Synthesis of Sulfamide Analogues of DPA in Anti-TB Drug Development

A thesis submitted in partial fulfilment of the requirements for the degree of Master of Science in Chemistry University of Canterbury

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Fang Liu

Summary

In 2009, approximately 1.7 million people died of tuberculosis.[1] The emergence of drug-resistant strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) has created an urgent demand for the development of new anti-tuberculosis (anti-TB) drugs and treatments.[2] *M. tuberculosis*, the causative agent, has a protective complex cell wall structure that is essential for its survival. One of the major building blocks of the cell wall structure is an arabinofuranosyl polysaccharide called arabinan. Since arabinan is not present in mammals, it has become a promising target for anti-TB drug development.[3] The arabinan component is biosynthesized by a family of arabinofuranosyltransferases (araTs) using the substrate decaprenolphosphoarabinose (DPA) as the donor of arabinose. (Figure S.1a).[4,5]

This project targets the biosynthesis of arabinan by synthesizing analogues of DPA as potential inhibitors of araTs. A sulfamide moiety was chosen as an isosteric replacement of the phosphate group of DPA. To mimic the polyprenyl chain of DPA, a series of alkyl chains of varying length and a triethylene glycol (TEG) derived chain were used (Figure S.1b).

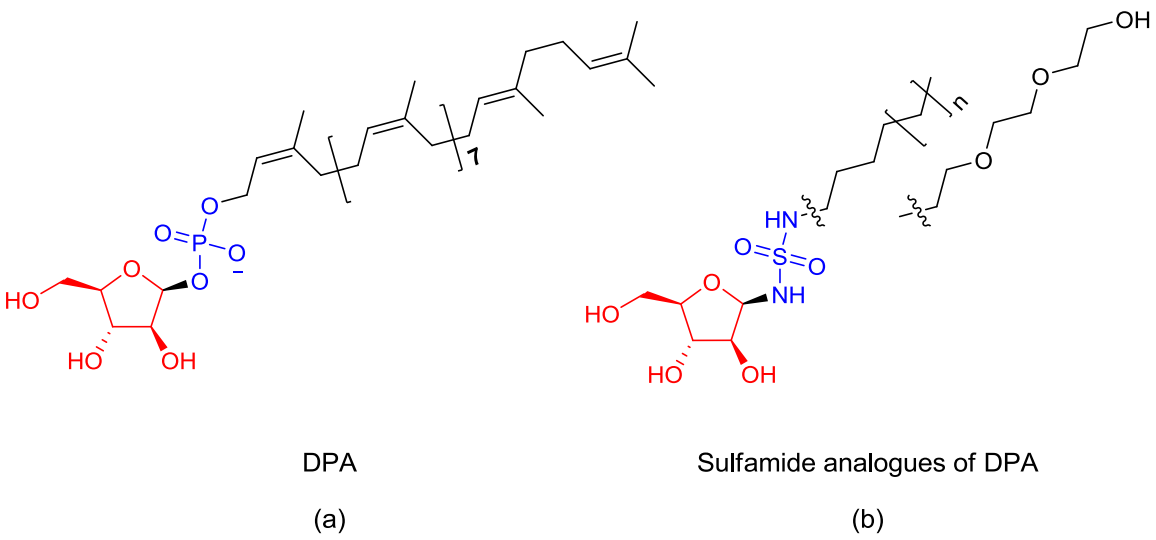

Figure S.1. (a) The structure of DPA. (b) The structure of sulfamide analogues of DPA.

References

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Finally I would like to thank my boyfriend Gérald for his help in chemistry and his support and trust through the good time and the difficult time.

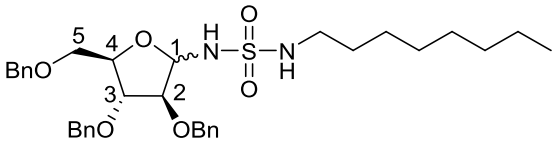
Abbreviations

Ac	acetyl	DPA	decaprenyl phosphoarabinose
AG	arabinogalactan	EMB	ethambutol
anti-TB	anti-tuberculosis	eqv.	equivalent
Aq	apparent quartet	ESI	electrospray ionization
Ara*f*	arabinofuranose	*et al*.	*et alia* (and co-workers)
araT(s)	arabinofuranosyltransferase(s)	ether	diethyl ehter
Bn	benzyl	EtOAc	ethyl acetate
Bu	butyl	Gal*f*	galactofuranose
Bz	benzoyl	GlcN-c	2-acetyl-2-amino-glucopyranoside
c	concentration	h	hour(s)
d	doublet	Hz	hertz
DCM	dichloromethane	IR	infrared
dd	doublet of doublets	J	coupling constant
DIPEA	*N*,*N*-Diisopropylethylamine	LAM	lipoarabinomannan
DMAP	4-(dimethylamino)pyridine	m	mutiplet
DMF	*N*,*N*-dimethylformamide	mAG	mycolyl-arabinogalactan

ManLAM	mannan capped lipoarabinomannan	petrol	petroleum ether boiling in the range of 40 - 60 °C
Man*p*	mannopyranose	quin.	quintet
M. bovis BCG	*Mycobacterium bovis* Bacillus Calmette-Guérin	R	generic group
mCPBA	3-chloroperbenzoic acid	R_f	retention factor
MDR-TB	multidrug-resistant tuberculosis	r.t.	room temperature
Me	methyl	s	strong (in IR spectroscopy)/ singlet (in NMR spectroscopy)
MHz	megahertz	t	triplet
MIC	minimum inhibitory concentration	TB	Tuberculosis
min	minute(s)	TEG	triethylene glycol
m.p.	melting point	TMSBr	trimethylsilyl bromide
M. smegmats	*Mycobacterium smegmatis*	TMSOTf	trimethyl triflate
M. tuberculosis	*Mycobacterium tuberculosis*	*t*BuH	*tert*-butyl alcohol
m/z	mass/charge ratio	THF	tetrahydrofuran
NMR	nuclear magnetic resonance	TTBP	2,4,6-tri-*tert*-butylpyrimidine
Pd-black	palladium black	XDR-TB	extensively drug resistant tuberculosis
Pd-C	palladium on carbon		

Explanatory Note

The carbohydrate and their derivatives detailed in the thesis are numbered according to the carbohydrate convention and named as suggested by the IUPAC recommendations of 1996 (*Pure Appl. Chem*. **1996**, *68*, 1919). The two protons on C-5 for pentose sugars are labeled H-5 and H-5'.



***N*-octyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 67**

Contents

Chapter 1: Introduction

1.1 Tuberculosis

Tuberculosis (TB) is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years. In 2009, 1.7 million people died from TB, a figure that is equivalent to 4700 deaths a day.[1] A major global issue is the emergence of drug-resistant strains of TB, multidrug-resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB).[1,6-8] MDR-TB is a form of TB that is difficult and expensive to treat, and fails to respond to standard front-line drugs.[1] The current front-line drugs are isoniazid **1**, rifampicin **2**, pyrazinamide **3**, ethambutol (EMB) **4** and streptomycin **5** (Figure 1.1).[3] The standard treatment for TB consists of dosage with isoniazid, rifampicin, and pyrazinamide for two months, followed by continuation of dosage with isoniazid and rifampicin for six months.[9] This treatment is generally supplemented with EMB or streptomycin, and requires strict adherence to the regime.[3] Poor management of the treatment regime is one of the factors that gives rise to MDR-TB. For the treatment of MDR-TB, the regime must be altered, and second-line antibiotics are often employed.[10] Extensively drug-resistant TB (XDR-TB) is said to occur when resistance to second-line drugs develops on top of MDR-TB. To date, XDR-TB cases have been confirmed in 58 countries.[1] New anti-TB drugs as well as new drug targets against TB are therefore in urgent need.

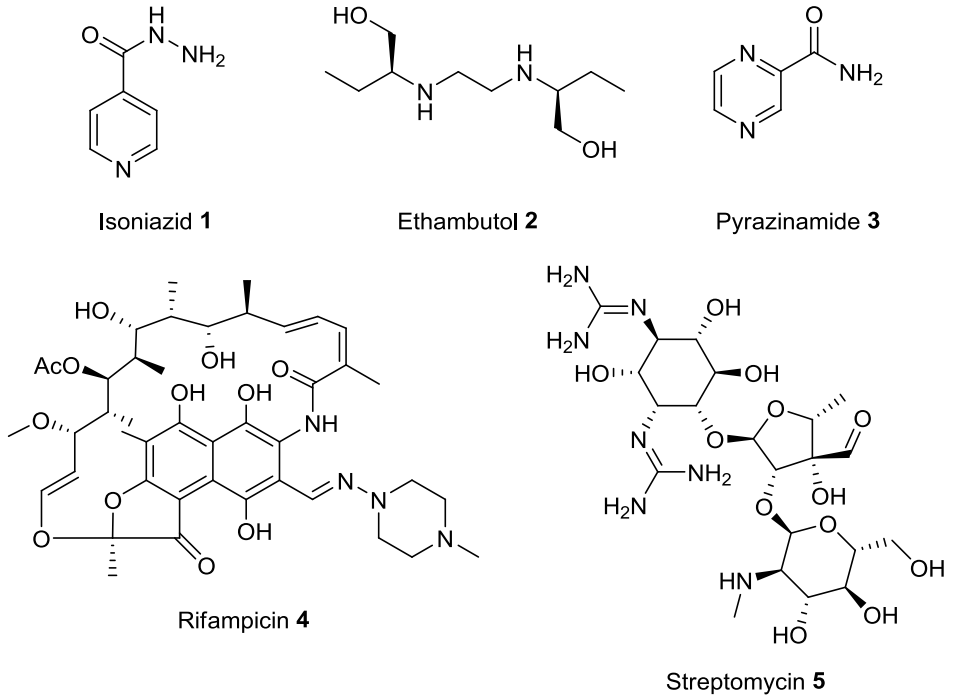


Figure 1.1. The structures of the first line anti-TB drugs.[3]

Polysaccharides composed of furanose residues are important constituents of glycoconjugates of many bacteria,[11] protozoa,[12] fungi[13] and plants.[14] In *Mycobacterium* species, galactose and arabinose are the most common sugars found in the cell wall. In *M. tuberculosis*, lipoarabinomannan (LAM) and mycolyl-arabinogalactan (mAG) are the two major building blocks of the cell wall (Figure 1.2).[3] LAM is a polymer of mannopyranose (Man*p*) and arabinofuranose (Ara*f*) residues, and is attached to the plasma membrane through a phosphatidyl inositol anchor. The mAG complex consists of a polymer of galactofuranose (Gal*f*) and ara*f* residues covalently linked to the peptidoglycan at the reducing end, which is esterified at the non-reducing end with mycolic acids and branched-chain lipids found in mycobacteria and other actinomycetes. Other components of the cell wall complex of mycobacteria include peptidoglycan, a polymer of *N*-acetylglucosamine, *N*-glycolylmuramic acid and short cross-

linked peptides, and glycolipids that are bound through noncovalent interactions with mycolate esters.[15,16,17]

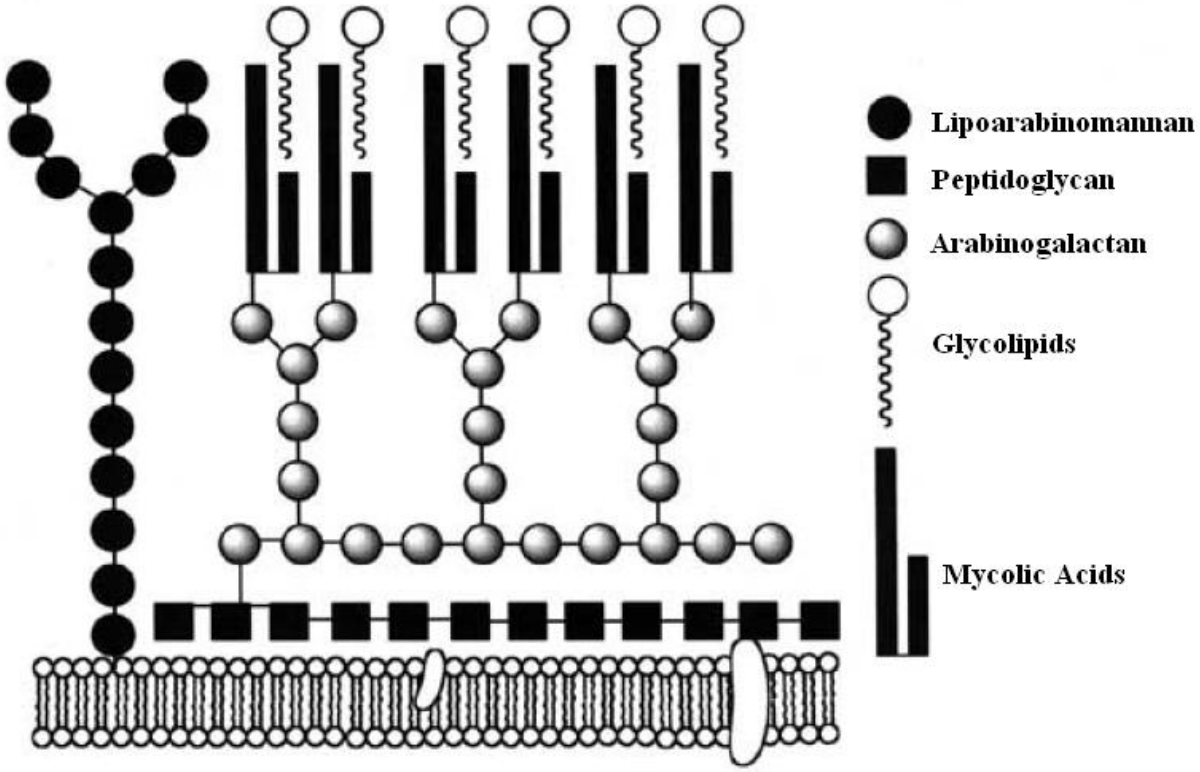


Figure 1.2. Schematic representation of the general structure of the mycobacterial cell wall.[3]

The thick, multilayered cell wall complex serves as a protective shell against threats from the surrounding environment including many classes of antibiotics.[18] The integrity of the cell wall is essential for bacterial survival. In fact the front-line anti-TB drugs EMB **2** and isoniazid **1** interrupt cell wall biosynthesis and thus allowing other drugs (eg, rifampicin **4** or streptomycin **5**) to enter the organism more easily. Mycobacterial viability is dependent upon the ability of the organism to produce an intact wall.[3] The biosynthesis of cell wall is therefore an attractive target for the development of new drugs for treating tuberculosis. This project focuses on inhibition of

the biosynthesis of arabinan, which is one of the major and essential components of the cell wall and which is not present in mammals.[19]

1.2 Arabinan

In *M. tuberculosis* the arabinan domain, which is composed of entirely arabinose residues in the furanose ring form, found in both LAM and mAG. In mAG the arabinan is predominantly an α-(1→5) linked linear polysaccharide of ara*f* units with critically positioned α-3,5-branch sites to which another linear chain is attached via the 3 position. A β-(1→2) linkage marks the "end point" of the arabinan biosynthesis before decoration with mycolic acid.[20] The non-reducing termini of these arabinan chains are capped with a unique Ara_6 motif composed of a branched hexasaccharide Ara*f*β-(1→2)Ara*f*α-(1→5)[Ara*f*β-(1→2)Ara*f*α-(1→3)]-Ara*f*α-(1→5)Ara*f*α-(1→ (Figure 1.3a) of which approximately two-thirds have mycolic acid residues which are esterified at all four primary hydroxyl groups, whilst the remaining hexasaccharide motifs are unsubstituted (Figure 1.3b).[3,16,21] The arabinan domain of LAM is a structure similar to that of AG in which similar linkages of Ara*f* units are found.[22] One of the distinctive features is that a linear Ara_4 motif Ara*f*β-(1→2)Ara*f*-α(1→5)Ara*f*α-(1→5)Ara*f*α-(1→ coexists with the hexasaccharide motif at the non-reducing termini of the arabinan, and these oligosaccharide are not esterified with mycolic acids. Instead, the two motifs are either unsubstituted or further glycosylated with either a mono Man*p*, a dimannoside Man*p*α-(1→2)Man*p*α or a trimannoside Man*p*α-(1→2)Man*p*α-(1→2)Man*p*α to give ManLAM (Figure 1.3c).[18,20] The terminal mannose residues are believed to be involved in the infection process through the binding to human mannose lectins.[3,23,24]

The arabinan domain is synthesized by a family of enzymes called arabinofuranosyltransferases (araTs).[3]

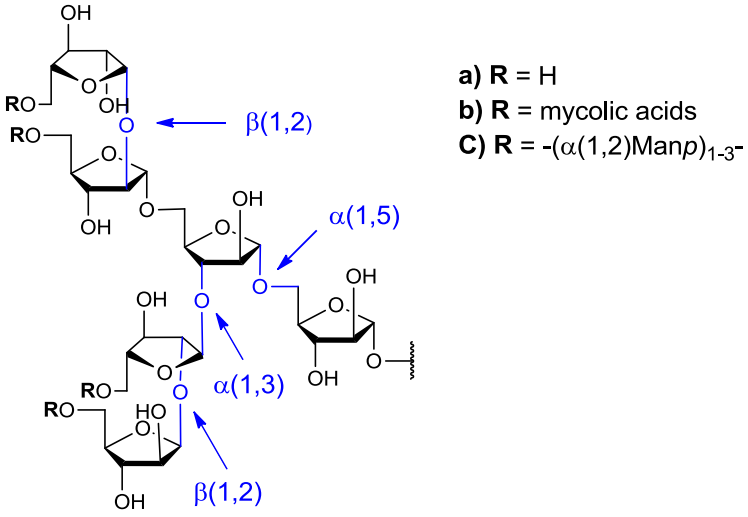


Figure 1.3. The structure of non-reducing termini Ara_6 motif: a) unsubstituted Ara_6 motif; b) Ara_6 motif esterified with mycolic acids; c) Ara_6 motif glycosylated with Man*p* residues.[18,20]

1.3 Arabinofuranosyltransferase

AraTs have been able to be identified as integral membrane enzymes with the active sites located on the periplasmic side of the plasma membrane. They belong to the glycosyltransferase GT-C superfamily, carrying the proposed GT-C motif of polyprenyl-dependent glycosyl transferases.[25,26] To date none of the araTs has been successfully isolated. However through microbiological studies and cell free-assays several araTs in *M. tuberculosis* have been able to be identified and characterised.[27,28,29] The identified araTs could be devided into two groups. One group known as being the targets of the anti-TB drug EMB **2** includes EmbA, EmbB, EmbC; The other group which is insensitive to EMB **2** includes AftA, AftB, AftC and AftD.[30-34] Each of the enzymes is responsible for synthesizing one part of the arabinan domain of AG or LAM in *M. tuberculosis*, although some parts of the arabinan may require the combined activity of two or

more enzymes. EmbA and EmbB acted in coordination to synthesize and transfer the disaccharide Ara*f*β-(1→2)Ara*f*α onto the 3-arm of the linear Ara*f*β-(1→2)Ara*f*α-(1→5)Ara*f*α-(1→5)Ara*f*α-(1→ to complete the formation of hexasaccharide Ara_6 motif at the non-reducing termini of AG;[35,36] EmbC is involved in the elongation of the arabinan domain of LAM;[31] AftA catalyzes the addition of the first key ara*f* residue onto the galactan domain of AG, thus "prime" the galactan backbone for the further attachment of α-(1→5) linked ara*f* residues;[37] AftB is required for forming terminal β-(1→2) linked ara*f* residues, which marks the end point of AG arabinan biosynthesis;[38] AftC is involved in the synthesis of internal α-(1→3) branchings of AG arabinan;[39] AftD, a recently discovered araT, is believed to catalyze the internal α-(1→3)-branching of arabinan of both AG and LAM.[20] Figure 1.4a shows the catalytic roles of each araT in the biosynthesis of arabinan of AG.[38]

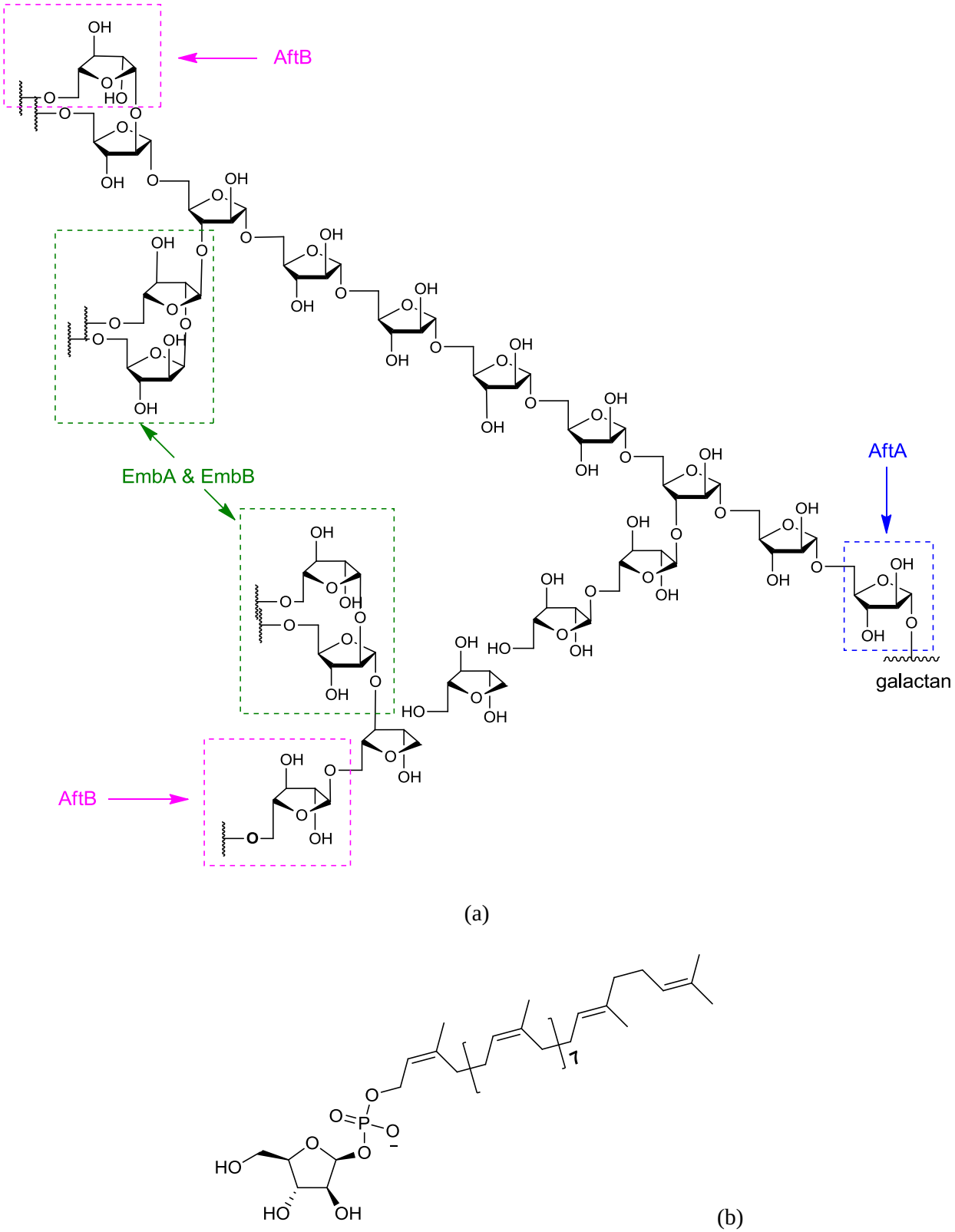


Figure 1.4. (a) The roles of each araT in the biosynthesis of arabinan of AG.[38] (b) The structure of the substrate donor DPA.[4]

Although considerable progress has been made towards understanding the biosynthetic pathway of arabinan domain of AG and LAM, there is still much that remains unknown.[25,40,41] How the arabinan and other domains of AG and LAM are assembled. For example if the arabinan grows stepwise from the reducing end towards the nonreducing end through the sequential addition of glycosyl residues, or if it is assembled through the polymerization of building blocks.[23] Nevertheless it is believed that all of the araT use one Ara*f* donor substrate, decaprenyl phosphoarabinose (DPA) (Figure 1.4b).[4] The acceptor substrates for the araTs are the growing arabinogalactan polysaccharides. Although the natural acceptor substrates for these enzymes are lipid-bound intermediates, these AraTs also recognize small oligosaccharides.[27,42]

The traditional anti-TB drugs like EMB target three or more of the araTs involved in arabinan biosynthesis. The synthesis of DPA analogues would provide potential inhibitors that could target all araTs, which would be particularly important for treating MDR-TB and XDR- TB. In fact, in recent years most of research effort aimed at inhibition of arabinan biosynthesis has focused on the development of DPA analogues.[18] Work done by Lowary *et al*. has been particularly remarkable in this field. In 2002 they synthesized a group of *C*-phosphonate analogues of DPA (Figure 1.5), which were tested against *M. tuberculosis* strain H_{37}Rv using microplate "Alamar Blue" Assay.[43] "Alamar Blue" assay is a nonradioactive, rapid, inexpensive, and high-throughput method for screening new drug candidates. The Alamar blue oxidation-reduction dye (alamarBlue®) is a general indicator of cellular growth and/or viability. It is added to the living culture containing the test compound which is present in increasing concentrations, and then incubated for at least 12 hours at 37^{o}C. The natural reducing power of the living cells normally reduces the dye from its blue, non-fluorescent oxidized form to the reduced form which

is fluorescent and pink in color. The nonviable and damaged cells in contrast have none or limited ability to reduce the blue dye. Changes in color are measured with a fluorometer or spectrophotometer or determined by a visual color change and a value of minimum inhibitory concentration (MIC) of the test compound can therefore be obtained.[44] During the "Alamar Blue" assay, compounds **6-9** were inactive towards the growth of the bacteria whilst compound **10** was found to have a MIC value of 3.13 μg/mL. Based on these results, the *C*-phosphonate **10** is currently being tested for efficacy in tuberculosis-infected mice.[43]

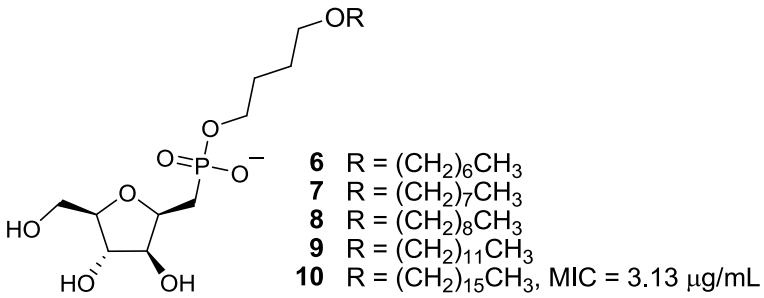
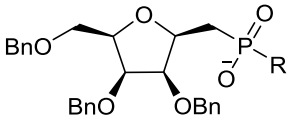
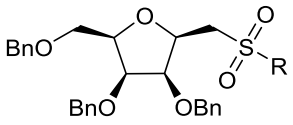


Figure 1.5. *C*-phosphonate analogues of DPA synthesized by Lowary *et al*.[43]

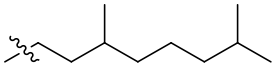
Given this success, T. Lowary *et al.* synthesized a series of glycosyl sulfone DPA analogues[45] and phosphinic acid-containing DPA analogues[46] (Table 1.6a), which were then tested against *M. tuberculosis* strain H_{37}Rv in the "Alamar Blue" assay. However compounds **11** - **22** showed only low to moderate activity towards the growth of bacteria, and none of them was found to be as a potent inhibitor as *C*-phosphonate analogue **10** (Table 1.6b). Lowary concluded at that point that there was no clear correlation between structure and the biological activity.[45]



18, R = $(CH_2)_7CH_3$
19, R = $(CH_2)_9CH_3$
20, R = $(CH_2)_{11}CH_3$
21, R = $(CH_2)_{15}CH_3$
22, R = $(CH_2)_{19}CH_3$



11, R = $(CH_2)_8CH_3$
12, R = $(CH_2)_9CH_3$
13, R = $(CH_2)_{11}CH_3$
14, R = $(CH_2)_{15}CH_3$
15, R = $(CH_2)_{19}CH_3$
16, R = $(CH_2)_{10}O(CH_2)_{15}CH_3$

17, R = 

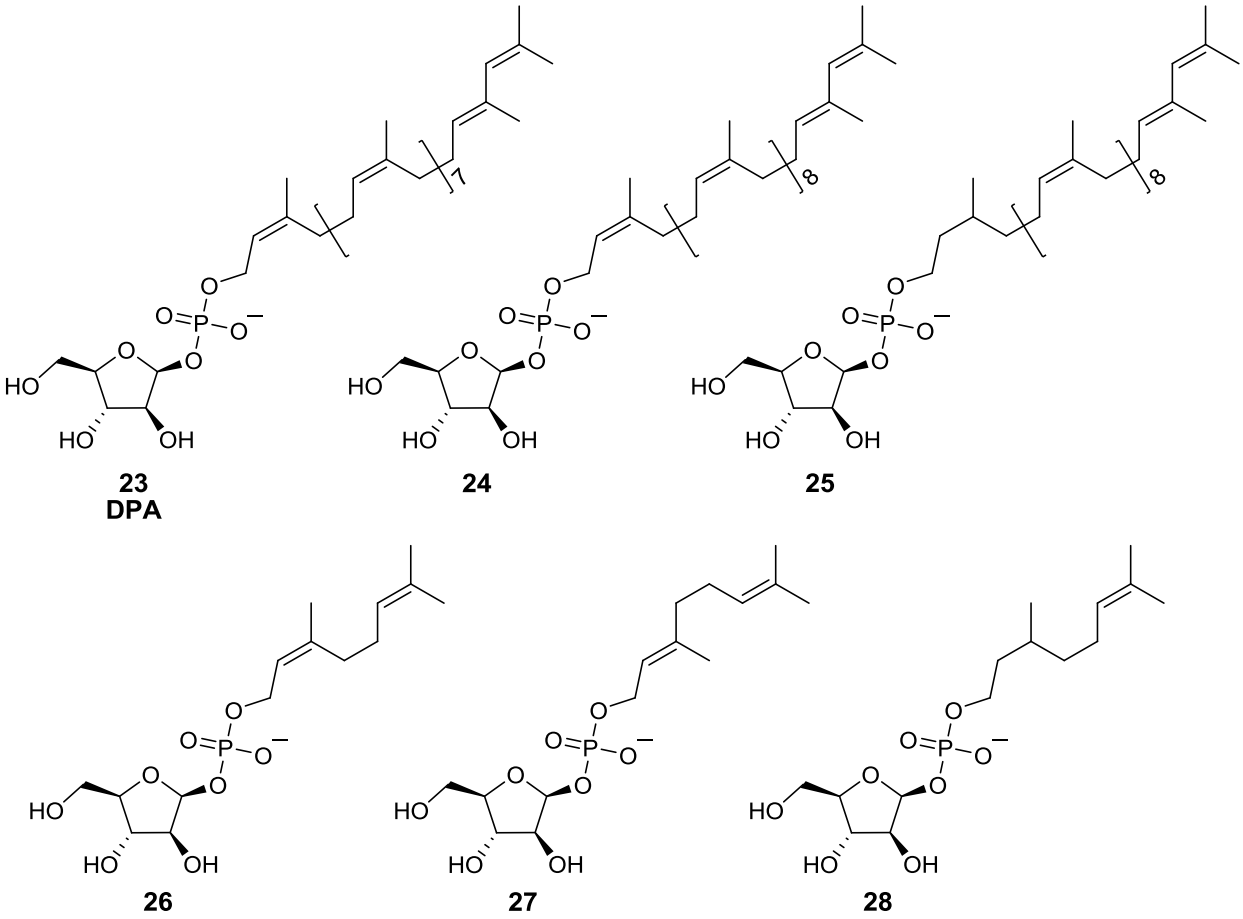
(a)

Compound	% Inhibition
10 (MIC = 3.13 μg/mL)	92
11	0
12	21
13	45
14	0
15	4
16	0
17	20
18	0
19	0
20	17
21	0
22	0

(b)

Table 1.6. (a) The structures of sulfone analogues of DPA (**11** – **17**)[48] and phophinic acid-containing analogues of DPA (**18** – **22**) synthesized by Lowary *et al*.[49] (b) The MIC values of DPA analogues **10** – **22** against the growth of *M. tuberculosis* strain H_{37}Rv obtained in the "Alamar Blue" assay.[45]

In contrast to Lowary's work, Besra synthesized a series of phosphate DPA analogues with polyprenol chain of varying length **(24 - 28)** (Figure 1.7), which were tested in a cell free assay with extracted araTs of *Mycobacterium smegmatis* (*M. smegmatis*) and synthetic acceptors. It was found that only the long chain polyprenol analogues **24** and **25** were recognized by the active site of araTs as arabinose donor substrate. Thus it was concluded that the hydrophobicity of the side chain plays an important role in substrate recognition.[28]



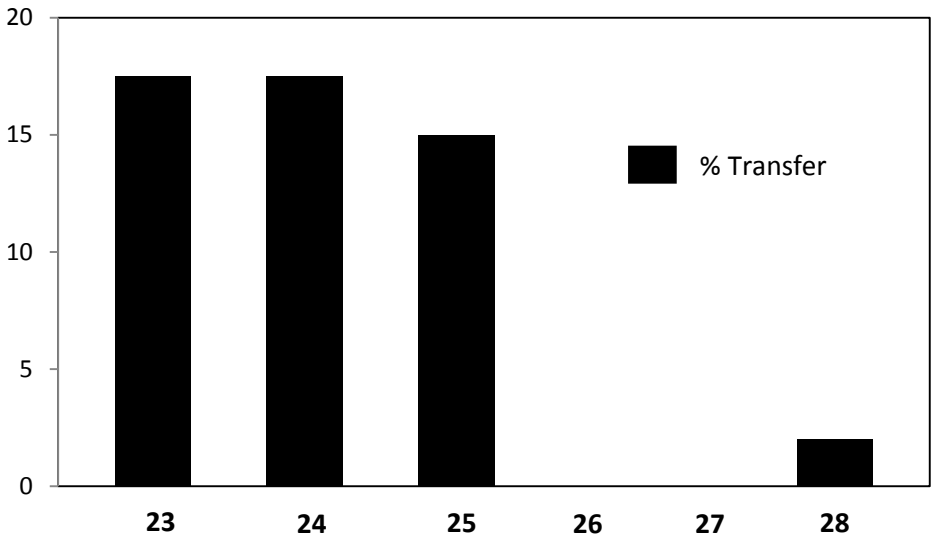


Figure 1.7. Phosphate analogues of DPA synthesized by Bersa G. C. *et al.* and the activity of each compound in the cell free assay of araTs of *M. smegmatis*.[28]

1.4 Aim of the project

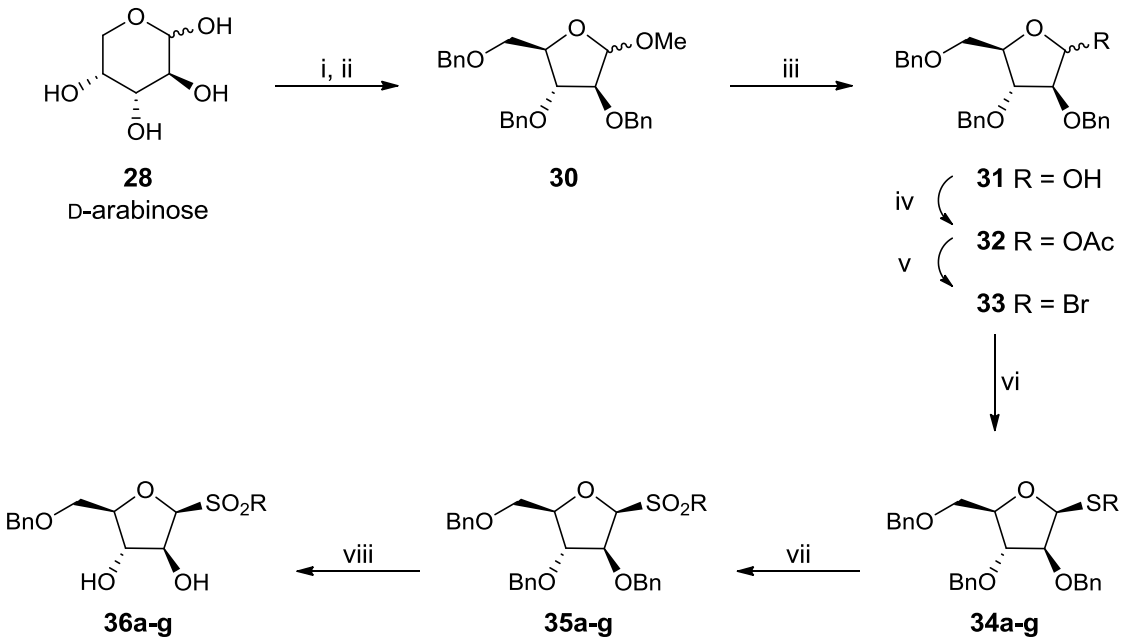
When designing DPA analogues as potential araT inhibitors, three factors should be considered. Firstly, the compound should bind well to the enzyme active site. Secondly, the compound must not be able to donate arabinose residues to the acceptor substrate. Thirdly, the compound should be stable and non-hydrolysable in a biological environment. With these three attributes, such a compound could potentially bind to all araT active sites without being turned over, therefore effectively inhibiting arabinan biosynthesis for both AG and LAM.

The aim of this project was to synthesize novel sulfamide analogues of DPA and to test their biological activity with "Alamar Blue" assay. Based on the work of Besra[28] and Lowary,[45,46] the effects of increasing the alkyl chain length as well as the insertion of oxygen atoms into the linear alkyl chain on the inhibition of mycobacterial growth were also investigated.

Chapter 2: Results and discussion

2.1 Synthesis of Glycosyl Sulfone DPA Analogues

Ayers, a former member of the Fairbanks group, synthesized sulfone DPA analogues (scheme 2.1) which were tested against the growth of *Mycobacterium bovis* Bacillus Calmette-Guérin (*M. bovis* BCG) using the "Alamar Blue" assay.[47]



34a, 35a, 36a R = $(CH_2)_3CH_3$
34b, 35b, 36b R = $(CH_2)_5CH_3$
34c, 35c, 36c R = $(CH_2)_7CH_3$
34d, 35d, 36d R = $(CH)_9CH_3$
34e, 35e, 36e R = $(CH)_{11}CH_3$
34f, 35f, 36f R = $(CH)_{13}CH_3$
34g, 35g, 36g R = $(CH)_{15}CH_3$

Scheme 2.1. The synthesis of sulfone DPA analogues by Ayers. Reagents and conditions: (i) AcCl, MeOH r.t., 6 h, 80%, α:β, 4:1; (ii) NaH, BnBr, DMF, r.t., 16 h, 87%; (iii) 80% AcOH (aq), 115°C, 48 h, 73%; (iv) Ac_2O, pyridine, r.t., 16 h, 94%, α:β, 1.7:1; (v) TMSBr, DCM, 40°C to r.t., 0.5 h, α:β, 4:1; (vi) RSH, TTBP, CH_2Cl_2, r.t., 16–17 h; **34a**, 94%, **34b**, 85%, **34c**, 83%, **34d**, 80%, **34e**, 63%, **34f**, 97%, **34g**, 80% (all over two steps); (vii) mCPBA, $NaHCO_3$, DCM, 16 h; **35a**, 83%, **35b**, 78%, **35c**, 84%, **35d**, 88%,

35e, 87%, **35f**, 83%, **35g**, 86%; (viii) H_2, 10% Pd on C, MeOH or MeOH:EtOAc, 1:1, or EtOAc, r.t., 24 h; **36a**, 72%, **36b**, 82%, **36c**, 80%, **36d**, 75%, **36e**, 94%, **36f**, 88%, **36g**, 81%.[47]

The thioglycosides were synthesized from reaction of glycosyl bromide **33** and a series of alkyl thiols in the presence of TTBP. This reaction was completely stereoselective and afforded only the β-anomers **34a - g** in excellent yields (63-94% over two steps). It is believed that the β anomeric configuration of the sugar donor is important for the substrate binding to the active site of araTs. In the "Alamar Blue" assay, compounds **36a - g** exhibited low to moderate inhibitory activity towards the the growth of *M. bovis* BCG (Table 2.1).[47] However, an increase in the inhibitory activity along with the increase in the alkyl chain length was observed from compound **36a - e**, indicating a possible correlation between the alkyl chain length and the inhibitory activity of the compound.

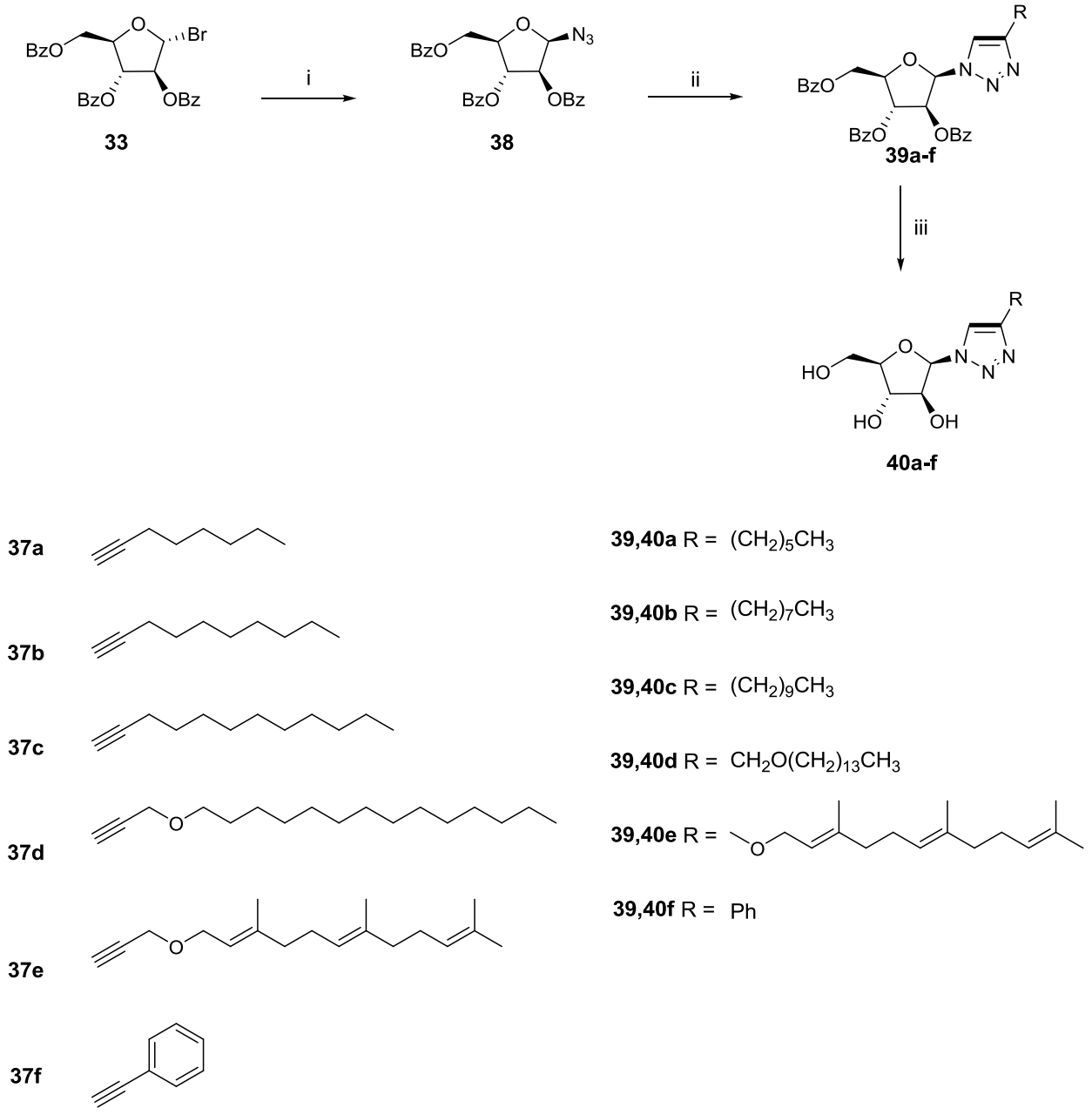
Sulfone DPA analogues	MIC (μg/mL)
36a	2000
36b	500
36c	250
36d	125 > X> 62
36e	62
36f	250
36g	250 > X > 125

Table 2.1. The MIC values of sulfone DPA analogues **36a** – **36g** against the growth of *M. bovis* BCG obtained in the "Alamar Blue" assay**.**[47]

2.2 Synthesis of Glycosyl Triazole DPA analogues

Wilkinson, another Fairbanks former group member, synthesized a series of glycosyl triazole analogues of DPA (Scheme 2.2)[48] and two sulfamide analogues of DPA (unpublished work).

