Nucleophilic Addition Reactions on Glycosyl 1,2-Orthoesters

Thesis Submitted towards the partial fulfillment of

BS-MS dual degree programme

by

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20091028

Under the guidance of

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CERTIFICATE

This is to certify that this dissertation entitled Nucleophilic Addition Reactions on Glycosyl 1,2-Orthoesters towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents original research carried out by **Ravi Raja Adhikari Panda**, IISER Pune under the supervision of **Dr. Srinivas Hotha**, Associate Professor - Chemistry, IISER Pune during the academic year 2013-2014.

Date : 02.04.2014

Place: Pune

Srinivas Hotha, Ph. D.
Associate Professor - Chemistry

DECLARATION

I hereby declare that the matter embodied in the report entitled Nucleophilic Addition Reactions on Glycosyl 1,2-Orthoesters are the results of the investigations carried out by me at the Department of Chemistry, IISER Pune, under the supervision of Dr. Srinivas Hotha and the same has not been submitted elsewhere for any other degree.

Date: 02.04.2014

Ravi Raja A.P

Place: Pune

BS-MS Dual Degree Program, IISER Pune

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Ravi Raja A. P.

Contents

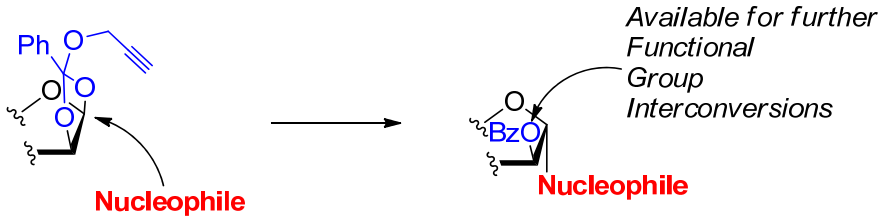
Abbreviations

TLC	Thin Layer Chromatography
M. S.	Molecular Sieves
NMR	Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectrometry
J	Coupling Constant
Hz	Hertz
MHz	MegaHertz
Ac	Acetyl
Bz	Benzoyl
Bn	Benzyl
DMF	N, N-dimethylformamide
DCM	Dicholoromethane
mg	Milligram
g	Gram
h	hour
M	Molar
mL	Millilitre
mol	Mole
Me	Methyl
THF	Tetrahydrofuran

Abstract

1,2-*trans* glycosides can be synthesized in a stereoselective manner through glycosyl 1,2-orthoesters. The utility of the protocol was demonstrated by the stereoselective synthesis of various carbohydrate epitopes present in infectious bacteria exploiting salient features of gold(III) catalysis. 1,2-orthoesters are stable and can be stored for longer periods without any degradation or decomposition. We envisioned that 1,2-orthoesters are highly useful synthons for the synthesis of those azido glycosides and cyano compounds where the *C*-2 hydroxyl group needs to become free for further chemistry. In this study, we explored utility of gold (III) catalysis for opening of propargyl 1,2-orthoesters by N- and C- nucleophiles.

Graphical Abstract



Introduction

Carbohydrates are the most voluminous class of organic compounds found in all living organisms.[1] They spring up as products of photosynthesis which is an endothermal process.[1] The consumption of these carbohydrates is the main source of energy in living forms. Carbohydrates are classified as monosaccharides, oligosaccharides and polysaccharides depending on the number of monosaccharide residues.

Tuberculosis is a disease caused by *Mycobacterium tuberculosis* (MTb), a bacterium.[2] MTb usually attacks lungs but can also attack other parts of the body such as kidneys, brain etc.[2] MTb transmits mainly through air when the person with TB coughs or sneezes and people nearby breathe the bacteria and get infected. TB has the second highest mortality after AIDS. It kills more than 3 million people every year and millions of them are getting infected. This coupled with the emergence of multiple drug resistant strains (MDR), extensively drug resistant strains (XDR) and immunocompromised patients (HIV/AIDS) escalated number of deaths because of MTb to alarming levels.[2]

Discovered by Robert Koch in 1882, MTb commonly attacks the lung but also known to affect the central nervous and lymphatic systems, bones and skin.[3] MTb belongs to the actinobacteria genus comprising gram positive bacteria with high GC content and is one of the largest taxonomic units within the domain.[4] Among the Actinobacteria, the genera *Corynebacterium, Mycobacterium* and *Nocardia* forms are identified by an unusually thick waxy capsular glycolipids mainly composed of unique long chain fatty acids called mycolic acids.[2] *Mycobacterium* genus is highly diverse comprising 85 different species among which majority are non-pathogenic environmental bacteria but a few such as MTb and *M. leprae* are slow growing and deadly.[2] MTb spreads via aerosol and is taken up by alveolar macrophages once it reaches the lung. MTb is a slow growing aerobic, prototrophic rod shaped bacterium of 0.3-0.5 μm diameter and of capricious length. MTb grows very slowly (doubling time ~23 h), shows ruffled colonies when cultured on artificial media indicating the

characteristic lipid rich cell wall and has very low metabolic activity. Furthermore, MTb tends to switch to a state of dormancy under extreme stress environments in the host which becomes very difficult to detect and treat as well.

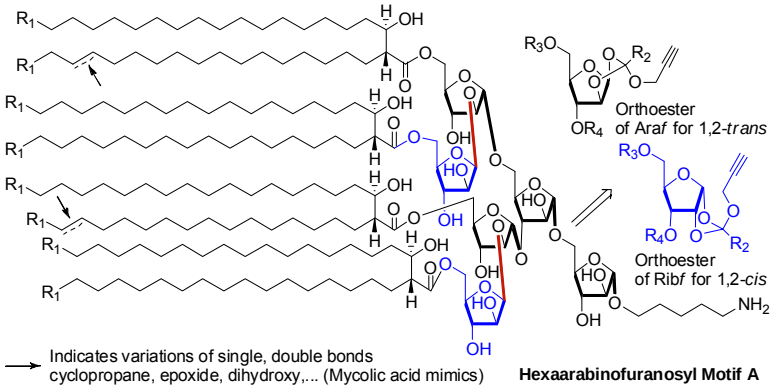


Figure 1. Part Structure of Arabinogalactan present of *M. tuberculosis* (MTb)

Mycobacterial Capsular Glycolipids

The complex and characteristic cell wall glycolipids of MTb make up about 40% of dry weight of bacterial cells which are made mostly of unusual sugars, mycolic acids and mycocerosic acids.[5] The capsular envelop also gains special significance being at the interface between the pathogen and the host mediating their interactions and promoting the pathogen's survival in the host.

The complete chemical structure of the cell wall of MTb has been unraveled.[6] Broadly, the glycan part of the capsular glycolipid has two components viz. lipoarabinomannan (LAM) and arabinogalactan (AG) which in turn have arabinose, galactose, mannose, rhamnose prominently.[6] Among these, arabinose and galactose exist in furanosyl forms which make the cell wall structure of MTb different from several other infectious bacteria and also important to note that ara*f*- and gal*f*- are xenobiotic to humans thereby making the unique cell wall a target for the development of novel therapeutic agents.[7] For example, ethambutol was shown to inhibit the arabinan biosynthesis that could in turn inhibit the growth of MTb cells.[7] Both AG and LAM contain arabinan domain of similar structure; however, arabinan structure in AG is more conserved (Figure 1) and structured when compared to LAM. Recent report by Shi *et al.* suggests that a key intermediate in the biosynthesis of arabinan is an octadecamer of Ara*f* having 10 of α-(1→5), 4 of β-(1→2) and 3 of α-

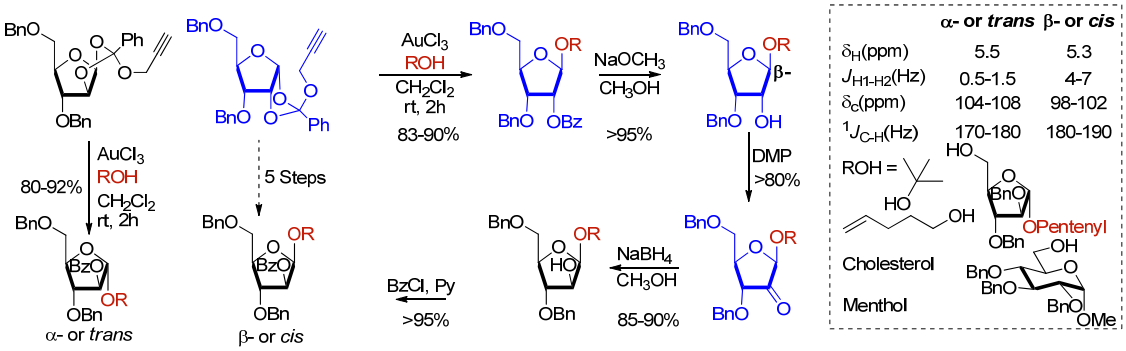
(1→3) linkages.[8] The terminal ara*f*- residues are linked to mycolic acids as esters (Figure 1). Ever since the identification of AG structure, unique and xenobiotic nature attracted the attention of synthetic carbohydrate chemists and several elegant strategies were developed for the synthesis of AG fragments using existing synthetic methodologies.[9]

Gold catalyzed glycosidation

From our laboratory, we discovered that propargyl glycosides can be activated in the presence of catalytic amount of gold(III) salts to undergo transglycosidation reaction.[10] The protocol has been tested with about 50 different aglycons thus far comprising aliphatic, aromatic, alicyclic, steroidal and carbohydrate alcohols to obtain excellent yields.[10] Later observations from the group proved that even methyl glycosides can also undergo similar transglycosidation at 70^{o}C in the presence of gold(III) catalysts under the aforementioned protocol.[10] The gold catalyzed transglycosidation reaction yields a mixture of both 1,2-*trans* and 1,2-*cis* isomers and it is found to be very difficult to separate them especially when number of saccharide residues increase to more than three. Thus, alkyne bearing 1,2-*O*-orthoesters were successfully explored for the synthesis of 1,2-*trans* glycosides in a stereoselective fashion.[10d,e]

Terminal carbohydrate epitope of MTb is a hexaarabinofuranosyl motif A. However, the chemistry of pyranosides and furanosides differs phenomenally as former compounds exhibit strong stereoelectronic effects whereas the selectivity in the latter depends primarily on steric factors. Indeed, propargyl and methyl rib*f*- and lyx*f*-donors resulted in the formation of only 1,2-*trans* glycosides where as 1,2-*trans* and 1,2-*cis* glycosides were noticed with corresponding ara*f*- and xyl*f*- donors. Thus the direct transglycosidation reaction cannot be used for the stereoselective synthesis of arabinofuranosides present in the Motif A. The attention was then redirected to apply the 1,2-*O*-orthoester strategy for making three of the 1,2-*trans* arabinofuranosides. Accordingly, propargyl orthoester of arabinose was subjected to the gold(III) catalysis to observe clean conversion of 1,2-*trans*- or α-arabinofuranosides. A number of substrates were checked to find out clean conversion to 1,2-*trans* isomers. The attention was then shifted for development of

novel method for the 1,2-cis or β-arabinofuranosides. 1,2-*cis* Arabinofuranosides (similar to β-mannopyranosides) are one of the toughest glycosides and the literature is abounding with various glycosyl donors such as *n*-pentenyl, thio-, sulfoxides-, aglycon delivery. However, the existing methods are low yielding or the preparation of the substrate is cumbersome.



Synthesis of α & β -arabinofuranosides from Propargyl 1,2-Orthoesters

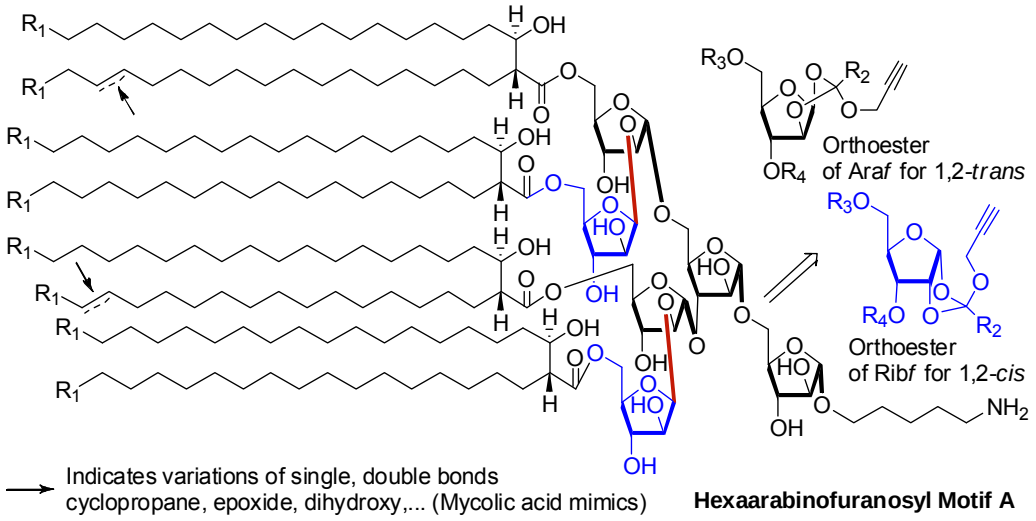
As delineated above, the synthesis of 1,2-*trans* ribfuranosides is a very easy proportion either by the transglycosidation reaction with propargyl/methyl ribofuranoside or by the use of 1,2-orthoester strategy. The challenging 1,2-*cis* arabinofuranosides can be envisaged by oxidoreduction strategy from 2-ulose derivatives of 1,2-*trans* ribofuranose derivatives. Earlier studies noticed that 2-ulose derivatives of α- or (1,2-*trans*)- ara*f* would result in both rib*f*- as well as ara*f*-configurations.[11] However, we anticipated that the reduction of β(1,2-*trans*) rib*f*-derived 2-ulose shall give 1,2-*cis* arabinofuranoside as the hydride attack can take place in *endo*- or the least sterically hindered fashion only.[11] Accordingly, 1,2-*O*-orthoesters of arab*f*- and rib*f*- were treated with $AuCl_3$ in various aglycons to give respective 1,2-*trans* glycosides in excellent yields.

For the β- or *cis*-ara*f*, *trans*-rib*f* was saponified under Zemplén deacetylation conditions and thus obtained secondary hydroxyl group was oxidized to 2-ulose derivative using Dess-Martin Periodinane (DMP) which was subsequently reduced with sodium borohydride to notice the formation of single 1,2-*cis* or β-arabinofuranoside in excellent yield.[11]

Significance of Arabinogalactan

Arabinogalactan is synthesized by several arabinofuranosyl transferases of MTb. Well known drugs such as Ethambutol and Isoniazide are shown to inhibit cell wall biosynthesis, for ex: isoniazide arrests the growth of mycobacterium TB by inhibiting the mycolic acid synthesis whereas ethambutol kills MTb by inhibiting the arabinan synthesis.[12] Importantly ethambutol inhibits arabinofuranosyl transferases involved in the synthesis of branching arabinans.

Several groups have synthesized various furanosyl motifs present in micobaterial cell surfaces. Many carbon-analogs of motifs C were synthesized as competitive inhibitors of arabinofuranosyl transferases. This promising strategy could lead to new therapeutic agents. Normally *O*-glycosides are susceptible for hydrolysis by either glycosidases or non enzymatic processes. Hence replacement of hydrolysable glycosidases by non-hydrolysable *C*-glycosides or *N*-glycosides would be ideal. As delineated above, Ethambutol works by inhibiting the branched arabinan synthesis. Thus synthesizing *C*- or *N*- analogs of motif B is a promising strategy rather than making *C*- or *N*- analogs of motif C as explored by others.[13]



Hexaarabinofuranosyl Motif A

Branching Motif B, requires installation of two 1,2-trans linkages which can be realized through glycosyl 1,2-orthoester strategy. The kind of glycosides generated when a sugar is linked with an aglycan establishing a C-O-C linkage are called O-glycosides. These glycoside linkages are normally found in nature.

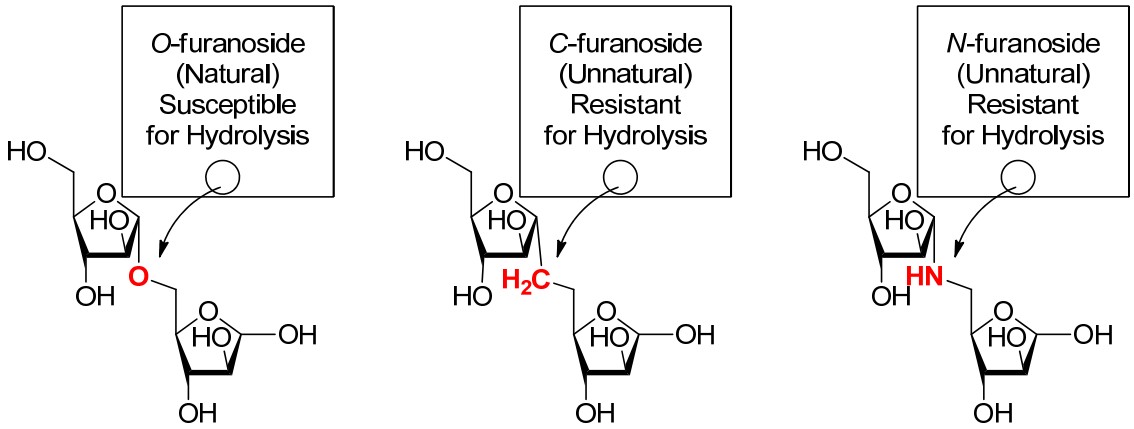


Figure 1. *O*-, *C*- and *N*- di arabinofuranosides

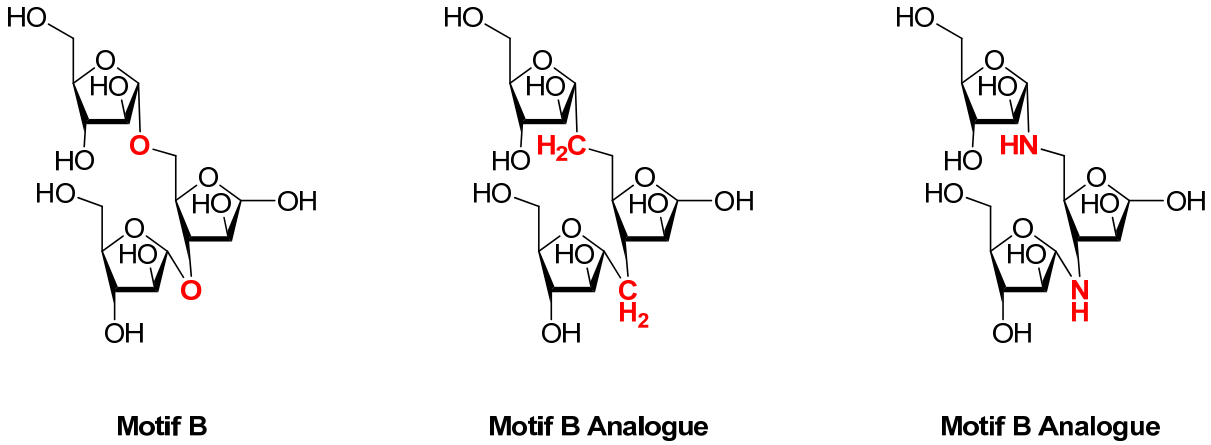


Figure 2. Target molecules

The kind of glycosides generated when a sugar is linked with an aglycan establishing a C-C-C linkage are called C-glycosides. These compounds are actually obtained by isosteric replacement of exocyclic oxygen with a CH_2- group (Figure 1). In addition, if the exocyclic oxygen is replaced isosterically with a NH group then these are called as *N*-glycosides (Figure 1).

