Regio- and Stereoselective Syntheses of Chiral Carbohydrate Building Blocks and R-(-)-Anamarine; Identification of Three New Diterpene Esters from *Euphorbia Decipiens*

Regio- und stereoselektive Synthesen von chiralen Kohlenhydratderivaten und R-(-)-Anamarin; Identifizierung von drei neuen Diterpenestern aus *Euphorbia Decipiens*

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Dedicated

to my brother

Mian Muhammad Afzaal (Late)

Who supported and encouraged me at every moment of my life

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ABBREVIATIONS

Ac	acetyl
AcONa	sodium acetate
aq.	aqueous
as	asymmetric
Bn	benzyl
BuLi	butyl lithium
Bz	benzoyl
cat.	catalytic
conc.	concentrated
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DMF	N,N´-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equation
equiv.	equivalent
EtOAc	ethyl acetate
EtOH	ethanol
GASP	gated spin echo
h	hour
LDA	lithium diisopropylamide
M	molar

m.p.	melting point
m-CPBA	meta-chloroperbenzoic acid
MeOH	methanol
min	minute
Ms	mesyl
n	normal
NMR	nuclear magnetic resonance
P	para
ppm	part per million
Py	pyridine
rt	room temperature
s	singlet
t	triplet
TEA	triethylamine
tert	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
TsOH	-toluenesulfonic acid

A. INTRODUCTION

Chirality at the molecular level has emerged as one of the major issues in the development of chemical technology, especially in the area of drug synthesis and advanced materials. The push to use only optically pure intermediates in drugs and to conserve the integrity of chiral centers in subsequent transformations has placed very high technical and economical constraints on the development of new drug candidates.

The four common ways by which chirality is integrated into molecular targets are, by performing transformations on a chiral core, integrating a performed fragment or chiral synthone into the target, using a chiral catalyst or using a chiral auxiliary. The chiral pool approach, where chiral substructures are carved or derived from readily available, cheap, renewable materials, such as carbohydrates, amino acids, organic acids and terpenes, is especially important [1].

Carbohydrates are specially ideal as chirones for natural product synthesis. The combination of natural chirality and topology of cyclic sugar derivatives permit a high degree of regio- and stereo-controlled systematic functionalization of the chosen reaction centre [2,3]. There are two main strategies for the use of carbohydrates in asymmetric synthesis. The first is to employ them as scaffolds, cores, or templates on which structural transformations are performed transforming them into new entities that share reasonably close structural similarity with the starting species. In the second strategy carbohydrates are totally transformed to often-unrelated compounds that are then used in different synthetic applications.

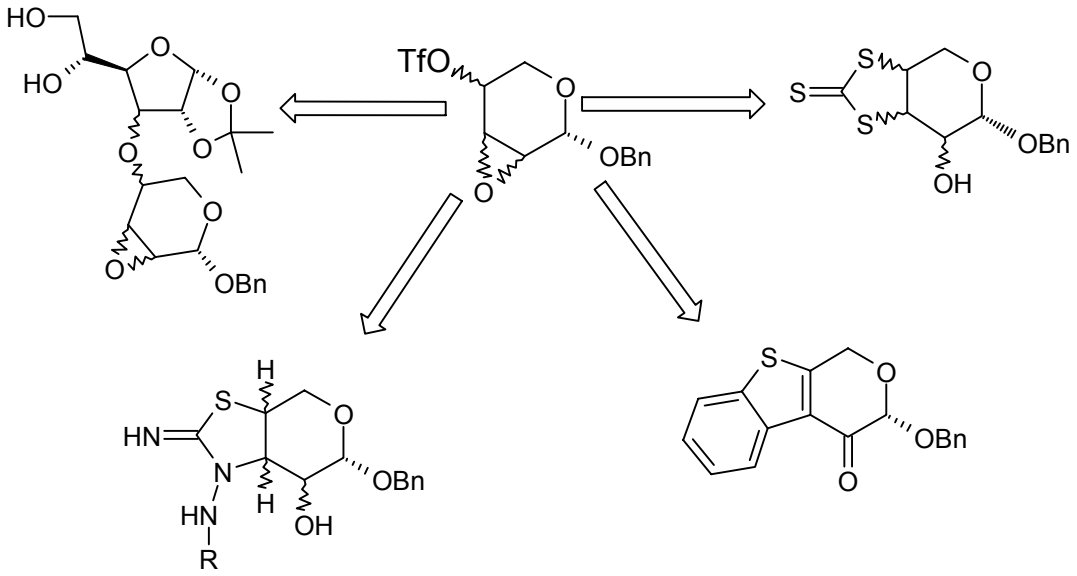


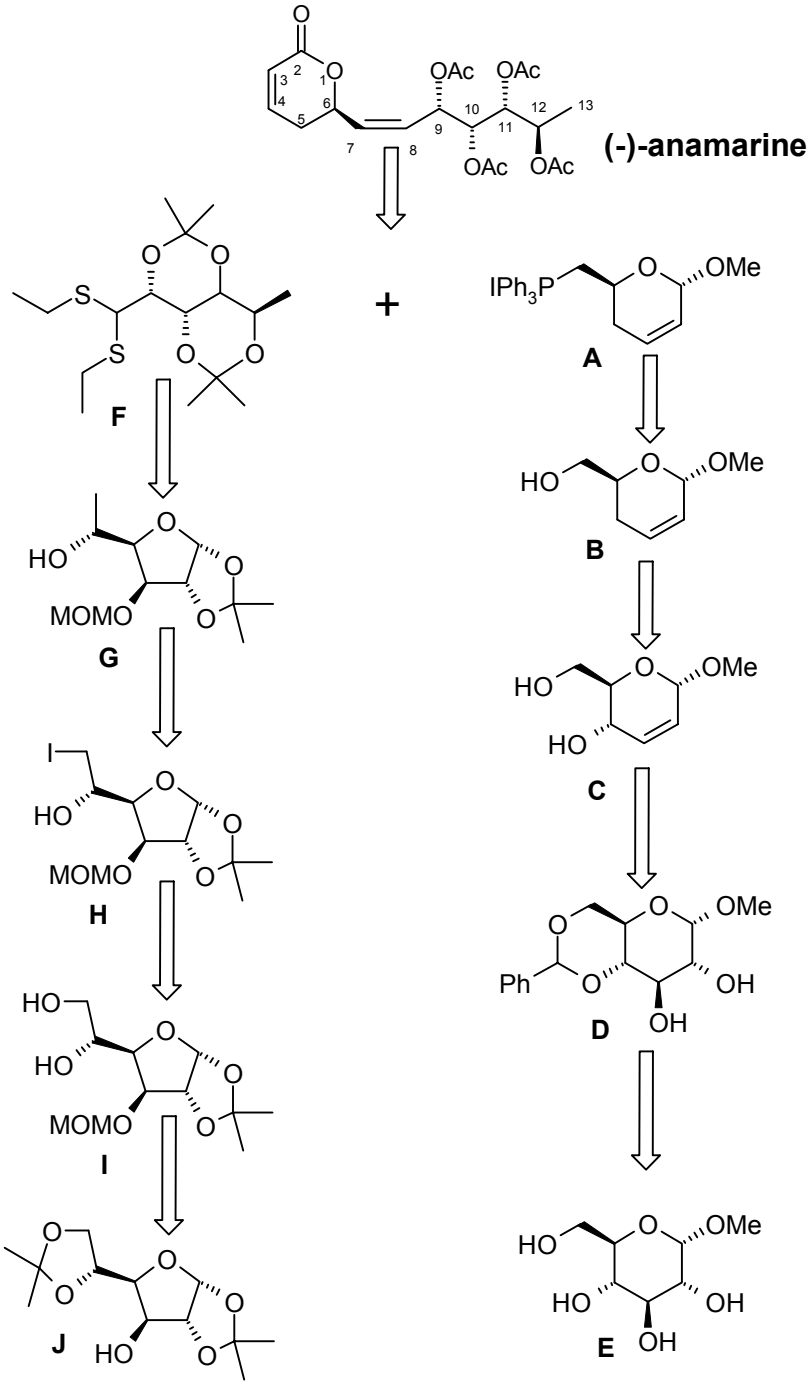
Fig. 1. Representation of new targets, synthesized from a 2,3-anhydro-pentose, used as "chiron" in this thesis.

The work presented in the synthetic part of this thesis relates a variety of examples for regio- and stereoselective transformations of 2,3-anhydropentoses giving chiral heterocyclic systems. Such carbohydrate-derived chiral templates can be further transformed into naturally occurring compounds or to interesting biologically active drugs [1-3]. A series of tri-substituted chiral thiazolidines with anti-tumour activity, trithiocarbonate derivatives as versatile intermediates for the synthesis of dithiosugars and dideoxysugars and a set of 3,4-disaccharides with the possible different potential biological activities have been synthesized (Fig. 1).

6-substituted 5,6-dihydro-α-pyrones, so-called α,β-unsaturated δ-lactones are widely distributed in plants as well as fungi and have been isolated from thirteen families of plants and twenty fungal species. They possess a diverse range of biological activities and have been reported as plant growth inhibitors, insect antifeedants, antifungal and antitumour agents [4].

The total synthesis of R-(-)-argentilactone, S-(+)-argentilactone R-(-)-massoilactone, (+)-osmundalactone has been achieved in Prof. Voelter's group, recently[5].

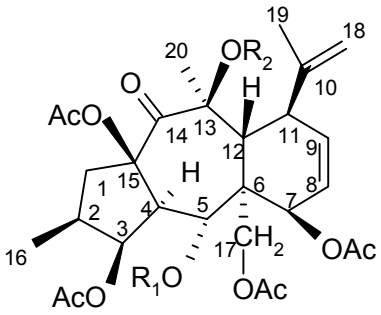
As a continuation to the synthesis of α,β-unsaturated δ-lactones, this thesis suggests an asymmetric synthesis of (-)-anamarine (Scheme 1).



Scheme 1. Reterosynthetic analysis of (-)-anamarine.

Reterosynthetically it can be envisioned (Scheme 1) that the intermediate alcohol **B**, can be a common precursor for the synthesis of α,β-unsaturated δ-lactones. The lactones containing double bond between C_7-C_8 can be constructed *via* a Wittig reaction between phosphonium salt **A** and aldehyde of **F**. The alcohol **B** can be constructed *via* a ring opening reaction on the benzylidene acetal **D**. The side chain can be synthesized by the acidic ring opening of deoxygenated alcohol **G**, which itself can be constructed *via* reduction of iodo-alcohol **H** (Scheme 1). As it become obvious from the scheme 1, methyl-α-D-glucopyranoside (**E**) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranoside (**J**) can be selected as the starting materials for the total synthesis of (-)-anamarine.

The second part of this thesis describes the isolation and chracterization of three new myrsinane type diterpene esters from *Euphorbia decipiens* (Fig. 2).



R_1	R_2
Bu	H
Bz	H
Bu	Ac

Fig. 2. Three new diterpene esters from *Euphorbia decipiens*.

Euphorbia is the largest genus of *Euphorbiaceae* family. Among the different types of compounds isolated from them, the bioactive, skin irritant polycyclic

diterpenoids, e.g. of the tigliaine and ingenane type, are common in their milky latex. Some of the plants belonging to the genus *Euphorbia* are used in folk medicine in order to cure some skin diseases, gonorrhea, migraine, intestinal parasites and warts. The dried roots of *E. kansui* are recorded in Sheng Nung's Herbal as low-grade drug and considered as a herbal remedy for edema, ascites and cancer in China. Some esters of myrsinol, a tetracyclic diterpenoid isolated from *E. myrsinites* showed anti HIV-1 reverse transcriptase (RT) inhibition [6-8].

The skin-irritant, tumor-promoting and anti-tumour and recently anti-HIV activities of these plants prompted us to reinvestigate *Euphorbia decipiens* Boiss for their chemical constituents.

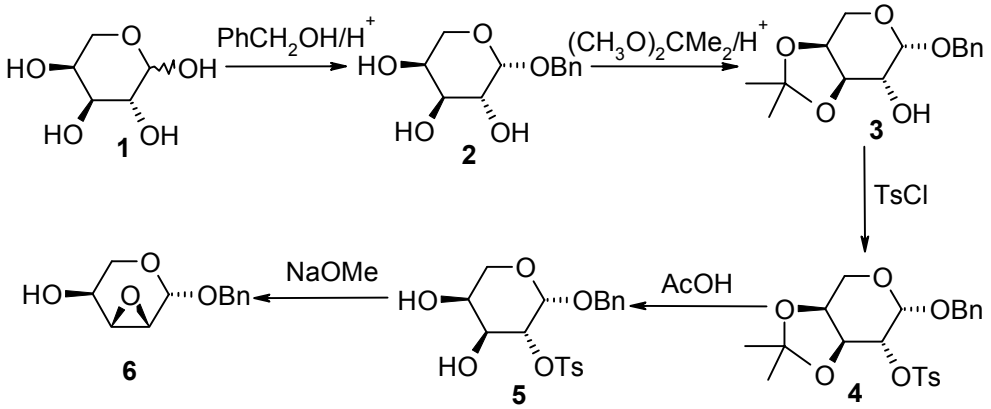
B. RESULTS AND DISCUSSION

B.I. 2,3-Anhydropentoses: Synthesis of Starting Materials

This part of the thesis demonstrates a variety of examples for regio- and stereoselective transformations of 2,3-anhydropentoses delivering a series of chiral targets (Fig. 1).

B.I.1. Synthesis of benzyl 2,3-anhydro-β-L-ribopyranoside (6) [9a]

Compound **6** was synthesized in 6 steps, starting from commercially available L-arabinose. Benzylation of L-arabinose in the presence of hydrogen chloride



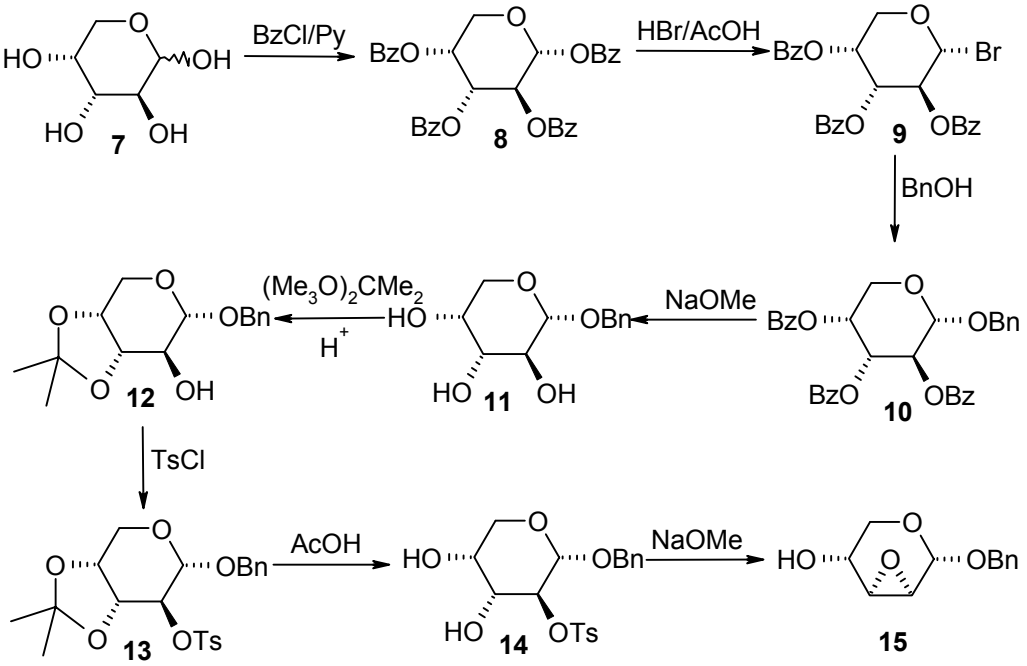
Scheme 2. Synthesis of benzyl 2,3-anhydro-β-L-ribopyranoside (**6**) from L-arabinose (**1**) *via* benzyl-β-L-arabinopyranoside (**2**), benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**), benzyl 3,4-*O*-isopropylidene-2-*O*-*p*-tosylsulphonyl-β-L-arabinopyranoside (**4**) and benzyl 2-*O*-*p*-tosylsulphonyl-β-L-arabinopyranoside (**5**).

leads to the anomerically protected benzyl β-L-arabinopyranoside (**2**) [10]. The two hydroxyl groups at C-3 and C-4 were protected *via* 2,2-dimethoxypropane and *p*-toluenesulphonic acid in acetone which formed benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**). The left behind free hydroxyl group at C-2 was tosylated with *p*-toluene sulphonyl chloride in

pyridine, giving compound **4**. The isopropylidene protecting group was selectively removed from **4** with 90% acetic acid to yield **5** [11]. The target compound **6** was finally obtained by the action of sodium methoxide in methanol on compound **5**, followed by neutralization with dilute hydrochloric acid (Scheme 2).

B.I.2. Synthesis of benzyl 2,3-anhydro-α-D-ribopyranoside (**15)**[9a]

The synthesis of compound **15** was achieved from D-arabinose (**7**), whereby it is known that the direct benzylation does not yield the α-anomer in high quantity due to the anomeric effect. In order to overcome this problem, one has to follow an alternative procedure (Scheme 3) [12] in which **7** was converted into the tetrabenzoyl derivative **8** by the action of benzoyl chloride

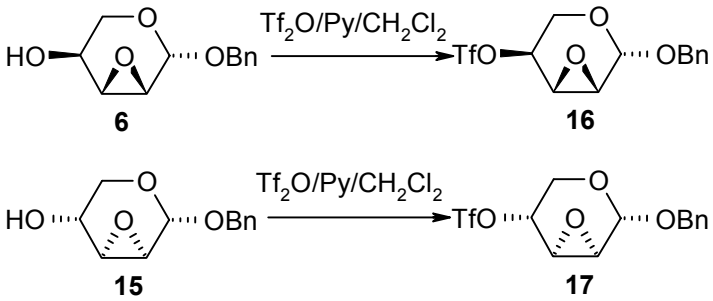


Scheme 3. Synthesis of benzyl 2,3-anhydro-α-D-ribopyranoside (**15**) *via* D-arabinose (**7**), tetrabenzoate of benzyl arabinopyranoside (**8**), 2,3,4-tri-O-benzoyl-β-D-arabinopyranosyl bromide (**9**), benzyl 2,3,4-tri-*O*-benzoyl-α-D-arabinopyranoside (**10**). benzyl α-D-arabinopyranoside (**11**), benzyl 3,4-*O*-isopropylidene-α-D-arabinopyranoside (**12**), benzyl 3,4-*O*-isopropylidene-2-*O*-p-tosylsulphonyl-α-D-arabinopyranoside (**13**) and benzyl 2-O-p-tosyl-sulphonyl-α-D-arabinopyranoside (**14**).

in pyridine. The anomeric mixture of compound **8** was treated with hydrogen bromide in 30% acetic acid to furnish **9**, which, *via* S_N2 reaction with benzyl alcohol, affords the α-D-benzyl glycoside. The benzoyl groups in **10** were removed by sodium methoxide in methanol, to give benzyl α-D-arabinopyranoside (**11**). The target compound **15** was obtained following analogous reaction sequences as described for the syntheses of compound **6** (Scheme 3) [9a].

B.I.3. Synthesis of benzyl 2,3-anhydro-4-*O*-triflylribopyranosides [9a]

Triflation of the free hydroxyl group in **6** and **15** was successfully achieved at low temperature (-20°C) *via* treatment with trifloromethansulphonic anhydride in dichloromethane. The triflates **16** and **17** were obtained in high yield upon basic work up at 0°C (Scheme 4).



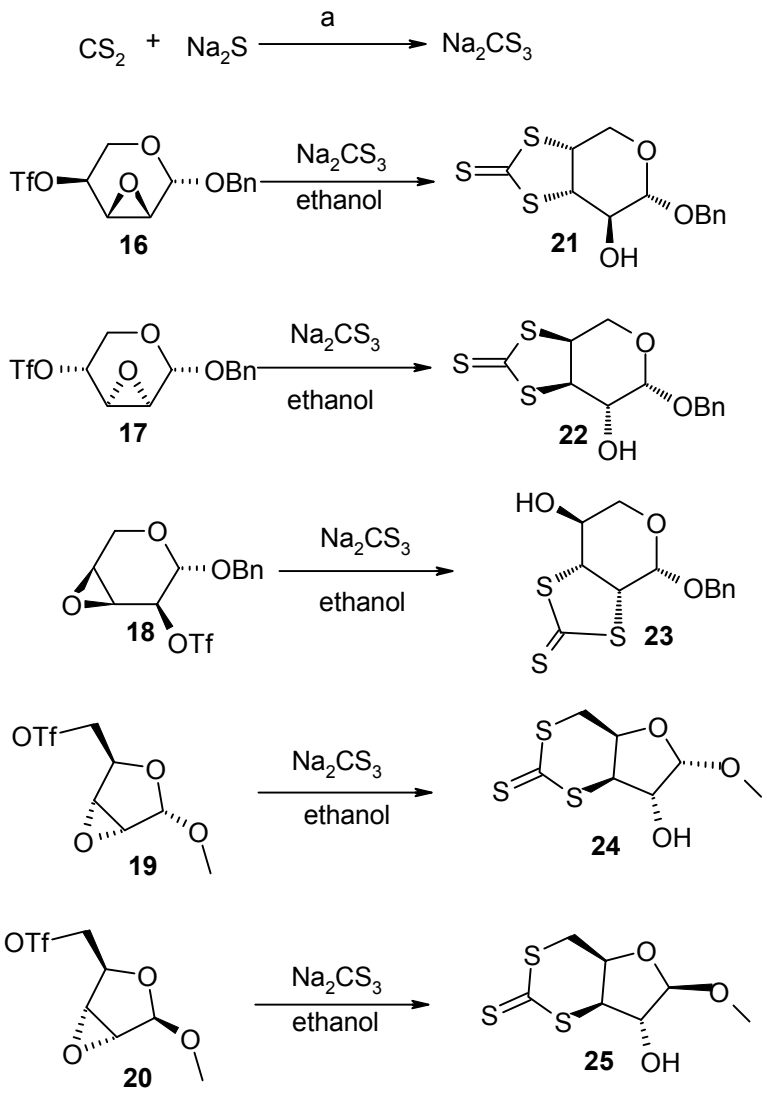
Scheme 4. Synthesis of benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**16**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**17**) from benzyl 2,3-anhydro-β-L-ribopyranoside (**6**) and benzyl 2,3-anhydro-α-D-ribopyranoside (**15**), respectively.

B.II. A Convenient Method for the Synthesis of Cyclic Trithiocarbonates on Carbohydrate Scaffold

The preparation of monosaccharides, in which one or more oxygen atoms have been replaced by a sulphur atom, has received considerable attention, primarily due to the fact that these compounds provide a route to the synthesis of deoxy sugars [13]. Trithiocarbonate derivatives of carbohydrates are versatile intermediates for the synthesis of dithiosugars [14] and dideoxysugars [15]. Many non-carbohydrate organic compounds containing trithiocarbonates has been reported to posses interesting biological activities [16-19]. However to the best of our knowledge, no sugar-embedded Trithiocarbonate has been reported for its biological activity. Moreover, only a few methods are available for the synthesis of such carbohydrate derivatives, such as the reaction of potassium methylxanthate on epoxides [20] and episulphides [21] or in some cases the use of toxic thiophosgene gas [22].

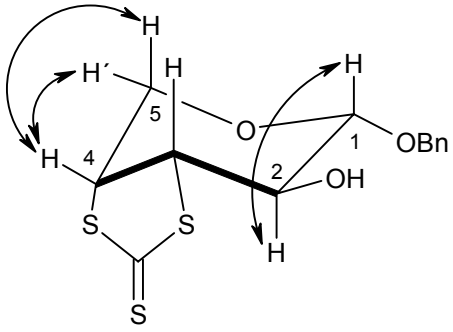
The reaction of organic halides with sodium trithiocarbonate has been widely used for the preparation of disubstituted trithiocarbonates [23]. Moreover, alkyl mono- and dihalides, upon treatment with sodium trithiocarbonate, could easily be converted into the corresponding mono- or dimercaptans [24]. Recent efforts towards the preparation of dialkyl trithiocarbonates [25] prompted us to investigate the epoxy triflates **16** and **17** for possible candidates of sugar-based trithiocarbonates. In the past, the triflates of the 2,3-anhydro-ribopyranosides **16** and **17** have been used by Prof. W. Voelter's research group as starting materials towards the synthesis of either new useful chiral building blocks or biologically active natural

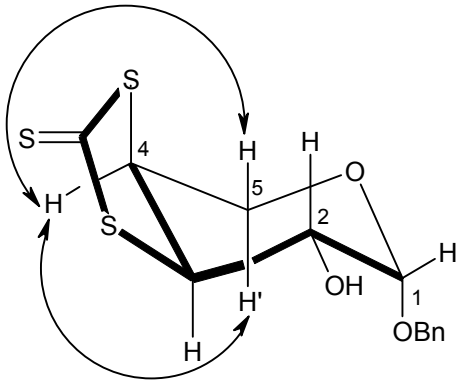
products [26-28]. The strategy banks upon the difference in the reactivity between the cis-oriented triflate at C-4 as a powerful leaving group and the epoxide. This strategy enables us to control the regioselective nucleophilic displacement of the triflate group forming trans-oriented systems that can be further modified by chemical transformations. In this chapter, a simple and efficient route for the synthesis of cyclic trithiocarbonates **21** and **22** from the anhydrotriflates **16** and **17** is described (scheme 5). The simple one



Scheme 5. Synthesis of sugar trithiocarbonates **21, 22, 23, 24** and **25** from epoxy triflates **16**, **17**, **18**, **19** and **20**, respectively. *Reagents and conditions*: a) H_2O, aliquat 336®, 40°C, 90 min [29].

pot reaction involves the addition of red-coloured aqueous solution of Na_2CS_3 to a stirred solution of benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**16**) (354 mg, 1 mmol) in ethanol (5 ml) at room temperature over a period of 10 min. Na_2CS_3 can be produced by reacting Na_2S (2.44 gm, 10 mmol) in water (5 ml) with CS_2 (0.608 ml, 10 mmol) with or without a phase transfer catalyst e.g. trioctylmethylammonium chloride (aliquat 336®) (22.5 μl) [29]. The nucleophilic displacement of the triflyl group at C-4 by sulphur was followed by the simultaneous interamolecular ring opening of the epoxide to afford benzyl 3,4-dideoxy-3,4-S-thiocarbonyl-α-D-arabinopyranoside (**21**) in 90% yield. The reaction was then tested for the triflate of the other anhydro sugars. Benzyl 3,4-anhydro-2-O-triflyl-β-L-arabinopyranoside (**18**) was prepared from **6** in two steps [30]. After treatment with the solution of Na_2CS_3, **18** is converted into the trithiocarbonate sugar **23** in good yield. However, the anhydrofuranoside **19** and **20** [31] gave a sluggish reaction to yield the trithiocarbonates **24** and **25**





21
$^1C_4$- Conformation
$J_{5,5'}$ = 13.4 Hz
$J_{4,5}$ = 3.05 Hz
$J_{4,5'}$ = 3.05 Hz
$J_{1,2}$ = 6.41 Hz

22
$^4C_1$- Conformation
$J_{5,5'}$ = 13.4 Hz
$J_{4,5}$ = 1.8 Hz
$J_{4,5'}$ = 3.05 Hz

Fig. 3. Preferred conformations of the pyranose ring in **21** and **22**.

in less than 50% yields containing other impurities (scheme 5).

The structures of all the products were established through MS, elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. The conformation adopted by the pyranoside rings in the products **21** and **22** were determined by the vicinal coupling constants and chemical shifts of their ^{1}H NMR spectra. 5-H and 5´-H were recognized from their large geminal coupling constant (~13 Hz) at δ = 4.30 and 3.87 ppm, respectively in **21**, and at δ = 4.15 and 3.38 ppm, respectively in **22**. A symmetrical ddd pattern appeared for H-4 of **21** with, $J_{4,5'}$ = 3.05 and $J_{4,5}$ = 3.05 and $J_{3,4}$ = 4.27 Hz. This indicates a quasi equatorial-quasi equatorial relation between 4-H and 5´-H and a quasi equatorial-axial relationship between 4-H and 5-H; conformation of

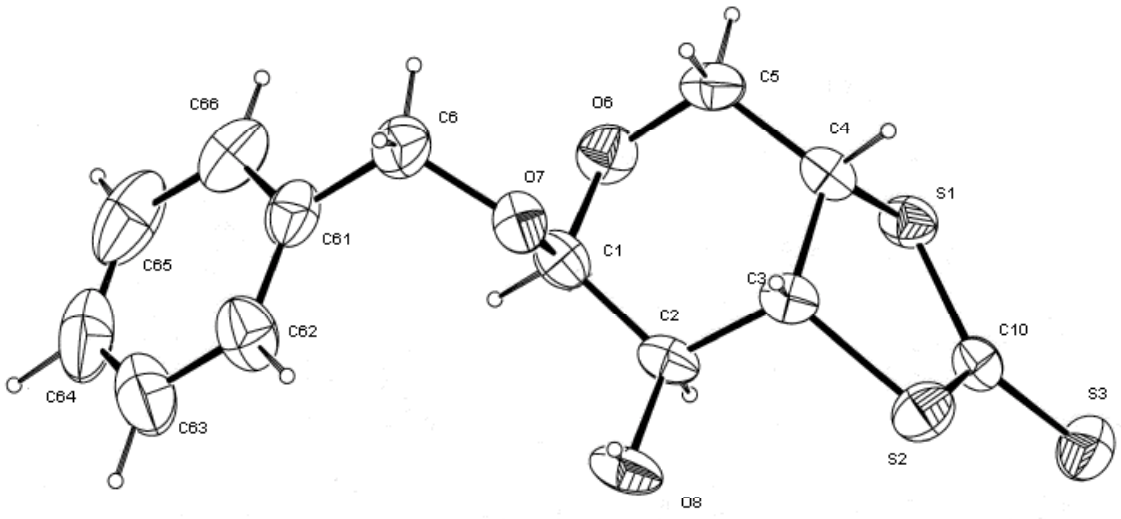


Fig. 4. Molecular structure of **22**. Selected bond length (Å) and angles (°): C(2)-O(8) 1.421, C(3)-S(2) 1.817(3), S(2)-C(10) 1.734(3), C(10)-S(3) 1.640(3), S(1)-C(10) 1.742(2), S(1)-C(4) 1.825(3); O(8)-C(2)-C(3) 111.3(2), C(2)-C(3)-S(2) 110.2(2), S(2)-C(10)-S(1) 114.8(2), S(1)-C(10)-S(3) 122.9(2), C10-S(1)-C(4) 96.8(12), S(1)-C(4)-C(5) 113.3(2).

pyranoside ring in **21** is, therefore, predominately $^{1}C_{4}$. This is further supported by large axial-axial coupling ($J_{1,2}$ = 6.41 Hz) for H-1 and H-2.

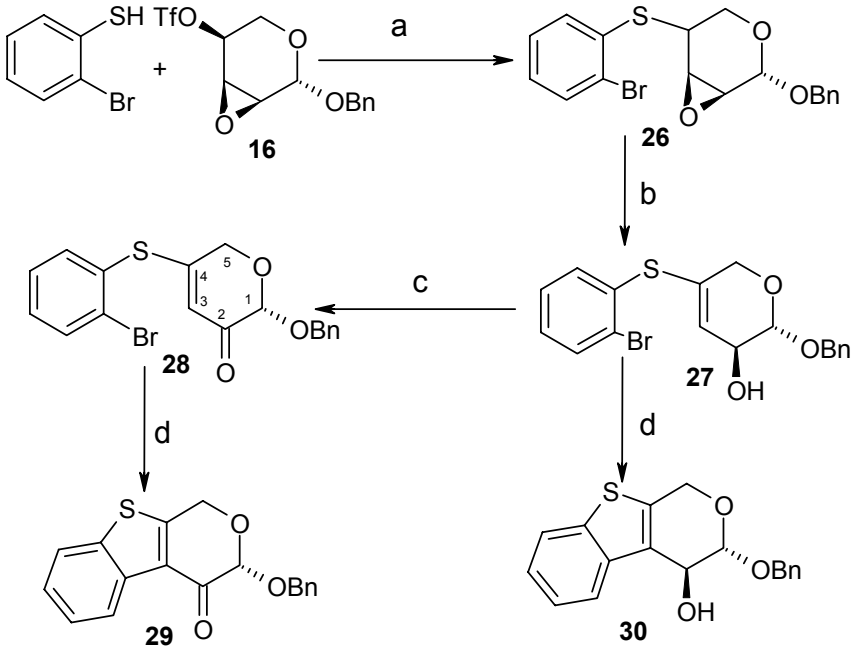
On the other hand in **22** 4-H appeared as a multiplet at δ = 4.81 ppm buried in the signal of the benzylidene protons. Although the direct calculation of the coupling constant is not possible in this case, the coupling interactions of 4-H with 5-H and 5´-H were calculated from dd patterns observed for the latter protons, revealing a 1.83 Hz value for $J_{4,5}$ and a 3.06 Hz value for $J_{4,5'}$. From these assignments, a quasi equatorial position for 4-H is assumed. Hence the pyranoside ring in **22** occurred predominately in the $^{4}C_{1}$ conformation (Fig. 3). Fig 4 shows the ORTEP diagram of compound **22** with selected bond lengths and bond angles.

In summary, our new template **21**-**25** will allow further elaboration to other targets through chemical modification on the trithiocarbonate part of the molecules.

