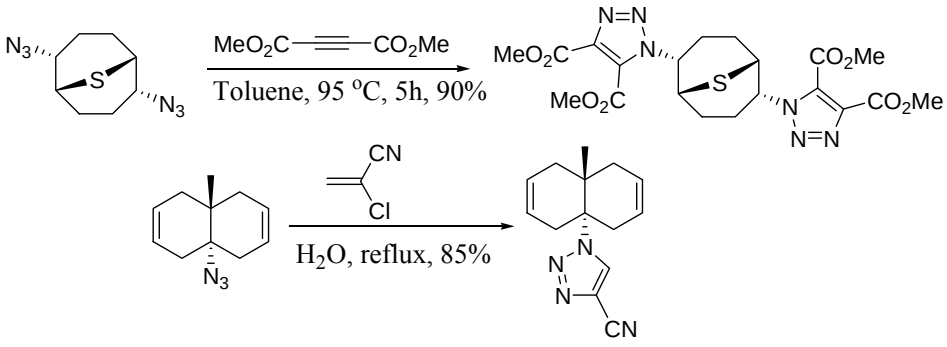
The Huisgen 1,3-dipolar cycloaddition between a terminal alkyne and an azide has rapidly become the most popular click reaction in current era.[2c] The formation of triazoles via the cycloaddition of azide and acetylene was first reported by Dimroth in the early 1900's but the generality, scope, and mechanism of these cycloaddition was not fully realized until the 1960's.[7] The reaction generates a mixture of 1,4- and 1,5-disubstituted triazoles. Rolf Huisgen reported a 1,3-dipolar cycloaddition reaction in his paper where the outcome of reaction shown the dependence of electronic and steric effects (Scheme 1).[7c]

Scheme 1: Thermal and Cu(I) -Catalyzed 1,3-Dipolar cycloaddition



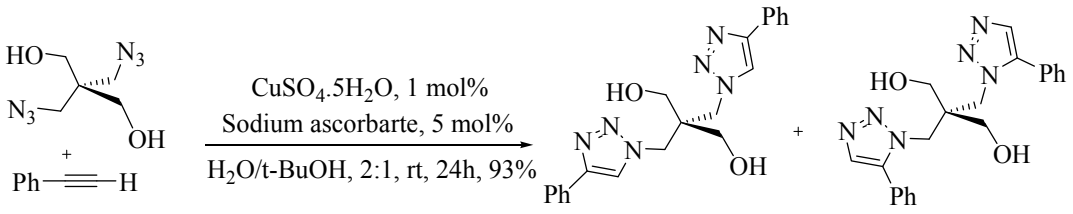
Various attempts to control the regioselectivity have been reported without much success until the discovery of the copper (I)-catalyzed reaction in 2002, which exclusively yields the 1,4-disubstituted 1,2,3-triazole.[2b,9] Sharpless and co-workers[2a] reported azide cycloaddition where azido molecule readily adds to alkyne. In these cases the alkyne bonds are substituted by electron withdrawing groups, which make the alkyne group more reactive. Azide reacts with the cyanoacetylene equivalent, 2-chloroacrylonitrile, to give only one regioisomer of triazole (Scheme 2).

Scheme 2



Recently Sharpless[2b] reported copper-(I) catalyzed reaction sequence which regiospecifically couples azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3-triazoles (Scheme 3). The process is experimentally simple and appears to have enormous scope. The use of Cu(I) catalyst dramatically accelerated the rate of the azido-alkyne coupling. Another advantage of this procedure is use of water as solvent which is benign and product can be just filtered, rendering purification unnecessary.

Scheme 3

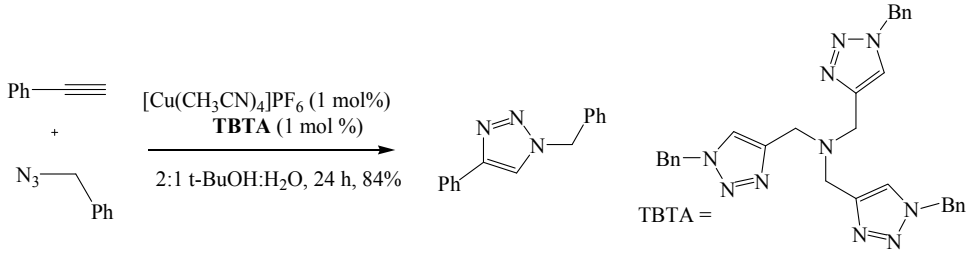


Sharpless and co-workers found that the catalyst is better prepared in situ by reduction of Cu (II) salts using sodium ascorbate as reductant. The procedure was found to be high yielding at catalytic amount of Cu(II) salts. The reaction conditions were very simple. The reaction proceeds at ambient temperature, wide choice of solvent, independent of pH, reaction completes in 6 to 36 hours. In other words, this is a very robust catalytic process, which is so insensitive to the usual reaction parameters. Another scope of this copper-catalyzed triazole synthesis is the lack of functional group interference.

Copper (I) salts, for example, CuI, $CuOTf.C_6H_6$, and $[Cu(NCCH_3)_4][PF_6]$, can also be used directly in the absence of a reducing agent. These reactions use acetonitrile as co-solvent and one equivalent of a nitrogen base (for example, 2,6-lutidine, triethylamine, *N,N*-diisopropylethylamine, or pyridine). However, the formation of undesired byproducts, such as diacetylenes, bis-triazoles, and 5-hydroxy-triazoles was often observed. Therefore Cu(II)/sodium ascorbate catalyst system found to be more reliable in aqueous condition.

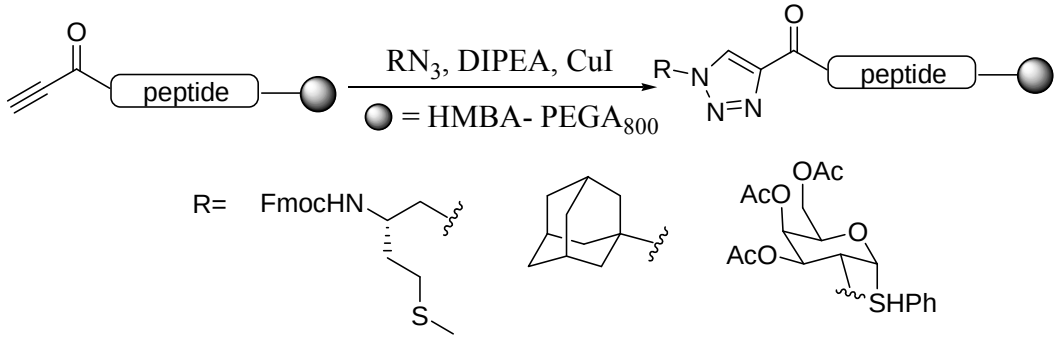
In the latter studies Fokin group[2b] developed oligotriazole ligands such as *tris*-(benzyltriazolylmethyl)amine (TBTA) for protecting Copper(I) catalyst under aerobic aqueous conditions and promoting Cu(I) catalyzed transformations (Scheme 4). The TBTA has also been successfully applied in bioconjugation studies.

Scheme 4



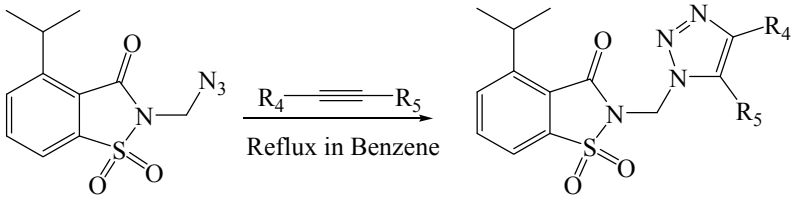
Meldal *et al.* reported peptidotriazole synthesis on solid phase using copper iodide and *N,N*-diisopropylethylamine obtained regiospecifically 1,4-disubstituted products in quantitative yields (Scheme 5).[9]

Scheme 5



In contrast to the Cu(I) catalyzed regiospecific 1,3-dipolar cycloaddition reaction, Hlasta and coworker reported synthesis of a new class of human leukocyte elastase inhibitors by 1,3-dipolar cycloaddition reaction of an (azidomethyl) benzisothiazolone with trimethylsilyl substituted acetylenes (Scheme 6). He reported the trimethylsilyl controlled regioselectivity over the electron deficient sulfonyl group. The influence of trimethylsilyl group is attributed to their steric effect and stabilization of a partial positive charge on the acetylene β carbon.[10]

Scheme 6

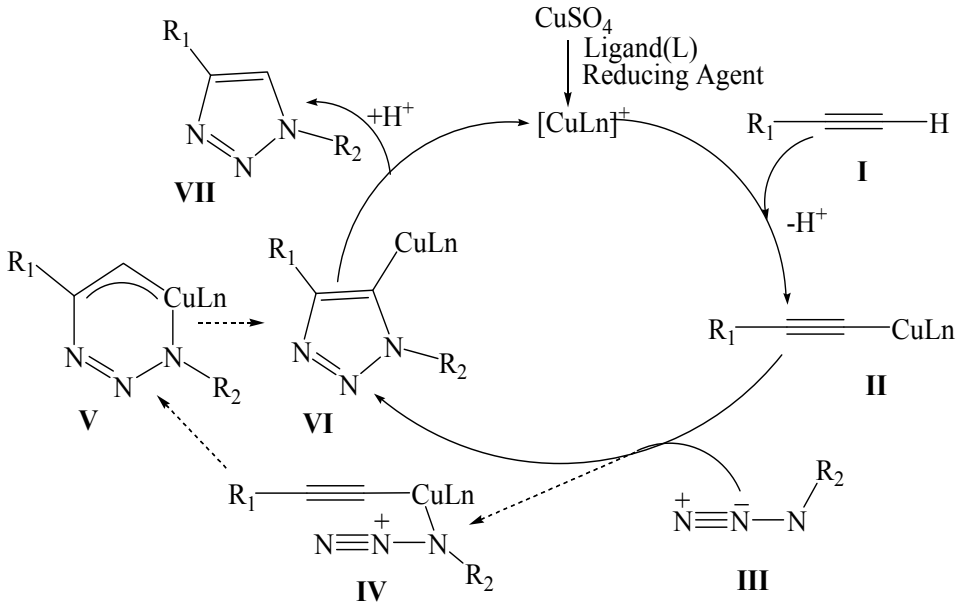


R_4	R_5	Yield %
TMS	H	81
TMS	SO_2Ph	73

Mechanism:

It is known that copper (I) readily inserts into terminal alkynes in the presence of base, e.g. the Sonogashira coupling. The polarization of the terminal triple bond by the covalently bound copper (I) catalyzes the cycloaddition which probably changes from a concerted reaction into a stepwise addition. Sharpless and coworkers proposed a catalytic cycle for Cu(I) catalyzed 1,3-dipolar cycloaddition reaction (Figure 2). It begins with formation of the copper (I) acetylide **II**. According to density functional theory calculations copper catalyzed reaction disfavors the concerted [3+2] cycloaddition and favors to a stepwise, annealing sequence, hence the term "ligation", which proceeds via the six membered copper-containing intermediate **V**. Insertion of azide leading to the six-membered metallocycle (**V**) is the key step.[2b,11]

Figure 2: Mechanism of Cu(I) Catalyzed 1,3-Dipolar Cycloaddition



Click chemistry and drug discovery:

Click chemistry is being used increasingly in biomedical research, ranging from lead discovery and optimization to tagging of biological systems, such as proteins, nucleotides and whole organisms. The development of the copper(I)-catalyzed cycloaddition reaction between azides and terminal alkynes has led to many interesting applications of click reactions including the synthesis of natural product derivatives. Although azides and alkynes display high mutual reactivity, individually these functional groups are two of the least reactive in organic synthesis. They have been termed bioorthogonal because of their stability and inertness towards the functional groups typically found in biological molecules.[2c] This bioorthogonality has allowed the use of the azide-alkyne [3 + 2] cycloaddition in various biological applications including target guided synthesis[12] and activity-based protein profiling.[13] Majority of therapeutically useful medicinal agents and naturally occurring biologically active substances contains one or more heterocyclic rings. In this universe of heterocyclic substances, the presence of 1,2,3-triazole nucleus is significant. The motifs containing these ring systems have shown enormous, range of biological activities. Triazole containing compounds exhibited anti HIV, anticancer, antibacterial, antiallergic, fungicidal, glycosidase inhibitory activities, etc. The azido and terminal alkyne compounds which form 1,2,3-triazole are regarded as bioorthogonal chemical reporters[14a,b] and used in designing bioconjugates.

Triazole as amide surrogate: electronic similarities

This kind of transformation is significantly useful for drug discovery, because of not only its reliability, but also due to the favorable physicochemical properties of triazoles. 1,4-Disubstituted 1,2,3-triazoles are regarded as amide surrogates because of their rigid linkage (Figure 3). Unlike amides, triazoles cannot be cleaved by hydrolysis. They are impossible to oxidize or reduce as in the case of benzenoid and related aromatic heterocycles. These facts demonstrates the metabolic stability of 1,2,3-triazoles.

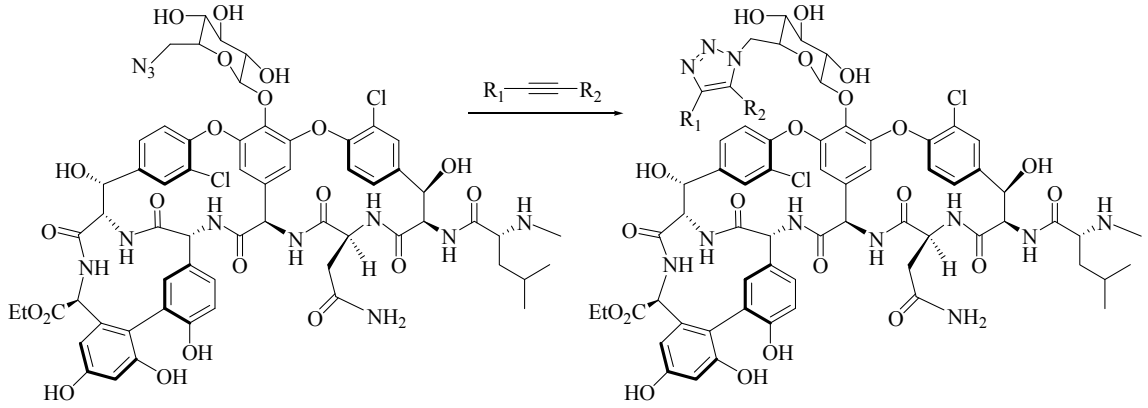
Figure 3

1,4-Disubstituted 1,2,3- triazoles also possess a large dipole moment of about 5 Debye and interestingly nitrogen atoms two and three (Figure 3) function as weak hydrogen bond acceptor. Thus 1,2,3-triazoles can participate in the hydrogen bonding which can enhance the affinity of drug molecules to the target receptors and also modify the solubility.[2c]

Generation of natural product derivatives:

Click reactions can be utilized to construct building blocks for the rapid synthesis of 1,2,3-triazoles containing molecules with diverse structure and function. The significant profiles of triazoles are not only limited to biology or therapeutics. The applications of these motifs are also extended to other face of the chemical science. These are explored and utilized as ligands for Pd catalyst, in material science such as cyclic peptides, nanoparticles, functionalized polymers, dendrimers, molecular electronic devices, etc.

Scheme 7: Generation of Vancomycin Analogs

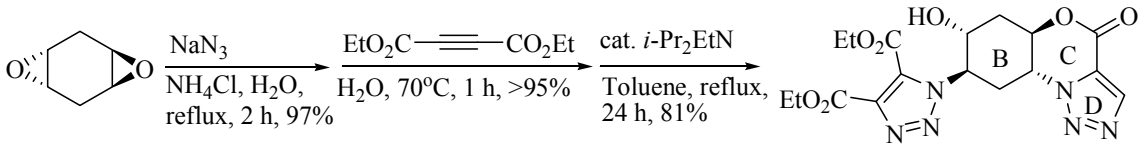


Thorson and co-workers recently utilized the Huisgen 1,3-dipolar cycloaddition of azide and acetylenes to generate fifty triazole analogs of the clinically used antibiotic vancomycin (Scheme 7).[15] Antibacterial screens of these compounds revealed several

vancomycin derivatives that possessed similar biological activity to the natural product and could possibly be utilized against vancomycin resistant bacterial strains as these analogs have a different target than the parent compound.

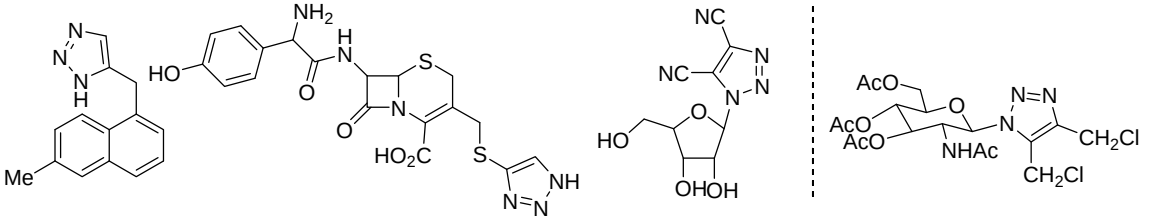
Similarly, the copper-catalyzed azide-alkyne cycloaddition was utilized to create derivatives of the non-ribosomal decapeptide antibiotic tyrocidine.[16] Sharpless and co-workers demonstrated the power of nucleophilic ring opening and 1,3-dipolar cycloaddition click reactions in the construction of steroid-like skeletons from diepoxides (Scheme 8).[2a]

Scheme 8: Formation of Steroid Mimics



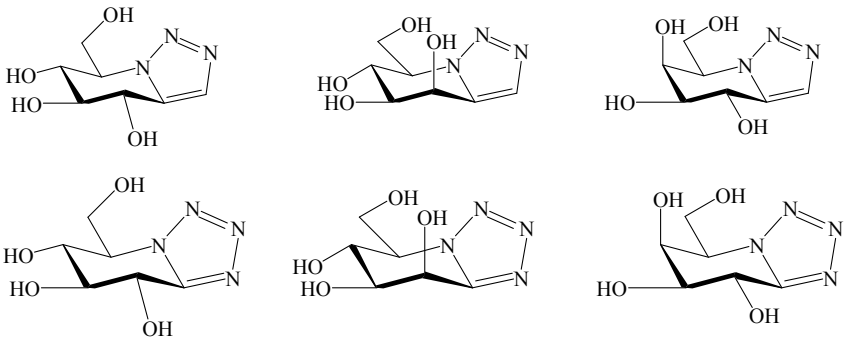
Cifatrizin is cephalosporin antibiotic which has activity against 342 different germs. 1,2,3-triazole-1,8-naphthyridine derivatives have been synthesized and reported to have analgesic, sedative and fungicidal activity. 1,2,3-triazole-nucleosides such as found to possess antibacterial and *in vitro* antiviral activity against herpes and measles virus and *N*-glycosyl (halomethyl)-1,2,3-triazole have been detected as alkylating agent showing cytostatic activity (Figure 4).[17]

Figure 4



Vasella group reported the synthesis of triazole and tetrazole fused bicyclic compounds derived from carbohydrate substrates. These compounds have shown strong β-glycosidase and glycogen phosphorylase b inhibitory activities (Figure 5).[18]

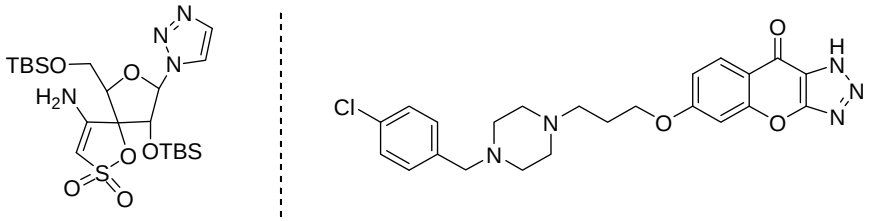
Figure 5



Camarasa *et al.* reported a series of 1,2,3-triazole spirocyclic ribofuranosyl nucleosides derivatives were synthesized and evaluated for their inhibitory activity on HIV-1 and HIV-2 induced cytopathicity in MT-4 cells and syncytium formation in CEM Cell cultures. The unsubstituted 1,2,3-triazole TSAO found active and had an EC50 for HIV-1 in MT-4 cells and CEM cells of 3.7 and 3.4pM respectively (Figure 6).[19]

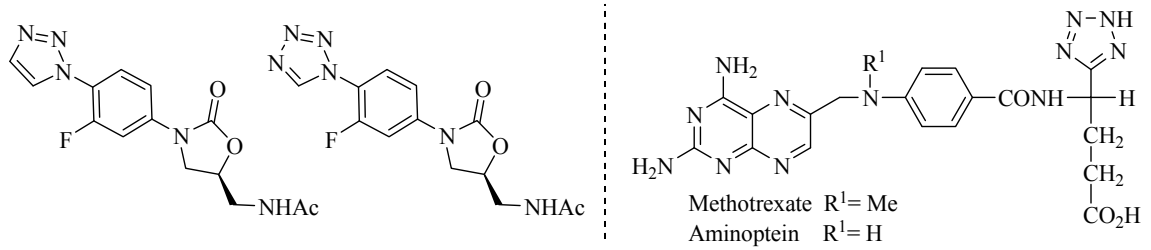
Buckle and co-workers[20] reported the H1-antihistamine activity for 1,2,3-triazole containing benzopyranone derivatives. Compound was found to have potent H1-antihistamine activity comparable to that of mepyramine (Figure 6).

Figure 6



On the other hand, Genin and co-workers[21] reported the synthesis of oxazolidinones containing 1,2,3-triazole and tetrazole ring (Figure 7) and these possess antibacterial activity of against both gram positive and gram negative organisms including *S. aureus, H. influenzae, S. pneumoniae* etc.

Figure 7

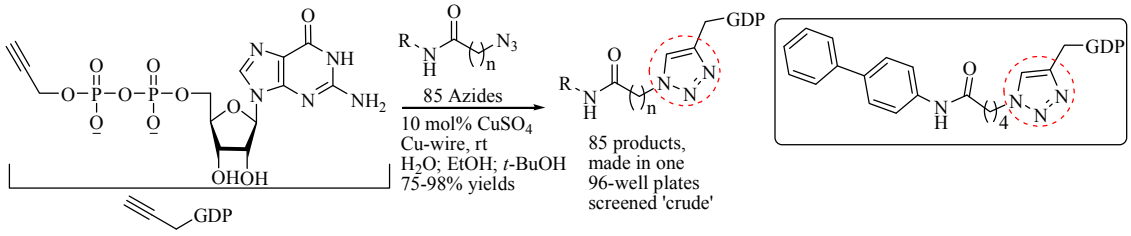


Kalman and co-workers[22] synthesized tetrazole isoster of antimetabolite agents methotrexate and aminopterin (Figure 7) and these have shown potent inhibition of growth of CCRF-CEM and K562 human leukemia cell lines.

Fucosyltransferase inhibitor:

Cell surface glycoconjugates bearing the sialyl Lewis^x and sialyl Lewis^a tetrasaccharide epitopes mediate a variety of crucial processes.[23] The fucosyltransferases catalyzed biosynthesis of these carbohydrates involves the transfer of an L-fucose moiety from guanosine diphosphate *β*-L-fucose (GDP-fucose) to a specific hydroxyl group of sialyl N-acetyl-lactosamine. Selective inhibitors of these enzymes might provide drugs by blocking the synthesis of fucosylated end-products, and the pathology they trigger.[24]

Scheme 9

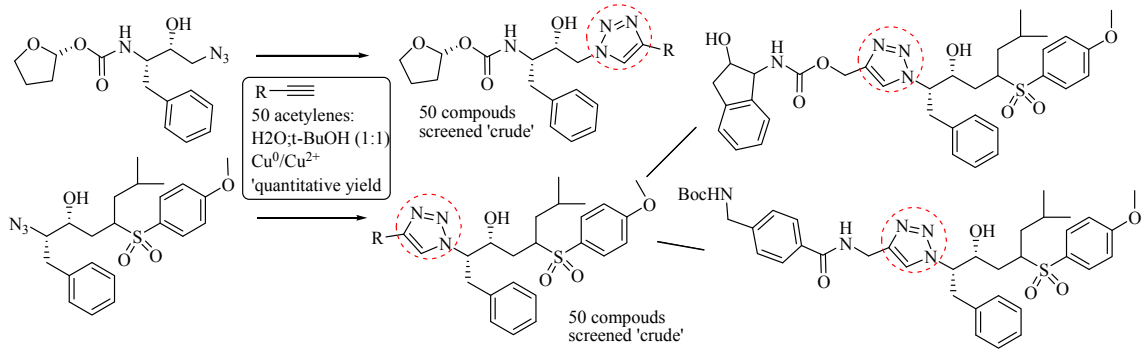


Wong *et al.* identified nanomolar inhibitors from a library of 85 test compounds that was prepared by linking GDP derived acetylene to a library of azides, using the copper-(I)-catalyzed triazole formation (Scheme 9). Hit follow-up, conducted on purified compounds against a panel of fucosyl and galactosyl transferases and kinases, revealed biphenyl derivative as the most potent inhibitor of human α-1,3-fucosyltransferase VI that has been found to date.[25]

Development of HIV protease inhibitors: [26-29]

HIV protease is responsible for the final stages of virus maturation and, thus, its inhibitors are useful drugs for the treatment of AIDS. Wong *et al.* prepared two focused libraries of 50 compounds each, based on hydroxyethylamine peptide isosteres (Figure 10). These libraries, which were already in aqueous solution from the synthesis step, were used directly, for screening against wild type HIV-1 protease and three mutants (G48V, V82F, V82A). Two of these compounds strongly inhibited all four proteases tested, with activities in the low nanomolar range (purified compounds).

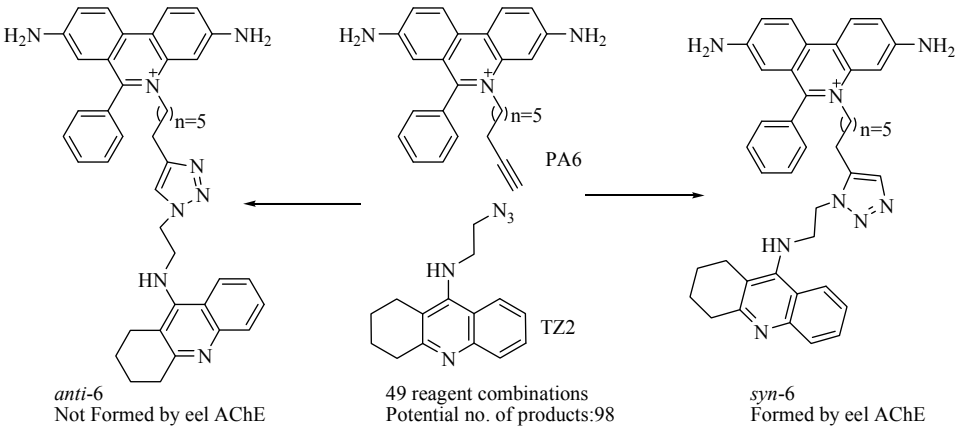
Scheme 10



In situ click chemistry*:*

Click chemistry methods demonstrate the promise of creating natural product derivatives quickly and efficiently and in addition, is now been employed in *in situ* synthesis in biomolecular active sites. Kolb and co-workers[30] discovered potent acetylcholine esterase inhibitors by in situ screening using acetylcholine esterase enzyme as a test system. The enzyme AChE catalyzes the formation of its own inhibitor.

Figure 8

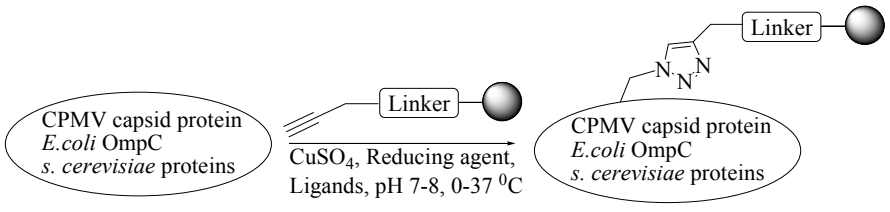


Whereas the less active *anti*-triazole (*anti*-6), which is not formed *in situ*, does not alter the conformational state of the enzyme, the highly potent *syn*-triazole (*syn*-6), formed *in situ*, traps the enzyme in a 'new' conformational state, which is probably a low abundance one in the absence of *syn*-6 (Figure 8). The in situ products *syn*-TZ2PA6 and *syn*-TA2PZ5 are the some examples derived from tacrine and phenylphenanthridinium acetylene and azide respectively.

Tagging of live organisms and proteins:

The application of mild methods for the chemical modification of components in, or on, living cells under physiological conditions has been pioneered by the Bertozzi group.[31] Finn *et al.* recently succeeded in using the new copper-(I)-catalyzed 1,2,3-triazole formation for labelling intact Cowpea mosaic virus particles (CPMV) with fluorescein (Scheme 11).[32] Tirrell and Link have recently disclosed how, using an ingenious sequence of molecular biology techniques, they forced *Eschericia coli* cells into making and displaying an azide-bearing outer membrane protein C (OmpC). These bacterial cells, now presenting azide groups to the extracellular milieu, were successfully biotinylated, under the special copper-catalyzed conditions.[33]

Scheme 11

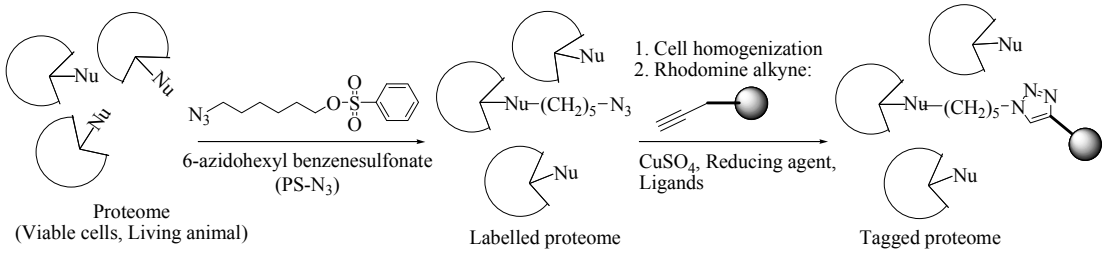


The Schultz laboratory then reported that their method for genetically-encoded incorporation of the azide and acetylene tyrosine analogs into proteins of *Saccharomyces cerevisiae,* could be followed up by capture of dyes, using the copper-(I)-catalyzed azide–alkyne triazole-coupling, as optimized by Finn *et al.*[32] for *in situ* bioconjugations.[34]

Activity-based protein profiling (ABPP):

Activity-based protein profiling (ABPP) utilizes active site-directed chemical probes with broad target selectivity to label active proteins within various enzyme classes and allows for the discovery of new drug targets.[35] However, the bulky reporter tags that are currently used require cell homogenization before analysis, thereby, preventing measurements in living organisms.[36] Cravatt *et al.* have solved this problem with small, cell-permeable reagents that carry an azide group for later dye attachment via the bio-orthogonal, copper-(I) catalyzed reaction with acetylenes (Scheme 12).[13] In fact, the use of click chemistry in ABPP resulted in the isolation of several enzymes in breast cancer cell lines that were never identified *in vitro* and can possibly serve as markers or novel targets for this disease.

