SAKARYA UNIVERSITY
INSTITUTE OF SCIENCE AND TECHNOLOGY

THE SYNTHESIS OF AZIDO AND AMINO CARBASUGARS

M.Sc. THESIS

Khamis ALLY

Department : CHEMISTRY

Field of Science : ORGANIC CHEMISTRY

Supervisor : Assoc. Prof. Dr. Arif BARAN

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This thesis has been accepted unanimously by the examination committee on 04.02.2014

Doç.Dr. Arif BARAN Doç.Dr. Mustafa ÇAĞ Doç.Dr. Şule BARAN

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Head of Jury	**Jury Member**	**Jury Member**

ACKNOWLEDGMENTS

This study was conducted at the Department of chemistry, Institute of natural sciences, Sakarya university, Sakarya from 2012-2014.

First of all I would like to express my feelings of gratitude to my supervisor Doç. Dr. Arif Baran for his skillful guidance, endless patience, encouragement and support throughout this study. It was a great pleasure for me to be a student of him.

I owe my thanks to may lab-mates and who are at the same time Ph.D. students Gokay Aydin, Tahir Savran and Sedat Sevmezler for their valuable assistances, supports and extraordinary work for my NMR spectra through out this study.

I also thank all the staffs of the Department of Chemistry, Faculty of Science and Art, Sakarya University, for their supports.

I would like to express my thanks to Dr. Asena Özer Boztaş, Kurşat Çapraz and Dişlikaya, Çakir, Karakaya families for their valuable supports, without forgetting my Nigerians friends Mohammed H. Abdallah, Saleh Abubakar, Haruna Ali, Mohammed Saidu, Mohammed A. Saban, Mohammed Gambo and Abdıllah Mohammed.

Lastly but mostly, my thanks are devoted to my mother, father and uncles for tolerating, supporting and encouraging me in anything I want to do.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ac_2O	: Acetic anhydride
AcCl	: Acetic chloride
AcOH	: Acetic Acid
br	: Broad
br.s	: Broad singlet
Br_2	: bromine
^0C	: Degree Celsius
d	: Doublet
DBU	: 1,8-diaza-bicyclo[5.4.0]-undec-7-en
dd	: Doublet of doublets
dm	: Doublet of multiplets
Dt	: Doublet of triplets
h	: Hour
$LiAlH_4$	: Lithium Aluminium Hydride
m	: multiplet
NH_2SO_3H	: Sulfamic Acid
OAc	: Acetate
q	: Quartet
rt	: Room temperature
Ra-Ni	: Raney-Nikel
s	: Singlet
THF	: Tetrahydrofuran
TPP	: Tetraphenilporfirin

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ÖZET

Anahtar kelimeler: Siklitoller, karbaşekerler, azido karbaşekerler, amino karbaşekerler

Öncelikle, azido ve amino karbaşekerlerin sentez yöntemine hazır olarak elde edilebilen anhidrit bileşiğinden 83 çıkılarak bir kaç adımda sentezlenen anahtar bileşiğin 90 oluşumu ile başlandı. 90 nolu bileşik etanol içinde azid iyonu ile reaksiyonu 91 ve 92 nolu bileşikleri vermiştir. Bu iki bileşiğin hidrolizi sonucunda 93 ve 94 nolu bileşikler oluşmuştur. Daha sonra 94 nolu bileşiğin hidrojenasyonuyla 95 nolu bileşik elde edilmiştir.

İkinci aşamada 92 nolu bileşikteki furan halkası sülfamik asit içinde reaksiyonu ile açılıp asetillenmesiyle 96 nolu bileşik elde edilmiştir. Daha sonra bu bileşiğin hidrolizi 97 nolu bileşiği vermiştir. Son olarak 97 nolu bileşiğin hidrojenasyonu sonucu 98 nolu bileşik elde edilmiştir.

THE SYNTHESIS OF AZIDO-AMINO CARBASUGARS

SUMMARY

Key words:Cyclictols, carbasugars, azido carbasugars, amino carbasugars

Firstly the method of preparing azido and amino carbasugars with their derivatives began with the formation of the key compound 90 which synthesized after several steps from readily available anhydride compound 83. The compound 90 was reacted with azide ion in etharnol to give compounds 91 and 92, the compounds 91 and 92 were hydrolized to produce compounds 93 and 94, finally a compound 94 was hydrogenized to afford compound 95.

Secondly furan ring of the compound 92 was cleaved by the acetylation reaction in sulfamic acid to produce compound 96 and then hydrolized to give compound 97. Lastly the compound 97 was hydrogenized to afford compound 98.

CHAPTER 1. INTRODUCTION

Since the beginning of organic synthesis, chemists have dreamed of preparing complex molecules in an elegance and efficiency similar to that of Nature. Examination of the chemical building blocks, modes of substrate activation, and biosynthetic pathways in Nature provides insight for achieving similar transformations by chemical synthesis. In doing so, chemists have designed many biomimetic natural product syntheses and biomimetic catalytic processes [1]. Azido and Amino carbasugars are examples of the complex organic molecules which are a subclass of the largely represented family of cyclitols.

Cyclitol is a generic term used to describe polyhydroxy cycloalkanes. Many biologically important molecules and natural products contain polyhydroxylated carbocycles. A number of them have been used as sweeteners, antibiotics, antiviral, antidiabetic, and anticancer agents [2].

Azido and amino cyclitols (carbasugars) are a group of natural products with remarkable biological activities. Over the last years, significant efforts have been made to develop synthetic methodologies directed not only towards their total synthesis but also towards the design of structural analogues with improved or novel biological properties [3].

The aim of this study is to provide a concise update of the relevant methods for the synthesis of azido and amino carbasugars.

CHAPTER 2. GENERAL INFORMATION

2.1. Cyclitols

Cyclitols is the general name used for the polyhydroxy cycloalkanes (Figure 2.1). Cyclitols or carbocyclic polyols have emerged as an important, rapidly expanding and diversified family of bioactive entities that include inositols, conduritols, quersitols and carbasugars among other variants. These molecules are involved in the function and regulation of a number of biological processes, critical for the sustenance of life, such as cellular recognition, signal transduction and selective inhibition of carbohydrate processing enzymes (glycosidases). These attributes make cyclitols and carbasugars desirable substrates for targeting many key pathways that have been implicated in disorders ranging from diabetes to viral infections and cancer. Hence, it is hardly surprising that there has been a sustained interest over the past few decades in synthetic endeavors directed toward creating diversity within the basic framework of these polyhydroxylated entities. Amino substituted siblings of cyclitols and carbasugars, such as 1 and 2, have invoked particular attention in this regard as their scaffolds have proved to be quite promising in drug discovery and development [4].

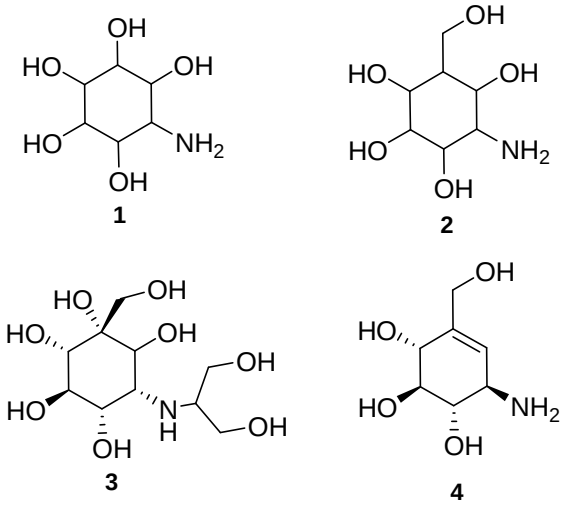


Figure 2.1. Some Cyclitol structures

2.2. Inositols

Inositols (cyclohexanehexols) are sugar-like molecules. There are nine stereoisomers, all of which may be referred to as inositol (Figure 2.2). The most prominent naturally occurring form is *myo*-inositol, *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol, and it is actively involved in cellular events and processes. Other naturally occurring isomers are *scyllo*-, *chiro*-, *muco*-, and *neo*-inositol.

It is assumed that these isomers may be made from myo-inositol by inversion of the configuration (epimerization) of one or two hydroxyl groups [5].

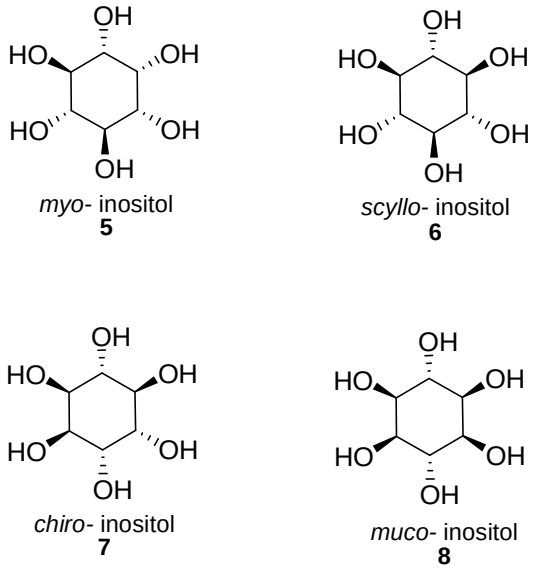


Figure 2.2. Some Inositol isomers

2.3. Conduritols

Conduritols 9–14 (cyclohex-5-ene-1,2,3,4-tetrols) are a class of polyols valuable as starting materials for the synthesis of biologically active compounds. The ten possible stereoisomers, two meso-forms (conduritols A and D) and four couples of enantiomers (conduritols B, C, E and F), have been obtained in enantiomerically pure forms (Figure 2.3). In nature, the occurrence of only two conduritols A and F, has been established [6].

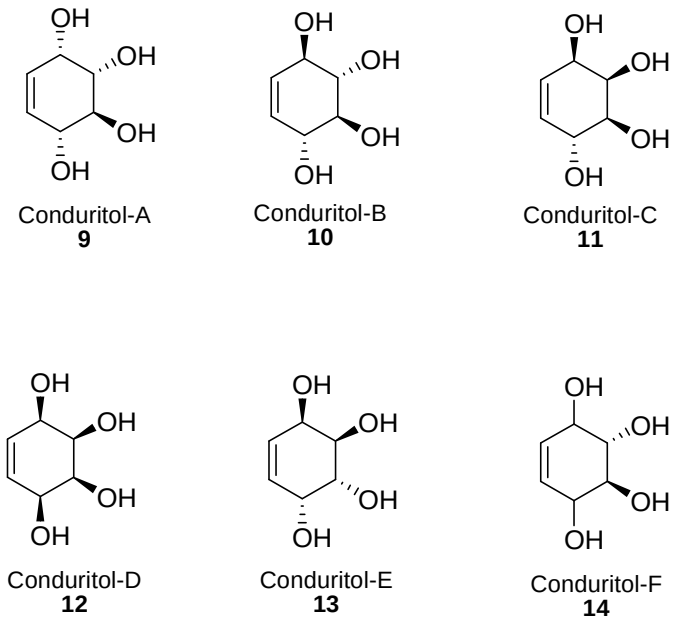


Figure 2.3. Conduritol diastereomers

2.3.1. Aminoconduritols

Conduramines are purely synthetic aminocyclohexenetriols, formally derived from conduritols, in which one of the OH groups is exchanged for an amino moiety (Figure 2.4). Conduramines and their analogues are important intermediates in the synthesis of amino- and diaminocyclitols. Some aminoconduritols have shown interesting inhibitory activities towards glycosidases [6].

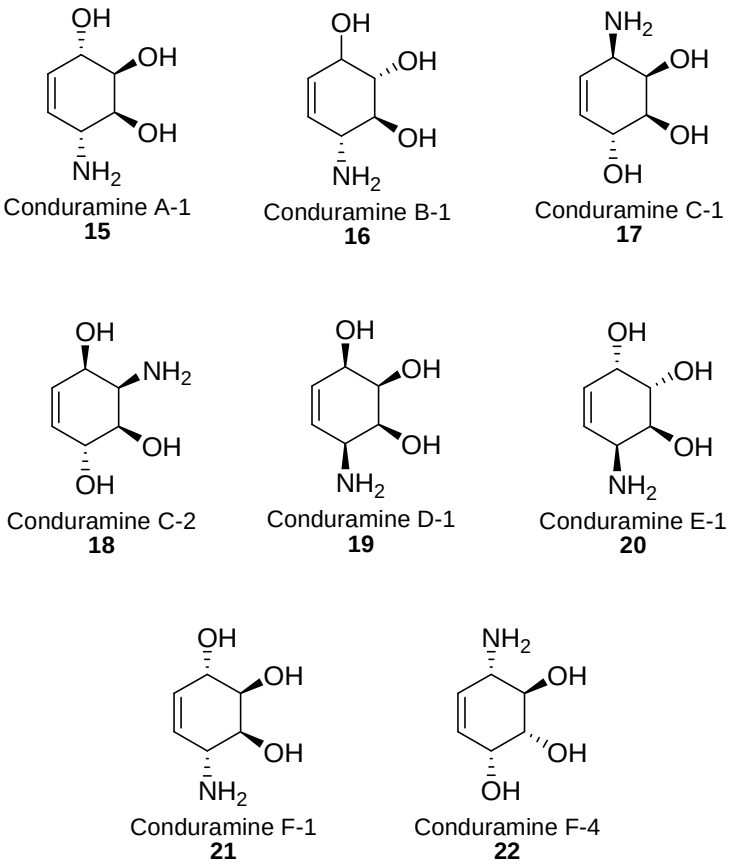


Figure 2.4. Conduramine structures

2.4. Quercitols

Quercitol has been used as a generic term for cyclohexane pentols. Quercitols are basically deoxyinositols and can exist in 16 stereoisomeric forms, of which 4 are symmetric with the 12 others being grouped in 6 pairs of optical images (Figure 2.5). Only three optically active quercitols have so far been found in nature and they only exist in plants [7].

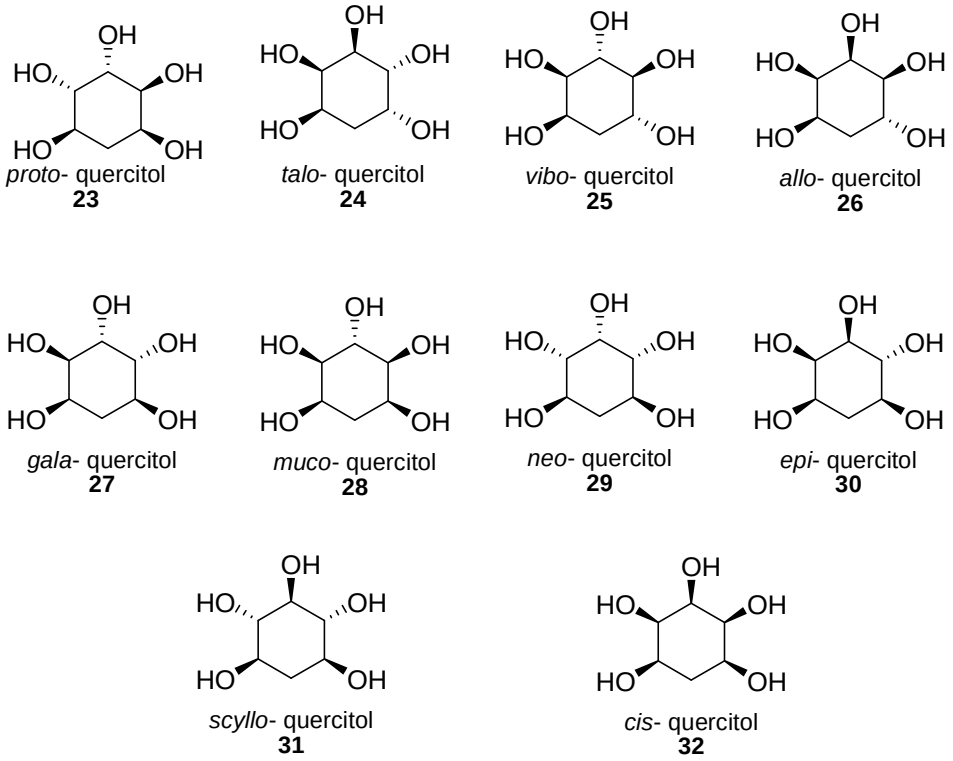


Figure 2.5. Quercitol stereoisomers

2.5. Pseudo-sugars (Carbasugars)

The term carbasugar refers to the carbocyclic analogues of monosaccharides, where the ring oxygen is replaced by a methylene group.

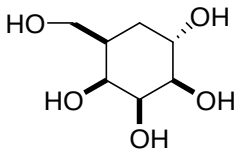
The pseudo-sugars and carba-sugars terms, introduced by McCasland et al. and Ogawa and Suami respectively, to indicate a class of carbocyclic analogues of monosaccharides containing a methylene group in the place of the pyranose ring oxygen atom and showing very important biological activities [8].

McCasland envisioned that his modified carbohydrates would be recognized by enzymes much like carbohydrates, although they would be stable to hydrolysis due to their lack of an acetal or hemiacetal functionality [9].

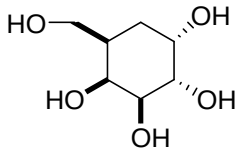
Professor G. E. McCasland's group synthesized 5a-carba-α-DL-talopyranose (33) (the first reported carbasugar), 5a-carba-α-DL-galactopyranose (34), and 5a-carba-α-

DL-gulopyranose (35) (Figure 2.6). It is noteworthy that, 7 years later, 5a-carba-R-D-galactopyranose was isolated as a true natural product from a fermentation broth of Streptomyces sp. MA-4145.1 [10].

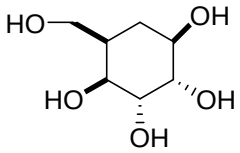
To date, many of the carbasugar analogues of common pyranose monosaccharides have been synthesised. Although carbahexopyranoses and carbapentofuranoses have been extensively studied, carbahexofuranoses are considered to a lesser extent [9].



