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Carbohydrates as future drugs. Synthesis of (2-naphthyl) β-D-xylopyranoside or XylNap and subsequent transformation of 2- and 4-positions

BACHELOR'S THESIS

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ABSTRACT

Carbohydrate chemistry has important implications for the biochemistry of living organisms. The present work describes the development of methodology towards the selective modification of the 2- and 4-positions of xylose.

First of all, (2-naphthyl) β-D-xylopyranoside (XylNap) was synthesized from xylose. In order to achieve this, glycosylation, protection and deprotection reactions have been developed. Further reaction of XylNap to selectively protect two of the three hydroxyl groups lead to a mixture of two isomers: one isomer with an unprotected hydroxyl group in the 2-position and one with the hydroxyl group in the 4-position.

The selective inversion of the stereochemistry of the unprotected hydroxyl groups was attempted on the mixture of the two isomers. This resulted in a mixture of products. It was possible to observe the desired products, where inversion of the sterocentre has occurred. However there was also a significant amount of dehydration byproduct observed.

LIST OF ABBREVIATIONS AND SYMBOLS

α	Alpha
β	Beta
σ*	Antibonding orbital
NMR	Nuclear Magnetic Resonance
$CDCl_3$	Chloroform-d
C_6D_6	Benzene-d_6
^1H	Proton
Ac_2O	Acetic anhydride
KOAc	Potassium acetate
SiO_2	Silica
EtOH	Ethanol
MeOH	Methanol
NaOMe	Sodium methoxide
$NaHCO_3$ (sat. aq.)	Sodium bicarbonate
NaCl (sat. aq.)	Sodium chloride
$BF_3{\cdot}OEt_2$	Boron trifluoride diethyl etherate
Et_3N	Triethylamine
CH_2Cl_2	Dichloromethane
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
$MgSO_4$	Magnesium sulphate
Na_2SO_4	Sodium sulphate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
$NaBH_4$	Sodium borohydride
Tf_2O	Trifluoromethanesulfonic anhydride
QNO_2	Tetrabutylammonium nitrate
CsOAc	Cesium acetate
C_5H_5N	Pyridine
S_N2	Bimolecular nucleophilic substitution

CONTENTS

1. OBJECTIVES

The proposed objectives of this project are:

- Synthesize (2-naphthyl) β-D-xylopyranoside from xylose
- Synthesize analogues of XylNap bearing a single unprotected hydroxyl group. The hydroxyl group being located at either the sterogenic 2- or 4-postion of the sugar ring.
- Develop methodology for the selective inversion of stereochemistry at the unprotected 2- and 4-positions of the isomers obtained.

2. INTRODUCTION

2.1 CARBOHYDRATES BACKGROUND INFORMATION

Carbohydrates are the most abundant class of organic compounds found in living organisms, because they are a major source of metabolic energy. The role of carbohydrates in biological systems is complex. They are involved in many biochemical processes such as biological recognition processes, selective transport or specific regulation of biomolecules as well as a structural components of some proteins.[1]

Proteoglycans (PGs) are polyanionic proteins consisting of a core protein substituted with carbohydrate chains, that is, glycosaminoglycans (GAGs).[2] The point of attachment is a serine (Ser) residue to which the GAGs are joined through a tetrasaccharide, where xylose is the saccharide unit linking the GAGs to the serine residue. The chains are long and unbranched carbohydrate polymers that are negatively charged under physiological conditions (Figure 2.1). Those proteins are a major component of the animal extracellular matrix existing between cells in an organism.

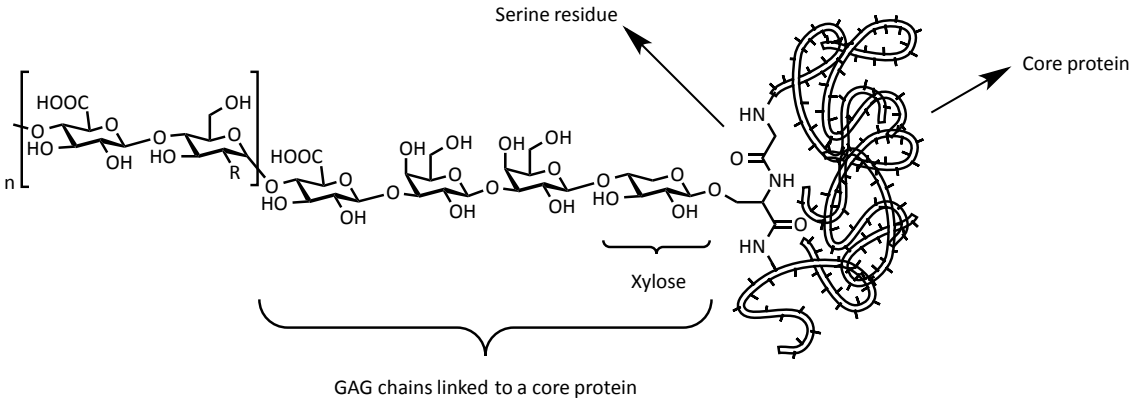


Figure 2.1. *Proteoglycans structure. GAG chains linked to a core protein by xylose.*

It has been suggested that GAG chains have the potential to inhibit the proliferation of certain types of tumors. The Ellervik group has previously investigated the use of analogues of xylose, xylosides, as agents for inhibiting the growth of tumor cells. The xyloside analogues were shown to induce the production of specific GAG chains within cancer cells. These GAG chains were then shown to migrate to cell nuclei and induce apoptosis. Different xylosides were shown to create different GAG chains with different anticancer properties.[1] In order to

produce new xylosides, with potentially greater anticancer properties, it is important to develop methodologies for the modification of the xylose moiety.

Xylose is a monosaccharide of the aldopentose type, which means that it contains five carbon atoms and includes an aldehyde functional group. Depending on conditions, it can adopt several structures so it can be found either as acyclic form or as cyclic hemiacetal isomers. Contrary to glucose or galactose, xylose is composed of four secondary hydroxyl groups with very similar reactivity. Seeing that, protective group strategies are essential during the development of synthetic protocols to modify selectively those groups.[3]

Previously modification of XylNap xylosides has revolved around obtaining analogues were there has been substitution of one of the hydroxyl groups at the 2-, 3- or 4-positions of the xylose moiety. These substituted analogues have borne no more than one of their functional groups in the axial position. In this work it was attempted to produce analogues of the xylose moiety with two functional groups in axial positions. To do this first xyloside analogues were produced with a protected, axial hydroxyl funcationality in the 3-position, and only one of either the equatorial 2- or 4-hydroxyl groups unprotected. Then it was attempted to perform substitutions of the unprotected, equatorial, hydroxyl groups at either the 2- or 4-positions with an inversion of the sterogenic centre. The development of these procedures will allow future synthesis of a wide range of new xylosides, which can be trialed for their anticancer properties.

2.2 BASIC LABORATORY TECHNIQUES

2.2.1 Thin-layer chromatography (TLC)

Thin-layer chromatography (TLC) is a chromatography technique used to separate components of non-volatile mixtures. This technique is used in organic chemistry to analyse crude reaction mixtures, identify the number of compounds present in the given mixture. It can also be used to monitor the progress of a reaction and to determine conditions for purification by column chromatography. [4]

Thin-layer chromatography is performed on a sheet of aluminium foil covered by a layer of adsorbent material as silica gel, known as the stationary phase. After the sample has been applied on the plate, the bottom of the plate is placed into a mixture of solvents known as mobile phase. The mobile phase moves up the plate by capillarity action. The analytes ascend the TLC plate, pulled along by the mobile phase, at different rates and separation is achieved depending on the affinity of the compounds with the stationary phase.

Projecting ultraviolet light onto the sheet can be useful in order to visualize where the components have ended up on the plate. However, some compounds are not ultraviolet active and it requires using chemical processes to achieve a visualization of the spots. For example in this project a solution of anisaldehyde and sulphuric acid is used to form coloured adducts which will be burned to leave a dark and visible spots. Other chemical processes can also be used for visualization.

2.2.2 Flash chromatography

Flash chromatography is a fast and simple method used to purify an individual chemical compound from mixtures which have similar polarities.[5] The mixture of components is washed through a column consisting of a stationary phase; typically composed of silica gel, with a mixture of solvents, known as the mobile phase. The individual components run at different speeds through the column due to their differing affinity with the stationary phase. The elute of the column therefore contains the separated components of the mixture as different times, allowing isolation of individual compounds.

The mobile phase is either a pure solvent or a mixture of solvents with different polarities. This solvent system has to be chosen so that the different compounds can be easily separated. For that reason, a small-scale test is developed using TLC in order to optimize the conditions.

Finally, to minimize the time and the amount of eluent to run the flash chromatography, the retention factor value of the interesting compound has to be roughly around 0.2-0.3.

3. EXPERIMENTATION

Here is described the experimental procedure carried out to develop the new synthetic route for the synthesis of new xylose analogues (Figure 3.1). Starting from xylose **1**, (2-naphthyl) β-D-xylopyranoside (XylNap) **4** has been prepared, followed by the synthesis of xylopyranosides analogues **7** and **8**. New procedures were trialed to develop a method for the selective transformation of the 2- and 4-positions of **7** and **8** to yield **9**, **10**, **11** and **12**.

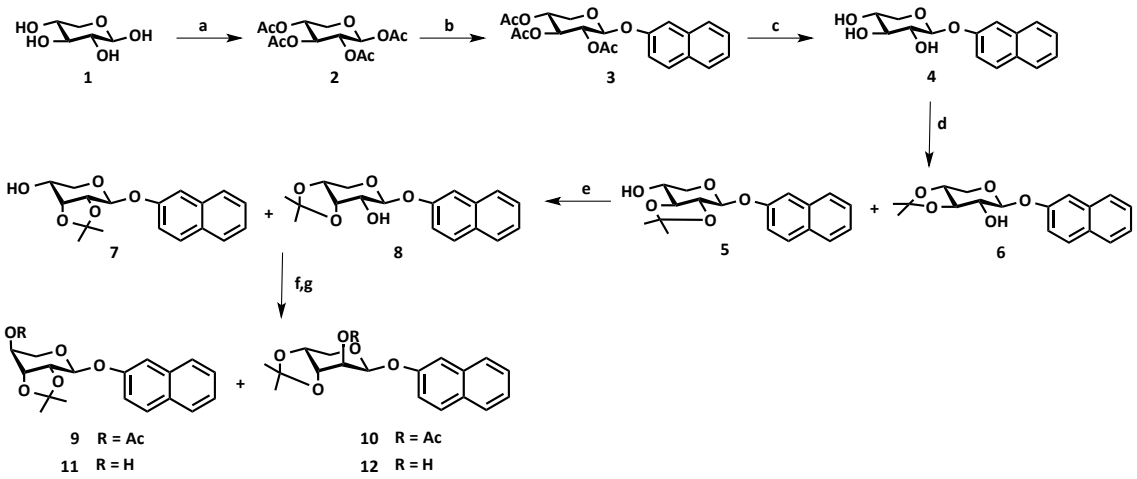
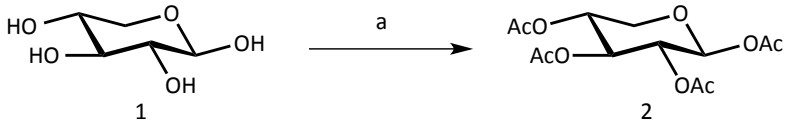


Figure 3.1. *Synthetic route developed to prepare (2-naphthyl) β-D-xylopyranoside **4** and analogues.*

3.1 PREPARATION OF 1,2,3,4-TETRA-*O*-ACETYL-β-D-XYLOPYRANOSIDE FROM XYLOSE

The alcohol functionalities of xylose were reacted with acetic anhydride to form the corresponding ester. It is most commonly performed with a large exces of Ac_2O in the presence of a catalytic amounts of KOAc.[1]

3.1.1 Synthetic scheme



Scheme 3.1.1. *Reagents and conditions: (a) Ac_2O, KOAc, 122 ºC.*

Reagents	1	Ac_2O	KOAc	**Products**	2
Formula	$C_5H_{10}O_5$	$C_4H_6O_3$	KOAc	Formula	$C_{13}H_{18}O_9$
MW	150.13	102.09	98.14	MW	318.13
Equivalents	1	18.7	1.2	Equivalents	1
Mols (mmol)	8.10	150.98	9.85	Mols (mmol)	8.10
Weight (g)	1.22		0.97	Weight (g)	2.58
Volume (ml)		10		Volume (ml)	
Density (g/cm^3)		1.08		Density (g/cm^3)	
Purity (%)	≥99	≥98	≥99	Purity (%)	

3.1.2 Safety

Reagent	**Pictograms**	**Specifications**
Ac_2O		Flammable liquid. It may cause serious eye damage. Harmful if contact with skin and toxical if inhalation. Work in the fumehood and wear personal protective equipment.
CH_2Cl_2		Acute toxicity. It may cause serious eye and skin irritation. Causes serious repiratory sensitization and it is harmful if inhaled. Work in the fumehood and wear personal protective equipment.
EtOH		Flammable liquid. Work in the fumehood and wear personal protective equipment.