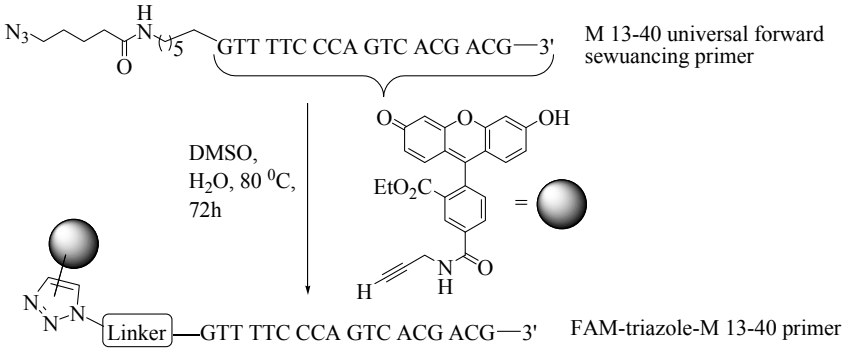
Scheme 12



Labeling of DNA:

Ju *et al.* prepared primers for the Sanger dideoxy chain termination reaction for DNA sequencing, by tagging the M13–40 universal forward sequencing primer at its 5′-end, with alkynyl 6-carboxyfluorescein (FAM), using the concerted thermal 1,3-dipolar cycloaddition process (Scheme 13).[37] The FAM-triazole-M13–40 primer was successfully used in the Sanger method, terminating with biotinylated dideoxyATP (ddATP-Biotin), to produce DNA sequencing fragments, using PCR-amplified DNA as a template.

Scheme 13



*****

Chapter 3: Present Work

Efficient carbohydrate conjugation to scaffold molecules is one of the important goals in bio-organic chemistry. Glycoconjugates[38] are playing increasingly important roles in the interference with protein–carbohydrate interactions,[39] carbohydrate vaccines,[40] functionalized glycochips and related surfaces,[41] and probes for (glyco)proteomics purposes.[42] Multivalent display of carbohydrates is more and more frequently used as a method to increase affinities[43] in various contexts such as the binding of bacteria,[44] bacterial toxins,[45] galectins[46] and other lectins,[47] offering a host of attractive drug discovery opportunities. In addition, glycosylation of proteins and lipids are key factors in modulating their structures and functions. Synthesis of such glycopeptides[48] is complicated by the sensitivity of the glycosidic linkage between the (oligo)saccharide and the peptide toward chemical and enzymatic hydrolysis. Synthesis of (unnatural) amino acids, with the amino acid side chain connected to the sugar unit via an isosteric linkage, may lead to chemically and metabolically more stable analogues with potential biological activity[49] (e.g., inhibitory activity toward glycosidases) or provide means to elucidate biochemical pathways. In order to study the functions of glycoconjugates in molecular detail, numerous methods for the synthesis of glycoconjugates have been developed for the assembly of complex glycoconjugates.[50] However, the traditional protocol for regio- and stereo-control in glycoside bond-forming process often leads to laborious synthetic transformations and tremendous protecting group manipulations, which complicate the overall synthetic process and decrease the synthetic efficiency.[51] Hence, development of new strategies and tactics in glycoconjugate syntheses are of growing importance.[52]

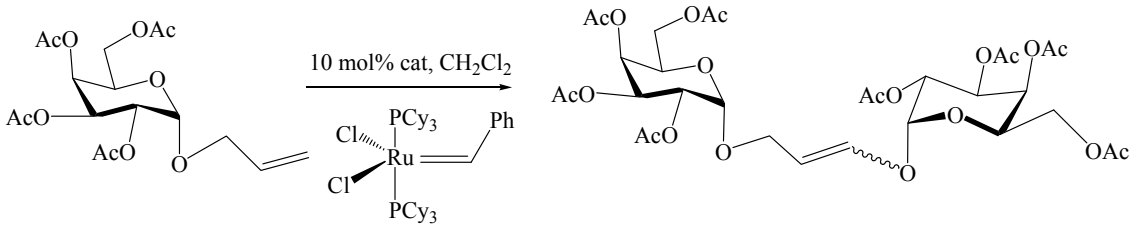
Click chemistry, in particular, the copper-(I)-catalyzed ligation of azides and acetylenes, promises to greatly simplify and accelerate the discovery of high-affinity carbohydrate mimetics. In carbohydrate chemistry this methodology has been successfully applied for the synthesis of multivalent neoglycoconjugates and cyclodextrine analogues. Applications of these multivalent neoglycoconjugates include neutralization of viruses and toxins, carbohydrate-based anticancer therapy and prevention of early adhesion of neutrophils to endothelial surfaces. Moreover, these glycoconjugates are also emerging as potential carbohydrates based therapeutic agents[53] and utilized to probe and enhance carbohydrate-protein interactions at molecular level.[53] A recent survey identified that synthetic oligosaccharides covalently attached to proteins facilitate the development of vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitides* group

C.[54] Lack of sufficient quantities of oligosaccharides and peptides often limit the efficient conjugation of oligosaccharides to oligosaccharides/peptides. It is anticipated that such homo and hetero dimeric glycoconjugates will be excellent probes which can act as potent reversible cross-linking reagents and also to measure the distances between carbohydrate binding sites in polyvalent recognition sites.[53a] Here in this chapter, an effort to synthesize 1,2,3-triazole compounds from carbohydrate templates is described.

Some of methods for homo and hetero dimerization:

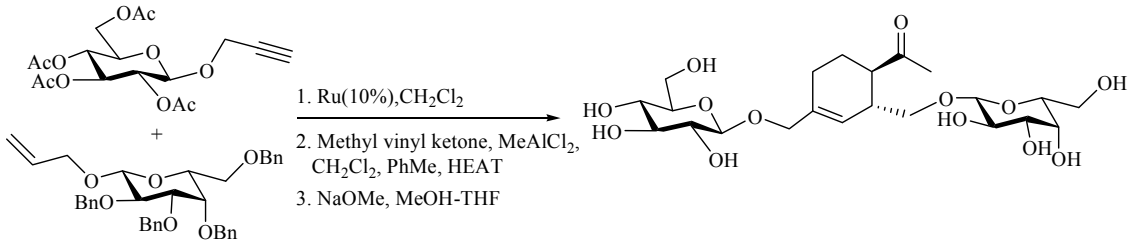
Rene Roy and co-workers applied Grubbs's ruthenium benzylidene catalyzed olefin metathesis reaction toward the synthesis of polyfunctionalized carbohydrate homodimers for the preparation of potential cross-linkers for signal transduction (Scheme 14).[55a]

Scheme 14: Alkenyl *O*- and *C*-glycopyranosides homodimerization by olefin metathesis reaction



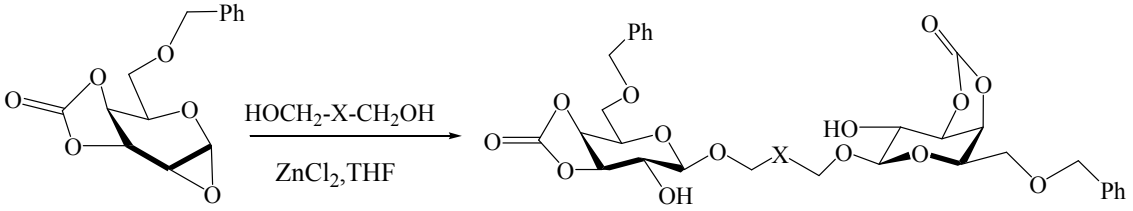
Siegfried Blechert *et al.* developed a general sequence of selective yne-ene cross metathesis, Diels-Alder transformation and equilibration-deprotection for the synthesis of various biologically interesting carbohydrate derivatives. The combination of different monosaccharide building blocks and dienophiles has been demonstrated and should potentially give rise to a large number of *pseudo*-oligosaccharides of the types presented (Scheme 15).[55b]

Scheme 15: *Pseudo*-oligosaccharides by a sequence of yne-ene cross metathesis and Diels–Alder reaction



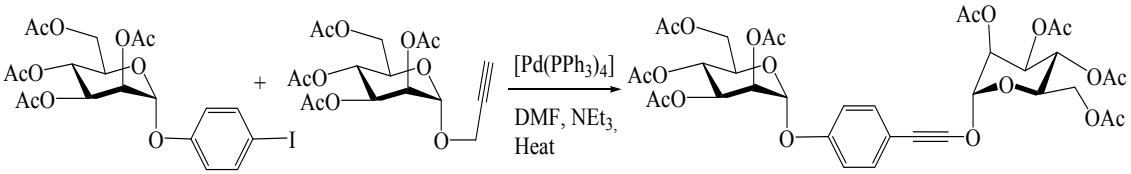
Raymond Patch and co-workers synthesized Spacer-Linked 1,1'-Bis -and 1,1',1''-Tris-*β*-glycosides in a highly stereoselective fashion using Danishefsky's elegant glycal epoxide glycosidation methodology under mild conditions (Scheme 16). [55c]

Scheme 16: Convenient Syntheses of Spacer-Linked Tris-*β*-glycosides by the Glycal Epoxide Glycosidation



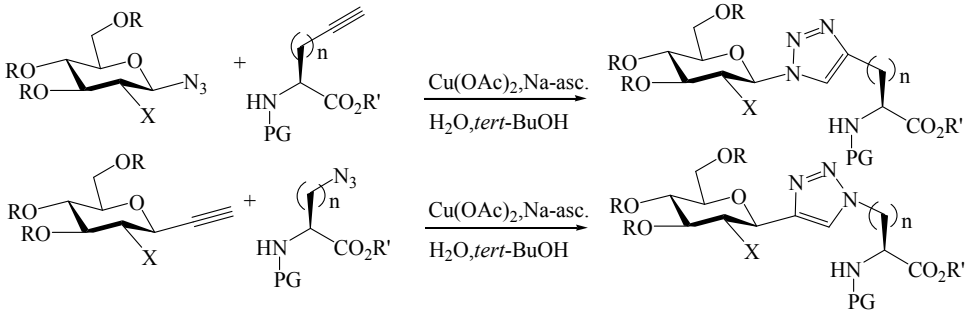
Rene Roy *et al.* applied tetrakis (triphosphine)-palladium-catalyzed Sonogashira cross coupling reaction between an alkyne and a halogen bearing sp^2-carbon for the efficient synthesis of rigid divalent or heterobifunctional "Sugar-rods" which exhibited great potential as protein or receptor cross-linker. Dimeric mannose-containing "sugar-rods" showed a strong and fast cross-linking ability towards the tetrameric plant lectin from *canavalia ensiformis* (Con A). Moreover, these heterodimers "sugar-rods" showed better inhibitory properties than their more flexible counter-part dimannoside in the inhibition of the hemagglutination of rabbit erythrocytes by two plant lectins that have similar affinities towards *α*-D-mannopyranosides (Scheme 17).[55d]

Scheme 17: Synthesis of ''Sugar-Rods'' using Palladium-Catalyzed Sonogasira Coupling



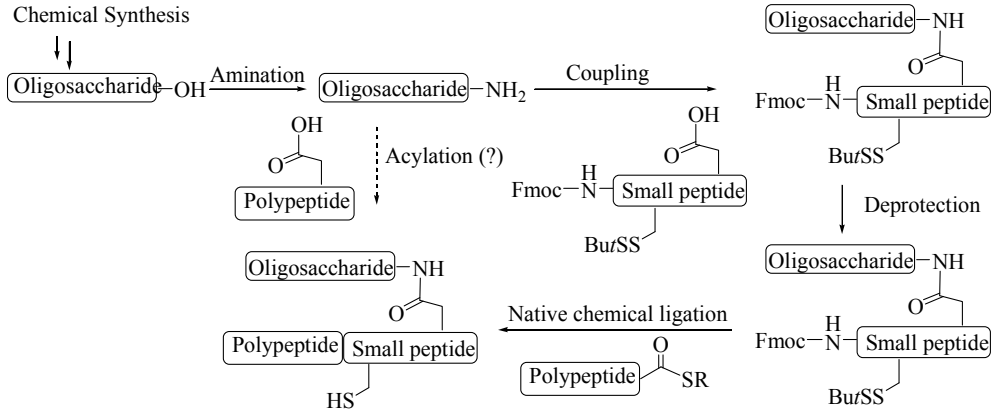
Rutjes *et al.* have developed a straightforward, versatile, and high-yielding method for the synthesis of a novel class of triazole-linked glycopeptides. These novel and stable glycopeptide mimics were prepared via Cu(I)-catalyzed [3 + 2] cycloaddition of either azide-functionalized glycosides and acetylenic amino acids or acetylenic glycosides and azide-containing amino acids. Both *α*- and *β*-triazole-linked glycopeptides can be efficiently prepared using a variety of suitably functionalized (oligo)saccharides and (oligo)peptides (Scheme 18).[55e]

Scheme 18: Cu(I)-catalyzed [3 + 2] cycloaddition for the synthesis of triazole-linked glycopeptides.



On the other hand, Danishefsky and co-workers presented a highly convergent route for the production of substantial quantities of homogeneous N-linked glycopolypeptides which offers the ability to introduce structural modifications for the purpose of understanding the role of stereochemistry in glycoconjugate recognition (Figure 9).[55f]

Figure 9

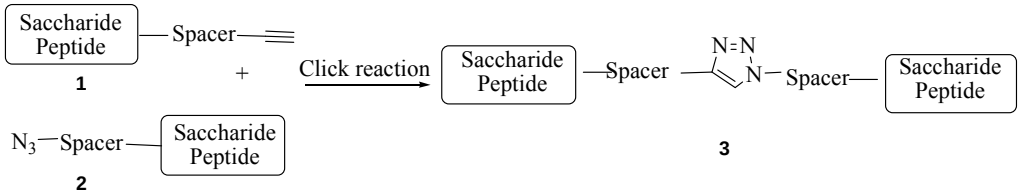


Aforementioned methods vary in efficiency and their compatibility with functional groups, and yield side-products, undesirable in couplings involving precious carbohydrate structures. With the recent improvement of the Huisgen cycloaddition by copper catalysis, this 1,4-disubstituted 1,2,3-triazole[4]-forming "click" reaction[2] has all of the earmarks to become a premier conjugation method for protected and unprotected carbohydrates. Application of this protocol to carbohydrate substrates has recently begun and most of the reports are concerned with the use of anomeric azides.[55,56] However, introduction of a spacer between the sugar moiety and the protein is required and currently available methods will not enable us to do so. Also it would be advantageous if the linker is at the terminus of the saccharide chain, the conjugation reaction must proceed at equimolar ratio, should not yield offensive by-products and the method should enable recovery or the removal of the unreacted conjugation partners.

Recently, it was found that inhibition of hemagglutination by dimeric saccharides synthesized *via* cross metathesis reaction was superior compared to their corresponding monomeric glycosides.[55d] Apart from the synthetic promise, triazole moieties are also interesting conjugation entities as they are proven to be relatively stable to metabolic degradation and the triazole ring also can participate in the hydrogen bonding, which can be excellent in the context of biomolecular targets and solubility.[57] In view of the above facts, fascinating biological significance and continued interest[56a] in the application of "click" chemistry to carbohydrate substrates prompted us to develop an efficient procedure for the conjugation of oligosaccharides to oligosaccharides/amino acids (Figure 10).

In our approach towards the chemical ligation of carbohydrates to carbohydrates/peptides, we employed Huisgen's 1,3 -dipolar cycloaddition reaction between terminal alkynyl (**1**) and azidoethyl (**2**) glycosides in the presence of CuI to obtain 1,2,3-triazole bridged homo- and hetero- dimeric oligosaccharides (**3)** (Figure 10).[56c]

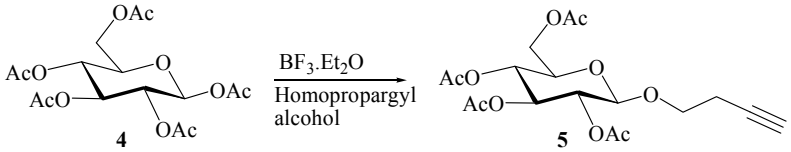
Figure 10



To begin our investigation, our approach required homopropargyl glycoside and azidoethyl glycoside precursors for the 1,3-dipolar cycloaddition which were synthesized by standard procedure. For a pilot study, we synthesized 3-butynyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (**5**) as an alkyne component using a $BF_3.Et_2O$ mediated glycosylation.[58] Accordingly, commercially available and stable penta-*O*-acetyl-β-D-glucopyranoside (**4**) has been reported to react with homopropargyl alcohol (3-5 mole equivalent) in the presence of $BF_3.Et_2O$ (2-5 mole equivalents) to form corresponding 3-butynyl 2,3,4,6 tetra-*O*-acetyl-*β*-D-glucopyranoside (**5**) (Scheme 19).

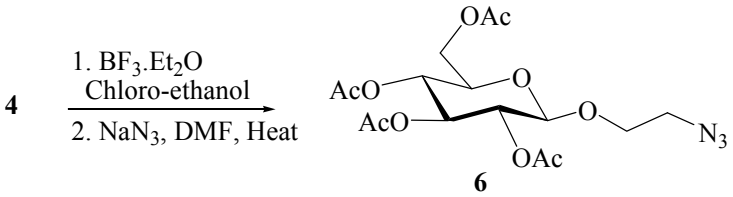
The ^1H NMR spectrum of **5** showed the appearance of the anomeric proton at δ 4.58 ppm as a doublet with coupling constant of J = 7.80 Hz and the acetylenic methine proton at δ 1.97 ppm as a triplet (J = 2.63 Hz) integrating for one proton along with the presence of all other proton resonances in complete agreement with the assigned structure. In the ^{13}C NMR spectrum of compound **5,** anomeric carbon was evident at δ 100.51 ppm whilst all the other resonances were in complete agreement with that of assigned structure. Furthermore, the DEPT NMR spectrum of compound **5** unambiguously confirmed the presence of three $-CH_2-$ groups (inversely intense) by showing the resonance at δ 19.4, 61.6, 67.7 ppm. In addition, structure of **5** was determined in the course of data comparison with the literature reports and by means of mass spectral [MALDI-TOF spectrum shows relative intense peak at 423.90 (M^+ + 23; Calcd for $C_{18}H_{24}O_{10}$: 400.38)] and elemental analysis data as well. IR spectrum of compound **5** showed the acetylenic -CH transmittance at 3269 cm^{-1} and carbonyl stretches at 1745 cm^{-1}.

Scheme 19



The other coupling partner for Huisgen's 1,3-dipolar cycloaddition, 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (**6**) was synthesized in two steps from penta-*O*-acetyl-*β*-D-glucopyranoside (**4**). Firstly, per-*O*-acetylated 2-chloroethyl *β*-D-glucoside was synthesized from **4** which was subsequently converted to azido derivative (**6**) using NaN_3 in anhydrous DMF at 80 ^oC for 12 h (Scheme 20).

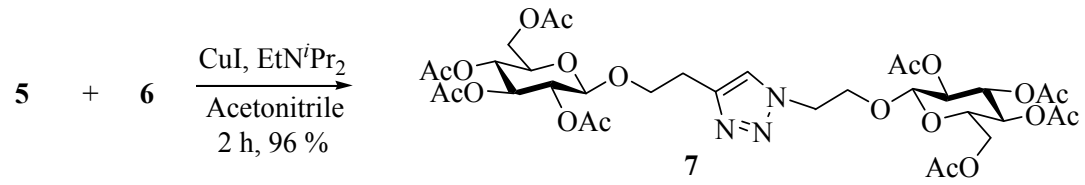
Scheme 20



The ^1H NMR spectrum of compound **6** showed the characteristic resonances corresponding to anomeric proton at δ 4.60 ppm as a doublet with coupling constant of J = 7.81 Hz and at the same time resonances due to four acetyl groups were observed at δ 2.01, 2.03, 2.05 and 2.09 ppm along with the other proton resonances in the complete agreement with the assigned structure. In the ^{13}C NMR spectrum of compound **6,** the anomeric carbon was identified at δ 100.4 ppm and the azido-methylene group was noticed at δ 50.3 ppm along with other resonances in accordance with the assigned structure. Furthermore, the DEPT NMR spectrum of **6** unambiguously confirmed the presence of three inversely intense methylene groups ($-CH_2-$) by showing resonances at δ 50.3, 61.6, 68.4 ppm along with all other signals in accordance with the assigned structure. In addition to this, compound **6** gave satisfactory elemental analysis and molecular weight [m/z: 457.88 (M^+ + 39 for K)]. The presence of azido group was also evident from the IR spectrum wherein transmittance due to the azido group was observed at 2102.26 cm^{-1}.

In the early effort, we planned to utilize the copper mediated azide alkyne cycloaddition (CuAAC) between sugar and peptide derived terminal alkyne and azide for chemical ligation of carbohydrates to carbohydrates/peptides to make *pseudo*-oligosaccharides and amino acid glycoconjugates. After successful preparation of two coupling partners, we utilized 3-butynyl 2,3,4,6 tetra-*O*-acetyl-*β*-D-glucopyranosidel (**5**) and 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (**6**) for the synthesis of *pseudo*-oligosaccharide using click reaction. The crucial Huisgen's 1,3-dipolar cycloaddition carried-out between carbohydrate derived alkyne (**5**) and azide (**6**) in acetonitrile using stoichiometric amount of CuI in the presence of *N,N*-diisopropylethylamine.[59] Huisgen reaction was found to be highly regioselective yielding 1,4-disubstituted 1,2,3-triazole containing *pseudo*-oligosaccharide (**7**) in 96 % yield (Scheme 21).

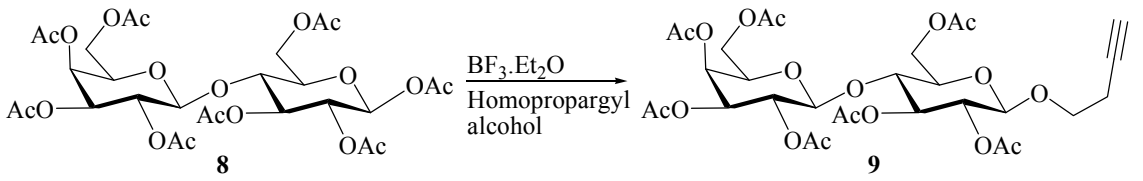
Scheme 21



The ^{1}H NMR spectrum of *pseudo*-disaccharide **7** showed resonances corresponding to the acetyl group between δ 1.95 ppm and 2.10 ppm as singlets, allylic methylene resonances were observed at δ 3.00 ppm (t, 2 H, J = 6.53 Hz) and at the same time the characteristic resonances corresponding to the olefinic proton associated with the 1,2,3-triazole moiety was identified δ 7.43 ppm as a singlet along with other resonances in accordance with the assigned structure. The ^{13}C NMR spectrum of compound **7** confirmed the presence of conjugated product as the two anomeric carbons were identified at δ 100.4 and 100.2 ppm and olefinic carbons of triazole part were characterized at δ 123.2 and 143.8 ppm. The DEPT spectrum revealed that the resonances at δ 143.8 were absent (a quarternary olefinic carbon) along with inversely phased signals attributable to six methylene (-CH_2-) groups (δ 26.0, 49.5, 61.4, 61.6, 67.5 and 68.4 ppm) thereby confirming the product. In addition, the structure of conjugated product **7** was established by means of elemental and mass spectral analysis [MALDI-TOF: mol wt calcd 817.75, Found 840.83 (M^+ + 23 for Na)]. Moreover, IR spectrum of **7** revealed the absence of characteristic transmittance due to acetylenic -CH and azido group at 3269 cm^{-1} and 2102 cm^{-1} respectively.

In continuation of above stated protocol for the chemical ligation of oligosaccharides, we did an initial substrate compatibility survey using various carbohydrate derived alkynyl (**9**) and azidoalkyl (**10** and **12**) saccharides. During the progress of this endeavor, we synthesized 3-butynyl per-*O*-acetyl-*β*-D-lactopyranoside (**9**) and 2-azidoethyl per-*O*-acetyl-*β*-D-lactopyranoside (**10**) using aforementioned procedure.[58] Accordingly, *β*-D-lactopyranose octaacetate (**8**) was reacted with homopropargyl alcohol (1.2 mole equivalent) in dry dichloromethane at room temperature using $BF_3.Et_2O$ (1.5 mole equivalent) for 2 h to obtain 3-butynyl hepta-*O*-acetyl-*β*-D-lactopyranoside (**9**) in good yield (Scheme 22).[58] Formation of the undesired *α*-anomer was not observed by TLC and ^{1}H NMR. Compound **9** was characterized by the appearance of the resonances corresponding to the acetyl group between δ 1.95 ppm and 2.16 ppm as singlets, whilst anomeric proton was identified at δ 5.35 as a doublet (J = 3.24 Hz) integrating for one proton along with all other proton resonances in accordance with the assigned structure.

Scheme 22

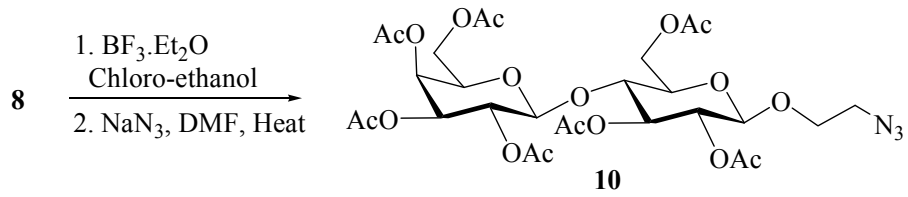


8 **9**

Furthermore, the ^{13}C NMR spectrum of compound **9** showed the characteristic resonances of two anomeric carbons at δ 100.4 and 100.9 ppm and seven carbonyl resonances were noticed at δ 169.0, 169.5, 169.7, 169.9, 170.0, 170.2, 170.2 ppm, whilst all the other resonances were in complete agreement with the assigned structure. The DEPT spectrum of compound **9** revealed the presence of four inversely phased signals attributable to methylene (-CH_2-) groups (δ 19.7, 60.7, 61.2, 67.8 ppm) thereby confirming the product. In addition, the structure of product **9** was recognized by means of elemental and mass spectral analysis [MALDI-TOF: mol wt calcd 688.63, found 711.28 (M^+ + 23 for Na)]. Moreover**,** IR spectrum of **9** showed the acetylenic -CH transmittance at 3284 cm^{-1} and carbonyl stretches at 1747 cm^{-1}.

Likewise, 2-azidoethyl per-*O*-acetyl-*β*-D-lactopyranoside (**10**) was synthesized from *β*-D-lactopyranose octaacetate (**8**) in two steps. Firstly, 2-chloroethyl per-*O*-acetyl-*β*-D-lactopyranoside was prepared from **8** using aforementioned $BF_3.Et_2O$ mediated glycosylation, which was subsequently converted to azido derivative (**10**) using NaN_3 in anhydrous DMF at 80 ^oC for 16 h (Scheme 23).

Scheme 23



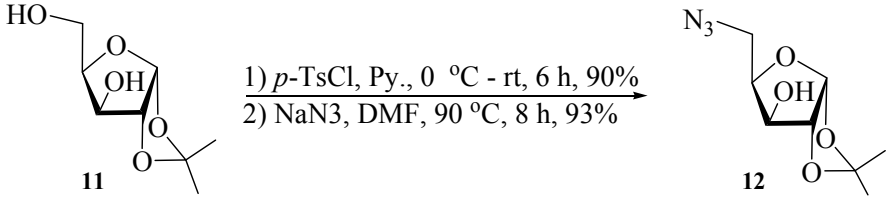
10

The ^1H NMR spectrum of compound **10** showed the characteristic resonances corresponding to anomeric proton at δ 5.35 ppm as a doublet with a coupling constant of J = 3.02 Hz and at the same time resonances due to the acetyl group were observed between δ 1.97 ppm and 2.16 ppm as singlets along with the other proton resonances in complete agreement with the assigned structure. In the ^{13}C NMR spectrum of compound **10**, seven carbonyl resonances were noticed at δ 169.0, 169.7, 169.7, 170.0, 170.1, 170.3, 170.3 ppm, whilst the anomeric carbon was identified at δ 100.7 and 100.8 ppm and the azido methylene group was noticed at δ 42.3 ppm along with other resonances in accordance with the assigned structure. Furthermore, the DEPT NMR spectrum of lactoside **10** unambiguously confirmed the presence of four -CH_2- groups (inversely intense) by showing the resonances at δ 42.3, 60.7, 61.7, 69.9 ppm along with all other signals accordance with the assigned structure. The presence of azido

group was also evident from the IR spectrum wherein transmittance due to the azido group was observed at 2108 cm^{-1}. In addition to this, compound **10** gave satisfactory elemental analysis and MALDI-TOF: mol wt calcd 698.29, found 721.43 (M^+ + 23 for Na).

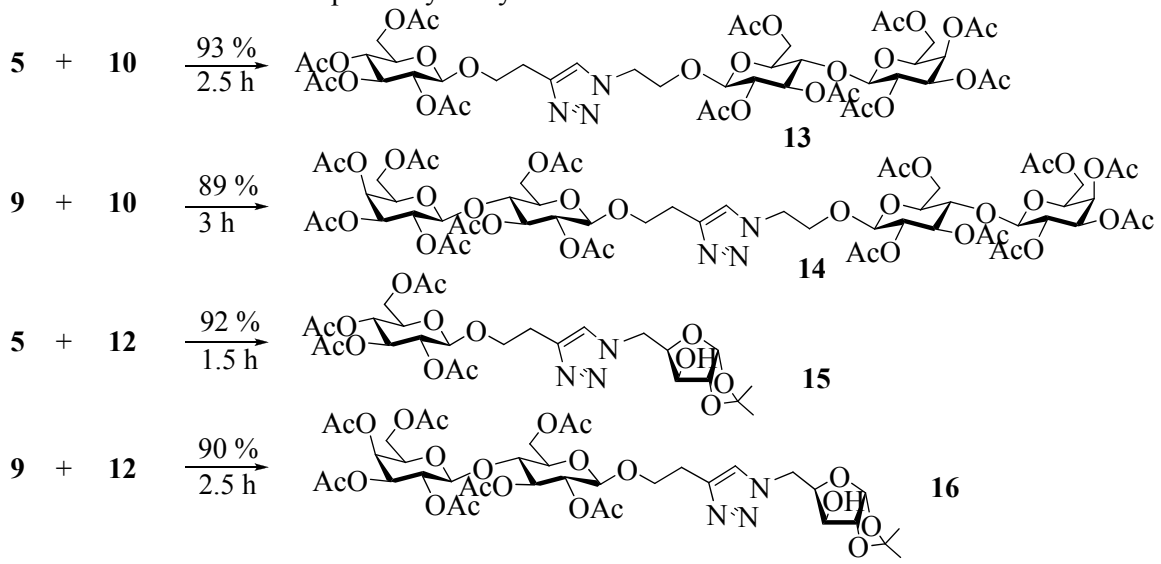
In another set of reactions, 5-*deoxy*-5-azidoxylofuranoside (**12**) was prepared by literature procedure.[56a] It involves synthesis of *α*-D-xylofuranose derived 5-*O*-tosylate by treating 1,2-*O*-isopropylidene-*α*-D-xylofuranose (**11**) with *p*-tosyl chloride in pyridine at 0 ^oC for 6 h in 90% yield. Subsequently, Xylofuranose tosylate was transformed into 5-deoxyazidoxylofuranoside (**12**) by S_N2 displacement of tosyl group in the presence of NaN_3 in 93% yield (Scheme 24). The azido substrate (**12**) showed characteristic stretching peak for azide group in IR spectrum at 2104 cm^{-1}.

