SYNTHESIS OF CARBOHYDRATES DERIVATIVES RELATED TO L-FUCOSE

M.sc Organic Chemistry Project Dissertation

Submitted to St. Francis College for Women in the partial fulfillment of the Requirements for the award of the Degree of

Master of Science

BY

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This is to certify that this bonafide project work titled "Synthesis of Carbohydrates Derivatives Related to L- FUCOSE" has been carried out by Puli. Hema bearing Roll No:121321035013 towards partial fulfillment of the requirements for the award of Degree of Master's in Organic Chemistry from St. Francis College for Women, Begumpet in the academic year 2022-23.

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DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**SYNTHESIS OF CARBOHYDRATES DERIVATIVES RELATED TO L – FUCOSE**" in fulfillment of the requirements for the award of the degree of Master of Sciences in Organic Chemistry submitted to St. Francis College for Women, Begumpet, Hyderabad, an authentic record of my work carried out during a period from November 2022 to February 2023 under the supervision of **Dr. Abhishek Santra**, Scientist, CSIR-Indian Institute of Chemical Technology, Hyderabad. The matter embodied in this thesis has not been submitted for this award to any other degree or any other University/ Institute.

Date:

Place: HYDERABAD

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MINISTRY OF SCIENCE AND TECHNOLOGY, GOVERNMENT OF INDIA

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This is to certify that the dissertation work carried out by PULI.HEMA bearing Roll No: 121321035013 at CSIR-IICT, Hyderabad from November 2022 to February 2023. The Thesis entitled "Synthesis of Carbohydrates Derivatives of L- FUCOSE" in partial fulfillment of Master of Sciences in Organic chemistry is a bonafide research work carried out by the candidate under my supervision. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Place: Hyderabad

Date:

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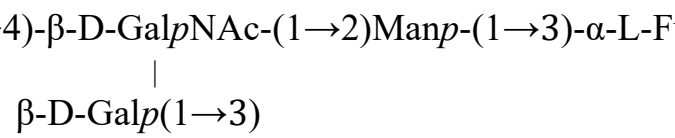
PULI HEMA

ABSTRACT

The present research work has been carried out as a part of the efficient synthesis of O-antigen polysaccharide of *Escherichia coli* O125ac



The required protected L-fucose monosaccharide building block was synthesized from commercially available L-fucose using protection and deprotection reaction. In the future, this synthesized building block will be used for the total synthesis of the pentasaccharide *Escherichia coli* O125ac.

LIST OF FIGURES

ABBREVIATIONS:

$CDCl_3$: Deuterated chloroform

DMSO: Dimethyl sulfoxide

NMR: Nuclear Magnetic Resonance

M.P: Melting Point

RT: Room Temperature

TLC: Thin Layer Chromatography

CHAPTER-1

INTRODUCTION

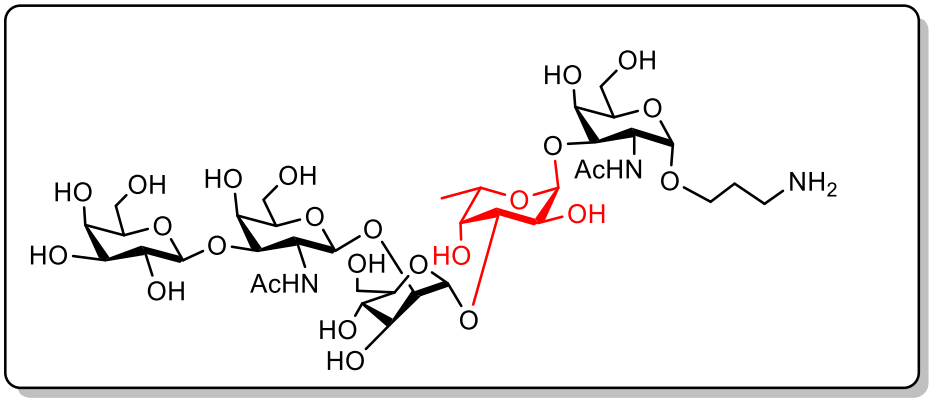
1.0 INTRODUCTION

Escherichia coli (E. coli) is a group of gram-negative bacteria that colonize an infant's gastrointestinal tract within hours of life.[1] *Escherichia* as a genus is defined by a series of physiological and morphological behaviors. But it is very difficult to describe accurately a single strain without knowing its serotyping due to the presence of high heterogenecity of this genus. The subdivision of the immunologically active site of the bacterial surface structure was introduced by Kauffmann.[2,3] He characterized the *E. coli* group based on the serotyping scheme. *E. coli* strains have been classified based on three types of antigens which are as follows: (i) somatic (*O*) antigen, (ii) capsular (K) and,igen, and (iii) flagellar (*H*) antigen. Initially, Kauffmann described 25 *O*, 5, *K,* and 20 *H* antigens.[4] Because of the emergence of several strains of *E. coli* currently 173 *O* antigens, *K* antigens 10,,3, and *H* antigens 56 are present in the literature.[5,6] The somatic *O*-antigens are composed of lipopolysaccharide complexes, which are an important component of the cell wall of *E. coli*. The immunogenicity of the cell wall polysaccharides appears from the *O*-antigens. Kauffmann and Vahlne introduced the term *K*-antigen as a symbol for the envelope or capsular antigens.[7] In general, *K*-antigens are acidic polysaccharides, serologically different from the *O*-antigens. Acidic capsular polysaccharides of *E. coli* are divided into two groups: group I polysaccharides similar to the capsule of *Klebsiella* species and Group II polysaccharides similar to the capsule of *Haemophilus influenza* and *Neisseria meningitidis*.[8,9] The antigenic diversity of *H*-antigens is based on the different types of flagellin present in the flagellar structure. The *O*, *K*, and *H* antigens can be found in nature in many possible combinations. Although the final number of *E. coli* serotypes is very high 50,000-100,000 or more,[2] the numbers of pathogenic serotypes are limited.

E. coli are versatile bacteria, which are a typicacomponentsnt of human colonic flora. The diversity of *E. coli* pathotypes is due to the presence of specific subsets of virulence-associated genes, which are considered to be largely absent from the normal-flora *E. coli* strains. These virulence genes are usually carried by a variety of pathogenicity islands (PAIs), bacteriophages, plasm, ids, and/or transposons.[10] However, the pathogenic types of *E. coli* can cause both enteric and diarrhoeadiseasesse. Based on other natures of infections, the enteropathogenic strain of *E.*

coli have been classified inintoeveral classes,[11,12] which include (a) enteropathogenic *E. coli* (EPEC), (b) enteroinvasive *E. coli* (EIEC), (c) enterotoxigenic *E. coli* (ETEC), (d) enteroaggregative *E. coli* (EAEC), (e) diffusely adherent *E. coli* (DAEC), and (f) enterohemorrhagic *E. coli* (EHE, C), etc. Enterohemorrhagic *E. coli* (EHEC) are mostly responsible for diarrhea and wilife-threateninging complications e.g. hemorrhagic colitis (HC) and hemolytic-uraemic syndrome (HUS).[11,12] EHEC strains are also called "verotoxigenic *E. coli*" (VTEC) because of their toxic effect on the cultured Vero cells. They also produce a bacteriophage-mediated Shiga-like toxin and are termed "Shiga toxin-producing *E. coli*" (STEC).[13] The pathological symptoms due to the HC and HUS are the result of the action of Shiga toxin (Stx) on endothelial cells. The best-known Shigatoxin-producing EHEC strain is *E. coli* O157:H7, which is the frequent cause of fatal intestinal infections and is associated with several outbreaks of disease in Europe, America, and, Japan.[14-17] It is the major cause of hemolytic–uremic syndrome (HUS), a multisystemic disorder that is characterized by the onset of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. The majority of outbreaks of human *E. coli* O157:H7 HUS cases resulted from the consumption of undercooked meat, raw milk, water, contaminated food or by direct contact with animals or people infected with the bacterium and EHEC epidemiology is invariably associated with the *E. coli* being an intestinal reservoir in cattle and other animals. The key virulence factors of the *E. coli* O157:H7 pathogen include verotoxins (Vt) together with effectors and adhesions associated with type III secretion systems, while the role of LPS in the EHEC pathogenesis appears to be relatively minimal. Besides *E. coli* O157:H7, several other *E. coli* serotypes have been reported to be associated with the STEC category.[18-21] Although, *E. coli* is confined to the intestinal lumen, it causes infection in a debilitated or immuno-suppressed host or when the bacteria are introduced to other tissues, even normal "nonpathogenic'' strains of *E. coli* can cause infection.[19] *E. coli* infections may be limited to the mucosal surface or can disseminate throughout the body. The three general clinical syndromes caused by the pathogenic *E. coli* strains are urinary tract infections, sepsis/meningitis, and enteric/diarrheal diseases.[22]

In the recent past, glycoconjugates derived from the *O*-antigenic oligosaccharides from the bacterial cell wall have been used to develop antibacterial vaccine candidates.[23-29] Several biological experiments are necessary for a detailed understanding of the relationship between the *O*-antigen with the pathogenicity of a particular bacterial strain, which in turn demands substantial quantities of oligosaccharides in hand. The oligosaccharides isolated from the natural source can not meet such requirements. Therefore, the development of a concise chemical synthetic strategy is essential to provide a large quantity of a particular oligosaccharide. In this context, oligosaccharide structures of cell-wall of the following strains have been selected for chemical synthesis using several recently developed synthetic methodologies:



→4)-β-D-Gal*p*NAc-(1→2)Man*p*-(1→3)-α-L-Fuc*p*-(1→3)-α-D-GalpNAc-(1→
|
β-D-Gal*p*(1→3)

In this connection, we would like to synthesize the cell wall polysaccharide structure of *Escherichia coli* O125ac. The propylamine linker at the reduction will help it to couple it with a carrier protein to evaluate its biological activity towards the development of a possible vaccine candidate against *Escherichia coli* infection.