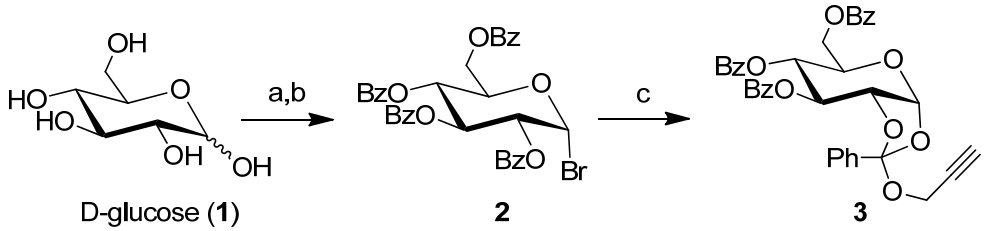
Importantly, *C*-glycosides and *N*-glycosides are chemically stable in metabolic processes and in addition, they can also inhibit carbohydrate processing enzymes unlike the glycans involved in intra and inter-cellular processes.

Methods that enable synthesis of these compounds will be highly useful for synthesizing many other C- or N-glycosides that are frequently noticed in natural products and pharmaceutical ingredients.

Earlier studies from our group showed that propargyl 1,2-orthoesters are very good glycosyl donors for giving 1,2-trans glycosides in a stereoselective manner. In addition, they also enable easy access to *C*-2 functionalizable glycosides upon saponification under Zémplen deacetylation conditions. Since their discovery by Kochetkov in early 1960s, all the synthetic endeavours have been placed on the utilization of 1,2-orthoesters for the synthesis of *O*-glycosides only except a recent report by Lopez group which reported the synthesis of nucleosides using *n*-pentenyl 1,2-orthoesters. The above delineated discussion prompted to investigated utility of propargyl 1,2-orthoesters for the synthesis of *N*- and *C*- glycosides enroute to the synthesis of unnatural motif B present in the Mycobacterium tuberculosis cell surface.

Accordinlgy, propargyl orthoesters of arabinose, ribose, xylose, glucose, galactose, mannose and lactose were synthesized in two steps via glycosyl bromide intermediate. The preparation of orthoesters in furanosyl form is a challenging one as most of the reported reaction conditions would enable preparation of 1,2-orthesters of pyranosides only. For example, treatment of aldose (**1**) with benzoyl chloride in pyridine ensues in the formation of the per-*O*-benzoylated glucopyranoside which can further be converted to corresponding bromosyl glucopyranoside (**2**) which can be subsequently transformed to alkyl 1,2-orthoester (**3**) in the presence of 2,6-lutidine and TBAI at reflux temperature (Scheme 1).

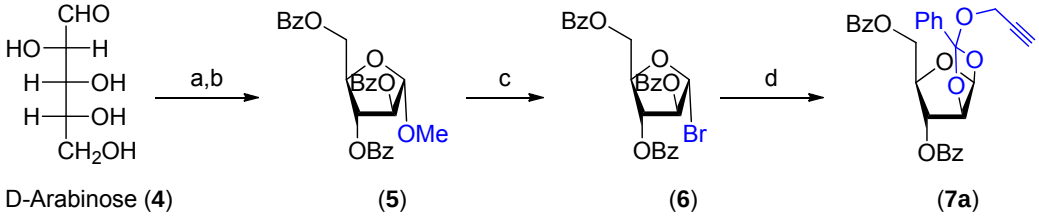
Scheme 1: Synthesis of Pyranosyl 1,2-Orthoester



Reagents: a) BzCl, Py, CH_2Cl_2, 0 ^oC to r.t., 12 h, b) HBr.AcOH, Ac_2O, CH_2Cl_2, 0 ^oC to r.t., 8 h (70% over two steps) c) Propargyl alcohol, 2,6-lutidine, TBAI, reflux, 24 h, 65%.

However, synthesis of bromosyl furanosides requires initial conformation locking and then subsequent conversion to the bromide in order to ensure the 1,2-orthoester of furanoside only. Accordingly, the synthetic endeavour started with the synthesis of propargyl 1,2-orthoesters starting from pentoses. For example, propargyl 1,2-orthoester of arabinose was obtained in four convenient steps with an overall yield of 70%. Arabinose (**4**) was converted into methyl arabinofuranoside under Fischer's acid mediated glycosidation condition, per-*O*-benzoylation to obtain compound **5** followed by bromination using HBr. AcOH to obtain bromosyl arabinofuranoside (**6**) which was refluxed in propargyl alcohol, 2,6-lutidine and catalytic amount of TBAI for 24h to obtain the 1,2-orthoester **7a** (Scheme 2).

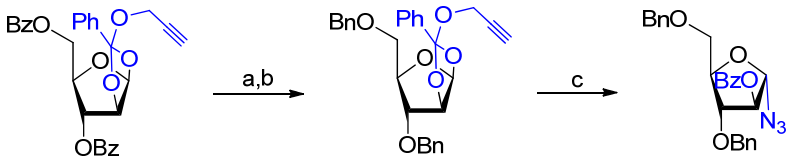
Scheme 2: Synthesis of furanosyl 1,2-Orthoester



Reagents: a) AcCl, MeOH, 0 °C, 6.5 h; b) BzCl, Py, 0 °C to rt, 12 h; c) AcBr, MeOH, 0 °C, 2 h; d) Propargyl alcohol, 2,6-lutidine,TBAI, CH_2Cl_2, reflux, 4 h, rt

Similar procedure was adopted for the synthesis of orthoesters from ribose (**8b**), xylose (**8c**), galactose (**8f**), glucose (**8d**), mannose (**8e**) and lactose (**8g**). All orthoesters were thoroughly confirmed by ^{1}H, ^{13}C NMR spectral analysis and also matched with that of reported values. For example, characteristic resonances at δ 121.3 ppm for the orthoester methine and three carbonyls δ 166.7 ppm confirmed the formation of 1,2-orthoester.

Scheme 3. Per-*O*-benzyl propargyl orthoester of arabinose



Reagents: (a) NaOMe, MeOH, rt, 1 h, 92%; (b) NaH, BnBr, DMF, TBAI, 0 °C-rt, 12 h, 95 %; (c) $TMSN_3$, $AuBr_3$, CH_2Cl_2, 4 Å Molecular Sieves Powder, 25 ºC, 30min, 95%.

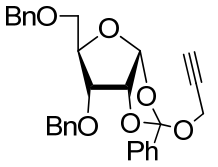
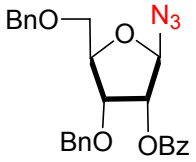
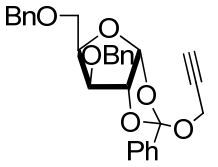
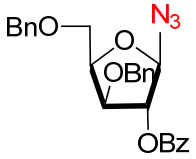
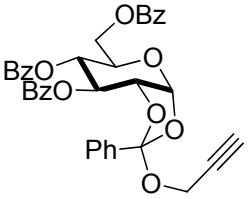
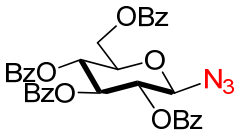
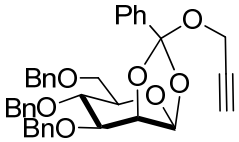
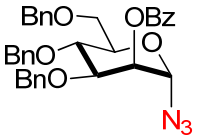
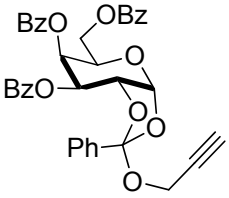
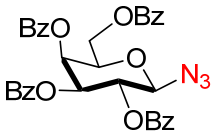
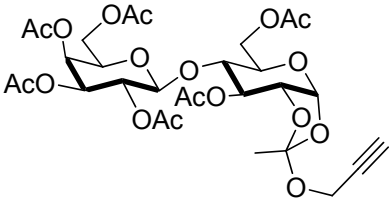
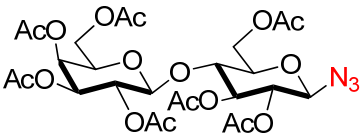
For the convenient deprotection of the *C*-2 position, the orthoester **7a** was converted into per-*O*-benzyl 1,2-orthoester **8a** in two steps (Scheme 3). Suresh and Hotha have shown earlier that propargyl 1,2-orthesters yield 1,2-trans glycosides in the presence of $AuCl_3$ (7 mol%) and aglycon under Argon atmosphere for 4h at room temperature. Addition of freshly activated 4 Å molecular sieves powder was found to be beneficial to avoid formation of lactol as a side product. The same observations were noticed when molecular sieves were improperly activated. In addition, good quality $AuBr_3$ is also essential in order to avoid the formation of trans-orthoester product.

Synthesis of *N*-glycosides was initially investigated after synthesizing sufficient quantities of all required propargyl 1,2-orthoesters. To begin, arabinofuranosyl orthoester **9a** was treated with 20 equivalents of $TMSN_3$ under standard gold catalysis conditions [$AuBr_3$ (7 mol%), CH_2Cl_2, 4Å molecular sieves powder at room temperature] for 30 min to obtain clean conversion to azido-arabinofuranoside (**9a**) in an excellent yield. Azide presence was confirmed with characteristic IR stretching frequency ν 2106 cm^{-1} which was observed in its IR spectrum. In the ^1H NMR spectrum, characteristic resonances corresponding to the anomeric proton were identified at δ 5.52 (d, J = 0.9 Hz, 1H) ppm and the ^{13}C NMR showed resonances due to anomeric carbon at δ 81.6 ppm. In addition, benzylic protons were noticed as quartets from 4-5ppm region in the ^1H NMR spectrum and the presence of lone benzoyl group was evident in the ^{13}C NMR spectrum wherein carbonyl resonances were observed at 165.6 ppm. All other sugar protons and carbons were observed in respective regions. In addition, the azide-derivative **9a** gave good matching of molecular weight in the HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}N_3O_5+Na]^+$: 482.1692; Found: 482.1694.

Furthermore, the utility of the protocol was weighed with a selected panel of 1,2-orthoesters **8b-8g** synthesized *vide supra*. In all the cases, the reaction proceeded smoothly, very efficiently and in a fully diastereoselective fashion to give corresponding 1,2-*trans* azido glycosides **9b**-**9f**. Gratifying to note that the reaction worked well even on the lactose (a disaccharide) derived orthoester **8g** to give azide **9g** at the anomeric position in 87% yield. Acetates, benzyl and benzoate protecting groups are tolerated under the identified reaction conditions (Table 1). All reactions

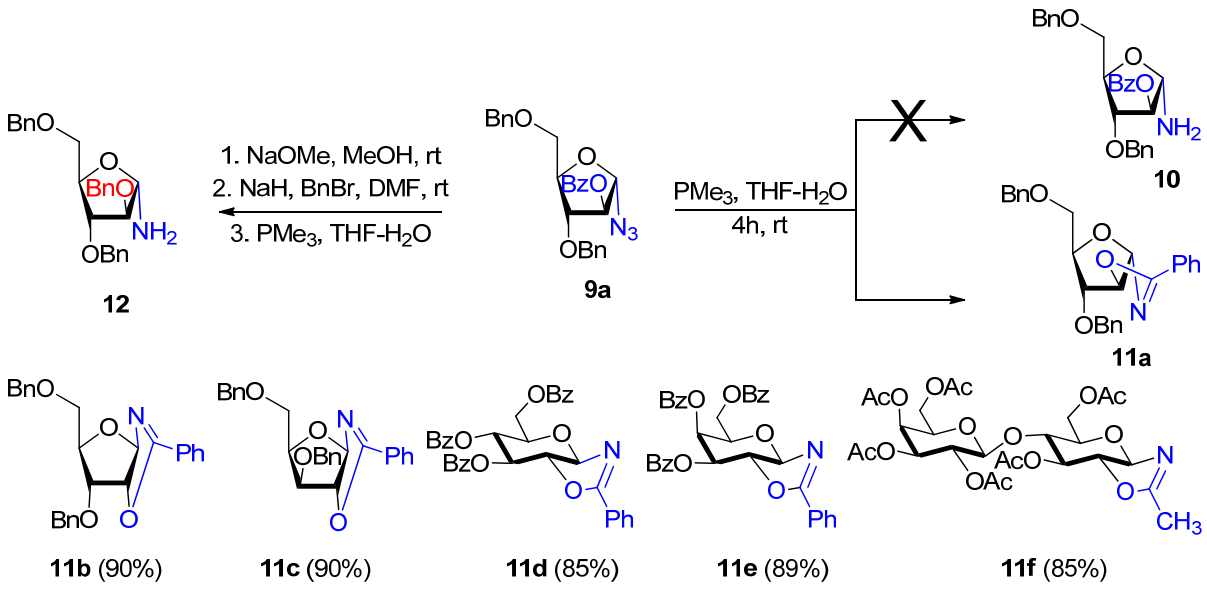
proceeded to give more than 85% yield and in a fully diastereoselective fashion. The reaction is catalytic and does not require harsh reaction conditions.

Table 1. Stereoselective synthesis of azido glycosides

S. No.	1,2-Orthoester	Azido-glycoside	% Yield
1	 **8b**	 **9b**	93
2	 **8c**	 **9c**	92
3	 **8d**	 **9d**	95
4	 **8e**	 **9e**	95
5	 **8f**	 **9f**	90
6	 **8g**	 **9g**	87

In continuation, reduction of anomeric azide to amine is required for which many reagents were considered, for example, THF-H_2O, Pd/C–H_2, $LiAlH_4$ etc. The best reaction conditions were found to be PMe_3 in THF-H_2O as solvent for the synthesis

of amine **10**. In the ^{1}H NMR spectrum of **10**, characteristic resonances of NH_2-compound were not noticed; but, the compound was found to be the oxazoline **11a**. In the 1H NMR spectrum of compound **11a**, the anomeric proton was observed around δ 6.22 (d, *J* = 5.6 Hz, 1H) ppm as singlet. In the ^{13}C NMR spectrum, resonances due to methine present in the oxazoline ring were noticed around δ 126.5 ppm.

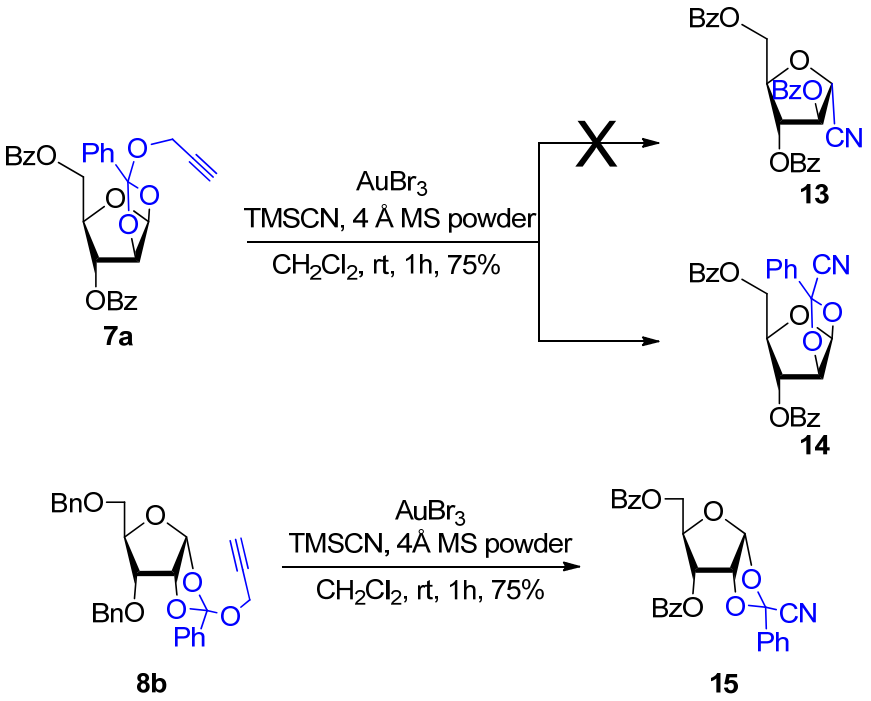


Pertinent to mention that the literature reports showed that oxazoline ring can form when ester group is present in the *C*-2 position as shown for the preparation of compound. Hence, anomeric amine can be synthesized if the C-2 position contains ether instead of ester. With this objective, saponification of azide **9a** was carried out with NaOMe in MeOH at room temperature followed by its conversion to the corresponding benzyl ether gave the requisite compound for the conversion of azide to amine. In continuation, PMe_3, THF-H_2O reaction resulted into the formation of required aminoglycoside **12** in very good yield which was thoroughly confirmed by various spectroscopic techniques.

Synthesis of C-Furanosides

C-Glycosides are envisioned by the use of TMSCN in place of $TMSN_3$. As a model reaction, arabinofuranosyl 1,2-orthoester **7a** was treated with TMSCN, $AuBr_3$, 4 Å MS powder, CH_2Cl_2, at room temperature for 1h to obtain a product which was

supposed to be the –CN glycoside **13**. However, the thorough NMR spectral analysis confirmed that the resulting compound as transorthoester product **14**.



In the ^{1}H NMR spectrum of compound **14**, anomeric proton was noticed at δ 6.30 (d, *J* = 4.1 Hz, 1H) ppm and in the ^{13}C NMR spectrum, resonances due to the anomeric carbon were identified at δ 107.3 ppm and gave very good matching with the high resolution mass spectroscopic analysis [m/z calcd for [$C_{27}H_{21}NO_7$+Na]+: 494.1216; Found: 494.1210]. Similar reaction carried out on the ribofuranosyl orthoester **8b** gave compound **15** in 75% yield. In the ^{1}H NMR spectrum of compound **15**, anomeric proton was noticed at δ 6.46 (d, *J* = 4.2 Hz, 1H) ppm and in the ^{13}C NMR spectrum, resonances due to the anomeric carbon were identified at δ 107.3 ppm and gave very good matching with the high resolution mass spectroscopic analysis [m/z calcd for [$C_{27}H_{21}NO_7$+Na]$^{+}$: 494.1216; Found: 494.1211].

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- All the chemicals were purchased from Sigma-Aldrich, RanKem and Spetrochemicals.
- ^{1}HNMR, ^{13}CNMR and DEPT spectra were recorded on Jeol-400 MHz spectrometer using tetramethylsilane (TMS) as an integral standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ESI HRMS data were recorded on Waters Synapt G2 spectrometer.
- Optical rotations were measured with a JACSO DIP 670 digital polarimeter.
- All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV-light, staining with I_2 and anisaldehyde in ethanol and ninhydrine.
- All reactions were carried out under nitrogen atmosphere with dry solvents purchased from Merck and Finar.
- All evaporations were carried out under reduced pressure on Büchi rotatory evaporator below 40 ^{o}C unless otherwise specified.
- Silica gel (100 -200) mesh were used for column chromatography.

Preparation of Hexose orthoesters (3, 8d, 8e, 8f, 8g): To a suspension of D-lactose (10.0 g, 27.8 mmol) in glacial acetic acid (50 mL) was added acetic anhydride (24 mL, 249.8 mmol) followed by catalytic amount of conc. H_2SO_4 and the reaction mixture was stirred at room temperature for 30 min. Then a solution of 33 % hydrobromic acid in glacial acetic acid (75 mL) was added at 0 °C and the resulting solution was stirred for an additional 5 h at room temperature. After completion of the reaction as judged by TLC, the reaction mixture was poured into ice and extracted with dichloromethane (2×100 mL). Combined organic layers were washed with water (3×200 mL), saturated NaHCO3 solution, water, dried over anhydrous sodium sulfate and concentrated in vacuo to give hepta-O-acetyl-α-D-lactopyranosyl bromide (18.3 g) that was redissolved in anhydrous dichloromethane (50 mL). To that, 2,6-lutidine (10 mL), propargyl alcohol (7.6 mL, 130.82 mmol) followed by a catalytic amount of tetra-n-butylammonium iodide (0.2 g) were added at room temperature under argon atmosphere. The reaction mixture was stirred at 70 °C for 36 h under argon atmosphere, quenched with a saturated solution of oxalic acid and extracted with dichloromethane (2× 100 mL). Combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate and concentrated in vacuo to obtain a brownish black residue, which was purified by silica gel column chromatography using petroleum ether-ethyl acetate as the mobile phase to give the corresponding lactose propargyl 1,2-orthoacetate **8g**.