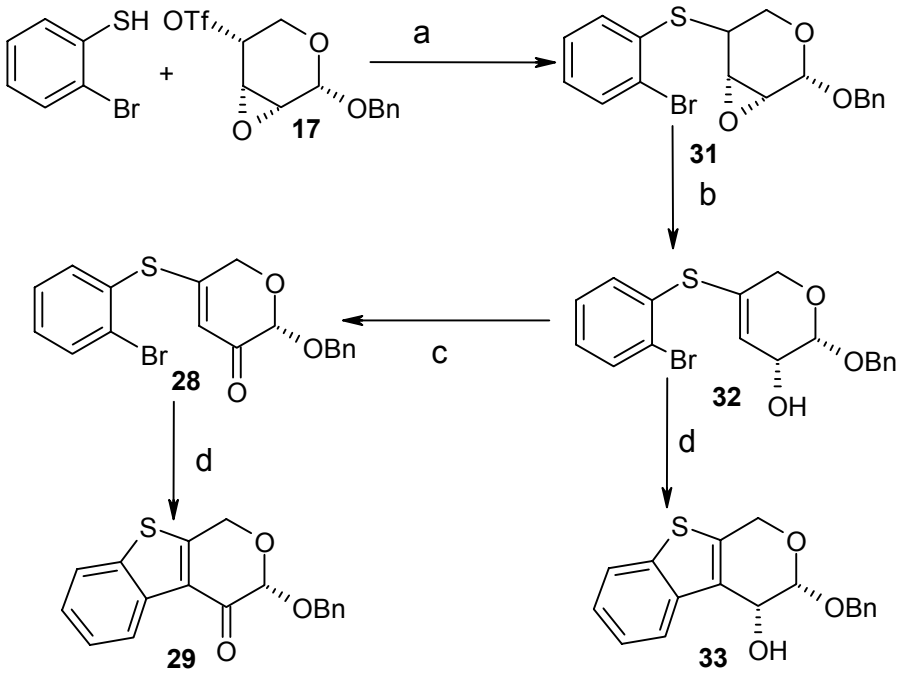
B.III. Approach for the Synthesis of Benzothiophene Fused to the Carbohydrate Skeleton

Derivatives of benzothiophene are known to be biologically active [32,33]. Polycyclic aromatic hydrocarbons have been widely studied because of adverse biological activity e.g. multigenic and/or carcinogenic. Analogous sulphur heterocycles, in which one aromatic ring has been replaced by a thiophene ring, also have shown carcinogenic and mutagenic activities [33,34]. Sugar moieties are naturally present in many biologically active molecules. Therefore fusing a sugar moiety to the benzothiophene system attracted us to synthesize some of such derivatives from 2-bromothiophenol and benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**16**), or benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**17**). The 2-bromo benzosulfonyl anion was generated with Na_2CO_3 in CH_3CN and made to attack on the triflate of epoxy sugar to get **26** (Scheme 6 & 7). Which was further treated with BuLi at -40 °C to form **27**. In **26** the ^{13}C NMR signal at δ = 39.0 indicates the presence of sulphur at C-4. While the presence of two signals at δ = 54.2 and 50.2 indicate the presence of an epoxy ring in the molecule.

The anomeric signal of **27** is located at δ = 4.81 (d, J = 2.1 Hz) indicating the axial-equitorial relation in H-1and H-2 while the olefinic signal was found at δ = 6.14 (d, J = 4.6 Hz). As H-2 in both the cases (**27** and **32**) gave a br. singlet so the direct calculation of coupling constant was not possible. The coupling constant of H-2 in **27** was calculated indirectly and found $J_{1,2}$ = 2.1 and $J_{2,3}$ = 4.6. The anomeric and olefinic protons of **32** were found at δ = 4.99 (d, J = 4.1 Hz) and 6.10 (d, J = 2.2 Hz) respectively.



Scheme 6. Synthesis of benzothiophene derivatives **29** and **30** from benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**16**) and 2-bromothiophenol. *Reagents and conditions*: a) Na_2CO_3/CH_3CN, 0°C, 8h, b) BuLi/THF, -40°C, 5h, c) pyridinium chorochromate, CH_2Cl_2, reflux, 5h, d) $Pd(OAc)_2(PPh_3)_2$, $NaHCO_3$, CH_3CN, reflux.



Scheme 7. Synthesis of benzothiophene derivatives **29** and **33** from benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**17**) and 2-bromothiophenol. *Reagents and conditions*: a) Na_2CO_3/CH_3CN, 0°C, 8h, b) BuLi/THF, -40°C, 5h, c) pyridinium chlorochromate, CH_2Cl_2, reflux, 5h, d) $Pd(OAc)_2(PPh_3)_2$, $NaHCO_3$, CH_3CN, reflux.

The coupling constant of H-2 in **32** was calculated indirectly and found $J_{1,2}$ = 4.1 and $J_{2,3}$ = 42.2 Hz. The alcohols **27** and **32** were oxidized to ketone in quantitative yield [35]. Having **27**, **28** or **32** in hand, we planned to do an intramolecular Heck reaction [36-37] to get the required compounds **29, 30** or **33**.

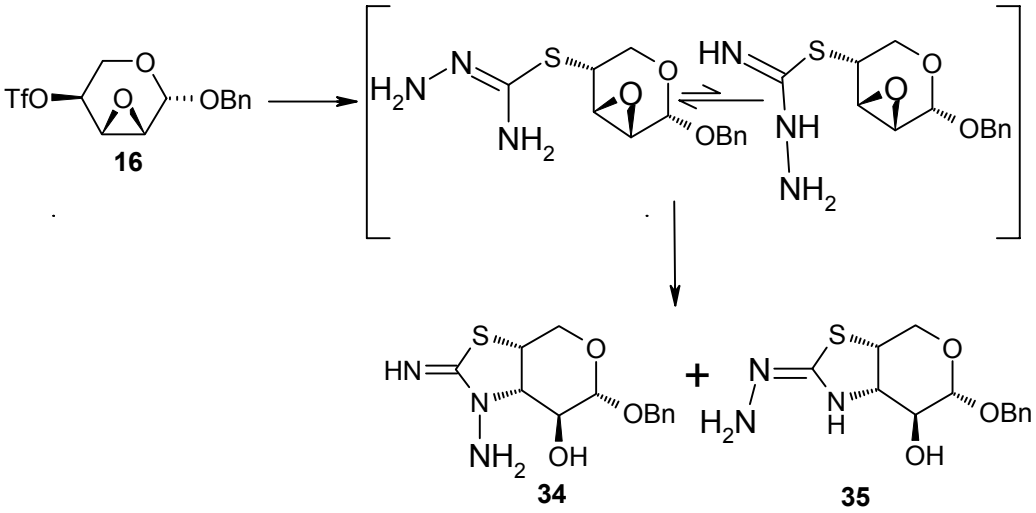
B.IV. An Expeditious Synthesis of Highly Functionalized Tri-substituted Chiral Thiazolidines

Substituted thiazolidine derivatives represent important key intemediates for the synthesis of numerous pharmacologically active drugs [38-40]. A number of thiazolidines has been claimed to be retroviral protease inhibitors [41,42]. Substituted thiazolidine derivatives have been supposed as substitutes for the carbohydrate moiety in the synthesis of new antiviral nucleosides [43].

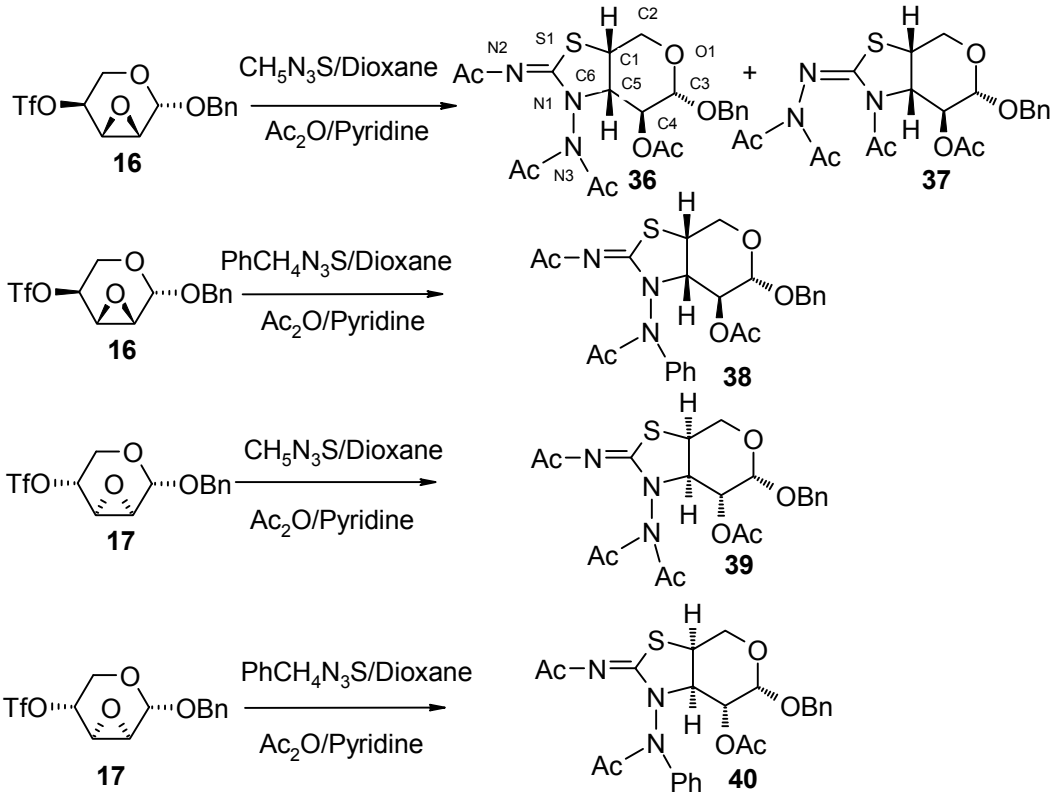
Many non-carbohydrate organic compounds containing thiazolidines have been reported to possess interesting biological activities [37-43], but, to the best of our knowledge, no sugar-embedded thiazolidine has been reported for its biological activity. In the past, much attention has been given to the synthesis of substituted thiazolidene-4-ones, as they have been recognized as fundamental heterocyclic compounds, comprising, for example, an anti-PAF (Platelet Activating Factor) drug, a key intermediate for β-lactams, sulphur containing mimic of D-ribose, and oxygenase inhibitors [44]. Thiazolidine-4-ones show a large spectrum of biological activities and can be used as a precursor in the synthesis of heterocyclic compounds [45-47].

Developing new strategies by using the novel chiral synthons benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside **16** and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside **17** thereof leading to novel synthetic approaches to chiral heterocyclic systems is an attractive approach. In this thesis, a one pot procedure for the synthesis of chiral substituted thiazolidines is described (Scheme 9). The unexplored chemistry and bioactivity of the

thiazolidines **34-40** led us to synthesize these compounds from thiosemicarbazide/4-phenylthiosemeicarbazide and epoxy triflates (Scheme 9). Thiosemicarbazide and β-epoxy triflate **16** are used for the synthesis of **34-35** in 1,4-dioxane (Scheme 8).



Scheme 8. The two possible *S*-substituted thiosemicarbazide intermediate in the thazolidine formation reaction.



Scheme 9. Synthesis of acetylated thiazolidine **36-40**

The intermediate is presumably an *S*-substituted thiosemicarbazide derivative, which leads to an opening of the epoxy ring by the participation of the nitrogen atom. However, the intermediates could not be isolated despite numerous attempts (Scheme 8).

After the completion of the reaction (TLC controlled), the reaction mixture was concentrated under reduced pressure and acetylation was carried out without purification of the product so as to protect the free amino, imino and alcoholic groups. The anomeric proton in **40** appeared as doublet at δ = 5.06 (d, J = 3.05 Hz) and the H-2 at 5.18 (dd, J = 3.05, 7.92 Hz). The coupling constant between H-2/H-3 (7.92 Hz) indicated the axial-axial relation between the two protons, therefore $^4C_1$ is the predominant conformation in **40**, while the anomeric and H-2 protons in **36**, **37** and **38** gave a singlet.

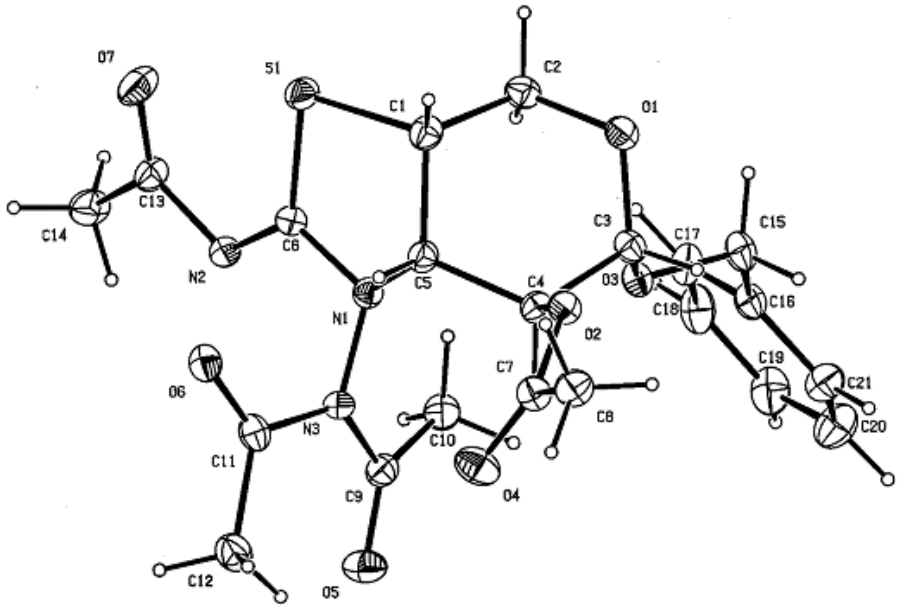


Fig. 5. Molecular structure of **36.** Selected bond lengths (Å) and bond angles (°); S(1)-C(6) 1.738(7); N(1)-C(5) 1.474(9); S(1)-C(1) 1.814(8); N(1)-C(6) 1.388(9); C(1)-C(5) 1.523(11); N(3)-C(11) 1.419(10); N(3)-C(9) 1.411(9); N(2)-C(13) 1.399(9); O(2)-C(4) 1.437(8); C(6)-S(1)-C(1) 91.6(3); C(6)-N(1)-C(5) 114.8(5); N(3)-C(11)-C(12) 118.7(7); N(3)-C(9)-C(10) 116.1(7); C(3)-O(3)-C(15) 111.6(5); C(6)-N(1)-N(3) 115.9(5); C(5)-C(1)-C(2) 112.6(6).

The x-ray diagram, however indicated the $^1C_4$ conformation in **36**, with expected coupling constant of ~ 6.5 Hz. After column chromatography, the thiazolidine **36** was crystallized from ethanol:water system and then subjected for x-ray crystallography. Figure 5 shows the ORTEP diagram of compound **36** with selected bond lengths and angles. C(1)-S(1) and N(1)-C(5) are found to have bond length values of 1.388(9) and 1.474(9) Å, respectively. A shorter bond length of the bond N(2)-C(6) is found with the value 1.289(9) Å indicating C=N bond.

A mixture of thiazolidine **34** and **35** was submitted for the anti-tumour activity against SK-N-LO cell line and found to be 88% active (Fig. 5).

B.IV.1. MTT Assay

B.IV.1.1. Principles of the MTT assay

MTT is used for the quantitative determination of cellular proliferation and activation e.g. in response to growth factors and cytokines such as IL-2 or IL-6. In cancer research, the MTT assay is used for quantification of in *vitro* chemoselectivity of tumour cells and the screening of anti-cancer compounds. The assay is based on the mitochondrial conversion of a water-soluble tetrazolium salt, 3-[4,5-dimethylthiazol-2-y1]-2,5-diphenyltetra-zolium bromide (MTT) into a water-insoluble formazan. The assay is based on the cleavage of the yellow tetrazolium salt MTT to purple formazan crystals by metabolic active cells. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, coloured formazan product. This cellular reduction involves the pyridine nucleotide cofactors NADH and NADPH. An increase in the number of living cells results in an

increase in the total metabolic activity in the sample and the level of activity is a measure of the viability of the cell. This increases directly correlates to the amount of the purple formazan crystals formed as monitored by the absorbance. These salt crystals are insoluble in aqueous solution, but may be solubilized by adding the solubilization solution and incubating the plates overnight in humidified atmosphere (e.g. 37°c, 5% CO_2). The solubilized formazan product is spectrophotometrically quantified at 550 nm using an ELISA plate reader.

B.IV.1.2. Preparation of the MTT solution

5mg of MTT are dissolved in 1 ml of PBS (Phosphate buffered saline). The solution should be filtered through a 0.2 μm filter, wrapped in aluminum foil (MTT is a light sensitive substance) and stored at 4°C.

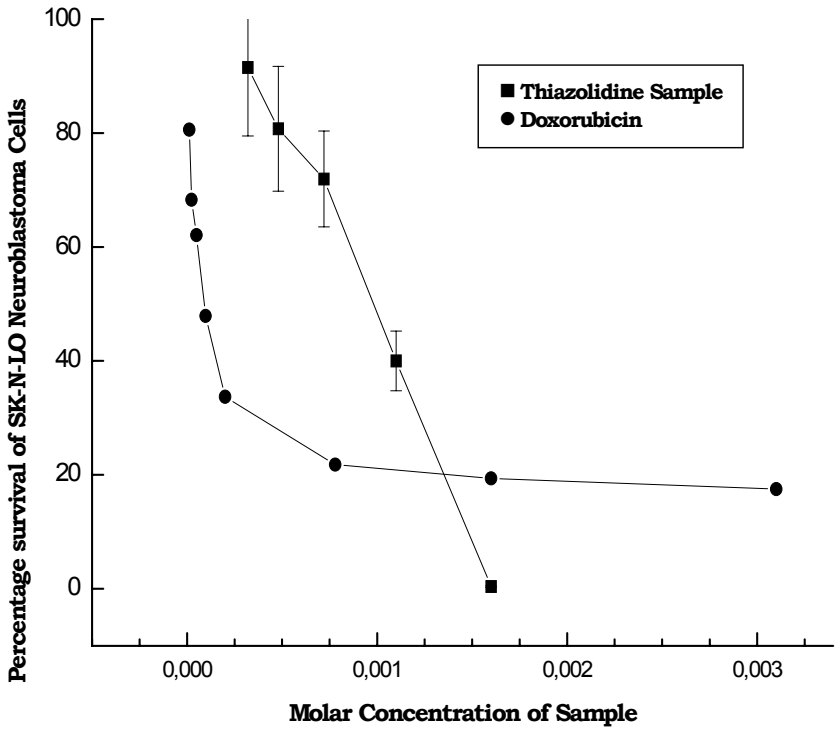


Fig. 6. Cytotoxic effect of thiazolidines **34** and **35** on the human neuroblatoma cell line SK-N-LO.

B.IV.1.3.Preparation of Ispropanol-triton X-100 solution

In order to get this solution 0.10 M HCl in isoprpopanol +10% Triton X-100 should be mixed. This solution should be stored at room temperature.

B.IV.1.4. MTT assay with neuroblastoma cells

1. 200 μL of a cell suspension (2 x 10^5 cells/ml of cell culture medium) are placed with a dispenser multipipette (Eppendorf) into each well of the 96 well microtiter plate, 3wells are filled with cell culture medium only and are used as BLANK: the plate is incubated overnight in an incubator at 37°C, 5% CO_2.
2. After 24 hours, the substance which effects have to be investigated are added in 10μL volumes. In the control wells the same volumes of PBS were added instead of substance. The 96 well microtiter plate is further incubated for 48 hours at 37°C, 5% CO_2.
3. After an incubation of 48 hours, the cell culture medium was removed completely by a Pasteur pipette, which is installed on a vacuum pump. A further 100μl of an MTT solution (MTT stock solution should be diluted 1:9 with RPMI-1640) is added into each well.
4. The microtiter plate was further incubated for 3 hours in the incubator. During this time, MTT is transformed into formazan, wich microscopically represents blue crystals between the cells at the bottom of the wells.
5. Then, 100μl of isopropanol solution were added to each well and the plate was shaken horizontally for further 8-10 hours (usually over night) at room temperature. During this time, formazan crystals are dissolved after

this step, microscopically, no crystals should be observed in any well. In all wells there should be homogenous colour observed.

6. Finally, the absorbance of the colour in each well was measured by a microplate reader (MR700) in a dualmode with a reference wavelength at 550 nm (filter number 5) and a rest wavelength at 630 nm (filter number 4).

B.V. Approach to the Total Synthesis of R-(-)-Anamarine, the Non-natural Enantiomer of Anamarine (42)

Anamarine was isolated in 1979 from the flowers and leaves of a *Peruvian hyptis* was shown to have the structure **41** (Fig. 7). Anamarine has been synthesised from D-glucose as starting material [48,49].

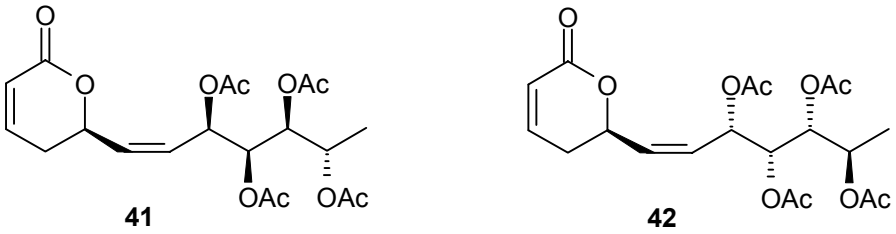
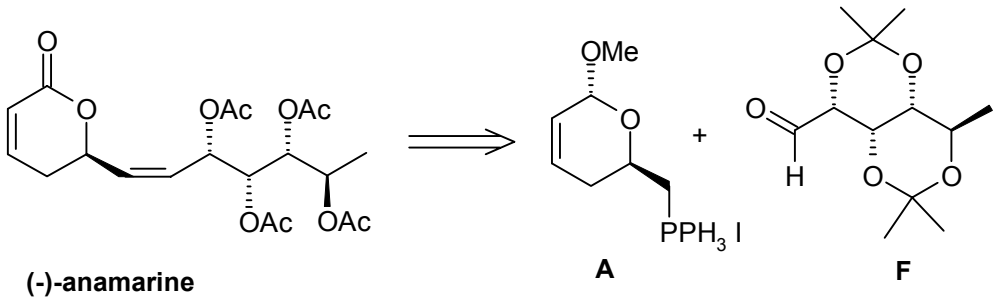


Fig.7. Structure of (+)-anamarine (**41**) and (-)-anamarine (**42**).

Here we report the synthesis of (-)-anamarine using methyl α-D-glucopyranoside as carbohydrate template (schemes 1 and 10).

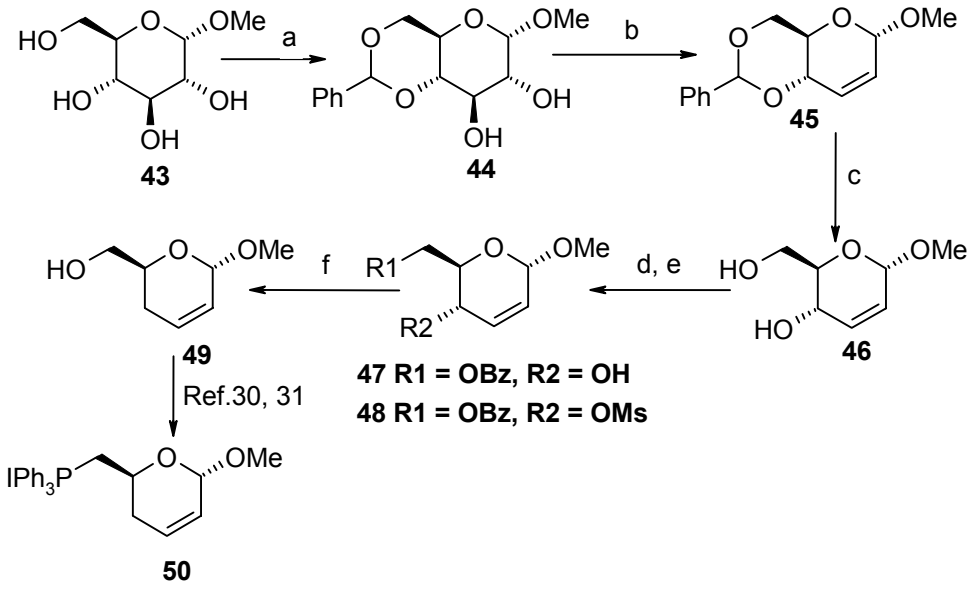


Scheme 10. Reterosynthesis of (-)-anamarine.

B.V.1. Synthesis of part A of (-)-anamarine

According to the reteroanalysis (Scheme 1 and 11), methyl-α-D-glucopyranoside (**43**) can be a potential starting material for the synthesis of δ-lactones. So it was efficiently converted into methyl-4,6-di-*O*-benzylidene-α-D-glucopyranoside (**44**) in 90 % Yield (scheme 11). The vicinal diol **44** was

now ready to undergo 2,3-dideoxygenation and we applied, firstly, the conditions described by Garegg and Samualsson [50a]. The reaction was not, however, clean and an impure product with a low yield was obtained. As a second choice, we found that Iodoform/imidazole/triphenyl-phosphene in toluene [50b] is an excellent reagent to produce **45** (87% yield) as nice crystals (Scheme 11). Hydrolysis of **45** was carried out by $AlCl_3$/t-BuOOH in CH_2Cl_2 at –40°C in 80% yield. Stereoselective protection of diol **46** at primary position with benzoyl chloride at 0°C and mesylation of the secondary alcohol was carried out to produce **48** in 90% yield over two steps (Scheme 11). The mesyl group was displaced with superhydride® (lithium triethylborohydride, 1M solution in THF) to get **49** in 70% yield. The alcohol **49** can be converted to **50** over two steps according to references [48,49].



Scheme 11. Synthesis of **A** part of (-)-anamarine. *Reagent and conditions*: a) α,α-dimethoxytolune, *p*-toluenesulphonic acid, DMF, reflux under reduced pressure, 1h; b) PPh_3, imidazole, CHI_3, toluene, 2h; c) $AlCl_3$, t-BuOOH, CH_2Cl_2, -40°C, 30 min; d) benzoyl chloride, pyridine, 0°C, 8h, 90%; e) MsCl, pyridine, 5°C, 4h; f) lithium triethylborohydride, THF, 12h.

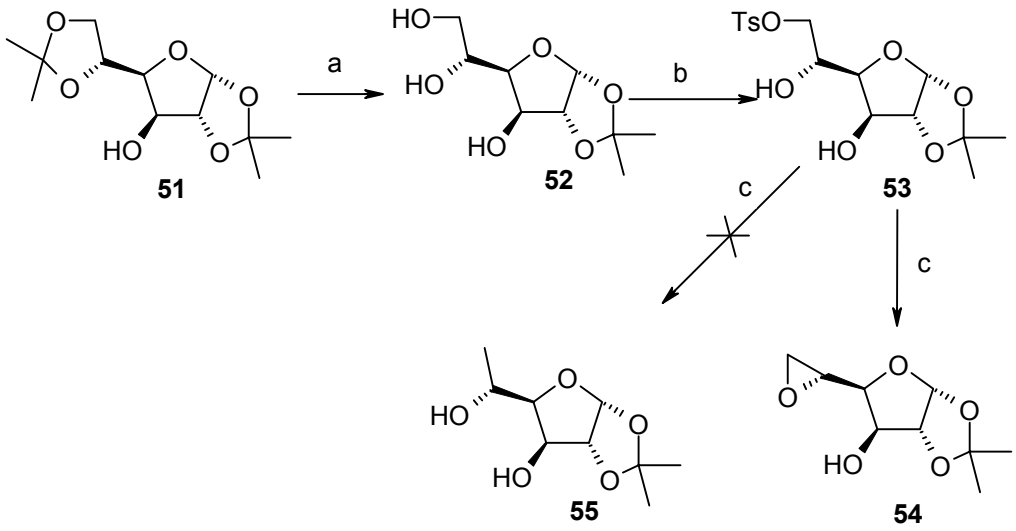
B.V.2. Synthesis of side chain (part F) of (-)-anamarine

Synthesis of side chain was carried out from D-glucose according to scheme 1. The free OH-groups of D-glucose were protected with the isopropylidene group by using $ZnCl_2$ and phosphoric acid as catalyst in dry acetone to get 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranoside (**51**)[51]. The two OH-groups at C-5 and C-6 were selectively deprotected with 20% acetic acid at 25°C to get 1,2-*O*-isopropylidene-α-D –glucofuranoside (**52**) [52]. Then, the primary OH-group at C-6 was tosylated in pyridine to get 1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranoside (**53**) [48]. The structure of the diol **53** was confirmed by melting point, mass spectroscopy, optical rotation and NMR spectroscopy, as reported in reference (Scheme 12) [48].

B.V.3. Synthesis of epoxide 54

Powdered **50** was added to a suspension of $LiAlH_4$ in anhydrous ethyl ether, according to ref. [48]. The mixture was boiled under reflux for six hours. The product was purified in 78% yield by column chromatography. The product obtained in this way was an epoxide with the melting point of 133-134°C. Ref. [48] Indicates the formation of methyl group at C-5 but we get an epoxide under the reported conditions. We repeated the reaction three times, so as to confirm the new product. The formation of epoxide **54** from **53** using $LiAlH_4$ has not yet been reported (Scheme 12).

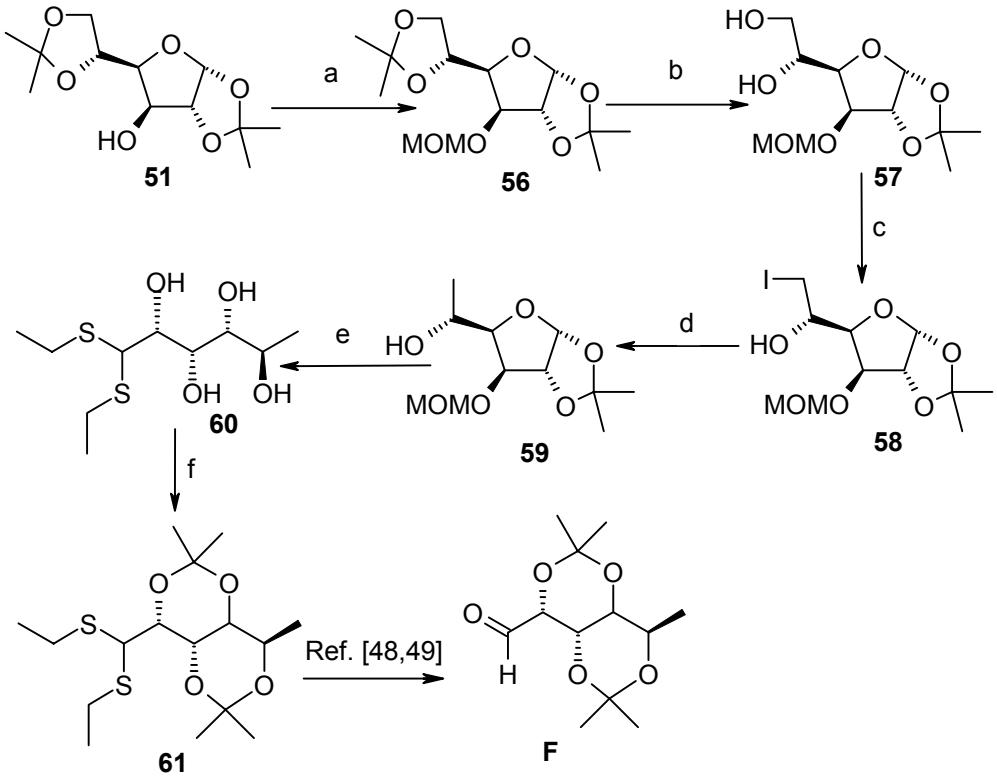
5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranoside (**54**) was confirmed by two carbon signals at 50.1 and 46.1 ppm for C-5 and C-6 respectively. The physical and spectroscopic data of **54** were found to be similar with those of reference [53].



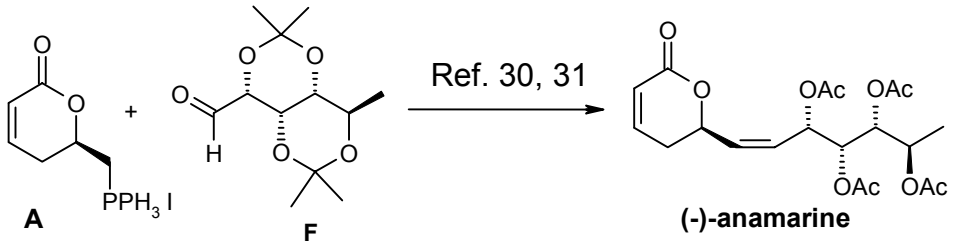
Scheme 12. Synthesis of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranoside (**54**). *Regents and conditions*: a) 20% acetic acid, 25°C, 12h; b) TsCl, pyridine, 0°C→rt, 12h; c) $LiAlH_4$, diethyl ether, 0°C→r.t, 12h.

B.V.4. Modifying the route for side chain synthesis

As **53** did not give the desired product **55,** the synthetic route was modified and instead of tosylation at C-6 (Scheme 13), we planned to do iodination with I_2, imidazole and PPh_3 [54a]. Reduction of the iodo product **58** was carried out with $NaBH_4$ in diglyme to get the required deoxygenated product 3-*O*-methoxymethyl-6-deoxy-1,2-isopropylidene-α-D-glucofuranosid (**59**) (4b]. **59** was treated with a small amount of concentrated HCl in ethylthiol to get dithioacetal (**60**) [48]. The free OH-groups in **60** were readily protected by isopropylidene group in acidic media to form **60**. The thioketal protective group from **60** can be removed by $HgCl_2$ [48]. Employing Wittig reaction on **A** and **F**, according to the ref.[48,49], can give (-)-anamarine (Scheme 14).