Scheme 24



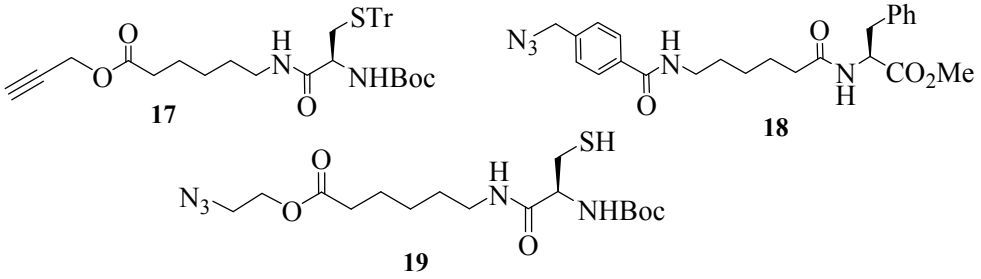
As depicted in Figure 10, we could extrapolate our efforts to conjugate *gluco*-, *lacto*- and *xylo*- derived alkynes and azides to 1,2,3-triazole conjugated oligosaccharides (**13-16**) successfully. It is worth mentioning here that present Huisgen's 1,3-dipolar cycloaddition reaction between carbohydrate derived alkynes and azides resulted in the formation of respective 1,4-disubstituted 1,2,3-triazole containing *pseudo*-oligosaccharide (**13-16**) in highly regioselective manner and in excellent yields (Scheme 25). The structures of all conjugated products were established by ^1H, ^{13}C, DEPT NMR, elemental and mass spectral analysis.

Scheme 25: Substrate compatibility study



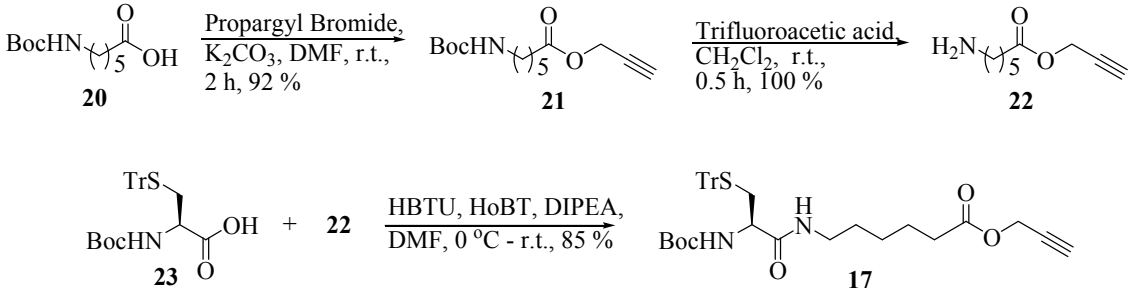
Our next endeavors were devoted towards ligating oligosaccharides to amino acid derived azides and alkynes. We anticipate that the current attempt will play a pivotal role in the chemical ligation of amino acid derived alkyne/azides. In our continuing and systematic studies, we chose to perform the 1,3-dipolar cycloaddition between carbohydrate derived alkyne/azides with peptides containing an azide/alkyne. Towards this, we have designed and synthesized alkynyl (**17**) and azide (**18**, **19**) containing peptides using the traditional *tert*-Boc chemistry and utilized them in the "click chemistry" guided conjugation reaction successfully. The reactive site (azide or alkyne) was separated from the cysteine or phenyl alanine by a 6-aminocaproic acid linker (Figure 11).

Figure 11: Peptide building blocks



The synthesis of peptide building block containing acetylenic terminal group (**17**) started with the esterification of commercially available *tert*-butoxycarbonyl protected amino caproic acid **20** with propargyl bromide in the presence of potassium carbonate and DMF at room temperature for 2 h to afford propargyl ester **21** in 92 % yield (Scheme 26). After usual work-up, the product was isolated by silica gel column chromatography using light petroleum ether (boiling range 60-80 ^{o}C) and ethyl acetate.

Scheme 26



In the ^{1}H NMR spectrum of compound **21**, resonances corresponding to *tert*-butoxy group were noticed at δ 1.44 ppm as a singlet (9 H) and those of acetylenic proton were characterized at δ 2.51 ppm as a triplet with a coupling constant of J = 2.47 Hz along with other resonances in accordance with the assigned structure. In the ^{13}C NMR spectrum of compound **21**, *tert*-butoxycarbonyl group was confirmed by the resonances at δ 155.6 ppm and

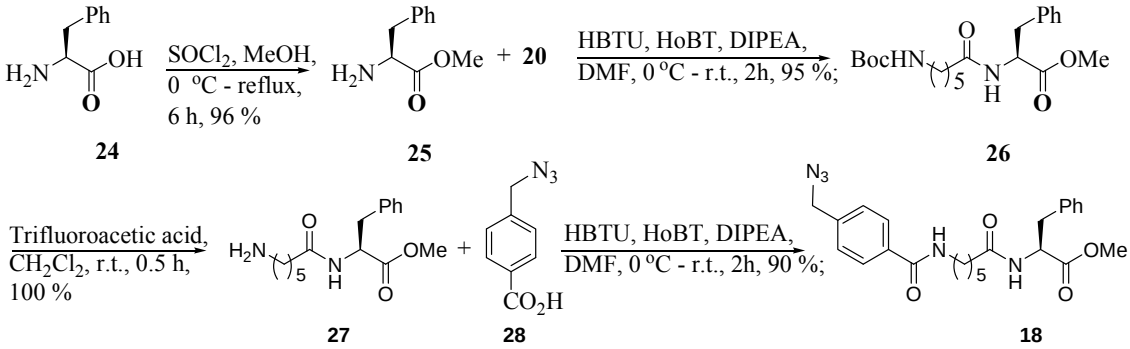
at the same time resonances of the ester group was observed at δ 172.1 ppm besides all other resonances in accordance with the assigned structure. In addition, the DEPT spectrum confirmed the presence of six inversely intense methylene groups (-CH_2). Furthermore, compound **21** gave satisfactory elemental analysis and IR spectrum showed the acetylenic -CH transmittance at 3297 cm^{-1} and carbonyl stretches at 1705 cm^{-1}.

Subsequently deprotection of *tert*-butoxycarbonyl group (*Boc*) from propargyl ester **21** was effected using trifluoroacetic acid and after the basic work up, the free amine **22** was directly used for the next step without any further purification. BocCys(Tr)COOH (**23**) was prepared by literature reported methods whose spectral characteristics matched with those of reported values.[60] The crucial peptide coupling reaction[60] was carried out between BocCys(Tr)COOH **23** and amine **22** prepared *vide supra* in the presence of HBTU/DIPEA/HoBT as the activating reagent to furnish the desired peptide **17** in 85 % yield (Scheme 26). In the ^{1}H NMR spectrum of peptide **17,** resonances corresponding to the *tert*-Boc group and trityl moiety were present respectively at δ 1.41 and 7.18-7.50 ppm whilst acetylenic methine proton was characterized at δ 2.47 ppm as a triplet (J = 2.24 Hz) along with all other resonances in accordance with the assigned structure.

In the ^{13}C NMR spectrum of compound **17**, three carbonyl resonances were noticed at δ 172.0, 170.0, 154.9 ppm, carbons of trityl group appeared around δ 126.38-129.16 ppm and δ 144.14 ppm whilst resonances corresponding to the *tert*-butoxy carbonyl group were identified at δ 154.9 ppm. Furthermore, in the DEPT spectrum of compound **17**, seven inversely intense methylene groups were noticed and at the same time, nine quarternary carbons (absent from ^{13}C NMR) were identified. In addition to this, compound **17** gave satisfactory elemental analysis and molecular weight [m/z: 637 (M^+ + 23)] whilst IR spectrum showed the acetylenic -CH transmittance at 3297.99 cm^{-1}, carbonyl stretches at 1705.09 cm^{-1} and amide group at 1668.30 cm^{-1}.

The synthesis of the azide containing coupling partner for the click reaction commenced with the esterification of phenyl alanine (**24)** using thionyl chloride in the presence of methanol at 0 ^{o}C to reflux for 6 h. The reaction mixture was carefully evaporated *in vacuo* to obtain the methyl ester of phenyl alanine as a hydrochloride salt that was neutralized using triethyl amine to afford the free amine **25** and directly used in the next step. Commercially available *tert*-butoxycarbonyl protected amino caproic acid **20** was coupled with methyl ester of phenyl alanine (**25)** in the presence of HBTU/DIPEA/HoBT/DMF (0 ^{o}C - room temperature) as a coupling reagent in order to obtain the *tert*-Boc-protected dipeptide **26** in 95 % yield (Scheme 27).

Scheme 27



24 **25** **26** **27** **28** **18**

In the ^{1}H NMR spectrum of dipeptide **26**, resonances corresponding to the methyl ester were noticed at δ 3.69 ppm as a singlet integrating for three protons, *tert*-Boc group was observed at δ 1.43 ppm and methylenes at δ 1.25, 1.57, 2.16 ppm as multiplets integrating for six protons. In the ^{13}C NMR spectrum of compound **26**, resonances corresponding to the *tert*-Boc group appeared at δ 27.9 ppm, aromatic signals were noticed around 126.4-135.9 ppm and resonances corresponding to the *tert*-butoxycarbonyl group were identified at δ 155.6 ppm whilst two other carbonyl groups were characterized at δ 171.8, 172.3 ppm. DEPT spectrum of dipeptide **26** revealed the presence of seven methylene groups (inversely intense) and eight quarternary carbons (absent in the DEPT spectrum when compared with ^{13}C NMR). Furthermore, compound **26** was confirmed by IR and CHNS analysis.

tert-Boc group of compound **26** was deprotected using trifluoroacetic acid in CH_2Cl_2, was neutralized using triethylamine to obtain the free amine **27** that was directly used in the next step without further purification. The next step involves the introduction of azido carboxylic acid as an amide linkage. After a lot of unsuccessful attempts with bromoacetyl bromide, bromoacetyl chloride and bromoacetic acid under variety of conditions, finally it was thought to utilize 4-azidomethyl benzoic acid (**28**) which in turn can be synthesized from *p*-toluoic acid.[7] Accordingly, *p*-toluoic acid was subjected to photochemical reaction using bromine under photochemical conditions in order to get 4-bromomethyl benzoic acid by literature reported method[7], which was then treated with NaN_3 in DMF to yield the 4-azidomethyl benzoic acid (**28**) in 65 % yield. The amide formation between amine **27** and acid **28** was performed using HBTU/DIPEA/HoBT/DMF at 0 °C to room temperature for 2 hr to obtain the dipeptide **18** in 90 % yield.

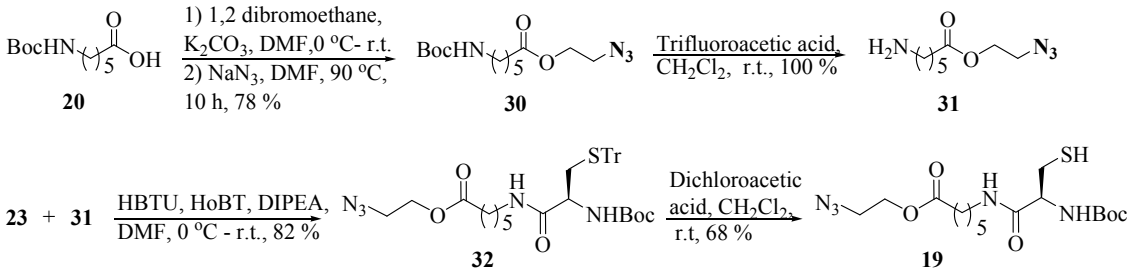
In the ^{1}H NMR spectrum of dipeptide **18**, characteristic resonances for methyl ester group were recognized at δ 3.69 ppm as a singlet and azidobenzylic -CH_2 group was noticed at δ 4.38 ppm as a singlet integrating for two protons along with all other resonances in accordance with the assigned structure. Furthermore, the ^{13}C NMR and DEPT spectra of **18**

unambiguously confirmed the presence of seven inversely intense methylene groups (-CH_2) and six quarternary carbons (absent in the DEPT spectrum when compared with ^{13}C NMR). IR spectrum of dipeptide **18** confirmed the presence of azido group by showing transmittance at 2092.62 cm^{-1}. In addition to this, compound **18** gave satisfactory elemental analysis and molecular weight (m/z) as 474.06 (M^+ + 23).

The other azide containing peptide (**19**) was synthesized in two steps, started with the esterification of commercially available *tert*-butoxycarbonyl protected amino caproic acid (**20)** with 1,2 dibromoethane in the presence of 2.5 equivalent of potassium carbonate and DMF at room temperature for 3 h to afford corresponding bromoethyl ester **29**, followed by subsequently conversion of bromoethyl derivative (**29**) to azido derivative (**30**) using NaN_3 in anhydrous DMF at 80 ^oC for 10 h gives 78 % of overall yield after two steps**.** Consequently removal of *tert*-Boc group from **30** was effected using trifluoroacetic acid and after the basic work up, the free amine **31** was directly used for the next step without any further purification. Next, coupling reaction was carried out between acid **23** and amine **31** prepared *vide supra* using standard reaction conditions (HBTU/DIPEA/HoBT) furnished the preferred peptide **32** in 82 % yield (Scheme 28).

The ^1H NMR spectrum of dipeptide **32** showed the resonances corresponding to the *tert*-Boc group and trityl moiety at δ 1.41 and 7.15-7.44 ppm respectively with all other resonances in accordance with the assigned structure. In the ^{13}C NMR spectrum of compound **32**, resonances corresponding to the *tert*-Boc group identified at δ 27.9 ppm, *tert*-butoxycarbonyl was observed at δ 155.6 ppm whilst two other carbonyl groups were characterized at δ 170.1 and 172.7 ppm. Furthermore, the DEPT spectrum of **32** confirmed the presence of eight -CH_2 groups (negative intensity) and eight quarternary carbons as compared with ^{13}C NMR. In addition to this, compound **32** gave satisfactory elemental analysis and molecular weight [m/z: 668.19 (M^+ + 23)] whilst IR spectrum showed transmittance due to azido group at 2106.12 cm^{-1}, carbonyl stretches at 1703.03, 1737.74 cm^{-1} and amide group at 1666.38 cm^{-1}.

Scheme 28



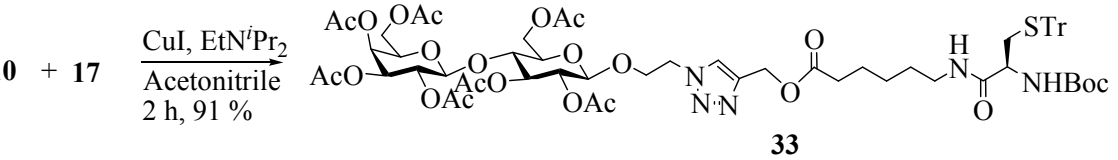
Selective deprotection of the *trityl* group in presence of *tert*-Boc in compound **32** under a number of conditions was unsuccessful. After a lot of efforts, *trityl* group in compound **32** was selectively removed by using stoichiometric amount of dichloroacetic acid in CH_2Cl_2 to produce corresponding free thiol containing dipeptide (**19**), which was purified by conventional silica gel chromatography in 68% yield (Scheme 28).

The ^{1}H NMR spectrum of **19** showed the characteristic resonances corresponding to *tert*-butoxy group at δ 1.46 ppm as a singlet integrating for nine protons along with the other resonances in accordance with the assigned structure. In the ^{13}C NMR spectrum of compound **19**, *tert*-butoxy group was confirmed by showing the resonances at δ 28.2 ppm and at the same time, carbonyl groups were observed at δ 155.5, 169.9 and 173.1 ppm for *tert*-butoxycarbonyl, amide and ester groups respectively. The DEPT NMR study of compound **19** unambiguously proved the presence of eight methylene groups (inversely intense) and absence of four quarternary carbons (compared with ^{13}C NMR) confirmed the assigned structure. In addition to this, compound **19** gave satisfactory elemental analysis and molecular weight [m/z: 426.10 (M^+ + 23)]. IR spectrum of **19** showed transmittance due to azido group at 2108.05 cm^{-1}, carbonyl stretches at 1731.96, 1704.96 cm^{-1} and amide group at 1662.52 cm^{-1}.

After the successful preparation of peptide derived alkyne (**17**) and azides (**18**, **19**), we thought of extending the chemical ligation procedure to these amino acid derived alkyne/azide (**17-19**) with carbohydrate alkyne/azide (**5**, **6**, **9**, **10**) in different combinations. Accordingly, azidoethyl lactoside (**10**) was reacted with amino acid anchored alkyne (**17**) in the presence of CuI to obtain the ligated glycoconjugate **33** in 91% yields (Scheme 29). In the ^{1}H NMR spectrum of compound **33**, resonances corresponding to the seven acetyl groups were noticed between δ 1.96 and 2.15 ppm and that of *tert*-butoxy group were characterized at δ 1.41 ppm as a sharp singlet integrating for nine protons. Also, the characteristic resonances corresponding to the olefinic proton of 1,2,3-triazole were identified at δ 7.63 ppm as a singlet and at the same time, anomeric proton resonances of lactose moiety were observed at δ 5.35 as a doublet (J = 3.45 Hz) along with all other proton resonances in accordance with the assigned structure. In the ^{13}C NMR spectrum of compound **33**, the anomeric carbons were noticed at δ 100.2 and 100.8 ppm, aromatic carbons were observed from δ 126.7 to 129.4 ppm. In addition to this, DEPT spectrum revealed the presence of eleven -CH_2 groups (inversely intense) thereby confirming the conjugated product. Furthermore, characteristic resonances corresponding to olefin carbons of 1,2,3-triazole ring were observed at δ 124.7 and 142.5 (quarternary) ppm along with all other resonances in accordance with the assigned structure. IR spectral analysis of **33** showed carbonyl stretches at 1751 cm^{-1} and that of amide at 1670 cm^{-1}. In addition,

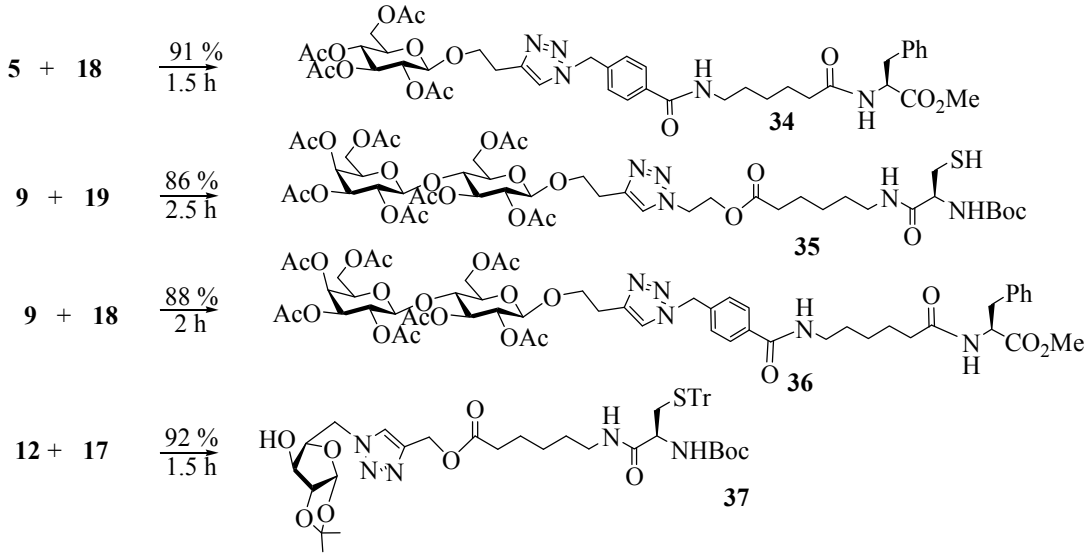
glycoconjugate **33** gave satisfactory elemental analysis and molecular weight [m/z: 1345.44 (M^+ + 23)].

Scheme 29: Synthesis of Amino acid Glycoconjugates



Furthermore, the ligation protocol was exploited successfully to other amino acid-derived azides (**18** and **19**) and synthesized various glycoconjugates (**34**-**37**) (Scheme 30). It is significant to mention that present 1,3-dipolar cycloaddition reaction between carbohydrate derived alkyne/azides and amino acid derived alkyne/azides resulted in the formation of respective 1,4-disubstituted 1,2,3-triazole containing amino acid glycoconjugates (**34-37**) in highly regioselective manner and in excellent yields. The structures of all conjugated products were established by ^{1}H, ^{13}C, DEPT NMR, elemental and mass spectral analysis.

Scheme 30: Substrate compatibility study



In summary, we have developed a practical procedure for the ligation of oligosaccharides to oligosaccharides/peptides under neutral reaction conditions.[56c] We anticipate that the 1,2,3-triazole containing dimeric saccharides and amino acid glycoconjugates may show a variety of bioactivities as several compounds containing 1,2,3-triazoles display broad spectra of biological activities including antibacterial, herbicidal and fungicidal, antiallergic, and anti-HIV. A combination of different monosaccharide and peptide building blocks has been showed and should potentially give rise to a large number of *pseudo*-oligosaccharides and amino acid glycoconjugates.

*****

General Experimental procedure for Click reaction:[59]

To a solution of an alkyne (1 mmol) and an azide (1 mmol) in 10 mL of anhydrous acetonitrile was added CuI (2 mmol) and *N,N*-diisopropylethylamine (3 mmol) at room temperature and stirred for specified time. At the end of the reaction as judged by the TLC analysis, the reaction mixture was diluted using 25 mL of water and 10 mL of NH_4Cl, the aqueous layer was extracted with ethyl acetate (3 x 50 mL), combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and concentrated *in vacuo* to obtain a crude residue which was purified by silica gel column chromatography using a gradient of ethyl acetate and petroleum ether (60-80 ^oC) to obtain the desired 1,4-disubstited 1,2,3-triazole as white solid.

General experimental Procedure for N-*tert*-Boc protection:[60]

To a solution of Amino Acid (1 mmol) in 70:25 mL dioxane-water at 0 ^oC was added NaOH (2.5 mmol) in 15 ml water and stirred for 15-20 minutes at 0 ^oC. The reaction mixture was stirred for 20 min and di-*tert*-butyl pyrocarbonate (1 mmol) was added dropwise for half an hour. Stirred the reaction mixture for 3 hours and concentrated the reaction mixture *in vacuo* and again cooled to 0 ^oC. To the crude reaction mixture, 60 mL of ethyl acetate and 50 ml of water and adjusted the pH to 2-3 using $KHSO_4$. The solution was transferred to separating funnel and extracted with ethyl acetate (3 x 50 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated *in vacuo* to get *tert*-Boc protected amino acid in good yield.

General experimental Procedure for propargyl ester:

To a solution of Boc Protected amino acid (1 mmol) prepared *vide supra* in 10 mL of anhydrous *N,N*-dimethylformamide at 0 ^oC was added K_2CO_3 (2.5 mmol), propargyl bromide (1.53g, 1.5 mmol) and stirred for 2 h at room temperature. At the end of the reaction (monitored by TLC), 50 ml of water was added and extracted the aqueous layer with ethyl acetate (3 x 50 mL), combined organic layers were washed with water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo* to obtain a residue which was directly used for next step without further purification.

General experimental Procedure for *tert*-Boc protection:[60]

To a solution of compound Boc protected amino acid (1 mmol) in 10 mL of CH_2Cl_2 at 0 ^oC, 50 % TFA in 5 mL of CH_2Cl_2 was added, stirred at room temperature for 0.5 h. The

reaction mixture was poured into a separatory funnel and work up using triethyl amine was carried out to obtain free amine that was directly used for the next step without any further purification.

General experimental Procedure for peptide coupling: [60]

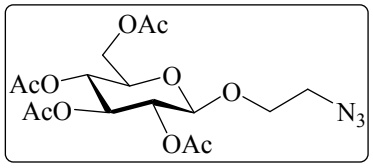
To a solution of *N*-protected amino acid (1 mmol) prepared *vide supra* in 10 mL of anhydrous *N,N*-dimethylformamide at 0 ^{o}C was added HBTU (1.2 mmol), HoBt (1.2 mmol) and DIPEA (1.2 mmol). After 10 minutes, free amine containing compound (1.1 mmol) in 10 mL of DMF was introduced at 0 ^{o}C and stirred for 2 hours at room temperature. At the end of the reaction as judged by TLC, 50 mL of water was added and extracted the water layer with ethyl acetate (3 x 50 mL), washed the combined organic layer with water (2 x 20 mL), combined organic layers were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using ethyl acetate and light petroleum ether mixture to afford desired dipeptide.

Preparation of 4-azido-methyl benzoic acid:[61]

According to the literature reported method, *p*-toluoyl chloride was prepared by refluxing, *p*-toluic acid (13.6g, 0.1 mmol) with thionyl chloride (12 mL) untill the free acid dissolved completely. The resulting solution was heated to 160 ^{o}C to remove excess thionyl chloride. Liquid bromine was added dropwise to the *p*-toluoyl chloride in a beaker at 160 ^{o}C untill the uptake of bromine (15.8g, 0.1 mmol) corresponded to 2 gram-atoms per mole of acid chloride. The bromination was done under bright tungusten illumination. The resulting ω-bromo-*p*-toluoyl bromide hydrolyzed with 85% formic acid (50 mL) by heating on the steam bath to approximately 40 ^{o}C. The excess formic acid was then allowed to evaporate leaving 21g of crude ω-bromo-*p*-toluic acid.

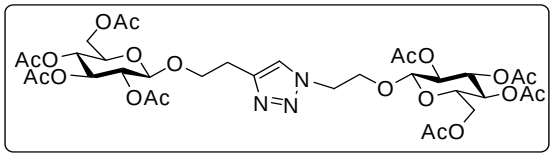
To a solution of ω-bromo-*p*-toluic acid (1g, 4.6 mmol) in DMF, was added sodium azide (3g, 46.5 mmol) and refluxed for 6h at 80 ^{o}C. At the end of reaction as adjudged by TLC examination, the reaction mixture was cooled to room temperature, 50 mL of water was added and the reaction mixture was extracted with ethyl acetate (3 x 50 mL), washed the combined organic layer with water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. The resulting crude residue was purified by silica gel column chromatography using ethyl acetate and petroleum ether mixture (1:1) to obtain the 4-azido-methyl benzoic acid (0.52g, 65%) as a solid.

2-Ethyl azido 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (6):



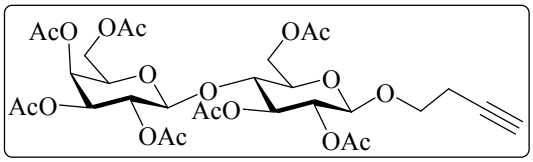
$[\alpha]_D^{25}$ = -20.13 (*c,* 1.20, $CHCl_3$); IR ($CHCl_3$): 2102.26, 1758.96, 1747.39, 1731.96, 1226.60 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 2.01, 2.03, 2.05, 2.09 (4 s, 12H), 3.29 (ddd, 1H, *J* = 3.46, 4.81 Hz), 3.51 (ddd, 1H, *J* = 3.50, 8.20 Hz), 3.64-3.76 (m, 2H), 3.99-4.09 (m, 1H), 4.16 (dd, 1H, *J* = 2.59, 12.21 Hz), 4.29 (dd, 1H, *J* = 4.61, 12.29 Hz), 4.60 (d, 1H, *J* = 7.81 Hz), 4.98-5.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3, 20.3, 20.4, 20.5, 50.3, 61.6, 68.1, 68.3, 70.8, 71.7, 72.5, 100.4, 169.1, 169.1, 170.0, 170.1; CHNS Anal. Calcd for $C_{16}H_{23}N_3O_{10}$: C, 46.04; H, 5.55; N, 10.07; O, 38.33; Found: C, 46.39; H, 5.62; N, 10.12; MALDI-TOF: mol wt calcd for $C_{16}H_{23}N_3O_{10}$: 417.37; Found 457.88 (M^+ + 39 for K).

Characterization data of compound 7:



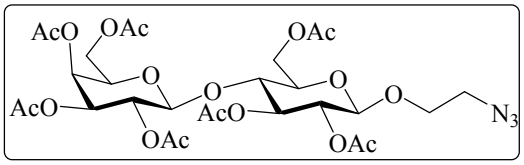
m.p. = 115-118 °C; $[\alpha]_D^{25}$ = -15.30 (*c,* 1.10, $CHCl_3$); IR (Nujol film): 1753 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.95, 2.00, 2.02, 2.09 (4s, 24H), 3.00 (t, 2H, *J* = 6.53 Hz), 3.72 (m, 2H), 3.89 (m, 2H), 4.07-4.33 (m, 6H), 4.45-4.58 (m, 4H), 4.90-5.25 (m, 6H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.2-20.5, 26.0, 49.5, 61.4, 61.6, 67.5, 67.9, 68.0, 68.5, 70.6, 70.9, 71.4, 71.6, 72.1, 72.4, 100.2, 100.4, 123.2, 143.8, 168.9, 169.0, 169.1, 169.2, 169.8, 169.9, 170.2, 170.3; CHNS Anal. Calcd for $C_{34}H_{47}N_3O_{20}$: C, 49.94; H, 5.79; N, 5.14; O, 39.13; Found: C, 50.13; H, 5.49; N, 4.92; MALDI-TOF: mol wt calcd for $C_{34}H_{47}N_3O_{20}$: 817.75; Found 840.83 (M^+ + 23 for Na).

3-Butynyl 2,3,4,6,2', 3', 6',-hepta-*O*-acetyl-*β*-D-lactopyranoside (9):



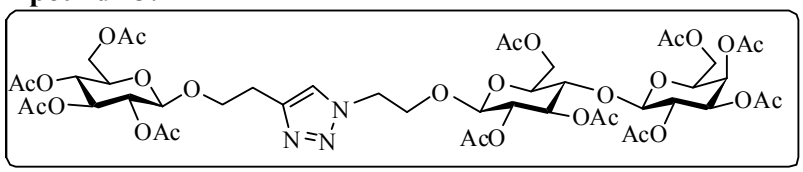
$[\alpha]_D^{25}$ = -1.79 (*c,* 1.10, $CHCl_3$); IR ($CHCl_3$): 3284.55, 1766.67, 1755.10, 1747.39, 1737.74, 1731.96, 1371.29 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.97 (t, 1H, *J* = 2.48 Hz), 1.97, 2.05, 2.05, 2.06, 2.13, 2.15, 2.15 (7 s, 21H), 2.46 (td, 2H, *J* = 6.78, 2.58 Hz), 3.58-4.08 (m, 4H), 4.12 (t, 2H, *J* = 3.56 Hz), 4.51 (t, 3H, *J* = 8.90 Hz), 4.85-5.25 (m, 6H), 5.35 (d, 1H, *J* = 3.24); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 19.7, 20.3, 20.5, 20.5, 20.5, 20.6, 20.6, 20.7, 60.7, 61.8, 66.5, 67.8, 68.9, 69.4, 70.5, 70.8, 71.3, 72.5, 72.5, 76.0, 80.4, 100.4, 100.9, 169.0, 169.5, 169.7, 169.9, 170.0, 170.2, 170.2; CHNS Anal. Calcd for $C_{30}H_{40}O_{18}$: C, 52.32; H, 5.85; O, 41.82; Found: C, 52.39; H, 5.82; MALDI-TOF: mol wt calcd for $C_{30}H_{40}O_{18}$: 688.63; Found 711.28 (M^+ + 23 for Na).

