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EGE UNIVERSITY

Graduate School of Applied and Natural Science

ASYMMETRICAL HENRY REACTION OF THREE DENDATE LIGANDS OF AMINO SUGAR DERIVATIVES VIA Cu(II) IONS

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Sevda ALKAN KISAÇ tarafından **yüksek lisans** tezi olarak sunulan "**Asymmetrical Henry Reaction Of Three Dendate Ligands Of Amino Sugar Derivatives Via Cu(II) Ions**" başlıklı bu çalışma EÜ Lisansüstü Eğitim ve Öğretim Yönetmeliği ile EÜ Fen Bilimleri Enstitüsü Eğitim ve Öğretim Yönergesi'nin ilgili hükümleri uyarınca tarafımızdan değerlendirilerek savunmaya değer bulunmuş ve .....tarihinde yapılan tez savunma sınavında aday oybirliği/oyçokluğu ile başarılı bulunmuştur.

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20 / 08 / 2019

Sevda ALKAN KISAÇ

ÖZET

AMİNO ŞEKER TÜREVLERİNİN ÜÇ DİŞLİ LİGANTLARININ Cu(II) ARACILIĞI İLE ASİMETRİK HENRY REAKSİYONU

ALKAN KISAÇ, Sevda

Yüksek Lisans Tezi, Kimya Bölümü

Tez Yöneticisi: Doç. Dr. A. Yeşim SALMAN

Ağustos 2019, 69 sayfa

Bu çalışmada D-glukoz ve D-galaktoz başlangıç şekerleri olarak kullanılmıştır. Öncelikle deneysel çalışmalar, 1,2-*O*-(R)-trikloroetiliden-α-D-glukofuranoz (α-kloraloz) ve 1,2-*O*-(S)-trikloroetiliden-α-D-galaktofuranoz'un 6-amino türevlerinin sentezleri üzerinde oluşturulmuştur.

D-glukoz ve D-galaktoz'un trikloroetiliden acetalleri, susuz kloral ve şekerlerle reaksiyonu sonucu hazırlanmıştır. D-glukoz ve D-galaktoz'un trikloroetiliden acetallerinin tosil türevleri p-toluensülfonilklorür ile reaksiyon sonucu elde edimiştir ve daha sonra bu tosil türevleri nükleofilik yerdeğiştirme tepkimesi ile azit formuna dönüştürülmüştür. Elde edilen azit bileşikleri, ilgili amino şeker türevini elde etmek için indirgeyici reaktif olan trifenilfosfin ile reaksiyona sokulmuştur. Ayrıca bu amino şekerlerin C-3 hidroksil grupları metillenmiş olan türevleride benzer yöntemle sentezlenmiştir.

Daha sonra Schiff bazı sentezlemek amacı ile, MeOH içinde aldehit (salisilaldehit veya 3,5-ditbutilsalisilaldehit) çözeltisi 5 ml MeOH'deki amino şeker türevi çözeltisi içine damlatılarak ilave edilmiştir.

Henry reaksiyonunu gerçekleştirmek amacıyla belirtilen sıcaklıkta ligant olan Schiff bazı ve çözgen, $Cu(OAc)_2.nH_2O$ üzerine eklenmiştir. Daha sonra aldehit (4-nitrobenzaldehit) ve nitrometan bu çözeltiye ilave edilmiştir. Reaksiyon tamamlandıktan sonra solvent buharlaştırılarak istenen Henry ürünü, hekzan ve etilasetat kullanılarak kolon kromatografisi ile saflaştırılmıştır. Enantiyomerik fazlalık değerleri Chiralcel OD-H kolon kullanılarak HPLC'de belirlenmiştir.

Bütün bileşiklerin yapıları ^{1}H-NMR, ^{13}C-NMR ve IR gibi spektroskopik yöntemlerle belirlenmiştir.

Anahtar kelimeler: Kloraloz, Asimetrik Henry reaksiyonu, Kiral Schiff bazı, Amino şeker

ABSTRACT

ASYMMETRICAL HENRY REACTION OF THREE DENDATE LIGANDS OF AMINO SUGAR DERIVATIVES VIA Cu(II) IONS

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MSc in Department of Chemistry

Supervisor: Assoc. Prof. Dr. A. Yeşim SALMAN

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In this study, D-glucose and D-galactose were used as starting sugar. Firstly, the experimental works were constituted on the simple synthesis of the 6-amino derivatives of 1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (α-chloralose) and 1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose.

The trichloroethylidene acetals of D-glucose and D-galactose were prepared from the reaction of sugars and anhydrous chloral. Tosyl derivates of trichloroethylidene acetals of D-glucose and D-galactose were obtained through the reaction of these compounds with p-toluenesulfonylchloride and then, these tosyl derivates were converted to the azide form by following nuclephilic substitution reaction. Obtained azide derivates were reacted with triphenylphosphine as reducing agent in order to get the related amino-sugars derivates. Also the same amino-sugars were synthesized in the C-3 hydroxy groups are methylated to derivatives by the same method.

Then, in order to synthesize Schiff bases; the homogeneous mixture aqua form of aldehyde (salicylaldehyde or 3,5-ditbutylsalicylaldehyde) in MeOH was added dropwise into the solution of amino sugar derivative in 5mL of MeOH. Schiff bases were synthesized at the last of reaction.

For to perform Henry reaction; to a solution of shiff bases as a ligand and solvent at the given temperature was added $Cu(OAc)_2.nH_2O$. Then the aldehyde(4-nitrobenzaldehit) and nitromethane were added into the solution.

Subsequential of the completion, to afford the desired Henry product the solvent was evaporated and the residue was purified by column chromatography using hexane:ethyl acetate. HPLC using a Chiralcel OD-H column used to determine the enantiomeric excess values.

Spectroscopic analysis, like ^{1}H-NMR, IR and^{13}C-NMR, helped us to learn the structures of all the compounds.

Keywords: Chloralose, Asymmetric Henry reaction, Chiral Schiff base, Amino sugar

PREFACE

In this study amino chloraloses derivatives of D-glucose and D-galactose were synthesized. A series of chiral Schiff bases were prepared as ligand by using this amino sugar derivatives.

The prepared Schiff bases ligands were used as the catalyst in asymmetric Henry reaction in the presence of Cu (II) ions. The product of Henry reaction was purified by Column Chromatography. The enantiomeric excess of the product Henry were determined by HPLC using chiralcel OD-H colon. The structures of all synthesized compounds were determined by spectroscopic methods such as ^{1}H-NMR, ^{13}C-NMR and IR.

In the performed Henry reaction; the effects of the structure of synthesized Schiff bases, aldehyde used in the reaction, ambient conditions and the solvent used on enantiomeric control were investigated. It is revealed that there is an interesting solvent dependence on the enantiomeric control. The best enantiomeric excess (up to 92%) were obtained in the presence of water.

Some parts of the results of this thesis were published in the journal Carbohydrate Research 407 (2015), 97-103.

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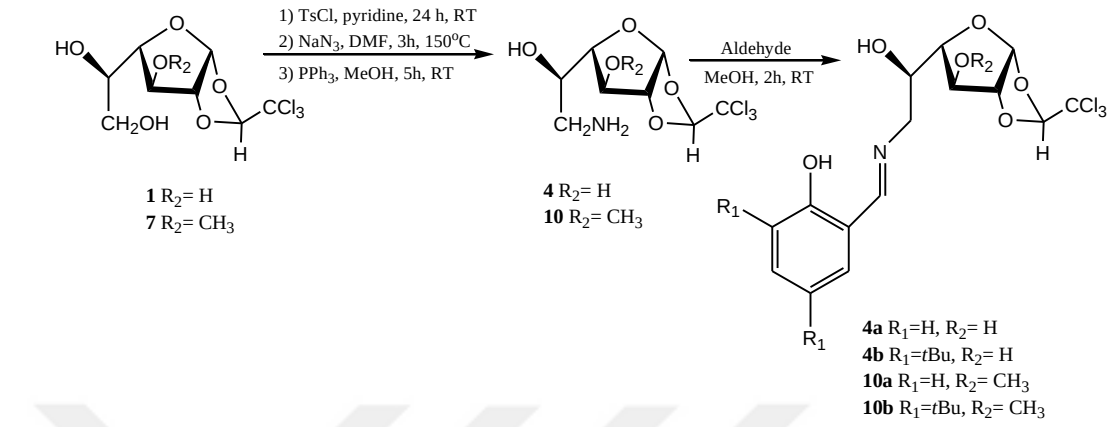
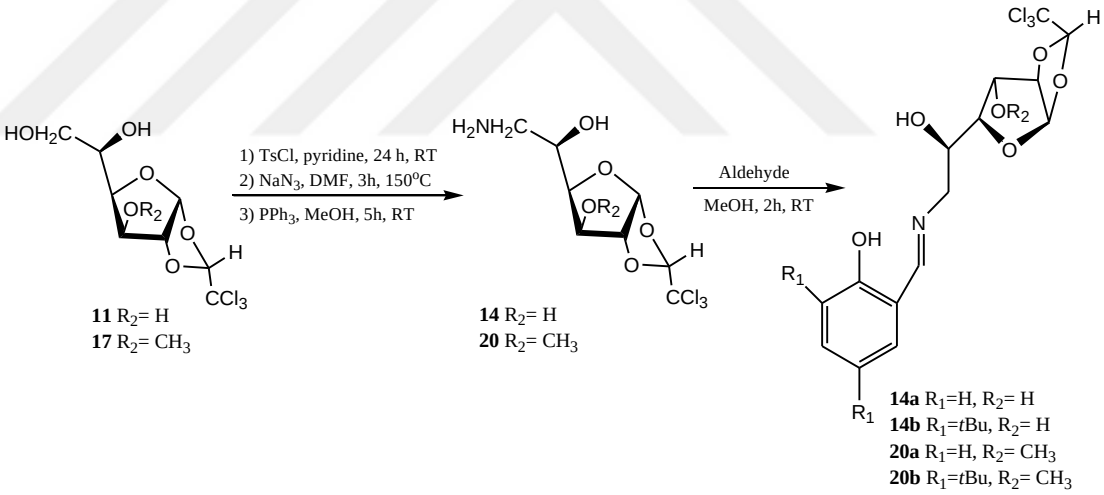


1 R_2= H
7 R_2= CH_3

4 R_2= H
10 R_2= CH_3

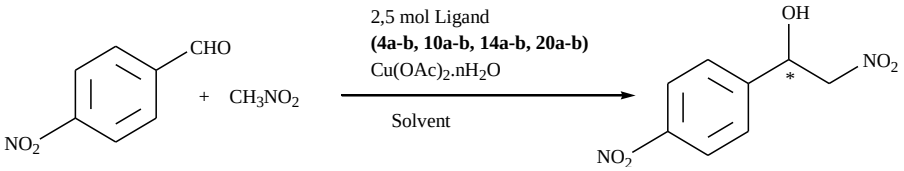
4a R_1=H, R_2= H
4b R_1=*t*Bu, R_2= H
10a R_1=H, R_2= CH_3
10b R_1=*t*Bu, R_2= CH_3



11 R_2= H
17 R_2= CH_3

14 R_2= H
20 R_2= CH_3

14a R_1=H, R_2= H
14b R_1=*t*Bu, R_2= H
20a R_1=H, R_2= CH_3
20b R_1=*t*Bu, R_2= CH_3



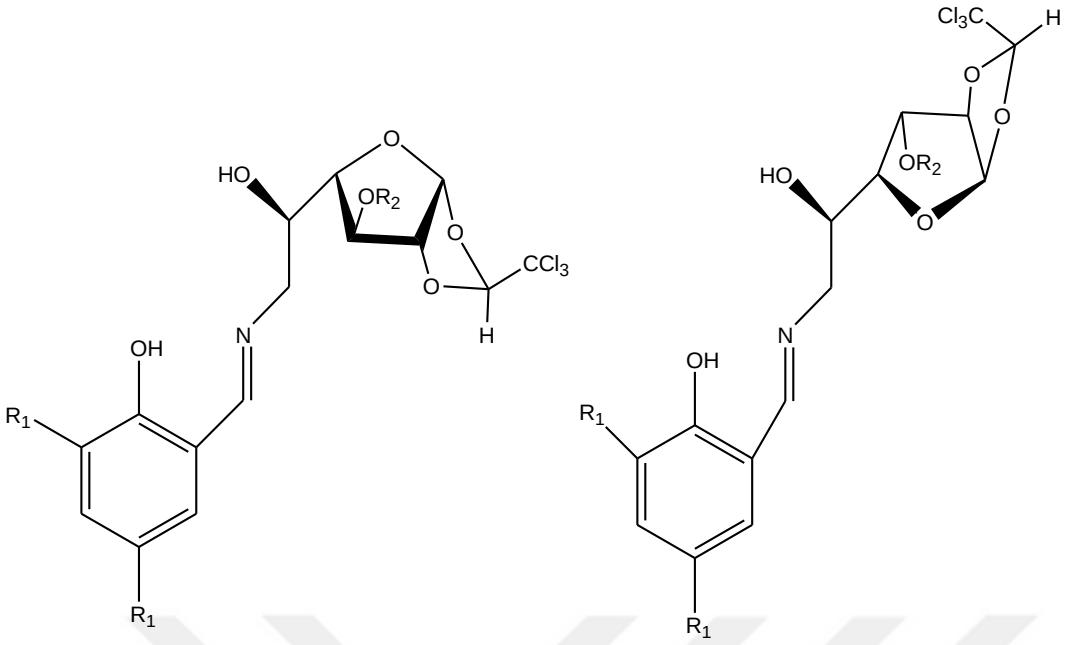
ABBREVIATIONS

Abbreviation	Explanation
2,2-DMP	2,2-Dimethoxypropane
DMF	N,N-Dimethylformamide
Equ	Equivalent
IR	Infrared Spectroscopy
h	Hours
H_2SO_4	Sulfuric acid
Mp	Melting point
Me	Methyl
mL	milliliter
Min.	Minute
mol	Mole
mmol	Millimole
NaN_3	Sodium azide
NMR	Nuclear Magnetic Resonance Spectroscopy
PTSA	*p*-Toluene sulphonic acid
Pyr	Pyridine
RT, rt	Room temperature
TLC	Thin Layer Chromatograhy
PPh_3	Triphenylphosphine
Tol	Toluene
Ts	*p*-toluene sulfonyl “tosyl”
Et	Ethyl
IPA	isopropyl alcohol
TBME	tert-butyl metyl ether

1. INTRODUCTION

The nitroaldol (Henry) reaction is a convenient method of C-C bond formation which affords useful products for organic synthesis. As a result, considerable research effort has been invested into finding suitable methods for carrying out this reaction in high yields and stereocontrol. Such methods include applications of organocatalysts, enzymes, and transition metal-chiral ligand complexes. In particular, Cu(II) complexes of a variety of bidentate and tridentate ligands have recently been utilised to good effect. Using these catalysts, it is generally believed that the transition state consists of a square pyramidal copper (II) center that is coordinated by the chiral ligand, the substrate aldehyde and nitroalkane and in some cases a counteranion such as acetate and that it is the subsequent combination of the apically coordinated nitronate and equatorially bonded aldehyde that results in the formation of the desired β-nitroalcohols in good yields and with good stereocontrol. Further studies have indicated that the presence of bulky groups near to the metal center can also play an important role.

In consideration of this information, we decided to prepare Schiff base ligands (**10a-20a**, **10b-20b**) from aminochloralose derivatives of glucose and galactose (Figure 1.1). Thus, it was anticipated that we could learn about the applicability of chloraloses in asymmetric synthesis and learn more about the effect of the proximal hydroxy groups (OR_2, R_2 = H) which are present in ligands **14a-b** and **4a-b**.



4a (R_1=H, R_2=H)
4b (R_1= *t*Bu, R_2=H)
10a (R_1=H, R_2=CH_3)
10b (R_1= *t*Bu, R_2=CH_3)

14a (R_1=H, R_2=H)
14b (R_1= *t*Bu, R_2=H)
20a (R_1=H, R_2=CH_3)
20b (R_1= *t*Bu, R_2=CH_3)

Figure 1.1 Structure of Schiff base ligands (**4a-b, 10a-b, 14a-b, 20a-b**) from aminochloralose of glucose and galactose

2. LITERATURE SURVEY

2.1 Sugar Acetals and Ketals

The condensation of aldehydes and ketones with alcohols and polyols is an organic chemistry reaction. Wurtz (acetaldehyde and ethylene glycol), and Meunier (acid catalysis) directed a work before Emil Fischer described in 1895 the formation of acetals of glycoses (1st form D-fructose and acetone). From that day forward, organic chemistry is using this protecting group, in general, and carbohydrate chemistry, in particular.

Alteration of polyols into cyclic acetals as a form for temporary protection is succeeded mainly by the help of these reasons: approachability and cost-effective of the reagents, convenience of produce to lead quick and high yield to the protected derives, inertness of the protecting group to a big variety of reagents which are used in the substrate structural modifications, simple and good-yielding foot for deprotection.

O-isopropylidene and *O*-benzylidene sugars were the most important derivatives in carbohydrate chemistry. Several methods to synthesize *O*-isopropylidene derivates have been reported in literature. The conventional method consists of condensation of diol with acetone existence of a catalyst in anhydrous situation. As catalyst several agents have been used such as mineral acid, anhydrous zinc chloride together with phosphoric acid, ion exchange resins, anhydrous copper (II) sulfate, iodine, anhydrous ferric chloride boron trifluoride etherate, anhydrous aluminium chloride and HY type zeolite (Rauter *et al*, 1995).

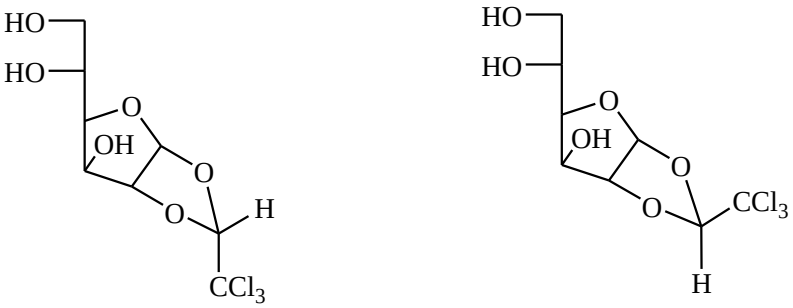
2.2 Trichloroethlidene Acetals (Chloraloses)

Furanose-type cyclic asetals of pentoses and hexoses containing to 1,2-*O*-trichloroethylidene circle form chloraloses. Heffter Arthur firstly synthesized chloralose in the year of 1889 by the condensation of D-glucose and trichloroacetaldehyde (choral) existence of an acid catalyst (Heffter, 1889).

A mixture of two diastereomers was obtained from glucose which α-glucochloralose (α-chloralose) and β-glucochloralose (β-chloralose). If trichloromethyl (CCl_3) substituent has endo orientation, this compound is called α-chloralose and exo orientitation is β-chloralose (Fig.2.1). (α-) and (β-) terms show the configuration on the acetal carbon. Trichloroethylidene rings are very stable in acidic and slightly basic conditions (Ay *et al*., 2007) but they are not stable in strongly basic condition like potassium *tert*-butoxide. Cylic ketene acetal occurred by getting HCl from trichloroethylidene ring of chloralose with alkoxide (strong-base) (Salman et al., 1994; Salman et al., 2004) and elimination of trichloroethylidene group may be accomplished by reaction of hydrogenation using of Raney nickel, before the acidic hydrolysis (Forsen *et al*., 1965).

Trichloroethylidene acetals are potential active compounds in biologically; so a hypnotic drug which is α-chloralose (1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose) has been employed in the manner of an anesthetic agent in laboratory animals (Zosimo-Landolfo and Tronchet, 1999). It also was used in human beings until the beginning of the 1900s (Krasowski, 2003). Used as a commercial drug α-chloralose is also widely used in bird repellent, rodenticide, veterinary medicine and neuroscience for loss of sensation named sedative and anesthetic (Forsen *et al*., 1965; Zosimo-Landolfo *et al*., 1999).

Surprisingly, Overton found that anesthetic differences between α-chloralose and its structure isomer β-chloralose were hard to explain. The phenomena of narcosis with α-chloralose are not easy to interpret. β-chloralose, which is only very slightly soluble in water in most solutions, has no narcotic effect (Fig.2.1) It is a molecule that has a potent of busy central nervous system activity, and examined in human and animals, relating to therapeutic features (Segev *et al*., 2006; Aburto-Luna *et al*., 2008).



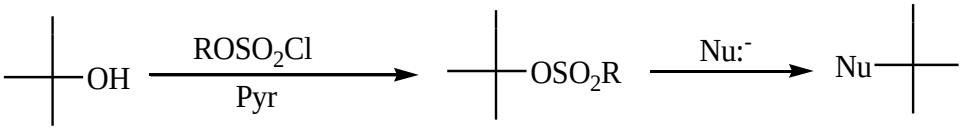
α-chloralose (anaesthetic) β-chloralose (not anaesthetic)

Figure 2.1 Molecular Structures of α-Chloralose and β-Chloralose

Additionally, because of the anesthesia effects of it, arabinochloralose is used as an intermediate compound to develop an anti-tuberculosis drugs in pharmacological study (Sanchez et al., 2000). *Spiro*-endoperoxide chloraloses has been produced and researched in regard to anti-microbial act against microscopic life forms (Yenil et al., 2008; Çetin et al.,2005). Then trichloroethylidene asetals are not used mainly as protecting group but because of their interesting biological activities.

2.3 Sulfonates

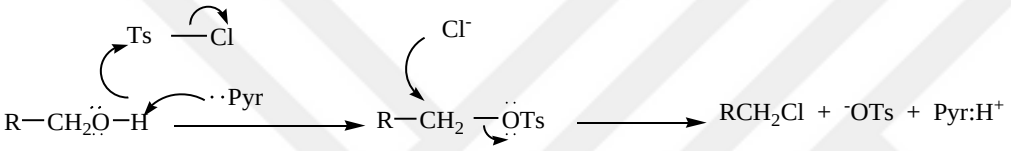
This group of esters is characterized not all by its protection of hydroxyl group but, rather, by its activation of group towards nucleophilic substitution i.e. the very great importance of sulfonate esters in carbohydrate chemistry comes from the excellent "leaving properties" of sulphoxy groups in nucleophilic displacements rections (Ferrier and Collins, 1972).



Scheme 2.1 Nucleophilic Substitution of Sulfonate Esters

Sulfanates are stable toward mild acids and mildly basic conditions, but are cleaved with aqueous alkali. The sulfonates are reconverted to the alcohols by treatment with sodium amalgam or Raney Nikel. Tosylate may be cleaved photolytically in the presence of methoxide to give alcohols (Ferrier and Collins, 1972).

In this group, there are three common sulfanates: ***Tosylate;*** (4-toluensulfonate), ***Mesylate;*** (methanesulfonate) and ***Triflate;*** (trifluoromethanesulfonate). Sulfonate esters of polyhydroxyl compounds give S_N2 reaction by nucleophiles:



Scheme 2.2 S_N2 Reaction of Sulfonate Esters

At lower temperatures, a tosylate is formed from the reaction of *p*-toluensulphonyl chloride and an alcohol. The new bond is formed between the toluenesulphonyl group and oxygen of alcohol. At higher temperatures, the chloride anion can displace the –OTs group, which is an excellent leaving group, to form an orgonochloride.

Sulfonates are usually prepared by use of acid chloride in cold pyridine and under these conditions the reagent show marked selectivity for primary hydroxyls group (Ferrier and Colllins, 1972). But it could be said that because of stereochemistry of carbohydrates, streric effects are very important as much as the degree of hydroxyl groups of sugar.

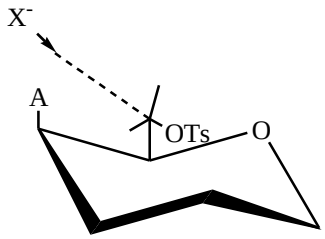


Figure 2.2 Displacement Reactions on Pyranoid Rings

Generally displacement reactions on the pyranoid rings are more difficult than displacement reaction on furanoid rings. At a pyranoid rings during the time form the ground state to the transition state, the great bending tension is observed among nonbonding substituents in addition to unfavorable interactions. Whereas furanoid rings have a bending tension in any case but it is not observed extra tension in tension state. Because of this, the displacement reactions are more easily formed on furanoid rings.

2.4 The Synthesis of Azides

The halide displacement by azide ion is the most commonly applied route especially to alky azides (Scriven and Turnboll, 1988; Sasaki at al., 1982). It is also applicable to acyl azide preparation by using sodium azide (NaN_3) and acyl chloride (Holden, 1984; Gmulka et al .,1985).

The displacement of sulfonates by azide ion is another important route to organic azides : Alkyl azides can be prepared from alcohols in a two steps process involving conversation of alcohols to sulfonates and displacement of the sulfonate group to azides. At high temperature in polar aprotic solvent for example in DMF, the azide compounds are prepared in good yields by the action of NaN_3 on tosylates or mesylates. (Holden, 1984; Gmulka et al .,1985).

The displacement of primary sulfonyloxy groups by azide is usually facile in solvent such as acetone and butatone except in certain cases, D-galactopyranoses, where unfavorable steric and polar factors operate.

Replacement of seconder sulfonyloxy groups is more difficult and required the use of aprotic solvent polar, like N,N-dimethylformamide, N-methylpyrrolidone, or hexamethylphosphoramide. The later is the most effective (Normant, 1967) solvent for these reactions. The factor is the greater solubility of sodium azide in HMPA (2.68g per 100 mL) than in DMF (0.74 g per 100 mL at 1200 ^{o}C) but its use is hampered by its high boiling point which makes it difficult to remove from the reaction product (Normant, 1967).

The epoxides can be also starting compound for preparation of azides but present disadvantage in case they lead to formation of bifunctional group of azide and alcohol (Zambani and Rokach, 1984; Scriven and Thumboll, 1988). Carboxylic acids (Lemmens et al ., 1982) and amino or hydrazines (Kim et al.,1986) may be also used as beginning compounds to produce of alkyl azides.

2.5 Amino Sugars

Carbohydrates and their analogues are considerable synthetic aims because they are so functional for living beings. These Carbohydrates derivatives including an amino substituent in their body are called amino sugars. Some biologically active compounds contain these sugars like biopolymers and antibiotics. Amino sugars are so important for proteins and enzymes because they have very essential trick as receptors on the cell surface. They also interact with DNA backbone phosphate or RNA.

We can understand here that amino sugars have been concerned in the manner of major target molecules during the past years because of medical and biological significance of them.

Amino sugars are aldoses or ketoses which have a hydroxyl group replaced by an amino group at any position other than the anomeric carbon. These glycosylamines are named from the sugar from which they are derived by used of the enumerated term “aminodeoxy” (Guthrie and Honeyman, 1968).

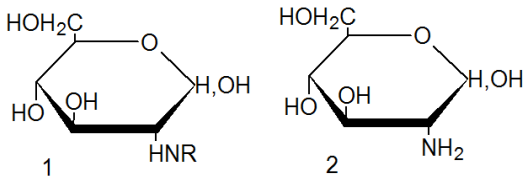


Figure 2.3 Some Aminodeoxy- Sugars

2- Amino-2-deoxy-D-glucose (D-glucoseamine or chitosamine 1, R=H) is abundant nature appearing in particular in polysaccharide chitin as its N-acetyl derivative (1, R=Ac).

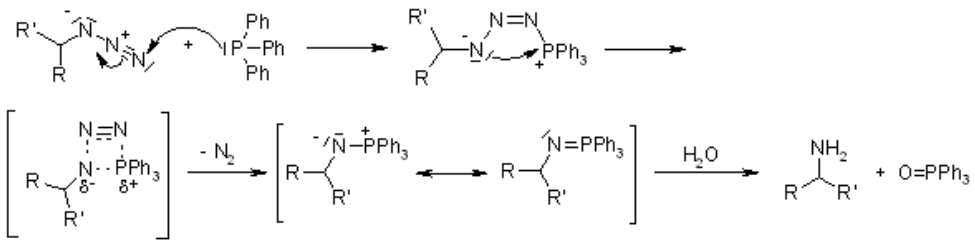
2.6 The Synthesis of Amino Products

Preparation of amino products contains three very standard steps:

- Changing of alcohols to related halides sulfonates;
- Azide anion's nucleophilic subtitution and
- Azide to amine reaction of reduction by the help of different reagents.

The unit of an azide with a phosphine or phosphite produces in iminophosphorane intermediate is a chemical reaction called The **Staudinger reaction** or **Staudinger reduction** (Tian et al., 2004; Bergman et al., 2005). United of the hydrolysis of aza-ylide to make a phosphine oxide and an amine, a calm technic of reducing an azide to an amine. Triphenylphosohine usually works as the reducing agent, yielding triphenylphosphine oxide in the role of the side product added to the amine.