CHAPTER-2

LITERATURE REVIEW

2.0. REVIEW OF THE LITERATURE ON THE SYNTHESIS OF THE SUGAR

2.1 Previous reports

Thioglycosides are amongst the most widely used choices of glycosyl donors in synthetic carbohydrate chemistry. Their popularity can be defined as their ready synthesis, thermal stability, and acting as a precursor to other glycosyl donors. Thiglycosides are known to be very less abundant in nature, only a few simple alkyl and aryl thioglycosides have been found as constituents of antibiotics from *Streptomyces* species.[1-3] Glucosinolates (althougeally thioglycosides) with aatomicmcsulfurr, sulfur well-known natural compounds.[4,5] Despite their low availability in nature, for a long time thioglycosides and their chemistry have been a field of interest for many researchers. The first thioglycoside was synthesized in 1909,[6] but their glycosyl donor capability has recently been recognized. Using thioglycoside as a glycosyl donor, the first successful synthesis of a disaccharide[7] was performed at the beginning of the seventies**.** But it was not until the middle of the eighties that enough efficient promoters were discovered to make glycosylation with thioglycoside donors into a general and accepted method. In the last decade, sugars have widely been used in biochemical and structural investigations of glycosidases due to their close structural similarity to the natural *O*-glycosides.[8-12] But their chemical reactivities are quite different from their *O*-glycoside counterpart.[13,14] A wide array of properties of thioglycosides makes them versatile glycosyl donors ie synthetic carbohydrate chemistry, particularly in oligosaccharide synthesis.[15-17]

The preparation of thioglycosides is relatively easy, they are stable under most of the reaction conditions and are relatively easy to handle. Thioglycosides can act as precursors for various glycosyl derivatives such as glycals,[18] hemiacetals[19-24], glycosyl fluorides,[25] sulfoxides[26-34], and sulfones[35-3,7], etc (Figure 1), which are used as glycosyl donors for *O*- and *C*-glycosylation.[38-40] The success of using thioglycosides in the oligosaccharide synthesis originates from the stability of the anomeric thio functionality towards a wide range of reaction conditions used for the

protecting group manipulations in the synthetic carbohydrate chemistry. In addition, the thio group can be activated using a range of electrophiles to provide a reactive glycosyl donor. The thioacetal function thus conveniently combines the role of an anomeric protecting group as well as an efficient leaving group. This fact makes thioglycosides versatile agents in the synthesis of oligosaccharides.[41-58]

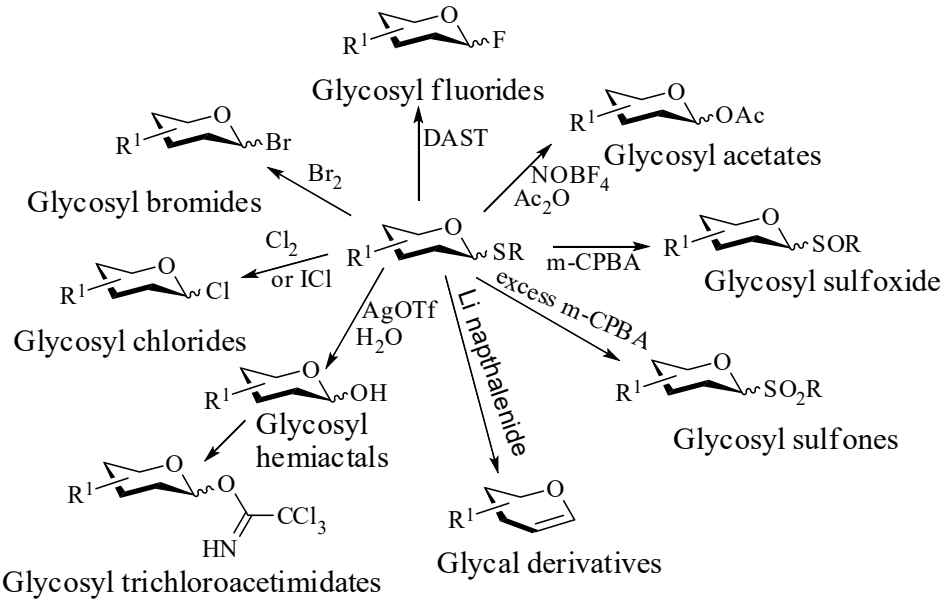


Figure 1: Thioglycosides as a precursor for various glycosyl donors.

As in the case of thioglycosides, selenoglycosides have also been widely used in the biochemical and structural investigations of glycosidases.[59,60] Being very effective and stable glycosyl donors 1,2-selenoglycosides have found many applications in the field of carbohydrate chemistry.[61-63] As for thioglycosides, selenoglycosides can also act as precursorsr various glycosyl derivatives such as glycosyl fluorides,[64] bromides,[65] iodides,[66] hemiacetals,[67], etc (Figure 2).

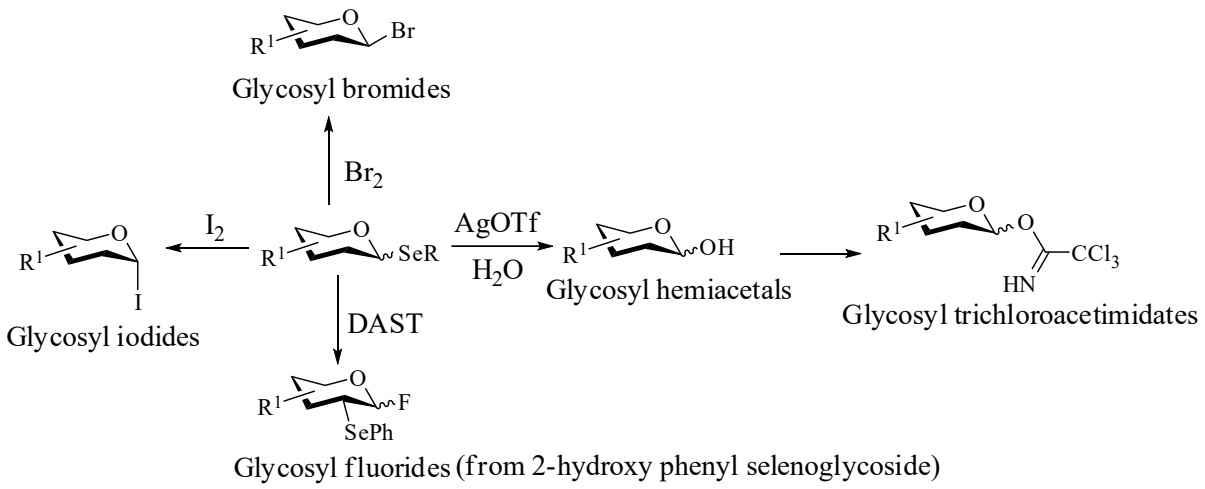
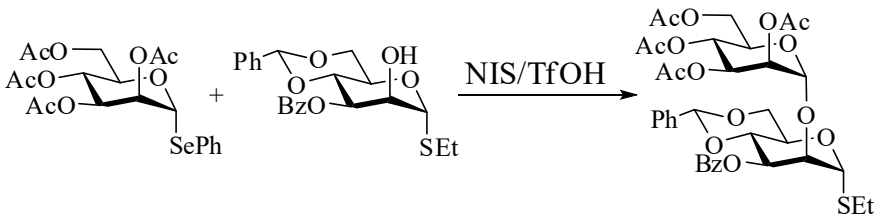


Figure 2: Selenoglycosides as a precursor for various glycosyl donors.

Selenoglycosides can be selectively activated in the presence of thioglycosides, which makes them an attractive intermediate in oligosaccharide synthesis (Scheme 1). Besides their use in the glycosylation chemistry as glycosyl donors they have also been used as preprecursorsr the preparation of functionalized glycals, *C*-glycoside glycoconjugatesatese, s, etc.[68-70]



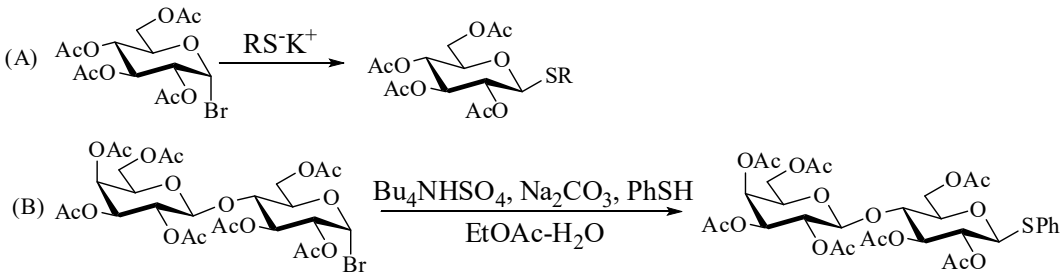
Scheme 1: Chemoselective glycosylation of selenoglycoside in the presence of thioglycoside.

Given the importance of thio- and selenoglycosides a plethora of methods are available in liter nature for their preparation. Those are categorized as follows:

5.1.1. Synthesis of thioglycosides

(a) From glycosyl halides

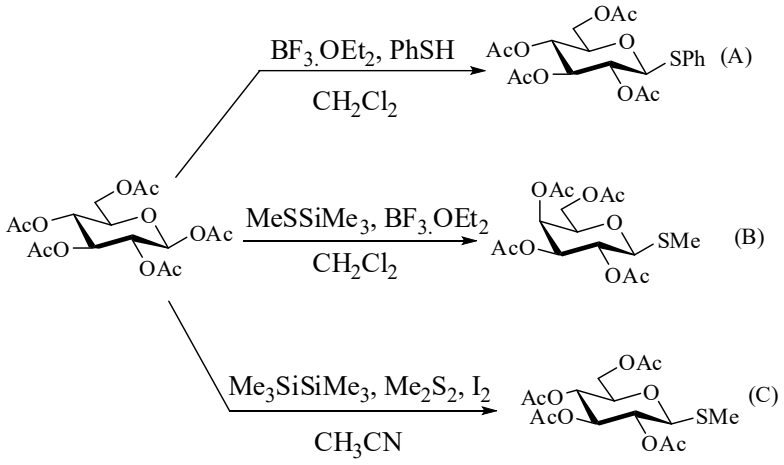
For the synthesis of thioglycoside, an S_N2 displacement of a per-*O*-acetylated glycosyl halide by thioalkoxide reagent has been introduced (Eq. A, Scheme 2).[71-75] However, due to the possibility of the formation of by-product through partial de-*O*-acylation, a phase transfer reaction condition has also been introduced to overcome the drawback (Eq. B, Scheme 2).[76-78]



Scheme 2: Reaction of glycosyl halides with thiolate anion.

(b) From anomeric acylates

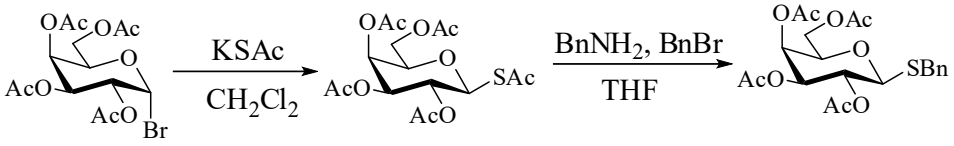
Lewis acid-mediated displacement of anomeric acetate group with a thioalkyl/aryl group is the most commonly used method for the synthesis of thioglycosides (Eq. A, Scheme 3).[79-84] However, the major drawback of the above procedure is the use of toxic and malodorous thiols and formaisomerizedomerized products. As a modification of this proc procedure, the trimethylsilylmarcaptans instead of thiol were subsequently introduced (Eq. B, Scheme 3 order to avoid the use of expensive trimethylsilylmarcaptans, an iodine iodinemediatedodology has also been introduced (Eq. C, Scheme 3).[87]



Scheme 3: Reaction of anomeric acylates with thiols or trimethylsilyl mercaptans.