2-Ethylazido 2,3,4,6,2', 3', 6',-hepta-*O*-acetyl-*β*-D-lactopyranoside (10):



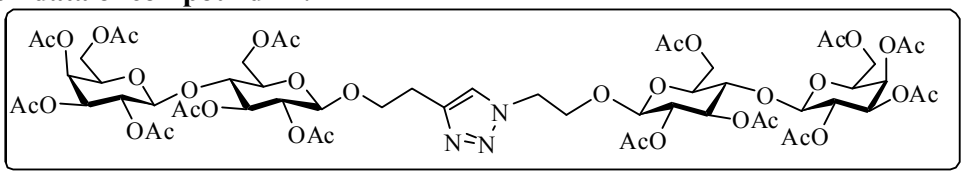
$[\alpha]_D^{25}$ = +5.12 (*c,* 1.20, $CHCl_3$); IR ($CHCl_3$): 2108.05, 1770.53, 1755.10, 1737.74, 1731.96,1714.60 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.97, 2.05, 2.05, 2.06, 2.07, 2.13, 2.16 (7 s, 21H), 3.42 (t, 1H, *J* = 4.86 Hz), 3.58-3.80 (m, 6H), 3.86 (dd, 1H, *J* = 7.05, 12.31 Hz), 4.00-5.19 (m, 3H), 4.51 (dd, 2H, *J* = 7.82, 10.17 Hz), 4.87-4.99 (m, 2H), 5.07-5.26 (m, 2H), 5.35 (d, 1H, *J* = 3.02); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.5, 20.6, 20.6, 20.6, 20.7, 20.7, 20.8, 42.4, 60.7, 61.7, 66.5, 68.6, 69.0, 69.9, 70.6, 70.9, 71.2, 72.6, 76.1, 100.7, 100.8, 169.0, 169.7, 169.7, 170.0, 170.1, 170.3, 170.3; CHNS Anal. Calcd for $C_{28}H_{39}N_3O_{18}$: C, 47.66; H, 5.57; N, 5.96; O, 40.81; Found: C, 47.71; H, 5.82; N, 6.02; MALDI-TOF: mol wt calcd for $C_{28}H_{39}N_3O_{18}$: 698.29; Found 721.36 (M^+ + 23 for Na).

Characterization data of compound 13:



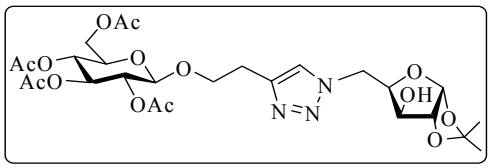
m.p. = 158-162 °C; $[\alpha]_D^{25}$ = -4.58 (*c*, 1.00, $CHCl_3$); IR (Nujol film): 1753 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.94, 1.95, 1.97, 2.00, 2.03, 2.04, 2.05, 2.06, 2.09, 2.13, 2.15 (11s, 33H), 2.99 (t, 3H, *J* = 6.48 Hz), 3.45-3.98 (m, 5H), 4.00-4.36 (m, 8H), 4.51 (m, 5H), 4.81-5.27 (m, 7H), 5.35 (d, 1H, *J* = 2.92 Hz), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.4-20.7, 26.1, 49.6, 60.6, 61.6, 61.7, 66.4, 67.7, 68.2, 68.7, 68.9, 70.5, 70.8, 71.0, 71.1, 71.6, 72.3, 72.6, 72.6, 75.9, 100.2, 100.6, 100.9, 123.3, 143.9, 168.9, 169.1, 169.3, 169.3, 169.5, 169.9, 170.0, 170.1, 170.2, 170.2, 170.5; CHNS Anal. Calcd for $C_{46}H_{63}N_3O_{28}$: C, 49.95; H, 5.74; N, 3.80; O, 40.50; Found: C, 50.01; H, 5.86; N, 3.76.

Characterization data of compound 14:



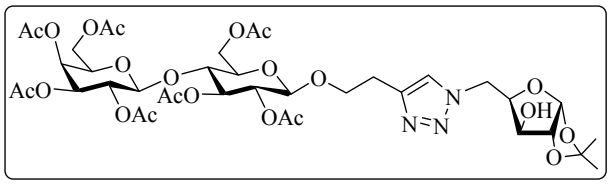
m.p. = 122-125 °C; $[\alpha]_D^{25}$ = +1.14 (*c*, 1.20, $CHCl_3$); IR (Nujol film): 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 20013 MHz): δ 1.93-2.17 (14s, 42H), 2.98 (t, 2H, *J* = 6.42 Hz), 3.59 (m, 2H), 3.72-3.91 (m, 6H), 4.00-4.20 (m, 8H), 4.32-4.61 (m, 7H), 4.81-5.23 (m, 9H), 5.34 (dd, 2H, *J* = 0.61, 3.02 Hz), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3-20.7, 26.1, 49.7, 60.6, 60.6, 61.6, 61.8, 66.4, 66.4, 67.7, 68.6, 68.9, 68.9, 70.4, 70.5, 70.6, 70.8, 70.9, 71.1, 71.4, 72.3, 72.5, 72.5, 75.8, 76.0, 100.2, 100.4, 100.8, 100.9, 123.3, 143.9, 168.8-170.5; CHNS Anal. Calcd for $C_{58}H_{79}N_3O_{36}$: C, 49.96; H, 5.71; N, 3.01; O, 41.31; Found: C, 50.20; H, 5.49; N, 3.07.

Characterization data of compound 15:



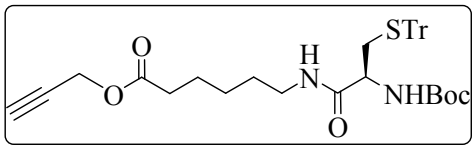
m.p. = 138-142 ^{o}C; $[\alpha]_D^{25}$ = -26.34 (*c*, 1.10, $CHCl_3$); IR (Nujol film): 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.31 (s, 3H), 1.46 (s, 3H), 1.97, 2.00, 2.03, 2.07 (4s, 12H), 3.01 (t, 2H, *J* = 6.19 Hz), 3.65-3.78 (m, 1H), 3.81 (m, 1H), 3.92 (d, 1H, *J* = 5.05 Hz), 4.07-4.20 (m, 3H), 4.28 (dd,1H, *J* = 4.81, 12.39 Hz), 4.45-4.63 (m, 4H), 4.73 (dd, 1H, *J* = 7.70, 13.43 Hz), 5.01 (dd, 1H, *J* = 9.13, 17.37 Hz), 5.12 (d, 1H, *J* = 16.30 Hz), 5.18 (ABq, 1H, *J* = 9.31 Hz), 5.99 (d, 1H, *J* = 3.41 Hz), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3, 20.4, 20.5, 20.6, 26.0, 26.2, 26.6, 48.4, 61.7, 68.2, 68.5, 71.2, 71.7, 72.5, 74.1, 79.1, 85.2, 100.6, 105.0, 111.8, 123.6, 144.3, 169.3, 169.5, 170.1, 170.6; CHNS Anal. Calcd for $C_{26}H_{37}N_3O_{14}$: C, 50.73; H, 6.06; N, 6.83; O, 36.39; Found: C, 50.44; H, 6.47; N, 6.67.

Characterization data of compound 16:



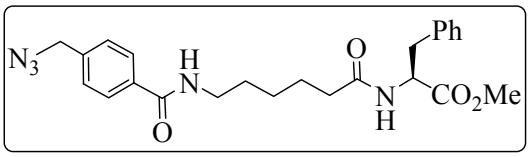
m.p. = 145-150 ^{o}C; $[\alpha]_D^{25}$ = -7.53 (*c*, 1.00, $CHCl_3$); IR (Nujol film): 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.31 (s, 3H), 1.45 (s, 3H), 1.97, 1.98, 2.05, 2.06, 2.07, 2.12, 2.16 (7s, 21H), 2.99 (t, 2H, *J* = 5.92 Hz), 3.65 (m, 1H), 3.70-3.95 (m, 4H), 4.01-4.19 (m, 5H), 4.40-4.65 (m, 6H), 4.71 (dd, 1H, *J* = 7.70, 13.38 Hz), 4.78-5.25 (m, 4H), 5.35 (d, 1H, *J* = 2.84 Hz), 5.99 (d, 1H, *J* = 3.40 Hz), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.4-20.9, 26.1, 26.3, 26.7, 48.1, 60.7, 61.8, 66.5, 68.5, 69.0, 70.6, 70.9, 71.6, 72.5, 72.6, 74.2, 76.1, 79.1, 85.2, 100.5, 101.0, 105.1, 111.9, 123.6, 144.5, 169.0, 169.7, 169.9, 170.0, 170.1, 170.3, 170.4; CHNS Anal. Calcd for $C_{38}H_{53}N_3O_{22}$: C, 50.50; H, 5.90; N, 4.65; O, 38.94; Found: C, 50.55; H, 5.67; N, 4.78.

Characterization data of compound 17:



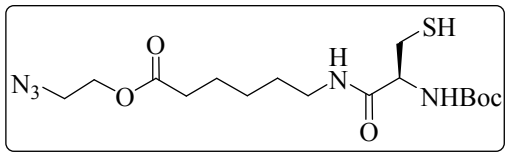
$[\alpha]_D^{25}$ = +13.26 (*c*, 1.10, $CHCl_3$); IR ($CHCl_3$): 3307.37, 1739.24, 1705.09, 1668.30, 1492.39, 1163.65, 756.10 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.25-1.34 (m, 2H), 1.41 (s, 9H), 1.38-1.50 (m, 2H), 1.62 (m, 2H), 2.30 (t, 2H, *J* = 7.32 Hz), 2.47 (t, 1H, *J* = 2.15 Hz), 2.50 (dd, 1H, *J* = 5.83, 13.18 Hz), 2.70 (m, 1H), 3.17 (q, 2H, *J* = 6.65, 13.09 Hz), 3.82 (t, 1H, *J* = 5.94 Hz), 4.65 (d, 2H, *J* = 2.21 Hz), 4.87(d, 1H, *J* = 7.18 Hz), 6.08 (t, 1H, *J* = 5.85 Hz), 7.18-7.42 (m, 15H); ^{13}C NMR (75.48 MHz, CDCl3): 23.9, 25.7, 27.9, 28.6, 33.3, 33.9, 38.7, 51.3, 53.2, 66.6, 74.7, 77.5, 79.5, 126.4, 127.6, 129.2, 144.1, 154.9, 170.0, 172.0; CHNS Anal. Calcd for $C_{36}H_{42}N_2O_5S$: C, 70.33; H, 6.89; N; 4.66 S, 5.22; Found: C, 70.29; H, 6.92; N, 4.62; S, 5.18; m/z: 637.53 (M^+ + 23 for Na).

Characterization data of compound 18:



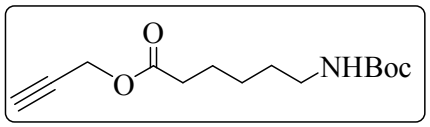
m.p. = 105 ^{0}C; $[\alpha]_D^{25}$ = +43.00 (*c*, 1.1, $CHCl_3$); IR (Nujol film): 3311.55, 2092.62, 1741.16, 1650.95, 1645.17, 1633.59, 1461.94, 1377.08 cm^{-1}; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 1.26-1.39 (m, 2H), 1.52-1.68 (m, 4H), 2.19 (t, 2H, *J* = 7.14 Hz), 3.07 (dq, 2H, *J* = 5.71, 13.80 Hz), 3.35-3.45 (m, 2H), 3.69 (s, 3H), 4.38 (s, 2H), 4.82 (t, 1H, *J* = 6.69 Hz), 7.07-7.84 (m, 9H); ^{13}C NMR (75.48 MHz, CDCl3): 24.5, 25.7, 28.4, 35.3, 37.23, 39.2, 51.7, 53.0, 53.8, 126.6, 127.2, 127.7, 128.1, 128.7, 134.1, 135.9, 138.4, 167.3, 172.0, 173.3; CHNS Anal. Calcd for $C_{24}H_{29}N_5O_4$: C, 63.84; H, 6.47; N, 15.50; Found: C, 63.86; H, 6.48; N, 15.55; m/z: 474.06 (M^+ + 23 for Na).

Characterization data of compound 19:



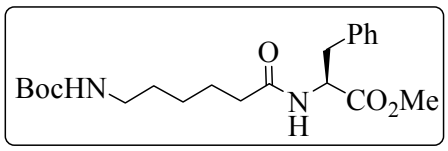
$[\alpha]_D^{25}$ = -7.59 (*c*, 1.10, $CHCl_3$); IR ($CHCl_3$): 3417.63, 3325.05, 2108.05, 1731.96, 1704.96, 1662.52, 1504.37.80, 1164.92, 754.042 cm^{-1}; ^{1}H NMR(200.13 MHz, $CDCl_3$): δ 1.25-1.42 (m, 2H), 1.46 (s, 9H), 1.51-1.58 (m, 2H), 1.59-1.76 (m, 2H), 2.37 (t, 2H, *J* = 7.36 Hz), 2.71 (ddd, 1H, *J* = 6.24, 13.76 Hz), 3.09 (ddd, 1H, *J* = 4.56, 7.58 Hz), 3.29 (q, 2H, *J* = 6.72, 12.87 Hz), 3.48 (t, 2H, *J* = 5.07 Hz), 4.25 (t, 2H, *J* = 5.18 Hz), 4.25 (dd, 1H, *J* = 1.76, 3.78 Hz), 5.48 (d, 1H, *J* = 8.35 Hz), 6.48 (t, 1H, *J* = 5.90 Hz); ^{13}C NMR (75.48 MHz, CDCl3): 24.2, 26.2, 26.9, 28.2, 29.0, 33.8, 39.2, 49.7, 55.6, 62.8, 80.5, 155.0, 170.0, 173.1; CHNS Anal. Calcd for $C_{16}H_{29}N_5O_5S$: C, 47.63; H, 7.24; N; 17.36; O, 19.83; S, 7.95; Found: C, 47.59; H, 7.29; N, 17.41; S, 7.89; m/z: 626.10 (M^+ + 23 for Na).

Characterization data of compound 21:



IR ($CHCl_3$): 3368.93, 3297.99, 1742.90, 1705.58, 1519.18, 1166.96 cm^{-1}; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 1.27-1.58 (m, 4H), 1.44 (s, 9H), 1.67 (m, 2H), 2.37 (t, 2H, *J* = 7.37 Hz), 2.51 (t, 1H, *J* = 2.41 Hz), 3.10 (q, 2H, *J* = 6.45 Hz), 4.67 (d, 2H, *J* = 2.49 Hz). ^{13}C NMR (75.48 MHz, $CDCl_3$): 24.0, 25.7, 28.0, 29.2, 33.3, 39.9, 51.2, 74.6, 77.4, 78.3, 155.6, 172.1; CHNS Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20; Found: C, 62.42; H, 8.65; N.5.24.

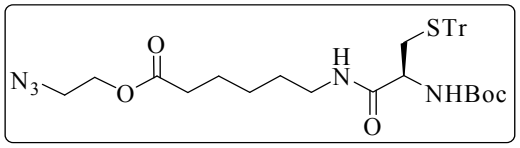
Characterization data of compound 26:



m.p. = 145 ^{0}C; $[\alpha]_D^{25}$ = +42.70 (*c*, 1.12, $CHCl_3$); IR ($CHCl_3$): 3320.15, 1744.23, 1692.94, 1659.20, 1529.06, 1172.89, 755.67 cm $^{-1}$; ^{1}H NMR(300.13 MHz, $CDCl_3$): δ 1.20-1.30 (m, 2H), 1.43 (s, 9H),

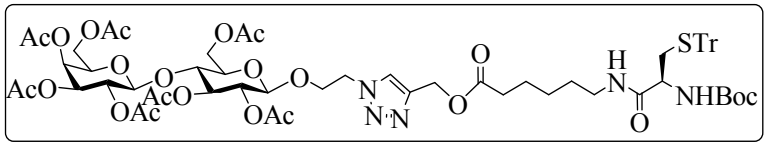
1.52-1.62 (m, 2H), 2.16 (t, 2H, *J* = 6.67 Hz), 2.98-3.107 (m, 2H), 3.14 (dd, 2H, *J* = 5.88, 13.96 Hz), 3.69 (s, 3H), 4.86 (dd, 1H, *J* = 6.58, 13.16 Hz), 4.93 (t, 1H, *J* = 5.47 Hz), 6.53 (d, 1H, *J* = 8.09 Hz), 7.11-7.29 (m, 5H); ^{13}C NMR (75.48 MHz, CDCl3): δ 24.6, 25.7, 27.9, 29.2, 35.4, 37.3, 39.9, 51.6, 52.7, 78.1, 126.4, 127.9, 128.6, 135.9, 155.6, 171.8, 172.3; CHNS Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14; Found: C, 64.29; H, 8.19; N, 7.10.

Characterization data of compound 32:



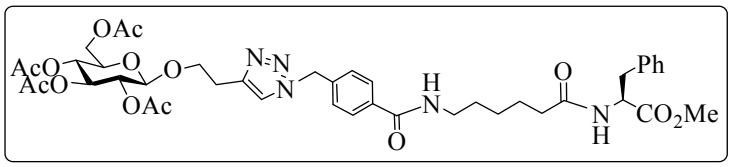
$[\alpha]_D^{25}$ = +14.28 (*c*, 1.00, $CHCl_3$); IR ($CHCl_3$): 3419.56, 3334.69, 2106.12, 1737.74, 1703.03, 1666.38, 1492.80, 1164.92, 754.12 cm^{-1}; ^{1}H NMR(200.13 MHz, $CDCl_3$): δ 1.22-1.50 (m, 4H), 1.41 (s, 9H), 1.55-1.72 (m, 2H), 2.31 (t, 2H, *J* = 7.35 Hz), 2.52 (dd, 1H, *J* = 5.52, 12.70 Hz), 2.69 (dd, 1H, *J* = 6.91, 12.67 Hz), 3.18 (q, 2H, *J* = 6.63, 12.79 Hz), 3.43 (t, 2H, *J* = 5.37 Hz), 3.84 (q, 1H, *J* = 6.47, 12.94 Hz), 4.22 (t, 2H, *J* = 5.36 Hz), 4.89 (d, 1H, *J* = 7.58 Hz), 6.08 (t, 1H, *J* = 5.68 Hz), 7.15-7.44 (m, 15H); ^{13}C NMR (75.48 MHz, CDCl3): 24.0, 25.9, 28.0, 28.7, 33.5, 33.9, 38.8, 49.4, 53.3, 62.4, 66.8, 79.7, 126.5, 127.7, 129.3, 144.2, 155.0, 170.1, 172.7; CHNS Anal. Calcd for $C_{35}H_{43}N_5O_5S$: C, 65.09; H, 6.71; N; 10.84; O, 12.39; S, 4.97; Found: C, 65.14; H, 6.69; N, 10.89; S, 4.92; m/z: 668.19 (M^+ + 23 for Na).

Characterization data of compound 33:



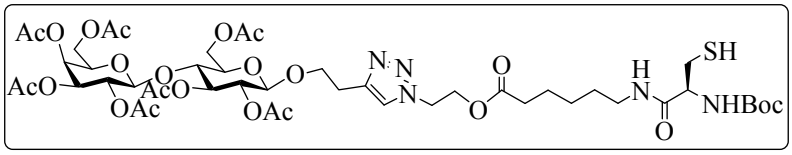
m.p. = 98-102^{o}C; $[\alpha]_D^{25}$ = +10.36 (*c*, 1.10, $CHCl_3$); IR (Nujol film): 1751, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.26 (m, 3H), 1.41 (s, 9H), 1.59 (dd, 3H, *J* = 7.36, 15.13 Hz), 1.96, 1.97, 2.03, 2.04, 2.06, 2.12, 2.15 (7s, 21H), 2.29 (t, 2H, *J* = 7.20 Hz), 2.50 (dd, 1H, *J* = 5.44, 12.75 Hz), 2.70 (dd, 1H, *J* = 6.93, 12.81 Hz), 3.17 (q, 2H, *J* = 6.66, 12.97 Hz), 3.61 (m, 1H), 3.72-3.97 (m, 4H), 4.01-4.26 (m, 4H), 4.40-4.63 (m, 5H), 4.80-5.25 (m, 7H), 5.35 (d, 1H, *J* = 3.09 Hz), 6.08 (t, 1H, *J* = 5.47 Hz), 7.15-7.45 (m, 15H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3-20.7, 24.2, 26.0, 28.1, 28.8, 33.7, 33.8, 39.0, 49.9, 53.4, 57.2, 60.6, 61.5, 66.4, 66.9, 67.6, 68.9, 70.5, 70.7, 71.1, 72.3, 72.6, 75.8, 80.0, 100.2, 100.8, 124.7, 126.7-129.4, 142.5, 144.2, 155.1, 168.9, 169.4, 169.5, 169.9, 170.0, 170.1, 170.1, 170.2, 173.1; CHNS Anal. Calcd for $C_{64}H_{81}N_5O_{23}S$: C, 58.20; H, 6.18; N, 5.30; O, 27.88; S, 2.43; Found: C, 57.95; H, 6.52; N, 6.62; S, 2.20.

Characterization data of compound 34:



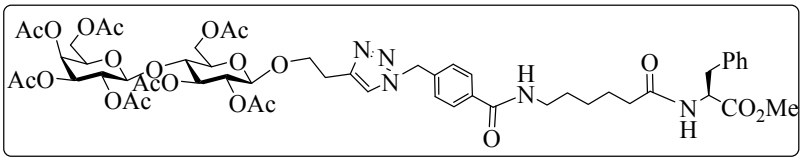
m.p. = 128-132°C; $[\alpha]_D^{25}$ = +6.65 (*c*, 1.00, $CHCl_3$); IR (Nujol film): 1747, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.35 (m, 2H), 1.64 (m, 4H), 1.89, 1.99, 2.02, 2.05 (4s, 12H), 2.19 (t, 2H, *J* = 6.99 Hz), 2.99 (t, 2H, *J* = 6.33 Hz), 3.09 (t, 2H, *J* = 6.00 Hz), 3.42 (dd, 2H, *J* = 6.45, 12.37 Hz), 3.66 (m, 1H), 3.71 (s, 3 H), 3.85 (m, 1H), 4.08 (m, 2H), 4.23 (dd, 1H, *J* = 4.77, 12.22 Hz), 4.50 (d, 1H, *J* = 7.94 Hz), 4.80-5.25 (m, 4H), 5.54 (bs, 2H), 6.01 (d, 1H, *J* = 7.31 Hz), 6.62 (m, 1H), 7.08 (m, 2H), 7.26 (m, 3H), 7.30 (d, 2H, *J* = 8.28 H), 7.37 (s, 1H), 7.80 (d, 2H, *J* = 8.27 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.4-20.6, 24.6, 26.1, 26.3, 28.8, 35.8, 37.6, 38.5, 39.5, 52.2, 52.9, 53.3, 61.8, 68.2, 68.5, 71.1, 71.6, 72.6, 100.6, 123.3, 126.8-129.1, 134.9, 135.8, 137.9, 144.9, 166.7, 169.3, 169.4, 170.1, 170.5, 172.1, 172.5; CHNS Anal. Calcd for $C_{42}H_{53}N_5O_{14}$: C, 59.21; H, 6.27; N, 8.22; O, 26.29; Found: C, 59.43; H, 6.35; N, 8.25.

Characterization data of compound 35:



m.p. = 78-82°C; $[\alpha]_D^{25}$ = +6.48 (*c*, 1.00, $CHCl_3$); IR (Nujol film): 1749, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.27 (m, 2H), 1.46 (s, 9H), 1.58 (m, 4H), 1.96, 1.97, 2.04, 2.05, 2.06, 2.12, 2.15 (7s, 21H), 2.31 (t, 2H, *J* = 7.42 Hz), 3.00 (m, 4H), 3.22 (m, 2H), 3.48-3.90 (m, 5H), 4.00-4.30 (m, 5H), 4.32-4.63 (m, 7H), 4.65-5.25 (m, 4H), 5.35 (d, 1H, *J* = 2.75 Hz), 5.64 (d,1H, *J* = 9.11 Hz), 7.45 (s, 1H), 7.72 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3-20.8, 24.3, 26.3, 28.3-28.4, 29.3, 33.6, 33.7, 39.3, 46.8, 49.0, 54.7, 60.7, 62.1, 66.6, 68.7, 69.1, 70.6, 70.9, 71.6, 72.6, 72.7, 76.2, 80.0, 100.6, 101.0, 122.6, 144.6, 155.8, 169.0, 169.6, 170.0-170.3, 172.8; CHNS Anal. Calcd for $C_{46}H_{69}N_5O_{23}S$: C, 50.59; H, 6.37; N, 6.41; O, 33.69; S, 2.94; Found: C, 50.24; H, 6.23; N, 6.25; S, 2.79.

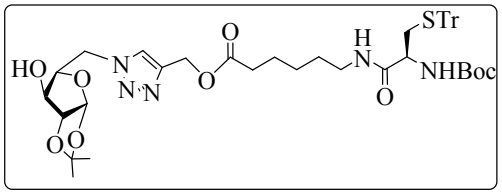
Characterization data of compound 36:



m.p. = 135-140°C; $[\alpha]_D^{25}$ = +10.12 (*c*, 1.10, $CHCl_3$). IR (Nujol film): 1751, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.36 (m, 2H), 1.62 (m, 4H), 1.90, 1.96, 2.03, 2.04, 2.06, 2.08, 2.15 (7s, 21H), 2.19 (t, 2H, *J* = 7.40 Hz), 2.98 (t, 2H, *J* = 6.19 Hz), 3.09 (t, 2H, *J* = 6.19 Hz), 3.43 (q, 2H, *J* = 6.61, 12.81 Hz), 3.58 (m, 1H), 3.70 (s, 3H), 3.74-3.94 (m,

3H), 4.01-4.15 (m, 4H), 4.48 (t, 3H, *J* = 6.19 Hz), 4.76-5.04 (m, 3H), 5.04-5.22 (m, 2H), 5.35 (d, 1H, *J* = 2.99 Hz), 5.53 (bs, 2H), 6.02 (d, 1H, *J* = 7.26 Hz), 6.63 (d, 1H, *J* = 5.00 Hz), 7.07 (m, 2H), 7.27 (m, 3H), 7.29 (d, 2H, *J* = 8.31 Hz), 7.35 (s, 1H), 7.80 (d, 2H, *J* = 8.30 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.2-20.6, 24.5, 25.9, 26.1, 28.7, 35.6, 37.5, 38.3, 39.4, 52.0, 52.9, 53.2, 60.6, 61.7, 66.4, 68.4, 68.9, 70.3, 70.7, 71.3, 72.4, 75.9, 100.2, 100.7, 122.2, 126.7-129.0, 134.7, 135.8, 137.9, 144.8, 166.6, 168.9, 169.5, 169.6, 169.8, 169.9, 170.1, 170.2, 172.0, 172.6; CHNS Anal. Calcd for $C_{54}H_{69}N_5O_{22}$: C, 56.89; H, 6.10; N, 6.14; O, 33.87; Found: C, 56.64; H, 6.47; N, 5.99.

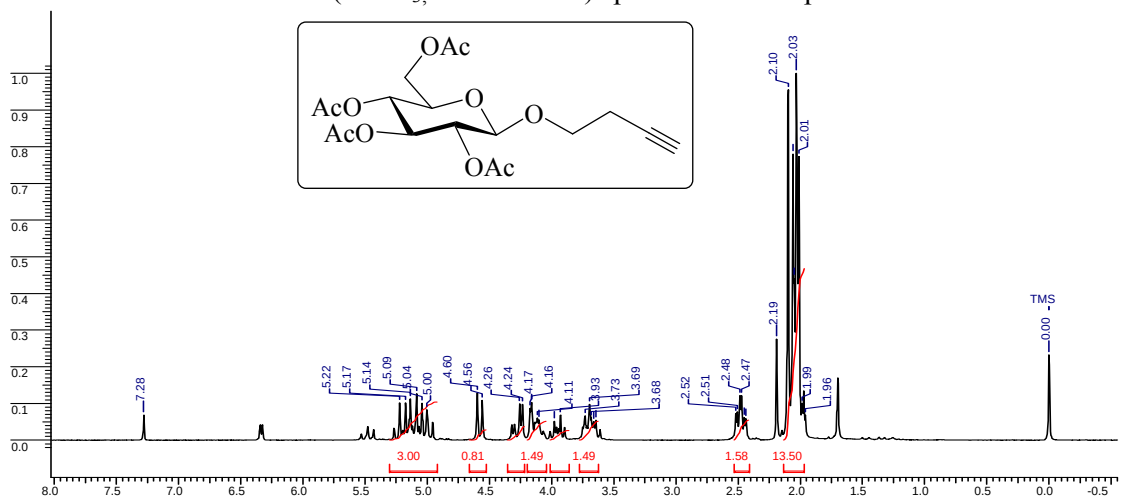
Characterization data of compound 37:



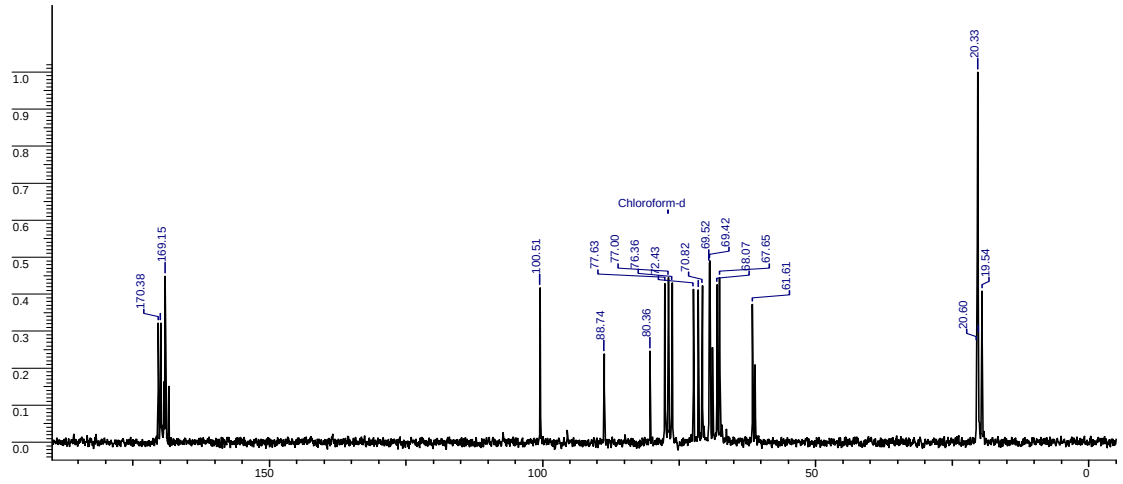
m.p. = 78-84°C; $[\alpha]_D^{25}$ = + 2.10 (*c*, 1.10, $CHCl_3$); IR (Nujol film): 1710, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.26-1.28 (m, 2H), 1.28 (s, 3H), 1.40 (s, 9H), 1.44 (s, 3H), 1.60 (m, 4H), 2.30 (t, 2H, *J* = 7.08 Hz), 2.50 (dd, 1H, *J* = 5.37, 12.59 Hz), 2.68 (dd, 1H, *J* = 7.04, 12.96 Hz), 3.18 (q, 2H, *J* = 6.22, 12.57 Hz), 3.87 (q, 1H, *J* = 6.74, 12.78 Hz), 4.07 (m, 2H), 4.45-4.88 (m, 4H), 4.96 (q, 1H, *J* = 7.05, 14.61 Hz), 5.20 (dd, 2H, *J* = 12.89, 17.81 Hz), 5.96 (d, 1H, *J* = 3.58 Hz), 6.21 (m, 1H), 7.15-7.46 (m, 15H), 7.74 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 24.2, 25.9, 26.1, 26.7, 28.1-28.2, 28.8, 33.7, 33.8, 39.1, 48.6, 53.5, 57.3, 67.0, 74.2, 79.1, 80.3, 85.3, 105.0, 111.8, 125.0, 126.7-129.5, 142.8, 144.2-144.3, 155.29, 170.6, 173.2; CHNS Anal. Calcd for $C_{44}H_{55}N_5O_9S$: C, 63.67; H, 6.68; N, 8.44; O, 17.35; S, 3.86; Found: C, 63.98; H, 6.95; N, 8.28; S, 3.63.