To produce a phosphazide that leaves N_2 to figure iminophosphorane, triphenylphosphine reacts with azide. Additionally aqueous phase development heads to amine and the phosphine oxide which is very stable.



Scheme 2.3 An Example of Staudinger Reduction

There is an other way as an alternative to produce these which includes two steps :

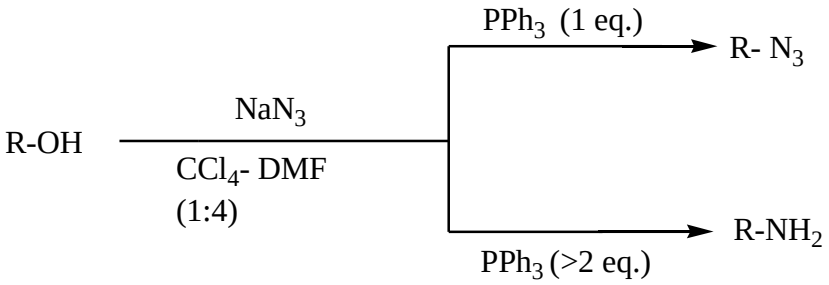
- Transform of alcohol to azide by Mitsunobu reaction using hydrazoic acid, to which correspondence should be located triphenyphosphine and diethylazodicarboxylate (DEAD)
- Azide to amine reaction of reduction

Even if this method is well running, extra time consuming to isolate intermediate products causes to reduce overall yields, and takes the disadvantage of the risk to handle explosive azides.

Herein, reported also a procedure for the transformation of alcohols to azide and amines applying NaN_3 and PPh_3 in CCl_4-DMF (1:4). Dealing alcohols with NaN_3 and two equivalents of PPh_3 in CCl_4-DMF (1:4) at 90 ^oC allowed amines in an perfect yield (85-95%).

Construction of amines can be imagined as the initial azide formation that would react with second equivalent of PPh_3 which gives the iminophosphorane that in turn transferred to the amine by treating with water.

Conduct of alcohols with one molar equivalent of PPh_3 produced azides exclusively in satisfactory yields. The reaction of primary alcohols needed 4-6 h, whereas secondary alcohols lasted much more time (8-10h).



Scheme 2.4 Onepot Protocol Conversion of Alcohols into Azide and Amines

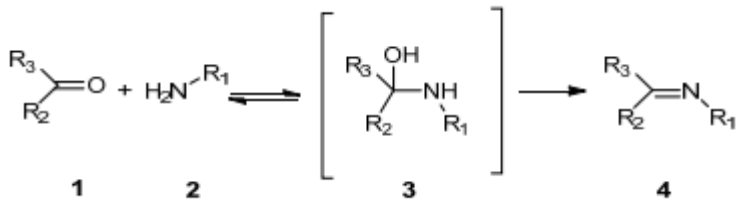
By a diazotransfer reaction azides ,which is known in chemical syntheses to be useful to indicate the amines as followers, may be introduced by displacement of direct conversion of an existing amine or a fit nucleofuge. Moreover azides can be reduced to amines effortlessly one orthogonally or the other generally (hydrides- metal hydrogenation, etc.) (Staudinger and Meyer, 1919).In addition to that they are very strong against to so many conditions of reaction.

2.7 Schiff Bases (Imines)

Schiff's bases, which are also called imines, are an essential arm of organic compounds .In 1864 Hugo Schiff reported them firstly. Condensation products of carbonyl compounds with primary amines are Schiff's bases.Well-known structural detail of these compounds is the azomethine group which has the general formula RHC = N-R_1, where R and R_1 are aryl, alkyl, heterocyclic, or cycloalkyl groups. In skeleton of a Schiff's base (also known as azomethine) is a nitrogen derivative of an aldehyde or ketone where the carbonyl group (>C = O) is changed by azomethine group or an imine. Showing the exhibition which is a wide range of biological activities that contains antifungal, antimalarial, antiproliferative, anti-pyretic, antibacterial, antiviral and anti-inflammatory properties is the feature of the Schiff's bases. Different natural or non-natural and naturally derived compounds have azomethine or imine groups in them and these imine groups present in such compounds are so important for their biological activities. Because of their broad range of applications in industrial, Schiff's bases are critical compounds.

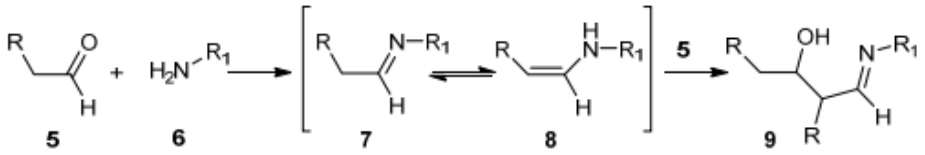
2.8 Preparations of Imines

Original reaction discovered by Schiff is a well-known method in order to prepare imines. In a fundamental manner it composes an aldehyde reaction (respectively a ketone) with a primary amine and discarding of a H_2O molecule (Scheme 2.5). Acid catalysis may accelerate this reaction. The reaction is performed in a Dean Stark apparatus for removing water by refluxing a mix of a carbonyl compound (**1**) and an amine (**2**). The water removal is critical because of the alteration of reversible aminal (**3**) into imine (**4**) (Scheme 2.5). In that respect some agents of dehydrating like molecular sieves and sodium sulphate have been successfully applied. As a alternative way some in situ methods have been reported very satisfactory.These are including dehydrating solvents like trimethyl orthoformate or tetramethyl orthosilicate. Furthermore if it is a need of using acid catalyst,organic acids such as *p*-toluene sulphonic acids or pyridinium *p*-toluenesulphonate,mineral acids, like H_2SO_4 or HCl, acid resin, montmorillonite or even Lewis acids like $TiCl_4$, BF_3Et_2O, $MgSO_4$, $SnCl_4$, $ZnCl_2$, $Mg(ClO_4)_2$, etc., have been reported.



Scheme 2.5. Preparation of imines by Schiff reaction

During the preparation of imines there is a way we can say about it like that: If aliphatic aldehydes which is a common competitive reaction are used, because of the building of a condensation product deriving from an aldol kind reaction, it would be very good (Scheme 2.6).

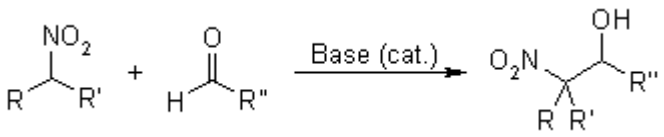


Scheme 2.6 Aliphatic aldehydes' Aldol like condensation

Because higher temperatures of reaction and much more reaction time are necessary for the reaction of aliphatic ketones, reaction of aldehydes with amines to produce imines is more quickly than aliphatic ketones. For increasing the reaction yields to 80%–95% values, taking away of water from the reaction mixture and using acid catalysts are essential. Aliphatic ketones are more reactive than aromatic ones. Aromatic ketones need rough conditions to be transformed to imines. Some new methods to synthesize imines have been published, consisting of microwave irradiation, without solvent, clay, molecular sieves, medium of water suspension, liquid crystals, infrared and ultrasound irradiation, in recent times.

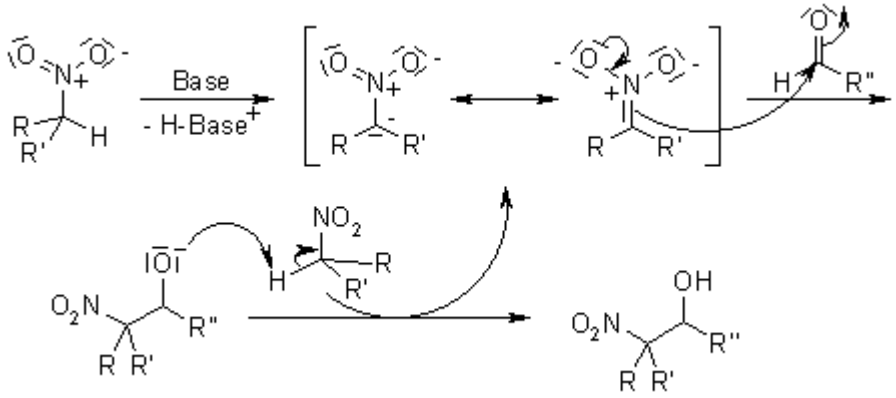
2.9 Defination of Henry Reaction

It has also mentioned as the Nitro Aldol Reaction, base-catalyzed C-C bond-forming reaction between aldehydes or ketones and nitroalkanes and all these have the resemblance to the Aldol Addition is Henry reaction.



Scheme 2.7 Henry Reaction Display

The products show the behavior of eliminating water to give nitroalkenes, if there are acidic protons (i.e. when R = H). Thus, if the isolation of the β-hydroxy-nitro-compounds is planned, base should be used only in little amounts.



Scheme 2.8 Henry Reaction Mechanism

In 1991 Henry reaction's first asymmetric version was briefed by Sasai *et al*. From that day forward, there is a great interest in this area noticeably and different articles have been continually entering in the academic world for the asymmetric Henry reaction on advancement of various bases of metal and nonmetal catalysts.

Pharmaceutical industries uses chiral nitroaldol products in so many applications, it is a real display. The synthetic gain of the chiral nitroaldol reaction is depend on changeability skill of the 1,2-nitroalcohols, which may be altered in to 1,2-amino alcohols, nitroalkenes, amino sugars carboxylic acids, nitroketones, α,β-unsaturated nitrocompounds, ketones, in the chemical reactions of compounds to form more complex compounds of natural products, polyhydroxy lated amides and poly amino alcohols.

These converted products getting from synthesis are very essential pioneer of bio-active compounds. In the production of various pharmaceuticals a great deal of these utilization have been used with the inclusion of making of the carbohydrate sub-unit of the anthracycline class of antibiotics, L-acosamine, the

β-blocker (S)-propranolol and the HIV protease inhibitor Amprenavir (Ananthi *et al*., 2011)

Both aromatic chiral nitro-aldols and aliphatic nitro-aldols have important role for synthetic organic chemistry. As a result, considerable research effort has been invested into finding suitable methods for carrying out this reaction in high yields and stereocontrol. Such methods include applications of organocatalysts, enzymes, and transition metal-chiral ligand complexes. In particular, Cu(II) complexes of a variety of bidentate and tridentate ligands have recently been utilized with good results. Using these catalysts, it is generally believed that the transition state consists of a square pyramidal copper (II) center that is coordinated by the chiral ligand, the substrate aldehyde and nitroalkane and in some cases a counteranion such as acetate and that it is the subsequent combination of the apically coordinated nitronate and equatorially bonded aldehyde that results in the formation of the desired B-nitroalcohols in good yields and with good stereocontrol. Further studies have indicated that the presence of bulky groups near to the metal center can also play an important role.

2.10 Enantiomeric Excess Definition

If a sample is optically active and consists of a single enantiomer , it is called to be pure enantiomerically which means that have an enantiomeric excess of a hundred per cent.

Known as the optical purity, definition of the enantiomeric excess (ee) is like this:

$$\%\ \text{Enantiomeric excess} = \frac{\text{one enantiomer moles} - \text{other enantiomer moles}}{\text{both enantiomers moles totally}}\ x100$$

From optical rotations the enantiomeric excess may be evaluated:

$$\%\ \text{Enantiomeric excess} = \frac{\text{considered specific rotation}}{\text{the pure enantiomer specific rotation}}\ x100$$

Half of the mix formed of the (+) enantiomer (the excess) and other half formed of the racemic means enantiomeric excess of this mixture is 50%.

Because the optical rotations cancel one another out for the half that is racemic, only the 50% of the mix that is formed of the (+) enantiomer partakes to the optical rotation estimation. Hence the detected rotation is 50% (or one-half) of what it is if the mix is formed only of the (+) enantiomer.

Enantiomeric excess shows the success of an asymmetric synthesis. It is an important indicator for these productions. Concerning diastereomers mixtures there are similar decribings and usages for diastereomeric excess and percent diastereomeric excess.

If we need to give an example about this, think about a sample together with percent of 70 of R isomer and percent of 30 of S eventually enantiomeric excess of this sample will be percent of 40. Also this may be thought as a mix of 60% of a racemic mix with 40% pure R (which contributes 30% S and 30% R to entire composition).

Theoretically the contribution of each part of the mixture to the total optical rotation is directly proportional to its mole fraction, and thus the enantiomeric excess is identical to the numerical value of the optical purity. Informally this leads to use the two terms as substitutable in mutual respect, especially owing to the common way to measure enantiomeric excess was optical purity. Nevertheless, for measuring the amount of each enantiomer, other technics like NMR spectroscopy andnchiral column chromatography can now be utilized, independently.

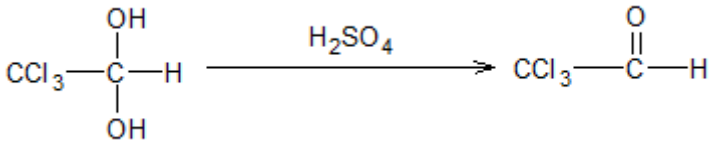
3. MATERIAL AND METHODS

3.1 General Techniques

- Melting points had been recorded with Gallekamp elecrotermal melting point appliance.
- Silica gel (Merck 5554) was used for the instrument which is thin layer chromatography. TLC spots were developed by spraying 5 percent of aqueous sulphuric acid and by heating the plates higher than 120 ^{o}C in the time of 3 minutes approximately.
- Starting compounds and reagent were obtained from Merck and Carlo Erba; and solvents like toluene, methanol, dichloromethane etc. were obtained from industrial grade solvents which were further purified by distillation.
- Solvents were dried with molecular sieve (typt 4 ^{o}A). Anhydrous sodium sulphate was also used for used for drying organic solvent extracts. All solvents were evaporator.
- IR spectra were get by Perkin Elmer Spectrum 100 FTIR Spectrometer.
- ^{1}H-NMR (400 MHz) and ^{13}C-NMR (400 MHz) were obtained on a Varian AS 400 instrument.
- Optical rotation measurements were performed on a Schmidt-Haensch Polartonic E polarimeter.
- HPLC using a Chiralcel OD-H column was used to calculate the enantiomeric excess values.
- Optical rotation measurements were evaluated by the help of a Rudolph Analytical Autopol I automatic polarimeter.

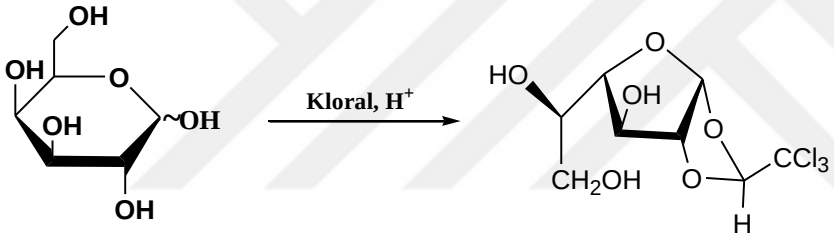
3.2 Experiments

3.2.1 Preparations of anhydrous chloral



Concentrated H_2SO_4 (245 ml, d=1.84) was added on chloral hydrate (430 g, 2,6 mol) and refluxed for about 2 hours at max. 97 °C. Distillation provided pure anhydrous chloral (216 ml, d=1,512; 327 g) with 92 % yield.

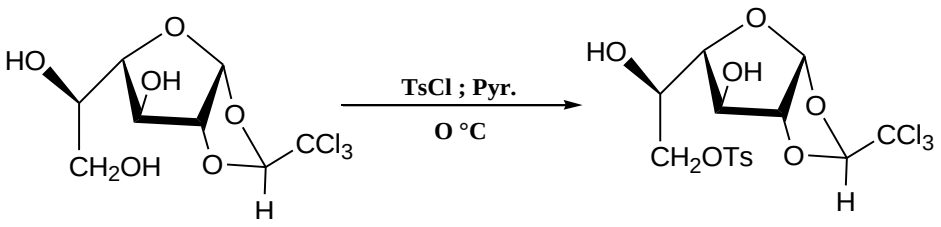
3.2.2 1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (1)



1

D-galactose (54.25 g; 300.4 mmol) was added on anhydrous chloral (166 mL; d=1.512; 250 g) under stirring. Conc. sulphuric acid (1 mL) was joined and reflux of the mixture lasted 2 hours and 30 minutes. The mix was then poured into a flask. The remaining solide was taken with dichloromethane and added to the first portion until all solid was taken. Excess chloral and dichloromethane were evaporated and bloack coloured syrup was obtained. Methanol (400 mL) was added for dissolving all hardened and solidified substance. The solution was heated about 1h 30min. and then decolourised with activated charcoal. After evaporation of solvent the product **(1)** was get as colourless crystals from hot solution of methanol (83 g; 88%); Mp:207-209 °C, $[\alpha]^{21}_{D}$:-31.7 ° (*c* 1.07, MeOH).

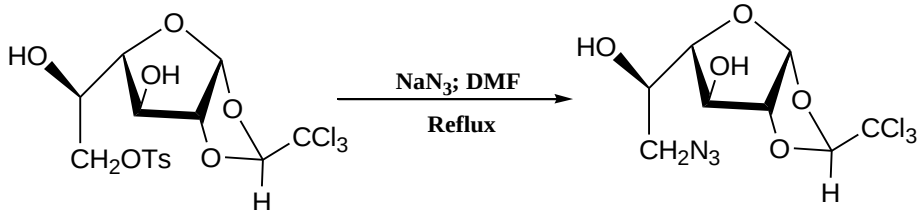
3.2.3 6-*O*-tosyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (2)



1 **2**

A solution of **1** (4.4 g, 0.014 mol) in pyridine was chilled with bath of ice and 1.2 equivalent of *p*-toluenesulfonyl chloride dissolves in pyridine was joined dropwise. The mix stirred for 24 h at 0 °C for the reaction; TLC (toluene-MeOH 9:1) indicated completely disappeared of the starting sugar with two spots. The mixture of reaction was reduced to half volume by evaporation of the solution and so concentrated and poured into ice-water (200 mL). Afterwards, it was extracted with CH_2Cl_2 (3x 100 mL). Washing of organic phase was completed with H_2O and dried over anhydrous and Na_2SO_4. After filtered off, evaporating under deflating pressure was done. Purifiying of the crude syrupy product was done by the help of silica column chromatography that contains CH_2Cl_2-MeOH as eluting system giving product **2** as colorless crystals product (6.1 g; 74%), Mp:166-167°C, $[\alpha]^{21}_D$:-16° (*c* 1, MeOH).

3.2.4 6-Azido-6-deoxy-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (3)

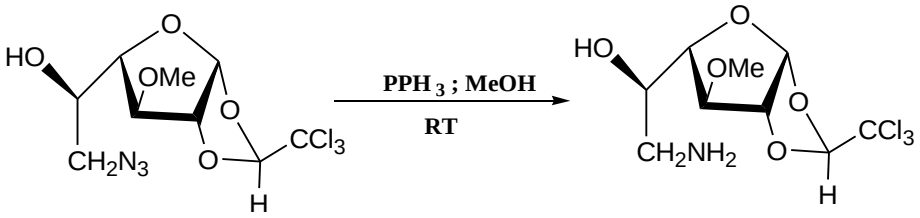


2 **3**

To 7.8 mmol (3.6 g) of **2** dissolved in dried DMF (20 mL); was joined NaN_3 (1.02 g, 15.6 mmol) and the mix was refluxed at 150 °C for 3 h. Then, TLC (toluene-MeOH, 9:1) showed completion of the reaction with 1 product. The reaction was poured into ice-water (50 mL) and extracted twice with CH_2Cl_2-water. Filtered off after drying over anhydrous sodium sulfate; evaporation of the

organic phase was giving colourless crystals as pure compound **3** (2.25 g, 80%), Mp:159-161°C, $[\alpha]^{21}_{D}$:-45.7 ° (*c* 0.7, MeOH).

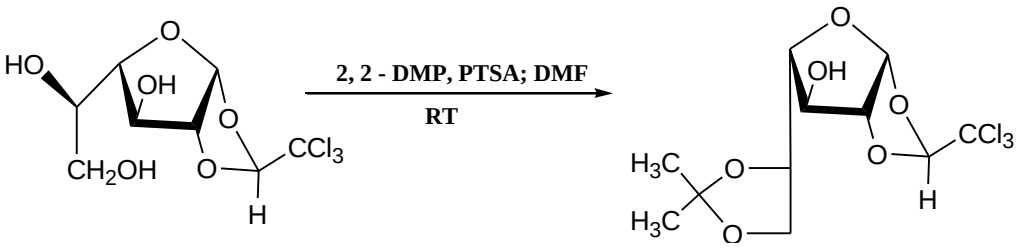
3.2.5 6-Amino-6-deoxy-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (4)



3 **4**

To a solution of **3** (1.2 g, 3.4 mmol) in MeOH (30 mL) had been added triphenylphosphine (1 g; 4.2 mmol). Mixture of reaction was agitated for five hours at room temperature. TLC (Toluene-MeOH, 9:1) showed completed of the reaction. Evaporated, the mixture of reaction managed amine almost purely, which were transited a short pad of silica gel with Toluene/MeOH: 5/1 to give pure amine **4** as colourless crystals (0.75 g, 72%), Mp: 120-121°C, $[\alpha]_{D}^{20}$:-14.0 (c 0.4, MeOH).

3.2.6 5,6-*O*-isopropylidene-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (5)

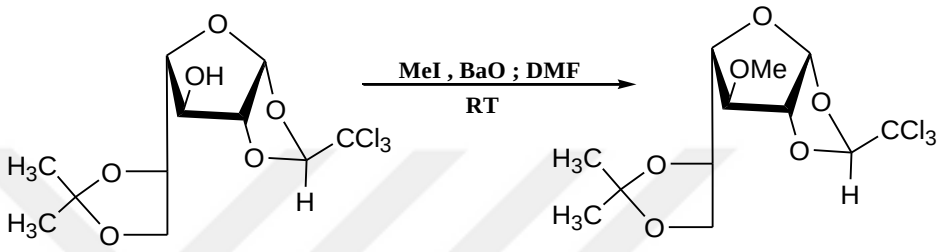


1 **5**

A solution of **1** (10 g, 32.4 mmol) in DMF (25 ml) were added 2,2 DMP (8 mL, 64.8 mmol) and PTSA (5 mg) as a catalyst. The mixture was agitated for 24 hours at room temperature afterward neutralized with aqueous saturated sodium bicarbonate solution. Then the solvent was moved away under deflated pressure to

give a syrupy which was dissolved in neutral methanol and crystallized after the addition of water until slight cloudiness at 0 °C and white powder crystals of compound **5** was obtained (8.68 g, 74 %), Mp:188-189 °C, $[\alpha]^{25}_{D}$: -12 (*c* 1, MeOH).

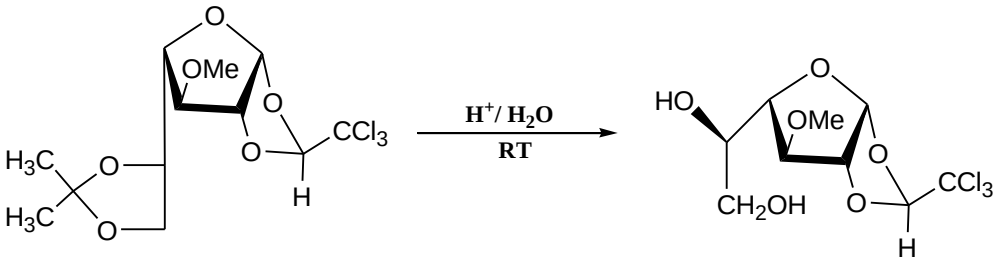
3.2.7 5,6-*O*-isopropylidene-3-*O*-Methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (6)



5 **6**

A solution of **5** (7.6 g, 22 mmol) in DMF (50 ml) and methyl iodide (2.72 ml, 44 mmol) and BaO (6.7 g, 44 mmol) were joined together. The mixture was blended for 24 hours at room temperature. The filtered salts were washed with dichloromethane and after the combination of filtration and the washings evaporating applied at 50 °C. The residue was introduced with dichloromethane, decolourized with sodium thiosulfate solution after washing with water it was dried. The discharging of the solvent served a syrupy residue (7.2 g, 90%), $[\alpha]^{21}_{D}$:-17.2 (*c* 1, MeOH).

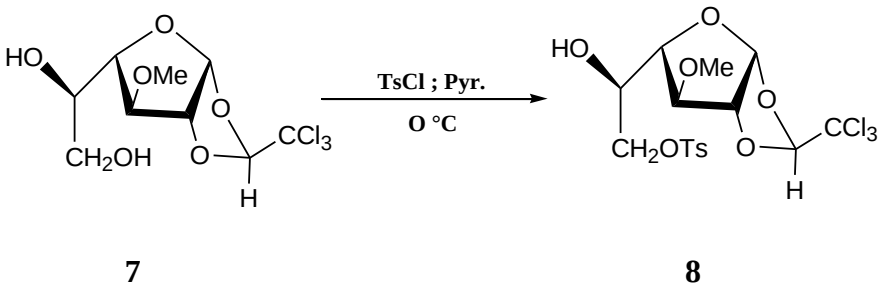
3.2.8 3-*O*-Methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (7)



6 **7**

5,6-*O*-isopropylidene-3-*O*-methyl which was get **(6)** from the former experiment (6 g, 16.6 mmol) was blended with methanol (200 ml), water (20 ml) and concentrated HCl (three drops). All of the dissolution process occurred as the progress of hydrolysis. TLC (toluene- methanol, 9:1) displayed the hydrolysis. After neutralization with $NaHCO_3$ most of methanol was discharged and the extracting of the aqueous residue was made with dichloromethane (4x25 ml). After drying the solution, it was concentrated and due to the removal of the solvent, it gave a syrupy residue (4.7 g, 89%), $[\alpha]^{21}_{D}$:-18.6° (*c* 1, MeOH).

3.2.9 6-*O*-tosil-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (8)

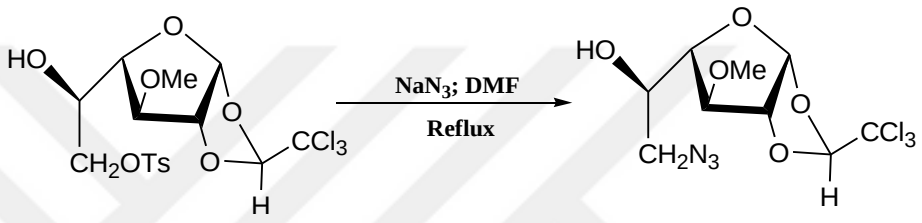


7 **8**

Ice bath was used to cool a solution of **7** (4.5 g, 14 mmol) in pyridine and 1.2 equivalent of *p*-toluenesulfonyl chloride dissolves in pyridine was added dropwise. The reaction mixture stirred for 24 h at 0 °C; TLC (toluene-MeOH 9:1) showed the completely disappeared of the starting sugar with two spots. The mixture of reaction was concentrated by the way of reducing the volume to half by evaporation of the solution and immerged to ice-water (200 mL). Later,

extraction was made with CH_2Cl_2 (3x 100 mL). Water was used to wash organic phase and then dried over anhydrous sodium sulfate. After filtered off, evaporation was completed under reduced pressure. The column chromatography was used to purify the crude syrupy product, with CH_2Cl_2-MeOH as eluting system giving product **8** as colorless crystals product. (5.15 g; 77%), Mp:159-160°C, $[\alpha]^{21}_D$:-17° (*c* 1, MeOH).

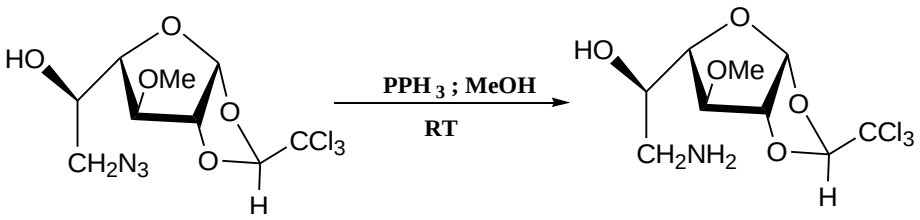
3.2.10 6-Azido-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (9)



8 **9**

To 8.4 mmol (4 g) of **8** dissolved in dried DMF (20 mL); was added NaN_3 (1.1 g, 16.8 mmol) and this mix was refluxed at 100 °C for 6 h. Then, TLC (toluene-MeOH, 9:1) showed completion of the reaction with 1 product. The reaction was poured into ice-water (50 mL) and extracted twice with CH_2Cl_2-water. After drying over anhydrous sodium sulfate and filtered off; the evaporation of organic phase was giving colourless syrupy as pure compound **9** (2.2 g, 76%), $[\alpha]^{21}_D$:-42 ° (*c* 0.8, MeOH).

