# The Selective Dehydration of Sugars in the Sustainable Synthesis of Chiral Fragments and Fluoroalkane Generation from Prochiral Substrates.

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of the requirements for the degree of

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University College London

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I, Rachel Szpara, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

*"An artists heart is his head... our business is to realise the world as we see it, not reform it as we know it."*

- Oscar Wilde

# Abstract

Waste biomass is abundant in sugars (both hexoses and pentoses), making them a renewable source of chiral building blocks which may be utilised in synthetic chemistry. Although large percentages of waste biomass are useful (~17% sugar by weight),[1] large-scale production of drug precursors and THF-containing molecules often utilise alternative synthetic routes.

Trapping of sugars in their open-chain form allows them to be treated as chiral polyol reagents for attaching chiral centres. A variety of different sugar thioacetals may be selectively dehydrated to produce the corresponding ketene thioacetals under mild basic conditions. The reactivity of the resulting ketene thioacetals has been explored, with cyclisation induced to produce a range of novel heterocycles. Further selective dehydration has been carried out in some cases. Insight into the mechanism of dehydration has been provided, with studies into the intermediate structures. With the demand for chiral heterocyclic rings increasing in pharmaceuticals, we present sustainable methods for the synthesis of useful compounds from innately chiral fragments.

In addition, studies into the formation of chiral fluorine compounds have been explored, with the application of ene-reductase biocatalysis in an effort for a more sustainable approach to synthetic chiral fluorine generation.

# Impact Statement

My research undertaken at UCL involves the dehydration of sugars and the application of novel sugar-derived compounds to make chiral building blocks, in particular, compounds containing 5/6-membered rings (THFs and THPs respectively). The objective was to create complex, chiral building blocks (containing structures commonly found in drug molecules) from renewable starting materials which are desirable for use in medicinal chemistry in the pharmaceutical industry. The synthesis of these building blocks often requires harsh conditions and long reaction sequences. This work will have positive impacts on the environment and renewables research through the repurposing of waste biomass from agricultural processes. It also provides valuable contributions to the pharmaceutical industry through improving knowledge of the production of novel chiral compounds which are useful intermediates in the synthesis of drugs. It also provides novel synthetic routes for their synthesis in a more sustainable manner through the usage of lower temperatures and more environmentally friendly organic solvents. This work was published and is available online for other researchers to access the chemistry and its applications. In addition to this, I have conducted research around the screening of substrates for acceptance with engineered ene-reductase enzymes. The potential of using biocatalysts in the place of metal catalysts in favour of more sustainable synthesis is valuable for the growing demand for sustainable research. Although the compounds were found not be ideal substrates, this work helped develop methods for the efficient synthesis of fluoroalkene substrates.

# Acknowledgements

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It only feels right to leave in the statement that has been in my acknowledgments section from when I first started writing my thesis 3 years ago: Thanks, Rachel, for writing this.

# Contents

# Abbreviations

| | |
|---|---|
| 1,4-DMB | 1,4-Dimethoxybenzene |
| ADH | Alcohol Dehydrogenase |
| Ala | Alanine |
| Boc | *tert*-butoxycarbonyl |
| CAP-1 | Adenylyl Cyclase-Associated Protein 1 |
| D-ery | D-Erythrose |
| D-fru | D-Fructose |
| D-gal | D-Galactose |
| D-galA | D-Galacturonic Acid |
| D-glcA | D-Glucuronic Acid |
| D-glc | D-Glucose |
| D-lyx | D-Lyxose |
| D-man | D-Mannose |
| D-rha | D-Rhamnose |
| D-rib | D-Ribose |
| D-sor | D-Sorbose |
| D-tho | D-Threose |
| D-xyl | D-Xylose |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCE | Dichloroethane |
| DFT | Density Functional Theory |
| DIPEA | *N,N*-Diisopropylethylamine |
| DOS | Diversity-Oriented Synthesis |
| DMAP | 4-Dimethylaminopyridine |
| DMC | Dimethyl carbonate |
| dTBP | Di-*tert*-butylpyridine |
| dTDP | Deoxythymidine diphosphate |

| | |
|---|---|
| DMC | Dimethyl carbonate |
| EDCI | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| EOR | Enoate-Reductase |
| ER | Ene-Reductase |
| Et | Ethyl |
| EWG | Electron-Withrawing Group |
| FAD | Flavin Adenine Dinucleotide |
| G6PNa | D-Glucose-6-Phosphate Sodium Salt |
| G6PDH | D-Glucose-6-Phosphate Dehydrogenase |
| HIV | Human immunodeficiency virus |
| HEPES | (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid |
| HMF | Hydroxymethylfurfural |
| HPLC | High Performance Liquid Chromatography |
| HWE | Horner-Wadsworth-Emmons |
| Ile | Isoleucine |
| IPTG | Isopropyl β-D-1-thiogalactopyranoside |
| L-ara | L-Arabinose |
| L-rha | L-Rhamnose |
| L-xyl | L-Xylose |
| LCMS | Liquid Chromatography-Mass Spectrometry |
| Li-HPA | Li-β-hydroxypyruvate |
| LPS | Lipopolysaccharides |
| GlcNAc | *N*-Acetylglucosamine |
| Me | Methyl |
| MeTBD | Methyl Triazabicyclodecene |
| MraY | phosphor-MurNAc-pentapeptide transcolase |
| NAD | Nicotinamide Adenine Dinucleotide |
| NADP | Nicotinamide Adenine Dinucleotide Phosphate |
| NBS | *N*-Bromosuccinamide |
| NMR | Nuclear Magnetic Resonance |
| $OD_{600}$ | Optical Density at $\gamma$ = 600 nm |
| OYE | Old Yellow Enzyme |
| SAM | S-Adenosyl Methionine |

| | |
|---|---|
| SAR | Structure-Activity Relationship |
| TA | Transaminase |
| TAME | *tert*-Amyl methyl ether |
| $^{t}$BuOK | Potassium *tert*-butoxide |
| TBD | Triazabicyclodecene |
| TBDMS | *tert*-Butyldimethylsilyl |
| TBDMSCl | *tert*-Butyldimethylsilyl chloride |
| TCDI | 1,1'-Thiocarbonyldiimidazole |
| TFA | Trifluoroacetic Acid |
| THF | Tetrahydrofuran |
| TK | Transketolase |
| TOS | Target-Oriented Synthesis |

# Chapter 1

# Introduction

## 1.1 Research Question and Hypothesis

The main objectives of this project are to develop novel methods for the conversion of sugars into useful heterocycles, with the retention of their chiral centres. Specifically, the synthesis of readily accessible chiral building blocks will be pursued with a focus on limiting the number of protecting groups and on using mild conditions.

The utilisation of sugars in the synthesis of chiral fragments and natural products to produce single isomers is well-established.[2] By exploiting the chirality of such structures as building blocks, it is hoped that open-chain sugars can be selectively dehydrated to give a wide variety of chiral scaffolds (**Figure 1**). Such fragments are important in the synthesis of drug precursors and natural products.[3,4] Specifically, we endeavour to develop a method for the production of chiral heterocycles from sugars, to produce key intermediates in the synthesis of antivirals such as HIV drugs.

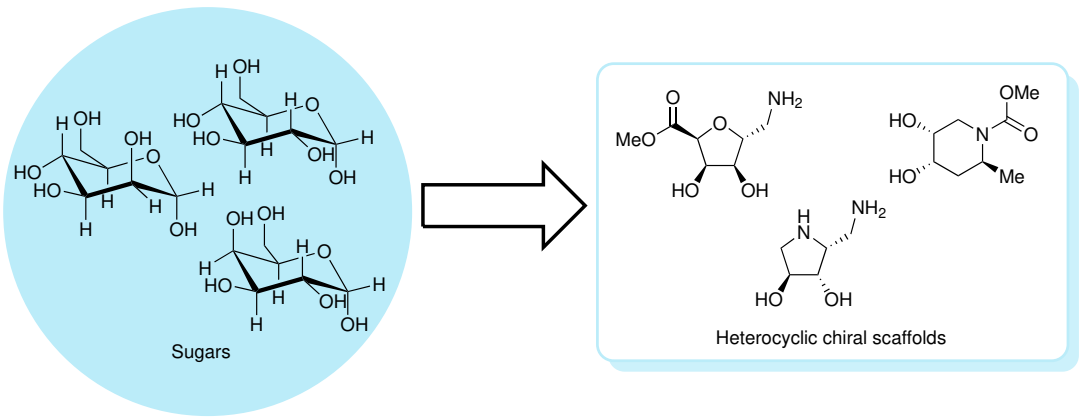



**Figure 1** General scheme of sugars (available from waste biomass) being transformed into chiral scaffolds.

## 1.2 Carbohydrate Derivatives

A brief literature review into the main uses of carbohydrates in modern pharmaceuticals reveals their potency as both antibiotics and antivirals. In the pursuit of novel drugs, studies into the role of carbohydrates in the life cycle of bacteria and viruses prove highly valuable.[5] This chapter will review key examples of sugar moieties in pharmaceutically useful compounds and their applications. It is the aim of this project to develop methods for the synthesis of chiral heterocycles from sugars and simple carbohydrates for their application in constructing pharmaceuticals such as antivirals.

### 1.2.1 Antibiotics

Carbohydrates attached onto the surface of bacteria act as receptors or as substrates for external receptors.[6] These carbohydrate interactions present opportunities for antibiotic activity through interruption. Their structures may resemble the natural substrates within bacteria, thereby leading to higher likelihood of similar interactions.[7] Specific interactions can enable death of the bacterial cell, depending on the potency of the drug. Often, cell death is triggered by abnormal gene expression due to administration of the drug, resulting in apoptosis.[8] An example of a common target for modern antibiotics is based on an interaction with a protrusion on the outer leaflet of bacteria known as lipopolysaccharides (LPS). Rigidity of the envelope as a result of the interaction may be induced, causing eruption of the cell as a product of high osmotic pressure.[6] Strategies employed to target the inhibition of LPS biosynthesis act as a preventative route, meaning the microbe can no longer target other organisms.[7] Strategies which target the lipid section of the LPS focus on interrupting the biosynthesis of O-antigens (commonly containing deoxysugars) where L-rhamnose is one of the major components. If LPS is no longer present in the cell wall, this allows structural weakening of the carbohydrate and efficient disruption of the affected cells.[5] LPS inhibitors commonly contain saturated heterocycles or are derived from sugars to mimic the compounds involved in the cell's normal pathways (**Figure 2**).

Methods that target non-human enzymes are often preferential as it means that human cells are less likely to be targeted. An example of a non-human enzyme target is the dTDP-L-rhamnose biosynthetic pathway, which presents a reduced number of side effects and versatile potency towards many species of bacteria. These treatment

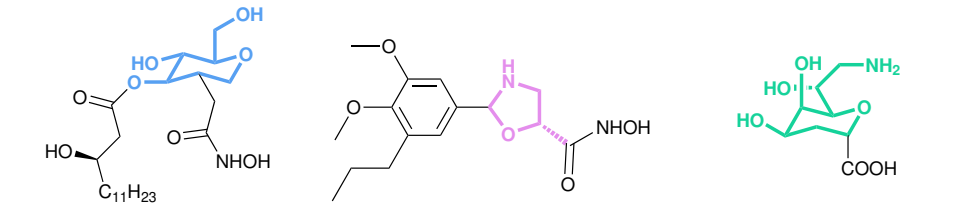



**Figure 2** Inhibitors of LPS biosynthesis with their corresponding targets. Sugar-derived components are highlighted.

methods highlight the importance of carbohydrates in medicine and represent a future in drug production from renewable, chiral starting materials. LPS inhibitors such as dTDP-L-rhamnose pathway inhibitors are examples of antibiotics that contain chiral heterocyclic rings and are derived from sugars (as highlighted in **Figure 2**). This creates an opportunity for a sustainable synthesis of LPS inhibitors from renewable sources.

Well-known antibiotic drugs such as penicillins and cephalosporins target the cross-linking stage of transpeptidases.[9] Many bacteria are now resistant to these classical drugs through the induction of β-lactamases. This observation has led to an increased desire to inhibit earlier steps in the peptidoglycan biosynthetic pathway.[9,10] Inhibition of the biosynthetic pathway of the peptidoglycan layer is popular amongst currently marketed drugs, specifically, inhibitors of phosphor-MurNAc-pentapeptide translocase (MraY) (**Figure 3**).[11] Sugar moieties present in liposidomycins are able to mimic the pyrophosphate group of a pentapeptide on the nucleoside substrate. The analysis of structural activity relationships has proven that a central "enamide" group is responsible for the binding of the nucleoside to the peptide portion of the drug. This functionality tautomerises under the natural acidic conditions found inside cells, to form *N*-acyl imminium ions. This functionality then acts as a potent electrophile, leading to formation of an irreversible covalent bond to the peptide.[6] The selective and robust activity of competitive inhibitors can often be a result of the inhibitors having similar structures to the natural substrates of the enzymes.[12] This resemblance signifies the importance of research surrounding natural product synthesis and also the need for sustainable routes to these compounds.

### 1.2.2 HIV Drugs

Antibiotics are not the only area of medicinal chemistry which have utilised carbohydrate motifs in active drug structures. Since the widespread outbreak of human

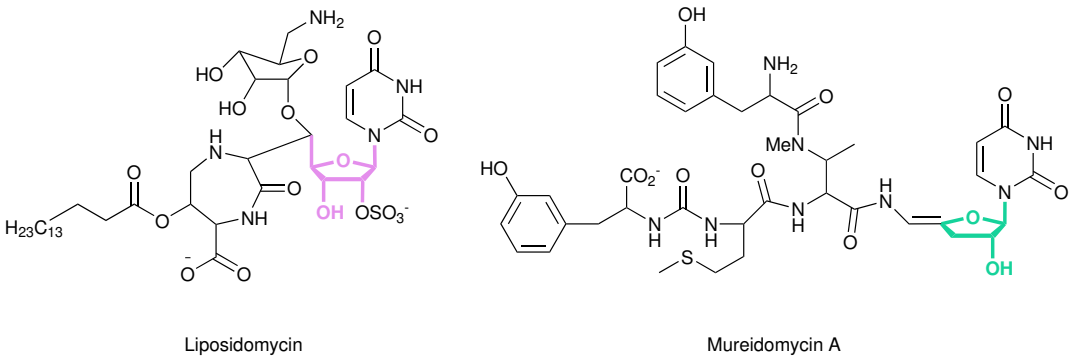



**Figure 3** Examples of MraY (translocase) inhibitors composed of carbohydrate centres (highlighted).

immunodeficiency virus (HIV) in the 1980s,[13] various methods of treatment have been employed. The first drug that was used to treat HIV infection was azidothymidine (AZT), originally developed as a potential cancer therapy. In a screening for HIV/AIDS treatments, AZT (commercially known as Zidovudine) was found to suppress HIV replication without damaging normal cells via inhibiting nucleoside reverse transcriptase enzymes required for HIV replication.[14] The success of AZT led to the production of a variety of nucleoside inhibitors bearing sugar moieties (**Figure 4**) that do not possess a 3'-OH, thereby preventing a phosphodiester link and inducing chain termination.

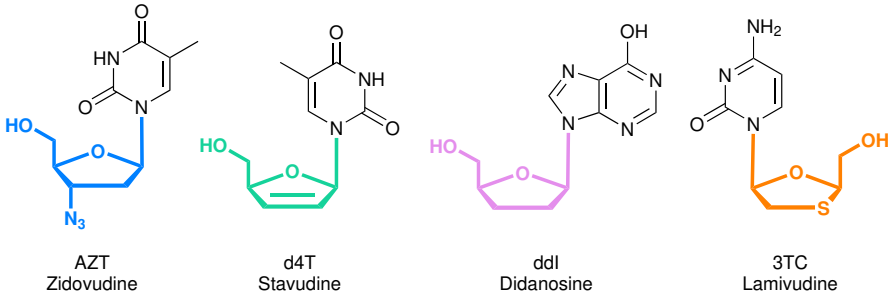



**Figure 4** Approved nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV therapy (carbohydrate motif highlighted).

Treatments commonly involve the inhibition of different stages of the virus's lifecycle. A combination of treatments such as: reverse transcriptase inhibitors, integrase inhibitors and HIV protease inhibitors, are usually given to patients.[15] In order to inhibit vital elements in the maturation of the virus, subsections of the protein structure of proteases are mapped and potential drugs screened for efficacy. In particular, scaffolds including chiral alcohols, lactone rings and functionalised heterocyclic rings have proven to possess potent pharmacological activity (**Figure 5**). Protease inhibitors bind to hydroxyl groups present in the drug to the carboxyl group

in the active site via hydrogen bonding[15] (shown in green on **Figure 5**). By mimicking the natural substrates of the enzyme, it is able to irreversibly bind to the active site and prevent any further enzyme activity, thereby ceasing protease function which is vital for the life cycle of the virus.

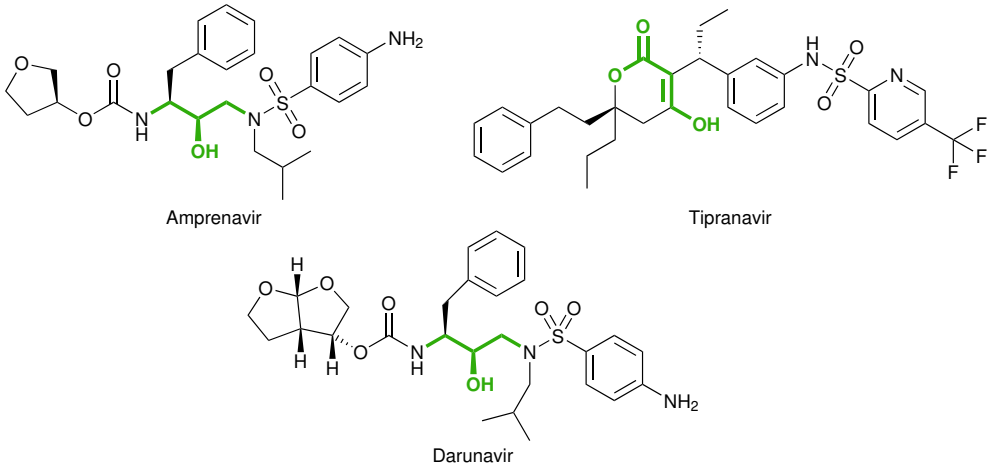



**Figure 5** Successfully marketed HIV drugs containing functionalised heterocyclic rings.

The drug tipranavir utilises a novel method which involves substitution of the water molecule which interconnects the inhibitor to the protease flaps (**Figure 6**). Interaction between an amino acid residue in the flap region of the protease with the lactone oxygen of the dihydropyrone ring stabilises the protease-inhibitor complex. This interaction causes irreversible inhibition of the HIV-1 protease, which has developed resistance to alternative inhibitors.

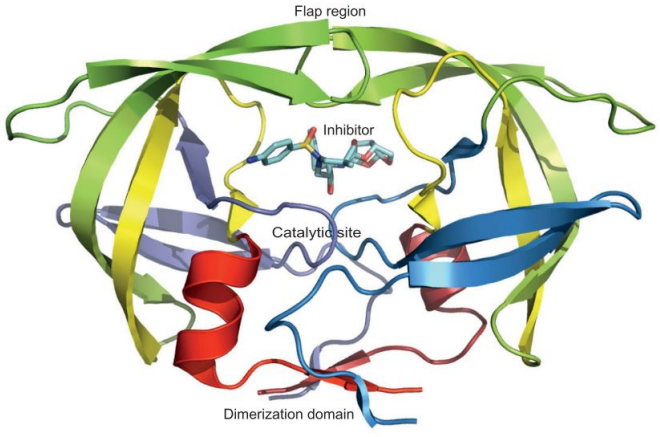



**Figure 6** A pictoral depiction of the HIV protease active-site, with interaction between an inhibitor and flap region of the enzyme shown.[15]

Even simple carbohydrates have been shown to have antiviral properties and potential as anti-HIV drugs. Sugar derivatives 2-deoxy-D-glucose and 2-fluoro-2-deoxy-D-mannose (**Figure 7**) were found to inhibit normal *N*-glycosylation pathways

on the external domain of the virus, leading to a disruption in the virus' ability to pass from cell to cell.[16] It has been suggested that these drugs may give wider utility and be of lower cost than drugs which are designed as specific targets to HIV proteins.

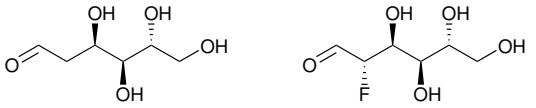



**Figure 7** Potential fusogenic virus drugs derived from sugars.[16]

Small molecules rich in heteroatoms often mimic natural products in the virus's biochemical pathways. These heterocycles induce therapeutic effects via stabilisation effects with *in situ* amino acids through hydrogen bonding, which lead of prevention of replication. The addition of heterocycles can also improve the solubility of drug candidates,[17] once again, making investigation into their synthesis very desirable. It has also been determined that three-dimensional structures with an increased number of rings, geminal substitutions and an abundance of chiral centres often contributes to the potency of drugs.[4] For these reasons, we aim to develop methods for the synthesis of antivirals from sugar starting materials.

### 1.2.3 Carbohydrates as Chiral Synthon Precursors

The traditional method for the design of drug molecules often begins with a screening of small molecules against a pre-selected biological target; a process known as target-oriented synthesis (TOS). An alternative method of drug design is to screen small molecules and determine their efficacy in modulating a biological pathway, regardless of the target. This latter process is known as diversity-oriented synthesis (DOS).[18] In contrast to TOS, DOS aims to create as complex and diverse substrates as possible, using divergent mechanisms which combine small molecules in many different combinations. Carbohydrates offer an abundant source of chiral compounds and have been described as 'underdeveloped' and 'under explored' in synthetic strategies employed for generating chemical diversity.[19] A pioneering example of carbohydrates used as molecular templates is R. Hirschmann's work on D-glucose somatotropin release inhibiting factor (SRIF) mimetics.[20] This example highlights the use of a pharmacophore with a well-defined spatial orientation due to conformational strain, showing effective application as an inhibitor. It is due to their specific conformations that these compounds are able to mimic the natural substrates and be accepted into

the active sites of their targets, thus resulting in inhibitory character.

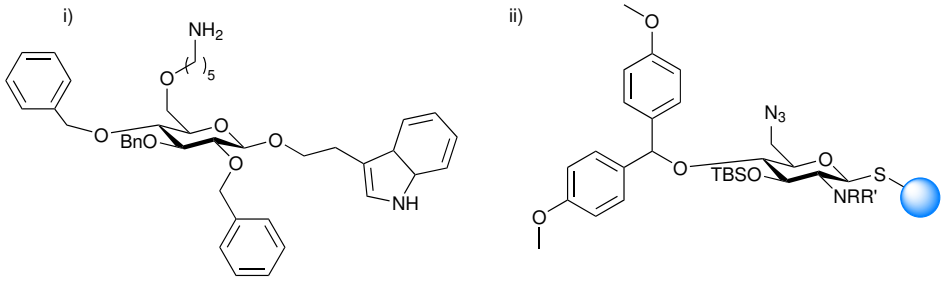



**Figure 8** (i) R Hirschmann's SRIF mimetic with a glucose core. (ii) H Kunz's diaminoglucose substrate used in combinatorial solid-phase sythesis.[20,21]

## 1.3 Sugars as Synthetic Starting Materials

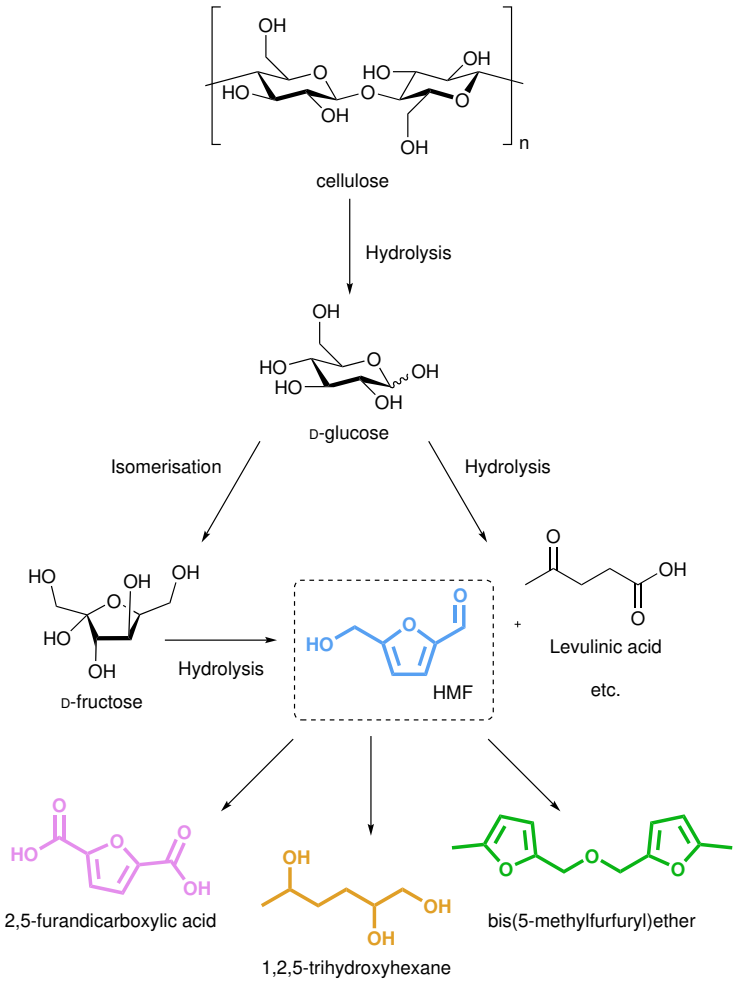
### 1.3.1 Carbohydrates from Renewable Feedstocks and their Chemical Manipulation

Chiral motifs are highly prevalent in nature (e.g. NAD, FAD, and antibiotics such as ribostamycin).[23] Heterocycles that possess chirality have been shown to be ideal competitive inhibitors for enzymatic pathways such as those used in the treatment of HIV (highlighted previously in **Figure 5**).[4] However, access to diverse libraries of chiral saturated heterocycles is a limiting factor in many medicinal chemistry programmes.

Saturated heterocycles such as THPs, THFs, piperidines and pyrrolidines can often be challenging to make, especially when selectively incorporating chiral centres onto the ring structure. Typical methods for the manufacture of heterocyclic structures, and those containing chiral functionalities, frequently involve use of transition-metal catalysis[24] to form C-C bonds. Asymmetric chemistry is then employed in order to insert chirality.[25] However, the use of renewable feedstocks which are abundant in carbohydrates (waste biomass such as sugar beet pulp) provides a source of chirality present in the starting material.

With carbohydrates existing as a large percentage of waste biomass, they constitute a renewable source of innate chirality which may be functionalised and adapted.[26,27]

Much research has gone into the study of introducing more complex chemical groups onto sugars, but these are typically not implemented on an industrial scale due to difficulties in separation of matter.[28] Substantial research has been carried out in



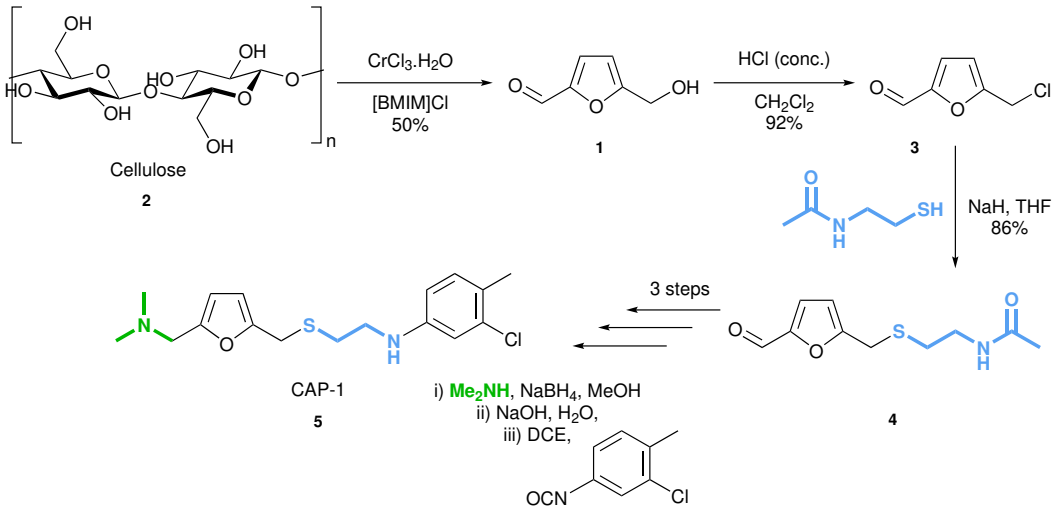

**Scheme 1** Hydrolysis of cellulose into platform chemicals, and further hydrolysis into useful products.

the breakdown of polysaccharides, specifically, the de-polymerisation of cellulose. Cellulosic material may be broken down into monomeric components such as D-glucose and D-fructose, which may be utilised for their chirality, or further broken down into useful platform chemicals (**Scheme 1**).

For example, following large-scale hydrolysis, D-glucose may be efficiently converted to platform chemical hydroxymethylfurfural (HMF), following isomerisation to D-fructose.[29,30] With 90% of all cotton extracts and 50% of trees (by weight) consisting of cellulose,[31] renewable generation of heterocycles such as HMF and its derivatives is economically and environmentally viable. For example, de-polymerisation of crystalline cellulose to glucose, prior to fermentation/condensation, leads to the production of ethanol/HMF respectively. These can then be functionalised into more valuable target molecules relevant to industrial applications such as jet fuels.[32]

Previous syntheses involving the production of HIV protease antagonists from carbohydrates demonstrate the ability to create valuable, chiral substrates from in-

expensive and highly abundant starting materials from renewable feedstocks such as waste biomass. Antagonist adenylyl cyclase-associated protein-1 (CAP-1) which inhibits the HIV-1 protein capsid assembly is an example of a heterocyclic compounds that can be produced from cellulosic material. CAP-1 operates by inhibiting the cleavage from Gag-pol proteins, which prevents its digestion by protease and other essential enzymes, meaning it is left in an inactive form. An active hydroxyl group in the inhibitor interacts with the carboxyl group of protease active site residues via hydrogen bonding. The residues in contact with the inhibitor of HIV proteases are relatively conserved, however, accumulation of mutations alters the structure of HIV protease and causes treatment failure due to drug-resistance. The CAP-1 core exists as a 2,5-disubstituted furan ring which can easily be accessed via the platform chemical 5-HMF (5-(hydroxymethyl)furfural) **1** (**Scheme 2**). From this stage the functionality of the molecule can be readily altered at the 2- and 5-positions.

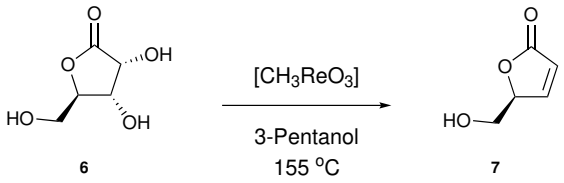



**Scheme 2** Synthetic strategy for the generation of CAP-1 inhibitor from cellulose.

CAP-1 can be synthesised in six steps from renewable starting material **2** extracted from waste biomass[33] without the need for metal catalysis or harsh conditions, with reasonable yield (31% overall yield). This chemistry highlights the large applicability of natural building blocks into process chemistry, although in this example, failing to utilise the innate chirality of the initial building blocks.[33]

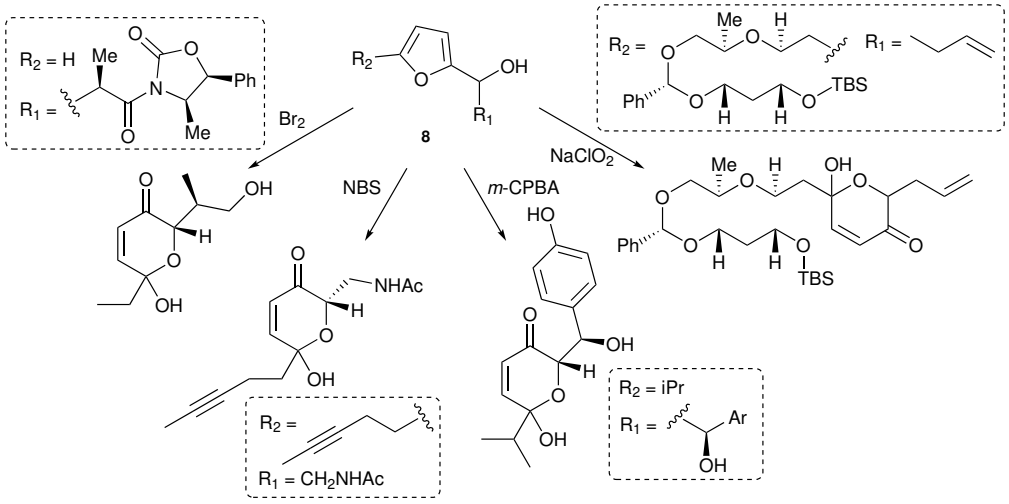
In order to achieve a more diverse array of sugar-derivatives, dehydration may be carried out to produce alkanes, alkenes, and also 1,4-conjugated systems. Toste *et al.* developed a dehydration strategy to selectively dehydrate at positions adjacent to

carbonyls in five and six-membered rings, creating pyranones/furanones respectively, without the need for protecting groups (**Scheme 3**). By exposing the substrate to a rhenium catalyst developed within the group, chiral triols such as **6** may be selectively converted to furanone **7**.[34]




**Scheme 3** Selective dehydration of a chiral triol, to create furanone **7**.[34]

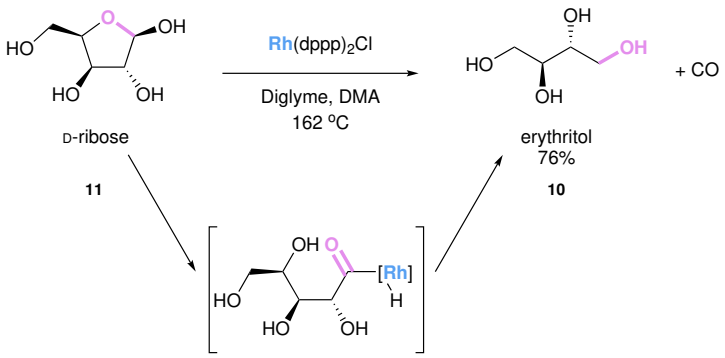
Efficient production of carbonyl groups can be a powerful tool when building structurally complex units. Aldehydes and ketones are present in cellulosic building blocks and are frequently involved in transformations such as condensation and retro-aldol reactions. A similar strategy for synthesising interesting carbonyl products derived from waste biomass was recently developed by Ghosh *et al.*, to create synthetically versatile dihydropyrones. They have developed a catalytic Achmatowicz reaction whereby furfuryl alcohols **8** (biomass-derived) can be converted into a diverse array of chiral pyranones under mild conditions (**Scheme 4**).[35]




**Scheme 4** Achmatowicz rearrangements of furfuryl alcohols into chiral pyranones.[35,36,37,38,39]

The use of metal catalysis on sugar starting materials (such as D-ribose which is highly abundant in waste biomass) proves useful in decarbonylation reactions (loss of CO). The Madsen group developed a decarbonylation strategy of cellulosics without the need for protecting groups. They were able to reduce the length of the carbon

chain in a variety of different sugars (including hexose, pentose and *N*-acetylated) sugars by exposure to a Rh(I)-catalyst and heated in the presence of diglyme. The reaction of pentose sugar D-ribose **9** under these conditions gave erythritol **10** in good yield (**Scheme 5**).[40] This provides an accessible route to chiral polyols, and proves useful in the synthesis of complex chiral moieties such as in the production of antivirals.




**Scheme 5** Protection group-free synthesis of erythritol via Rh-catalysed decarbonylation of D-ribose.[40]

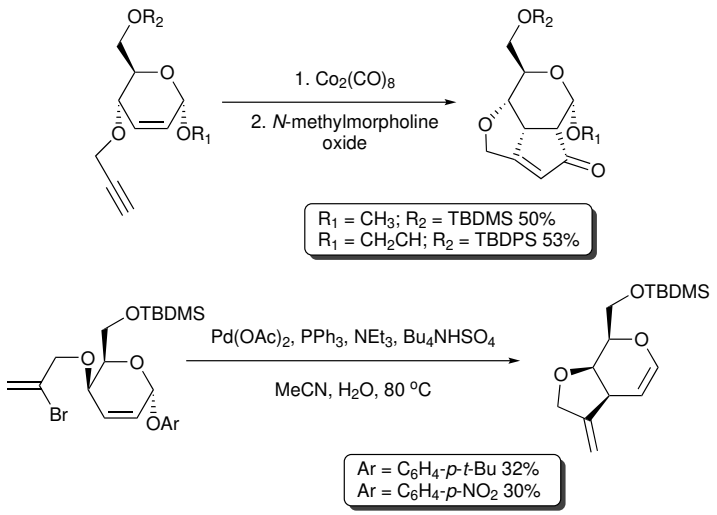
### 1.3.2 Carbohydrate Chemistry Limitations

Despite carbohydrates being attractive starting materials for the synthesis of chiral compounds, syntheses involving sugars also carries its limitations. For example, only a limited sector in the world of pharmacopeia involves sugar-derived compounds, with a large number of carbohydrate-protein interactions yet to be investigated. In terms of drug delivery, issues involving the oral availability and plasma stability have been especially relevant for carbohydrate-based pharmaceuticals.[19]

The most obvious advantage of carbohydrate chemistry is the utilisation of waste biomass. However, the two most popular methods for conversion of biomass are fermentation and high-temperature pyrolysis. Although both procedures make use of raw, complex mixtures of carbohydrates, they are limited in the range of products that can be acquired from the processes and are both largely endothermic processes. The sustainability of these operations therefore has to be examined.[22]

Many syntheses that utilise renewable starting materials often require expensive and non-renewable materials such as metal catalysts. Sinou et al.'s 2006 review highlights the limits of carbohydrate chemistry and its requirement for materials from non-renewable feedstocks. THPs with appended alcohols that are derived from carbohydrates have been shown to further cyclise using metal catalysis. **Scheme 6**

shows examples of Co- and Pd-catalysed cyclisations.

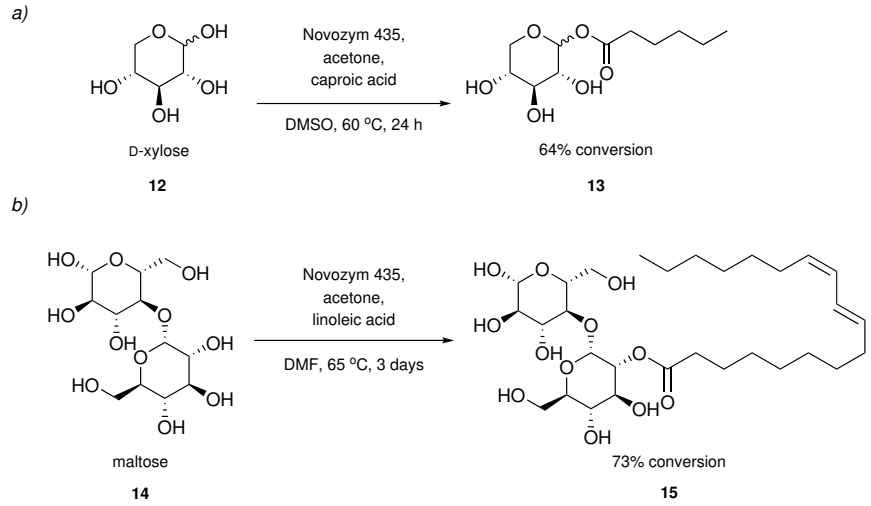



**Scheme 6** Examples of carbohydrate-based cyclisations which require non-renewable metal catalysts

### 1.3.3 Biocatalytic Manipulation of Sugars

Modifications of carbohydrates to give sugar fatty acid esters (SFEA's) is a current area of interest due to their applications as non-ionic surfactants. They are particularly useful due to their wide range in hydrophilic-lipophilic balance (HLB) values, an index expressing the properties of the surfactant, thereby demonstrating the wide applicabiltiy of SFEA's.[41] SFEA's are often chosen for their versatility and for being: biodegradable, non-toxic, non-irritant and tasteless in nature.[42] SFEA surfactants are in demand from both the food industry and cosmetic consumers.[43] The enzymatic methods for producing these esters offer high regioselectivity and mild conditions relative to chemical synthesis. Abdulmalek *et al.* gave optimised conditions for lipase-catalysed transformation of D-xylose to the corresponding caproic ester (**Scheme 7a**).[44] Not only are the reactions carried out under mild conditions, the use of organic solvent DMSO highlights the versatility of the enzymes used. The esters are produced efficiently with good conversion and short incubation time.

It is also possible to produce the SFAE of disaccharides. Fischer *et al.* performed the esterification under lipase-catalysed conditions to produce the linoleic ester (**Scheme 7b**). Although on average requiring a longer reaction time, the production may still be carried out under mild conditions and in good conversion.[45] The lipases are used in their immobilised form, allowing for good recyclability and reusability, emphasising the green alternative of biocatalysis. In both cases, the

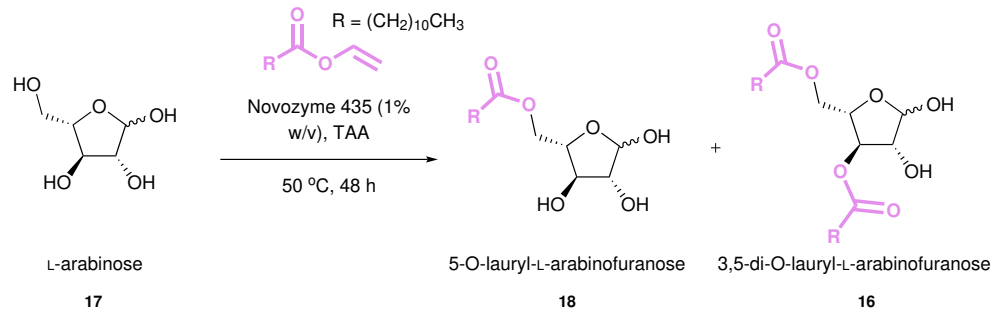



**Scheme 7** Lipase-catalysed synthesis of SFAE surfactants. a) Synthesis of D-xylose caproic ester.[44] b) Synthesis of maltose-derived linoleic ester.[45]

methods may be scaled up for industrial applications.

The large majority of enzyme-catalysed synthesis of esters and amide bonds in organic solvent systems are carried out by a robust family of enzymes known as hydrolases (e.g. proteases and lipases).[46] Studies into the biocatalysed formation of fatty-acid esters from hexoses has been studied extensively, but the pentose-derived esters, less so. Often, structural data of these molecules are not described.[47] With pentose sugars such as D-ribose and L-arabinose being main components of lignocellulosic plant walls, application of enzymes to these monomers offers the opportunity for large-scale, renewable applications. Research by Deleu *et al.* reports the lipase-catalysed formation of laurate pentose esters from D-ribose and L-arabinose, as well as providing detailed information of their structures and surface-active properties. Using a low loading of enzyme (Novozym 435) and mild conditions, the Deleu group provide optimised conditions for the transesterification of pentose sugars (**Scheme 8**). In the case of L-arabinose ester, a good yield of 59% conversion is reported, with diester **16** being the major product and maximum conversion seen at just 4 hours.

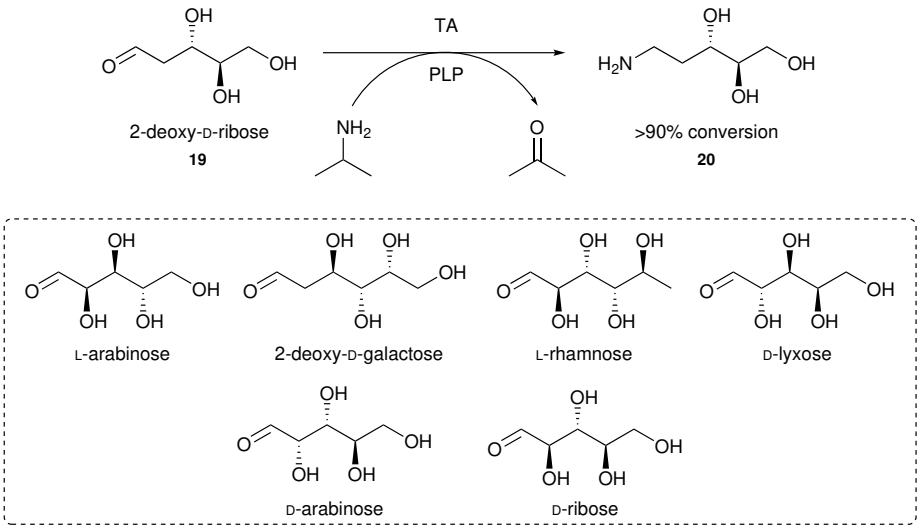
Properties of the pentose esters were acquired and compared with those of the hexose sugars. The critical aggregation concentration (CAC)[48] measures the effect of solvents on the structure of the molecules. The relatively low CACs of D-xylose and L-arabinose furanose esters indicate interesting properties for these molecules as surfactants, as they are lower than the commercially available sugar esters such as Tween 20.[49] A low CAC is desirable as it means a lower loading of the surfactant




**Scheme 8** Lipase-catalysed transesterifcation of pentose sugar, L-arabinose and vinyllaurate.[47]

molecules is required for aggregation.

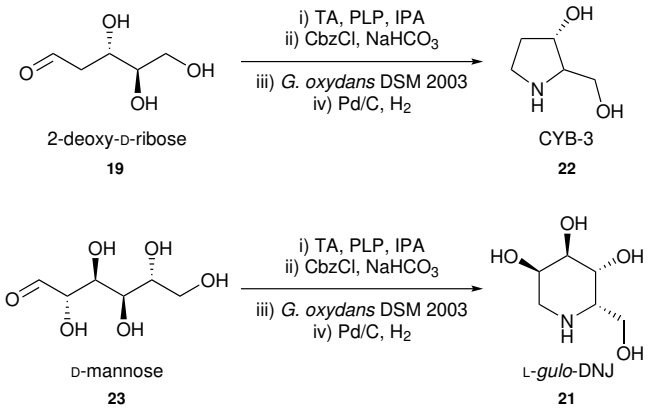
Research by the O'Reilly group reported the ability for transaminases (TAs) to convert the carbonyl functionality in aldoses to primary amines, enabling access to a variety of aminopolyols (**Scheme 9**).[50] Biotransformations were performed with commercially available and cost effective amine donor, isopropyl amine. The transformations were also successful when performed on a preparative scale using commercially available transaminase ATA256, providing the amino alcohols in high levels of conversion (up to 94%). This work demonstrated the direct conversion of cyclic aldose sugars to the corresponding amino alcohols using commercially available TA enzymes.




**Scheme 9** The direct amination of 2-deoxy-D-ribose using a transaminase biocatalyst. A variety of accepted sugar substrates are shown.

Also within the O'Reilly group, a recent study by Kuska *et al.* detailed the synthesis of biologicially important iminosugars from readily available aldoses such as 2-deoxy-D-ribose, D-ribose and D-mannose,[51] utilising the previously established

TA activity.[50] Kuska was able to demonstrate an expansion upon the substrate scope seen previously with the TA's, to develop a two-enzyme, four-step sequence for the production bioactive iminosugars (**Scheme 10**). The production of aminopolyols such as the precursor to α-glucosidase inhibitor, 1-deoxynojirimycin **21** (L-*gulo*-DNJ) was carried out diastereoselectively with excellent conversion and isolated yields. This work was able to expand the substrate range for the oxidative whole-cell catalyst *G. oxydans DSM 2003* and biocatalysed amination. They were able to develop a four-step sequential cascade to provide valuable iminosugars from readily available carbohydrates.




**Scheme 10** Chemoenzymatic synthesis of iminosugars from aldose sugars 2-deoxy-D-ribose and D-mannose.[51]

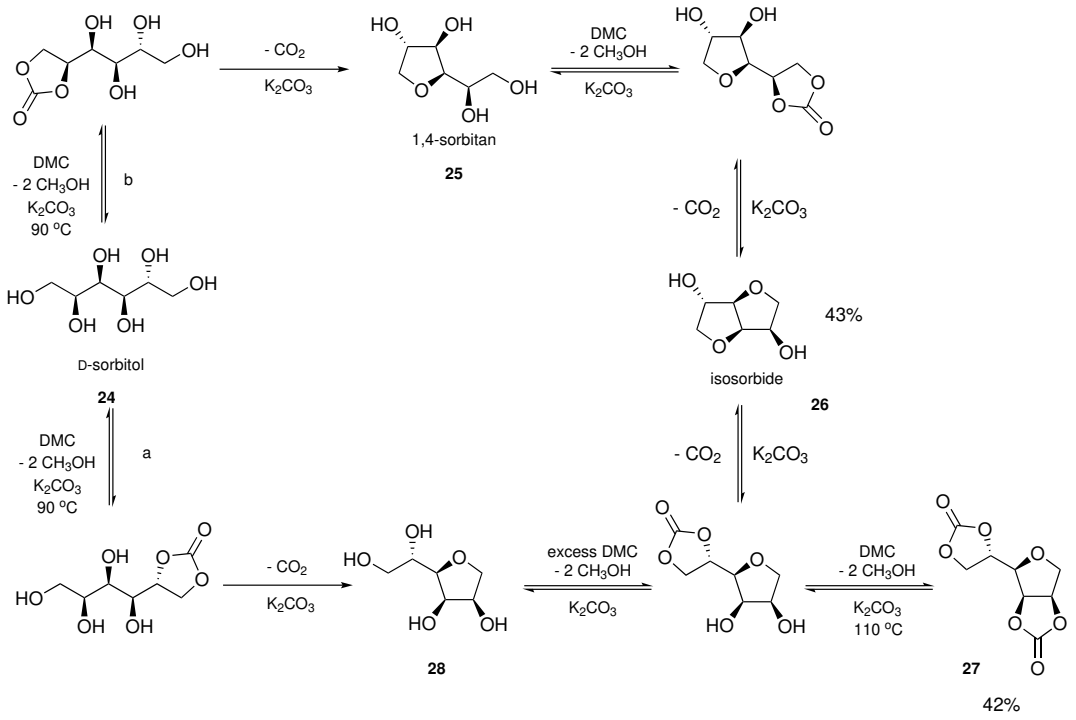
# 1.4 Chiral Fragment Chemistry

## 1.4.1 Dihydroxytetrahydrofuran Ring Formation

Dihydroxytetrahydrofuran rings (dhTHF's) are building blocks which may be functionalised in a multitude of fashions, yielding accessible routes to natural products and drug precursors.[52] Techniques have been developed to produce and alter these fragments through the formation of carbonate species and their subsequent decarboxylation.[53] Tomczyk and co-workers developed a synthetic strategy whereby sugar substrates (in particular, sugars lacking carbonyl functionality) may be converted to the dhTHF species in one step under mild conditions (**Scheme 11**).

By simply controlling the quantity of reagents and temperatures used, various scaffolds may be obtained by isolation at different points within the pathway. The reaction pathway of D-sorbitol with DMC and $K_2CO_3$ that may take one of two paths. One pathway involves initial cyclisation at the 1-position of the sugar (pathway **a**),

and the other forms a carbonate at the 6-position (pathway **b**) (**Scheme 11**).

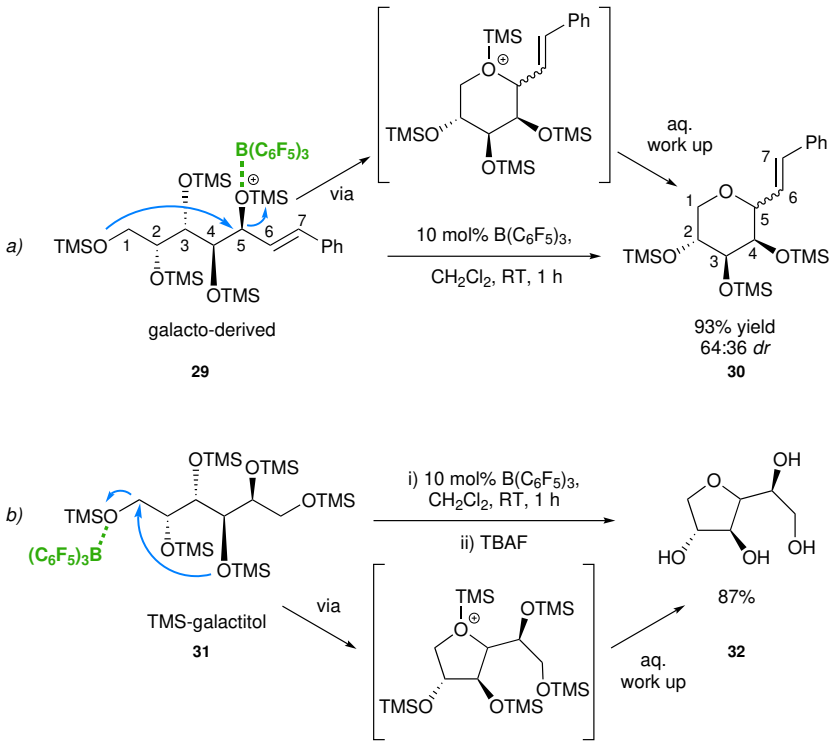



**Scheme 11** Production of isosorbide from the reaction of D-sorbitol with dimethyl carbonate under basic conditions.[53]

Only pathway **a** allows access to structures such as product **28**. Intermediate **25** of pathway **b** would not lead to a 5-membered carbonate due to the high strain which would be present in the cyclised structure, this being due to the *trans* relationship of its hydroxy moieties in the starting material. However, both pathways lead to formation of bicyclic structure isosorbide **26** in reasonable yield, either through intramolecular etherification or using excess DMC. An increase in the temperature of the reaction (to 110 °C) in pathway **a** allows formation of structurally-interesting isosorbide derivative **27** in reasonable yield also. Isosorbide provides a gateway to a variety of functionality and has great utility in medicinal chemistry as a treatment for angina.[54]

Recent work published on the formation of heterocycles from polyols described the $B(C_6F_5)_3$-catalysed cyclisation of protected, functionalised substrates via deoxygenation cyclisation (**Scheme 12a**).[55]

The work includes substrates which are often derived from sugars/products of waste biomass. It is thought that the reaction proceeds through an $S_N2$-type mechanism upon activation of C-O bonds by the borane catalyst, encouraging attack by the C-**1** silyl ether. The mechanism proceeds via intramolecular attack of a




**Scheme 12** $B(C_6F_5)_3$-catalysed intramolecular condensative cyclisation.[55,56]

primary silyloxonium ion onto the most activated position, (C-5 of **30**) leading to tetrahydropyran (THP) formation. Or in the case of TMS-galactitol, which possesses a shorter carbon-chain, tetrahydrofuran (THF) formation. It was observed that the alkenyl-derived silyl sugars exhibit regiopreference for THPs (compound **30**).

Later work by Gagné and coworkers[56] expanded further on the utility of $B(C_6F_5)_3$-catalysed cyclisations, using saturated sugars to form anhydrosugars (compound **32**) via intramolcular condensative cyclisation (**Scheme 12b**). The use of saturated sugars enabled the selective formation of THFs via activation of the primary silyl ether with the Lewis acid, leading to the cyclised intermediate. It was proposed that the mechanism of the reaction occurs via activation of one of the symmetry equivalent C-O bonds by $B(C_6F_5)_3$, which initiates intramolecular attack by the C4 silyl ether. From this intermediate (shown in **Scheme 12b**), $(R_3Si)_2O$ is extruded to produce **32**. The mechanistic theory was supported by isolation of the displayed THF intermediate (**Scheme 12b**). A wide range of linear silylated sugars were explored such as galactitol, sorbitol, mannitol and aranitol, as well as tetraols such as man-tetral (biomass derived).[56] This reactivity provides a useful synthesis of dihydroxytetrahydrofuran (dhTHF) units which are frequently found in bioactive natural products with antiviral/antitumour activity, including (+)-varitriol, tiazofurin, and goniothalesdiol

(**Figure 9**).

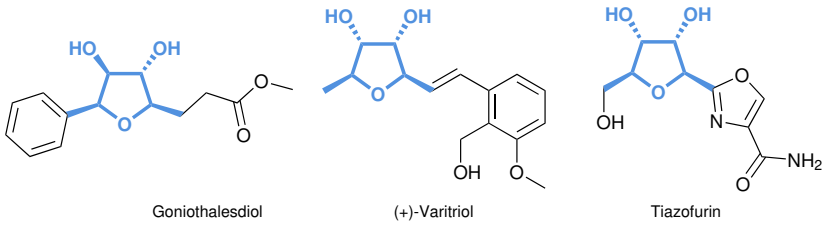



**Figure 9** Natural product (+)-varitriol and other natural products containing a dihydroxytetrahydrofuran (dhTHF) subunit.

Following on from the Gagné group's work involving the catalytic $B(C_6F_5)_3$–silane system, research by Zhang *et al*, displays the first application of bis(pentafluorophenyl)borane, ($(C_6F_5)_2BH$, also known as Piers' borane), as a single hydrosilylative reduction catalyst **(Figure 10)**.[57]

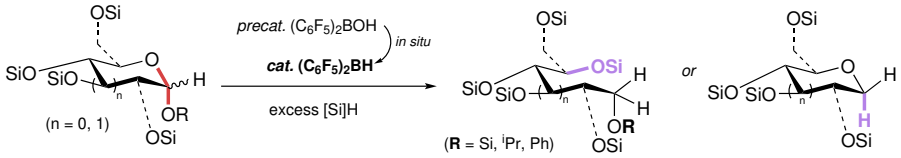
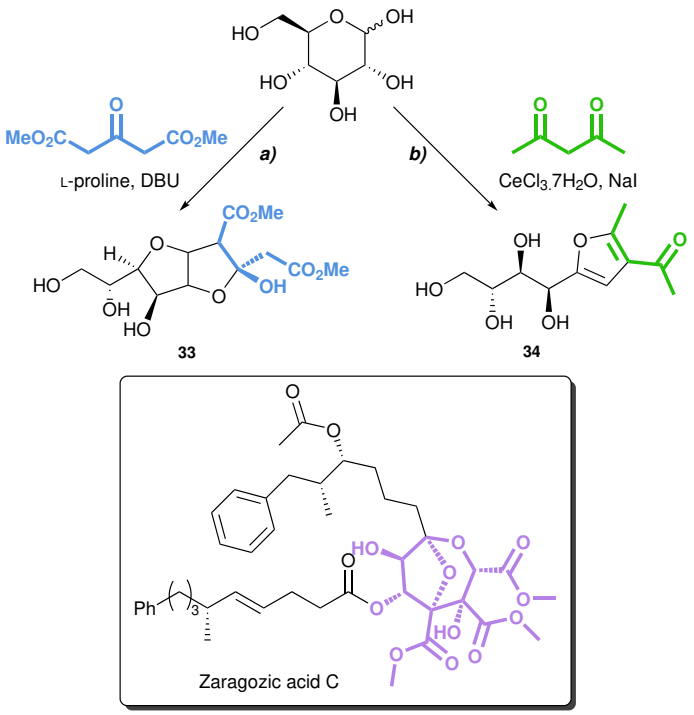



**Figure 10** Hydrosilylative C-O bond cleavage of sugars promoted by *in situ*-generated bis(pentafluorophenyl)borane.

This hydrosilylative C-O bond cleavage of sugars uses Piers' Borane catalyst, generated *in situ* from $(C_6F_5)_2BOH$, to provide a range of polyols with superb chemo- and regioselectivities from both 5 and 6-carbon sugars.

The steric environment present in the sugar starting materials allows for unique stereocontrol which may be harnessed in the creation of chiral aliphatic molecules, even on a disaccharide/oligosaccharide scale (producing a mixture of acyclic and cyclic chiral polyols). The addition of nucleophiles to sugars increases the chemical complexity of the molecules and provides more diverse chiral fragments. Direct catalysis by the addition of carbon-based nucleophiles has been carried out on D-glucose to give an array of useful molecules, such as the complex bicyclic sugar **33**. This substrate can be made via proline-catalysed addition of an ester in a Knoevenagel condensation-cyclisation reaction under mild conditions (pathway **a** of Scheme 13).[58]

By varying the nucleophile, different reactivity of the sugar is observed. Opening of the sugar occurs upon exposure to Lewis acidic conditions to yield a THF with a




**Scheme 13** Diversification of D-glucose via catalytic addition of carbon-based nucleophiles.[58,59] The core of zaragozic acid is highlighted for its structural similarity.

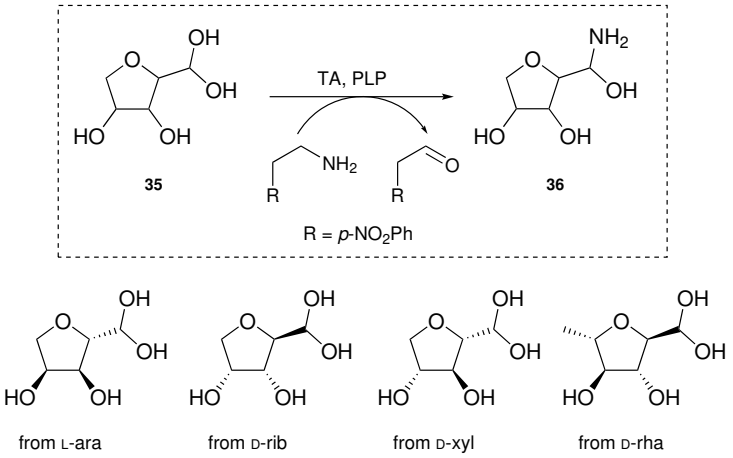
chiral polyol tail (pathway **b** of **Scheme 13**).[59] Furanyl sugar **34** is made from glucose via the addition of a dicarbonyl and subsequent dehydration in a Garcia-Gonzalez reaction. Not only can the reactivity seen here be applied to various pentose and hexose sugars (e.g. arabinose, ribose, xylose and galactose), this research highlights the versatility in reactivity and applicability of just one carbohydrate depending on the conditions. These scaffolds are useful in construction of bioactive molecules such as the core of 7-deoxy zaragozic acid (**Scheme 13**).[60,61]

## 1.5 Previous Research Within the Group

### 1.5.1 Enzyme-Catalysed Reactions from Renewable Feedstocks

Aminosugars represent high-value derivatives of their carbohydrate relatives due to their application as carbohydrate mimetics for antivirals, antitumour agents and the treatment of diabetes.[62] The use of polyhydroxylated amines and aminosugars highlights the accessibility of drug candidates from renewable feedstocks such as sugar beet pulp.[63,64] Methods for the production of aminopolyols traditionally use chemical reductive amination whereby alkylation events also occur, consequently creating unwanted alkylated adducts.[65] The production of aminopolyols via transamination

and the use of biocatalysis has provided a significantly more sustainable approach to the construction of these useful scaffolds. Previous research within the group by F. Subrizi introduces the production of aminopolyols from biomass-derived cyclic aldehydes.[66] Their methodology involves using TA's, provided as crude cell lysates, following screening of the aldehydes with a colorimetric assay. The conversion of cyclic aldehydes derived from an array of sugars to the corresponding aminosugar is carried out under mild conditions with good yields of 60–80% (**Scheme 14**).[66]

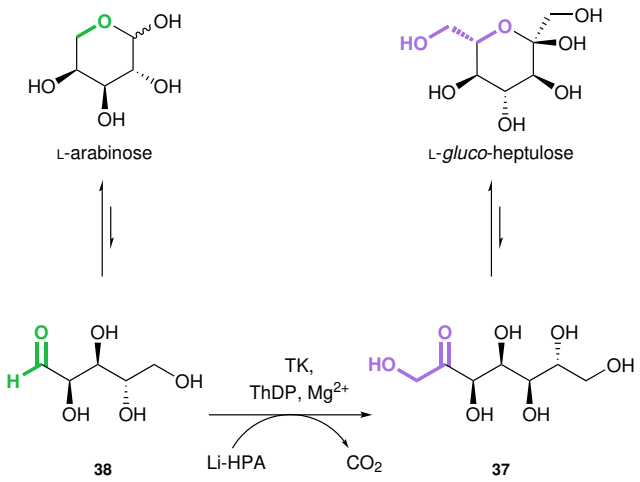



**Scheme 14** Synthesis aminopolyols **36** from cyclic sugar aldehydes **35**.[66]

The research conducted by Subrizi *et al.* involved the use of 2-(4-nitrophenyl)ethan-1-amine as the amine donor, which produces a vivid red precipitate when converted to the corresponding aldehyde, indicating successful amination. Several different TAms were found to accept the sugar-derived substrates, with cost-effective amine donors such as isopropyl amine (IPA) also tolerated. Overall, they show the conversion of sugar THFs available from waste biomass into valuable aminopolyols in good yield.

Arabitol is one of the top commodity biochemicals from biomass, noted as one of the 12 top value-added chemicals from biomass in the production of polyester resins.[67] From the abundance of arabinose and its derivatives, methods have been created for converting arabinose into useful starting materials for medicinal chemistry as well as in the production of plastisisers and polyesters.[6869] Fernandez *et. al* have developed a technique which uses transketolase enzymes (TK) as a method for creating carbon-carbon bonds in a stereospecific manor, using sugars as substrates. TK's use thiamine diphosphate (ThDP) as a cofactor, in this case, Li-β-hydroxypyruvate (Li-HPA) as a ketol donor, and L-arabinose as the aldehyde acceptor (**Scheme 15**). TK's perform an

irreversible reaction via the loss of $CO_2$, making its application desirable to industry. The result of this reaction is L-gluco-heptulose, known for its value in the manufacture of cancer and hypoglyaemia drugs.[70]



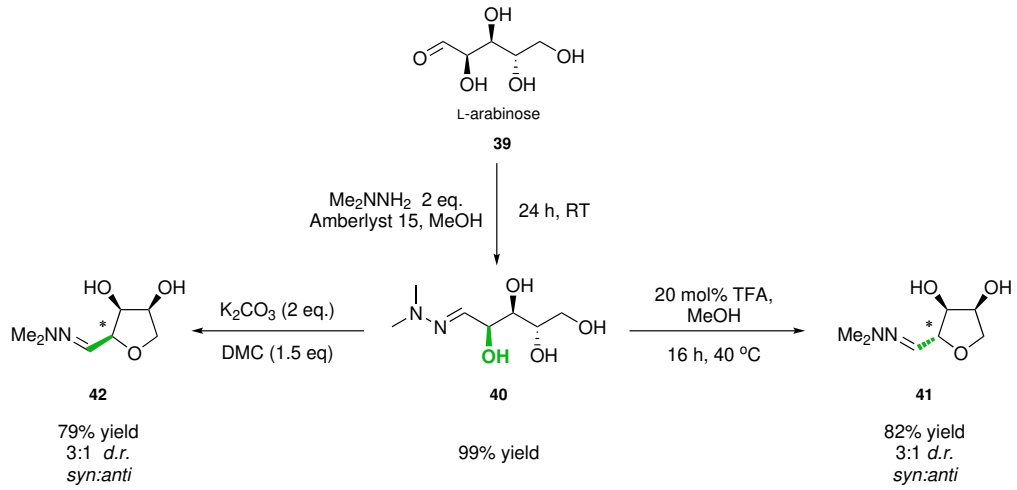

**Scheme 15** Synthesis of ketoheptose L-gluco-heptulose via transketolation of L.

For wild type TKs, only phosphorylated aldoses are efficiently accepted as substrates, therefore, the group used docking studies and colorimetric assays to obtain optimal conditions with unphosphorylated sugars such as arabinose. The strain of *E*-coli TK with the highest specific activity gave isolated yields of up to 45%. Characterisation of the product showed incredible diastereoselecitvity, which is consistent with TK reactions with other aldoses.[71] This work presents another valuable method of upgrading arabinose-rich waste biomass into potentially therupatic applications.[68]

### 1.5.2 Sustainable Sugar Dehydration

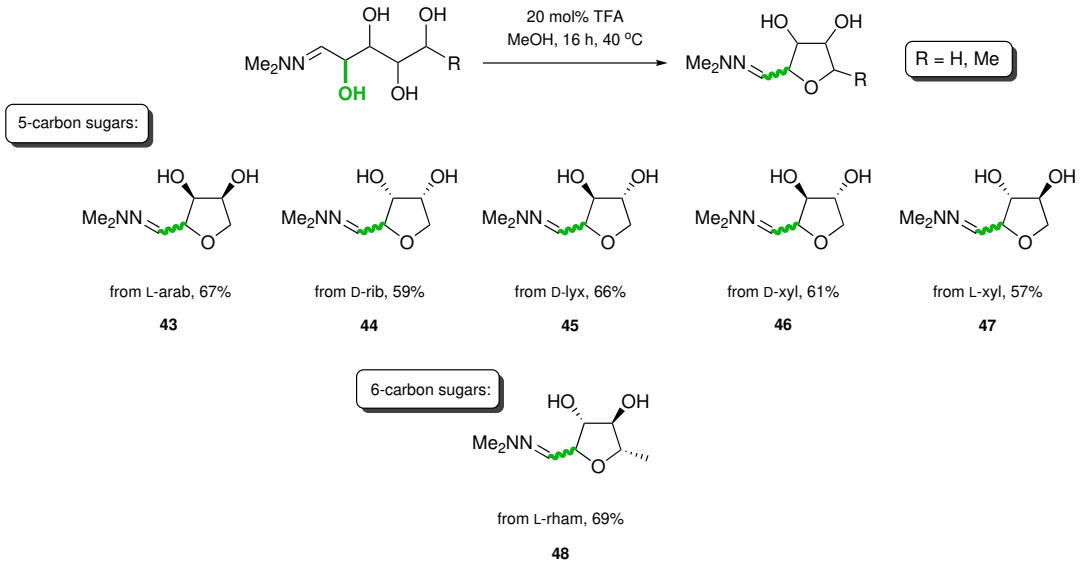
Heterocyclic rings such as THFs which are functionalised with chiral centres are often more complex to produce due to the difficulty in maintaining stereochemistry post-cyclisation. Research carried out within the group by R. Foster provided a sustainable and selective approach to the production of THFs and furfurals from waste biomass.[69] Two of the major components of waste biomass are cellulose (polymeric D-glucose) and hemicellulose (which is abundant in L-arabinose and D-xylose).

The synthesis shown in **Scheme 16** highlights the simple conversion of the sugar L-arabinose **39** into the dimethylhydrazone derivative **40**, which is then able to cyclise under acidic conditions to give THF **41**, in a moderate overall yield. However, when exposed to basic conditions, the diastereomeric product **42** is formed. The resulting



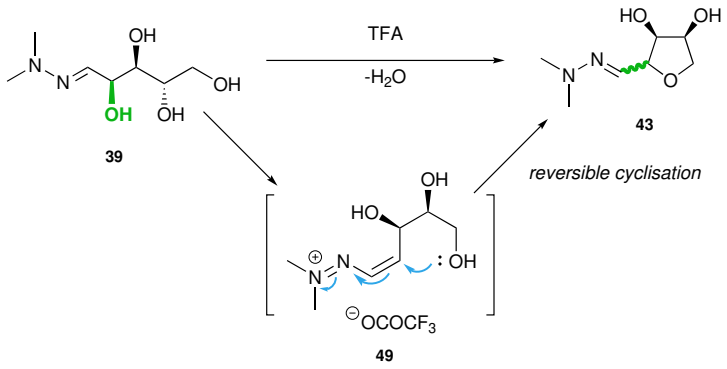

**Scheme 16** Hydrazone production and subsequent acid- or base-catalysed cyclisation of L-arabinose.

stereochemistry can be determined by the choice of conditions employed (whether acid base) and the stereochemistry of the alcohols in the sugar starting material. Foster applied this cyclisation chemistry to a variety of sugar-derived hydrazones to create an array of chiral THFs (**Scheme 17**).



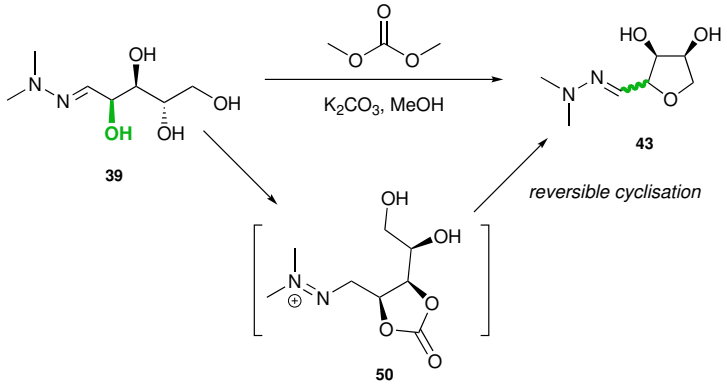

**Scheme 17** A variety of THF hydrazones formed via treatment of sugar hydrazones under acidic conditions.

It is thought that the mechanism proceeds via activation of the alcohol at the C2 position under the acidic conditions (**Scheme 18**). The resulting cation is stabilised by the adjacent *N*,*N*-dialkylhydrazone group, forming vinyldiazenium intermediate **49**.



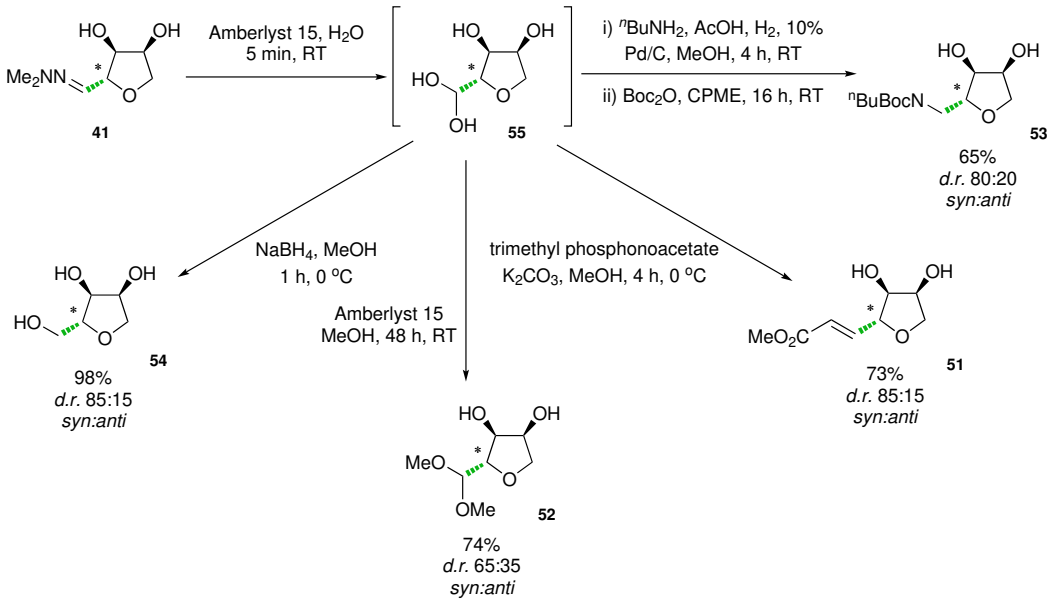

**Scheme 18** A proposed mechanism for the formation of chiral THFs from sugar-derived hydrazones under acidic conditions.

Alternatively, application of basic conditions is likely to proceed via a different mechanism. It is thought that the a cyclic carbonate forms between alcohols at C2 and C3, similar to that seen earlier in **Scheme 11**. Formation of cyclic carbonate **50** is involved in a nucleophilic substitution mechanism with attack from the primary alcohol, resulting in THF formation. However, no mechanistic studies were carried out, nor mechanism for removal of the C2-OH given.



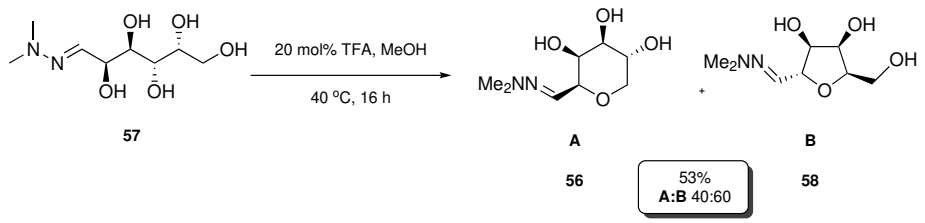

**Scheme 19** A proposed mechanism for the formation of chiral THFs from sugar-derived hydrazones under basic conditions.

Once cyclised, THF hydrazone **41** may be transformed into various THFs (**Scheme 20**). For example, the hydrazone **41** may be transformed to methyl ester **51**, acetal **52**, a Boc-protected amine **53** which can be functionalised further and also primary alcohol species **54**. Interestingly, the corresponding primary alcohol species produced from L-rhamnose-derived THF **48** provides a potential sustainable synthetic route to natural product 3*R*-3-hydroxymuscarine in only two steps.



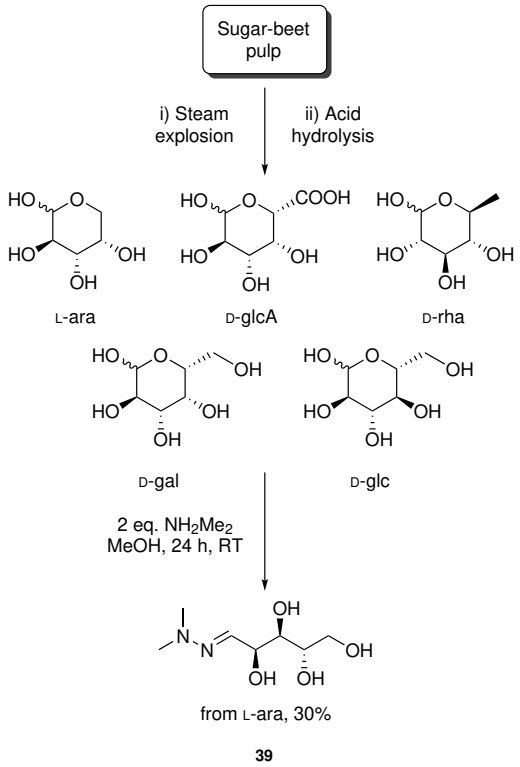

**Scheme 20** Functionalisation of sugar-derived hydrazones into a variety of synthetically useful THFs.

Foster and co-workers also showed that readily available hexose sugars such as D-galactose could cyclise under the same conditions (**Scheme 21**). This further extends the methodology to an even larger array of functionalised heterocycles (including six-membered rings, e.g. **56**), providing an effective approach to low-molecular weight chiral molecules from biomass feedstock origins. However, the scope of this chemistry was also limited to only a few hexose sugars (D-galactose and L-rhamnose) due to low conversion to the corresponding hydrazones. This leaves areas for research in the formation of alternative protecting groups for hexose sugars, followed by application of the same acidic/basic conditions. The ability to form the hydrazone varies depending on the sugar, with steric bulk possibly being an issue in some cases (e.g. D-fructose). Ultimately, an effective and broad methodology is still required. Areas for further study include the use of alternative aldose sugars such as erythrose and glucose, as well as exploring the reactivity of the hydrazones under a wider variety of conditions.




**Scheme 21** Transformation of D-galactose dimethyl hydrazone into heterocyclic rings under acidic conditions.

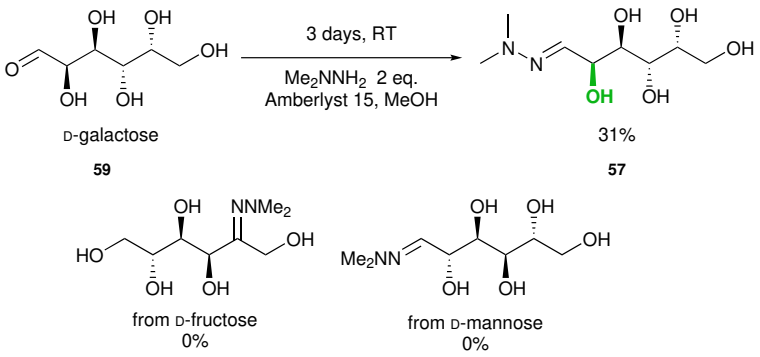
As an expansion on their work, Foster was able to demonstrate the direct application of their chemistry to waste biomass. A sample of solubilised sugar-beet pulp was treated to give its component sugars and then directly exposed to Fosters' hydrazone conditions (**Scheme 22**).[2] An acceptable yield of 30% of L-arabinose hydrazone was produced directly from a renewable source in just three steps. Overall, great selectivity was seen with regards to L-arabinose hydrazone, with only traces of D-rhamnose hydrazone detected.




**Scheme 22** Breakdown and subsequent hydrazone formation from solubilised sugar-beet pulp, producing L-arabinose hydrazone.

Unfortunately, their general methodology was limited almost entirely to pentose sugars. Issues in forming the hydrazones of hexoses were experienced in all cases, aside from L-rhamnose dimethylhydrazone (differs structurally by the presence of

a terminal methyl group) which was isolated in 99% yield.[72] Although hydrazone formation was previously reported with D-galactose, this generally required long reaction times and extra purification steps. Production of D-galactose dimethyl hydrazone **57** was far more sluggish (reaction time of three days), with a much more modest yield of 31% after purification by column chromatography (**Scheme 23**). Generally, hexose sugars showed much slower reaction times than their pentose counterparts. In the case of D-galacturonic acid, the low solubility of the acid in MeOH and low reactivity meant that no hydrazone formation took place. When applying the optimised hydrazone conditions with hexose sugars such as fructose, very little conversion was seen, with additional heating of the reaction only leading to a complex mixture of products.




**Scheme 23** Transformation of hexose sugars into the corresponding dimethyl hydrazone.

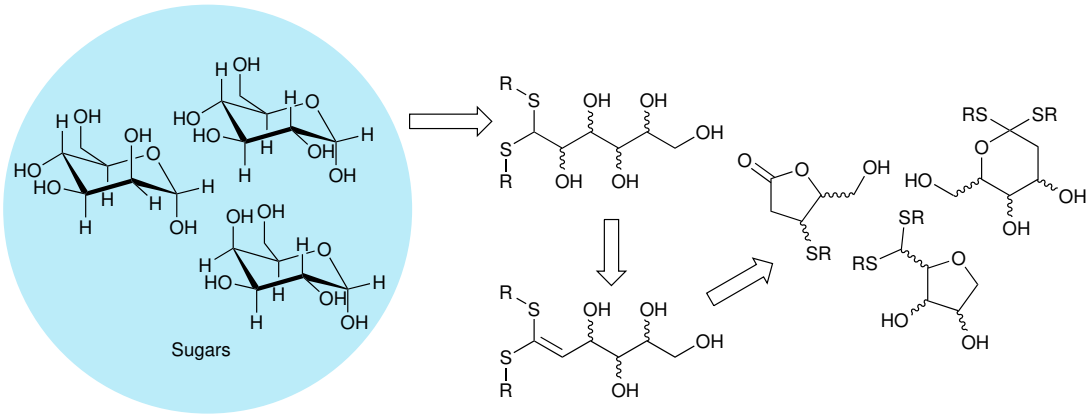
The aim of this project is to expand the scope of these recently discovered dehydration reactions of sugar thioacetals, exploring the full reactivity of the products and to functionalise the resulting novel compounds. It is hoped that open-chain sugars of hexoses will be produced that weren't accessible using hydrazone protecting groups, as well as open-chains of pentose sugars which henceforth haven't been accessible (e.g. D & L-xylose)), thereby presenting a route to a wider variety of dehydrated sugars. As well as this, it is aimed to identify conditions under which sugar hydrazones may be selectively deoxygenated and further cyclised into useful chiral fragments.

# Chapter 2

# Results and Discussion

## 2.1 Project Aims

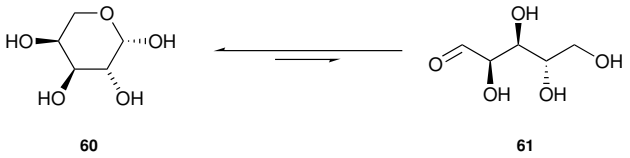
To follow on from research by R. Foster, it is intended that this work will provide access to a more diverse array of open-chain sugars, including hexoses. Treatment of these open-chain sugars with basic conditions to selective dehydrate them will be carried out, followed by the optimisation of this reaction for the array of sugars. Reactivity of the resulting ketene thioacetals will be explored. A major aim of this work is to produce chiral heterocycles from the sugar starting materials; thereby producing potentially useful chiral compounds from renewable starting materials. A general scheme of the aims of this work for the manipulation of sugars has been shown in **Scheme 24**.




**Scheme 24** A general scheme showing the project aims of this work; involving the conversion of sugars to their open-chain form, selectively dehydration at C-2 and subsequent cyclisations.

## 2.2 Open-Chain Sugar Protection

Sugar molecules exist in a equilibrium between the cyclised form **60** (furanose/pyranose for 5/6-membered rings respectively) and the open-chain form **61** (**Scheme 25**). In order to access a broader reactivity of sugars, they should be trapped in their open form (as an open-chain), creating a polyol coupled to a masked aldehyde (**Scheme 25**).

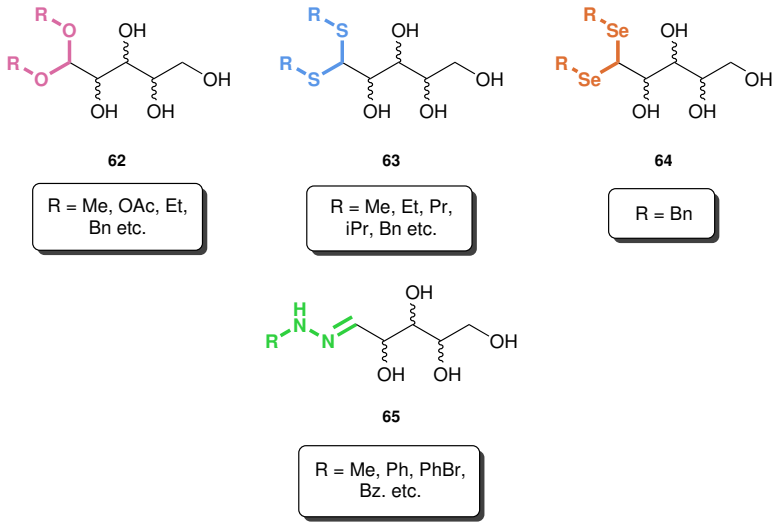



**Scheme 25** The existing equilibrium between L-arabinose open-chain and the cyclised pentose.

Trapping of sugars in their open-chain form enables the formation of new rings through cyclisation at different positions in the ring. With sugars existing predominantly in their cyclic form, new cyclisations cannot occur unless they are first locked in their open-chain form. The most common way of trapping a sugar as an open-chain is to install a hydrazone, an acetal or dithioacetal group. However, creating these open-chains can be challenging because of the strongly thermodynamically favoured cyclic form (e.g. **60**).

Ketose sugars (those with only one secondary carbonyl group per molecule[73]) and aldose sugars (those with a carbonyl on the first carbon of the sugar - an aldehyde) are the most commonly encountered sugars. There are numerous literature examples of many varieties of protected sugars, with large flexibility in the attached R groups (**Scheme 26**). In particular, acetals can be made readily with R groups including OAc, Me and Et (structure **62**).[74,75] Acetals such as dibenzyl acetals have potential utilisation as synthetic intermediates and as potential pharmaceuticals in cancer treatment.[76] However, synthesis of acetals can often be troublesome. Acidic conditions with a nucleophile such as methanol lead to substitution at the carbonyl without the result of an open chain. It is for this reason that chemists often turn to sulphur chemistry. Thioacetal derivatives offer different reactivity, with a sulphur atom in the place of oxygen. Unlike acetals, thioacetals are stable under acidic conditions and therefore offer more robust reactivity.[77] As a result of their stability, deprotection requires harsher conditions such as using mercuric chloride. However, desulphurisation may

be carried out using Raney Ni to give the corresponding hydrocarbon.[77] Variants include different alkyl groups and aromatics **63**.[78,79]




**Scheme 26** Literature examples of open-chain sugars using a variety of aldehyde protecting groups.

With similar character to thioacetals, diselenanes can also be formed (structures **64**),[80] with a wide array of 1,3-diselenanes available on non-sugar susbtrates.[81] As they are in the same group as sulphur, selenium and tellurium derivatives offer similar reactivity, however, the toxicity and cost inefficiency may explain the lack of research into their analogues.