(c) From anomeric thioacetates

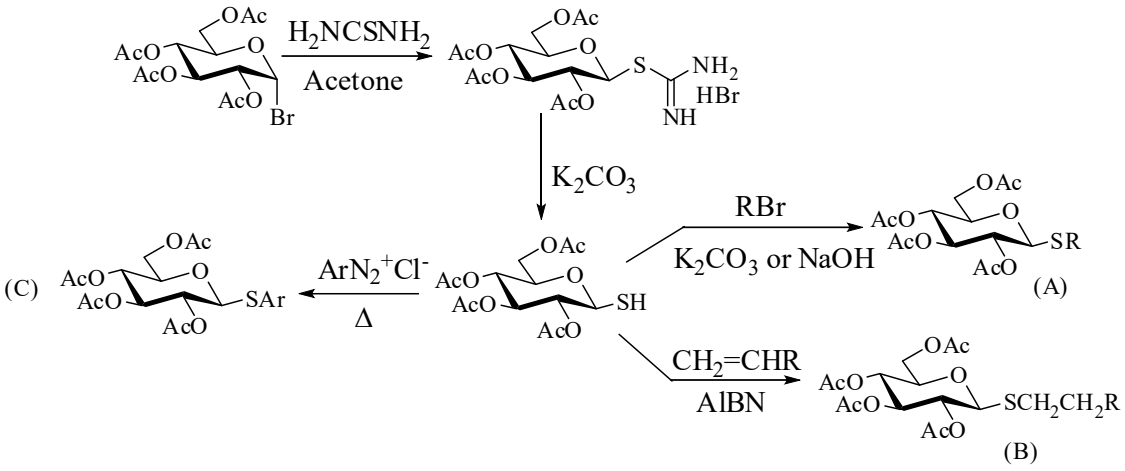
In this case, thioglycosides can be prepared through the formation of glycosyl thioacetates from glycosyl halides, followed by alkylation/arylation of the thiol generated *in situ* by selective de-*S*-acetylation (Scheme 4).[88]



Scheme 4: Reaction of 1-thioacetates with alkyl/aryl halides.

(d) From glycosyl tiotropium salt

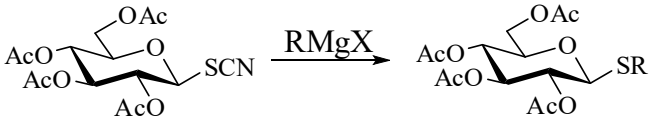
An isothiouronium salt is prepared by the treatment of acylated glycosyl halide with thiourea, which upon hydrolysis with aqueous potassium carbonate yields acylated 1-thioglycopyranose having the 1,2-*trans* configuration.[89] Reaction of the acylated 1-thiopyranose with an alkyl halide yields 1,2-*trans*-alkyl-1-thioglycoside (Eq. A, Scheme 5). This method is particularly useful for the preparation of thioglycosides avoiding the use of thiols.[90,91] Reaction of the acetylated 1-thioaldoses with alkenes in the presence of azobis(isobutyronitrile) (AIBN) also produces acylated 1-thioglycosides (Eq. B, Scheme 5).[92] Acylated aryl 1-thioglycoside can be prepared by the reaction of acylated 1-thio-glucopyranose with an aryldiazonium salt and subsequent thermal decomposition of the intermediate diazonium compound (Eq. C, Scheme 5).[93]



Scheme 5: Reaction of acylated glycosylthiouronium salt.

(e) From glycosyl thiocyanates

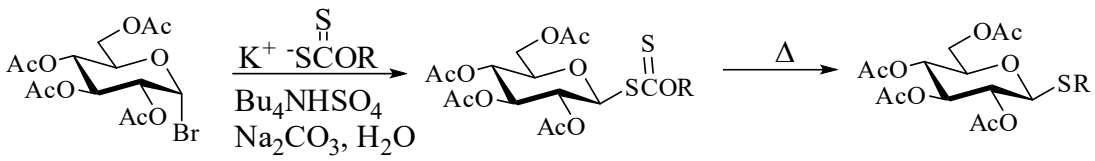
The reaction of acetylated glucopyranose halides with potassium thiocyanate produces the corresponding 1-thiocyanates, which on treatment with Grignard reagents at −40°C afford 1-thioglycosides (Scheme 6).[94] This is an indirect method for the preparation of thioglycosides.



Scheme 6: Reaction of glycosyl thiocyanates with the Grignard reagent.

(f) From Glycosyl Xanthates

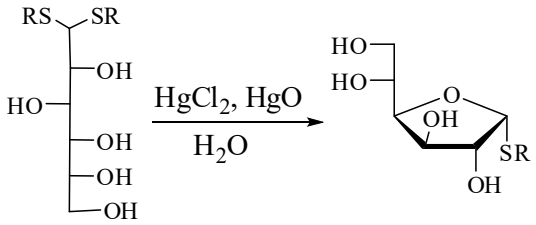
Glycosyl xanthate can be prepared by the treatment of glucopyranose halide with a potassium alkylxanthate[95] either in solution or under phase-transfer conditions[96] or by treatment oftra-*O*-alkylateglucopyranosese with *p*-toluenesulfonyl chloride and potassialkyl xanthate under phase-transfer conditions.[97] The glycosyl xanthates then thermally decompose to furnish 1-thioglycosides (Scheme 7).



Scheme 7: Decomposition of glycosyl xanthates to the thioglycosides.

(g) From glycosyl dithioacetals

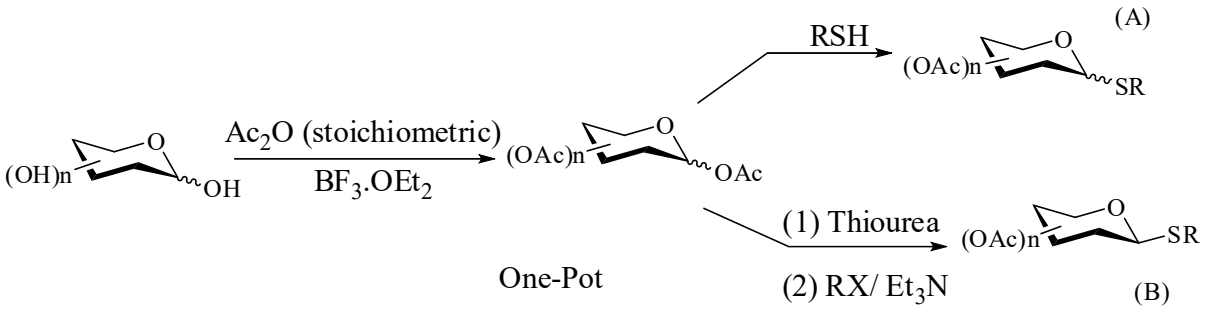
Mercury (II) salts mediated partial desulfurization of glycosyl dithioacetals is a useful procedure for the preparation of 1-thioglycosides having the 1,2-*cis* configuration, which is as difficult to achieve by the conventional methods. As this transformation involves thermodynamic ring-cyclization, it has been used successfully for the preparation of furanosidic thioglycosides (Scheme 8).[98]



Scheme 8: Partial hydrolysis of glycosyl dithioacetals and formation of thiofuranosides.

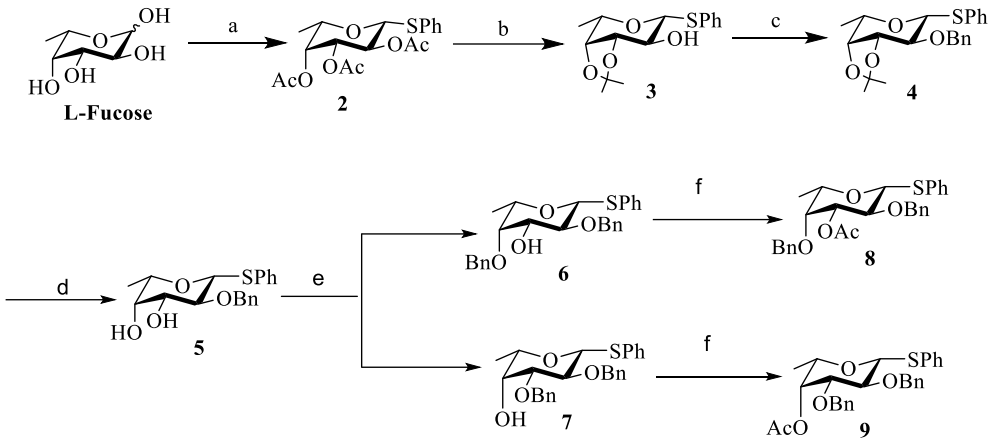
(h) From reducing sugars

Thioglycosides can also be prepared directly from unprotected reducing sugars following acetylation using a stoichiometric amount of acetic anhydride in the presence of boron trifluoride diethyl etherate and subsequent reaction with alkyl/aryl thiols (Eq. A, Scheme 9).[99] In another aspect, 1,2-*trans* thioglycosides can also be prepared in the same way but instead of using alkyl/aryl thiols it goes through the formation of *S*-glycosyl isothiouronium salts *in situ,* and subsequent reaction with alkyl halides (Eq. B, Scheme 9).[100]



Scheme 9: Lewis acids mediated the formation of thioglycosides from reducing sugars in one pot.

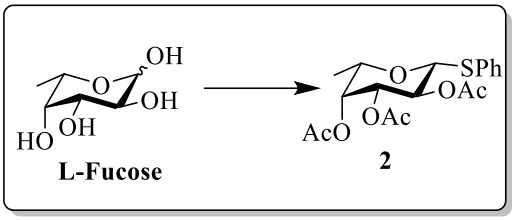
2.2 PRESENT WORK:



Scheme 10. Reagents: (a) (i) Acetic anhydride, Pyridine, r t, 8 h; (ii) PhSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 5-10 °C, 4 h, 86% in two steps; (b) (i) 0.1 M CH_3ONa, CH_3OH, r t, 3 h; (ii) 2,2-dimethoxy propane, acetone, CSA, r t, 3 h, 77 % in two steps; (c) benzyl bromide, NaOH, DMF, r t, 3 h, 93%; (d) 80% aq. AcOH, 80 °C, 1.5 h, 92%; (e) 5% NaOH, DCM, BnBr, r t, 12 h; (f) Acetic anhydride, Pyridine, r t, 8 h, 95%

Preparation and spectral data of compounds 1-8

Synthesis of 1,2,3,4-tetra-O-acetyl-L-Fucopyranoside:



PROCEDURE: -

To an ice-cooled suspension of L-fucose, **1** (5 g, 0.030 mmol) in Pyridine (25 mL), acetic anhydride (10 mL) was added dropwise. The resulting mixture was stirred for 9 h at room temperature and subsequently poured into iced water. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with cold 1M HCl, saturated aqueous $NaHCO_3$, and brine successively, and finally dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was isolated as a gummy liquid in quantitative yield and used in the next step without further purification.