Similar protocol have been followed for D-glucose **3** (10.0 g, 55.55 mmol) or D-galactose (10.0 g, 55.55 mmol) or D-mannose (10.0 g, 55.55 mmol) to prepare the respective orthoesters **8d**-**8g**.

Preparation of Pentose orthoesters **8a**-**8c:** Acetyl chloride (12 mL, 0.17 mol) was treated with MeOH (10 mL) at 0 ^{o}C for 30 min to give MeOH:hydrochloric acid solution. Further this solution was added to the D-arabinose **4** (20.0 g, 0.13 mol) in MeOH (125 mL) at 0 ^{o}C and warmed to room temperature. Progress of the reaction was monitored by the TLC (EtOAc:MeOH:*n*BuOH) until disappearance of the starting material. After completion of the reaction (6.5 h), the reaction mixture was quenched with pyridine (40 mL) and concentrated *in vacuo* and obtained a crude residue of

α:β methyl arabinofuranosides along with some amount of pyranoside (less than 10%). Crude methyl arabinofuranoside was dissolved in anhydrous pyridine (200 mL) and cooled to 0 ^{o}C, and slowly treated with benzoyl chloride (60 mL, 0.53 mol). Further, the reaction mixture was stirred for overnight at room temperature and few ice pieces were added to the reaction mixture; stirred for another 30 min at room temperature and then extracted with CH_2Cl_2 (2x). The extract was washed with 3N H_2SO_4, sat. sodium bicarbonate solution and organic layer was collected and dried sodium sulphate, concentrated in vacuo to yield crude α:β methyl 2,3,5-tri-O-benzoyl arabinofuranosides. This α,β mixture was dried under high vacuum and dissolved in hot EtOH (5%). The EtOH solution was kept at room temperature for 15 h and settled out solid was collected through filtration to give pure Methyl α-D-2,3,5-tri-O-benzoyl arabinofuranoside **5** as a white solid (31 g, 48.8%, m.p. 100 ^{o}C). Methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (31.0 g, 0.065 mol) prepared *vide supra* was redissolved in CH_2Cl_2 (150 mL) and cooled to 0 ^{o}C. Acetyl bromide (26.7 mL, 0.36 mol) was added to the reaction mixture followed by the drop wise addition of MeOH (11.9 mL, 0.29 mol) with constant stirring at 0 ^{o}C. Additionally, the reaction mixture was stirred for 2 h at 0 ^{o}C before dilution with CH_2Cl_2 (500 mL). The reaction mixture was poured into the cold water and aqueous layer was extracted with CH_2Cl_2 (2x250 mL) and organic layer was washed with cold sat. sodium bicarbonate solution, dried over sodium sulphate and concentrated under reduced pressure to give 2,3,5-tri-*O*-benzoyl arabinofuranosyl bromide **6** as white foam which was immediately used in the next step without any purification. The crude arabinofuranosyl bromide **6** was dissolved in 200 mL anhydrous CH_2Cl_2, propargyl alcohol (5.6 mL, 0.097 mol) and 2, 6-lutidine (15.1 mL, 0.13 mol). Tetra *n*-butyl ammonium iodide (1.44 g, 3.9 mmol) was added to the reaction and stirred for 4 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (250 mL) and water (500 mL) and the aqueous layer was extracted with CH_2Cl_2 (2x) and the organic extract was washed with sat. oxalic acid solution, sat. sodium bicarbonate solution. The organic phase was collected, dried over sodium sulphate and concentrated *in vacuo*. The crude residue of orthoester was purified by silica gel column chromatography (EtOAc:pet ether 20:80) to obtain **7a** (25.0 g, 76.8% over two steps) as white solid.

Preparation of *N*-glycosides 9a-9g from orthoesters: The propargyl orthoester **8a** in anhydrous CH_2Cl_2 was added 4 Å activated molecular sieves powder and then $TMSN_3$ is added drop wise at room temperature followed by addition of $AuBr_3$ and stirred for 30 min. After the work up, the crude residue was purified by silica gel column chromatography to obtain N-glycosides **9a**-**9g** in very good yields.

Preparation of Oxazolines from N_3: Azide **9a** was dissolved in THF and PMe_3 is added and stirred for 4 h in the presence of 4 Å molecular sieves powder. The reaction mixture was concentrated *in vacuo* and the resulting residue was redissolved in ethyl acetate and washed with water. Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography (EtOAc:pet ether 5:95) to obtain the oxazoline products **11a**-**11e**.

Preparation of *C*-glycosides from orthoester: The propargyl orthoester **8a** in anhydrous CH_2Cl_2 was added 4Å activated molecular sieves powder and then TMSCN is added drop wise at room temperature followed by addition of $AuBr_3$ and stirred for 30 min. After the work up, the crude residue was purified by silica gel column chromatography to obtain N-glycosides **9a**-**9g** in very good yields.

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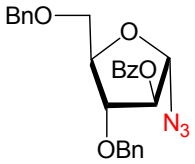
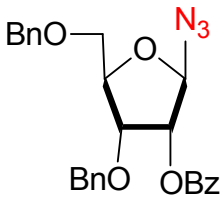
Azido-2-*O*-benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranoside (9a):



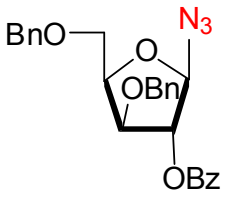
$(\alpha)^{25}_{D}$ ($CHCl_3$, *c* 1.0) +43.6; IR(cm^{-1}, $CHCl_3$): 3037, 2924, 2449, 2110, 1589, 1257, 1087; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 10.8, 4.5 Hz, 1H), 3.72 (dd, *J* = 10.8, 2.7 Hz, 1H), 4.28–4.38 (m, 2H), 4.40–4.64 (m, 4H), 5.32 (dd, *J* = 4.0, 1.2 Hz, 1H), 5.52 (d, *J* = 0.9 Hz, 1H), 7.17–7.25 (m, 5H), 7.28–7.38 (m, 5H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.56–7.62 (m, 1H), 8.07 (dd, *J* = 8.3,1.1 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 69.7 (CH_2), 73.2 (CH_2), 73.6 (CH_2), 74.7 (CH), 76.8 (CH), 81.6 (CH), 93.1 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 128.1 (CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 129.4 (C), 130.0 (CH), 130.0 (CH), 133.6 (CH), 137.2 (C), 138.1 (C),165.6 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}N_3O_5+Na]^+$: 482.1692; Found: 482.1694.

Azido-2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranoside (9b):



$(\alpha)^{25}_{D}$ ($CHCl_3$, *c* 1.0) -0.2; IR(cm^{-1}, $CHCl_3$): 3430, 2921, 2113, 1726, 1260, 1113, 742; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.56 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.71 (dd, *J* = 10.8, 2.7 Hz, 1H), 4.26–4.40 (m, 2H), 4.45–4.62 (m, 4H), 5.32 (dd, *J* = 4.0, 1.0 Hz, 1H), 5.52 (d, *J* = 1.0 Hz, 1H), 7.18–7.23 (m, 5H), 7.26–7.38 (m, 5H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.58 (m, *J* = 7.4 Hz, 1H), 8.05–8.08 (dd, *J* = 6.9, 1.2 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 69.7(CH_2), 73.2 (CH_2), 73.5 (CH_2), 74.7 (CH), 76.8 (CH), 81.6 (CH), 93.1 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 128.1 (CH) , 128.1 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 129.4 (C), 130.0 (CH), 130.0 (CH), 133.6 (CH), 137.2 (C), 138.1 (C), 165.6 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}N_3O_5+Na]^+$: 482.1692; Found: 482.1689.

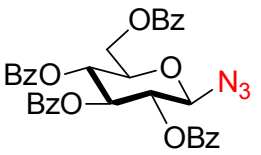
Azido-2-*O*-benzoyl-3,5-di-O-benzyl-β-D-xylofuranoside (9c):



$(\alpha)^{25}_{D}$ ($CHCl_3$, *c* 1.0) -111.8; IR(cm^{-1}, $CHCl_3$): 2919, 2115, 1726, 1248, 1100,7 06; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.85 (s,1H), 3.86 (d, J = 1.2 Hz, 1H) , 4.55–4.51 (m, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.61 (d, *J* = 10.7 Hz, 1H), 4.64 (d, *J* = 10.4 Hz,1H), 4.87 (d, *J* =12 .2 Hz, 1H), 5.34 (s, 1H), 5.41 (s, 1H), 7.37 – 7.22 (m, 10H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.60 (tt, *J* = 7.1, 1.2 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.3 Hz, 2H); ^{13}CNMR(100.53MHz, $CDCl_3$) δ 68.4 (CH_2), 72.1 (CH_2), 73.7 (CH_2), 80.0 (CH), 80.1 (CH), 82.8 (CH), 93.8 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH),128.7 (CH), 128.7 (CH), 128.7 (CH), 128.9 (C), 129.9 (CH), 129.9 (CH), 133.9

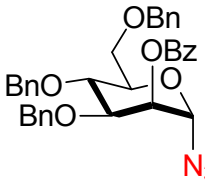
(CH), 137.2 (C), 138.0 (C),165.3 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}N_3O_5+Na]^+$: 482.1692; Found: 482.1685.

Azido-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (9d):



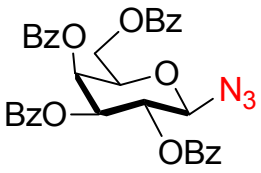
$(\alpha)^{25}_D$ (CHCl3, c 1.0) 13.5; IR(cm^{-1}, $CHCl_3$): 2119, 1729, 1264, 1097, 707; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.25 (ddd, *J* = 9.9, 5.0, 3.0 Hz, 1H), 4.51 (dd, *J* = 12.3, 5.1 Hz, 1H), 4.67 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.97 (d, *J* = 8.8 Hz, 1H), 5.49 (dd, *J* = 9.6, 8.9 Hz, 1H), 5.71 (t, *J* = 9.8 Hz, 1H), 5.93 (t, *J* = 9.7 Hz, 1H), 7.45–7.19 (m, 7H), 7.45–7.19 (m, 5H), 7.81 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.95 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.03 (dd, *J* = 8.3, 1.3 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 62.9 (CH_2), 69.2 (CH), 71.3 (CH), 72.8 (CH), 71.3 (CH), 74.5 (CH), 88.4 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.6 (C), 128.6 (C), 128.8 (C), 129.5 (C), 129.9 (CH), 129.9 (CH), 129.9 (CH), 129.9 (CH), 129.9 (CH), 129.9 (CH), 130.0 (CH), 130.0 (CH), 130.0 (CH), 133.3 (CH), 133.5 (CH), 133.7 (CH), 133.7 (CH), 162.1 (C=O), 165.2 (C=O), 165.8 (C=O), 166.2 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{34}H_{27}N_3O_9+Na]^+$: 644.1645; Found: 644.1646.

Azido-2-*O*-benzoyl-2,3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (9e):



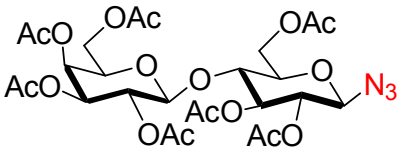
$(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0): 7.7; IR(cm^{-1}, $CHCl_3$): 2915, 2115, 1729, 1261, 1091, 744; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.64 (ddd, *J* = 9.4, 4.1, 2.2 Hz, 1H), 3.87–3.71 (m, 4H), 4.69–4.52 (m, 5H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 5.27–5.18 (m, 1H), 7.14–7.09 (m, 5H), 7.20–7.15 (m, 2H), 7.37–7.27 (m, 8H), 7.47–7.41 (m, 2H), 7.60–7.55 (m, 1H), 8.01 (dd, *J* = 8.5, 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): 68.4 (CH_2), 73.2 (CH), 73.7 (CH_2), 75.3 (CH_2), 75.4 (CH_2), 77.5 (CH), 77.6 (CH), 82.3 (CH_2), 88.3 (CH_2), 127.9 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.0 (CH),128.1 (CH), 128.1(CH), 128.4 (CH), 128.4 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 129.5 (C), 130.0 (CH), 130.0 (CH), 133.5 (CH), 137.7 (C), 137.8 (C), 138.0 (C), 165.2 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{34}H_{33}N_3O_6+Na]^+$: 602.2267; Found: 602.2266.

Azido-2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (9f):

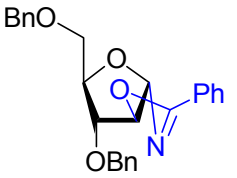


$(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0): 7.4; IR (cm^{-1}, $CHCl_3$): 3067, 2930, 2104, 1726, 1597, 1453, 1300, 1035, 709; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.48–4.43 (m, 2H), 4.66 (ddd, *J* = 9.9, 6.8, 2.9 Hz, 1H), 4.97 (d, *J* = 8.7 Hz, 1H), 5.64 (dd, *J* = 10.4, 3.3 Hz, 1H), 5.76 (dd, *J* = 10.4, 8.7 Hz, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 7.27–7.20 (m, 2H), 7.46–7.34 (m, 5H), 7.58–7.46 (m, 5H), 7.77 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.96 (dd, *J* = 8.4, 1.1 Hz, 2H), 8.02 (dd, *J* = 8.2, 1.3 Hz, 2H), 8.07 (dd, *J* = 8.2, 1.3 Hz, 2H). ^{13}C NMR (100.53 MHz, $CDCl_3$): 61.7 (CH_2), 67.7 (CH), 68.8 (CH), 71.3 (CH), 73.3 (CH), 88.4 (CH), 128.2 (CH), 128.2 (CH), 128.3 (C), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.4 (C), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.6 (C), 129.1 (CH), 129.1 (C),

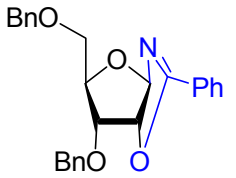
129.6 (CH), 129.6 (CH), 129.7 (CH), 129.8 (CH), 129.8 (CH), 133.2 (CH), 133.3 (CH), 133.4 (CH), 133.6 (CH), 165.0 (C=O), 165.2 (C=O), 165.2 (C=O), 165.9 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{34}H_{27}N_3O_9+Na]^+$: 644.1645; Found: 644.1641.



Azido per-*O*-acetyl-β-D-lactose (9g): $(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0) -11.5; IR(cm^{-1}, $CHCl_3$): 2922, 2120, 1750, 1373, 1231, 1059; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ1.93 (s, 3H), 2.02 (s, 6H), 2.03 (s, 3H), 2.04 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 3.70–3.65 (m, 1H), 3.88–3.75 (m, 2H), 4.13–4.01 (m, 3H), 4.51–4.41 (m, 2H), 4.60 (d, *J* = 8.7 Hz, 1H), 4.83 (d, *J* = 9.2 Hz, 1H), 4.93 (dd, J = 10.4, 3.5 Hz, 1H), 5.07 (dd, *J* = 10.4, 7.9 Hz, 1H), 5.18 (t, *J* = 9.2 Hz, 1H), 5.32 (dd, *J* = 3.5, 0.9 Hz, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 20.6 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 60.9 (CH_2), 61.8 (CH_2), 66.6 (CH), 69.1 (CH), 70.8 (CH), 71.0 (CH), 71.0 (CH), 72.6 (CH), 74.9 (CH), 75.9 (CH), 87.8 (CH), 101.2 (CH), 170.4 (C=O), 170.4 (C=O), 170.2 (C=O), 170.1 (C=O), 169.7 (C=O), 169.6 (C=O), 169.1 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{35}N_3O_{17}+Na]^+$: 684.1864; Found: 684.1926.

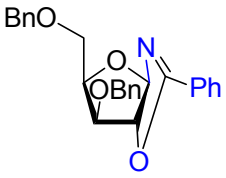


3,5-di-*O*-benzyl-1,2-phenyl oxazoline-α-D-arabinofuranoside (11a): $(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0): 154.1; IR(cm^{-1}, $CHCl_3$): 2918, 1634, 1451, 1360, 1090, 1025, 738; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.63 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.81 (dd, *J* = 11.1, 2.1 Hz, 1H), 3.76–3.68 (m, 1H), 4.11 (dd, *J* = 9.1, 5.4 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.61 (dd, *J* = 11.6, 4.8 Hz, 2H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.92 (t, *J* = 5.5 Hz, 1H), 6.22 (d, *J* = 5.6 Hz, 1H), 7.34–7.23 (m, 6H), 7.40–7.35 (m, 4H), 7.44–7.39 (m, 2H), 7.51 (tt, *J* = 7.6, 1.2 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.2 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 67.4 (CH_2), 72.4 (CH_2),73.6 (CH_2),76.6 (CH), 78.1 (CH), 78.6 (CH), 100.6 (CH), 126.5 (C), 127.7 (CH), 127.8 (CH), 127.8 (CH), 128.1 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 129.1 (CH),129.1 (CH), 132.4 (CH),137.6 (C),138.1 (C),167.9 (C=N); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}NO_4+H]^+$: 416.1862; Found: 416.1858.

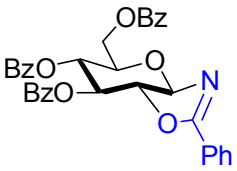


3,5-di-*O*-benzyl-1,2-phenyl oxazoline-β-D-ribofuranoside (11b): $(\alpha)^{25}_D$ (CHCl3, *c* 1.0): 171.3; IR(cm^{-1}, $CHCl_3$): 2868, 1644, 1452, 1360, 1085, 739; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 11.2, 3.7 Hz, 1H), 3.71 (ddd, *J* = 9.1, 3.6, 2.2 Hz, 1H), 3.82 (dd, *J* = 11.1, 2.1 Hz, 1H), 4.11 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.61 (dd, *J* = 11.6, 3.6 Hz, 2H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.92 (t, *J* = 5.5 Hz, 1H), 6.22 (d, *J* = 5.7 Hz, 1H), 7.46–7.24 (m, 12H), 7.55 – 7.48 (tt, *J* = 7.6,1.2 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.2 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 67.4 (CH_2), 72.4 (CH_2), 73.6 (CH_2), 76.6 (CH),78.1 (CH), 78.6 (CH), 100.6 (CH),126.5 (C),127.7

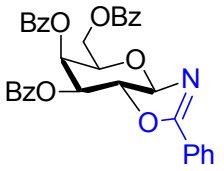
(CH), 127.8 (CH), 127.8 (CH),128.1 (CH),128.2 (CH),128.5 (CH),128.5 (CH),128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 129.1 (CH), 129.1 (CH),129.1 (CH),132.4 (CH),137.6 (C),138.1 (C),167.9 (C=N); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}NO_4+H]^+$: 416.1862; Found: 416.1860.



3,5-di-*O*-benzyl-1,2-phenyl oxazoline-β-D-xylofuranoside (11c): $(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0) -9.1; IR(cm^{-1}, $CHCl_3$): 2921, 1645, 1453, 1351, 1088, 698; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 3.94–3.77 (m, 3H), 4.14 (d, *J* = 3.1 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 5.7 Hz, 1H), 6.32 (d, *J* = 5.7 Hz, 1H), 7.38–7.22 (m, 10H), 7.44–7.38 (m, 2H), 7.51 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.98 (dd, *J* = 8.2, 1.1 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 67.1 (CH_2), 72.4 (CH_2), 73.7 (CH_2), 77.4 (CH), 81.6 (CH), 83.9 (CH),100.7 (CH), 126.5 (C), 127.8 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.9 (CH), 128.9 (CH),132.4 (CH), 137.5 (C), 138.6 (C), 166.5 (C=N); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{25}NO_4+H]^+$: 416.1862; Found: 416.1860.