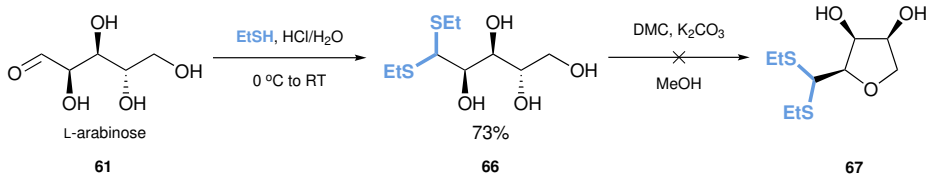
As previously mentioned in research by Foster *et al.*, hydrazones may also be formed to trap sugars in their open-chain form (structures **65**).[69] Other variants have also been cited bearing phenyl groups etc.[79,82,83] However, the limits of hydrazones are made apparent when trying to form the hydrazones on different sugars, with the scope proven to be limited.

#### 2.2.0.1 Previous Work

To begin the investigation, a Master's student within the Sheppard group, Alex Goyder, began with the protection of L-arabinose, trialling a small variety of thiol protecting groups. Thioacetals of L-arabinose exist in the literature with both ethanethiol and thiophenol functionalisation. These thioacetals were produced as initial substrates to test Foster's dehydration conditions.[69]

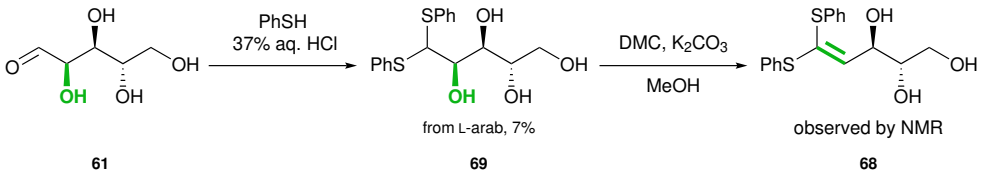
In an initial search for a thiol protecting group, Goyder tested thioethanol with model sugar L-arabinose. Although protection was carried out successfully (73%,

compound **66**), implentation of Foster's conditions (step 2 of **Scheme 27**) gave no selective reactivity. No cyclisation was seen when exposed to both basic and acidic conditions, with only complex mixtures of products seen.[84]




**Scheme 27** Formation of L-arabinose diethyldithioacetal, followed by application of established dehydration conditions.[69]

Following this, Goyder produced thiophenol-protected L-ara and exposed it to the same conditions (**Scheme 28**). Selective reactivity in the dehydration step was found when using diphenylthioacetals, meaning these were used henceforth in his research as the preferential route for open-chain trapping and subsequent dehydration. In addition to this, simple purification via recrystallisation of the phenylthioacetals worked effectively, as opposed to the requirement for column chromatography for ethylthioacetals. Interestingly, instead of forming a THF, as predicted, ketene thioacetal **68** was observed. To lead on from Goyder's work, we endeavoured to explore the reactivity of **68**, and the corresponding dehydration reaction applied to a multitude of pentose and hexose sugars.

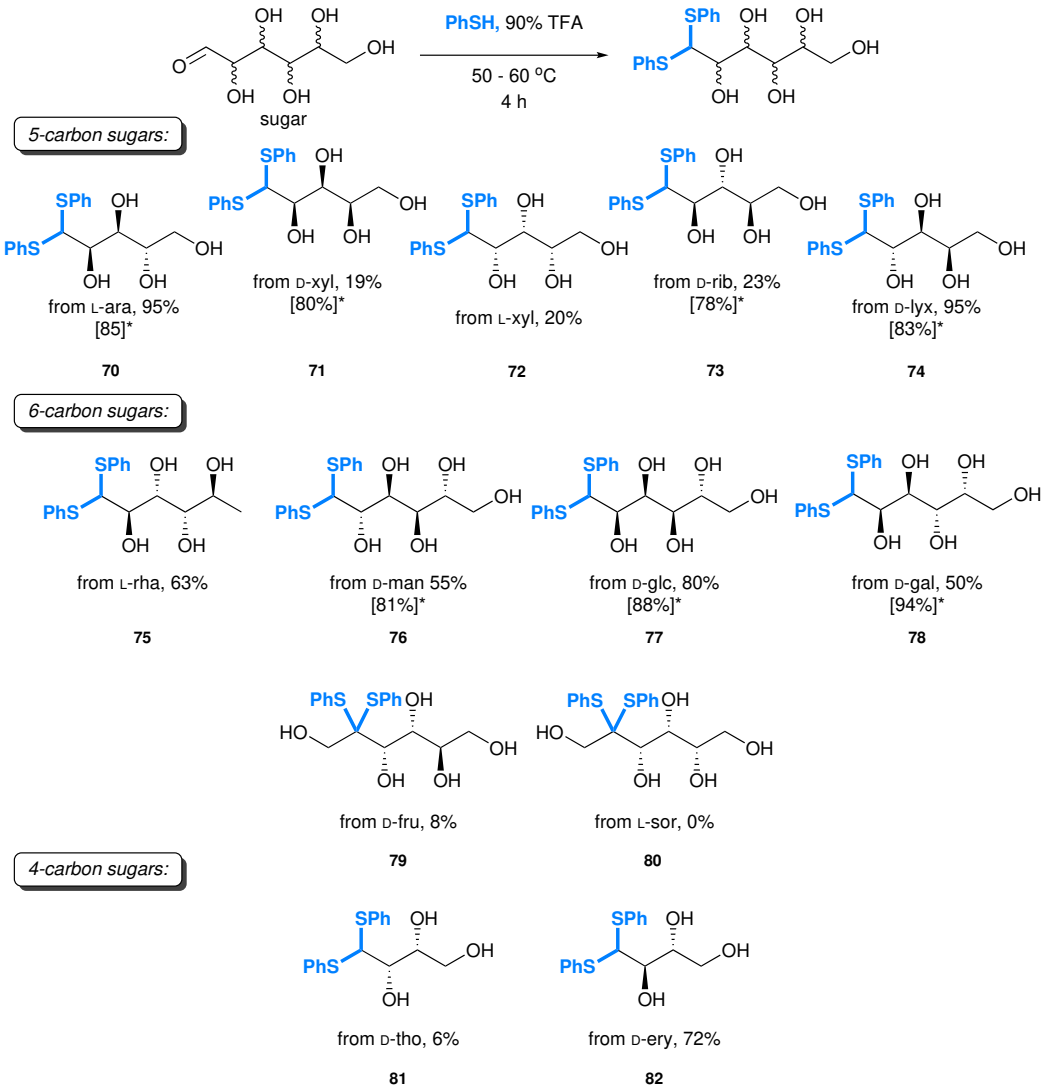



**Scheme 28** Formation of a diphenyldithioacetal, derived from L-arabinose, followed by application of basic, dehydration conditions.[84]

### 2.2.1 Thiophenol-protected Sugars – This Work

To begin the investigation, we generated a series of dithioacetals by the reaction of sugars with thiophenol under optimised conditions (**Scheme 29**).[78] In order to test the reactivity of the protected sugar, a model sugar (L-arabinose) was subjected to cyclisation conditions (used by Foster *et al.*) and the products' reactivity explored.[84] A broader scope of cyclised products (than achieved from hydrazones) may be obtained

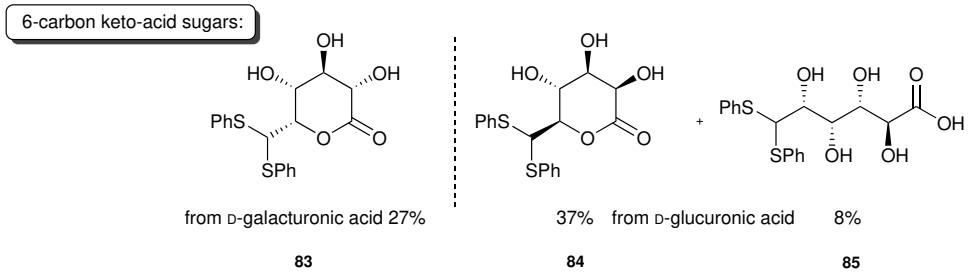
using alternative open-chain trapping agents. Major aims of the project include: protection of a wide variety of sugars to trap them in their open-chain form, treating the sugars with dehydration conditions and exploring the reactivity/finding potential applications of the resultant molecules.




**Scheme 29** Isolated diphenyldithioacetals produced from a variety of sugars. Literature yields shown in square brackets.[78]

Pure dithioacetal products from a wide variety of sugars were produced in reasonable yield (**Scheme 29**).[85] A range of sugars (both aldose and ketose) were converted to the corresponding diphenyldithioacetals via treatment with thiophenol under acidic conditions.[78] The thioacetals were produced in low to good yield with aldose sugars generally performing better than ketose sugars and crystallising upon formation. Generally, there was no difference in reactivity observed between pentoses or hexoses (**Scheme 29**). However, it should be noted that the thioacetals with lowest

yields were those that possessed *syn* stereochemistry at positions -2 and -3 (from xyl, fru, sor and tho). Though the reason for this is unclear, such reactivity may suggest that specific orientation of the sugar is required for optimal thioacetalisation. Most yields found in the literature[78] were higher than found in the laboratory, primarily due to low conversion, shown by recovery of sugar starting material in most cases. For example, from D-ribose, whereby 9 g of the 13 g starting material was recovered post-reaction, due to its low conversion (24% of **73**). Protection of ketose sugars such as fructose and sorbose was also investigated. However, these exhibited limited reactivity due to steric hindrance around the carbonyl, giving little or no product formation (in the case of sorbose, **Scheme 29**).

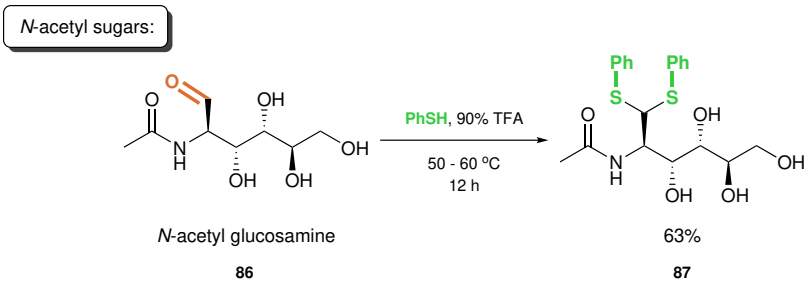



**Scheme 30** Isolated products of the diphenyldithioacetal formation of keto-acid sugars.[78]

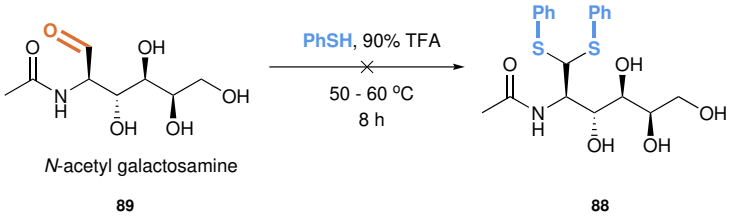
It was noticed that upon dithioacetal formation from glucuronic and galacturonic acids, spontaneous cyclisation occurs to yield 6-membered lactone products **83** and **84** (**Scheme 30**). In these cases, cyclisation was much more probable due to the reactive carboxylic acid side chain in the starting material. In the case of D-glucuronic acid, an open chain thioacetal was also isolated. All products were formed in low yield (8 - 37%), primarily due to low conversion from sugar starting materials.

To explore substrates containing nitrogen, *N*-acetylglucosamine **86** was reacted with thiophenol under the same thioacetal-forming conditions[78] to give compound **87** (**Scheme 31**). Similarly, *N*-acylated sugar *N*-acetylgalactosamine was reacted with thiophenol under acidic conditions to form a protected, thioacetal **88** (**Scheme 32**). Unfortunately, only a complex mixture was obtained from the reaction, and therefore, no further investigation on this sugar was carried out.

Due to the lack of selective reactivity, the effect of the altered stereochemistry between **86** and **89** on the subsequent cyclisation was unable to be explored.



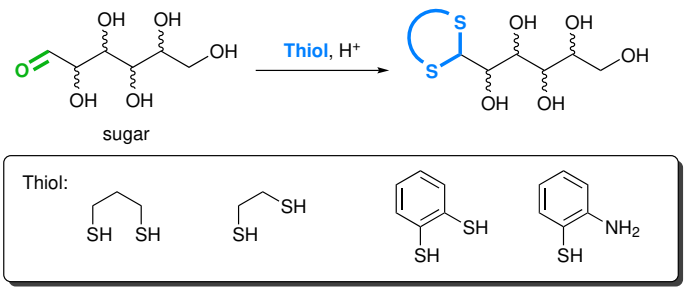

**Scheme 31** Isolated products of the diphenyldithioacetal formation of *N*-acetyl glucosamine.[78]




**Scheme 32** Reaction to form *N*-acetyl galactosamine dithioacetal **88**, with no selective reaction taking place.

## 2.2.2 Dithiol-protected Sugars

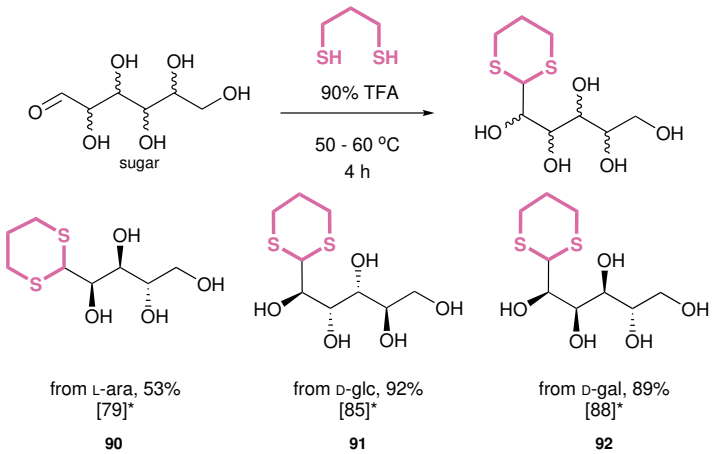
Dithiols were also explored as protecting groups for the sugars to explore if the resulting structures differed in reactivity to their monodentate counterparts. With monodentate nucleophiles there are added steric pressures that must be overcome with the attack of two equivalents of thiol. It was thought that the use of a bidentate thiol protecting group would help drive the reaction and give higher conversions. After initial attack of one thiol group, the second tethered thiol group should readily attack to form a sulphur-containing heterocycle. Multiple dithiols were tested for their reactivity with model sugar L-arabinose under various acidic conditions to create a cyclic dithiol (**Scheme 33**).




**Scheme 33** A general scheme showing the possible bidentate thioacetal protecting groups of L-arabinose.

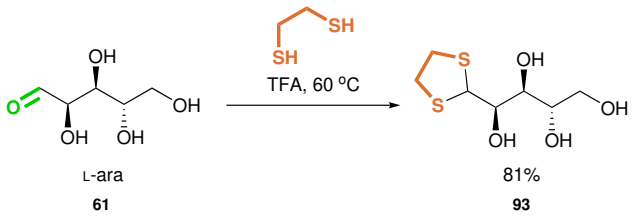
It was thought that 1,2-benzenedithiol would possess similar reactivity and characteristics to the corresponding thiophenol derivative, due to its structural similarity. However, there is no literature precedence for this as a protecting group for sugars, and no success was found when performing the reaction under a variety of acidic conditions.[86,87] In both cases, only starting material was recovered from the reaction. This may be due to strained bond angles in the dithiane product, making the reaction energetically unfavourable. Due to this lack of reactivity, as well as high cost, we explored different thiols.

In 1986, the Takano group reported a large array of sugars with thiol protecting groups, including both mono and bidentate thiols. Using the same conditions, we were able to produce an array of diphenyldithioacetals, as mentioned previously (**Scheme 29**). The same literature conditions (90% aq. TFA + thiol) were used 1,3-propanedithiol to create a range of sugar-derived sulphur-containing heterocycles in good yields.[86] However,Takano's research was only carried out on a select number of sugars, allowing this work to expand the scope for both propanedithiol as well as thiophenol protected sugars. Certain sugars, such as D-ribose, were proven to be inert under such conditions and were therefore no longer explored.




**Scheme 34** A general scheme showing the thioacetalisation of pentose and hexose sugars using 1,3-propanedithiol. Literature yields shown in square brackets.[86]

The protection of five-carbon sugar L-arabinose using 1,2-ethanedithiol was produced in good yield (**Scheme 34**). We intended to produce the corresponding thioacetals for hexose sugars D-glucose and D-galactose in order to establish the difference in reactivity when exposed to dehydration conditions.

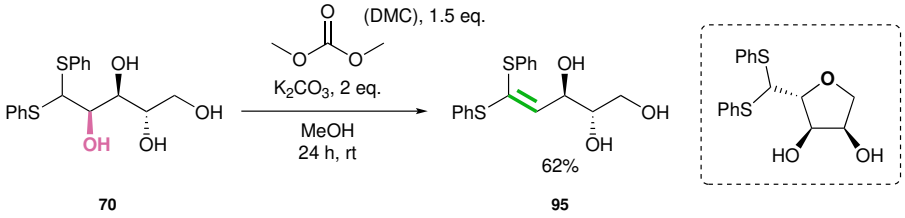



**Scheme 35** Thioacetalisation of L-arabinose using bidentate trapping agent 1,2-ethanedithiol.[86]

After trialling numerous thiols to trap the sugars in their open-chain form, the thiophenol-derived thioacetals were found to give the most reliable and uniform reactivity, in terms of formation of the thioacetal and subsequent dehydration across all tested sugars. Reactions with propanedithiol and ethanedithiol, although occurring readily, proved to make more unstable products, with little uniformity across pentose/hexose sugars. Hexose thioacetals were generally produced in a better yield than pentoses. This could be due to the difference in time that the hexose sugar spends in the open-chain form, leading to a larger attack window for the thiol nucleophile and therefore, greater yield.

### 2.2.3 Thioacetal Dehydration

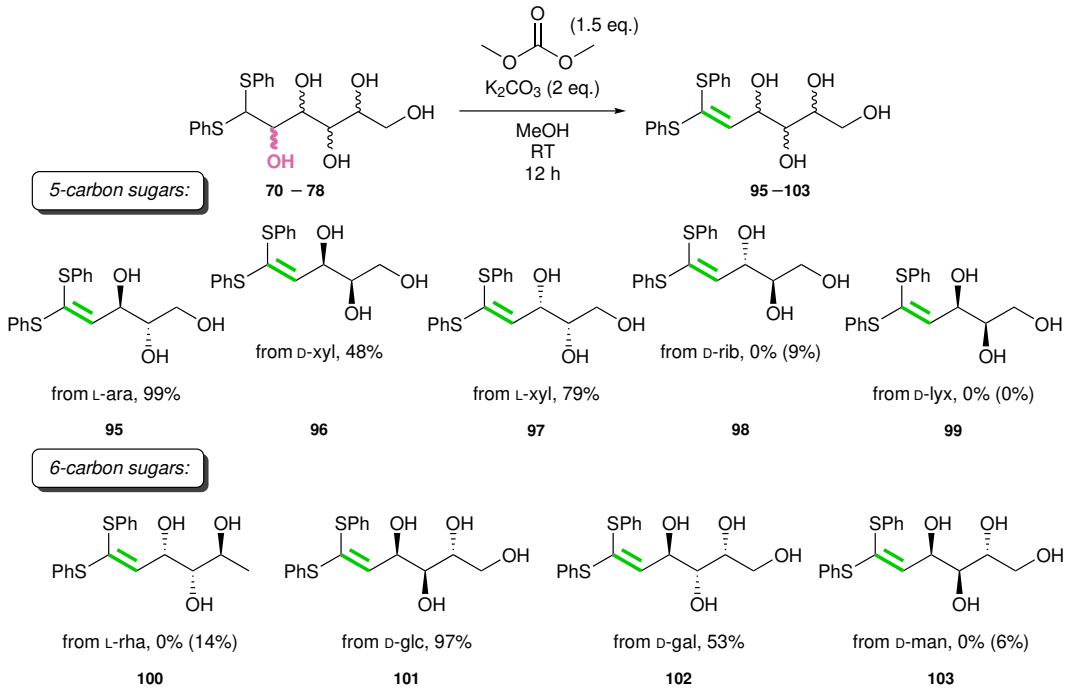
Previous work in the group involving hydrazone-protected sugars (**Scheme 16**) was limited to only a few aldose sugars.[69] It was proposed that sugar dithioacetals, under the same conditions which allow cyclisation of the hydrazone ($K_2CO_3$, DMC), should result in the analogous cyclised product (encircled in **Scheme 36**) with a broader substrate scope.[88]




**Scheme 36** Reaction of L-Arabinose diphenyldithioacetal with dimethyl carbonate under basic conditions.[84] Initial predicted cyclised product based on previous work by Foster *et al.* is highlighted.

L-arabinose was selected as a model compound to be carried forward in dehydration reactions due to its relative stability, high yield and ease of recrystallisation. When these basic conditions were applied to the protected sugar (compound **70**),

we found the selective dehydration to produce ketene dithioacetal **95**.[84] Under unoptimised conditions, the reaction went to full conversion with a good yield of 62% following purification.

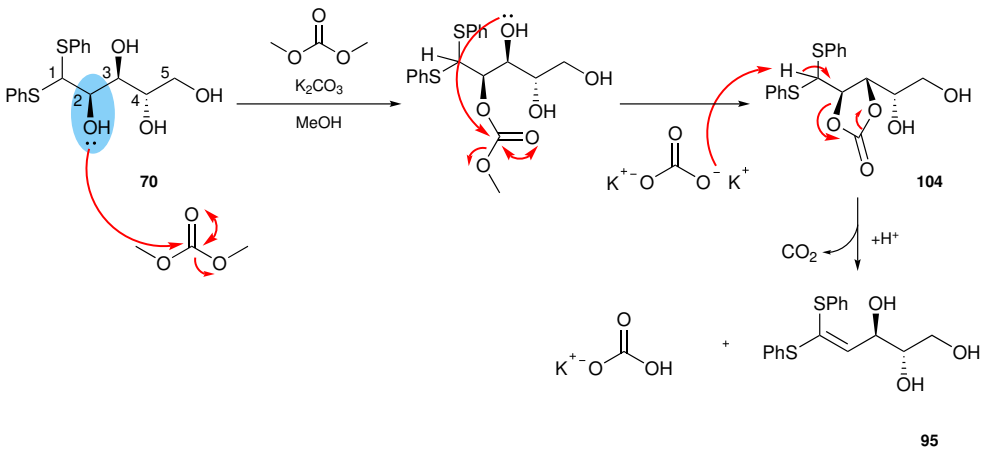



**Scheme 37** Isolated products of the reaction between sugar diphenyldithioacetals and $K_2CO_3$ with DMC in MeOH. NMR conversions included in parentheses.[85]

The ketene thioacetal was found to be unstable to column chromatography initially used for purification. The reaction was repeated with crystallisation as the method of purification, vastly improving the yield (**Scheme 37**). This selective dehydration was carried out with an array of sugar dithioacetals (**Scheme 37**) in good to excellent yields. A wide variety of reactivity was seen with the sugar dithioacetals, with ketene thioacetal products isolated in most cases. However, lack of reactivity was noticed with sugars which readily formed dithioacetals in the initial straight-chain formation step. Derivatives such as L-rhamnose and D-ribose gave little to no conversion to the alkene and only starting materials (**75** and **73** respectively) were present after 24 h.

It is thought that the dehydration takes place through the formation of a carbonate species by reaction of the polyol with dimethyl carbonate, which then subsequently eliminates at the most stabilised position to liberate $CO_2$ (**Scheme 38**).

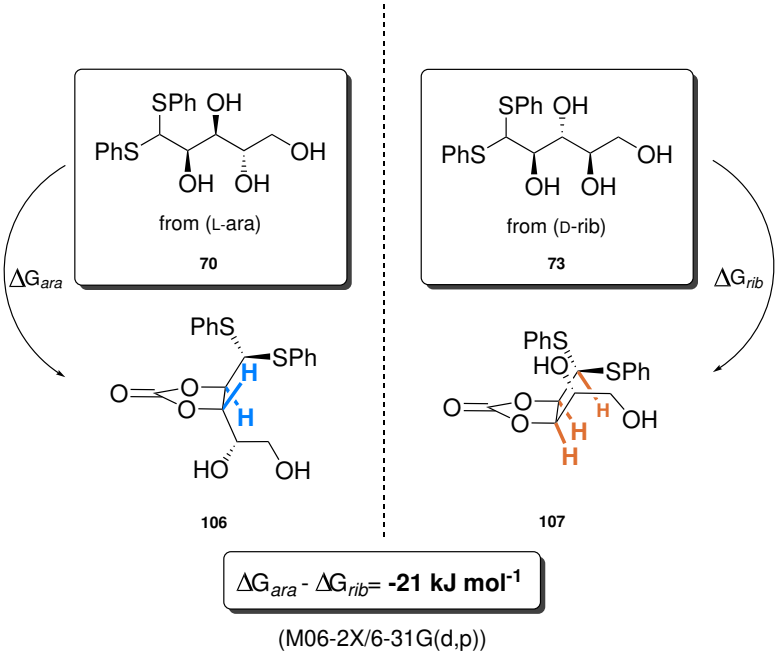
Isolation of the intermediate carbonate species **104** was not possible. However, the difficulty we observed for sugars containing *anti* stereochemistry at the α- and




**Scheme 38** Proposed mechanism for the selective dehydration of sugar dithioacetals, with the most stabilised site for dehydration circled in green.

β-positions gives weight to our proposed mechanism to form the ketene thioacetal. By looking at the geometry of the carbonate structures (**104**) of both *anti* and *syn* sugars, it can be seen more easily how the mechanism of cleavage of *syn*-sugar thioacetals is favoured (**Scheme 39**). As shown by structure **107** derived from *anti* sugar D-rib, we can see that a carbonate is more sterically hindered and therefore less likely to form. This orientation may also hinder the alignment of the C-1 proton into the correct position for the proceeding $E_2$ elimination. In contrast, the carbonate derived from *syn* sugar L-ara **106** adopts as less-hindered cyclic structure whereby the hydrogen atoms adjacent to the carbonate are more exposed. This allows ready adoption into the required conformation for basic attack, and subsequent elimination to yield the alkene. This suggests that formation of intermediates such as **104** are vital for the dehydration to take place under these conditions.

To gain mechanistic insight into the dehydration, computational studies were carried out by M. Porter to measure the change in free-energy between the sugar thioacetals and their corresponding carbonate intermediates ($\Delta G_{ara}$ and $\Delta G_{rib}$).[85] DFT calculations were carried out to model the free energy of sugar thioacetals **70** and **73** (**Scheme 29**), and their relative energies to carbonate intermediates **106** and **107** respectively. The thioacetal starting materials possess similar ground state energies (differing by 0.3 kJ $mol^{-1}$). The free energy change in going from **70** to **106** is ca. 21 kJ $mol^{-1}$ more negative than that going from *anti* thioacetal **73** to the cyclic intermediate **107**. These data indicate that the transition from an *anti* diol to the cyclic carbonate is about 21 kJ $mol^{-1}$ more endergonic than for its *syn* counterpart when in



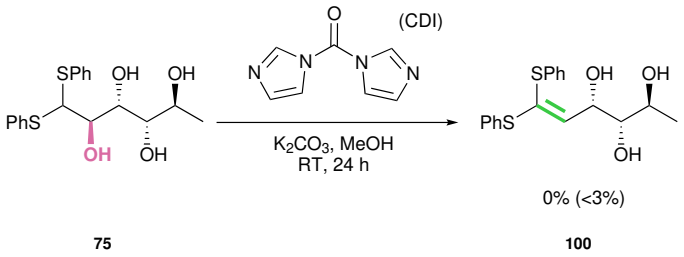

**Scheme 39** Illustrations of 3D structures of intermediate carbonates formed with *anti* and *syn* sugar thioacetals. Key stereochemical features are encircled in red.[85]

solution in MeOH. From this, we can deduce that the *syn* carbonate **107** is far less likely to form than *anti* **106**, which is in alignment with our experimental outcomes.[85]

We therefore postulate that in sugars that exhibit an *anti* relationship at 2-OH and 3-OH, such as L-rhamnose and D-ribose, that it is unlikely for a strained, cyclic carbonate to form. Therefore, very litte thioacetal ketene would be observed .

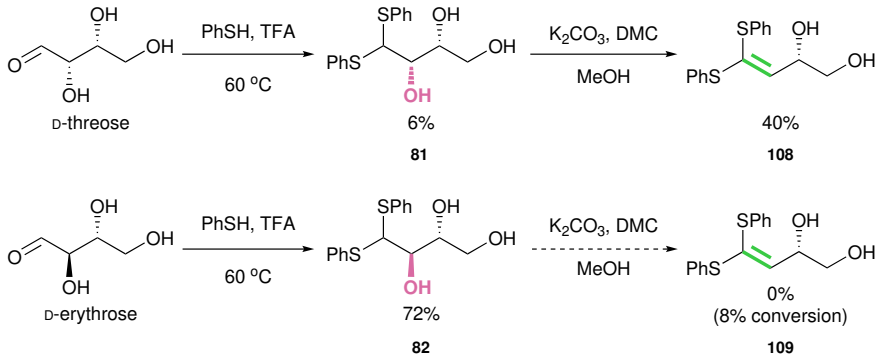
In order to test if the lack of reactivity is caused by the unfavourable formation of the carbonate, a more reactive carbonate species, carbonyldiimidazole (CDI) was used with the 2,3-*anti* compound derived from L-rhamnose **75**. Analogous conditions with CDI in place of DMC gave similarly poor results (**Scheme 40**) with less than 3% conversion to the ketene thioacetal observed by $^{1}$H NMR and only starting material recovered after purification.

To probe our hypothesis, the dehydration of tetrose/4-carbon (4C) sugars was investigated (**Scheme 41**). It would be expected that the D-threose thioacetal would eliminate under DMC and $K_2CO_3$ conditions (due to its *syn* stereochemistry at the 2- and 3-positions), but that the D-erythrose thioacetal would be unreactive under these conditions (due to it's *anti* stereochemistry, hampering formation of the carbonate intermediate). As predicted, this occurred with full conversion of the D-threose thioacetal **81** to the ketene thioacetal **108**, whereas only 8% conversion was observed




**Scheme 40** The use of CDI as carbonate source in the formation of L-rhamnose ketene thioacetal, showing only trace reactivity, NMR conversion included in parentheses.

in the corresponding reaction with D-erythrose thioacetal **82**. It should be noted that in many cases, the purification of ketene thioacetals was challenging based on decomposition of the materials on silica, meaning a lower isolated yield. In cases of high yield, purification via recrystallisation was possible.

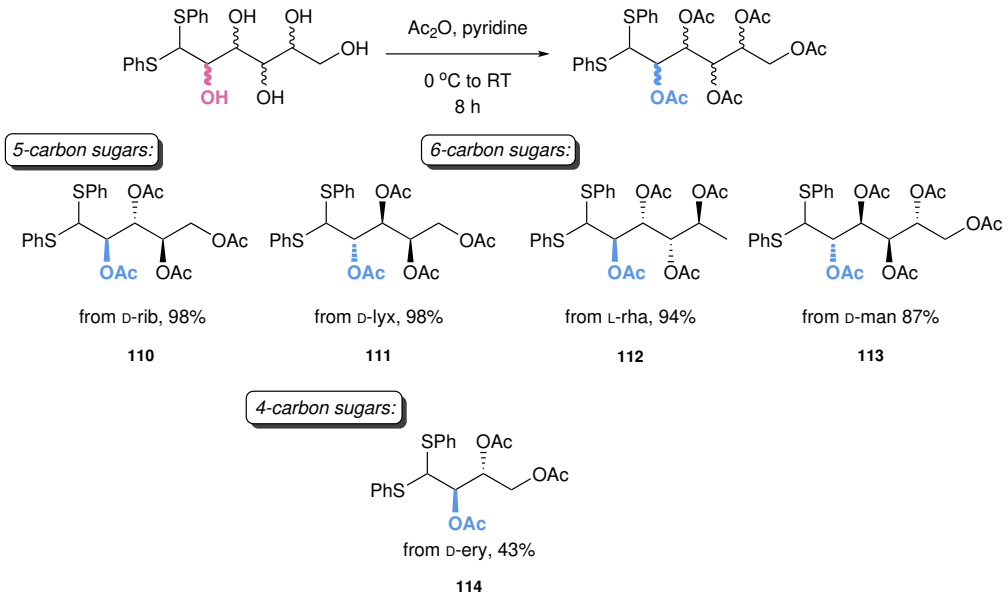



**Scheme 41** Thioacetal formation of 4C sugars D-threose and D-erythrose, followed by application of dehydration conditions ($K_2CO_3$ and DMC in MeOH). Difference in activity between *syn* and *anti* sugars is shown.

In order to expand the scope such that 2,3-*anti* sugars were compatible, we proposed creating an alternative leaving group on the molecule that would encourage dehydration, thus allowing the formation of ketene thioacetals. Based on literature precedence for success in the acetylation of sugars with pyridine/acetic anhydride,[89,90] acetylation of *anti*-sugars was carried out (**Scheme 42**).

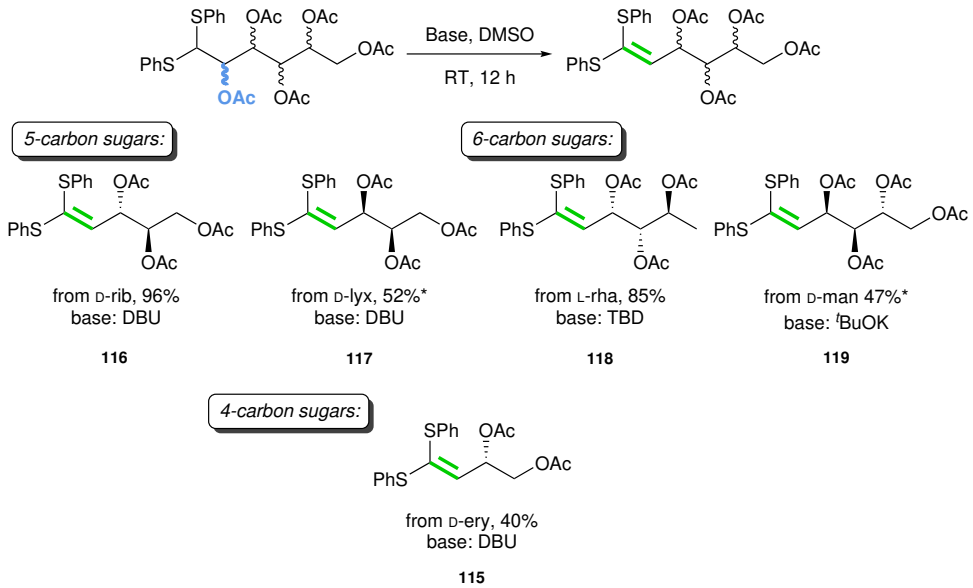
Acetylation of the thioacetals was carried out in good to excellent yields for all sugar-derivatives (72–98%). Clean, selective reactions were seen, meaning no purification steps were required following aqueous workup in all cases. A slightly lower yield was observed in the case of tetrose sugar D-erythrose likely due to instability of the sugar substrate.

Following acetylation, the protected sugars were stirred under basic conditions




**Scheme 42** Acetylation of sugar alcohols on a variety of thioacetal-protected 2,3-*anti*-sugars.

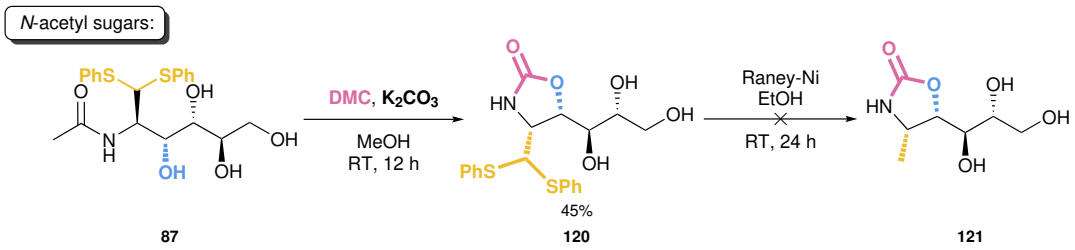
and monitored for ketene thioacetal formation. Although still unreactive with $K_2CO_3$, the use of organic, amine bases 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triazabicyclodecene (TBD) and 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MeTBD), as well as $^t$BuOK gave formation of the desired alkene products. Depending on the sugar, the base was varied to give reasonable yields, (**Scheme 43**). It should be noted that for the derivative of tetrose sugar, erythrose **115**, due to its' instability and low purity, this structure is only the proposed major product.




**Scheme 43** Isolated acetylated ketene thioacetals from a variety of *anti*-sugars. NMR yields shown by an asterisk.

By acetylation of *anti* sugars prior to the application of basic conditions, it is possible to access novel ketene thioacetals of the most abundant sugars found in biomass.[2] Moreover, this can be applied to more unusual 4C sugars, which may be used to create small chiral scaffolds upon further functionalisation. Dehydration that is only possible via prior acetylation provides valuable insight into the mechanism. From our studies, it can be shown that 2,3-*anti*-sugars are inactive in forming cyclic carbonates on the 2 and 3 positions prior to elimination (**Scheme 38**), and therefore, must be activated in an alternative way if the dehydration should take place. Dehydration via this route gave ketene thioacetals from previously unsuccessful sugar-derivates such as D-ribose and L-rhamnose in excellent yields of 96% and 85% respectively.

Due to the abundance of *N*-containing heterocycles in nature,[91] it is desirable to explore methods which incorporate nitrogen into ring systems. The reaction of *N*-acetylglucosamine thioacetal **87** under dehydration conditions[84] yielded the carbamate product **120** in a 45% yield (**Scheme 44**). Reduction of **120** under Raney-Ni conditions was attempted in order to obtain a chiral, cyclic carbamate with a methyl group attached to a stereocentre. This methyl group is an interesting motif which could be synthesised in three steps from a renewable starting material. However, upon analysis of the crude mixture by NMR, a complex mixture of products was seen without isolation of **121**. This pathway may be more successful by prior acetylation of the carbamate, followed by reduction, in order to ease the purification process.

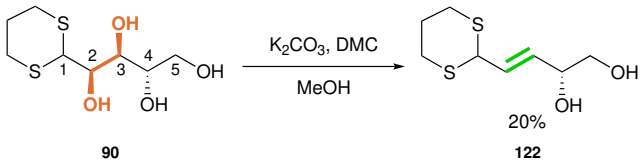



**Scheme 44** Reaction between *N*-acetyl glucosamine dithioacetal **87** and $K_2CO_3$ with DMC in MeOH, followed by desulphurisation using Raney-Ni.

*N*-Acetylglucosamine (**86**) is a chiral building block which contains a nitrogen handle which may be manipulated. Although a similar analogue to our thioacetylated sugar has been produced before **120** (possessing an ethanethiol protecting group[92]), no exploration into the utility of these compounds has been conducted. Formation

of chiral, substituted carbamate **120** (**Scheme 44**) raises the possibility for directed functionalisation of the adhered chiral alcohols. Unfortunately, an attempted reduction with Raney-Ni gave no reaction, possibly caused by a deactivating effect of the nitrogen on the Ni-catalyst.

When trialling alternative thioacetals under the same dehydration conditions, loss of hydroxyl functionality takes place at both positions 2 and 3 when exposed to base (**Scheme 45**). Dehydration of **90** gives novel alkene **122**, isolated in low yield in unoptimised conditions. The notably low yield is due to the formation of unisolable by-products, likely a result of dehydration occurring at various parts of the molecule leading to reactive intermediates. We postulate that the mechanism for this reaction involves the initial formation of a cyclic carbonate at C-2/C-3, which may then be protonated upon purification and eliminate to give the alkene and release $HCO_3$ as a by-product.

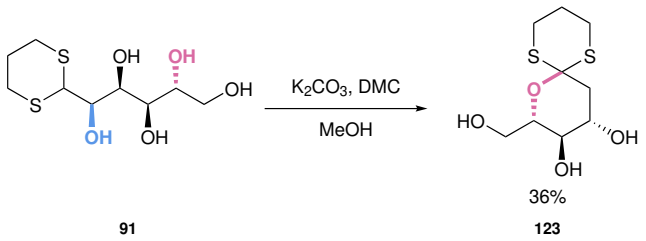



**Scheme 45** Application of dehydration conditions[69] to propanedithiol-protected L-arabinose, yielding a *trans* alkene.

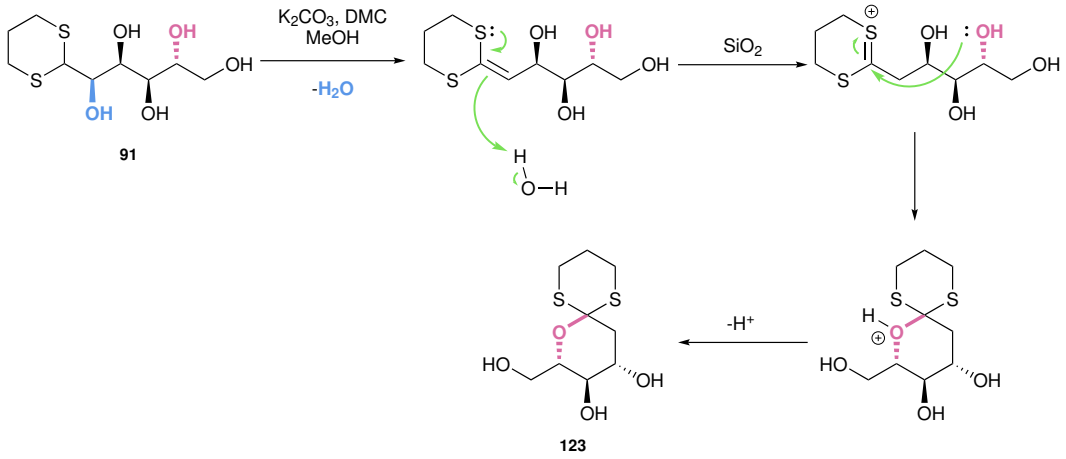
The thioacetal that forms from reaction of D-glucose and propanedithiol **91** was also exposed to the dehydration conditions of DMC, $K_2CO_3$ in MeOH. The outcome, however, differed to that of the arabinose derivative **90**, with spiro compound **123** formed instead. Based on the stereochemistry of the THP, it appears to have formed via intramolecular attack of the terminal OH group onto a transient ketene thioacetal intermediate (**Scheme 46**). THP **123** was formed in a modest yield due to low conversion from starting material under unoptimised conditions. The use of a stronger base or converting the alcohols to the acetates prior to exposure to basic conditions may improve the yield.

We postulate that the formation of **123** takes place via inital formation of a thioacetal ketene followed by attack of the C-5 OH, catalysed by $H^+$ during purification (**Scheme 47**).

Although not reported in the literature, similar compounds to **123** have been pub-



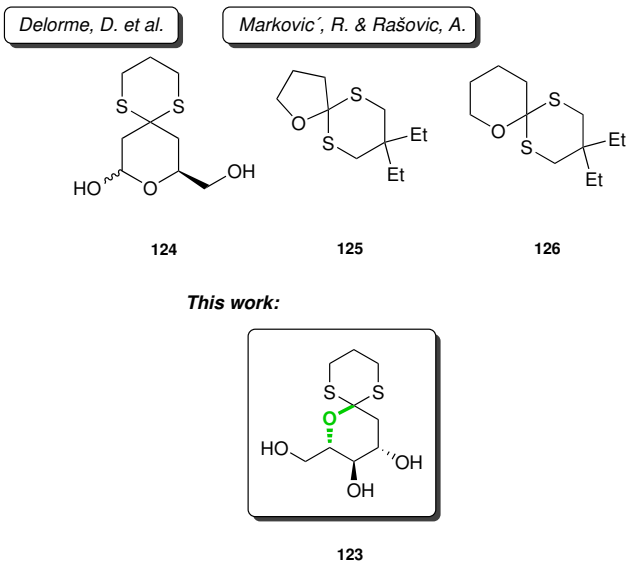

**Scheme 46** Application of dehydration conditions[69] to D-glucose dithiane, yielding chiral THP **123**.




**Scheme 47** Postulated mechanism for the formation of chiral THP **123**.

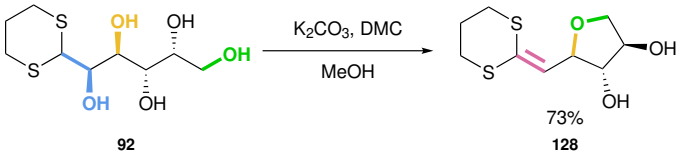
lished with minor structural differences. Key reports include the use of similar THPs as thioacetal-based linker for solid-phase synthesis.[93] A variety of 1,2-dithiolanes were investigated in the literature for their potential use in solid-phase synthesis, with novel spiro 1,3-dithianes isolated as by-products from their reactions (**Scheme 48**). Another reported molecule of similar structure was discovered in the exploration of the structure activity relationship (SAR) of naphthalenic lignan lactone (L-702,539), a potent and selective 5-lipoxygenase (5-LO) inhibitor.[94] The study aimed the improve the metabolic stability for this series and, in the process, produced and characterised glycoside **124** as an intermediate. However, it is unknown if the pharmaceutical potential of THPs such as this one have been investigated.

If the stereochemistry at the 4-position is altered (as is the case in D-galactose) a different cyclised product is produced. Instead of THP formation, an intramolecular cyclisation occurs via attack from the 3-position, creating a THF adjacent to the ketene thioacetal, similar to glucose-derived **127**. (**Scheme 49**) It differs from the D-glucose derivative in that the formation of the ketene thioacetal seems to occur alongside cyclisation without interaction between the two parts of the molecule (due




**Scheme 48** Spiro THPs reported in the literature which resemble novel THP **123** discovered in this work.[93 ,94]

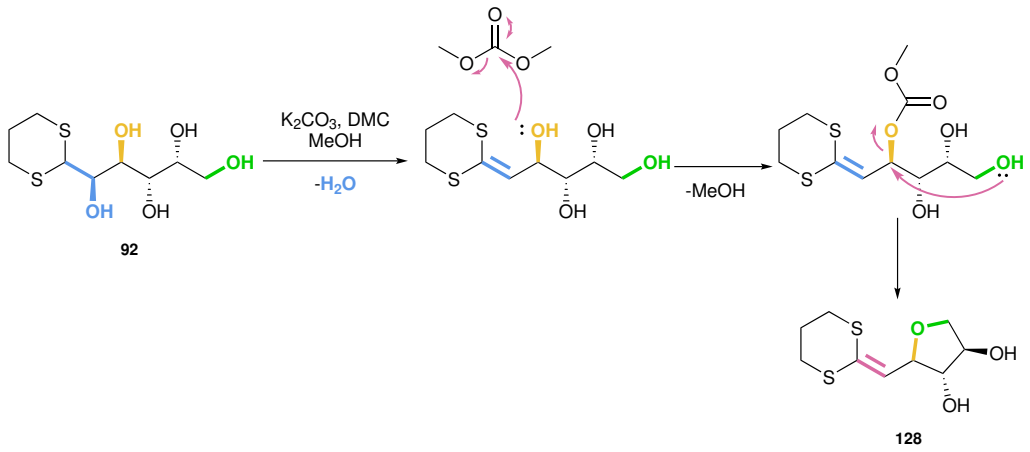
to altered stereochemistry and orientation of the carbon backbone in space), thereby leading to a difference in reactivity.




**Scheme 49** Application of dehydration conditions[69] to D-galactose dithiane, yielding chiral THF **128**.

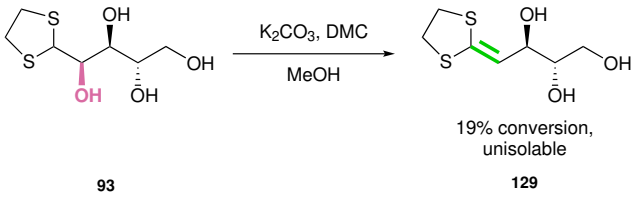
Although complete consumption of starting material occurred at room temperature, large numbers of non-selective reactions took place without the isolation of any by-products, accounting for a low isolated yield of THF **128**. The difference in reactivity seen here between D-gal and D-glc must be as a result of the difference in stereochemistry at the 4-position. It seems that by having the alcohol group at this position and *anti* relative to 3-OH, it allows for the formation of a smaller, more strained 5-membered ring. Due to the *trans* relationship of the two alcohols at positions 3 and 4, there should be less steric interaction in the cyclic transition state, and therefore, should form a THF more readily. It is thought that under mildly acidic conditions during purification that cyclisation occurs in a similar mechanism to that seen with hydrazone formation (**Scheme 50**).

The corresponding dehydration of ethanedithiol-protected sugar L-arabinose **93** was trialled **(Scheme 51)** which, like its propanedithiol analogue (**Scheme 45**),




**Scheme 50** Postulated mechanism for the formation of chiral THF **128**.

formed an alkene. In this case, a ketene thioacetal was formed via single dehydration at the 2-position in a selective manner.




**Scheme 51** Application of dehydration conditions[69] to ethanedithiol-protected L-arabinose, yielding an unstable ketene thioacetal.

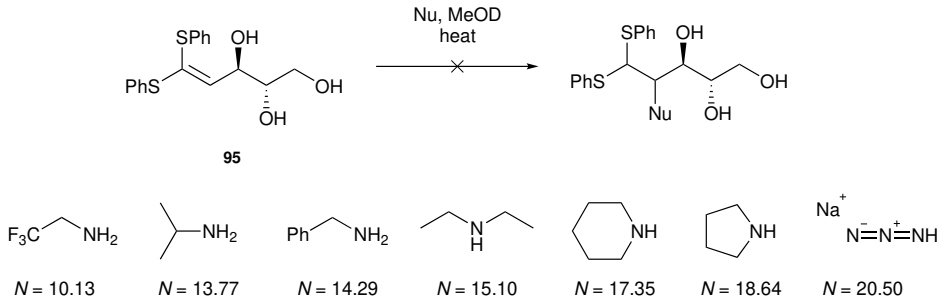
Unfortunately, novel ketene thioacetal **129** was unstable to purification conditions, possibly due to the reactive nature of the alkene attached to the 5-membered ring. Structure **129** was only seen as a crude product, with relatively low conversion. Therefore, exploration into ethanethiol-derived thioacetals was not pursued.

## 2.3 Ketene Thioacetal Reactivity Scope

### 2.3.1 Ketene Thioacetals in the Literature

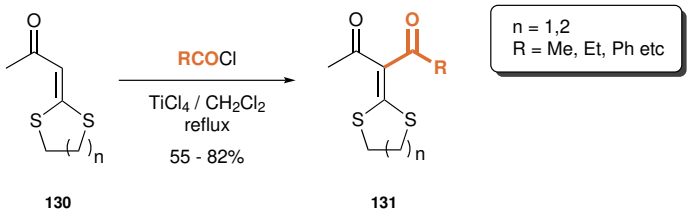
To explore the potential application of the sugar ketene thioacetals in the formation of chiral heterocycles, L-arabinose derivative **95** was reacted with a variety of nucleophiles and electrophiles. It was thought that the resulting anion formed upon attack of the nucleophile/electrophile would be stabilised by the two adjacent sulphur atoms, leading to interesting reactivity. Despite the lack of literature precedence, **95** was reacted with a variety of nucleophiles (**Scheme 52**). However, no electrophilic character was seen, even with very reactive nucleophiles (e.g sodium azide), suggesting

nucleophilic character of the ketene thioacetal functionality.



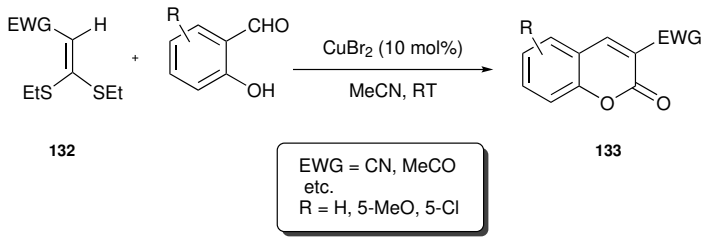

**Scheme 52** The screening of **95** with a variety of nucleophiles. Nucleophilic reactivities for each nucleophile are quoted below each structure.[95]

There is literature precedence that demonstrates the nucleophilic behaviour of ketene thioacetals. Liu *et al.* found that the olefinic functionality can be activated by the presence of alkylthiol groups through p-π conjugation, thus making the α-carbon more nucleophilic than ethylene.[96] A wide variety of versatile intermediates may be formed through functionalisation at the alpha position, such as α-oxo ketene thioacetal **130**, which serve as 1,3-electrophilic synthons.[97] Fu *et al.* demonstrated multiple useful transformations including acetylation (**Scheme 53**). Ketene thioacetals may be functionalised to create a diverse array of substrates, incorporating functional groups such as sulphonyl, chloro/bromo/iodo and silyl.



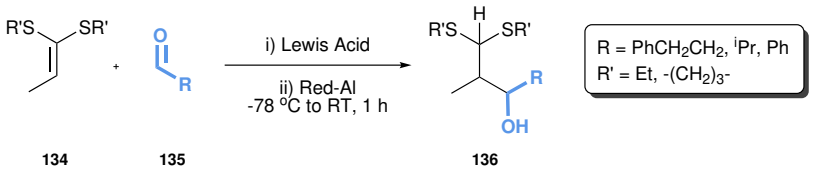

**Scheme 53** Acetylation of ketene thioacetals under Lewis acidic conditions in research by Fu *et al.*[97]

The group were also able to use their α-oxo ketene thioacetals to form coumarin derivatives and a variety of useful substituted products (**Scheme 54**).[98]



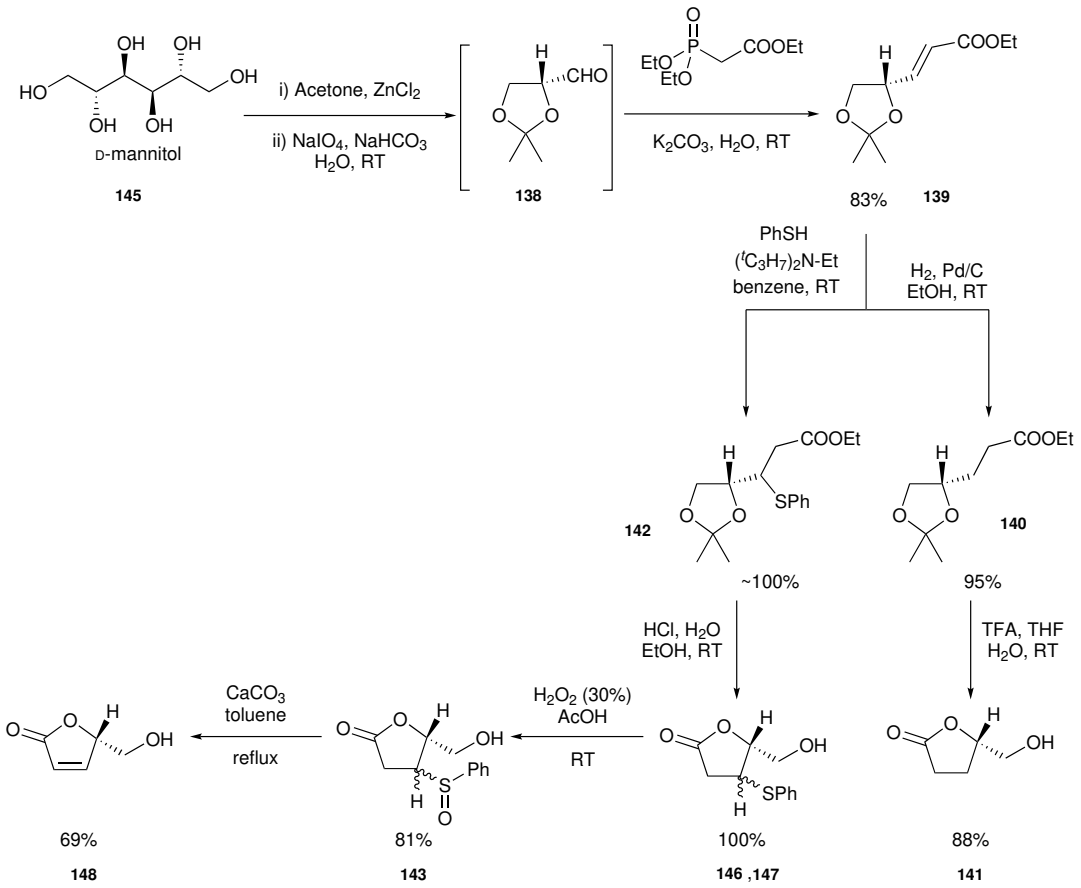

**Scheme 54** Synthesis of coumarin derivatives from ketene thioacetals in research by Yuan *et al.*[98]

Literature reactions involving dimethyl and diethyldithioacetal ketenes show nucleophilic character for this functionality. When exposed to aldehydes under Lewis acidic conditions and in the presence of a reducing agent, the ketenes form β-hydroxy-thioacetal adducts (**Scheme 55**).[99]




**Scheme 55** The formation of β-hydroxy dithioacetals from dithioacetals and aldehydes under Lewis acidic conditions, in research by Saitoh *et al.*[99]

Takano *et al.* reported the synthesis of chiral lactone species from chiral starting material D-mannitol, in a one-pot sequential procedure (**Scheme 56**).[86] This method involves four steps from the sugar to a cyclised lactone species. The pathway includes iodination, hydrogenation, Horner-Wadsmorth-Emmons reactions, epimerisation and other reactions with poor atom economy.[100]



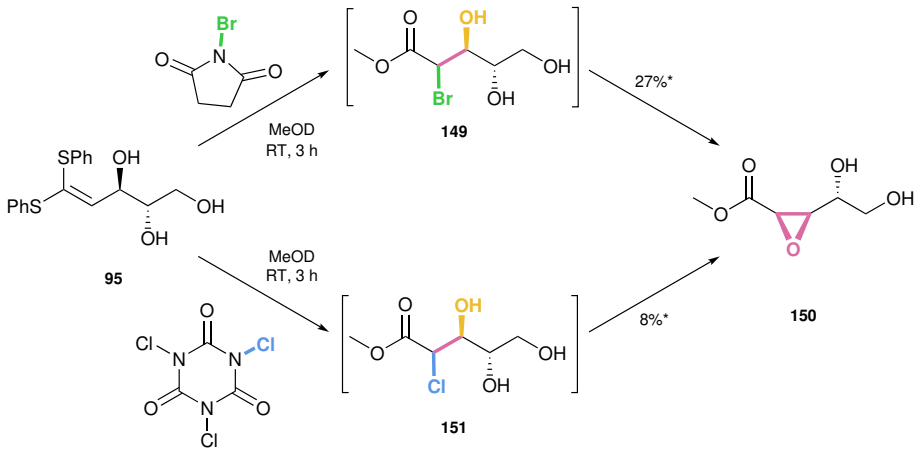

**Scheme 56** Synthesis of optically active lactone species from D-mannitol, published by Takano *et al.*[86]

Cyclisation and oxidative cleavage of the sugar gives the optically active lactone precursors, and provides a possible route to useful materials in large-scale synthesis. However, yields of the final products were moderate considering the number of steps involved in the synthetic route. Not only is this route's atom economy poor, it requires harsh reagents in work-up steps, such as hydrogen peroxide, as well as the use of carcinogenic reaction solvents (e.g. benzene). However, this work does provide a possible synthetic route for creating (*S*)-hydroxy-2-penten-4-olide **148** and other analogues, but leaving areas for research in producing such molecules in a more sustainable and efficient way.

## 2.3.2 Electrophilic Reactions

In order to begin our investigation into the nucleophilic reactivity of our sugar-derived thioacetal ketenes, we initially exposed **95** to electrophilic halogenating agents. Reaction with electrophile *N*-bromosuccinimide (NBS) gave a monobrominated methyl ester intermediate **149** (**Scheme 57**) which readily cyclised to form epoxide

species **150** (determined via $^1$H NMR fine coupling). The epoxide product was unstable to column chromatography and was unable to be isolated. A similar reaction took place with chlorinating agent trichloroisocyanuric acid, producing epoxide **150**. This reactivity confirmed the nucleophilic character of the alkene and led to further investigation.

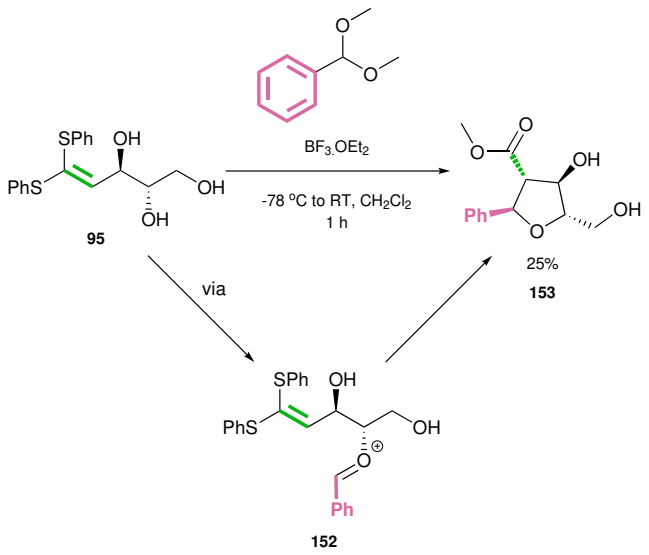



**Scheme 57** The halogenation of L-arabinose ketene thioacetal, resulting in subsequent elimination to give an epoxide methyl ester. Yields shown for top and bottom routes respectively, NMR yields indicated by an asterisk.

### 2.3.3 Lewis Acid-Catalysed Reactions

Lewis acidic conditions were applied to L-arabinose ketene thioacetal **95**. However, no β-hydroxy acetal was produced (as in **Scheme 55**), with no selective reaction taking place. To encourage nucleophilic attack, a dimethylacetal was used in the place of an aldehyde, to act as an activated aldehyde (**Scheme 58**). It was thought that this analogue would offer more selectivity via coordination prior to attack (intermediate **152**), encouraging intramolecular attack. This yielded the functionalised, cyclised methyl ester **153** in low yield (**Scheme 58**). Unexpectedly, only a single isomer was recovered from the reaction, suggesting stereoselectivity. This may be the case because of the orientation of the protons based on the stereochemistry of the sugar, thereby driving attack preferencially onto one face of the molecule. It is thought that the mechanism proceeds via the attack of 4-OH to give intermediate **152**. Electron-density from the sulphur then drives the attack of the coordinated acetal by the alkene, followed by methanolysis of the dithiacetal to give the methyl ester.

Initially, benzaldehyde was used and in an attempt to improve the yield, *para*-

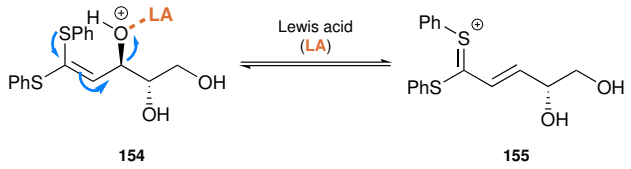



**Scheme 58** Formation of cyclised methyl ester **153**, via hydrolysis of *in situ* β-methoxylacetal with methanol.

anisaldehyde dimethylacetal was tested as an electrophilic coupling partner with **95**. However, upon analysis of the reaction mixture, a complex mixture of products was observed by $^{1}$H NMR. From here, the effect of electron-withdrawing substituents on the benzene ring of the acetal should be explored in order to widen the substrate scope of the reaction. As well as attempting the reaction with electron-withdrawing substituents, less sterically-demanding substrates should also be tried. For example, aliphatic aldehydes/acetals offer less-bulky alternatives which could possibly increase the likelihood for attack at their electrophilic centres (as well as subsequent cyclisation).

Under Lewis-acidic conditions, it is likely that the ketene thioacetals of the sugars exist in an equilibrium between a ketene thioacetal form and a thionium ion (**Scheme 59**). In the presence of a Lewis acid, the β-hydroxyl group is activated (structure **154**), enabling formation of a conjugated thionium ion (structure **155**) which could react with a nucleophile. This reactivity may explain reactivity observed previously (**Scheme 58**).

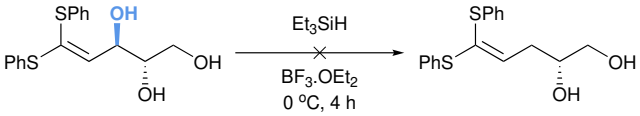
In work by Ewing and Robins,[101] it was shown that treatment of sugars with triethylsilane in the presence of a Lewis acid caused selective reduction of activated hydroxyl groups. It was thought that under the same conditions, thionium ion formation and subsequent reduction might take place with ketene thioacetals (**Scheme 60**). To test this theory, L-arabinose ketene thioacetal was subjected to the




154 155

**Scheme 59** Putative equilibrium of ketene thioacetal **156** with a conjugated thionium ion, under Lewis acid conditions.

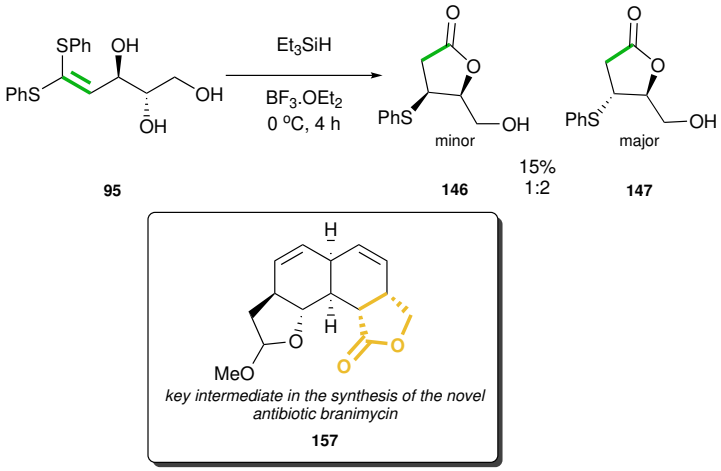
literature conditions[101] in the hope of forming a selectively-reduced sugar at the 3-position. The major products of the reaction were lactones, formed as a result of intramolecular nucleophilic attack, and the reduced sugar was not formed (**Scheme 61**). Chiral lactones **146** and **147** were isolated from the mixture in a low yield in an initial finding. They are interesting structures which may be useful in the stereoselective synthesis of branimycin precursor **157**, as shown by their structural similarity.




95 158

**Scheme 60** Attempted reduction of L-arabinose ketene thioacetal under literature-reported conditions.[101]

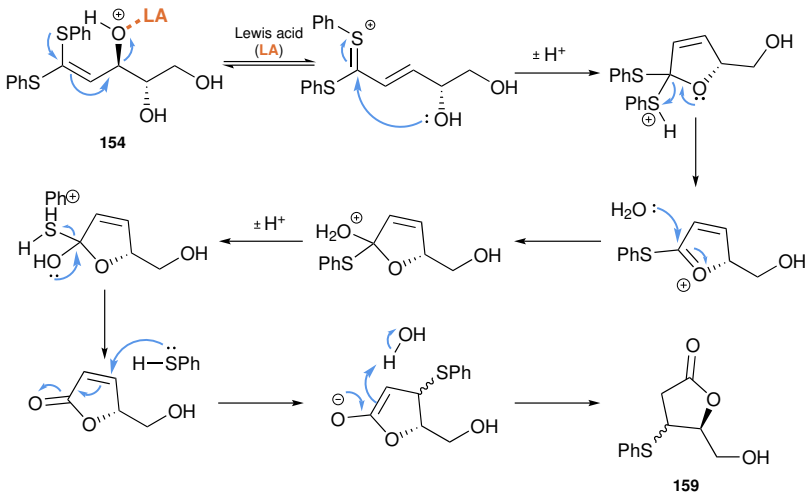
After purification, the lactone species were recovered as a mixture of two isomers, with no success in separation of the two. The lactone products (**146** and **147**) (**Scheme 61**) exist in the literature with only one preparation procedure consisting of six steps, as mentioned in (**Scheme 56**).[85,86]




95 146 147 157

**Scheme 61** Reaction of ketene thioacetal **95** with triethylsilane under Lewis-acid conditions.[101] Structurally similar arabinose-derived lactone scaffold highlighted in yellow.

Despite the low yield of our recently developed procedure, lactones **146** and **147** are created in only three steps from an abundant sugar starting material. It is obvious from the structure that no reduction is taking place, therefore, the reaction was repeated in the absence of triethylsilane, giving a slight increase in selectivity and yield. For this reason, it is expected that the reaction proceeds through the initial formation of a thionium ion (**Scheme 59**) which then allows intramolecular attack and subsequent hydrolysis of the thiophenol groups (**Scheme 62**).



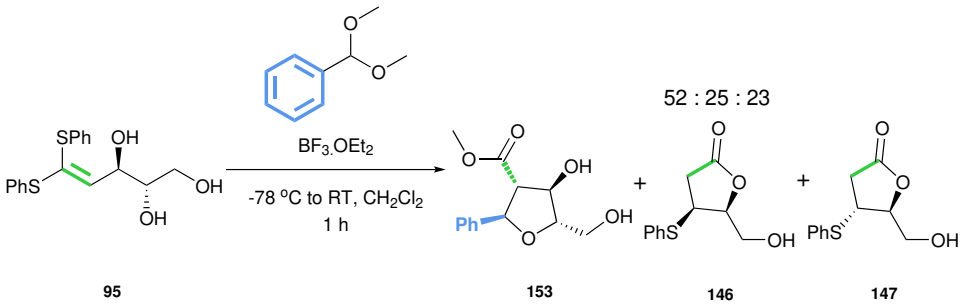

**Scheme 62** Proposed mechanism for the formation of lactones **159** from L-arabinose derivative **154**.

**Table 1** A table showing the alteration of conditions in order to optimise formation of lactones **146** and **147** (**Scheme 61**) from **95**. NMR yields (calculated via addition of an internal standard) are shown by an asterisk.

| Entry | Lewis acid | Eq. | Solvent | Yield/ % |
|---|---|---|---|---|
| 1 | $BF_3 \cdot OEt_2$ + $Et_3SiH$ | 4 | $CH_2Cl_2$ | 15 |
| 2 | $BF_3 \cdot OEt_2$ | 4 | $CH_2Cl_2$ | 17 |
| 3 | $AlCl_3$ | 4 | $CH_2Cl_2$ | 2 |
| 4 | $In(OTf)_3$ | 4 | $CH_2Cl_2$ | 37 |
| 5 | $BF_3 \cdot OEt_2$ | 4 | MeCN | 25 |
| 6 | $BF_3 \cdot OEt_2$ | 1 | MeCN | 28 |
| 7 | $In(OTf)_3$ | 1 | MeCN | n.r |
| 8 | $In(OTf)_3$ | 1 | THF | 38 |
| 9 | $BF_3 \cdot OEt_2$ | 1 | THF | 25* |
| 10 | $BF_3 \cdot THF$ | 1 | THF | 18* |
| 11 | $BF_3 \cdot OEt_2$ + dTBP | 2 | THF | 10* |
| 12 | TMSOTf | 1 | THF | 23* |
| 13 | $BF_3 \cdot OEt_2$ | 0.5 | neat | 28 |
| 14 | $In(OTf)_3$ | 1.4 | neat | 41 |
| 15 | $In(OTf)_3$ | 2.5 | neat | 53 |
| 16 | $Fe(OTf)_3$ | 4 | neat | n.r |

A variety of Lewis acids and solvents were tested for their effect on the yield of the lactone-forming reaction shown in (**Scheme 61**), as shown in **Table 1**. $BF_3 \cdot OEt_2$ offered the cleanest crude mixture when analysed by $^1$H NMR. An issue of solubility was evident with solid Lewis acids such as $AlCl_3$ and $In(OTf)_3$ (entries 3, 4 and 7), which in the case of $In(OTf)_3$ was improved through alteration of solvent (entry 8). A change of solvent from $CH_2Cl_2$ to THF not only improved the solubility, but also meant that a greener solvent could be used for the reaction. Liquid Lewis acids TMSOTf and $BF_3$-derivatives (entries 5-6 and 9-13) had no issues with solubility and gave relatively clean crude mixtures, but low conversion to the lactone products. Upon close inspection, it was noticed that the lactone products were formed upon concentration of the solution *in vacuo*. Quenching the reaction with base ($NEt_3$) prior to concentration results in no lactone formation and only the presence of starting materials.

Once this Lewis acid-dependent cyclisation was identified, the $^1$H NMR spectrum of the crude reaction products for the reaction of **Scheme 58** were inspected for the presence of lactone products **146** and **147**. It was found that an equal quantity of the lactones as the ester were also produced during the dimethylacetal reactions (**Scheme 63**), explaining the lack of selectivity observed previously.



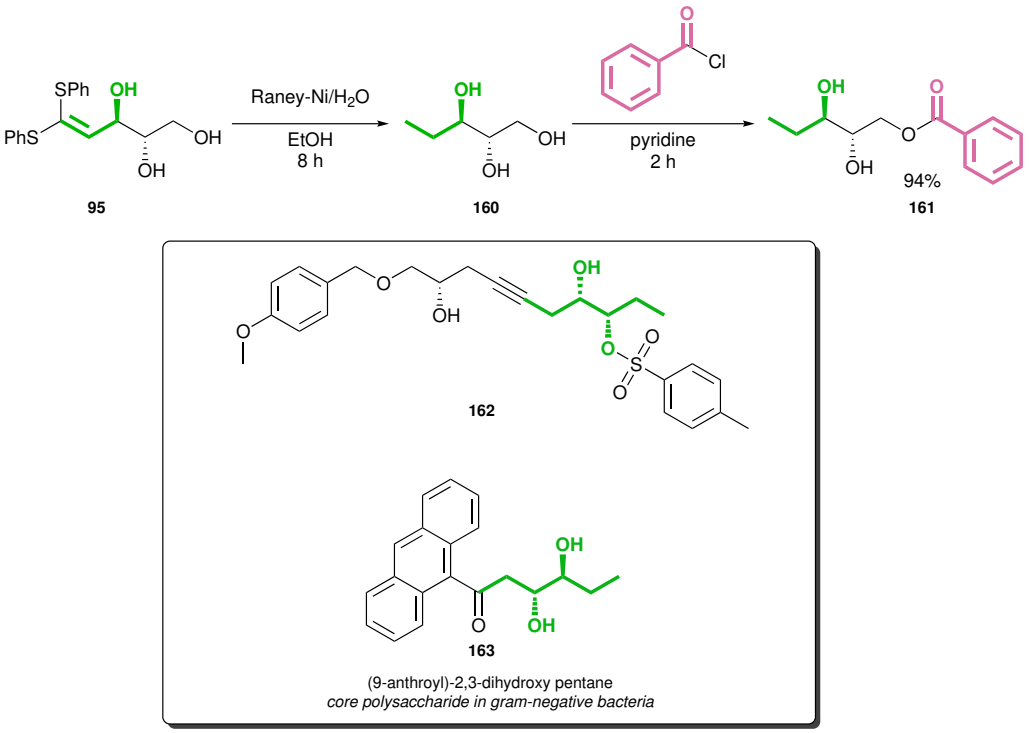

**Scheme 63** Revised reaction scheme for mixture of **95** with Lewis acid and a dimethylacetal, yielding a methyl ester and lactone species **146** and **147**.

From this insight, it should be possible to alter the conditions used in dimethylacetal cyclisation to form **153** more selectively in future research.

### 2.3.4 Reduction Reactions

Following selective dehydration of thioacetal **70** to yield ketene thioacetal **95**, reduction was carried out using Raney-Ni (**Scheme 64**). Deprotection of the thioacetal group is often carried out by hydrolysis using heavy-metal reagents such as mercury(II) salts, or by oxidation, due to the stability of thioacetals to acid and base.[102]

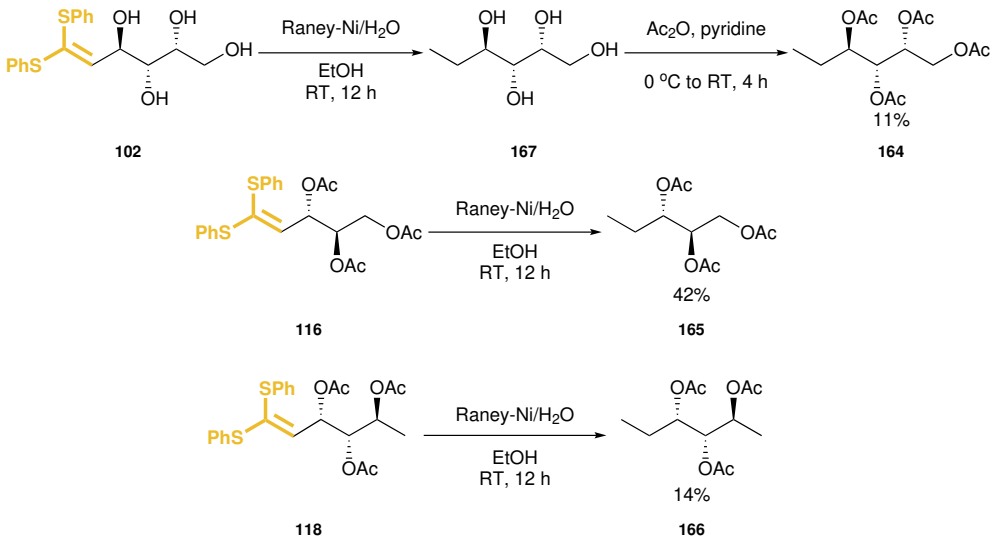
However, hydrolysis would yield the aldehyde moiety, possibly leading to cyclisation of the sugar backbone once again. Use of Raney-Ni is not only a less-toxic route, but yields a less reactive alkane species. The reduction of the thioacetal and alkene functionalities with Raney-Ni produced a hygroscopic triol **160**. This was isolated as ester **161** in excellent yield after subsequent benzoylation to ease the purification process (**Scheme 64**). Structures of this form are useful in the synthesis of natural products as a source of chiral ethyl and alcohol groups, in compounds such as eicosatetraenoic acid,[103] polysaccharides found in gram-negative bacteria,[104] and in cholesterol side-chains (dihydroxyvitamins).[105]




**Scheme 64** Reaction scheme showing the reduction of L-arabinose ketene thioacetal **95** using Raney-Ni, followed by benzoylation to give **161**. Chiral motifs found in organic molecules are highlighted.

In the same manner, protection and subsequent reduction was carried out on the 6C sugar ketene thioacetal derived from D-galactose. Initially, benzoylation of the sugar was carried out to ease the purification process, however, low proportions are protection were achieved. Previous successes with acetylation of sugar derivatives (**Scheme 42**) meant this method of protection was used as an alternative. Reaction with Raney-Ni followed by immediate acetylation gave polyol **164**. The low yield of this reaction may be improved through use of a large excess of acetic anhydride in order to force formation of a fully acetylated product, which should be carried

out in future research. Analogous reduction of the corresponding D-gal, D-rib and L-rha derivatives was conducted in order to obtain the acetylated polyols differing in specific stereochemistry (**Scheme 65**). Despite the low yields, these selectively-reduced polyols (compounds **164**, **165** and **166**) are evidence of sugar utility in short pathways to novel, useful products from renewable starting materials in as little as four steps.

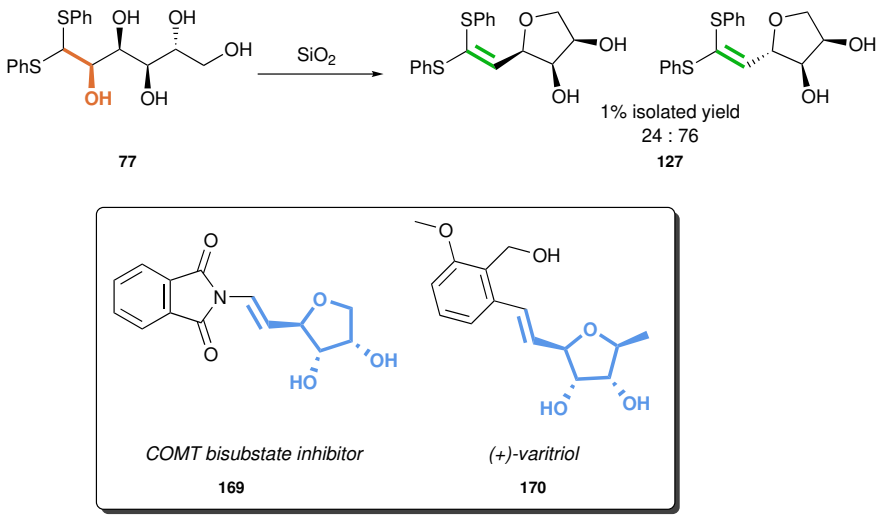



**Scheme 65** The reduction of D-galactose, D-ribose and L-rhamnose ketene thioacetals, **168**, **116** and **118** respectively, using Raney-Ni.

Further investigation showed that the hexose-derived ketene thioacetals, such as **77** were unstable under acidic conditions, tending to decompose during the purification process when purifying via flash chromatography. Purification was henceforth carried out using recrystallisation. Some interesting by-products of the decomposition of the D-glucose derivative were isolated, such as THFs **127** (**Scheme 66**).

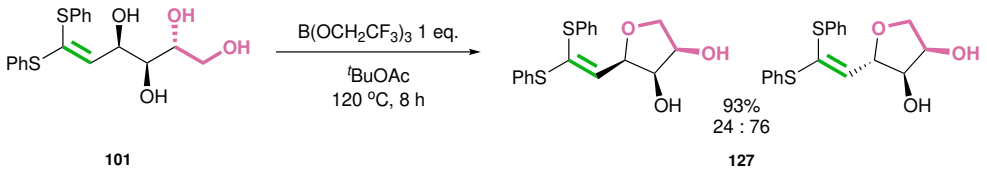
Interestingly, glucose-derived compound **127** bears a structural resemblance to anti-tumour natural product (+)-varitriol **170**[107] and to the backbone catechol-O-methyltransferase (COMT) bisubstrate inhibitor **169** (**Scheme 66**).

It is known that borate esters such as $B(OCH_2CF_3)_3$ can assist in condensation reactions, for example to promote direct formation of amides.[108] In order to try and selectively produce the cyclised structures, borate ester $B(OCH_2CF_3)_3$ was used to assist the condensation and cyclisation of **101**, (**Scheme 67**). At reflux, in the presence of the aerated borate ester,[108] complete conversion of **101** occurred with selective reactivity, to produce **127**. The THFs were seen in an identical ratio of the two diastereomers as previously isolated, as described in **Scheme 66**. In both




**Scheme 66** Isolated cyclised THFs, formed upon purification of D-glucose ketene thioacetal. Structurally similar aspects of natural products catechol-O-methyltransferase (COMT) bisubstrate inhibitor,[106] (+)-varitriol and its derivatives[107] are highlighted.

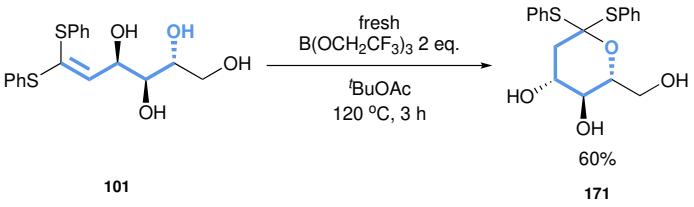
cases, the cyclised diastereomers could not be separated by chromatographic methods.




**Scheme 67** The cyclisation of D-glucose ketene thioacetal upon treatment with aerated borate ester $B(OCH_2CF_3)_3$ at reflux in $^t$BuOAc.

However, upon repetition, it was found that new batches of the borate ester failed to produce the same alkenyl THF product. Instead, chiral THP **171** was made in a reasonable yield under unoptimised conditions (**Scheme 68**). It is possible that over time, borate ester $B(OCH_2CF_3)_3$ hydrolysed to boric acid and trifluoroethanol and that this is responsible for the cyclisation stated in **Scheme 66**. This would be feasible considering the acidic nature of $SiO_2$ and the previous reactivity seen. However, the impurities that may have caused this reactivity remain undetermined. In order to rule out the possibility that residual $K_2CO_3$ present from the formation of the starting material was not catalysing the newfound cyclisation, excess $K_2CO_3$ was added in a repeat reaction with fresh borate ester, with no reaction seen and full recovery of starting material.

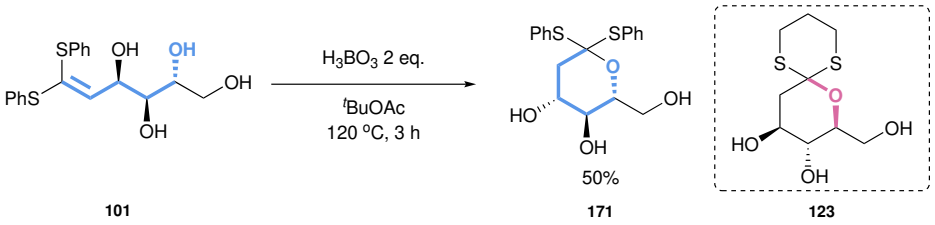
A fresh batch of the catalyst was made, yielding a different result (**Scheme 68**).




**Scheme 68** Reaction scheme showing the cyclisation of D-glucose ketene thioacetal upon treatment with fresh borate ester $B(OCH_2CF_3)_3$ at reflux in $^t$BuOAc.

It was found that the cyclised product **171** was formed via attack of the C-5 alcohol onto the quaternary centre to yield a THP. Although different to the desired THF, this structure presents an interesting route to chiral THP's and subsequent hydrolysis of this could lead to a 6-membered lactone, or a THP if the thioacetal is removed.

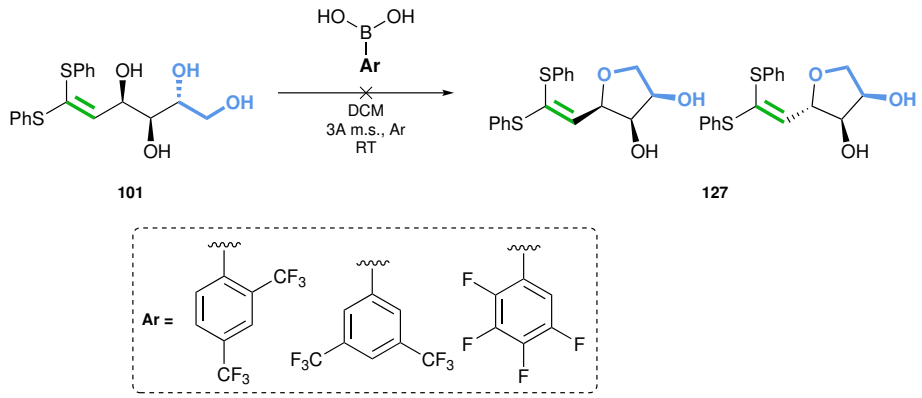
The reaction of boric acid with glucose-derived ketene thioacetal **101** was carried out with the idea that a similar cyclisation would occur to that shown in **Scheme 68**. It was found that cyclised product **171** formed via the attack of the C-5 alcohol onto the quaternary centre to yield the THP, in an equally efficient method (**Scheme 69**). This novel THP resembles the cyclised product seen previously (**Scheme 46**) with a bidentate thiol protecting group (highlighted).




