Imam Muhammad ibn Saud Islamic University
College of Sciences
Department of Chemistry

Preparation of 1,2:3,4-di-O-isopropylidene-α-D-galopyranose

A graduation research project

submitted to the Department of Chemistry in partial fulfillment of the requirements for the completion of the degree of Bachelor of Science in Chemistry

By

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Under supervision

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Abstract

The preparation of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose has been carried out through two methods. The first method, describe the synthesis of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose by the *O*-isopropylidination reaction of galactose using iron chloride as a catalyst. The second method, consist to used iodine as a good catalyst in the *O*-isopropylidination of α-D-galopyranose.

The structural study of the synthesized 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose has been confirmed based on ^{1}H NMR spectroscopy analysis.

الخلاصة

تم تحضير مركب الكلكتوز ايزوبيرانوز من خلال طريقتين مختلفتين. اعمدنا في الطريقة الأولى على استعمال كلوريد الحديد الثلاثي كمحفز لتفاعل الكلكتوز باستعمال الأسيتون كمذيب ومتفاعل. بين من خلال الطريقة الثانية انه يمكن اجراء التفاعل باستبدال كلوريد الحديد باليود. تمت دراسة صيغة المركب من خلال تحليل الطيف الرنين المغناطيسي النووي.

Chapter 1 :

INTRODUCTION

1.1. Introduction

Carbohydrates represent an extensive group of organic substances which comprise the celluloses, gums, starches, and sugars. The joint characteristics of carbohydrates are that they comprise only the elements carbon (C), hydrogen (H) and oxygen (O), and that their combustion will produce carbon dioxide (CO_2) and Water (H_2O) [1,2].

Carbohydrates are of an impressive economic rank, presence found for the industrial development of viscose, paper, and textile. Chemically changed carbohydrates, are also castoff in the production of compounds such as polymers, while some of the other cellulose derivatives comprise adhesives (e.g., carboxymethyl cellulose and methyl cellulose), thickeners, emulsifiers, and stabilizers in processed [3]. Also, other several biologically active products contained carbohydrates have been prepared. By motive of their biological rank, the synthesis of sugars becomes a significant topic in organic chemistry. Greatest of these products are not plentiful in nature and / or are not gamely available from molecules which are abundant. Usually, these products are prepared via synthetic multi-step methods from mutual carbohydrates (D-mannose, D-lactose, D-galactose, L-fucose, etc.) [4].

1.2. Aims of the project

Having recognized the practicality of carbohydrate derivatives from a biological and synthetic point of view, the development of selective and effective synthesis technic is relevant. In this line, an impressive effort has been devoted to the synthetic application of the carbohydrates. In this report, we present synthesis of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose.

1.3. Arrangement of the project

In agreement with the aims defined for the present project, the manuscript began with a general introduction, and then a bibliographic revision is made, in chapter 1, concerning the most relevant topics related to the synthesis of carbohydrates.

The second part presents the general methods and the materials utilized in the scope of this project.

The third part contains a general discussion, the major results, and conclusions.

Chapter 2 :

Review of Literature

2.1. Introduction

2.1.1. Diabetes

Affording to the World Health Organization, the number of diabetics in the world is predictable to more than double by 2025. The medium and long-term difficulties of diabetes are the cardiovascular dangers and neurological. The harshness and frequency of these difficulties are a thoughtful public health problematic. The organization of diabetes is a main social and economic issue, creation it urgent to set up screening approaches and the detection of new drugs, real and easy to manage. Liable on whether patients yield insulin or not, diabetes is divided into two main types: type I, or insulin-dependent diabetes mellitus (IDD) and type II, or non-insulin-dependent diabetes mellitus (DNID) much more frequent since accounting for ~90% of diabetes [5-7].

2.2. Type of Diabetes

2.2.1. Type I diabetes (DID)

Type I diabetes is understood most frequently in young individuals. It looks rapidly, frequently before the age of 15. It comes from a annihilation of β cells of the pancreatic islets, fabricating insulin. This diabetes is called insulin-dependent since the management of insulin is the only way to supplement lack of insulin creation. DID is an autoimmune disease where the β cells of the islets of Langerhans of the pancreas do not secrete any insulin, so that in the nonappearance of hormone, the tissues are incapable to metabolize glucose. It collects in the blood. The body responds, with an upsurge in blood volume by water absorption, plentiful and glucose-rich urine. As glucose no lengthier enters the cells, they turn to other energy-generating metabolic pathways such as the use of ketone products. formed by the liver. Thus, their concentration increases in the blood and urine. Weight loss and muscle weakness are detected with more long-term, cardiovascular, kidney, nervous and visual difficulties. The diabetes of type I, declared early, require the injection of insulin, an effective therapy but binding [8-10].

