Arabinofuranose 1-Deoxy-β-1-*C*-Sulfonic Acid

by

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ABSTRACT OF THE THESIS

ARABINOFURANOSE 1-DEOXY-β-1-*C*-SULFONIC ACID

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Thesis Director:

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Utilizing the tools of bioisosteres, we were able to rationally design a sulfonic acid that can possibly mimic the natural arabinosyltransferase donor, β-1,2-*cis*-decaprenolphoarabinose. The sulfur replacement provides a more enzymatically stable donor that can possibly inhibit the actions of arabinosyltransferases upon binding and thus prevent the biosynthetic pathway of the arabinogalactan cell wall that is essential to the viability of *Mycobacterium* tuberculosis. We have successfully synthesized β-1-*C*-sulfonic acid from a new 1-thio-$_D$-arabinofuanose acetate. Incorporating the ideas from previously published routes to the key intermediates, we describe the successes and failures in our approach to the target sulfonic acid. The route includes a useful method of oxidizing acid-sensitive substrates.

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List of Abbreviations

ACN	acetonitrile
AcOH	acetic acid
Ac_2O	acetic anhydride
AG	arabinogalactan
Ara_f	arabinofuranose
Bn	benzyl
BnBr	benzyl bromide
Bz	benzoyl
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
DCE	dichloroethane
DCM	dichloromethane
DMDO	dimethyldioxirane
DMF	dimethylformamide
DNA	deoxyribonucleic acid
DPA	decaprenolphosphoarabinose
EMB	ethambutol
ESI	electrospray ionization
EtOAc	ethylacetate
EtOH	ethanol
Gal_f	galactofuranose
HBr	hydrogen bromide

HCl	hydrogen chloride
Hex	hexanes
H_2SO_4	sulfuric acid
IC_{50}	50% inhibitory concentration
INH	isoniazid
KSAc	potassium thioacetate
LAM	lipoarabinomannan
MeOH	methanol
MIC	minimal inhibiting concentration
µg	microgram
MHz	megahertz
mL	milliliter
mM	millimolar
mmol	millimoles
mRNA	messenger ribonucleic acid
MS	mass spectrometer
NaH	sodium hydride
NaOMe	sodium methoxide
nM	nanomolar
NMR	nuclear magnetic resonance
Pd-C	palladium on carbon
py	pyridine
R_f	retention factor

RIF	rifampin
RNA	ribonucleic acid
r.t.	room temperature
pH	- log of $[H^+]$
PZA	pyrazinamide
SiO_2	silicon dioxide
$SOCl_2$	thionyl chloride
TB	tuberculosis
TEA	triethylamine
TLC	thin layer chromatography
TMS-Br	trimethylsilyl bromide

Chapter 1. Introduction

1.1 Bioisosteres

Bioisosterism is an approach used by medicinal chemists to rationally modify lead compounds to find a compound with better overall biological profile. Bioisosteres are broken down into two categories: classical and nonclassical. Classical bioisosteres follow the original isostere ideas of Grimm, H.G., and Erlenmeyer, H. Grimm's law states: "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right." Erlenmeyer then added to Grimm's Law with isosteres as being atoms, ions, and molecules with the same number of peripheral layers of electrons. Unlike the classical bioisosteres, nonclassical bioisosteres do not follow these ideas. These modifications mimic the biological spatial arrangement, electronic properties, and/or physicochemical properties of a group or molecule in order to maintain similar, modified, or enhanced biological activities.[1]

1.2 Phosphates / Phosphonates

Phosphonate mimics of phosphate groups are one example where bioisosteres have proven useful. Replacing the linking oxygen in phosphates with a methylene to form a phosphonate provides a more hydrolytically stable

bond. In nature, many glycosides contain glycosidic bonds to phosphates. Phosphate groups play important roles in a variety of biological processes. Decaprenol-P-β-arabinofuranose is naturally occurring donor substrate involved in the biosynthesis of the *Mycobacterium tuberculosis'* arabinogalactan cell wall. Lowary's group has synthesized mimics of this phosphate donor, including most notably an active *C*-phosphonate donor analogue.

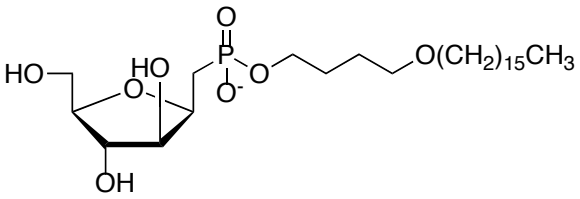


Fig 1.1 Example of an active *C*-phosphonate donor analogue.[2]

This potent analogue was tested in vitro for the ability to prevent growth of *Mycobacterium tuberculosis* strain H_{37}Rv and was shown to have an MIC of 3.13 μg/ml. Rational designs such as this C-phosphonate analogue demonstrate the potential of bioisosteres.[2]

Bioisosteres can also address issues of cellular bioavailability. Phosphates and phosphonates are highly charged dianionic species that may cause poor cellular permeability. Carboxylates have been used as bioisosteres of phosphorus functional groups to provide an alternative phosphate-like electrostatic interactions, but improved cellular bioavailability. Conversely, phosphonate groups can be used as bioisosteres of carboxylates when a stronger electrostatic interaction is desired. Recent work done in Wong's group

describes a phosphonate mimic of the important influenza drug Tamiflu, which contains an esterified carboxylate group, to increase the potency of the anti-influenza activity (Table 1.1). Tamiflu undergoes in vivo hydrolysis to the oseltamivir, exposing the active carboxylate group.

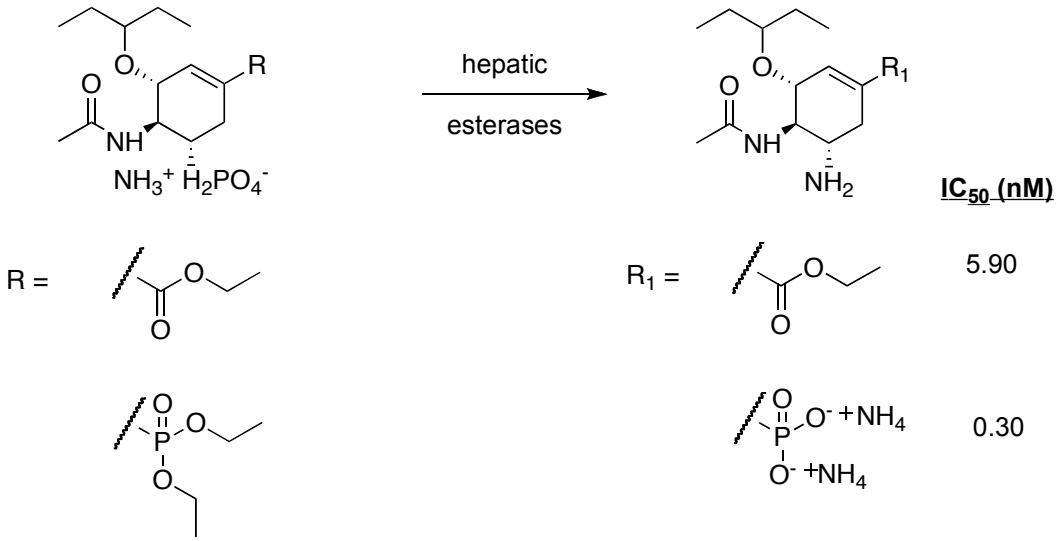


Table 1.1 Inhibition activity of the phosphonate analogue versus oseltamivir.[4]