*****

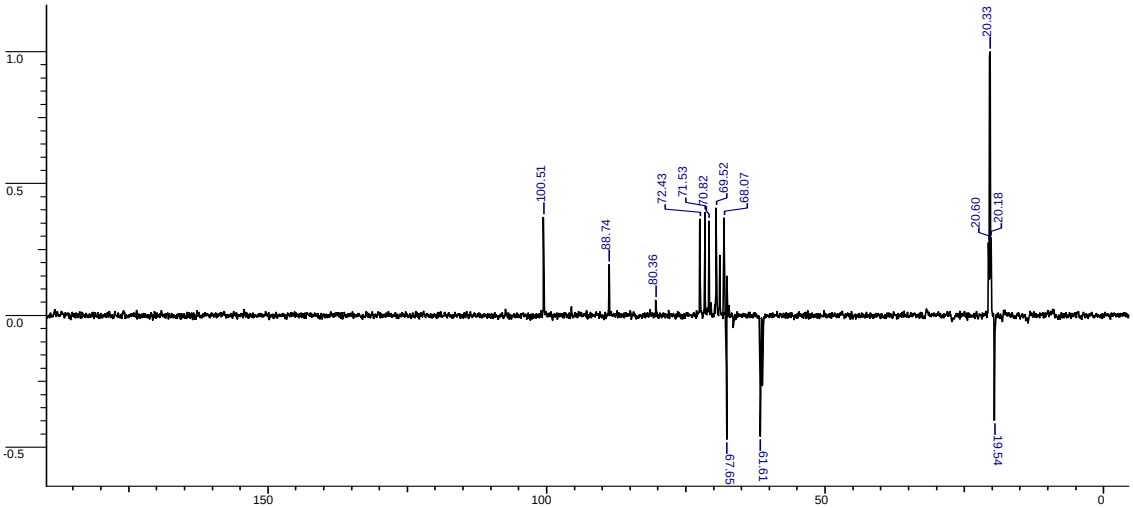
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **5**



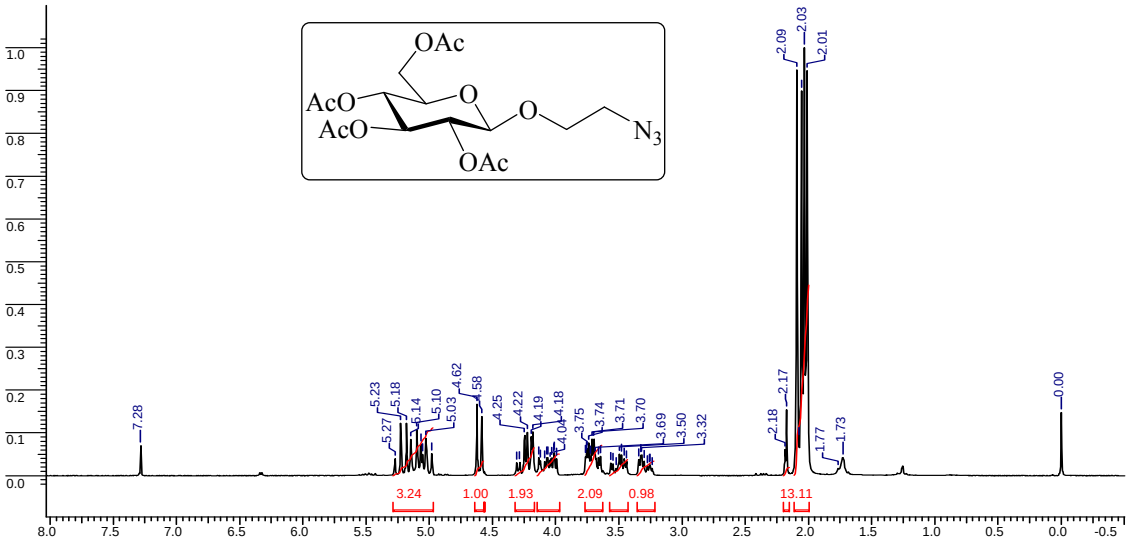
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **5**



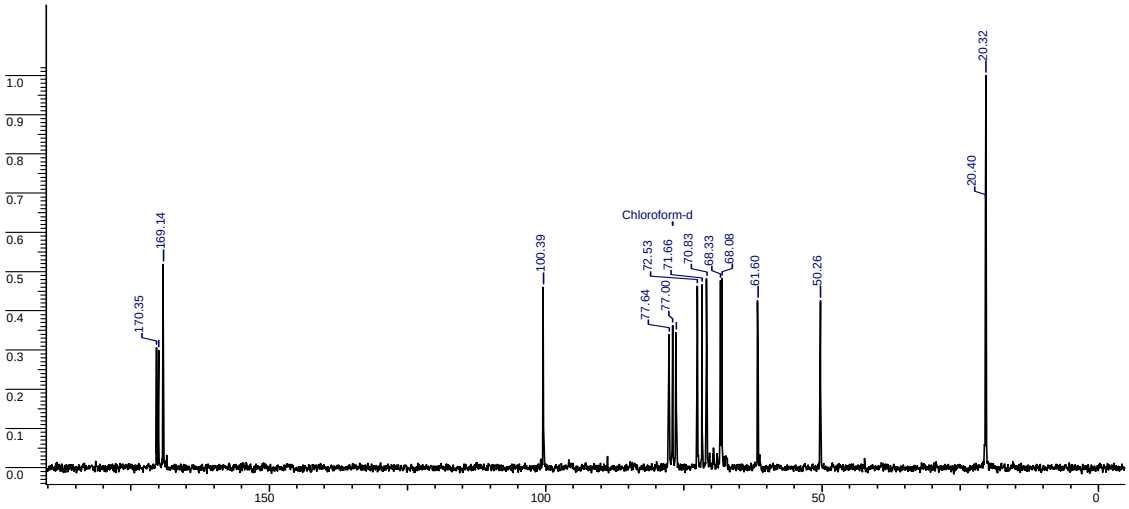
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **5**



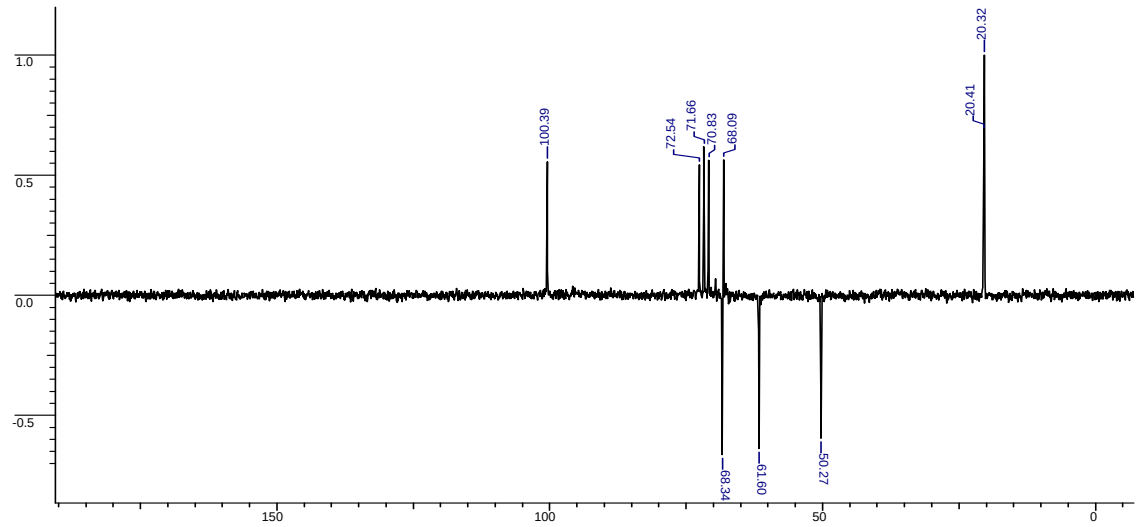
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **6**



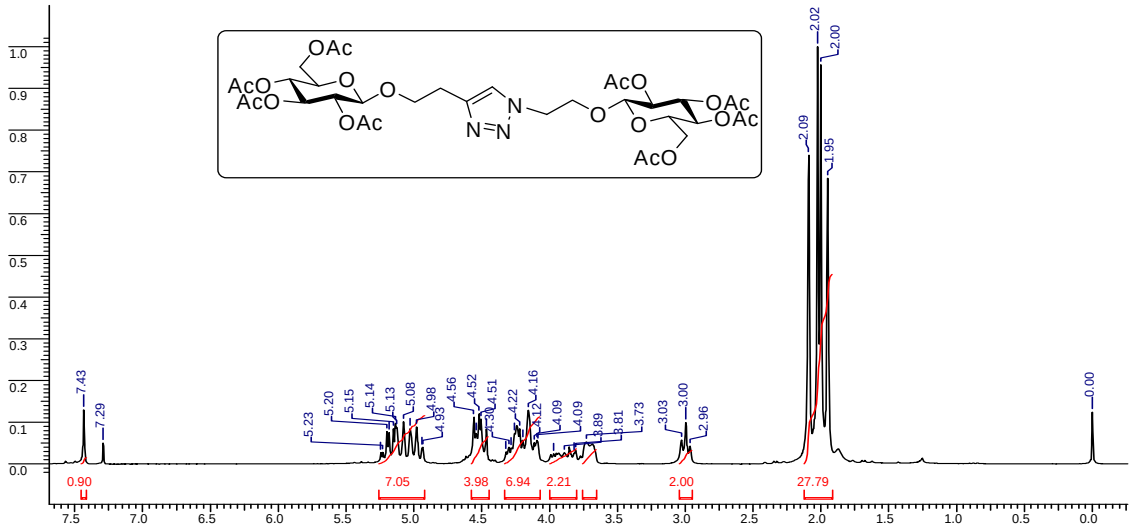
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **6**



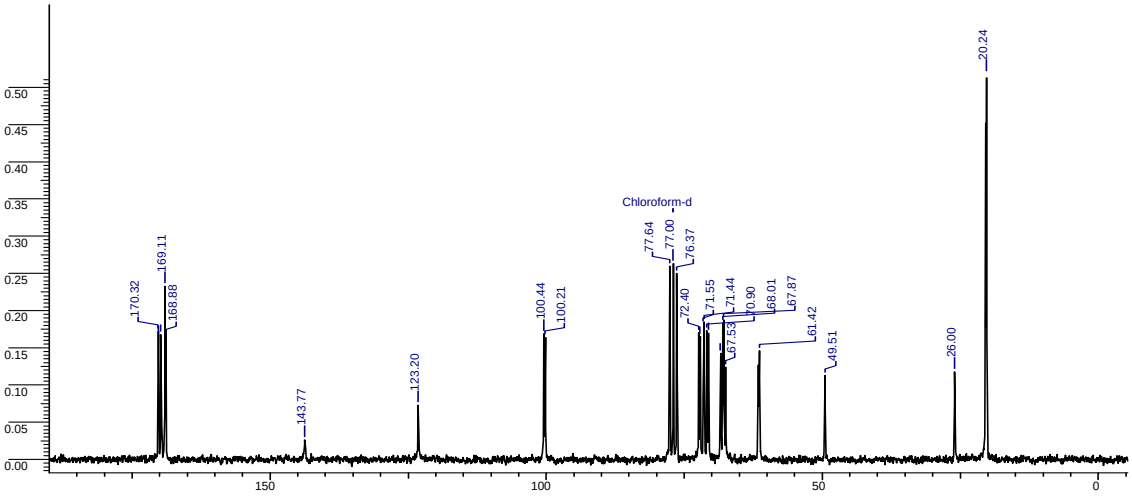
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **6**



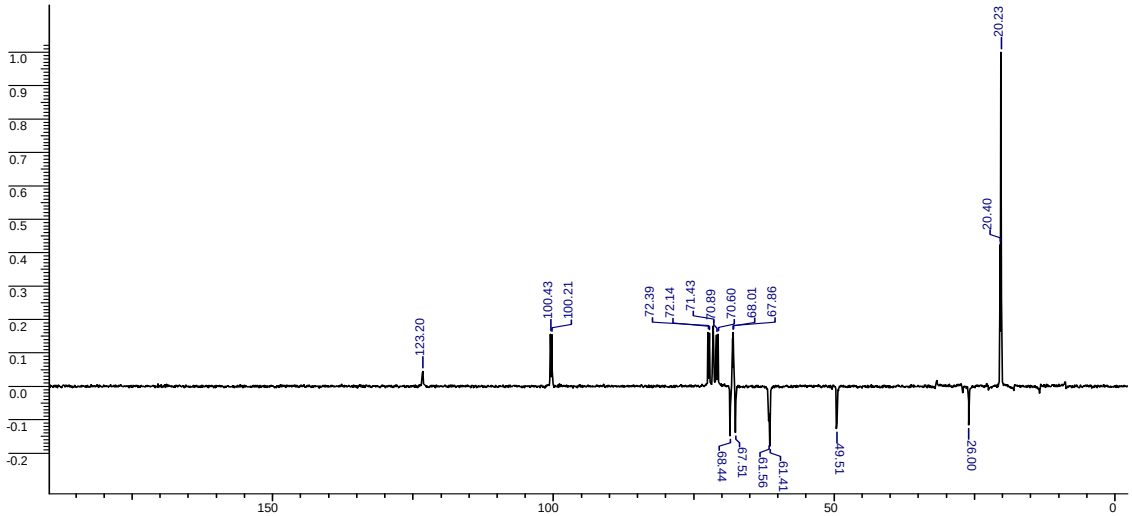
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **7**



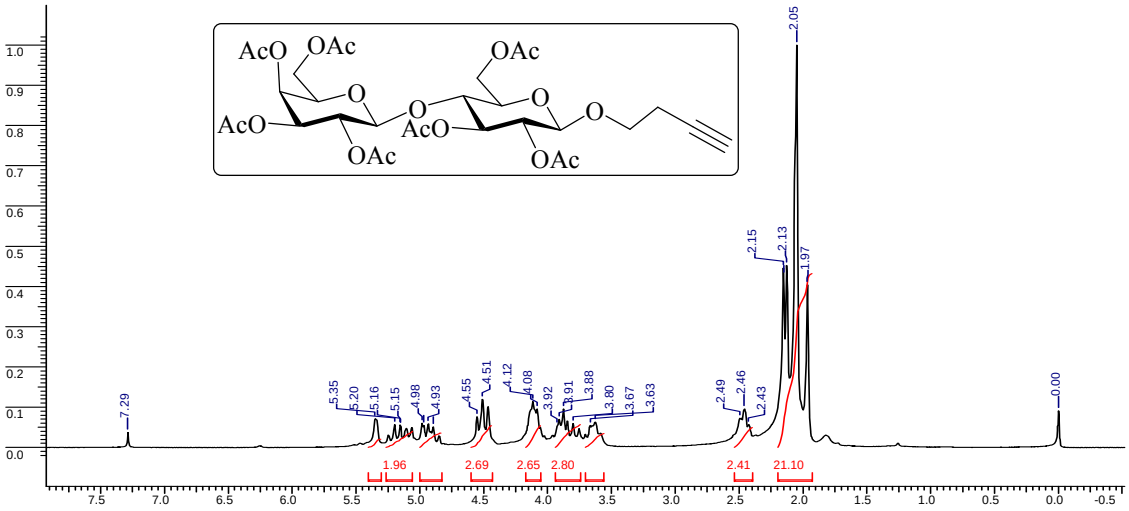
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7**



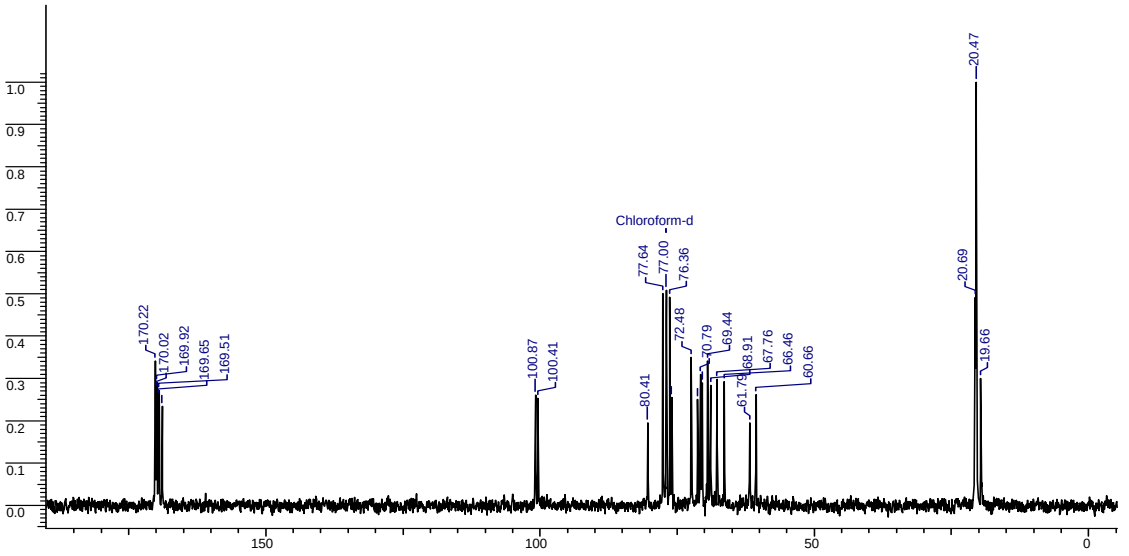
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **7**



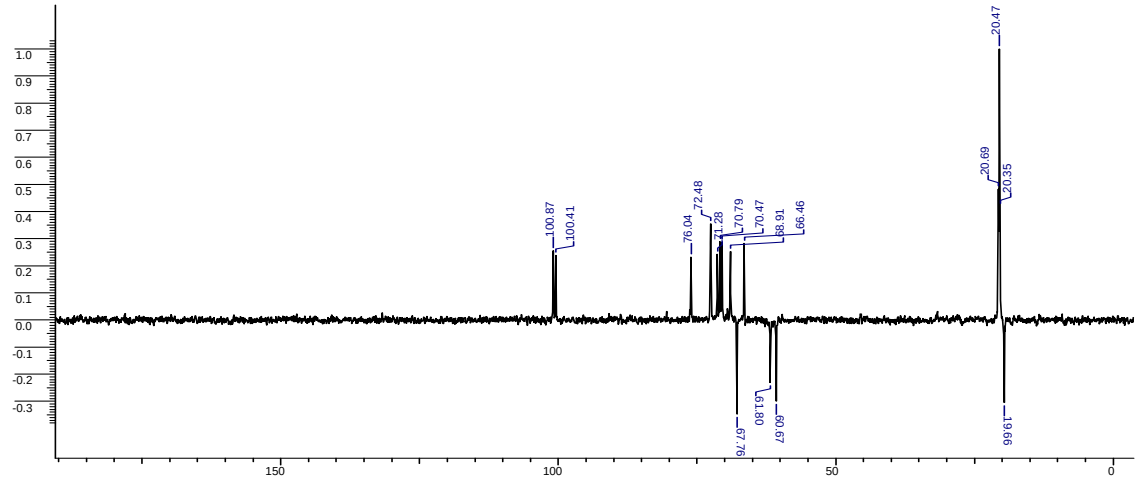
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **9**



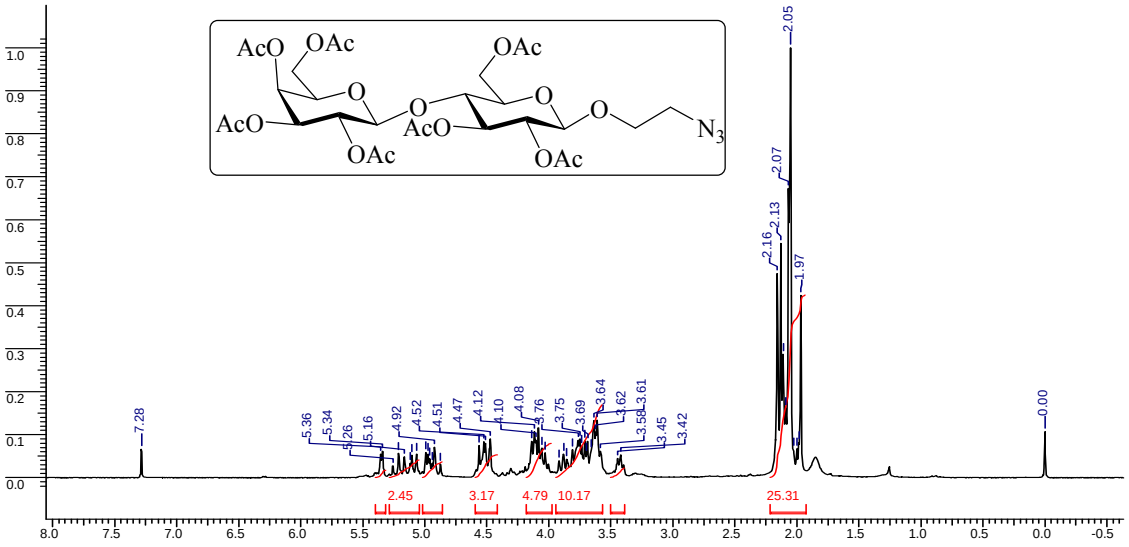
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



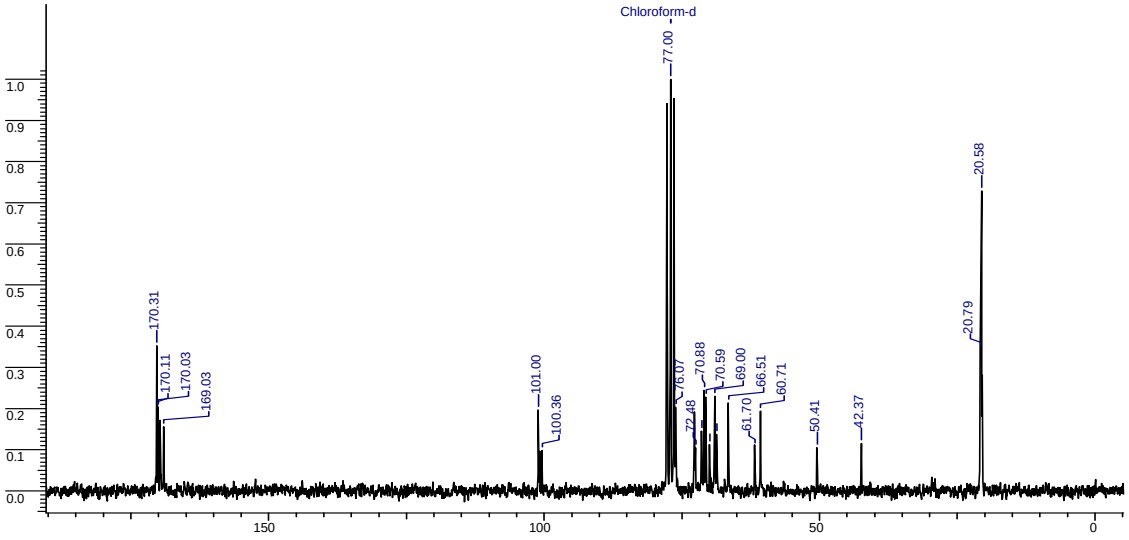
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **9**



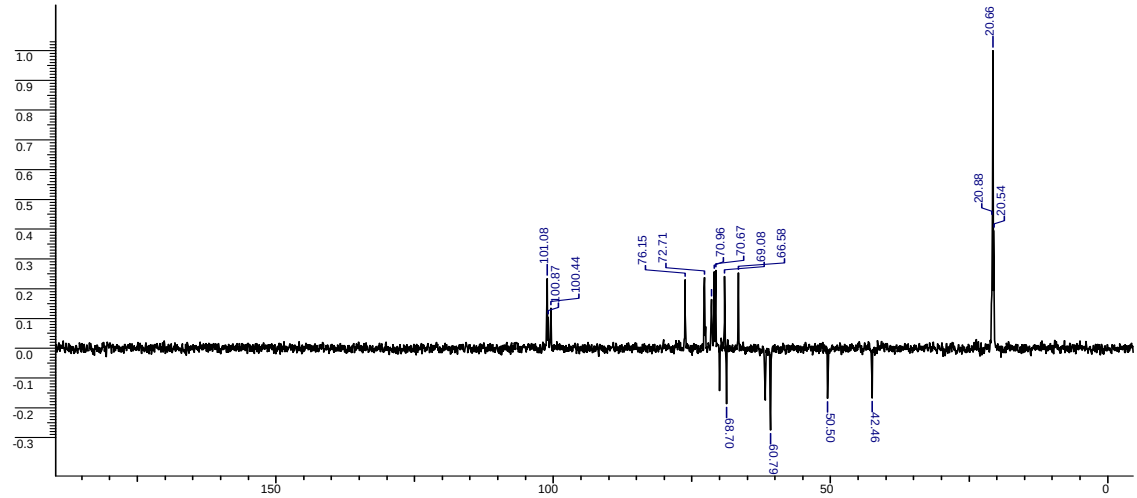
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **10**



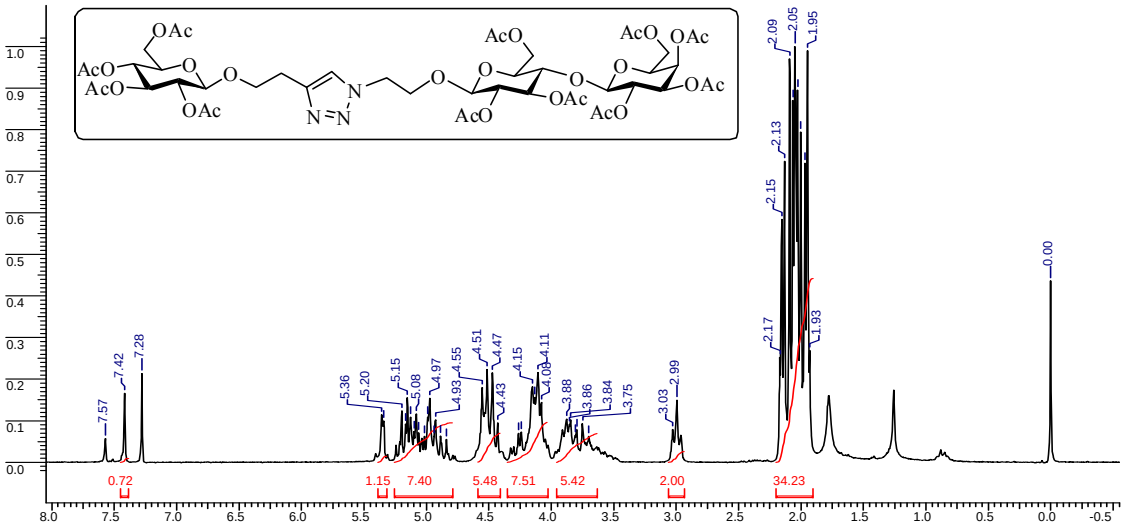
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **10**



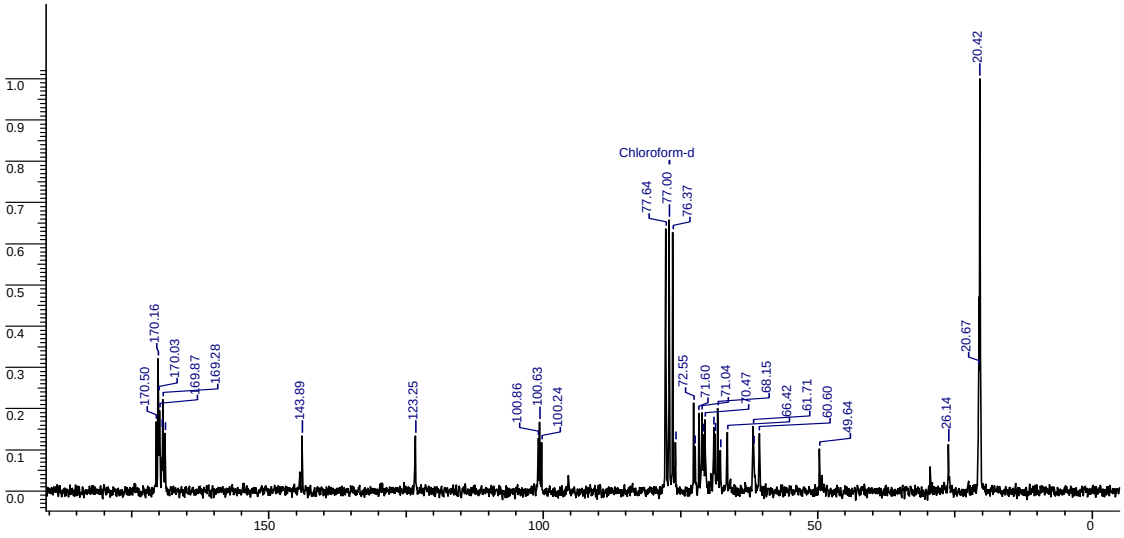
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **10**



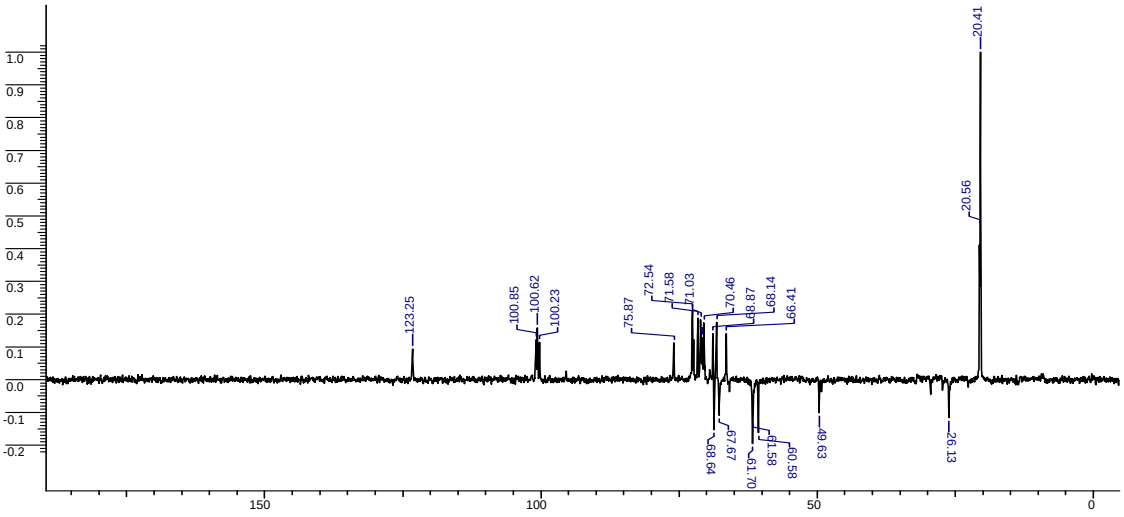
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **13**



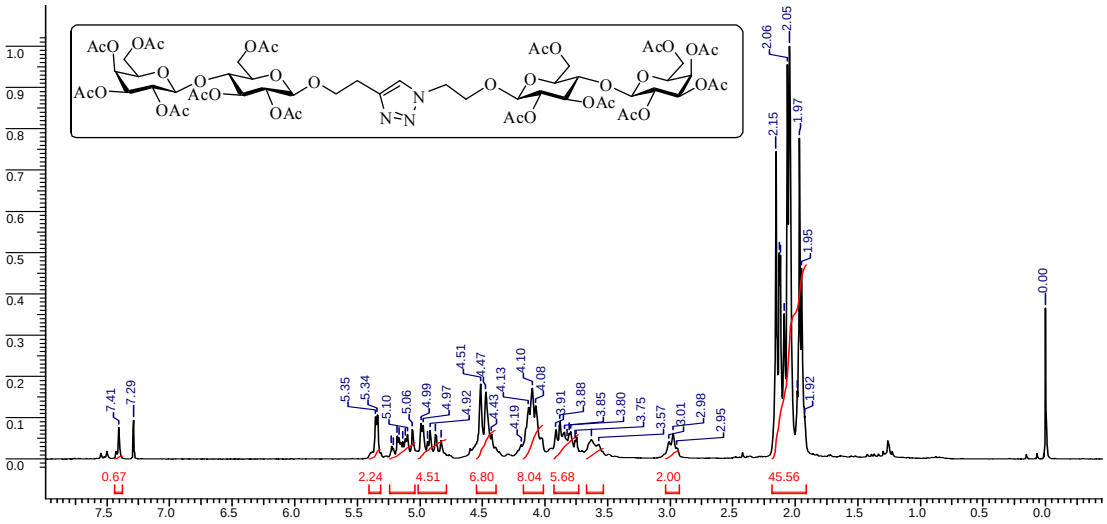
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **13**