5a-carba-α-DL-talopyranose
33



5a-carba-α-DL-galactopyranose
34



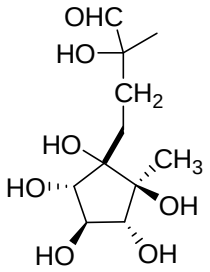
5a-carba-α-DL-gulopyranose
35

Figure 2.6. Carbasugars structures

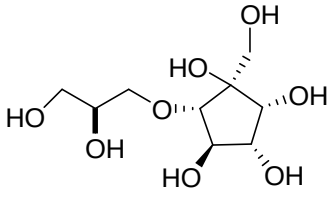
2.5.1. Natural Occurrence of Carbasugars

2.5.1.1. Natural Carbafuranoses

Carbafuranoses have not been found free in Nature but are subunits of products isolated from natural sources, in particular carbanucleosides. These compounds have been the subject of several recent reviews. It should be pointed out, however, that five-membered cyclitols, such as caryose (36) or calditol (37) (Figure 1.7), have been isolated as natural products. No other examples of five-membered carbocyclic carbohydrate analogues from natural sources have been reported [10].



Caryose
36



Calditol
37

Figure 2.7. Naturally occurring carbafuranoses

2.5.1.2. Natural Carbapyranoses

Carbapyranoses have been scarcely found in Nature; however, they are abundant as subunits of other natural products. Compounds such as carba-α-D-galactopyranose (33) (isolated from Streptomyces sp. MA-4145),15 cyclophellitol (38) (isolated from Phellinus sp.) or MK7607 (39) (isolated from CurVularia eragestrides) (Figure 2.8) were isolated directly from natural sources [10].

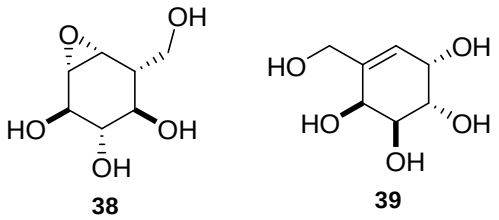


Figure 2.8. Naturally occurring carbapyranose derivatives

2.5.1.3. Azido carbasugars and Amino Carbasugars

Aminocyclitols are a group of natural products of significant relevance in medicinal chemistry, as they are structural components of a variety of antibiotics, glycosidase inhibitors, and other families of biologically active compounds. From a structural point of view, aminocyclitols are cycloalkanes containing at least one free or one substituted amino group and three additional hydroxy groups on the ring atoms. Because of their close structural relationship with sugars, aminocyclitols are also regarded as aminocarbasugars.

Natural aminocyclitols are secondary metabolites foundas structural subunits in some complex natural products, such as validamycins, a family of antibiotics isolated from the fermentation culture of Streptomyces hygroscopicus. A validamycin is composed of one valienamine unit, together with an additional unit variously of validamine, valiolamine, or hydroxyvalidamine (Figure 2.9). The α-amylase inhibitor acarbose is another complex natural product containing an aminocyclitol unit (valienamine), linked in this case to a trisaccharide [3].

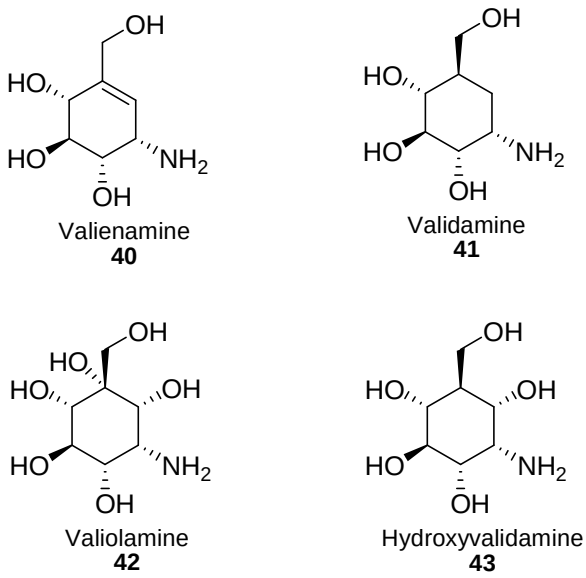


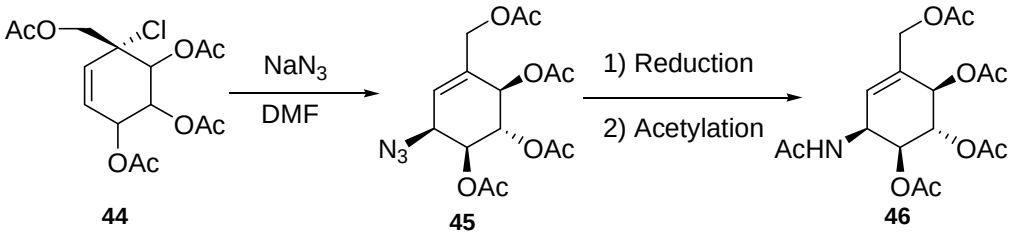
Figure 2.9. Amino carbasugar structures

Aminocarbasugars such as validamine (41) (Figure 2.9) are some of the most important and attractive members of the carbasugar family due to their enzyme inhibitory activity against various glucose hydrolase.

Aminocarbasugars are also constituents of the antibiotic validamycin complexes isolated from the fermentation broth of streptomyces hygroscopicus subsp. limonenus, which shows growth inhibition activity against bacterial diseases of rice plants [11].

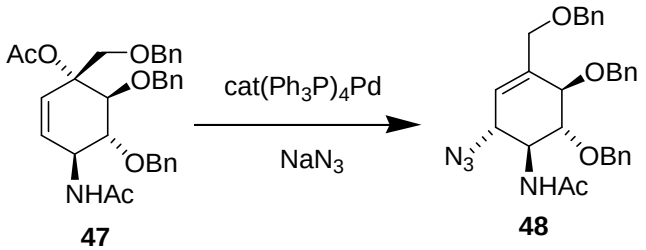
At the same time speaking about azido carbasugar, is the kind of carbasugar which contain azido group instead of amino group. Yet there are no much studies in the lituretures concerning azido carbasugars than amino carbasugars. In this study firstly azido carbasurgars are synthesized then by hydrogenizing them amino carbasugars are formed.

2.6. Synthesis of some azido cyclitols (azido carbasugars) and their derivatives from literatures



Scheme 2.1. Azidocyclitol by S_N2' displacement of an allylic chloride.

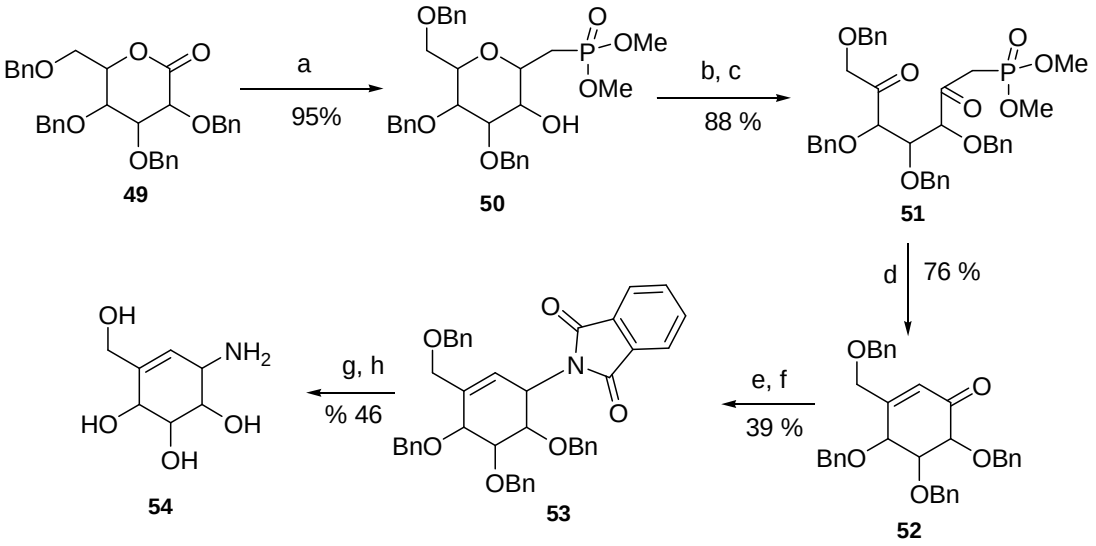
Nucleophilic displacement of an activated inositol derivative by a nitrogen nucleophile is a widely used method for the synthesis of aminocyclitols. In a very straightforward approach, a racemic 1, -diaminoinositol was obtained by nucleophilic S_N2 displacement from a protected inositol bismesylate. A similar approach has been used in the synthesis of aminocarbasugars from precursors originating from rearrangement of norbornyl derivatives, 2-deoxy-streptamine analogues, and several mono- and diazido and –amino inositols, and also to prepare a deuterated valiolol analogue for biochemical studies. Examples of S_N2' displacements have been described, as in the synthesis of paracetylated valienamine reported by Ogawa et al. from allylic chloride 44 and sodium azide (scheme 2.1) [3].



Scheme 2.2. Azidocyclitol by Azidocyclitols (azidocarbasugars) by palladium-catalyzed allylic amination.

The Pd-catalyzed reaction of sodium azide with a suitable allylic acetate(47) to give allylic azide (48) [3].

2.7. Synthesis of some aminocyclitols (amino carbasugars) and their derivatives from literatures

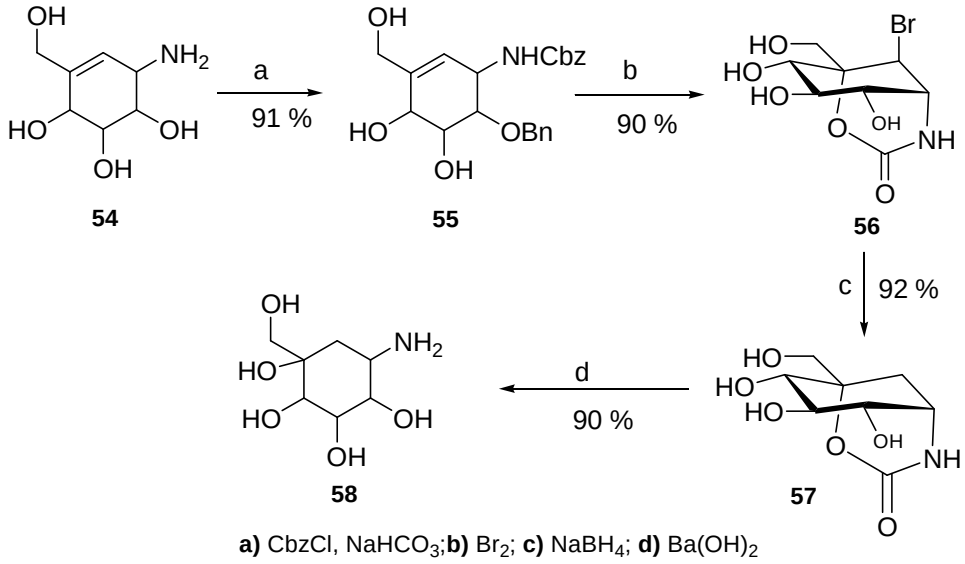


a)$(MeO)_2P(O)CH_2Li$; **b)** $NaBH_4$,; **c)** DMSO, TFAA, Et_3N; **d)** K_2CO_3, 18-crown-6; **e)** $NaBH_4$,$CeCl_3$
f) Phthalimide, DEAD, Ph_3P; **g)** H_2NNH_2,H_2O; **h)** Na, liq. NH_3.

Scheme 2.3. Synthetic route of valienamine (54) from gluconolactone (49)

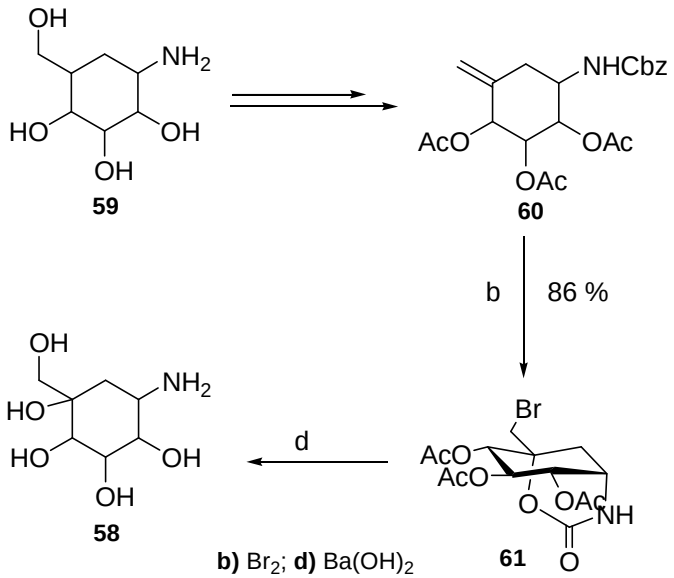
Meanwhile, Fukase and his colleagues focused on developing a practical way of synthesizing 54 from an inexpensive starting material . First, tetra-O-benzylated D-glucono-1,5-lactone (49) was treated with lithium dimethyl methylphosphonate to afford phosphoryheptulose (50), which was once reduced with sodium borohydride and successively oxidized with DMSO and trifluoroacetic anhydride in the presence of triethyl amine to give 2,6 heptodiulose 51. A subsequent intramolecular Horner-Emmons reaction with potassium carbonate and 18-crown-6 yielded the branched unsaturated inosose 52. Luche reduction of 52 using sodium borohydride and cerous chloride, followed by substitution of the newly generated hydroxyl group with phthalimide under the Mitsunobu condition gave the fully protected target molecule 53 Removal of the phthaloyl group with hydrazine hydrate and benzyl group by Birch reduction afforded 54 (Scheme 2.3) [12].

Route 1



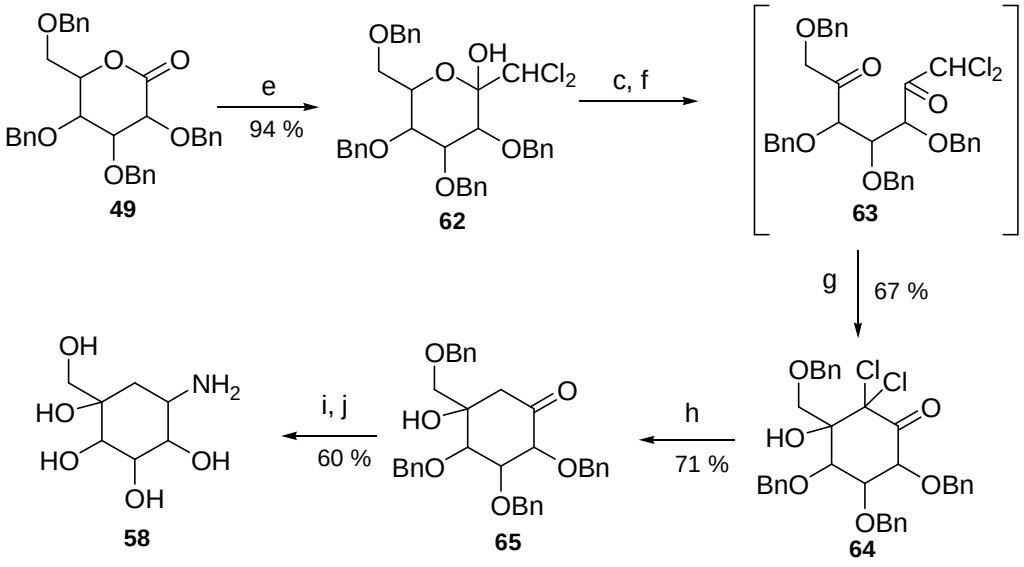
Scheme 2.4. Synthetic route 1 of valiolamine (58)

Route 2



Scheme 2.5. Synthetic route 2 of valiolamine (58)

Route 3



c) $NaBH_4$;**e)** $LiCHCl_2$; **f)** DMSO, TFAA, Et_3N; **g)** base, THF
h) n-Bu_3SnH, AIBN; **i)** NH_2OH, Raney Ni; **j)**Pd, HCO_2H

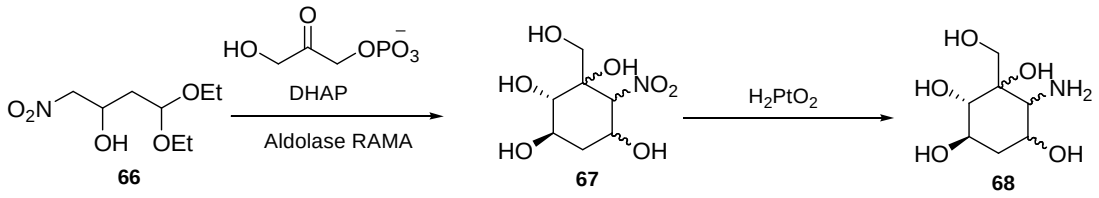
Scheme 2.6. Synthetic route 3 of valiolamine (58)

The valiolamine (58) was prepared by three different routes. The first method (route 1) was started with protection of the amino group of 54 with Cbz chloride, followed by the treatment of N-protected valienamine (55) with bromine to afford oxazoline (56). Reduction of 56 with sodium borohydride, and successive hydrolysis with barium hydroxide gave 58 (Scheme 2.3).

The second method (route 2) was similar to the first one except for starting with validamine (59) (Scheme 2.4).