3.1.3 Mechanism

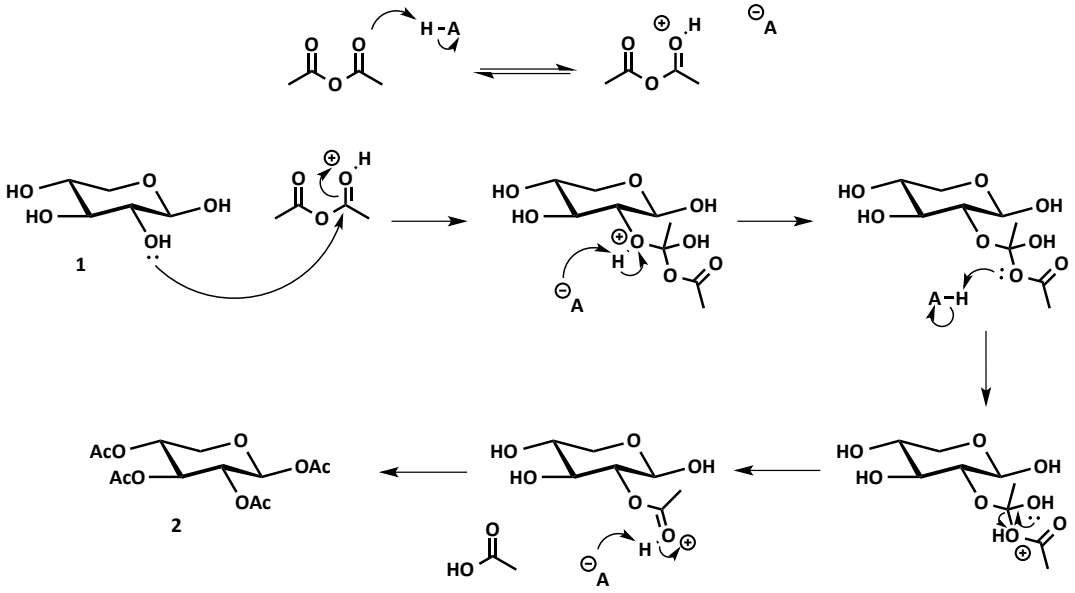


Figure 3.1.3. *Acetylation of β-D-xylose **1** mechanism.*

3.1.4 Experimental procedure

KOAc (0.97 g, 9.85 mmol) was dissolved in Ac_2O (10 ml) and heated to 122 ºC. β-D-xylose **1** (1.22 g, 8.10 mmol) was added to mixture in 5 portions over 10 minutes. After 30 minutes, the reaction mixture was allowed to reach room temperature and was then, poured onto ice (16 g) and it was left over night.

The mixture was extracted three times with CH_2Cl_2 (15 ml) and the combined organic layers were washed with 40 ml $NaHCO_3$ (sat. aq.), dried over $MgSO_4$ and filtered. Activated charcoal was added and the mixture was filtered through a short plug of SiO_2, eluted with CH_2Cl_2 and concentrated. Finally, the residue was recrystallized from EtOH to give a white solid, 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranoside **2** (0.51 g, 8.10 mmol, 20%).

3.1.5 Results

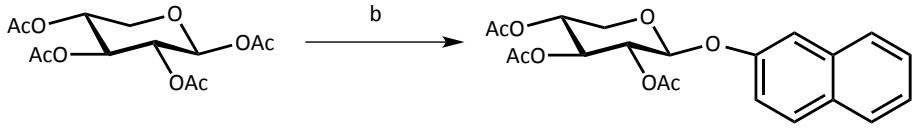
Table 3.1.5. *Obtained results from acetylation of β-D-xylose (**1**) by Ac_2O.*

	1	**2**
Initial weight (g)	1.22	-
Theoretical weight (g)	-	2.58
Obtained weight (g)	-	0.51
Yield		**20%**
Initial weight (g)	5	-
Theoretical weight (g)	-	10.59
Obtained weight (g)	-	2.68
Yield		**25%**

3.2 PREPARATION OF (2-NAPHTHYL) 2,3,4-TRI-*O*-ACETYL-β-D-XYLOPYRANOSIDE

Glycosylation of 2-naphthol by **2**, yielded the correspondent glycoside **3**. Initially reaction of a Lewis acid with the ester at the anomeric position of the ring of **2** generates an oxocarbenium cation. A lone pair of the 2-naphthol, hydroxyl group, then attacks this oxocarbenium cation.

3.2.1 Synthetic scheme



2 3

Scheme 3.2.1. *Reagents and conditions: (b) CH_2Cl_2, 2-naphthol, Et_3N, $BF_3{\cdot}OEt_2$, 3 h.*

Reagents	2	2-naphthol	Et_3N	$BF_3{\cdot}OEt_2$	**Products**	3
Formula	$C_{13}H_{18}O_9$	$C_{10}H_7OH$		$BF_3{\cdot}O(C_2H_5)_2$	Formula	$C_{21}H_{22}O_8$
MW	318.13	144.17	101.19	141.93	MW	402.30
Equivalents	1	1.5	0.5	2.5	Equivalents	1
Mols (mmol)	2.73	4.10	1.37	6.83	Mols (mmol)	2.73
Weight (g)	0.87	0.59			Weight (g)	1.10
Volume (ml)			0.19	0.84	Volume (ml)	
Density (g/cm^3)			0.73	1.12	Density (g/cm^3)	
Purity (%)		99	≥99		Purity (%)	

3.2.2 Safety

Reagent	Pictograms	Specifications
(2)-naphthol		Acute toxicity. It may cause serious eye and skin irritation and has hazardous effects to the aquatic environment. Work in the fumehood and wear personal protective equipment.
Et_3N		Extremely flammable liquid and vapor. It may cause serious eye and skin irritation and corrosion. Work in the fumehood and wear personal protective equipment.
$BF_3{\cdot}OEt_2$		Extremely flammable liquid and vapor. Causes serious eye damage, skin corrosion and it is harmful if inhaled. Work in the fumehood and wear personal protective equipment.
EtOAc		Flammable liquid. It may cause serious eye and skin irritation and sensitization. Work in the fumehood and wear personal protective equipment.

3.2.3 Mechanism

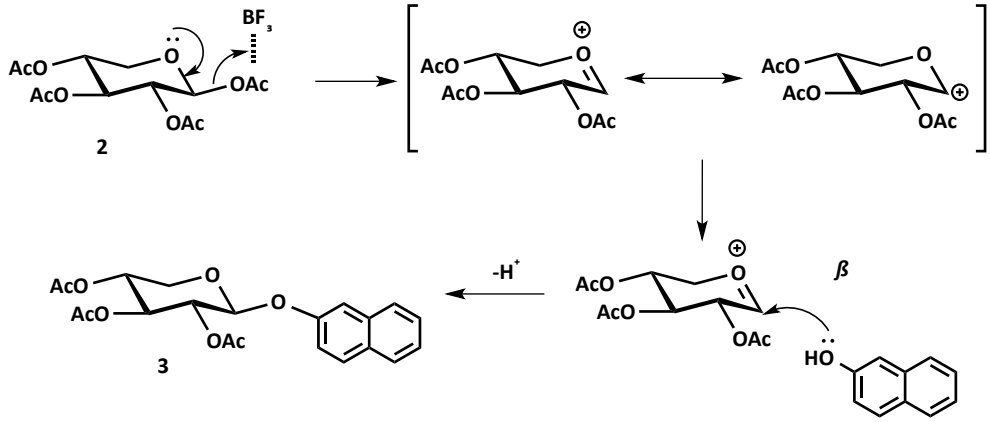


Figure 3.2.3. *Glycosylation of 1,2,3,4-tetra-O-acetyl-β-D-xylopyranoside* ***2*** *mechanism.*

3.2.4 Experimental procedure

1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranoside **2** (0.87 g, 2.73 mmol) was dissolved in CH_2Cl_2 (20 ml) under N_2-atmosphere. After that, 2-naphthol (0.59 g, 4.10 mmol) was added and followed by Et_3N (0.19 ml, 1.37 mmol) and $BF_3{\cdot}OEt_2$ (0.84 ml, 6.83 mmol).

After stirring for 3 hours, the reaction mixture was quenched by addition of 8 ml $NaHCO_3$ (sat. aq.) and extracted with EtOAc (15 ml) twice. The combined organic layers were dried over $MgSO_4$, filtered and the collected fraction was concentrated. Lastly, the residue was recrystallized from EtOH to give a white solid, (2-naphthyl) 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **3** (0.83 g, 2.06 mmol, 76%).

3.2.5 Results

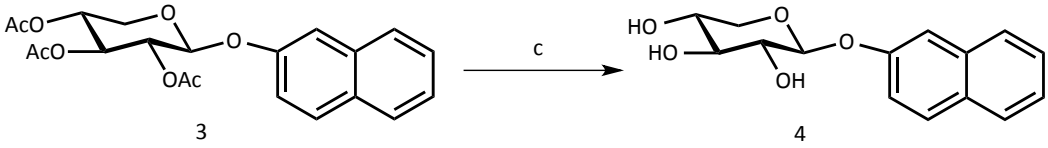
Table 3.2.5. *Obtained results from glycosylation of 1,2,3,4-tetra-O-acetyl-β-D-xylopyranoside* ***2****.*

	2	**3**
Initial weight (g)	0.87	-
Theoretical weight (g)	-	1.10
Obtained weight (g)	-	0.83
Yield	**76%**	
Initial weight (g)	2.29	-
Theoretical weight (g)	-	2.90
Obtained weight (g)	-	1.02
Yield	**35%**	

3.3 PREPARATION OF (2-NAPHTHYL) β-D-XYLOPYRANOSIDE (XylNap)

In order to obtain (2-naphthyl) β-D-xylopyranoside **4** from compound **3**, a Zemplén deacetylation has been performed. The efficient removal of the *O*-acetyl protecting groups is achieved by treatment of the protected substance in methanol with a catalytic amount of sodium methoxyde at room temperature.[6]

3.3.1 Synthetic scheme



Scheme 3.3.1. *Reagents and conditions: (c) MeOH, NaOMe, 30 min.*

Reagents	3	MeOH	NaOMe	**Products**	4
Formula	$C_{21}H_{22}O_8$	CH_4O	CH_3ONa	Formula	$C_{15}H_{16}O_5$
MW	402.30	32.04	54.02	MW	276.28
Equivalents	1	82	0.2	Equivalents	1
Mols (mmol)	2.06	169.60	0.35	Mols (mmol)	2.06
Weight (g)	0.83			Weight (g)	0.57
Volume (ml)		6.87	3.50	Volume (ml)	
Density (g/cm^3)		0.791		Density (g/cm^3)	
Purity (%)		99.80		Purity (%)	
Molar concentration (M)			1	Molar concentration (M)	

3.3.2 Safety

Reagent	**Pictograms**	**Specifications**
MeOH		Flammable liquid. Acute toxicity and harmful if inhaled. Work in the fumehood and wear personal protective equipment.
NaOMe		Flammable liquid. It may cause serious eye damage and skin corrosion and irritation. Work in the fumehood and wear personal protective equipment.
CH_3COOH		Flammable liquid. It may cause serious eye damage and skin corrosion and irritation. Work in the fumehood and wear personal

$C_6H_5CH_3$

protective equipment.
Highly flammable liquid and vapor. It may cause dizziness and damage to organs through repeated or prolongued exposure. It may be fatal if it is swallowed and causes skin irritation. Work in the fumehood and wear personal protective equipment.

3.3.3 Mechanism

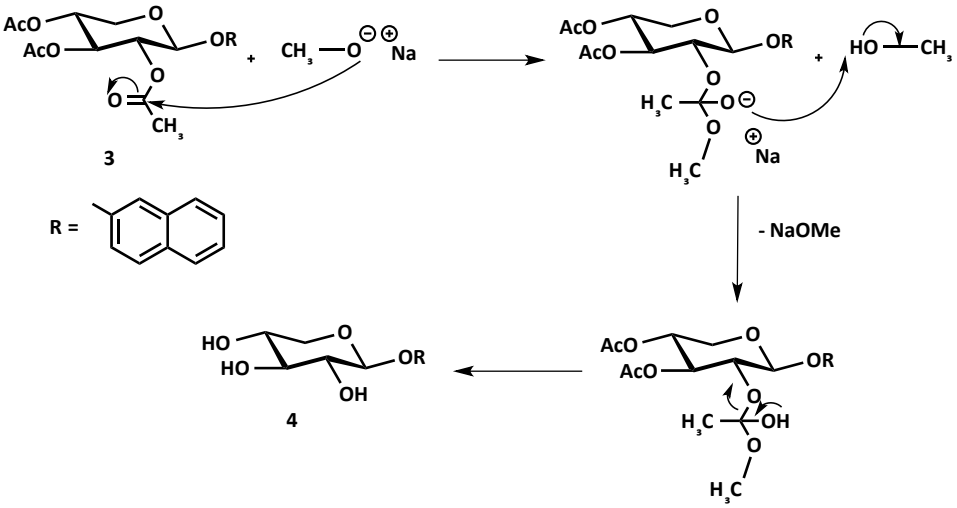


Figure 3.3.3. *Deacetylation of (2-naphthyl) 2,3,4-tri-O-acetyl-β-D-xylopyranoside **3** mechanism.*

3.3.4 Experimental procedure

(2-naphthyl) 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **3** (0.83 g, 2.06 mmol) was dissolved in NaOMe 1M (3.5 ml) and stirred for 30 minutes. The reaction was quenched by addition of as many drops as glacial acetic acid as needed to achieve a neutral pH. The reaction mixture was concentrated and diluted with toluene to remove the leftover glacial acetic acid.