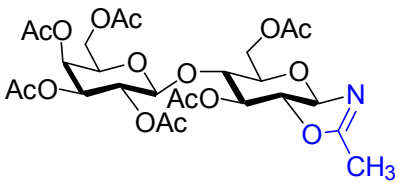


3,4,6-tri-*O*-benzyl-1,2-phenyl oxazoline-α-D-glucopyranoside (11d): $(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0): 11.6; IR(cm^{-1}, $CHCl_3$): 1727, 1264, 1100, 705; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.14–4.04 (m, 1H), 4.54 (dd, *J* = 12.0, 4.9 Hz, 1H), 4.66 (dd, *J* = 11.9, 3.5 Hz, 1H), 4.84 (ddd, *J* = 7.8, 3.6, 1.2 Hz, 1H), 5.57 (ddd, *J* = 7.5, 3.3, 0.9 Hz, 1H), 5.78 (t, *J* = 3.5 Hz, 1H), 6.25 (d, *J* = 7.8 Hz, 1H), 7.31–7.17 (m, 4H), 7.52–7.38 (m, 6H), 7.64–7.55 (m, 2H), 7.82 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.13–8.06 (m, 4H); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 64.6 (CH_2), 67.6 (CH), 68.5 (CH), 69.4 (CH), 74.8 (CH), 93.3 (CH), 126.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH),128.9 (C), 129.0 (C), 129.2 (CH), 129.7 (C), 129.8 (CH), 129.8 (CH), 129.9 (CH), 129.9 (CH), 130.1 (CH), 130.1 (CH), 132.9 (CH), 133.1 (CH), 133.5 (CH), 133.8 (CH), 165.0 (O-C=N), 165.1 (C=O), 166.3 (C=O), 167.1(C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{34}H_{27}NO_8+H]^+$: 578.1815; Found: 578.1813.

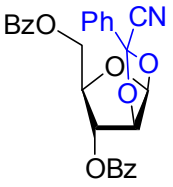


3,4,6-tri-*O*-benzyl-1,2-phenyl oxazoline-β-D-galactopyranoside (11e): $(\alpha)^{25}_D$ (CHCl3, c 1.0) 57.4; IR(cm^{-1}, $CHCl_3$): 3422, 2959, 2115, 1726, 1265, 1095; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 10.9, 6.3 Hz, 1H), 4.62 (td, *J* = 6.3, 2.5 Hz, 1H), 4.68 (dd, *J* = 10.8, 6.3 Hz, 1H), 4.98 (t, *J* = 7.0 Hz, 1H), 5.54 (dd, *J* = 7.0, 3.2 Hz, 1H), 6.00 (t, *J* = 2.8 Hz, 1H), 6.30 (d, *J* = 7.1 Hz, 1H), 7.47–7.33 (m, 8H), 7.63–7.48 (m, 4H), 8.05–7.92 (m, 8H); ^{13}C NMR (100.56 MHz, $CDCl_3$): 62.1 (CH_2), 67.3 (CH), 67.0 (CH), 72.3 (CH), 77.4 (CH), 94.4 (CH), 126.6 (C), 128.4 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 129.0

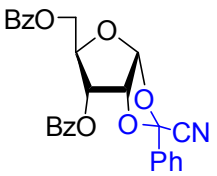
(CH), 129.0 (CH), 129.1 (C), 129.2 (C), 129.5 (C), 129.9 (CH), 129.9 (CH), 129.9 (CH), 129.9 (CH), 130.0 (CH), 130.0 (CH), 132.8 (CH), 133.2 (CH), 133.5 (CH), 133.7 (CH), 165.4 (C=O), 165.6 (C=O), 166.1 (C=O), 166.7 (C=N). HRMS (Waters Synapt G2): m/z calcd for $[C_{34}H_{27}NO_8+H]^+$: 578.1815; Found: 578.1815.

Per-*O*-acetyl-1,2-methyl oxazoline lactose (11f): 

$(\alpha)^{25}_D$ ($CHCl_3$, *c* 1.0): 4.2; IR(cm^{-1}, $CHCl_3$): 3408, 2923, 1757, 1372, 1232, 1053, 757; ^{1}H NMR(399.78 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.01 (s, 3H), 2.01 (s, 3H), 2.03 (s, 6H), 2.09 (s, 3H), 2.12 (s, 3H), 3.53–3.62 (m, 1H), 3.66–3.73 (m, 1H), 3.80–3.86 (m, 1H), 4.02–4.16 (m, 4H), 4.39–4.47 (m, 2H), 4.65–4.73 (m, 1H), 4.91 (dd, *J* = 10.4, 3.5 Hz, 1H), 5.03–5.10 (m, 1H), 5.19 (t, *J* = 9.4 Hz, 1H), 5.33 (ddd, *J* = 13.7, 3.4, 0.9 Hz, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 20.6 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 60.9 (CH_2), 62.1 (CH_2), 66.7 (CH), 69.2 (CH), 70.7 (CH), 71.1 (CH), 72.5 (CH), 73.0 (CH), 73.7 (CH), 76.7 (CH), 84.7 (CH), 101.1 (CH), 170.4 (C=O), 170.4 (C=O), 170.2 (C=O), 170.1 (C=O), 169.7 (C=O), 169.5 (C=O), 169.1 (C=O); HRMS (Waters Synapt G2): m/z calcd for $[C_{26}H_{35}NO_{16}+H]^+$: 618.2034; Found: 618.2037.

3,5-di-*O*-benzoyl arabinofurano-1,2-cyano orthoester (14): $(\alpha)^{25}_D$ 

($CHCl_3$, *c* 1.0) 108.3; IR(cm^{-1}, $CHCl_3$): 2955, 2128, 1727, 1269, 1110, 708; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.43–4.56 (m, 2H), 4.72 (dd, *J* = 12.1, 3.0 Hz, 1H), 5.19 (dd, *J* = 9.1, 5.1 Hz, 1H), 5.33–5.45 (m, 1H), 6.30 (d, *J* = 4.1 Hz, 1H), 7.33 – 7.50 (m, 7H), 7.51–7.60 (m, 2H), 7.67–7.73 (m, 2H), 7.95–8.08 (m, 4H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 62.3 (CH_2), 72.5 (CH), 76.7 (CH), 78.7 (CH), 102.8 (C), 105.5 (CH), 116.4 (CN), 125.9 (CH),125.9 (CH), 128.5 (CH),128.5 (CH), 128.7 (CH),128.7 (CH), 128.8 (C), 129.0 (CH), 129.0 (CH),129.4 (C), 129.8 (CH),129.8 (CH), 130.0 (CH),130.0 (CH), 131.3 (C), 133.4 (CH), 133.4 (CH), 133.9 (CH), 165.5 (C=O), 166.1 (C=N); HRMS (Waters Synapt G2): m/z calcd for $[C_{27}H_{21}NO_7+Na]$+: 494.1216; Found: 494.1210.

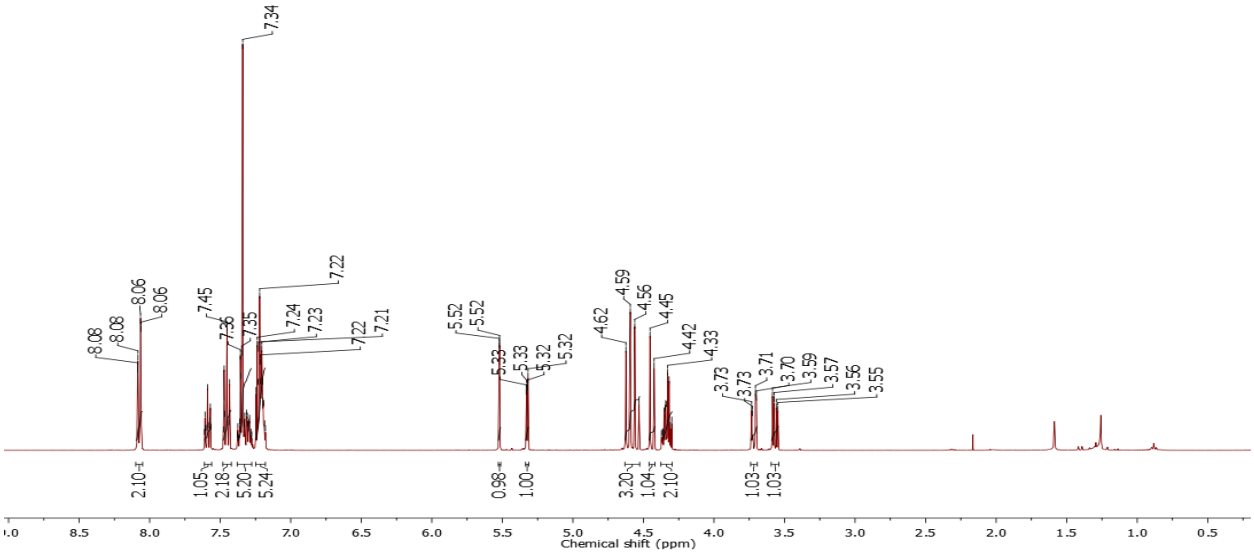
3,5-di-*O*-benzoyl ribofurano-1,2-cyano orthoester (15): $(\alpha)^{25}_D$ 

($CHCl_3$, *c* 1.0): 102.4; IR(cm^{-1}, $CHCl_3$): 3447, 2928, 1714, 1269, 1111, 713; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 7.0, 3.4 Hz, 2H), 4.73 (t, *J* = 7.0 Hz, 1H), 5.25 (d, *J* = 4.1 Hz, 1H), 5.58 (s, 1H), 6.46 (d, *J* = 4.2 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.44–7.50 (m, 5H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 2H), 8.00–8.06 (m, 4H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 63.6 (CH_2), 77.0 (CH), 85.4 (CH), 86.0 (CH), 102.6 (C), 107.3 (CH), 116.3 (CN), 125.9 (CH), 125.9 (CH), 128.5 (CH), 128.5 (C), 128.6 (CH), 128.7 (CH),128.7 (CH),129.1 (CH), 129.1 (CH), 129.5 (C), 129.9 (CH), 129.9 (CH),130.0 (CH),130.0 (CH), 131.4 (CH), 132.7 (C), 133.3 (CH), 134.0 (CH), 165.3 (C=O), 165.9 (C=N); HRMS (Waters Synapt G2): m/z calcd for $[C_{27}H_{21}NO_7+Na]^+$: 494.1216; Found: 494.1211.

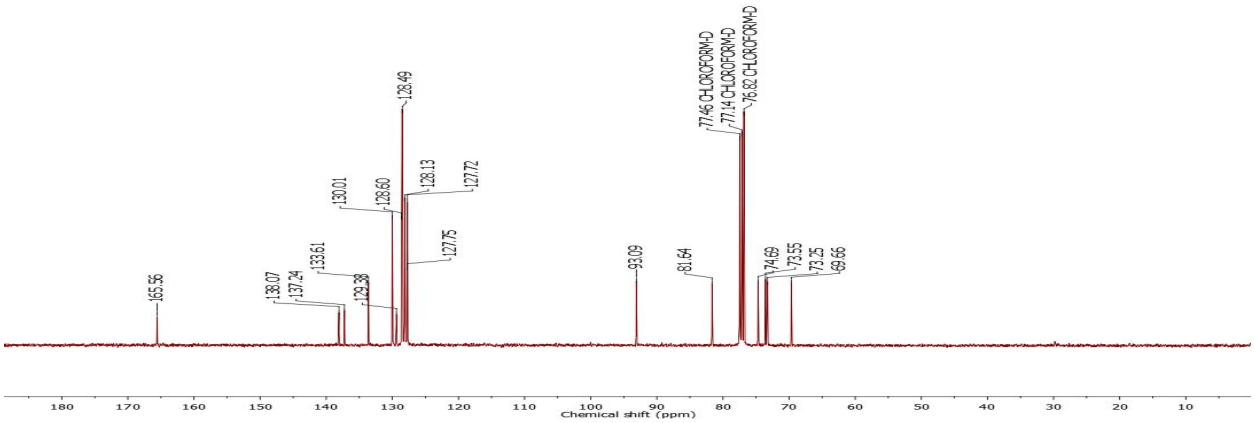
Conclusions

1,2-*trans* glycosides are synthesized in a stereoselective manner through glycosyl 1,2-orthoesters by gold(III) catalysis. The utility of the protocol was demonstrated by the stereoselective synthesis of 1,2-*trans* *N*-glycosides. 1,2-orthoesters are stable and can be stored for longer periods without any degradation or decomposition. 1,2-Orthoesters are shown to be highly useful synthons for the synthesis of azido glycosides and where the *C*-2 hydroxyl group needs to become free for further chemistry. Reduction of the azide group resulted into the formation of 1,2-oxazoline compounds which could have interesting biological properties. In addition, C-glycosidation reaction using TMSCN resulted in the nucleophilic displacement of propargyloxy group with nitrile giving access one of the unique set of compounds.

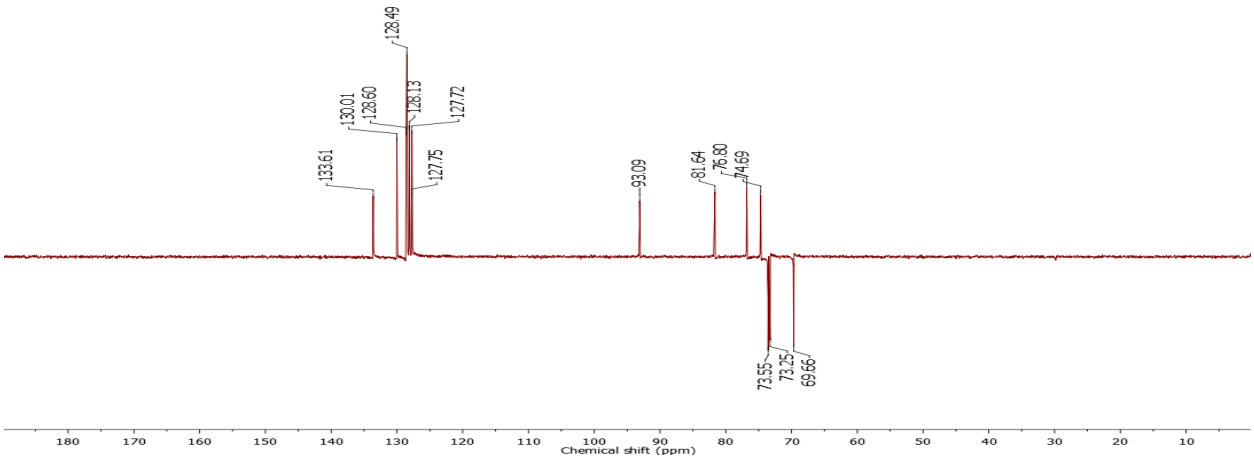
^{1}H NMR Spectrum of Compound **9a** (399.78 MHz, $CDCl_3$)



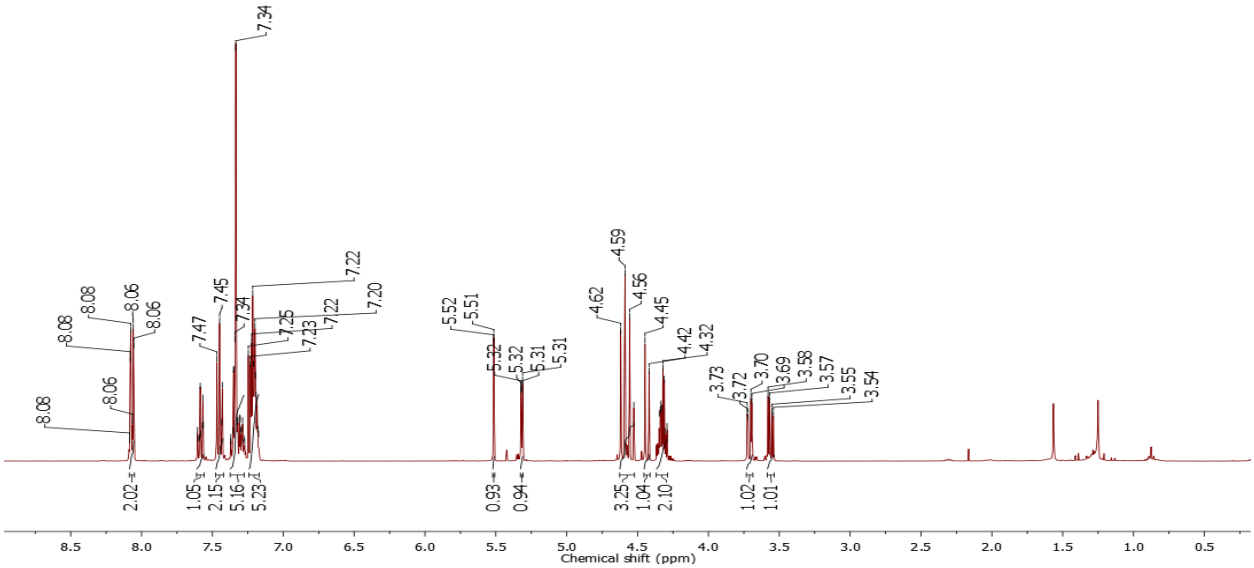
^{13}C NMR Spectrum of Compound **9a** (100.56 MHz, $CDCl_3$)



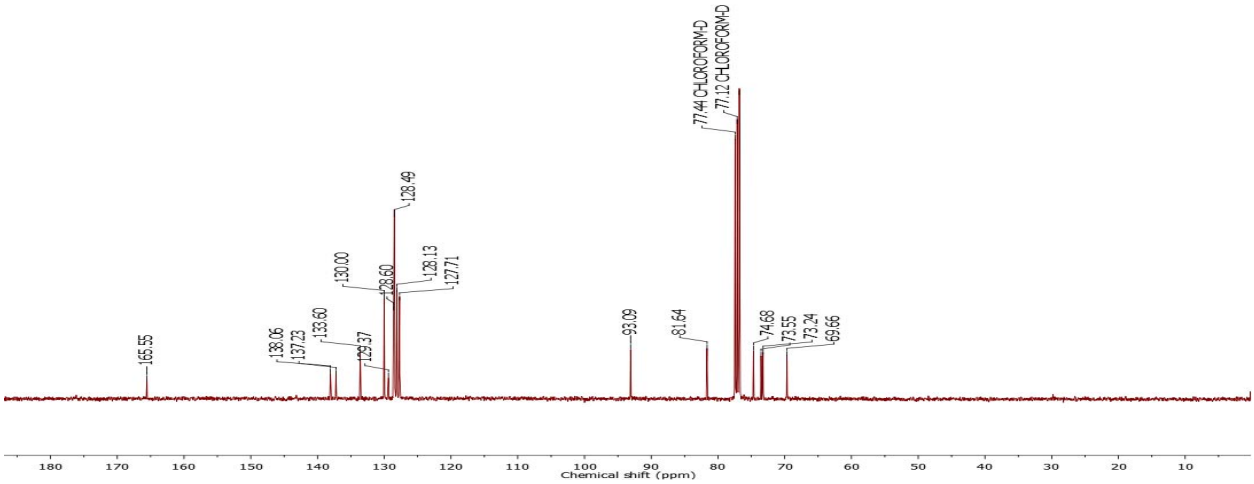
^{13}C-DEPT NMR Spectrum of Compound **9a** (100.56 MHz, $CDCl_3$)