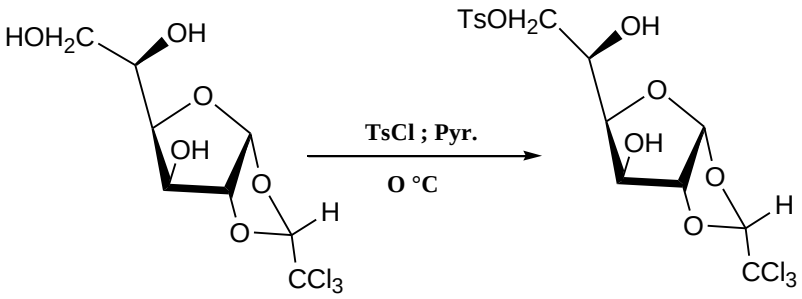
3.2.11 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (10)



9 **10**

A solution of **9** (1.1 g, 3.2 mmol) in MeOH (30 mL) was added to triphenylphosphine (1 g; 4 mmol). Mix of reaction was blended for 5 hours at room temperature. TLC (toluene-MeOH, 9:1) showed the completed reaction. Evaporated, the reaction mixture afforded amine nearly in a form of pure, which were gone through a short pad- silica gel with Toluen/MeOH: 5/1 to give pure amine **10** as colourless syrupy (0.8 g, 78%), $[\alpha]_D^{25}$: -21.0, (c 1.0, MeOH).

3.2.12 6-*O*-Tosyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (12)

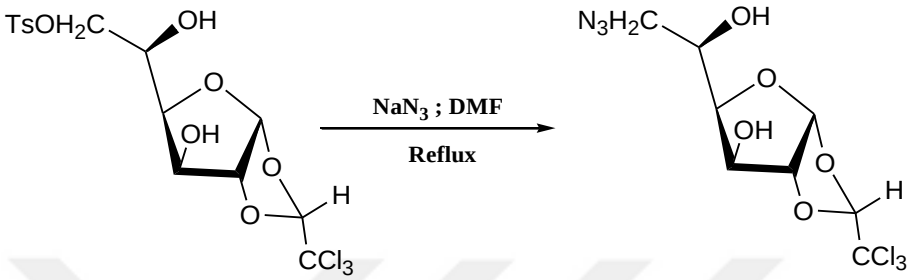


11 **12**

A solution that is purchased commercially α-chloralose **(11)** (4 g, 13 mmol) in pyridine was chilled with ice-bath and 1.2 equivalent of *p*-toluenesulfonyl chloride dissolves in pyridine was added dropwise. The mix of reaction stirred for 24 hours at 0 °C; TLC (toluene-MeOH 9:1) showed the completely disappeared of the starting sugar with two spots. The mix of reaction was concentrated to half volume by evaporation of the solution and poured into ice-water (200 mL). Then, it was extracted with CH_2Cl_2 (3x 100 mL). Water was used to wash organic phase and after that dried over anhydrous Na_2SO_4. Filtered off, evaporated under

reduced-pressure. The purification of crude syrupy product was done by column chromatography with CH_2Cl_2-MeOH as eluting system giving product **12** as colorless crystals product (4.52 g; 75%), Mp:166-167 °C, $[\alpha]^{21}_D$:16° (*c* 1, MeOH).

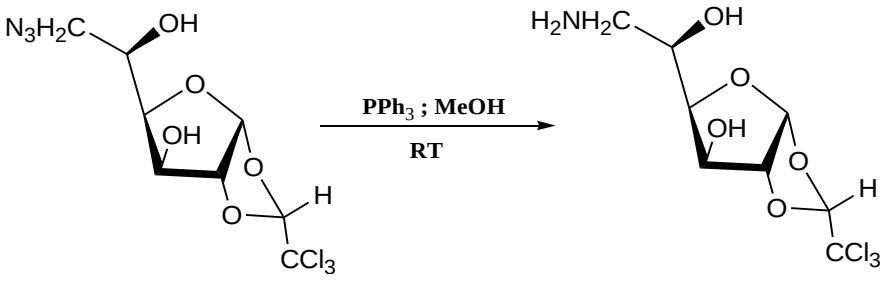
3.2.13 6-Azido-6-deoxy-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (13)



12 **13**

To 6.7 mmol (3 g) of **12** dissolved in dried DMF (20 mL); was added NaN_3 (0.87 g, 13.4 mmol) and the mixture was refluxed at 150 °C for 3 h. Then, TLC (toluene-MeOH, 9:1) showed reaction completion of with 1 product. The reaction was poured into ice-water (50 mL) and extracted twice with CH_2Cl_2-water. Dried over anhydrous sodium sulfate and filtered off; the phase-organic was evaporated giving colourless crystals as pure compound **13** (1.56 g,70%), Mp:159-161 °C, $[\alpha]^{21}_D$:-45.7 ° (*c* 0.7, MeOH).

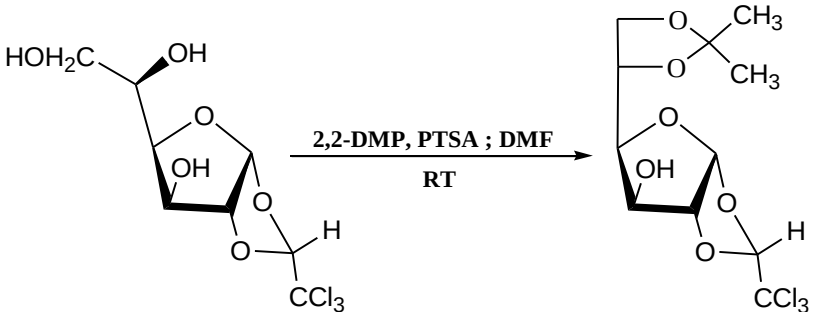
3.2.14 6-Amino-6-deoxy-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (14)



13 **14**

To a solution of **13** (1.1 g, 3.3 mmol) in MeOH (30 mL) was added triphenylphosphine (1.07 g; 4.1 mmol). The mix of reaction was stirred for 5 hours at room temperature. TLC (toluene-MeOH, 9:1) showed the completed reaction. Evaporated, the reaction mixture afforded amine almost in pure form, which were passed through a short pad of silica gel with Toluen/MeOH: 5/1 to give pure amine **14** as colourless crystals (0.7 g, 69%), Mp: 75-76 °C, $[\alpha]_D^{20}$:+12.0, (c 0.5, MeOH).

3.2.15 5,6-*O*-isopropylidene-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (15)

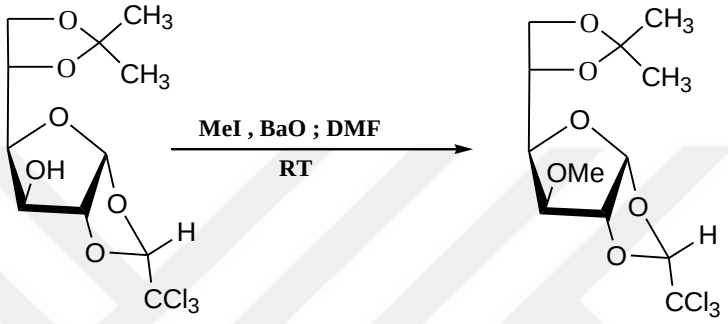


11 **15**

Commercial α-chloralose **(11)** was purified (β- chloralose) by crystallization from hot water and dried at r.t. A solution of α-chloralose (10 g, 32.4 mmol) in DMF (30 ml) were added 2,2 DMP (8 mL, 64.8 mmol) and PTSA (5 mg) as a catalyst. The mixture was stirred for a day-24 hours at room temperature and then neutralized with aqueous saturated sodium bicarbonate solution. The solvent was

removed under reduced pressure to give a syrup that was dissolved in neutral methanol and crystallization completed after the addition of water until slight cloudiness at 0 °C and white powder crystals of compound was obtained. (8.10 g, 72 %), Mp: 107-108 °C, $[\alpha]^{25}_{D}$: +12 (*c* 1, MeOH)

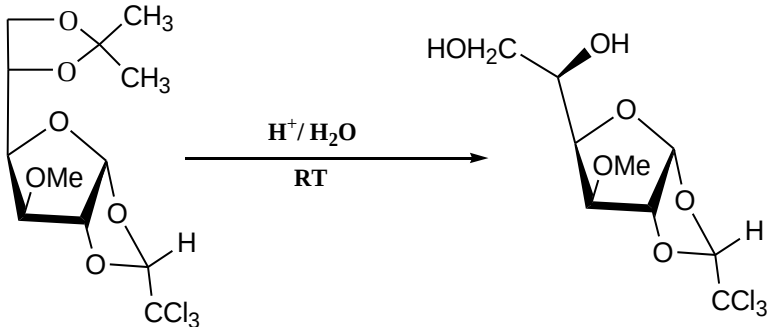
3.2.16 5,6-*O*-isopropylidene-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (16)



15 **16**

A solution of **15** (7 g, 20 mmol) in DMF (25 ml) was added to methyl iodide (2.5 ml, 40 mmol) and BaO (6.1 g, 40 mmol). The mix was agitated for a day at room temperature. Filtration of salts and washing with dichloromethane and filtrate and the washings were incorporated and then evaporated at 50 °C. The resudie was got into dichloromethane, after decolorization with sodium thiosulfate solution, water washing done and then dried. The discharging of the solvent provided a syrupy residue (6.5 g, 90%), $[\alpha]^{25}_{D}$:-17.2° (*c* 1.16, MeOH).

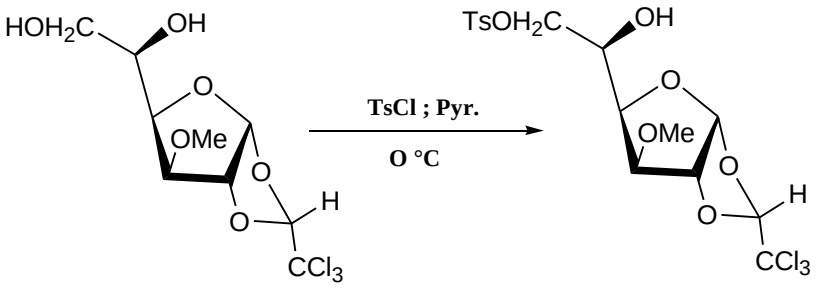
3.2.17 3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (17)



16 **17**

5,6-*O*-isopropylidene-3-*O*-methyl which is got from the before experiment (5 g, 13.8 mmol) was mixed with methanol (200 ml), water (20 ml) and concentrated HCl (three drops). All of the dissolution happened as the hydrolysis progressed. Hydrolysis was displayed by TLC (toluene- methanol, 9:1). The most of methanol was discharged after $NaHCO_3$ –neutralization and the aqueous residue was extracted with dichloromethane (4x25 ml). Dried solution was concentrated and removal of the solvent provided us a syrupy residue (4 g, 90%), $[\alpha]^{25}_{D}$:-18.6° (*c* 1, MeOH).

3.2.18 6-*O*-Tosyl-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (18)

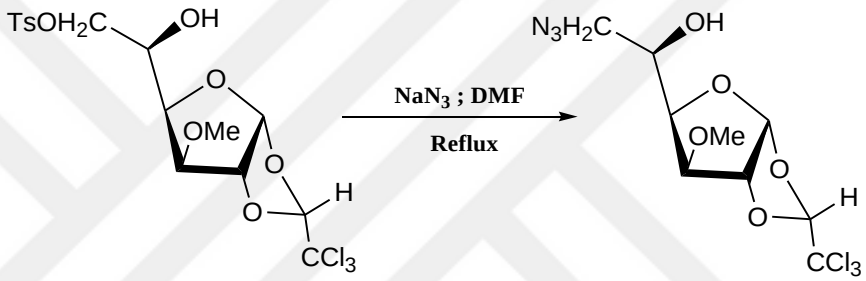


17 **18**

A solution of 3-*O*-methyl-1,2-*O*-(*R*)- trichloroethylidene-α-D-glucofuranose **(17)** (4 g, 12.4 mmol) in pyridine was cooled with ice-bath and 1.2 equivalent of *p*-toluenesulfonyl chloride dissolves in pyridine was added dropwise. The reaction mixture stirred for 24h at 0 °C; TLC (toluene-MeOH 9:1) showed the completely

disappeared of the starting sugar with two spots. Reaction-mix was concentrated reducing to half volume by evaporation of the solution and poured into ice-water (200 mL). Then, it was extracted with CH_2Cl_2 (3x 100 mL). Organic phase was washed with water and dried over anhydrous Na_2SO_4. Filtered off, evaporated under reducing pressure. The crude syrupy product was purified by column chromatography with CH_2Cl_2-MeOH as eluting system giving product **18** as colorless crystals product (4.3 g, 72%), Mp:153-154 °C, $[\alpha]^{25}_D$:-14° (*c* 1, MeOH).

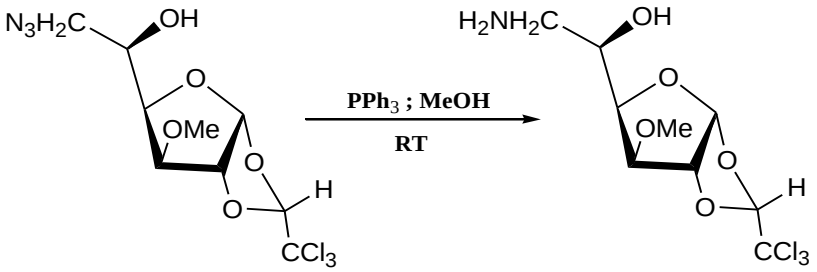
3.2.19 6-Azido-6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (19)



18 **19**

To 8.4 mmol (4g) of **18** dissolved in dried DMF (20 mL); was added NaN_3 (1,1 g, 16.8 mmol) and the mixture was refluxed at 150 °C for 3 h. Then, TLC (toluene-MeOH, 9:1) showed completion of the reaction with 1 product. The reaction was poured into ice-water (50 mL) and extracted twice with CH_2Cl_2-water. Dried over anhydrous sodium sulfate and filtered off; the phase-organic was evaporated giving colourless syrupy as pure compound **19** (2,4 g, 82%), $[\alpha]^{21}_D$:-8 ° (*c* 1, MeOH).

3.2.20 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (20)



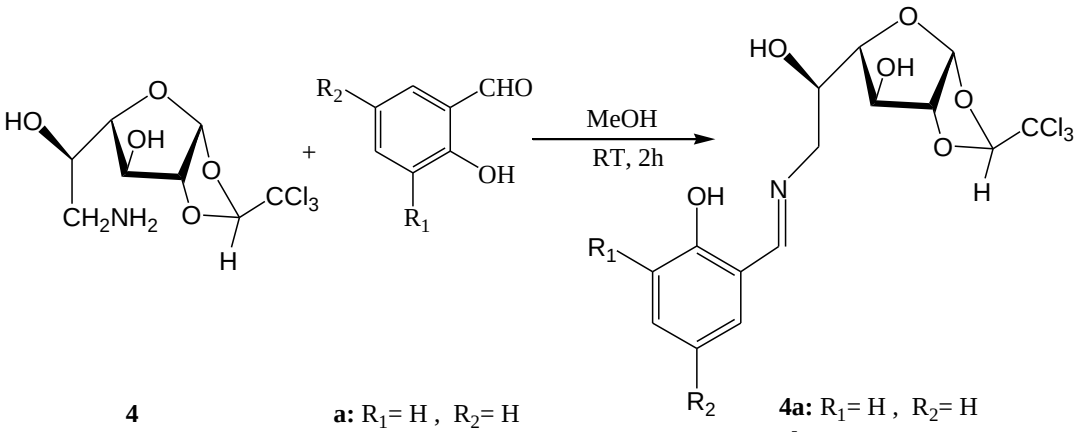
19 **20**

To a solution of **19** (2,1g, 6.2mmol) in MeOH (20 mL) was added triphenylphosphine (2 g; 7,8 mmol). The reaction mixture was stirred at room temperature for 5 h. TLC (toluene-MeOH, 9:1) showed the completed reaction. Evaporated, the reaction mixture afforded amine almost in pure form, which were passed through a short pad of silica gel with CH_2Cl_2/MeOH: 8/2 to give pure amine **20** as colourless syrupy (1.2 g, 60%), $[\alpha]^{20}_D$:-35° (*c* 0.4, MeOH).

3.2.21 General procedure for the preparation of chiral Schiff bases

The solution of aldehyde (1 mmol) in MeOH was added dropwise into the solution of amino sugar derivative (1 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 2h at room temperature. Evaporation of the solvent provided a residue, which was crystallized from CH_2Cl_2:hexane to give yellow or orange crystals (81%-97% yields).

3.2.22 Schiff bases synthesized from Compound 4



4 **a:** R_1= H , R_2= H
b: R_1= *t*-Bu , R_2= *t*-Bu

4a: R_1= H , R_2= H
4b: R_1= *t*-Bu, R_2= *t*-Bu

Table 3.1 Properties of Schiff bases 4a-b

No	The name of the compound		Mp (°C)	$[\alpha]_D$
	The appearance	Yield		
4a	6-deoxy-1,2-*O*-(*S*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose		128-129	$[\alpha]_D^{19}$= -30.0 (c 0.1, MeOH)
	Yellow crystals	81% (150 mg)		
4b	6-deoxy-1,2-*O*-(*S*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-galactofuranose		78-79	$[\alpha]_D^{18}$= +2.5 (c 0.4, CH_2Cl_2)
	Yellow crystals	89 % (210mg)		

3.2.23 Schiff bases synthesized from Compound 10

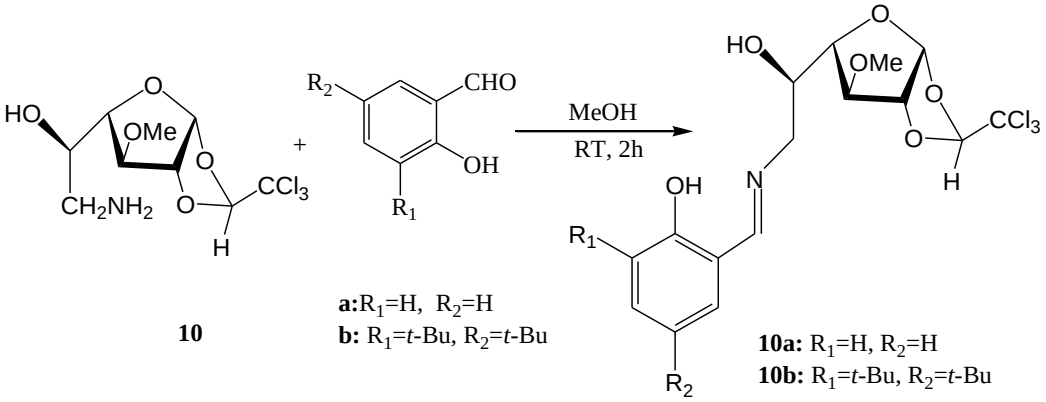


Table 3.2 Properties of Schiff bases 10a-b

No	The name of the compound		Mp (°C)	$[\alpha]_D$
	The appearance	Yield		
10a	6-deoxy-3-*O*-methyl-1,2-*O*-(*S*)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-galactofuranose		119-120	$[\alpha]_D^{19}$= -9.0 (c 0.4, CH_2Cl_2)
	Yellow crystals	89% (300mg)		
10b	6-deoxy-3-*O*-methyl-1,2-*O*-(*S*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose		103-104	$[\alpha]_D^{18}$= -22.5 (c 0.4, CH_2Cl_2)
	Yellow crystals	93% (700mg)		

3.2.24 Schiff bases synthesized from Compound 14

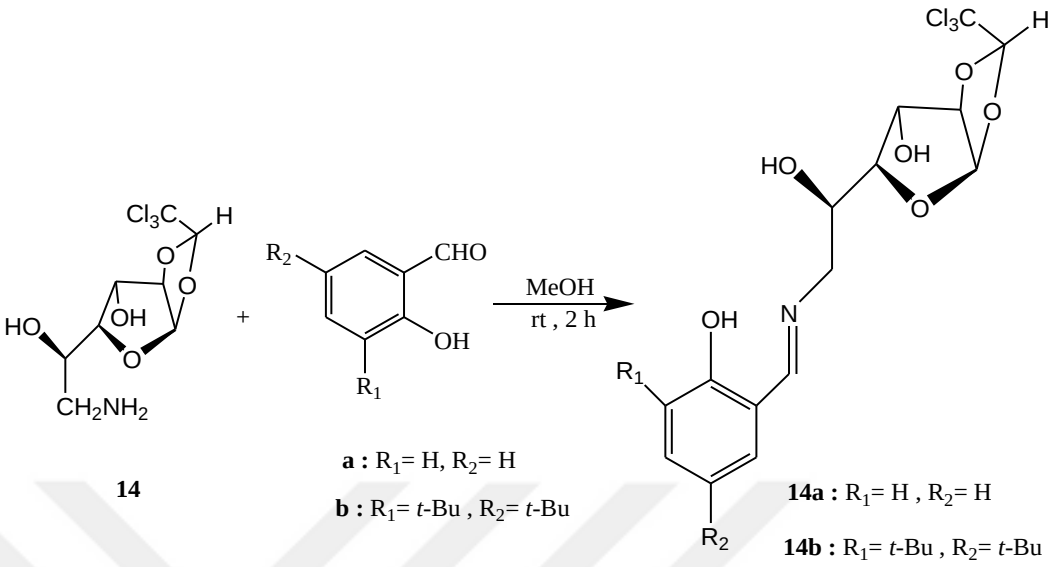


Table 3.3 Properties of Schiff bases 14a-b

No	The name of the compound		Mp (°C)	$[\alpha]_D$
	The appearance	Yield		
14a	6-deoxy-1,2-*O*-(*R*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-glucofuranose		90-91	$[\alpha]_D^{19}$= +30.0 (c 0.4, CH_2Cl_2)
	Yellow crystals	89% (218mg)		
14b	6-deoxy-1,2-*O*-(*R*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-glucofuranose		55-58	$[\alpha]_D^{19}$= +20.0 (c 0.4, CH_2Cl_2)
	Yellow crystals	94 % (296mg)		

3.2.25 Schiff bases synthesized from Compound 20

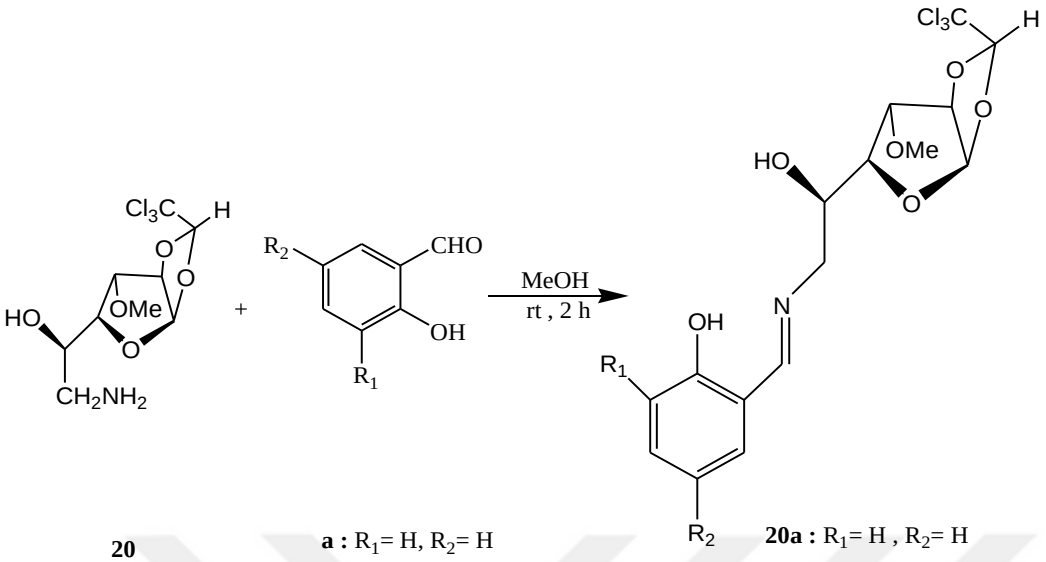


Table 3.4 Properties of Schiff bases 20a-b

No	The name of the compound		Mp (°C)	$[\alpha]_D$
	The appearance	Yield		
20a	6-deoxy-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-glucofuranose		-	$[\alpha]_D^{19}$= +102.5 (c 0.4, CH_2Cl_2)
	Yellow syrupy	97% (280 mg)		
20b	6-deoxy-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-glucofuranose		84-85	$[\alpha]_D^{26}$= +6.0 (c 1.0, CH_2Cl_2)
	Yellow crystals	91% (300mg)		

3.2.26 The asymmetric Henry reaction General procedure

To a solution of ligand **[4a-b, 10a-b, 14a-b, 20a-b]** (0.01 mmol) and 1 mL of solvent at the assumed proper temperature was joined $Cu(OAc)_2.nH_2O$ (0.01 mmol). The mix was admitted to agitate for 5 hours. The aldehyde (0.5 mmol) and nitromethane (5 mmol) were also added into this solution. TLC applied to monitore the reaction- progress. Later completion of reaction was seen, evaporation of the solvent was waited and by the help of using hexane:ethyl acetate (5:1) column chromatography the residue was purified to afford the desired product of Henry. The values of enantiomeric excess were figured by the help of using a Chiralcel OD-H column HPLC.

3.2.27 The Enaantiomeric Excess Value of 4a-b Catalyzed Henry Reaction

The asymmetric Henry reaction realized between nitromethane and 4-nitro benzaldehyde in the existence of 10% mol ligand 4a-b and $Cu(OAc)_2.nH_2O$.

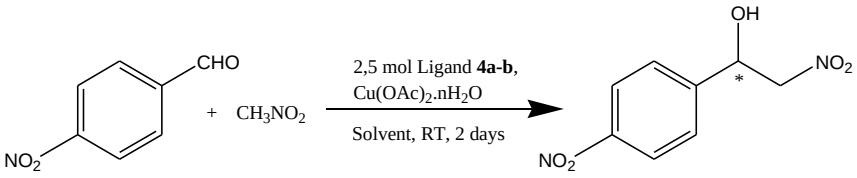


Table 3.5 The ee value of Henry reaction in the percence of 10%mol ligand 4a-b

Entry	Ligand	Solvent	Yield[a] (%)	ee[b] (%)	Config.[c]
1	4a	EtOH	65	1.5	R
2	4b	EtOH	92	41	R
3	4b	CH_2Cl_2	72	12	R
4	4b	IPA	78	12	R
5	4b	TBME	53	8	R
6	4b	ACN	70	20	R
7	4b	MeOH	80	58	R
8	4b	MeOH/H_2O (10/1)	72	30	R
9	4b	MeOH/H_2O (1/5)	76	42	R
10	4b	MeOH/H_2O (1/1)	71	70	R
11	4b	MeOH/H_2O (6/10)	65	78	R
12	4b	MeOH/H_2O (1/3)	75	83	R
13	4b	CH_3NO_2	60	68	R
14	4b	CH_3NO_2/H_2O(1/10)	82	60	R
15	4b	CH_3NO_2/H_2O(10/1)	74	80	R
16	4b	CH_3NO_2/H_2O(5/1)	68	82	R
17	4b	IPA/H_2O (1/3)	87	82	R
18	4b	*t*-BuOH/H_2O (1/3)	85	85,2	R
19	4b	EtOH/H_2O (1/3)	78	80	R
20	4b	CH_3NO_2/H_2O(1/1)	72	86	R
21	4b	CH_3NO_2/H_2O(1/3)	70	90	R
22	4b	CH_3NO_2/H_2O(1/5)	74	85,2	R
23	4b	CH_3NO_2/H_2O(5/2)	75	78	R
24	4b	CH_3NO_2/H_2O(3/5)	78	84	R
25	4b	H_2O/*t*-BuOH (1/9)	81	86,5	R

3.2.28 The Enaantiomeric Excess Value of 10a-b Catalyzed Henry Reaction

The asymmetric Henry reaction realized between nitromethane and 4-nitro benzaldehyde in the existence of 10% mol ligand 10a-b and $Cu(OAc)_2.nH_2O$.