The phosphonate mimic is nearly 18 folds more potent than oseltamivir against wild-type influenza virus neuraminidases.[4]

1.3 *Mycobacterium tuberculosis*

Inhibitory biomimetics associated with *Mycobacterium tuberculosis* could prove to have important applications in tuberculosis (TB) treatment. The latest global estimates from 2002 reveal that roughly 24,000 people developed an active form of the disease, and close to 5,000 people died from tuberculosis, every day. The situation is exacerbated because TB often coinfects with HIV,

and nearly 31% of AIDS deaths are caused by TB. Further, multidrug-resistant strains of *Mycobacterium tuberculosis* have emerged. Currently, the best available treatment is a cocktail of drugs (Figure 1.2) that includes isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). However, it can take up to 12 weeks to determine any resistance to these drugs. The need to improve drug delivery with new antituberculars is apparent.[5]

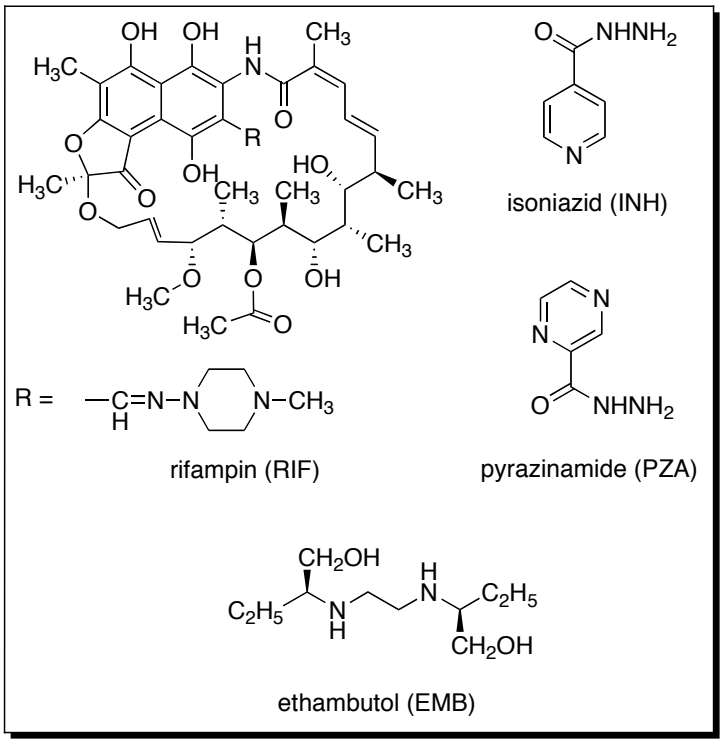


Fig 1.2 Current compounds used for treatment of *Mycobacterium tuberculosis*.[5]

	Mechanism of Action
Rifampin[6]	- inhibits DNA-dependent RNA polymerase, thus preventing mRNA transcription
Isoniazid[7]	- inhibits synthesis of mycolic acids
Pyrazinamide[8]	- inhibits the fatty acid synthesizing enzyme which prevents the bacteria to grow
Ethambutol[9]	- unknown

Table 1.2 Mechanisms of actions for the current treatments of *Mycobacterium tuberculosis.*

Among the current treatments, the mechanism of action for EMB is still unknown. However, it is suggested that EMB is responsible for reducing the amount of arabinan in the biosynthesis of the cell wall.[9] The ability of the organism to synthesize its complicated cell wall is required for *Mycobacterium tuberculosis* viability. The cell wall of the mycobacteria mainly consists of the polysaccharides arabinogalactan (AG) and lipoarabinomannan (LAM). Both are arabinan-containing polysaccharides that differ in their location and role in the cell wall. The AG is known to be in the core of the cell wall, and to provide the central support system for the cell wall. The LAM, which is known to be anchored in the cell membrane, is the major antigenic part of the cell wall. Figure 1.3 shows the biosynthetic pathway of the arabinogalactan cell wall core in *Mycobacterium tuberculosis*.[10]

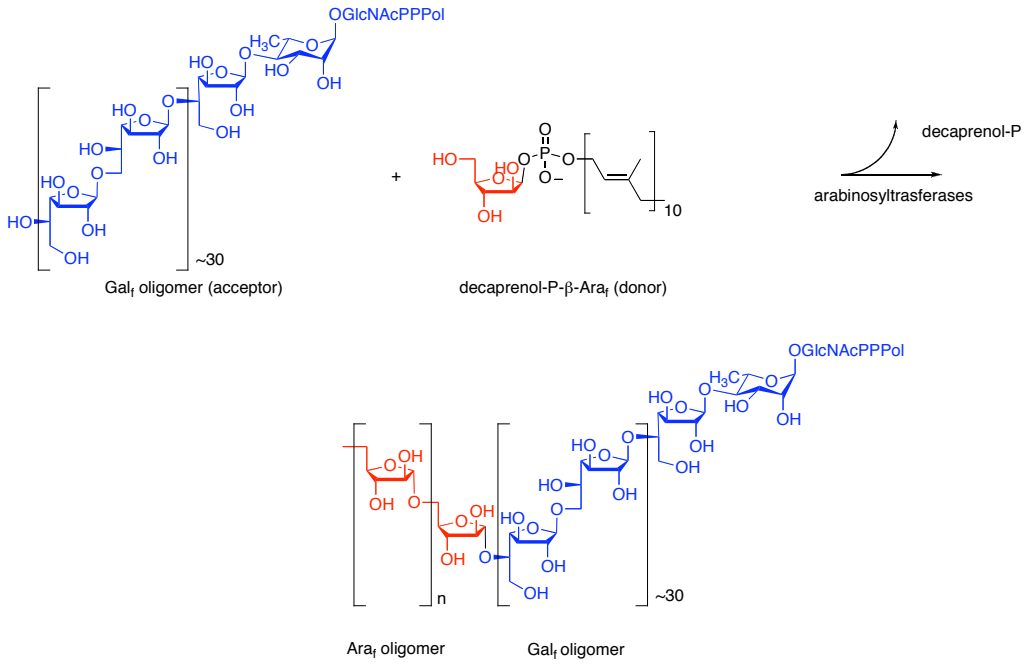


Fig 1.3 Biosynthetic pathway of arabinofuranoside polysaccharide in the AG.[10]