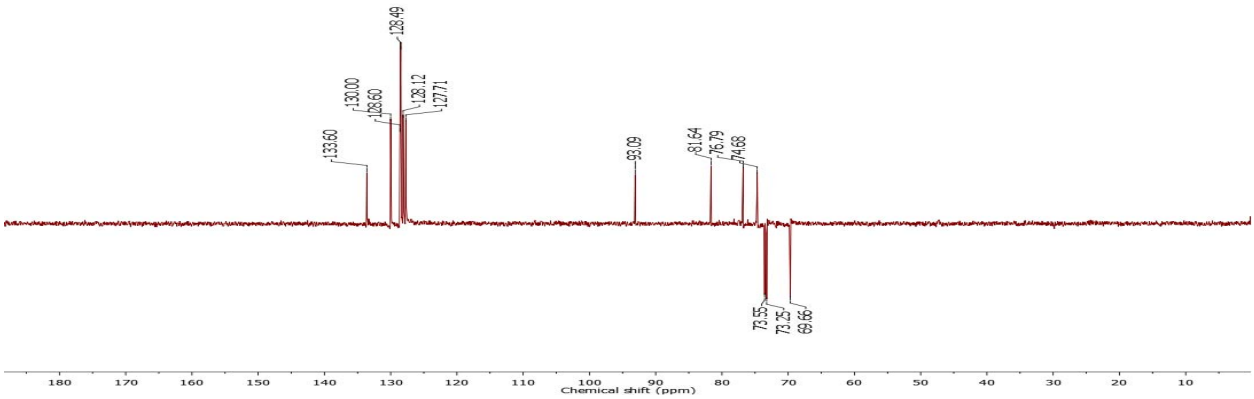
^{1}H NMR Spectrum of Compound **9a** (399.78 MHz, $CDCl_3$)



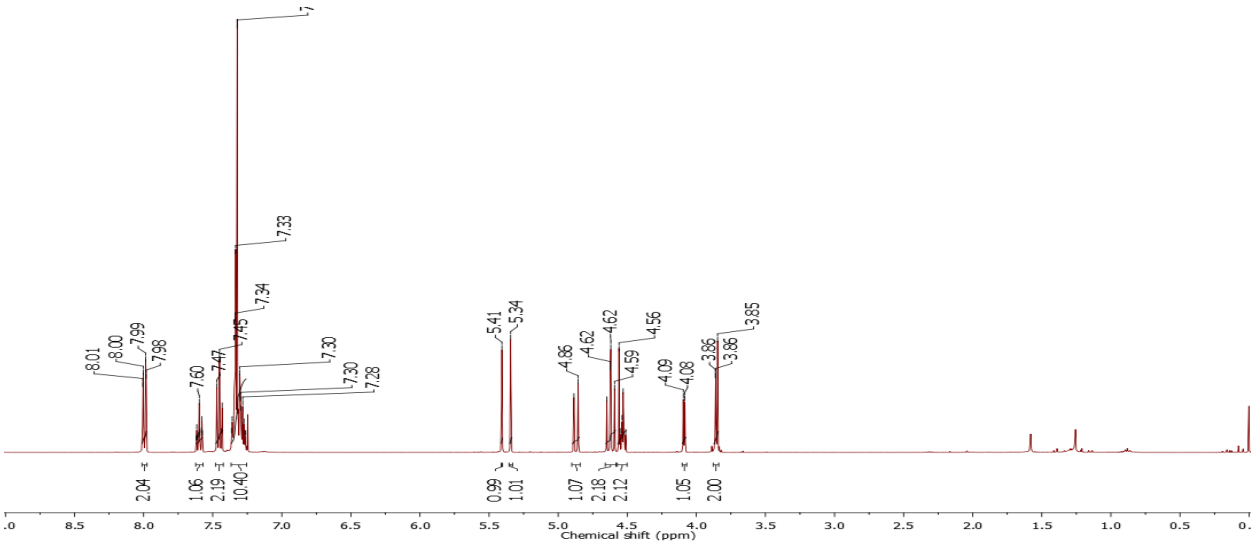
^{13}C NMR Spectrum of Compound **9b** (100.56 MHz, $CDCl_3$)



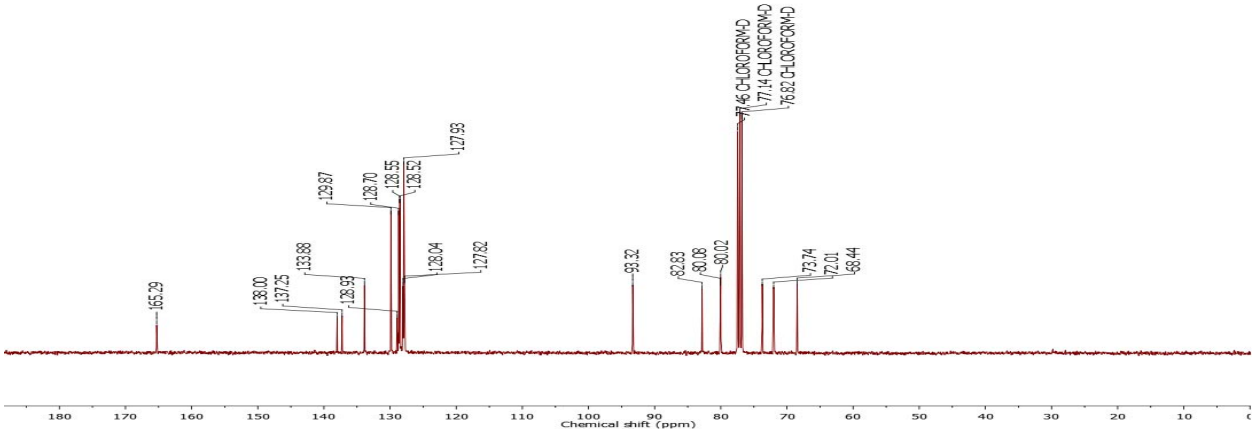
^{13}C-DEPT NMR Spectrum of Compound **9b** (100.56 MHz, $CDCl_3$)



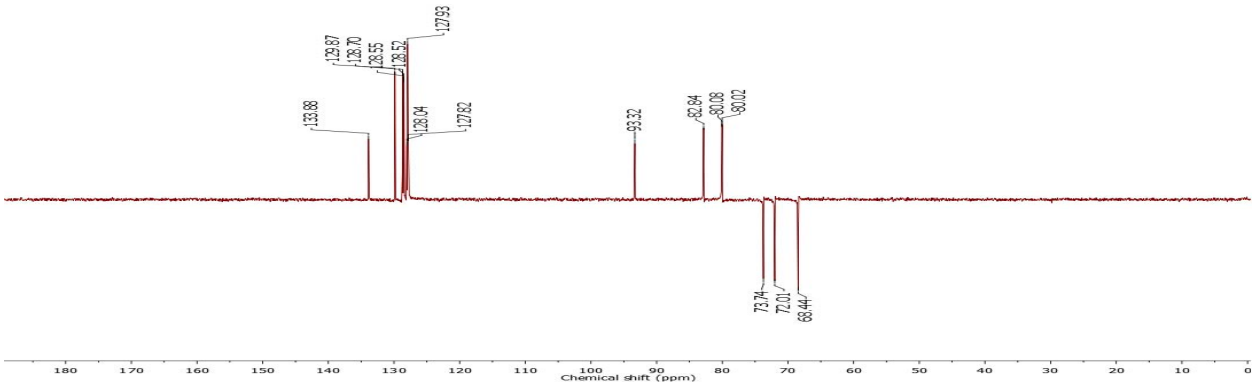
^{1}H NMR Spectrum of Compound **9c** (399.78 MHz, $CDCl_3$)



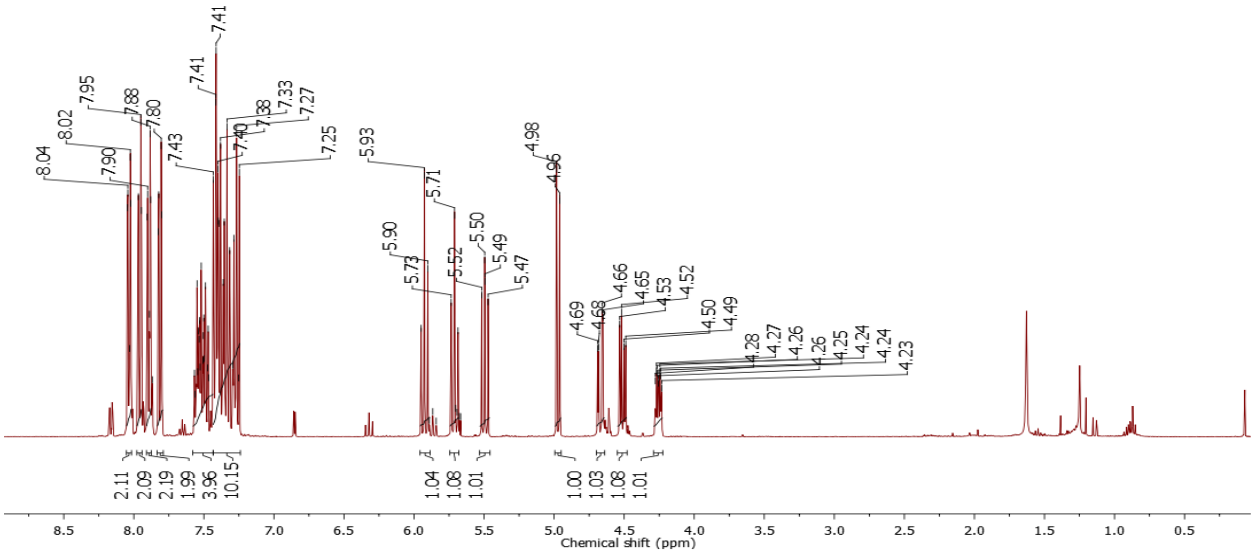
^{13}C NMR Spectrum of Compound **9c** (100.56 MHz, $CDCl_3$)



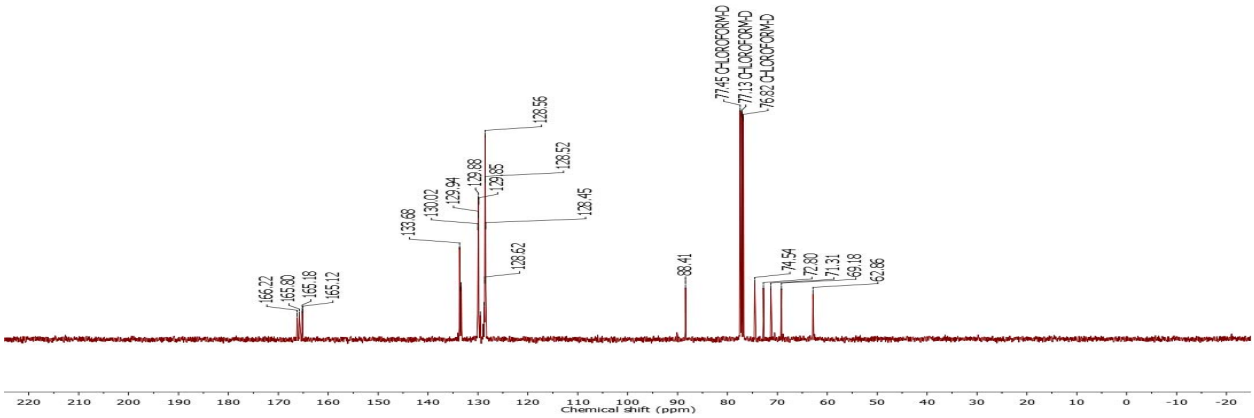
^{13}C-DEPT NMR Spectrum of Compound **9c** (100.56 MHz, $CDCl_3$)



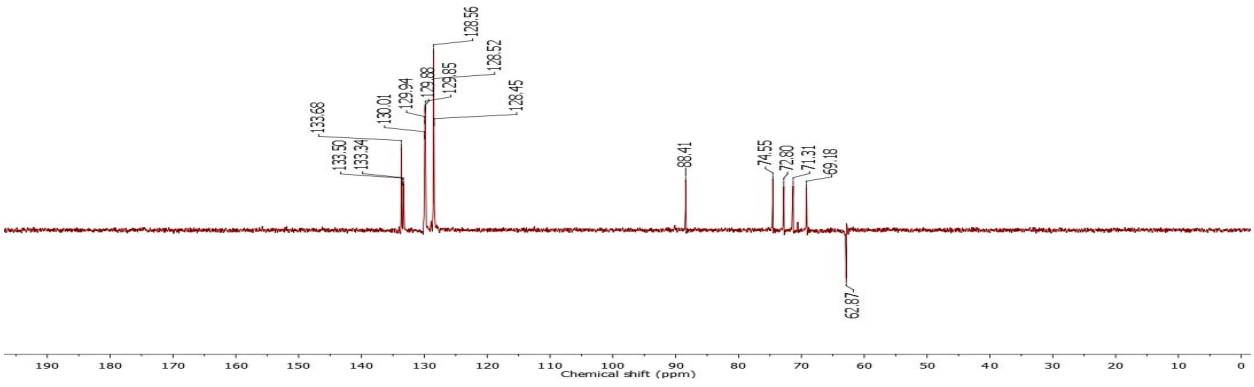
^{1}H NMR Spectrum of Compound **9d** (399.78 MHz, $CDCl_3$)



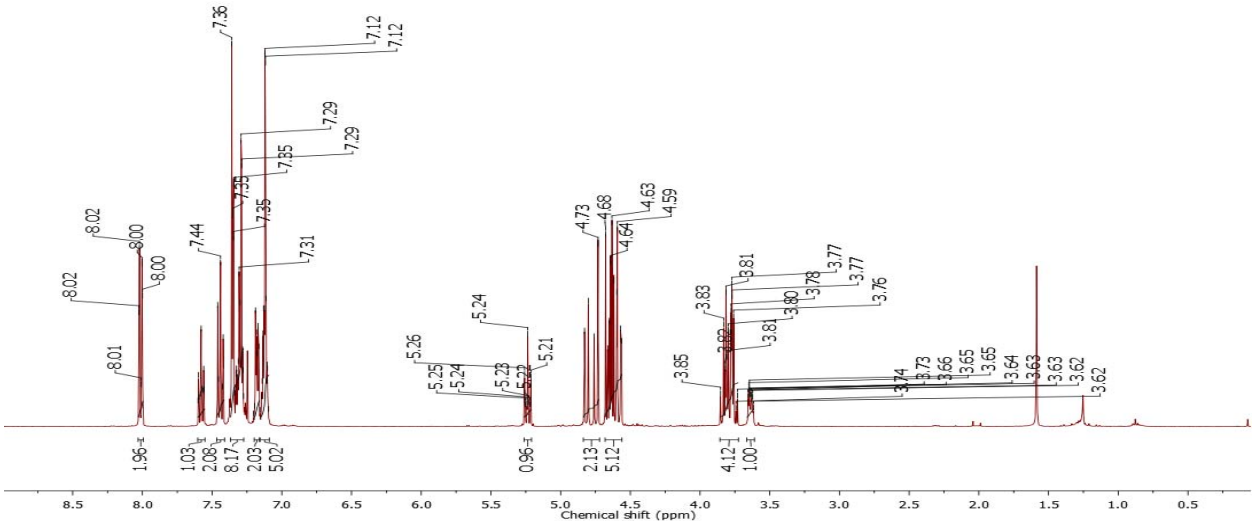
^{13}C NMR Spectrum of Compound **9d** (100.56 MHz, $CDCl_3$)



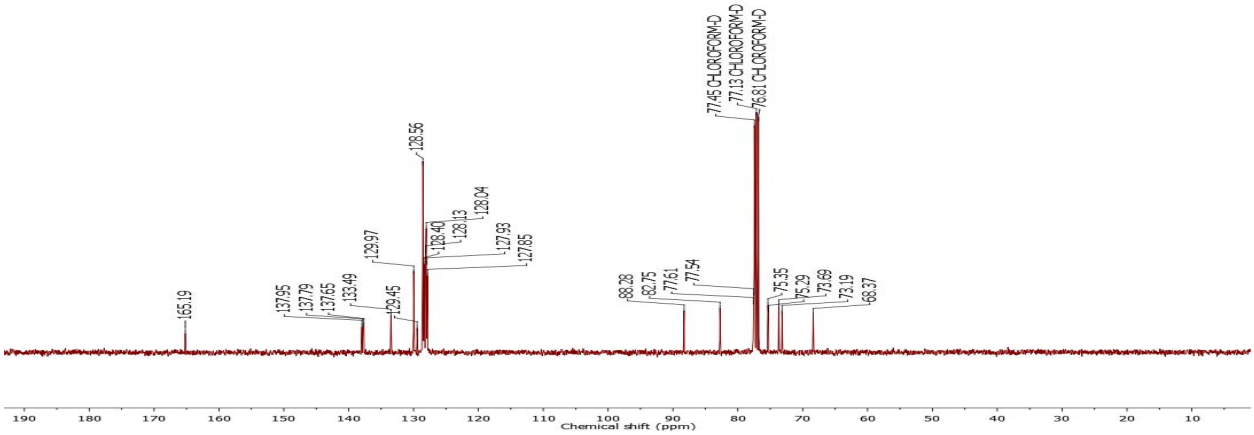
^{13}C-DEPT NMR Spectrum of Compound **9d** (100.56 MHz, $CDCl_3$)



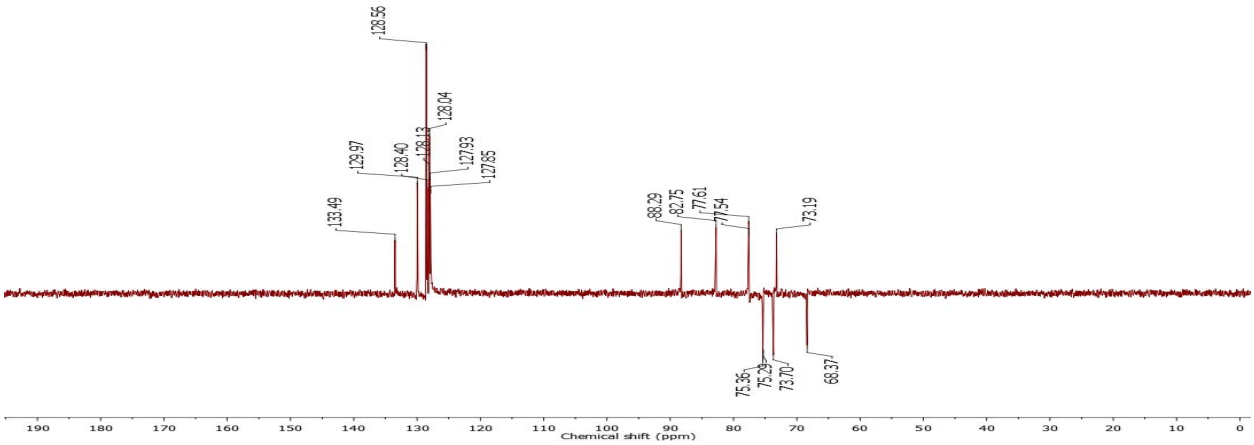
^{1}H NMR Spectrum of Compound **9e** (399.78 MHz, $CDCl_3$)



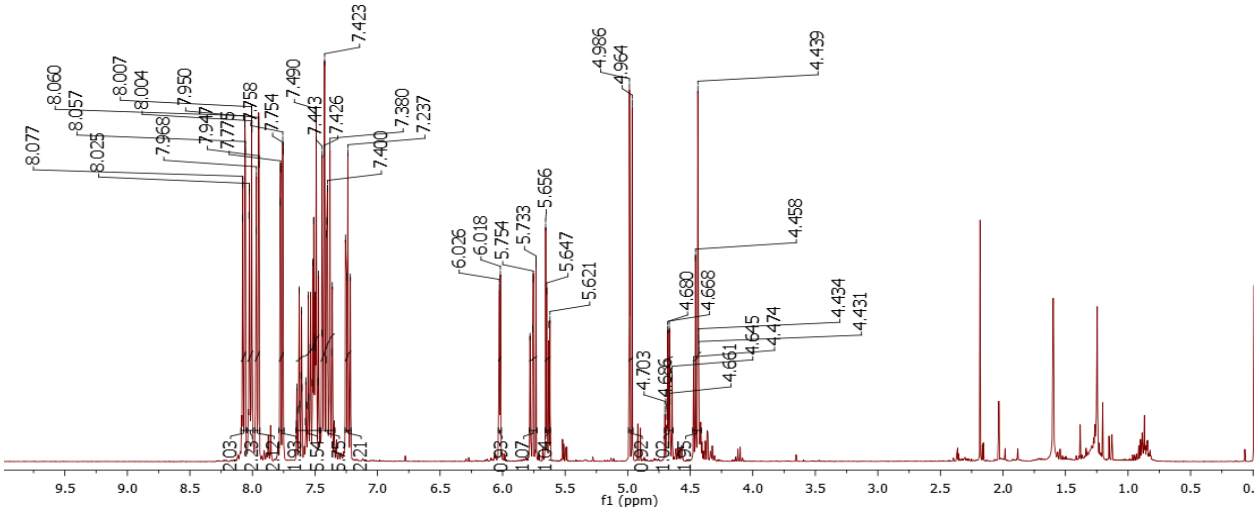
^{13}C NMR Spectrum of Compound **9e** (100.56 MHz, $CDCl_3$)