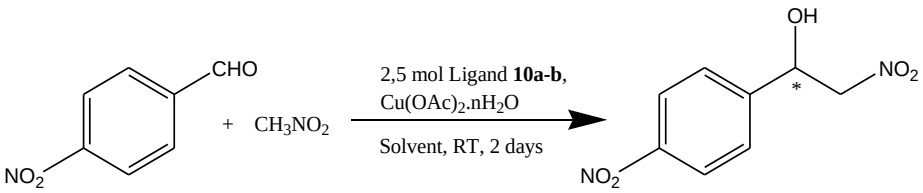


Table 3.6 The ee value of Henry reaction in the presence of 10%mol ligand 10a-b

Entry	Ligand	Solvent	Yield[a] (%)	ee[b] (%)	Config.[c]
1	10a	EtOH	88	20	R
2	10b	EtOH	73	68	R
3	10a	$CH_3NO_2/H_2O(1/3)$	92	45	R
4	10b	$CH_3NO_2/H_2O(1/3)$	67	66	R

3.2.29 The Enaantiomeric Excess Value of 14a-b Catalyzed Henry Reaction

The asymmetric Henry reaction realized between nitromethane and 4-nitro benzaldehyde in the existence of 10% mol ligand 14a-b and $Cu(OAc)_2.nH_2O$.

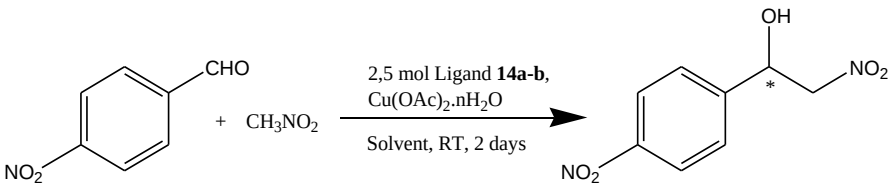


Table 3.7 The ee value of Henry reaction in the 10%mol ligand 14a-b presence

Entry	Ligand	Solvent	Yield[a] (%)	ee[b] (%)	Config.[c]
1	14a	EtOH	34	1	S
2	14b	EtOH	80	4	R

3.2.30 The Enaantiomeric Excess Value of 20a-b Catalyzed Henry Reaction

The asymmetric Henry reaction realized between nitromethane and 4-nitro benzaldehyde in the presence of 10% mol ligand 14a-b and $Cu(OAc)_2.nH_2O$.

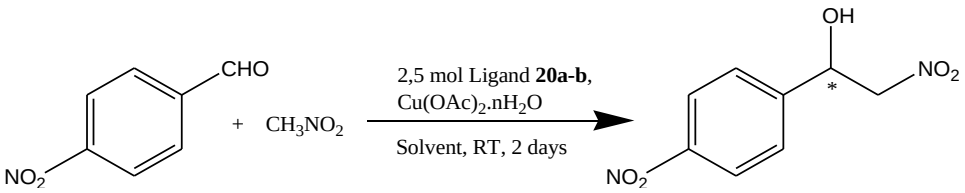


Table 3.8 The ee value of Henry reaction in the presence of 10%mol ligand 20a-b

Entry	Ligand	Solvent	Yield[a] (%)	ee[b] (%)	Config.[c]
1	20a	EtOH	50	10	R
2	20b	EtOH	39	30	R
3	20a	$CH_3NO_2/H_2O(1/3)$	68	13	S
4	20b	$CH_3NO_2/H_2O(1/3)$	74	24	S

a Isolated yields by the column chromatography using 5:1 hexane:ethyl acetate.

b Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

c Absolute configurations were determined by comparison of the values with the literature values.

4. RESULTS AND DISCUSSION

Our prepararative routes to the Schiff base ligands involved formation of aminochloraloses by selective tosylation of the appropriate chloralose followed by azidation and reduction reactions as can be seen in Figure 4.1. Subsequent reaction with either salicylaldehyde or 3,5-ditbutylsalicylaldehyde afforded the desired Schiff base ligands.

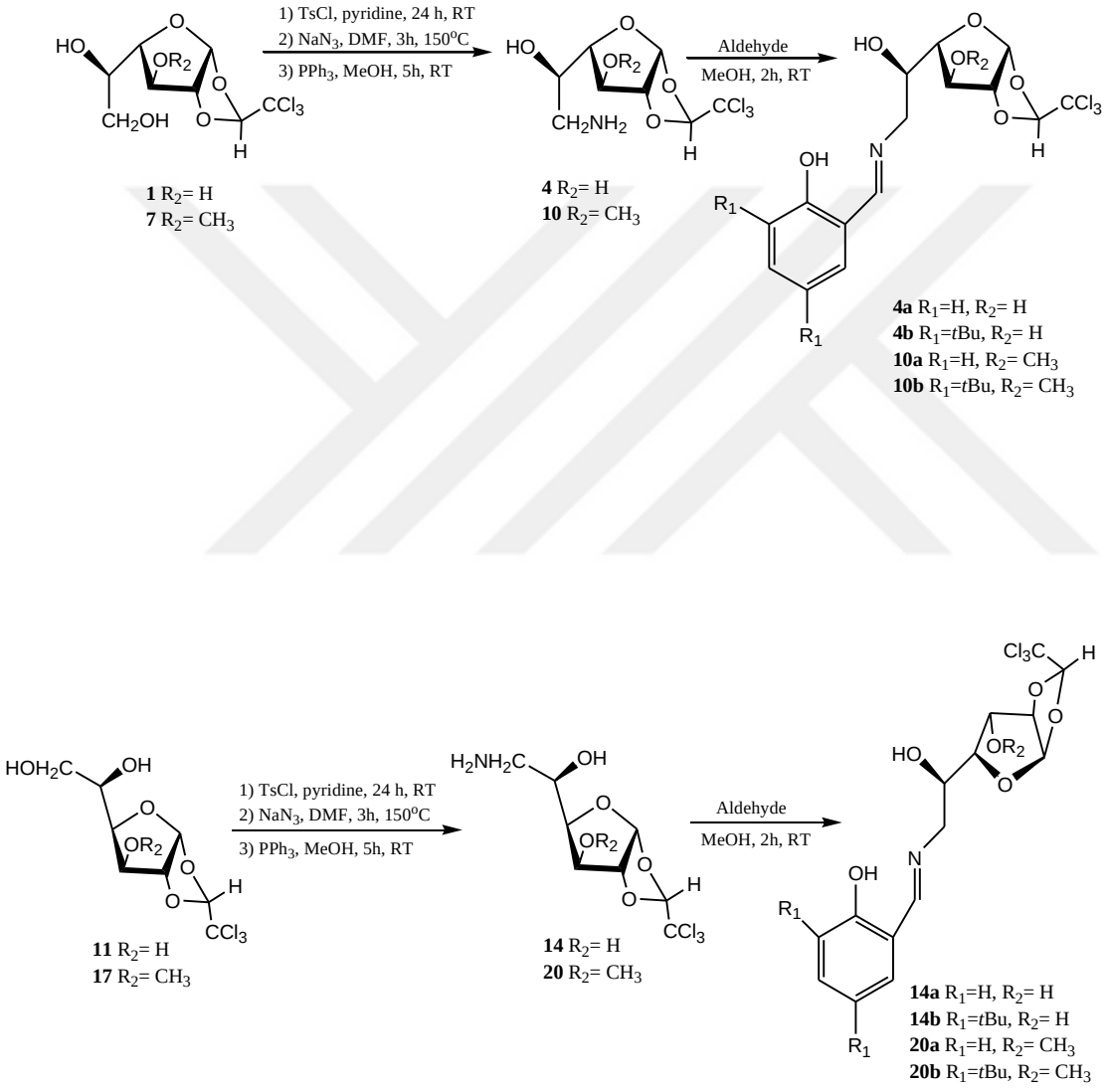


Figure 4.1 Syntheses of aminosugar derivatives **(4, 10, 14, 20**) and Schiff base derivates (**4a-b, 10a-b, 14a-b, 20a-b**)

Once the ligands had been prepared, they were used as catalysts for the Henry reaction in ethanol solvent in the presence of $Cu(OAc)_2$ (Table 4.1).

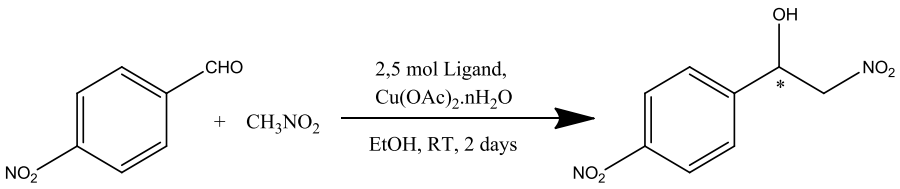


Table 4.1 Optimization of catalytic ligands (**4a-4b**, **14a-14b**) effect on the asymmetric Henry reaction**.**

Entry[a]	Ligand	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**14a**	rt	2	34	1	S
2	**14b**	rt	2	80	4	R
3	**4a**	rt	2	65	1	R
4	**4b**	rt	2	92	41	R

[a] All reactions were performed with 0.5 mmol 4-Nitro-benzaldehyde, 2.5% mol ligand and $Cu(OAc)_2.nH_2O$, and 5 mmol nitromethane in 1 ml of EtOH at room temperature.

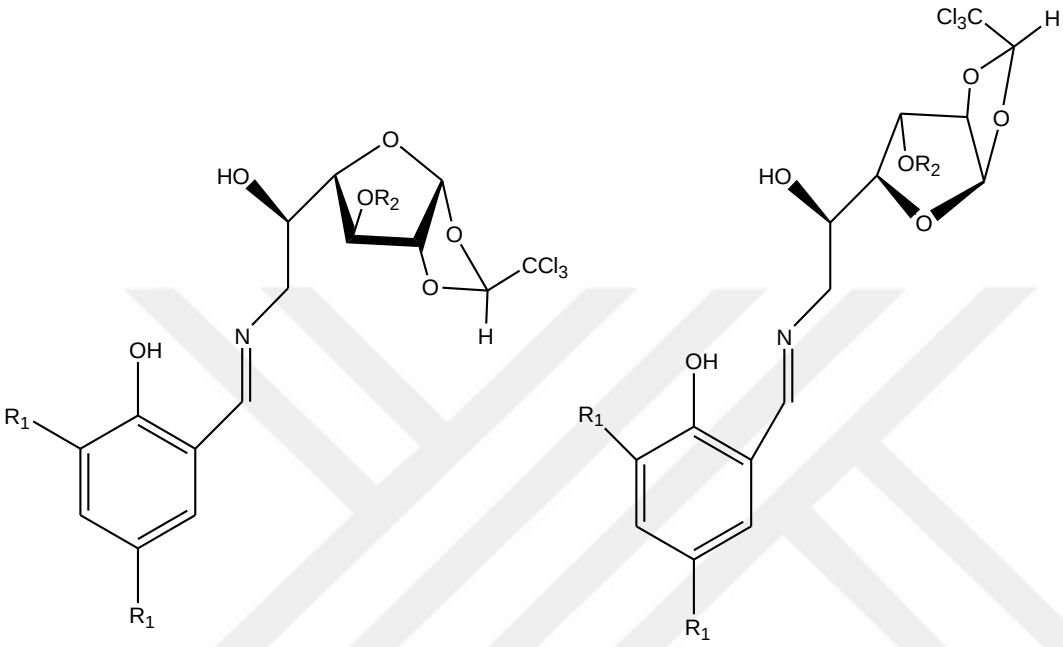
[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.

Surprisingly, ligand **14** gave very disappointing results. For ligands **14a** and **14b**, molecular models had confirmed that the hydroxy group (OR_2, R_2 = H) is capable of acting as a fourth donor site, thus turning the tridentate ligand into a potential tetradentate ligand. The only ligand that gave a promising e.e. was ligand **4b**. As can be seen in Figure 4.2, for ligand **4b**, it is clearly not possible for the β-hydroxy group (OR_2, R_2 = H) to coordinate to the Cu^{2+} ion. This can be taken to indicate that for these examples, the presence of a beta hydroxy group which can potentially act as a fourth donor site is not an important requirement to

obtain high enantiocontrol. It is also noteworthy that **4b** contains a tertiary butyl group *ortho* to the phenolic group. These observations suggest that it may be the overall steric nature of substituents that have an influence on the active site which may be important for high enantiomeric control.



4a (R_1=H, R_2=H)
4b (R_1= *t*Bu, R_2=H)
10a (R_1=H, R_2=CH_3)
10b (R_1= *t*Bu, R_2=CH_3)

14a (R_1=H, R_2=H)
14b (R_1= *t*Bu, R_2=H)
20a (R_1=H, R_2=CH_3)
20b (R_1= *t*Bu, R_2=CH_3)

Figure 4.2 Structure of Schiff base ligands (**4a-b, 10a-b, 14a-b, 20a-b**) from aminochloralose of glucose **(14, 20)** and galactose **(4, 10)**

It was subsequently decided to investigate the effect of the solvent on the reaction and the results of these experiments are given in Table 4.2.

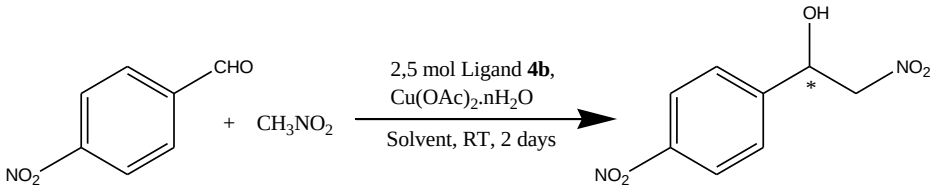


Table 4.2 The solvent effect on the asymmetric Henry reaction between nitromethane and 4-nitrobenzaldehdye in the presence of 10% mol ligand **4b** and $Cu(OAc)_2 .nH_2O$.

Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)	Config.[d]
1	CH_2Cl_2	72	12	R
2	IPA	78	12	R
3	ACN	70	20	R
4	TMBE	53	8	R
5	EtOH	92	40	R
6	MeOH	80	58	R
7	$MeOH/H_2O$ (10/1)	72	30	R
8[e]	$MeOH/H_2O$ (1/1)	71	70	R
9	$MeOH/H_2O$ (1/3)	75	83	R
10	CH_3NO_2/H_2O (1/3)	70	90	R
11[e,f]	$EtOH/H_2O$ (1/3)	78	80	R
12	IPA/H_2O (1/3)	87	82	R
13	$t\text{-}BuOH/H_2O$ (1/3)	85	85.2	R

[a] Reactions were performed with 0.5 mmol 4-Nitro-benzaldehyde, 10% mol ligand and $Cu(OAc)_2.nH_2O$, and 0.25 mL (5 mmol) nitromethane in 1 mL of solvent unless otherwise stated.

[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literatüre.

[e] 0.5 mL nitromethane used.

[f] Overall solvent composition = 0.25 mL EtOH:0.75 mL H_2O:0.5 mL nitromethane.

As can be seen, the observed enantiomeric excess of the products showed a strong solvent dependency: The non-protic solvents dichloromethane, acetonitrile and tert-butyl methyl ether all gave disappointing results whereas mixed results were obtained for alcoholic solvents: Methanol afforded an enantiomeric excess (58%) significantly more promising than ethanol (40%) while isopropyl alcohol (12%) was as disappointing as the non-protic solvents. With these results in mind, it was decided to employ methanol/water mixtures as solvents for the reaction and some interesting results were obtained from these experiments. Thus, use of a 10/1 MeOH/H_2O mixture resulted in a quite dramatic decrease in e.e. to 30%. However, when a 1/1 mixture of MeOH/H_2O was employed, a biphasic system was obtained whereby the dark green coloured catalyst remained entirely in the lower organic (nitromethane) phase and in this experiment it was observed that the enantiomeric excess increased to 70%. Interestingly, addition of further water to the biphasic system resulted in a further increase and an optimum value of 83% was reached when the ratio of MeOH/H_2O was 1:3. Similar results were observed for mixtures of different alcohols and water. Finally, when water was added to the reaction mixture in the absence of an alcohol, the observed enantiomeric excess obtained from the biphasic system increased to 90%. Further experiments showed that decreasing the amount of nitromethane in the reaction in order to obtain a homogeneous solution failed to yield higher enantiomeric excesses.

Thus, it appears that for these reactions, the best results were obtained in nitromethane solution that was saturated with water, and this is most easily achieved in a biphasic system. This would appear to indicate that the presence of water has an effect on the transition state. This may be a direct effect such as coordination to the copper or it could conceivably be a more subtle effect such as changing the most stable conformation of the galactochloralose moiety by rotation around the C4-C5 bond. Such solvent-dependent conformational chages are well-known in biological systems such as peptides and proteins but have only rarely found applications in metal ion-catalyzed asymmetric reactions.

Our next stage in the investigation was to prepare the methoxy derivatives **20** and **10** to see what effect loss of the hydroxy function on the furanose ring would have. As can be seen in Table 4.3, the results obtained with the methoxy

substituted ligands showed a similarity to their parent hydroxy substituted compounds. This is consistent with our suggestion that in these cases, the steric nature of substituents rather than the presence of an additional hydroxyl group may be responsible for determining the degree of enantiocontrol.

Table 4.3 Effect of OMe group on the value of ee.

Ligand[a]	Solvent	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config.[d]
20a	EtOH	rt	2	50	10	R
	H_2O	rt	2	68	13	S
20b	EtOH	rt	2	39	30	R
	H_2O	rt	2	74	24	S
10a	EtOH	rt	2	88	20	R
	H_2O	rt	2	92	45	R
10b	EtOH	rt	2	73	68	R
	H_2O	rt	2	67	66	R

[a] All reactions were performed with 0.5 mmol 4-Nitro-benzaldehyde, 10% mol ligand and $Cu(OAc)_2.nH_2O$, and 5 mmol nitromethane in 1 ml of solvent..

[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.

Finally, we applied our method using catalyst **4b** to a variety of aromatic aldehydes at different temperatures. Moderate to good enantiomeric excesses were obtained in all cases, although in some cases, such as *ortho*-substituted aldehydes, the obtained yields at room temperature were dissapointing.(Table 4.4)

Table 4.4 Range of the aldehydes used in the Henry reactions in the presence of 10% mol ligand **4b** and $Cu(OAc)_2 .nH_2 O$.

Entry[a]	Aldehyde	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	4-nitrobenzaldehyde	rt	2	70	90	R
2	4-nitrobenzaldehyde	5	3	67	89	R
3	2-nitrobenzaldehyde	rt	5	95	72	R
4	3-nitrobenzaldehyde	rt	5	90	91	R
5	2-chlorobenzaldehyde	rt	5	10	60	R
6	4-chlorobenzaldehyde	rt	5	12	40	R
7	p- anisalaldehyde	rt	5	10	70	R
8	p- anisalaldehyde	40	5	60	54	R
9	o- anisalaldehyde	40	5	55	60	R

[a] All reactions were performed with 0.5 mmol aldehyde, 10% mol ligand and $Cu(OAc)_2.nH_2O$, and 5 mmol nitromethane in 1 ml of H_2O.

[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.

As a result, Schiff base ligands containing chloralose substructures can be easily prepared from aminochloraloses and salicylaldehyde derivatives. Our results show that these ligands in the presence of metal ions show considerable promise as catalysts in asymmetric synthesis.

5. SPECTROSCOPIC DATA

IR spectra were recorded on a Perkin Elmer 100 FTIR spectrometer. All ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature.

5.1 6-Amino-6-deoxy-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 4)

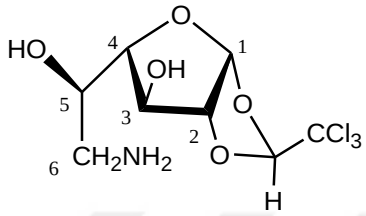


Table 5.1.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 4**

IR	
Functional Groups	**cm^{-1}**
NH_2 and OH	3444
N-H	1574
^{13}C-NMR	
Location of Atoms	**δ in ppm**
HC-CCl_3, C_1	108.3, 106.7
HC-CCl_3	99.7
C_2, C_3 and C_4	89.9, 85.6, 75.2
C_5	71.1
C_6	46.2

Table 5.1.2 ^{1}H-NMR **(**DMSO-d_6, δ ppm) of **Compound 4**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
H_1	6.16 (d)	1H, $J_{1,2}$=4.0 Hz
$HCCl_3$	5.72 (s)	1H
H_2	4.74 (d)	1H
H_3	4.18 (d)	1H, $J_{3,4}$=2.8 Hz
H_4	3.80 (br s)	1H
H_5	3.43 (m)	1H
-NH_2, -OH	3.20 (br s)	3H
H_{6a}	2.65 (dd)	1H
H_{6b}	2.75 (dd)	1H, $J_{6a,6b}$=16 Hz,

5.2 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 10)

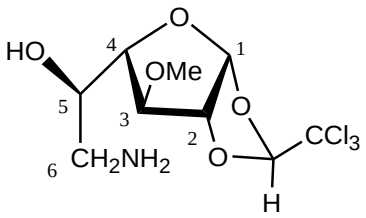


Table 5.2.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 10**

IR	
Functional Groups	**cm^{-1}**
NH_2 and OH	3368
N-H	1670
OMe	1100
^{13}C-NMR	
Location of Atoms	**δ in ppm**
HC-CCl_3, C_1	108.6, 107.0
HC-CCl_3	99.6
C_2, C_3 and C_4	87.5, 86.7, 85.1
C_5	70.9
OCH_3	57.3
C_6	44.5

Table 5.2.2 ^{1}H-NMR **(**DMSO-d_6, δ ppm) of **Compound 10**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants**
H_1	6.14 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.75 (s)	1H
H_2	4.88 (d)	1H
H_4	4.24 (br s)	1H
H_3	3.93 (br s)	1H
H_5	3.89 (m)	1H
-NH_2, -OH	4.24 (br s)	3H
H_{6a}	3.57 (dd)	1H
OCH_3	3.31 (s)	3H
$1H_{6b}$	2.75 (dd)	1H $J_{6a,6b}$=12 Hz ,

5.3 6-Amino-6-deoxy-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (Compound 14)

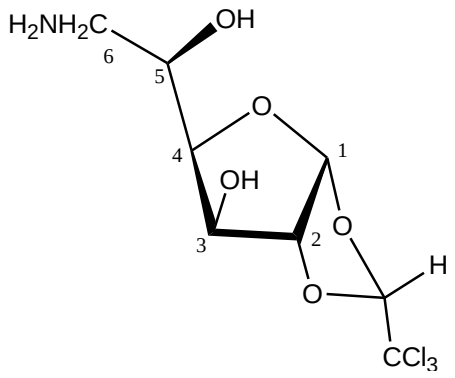


Table 5.3.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 14**

IR	
Functional Groups	**cm^{-1}**
NH_2 and OH	3372
N-H	1598
^{13}C-NMR	
Location of Atoms	**δ in ppm**
HC-CCl_3, C_1	106.3, 105.8
HC-CCl_3	97.7
C_2, C_3 and C_4	87.3, 83.7, 73.0
C_5	68.7
C_6	45.5

Table 5.3.2 ^{1}H-NMR **(**DMSO-d_6, δ ppm) of **Compound 14**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
H_1	6.00 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.39 (s)	1H
H_2	4.59 (d)	1H
H_4	4.18 (d)	1H, $J_{4,5}$=8.0 Hz
H_3	4.11 (s)	1H, $J_{3,4}$=0 Hz
H_5	3.61 (m)	1H
H_{6a}	3.59 (dd)	1H
H_{6b}	2.70 (dd)	1H $J_{6a,6b}$=12 Hz ,

5.4 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (Compound 20)

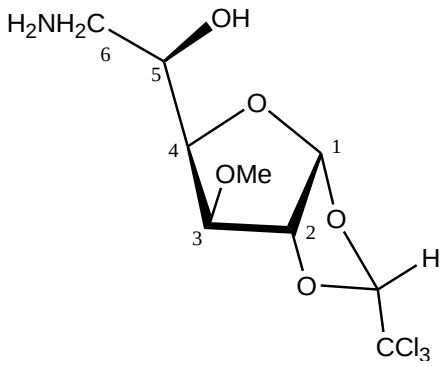


Table 5.4.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 20**

IR	
Functional Groups	**cm^{-1}**
NH_2 and OH	3299
N-H	1591
OMe	1100
^{13}C-NMR	
Location of Atoms	**δ in ppm**
HC-CCl_3, C_1	106.7, 107.7
HC-CCl_3	97.4
C_2, C_3 and C_4	83.7, 83.4, 82.4
C_5	64.3
OCH_3	58.1
C_6	43.3

Table 5.4.2 ^{1}H-NMR **(**DMSO-d_6, δ ppm) of **Compound 20**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
H_1	6.00 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.42 (s)	1H
H_2	4.80 (d)	1H
H_4	4.22 (dd)	1H, $J_{4,5}$=9.0
H_3	3.85 (d)	$J_{3,4}$=2.8 Hz
H_5	3.64 (m)	1H
OCH_3	3.36 (s)	3H
H_{6a}	3.30 (dd)	1H
-NH_2, -OH	3.29 (br s)	3H
H_{6b}	2.75 (dd)	1H, $J_{6a,6b}$=13 Hz,

5.5 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 4a)

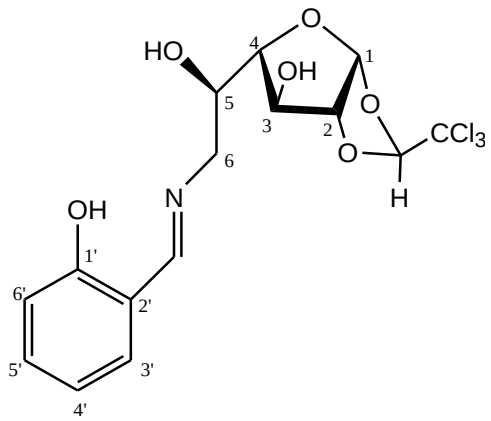


Table 5.5.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 4a**

IR	
Functional Groups	**cm^{-1}**
OH	3460
Ar-H	3060
CH	2940
C=N	1635
C-O	1152
disubs. Ar-H	808
C-Cl	751
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N, $C_{1'}$	167.6, 161.3
$C_{2'}$ - $C_{3'}$ - $C_{4'}$- $C_{5'}$ - $C_{6'}$	133.0, 132.1, 119.1, 118.8, 117.0
HC-CCl_3, C_1	108.4, 106.8
CCl_3	99,7
C_2, C_3,C_4, C_5, C_6	90.0, 89.9,75.2, 70.2, 62.3

Table 5.5.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 4a**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.41 (s)	1H
Ar-H	7.57 (dd)	J= 3.2Hz, 6 Hz, 1H
Ar-H	7.34 (m)	1H
Ar-H	7.29 (m)	1H
Ar-H	7.91 (m)	1H
H_1	6.11 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.56 (s)	1H,
H_2	4.95 (d)	1H
H_3	4.51 (d)	1H, $J_{3,4}$=3.6 Hz
H_4	3.15 (d)	1H, $J_{3,4}$=2.8 Hz
H_5	3.93 (m)	1H
H_{6b}	3.84 (dd)	1H
H_{6a}	3.75 (dd)	1H, $J_{6a,6b}$=12.6 Hz
OH	2.41 (s)	2H

5.6 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 4b)

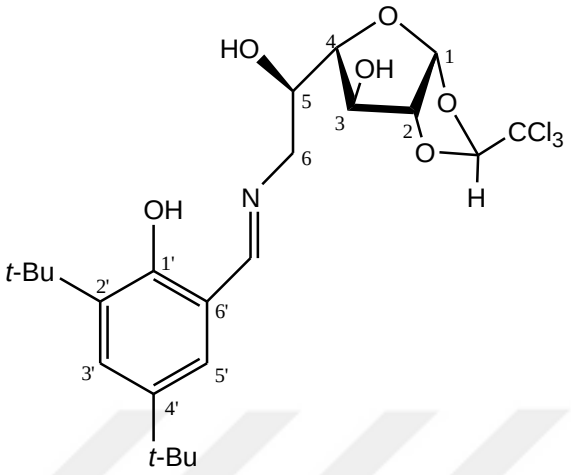


Table 5.6.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 4b**

IR	
Functional Groups	**cm^{-1}**
OH	3412
Ar-H	2961
CH	2872
C=N	1630
t-Bu	1470-1442
C-O	1161
disubs. Ar-H	830-805
C-Cl	764
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N, $C_{1'}$	168.8, 158.0
$C_{2'}$- $C_{4'}$	140.4, 136.8
$C_{3'}$ - $C_{5'}$ - $C_{6'}$	131.9, 127.9, 127.5
HC-CCl_3, C_1	109.4, 107.1
CCl_3	99,3
C_2, C_3, C_4, C_5,C_6	89.7, 89.5, 76.3,70.2, 62.1
t-Bu	35.0, 34.1, 31.5, 31.3, 29.4, 29.3

Table 5.6.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 4b**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.43 (s)	1H
Ar-H	7.39 (d)	J= 2.4 Hz, 1H
Ar-H	7.09 (d)	1H
H_1	6.30 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.70 (s)	1H,
H_2	5.00 (d)	1H
H_3	4.48 (s)	1H
H_4	4.17 (dd)	1H, $J_{4,5}$=6.8 Hz
H_5	3.93 (dd)	1H, $J_{5,6a}$=5.6 Hz
H_{6b}	3.75 (dd)	1H, $J_{6a,6b}$=11.2 Hz
H_{6a}	3.80 (dd)	1H
OH	2.48 (s)	2H