The intermediate glycosyl azide **38** was synthesized by reaction of glycosyl bromide **33** with sodium azide. In contrast to the synthesis of **34a - g**, the reaction did not proceed with complete stereoselectivity. Instead, the reaction afforded compounds **39a - g** as anomeric mixtures with the desired β-anomer predominating (α:β, 1:2).



Scheme 2.2. The synthesis of triazole DPA analogues by Wilkinson. (i) NaN_3 (5.0 equiv), Bu_4NHSO_4 (1.0 equiv), 1:1 DCM:$NaHCO_3$ (aq), α:β, 1:2, 43% β; (ii) **37a – f** (5–10 equiv), CuI (1.0 equiv), DIPEA (1.0 equiv), 110°C, 72–92%; (iii) $NaOCH_3$ (0.4 equiv), MeOH and THF (2:1 v/v), 92–100%.[48]

In the assay, compounds **40a-f** exhibited low to moderate inhibitory activity towards the growth of *M. bovis* BCG (Table 2.2).[48] Amongst all of the triazole DPA analogues compound **39d** has

the lowest MIC value which possibly indicates that the active site of araTs favor the hydrophobic chain of a certain length.

Triazole DPA analogues	MIC (μg/ml)
40a	500
40b	62
40c	250
40d	31
40e	62
40f	No activity

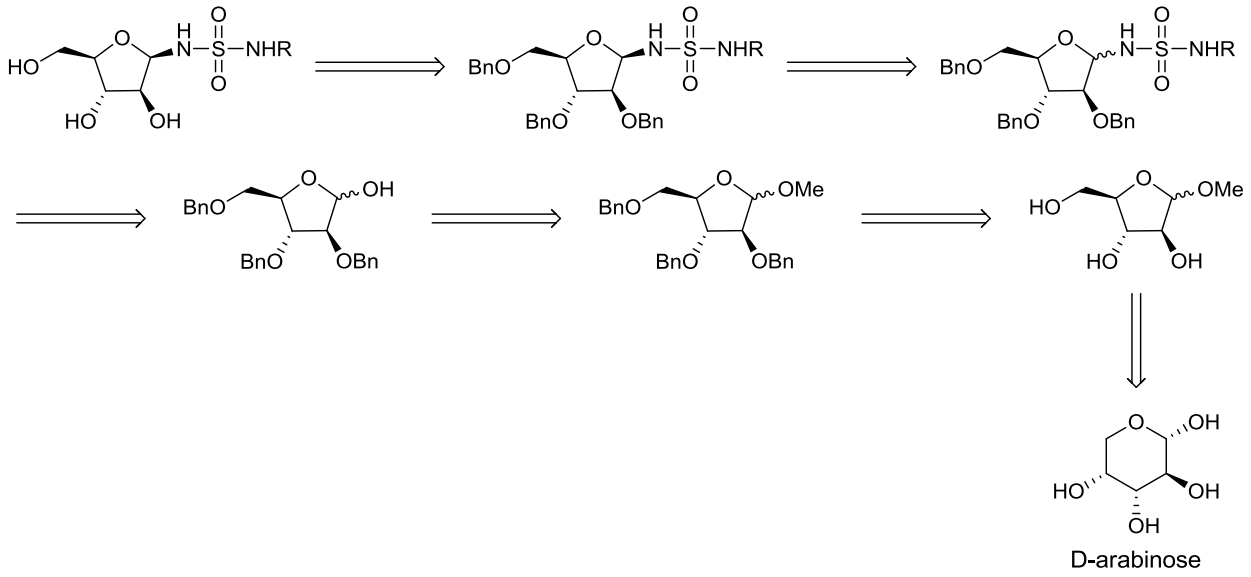
Table 2.2. The MIC values of sufone DPA analogues **40a** – **40f** against the growth of *M. bovis* BCG obtained in the "Alamar Blue" assay.[48]

2.3 Synthesis of Sulfamide DPA Analogues

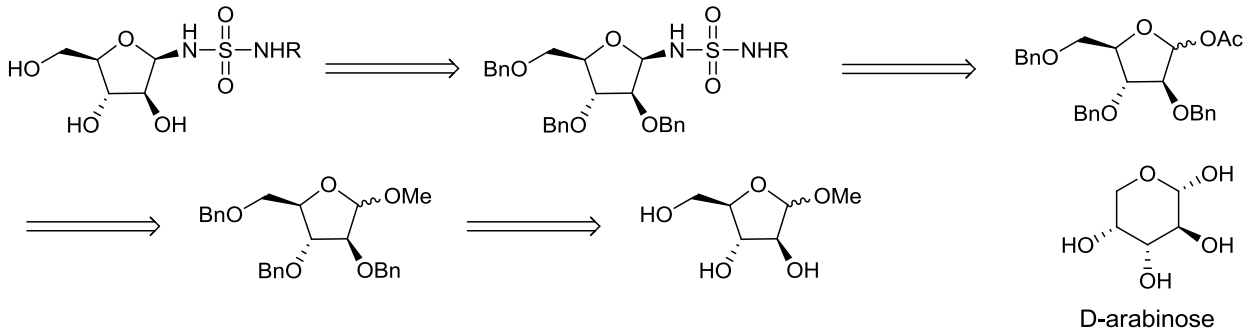
2.3.1 Synthetic Strategy

In the cell wall of *M. tuberculosis*, all the arabinose residues are in their furanose-ring form. Commercially available D-arabinose exists in solution as an equilibrium mixture of acyclic and cyclic forms, with the later as the majority. Cyclic D-arabinose consists of both pyranose and furanose isomers and at equilibrium, the pyranose form predominates.[49] To obtain the desired arabinofuranose, the first step of the synthetic pathway was to constrain the D-arabinose into the furanose configuration. Appropriate protecting groups were then used for the hydroxyls to afford a donor suitable for glycosylation with a sulfamide acceptor incorporating a variety of side chains. The sulfamide group was chosen as a potential isosteric mimic of the metabolically labile phosphate group of DPA.[50] The sulfamide acceptors were prepared from the commercially available chlorosulfonyl isocyanate and a range of commercially available alkyl amines, or a

TEG derived amine which was synthesized in the laboratory.[51] The anomeric configuration of the glycosyl sulfamide final product must be β in order to be isostructural with DPA. This could be potentially achieved either by stereoselective sulfamidoglycosylation (Scheme 2.3a), or through the direct sulfamidoglycosylation followed by isolation of the β-anomer using flash chromatography (Scheme 2.3b).



(a)

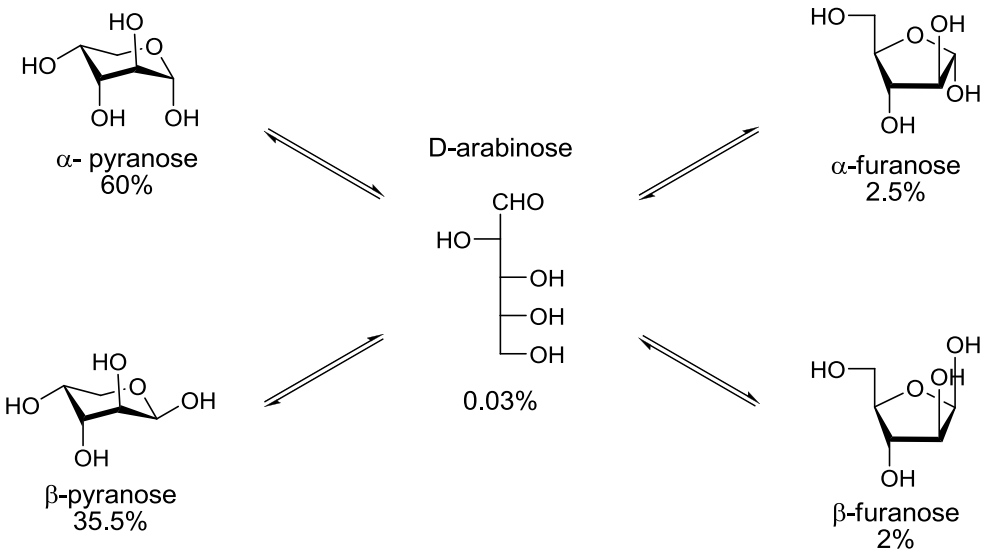


(b)

Scheme 2.3. (a) Retrosynthetic pathway for direct synthesis of sulfamide. (b) Retrosynthetic pathway for stereoselective synthesis of sulfamide.

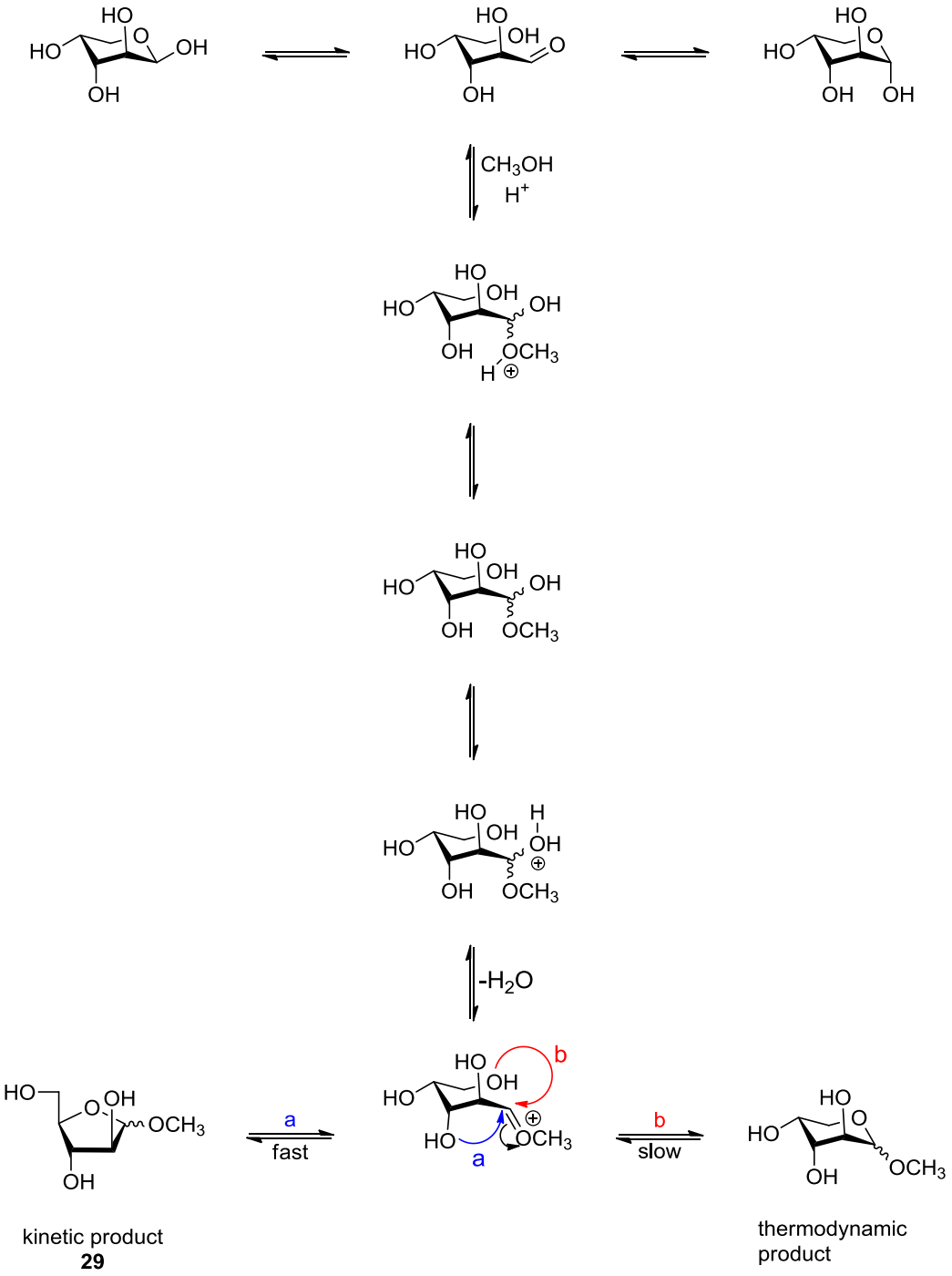
2.3.2 Preparation of the Arabinose Donor

The starting material D-arabinose **28** is mainly in its pyranose form when dissolved in the solution (Scheme 2.4)[52]



Scheme 2.4. The forms of D-arabinose dissolved in the solution.[52]

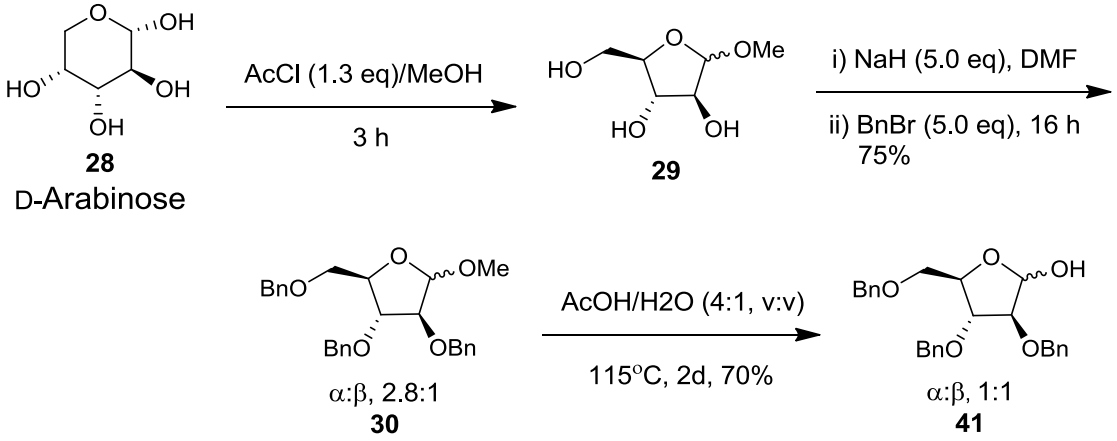
A Fischer glycosylation was used to afford the methyl-α,β-D-arabinofuranoside **29**. The reaction mechanism is shown in scheme 2.5.[53] The starting material D-arabinose was stirred in methanol under acidic conditions (AcCl 1.3 eqv.). The furanoside **29** was the kinetic product and formed fast through pathway a. The reaction progress was monitored by t.l.c. using a mobile phase of DCM : MeOH, 4:1. The reaction was quenched with pyridine after a three-hour period to avoid the formation of the undesired pyranose form (thermodynamic product).[49]



Scheme 2.5. Compound **29** obtained by Fisher glycosylation.[53]

The benzyl ether was chosen as the protecting group for the rest of the hydroxyls of **29**. Other common protecting groups like *tert*-butyl dimethyl silyl ether (TBDMS) and benzoyl ether were

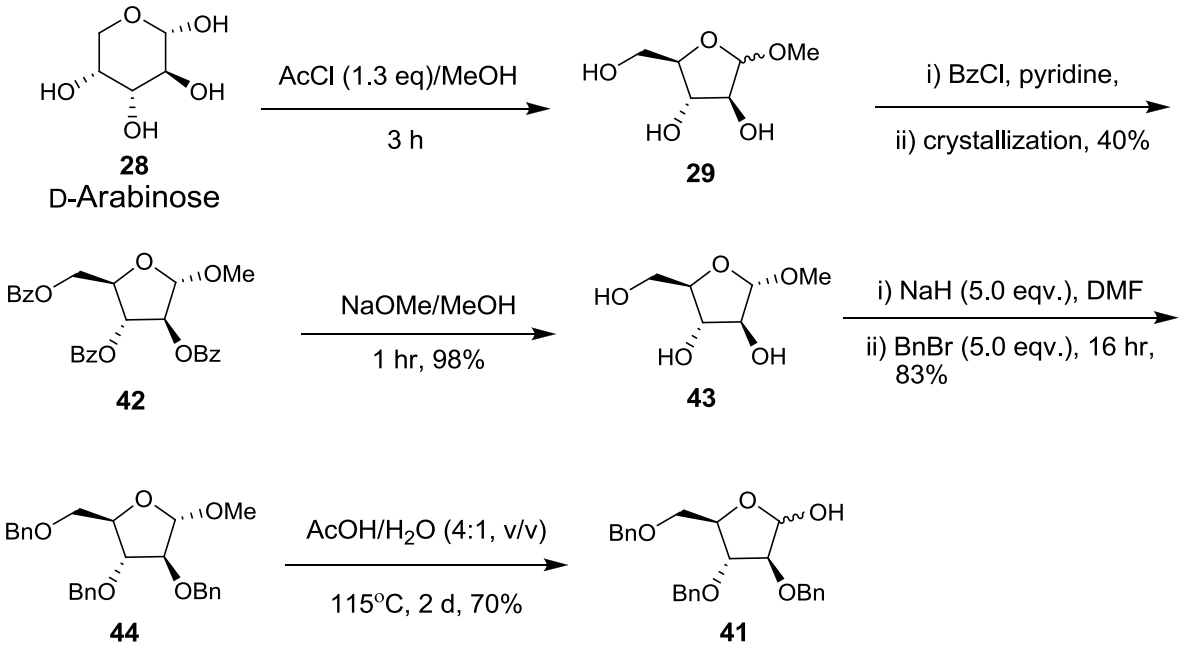
not suitable in this project: TBDMS would not be stable to the required acid hydrolysis step needed for the synthesis of compound **41**, whilst the use of benzyl ether protecting group would result in the formation of the undesired α-anomer as the predominant product which was due to the neighboring group participation. Methyl-α,β-D-arabinofuranoside **29** was submitted to standard benzylation conditions to afford methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **30** (70%, α:β, 2.8:1). The anomeric ratio was determined by ^{1}H-NMR (H-1β, 4.89 ppm, d, $J_{1\text{-}2}$ 4.1Hz; H-1α, 4.95 ppm, s). The position of the anomeric proton of compound **75** in ^{1}H-NMR was determined by 1D-Noesy NMR, which was used to help to determine the position of anomeric proton of all the other products in ^{1}H-NMR. The methyl glycoside was then hydrolyzed by stirring in an 80% acetic aqueous solution for two days at 115^{o}C, affording compound **41** (75%, α;β, 1:1.5). The anomeric ratio was determined by ^{1}H-NMR (H-1α, 5.02 ppm, d, $J_{1,OH}$ 8.5 Hz; H-1β, 5.40 ppm $J_{1,2}$ 4.5Hz, $J_{1,OH}$ 8.0 Hz) (Scheme 2.6).



Scheme 2.6. The synthesis of the arabinose donor.

Purification of methyl glycoside **30** by flash chromatography had to be repeated three times in order to obtain the pure compound. An alternative strategy was therefore investigated in order to increase the efficiency of the synthetic route to **41** (Scheme 2.7).[54]

In this alternative synthetic route, compound **29** was initially perbenzoylated. Because methyl-2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside **42** is a crystalline solid, it could be fully purified easily by crystallization (the β-anomer of **42** is an oil).[49] However the crystallization of compound **42** was not as straight forward as described in the literature. Because the reaction was done on a large scale, during the crystallization some of the β-anomer co-crystallized, resulting in yellow colored crystal. A second recrystallization was performed to obtain pure methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside **42** (yield 40%). Deprotection of **42** in a solution of NaOMe and MeOH was complete in 1 hour, and afforded methyl-α-D-arabinofuranoside **43** in a good yield (98%). It was expected that with pure methyl-α-D-arabinofuranoside **43**, the benzylation reaction would afford a cleaner product. The benzylation of **43** was in fact cleaner as shown by t.l.c., and a single purification by flash chromatography yielded the pure product **44** in 88%. The synthesis of **41** from **44** followed the same procedure as that described in the first synthetic route (75%). Compare the two synthetic routes the earlier method produced a higher yield, whilst the later method consumed less time and effort.

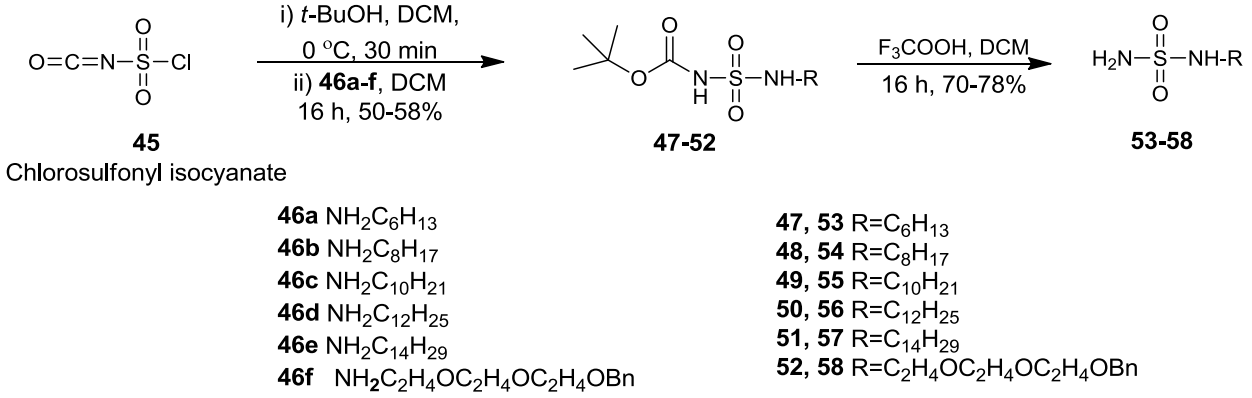


Scheme 2.7. The alternative synthetic pathway for synthesizing 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose **41**.

2.3.3 Synthesis of Sulfamide Acceptors

The sulfamide acceptors were synthesized following a published procedure involving the commercially available chlorosulfonyl isocyanate **45** (1.0 eqv.), and a variety of amines incorporating different side chains (Scheme 2.8).[51] In the first step, *tert*-butyl alcohol (*t*-BuOH) was used to form the NH-Boc protected intermediate. Amines **46a - f** were then added into the same reaction vessel to afford compounds **47 - 52**. The yields for these steps were consistently moderate (50-58%), probably due to the fact that the starting material **45** is extremely reactive and moisture sensitive. Pure compound **52** was impossible to obtain even after several purification steps. However it was proved that the impurities did not affect the later reactions. The NHBoc protected sulfamides **47 - 52** were deprotected by treatment with trifluoroacetic acid (5.0 eqv.) to give sulfamides **53 - 58** in excellent yields (70-88%). Amine 2-(2-(2-

(benzyloxy)ethoxy)ethoxy)ethylamine **46f** was synthesized by monobenzylation of commercially available TEG **46g** in four steps (Scheme 2.9).

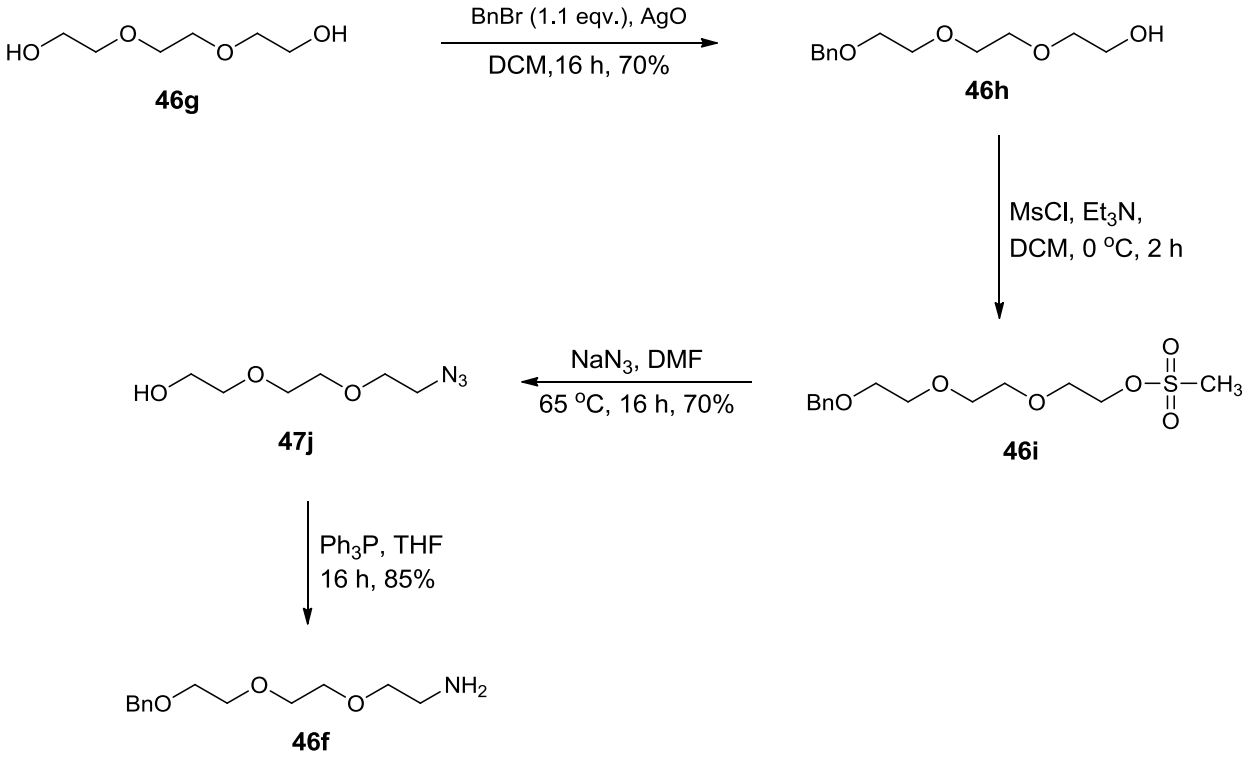


Scheme **2.8.** The synthesis of sulfamide acceptors.

2.3.4 The Synthesis of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethylamine 46f

In the first step one of the hydroxyl groups of TEG **46g** was protected as a benzyl ether following a published method.[55] The Ag_2O required in this step was freshly made, which was also commercially available. Although the literature stated the usage of freshly made Ag_2O was important, it was found that using commercial Ag_2O produced **46h** in a similar yield (70%). In the second step, the free hydroxyl group of **46h** was converted into a good leaving group (mesylate) using mesyl chloride (2.0 eqv.) in the presence of triethylamine (1.5 eqv.) in dry DCM.[56] The reaction was completed in just two hours. Compound **46i** was then used directly in the next step without further purification. In the next step, the mesylate was replaced by an azide by the treatment with sodium azide in DMF to give **46j** (70%). In the final step, the azide of **46j** was reduced to an amine using triphenylphosphine in DCM to afford **46f** 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethylamine. Initial attempts to purify **46f** by flash chromatography used WIPE (water, isopropane, ethyl acetate) and acetic acid of a ratio 10:60:30:2 as the eluting

solvent, but it was found that compound **46f** formed into an acetate salt with acetic acid, which affected the later reactions. A different solvent system (ethyl acetate → ethyl acetate: acetone, 3:2) was then used as eluent for the flash chromatography and compound **46f** was finally obtained in an excellent yield (85%).

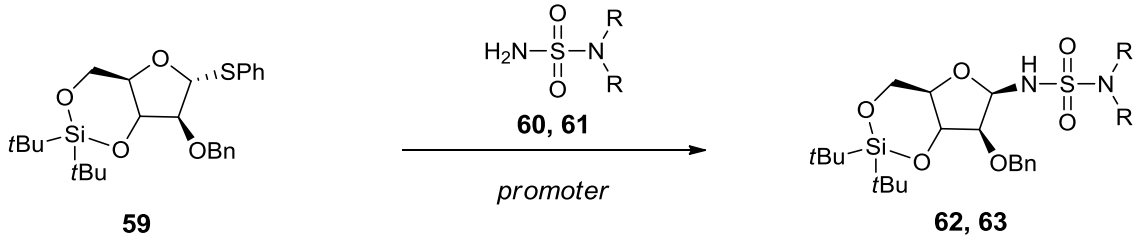


Scheme 2.9. The synthesis of a TEG **46g** derived amine 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethylamine **46f**.

2.3.5 Synthesis of Sulfamidoglycosides

Little work has been reported on the use of sulfamide as an isosteric replacement for the phosphate group of DPA for anti-TB drug design. In fact only one example exists in the literature concerning about the potential use of sulfamides in anti-TB drug design.[57] The first work done in the group on this topic was by Wilkinson (unpublished work). Initially he

attempted to synthesize two sulfamidoglycosides **62** and **63** by the stereoselective sulfamidoglycosylation of a conformationally constrained thioglycoside **59**[58] with the sulfamides incorporating alkyl chains **60** and **61** (Scheme 2.10).[59,60] However the stereoselectivity was poor (α:β, 1:2 at best) and the yields of this step were moderate (55-76%) even though a variety of activation conditions were investigated (Table 2.3). Furthermore, the sulfamidoglycosylation employing the thioglycoside **59** was not clean and the product required repeated chromatographic purification.



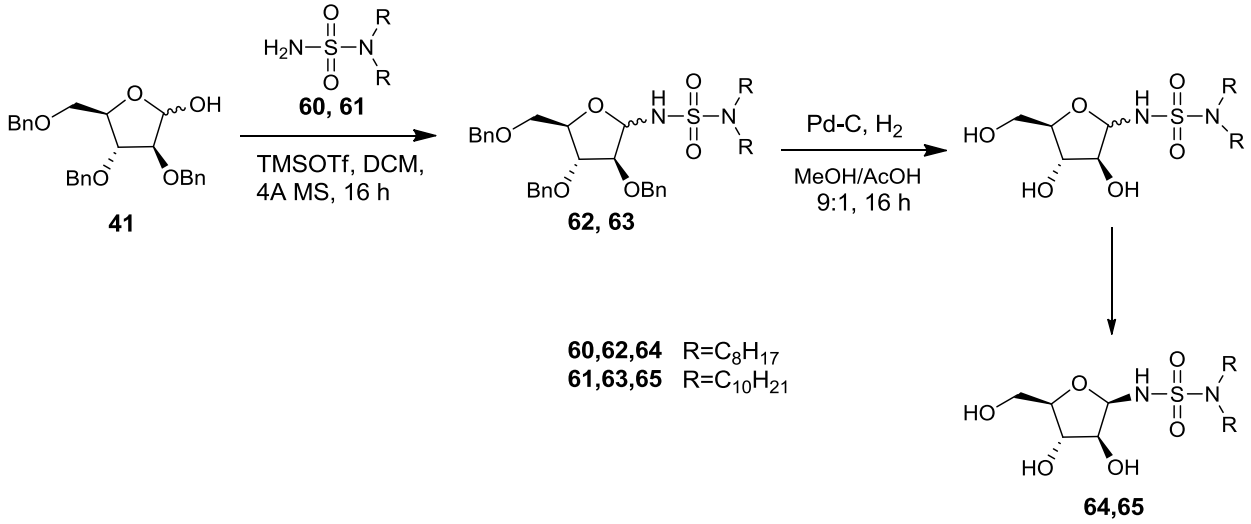
60, 62 R = C_8H_{17}
61, 63 R = $C_{10}H_{21}$

Scheme 2.10. Stereoselective synthesis of glycosyl sulfamides **62, 63** from the conformational constrained thioglycoside **59** by Wilkinson.

Entry	Conditions	Acceptor (R)	Yields (%)
1	NIS (1.5 eq.), AgOTf (0.5 eq.), DCM, 4Å MS, -78 ºC → r.t.	C_8H_{17}	55 (α:β, 1:1.7)
2	NIS (1.5 eq.), AgOTf (0.5 eq.), DCM, 4Å MS, -78 ºC → r.t.	C_8H_{17}	62 (α:β, 1:2)
3	I_2 (1.0 eq.), AgOTf (2.0 eq.), DTBMP (2.0 eq.), 3 Å MS, Et_2O, -78 ºC → r.t	$C_{10}H_{21}$	76 (α:β, 1:1)

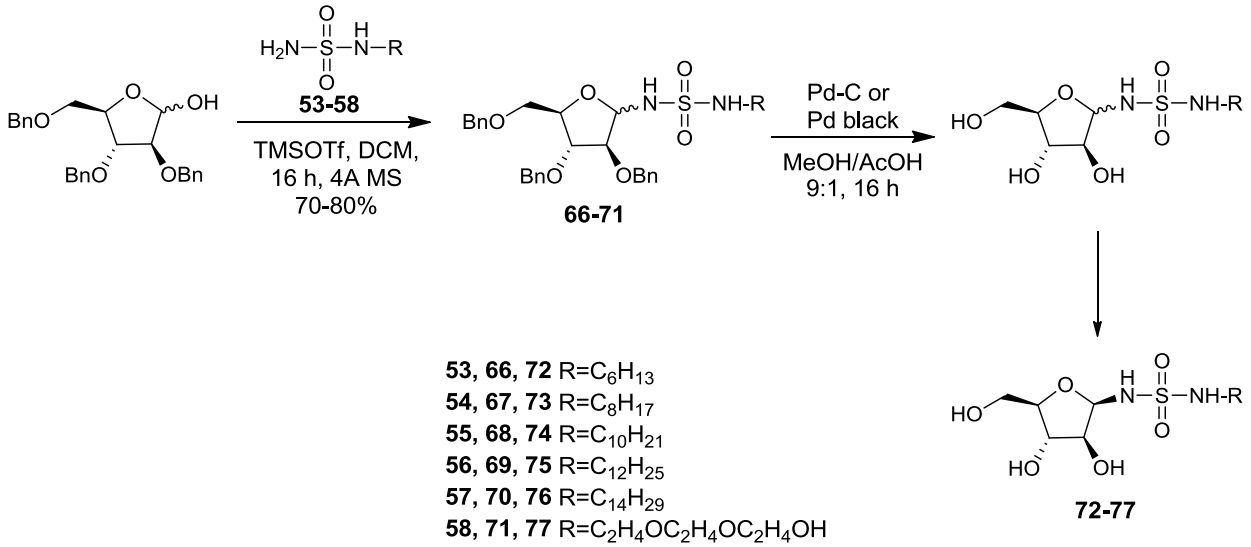
Table 2.3. Attempted stereoselective sulfamidoglycosylation with donor **61**, **62** by Wilkinson.

Therefore Wilkinson adopted a direct sulfamidoglycosylation method (Scheme 2.11**),** with which he synthesized compounds **62** (87%) and **63** (94%). Compound **62** and **63** were formed as mixtures of α- and β-anomers (α:β, 1:1) and they were not separable by flash chromatography at this stage. Hydrogenation of **62** and **63** was achieved in a solvent mixture of methanol and acetic acid (9:1, v/v) in the presence of Pd-C (10% Pd) under an atmosphere of hydrogen. These reactions afforded products that were mixtures of α-and β-anomers which were separable by flash chromatography. The β-anomers of **64** and **65** were isolated and purified by flash chromatography in good yields (87%-88% based on the β anomer). Compounds **64** and **65** were then tested against the growth of *M. bovis* BCG using the "Alamar Blue" assay, and were both found to have an MIC value of 31μg/mL.



Scheme 2.11. The synthesis of **64**, **65** by direct sulfamidoglycosylation by Wilkinson.

Following the success achieved by Wilkinson for the synthesis of the two β-sulfamidoglycosides, a new series of β-sulfamidoglycosides from D-arabinose donor **41** and sulfamide acceptors **53 - 58** were attempted to be synthesized by the direct sulfamidoglycosylation method (Scheme 2.12).



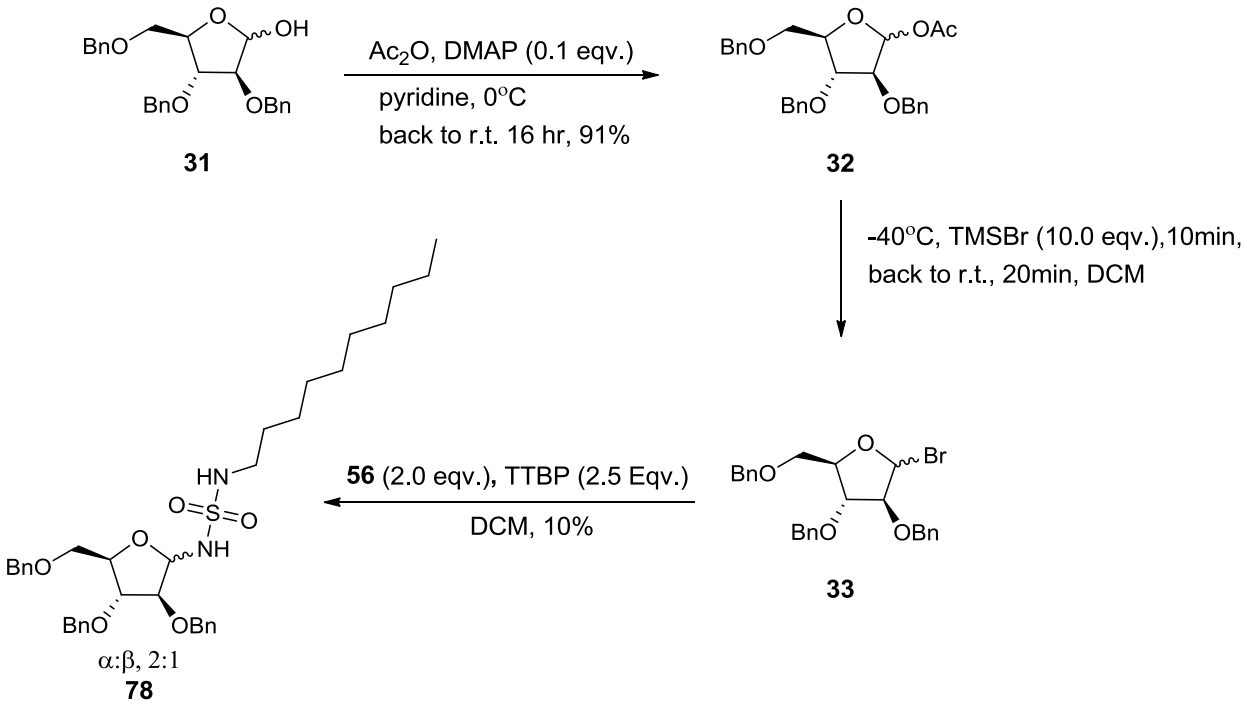
Scheme 2.12. The synthesis of compounds **72** – **77** by direct sulfamidoglycosylation.

Direct sulfamidoglycosylation proceeded in dry DCM and in the presence of TMSOTf (1.0 eqv) and crushed activited 4Å molecular sieves as moisture severely compromised reaction yields (mentioned in the unpublished work of Wilkinson). These reactions afforded compounds **66 - 71** as anomeric mixtures in good yields (70%-80%, α:β, 1:1.3 to 1:2 for compounds **66 - 70**, α:β, 1:20 for compound **71)**. The anomeric ratios were determined by ^{1}H-NMR (H-1α, s; H-1β, d, $J_{1\beta\text{-}2}$ 4.1 Hz). The α- and β-isomers showed no chromatographic resolution by t.l.c., and thus they were not separable by flash chromatography. Compounds **66 - 71** were then deprotected by hydrogenation in a solution of methanol and acetic acid (9:1, v/v) in the presence of 10% Pd-C (40% by the weight of **66 - 71**) or Pd-black (5% by the weight of **66 - 71**) under an atmosphere of hydrogen. Occasionally the hydrogenation process stopped, and the reaction did not proceed any further. In these cases, the reaction mixture was filtered through celite®, concentrated *in vacuo*, and then redissolved in fresh solvent. The hydrogenation reaction was then restarted with new reagents and under the same conditions. After deprotection was completed, the pure β-

anomers **72 - 77** were isolated by flash chromatography in reasonable yields (50%-65%, H-1, d, $J_{1\text{-}2} \sim 7.0$ Hz, $J_{1\text{-NH}} \sim 10$ Hz).

2.3.6 Stereoselective Synthesis of Sulfamidoglycoside from Glycosyl Bromide

As described earlier, the synthesis of thioglycosides (**34a - g**) from the glycosyl bromide **33** and alkyl thiols in the presence of TTBP were completely stereoselective giving only the β-anomers.[47] Thus, the same scheme was tried in order to synthesize sulfamidoglycoside stereoselectively (Scheme 2.13).



Scheme 2.13. The sulfamidoglycosylation from glycosyl bromide **33** and sulfamide acceptor **56.**

The synthesis of glycosyl bromide **33** from 2,3,5-tri-*O*-benzyl-α,β-D-arabinose **31** followed the procedure described in the work of Ayers.[47] Glycosyl bromide **33** was used in the sulfamidoglycosylation with the sulfamide acceptor **56** without further purification. However,

after 16 hours, the reaction had not proceeded significantly by t.l.c. and multiple spots were shown on the t.l.c. plate. The reaction was worked up and compound **78** was isolated by flash chromatography in a very poor yield (10%). ^{1}H-NMR analysis showed that compound **78** had been formed as a mixture of α- and β-anomers with α-anomer predominating (α:β, 2:1). The anomeric ratio was obtained by ^{1}H-NMR (H-1β, 5.21 ppm, dd, $J_{1\text{-}2}$ 4.5 Hz, $J_{1\text{-}NH}$ 10.5 Hz; H-1α, 5.30 ppm, d, $J_{1\text{-}NH}$ 11.5 Hz,). This route was therefore abandoned.

2.4 Biological Testings

Compounds **72 - 77** were tested by Priya Deri (Hon. 2011) against the growth of *M. bovis* BCG as the model for *M. tuberculosis* using the "Alamar Blue" assay.[61] The MIC values obtained for compounds **73** and **74** are shown in Table 2.4. Unfortunately the assays on the rest of the compounds had not been completed in time for inclusion in this thesis.

Compound	MIC (μg/mL)
73	125
74	31

Table 2.4. The MIC values of compounds **73** and **74** against the growth of *M. bovis* BCG obtained in the "Alamar Blue" assay.

It can be seen that both compounds inhibit bacterial growth. Presumably this is a result of inhibition of araTs involved in cell wall biosynthesis, though this last must be confirmed by further study.

These results go some way to validate the use of the sulfamide group as an isosteric replacement for the phosphate in DPA. However even the most active compound is still an order of magnitude less active than current front-line anti-TB drugs.