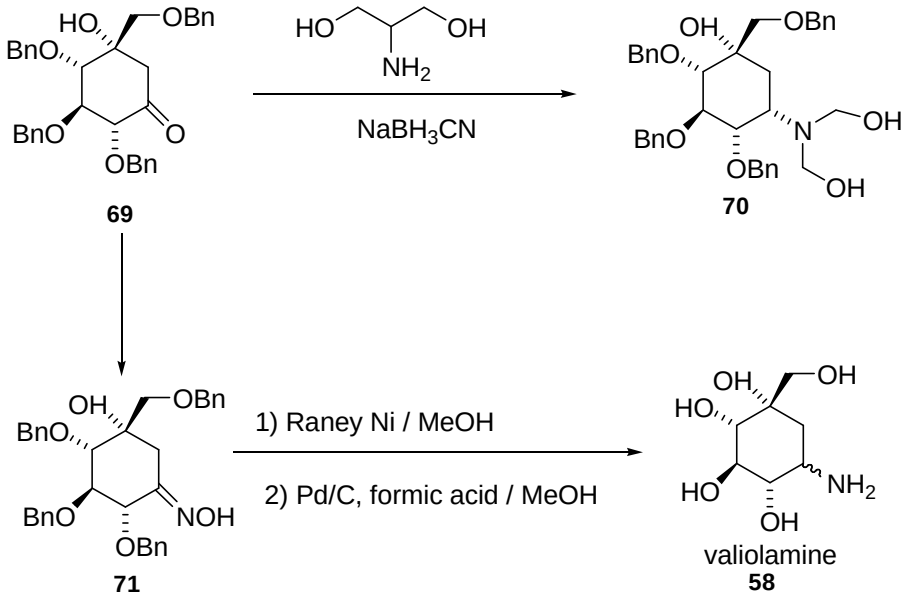
The third method (route 3) applied to the synthesis of labeled compounds started with gluconolactone (49). Namely, 49 was treated with dichloromethyllithium to afford 62, which was once reduced with sodium borohydride and oxidized. After treating the reaction residue, which should mainly contain 63, with a base to facilitate intramolecular aldol condensation, the geminal dichloro methylene group of the cyclized compound 64 was reduced with tri-butyltin hydride to give 65. Reductive

amination of 65 with hydroxylamine in the presence of Raney-Ni, followed by debenzylation by catalytic hydrogenation yielded 58 (Scheme 2.5) [12].



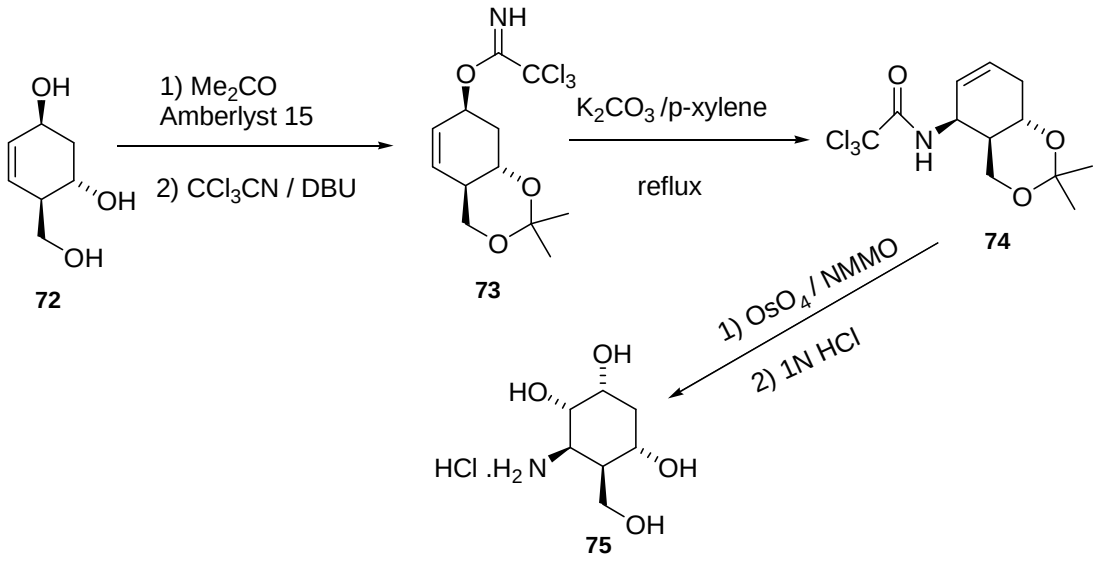
Scheme 2.7. Intramolecular chemoenzymatic nitroaldol condensation

Another noteworthy contribution to the field is the nitroaldol-type intramolecular cyclization between a masked 3-hydroxy-4-nitrobutyraldehyde 66 and dihydroxyacetone phosphate (DHAP) catalyzed by fructose-1,6-bisphosphate aldolase (RAMA) (Scheme 2.6). This transformation was applied to the synthesis of the diastereomeric mixture of nitrocyclitols 67, which were separated and reduced to the corresponding aminocyclitols 68, structural analogues of the glycosidase inhibitor valiolamine [3].



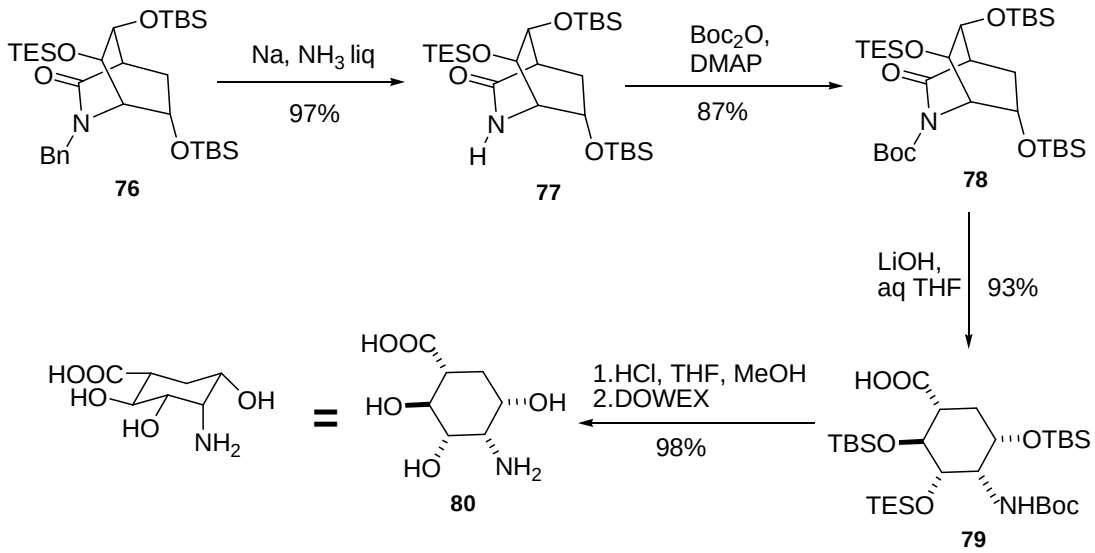
Scheme 2.8. Aminocyclitols (amino carbasugars) by reductive amination of cyclohexenones and ketoxime reduction.

In one of the synthesis of valiolamine and several N-substituted derivatives, reductive amination of a functionalized cyclohexanone derivative 69 in the presence of $NaBH_3CN$ allowed the introduction of an alkylamino side chain with total stereocontrol through attack of the reducing agent on the less hindered side of the intermediate Schiff's base. However, ketoxime formation from the above cyclohexanone, followed by catalytic hydrogenation, led to a mixture of epimeric aminocyclitols in an α/β ratio of 16:1 (Scheme 2.7) [3].

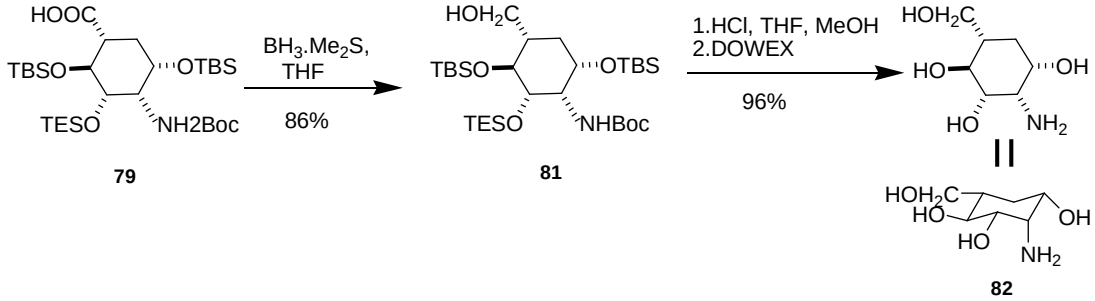


Scheme 2.9. Aminocyclitols through sigmatropic rearrangements of allylic imidates

The sigmatropic rearrangement of allylic imidates, classically known as the aza-Claisen or Claisen-imidate rearrangement and nowadays also called the Overman rearrangement, has also been used to provide access to aminocyclitol systems from suitable precursors. The process can be carried out either thermally or in the presence of Hg^{II} or Pd^{II} catalysts. Mehta et al. have used this rearrangement to convert trichloroacetimidate 73 into trichloroacetamide 74 under thermal conditions en route to aminocarbasugar Analogues 75 (Scheme 2.9) [3].



Scheme 2.10. Synthesis of carbapyranuronic amino acid (80)



Scheme 2.11. Synthesis of carbapyranosylamine (82)

To complete the synthesis of both carbapyranuronic amino acid 80 and carbapyranosylamine 82, conversion of 76 into the protected amino acid 79 (a common predecessor) was planned (Scheme 2.10). Thus, benzyl-substituted bicycle 76 was transformed into the N-Boc derivative 78 in a 84% global yield via debenzylation with Na in liquid ammonia (i.e. 76-77) followed by N-Boc reprotection (Boc_2O, MeCN, DMAP). Hydrolysis of 78 with LiOH in THF/water then provided protected amino acid 79 (93% yield), which was fully deprotected to 80 by exposure to 6 N HCl in THF/MeOH (1:2:1 ratio) followed by DOWEX (98% yield).

In a divergent way (Scheme 2.1I), acid 79, when treated with an excess of a 2 M solution of BH_3DMS in THF (8 mol equiv), delivered the protected amino alcohol 81 (86% yield), which was liberated by acidic treatment to furnish amine 82 in 96% yield [13].

CHAPTER 3. MATERIALS AND METHODS

3.1. General

In experimental studies, Heidolph MR Hei-Standart magnetic mixer with heater was used as heat source. Solvents were removed under vacuum with Heidolph Laborota 4000 and Bibby rotated evaporator. The ^{1}H and ^{13}C NMR spectra were recorded on a VARIAN instrument at 300 MHz in $CDCl_3$, C_6D_6, and D_2O. Chemical shifts are reported in parts per million (δ) downfield from TMS as internal standart reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols; s:singlet, d:doublet, t:triplet, q:quartet and m:multiplet. Melting points were determined on Barnstead Electrothermal capillary melting apparatus and are uncorrected. IR was obtained from KBr or film on PerkinElmer FT-IR spectrophotometer. Column Chromatograpy to purify target molecules was carried out a silica gel 60 (Merck 7734). TLC was conducted on pre-coated silica gel 60 F_{254} aluminium sheets (Merck 5554) plates.

Solvents and chemicals were supplied with Fluka, Merck, Alfa Aesar ve Sigma Aldrich companies.

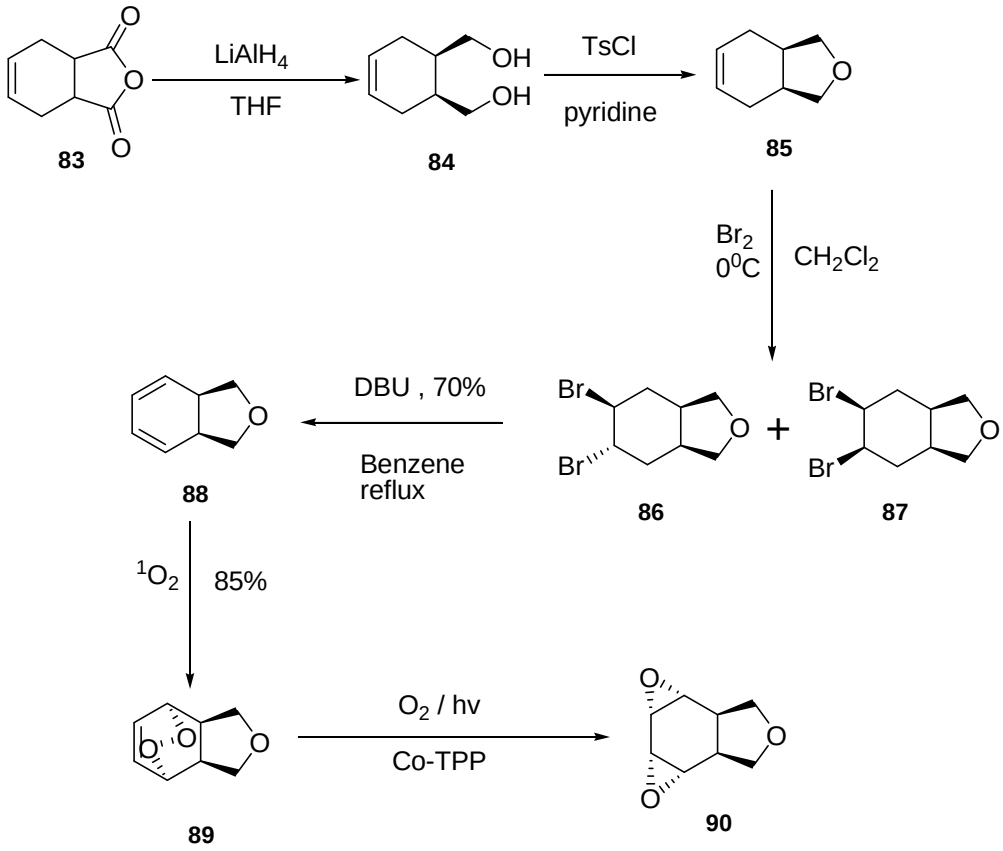
3.2. Experimental Studies

3.2.1. Synthesis of Azido and Amino Carbasugars using a new method

In this study, novel synthetic strategies leading to azido and amino carbasugar's derivatives were aimed and investigated. The syntheses of azido and amino carbasugar's derivatives were achieved successfully.

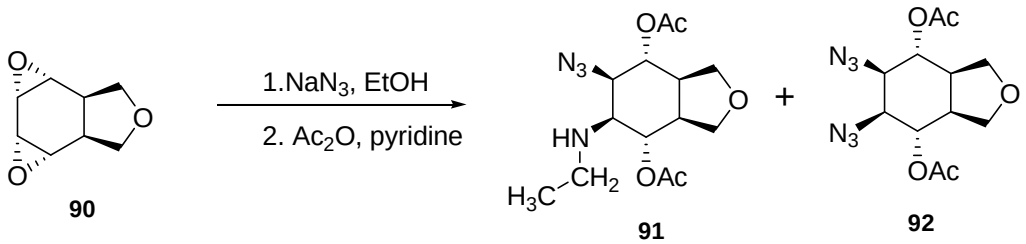
For the synthesis of both azido and amino carbasugar's derivatives, The compound 90 was synthesized as a key compound.

The synthesis of the key compound 90 used in the synthesis of azido and amino carbasugars began with readily available anhydride 83 and was followed by the sequence of steps. Treatment of the anhydride 83 obtained by the addition of maleic anhydride to in situ generated butadiene, with $LiAlH_4$ yielded the diol 84. The diol 84 was successfully converted to the desired tetrahydrofuran derivative 85 by treatment of 84 with tosyl chloride in pyridine. The resulting compound 85 was brominated at low temperature to give cis-dibromo 87 and trans-dibromo compound 86 in high yield. Hydrogen bromide elimination with 1,8-biazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at 0 °C gave the diene 88. Photooxygenation of 88 in methylene chloride (500 W, projection lamp) at room temperature using tetraphenylporphyrin (TPP) as the sensitizer afforded the bicyclic endoperoxide 89 in a yield of 85%. To a magnetically stirred solution of bicyclic endoperoxide 89 in CH_2Cl_2 was added a solution of cobalt meso-tetraphenylporphyrin (Co-TPP) in CH_2Cl_2 at 0 °C. After complete addition (10 min), the mixture was stirred for 2 h at room temperature. Removal of solvent and chromatography of the residue on 50 g of silica gel eluting with hexane/EtOAc (2:3) gave the diepoxide 90 (1.68 g, 84%), which was crystallized from chloroform: colorless crystals (scheme. 3.1)



Scheme 3.1. Synthesis of Azido and Amino Carbasugars using a New Method

3.2.2. The synthesis of monoazide diacetate furan (91) and diazide diacetate furan (92)

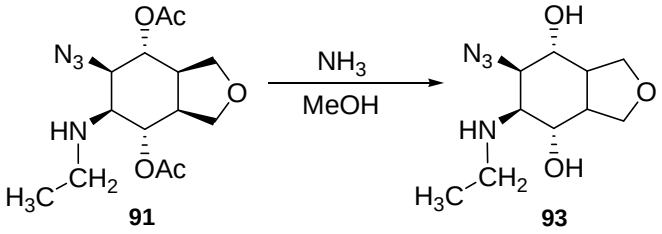


Scheme 3.2. The synthesis of monoazide diacetate furan (91) and diazide diacetate furan (92)

Cis-Bisepoxide 90 (1.2 g, 7.79 mmol) was dissolved in absolute ethanol (50 mL), Sodium azide (1.26 g, 19.38 mmol) was added to the solution. The reaction mixture was refluxed for 1 day and then cooled to room temperature. The reaction was completed, and ethanol removed under reduced pressure. The remaining residue was filtered on a short silica gel column with EtOAc. After evaporation of the ethyl acetate, without any additional purification, the residue was dissolved in pyridine

(4 ml) and acetic anhydride (4.5 ml), and stirred magnetically at rt for 12 h. At the end of this period dichloromethane (200 ml) was added to the solution and stirred for 5 min. The mixture was hydrolyzed with iced-HCl (100 mL 5%) and washed with saturated $NaHCO_3$ (2x100 mL) and water (3x200 mL), and dried on Na_2SO_4. After removal of the solution, the residue filtered on a short column with silica gel (20 g) eluted with hexane /ethyl acetate (2:1) to give monoazide diacetate furan 91 and diazide diacetate furan 92 respectively.