The arabinosyltransferases binds the β-1,2-cis-decaprenolphosphoarbinose donor with the galactofuranose oligomer acceptor in the enzyme active site. The donor is then transferred to the acceptor (with loss of the decreprenolphosphoryl group) to form another oligomer acceptor capable of continuing the construction of the arabinogalactan cell wall. Targeting and inhibiting this biosynthetic pathway may represent a mean for eliminating new incidences of TB. EMB might be working as either an inhibitor of the arabinosyltransferases, which are responsible for the biosynthesis of AG & LAM, or of an arabinase-type enzyme that can cleave the arabinan in the cell wall as it is biosynthesizing.[11]

1.4 Possible Mimic of DPA Donor

Mimics of the naturally occurring glycotransferase acceptors have been explored extensively; however, the donor mimics have not been explored as widely, inasmuch as a particular glycosyl donor might be a substrate for a number of glycosyltransferases. Mimics of the decaprenolphosphoarbinose donor can potentially block specific biosynthetic steps and thus might prove to be potent antibacterial agents. By considering the ideas of bioisostereoisomerism as well as what we know so far about possible EMB's mechanism of action, we propose an arabinofuranose sulfonate DPA donor mimic. Here we describe the synthesis of this new compound (Figure 1.4). The sulfonate differs from the natural donor in that it is missing an atom bridging the oxido negative charge to

the furanoses, is singly charged, and is lacking in the leaving group. It is expected, however, to be completely resistant to phosphatases.

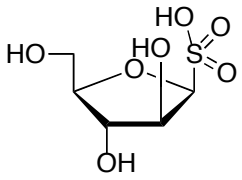


Fig 1.4 Sulfonic acid arabinofuranoside phosphate donor mimic.

Currently, there is great interest in bioorgano sulfur chemistry, including specifically the replacement of the oxygen of the glycosidic bond with sulfur to provide thioglycosides-based inhibitors. The sulfur atom replacement conveys stability against acid/base and enzyme degradation. Applications of thioglycosides include the syntheses of several α-linked thioglycosides as potential anti-HIV agents in either CEM or MT-2 cells (Table 1.3).

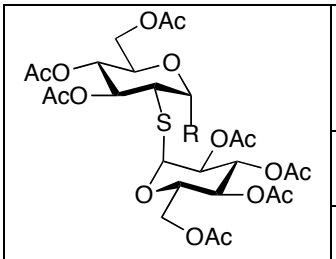
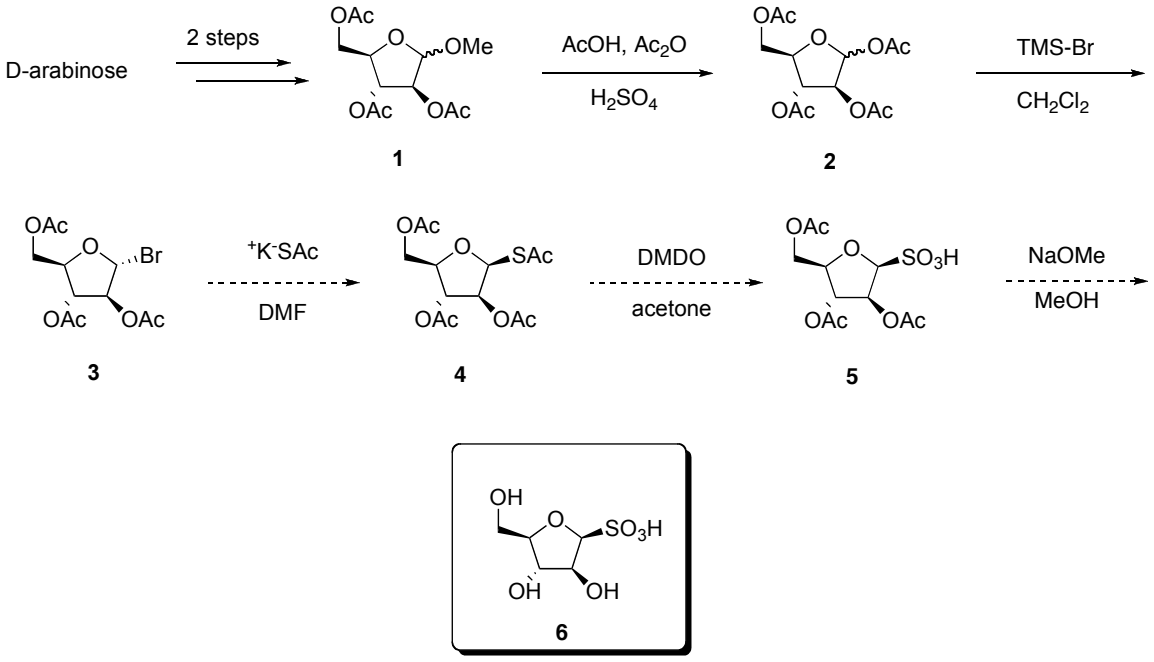
	**R**	**IC50 (ug/mL)**	
		CEM	MT-2
	OAc	51.4	8.0
	SAc	48.0	-

Table 1.3 Results of inhibition activity in CEM cells.[12]

The simple replacement of the anomeric oxygen with sulfur increases the activity in CEM cells, cell line derived from human T cells. The activity in MT-2 cells, a type of adult T-cell leukemia, is negligible.[12]

Chapter 2. Attempted Routes to the Anomeric Thioacetate

2.1 Initial Efforts to the β-Thioacetate



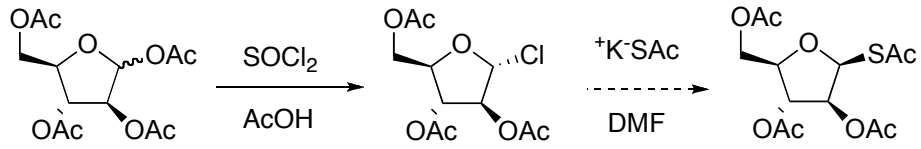
Scheme 2.1 Initial route to the target β-1-*C*-sulfonic acid[14,15,16]

The planned route, (Scheme 1.1), began with the commercially available D(+)-arabinose sugar. Acetylated methyl glycoside **1** was synthesized in two steps following literature procedures, and produced a mixture of α and β anomers. Due to the difficulty of separating the anomers, **1** was carried on as a mixture to the anomeric acetate **2**, which was isolated as predominately the α-anomer (10:1 α:β). The α-bromide **3**, is formed exclusively upon substitution promoted by TMS-Br. Due to the instability of **3**, the bromination reaction mixture was concentrated in vacuo and subjected directly to the nucleophilic

displacement reaction with KSAc in DMF. TLC and ^{1}H of the crude reaction mixture indicated no product after 12 h. Instead only the starting anomeric acetate **2** and the corresponding reducing sugar (anomeric -OH) was recovered.

2.2 Attempt to Displace the Anomeric Chloride

Given the possible stability issue of the anomeric bromide we looked into a more stable halide, the anomeric chloride **5**. Following literature procedures, **5** was synthesized from **2** by treatment with thionyl chloride and acetic acid. TLC analysis showed a streaking lower R_f product, and only traces of **2**. The instability of the anomeric chloride on silica could explain the streaking TLC. According to ^{1}H NMR analysis of the crude reaction mixture, mainly the α-anomer is formed. Without any purification, the crude product was subjected to the nucleophilic displacement conditions used previously (Scheme 1). The reaction again yielded almost equal amounts of the starting anomeric acetate **3** and the reduced sugar.