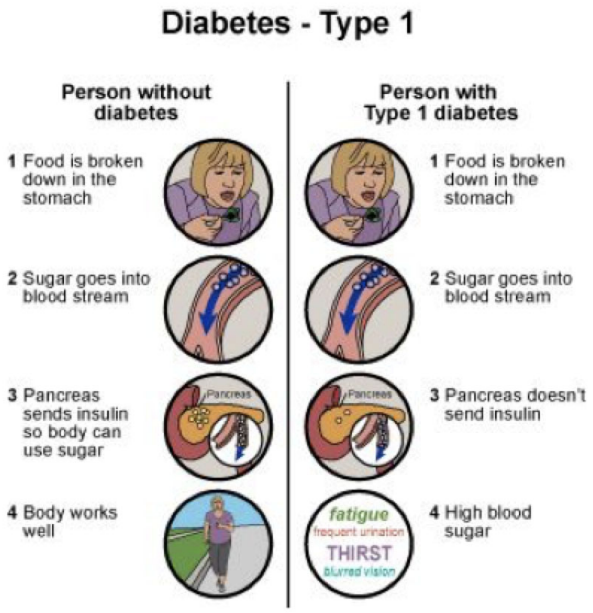


Figure 1 Diabetes Type I

2.2.2. Type II diabetes (DNID)

Non-insulin-dependent diabetes (DNID, type II diabetes) balance sheet for about 90% of the diabetic population and mostly touches people over 40 years. It is measured a disease of middle age. This type of diabetes is classified into two subtypes: IIa (not obese, 15% of NIDs) and IIb (obese, weight >120% of ideal weight). Unlike DID, patients with DNID yield insulin but in deficient quantity, version inadequate the compensatory reply of the hormone to elevations in glucose levels, resultant in hyperglycemia fast. This anomaly of insulin emission is related with insulin resistance of peripheral tissues whose ability to use glucose is diminished. It should be noted that hyperglycemia associated with NIDDM, if left untreated, tends to accentuate the deficit of insulin secretion. In fact, high levels of glucose circulating are toxic (glucotoxicity) and cause both a decrease in β-cell secretory function and augmented insulin resistance. Expression of the DNID phenotype results from a combination of genetics and factors environmental. The mode of transmission would be polygenic in a population important and genetically heterogeneous (Western world), and more possibly monogenic in very high-risk human isolates [10].

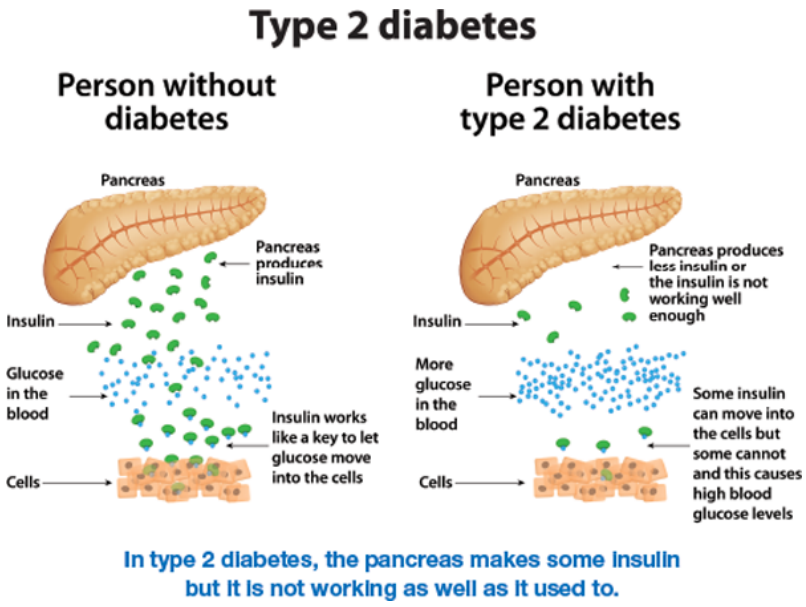


Figure 2 Diabetes Type II

2.3. Pharmacological actions for non-insulin-dependent diabetes (DNID)

In many cases and particularly in the case of obese patients, the rate of glucose can be measured with a composed diet and exercise. If that proves unsuccessful, these patients should syndicate oral antidiabetics with a healthy lifestyle. The primary goal of action is to maintain homeostasis of the glucose to defend, in the long term, sensitive tissues such as the arteries. The 1990s were visible by major advances in the field of oral hypoglycemic drugs, which can be congregated into three classes:

a. Biguanides

b. Sulfonylureas

c. Alpha-glucosidase inhibitors

Riveted carbohydrates are broken down by salivary and pancreatic amylase into disaccharides (sucrose, lactose, maltose) then by α-glucosidases (maltase, lactase, sucrase or invertase) into monosaccharides. Certainly, only monosaccharides can cross the intestinal barrier. α-glucosidase inhibitors inhibit the last stage of sugar digestion. These cannot be engrossed; they continue their journey through the intestine and undergo bacterial colonic fermentation into fatty acids volatile or are eliminated in the stool. The purpose of this type of product is therefore to limit postprandial

hyperglycaemia. Therefore, they must be taken at the start of a meal. The α-glucosidase inhibitors are the main representative of this new therapeutic class acarbose (GLUCOR®). However, miglitol (DIASTABOL®), received FDA approval in 1996. It is the only inhibitor of this family must be completely absorbed and to cross the intestinal barrier. He introduces far fewer opposing side properties than acarbose.

2.4. Generality on carbohydrates

Carbohydrates are quite plentiful in nature. More than half of the carbon found in existing organisms is confined in carbohydrate molecules, most of which are presenting plants. Carbohydrates are also mentioned to sugars or saccharides [11]. Carbohydrates are imperative givers to usual compounds and biological chemistry because of their role incell–cell adhesion, cell–cell credit and molecular directing.

2.4.1. Monosaccharide Definition

A monosaccharide is the maximum basic form of carbohydrates. Monosaccharides are also mentioned to as modest sugars. They have the general chemical formula of $C_n(H_2O)_n$; where n (the number of carbon atoms) can be three to seven. They are ketones or aldehydes [12,13].

2.4.2. Types of Monosaccharide

a- Mannose

Mannose is a sugar monomer. It is a C-2 epimer of glucose [5]. Mannose is significant in human metabolism, particularly in the glycosylation of certain proteins. Numerous congenital disorders of glycosylation are related with mutations in enzymes intricate in mannose metabolism. Mannose is not an important nutrient; it can be fashioned in the human body from glucose, or transformed into glucose. We existing in the following figure the fischer structure of D-mannoseand L-Mannose [14].

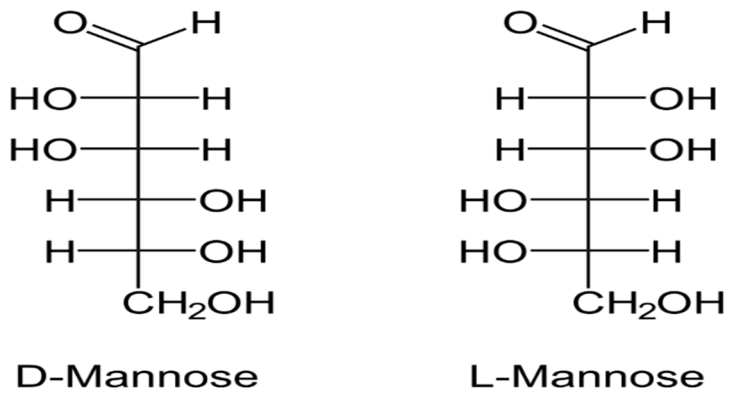


Figure 3 Mannose as Fischer structure

b- Glucose

D-Glucose is also identified as dextrose or D-GLC, belongs to the type of organic products known as hexoses. These are monosaccharides in which the sugar unit is a is a six-carbon covering moiety. D-Glucose happens as a solid, soluble in water, and a actual weakly acidic product. D-Glucose has been originating throughout greatest human tissues, and has also been noticed in maximum biofluids, counting sweat, saliva, blood, and urine. Within the cell, D- glucose is primarily situated in the lysosome, endoplasmic reticulum, golgi and myelin sheath. D-glucopyranose is a glucopyranose having D- configuration. We existing in the following its Haworth and fischer structures [15].