3.2.3. The synthesis of monoazide diol furan (93).

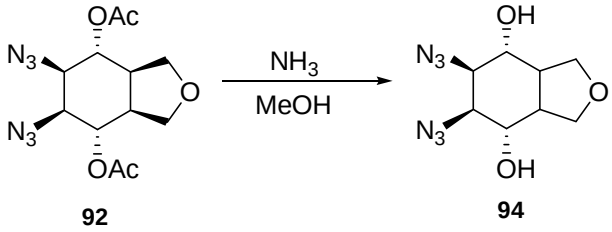


91 **93**

Scheme 3.3. The synthesis of monoazide diol furan (93)

Monoazide diacetate 91 was dissolved in absolute methanol (15 mL) in a 25 mL flask. NH_3(g) was passed through the reaction during 1.5h. The reaction flask was closed with a stopper and stirred for 12 h additionally at the same temperature. The completion of the reaction and removal of the MeOH and forming acetamide under vacuum gave monoazide diol furan 93 yellowish, viscous.

3.2.4. The synthesis of diazide diol furan (94)

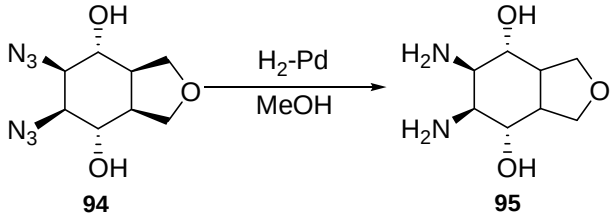


92 **94**

Scheme 3.4. The synthesis of diazide diol furan (94)

Diazide diacetate furan 92 was dissolved in absolute methanol (15 mL) in a 25 mL flask. NH_3(g) was passed through the reaction during 1.5 h. The reaction flask was closed with a stopper and stirred for 12 h additionally at the same temperature. The completion of the reaction and removal of the MeOH and forming acetamide under vacuum gave diazide diol furan 94 dark brown, viscous.

3.2.5. The synthesis of diamino diol furan (95)

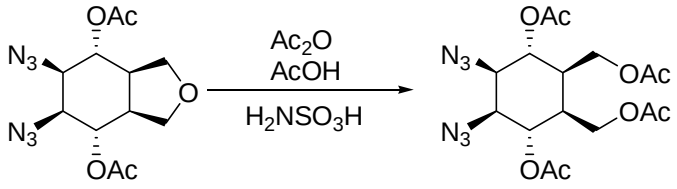


94 **95**

Scheme 3.5. The synthesis of diamino diol furan (95)

A mixture of diazide diol furan 94 and Pd (0.25 mg) in methanol (15 mL) was stirred at rt for 18 h under hydrogen atmosphere. The completion of the reaction, methanol was removed under reduced presure. The residue was dissolved in water and filtered on a short cotton column with water. Water was removed under vacuum, gave diamino diol furan 95 brown, viscous which was crystillated from ethanol as white solid.

3.2.6. The Synthesis of diazide tetraacetate (96)



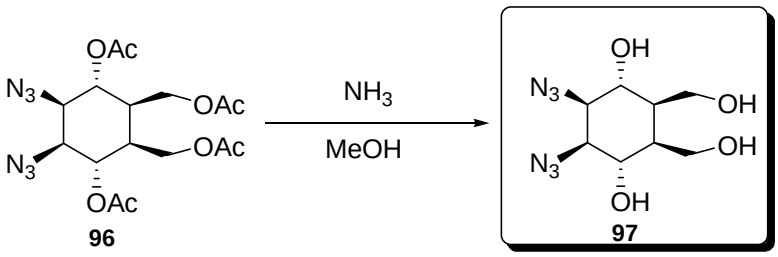
92 **96**

Scheme 3.6. The Synthesis of diazide tetraacetate (96)

To a stirred solution of diazide diacetate furan 92 in Ac_2O/AcOH (10 mL 1:1) was added sulfamic acid (40 mg) at room temperature, followed by heating at reflux temperature for 24 h. After the mixture was cooled to room temperature, HCl was

added (100 mL, 5%) and extracted with ethyl acetate (350 mL). The organic phase was washed with water (2 x 300 mL) and saturated $NaHCO_3$ (2 x 100 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (20 g) with DCM to give diazide tetraacetate 96 colorless, liquid which was crystillated from ethyl acetate**.**

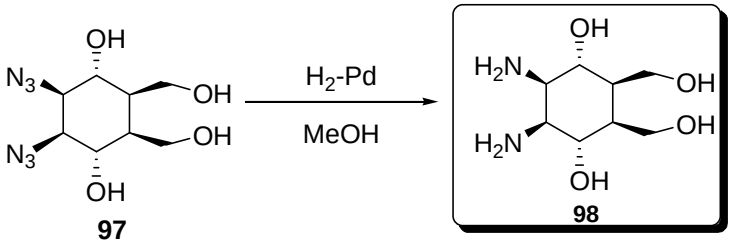
3.2.7. The synthesis of diazide tetrol (97)



Scheme 3.7. The synthesis of diazide tetrol (97)

Diazide tetraacetate 96 was dissolved in absolute methanol (15 mL) in a 25 mL flask. NH_3(g) was passed through the reaction during 1.5 h. The reaction flask was closed with a stopper and stirred for 12 h additionally at the same temperature. The completion of the reaction and removal of the MeOH and forming acetamide under vacuum gave diazide tetrol 97 brown, liquid.

3.2.8. The synthesis of diamino tetrol (98)

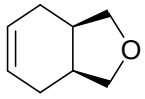


Scheme 3.8. The synthesis of diamino tetrol (98)

A mixture of diazide tetrol 97 and Pd (0.25 mg) in methanol (15 mL) was stirred at rt for 18h under hydrogen atmosphere. The completion of the reaction, methanol was removed under reduced presure. The residue was dissolved in water and filtered on a

short cotton column with water. Water was removed under vacuum, gave diamino tetrol 98 light brown, liquid.

CHAPTER 4. EXPERIMENTAL RESULTS



85

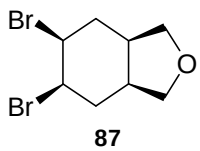
tetrahydrofuran

Hexahydrobenzofuran derivative (85) was prepared according to same procedure as described in the literature 11.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.69 (s, 2H), 3.89 (dd, A-part of AB-system, J =7.5 and 6.4 Hz, 2H), 3.54 (dd, B-part of AB-system, J) 7.5 and 5.6 Hz, 2H), 2.36 (m, 2H), 2.26-2.22 (m, 2H), 1.95 (dd, J =16.0 and 3.4 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 124.9, 73.1, 35.3, 24.1;

IR (KBr, cm-1); 3025, 2927, 2857, 1485, 1437, 1377, 1309, 1209, 1189, 1175, 1120, 1088, 1055, 1019, 968, 951, 899. Anal. Calcd for $C_8H_{12}O$; C, 77.38; H, 9.74. Found: C, 77.4; H, 9.7.



87

cis-dibromo

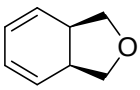
To magnetically stirred solution of 85 (10.0 g, 80,65 mmol) in 300 mL of dry CH_2Cl_2 at 0 °C a solution of bromine (13.0 g, 81.2 mmol) was added dropwisely in

200 mL of CH_2Cl_2 over a period of 1 h. The reaction mixture was stirred for an additional 2 h at room temperature. The solvent was evaporated. Crystallization of the residue from ether at 0 °C gave 17.87g of pure 87 (78% after crystallization) as white crystals. Mp 58-60 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.42-4.37 (m, 1H), 4.29-4.24 (m, 1H), 3.92-3.81 (m, 3H), 3.69-3.65 (m, 1H), 2.61-2.46 (m, 3H), 2.42-2.36 (m,1H), 2.25-2.15 (m, 1H), 2.12-2.05 (m, 1H);

^{13}C NMR (100 Mhz, CDCl3) δ = 72.4, 70.2, 53.2 (2x), 38.3, 37.2, 34.5, 33.2;

IR (KBr, cm-1); 2 926, 2871, 1306, 1286, 1246, 1169, 1158, 1118, 1069, 1041, 1029, 1013, 980, 942, 934, 903. Anal. Calcd for $C_8H_{12}Br_2O$: C, 33.83; H, 4.26. Found: C, 34.00; H, 4.23.



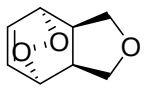
88

diene

To solution of dibromide 87 (15.0g, 52.82 mmol) in 400 mL of dry benzene a solution of 1,8-diazabicyclo[5.4.0]undec-7- ene (36.0 g, 236 mmol) was added in 400 mL of dry benzene at room temperature. The reaction mixture was refluxed for 6 h and then cooled to room temperature. The solid was filtered off. The benzene phase was poured into water (1000 mL) and extracted with ether (3 x 500 mL). The combined organic phase was washed with saturated aqueous sodium bicarbonate (3 x 500 mL), dried (Na_2SO_4), and evaporated in vacuum to give 4.51g of 88 (70%) as a colorless liquid [11].

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.86-5.80 (m, 2H), 5.62-5.59 (m 2H), 4.16-4.12 (m, 2H), 3.60-3.57 (m, 2H), 2.96 (bs, 2H);

^{13}C NMR (100 MHz, $CDCl_3$). δ = 126.2, 122.3, 75.0.



89

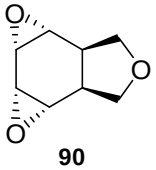
bicyclic endoperoxide

A stirred solution of cyclohexadiene derivative 88 (10.0g, 81.9 mmol) and 200 mg of tetraphenylporphyrine (TPP) in 250mL of CH_2Cl_2 was irradiated with a projection lamp (500 W) while oxygen was passed through the solution The reaction completed after 12 h. Evaporation of solvent (30 °C, 20 mmHg) and crystallization of the residue from ether gave 10.7 g of pure endoperoxide 89 (85%) as colorless crystals. Mp 123-126 °C;

^1H NMR (400 MHz, CDCl3) δ = 6.68 (quasi t, A-part of AA′XX′-system, 2H), 4.71 (m, X-part of AA′XX′-system, 2H), 3.73 (m, 2H), 3.50 (dd, J3,3′(5,5′)) 9.3 and 2.6 Hz, 2H), 3.03 (m, 2H);

^{13}C NMR (100MHz, CDCl3) δ = 131.9, 72.4, 70.0, 39.9;

IR (KBr, cm-1); 3079, 2958,2923, 2861, 1475, 1465, 1377, 1277, 1198, 1129, 1075, 1040, 1029,965, 950. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C,62.03; H, 6.59.



90

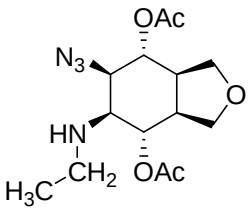
cis-bisepoxide

To magnetically stirred solution of bicyclic endoperoxide 89 (2.0 g, 13 mmol) in 40 mL of CH_2Cl_2 a solution of cobalt meso-tetraphenylporphyrin (60 mg) was added in 10 mL of CH_2Cl_2 at 0 °C. After complete addition (10 min), the mixture was stirred for 2 h at room temperature. Removal of solvent and chromatography of the residue on 50 g of silica gel eluting with hexane/EtOAc (2:3) gave bisepoxide 90 (1.68 g, 84%), which was crystallized from chloroform: colorless crystals; mp 73−75 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.91 (br t, A-part of AB-system, J = 7.6 Hz, 2H), 3.62 (dd, B-part of AB-system, J = 8.4 and 4.5 Hz, 2H), 3.41 (d, J =1.3 Hz, 2H), 2.87 (br d, J = 1.3 Hz, 2H) 2.64−2.58 (m, 2H);

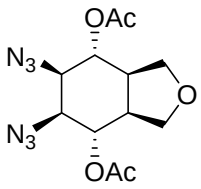
^{13}C NMR (100 MHz, $CDCl_3$) δ = 71.0, 50.4, 47.6, 36.8;

IR (KBr, cm^{-1}); 3003, 2956,2879, 1423, 1365, 1267, 1195, 1070.49, 1049, 1033, 952, 929, 894. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.36; H,6.65.



91

monoazide diacetate furan



92

diazide diacetate furan

cis-Bisepoxide 90 (2.4 g, 15.58 mmol) was dissolved in absolute ethanol (75 mL). Sodium azide (2.52 g, 38.76 mmol) was added to the solution. The reaction mixture was refluxed and conversion was controled with TLC. After 24h the conversion was completed, the mixture cooled to room temperature. Ethanol was removed under reduced pressure. The remaining residue was filtered on a short silica gel column with ethyl acetate. After evaporation of the ethyl acetate, without any additional purification, the residue was dissolved in pyridine (5 mL) and acetic anhydride (6 mL), and stirred magnetically at rt for 12 h. At the end of this period dichloromethane (200 ml) was added to the mixture and stirred for 5 min. The mixture was hydrolyzed with iced-HCl (100 mL 5%) and neutralized with $NaHCO_3$

(300 mL) and washed with water (3x400 mL), and dried over Na_2SO_4. After removal of the solution, the residue (5.12 g) was loaded on column on silica gel (60 g) and eluted with hexane /ethyl acetate (4:1). The column was repeated and fractions was combined, evaporation of the solution gave ethylamino-monoazide diacetate furan 91 as a first fraction and diazide diacetate furan 92 as a second fraction respectively.

The first fraction 91: (0.72 g, 14%) yellow liquid. M.p: 86-88^oC. Anal.Calcd for $C_{14}H_{22}N_4O_5$: C, 51.52; H, 6.79; found: C; 51.79; H, 6.88.

^{1}H-NMR (300 MHz, in $CDCl_3/C_6D_6$: 1/1) δ = 5.39 (t, J=10.0 Hz, 1H), 4.94 (t, J=3.1 Hz, 1H), 3.83 (dd, J=9.7, 8.0 Hz, 1H), 3.76 (dd, J=8.7, 1.4 Hz, 1H), 3.64 (t, J=8.7 Hz, 1H), 3.52 (dt, J=3.8, 1.2 Hz, 1H), 3.47 (dd, J=8.8, 5.0 Hz, 1H), 3.29 (q, 2H), 3.18 (dd, J=10.2, 2.9 Hz, 1H), 2.23-2.12 (m, 1H), 2.11-2.05 (m, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 0.92 (t, 3H).

^{13}C- NMR(75 MHz, $CDCl_3$) δ = 170.4 (2C), 169.9 (2C), 79.4, 70.8, 69.6, 68.6, 67.4, 67.2, 60.9, 43.4, 42.9, 21.3 (2C), 21.2 (2C), 15.5.

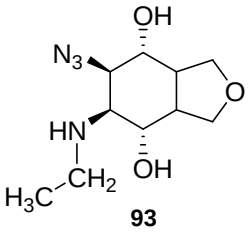
IR (KBr, cm^{-1}); 2983, 2940, 2914, 2102, 1736, 1434, 1375, 1227, 1218, 1107, 1096, 1062, 1030, 935, 887, 648.

The second fraction 92: (1.46 g, 58%) a colorless liquid which was crystillated from ethyl acetate (3.90 g, 76%). M.p: 149-151^oC. Anal.Calcd for $C_{12}H_{16}N_6O_5$: C, 44.44; H, 4.97; found: C; 44.10; H, 4.75.

^{1}H-NMR (300 MHz, in $CDCl_3/C_6D_6$: 2/1) δ = 5.08 (t, J=5.3 Hz, 2H), 3.77 (dd, J=8.5, 5.3 Hz, 2H), 3.70 (bd, J=5.5 Hz, 2H), 3.63-3.57 (m, 2H), 2.25 (dd, J=9.4, 5.3 Hz, 2H), 1.92 (s, 2x3H).

^{13}C- NMR(75 MHz, in $CDCl_3/C_6D_6$: 2/1) δ = 169.6 (2C), 68.2 (2C), 69.1 (2C), 62.2 (2C), 43.0 (2C), 20.9 (2C).

IR (KBr, cm^{-1}); 2971, 2912, 2873, 2111, 1740, 1428, 1371, 1303, 1262, 1216, 1067, 1039, 1023, 921, 880, 783, 688.



93

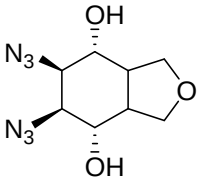
monoazide diol furan

Monoazide diacetate 91 (0.54 g, 1.66 mmol) was hydrolyzed with NH_3 in absolute MeOH to give monoazide diol furan 93 (0.37 g, 92%) yellowish, viscous. Anal.Calcd for $C_{10}H_{18}N_4O_3$: C, 49.57; H, 7.49; found: C; 48.97; H, 7.72.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 4.00 (t, j=2.9 Hz, 1H), 3.85 (d, j=8.5 Hz, 1H), 3.76 (d, j=9.4 Hz, 1H), 3.69-3.60 (m, 2H), 3.54-3.49 (m, 2H), 3.46-3.34 (m, 2H), 2.93 (dd, j=10.6, 3.5 Hz, 1H), 2.49-2.43 (m, 1H), 2.19-2.09 (m, 1H), 0.97 (t, j=7.0 Hz, 3H)

^{13}C- NMR(75 MHz, $CDCl_3$) δ = 80.7, 71.0, 68.4, 68.3, 66.5, 63.9, 52.5, 44.7, 43.3, 14.6

IR (KBr, cm^{-1}); 3291, 2971, 2930, 2882, 2108, 1739, 1565, 1405, 1366, 1229, 1206, 1094, 1063, 914, 886, 717, 648.



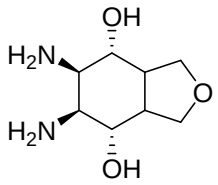
94

diazide diol furan

Diazide diacetate furan 92 (0.72 g, 2.22 mmol) was hydrolyzed with NH_3 in absolute MeOH to give diazide diol furan 94 (0.48 g, 90%) dark brown, viscous. Anal.Calcd for $C_8H_{12}N_6O_3$: C, 40.00; H, 5.04; found: C; 40.31; H, 5.15;

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 3.87 (d, j=6.0 Hz, 2H), 3.83-3.69 (m, 6H), 2.36 (dt, j=11.7, 7.0 Hz, 2H).