Lastly, the obtained residue was recrystallized from EtOH to give a white solid, (2-naphthyl) β-D-xylopyranoside or XylNap **4** (0.11 g, 0.41 mmol, 20%).

3.3.5 Results

Table 3.3.5. *Obtained results from deacetylation of (2-naphthyl) 2,3,4-tri-O-acetyl-β-D-xylopyranoside **3**.*

	3	**4**
Initial weight (g)	0.83	
Theoretical weight (g)	-	0.57
Obtained weight (g)	-	0.11
Yield	**20%**	
Initial weight (g)	1.01	-
Theoretical weight (g)	-	0.69
Obtained weight (g)	-	0.52
Yield	**75%**	

3.4 PREPARATION OF (2-NAPHTHYL) 2,3- AND 3,4-*O*-ISOPROPYLIDENE-β-D-XYLOPYRANOSIDE FROM XylNap

In order to selectively react the hydroxyl groups at the 2- and 4-positions of the xylose moiety the other secondary hydroxyl groups must be protected.[1]

Isopropylidene acetal is an important protecting group for 1,2- and 1,3-diols and under specific conditions, thermodynamic product is most often formed. Regarding glycosides, 1,2-derivates are usually favoured over 1,3-derivates. Nevertheless, 1,2-*cis*-diols are preferentially protected over 1,2-*trans*-diols.[7] 2-Methoxy propene is the most commonly used reagent and the reaction is performed under acidic conditions, with catalytic amounts of *p*-toluenesulfonic acid (*p*TSA) or camphorsulfonic acid (CSA).[7,8] Both methods were carried out and are described in this section. The reaction of **4** under both sets of conditions led to the production of a mixture of two isomers, compounds **5** and **6**. Each isomer is produced by a 1,2-protection of the xylose moiety, leaving one unprotected hydroxyl group. One isomer has the hydroxyl group at the 2-position and the other isomer at the 4-position.

The two isomers were not separated from each other due to their co-elution during column chromatography and it is expected that the subsequent reactions will not be compromised by the use of the mixture.

3.4.1 Mechanism

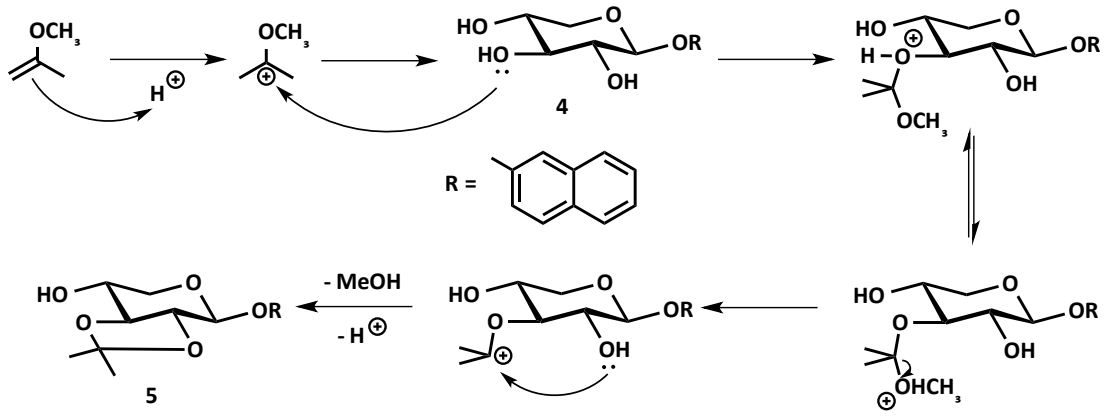


Figure 3.4.1. *Isopropylidene acetal protection of XylNap **4** mechanism.*

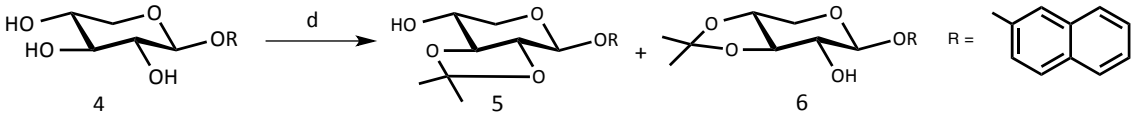
3.4.2 Safety

Reagent	Pictograms	Specifications
C_4H_8O		Extremely flammable liquid and vapor. It may form explosive peroxides. Work in the fumehood and wear personal protective equipment.
*p*TSA		It may cause severe skin burns and eye damage. Work in the fumehood and wear personal protective equipment.
DMF		Flammable liquid and vapor. It may cause serious eye irritation and it is harmful if inhaled. Work in the fumehood and wear personal protective equipment.

CSA  It may cause severe skin burns and eye damage. Work in the fumehood and wear personal protective equipment.

3.4.3 Preparation of (2-naphthyl) 2,3- and 3,4-*O*-isopropylidene-β-D-xylopyranoside using *p*-toluenesulfonic acid

3.4.3.1 Synthetic scheme



Scheme 3.4.3. *Reagents and conditions: (d) 2-Methoxy propene, pTSA, DMF, 80 ºC.*

Reagents	4	C_4H_8O	*p*TSA	DMF	**Products**	5 and 6
Formula	$C_{15}H_{16}O_5$	C_4H_8O	$C_7H_8SO_3 \cdot H_2O$	C_3H_7NO	Formula	$C_{18}H_{20}O_5$
MW	276.28	72.11	190.22	73.09	MW	316.35
Equivalents	1	3	0.02		Equivalents	1
Mols (mmol)	1.81	5.43	0.04		Mols (mmol)	1.81
Weight (mg)	500		7.4		Weight (mg)	573
Volume (µl)		511		2500	Volume (µl)	
Density (g/cm^3)		0.77			Density (g/cm^3)	
Purity (%)		97	≥98.50	99.80	Purity (%)	

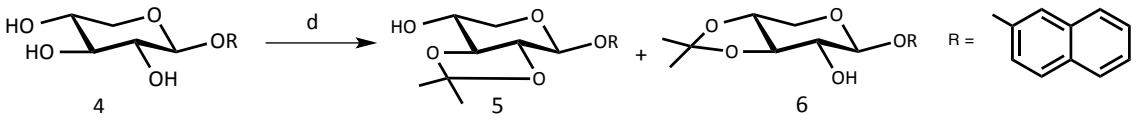
3.4.3.2 Experimental procedure

Compound **4** (500 mg, 1.81 mmol) and *p*TSA (7.4 mg, 0.04 mmol) were suspended in dry DMF (2.5 ml) and heated to 80 ºC under stirring, generating a solution. In the meantime, 2-methoxy propene (511 µl, 5.43 mmol) was added to the mixture in 6 portions, leaving 10 minutes between each addition. After that, Et_3N (0.2 ml) and toluene were added and the mixture was reduced in vacuo to yield a white solid.

The residue was lately purified by flash chromatography (Et_2O-Petroleum ether, 50%-50% to 70%-30%, with 2% of Et_3N) to give the pure mixture of **5** and **6** (256 mg, 1.81 mmol, 45%).

3.4.4 Preparation of (2-naphthyl) 2,3- and 3,4-*O*-isopropylidene-β-D-xylopyranoside using camphorsulfonic acid

3.4.4.1 Synthetic scheme



Scheme 3.4.4. *Reagents and conditions: (d) 2-Methoxy propene, CSA, DMF, rt.*

Reagents	4	C_4H_8O	CSA	DMF	**Products**	5 and 6
Formula	$C_{15}H_{16}O_5$	C_4H_8O	$C_{10}H_{16}O_4S$	C_3H_7NO	Formula	$C_{18}H_{20}O_5$
MW	276.28	72.11	232.30	73.09	MW	316.35
Equivalents	1	2.7	0.15	-	Equivalents	1
Mols (mmol)	0.36	0.97	0.05		Mols (mmol)	0.36

Weight (mg)	100		12.54		Weight (mg)	113.89
Volume (μl)		92		600	Volume (μl)	
Density (g/cm^3)		0.77			Density (g/cm^3)	
Purity (%)		97	99	99.80	Purity (%)	

3.4.4.2 Experimental procedure

Compound **4** (100 mg, 0.36 mmol) and CSA (12.54 mg, 0.05 mmol) were suspended in dry DMF (0.60 ml). After that, 2-methoxy propene (92 μl, 0.97 mmol) was added to the mixture in 4 portions, leaving 20 minutes between each addition and generating a totally clear solution. The reaction was quenched by addition of Et_3N (0.02 ml) and the reaction mixture was coevaporated with toluene under vacuo to yield a white solid.

The residue was lately purified by flash chromatography (Et_2O-Petroleum ether, 3:4, with 0.2% of Et_3N) to give the pure mixture of **5** and **6** (59.20 mg, 0.36 mmol, 52%).

3.4.5 Results

Table 3.4.5. *Obtained results from isopropylidene acetal protection of XylNap* ***4****.*

Entry	Reagents	Solvent	Initial weight (mg)	2-methoxy propene addition intervals (min)	Obtained weight (mg)	Yield
1	*p*TSA	DMF	500	10	299	52%
2	*p*TSA	DMF	500	10	256	45%
3	*p*TSA	DMF	500	10	207.70	36%
4	*p*TSA	DMF	500	10	26.50	5%
5	*p*TSA	DMF*	500	15	175	31%
6	CSA	DMF	100	20	59.20	52%

* Filtered through Al_2O_3

Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 – 7.42 (m, 6H), 1.53 (s, 6H, $(CH_3)_2C$), 2.50-2.52 (d, 1H, 4-OH), 5.45 (d, 1H, C1, J=8-10 Hz), 3.70 (t, 1H, C2, J=8-10 Hz), 3.72 (t, 1H, C3, J=8-10 Hz), 4.07 (td, 1H, C4, J=8-10 Hz/J=2-3 Hz), 4.21 (d, 1H, C5, J=8-10 Hz), 3.50 (d, 1H, C5, J=2-3 Hz).

Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.46 (m, 6H), 1.50 (s, 6H, $(CH_3)_2C$), 2.54-2.56 (d, 1H, 2-OH), 5.04 (d, 1H, C1, J=8-10 Hz), 3.72 (t, 1H, C2, J=8-10 Hz), 3.70 (t, 1H, C3, J=8-10 Hz), 4.03 (td, 1H, C4, J=8-10 Hz/J=2-3 Hz), 4.29 (d, 1H, C5, J=8-10 Hz), 3.74 (d, 1H, C5, J=2-3 Hz).[1]

3.5 SWERN OXIDATION, ISOMERIZATION AND IN SITU REDUCTION

The inversion of the sterocentre at the 3-postion was carried out by sequential oxidation and reduction of the remaining alcohol. Epimerization of α-position is a well-known side reaction of the Swern oxidation in the presence of a base.[7] The mixture of **5** and **6** brought forward from the previous step was oxidized under Swern conditions and the corresponding ketones formed were then reduced in situ.

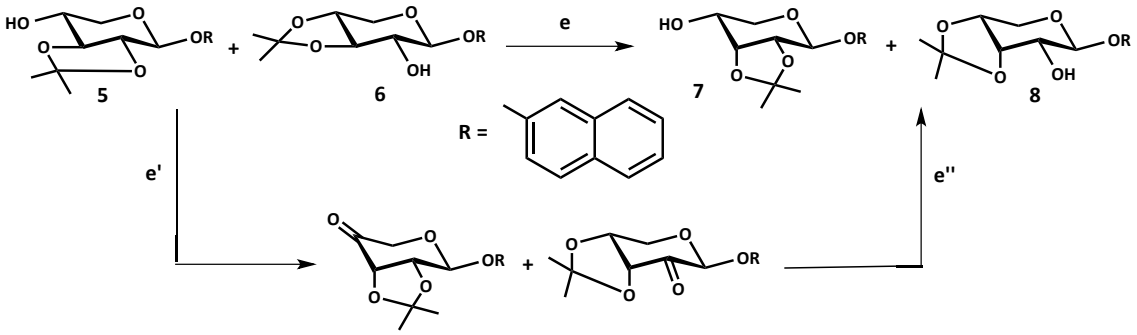
It is known that complete inversion of the 3-position of the ketone intermediate is achieved when using Et_3N and long reaction times. Therefore, epimerization was carried out for 12 hours before reduction of the ketone with $NaBH_4$ regenerates the equatorial hydroxyl groups

[1] Appendant ^{1}H NMR spectra

at the 4- and 2-postions for compounds **7** and **8** respectively.[7] Again due to co-elution during column chromatography the products **7** and **8** were not separated. Also it was again envisioned that subsequent reaction would not be compromised by use of this mixture.

This sequence is carried out one-pot. In chemistry, one-pot synthesis is a strategy to improve the efficiency of a chemical reaction. It is based on subjecting a reactant to successive chemical reactions in just one reactor. This process avoids the separation and purification of intermediate compounds as well as, saves time, resources and increases performance.