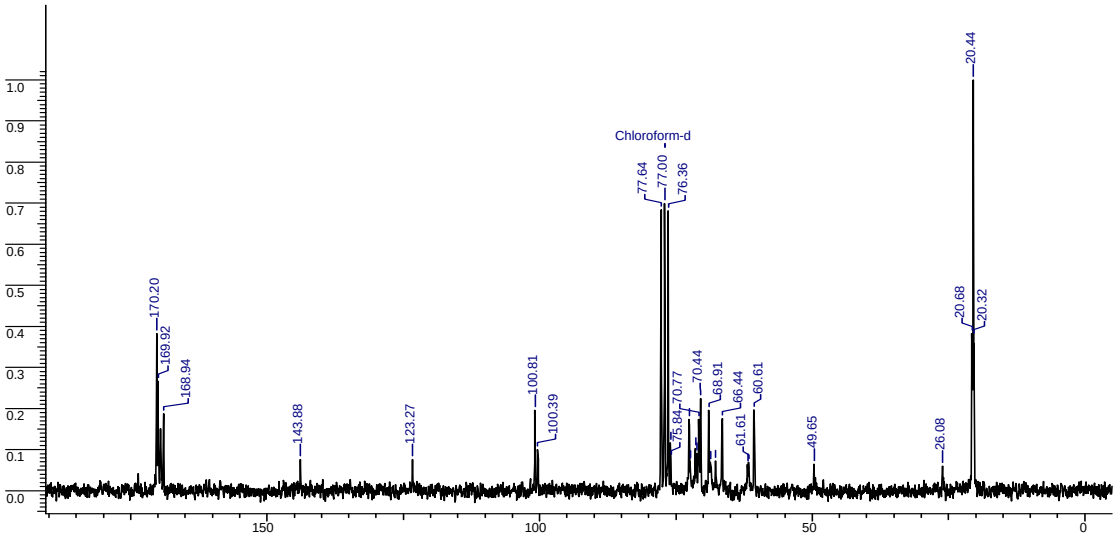
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **13**



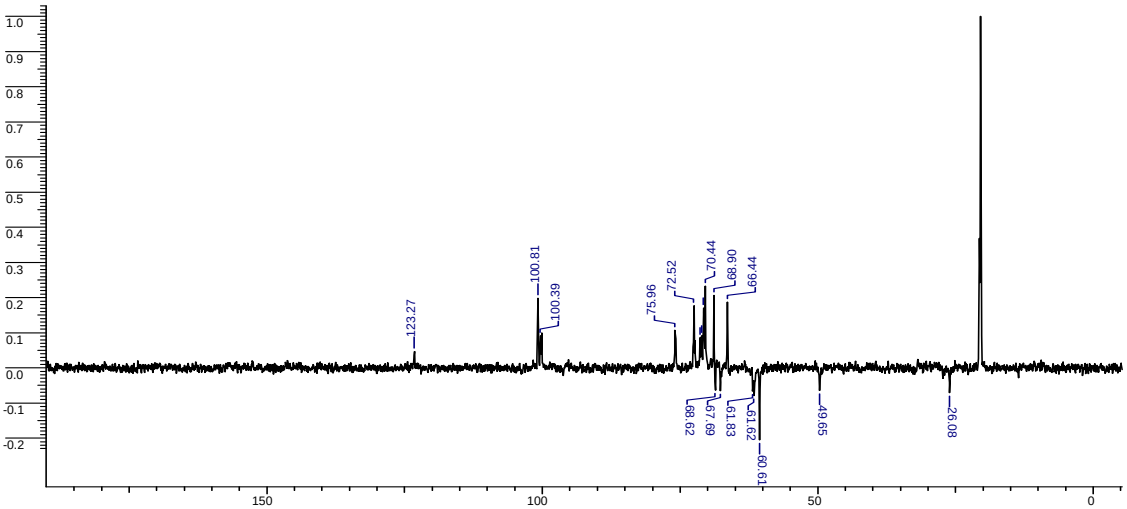
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **14**



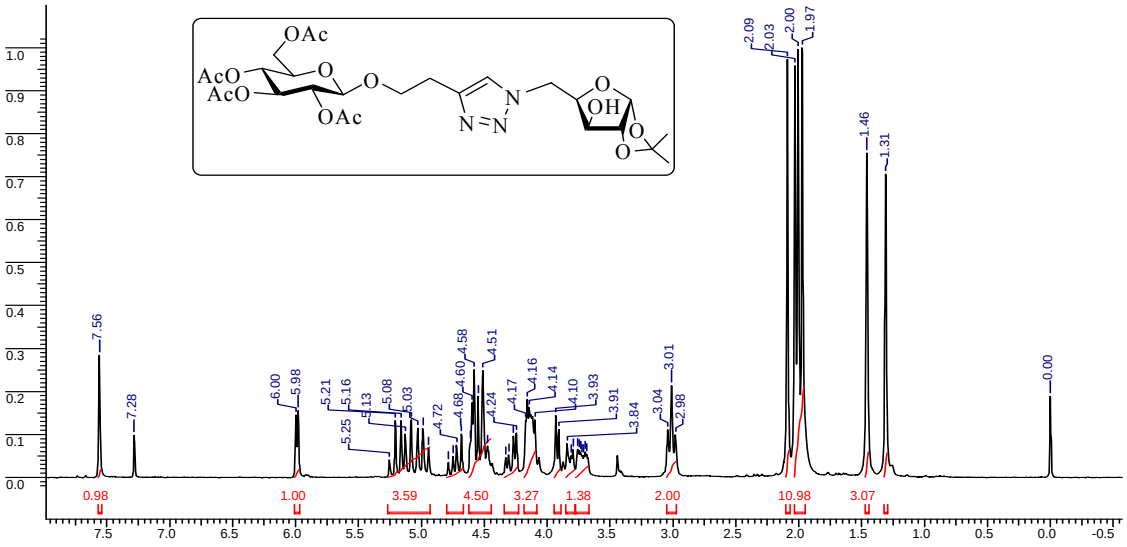
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



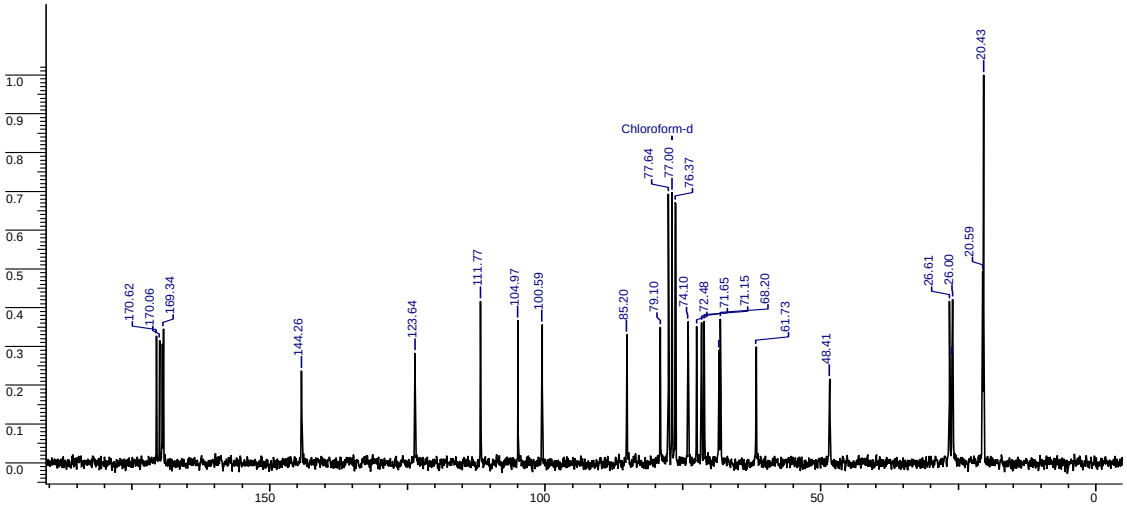
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **14**



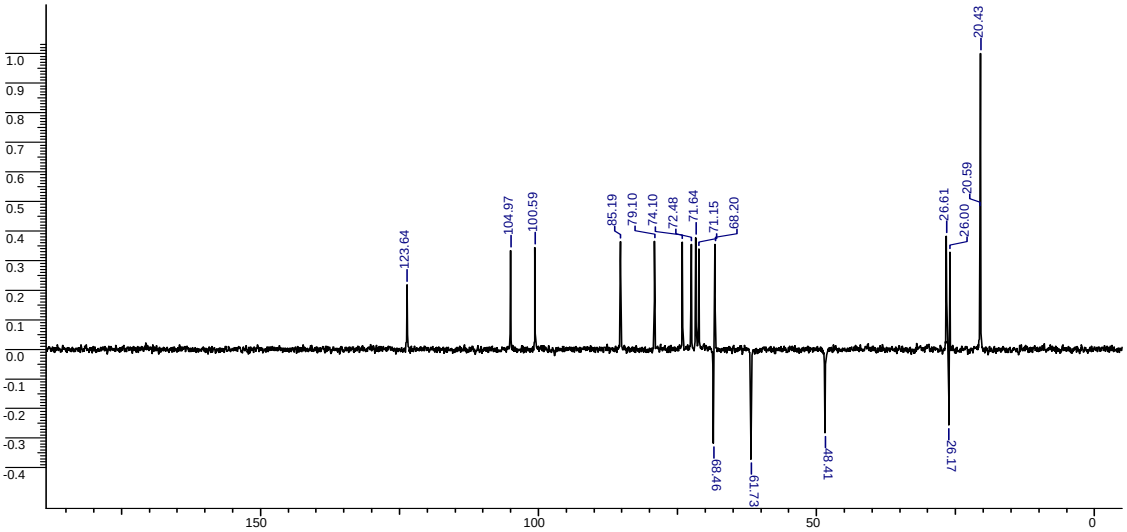
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **15**



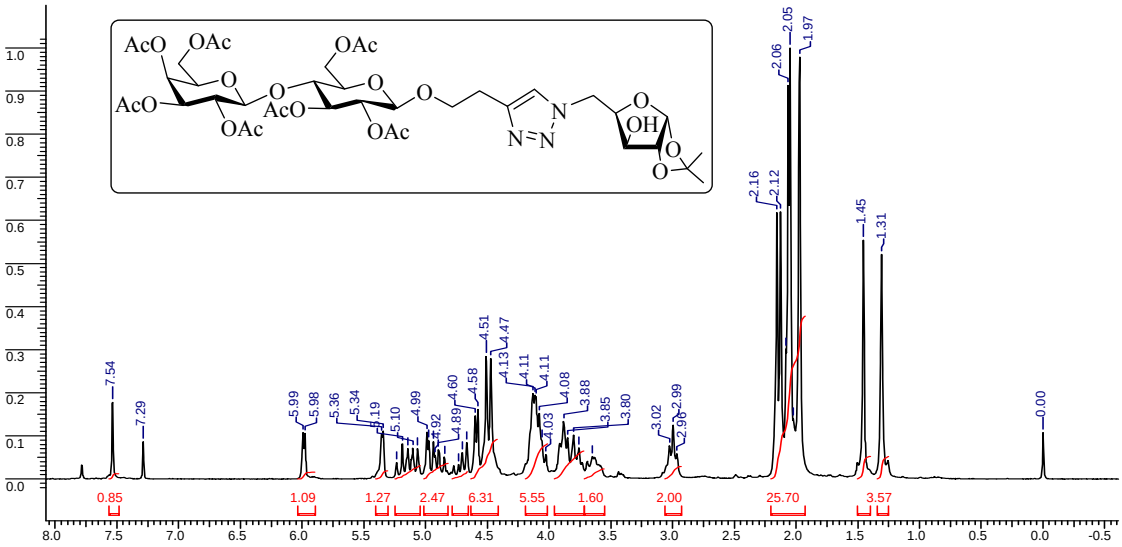
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



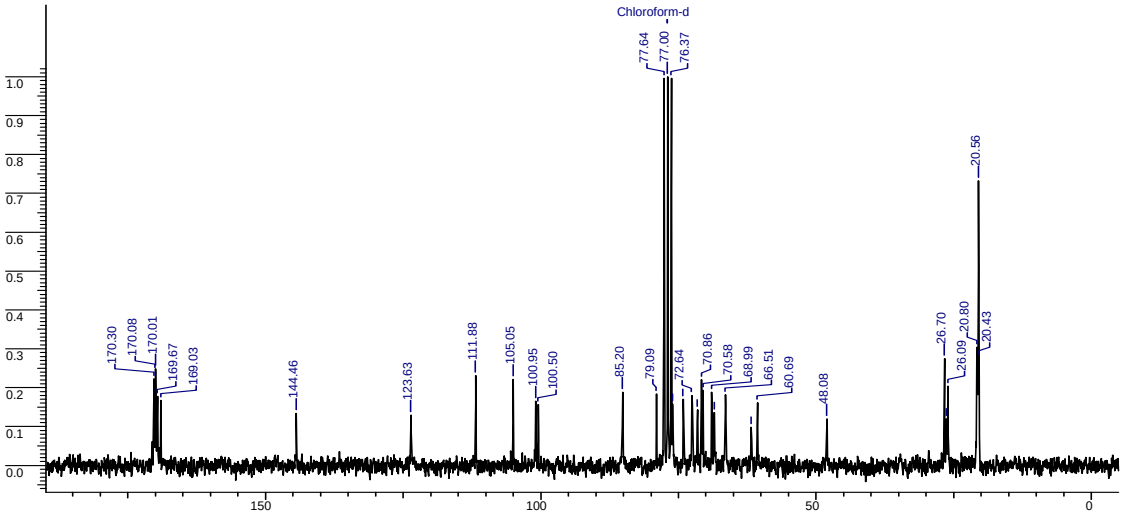
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **15**



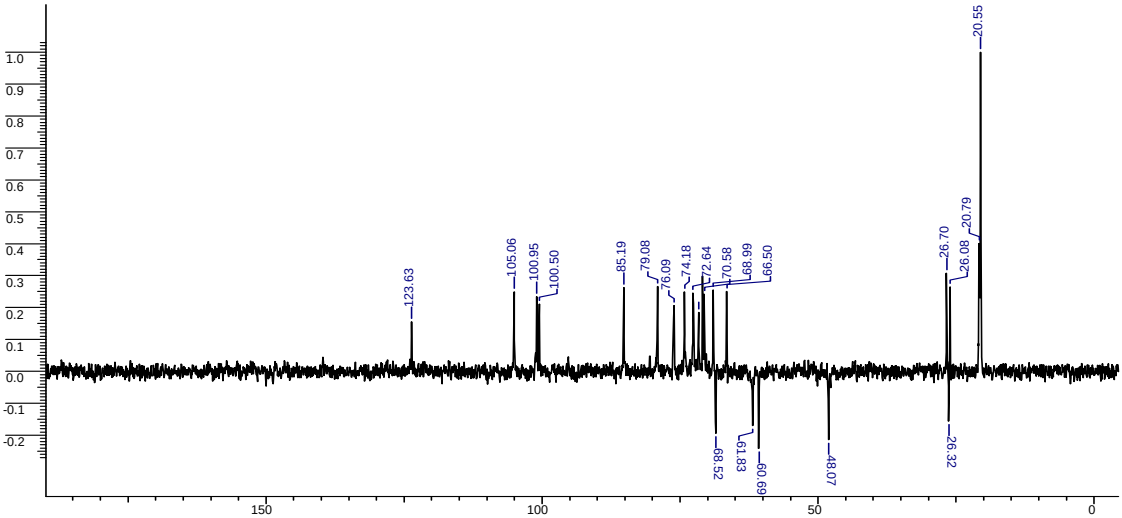
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **16**



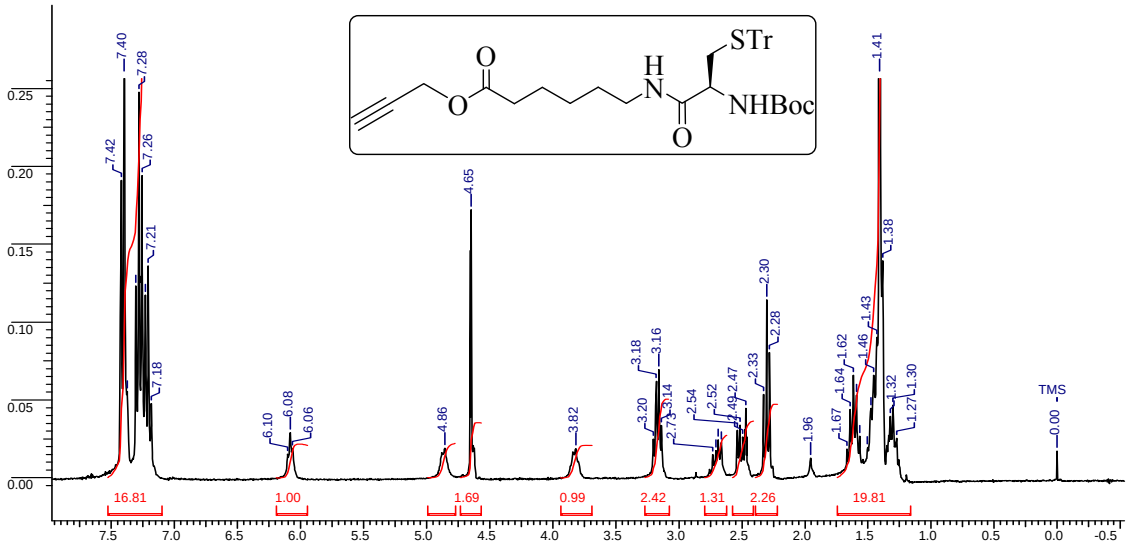
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **16**



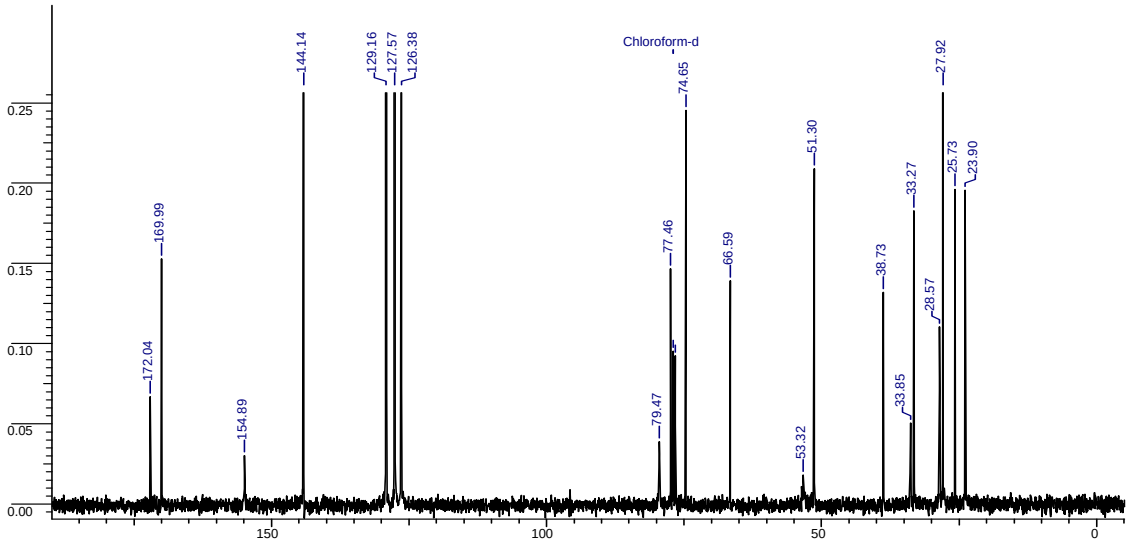
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **16**



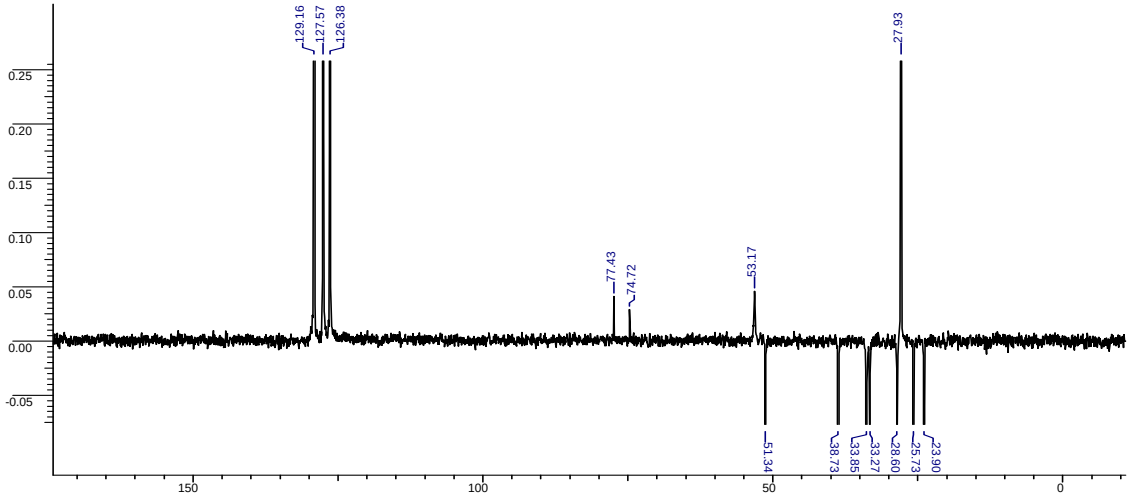
^{1}H NMR ($CDCl_3$, 300.13 MHz) spectrum of compound **17**



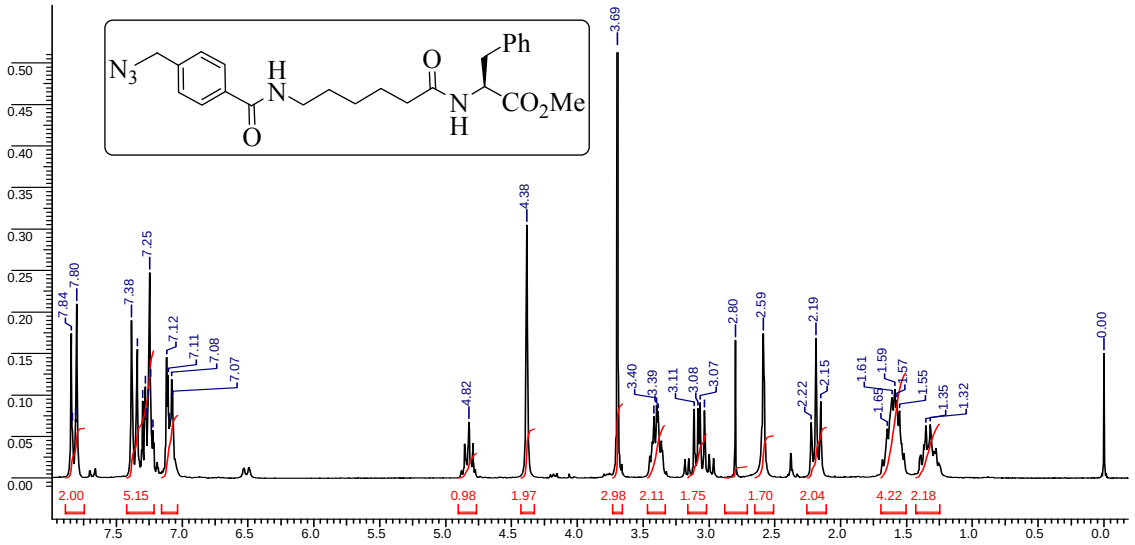
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **17**



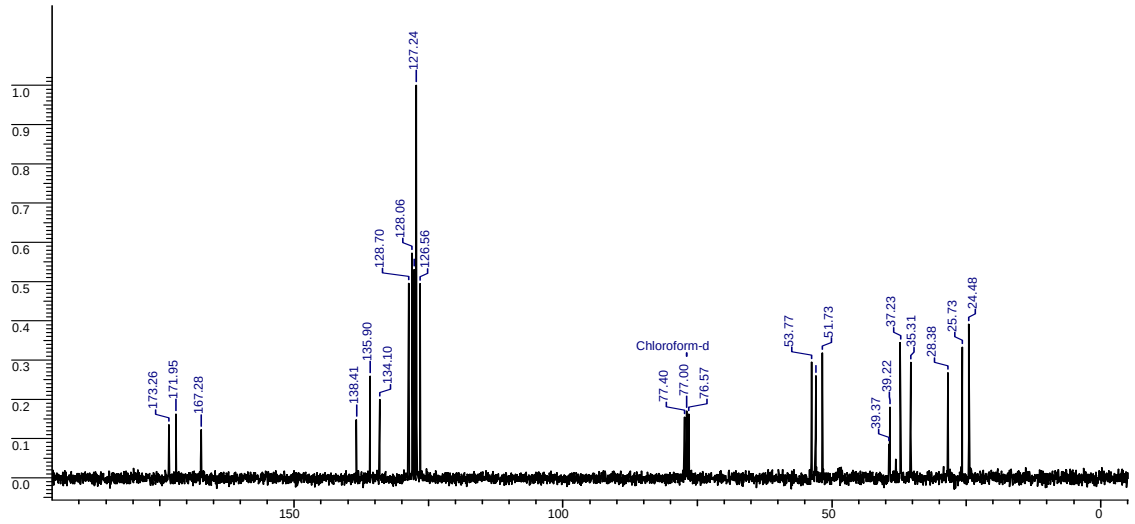
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **17**



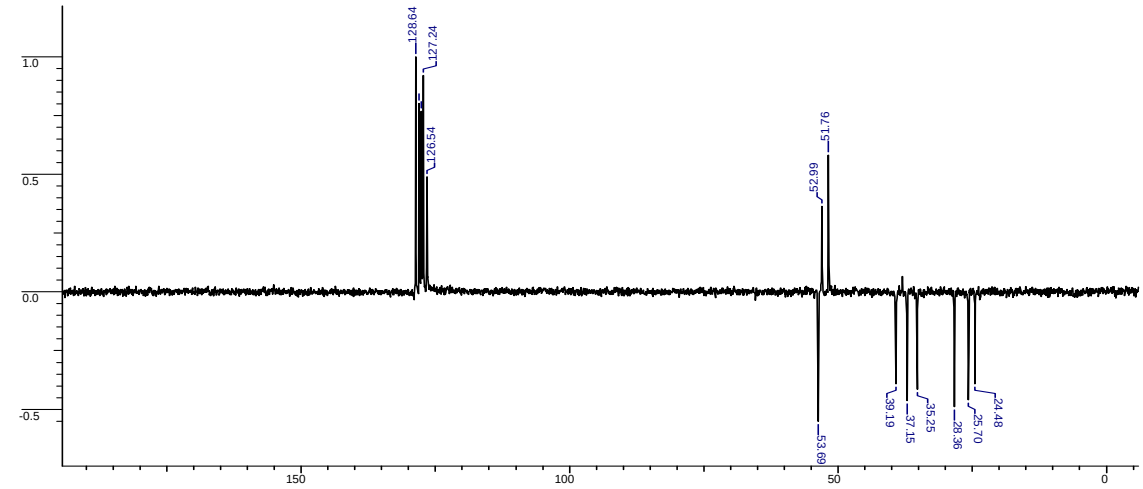
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **18**



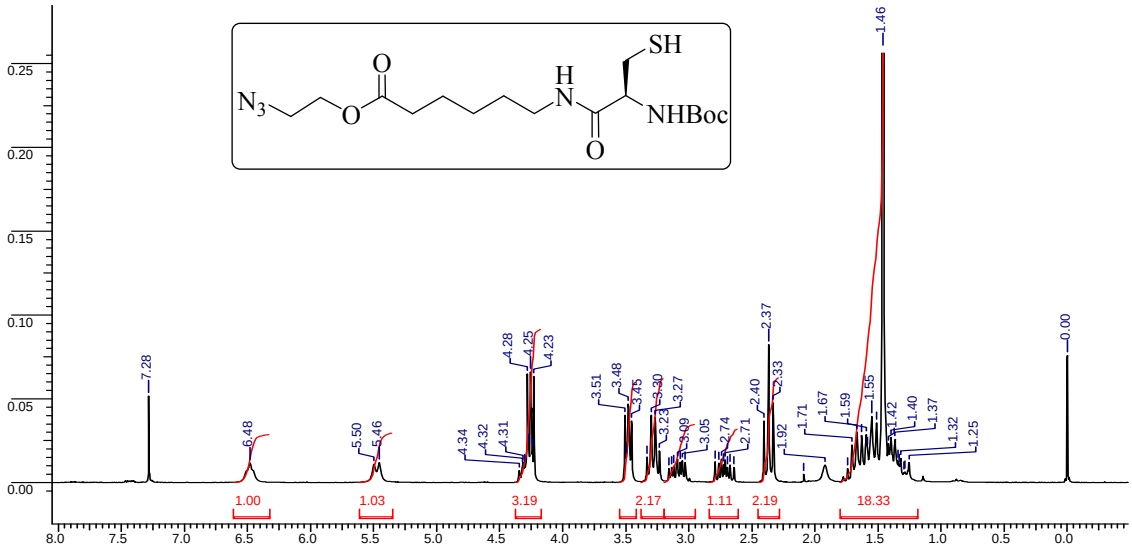
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **18**



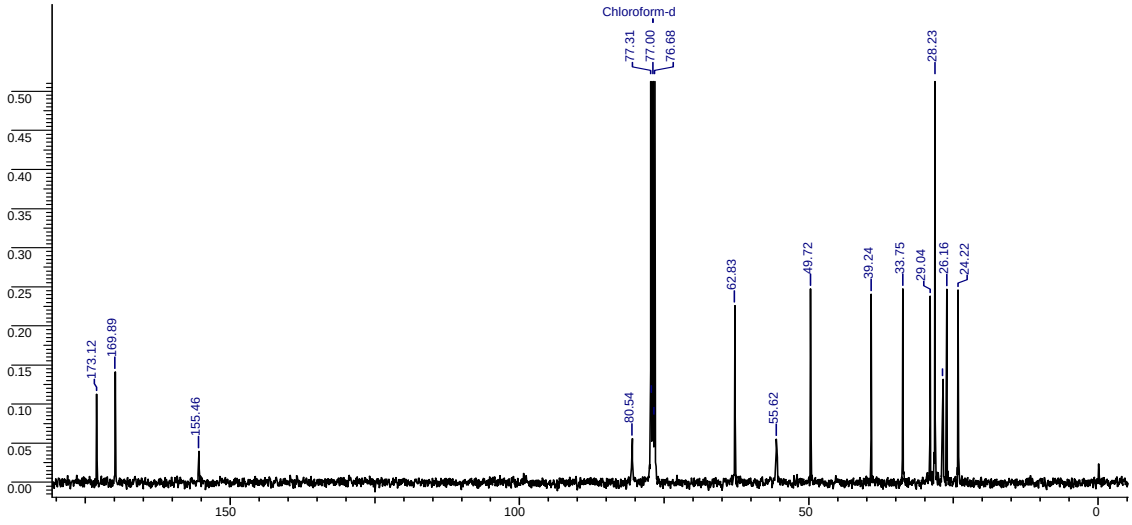
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **18**