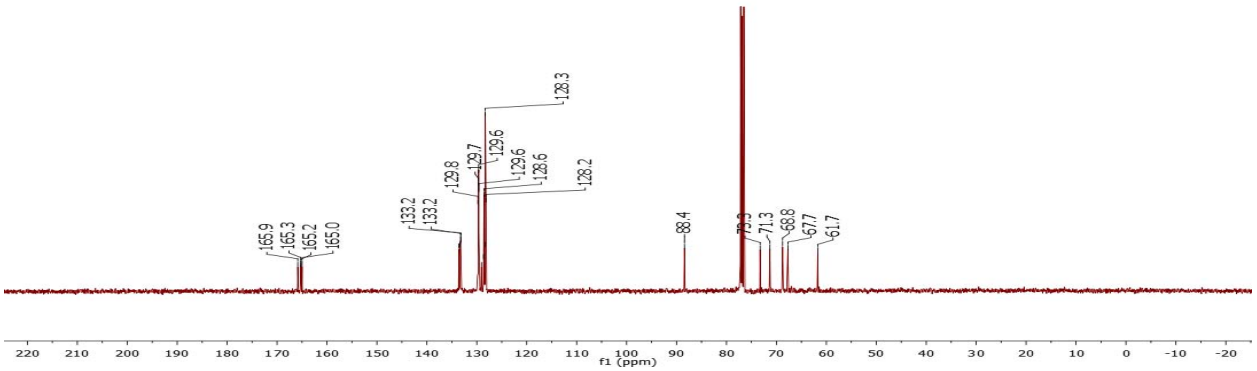
^{13}C-DEPT NMR Spectrum of Compound **9e** (100.56 MHz, $CDCl_3$)



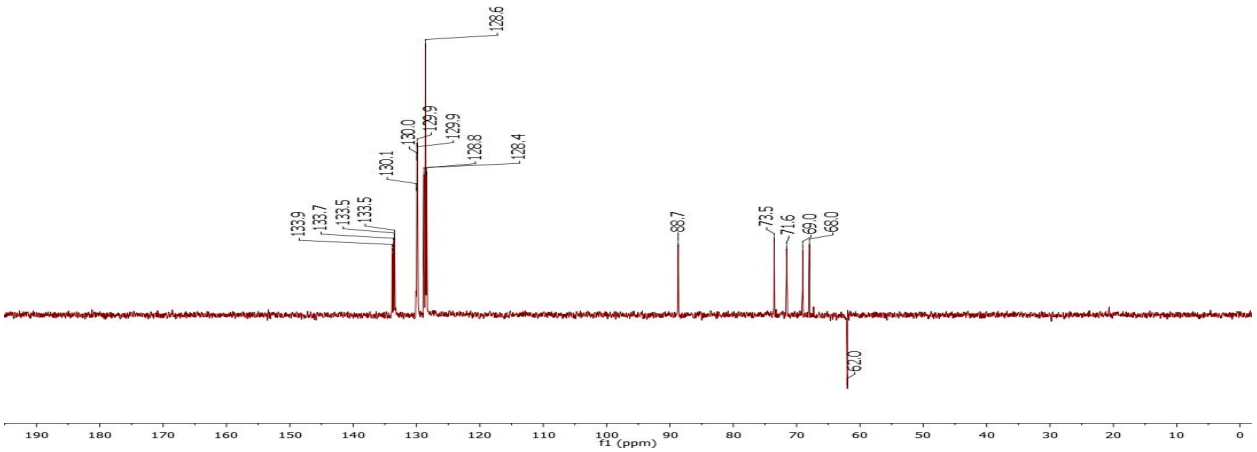
^{1}H NMR Spectrum of Compound **9f** (399.78 MHz, $CDCl_3$)



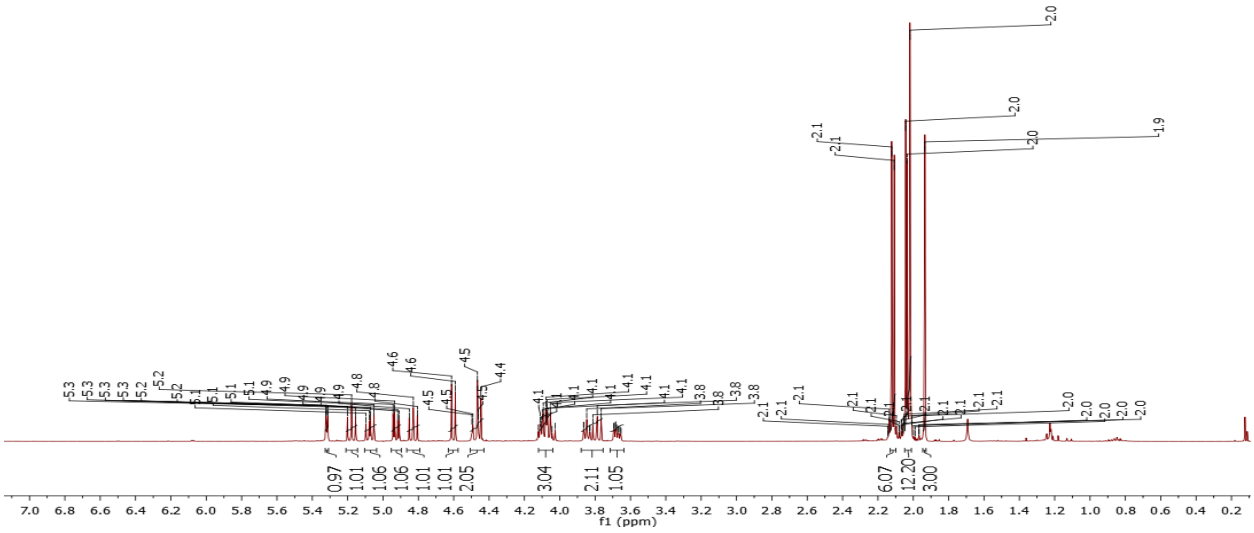
^{13}C NMR Spectrum of Compound **9f** (100.56 MHz, $CDCl_3$)



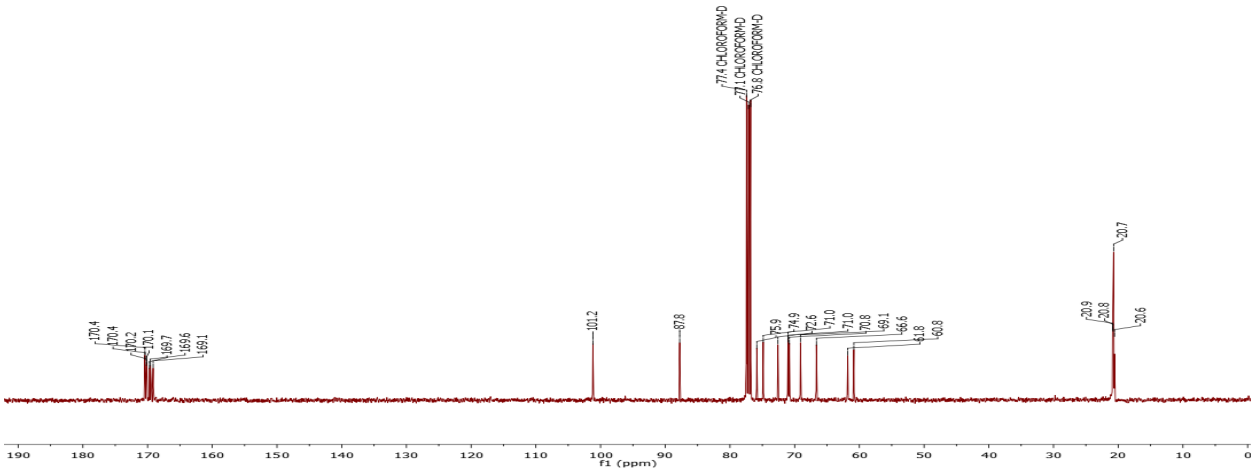
^{13}C-DEPT NMR Spectrum of Compound **9f** (100.56 MHz, $CDCl_3$)



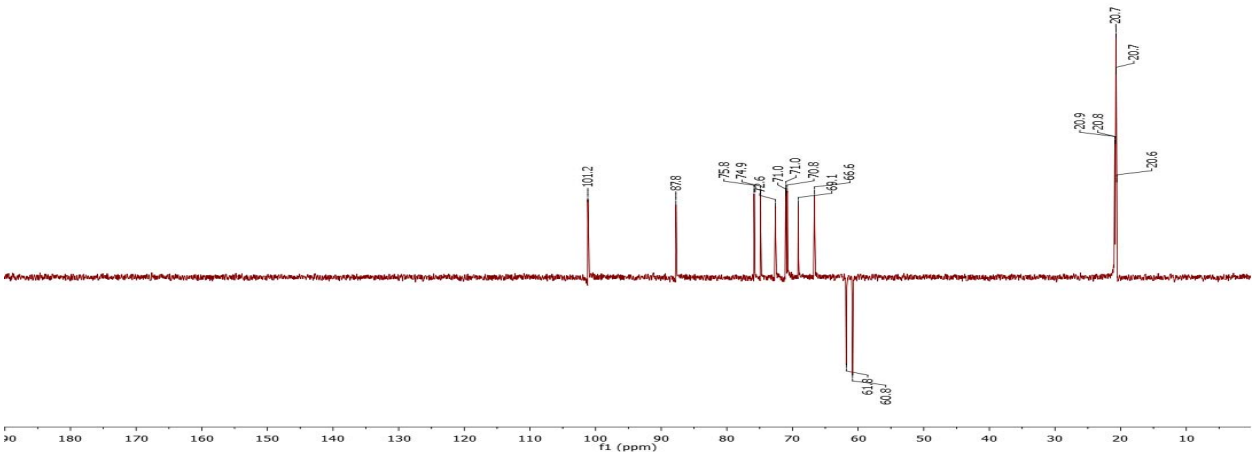
^{1}H NMR Spectrum of Compound **9g** (399.78 MHz, $CDCl_3$)



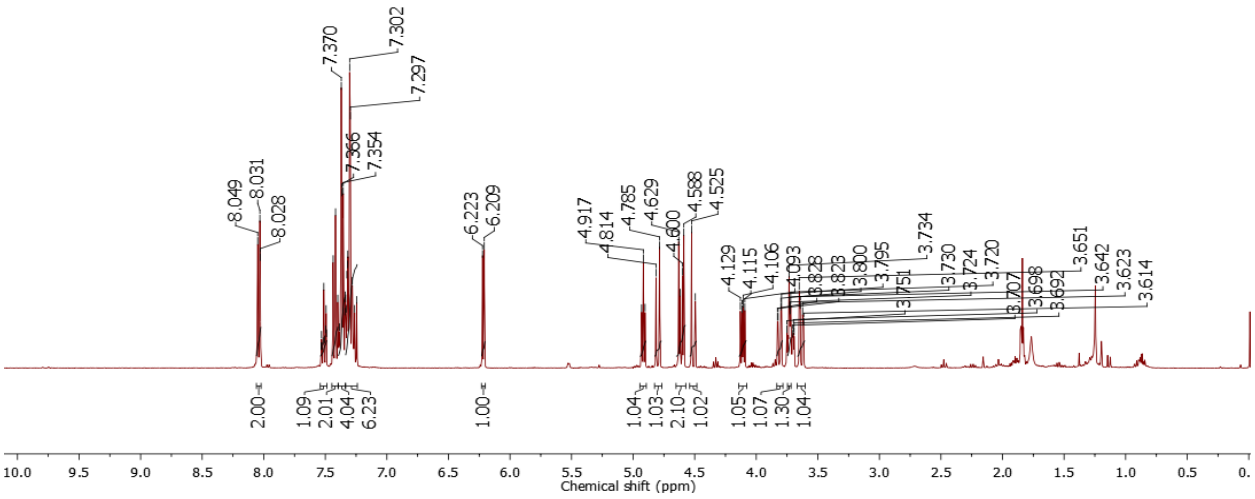
^{13}C NMR Spectrum of Compound **9g** (100.56 MHz, $CDCl_3$)



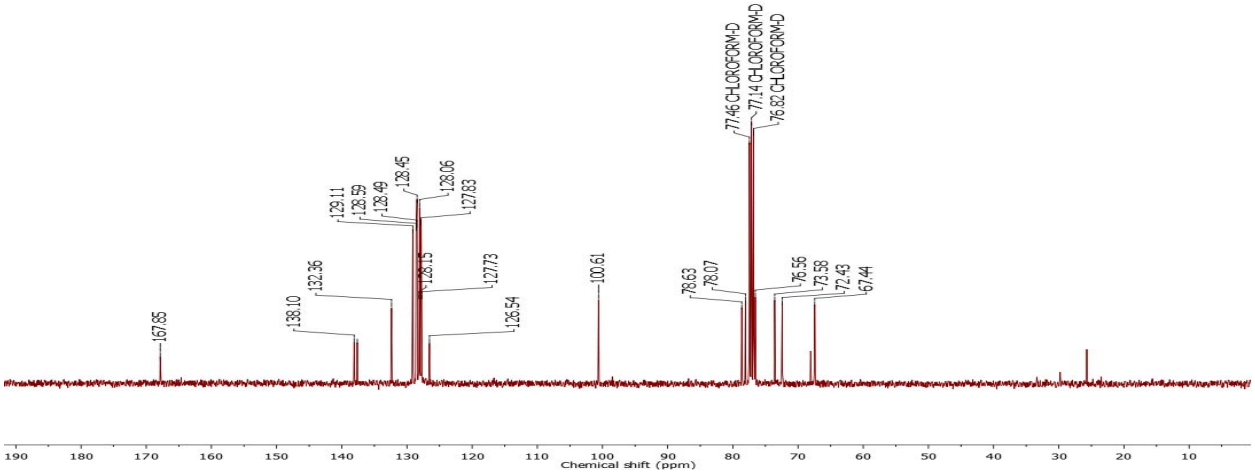
^{13}C-DEPT NMR Spectrum of Compound **9g** (100.56 MHz, $CDCl_3$)



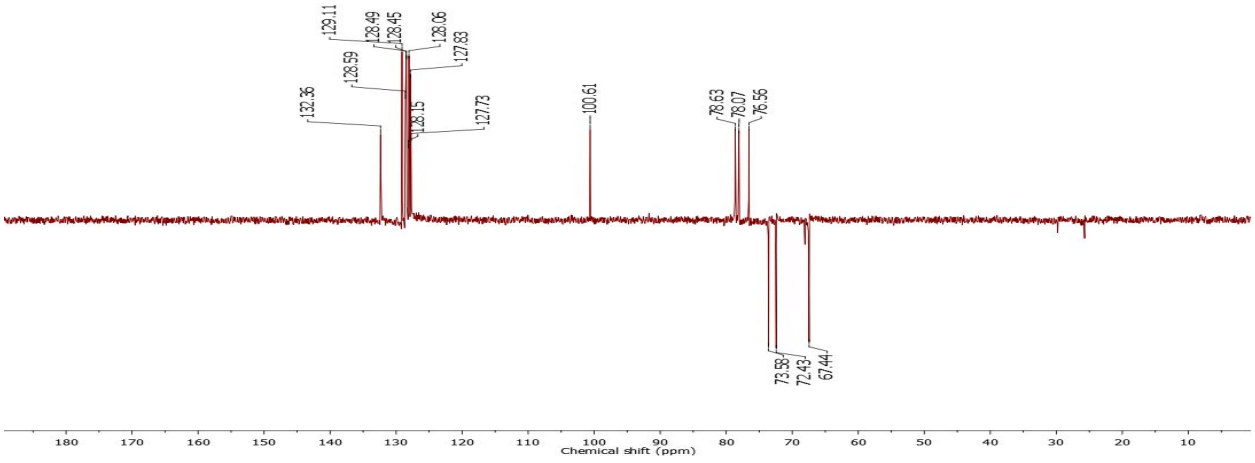
^{1}H NMR Spectrum of Compound **11a** (399.78 MHz, $CDCl_3$)



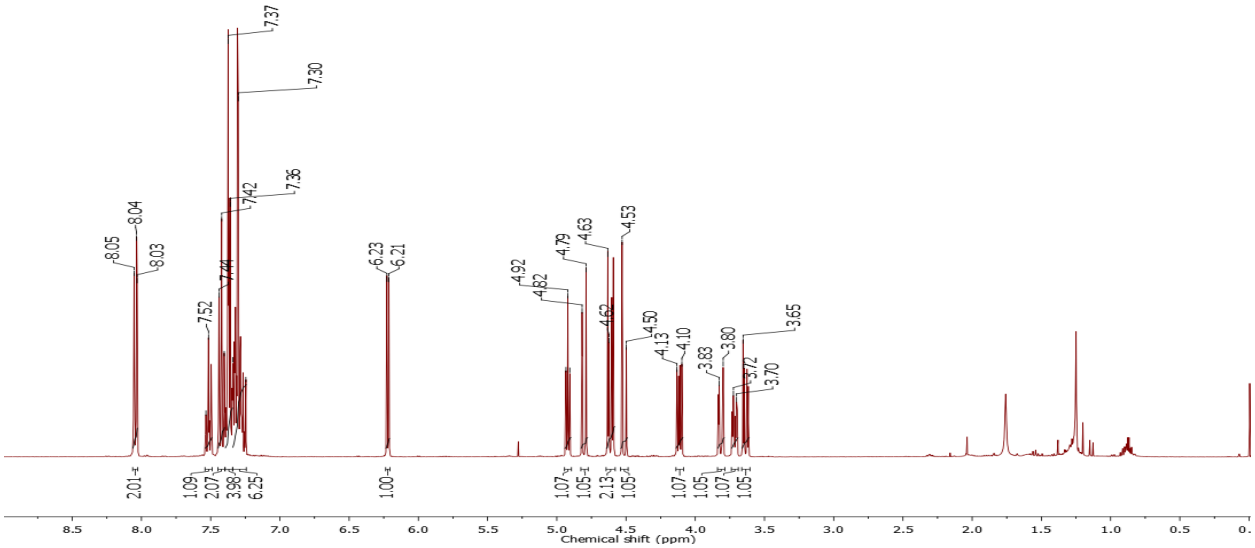
^{13}C NMR Spectrum of Compound **11a** (100.56 MHz, $CDCl_3$)