6.7 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 10a)

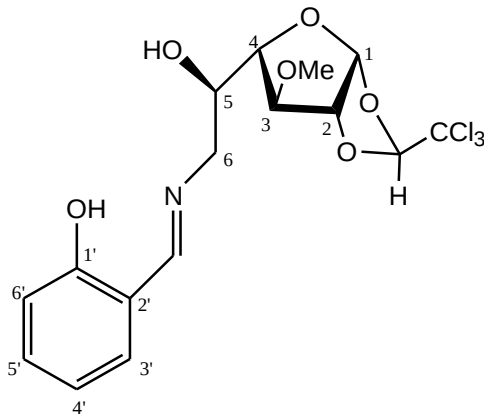


Table 5.7.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 10a**

IR	
Functional Groups	**cm^{-1}**
OH	3390
Ar-H	3060
C-H	2937-2836
N=C	1634
C-O	1159
C-Cl	757
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N,$C_{1'}$	167.6, 161.0
$C_{2'}$ - $C_{3'}$ - $C_{4'}$- $C_{5'}$ - $C_{6'}$	132.7, 131.6 118.7, 118.6, 117.0
HC-CCl_3, C_1	109.4, 107.2
CCl_3	99,3
C_2, C_3 and C_4	87.3, 86.7, 85.4
C_5	70,6
OCH_3	62,3
C_6	57,7

Table 5.7.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 10a**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.39 (s)	1H
Ar-H	7.31 (dd)	1H, J= 3.20 Hz, 6 Hz
Ar-H	7.31 (m)	1H
Ar-H	6.96 (d)	1H ,J= 6 Hz,
Ar-H	6,88 (m)	1H
H_1	6.16 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.64 (s)	1H,
H_2	4.93 (d)	1H
H_4	4.18 (dd)	1H, $J_{4,5}$=8.0 Hz
H_3	3.99 (d)	1H, $J_{3,4}$=3.6 Hz
H_5	3.95 (m)	1H
H_{6b}	3.78 (dd)	1H
H_{6a}	3.73 (dd)	1H, $J_{6a,6b}$=12.6 Hz
OCH_3	3.40 (s)	3H

5.8 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 10b)

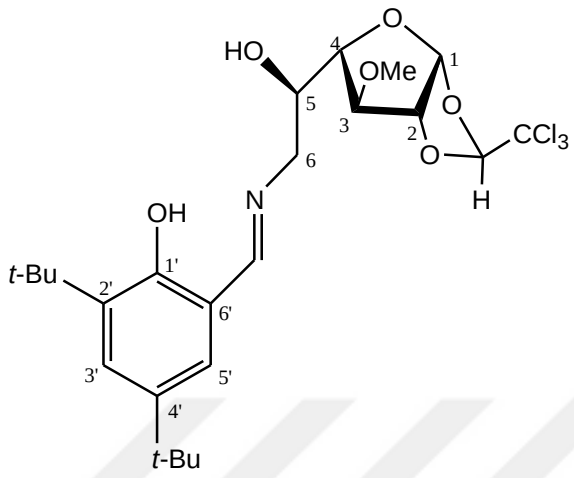


Table 5.8.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 10b**

IR	
Functional Groups	**cm^{-1}**
OH	3412
Ar-H	2959
CH	2872
C=N	1631
t-Bu	1470-1442
C-O	1161
C-Cl	750
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N,$C_{1'}$	168.8, 157.9
$C_{2'}$- $C_{4'}$	140.3, 136.7
$C_{3'}$- $C_{5'}$ - $C_{6'}$	131.9, 127.9, 127.3
HC-CCl_3, C_1	109.4, 107.2
CCl_3	99,3
C_2, C_3 and C_4	87.5, 86.8, 85.5
C_5	62,4
OCH_3	57,7
C_6	58,1
t-Bu	35.0, 34.2, 34.1, 31.5, 29.4, 29.3

Table 5.8.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 10b**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.43 (s)	1H
Ar-H	7.40(d)	1H, J= 4 Hz
Ar-H	7.12 (d)	1H
H_1	6.26 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.73 (s)	1H,
H_2	5.00(d)	1H
H_4	4.20 (dd)	$J_{4,5}$=8.0 Hz
H_3	4.01 (d)	1H, $J_{3,4}$=3.6 Hz
H_5	3.99 (dd)	1H, $J_{5,6a}$=4 Hz
H_{6b}	3.80 (dd)	1H, $J_{6a,6b}$=12.4 Hz
H_{6a}	3.77 (d)	1H
OCH_3	3.49 (s)	3H

5.9 6-deoxy-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-glucofuranose (Compound 14a)

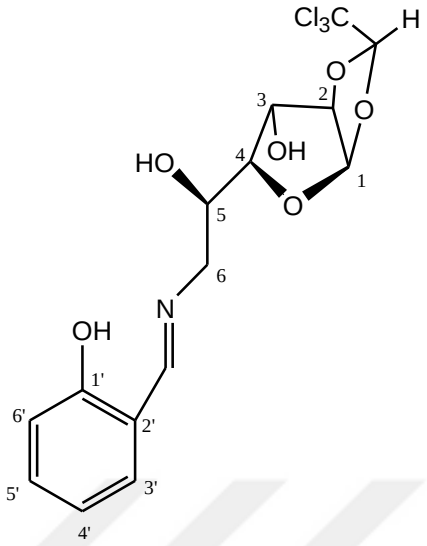


Table 5.9.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 14a**

IR	
Functional Groups	**cm^{-1}**
OH	3372
Ar-H	2954
N=C	1635
C-O	1158
disubs. Ar-H	828-806
C-Cl	756
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N ,$C_{1'}$	167.5, 165.8
$C_{2'}$ - $C_{3'}$ - $C_{4'}$ - $C_{5'}$ - $C_{6'}$	134.6, 132.4, 118.8, 117.8
HC-CCl_3, C_1	107.1, 105.8
CCl_3	96,8
C_2, C_3 and C_4	87.5, 82.1, 74.1
C_5, C_6	68.4, 59.7

Table 5.9.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 14a**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.22 (s)	1H
Ar-H	7.32 (m)	1H
Ar-H	7.18 (dd)	J= 8.0 Hz,6 Hz, 1H
Ar-H	6,85 (d)	J= 8.0 Hz 1H
Ar-H	6.77 (m)	1H
H_1	6.10 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.26 (s)	1H,
H_2	4.69 (d)	1H
H_3	4.56 (d)	1H, $J_{3,4}$=3.6 Hz
H_4	4.35 (d)	1H, $J_{3,4}$=2.8 Hz
H_5	4.24 (m)	1H
H_{6b}	3.95 (dd)	1H
H_{6a}	3.68 (dd)	1H, $J_{6a,6b}$=12.6 Hz

5.10 6-deoxy-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl] phenol-α-D-glucofuranose (Compound 14b)

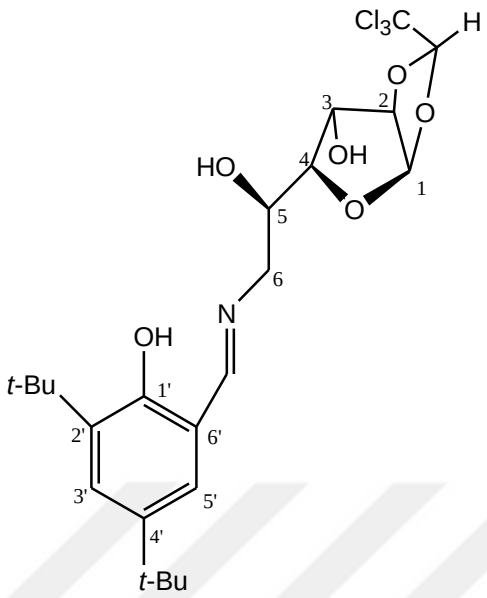


Table 5.10.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 14b**

IR	
Functional Groups	**cm^{-1}**
OH	3407
Ar-H	2961
CH	2871
C=N	1651
t-Bu	1469-1441
C-O	1170
disubs. Ar-H	828-802
C-Cl	771
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N, $C_{1'}$	169.2, 159.1
$C_{2'}$- $C_{4'}$	140.4, 136.9
$C_{3'}$ - $C_{5'}$ - $C_{6'}$	131.9, 127.6, 126.3
HC-CCl_3, C_1	107.1, 105.7
CCl_3	96,7
C_2, C_3 and C_4	87.4, 81.4, 74.8
C_5	69,6
C_6	61,9
t-Bu	35.0, 34.1, 31.5, 31.3, 29.4, 29.3

Table 5.10.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 14b**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.43 (s)	1H
Ar-H	7.41 (d)	1H, $J_{1,2}$=2.4 Hz
Ar-H	7.10 (d)	1H
H_1	6.10 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.26 (s)	1H
H_2	4.71 (d)	1H
H_4	4.60 (m)	1H
H_3	4.57 (d)	1H, $J_{3,4}$=4.0 Hz
H_5	4.32 (dd)	1H, $J_{5,6a}$=8 Hz
H_{6b}	3.95 (dd)	1H, $J_{6a,6b}$=12.4 Hz
H_{6a}	3.38 (dd)	1H

5.11 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20a)

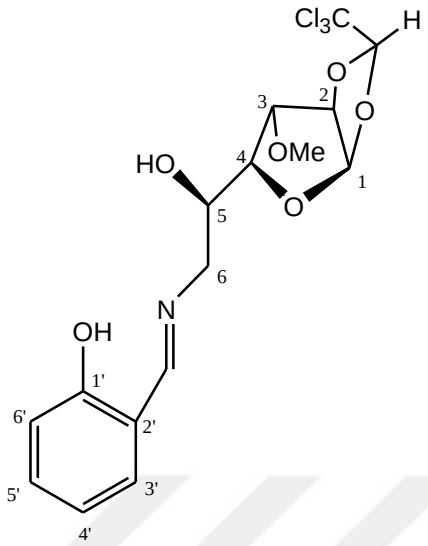


Table 5.11.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 20a**

IR	
Functional Groups	**cm^{-1}**
OH	3390
Ar-H	3060
C-H	2937-2836
N=C	1634
C-O	1159
C-Cl	757
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N , $C_{1'}$	167.6, 161.4,
$C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$	133.0, 132.9, 131.6, 129.7,118.6
HC-CCl_3, C_1	107.1, 105.9
CCl_3	96,7
C_2, C_3, C_4, C_5, C_6	83.7, 83.5, 81.8,68.3,58.1
OCH_3	62,3

Table 5.11.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 20a**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.38 (s)	1H
Ar-H	7.70 (m)	1H
Ar-H	7.60 (m)	1H
Ar-H	7.28 (dd)	1H, J= 8 Hz
Ar-H	6,88 (m)	1H
H_1	6.10 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.28 (s)	1H,
H_2	4.75 (d)	1H
H_4	4.54 (dd)	$J_{4,5}$=8.0 Hz
-OH	4.38 (br s)	1H
H_5	4.22 (m)	1H
H_3	4.08 (d)	1H, $J_{3,4}$=3.6 Hz
H_{6b}	4.01 (dd)	1H
-OH	3.99 (br s)	1H
H_{6a}	3.68 (dd)	1H, $J_{6a,6b}$=12.6 Hz
OCH_3	3.46 (s)	3H

5.12 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20b)

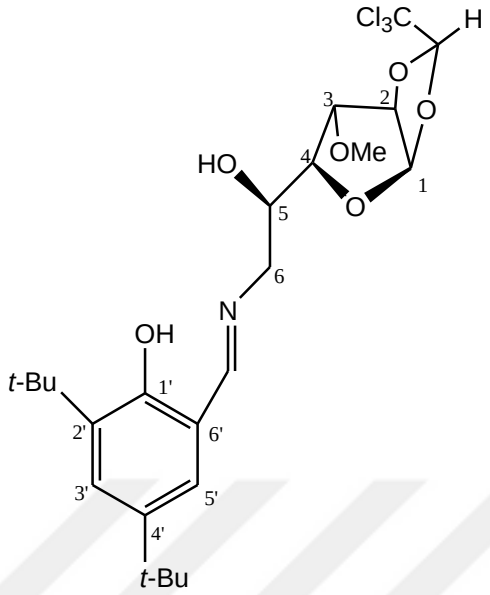


Table 5.12.1 IR (cm^{-1}) and ^{13}C-NMR (δ in ppm) of **Compound 20b**

IR	
Functional Groups	**cm^{-1}**
OH	3412
Ar-H	2937
CH	2872
C=N	1634
t-Bu	1470-1442
C-O	1161
disubs. Ar-H	830-805
C-Cl	772
^{13}C-NMR	
Location of Atoms	**δ in ppm**
C=N , $C_{1'}$	168.9, 157.9
$C_{2'}$- $C_{4'}$	140.2 , 136.7
$C_{3'}$ - $C_{5'}$ - $C_{6'}$	131.9, 127.2, 126.2
HC-CCl_3, C_1	107.1, 105.9
CCl_3	96,7
C_2, C_3 and C_4	83.7, 83.5, 81.6
C5	68,4
OCH_3	62,5
C_6	58,1
t-Bu	35.0, 34.1, 31.5, 31.3, 29.4, 29.3

Table 5.12.2 ^{1}H-NMR ($CDCl_3$, δ ppm) of **Compound 20b**

^{1}H-NMR		
Location of Atoms	**δ in ppm**	**H and Coupling Constants (Hz)**
-CH=N-	8.42 (d)	1H
Ar-H	7.39 (d)	J= 2.4 Hz, 1H
Ar-H	7.09 (d)	1H
H_1	6.12 (d)	1H, $J_{1,2}$=3.6 Hz
$HCCl_3$	5.31 (s)	1H,
H_2	4.76 (d)	1H
H_4	4.58 (dd)	$J_{4,5}$=8.8 Hz
-OH	4.23 (br s)	2H
H_3	4.12 (d)	1H, $J_{3,4}$=3.6 Hz
H_5	3.93 (dd)	1H, $J_{5,6a}$=8 Hz
H_{6b}	3.75 (dd)	1H, $J_{6a,6b}$=12.4 Hz
OCH_3	3.49 (s)	3H
H_{6a}	3.47 (d)	1H

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Ağustos 2019

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APPENDIX A

FT-IR SPECTRUMS OF THE PRODUCTS

Figure A.1 IR spectrum of 6-Amino-6-deoxy-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 4)

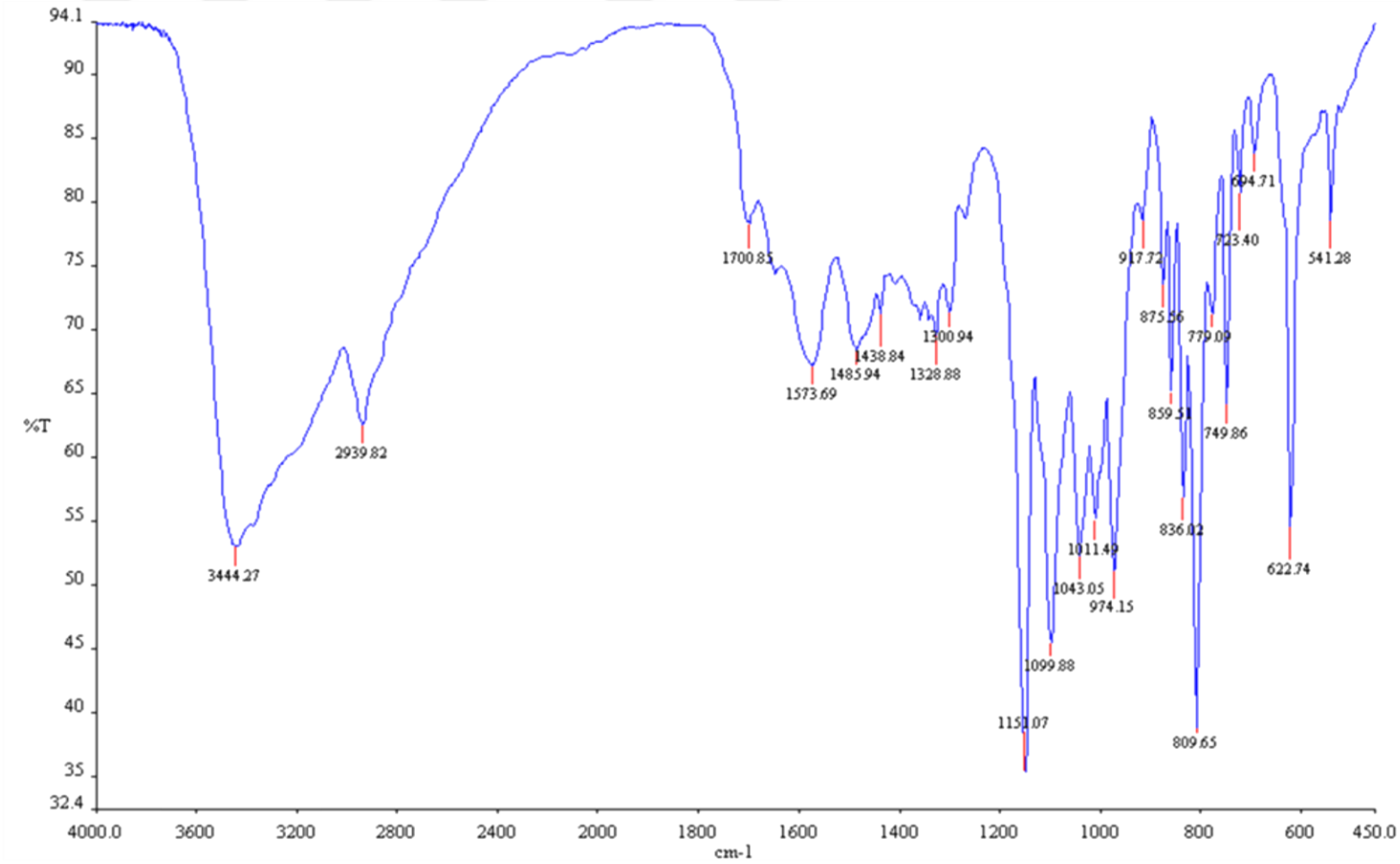


Figure A.2 IR spectrum of 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 10)

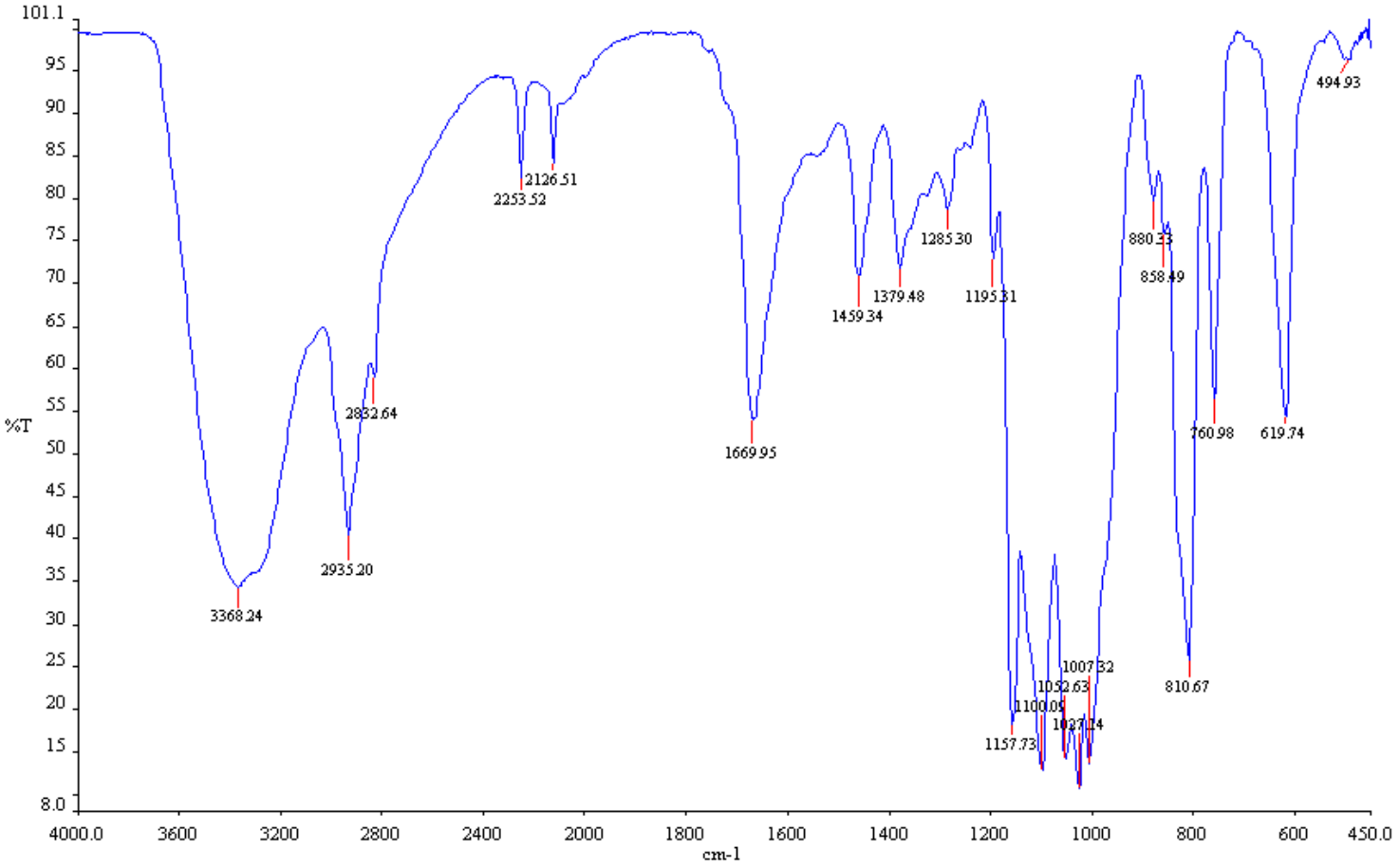


Figure A.3 IR spectrum of 6-Amino-6-deoxy-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (Compound 14)

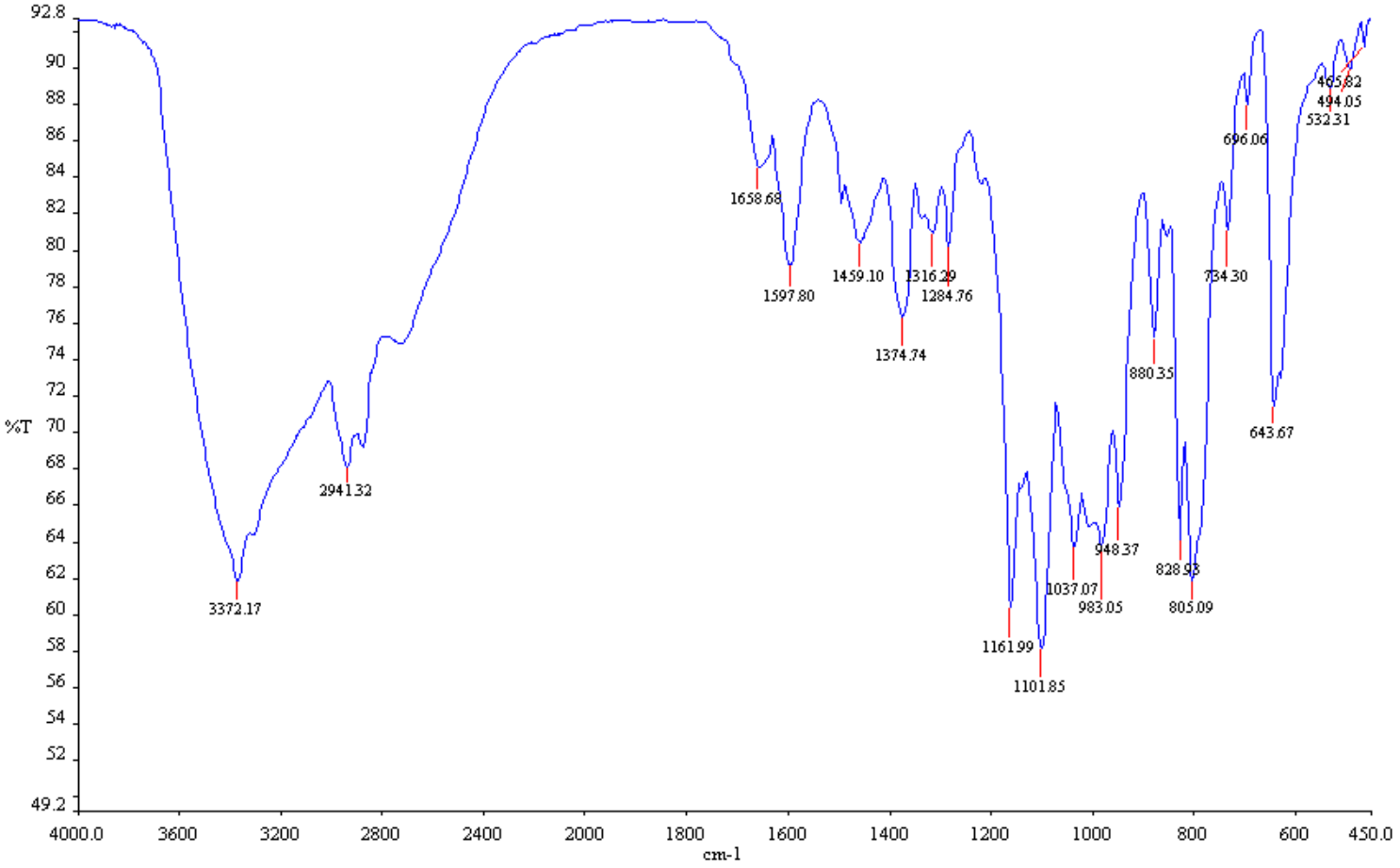


Figure A.4 IR spectrum of 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-α-D-glucofuranose (Compound 20)

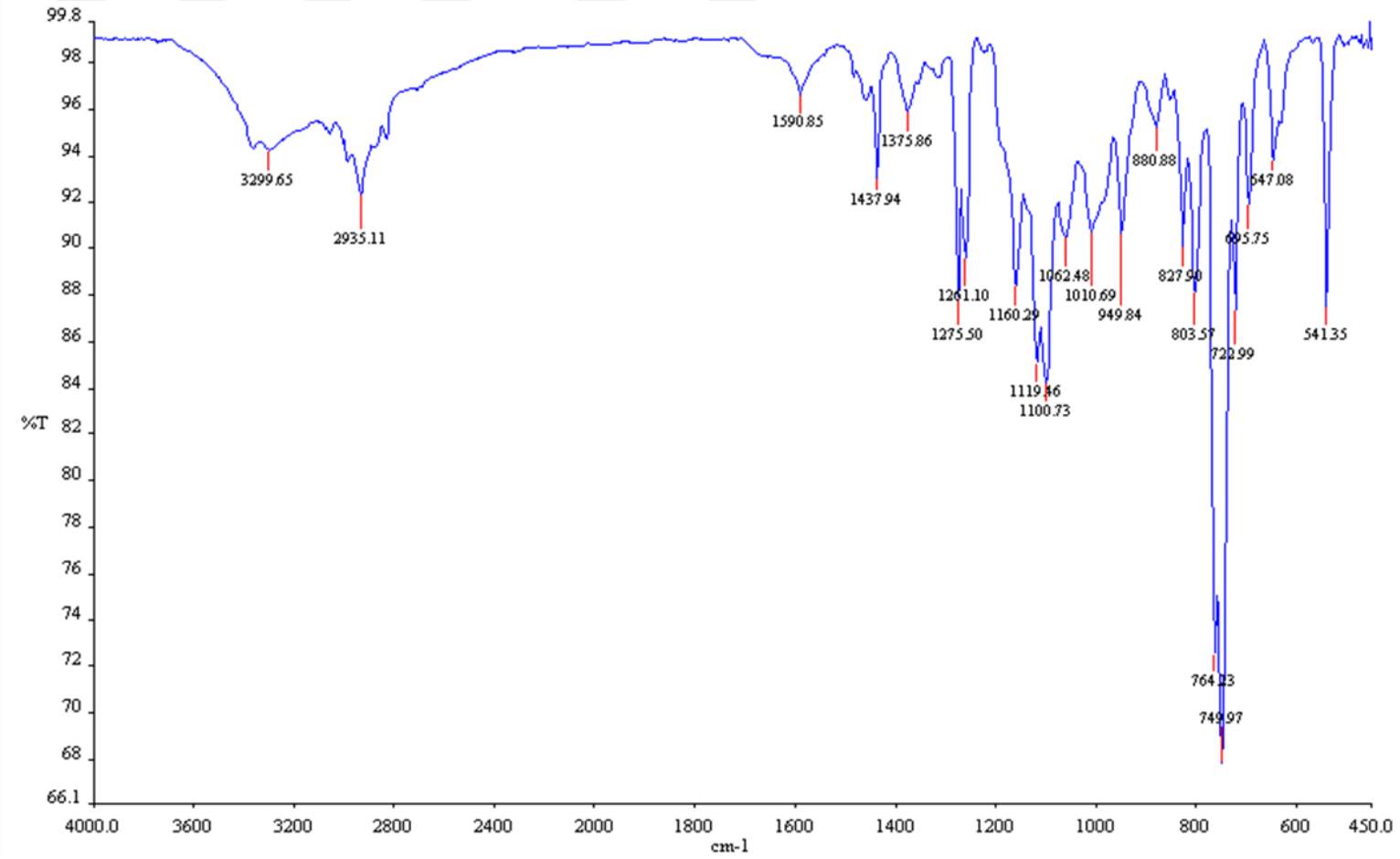


Figure A.5 IR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 4a)