^{13}C- NMR(75 MHz, $CDCl_3$) δ = 69.6, 67.4, 64.1, 44.1.



95

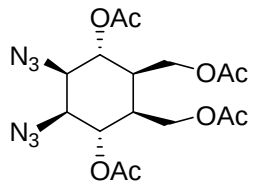
diamino diol furan

Diazide diol furan 94 (0.63 g, 2.61 mmol) and Pd (0.30 mg, 10% on activated carbon powder) in absolute methanol (50 mL) was stirred, and hydrogen was bubbled through the solution and followed by stirring under hydrogen to give diamino diol furan 95 (0.42 g, 87%) brown, viscous which was crystalized from ethanol gave colorless crystals (0.33 g, 67%), M.p: 213-215^{o}C. Anal.Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; found: C; 50.95; H, 8.63;

^{1}H-NMR (300 MHz, D_2O) δ = 3.76 (t, j=5.6 Hz, 6H), 3.48 (t, j=6.2 Hz, 2H), 2.94 (d, j=6.1 Hz, 2H), 2.33 (dt, j=13.0,7.6 Hz, 2H).

^{13}C- NMR(75 MHz, D_2O) δ = 70.6, 70.3, 54.4, 44.2.

IR (KBr, cm^{-1}); 3380, 3072, 2959, 2932, 2889, 2874, 1628, 1599, 1565, 1468, 1359, 1254, 1229, 1059, 917, 809, 731.



96

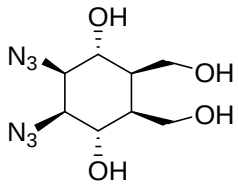
diazide tetraacetate

To stirred solution of diazide diacetate furan 92 (1.65 g, 5.09 mmol) in Ac_2O/AcOH (10 mL 1:1) sulfamic acid (40 mg) was added at room temperature, followed by heating at reflux temperature for 24h to give diazide tetraacetate 96 (1.56 g, 72%) colorless, liquid which was crystallized from ethyl acetate, gave salty crystals (1.35 g, 62%). M.p: 93-95^{o}C. Anal.Calcd for $C_{16}H_{22}N_6O_8$: C, 45.07; H, 5.20; found: C; 45.40; H, 5.00;

^{1}H-NMR (300 MHz, $CDCl_3$) δ; 5.29 (t, j=6.1 Hz, 2H), 4.31 (dd, j=11.7, 6.8 Hz, 2H), 4.11 (dd, j=11.7, 4.7 Hz,2H), 3.93 (d, j=5.6 Hz, 2H), 2.43 (dd, j=11.5, 6.1 Hz, 2H), 2.13 (s, 2x3H), 2.06 (s, 2x3H);

^{13}C- NMR(75 MHz, $CDCl_3$) δ = 170.8, 169.7, 69.3, 62.6, 61.8, 21.2, 21.1.

IR (KBr, cm^{-1}): 2989, 2108, 1736, 1702, 1429, 1370, 1217, 1027, 915, 672, 642.



97

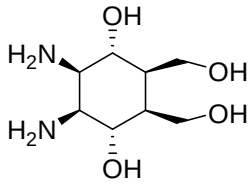
diazide tetrol

Diazide tetraacetate 96 (0.45 g, 1.05 mmol) was hydrolyzed with NH_3 in absolute MeOH to give diazide tetrol 97 (0.25 g, 92%) brown, viscous. Anal.Calcd for $C_8H_{14}N_6O_4$: C, 37.21; H, 5.46; found: C; 37.37; H, 5.12;

^{1}H-NMR (300 MHz, D_2O) δ = 3.83 (m, 4H), 3.60 (m, 4H), 3.60 (m, 4H), 2.03 (m, 2H).

^{13}C- NMR(75 MHz, D_2O) δ = 67.9, 64.6, 59.7, 42.5.

IR (KBr, cm^{-1}); 3276, 2874, 2094, 1731, 1661, 1611, 1248, 1047, 1019, 881, 785, 747.



98

diamino tetrol

Diazide tetrol 97 (0.32 g, 1.24 mmol). and Pd (0.20 mg, 10% on activated carbon powder) in absolute methanol (50 mL) was stirred, and hydrogen was bubbled through the solution and followed by stirring under hydrogen to give diamino tetrol 98 (0.23 g, 88%) light brown, viscous. Anal.Calcd for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80; found: C; 46.78; H, 8.72;

^{1}H-NMR (300 MHz, D_2O) δ = 3.65 (dd, j=11.7, 3.2 Hz, 2H), 3.55 (t, j=5.4 Hz, 2H), 3.39 (dd, j=11.7, 4.7 Hz, 2H), 2.90 (d, j=4.7 Hz, 1H), 1.89 (m, 2H).

^{13}C- NMR(75 MHz, D_2O) δ = 72.25, 60.1, 53.4, 42.5;

IR (KBr, cm^{-1}); 3277, 2889, 1585, 1438, 1378, 998, 936, 684.

CHAPTER 5. CONCLUSIONS

In conclusion, Cyclitols concerning a large group of natural products are of great importance due to their known and potential biological activities as well as their synthetic usefulness in the synthesis of other natural or pharmaceutical compounds. Carbasugars known also pseudo-sugars form an important subclass of cyclitols and are thought to be more potent drug candidates than natural sugars as they are much more stable towards hydrolysis. Moreover, these compounds constitute the key structural fragments of aminoglycoside antibiotics and are potential glycosidase inhibitors, mediation of cellular communication as well as antiviral agents. Amino-carbasugars as aminocyclitols , their chemistry has greatly benefited from knowledge acquired on the synthesis of carbohydrates and carbocyclic-derived compounds. Hence, to develop new and efficient synthesis leading to cyclitols and their derivatives is a field of interest. In other words, Various methodologies have been developed for the synthesis of pure cyclitols and their analogues.

Thus, the azido carbasugar (97) and the amino carbasugar (98) were synthesized succesfully from easily available and less expensive starting material (83) through five or six steps with relatively high to moderate yields in this study. The readily available starting material (83), high yielding and stereoselective steps make our synthetic route more practicable and efficient for the synthesis of new analogues of aminocyclitols. We assume that these compounds may have important biological activities and can also be used prospectively for pharmacological researches. The studies of the biological activities of these compounds are currently ongoing and will be reported in due course.

Last of all, the diepoxide (90) as the key compound undergo regio- and stereospecific epoxide ring opening with azide ion in EtOH to give the corresponding azidocyclitol

(91) and aminocyclitol (92) in good yields, and the structures were determined by using spectroscopic techniques (IR, ^{1}H NMR and ^{13}C NMR).

CHAPTER 6. DISCUSSIONS AND SUGGESTIONS

In this thesis, the diepoxide furan (90) was used as a key compound for the synthesis of various azido and amino carbasugars derivatives. The diene (88) was subjected to an epoxidation reaction for further functionalization of the diene unit.

The previously known diene 88 [5] was prepared in five steps starting with the addition of maleic anhydride to in situ generated butadiene. The reduction of the anhydride functionality in 83 followed by tosylation of diol 84 afforded the desired tetrahydrofuran derivative 85. Bromination of the resulting tetrahydrofuran, and 1,8-biazabicyclo[5.4.0]undec-7- ene (DBU) induced elimination furnished diene 88. Addition of singlet oxygen to the diene moiety in 88 afforded bicyclic endoperoxide 89 as the sole product (Scheme 3.1). Unsaturated bicyclic endoperoxides can be conveniently converted into the corresponding diepoxides with synconfiguration by treatment with cobalt(II) tetraphenylporphyrin (CoTPP). The reaction of the endoperoxide 89 with CoTPP at 0 °C resulted in the formation of bisepoxide 90 in 84% yield. The symmetrical structure was confirmed by the ^{13}C NMR spectrum consisting of four carbon resonances.

The bisepoxide 90 was subjected to sodium azide ring-opening reaction in the presence of Ethanol followed by acetylation with acetic anhydride in pyridine resulting in the formation of three separable monoazide diacetate (91) and diazide diacetates (92) (one of them with a symmetrical structure: 92) (Scheme 3.2).

The methodology detailed herein resulted in the convenient conversion of the diene 85 into various carbasugar derivatives (97 and 98). The oxygen functionalities were introduced by an epoxide-ring-opening reaction with sodium azide in the presence of Ethanol. This methodology opens up also an entry to the synthesis of aminocylitols.

These compounds will be used for biological studies and may be readily served as intermediates for synthesis of antibiotics.

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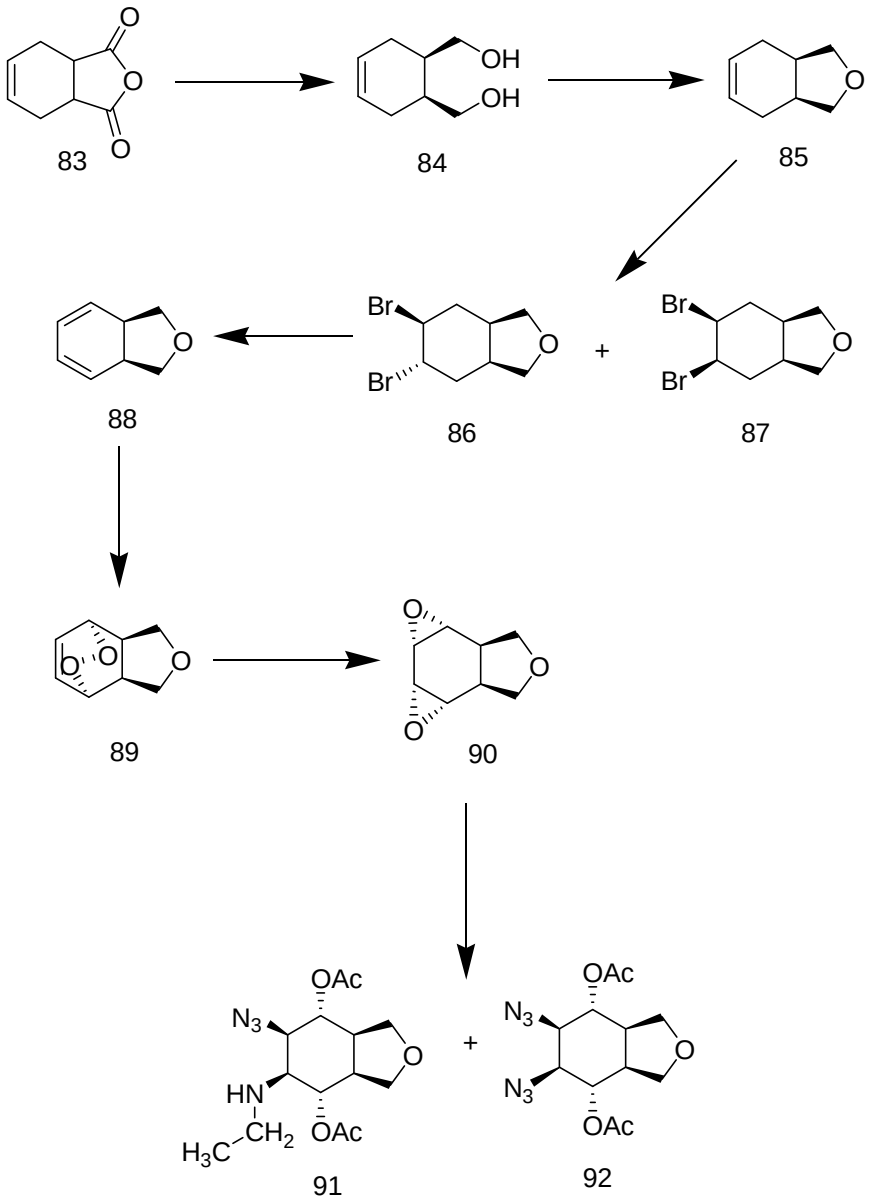
ANNEX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89
O
O
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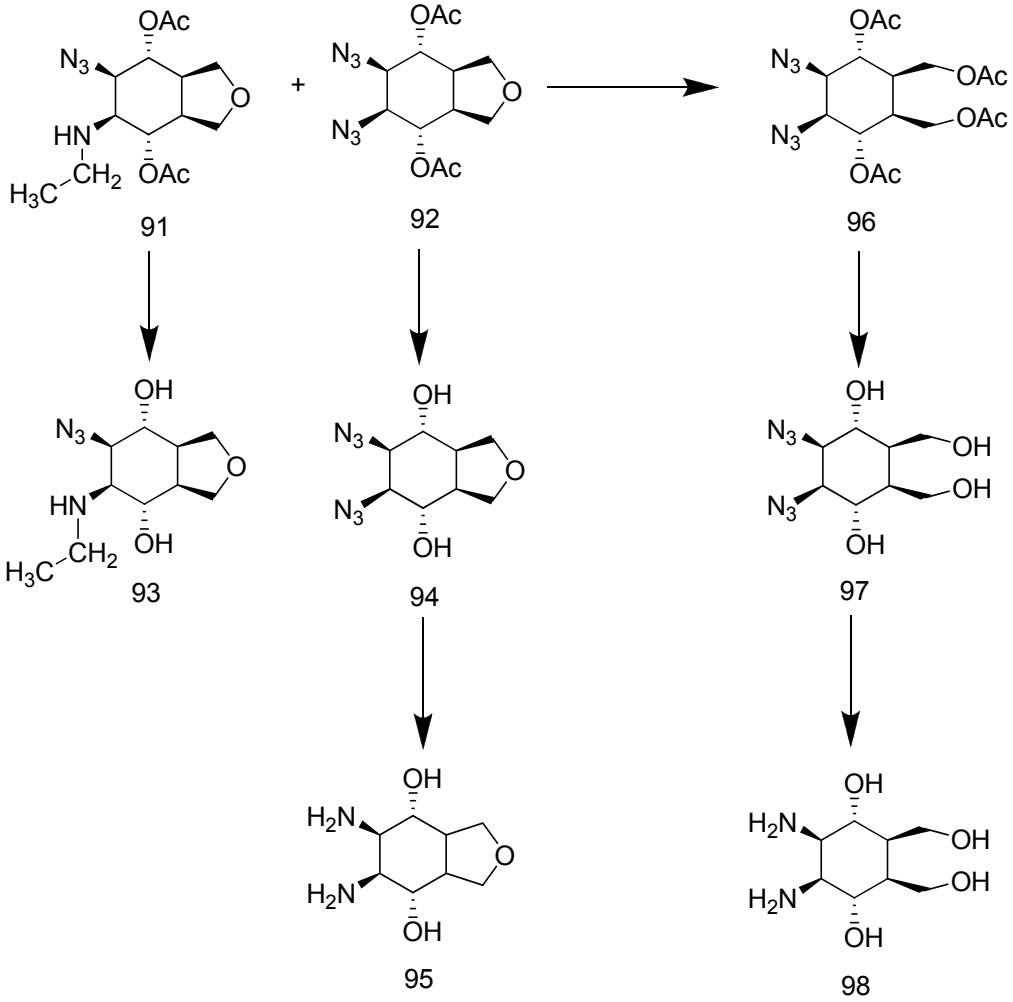
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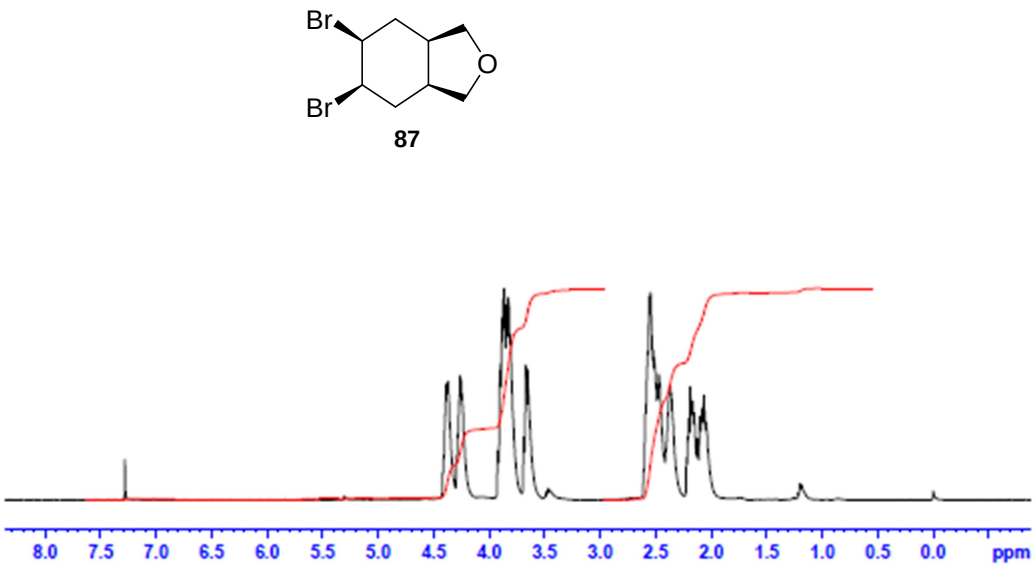


Figure 6.1.^{1}H NMR Spectrum of Compound 87 (in $CDCl_3$)