3.5.1 Synthetic scheme



Scheme 3.5.1. *Reagents and conditions: (e') i) oxalyl chloride, DMSO, anhyd CH_2Cl_2, -78 ºC, 2 h, ii) Et_3N, rt, 12 h; (e'') in situ: $NaBH_4$, anhyd MeOH, 0 ºC, 4 h.*

Reagents	5 and 6	$(COCl)_2$	DMSO	Et_3N	$NaBH_4$	**Products**	7 and 8
Formula	$C_{18}H_{20}O_5$	$C_2Cl_2O_2$	$(CH_3)_2SO$	$(C_2H_5)_3N$	$NaBH_4$	Formula	$C_{18}H_{20}O_5$
MW	316.35	126.93	78.13	101.19	37.83	MW	316.35
Equivalents	1	3	6	10	2.7	Equivalents	1
Mols (mmol)	0.16	0.48	0.94	1.62	0.52	Mols (mmol)	0.16
Weight (mg)	50				20	Weight (mg)	50
Volume (ml)		0.24	0.07	0.21		Volume (ml)	
Density (g/cm^3)			1.1	0.78		Density (g/cm^3)	
Purity (%)			≥99.9	≥99	≥98	Purity (%)	
Molar concentration (M)		2				Molar concentration (M)	

3.5.2 Safety

Reagent	**Pictograms**	**Specifications**
$(COCl)_2$		Acute toxicity. It may cause eye damage or skin corrosion. Work in the fumehood and wear personal protective equipment.
$NaBH_4$		Flammable solid, toxic if contact with skin and harmful if it is inhaled or swallowed. It may cause skin corrosion or eye irritation and respiratory sensitization. Work in the fumehood and wear personal protective equipment

3.5.3 Mechanism

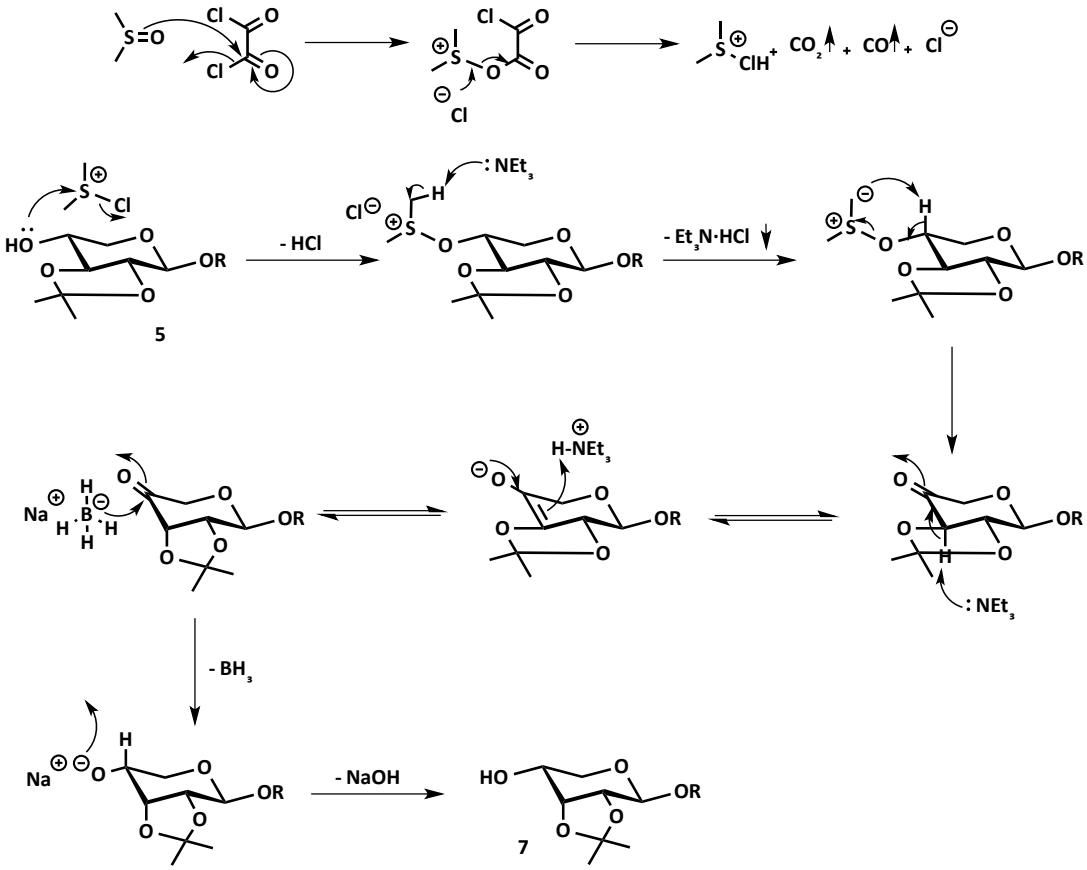


Figure 3.5.3. *Swern oxidation-Isomerization-Reduction of compound **5** mechanism.*

3.5.4 Experimental procedure

Anhydrous DMSO (0.07 ml, 0.94 mmol) was added to a stirred solution of oxalyl chloride 2M (0.24 ml, 0.48 mmol) at -78 ºC under N_2. After 1 hour, the mixture of **5** and **6** (50 mg, 0.16 mmol) was dissolved in anhydrous CH_2Cl_2 and added to the reaction flask.

After 2 hours at -78 ºC, the reaction was quenched by addition of Et_3N (0.21 ml, 1.62 mmol) and 30 minutes later, the reaction mixture was allowed to reach room temperature.

Anhydrous MeOH (0.63 ml) was added after approximately 12 hours and it was cooled to 0 ºC, before addition of $NaBH_4$ (16 mg, 0.43 mmol). After 4 hours under stirring, H_2O (10 ml) was added to the flask and the reaction mixture was allowed to reach room temperature before extraction with CH_2Cl_2 four times (10 ml). Then, the combined organic layers were dried over Na_2SO_4, filtered and the collected fraction was concentrated under reduced pressure.

Lastly, the residue was purified by flash chromatography (EtOAc-Heptane, 1:1, with 2% of Et_3N) to give the pure mixture of compounds **7** and **8** (18 mg, 0.16 mmol, 36%).

3.5.5 Results and discussion

Table 3.5.5. *Obtained results from Swern oxidation-isomerization-reduction of **5** and **6**.*

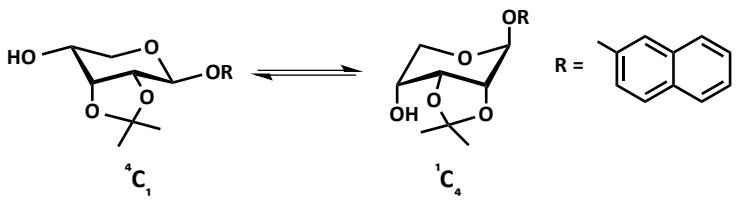
	5 and 6	**7 and 8**
Initial weight (mg)	50	-
Theoretical weight (mg)	-	50
Obtained weight (mg)	-	18
Yield	**36%**	
Initial weight (mg)	96	-
Theoretical weight (mg)	-	96
Obtained weight (mg)	-	41
Yield	**43%**	
Initial weight (mg)	100	-
Theoretical weight (mg)	-	100
Obtained weight (mg)	-	5
Yield	**5%**	
Initial weight (mg)	59.20	-
Theoretical weight (mg)	-	59.20
Obtained weight (mg)	-	38.20
Yield	**65%**	

Compound **7**: ^{1}H NMR (400 MHz, C_6D_6): δ = 7.52 – 7.56 (m, 4H), 7.19 – 7.50 (m, 3H), 5.59 (d, 1H, C1, J=2-5 Hz), 3.97 (m, 1H, C4), 4.14 - 4.16 (m, 1H, C2-C3, J=2-5 Hz), 3.64 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 3.58 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 1.15 - 1.45 (s, 6H, $(CH_3)_2C$).

Compound **8**: ^{1}H NMR (400 MHz, C_6D_6): δ = 7.55 – 7.59 (m, 4H), 7.30 – 7.34 (m, 3H), 5.60 (d, 1H, C1, J=2-5 Hz), 3.71 (m, 1H, C2), 4.16 (m, 1H, C3, J=2-5 Hz), 3.60 (m, 2H, C4), 3.43 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 3.43 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 1.17 - 1.53 (s, 6H, $(CH_3)_2C$).[2]

It is known that pyranose system can exist in five different conformers: Chair (C), Boat (B), Skew (S), Half-Chair (H) or Envelope (E). In all cases there are four or more atoms that make up a plane. It is also possible to interconvert between conformations. The conformation predomenately adopted is due to steric and stereoelectronic effects such as the anomeric effect or 1,3 diaxial interactions.

Since xylopyranose is lacking a hydroxymethyl group present in glucose, several conformations need to be considered due to its ring flexibility.[2] The chair conformation of six membered rings is the most stable conformer. There are two possible chair conformations. Conformations with 1,3 diaxial interactions are usually disfavored due to steric congestion and can shift equilibrium to the other chair form (Scheme 3.5.5).



Scheme 3.5.5. *Conformational behaviour of compound **7**.*

[2] Appendant ^{1}H NMR spectra

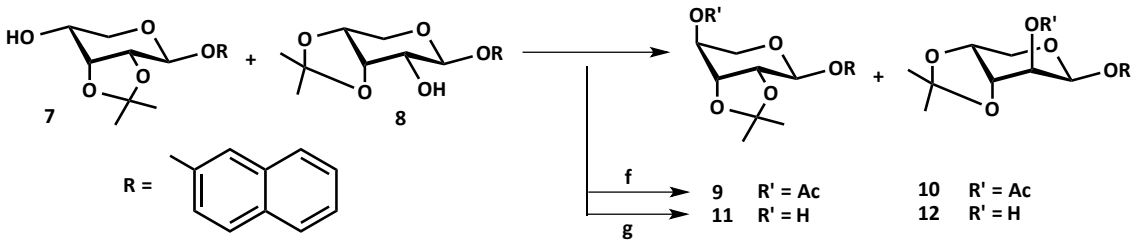
The ^{1}H NMR spectra of the products of the reaction performed are suggestive of the $^{1}C_4$ conformation. The coupling constant between the hydrogen atoms located on the C1 and C2 atoms are in the order of 2-3 Hz suggesting the protons are in equatorial positions. Expected values of this coupling constant where these protons are located in axial positions would be in the region of 8-10 Hz.

3.6 SELECTIVE TRANSFORMATIONS OF 2- AND 4-POSITIONS

It has been shown that it is possible to invert and if desired susbstitute the hydroxyl groups of sugars.[2,8,9] First converting them to their corresponding trifluoromethansulfonate ester or triflate and then perfoming a S_N2 nucleophilic substitution reaction, with the appropriate nucleophile, displacing the triflate. The S_N2 nucleophilic substitution ensures the desired stereochemistry is obtained: inverted compared to the starting material. Triflic anhydride is the most common reagent to prepare triflates derived from sugars and requires the addition of a base, usually pyridine, to neutralize the triflic acid produced.

Reactions were carried out were a mixture of compounds **7** and **8** was reacted with triflic anhydride and subsequently with a different oxygenated nucleophile (Scheme 3.6.1).

3.6.1 Synthetic scheme



Scheme 3.6.1. *Reagents and conditions: (f) Tf_2O, CH_3COOH, DBU, toluene, 95 ºC, 12 h; (f) Tf_2O, CsOAc, DMF, 50 ºC, 3 days; (g) Tf_2O, QNO_2, DMF, 50 ºC, 16 h.*

3.6.2 Safety

Reagent	Pictograms	Specifications
Tf_2O		Acute toxicity. It may cause eye damage or skin corrosion. Work in the fumehood and wear personal protective equipment.
DBU		Toxic liquid if contact with skin and harmful if it is inhaled or swallowed. It may cause skin corrosion or eye irritation and respiratory sensitization. Work in the fumehood and wear personal protective equipment.
QNO_2		Oxidizing solid. It may cause skin irritation or eye damage. Work in the fumehood and wear personal protective equipment.
C_5H_5N		Flammable liquid. It may cause skin irritation or eye damage. Work in the fumehood and wear personal protective equipment.
CsOAc	-	Work in the fumehood and wear personal protective equipment.