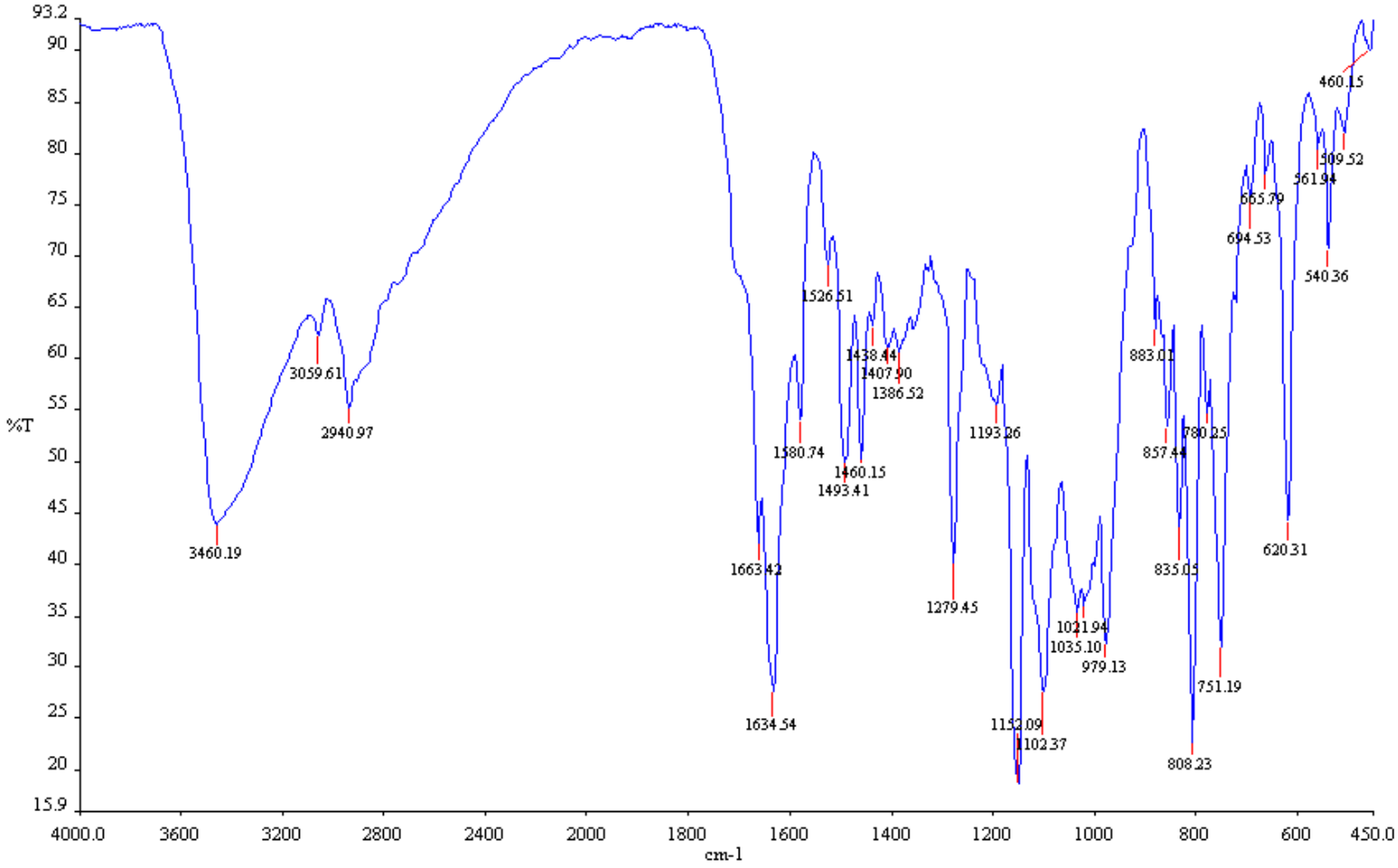


Figure A.6 IR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 4b)

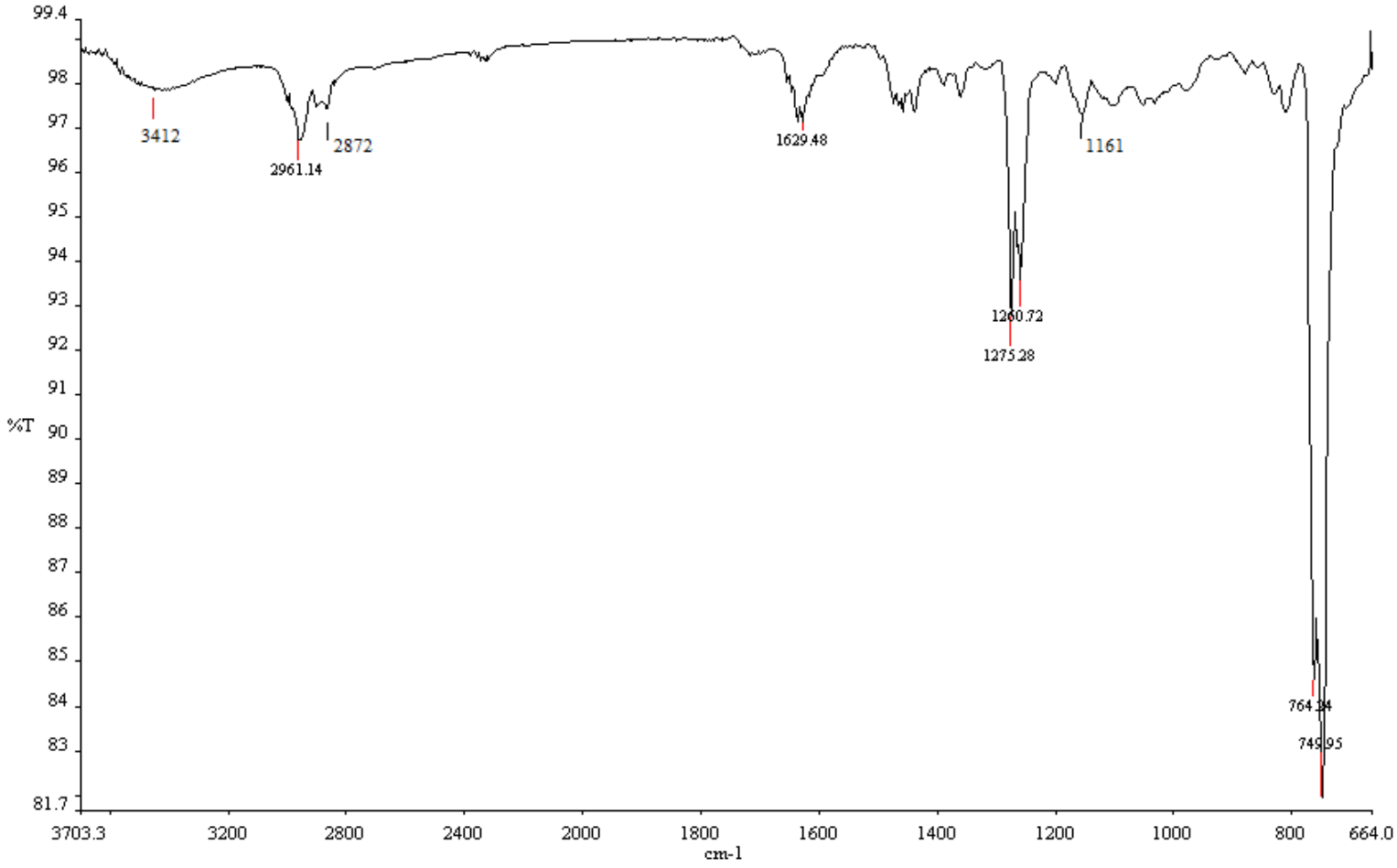


Figure A.7 IR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 10a)

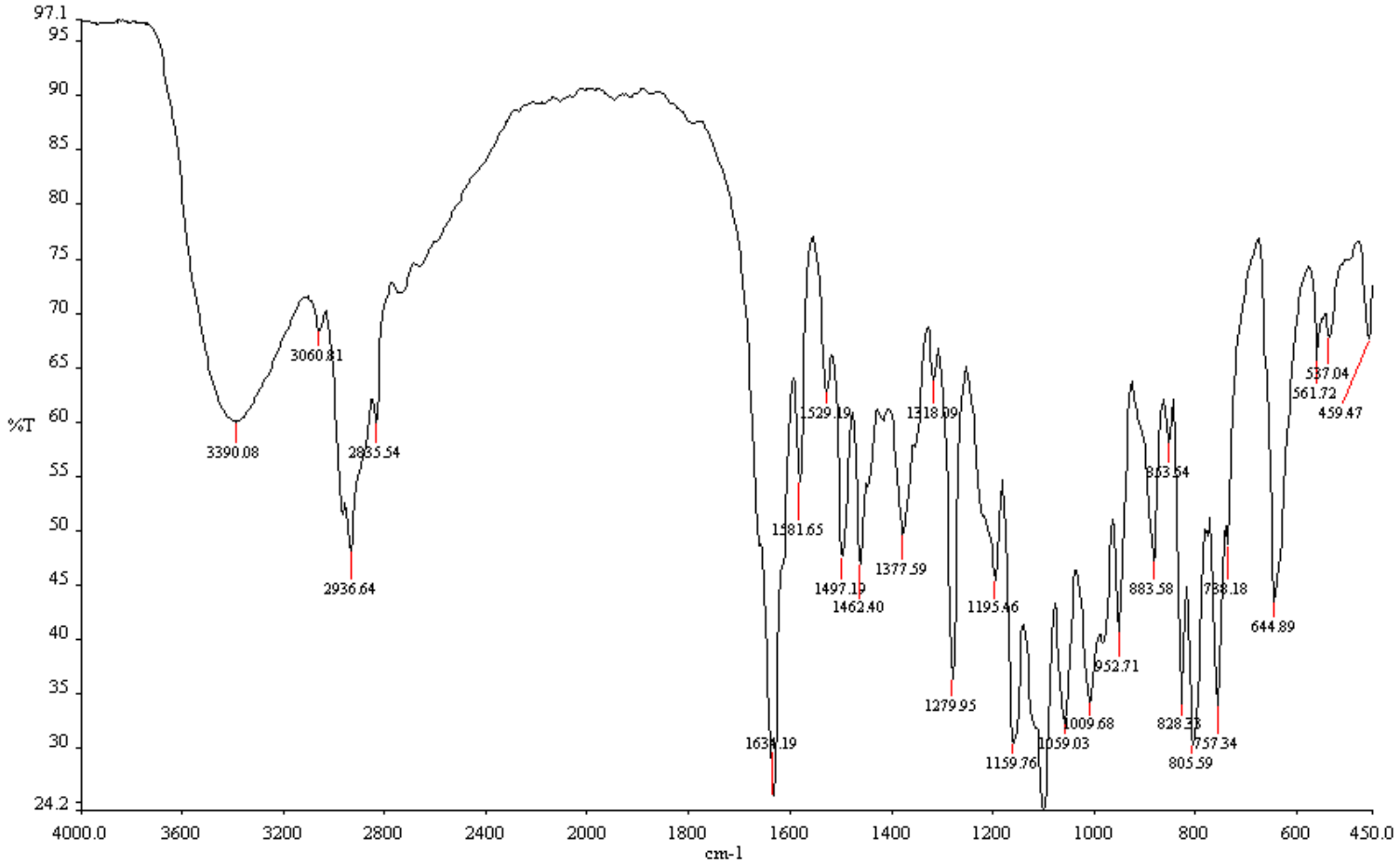


Figure A.8 IR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 10b)

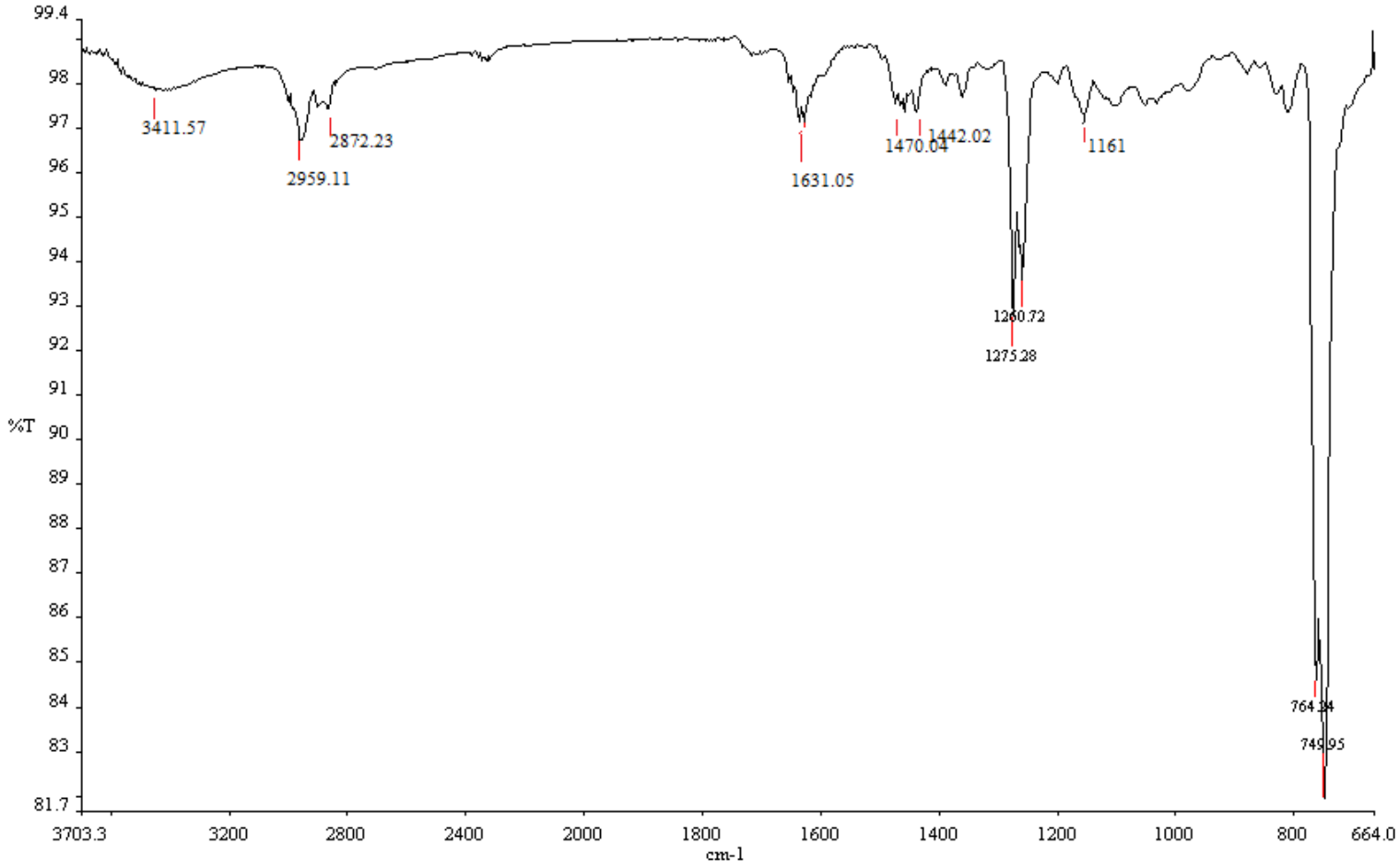


Figure A.9 IR spectrum of 6-deoxy-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-glucofuranose (Compound 14a)

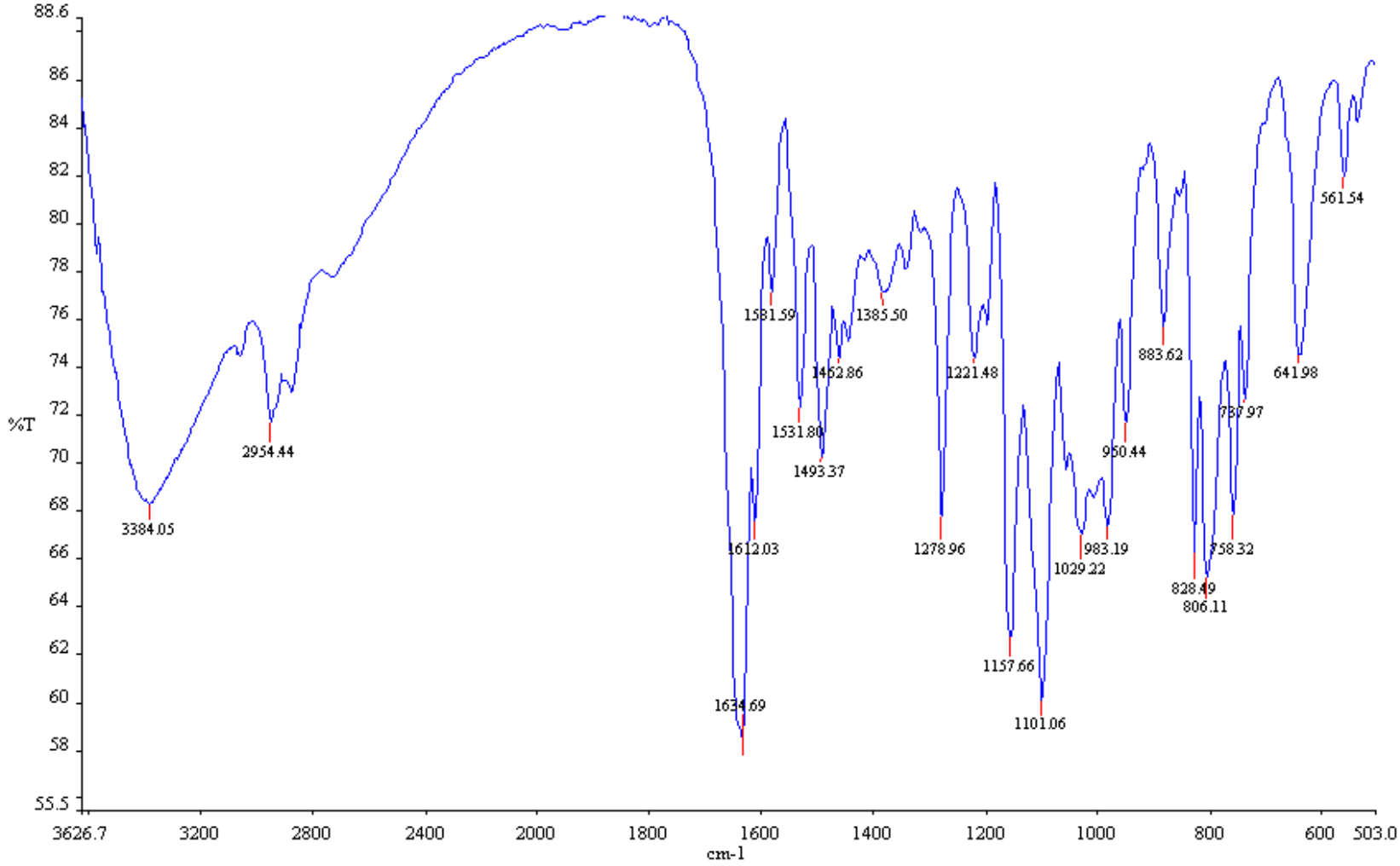


Figure A.10 IR spectrum of 6-deoxy-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl] phenol-α-D-glucofuranose (Compound 14b)

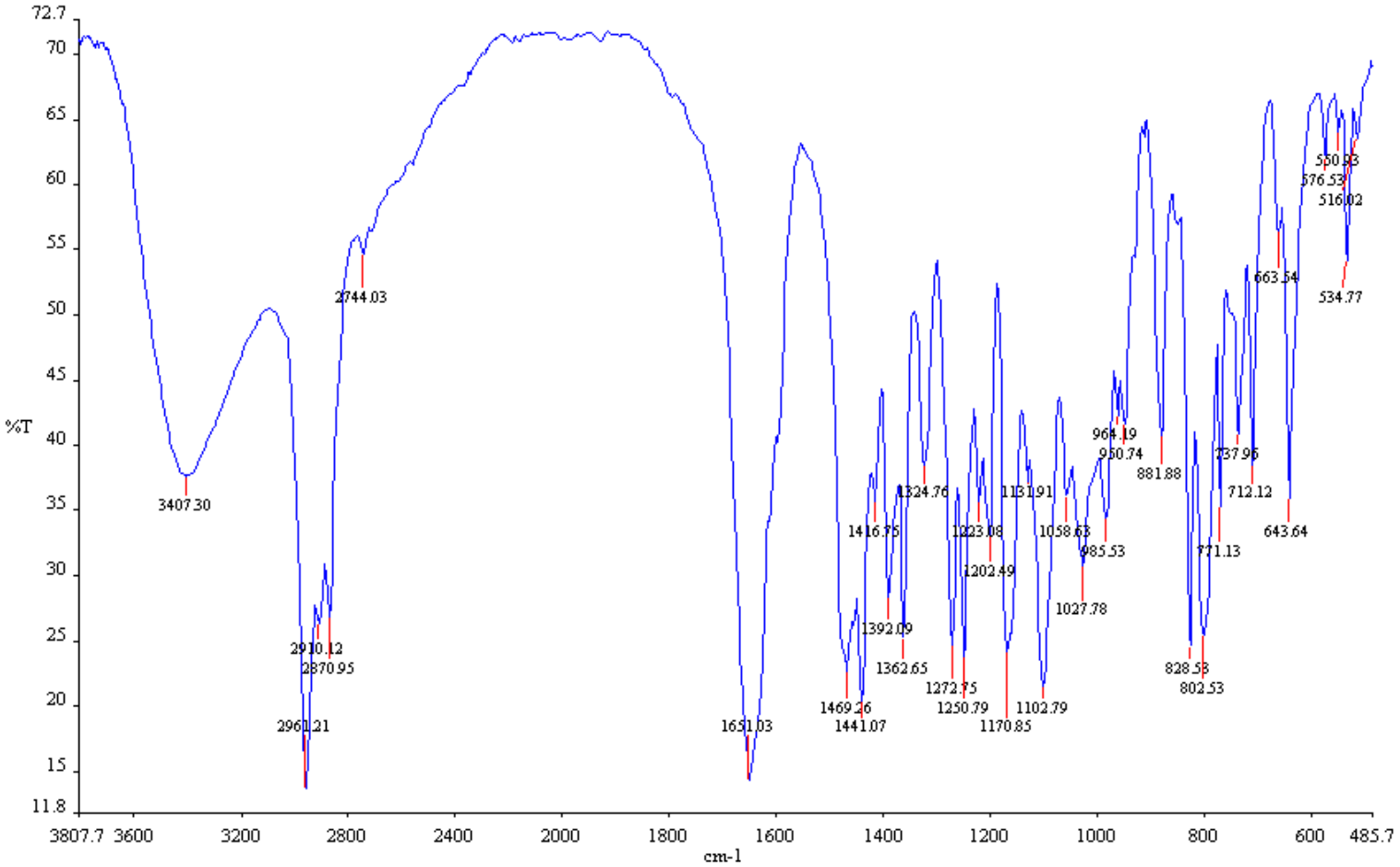


Figure A.11 IR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20a)

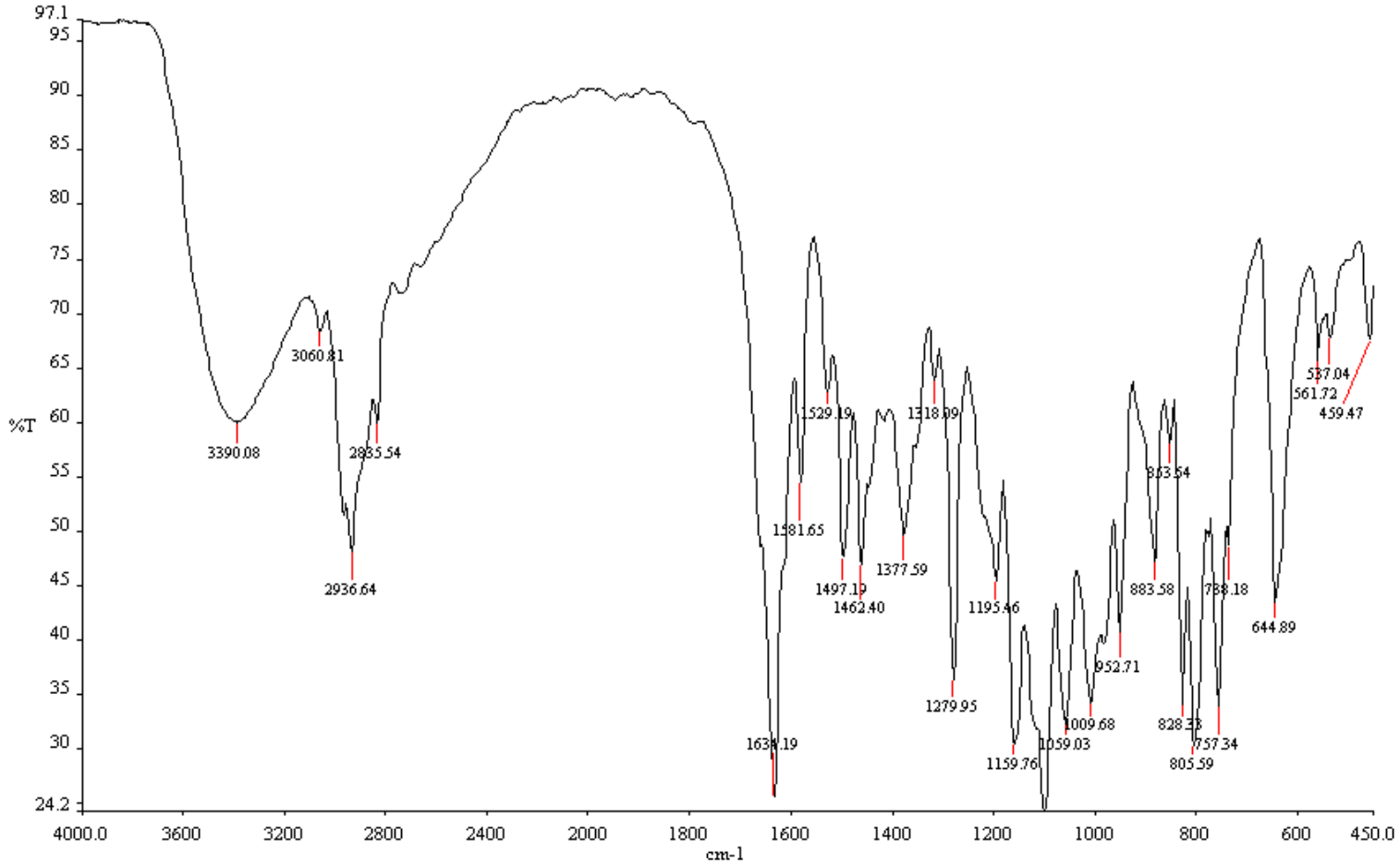
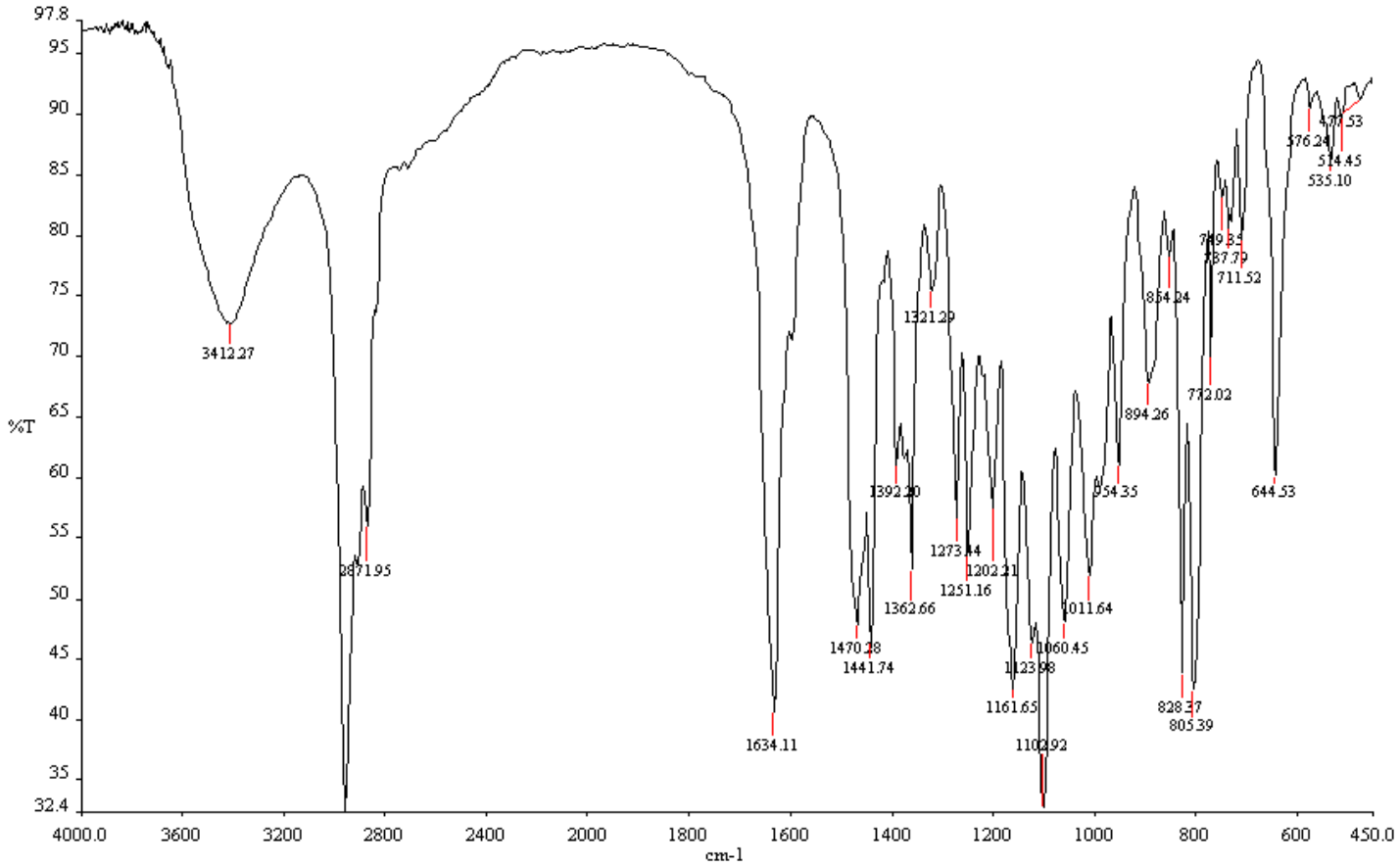