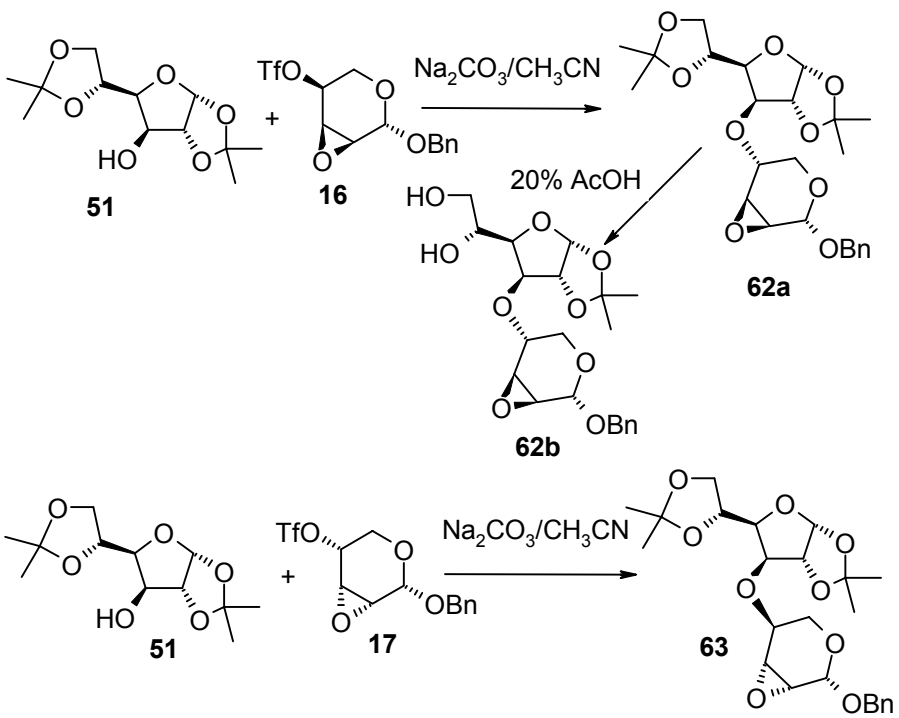
Scheme 13. Synthesis of dithioacetal (**61**) *via* 1,2:5,6-di-*O*-isopropylidene-α -D-glucofuranoside (**51***). Reagents and conditions*: a) NaH, MOM-Cl, 0°C, 6h; b) 20% acetic acid, 25°C, 12h; c) PPh_3, imidazole, I_2, CH_3CN, 40°C, 5h; d) $NaBH_4$, diglyme, reflux, 6h; e) conc. HCl, C_2H_5SH, r.t., 40 min; f) cat. $HClO_4$, acetone, 12h.



Scheme 14. Coupling **A** and **F** to get the (-)-anamarine**.**

B.VI. Synthesis of 3,4-Disaccharides.

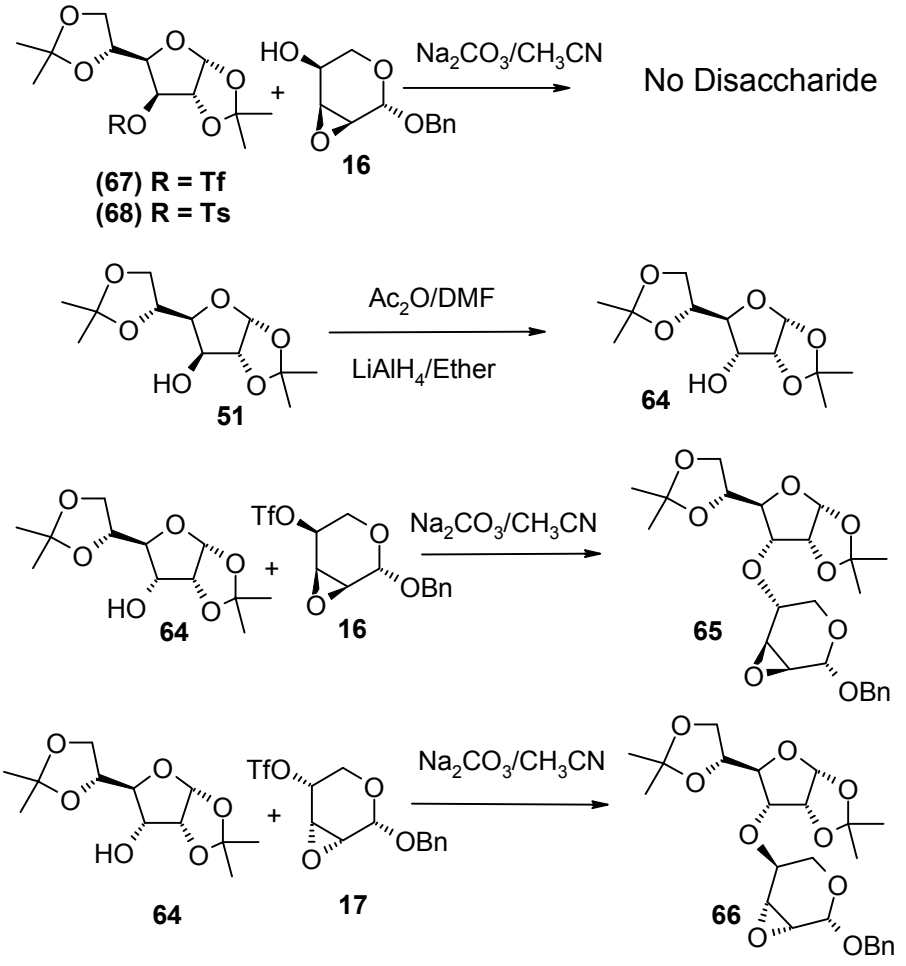
3-*O*-alkyl-1,2-*O*-isopropylidene-α-D-glucofuranoside has been shown to exhibit several biological activities. For example, it can reduce *intra*-membrane charge movement, required for signal tranduction between the sarcolemma and the sarcoplasmic reticulum, thereby inhibiting the excitation-calcium release mechanism, (muscle relaxant activity) [55]. Besides it has strong inhibitory effect on the enzyme β-galactosidase from *Escherichia coli* [56]. The oxirane ring- containing carbohydrates are enzyme inhibitors, i.e. 2,3-epoxypropyl-β-D-glucosides of 2-acetamido-2-deoxy-D-glucose and its oligomers are inhibitors of hen's egg-white lysozyme [57-59].



Scheme 15. Synthesis of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-gluco-furanoside-3-yl benzyl 2,3-anhydro-α-D-lyxopyranoside (**62a**) and 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranoside-3-yl benzyl 2,3-anhydro-β-L-lyxopyranoside (**63**).

2,3-Epoxypropyl-α-D-glucopyronside irreversibly inhibits yeast hexokinase [60]. Similarly, derivatives of cellobiose and cellotriose show inhibiting activity against enzyme cellulase [61].

Recently, a variety of sugar derivatives [62] have been examined as possible inhibitors for a new thermostable neutral proteinase, isolated from *Saccharomonospora canesecns*. Among all tested compounds, benzyl 2,3-anhydro-β-L-ribopyranoside (**6**) and benzyl 2,3-anhydro-α-D-ribopyranoside (**15**) exhibited the highest inhibiting activity. Therefore it was decided to



Scheme 16. Synthesis of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-allofuranoside-3-yl benzyl 2,3-anhydro-α-D-lyxopyranoside (**65**) and 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-allofuranoside-3-yl benzyl 2,3-anhydro-β-L-lyxopyranoside (**66**).

couple 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranoside (**51**) and epoxy-triflate **16** or **17** to get new compounds with different potential biological activities (Scheme 15 and 16).

Disaccharides **62** and **63** were synthesized by the nucleophilic attack of **51**, produced by using mild conditions, (Na_2CO_3/CH_3CN) at C-4 of epoxytriflates **16** or **17** (Scheme 15).

For the other two disaccharides **65** and **66**, triflate **67** [48] and tosylate **68** [63], were tried. The nucleophilic attack of the epoxy sugar anion on the activated C-3 carbon of **67** or **68** was found to be impossible due to the crowding around C-3 of **67** or **68**. As it gave the triflate or tosylate of the epoxy sugar **6** and **15**, so it was decided to change the stereochemistry of the C-3 OH- group from $\beta \rightarrow \alpha$ [64] for the other two isomers (**65** and **66**) of the 3,4-disaccharides (Scheme 16).

B.VII. Testing Formaldehyde Acetals on Carbohydrates

Acetalation is one of the most applied reaction in the carbohydrate chemistry. Acid-catalyzed acetylation and transe acetalation are common [65] for the preparation of different acetals, but they give very poor yield in case the of methylene derivatives [66]. Brimacombe et al.[67] used sodium hydride CH_2X_2 in DMF. Hanessian et. al [68,69] And Munavu [70] used DMSO/NBS or DMSO/Br_2 for the preparation of methylene acetals utilising the Pummerer rearrangement of an initially formed bromo sulphonium ion to give an α-alkoxy sulphoxide intermediate. Phase transfer catalysis also proved to be a very useful method for the methylation of catechol [71] Andras Liptak et.al [72] used KOH/DMSO in CH_2Br_2 for the acetalation of different carbohydrates in good yield.

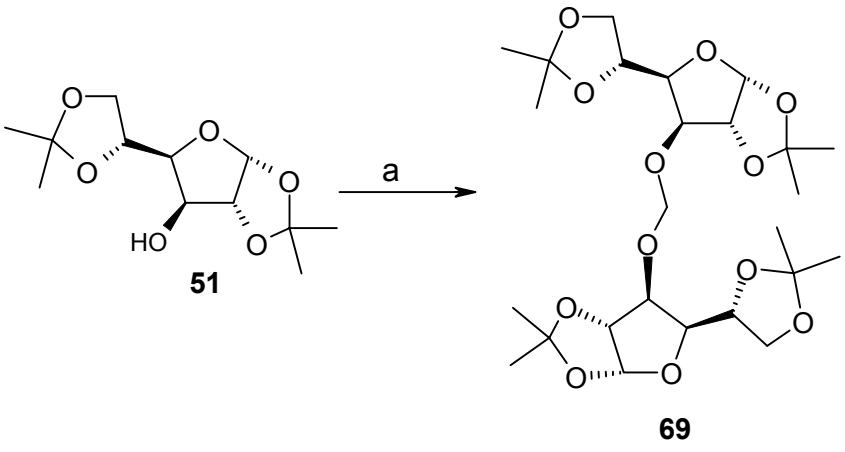
We used NaOH/DMF in CH_2X_2 for methylene acetal formation of carbohydrates, but inter-molecular as well as intra-molecular methylene acetals can be formed depending upon the number of free hydroxyl groups present in the sugar molecule. All the compounds were synthesized by adding NaOH Pellet in CH_2X_2 and DMF followed by addition of alcohol. The reaction mixture was heated to 30°C in case of CH_2Br_2 and 65°C for CH_2Cl_2 (Table 1).

The structure of **69** was confirmed by mass spectroscopy and ^{1}H NMR: there was equal integration for the anomeric proton and for the methylenic proton, which indicated the formation of symmetric molecule i.e. the two anomeric proton of the two sugar units are in the same chemical environment thus resonating on the same chemical shift in ^{1}H NMR (Scheme 17).

Table 1. Substrates and reaction conditions employed in the methylene acetal formation reaction.

Comp.	Base	Solvent	Time	Temp.(°C)	Yield(%)
69	NaH	CH_2Cl_2	24	r.t	91
69	NaOH	CH_2Cl_2	30	65	76
69	NaOH	CH_2Br_2	12	30	83
70	NaOH	CH_2Cl_2	30	65	72
70	NaOH	CH_2Br_2	16	30	84
73	NaOH	CH_2Cl_2	30	65	69
73	NaOH	CH_2Br_2	12	30	76
75	NaOH	CH_2Cl_2	30	65	three products
75	NaOH	CH_2Br_2	7	30	67

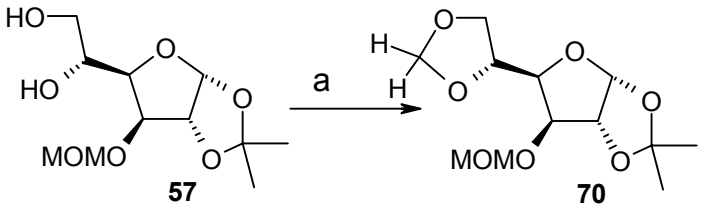
1,2-Isopropylidene-3-methoxymethyl-5,6-methylidene-α-D-glucopyranoside (**70**) was made from **57** in excellent yield (Scheme 18) and was confirmed by



Scheme 17. Synthesis of **69**. *Reagents and conditions*: a) NaH, CH_2Cl_2, DMF, 30°C, 24h.

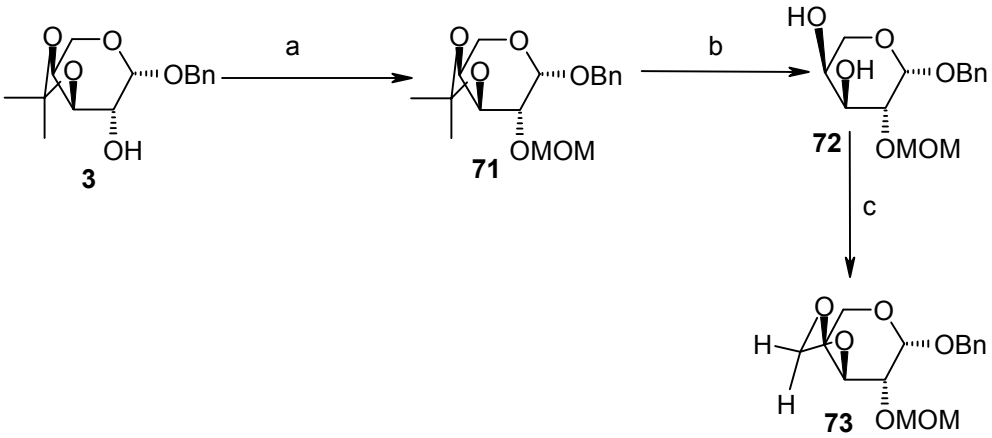
the anomeric signal at δ 5.89 (d, J = 3.65 Hz, 1H), two methylene signals δ = 5.02 (s, 1H), 4.84 (s, 1H) and 4.73 (s, 2H). The two-methylene signals appeared at 96.1 and 95.2 in the ^{13}C NMR.

For the synthesis of **73**, benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**) was treated with MOM-Cl in NaH/THF to protect the free OH-group. Then, the isopropylidene group was removed selectively and the product subjected for the methylene acetal formation reaction (Scheme 19).



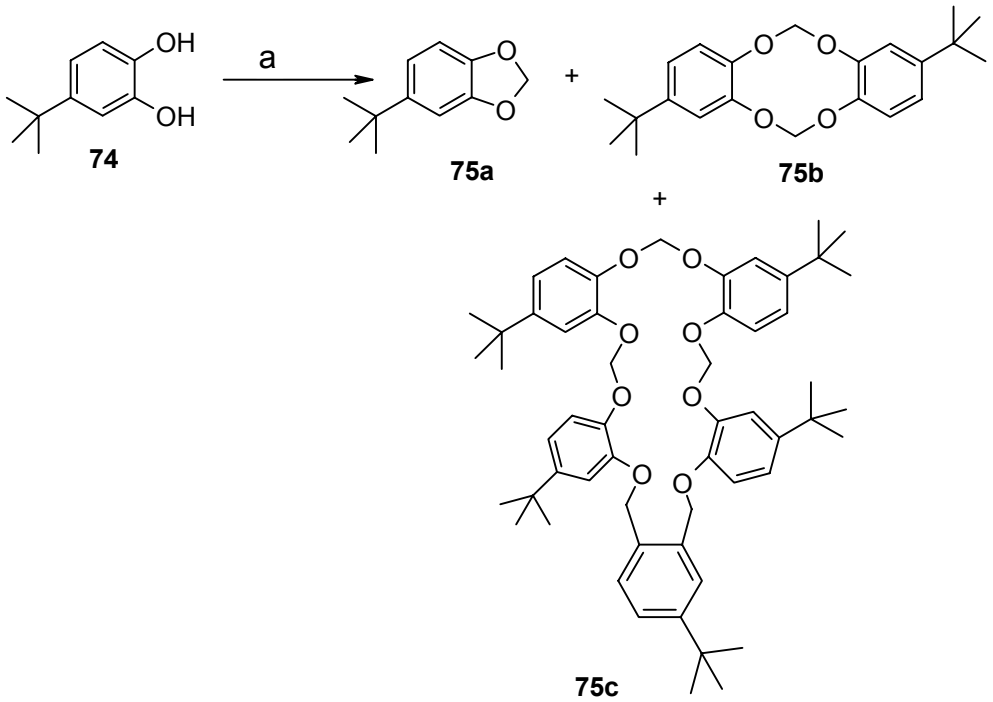
Scheme 18. Synthesis of 1,2-acetanolide-3-methoxymethyl-5,6-methylidene-α-D-glucofuranoside (**70**) from 3-*O*-methoxymethyl-1,2-*O*-isopropylidene-α-D-glucofuranoside (**57**). *Reagents and conditions*: a) NaOH, CH_2Br_2, DMF, 30°C, 16h.

The structure of **73** was proved by the mass as well as NMR spectroscopy. The signal at δ = 4.77 (d, J = 2.9 Hz, 1H) represent the anomeric proton



Scheme 19. Synthesis of benzyl 2-*O*-methoxymethyl-3,4-*O*-methylidene-β-L-arabinopyranoside (**73**) from benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**). *Reagents and conditions*: a) NaH/MOM-Cl, THF, 0°C-r.t.; b) 20% AcOH; c) NaOH, CH_2Br_2, DMF, 30°C, 12h.

while the signal at δ = 5.20 (s, 1H), 4.79 (s, 1H) and 4.99 (s, 2H) indicated the presence of two methylene groups. The 4-isobutyl-catechol (**74**) was also tested against the methylene formation reaction. The number of products formed in this reaction depends upon the dilution of the reaction mixture and also on the solvent used. For example dichloromethane gave three products **75**a→c while the same reactant in the same dilution with dibromomethane gave one major product (**75**a) (Scheme 20).



Scheme 20. Synthesis of 4-isobutyl-1,2-methylene catechol (**75a**), diactal **75b** and polyacetal **75c**. a) *Reagents and conditions*: NaOH, CH_2Cl_2, DMF, 65°C, 30h.

The structures were confirmed by FD-mass and NMR spectroscopy. 1,2-methylene-4-isobutyl catechol (**75a**) was confirmed by ^1H NMR signal at 5.88 (s, 2H) indicating the methylene protons. The three methyls resonate at 1.27 (s, 9H). The acetal **75b** was confirmed by the methylene signal at 5.67 (s, 4H) and six-methyl at 1.32 (s, 18H). The acetal **75c** was proposed due to the five

methylene carbons resonating between 93.5-93.4 and also the FD mass spectroscopy revealed that the product contain five catechol units.

C. EXPERIMENTAL

C.I. Synthesis of 2,3-anhydro-β-L-ribopyranosides

C.I.1. Benzyl 2,3-anhydro-β-L-arabinopyranoside (6)

C.I.1.1. Benzyl β-L-arabinopyranoside (2)

2 was prepared from 50 g (0.33 mol) of L-arabinose (1) and 250 ml benzyl alcohol and 1L of abs. ether as described in ref. [9a]: Yield 71 g (88.5%); m.p. 172°C (ethanol/water), ref. [9a]: 168-171°C (ethanol); $[\alpha]_D$= +208° (c = 1, water), ref. [9a]: +206° (c = 0.3, water)

$C_{12}H_{16}O_5$ (240.23)

Calculated C 59.99 H 6.7%,

Found C 59.55 H 6.50%.

C.I.1.2. Benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (3)

3 was prepared from 70 g of benzyl-β-L-arabinopyranoside (0.29 mol), 500 ml 2,2-dimethoxypropane and 1.0 g. *p*-toluenesulphonic acid in 500 ml acetone. The resultant product **3** was used as such for the next step. Yield: 49 g (82.2%).

C.I.1.3. Benzyl 3,4-O-isopropylidene-2-*O*-*p*-tolylsulphonyl-β-L-arabinopyranoside (4)

4 was prepared from 100 g (0.36 mol) of **3**, in 670 ml pyridine and 270 g *p*-toluenesulphonyl chloride as described in ref. [9a]. Yield: 139 g (88%); m.p. 92°C (ethanol/water), ref. [9a]: 93-94°C (ethanol/water); $[\alpha]_D$ = +185° (c = 1, $CHCL_3$), ref. [9a]: +183° (c = 1, $CHCl_3$)

$C_{22}H_{26}O_7S$ (434.47)

Calculated C 60.81 H 7.37%,

Found C 60.61 H 7.15%.

C.I.1.4. Benzyl 2-*O*-*p*-tolylsulphonyl-β-L-arabinopyranoside (5)

5 was prepared from 135 g (0.31 mol) of **4** and 100 ml 90% acetic acid as described in ref. [9a]. Yield: 110.4 g (90%); $[\alpha]_D$ = +125° (c = 1, $CHCL_3$), ref. [9a]: +134° (c = 1, $CHCl_3$)

$C_{19}H_{22}O_7S$ (394.41)

Calculated C 51.81 H 8.12%,

Found C 57.71 H 8.05%.

C.I.1. Benzyl 2,3-anhydro-β-L-arabinopyranoside (6)

6 was prepared from 110 g (0.28 mol) of 5, 1.2 L methanol and 8.9 g (0.37 mol) sodium. as described in ref. [9a]. Yield: 38.7 g (66%); m.p. 78°C (EE), ref [1a]: 76-77°C (EE); $[\alpha]_D$ = -15° (c = 1, EE), ref. [9a]: -13° (c = 1, EE)

$C_{12}H_{14}O_4$ (222.22)

Calculated C 64.86 H 6.34%,

Found C 64.32 H 6.32%.

C.I.2. Benzyl 2,3-anhydro-α-D-ribopyranoside (15)

C.I.2.1. Tetrabenzoate of *β*-D-arabinopyranoside (8)

8 was prepared from 50 g (0.33 mol) D-arabinose (**7**) and 300 ml CH_2Cl_2, 100 ml pyridine and 250 ml benzoyl chloride as described in ref. [9a]. Yield 174 g (93%); m.p. 172°C (ethanol), ref. [9]: 175°C (ethanol); $[\alpha]_D$= -318° (c = 1, $CHCl_3$), ref. [9a]: -321° [c = 0.3, $CHCl_3$), $C_{33}H_{26}O_9$ (566.56)

Calculated C 69.96 H 4.63%,

Found C 70.35 H 4.52%.

C.I.2.2. 2,3,4-Tri-*O*-benzoyl-β-D-arabinopyranosyl bromide (9)

9 was prepared from 173 g (0.30 mol) **8**, 200 ml CH_2Cl_2 and 325 ml HBr/acetic acid as reported in ref. [9a]. Yield 125 g (78%); m.p. 143°C (CH_2CL_2/EE), ref. [12a]: 146-148°C (EE); $[\alpha]_D$= -348° (c = 1, $CHCl_3$), ref. [12a]: -353° [c = 1.4, $CHCl_3$), $C_{26}H_{21}BrO_9$ (566.56)

Calculated C 59.44 H 4.03 Br 15.21%,

Found C 59.68 H 4.00 Br 15.09%.

C.I.2.3. Benzyl 2,3,4-tri-*O*-benzoyl-α-D-arabinopyranoside (10)

10 was prepared from 124 g (0.22 mol) of **8**, 1 L benzyl alcohol, as described in ref. [12a]. Yield 110 g (92%); m.p. 144°C (ethanol), ref. [12a]: 143-144°C (ethanol); $[\alpha]_D$= -143° (c = 1, $CHCl_3$), ref. [12a]: -146.7° [c = 2.11, $CHCl_3$)

$C_{33}H_{28}O_8$ (552.55)

Calculated C 71.73 H 5.11%,

Found C 72.26 H 5.07%.

C.I.2.4. Benzyl α-D-arabinopyranoside (11)

11 was prepared from 110 g (0.20 mol) of **10**, 365 ml CH_2Cl_2 and 250 ml MeOH as described in ref. [9].Yield 45 g (93%); m.p. 136°C (ethanol), ref. [9a]: 140-141°C (ethanol); $[\alpha]_D$= +13° (c = 1, water), ref.[9a]: +12.3° (c = 1.4, water). $C_{12}H_{16}O_5$ (240.23)

Calculated C 59.99 H 6.71%,

Found C 59.80 H 6.50%.

C.I.2.5. Benzyl 3,4-*O*-isopropylidene-*α*-D-arabinopyranoside (12)

12 was prepared from 44 g (0.18 mol) of **11**, 500 ml acetone, 300 ml 2,2-dimethoxypropane and 1.0 g. *p*-toluenesulphonic acid as described in ref. [1a]. Yield: 45 g (89%). The product was used directly for the next step.

$C_{15}H_{20}O_5$ (280.31).

C.I.2.6. Benzyl 3,4-*O*-isopropylidene-2-*O*-tolylsulphonyl-α-D-arabinopyranoside (13)

13 was prepared from 44 g (0.157 mol) of **12**, 600 ml pyridine and 190 g *p*-toluenesulphonyl chloride as described in ref. [9a].Yield 55 g (80%); m.p. 80°C (ethanol/water), ref. [9a]: 80-82°C (ethanol/water); $[\alpha]_D$= -8° (c = 1, $CHCl_3$), ref.[9a]: -7° [c = 1, $CHCl_3$), $C_{22}H_{26}O_7S$ (434.47)

Calculated C 60.81 H 6.02 S 7.37%,

Found C 61.02 H 6.00 S 7.20%.

C.I.2.7. Benzyl 2-*O*-tolylsulphonyl-α-D-arabinopyranoside (14)

14 was prepared from 54 g (0.124 mol) of **13**, 110 ml 90% acetic acid as described in ref. [9a]. Yield: 42 g (86%); m.p. 118°C (ethanol/water), ref. [9a]: 116-117°C (ethanol/water); $[\alpha]_D$= +22° (c = 1, $CHCl_3$), ref. [9a]: +25° [c = 1, $CHCl_3$), $C_{19}H_{22}O_7S$ (394.41)

Calculated C 57.81 H 5.61 S 8.12%,

Found C 57.64 H 5.60 S 8.02%.

C.I.2. Benzyl 2,3-anhydro-α-D-ribopyranoside (15)

15 was prepared from 40 g (0.102 mol) of **14**, 910 ml methanol and 3.0 g sodium as described in ref. [9a]. Yield: 15 g (63%); m.p. 97°C (EE/PE), ref. [9a]: 97-98°C (PE); $[\alpha]_D$= +190° (c = 1, EE), ref. [9a]: +188° [c = 1, EE), $C_{12}H_{14}O_4$ (222.22)

Calculated C 64.86 H 6.34%,

Found C 64.56 H 6.22%.

C.I.3. Benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (16) and Benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (17)

16 and **17** were prepared from 2.2 g (10 mmol) **6** and 15 respectively, 75 ml CH_2Cl_2, 2 ml pyridine and 1.8 ml (10.97 mmol) trifloromethansulphonic anhydride as described in ref. [9a].

C.I.3.1 Benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (16)

Yield: 3.2 g (91%); m.p. 81°C (ethanol), ref. [9a]: 82-83°C (ethanol); $[\alpha]_D$= +15° (c = 1, $CHCl_3$), ref. [9a : +16° [c = 1, $CHCl_3$), $C_{13}H_{13}F_3O_6S$ (354.29)

Calculated C 44.07 H 3.69 S 9.04%,

Found C 43.85 H 3.60 S 9.25%.

C.I.1.2. Benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (17)

Yield: 3.3 g (94.3%); m.p. 65°C (ethanol), ref. [9a]: 66-68°C (ethanol); $[\alpha]_D$= +129° (c = 1, $CHCl_3$), ref. [9a]: +128° [c = 1, $CHCl_3$), $C_{13}H_{13}F_3O_6S$ (354.29)

Calculated C 44.07 H 3.69 S 9.04%,

Found C 43.85 H 3.60 S 9.25%.

C.II. General Procedure for the Preparation of Trithiocarbonates

The thiocarbonate salt was prepared by mixing (4.97 mg, 2 mmol) sodium sulphide in 10 mL of water and then 189 mg (2.5 mmol) carbon disulphide was added into it. The reaction mixture was warmed to 40°C and allowed to stir for 6h. The excess carbon disulfide was removed by evaporation at reduced pressure. To the resulting red-coloured solution was dropped slowly a solution of 354 mg (1 mmol) triflate **16** or **17**, dissolved in small amounts

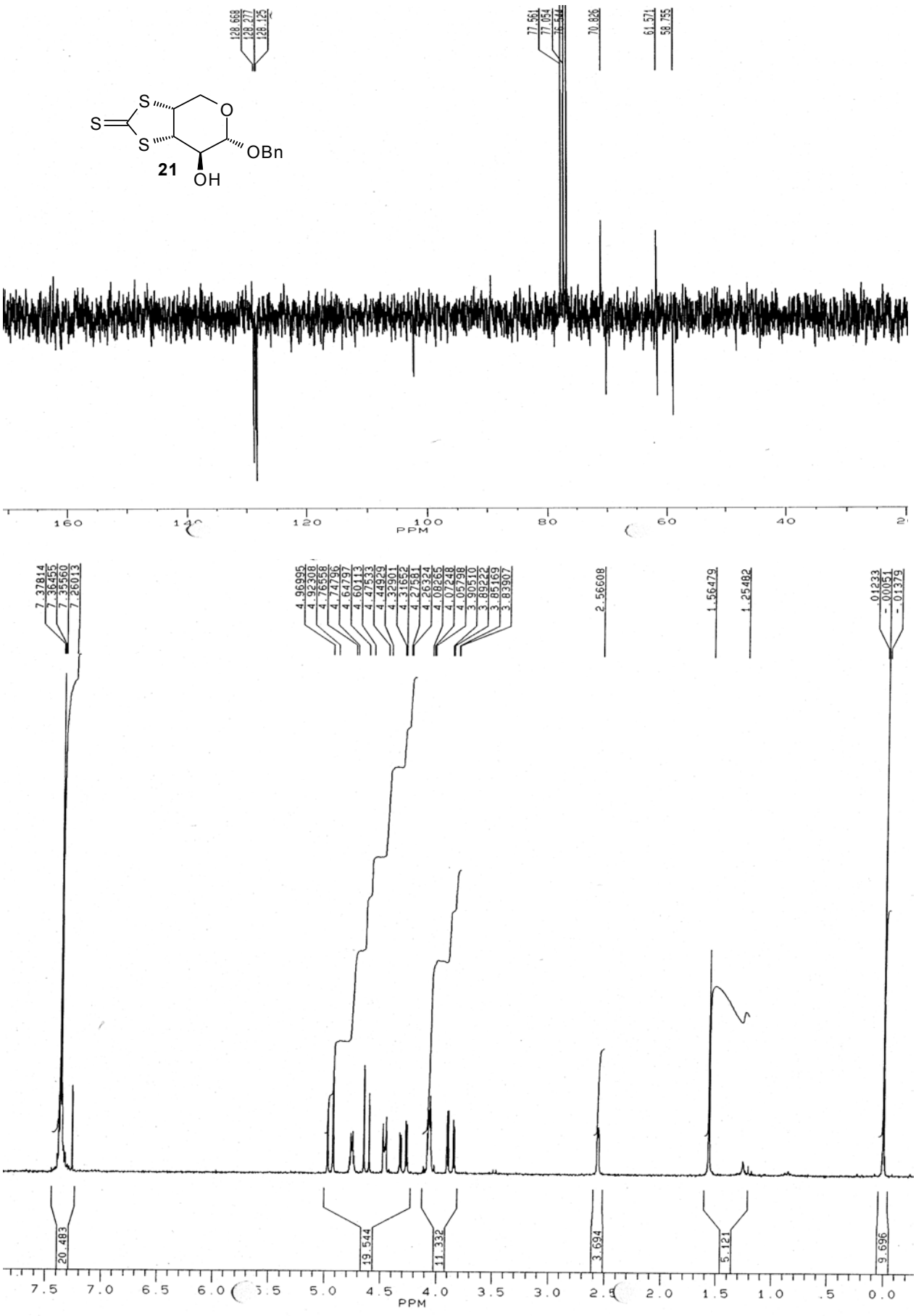


Fig 8. ^{1}H and ^{13}C NMR spectra of trithiocarbonate **21**.

of ethanol, respectively. Stirring at room temperature for 10 min produced the yellow colored precipitates of trithiocarbonate sugars.

C.II.1. Benzyl 3,4-dideoxy-3,4-*S*-thiocarbonyl-α-D-arabinopyranoside (21)

Yellow crystals, mp 131-133°C, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36-7.38 (m, 5H), 4.95 (d, J = 11.9 Hz, 1H), 4.76 (ddd, J = 3.05, 4.27, 6.18 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 6.41 Hz, 1H), 4.30 (dd, J = 3.05, 13.42 Hz, 1H), 4.07 (m, 2H), 3.87 (dd, J = 3.35, 13.42 Hz, 1H); ^{13}C NMR (63MHz, $CDCl_3$): δ = 162.1 (C=S), 128.1, 128.3, 128.7 (Ph), 102.3 (C-1), 70.8 (*C*HHPh), 69.9 (C-2), 61.6 (C-5), 61.4 and 58.7 (C-3, C-4). FAB-MS: m/z = 314.1 (M^+)

$C_{13}H_{14}O_3S_3$ (314.45)

Calculated C 49.66 H 4.49 S 30.59%,

Found C 49.58 H 4.45 S 30.56%.

C.II.2. Benzyl 3,4-dideoxy-3,4-*S*-thiocarbonyl-β-L-arabinopyranoside (22)

Yellow crystals**,** m.p. 162.3°C, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34-7.42 (m, 5H), 5.07 (br s, 1H), 4.82 (d, J = 11.59 Hz, 1H), 4.81 (m, 1H), 4.61 (d, J = 11.59, 1H), 3.88 (dd, J = 1.83, 13.42 Hz, 1H), 4.17 (m, 3H); ^{13}C NMR (63MHz, $CDCl_3$): δ = 128.8, 128.35, 128.1 (Ph), 97.1 (C-1), 70.4 (CHHPh), 68.3 (C-2), 60.9, 60.38 (C-3, C-4), 56.8 (C-5). FAB-MS: m/z = 314.1 (M^+)

$C_{13}H_{14}O_3S_3$ (314.45)

Calculated C 49.66 H 4.49 S 30.59%,

Found C 49.58 H 4.45 S 30.56%.