**Scheme 69** Reaction scheme showing the cyclisation of D-glucose ketene thioacetal upon treatment with boric acid at reflux in $^t$BuOAc. Similar cyclisation product **123** is highlighted.

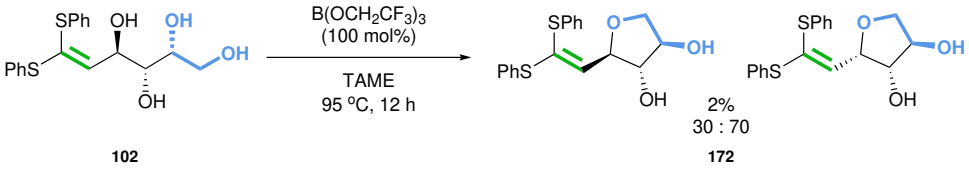
Catalytic amounts of boronic acids are also able to promote activation of alcohols for use in rearrangement chemistry and dehydration reactions.[109,110] This chemistry was applied to our D-glucose-derived thioacetals using a variety of boronic acids (**Scheme 70**). However, even in excess, cyclisation did not take place in the presence of the boronic acids, with only starting materials recovered in all cases.

With both boronic acids and the borate ester, different solvents (such as DCM, MeCN, TAME and $^t$BuOAc) were tested for their effect on the success of the reaction, it was found that $^t$BuOAc was most optimal for THF formation. In order to widen the applicability of the THF formation, it was tested if the same cyclisation would




**Scheme 70** The cyclisation of D-glucose ketene thioacetal upon treatment with boronic acids.

take place with the corresponding ketene thioacetal of D-galactose. Under the same conditions as with the D-glucose derivative, a complex mixture of products was produced with no THF isolated. Alteration of the solvent to *tert*-amyl methyl ether (TAME) allowed reflux at a lower temperature, leading to isolation of the product in a very low yield (**Scheme 71**). The reduced activity could be due to the alternative stereochemistry at the 4-position of the sugar, which may influence the angle at which the secondary alcohol can attack, thereby altering the likelihood of THF formation.




**Scheme 71** The cyclisation of D-galactose ketene thioacetal upon treatment with borate ester $B(OCH_2CF_3)_3$ at reflux in TAME.

Unfortunately, due to the small quantity of **172** produced, not all data was obtained for these compounds. Future work would involve optimisation of this procedure and carrying out the reaction on a larger scale to fully characterise the THF products. As a mixture of stereoisomers were obtained following each reaction and recrystallisation of the mixtures may allow separation of the products and properties/reactivity of the individual analogues to be determined. Reduction of the cyclised D-glucose and D-galactose derivatives (e.g using Raney-Ni) could be carried out, to yield an alkane tethered to a chiral THF.

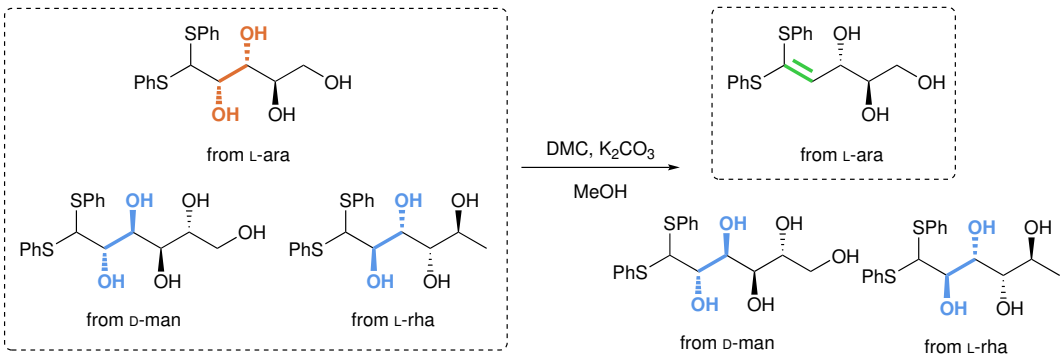
## 2.4 Sugar Selectivity Towards Thioacetal Ketene Formation

### 2.4.1 Sugar-Beet Pulp Biomass

Sugar beet pulp is a renewable source of sugars, and by weight, mostly contains uronic acids, along with large percentages of pentose and hexose sugars.[1] To access the sugars, pulp polysaccharides are fractionated into pectin, hemicellulose and cellulose. The pectin fractions are rich in arabinose, galactose and uronic acids, and the hemicellulose fibres rich in xylose and glucose (**Figure 12**).

An aim of this research is to carry out the sugar manipulation chemistry in as few steps as possible. Therefore, it will be investigated if our protection and dehydration reactions can be performed whilst exhibiting selectivity between sugars based on their stereochemistry.

Initially, a mixture of thioacetals were chosen that were expected to exemplify selectivity between *syn* and *anti* sugars. For this, thioacetals of L-ara, D-man and L-rha were combined to determine if selectivity between the sugars occurred *in situ*. In theory, only L-ara should dehydrate. Due to its *syn* stereochemistry at positions 1' and 2', L-ara can readily form the carbonate intermediate at that position and subsequently dehydrate. D-man and L-rha should display little-to-no conversion to the ketene thioacetals due to their *anti* stereochemistry at positions 1' and 2'.




**Scheme 72** Initial selectivity study where 1,2-*syn* sugar L-ara and 1,2-*anti* sugars D-man and L-rha were exposed to the established dehydration conditions.

As previously, the *anti* sugars, D-man and L-rha, showed slight conversion to the ketene thioacetal, the maximum conversion being 14% for D-man in 1.5 eq. of DMC (entry 1 of **Table 2**). However, largest conversion to the corresponding thioacetal

ketene was seen for L-ara, with 51% of the starting material being converted to the product (entry 1).

**Table 2** A table showing the conversion (%) of sugar thioacetals to their corresponding ketene thioacetals, with varying amounts of DMC.

| Entry | Amount of DMC | from L-ara | from L-rha | from D-man |
|---|---|---|---|---|
| 1 | 1.5 eq. | 51 | 5 | 14 |
| 2 | 1.5 eq. | 39 | 0.4 | 2 |
| 3 | 8 eq. | 30 | 5 | 3 |
| 4 | 8 eq. | 23 | 0.4 | 0.4 |

When increasing the amount of DMC in the reaction, there appeared to be more side product formation, and lower proportions of ketene thioacetals for all three sugars (entries 3 and 4). Therefore, henceforth, the amount of DMC was limited to 1.5 eq. Although not proceeding with as high yields as in isolated reactions, dehydration of the L-ara thioacetal is still favoured. The preference for L-ara is highlighted, visually, in **Figure 11**.

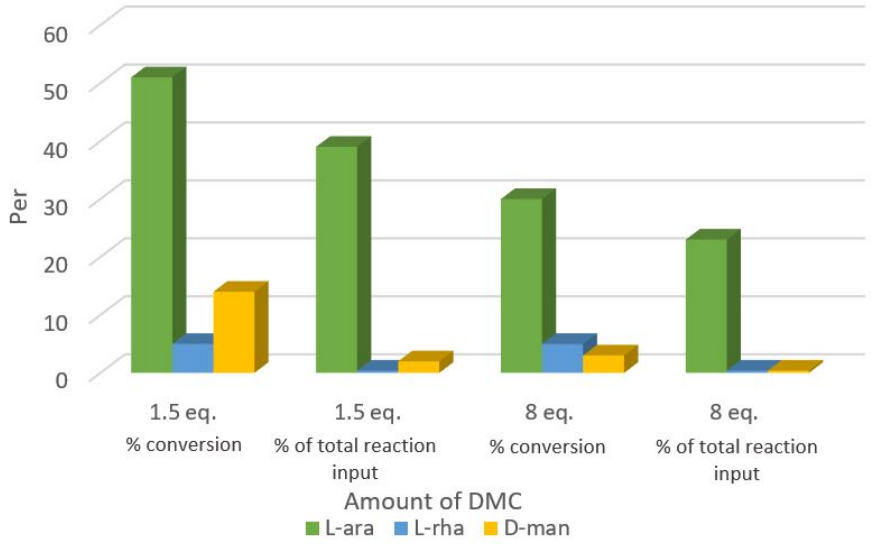
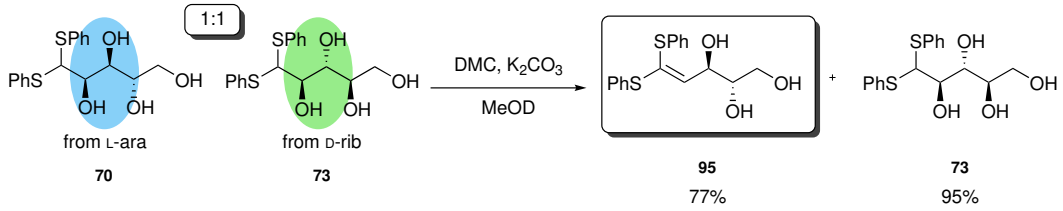



**Figure 11** A bar chart showing data from **Table 2**, highlighting the conversion (%) of sugar thioacetals to their corresponding ketene thioacetals, with varying amounts of DMC.

It is thought the low conversion of L-ara thioacetal to the corresponding ketene thioacetal may be due to the formation of side products and the consumption of reagents in alternative reaction pathways. Further analysis of the NMR data for the reaction showed traces of lactone formation, with at 2:1 ratio of L-ara ketene thioacetal to lactone **173**, as seen when exposed to Lewis acids (**Scheme 63**).

To further the analysis of the selective dehydration, pentose sugars with a *syn*

and *anti* relative stereochemistry at the 2- and 3- positions were used to observe a difference in reaction progress. Firstly, a 1:1 mixture of L-arabinose and D-ribose thioacetals (**70** and **73** respectively) were stirred under the basic dehydration conditions and conversion monitored over time using an internal standard (**Scheme 73**).



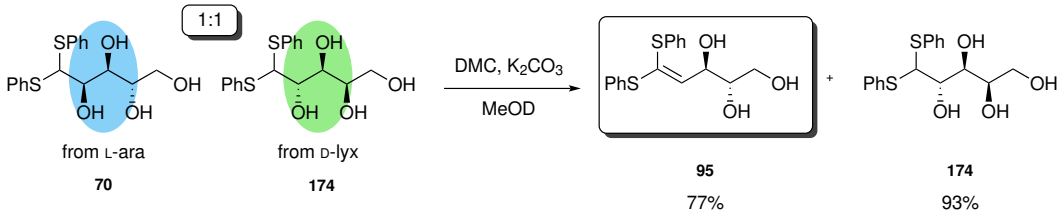

**Scheme 73** A 1:1 mixture of L-arabinose and D-ribose thioacetals under basic conditions, highlighting the expected selectivity.

It was found that within 2 h, L-arabinose began to selectively dehydrate at the 2-position, with very little depletion in the amount of D-ribose thioacetal. Specifically, 82% of **70** was depleted, with 95% of **73** remaining in solution. Due to the dehydration products of both sugars being enantiomers of each other, they are indistinguishable via NMR. Therefore, conversion of **70** to the ketene thioacetal cannot be measured directly via integration of the alkene peak. We have allowed the assumption that 95% of D-rib derived starting material was remaining, deducing that L-ara was converted to the alkene (**95**) in a yield of 77%. Controls were carried out in the absence of **70**, observing that under the same conditions (DMC and $K_2CO_3$ now in excess), 83% of D-rib derived starting material was remaining.

In order to more accurately measure the conversion of *syn* vs *anti* sugars to their corresponding ketene thioacetal, sugars which would dehydrate to give diastereomers were used. Sugar D-lyxose was chosen based on its stereochemistry. As it is an *anti* sugar, we expected that little to no dehydration should take place, and if this did occur, then the product will be distinguishable by NMR analysis.

The sugars were mixed at a 1:1 ratio to allow for measurable conversion via an internal standard (**Scheme 74**). It was expected that only the sugar with *syn* stereochemistry will dehydrate at the 2- position due to a more accessible elimination of the carbonate in the intermediate. The thioacetal of pentose sugar lyxose was synthesised, giving D-lyxose diphenyldithioacetal in excellent yield (95%) following a literature procedure.[78]

It was found that within 2 h, arabinose-derived ketene thioacetal began to form, with depletion of the starting material. After 24 h, 93% of lyxose thioacetal remained




**Scheme 74** A 1:1 mixture of L-arabinose and D-lyxose thioacetals under the optimised basic conditions.

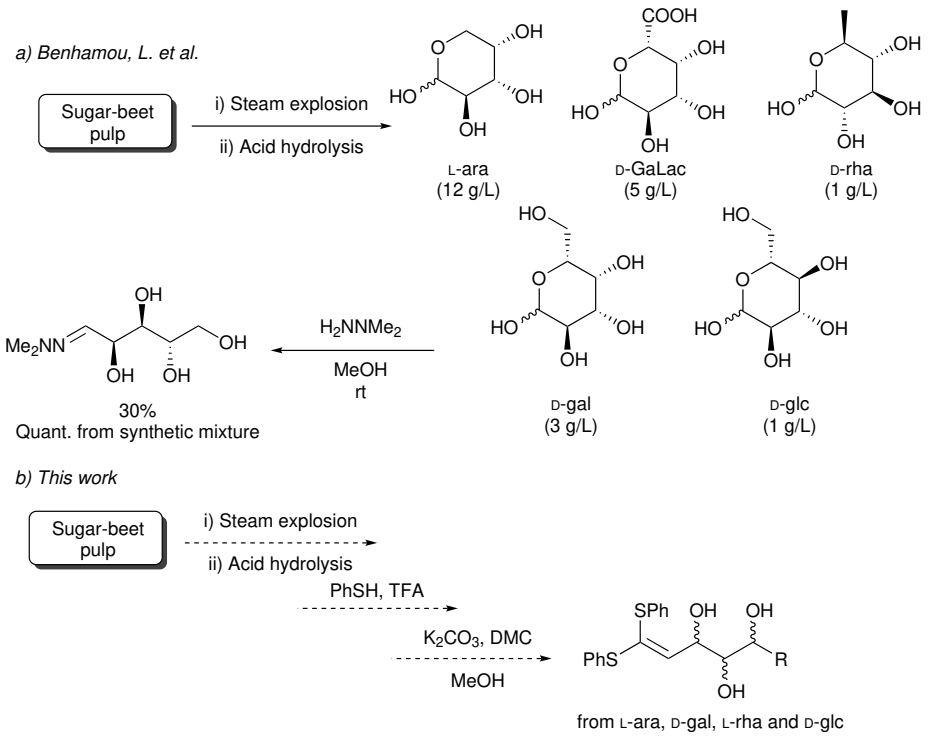
in solution, and with loss accounted for by reaction with the DMC present. Over this same period of time, 77% conversion of arabinose thioacetal was converted to the ketene thioacetal with 10% starting material remaining. It is worth nothing that there is slightly lower yield than for the isolated dehydrated reaction. This data clearly shows selectivity of the *syn*-sugar L-ara over *anti*-sugar D-lyx derivatives for dehydration under these specific conditions. Such selectivity may be very useful in cases whereby sugars cannot be separated from one another, or extra steps may be avoided in order to limit time and resources for sustainable synthesis.

### 2.4.2 Pentose Sugar Extraction

Work carried out by Benhamou, L. *et al.* in 2019 took a solubilised sample of sugar-beet pulp and selectively synthesised the hydrazone of pentose sugar L-arabinose.[2] This presented a scalable synthesis of chiral functionalised tetrahydrofuran building blocks from raw materials in a sustainable way (**Scheme 75a**).

An aim of this work is to follow an analogous pathway to form the sugar thioacaetals from the sugar beet mixture (**Scheme 75b**). Once in their open-chain form, it is hoped that selective reactions with *syn* and *anti* sugars, should only form ketene thioacetals of *syn* sugars. This would provide a separation method of *syn* and *anti* sugars thioacetals from the sugar-beet pulp in only a few steps.

Following the same strategy as presented by Benhamou *et al.*, it is proposed that sugar beet pulp would be solubilised, subjected to steam explosion, followed by acid hydrolysis, which should give a mixture of five different sugars and excess $NaSO_4$ (a byproduct of the hydrolysis process) (**Scheme 75b**). It was the intention for the mixture of sugars to be exposed to thioacetal forming conditions, washed to remove excess thiophenol and TFA, then subjected to dehydration conditions to selectively form ketene thioacetals of *anti*-sugars.




**Scheme 75** *Part a* - The synthesis of L-arabinose hydrazone from a solubilised sample of sugar beet pulp, as reported by Benhamou *et al.*[2] *Part b* - The proposed synthesis of L-arabinose thioacetal ketene from a solubilised sample of sugar beet pulp.

In order to investigate this, a representative ratio of sugar thioacetals (**Figure 12**) from sugar beet pulp was mixed under dehydration conditions to highlight the regioselectivity of the *syn*/*anti* mechanistic preference.

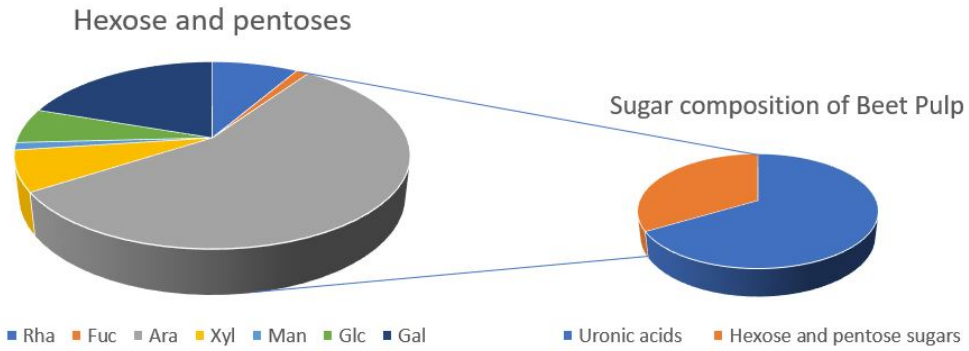
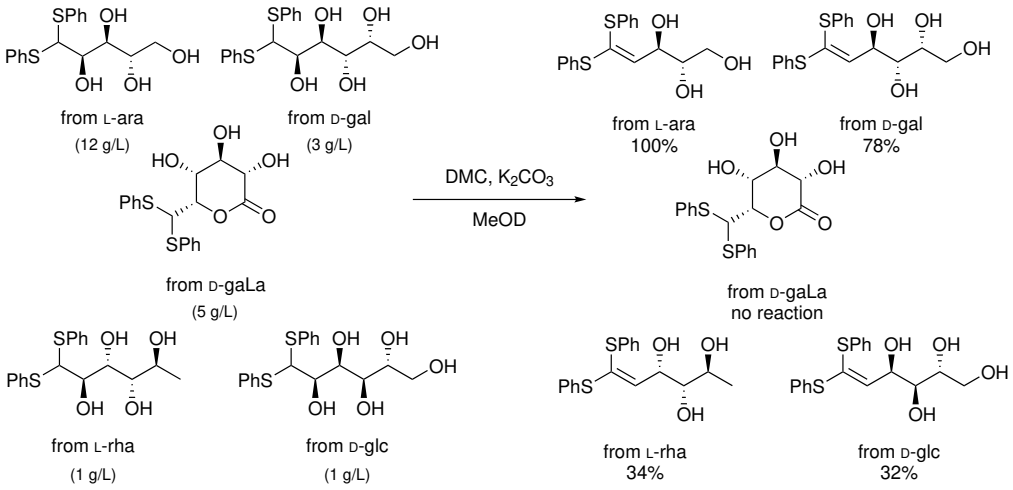



**Figure 12** Pie charts showing the relative quantities of sugars in the sugar beet pulp.[1]

As the thioacetalisation step can result in complex mixtures for some sugar derivatives, mixture of the sugars already in their open-chain form (as their corresponding thioacetals) were combined and subjected to the basic conditions. This was done to enable reference peaks to be detected in the NMR spectra for easier

classification if we were to conduct the study from the beginning of the pathway. Thioacetals of arabinose, galactose, galacturonic acid, rhamnose and glucose were combined under basic conditions (**Scheme 76**). Conversion to the corresponding thioacetal ketene was effective for 1,2-*syn*-sugars L-ara, D-gal and D-glc, with L-ara showing complete conversion to the alkene.



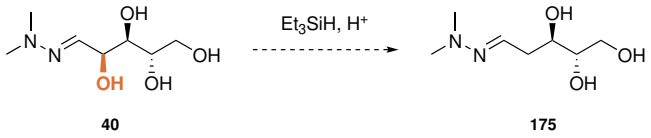

**Scheme 76** Sugar-derived thioacetals under basic condition, giving ketene thioacetals. All yields approximated by NMR analysis via addition of an internal standard.

Due to the overlap of peaks and lack of clarity in the NMR spectra, yields are not highly accurate but give an idea of the selectivity between the sugars. The 1,2-*syn*-sugar derivative of L-rha gave low conversion to the ketene thioacetal as expected, meaning it would likely be removable in an aqueous workup, alongside D-GaLa derivative which was present as unreacted starting material. The hexose and pentose ketene thioacetals have different $R_f$ values and should easily be separable by column chromatography. Therefore, this work presents an efficient way to selectively produce L-arabinose derived ketene thioacetal **95** with minimal purification until the final step. In future work, the entire pathway, from sugar-beet pulp to ketene thioacetals (**Scheme 75b**) would be conducted to determine if this work presents a viable separation method of *syn* and *anti* sugar thioacetals.

## 2.5 Sugar Hydrazones

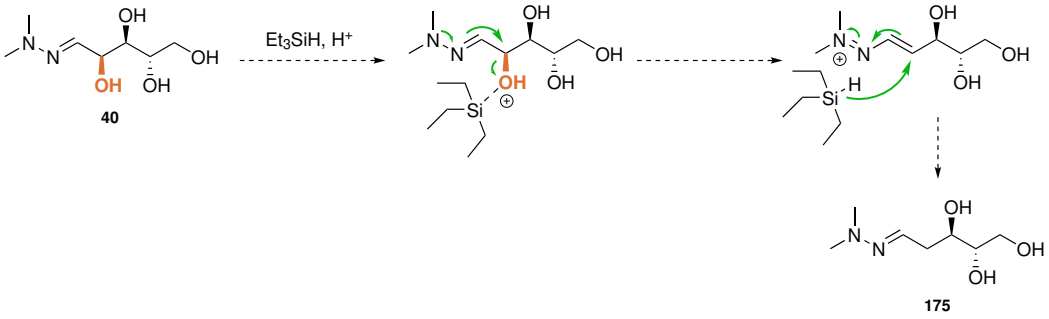
In previous work within the group, it was found that the trapping of sugars in their open-chain form through hydrazone formation led to cyclisation upon treatment with acidic or basic conditions. This work highlights the utility of protected sugar substrates for producing chiral substrates, as shown by Foster *et al.* in the formation of chiral

THFs (**Scheme 16** in Chapter 1.4.2).[69] In addition to this, preliminary investigations into the selective reduction of hydrazones showed that the activation effect of the hydrazone functionality allowed reduction to occur selectively at the $\alpha$ position. It was predicted that if these same hydrazones were treated with a reducing agent such as triethylsilane under acidic conditions, that selective reduction at the $\alpha$-position would occur (**Scheme 77**). This reaction would thereby create a useful chiral aminopolyol after hydrazone reduction.[111]




**Scheme 77** The proposed synthesis of a dimethylhydrazone-1,2,3-triol via reduction of L-arabinose dimethylhydrazone **40**.

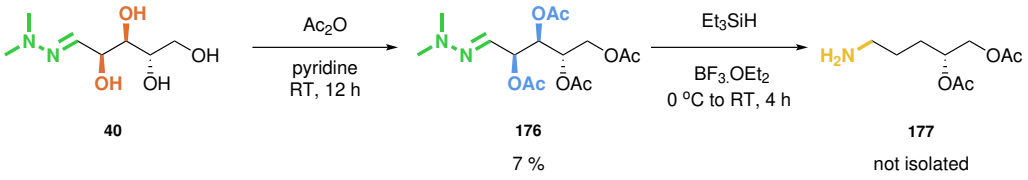
It is thought that the reduction mechanism could proceed via a stepwise, polar mechanism whereby the $\alpha$-hydroxyl group is eliminated under the acidic conditions, followed by attack of a hydride at the same position (**Scheme 78**). The hydrazone moiety is proposed to stabilise the electron density along the sugar backbone before hydride substitution.




**Scheme 78** The proposed mechanism of a dimethylhydrazone-1,2,3-triol production via reduction of L-arabinose dimethylhydrazone **40**.

As demonstrated in previous work,[69] a variety of sugar-hydrazone derivatives can be synthesised (**Scheme 20**). L-Arabinose and L-rhamnose dimethylhydrazone substrates were synthesised in order to test the proposed reactivity. Unfortunately, solubility issues were present upon mixing of the sugars with triethylsilane at low temperatures with acids such as TFA and acetic acid. In order to combat these issues, protection of the alcohols was carried out to make the molecule less polar.

Formation of boronic esters proved unsuccessful, however successful acetylation of **40** was carried out using acetic anhydride in pyridine to afford compound **176** (**Scheme 79**). Reduction was then carried out under the same conditions. The acetylated hydrazone **176** displayed significantly improved solubility in dichloromethane but was prone to elimination of acetyl groups under the acidic conditions. It was also noticed that there seemed to be over-reduction (compound **177**) though the reason for this is unclear. Alternative protecting groups were then explored.

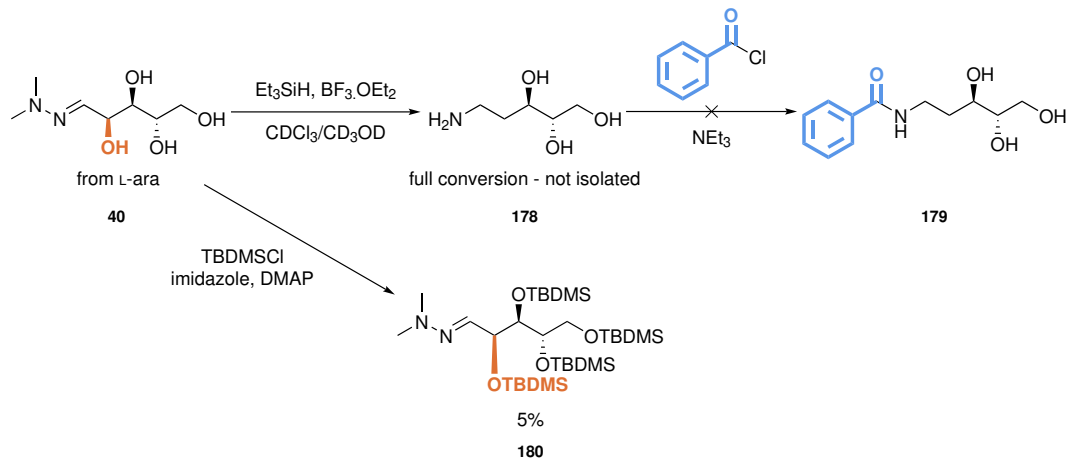



**Scheme 79** Reaction scheme showing the acetylation and reduction of arabinose hydrazone **40**.

The use of Lewis acid, $BF_3 \cdot OEt_2$, gave good solubility with the non-protected **40** and displayed reduction at the $\alpha$-position (**Scheme 80**). Crude analysis of the mixture indicated reduction of the hydrazone and reduction of the $\alpha$-alcohol. Lack of UV active groups and non-staining functionality meant that the reduced product proved difficult to isolate. Benzoylation of aminopolyol **178** was unsuccessful due to the lack of any selective reactivity, with any residual starting material lost during purification (**Scheme 80**). Production of a soluble, more stable protected aminopolyol was also attempted by formation of a silyl ether followed by subsequent reduction, to enable simpler purification. However, formation of a silyl ether, in the case of TBDMS, was unsuccessful. Silylation of the hydrazone was found to be non-selective with poor recovery of the material, and therefore, no further reactions were pursued.

## 2.6 Aminosugar Formation

Heterocycles are some of the most common functionalities present in active pharmaceuticals.[17] These constituents are ideal in the synthesis of biologically-active chemicals based on their utility as isosteres/bioisosteres for carbon structures such as aliphatic functionality or heterocycles.[17] In terms of popularity, nitrogen heterocycles of various geometries and positional combinations are utilised the most, along with




**Scheme 80** The reduction of arabinose hydrazone **40** and subsequent benzoylation to give protected compound **179**. Silylation of **40** to give protected compound **181** in low yield.

oxygen sulphur-containing heterocycles. With 85% of bioactive molecules containing some form of a heterocycle, synthetic routes to form such motifs becomes evermore important.

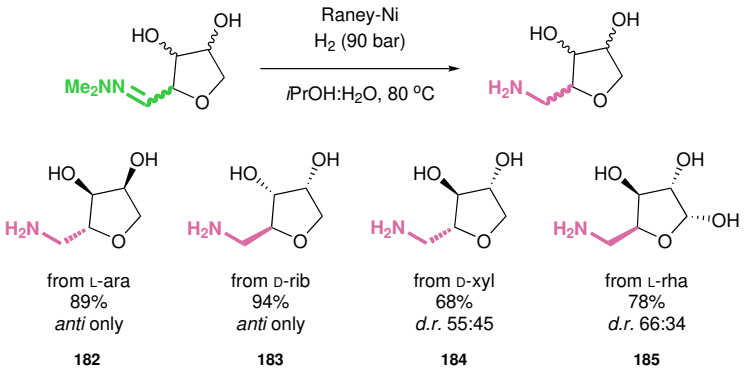
The creation of heterocycles in few steps, especially from organic waste material, allows for the sustainable production of useful bioactive molecules. Although oxygen heterocycles have already been explored in this work, the incorporation of nitrogen has not. It is believed that current methods for cyclisation of sugars shown in this work may be applied to aminosugars to yield nitrogen heterocycles, via chemical or biochemical methods.

## 2.6.1 Nitrogen Incorporation

### 2.6.1.1 Chemical Methods

Research within the group, conducted by R. Foster, showed that nitrogen functionality in sugars can readily be accessed, in their case, via hydrazone formation and subsequent reduction to the amine, on a variety of sugar-derived THFs (**Scheme 81**).[69,2] They were able to reduce the hydrazone in very good yields to give an array of aminosugars.

However, incorporation of nitrogen into the ring itself can be somewhat challenging. Nitrogen heterocycles are highly important scaffolds for a range of existing medicinal chemistry applications, in particular, chiral pyrrolidines, piperidines and azetidines.[112] Lobeline and its derivatives (**Figure 13**) are potent inhibitors of vesicular dopamine uptake, for potential use in the treatment of methamphetamine




**Scheme 81** Synthesis of amino THFs via Raney Ni reduction, using flow chemistry, in research by Benhamou *et al.*[2]

addiction.[113]

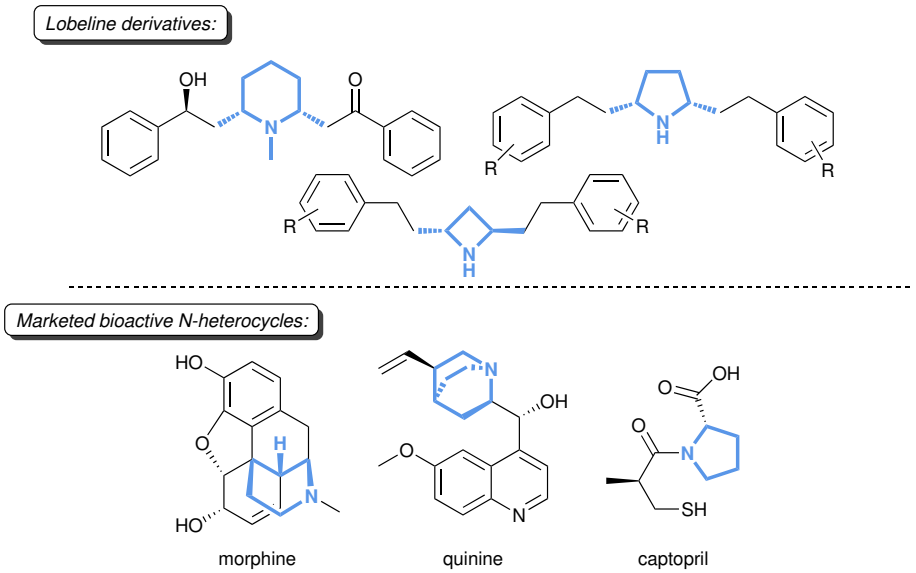



**Figure 13** Structures of pharmaceutically useful molecules containing nitrogen-heterocycle cores (highlighted in blue).[112,114]

The *N*-heterocycles interact with several central nervous system targets and therefore offer large pharmaceutical potential.[112] Key examples of marketed drugs that contain saturated *N*-heterocycles include morphine and chloroquinine (**Figure 13**).[114]

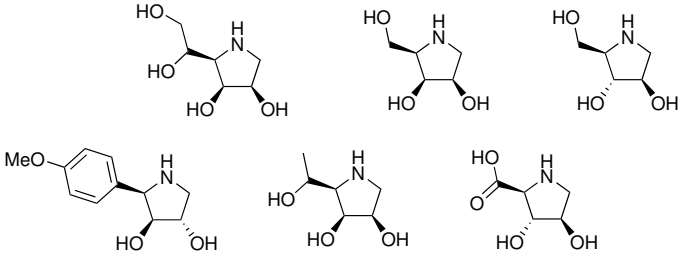
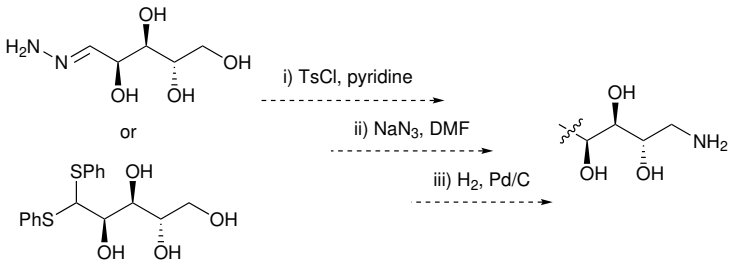


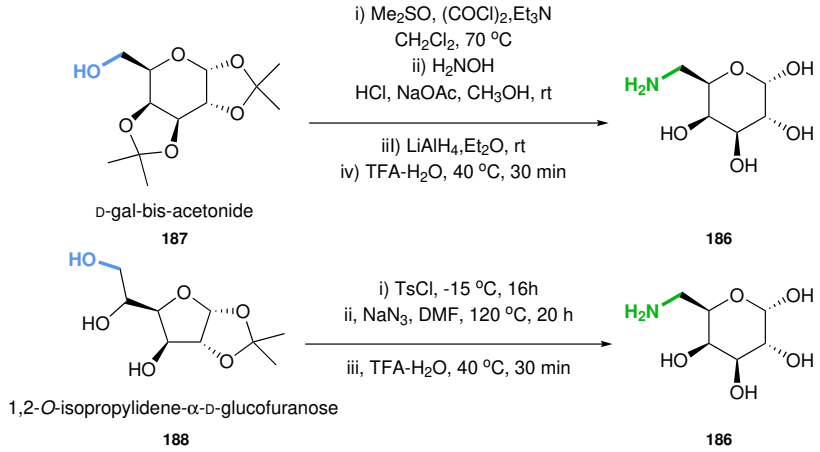
**Figure 14** Examples of sugar-derived pyrrolidines.[115,116,117]

Issues with the synthesis of such structures presents itself when trying to control the relative and absolute stereochemistry in the formation of the heterocycle. In theory, the simplest approach to create chiral azetidines, pyrrolidines and piperidines from sugars (for example **Figure 14**) would be to trap the sugar into its open-chain form, convert the primary alcohol into an amine and then perform a cyclisation. More direct routes to *N*-heterocycles may be explored, such as selective reaction of the primary alcohol in hydrazone protected sugars or thioacetals, followed by azide displacement and reduction (**Scheme 82**).




**Scheme 82** A general scheme showing the planned conversion of sugar hydrazones or sugar thioacetals to the corresponding protected aminosugar via tosyl displacement.

There is large literature precedence for functionalisation at the primary alcohol, often involving acetonide-protected hexose sugars.[57] For example, work by Streicher *et al.*, provided access to hexose-derived heterocycles such as **186** using protecting group chemistry (**Scheme 83**).

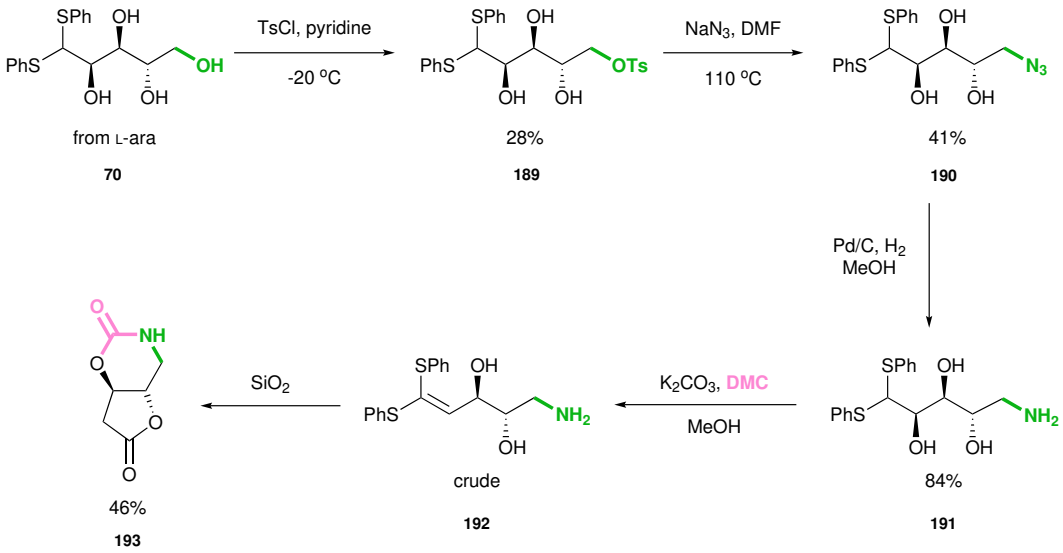



**Scheme 83** Literature methods for the creation of hexose aminosugars from commercially available starting materials.[118,119]

Swern oxidation of the bisacetonide gave the aldehyde which was then reacted with hydroxylamine to give the oxime, and then reduced to the amine using $LiAlH_4$.

Amines were able to be converted to the corresponding amide using various carboxylic acid chlorides (**Scheme 83**).[118] Jose *et al.* were also able to produce glucose-derived THP using protection of the primary alcohol of **188** and azide displacement (**Scheme 83**).

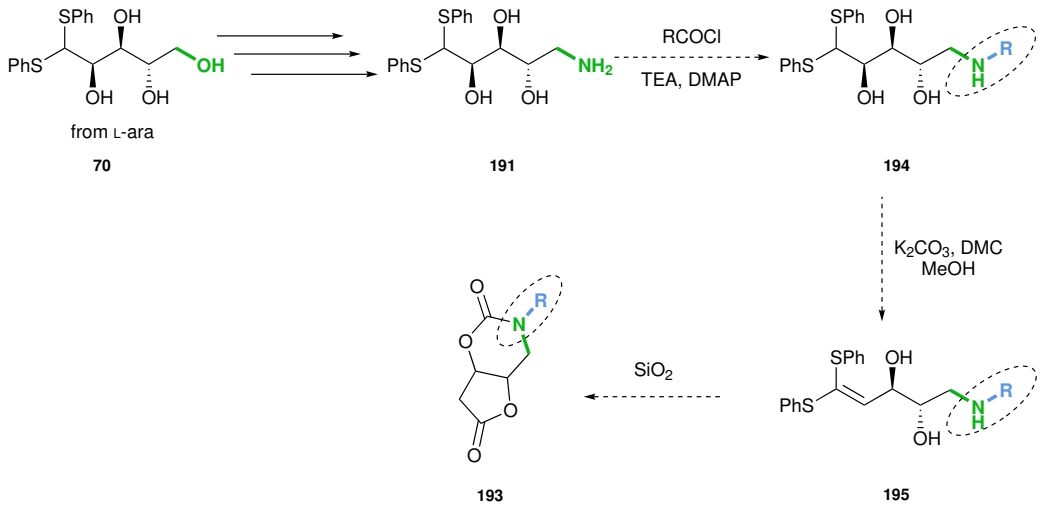
Initially, tosylation and azide displacement was tested on thioacetals of both L-arabinose (**Scheme 84**) and D-glucose (**Scheme 84**). Tosylation of the thioacetals was proven to be low yielding and in the case of D-glucose thioacetal, unstable. A complication with selectivity for the primary alcohol was encountered, with over-tosylation occurring in some cases, giving an average yield of around 28% (for L-ara).




**Scheme 84** Chemical pathway to the formation of aminosugar **191**, followed by cyclisation under dehydration conditions to give fused lactam/lactone **193**. Functional group conversion is highlighted in green.

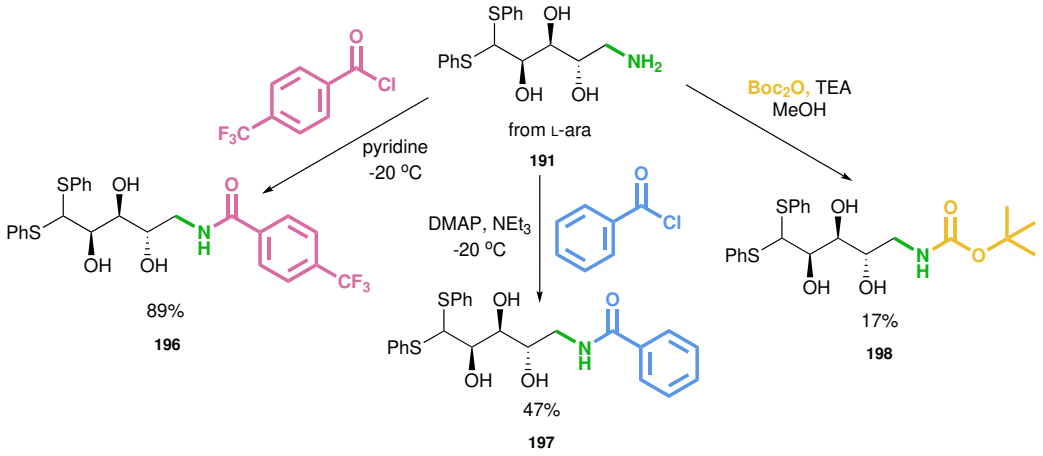
Tosylation, azide formation and subsequent hydrogenation prove to be more selective and higher yielding, with no purification required following hydrogenation. Application of our dehydration conditions ($K_2CO_3$/DMC in MeOH) resulted in the selective dehydration at the 2' position, as seen when **70** is placed under the same conditions. Crude dehydration product **192** then cyclised upon purification with silica, to form fused lactam/lactone **193** in a reasonable yield. It is assumed that stereochemistry has been retained during the cyclisation based on the observation of only one product forming. However, it should be noted that due to the low purity of **193**, its structure is only the proposed major product. Further development is required to establish a reproducible synthetic method.

With cyclisation of **192** occurring upon purification, it was seen if functionalisation of the nitrogen prior to exposure to silica would have an effect on the product retrieved from the column (**Scheme 85**).




**Scheme 85** Chemical pathway to the formation of aminosugar **191**, followed by proposed cyclisation under dehydration conditions to give fused lactam/lactone **193**. Functional group conversion is highlighted in green.

Functionalised nitrogen heterocycles are incredibly useful motifs in the construction of pharmaceutically relevant molecules,[112] therefore, screening of the influence of different functional groups attached to the amine was carried out on model sugar L-arabinose thioacetal **70**. Following this, the compounds were exposed to basic, dehydration conditions.

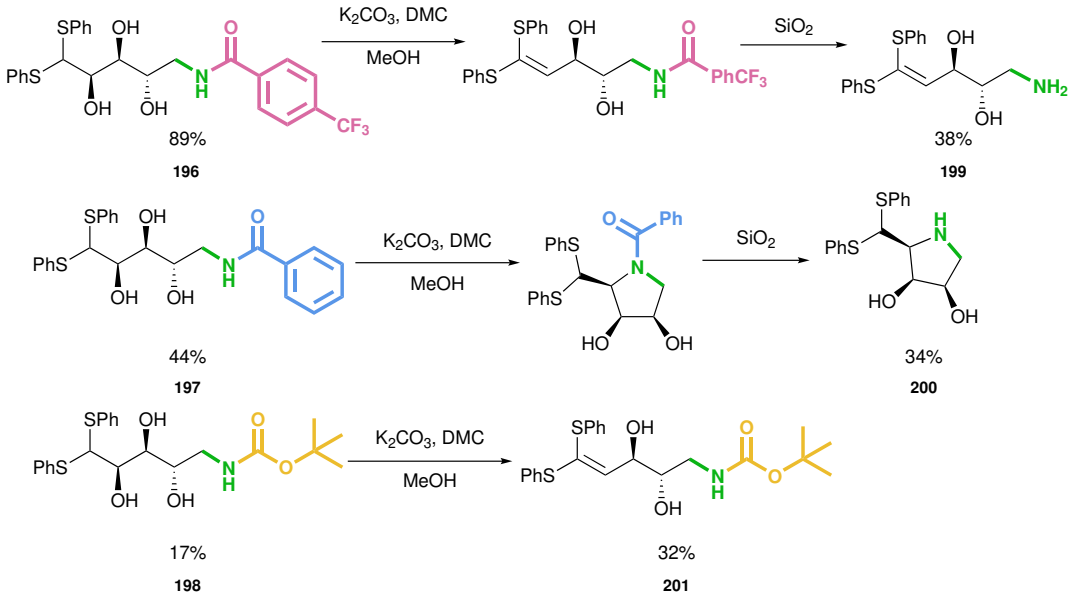



**Scheme 86** Amide formation of L-arabinose derived aminosugars.

Functionalisation such as amide, carbamate and sulphonamides were explored in order to alter the activity of the amine. This should open up a variety of possible

cyclisations to occur based on the conditions. Initially, amides were create via benzoylation before exposure to cyclisation conditions (**Scheme 86**).

Novel benzoylation products **197** and **196** were achieved in reasonable yields. The processes were not optimised, as enough material was obtained for testing their reactivity. Additionally, alternative amides such as Boc-protected amines were made in reasonable yield. Compounds **197** and **196** were exposed to our basic dehydration conditions ($K_2CO_3$/DMC in MeOH) to assess whether cyclisation could occur (**Scheme 87**).



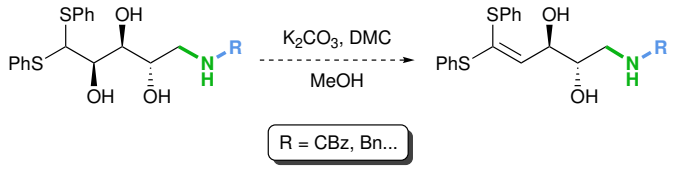

**Scheme 87** Dehydration of protected aminosugars under basic conditions.

For 4-trifluoromethyl benzoyl protected aminosugar **199**, selective dehydration took place at the C-2 position, yielding a ketene thioacetal. Although no cyclisation took place, access to this novel ketene thioacetal in reasonable yield considering no optimisation has been done. This route gives a clean and selective reaction, thereby allowing the crude, protected aminosugar to be utilised without the need for purification. Alternatively, it may be deprotected, which occurs during exposure to silica when columned.

For benzoyl protected aminosugar **197**, no ketene thioacetal was detected, with cyclisation occurring at the C-2 position, to yield functionalised pyrrolidine **200**. This reactivity was not expected due to the electrophilic character of the alkene (which exists in the transition state) seen previously. However, in this case, the tethered character of the amine allows for cyclisation and creation of a stable 5-membered

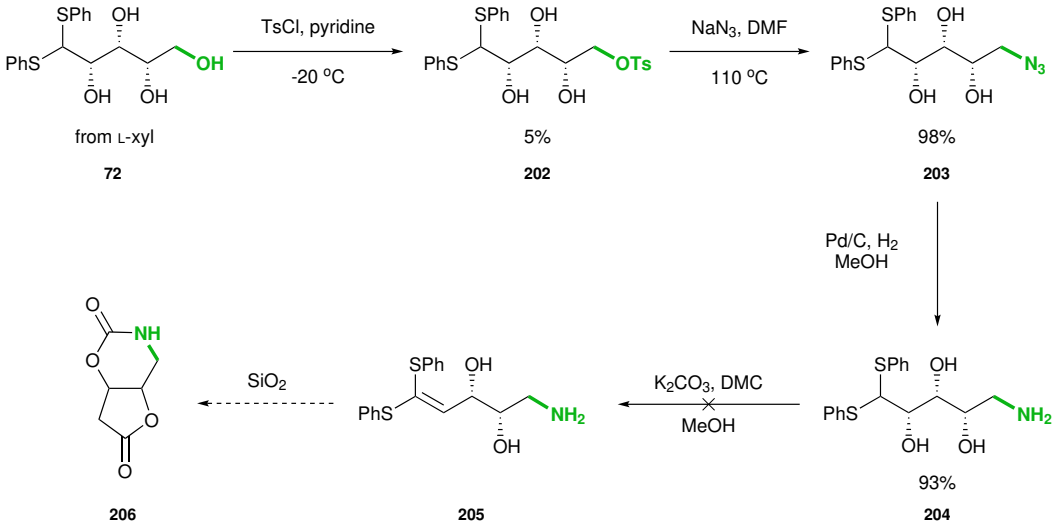
ring. As with compound **199**, deprotection occurred upon purification via silica gel chromatography, providing the unprotected pyrrolidine in a reasonable yield. Further development is required to establish a reproducible synthetic method.

In the case of Boc-protected aminosugar **198**, dehydration took place selectively at the C-2 position to yield the ketene thioacetal, as it does with the non nitrogen-containing sugar thioacetals. Unlike the other protected aminosugars, the alkene was stable to purification methods and the ketene thioacetal was isolated in moderate yield.




**Scheme 88** Future research to be carried out on the functionalisation of the amino group on aminosugars prior to dehydration conditions.

Future research on this topic would include further functionalisation of the amino group and explore other possible cyclisations of the compounds (**Scheme 88**). A more diverse array of protecting groups on the amine moiety would be applied prior to dehydration, such as Cbz, FMoc, Bn and Ts.

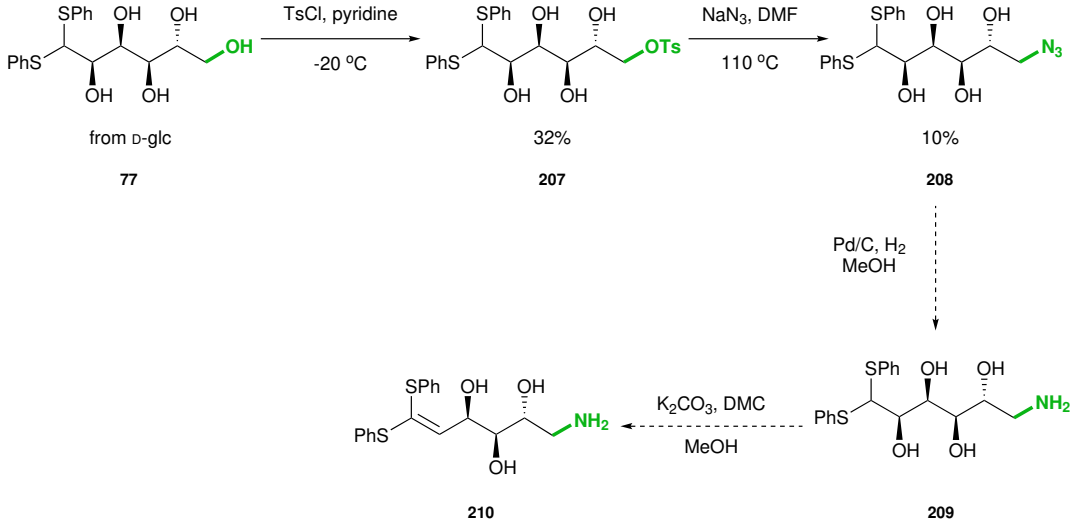



**Scheme 89** Proposed chemical pathway to the formation of aminosugar from L-xylose thioacetal. Functional group conversion is highlighted in green.

The derivatives of pentose sugar L-xylose behaved in a similar manner. Tosylation and subsequent azide displacement, followed by hydrogenation achieved the

aminosugar in good yield over 4 steps from the sugar (**Scheme 89**). However, it should be noted that due to the low purity of **202**, its structure is only the proposed major product.

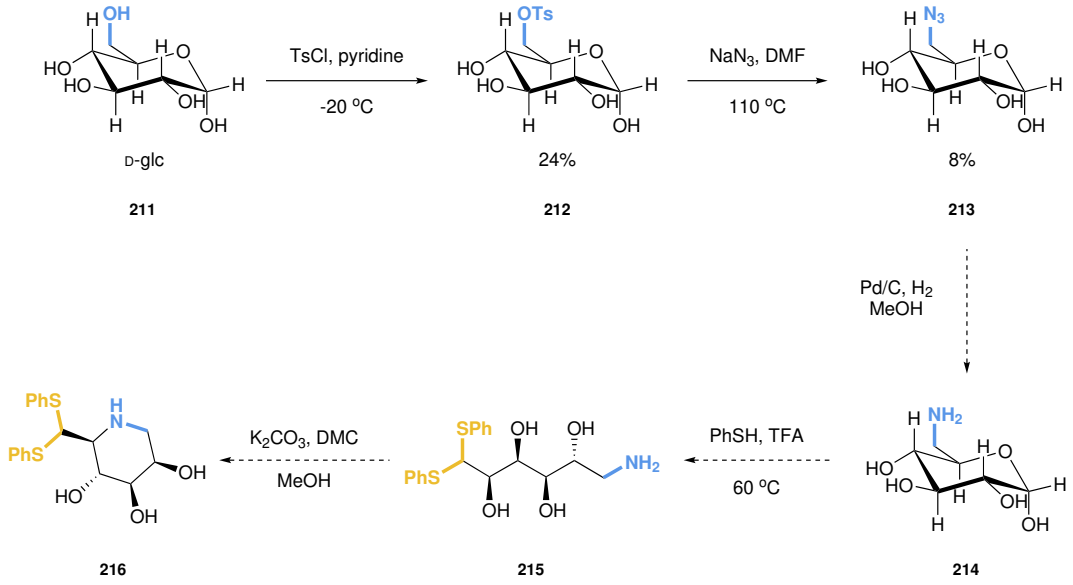
Aminosugar **204** was notably unstable, and no conversion to the corresponding ketene thioacetal was seen. The same pathway was carried out on the thioacetal of six-carbon sugar, D-glucose (**Scheme 90**). Due to over-tosylation, the first step of the pathway proved problematic. Although **207** was produced in enough substance to perform the next step, difficulty in separation from its polytosylated counterparts was impractical.




**Scheme 90** Proposed chemical pathway to the formation of aminosugar **209**. Functional group conversion is highlighted in green.

Azide **208** was produced in a low yield, with insufficient material to carry the pathway forward to produce aminosugar **209**. Tosylation of the sugar prior to thioacetalisation was then carried out, as selectivity to the primary alcohol should be higher due to steric effects as a result of the cyclic geometry (**Scheme 91**). Other pentose sugars which experienced problematic tosylation such as D-ribose, will also be treated in this manor.

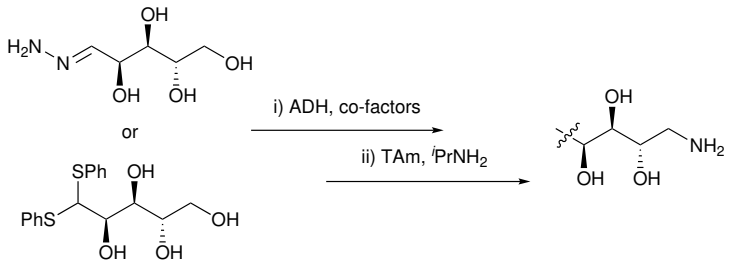
However, due to low yielding tosylation and azo formation steps, this route was carried no further. Further investigation into the hydrazone/thioacetal open-chain of these derivatives should be explored.




**Scheme 91** The formation of closed-ring aminosugars, prior to thioacetal protection. Functional group conversion is highlighted.

### 2.6.1.2 Biochemical Methods

An alternative way to create the same sugar-derived amines (**Scheme 82**), can be through the utilisation of biocatalysts. Not only are they a more sustainable approach, but would produce the amine within two steps, as opposed to three (**Scheme 92**). Mixing of the hydrazone/thioacetal with an alcohol dehydrogenase (ADH) should selectively oxidise at the primary alcohol. Transamination of the aldehyde to the amine using a transaminase (TAm) and amine donor, should give the aminosugar. This, under basic, dehydration conditions, should then cyclise to form a fused lactam/lactone seen previously (**Scheme 84**). This protecting group chemistry has led to the development of a simple method for creating protected azasugars.




**Scheme 92** A general scheme showing the conversion of sugar hydrazones or sugar thioacetals to the corresponding protected aminosugar via biocatalysis.

## 2.7 Conclusions

In this work, we have established a method for creating ketene thioacetals for a wide variety of sugars, including hexose, pentose and tetrose sugars. Insight into the mechanism of formation of the ketene thioacetals has been given by collaborative computational studies. A relationship between the relative stereochemistry at positions 2 and 3 and the ability to dehydrate under our established conditions has been determined. This has led to selective dehydration when reacting mixtures of the sugars (representative of waste biomass) and the ability to predict the reactivity of carbohydrates when using our dehydration method.

The applicability of arabinose ketene thioacetal **95** has been studied, including the discovery of novel reactivity under Lewis acidic conditions. Cyclisations of the open-chain sugars has been explored to create a variety of chiral THFs and THPs. The key structures that were developed in this work has been summarised in **Figure 15**.

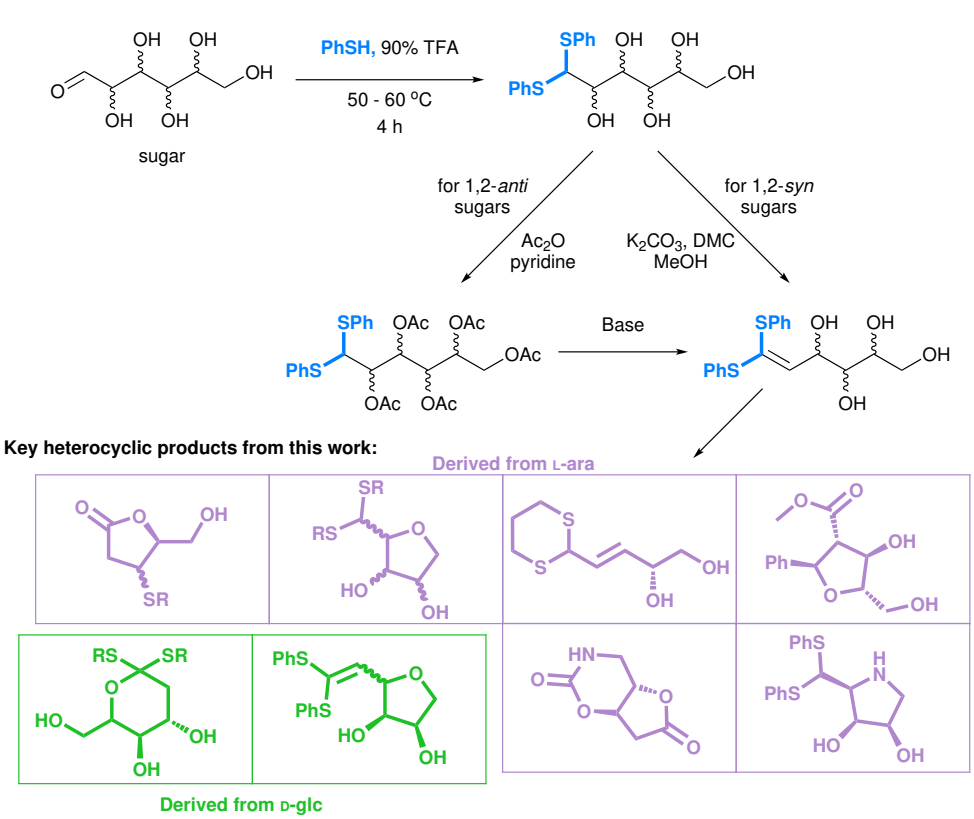
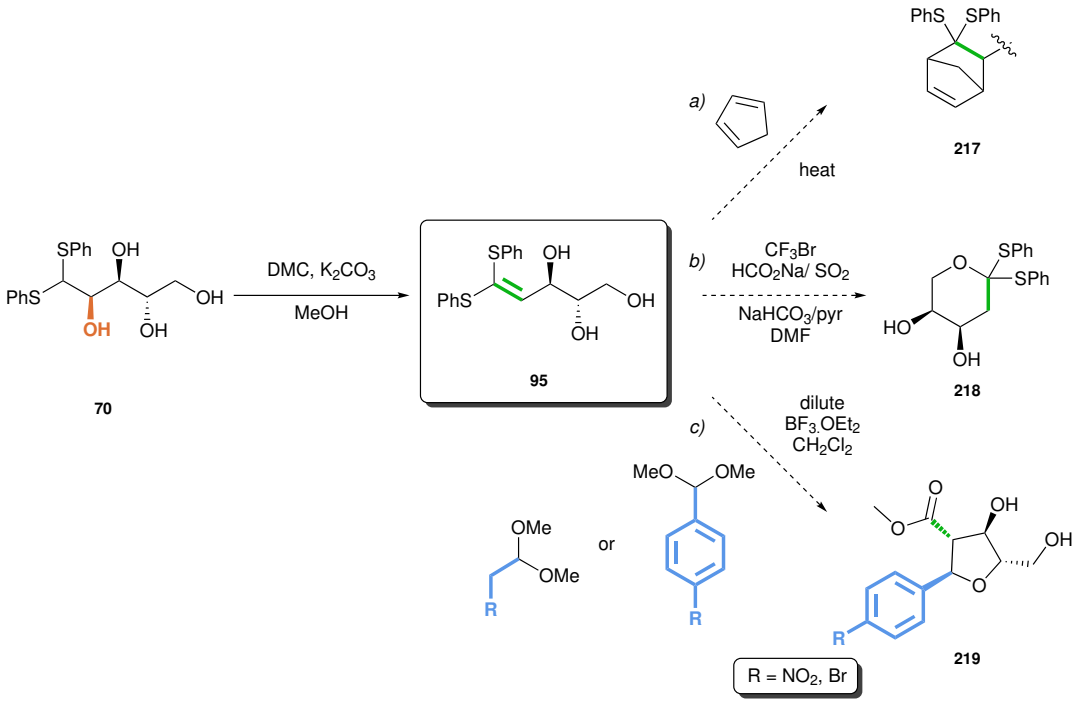



**Figure 15** A summary of this work, including a table of key novel heterocycles.

Conversion of **95** to the corresponding aminosugar has also been carried out, with cyclisation occurring upon exposure of the protected aminosugar to our established dehydration conditions. Depending on the protecting group used, different reactivity

was seen. We have established a method for the production of chiral pyrrolidines such as **200**.

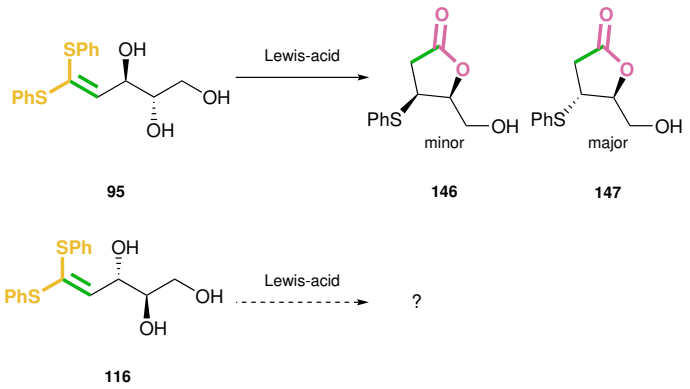
Outlined in **Scheme 93** are areas for future work, such as to explore the reactivity of the double-bond present in ketene thioacetal **95**. Research by De Lucchi *et al.* revealed that aryl-substituted ketenedithioacetal tetroxides display Diels-Alder reactivity with cyclopentadiene,[120] resulting in fused-ring products (*pathway a*). Similar conditions may be employed to test for such reactivity, with adjustment of the chosen diene and exploring electron-poor systems.




**Scheme 93** Proposed reaction pathways as applications of arabinose ketene thioacetal **95**. *a)* Diels-Alder reaction,[120] *b)* radical cyclisation,[121] *c)* cyclised ester formation.[99]

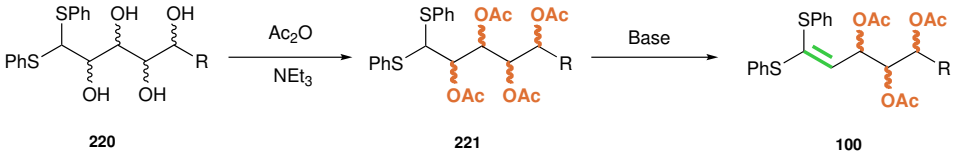
So far, the potential for **95** to act in radical reactions has yet to be explored. Interesting research involving ketene dithioacetals has shown reactivity with radical species, leading to cyclisation of the sugar to form heterocyclic product **218**.[121] Future work would include testing if cyclisation of the 5-C sugar also takes place (*pathway b* of **Scheme 93**).

As previously mentioned, **95** reacted with an activated aldehyde (**Scheme 58**). Future research could involve optimisation with variation in Lewis acid (to reduce lactone products mentioned in **Scheme 61**), concentration, solvent and quantities of reagents. For example, using largely dilute reactions to minimise lactone formation.




**Scheme 94** Cyclisation of ketene thioacetal **95** under Lewis acidic conditions.

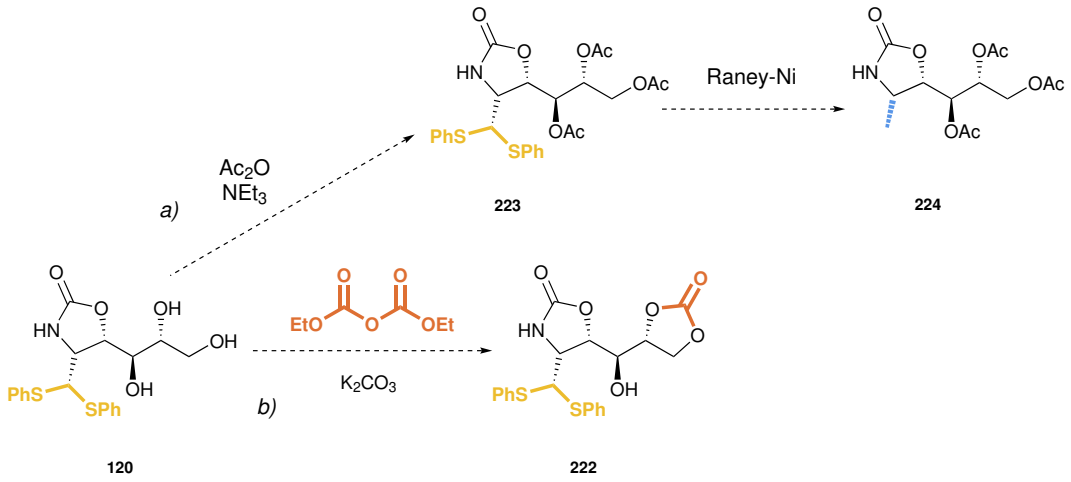
The implementation of *para* electron-withdrawing groups in order to favour product formation and obtain a higher yield should also be investigated, as well as the use of aliphatic acetals (*pathway c* of **Scheme 93**). In future work, the lactonisation reaction (**Scheme 94**) itself should be optimised to increase the yield, for example, by using catalytic quantities of $AlCl_3$ in a variety of solvents under dilute conditions. It could also be tested if the ketene thioacetal derived from D-ribose **116** cyclises in a similar fashion, creating alternative stereocentres.




**Scheme 95** Acetylation of L-rhamnose thioacetal **220** followed by subsequent elimination, yielding an alkene.

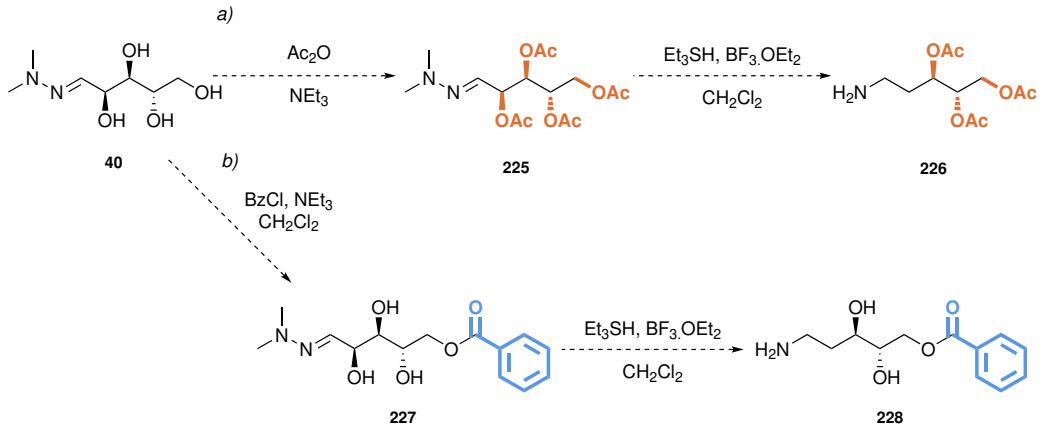
It was found that sugar dithioacetals which possess *anti*-configured alcohols about the 2- and 3- positions were unreactive with regards to ketene dithioacetal formation unless first acetylated. Acetylation of the alcohols seemed to give a higher propensity for dissociation, favouring alkene formation. However, yields of these reactions are poor for certain sugars, and therefore should be optimised in future research through alteration of solvents and temperature (**Scheme 95**).

Application of cyclised *N*-acetylglucosamine product **120** could be explored in order to try and create a further cyclic carbonate (*pathway b* of **Scheme 96**). By installing a second carbonate (**223**) it introduces another site for electrophilic attack but also leaves one free alcohol which may selectively be functionalised.




**Scheme 96** Proposed reaction of cyclised *N*-acetylglucosamine dithioacetal **120** with DEC, followed by further cyclisation under basic conditions to form **223**.

It is thought that cyclisation may also occur upon hydrolysis of the thioacetal. Reduction using Raney-Ni (as done previously with L-arabinose derivative **95**) could create a novel chiral scaffold. Acetylation could be carried out prior to reduction in order to ease purification, creating scaffold **224**.

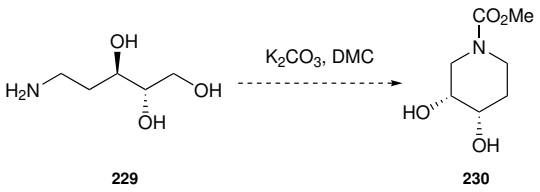



**Scheme 97** Protection and subsequent reduction of **40** in order to isolate β-reduced aminopolyols.

A major aim of the project was to isolate a reduced form of arabinose hydrazone **40** (**Scheme 97**). In order to combat difficulty in purification of the aminopolyol, benzoylation of starting material **40** prior to reduction should be tested. As well as this, protection of the sugar alcohols to form acetyl groups under the new successful acetylation conditions before reduction could be carried out.

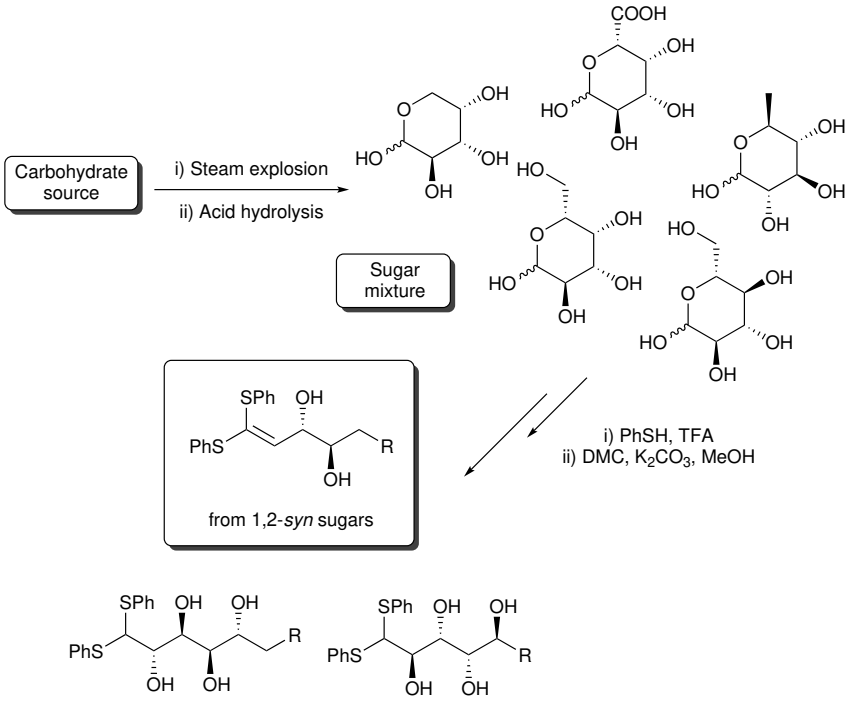
*In situ* reduction of the acetyl/alcohol adjacent to an aldose hydrazone will provide a valuable route to deoxygenated sugars which can potentially then be con-

verted into valuable saturated heterocycles by cyclisation under basic conditions (**Scheme 98**).




**Scheme 98** Cyclisation of reduced, deoxygenated hydrazone **229** under basic conditions.

Future work would include implementing the thioacetal formation procedure on the mixture of sugars obtained directly from other waste carbohydrate sources than sugar beet pulp (**Scheme 99**). Waste sources such as agro-industrial oil (soy, palm oil), food agro-industrial (corn, orange, coconut, cashew) or wood agro-industrial (wood, sisal) and contain chemical potential in the form of lignin, cellulose and other carbohydrate aggregates.[122]




**Scheme 99** The proposed selective isolation of sugars from waste biomass.

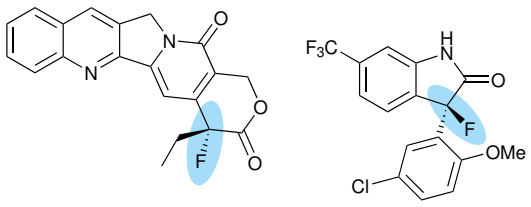
Applying our established basic conditions and trying to use this to selectively isolate ketene thioacetals of L-ara, D-glc and D-gal would be an incredible example of the utility of our chemistry.

# Chapter 3

# Ene-Reductase Bioreduction to Generate Chiral Fluorine Compounds

### 3.0.1 Project Aims & Previous Work

Since the introduction of the first fluoro-pharmaceutical in 1954, fluorochemicals in the pharmaceutical industry have become increasingly prevalent, with an estimated 20% of marketed drugs in 2020 being a fluoro-pharmaceutical.[123] Fluorine-containing drugs have wide applicability in terms of therapeutic effect, such as use as antimicrobials, antitumour agents and anti-inflammatories (**Figure 16**). With over 50% of current market drugs being chiral compounds,[124] the relevance of chiral fluoro compounds should be explored. Inoue *et al.* identified over 60 fluoro-pharmaceuticals with a chiral fluorine motif,[123] making their direct synthesis a valuable area for research.

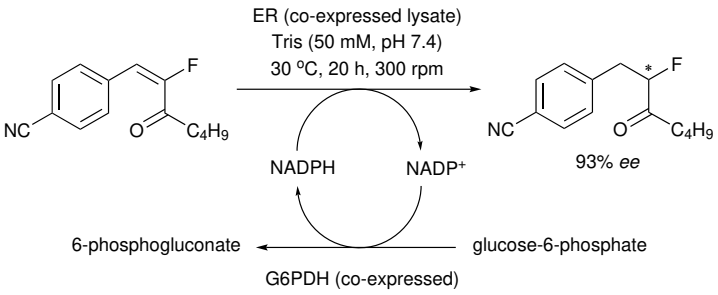



Fluorocamptothecin BMS-204352

**Figure 16** Examples of chiral-fluorine centres in pharmaceutically active compounds.[125]

Research within the group by A. King demonstrated the ability to access valuable chiral fluorinated molecules in a stereoselective manner using biocatalysis. Her work gave insight into the bioreduction of fluoroalkenes when using ene-reductases (ERs) on a variety of different fluoroalkenes.[126] Initially, her work began with a

preliminary screening of an (*E*)-α-fluoro-β-arylenone (containing small quantities of the *Z*-isomer) bearing a *para*-CN on the aromatic ring (**Scheme 100**).



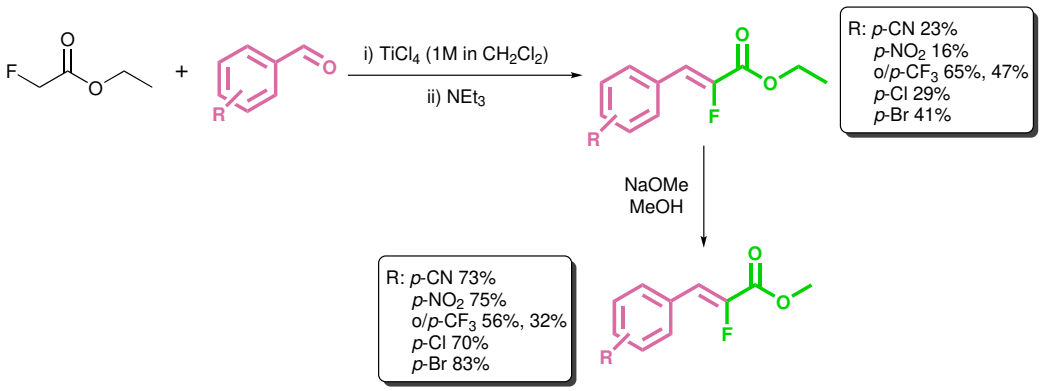

**Scheme 100** Bioreduction of α-fluoro-β-arylenone, (*E*)-4-(2-fluoro-3-oxohept-1-en-1-yl)benzonitrile with co-expressed clarified lysates, carried out by A. King.

The *E*-fluoroenone was readily accepted by the enzyme NCR+pQR1811 (with no acceptance of the *Z*-isomer) and product formation was observed by chiral HPLC and $^{19}$F NMR. Synthesis of the reduced product (racemic) confirmed formation of the product in the biotransformation by HPLC analysis, giving the reduced compound in 93% *ee*. The formation of byproducts occurred, with A. King suggesting that these were formed as a result of alcohol dehydrogenase (ADH) enzymes present in the *E. coli* clarified lysates acting on the substrates.

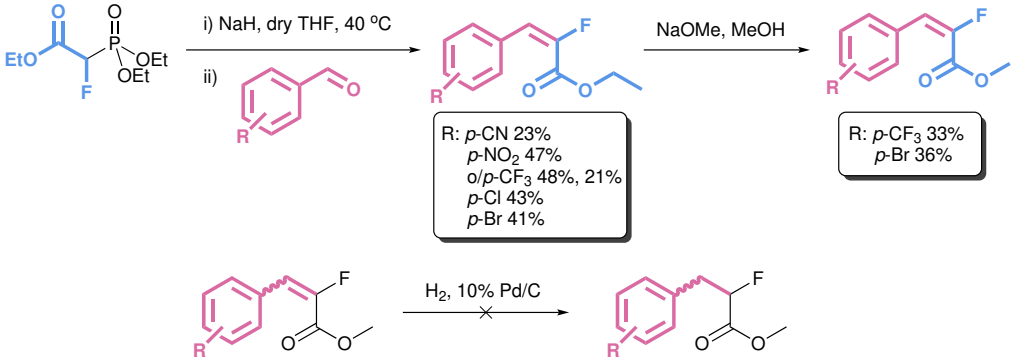
Following this success, she then turned to testing *E*- and *Z*-α-fluoro-β-arylenoates bearing a variety of *para*-substituted EWGs. The stereoselective formation of *Z*-fluoroarylenotes was carried out via the asymmetric aldol condensation of ethyl fluoroacetate with substituted aldehydes (**Scheme 101**) achieving moderate yields of 23–65%. The ethyl esters were then transesterified to the corresponding methyl ester in good yields (32–83%).

*E*-Fluoro arylenotes were produced through the use of commercially available diethylphosphoryl-2-fluoroacetate in a Horner-Wadsworth-Emmons (HWE) reaction, to provide an array of ethyl esters (**Scheme 102**) in reasonable yields (23–49%). The substrates were then subjected to transesterification conditions to obtain the methyl esters (33–36%). Hydrogenation of the esters using Pd/C with $H_2$ to obtain the corresponding reduced compound was attempted in order to gain the authentic sample for analytical purposes, however, no reaction occurred. As a result, reaction success was determined based on consumption of starting material.

A. King selected strong electron-withdrawing functionality such as $CF_3$ and $NO_2$ for substitution on the aromatic ring based on previous research suggesting that



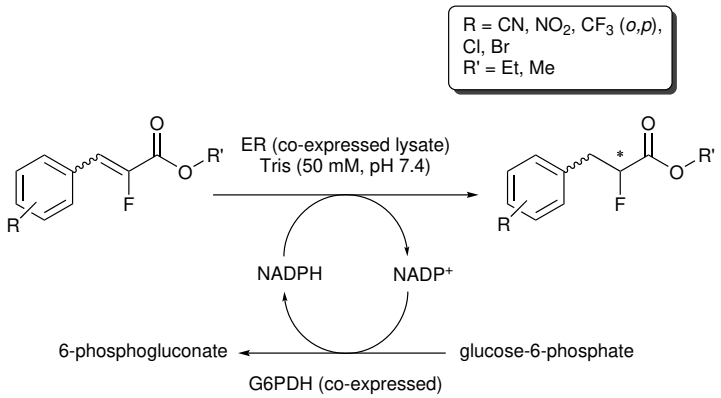

**Scheme 101** General scheme showing asymmetric aldol condensations of ethyl fluoroacetate with substituted aldehydes to generate substituted (*Z*)-α-fluoro-β-arylenoates. Transesterifcation was then carried out to provide the methyl ester, carried out by A. King.[126]




**Scheme 102** General scheme showing the Horner-Wadsworth-Emmons reaction to afford substituted (*E*)-α-fluoro-β-arylenoates. Transesterifcation was then carried out to provide the methyl ester.[126] Hydrogenation of the alkenes to the reduced compounds using Pd/C was attempted. Work carried out by A. King.

electron-poor alkenes were more readily accepted by the enzymes.[127] The α-fluoro-β-arylenonoates (ethyl esters) bearing EWGs on the phenyl ring were screened against the ERs, revealing little or no acceptance ( 1–5%) by the enzymes for *Z* isomers (**Scheme 103**). However, for the (*E*)-α-fluoro-β-phenylenoates, moderate acceptance by the enzymes was observed (approximately 30% for all), with preliminary *ee*'s of 49–69%. Given the success of the *E*-fluoro arylenoates bearing ethyl esters, the corresponding methyl esters were then also screened.

Specifically, (*E*)-α-fluoro-β-phenylenoates bearing either a *para*-$CF_3$ group or Br were selected as potential substrates for the strongly withdrawing component and their utility in cross-coupling reactions. These substrates showed moderate acceptance by the ERs and good provisional *ee*s of 71% and 61% respectively. The methyl esters exhibited nearly full conversion (not quantified) by HPLC analysis, showing promise




**Scheme 103** Bioreduction of α-fluoro-β-arylenoates with co-expressed clarified lysates. Both *E* and *Z* isomers were tested as substrates, with a variety of *p*-EWGs on the aromatic ring. Work carried out by A. King.[126]

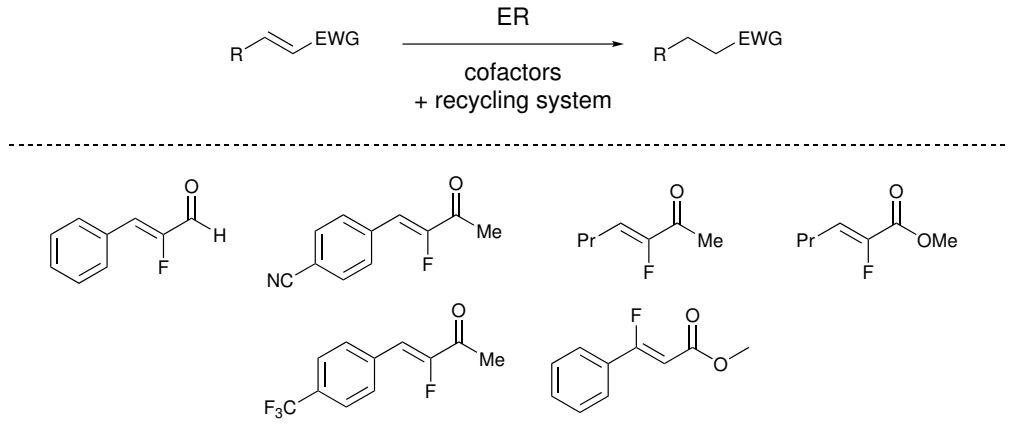
for (*E*)-α-fluoro-β-phenylenoates with electron-withdrawing substituents.

It is the aim of this work to build upon this research and produce a number of novel substrates for ERs and test their viability for acceptance by the ER enzymes. To do this, the synthesis of α- and β-fluorocarbonyl compounds will be carried out. The corresponding reduced compounds will be prepared alongside the fluoroalkenes in efforts to determine the absolute stereochemistry of the enzyme-produced products and for use as reference samples (**Scheme 104**). Specifically, we aim to test novel ketone substrates with the enzymes following previous success (**Scheme 100**). To do this, we aim to develop a route for the synthesis of a methyl ketone substrate as the previous synthetic route for the butyl ketone (shown in **Scheme 100**) was carried out from alkyne starting material, hexyne.[126] However, applying this pathway to a methyl ketone would involve the use of propyne gas and therefore will be avoided. Following synthesis, the novel ketone substrate will be tested for acceptance with our ERs.

The viability of non-substituted phenyl rings in α-fluoro-β-phenylenoates as substrates will be explored, to see if a *para*-EWG is required for acceptance by the enzymes. Additionally, the effect of the position of the fluorine relative to the carbonyl functionality on acceptance by the enzyme will be investigated through the synthesis and screening of a β-fluoroester. Aldehyde substrates will also be screened as potential substrates, following their synthesis.

An additional objective of this work is to develop an efficient method for the production of α-fluoroenones, using similar chemistry to that used previously, such as Horner-Wadsworth-Emmons reactions. As well as fluoroenones, it is the aim to also use this chemistry to produce α-fluoroenones with aliphatic chains attached to

them, to explore if the aromatic ring is essential for acceptance by the ERs.




**Scheme 104** A general scheme and scope of potential substrates to be tested for their reduction using novel ene-reductase enzymes.

The overall aim of this project is to provide deeper insight into the functionality required for acceptance by ERs, to explore synthetic techniques to create fluoroalkenes, and to expand the substrate scope for enzymes NCR+pQR1811. Moreover, this work aims to develop new routes to chiral $sp^3$-fluorides in a sustainable approach.