Figure A.12 IR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20b)



APPENDIX B

^{13}C-NMR SPECTRUMS OF THE PRODUCTS

Figure B.1 ^{13}C-NMR spectrum of 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 10)

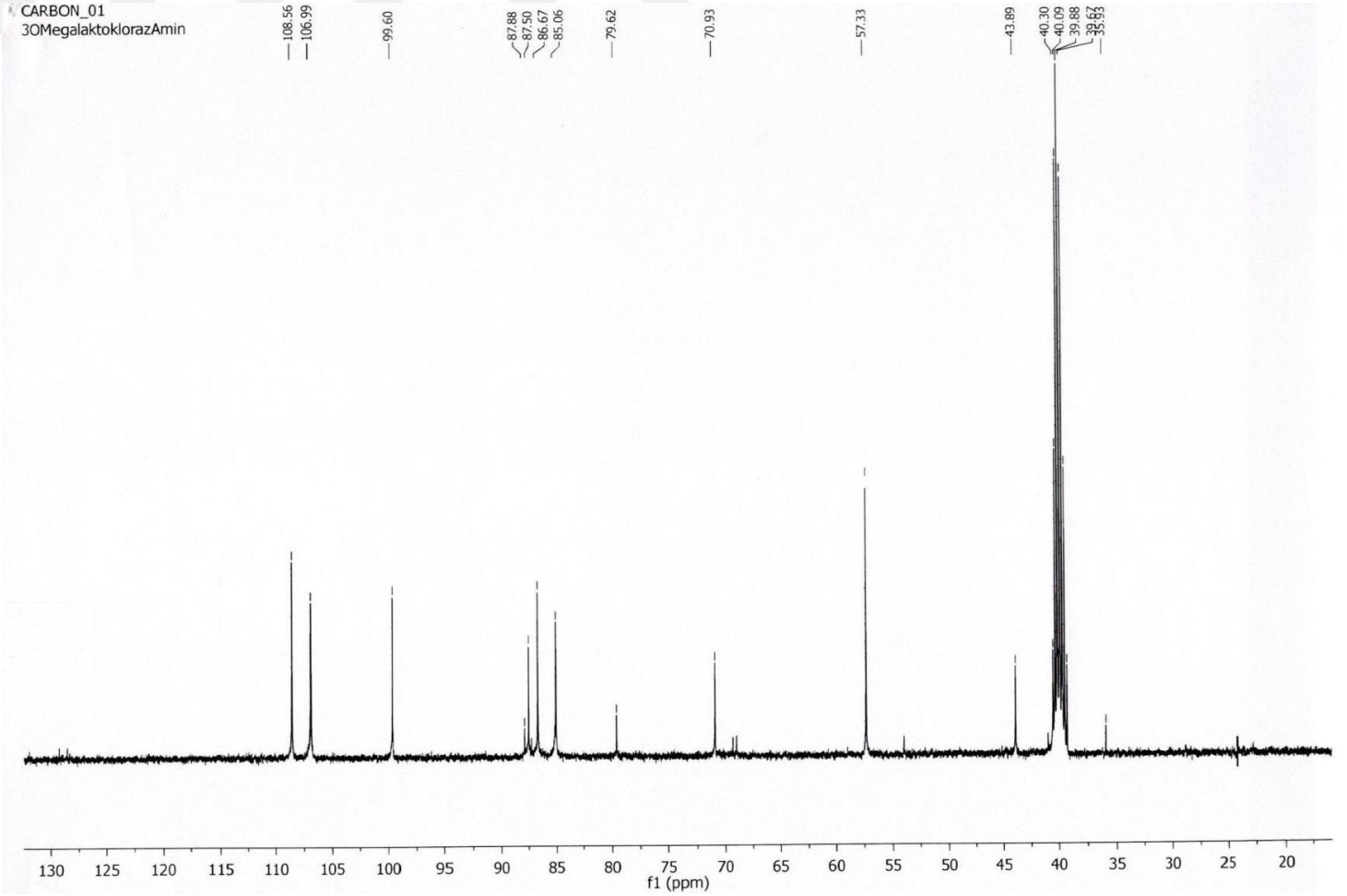


Figure B.2 ^{13}C-NMR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 4a)

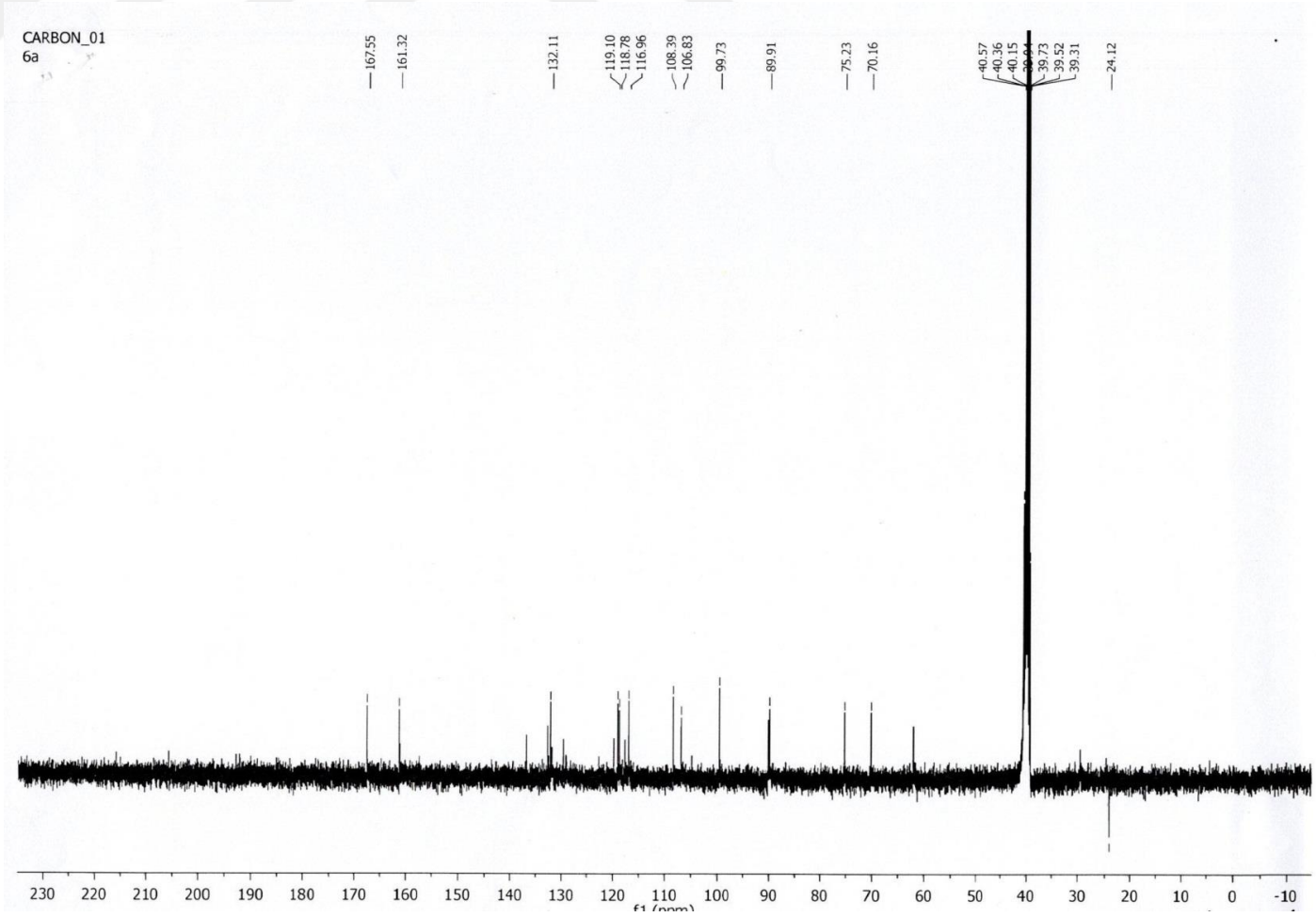


Figure B.3 ^{13}C-NMR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 4b)

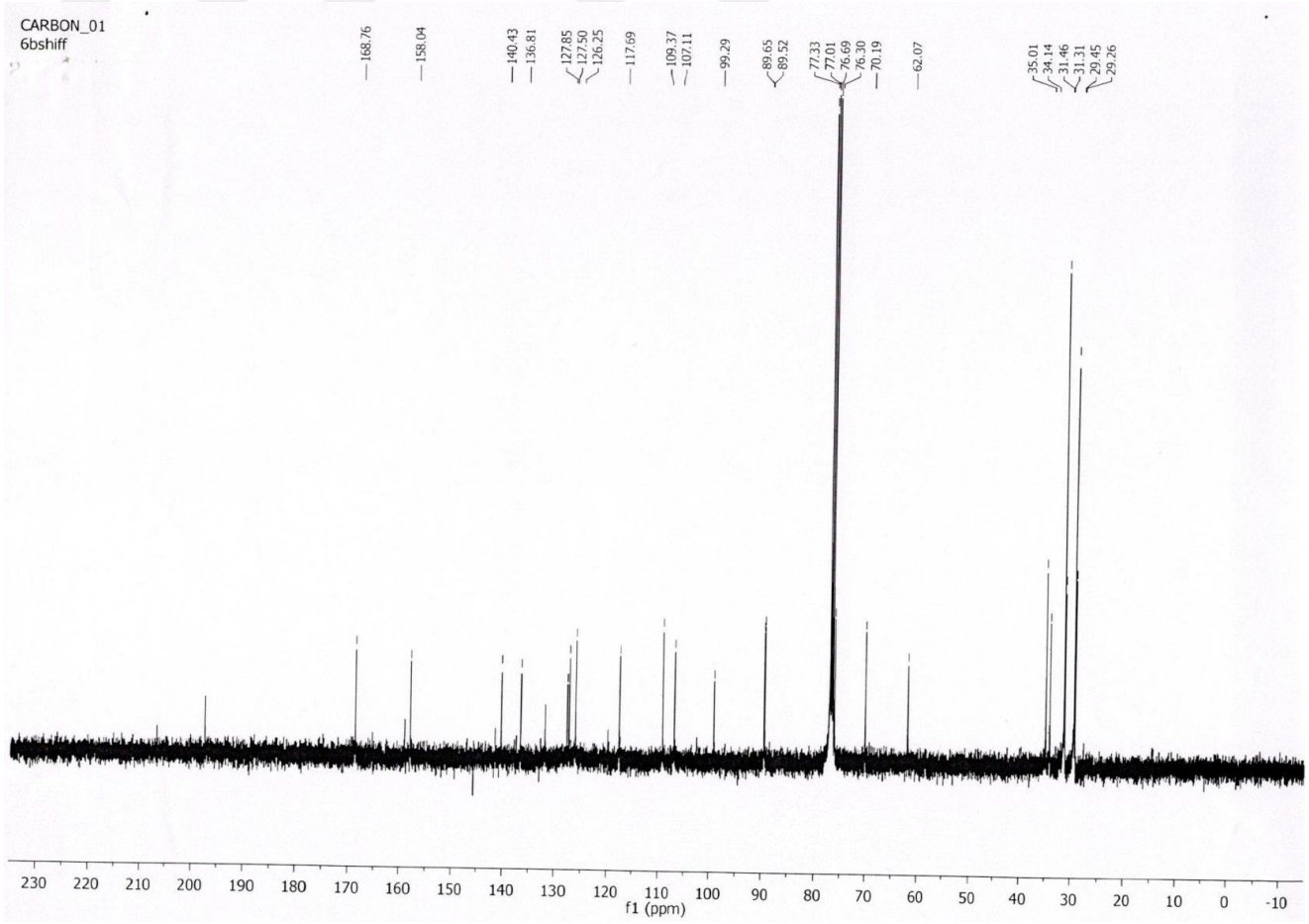


Figure B.4 ^{13}C-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 10a)

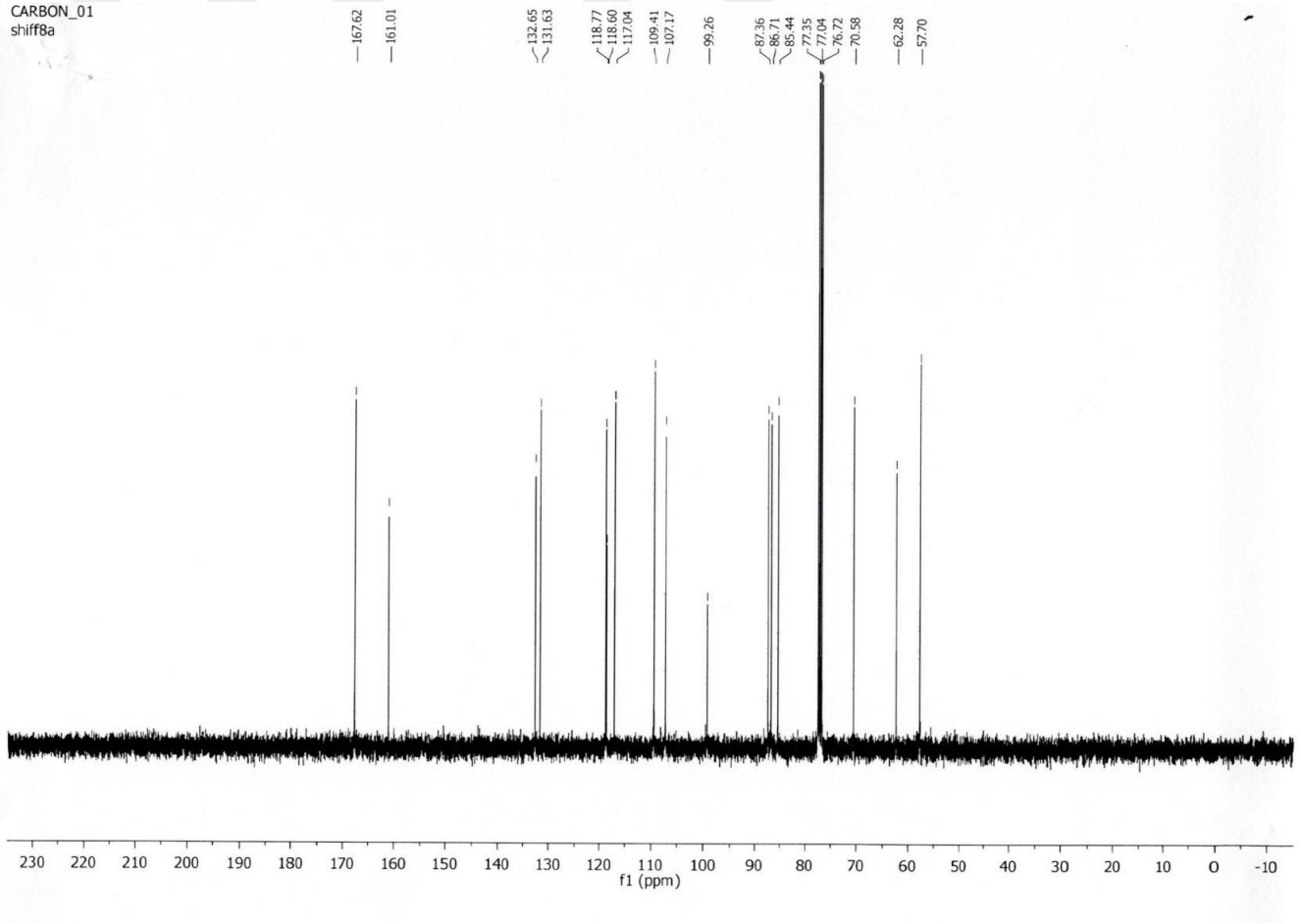


Figure B.5 ^{13}C-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 10b)

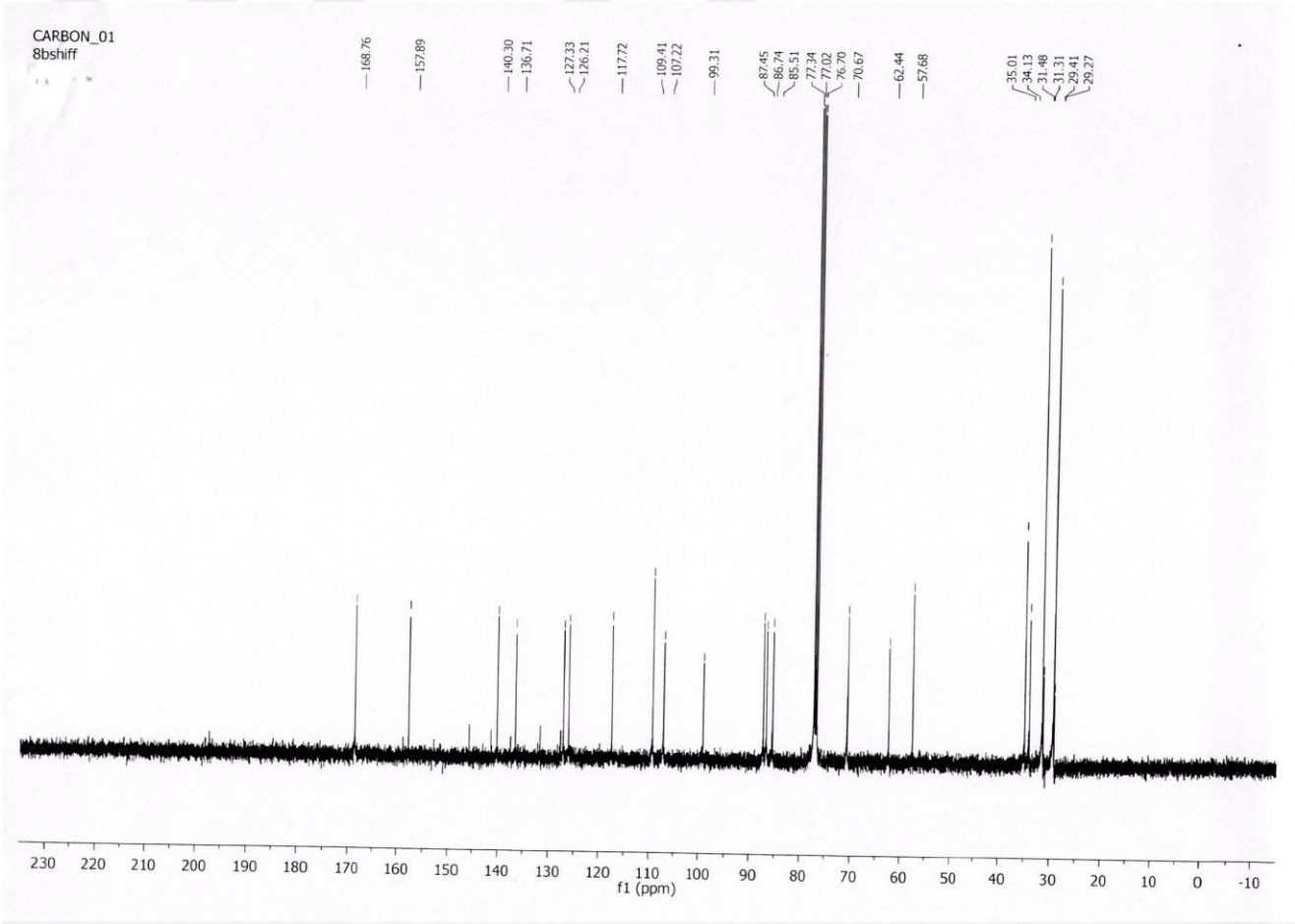


Figure B.6 ^{13}C-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20a)

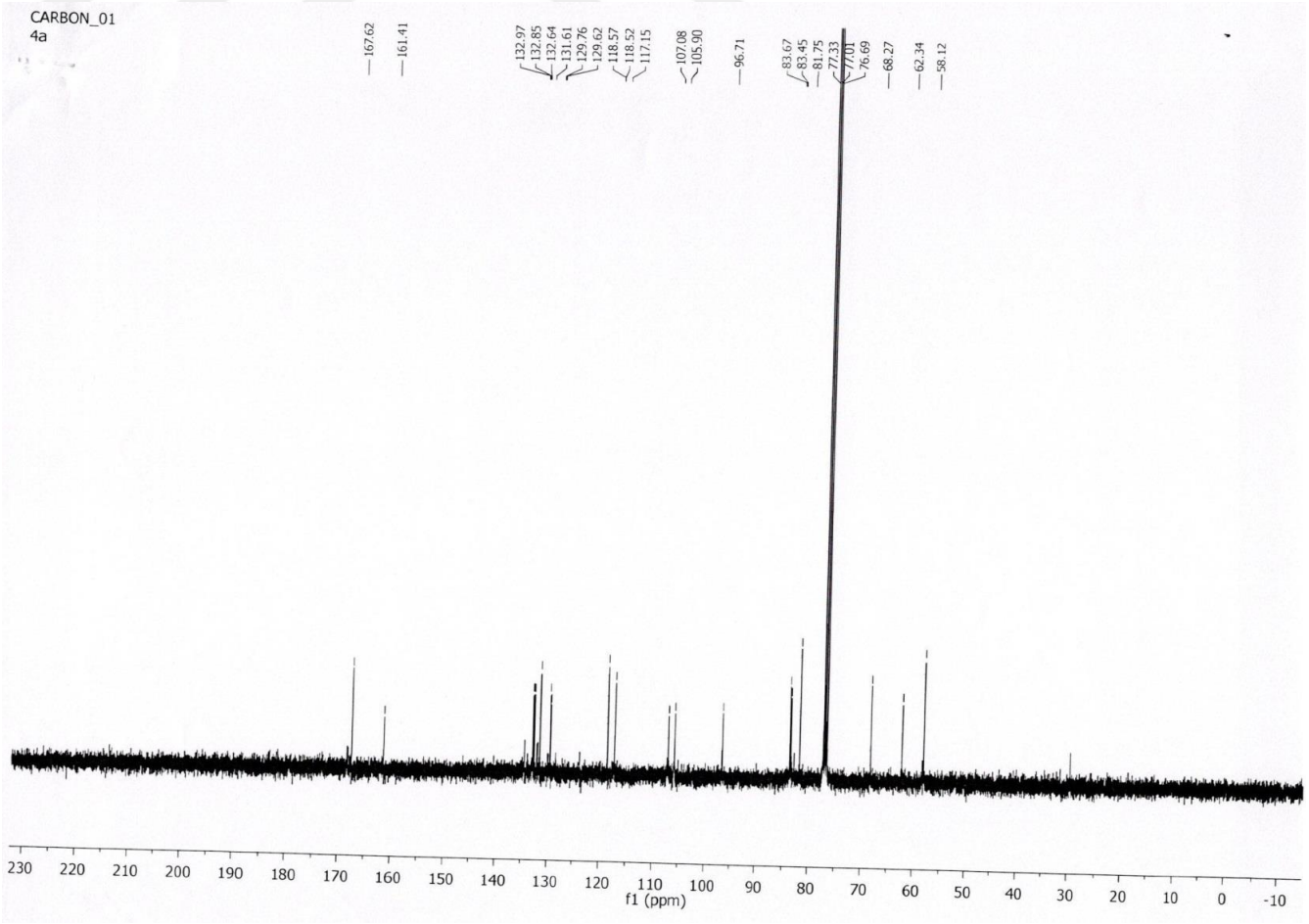
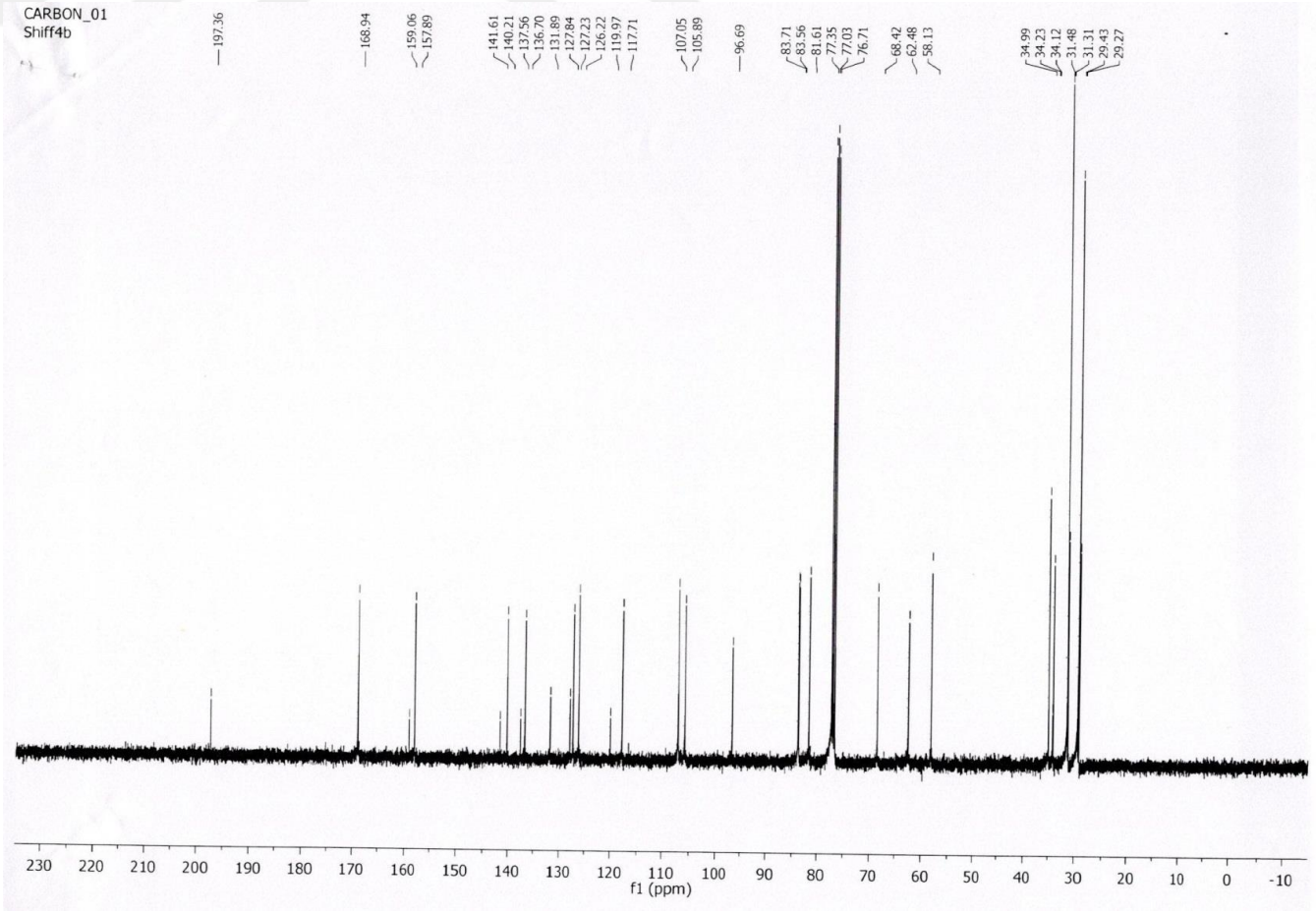