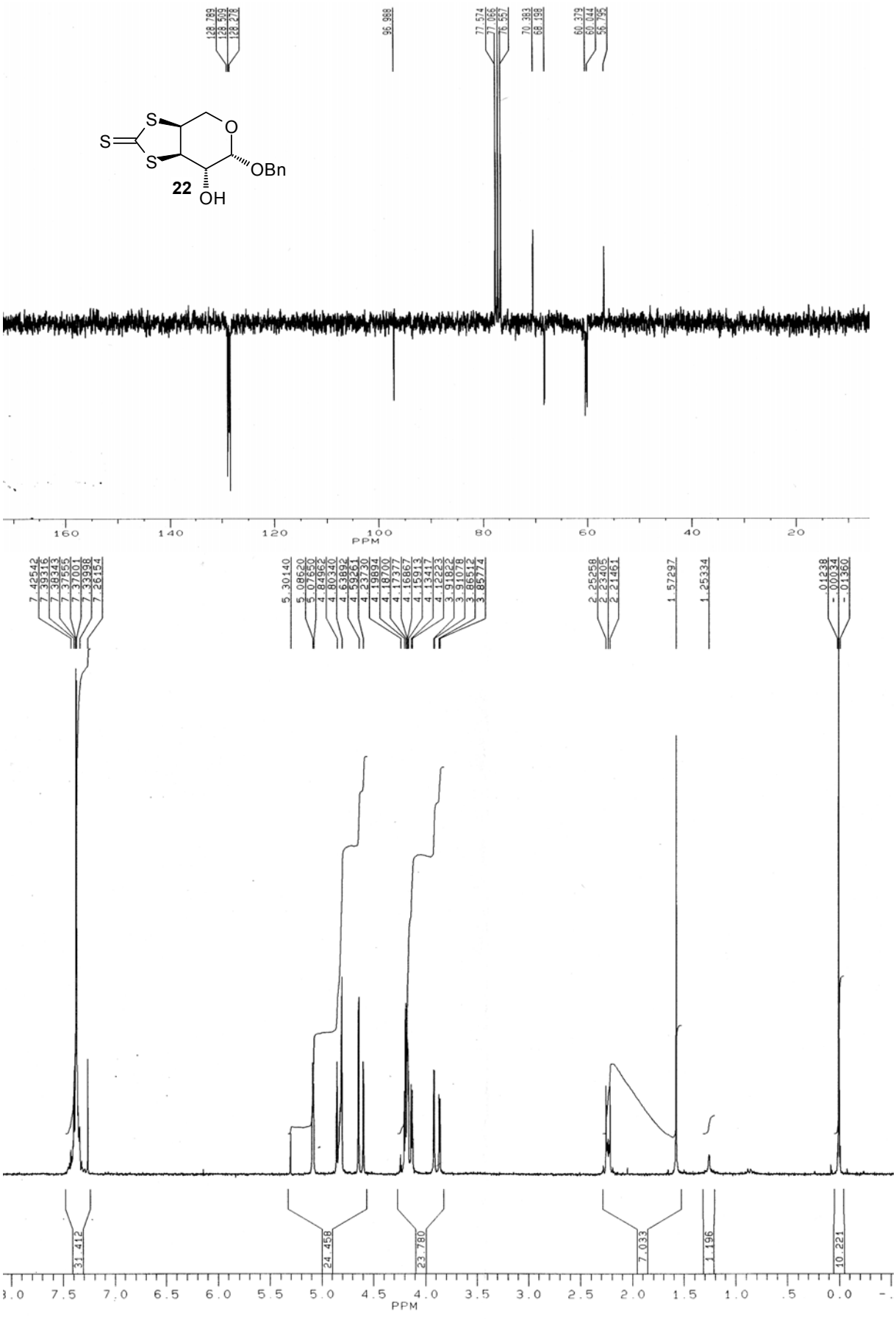


Fig 9. ^{1}H and ^{13}C NMR spectra of trithiocarbonate **22**.

C.II.3. Methyl 3,5-dideoxy-3,5-S-thiocarbonyl-α-D-xylofuranoside (24)

Yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.23 (s, 1H), 4.29 (t, J = 7.3 Hz, 1H), 3.66 (m, 2H), 3.52 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (63MHz, $CDCl_3$): δ = 102.7 (C-1), 75.7 (C-2), 56.1 (OCH_3), 55.7 (C-3), 38.6 (C-5). FAB-MS: m/z = 207.1 (M^+-OCH_3), $C_7H_{10}O_3S_3$ (238.1)

Calculated C 35.27 H 4.23 S 40.36%,

Found C 35.15 H 4.16 S 40.34%.

C.III. General Method of Synthesis of Benzothiophene Derivatives

2-Bromothiophenol (1.1 mmol) was added to an efficiently stirred suspension of Na_2CO_3 (1.1 mmol) in 20 mL CH_3CN at 0°C. The reaction mixture was stirred at this temperature for 15 min and then 1 mmol of β-epoxytriflate **16** or **17,** dissolved in 5 mL of CH_3CN, was added into it dropwise. The reaction mixture was stirred at the same temperature for two hours and then overnight at room temperature. Completion of the reaction was confirmed by TLC [dichloromethane:pet. ether (4:6)] indicating the formation of a new spot just below the epoxy triflate spot (Rf = 0.6). The reaction was quenched with NH_4Cl solution and extracted with water. The organic phase was separated and dried over Na_2SO_4 and concentrated to a syrup which was further purified by column chromatography giving 80-88% pure product.

C.III.1. Benzyl 2,3-anhydro-4-(2-bromo phenyl sulphonyl)-β-L-ribopyra-noside (26)

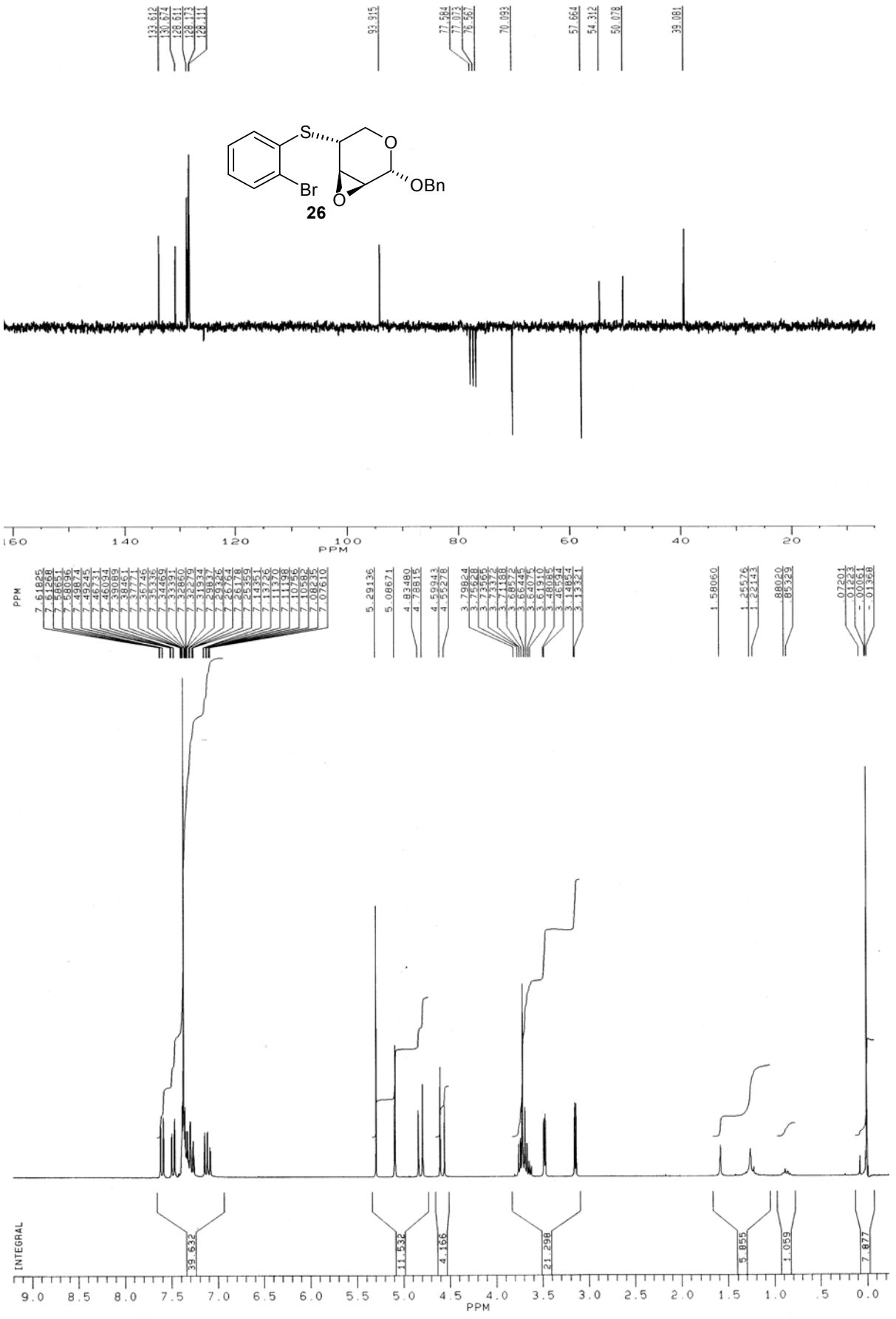


Fig 10. ^{1}H and ^{13}C NMR spectra of benzothiophene **26**.

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.50-7.47 (dd, J = 1.2, 7.9 Hz, 1H aromatic), 7.39-7.35 (dd, J = 1.2, 6.5 Hz, 1H aromatic), 7.02-9.96 (ddd, J = 1.5, 7.6, 9.1 Hz, 1H), 4.97 (s, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 3.79-3.61 (m, 3H), 3.37 (d, J = 3.6 Hz, 1H), 3.04 (d, J = 3.6 Hz, 1H), ^{13}C NMR (63 MHz, $CDCl_3$) δ: 137.0-125.4 (12x*C*, Aromatic), 93.8 (C-1), 70.0 (*C*HHPh), 57.6 (C-5), 54.2, 50.2 (C-2, C-3), 39.0 (C-4).

$C_{18}H_{17}BrO_3S$, (392.9), $[\alpha]_D$ = +336.5° (c = 1, CH_2Cl_2).

Calculated C 56.03 H 4.71%,

Found C 56.46 H 4.50%.

C.III.2. 4-(2-Bromo phenyl sulphonyl)-2-benzyloxy-3,6-dihydro-2-H-pyran-3-ol (27)

50 mg (0.127 mmol) of benzyl 2,3-anhydro-4-(2-bromo phenyl sulphonyl)-β-L-ribopyranoside (**20**) was added in 5 ml THF under nitrogen atmosphere and cooled to -78°C. Then 40 μL of n-BuLi (1.6 M in hexane) was added in the reaction mixture and stirred for 6h. TLC (8% ethyl acetate:dichloromethane) indicated the completion of reaction. The reaction mixture was neutralized with NH_4Cl, extracted with dichloromethane:water and concentrated to a syrup. The product was purified by column chromatography in 74% yield.

C.III.3. 4-(2-Bromo phenyl sulphonyl)-2-benzyloxy-3,6-dihydro-2H-pyran-3-ol (31)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.47-6.92 (m, 9H aromatic), 6.10 (br. s, 1H), 4.99 (d, J = 4.1 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.28 (br. s, 1H), 4.13-3.90 (m, 2H). ^{13}C NMR (62.8 MHz,

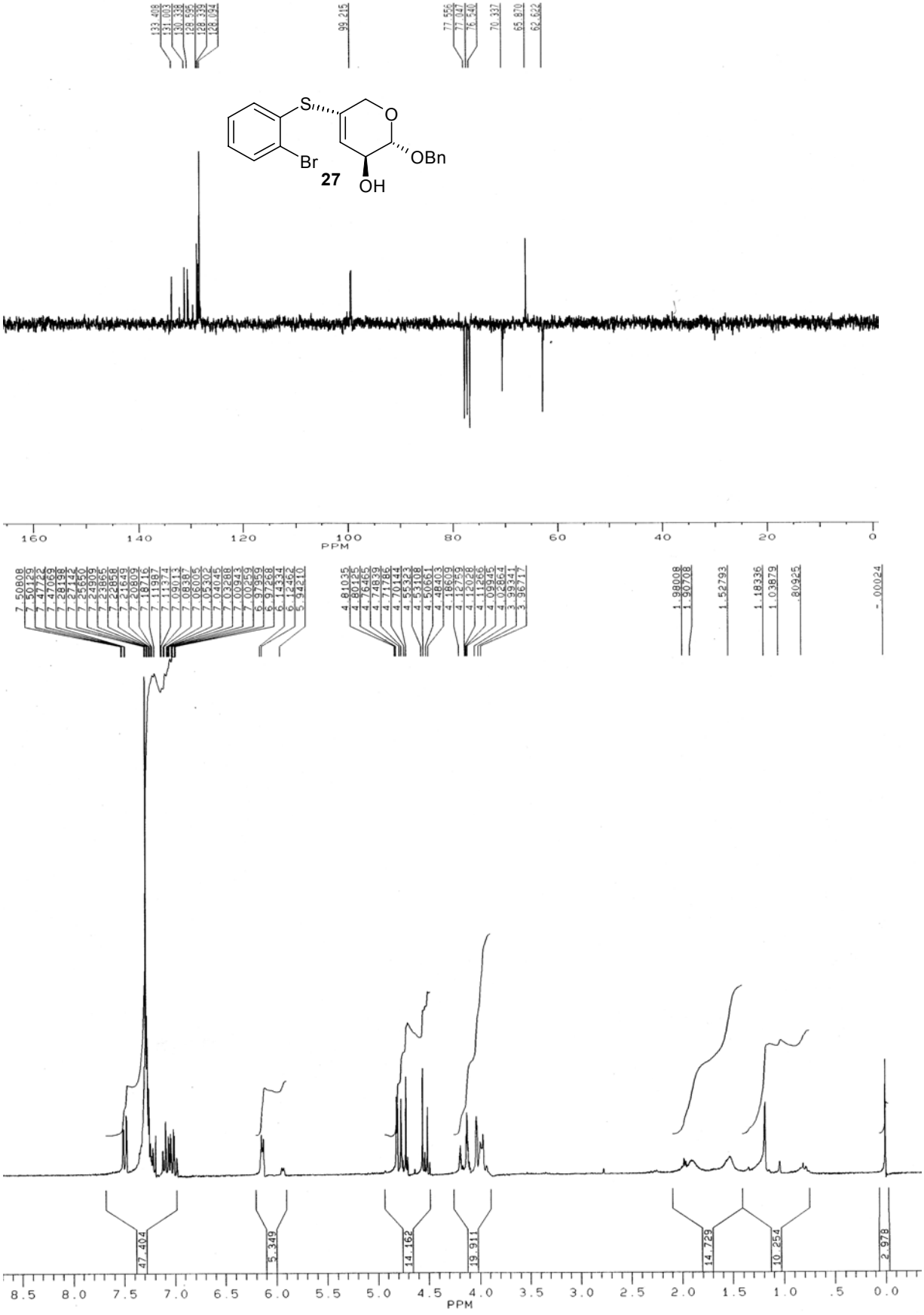


Fig 11. ^{1}H and ^{13}C NMR spectra of benzothiophene **27**.

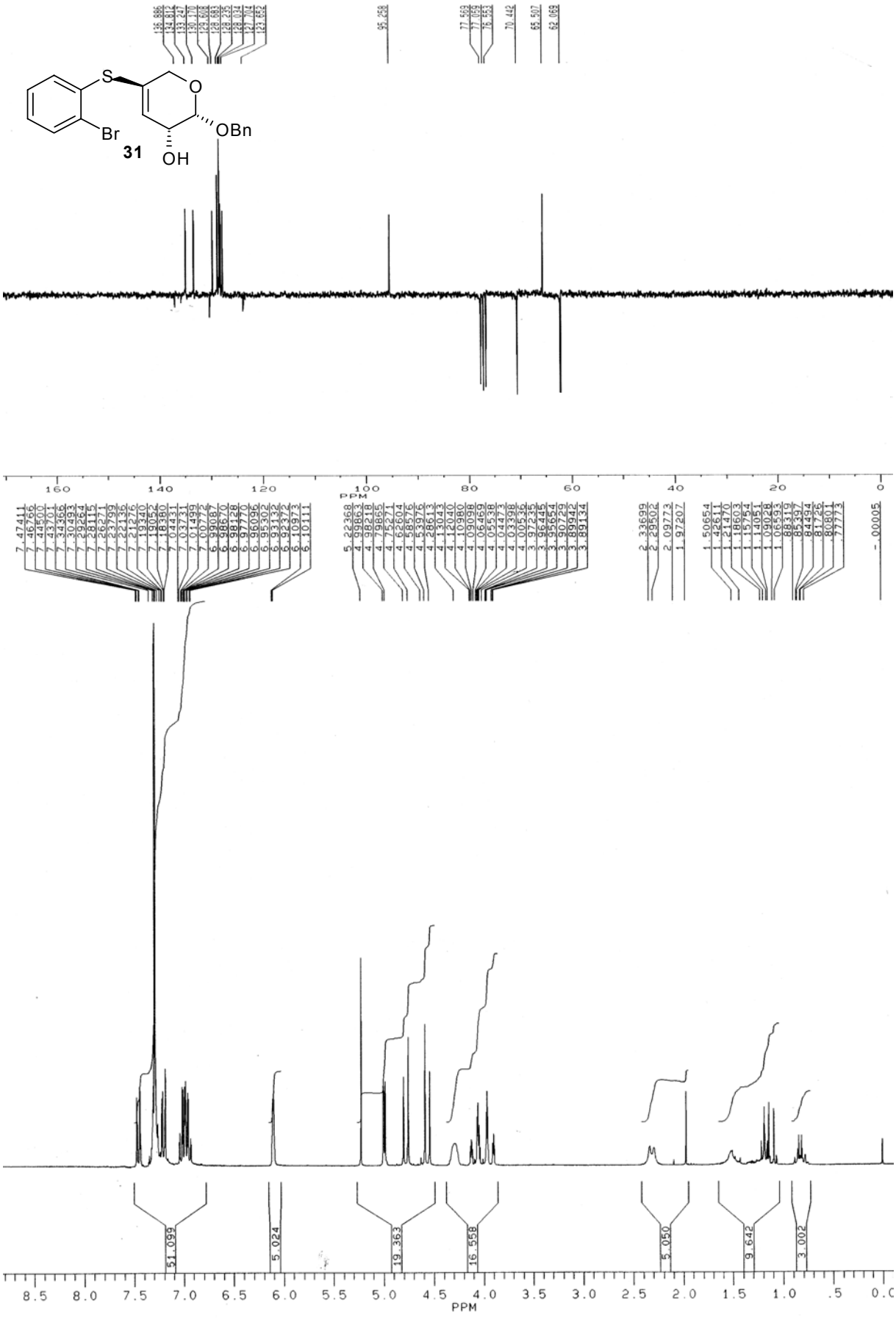


Fig 12. ^{1}H and ^{13}C NMR spectra of benzothiophene **31**.

$CDCl_3$) δ: 136.8-127.7 (12x*C*, Aromatic + C-3, C-4); 95.2 (C-1), 70.4 (*C*H_2Ph), 65.5 (C-2), 62.0 (C-5)

$C_{18}H_{17}BrO_3S$ (392.9), $[\alpha]_D$ = +62.3 (c = 1, CH_2Cl_2).

C.III.4. α,β-Unsaturated ketone 32

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.68-7.18 (m, 9H aromatic), 5.45 (d, J = 1.86 Hz, 1H), 4.82 (s, 1H), 4.76 (d, J = 11.6 Hz, 1H, C*H*HPh), 4.67-4.59 (m, 2H), 4.18 (d, J = 11.6 Hz, 1H, CH*H*Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 137.6-128.1 (13x*C*; Aromatic + C-3 and C-4); 96.6 (C-1), 70.9 (-*C*H_2Ph), 60.9 (C-5)

$C_{18}H_{15}BrO_3S$ (391.29).

C.IV. General Method of Preparation of Thiazolidines

The thiosemicarbazide or 4-phenylthiosemicarbazide (0.55 mmol) was added in 10 mL of 1,2-dioxane. After stirring 15 min., 177 mg (0.5 mmol) of β-epoxytriflate **16** or **17** in 5 mL THF, was added dropwise. The reaction mixture was stirred at room temperature overnight and then concentrated to a syrup. Column chromatography with 10% methanol:dichloromethane as eluent gave a mixture of two products, very near to one another. Thiazolidines **36** and **37** were purified, after acetylation with pyridine-acetic anhydride, on a small column using dichloromethane as eluent.

C.IV.1. Thiazolidine 36

Colourless crystals, m.p. 187°C, yield: 74%. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.33-7.20 (m, 5H), 5.22 (s, 1H), 4.81(br. s, 1H), 4.78 (br. s, 1H), 4.62 (d, J = 11.1 Hz, 1H, C*H*HPh), 4.39 (d, J = 11.1 Hz, 1H, CH*H*Ph), 4.06 (m, 1H), 4.37-3.61 (m, 2H), 2.50 (s, 3H), 2.08 (s, 3H), 2.00 (s, 6H). ^{13}C NMR (62.8 MHz,

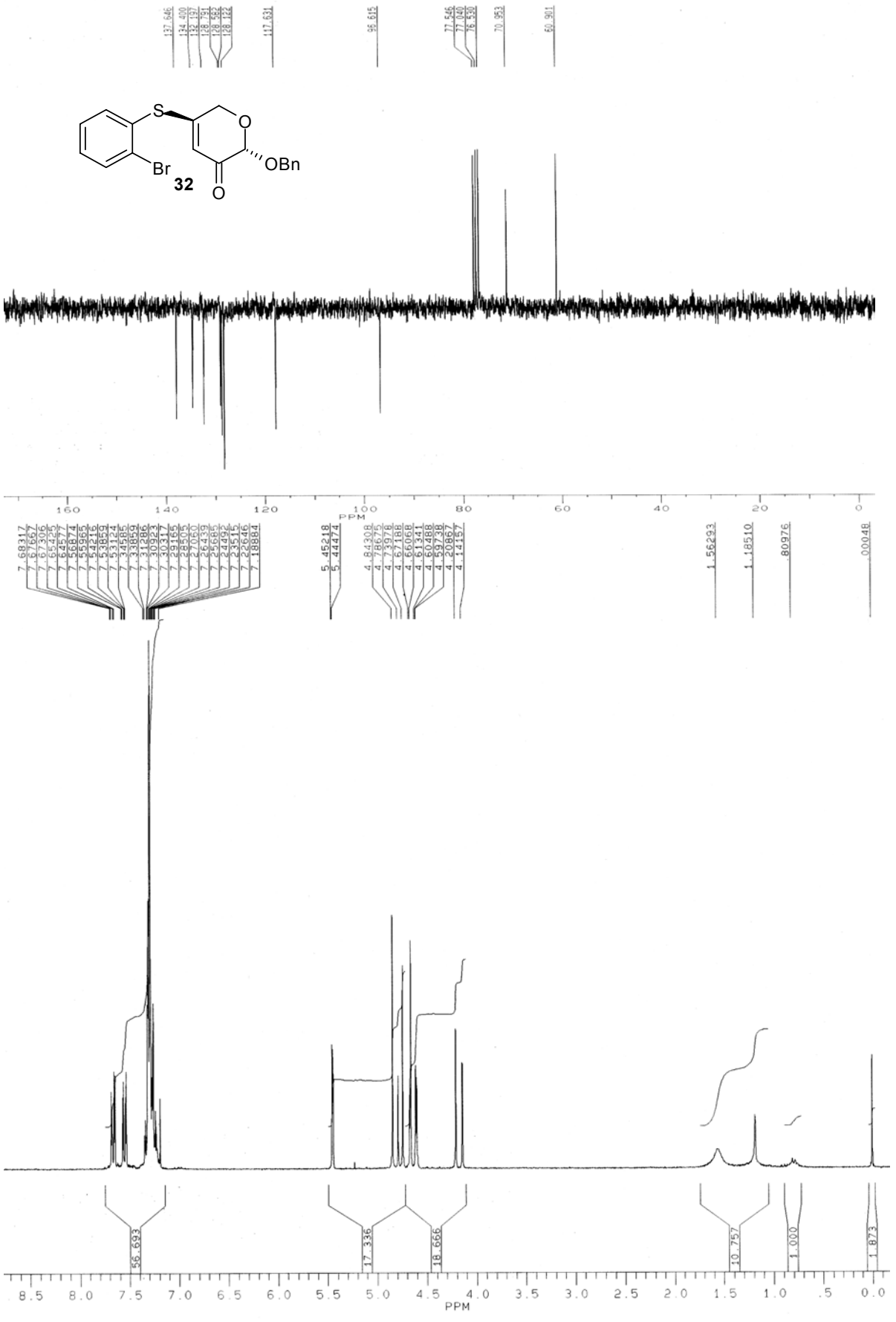


Fig 13. ^{1}H and ^{13}C NMR spectra of benzothiophene **32**.

$CDCl_3$) δ: 95.5 (C-1), 70.2 (C-CH_2Ph), 65.5 (C-2), 58.3 (C-4), 58.1 (C-5), 35.2 (C-3), 27.7, 26.5, 23.1 and 20.8 (4x*C*H_3). (Five quaternary signals at δ 183.0, 174.5, 169.5, 169.2 and 135.5 ppm)

$C_{21}H_{25}N_3O_7S$ (464.4), $[\alpha]_D$ = +167.3° (c = 1, CH_2Cl_2)

Calculated C 53.95 H 6.25 N 8.9 S 5.86%

Found C 53.49 H 6.137 N 8.259 S 5.352%.

C.IV.2. Thiazolidine 37

Purified after acetylation with pyridene-acetic anhydride on a small column, using 2% ethyl acetate:dicholoromethane, in 16% yield.

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 5H), 5.22 (s, 1H), 4.99(br. s, 1H), 4.76 (br. s, 1H), 4.56 (d, J = 11.1Hz, 1H), 4.36 (d, J = 11.1Hz, 1H), 4.00 (m, 1H), 3.72-3.29 (m, 2H), 2.06 (s, 6H), 1.97 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 95.8 (C-1), 70.6 (*C*H_2Ph), 66.2 (C-2), 61.7 (C-4), 59.2 (C-5), 35.2 (C-3), 27.6, 24.9, 21.8 and 20.9 (4x*C*H_3). (Five quaternary signals at δ 183.0, 177.5, 169.4, 164.5 and 136.4 ppm)

$C_{21}H_{25}N_3O_7S$ (464.4), $[\alpha]_D$ = +15.3° (c = 1, CH_2Cl_2)

Calculated C 53.95 H 6.25 N 8.9 S 5.86%

Found C 53.49 H 6.137 N 8.259 S 5.352%.

C.IV.3. Thiazolidine 38

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.45-6.78 (m, 10H), 4.87 (s, 1H), 4.81 (s, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.30 (br. s, J = 5.47 Hz, 1H), 3.92-3.56 (m, 3H). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 95.7 (C-1), 70.1 (C-2), 66.5 (*C*H_2Ph), 59.1 (C-3), 59.0 (C-5), 35.1 (C-3), 26.9, 23.4 and 20.8 (3x*C*H_3); $C_{25}H_{29}N_3O_6S$ (499.4).

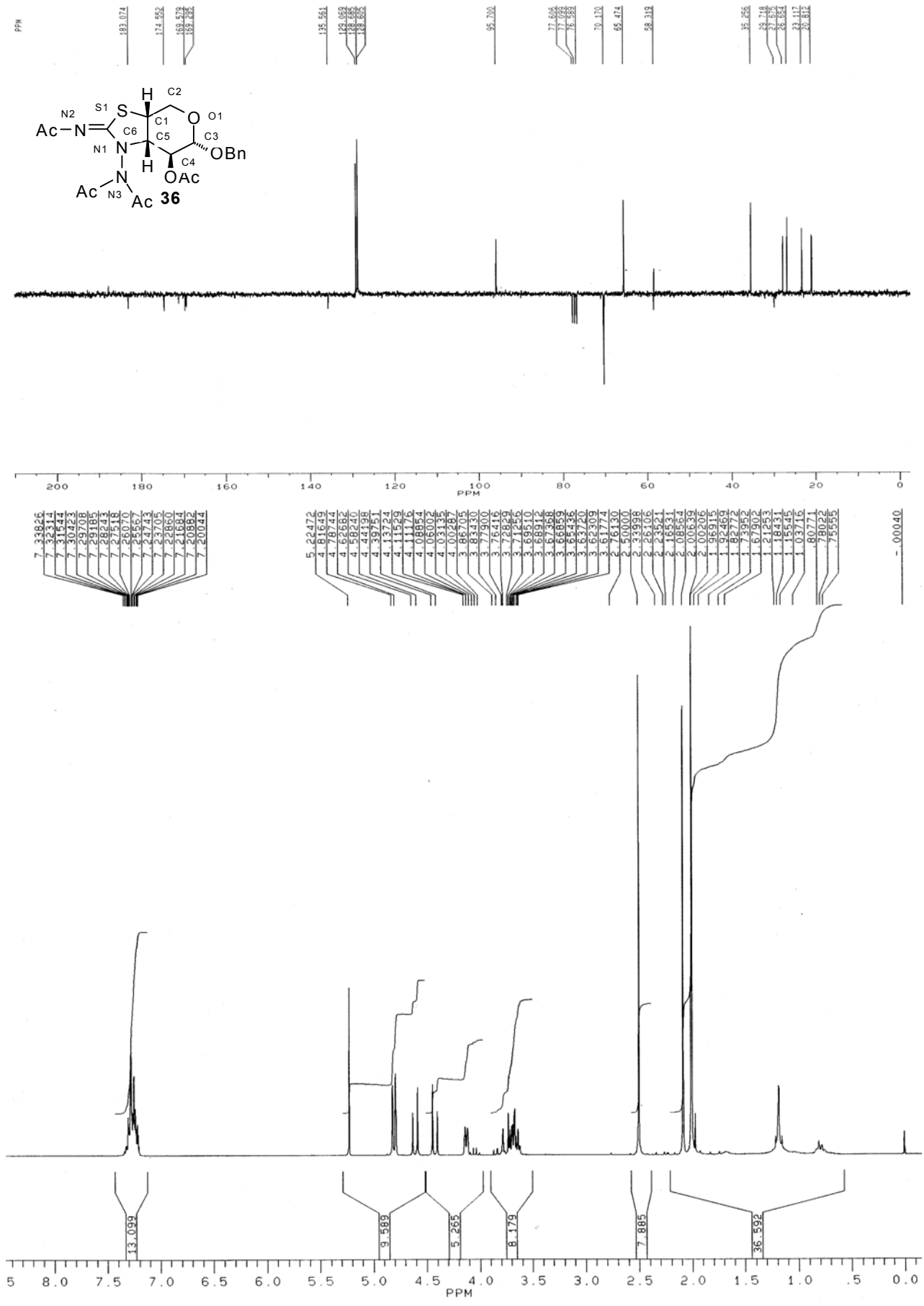


Fig. 14. ^{1}H and ^{13}C NMR spectra of thiazolidine **36**.

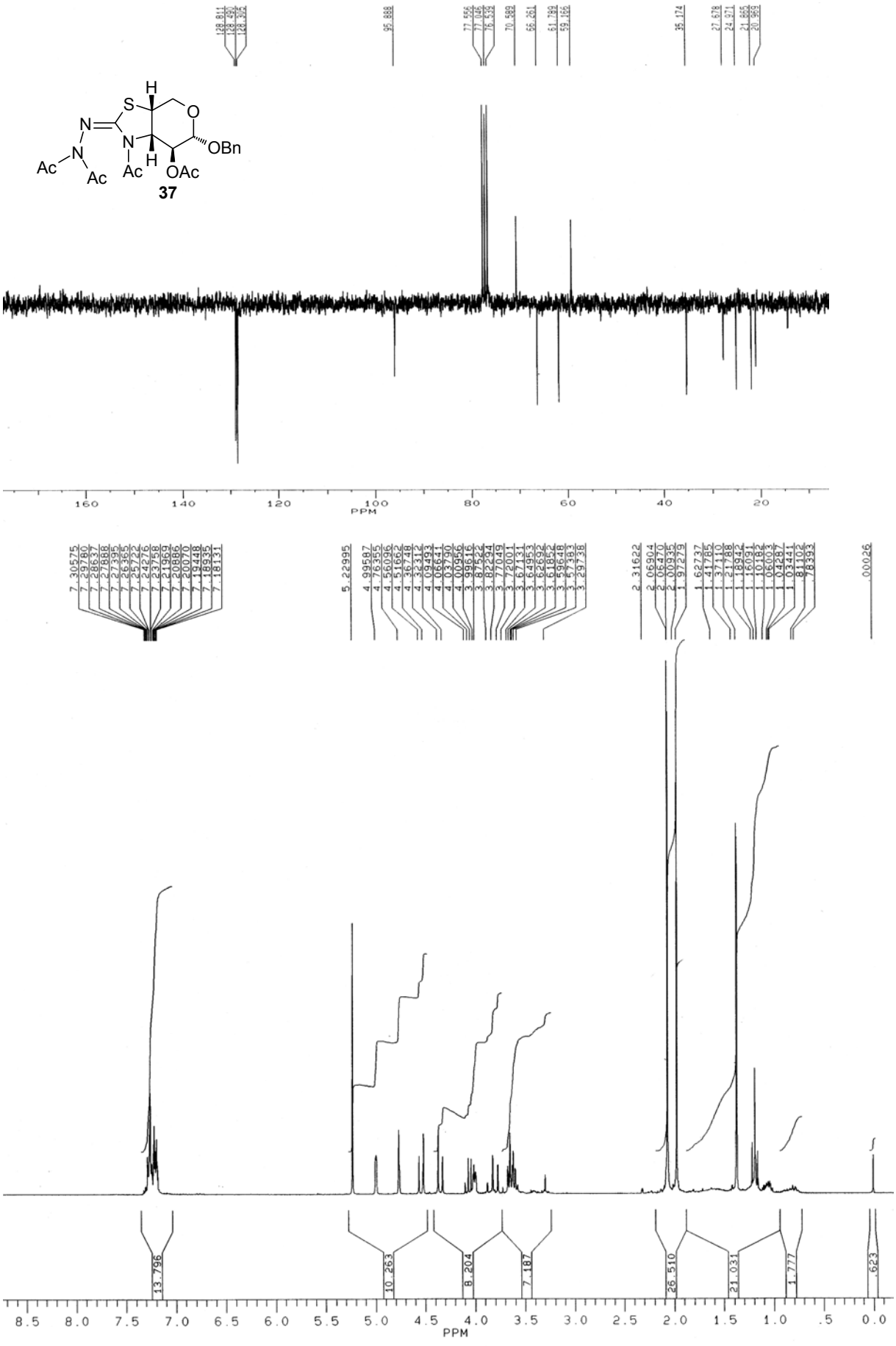


Fig. 15. ^{1}H and ^{13}C NMR spectra of thiazolidine **37**.