## 3.0.2 Chemical Fluorination Techniques

Existing research on stereoselective fluorination typically involves either transition metal catalysis or intramolecular stereocontrol with retention of stereochemistry of the enantiomerically pure substrate.[125] Examples of attached chiral auxiliaries, acting as temporary chiral motifs, include: oxazolidinones, ephedrine and 8-phenylmenthol, all of which demonstrate very good diastereoselectivity.[128]

### 3.0.2.1 Enantioselective Electrophilic Fluorination

Among the most successful are derived from *Cinchona* alkaloids, with *N*-fluoroammonium salts of Cinchona alkaloids being easily prepared using fluorinating agents (**Figure 17**). Prochiral substrates are readily transformed to non-racemic chiral products with concomitant creation of a C-F chiral centre using such methods.[129,125]

The use of transition metals with chiral ligands present greatly efficient methods for enantioselective fluorination in the presence of electrophilic fluorine (e.g Selectfluor, *N*-fluorobenzenesulphonimide, *N*-fluoropyridinium triflate). However, limitations such as the requirement of active methylene compounds reduces the applicability of such methods.[125] To date, a large array of organocatalysts have been developed for asymmetric fluorination, with a multitude of transition metals

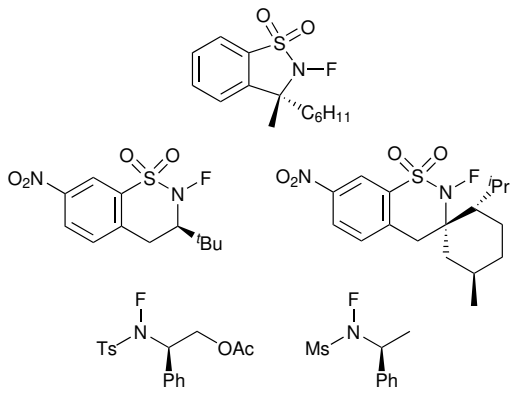


**Figure 17** *Cinchona* alkaloid-derived chiral electrophilic fluorinating agents, discovered by Takeuchi et al.[129]

(**Figure 18**) For example, the catalyst developed by Togni is a powerful catalyst for the enantioselective fluorination of β-ketoesters (up to 93%), whilst Cahard's aluminium/lithium BINOL catalyst provides α-fluoro-β-ketoesters in high yield and 67% *ee*.[130,125]

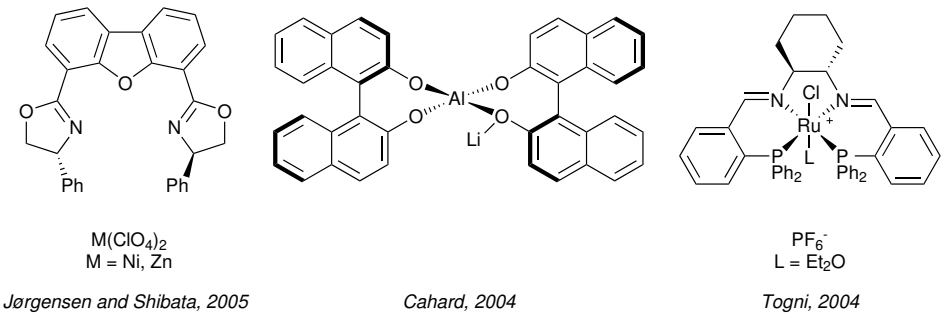



**Figure 18** Examples of organocatalysts used in enantioselective electrophilic fluorination.[131,128,132]

### 3.0.2.2 Organocatalysis

Organocatalysis is an alternative method that offers high to very high enantioselectivies.[125] For example, the enantioselective α-fluorination of linear aldehydes provides access to tertiary C-F centres with selectivities of up to 99% using proline or imidazolidinone derivatives as organocatalysts (**Figure 19**).[130]

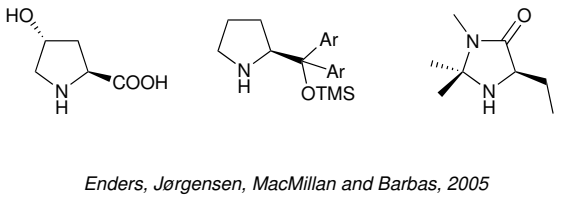



**Figure 19** Examples of organocatalysts used in organocatalytic fluorination.

Due to instability, α-fluoro aldehydes are often reduced to the corresponding α-

fluoro alcohols or trapped, resulting in the allyl or propargylic fluorides. An example of this using a proline-derived organocatalyst is highlighted in **Figure 20**.[133]

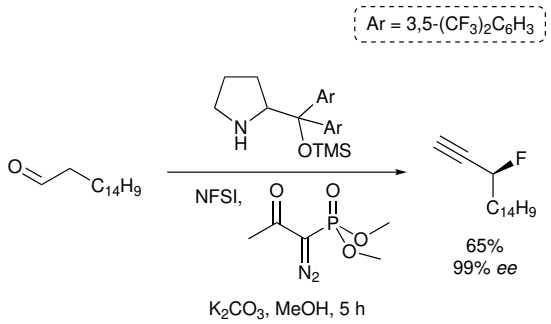



**Figure 20** Examples of organocatalysts used in the synthesis of propargylic fluorides.

### 3.0.2.3 Asymmetric Hydrogenation of Fluoroalkenes

The synthesis of fluoroalkanes can also be approached through selectively hydrogenating a fluoroalkene using a chiral complex such as *R*-BINAP. In 1992, Saburi *et al.* reported an example of asymmetric hydrogenation of fluorinated olefins *E*- and *Z*-2-fluoro-2-hexenoic acid (**Figure 21**), providing insight into the affect of substrate geometry on the resulting stereochemistry.[134] It was found that regardless of the geometry of the alkene, the same enantiomer was formed with high enantiomeric purities (up to 90% *ee*). Since this work has been published, many other examples of asymmetric hydrogenation have been reported.[135,136,125]

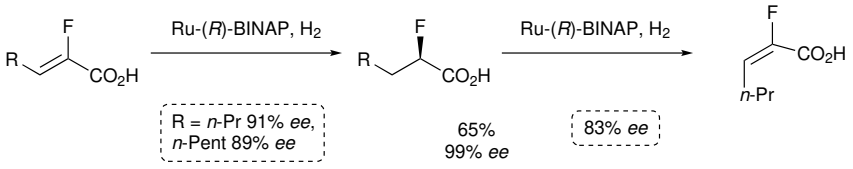
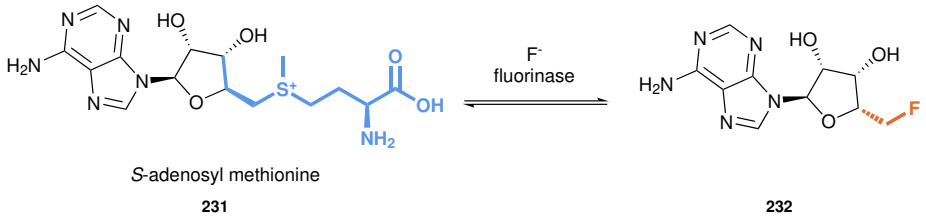



**Figure 21** Examples of the asymmetric hydrogenation of fluoroalkenes using a Ru-BINAP complex.

## 3.0.3 Biocatalytic Fluorination Techniques

The first example of fluorination using enzymes was reported by Zechel, Withers and co-workers in 2001[137] after mutagenesis experiments were carried out on glycosyl transferase enzymes. A fluoride anion was added at a high concentration to the assay, yielding a fluorinated product. Although fluorinases were thought to exist in nature, e.g in the fluorometabolic biosynthesis of fluoroacetone in *S. cattleya*, the first "fluorinase" was not isolated until 2002 from this very pathway.[138] The catalytic fluorination occurs via an $S_N2$ substitution mechanism whereby a fluoride ion initiates

a nucleophilic attack on the on 5'-C on the ring of *S*-adensoyl methionine (SAM) **231** to give **232** (**Scheme 105**).




**Scheme 105** Biocatalytic fluorination of SAM occurring in the metabolic pathway of soil bacteria *Streptomyces cattleya*, with the substitution highlighted in orange.[138]

Since its discovery, additional fluorinase enzymes have been reported from multiple different bacterial strains via genome mining. Between 2011 and 2013, four new fluorinases were discovered, with the fluorinase gene (*flA*) having >80% homology to the original fluorinase found in *S. cattleya*.[139,140,] Unfortunately, there remains limited availability of fluorinases for use in synthetic strategies, as well as restriction of the scope for activated sites in the target molecule. This has led to increased enthusiasm for the development of alternative methods.

### 3.0.4 Oxidoreductases and Their Substrates

Enoate-reductases (EORs) catalyse the bioreduction of unactivated or poorly activated alkene substrates, typically those with adjacent carboxylic acid or ester functionalisation.[141] Despite having a wide substrate-scope, utility of EORs is limited due to sensitivity to oxygen and the requirement for oxygen-free buffers/inert atmospheres. Extensive study into the family of the Old Yellow Enzyme (OYE) found that Ene-reductases (ERs) could perform asymmetric reduction to generate single isomer products. With both EORs and ERs belonging to the flavin-containing oxidoreductase family of enzymes (EC 1.6.99.1),[142] the reduction is carried out in the presence of cofactors NADH and NADPH respectively (a computer-generated image of the active site is shown in **Figure 22**). Both mechanisms proceed via stereospecific routes to produce enantioenriched alkanes. Advantageously, ER-catalysed reductions may be carried out under standard conditions, with the drawback being the requirement for an electron-withdrawing group (EWG) adjacent to the alkene. The selectivity of these methods is comparable to that seen with traditional hydrogenation reactions, therefore offering sustainable methods for asymmetric reduction. Substrates containing an EWG that are currently known to be accepted by ERs include ketones, acids, esters

and aldehydes.[127]

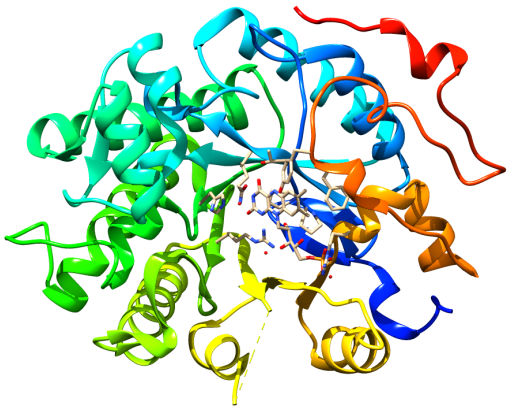


**Figure 22** A visual representation of the Old Yellow Enzyme active site, showing its flavin-derived core.

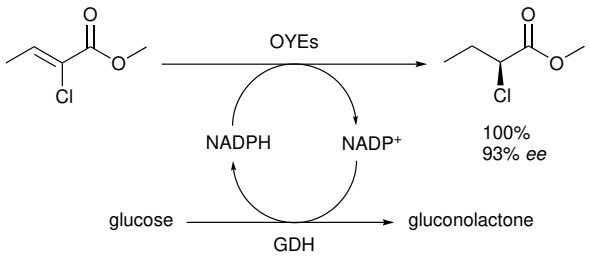
Recent work carried out by Dobrijevic *et al.* involving mining a drain metagenome led to the discovery of novel ERs, two of which exhibited high activities and reasonable tolerance to DMSO and methanol as co-solvents.[127] Great efficiency was seen in preparative scale reactions, as well as acceptance of bulky substrates such as bicyclic ketones, showing complete selectivity.[127] Activating groups such as halogens have been explored, such as bromo- and chloro-enoates,[143] with fluoro-activating groups yet to be fully explored.

### 3.0.5 Fluoroalkene Substrates

Enones with adjacent Br and Cl moieties have been reported in the literature,[144,145] however, there is limited investigation into α- and β-substituted fluoroalkenes. It was found that in the cases of 2-chloro-2-alkenoates, the α-chlorine group attached to the alkene substrate was vital for the bioreduction to take place (an example is given in **Scheme 106**).[146] Fluorine is a relatively inert functional group that acts as a highly electron-withdrawing substituent. It is thought that because of this, and its small size, that fluoroalkenes will be readily accepted as substrates for ER bioreduction to produce enantioenriched fluoroalkenes.

#### 3.0.5.1 Fluoroketone Synthesis

In this work, we will be furthering the substrate scope for the ER NCR+pQR1811. Specifically, work will involve the production of a variety of fluoroalkene species with a variety of different adjacent functionalities such as ketones, aldehydes and esters. The effect of substitution on the aromatic rings will be explored. A variety of α-fluoroenones will be tested for their acceptance as substrates for biocatalytic



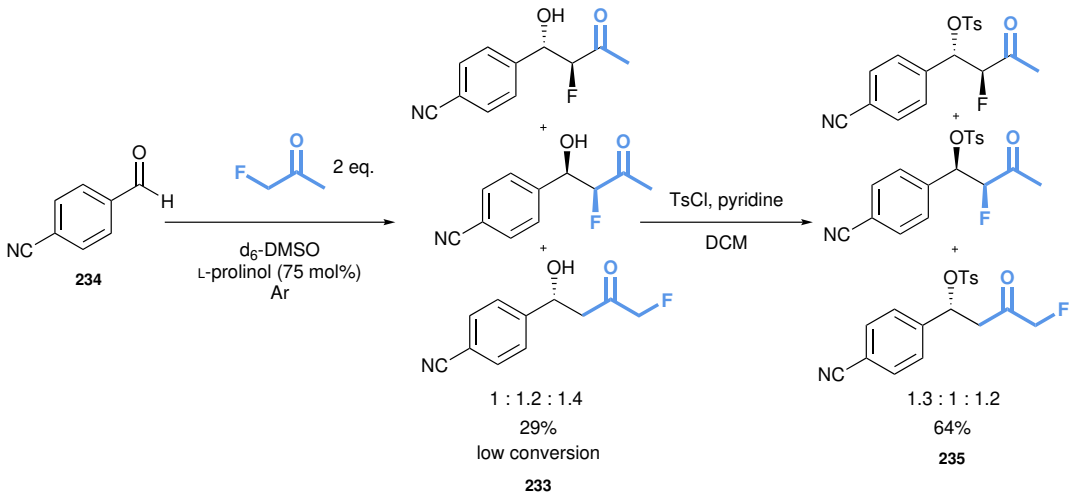

**Scheme 106** The biocatalysed reduction of a *Z*-α,β-unsaturated ester methyl (*Z*)-2-chlorobut-2-enoate using OYEs, in research by Brenna *et al.*

reduction with ERs, in order to provide a straightforward method of accessing chiral centres bearing a C-F bond.

Substrates selected for synthesis were chosen based on their resemblance to previously successful substrates with ERs, discovered by A. King. Initially, α,β-unsaturated phenyl enones were explored based on the positive result seen previously with a phenyl enone with an adjacent butyl ketone. Therefore, the corresponding methyl ketone of King's substrate, a *Z*-alkene bearing a *p*-CN group, was first investigated. By only altering one aspect of the substrate, this would help to determine if the catalytic activity of the enzyme was limited only to ketone substrates.

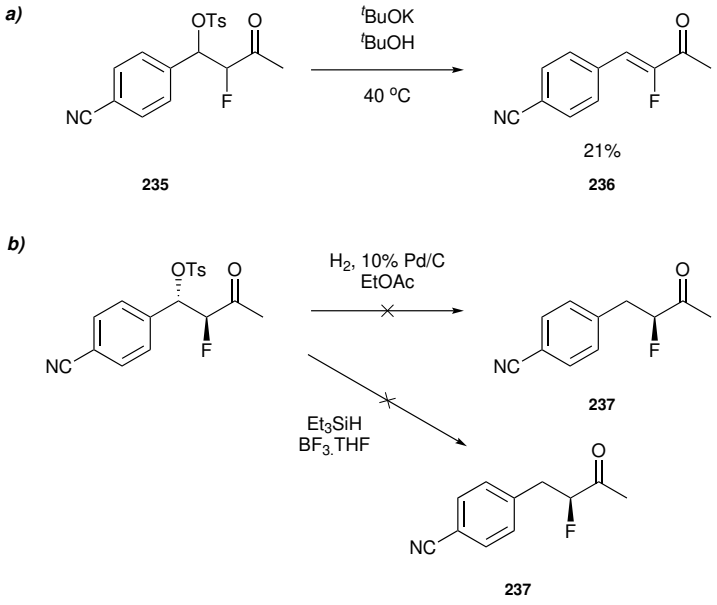
Synthesis of the backbone of the ketone substrate was carried out via an aldol reaction, using organocatalyst L-prolinol (**Scheme 107**).[147] The use of the chiral catalyst was chosen in the hope of using this route to make an enantioenriched fluoroketone which could then be used to determine the absolute stereochemistry from the enzyme reaction. The L-prolinol produced compounds **233** as a mixture of diastereoisomers (*syn* and *anti* compounds) Unfortunately, a regioisomer also formed (derived from formation of the enamine at the methyl group) as a result of an aldol reaction on the other side of the fluoroacetone molecule, leading to a lower yield of the desired product. Each of the three compounds are thought to be enantioenriched as it was in the reported literature procedure.[147] However, this specific substrate was not reported in the literature and so we were not able to accurately determine the major enantiomer in each case. The reaction involves the use of two equivalents of fluoroacetone, which may be altered in optimisation to determine if selectivity is affected.

Following aldol condensation to produce compounds **233** as a mixture of isomers, the alcohol was converted to a better leaving group for subsequent elimination via formation of the tosylate.[148] The tosylates **235** were produced in moderate yield,




**Scheme 107** Aldol condensation and subsequent tosylation to give **235** as a mixture of isomers, activated for elimination.

containing a mixture of stereoisomers and regioisomers (**Scheme 107**). To produce the alkene substrate for the ene-reductase, basic conditions were applied to mixture **235** to encourage elimination of the tosylates. Selective elimination gave alkene **236** in moderate yield (**Scheme 108**).[149]

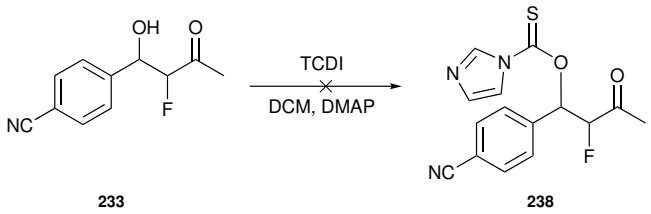



**Scheme 108** Elimination (part *a*) and reduction pathways (part *b*) of **235** to give enzyme substrate **236** and analysis standard **237**.

As previously mentioned, the corresponding alkane is required as a standard for analysis of the biotransformation and also, if the sample is enantioenriched, to determine the stereochemistry of the C-F bond. This data would then be used to learn the stereochemistry produced by the enzyme. Unfortunately, reduction of tosylate

**235** by use of palladium catalysed hydrogenation or triethylsilane/$BF_3 \cdot THF$ did not give any of the desired reference standard **237**.

An alternative means of encouraging elimination of the β-hydroxyl group to the ketone is through the formation of a leaving group such as an adduct with 1,1'-thiocarbonyldiimidazole (TCDI) (**Scheme 109**). This protected alcohol could then be reduced to give the fluoroalkane. However, reaction of **233** with TCDI yielded a complex mixture of products, with no selective protection of the free alcohol taking place. Due to reactivity issues with the β-hydroxy-α-fluoro ketone, no further research was conducted surrounding this route.



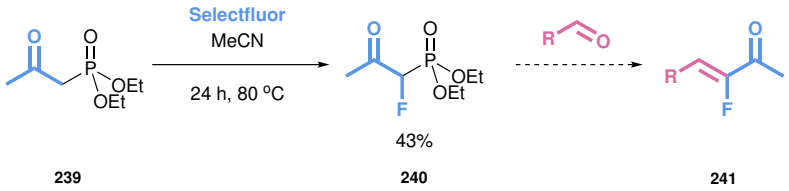

**233** **238**

**Scheme 109** The protection of a secondary alcohol using TCDI.

### 3.0.5.2 Horner-Wadsworth-Emmons Coupling Reactions

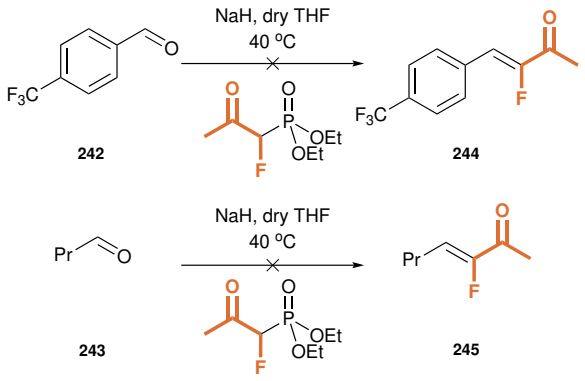
In order to access a variety of fluorinated compounds, the creation of a fluorinated phosphonate ester compound was first explored in the hope of creating an array of α-fluoroenones (**Scheme 110**) in similar action to that seen previously (**Scheme 102**). Although a HWE reaction should work for making an array of fluoroketones, there is not much literature precedence for this reaction. Existing examples for alkene formation via this method was carried out with a phosphonate ester bearing propyl groups on phosphorous,[150] which reports a mixtures of isomers. In this work, the fluorination of commercially available diethyl (2-oxopropyl)phosphonate **239** was carried out in low yield with unoptimised conditions to give compound **240**.[151] This phosphonate ester could then be used to attach an α-fluoro ketone onto an aldehyde via HWE coupling in a similar manner.[126,150] Although this phosphonate has been made before, it was not used for alkene formation, so the viability of this phosphonate ester as a coupling partner will be explored.

Fluorophosphonate **240** was tested in HWE reactions with an aryl and alkyl aldehyde using conditions developed by Coutrot *et al* for analogous ethyl esters (**Scheme 111**).[150] Unfortunately, neither 3-trifluoromethylbenzaldehyde **242** or hexenal **243** afforded any of the desired products and only the starting materials were



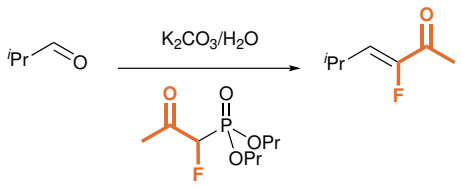

**Scheme 110** The fluorination of diethyl (2-oxopropyl)phosphonate, providing a potential route to alkenyl α-fluoro ketones.

observed in the crude reaction mixture. It appears, from NMR observation, that formation of the anion is occurring but with no enone product formation occurring. This may be caused by the sterically-crowded geometry of the structures in the cyclic transition state formed with the phosphonate ester. It may also be due to the somewhat electron-poor nature of the substrates or generally low reactivity of the phosphonate ester. In future work, this reaction would be tested with alternative aldehyde substrates and different phosphonate esters.




**Scheme 111** The synthesis of α-fluoro ketones via HWE-like coupling of aldehydes with a phosphonate ester.

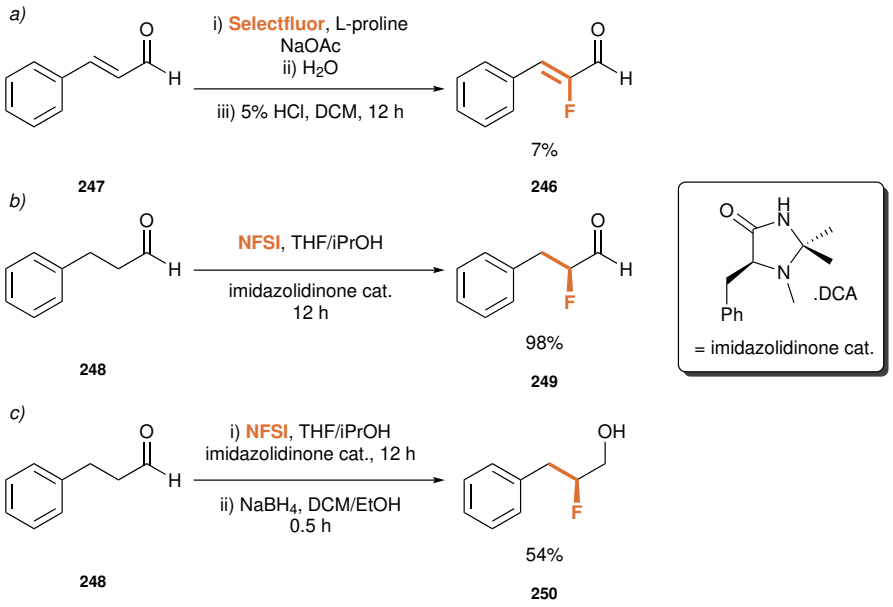
Previous work by Coutrot *et al* showed success with the coupling of an aldehyde to a similar phosphonate ester (dipropyl (1-fluoro-2-oxopropyl)phosphonate), under mildly basic conditions, to give the corresponding fluoroketone (**Scheme 112**). However, application of these conditions with compound **242** also resulted in no reaction. This method has the potential to be an incredibly useful tool for accessing a diverse array of fluorinated products from commercially available starting materials. Variation of either the aldehyde coupling partner or the functionality on the phosphonate ester may be performed with ease using this method, if successful.




**Scheme 112** The synthesis of α-fluoro ketones via HWE-like coupling of aldehydes with a phosphonate ester by Coutrot *et al.*[150]

### 3.0.5.3 Fluoroaldehyde Synthesis

The fluorination of α,β-unsaturated aldehydes was carried out to access α-fluoroenal substrates (**Scheme 113**). Initially, an aromatic substrate reported in the literature (**246**) was produced, before attempting to apply the procedure to additional aldehyde substrates.[152] Fluorination of the alkene adjacent to aldehyde was carried out in low yield using Selectfluor and a L-proline catalyst according to the literature procedure to produce **246** (**Scheme 113a**). However, in the literature, aldehyde **246** was immediately reduced to the alcohol for stability reasons.

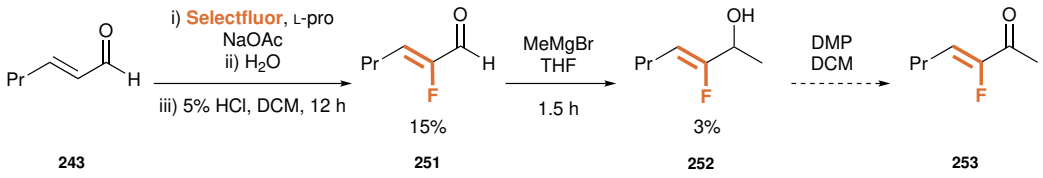



**Scheme 113** *Parts a, b:* The fluorination of dihydrocinnamaldehyde and fluorination to yield the analogous α-fluoro aldehydes. *Part c:* Reduction of the alkyl aldehyde substrate gives primary alcohol **250** for use in stereochemistry determination.

If **246** is accepted as a substrate with the engineered ER enzymes, the fluoroalkene will be reduced to the alkylfluoro species to give a chiral fluoroalkane (e.g. **249**). It is not yet known which isomer will be produced by the ER enzymes; HPLC data gathered from the enzymatic reaction must be compared with that of the reduced

compound (**Scheme 113b**) to determine the enantioselectivity of the biotransformation. Compound **249** was synthesised in excellent yield from commercially available **248** to give the α-fluoro aldehyde of known stereochemistry.[153] However, it should be noted that due to the low purity of **249**, its structure is only the proposed major product. Future research will lead to comparison of this data to HPLC data post-enzymatic reactions. However, it is likely that latent ADH enzymes exist within the enzyme sample and that aldehyde substrates may be reduced as a consequence. In response to this, synthesis of α-fluoro alcohol **250** was also carried out to obtain comparative data (**Scheme 113c**). When analysing these aldehydes using HPLC for use as reference compounds for biotransformations, it appeared that hydrates were formed, complicating the analytical process. Future work would involve running these substrates with alternative chiral columns in the hope of less complicated data and as a result, compounds which were more easily analysed by HPLC were focussed on.

This method of fluorination was also used to produce aliphatic substrate **251** from (*E*)-2-hexenal (**Scheme 114**). Although low yielding, this reaction highlights the selectivity of fluorination chemistry using Selectfluor with a simple L-proline catalyst. This aldehyde will be tested as a substrate for use with the ERs. Additionally, the aldehydes present a possible route to the corresponding ketone via Grignard chemistry to produce **252** (**Scheme 114**) which could be oxidised to form the corresponding methyl ketone **253**.

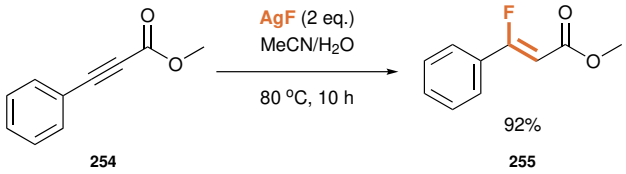



**Scheme 114** Fluorination of aliphatic aldehyde **243**, followed by Grignard addition and oxidation to yield a methyl ketone substrate.

Unoptimised conditions gave the secondary alcohol from the fluorinated aldehyde in a low yield. Conversion to methyl ketone **253** may be carried out via oxidation using Dess-Martin periodinane. This would provide the α-fluoro ketone to be tested as a potential ER substrate in future research.

#### 3.0.5.4 Metal-Assisted Fluorination

Additionally, β-fluoroenoates were targeted in order to expand the scope of the substrate screening and further test the versatility of ERs. Although not yet reported in the literature, it was thought that the use of β-fluoroenoates could provide access to interesting fluorinated materials if readily accepted, opening up the scope of these ER biotransformations to a new branch of substrates. Recently, fluorination of electron deficient alkynes was reported using AgF as the fluoride source under mild conditions.[154] The procedure presents an efficient way to access fluoroalkenes and also functionalise alkynes depending on the halogen source used.




**Scheme 115** Synthesis of β-fluoroalkenes using AgF as a fluoride source.[154]

Reported substrate **255** was synthesised from commercially available phenyl methylpropiolate **254** in excellent yield (**Scheme 115**). As of yet, β-fluoroenoates have not been tested as substrates for ER enzymes pQR1440+1811. A methyl ester was selected as the adjacent EWG to provide minimal hindrance for the enzyme. This fluorination chemistry provides an efficient pathway to a wide array of β-fluoro-β-phenylenoates from commercial starting materials, should trial substrate **255** be accepted.

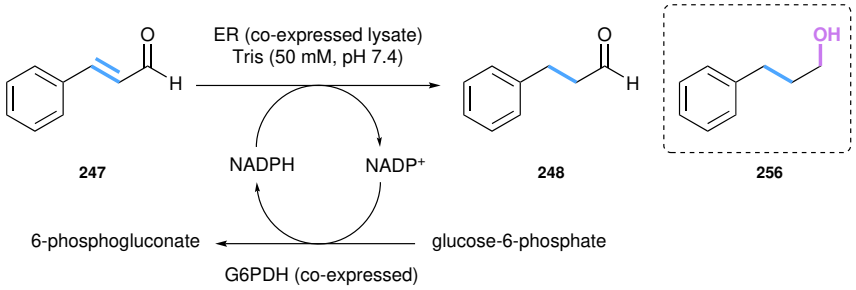
### 3.0.6 Biocatalytic Reduction of Fluoroalkenes

#### 3.0.6.1 Preliminary Substrate Screening

Initially, previously successful conditions[126] were employed to screen compounds. A "coupled enzyme" strategy was employed for the recycling of costly enzyme cofactor NADPH by G6PDH (commercial). It has been reported that NADH shows dominance in ER biotransformations[155] and so was avoided in the choice of cofactor.

A preliminary screen was carried out with cinnamaldehyde **247** as a model substrate based on its well recognised high activity with enzymes from the OYE family, in particular, ERs.[156,157] Cinnamaldehyde was subjected to King's reduction conditions[126] with purified enzymes to compare productivity (**Scheme 116**), and

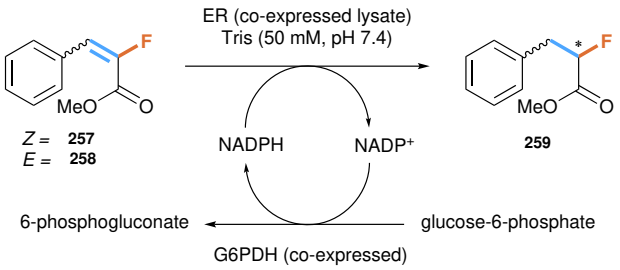
converted to the corresponding reduced product **248**. Previous work in the group found that the reduced cinnamyl products had identical retention times via HPLC and so the reaction was monitored by chiral GC.[126] The reaction was monitored by chiral GC using our established Chiral GC Method, which confirmed that there was full consumption of the alkene starting material. It has been reported within the group (unpublished) that commercial G6PDH sometimes show signs of contamination with ADH's, thereby leading to reduced alcohols as side-products. With this is mind, the corresponding alcohol **256** was run as a standard and compared against the GC data. It was found that reduced product **256** was formed as 31% of the reaction mixture from the latent ADH's present in the reaction mixture. Alcohol **256** was also found in the control experiments which did not contain ERs, thereby supporting the earlier statement of contaminated G6PDH.




**Scheme 116** Bioreduction of cinnamaldehyde with purified, ER+G6PDH. Biotransformations were performed in triplicate at 30 °C, 300 rpm for 20 h at a scale of 250 µL. Final concentrations were G6PNa (100 mM), NADP+ (3 mM), and alkene substrate (10 mM) in 50 mM Tris.HCl (pH 7.4) with DMSO. Co-expressed clarified lysate was applied at final concentrations of 1 mg/mL. Reactions were analysed by Chiral GC.

Given the success of biotransformations using substituted (*E*)-α-fluoro-β-arylenoates with ERs (mentioned previously in **Scheme 103**), initial screening of non-substituted α-fluoro-β-phenylenoates was carried out for both (*Z*) and (*E*) isomers (**Scheme 117**). Preliminary screenings of substrates **257** and **258** (synthesised by Dr Helen Allan) were carried out in triplicate and analysed by chiral HPLC. Conversions of the biotransformations were compared with known, readily accepted substrate methyl (*E*)-3-(4-cyanophenyl)-2-fluoroacrylate, seen previously in A. King's research.[126]

Previous research by King found that (*Z*)-α-fluoro-β-arylenoates were not readily accepted as substrates, however, *Z*-fluoroalkenes with non-substituted aromatic rings were yet to be explored.[126] For *(Z)*-fluoroalkene **257**, we saw no consumption of




**Scheme 117** Bioreduction of (*E/Z*)-α-fluoro-β-arylenoates with purified, ER+G6PDH. Biotransformations were performed in triplicate at 30 °C, 300 rpm for 20 h at a scale of 250 µL. Final concentrations were G6PNa (100 mM), NADP+ (3 mM), and alkene substrate (10 mM) in 50 mM Tris.HCl (pH 7.4) with DMSO. Co-expressed clarified lysate was applied at final concentrations of 1 mg/mL. Reactions were analysed by Chiral HPLC.

the starting material (retention time of 8.65 min), with no formation of the corresponding fluoroalkane **259** (retention time of 8.99 min). In alignment with King's findings, when testing *(E)*-fluoroalkene **258** with our ERs, some conversion to reduced product **259** occurred. As the *E*- starting material was contaminated with small quantities of *Z*-alkene, conversion of the *E* SM (retention time of 5.79 min) can be seen based on its depletion relative to the *Z* SM peak in the HPLC trace (**Figure 23**). The peak of **259** cannot be seen clearly in the chromatogram, as it is likely under the large peak of the *Z* alkene, and therefore its presence cannot be certified from this HPLC trace. From this experiment, we propose that EWGs are not required on the phenyl ring for acceptance of the substrate by the enzyme and that an *E* geometry is necessary for enzyme-catalysed reduction to take place. It should be noted that these HPLC results are preliminary and the nature of these observed compounds has not been confirmed by co-injection of chemical standards, or other means of verification.

Given the lack of literature precedence for β-fluoro compounds as substrates with ERs, β-fluoro-β-phenylenoate **255** was tested as a potential substrate, and the effect of fluorine placement in relation to the EWG explored. Initially, novel β-fluoro compound **255** (synthesis shown in Scheme 115) was subjected to ER biotransformation conditions (**Scheme 118**). The mixture was analysed by HPLC, to reveal that the substrate was not accepted by the ERs, leaving only starting material (**255**). Although no reduction of β-fluoroenoate **255** took place, this result gives insight into the potential pool of substrates which could be accepted by our ERs, and a result, gives insight into the scope of reduced fluoroalkane compounds which may be produced by this method. This lack of acceptance is likely to be caused by the

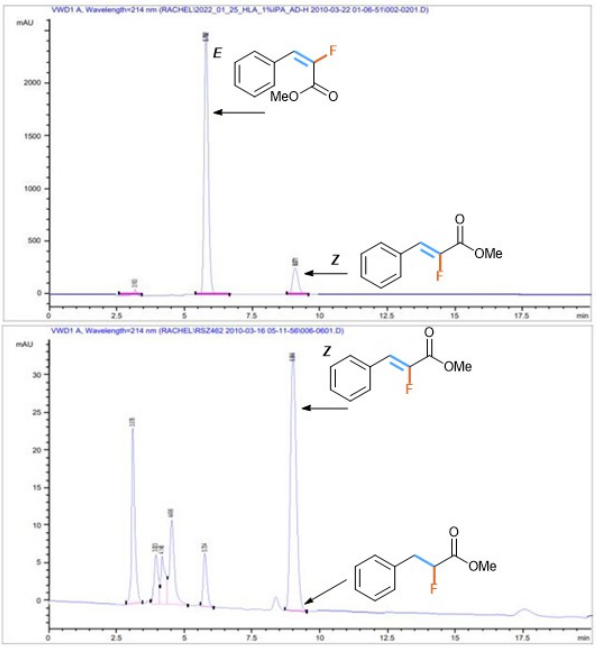
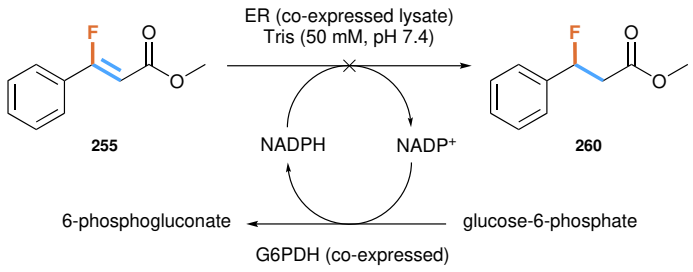



**Figure 23** Chromatograms (analytical HPLC) of the **258** and the small scale ER bioreduction of **258**, showing consumption of SM. Retention times: **258** 5.79 min, **259** 8.99 min.

*Z*-geometry of the alkene rather than the placement of the (relatively small) fluorine moiety, based on prior knowledge of *Z*-alkenes not being readily accepted by the enzymes. From this, we can infer qualities about the active site of the enzymes and the steric requirement of the substrates. It is worth noting that in previous research, A. King found that *Z*-enones weren't readily accepted by the enzymes. In this work, having exclusively produced the *Z*-β-fluoroenoate as a result of the synthetic route, we expected similar results and observed a lack of acceptance. As such, creation of the *E*-isomer of the β-fluoroenoate should be explored.




**Scheme 118** Bioreduction of β-fluoro compound, methyl (*Z*)-3-fluoro-3-phenylacrylate, with purified, co-expressed ER+G6PDH. Biotransformations were performed in triplicate at 30 °C, 300 rpm for 20 h at a scale of 250 µL. Final concentrations were G6PNa (100 mM), NADP+ (3 mM), and alkene substrate (10 mM) in 50 mM Tris.HCl (pH 7.4) with DMSO. Co-expressed clarified lysate was applied at final concentrations of 1 mg/mL. Reactions were analysed by Chiral HPLC.

The primary method of analysis for these biotransformations was via chiral HPLC. In order to obtain additional data, $^{19}$F NMR was attempted with the reaction mixtures. However, due to small quantities used in the reactions, the amount of material was not sufficient for NMR to be obtained. Future work would involve a scale up of the reaction to observe reaction progress by a shift in the $^{19}$F NMR spectrum.

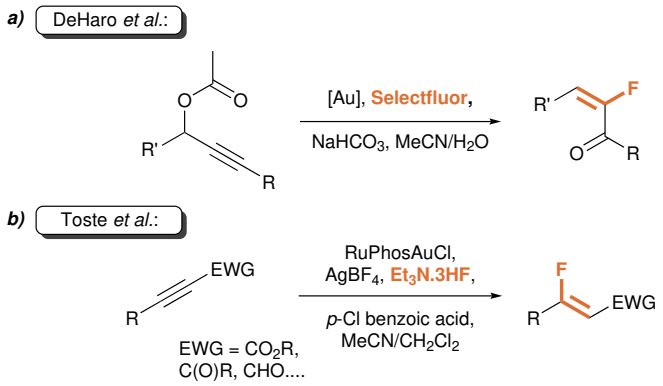
## 3.1 Conclusions

With the utility of fluorinated compounds becoming increasingly prevalent, a more sustainable and efficient synthesis becomes highly sought after. In summary, we have explored novel syntheses of fluoro-compounds for their use in enzyme-catalysed reduction reactions and subsequent utility as useful, chiral building blocks. We have explored the substrate scope for ERs NCR+pQR1811 with α-fluoro-β-phenylenoates without substitution on the aromatic ring, and have established that EWGs on the aromatic ring are not required for acceptance of the substrate by the ERs. We have also explored the acceptance of novel substrates with the ERs such as β-fluoro-β-phenylenoates. Additionally, we have explored the synthesis of enantioenriched fluoroalkanes and methods for creating a diverse array of fluoroalkene substrates through the testing of a fluorophosphonate species with a variety of aldehydes for HWE couplings. We have also proposed new areas for research in the synthesis of fluoroalkene substrates.

In this example, the β-fluoro-β-enoate was not accepted as a substrate for ERs, however, further research should be carried out with more electron-deficient β-fluoro-β-phenylenoates, such as those possessing *para* nitrile groups on the aromatic ring. The influence of the positioning of the fluorine atom relative to the alkene on acceptance by the enzymes should also be explored. In order to increase the accuracy of these experiments, fresh enzymes should be purified prior to testing.

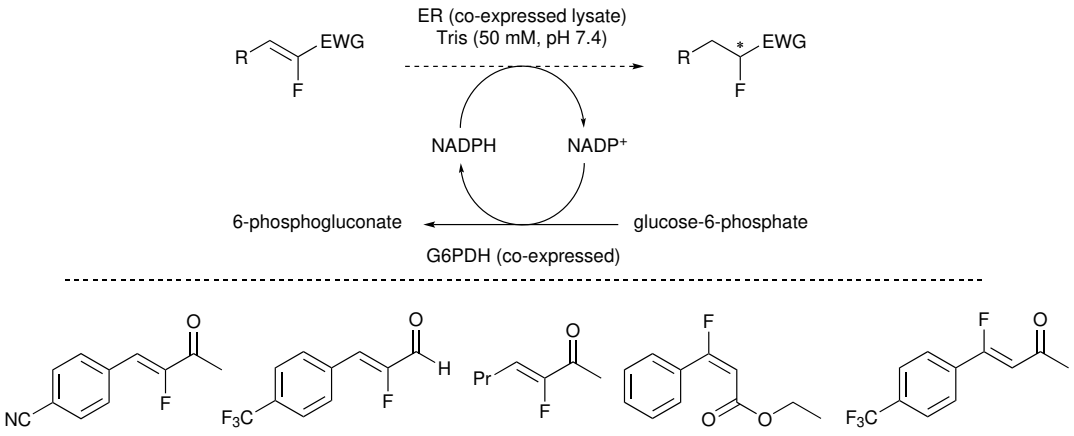
The syntheses of other fluoroalkene substrates may be carried out by alternative metal-catalysed processes such as the gold-catalysed rearrangement of propargyl acetates, as reported by DeHaro *et. al* (**Scheme 119a**). It was this method that was used to produce the butyl ketone substrate used in A. King's work.[126] Additionally, silver catalysed fluorination of aldehydes was reported via the fluorination of electron-deficient alkynes to give β-alkyl, β-fluoro Michael acceptors.[158] Not only does this procedure work for producing β-fluoro-α,β-unsaturated ketones and esters, but also

nitriles, amides and aldehydes (**Scheme 119b**).[158]




**Scheme 119** Synthesis of β-fluoroalkenes using Selectfluor (*part a*) and a HF-derivative (*part b*) as fluoride sources, catalysed by gold and silver respectively.[159,158]

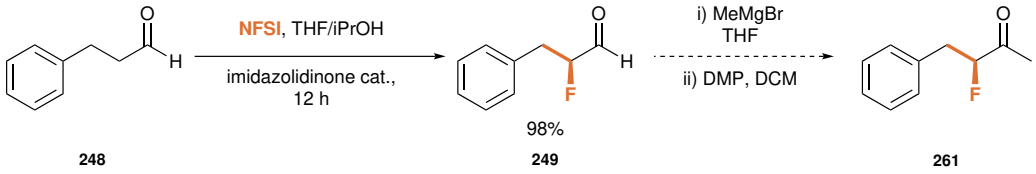
In order to expand on this research, a wider variety of electron-deficient α- and β-fluoroalkene substrates would be tested for their acceptance with novel ERs and conditions would be varied to optimise the reaction. For example, the analogous ketone of the β-fluoroenoate should be synthesised, as well as the corresponding *Z*-isomer, both to be tested as substrates (**Scheme 120**). This scheme shows substrates which were synthesised during this research but were not yet tested with the enzymes.




**Scheme 120** A general scheme for the transformation of an electron-deficient alkene to the corresponding alkane using novel ene-reductase enzymes with possible substrates shown below.

The synthesis of the *E*-fluoroenone could be carried out by reducing ester **255** to the corresponding aldehyde and converting to the ketone via Grignard chemistry. Formation of the *Z*-fluoroenoate could be carried out by utilising chemistry demonstrated by DeHaro (**Scheme 119**) through the use of gold catalysis and Selectfluor on alkyne starting materials. Based on these results, it is thought that *E*-substrates will be more

likely to be accepted by the enzymes and so focus for future research should be on this geometry. HPLC analysis of the reaction mixtures would be compared to retention times of the corresponding alkanes (including β-fluoro alcohols in the presence of latent ADHs) to confirm the stereochemistry produced by the ERs. For example, these aldehydes could be used to access a variety of ketones through addition of a Grignard, followed by oxidation (**Scheme 121**). The reduced compound produced by Grignard reaction on an enantioenriched alkyl aldehyde could be used for confirming stereochemistry produced by the enzyme.




**Scheme 121** The proposed synthesis of α-fluoroketone **261** using Grignard chemistry.

Future work should involve the development of improved GC conditions, due to difficulty with distinguishing between enantiomers based on similar retention times with the current methods. Previously, issues with aldehydes forming hydrates during HPLC analysis proved problematic, therefore future work with alteration of the chiral column used for analysis would also be carried out.

# Chapter 4

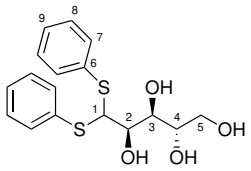
# Experimental

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific, Fluorochem or Acros Organics and used as supplied unless otherwise noted. Resins (Amberlite IRA743) were pre-washed with EtOAc, $Et_2O$ and $CH_2Cl_2$ and dried *in vacuo* prior to use. All reactions were monitored by TLC or $^1$H NMR. TLC analysis was conducted using aluminium plates pre-coated with silica gel 60 F254 (Merck KGaA). The spotted TLCs were visualised by UV light at 254 nm or appropriate staining agents. Column chromatography purification was performed using a Biotage Isolera flash purification system with Buchi FlashPure flash cartridges pre-packed with silica gel (40-60 μm). Petrol mentioned in procedures is petroleum ether b.p 40-60 °C. $^1$H NMR and $^{13}$C NMR spectra were recorded at 400, 500, 600 or 700 MHz (for $^1$H) and 151 or 176 MHz (for $^{13}$C) on a Bruker AMX400, AMX500, AMX600, AMX700 spectrometers at ambient temperature, unless otherwise indicated. Peaks are assigned as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), or multiplet (m). All shifts are reported in parts per million (ppm) and compared against residual solvent signals: $CHCl_3$ ($\delta$ = 7.26 ppm, s), MeOH ($\delta$ = 3.31 ppm, qn) or DMSO ($\delta$ = 2.50 ppm, qn) as the internal standard. Coupling constants ($J$) are quoted in Hertz (Hz) to one decimal place. Mass spectrometry was performed by the UCL Chemistry Mass Spectrometry Facility using either a Agilent LC- 6510 Q-TOF mass spectrometer (ThermoFischer Scientific) with a TOF mass analyser or the OrbitrapTM Q Exactive mass spectrometer with a FTMS mass analyser (ES+, CI, ES- modes). Infra-red spectra were obtained using a Perkin-Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode, all frequencies given in reciprocal centimetres ($cm^{-1}$). Melting points were measured with a Gallenkamp heating block and are uncorrected. Optical rotation was measured using an AA-65 Optical Activity

Ltd Polarimeter with working wavelength 589.44 nm, all $[\alpha]_D$ values were obtained using 10 mg/mL solutions unless otherwise stated and are given in degrees m $cm^3$ $g^{-1}$ $dm^{-1}$. Literature data is given in square parentheses.

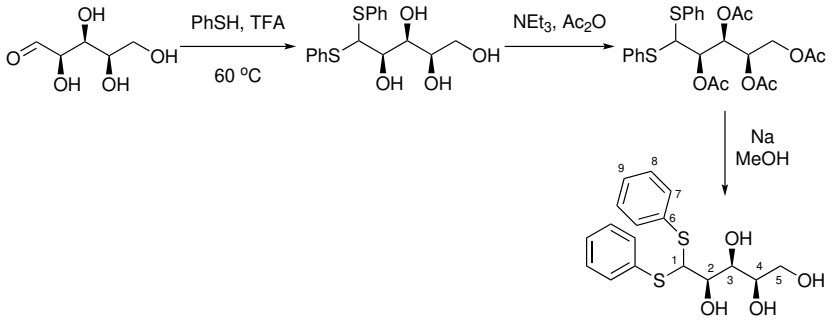
## 4.1 Sugar-Derived Compounds

L-Arabinose diphenyldithioacetal, (2S,3*S*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **70**:[78]




A mixture of L-arabinose (9.00 g, 60.0 mmol) and thiophenol (13.3 mL, 130 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (5.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 10.0 mL) to yield the desired dithioacetal (19.7 g, 56.0 mmol, 95%): M.p: 180–183 °C (EtOAc) [183–186 °C], $[\alpha]_D^{21}$ = -20 (*c* = 1.00, pyridine) [-23]; $^1$H NMR (700 MHz, $CD_3OD$) δ 7.46–7.42 (m, 4H, H-Ar), 7.31–7.20 (m, 6H, H-Ar), 4.76 (d, *J* = 7.7 Hz, 1H, H-1), 4.12 (d, *J* = 2.1 Hz, 1H, H-3), 4.01 (dd, *J* = 7.7, 2.1 Hz, 1H, H-2), 3.78 (d, *J* = 11.2 Hz, 1H, H-5), 3.70–3.65 (m, 1H, H-4), 3.62 (d, *J* = 11.2 Hz, 1H, H-5). $^{13}$C NMR (176 MHz, $CD_3OD$) δ 136.8 (Ar-Cq), 133.8 (Ar-C), 129.7 (Ar-C), 128.4 (Ar-C), 73.2 (C-2), 72.8 (C-3), 72.0 (C-4), 64.9 (C-5), 64.5 (C-1). $\nu_{max}$ (solid/$cm^{-1}$) 3300 (O-H), 1640 (Ar C=C), 1437 ($CH_2$), 1085 (C-O). Data is in accordance with the literature.

D-Xylose diphenyldithioacetal, (2*R*,3*S*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **71**:[78]

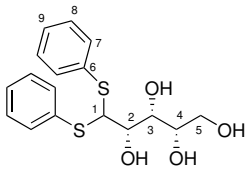



A mixture of D-xylose (3.00 g, 20.0 mmol) and thiophenol (4.51 mL, 40.0 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (3.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to give the crude xylose diphenyldithioacetal. A solution of the crude xylose diphenyldithioacetal (8.70 g, 24.0 mmol) in $NEt_3$ (48.0 mL, 0.34 mol) and acetic anhydride (16 mL, 0.17 mol) was stirred at room temperature for 12 h. The mixture was then poured onto ice-water (600 mL). After 15 min, the mixture was extracted into $CH_2Cl_2$ (2 × 50 mL) and the combined extracts were dried over $MgSO_4$ before concentrating to near dryness *in vacuo*. A solution of the product in $CH_2Cl_2$ was filtered through a pad of silica, washing with $CH_2Cl_2$. Evaporation of the filtrate and crystallisation of the product from a 4:1 ether/petrol mixture (50 mL) at 0 °C gave a white solid as a crude product. The crude material was then purified via silica-gel chromatography (2:1 EtOAc/petrol) to give D-xylose diphenyldithioacetal tetraacetate (959 mg, 160.0 mmol, 19%).

To a solution of D-xylose diphenyldithioacetal tetraacetate (959 mg, 160 mmol) in methanol (50 mL) was added sodium (10.0 mg); after stirring for 6 h, dry ice (2 g) was added and the mixture was filtered. The filtrate was evaporated to leave a residue, trituration of this solid with ethanol caused it to crystallise to an orange waxy solid (482 mg, 1.37 mmol, 86% crude). Recrystallisation from hot methanol gave the product as fine white crystals (134 mg, 0.38 mmol, 24%): M.p: 113-118 °C (EtOH) [100-101 °C]; $[\alpha]_D^{21}$ = -12 (*c* = 1.00, pyridine) [-8]; $^1$H NMR (600 MHz, $CD_3OD$) δ 7.45–7.39 (m, 4H, H-Ar), 7.32—7.20 (m, 6H, H-Ar), 4.74 (d, *J* = 5.0 Hz, 1H, H-1), 4.15–4.10 (m, 2H, H-5), 4.07 (m, 1H, H-3), 3.97 (t, *J* = 5.0 Hz, 1H, H-2), 3.88 (m, 1H, H-4); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 136.0 (Ar-Cq), 133.2 (Ar-C), 130.2 (Ar-C), 128.8 (Ar-C), 74.5 (C-2), 72.8 (C-3), 71.7 (C-4), 66.9 (C-5), 64.3 (C-1); $\nu_{max}$

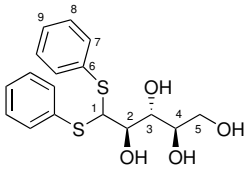
(solid/$cm^{-1}$) 3216 (O-H), 1578 ($CH_2$), 1045 (C-O). Data is in accordance with the literature.

L-Xylose diphenyldithioacetal, (2*S*,3*R*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **72**:




A mixture of L-xylose (3.00 g, 20.0 mmol) and thiophenol (4.52 mL, 40.0 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (5.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from $CH_2Cl_2$ before washing with diethyl ether (2 × 10.0 mL) and drying *in vacuo* to yield the product as a fine white powder (1.32 g, 3.7 mmol, 20%): M.p: 114-117 °C ($CH_2Cl_2$); $[\alpha]_D^{21}$ = +12 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.46–7.41 (m, 4H, H-Ar), 7.28–7.21 (m, 6H, H-Ar), 4.76 (d, *J* = 5.3 Hz, 1H, H-1), 4.12 (dd, *J* = 4.7, 3.7 Hz, 1H, H-2), 3.96-3.92 (m, 1H, H-3), 3.71 (ddd, *J* = 6.4, 5.0, 3.7 Hz, 1H, H-4), 3.62 (dd, *J* = 11.2, 5.0 Hz, 1H, H-5), 3.54 (dd, *J* = 11.2, 6.4 Hz, 1H, H-5); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 135.9 (Ar-Cq), 133.5 (Ar-C), 129.9 (Ar-C), 128.5 (Ar-C), 74.8 (C-2), 73.9 (C-3), 72.4 (C-4), 64.2 (C-5), 63.9 (C-1). $\nu_{max}$ (solid/$cm^{-1}$) 3384 (O-H), 2919 (O-H), 1084 (C-O); Calc'd for $C_{17}H_{21}O_4S_2$ $[M + H]^+$ 353.0803, found 353.0799.

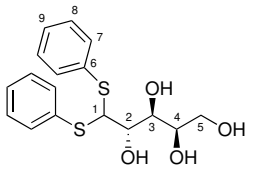
D-Ribose diphenyldithioacetal, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **73**:[78]




A mixture of D-ribose (13.0 g, 86.0 mmol) and thiophenol (19.5 mL, 190 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (21.0 mL) was warmed at 50–60 °C for 12 h whilst stirring. The reaction solution was concentrated *in vacuo* to a solid

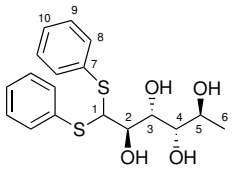
residue, which was then purified using silica gel chromatography (EtOAc/petrol 2:3) to yield the product as a yellow oil (6.98 g, 19.8 mmol, 23%): $[\alpha]_D^{21}$ = +100 (*c* = 1.00, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.51–7.47 (m, 2H, H-Ar), 7.34 (d, *J* = 7.6 Hz, 2H, H-Ar), 7.28–7.18 (m, 6H, H-Ar), 5.02 (d, 3.2 Hz, 1H, H-1), 4.41–4.39 (m, 1H, H-2), 4.18 (dt, *J* = 8.4, 4.3 Hz, 1H, H-4), 3.94 (dd, *J* = 7.9, 7.1 Hz, 1H, H-5), 3.85 (dd, *J* = 7.8, 7.2 Hz, 1H, H-5), 3.75 (d, *J* = 8.7 Hz, 1H, H-3); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 136.5 (Ar-Cq), 132.9 (Ar-C), 130.1 (Ar-C), 128.5 (Ar-C), 78.2 (C-2), 75.8 (C-3), 71.4 (C-4), 65.4 (C-5), 64.1 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 3426 (O-H), 1434 ($CH_2$), 1064 (C-O); Data is in accordance with the literature.

D-Lyxose diphenyldithioacetal, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **74**:[78]



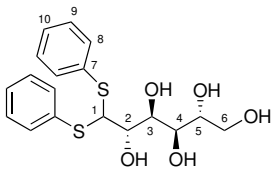

A mixture of D-lyxose (3.00 g, 0.02 mol) and thiophenol (4.50 mL, 0.044 mol, 2.2 eq.) in 90% trifluoroacetic acid in water (10.0 mL) was warmed at 50–60 °C for 1 h whilst stirring. The reaction solution was then concentrated *in vacuo* to a solid residue which crystallised to yield the product as a white solid (6.67 g, 0.019 mmol, 95%): $[\alpha]_D^{21}$ = +24 (*c* = 1.00, MeOH); $^1$H NMR (300 MHz, $CD_3OD$) δ 7.59–7.43 (m, 2H, H-Ar), 7.36–7.17 (m, 8H, H-Ar), 5.07 (d, *J* = 1.5 Hz, 1H, H-1), 4.12 (dd, *J* = 9.1, 1.3 Hz, 1H, H-5), 3.97–3.89 (m, 2H, H-5, H-2), 3.63–3.60 (m, 2H, H-3, H-4). $^{13}$C NMR (75 MHz, $CD_3OD$) δ 136.8 (Ar-Cq), 136.8 (Ar-Cq), 132.9 (Ar-C), 132.8 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 74.0 (C-2), 72.1 (C-3), 71.5 (C-4), 65.0 (C-5), 64.8 (C-1). $\nu_{max}$ (film/cm$^{-1}$) 3383 (O-H), 1438 ($CH_2$), 1067 (C-O); HRMS Calc'd for $C_{17}H_{20}O_4S_2{}^+Na$ $[M + Na]^+$ 375.0695, found 375.0686. Data is in accordance with the literature.

L-Rhamnose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol **75**:



A mixture of L-rhamnose (1.94 g, 0.01 mol) and thiophenol (2.3 mL, 0.02 mol, 2.2 eq.) in 90% trifluoroacetic acid in water (5.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 10.0 mL) and drying *in vacuo* to yield the product as white crystals (2.50 g, 6.00 mmol, 63%): M.p: 122-126 °C (EtOAc), $[\alpha]_D^{21}$ = +136 (*c* = 1.00, MeOH); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.54-7.49 (m, 2H, H-Ar), 7.37-7.32 (m, 2H, H-Ar), 7.30-7.15 (m, 6H, H-Ar), 5.08 (d, *J* = 1.5 Hz, 1H, H-1), 4.23-4.19 (m, 1H, H-2), 4.12-4.07 (m, 1H, H-3), 3.81-3.74 (m, 1H, H-4), 3.56 (m, 1H, H-5), 1.28-1.24 (m, 3H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 136.7 (Ar-Cq), 132.7 (Ar-C), 129.2 (Ar-C), 128.0 (Ar-C), 74.7 (C-2), 74.1 (C-3), 71.0 (C-4), 69.0 (C-5), 64.7 (C-1), 20.5 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3237 (O-H), 1064 (C-O). HRMS (ESI) Calc'd for $C_{18}H_{22}O_4S_2Na$ [M + Na]$^+$ 389.0857, found 389.0850.

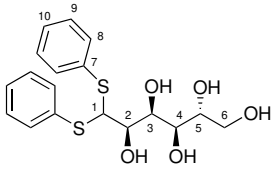
D-Mannose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-6-(cyclohexa-2,4-dien-1-ylthio)-6-(phenylthio)hexane-1,2,3,4,5-pentaol, **76**:[78]



A mixture of D-mannose (3.00 g, 0.017 mmol) and thiophenol (3.84 mL, 0.037 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (4.30 mL, 3.3 eq.) was stirred at 50–60 °C for 12 h. The reaction solution was then concentrated *in vacuo*. Addition of diethy ether (10.0 mL) resulted in crystallisation of the product as a white solid (3.55 g, 9.30 mmol, 55%): M.p: 116–119 °C ($Et_2O$) [140–141 °C]; $[\alpha]_D^{21}$ = -20 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.53-7.49 (m, 2H, H-Ar), 7.36-7.34 (m,

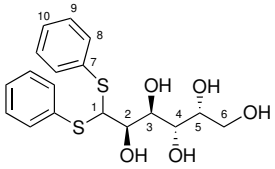
2H, H-Ar), 7.29-7.16 (m, 6H, H-Ar), 5.07 (d, $J$ = 1.4 Hz, 1H, H-1), 4.19 (dd, $J$ = 9.4, 0.8 Hz, 1H, H-3), 4.10 (dd, $J$ = 9.4, 1.4 Hz, 1H, H-2), 3.81 (dd, $J$ = 8.1 Hz, 0.8 Hz, 1H, H-4), 3.79 (dd, $J$ = 11.1, 3.6 Hz, 1H, H-6), 3.67-3.64 (m, 1H, H-5), 3.63-3.59 (m, 1H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 136.8 (Ar-Cq), 136.7 (Ar-Cq), 132.8 (Ar-C), 132.7 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 73.9 (C-2), 73.1 (C-3), 71.2 (C-4), 71.0 (C-5), 65.0 (C-1), 64.8 (C-6). $\nu_{max}$ (solid/cm$^{-1}$) 3355 (O-H), 1428 ($CH_2$), 1067 (C-O); HRMS (ESI) Calc'd for $C_{18}H_{22}O_5S_2Na$ [M + Na]$^+$ 405.0802, found 405.0802. Data is in accordance with the literature.

D-Glucose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol, **77**:[78]



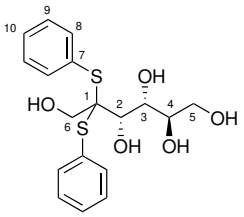

A mixture of D-glucose (1.00 g, 5.60 mmol) and thiophenol (1.3 mL, 12.3 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (2.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 10.0 mL) and drying *in vacuo* to yield the product as fine white crystals (12.8 g, 34.0 mmol, 80%): M.p: 153–156 °C (EtOAc) [158–160 °C]; $[\alpha]_D^{21}$ = +44 ($c$ = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.48-7.45 (m, 2H, H-Ar), 7.44-7.41 (m, 2H, H-Ar), 7.29-7.21 (m, 6H, H-Ar), 4.72 (d, $J$ = 4.9 Hz, 1H, H-1), 4.37-4.33 (m, 1H, H-3), 4.02-3.98 (m, 1H, H-2), 3.78-3.73 (m, 1H, H-4), 3.73-3.67 (m, 1H, H-5), 3.62-3.58 (m, 2H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 135.8 (Ar-Cq), 133.5 (Ar-C), 129.8 (Ar-C), 128.4 (Ar-C), 75.8 (C-2), 73.5 (C-3), 72.9 (C-4), 71.4 (C-5), 64.6 (C-1), 64.1 (C-6). $\nu_{max}$ (solid/cm$^{-1}$) 3286 (O-H), 2931 (O-H), 1438 ($CH_2$), 1167 (C-O). Data is in accordance with the literature.

D-Galactose diphenyldithioacetal, (2*R*,3*S*,4*S*,5*R*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol **78**:[78]



A mixture of D-galactose (1.80 g, 10.0 mmol) and thiophenol (2.26 mL, 22.0 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (3.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 10.0 mL) and drying *in vacuo* to yield the product as a white solid (1.93 g, 5.00 mmol, 50%): M.p: 170–174 °C (EtOAc) [175–176 °C]; $[\alpha]_D^{21}$ = -24 (*c* = 1.00, pyridine); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.48–7.39 (m, 4H, H-Ar), 7.31–7.21 (m, 6H, H-Ar), 4.77 (d, *J* = 8.1 Hz, 1H, H-1), 4.28 (dd, *J* = 9.1, 1.7 Hz, 1H, H-3), 4.04 (dd, *J* = 8.1, 1.7 Hz, 1H, H-2), 3.93 (td, *J* = 6.3, 1.6 Hz, 1H, H-5) 3.66 (dd, *J* = 9.1, 1.6 Hz, 1H, H-4), 3.64 (d, *J* = 6.3 Hz, 2H, H-6); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 136.4 (Ar-Cq), 133.9 (Ar-C), 129.8 (Ar-C), 129.0 (Ar-C), 73.1 (C-2), 71.9 (C-3), 71.8 (C-4), 70.8 (C-1), 65.0 (C-5), 64.7 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3256 (O-H), 1068 (C-O). Data is in accordance with the literature.

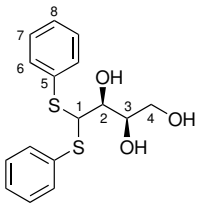
D-Fructose diphenyldithioacetal, (2*R*,3*R*,4*S*)-5,5-bis(phenylthio)hexane-1,2,3,4,6-pentaol **79**:



A mixture of D-fructose (1.00 g, 5.60 mmol) and thiophenol (1.30 mL, 12.3 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (2.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 10.0 mL) and drying *in vacuo* to yield the product as a pink solid (160 mg, 0.34 mmol, 8%): M.p: 107–110 °C (EtOAc), $[\alpha]_D^{21}$ = +64 (*c* = 1.00, pyridine); $^1$H NMR (700

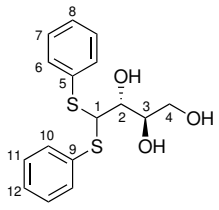
MHz, $CD_3OD$) δ 7.52–7.48 (m, 5H, H-Ar), 7.23–7.20 (m, 2H, H-Ar), 7.16–7.13 (m, 2H, H-Ar) 7.10–7.06 (m, 1H, H-Ar), 4.48 (d, *J* = 10.1 Hz, 1H, H-6), 4.42 (dd, *J* = 10.1, 1.4 Hz, 1H, H-6), 3.98–3.96 (m, 1H, H-2), 3.88 (dd, *J* = 10.1, 2.9 Hz, 1H, H-3), 3.79–3.76 (m, 1H, H-4), 3.60-3.54 (m, 1H, H-5), 3.24 (d, *J* = 13.7 Hz, 1H, H-5); $^{13}C$ NMR (176 MHz, $CD_3OD$) δ 137.0 (Ar-Cq), 130.1 (Ar-C), 129.7 (Ar-C), 129.4 (Ar-C), 97.1 (C-2), 71.9 (C-3), 70.7 (C-4), 70.3 (C-6), 66.7 (C-5), 42.8 (C-1); $\nu_{max}$ (solid/$cm^{-1}$) 3404 (O-H), 1039 (C-O). HRMS (ESI) Calc'd for $C_{18}H_{23}O_5S_2$ $[M + H]^+$ 382.0909, found 382.1096.

D-Threose diphenyldithioacetal, (2*R*,3*S*)-4,4-bis(phenylthio)butane-1,2,3-triol **81**:



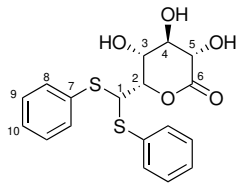

A mixture of D-threose (300 mg, 2.50 mmol) and thiophenol (565 μL, 5.50 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (632 μL, 8.25 mmol, 3.3 eq.) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then recrystallised from boiling ethyl acetate before washing with diethyl ether (2 × 5.00 mL) to yield the product as a white solid (48 mg, 0.15 mmol, 6%): M.p: 87-89 °C (EtOAc); $[\alpha]_D^{21}$ = -16 (*c* = 1.00, ethanol); $^1H$ NMR (700 MHz, $CDCl_3$) δ 7.44–7.36 (m, 4H, H-Ar), 7.32–7.25 (m, 6H, H-Ar), 4.59 (d, *J* = 7.5 Hz, 1H, H-1), 4.27 (ddd, *J* = 7.3, 6.1, 2.1 Hz, 1H, H-2), 3.76 (dd, *J* = 7.6, 2.1 Hz, 1H, H-3), 3.16–3.09 (m, 2H, H-4); $^{13}C$ NMR (176 MHz, $CDCl_3$) δ 133.5 (Ar-Cq), 133.0 (Ar-C), 130.2 (Ar-C), 129.3 (Ar-C), 72.8 (C-2), 68.9 (C-3), 66.0 (C-1), 63.9 (C-4); $\nu_{max}$ (solid/$cm^{-1}$) 3425 (O-H), 2917 (O-H), 1477 ($CH_2$), 1067 (C-O); HRMS (ESI) Calc'd for $C_{16}H_{19}O_3S_2$ $[M + H]^+$ 322.0697, found 322.0619.

D-Erythrose diphenyldithioacetal, (2*R*,3*R*)-4,4-bis(phenylthio)butane-1,2,3-triol **82**:



A mixture of D-erythrose (300 mg, 2.50 mmol) and thiophenol (565 μL, 5.50 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (632 μL, 3.3 eq.) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then purified via silica-gel chromatography (3:2 EtOAc/Petrol) to yield the product as a pink oil (582 mg, 1.81 mmol, 72%): $[\alpha]_D^{21}$ = +76 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.53–7.48 (m, 2H, H-Ar), 7.35 (m, 2H, H-Ar), 7.27–7.16 (m, 6H, H-Ar), 5.05 (d, *J* = 3.0 Hz, 1H, H-1), 4.05-3.97 (m, 1H, H-2), 3.95–3.91 (m, 1H, H-3), 3.82 (dd, *J* = 11.5, 3.1 Hz, 1H, H-4), 3.67-3.59 (dd, *J* = 11.4, 3.1, 1H, H-4); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 136.6 (Ar-Cq), 136.5 (Ar-Cq), 133.1 (Ar-C), 133.0 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 74.9 (C-2), 73.1 (C-3), 65.0 (C-1), 64.6 (C-4); $\nu_{max}$ (film/cm$^{-1}$) 3404 (O-H), 1581 (C-H), 1439 ($CH_2$), 1067 (C-O); HRMS (ESI) Calc'd for $C_{16}H_{19}O_3S_2$ $[M + H]^+$ 321.0697, found 321.0618.

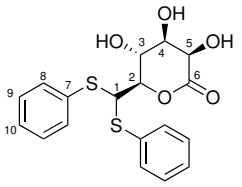
D-Galacturonic acid diphenyldithioacetal lactone, (3*S*,4*R*,5*R*,6*S*)-6-(bis(phenylthio)methyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-one **83**:



A mixture of D-galacturonic acid (8.00 g, 41.2 mmol) and thiophenol (9.30 mL, 90.6 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (3.50 mL, 45.3 mmol, 1.1 eq.) was stirred at 50–60 °C for 3 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a white solid (4.219 g, 11.15 mmol, 27%): $[\alpha]_D^{21}$ = +44 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.56–7.50 (m, 2H, H-Ar), 7.43–7.37 (m, 2H, H-Ar), 7.34–7.25 (m, 6H, H-Ar), 4.76 (dd, *J* =

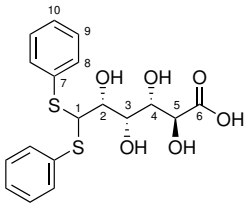
8.2, 3.4 Hz, 1H, H-3), 4.72 (d, *J* = 6.9 Hz, 1H, H-1), 4.36 (d, *J* = 8.9 Hz, 1H, H-5), 4.16 (t, *J* = 8.6 Hz, 1H, H-4), 3.86 (dd, *J* = 6.9, 3.4 Hz, 1H, H-2); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 175.8 (C=O), 133.6 (Ar-Cq), 132.6 (Ar-C), 129.2 (Ar-C), 128.5 (Ar-C), 79.4 (C-2), 74.8 (C-3), 74.1 (C-4), 67.0 (C-5), 63.0 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 3365 (O-H), 2070 (Ar-CH), 1708 (C=O), 1119 ($CH_2$); HRMS (ESI) Calc'd for $C_{18}H_{18}O_5S_2Na$ $[M + Na]^+$ 401.0493, found 401.0487.

D-Glucuronic acid diphenyldithioacetal lactone, (3*R*,4*R*,5*R*,6*R*)-6-(bis(phenylthio)methyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-one **84**:



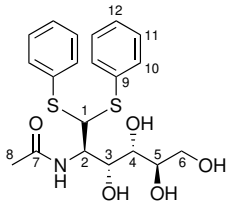

A mixture of D-glucuronic acid (2.00 g, 10.0 mmol) and thiophenol (2.30 mL, 20.0 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (5.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then purified using silica gel chromatography (acetone/$CH_2Cl_2$ 2:3) with pure product isolated as a brown oil (1.48 g, 3.74 mmol, 37%). Product contaminated with EtOAc, unable to isolate upon replication. $[\alpha]_D^{21}$ = +8 (*c* = 1.00, pyridine); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.57–7.53 (m, 4H, H-Ar), 7.33–7.25 (m, 6H, H-Ar), 5.38 (d, *J* = 2.2 Hz, 1H, H-1), 4.88 (dd, *J* = 5.3, 3.8 Hz, 1H, H-4), 4.82 (d, *J* = 3.8 Hz, 1H, H-3), 4.60 (d, *J* = 5.3 Hz, 1H, H-5), 4.36 (d, *J* = 2.2 Hz, 1H, H-2); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 176.8 (C=O), 135.8 (Ar-Cq), 133.0 (Ar-C), 130.0 (Ar-C), 128.6 (Ar-C), 95.7 (C-2), 85.8 (C-3), 80.9 (C-4), 71.1 (C-5), 61.6 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 3421 (O-H), 1779 (C=O), 1069 (C-O); HRMS (ESI) Calc'd for $C_{18}H_{18}O_5S_2Na$ $[M + Na]^+$ 401.0493, found 401.0493.

D-Glucuronic acid diphenyldithioacetal, (2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6,6-bis(phenylthio)hexanoic acid **85**:



A mixture of D-glucuronic acid (1.00 g, 5.15 mmol) and thiophenol (1.16 mL, 11.3 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (3.00 mL) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which was then purified using silica gel chromatography (acetone/$CH_2Cl_2$ 2:3) to yield the product as a brown oil (155 mg, 0.39 mmol, 8%): $[\alpha]_D^{21}$ = +8 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.52–7.48 (m, 2H, H-Ar), 7.34–7.25 (m, 8H, H-Ar), 5.27 (d, *J* = 4.2 Hz, 1H, H-1), 4.46 (dd, *J* = 7.6, 2.3 Hz, 1H, H-4), 4.45–4.41 (m, 1H, H-3), 4.38 (d, *J* = 2.4 Hz, 1H, H-5), 4.11–4.06 (m, 1H, H-2); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 174.2 (C=O), 133.7 (Ar-Cq), 133.0 (Ar-C), 130.0 (Ar-C), 128.6 (Ar-C), 93.3 (C-5), 86.9 (C-3), 71.9 (C-4), 59.3 (C-2), 51.3 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 3446 (O-H), 2920 (O-H) 1725 (C=O) 1477 (C-H), 1437 (COOH), 1023 (C-O); HRMS (ESI) cald for $C_{18}H_{19}O_6S_2$ $[M]^-$ 395.0623, found 395.0622.

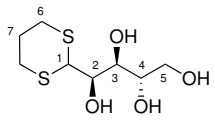
*N*-Acetylglucosamine diphenyldithioacetal, N-((2*R*,3*R*,4*S*,5*R*)-3,4,5,6-tetrahydroxy-1,1-bis(phenylthio)hexan-2-yl)acetamide **87**:



A mixture *N*-acetylglucosamine (100 mg, 0.61 mmol) and thiophenol (138 μL, 1.34 mmol, 2.2 eq.) in 90% trifluoroacetic acid in water (1.00 mL) was warmed at 50–60 °C for 12 h whilst stirring. The reaction solution was then concentrated *in vacuo* to a solid residue, which was then precipitated from $CH_2Cl_2$ before washing with diethyl ether (2 × 5.00 mL) to yield the product as a white solid (163 mg, 0.39 mmol, 63%): M.p: 128-132 °C ($CH_2Cl_2$); $[\alpha]_D^{21}$ =-8 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.50–7.46 (m, 4H, H-Ar), 7.31–7.27 (m, 4H, H-Ar), 7.25–7.22 (m, 2H, H-Ar), 4.77 (d, *J* = 10.4, 1H, H-1), 3.88–3.85 (m, 1H, H-6), 3.83–3.72 (m,

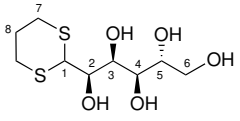
2H, H-2, H-3), 3.70–3.65 (m, 1H, H-6), 3.50–3.44 (m, 1H, H-4), 3.36–3.32 (m, 1H, H-5), 1.99 (s, 3H, H-8); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 173.5 (C=O), 135.8 (Ar-Cq), 131.0 (Ar-C), 129.8 (Ar-C), 127.9 (Ar-C), 88.3 (C-3), 82.0 (C-4), 77.3 (C-5), 71.7 (C-6), 62.7 (C-2), 56.1 (C-1), 22.8 (C-8); $\nu_{max}$ (film/cm$^{-1}$) 3304 (O-H), 2919 (N-H), 2037 (Ar-CH), 1670 (C=O), 1428 ($CH_2$), 1066 (C-O); HRMS (ESI) Calc'd for $C_{20}H_{26}NO_5S_2$ $[M + H]^+$ 424.1247, found 424.1244.

L-Arabinose 1,3-dithiane, (1*R*,2*S*,3*S*)-1-(1,3-dithian-2-yl)Butane-1,2,3,4-tetraol **90**:




A mixture of L-arabinose (3.00 g, 20.0 mmol) and 1,3-propanedithiol (2.20 mL, 22.0 mmol, 1.1 eq.) in 90% trifluoroacetic acid in water (7.70 mL, 5 eq.) was stirred at 50–60 °C for 12 h. The reaction solution was concentrated *in vacuo* to a solid residue, which then crystallised to give the dithiane as a white crystalline solid. The solid was washed with $Et_2O$ and dried to yield the product as white crystals (2.55 g, 4.00 mmol, 53%): M.p: 138–140 °C ($Et_2O$); $[\alpha]_D^{21}$ = -28 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CD_3OD$) δ 4.35 (dd, *J* = 11.5, 2.5 Hz, 1H, H-5), 4.14 (dd, *J* = 11.5, 6.1 Hz, 1H, H-5), 4.09 (d, *J* = 9.6, Hz, 1H, H-2), 4.05 (dd, *J* = 9.6, 1.0 Hz, 1H, H-3), 3.95 (dd, *J* = 9.5, 1.0 Hz, 1H, H-1), 3.90 (dd, *J* = 6.1, 2.5 Hz, 1H, H-4), 2.97–2.87 (m, 2H, H-6), 2.78–2.70 (m, 2H, H-6), 2.06–2.01 (m, 1H, H-7), 1.95–1.88 (m, 1H, H-7); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 71.0 (C-2), 70.7 (C-3), 70.3 (C-4), 67.7 (C-5), 28.7 (C-1), 28.4 (C-6), 26.9 (C-6), 20.7 (C-7); $\nu_{max}$ (solid/cm$^{-1}$) 3400 (O-H), 2931 (R-CH) 1785 (R-CH), 1220 (C-O); HRMS (ESI) Calc'd for $C_8H_{16}O_4S_2Na$ $[M + Na]^+$ 263.0382, found 263.0381.

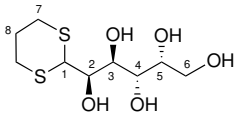
D-Glucose 1,3-dithiane, (1*R*,2*S*,3*R*,4*R*)-1-(1,3-dithian-2-yl)pentane-1,2,3,4,5-pentaol **91**:




A mixture of D-glucose (3.00 g, 16.7 mmol) and 1,3-propanedithiol (1.80 mL, 18.3

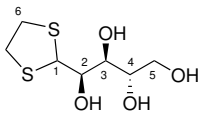
mmol, 1.1 eq.) in 90% trifluoroacetic acid in water (6.40 mL, 5 eq.) was stirred at 50–60 °C for 4 h. The reaction solution was concentrated *in vacuo* to a solid residue, which then crystallised to give the dithiane as a white crystalline solid. The solid was washed with $Et_2O$ and dried to yield the product as white crystals (4.12 g, 15.2 mmol, 92%): M.p: 137–139 °C ($Et_2O$), $[\alpha]_D^{21}$ = +40 (*c* = 1.00, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 4.19 (dd, *J* = 4.0, 2.9 Hz, 2H, H-1, H-5), 3.94 (dd, *J* = 7.9, 4.0 Hz, 1H, H-2), 3.77 (dd, *J* = 11.1, 3.5 Hz, 1H, H-6), 3.70 (ddd, *J* = 7.9, 5.8, 3.5 Hz, 1H, H-4), 3.66 (dd, *J* = 7.9, 5.8 Hz, 1H, H-3), 3.62 (dd, *J* = 11.1, 2.9 Hz, 1H, H-6), 2.95–2.88 (m, 2H, H-7), 2.84–2.75 (m, 2H, H-7), 2.08–2.02 (m, 1H, H-8), 1.94–1.85 (m, 1H, H-8); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 75.3 (C-2), 74.2 (C-4), 73.0 (C-5), 70.2 (C-3), 64.7 (C-6), 50.1 (C-1), 29.6 (C-7), 29.0 (C-7), 27.0 (C-8); $\nu_{max}$ (solid/cm$^{-1}$) 3346 (O-H), 2889 (C-H str), 1416 (C-H b), 1082 (C-O), 1024 (C-O); HRMS (ESI) Calc'd for $C_9H_{18}O_5S_2$ $[M + Na]^+$ 293.0488, found 293.0488.

D-Galactose 1,3-dithiane, (1*R*,2*S*,3*S*,4*R*)-1-(1,3-dithian-2-yl)pentane-1,2,3,4,5-pentaol **92**:



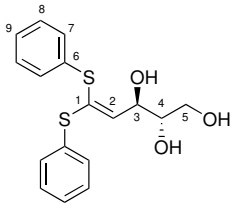

A mixture of D-galactose (3.00 g, 16.7 mmol) and 1,3-propanedithiol (1.80 mL, 18.3 mmol, 1.1 eq.) in 90% trifluoroacetic acid in water (6.40 mL, 5 eq.) was stirred at 50–60 °C for 4 h. The reaction solution was concentrated *in vacuo* to a solid residue, which then crystallised to give the dithiane as a white crystalline solid. The solid was washed with $Et_2O$ and dried to yield the product as white crystals (4.00 g, 14.8 mmol, 89%): M.p: 185–187 °C ($Et_2O$), $[\alpha]_D^{21}$ = +52 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CD_3OD$) δ 4.53 (dd, *J* = 10.9, 8.1 Hz, 1H, H-6), 4.42 (dd, *J* = 11.0, 4.9 Hz, 1H, H-6), 4.21 (ddd, *J* = 8.1, 4.9, 1.5 Hz, 1H, H-5), 4.12–4.09 (m, 2H, H-3, H-1), 3.66 (d, *J* = 1.6 Hz, 1H, H-4), 3.66–3.63 (m, 1H, H-2), 3.01–2.87 (m, 2H, H-7), 2.81–2.68 (m, 2H, H-7), 2.11–1.99 (m, 1H, H-8), 1.93–1.83 (m, 1H, H-8); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 78.3 (C-5), 71.7 (C-2), 71.3 (C-4), 70.9 (C-1), 70.2 (C-6), 68.7 (C-1), 28.7 (C-7), 28.4 (C-7), 26.1 (C-8). $\nu_{max}$ (solid/cm$^{-1}$) 3366 (O-H), 2928 (C-H str), 1422 (C-H b), 1026 (C-O); HRMS (ESI) Calc'd for $C_9H_{18}O_5S_2Na$ $[M + Na]^+$ 293.0488, found 293.0484.

L-Arabinose 1,2-dithiane, (1*R*,2*S*,3*S*)-1-(1,3-dithiolan-2-yl)butane-1,2,3,4-tetraol **93**:




A mixture of L-arabinose (3.00 g, 20.0 mmol) and 1,2-ethanedithiol (1.85 mL, 22.0 mmol, 1.1 eq.) in 90% trifluoroacetic acid in water (7.70 mL, 5 eq.) was stirred at 50–60 °C for 4 h. The reaction solution was concentrated *in vacuo* to a solid residue, which then crystallised to give the dithiane as a white crystalline solid. The solid was washed with $Et_2O$ and dried to yield the product as white crystals (3.66 g, 16.2 mmol, 81%): M.p: 152–156 °C ($Et_2O$), $[\alpha]_D^{21}$ = +36 (*c* = 1.00, MeOH); $^1$H NMR (400 MHz, $CD_3OD$) δ 4.66 (d, *J* = 9.7 Hz, 1H, H-1), 3.79 (dd, *J* = 10.7, 2.9 Hz, 1H, H-5), 3.73 (dd, *J* = 9.7, 1.2 Hz, 1H, H-2), 3.69 (d, *J* = 8.5 Hz, 1H, H-3), 3.66 (dd, *J* = 8.5, 2.9 Hz, 1H, H-4), 3.61 (d, *J* = 10.8 Hz, 1H H-5), 3.23–3.15 (m, 4H, H-6); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 75.8 (C-4), 73.1 (C-2), 65.1 (C-5), 57.0 (C-1), 39.3 (C-3), 38.6 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3303 (O-H), 2923 (C-H str), 1387 (C-H b), 1076 (C-O); HRMS (ESI) Calc'd for $C_7H_{15}O_4S_2$ $[M + H]^+$ 227.0406, found 227.0406.

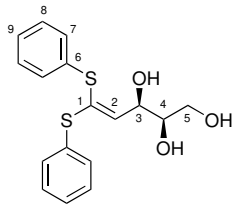
L-Arabinose diphenyldithioacetal alkene, (2*S*,3*R*)-5,5-bis(Phenylthio)pent-4-ene-1,2,3-triol **95**:[84,85]




To a mixture of L-arabinose diphenyldithioacetal (5.57 g, 15.8 mmol) in MeOH (30.0 mL), was added dimethyl carbonate (6.20 mL, 110.6 mmol, 7 eq.) and $K_2CO_3$ (4.37 g, 31.6 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being filtered. The residue was washed with acetone (2 × 10.0 mL) and the filtrate concentrated under reduced pressure to yield the product as a pale-yellow solid (5.24 g, 15.7 mol, 99%): M.p: 178-181 °C (MeOH), $[\alpha]_D^{21}$ = +60 (*c* = 1.00, pyridine); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.33–7.19 (m, 10H, H-Ar), 6.29 (d, *J* = 8.7 Hz, 1H, H-2), 4.87–4.82 (m, 1H, H-3), 3.68–3.60 (m, 2H, H-5), 3.64–3.56

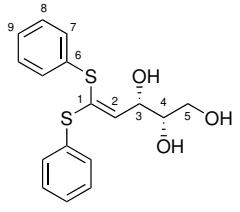
(m, 1H, H-4); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 140.7 (C-1), 133.4 (Ar-Cq), 132.4 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 128.9 (C-2), 76.2 (C-3), 72.2 (C-4), 64.4 (C-5); $\nu_{max}$ (solid/cm$^{-1}$) 3265 (O-H), 1610 (Ar-CH), 1022 (C-O); HRMS (ESI) Calc'd for $C_{17}H_{19}O_3S_2$ $[M + H]^+$ 335.0770, found 335.0777.