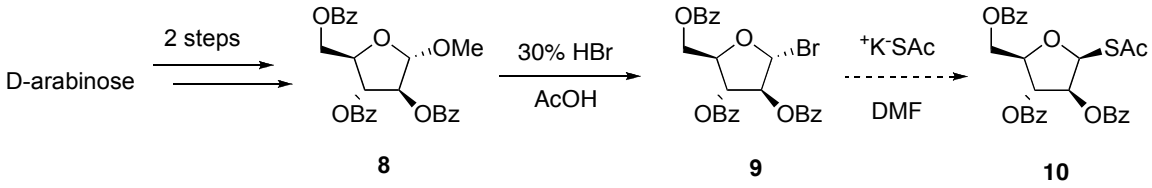


2 **7** **4**

Scheme 2.2 Synthesis of a more stable anomeric chloride[15,17]

2.3 Utilizing Benzoyl Protecting Group

Unable to detect any trace of the desired thioacetate from either halides **3** or **5**, we turned our attention to an alternate, bulkier protected halide intermediate, the benzoyl protected bromide **9**. This route was one step shorter in that the halogenation could be done on the anomeric methyl glycoside, **8**, directly. Further, **8**, was cleanly isolated in pure form by crystallization from the mixture of α and β-anomeric methyl glycosides. By following published procedures, we brominated **8** by using 30% HBr in glacial acetic acid to afford mainly the α-bromide **9**, without the need for any further purification. However, the stability of **9** was an issue in that after storage of the bromide in the refrigerator overnight, TLC analysis showed an increase in the reducing sugar. Therefore, immediately after concentration of the bromination reaction in vacuo, the crude bromide was subjected to the nucleophilic displacement reaction with KSAc in DMF. According to the ^{1}H NMR spectrum of the crude product, the reaction gave only the α-thioacetate and the reducing sugar with no traces of the β-thioacetate **10**. This suggests that the nucleophilic substitution is not undergoing the desired S_N2 pathway exclusively, but rather there is significant S_N1 conversion. The resulting C-1,2-*trans* thioglycoside (the α-thioacetate) would be the more stable anomer. The dissociation is most likely due the to acyl participation at C-1 by the C-2 *O*-benzoate. This can also explain the instability issues of the chloride and bromide in the *O*-Ac protected substrates previously presented.

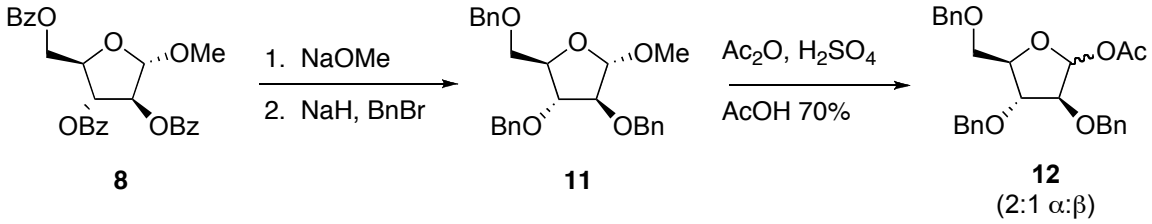


Scheme 2.3 Synthesis of benzoyl protecting group[15,18,19]

Chapter 3. Utilizing a Non-acyl Protecting Group

3.1 Route to the Benzyl Protected Thioacetate

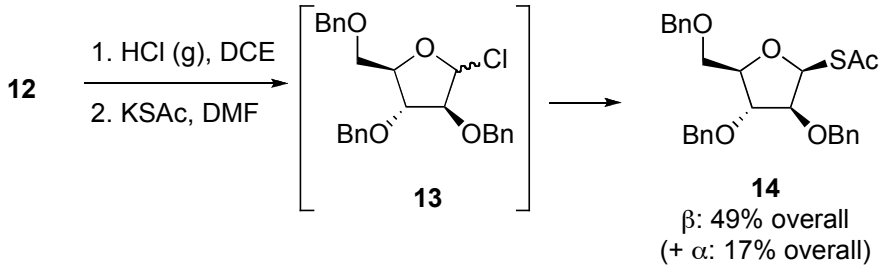
Based on previously published procedures, the plan was to go from the pure benzyl protected α-OMe glycoside **8** to the benzyl protected α-OMe glycoside **11**. The procedure involves the deprotection of the benzoates and then protecting with benzyl bromide which affords an almost quantitative yield of **11**. Acetylation from **11** to the anomeric acetate **12**, produced a 2:1 α:β mixture. We found that it was critical to use catalytic amount of sulfuric acid in the acetylation reaction for optimal yield.



Scheme 3.1 Conversion to the benzyl protected anomeric acetate[14,20]

By using recent procedures from the Lowary group, the anomeric acetate was chlorinated to give predominately the α-chloride **13**, which was carried on as

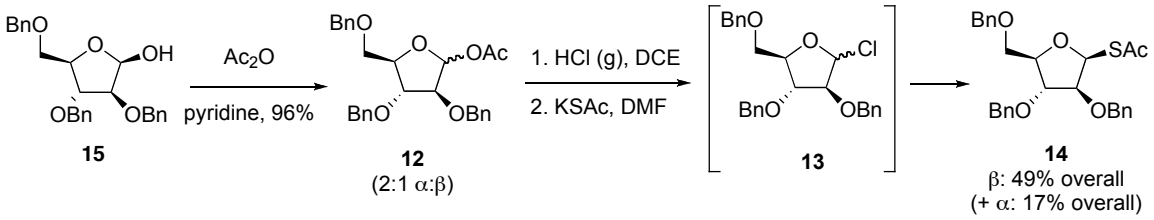
the crude product to the displacement reaction without any further purification. Chlorination entailed bubbling in HCl gas into a solution of anomeric acetate **12** in dichloroethane at room temperature until all the anomeric acetate was consumed. Once the starting material was consumed, the reaction mixture was concentrated in vacuo to afford a light yellow syrup. The crude chloride was dissolved in dry DMF then cannulated over to a flask containing KSAc dissolved in minimal amount of dry DMF. After 12 h of reaction time, the reaction mixture was quenched and chromatographed to give almost 50% overall yield of the β-thioacetate **14** along with 17% of the α-thioacetate (Scheme 2.2).



Scheme 3.2 Successful synthesis of the β-thioacetate[15,22]

3.2 Reducing Sugar as the Late Stage Intermediate

Starting from the commercially available benzyl protected arabinofuranoside **15**, acetylation at the anomeric position yielded almost quantitative amount of the anomeric acetate **12**. This improved the overall yield of the desired β-thioacetate **14** (Scheme 2.3). Thioacetate **14** was characterized by mass spectroscopy and ^{1}H and ^{13}C NMR analysis (Figure 6.3 & 6.4).