3.6.3 Mechanism

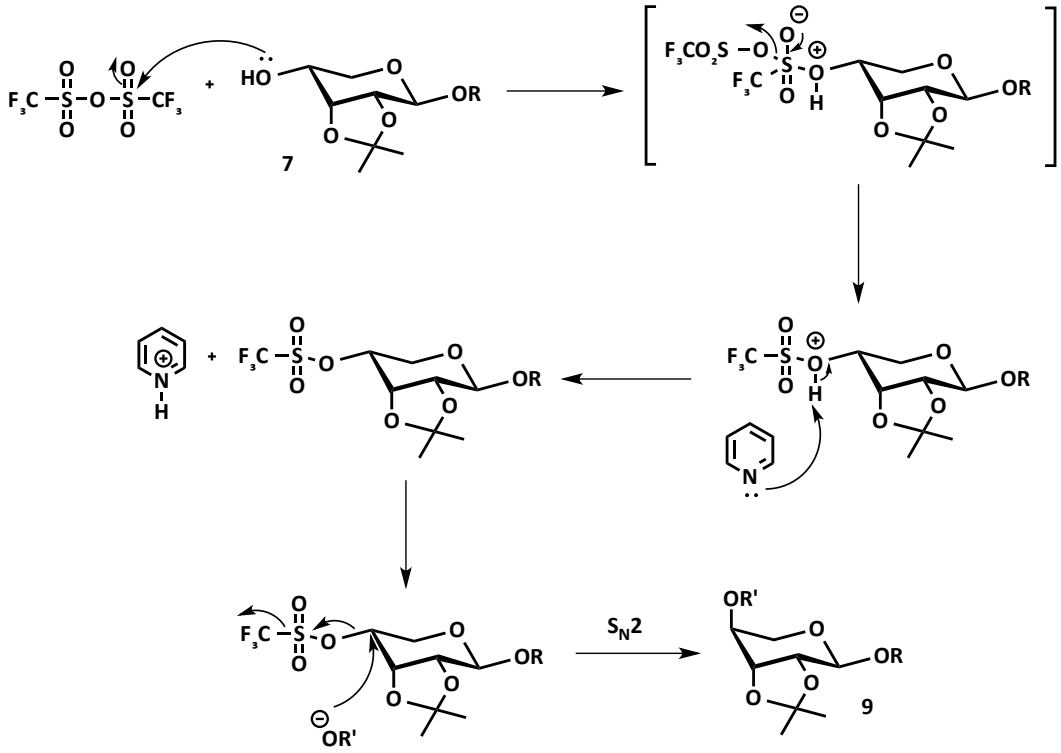


Figure 3.6.3. *Inversion of 4-position in compound **7** mechanism.*

3.6.4 Experimental procedure

3.6.4.1 Inversion of 2- and 4-positions with a tunable complex of acetic acid and DBU

Reagents	7 and 8	Tf_2O	CH_3COOH	DBU	**Products**	9 and 10
Formula	$C_{18}H_{20}O_5$	$(CF_3SO_2)_2O$	$C_2H_4O_2$	$C_9H_{16}N_2$	Formula	$C_{20}H_{22}O_6$
MW	316.35	282.14	60.05	152.24	MW	358.39
Equivalents	1	2.43	11.74	5.87	Equivalents	1
Mols (mmol)	0.06	0.18	0.70	0.40	Mols (mmol)	0.06
Weight (mg)	20				Weight (mg)	22.58
Volume (ml)		0.03	0.04	0.06	Volume (ml)	
Density (g/cm^3)		1.68	1.05	1.02	Density (g/cm^3)	
Purity (%)		≥99	≥99.5	98	Purity (%)	

Compounds **7** and **8** (20 mg, 0.06 mmol) were dissolved in anhydrous CH_2Cl_2 (3.40 ml) and pyridine (0.40 ml). The mixture was cooled to 0 ºC and followed by the addition of Tf_2O (30 μl, 0.18 mmol). After 2 hours and a half stirring under N_2, anhydrous MeOH (1.50 ml) and anhydrous CH_2Cl_2 (1.50 ml) were added and the reaction mixture was washed with $NaHCO_3$ (sat. aq.) (5 ml) and NaCl (sat. aq.) (5 ml). The organic layers were dried over Na_2SO_4, filtered and the collected fraction was concentrated under reduced pressure to get the crude triflate.

Acetic acid (0.04 ml, 0.70 mmol) and DBU (0.06 ml, 0.4 mmol) were added to anhydrous toluene (3.60 ml) while stirring and under N_2. After 35 minutes, the reaction mixture was poured into onto the crude triflate and heated to 95 ºC during 12 hours.

Finally, after that time the reaction mixture was allowed to reach room temperature and then it was washed with 1M HCl (2.40 ml), $NaHCO_3$ (sat. aq.) (2.40 ml), NaCl (sat. aq.) (2.40 ml) and dried over Na_2SO_4. The collected fraction was concentrated under pressure.

3.6.4.2 Inversion of 2- and 4-positions with tetrabutylammonium nitrate

Reagents	7 and 8	Tf_2O	C_5H_5N	QNO_2	**Products**	11 and 12
Formula	$C_{18}H_{20}O_5$	$(CF_3SO_2)_2O$	C_5H_5N	$(C_4H_9)_4N(NO_3)$	Formula	$C_{18}H_{20}O_5$
MW	316.35	282.14	79.10	304.47	MW	316.35
Equivalents	1	2	8	4	Equivalents	1
Mols (mmol)	0.10	0.21	0.83	0.42	Mols (mmol)	0.10
Weight (mg)	32.80			127	Weight (mg)	32.80
Volume (ml)		0.04	0.07		Volume (ml)	
Density (g/cm^3)		1.68	0.98		Density (g/cm^3)	
Purity (%)		≥99	≥99	97	Purity (%)	

Compounds **7** and **8** (32.80 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (1.64 ml) and the solution was cooled to -78 ºC under N_2, while stirring. Pyridine (0.07 ml, 0.83 mmol) and Tf_2O (0.04 ml, 0.21 mmol) were added to the flask and the temperature was raised to 0 ºC. After 3 hours, CH_2Cl_2 (5 ml) was added and the reaction mixture was washed with $NaHCO_3$ (sat. aq.) (5 ml), dried over Na_2SO_4 and filtered. After that, solvents were evaporated and the remaining crude triflate was submitted to subsequent reaction.

Therefore, the crude was dissolven in DMF (2.6 ml) and QNO_2 (127 mg, 0.42 mmol) was introduced while stirring, under N_2. The reaction mixture was heated to 50 ºC for 16 hours. After that time, the mixture was allowed to reach room temperature, H_2O was added (7 ml) and the solution was extracted three times from EtOAc (10 ml). The combined organic layers were dried over Na_2SO_4, filtered and the collected fraction was concentrated under reduced pressure yielding an oil. Lastly, the residue was purified by flash chromatography (EtOAc-Heptane, 1:3).

3.6.4.3 Inversion of 2- and 4-positions with cesium acetate

Reagents	7 and 8	Tf_2O	C_5H_5N	CsOAc	**Products**	9 and 10
Formula	$C_{18}H_{20}O_5$	$(CF_3SO_2)_2O$	C_5H_5N	CH_3CO_2Cs	Formula	$C_{20}H_{22}O_6$
MW	316.35	282.14	79.10	191.95	MW	358.39
Equivalents	1	2	8	5	Equivalents	1
Mols (mmol)	0.10	0.21	0.83	0.52	Mols (mmol)	0.10
Weight (mg)	32.80			99.81	Weight (mg)	37.30
Volume (ml)		0.04	0.07		Volume (ml)	
Density (g/cm^3)		1.68	0.98		Density (g/cm^3)	
Purity (%)		≥99	≥99	≥99.99	Purity (%)	

Compounds **7** and **8** (32.80 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (1.64 ml) and the solution was cooled to -78 ºC while stirring and under N_2. Pyridine (0.07 ml, 0.83 mmol) and Tf_2O (0.04 ml, 0.21 mmol) were added to the flask and the temperature was raised to 0 ºC. After 3 hours, CH_2Cl_2 (5 ml) was added and the reaction mixture was washed with $NaHCO_3$ (sat. aq.) (5 ml), dried over Na_2SO_4 and filtered. After that, solvents were evaporated and the remaining crude triflate was submitted to subsequent reaction.

Therefore, the crude was dissolven in DMF (2.6 ml) and CsOAc (99.80 mg, 0.52 mmol) was introduced while stirring, under N_2. The reaction mixture was heated to 50 ºC for 2 days. After that time, the mixture was allowed to reach room temperature and then the solvents where evaporated to yield an oil. Lastly, the residue was purified by flash chromatography (EtOAc-Heptane, 1:4).

3.6.5 Results and discussion

Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.85 (m, ArH), 5.65 (d, 1H, C1, J=2-5 Hz), 4.45 (m, 2H, C2-C3), 5.05 (m, 1H, C4), 3.70 (dd, 1H, C5, J=12-15 Hz/J=8-10 Hz), 3.85 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 2.11-2.14 (s, 3H, -$OOCCH_3$), 1.20 - 1.60 (s, 6H, $(CH_3)_2C$).

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 – 7.85 (m, ArH), 5.75 (d, 1H, C1, J=2-5 Hz), 5.15 (m, 1H, C2), 4.65 (dd, 1H, C3, J=2-5 Hz), 4.40 (dt, 1H, C4, J= 8-10 Hz/J=2-5 Hz), 4.10 (dd, 1H, C5, J=12-15 Hz/J=8-10 Hz), 4.15 (dd, 1H, C5, J=12-15 Hz/J=2-5 Hz), 2.11-2.14 (s, 3H, $OOCCH_3$), 1.20 - 1.60 (s, 6H, $(CH_3)_2C$).

Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 – 7.85 (m, ArH), 5.45 (d, 1H, C1, J=8-10 Hz), 4.30 (m, 1H, C2), 4.75 (m, 1H, C3, J=6 Hz/J=2-5 Hz), 5.20 (dd, 1H, C4, J=6 Hz/J=2-5 Hz), 6.50 (dd, 1H, C5, J=6 Hz), 1.20 - 1.60 (s, 6H, $(CH_3)_2C$).

Compound **7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 – 7.85 (m, ArH), 5.25 (d, 1H, C1, J=8-10 Hz), 4.65 (m, 1H, C2), 4.85 (dt, 1H, C4, J=6 Hz/J=2-5 Hz), 4.50 (m, 2H, C5), 1.20 - 1.60 (s, 6H, $(CH_3)_2C$).[3]

When the reaction was carried out in toluene and a mixture of CH_3COOH and DBU, used to generate the oxygen nucleophile, deglycosylation of the sugar moiety occurred. By comparison of R_f values in TLC it was possible to see free 2-naphthol, suggesting cleavage of the ester. This showed this method to be unsuitable for the desired chemistry.

As the mixture of CH_3COOH and DBU may be causing the cleavage of naphyl ester, CsOAc was trialed as a nucleophile for the reaction in DMF.[2] The reaction gave a mixture of products by ^{1}H NMR spectroscopy. These products are assigned at compounds **7a**, **7b**, **9** and **10** (Figure 3.6.5). It was not possible by column chromotography to separate each individual product. This resulted in two samples, one a mixture of **7a**, **7b** and **9** and the other a mixture of **9** and **10**. The identity of these compounds is assigned from the ^{1}H NMR and COSY spectra.

[3] Appendant ^{1}H NMR spectra

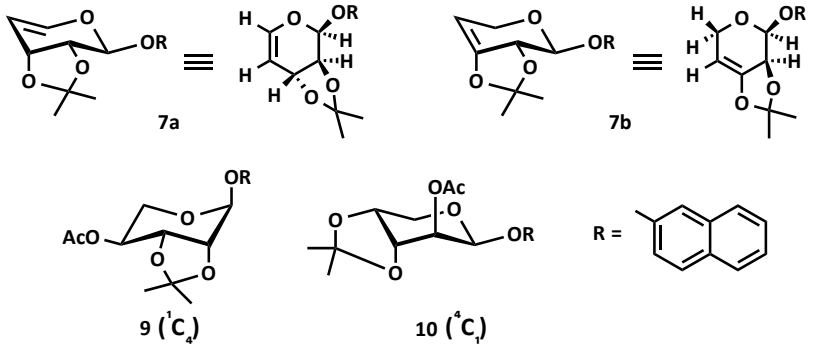


Figure 3.6.5. *Structures of the obtained products. Chemical shifts assignment through 2D ^{1}H COSY NMR.*

The S_N2 reaction mechanism is based on the breaking of a relatively polar bond, while concertedly forming a new bond without creating intermediate species. This occurs when a nucleophle attacks the σ* orbial of the carbon-leaving group bond. Simultaneously through a planar transition state, the nucleophile attacks the opposite side of the carbon to the leaving group, which is pushed off giving the product with the inverted configuration.

Elimination reactions are a common side reaction when S_N2 chemistry is desired. Where a base is present in reaction, the abstraction of a proton on the β carbon can occur followed by loss of the leaving group to give an alkene. Elimination is favoured if the α carbon, where substitution is to occur, is sterically hindered compared to β carbon where deprotonation can occur.

The presence of bulky substituents and steric crowding around the carbon atoms bearing the hydroxyl groups, due to the $^1C_4$ conformation of compounds **7** and **8**, is suggested as a reason and elimination products are observed during the CsOAc reaction.

Reaction of the triflic esters with QNO_2 has previously been shown to yield the hydroxyl product with inversion of stereochemistry.[2] Triflic esters of **7** and **8** were reacted with QNO_2. Even though the TLC was suggesting two spots with identical R_f values as the spots observed in the previous reaction with CsOAc, corresponding to the elimination products, the ^{1}H NMR was suggesting the same mixture among some other by-products. For this reason, the ^{1}H NMR interpretation was not carried out.

4. CONCLUDING REMARKS

The synthesis of (2-naphthyl) β-D-xylopiranoside from xylose has been successfully performed. Furthermore, the scale was increased from when the reaction was previously carried out.

Different methods have been trialed for the synthesis of XylNap analogues **5** and **6** due to the variety in the obtained yields (Table 3.4.5). Modification of both the acid used and the time between 2-methoxipropene additions has shown that using CSA gave more consistent performance in order to produce compounds **5** and **6**.

The epimerization step yielded the desired product. However, the products obtained were in unexpected conformations. That fact produced that the last step was performed with

difficulties and for that, new challenges should be considered in order to improve the inversion step.

Finally, despite knowing that carbohydrates are interesting molecules for the development of new drugs and that fact has stimulated renewed interest in chemistry, it is also well-known that is a complex field due to their structural and synthetic complexity. Thus, the project could not go further and achieve the synthesis of xylosides with two functional groups in axial positions, which can be trialed for their anticancer properties, because each synthetic step has represented a new challenge.