D-Xylose diphenyldithioacetal alkene, (2*R*,3*R*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol **96**:[85]




To a mixture of D-xylose diphenyldithioacetal (35.0 mg, 0.10 mmol) in MeOH (2.00 mL), was added dimethyl carbonate (10.0 μL, 0.15 mmol, 1.5 eq.) and $K_2CO_3$ (28.0 mg, 0.20 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (acetone/$CH_2Cl_2$ 2:3) to yield the product as a yellow oil (160 mg, 0.05 mmol, 48%): $[\alpha]_D^{21}$ = -44 (*c* = 1.00, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.31–7.23 (m, 10H, H-Ar), 6.23 (d, *J* = 8.8 Hz, 1H, H-2), 4.80 (dd, *J* = 8.7, 4.6 Hz, 1H, H-3), 3.62 (dd, *J* = 10.9, 6.9 Hz, 1H, H-5), 3.59–3.55 (m, 1H, H-4), 3.50 (dd, *J* = 10.9, 6.7 Hz, 1H, H-5); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 140.3 (C-1), 134.7 (Ar-Cq), 134.5 (Ar-Cq), 134.3 (Ar-C), 133.5 (Ar-C), 132.2 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 129.0 (Ar-C), 128.3 (C-2), 76.1 (C-3), 71.6 (C-4), 64.2 (C-5); $\nu_{max}$ (film/cm$^{-1}$) 3329 (O-H), 1640 (Ar-CH), 1580 (C=C), 1474 ($CH_2$), 1023 (C-O); HRMS (ESI) Calc'd for $C_{17}H_{19}O_3S_2$ $[M + H]^+$ 335.0770, found 335.0776.

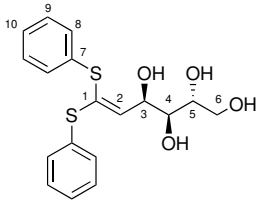
L-Xylose diphenyldithioacetal alkene, (2*S*,3*S*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol **97**:[85]




To a mixture of L-xylose diphenyldithioacetal (300 mg, 0.85 mmol) in MeOH (2.00

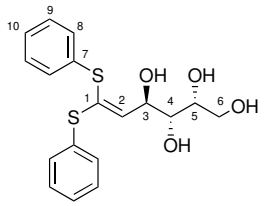
mL), was added dimethyl carbonate (71.0 μL, 1.28 mmol, 1.5 eq.) and $K_2CO_3$ (235 mg, 1.70 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being filtered and washed with MeOH (2 × 5.00 mL). The residue was then concentrated under reduced pressure to yield the product (224 mg, 0.67 mmol, 79%): M.p: 196-198 °C (MeOH), $[\alpha]_D^{21}$ = +64 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.32–7.23 (m, 10H, H-Ar), 6.23 (d, *J* = 8.8 Hz, 1H, H-2), 4.79 (dd, *J* = 8.8, 4.7 Hz, 1H, H-3), 3.62 (dd, *J* = 10.8, 4.6 Hz, 1H, H-5), 3.59–3.56 (dd, *J* = 6.8, 4.7 Hz, 1H, H-4), 3.52–3.48,(dd, *J* = 10.8, 6.8 Hz 1H, H-5); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 140.3 (C-1), 134.7 (Ar-Cq), 134.5 (Ar-Cq), 134.3 (Ar-C), 133.5 (Ar-C), 132.2 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 129.0 (Ar-C), 128.2 (C-2), 76.2 (C-3), 71.6 (C-4), 64.2 (C-4); $\nu_{max}$ (solid/cm$^{-1}$) 3364 (O-H), 1580 (C=C), 1475 ($CH_2$), 1068 (C-O); HRMS (ESI) Calc'd for $C_{17}H_{19}O_3S_2$ $[M + H]^+$ 335.0770, found 335.0777.

D-Glucose diphenyldithioacetal alkene, (2*R*,3*S*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol **101**:[85]



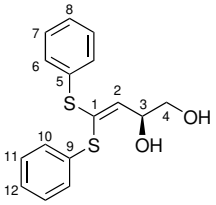

To a mixture of D-glucose diphenyldithioacetal (3.54 g, 9.26 mmol) in MeOH (8.00 mL), was added dimethyl carbonate (0.81 mL, 18.5 mmol, 1.5 eq.) and $K_2CO_3$ (2.56 g, 18.5 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and recrystallised from boiling EtOAc and washed with $Et_2O$ (2 × 5.00 mL) to yield the product (3.19 g, 8.78 mmol, 97%): M.p: 144-148 °C (EtOAc), $\alpha]_D^{25}$ = -32 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.30–7.20 (m, 10H, H-Ar), 6.42 (d, *J* = 8.6 Hz, 1H, H-2), 5.07 (dd, *J* = 8.6, 2.6 Hz, 1H, H-3), 3.78 (dd, *J* = 11.1, 3.3 Hz, 1H, H-6), 3.70 (ddd, *J* = 7.9, 6.0, 3.3 Hz, 1H), 3.66 (dd, *J* = 11.1, 6.0 Hz, 1H, H-4), 3.47 (dd, *J* = 7.9, 2.6 Hz, 1H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 141.4 (C-1), 133.6 (Ar-Cq), 133.3 (Ar-C), 132.2 (Ar-C), 130.0 (Ar-C), 129.7 (C-2), 72.5 (C-3), 69.4 (C-4), 63.3 (C-5), 62.4 (C-6); $\nu_{max}$ (film/cm$^{-1}$) 3253 (O-H) 1641 (Ar-CH), 1013 (C-O); HRMS (ESI) Calc'd for $C_{18}H_{21}O_4S_2$ $[M + H]^+$ 365.0876, found 365.0898.

D-Galactose diphenyldithioacetal alkene, (2*R*,3*R*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol **102**:[85]



To a mixture of D-galactose diphenyldithioacetal (100 mg, 0.26 mmol) in MeOH (15.0 mL), was added dimethyl carbonate (33.0 μL, 0.39 mmol, 1.5 eq.) and $K_2CO_3$ (72.0 mg, 0.52 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (acetone/$CH_2Cl_2$ 1:5) to yield the product (53.0 mg, 0.14 mmol, 53%): M.p: 80-84 °C ($CH_2Cl_2$), $[\alpha]_D^{21}$ = +28 (*c* = 1.00, pyridine); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.34–7.17 (m, 10H, H-Ar), 6.32 (d, *J* = 8.7 Hz, 1H, H-2), 4.90 (dd, *J* = 8.7, 7.2 Hz, 1H, H-3), 3.87 (td, *J* = 6.5, 2.5 Hz, 1H, H-5), 3.65 (dd, *J* = 10.9, 6.4 Hz, 1H, H-6), 3.62 (dd, *J* = 10.9, 6.5 Hz, 1H, H-6), 3.55 (dd, *J* = 7.2, 2.5 Hz, 1H, H-4); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 141.9 (C-1), 135.0 (Ar-Cq), 135.0 (Ar-Cq), 134.8 (Ar-C), 133.2 (Ar-C), 132.4 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 128.8 (Ar-C), 128.3 (C-2), 74.4 (C-3), 72.2 (C-4), 71.5 (C-5), 64.7 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3336 (O-H), 1578 (Ar-CH), 1438 ($CH_2$); HRMS (ESI) Calc'd for $C_{18}H_{21}O_4S_2$ $[M + H]^+$ 365.0676, found 365.0668.

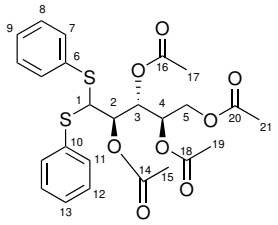
D-Threose diphenyldithioacetal alkene, (2*R*,3*S*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol **108**:



D-Threose diphenyldithioacetal (24 mg, 0.075 mmol) was dissolved in MeOH (2 mL) followed by addition of DMC (30 μL, 0.60 mmol, 8 eq.) and $K_2CO_3$ (104 mg, 0.75 mmol, 10.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified via silica gel

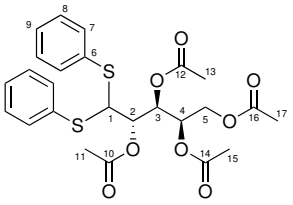
chromatography (Petroleum ether/EtOAc 3:2) to yield the product as a yellow oil, observed by $^1$H NMR (9 mg, 0.03 mmol, 40%): $^1$H NMR (700 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H, H-Ar), 7.31–7.21 (m, 8H, H-Ar), 6.04 (d, *J* = 8.2 Hz, 1H, H-2), 4.89 (td, *J* = 8.2, 4.2 Hz, 1H, H-3), 3.19 (dd, *J* = 13.9, 4.2 Hz, 1H, H-4), 2.96 (dd, *J* = 13.9, 8.2 Hz, 1H, H-4); HRMS (ESI) Calc'd for $C_{16}H_{17}O_2S_2$ $[M + H]^+$ 305.0670, 305.0667 found.

D-Ribose diphenyldithioacetal tetraacetate, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetrayl tetraacetate **110**:[85]



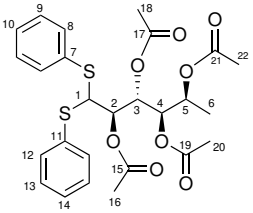
To a mixture of D-ribose dithioacetal (1.27 g, 3.56 mmol) in dry pyridine (10.0 mL) was added acetic anhydride (1.70 mL, 18.0 mmol, 5 eq.) and the mixture kept overnight with stirring. The mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo* to give pure product as a colourless oil (1.81 g, 3.50 mmol, 98%): $[\alpha]_D^{21}$ = +52 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 $CDCl_3$) δ 7.45–7.43 (m, 2H, H-Ar), 7.36–7.32 (m, 2H, H-Ar), 7.28–7.19 (m, 6H, H-Ar), 5.66 (dd, *J* = 7.4, 3.5 Hz, 1H, H-2), 5.4 (dd, *J* = 7.3, 3.8 Hz, 1H, H-3), 5.27 (dt, *J* = 7.3, 3.8 Hz, 1H, H-4), 4.44 (d, *J* = 3.5 Hz, 1H, H-1), 4.23 (dd, *J* = 12.1, 3.8 Hz, 1H, H-5), 4.04 (dd, *J* = 12.1, 7.3 Hz, 1H, H-5), 2.07 (s, 3H, $CH_3$), 1.95 (s, 3H, $CH_3$), 1.94–1.91 (s, 3H, $CH_3$), 1.91 (s, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.5 (C=O), 169.9 (C=O), 169.7 (C=O), 169.2 (C=O), 133.8 (Ar-Cq), 132.6 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 72.38 (C-1), 70.6 (C-2), 70.1 (C-3), 61.8 (C-4), 61.3 (C-5), 20.8 ($CH_3$), 20.7 ($CH_3$), 20.7 ($CH_3$), 20.6 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1739 (C=O), 1643 (Ar-CH), 1367 ($CH_2$), 1197 (C-O); HRMS (ESI) Calc'd for $C_{25}H_{29}O_8S_2$ $[M + H]^+$ 521.1226, found 521.1336.

D-Lyxose diphenyldithioacetal tetraacetate, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetrayl tetraacetate **111**:[85]



To a mixture of D-lyxose thioacetal (2.23 g, 6.32 mmol) in dry pyridine (15.0 mL) was added acetic anhydride (20.3 mL, 31.6 mmol, 5 eq.), and this addition repeated every hour for 4 h. The mixture was kept stirring for 5 h. The mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo* to give pure product as a colourless oil (3.22 g, 6.20 mmol, 98%): $[\alpha]_D^{25}$ = +12 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.56–7.50 (m, 2H, H-Ar), 7.34–7.29 (m 6H, H-Ar), 7.27–7.24 (m, 2H, H-Ar), 5.75 (dd, $J$ = 8.8, 2.0 Hz, 1H, H-2), 5.41 (dd, $J$ = 8.8, 2.6 Hz, 1H, H-3), 5.32 (ddd, $J$ = 7.4, 5.1, 2.0 Hz, 1H, H-4), 4.37 (d, $J$ = 2.6 Hz, 1H, H-1), 4.24 (dd, $J$ = 11.6, 5.1 Hz, 1H, H-5), 3.86 (dd, $J$ = 11.6, 7.4 Hz, 1H, H-5), 2.06 (s, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 1.95 (s, 3H, $CH_3$); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.2 (C=O), 170.6 (C=O), 170.4 (C=O), 169.7 (C=O), 169.7 (C=O), 137.5 (Ar-Cq), 133.5 (Ar-C), 133.1 (Ar-C), 129.3 (Ar-C), 129.2 (C-Ar), 124.4 (Ar-C), 71.2 (C-2), 69.9 (C-3), 68.2 (C-4), 62.3 (C-1), 61.7 (C-5), 21.3 ($CH_3$), 20.8 ($CH_3$), 20.8 ($CH_3$), 20.6 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1746 (C=O), 1370 ($CH_2$), 1209 (C-O); HRMS (ESI) Calc'd for $C_{25}H_{28}O_8S_2Na$ [M + Na]$^+$ 543.1118, found 543.1112.

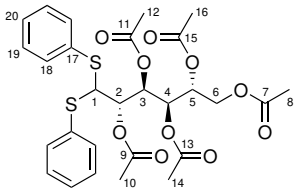
L-Rhamnose diphenyldithioacetal tetraacetate, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetrayl tetraacetate **112**:[85]



To a mixture of L-rhamnose dithioacetal (500 mg, 1.26 mmol) in dry pyridine (5.00

mL) was added acetic anhydride (596 μL, 6.30 mmol, 5 eq.) and the mixture stirred at rt for 4h. To the mixture, acetic anhydride (596 μL, 6.30 mmol, 5 eq.) was added additionally and the mixture stirred for a further 4h. The resulting mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo*. The mixture was purified via column chromatography (3:2 EtOAc/Petrol) to give pure product as a yellow oil (630 mg, 1.18 mmol, 94%): $[\alpha]_D^{25}$ = +92 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2H, H-Ar), 7.36–7.30 (m, 5H, H-Ar), 7.26 (m, 3H, H-Ar), 5.88 (dd, *J* = 8.6, 1.8 Hz, 1H, H-3), 5.33 (dd, *J* = 8.6, 2.9 Hz, 1H, H-2), 5.20 (dd, *J* = 8.3, 1.8 Hz, 1H, H-4), 4.85 (dq, *J* = 8.3, 6.4 Hz, 1H, H-5), 4.38 (d, *J* = 2.9 Hz, 1H, H-1), 2.06 (s, 3H, $CH_3$), 2.01 (s, 3H, $CH_3$), 1.98 (s, 6H, $CH_3$ x 2), 1.16 (d, *J* = 6.4 Hz, 3H, H-6); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.4 (C=O), 170.2 (C=O), 169.8 (C=O), 169.6 (C=O), 134.2 (Ar-Cq), 133.9 (Ar-Cq), 133.4 (Ar-C), 133.4 (Ar-C), 129.2 (Ar-C), 129.2 (Ar-C), 128.4 (Ar-C), 128.4 (Ar-C), 71.5 (C-2), 71.4 (C-3), 69.0 (C-4), 67.3 (C-5), 61.6 (C-1), 21.3 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.8 ($CH_3$), 16.6 (C-6); $\nu_{max}$ (film/cm$^{-1}$) 1730 (C=O), 1371 ($CH_3$), 1235 (C-O), 1043 (C-O); HRMS (ESI) Calc'd for $C_{26}H_{30}O_8S_2Na$ $[M + Na]^+$ 557.1274, found 557.1274.

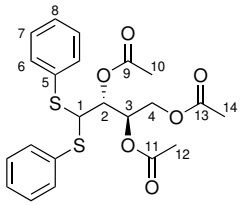
D-Mannose diphentythioacetal pentaacetate, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentayl pentaacetate **113**:[85]



To a mixture of D-mannose dithioacetal (293 mg, 0.77 mmol) in dry pyridine (3.00 mL) was added acetic anhydride (1.74 mL, 18.4 mmol, 24 eq.), added over 4 h. The mixture was kept overnight with stirring. The mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo* to give pure product as a colourless oil (421 mg, 0.765 mmol, 99%): $\alpha]_D^{25}$ = +32 (*c* = 1.00, $CHCl_3$); $^1$H

NMR (700 MHz, $CD_3OD$) δ 7.58–7.53 (m, 4H, H-Ar), 7.38–7.23 (m, 6H, H-Ar), 5.84 (dd, *J* = 8.3, 1.3 Hz, 1H, H-3), 5.44 (dd, *J* = 9.1, 1.3 Hz, 1H, H-4), 5.33 (dd, *J* = 8.3, 3.5 Hz, 1H, H-2), 5.02 (ddd, *J* = 9.1, 5.1, 2.7 1H, H-5), 4.42 (d, *J* = 3.5 Hz, 1H, H-1), 4.19 (dd, *J* = 12.5, 2.7 Hz, 1H, H-6), 4.03 (dd, *J* = 12.5, 5.1 Hz, 1H, H-6), 2.10 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 1.99 (s, 3H, $CH_3$), 1.96 (s, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 170.7 (C=O), 170.1 (C=O), 170.1 (C=O), 169.74 (C=O x 2), 134.0 (Ar-Cq), 133.8 (Ar-Cq), 133.5 (Ar-C), 133.4 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 71.5 (C-3), 69.0 (C-5), 68.1 (C-2), 67.7 (C-4), 62.0 (C-6), 61.3 (C-1), 21.1 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1744 (C=O), 1667 (Ar-CH), 1368 ($CH_2$), 1209 (C-O), 1043 (C-O); HRMS (ESI) Calc'd for $C_{26}H_{30}O_9S_2Na$ $[M + Na]^+$ 573.1223, found 573.1223.

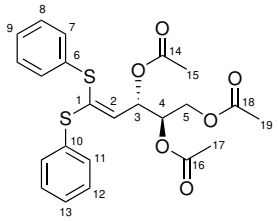
D-Erythrose diphenyldithioacetal alkene, (2*R*,3*R*)-4,4-bis(Phenylthio)butane-1,2,3-triyl triacetate **114**:




To a mixture of D-erythrose dithioacetal (100 mg, 0.31 mmol) in pyridine (5.00 mL) was added acetic anhydride (117 μL, 1.24 mmol, 5 eq.) and the mixture was left to stir for 12 h. The mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo* to give pure product as a colourless oil (59 mg, 0.13 mmol, 43%): $[\alpha]_D^{25}$ = +68 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H, H-Ar), 7.41 (m, 2H, H-Ar), 7.35–7.27 (m, 6H, H-Ar), 5.58 (ddd, *J* = 7.6, 5.1, 2.8 Hz, 1H, H-3), 5.50 (dd, *J* = 7.6, 2.8 Hz, 1H, H-2), 4.49 (d, *J* = 3.5 Hz, 1H, H-1), 4.33 (dd, *J* = 12.5, 3.5 Hz, 1H, H-4), 4.16 (dd, *J* = 12.5, 5.1 Hz, 1H, H-4), 2.01 (s, 1H, $CH_3$), 2.00 (s, 1H, $CH_3$), 1.93 (s, 1H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.7 (C=O), 169.8 (C=O), 169.7 (C=O), 134.4 (Ar-Cq), 133.7 (Ar-Cq), 133.7 (Ar-C), 132.8 (Ar-C), 129.3 (Ar-C), 129.3 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 72.4 (C-3), 70.6 (C-2), 61.9 (C-4), 61.5 (C-1), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$);

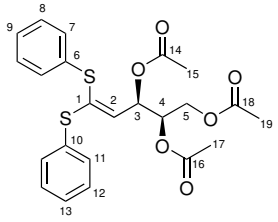
$\nu_{max}$ (film/cm$^{-1}$) 1740 (C=O), 1649 (Ar-CH), 1367 ($CH_2$); HRMS (ESI) Calc'd for $C_{22}H_{24}O_6S_2Na$ $[M + Na]^+$ 471.0907, found 471.0907.

D-Ribose diphenyldithioacetal alkene, (2*R*,3*S*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol **116**:[85]



D-Ribose diphenyldithioacetal tetraacetate (1.80 g, 3.50 mmol) was dissolved in DMSO-$d_6$ (10.0 mL), followed by addition of DBU (1.10 mL, 7.00 mmol, 2.0 eq.). The resulting mixture was stirred at rt for 12 h to yield the thioacetal ketene. The mixture was added to water (10.0 mL) and the product extracted with $Et_2O$ (5 x 10.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the isolated product as a yellow oil (1.55 g, 3.4 mmol, 96%): $[\alpha]_D^{21}$ = +96 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.36–7.21 (m, 10H, H-Ar), 6.11 (dd, *J* = 8.8, 5.7 Hz, 1H, H-2), 5.83 (d, *J* = 8.8 Hz, 1H, H-4), 5.28 (ddd, *J* = 6.4, 5.7, 3.6 Hz, 1H, H-3), 4.26 (dd, *J* = 12.0, 3.6 Hz, 1H, H-5), 4.17 (dd, *J* = 12.0, 6.4 Hz, 1H, H-5), 2.07 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.7 (C=O), 170.0 (C=O), 169.6 (C=O), 140.4 (C-1), 133.4 (Ar-Cq), 132.7 (Ar-Cq), 132.5 (Ar-C), 132.4 (Ar-C), 129.5 (Ar-C), 129.2 (Ar-C), 128.9 (Ar-C), 128.5 (Ar-C), 128.0 (C-2), 71.3 (C-3), 70.8 (C-4), 62.2 (C-5), 21.0 ($CH_3$), 21.0 ($CH_3$), 20.9 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1745 (C=O), 1672 (C=C), 1370 ($CH_2$), 1024 (C-O); HRMS (ESI) Calc'd for $C_{23}H_{25}O_6S_2$ $[M + H]^+$ 461.1048, found 461.1113.

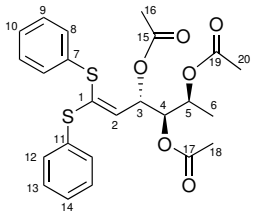
D-Lyxose diphenyldithioacetal alkene **117**:[85]



D-Lyxose diphenyldithioacetal tetraacetate (26.5 mg, 0.057 mmol) was dissolved

in DMSO-$d_6$ (1.30 mL), followed by addition of DBU (43.0 μL, 0.29 mmol, 0.7 eq.). The resulting mixture was stirred at rt for 12 h to yield the thioacetal ketene. The mixture was added to water (5.00 mL) and the product extracted with $Et_2O$ (5 x 5.00 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude ketene thioacetal as a colourless oil (23.0 mg, 0.029 mmol, 52%). Yield calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB). $[\alpha]_D^{21}$ = +60 (*c* = 1.00, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.38–7.19 (m, 10H, H-Ar), 6.00 (dd, *J* = 8.8, 5.6 Hz, 1H, H-2), 5.89 (d, *J* = 8.8 Hz, 1H, H-3), 4.20 (dd, *J* = 11.7, 3.8 Hz, 1H, H-5), 4.10 (dd, *J* = 11.7, 6.2 Hz, 1H, H-5), 3.99–3.94 (m, 1H, H-4), 2.09 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.3 (C=O), 171.2 (C=O), 170.1 (C=O), 139.4 (C-1), 133.0 (Ar-Cq), 132.5 (Ar-Cq), 132.1 (Ar-C), 130.5 (Ar-C), 129.2 (Ar-C), 128.9 (Ar-C), 128.4 (Ar-C), 127.9 (Ar-C), 73.3 (C-2), 71.7 (C-3), 65.1 (C-4), 60.5 (C-5), 21.1 ($CH_3$), 21.1 ($CH_3$), 20.9 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1740 (C=O), 1581 (C=C), 1228 (C-O); HRMS (ESI) Calc'd for $C_{23}H_{24}O_6S_2$ [M + H]$^+$ 459.0936, found 459.0907.

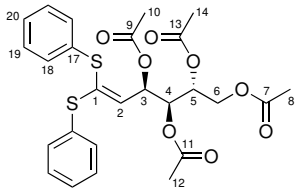
L-Rhamnose diphenyldithioacetal triacetate ketene, (2*S*,3*R*,4*S*)-6,6-bis(Phenylthio)hex-5-ene-2,3,4-triyl triacetate **118**:[85]




(2*R*,3*R*,4*S*,5*S*)-1,1-bis(Phenylthio)hexane-2,3,4,5-tetrayl tetraacetate (900 mg, 1.68 mmol) was dissolved in DMSO-$d_6$ (10.0 mL), followed by addition of triazabicyclodecene (350 mg, 2.52 mmol, 2.0 eq.). The mixture was added to water (10.0 mL) and the product extracted with $Et_2O$ (5 x 10.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the pure product as a yellow oil (680 mg, 1.43 mmol, 85%): $[\alpha]_D^{25}$ = +96 (*c* 0.80, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.36–7.28 (m, 10H, H-Ar), 6.17 (dd, *J* = 8.7, 5.0 Hz, 1H, H-3), 5.69 (d, *J* = 8.7 Hz, 1H, H-2), 5.17 (dd, *J* = 6.4, 5.0 Hz, 1H, H-4), 5.03 (p, *J* = 6.4 Hz, 1H, H-5), 2.07 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 1.23 (d, *J* = 6.4 Hz, 3H, H-6); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.2 (C=O), 170.0 (C=O), 169.7 (C=O), 133.8 (Ar-Cq), 132.2

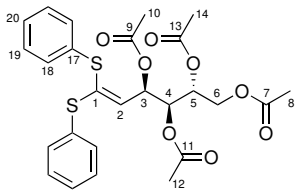
(Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.6 (C-1), 127.9 (C-2), 74.7 (C-3), 70.3 (C-4), 67.9 (C-5), 21.2 ($CH_3$), 21.1 ($CH_3$), 20.8 ($CH_3$), 16.0 (C-6); $\nu_{max}$ (film/cm$^{-1}$) 1746 (C=O), 1653 (C=C), 1370 ($CH_3$), 1217 (C-O), 1056 (C-O); HRMS (ESI) Calc'd for $C_{24}H_{27}O_6S_2$ $[M + H]^+$ 475.1244, found 475.1250.

D-Mannose diphenylthioacetal tetraacetate ketene, (2*R*,3*S*,4*R*)-6,6-bis(Phenylthio)hex-5-ene-1,2,3,4-tetrayl tetraacetate **119**:[85]



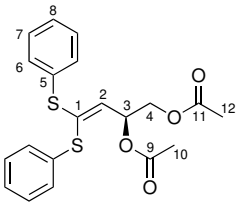
D-Mannose diphenyldithioacetal pentaacetate (21.0 mg, 0.0382 mmol) was dissolved in DMSO-$d_6$ (1.00 mL), followed by addition of $^t$BuOK (10.0 mg, 0.087 mmol, 4.4 eq.). The resulting mixture was stirred at rt for 12 h to yield the thioacetal ketene. The mixture was added to water (5.00 mL) and the product extracted with $Et_2O$ (4 × 5.00 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the product as an inseparable mixture of the product with starting material as a yellow oil (4.00 mg, 0.018 mmol, 47%). Yield calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB). The product was characterised by preparation of an authentic sample via acetylation of glucose thioacetal ketene (see below). $^1$H NMR (700 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H, H-Ar), 6.20 (dd, *J* = 8.5, 3.6 Hz, 1H, H-3), 5.62 (d, *J* = 8.5 Hz, 1H, H-2), 5.30 (dd, *J* = 8.0, 3.6 Hz, 1H, H-4), 5.21 (ddd, *J* = 8.0, 5.3, 2.7 Hz, 1H, H-5), 4.23 (dd, *J* = 12.4, 2.7 Hz, 1H, H-6), 4.16 (dd, *J* = 12.4, 5.3 Hz, 1H, H-6), 2.06 (s, 3H, $CH_3$, 2.05 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.7 (C=O), 170.0 (C=O), 169.7 (C=O), 169.5 (C=O), 139.1 (C-1), 133.6 (C-2), 133.5 (Ar-Cq), 132.8 (Ar-Cq), 132.0 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 127.9 (Ar-C), 71.3 (C-4), 70.0 (C-5), 68.7 (C-3), 62.1 (C-6), 21.1 ($CH_3$), 21.0 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$); HRMS (ESI) Calc'd for $C_{26}H_{29}O_8S_2$ $[M + H]^+$ 533.1298, found 533.1297.

D-Glucose diphenylthioacetal tetraacetate ketene, (2*R*,3*S*,4*R*)-6,6-bis(Phenylthio)hex-5-ene-1,2,3,4-tetrayl **262** (Reference compound):[85]



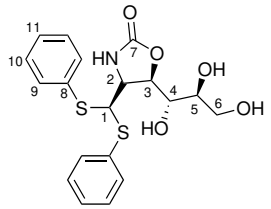
To a mixture of D-glucose dithioacetal ketene (100 mg, 0.275 mmol) in dry pyridine (1.00 mL) was added acetic anhydride (130 μL, 1.37 mmol, 6 eq.), and this addition repeated every hour for 4 h. The mixture was kept overnight with stirring. The mixture was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15% $CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo* to give the pure product as a colourless oil (64.0 mg, 0.12 mmol, 44%): $[\alpha]_D^{25}$ = -20 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H, H-Ar), 7.33–7.26 (m, 8H, H-Ar), 6.20 (dd, *J* = 8.5, 3.6 Hz, 1H, H-3), 5.62 (d, *J* = 8.5 Hz, 1H, H-2), 5.30 (dd, *J* = 8.0, 3.6 Hz, 1H, H-4), 5.21 (ddd, *J* = 8.0, 5.3, 2.7 Hz, 1H, H-5), 4.22 (dd, *J* = 12.4, 2.7 Hz, 1H, H-6), 4.16 (dd, *J* = 12.4, 5.3 Hz, 1H, H-6), 2.06 (s, 1H, $CH_3$), 2.05 (s, 1H, $CH_3$), 2.04 (s, 1H, $CH_3$), 2.04 (s, 1H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.7 (C=O), 170.0 (C=O), 169.7 (C=O), 169.5 (C=O), 139.1 (C-1), 133.6 (C-2), 132.8 (Ar-Cq), 132.2 (Ar-Cq), 132.0 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 127.9 (Ar-C), 71.3 (C-4), 70.0 (C-5), 68.7 (C-3), 62.1 (C-6), 21.0 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1744 (C=O), 1660 (C=C), 1370 ($CH_2$), 1210.0 (C-O), 1024 (C-O), 774 (C=C); HRMS (ESI) Calc'd for $C_{26}H_{29}O_8S_2$ $[M + H]^+$ 533.1298, found 533.1298. Data is in accordance with Compound **101**.

D-Erythrose diphenylthioacetal tetraacetate ketene, (*S*)-4,4-bis(Phenylthio)but-3-ene-1,2-diyl diacetate **115**:



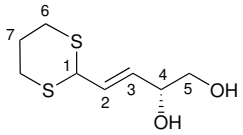
To a mixture of (2*R*,3*R*)-4,4-bis(phenylthio)butane-1,2,3-triyl triacetate (20.0 mg, 0.045 mmol) in DMSO-$d_6$ (1.00 mL) was added DBU (14.0 μL, 0.09 mmol, 2.0 eq.). The resulting mixture was stirred at rt for 12 h. The mixture was added to water (5.00 mL) and the product extracted with $Et_2O$ (4 x 5.00 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product, observed by $^1$H NMR (7.00 mg, 0.018 mmol, 40%). Yield calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB). $^1$H NMR (700 MHz, $CDCl_3$) δ 7.30–7.28 (m, 4H, H-Ar), 7.24–7.20 (m, 6H, H-Ar), 6.08 (d, *J* = 7.9 Hz, 1H, H-2), 5.21 (dd, *J* = 7.9, 7.3 Hz, 1H, H-3), 4.08 (dd, *J* = 8.5, 6.4 Hz, 1H, H-4), 3.58 (dd, *J* = 8.5, 7.3, 1H, H-4), 2.27 (s, 3H, $CH_3$), 1.99 (s, 3H, $CH_3$); HRMS (ESI) Calc'd for $C_{20}H_{21}O_4S_2$ $[M + H]^+$ 389.0837, found 389.0891. Due to this compound's low level of purity, this structure is only the proposed major product

*N*-Acetyl glucosamine carbamate, (4*R*,5*R*)-4-(bis(phenylthio)methyl-5-((1*S*,2*S*)-1,2,3-trihydroxypropyl)oxazolidin-2-one **120**:



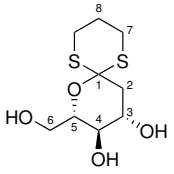

To a mixture of *N*-acetylgluocsamine diphenyldithioacetal (50.0 mg, 0.12 mmol) dissolved in MeOH (15.0 mL), was added dimethyl carbonate (11 μL, 0.18 mmol, 1.5 eq.) and $K_2CO_3$ (34.0 mg, 0.24 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (acetone/$CH_2Cl_2$ 2:3) to yield the product as a yellow oil (22.0 mg, 0.05 mmol, 45%): $[\alpha]_D^{25}$ = -40 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.50–7.45 (m, 4H, H-Ar), 7.35–7.28 (m, 6H, H-Ar), 5.04 (dd, *J* = 4.5, 1.5 Hz, 1H, H-3), 4.60 (d, *J* = 3.9 Hz, 1H, H-1), 4.18 (dd, *J* = 4.5, 3.9 Hz, 1H, H-2), 3.77 (dd, *J* = 11.4, 3.0 Hz, 1H, H-6), 3.69 (ddd, *J* = 9.1, 5.4, 3.0 Hz, 1H, H-5), 3.62 (dd, *J* = 11.4, 5.4 Hz, 1H, H-6), 3.47 (dd, *J* = 9.1, 1.5 Hz, 1H, H-4); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 161.5 (C-7), 134.6 (Ar-Cq), 134.0 (Ar-C), 130.2 (Ar-C), 129.2 (Ar-C), 80.0 (C-3), 73.7 (C-5), 64.7 (C-4), 58.8 (C-6), 55.9 (C-1), 54.7 (C-2); $\nu_{max}$ (film/cm$^{-1}$) 3292 (O-H), 1720 (C=O), 1651 (Ar-CH), 1436 ($CH_2$), 1082 (C-O); HRMS (ESI) Calc'd for $C_{20}H_{24}NO_4S_2$ $[M + H]^+$ 406.1141, found 406.1142.

L-Arabinose dithiane alkene, (*R*,*E*)-4-(1,3-dithian-2-yl)but-3-ene-1,2-diol **122**:




To a mixture of L-arabinose dithiane **90** (500 mg, 2.08 mmol) in MeOH (3.00 mL), was added dimethyl carbonate (175 μL, 3.12 mmol, 1.5 eq.) and $K_2CO_3$ (575 mg, 4.18 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being filtered. The residue was purified using silica gel chromatography (EtOAc/Petrol 2:3) to yield the product as a colourless oil (87.0 mg, 0.42 mmol, 20%): $[\alpha]_D^{21}$ = +28 (*c* = 1.00, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 5.99 (dd, *J* = 15.7, 5.3 Hz, 1H, H-2), 5.78 (dd, *J* = 15.7, 1.6 Hz, 1H, H-3), 4.17 (dtd, *J* = 6.8, 5.3, 1.6 Hz, 1H, H-1), 3.47 (dd, *J* = 11.3, 4.9 Hz, 1H, H-5), 3.44 (dd, *J* = 11.3, 6.8 Hz, 1H, H-5) 3.30–3.27 (m, 1H, H-4), 3.21–3.14 (m, 2H, H-6), 2.64–2.59 (m, 2H, H-6), 2.10–2.07 (m, 1H, H-7), 1.89–1.82 (m, 1H, H-7); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 135.8 (C-2), 131.4 (C-3), 73.0 (C-1), 66.9 (C-5), 52.6 (C-4), 28.0 (C-6), 25.5 (C-8); $\nu_{max}$ (film/cm$^{-1}$) 3373 (O-H), 2918 (C=C), 1717 (R-CH), 1420 (R-CH), 1275 (C-O); HRMS (ESI) Calc'd for $C_8H_{15}O_3S_2$ $[M + H]^+$ 205.0351, found 205.0352.

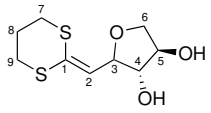
8-(Hydroxymethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane-9,10-diol, **123**:




To a mixture of D-glucose dithiane **91** (200 mg, 0.74 mmol) in MeOH (5.00 mL), was added dimethyl carbonate (63.0 μL, 1.11 mmol, 1.5 eq.) and $K_2CO_3$ (205 mg, 1.48 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being filtered. The residue was purified using silica gel chromatography (EtOAc/Petrol 2:3) to yield the product (62.0 mg, 0.26 mmol, 36%): $[\alpha]_D^{21}$ = +56 (*c* = 1.00, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.78 (dd, *J* = 7.3, 5.5 Hz, 1H, H-3), 4.71 (t, *J* = 5.5 Hz, 1H, H-4), 4.21 (q, *J* = 5.5 Hz, 1H, H-5), 3.87 (dd, *J* = 9.5, 5.5 Hz, 1H, H-6), 3.75 (dd, *J* = 9.5, 6.1 Hz, 1H, H-6), 3.44 (ddd, *J* = 13.8, 12.6, 2.6

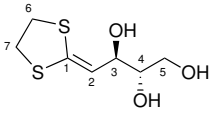
Hz, 1H, H-7), 3.34 (ddd, *J* = 13.8, 12.6, 2.6 Hz, 1H, H-7), 2.82–2.65 (m, 2H, H-7), 2.62 (dd, *J* = 14.8, 7.3 Hz, 1H, H-2), 2.30 (dd, *J* = 14.8, 3.2 Hz, 1H, H-2), 2.21–2.13 (m, 1H, H-8), 2.01–1.93 (m, 1H, H-8); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 93.2 (C-1), 83.2 (C-5), 72.1 (C-4), 49.2 (C-3), 28.9 (C-6), 27.9 (C-2), 26.9 (C-7), 24.3 (C-8); $\nu_{max}$ (film/cm$^{-1}$) 3419 (O-H), 2923 (C-H), 1777 (R-CH), 1423 (R-CH), 1062 (C-O); HRMS (ESI) Calc'd for $C_9H_{16}O_3S_2$ $[M + H]^+$ 235.0457, found 235.0450.

(3*S*,4*R*)-2-((1,3-Dithian-2-ylidene)methyl)tetrahydrofuran-3,4-diol, **128**:




To a mixture of D-galactose dithiane **92** (290 mg, 1.07 mmol) in MeOH (15.0 mL), was added dimethyl carbonate (91.0 μL, 1.16 mmol, 1.5 eq.) and $K_2CO_3$ (296 mg, 2.14 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being filtered. The residue concentrated *in vacuo* and was washed with water (5.00 mL) to give the product as a white solid (182 mg, 0.78 mmol, 73%): $[\alpha]_D^{21}$ = +44 (*c* = 1.00, MeOH); $^1$H NMR (400 MHz, $CD_3OD$) δ 5.95 (d, *J* = 8.6 Hz, 1H, H-2), 4.97 (dd, *J* = 8.6, 3.2 Hz, 1H, H-3), 4.18 (d, *J* = 4.3 Hz, 1H, H-5), 4.12 (dd, *J* = 9.4, 4.3 Hz, 1H, H-6), 3.89 (d, *J* = 3.2 Hz, 1H, H-4), 3.60 (d, *J* = 9.4 Hz, 1H, H-6), 3.03–2.82 (m, 4H, H-7), 2.21–2.08 (m, 2H, H-8); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 134.7 (C-1), 126.9 (C-2), 79.1 (C-4), 79.0 (C-3), 78.6 (C-5), 74.1 (C-6), 30.4 (C-7), 30.0 (C-9), 25.7 (C-8); $\nu_{max}$ (film/cm$^{-1}$) 3373 (O-H), 970 (C=C); HRMS (ESI) Calc'd for $C_9H_{16}O_3S_2$ $[M + H]^+$ 235.0457, found 235.0456.

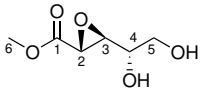
(2*S*,3*R*)-4-(1,3-Dithiolan-2-ylidene)butane-1,2,3-triol **129**:




To a mixture of **93** (200 mg, 0.88 mmol) in MeOH (5.00 mL), was added dimethyl carbonate (75.0 μL, 1.33 mmol, 1.5 eq.) and $K_2CO_3$ (243 mg, 1.76 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure. The product was observable by NMR (19% conversion): $^1$H

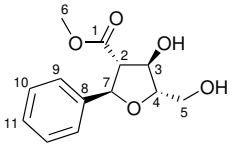
NMR (400 MHz, $CD_3OD$) δ 4.68 (d, *J* = 10.4 Hz, 1H, H-2), 3.79 (dd, *J* = 6.8, 5.3 Hz, 1H, H-5), 3.74 (dd, *J* = 6.8, 3.0 Hz, 1H, H-5), 3.66 (m, 2H, H-3, H-4), 3.25–3.13 (m, 4H, H-6); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 161.2 (C-1), 75.7 (C-2), 64.8 (C-4), 57.0 (C-3), 53.4 (C-5), 39.75 (C-6), 38.6 (C-7).

Methyl(2*R*,3*R*)-3-((*S*)-1,2-dihydroxyethyl)oxirane-2-carboxylate **150**:




To a mixture of **95** (67.0 mg, 0.20 mmol) in methanol (1.00 mL), NBS (43.0 mg, 0.24 mmol, 1.2 eq.) was added at rt and left to stir for 24 h. The product was observed by $^1$H NMR (9.00 mg, 0.05 mmol, 27%)). Yield calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB): $^1$H NMR (700 MHz, $CDCl_3$) δ 4.74–4.70 (d, *J* = 7.8 Hz, 1H, H-2), 4.48–4.43 (d, *J* = 7.8 Hz, 1H, H-3), 4.33–4.28 (m, 1H, H-4), 3.90 (dd, *J* = 13.3, 3.2 Hz, 1H, H-5), 3.74 (dd, *J* = 13.3, 4.4 Hz, 1H, H-5), 3.35 (s, 3H, H-6); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 181.4 (C-1), 86.2 (C-2), 76.0 (C-3), 73.9 (C-4), 61.1 (C-5), 49.8 (C-6).

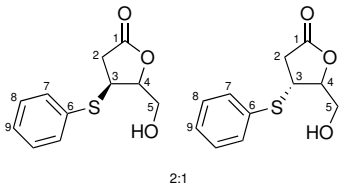
Methyl-(2*R*,3*R*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)-2-phenyltetrahydro furan-3-carboxylate **153**:




A mixture of **95** (50.0 mg, 0.15 mmol) in $CH_2Cl_2$ under argon was stirred at -78 °C for 5 min before the addition of benzaldehyde dimethylacetal (24.0 μL, 0.16 mmol) and boron trifluoride etherate (18.0 μL, 0.16 mmol). The solution was left to stir for 1 h. The solution was concentrated *in vacuo*, followed by addition of EtOAc (5.00 mL). The product was extracted with EtOAc (3 × 10.0 mL), washed over brine (10.0 mL) and dried over $MgSO_4$. The product was purified via silica gel chromatography in a gradient of EtOAc/Petrol and isolated as a yellow oil (12.0 mg, 0.04 mmol, 25%): $[\alpha]_D^{25}$ = -60 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5H, H-Ar), 5.14 (d, *J* = 8.9 Hz, 1H, H-7), 4.21–4.18 (m, 1H, H-4), 4.07–4.01 (m, 1H, H-3), 3.88 (dd, *J* = 12.0, 5.3 Hz, 1H, H-5), 3.79–3.72 (m, 1H, H-5), 3.56 (s, 3H, H-6),

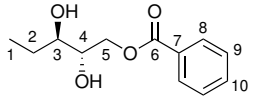
3.12 (dd, *J* = 10.0, 8.9 Hz, 1H, H-2); $^{13}$C NMR (176 MHz, CDCl3) δ 171.6 (C-1), 134.0 (Ar-Cq), 129.3 (Ar-C), 128.8 (Ar-C), 125.9 (Ar-C), 84.7 (C-4), 83.4 (C-7), 62.4 (C-3), 60.2 (C-5), 52.4 (C-6), 50.9 (C-2); $\nu_{max}$ (film/cm$^{-1}$) 2919 (O-H), 1734 (C=O), 1461 ($CH_2$); HRMS Calc'd for $C_{13}H_{16}O_5Na$ $[M]^-$ 251.0697, found 251.0875.

(4*S*)-5-(Hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one **146**, (4*R*)-5-(hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one **147**:




A mixture of **95** (100 mg, 0.33 mmol) and $In(OTf)_3$ (467 mg, 0.8 mmol, 2.5 eq.) were combined and stirred neat at rt for 4 h. The crude mixture was purified using column chromatography (2:1 EtOAc/Petrol) to yield the isolated lactone as an oil, a mixture of two isomers (2:1) (39.0 mg, 0.174 mmol, 53%): (4*R*): $^1$H NMR (700 MHz, $CDCl_3$) δ 7.53—7.10 (m, 5H, H-Ar), 4.45–4.41 (m, 1H, H-4), 3.98–3.91 (m, 2H, H-5, H-3), 3.69–3.63 (dd, *J* = 13.3, 3.5 Hz, 1H, H-5), 3.08–2.99 (dd, *J* = 17.5, 8.5 Hz, 1H, H-2), 2.63–2.56 (dd, *J* = 17.5, 8.5 Hz, 1H, H-2); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 174.6 (C-1) 133.1 (Ar-Cq), 131.4 (Ar-C), 129.6 (Ar-C), 128.7 (Ar-C), 85.0 (C-4), 62.5 (C-2), 42.2 (C-3), 36.4 (C-5); (4*S*): $^1$H NMR (700 MHz, $CDCl_3$) δ 7.53–7-.10 (m, 5H, H-Ar), 4.77–4.74 (m, 1H, H-4), 4.19–4.13 (m, 2H, H-5), 4.11 (dd, *J* = 12.6, 4.5 Hz, 1H, H-3), 4.00–3.96 (m, 1H, H-4), 2.90 (dd, *J* = 17.6, 8.7 Hz, 1H, H-2), 2.76 (dd, *J* = 17.6, 8.6 Hz, 1H, H-2); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 174.4 (C-1), 131.5 (Ar-Cq), 129.7 (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 81.8 (C-4), 62.5 (C-2), 44.6 (C-3), 29.8 (C-5); $\nu_{max}$ (film/cm$^{-1}$) 3390 (O-H), 1781 (C=O), 1651 (Ar-CH), 1176 ($CH_2$); HRMS Calc'd for $C_{11}H_{13}O_3S$ $[M + H]^+$ 225.0580, found 225.0580. Data is in accordance with literature.

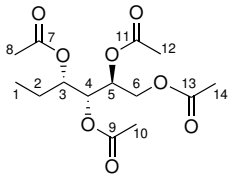
(2*S*, 3*R*)-Dihydroxypentyl benzoate **161**:




A solution of **95** (67.0 mg, 0.20 mmol) in EtOH (2.00 mL) with Raney-Ni (2.00 g)

was stirred at room temperature for 12 h. The mixture was filtered through a plug of silica and washed with EtOH (5.00 mL). The filtrate was concentrated *in vacuo* and dissolved in pyridine (3.00 mL) at 0 °C under an inert atmosphere. To the stirred solution was added benzoyl chloride (23 μL, 0.2 mmol) dropwise. The mixture was stirred at 0 °C for 2 h and then at rt for 12 h. The solvent was evaporated and then co-evaporated with toluene (5.00 mL). The residue was slowly poured into vigorously stirring water. The product was extracted with ethyl acetate (3 × 5.00 mL) before washing with brine (5.00 mL) and saturated aqueous sodium bicarbonate (5.00 mL). The mixture was dried using $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography (20% EtOAc/petrol) to yield the product as a colourless oil (42.0 mg, 0.19 mmol, 94%): $[\alpha]_D^{25}$ = +4 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 2H, H-8), 7.59 (t, *J* = 7.4 Hz, 1H, H-10), 7.46 (t, *J* = 7.5 Hz, 2H, H-9), 4.52 (d, *J* = 4.8 Hz, 2H, H-5), 3.94–3.88 (m, 1H, H-4), 3.67 (m, 1H, H-3), 2.54 (d, *J* = 4.7 Hz, 1H, OH), 2.15 (d, *J* = 4.5 Hz, 1H, OH), 1.72–1.65 (m, 1H, H-2), 1.61–1.56 (m, 1H, H-2), 1.04 (t, *J* = 7.4 Hz, 3H, H-1); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 167.4 (C=O), 133.5 (Ar-Cq), 130.0 (Ar-C), 129.8 (Ar-C), 128.6 (Ar-C), 74.0 (C-5), 73.1 (C-4), 66.3 (C-3), 25.6 (C-2), 10.3 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 3386 (O-H), 1680 (C=O), 1582 ($CH_2$), 1067 (C-O); HRMS (ESI) Calc'd for $C_{12}H_{16}O_4Na$ $[M + Na]^+$ 247.0941, found 247.0941.

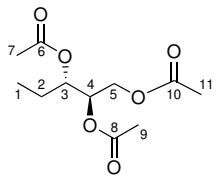
(2*S*,3*R*,4*S*)-Hexane-1,2,3,4-tetrayl tetraacetate **164**:




A solution of **102** (300 mg, 0.82 mmol) in EtOH (5.00 mL) with Raney-Ni (2.00 g) was stirred at room temperature for 12 h. The mixture was filtered through a plug of silica and washed with EtOH (10.0 mL). The filtrate was concentrated *in vacuo* and dissolved in pyridine (3.00 mL) at rt under an inert atmosphere. To the solution was added acetic anhydride (388 μL, 4.10 mmol, 5 eq.) and the mixture kept overnight with stirring. To the mixture, acetic anhydride (388 μL, 4.1 mmol, 5 eq.) was added and the mixture stirred for a further 4 h. The solution was poured onto crushed ice and mixed with $CH_2Cl_2$ (10.0 mL). The organic layer was washed with aq. 15%

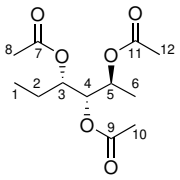
$CuSO_4$ solution (10.0 mL) followed by brine (10.0 mL) before drying over $MgSO_4$. The mixture was filtered through silica and concentrated *in vacuo*. The crude product was purified via column chromatography (3:2 EtOAc/Petrol) to give the pure product as a colourless oil (30.0 mg, 0.09 mmol, 11%): $[\alpha]_D^{25}$ = +44 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 5.34 (ddd, *J* = 7.1, 5.1, 3.2 Hz, 1H, H-5), 5.23 (dd, *J* = 7.8, 3.2 Hz, 1H, H-4), 4.99 (td, *J* = 7.8, 3.5 Hz, 1H, H-3), 4.23 (dd, *J* = 11.7, 5.1 Hz, 1H, H-6), 3.94 (dd, *J* = 11.7, 7.1 Hz, 1H, H-6), 2.11 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$), 2.03 (s, 6H, 2 x $CH_3$), 1.64–1.59 (m, 1H, H-2), 1.55–1.49 (m, 1H, H-2), 0.87 (t, *J* = 7.4 Hz, 3H, H-1); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 170.6 (C=O), 170.4 (C=O), 170.3 (C=O), 170.0 (C=O), 71.2 (C-3), 71.0 (C-4), 68.4 (C-5), 62.2 (C-6), 23.5 (C-2), 21.0 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 20.7 ($CH_3$), 9.3 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 1738 (C=O), 1368 ($CH_2$), 1211 (C-H); HRMS (ESI) Calc'd for $C_{14}H_{23}O_8$ $[M + H]^+$ 319.1348, found 319.1393.

(2*R*,3*S*)-Pentane-1,2,3-triyl triacetate **165**:



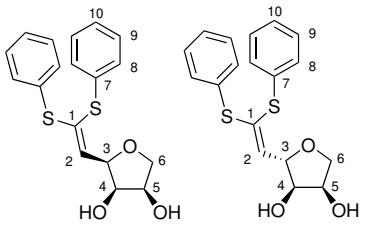

A solution of **110** (300 mg, 0.65 mmol) in EtOH (5.00 mL) with Raney-Ni (2.00 g) was stirred at room temperature for 12 h. The mixture was filtered through a plug of silica and washed with EtOH (10.0 mL). The mixture was concentrated *in vacuo* and crude product purified via column chromatography (3:2 EtOAc/Petrol) to give the pure product as a colourless oil (66.0 mg, 0.27 mmol, 42%): $[\alpha]_D^{25}$ = +72 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.17–5.11 (m, 1H, H-4), 5.03 (dt, *J* = 8.5, 4.7 Hz, 1H, H-3), 4.28 (dd, *J* = 12.0, 3.1 Hz, 1H, H-5), 4.13 (dd, *J* = 12.0, 7.5 Hz, 1H, H-5), 2.06–2.05 (m, 6H, 2 x $CH_3$), 2.04 (s, 3H, $CH_3$), 1.68–1.53 (m, 2H, H-2), 0.90 (t, *J* = 7.4 Hz, 3H, H-1); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O), 170.4 (C=O), 170.3 (C=O), 73.1 (C-4), 71.7 (C-3), 62.1 (C-5), 23.4 (C-2), 20.9 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_3$), 9.7 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 1736 (C=O), 1369 ($CH_2$), 1213 (C-H); HRMS (ESI) Calc'd for $C_{11}H_{18}O_6Na$ $[M + Na]^+$ 269.0996, found 269.0999.

(2*S*,3*S*,4*S*)-Hexane-2,3,4-triyl triacetate **166**:



A solution of **263** (300 mg, 0.63 mmol) in EtOH (5.00 mL) with Raney-Ni (2.00 g) was stirred at room temperature for 12 h. The mixture was filtered through a plug of silica and washed with EtOH (10.0 mL). The mixture was concentrated *in vacuo* and crude product purified via column chromatography (3:2 EtOAc/Petrol) to give pure product as a colourless oil (23.0 mg, 0.09 mmol, 14%): $[\alpha]_D^{25}$ = +48 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.13 (dd, *J* = 7.1, 3.7 Hz, 1H, H-4), 5.10–5.04 (m, 1H, H-3), 4.97 (p, *J* = 6.4 Hz, 1H, H-5), 2.12 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.01 (s, 3H, $CH_3$), 1.57–1.48 (m, 2H, H-2), 1.19 (d, *J* = 6.4 Hz, 3H, H-6), 0.90 (t, *J* = 7.5 Hz, 3H, H-1); $^{13}$ NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O), 170.3 (C=O), 170.2 (C=O), 73.9 (C-4), 72.1 (C-3), 67.6 (C-5), 27.0 (C-2), 24.0 ($CH_3$), 21.1 ($CH_3$), 20.9 ($CH_3$), 16.1 (C-6), 9.5 (C-1); $\nu_{max}$ (film/cm$^{-1}$) 1737 (C=O), 1371 ($CH_2$), 1218 (C-H); HRMS (ESI) Calc'd for $C_{12}H_{19}O_6$ $[M + Na]^+$ 282.1074, found 282.2785.

D-Glucose dithioacetal alkenyl THF, (2*R*,3*R*,4*R*)-2-(2,2,-bis(phenylthiol)vinyl) tetrahydrofuran-3,4-diol), (2*S*,3*R*,4*R*)-2-(2,2,-bis(phenylthiol)vinyl) tetrahydrofuran-3,4-diol) **127**:

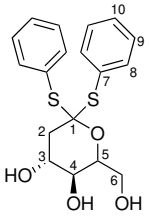


24:76

A mixture of **101** (50.0 mg, 0.14 mmol) in $^t$BuOAc (1.40 mL) with $B(OCH_2CF_3)_3$ (30.0 μL, 100 mol%) was stirred at 120 °C for 6 h. The mixture was cooled to rt. To the stirring solution, Amberlite IRA743 (0.50 g) was added; the resulting suspension was stirred for 30 min before drying over $MgSO_4$. The solvent was removed under reduced pressure. The product precipitated as an oily solid, consisting of a mixture (24:76) of two disastereomers (45.2 mg, 0.13 mmol, 93%): (2*S*) (minor): $^1$H NMR

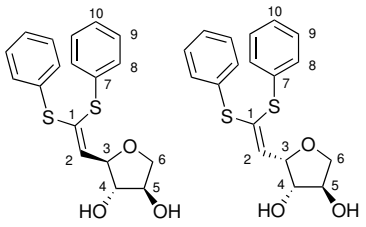
(700 MHz, $CD_3OD$) δ 7.51–7.45 (m, 2H, H-Ar), 7.39–7.28 (m, 8H, H-Ar), 6.01 (d, *J* = 8.7 Hz, 1H, H-2), 4.92 (dd, *J* = 8.7, 7.5 Hz, 1H, H-3), 4.16 (dt, *J* = 4.9, 2.7 Hz, 1H, H-5), 4.09–4.06 (m, 1H, H-6), 3.86 (dd, *J* = 7.5, 4.9 Hz, 1H, H-4), 3.73 (dd, *J* = 9.6, 2.7 Hz, 1H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 138.0 (C-1), 135.1 (Ar-Cq), 134.9 (Ar-C), 134.3 (Ar-C), 133.7 (Ar-C), 132.3 (C-2), 80.6 (C-3), 78.0 (C-4), 74.0 (C-5), 54.7 (C-6); (2*R*) (major): $^1$H NMR (700 MHz, $CD_3OD$) δ 7.31–7.21 (m, 10H, H-Ar), 6.35 (d, *J* = 8.3 Hz, 1H, H-2), 5.02 (dd, *J* = 8.3, 4.7 Hz, 1H, H-3), 4.31 (dt, *J* = 6.3, 4.7 Hz, 1H, H-5), 4.09 (t, *J* = 4.7 Hz, 1H, H-4), 3.88 (dd, *J* = 8.7, 6.3 Hz, 1H, H-6), 3.72–3.69 (m, 1H, H-6); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 137.9 (C-1), 133.5 (Ar-Cq), 131.7 (Ar-C), 123.0 (Ar-C), 129.7 (Ar-C), 128.9 (C-2), 80.8 (C-3), 74.3 (C-4), 73.0 (C-5), 72.3 (C-6);
$\nu_{max}$ (film/cm$^{-1}$) 3390 (O-H), 2924 (=C-H), 2921 (O-H), 1622 (Ar-CH), 1104 (C-O); HRMS Calc'd for $C_{18}H_{19}O_3S_2$ $[M + H]^+$ 347.0697, found 347.0770.

(3*S*,4*R*)-2-(hydroxymethyl)-6,6-bis(phenylthio)tetrahydro-2H-pyran-3,4-diol **171**:



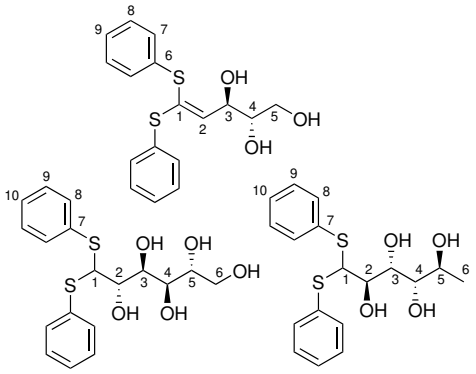

A mixture of (87.0 mg, 0.238 mmol) in $^t$BuOAc (8.00 mL) with $B(OCH_2CF_3)_3$ (147 μL, 200 mol%) was stirred at 120 °C for 3 h. The mixture was cooled to rt. To the stirring solution, Amberlite IRA743 (1.00 g) was added; the resulting suspension was stirred for 30 min before drying over $MgSO_4$. The solvent was removed under reduced pressure to give the product (52.0 mg, 0.143 mmol, 60%): $[\alpha]_D^{25}$ = +16 (*c* = 1.00, $CHCl_3$); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.68–7.66 (m, 2H, H-Ar), 7.65–7.61 (m, 2H, H-Ar), 7.42–7.33 (m, 6H, H-Ar), 4.69–4.67 (m, 1H, H-5), 4.57 (t, *J* = 4.9 Hz, 1H, H-4), 4.13 (ddd, *J* = 9.4, 6.8, 4.9 Hz, 1H, H-3), 3.64–3.57 (m, 1H, H-2), 3.15–3.09 (m, 1H, H-2), 2.58 (dd, *J* = 15.0, 7.2 Hz, 1H, H-6), 2.28 (dd, *J* = 15.0, 3.2 Hz, 1H, H-6); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 138.0 (Ar-Cq), 137.2 (Ar-C), 130.4 (Ar-C), 130.2 (Ar-C), 104.7 (C-1), 84.6 (C-4), 83.3 (C-5), 72.9 (C-3), 70.5 (C-2), 48.1 (C-6); $\nu_{max}$ (film/cm$^{-1}$) 3450 (O-H), 1068 (C-O); HRMS Calc'd for $C_{18}H_{21}O_4S_2$ $[M + H]^+$ 365.0803, found 365.0876.

D-Galactose dithioacetal alkenyl THF, (2*R*,3*S*,4*R*)-2-(2,2-bis(Phenylthio)vinyl)tetra hydrofuran-3,4-diol, (2*S*,3*S*,4*R*)-2-(2,2-bis(phenylthio)vinyl)tetrahydrofuran-3,4-diol **172**:



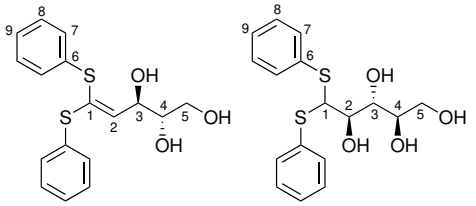

A mixture of **102** (25.0 mg, 0.07 mmol) in *tert*-amyl methyl ether (1.40 mL) with $B(OCH_2CF_3)_3$ (30.0 μL, 200 mol%) was stirred at 120 °C for 6 h. The mixture was cooled to rt. To the stirring solution, Amberlite IRA743 (0.50 g) was added; the resulting suspension was stirred for 30 min before drying over $MgSO_4$. The solvent was removed under reduced pressure, and the crude mixture was purified via silica chromatography (1:1 EtOAc/Petrol) to give a mixture (76:24) of two disastereomers (3.00 mg, 0.01 mmol, 2%): (2*R*,3*S*,4*R*): $^1$H NMR (700 MHz, $CDCl_3$) 7.34–7.27 (m, 10H, H-Ar), 6.20 (d, *J* = 7.9 Hz, 1H, H-2), 4.86 (dd, *J* = 7.9, 3.5 Hz, 1H, H-3), 4.25 (m, 1H, H-4), 4.03 (dd, *J* = 10.0, 4.2 Hz, 1H, H-6), 4.00 (m, 1H, H-5), 3.87 (dd, *J* = 10.0, 1.9 Hz, 1H, H-6); (2*S*,3*S*,4*R*): $^1$H NMR (700 MHz, $CDCl_3$) 7.34–7.27 (m, 10H, H-Ar), 6.11 (d, *J* = 7.5 Hz, 1H, H-2), 5.18 (dd, *J* = 7.5, 3.5 Hz, 1H, H-3), 4.32 (m, 1H, H-4), 4.22 (dd, *J* = 10.0, 4.4 Hz, 1H, H-6), 4.09 (m, 1H, H-5) 3.71 (dd, *J* = 10.0, 1.6 Hz, 1H, H-6); HRMS Calc'd for $C_{18}H_{19}O_3S_2$ $[M + H]^+$ 347.0770, found 347.0770.

(2*S*,3*S*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **95**, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol **76**, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol **75**:



To a mixture of L-arabinose diphenyldithioacetal (500 mg, 1.42 mmol), L-rhamnose diphenyldithioacetal (60.0 mg, 0.15 mmol) and D-mannose diphenyldithioacetal (100 mg, 0.26 mmol), in MeOH (20 mL), was added dimethyl carbonate (820 μL, 14.6 mmol, 8 eq. per sugar derivative) and $K_2CO_3$ (506 mg, 3.66 mmol, 2 eq. per sugar derivative). The resulting mixture was concentrated under reduced pressure. Yield of **95** calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB), (141 mg, 0.42 mmol, 30%): $^1$H NMR (600 MHz, $CD_3OD$) δ 7.33–7.19 (m, 10H, H-Ar), 6.29 (d, *J* = 8.7 Hz, 1H, H-2), 4.87–4.82 (m, 1H, H-4), 3.70 (m, 2H, H-5), 3.64-3.56 (m, 1H, H-3); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 140.7 (C-1), 133.4 (Ar-Cq), 132.4 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 128.9 (C-2), 76.2 (C-3), 72.2 (C-4), 64.4 (C-5).

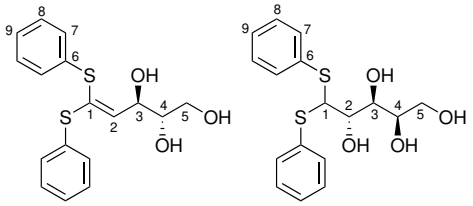
(2*S*,3*R*)-5,5-Bis(phenylthio)pent-4-ene-1,2,3-triol **95**, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol **73**:



To a mixture of L-arabinose diphenyldithioacetal (4.00 mg, 9.70 μmol) and D-ribose diphenyldithioacetal (2.00 mg, 1.90 μmol) in $CD_3OD$ (1.10 mL), was added dimethyl carbonate (5.00 μL, 0.09 mmol, 1.5 eq. per sugar derivative) and $K_2CO_3$ (16.0 mg, 0.12 mmol, 2 eq. per sugar derivative). The resulting mixture was concentrated under reduced pressure. Yield of **95** calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB), (3.00 mg, 7.50 μmol, 77%): $^1$H NMR (600 MHz, $CD_3OD$) δ 7.33–7.19 (m, 10H, H-Ar), 6.29 (d, *J* = 8.7 Hz, 1H, H-2), 4.87–4.82 (m, 1H, H-4), 3.70 (m, 2H, H-5), 3.64-3.56 (m, 1H, H-3); $^1$H NMR (700 MHz, $CD_3OD$) δ

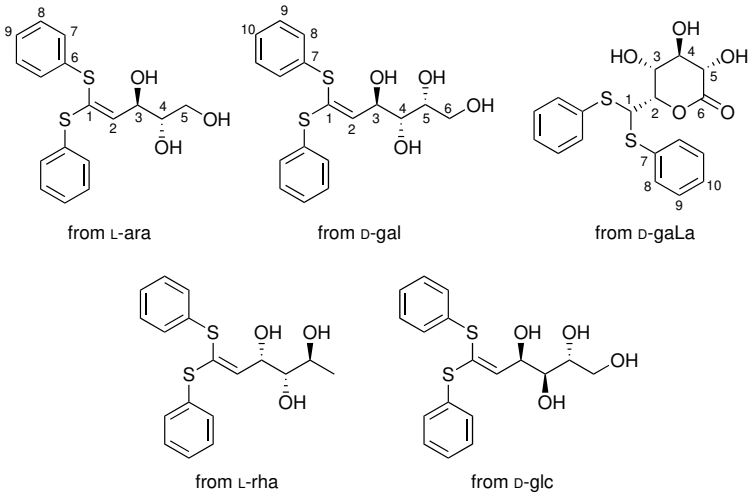
7.51–7.47 (m, 2H, H-Ar), 7.34 (d, *J* = 7.6 Hz, 2H, H-Ar), 7.28–7.18 (m, 6H, H-Ar), 5.02 (d, *J* = 3.2 Hz, 1H, H-1), 4.41–4.39 (m, H-2), 4.18 (dt, *J* = 8.7, 4.3 Hz, 1H, H-4), 3.94 (dd, *J* = 7.9, 7.2 Hz, 1H, H-5), 3.85 (dd, *J* = 7.9, 7.2 Hz, 1H, H-5), 3.75 (d, *J* = 8.7 Hz, 1H, H-3).

(2*S*,3*R*)-5,5-Bis(phenylthio)pent-4-ene-1,2,3-triol **95**, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio) pentane-1,2,3,4-tetraol **74**:



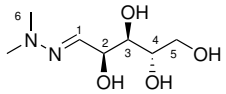
To a mixture of L-arabinose diphenyldithioacetal (7.00 mg, 21 μmol) and D-lyxose diphenyldithioacetal (13.0 mg, 38.0 μmol) in $CD_3OD$ (2.26 mL), was added dimethyl carbonate (10.0 μL, 0.18 mmol, 1.5 eq. per sugar derivative) and $K_2CO_3$ (32.0 mg, 0.23 mmol, 2 eq. per sugar derivative). The resulting mixture was concentrated under reduced pressure. Yield of **95** calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB), (5.00 mg, 16.0 μmol, 77%): $^1$H NMR (600 MHz, $CD_3OD$) δ 7.33–7.19 (m, 10H, H-Ar), 6.29 (d, *J* = 8.7 Hz, 1H, H-2), 4.87–4.82 (m, 1H, H-4), 3.72–3.69 (m, 2H, H-5), 3.64–3.56 (m, 1H, H-3); $^1$H NMR (300 MHz, $CD_3OD$) δ 7.59–7.43 (m, 2H, H-Ar), 7.36–7.17 (m, 8H, H-Ar), 5.07 (d, *J* = 1.5 Hz, 1H, H-1), 4.12 (dd, *J* = 9.1, 1.3 Hz, 1H, H-5), 3.97–3.89 (m, 2H, H-5, H-2), 3.63–3.60 (m, 2H, H-3, H-4).

(2*S*,3*S*,4*R*)-5,5-Bis(phenylthio)pentane-1,2,3,4-tetraol **95**, (2*R*,3*R*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol **102**, (2*S*,3*R*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6,6-bis(phenylthio)hexanoic acid **83**, (2*S*,3*S*,4*S*)-6,6-bis(phenylthio)hex-5-ene-2,3,4-triol **75**, (2*R*,3*S*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol **101**,




To a mixture of thioacetals (quantities measured by T=0 $^1$H NMR via addition of internal standard 1,4-DMB) of L-arabinose (1.29 mmol), D-galactose (0.85 mmol), D-galacturonic acid (0.45 mmol), L-rhamnose (0.48 mmol) and D-glucose (0.36 mmol) in $CD_3OD$ (10.0 mL), was added dimethyl carbonate (62.0 μL, 1.09 mmol, 1.5 eq. per sugar derivative) and $K_2CO_3$ (202 mg, 1.46 mmol, 2 eq. per sugar derivative). The resulting mixture was analysed by NMR to give the yield of **95** calculated by $^1$H NMR, via addition of an internal standard (1,4-DMB), (1.29 mmol, 100%), D-galactose alkene (0.66 mmol, 78%), L-rhamnose alkene (0.17 mmol, 34%) and D-glucose alkene (0.12 mmol, 32%): L-arabinose thioacetal ketene: $^1$H NMR (600 MHz, $CD_3OD$) δ 6.31 (d, *J* = 8.7 Hz, 1H, H-2); D-galactose thioacetal ketene: $^1$H NMR (600 MHz, $CD_3OD$) δ 6.27 (d, *J* = 8.7 Hz, 1H, H-2); D-galacturonic acid thioacetal: $^1$H NMR (600 MHz, $CD_3OD$) δ 4.35 (d, *J* = 8.9 Hz, 1H, H-5); L-rhamnose thioacetal ketene: $^1$H NMR (600 MHz, $CD_3OD$) δ 6.37 (d, *J* = 8.7 Hz, 1H, H-2); D-glucose thioacetal ketene: $^1$H NMR (600 MHz, $CD_3OD$) δ 6.45 (d, *J* = 8.6 Hz, 1H, H-2).

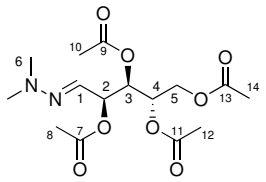
L-Arabinose dimethylhydrazone, (2*S*,3*R*,4*S*,*E*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetraol, **40**:[69]



To a solution of L-arabinose (4.50 g, 30.0 mmol) in methanol (15.0 mL), was added *N*,*N*-dimethylhydrazine (4.60 mL, 0.06 mol, 2 eq.) and Amberlyst 15 (3.00 g). The resulting mixture was stirred at rt for 24 h before filtration. The clear solution was

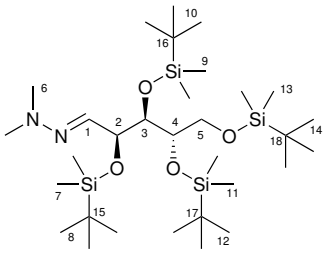
then concentrated *in vacuo* and the product washed with $Et_2O$ (2 × 15.0 mL), yielding a white solid (4.16 g, 22.0 mmol, 72%): M.p: 101–104 °C ($Et_2O$), $[\alpha]_D^{25}$ = +20 (*c* = 1.00, pyridine); $^1$H NMR (600 MHz, $CD_3OD$) δ 6.77 (d, *J* = 5.5 Hz, 1H, H-1), 4.40 (dd, *J* = 5.5, 2.6 Hz, 1H, H-2), 3.79 (dd, *J* = 11.2, 3.5 Hz, 1H, H-5), 3.71 (ddd, *J* = 8.0, 6.0, 3.5 Hz, 1H, H-4), 3.65 (dd, *J* = 11.2, 6.0 Hz, 1H, H-5), 3.56 (dd, *J* = 8.0, 2.6 Hz, 1H, H-3), 2.77 (s, 6H, H-6); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 139.1 (C-1), 74.9 (C-2), 72.9 (C-3), 72.2 (C-4), 64.8 (C-5), 43.1 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3390 (O-H), 3246 (N=C-H), 2938 (C=N); Data is in accordance with the literature.

L-Arabinose dimethylhydrazone tetraacetate, (2*S*,3*R*,4*S*,*E*)-5-(2,2-dimethylhydrazin eylidene)pentane-1,2,3,4-tetraacetate, **176**:



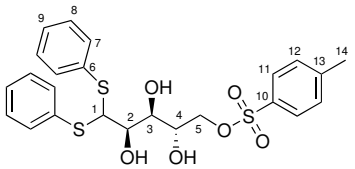
A mixture of L-arabinose dimethylhydrazone (500 mg, 2.60 mmol) and acetic anhydride (1.97 mL, 20.8 mmol) in pyridine (10.0 mL) was left to stir at 50 °C for 10 h before being poured over ice-water. The aqueous layer was extracted with ethyl acetate (3 × 10.0 mL). The organic extracts were washed with 1 M HCl (5.00 mL), sat. aq. $NaHCO_3$ (10.0 mL) and brine (10.0 mL) before drying over $MgSO_4$. Solvent was removed *in vacuo* yielding a crude orange syrup. Crude material was purified via column chromatography to yield the pure product as an orange oil (67.0 mg, 0.18 mmol, 7%): $[\alpha]_D^{25}$ = -40 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.31 (m, 1H, H-1), 6.50 (dd, *J* = 15.2, 8.9 Hz, 1H, H-3), 6.01–5.94 (dd, *J* = 15.2, 6.7 Hz, 1H, H-2), 5.64–5.58 (m, 1H, H-4), 4.31–4.27 (m, 1H, H-5), 4.16–4.13 (m, 1H, H-5), 3.22 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 173.0 (C=O), 171.3 (C=O), 170.7 (C=O), 170.4 (C=O), 139.1 (C-1), 132.7 (C-2), 131.4 (C-3), 71.2 (C-4), 64.6 (C-5), 42.6 (N-$CH_3$), 27.6 ($CH_3$), 21.5 ($CH_3$), 21.1 ($CH_3$), 20.9 ($CH_3$); $\nu_{max}$ (film/cm$^{-1}$) 2929 (N=C-H), 1741 (C=O), 1463 ($CH_2$), 1002 (C-O); HRMS (ESI) Calc'd for $CH_{15}H_{25}N_2O_8$ $[M + H]^+$ 361.1566, found 361.1611.

(*E*)-1,1-Dimethyl-2-((2*S*,3*R*,4*S*)-2,3,4,5-tetrakis((tert-butyldimethylsilyl)oxy)pentylidene) hydrazine **180**:



To a stirred solution of hydrazone (100 mg, 0.61 mmol), imidazole (166 mg, 2.44 mmol) and DMAP (9.00 mg, 0.07 mmol) in $CH_2Cl_2$ (2.00 mL), was added TBDMSCl (475 μL, 2.74 mmol) dissolved in $CH_2Cl_2$ (2.00 mL) at 0 °C. The mixture was then heated to reflux for 4 h. The reaction mass was concentrated under reduced pressure and purified via column chromatography (20% Acetone/$CH_2Cl_2$) to give the pure product as a yellow oil (20.0 mg, 0.03 mmol, 5%): $[\alpha]_D^{25}$ = +12 (*c* = 1.00, pyridine); $^1$H NMR (700 MHz, $CDCl_3$) δ 6.58 (d, *J* = 6.6 Hz, 1H, H-1), 4.40 (dd, *J* = 6.6, 3.6 Hz, 1H, H-2), 3.81 (d, *J* = 3.6 Hz, 1H, H-5), 3.76–3.73 (m, 2H, H-4, H-5), 3.69–3.65 (m, 1H, H-3), 2.77 (s, 6H, H-6), 0.90–0.87 (m, 36H, $^t$-$CH_3$), 0.14–0.10 (m, 6H, $CH_3$ x 2), 0.09 (s, 12H, $CH_3$ x 4), 0.06 (s, 6H, $CH_3$ x 2); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 135.0 (C-1), 76.2 (C-2), 74.0 (C-3), 72.6 (C-4), 64.6 (C-6), 43.0 ($NCH_3$ x 2), 26.1 ($^t$-$CH_3$ x 4), 18.5 (Cq), 18.2 (Cq), 18.1 (Cq), 18.0 (Cq), -3.9 ($SiCH_3$), -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -4.8 ($SiCH_3$), -5.0 ($SiCH_3$), -5.1 ($SiCH_3$), -5.2 ($SiCH_3$), -5.3 ($SiCH_3$); $\nu_{max}$ (film/cm$^{-1}$) 2927 (N=C-H), 1470 ($CH_2$), 1103 (C-O); HRMS (ESI) Calc'd for $C_{31}H_{73}N_2O_4Si_4$ $[M + H]^+$ 649.4647, found 649.4667.

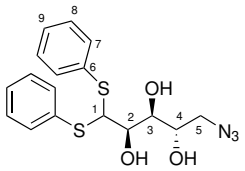
(2*S*,3*S*,4*R*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl 4-methylbenzenesulfonate **189**:



To a solution of L-arabinose diphenyl dithioacetal **70** (600 mg, 1.70 mmol) in pyridine (4.00 mL) at -20 °C, was added a solution of tosyl chloride (650 mg, 3.40 mmol, 2 eq.) in pyridine (4.00 mL). After 2 h, water (5 drops) was added and the solution was

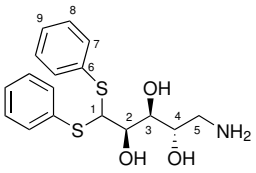
concentrated to dryness and co-concentrated with toluene to give the crude mixture. The residue was then purified via column chromatography to give the pure product as a white solid (240 mg, 0.50 mmol, 28%): M.p: 119–123 °C ($Et_2O$), $[\alpha]_D^{21}$ = 120 ($c$ = 1.00, $CHCl_3$); $^H$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J$ = 8.3 Hz, 2H, H-Ar), 7.49–7.41 (m, 4H, H-Ar), 7.34 (d, $J$ = 8.0 Hz, 2H, H-Ar), 7.33–7.28 (m, 6H, H-Ar), 4.60 (d, $J$ = 8.1 Hz, 1H, H-1), 4.31 (dd, $J$ = 10.6, 3.0 Hz, 1H, H-5), 4.19 (dd, $J$ = 10.6, 6.0 Hz, 1H, H-5), 4.12 (dd, $J$ = 8.1, 1.5 Hz, 1H, H-2), 3.96–3.89 (m, 2H, H-3, H-4), 2.43 (s, 3H, H-14); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 133.6 (Ar-Cq), 133.3 (Ar-Cq), 133.1 (Ar-C), 132.6 (Ar-C), 132.2 (Ar-C), 130.1 (Ar-C), 129.3 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 71.8 (C-5), 70.7 (C-4), 70.6 (C-3), 69.8 (C-2), 63.8 (C-1), 21.8 ($CH_3$); $\nu_{max}$ (solid/cm$^{-1}$) 3464 (O-H), 1438 (R-CH), 1353 (S=O), 1173 (C-O); HRMS (ESI) Calc'd for $C_{24}H_{26}O_6S_3Na$ $[M + Na]^+$ 529.0784, found 529.0783.

(2*R*,3*S*,4*S*)-5-Azido-1,1-bis(phenylthio)pentane-2,3,4-triol, **190**:



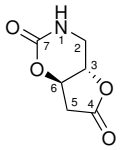

To a stirred solution of **189** (220 mg, 0.44 mmol) in DMF (2.50 mL) was added sodium azide (57.0 mg, 0.87 mmol, 2 eq.). The mixture was heated at 110 °C for 3 h. Then, the solvent was evaporated and the residue partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography to give the product as a yellow solid (69.0 mg, 0.18 mmol, 41%): M.p: 91–96 °C ($Et_2O$), $[\alpha]_D^{21}$ = +96 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H, H-Ar), 7.47–7.45 (m, 2H, H-Ar), 7.33–7.31 (m, 6H, H-Ar), 4.63 (d, $J$ = 8.0 Hz, 1H, H-1), 4.13 (dd, $J$ = 6.3, 1.7 Hz, 1H, H-4), 3.92 (dd, $J$ = 8.0, 1.7 Hz, 1H, H-2), 3.86–3.82 (m, 1H, H-3), 3.59 (dd, $J$ = 12.6, 3.6 Hz, 1H, H-5), 3.52 (dd, $J$ = 12.6, 6.3 Hz, 1H, H-5); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 133.7 (Ar-Cq), 133.3 (Ar-Cq), 133.2 (Ar-C), 132.2 (Ar-C), 131.8 (Ar-C), 129.3 (Ar-C), 128.8 (Ar-C), 128.5 (Ar-C), 71.9 (C-3), 71.0 (C-4), 70.7 (C-2), 63.9 (C-1), 54.3 (C-5); $\nu_{max}$ (solid/cm$^{-1}$) 3405 (O-H), 2923 (R-CH), 2102 (N=N=N), 1438 (R-CH), 1069 (C-N), 1051 (C-O); HRMS (ESI) Calc'd for $C_{17}H_{19}N_3O_3S_2Na$ $[M + Na]^+$ 400.0760, found 400.0752.

(2*R*,3*S*,4*S*)-5-Amino-1,1-bis(phenylthio)pentane-2,3,4-triol **191**:




A solution of **190** (135 mg, 0.36 mmol) in MeOH (9.00 mL) was hydrogenated with Pd-C (10%, 16.0 mg) at 1 atm for 12 h. The catalyst was filtered off and the solvent concentrated to give the product as a colourless oil (106 mg, 0.30 mmol, 84%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2H, H-Ar), 7.47–7.43 (m, 2H, H-Ar), 7.33–7.29 (m, 6H, H-Ar), 4.63 (d, *J* = 7.9 Hz, 1H, H-1), 4.12 (d, *J* = 7.1 Hz, 1H, H-2), 3.92 (d, *J* = 7.9 Hz, 1H, H-3), 3.86–3.82 (m, 1H, H-4), 3.56 (dd, *J* = 12.6, 3.4 Hz, 1H, H-5) 3.51 (dd, *J* = 12.6, 6.2 Hz, 1H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 133.6 (Ar-Cq), 133.2 (Ar-Cq), 133.1 (Ar-C), 132.2 (Ar-C), 129.3 (Ar-C), 129.3 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 71.8 (C-4), 70.9 (C-3), 70.7 (C-2), 63.9 (C-1), 54.2 (C-5); $[\alpha]_D^{21}$ = 16 (*c* = 1.00, $CHCl_3$); $\nu_{max}$ (solid/cm$^{-1}$) 3399 (O-H), 1438 (R-CH), 1069 (C-N); HRMS (ESI) Calc'd for $C_{17}H_{23}NO_3S_2$ $[M + H]^+$ 352.1036, found 352.1029.

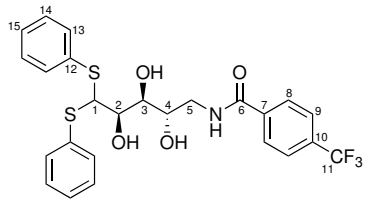
Tetrahydro-2H-furo[2,3-e][1,3]oxazine-2,6(3H)-dione **193**:




To a mixture of **191** (34.0 mg, 0.10 mmol) dissolved in MeOH (2.00 mL) was added dimethyl carbonate (22.0 μL, 0.15 mmol, 1.5 eq.) and $K_2CO_3$ (27.0 mg, 0.19 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a colourless oil (15.0 mg, 0.05 mmol, 46%): $[\alpha]_D^{21}$ = +8 (*c* = 1.00, $CHCl_3$); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.52–4.44 (m, 2H, H-3, H-6), 3.67 (dd, *J* = 13.2, 4.2 Hz, 1H, H-2), 3.60 (dd, *J* = 13.2, 3.8 Hz, 1H, H-2), 2.96 (dd, *J* = 18.1, 7.1 Hz, 1H, H-5), 2.55 (dd, *J* = 18.1, 4.0 Hz, 1H, H-5); $^{13}$C

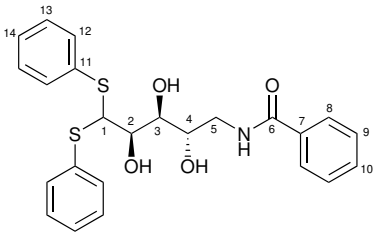
NMR (101 MHz, $CDCl_3$) δ 174.0 (C-7), 153.1 (C-4), 84.5 (C-3), 69.5 (C-6), 52.0 (C-2), 38.0 (C-5); $\nu_{max}$ (solid/$cm^{-1}$) 3433 (O-H), 1779 (C=O); HRMS (ESI) Calc'd for $C_6H_8NO_4$ $[M + H]^+$ 157.0370, found 157.0354. Due to this compound's low level of purity, this structure is only the proposed major product.