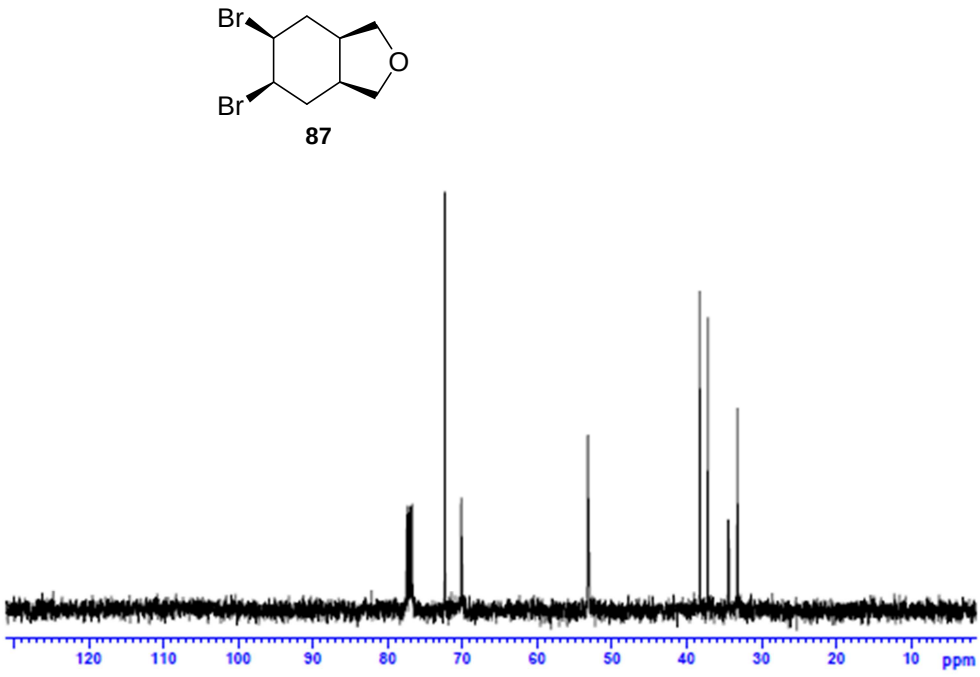


Figure 6.2.^{13}C NMR Spectrum of Compound 87 (in $CDCl_3$)

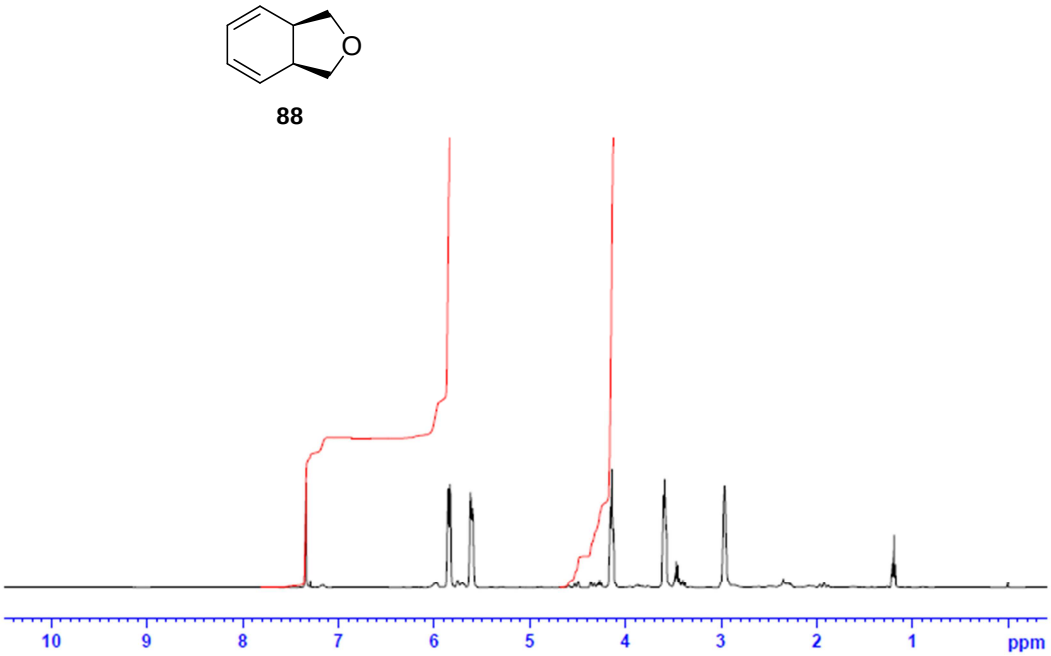


Figure 6.3.^{1}H NMR Spectrum of Compound 88 (in $CDCl_3$)

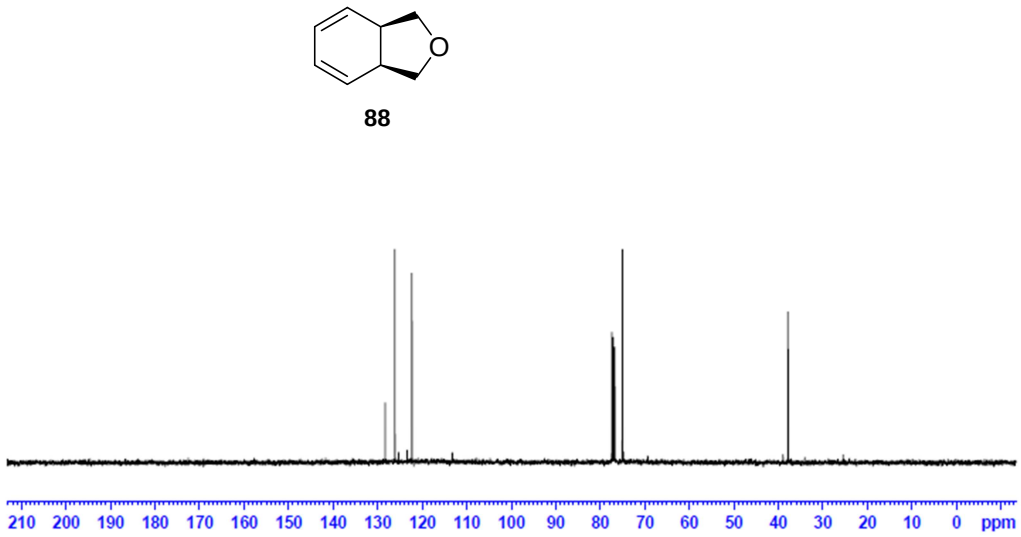
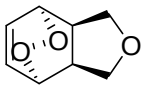


Figure 6.4.^{13}C NMR Spectrum of Compound 88 (in $CDCl_3$)



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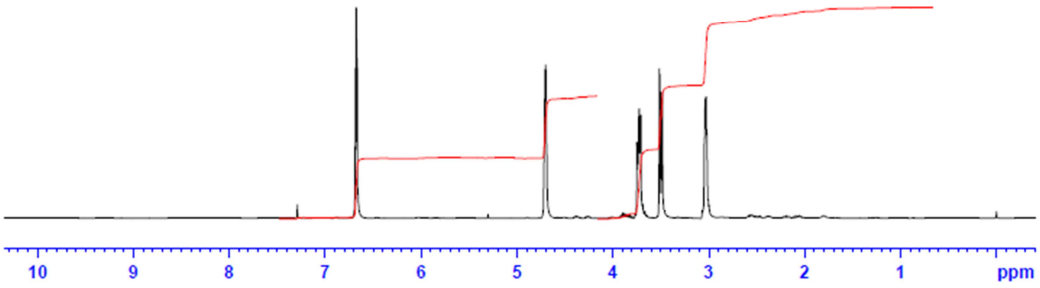
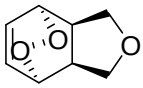


Figure 6.5. ^{1}H NMR Spectrum of Compound 89 (in $CDCl_3$)



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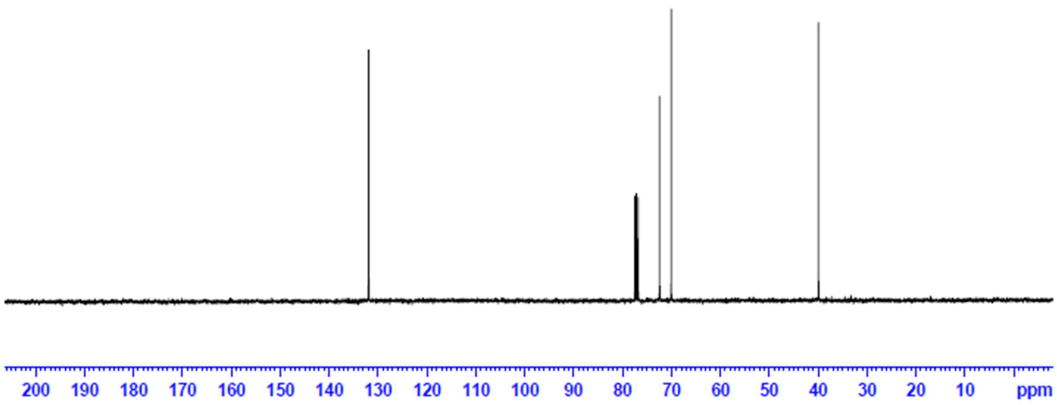


Figure 6.6. ^{13}C NMR Spectrum of Compound 89 (in $CDCl_3$)

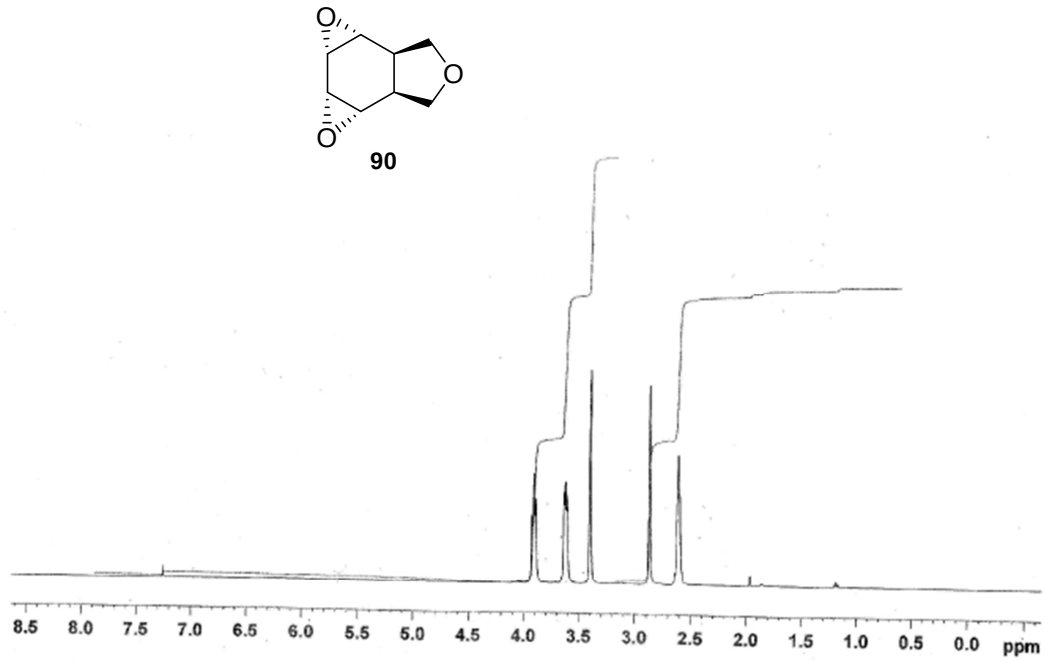


Figure 6.7. ^{1}H NMR Spectrum of Compound 90 (in $CDCl_3$)

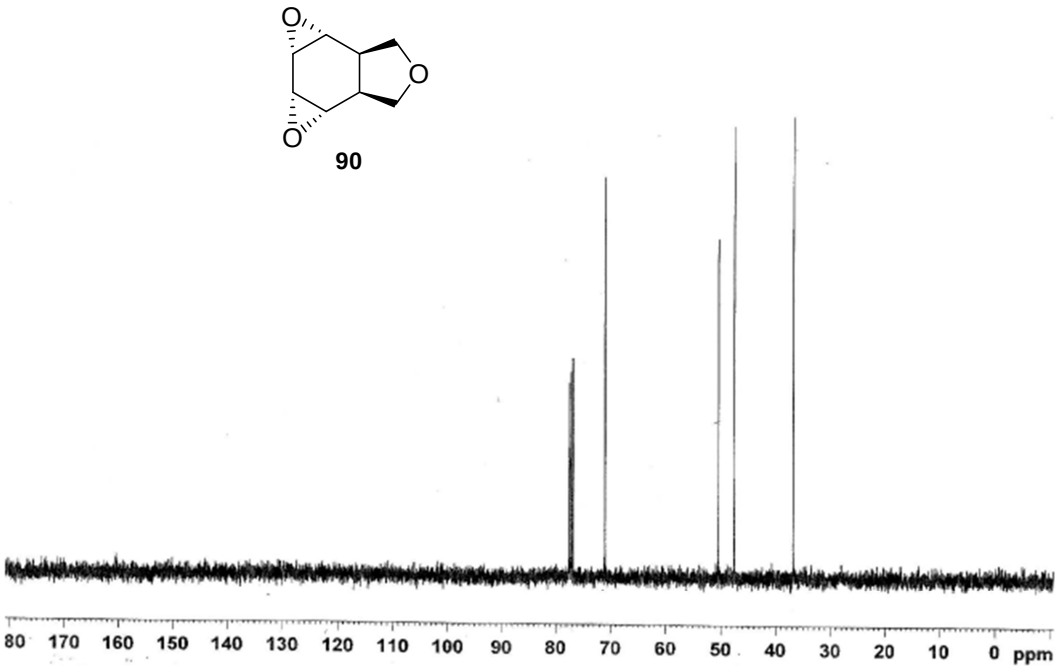


Figure 6.8. ^{13}C NMR Spectrum of Compound 90 (in $CDCl_3$)

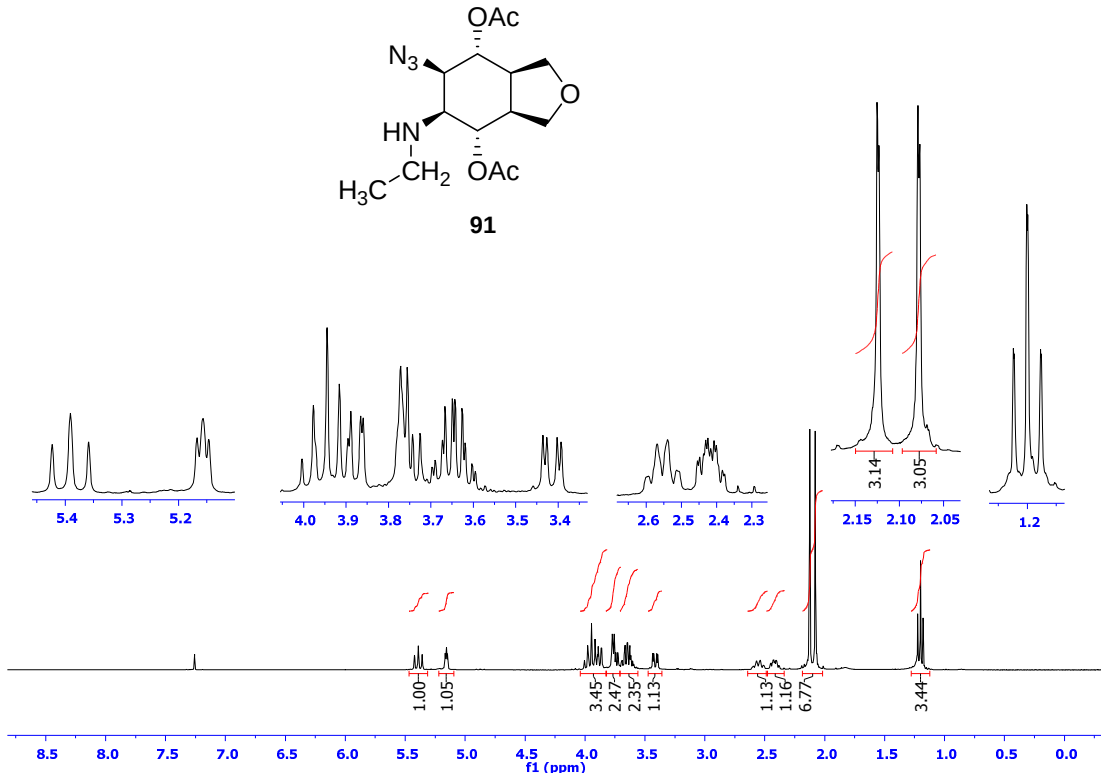


Figure 6.9. ^{1}H NMR Spectrum of Compound 91 (in $CDCl_3$)

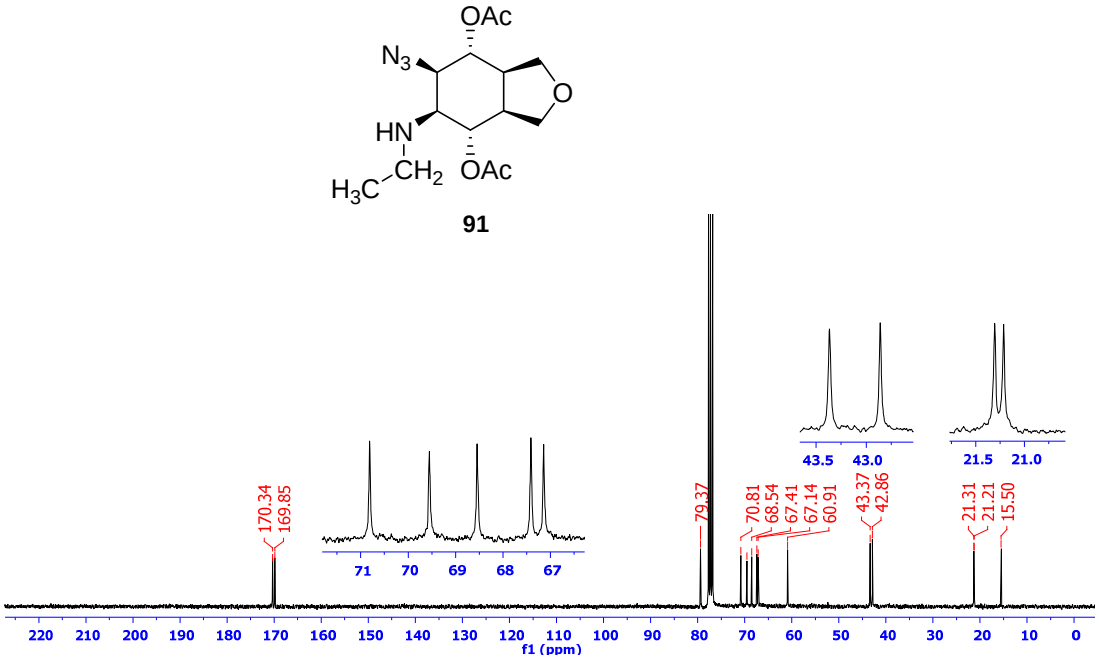
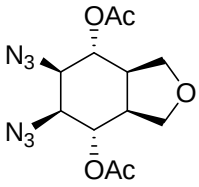