2.4 Conclusions and Future Work

During this research program, six novel sulfamide analogues of DPA were synthesized. Two of these sulfamide analogues and the two previously synthesized sulfamide analogues were tested against the growth of *M. bovis* BCG using the "Alamar Blue" assay, and all compounds were found to be active. This project aims to investigate the inhibitory potential of glycosyl sulfamides and also the impact of varying the chain length on the inhibitory activities. Unfortunately because of the delays in obtaining the assay results for the other four sulfamide analogues, we cannot yet conclude as to whether the side chains of the sulfamide analogues play an important part in their inhibitory activity.

Anti-TB drug development based on sulfamides is an exciting new topic. In future research in this area, some sulfamide analogues with longer side chains and side chains possessing unsaturation could be synthesized to access better mimics of the decaprenol chain in DPA.

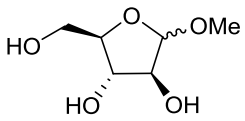
Chapter 3: Experimental

3.1 General Experimental

Solvents and Reagents: All chemicals were purchased from Sigma Aldrich, Merck, BHD, or Scharlau. Water was distilled. All other solvents were used as supplied (Analytic or HPLC grade) without further purification. TTBP was recrystallised from methanol. 'Petrol' refers to the fraction of light petroleum ether boiling in the range of 40 - 60 °C. **Chromatography:** Thin layer chromatography (t.l.c.) was performed on Merck Kieselgel $60F_{254}$ pre-coated aluminum-backed plates. Visualisation of the plates was achieved using a u. v. lamp (λ_{max} = 365 nm), and ammonium molybdate (5% in 2M H_2SO_4) or sulfuric acid (5% in EtOH) or ninhydrin (0.37% in 0.5 M acetic acid in n-butanol). Flash chromatography was performed using Merck silica gel 60 (0.063 - 0.200 mm). **Melting Points:** Melting points were recorded on an Electrothermal Melting Point Apparatus. Temperatures are given in °C. **Optical Rotations:** Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. **Infrared Spectroscopy:** Infrared spectra were recorded on Perkin-Elmer Diffuse Reflectance FT-IR spectrophotometer. Peaks are given in cm^{-1}. **NMR Spectroscopy:** Proton nuclear magnetic resonance spectra (δ_H) were recorded on a Varian As500 (500 MHz) spectrometer and were calibrated according to the chemical shift of the deuterated solvent stated or TMS (0.0 ppm). Carbon nuclear magnetic resonance spectra (δ_C) were recorded on a Varian As500 (125 MHz) spectrometer and were calibrated according to the chemical shift of the deuterated solvent stated. All chemical shifts are quoted in ppm and coupling constants (*J*) in Hz. The abbreviations used to denote multiplicities can be found in the Abbreviations section. **Mall Spectrometry:** Low-resolution and high-resolution mass spectra were recorded on a Bruker

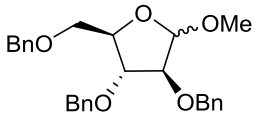
Maxis micrOTOF (ESI) spectrometer. **Biological Test**: The "Alamar Blue" assay was performed by Priya Deri in Biology Department of the University of Canterbury.

3.2 Experimental Methods



methyl-α,β-D-arabinofuranoside 29

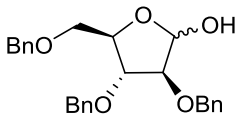
D-arabinose (10.0 g, 66.6 mmol, 1.0 equiv.) was suspended in methanol (195 mL) and stirred under nitrogen at room temperature. Acetyl chloride (6.0 mL, 84.0 mmol, 1.3 equiv.) was added slowly and the reaction was stirred vigorously for 3 hours. T.l.c. (DCM:MeOH, 4:1) indicated formation of two products, a major product methyl-α,β-D-arabinofuranoside (R_f 0.3) and a minor product methyl-α,β-D-arabinopyranoside (R_f 0.4) and complete consumption of starting material (R_f 0.0). The mixture was neutralized by adding solid K_2CO_3 (11.2 g, 81.0 mmol), filtered and the filtrate was concentrated *in vacuo* and co-evaporated with toluene (3 x 100 mL) to afford a crude mixture of methyl- α,β-D-arabinofuranoside **29** and methyl- α,β-D-arabinopyranoside as a brown oil which was used in the next step without further purification.



methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside 30

A solution of methyl-α,β-D-arabinofuranoside **29** (10.8 g, 66.8 mmol, 1.0 equiv.) in DMF (75 mL) was added dropwise to a solution of sodium hydride (60% disperse in mineral oil, 11.8 g, 294.9 mmol, 4.5 equiv.) in DMF (75 mL) under nitrogen. The mixture was stirred vigorously for 1 hour before the dropwise addition of benzyl bromide (35.3 mL, 297.2 mmol, 4.5 equiv.). The mixture was allowed to stir over night. T.l.c. (petrol:ethyl acetate, 7:1) indicated formation of a single product (R_f 0.5) and consumption of starting material (R_f 0.1). The reaction mixture was

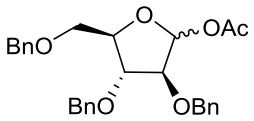
quenched in ice bath by slow addition of ethanol (60 mL), methanol (60 mL) and water (240 mL), and concentrated *in vacuo*. The residue was diluted with diethyl ether (200 mL) and washed with brine (3 x 70 mL of a saturated solution). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 7:1) to afford a mixture of methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **30** (21.7 g, 75%, α:β, 2.8:1) as a clear oil. δ_H (500 MHz, acetone-d_6) 3.29 (3H, s, alkyl CH_3-β), 3.32 (8.4H, s, alkyl CH_3-α), 3.61-3.69 (7.6H, m, H-5α, H-5'α, H-5β, H-5'β), 3.96 (2.8H, dd, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 6.5 Hz, H-3α), 4.03 (2.8H, d, $J_{2,3}$ 2.5 Hz, H-2α), 4.03-4.08 (3H, m, H-2β, H-3β, H-4β), 4.12-4.16 (2.8H, aq, *J* 5.5Hz, H-4α), 4.53-4.67 (22.8H, m, $PhCH_2$-α, $PhCH_2$-β), 4.89 (1H, d, $J_{1,2}$ 4.0 Hz, H-1β), 4.95 (2.8H, s, H-1α), 7.25-7.40 (57H, m, Ar-H). m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 457.1984 (100%), peak calculated : 457.1985.



2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose 31

Methyl 2,3,5-tri-*O*-benzyl-α, β-D-arabinofuranoside **30** (14 g, 32.2 mmol) was dissolved in an mixed solvent of water and acetic acid (250 mL, 4:1, v/v). the reaction was stirred at 115℃ for 2 days. After this time, T.l.c. (petrol:ethyl acetate, 3:1) indicated formation of one product (R_f 0.1) and consumption of starting marterial (R_f 0.4). The reaction mixture was poured onto ice-water mixture (500 mL) and the mixture was extracted with diethyl ether (3 x 400 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford a mixture of

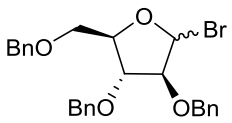
2,3,5-tri-*O*-benzyl-α, β-D-arabinofuranoside **31** (9.5 g, 70%, 1:1.5 α:β) as a white solid . δ_H (500 MHz, acetone-d_6), 3.60-3.66 (5H, m, H-5α, H-5'α, H-5β, H-5'β), 4.01- 4.05 (5H, m, H-2α, H-3α, H-2β, H-3β), 4.12-4.17 (1.5H, m, H-4β), 4.55-4.73 (16H, m, $PhCH_2$, H-4α), 5.02 (1H, d, $J_{1,OH}$ 8.5 Hz, H-1α), 5.4 (1.5H, dd, $J_{1,2}$ 4.5Hz, $J_{1,OH}$ 8.0 Hz, H-1β), 7.26-7.35 (37.5H, m, Ar-H). m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 443.1851 (100%), peak calculated : 443.1829.



acetyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside 32

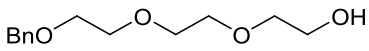
2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **31** (1.5 g, 3.6 mmol) was dissolved in pyridine (15mL) and DMAP (44 mg, 0.4 mmol) was added. The solution was stirred under hydrogen at 0℃ and Ac_2O (0.7 mL, 7.2 mmol) was added slowly. The reaction was allowed to return to r.t. and stirred for 16 h. T,l.c. (petrol:ethyl acetate, 5:1) indicated formation of one product (R_f 0.5) and complete consumption of starting material (R_f 0.1). The reaction was cooled to 0°C and quenched with EtOH (10 mL). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3 x 20 mL). The residue was purified by flash chromatography (petrol:ethyl acetate, 5:1) to afford a mixture of acetyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **32** (1.5 g, 91%, α:β, 1:5.3) as a clear oil. δ_H (500 MHz, $CHCl_3$-*d*) 2.02 (15.9H, s, $COCH_3$-β), 2.08 (3H, s, $COCH_3$-α), 3.61-3.62 (10.6H, m, H-5β, H-5'β), 3.66-3.67 (2H, m, H-5α, H-5'α), 4.02 (1H, d, $J_{3,4}$ 5.8 Hz, H-3α), 4.11-4.26 (11.6H, m, H-2α, H-2β, H-3β), 4.20-4.46 (1H, aq, *J* 5.1 Hz, 4α), 5.54-5.74 (43.1H, m, $PhCH_2$-α, $PhCH_2$-β, H-4β), 6.31 (1H, s, H-1α), 6.33

(5.3H, d, $J_{1,2}$ 4.0 Hz, H-1β), 7.24-7.41 (94.5H, m, Ar-H); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 485.1940 (100%), peak calculated : 485.1935.



2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl bromide 33

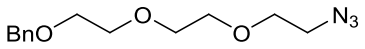
Acetyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **32** (429.2 mg, 1.85 mmol) was dissolved in dry DCM (10 mL) and cooled to -40°C under an atmosphere of nitrogen. TMSBr (1.3 mL, 18.5 mmol) was added, the reaction stirred for 10 min and allowed to return to r.t.. After 10 min t.l.c. (petrol:ethyl acetate, 5:1) indicated formation of one major product (R_f 0.1) and complete consumption of starting material (R_f 0.5). The reaction mixture was concentrated *in vacuo* and unreacted TMSBr co-evaporated with toluene (3 x 5 mL). This afforded a crude mixture of 2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranosyl bromide **33** (α:β, 7.5:1) as an orange oil, used in the next step without further purification. δ_H (500 MHz, $CHCl_3$-*d*) 3.50-3.61 (17H, m, H-5α, H-5'α, H-5β, H-5'β), 3.82-3.88 (7.5H, d, $J_{3,4}$ 5.8 Hz, H-3α), 4.00-4.25 (2H, m, H-2β, H-3β), 4.28-4.66 (67H, m, H-2α, H-4α, H-4β), 6.41 (7.5H, s, H-1α), 6.52 (1H, d, $J_{1,2}$ 3.0 Hz, H-1β) 7.08-7.28 (127.5H, m, Ar-H).



2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol 46h

Tri(ethylene) glycol (4.8 mL, 36 mmol) was added to a suspension of silver oxide (12.6 g, 54.0 mmol) in dry DCM (150 mL) under nitrogen. Benzyl bromide (4.8 mL, 39.6 mmol) was then added drop-wise at room temperature and the mixture was allowed to stir for 16 hours. T.l.c.

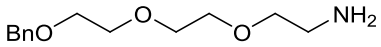
(petrol:ethyl acetate, 2:1) indicated formation of product (R_f 0.2) and consumption of starting material (R_f 0.0). The reaction mixture was filtered on Celite®, eluting with methanol and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 2:1) to afford product as a clear oil 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol **46h** (6.2 g, 72%). δ_H (500 MHz, acetone-d_6) 2.92 (1H, s, OH), 3.50-3.65 (12H, m, CH_2), 4.53 (2H, s, Ph-CH_2) 7.22-7.38 (5H, m, Ar-H); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 263.1260 (70%), peak calculated: 263.1254.



((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)benzene 46j

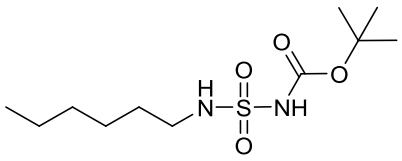
Mesylchloride (2.6 mL, 33.7 mmol,) was added dropwise to a solution of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol **46h** (5.4 g, 22.5 mmol, 1.0) in dry DCM (30 ml) at 0ºC under nitrogen. The reaction was allowed to return to room temperature and stirred for 2 hours. T.l.c. (petrol:ethyl acetate, 1:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting marterial (R_f 0.2). The reaction was quenched by the addition of methanol (20 mL). The reaction mixture was concentrated in *vacuo.* The residue was dissolved in DMF (50 mL) and stirred at room temperature under nitrogen. Sodium azide (1.46 g, 22.5 mmol) was then added into the solution. The reaction was heated up to 65 ˚C and allowed to stir at 65ºC for 16 hours. T.l.c. (petrol:ethyl acetate, 2:1) indicated formation of a single product (R_f 0.4) and consumption of starting material (R_f 0.3). The reaction mixture was diluted with water (30 ml) and extracted with ether (3 x 50 mL). The combined extracts were washed with brine (3 x 30 mL of a saturated solution), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a

yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 5:1) to afford ((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)benzene **46j** (4.2 g, 71%) as a clear oil. δ_H (500 MHz, $CDCl_3$) 3.37 (2H, t, *J* 5.0 Hz, CH_2), 3.63 - 3.71 (10H, m, CH_2), 4.57 (2H, s, Ph-CH_2), 7.18 - 7.44 (5H, m, Ar-H); *m/z* (ES^+) 288.1323 ($M+Na^+$, 100%); HRMS (ES^+) calculated for $C_{13}H_{19}N_3NaO_3$ ($M+Na^+$) 288.1323. Found 288.1319.



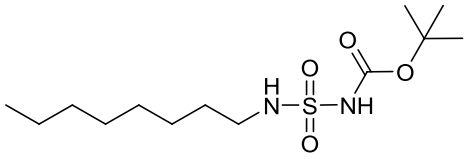
2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanamine 46f

Triphenylphosphine (8.8 g, 34.0 mmol) and water (0.6 mL, 34.0 mmol) was added to a solution of of ((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)benzene **46j** (4 g, 17.0 mmol) in THF (~ 50 mL) under nitrogen. The reaction was allowed to stir under nitrogen for 16 hours. T.l.c. (petrol:ethyl acetate, 2:1) indicated formation of a single product (R_f 0.0) and consumption of starting material (R_f 0.7). The reaction mixture was concentrated in *vacuo* to afford a yellow oil. The residue was purified by gradient flash chromatography (ethyl acetate → ethyl acetate:acetone, 3:2) to afford 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanamine **46f** (3.4 g, 85.0%) as a clear oil. δ_H (500 MHz, methanol-d_4) 2.76 (2H, t, *J* 5.32 Hz, C$\underline{H}_2$$NH_2$), 3.51 (2H, t, *J* 5.0 Hz, CH_2), 3.58 - 3.73 (8H, m, CH_2), 4.55 (2H, s, Ar-CH_2), 7.22 - 7.43 (5H, m, Ar-H); *m/z* (ES^+) 240.1600 ($M+H^+$, 100%); 262.1419 ($M+Na^+$, 100%); HRMS (ES^+) calculated for $C_{13}H_{22}NO_3$ ($M+H^+$) 240.1600. Found 240.1594. Calculated for $C_{13}H_{21}N_3NaO_3$ ($M+Na^+$) 262.1419. Found 262.1414.



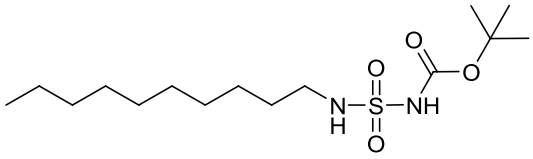
_N_-(hexyl)-_N_'-(_tert_-butoxycarbonyl)sulfamide 47

A stirred solution of chlorosulfonyl isocyanate (1.5 mL, 17.1 mmol, 1.0 equiv.) in dry DCM (20 mL) was cooled to 0˚C under nitrogen, and *tert*-butyl alcohol (2.3 mL, 24.0 mmol, 1.4 equiv.) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of hexylamine (2.3 mL, 17.1 mmol, 1.0 equiv.) and dry triethylamine (2.7 mL, 18.8 mmol, 1.1 equiv.) in dry DCM (20 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.5, streaking) and consumption of starting material (R_f ~ 0.1, streaking). The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and brine (3 x 50 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (DCM) to afford *N*-(hexyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **47** (2.7 g, 58.0%) as a white solid, m.p. 98-102 ºC (ethyl acetate/petrol. υ_{max} (diffraction) 3300 (s, N-H), 1709 (s, C=O), 1353 (s, S=O), 1170 (s, S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 0.89 (3H, t, *J* 7.2 Hz, CH_3), 1.30-1.31 (4H, m, $C\underline{H_2}C\underline{H_2}CH_3$), 1.36-1.39 (2H, m, $NHCH_2CH_2C\underline{H_2}$), 1.46 (9H, s, *tert*-Bu CH_3), 1.60 (2H, quin, *J* 7.6 Hz, $NHCH_2C\underline{H_2}$), 3.05 (2H, q, *J* 7.0 Hz, $NHC\underline{H_2}$); δ_C (126 MHz, acetone-d_6) 13.6 (CH_3), 22.5 (CH_2), 26.4 (CH_2), 27.5 (*tert*-Bu CH_3), 29.2 (CH_2), 31.5 (CH_2), 43.7 (CH_2), 81.7 (*tert*-Bu C), 150.9 (O=C); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 303.1349 (100%), peak calculated : 303.1354.



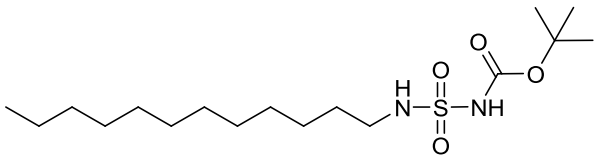
_N_-(octyl)-_N_'-(*tert*-butoxycarbonyl)sulfamide 48

A stirred solution of chlorosulfonyl isocyanate (1 mL, 11.4 mmol) in dry DCM (12 mL) was cooled to 0˚C under nitrogen, and *tert*-butyl alcohol (1.5 mL, 16.0 mmol) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of octylamine (1.9 mL, 11.4 mmol) and dry triethylamine (1.8 mL, 12.5 mmol) in dry DCM (12 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM:MeOH, 30:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.8, streaking) and consumption of starting material (R_f ~ 0.2, streaking). The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and brine (3 x 50 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by gradient flash chromatography (DCM → DCM:methanol, 20:1) to afford *N*-(octyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **48** (1.8 g, 51.6%) as a white solid. m.p. 102 ºC (ethyl actate/petrol). υ_{max} (diffraction) 3334 (w, N-H) 3292 (m, N-H), 1709 (s, C=O), 1350 (s, S=O), 1165 (s, S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 0.88 (3 H, t, *J*=6.42 Hz), 1.28-1.33 (10 H, m, CH_2), 1.47 (9 H, s, *tert*-Bu CH_3), 1.56 - 1.64 (2 H, m, $C\underline{H}_2CH_2NH$), 3.03 - 3.08 (2 H, t, *J*=7.0 Hz, $C\underline{H}_2NH$) 6.38 (1H, br. s, $CH_2N\underline{H}$); δ_c (126 MHz, acetone-d_6) 13.7 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 27.5 (*tert*-Bu CH_3), 29.2 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 43.7 (CH_2NH); *m/z* (ESI^+) 331.1669 ($M+Na^+$, 100%); HRMS (ESI^+) calculated for $C_{13}H_{28}N_2NaO_4S$ ($M+Na^+$) 331.1669. Found 331.1662.



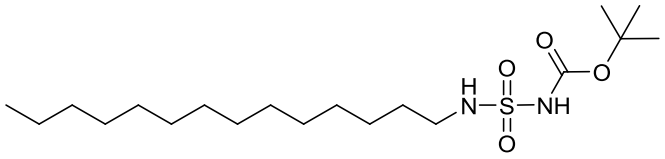
***N*-(decyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide 49**

A stirred solution of chlorosulfonyl isocyanate (2.0 mL, 22.8 mmol) in dry DCM (12 mL) was cooled to 0˚C under nitrogen and *tert*-butyl alcohol (3.0 mL, 16.0 mmol) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of decylamine (4.8 mL, 22.8 mmol) and dry triethylamine (3.6 mL, 25.1 mmol) in dry DCM (12 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM:MeOH, 30:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.80 streaking) and consumption of starting material (R_f ~ 0.20 streaking). The reaction mixture was diluted with DCM (100 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 70 mL) and brine (3 x 70 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by gradient flash column chromatography (DCM → DCM:methanol, 20:1) to afford *N*-(decyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **49** (3.8 g, 50%) as a white solid, m.p. 97-98 ˚C (ethyl acetate/petrol). υ_{max} (diffraction) 3327(w, N-H), 3289 (m, N-H), 1710 (s, C=O), 1350 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (500 Hz, $CDCl_3$) 0.88 (3H, t, *J*=6.97 Hz, CH_3), 1.19 - 1.39 (14H, m, CH_2), 1.50 (9H, s, *tert*-Bu CH_3), 1.54 - 1.64 (2H, m, $C\underline{H}_2CH_2NH$), 3.06 (2H, q, *J*=6.72 Hz, $C\underline{H}_2NH$), 5.03 (1H, t, *J*=5.87 Hz, NH), 7.07 (1H, br. s. NH); δ_C (126 MHz, acetone) 13.7 (CH_3), 22.7 (CH_2), 26.7 (CH_2) 27.5 (*tert*-Bu CH_3), 29.8 (CH_2), 30.0 (CH_2) 30.2 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 40.7 (CH_2), 81.7 (*tert*-Bu C), 150.9 (C=O); *m/z* (ESI^+) 359.1978 ($M+Na^+$, 100%); HRMS (ESI^+) calculated for $C_{15}H_{32}N_2NaO_4S$ ($M+Na^+$) 359.1978. Found 359.1975.



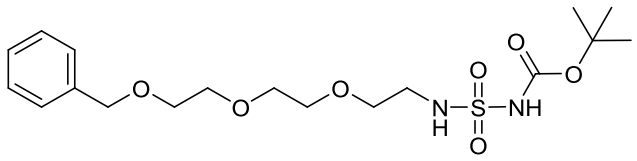
_N_-(dodecyl)-_N_'-(_tert_-butoxycarbonyl)sulfamide 50

A stirred solution of chlorosulfonyl isocyanate (1.0 ml, 11.4 mmol) in dry DCM (15 mL) was cooled to 0˚C under nitrogen, and *tert*-butyl alcohol (1.5 mL, 16.0 mmol) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of dodecylamine (2.2 g, 11.4 mmol) and dry triethylamine (1.8 mL, 12.5 mmol) in dry DCM (12 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.3, streaking) and consumption of starting material (R_f ~ 0.0). The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and brine (3 x 50 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by gradient flash chromatography (DCM → DCM:methanol, 30:1) to afford *N*-(dodecyl)-*N*'-(*tert*-butoxycarbonyl) sulfamide **50** (2.2 g, 52%) as a white solid, m.p. 91-93 ºC (petrol/ethyl acetate). υ_{max} (diffraction) 3325 (w, N-H), 3277 (m, N-H), 1710 (w, C=O), 1350 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (500 MHz, chloroform-*d*) 0.88 (3H, t, *J* 7.0 Hz, CH_3), 1.25-1.34 (22H, m, CH_2), 1.45 (9H, s, *tert*-Bu CH_3), 1.53-1.58 (2H, m, $NHCH_2C\underline{H}_2$), 3.05-3.06 (2H, m, $NHC\underline{H}_2$), 5.09 (1H, br. s, NH); δ_C (500 MHz, chloroform-*d*) 14.1 (CH_3), 22.7 (CH_2), 26.6 (CH_2), 28.0 (*tert*-Bu CH_3), 29.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 43.9 ($NHCH_2$), 83.8 (*tert*-Bu C), 150.2 (CO); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 415.2601 (66.5%), peak calculated: 415.2601.



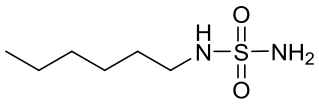
_N_-(tetradecyl)-_N_'-(*tert*-butoxycarbonyl)sulfamide 51

A stirred solution of chlorosulfonyl isocyanate (1.0 ml, 11.4 mmol) in dry DCM (10 mL) was cooled to 0˚C under nitrogen, and *tert*-butyl alcohol (1.5 mL, 16.0 mmol, 1.4 equiv.) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of dodecylamine (2.6 g, 11.4 mmol) and dry triethylamine (1.8 mL, 12.5 mmol) in dry DCM (10 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.3, streaking) and consumption of starting material (R_f ~ 0.0). The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and brine (3 x 50 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (DCM) to afford *N*-(tetradecyl)-*N*'-(*tert*-butoxycarbonyl) sulfamide **51** (1.9 g, 50%) as a white solid, m.p. 98-100 ºC (petrol/ethyl acetate). υ_{max} (diffraction) 3286 (m, N-H), 1714 (s, C=O), 1348 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (500 MHz, chloroform-*d*) 0.88 (3H, t, *J* 7.0 Hz, CH_3), 1.25-1.34 (22H, m, CH_2), 1.54-1.58 (2H, m, $NHCH_2C\underline{H}_2$), 3.04-3.06 (2H, m, $NHC\underline{H}_2$), 5.09 (1H, br. s, NH); δ_C (500 MHz, chloroform-*d*) 14.1 (CH_3), 22.7 (CH_2), 26.6 (CH_2), 28.0 (*tert*-Bu CH_3), 29.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 43.9 ($NHCH_2$), 83.8 (*tert*-Bu C), 150.2 (CO); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 415.2618 (65.5%), peak calculated: 415.2601.



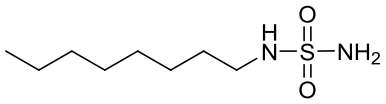
***N*-(2-(2-(2-(benzyloxyethoxy)ethoxy)ethyl-*N*'-(*tert*-butoxycarbonyl)sulfamide 52**

A stirred solution of chlorosulfonyl isocyanate (1.4 mL, 16.3 mmol) in dry DCM (15 mL) was cooled to 0˚C under nitrogen and *tert*-butyl alcohol (2.1 mL, 22.8 mmol) was added drop-wise. The solution was stirred for a further 30 minutes at 0 ˚C. A solution of 2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanamine **46f** (3.9 g, 16.3 mmol) and dry triethylamine (2.5 mL, 17.9 mmol) in dry DCM (20 mL) was then added dropwise. The reaction mixture was allowed to return to room temperature and stirred for 16 hours. T.l.c. (DCM:MeOH, 20:1, charring with ninhydrin) indicated formation of a major product (R_f ~ 0.4 streaking) and consumption of starting material (R_f ~ 0.1 streaking). The reaction mixture was diluted with DCM (25 mL), washed with saturated aqueous $NaHCO_3$ solution (3 x 25 mL) and brine (3 x 25 mL of a saturated solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by gradient flash column chromatography (DCM → DCM:methanol, 40:1) to afford *N*-benzyloxytriethoxy-*N'*-(tert-butoxycarbonyl) sulfamide **52** (3.7 g, 55%) as a clear oil. υ_{max} (diffraction) 3293 (m, N-H), 1715 (s, C=O), 1150 (s, S=O) cm^{-1}; δ_H (500 MHz, methanol-d_4) 1.44 - 1.54 (9 H, m, *tert*-Bu CH_3), 3.19 (1 H, t, *J* 5.30 Hz, $NH_2C\underline{H}_2$), 3.53 - 3.71 (8 H, m, CH_2), 4.10 (1 H, t, *J* 5.30 Hz, NH_2 $CH_2C\underline{H}_2$), 4.56 (2 H, s, Ar-CH_2), 7.22 - 7.43 (5 H, m, Ar); δ_C (126 MHz) 28.2 (*tert*-Bu CH_3), 44.2 (CH_2), 69.9 (CH_2), 70.4 (CH_2), 70.9 (CH_2), 71.2 (CH_2), 73.4 (CH_2), 82.6 (*tert*-Bu C), 128.1 (Ar-C), 128.4 (Ar-C), 129.0 (Ar-C), 139.8 (Ar-C), 151.7 (CO); *m/z* (ES^+) 441.1665 (M+Na, 100%); HRMS (ES^+) calculated for $C_{18}H_{30}N_2NaO_7S$ ($M+Na^+$) 441.1665. Found 441.1666.



_N_-(hexyl)-sulfamide 53

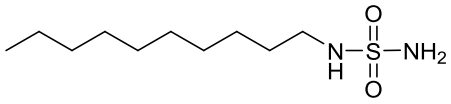
Trifluoroacetic acid (2.0 mL, 25.0 mmol) was added to a solution of *N*-(Hexyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **47** (1.4 g, 5.0 mmol) in DCM (40 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (petrol:ethyl acetate, 3:1, charring with ninhydrin) indicated formation of a major product (R_f ~ 0.6 streaking) and consumption of starting marterial (R_f ~ 0.2 streaking). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford *N*-(hexyl)-sulfamide **53** (0.6 g, 70%) as a white solid, m.p. 76-77 ºC (ethyl acetate/petrol). υ_{max} (diffraction) 3331 (w, N-H), 3289 (m, N-H), 1357 (s, S=O), 1130 (s, S=O); δ_H (500 MHz, acetone-d_6) 0.89 (3H, t, *J* 0.7 Hz, CH_3), 1.28-1.40 (6H, m, CH_2), 1.55-1.60 (2H, m, $NHCH_2C\underline{H}_2$), 3.03-3.07 (2H, m, $NHC\underline{H}_2$), 5.59 (1H, br. s, NH), 5.81 (2H, s, NH_2); δ_C (500 MHz, acetone-d_6) 13.6 (CH_3), 22.6 (CH_2), 26.6 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 43.4 ($NHCH_2$); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 203.0833 (74.0%), peak calculated : 203.0825.



_N_-(octyl)-sulfamide 54

Trifluoroacetic acid (1.8 mL, 23.0 mmol) was added to a solution of *N*-(Octyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **48** (1.0 g, 4.6 mmol) in DCM (16 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (DCM:MeOH, 30:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.3 streaking) and consumption of starting marterial (R_f ~ 0.8 streaking). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The

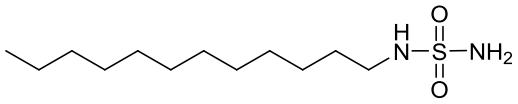
residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford *N*-(octyl)-sulfamide **54** (0.7 g, 72%) as a white solid. m.p. 66-68 ºC (ether). υ_{max} (diffraction) 3330 (w, N-H), 3281 (w, N-H), 1350 (w, S=O), 1141 (s, S=O); δ_H (500 MHz, acetone-d_6) 0.88 (3H, t, *J* 6.7Hz, CH_3), 1.29-1.39 (10H, m, CH_2), 1.50-1.61 (2H, m, $C\underline{H}_2CH_2NH$), 3.03-3.08 (2H, m, $C\underline{H}_2NH$), 5.59 (1H, br. s, $CH_2N\underline{H}$), 5.82 (2H, s, NH_2); δ_C (126 MHz, acetone-d_6) 13.7 (CH_3), 22.7 (CH_2), 26.9 (CH_2), 28.9 (CH_2), 29.4 (CH_2) 29.6 (CH_2), 29.6 (CH_2), 43.4 (CH_2NH); *m/z* (ESI^+) 231.1137 ($M+Na^+$, 100%); HRMS (ESI^+) calculated for $C_8H_{20}N_2NaO_2S$ ($M+Na^+$) 231.1137. Found 231.1138.



_N_-decyl sulfamide 55

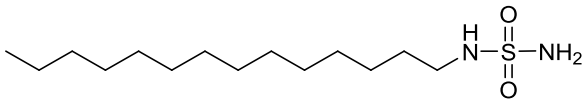
Trifluoroacetic acid (3 mL, 38.6 mmol) was added to a solution of *N*-(Decyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **49** (2.6 g, 7.7 mmol) in DCM (100 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (DCM:MeOH, 20:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.3 streaking) and consumption of starting marterial (R_f ~ 0.7 streaking). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford *N*-decyl sulfamide **55** (1.3 g, 72%) as a white solid, m.p. 75-76˚C (ethyl acetate/petrol). υ_{max} (diffration) 3330 (w, N-H), 3283 (w, NH), 1345 (w, S=O) 1135 (w, S=O) cm^{-1}; δ_H (500MHz ,acetone-d_6) 0.88 (3H, t, *J*=6.60 Hz, CH_3), 1.18 - 1.47 (14H, m, CH_2), 1.58 (2H, m, $C\underline{H}_2CH_2NH$), 3.07 (2H, q, *J*=6.97 Hz, $C\underline{H}_2NH$), 5.59 (1H, br. s. $CH_2N\underline{H}$), 5.82 (2H, br. s. NH_2); δ_C (126 MHz, acetone-d_6) 13.7 (CH_3), 22.7 (CH_2), 26.9 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.6

(CH_2), 29.7 (CH_2), 31.9 (CH_2), 43.4 (CH_2); *m/z* (ESI^+) 259.1445 ($M+Na^+$, 100%); HRMS (ESI^+) calculated for $C_{10}H_{24}N_2NaO_2S$; ($M+Na^+$) 259.1445. Found 259.1451.



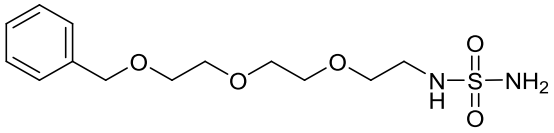
_N_-dodecyl sulfamide 56

Trifluoroacetic acid (1.9 mL, 24.7 mmol) was added to a solution of *N*-(Dodecyl)-*N*'-(*tert*-butoxycarbonyl)sulfamide **50** (1.8 g, 4.9 mmol) in DCM (80 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (petrol:ethyl acetate, 3:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.1 streaking) and consumption of starting marterial (R_f ~ 0.5 streaking). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford *N*-dodecyl sulfamide **56** (1.0 g, 78%) as a white solid, m.p. 84-88˚C (ethyl acetate/petrol). υ_{max} (diffration) 3338 (w, N-H), 3278 (w, NH), 1345 (w, S=O) 1136 (w, S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 0.88 (3H, t, *J 7.3* Hz, CH_3), 1.29-1.37 (18H, m, CH_2), 1.57-1.58 (2H, m, $NHCH_2C\underline{H}_2$), 3.04-3.05 (2H, m, $NHC\underline{H}_2$), 5.58 (1H, br s, $CH_2N\underline{H}$), 5.80 (2H, br s, NH_2); δ_C (500 MHz, acetone-d_6) 14.4 (CH_3), 23.3 (CH_2), 27.6 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 32.6 (CH_2), 44.1 (CH_2); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 287.1760 (100%), peak calculated: 287.1764.



_N_-tetradecyl sulfamide 57

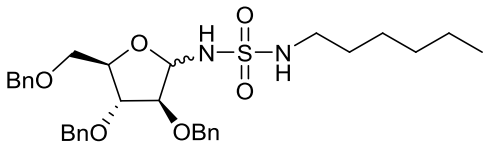
Trifluoroacetic acid (1.9 mL, 24.7 mmol) was added to a solution of *N*-(Tetradecyl)-*N*'-(tert-butoxycarbonyl)sulfamide **51** (2.6 g, 6.6 mmol) in DCM (50 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (petrol:ethyl acetate, 3:1, charring with ninhydrin) indicated formation of a single product (R_f ~ 0.1 streaking) and consumption of starting marterial (R_f ~ 0.7 streaking). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford *N*-tetradecyl sulfamide **57** (1.4 g, 70%) as a white solid, m.p. 93-95˚C (ethyl acetate/petrol). υ_{max} (thin film) 3330 (w, N-H), 3276 (m, NH), 1340 (w, S=O) 1134 (m, S=O) cm^{-1} δ_H (500 MHz, methanol-d_4) 0.90 (3H, t, *J* 7.3 Hz, CH_3), 1.29-1.37 (22H, m, CH_2), 1.55 (2H, quin., *J* 7.0 Hz, $NHCH_2C\underline{H}_2$), 3.01 (2H, t, *J* 7.2 Hz, $NHC\underline{H}_2$); δ_C (126 MHz, methanol-d_4) 14.4 (CH_3), 23.7 (CH_2), 27.9 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 44.3 (CH_2); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 315.2077 (100%), peak calculated: 315.2077.



_N_-((2-(2-(2-(benzyloxyethoxy)ethoxy)ethyl)-sulfamide 58

trifluoroacetic acid (1.7 mL, 21.5 mmol) was added to a solution of *N*-(2-(2-(2-(benzyloxyethoxy)ethoxy)ethyl- *N*'-(*tert*-butoxycarbonyl)sulfamide **52** (1.8 g, 4.3 mmol) in DCM (30 mL). The solution was stirred at room temperature for 16 hours. T.l.c. (ethyl acetate :

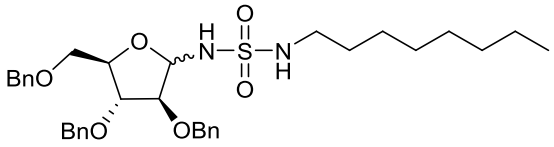
petrol, 2:1, charring with ninhydrin) indicated formation of a single product (R_f 0.2) and consumption of starting marterial (R_f 0.0). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash column chromatography (ethyl acetate : petrol, 2:1) to afford *N*-((2-(2-(2-(benzyloxyethoxy)ethoxy)ethyl)-sulfamide **58** (1.0 g, 73%) as a clear oil. υ_{max} (thin film) 3277 (m, NH), 1335 (w, S=O) 1132 (w, S=O) cm^{-1}; δ_H (500 MHz, methanol-d_4) 3.21 (2H, t, *J* 5.00 Hz, CH_2), 3.56 - 3.71 (10H, m, CH_2), 4.54 (2H, s, CH_2-Ar), 7.18 - 7.41 (5H, m, Ar-H); δ_C (126 MHz) 49.4 (CH_2), 69.3 (CH_2), 69.9 (CH_2), 70.0 (CH_2), 70.1 (CH_2), 70.2 (CH_2), 73.0 (CH_2), 127.5 (Ar-C), 127.8 (Ar-C), 128.2 (Ar-C), 138.4 (Ar-C); *m/z* (ES^+) 341.1141 (M+Na, 100%); HRMS (ES^+) calculated for $C_{13}H_{22}N_2NaO_5S$ ($M+Na^+$) 341.1141. Found 341.1142.



***N*-hexyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 66**

2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **31** (1.3 g, 3.0 mmol), *N*-(Hexyl)-sulfamide **53** in dry DCM (50 mL) stirred at room temperature under nitrogen. TMSOTF (0.6 mL, 3.3 mmol) was added drop-wise and the mixture was allowed to stir for 16 hours. T.l.c. (petrol:ethyl acetate, 5:1) indicated formation of a single product (R_f 0.3) and the consumption of starting material (R_f 0.1) . The reaction was neutralized by the drop-wise addition of excess triethylamine (~ 1.2 mL). The reaction mixture was filtered on celite®, eluting with ethyl acetate and concentrated in *vavuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 8:1) to afford *N*-hexyl-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl) sulfamide **66** (1.2 g, 70%, α:β, 1:2) as a waxy solid. υ_{max} (thin film) 3264 (w, N-H), 3289 (m, N-H), 1350 (w, S=O), 1158 (w,

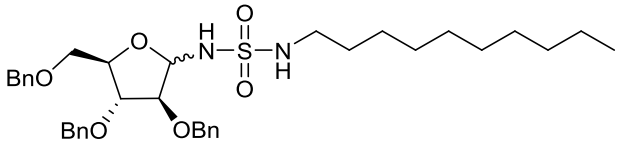
S=O) cm^{-1}; δ_H (500 MHz, chloroform-*d*) 0.85-0.88 (9H, m, CH_3-α, CH_3-β), 1.22-1.32 (18H, m, CH_2-α, CH_2-β), 1.45-1.54 (6H, m, $NHCH_2C\underline{H}_2\alpha$, $NHCH_2C\underline{H}_2\beta$), 2.97-3.05 (6H, m, $NHC\underline{H}_2\alpha$, $NHC\underline{H}_2\beta$), 3.46 (2H, dd, $J_{5\text{-}5'}$ 9.6 Hz, $J_{5\text{-}4}$ 7.5 Hz, H-5β), 3.50-3.52 (2H, m, H-5α, H-5'α), 3.56 (2H, dd, $J_{5'\text{-}5}$ 9.7 Hz, $J_{5'\text{-}4}$ 5.9 Hz, CH-5'β), 3.93-4.06 (6H, m, H-3α, H-3β, H-2α, H-2β), 4.08-4.14 (2H, m, H-4β), 4.16-4.20 (1H, m, $NH_2\alpha$), 4.22-4.26 (2H, m, $NH_2\beta$), 4.30-4.36 (1H, m, H-4α), 4.40-4.60 (18H, m, Ph-$C\underline{H}_2$), 5.36 (1.0H, dd, $J_{1\text{-}NH}$ 10.3 Hz, $J_{1,2}$ 4.4 Hz, H-1α), 5.41 (2H, d, $J_{1\text{-}NH}$ 10.8 Hz, H-1β), 5.55 (1H, d, $J_{NH\text{-}1}$ 10.3 Hz, NH-α), 5.59 (2H, $J_{NH\text{-}1}$ 10.8 Hz, NH-β), 7.22-7.34 (35.5H, m, Ar-H); δ_C (500 MHz, chloroform-*d*) 14.0 (CH_3), 22.5 (CH_2), 26.4 (CH_2), 29.4 (CH_2), 31.4 (CH_2), 43.4 (CH_2), 43.5 (CH_2), 71.8 (CH_2), 71.9 (CH_2), 72.3 (CH_2), 73.3 (CH_2), 80.8 (CH), 81.2 (CH), 81.8 (CH), 82.3 (CH), 83.3 (CH), 84.3 (CH), 84.7 (CH), 88.2 (CH), 127.7-138.0 (Ph-C); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 605.2656 (100%), peak calculated:605.2656.