5. REFERENCES

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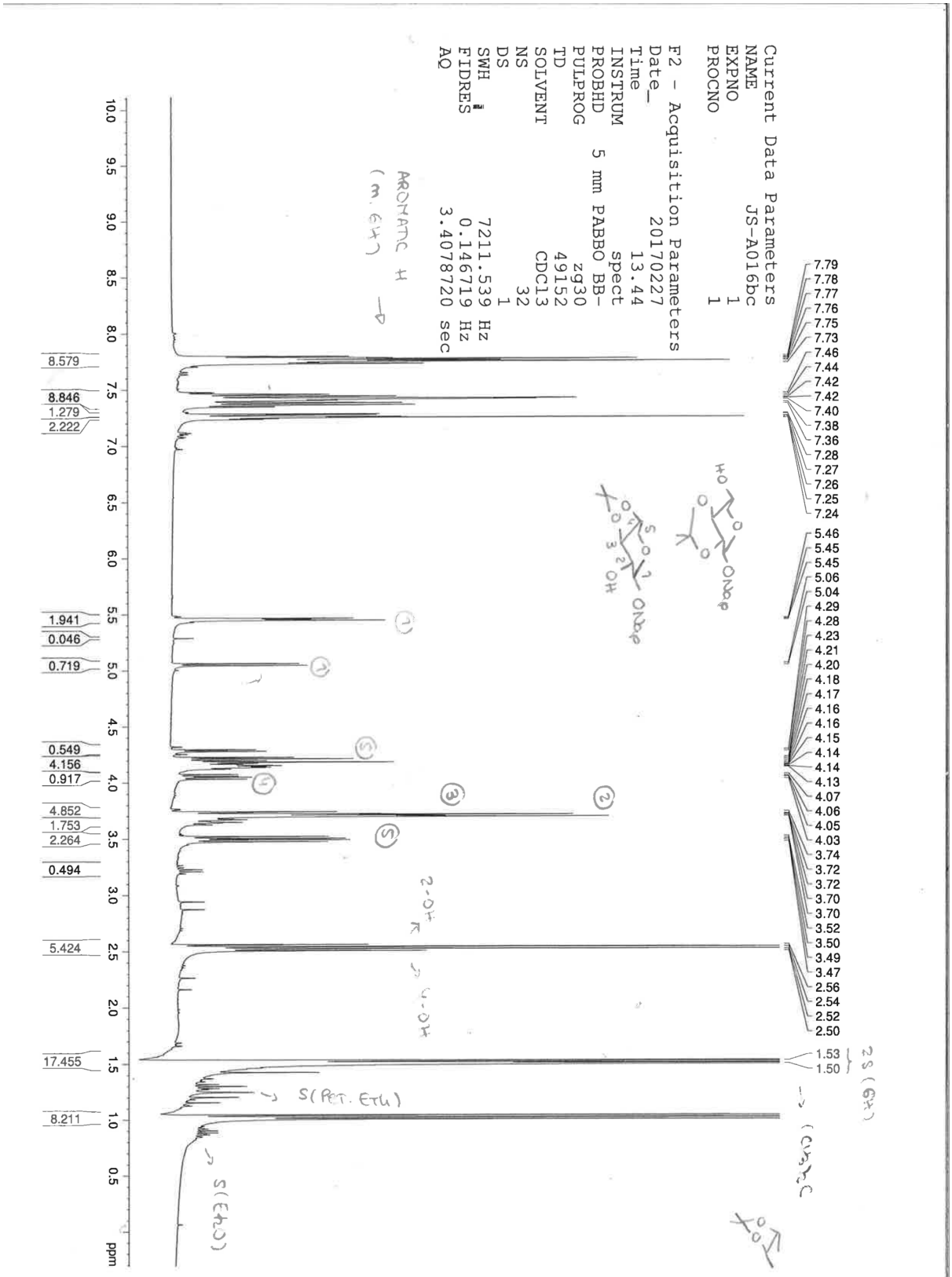
6. APPENDICES

Table 1. ^{1}H NMR Data[a]

	proton	mult	THF-d_8	CD_2Cl_2	$CDCl_3$	toluene-d_8	C_6D_6	C_6D_5Cl	$(CD_3)_2CO$	$(CD_3)_2SO$	CD_3CN	TFE-d_3	CD_3OD	D_2O
solvent residual signals			1.72 3.58	5.32	7.26	2.08 6.97 7.01 7.09	7.16	6.96 6.99 7.14	2.05	2.50	1.94	5.02 3.88	3.31	4.79
water	OH	s	2.46	1.52	1.56	0.43	0.40	1.03	2.84[b]	3.33[b]	2.13	3.66	4.87	
acetic acid	CH_3	s	1.89	2.06	2.10	1.57	1.52	1.76	1.96	1.91	1.96	2.06	1.99	2.08
acetone	CH_3	s	2.05	2.12	2.17	1.57	1.55	1.77	2.09	2.09	2.08	2.19	2.15	2.22
acetonitrile	CH_3	s	1.95	1.97	2.10	0.69	0.58	1.21	2.05	2.07	1.96	1.95	2.03	2.06
benzene	CH	s	7.31	7.35	7.36	7.12	7.15	7.20	7.36	7.37	7.37	7.36	7.33	
tert-butyl alcohol	CH_3	s	1.15	1.24	1.28	1.03	1.05	1.12	1.18	1.11	1.16	1.28	1.40	1.24
	OH	s[c]	3.16			0.58	0.63	1.30		4.19	2.18	2.20		
chloroform	CH	s	7.89	7.32	7.26	6.10	6.15	6.74	8.02	8.32	7.58	7.33	7.90	
18-crown-6	CH_2	s	3.57	3.59	3.67	3.36	3.39	3.41	3.59	3.51	3.51	3.64	3.64	3.80
cyclohexane	CH_2	s	1.44	1.44	1.43	1.40	1.40	1.37	1.43	1.40	1.44	1.47	1.45	
1,2-dichloroethane	CH_2	s	3.77	3.76	3.73	2.91	2.90	3.26	3.87	3.90	3.81	3.71	3.78	
dichloromethane	CH_2	s	5.51	5.33	5.30	4.32	4.27	4.77	5.63	5.76	5.44	5.24	5.49	
diethyl ether	CH_3	t, 7	1.12	1.15	1.21	1.10	1.11	1.10	1.11	1.09	1.12	1.20	1.18	1.17
	CH_2	q, 7	3.38	3.43	3.48	3.25	3.26	3.31	3.41	3.38	3.42	3.58	3.49	3.56
diglyme	CH_2	m	3.43	3.57	3.65	3.43	3.46	3.49	3.56	3.51	3.53	3.67	3.61	3.67
	CH_2	m	3.53	3.50	3.57	3.31	3.34	3.37	3.47	3.38	3.45	3.62	3.58	3.61
	OCH_3	s	3.28	3.33	3.39	3.12	3.11	3.16	3.28	3.24	3.29	3.41	3.35	3.37
dimethylformamide	CH	s	7.91	7.96	8.02	7.57	7.63	7.73	7.96	7.95	7.92	7.86	7.97	7.92
	CH_3	s	2.88	2.91	2.96	2.37	2.36	2.51	2.94	2.89	2.89	2.98	2.99	3.01
	CH_3	s	2.76	2.82	2.88	1.96	1.86	2.30	2.78	2.73	2.77	2.88	2.86	2.85
1,4-dioxane	CH_2	s	3.56	3.65	3.71	3.33	3.35	3.45	3.59	3.57	3.60	3.76	3.66	3.75
DME	CH_3	s	3.28	3.34	3.40	3.12	3.12	3.17	3.28	3.24	3.28	3.40	3.35	3.37
	CH_2	s	3.43	3.49	3.55	3.31	3.33	3.37	3.46	3.43	3.45	3.61	3.52	3.60
ethane	CH_3	s	0.85	0.85	0.87	0.81	0.80	0.79	0.83	0.82	0.85	0.85	0.85	0.82
ethanol	CH_3	t, 7	1.10	1.19	1.25	0.97	0.96	1.06	1.12	1.06	1.12	1.22	1.19	1.17
	CH_2	q, 7[d]	3.51	3.66	3.72	3.36	3.34	3.51	3.57	3.44	3.54	3.71	3.60	3.65
	OH	s[c,d]	3.30	1.33	1.32	0.83	0.50	1.39	3.39	4.63	2.47			
ethyl acetate	CH_3CO	s	1.94	2.00	2.05	1.69	1.65	1.78	1.97	1.99	1.97	2.03	2.01	2.07
	CH_2CH_3	q, 7	4.04	4.08	4.12	3.87	3.89	3.96	4.05	4.03	4.06	4.14	4.09	4.14
	CH_2CH_3	t, 7	1.19	1.23	1.26	0.94	0.92	1.04	1.20	1.17	1.20	1.26	1.24	1.24
ethylene	CH_2	s	5.36	5.40	5.40	5.25	5.25	5.29	5.38	5.41	5.41	5.40	5.39	5.44
ethylene glycol	CH_2	s[e]	3.48	3.66	3.76	3.36	3.41	3.58	3.28	3.34	3.51	3.72	3.59	3.65
H grease[f]	CH_3	m	0.85–0.91	0.84–0.90	0.84–0.87	0.89–0.96	0.90–0.98	0.86–0.92	0.90	0.82–0.88		0.88–0.94	0.86–0.93	
	CH_2	br s	1.29	1.27	1.25	1.33	1.32	1.30	1.29	1.24		1.33	1.29	
hexamethylbenzene	CH_3	s	2.18	2.20	2.24	2.10	2.13	2.10	2.17	2.14	2.19	2.24	2.19	
n-hexane	CH_3	t, 7	0.89	0.89	0.88	0.88	0.89	0.85	0.88	0.86	0.89	0.91	0.90	
	CH_2	m	1.29	1.27	1.26	1.22	1.24	1.19	1.28	1.25	1.28	1.31	1.29	
HMDSO	CH_3	s	0.07	0.07	0.07	0.10	0.12	0.10	0.07	0.06	0.07	0.08	0.07	0.28
HMPA	CH_3	d, 9.5	2.58	2.60	2.65	2.42	2.40	2.47	2.59	2.53	2.57	2.63	2.64	2.61
hydrogen	H_2	s	4.55	4.59	4.62	4.50	4.47	4.49	4.54	4.61	4.57	4.53	4.56	
imidazole	CH(2)	s	7.48	7.63	7.67	7.30	7.33	7.53	7.62	7.63	7.57	7.61	7.67	7.78
	CH(4,5)	s	6.94	7.07	7.10	6.86	6.90	7.01	7.04	7.01	7.01	7.03	7.05	7.14
methane	CH_4	s	0.19	0.21	0.22	0.17	0.16	0.15	0.17	0.20	0.20	0.18	0.20	0.18
methanol	CH_3	s[g]	3.27	3.42	3.49	3.03	3.07	3.25	3.31	3.16	3.28	3.44	3.34	3.34
	OH	s[c,g]	3.02	1.09	1.09			1.30	3.12	4.01	2.16			
nitromethane	CH_3	s	4.31	4.31	4.33	3.01	2.94	3.59	4.43	4.42	4.31	4.28	4.34	4.40
n-pentane	CH_3	t, 7	0.89	0.89	0.88	0.87	0.87	0.84	0.88	0.86	0.89	0.90	0.90	
	CH_2	m	1.31	1.30	1.27	1.25	1.23	1.23	1.27	1.27	1.29	1.33	1.29	
propane	CH_3	t, 7.3	0.90	0.90	0.90	0.89	0.86	0.84	0.88	0.87	0.90	0.90	0.91	0.88
	CH_2	sept, 7.3	1.33	1.32	1.32	1.32	1.26	1.26	1.31	1.29	1.33	1.33	1.34	1.30
2-propanol	CH_3	d, 6	1.08	1.17	1.22	0.95	0.95	1.04	1.10	1.04	1.09	1.20	1.50	1.17
	CH	sept, 6	3.82	3.97	4.04	3.65	3.67	3.82	3.90	3.78	3.87	4.05	3.92	4.02
propylene	CH_3	dt, 6.4, 1.5	1.69	1.71	1.73	1.55	1.55	1.58	1.68	1.68	1.70	1.70	1.70	1.70
	$CH_2(1)$	dm, 10	4.89	4.93	4.94	4.92	4.95	4.91	4.90	4.94	4.93	4.93	4.91	4.95
	$CH_2(2)$	dm, 17	4.99	5.03	5.03	4.98	5.01	4.98	5.00	5.03	5.04	5.03	5.01	5.06
	CH	m	5.79	5.84	5.83	5.70	5.72	5.72	5.81	5.80	5.85	5.87	5.82	5.90
pyridine	CH(2,6)	m	8.54	8.59	8.62	8.47	8.53	8.51	8.58	8.58	8.57	8.45	8.53	8.52
	CH(3,5)	m	7.25	7.28	7.29	6.67	6.66	6.90	7.35	7.39	7.33	7.40	7.44	7.45
	CH(4)	m	7.65	7.68	7.68	6.99	6.98	7.25	7.76	7.79	7.73	7.82	7.85	7.87
pyrrole	NH	br t	9.96	8.69	8.40	7.71	7.80	8.61	10.02	10.75	9.27			
	CH(2,5)	m	6.66	6.79	6.83	6.43	6.48	6.62	6.77	6.73	6.75	6.84	6.72	6.93
	CH(3,4)	m	6.02	6.19	6.26	6.27	6.37	6.27	6.07	6.01	6.10	6.24	6.08	6.26
pyrrolidine[h]	$CH_2(2,5)$	m	2.75	2.82	2.87	2.54	2.54	2.64		2.67	2.75	3.11	2.80	3.07
	$CH_2(3,4)$	m	1.59	1.67	1.68	1.36	1.33	1.43		1.55	1.61	1.93	1.72	1.87
silicone grease	CH_3	s	0.11	0.09	0.07	0.26	0.29	0.14	0.13	−0.06	0.08	0.16	0.10	
tetrahydrofuran	$CH_2(2,5)$	m	3.62	3.69	3.76	3.54	3.57	3.59	3.63	3.60	3.64	3.78	3.71	3.74
	$CH_2(3,4)$	m	1.79	1.82	1.85	1.43	1.40	1.55	1.79	1.76	1.80	1.91	1.87	1.88
toluene	CH_3	s	2.31	2.34	2.36	2.11	2.11	2.16	2.32	2.30	2.33	2.33	2.32	
	CH(2,4,6)	m	7.10	7.15	7.17	6.96–7.01	7.02	7.01–7.08	7.10–7.20	7.18	7.10–7.30	7.10–7.30	7.16	
	CH(3,5)	m	7.19	7.24	7.25	7.09	7.13	7.10–7.17	7.10–7.20	7.25	7.10–7.30	7.10–7.30	7.16	
triethylamine	CH_3	t, 7	0.97	0.99	1.03	0.95	0.96	0.93	0.96	0.93	0.96	1.31	1.05	0.99
	CH_2	q, 7	2.46	2.48	2.53	2.39	2.40	2.39	2.45	2.43	2.45	3.12	2.58	2.57