Crude per-acetylated L-fucose (10.9 gm, 45.14mmol) was dissolved in dry DCM (45 ml) and added p-thiophenol (4ml,53.05mml) was under a nitrogen atmosphere and stirred for 30 minutes in an ice bath. Then 12.5ml of $BF_3.OEt_2$ was added portion-wise and stirred for 12 hours at room temperature. After the complete consumption of starting material, the reaction mixture was extracted with DCM and washed with NaOH solution and brine solution successively. Then the organic layer was concentrated under reduced pressure and dried in a vacuum. The crude product was purified by column chromatography over silica gel (100-200mesh) (n-hexane/ethyl acetate = 3:1) to obtain a compound.

TLC: Ethyl acetate: Hexane (2:3), $\mathbf{R}_f$= 0.5

YIELD: 86%

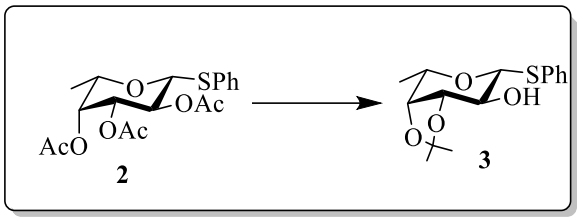
Molecular formula : $C_{18}H_{22}O_7S$

Molecular weight:382.11

1H NMR (500 MHz, CDCl3) : 1H NMR (400 MHz, CDCl3) δ 7.55 – 7.48 (m, 2H), 7.35 – 7.28 (m, 3H), 5.26 (ddd, J = 23.5, 16.3, 10.8 Hz, 2H), 5.05 (dd, J = 9.9, 3.4 Hz, 1H), 4.71 (d, J = 9.9 Hz, 1H), 3.84 (dd, J = 6.4, 0.9 Hz, 1H), 2.13 (d, J = 15.4 Hz, 3H), 2.11 – 2.07 (m, 3H), 1.98 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H).

13C NMR (CDCl3, 100 MHz): ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.65 (s), 170.17 (s), 169.53 (s), 132.92 (s), 132.35 (s), 128.90 (s), 127.97 (s), 86.51 (s), 73.19 (s), 72.46 (s), 70.36 (s), 67.39 (s), 20.90 (s), 20.69 (d, *J* = 4.4 Hz), 16.51 (s).

Synthesis of Phenyl-3,4-O-isopropylidene-1-thio-β-L-Fucopyranoside:



PROCEDURE: -

A solution of compound **2** (12.64 g, 0.031 mmol) in 0.1 M sodium methoxide in CH_3OH (30 mL) was allowed to stir at room temperature for 3 h. The reaction mixture was neutralized with acetic acid, and concentrated under reduced pressure.

To a solution of the crude mass in anhydrous acetone (70 mL) were added 2,2-dimethoxy propane (18.49 mL, 0.177 mmol) and *p*-toluenesulfonic acid (500 mg), and the reaction mixture was allowed to stir at room temperature for 3 h. After complete consumption of the starting material the reaction mixture was neutralized with trimethylamine and solvents were concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane-EtOAc (4:1) as eluant to give pure compound **3** (1.522 g, 77%).

TLC: Ethyl acetate: Hexane (1:1) $\mathbf{R_f}$= 0.3

YIELD: (1.522g, 77%)

Molecular formula $C_{15}H_{20}O_4S$

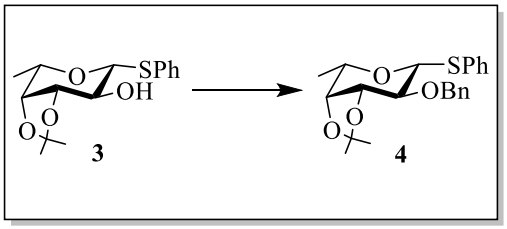
Molecular weight: 296.38

^{1}H NMR (500 MHz, $CDCl_3$) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.38 (dd, *J* = 29.2, 6.9 Hz, 2H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.26 – 4.21 (m, 1H), 4.05 (dd, *J* = 5.6, 2.1 Hz, 1H), 3.83 (dd, *J* = 6.6, 2.1 Hz, 1H), 3.50 (dd, *J* = 9.7, 6.5 Hz, 1H), 1.43 – 1.38 (m, 3H), 1.36 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz):

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.98 (s), 133.80 (s), 132.14 (s), 128.77 (s), 128.27 (d, J = 7.5 Hz), 127.73 (s), 127.38 (s), 109.72 (s), 86.14 (s), 79.86 (s), 78.14 (s), 76.45 (s), 73.48 (s), 72.42 (s), 27.91 (s), 26.42 (s), 16.92 (s).

Synthesis of Phenyl-2-O- Benzyl-O-Isopropylidine-1-thio-β-L-Fucopyranoside:



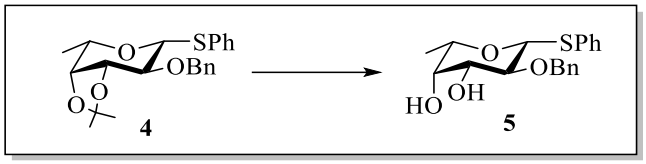
PROCEDURE: -

To an ice-cooled stirred solution of compound **3** (1.522 g,0.005 mmol) in dry THF (5 ml) and sodium hydride (0.37, 0.015mmol) was added portion wise and benzyl bromide (0.91ml,0.005 mmol) was added and the resulting reaction mixture was stirred for 1 hour at room temperature. After the complete consumption of starting material, the reaction mixture was quenched by adding an ammonium chloride solution. Then the quenched reaction mixture was extracted with CH_2Cl_2 (30 mL). The organic layer was, washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel (100-200mesh) (n-hexane/ethyl acetate = 3:1) to obtain a compound **4**.

TLC: Ethyl acetate: Hexane (1:1) $\mathbf{R_f}$= 0.3

YIELD: 93%, (4.133g)

Synthesis of Phenyl-2-O- Benzyl-1-thio-β-L-Fucopyranoside:



PROCEDURE: -

To compound **4** (4.133g) in CH_2Cl_2 (2 ml), 20% aqueous acetic acid (100 ml) was added and the reaction mixture was stirred at 80 ^{0}C for 1 hour. Upon completion, the solvent was removed under reduced pressure and co-evaporated with toluene (3×10ml). the compound was purified by column chromatography over silica gel (100-200mesh) (n-hexane/ethyl acetate = 3:1) to obtain compound **5**.

TLC: Ethyl acetate: Hexane (2:3) $\mathbf{R}_f$= 0.5

YIELD: 92% (5.75g)

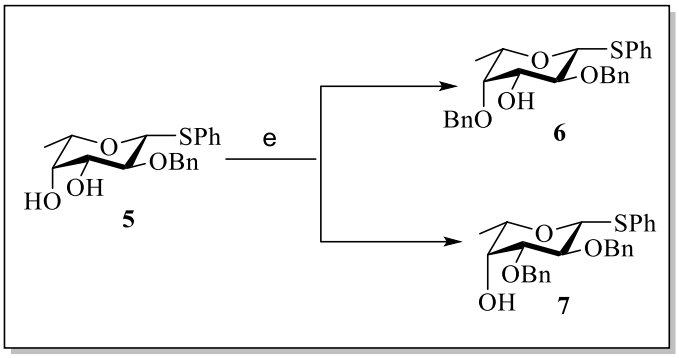
Molecular formula: $C_{19}H_{22}O_4S$

Molecular weight: 346.44

^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.41 – 7.27 (m, 7H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.61 (d, *J* = 9.6 Hz, 1H), 3.75 (d, *J* = 3.5 Hz, 1H), 3.73 – 3.59 (m, 2H), 3.54 (t, *J* = 9.3 Hz, 1H), 2.46 (d, *J* = 5.0 Hz, 1H), 2.13 (d, *J* = 4.8 Hz, 1H), 1.36 (d, *J* = 6.5 Hz, 3H).

Scheme -8

Synthesis of Phenyl-2,4-di-O- Benzyl-1-thio-β-L-Fucopyranoside:



PROCEDURE: -

To a solution of compound **5** (5.75g,0.016 mmol) in DCM, 7.5% (NaOH) solution (5ml) was added and stirred vigorously for 10 min and benzyl bromide (0.068 ml, mmol) was added and stirred for another 6 hours at room temperature. After the starting material was consumed, the reaction mixture was diluted with DCM (20 mL). The organic layer was, washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel (230-400mesh) (n-hexane/ethyl acetate = 3:1) to obtain compounds 6 and 7 in a 1:1 ratio.

TLC: Ethyl acetate: Toluene (1:4) $\mathbf{R}_f$= 0.2

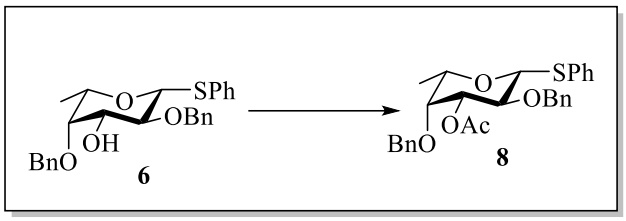
YIELD: 96% (5.75g)

Molecular formula :$C_{20}H_{24}O_3S$

Molecular weight: 344.47

^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 2H), 7.43 – 7.25 (m, 8H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.65 (dd, *J* = 30.8, 10.3 Hz, 2H), 3.68 (ddd, *J* = 19.2, 13.2, 4.6 Hz, 3H), 3.54 (t, *J* = 9.3 Hz, 1H), 2.46 (d, *J* = 5.0 Hz, 1H), 2.23 – 1.93 (m, 1H), 1.36 (d, *J* = 6.5 Hz, 3H).