***N*-octyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 67**

2,3,5-Tri-*O*-α,β-D-benzylarabinofuranose **31** (0.7 g, 1.7 mmol), *N*-(octyl)-sulfamide **54** (354 mg, 1.7 mmol) and crushed, activated 3Å molecular sieves (~ 400 mg) were suspended in dry DCM (20 mL) stirred at room temperature under nitrogen. TMSOTF (0.3 mL, 1.7 mmol) was added drop-wise and the mixture was allowed to stir for 16 hours. T.l.c. (petrol:ethyl acetate, 2:1) indicated formation of a single product (R_f 0.6) and consumption of starting material (R_f 0.3). The reaction was neutralized by the drop-wise addition of excess triethylamine (~ 0.6 mL). The reaction mixture was filtered on celite®, eluting with ethyl acetate and concentrated in *vavuo* to

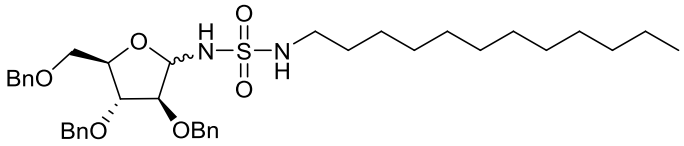
afford a yellow clear oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 10:1) to afford *N*-octyl-*N*'-2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide **67** (751 mg, 77%, α:β, 1:2) as a waxy solid. υ_{max} (thin film) 3259 (w, N-H), 3289 (m, N-H), 1355 (w, S=O), 1158 (s, S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.88 (9H, t, *J* 6.8, CH_3), 1.26 (30H, m, CH_2), 1.47 - 1.61 (6H, m, CH_2), 2.99 - 3.02 (6H, m, NHC$\underline{H}_2$ α and NHC$\underline{H}_2$ β), 3.44 - 3.50 (3H, m, H-5α and H-5β), 3.46 -3.60 (3H, H-5'α, and H-5'β), 3.94 – 4.05 (3H, m, H-3α and H-3β), 4.01 - 4.02 (3H, m, H-2α and H-2β), 4.03-4.05 (1H, m,H-4α), 4.33-4.35 (2H, m, H-4β), 4.46 - 4.58 (18H, m, PhC$\underline{H}_2$), 5.36 - 5.38 (2H, dd, J_{NH-1} 11.0 Hz, J_{1-2} 4.10 Hz, H-1β), 5.41-5.43 (1H, d, *J* 10.60 Hz, H-1α), 5.54-5.60 (3H, m, NH-α, NH-β), 6.98 - 7.53 (45H, m, Ar-Hα and Ar-Hβ); δ_C (126 MHz, $CDCl_3$) 14.1 (CH_3), 22.6, 26.7, 28.3, 29.9, 31.7, 43.4 (CH_2), 70.0, 70.0 (C-5α, C-5β), 71.7, 71.8 72.9, 72.3, 73.3, 73.4 (PhC$\underline{H}_2$), 80.8, 81.1 (C-2α, C-2β), 81.2 (C-3α of C-3β), 82.3 (C-4α), 83.3 (C-1β), 84.2 (C-3α or C-3β), 88.2 (C-1α), 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 127.9, 128.0, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6 (Ar-CH), 136.6, 136.7, 136.8, 137.4, 137,6, 137.8 (Ar-C); *m/z* (ESI^+) 633.2975 ($M+Na^+$, 7.32%); HRMS (ESI^+) calculated for $C_{34}H_{46}N_2NaO_6S$ ($M+Na^+$) 633.2975. Found 359.2969.



***N*-decyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 68**

2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **31** (0.5 g, 1.2 mmol), *N*-(Octyl)-sulfamide **55** (0.3 g, 1.2 mmol) and crushed, activated 3Å molecular sieves (~ 400 mg) was suspended in dry DCM (15 mL) under nitrogen. TMSOTF (220 μL, 1.2 mmol) was added drop-wise at room temperature and the mixture was allowed to stir for 16 hours. T.l.c. (petrol:ethyl acetate 5:1)

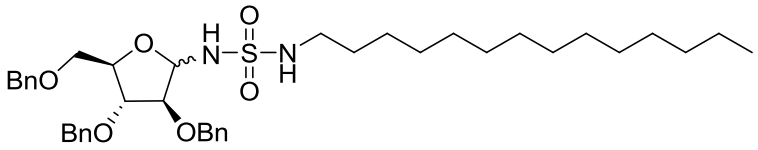
indicated formation of a single product (R_f 0.4) and consumption of starting material (R_f 0.1). The reaction was neutralized by the drop-wise addition of excess triethylamine (~ 0.6 mL). The reaction mixture was filtered on celite®, eluting with ethyl acetate and concentrated in *vavuo* to afford a yellow clear oil. The residue was purified by flash chromatography (petrol:ethyl acetate, 10:1) to afford *N*-decyl-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl sulfamide **68** (0.6 g, 78%, α:β, 1:1.3) as a waxy solid. υ_{max} (thin film); 3288 (w, NH), 1337 (s, S=O), 1155 (w, S=O) cm^{-1}; δ_H (500 MHz, methanol-d_4) 0.89 (6.9 H, CH_3 α and CH_3 β), 1.16 - 1.38 (32.2H, m, CH_2), 1.43 - 1.55 (4.6H, t, *J* 6.6 Hz, C<u>H</u>$_2$NH), 2.85 - 3.05 (4.6H, m, CH_2), 3.48 - 3.65 (4.6H, m, H-5α, H-5β, H-5'α, H-5'β), 3.86 - 4.29 (5.9H, m, H-2α, H-3α, H-2β, H-3β, H-4β), 4.39 - 4.74 (14.8H, m, $PhCH_2$, H-4α), 5.21 (1.3H, d, $J_{1,NH}$ 3.67 Hz, H-1β), 5.30 (1H, d, $J_{1,NH}$ 4.40 Hz, H-1α), 7.09 - 7.44 (34.5H, m, Ar-H); δ_C (126 MHz, methanol-d_4) 14.5 (CH_3), 20.9 (CH_2), 23.7 (CH_2), 27.9 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 44.0 (CH_2), 44.1 (CH_2), 61.5 (CH), 71.2 (CH), 71.7 (CH), 72.7 (CH), 73.0 (CH), 74.3 (CH), 81.6 (CH), 81.8 (CH), 82.7 (CH), 82.9 (CH), 83.6 (CH), 85.5 (CH), 88.0 (CH), 89.3 (CH), 89.3 (CH), 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.1, 129.2, 129.4, 129.5, 138.8, 139.1, 139.2, 139.3, 139.4 (Ar-C); *m/z* (ESI^+) 661.3280 ($M+Na^+$, 10%); HRMS (ESI^+) calculated for $C_{36}H_{50}N_2NaO_6S$ ($M+Na^+$) 661.3280. Found 661.3282.



_N_-dodecyl-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 69

2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **31** (1.4 g, 3.3 mmol), *N*-(Dodecyl)-sulfamide **56** (0.88 g, 3.3 mmol) and crushed, activated 3Å molecular sieves (~ 800 mg) was suspended in dry DCM

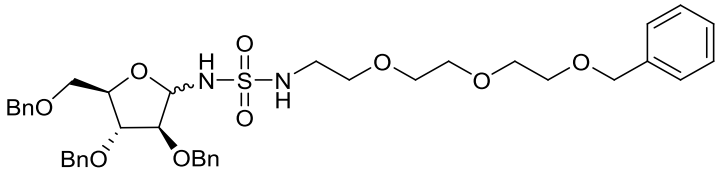
(25 mL) under nitrogen. TMSOTF (0.6 mL, 3.3 mmol) was added drop-wise at room temperature and the mixture was allowed to stir for 16 hours. T.l.c. (petrol:ethyl acetate 3:1) indicated formation of a single product (R_f 0.7) and consumption of starting material (R_f 0.2). The reaction was neutralized by the drop-wise addition of excess triethylamine (~ 1 mL). The reaction mixture was filtered on celite®, eluting with ethyl acetate and concentrated in *vavuo* to afford a yellow clear oil. The residue was purified by flash chromatography (petrol:ethyl acetate 8:1) to afford *N*-decyl-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl sulfamide **69** (1.8 g, 80%, α:β, 1:1.3) as a waxy solid. υ_{max} (thin film); 3296 (w, NH), 1341 (s, S=O), 1156 (w, S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 0.88 (6.9H, t, *J* 7.0 Hz, CH_3-α, CH_3-β), 1.27-1.51 (41.6H, m, CH_2), 1.53-2.05 (4.6H, m, $NHCH_2C\underline{H}_2\alpha$, $NHCH_2C\underline{H}_2\beta$), 2.99-3.07 (4.6H, m, $NHC\underline{H}_2\alpha$, $NHC\underline{H}_2\beta$), 3.58-3.62 (4.6H, m, CH-5α, CH5β, CH-5'α, CH-5'β), 3.98-4.03 (1.0H, m, CH-4α), 4.06-4.18 (5.6H, m, CH-2α, CH-2β, CH-3α, CH-3β), 4.27-4.31 (1.3H, m, CH-4β), 4.52-4.75 (13.8H, $PhC\underline{H}_2\alpha$, $PhC\underline{H}_2\beta$), 5.27 (1.3H, dd, J_{NH-1} 10.1 Hz, J_{1-2} 6.0 Hz, H-1β), 5.33 (1H, dd, J_{NH-1} 10.4 Hz, J_{1-2} 3.1 Hz, H-1α), 6.33 (1H, d, 10.5 Hz, NHα), 6.77 (1.3H, d, *J* 10.1 Hz, NHβ), 7.26-7.40 (34.5H, Ar-Hα, Ar-Hβ); δ_C (500 MHz, acetone-d_6) 13.7 (CH_3), 22.7 (CH_2), 26.9 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.6 (CH_2) 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.0 (CH_2), 43.2 (CH_2), 43.3 (CH_2), 70.5 (CH_2),71.0 (CH_2), 71.5 (CH_2), 71.7 (CH_2), 71.9 (CH_2), 72.0 (CH_2), 73.1 (CH_2), 73.1 (CH_2), 80.8 (CH), 81.3 (CH), 81.4 (CH), 82.0 (CH), 82.1 (CH), 83.1 (CH), 83.2 (CH), 84.7 (CH), 86.9 (CH), 88.5 (CH), 124.4-138.9 (Ar-CH); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 689.3573 (32%), peak calculated: 689.3595.



_N_-tetradecyl-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 70

2,3,5-Tri-O-benzyl arabinofuranose **31** (1.8 g, 4.3 mmol), *N*-(Tetradecyl)-sulfamide **57** (1.3 g, 4.3 mmol) and crushed, activated 3Å molecular sieves (~ 800 mg) was suspended in dry DCM (50 mL) under nitrogen. TMSOTF (0.8 mL, 4.3 mmol) was added drop-wise at room temperature and the mixture was allowed to stir for 16 hours. T.l.c. (petrol:ethyl acetate 5:1) indicated formation of a single product (R_f 0.3) and consumption of starting material (R_f 0.1) The reaction was neutralized by the drop-wise addition of excess triethylamine (~ 1 mL). The reaction mixture was filtered on celite®, eluting with ethyl acetate and concentrated in *vavuo* to afford a yellow clear oil. The residue was purified by flash chromatography (petrol:ethyl acetate 10:1) to afford *N*-tetradecyl-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl sulfamide **70** (1.9 g, 70%, α:β, 1:1.5) as a waxy solid. υ_{max} (thin film); 3295 (m, NH), 1344 (s, S=O), 1151 (w, S=O) cm^{-1}; δ_H (500 MHz, chloroform-*d*) 0.88 (7.5H, m, CH_3), 1.25-1.34 (55H, m, CH_2), 1.44-1.55 (5H, m, $NHCH_2C\underline{H}_2$), 2.95-3.05 (5H, m, $NHC\underline{H}_2$), 3.47 (1H, dd, $J_{5\text{-}5'}$ 9.3 Hz, $J_{5\text{-}4}$ 7.5 Hz, H-5β), 3.52 (2.5H, m, H-5α, H-5'α), 3.55-3.59 (1H, dd, $J_{5'\text{-}5}$ 9.7 Hz, $J_{5'\text{-}4}$ 5.8 Hz, H-5'β), 3.93-3.96 (2.5H, m, H-3α, H-3β), 3.97-3.98 (1.5H, m, H-2β), 3.99-4.01 (1H, m, H-2α), 4.02-4.06 (1H, m, H-4α), 4.09-4.14 (2.5H, m, NHα, NHβ), 4.20 (1H, t, *J* 6.2 Hz, $N\underline{H}CH_2\alpha$), 4.25 (1.5H, t, *J* 5.3 Hz, $N\underline{H}CH_2\beta$), 4.32-4.34 (1.5H, m, H-4β), 4.41-4.56 (15H, m, $PhC\underline{H}_2$), 5.36 (1H, dd, $J_{1\text{-}2}$ 4.4 Hz, $J_{1\text{-}NH}$ 10.3 Hz, H-1α), 5.41 (1.5H, d, *J* 10.6 Hz, H-1β), 5.55 (1H, d, *J* 10.2 Hz, NHα), 5.59 (1.5H, d, *J* 10.8 Hz, NHβ), 7.19-7.40 (37.5H, m, Ar-H); δ_C (500 MHz, chloroform-*d*) 14.3 (CH_3), 22.8 (CH_2), 26.8 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 43.5 (CH_2), 43.6 (CH_2), 70.2 (CH_2), 71.8

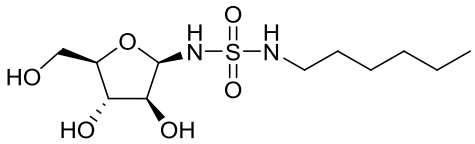
(CH_2), 71.9 (CH_2), 72.1 (CH_2), 72.5 (CH_2), 73.5 (CH_2), 73.6 (CH_2), 80.9 (CH), 81.3 (CH), 81.9 (CH), 82.5 (CH), 83.4 (CH), 84.4 (CH), 84.9 (CH), 88.4 (CH), 127.8-138.0 (Ar-C); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 717.3905 (100%), peak calculated: 717.3908.



***N*-(2-(2-(2-(benzyloxyethoxy)ethoxy)-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 71**

N-((2-(2-(2-(benzyloxyethoxy)ethoxy)ethyl)-sulfamide **58** (0.6 g, 1.8 mmol) and crushed, activated 3Å molecular sieves (~ 400 mg) was suspended in dry DCM (15 mL) stirred under nitrogen. TMSOTF (330 μL, 1.7 mmol) was added drop-wise at room temperature and the mixture was allowed to for 16 hours. T.l.c. (petrol:ethyl acetate, 1:1) indicated formation of a major product (R_f 0.4) and consumption of starting material (R_f 0.0). The reaction was neutralized by the drop-wise addition of excess triethylamine (0.6 mL). The reaction mixture was filtered on Celite®, eluting with ethyl acetate and concentrated in *vavuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol:ethyl acetate 2:1) to afford product *N*-monobenzyltri(ethylene-*N'*-(2,3,5-tri-O-benzyl-α,β-D-arabinofuranosyl) sulfamide **71** (0.9 g, 71%, α:β ~ 1:20); υ_{max} (thin film); 3286 (m, NH), 1341 (s, S=O), 1154 (w, S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 3.15-3.28 (5H, m, NHC<u>H</u>$_2$α, NHC<u>H</u>$_2$β), 3.53-3.64 (29H, m, CH_2, H-5α, H-5'α, H-5β, H-5'β), 3.99-4.03 (1H, m, H-4α), 4.07-4.10 (3.5H, m, H-2α, H-3α, H-3β), 4.16-4.18 (1.5H, m, H-2β), 4.31-4.34 (1.5H, m, H-4β), 4.47-4.71 (20H, m, PhC<u>H</u>$_2$), 5.30 (1.5H, dd, $J_{1\text{-}1'}$ 3.3 Hz, $J_{1\text{-}NH}$ 10.0 Hz, H-1β), 5.35 (1H, dd, $J_{1\text{-}1'}$ 4.4 Hz, $J_{1\text{-}NH}$ 10.7 Hz, H-1α), 5.75-5.80 (2.5H, m, NHα,

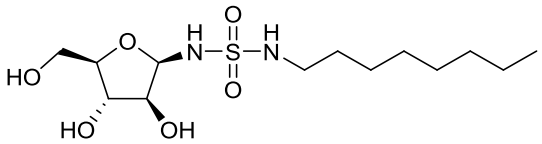
NHβ), 6.44 (1H, d, *J* 10.4 Hz, NH-1α), 6.82 (1.5H, d, *J* 9.9 Hz, NH-1β); δ_C (500 MHz, acetone-d_6) 43.1 ($NHCH_2\alpha$), 43.1 ($NHCH_2\beta$), 69.8 (CH_2), 70.2 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.8 (CH_2), 71.5 (CH_2), 71.7 (CH_2), 71.9 (CH_2), 72.0 (CH_2), 72.8 (CH_2), 73.1 (CH_2), 80.8 (CH), 81.3 (CH), 81.9 (CH), 82.1 (CH), 83.1 (CH), 84.8 (CH), 86.9 (CH), 88.6 (CH), 88.6 (CH),127.5-128.6 (Ar-CH), 138.2-139.2 (Ar-C); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 743.2983 (100%), peak calculated: 743.2973.



_N_-hexyl-_N'_-(β-D-arabinofuranosyl)sulfamide 72

Activated Pd-black (60 mg, 5% weight of **66**) was added slowly to a solution of *N*-Hexyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide **66** (600 mg, 1.0 mmol) in methanol:acetic acid (10 mL of a 9:1 v/v mixture). The flask was evacuated and purged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir for 2 days at room temperature. T.l.c. (ethyl acetate:acetone, 3:2) indicated formation of two products (R_f 0.4 and 0.3), corresponding to the α- and β-anomers and consumption of starting material (R_f 0.8). The flask was evacuated and placed under nitrogen. The mixture was filtered on Celite® (eluting with methanol ~30 mL) and concentrat *in vacuo* to afford a yellow oil. The residue was purified by flash column (ethyl acetate:acetone, 3:1) to afford and *N*-hexyl-*N'*-(β-D-arabinofuranosyl) sulfamide **72** (135 mg, 65%, from β anomer) as a white solid, m.p. 125-128˚C (ethyl acetate/petrol). $[\alpha]_D^{20}$ -25.2 (*c* 1.0 in MeOH); υ_{max} (diffraction) 3330 (br, OH), 3315 (N-H), 1328 (S=O), 1142 (S=O) cm^{-1}; δ_H (500 MHz, acetone-d_6) 0.85 (3H, t, *J* 7.0 Hz, CH_3), 1.23-1.35 (6H, m, CH_2), 1.51 (2H, m, $NHCH_2C\underline{H}_2$), 2.97-3.04 (2H, m, $NHC\underline{H}_2$), 3.56 (1H, d, *J* 12 Hz, H-

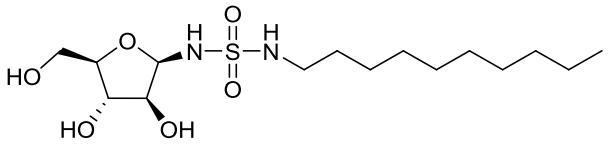
5'), 3.64-3.63 (2H, m, H-2, H-3), 3.83-3.88 (2H, m, H-4, H-5), 3.89 (1H, s, OH-5), 4.33 (1.5H, br. s, OH-2, OH-3), 4.41 (1H, d, *J* 7.4 Hz, H-1), 5.68 (1H, t, *J* 6.0 Hz, N<u>H</u>CH_2), 6.73 (0.5H, s, NH-1); δ_C (126 MHz, acetone-d_6) 14.2 (CH_3), 23.1 (CH_2), 27.0 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 43.6 (CH_2NH), 66.9 (CH-5), 66.9 (CH-5'), 68.5 (CH-4), 70.8 (CH-2 or CH-3), 74.0 (CH-2 of CH-3), 85.6 (CH-1); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 335.1262 (100%), peak calculated: 335.1247.



_N_-octyl-_N'_-(β-D-arabinofuranosyl)sulfamide 73

Activated Pd-black (45 mg, 5% weight of **67**) was added slowly to a solution of *N*-Octyl-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide **67** (640 mg, 1.1 mmol) in methanol:acetic acid (10 mL of a 9:1 v/v mixture). The flask was evacuated and purged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir for 2 days at room temperature. T.l.c. (petrol: ethyl acetate, 1:5) indicated formation of two products (R_f 0.21 and 0.23), corresponding to the α- and β-anomers and consumption of starting material (R_f 0.80). The flask was evacuated and placed under nitrogen. The mixture was filtered on Celite® (eluting with methanol ~ 30 mL) and concentrat in *vacuo* to afford a yellow oil. The residue was purified by flash column (petrol:ethyl acetate, 1:5) to afford and *N*-octyl-*N'*-(β-D-arabinofuranosyl)sulfamide **73** (150 mg, 60%, from β anomer) as a white solid, m.p. 125-128˚C (ethyl acetate/petrol). $[\alpha]_D^{20}$ -14.0 (*c*, 1.0 in MeOH); υ_{max} (diffration); 3330 (br, OH), 3310 (N-H), 1323 (S=O), 1142 (S=O); δ_H (500 MHz, acetone-d_6) 0.88 (3 H, t, *J* 6.60 Hz, CH_3), 1.17 - 1.44 (10H, m, CH_2), 1.49 - 1.63 (2H, m, C<u>H</u>$_2CH_2NH$), 2.82 (1H, OH-2 or OH-5), 2.85 - 3.06

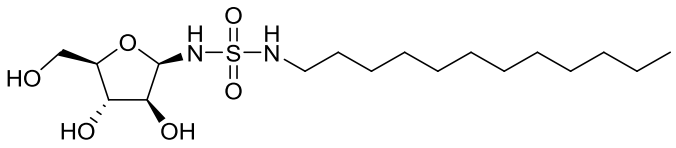
(2H, m, NC$\underline{H}_2$), 3.55 (2H, d, *J* 11.00 Hz, H-5), 3.63 - 3.65 (2H, m, H-2 and OH-3), 3.71 - 3.80 (1H, m, H-3), 3.80 - 3.84 (1H, m, H-5'), 3.84-3.89 (1H, m, H-4), 4.21 (1H, s, OH-2 or OH-5), 4.39-4.43 (1H, dd, $J_{1\text{-NH}}$ 9.8 Hz, $J_{1\text{-}2}$ 6.9 Hz, H-1β), 5.65 (1H, t, *J*=5.69 Hz, NH), 6.67 (1H, d, *J*=8.80 Hz, NH). δ_C (126MHz ,acetone-d_6) 14.3 (CH_3), 23.2 (CH_2), 27.2 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 30.2 (CH_2), 43.6 (NCH_2), 67.1 (C-5), 68.6 (C-4), 70.8 (C-2), 74.1 (C-3), 85.7 (C-1); *m/z* (ES^+) 363.1552 ($M+Na^+$, 70%); HRMS (ES^+) calculated for $C_{13}H_{28}N_2NaO_6S$ ($M+Na^+$) 363.1552. Found 353.1560.



***N*-decyl-*N'*-(β-D-arabinofuranosyl)sulfamide 74**

Activated Pd-black (40 mg, 5% weight of **68**) was added slowly to a solution of *N*-decyl-*N'*-(2,3,5-tri-O-benzyl-α,β-D-arabinofuranosyl) sulfamide **68** (0.6 g, 0.9 mmol) in methanol:acetic acid (10 mL of a 9:1 v/v mixture). The flask was evacuated and perged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir over night at room temperature under hydrogen. T.l.c. (petrol: ethyl acetate 1:5) indicated formation of two products (R_f 0.1 and 0.2), corresponding to the α- and β-anomers and consumption of starting material (R_f 0.8). The flask was evacuated and placed under nitrogen before filtration on celite® (eluting with methanol ~ 30 mL) and concentrated in *vacuo* to afford a yellow oil. The residue was purified with flash column (petrol:ethyl acetate 1:5) to afford *N*-decyl-*N'*-(β-D-arabinofuranosyl)sulfamide **74** (116 mg, 62%, from β anomer) as a white solid, m.p. 125-128˚C (ethyl acetate/petrol). $[\alpha]_D^{20}$ -32.4 (*c*, 1.0 in MeOH); υ_{max} (diffration); 3310 (br, OH), 1323 (s, S=O), 1142 (s, S=O); δ_H (500 MHz, acetone-d_6) 0.87 (3 H, t, *J* 6.60 Hz, CH_3), 1.17 - 1.43 (14H,

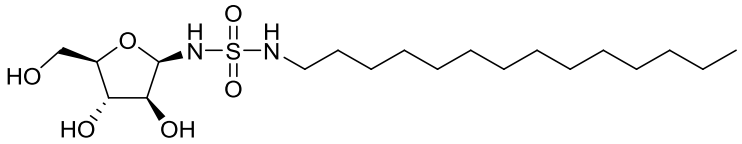
m), 1.54 (2 H, q, *J* 6.97 Hz, CH_2), 2.82 (1 H, s, OH-2 or OH-5) 2.94 - 3.15 (2 H, m, CH_2), 3.55 (1 H, d, *J* 11.37 Hz, H-5), 3.61 - 3.70 (2 H, m, H-2, OH-3), 3.77 (1 H, d, *J* 3.30 Hz, H-3), 3.80 - 3.94 (2 H, m, H-4, H-5'), 4.23 (1 H, br. s, OH-2 or OH-5), 4.41 (1 H, t, *J* 7.52 Hz, H-1β), 5.64 (1 H, t, *J* 5.69 Hz, NH-β), 6.68 (1 H, d, *J* 9.17 Hz, NH-α); ^{13}C NMR (126 MHz, acetone) δ_H ppm 13.7 (CH_3), 22.7 (CH_2), 26.9 (CH), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 43.2 (CH), 67.83 (CH), 70.65 (CH), 73.72 (CH), 85.09 (CH); *m/z* (ESI^+) 391.1872 ($M+Na^+$, 100%); HRMS (ESI^+) calculated for $C_{15}H_{32}N_2NaO_6S$ ($M+Na^+$) 391.1872. Found 391.1873.



_N_-dodecyl-_N'_-(β-D-arabinofuranosyl) sulfamide 75

Activated Pd/C (0.6 g, 40% weight of **69**) was added slowly to a solution of *N*-Dodecyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide **69** (1.2 g, 1.8 mmol) in methanol:acetic acid (20 mL of a 9:1 v/v mixture). The flask was evacuated and perged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir for two days at room temperature under hydrogen. T.l.c. (ethyl acetate:acetone, 3:2) indicated formation of two products (R_f 0.4 and 0.3), corresponding to the α- and β-anomers and consumption of starting material (R_f 0.8). The flask was evacuated and placed under nitrogen before filtration on celite® (eluting with methanol ~50 mL) and concentrated in *vacuo* to afford a yellow oil. The residue was purified with flash column (ethyl acetate:acetone, 3:1) to afford *N*-Dodecyl-*N'*-(α-D-arabinofuranosyl) sulfamide (40 mg) and *N*-dodecyl-*N'*-(β-D-arabinofuranosyl) sulfamide **75** (280 mg, 60%) as a white solid, m.p. 120-122˚C (petrol/ethyl acetate); $[\alpha]_D^{20}$ -22.2 (*c*, 1.0 in

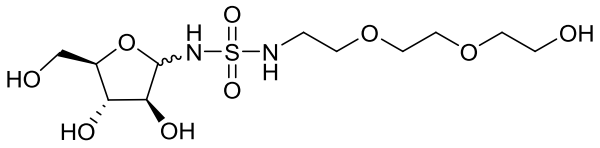
MeOH); υ_{max} (diffration); 3331 (br, OH), 3310 (N-H), 1321 (S=O), 1142 (S=O); δ_H (500 MHz, methanol-d_4) 0.90 (3H, t, *J* 7.0 Hz, CH_3), 1.29 (18H, m, CH_2), 1.51-1.54 (2H, m, $NHCH_2C\underline{H}_2$), 2.97-3.02 (2H, m, $NHC\underline{H}_2$), 3.52-3.58 (3H, m, H-2, H-3, H-5'), 3.82-3.85 (2H, m, H-4, H-5), 4.30 (1H, d, *J* 7.4, H-1); δ_C (126 MHz, methanol-d_4) 13.3 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.9 ($NHCH_2\underline{C}H_2$), 42.8 ($NHCH_2$), 67.0 (CH_2-5), 68.5 (CH_2-4), 70.2 (CH_2-2), 73.7 (CH_2-3), 85.4 (CH_2-1); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 419.2186 (100%), peak calculated: 419.2186.



_N_-tetradecyl-_N'_-(β-D-arabinofuranosyl) sulfamide 76

Activated Pd/C (0.6 g 40% weight of **70**) was added slowly to a solution of *N*-Tetradecyl-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl) sulfamide **70** (1.1 g, 1.6 mmol) in methanol:acetic acid (20 mL of a 9:1 v/v mixture). The flask was evacuated and perged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir for two days at room temperature under hydrogen. T.l.c. (ethyl acetate:acetone, 3:2) indicated formation of two products (R_f 0.4 and 0.3), corresponding to the α- and β-anomers and consumption of starting material (R_f 0.8). The flask was evacuated and placed under nitrogen before filtration on celite® (eluting with methanol ~ 50 mL) and concentrated in *vacuo* to afford a yellow oil. The residue was purified with flash column (ethyl acetate:acetone, 3:1) to afford *N*-tetradecyl-*N'*-(β-D-arabinofuranosyl)sulfamide **76** (244 mg, 60%, from β anomer) as a white solid, m.p. 119-120˚C (petrol/ethyl acetate); $[\alpha]_D^{20}$ -22.2 (*c*, 1.0 in MeOH); υ_{max} (diffration); 3335 (br, OH), 3310

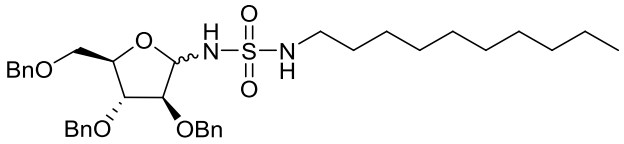
(N-H), 1142 (S=O); δ_H (500 MHz, methanol-d_4) 0.90 (3H, t, *J* 7.0 Hz, CH_3), 1.22-1.32 (22H, m, CH_2), 1.50-1.54 (2H, m, $NHCH_2C\underline{H_2}$), 2.96-3.02 (2H, m, $NHC\underline{H_2}$), 3.52-3.57 (3H, m, H-2, H-3, H-5'), 3.58-3.84 (2H, m, H-4, H-5), 4.09 (0.5H, aq, *J* 7.0 Hz, NH), 4.30 (1H, d, $J_{1,2}$ 7.5 Hz, H-1); δ_C (126 MHz, methanol-d_4) 13.3 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.9 ($NHCH_2\underline{C}H_2$), 42.8 ($NHCH_2$), 67.0 (CH_2-5), 68.5 (CH_2-4), 70.2 (CH_2-2), 73.7 (CH_2-3), 85.4 (CH_2-1); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 447.2499 (91%), peak calculated: 447.2505.



_N_-(2-(2-(ethoxy)ethoxy)ethanol -_N'_-(β-D-arabinofuranosyl)sulfamide 77

Activated Pd/C (400 mg 40% weight of **71**) was added slowly to a solution of *N*-octyl-*N*'-(2,3,5-tri-O-benzyl-α,β-D-arabinofuranosyl)sulfamide **71** (760 mg, 1.1 mmol) in methanol:acetic acid (10 mL of a 9:1 v/v mixture). The flask was evacuated and purged with nitrogen three times, before being placed under an atmosphere of hydrogen. The solution was allowed to stir for 2 days at room temperature. T.l.c. (ethyl acetate: acetone, 3:2) indicated formation of one product (R_f 0.2), corresponding to the mixture of α- and β-anomers and consumption of starting material (R_f 0.70). The flask was evacuated and placed under nitrogen. The mixture was filtered on Celite® (eluting with methanol ~ 30 mL) and concentrat in *vacuo* to afford a yellow oil. The residue was purified by flash column (DCM:methanol, 6:1) to afford *N*-(2-(2-(ethoxy)ethoxy)ethanol-*N'*-(α,β-D-arabinofuranosyl)sulfamide **77** (198 mg, 50%, β is the major anomer, α:β, ~ 1:20) as a clear oil. υ_{max} (thin film); 3334 (br, OH), 3314 (N-H), 1328 (S=O); δ_H (500 MHz, methanol-d_4) 3.15-3.30 (2H, m, $NHCH_2$), 3.55-3.72 (4H, m, CH_2, H-2, H-3, H-5),

3.84-3.87 (2H, m, H4, H-5), 4.33 (1H, d, $J_{1,2}$ 7.5 Hz, H-1); δ_C (500 MHz, methanol-d_4) 42.7 (CH_2), 61.0 (CH_2), 67.2 (CH_2), 68.6 (CH), 69.8 (CH_2), 69.9 (CH_2),70.2 (CH), 70.6 (CH), 72.5 (CH_2), 73.8 (CH), 85.5 (CH); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 383.1094 (100%), peak calculated: 383.1095.



_N_-decyl-_N'_-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 78

_N_-decyl sulfamide **55** (438.7 mg, 1.85 mmol) was added to a solution of cude 2,3,5-Tri-_O_-benzyl-α,β-D-arabinofuranosyl bromide **33** (0.92 mmol) and TTBP (576.3 mg, 2.3 mmol) in dry DCM (15 mL) under nitrogen. After 16 hr, t.l.c. (petrol:ethyl acetate, 5:1) indicated formation of a major product (R_f 0.3) and unreacted starting marterial **33** (0.1) and **33** (0.0). The reaction mixture was diluted in DCM (50 mL), washed with sodium bicarbonate (3 x 50 mL of a saturated solution) and brine (1 x 50 mL of a saturated solution). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (petrol,ethyl acetate, 5:1) to afford a mixture of _N_-decyl-_N'_-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide **78** (10%, α:β, 2:1) as a waxy solid. δ_H (500 MHz, $CHCl_3$-_d_) 0.88 (9 H, CH_3 α and CH_3 β), 1.24 - 1.30 (56H, m, CH_2), 1.42 - 1.58 (6H, m, CH_2), 2.94 - 3.01 (6H, m, CH_2), 3.40 - 3.60 6H, m, H-5α, H-5β, H-5'α, H-5'β), 3.86 - 4.38 (8H, m, H-2α, H-3α, H-2β, H-3β, H-4β), 4.40 - 4.74 (20H, m, $PhCH_2$, H-4α), 5.21 (1H, dd, $J_{1,NH}$ 10.5 Hz, $J_{1,2}$ 4.5 Hz, H-1β), 5.30 (1H, d, $J_{1,NH}$ 11.0 Hz, H-1α), 7.09 - 7.44 (45H, m, Ar-H); m/z (ESI^+) species observed ($M+Na^+$); ($M+Na^+$) peak observed: 661.3289 (100%), peak calculated: 661.3282.

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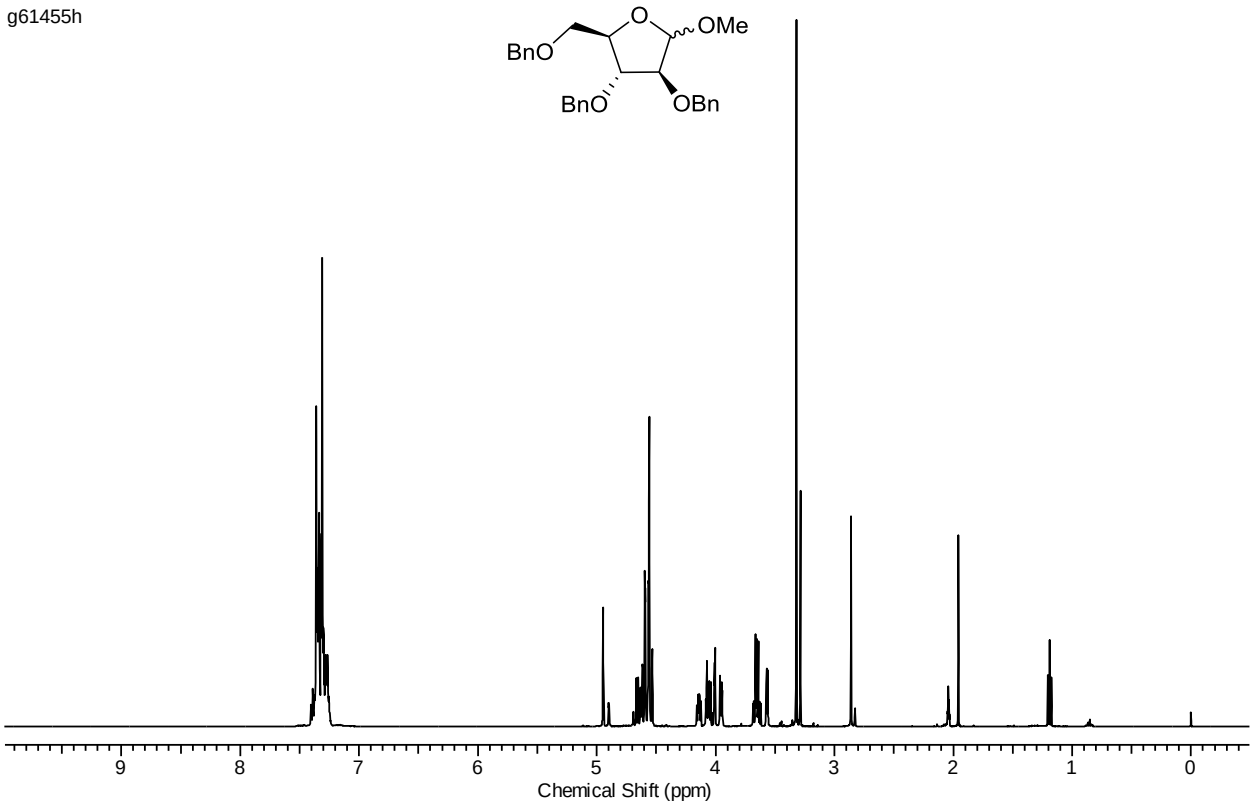
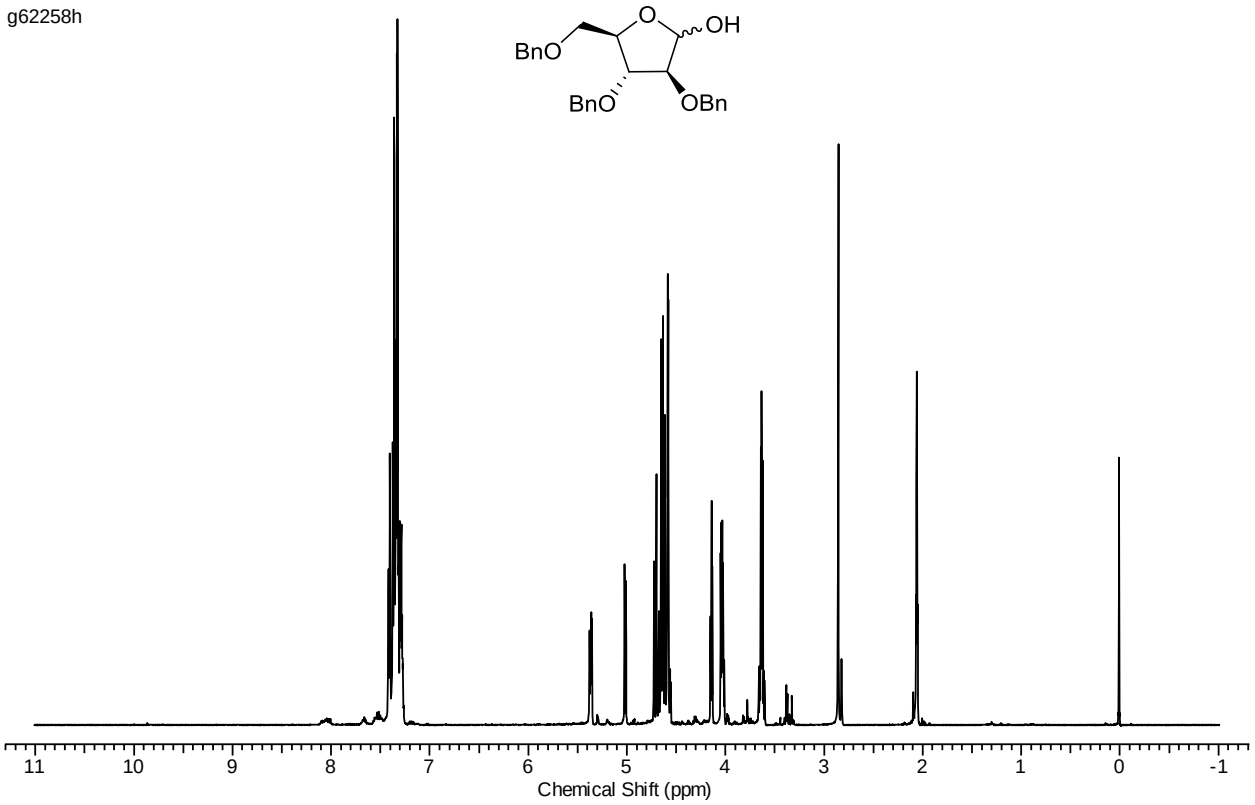
[1]H-NMR and [13]C- NMR Spectra