C.IV.4. Thiazolidine 39

Immidiatly acetylated with pyridene-acetic anhydride and then purified on TLC cards using 10% ethyl acetate:dicholoromethane, giving 66% yield of the **39**

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.33-7.20 (m, 5H), 5.22 (s, 1H), 4.99 (br. s, 1H), 4.76 (br. s, 1H), 4.56 (d, J = 11.1Hz, 1H, C*H*HPh), 4.36 (d, J = 11.1Hz, 1H, CH*H*Ph), 4.00 (m, 1H), 3.72-3.29 (m, 2H), 2.06 (s, 6H, 2xCH_3), 1.97 (s, 3H, -CH_3), 1.37 (s, 3H, -CH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 94.1 (C-1), 70.1 (*C*H_2Ph), 70.0 (C-2), 58.9 (C-4), 58.8 (C-5), 41.5 (C-3), 27.3, 25.4, 23.9 and 20.7 (4x*C*H_3), $C_{21}H_{25}N_3O_7S$ (464.4), $[\alpha]_D$ = +67.0° (c = 1, CH_2Cl_2)

Calculated C 53.95 H 6.25 N 8.9 S 5.86%

Found C 53.49 H 6.137 N 8.259 S 5.352%.

C.V. Synthesis of Anamarine

C.V.1.Synthesis of "A" part of anamarine

C.V.1.1. Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (44)

To a stirred suspension of methyl α-D-glucopyranoside (**43**) (60 g, 0.31 mol) in dry DMF (247 ml) was added α,α-dimethoxytoluene (47 ml, 0.31 mol) and *p*-toluenesulfonic acid (6.18 g, 0.03 mol). The mixture was then refluxed on a steam bath under vacuum, produced by water aspirator, for 1h. the solvent was evaporated at reduced pressure and the solid material was suspended in hot aqueous $NaHCO_3$. After cooling to room temperature, crystals of almost pure compound were obtained which were recrystallized in hot ethanol and dried in a desicator under vacuum at 70°C overnightto afford **44** as colourless crystalls. Yield 78.4 g (90%), m.p. 162-164°C (ethanol); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.33-7.87 (m, 5H), 5.5 (s, 1H), 4.76 (d, J = 3.9 Hz, 1H), 4.26 (dd, J

= 10.3, 9.7 Hz, 1H), 3.88 (dd, J = 9.5, 9.3 Hz, 1H), 3.72 (m, 2H), 3.61 (dd, J = 3.9, 9.5 Hz, 1H), 3.47 (dd, J = 9.3, 9.1 Hz, 1H), 3.02 (s, 1H, OH), 2.48 (s, 1H, OH); ^{13}C NMR (63 MHz,$CDCl_3$): δ = 126.2-129.7 (PhH), 101.8 (PhCH), 99.7(C-1), 80.9 (C-4), 72.8 (C-2), 71.6 (C-3), 68.8 (C-6), 63.3 (C-5), 55.4 (OCH_3)

$C_{14}H_{18}O_6$ (282.1), $[\alpha]_D^{20}$ +110° (c = 0.5, CH_2Cl_2).

C.V.1.2. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (45)

To a stirred solution of benzylidene acetal **44** (30 g, 0.11 mol) in toluene (300 ml) was added triphenylphosphine (115g, 0.44 mol), iodoform (86.6 g, 0.22 mol), and imidazole (15.0 g, 0.22 mol). The mixture was refluxed for 1h with vigorous stirring. The solution was cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was separated, dried over $MgSO_4$ and evaporated to dryness to yield a brown residue, which was extracted with hot hexane. The solid material was filtered and the filtrate evaporated. Purification on a column of silica gel and eluting with dichloromethane:pet. ether (80:20) gave **45** as a white solid. Yield 23.6 g (87%), m.p. 122°C (ethanol); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.52 (m, 5H, Ph*H*), 6.14(d, J = 10.37 Hz, 1H) 5.73 (dt, J = 10.37, 2.45 Hz 1H) 5.58 (s, 1H) 4.90 (brs, 1H) 4.31 (m, 1H), 4.12-4.17 (m, 1H), 3.74-3.88 (m, 2H), 3.46 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 130.9, 129.2, 128.4, 126.7, 126.3, 102.3, 96.2, 75.3, 69.5, 64.0 and 56.0

$C_{14}H_{16}O_4$ (248.2), $[\alpha]_D^{25}$ +115.2° (c = 0.7, CH_2Cl_2).

C.V.1.3. Methyl 2,3-didehydro-2,3-dideoxy-α-D-erythrohexoside (46)

To a stirred solution of **45** (20 g, 0.08 mol) in absolute CH_2Cl_2 (100ml) was added anhydrous t-BuOOH (14.5 ml, 5.5 M sol. in decane) under nitrogen. After 10 min, $AlCl_3$ (10.7 g, 0.08 mol) was added and stirring was continued

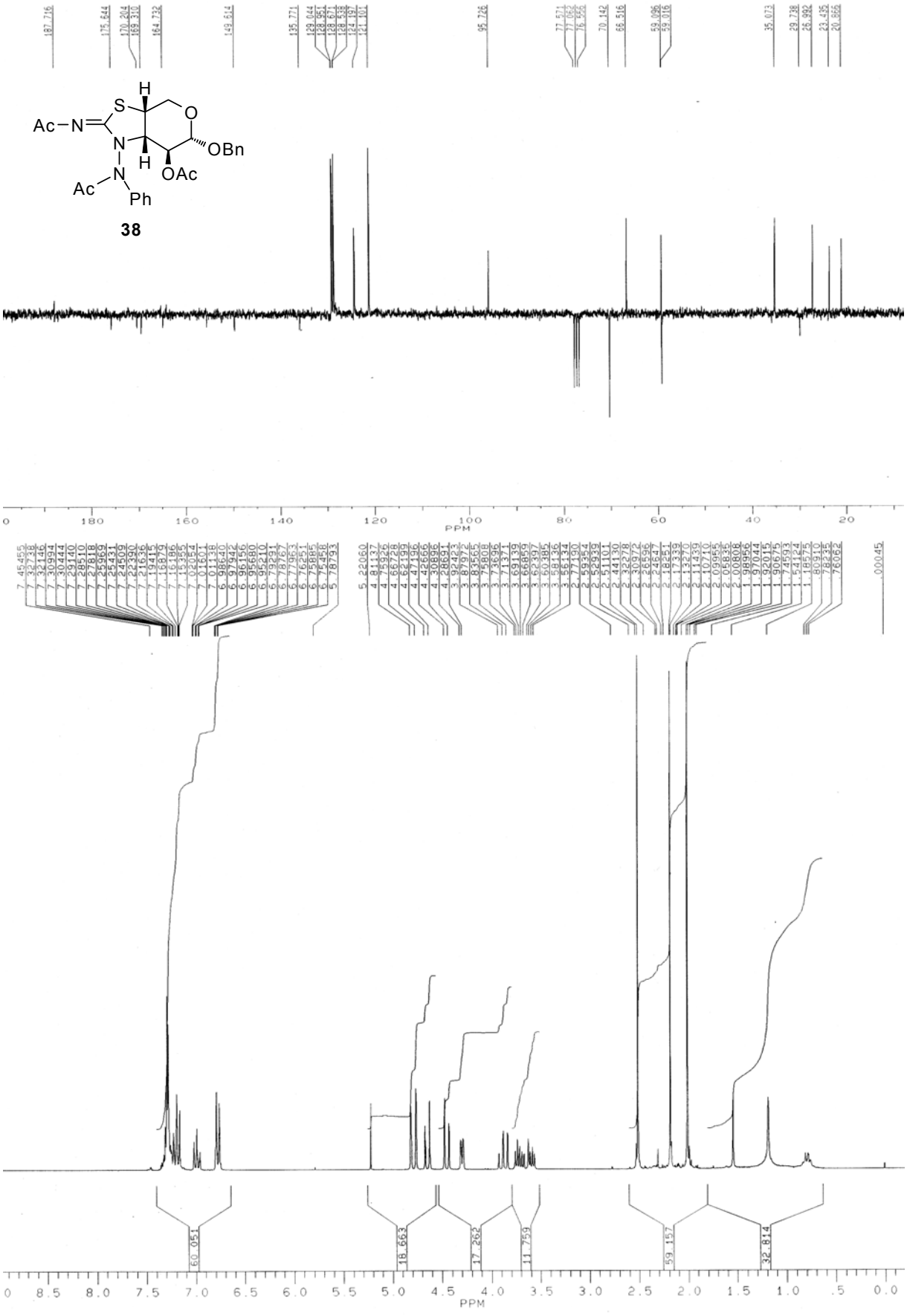


Fig. 16. ^{1}H and ^{13}C NMR spectra of thiazolidene **38**.

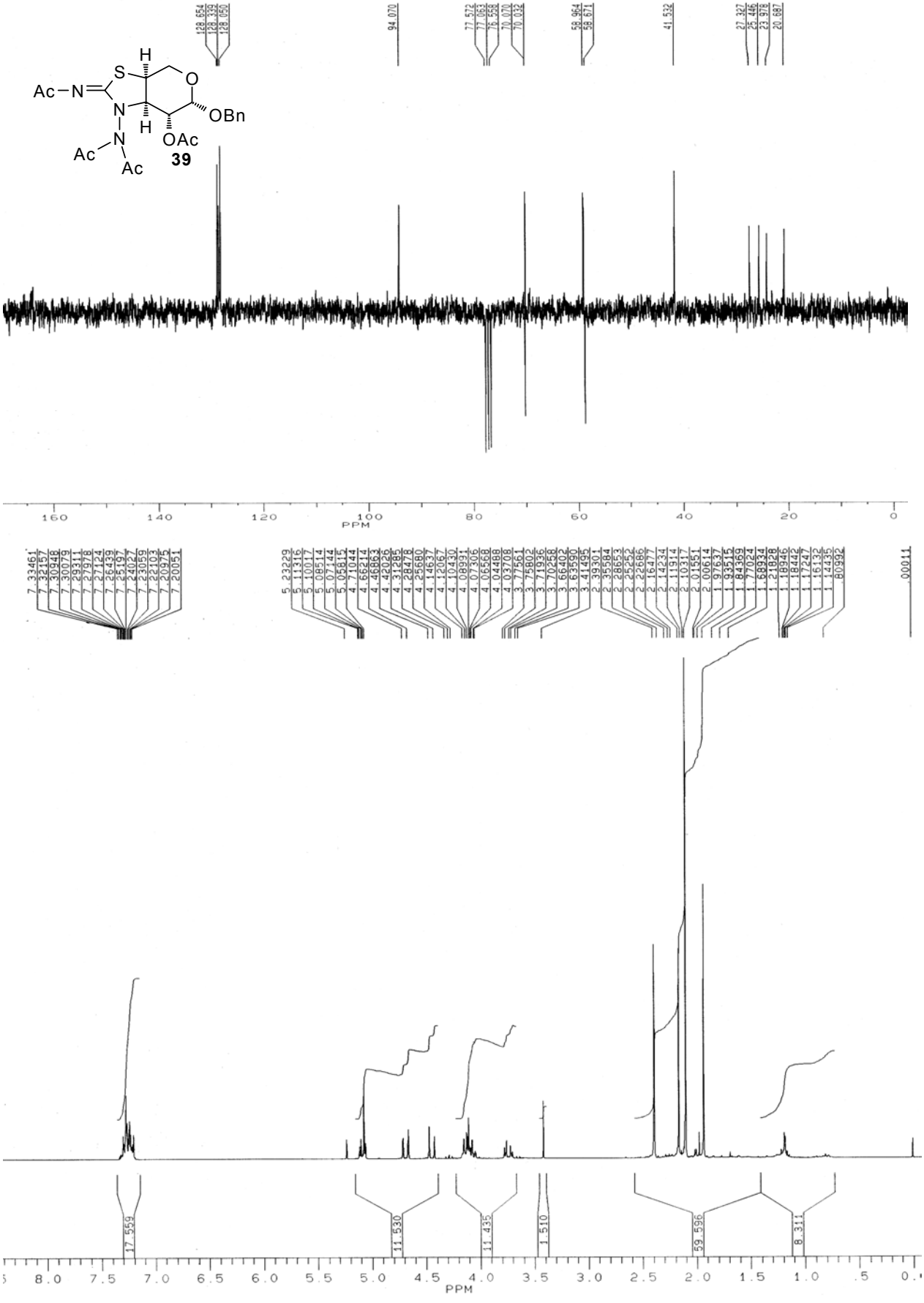


Fig. 17. ^{1}H and ^{13}C NMR spectra of thiazolidene **39**.

at the same temperature till TLC analysis showed no starting material. The reaction was quenched with slow addition of water and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under low pressure to yield almost pure **46** as a colourless oil. Yield 10.3 g (75%), ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.96 (d, J = 10.2 Hz, 1H), 5.74 (dt, J = 2.46, 10.2 Hz, 1H), 4.87 brs, 1H), 4.18 (m, 1H), 3.86 (brs, 2H), 3.64-3.72 (m, 1H), 3.44 (s, 3H), 3.00 (brs, 1H); ^{13}C NMR (63 MHz,$CDCl_3$): δ = 133.7, 126.0 (C-2, C-3), 95.4 (C-1), 71.5, 62.7 (C-4, C-5), 64.2 (C-6), 55.9 (O*C*H$_3$). FAB-MS: m/z = 159.0 (M^+-1), $C_{14}H_{18}O_6$ (160.2), $[\alpha]_D^{24}$ +104.3° (c = 1, methanol).

C.V.1.4. Methyl 6-*O*-benzoyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (47)

To a stirred solution of **46** (10.3 g, 0.06 mol) in absolute pyridine (25 ml) was added a solution of benzoylchloride (12.4 g, 0.09 mol) in CH_2Cl_2 (15 ml). In such a rate that temperature did not rise above -5°C. The reaction was stirred at the same temperature for 5h. The normal workup and purification of the crude material on the silica gel column with pure dichloromethane yielded **47** as a colourless oil. Yeild 15.1 g (90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-8.03 (m, 5H), 5.92 (br d, J = 10.37, 1H), 5.70 (dt, J = 2.44, 10.37 Hz, 1H), 4.85 (brs, 1H), 4.73 (dd, J = 4.88, 12.21 Hz, 1H), 4.45 (dd, J = 2.14, 12.21 Hz, 1H), 4.07 (d J = 8.85 Hz, 1H), 3.83-3.88 (m, 1H), 3.39 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 133.3, 133.1, 129.8, 128.4, 126.4, 95.6, 70.6, 64.3, 64.0, 55.9. FAB-MS: m/z =133.1(M^+-OMe)

$C_{14}H_{16}O_6$ (134.1), $[\alpha]_D^{24}$ +104.3° (c = 1, methanol)

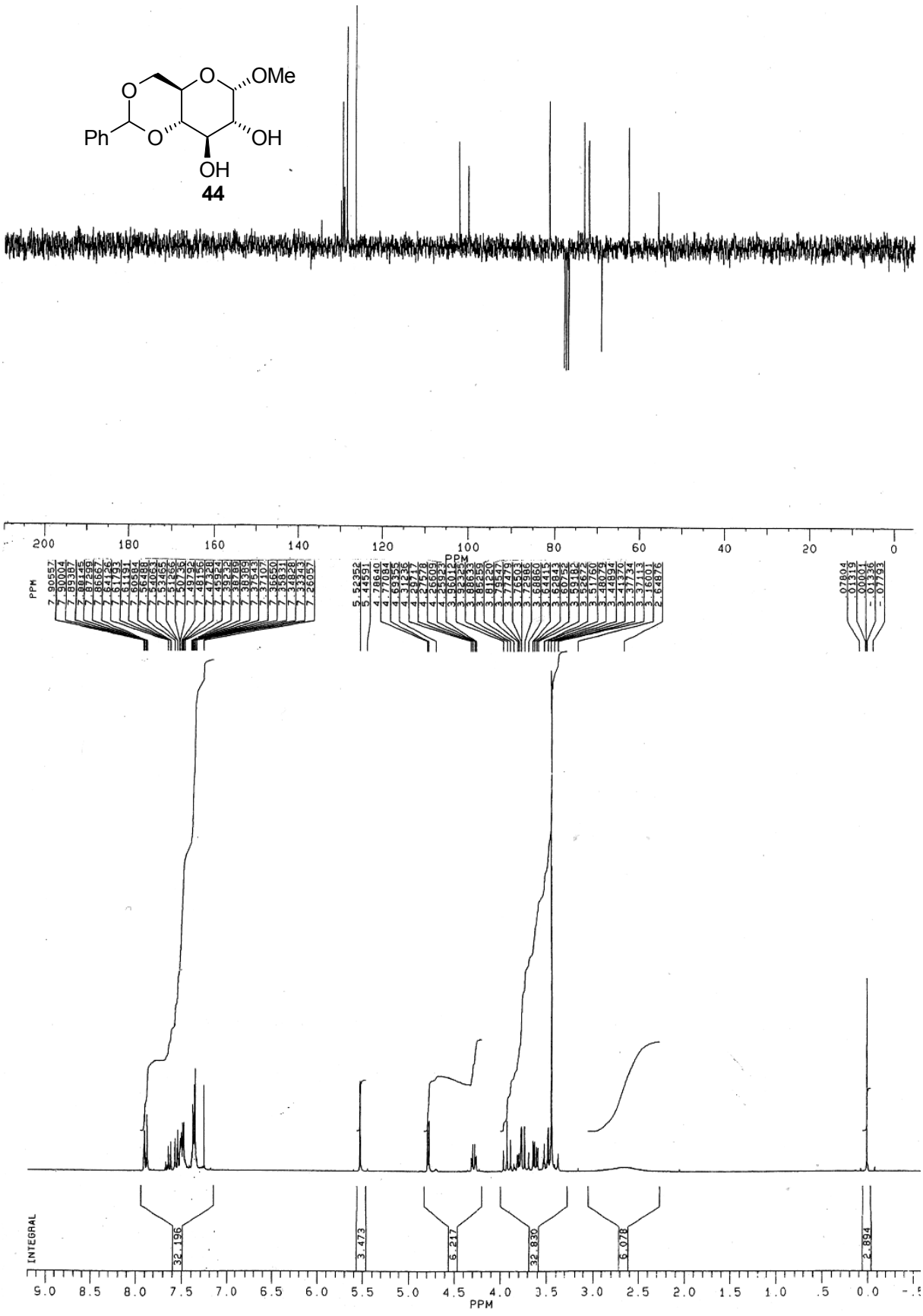


Fig. 18. ^{1}H and ^{13}C NMR spectra of Methyl-4,6-*O*-benzylidene-α-D-gluco-pyranoside (**44**).

C.V.1.5. 2(S)-Methoxy-6(S)-hydroxymethyl-5,6-dihydro-2H-pyran (49)

To a stirred solution of **48** (15 g, 0.057 mol) in absolute pyridine (25 ml) at 0°C was added a solution of mesyl chloride (5 ml). Stirring was continued at the same temperature for 4h. On completion of the reactions (TLC control), the mixture was poured into a beaker containing crushed ice. The aqueous solution was extracted with ether (2 x 50 ml) and the combined organic layers were washed successively with a cooled 2N HCl and saturated aqueous $NaHCO_3$ solution, and finally with water. After drying over anhydrous Na_2SO_4, the solvent was removed at low pressure. The crude material was dissolved in dry THF, under nitrogen atmosphere and gentle stirring, superhydride® (5 ml, 1M solution in THF) was added at 0°C. The temperature was slowly raised to 40°C after 3h the TLC showed no starting material. Excess hydride was destroyed with slow addition of water, then 3N NaOH solution (10 ml) was added, followed by the addition of 30% aqueous H_2O_2 solution (10 ml). The mixture was then brought into a separatory funnel and the THF layer was collected. The aqueous layer was further extracted with ether, the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed. After flash chromatography on a silica gel column by eluting with 5% ethylacetate in CH_2Cl_2. **49** was obtained as a colourless oil. Yield 5.76 g (70%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.09-5.98 (m, 1H), 5.81-5.70 (m, 1H), 4.90 (d, J = 2.00 Hz, 1H), 4.01 (m, 1H), 3.82-3.54 (m, 2H), 3.44 (s, 3H), 2.29 (brs, 1H), 2.25-2.04 (m, 1H), 1.99-1.81 (m, 1H); ^{13}C NMR (63 MHz,$CDCl_3$): δ = 128.6, 125.3, 95.7, 67.0, 76.2, 55.3, 26.0. EI-MS: m/z =113 (M^+-OMe)

$C_7H_{12}O_3$ (144), $[\alpha]_D^{25}$ –75.3° (c = 0.74, C_6H_6).

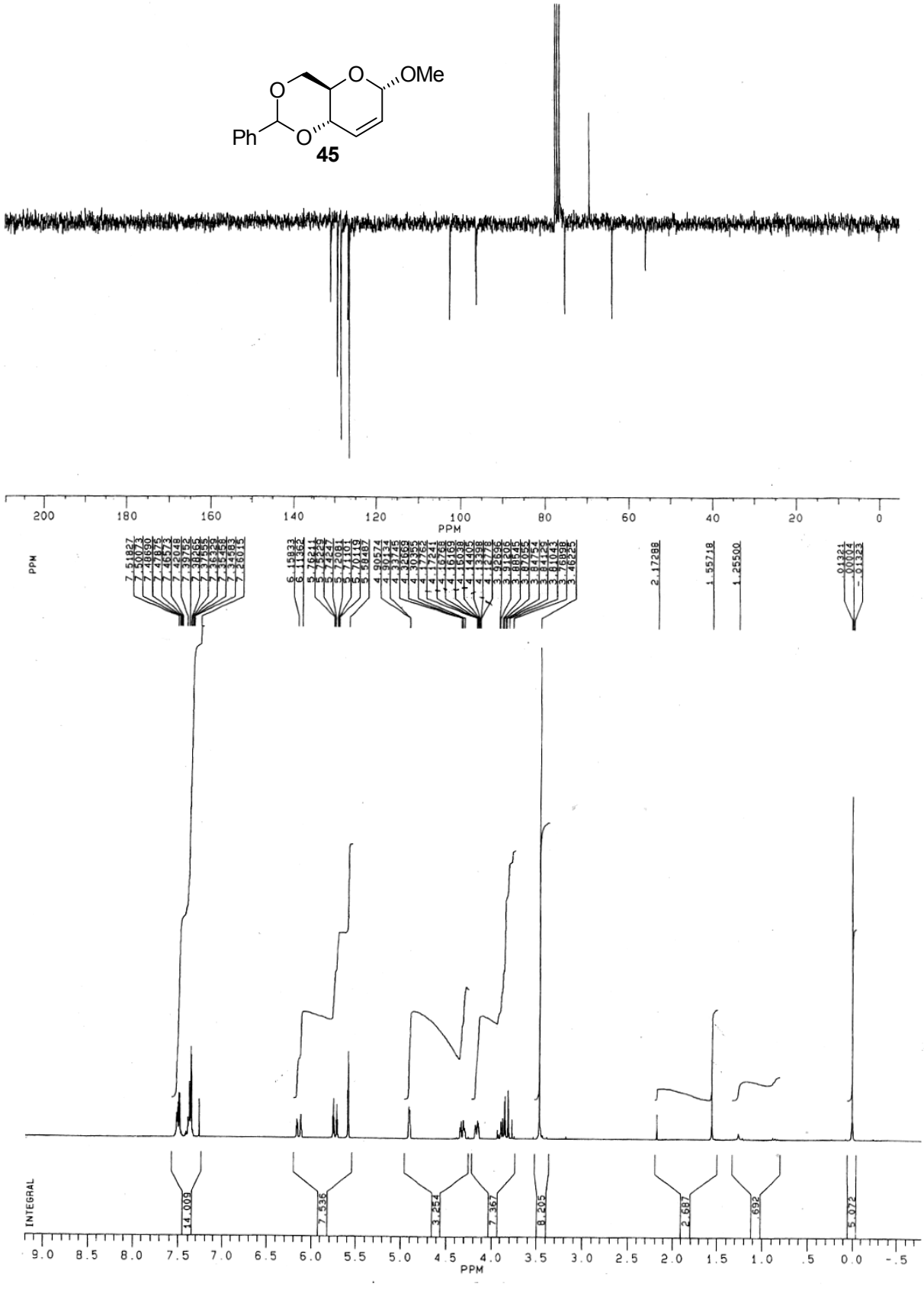


Fig. 19. ^{1}H and ^{13}C NMR spectra of Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (**45**).

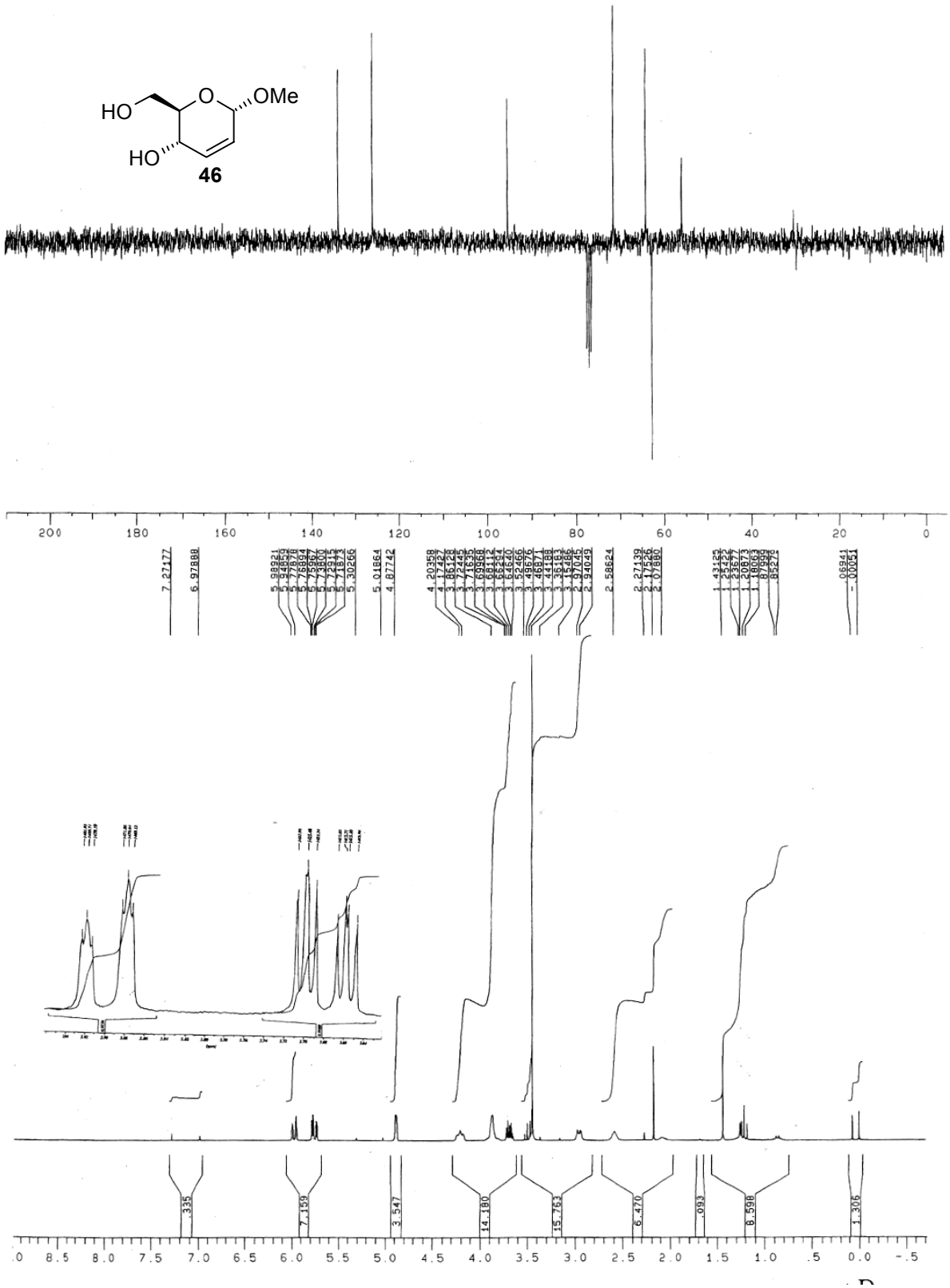


Fig. 20. ^{1}H and ^{13}C NMR spectra of Methyl 2,3-didehydro-2,3-dideoxy-α-D-erythrohexoside (**46**).

C.V.2. Synthesis of side chain (F)

C.V.2.1. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranoside (51)

To an efficiently stirred suspension of anhydrous D-glucose (150 g) in anhydrous acetone (1 liter) was added powdered anhydrous zinc chloride (120 g) followed by 7.2 g of 85% phosphoric acid. This mixture was stirred for 30 hours at room temperature, the undissolved D-glucose was filtered and washed with acetone. The filtrate was made slightly alkaline with NaOH solution at 0°C. The insoluble material was removed and the filtrate was concentrated to a syrup, which was extracted with dichloromethane:water. The organic phase was dried and concentrated to white crystalline residue of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside, which was further crystallized from petrol ether:dichloromethane.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.95 (d, J 3.62 Hz, 1H), 1.50 (s, C*H*$_3$), 1.47 (s, C*H*$_3$), 1.32 (s, C*H*$_3$), 1.24 (s, C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 105.3 (C-1), 73.5,75.2, 81.2, 85.1 (C-2 to C-5), δ 67.7 (C-6), 25.2, 26.2, 26.8, 26.9 (4 x *C*H$_3$). plus two signals of two quaternary acetonide carbons at δ 110 and δ 112 ppm.

$C_{12}H_{20}O_6$ (260.3), m.p.110-111°C. Lit. 109°C [27].

C.V.2.2. 1,2-*O*-Isopropylidene-α-D-glucofuranoside (52)

52 was synthesized by treating **51** with 20% acetic acid solution and stirring the reaction mixture at 25°C for overnight. Completion of the reaction was confirmed by TLC at 10% methanol:DCM indicating the complete conversion.

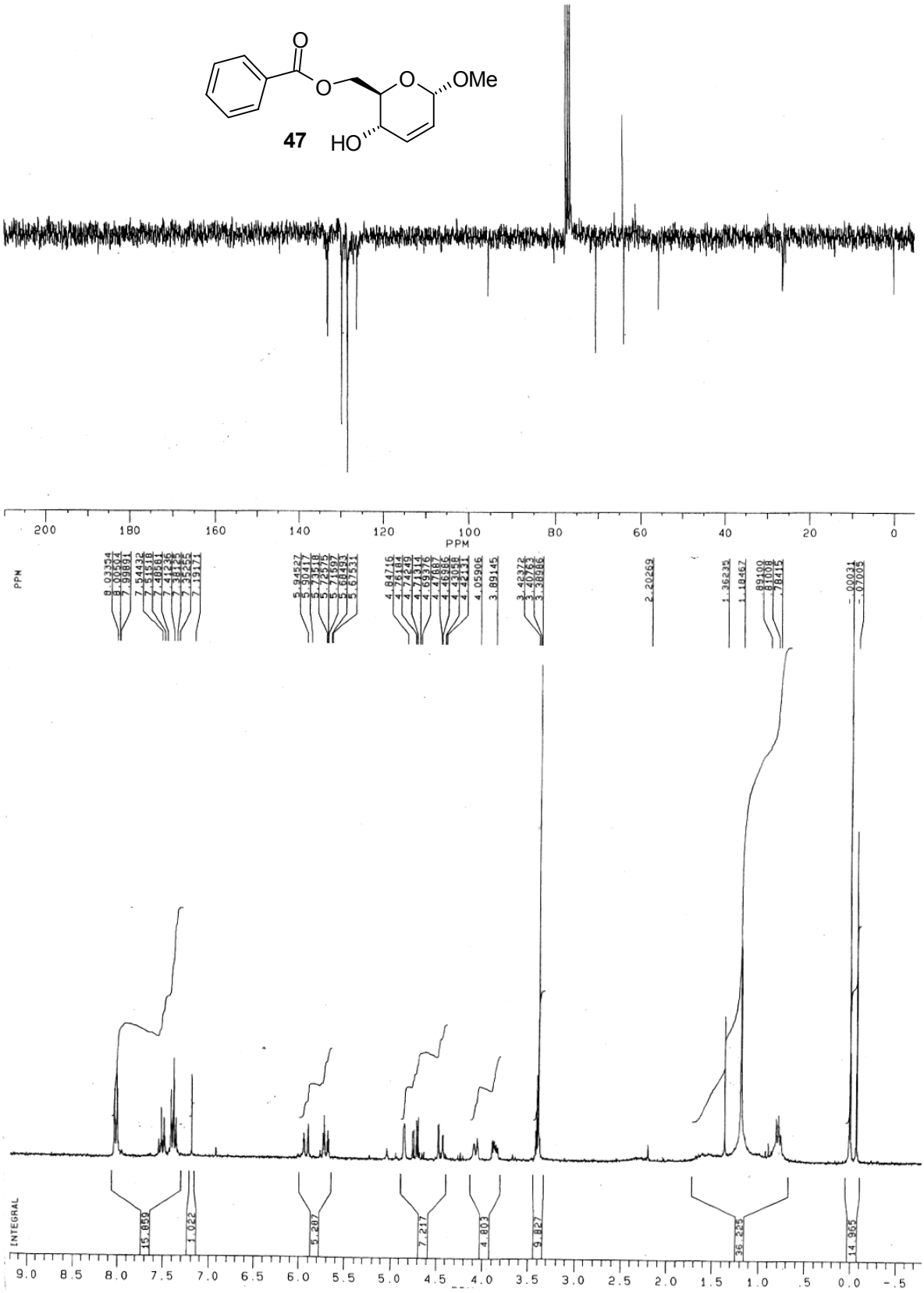


Fig. 21. ^{1}H and ^{13}C NMR spectra of Methyl 6-O-benzoyl-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside (**47**).