Synthesis of Phenyl-2,4-di-O- Benzyl-3-O-acetyl-1-thio-β-L-Fucopyranoside:



PROCEDURE: -

To an ice-cooled solution of compound **6** (2.875g,0.006mmol) in pyridine, acetic anhydride(16.9ml) was added and stirred for 3 hours. at room temperature. After the starting material was consumed, the reaction mixture was diluted with DCM (10 mL). The organic layer was, washed with bicarbonate solution, and brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel (230-400mesh) (n-hexane/ethyl acetate = 3:1) to obtain the compound

TLC: Ethyl acetate: Hexane (2:3) $\mathbf{R}_f$= 0.5

YIELD: 95% (2.518g)

Molecular formula :$C_{28}H_{30}O_5S$

Molecular weight: 478.18

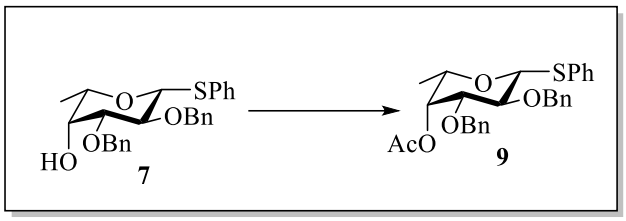
^{1}H NMR (500 MHz, $CDCl_3$):

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dt, *J* = 18.6, 8.3 Hz, 2H), 8.11 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.71 – 7.65 (m, 3H), 7.64 – 7.56 (m, 2H), 7.56 – 7.51 (m, 2H), 7.50 – 7.44 (m, 3H), 7.41 – 7.37 (m, 2H), 5.64 – 5.61 (m, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.77 – 4.70 (m, 2H), 4.66 (d, *J* = 9.4 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 3.86 – 3.81 (m, 1H), 3.76 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.71 (t, *J* = 9.3 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz):

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.86 (s), 138.30 (s), 137.63 (s), 133.83 (s), 132.08 (s), 128.81 (s), 128.32 (dd, *J* = 19.4, 7.8 Hz), 127.84 (d, *J* = 7.7 Hz), 127.47 (s), 87.61 (s), 81.30 (s), 76.62 (s), 75.74 (s), 73.04 (s), 71.91 (s), 69.79 (s), 22.73 (s), 20.97 (s), 16.90 (s), 14.16 (s), 0.04 (s).

Synthesis of Phenyl-2,3-di-O- Benzyl-4-O-acetyl-1-thio-β-L-Fucopyranoside:



PROCEDURE: -

To an ice-cooled solution of compound **7** (2.875mg,0.006 mmol) in pyridine, acetic anhydride(16.9ml) was added and stirred for 3 hours. at room temperature. After the starting material was consumed, the reaction mixture was diluted with DCM (10 mL). The organic layer was, washed with bicarbonate solution, and brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel (230-400mesh) (n-hexane/ethyl acetate = 3:1) to get compound **9**.

TLC: Ethyl acetate: Hexane (2:3) $\mathbf{R}_f$= 0.5

YIELD: 95%(2.518g)

Molecular formula :$C_{28}H_{30}O_5S$

Molecular weight: 478.18

^{1}H NMR (500 MHz, $CDCl_3$):

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dt, *J* = 18.6, 8.3 Hz, 2H), 8.11 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.71 – 7.65 (m, 3H), 7.64 – 7.56 (m, 2H), 7.56 – 7.51 (m, 2H), 7.50 – 7.44 (m, 3H), 7.41 – 7.37 (m, 2H), 5.64 – 5.61 (m, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.77 – 4.70 (m, 2H), 4.66 (d, *J* = 9.4 Hz, 1H), 4.53

(d, *J* = 11.3 Hz, 1H), 3.86 – 3.81 (m, 1H), 3.76 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.71 (t, *J* = 9.3 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz):

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.86 (s), 138.30 (s), 137.63 (s), 133.83 (s), 132.08 (s), 128.81 (s), 128.32 (dd, *J* = 19.4, 7.8 Hz), 127.84 (d, *J* = 7.7 Hz), 127.47 (s), 87.61 (s), 81.30 (s), 76.62 (s), 75.74 (s), 73.04 (s), 71.91 (s), 69.79 (s), 22.73 (s), 20.97 (s), 16.90 (s), 14.16 (s), 0.04 (s).

CHAPTER-3

METERIALS AND METHODS

3.0 MATERIALS AND METHODS:

3.1 CHEMICALS:

Table 1: The chemicals used in the present work are as listed in the table below

S.NO	CHEMICAL	CHEMICAL SUPPLIER	GRADE
1.	L-Fucose	Carbosynth	LR
2.	Pyridine	Loba Chemie	LR
3.	Acetic anhydrade	Finar	LR
4.	p-thiophenol	Avra	LR
5.	Dry DCM	Finar	AR
6.	2,2 Dimethoxy propane	Avra	LR
7.	Camphor sulphonic acid	Laba Chemie	LR
8.	Benzyl bromide	Avra	LR
9.	Benzoyl chloride	Avra	LR

3.2 METHODS:

All the required chemicals used were obtained mainly from Avra chemicals. All the solvents used were laboratory-grade.

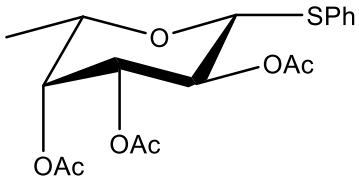
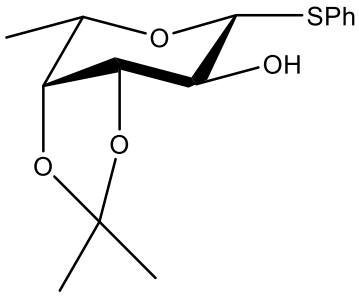
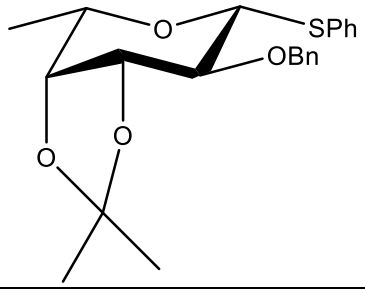
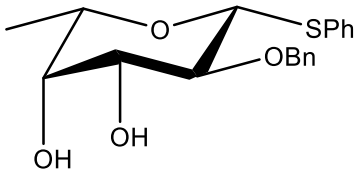
1. Melting points were determined on Stuart SMP10 melting point apparatus.
2. Proton magnetic resonance spectra were recorded on Avance 400 and Avance new 500 MHz instruments and the samples were made in CDCl3 using tetramethyl silane (Me4Si) as the internal standard.
3. Each reaction was monitored by TLC by using the appropriate solvent system, which was selected by trial and error method. Pre-coated TLC plates (0.25mm silica gel) were obtained from E. Merck.
4. All solvent extracts were washed with water, and brine, dried over anhydrous Na,2SO4, and concentrated at reduced pressures on Heidolph 4000 rotary evaporator below 40 °C.

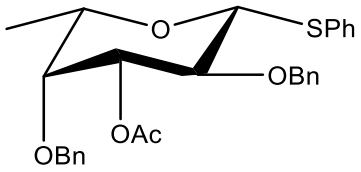
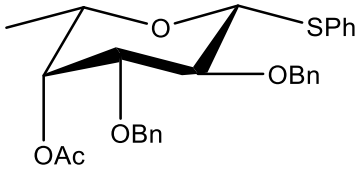
CHAPTER-4

RESULTS AND DISCUSSION

4.0. RESULTS AND DISCUSSION

4.1 Structures of the synthesized compounds:

S.NO	COMPOUND	IUPAC NAME	YIELD
1.		(2S,3R,4R,5S,6R)-2-Methyl-6-(phenylthiol)tetrahydro-2H-pyran-3,4,5-trial triacetate	86%
2.		(3aR,4S,6R,7S,7As)-2,2,4-trimethyl-6-(phenylthiol)tetrahydro-4H-(1,3)dioxolo(4,5-c)pyran-7-ol.	77%
3.		(3aR,4S,6R,7S,7aR)-7-(benzyloxy)-2,2,4-trimethyl -6-(phenylthiol)tetrahydro-4H-(1,3)doxology(4,5-c)pyran	93%
4.		(2S,3R,4R,5S,6R)-5-(benzyloxy)-2-Methyl-6-(phenylthiol)tetrahydro-2H-pyran-3,4-diol	92%

5.		(2S,3S,4R,5S,6R)-3,5-bis(benzyloxy)-2-methyl-6-(phenylthiol)tetrahydro-2-H-pyran-4-yl-acetate.	95%
6.		(2S,3S,4R,5S,6R)-4,5-bis(benzyloxy)-2-methyl-6-(phenylthiol)tetrahydro-2-H-pyran-4-yl-acetate	95%