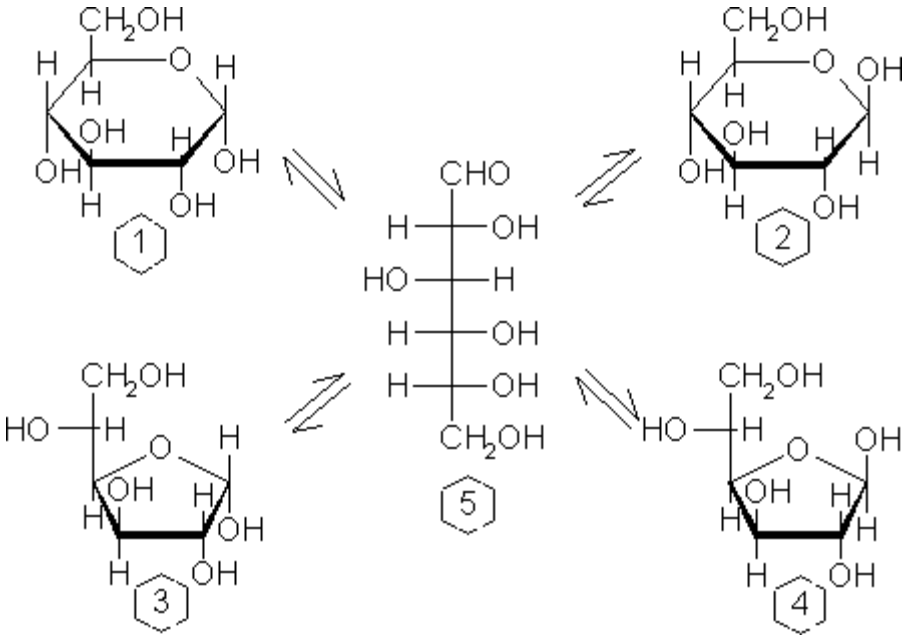


Figure 4 Haworth and Fischer structures of Glucose

c- Galactopyranose

D-galactopyranose taking D-configuration. It has a character as an Escherichia coli metabolite and a mouse metabolite. It is a D-galactose and a galactopyranose, also known as alpha-D-gal or alpha D-galactose, belongs to the type of organic products known as hexoses. These are monosaccharides in which the sugar unit is a is a six-carbon covering moiety [15].

d- Galactose

D-Galactose happens as a solid, soluble (in water), and a actual feebly acidic product. D-Galactose has been originating in human brain, prostate, and liver tissues, and has also been noticed in greatest biofluids, counting cerebrospinal fluid, feces, breast milk, and blood. Within the cell, D-galactose is mainly placed in the lysosome, mitochondria, and cytoplasm. D-Galactose occurs in all eukaryotes, reaching from yeast to humans. D- Galactose participates in several enzymatic reactions [16].

e- Carboxylic Acid Sugars

In a carboxylic acid sugar, an aldehyde of a monosaccharide has been substituted by a carboxyl group. This is complete by oxidation of aldehydes to carboxylic acids. D-glucose can be oxidized to yield D- gluconic acid.

2.4.3. Stereochemistry of Monosaccharaides

we present in the following Haworth structure and fischer structures [17].