Figure 6.10. ^{13}C NMR Spectrum of Compound 91 (in $CDCl_3$)



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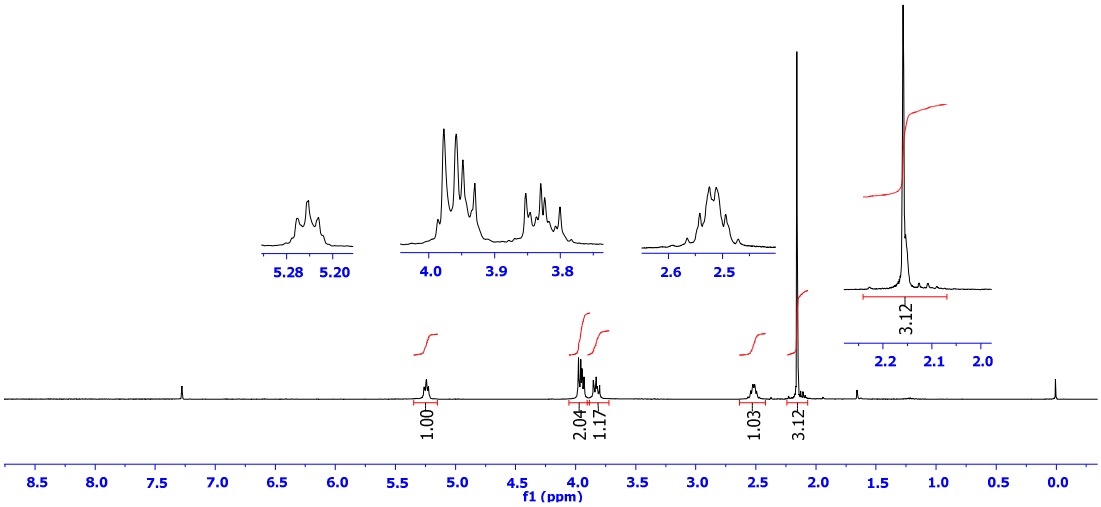
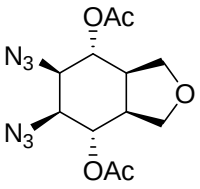


Figure 6.11. ^{1}H NMR Spectrum of Compound 92 (in $CDCl_3$)



92

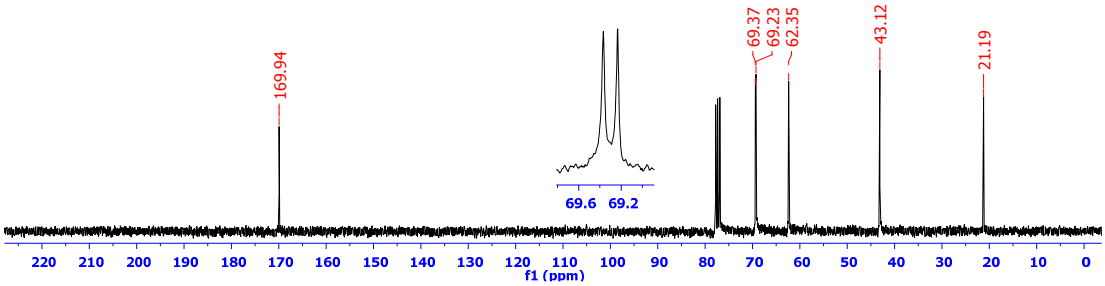


Figure 6.12. ^{13}C NMR Spectrum of Compound 92 (in $CDCl_3$)

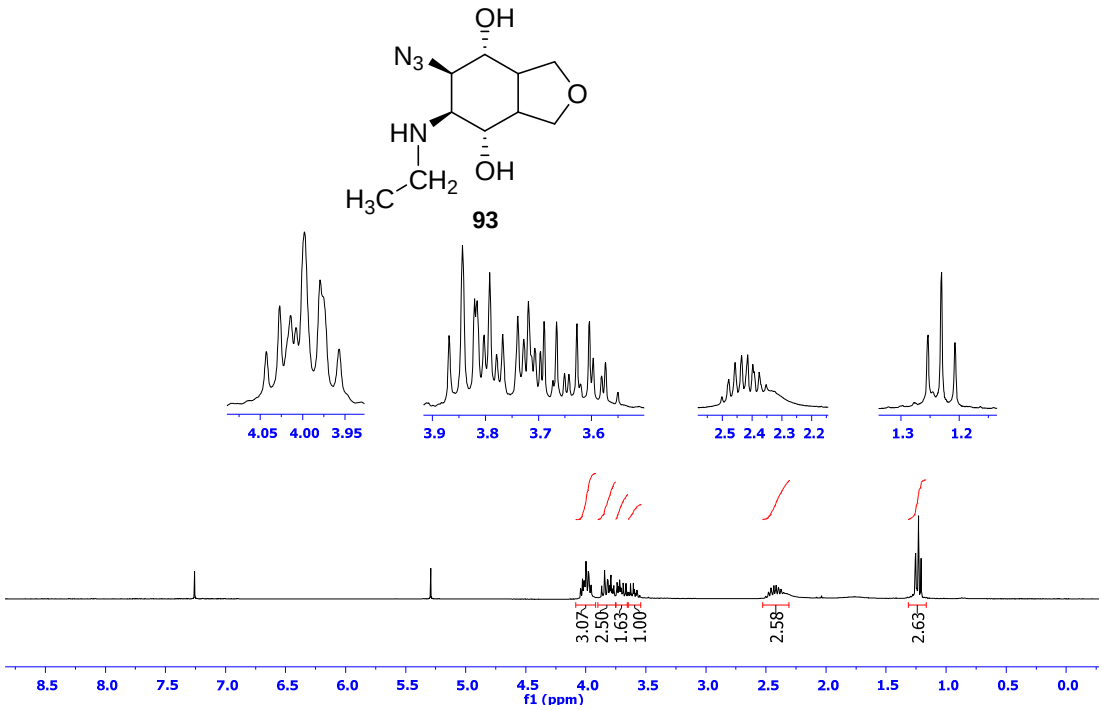


Figure 6.13. ^{1}H NMR Spectrum of Compound 93 (in $CDCl_3$)

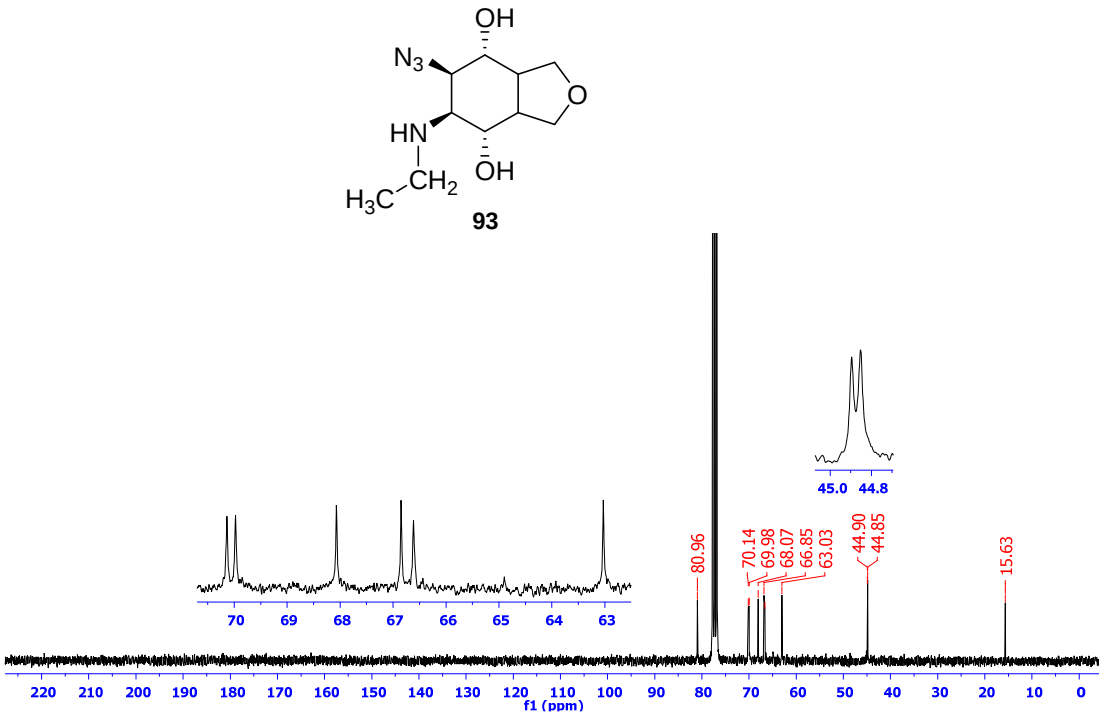


Figure 6.14. ^{13}C NMR Spectrum of Compound 93 (in $CDCl_3$)

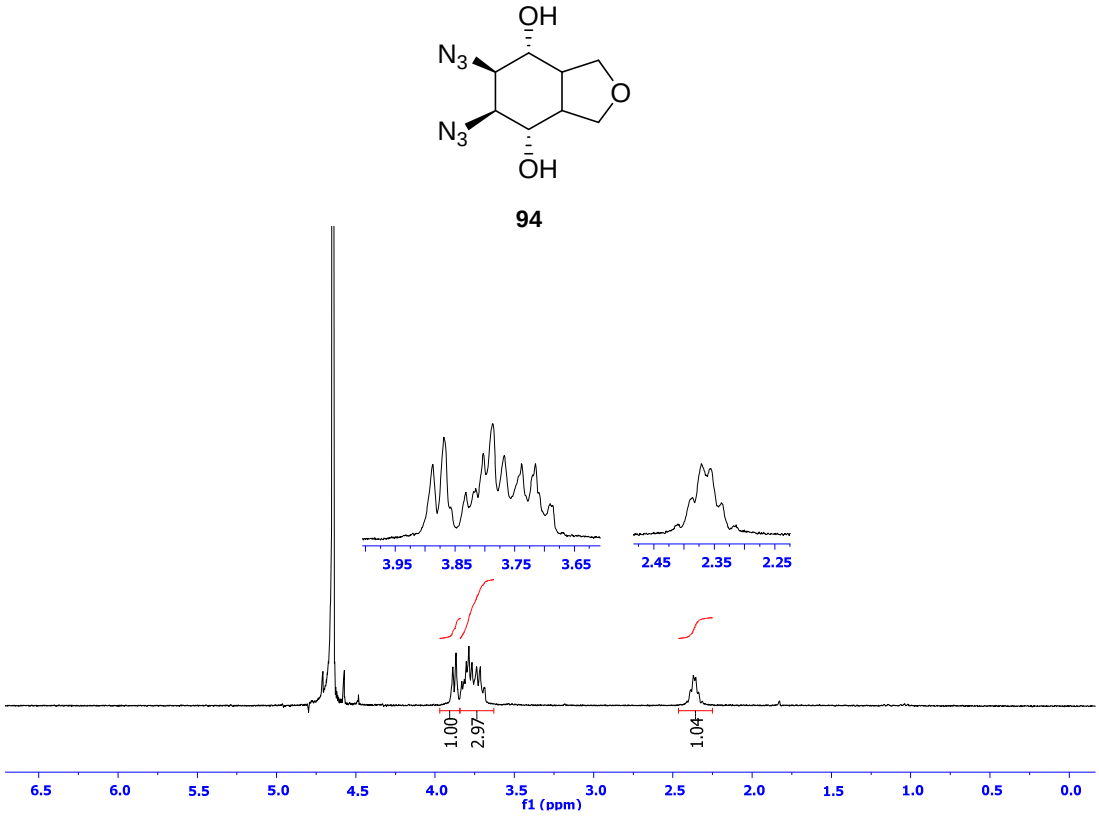


Figure 6.15. ^{1}H NMR Spectrum of Compound 94 (in D_2O)

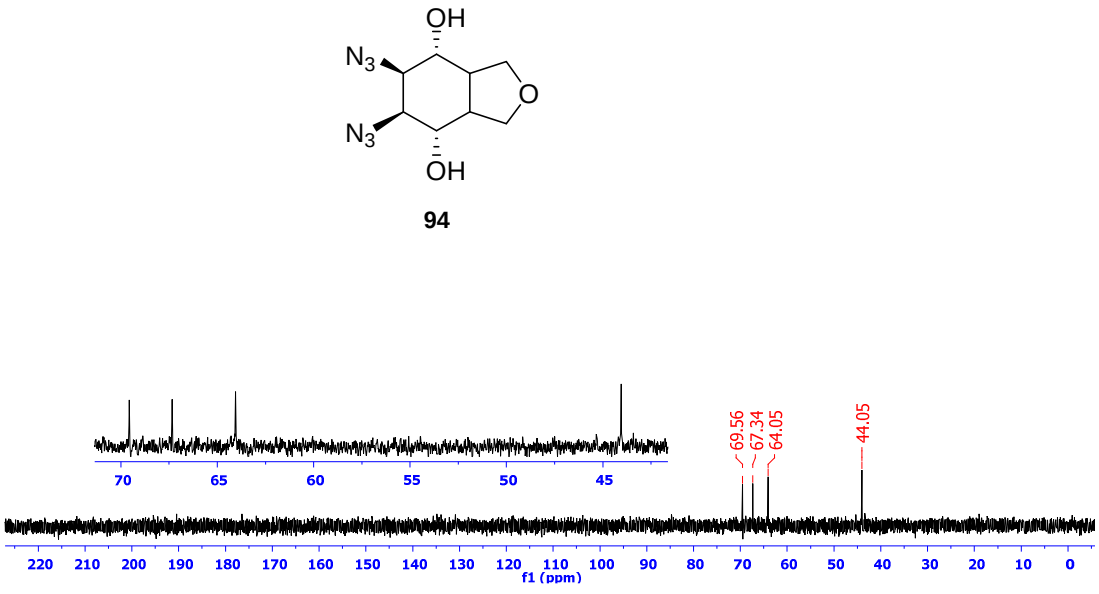


Figure 6.16. ^{13}C NMR Spectrum of Compound 94 (in D_2O)

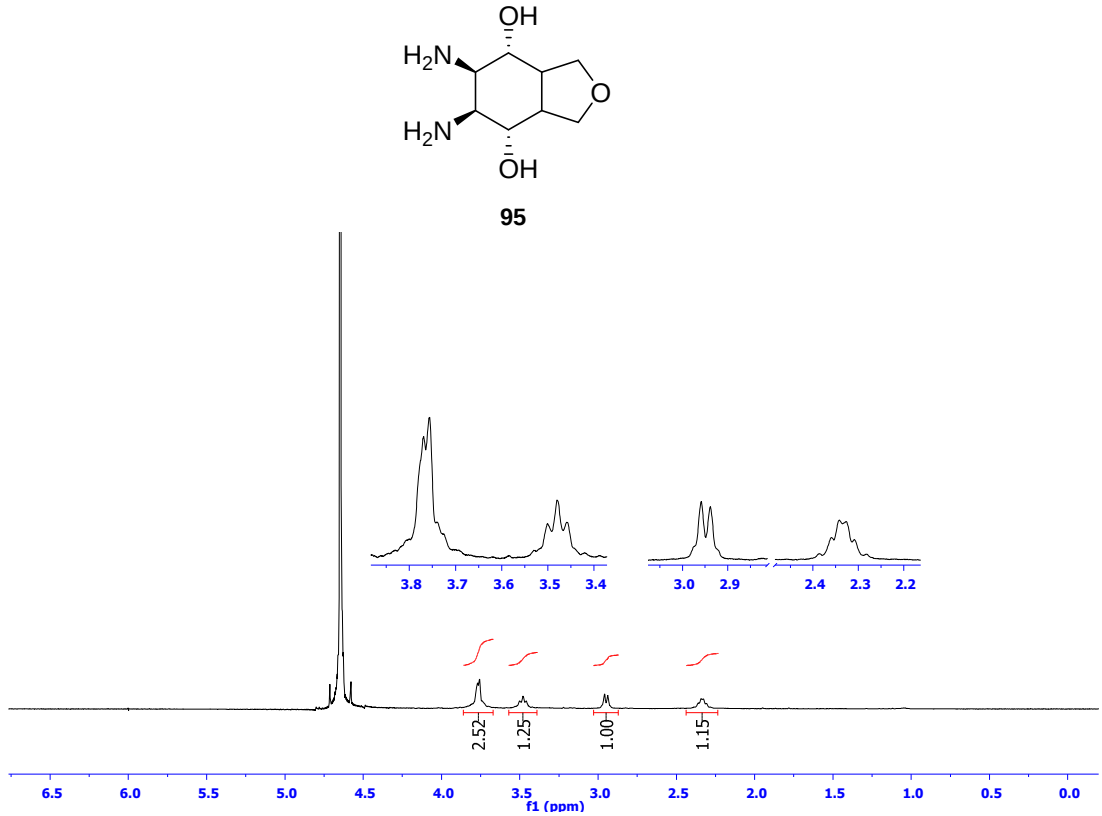


Figure 6.17. ^{1}H NMR Spectrum of Compound 95 (in D_2O)