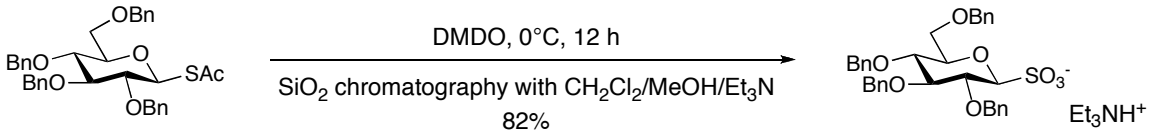


Scheme 3.3 Facile synthesis from commercially available reduced sugar[15,20,23]

Chapter 4. Oxidation to the Sulfonic Acid

4.1 Early Attempts at Oxidation

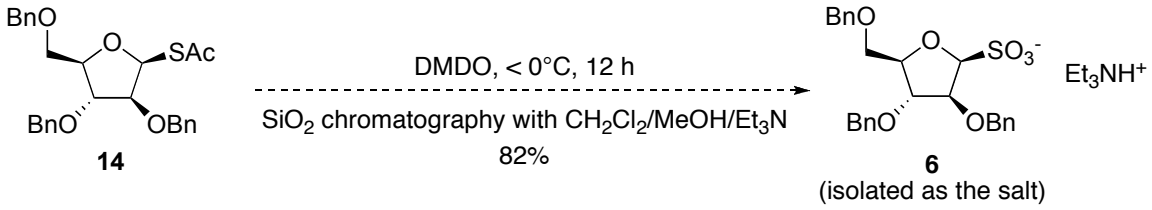
Furanosyl anomeric sulfonic acids are not known. However, the Knapp group has recently published an oxidation method (Scheme 4.1) taking *S*-acetyl-1-thiopyranoses to the corresponding sulfonic acids using dimethyldioxirane (DMDO).



Scheme 4.1 Published synthesis of 1-*C*-sulfonate using DMDO[16]

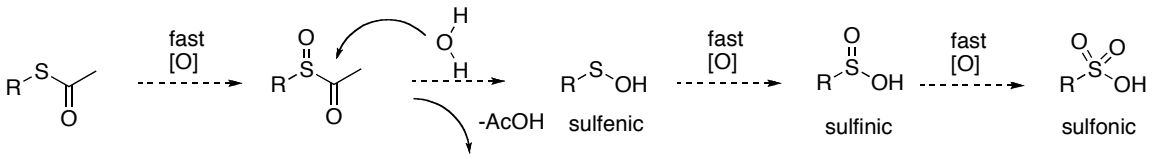
By using this method for oxidation, we attempted to transform thioacetate **14** to the target sulfonic acid **6**. DMDO was freshly prepared according to published procedures using oxone, sodium bicarbonate, acetone, and water. The starting thioacetate **14** was dissolved in freshly prepared DMDO solution in acetone at 0 °C, and was allowed to react overnight. TLC analysis of the reaction mixture the following day showed only the reducing sugar and small

amounts of the starting material. Repeated attempts at this oxidation at lower temperatures or with excess DMDO resulted in nothing more than the reduced sugar, and no more than slight traces of baseline material (possibly the desired product).



Scheme 4.2 Initial attempt of DMDO oxidation[16]

The presumed mode of action of DMDO on the thioacetate involves as many as three oxidations. The initial oxidation should be quick, forming an intermediate that is readily attacked by water to eliminate acetic acid and form the sulfenic acid. Then the second oxidation proceeds to form the sulfinic acid followed by the third oxidation to form the desired sulfonic acid (Scheme 3.3).



Scheme 4.3 Possible mechanism for DMDO oxidation[23]

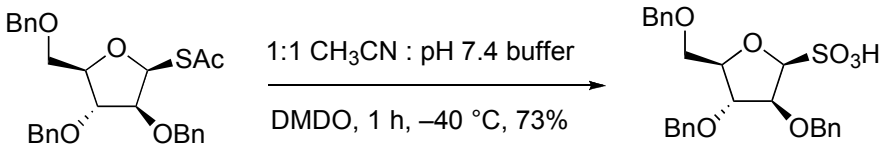
TLC analysis of the reaction mixture reveals that a product with an R_f slightly lower than that of the reducing sugar forms immediately after addition of DMDO in acetone. As the reaction continues, the reducing sugar becomes more

prominent on the TLC plate. The question as to whether the acidic condition lead to protonation of a sulfonic or sulfonic oxygen and thus elimination prior to the formation of the sulfonic acid is not answered by this experiment. It is evident from TLC analysis, however, that during the reaction the sulfonic acid never forms in large amounts. Assuming that more basic pH is needed for the sulfonic acid formation occur, we explored the conditions described by Shi's group to do asymmetric catalytic epoxidations under basic conditions. They reported epoxidations using chiral dioxiranes at increased pH, compared to their initial pH conditions, to improve the conversions to acid sensitive epoxides.

4.2 Successful Oxidation with a Basic Phosphate Buffer

Here we describe a higher pH method for oxidation of **14** to the sulfonic acid. By using sodium phosphate dibasic buffer at pH 7.4, the β-sulfonic acid **15** was formed in nearly 75% yield. The β-thioacetate was dissolved in a 1:1 mixture of CH_3CN and the phosphate buffer, and was treated with DMDO in acetone solution at -40 °C. The reaction mixture was stirred for 3 h to afford mainly the desired sulfonic acid with little if any of the reducing sugar. It was found that even after an hour, most of the sulfonic acid had formed in the same overall yield. Further, the resulting sulfonic acid was cleanly isolated by flash chromatography, as the free acid instead of the Et_3NH^+ salt, by eluting with 9:1 CH_2Cl_2 / MeOH. The free acid is apparently relatively stable since it can be stored for days in the freezer without any decomposition. Sulfonate **15** was

characterized by both mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy (Figure 6.5 & 6.6).

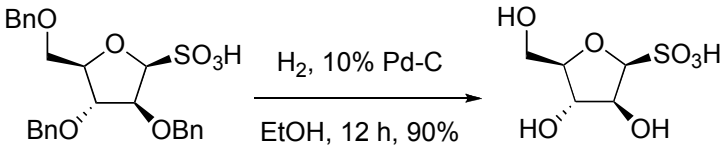


14 **15**

Scheme 4.4 Basic oxidation conditions using phosphate buffer[24]

4.3 Deprotection to the Target Sulfonic Acid

O-Benzyl's are removed by hydrogenation with palladium on carbon as the catalyst. Though divalent sulfur is known to poison the palladium catalyst, the sulfonic acid may not suffer from the same problem. The desired deprotected sulfonic acid should be highly water-soluble; therefore, ethanol was used for the deprotection step. A solution of the β-sulfonic acid **15** in EtOH was treated with a catalytic amount of 10% Pd-C. The reaction mixture was stirred overnight under an H_2 atmosphere. TLC analysis the following day indicated full consumption of the starting sulfonic acid **15**. The reaction mixture was filtered through a pad of celite, washed with EtOH a few times, and then concentrated in vacuo to yield a white solid. The ^{1}H NMR spectrum of the resulting solid showed cleanly deprotected desired triol product **6**. The yield of the reaction was exceptional at 90%. Sulfonate **6** was characterized by mass spectroscopy and ^{1}H and ^{13}C NMR analysis (Figure 6.1 & 6.2).