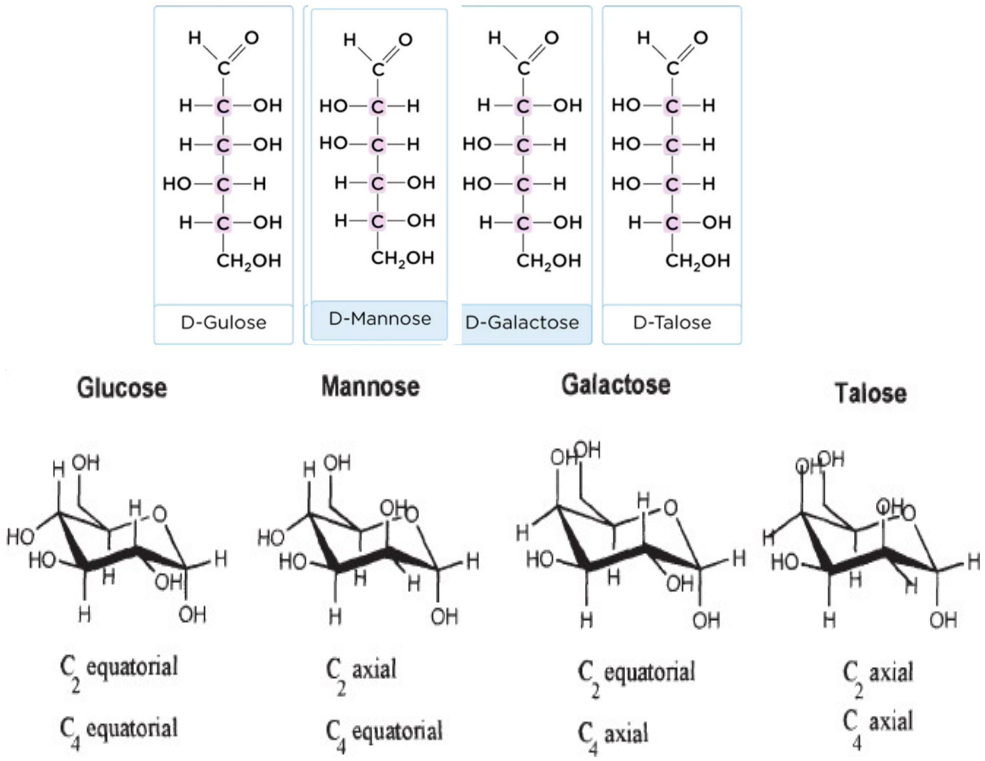


Figure 5 Structures of the four α-D epimers

Chapter 3

Experimental Part

3. Materials

3.1. Chemicals

Acetone, (+) *D-galactose*, iron chloride, sodium carbonate, chloroform, ethyl acetate, cyclohexane, dichloromethane, iodine, sodium sulfate and sodium thiosulfate were obtained from Sigma Aldrich (St Louis, MO, USA). TLC analysis was performed on Merck Kieselgel 60 F254 plates.

3.1.2. ^{1}H NMR Spectrometer

NMR spectra were obtained on a Bruker AC 300 spectrometer. Chemical shifts are given in parts per million relatives to tetramethylsilane (TMS). The spectrum was recorded in $CDCl_3$ as solvents at room temperature.

3.2. Methods

3.2.1. Synthesis of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose

The synthesis of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose has been approved out through two synthesis methods:

Method A

Iron chloride $FeCl_3$ (1.20 g, 7.5 mmol) was partially dissolved in acetone (100 mL) at room temperature. The whole was cooled in an ice-bath. The D-galactose (1.00 g, 5.1 mmol) was added and the resulting white suspension stirred for 1 hour at reflux. A solution of sodium carbonate (1.00 g) in water (5 mL) was added to the reaction mixture at 0 ºC. After filtration the solvent was removed in vacuo. The organic fraction was separated from the aqueous layer, followed by further extraction with chloroform (3 x 20 mL) to yield the protected galactose (oil, 1.2 g, 90 %). TLC R_f = 0.27 (hexane/ EtOAc 1:1)

Method B

(200 mg) of iodine I_2 was dissolved in (40 mL) of acetone; (1.00 g, 5.1 mmol) of (+) *D-galactose* was added, the whole was stirred at room temperature. Iodine was destroyed by addition of dilute aqueous sodium thiosulfate. The isopropylidene was extracted with dichloromethane (30 mL X 2),

dried with sodium sulfate, and concentrated under vacuum to yield the protected galactose (oil, 0.93 g, 70 %). TLC R_f = 0.27 (hexane/EtOAc 1:1).

3. 4. Spectroscopic Data

^{1}H NMR (300 MHz,$CDCl_3$) δ 5.47 (d, J_{H3a-8b} = 5.1, 1H, H_{3a}); 4.52 (dd, J_{H8a-8b} = 2.4, J_{H8a-5a} = 7.8, 1H, H_{8a}); 4.26 (dd, J_{H8b-3a} = 5.1, J_{H8b-8a} = 2.4, 1H, H_{8b}); 4.19 (dd, J_{H5a-8a} = 7.8, J_{H5a-5} = 2.1, 1H, H_{5a}); 3.95 (m, 1H, H_5); 3.65 (m, 2H, H_6); 1.46; 1.36 (s, 3H, CH_3); 1.26 (s, 6H, CH_3).