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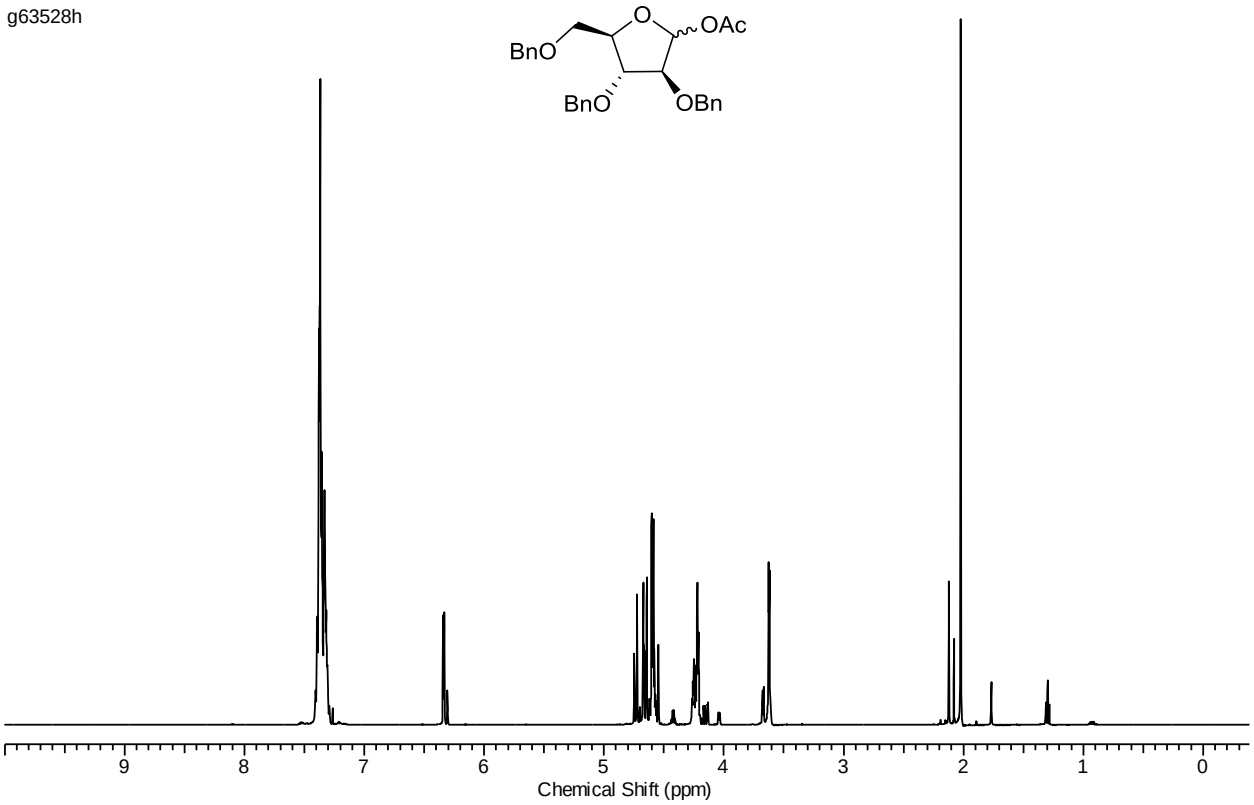
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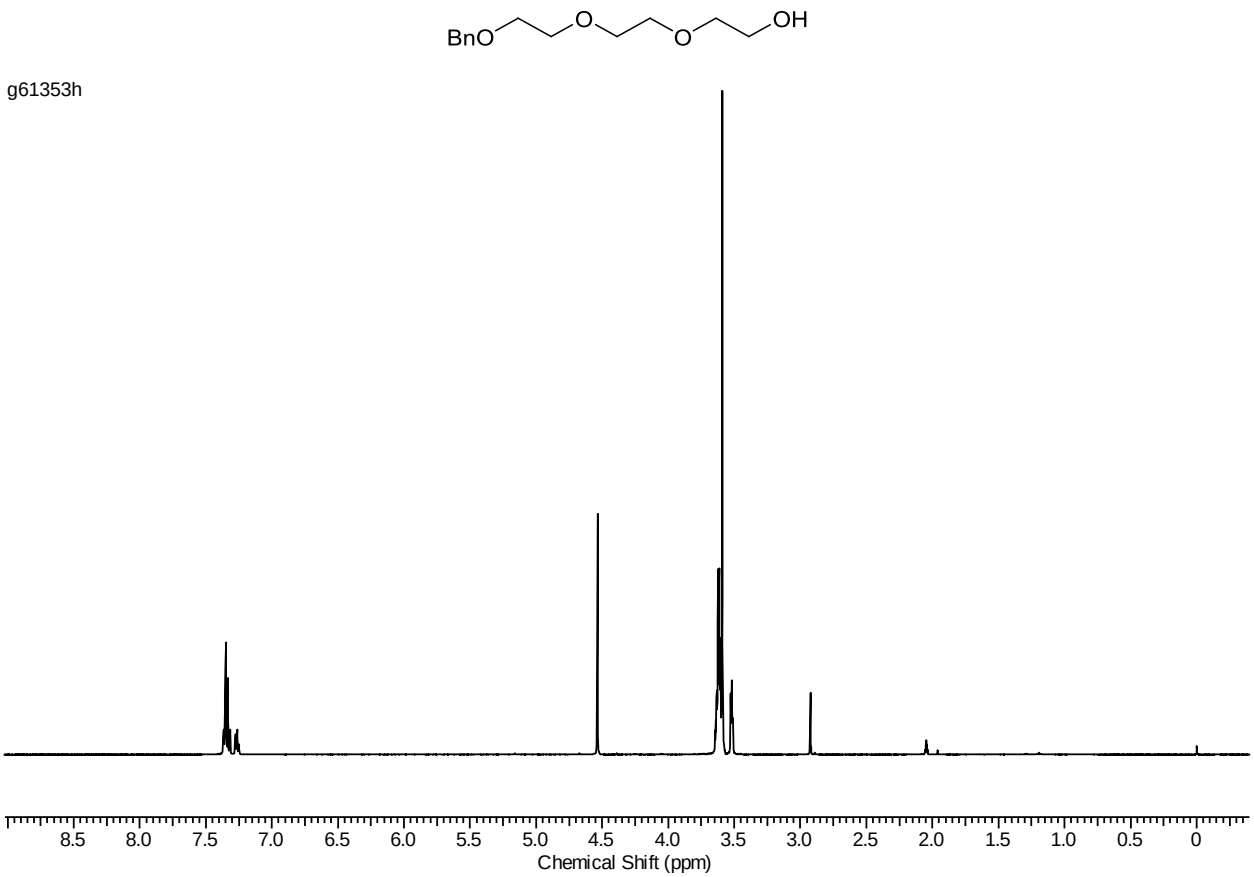
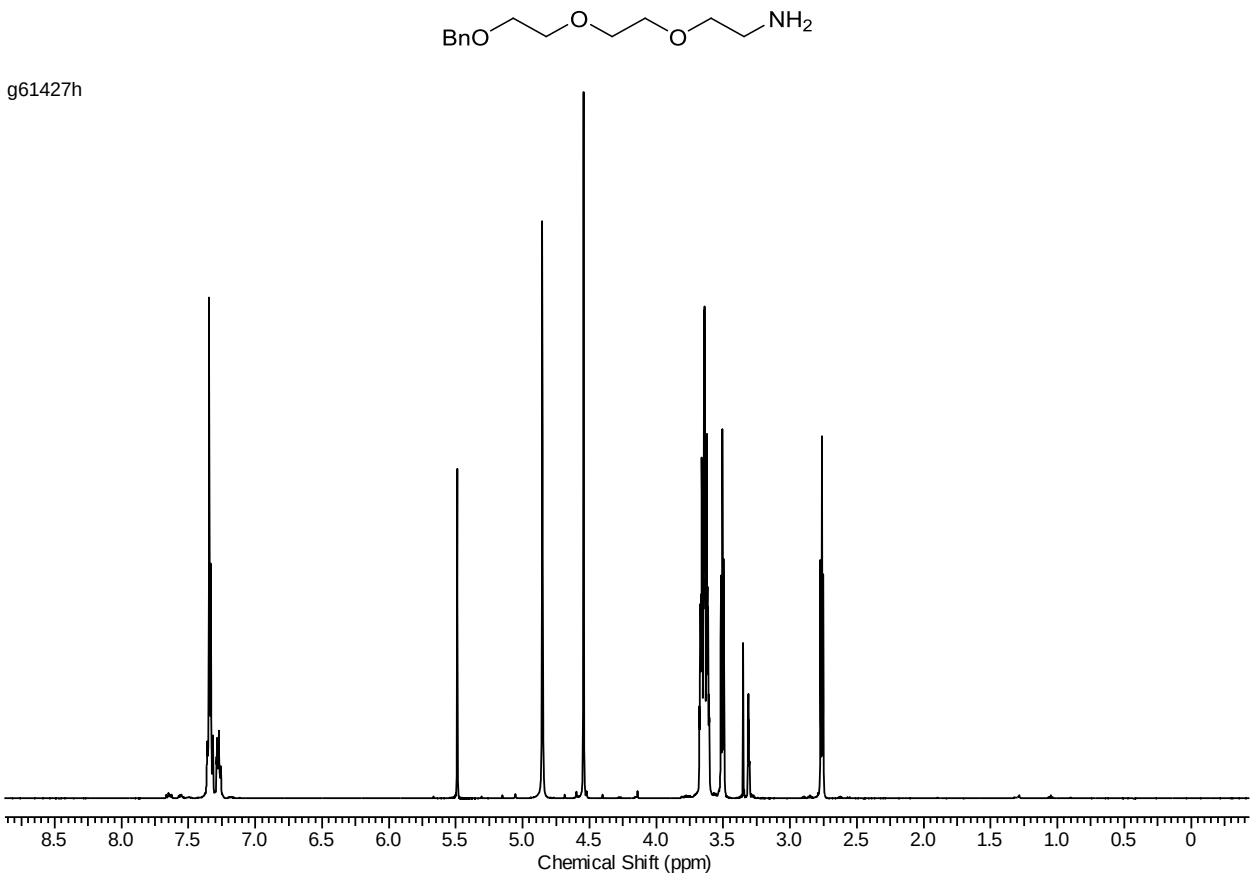
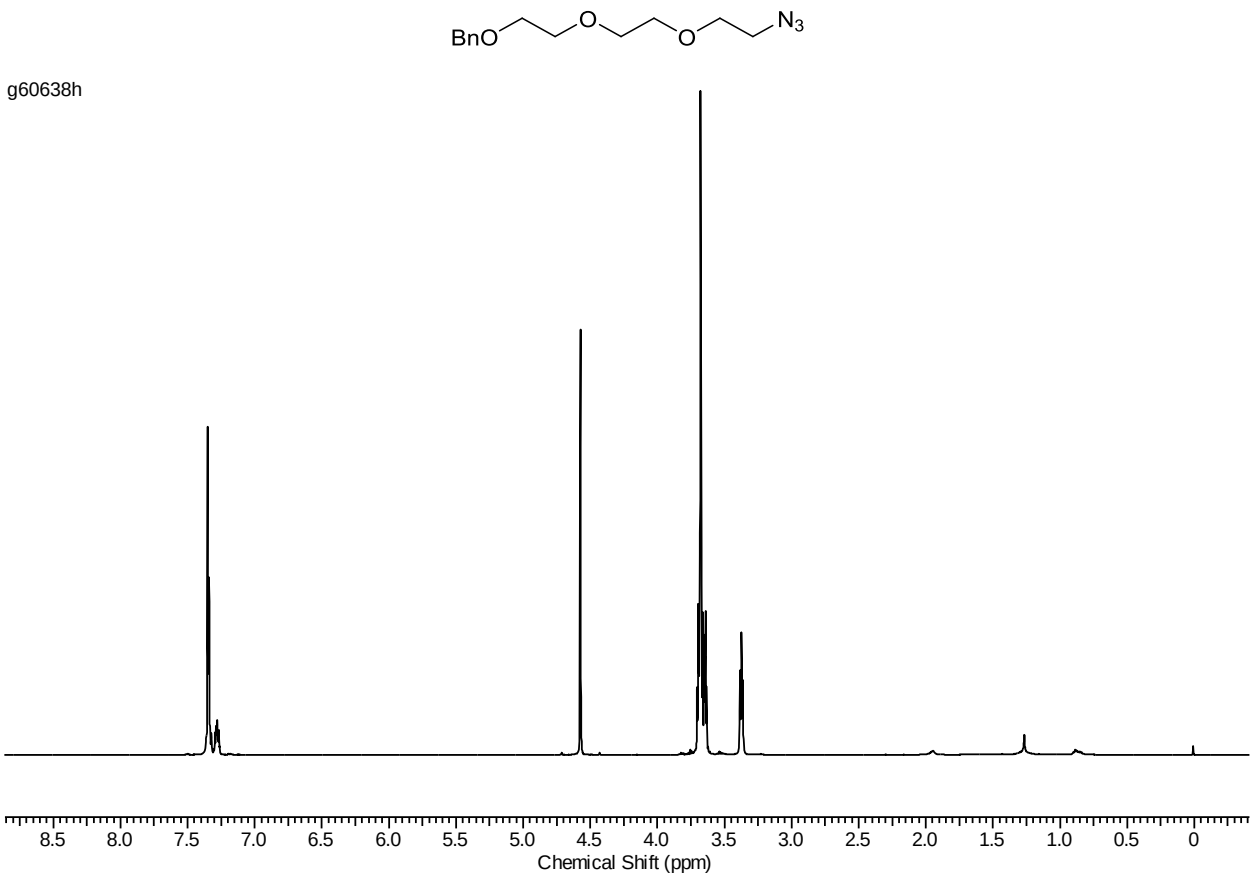
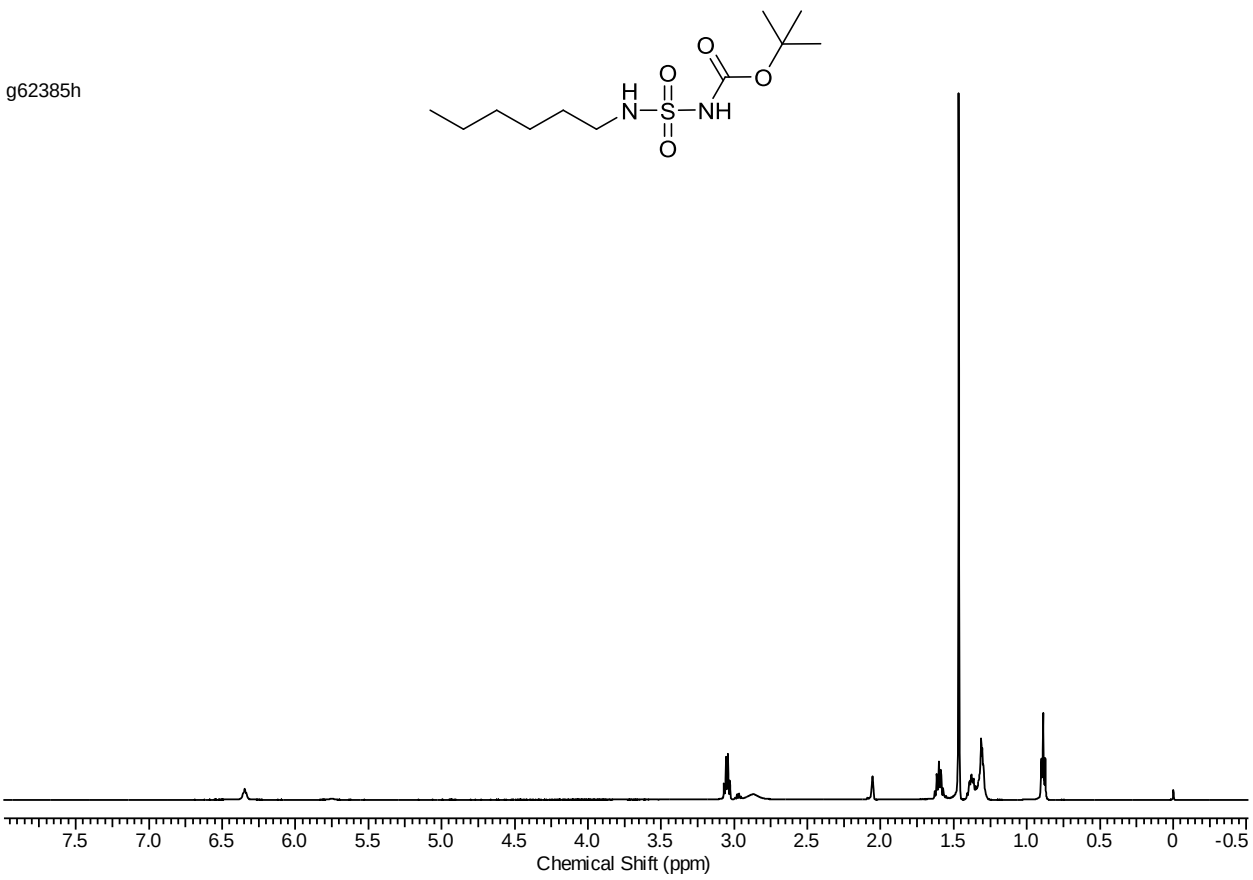

BnO
O
O
OH
g61353h
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

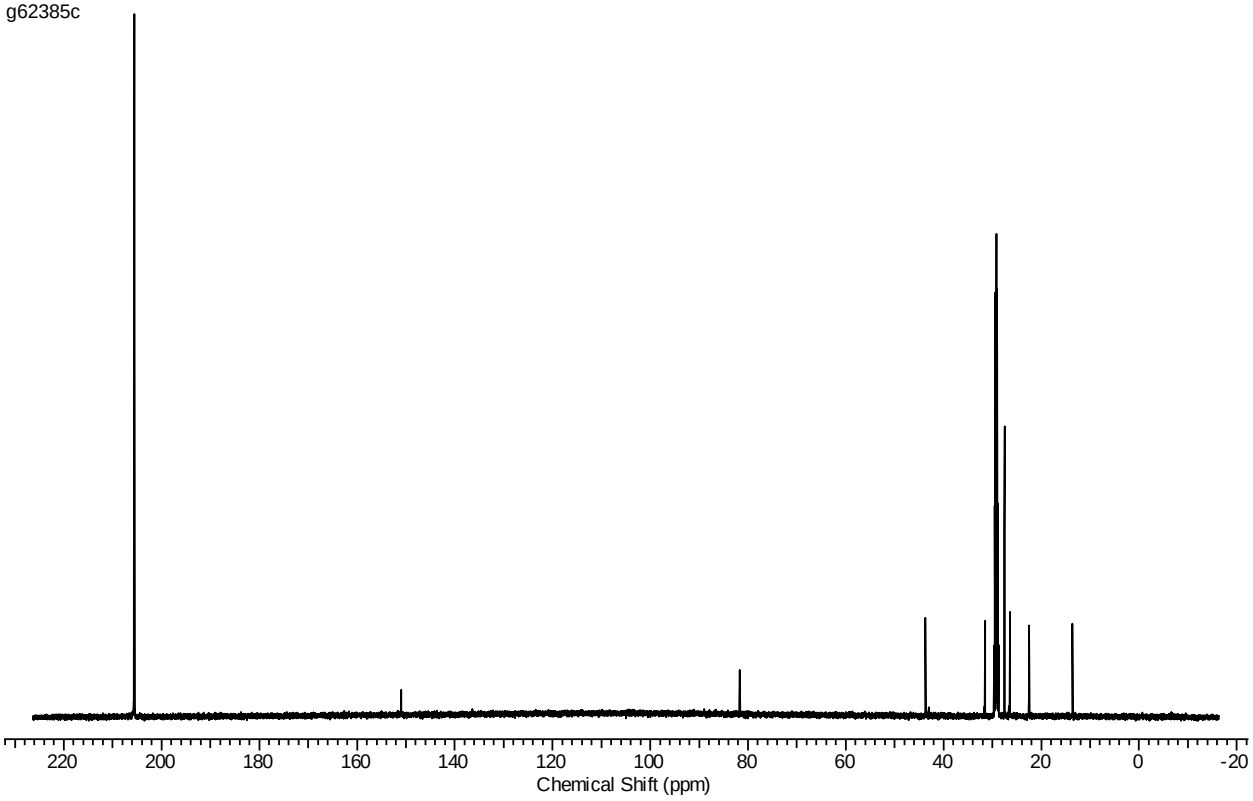

BnO
O
O
NH2
g61427h
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


BnO
O
O
N3
g60638h
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
Chemical Shift (ppm)