[a] Except for the compounds in solutions 8–10, as well as the gas samples, hexamethylbenzene, and the corrected values mentioned in the Supporting Information, all data for the solvents $CDCl_3$, C_6D_6, $(CD_3)_2CO$, $(CD_3)_2SO$, CD_3CN, CD_3OD, and D_2O were previously reported in ref 2. [b] A signal for HDO is also observed in $(CD_3)_2SO$ (3.30 ppm) and $(CD_3)_2CO$ (2.81 ppm), often seen as a 1:1:1 triplet ($^2J_{H,D}$ = 1 Hz). [c] Not all OH signals were observable. [d] In some solvents, the coupling interaction between the CH_2 and the OH protons may be observed (J = 5 Hz). [e] In CD_3CN, the OH proton was seen as a multiplet at 2.69 ppm, as well as extra coupling to the CH_2 resonance. [f] Apiezon brand H grease. [g] In some solvents, a coupling interaction between the CH_3 and the OH protons may be observed (J = 5.5 Hz). [h] Pyrrolidine was observed to react with $(CD_3)_2CO$.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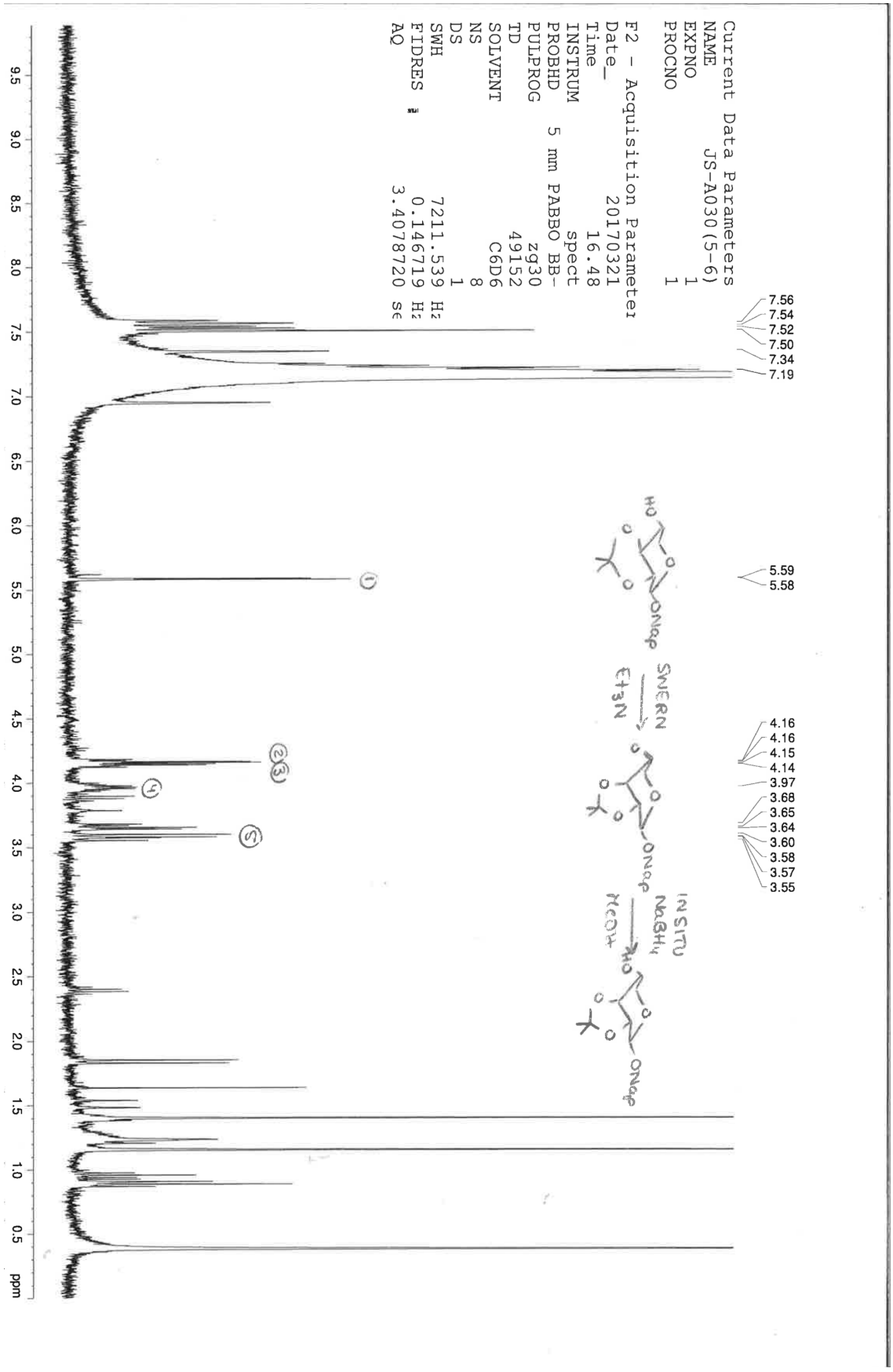
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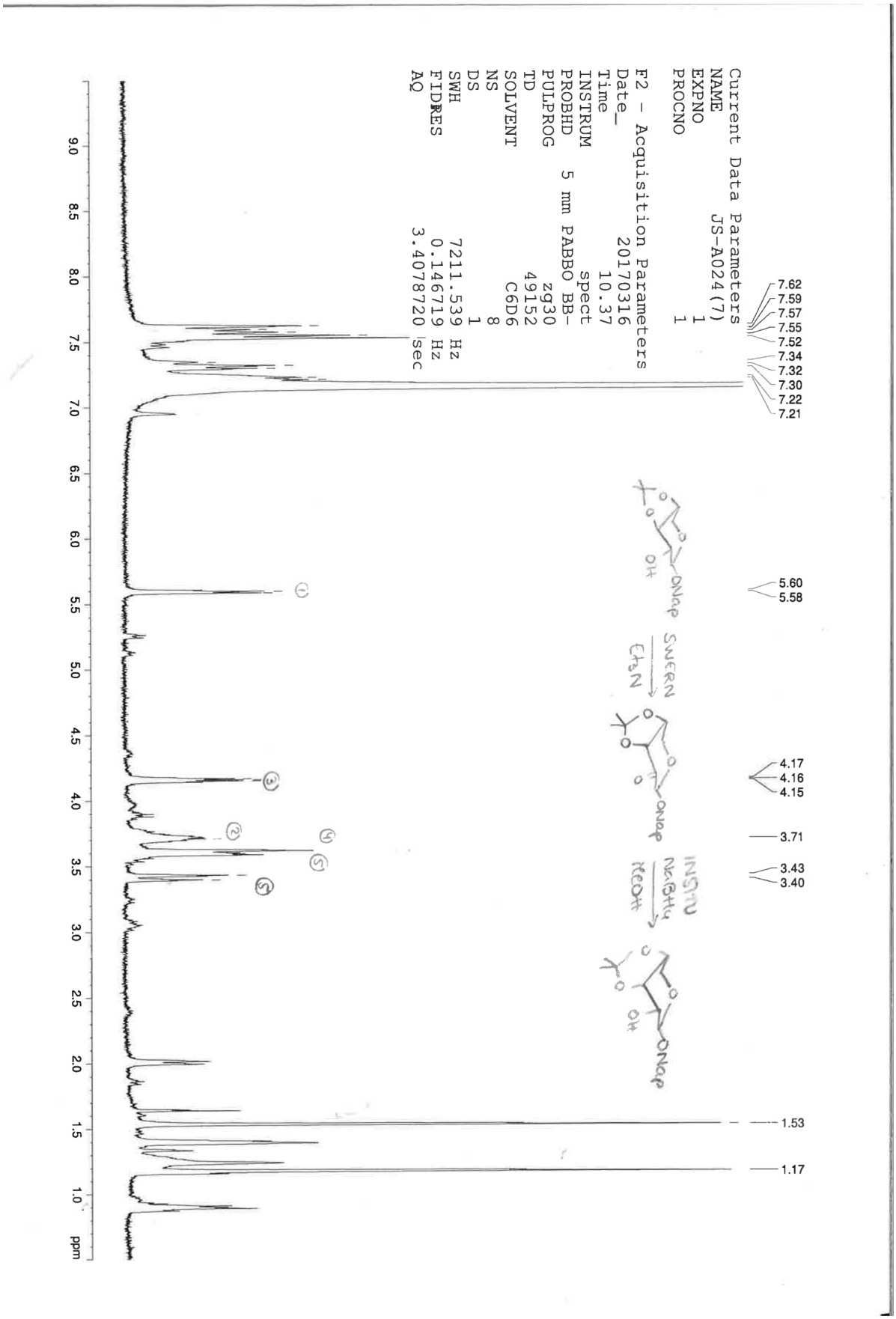
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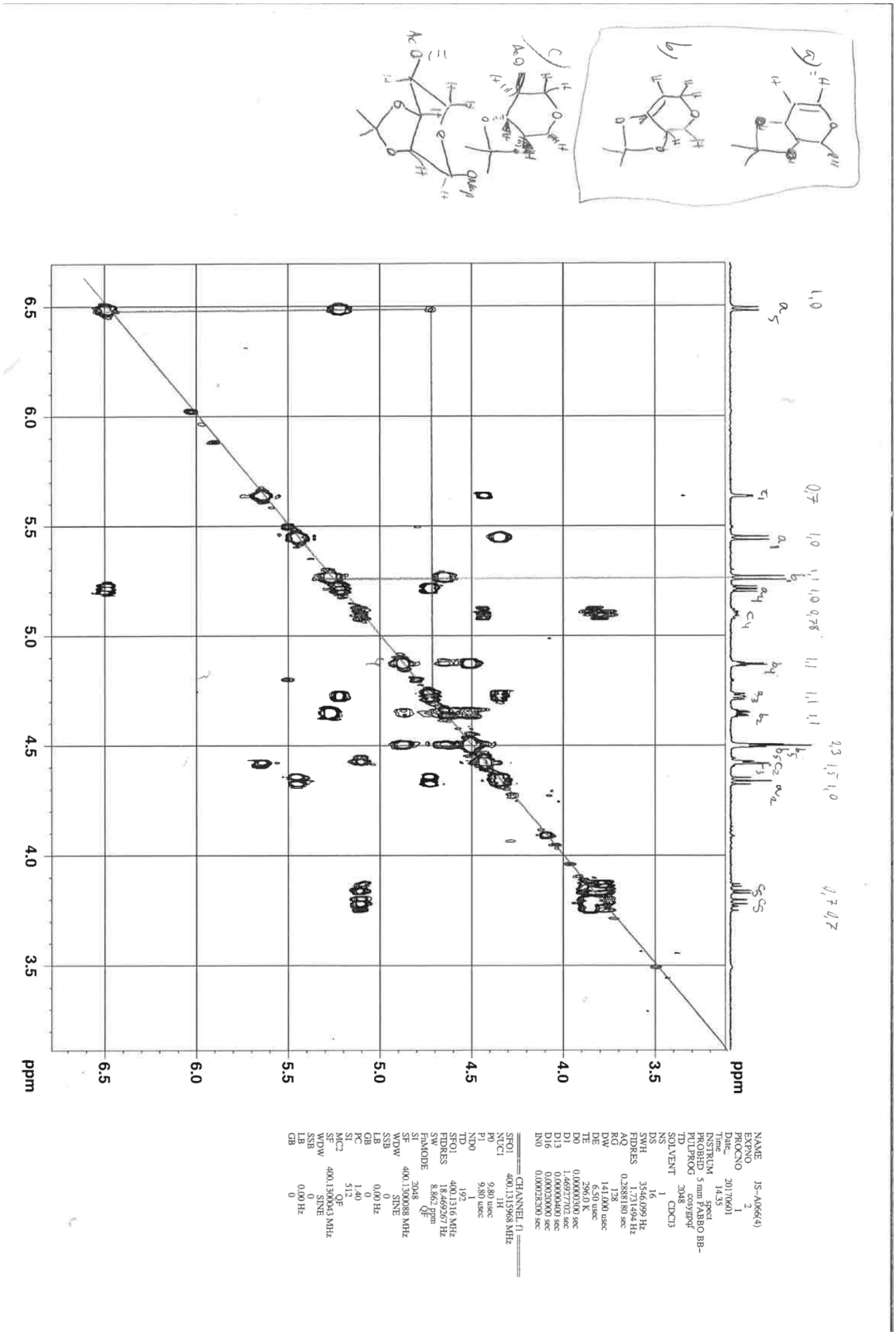
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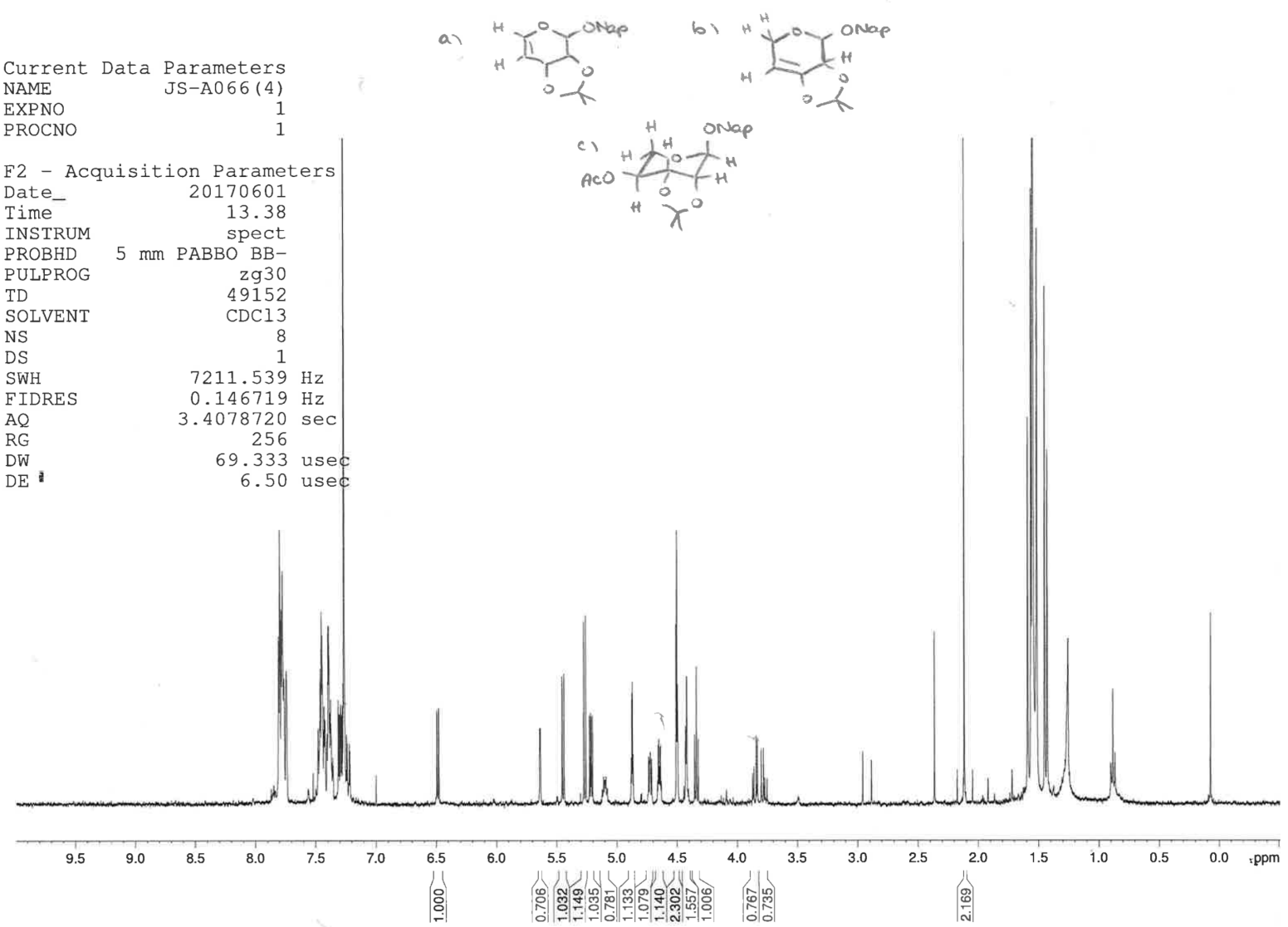
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b)