Chapter 4

Results and discussion

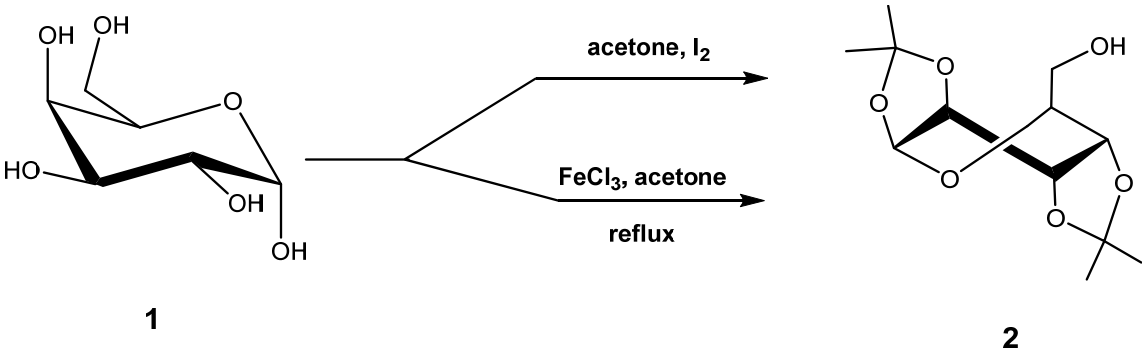
4.1. Synthesis of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose

4.1.1. Protection of α-D-galopyranose by the *O*-isopropylidination

This section designates the preparation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) by the *O*-isopropylidination reaction of D-(+)-galactose (**1**) using two methods.

The first method using anhydrous ferric (III) chloride as a catalyst. The protocol is efficient, fast, and selective. The product was obtained in good yield (90%) without need of further purification [18]. Results of the preparation of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose are shown in Scheme (1).

The second method consist to use iodine (I_2) as a good catalyst in the *O*-isopropylidination of α-D-galopyranose. 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose (6) was prepared according to the method of Kartha [19]. The isopropylidation of D-(+)-galactose has led to the exclusive production of *O*-isopropylidene sugar with good yields (70%).



Scheme 1 Protection of α-D-galopyranose by the *O*-isopropylidination

4.2. ^{1}H NMR study of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose

Analysis of the ^{1}H NMR spectrum recorded at 300 MHz in the $CDCl_3$ of the 1,2:3,4-di-O-isopropylidene-α-D-galopyranose **2** revealed the following signals (Figure 6):

Compound **2** showed three singlets at 1.46, 1.36 and 1.26 ppm which can be attributed to the methyl group proton. Compound **2** showed two multiples at 3.95 and 3.65 ppm H5 and H6. One peak as doublet at 5.47 ppm correspond to the proton H3a. Three doublets of doublet are observed at 4.52, 4.26 and 4.19 ppm can be attributed to the protons H8a H8b H5a.