Product was further purified by column chromatography using diethyl ether as eluent, in 91% yield.

^{1}H NMR (250 MHz, Acetone-d_6): δ = 5.77 (d, J = 3.65 Hz, 1H), 4.38 (d, J = 3.65 Hz, 1H), 4.10 (d, J = 2.75 Hz, 1H), 3.89 (dd, J = 2.45, 8.25 Hz, 1H), 3.79 (m, 1H), 3.65 (dd, J = 3.05, 11.6 Hz, 1H), 3.45 (dd, J = 5.8, 11.6 Hz, 1H), 3.19 (m, 1H), 1.30 (s, C*H*$_3$), 1.19 (s, C*H*$_3$); ^{13}C NMR (63 MHz, Acetone d_6): δ = 106.3 (C-1), 85.4, 81.2, 75.4, 70.3 (C-2 to C-5), 65.2 (C-6), 26.9, 25.3 (2x*C*H$_3$). Plus a signal of quaternary acetonide carbons at δ 112.6 ppm.

$C_9H_{16}O_6$ (220.2), m.p. 158°C.

C.V.2.3. 1,2-*O*-Isopropylidene-6-*O*-tosyl-α-D-glucofuranoside (53)

5 g of **52** was dissolved in pyridine (30 ml) and cooled to 0°C, then 4.7 g of *p*-toluensulphonic acid chloride was added portion wise. The reaction temperature was maintained at 0°C for further two hours and then stirred at room temperature overnight. The completion of the reaction was confirmed by TLC (10% ethyl acetate:dichloromethane). The reaction was poured on cold aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4 and concentrated to a syrup, which solidified immediately. Purification was carried out by column chromatography (4% ethyl acetate:dichloromethane).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 5.89 (d, J = 3.65 Hz, 1H), 5.30 (s, 1H), 4.50 (d, J = 3.65Hz, 1H), 4.34 (d, J = 2.63 Hz, 1H), 4.31-4.0 (m, 5H), 2.44 (s, C*H*$_3$-Aromatic), 1.50, 1.25 (s, 2xC*H*3).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 142.2, 132.2, 130.0, 128.0 (aromatic signals

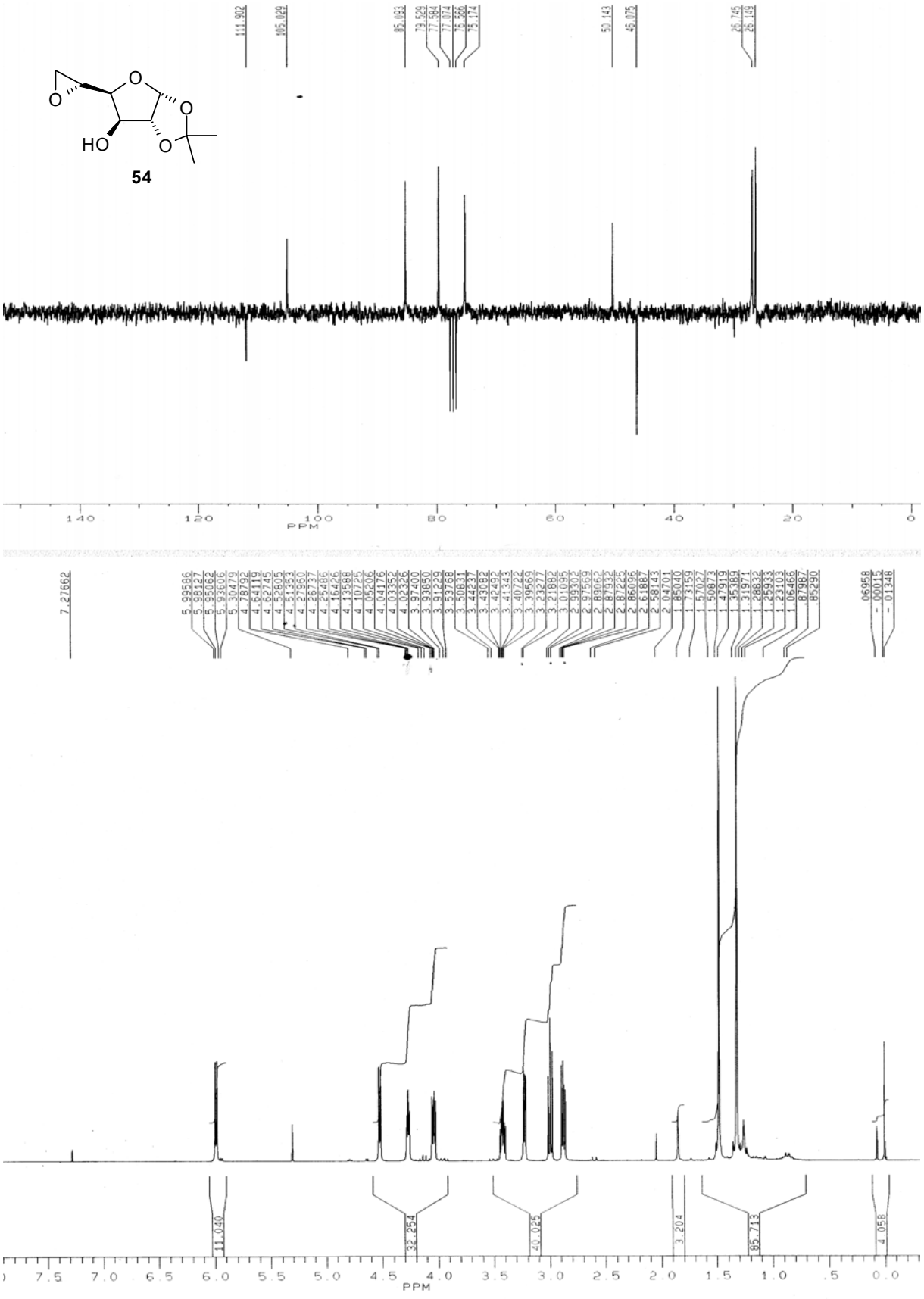


Fig. 22. ^{1}H and ^{13}C NMR spectra of 5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranoside (**54**).

of Ts.), 105.0 (C-1), 85.0, 79.2, 74.9 and 67.8 (C-2 to C-5), 72.2 (C-6), 28.8 and 26.2 (2x*C*H_3). Plus one signal of quaternary acetonide carbon at δ 111.9 ppm. $C_{15}H_{20}O_8S$ (360.4), m.p. 99.6°C, $[\alpha]_D$ = -7° (c = 1, CH_2Cl_2).

C.V.3. 5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranoside (54)

Powdered **53** (1.8 g, 5.26 mmol) was added to a suspension of $LiAlH_4$ (519 mg) in anhydrous ethyl ether, according to the ref. [30]. The mixture was boiled under reflux for six hours, cooled again and the excess of $LiAlH_4$ was destroyed by the addition of water and 15% NaOH. Solids were filtered off and the filtrate was dried over anhydrous Na_2SO_4 and evaporated to yield 78% of the product after column chromatography. m.p.134°C. $C_9H_{14}O_5$ (202.2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.99 (d, J = 3.6 Hz, 1H), 4.51 (d, J = 3.05 Hz, 1H), 4.26 (t, J = 3.05, 6.23 Hz, 1H), 4.27 (m, 1H), 4.02 (m, 1H), 3.42 (m, 1H), 3.21 (d, J = 3.48 Hz, 1H), 3.01-2.87 (m, 2H), 1.37, 1.31 (s, 2xC*H*3). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 105.0 (C-1), 85.1, 79.5, 75.1 (C-2 to C-4), 50.1 (C-5), 46.1 (C-6), 28.7 and 26.2 (2x*C*H_3). Plus a signal of quaternary acetonide carbon at δ 111.9 ppm.

C.V.4. Modifying the route for side chain synthesis

C.V.4.1. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-metoxymethyl-α-D-glucofuranoside (56)

1040 mg of **51** (4 mmol) was added to 50 mg of NaH (6 mmol) suspension in THF (50 ml) at 0°C followed by dropwise addition of MOM-Cl (0.5 ml). The reaction mixture was stirred overnight, excess of NaH was destroyed by addition of NH_4Cl solution and extracted with dichloromethane:water. Organic phase was dried with anhydrous Na_2SO_4, concentrated to a syrup and purified by column chromatography in 79% yield. $C_{14}H_{24}O_7$ (304.3)

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.89 (d, J = 3.64 Hz, 1H), 3.37 (s,-OC*H*$_3$, 3H), 1.50 (s, C*H*$_3$), 1.42 (s, C*H*$_3$), 1.32-1.37 (s, 2xC*H*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 105.3 (C-1), 96.2 (O-*C*H_2-O), 72.4,76.5, 81.1, 83.3 (C-2 to C-5), 67.5 (C-6), 56.3 (C-O*C*H_3), 26.9, 26.2, 25.4, 25.4 (4 x *C*H_3). Plus two signals of quaternary acetonide carbons at δ 110 and δ 112 ppm.

C.V.4.2. 3-*O*-Methoxymethyl-1,2-*O*-isopropylidene-α-D-glucofuranoside (57)

A solution of **56** in 20% acetic acid was stirred at 25°C for overnight and then reaction mixture was concentrated under reduced pressure to give 1,2-*O*-isopropylidene-3-methoxy methyl-α-D-glucopyranoside as a syrup in 90% yield. $[\alpha]_D$= +21°, $C_{11}H_{20}O_7$ (264.3)

C.V.4.3. 3-*O*-Methoxymethyl-6-deoxy-6-iodo-1,2-isopropylidene-α-D-gluco-furanoside (58)

The alcohol **57** was treated with 1.5 equiv. PPh_3, 1.5 equiv. of imidazole, 3 equiv. of iodine and heated up to 60°C for two hours. Then cooled to room temperature, diluted with ether, washed successively with water, aq. 10% $Na_2S_2O_3$ and saturated aq. NaCl solution. The solvent was evaporated under reduced pressure. The product, **58,** was obtained in 84% yield after chromatography. $C_{11}H_{19}IO_6$ (374.1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.87 (d = J 3.67 Hz, 1H), 3.40 (s, OC*H*$_3$, 3H), 2.0 (br. s, 2H), 1.29 (s, C*H*$_3$), 1.26 (s, C*H*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 105.2 (C-1), 97.2 (O-*C*H_2-O), 83.6, 82.3, 81.1, 67.6 (C-2 to C-5), 56.1 (-O*C*H_3), 26.9, 26.4 (2x*C*H_3), 14.2 (C-6). Plus a quaternary signal of acetonide carbon at δ 112.3 ppm.

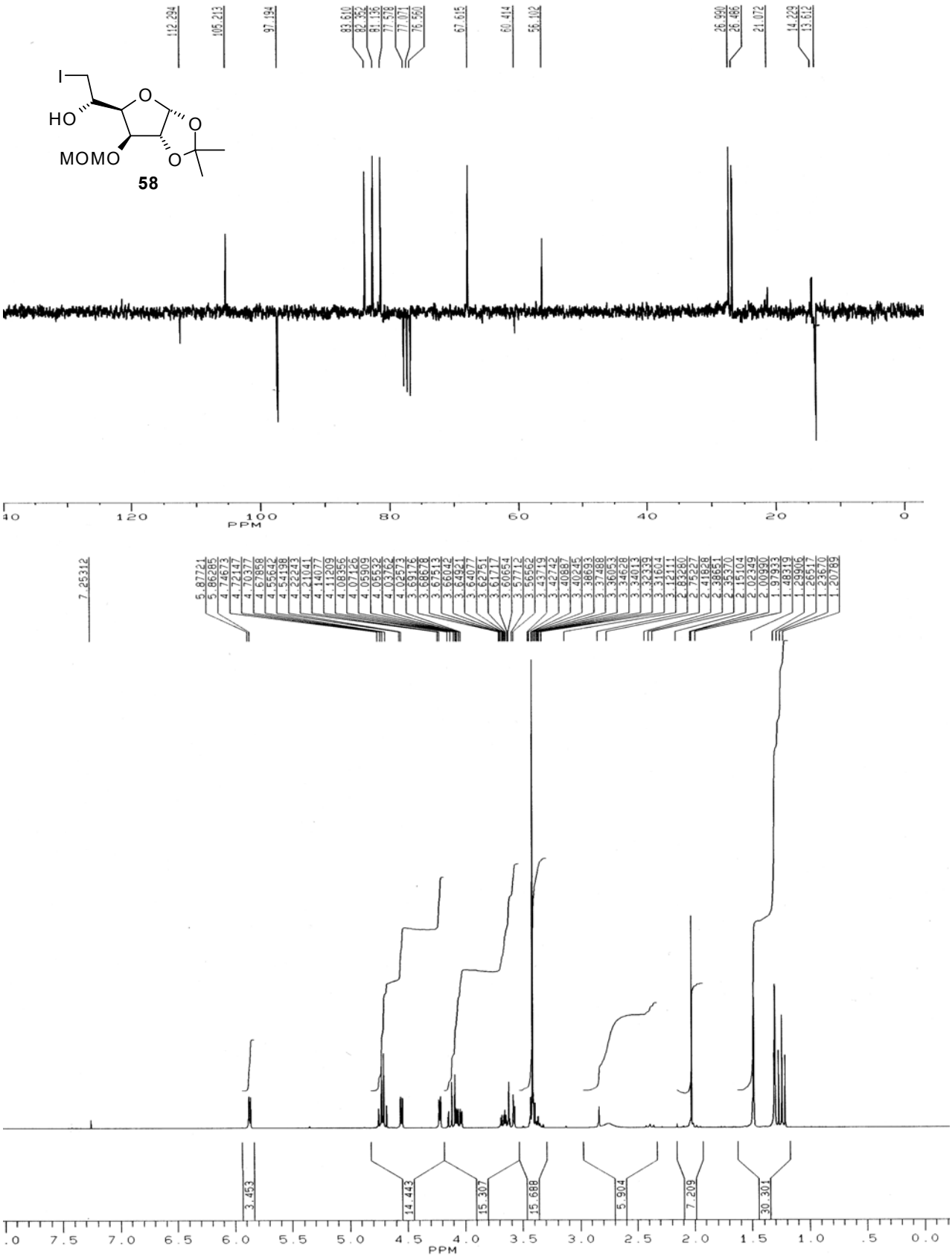


Fig. 23. ^{1}H and ^{13}C NMR spectra of 3-*O*-methoxymethyl-6-deoxy-6-iodo-1,2-isopropylidene-α-D-glucofuranoside (**58**).

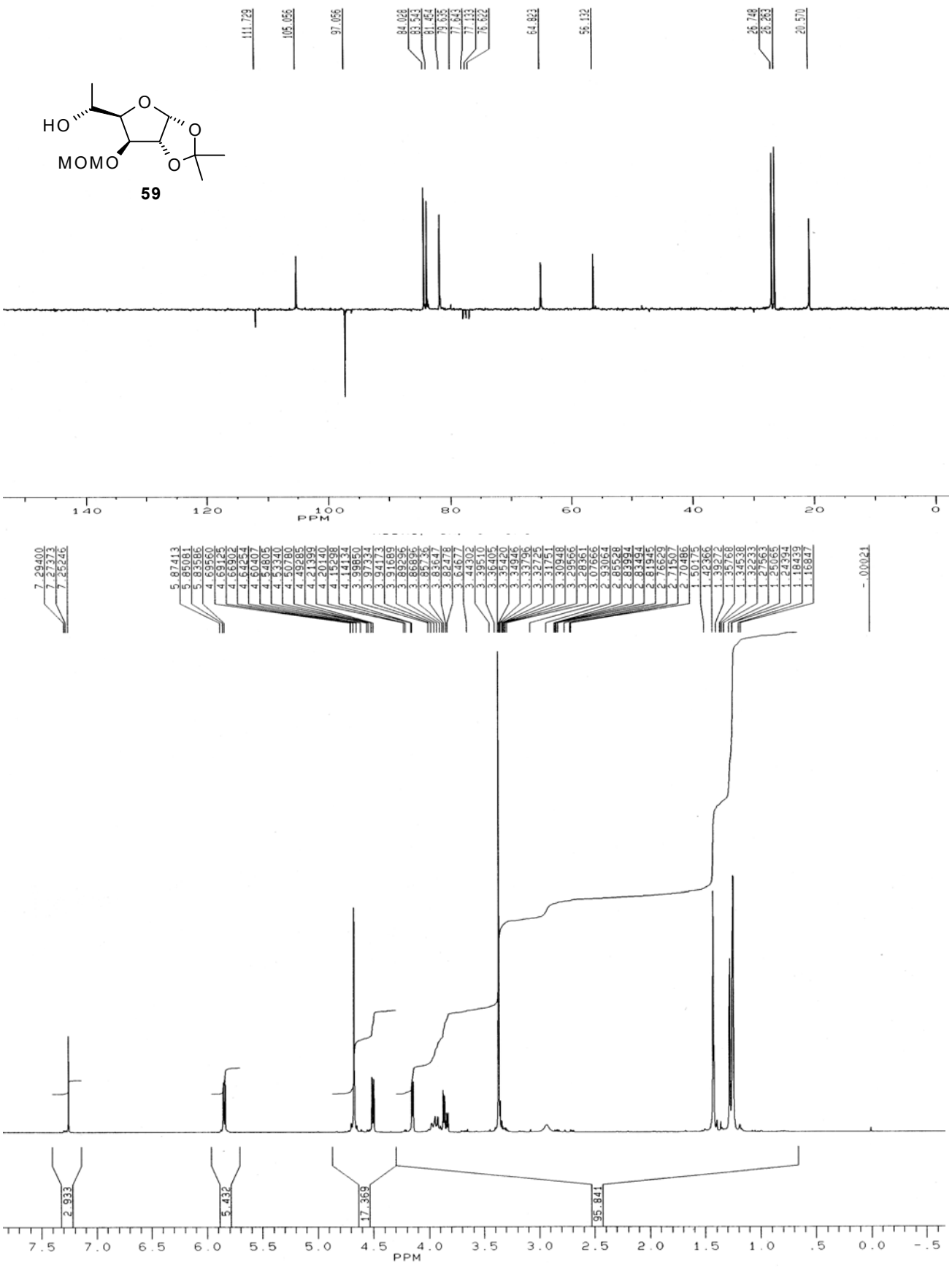


Fig. 24. ^{1}H and ^{13}C NMR spectra 3-*O*-methoxy methyl-6-deoxy-1,2-isopropylidene-α-D-glucofuranosid (**59**).

C.V.4.4. 3-*O*-Methoxymethyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranosid (59)

To a suspension of 1.5 equiv. of $NaBH_4$ in diglyme, 1.0 equiv. of **56** was added and heated upto 80°C for 6h and then cooled gradually to room temperature. The excess of $NaBH_4$ was destroyed with NH_4Cl solution extracted in dichloromethane:water, dried with anhydrous Na_2SO_4 and concentrated to a syrup. The product, 3-*O*-methoxymethyl-6-deoxy-1,2-isopropylidene-α-D-glucofuranoside, obtained in 81% yield after column chromatography.

^1H NMR (250 MHz, $CDCl_3$): δ = 5.87 (d, J = 3.73Hz, 1H), 3.35 (s, -OC*H*$_3$, 3H), 1.42 (s, C*H*$_3$), 1.18-1.16 (s, 2xC*H*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 105.0 (C-1), 97.0 (O-*C*H_2-O), 84.0, 83.5, 81.4, 64.8 (C-2 to C-5), 56.1 (C-O*C*H_3), 26.7, 26.2, 20.6 (3 x *C*H_3). Plus a quaternary signal of acetonide carbon at δ 111.7 ppm.

$C_{11}H_{20}O_6$ (248.3)

C.V.4.5. Dithioacetal (60) and di-*O*-isopropylidene dithioacetal (61)

The 6-deoxy product **59** (100 mg, 1.08 mmol) was added to a cooled flask containing ethylthiol (185 μL). Concentrated HCl (220 μL) was added to this and kept at 0-5°C for 10 minutes and then at room temperature for 40 minutes. Neutralisation with NH_4Cl and extraction with dichloromethane gave crude product, which was concentrated to a syrup. The crude compound was dissolved in anhydrous cold acetone and catalytic amount of $HClO_4$ was added into it. The solution was maintained at 0-5°C for one hour and then at room temperature for 20 hours. Reaction was quenched with few drops of pyridine and then product was purified on a small column giving 48% overall yield of the two steps.

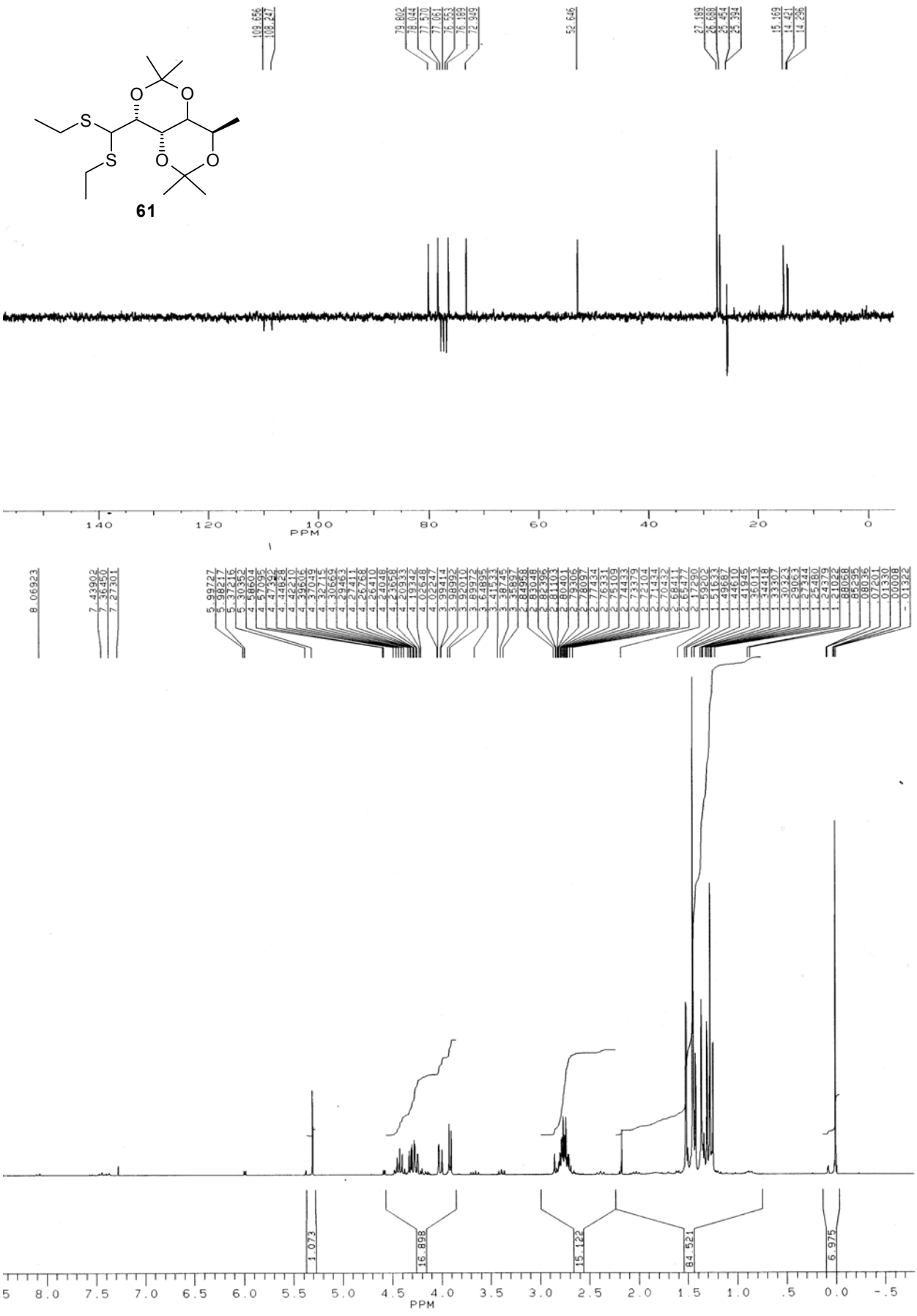


Fig. 25. ^{1}H and ^{13}C NMR spectra of Di-*O*-isopropylidene dithioacetal (**61**).

m.p. 53.6°C. $[\alpha]_D$ = -93° (c = 1, CH_2Cl_2). $C_{16}H_{30}O_4S_2$ (350.5), ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 79.8, 78.0, 76.2, 72.9 (C-2 to C-5), 52.6 (C-1), 15.2 (C-6). Plus two signals due to two S-CH_2 at 25.4, 25.3, two signals of S-CH_2CH_3 at 14.4, 14.3 and four signals of *C*-Me at 27.19, , 27.19, 27.19, 25.6 ppm.

C.VI. General Method for the Synthesis of 3,4-Disaccharides

1 mmol of **51** was added in 1.2 mmol of Na_2CO_3 suspension in dry CH_3CN at 0 °C. The mixture was stirred for 30 minutes and then 1.0 mmol of epoxy triflate (**16** or **17**) dissolved in 5 ml of CH_3CN was added dropwise into the reaction mixture at 0°C. The reaction mixture was stirred at this temperature for 30 minutes and then stirred at room temperature for 6h. After the completion of reaction, as indicated by TLC, the reaction mixture was neutralized with saturated solution of NH_4Cl and extracted with ethyl acetate. Dried over anhydrous Na_2SO_4 and concentrated to a syrup, and finally purified by column chromatography giving 82-48% yield.

C.VI.1. 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranoside-3-yl benzyl 2,3-anhydro-α-D-lyxopyranoside (62a)

Purified by column chromatography in 82% yield using 10% ethyl acetate:dichloromethane. Colourless oil; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.20 (5H-aromatic), 5.82 (d, J = 3.6 Hz, 1H), 4.92 (s, 1H), 4.73 (d, J = 11.6 Hz, 1H, -C*H*HPh), 4.51 (1H, d = J 3.35 Hz, 1H), 4.48 (d, J = 11.6 Hz 1H, -CH*H*Ph), 4.16-3.21 (m, 10H), 3.25 (d, J = 3.65 Hz, 1H), 3.07 (d, J = 3.67 Hz, 1H). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 105.3 (C-1´), 93.8 (C-1), 83.9, 82.2, 81.3,

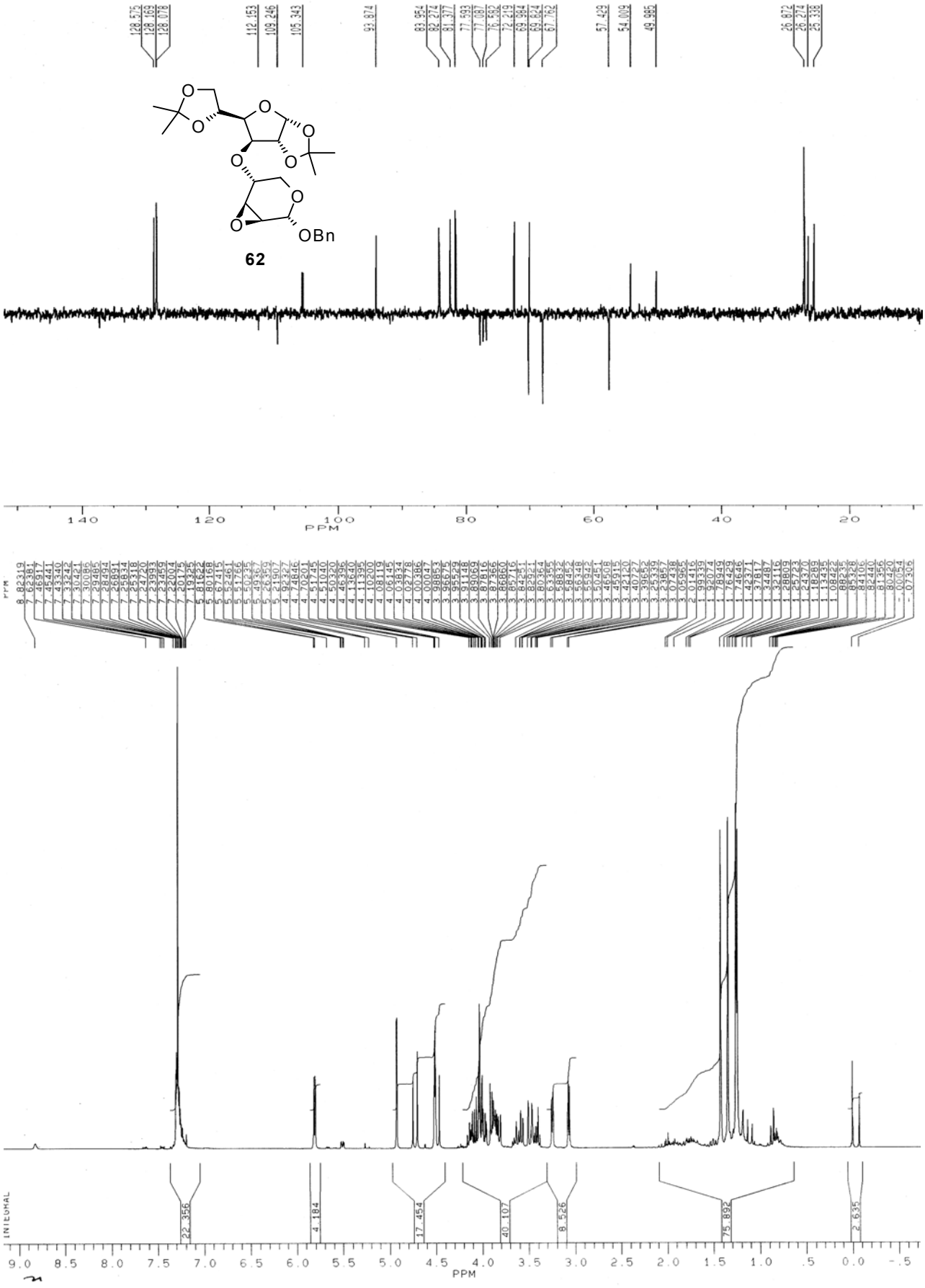


Fig. 26. ^{1}H and ^{13}C NMR spectra of disaccharide **62**.

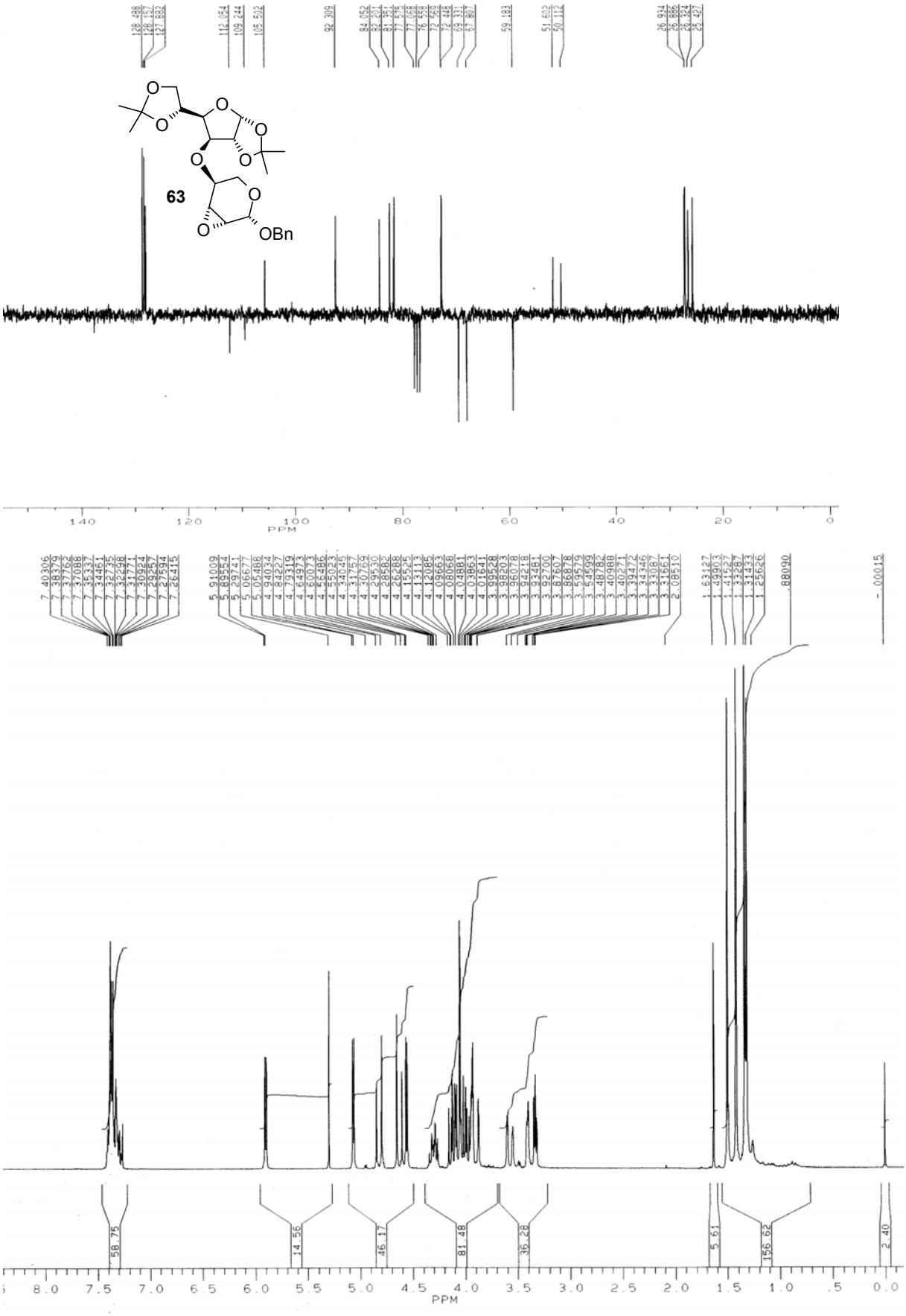


Fig. 27. ^{1}H and ^{13}C NMR spectra of disaccharide **63**.