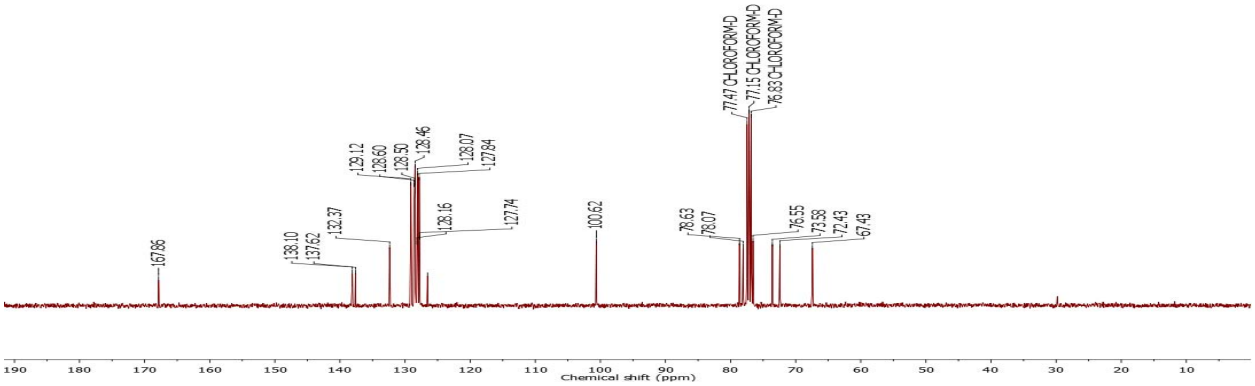
^{13}C-DEPT NMR Spectrum of Compound **11a** (100.56 MHz, $CDCl_3$)



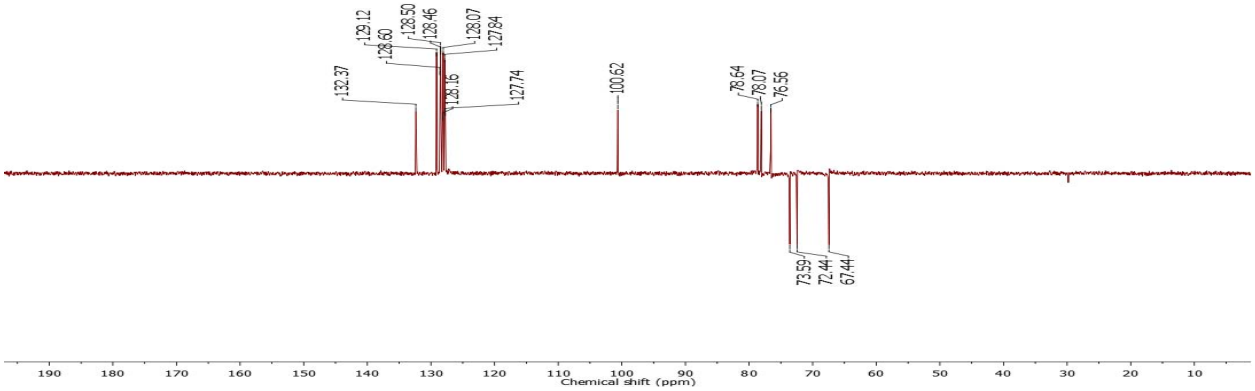
^{1}H NMR Spectrum of Compound **11b** (399.78 MHz, $CDCl_3$)



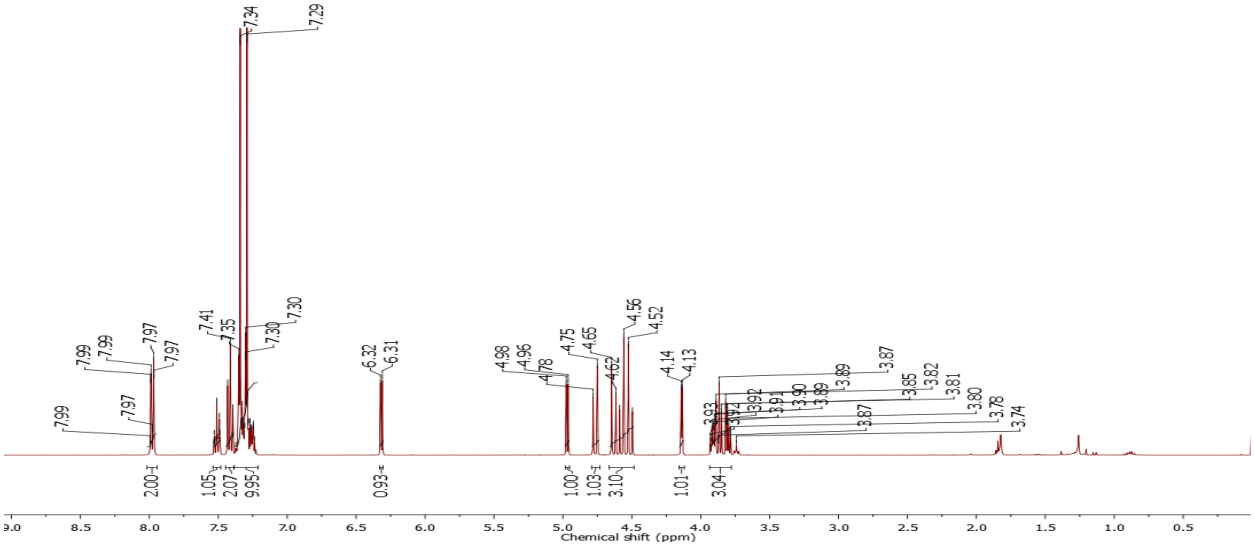
^{13}C NMR Spectrum of Compound **11b** (100.56 MHz, $CDCl_3$)



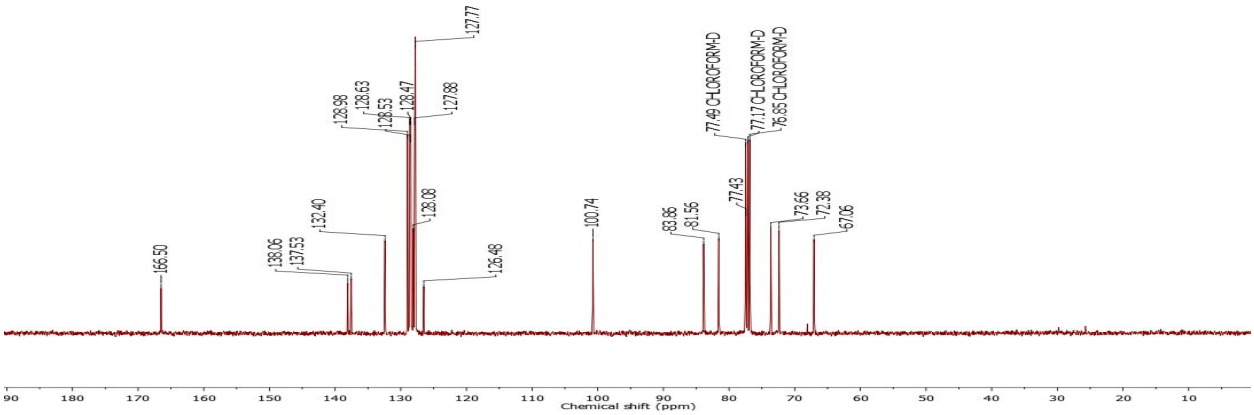
^{13}C-DEPT NMR Spectrum of Compound **9c** (100.56 MHz, $CDCl_3$)



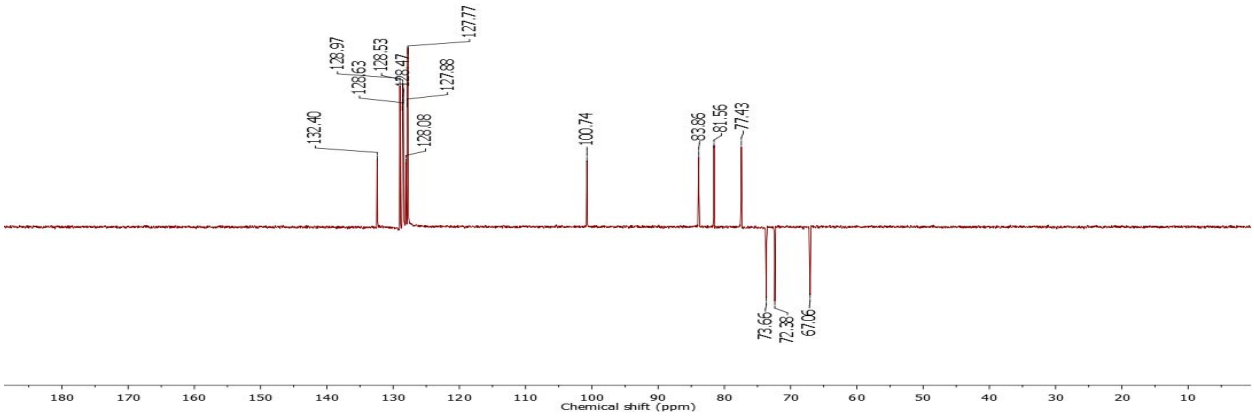
^{1}H NMR Spectrum of Compound **11c** (399.78 MHz, $CDCl_3$)



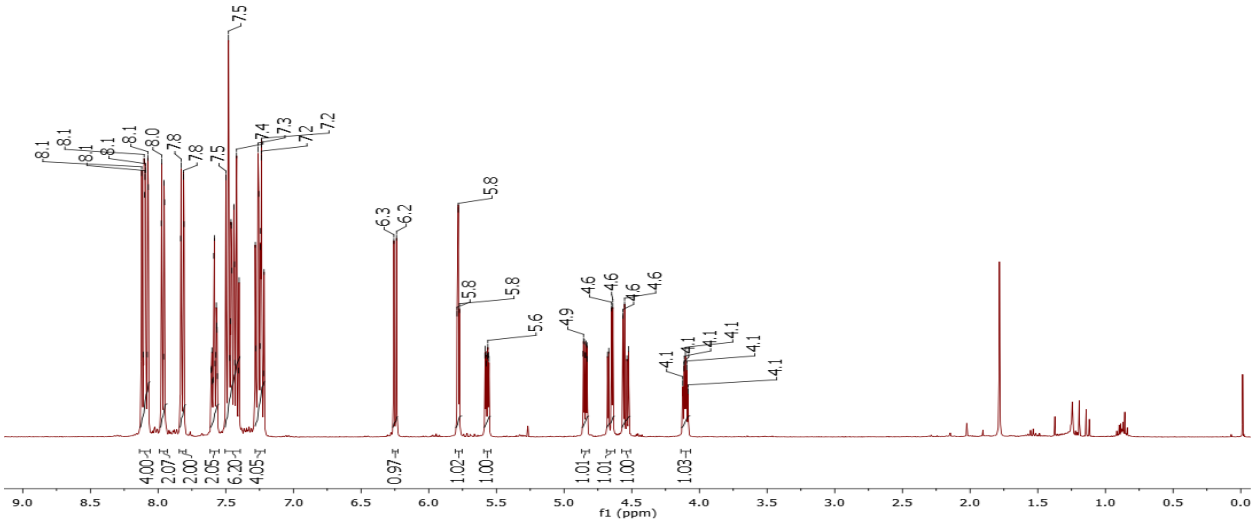
^{13}C NMR Spectrum of Compound **11c** (100.56 MHz, $CDCl_3$)



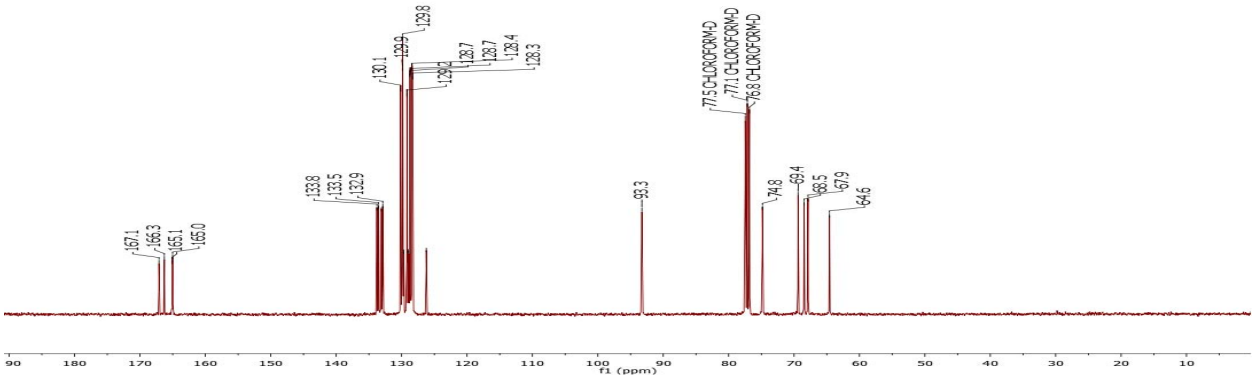
^{13}C-DEPT NMR Spectrum of Compound **11c** (100.56 MHz, $CDCl_3$)



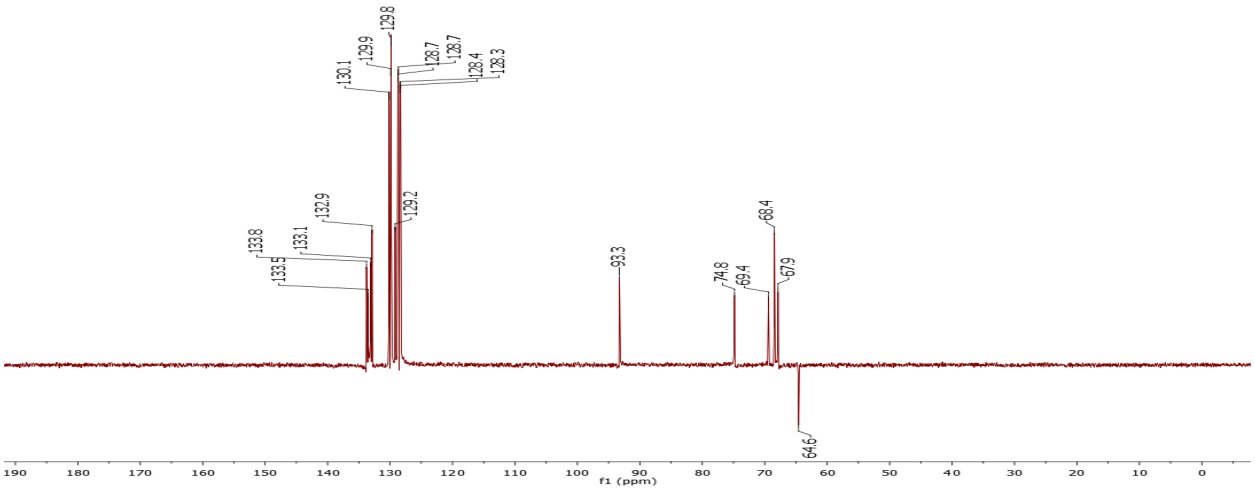
^{1}H NMR Spectrum of Compound **11d** (399.78 MHz, $CDCl_3$)



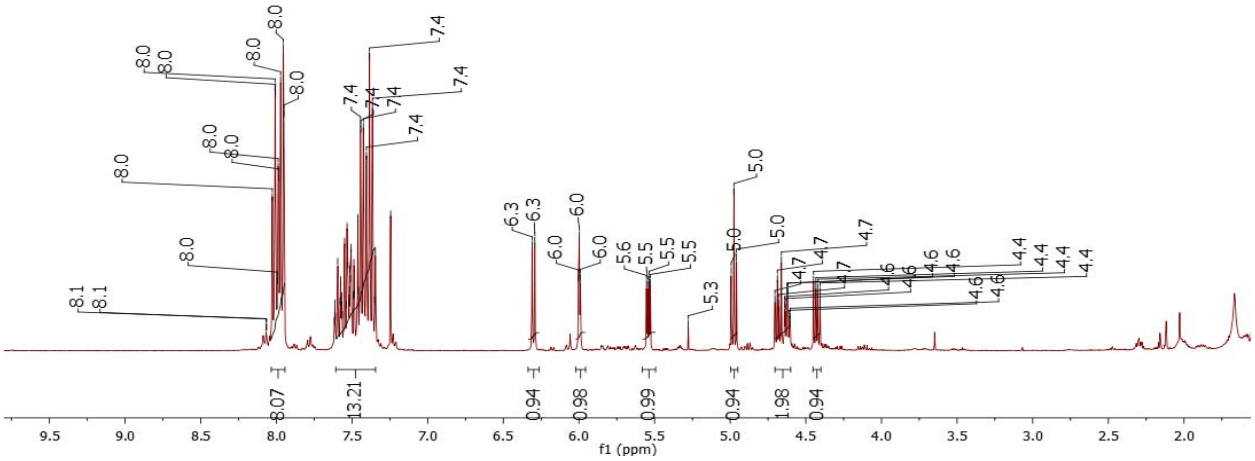
^{13}C NMR Spectrum of Compound **11d** (100.56 MHz, $CDCl_3$)



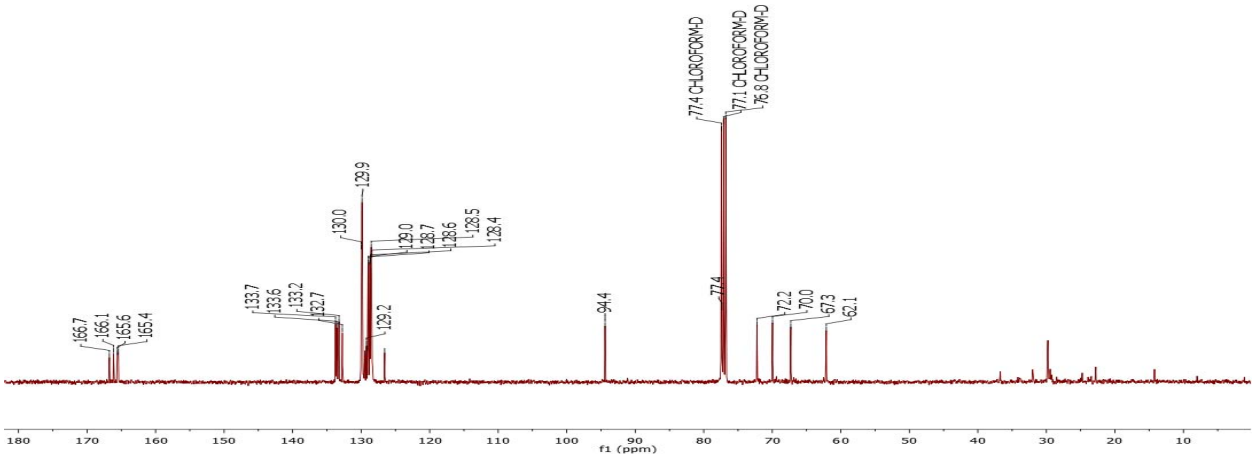
^{13}C-DEPT NMR Spectrum of Compound **11d** (100.56 MHz, $CDCl_3$)



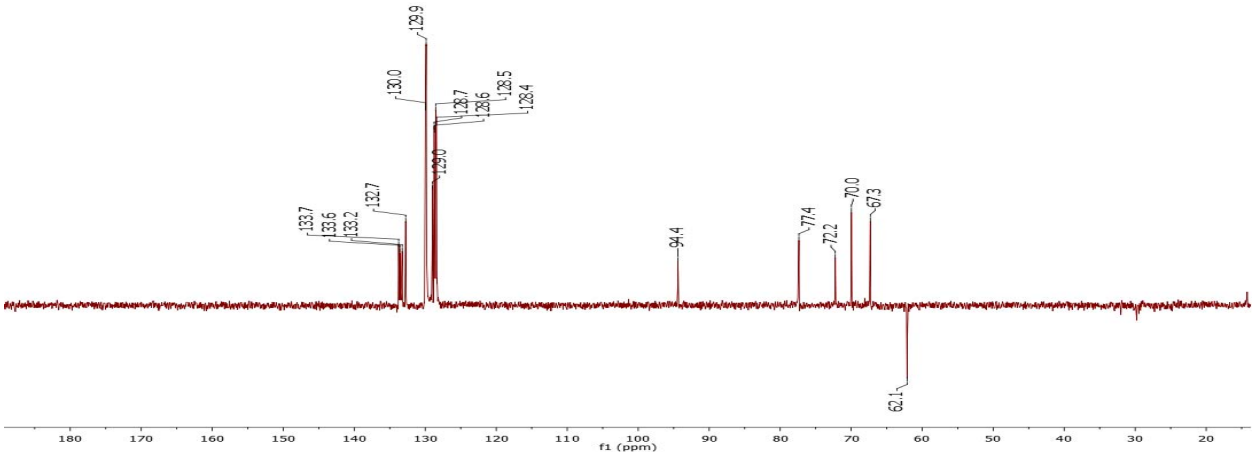
^{1}H NMR Spectrum of Compound **11e** (399.78 MHz, $CDCl_3$)