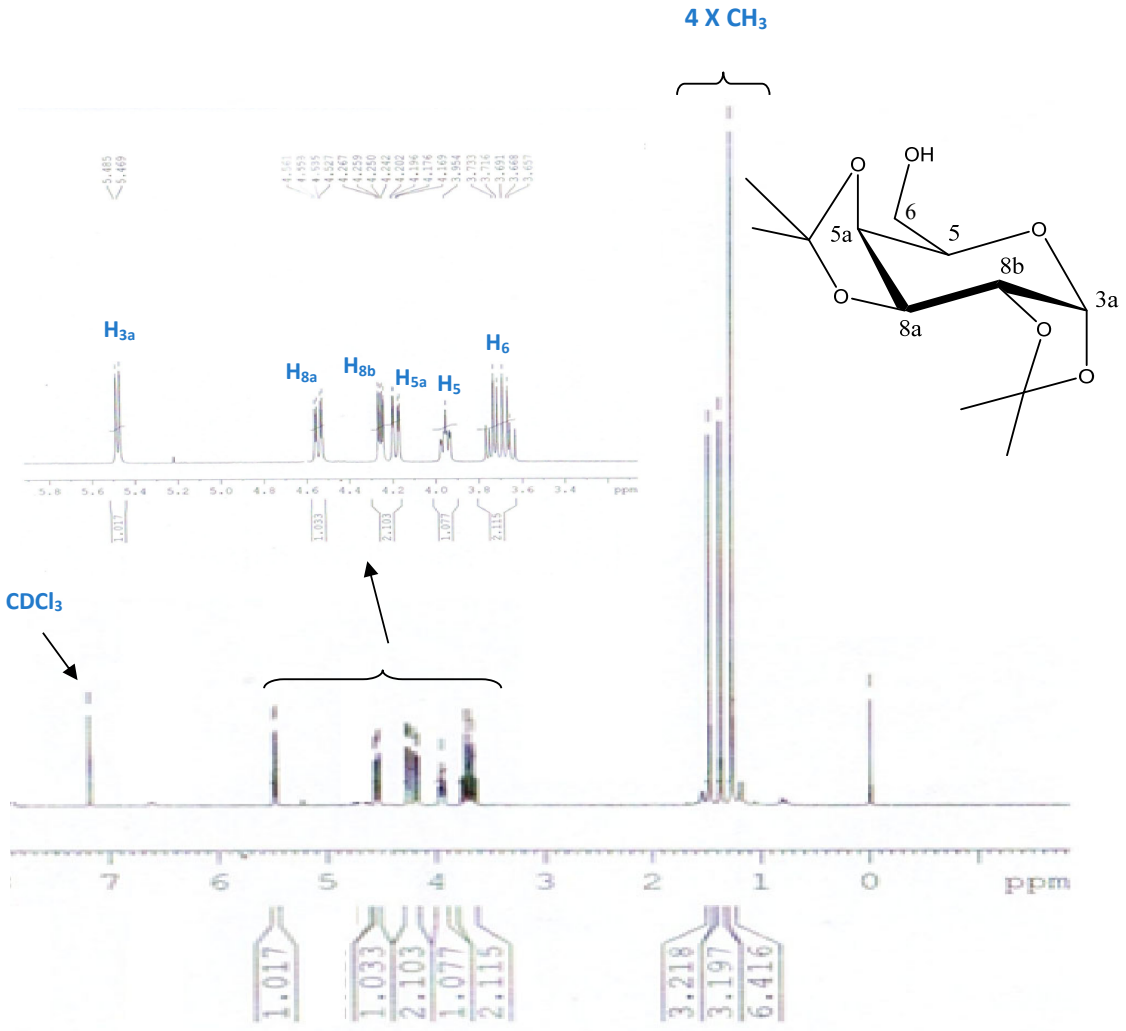
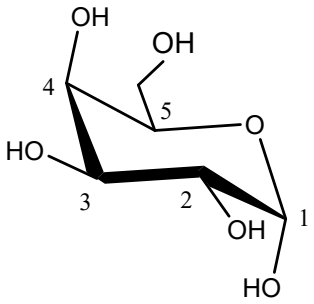


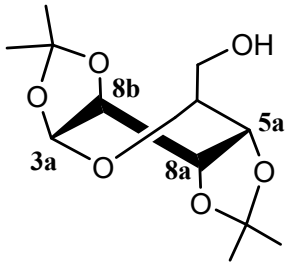
Figure 6 NMR ^{1}H spectrum of 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose

4.3. Conformation of the 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose

The conformational study of carbohydrate derivatives, and particularly the ring conformation, affects the biological activities, as well as physical and chemical properties of the substrates. The formation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose is known to change the preferred conformation of the galactose ring from chair conformer to a skew (twist-boat) conformer (Figure 7) [20].



chair conformer



twist-boat conformer

Figure 7 Conformation of the Galactose Ring

Table 1: Coupling constant of α-D-galactopyranose and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [20]

Sugar	Solvent	Conformer	$J_{H3a-H8b}$(Hz)	$J_{H8b-H8a}$ (Hz)	$J_{H5a-H8a}$ (Hz)
α-D-galactopyranose	D_2O	**Chair**	3.97	**10.33**	**3.42**
1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose	$CDCl_3$	**twist-boat**	5.1	**2.30**	**8.04**

CONCLUSION

Conclusion

In this project we propose to develop the preparation of 1,2:3,4-di-O-isopropylidene-α-D-galopyranose. The synthesis of has been approved out concluded two methods.

The first method, describe the synthesis of 1,2:3,4-di-O-isopropylidene-α-D- galactopyranose by the *O*-isopropylidination reaction of (+) D-galactose using iron chloride as a catalyst. The protocol is efficient, fast, and selective. The product was obtained in excellent yield (90%), For the second method, iodine serves as a good catalyst in the *O*-isopropylidination of (+) D-galactose.

The structural study of the synthesized 1,2:3,4-di-*O*-isopropylidene-α-D-galopyranose has been established based on ^{1}H NMR spectroscopy analysis.

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