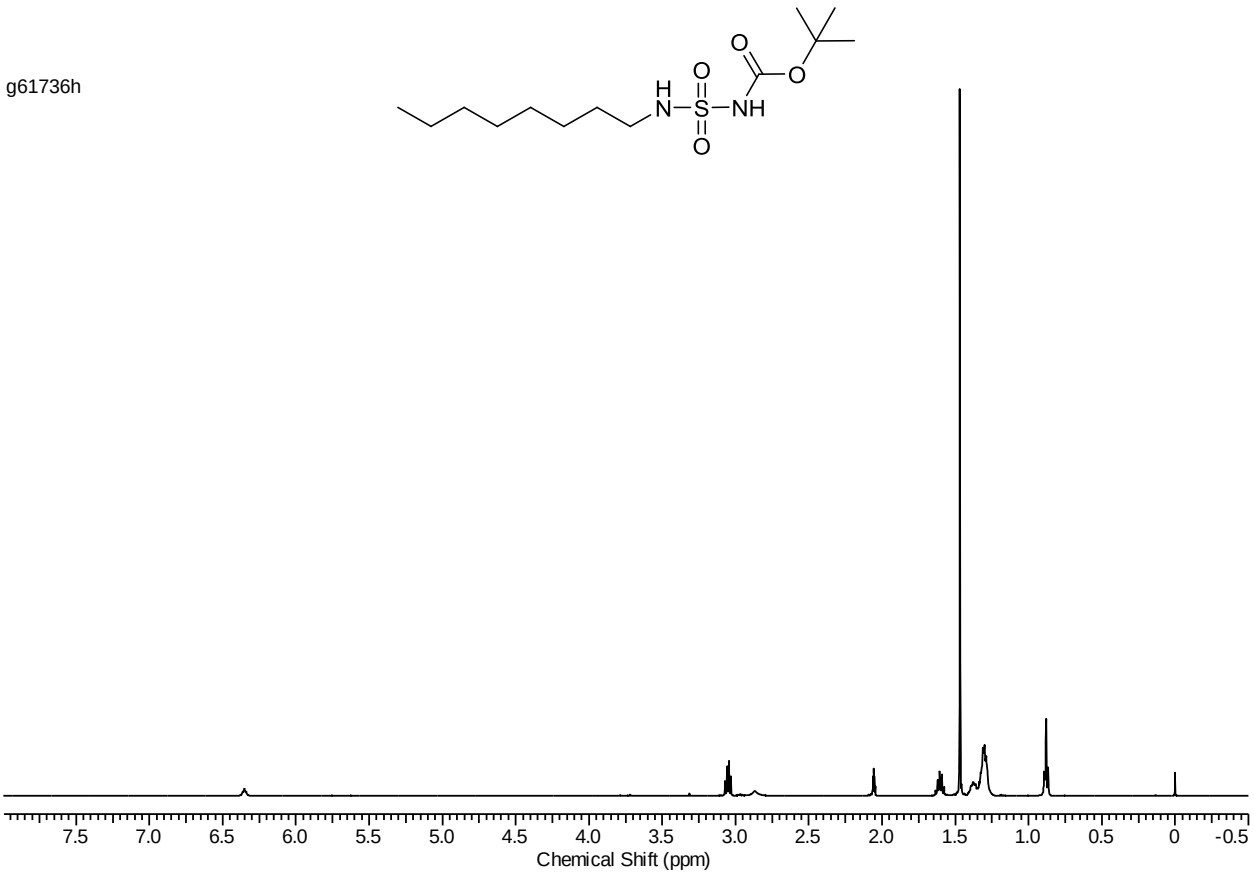
g62385h



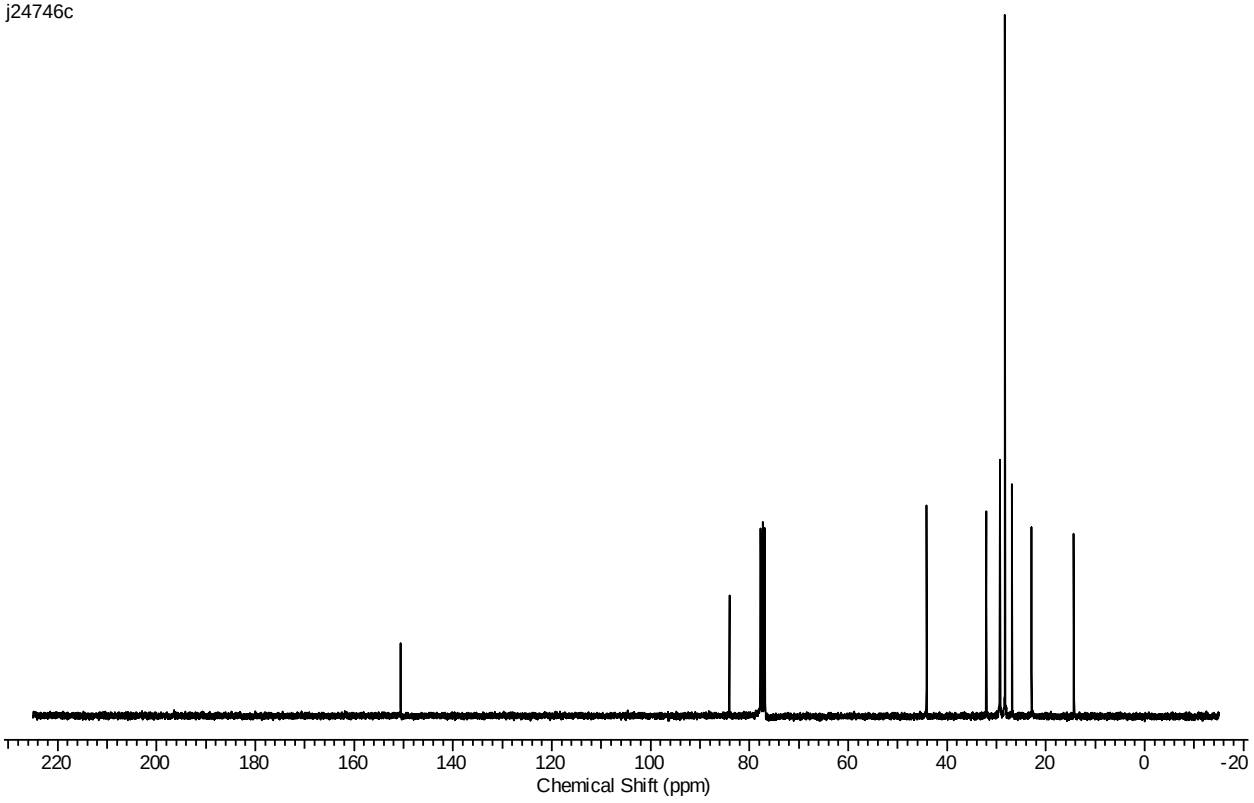
g62385c



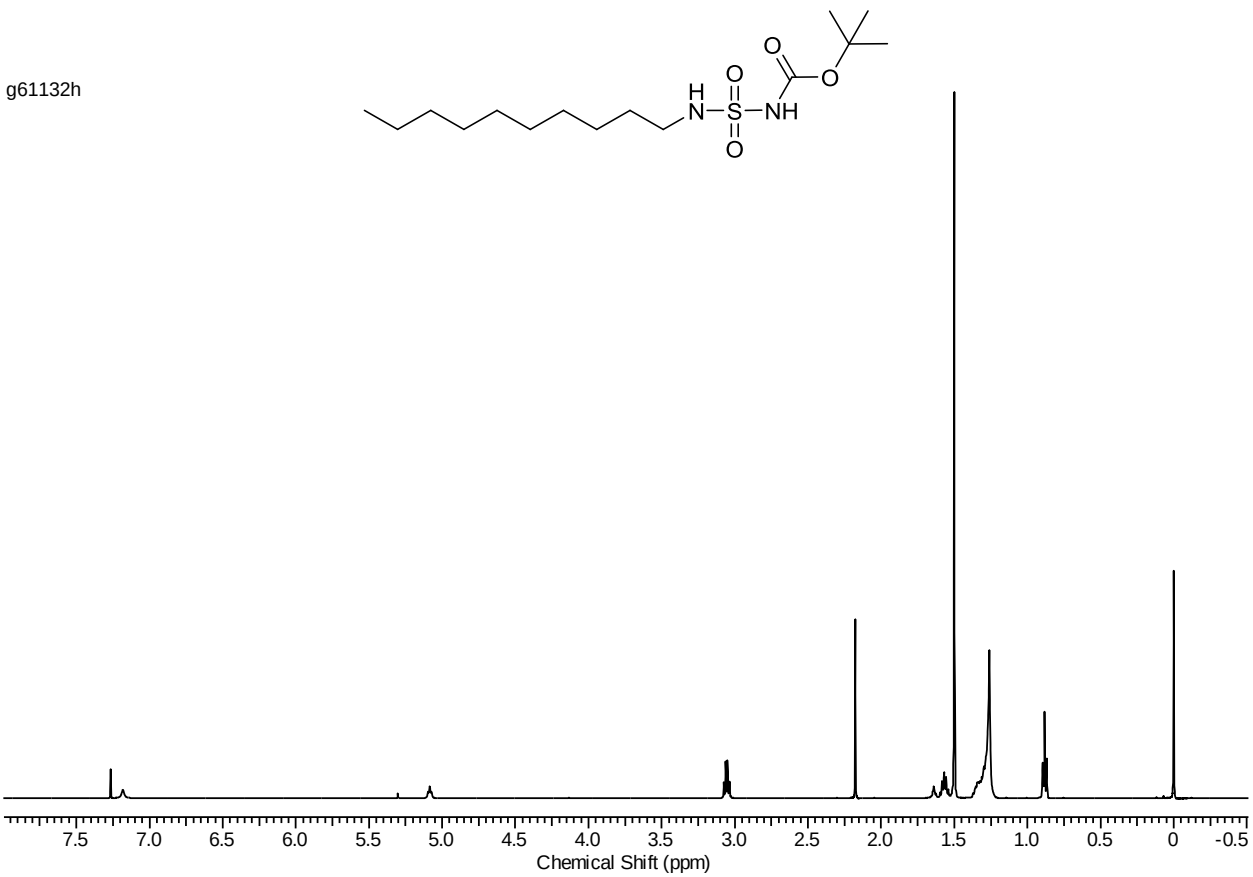
g61736h



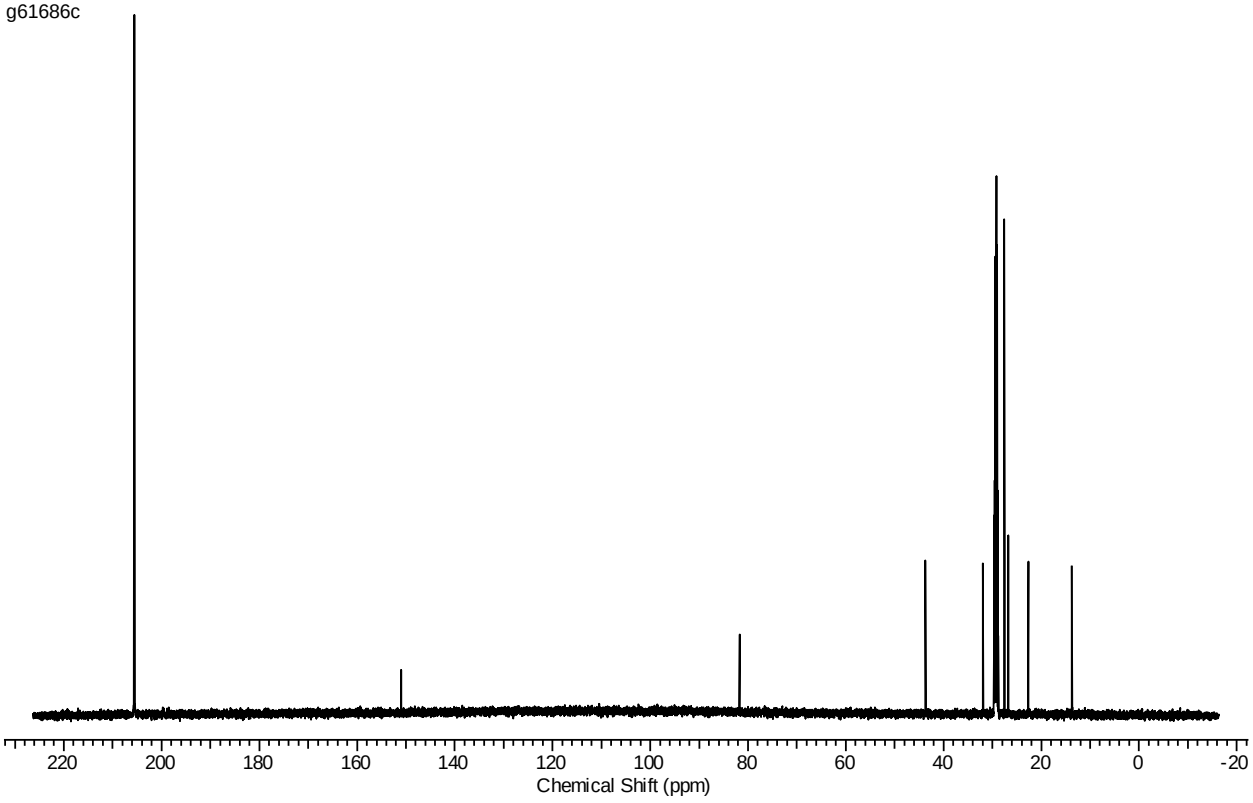
j24746c



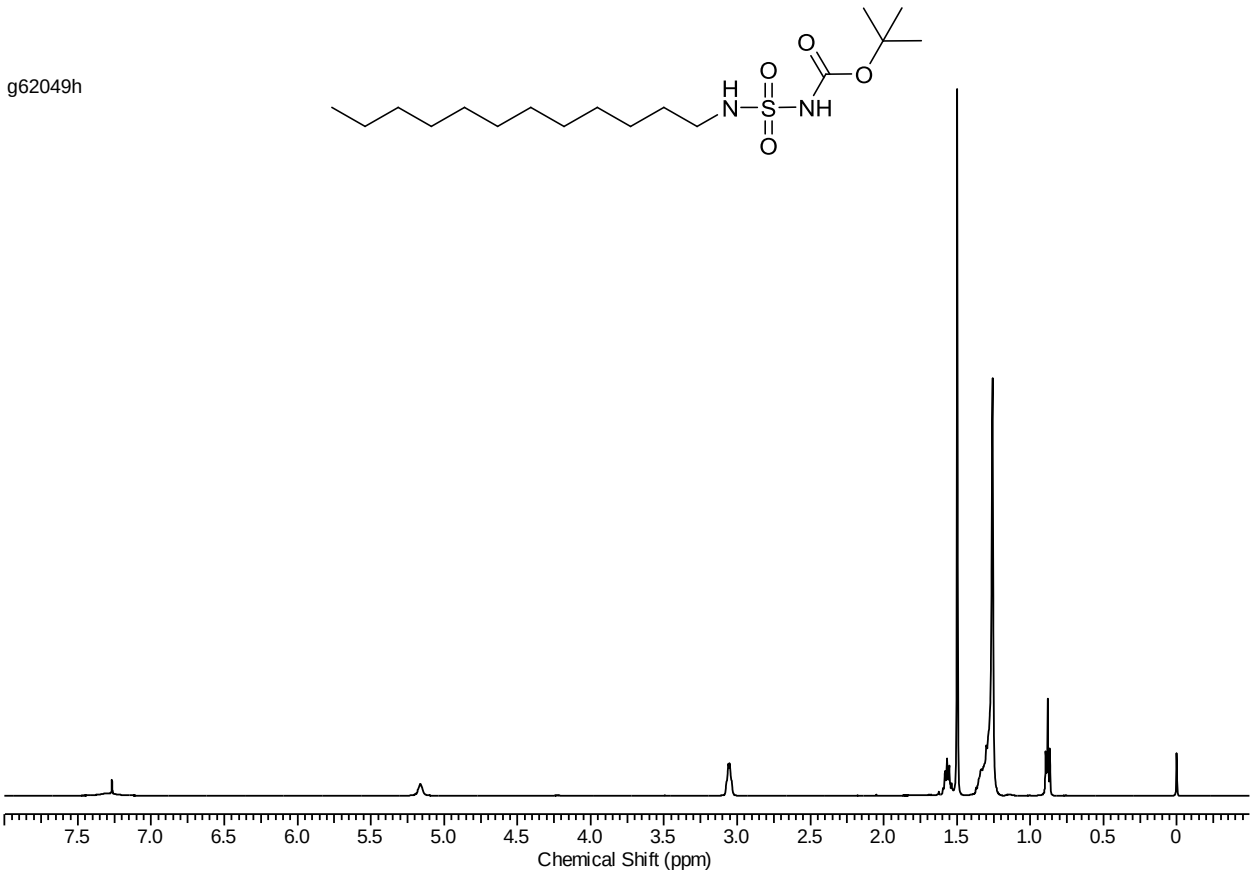
g61132h



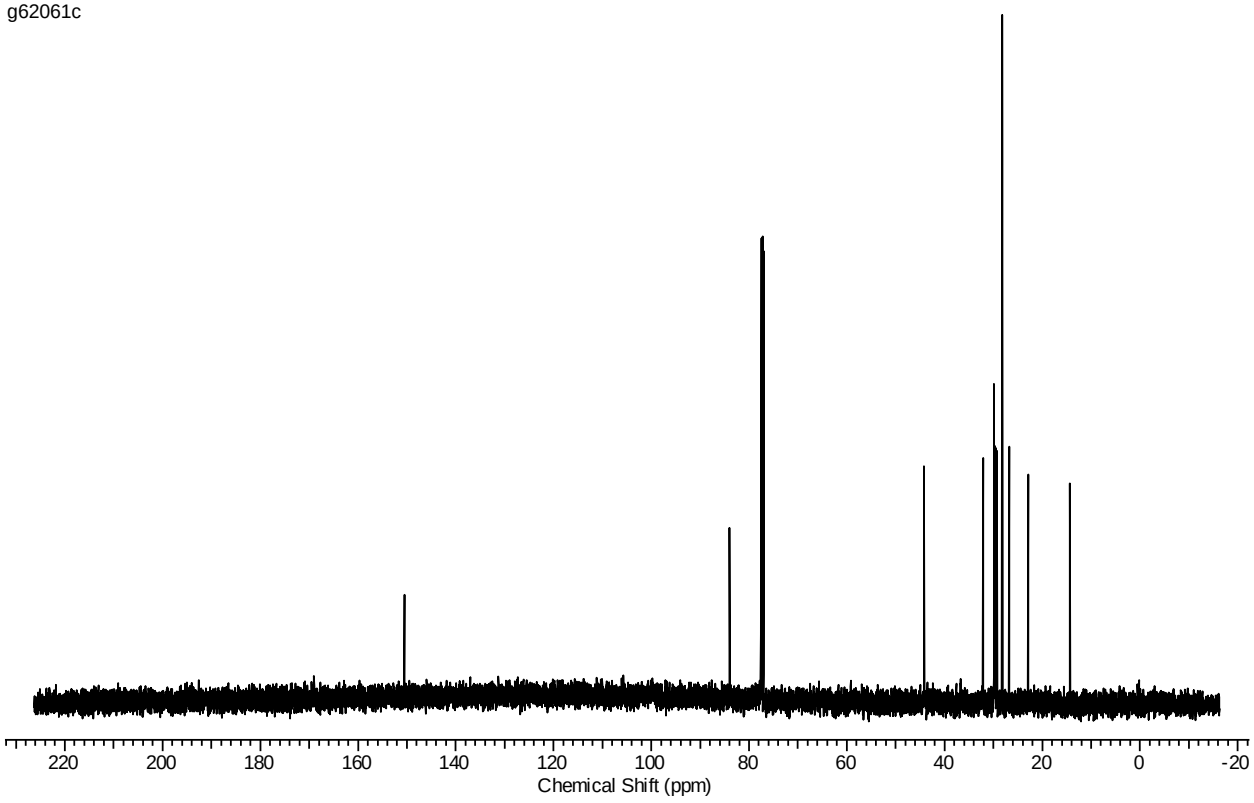
g61686c



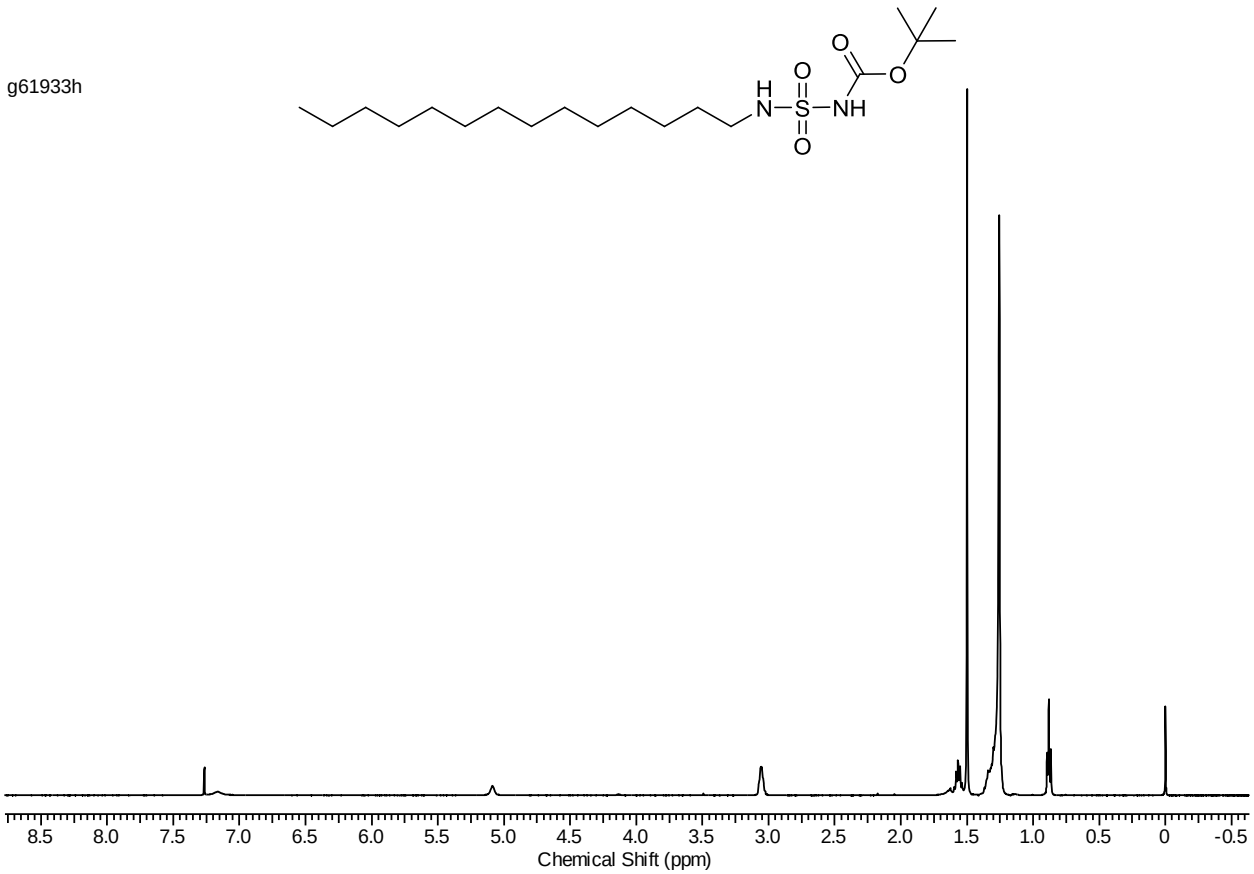
g62049h



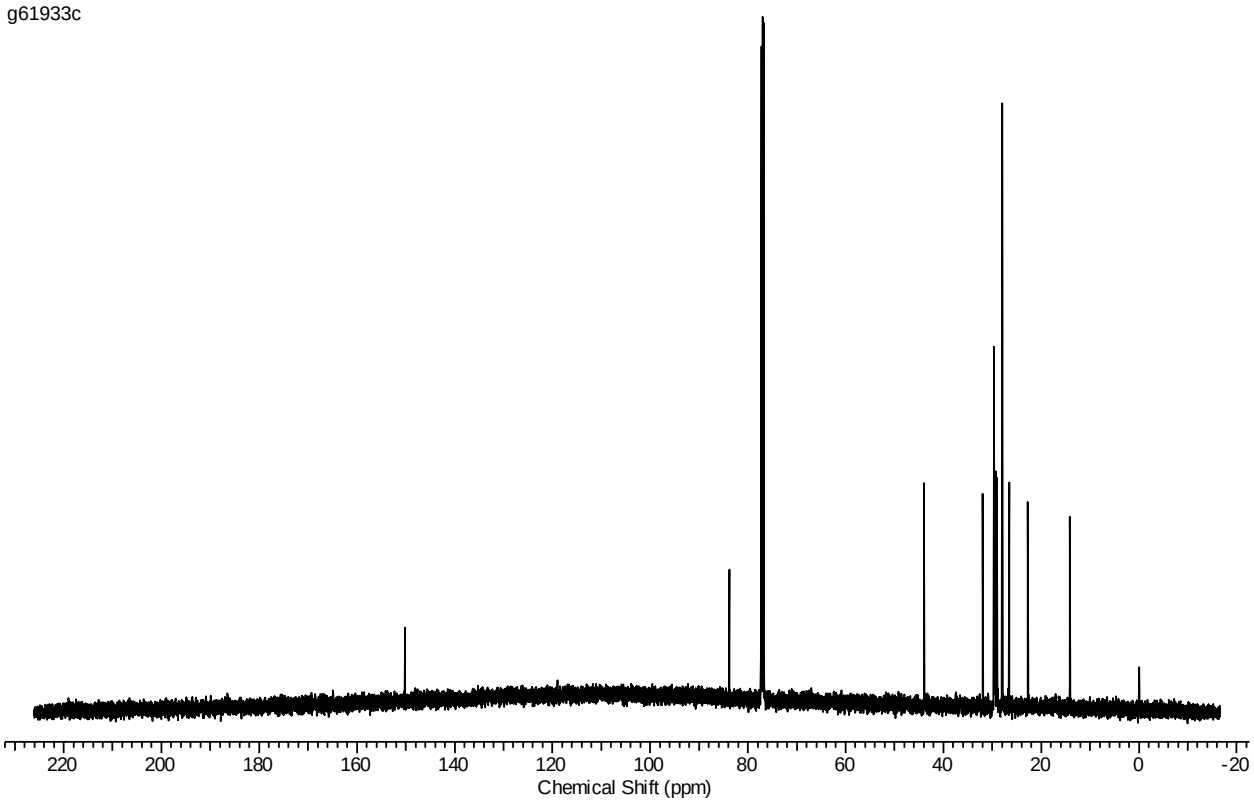
g62061c



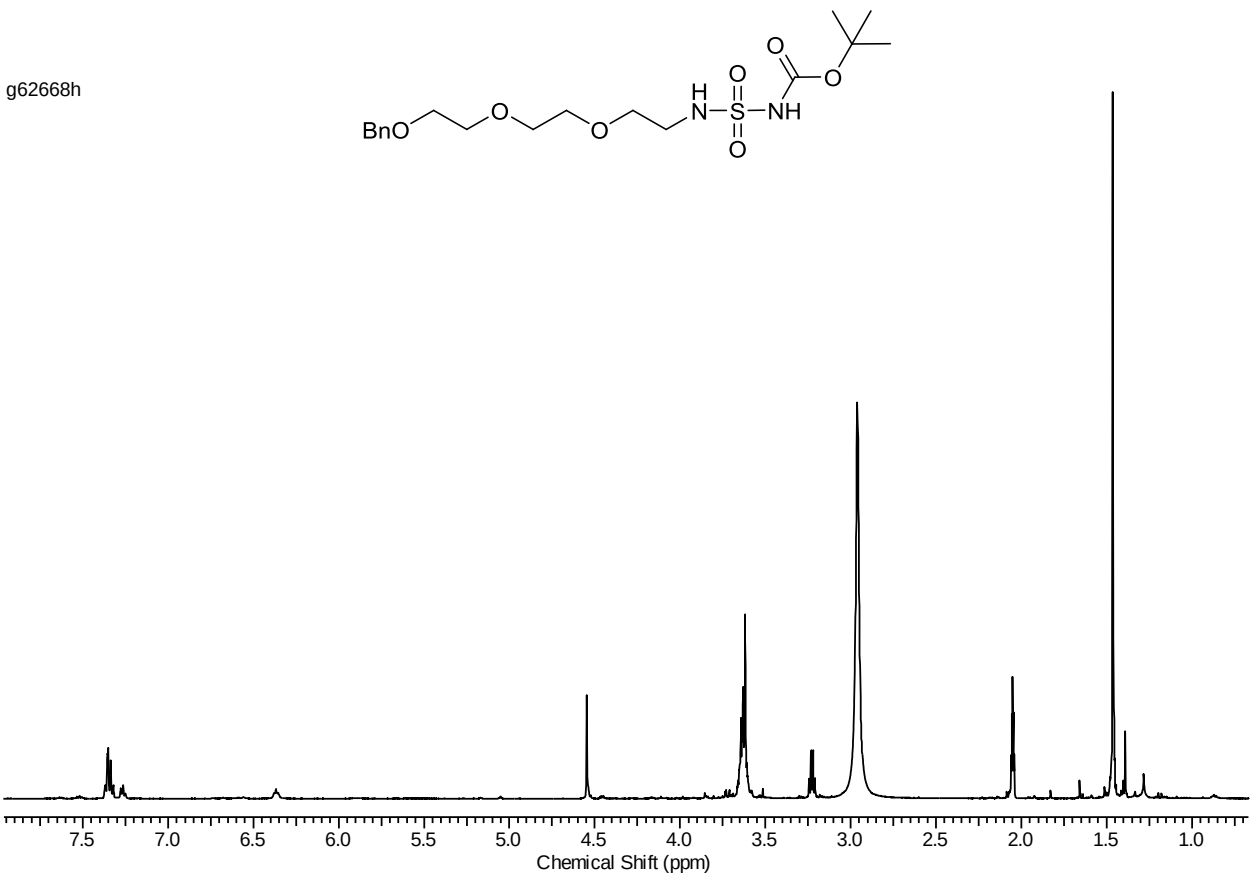
g61933h



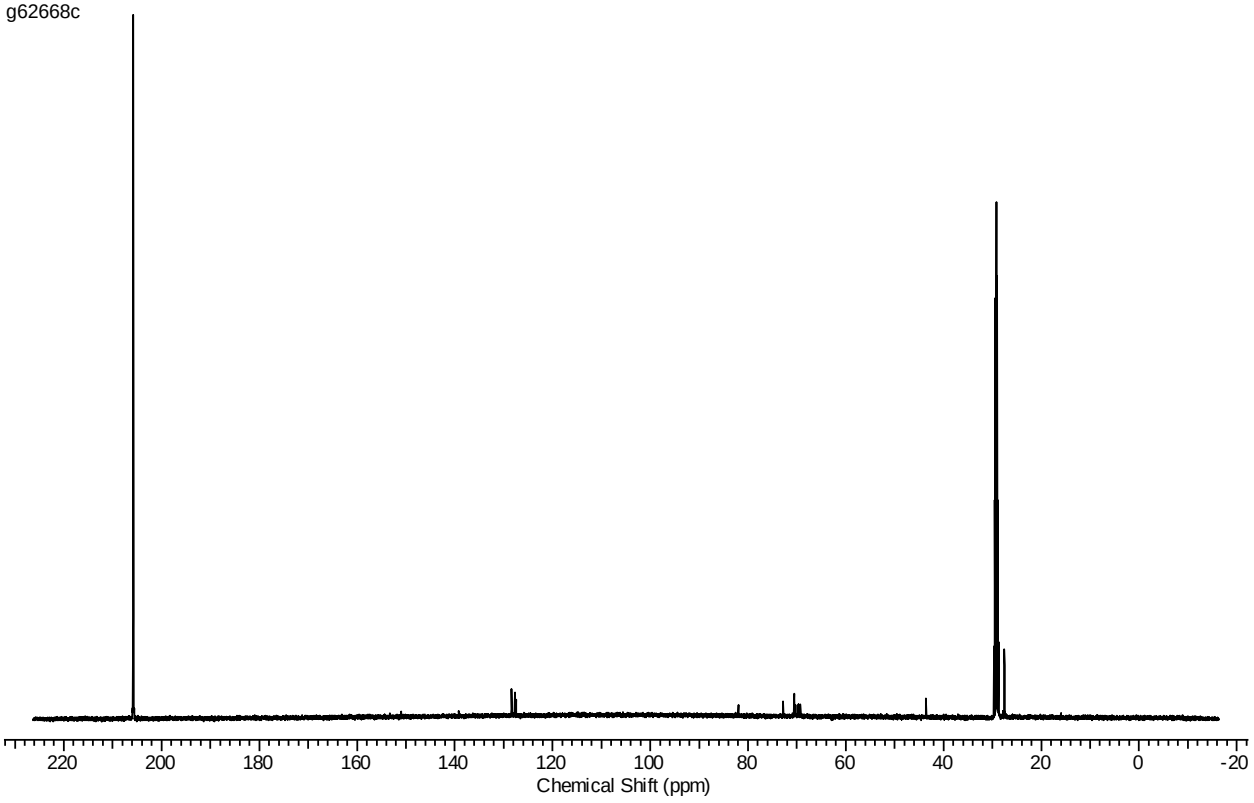
g61933c



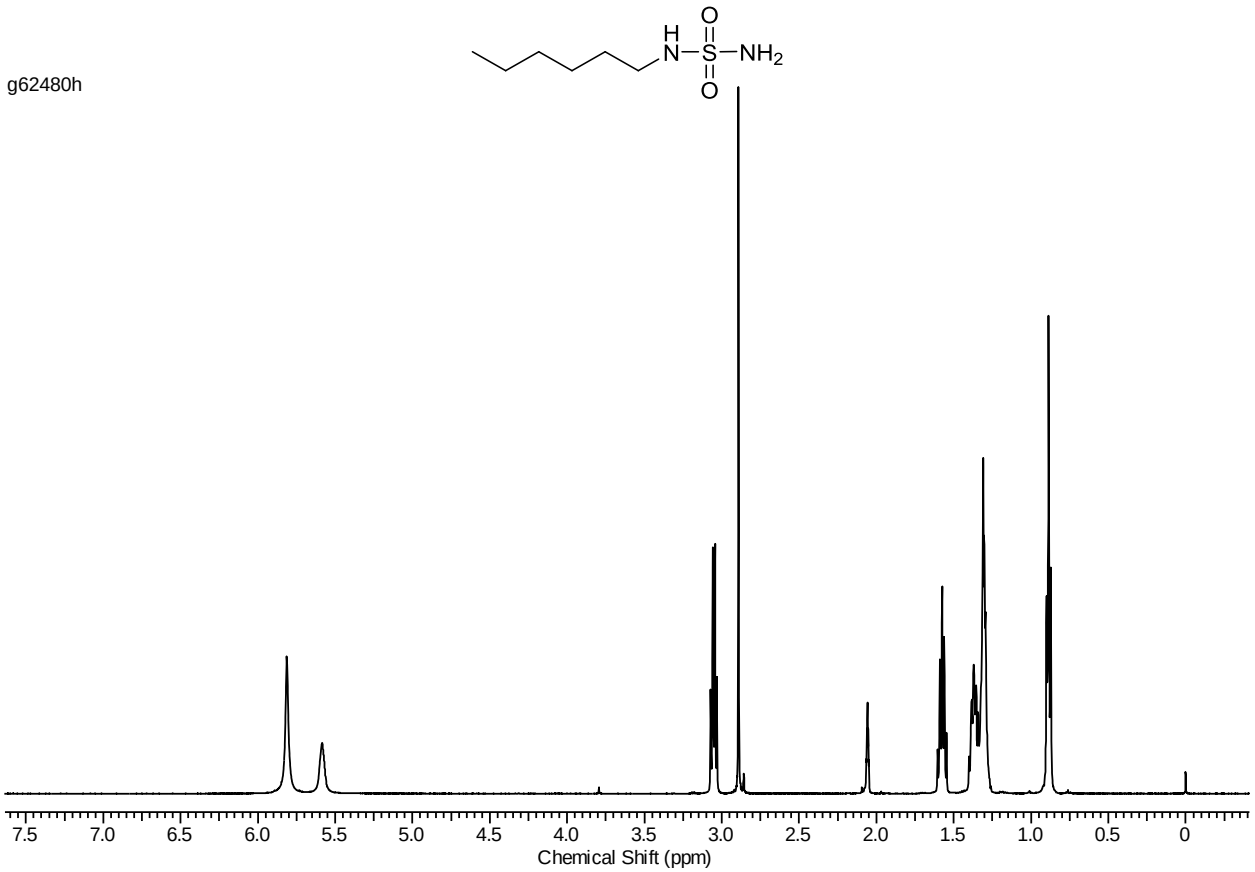
g62668h



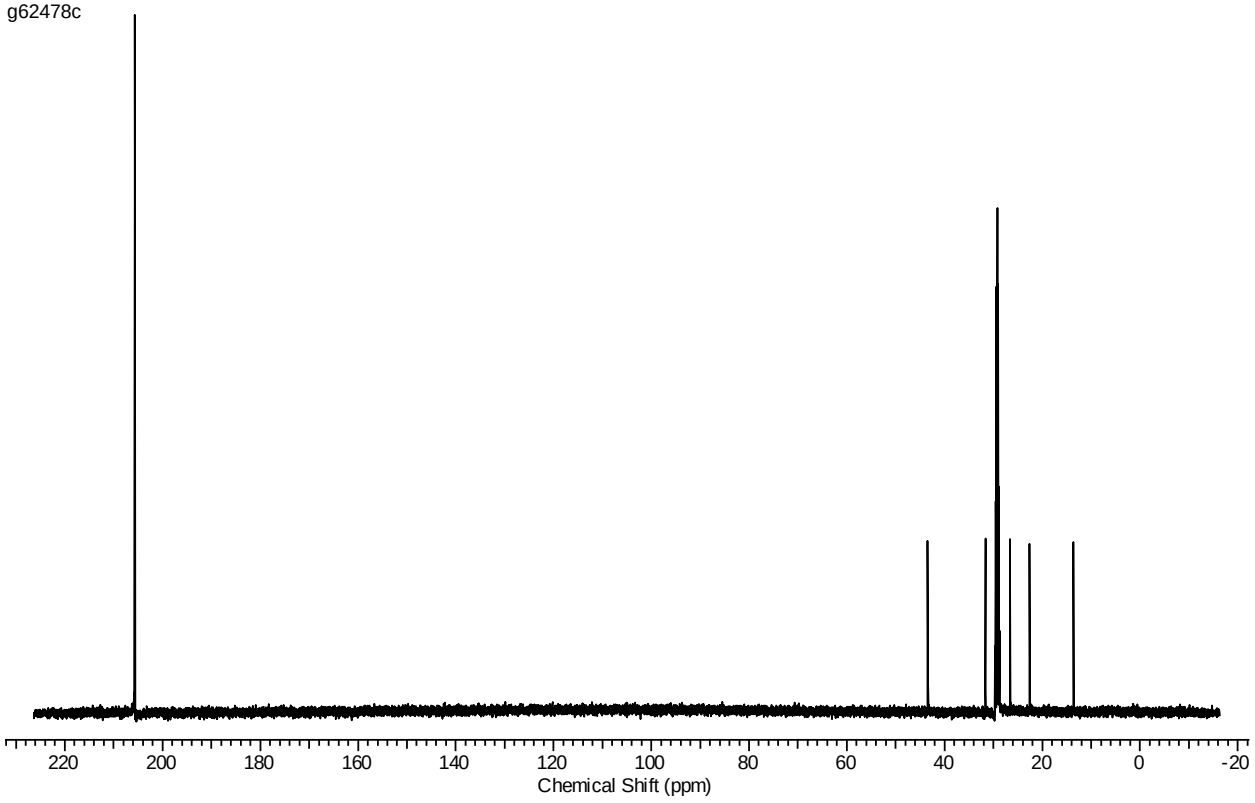
g62668c

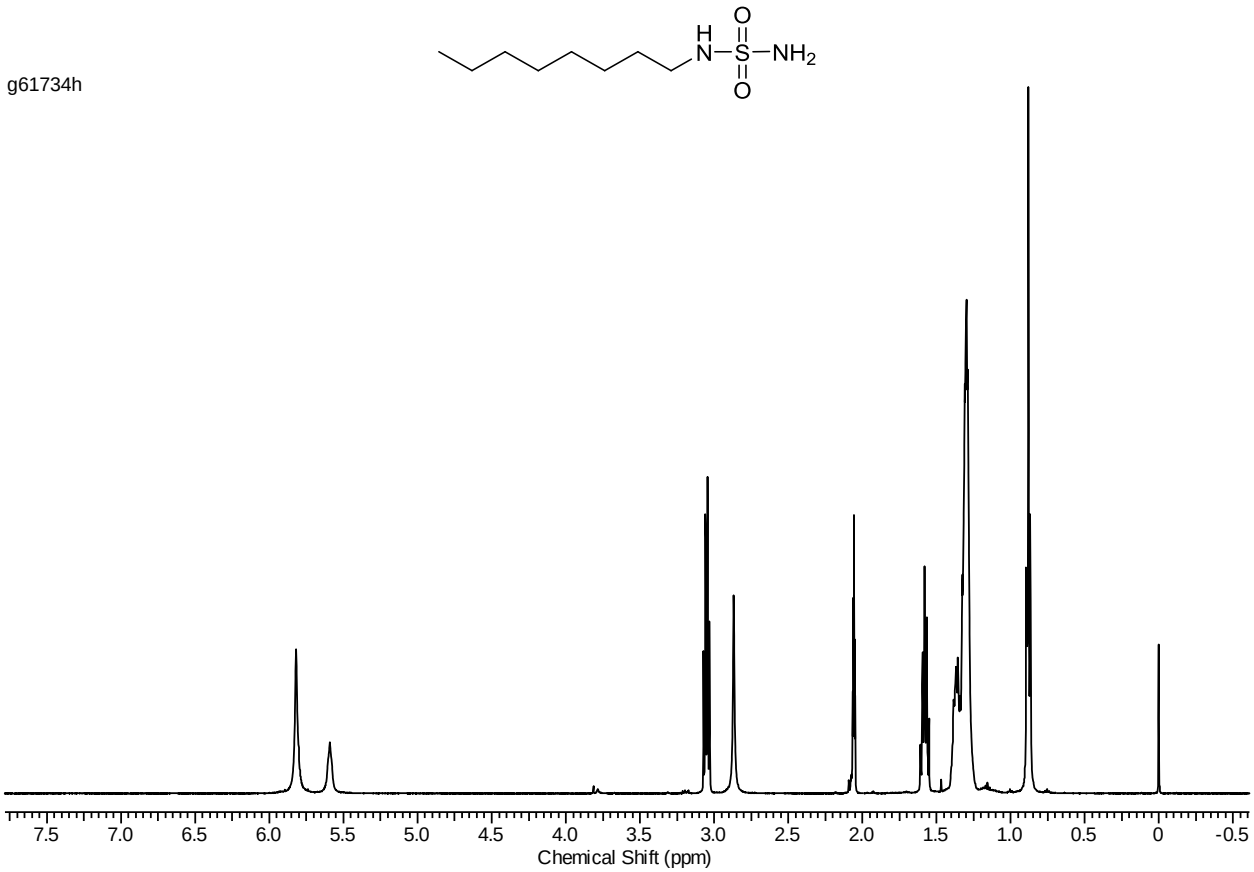


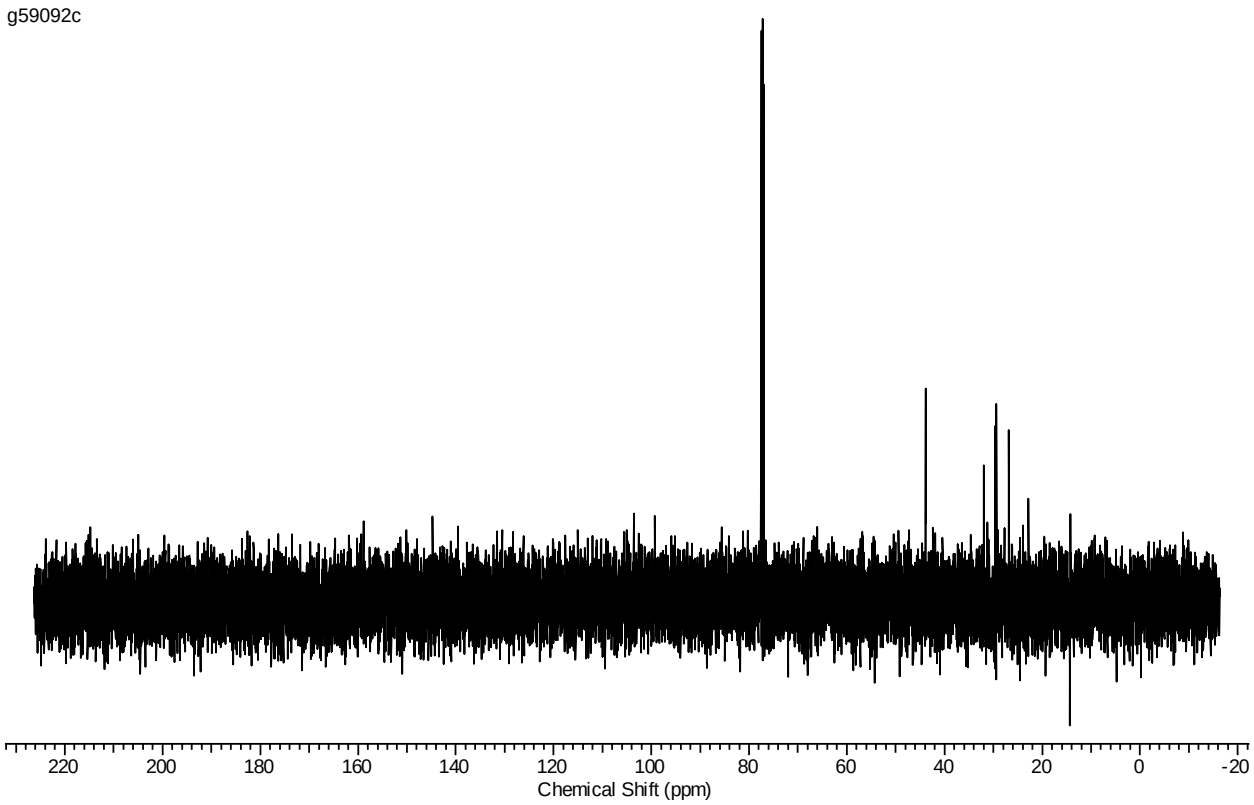
g62480h

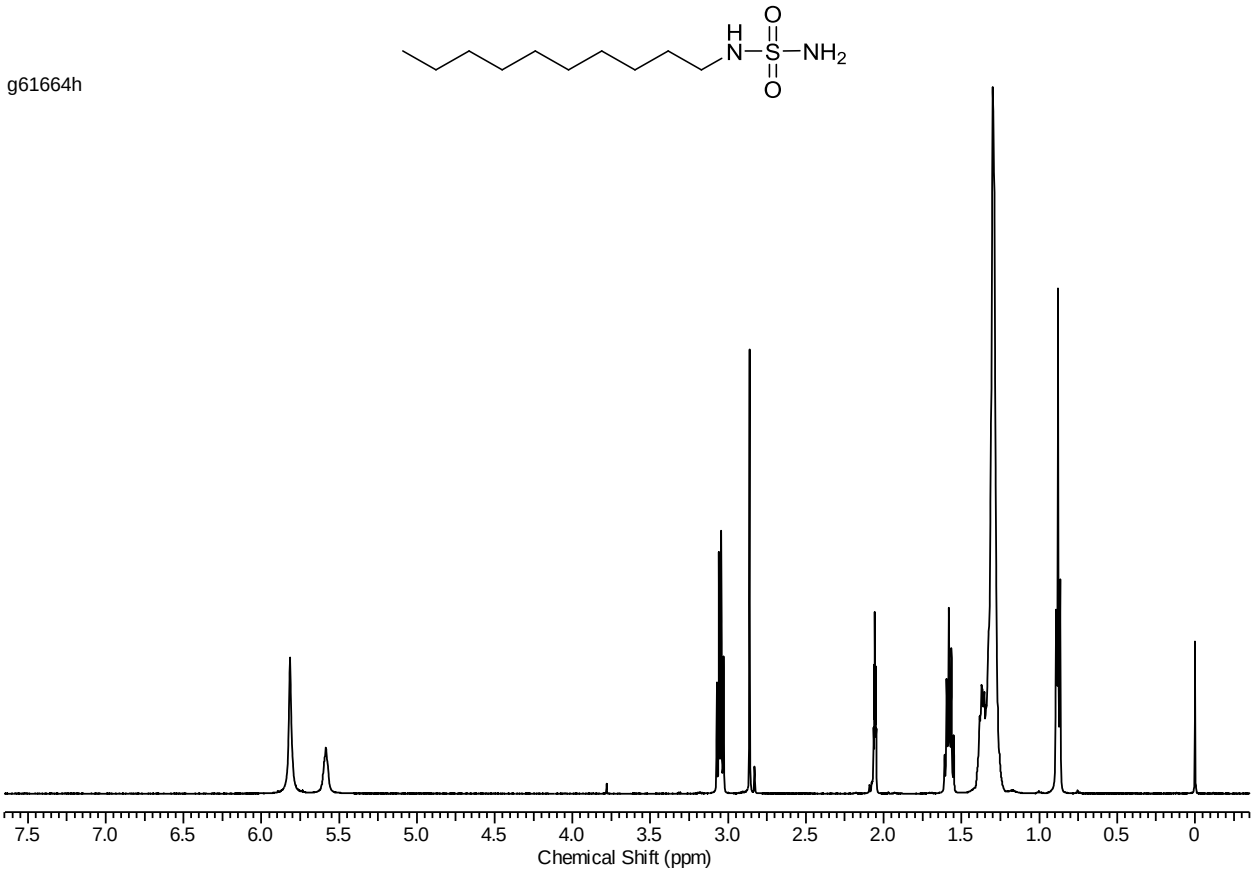


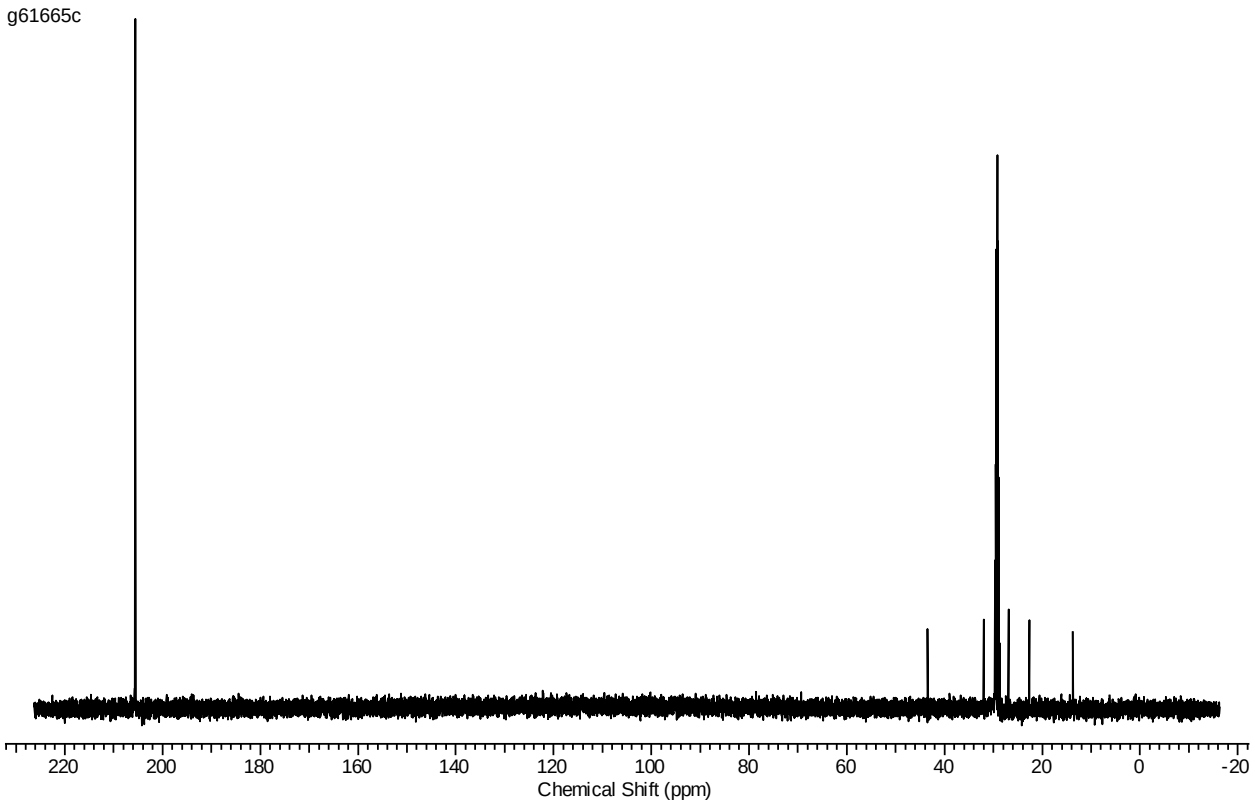
g62478c




g61734h
H
N
S
O
O
NH2
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
-0.5
Chemical Shift (ppm)


g59092c
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


g61664h
H
N
S
O
O
NH2
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
Chemical Shift (ppm)


g61665c
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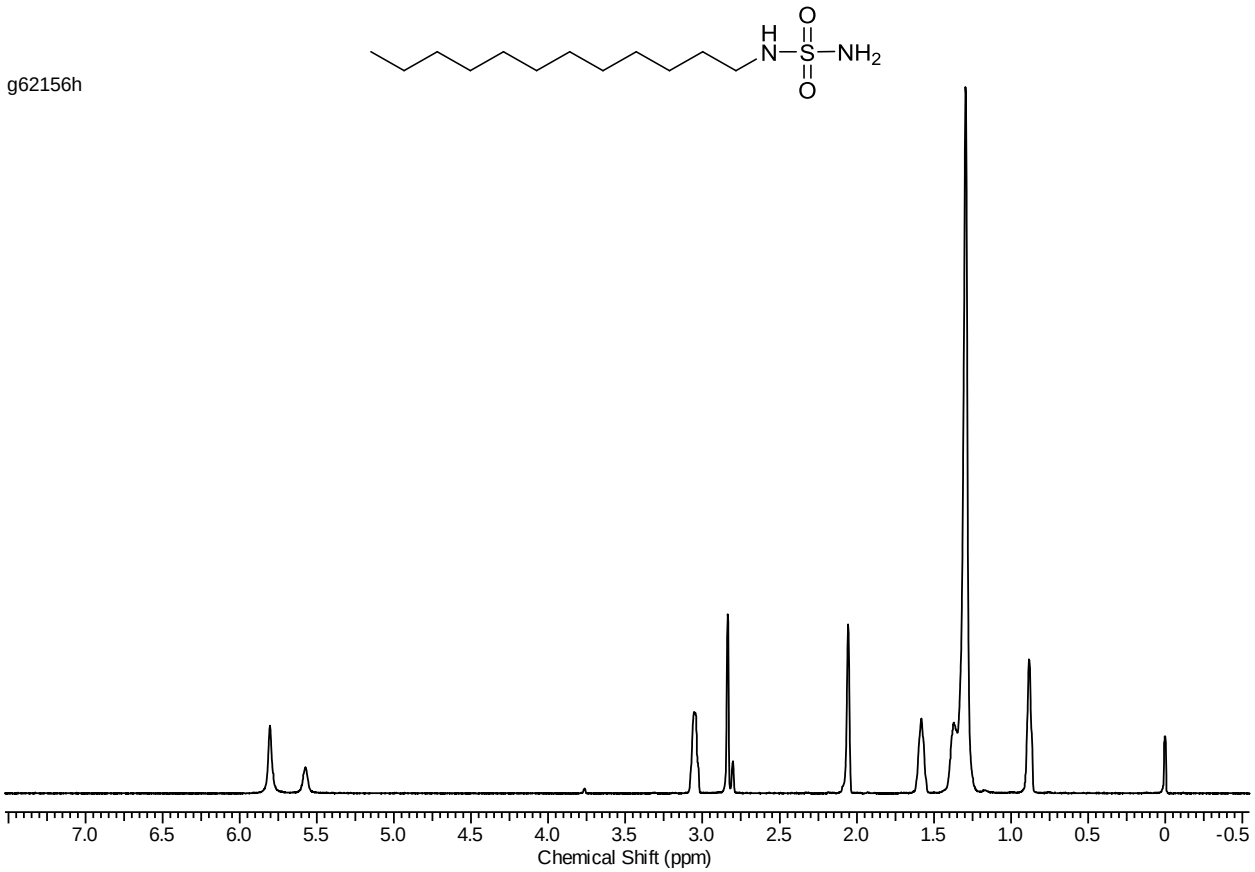
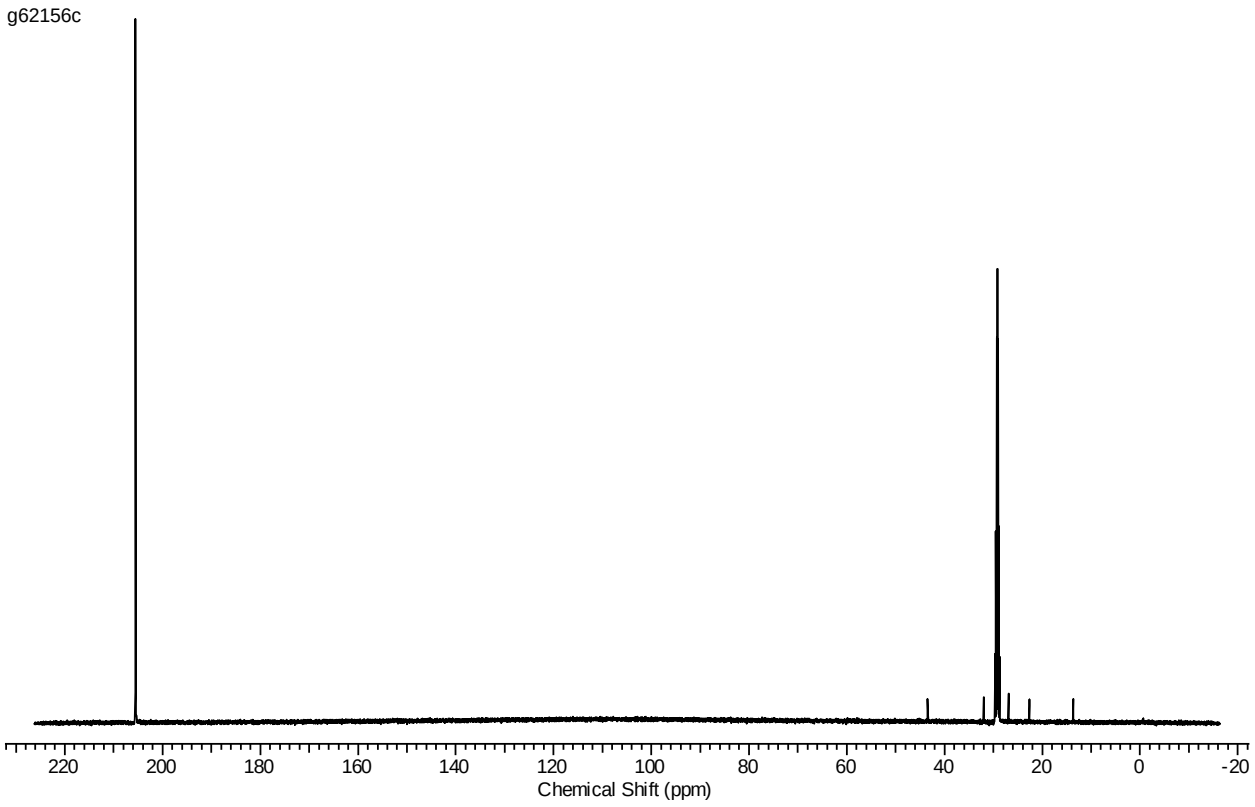
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


g62156h
H
N
S
O
O
NH2
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
-0.5
Chemical Shift (ppm)


g62156c
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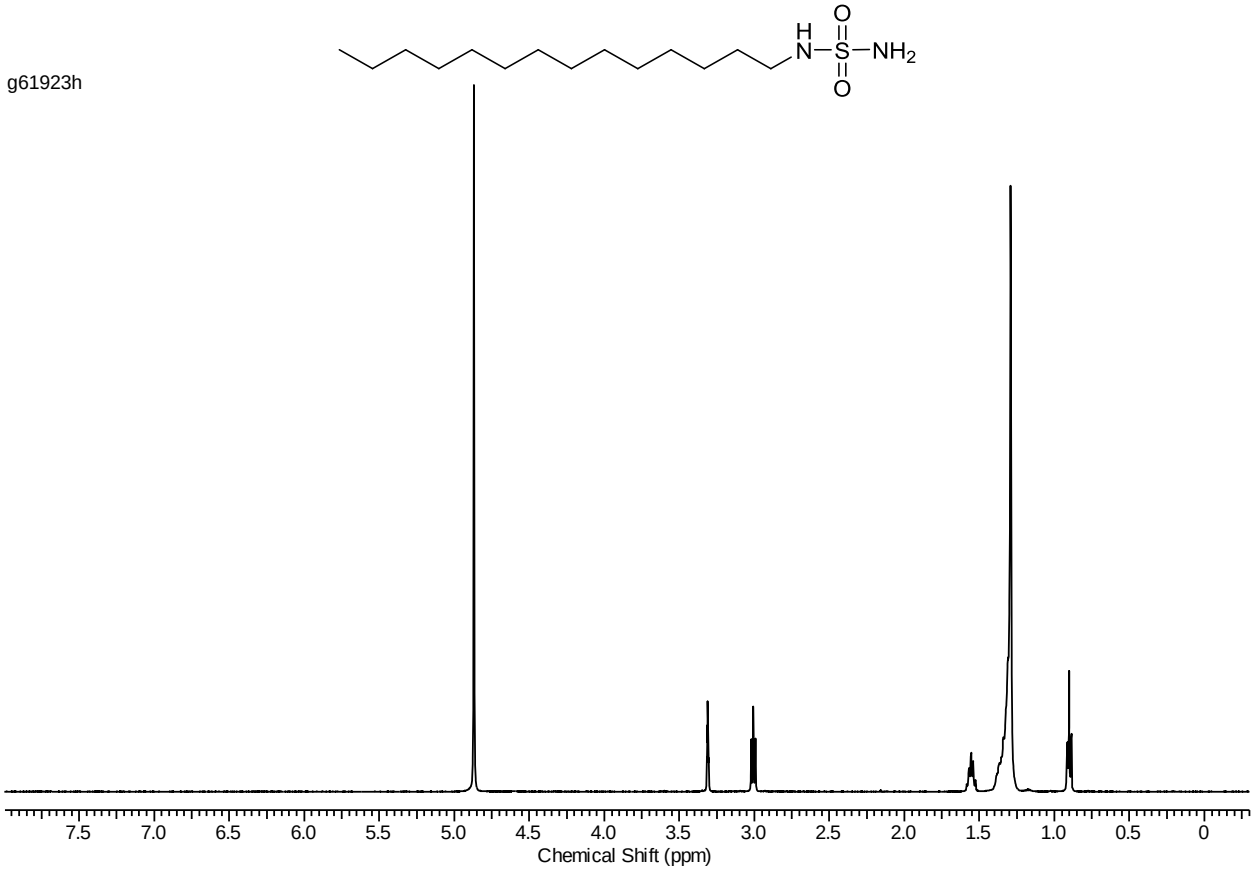
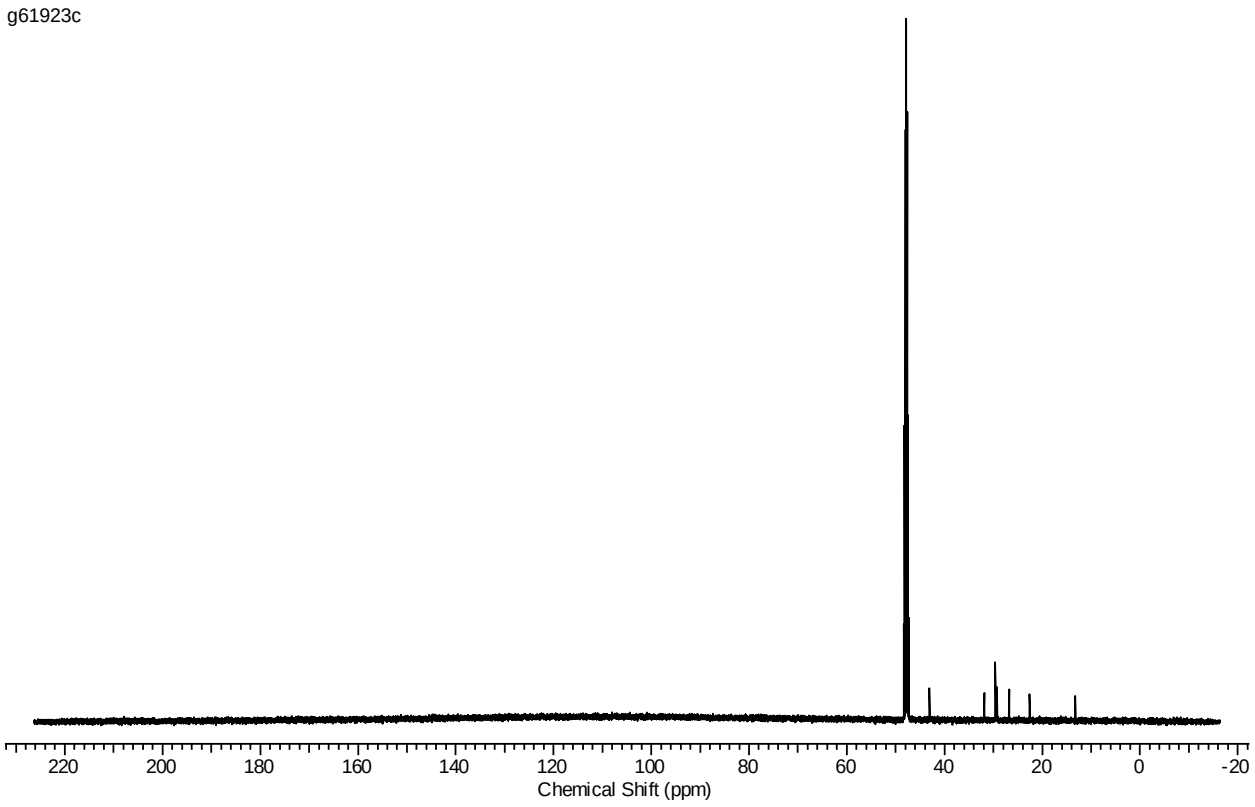
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


g61923h
O
H
N
S
NH2
O
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
Chemical Shift (ppm)


g61923c
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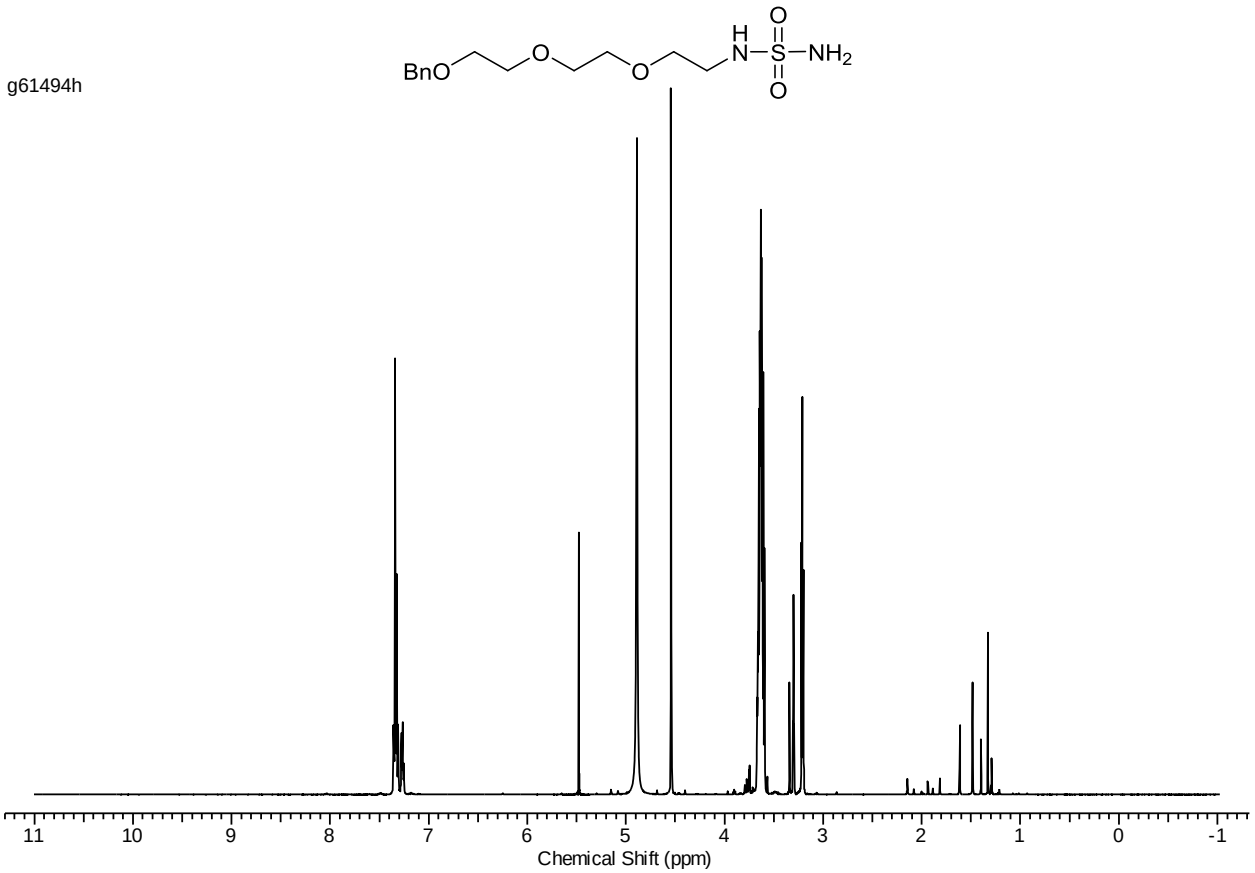
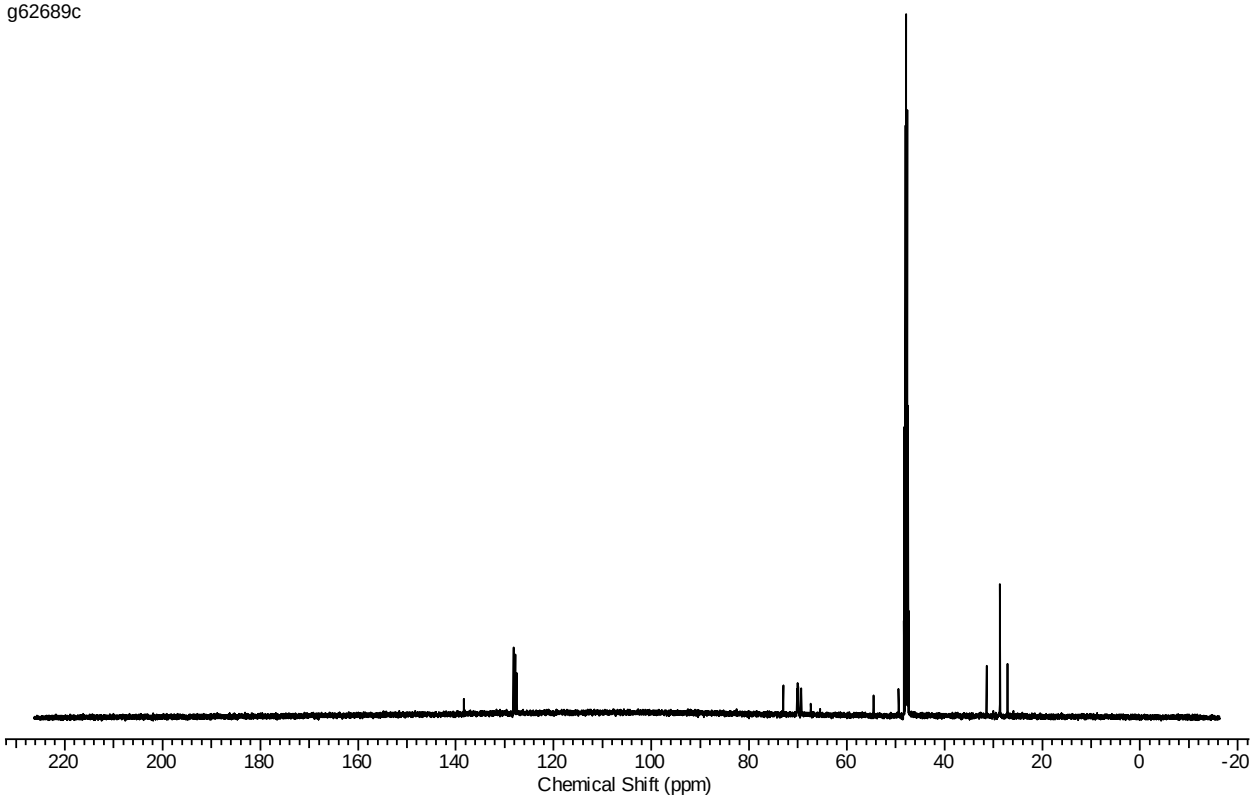
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