15 **6**

Scheme 4.5 Successful removal of the benzyl groups

Chapter 5. Experimental Procedures

5.1 Compound 12

To a solution of (1.0 g, 2.38 mmol) 2,3,5-tri-O-benzyl-α,β-D-arabinofuranose in 10 mL of pyridine was added 10 mL of acetic anhydride at 0°C. Reaction mixture was stirred at room temperature for 12 hrs. Reaction mixture was concentrated in vacuo. Flash chromatography (10:1 to 5:1 Hex / EtOAc) afforded 1.06 g (96%) of the resulting 1-O-acetyl-2,3,5-tri-O-benzyl-D-arabinofuranose as a colorless syrup in a 2:1 α:β ratio of anomers.

5.2 Compound 14

To a solution of (500 mg, 1.08 mmol) 1-O-acetyl-2,3,5-tri-O-benzyl-α,β-D-arabinofuranose in 10 mL of anhydrous dichloroethane was bubbled in HCl (g) at room temperature for 20 min. Reaction mixture was stirred at room temperature for 30 min under argon atmosphere and then concentrated in vacuo to afford 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride as a yellow syrup. No purification was done on the crude. To a solution of (1.23 g, 0.018 mol) potassium thioacetate in 10 mL of dry DMF was added a solution of the crude 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride in 5mL of dry DMF via cannulation at -40°C. Reaction mixture was stirred to room temperature for 12 hrs under argon atmosphere. After 12 hrs, the reaction mixture was concentrated in vacuo with heat. The crude was dissolved in CH_2Cl_2 and filtered through a pad of celite and the filtrate was concentrated in vacuo. Flash chromatography (10:1 Hex / EtOAc) afforded 254 mg (49%) of the 1-S-acetyl-2,3,5-tri-O-benzyl-β-D-arabinofuranose and 87 mg (17%) of the 1-S-acetyl-2,3,5-tri-O-benzyl-α-D-arabinofuranose.
Data (β-anomer): *Rf* 0.45 (4:1 Hex / EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.37 (m, 15H), δ 6.10 (d, 1 H, *J* = 5.2 Hz) δ 4.55 (s, 2 H), δ 4.55 and 4.51 (ABq, 2 H, *J* = 11.8 Hz), δ 4.50 and 4.60 (ABq, 2 H, *J* = 11.8 Hz), δ 4.20 (dd, 1 H, *J* = 4.6, 5.2 Hz), δ 4.18 (ddd, 1 H, *J* = 4.0, 5.6, 6.8 Hz), δ 4.04 (app t, 1 H, *J* = 4.0 Hz), δ 3.61 (dd, 1H, *J* = 5.2, 10.0 Hz), δ 3.55 (dd, 1H, *J* = 6.8, 10.4 Hz), δ 2.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 138.1, 137.7, 137.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 84.7, 83.4, 82.4, 82.3, 73.3, 72.3, 71.9, 70.0, 31.1; FAB-MS *m*/*z* 502 MNa^+.

5.3 Compound 15

To a solution of (200 mg, 0.418 mmol) 1-S-acetyl-2,3,5-tri-O-benzyl-β-D-arabinofuranose in 3 : 1 v/v CH_3CN : sodium phosphate dibasic buffer pH 7.41 (Aldrich) was added 20 mL of freshly prepared dimethyldioxirane (0.079 M solution in acetone) at -40°C. Reaction mixture is stirred for 1hr at -40°C.

Reaction mixture is concentrated in vacuo. Flash chromatography (9:0.5:0.5 CH_2Cl_2 / MeOH / Hex) afforded 148 mg (73%) of the 1-C-sulfonic acid.
Data: *Rf* 0.23 (9:0.5:0.5 CH_2Cl_2 / MeOH / Hex) ^{1}H NMR (400 MHz, CD_3OD) δ 7.15-7.43 (m, 15 H), δ 4.86 and 4.56 (ABq, 2 H, *J* = 12.6 Hz), δ 4.80 (d, 1 H, *J* = 5.2 Hz), δ 4.57 and 4.51 (ABq, 2 H, *J* = 11.6 Hz), δ 4.49 and 4.41 (ABq, 2 H, *J* = 12.0 Hz), δ 4.34 (dd, 1 H, *J* = 4.8, 5.2 Hz), δ 4.15 (app t, 1 H, *J* = 4.8 Hz), δ 4.08 (ddd, 1 H, *J* = 5.2, 6.0, 10.4 Hz), δ 3.77 (dd, 1 H, *J* = 6.4, 10.4 Hz), δ 3.67 (dd, 1 H, *J* = 6.0, 10.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 137.9, 137.9, 137.8, 128.1, 127.9, 127.8, 127.5, 127.4, 127.3, 127.2, 89.0, 82.6, 82.5, 82.2, 72.9, 72.8, 71.7, 70.6; NI-FAB-MS *m*/*z* 483 M^-.

5.4 Synthesis of Compound 6

To a solution of (148 mg, 0.305 mmol) of the 1-C-sulfonate in 10 mL of EtOH was added 15 mg of 10% Pd/C. Reaction mixture was stirred overnight under H_2 atmosphere. The reaction mixture was filtered through a pad of celite and washed with EtOH. The filtrate was concentrated in vacuo to afford 59 mg (90%) of the product as a white solid.
Data: mp 55-60°C $[\alpha]_D$ -7.0° (*c* 0.33, 1:1 EtOH/MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.72 (d, 1 H, *J* = 4.8 Hz), δ 4.26 (dd, 1 H, *J* = 3.6, 4.4 Hz), δ 4.11 (app t, 1 H, *J* = 4.0 Hz), δ 3.91 (ddd, 1 H, *J* = 4.4, 6.0, 8.4 Hz), δ 3.77 (dd, 6.4, 12.0 Hz), δ 3.71 (dd, 4.4, 12.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 89.1, 86.4, 77.1, 76.2, 62.1; NI-FAB-MS m/z 213 M^-.