72.2 (C-2´ to C-5´), 69.9 (C-4), 69.8 (C-*C*H_2Ph), 67.7 (C-6), δ 57.4 (C-5), 54.01 (C-3), 49.9 (C-2), 26.8, 26.8, 26.2, 25.3 (4x*C*H_3). FAB-MS: e/z 465.3 (M^+), $C_{24}H_{32}O_9$, $[\alpha]_D$ = +36.3° (c = 1, CH_2Cl_2).

Calculated C 62.06 H 5.94%

Found C 62.49 H 6.02%.

C.VI.2. 1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-glucofuranoside-3-yl benzyl 2,3-anhydro-β-L-lyxopyranoside (63)

Purified by column chromatography in 71% yield using 5% ethyl acetate:dichloromethane.

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.40-7.26 (5H-aromatic), 5.90 (d, J = 3.6 Hz, 1H, H-1´), 5.06 (d, J = 3.05, 1H, H-1), 4.80 (d, J = 12.2 Hz, 1H, C*H*HPh.), 4.62 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.65 (d, J = 3.67 Hz, 1H), 4.62-4.34 (m, 1H), 4.15-3.86 (m, 6H), 3.35 (br. d, J = 12.2 Hz, 1H), 3.40 (m, 1H), 1.49 (s, CH_3), 1.41 (s, CH_3), 1.33 (s, CH_3), 1.31 (s, CH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 127.8-128.4 (5x*C*-Aromatic), 105.5 (C-1´), 92.8 (C-1), 84.0,82.2, 81.3, 72.5 (C-2´ to C-5´), 72.4 (C-4), 69.3 (C-6´), 67.8 (*C*H_2Ph), 59.1 (C-5), 51.6 (C-3), 50.1 (C-2), 26.9, 26.8, 26.3, 25.4 (4x*C*H_3). FAB-MS: e/z 465.3 (M^+)

$C_{24}H_{32}O_9$,

Calculated C 62.06 H 5.94%

Found C 62.49 H 6.02%.

C.VI.3. 1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allofuranoside-3-yl benzyl 2,3-anhydro-α-D-lyxopyranoside (65)

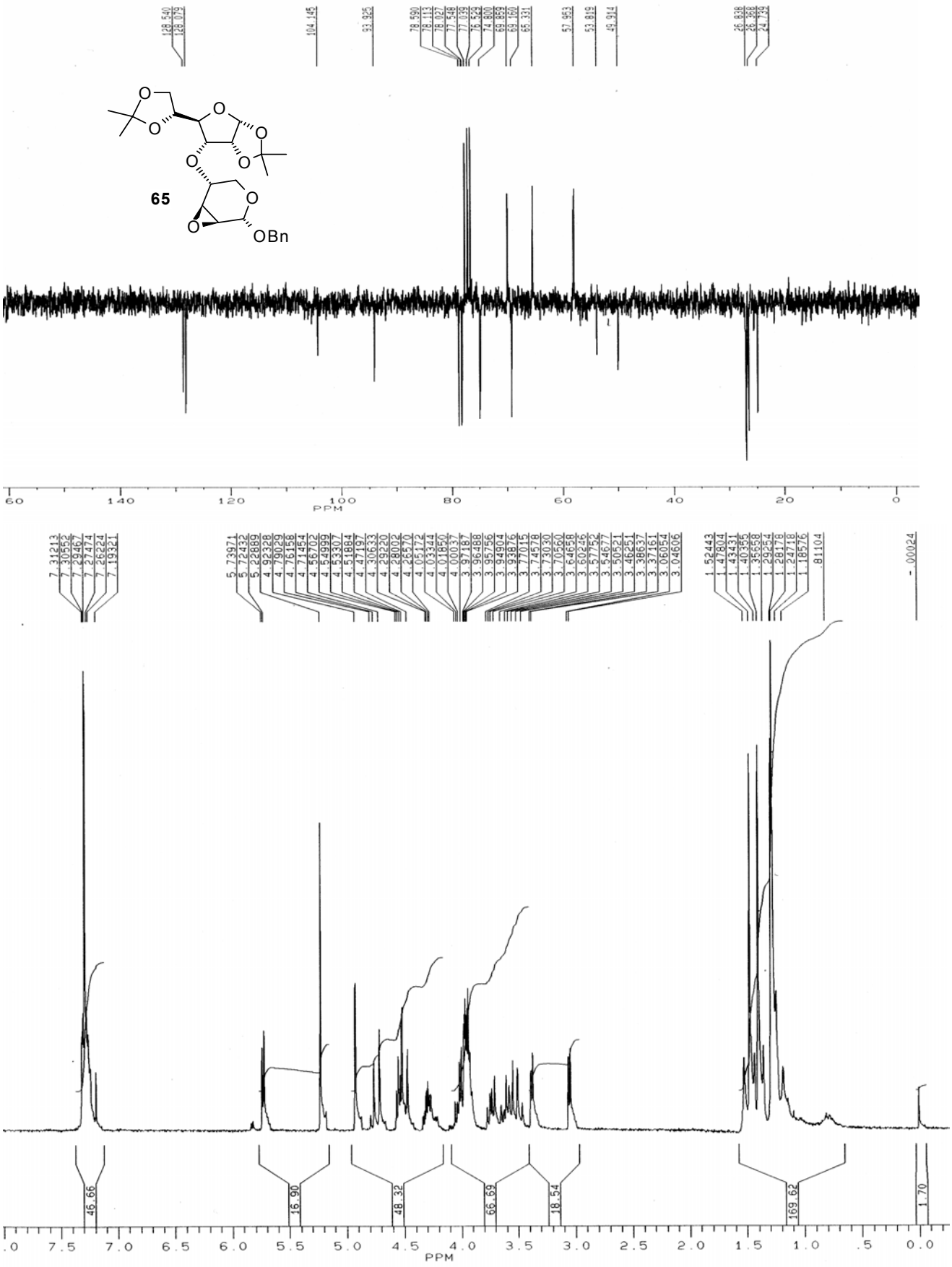


Fig. 28.. ^{1}H and ^{13}C NMR spectra of disaccharide **65**.

Purified by column chromatography in 54% yield using 10% ethylacetate:dichloromethane.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.35-7.20 (5H-aromatic), 5.73 (d, J = 3.67 Hz, 1H, H-1´), 5.22 (br. s, 1H, H-1), 4.92 (br. s, 1H), 4.77 (br. d, J = 11.9 Hz, 1H), 4.56-4.47 (m, 2H), 4.33-4.26 (m, 1H), 4.05-3.92 (m, 4H), 3.76-3.70 (d, J = 6.10 and 9.7 Hz 1H), 3.62-3.50 (m, 2H), 3.37 (d, J = 3.65 Hz 1H), 3.05 (d, J = 3.35 Hz, 1H), 1.47 (s, C*H*$_3$), 1.40 (s, C*H*$_3$), 1.29 (s, C*H*$_3$), 1.28 (s, C*H*$_3$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 104.1 (C-1´), 93.9 (C-1), 78.5, 78.1, 78.0, 74.7 (C-2´ to C-5´), 69.2 (C-4), 69.8 (C-CH_2Ph), 65.3 (C-6´), 57.9 (C-5), 53.8 (C-3), 49.9 (C-2), 26.8, 26.7, 26.3, 24.7 (4x*C*H$_3$). , FAB-MS: e/z 465.3 (M^+) $C_{24}H_{32}O_9$, $[\alpha]_D$ = +91.2° (c = 1, CH_2Cl_2),

Calculated C 62.06 H 5.94%

Found C 62.49 H 6.02%.

C.VI.4. 1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allofuranoside-3-yl benzyl 2,3-anhydro-β-L-lyxopyranoside (66)

Purified by column chromatography in 49% yield using 10% ethyl acetate:dichloromethane.

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32-7.19 (5H-aromatic), 5.77 (d, J = 3.6 Hz, 1H, H-1´), 4.99 (d, J = 3.05, 1H, H-1), 4.77 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.58 (d, J = 12.2 Hz, 1H, C*H*HPh), 4.01-3.96 (m, 3H), 3.85 (br. s, 2H), 3.52 (s, 3H), 3.29 (m, 1H), 1.49 (s, C*H*$_3$), 1.39 (s, C*H*$_3$), 1.31 (s, C*H*$_3$), 1.29 (s, C*H*$_3$). FAB-MS: e/z 465.3 (M^+), $C_{24}H_{32}O_9$, $[\alpha]_D$ = +86.1° (c = 1, CH_2Cl_2).

Calculated C 62.06 H 5.94%

Found C 62.49 H 6.02%.

C.VI.5. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-trifloromethylsulphonyl-α-D-glucofuranose (67)

The free -OH group in 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside was activated by triflation using general procedure as described earlier, yielding the product in 88% yield after recrystallization.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.99 (d, J = 3.69 Hz, 1H), 5.26 (br. s, 1H), 4.74 (t, J = 3.9, 7.6 Hz, 1H), 4.33-7.33 (m, 4H), 1.52, 1.42, 1.34 and 1.33 (4xCH_3) ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 105.0 (C-1), 88.1, 83.2, 79.9 and 71.7 (C-2 to C-5), 67.6 (C-6); 26.7, 26.5, 26.2 and 24.8 (4 x CH_3)

C.VI.6. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose (68)

1 g of **51** was dissolved in pyridine (7 ml) and cooled to 0°C, then 940 mg of *p*-toluensulphonic acid chloride was added portion-wise. The reaction temperature was maintained at 0°C for further two hours and then stirred over night at room temperature. Completion of the reaction was confirmed by TLC (4% ethyl acetate:chloroform). The reaction was poured on cold aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4 and concentrated to a syrup. Purification was carried out by column chromatography (chloroform).

The product was confirmed by mass spectroscopy.

450.0 (M+1), 399.0 (M-CH3), 357 (M-CH_3COCH_3), 298.9 (M-2CH_3COCH_3), 243 (M-OTs).

C.VI.7. 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranoside (64)[40]

A mixture of 40 mL of DMSO and 30 mL of acetic anhydride was treated with 6.55 g of **51** and stirred at room tempertature for 36 hours. Evaporation of the

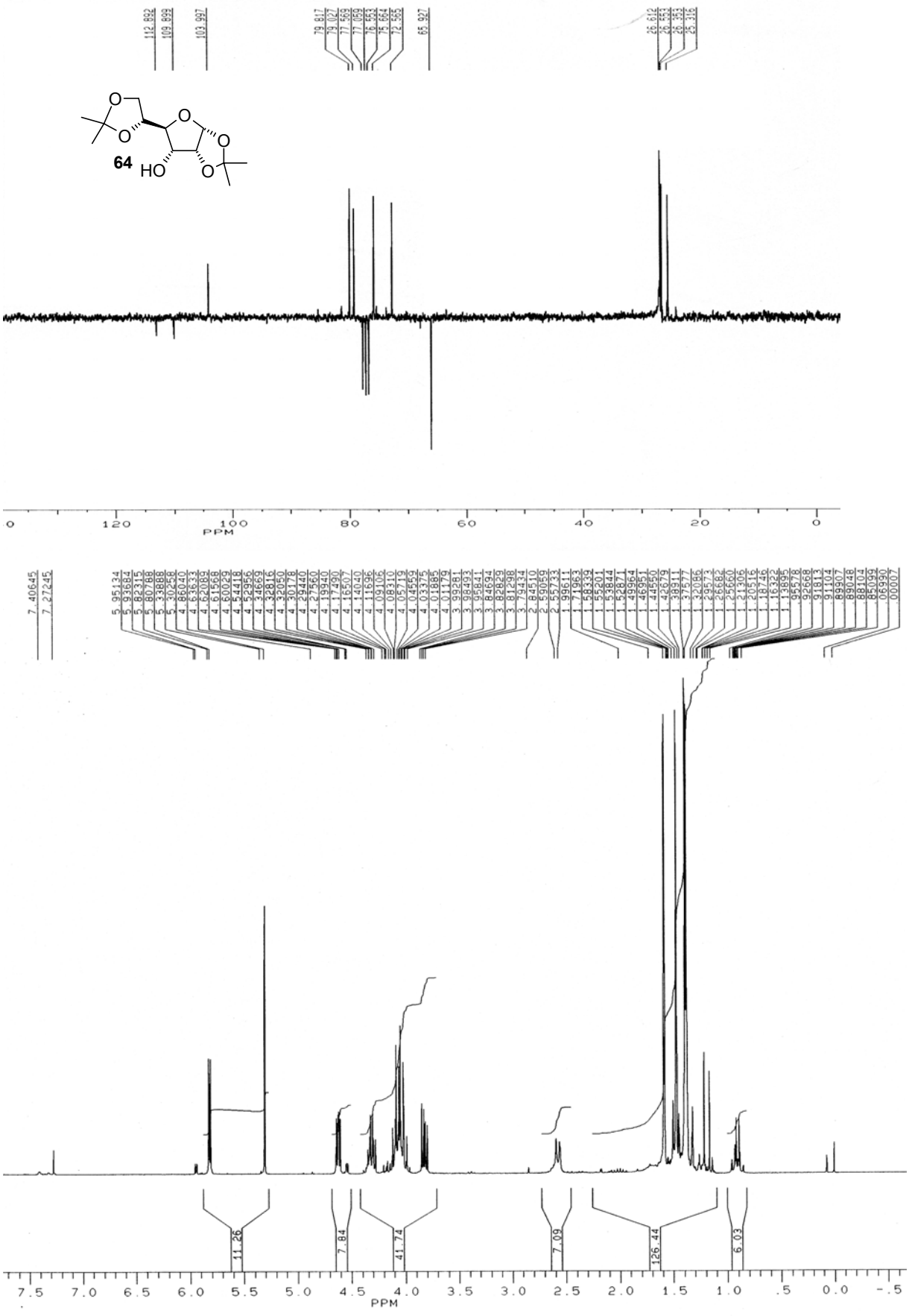


Fig. 29. ^{1}H and ^{13}C NMR spectra of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranoside. (**64**).

solvents under high vacuum gave a syrup, which was added dropwise to the stirred suspension of 1.4 g of $LiAlH_4$ in ether. After stirring overnight the excess of $LiAlH_4$ was destroyed first with ethylacetate then with ice. Extracted with dichloromethane:water, dried over Na_2SO_4 and purified in 38% yield by column chromatography using ethyl ether as eluent.

White solid, m.p. 77°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.82 (d, J = 3.97 Hz, 1H), 4.62 (dd, J = 3.95, 5.17 Hz, 1H), 4.32 (m, 1H), 4.09 (m, 3H), 3.95 (dd, J = 4.5, 8.5 Hz, 1H), 1.71 (s, C*H*$_3$), 1.52 (s, C*H*$_3$), 1.38 (s, C*H*$_3$), 1.37 (s, C*H*$_3$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 103.9 (C-1), 79.8,79.0, 75.6, 72.5 (C-2 to C-5), 65.9 (C-6), 26.6, 26.5, 26.3, 25.3 (4x*C*H$_3$), (plus two signals of two quaternary acetonide carbons at δ 112.8 and δ 109.8 ppm.

C.VII. General Method of Preparation of Formaldehyde Acetals on Carbohydrates

240 mg (6 mmol) of NaOH pellet was added in 10 mL of CH_2X_2 and 3 mL of DMF followed by 1 mmol of alcohol. The reaction mixture was heated to 30°C for 12 hours in case of CH_2Br_2. Progress of reaction was analyzed by TLC. Solvents were removed at low pressure to give a tarry material, which was purified by column chromatography.

C.VII.1. Acetal of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (69)

Purified by column chromatography in 91% yield using 10% ethyl acetate:dichloromethane as chromatographic system.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.83 (d, J = 3.65 Hz, 1H, H-1), 4.78 (s, 2H, O-C*H*$_2$-O), 4.49 (d, J = 3.65 Hz, 1H, H-2.), 4.29-4.21 (m, 2H, H-4, H-5), 4.09 (dd,

J = 3.67, 7.3 Hz 1H, H-3), 4.02-3.90 (m, 2H, H-6), 1.43,1.35, 1.27, 1.24 (s, 4xC*H*$_3$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 105.2 (C-1), 92.8 (O-*C*H_2-O), 83.0 (C-2), 81.0 (C-3), 78.7 (C-4), 72.5 (C-5), 67.1 (C-6), 26.8, 26.7, 26.2, 25.3 (4x*C*H_3). Plus two quaternary signals of acetonide carbons at δ 111.8 and δ 109.0 ppm. FAB-MS: e/z 447 (M-CH_3COCH_3), $C_{24}H_{38}O_{11}$, $[\alpha]_D$ = -36.2° (c = 1, CH_2Cl_2).

C.VII.2. 1,2-*O*-Isopropylidene-3-methoxymethyl-5,6-methylidene-α-D-glucofuranoside (70)

Purified by column chromatography in 84% yield using 8% ethyl acetate:dichloromethane as chromatographic system.

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.89 (d, J = 3.65 Hz, 1H, H-1), 5.02 (s, 1H, O-C*H*$_2$-O), 4.84 (s, 1H, O-C*H*$_2$-O), 4.73 (s, 2H, C*H*$_2$-MOM), 4.57 (d, J = 3.65 Hz, 1H, H-2.), 4.29-4.21 (m, 2H, H-4, H-5), 4.13 (m, H-3), 4.02-3.96 (m, 2H, H-6); 1.49,1.31 (s, 2x*C*H_3). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 105.2 (C-1), 96.1 (*C*H_2-MOM), 95.2 (O-*C*H_2-O), 83.0 (C-2), 80.4 (C-3), 79.2 (C-4), 71.9 (C-5), 67.8 (C-6), 55.8 (O-*C*H_3), 26.8, 26.2, (2x*C*H_3). Plus a quaternary signal of acetonide carbons at δ 111.9 ppm. FAM-MS: e/z 277.3 (M^+), $C_{12}H_{20}O_7$, $[\alpha]_D$ = -41.4° (c = 1, CH_2Cl_2),

Calculated C 52.17 H 7.30%

Found C 51.92 H 6.993%.

C.VII.3. Benzyl-2-methoxymethyl-3,4-*O*-methylidene-β-L-arabinopyranoside (73)

Purified by column chromatography in 76% yield using 4% ethyl acetate:dichloromethane as chromatographic system.

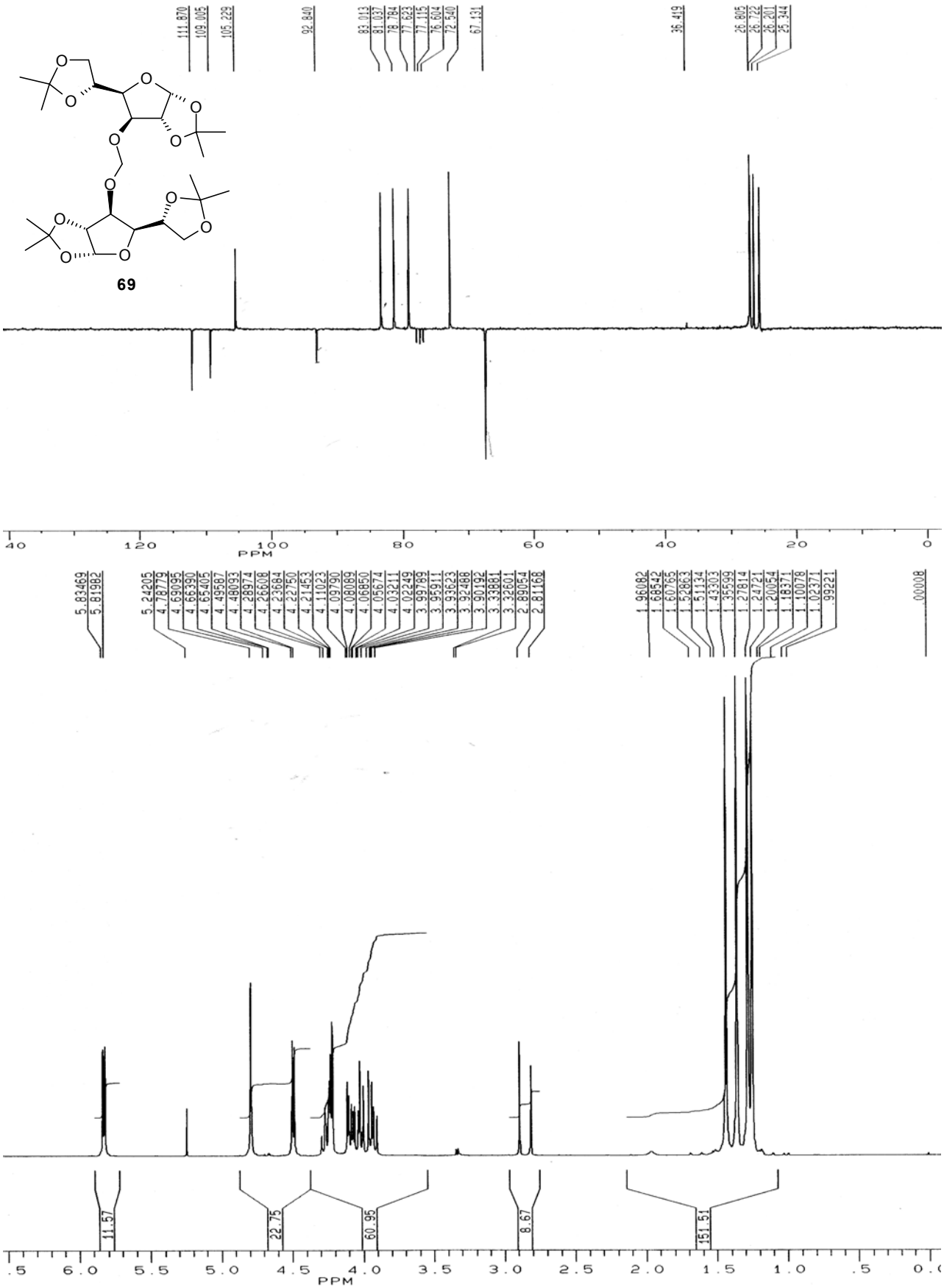


Fig.30. ^{1}H and ^{13}C NMR spectra of actal of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranoside. (**69**).

Colourless oil, ^{1}H NMR (250 MHz, $CHCl_3$): δ = 7.41-7.26 (m, 5H, Aromatic), 5.20 (s, 1H, OC*H*$_2$O), 4.99 (s, 2H, O-C*H*$_2$-O, MOM), 4.79 (s, 1H, OC*H*$_2$O), 4.77 (d, J = 2.9 Hz, 1H, H-1), 4.53 (d, J = 12.1, C*H*$_2$Ph), 4.38 (dd, J = 5.2, 7.9 Hz 1H, H-2), 4.07-3.98 (m, 3H, H-4, H-5), 3.63 (dd, J = 3.39, 7.97 Hz, H-3), 3.30 (s, 3H, OC*H*$_3$). FD-MS: e/z 296.1 $C_{15}H_{20}O_6$, $[\alpha]_D$ = +14.9° (c = 1, CH_2Cl_2).

Calculated C 60.80 H 6.80%

Found C 59.84 H 7.02%.

C.VII.4.1. 1,2-Methylene-4-isobutyl catechol (75a)

53a→c were purified by column chromatography using gradient of ethyl acetate:pet. Ether, Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.90 (d, J = 1.8 Hz, 1H), 6.70 (d, J = 7.9 Hz. 1H), 6.81 (dd, J = 1.8, 7.9 Hz, 1H), 5.88 (s, 2H, OC*H*$_2$O), 1.27 (s, 9H, 3 x C*H*$_3$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 145.7, 154.3, 143.4 (3xC, Aromatic), 106.3, 107.6, 117.8 (3xC, aromatic), 100.6 (O*C*H$_2$O), 31.6 (3 x *C*H$_3$). FD-MS e/z 122.1, $C_7H_6O_2$.

C.VII.4.2. Acetal of 1,2-methylene-4-isobutyl catechol (75b)

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25-7.08 (m, 6H aromatic), 5.67 (s, 4H, -OCH*H*O-), 1.32 (s, 18 x H, 6 x C*H*$_3$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 149.0 (6 x C, Aromatic), 126.5, 122.7, 120.6 (2 x 3C, aromatic), 98.5, 98.5 (2 x C, O*C*H$_2$O), 31.4 (6 x CH_3).FD-MS: e/z 341.4, $C_{21}H_{25}O_4$.

C.VII.4.3. Polyactal (75c)

Colourless oil; ^{1}H NMR (250 MHz, $CHCl_3$): δ = 7.15-6.89 (m, 15 x H aromatic), 5.61-5.14 (m, 10 x H, OC*H*$_2$O), 1.20 (s, 45H, 15 x CH_3). ^{13}C NMR (62.8 MHz,

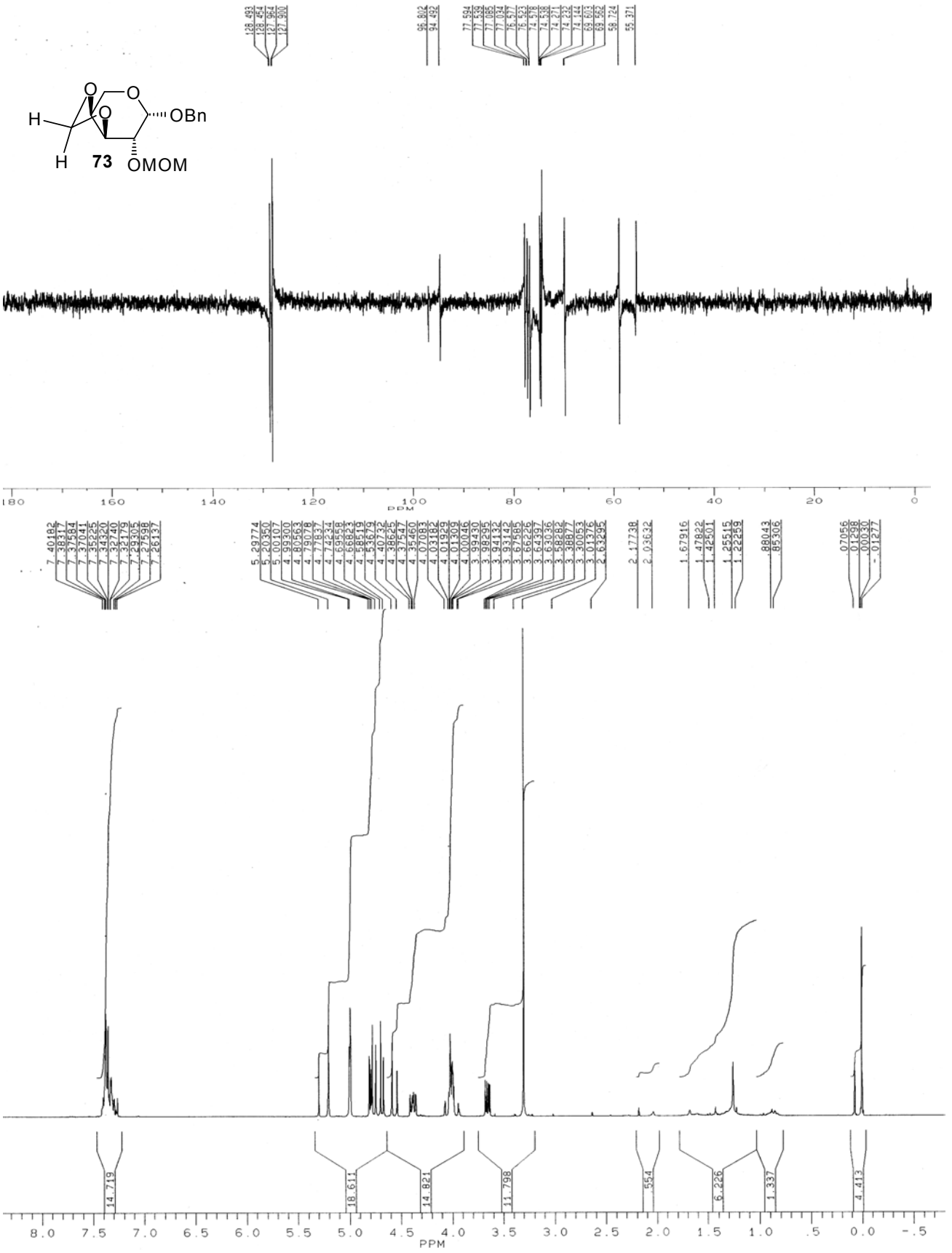


Fig.31. ^{1}H and ^{13}C NMR spectra of benzyl-2-methoxymethyl-3,4-*O*-methylidene-β-L-arabinopyranoside (**73**).

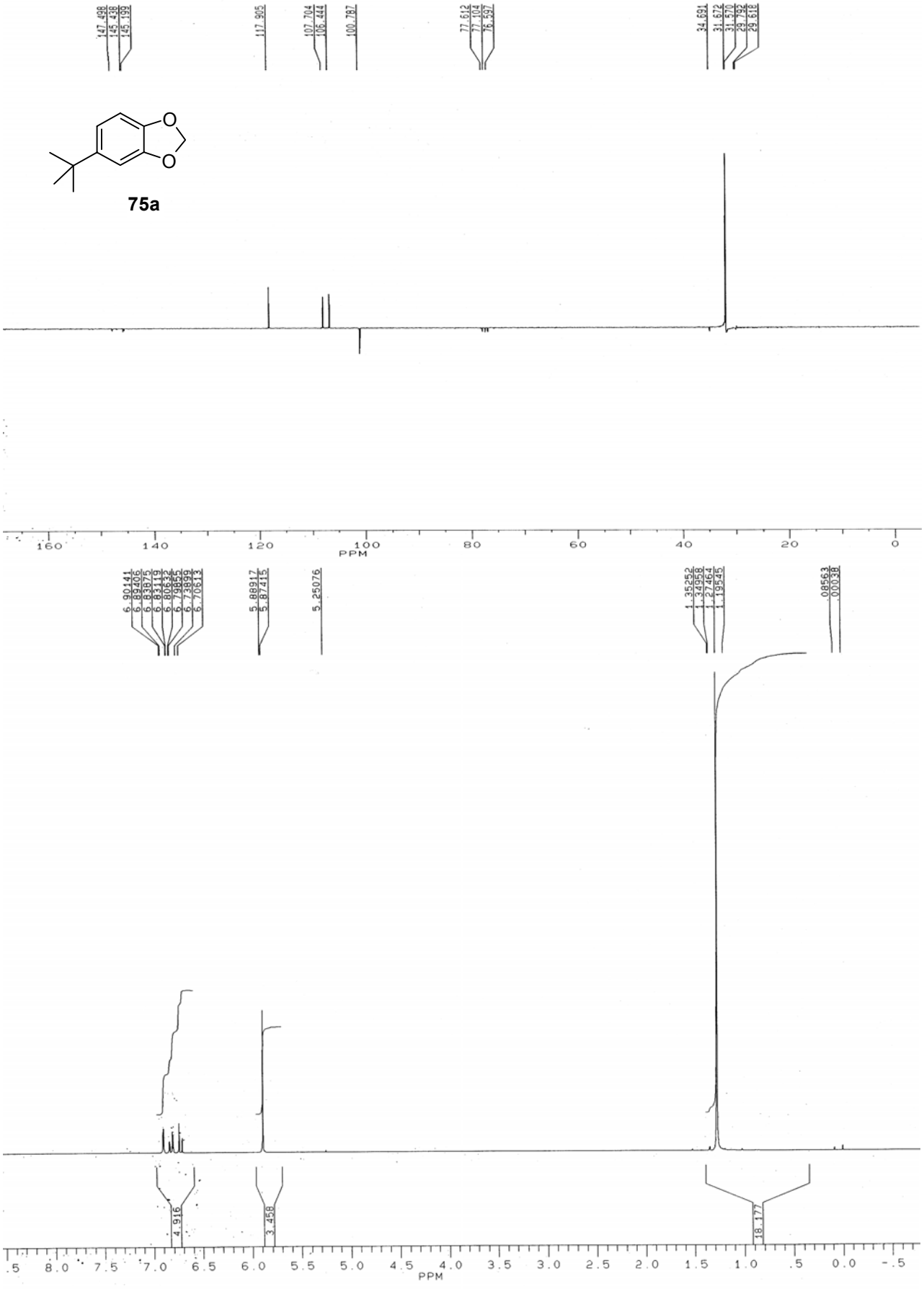


Fig. 32. ^{1}H and ^{13}C NMR spectra of 1,2-methylene-4-isobutyl catechol (**75a**).

$CHCl_3$): δ = 146.9 (15xC, Aromatic), 126.5-116 (15xC, aromatic), 93.5-93.4 (5xC, O*C*H_2O), 31.4, (15x*C*H_3)., FD-MS: e/z 844, $C_{54}H_{67}O_8$ (844.1).

D. ISOLATION PART

D.I. Phytochemical Investigation of *Euphorbia Decipiens*

D.I.1. Introduction

Our group has investigated *Euphorbia decipiens* Boiss. & Buhse previously and eight new diterpene esters were isolated from it [73–75]. In order to obtain the minor compounds, the plant was again collected and extracted with acetone [8]. The chloroform soluble fraction of the concentrated extract was subjected to different chromatographic procedures to purify compounds **76-80** (Fig. 38). Besides the previously isolated compounds, three new diterpene esters (**76**-**80**) were isolated and their structures were elucidated. The fine crystals of compounds **76** and **77** prompted us to subject both of the compounds to single crystal X-ray analysis, which resulted in the revised structures for decipinone **B** and **C** [75].