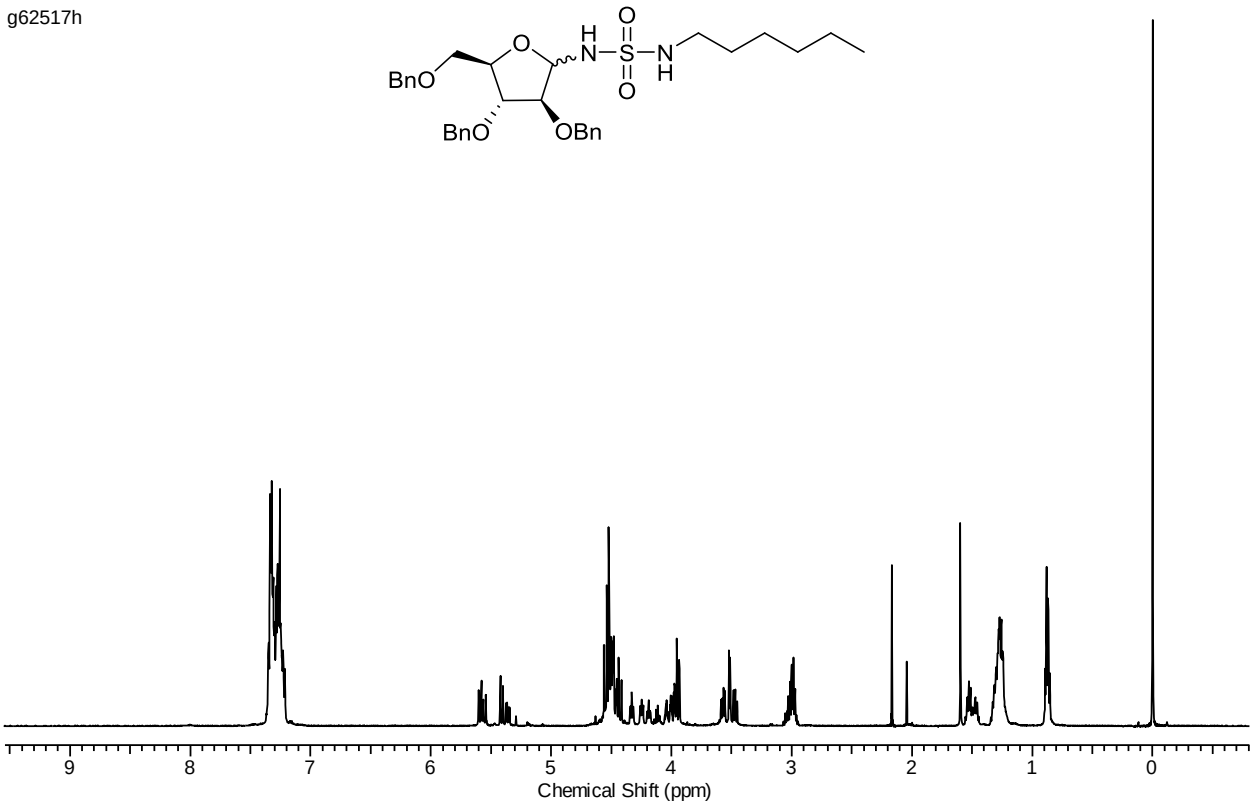
g61494h



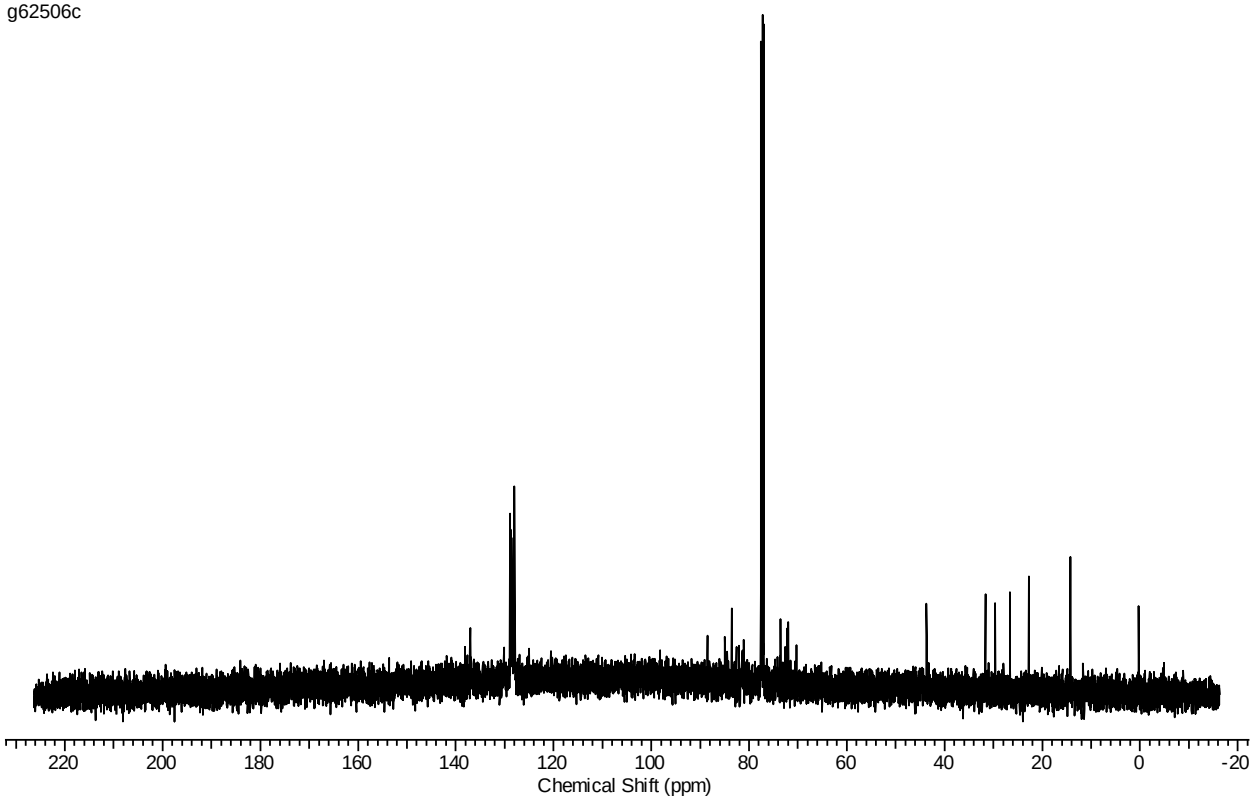
g62689c



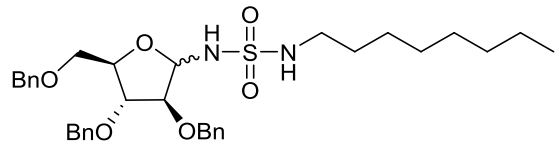
g62517h

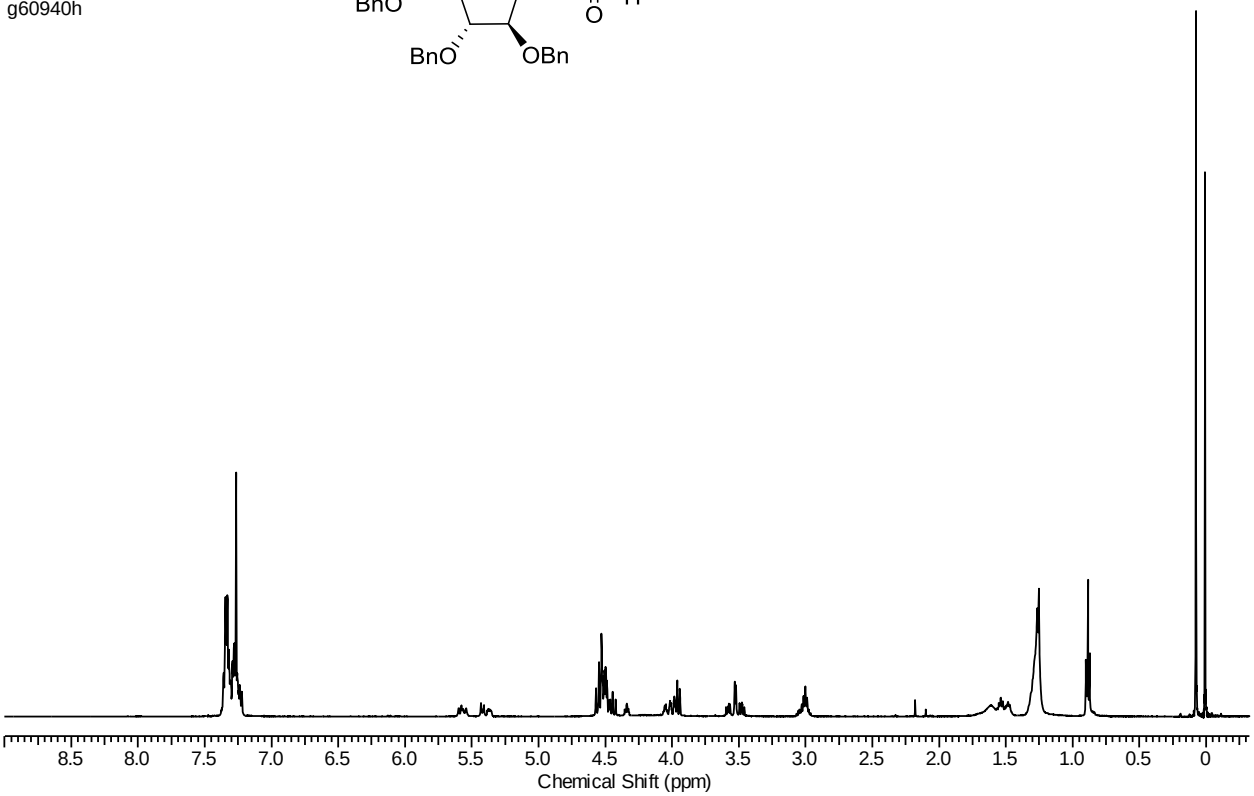


g62506c

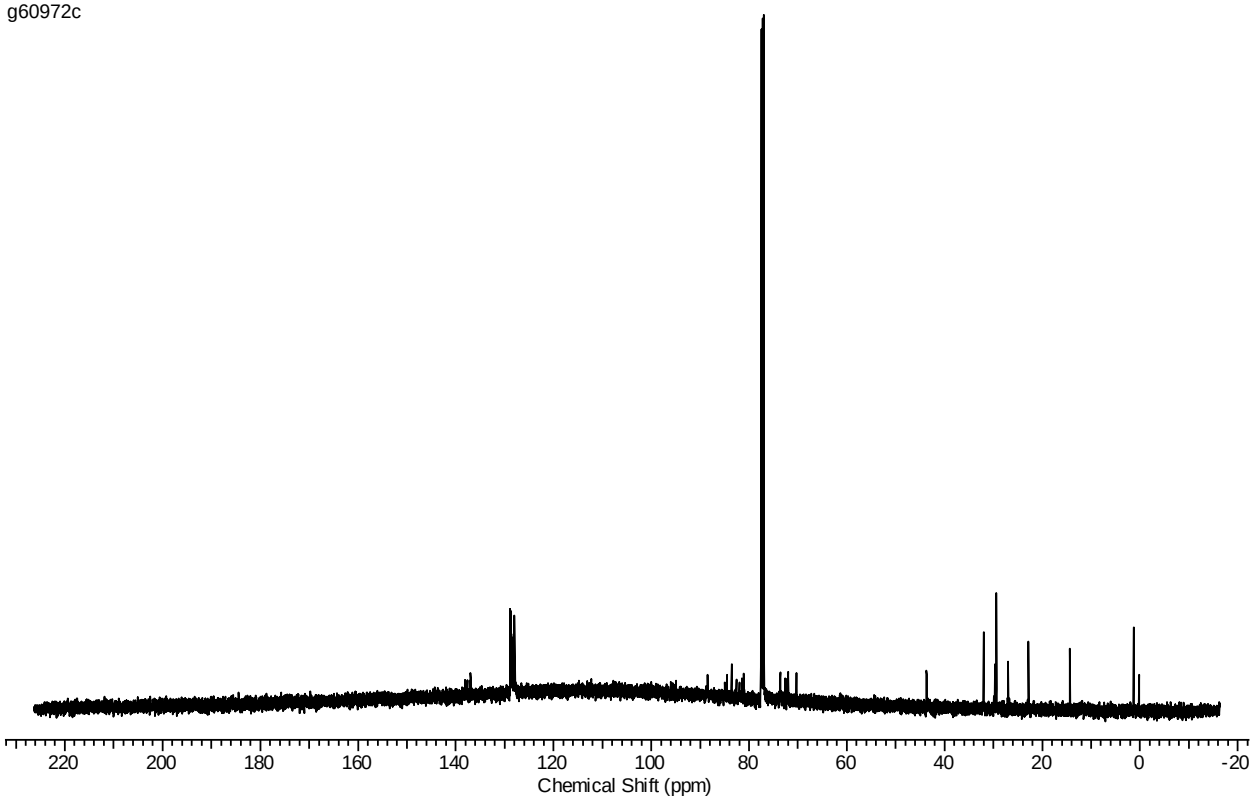


g60940h

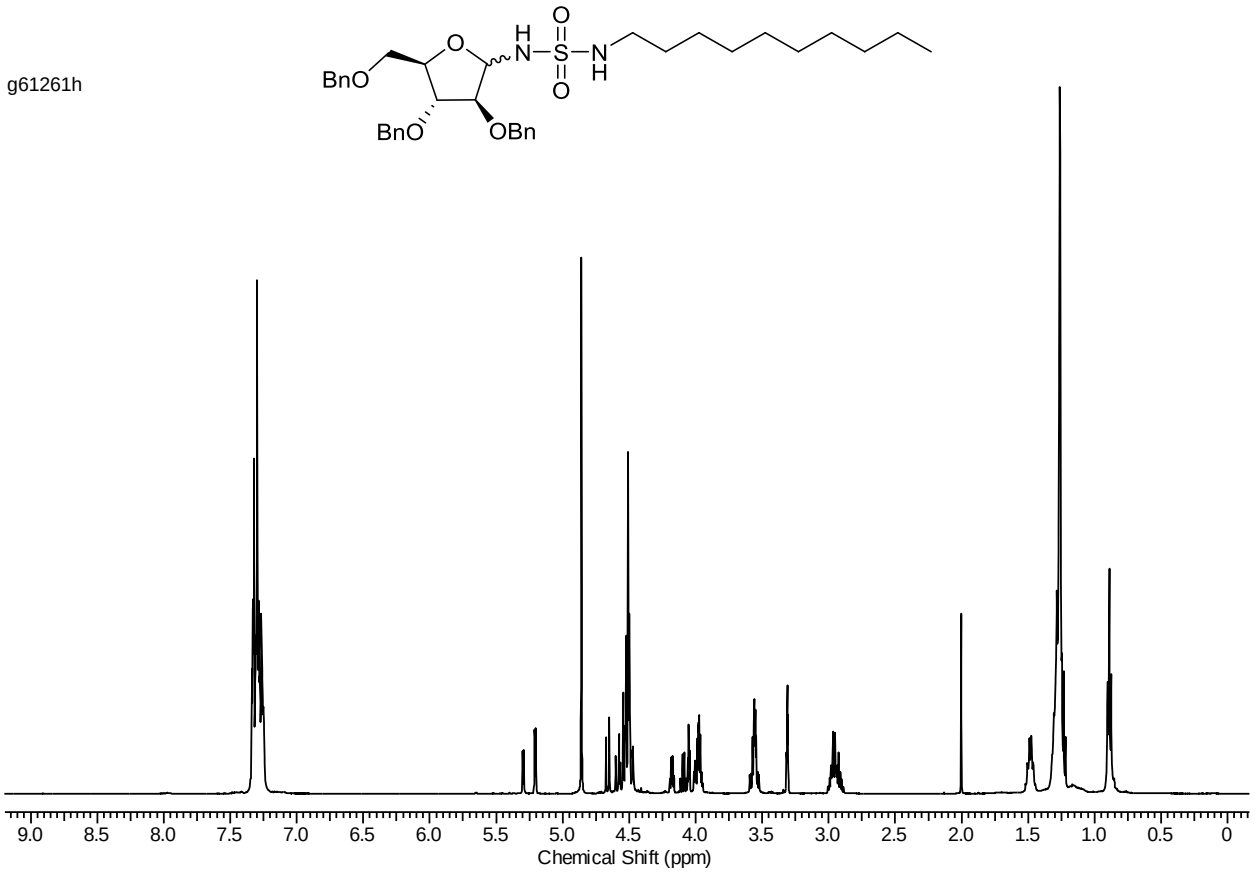




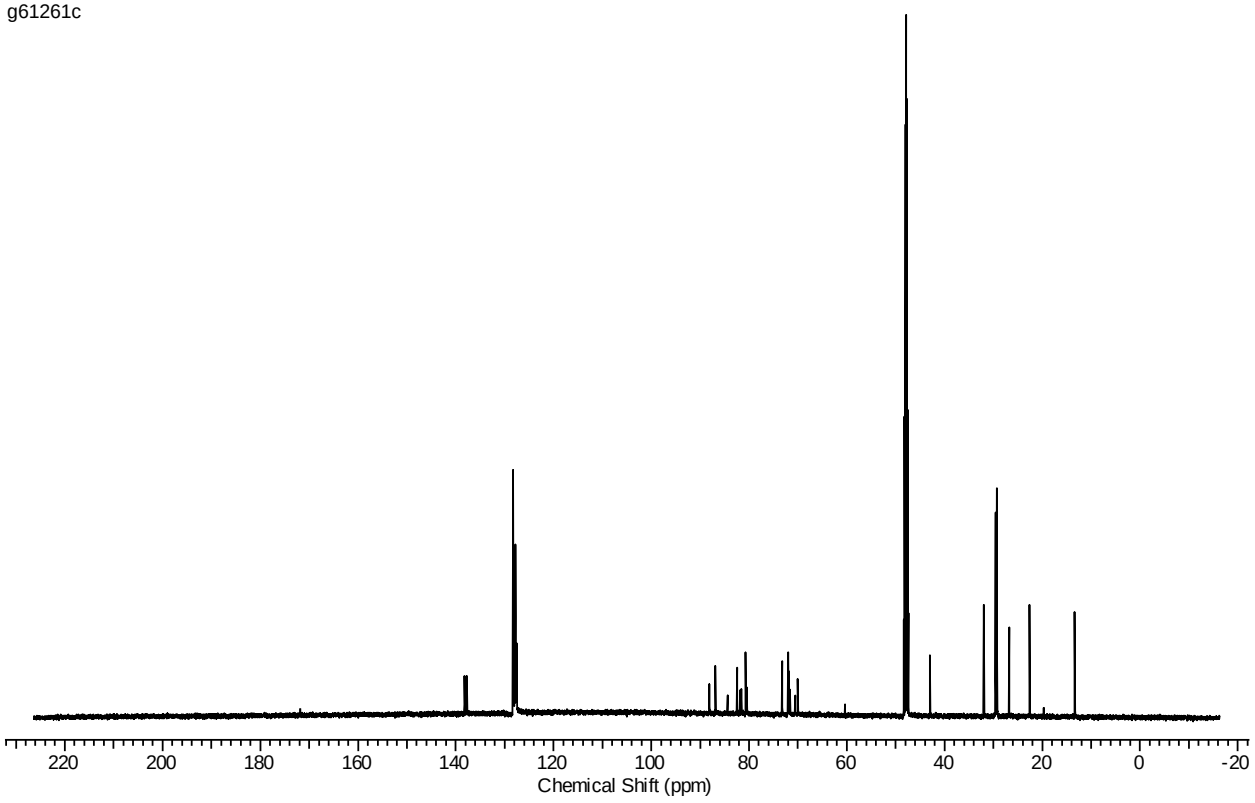
g60972c



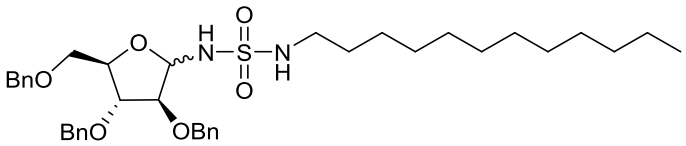
g61261h

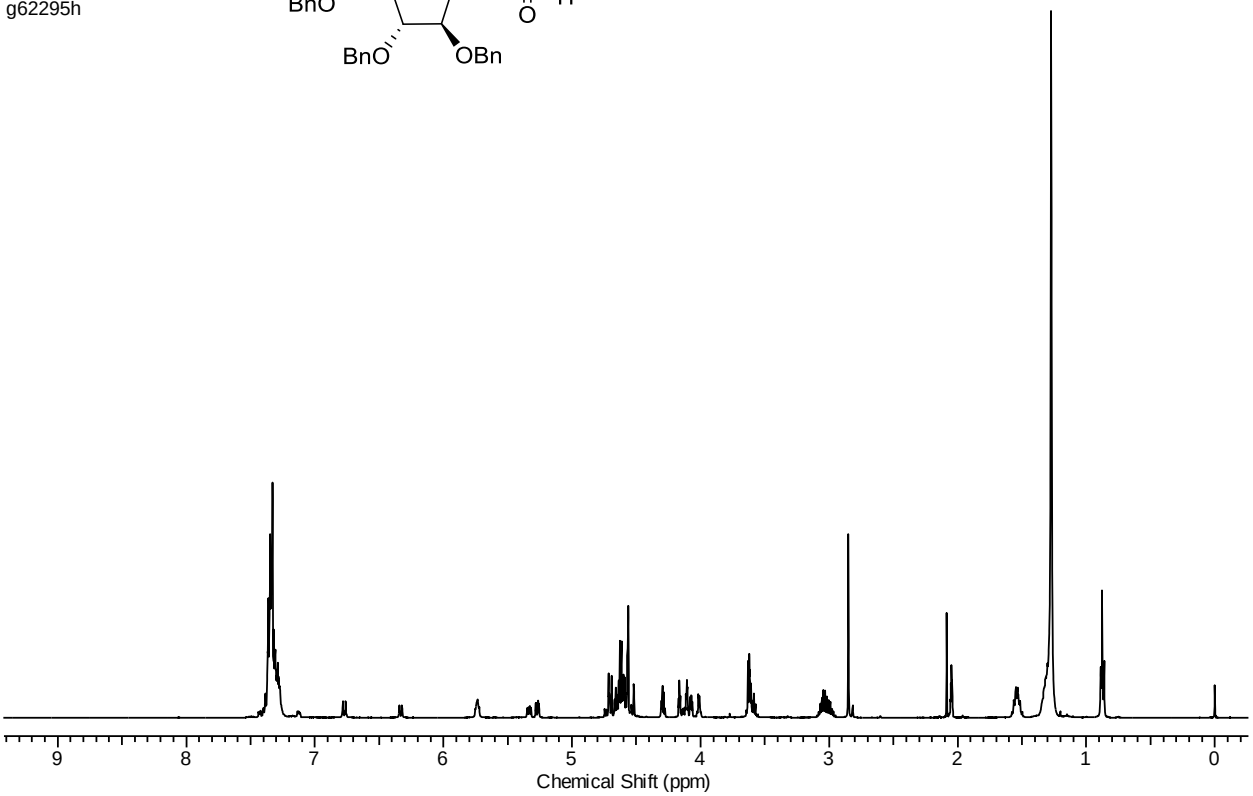


g61261c

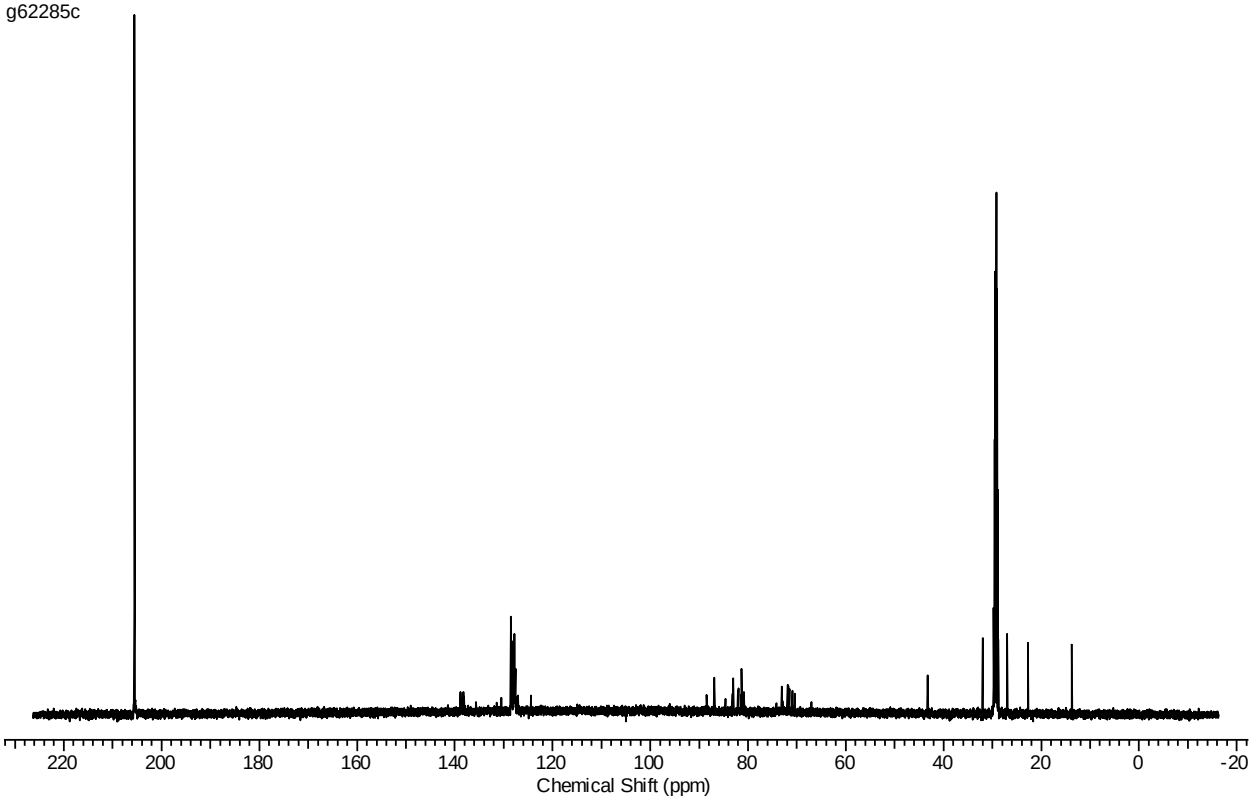


g62295h

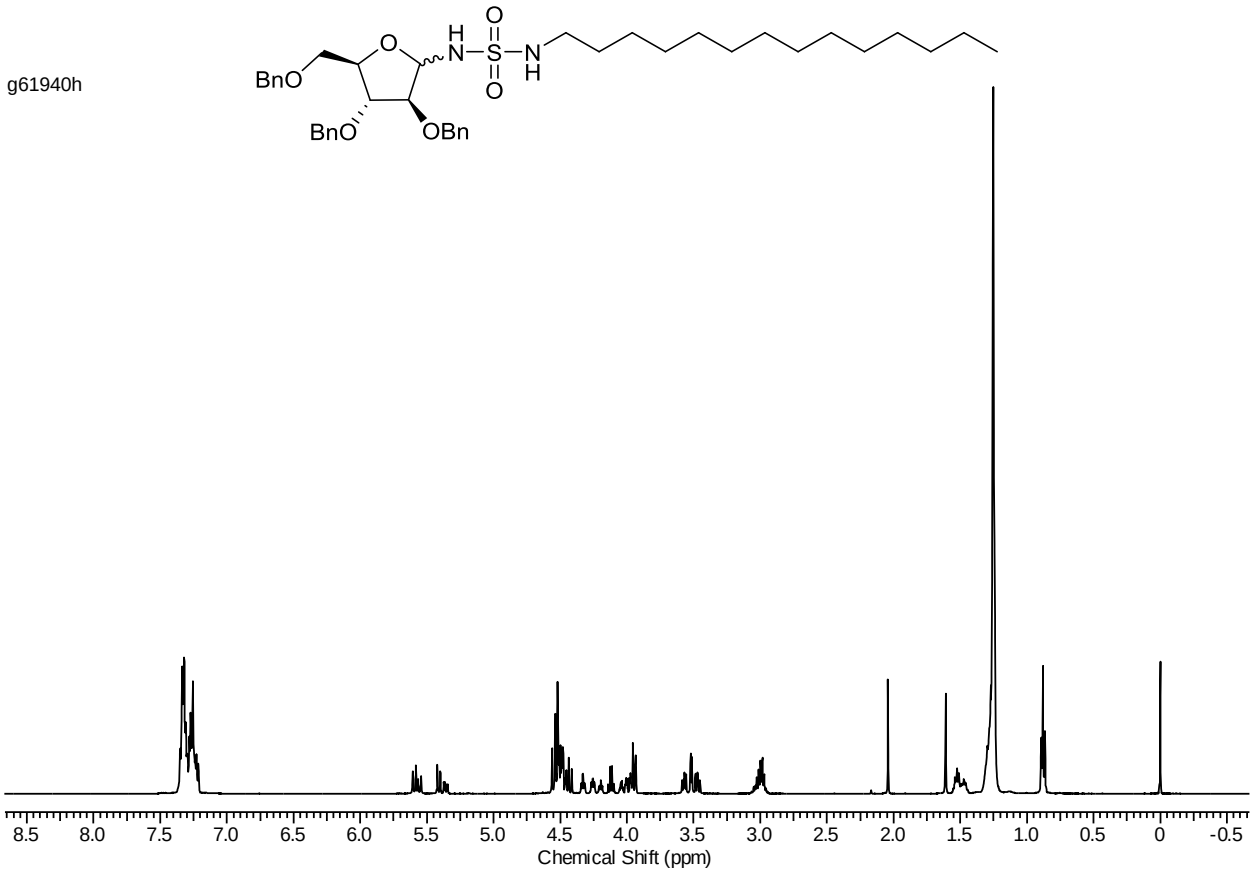




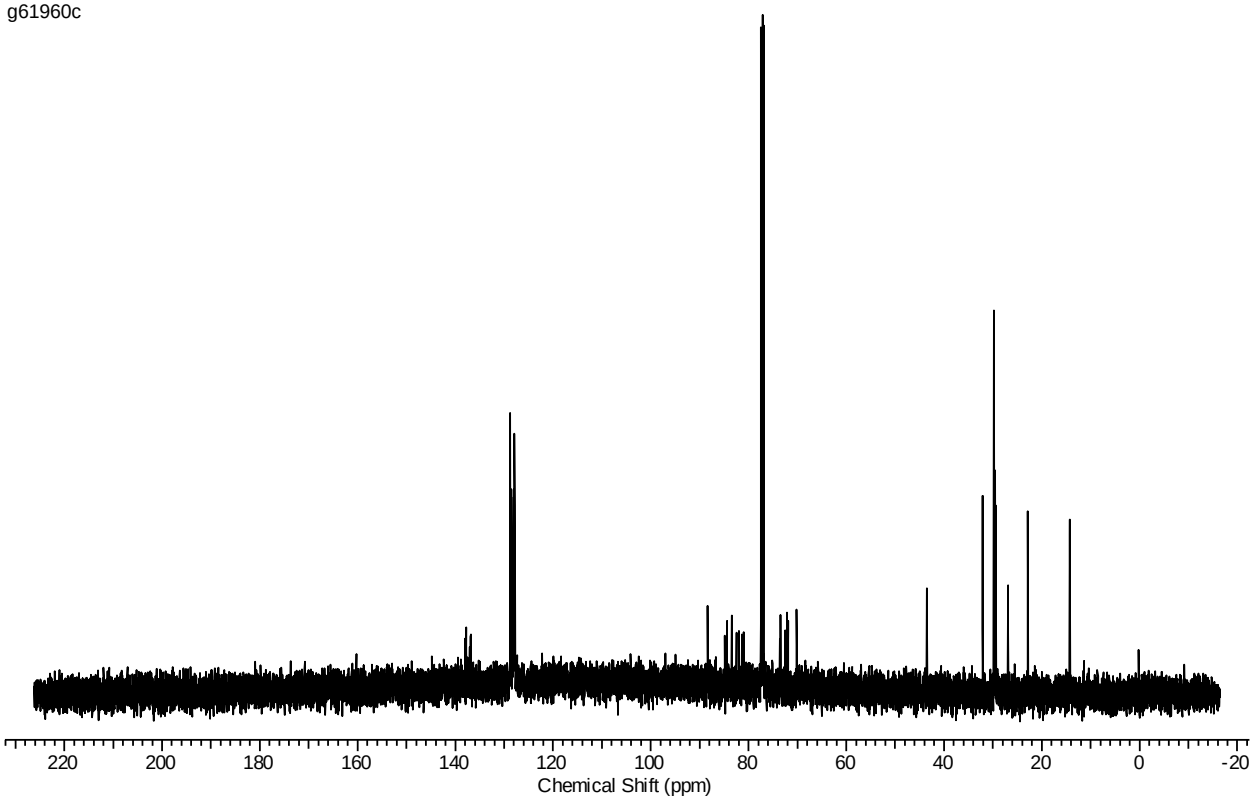
g62285c

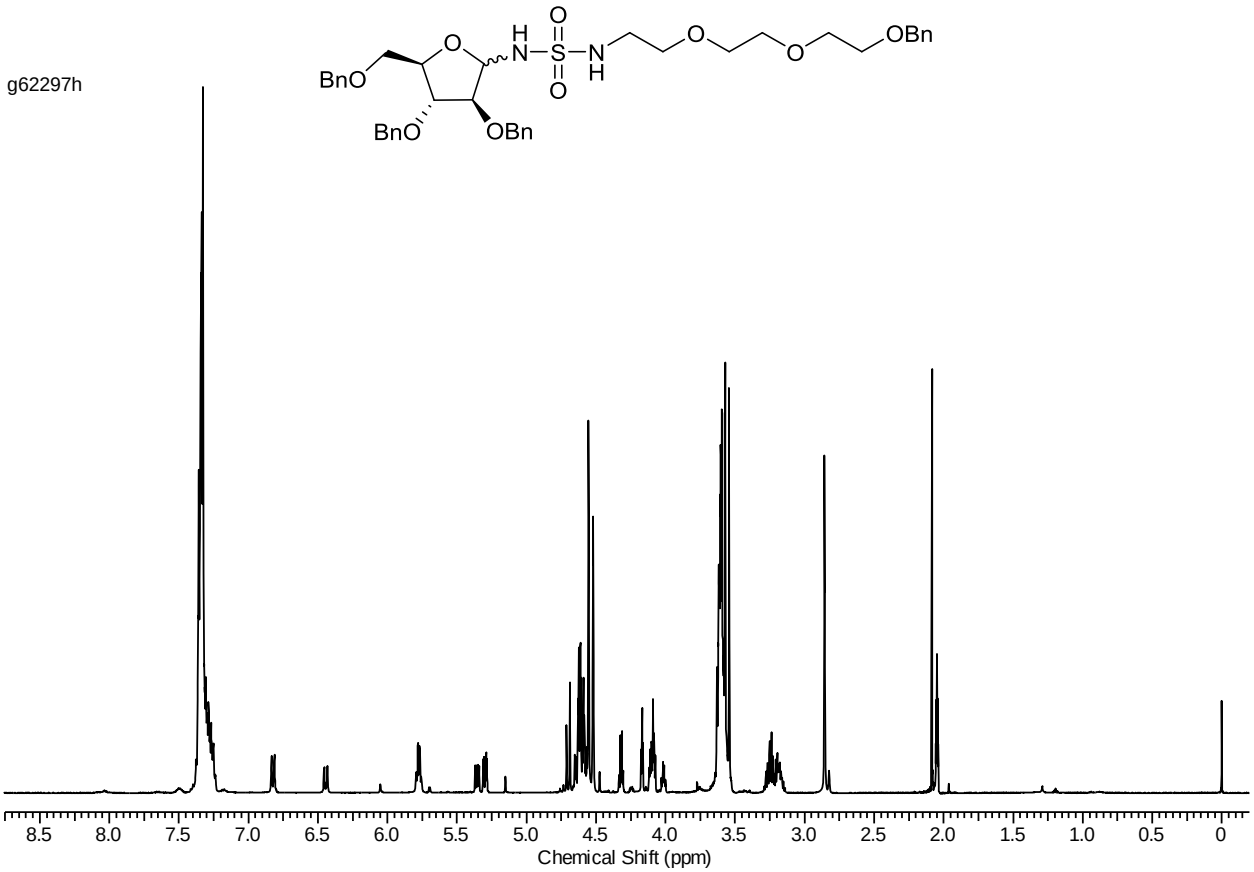


g61940h



g61960c




g62297h
BnO
BnO
OBn
H
N
S
O
O
N
H
O
O
OBn
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
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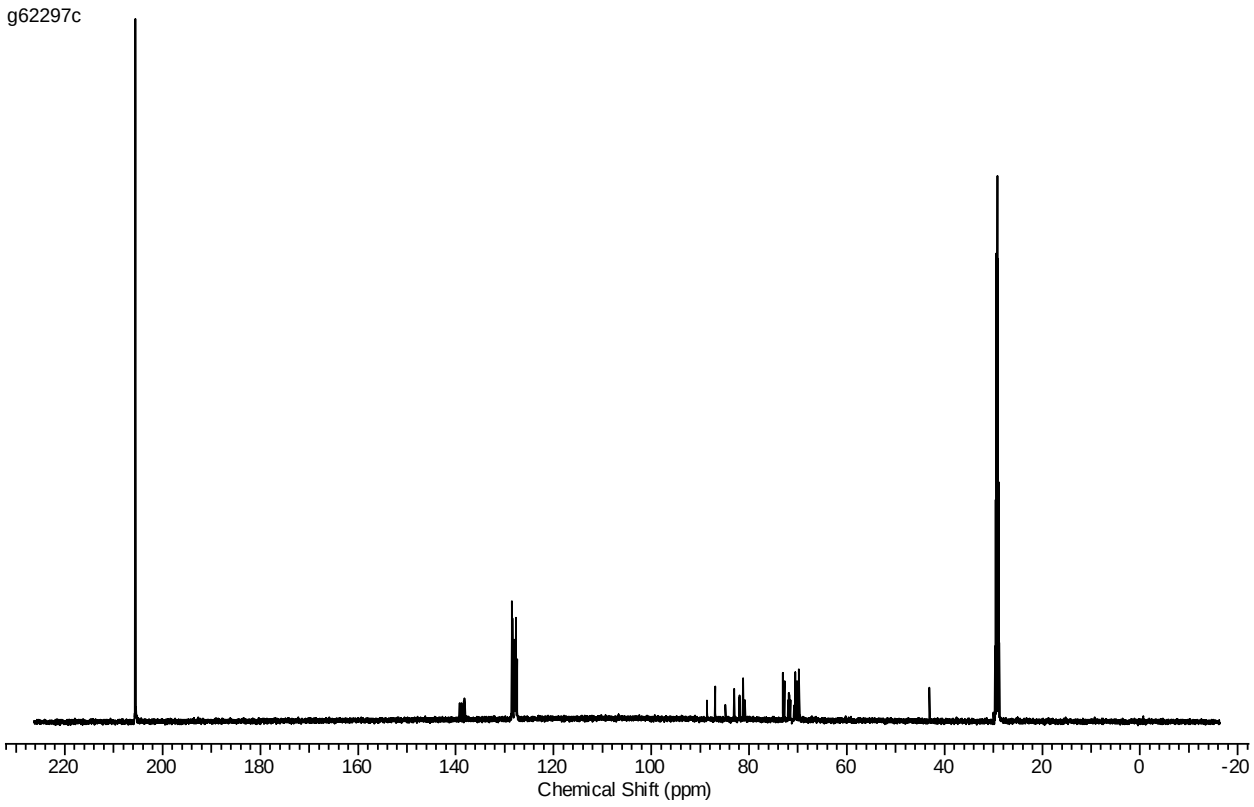
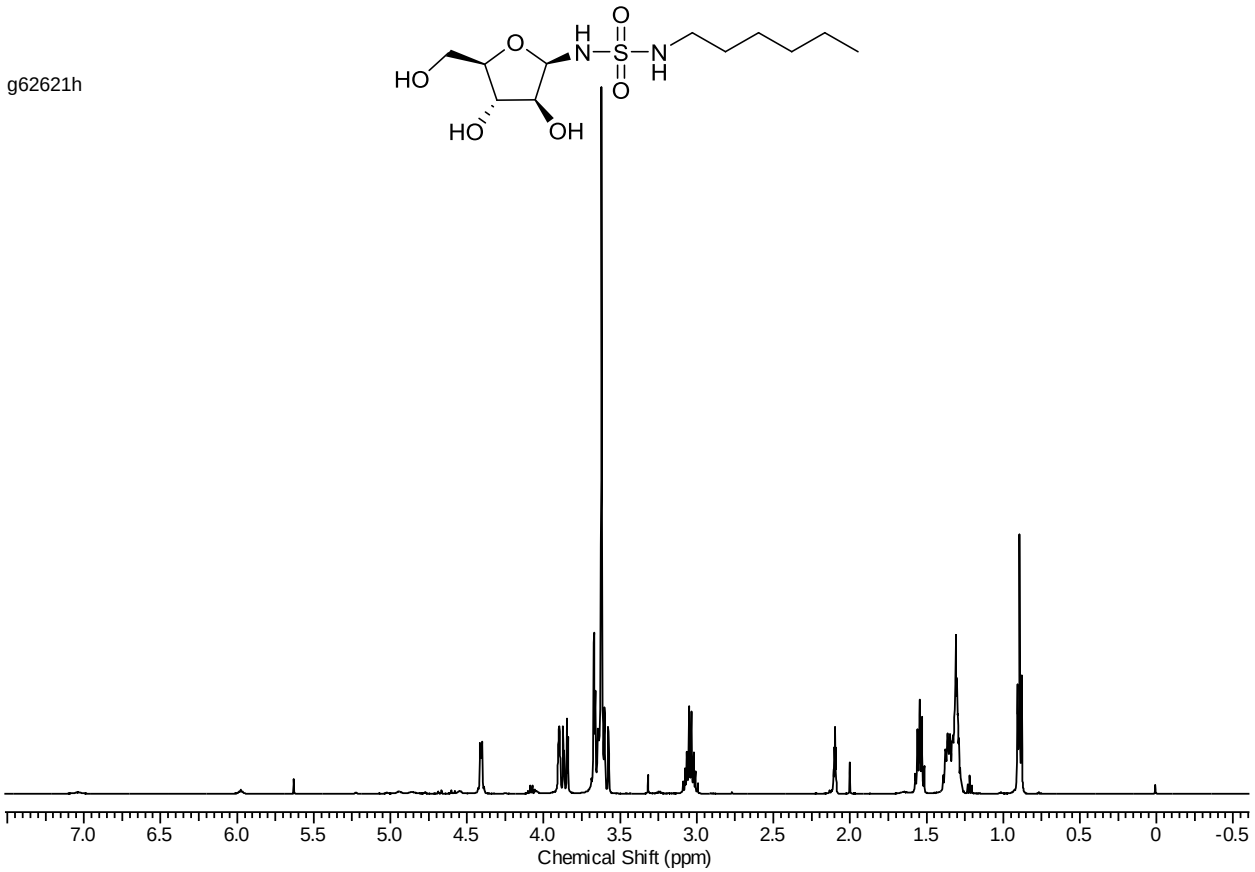
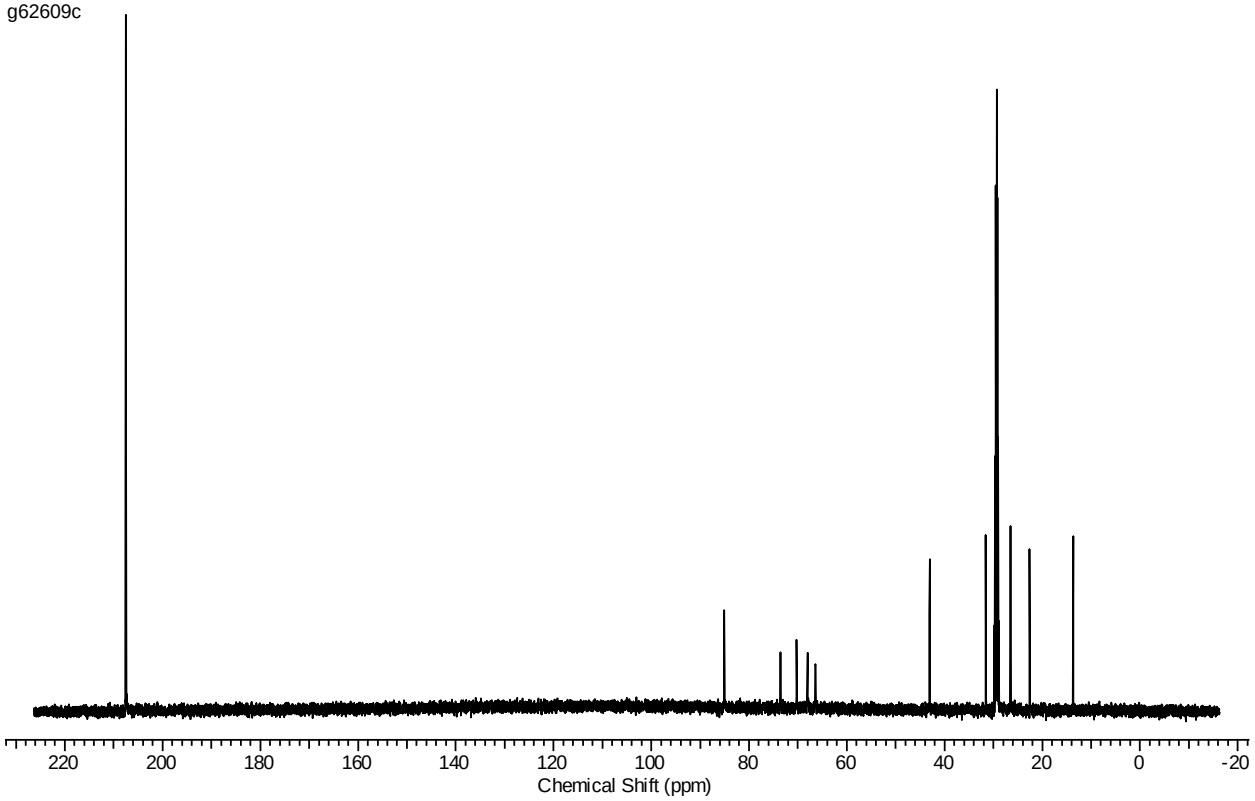
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


g62297c