^{1}H NMR DATA OF COMPOUND – 1

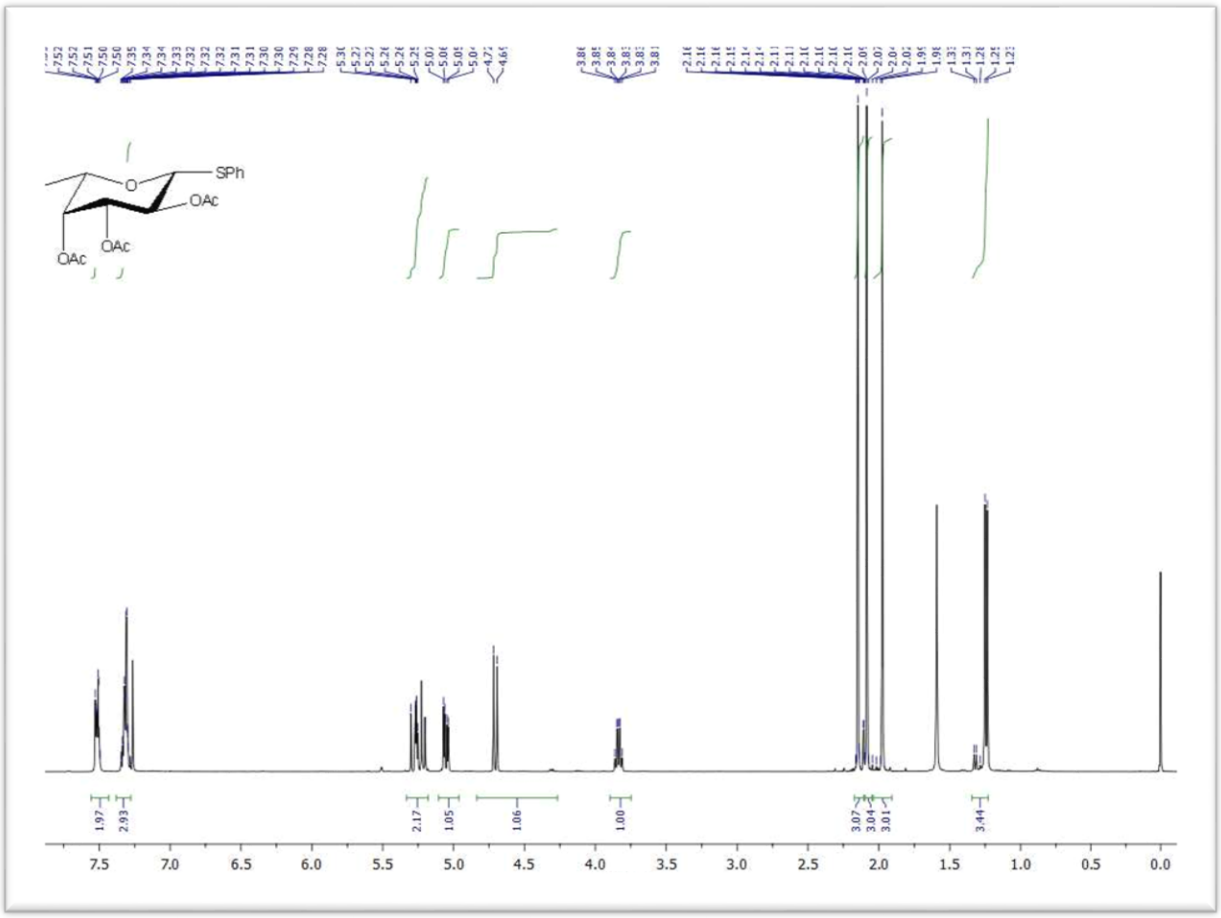


Figure.1

^{13}C NMR SPECTRA OF COMPOUND -1

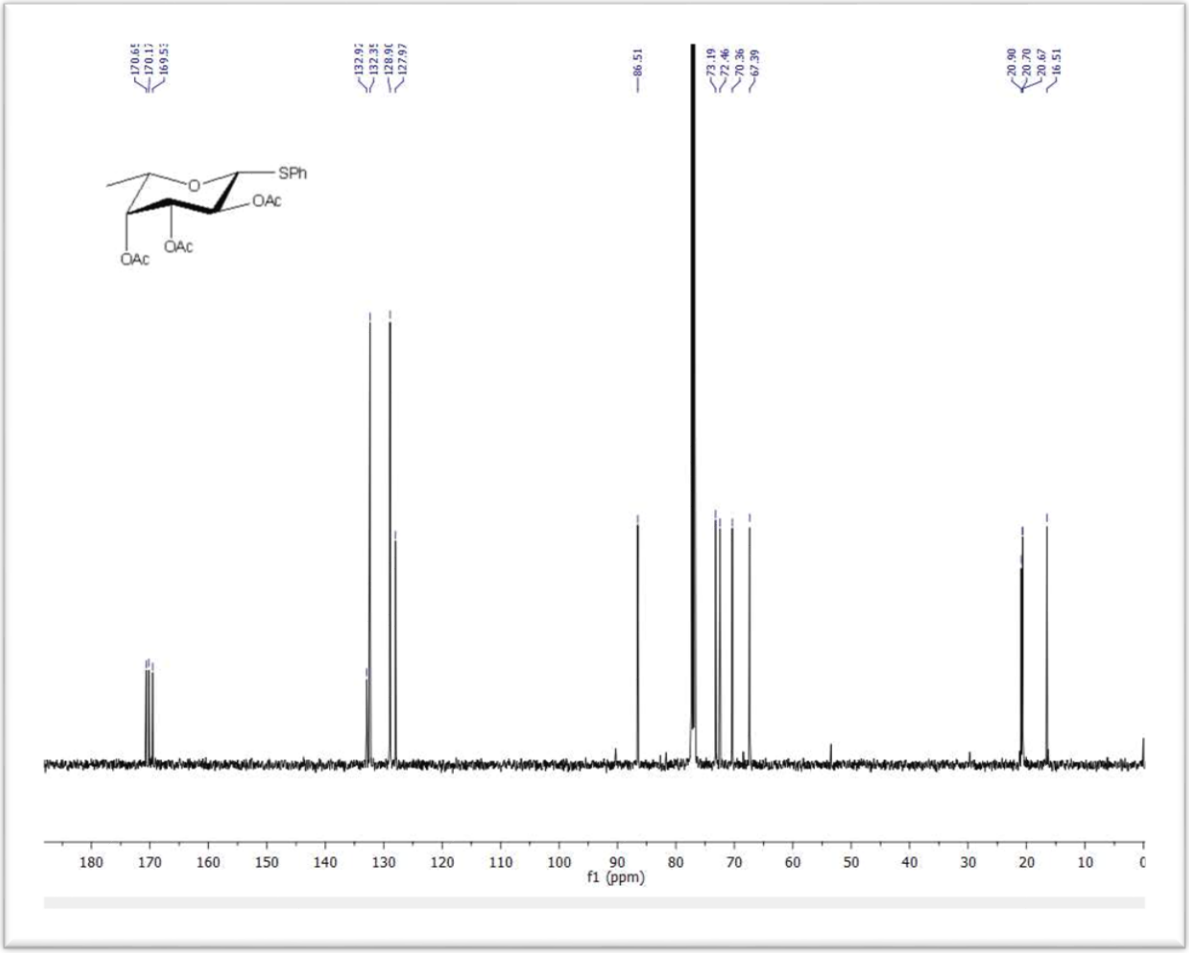


Figure.2

^{1}H NMR DATA OF COMPOUND – 2

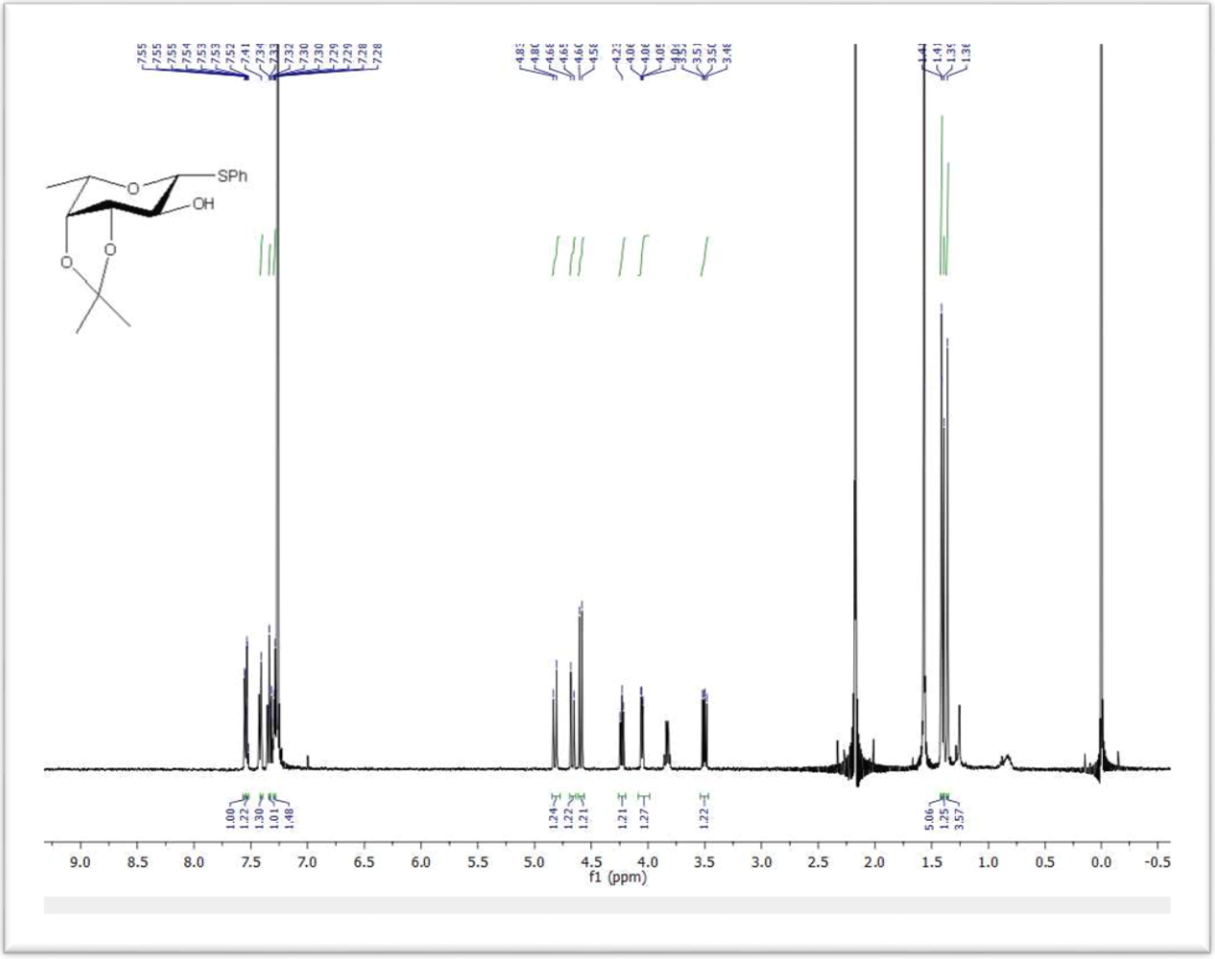


Figure.3

^{13}C NMR SPECTRA OF COMPOUND -2

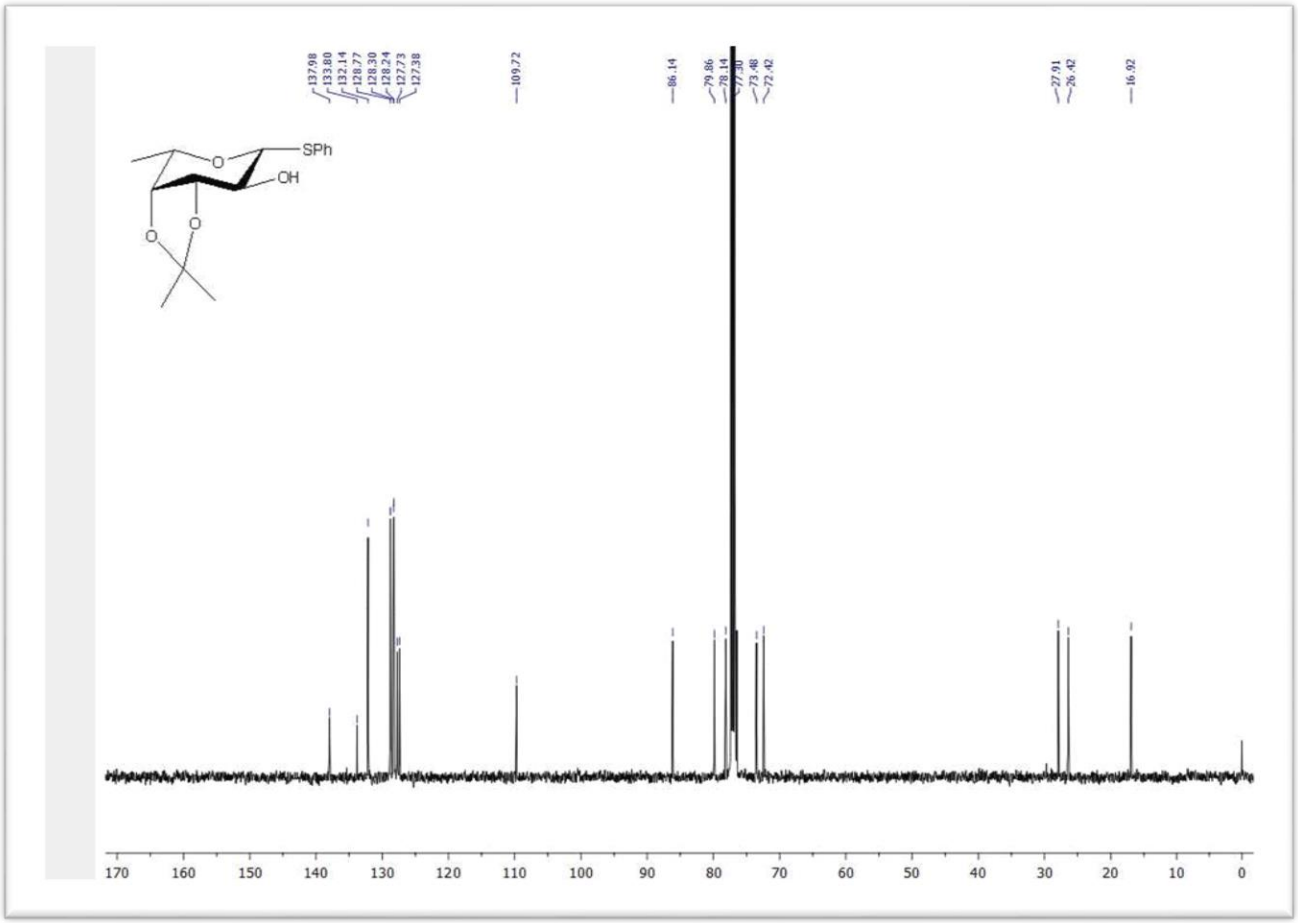


Figure.4

^{1}H NMR DATA OF COMPOUND – 3

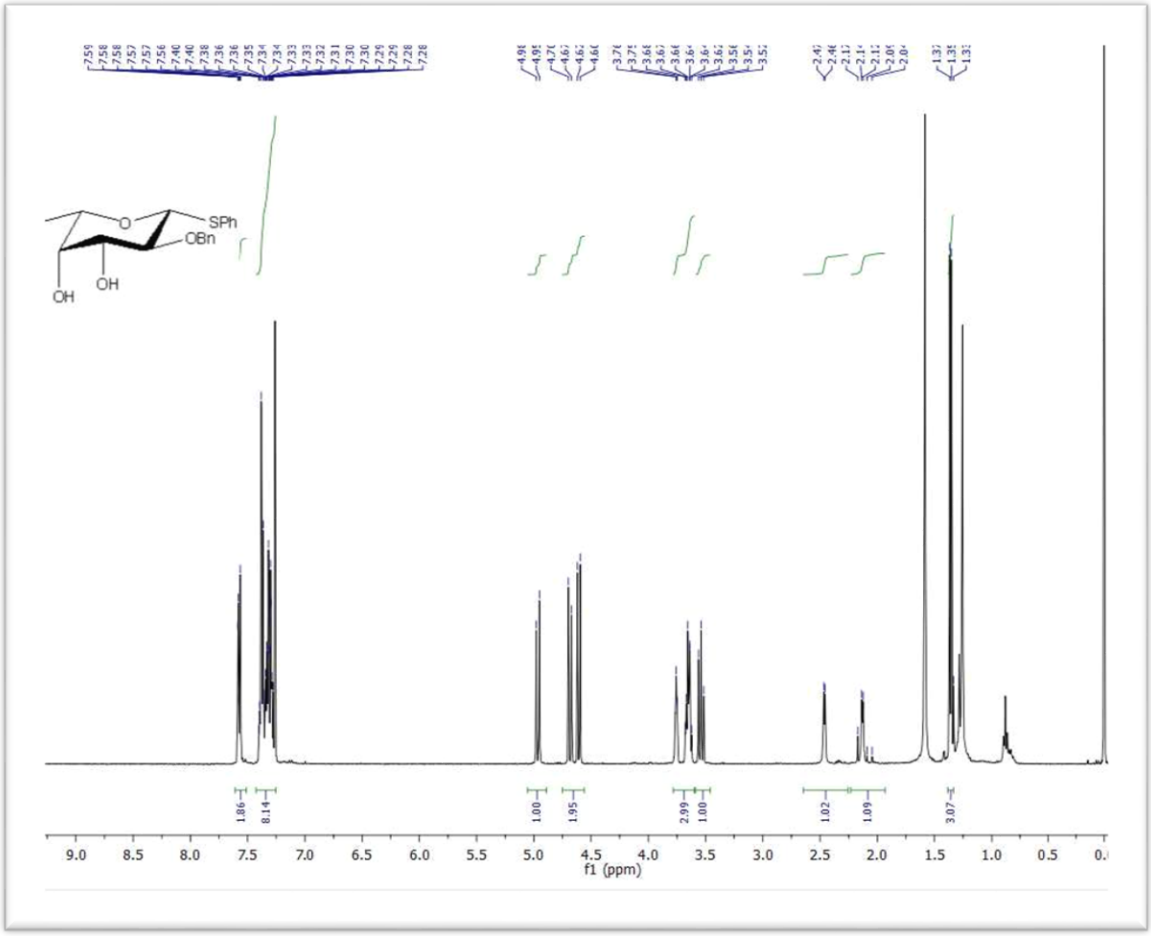


Figure.5

^{1}H NMR DATA OF COMPOUND – 4

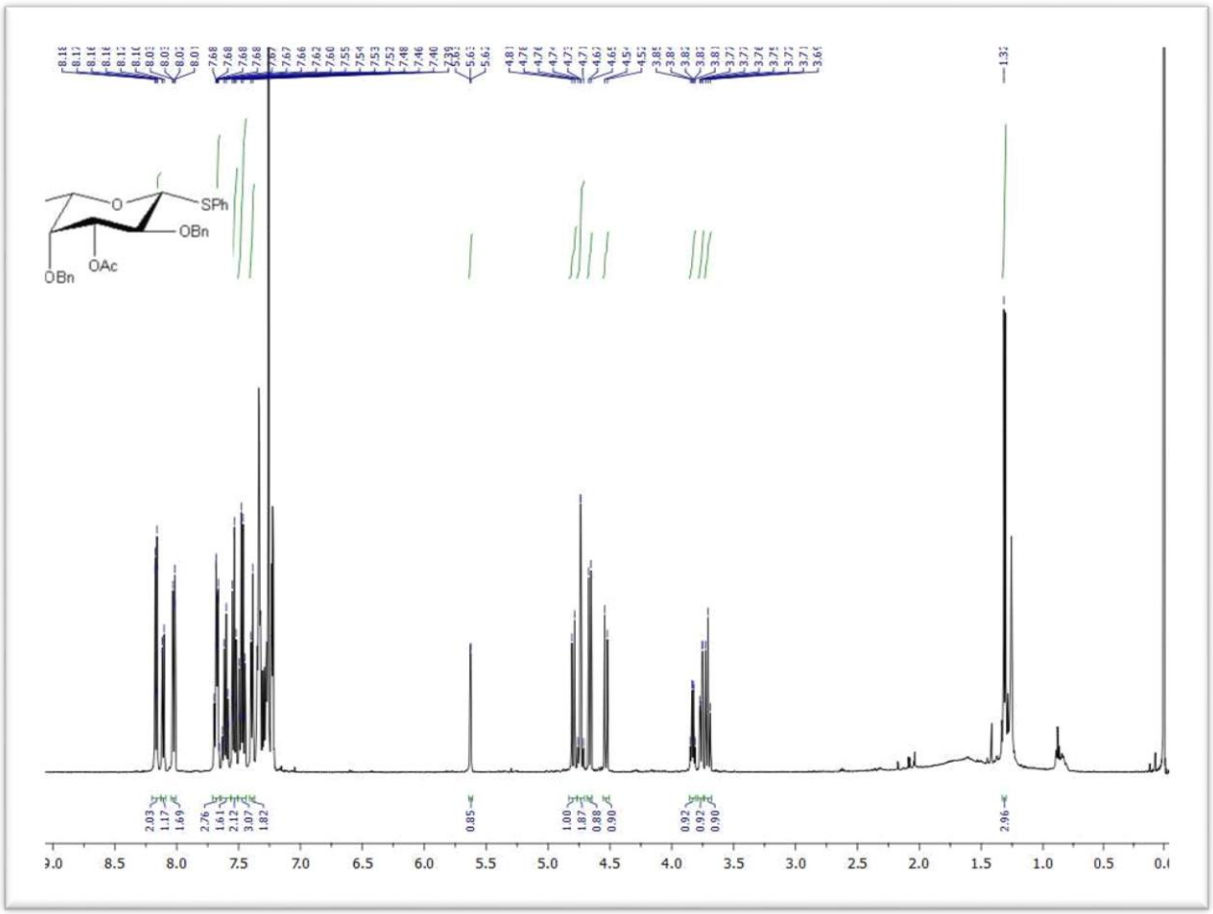