Figure B.7 ^{13}C-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20b)



APPENDIX C

^{1}H-NMR SPECTRUMS OF THE PRODUCTS

Figure C.1 ^{1}H-NMR spectrum of 6-Amino-6-deoxy-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 4)

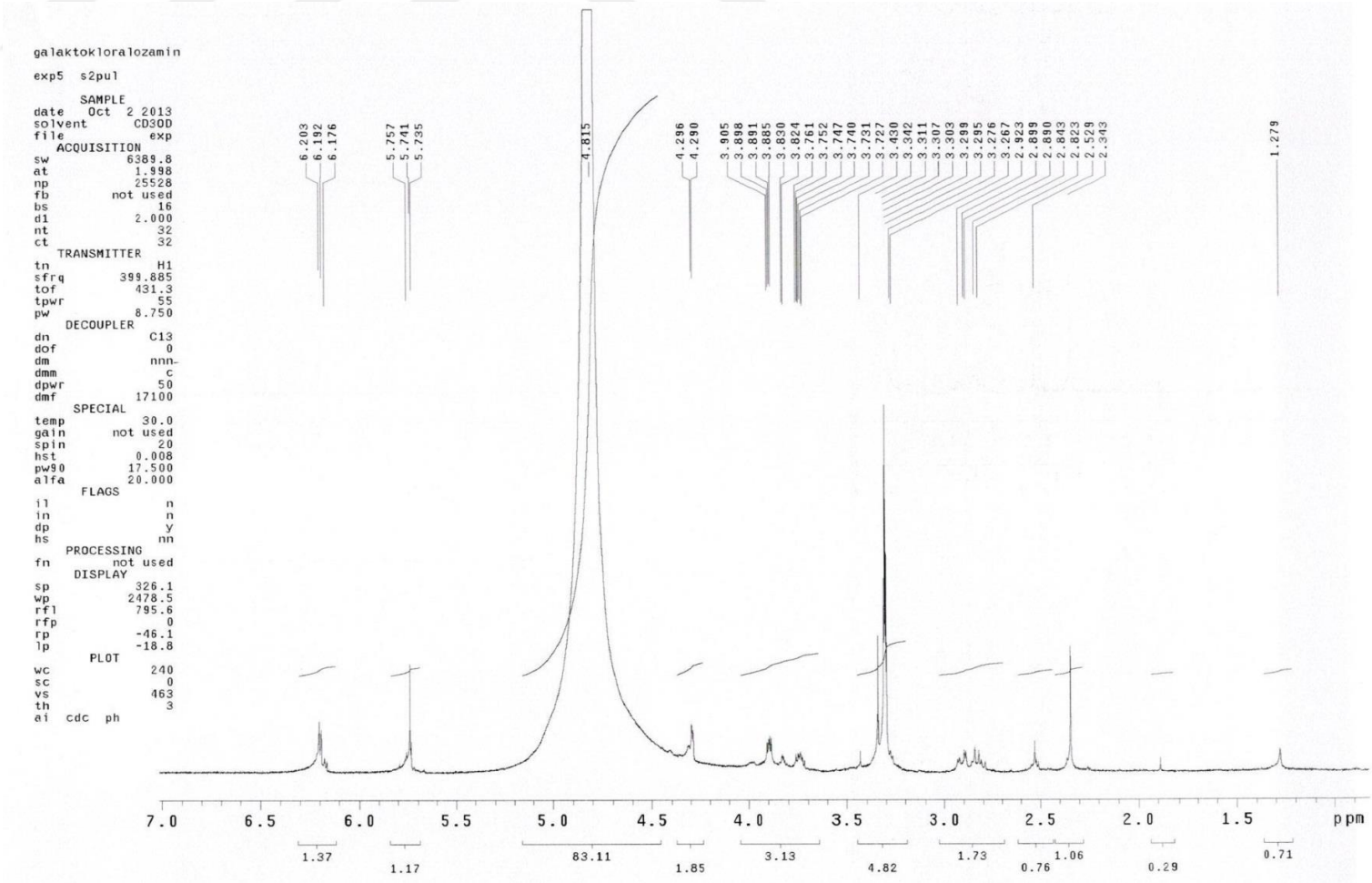


Figure C.2[1]H-NMR spectrum of 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-α-D-galactofuranose (Compound 10)

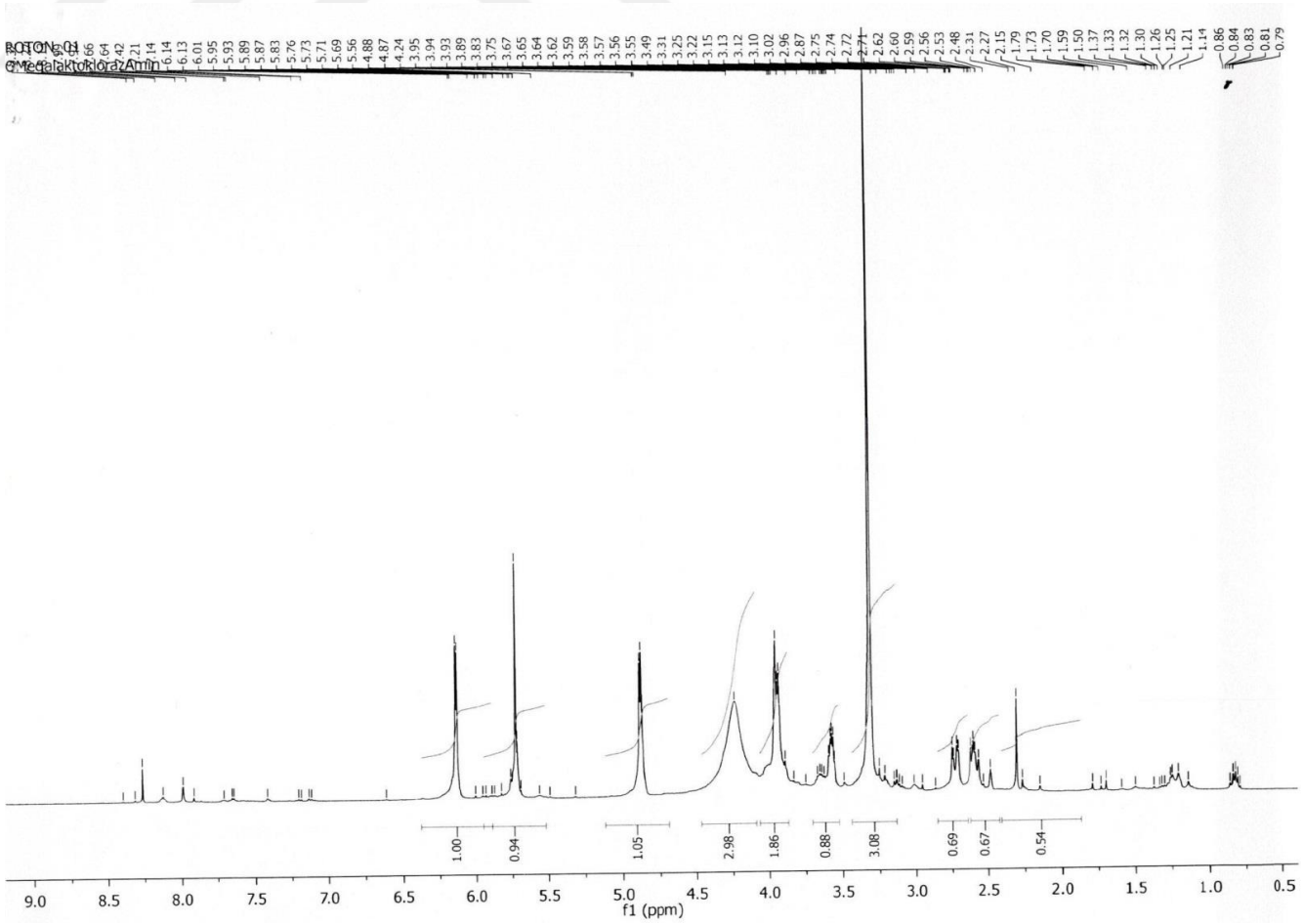


Figure C.3 ^{1}H-NMR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 4a)

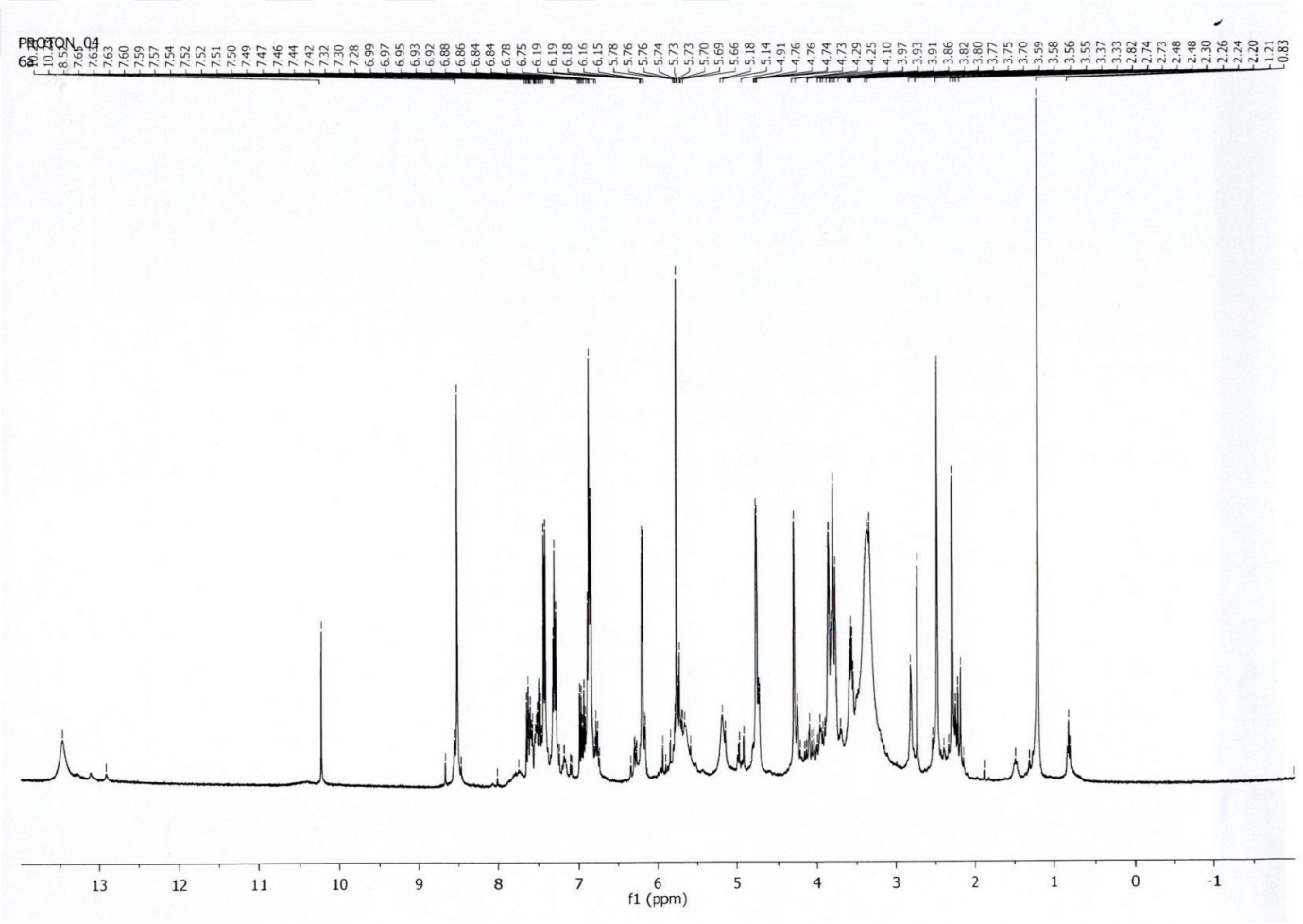


Figure C.4 ^{1}H-NMR spectrum of 6-deoxy-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-galactofuranose (Compound 4b)

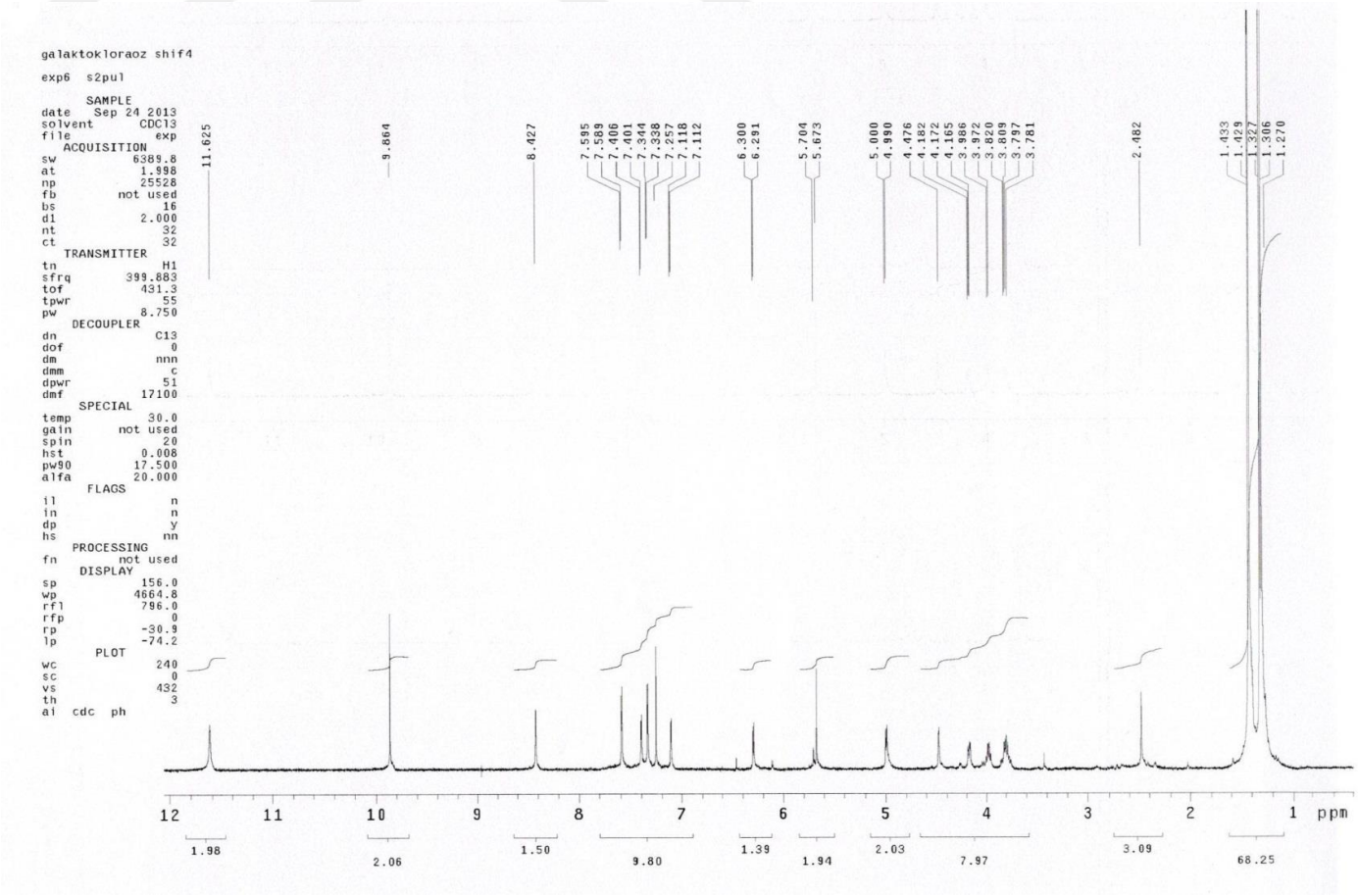


Figure C.5 ^{1}H-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-galactofuranose (10a)

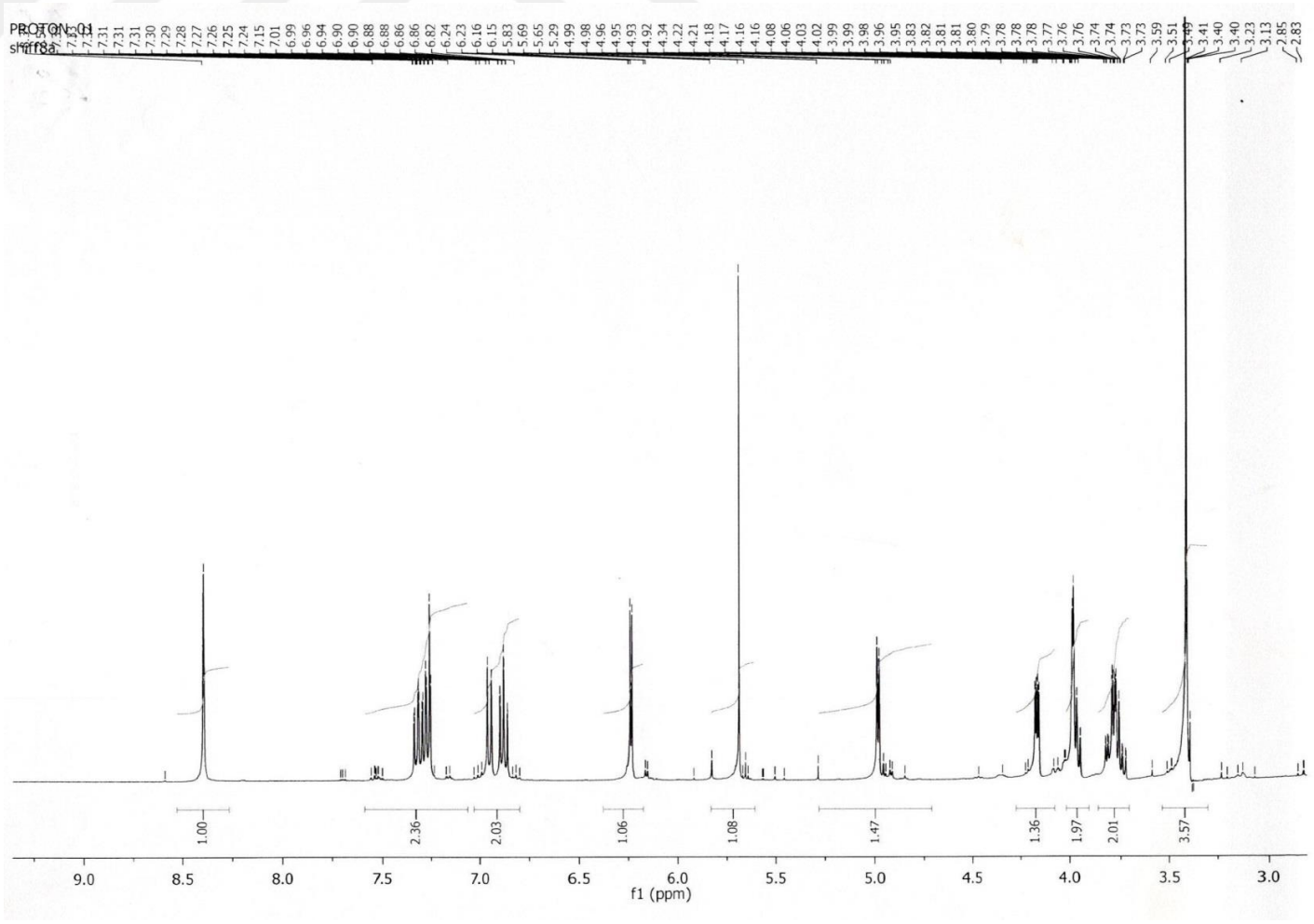


Figure C.6 ^{1}H-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(S)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (Compound 10b)

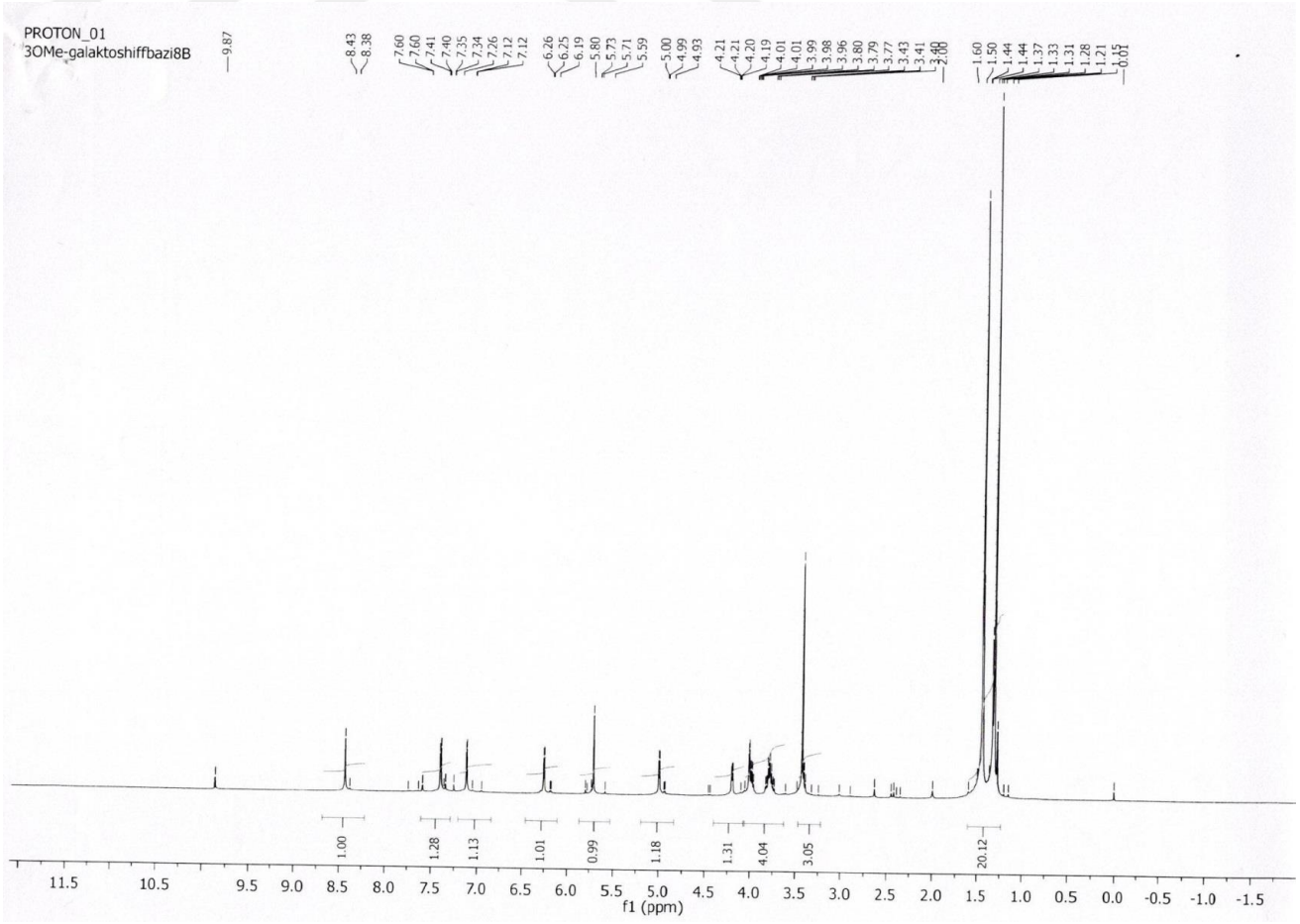


Figure C.7 [1]H-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[(2'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20a**)**

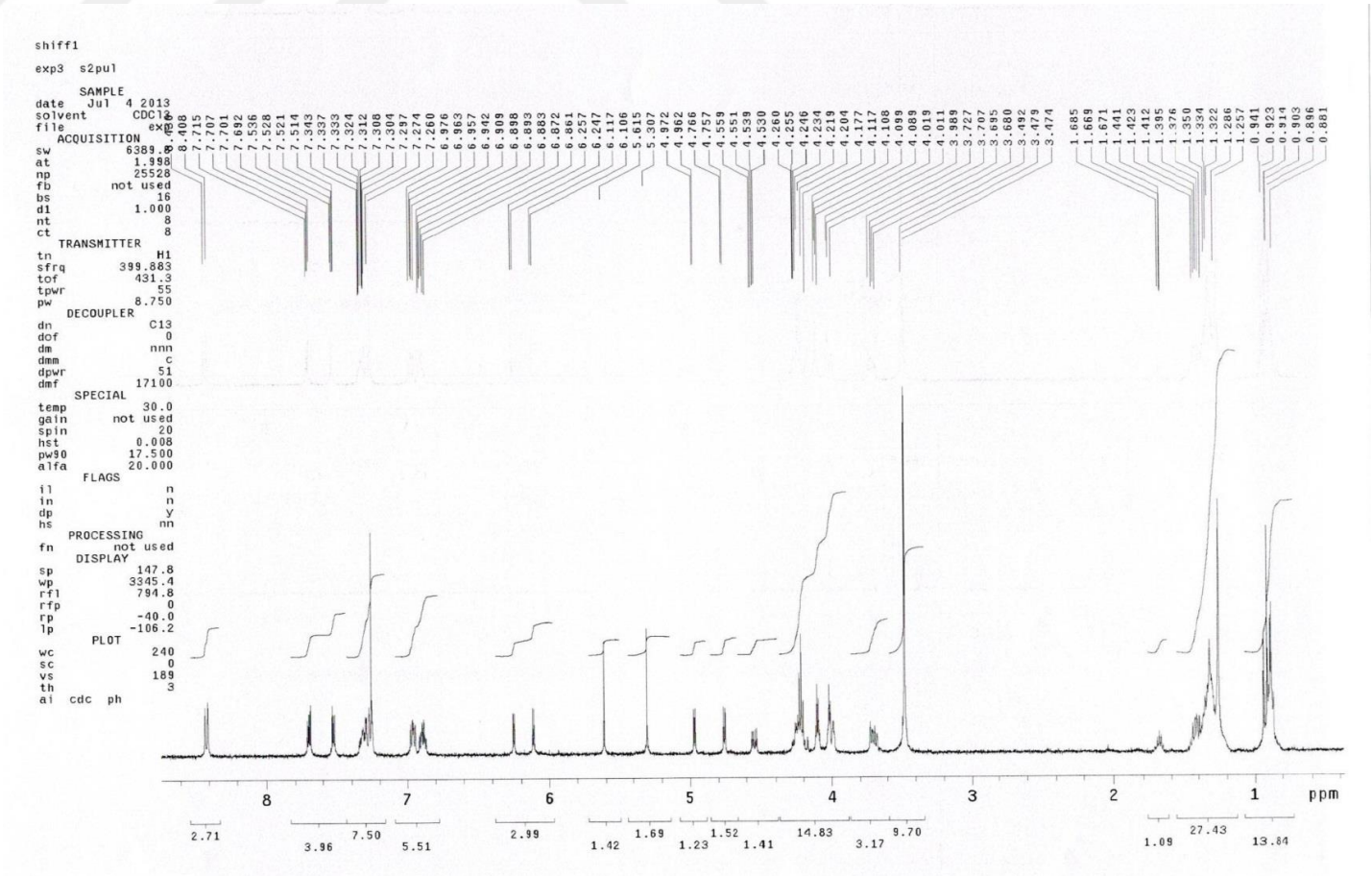


Figure C.8 ^{1}H-NMR spectrum of 6-deoxy-3-*O*-methyl-1,2-*O*-(R)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino) methyl]phenol-α-D-glucofuranose (Compound 20b)