c)
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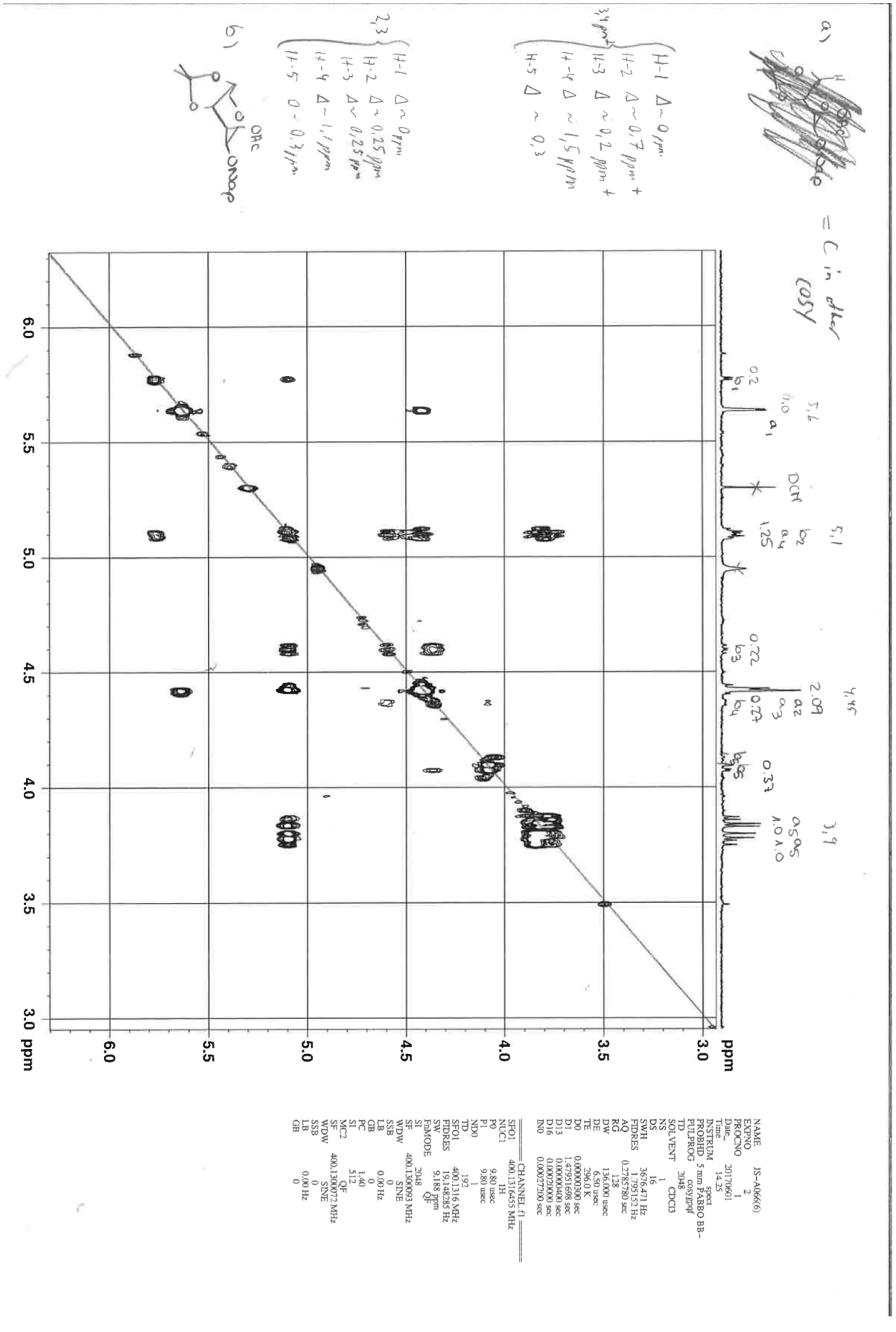
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cosy
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H-2 Δ~0,7 ppm +
3,4 ppm
H-3 Δ ~ 0,2 ppm +
H-4 Δ ~ 1,5 ppm
H-5 Δ ~ 0,3
2,3
H-1 Δ ~ 0,1ppm
H-2 Δ ~ 0,25 ppm
H-3 Δ ~ 0,25 ppm
H-4 Δ ~ 1,1 ppm
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b)
OAc
OAc
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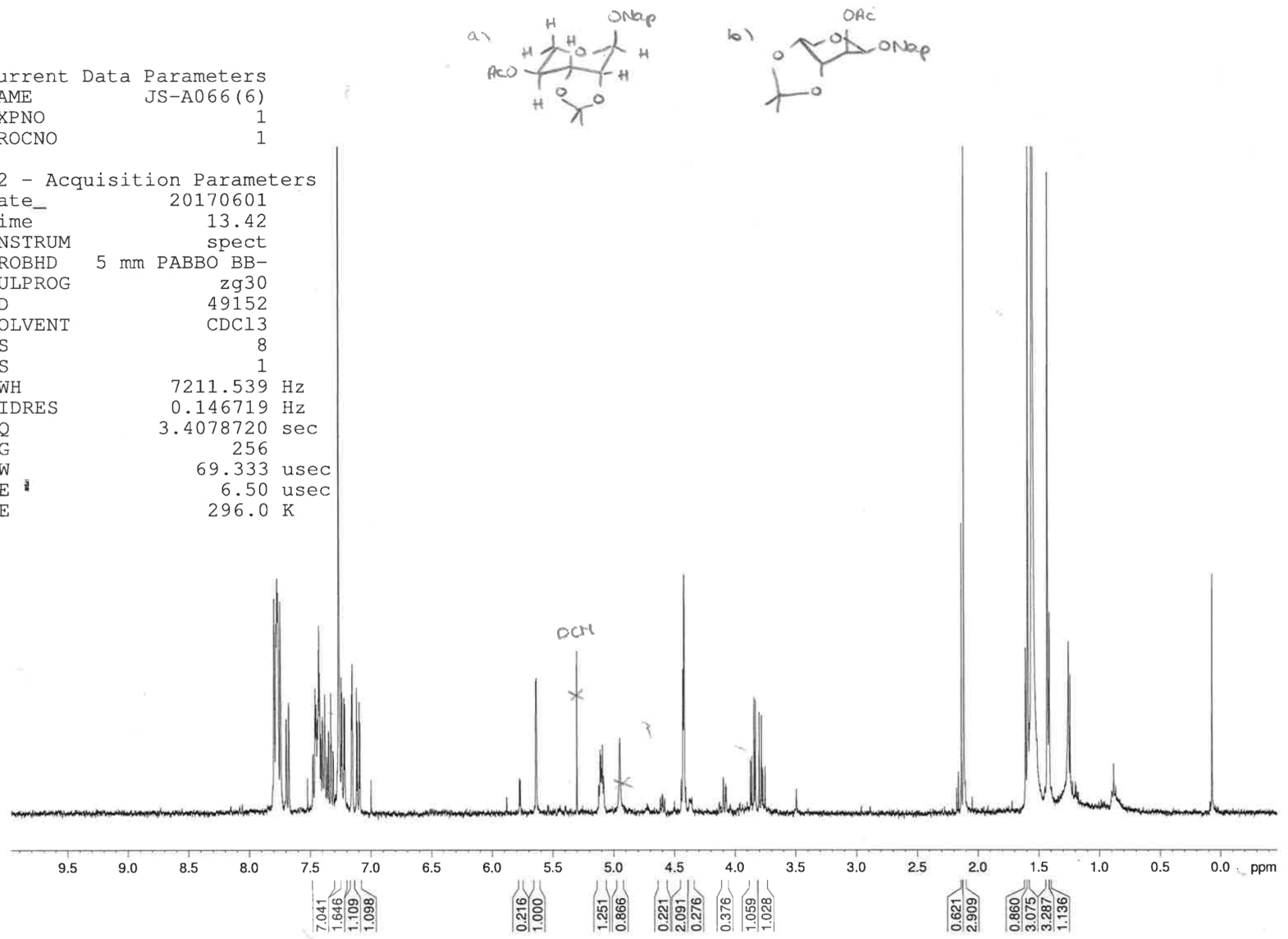
IN0 0.00027300 sec
======== CHANNEL f1 ========
SFO1 400.1316455 MHz
NUC1 1H
P0 9.80 usec
P1 9.80 usec
NDO 1
TD 192
SFO1 400.1316 MHz
FIDRES 19.148285 Hz
SW 9.188 ppm
FnMODE QF
SI 2048
SF 400.1300093 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
SI 512
MC2 QF
SF 400.1300073 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0


a)
ONap
AcO
b)
OAc
ONap
Current Data Parameters
NAME JS-A066(6)
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170601
Time 13.42
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 8
DS 1
SWH 7211.539 Hz
FIDRES 0.146719 Hz
AQ 3.4078720 sec
RG 256
DW 69.333 usec
DE 6.50 usec
TE 296.0 K
DCM
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
7.041 1.646 1.109 1.098
0.216 1.000
1.251 0.866
0.221 2.091 0.276
0.376
1.059 1.028
0.621 2.909
0.860 3.075 3.287 1.136