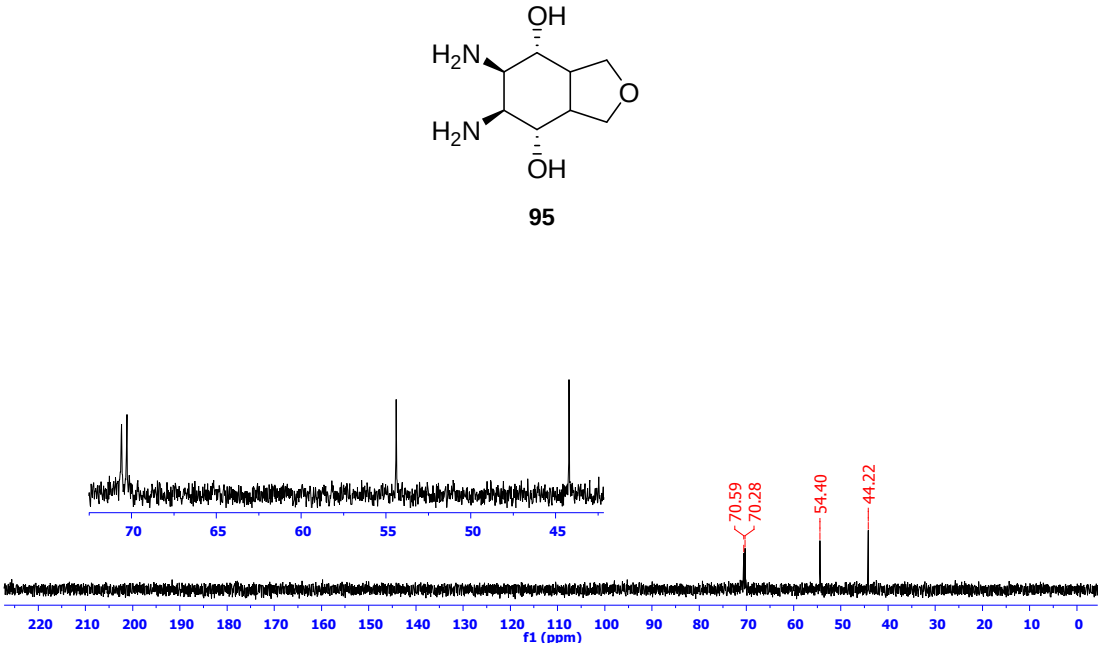


Figure 6.18. ^{13}C NMR Spectrum of Compound 95 (in D_2O)

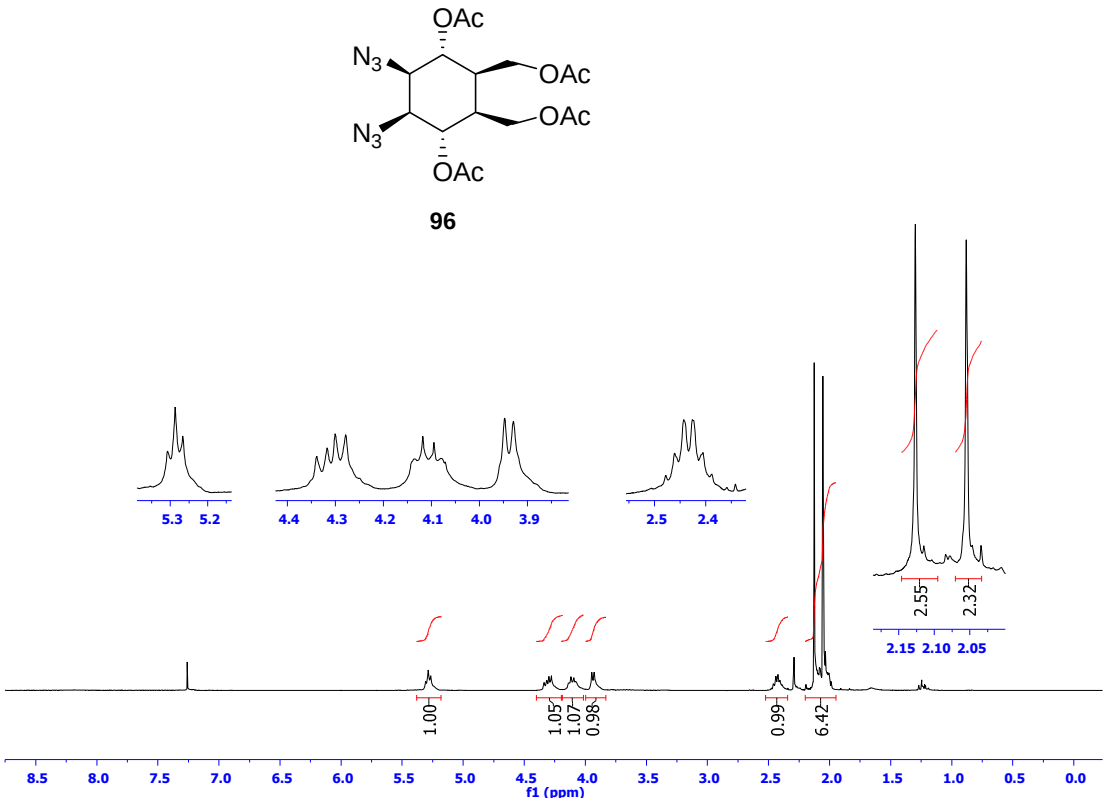


Figure 6.19. ^{13}C NMR Spectrum of Compound 96 (in $CDCl_3$)

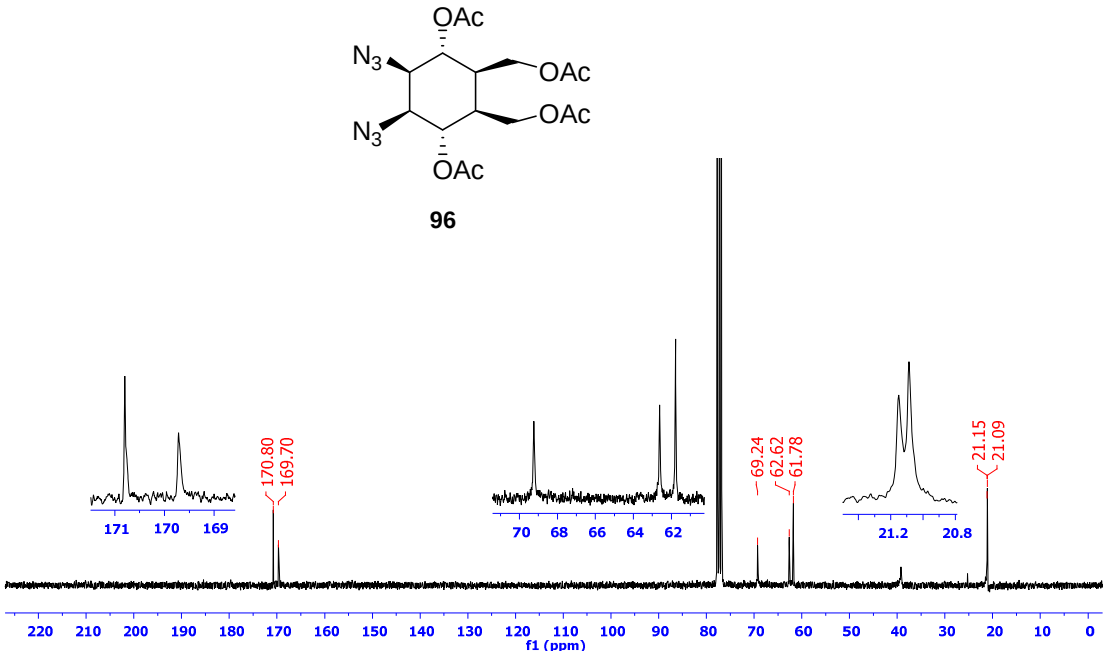


Figure 6.20. ^{13}C NMR Spectrum of Compound 96 (in $CDCl_3$)

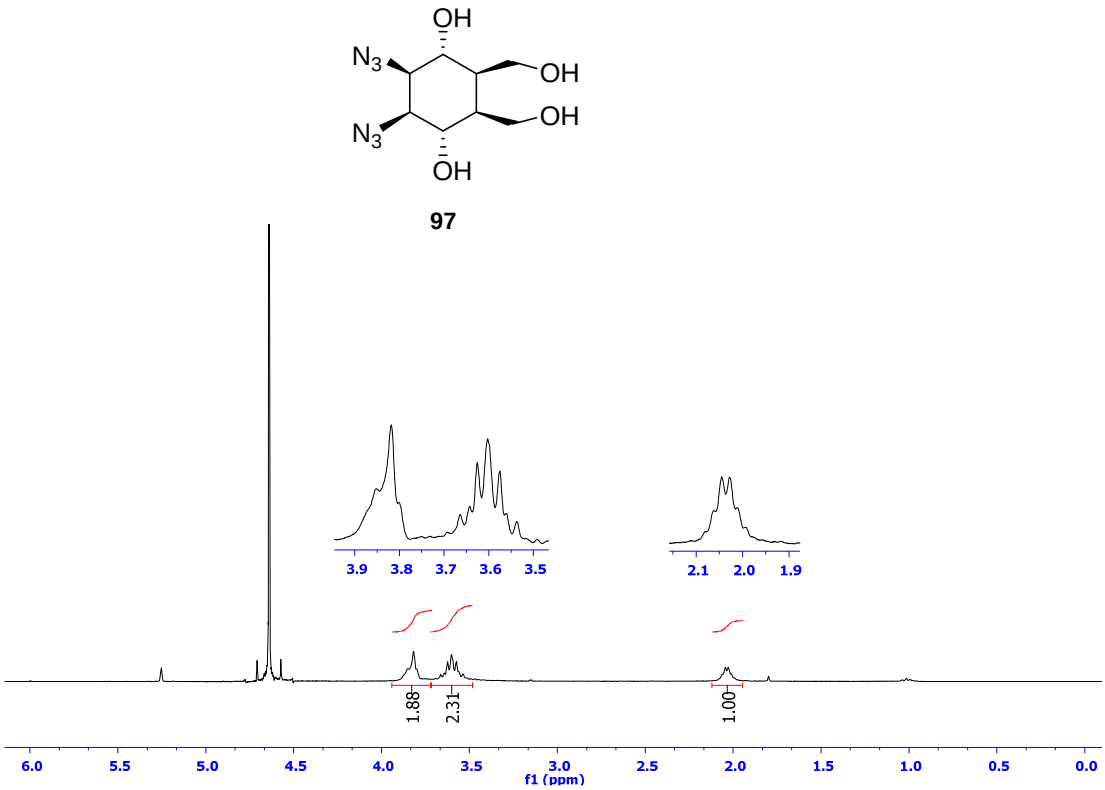


Figure 6.21. ^{1}H NMR Spectrum of Compound 97 (in D_2O)

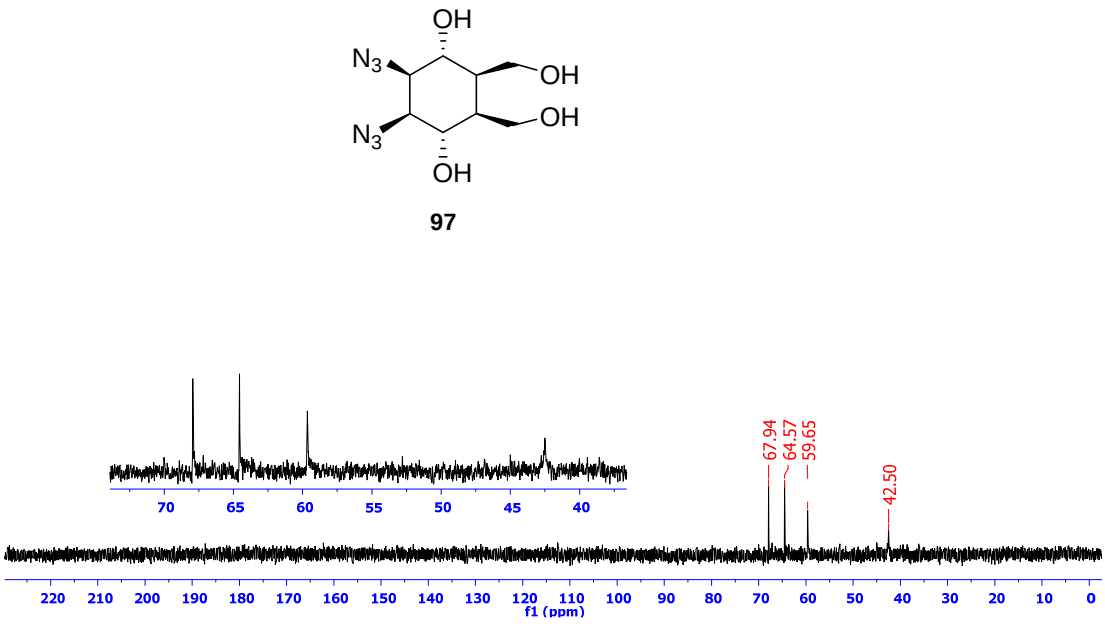


Figure 6.22. ^{13}C NMR Spectrum of Compound 97 (in D_2O)

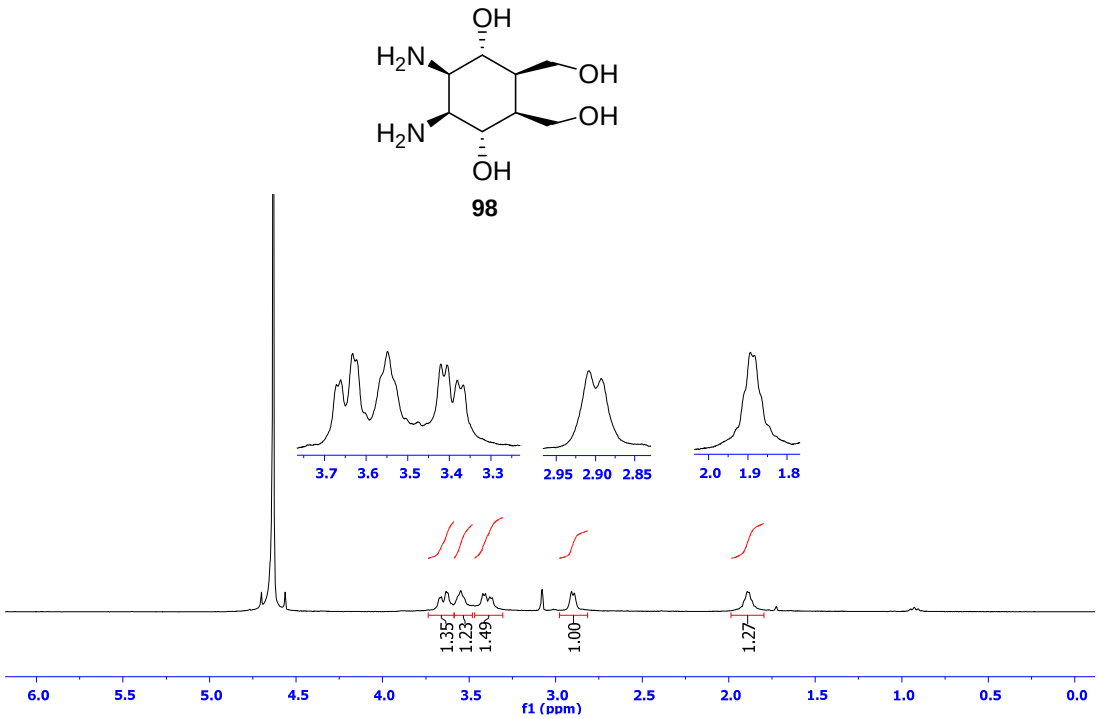


Figure 6.23. ^{1}H NMR Spectrum of Compound 98 (in D_2O)

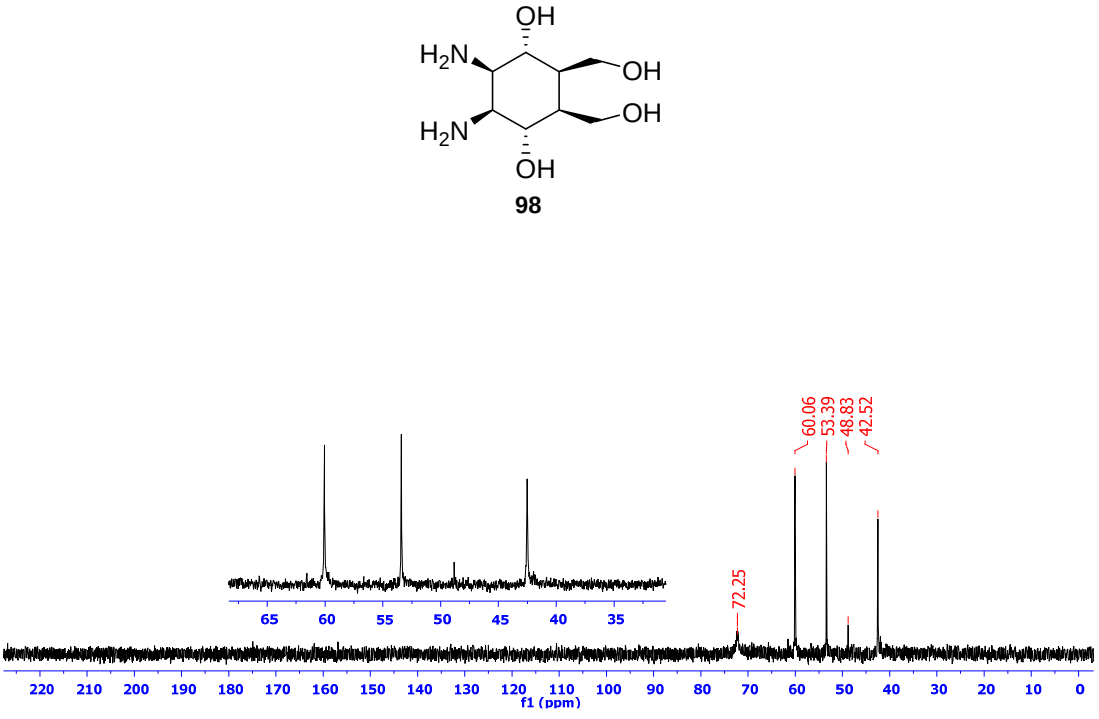


Figure 6.24. ^{13}C NMR Spectrum of Compound 98 (in D_2O)

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