Chapter 6. ^{1}H and ^{13}C Spectra for New Compounds

6.1 ^{1}H and ^{13}C Spectra for Compound 6

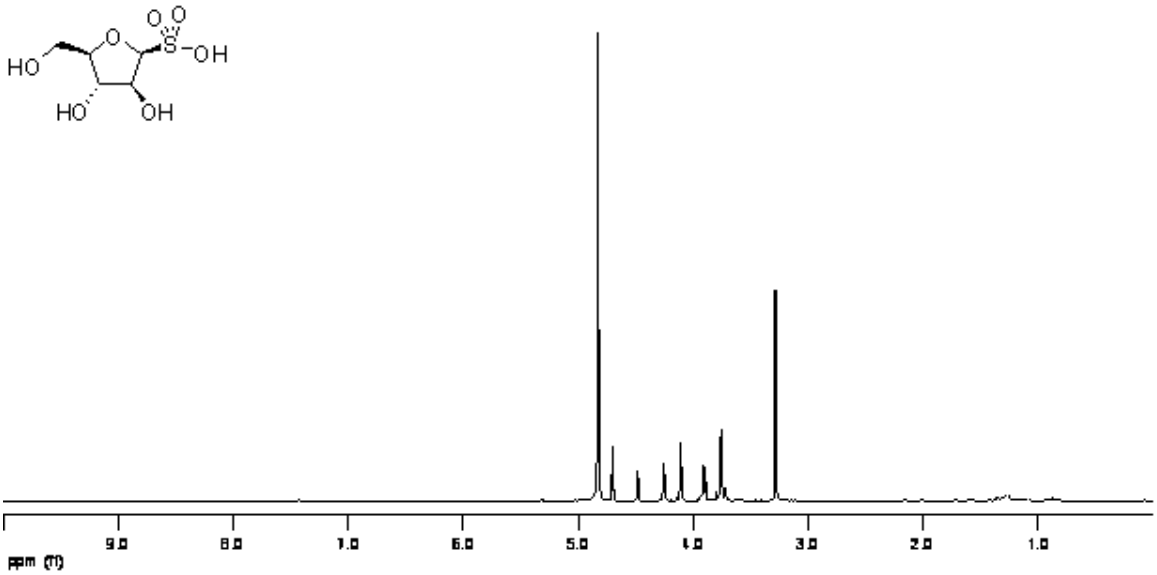


Fig 6.1 ^{1}H NMR of Compound 6 taken at 400 MHz in CD_3OD

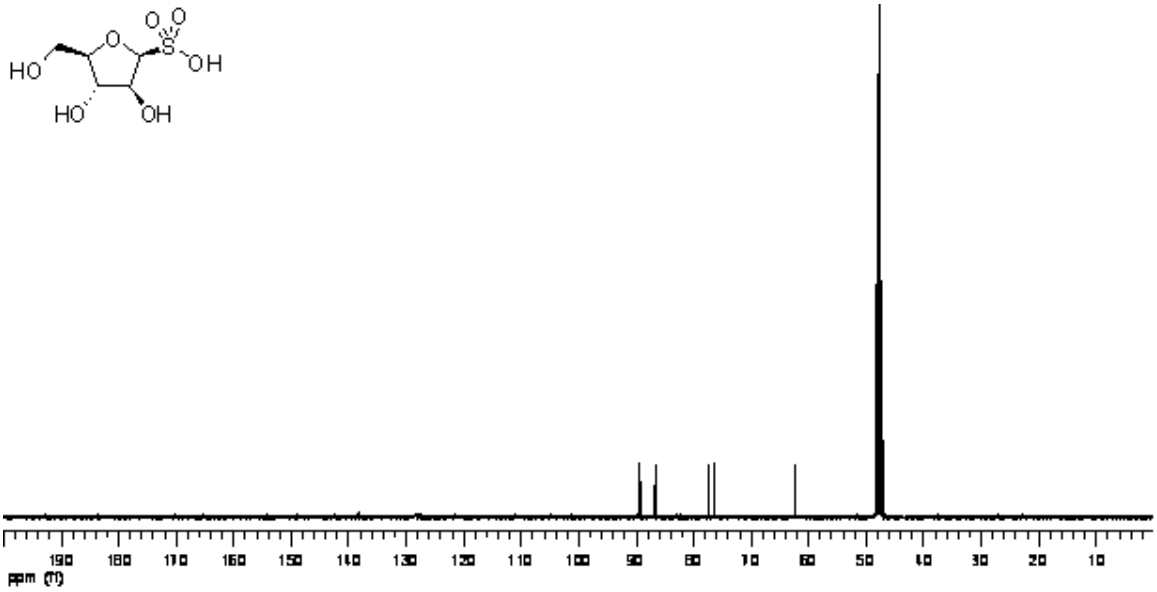


Fig 6.2 ^{13}C NMR of Compound 6 taken at 100 MHz in CD_3OD

6.2 ^{1}H and ^{13}C Spectra for Compound 14

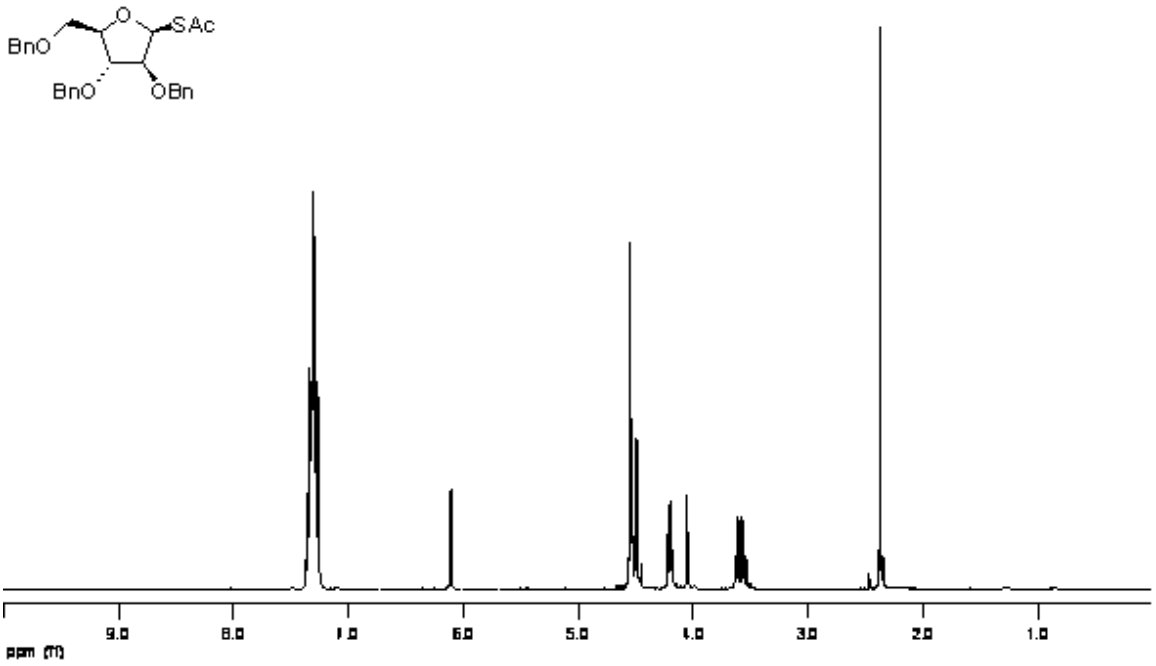


Fig 6.3 ^{1}H NMR of Compound 6 taken at 400 MHz in $CDCl_3$