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

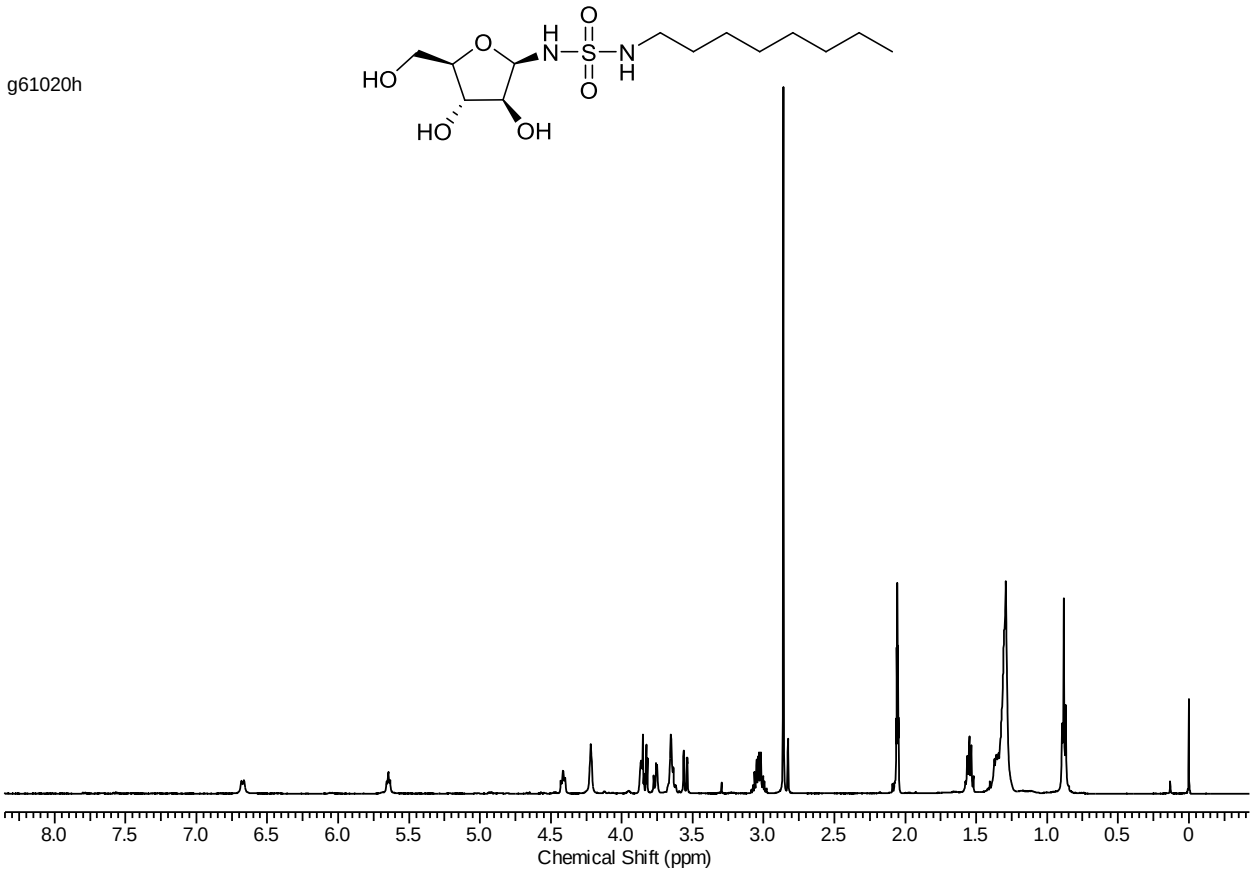
g62621h



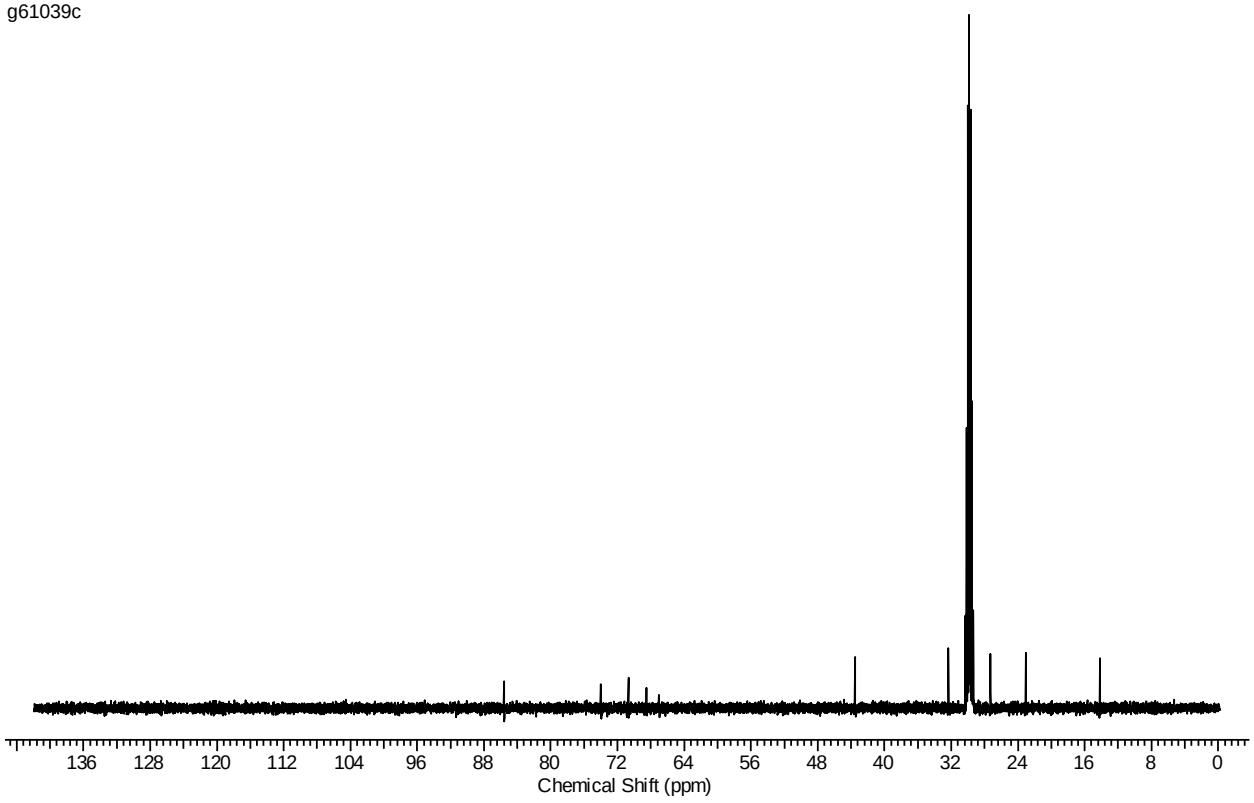
g62609c



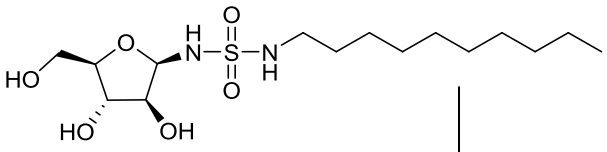
g61020h

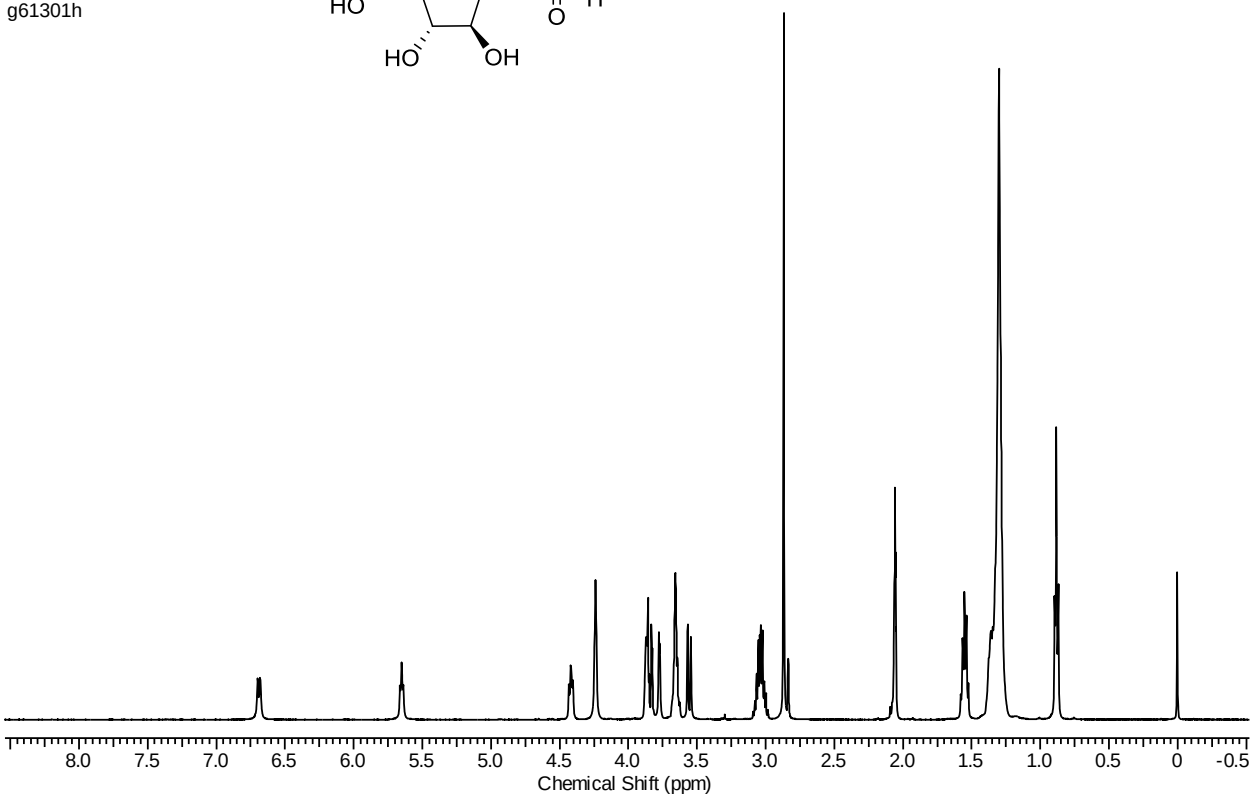


g61039c

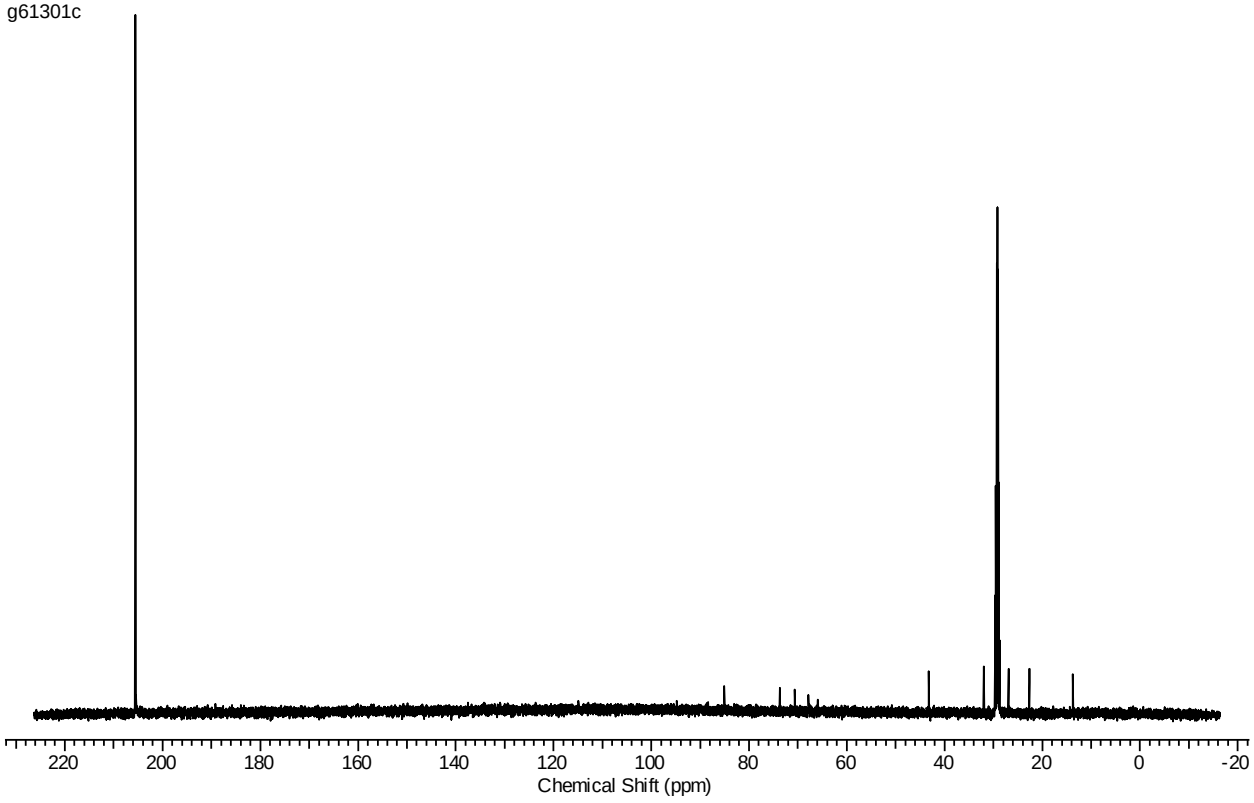


g61301h

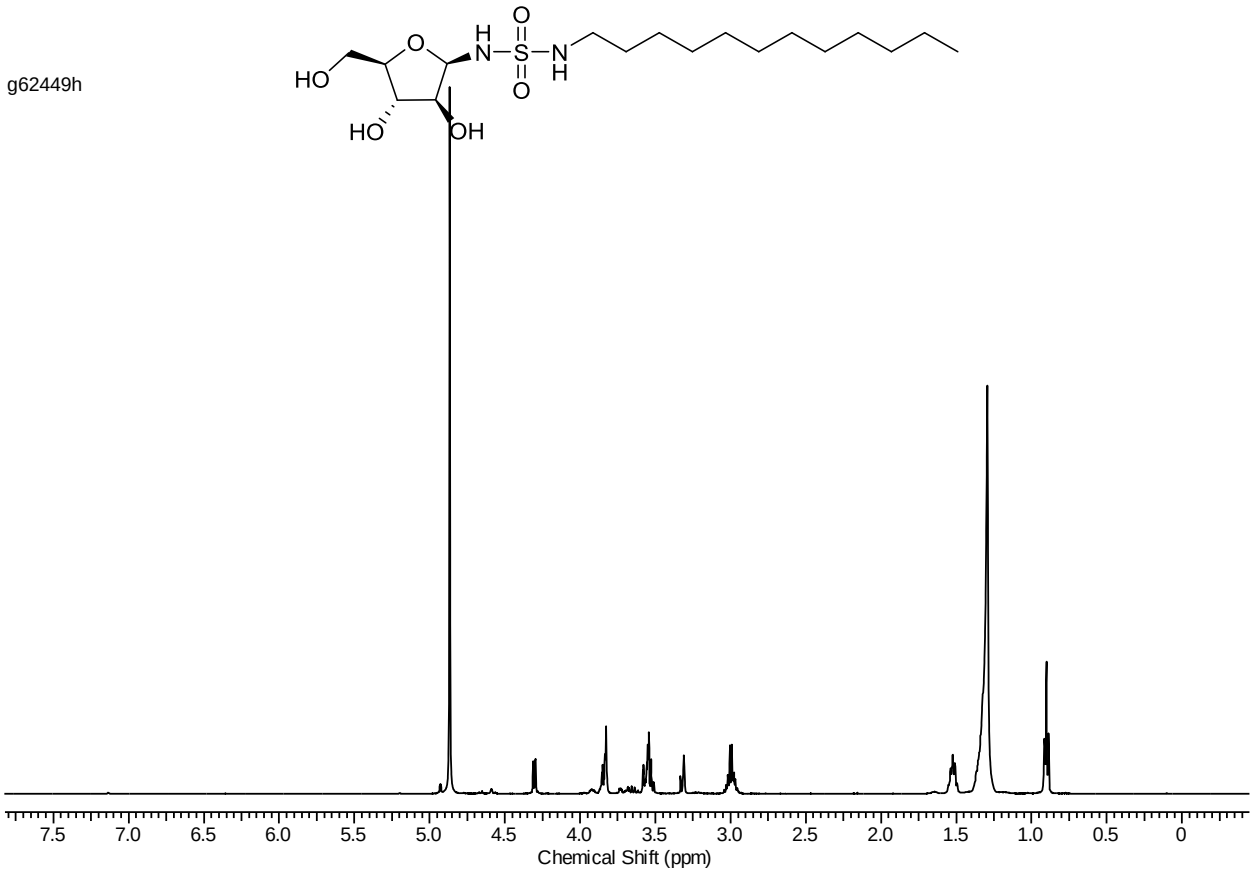




g61301c



g62449h



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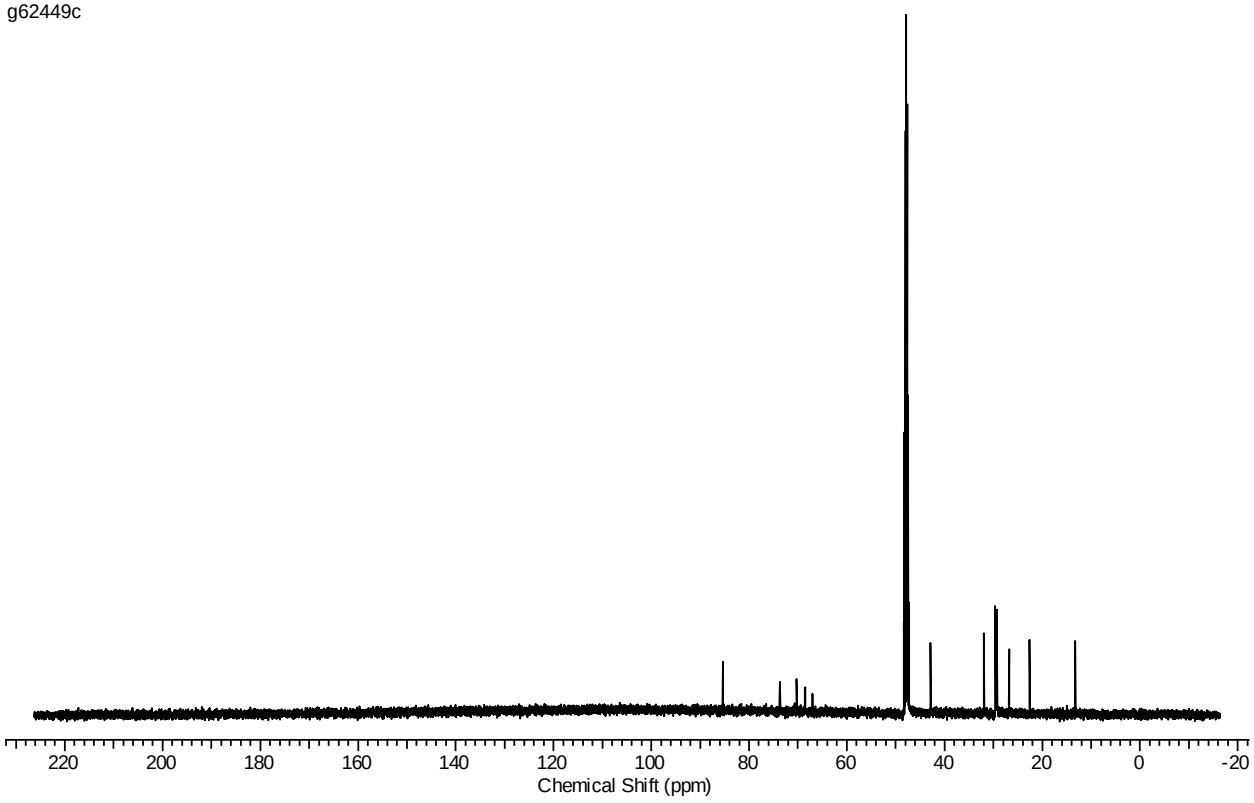

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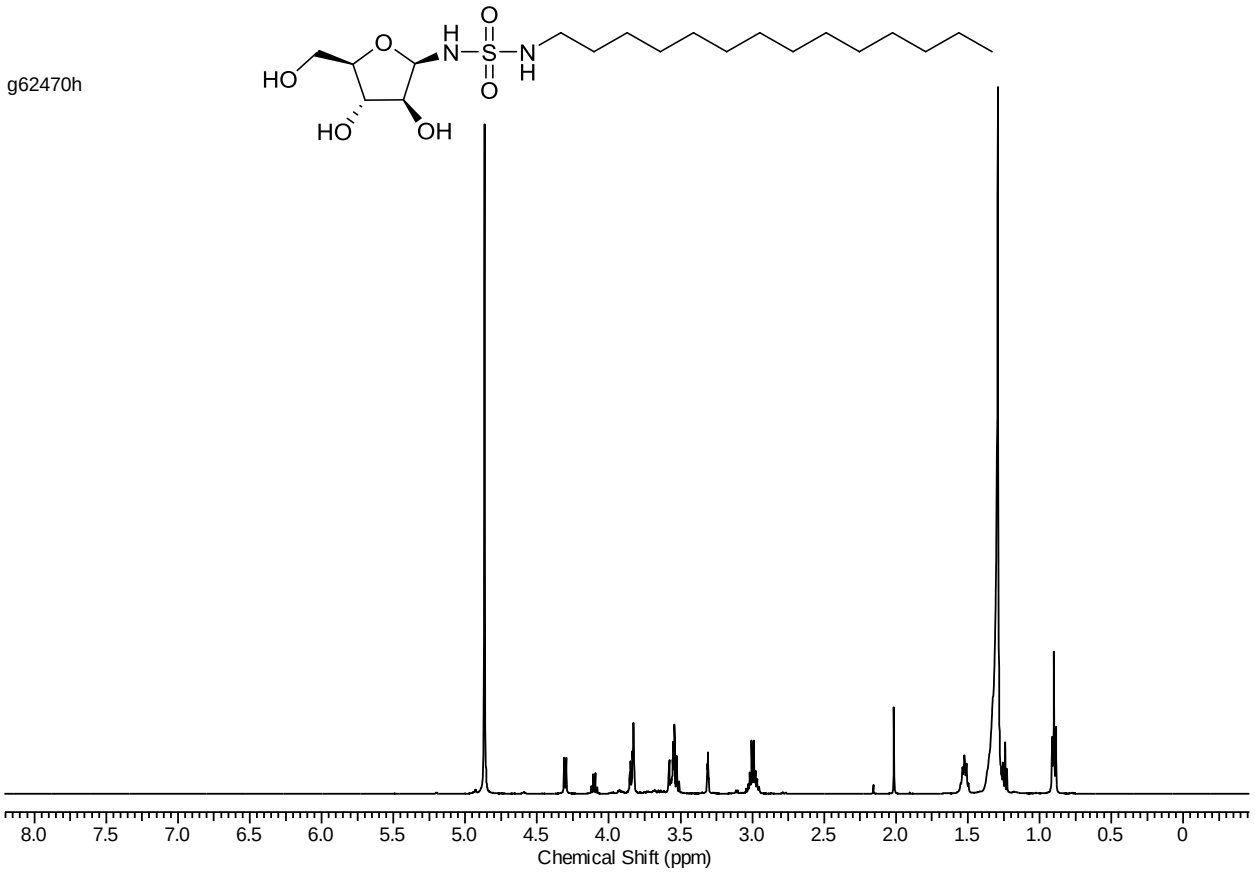

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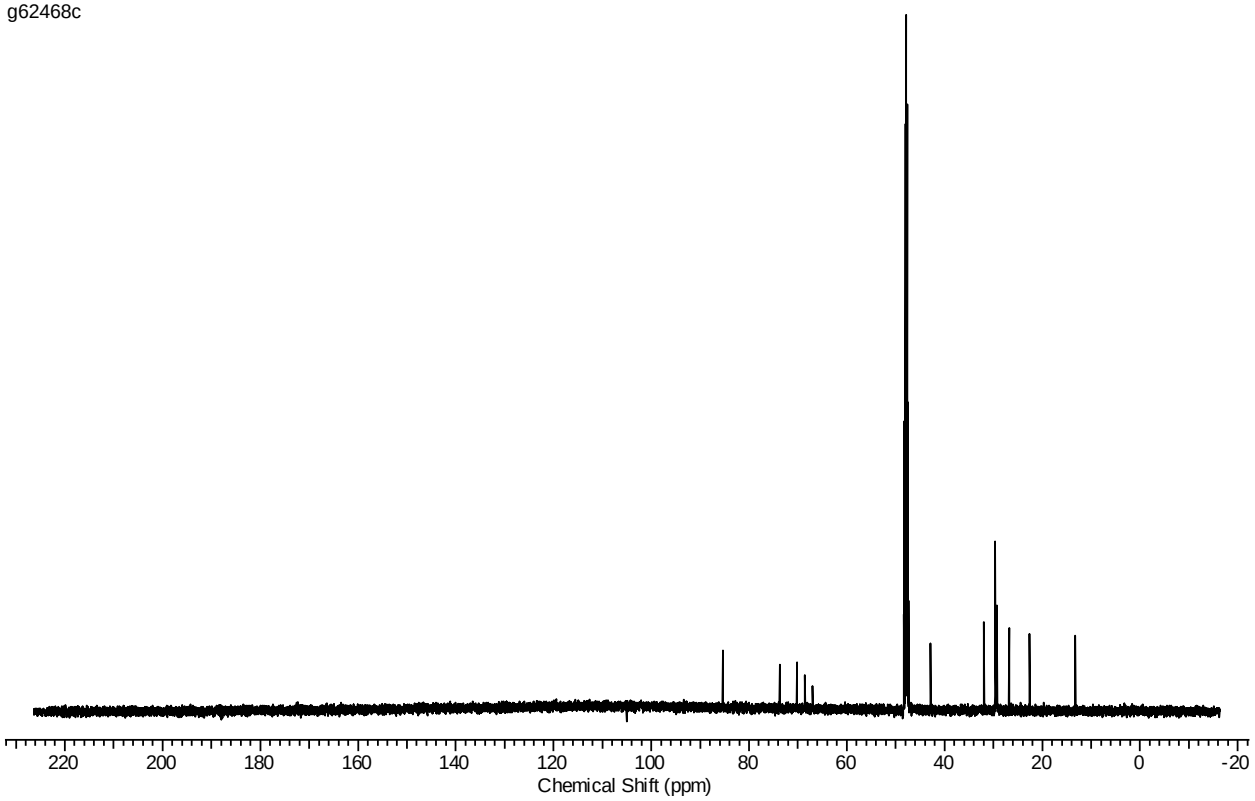

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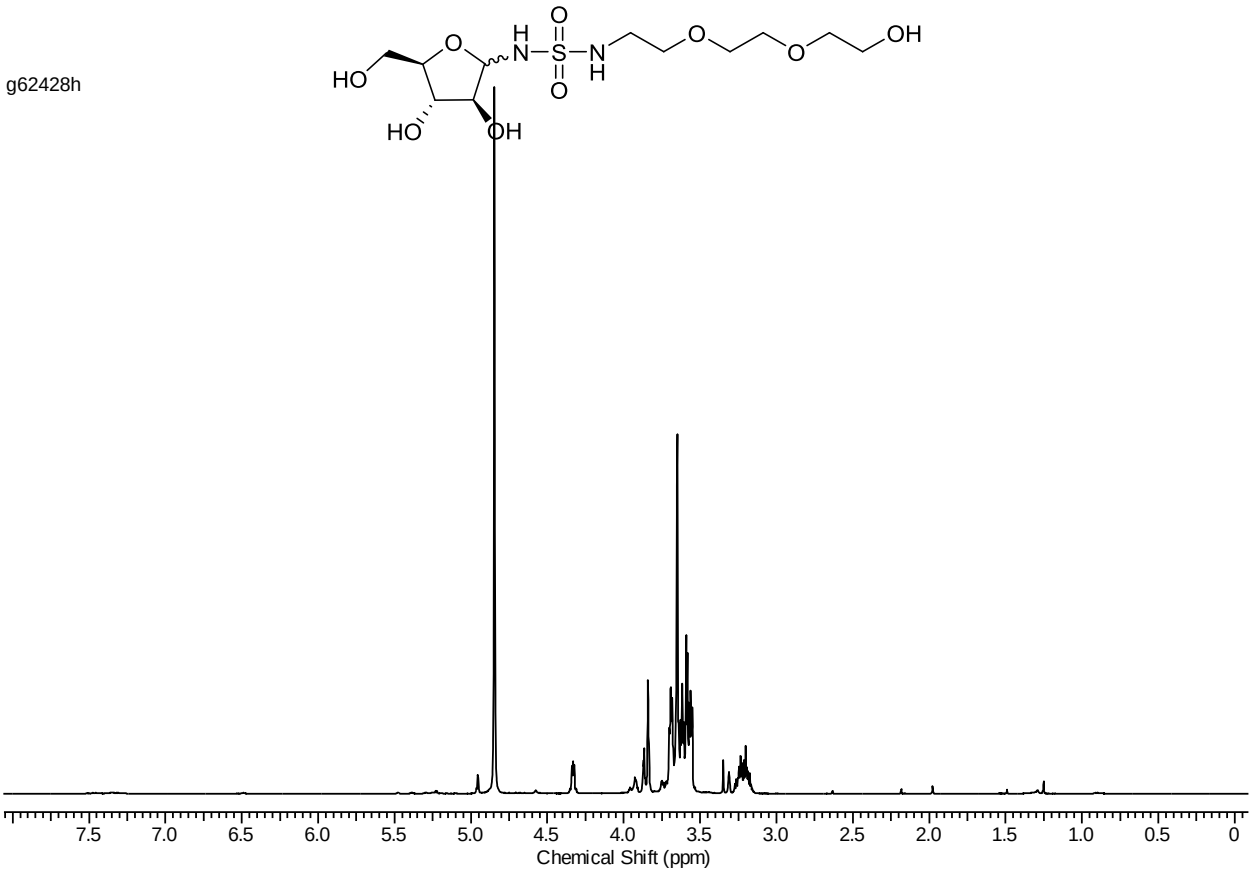

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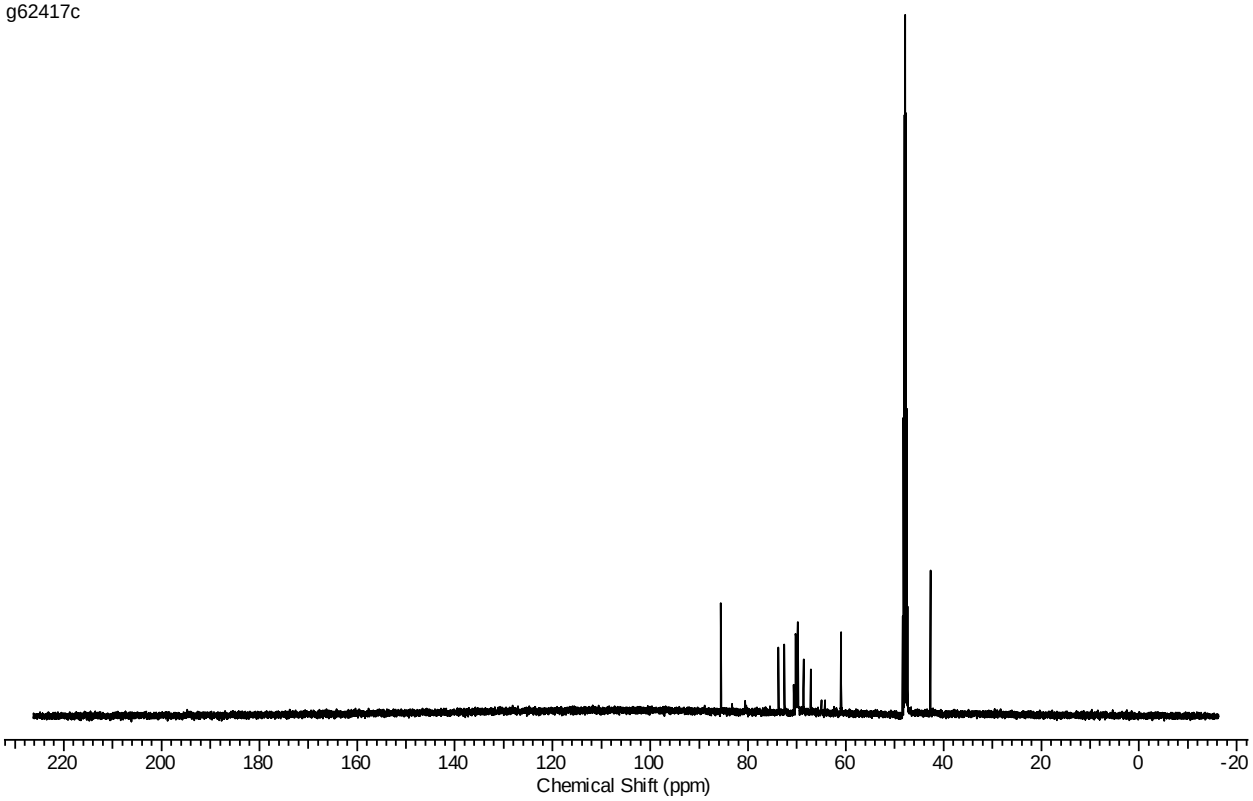

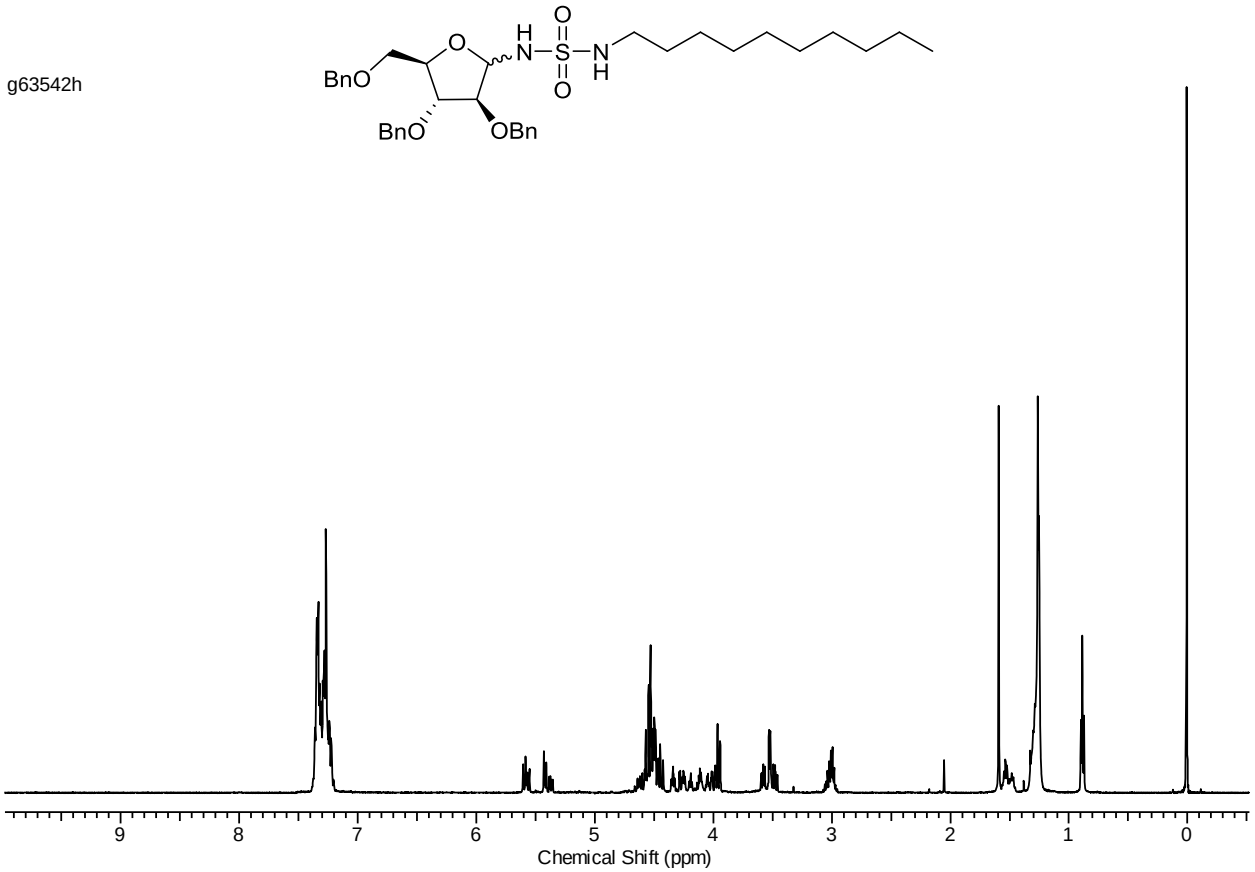
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1
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Chemical Shift (ppm)