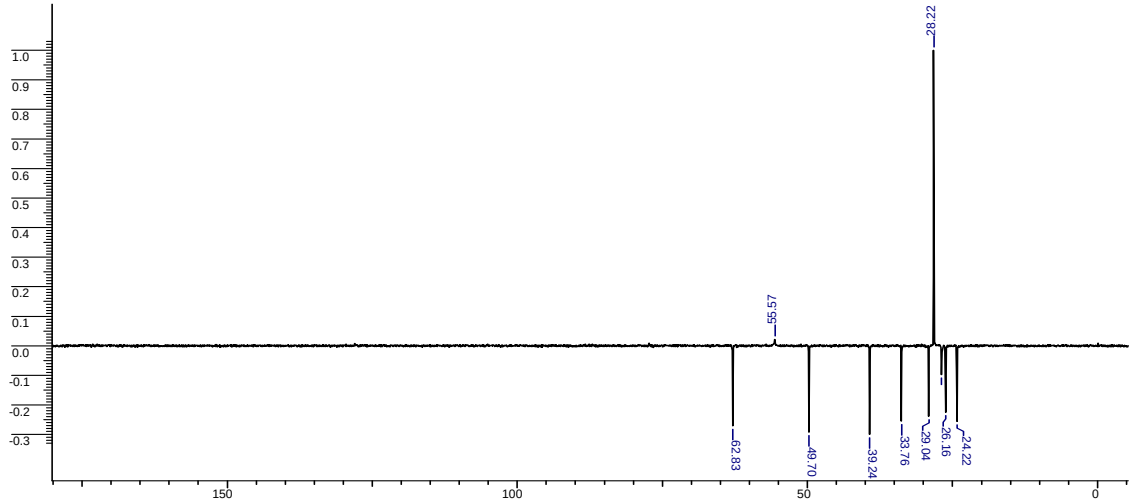
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **19**



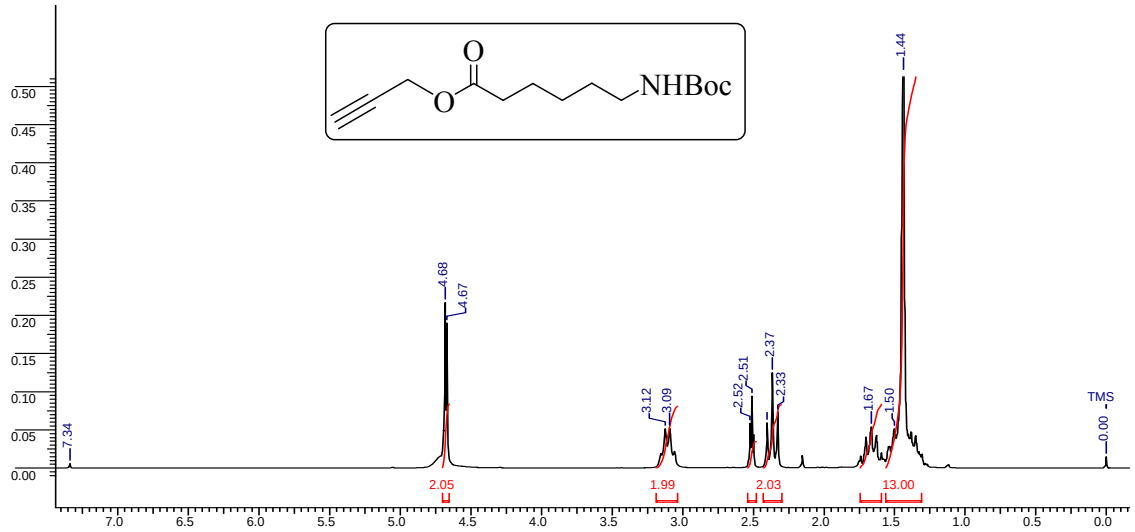
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **19**



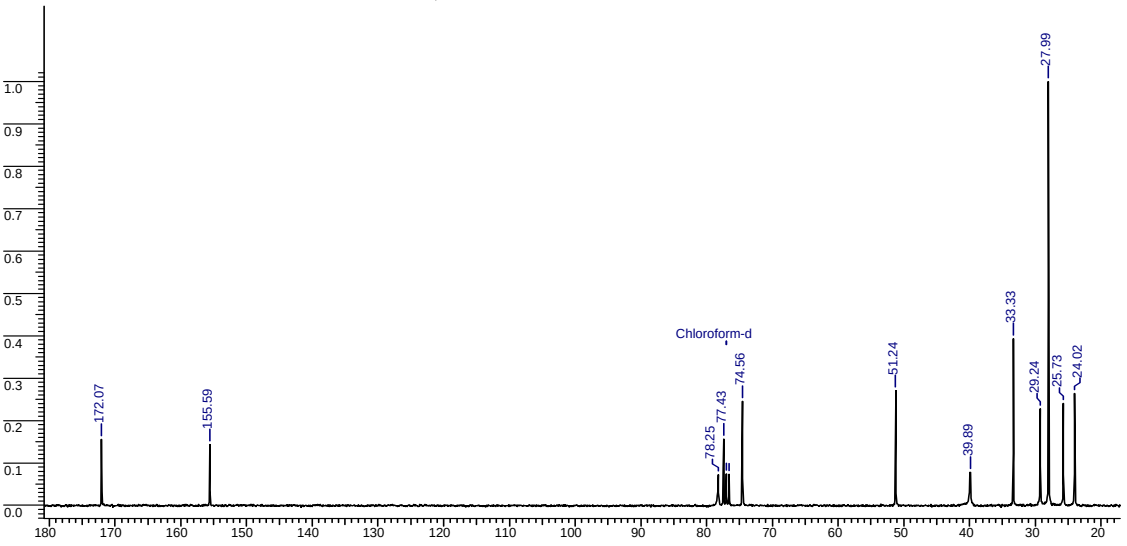
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **19**



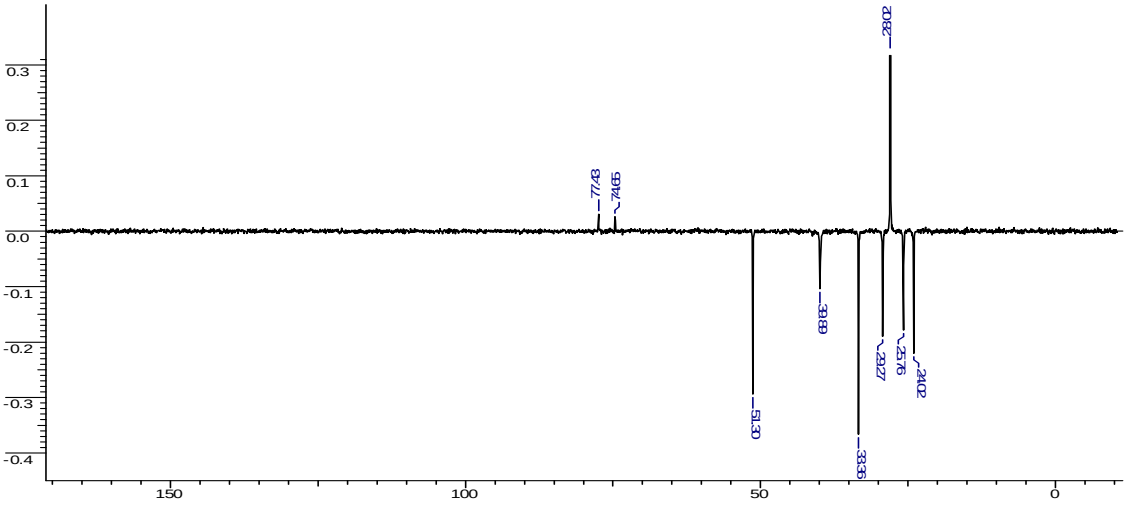
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **21**



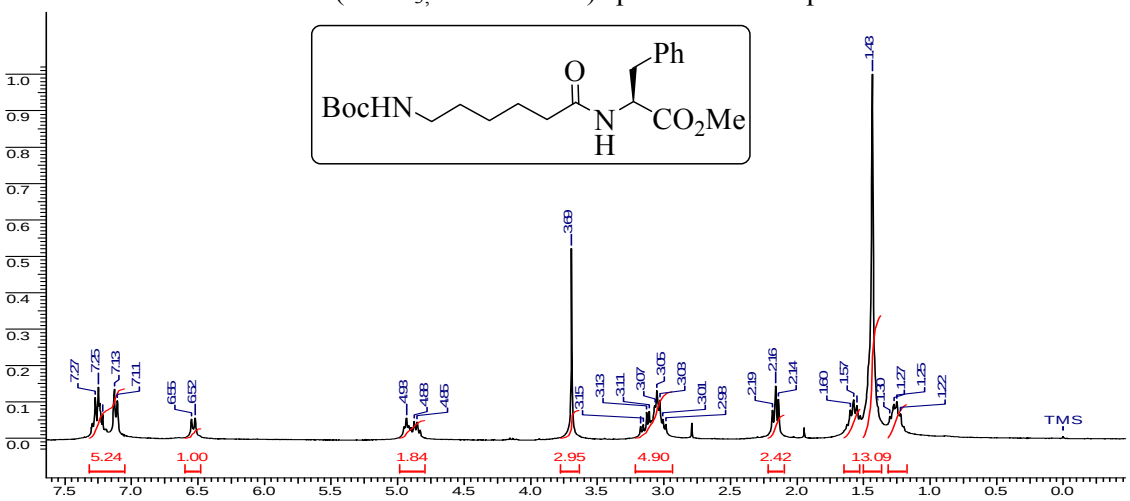
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **21**



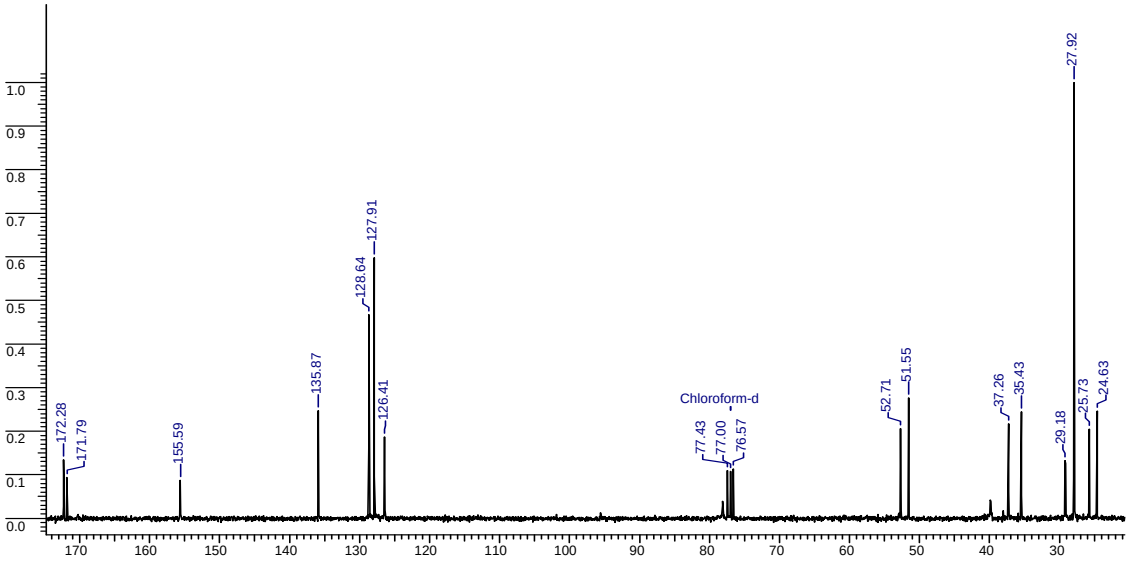
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **21**



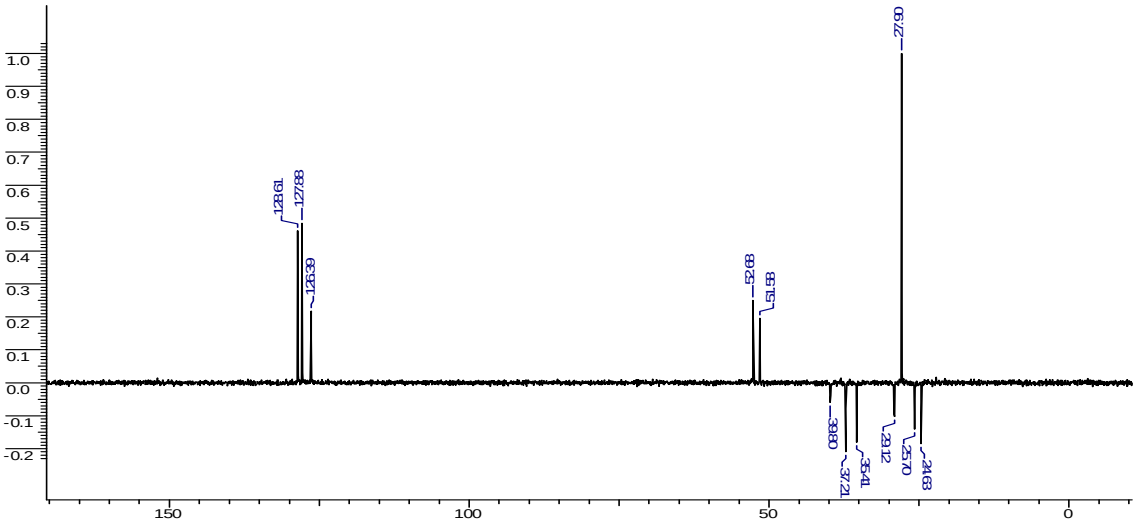
^{1}H NMR ($CDCl_3$, 300.13 MHz) spectrum of compound **26**



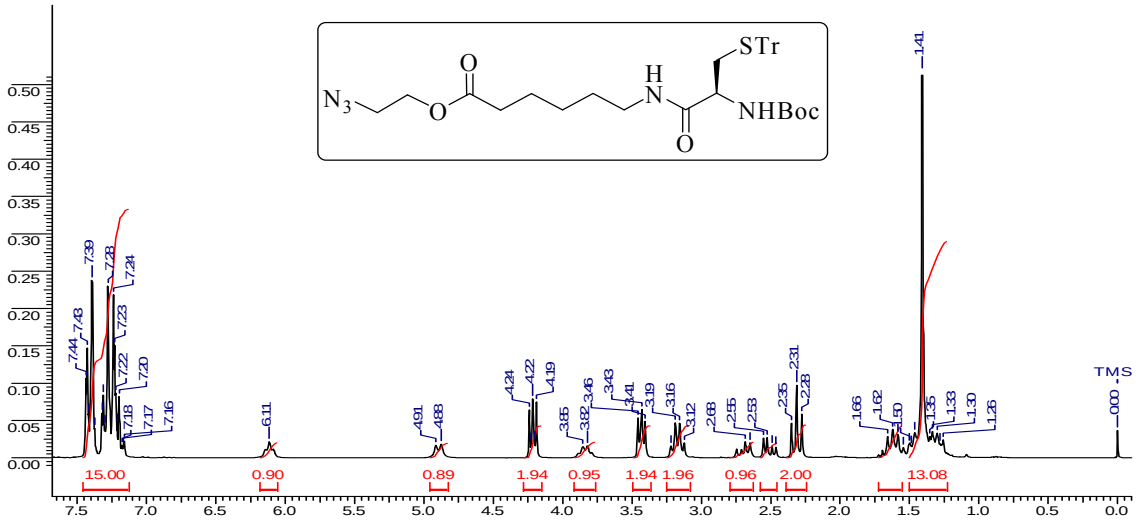
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **26**



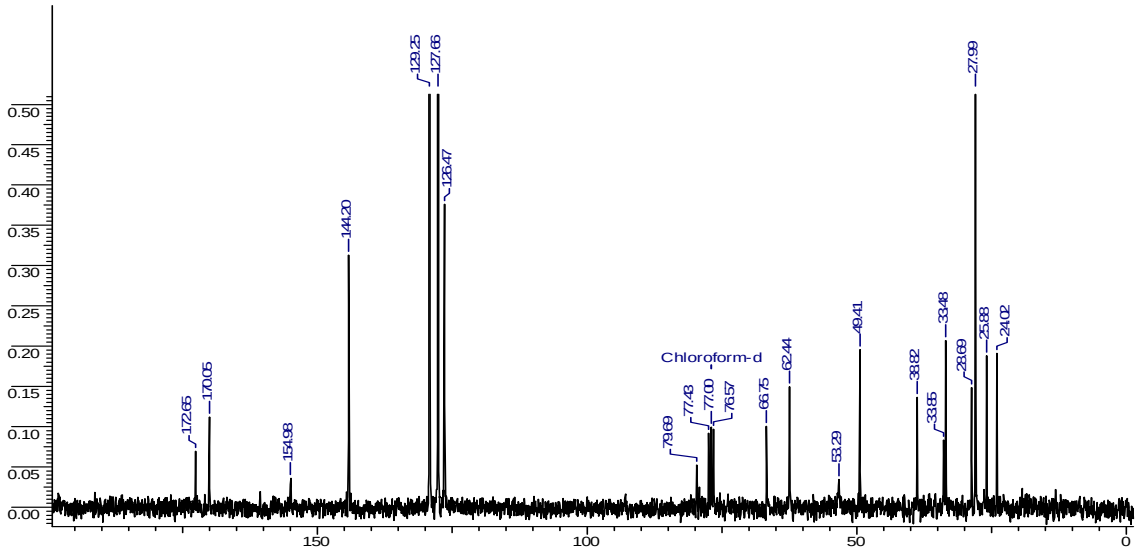
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **26**



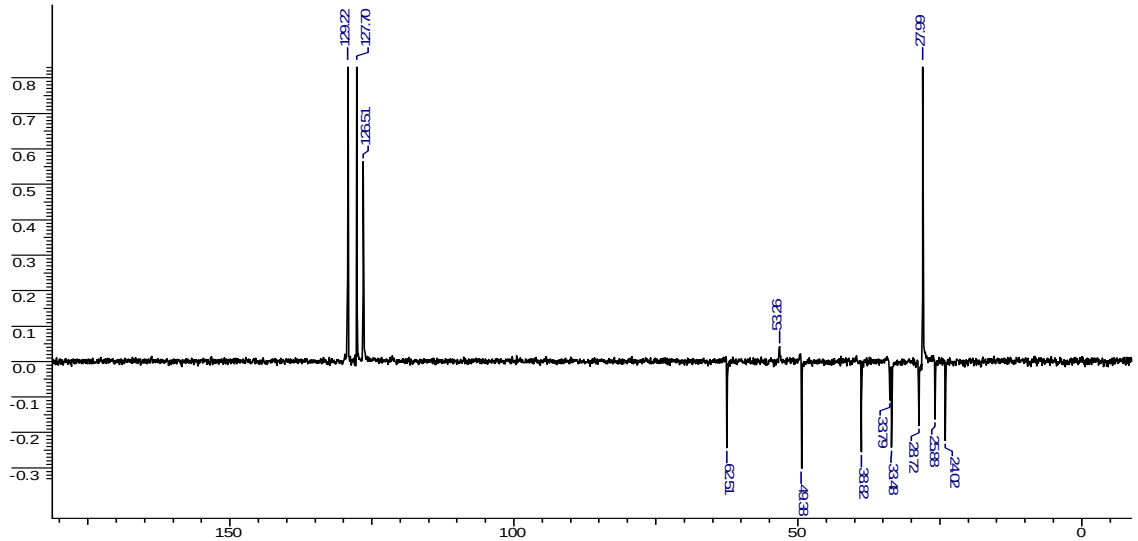
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **32**



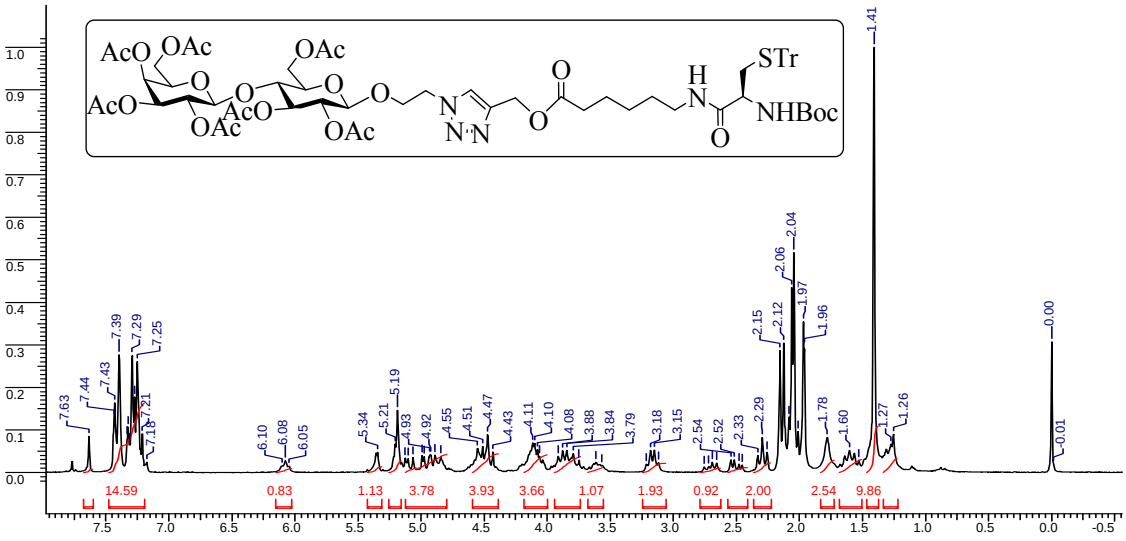
^{13}C NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **32**



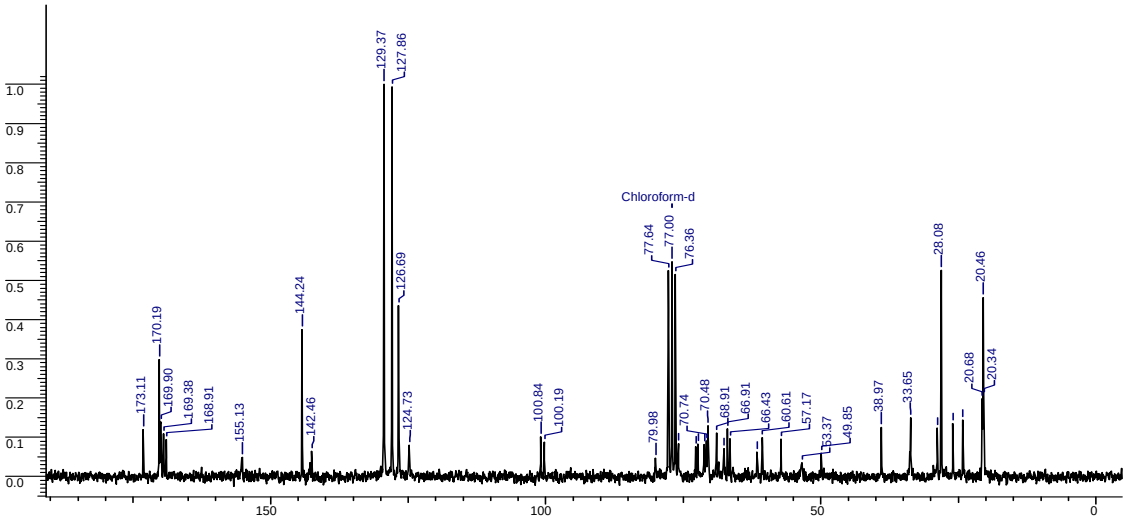
DEPT NMR ($CDCl_3$, 75.48 MHz) spectrum of compound **32**



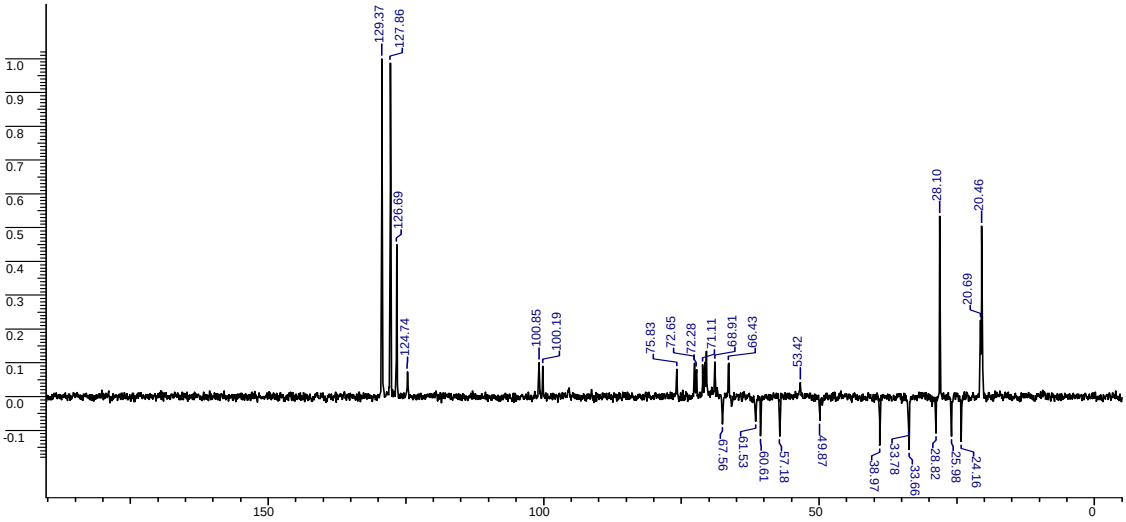
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **33**



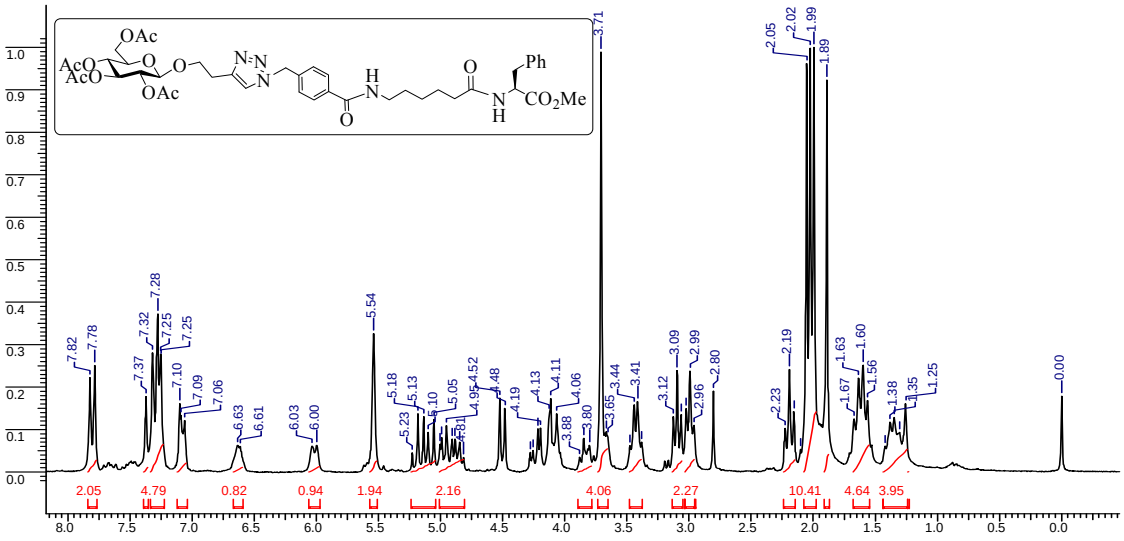
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **33**



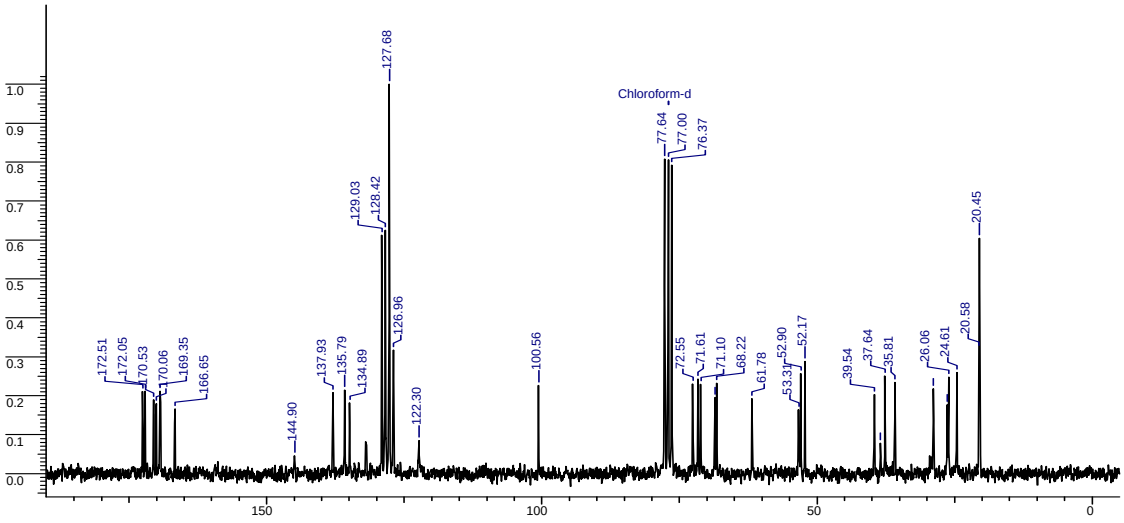
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **33**



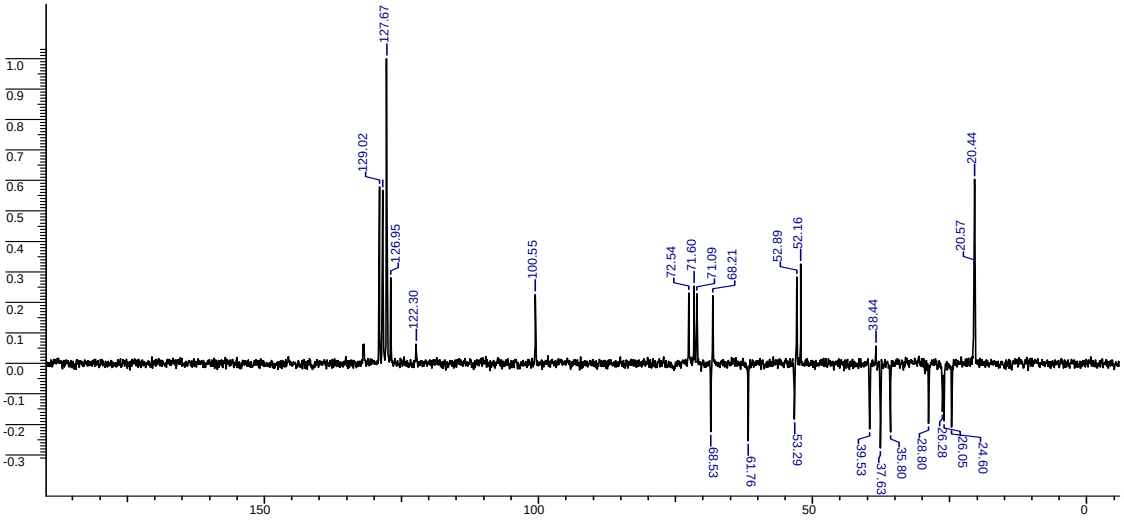
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **34**