D.I.2. Results and discussion

Decipinone B (**76**) and C (**77**) were purified as already described [75]. They were crystallized from methanol. The crystals were then subjected to X-ray analysis and 1D and 2D-NMR in $CDCl_3$ and CD_3OD for (**76**). The MS, IR, UV, and ^{1}H-NMR data of **76** were the same as described [75]. The molecular formula $C_{30}H_{42}O_{11}$ was assigned for **77** on the basis of EIMS, *m/z* 578[*M*]$^+$. The ions at *m/z* 560 [*M*-H_2O]$^+$, 518 *[M*-HOAc]$^+$, 490 *[M*-$C_3H_7CO_2H$]$^+$, 458 [M-2xHOAc]$^+$, and 71 [C_3H_7CO]$^+$ indicated the presence of -OH, acetate and butanoate moieties in the molecule. In reference [75] the structures of decipinones **B** and **C** (**76** and **77**)were suggested on the basis of NMR studies, and it is assumed that the peak due to ketonic group (C-14) in the IR

spectrum was masked by the strong absorption of the ester groups and this group was also not detected in the ^{13}C-NMR spectrum due to low concentration. However the structure of these two compounds are now being revised to **76** and **77**, respectively on the basis of the results of X-ray diffraction analyses (Fig. 36 and 37).

Three singlets at δ 77.8 (C-13), 100.1 (C-14), 98.0 (C-15) (in CD_3OD, for **76**), and 77.6 (C-13), 98.6 (C-14), 96.8 (C-15) (in $CDCl_3$, for **76** and **77**), clearly confirmed the presence of an oxygen bearing non-carbonyl carbon at C-14. The cross peaks between H-12/C-13, H-17'/C-14 and Me-20/C-14 confirmed the hemiacetal functionality in the HMBC spectrum of **76** (in CD_3OD).

13-Deacetylisodecipidone (**78**) showed a protonated molecular ion in the CIMS at m/z 579 representing molecular formula $C_{30}H_{42}O_{11}$. The base peak at m/z 519 indicated the loss of an acetate function from molecular ion. The ^{1}H and ^{13}C-NMR spectral data were very similar to those recorded for decipidone [73]. The upfield shift for C-13 and down field shift for C-15 at δ 81.6 (*s*) and 89.1 (*s*), respectively, were the main difference to the ^{13}C-NMR data of decipidone [73]. The above data confirm the position of the -OH and -OAc at C-13 and C-15, respectively.

13-Deacetylisodecipinone (**79**), the benzoyl analog of **78**, is elucidated with comparison of its ^{1}H and ^{13}C-NMR spectra (Tables 2 & 3) with the spectral data of decipinone [78] and **78**. The main difference was the signals of the benzoyloxy instead of those of a butanoyloxy group at C-5.

Isodecipidone **(80),** like isodecipinone [73], was obtained as a minor compound, in which, the acetate was transesterified from position C-17 in

decipidone [78] to position C-15. The CI-MS spectrum of **80** shows molecular ion at *m/z* 621 $[M+1]^+$ indicating the molecular formula $C_{32}H_{42}O_{12}$. In the ^{1}H-NMR spectrum of **80**, there are some differences with respect to those observed for decipidone. The upfield shift of H-12 at δ 3.63 (d, J = 9.7 Hz) and conversion of H-17, H-17´doublets signals to *AB* pattern at δ 3.91 (d, J = 12.0 Hz), and 4.07 (d, J = 12.0 Hz), confirms that the position of the acetate group changed from C-17 in decipidone to C-15 in **80**.

D.I.3. Experimental of isolation part

D.I.3.1. General column chromatography (CC)

silica gel, 70-230 mesh. Flash chromatography (FC): silica gel 230-400 mesh. TLC: pre-coated silica gel G-25-UV_{254} plates: detection at 254 nm, and by ceric sulphate reagent. Optical rotations: Jasco-DIP-360 digital polarimeter. UV and IR Spectra: Hitachi-UV-3200 and Jasco-320-A spectrophotometer, respectively. ^{1}H- and ^{13}C-NMR, COSY, HMQC and HMBC Spectra: *Bruker spectrometers* operating at 500 and 400 MHz; chemical shifts δ in ppm and coupling constants in Hz. Enraf-Nonius CAD-4 X-ray diffractometer with CuKα radiation. EI-, CI MS: JMS-HX-110 with a data system.

D.I.3.2. Plant material

The plants of *Euphorbia decipiens* Boiss. & Bushe. (Euphorbiaceae) was collected from the mountain Kandovan, north of Karaj, Iran, in the year of 1998. It was identified by Mr. Bahram Zehzad (Plant Taxonomist) at the Department of Biological Sciences, Shahid Beheshti University, Eveen, Tehran, Iran. A voucher specimen (no. 98112) has been deposited at the herbarium of the Biology Department of Shahid Beheshti University, Eveen, Tehran, Iran.

D.I.3.3. Extraction and isolation

The air-dried ground plant (4 kg) was exhaustively extracted with acetone at r.t. The extract was evaporated to yield the residue (62 g). The defatted extract (51 g) was extracted with chloroform. The chloroform extract (44 g) was subjected to CC over a silica gel column (880 g) using hexane with gradient of $CHCl_3$ upto 100% and followed by methanol. Twenty fractions were collected. Fraction 10 was loaded on $AgNO_3$ impregnated silica gel (flash silica 230-400 mesh) and eluted with pure $CHCl_3$. The fraction no. 20 thus obtained was again loaded on preparative plates using system of Hex.: EtOAc (70:30) to purify compounds **78** and **79**. Fraction 21 of the same column contained compounds **80**, was purified by PTLC using $CHCl_3$:Me_2CO (99:1) (Fig. 35).

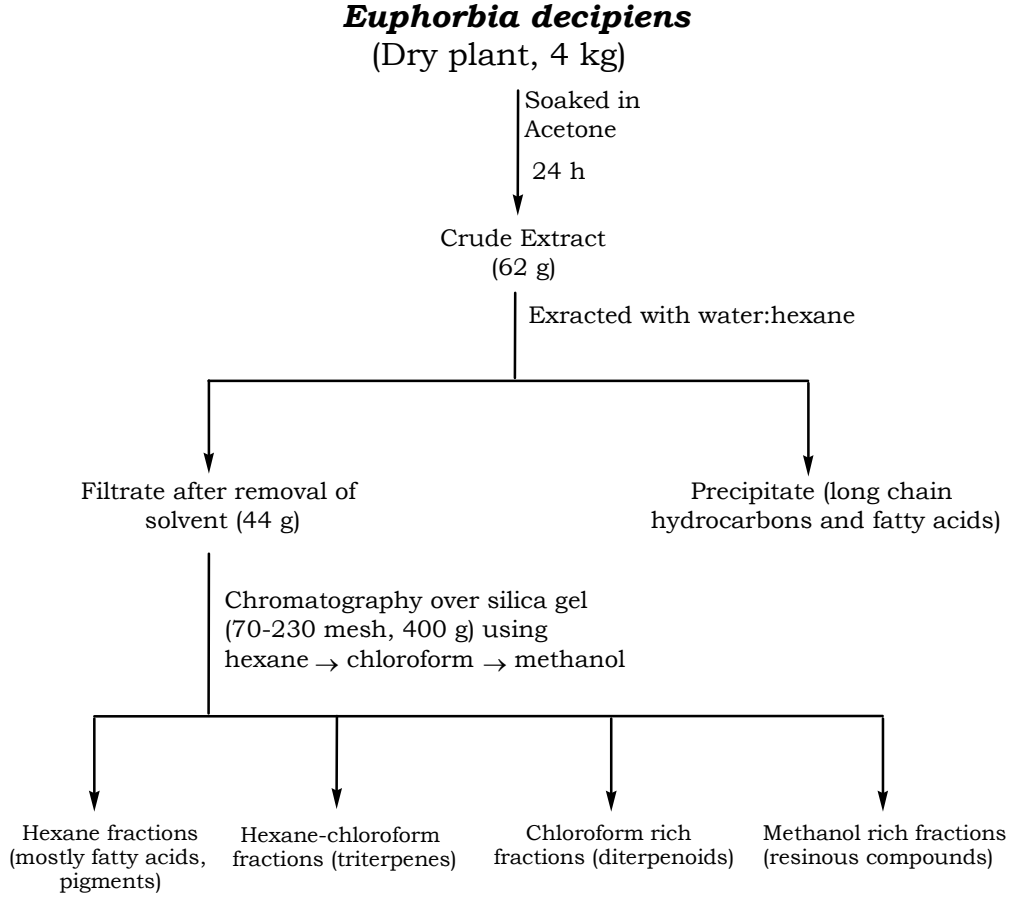


Fig.35. Scheme for the fractionation of plant material.

rel-(2R,3R,3aS,4S,4aS,5S,8R,8aS,9R,10R,10aS)-2,3,3a,4,-5,8,8a,9,10,10a-Decahydro-2,9-dimethyl-8-(methyl-ethenyl)-1H-10,4a-(epoxymethano)benz[f]-azul-ene-3,4,5,9,10,10a-hexol-3,5,10a-triacetate 4-Benzoate [76] (Decipinone **97**): 10.1 mg (yield 0.0006%). Colourless plate like crystals (MeOH). $C_{33}H_{40}O_{11}$.M.p. 190-192 ^{0} [75].

Crystal data of 76: $C_{33}H_{40}O_{11}$, Orthorombic, space group $P2_12_12_1$, **a** = 8.893 (4) Å, **b** = 17.509 (2) Å and **c** = 20.276 (4) Å, V = 3157(1) Å^3, CuK_α λ = 1.54178 Å, Z = 4, $D_{calc.}$ = 1.29 g/cm^3, F (000) = 1304.00, μ(CuKα) =8.05 mm^{-1}. Crystal size 0.50 × 0.48 × 0.22 mm^3. X-Ray diffraction data were collected at 293 (2) K° in the range = 5.0° to 68.0° ($0 \leq h \leq 10$, $0 \leq k \leq 21$, $0 \leq l \leq 24$) on *Enraf-Nonius CAD-4* diffractometer. The structure was solved by direct method and refined by Full-matrix least-squares on F^2 with the program SHELXTL 97. Anistropic thermal parameters were refined for all the non-hydrogen atoms. All the hydrogen atoms were located in the difference Fourier maps. Riding models were used to place the H-atoms in their idealized positions. The structure converged with R_1 = 0.064, wR_2 = 0.118 and GOF = 1.03 for the 1266 reflections with [$I > 2.0\sigma$ (I)] and 406 parameters. In the final difference Fourier synthesis, the electron density fluctuated in the range of 0.15 to –0.14 e/Å^3. An absolute structure could not be established in this analysis [Flack parameter 0.6 (7)].

Butanoic Acid rel-(2R,3R,3aS,4aS,5S,8R,8aS,9R,10R,10aS)-3,5,10a-tris(acety-loxy)-2,3,3a,4,5,8,8a,9,10,10a,-decahydro-9,10-dihydroxy-2,9-dimethyl-8-(1-methylethenyl)-1H-10,4a-(epoxymethano)benz[f]azulene-4yl ester [75,76] (decipinone **77**): 16.4 mg (yield .0004%). Colourless prismatic crystals (MeOH). M.p. 232-234^0. $[\alpha]^{24}_D$ +12.4 (c = 0.1, $CHCl_3$). UV (MeOH): 203.0 nm. IR ($CHCl_3$):

3450, 2900, 2840, 1736, 1728, 1712, 1640, 1450, 1370, 1280, 1150, 1100, 1020, 990, 970, 900, 600 cm^{-1}. EIMS *m/z* (rel. int.): 578 $[M]^+$ $(C_{30}H_{43}O_{11})^+$ (0.4), 560 $[M\text{-}H_2O]^+$ (1), 518 [*M*-HOAc] $^+$ (1), 490 $[M\text{-}C_3H_7CO_2H]^+$ (1), 458 [*M*-2 x HOAc]$^+$ (2), 714 $[C_3H_7CO]^+$ (100). ^1H-^{13}C NMR: see table **2** and **3**.

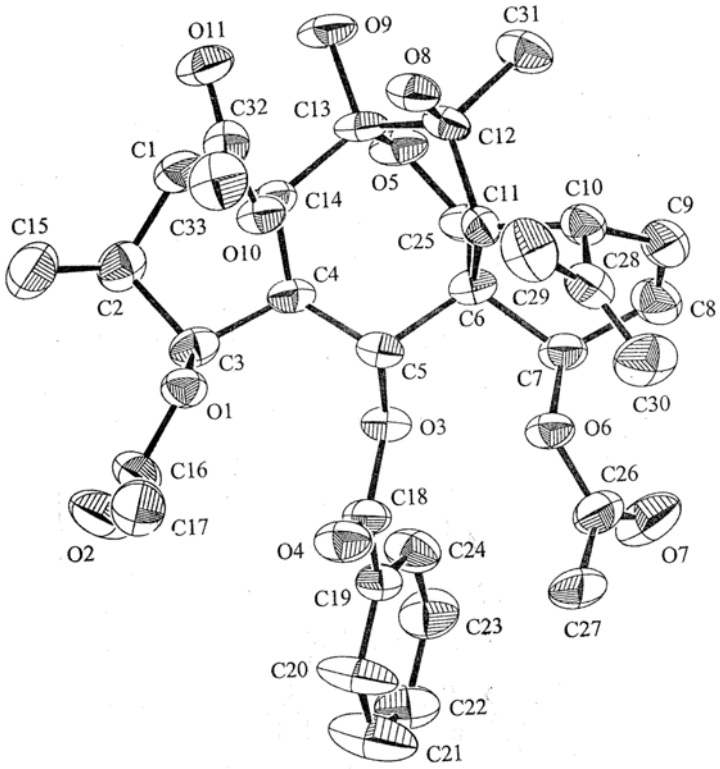


Fig. 36. Crystal structure of decipinol ester **76**.

Crystal data of 77: $C_{30}H_{42}O_{11}$, Orthorombic, space group $P2_12_12_1$, **a** = 8.877 (2) Å, **b** = 15.820 (2) Å and **c** = 21.696 (7) Å, V = 3046.9 (13) $Å^3$ (CuK_α λ = 1.5417 Å), Z = 4, $D_{calc.}$ = 1.261 Mg/m^3, F (000) = 1240, μ (Cu-Kα) = 0.797 mm^{-1}. Crystal size 0.35 × 0.30 × 0.25 mm^3. X-Ray diffraction data were collected at 293 (2) K° in the range = 5.0° to 68.0° $0 \leq h \leq 10$; $0 \leq k \leq 18$; $-26 \leq l \leq 26$) on Enraf-Nonius CAD-4 diffractometer. Structure was solved by direct method and refined by Full-matrix least-squares on F^2 with the program SHELXTL 97. Anistropic thermal parameters were refined for all the non-hydrogen atoms. All

the hydrogen atoms were located in the difference Fourier maps. Riding models were used to place the H-atoms in their idealized positions. The structure converged with R_1 = 0.052, wR_2 = 0.116 and GOF = 1.08 for the 3726 reflections with [$I > 2.0\sigma$ (I)] and 388 parameters. In the final difference Fourier synthesis, the electron density fluctuated in the range of 0.19 to –0.17 e/Å^3. An absolute structure was established for this compound [Flack parameter 0.0 (3)] using the Friedel pairs of reflections, which were not merged (Fig. 37).

Butanoic acid rel-(2R,3R,3aS,4S,4aS,5S,8R,8aS,9R,10aS)-3,5,10a-tris(acetyl-oxy)-1,2,3,3a,4,4a,5,8,8a,9,10,10a,-dodeca-hydro-9-hydroxy-4a-(hydroxydi-methyl)-2,9-dimethy-8-(1-meth-ylethenyl)-10-oxobenz[f]azulene-4-yl ester [75] (13-deacetylisodecipidone **78**): 12.1 mg (yield 0.0003%). $[\alpha]^{23}_D$ -15.61 (c = 0.448, $CHCl_3$). IR ($CHCl_3$): 3450, 1730, 1640 cm^{-1}. CIMS (CH_4) m/z: 579 [M+1]$^+$, ($C_{30}H_{43}O_{11}$)$^+$, 519 [M+1-HOAc]$^+$, ^{1}H-^{13}C NMR: see table 2 and 3.

rel-(2R,3R,3aS,4S,4aS,5S,8R,8aS,9R,10aS)-,3,5,10a-tris(acetyloxy-4-(benzyl-oxy)-2,3,3a,4,4a,5,8,8a,9,10a-decahydro-9-hydroxy-4a-(hydroxymethyl)-2,9-dimethyl-8-(1-methylethenyl) benz[f]azulene-10(1H)-one [75,76] (13-deacetyl-isodecipinone **79**): 4.5 mg (yield 0.00011%). $[\alpha]^{23}_D$ +15.35 (c = 0.717, $CHCl_3$). UV (MeOH): 272.3, 228.3. 198.1 nm. IR ($CHCl_3$): 3500, 2950, 1740, 1720, 1630, 1600 cm^{-1}. EIMS m/z (rel. int.): 612 [M] $^+$ ($C_{33}H_{41}O_{11}$)$^+$ (12), 491[M-121]$^+$ (23), 121[$C_6H_5CO_2$]$^+$ (10), 105[C_6H_5CO]$^+$ (100). CIMS (CH_4) m/z: 613 [M+1]$^+$, ^{1}H-^{13}C NMR: see table 2 and 3.

Butanoic acid rel-(2R,3R,3aS,4S,4aS,5S,8R,8aS,9R,10aS)-3,5,9,10a-tetrakis (acetyloxy)-1,2,3,3a,4,4a,5,8,8a,9,10,10a,-dodecahydro-4a-(hydroxymethyl)-2,9-dimethyl-8-(1-methylethenyl)-10-oxobenz[f]azulene-4-yl ester [75,76] (Iso-decipidone **80**): 2.8 mg (yield 0.00007%). M.p. 187-189 ^{0}C. $[\alpha]^{23}_D$ –22.8 (c =

0.48, $CHCl_3$). UV (MeOH): 264.5, 220.3. 200.1 nm. IR ($CHCl_3$): 3650, 3500, 1760, 1725, 1710, 1695 cm^{-1}. CIMS (CH_4) *m/z*: 621 $[M+1]^+$ $(C_{32}H_{45}O_{12})^+$, 561, 533, 519, 501, 473, 459, 441, 413, 371,353, 293, 311, 89, 61. ^1H NMR: see table 2.

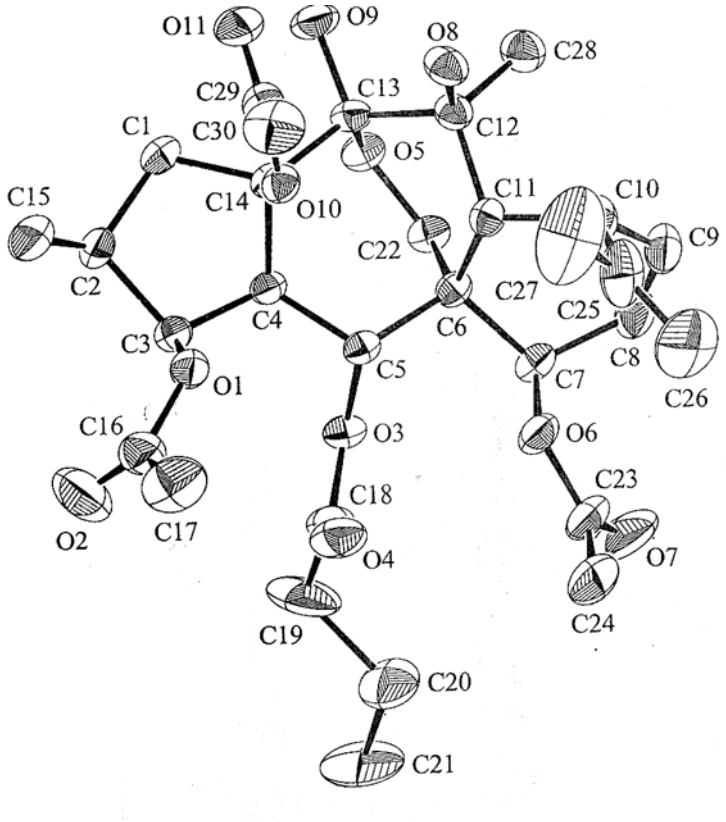


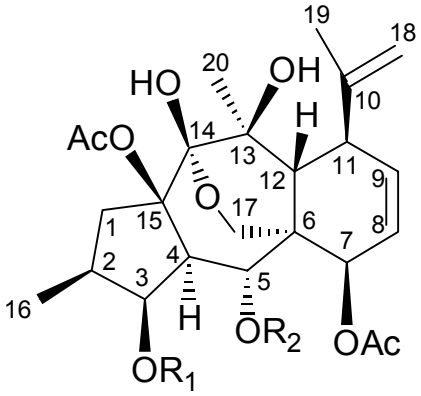
Fig. 37. Crystal Structure of decipinol ester **77**.

Table-2: ^{1}H NMR data of compounds **78**-**80** in $CDCl_3$. *J* in Hz.

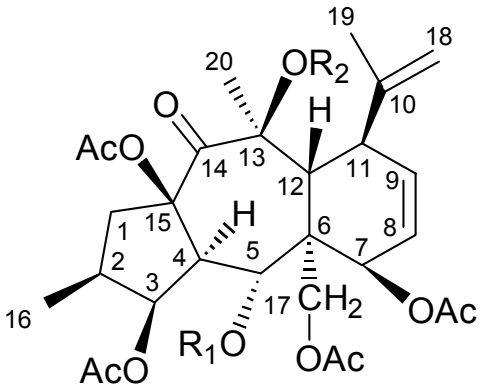
C. No	78	79	80
Hα-C(1)	3.30 (dd, J = 10.4, 14.8)	3.30 (dd, J = 10.4, 14.6)	3.34 (dd, J = 8.8, 14.9)
Hβ-C(1)	1.56 (dd, J = 6.8, 14.8)	1.58 (dd, j = 9.6, 15.0)	1.70 (dd, j = 6.9,14.9)
H-C(2)	2.10 (m)	2.10 (m)	2.10 (m)
H-C(3)	5.23 (t, 3.4)	5.23 (t, 3.4)	5.25 (t, 3.6)
H-C(4)	2.40 (dd, J = 3.2, 11.7)	2.45 (dd, J = 3.1, 11.6)	2.53 (dd, J = 3.2, 11.6)
H-C(5)	5.91 (d, J = 11.7)	6.18 (d, J = 11.6)	6.14 (d, J = 11.6)
	-	-	-
H-C(7)	4.77 (d, J = 6.4)	4.80 (d, J = 6.4)	4.59 (d, J = 6.4)
H-C(8)	6.03 (ddd, J = 1.6, 6.4, 9.6)	5.99 (ddd, J = 1.7, 6.4, 9.5)	5.99 (m)
H-C(9)	5.85 (dd, J = 4.2, 9.4)	5.83 dd, J = 4.8, 9.5)	5.76 (br.d, J = 9.6)
H-C(11)	3.46 (m)	3.50 (br.t, J = 5.5)	3.47 (m)
H-C(12)	3.46 (m)	3.55 (d, J = 7.0)	3.63 (d. J = 9.7)
H-C(16)	0.77 (d, J = 6.9)	0.94 (d, J = 6.9)	0.90 (d, J = 6.8)
H-C(17)	3.80 (d, J = 12.1)	4.03 (d, J = 12.1)	3.91 (d, J = 12.0)
H´-C(17)′	4.16 (d, J = 12.1)	4.13 (d, J = 12.1)	4.07 (d, J = 12.0)
H-C(18)	4.93 (br.s)	4.90 (br.s)	4.96 (br.s)
H´-C(18)′	4.90 (m)	4.94 (br.s)	4.86 (br.s)
H-C(19)	1.80 (s)	1.80 (s)	1.78 (s)
H-C(20)	1.40 (s)	1.40 (s)	1.56 (s)
Acetyl:		-	-
AcO	2.14 (s)	2.19 (s)	2.16(s)
AcO	2.00 (s)	2.03 (s)	2.08 (s)
AcO-C(3)	1.98 (s)	2.02 (s)	2.04 (s)
AcO			1.98 (s)
Benzoyl:			
H-C(2´)	-	7.89 (dd J = 1.3, 8.4)	-
H-C(6´)	-	7.40 (br.t, J = 8.2)	-
H-C(4´)	-	7.50 (dt, J = 1.4, 7.6)	-
Butanoyl			
CH_2(2´)	2.20 (m)	-	2.22 (m)
CH_2(3´)	1.50 (m)	-	1.56 (m)
Me(4´)	0.91 (t, J = 7.4)	-	0.93 (d, J = 7.2)

Table 3: ^{13}C NMR data of compounds **77**-**79** in $CDCl_3$.

C. No	77	78	79
C(1)	38.3	45.8	45.8
C(2)	33.2	37.6	27.6
C(3)	72.9	80.1	80.1
C(4)	54.5	85.3	55.5
C(5)	72.3	70.2	71.0
C(6)	45.9	47.9	48.2
C(7)	66.2	67.4	67.7
C(8)	127.3	122.7	122.7
C(9)	137.6	137.2	137.2
C(10)	147.6	147.8	147.9
C(11)	40.7	45.4	45.6
C(12)	40.9	44.9	45.5
C(13)	77.6	81.6	81.5
C(14)	98.6	203.0	203.1
C(15)	96.8	89.1	89.2
C(16)	16.1	14.8	14.8
C(17)	66.2	62.0	62.5
C(18)	110.6	112.8	112.8
C(19)	22.2	18.1	18.3
C(20)	22.5	21.1	20.8
Acetyl:			
*Me*COO	22.1	20.9	20.3
*Me*COO	20.8	20.8	21.2
*Me*COO-C(3)	20.8	20.2	21.1
Me*C*OO			21.0
Benzoyl:			
C(1´)			128.4
C(2´),C(6´)			129.2
C(3´),C(5´)			128.4
C(4´)			131.1
C=O			165.0
Me*C*OO	174.2	170.2	170.2
Me*C*OO	171.0	170.0	169.7
Me*C*OO	170.2	169.6	169.2
Me*C*OO			169.0
Butanoyl			
C(1´)	171.3		
C(2´)	36.1		
C(3´)	18.3		
C(4´)	13.7		



	R^1	R^2
(**76**)	Ac	Bz
(**77**)	Ac	Bu



	R^1	R^2
(**78**)	Bu	H
(**79**)	Bz	H
(**80**)	Bu	Ac

Fig. 38. Structures of diterpene esters **76**-**80**

E. ABSTRACT

This thesis describes the application of carbohydrates as chiral synthons for the stereoselective syntheses of, both, natural products and new synthetic classes of compounds.

Chapter II represents examples for the syntheses of chiral cyclic trithiocarbonates from the triflates of 2,3- and 3,4-anhydropentopyranosides. Sodium trithiocarbonate undergoes a nucleophilic displacement of the triflyl group, followed by a simultaneous ring opening reaction of the epoxide to produce 5- or 6-membered cyclic trithiocarbonates in good yield.

In chapter III, synthesis of benzothiophene derivatives was proposed from 2-bromo thiophenol and triflates of 2,3-anhydropyranosides. Bromothiophenol anion attacks the triflate to form an adduct. The C-4 hydrogen from this was removed with strong base, in good yield, to get the unsaturated alcohol. The secondary alcohol was further oxidized to a α,β-unsaturated ketone in quatitative yield. Intramolecular Heck reaction on this α,β-unsaturated ketone should give the required product.

Chapter IV, describes the synthesis of highly functionalized substituted thiazolidines. Thiosemicarbazide and 4-phenylthiosemicarbazide were used for their synthesis in 1,4-dioxane. The nucleophilic sulphur displaces the triflate of 2,3-anhydropyranoside to form a *S*-substituted thiosemicarbazide derivative, which simultaneously attacks the epoxide to form a substituted thiazolidine ring in acceptable to good yield. Thiazolidines, thus produced, were tested against human neuroblastoma SK-N-LO cells (MTT assay) and found to be active.

In chapter V, a total synthesis for non-natural R-(-)-anamarine is proposed, starting from methyl α-D-glucopyranoside. 2,3-Dideoxygenation of the benzylidene acetal was followed by the deprotection of benzylidene group and selective protection of the resulting diol at primary position. The secondary alcohol was mesylated and reductively displaced with superhydride®. The primary alcohol should then be deprotected and converted to a Wittig's ylide. The side chain of the anamarine was synthesized from D-glucose. The free hydroxyl groups in glucose were protected with isopropylidene. The selective deprotection of 5,6-hydroxyl group was performed with aq. acetic acid. Selective tosylation of primary alcoholic group followed by reduction gave, unexpectedly, the oxirane ring at 5,6-position. So the route was modified and, instead of tosylation, selective iodination followed by reduction at C-6 was carried out to get the required methyl at C-6. The acid hydrolysis of 6-deoxy product in ethanethiol followed by the protection of the free hydroxyl groups with isopropylidene was carried out in cat. $HClO_4$. The thioketal protective group should be removed and coupled with Wittig's ylide to get the (-)-anamarine.

As described in chapter VI, new 3,4-disaccharides were synthesized by the nucleophilic attack of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside anion at C-4 of epoxytriflates under mild conditions (Na_2CO_3/CH_3CN). These disaccharides show no inhibitory activity against SK-N-LO cell line.

Chapter VII demonstrates the utility of formaldehyde acetals in carbohydrate chemistry. We used NaOH, DMF in CH_2X_2 and found the reagent is quite effective in the formaldehyde acetal formation reaction. This reagent can be

used for inter- as well as for intra-molecular acetal formation reaction depending upon the number of free hydroxyl groups present in the molecule. Finally, the isolation part demonstrates the purification and characterisation of three new diterpene esters from *Euphorbia decipiens*. The chloroform soluble fraction of the concentrated extract was subjected to different chromatographic procedures to purify three new diterpene esters and their structures were elucidated by using highly sophisticated spectroscopic techniques such as X-ray, 1,2D-NMR, IR, UV and mass spectrometry.

F. ZUSAMMENFASSUNG

In der Dissertation werden einfache, natürliche Kohlenhydrate als chirale Synthone zur stereoselektiven Synthese von Naturstoffen und neuen Verbindungsklassen eingesetzt.

In Kapitel 2 wird eine Synthesenmethode für chirale zyklische Trithiocarbonate aus Triflaten von 2,3- und 3,4-Anhydropentopyranosiden beschrieben. Natriumtrithiocarbonat reagiert mit der Trflatgruppe in einer S_N2-Reaktion unter gleichzeitiger Ringöffnung der Epoxyde, wobei die zyklischen Trithiocarbonate mit hoher Ausbeute entstehen.

In Kapitel III wird eine Synthese von Benzothiophenderivaten aus 2-Bromthiophenol und Triflaten von 2,3-Anydropyranosiden vorgeschlagen. Das Bromthiophenolanion reagiert mit dem Triflat unter Bildung eines Addukts. Anschließend wird ein ungesättigter Alkohol hergestellt, aus welchem ein α, β-ungesättigtes Keton in quantitativen Ausbeuten gewonnen wird. Durch intramolekulare Heck-Reaktion sollten die erstrebten Benzothiophenderivate hergestellt werden.

In Kapitel 4 wird eine Methode beschrieben, welche zu stark funktionalisierten Thiazolidinen führt. Bei der Reaktion von Thiosemicarbazid bzw. 4-Phenylthiosemicarbazid mit Trifalten von 2,3-Anhydropyranosiden werden Thiosemicarbazidderivate gebildet, welche simultan mit dem Epoxydring substituierte Thiazolidine in guten Ausbeuten bilden. Diese Thiazolidine haben antitmorale Eigenschaften, wie die Ergebnisse im MTT-Test zeigen.

In Kapitel 5 wird eine Totalsynthese für R-(-)-Anamarin vorgeschlagen, wobei vom Methyl-α-D-Glycopyranosid ausgegangen wird. Nach Eliminierung der OH-Gruppen an C-2,3 der entsprechenden Benzylidenverbindung, Entfernung der Benzylidenschutzgruppe und selektivem Schutz des resultierenden Diols, wurde der sekundäre Alkohol mesyliert und mit Superhydrid reduziert. Aus dem primären Alkohol sollte anschließend ein Wittig-Reagenz hergestellt werden. Die Seitenkette von Anamarin wurde ebenfalls aus D-Glucose hergestellt. Die freien Hydroxylgruppen 1,2 und 5,6 wurden durch Isopropylidenreste geschützt, die selektive Entfernung der Schutzgruppe an 5,6 des Glucoserestes gelang mit wässriger Essigsäure. Dann wurde die primäre alkoholische Gruppe selektiv iodiert und reduziert. Anschließend erfolgte eine Umsetzung mit Ethylmercaptan, dann wurden die freien Hydroxylgrupppen durch Isopropylidenschutzgruppen geschützt. Nach Entfernung der Thioacetalgruppen mit $HgCl_2$ sollte eine Kupplung mit dem oben erwähnten Wittigs-Reagenz zum (-)-Anamarin führen.

In einem weiteren Kapitel wird die Synthese von neuen Disacchariden beschrieben, wobei 1,2-5,6-Di-*O*-isopropyliden-α-D-glucofuranose mit Epoxydtriflatzuckern umgesetzt wird.

In Kapitel 7 wird ein neues Reagenz zur Darstellung von Formaldehydacetalen entwickelt, welches in der Kohlenhydratchemie sehr gute Ausbeuten liefert.

Die Dissertation wird abgeschlossen durch die Isolierung von 3 neuen Diterpenestern aus der Pflanze *Euphorbia decipiens*. Die Reindarstellung dieser neuen Diterpenestern gelang durch verschiedene chromatographische Trennmethoden und die Strukturen wurden eindeutig durch Kernresonanz-,

IR-, UV- und Massenspektren aufgeklärt und schließlich durch Röntgenstukturanalyse bestätigt.

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