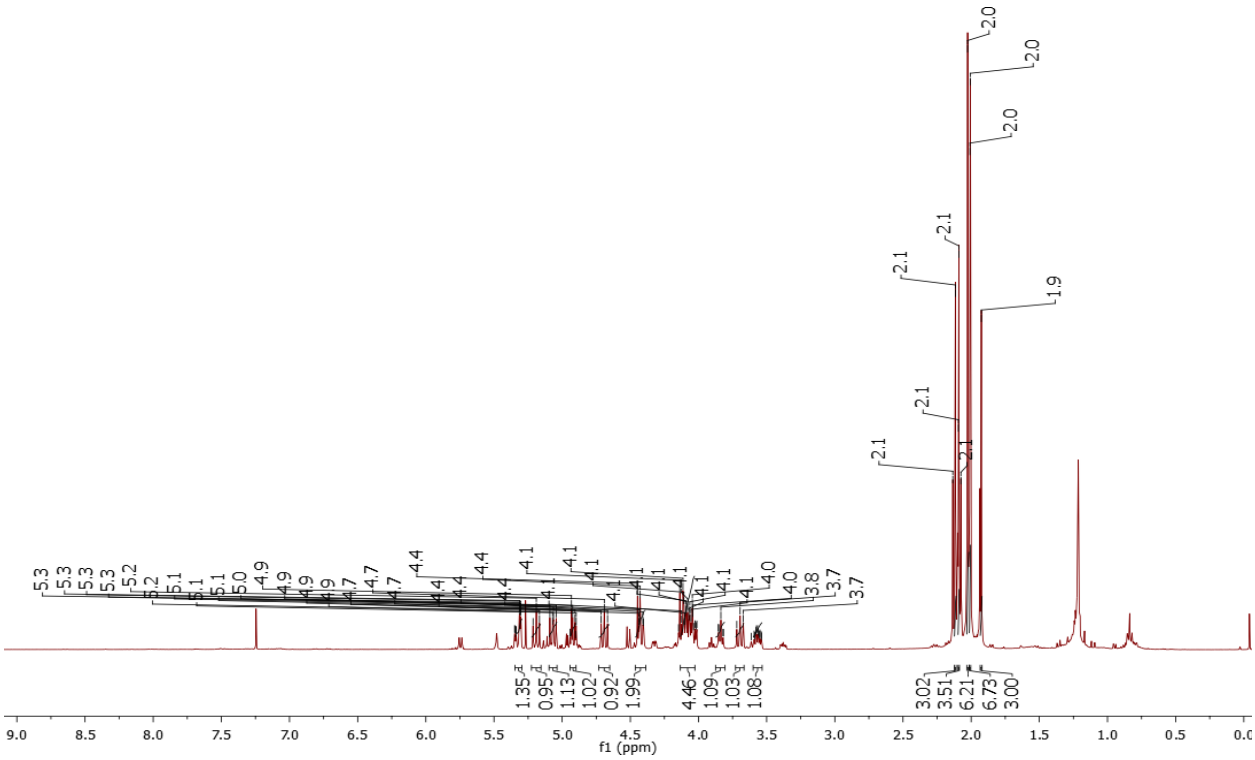
^{13}C NMR Spectrum of Compound **11e** (100.56 MHz, $CDCl_3$)



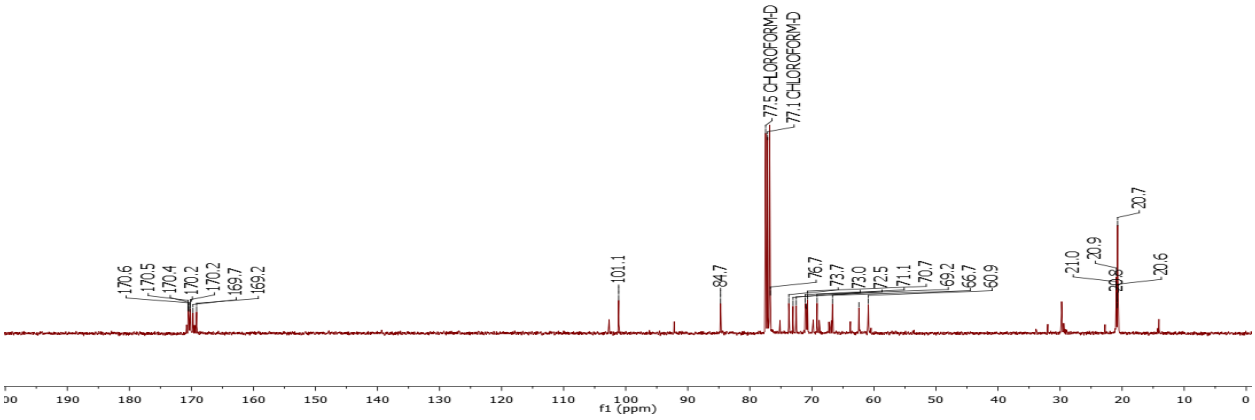
^{13}C-DEPT NMR Spectrum of Compound **11e** (100.56 MHz, $CDCl_3$)



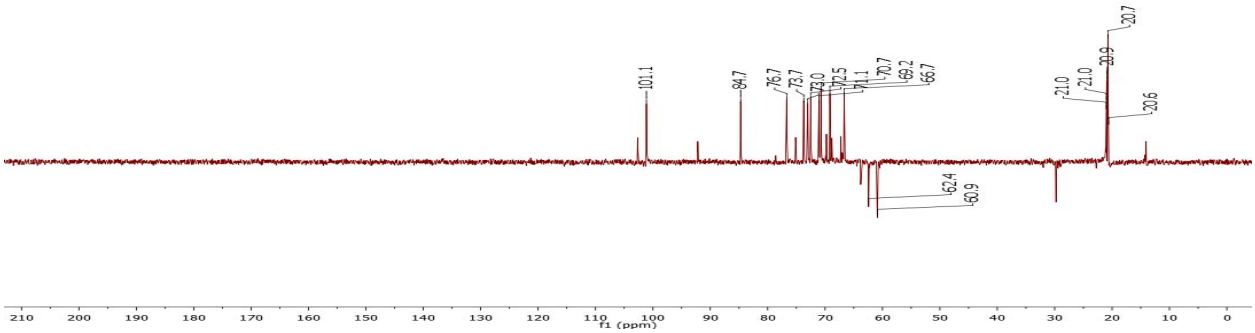
^{1}H NMR Spectrum of Compound **11f** (399.78 MHz, $CDCl_3$)



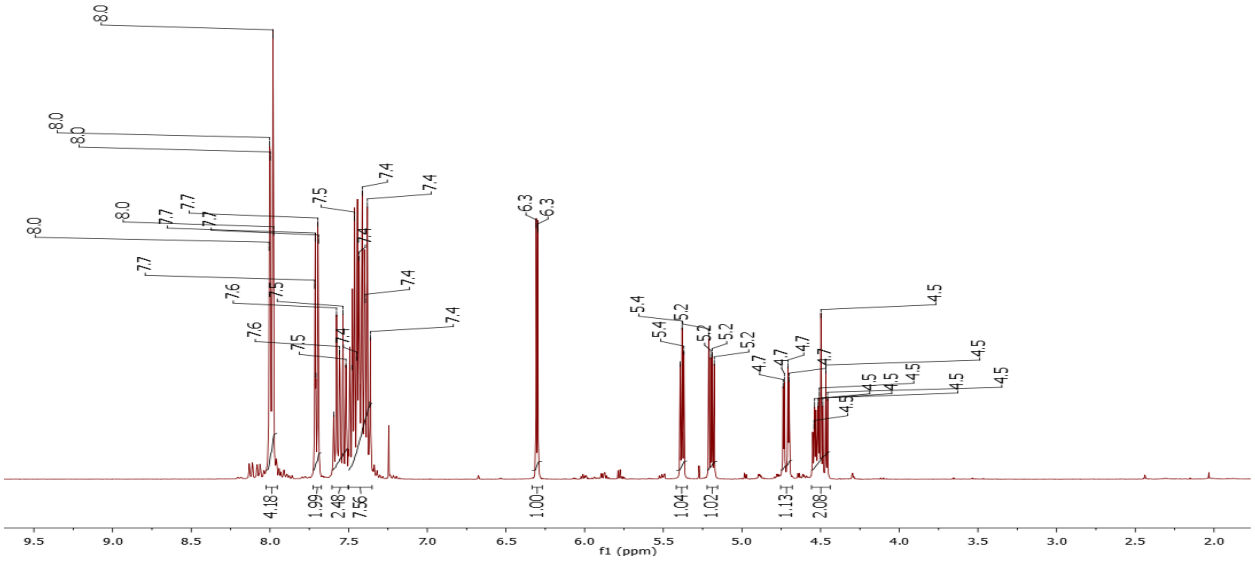
^{13}C NMR Spectrum of Compound **11f** (100.56 MHz, $CDCl_3$)



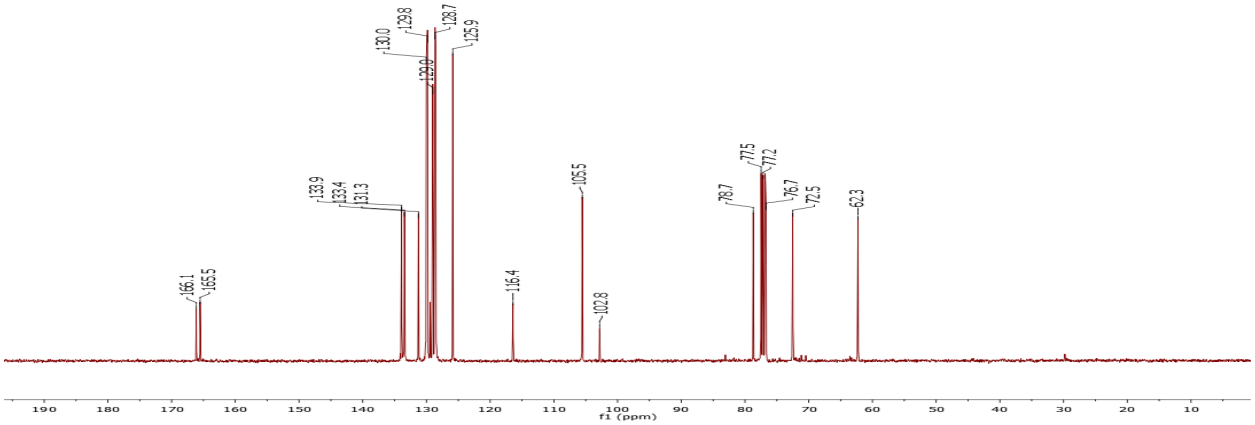
^{13}C-DEPT NMR Spectrum of Compound **11f** (100.56 MHz, $CDCl_3$)



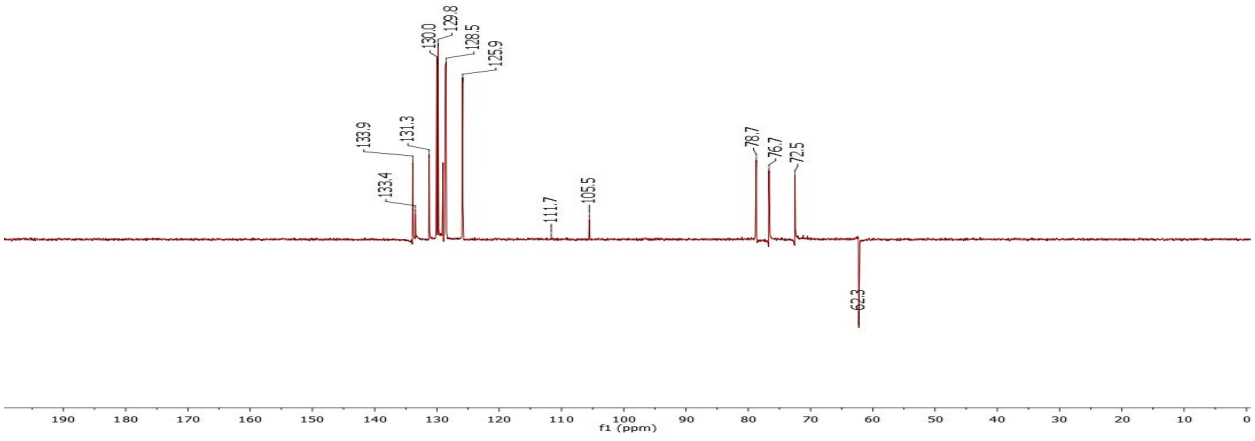
^{1}H NMR Spectrum of Compound **14** (399.78 MHz, $CDCl_3$)



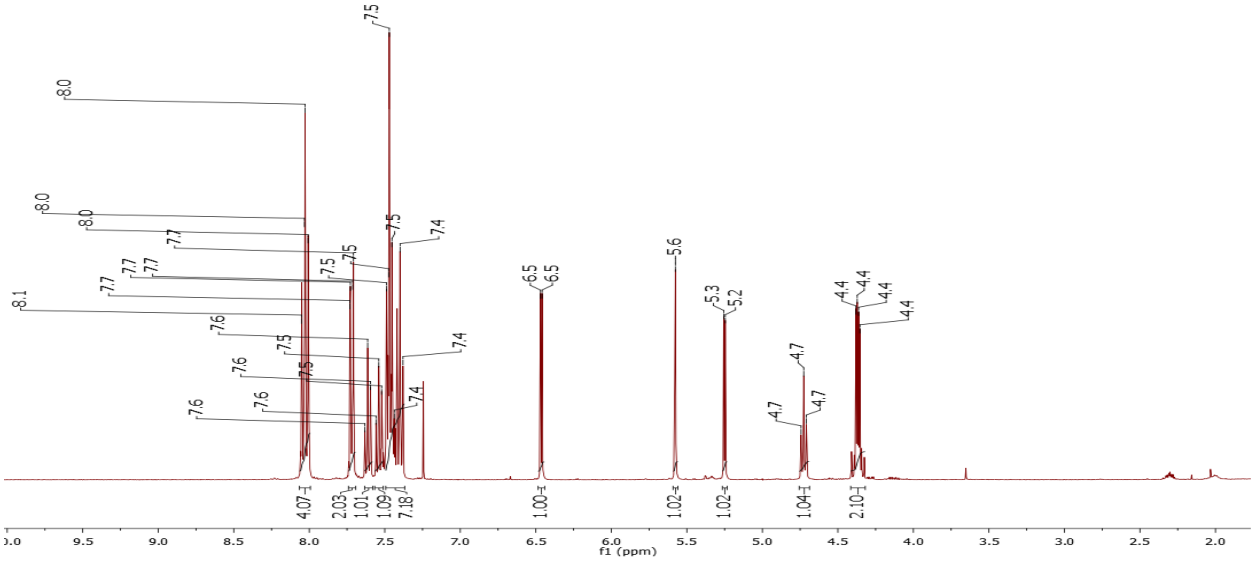
^{13}C NMR Spectrum of Compound **14** (100.56 MHz, $CDCl_3$)



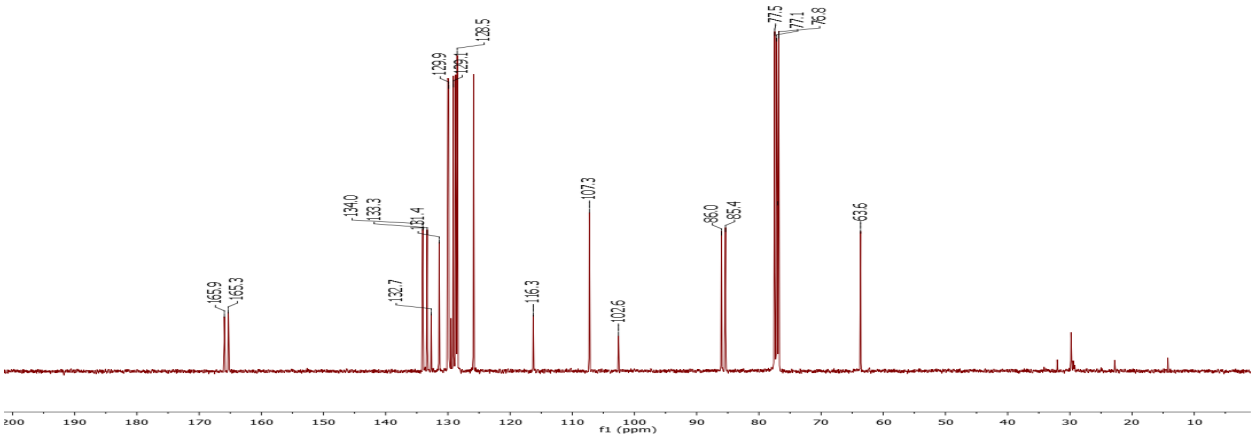
^{13}C-DEPT NMR Spectrum of Compound **14** (100.56 MHz, $CDCl_3$)



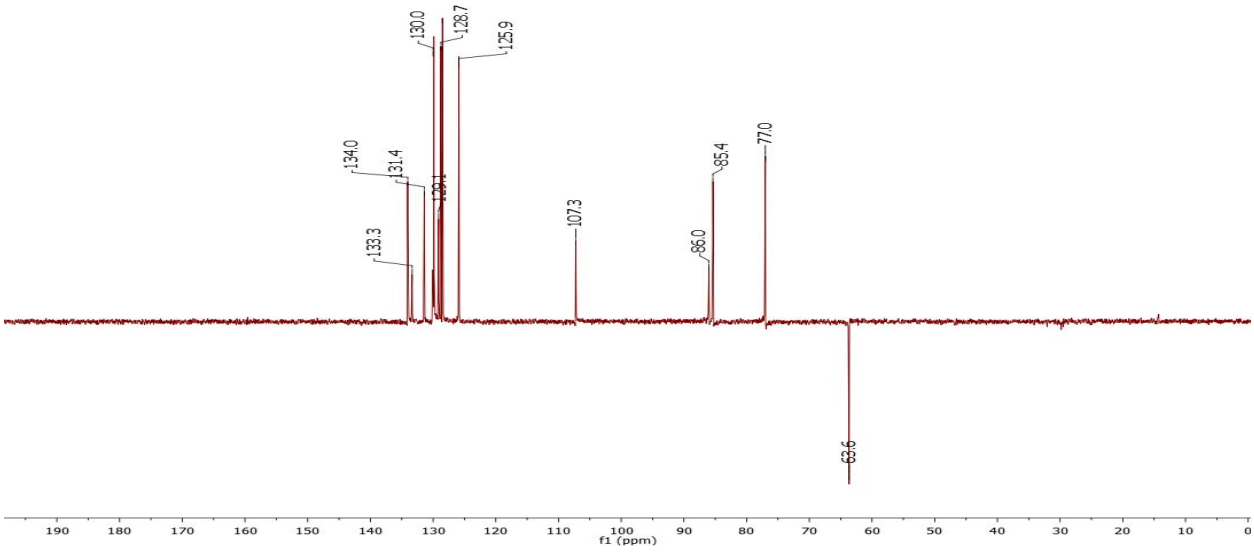
^{1}H NMR Spectrum of Compound **15** (399.78 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **15** (100.56 MHz, $CDCl_3$)



^{13}C-DEPT NMR Spectrum of Compound **15** (100.56 MHz, $CDCl_3$)



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