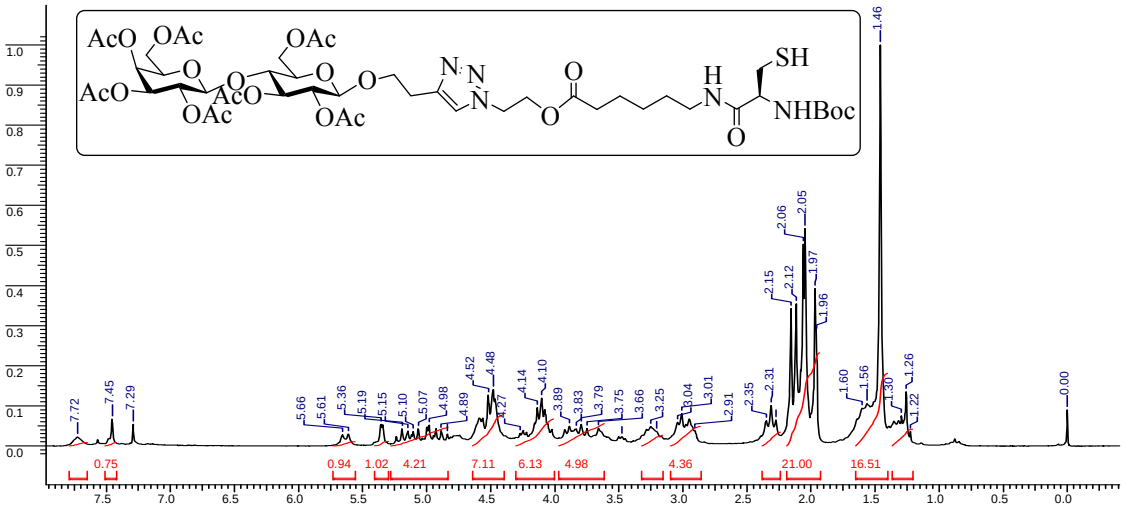
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **34**



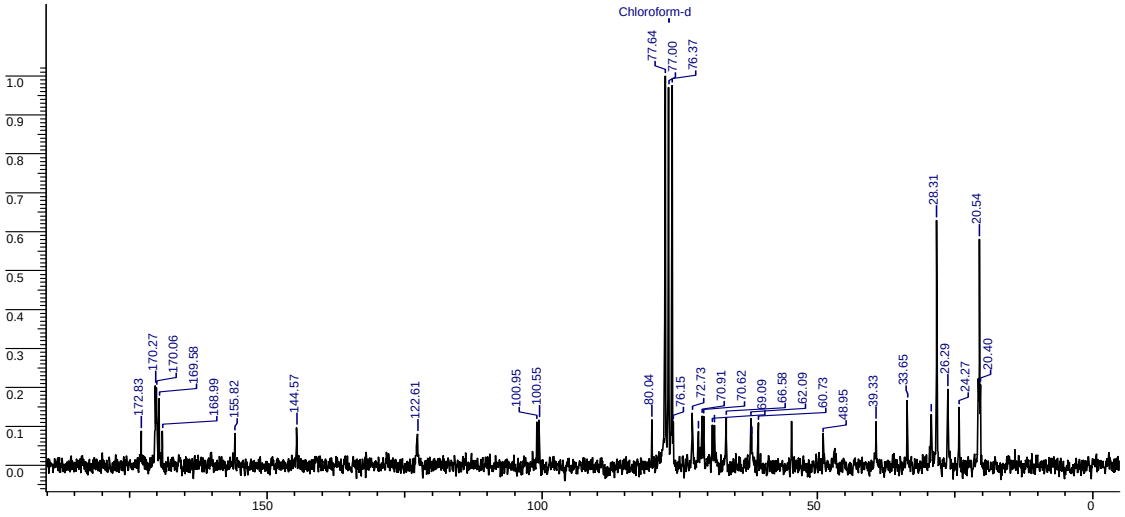
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **34**



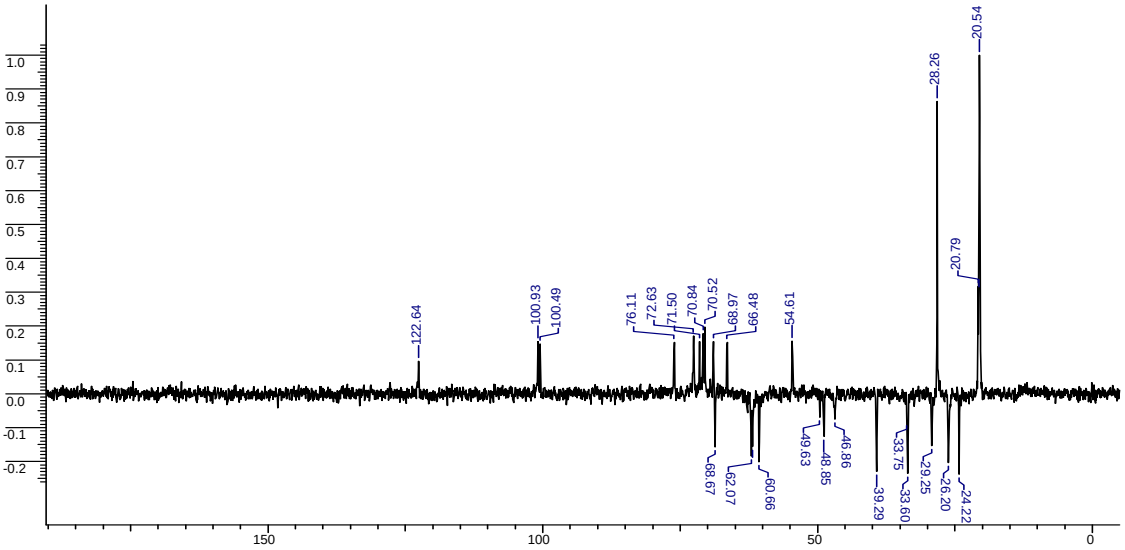
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **35**



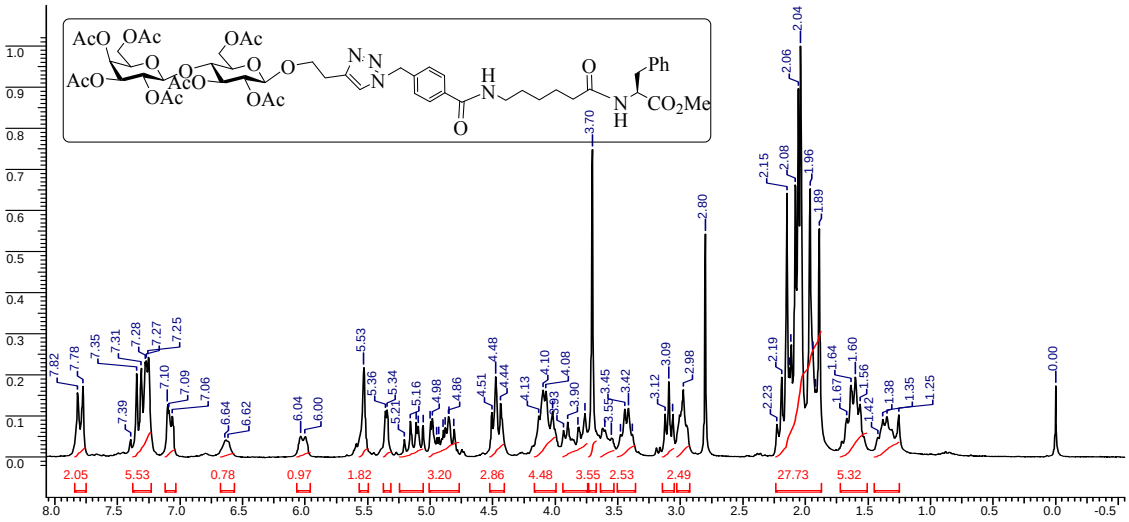
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **35**



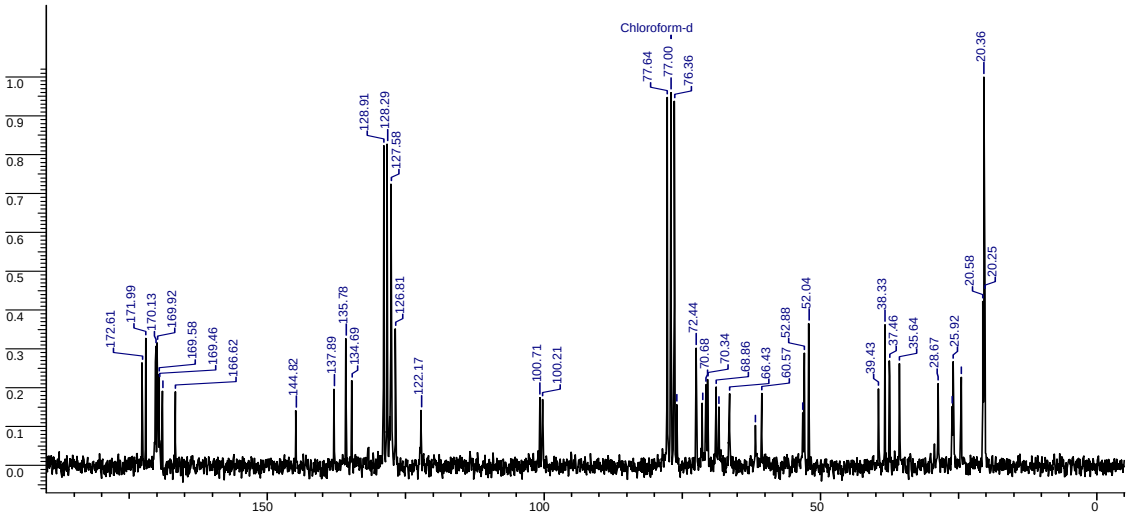
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **35**



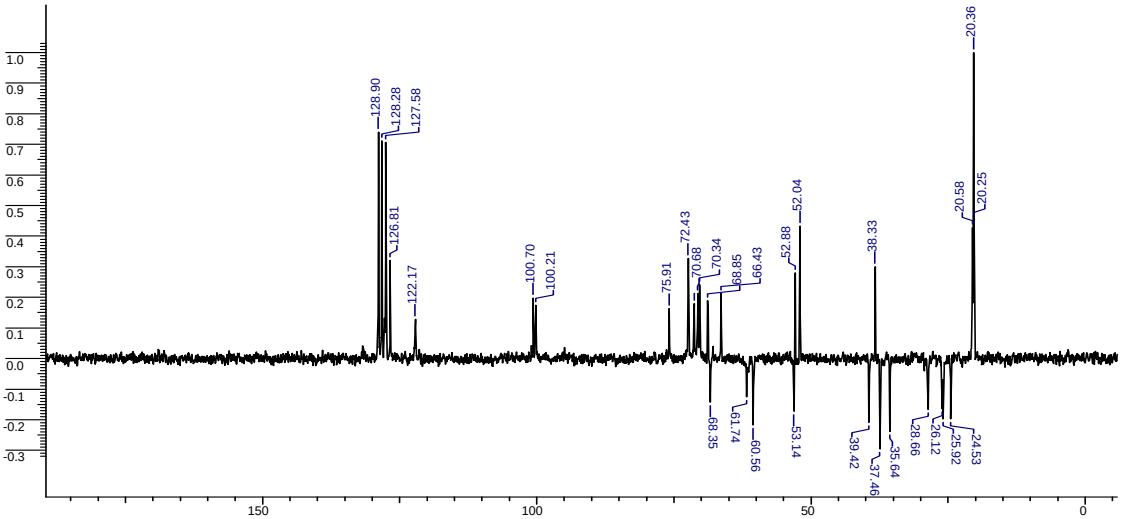
^{1}H NMR ($CDCl_3$, 200.13 MHz) spectrum of compound **36**



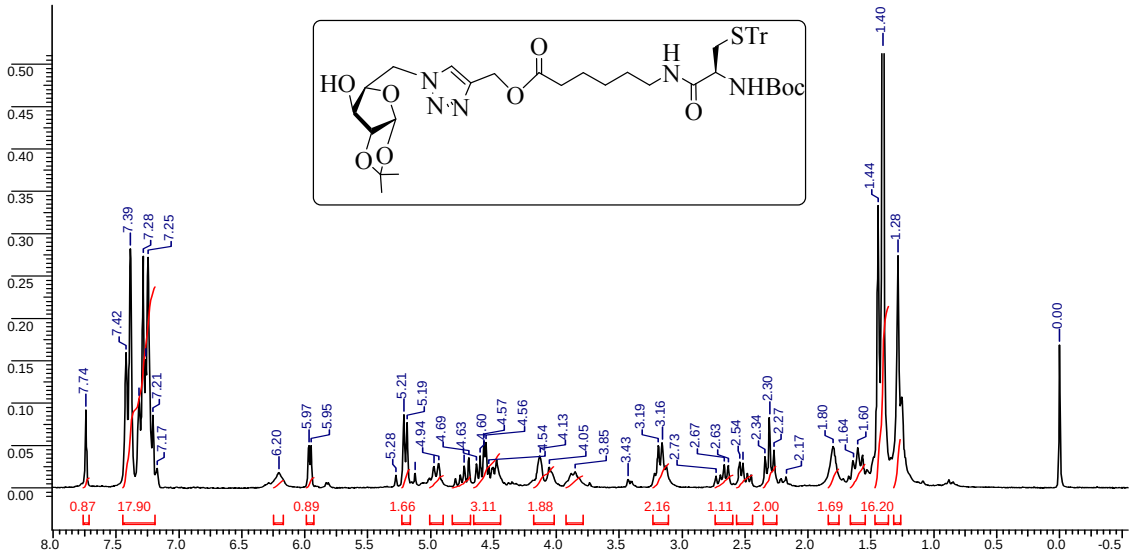
^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36**



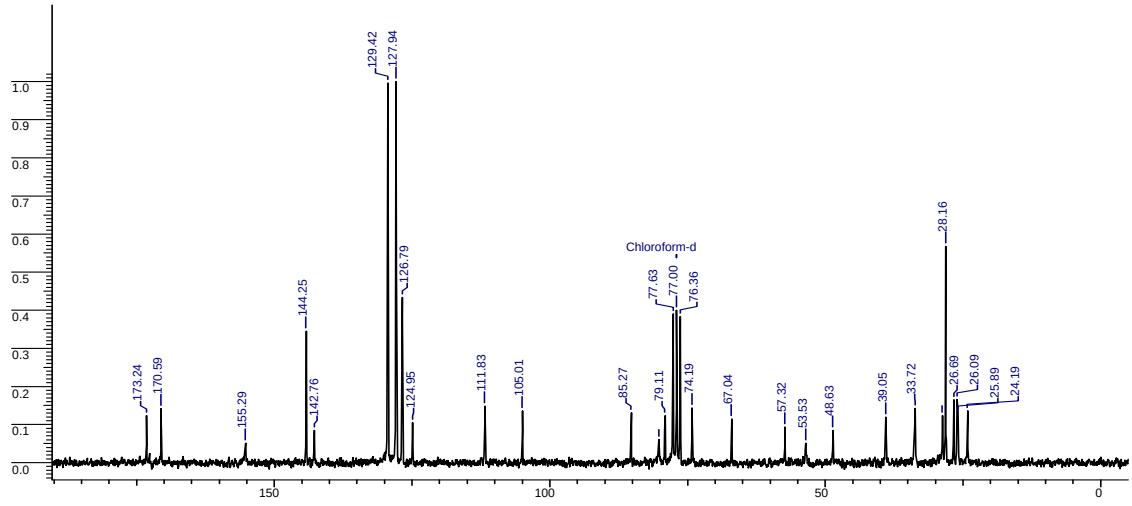
DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **36**



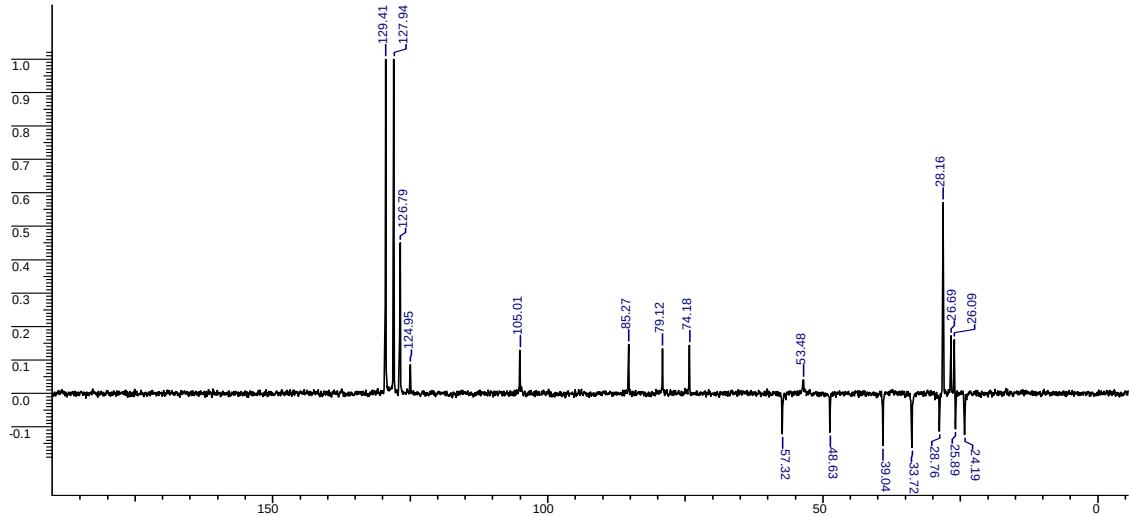
^{1}H NMR ($CDCl_3$, 200.13 MHz $_3$) spectrum of compound **37**



^{13}C NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37**



DEPT NMR ($CDCl_3$, 50.32 MHz) spectrum of compound **37**



Chapter 3: References

1. Barton, D.; Nakanishi, K. *Comprehensive Natural Products Chemistry.* Sankawa, U, Ed.; Elsevier: New York, **1999**.
2. (a) Kolb, H. C.; Finn, M. G. and Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004-2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V. and Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596-2599. (c) Kolb, H. C. and Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
3. (a) Sneader, W. In *Drug Prototypes and Their Exploitation*, John Wiley & Sons 3 Bemis, G.W. and Murcko, M.A. **1996**. (b) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996***, 39*, 2887–2893. (c) Seneci, P. In *Solid-Phase Synthesis and Combinatorial Technologies*. Wiley: New York, **2000**.
4. (a) Huisgen, R. *Angew. Chem., Int Ed.* **2001**, *7*, 321-328. (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*, Ed. Padwa, A., Wiley, **1984**, *1,* 1-176.
5. (a) Tietze, L. F.; Kettschau, G. *Topics in Current Chemistry* **1997**, *189*, 1-120. (b) Waldmann, H. *Synthesis* **1994**, 535-551. (c) Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3558–3588.
6. (a) Adolfsson, H.; Converso, A.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, *40*, 3991-3994. (b) Kolb, H.C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994***, 94*, 2483-2547. (c) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783-786. (d) Kühle, E. *Synthesis (Mass.) 11*, 563-586.
7. (a) Huisgen, R. *Proc. Chem. Soc*. **1961,** 367-369. (b) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613-628. (c) Huisgen, R. *Angew. Chern., Int. Ed., **1963,** 2,* 565.
8. Zhou, Z. and Fahrni, C. *J. Am. Chem. Soc.* **2004**, *126*, 8862-8863.
9. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057-3064.
10. (a) Hlasta, D. J,; James H. Ackerman, J. H. *J. Org. Chem*., **1994,** *59,* 6184. (b) Coat, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.,* **2005,** *7,* 1469.
11. Appukkuttan, P.; Dehaen, W.; Fokin, V.V.; Van der Eycken, E. *Org. Lett*. **2004**, *6*, 4223-4225.
12. Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2002**, *41*, 1053-1057.
13. Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc*. **2003**, *125*, 4686-4687.

14. (a) Prescher, J. A.; Bertozzi, C. R. *Nature Chem. Biol.,* **2005,** *1,* 13. (b) Rabuka, D.; Hubbard, S. C.; Laughlin, S. T.; Argade, S. P.; Bertozzi, C. R. *J. Am. Chem. Soc.,* ***2006*****,** *128,* 12078.
15. Yang, J.; Hoffmeister, D.; Liu, L.; Fu, Xun.; Thorson, J. S.; *Bioorg. Med. Chem*. **2004**, *12*, 1577-1584.
16. Lin, H.; Walsh, C. T. *J. Am. Chem. Soc*. **2004**, *126*, 13998-14003.
17. Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; *Katritzky*, A. R.; Rees, C. W. Eds.; Pergamon: Oxford, **1984**; *Vol. 5*, pp 669.
18. (a) Granie, T.; Panday, N.; Vasella, A. *Helv. Chem. Acta,* **1997,** *80,* 979. (b) Heightman, T. D.; Vasella, A.; Tsitsanou, K. E.; Zographos, S. E.; Skamnaki, V. T. Oikonomakos, N. G. *Helv. Chem. Acta,* **1998,** *81,* 853. (c) Mitchell, E. P.; Withers, S. G.; Ermert, P.; Vasella, A.; Garman, E. F.; Oikonomakos, N. G.; Johnson, L. N. *Biochemistry,* **1996,** *35,* 7341.
19. Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.,* **1994,** *37*, 4185.
20. Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.,* **1986,** *29,* 2262.
21. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stper, D.; Yagi, B. H. *J. Med. Chem*. **2000,** *43,* 953.
22. McGuire, J. J.; Russell, C. A.; Bolanowska, W. E.; Freitag, C. M.; Jones, C. S.; Kalman, T. I. *Cancer Res.* **1990**, *50,* 1726.
23. Sears, P.; Wong, C.H. *Cell. Mol. Life Sci.* **1998**, *54*, 223–252
24. (a) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077-3092. (b) Mitchell, M. L.; Tian, F.; Lee, L. V.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3041-3044.
25. Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588-9589.
26. Abdel-Rahman H.M.; Al-karamany G.S.; El-Koussi N.A.; Youssef A.F.; Kiso Y. *Curr. Med. Chem.* **2002**, *9*, 1905-1922.
27. Miller, V. *J. Acquir. Immune Defic. Syndr.* **2001**, *26*(Suppl. 1), S34–S50.
28. Brik, A. *et al. Chembiochem* **2003**, *4*, 1246-1248, **2005**, *6*, 1167-1169.
29. Tung, R. D. *et al. Infectious Disease and Therapy* **2002**, 25, 101-118.
30. Manetsch, R.; Krasinski, A.; Radic, Z.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126,* 12809.

31. (a) Mahal, L. K.; Yarema, K. J.; Bertozzi, C. R. *Science* **1997**, *276*, 1125-1128. (b) Vocadlo, D. J.; Hang, H. C.; Kim, E. J.; Hanover, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 9116-9121
32. Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193
33. Link, A. J.; Tirrell, D.A. *J. Am. Chem. Soc.* **2003**, *125*, 11164-11165
34. Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782-11783.
35. Cravatt, B. F.; Sorensen, E. J. *Current Opin. Chem. Biol*. **2000**, *4*, 663-668.
36. Manetsch, R.; Krasiński, A.; Radić, Z.; Raushel, J.; Taylor, P. Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc. 2004,* 126, 12809-12818
37. Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609-612
38. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215-3237.
39. Williams, S. J.; Davies, G. J. *Trends Biotechnol.* **2001**, *19*, 356-362.
40. Dudkin, V. Y; Orlova, M.; Geng, X.; Mandal, M.; Olson, W. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 9560-9562.
41. (a) Bryan, M. C.; Fazio, F.; Lee, H.-K.; Huang, C-Y.; Chang, A.; Best, M. D.; Calarese, D. A.; Blixt, O.; Paulson, J. C.; Burton, D.; Wilson, I. A.; Wong, C.-H. *J. Am. Chem. Soc.* **2004**, *126*, 8640-8641. (b) Park, S.; Lee, M.; Pyo, S.; Shin, I. *J. Am. Chem. Soc.* **2004**, *126*, 4812-4819.
42. Ballell, L.; Alink, K. J.; Slijper, M.; Versluis, C.; Liskamp, R. M. J.; Pieters, R. J. *ChemBioChem* **2005**, *6*, 291-295.
43. (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754-2794. (b) R. T. Lee, Y. C. Lee, *Glycoconjugate J.* **2000**, *17*, 543-551.
44. (a) Lindhorst, T. K.; Dubber, M.; Krallmann-Wenzel, U.; Ehlers, S. *Eur. J. Org. Chem.* **2000**, 2027-2034. (b) Nagahori, N.; Lee, R. T.; Nishimura, S.-I.; Pagé, D.; Roy, R.; Lee, Y. C. *ChemBioChem* **2002**, *3*, 836-844. (c) Autar, R.; Khan, A. S.; Schad, M.; Hacker, J.; Liskamp, R. M. J.; Pieters, R. J. *ChemBioChem* **2003**, *4*, 1317-1325. (d) Joosten, J. A. F.; Loimaranta, V.; Appeldoorn, C. C. M.; Haataja, S.; Ait El Maate, F.; Liskamp, R. M. J.; Finne, J.; R. Pieters, R. J. *J. Med. Chem.* **2004**, *47*, 6499–6508.
45. (a) Fan, E.; Zhang, Z.; Minke, W. E.; Hou, Z.; Verlinde, C. L. M. J.; Hol, W. G. J. *J. Am. Chem. Soc.* **2000**, *122*, 2663-2664. (b) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*,

669- 672. (c) Arosio, D.; Vrasidas, I.; Valentini, P.; Liskamp, R. M. J.; Pieters, R. J.; Bernardi, A. *Org. Biomol. Chem.* **2004**, *2*, 2113-2124.

46. (a) André, S.; Pieters, R. J.; Vrasidas, I.; Kaltner, H.; Kuwabara, I.; Liu, F.-T.; Liskamp, R. M. J.; Gabius, H.-J. *ChemBioChem* **2001**, *2*, 822-830. (b) Vrasidas, I.; S. André, S.; Valentini, P.; Böck, C.; Lensch, M.; Kaltner, H.; Liskamp, R. M. J.; Gabius, H.-J.; Pieters, R. J. *Org. Biomol. Chem.* **2003**, *1*, 803-810.
47. (a) Wittmann, V.; Seeberger, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 900–903. (b) Woller, E. K.; Walter, E. D.; Morgan, J. R.; Singel, D. J.; Cloninger, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 8820-8826.
48. (a) *Glycopeptides and Related Compounds: Synthesis, Analysis and Applications*; Large, D. G., Warren, C. D., Eds.; Marcel Dekker: New York, **1997**. (b) Kunz, H. *Angew. Chem., Int. Ed.* **1987**, *26*, *29*4. (c) Spiro, R. G. *Glycobiology* **2002**, *12*, 43R. (d) Seitz, O. *ChemBioChem* **2000**, *1*, 214.
49. (a) Wu, T. C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. (b) Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490.
50. (a) Gordon, E. J.; Sanders, W. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30. (b) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669. (c) Bovin, N. V.; Gabius, H. J. *Chem. Soc. Rev.* **1995**, *24*, 413. (d) Roy, R. *Curr. Opin. Struct. Biol.* **1996**, *6*, 69.
51. Paulsen, H. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 152.
52. Chittaboina, S.; Xie, F.; Wang. Q. *Tetrahedron Lett.* **2005**, *46*, 4585-4588 and references cited therein.
53. (a) Roy, R. In *Carbohydrate Chemistry*, *ed.* G. J. Boons, Chapman & Hall, UK, **1998**, p. 243. (b) Roy, R. *Curr*. *Opin*. *Struct*. *Biol*. **1996**, *6*, 692. (c) Kiessling L. L.; Pohl, N. L. *Chem*. *Biol*. **1996**, *3*, 71. (d) Bovin, N. V.; Gabius, H.-J. *Chem*. *Soc*. *Rev*. **1995**, *24*, 413. (e) Yarema, K. J.; Bertozzi, C. R. *Curr*. *Opin*. *Chem*. *Biol*. **1998**, *2*, 49. (f) Roy, R. In *Carbohydrates in Drug Design*, ed. Z. J. Witczak and K. A. Nieforth, Marcel Dekker, NY, **1997**, p. 83.
54. (a) Pozsgay, V. *Adv. Carbohydr. Chem. Biochem.* **2000**, *56*, 153-199. (b) Fernández-Santana, V.; Cardoso, F.; Rodriguez, A.; Carmenate, T.; Peña, L.; Valdés, Y.; Hardy, E.; Mawas, F.; Heynngnezz, L.; Rodríguez, M. C.; Figueroa, I.; Change, J.; Toledo, M. E.; Musacchio, A.; Hernández, I.; Izquierdo, M.; Cosme, K.; Roy, R.; Verez-Bencomo, V. *Infect. Immun.* **2004**, *72*, 7115-7123. (c) Peeters, C. C. A. M.; Evenberg, D.; Hoogerhout,

P.; Käyhty, H.; Saarinen, L.; van Boeckel, C. A. A.; van der Marel, G. A.; van Boom, J. H.; Poolman, J. T. *Infect. Immun.* **1992**, *60*, 1826-1833.

55. (a) Dominique, R.; Das, S. K.; Roy, R. *Chem. Commun.* **1998**, 2437-2438. (b) Schürer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203-1204. (c) Patch, R. J.; Chen, H.; Pandit, C. R. *J. Org. Chem.* **1997**, *62*, 1543-1546. (d) Roy, R.; Das, S. K.; Santoyo-González, F.; Hernández-Mateo, F.; Dam, T. K.; Brewer, C. F. *Chem. Eur. J.* **2000**, *6*, 1757-1762. (e) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123-3126. (f) Miller, J. S.; Dudkin, V. Y.; Lyon, G. J.; Muir, T. W.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 431-434.
56. (a) Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585-4588. (b) Joosten, J. A. F.; Tholen, N. T. H.; Maate, F. A. E.; Brouwer, A. J.; van Esse, G. W.; Rijkers, D. T. S.; Liskamp, R. M. J.; Pieters, R. J. *Eur. J. Org. Chem.* **2005**, 3182-3185. (c) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364 and 852.
57. (a) Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269-299. (b) Horne, W. S.; Yadav, M. K.; Stout, C.D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 15366-15367.
58. Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351-354
59. (a) TornØe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064. (b) Buchardt, J.; SchiØdt, C. B.; Krog-Jensen, C.; Delaissé, J.-M.; Foged, N. T.; Meldal, M. *J. Comb. Chem.* **2000**, *2*, 634-638.
60. Bodanszky, M. and Bodanszky, A. In *The Practice of Peptide Synthesis* (2 Edition) **1994**, pp.125-126.
61. Stewart, R. and Walker, L. G. *Can. J. Chem.* **1957**, *35*, 1561.

*****

List of Publications

Publications from the work described in this thesis:

1. Stereoselective synthesis of α-glucosides from 3-*O*-propargyl protected glucal exploiting alkynophilicity of $AuCl_3$: **Sudhir Kashyap** and Srinivas Hotha, *Tetrahedron Lett.* **2005,** *47,* 2021-2023.

2. "Click Chemistry" Inspired Synthesis of *pseudo*-Oligosaccharides and Amino Acid Glycoconjugates: Srinivas Hotha and **Sudhir Kashyap**, *J. Org. Chem.* **2005,** *71,* 364-367.

3. Propargyl Glycosides as Stable Glycosyl Donors: Anomeric Activation and Glycoside Syntheses: Srinivas Hotha and **Sudhir Kashyap**, *J. Am. Chem. Soc.* **2006,** *128,* 9620-9621.

4. Syntthesis of *C*-2 methylene glycosides from *C*-2 propargyloxymethyl glycals exploiting alkynophilicity of $AuCl_3$: **Sudhir Kashyap,** Srinivasa Rao Vidadala and Srinivas Hotha, *Tetrahedron Lett.* **2007,** *48,* 8960-8962.

5. Synthesis of Thioglycosides from Propargyl Glycosides Exploiting Alkynophilic Gold Catalyst: **Sudhir Kashyap**, Srinivasa Rao Vidadala and Srinivas Hotha (communicated).

Publications from the work NOT described in this thesis:

1. Gold Nanoparticle Networks with Photoresponsive Interparticle Spacings: Deepti S. Sidhaye, **Sudhir Kashyap**, Murali Sastry, Srinivas Hotha and B. L. V. Prasad, *Langmuir* **2005,** *21,* 7979-7984.

2. Enhanced Apoptotic Activity of Silica-Berberine-Nanoconjugates: Halimani, M.; Chandran, S. P.; **Sudhir Kashyap**; Jadav, V.; Prasad, B. L. V.; Hotha, S.; Maiti, S. (Communicated).

*****