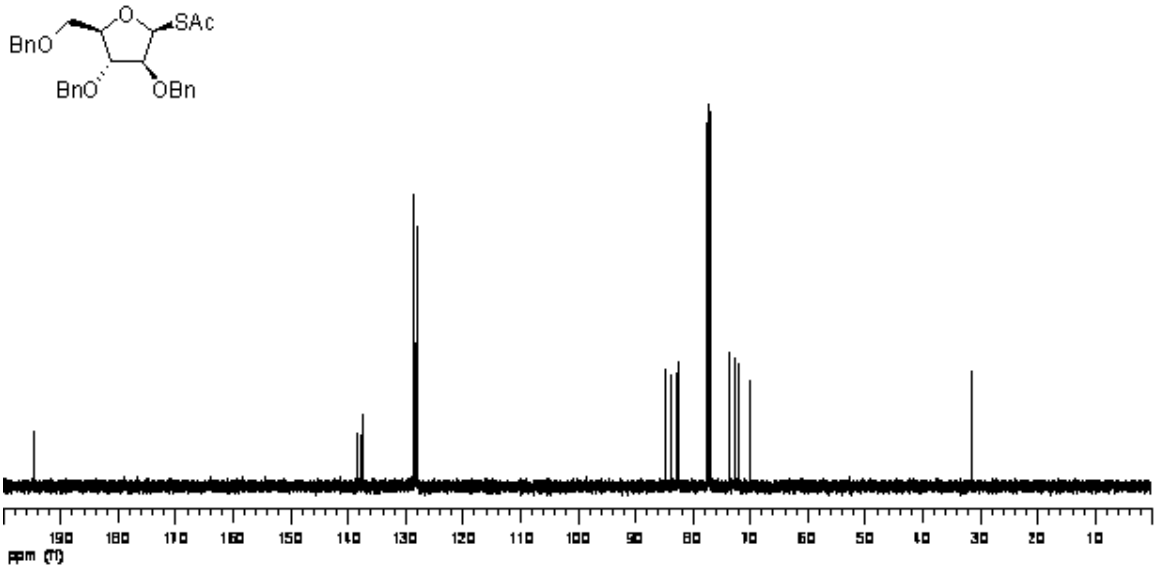


Fig .4 ^{13}C NMR of Compound 6 taken at 100 MHz in $CDCl_3$

6.3 ^{1}H and ^{13}C Spectra for Compound 15

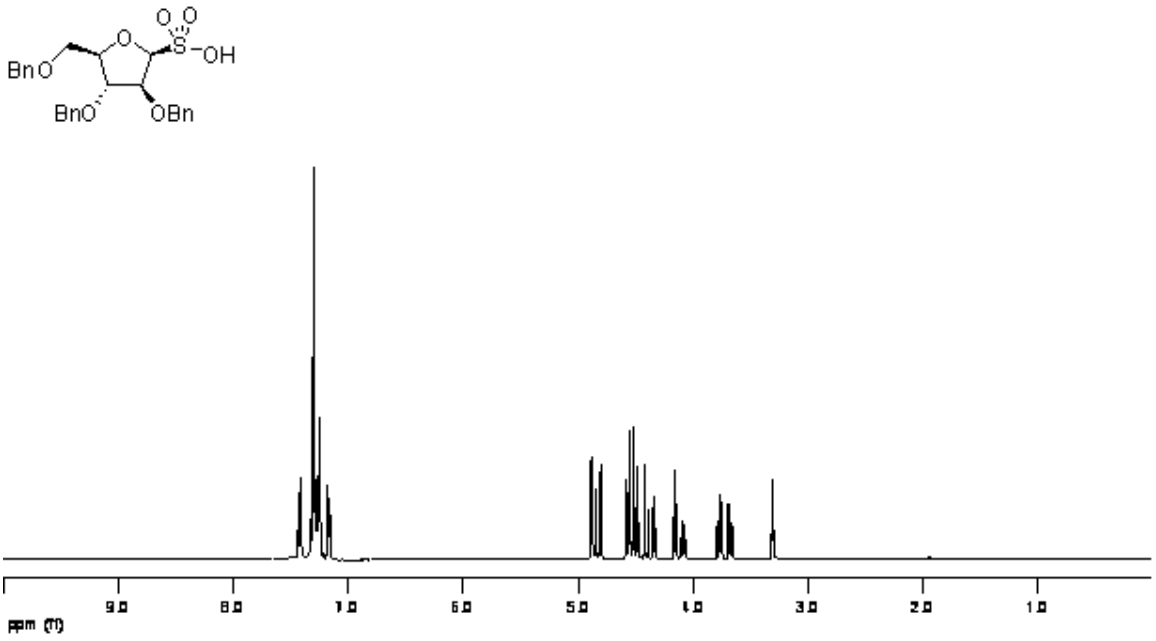


Fig 6.5 ^{1}H NMR of Compound 15 taken at 400 MHz in CD_3OD

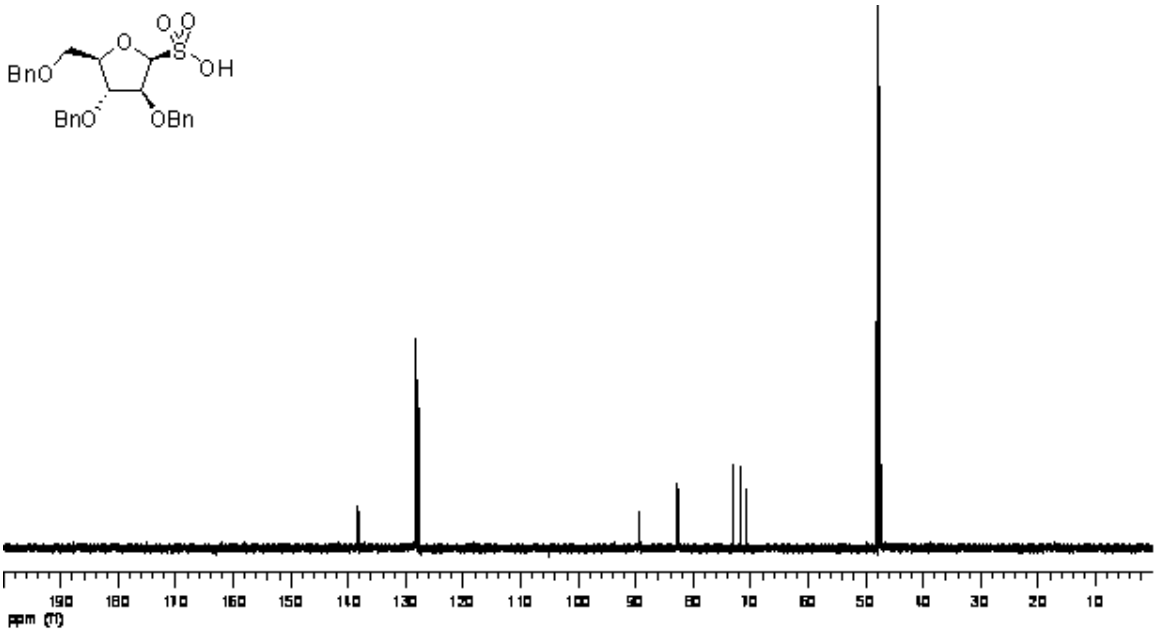


Fig 6.6 ^{13}C NMR of Compound 15 taken at 125 MHz in CD_3OD

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