Figure.6

^{13}C NMR SPECTRA OF COMPOUND -4

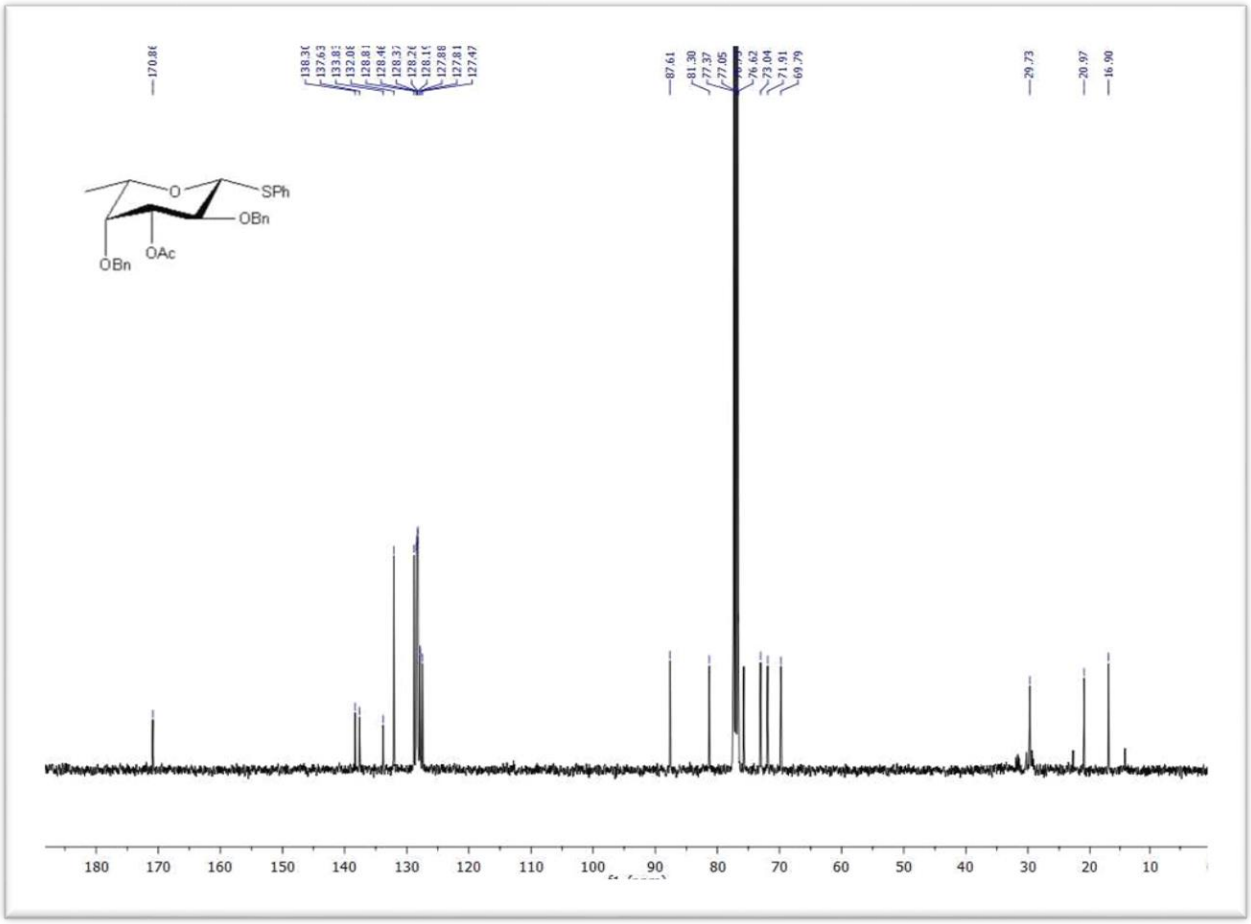


Figure.7

^{1}H NMR DATA OF COMPOUND – 5

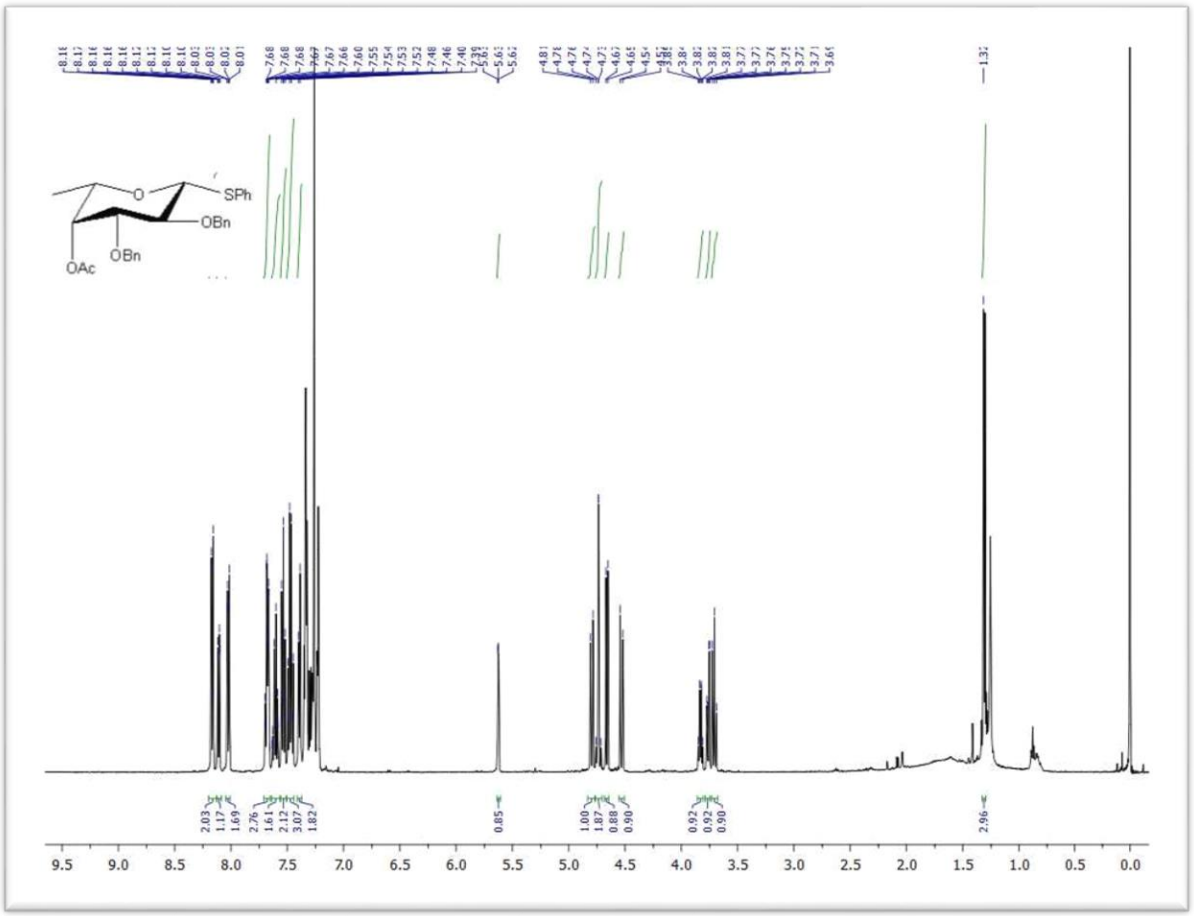


Figure.8

^{13}C NMR SPECTRA OF COMPOUND-5

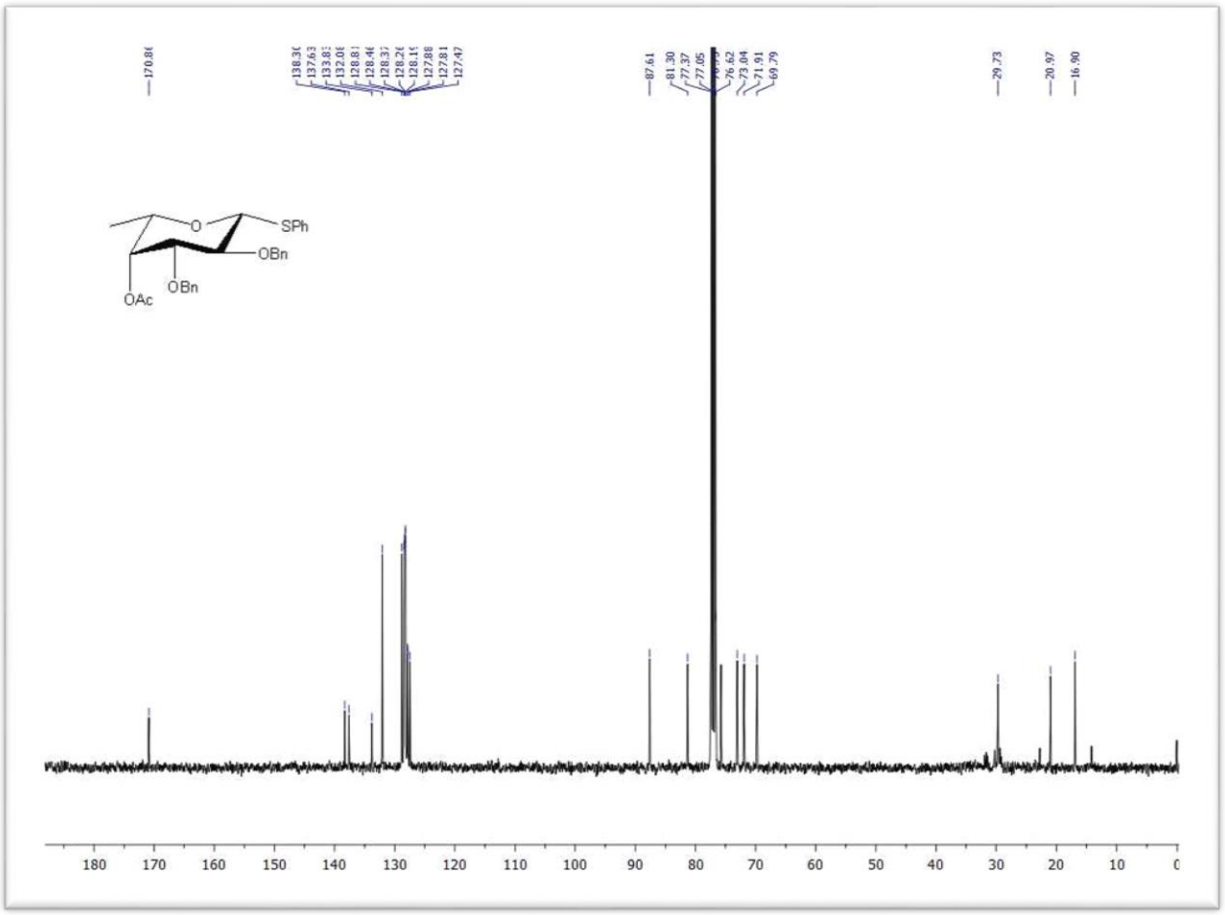


Figure.9

CHAPTER-5

CONCLUSION

Conclusion

Synthon is prepared normally in almost inert conditions. All the NMR data was collected using 400 & 500 MHz spectrophotometers and processed. Inert conditions are attained using nitrogen for the reaction medium. due to lack of time, I can synthesize only a limited part of the chain, and the data is recorded properly and accurately. There is no need to take any special precaution in either handling the catalyst or excluding moisture from the reaction medium. The prepared compounds were purified and characterized by analytical and spectral (^{1}H NMR, ^{13}C NMR) data.

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Chapter 2

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