4-(Trifluoromethyl)-*N*-((2*S*,3*S*,4*R*)-2,3,4-trihydroxy-5,5-bis(phenylthio)pentyl)benzamide **196**:



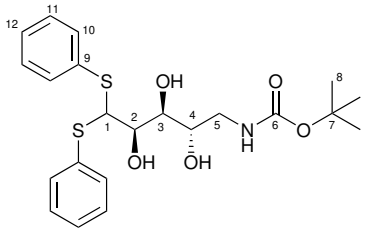

To a mixture of **191** (95.0 mg, 0.27 mmol) dissolved in pyridine (3.00 mL), 4-trifluormethylbenzoyl chloride (45.0 µL, 0.30 mmol, 1.1 eq.) was added dropwise at 0 °C. The mixture was stirred at 0 ° for 2 h and at rt overnight. The solvent was evaporated and co-evaporated with toluene. The residue was added to water, extracted with EtOAc and washed with brine, followed by aq. $NaHCO_3$. The residue was purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a colourless oil (123 mg, 0.24 mmol, 89%): $[\alpha]_D^{21}$ = +44 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, CDCl3) δ 8.02 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.97 (d, *J* = 8.0 Hz 1H, H-Ar), 7.65–7.60 (m, 2H, H-Ar), 7.54–7.41 (m, 2H, H-Ar), 7.30–7.21 (m, 6H, H-Ar), 5.53 (d, *J* = 6.9 Hz, 1H, H-1), 5.15 (dt, *J* = 8.8, 3.5 Hz, 1H, H-3), 4.97 (d, *J* = 6.9 Hz, 1H, H-2), 4.87 (dd, *J* = 8.8, 1.9 Hz, 1H, H-4), 3.82–3.70 (m, 1H, H-5), 3.60–3.47 (m, 1H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.4 (C=O), 133.7 (Ar-Cq), 133.5 (Ar-Cq), 133.3 (Ar-C), 132.8 (Ar-C), 132.4 (Ar-C), 132.1 (Ar-C), 130.5 (Ar-C), 130.2 (Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 125.4 (C-11), 73.3 (C-3), 72.5 (C-4), 69.0 (C-2), 59.9 (C-1), 52.5 (C-5); $\nu_{max}$ (solid/$cm^{-1}$) 3419 (O-H), 1732 (C=O); HRMS (ESI) Calc'd for $C_{25}H_{25}F_3NO_4S_2$ $[M + H]^+$ 524.1172, found 524.1171.

*N*-((2*S*,3*S*,4*R*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl)benzamide **197**:



To a mixture of **191** (50.0 mg, 0.142 mmol) dissolved in $CH_2Cl_2$ (5.00 mL) was added TEA (24.0 μL, 0.17 mmol, 1.2 eq.), DMAP (3.00 mg, 0.014 mmol, cat.) and benzoyl chloride (20.0 μL, 0.17 mmol, 1.2 eq.). The resulting solution was stirred and allowed to warm to rt for 18 h. The mixture was purified using silica gel chromatography (EtOAc/cyclohexane 1:1) to yield the product as a colourless oil (30.0 mg, 0.07 mmol, 47%): $[\alpha]_D^{21}$ = +48 (*c* = 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.3 Hz, 2H, H-Ar), 7.85 (dd, *J* = 8.4, 1.3 Hz, 2H, H-Ar), 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H, H-Ar), 7.52–7.44 (m, 3H, H-Ar), 7.42–7.35 (m, 3H, H-Ar), 7.32–7.20 (m, 4H, H-Ar), 5.54 (dd, *J* = 6.3, 1.9 Hz, 1H, H-2), 5.13 (dt, *J* = 8.5, 3.5 Hz, 1H, H-3), 4.90 (d, *J* = 6.3 Hz, 1H, H-1), 4.87 (dd, *J* = 8.5, 1.9 Hz, 1H, H-4),3.75 (dd, *J* = 13.5, 3.5 Hz, 1H, H-5), 3.69 (dd, *J* = 13.5, 4.3 Hz, 1H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.5 (C=O), 133.6 (Ar-Cq), 133.5 (Ar-Cq), 133.4 (Ar-C), 133.2 (Ar-C), 132.6 (Ar-C), 130.1 (Ar-C), 129.9 (Ar-C), 129.3 (Ar-C), 129.3 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 72.8 (C-3), 72.2 (C-4), 69.4 (C-2), 60.7 (C-1), 50.9 (C-5); $\nu_{max}$ (solid/cm$^{-1}$) 3481 (O-H), 1723 (C=O), 1212 (C-N); HRMS (ESI) Calc'd for $C_{24}H_{26}NO_4S_2$ $[M + H]^+$ 456.1298, found 456.1290.

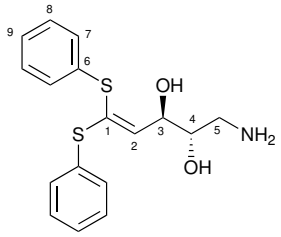
*tert*-Butyl ((2*S*,3*S*,4*R*)-2,3,4-trihydroxy-5,5-bis(phenylthio)pentyl)carbamate **198**:



To a mixture of **191** (150 mg, 0.43 mmol) dissolved in MeOH (5.00 mL) with TEA (4.00 mL) was slowly added a solution of of $Boc_2O$ (558 mg, 2.56 mmol, 6 eq.) in MeOH (3.00 mL). The resulting solution was stirred at 60 $^o$C 5 h. The

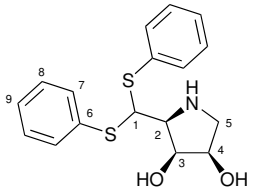
mixture was concentrated *in vacuo* and purified using silica gel chromatography (EtOAc/cyclohexane 1:1) to yield the product as a colourless oil (33.0 mg, 0.07 mmol, 17%): $[\alpha]_D^{21}$ = +40 (*c* = 0.90, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H, H-Ar), 7.46–7.42 (m, 2H, H-Ar), 7.30–7.26 (m, 6H, H-Ar), 5.06 (t, *J* = 5.8 Hz, 1H, N-H), 4.74 (d, *J* = 7.8 Hz, 1H, H-1), 4.04 (d, *J* = 8.2 Hz, 1H, H-4), 3.96 (d, *J* = 7.8 Hz, 1H, H-2), 3.82–3.76 (m, 1H, H-3), 3.52–3.45 (m, 1H, H-5), 3.36–3.30 (m, 1H, H-5), 1.44 (s, 9H, 3x$CH_3$); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 158.4 (C=O), 133.5 (Ar-Cq), 133.0 (Ar-C), 129.2 (Ar-C), 128.4 (Ar-C), 80.6 (C-7), 72.3 (C-3), 71.2 (C-4), 70.0 (C-2), 63.7 (C-1), 43.8 (C-5), 28.5 (C-8); $\nu_{max}$ (solid/$cm^{-1}$) 3365 (O-H), 1679 (C=O), 1249 (C-N); HRMS (ESI) Calc'd for $C_{22}H_{30}NO_5S_2$ $[M + H]^+$ 452.1559, found 452.1555.

(2*S*,3*R*)-1-Amino-5,5-bis(phenylthio)pent-4-ene-2,3-diol **199**:



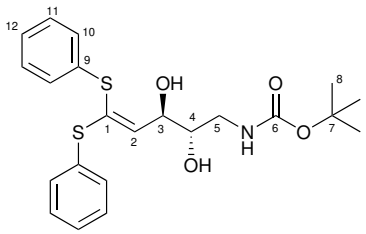

To a mixture of **196** (115 mg, 0.22 mmol) dissolved in MeOH (3.00 mL) was added dimethyl carbonate (19.0 μL, 0.33 mmol, 1.5 eq.) and $K_2CO_3$ (61.0 mg, 0.44 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a yellow oil (28.0 mg, 0.084 mmol, 38%): $[\alpha]_D^{21}$ = +72 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 10H, H-Ar), 6.01 (d, *J* = 8.4 Hz, 1H, H-2), 4.88 (dd, *J* = 8.4, 4.8 Hz, 1H, H-3), 3.88–3.80 (m, 1H, H-4), 3.41–3.36 (m, 2H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 137.2 (C-1), 134.0 (Ar-Cq), 133.4 (Ar-Cq), 133.0 (Ar-C), 132.2 (Ar-C), 131.1 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 127.7 (C-2), 73.1 (C-4), 71.4 (C-3), 53.0 (C-5); $\nu_{max}$ (solid/$cm^{-1}$) 3399 (O-H), 1356 (C-N); HRMS (ESI) Calc'd for $C_{17}H_{20}NO_2S_2$ $[M + H]^+$ 334.0891, found 334.0930.

(2*S*,3*S*,4*R*)-2-(Bis(phenylthio)methyl)pyrrolidine-3,4-diol **200**:



To a mixture of **197** (25.0 mg, 0.054 mmol) dissolved in MeOH (1.40 mL) was added dimethyl carbonate (5.00 μL, 0.082 mmol, 1.5 eq.) and $K_2CO_3$ (15.0 mg, 0.11 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a yellow oil (6.00 mg, 0.02 mmol, 34%): $[\alpha]_D^{21}$ = +88 (*c* = 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 4H, H-Ar), 7.31–7.22 (m, 6H, H-Ar), 4.73 (d, *J* = 8.0 Hz, 1H, H-1), 4.10 (dd, *J* = 8.8, 1.8 Hz, 1H, H-3), 3.99 (dd, *J* = 8.0, 1.8 Hz, 1H, H-2), 3.81 (ddd, *J* = 8.8, 6.6, 2.7 Hz, 1H, H-4), 3.51 (dd, *J* = 12.8, 2.7 Hz, 1H, H-5), 3.38 (dd, *J* = 12.8, 6.6 Hz, 1H, H-5); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 136.0 (Ar-Cq), 135.5 (Ar-Cq), 134.2 (Ar-C), 133.9 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 72.5 (C-3), 72.3 (C-2), 72.1 (C-4), 64.5 (C-1), 55.8 (C-5); $\nu_{max}$ (solid/cm$^{-1}$) 3414 (O-H), 2923 (C-N); HRMS (ESI) Calc'd for $C_{17}H_{20}N_1O_2S_2$ $[M + H]^+$ 334.0891, found 334.0930.

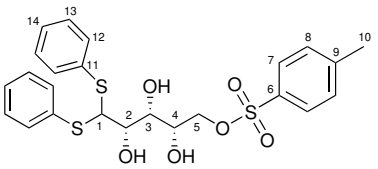
*tert*-Butyl ((2*S*,3*R*)-2,3-dihydroxy-5,5-bis(phenylthio)pent-4-en-1-yl)carbamate **201**:



To a mixture of **198** (30.0 mg, 0.07 mmol) dissolved in MeOH (1.40 mL) was added dimethyl carbonate (6.00 μL, 0.10 mmol, 1.5 eq.) and $K_2CO_3$ (19.0 mg, 0.13 mmol, 2 eq.). The resulting mixture was stirred at room temperature for 12 h before being concentrated under reduced pressure and purified using silica gel chromatography (EtOAc/cyclohexane 3:2) to yield the product as a yellow oil (9.00 mg, 0.02 mmol, 32%): $[\alpha]_D^{21}$ = +36 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 4H, H-Ar), 7.36–7.31 (m, 6H, H-Ar), 5.83 (d, *J* = 8.4 Hz, 1H, H-2), 5.06 (dd, *J* =

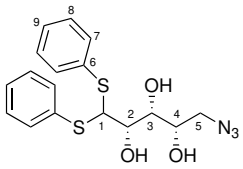
7.4, 4.6 Hz, 1H, H-4), 4.58 (d, *J* = 8.4 Hz, 1H, H-3), 4.34 (dd, *J* = 7.4, 1.5 Hz, 1H, H-5), 3.81 (dd, *J* = 8.4, 1.5 Hz, 1H, H-5), 1.27 (s, 3 x $CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.5 (C=O), 134.0 (C-1), 133.6 (Ar-Cq), 133.1 (Ar-C), 131.2 (Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 127.6 (Ar-C), 70.9 (C-7), 67.4 (C-4), 59.5 (C-3), 29.8 (C-5), 4.3 (C-8). $\nu_{max}$ (solid/cm$^{-1}$) 3420 (O-H), 1737 (C=O), 1023 (C-N); HRMS (ESI) Calc'd for $C_{17}H_{20}NO_2S_2$ $[M + H]^+$ 347.10, found 347.11.

(2*S*,3*R*,4*S*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl 4-methylbenzenesulfonate **202**:



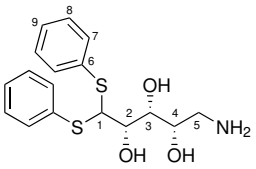

To a solution of L-xylose diphenyl dithioacetal **72** (2.26 g, 6.418 mmol) in pyridine (10.0 mL) at -20 °C, was added a solution of tosyl chloride (1.87 g, 9.79 mmol, 1.5 eq.) in pyridine (10.0 mL). After 24 h, the mixture was poured over ice-water and extracted into $CH_2Cl_2$ (5 x 10.0 mL), washed with aq. 15% $CuSO_4$ solution (10.0 mL), followed by brine (10.0 mL) and dried over $MgSO_4$. The solution was filtered through silica before concentrating *in vacuo*. The residue was then purified via column chromatography to give the pure product as a colourless oil (150 mg, 0.30 mmol, 5%): $[\alpha]_D^{21}$ = +48 (*c* = 1.00, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H, H-Ar), 7.44–7.40 (m, 2H, H-Ar), 7.31–7.23 (m, 10H, H-Ar), 4.66 (d, *J* = 9.1 Hz, 1H, H-1), 4.32 (dt, *J* = 4.2, 3.2 Hz, 1H, H-4), 4.29 (dd, *J* = 3.3, 1.4 Hz, 1H, H-3), 4.24 (dd, *J* = 9.9, 4.2 Hz, 1H, H-5), 4.15 (dd, *J* = 9.1, 3.3 Hz, 1H, H-2), 3.75 (dd, *J* = 9.9, 1.4 Hz, 1H, H-5), 2.42 (s, 3H, H-10); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 134.0 (Ar-Cq), 133.2 (Ar-Cq), 133.1 (Ar-C), 132.9 (Ar-C), 130.1 (Ar-C), 130.0 (Ar-C), 129.3 (Ar-C), 128.3 (Ar-C), 81.9 (C-2), 77.8 (C-3), 77.6 (C-4), 74.0 (C-5), 58.8 (C-1), 22.4 ($CH_3$); $\nu_{max}$ (solid/cm$^{-1}$) 3421 (O-H), 2037 (Ar-CH), 1360 (S=O), 1176 (C-O); HRMS (ESI) Calc'd for $C_{24}H_{25}O_6S_3$ $[M + H]^+$ 505.0807, found 505.0807. Due to this compound's low level of purity, this structure is only the proposed major product.

(2*S*,3*R*,4*S*)-5-Azido-1,1-bis(phenylthio)pentane-2,3,4-triol **203**:



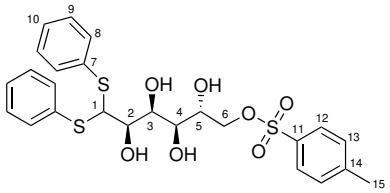
To a stirred solution of **202** (130 mg, 0.26 mmol) in DMF (2.00 mL) was added sodium azide (34.0 mg, 0.51 mmol, 2 eq.). The mixture was heated at 110 °C for 3 h. Then, the solvent was evaporated and the residue partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography to give the product as an unstable colourless oil (95.0 mg, 0.25 mmol, 98%): $[\alpha]_D^{21}$ = +20 (*c* = 1.00, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.32–7.27 (m, 10H, H-Ar), 4.65 (d, *J* = 9.0 Hz, 1H, H-1), 4.36–4.32 (m, 1H, H-4), 4.29–2.27 (m, 1H, H-3), 4.27 (dd, *J* = 10.0, 4.2 Hz, 1H, H-5), 4.17 (dd, *J* = 9.0, 3.4 Hz, 1H, H-2), 3.78 (dd, *J* = 10.0, 1.4 Hz, 1H, H-5). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 134.1 (Ar-Cq), 133.2 (Ar-Cq), 133.1 (Ar-C), 132.8 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.4 (Ar-C), 128.4 (Ar-C), 81.9 (C-2), 77.9 (C-3), 77.7 (C-4), 74.0 (C-5), 59.0 (C-1); $\nu_{max}$ (solid/cm$^{-1}$) 3428 (O-H), 2108 (N=N=N), 1261 (C-N).

(2*S*,3*R*,4*S*)-5-Amino-1,1-bis(phenylthio)pentane-2,3,4-triol **204**:



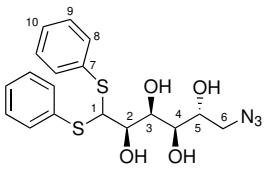
A solution of **203** (85.0 mg, 0.22 mmol) in MeOH (7.00 mL) was hydrogenated with Pd-C (10%, 11.0 mg) at 1 atm for 12 h. The catalyst was filtered off and the solvent concentrated to give the product as a colourless oil (73.0 mg, 0.21 mmol, 93%). $[\alpha]_D^{21}$ = +17 (*c* = 0.70, $CHCl_3$); $^1$H NMR (400 MHz, $CD_3OD$) δ 7.49–7.42 (m, 4H, H-Ar), 7.32–7.22 (m, 6H, H-Ar), 4.74 (d, *J* = 10.2 Hz, 1H, H-1), 4.26–4.18 (m, 3H, H-2, H-3, H-5), 4.03 (dd, *J* = 10.2, 2.9 Hz, 1H, H-5), 3.73–3.63 (m, 1H, H-4); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 135.2 (Ar-Cq), 134.7 (Ar-Cq), 134.5 (Ar-C), 134.4 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 83.2 (C-2), 78.4 (C-3), 77.6 (C-4), 75.0 (C-5), 59.4 (C-1); $\nu_{max}$ (solid/cm$^{-1}$) 3381 (O-H), 3370 (C-N).

(2*R*,3*R*,4*S*,5*R*)-2,3,4,5-Tetrahydroxy-6,6-bis(phenylthio)hexyl 4-methylbenzenesulfonate **207**:



To a solution of D-glucose diphenyl dithioacetal **77** (650 mg, 1.70 mmol) in pyridine (4.00 mL) at -20 °C, was added a solution of tosyl chloride (650 mg, 3.41 mmol, 2 eq.) in pyridine (4.00 mL). After 2 h, water (5 drops) was added and the solution was concentrated to dryness and co-concentrated with toluene to give the crude mixture. The residue was then purified via column chromatography to give the pure product as a white solid (290 mg, 0.54 mmol, 32%): M.p: 122–126 °C ($Et_2O$), $[\alpha]_D^{21}$ = +56 (*c* = 1.00, MeOH); $^1$H NMR (700 MHz, $CD_3OD$) δ 7.83–7.73 (m, 2H, H-Ar), 7.46–7.42 (m, 2H, H-Ar), 7.41–7.38 (m, 4H, H-Ar), 7.28–7.20 (m, 6H, H-Ar), 4.65 (d, *J* = 4.9 Hz, 1H, H-1), 4.28 (dd, *J* = 4.9, 2.1 Hz, 1H, H-3), 4.23 (dd, *J* = 10.1, 2.5 Hz, 1H, H-6), 4.03 (dd, *J* = 10.1, 6.3 Hz, 1H, H-6), 3.91 (t, *J* = 4.9 Hz, 1H, H-2), 3.83 (ddd, *J* = 8.6, 6.3, 2.5 Hz, 1H, H-5), 3.51 (dd, *J* = 8.5, 2.1 Hz, 1H, H-4), 2.42 (s, 3H, H-15); $^{13}$C NMR (176 MHz, $CD_3OD$) δ 146.3 (Ar-Cq), 135.9 (Ar-Cq), 135.8 (Ar-C), 134.2 (Ar-C), 133.8 (Ar-C), 133.5 (Ar-C), 130.9 (Ar-C), 130.7 (Ar-C), 129.9 (Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 75.8 (C-3), 73.6 (C-6), 72.9 (C-4), 71.0 (C-2), 70.4 (C-5), 64.2 (C-1), 21.5 ($CH_3$); $\nu_{max}$ (solid/cm$^{-1}$) 3437 (O-H), 1355 (S=O), 1174 (C-O).

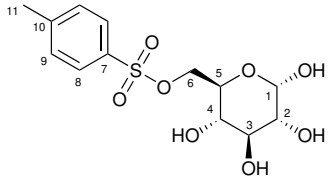
(2*R*,3*S*,4*R*,5*R*)-6-Azido-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol **208**:



To a stirred solution of **207** (280 mg, 0.52 mmol) in DMF (2.60 mL) was added sodium azide (68.0 mg, 1.04 mmol, 2 eq.). The mixture was heated at 110 °C for 3 h. Then, the solvent was evaporated and the residue partitioned between EtOAc and

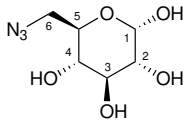
water. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography to give the product as a colourless oil (22.0 mg, 0.05 mmol, 10%): $[\alpha]_D^{21}$ = +68 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H, H-Ar), 7.48–7.44 (m, 2H, H-Ar), 7.36–7.30 (m, 6H, H-Ar), 4.66 (d, *J* = 8.0 Hz, 1H, H-1), 4.44 (dd, *J* = 2.6, 1.3 Hz, 1H, H-3), 3.89–3.85 (m, 1H, H-5), 3.75 (dd, *J* = 8.0, 2.6 Hz, 1H, H-2), 3.69 (dd, *J* = 7.6, 1.3 Hz, 1H, H-4), 3.59 (dd, *J* = 12.6, 3.4 Hz, 1H, H-6), 3.52 (dd, *J* = 12.6, 6.3 Hz, 1H, H-6); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 133.8 (Ar-Cq), 133.0 (Ar-C), 129.1 (Ar-C), 128.8 (Ar-C), 128.4 (Ar-C), 127.6 (Ar-C), 75.0 (C-3), 73.8 (C-6), 70.8 (C-4), 68.1 (C-2), 63.5 (C-5), 54.1 (C-1); $\nu_{max}$ (solid/$cm^{-1}$) 3395 (O-H), 2923 (R-CH), 2101 (N=N=N), 1438 (R-CH), 1071 (C-N), 1067 (C-O); HRMS (ESI) Calc'd for $C_{18}H_{19}N_3O_4S_2$ $[M]^-$ 406.0900, found 406.0887.

((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5,6-Tetrahydroxytetrahydro-2H-pyran-2-yl)methyl 4-methyl benzenesulfonate **212**:[160]




To a solution of D-glucose (1.50 g, 8.30 mmol) in pyridine (14.0 mL) at -20 °C, was added a solution of tosyl chloride (2.40 g, 12.5 mmol, 2 eq.) in pyridine (14.0 mL). After 2 h, water (5 drops) was added and the solution was concentrated to dryness and co-concentrated with toluene to give the crude mixture. The residue was then purified via column chromatography to give the product as a colourless oil (664 mg, 1.99 mmol, 24%): $[\alpha]_D^{21}$ = +56 (*c* = 1.00, MeOH); $^1$H NMR (600 MHz, $CD_3OD$) δ 7.83–7.80 (m, 2H, H-Ar), 7.77–7.75 (m, 2H, H-Ar), 5.02 (d, *J* = 3.5 Hz, 1H, H-1), 4.21 (dd, *J* = 10.8, 2.0 Hz, 1H, H-6), 4.14 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6) 3.97 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.86 (ddd, *J* = 10.1, 5.2, 2.0 Hz, 1H, H-5), 3.73–3.68 (m, 1H, H-3), 3.17 (dd, *J* = 10.1, 8.9 Hz, 1H, H-4), 2.45 (s, 3H, $CH_3$); $^{13}$C NMR (151 MHz, $CD_3OD$) δ 135.1 (Ar-Cq), 134.3 (Ar-C), 131.0 (Ar-C), 130.8 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 91.4 (C-1), 81.5 (C-2) 71.6 (C-3), 71.3 (C-4), 70.7 (C-6), 70.2 (C-5), 21.6 ($CH_3$); $\nu_{max}$ (solid/$cm^{-1}$) 3485 (O-H), 1356 (S=O), 1174 (C-O).

(2*R*,3*S*,4*R*,5*R*)-6-Azido-2,3,4,5-tetrahydroxyhexanal **213**:[119]

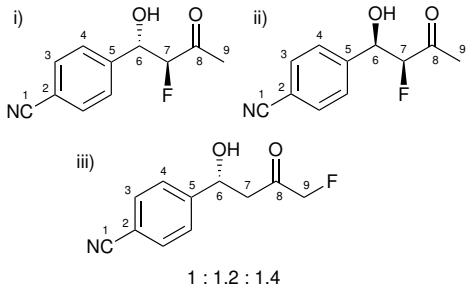



To a stirred solution of **212** (640 mg, 1.91 mmol) in DMF (6.00 mL) was added sodium azide (249 mg, 3.83 mmol, 2 eq.). The mixture was heated at 110 °C for 3 h. Then, the solvent was evaporated and the residue partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography to give the product as a colourless oil (32.0 mg, 0.16 mmol, 8%): $[\alpha]_D^{21}$ = +68 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, *J* = 2.9 Hz, 1H, H-1), 4.50 (t, *J* = 4.9 Hz, 1H, H-2), 4.15–4.08 (m, 2H, H-3, H-4), 4.02 (dd, *J* = 9.5, 2.9 Hz, 1H, H-5), 3.61 (dd, *J* = 12.9, 3.2 Hz, 1H, H-6), 3.55 (dd, *J* = 12.9, 5.8 Hz, 1H, H-6); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 95.7 (C-1), 79.7 (C-3), 76.2 (C-5), 71.3 (C-2), 70.0 (C-4), 54.0 (C-6); $\nu_{max}$ (solid/cm$^{-1}$) 3485 (O-H), 1356 (S=O), 1174 (C-O).

# 4.2 Fluorocompounds

## 4.2.1 Chemically-Derived Products

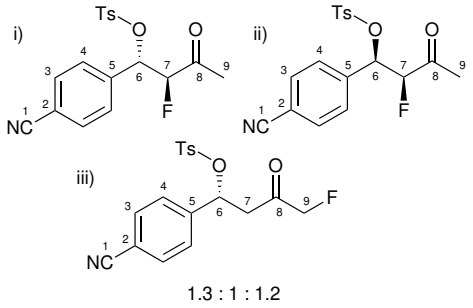
4-(2-Fluoro-1-hydroxy-3-oxobutyl)benzonitrile **233**:




To a solution of 4-cyanobenzaldehyde (3.00 g, 22.9 mmol) and fluoroacetone (3.30 mL, 45.8 mmol, 2 eq.) in anhydrous DMSO (7.00 mL), was added L-prolinol (1.68 mL, 17.2 mmol, 75 mol%). The resulting homogenous mixture was kept at rt for 24 h. Then, saturated $NH_4Cl$ solution (20.0 mL) was added. The reaction mixture was extracted with EtOAc (4 x 10.0 mL) and dried over $MgSO_4$. Evaporation of solvent was followed by purification via column chromatography (1:2 EtOAc/cyclohexane). A yellow oil was obtained, containing a mixture of isomers (1.39 g, 6.72 mmol, 29%). Isomer i: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.62–7.45 (m, 4H, H-Ar), 5.12 (dd, *J* = 16.9, 4.7 Hz, 1H, H-6), 4.84 (dd, *J* = 47.0, 4.5 Hz, 1H, H-7), 2.10 (dd, *J* = 4.9, 1.2 Hz, 3H, H-9); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 207.1 (d, *J* = 25.7 Hz, C=O), 133.1 (Ar-Cq), 132.6 (Ar-C), 132.4 (Ar-C), 132.3 (Ar-C), 118.7 (CN), 96.5 (d, *J* = 191.7 Hz, C-7), 73.0 (d, *J* = 21.6 Hz, C-6), 27.6 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -195.14 (dd, *J* = 49.3, 18.5 Hz) or -205.61 (dd, *J* = 48.1, 27.6 Hz); Isomer ii: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.62–7.45 (m, 4H, H-Ar), 5.18–5.12 (m, 1H, H-6), 4.80 (dd, *J* = 48.1, 2.1 Hz, 1H, H-7), 2.28 (dd, *J* = 5.0, 0.7 Hz, 3H, H-9); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 206.0 (d, *J* = 19.3 Hz, C=O), 130.1 (Ar-Cq), 127.9 (Ar-C), 127.4 (Ar-C), 126.5 (Ar-C), 118.7 (CN), 97.9 (d, *J* = 194.9 Hz, C-7), 72.9 (d, *J* = 19.0 Hz, C-6), 27.5 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -195.14 (dd, *J* = 49.3, 18.5 Hz) or -205.61 (dd, *J* = 48.1, 27.6 Hz); Isomer iii: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.62–7.45 (m, 4H, H-Ar), 5.32 (dd, *J* = 9.2, 2.9 Hz, 1H, H-6), 4.85 (dd, *J* = 49.4, 4.6 Hz, 2H, H-9), 2.96–2.91 (m, 1H, H-7), 2.85–2.81 (m, 1H, H-7); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 207.5 (d, *J* = 27.0 Hz, C=O), 144.7 (Ar-Cq), 143.4 (Ar-C), 133.1 (Ar-C), 130.1 (Ar-C), 118.7 (CN), 85.3 (d, *J* = 182.0 Hz, C-9), 68.7 (d, *J* = 2.7 Hz, C-6), 47.0

(C-7) $^{19}$F NMR (376 MHz, $CDCl_3$) δ no peaks observed, predicted to be outside of scanning range; HRMS (ESI) Calc'd for $C_{11}H_{11}FNO_2$ $[M + H]^+$ 208.0768, found 208.0769.

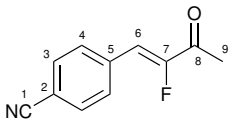
(2*S*)-1-(4-Cyanophenyl)-2-fluoro-3-oxobutyl 4-methylbenzenesulfonate, (*R*)-1-(4-cyanophenyl)-4-fluoro-3-oxobutyl 4-methylbenzenesulfonate **235**:




A solution of **233** (450 mg, 2.17 mmol) in pyridine and dry $CH_2Cl_2$ (4.50 mL) was cooled in an ice bath. TsCl (827 mg, 4.34 mmol, 2 eq.) dissolved in $CH_2Cl_2$ (2.00 mL) was added dropwise to the stirring cold solution. The reaction was allowed to warm to rt. After 24 h, the reaction was quenched with water and the aqueous layer extracted with EtOAc (3 x 15.0 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. A yellow oil was obtained, composed of a mixture of isomers (503 mg, 1.39 mmol, 64%). Isomer i: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (m, 4H, H-Ar), 7.25–7.20 (m, 4H, H-Ar), 5.82 (t, *J* = 2.4 Hz, 1H, H-6), 4.87 (dd, *J* = 153.2, 2.4 Hz, 1H, H-7), 2.48 (s, 3H, Ts-$CH_3$), 2.23 (d, *J* = 5.0 Hz, 3H, $CH_3$); Isomer ii: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94–7.88 (m, 2H, H-Ar), 7.41–7.37 (m, 4H, H-Ar), 5.89 (d, *J* = 2.5 Hz, 1H, H-6), 5.00 (dd, *J* = 156.0, 2.5 Hz, 1H, H-7), 2.48 (s, 3H, Ts-$CH_3$), 1.96 (d, *J* = 5.2 Hz, 3H, $CH_3$); Isomer iii: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93–7.89 (m, 4H, H-Ar), 7.40–7.37 (m, 4H, H-Ar), 5.29 (dd, *J* = 8.8, 3.6 Hz, 1H, H-6), 5.10–4.90 (dd, *J* = 77.0, 47.1. Hz, 1H, H-9), 4.97–4.78 (dd, *J* = 77.0, 2.5 Hz, 1H, H-9), 2.95 (dd, *J* = 8.8, 2.3 Hz, 1H, H-7), 2.92 (dd, *J* = 3.6, 2.3 Hz, 1H, H-7), 2.48 (s, 3H, Ts-$CH_3$); Isomers i, ii and iii: $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.3 (d, *J* = 6.2 Hz, C=O), 204.1 (d, *J* = 7.2 Hz, C=O), 194.6 (d, *J* = 20.3 Hz, C=O), 132.8 (Ar-Cq), 132.5 (Ar-Cq), 132.2 (Ar-C), 130.3 (Ar-C), 123.0 (Ar-C), 129.8 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 127.1 (Ar-C), 126.5 (Ar-C), 118.3 (CN), 118.1 (CN), 114.1 (CN), 113.3 (d, *J* = 82.9 Hz, C-F), 113.2 (d, *J* = 76.9

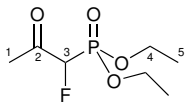
Hz, C-F), 84.1 (d, $J$ = 184.4 Hz, $CH_2$-F), 80.0 (C-OTs), 79.8 (C-OTs), 68.7 (C-OTs), 47.0 ($CH_2$), 27.2 (d, $J$ = 11.9 Hz, $CH_3$), 22.0 (d, $J$ = 16.1 Hz, $CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -195.14 (s, i/ii), -200.37 (s, i/ii), -204.00 (s, iii); HRMS (ESI) Calc'd for $C_{18}H_{17}FNO_4S$ $[M + H]^+$ 362.0857, found 362.0850.

(*Z*)-4-(2-Fluoro-3-oxobut-1-en-1-yl)benzonitrile **236**:[149]




To a solution of **235** (100 mg, 0.28 mmol) in *t*-BuOH (3.00 mL), *t*-BuOK (31.0 mg, 0.028 mmol, 0.1 eq.) was added and the mixture was left to stir at 75 °C for 2 h. The solution was cooled to rt and poured onto excess water. The mixture was extracted with $Et_2O$ (3 x 5.00 mL) and the organic extracts combined before drying over $MgSO_4$. The residue was concentrated *in vacuo* to yield the product as an oily yellow solid (11.0 mg, 0.06 mmol, 21%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H, H-Ar), 7.71–7.66 (m, 2H, H-Ar), 6.80 (d, $J$ = 35.5 Hz, 1H, H-6), 2.44 (d, $J$ = 3.7 Hz, 3H, H-9); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 192.4 (d, $J$ = 34.8 Hz, C=O), 154.8 (d, $J$ = 277.0 Hz, C-F), 135.6 (Ar-Cq), 132.6 (Ar-C), 130.9 (Ar-C), 130.0 (Ar-C), 118.4 (CN), 112.9 (d, $J$ = 5.7 Hz, C=C), 25.8 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -119.14—119.24 (m); $\nu_{max}$ (solid/cm$^{-1}$) 2250 (CN), 1687 (C=O), 1640 (C=C), 1253 (C-F); HRMS (ESI) Calc'd for $C_{11}H_9FNO$ $[M + H]^+$ 190.0663, found 190.0660. Data is in accordance with the literature.[149]

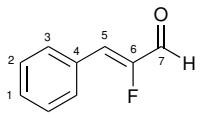
Diethyl (1-fluoro-2-oxopropyl)phosphonate **240**:[151]




In a PTFE flask, to a stirred solution of β-ketophosphonate (494 μL, 3.00 mmol) in dry MeCN (15.0 mL) at rt, was added Selectfluor (2.13 g, 6.00 mmol, 2 eq.). The vessel was heated to reflux and allowed to stir for 24 h. The reaction was cooled to rt and $Et_2O$ (10.0 mL) was added, followed by the addition of sat. aq. $NH_4Cl$. The layers were separated and the organic layer was washed with brine (2 x 15.0 mL) and

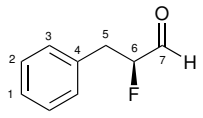
$H_2O$ (1 x 15.0 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The mixture was purified by column chromatography to give the product as a colourless oil (274 mg, 1.29 mmol, 43%). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, $^2J_{HF}$ = 48.0 Hz, $^2J_{HP}$ 14.3 Hz, 1H), 4.28–4.13 (m, 4H, H-4, 2 x $CH_2$), 2.32 (dd, $J$ = 4.4, 0.5 Hz, 3H, H-1, $CH_3$), 1.38–1.28 (m, 6H, H-5, 2 x $CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.7 (d, $J$ = 20.4 Hz, C=O), 91.7 (dd, $J_{CF}$ = 197.6 Hz, $J_{CP}$ 152.7 Hz, C-F), 64.3 ($CH_2$), 26.8 ($CH_3$), 16.4 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -207.44 (s); $^{31}$P NMR (162 MHz, $CDCl_3$) δ 9.99 (d, $^2J_{PF}$ = 71.7 Hz); $\nu_{max}$ (solid/cm$^{-1}$) 1731 (C=O), 1162 (C-O), 1016 (C-F); HRMS (ESI) Calc'd for $C_7H_{15}FO_4P$ $[M + H]^+$ 213.0687, found 213.0688.

(*Z*)-2-Fluoro-3-phenylacrylaldehyde **246**:[152]



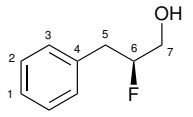

A PTFE vessel (Falcon Tube) was charged with cinnamaldehyde (132 μL, 1.00 mmol), L-proline (115 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol), Selectfluor (709 mg, 2.00 mmol, 2 eq.) and MeOH (5.00 mL) under a nitrogen atmosphere. MeCN was added and stirred for 30 min to give a yellow solution. The reaction was allowed to stir at 65 °C for 15 h, resulting in a dark brown solution. After cooling, excess water was added and the reaction product hydrolysed at rt for 1 h. The mixture was extracted into DCM (3 x 10.0 mL), with the organic extracts combined and concentrated. The mixture was redissolved in DCM (5.00 mL) and mixed with 5% aq. HCl (20.0 mL) before leaving to stir for 12 h. The mixture was extracted into DCM (3 x 10.0 mL), with the organic extracts combined and concentrated to give the product as a yellow oil (11.0 mg, 0.07 mmol, 7%). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, $J$ = 16.9 Hz, 1H, H-7), 7.75–7.65 (m, 2H, H-Ar), 7.51–7.40 (m, 3H, H-Ar), 6.62 (d, $J$ = 34.2 Hz, 1H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 184.1 (d, $J$ = 25.6 Hz, C-7), 156.3 (d, $J$ = 271.4 Hz, C-6), 131.1 (Ar-Cq), 131.0 (Ar-C), 130.8 (d, $J$ = 7.9 Hz, C-5), 126.9 (Ar-C), 121.2 (Ar-C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -128.5 (s); $\nu_{max}$ (solid/cm$^{-1}$) 1714 (C=O), 1156 (C-F), 827 (C=C); HRMS (ESI) Calc'd for $C_{11}H_{13}NO_3S$ $[M + H]^+$ 151.0554, found 151.0551. Data is in accordance with the literature.[161]

(*S*)-2-Fluoro-3-phenylpropanal **249**:[153]




A mixture of (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (70.0 mg, 0.20 mmol, 20 mol%) and *N*-fluorobenzenesulfonimide (1.58 g, 5.00 mmol, 5 eq.) was dissolved in THF (4.50 mL) and $^{i}$PrOH (0.50 mL). The mixture was stirred at rt until homogeneous, then cooled to -10 °C. 3-phenylpropanal (133 μL, 1.00 mmol) was added and stirred for 4 h. The reaction was cooled to -78 °C, diluted with $Et_2O$ (5.00 mL) and filtered through a pad of silica. $Me_2S$ (5.00 mL) was added, forming a white precipitate. The resulting mixture was washed with sat. $NaHCO_3$ (3 x 15.0 mL) and brine (1 x 15.0 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was purified via column chromatography to yield the product as a yellow oil (149 mg, 0.98 mmol, 98%). $[\alpha]_D^{21}$ = -21 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 5.5 Hz, 1H, H-7), 7.38–7.29 (m, 5H, H-Ar), 4.98–4.95 (m, 1H, H-6), 3.14–2.97 (m, 2H, H-5); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.9 (d, *J* = 34.9 Hz, C=O), 129.6 (Ar-Cq), 129.5 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 95.1 (d, *J* = 182.2 Hz, C-6), 36.8 (d, *J* = 20.3 Hz, C-5); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -197.63 (s); HRMS (ESI) Calc'd for $C_9H_{10}FO$ $[M + H]^+$ 152.06, found 152.09. Data is in accordance with the literature.[162] Due to this compound's low level of purity, this structure is only the proposed major product.

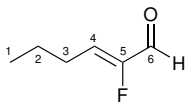
(*S*)-2-Fluoro-3-phenylpropan-1-ol **250**:[153]




To a mixture of (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (70.0 mg, 0.20 mmol, 20 mol%) and *N*-fluorobenezenesulfonimide (1.58 g, 5.00 mmol, 5 eq.) was added THF (4.50 mL) and $^{i}$PrOH (0.50 mL). The mixture was stirred at rt until homogenous then cooled to -10 °C. 3-Phenylpropanal (133 μL, 1.00 mmol) was added and the reaction mixture stirred for 12 h. The reaction was

cooled to -78 °C, diluted with $Et_2O$ (5.00 mL) and filtered through a pad of silica. $Me_2S$ (2.50 mL) was added, forming a white precipitate. The mixture was washed with sat. $NaHCO_3$ (3 x 20.0 mL) and brine (20.0 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was dissolved in DCM (6.00 mL) and EtOH (4.00 mL) and $NaBH_4$ (95.0 mg, 2.50 mmol, 2.5 eq.) was added. After 0.5 h, the reaction was cooled to °C and sat. $NH_4Cl$ (20.0 mL) was added. The mixture was warmed to rt and stirred for 12 h. The suspension was allowed to separate and diluted with DCM. The aqueous layer was extracted with DCM (3 x 20.0 mL) and the organic layers combined, before washing with sat. $NaHCO_3$ (3 x 20.0 mL) and brine (20.0 mL). The mixture was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting mixture was purified via column chromatography to give the alcohol as a yellow oil (83.0 mg, 0.54 mmol, 54%). $[\alpha]_D^{21}$ = -20 ($c$ = 1.00, $CHCl_3$) [-18, $c$ = 1.7, $CHCl_3$]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H, H-Ar), 7.28–7.21 (m, 3H, H-Ar), 4.78 (ddtd, $J$ = 48.7, 7.3, 5.9, 2.9 Hz, 1H, H-6), 3.84–3.60 (m, 2H, H-5), 3.10–2.84 (m, 2H, H-7), 2.28 (s, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 136.5 (d, $J$ = 6.0 Hz, Ar-Cq), 129.4 (Ar-C), 128.7 (Ar-C), 126.9 (Ar-C), 94.8 (d, $J$ = 171.1 Hz, C-6), 64.2 (d, $J$ = 21.6 Hz, C-7), 37.5 (d, $J$ = 21.3 Hz, C-5); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -187.44 (s); $\nu_{max}$ (solid/cm$^{-1}$) 3378 (O-H), 1050 (C-F); HRMS (ESI) Calc'd for $C_6H_{10}FO$ $[M + H]^+$ 117.0710, found 117.0705.

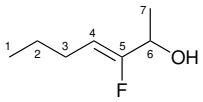
(*Z*)-2-Fluorohex-2-enal **251**:[152]




A PTFE flask was charged with *trans*-2-hexenal (118 μL, 1.02 mmol), L-proline (117 mg, 1.02 mmol), NaOAc (83.0 mg, 1.02 mmol), Selectfluor (723 mg, 2.04 mmol, 2 eq.) and MeOH (5.00 mL) under a nitrogen atmosphere. MeCN was added and stirred for 30 min to give a yellow solution. The reaction was allowed to stir at 65 °C for 15 h, resulting in a dark brown solution. After cooling, excess water was added and the reaction product hydrolysed at rt for 1 h. The mixture was extracted into DCM (3 x 10.0 mL), with the organic extracts combined and concentrated. The mixture was redissolved in DCM (5.00 mL) and mixed with 5% aq. HCl (20.0 mL) before leaving to stir for 12 h. The mixture was extracted into DCM (3 x 10.0 mL),

with the organic extracts combined, dried over $MgSO_4$, filtered and concentrated to give the crude product. The aldehyde was purified via column chromatography to give the fluoroalkene as a colourless oil (18.0 mg, 0.16 mmol, 15%). $^1$H NMR (700 MHz, $CDCl_3$) δ 9.22 (d, *J* = 18.1 Hz, 1H, H-6), 5.94 (dt, *J* = 32.4, 7.8 Hz, 1H, H-4), 2.38–2.34 (m, 2H, H-3), 1.58–1.55 (m, 2H, H-2), 0.98 (t, *J* = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 183.7 (d, *J* = 24.7 Hz, C=O), 157.9 (d, *J* = 155.7 Hz, C-5), 131.3 (d, *J* = 12.3 Hz, C-4), 51.0 (C-3), 27.0 (C-2), 13.8 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.67 (s); $\nu_{max}$ (solid/cm$^{-1}$) 2959 (C=CH), 2873 (CHO), 1714 (C=O), 1462 (C-F); HRMS (ESI) Calc'd for $C_6H_{10}FO$ $[M + H]^+$ 117.0710, found 117.0704. Data is in accordance with the literature.[152]

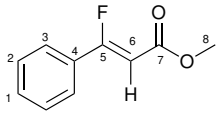
(*Z*)-3-Fluorohept-3-en-2-ol **252**:[152]




A PTFE flask was charged with (*E*)-2-hexenal (232 μL, 2.00 mmol), L-proline (230 mg, 2.00 mmol), NaOAc (164 mg, 2.00 mmol), Selectfluor (1.42 g, 4.00 mmol, 2 eq.) and MeOH (10.0 mL) under a nitrogen atmosphere. MeCN (6.00 mL) was then added and the mixture was left to stir at rt for 30 min. The reaction was heated to 65 °C for 12 h. After cooling, water (10.0 mL) was added and the reaction product was hydrolysed at rt for 3 h. The mixture was extracted with $CH_2Cl_2$ (3 x 10.0 mL) and dried over $MgSO_4$ to give the crude fluorinated aldehyde. The aldehyde was diluted in THF (5.00 mL) and cooled to -78 °C and treated with MeMgBr (2.4 eq.) before warming to rt and stirring for 1.5 h. The mixture was cooled to 0 °C and treated with water (1.00 mL per mmol aldehyde). The aqueous layer was extracted with $Et_2O$ (3 x 10.0 mL) and the layers combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified via column chromatography to give the product as a colourless oil (8.00 mg, 0.061 mmol, 3%). $^1$H NMR (700 MHz, $CDCl_3$) δ 5.07 (dq, *J* = 37.5, 7.8 Hz, 1H, H-4), 5.07 (dt, *J* = 37.5, 7.6 Hz, 1H, H-6), 3.40 (d, *J* = 1.1 Hz, 1H, OH) 2.14–2.07 (m, 2H, H-3), 1.43–1.39 (m, 3H, $CH_3$, H-7), 1.21–1.17 (m, 2H, H-2), 0.92 (t, *J* = 7.4 Hz, 3H, $CH_3$, H-1). $^{13}$C NMR (176 MHz, $CDCl_3$) δ 153.3 (d, *J* = 254.1 Hz, C-5), 109.2 (d, *J* = 11.3 Hz, C-4), 99.2 (d, *J* = 36.7 Hz, C-6), 53.2 (C-3), 25.2 (d, *J* = 4.2 Hz, C-2), 22.4 (d, *J* = 1.7 Hz, C-7), 13.8 (C-1);

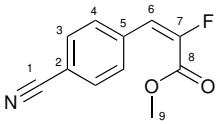
$^{19}$F NMR (376 MHz, $CDCl_3$) δ -126.90 (s); HRMS (ESI) Calc'd for $C_7H_{13}FONa$ [M + Na]$^+$ 155.0843, found 155.0157. Data is in accordance with the literature.[152]

Methyl (*Z*)-3-fluoro-3-phenylacrylate **255**:[154]




Methyl phenylpropiolate (73.0 μL, 0.50 mmol) and AgF (127 mg, 1.00 mmol, 2 eq.) in MeCN/$H_2O$ (2.00 mL/1.00 mL) were combined and the reaction mixture stirred at 80 °C for 10 h. After completion, the solution was diluted with EtOAc (5.00 mL), washed with $H_2O$ (5.00 mL) and brine (5.00 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The mixture was purified by column chromatography to give the product as a colourless oil (83.0 mg, 0.46 mmol, 92%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69–7.60 (m, 2H, H-Ar), 7.54–7.37 (m, 3H, H-Ar), 5.91 (d, *J* = 33.3 Hz, 1H, H-6), 3.79 (s, 3H, $CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 275.7 Hz, C-F), 164.5 (d, *J* = 2.8 Hz, C=O), 131.6 (Ar-C), 130.6 (d, *J* = 25.8 Hz, Ar-Cq), 128.9 (d, *J* = 2.0 Hz, Ar-C), 125.8 (d, *J* = 8.0 Hz, Ar-C), 96.9 (d, *J* = 7.2 Hz, C-6), 51.7 ($CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -95.64 (s); $\nu_{max}$ (solid/cm$^{-1}$) 1725 (C=O), 1661 (C=C), 1284 (C-F), 1165 (C-O); HRMS (ESI) Calc'd for $C_{11}H_9FO_2$ [M + H]$^+$ 181.0659, found 181.0658. Data is in accordance with the literature.[163]

Methyl (*E*)-3-(4-cyanophenyl)-2-fluoroacrylate **264**:[126]




To a solution of ethyl (*E*)-3-(4-cyanophenyl)-2-fluoroacrylate (synthesised by A. King[126]) (53.0 mg, 0.242 mmol) dissolved in MeOH (10.0 mL) was added NaOMe (4.00 mg, 0.061 mmol, 0.25 eq.) and the mixture left to stir at rt overnight. The mixture was concentrated *in vacuo* and resolubilised in $CHCl_3$ before filtering through a pad of silica. Concentration under reduced pressure gave the product as a fine white powder (41.0 mg, 0.202 mmol, 84%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H, H-Ar), 7.55 (d, *J* = 8.3 Hz, 2H, H-Ar), 6.89 (d, *J* = 20.9 Hz, 1H, H-6), 3.80

(s, 3H, H-9); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.5 (d, *J* = 35.3 Hz, C=O), 148.0 (d, *J* = 262.9 Hz, C-F), 135.8 (d, *J* = 9.9 Hz, Ar-C), 131.9 (Ar-C), 130.3 (d, *J* = 3.0 Hz, Ar-C), 112.0 (d, *J* = 26.9 Hz, C-6), 118.6 (CN), 112.4 (Ar-C), 52.7 ($CH_3$). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -113.50 (d, *J* = 20.8 Hz). HRMS (ESI) Calc'd for $C_{12}H_8FNO_2$ $[M + H]^+$ 206.0612, found 206.0613. Data is in accordance with the literature.[164]

### 4.2.2 Biocatalysed Reduction

General procedure for the preparation of clarified lysate and assay analytics: ERs were expressed by recombinant *E. coli* BL21 (DE3) cultivation. Cells were cultivated in TB medium at 37 °C until an $OD_{600}$ of 0.5–0.7 was attained, induced by addition of IPTG (0.5 mM), expressed at 25 °C for 24 h and then harvested via centrifugation. The medium was sonicated (10 rounds, 10 sec on/off, 18 W), with the pellets resuspended in HEPES buffer (30.0 mL). The cells were harvested by centrifugation and purified by Ni affinity column chromatography (Nickel NTA column) at a gradient of imidazole (10–500 mM). The proteins were desalted and further purified by size-exclusion chromatography. The concentration of the proteins were obtained by Bradford assay. The residue was concentrated with Pierce$^{TM}$ Protein Concentrator PES 10M MWCO (2–6 mL, 4,000 spm, 10 min intervals) until a concentration of 5.04 mg/mL was achieved as a clarified lysate. The term "clarified cell lysates" refers to the total soluble unpurified protein expressed by *E. coli*. Enzymes NCR+pQR1811 were stored at -80 ° for up to two weeks with no loss of activity, defrosted only once and kept at 0 °C prior to application. Purified enzyme concentrations were determined by performing a Bradford assay whereby the absorbance of the sample was measured at 600 nm and the concentration calculated from a calibration curve.

General procedure information: Biotransformations were carried out in triplicate. Reactions were performed in 2.00 mL eppendorf vials and incubated at 30 °C and 300 rpm for 20 h unless otherwise detailed. Bioreductions were quenched with 10% TFA (10.0 μL) and samples centrifuged (13,000 rpm, 4 °C) for 10 min. Solutions were extracted with EtOAc (250 μL) and centrifuged (13,000 rpm, 4 °C) for 10 min. The organic extract was dried ($Na_2SO_4$) and sampled (80.0 μL) by chiral GC. For chiral HPLC analysis, the sampled organic extract was concentrated *in vacuo* and redissolved in $^{i}$PrOH/hexane. Samples were stored at -20 °C if they were not able to be analysed immediately.

General biotransformation procedure with co-expressed recycling system

(NCR+pQR1811):[126] For small scale assays, stock solutions were prepared with Tris-HCl buffer (50.0 mM, pH 7.4). To a 2.00 mL eppendorf vial was added G6PNa (1.00 M, 25.0 μL), $NADP^+$ (15.0 mM, 50.0 μL, calculations based on anhydrous molecular weight) and alkene substrate (100 mM, 25.0 μL), followed by Tris.HCl buffer (50.0 mM, pH 7.4) and co-expressed ER with G6PDH to give a total volume of 250 μL with 10% MeOH at final concentrations of of G6PNa (100 mM), $NADP^+$ (3.00 mM), alkene substrate (10.0 mM) and co-expressed enzymes (0.60 mg/$mL^{-1}$, 30.0 μL) unless otherwise specified.

Analysis of chiral compounds: Quantitative analysis of biotransformations was carried out with chiral GC and HPLC. GC analysis was executed with Agilent 7820A with Supleco BetaDEX 225 capillary GC column (30 m × 250 μm × 0.25 μm) and flame ionisation detector at 300 °C. A linear temperature gradient and injection volume of 5 μL were used. Chiral HPLC analysis was executed with HP Series 1100 with Chiralpak AD-H column (5 μm, 4.5 mm, 250 nm).

Chiral GC Method: Initial temperature 90 °C held for 1 min, ramp 5 °C/min to 150 °C, ramp 20°C/min to 210 °C, hold for 2 min.

Chiral HPLC Method: Using ChiralPak AD-H column, UV detection at 214 nm and isocratic 1% $^i$PrOH/hexane at 1 mL/min over 20 min.

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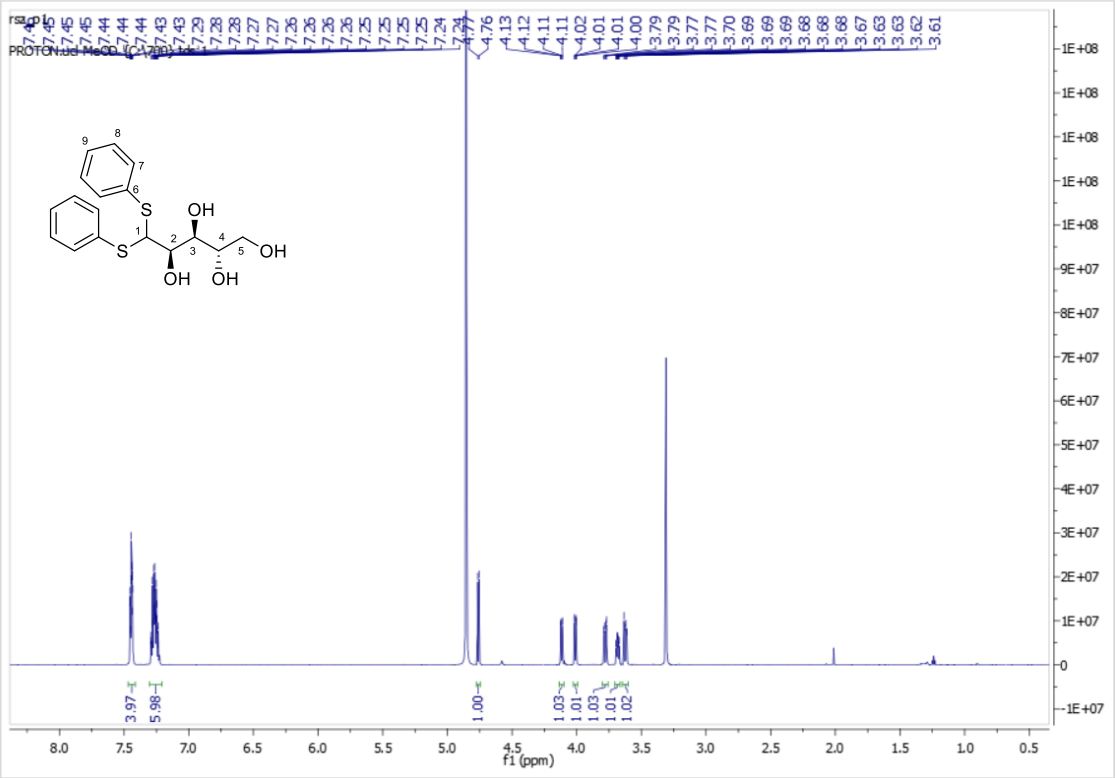
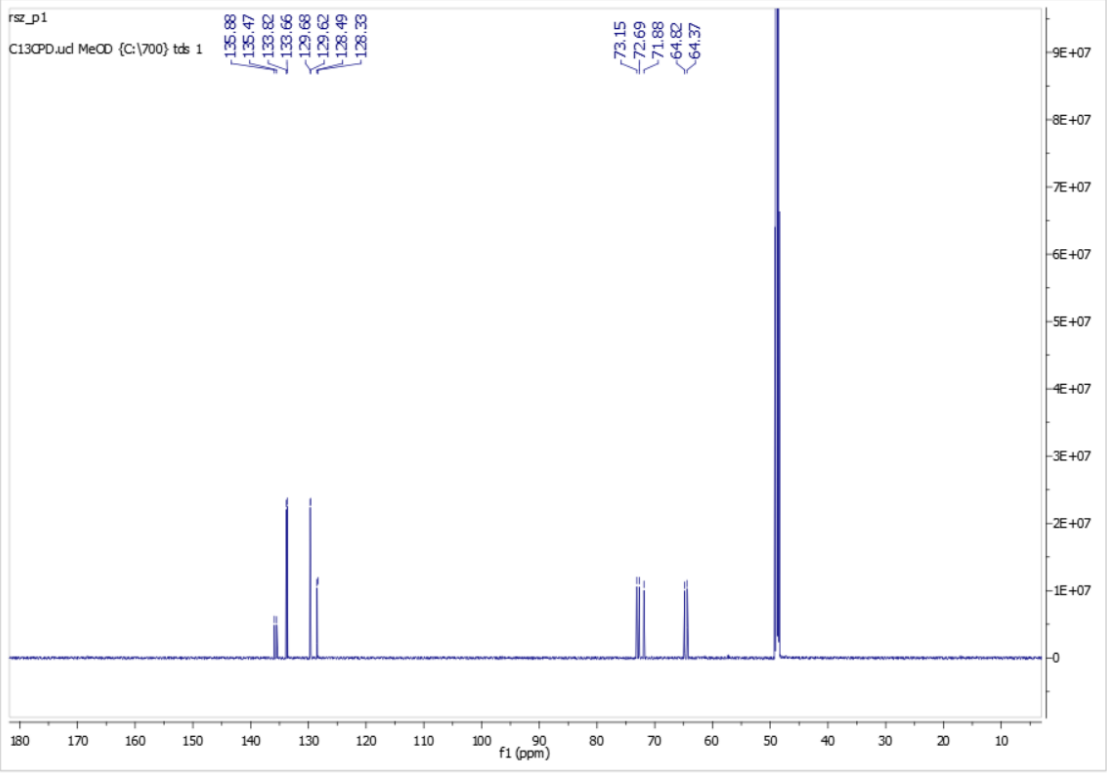
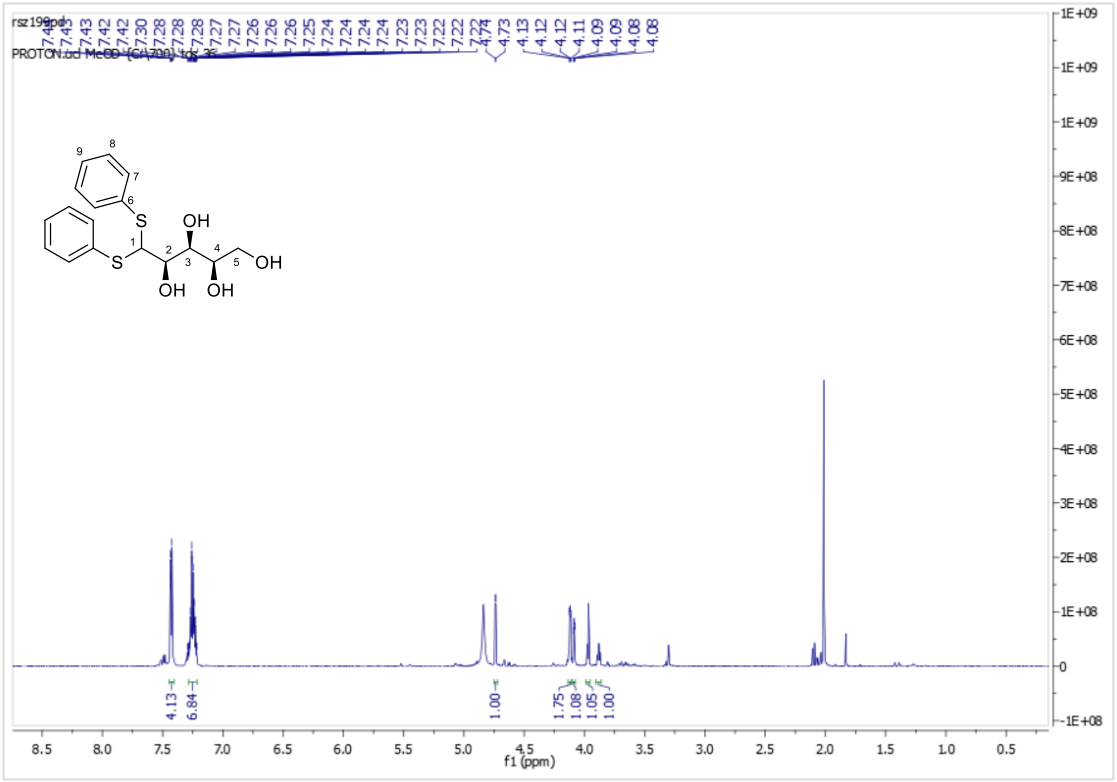
Supporting Information: $^{1}H$ &$^{13}C$ NMR

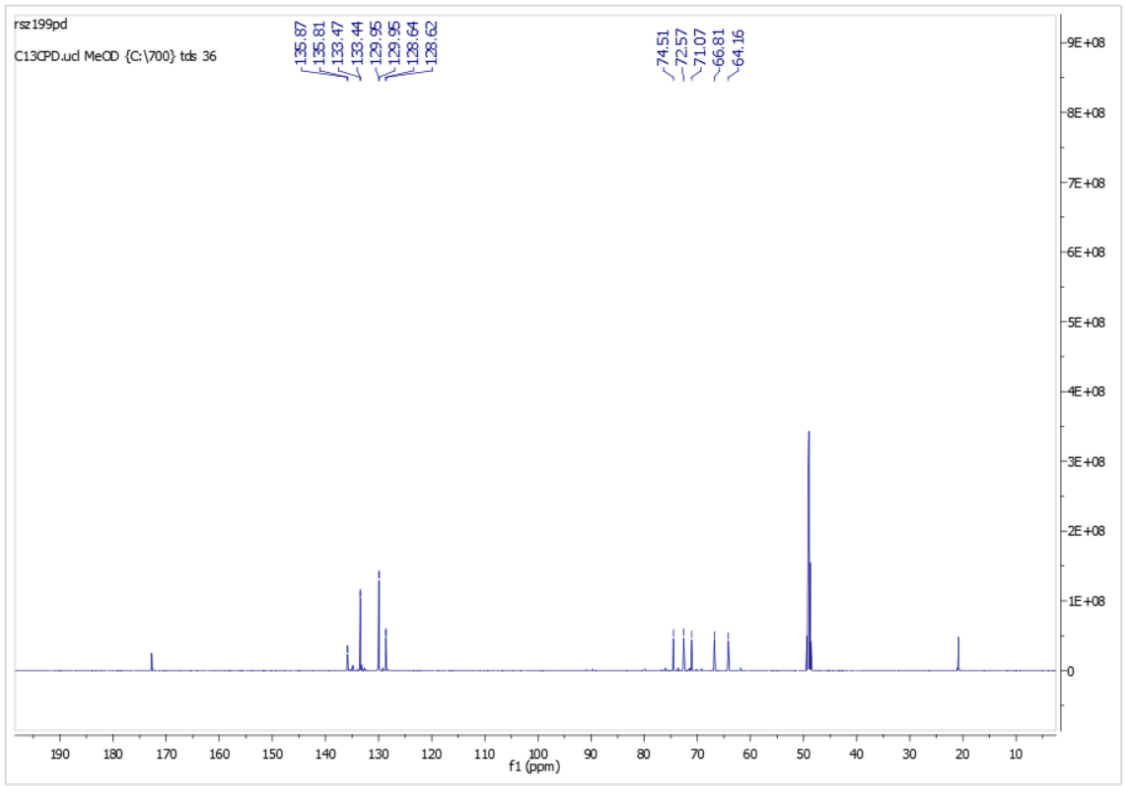
L-Arabinose diphenyldithioacetal, (2*S*,3*S*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**70**]:



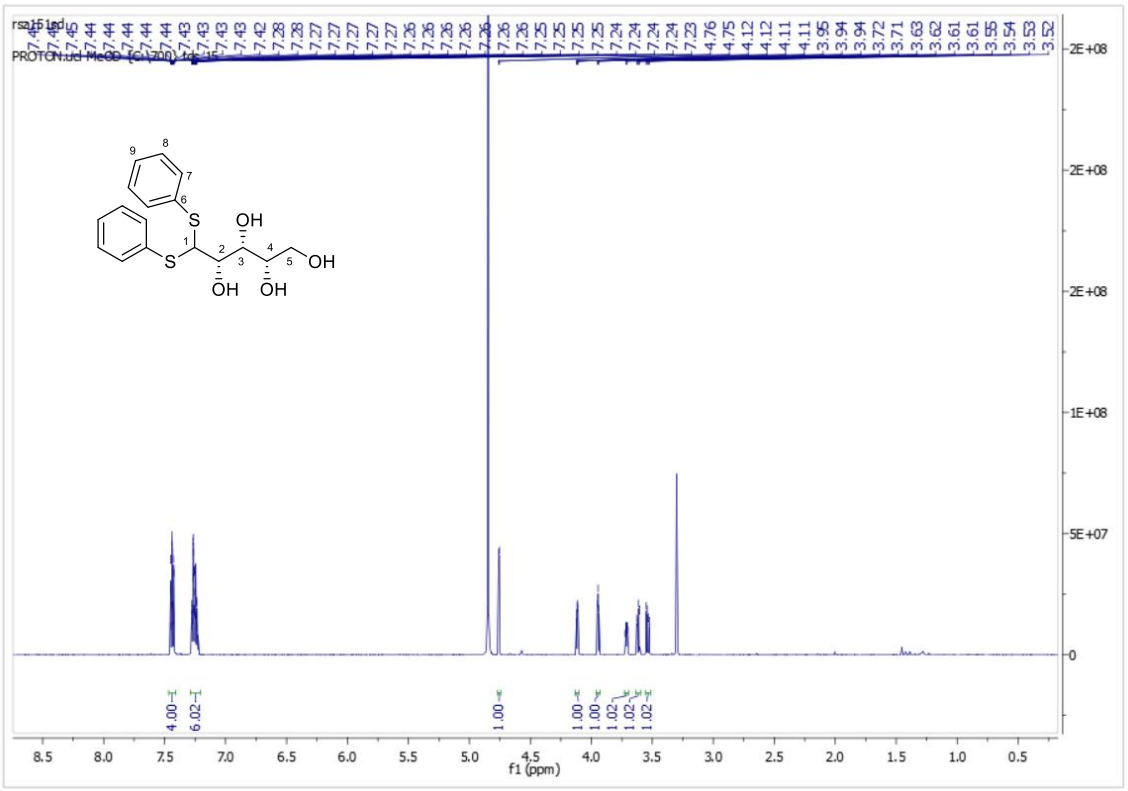



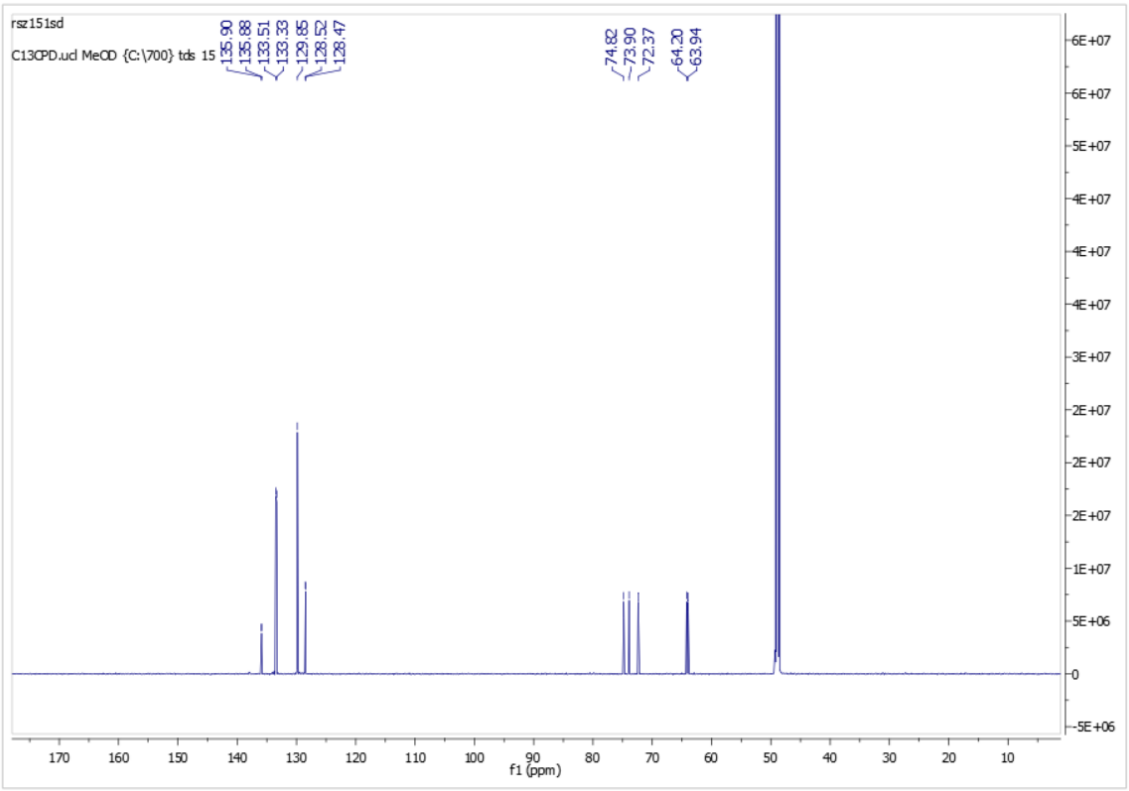
D-Xylose diphenyldithioacetal, (2*R*,3*S*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**71**]:



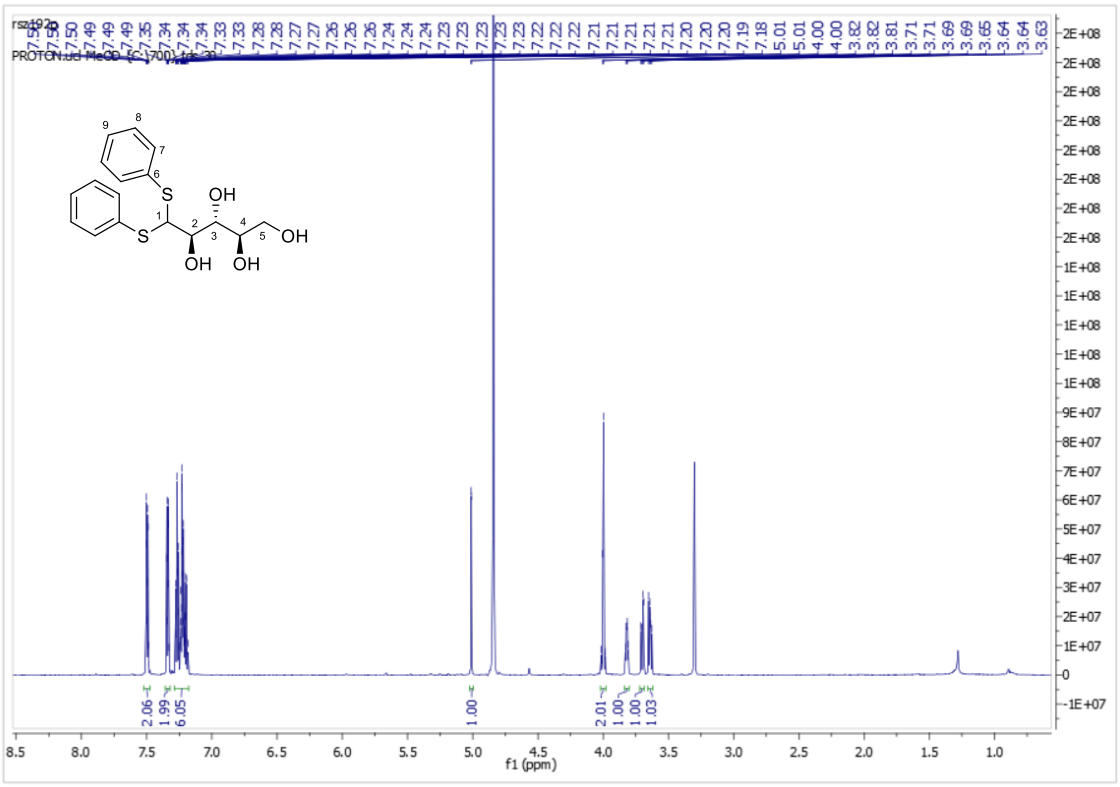



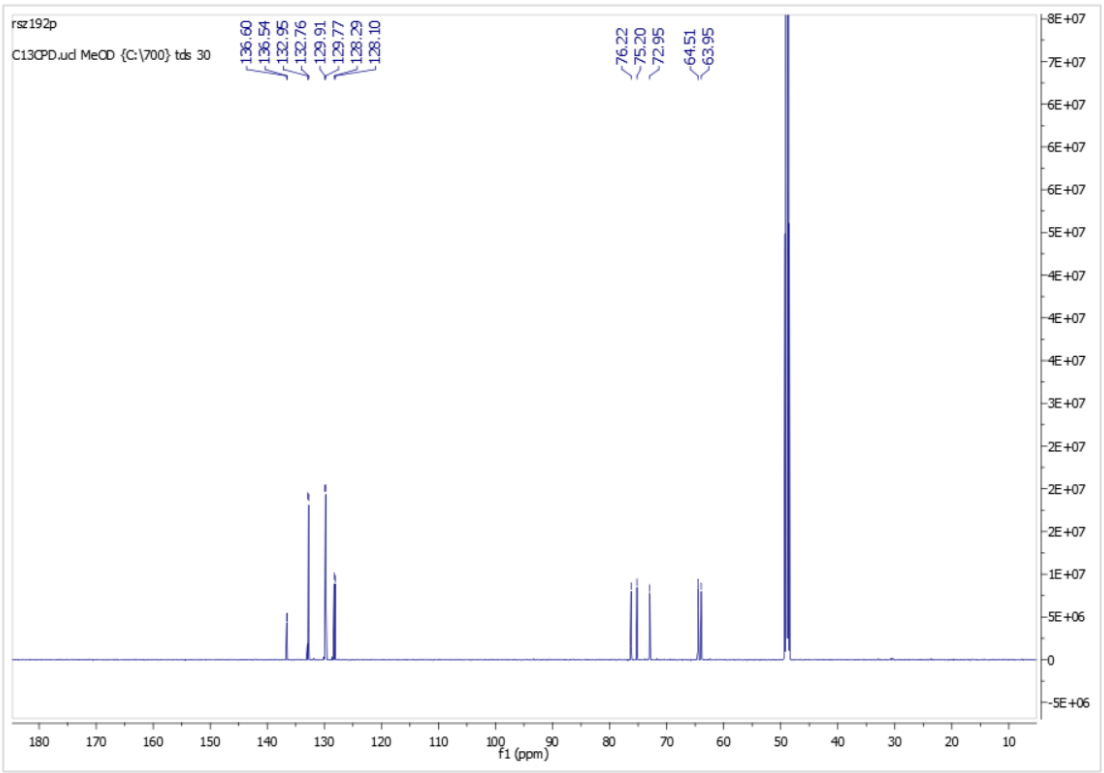
L-Xylose diphenyldithioacetal, (2*S*,3*R*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**72**]:



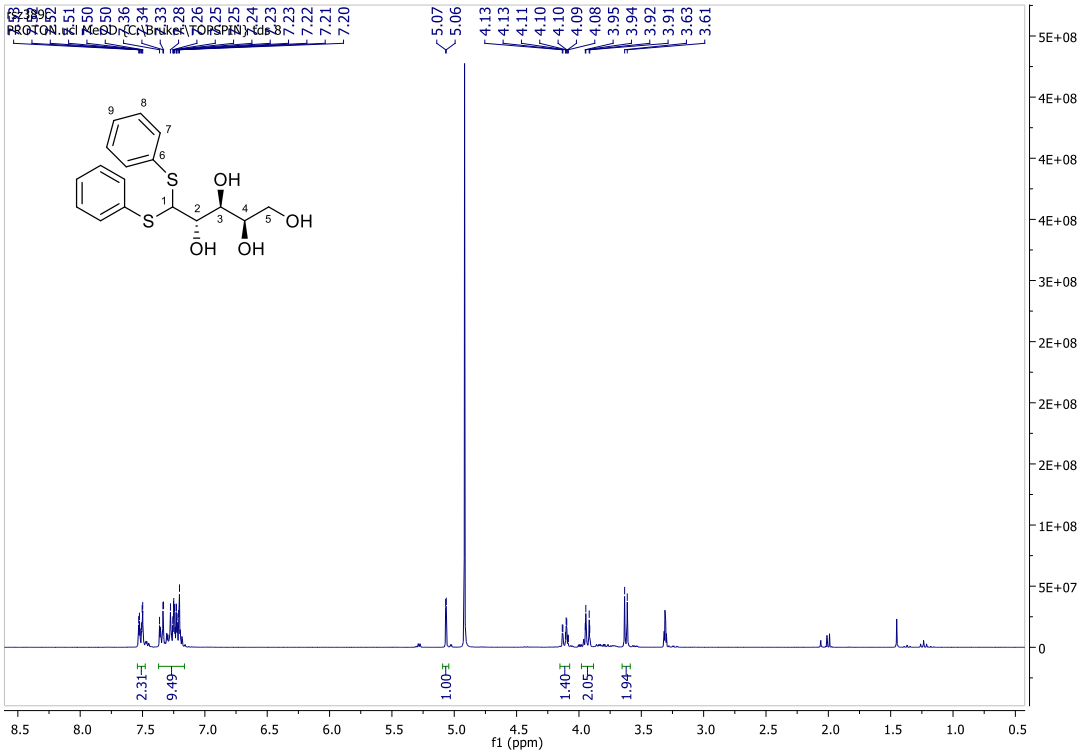



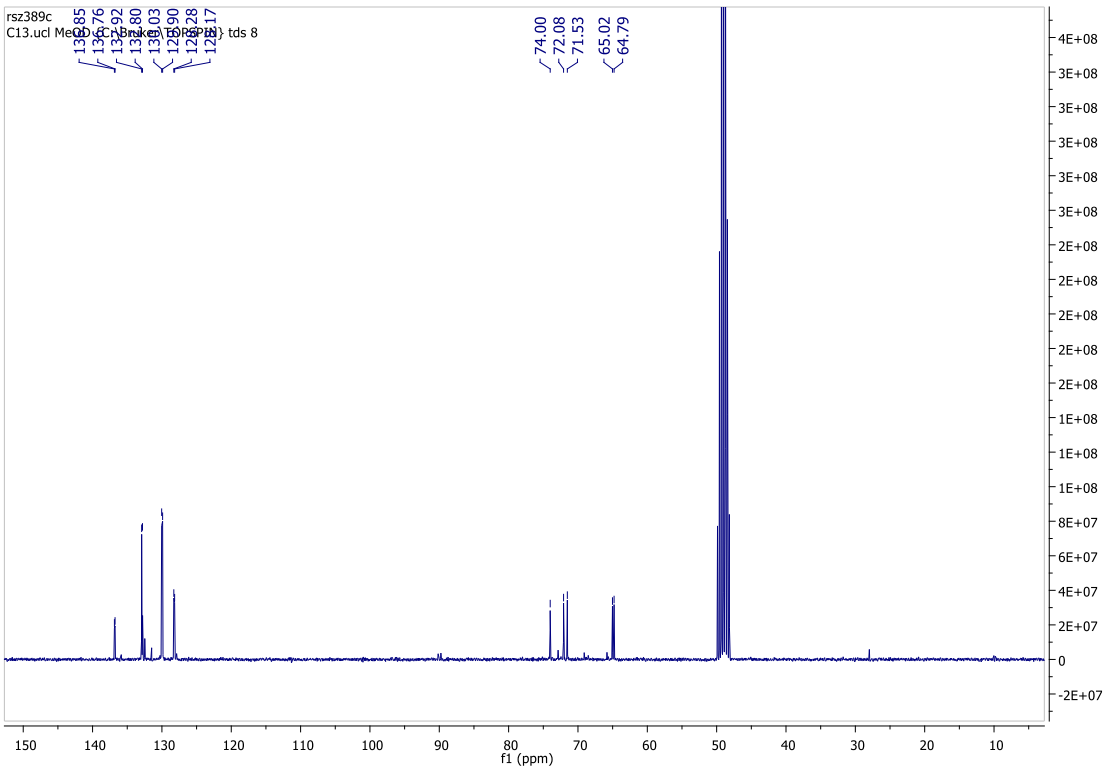
D-Ribose diphenyldithioacetal, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**73**]:



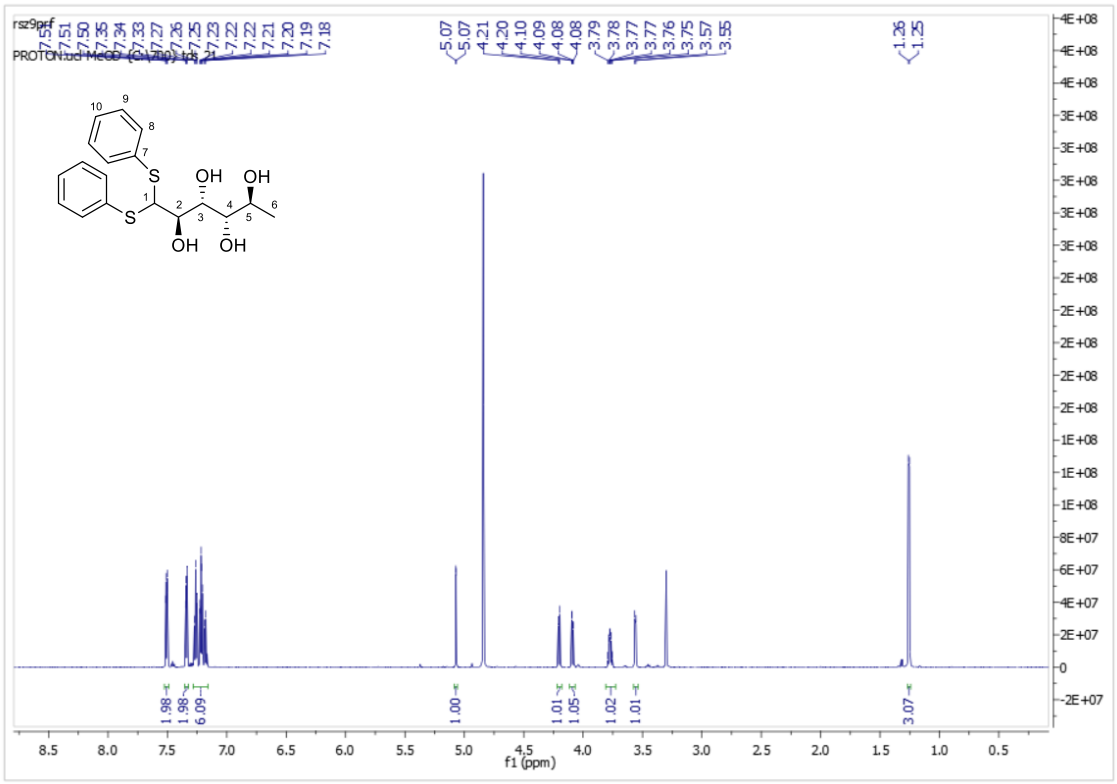



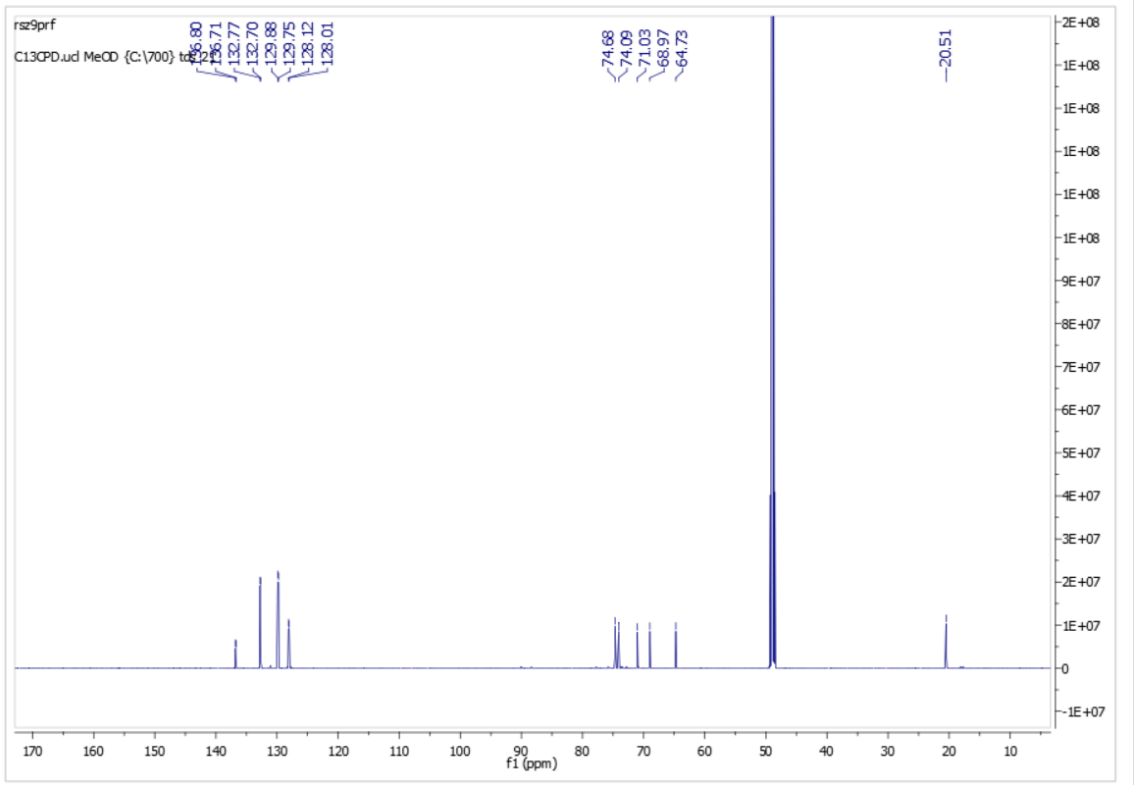
D-Lyxose diphenyldithioacetal, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**74**]:



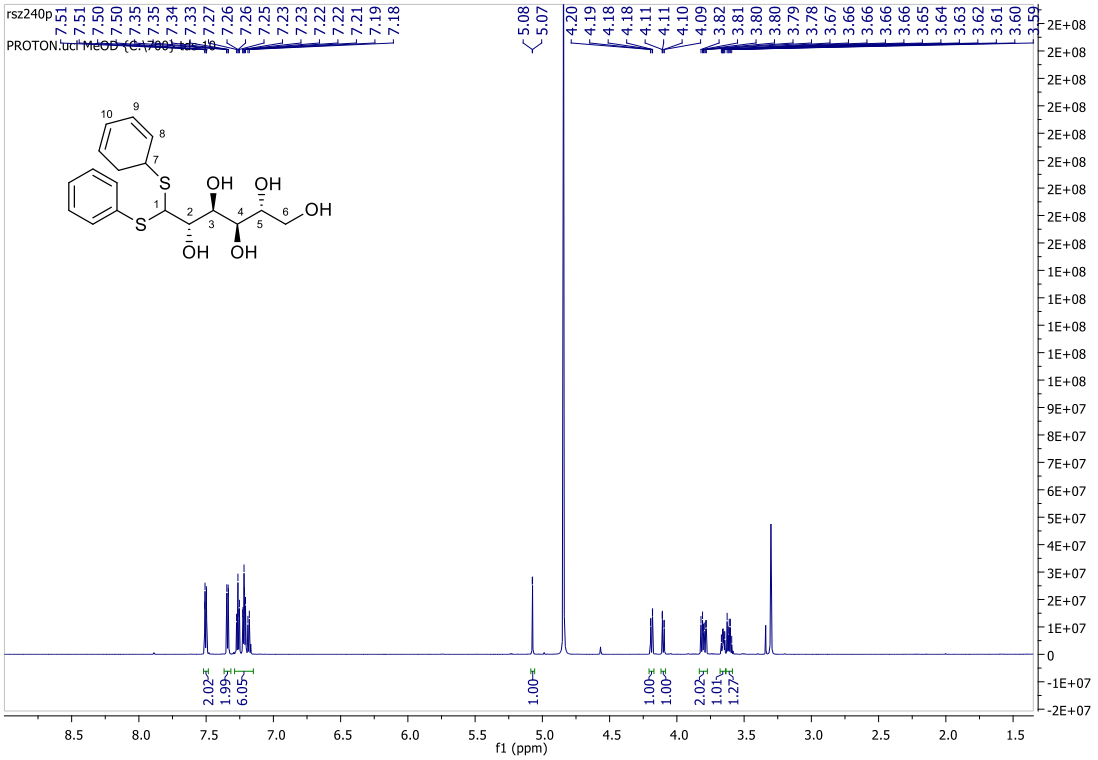



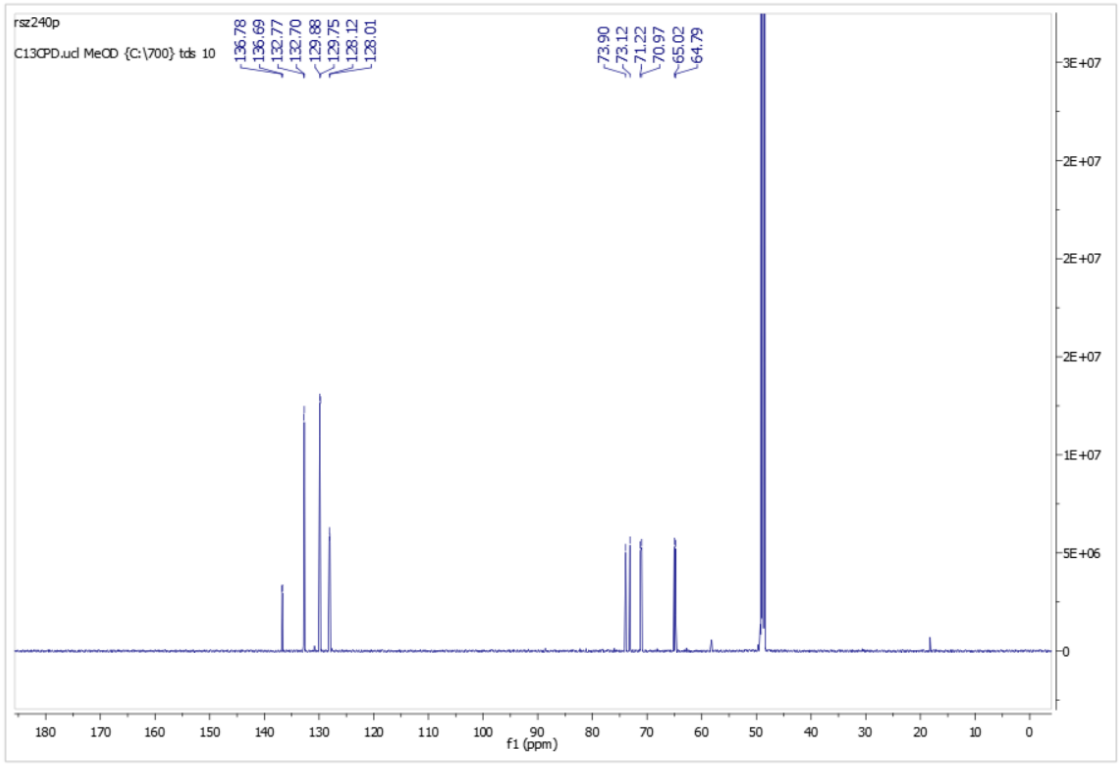
L-Rhamnose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol [**75**]:



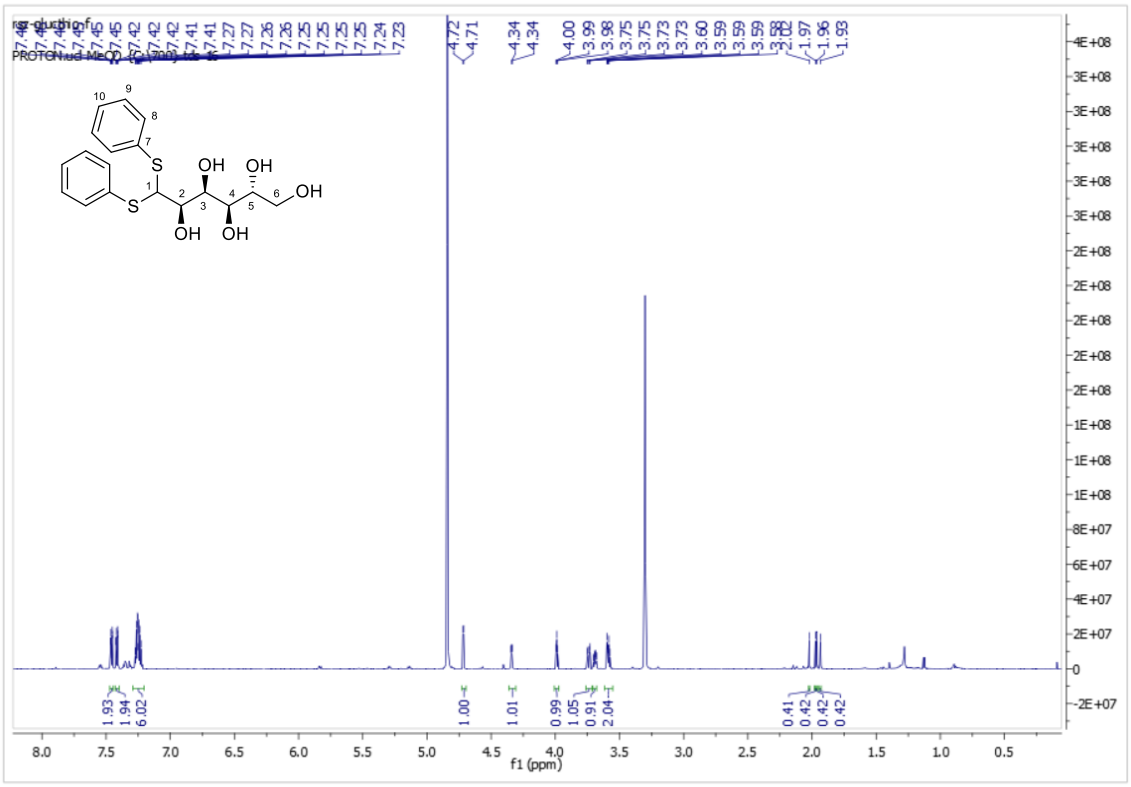



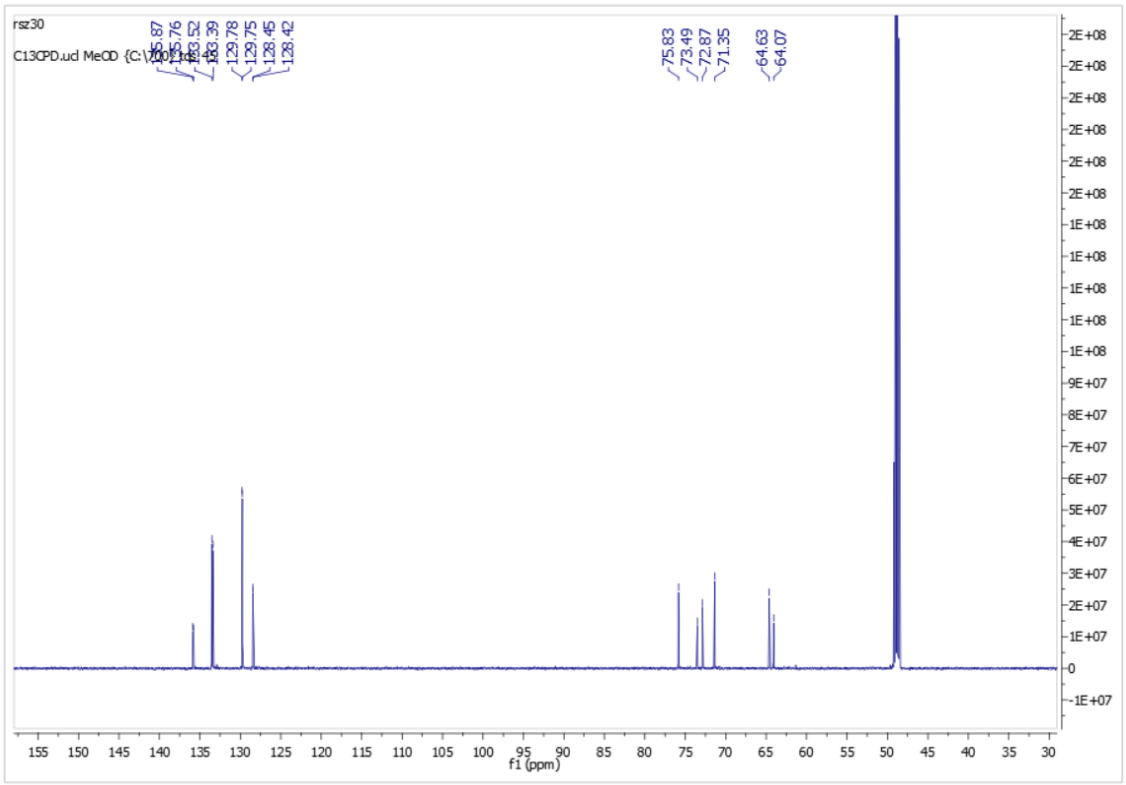
D-Mannose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-6-(cyclohexa-2,4-dien-1-ylthio)-6-(phenylthio)hexane-1,2,3,4,5-pentaol [**76**]:



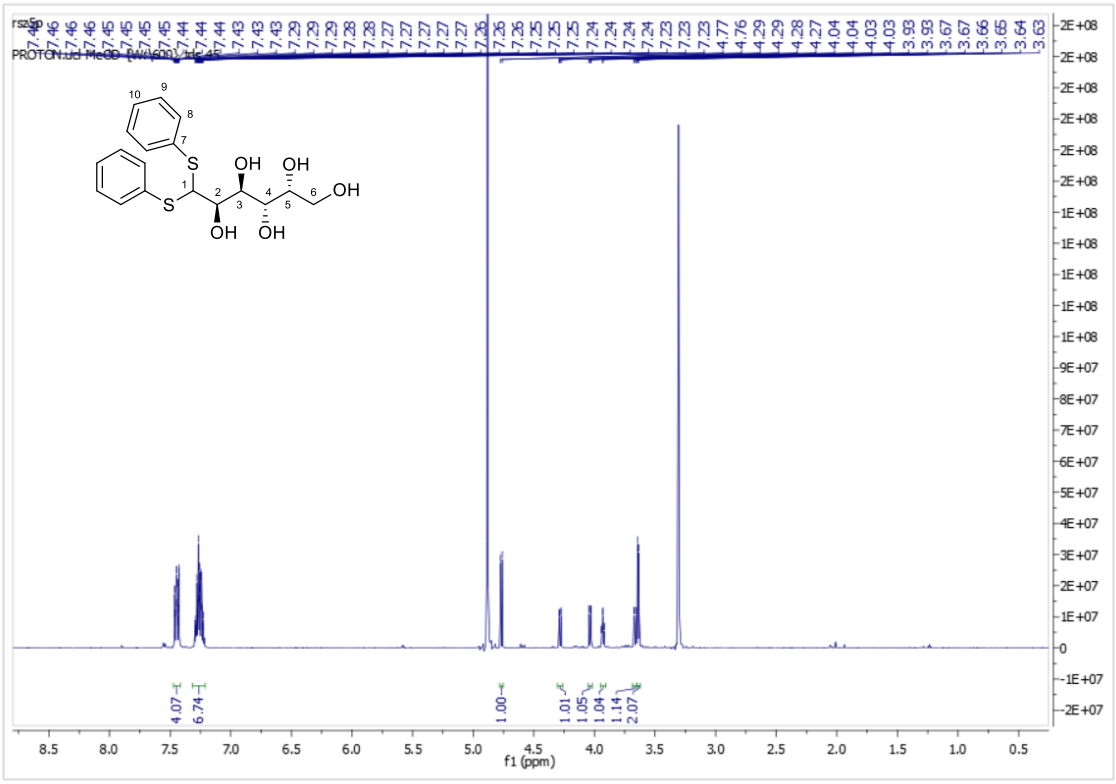



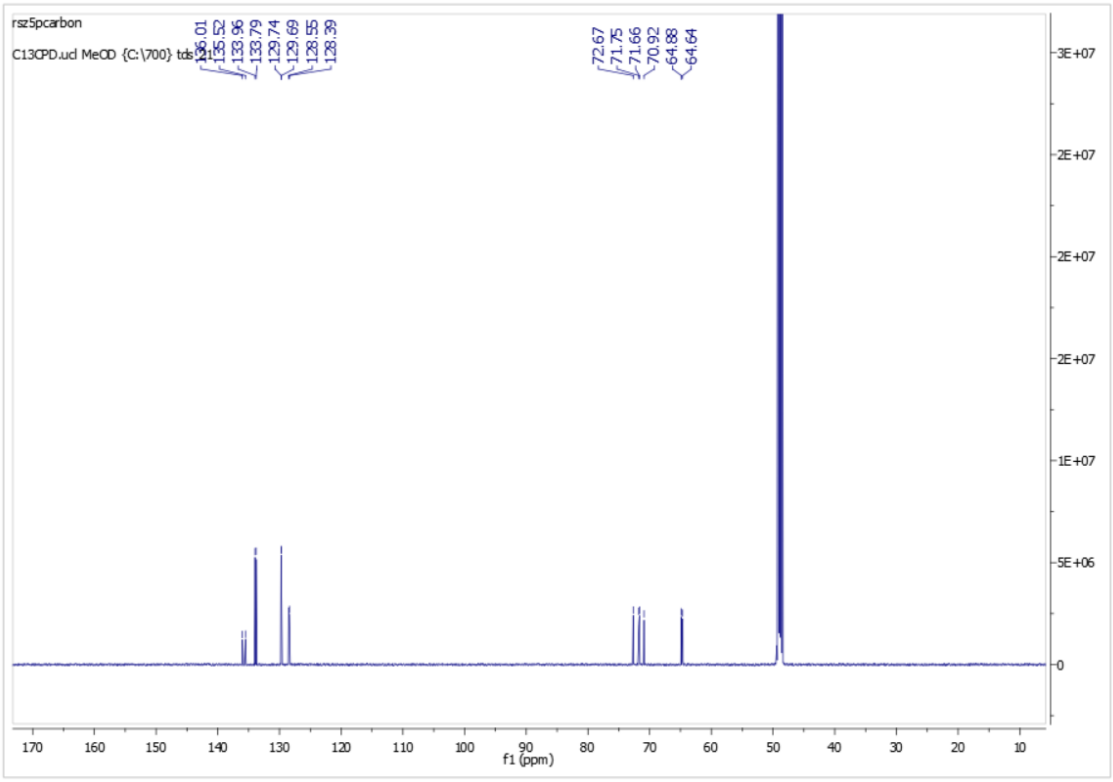
D-Glucose diphenyldithioacetal, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol [**77**]:



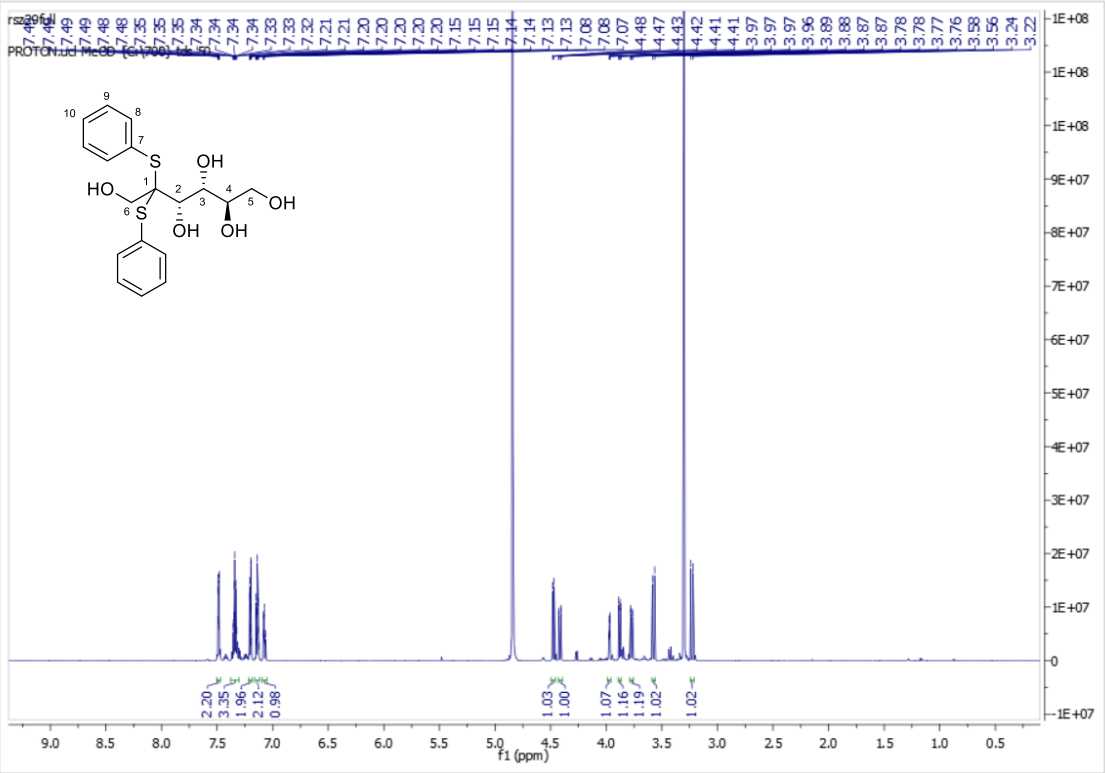



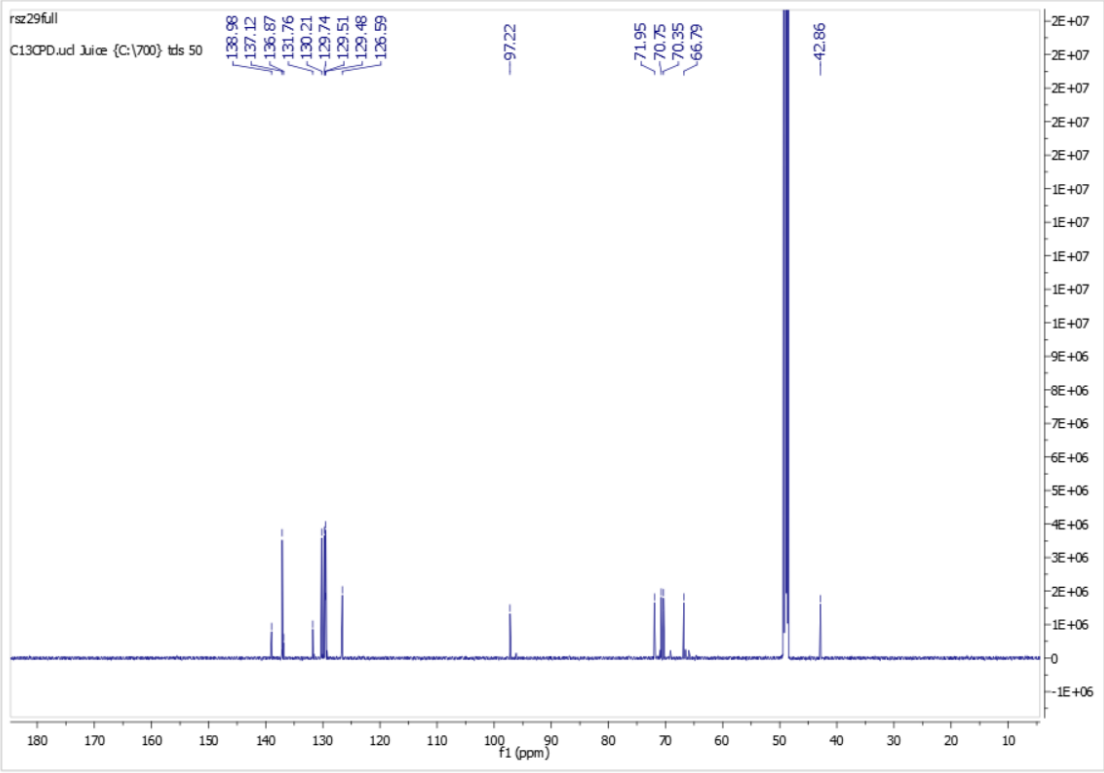
D-Galactose diphenyldithioacetal, (2*R*,3*S*,4*S*,5*R*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol [**78**]:



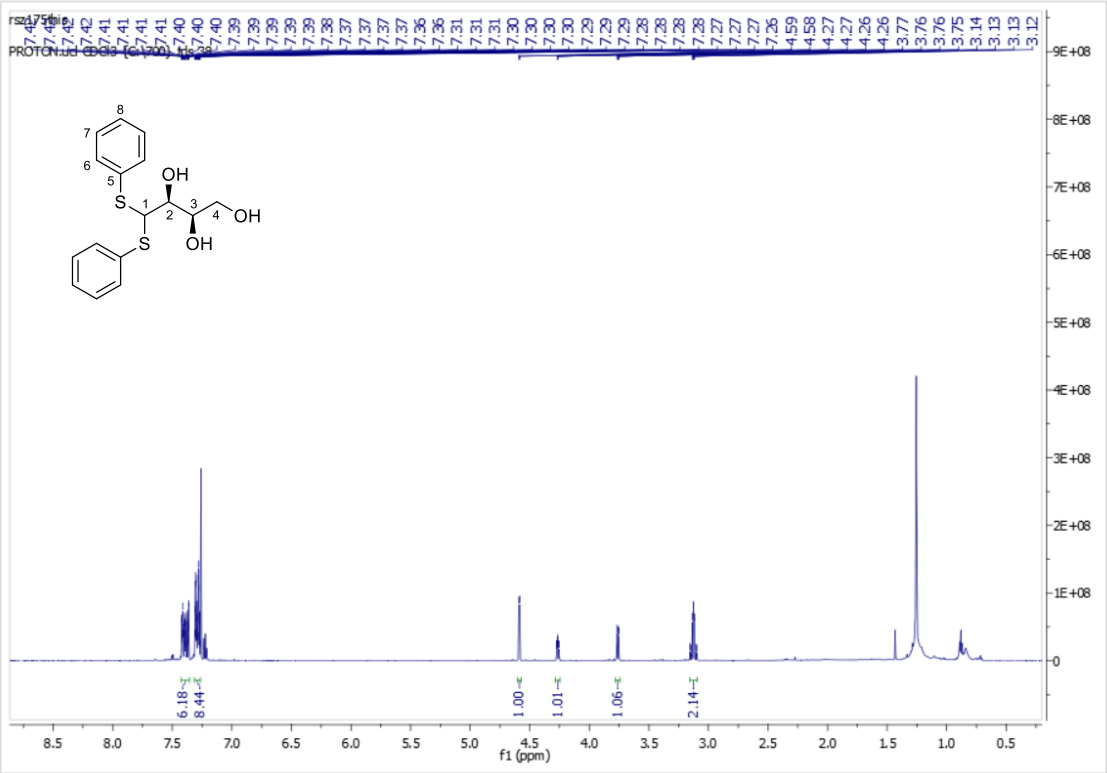



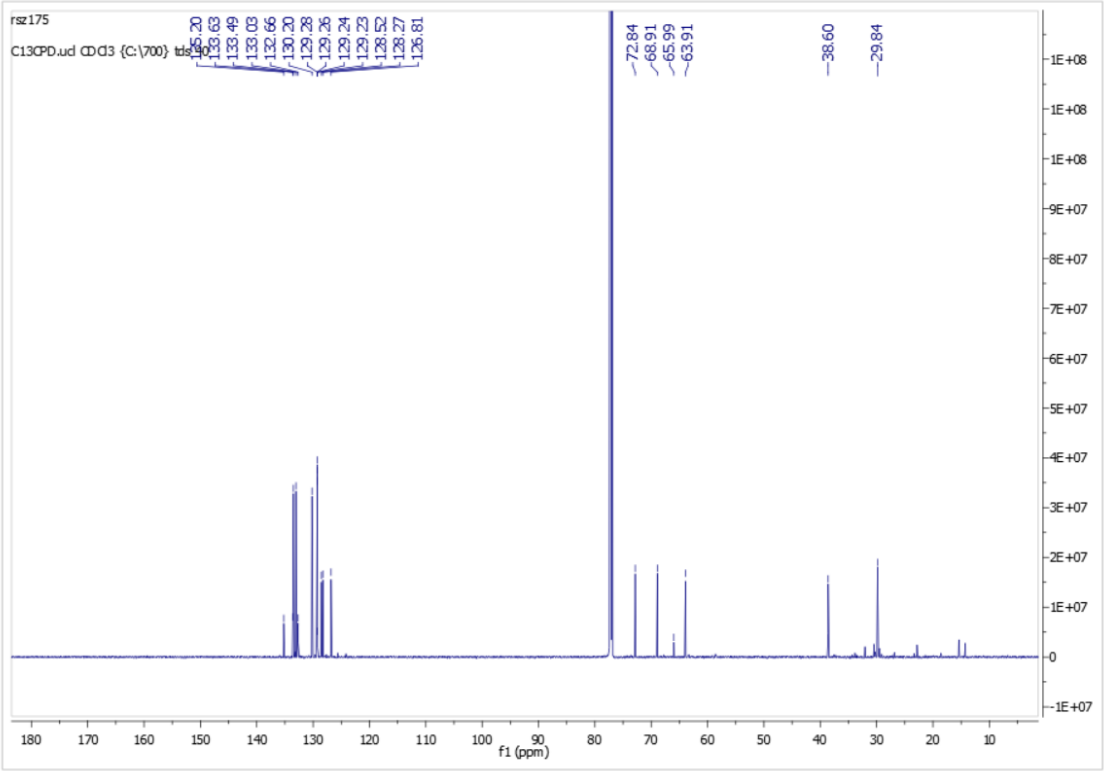
D-Fructose dithioacetal, (2*R*,3*R*,4*S*)-5,5-bis(phenylthio)hexane-1,2,3,4,6-pentaol [**79**]:



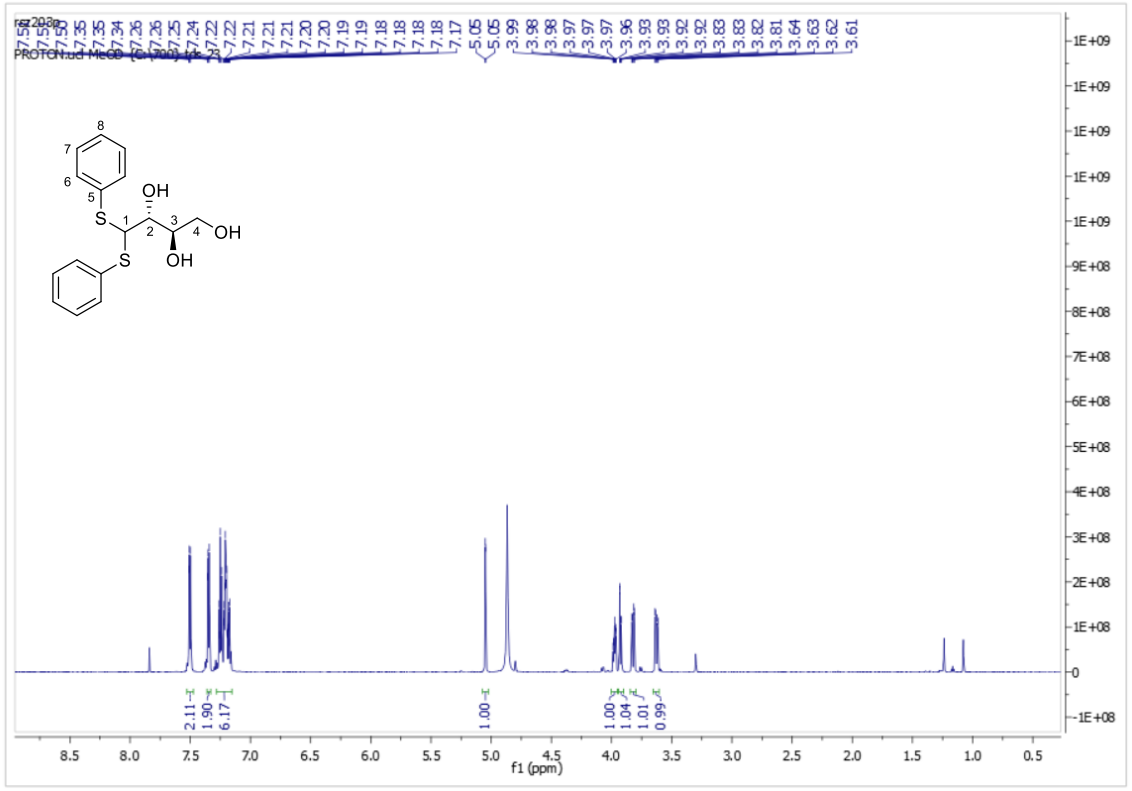



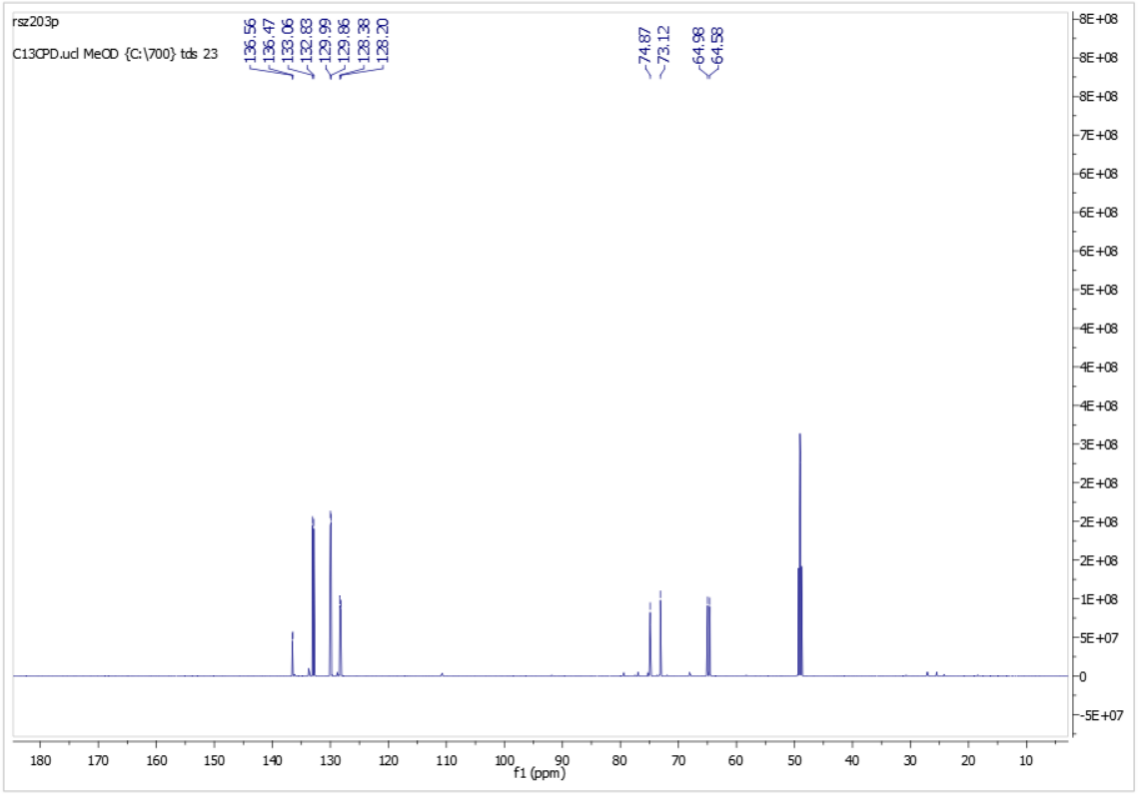
D-Threose diphenyldithioacetal, (2*R*,3*S*)-4,4-bis(phenylthio)butane-1,2,3-triol [**81**]:



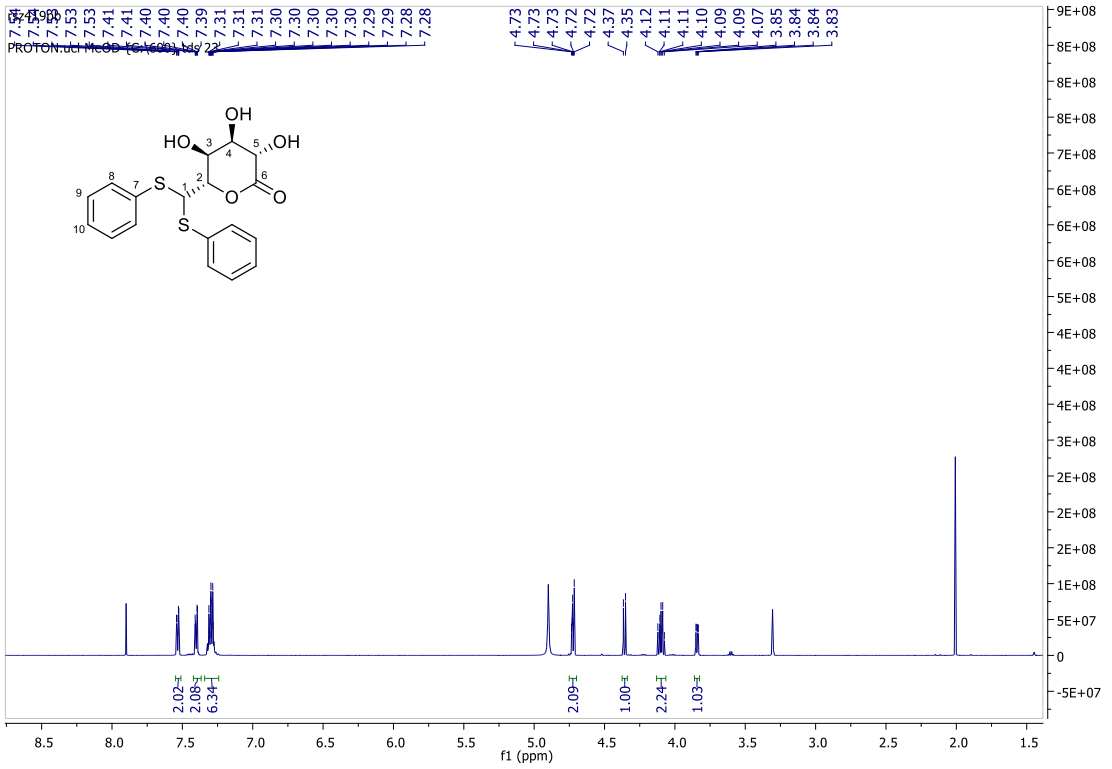



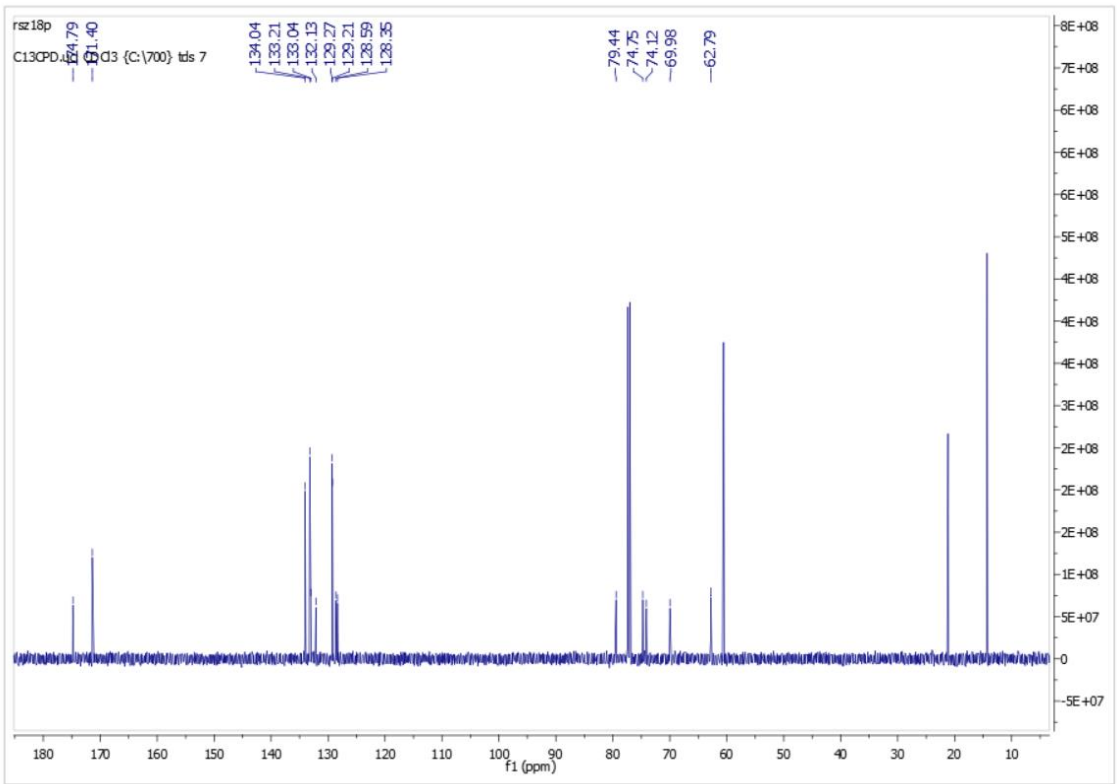
D-Erythrose diphenyldithioacetal, (2*R*,3*R*)-4,4-bis(phenylthio)butane-1,2,3-triol [**82**]:



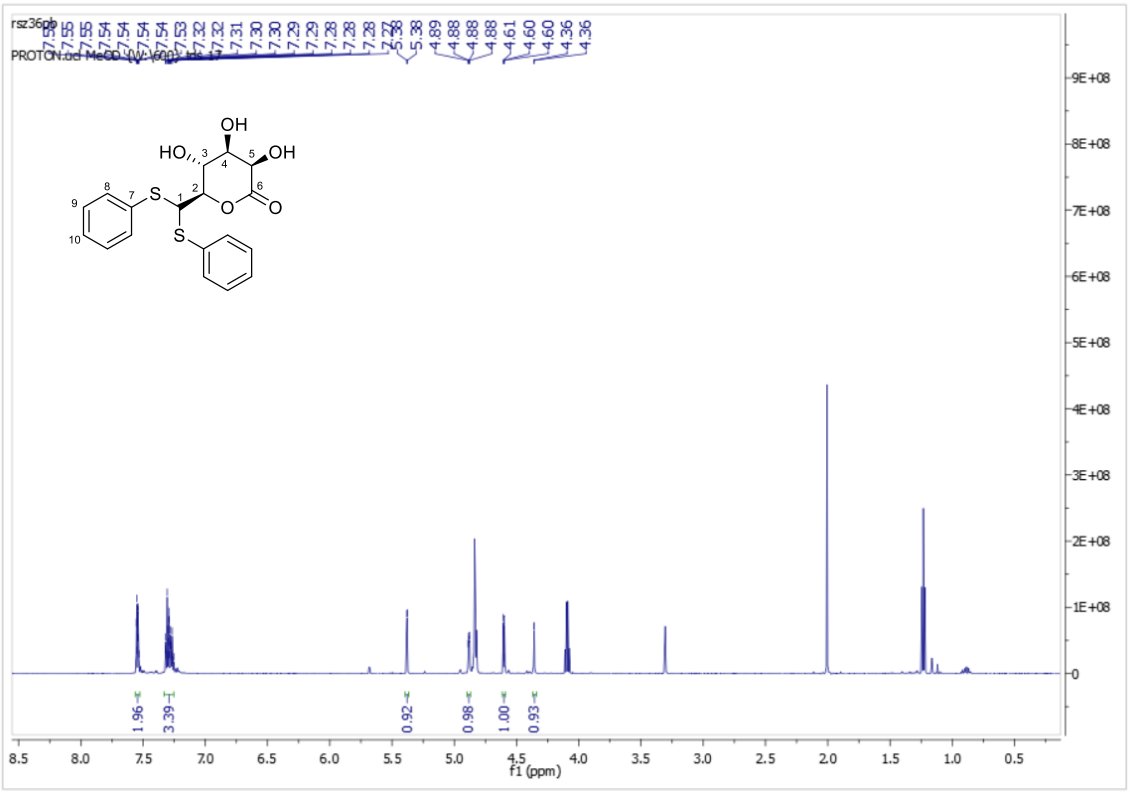



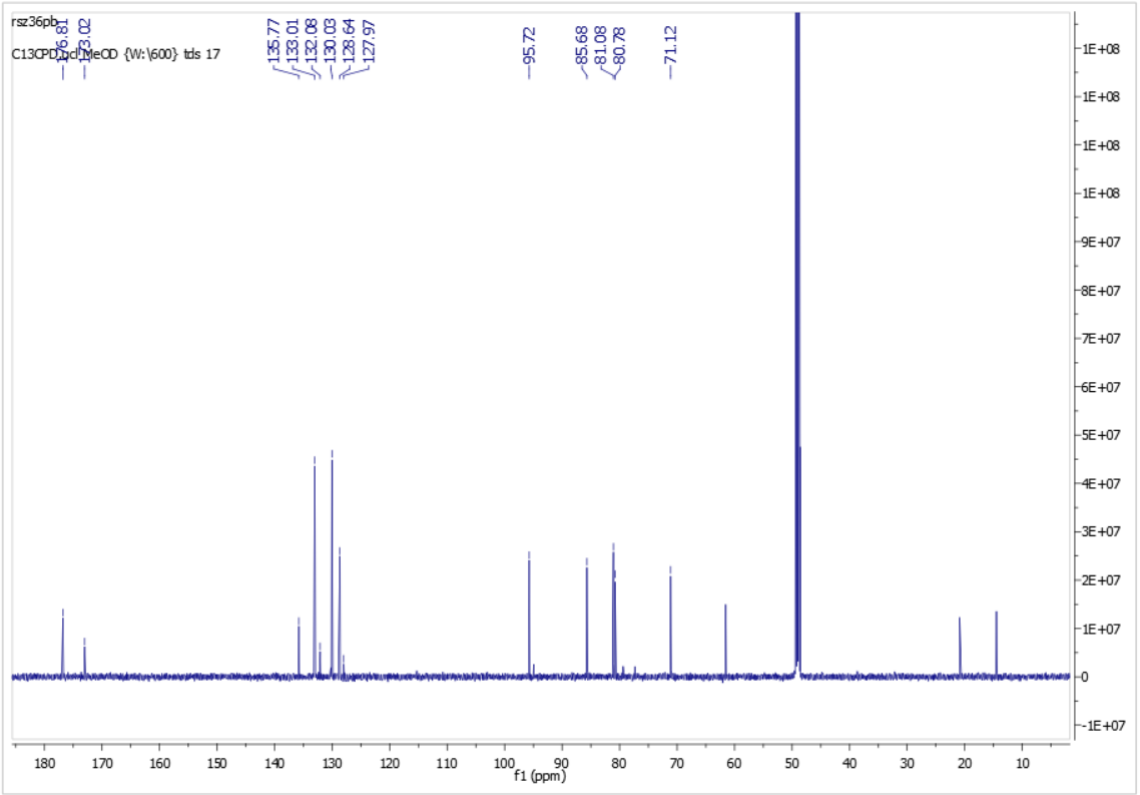
D-Galacturonic acid diphenyldithioacetal lactone, (3*S*,4*R*,5*R*,6*S*)-6-(bis(phenylthio)methyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-one [**83**]:



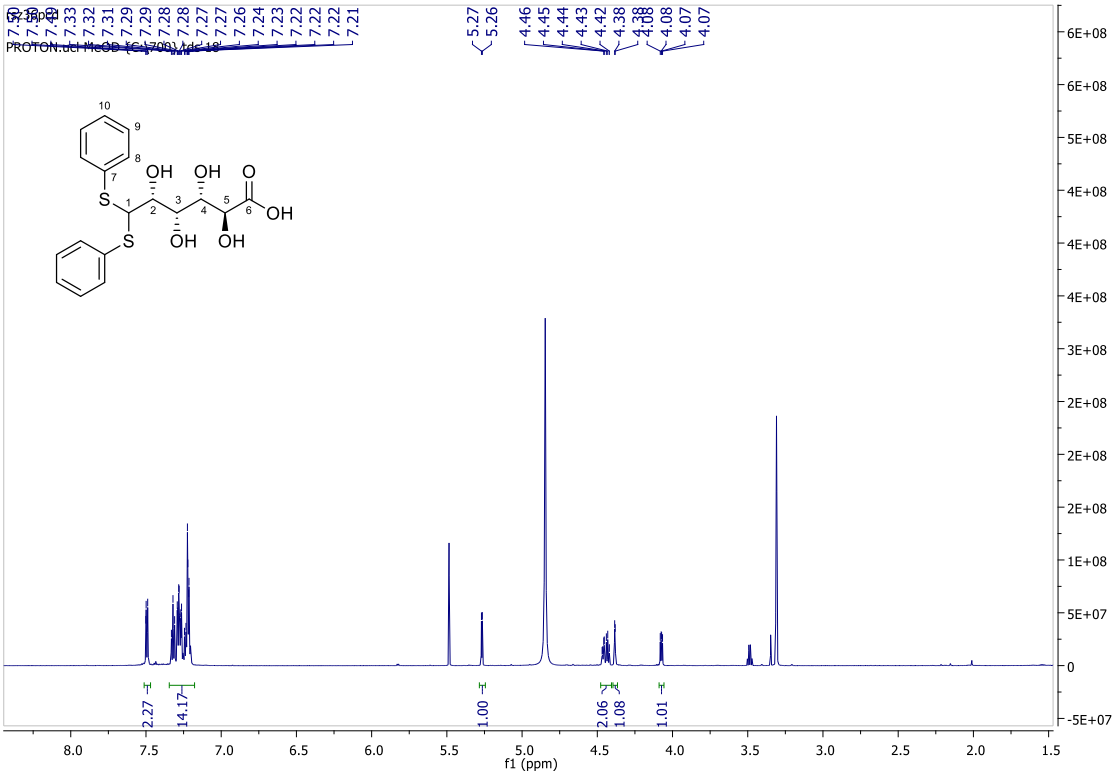



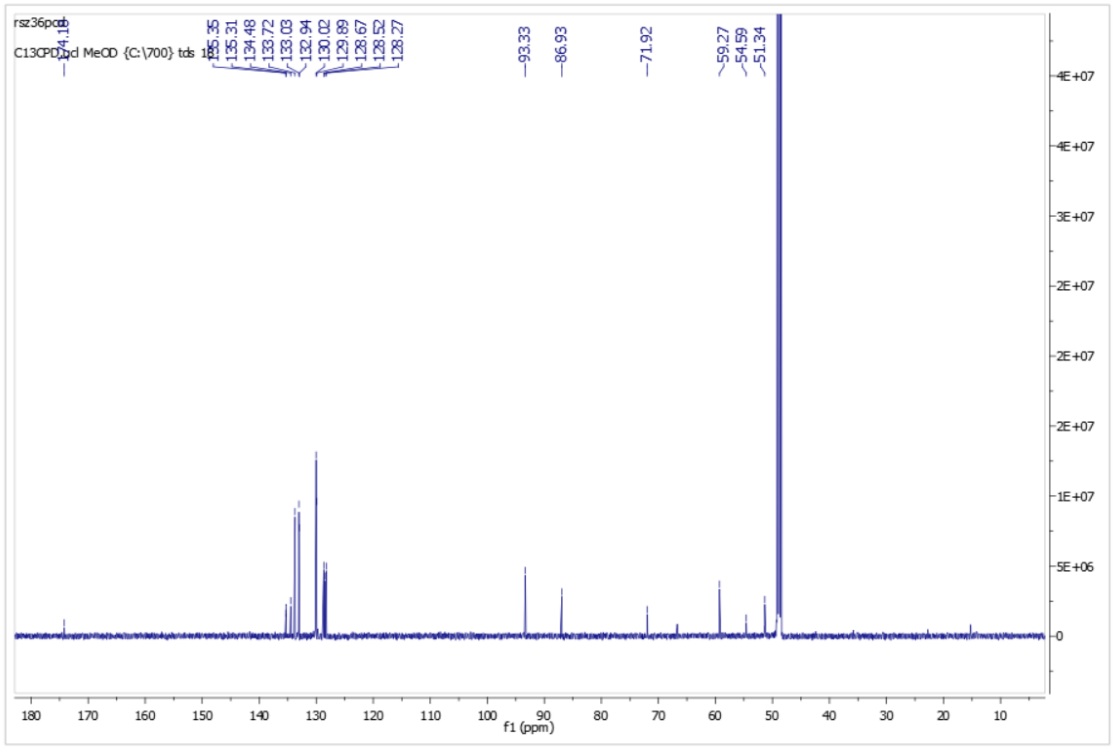
D-Glucuronic acid diphenyldithioacetal lactone, (3*R*,4*R*,5*R*,6*R*)-6-(bis(phenylthio)methyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-one [**84**]:



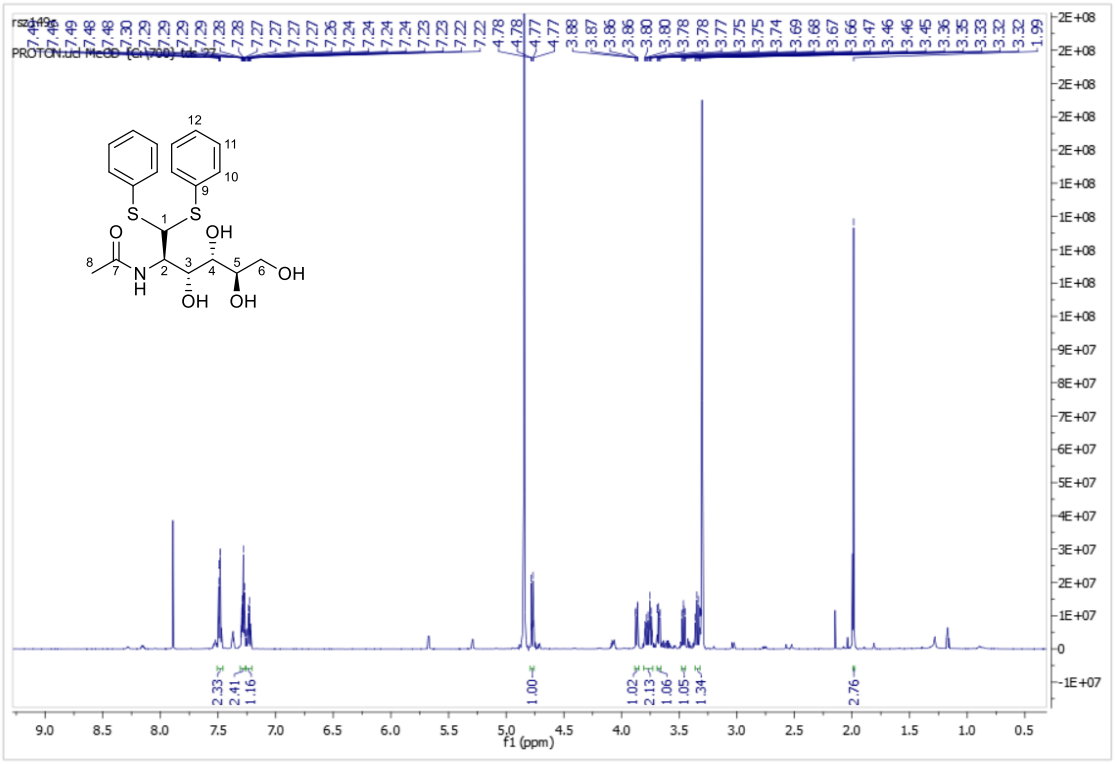



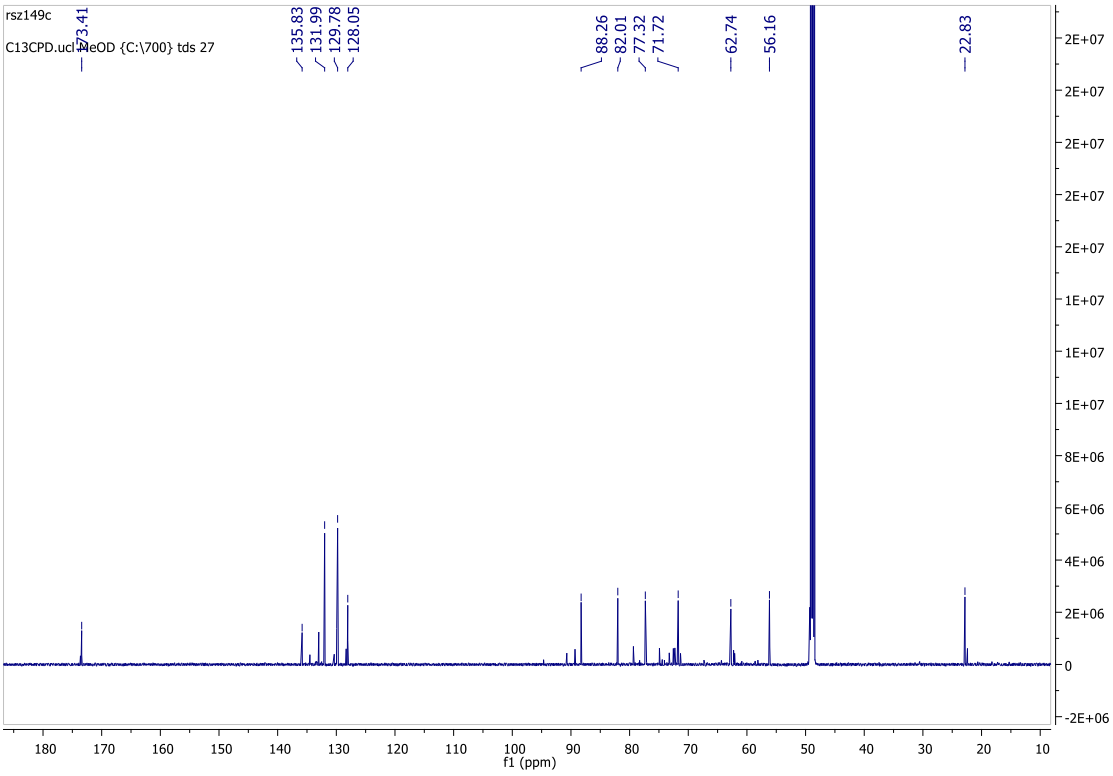
D-Glucuronic acid diphenyldithioacetal, (2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-6,6-bis(phenylthio)hexanoic acid [**85**]:



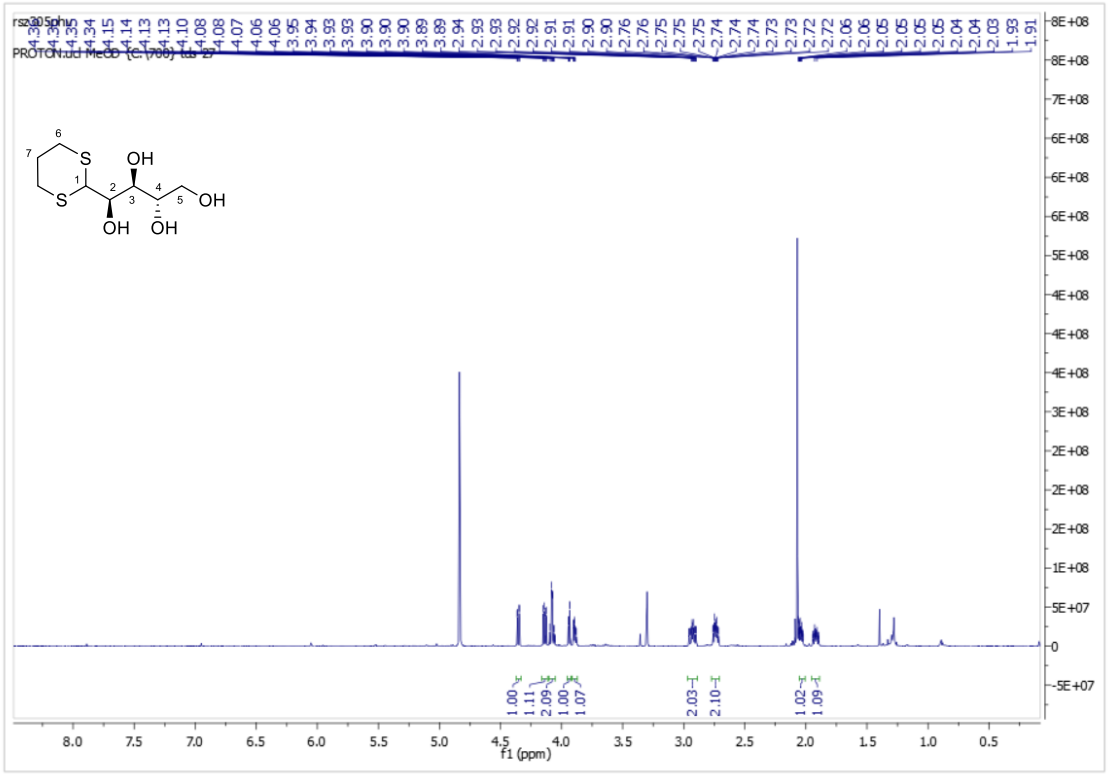



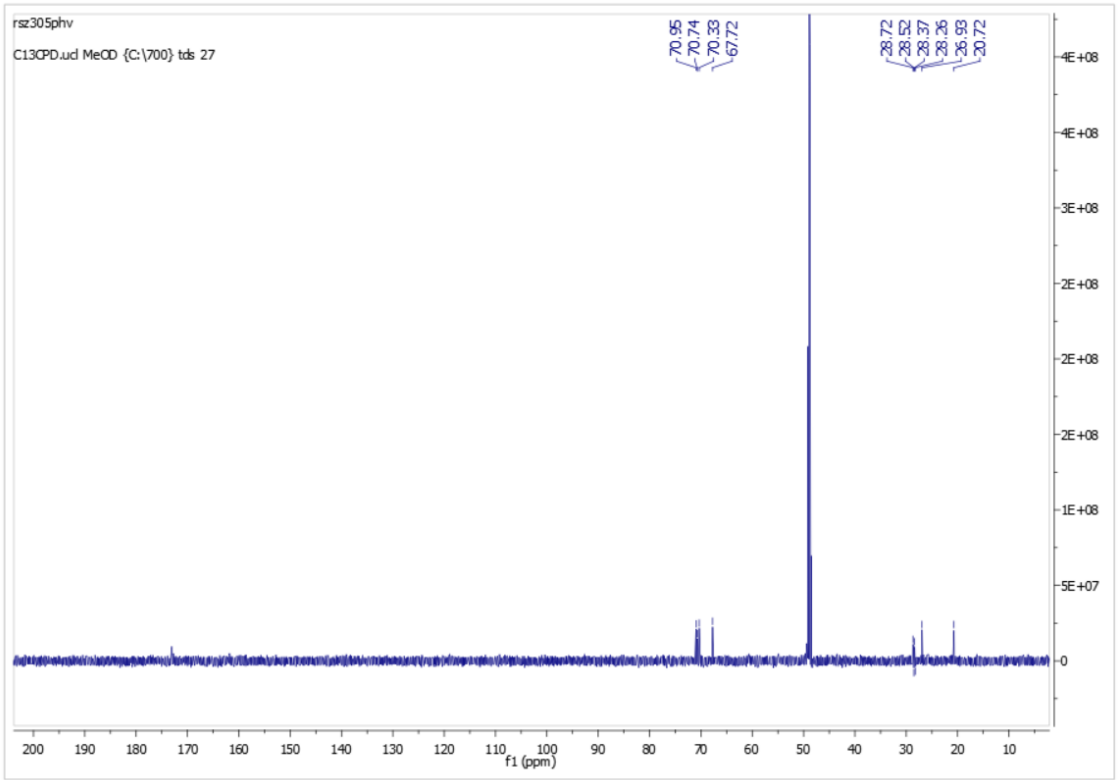
*N*-Acetyl glucosamine thioacetal, *N*-((2*R*,3*R*,4*S*,5*R*)-3,4,5,6-tetrahydroxy-1,1-bis(phenylthio)hexan-2-yl)acetamide [**87**]:



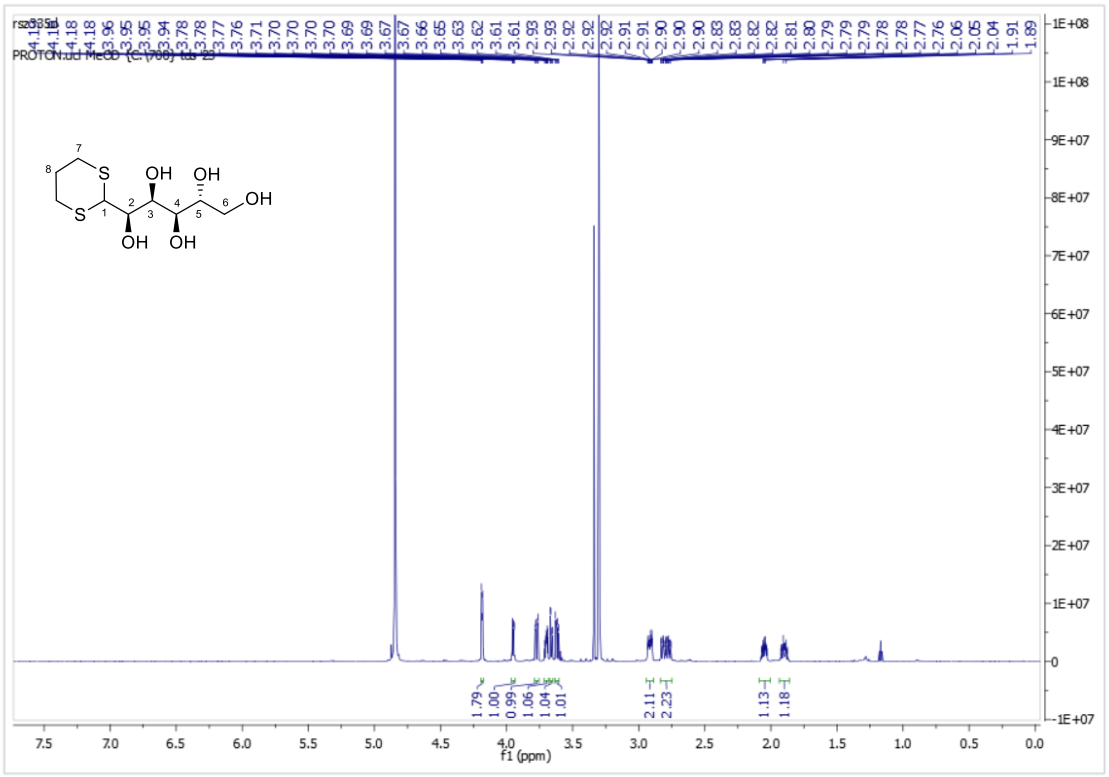



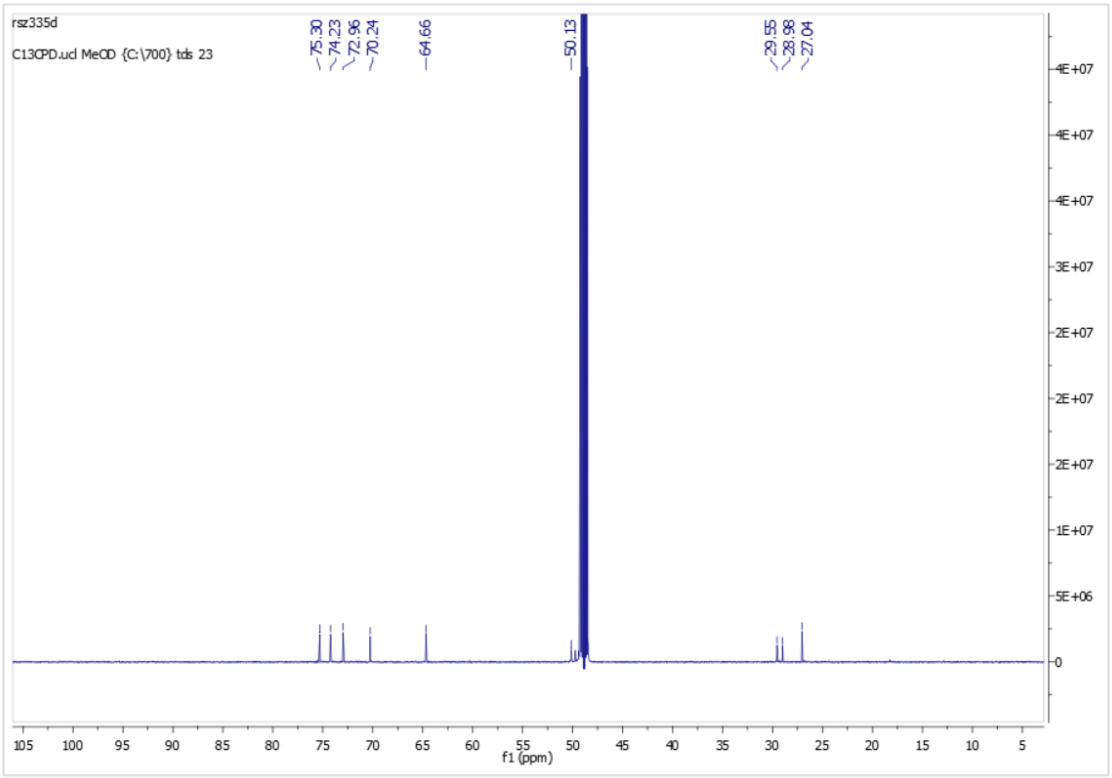
L-Arabinose 1,3-dithiane, (1*R*,2*S*,3*S*)-1-(1,3-dithian-2-yl)butane-1,2,3,4-tetraol [**90**]:



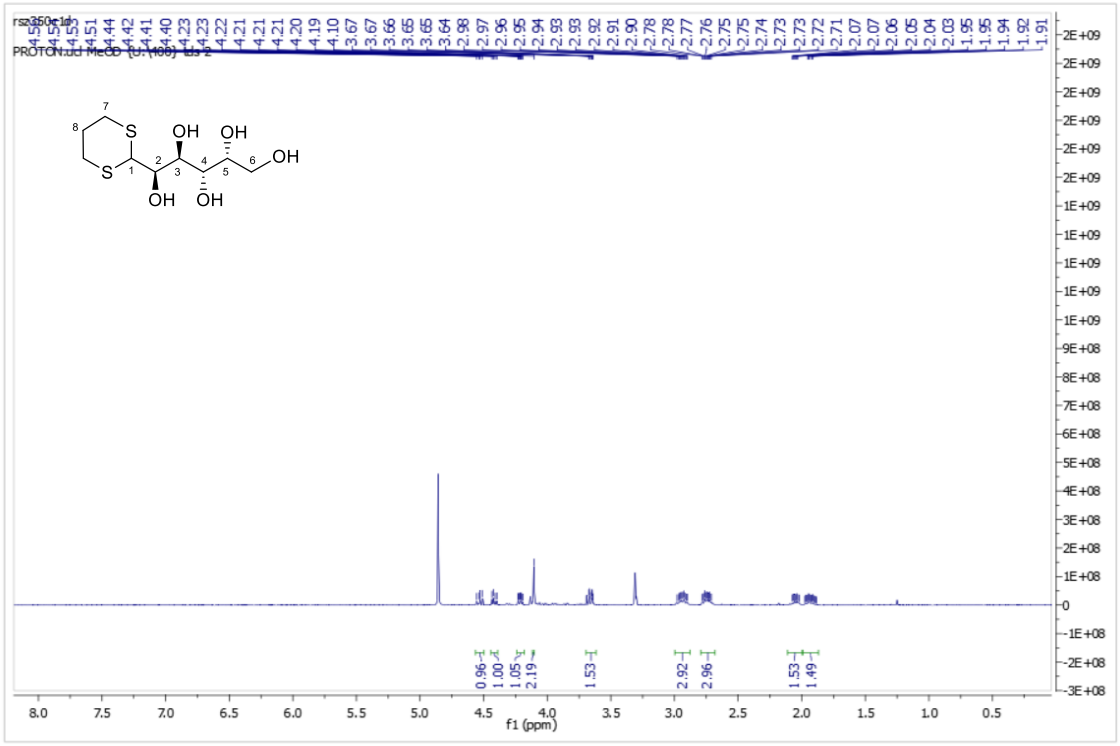



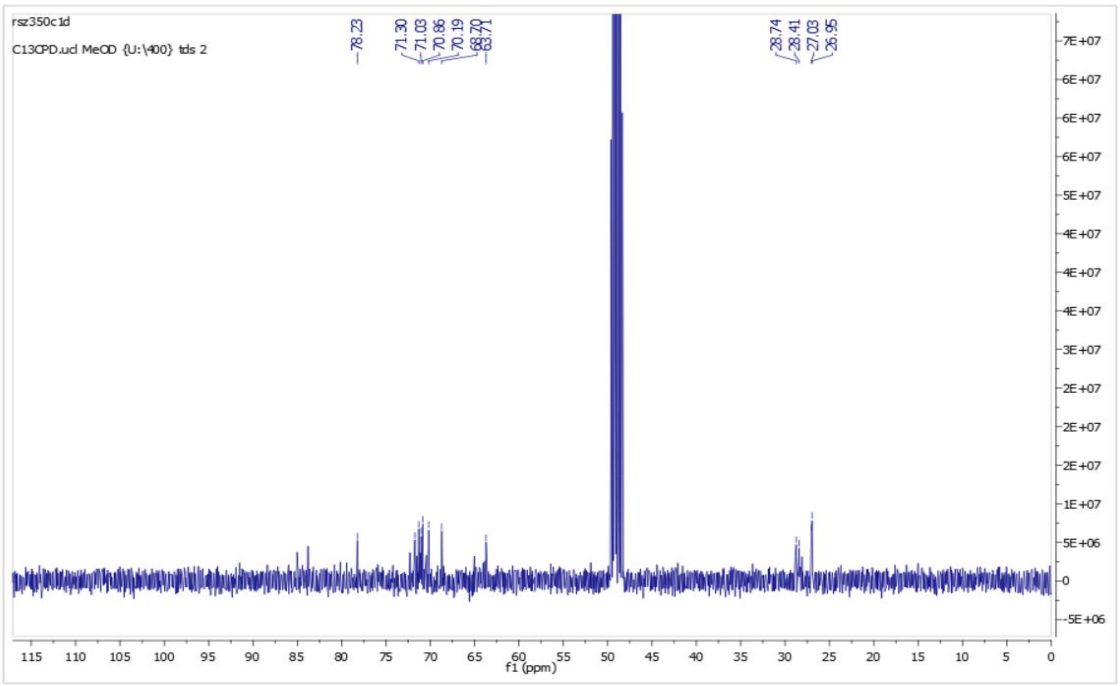
D-Glucose dithiane, (1*R*,2*S*,3*R*,4*R*)-1-(1,3-dithian-2-yl)pentane-1,2,3,4,5-pentaol [**91**]



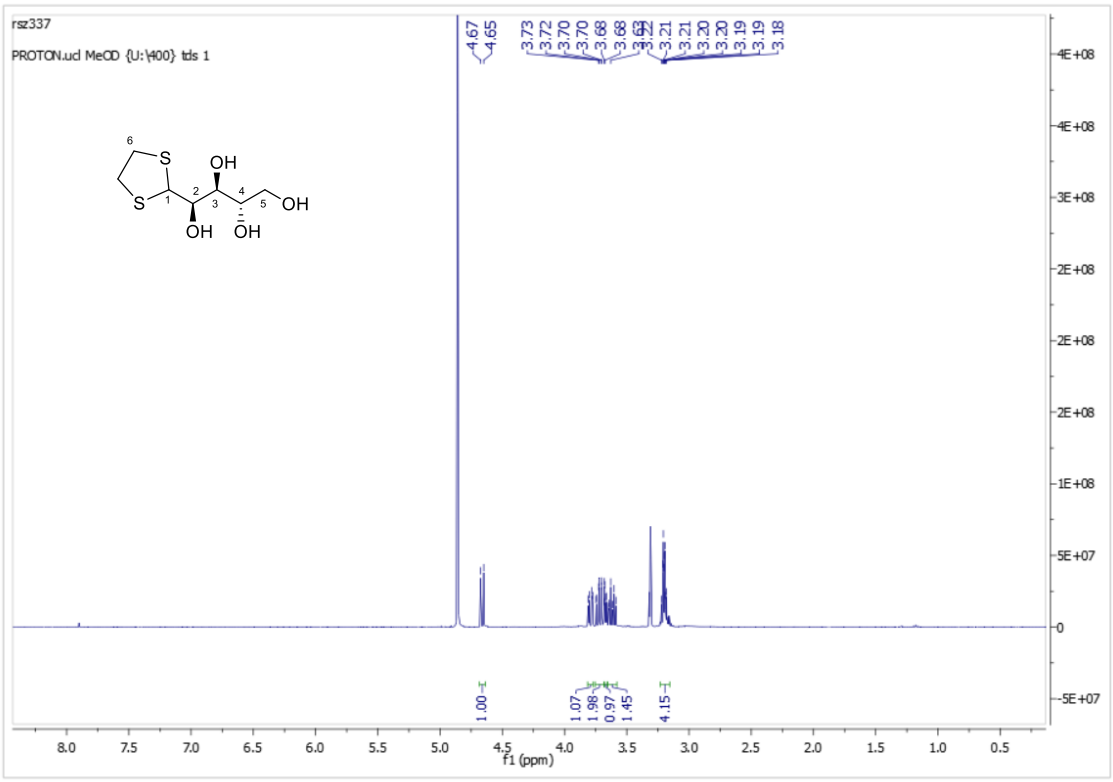



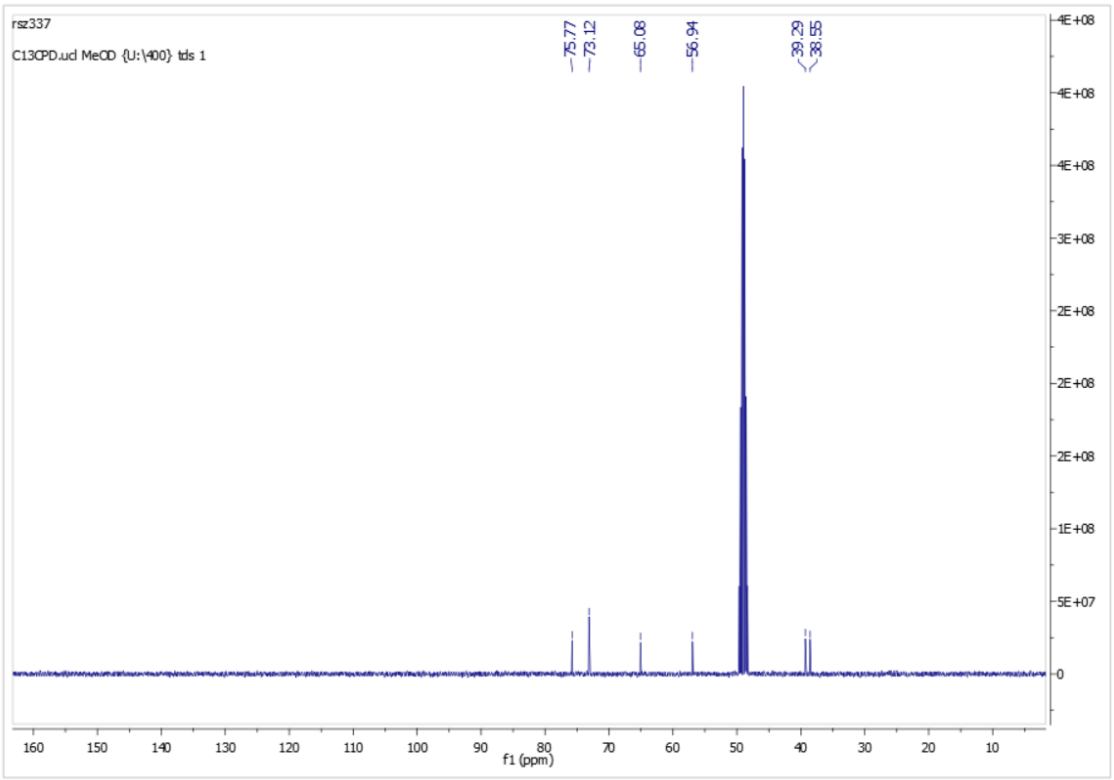
D-Galactose dithiane, (1*R*,2*S*,3*S*,4*R*)-1-(1,3-dithian-2-yl)pentane-1,2,3,4,5-pentaol [**92**]:



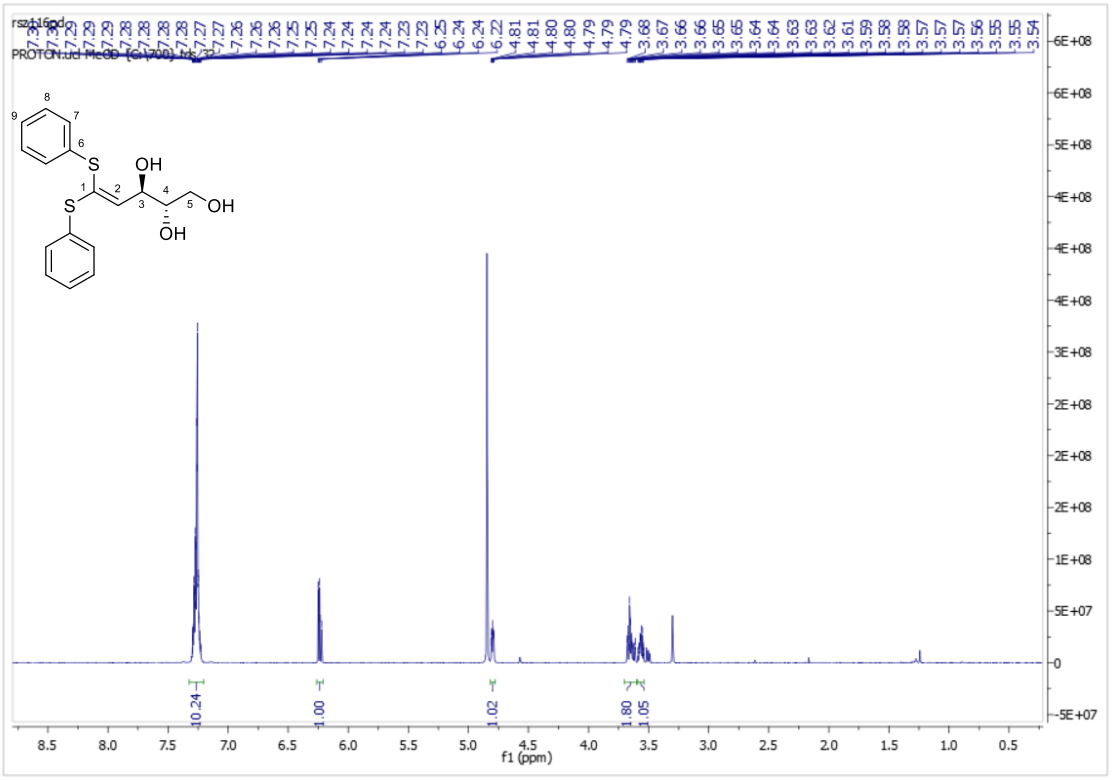



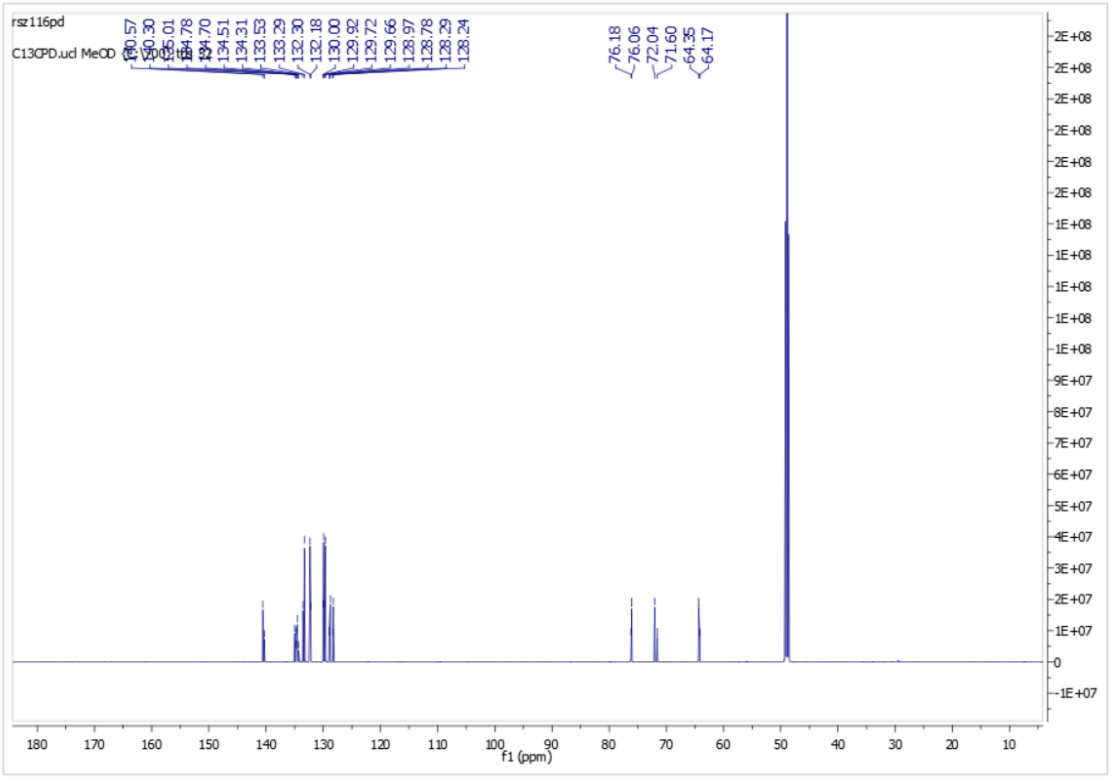
L-Arabinose dithiane, (1*R*,2*S*,3*S*)-1-(1,3-dithiolan-2-yl)butane-1,2,3,4-tetraol [**93**]:



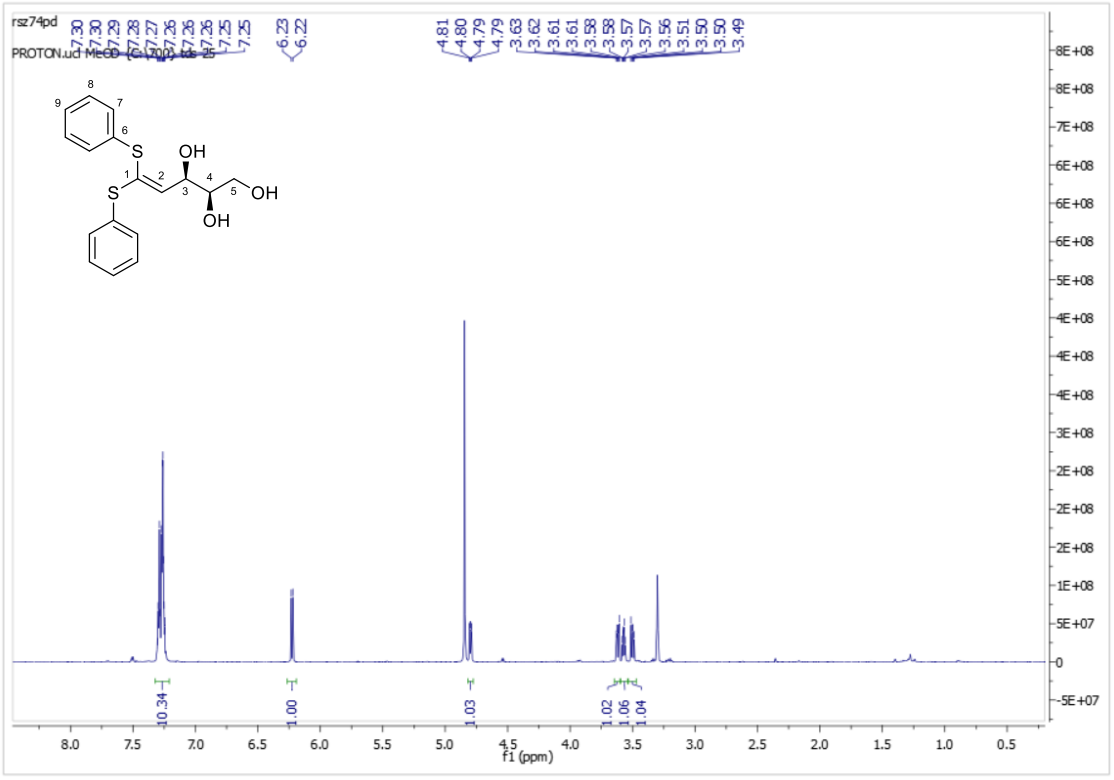



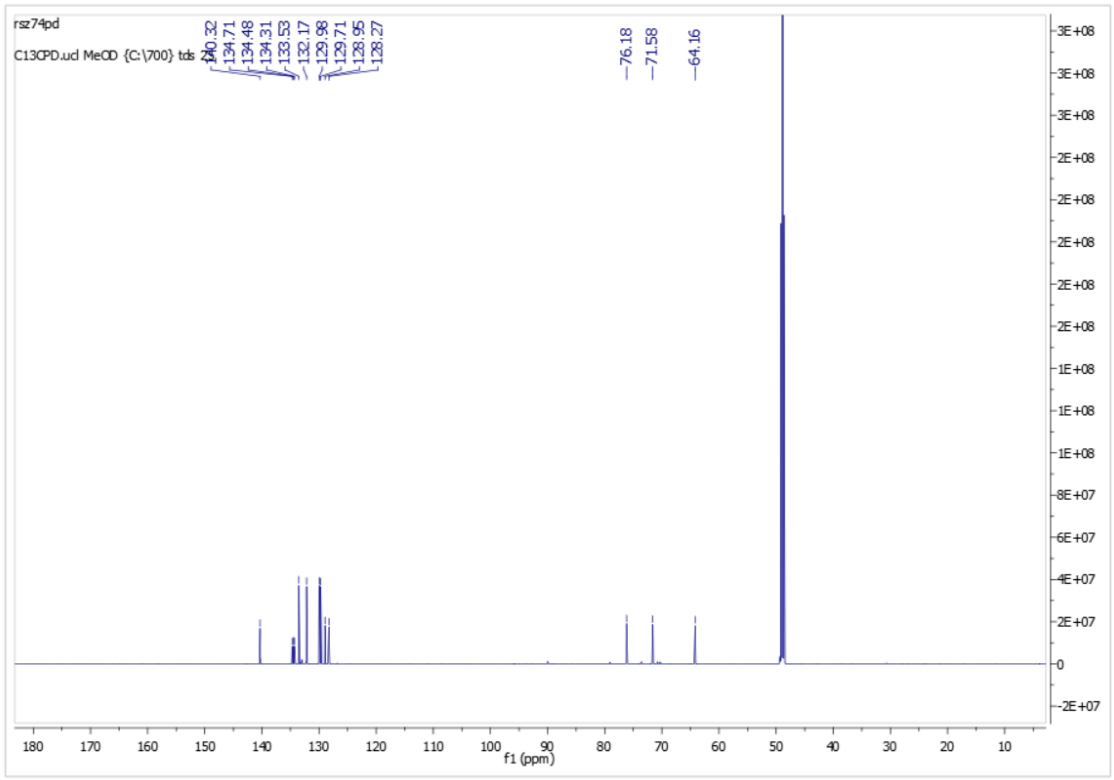
L-Arabinose thioacetal ketene, (2*S*,3*R*)-5,5-bis(Phenylthio)pent-4-ene-1,2,3-triol [**95**]:



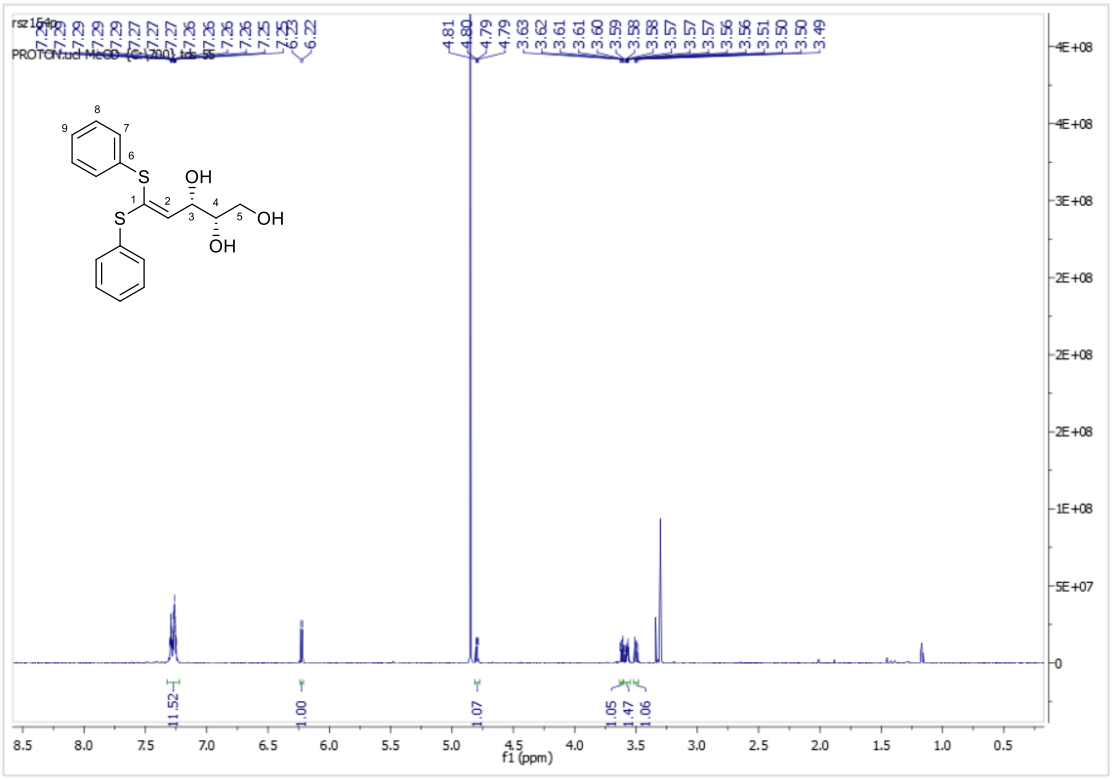



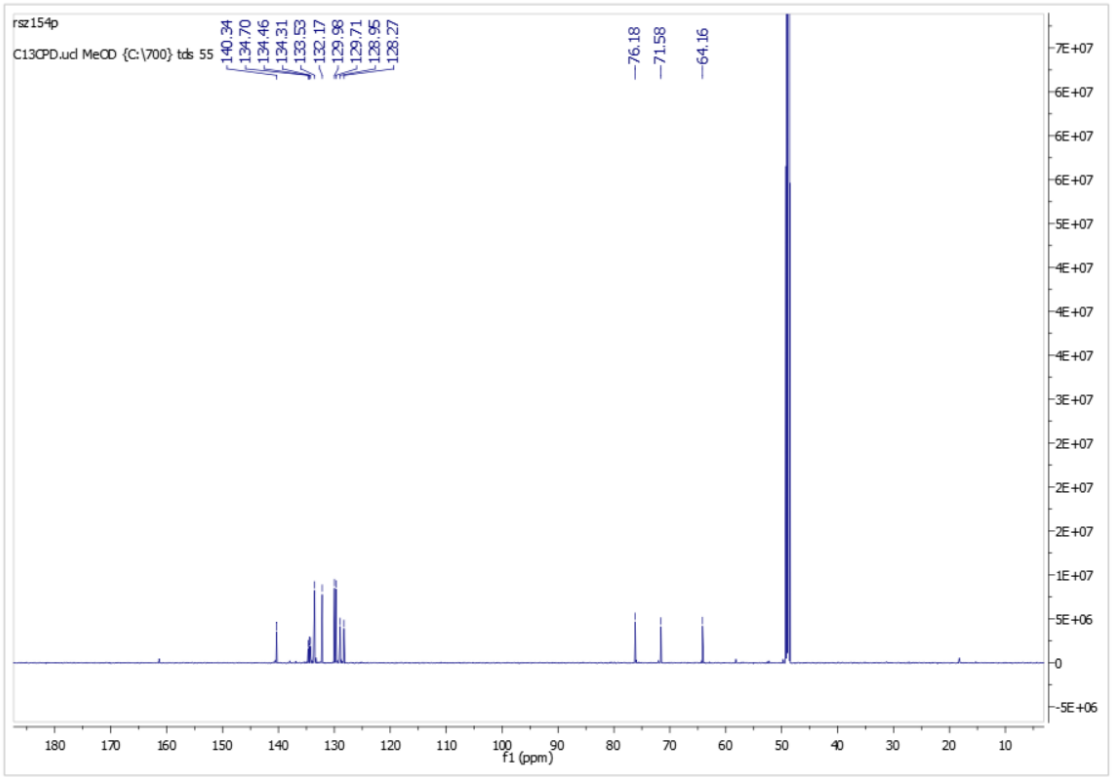
D-Xylose thioacetal ketene, (2*R*,3*R*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol [**96**]:



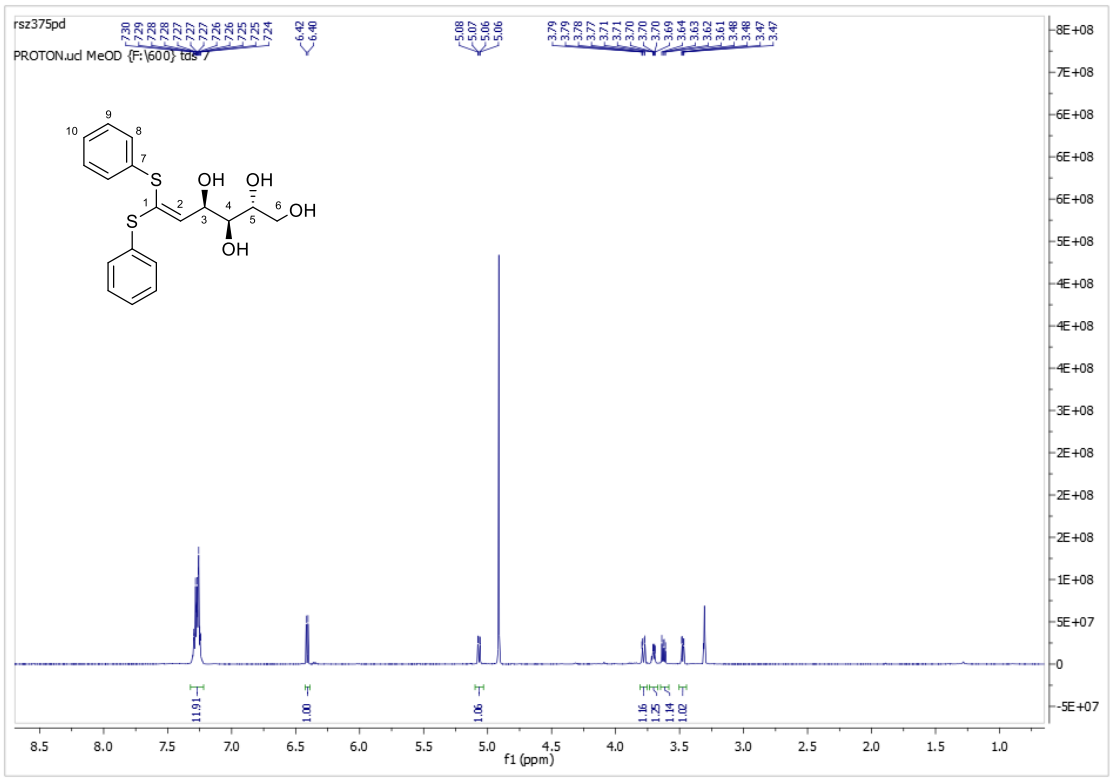



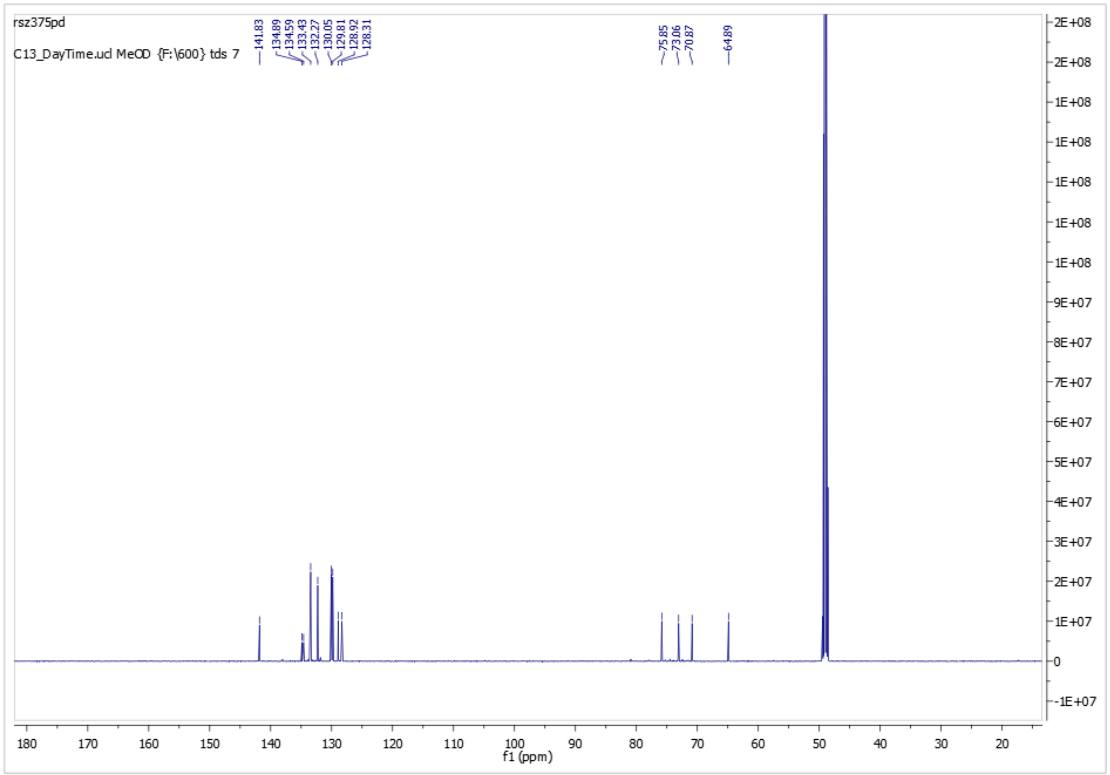
L-Xylose thioacetal ketene, (2*S*,3*S*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol [**97**]:



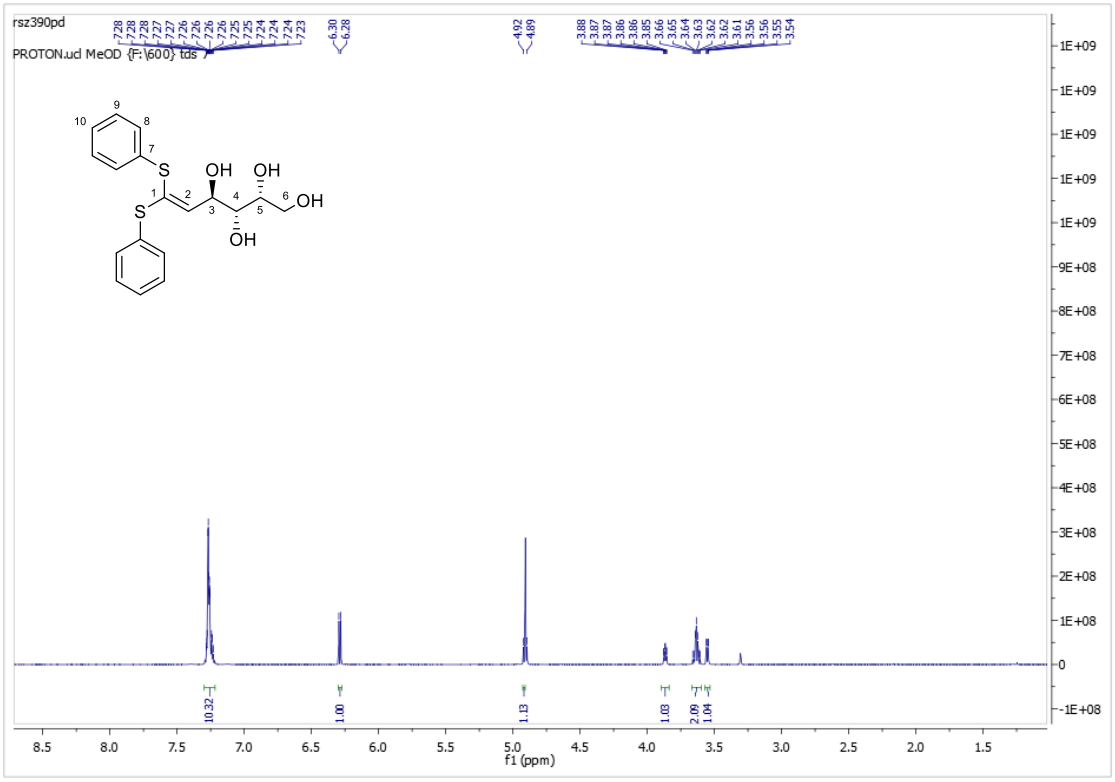



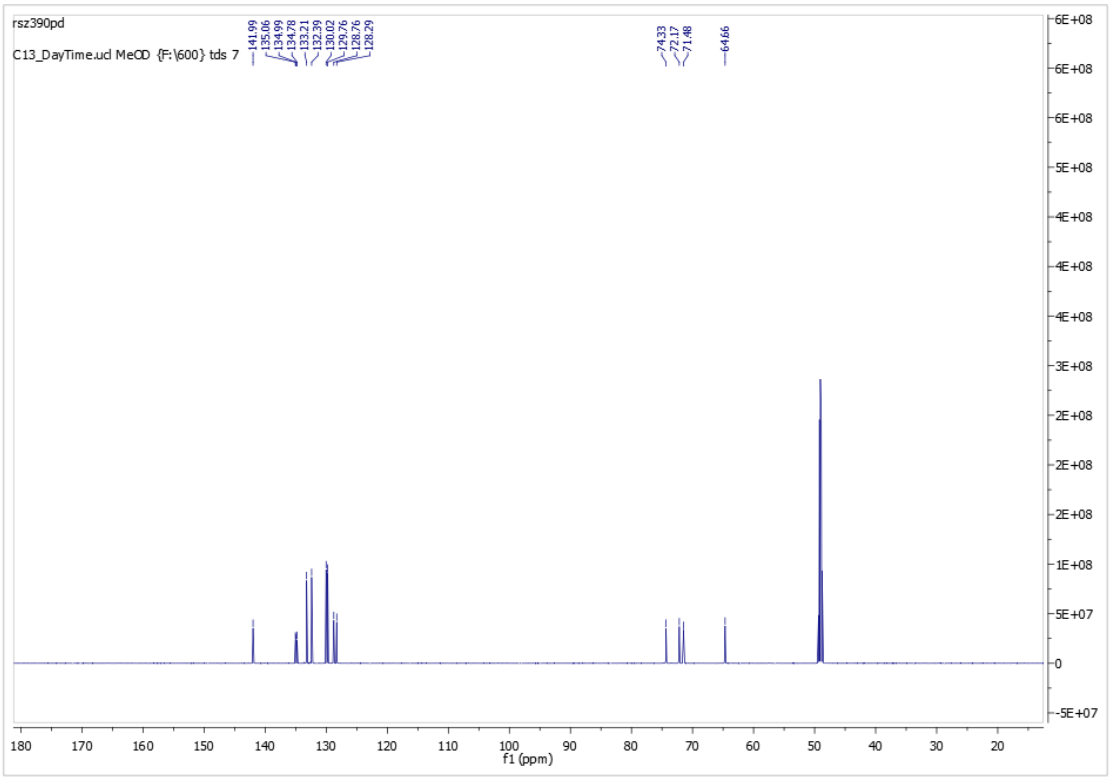
D-Glucose thioacetal ketene, (2*R*,3*S*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol [**101**]:



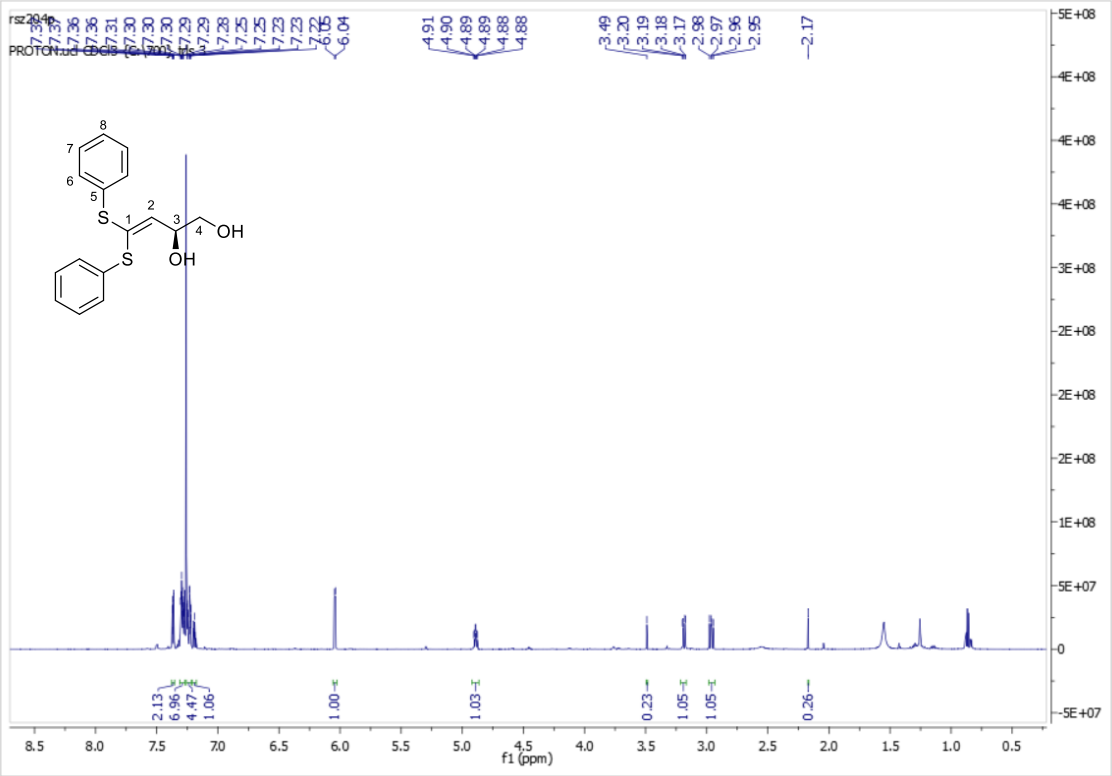



D-Galactose dithioacetal ketene, (2*R*,3*R*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetraol [**102]**:

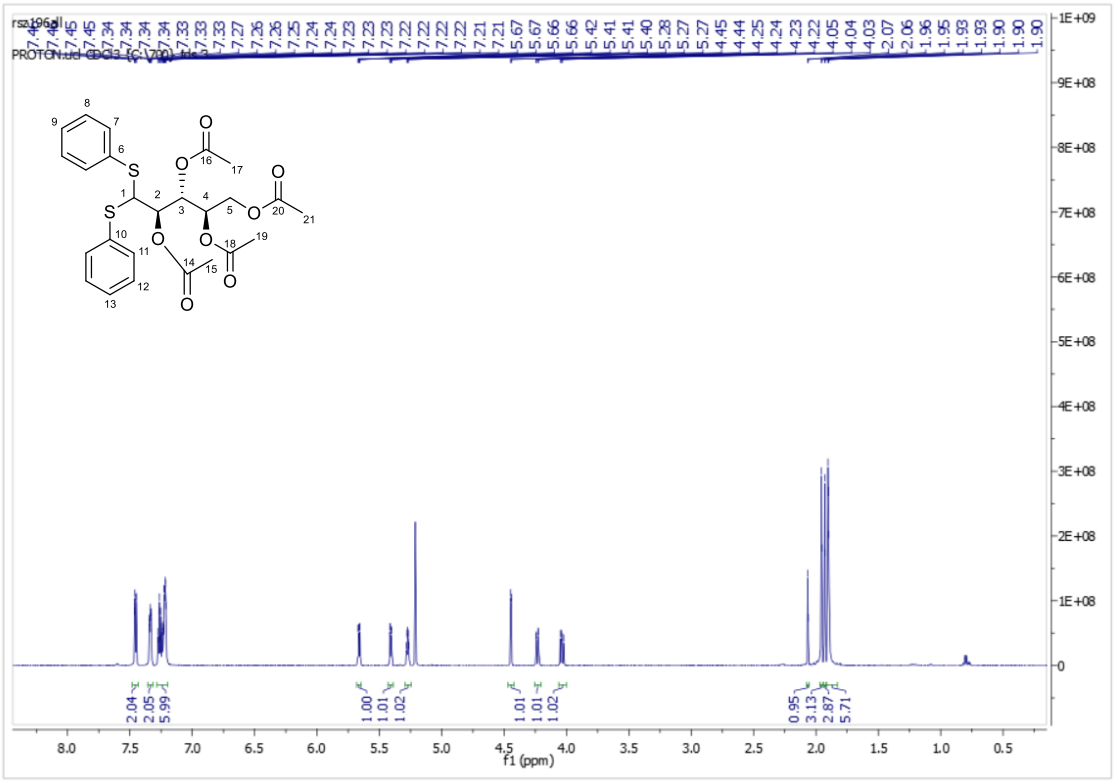


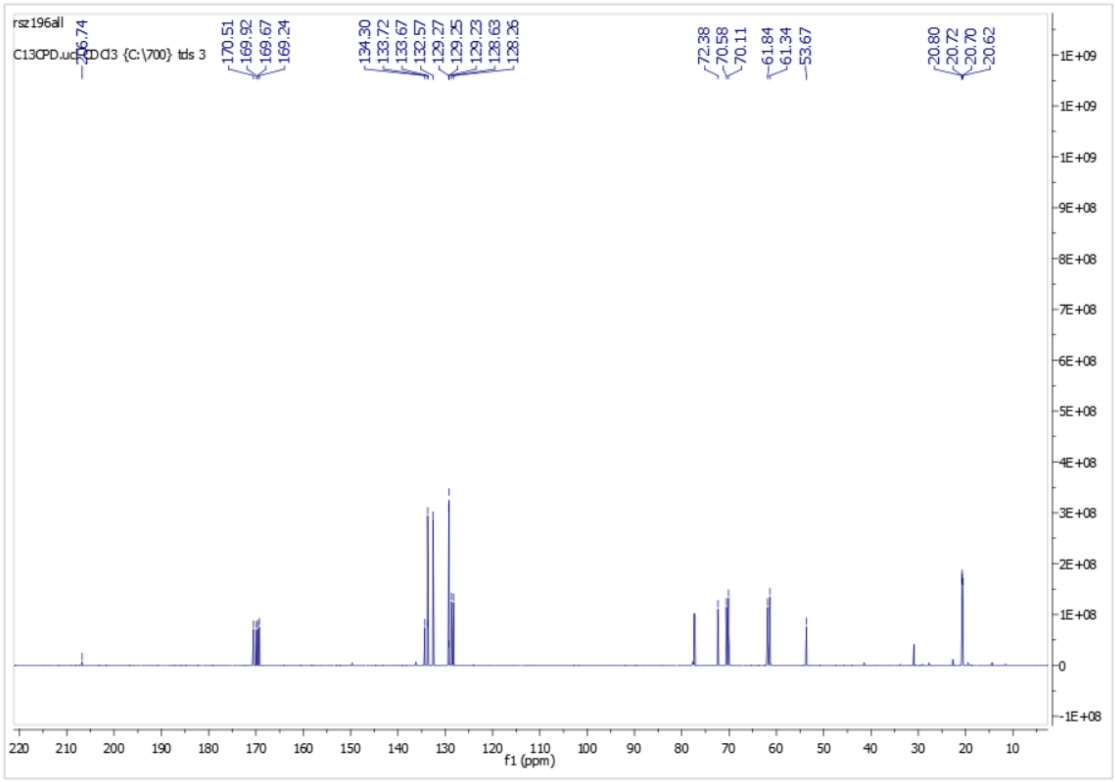



D-Threose diphenyldithioacetal ketene, (2*R*,3*S*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol [**108**]:

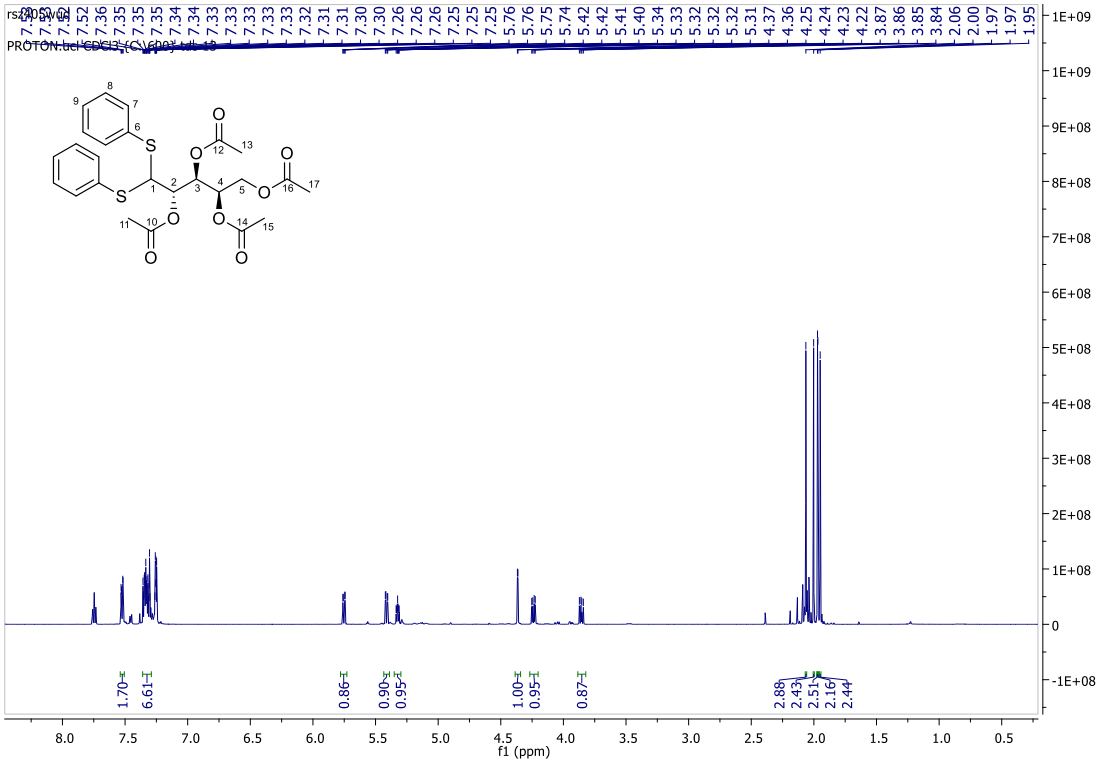


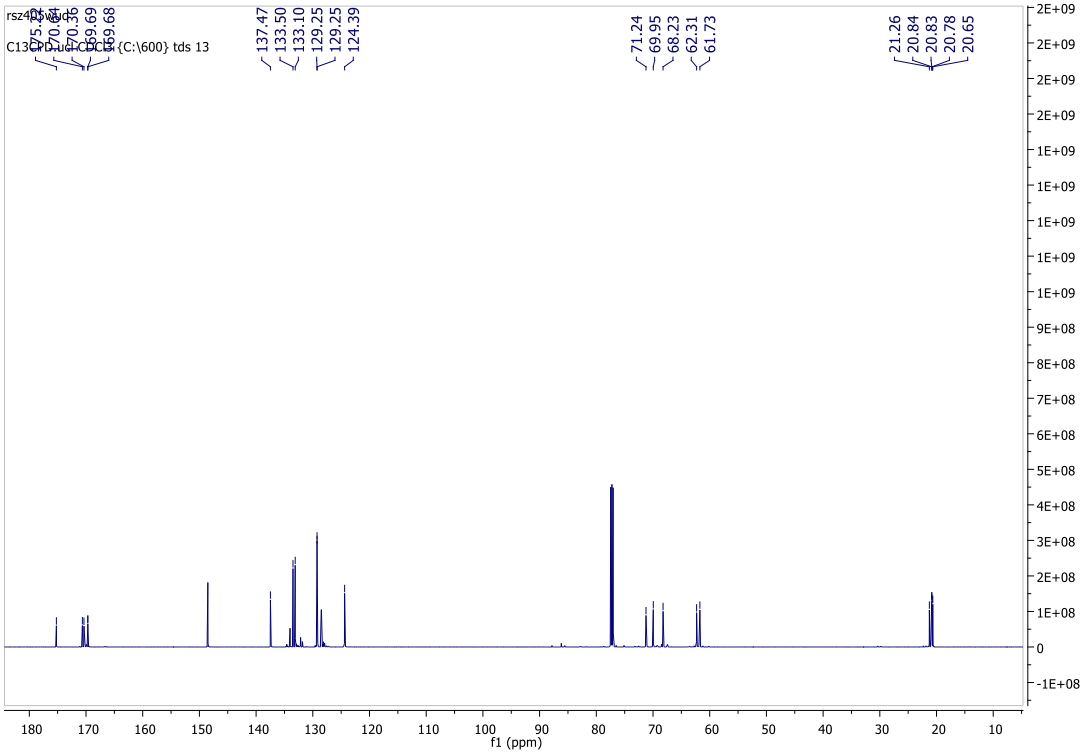
D-Ribose diphenyldithioacetal tetraacetate, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetrayl tetraacetate [**110**]:



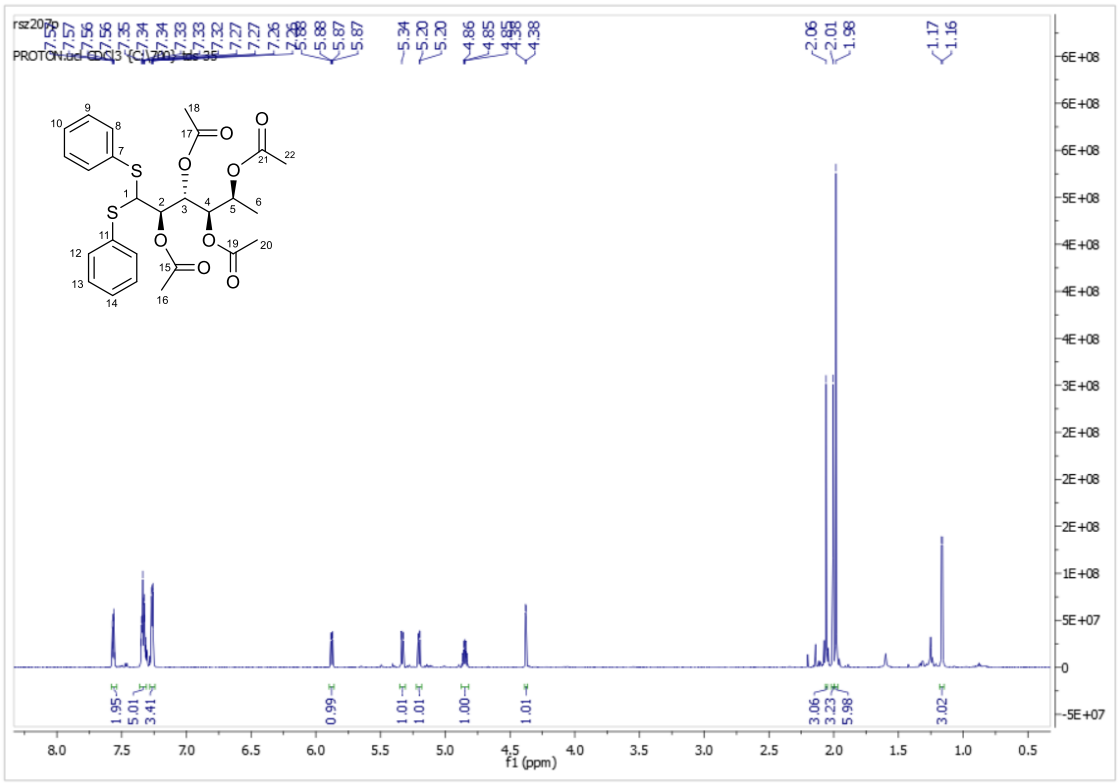


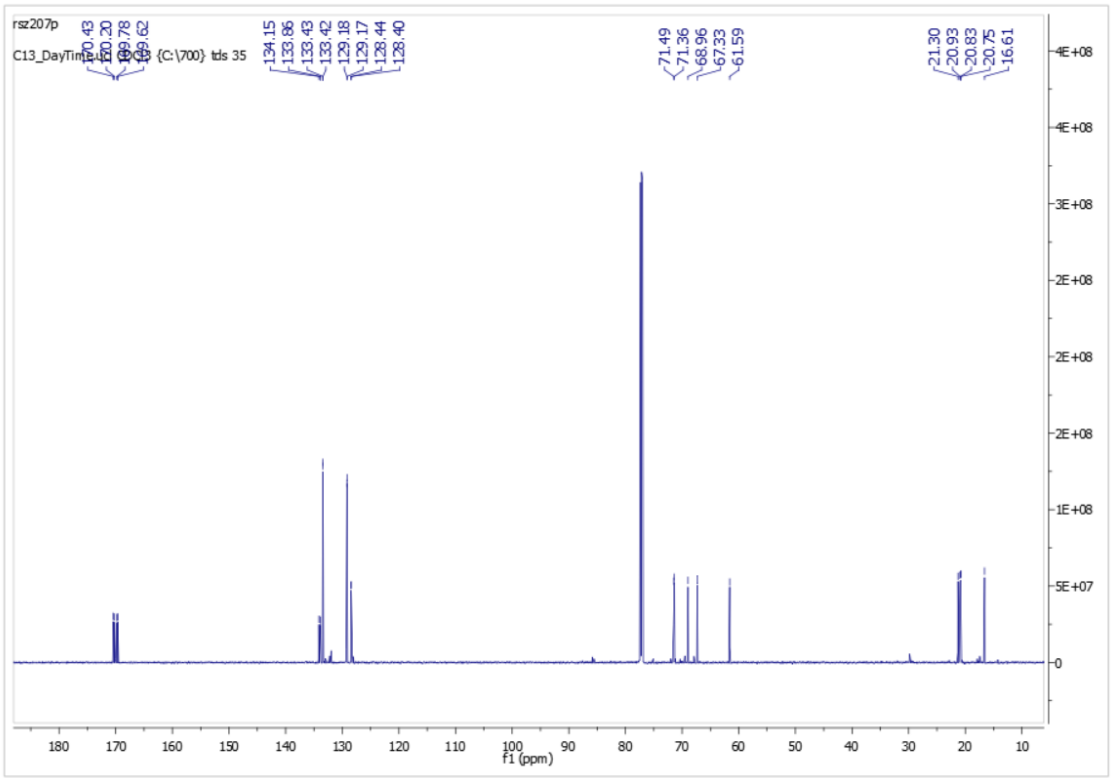
D-Lyxose diphenyldithioacetal pentaacetate, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetrayl tetraacetate [**111**]:



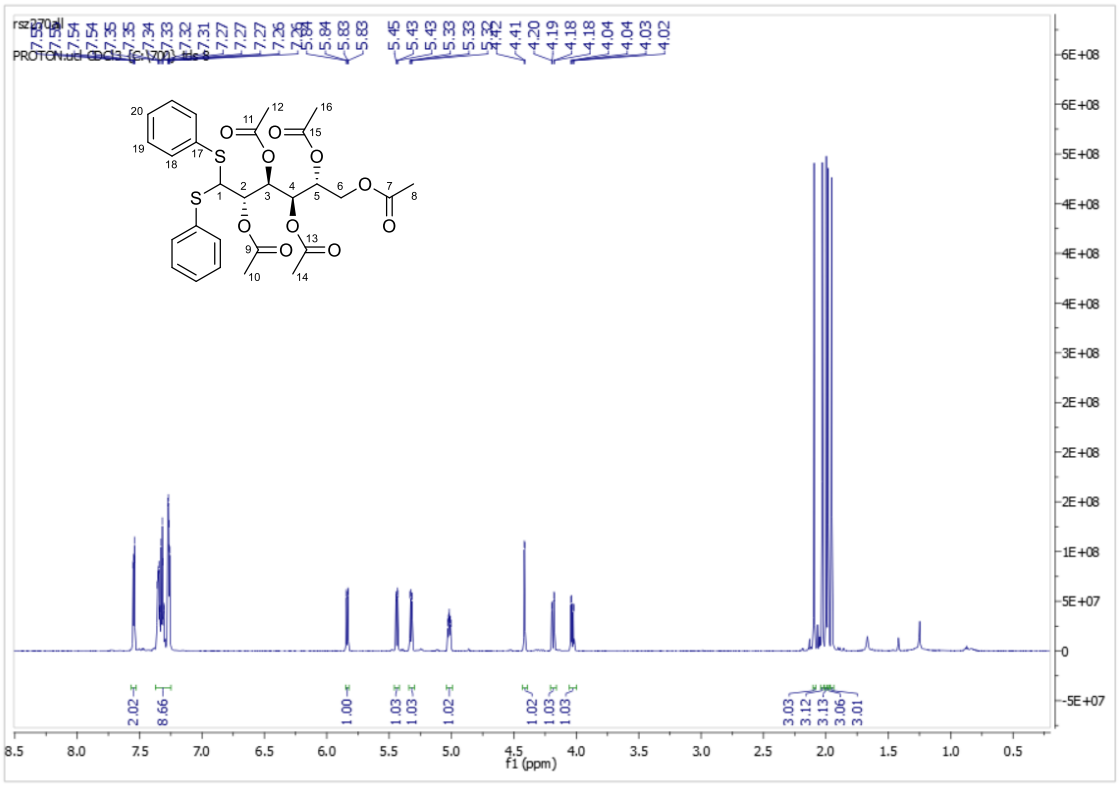



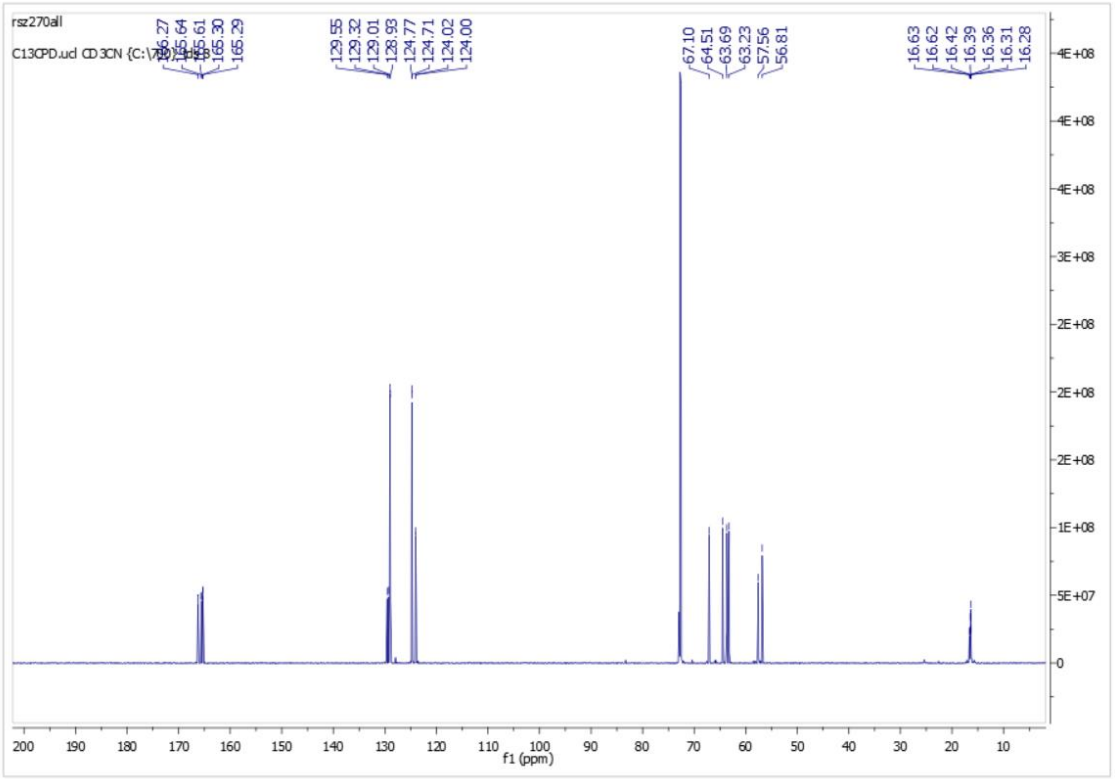
L-Rhamnose diphenyldithioacetal tetraacetate, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetrayl tetraacetate [**112**]:



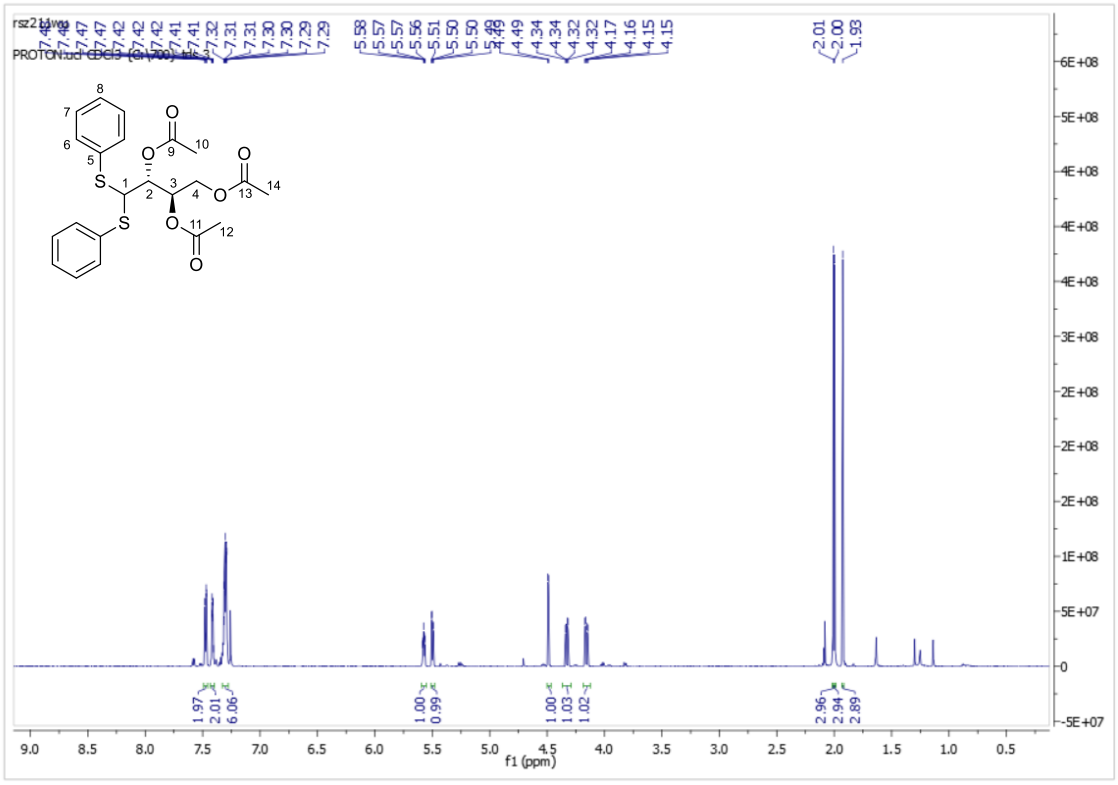



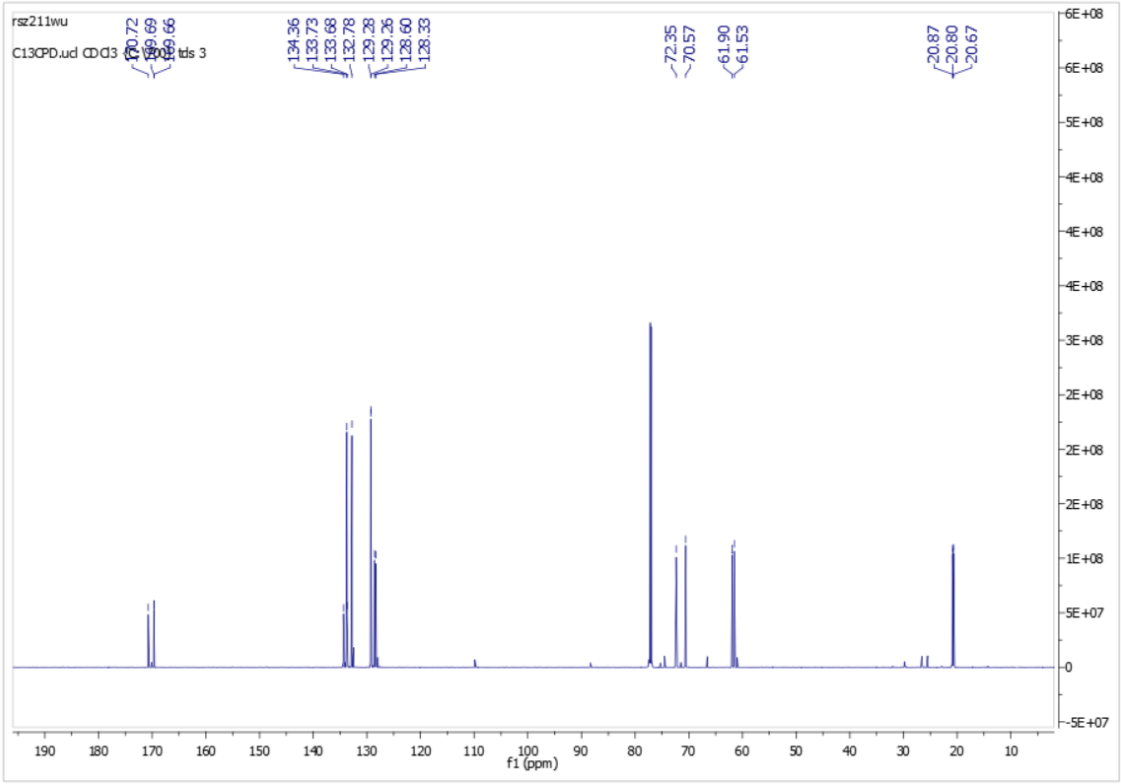
D-Mannose diphenyldithioacetal pentaacetate, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentayl pentaacetate [**113**]:



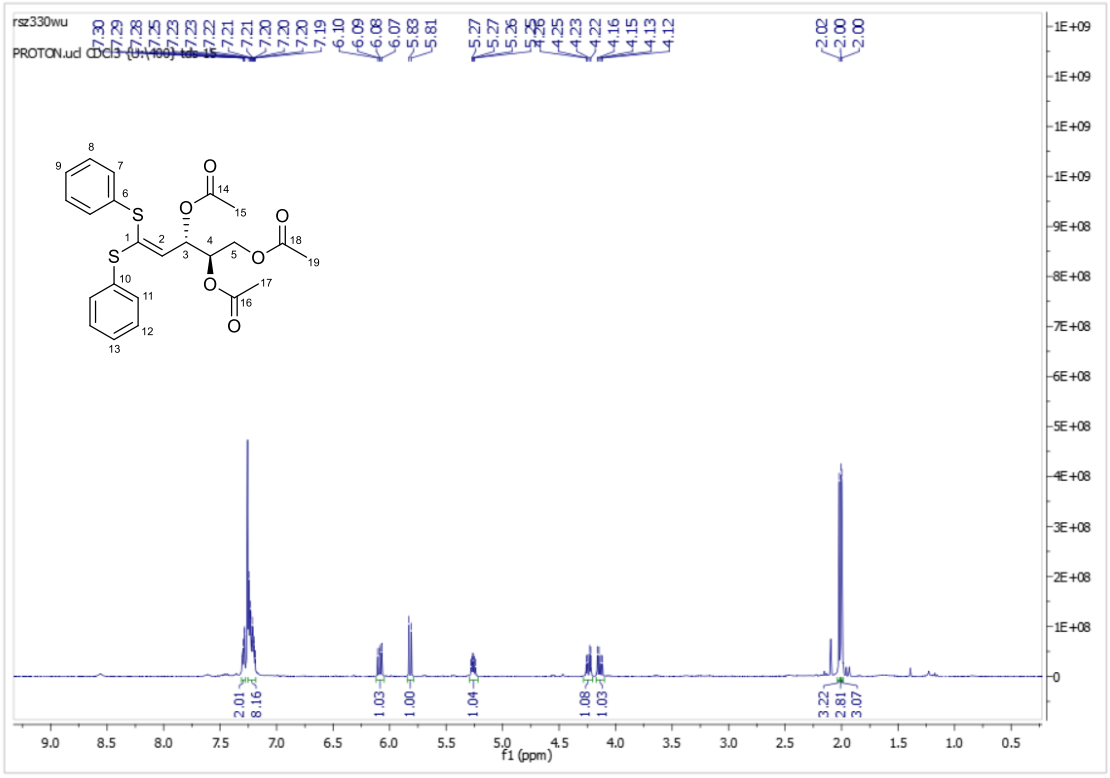



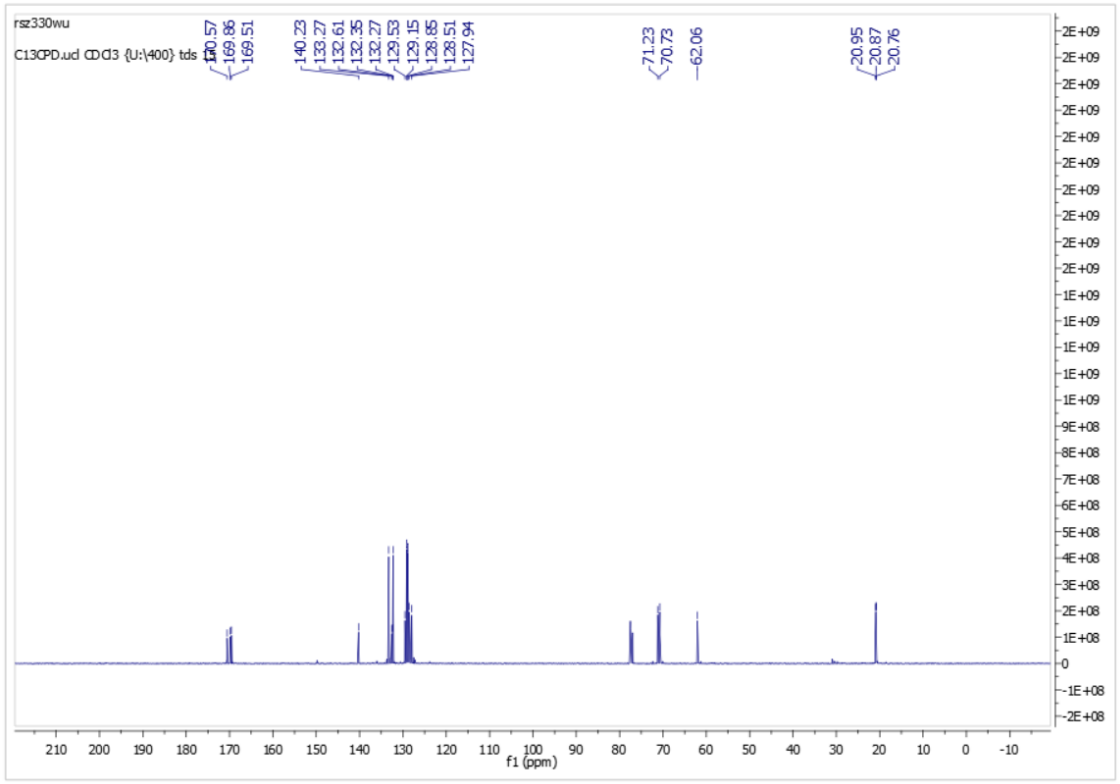
D-Erythrose triacetate, (2*R*,3*R*)-4,4-bis(phenylthio)butane-1,2,3-triyl triacetate [**114**]:



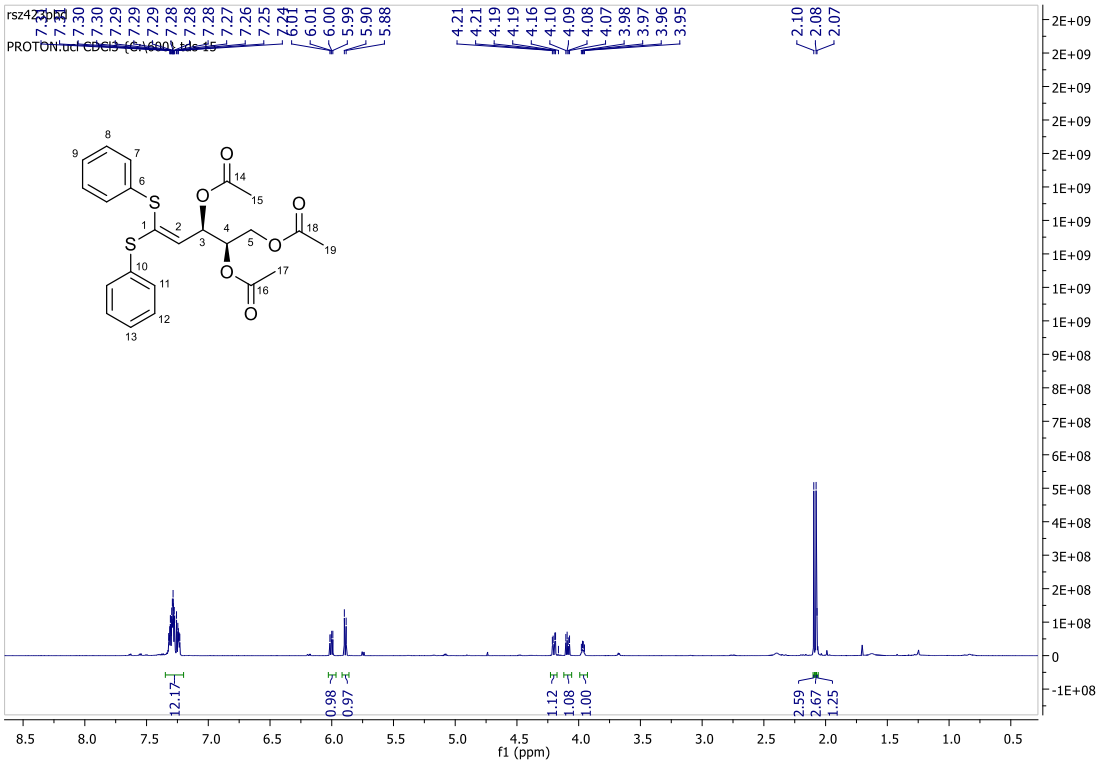



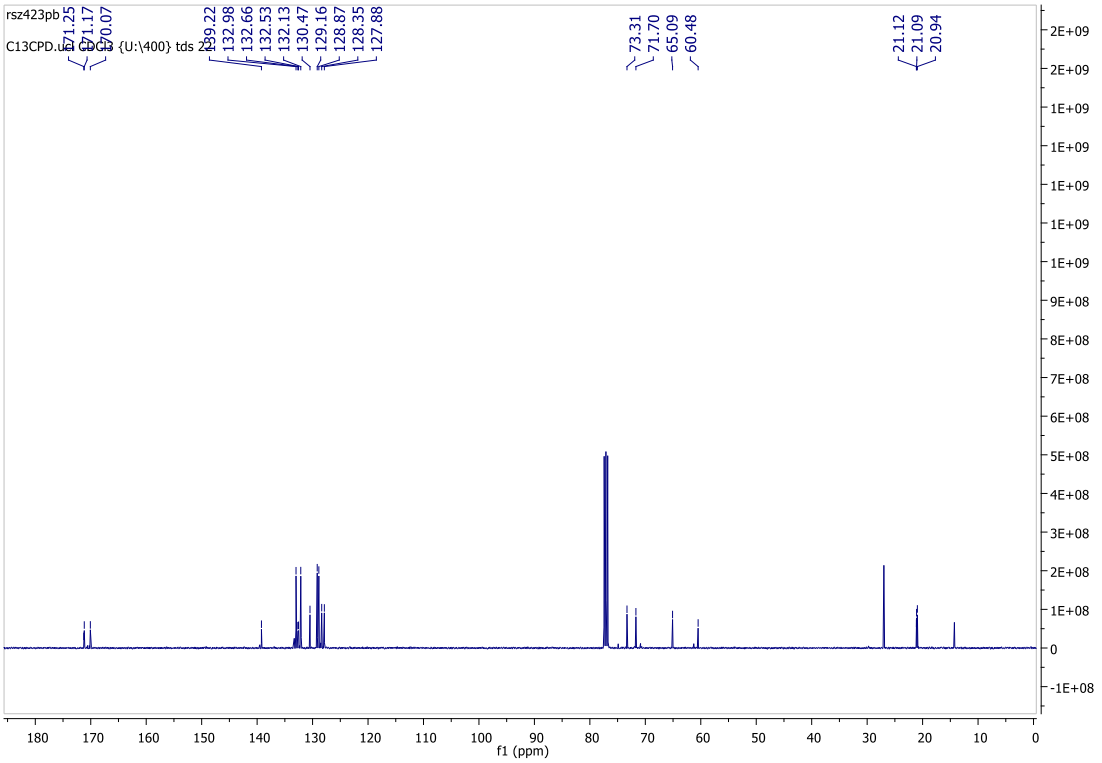
D-Ribose diphenyldithioacetal ketene, (2R,3S)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triol [**115**]:



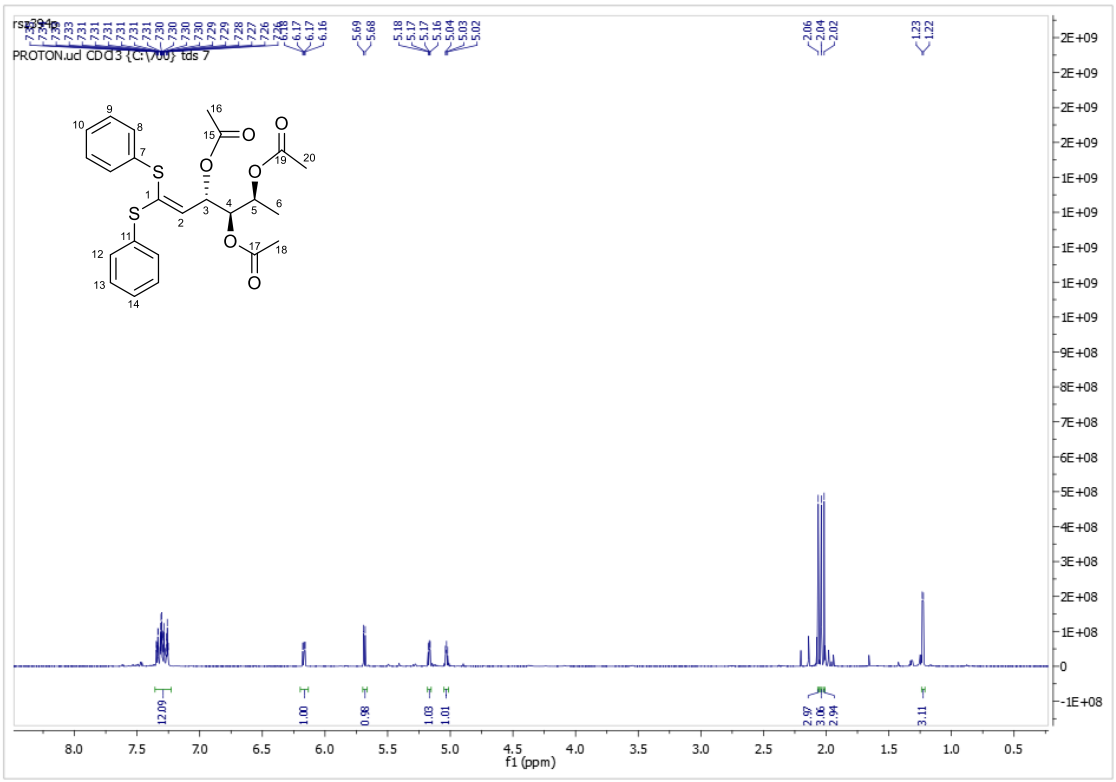



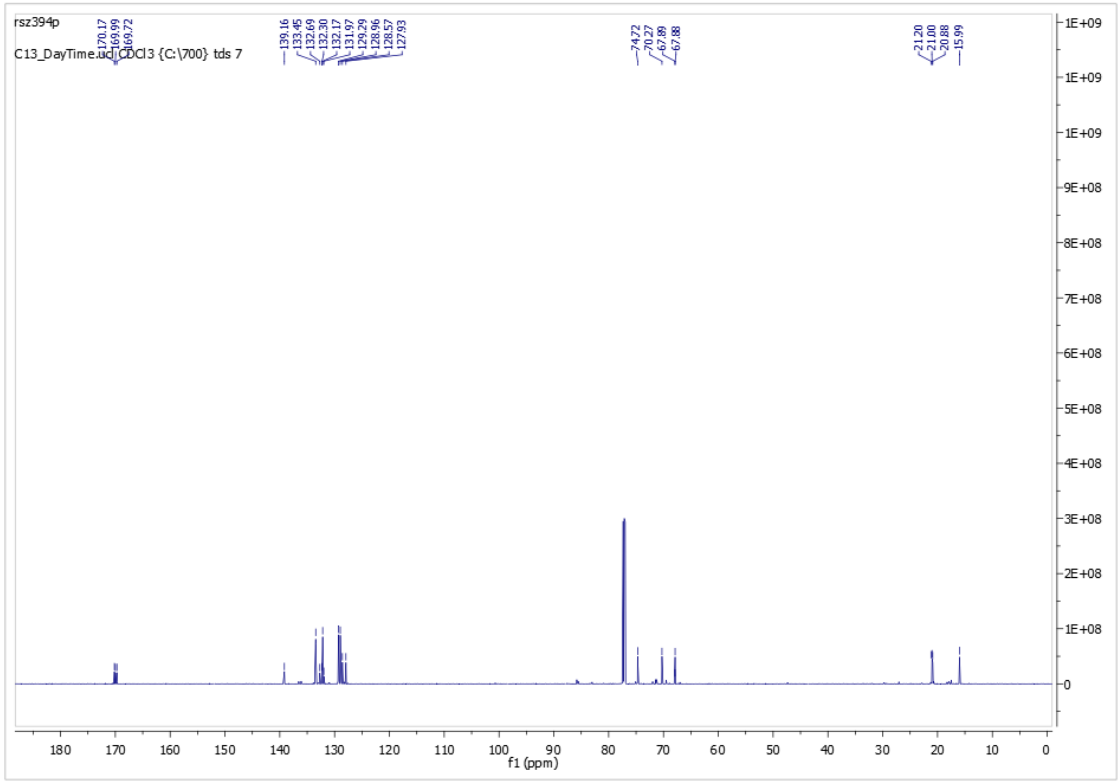
D-Lyxose diphenyldithioacetal ketene, (2*R*,3*R*)-5,5-bis(phenylthio)pent-4-ene-1,2,3-triyl triacetate [**116**]:



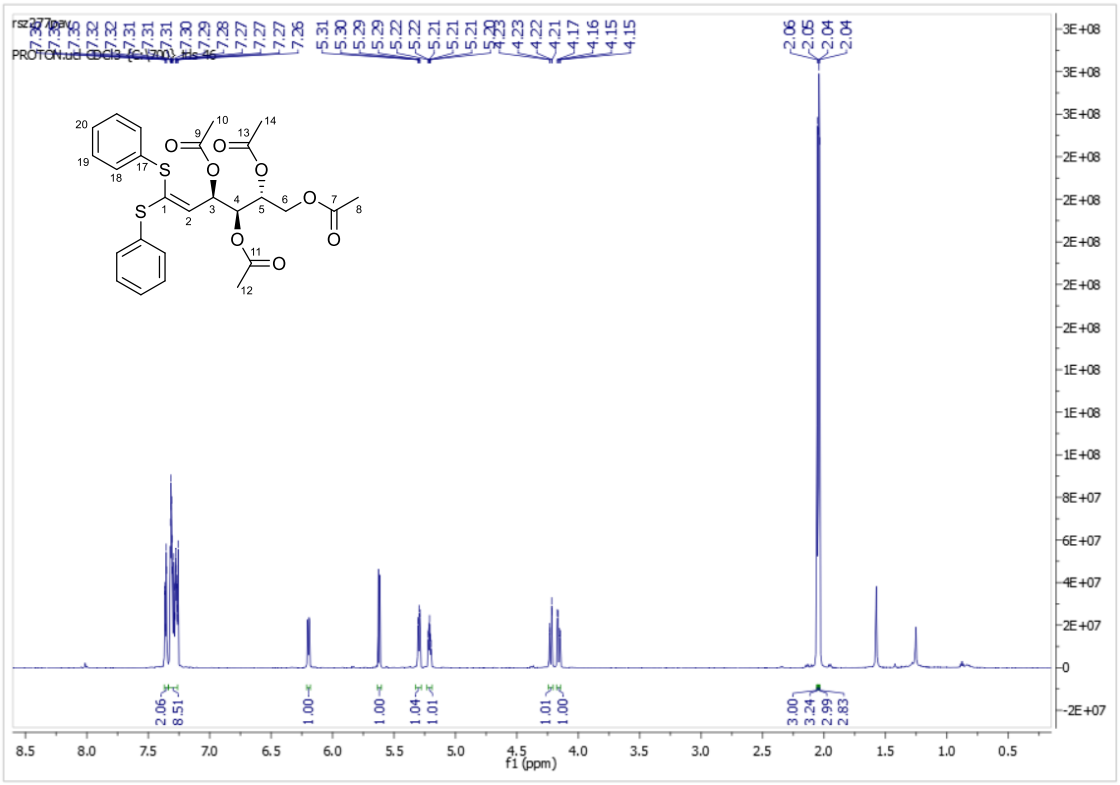



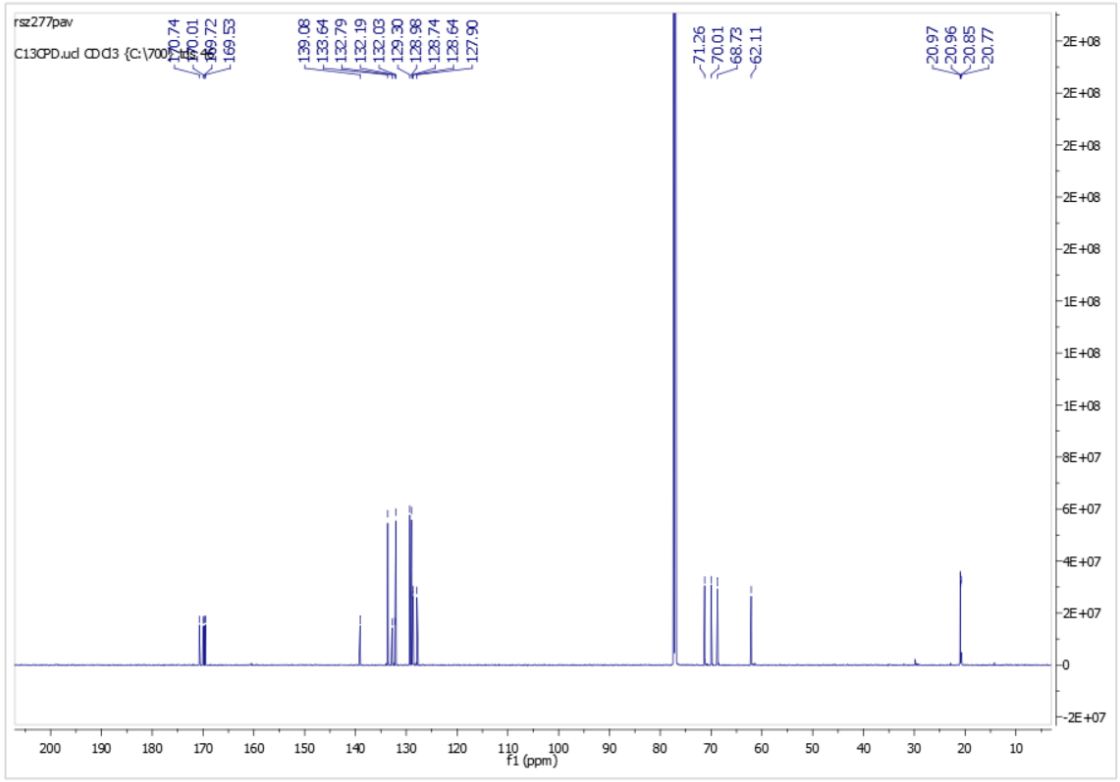
L-Rhamnose diphenyldithioacetal triacetate ketene, (2*S*,3*R*,4*S*)-6,6-bis(phenylthio)hex-5-ene-2,3,4-triyl triacetate [**117**]:



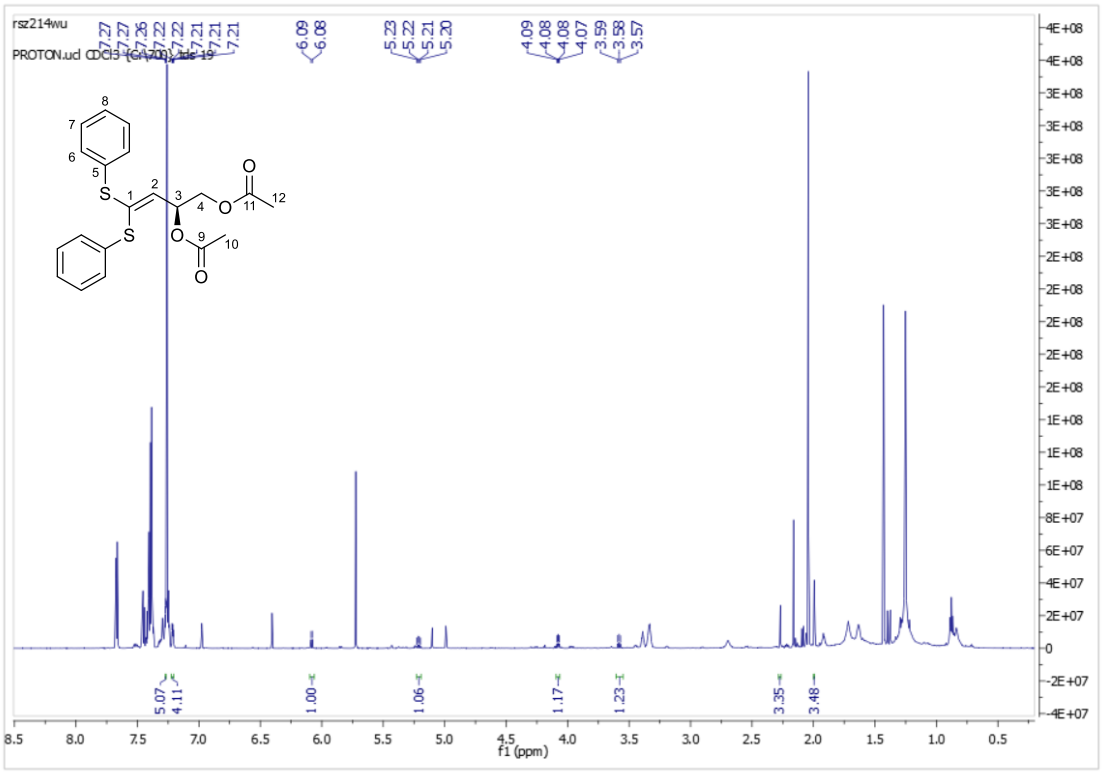



D-Mannose diphenylthioacetal tetraacetate ketene, (2*R*,3*S*,4*R*)-6,6-bis(phenylthio)hex-5-ene-1,2,3,4-tetrayl tetraacetate [**118**]:

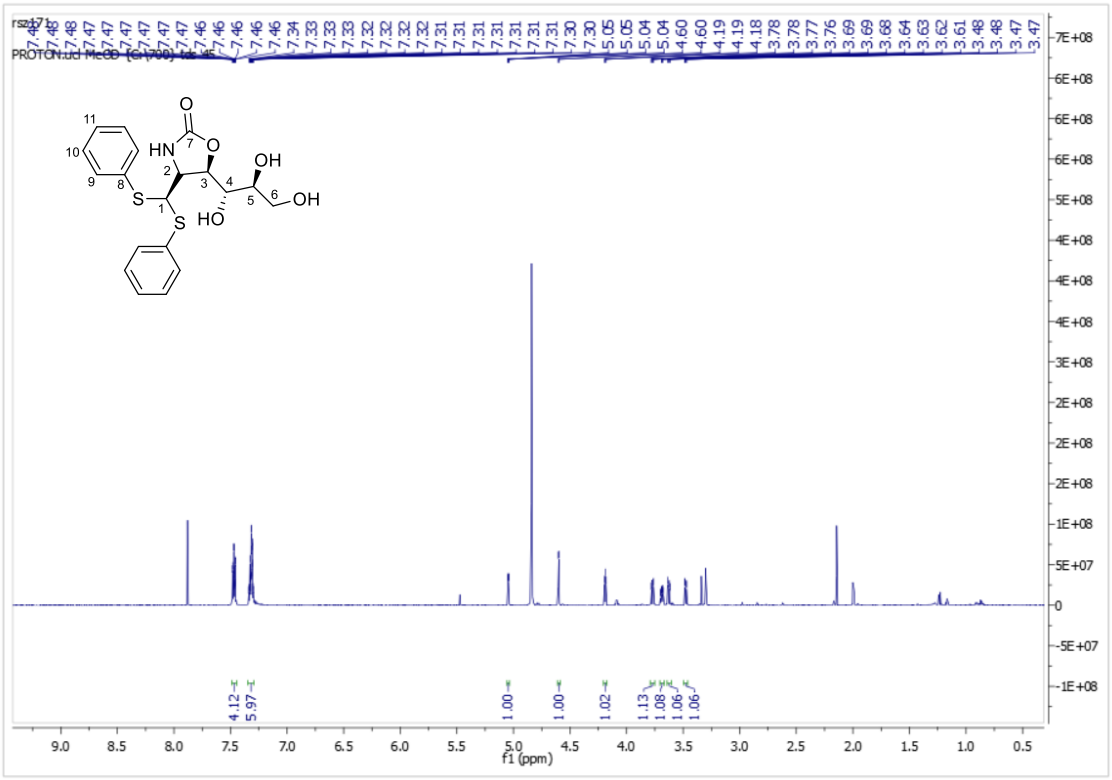


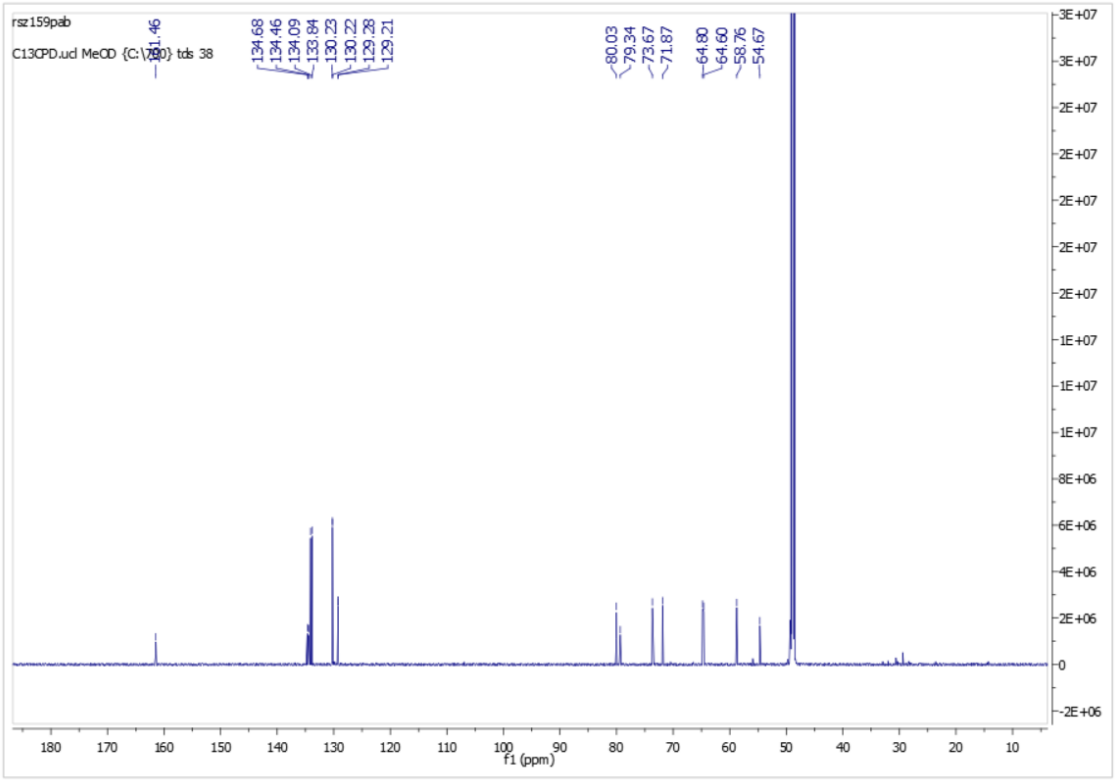



D-Erythrose diphenylthioacetal triacetate ketene, (*S*)-4,4-bis(phenylthio)but-3-ene-1,2-diyl diacetate [**119**]**:**

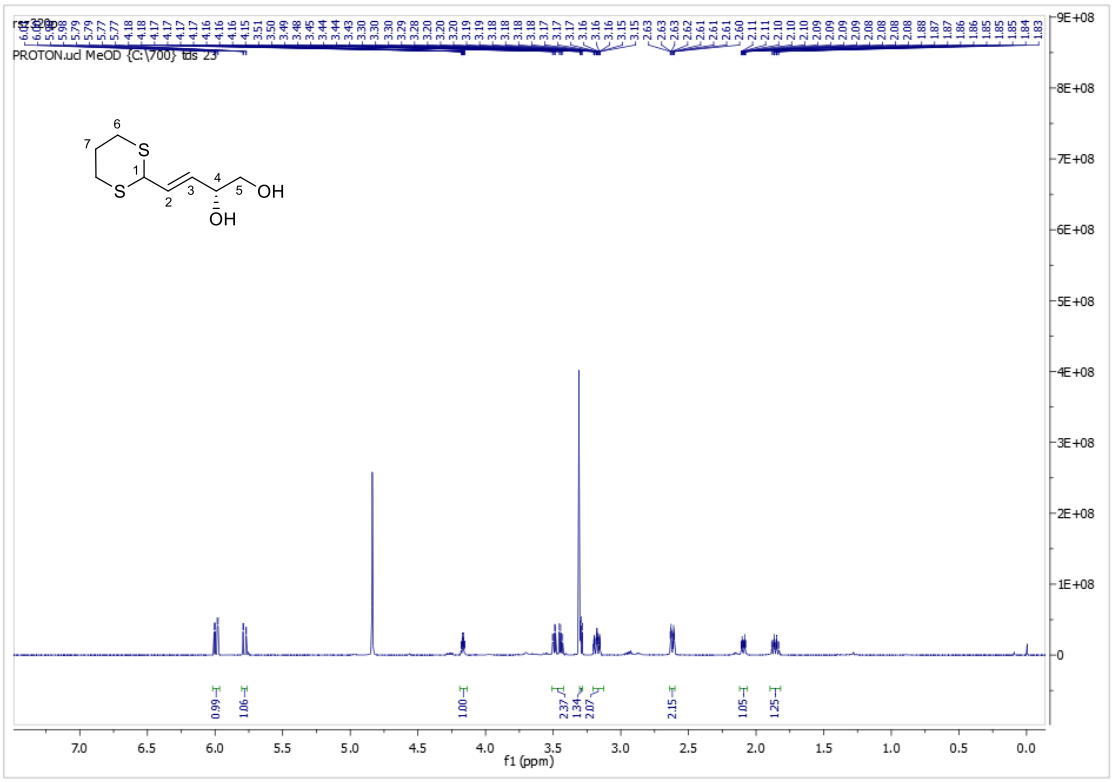


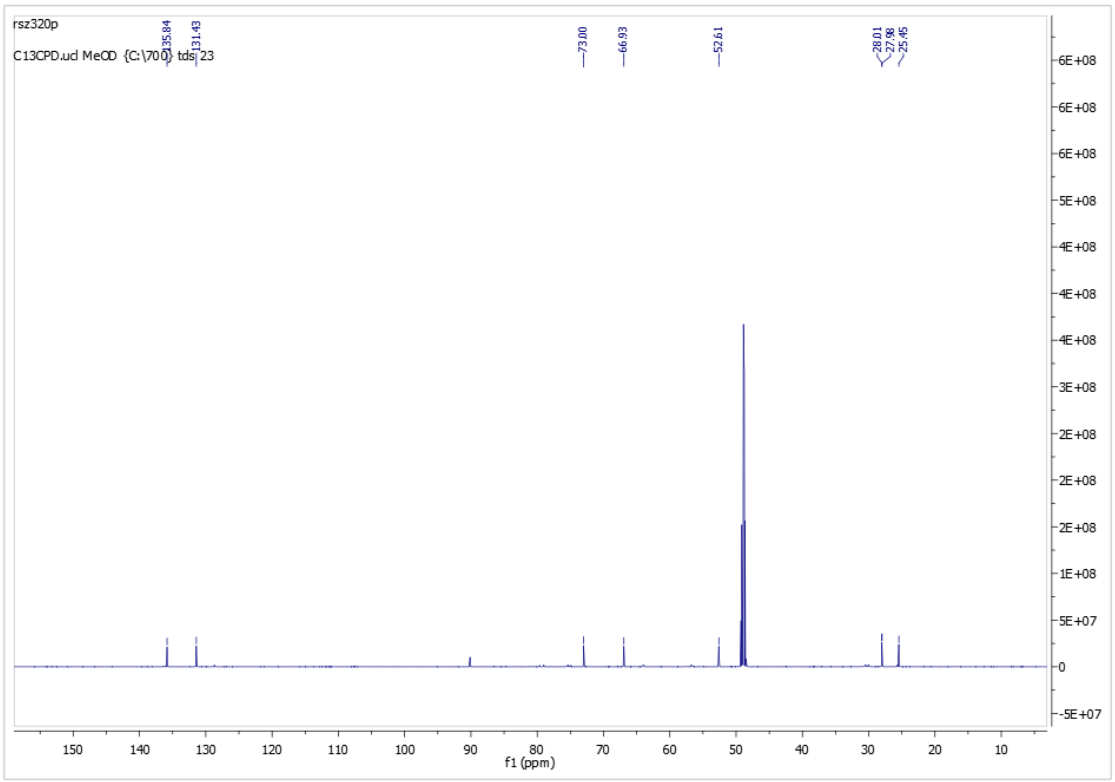
*N*-Acetyl glucosamine carbamate, (4*R*,5*R*)-4-(bis(phenylthio)methyl)-5-((1*S*,2*S*)-1,2,3-trihydroxypropyl)oxazolidin-2-one [**120**]:



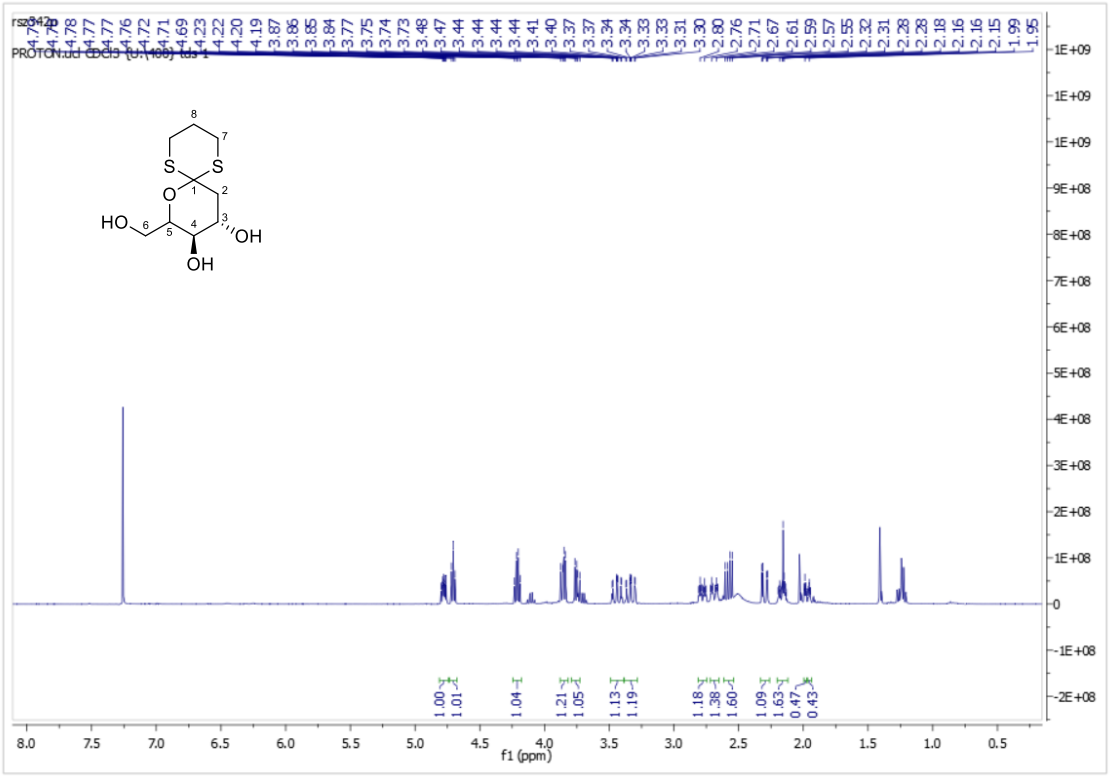



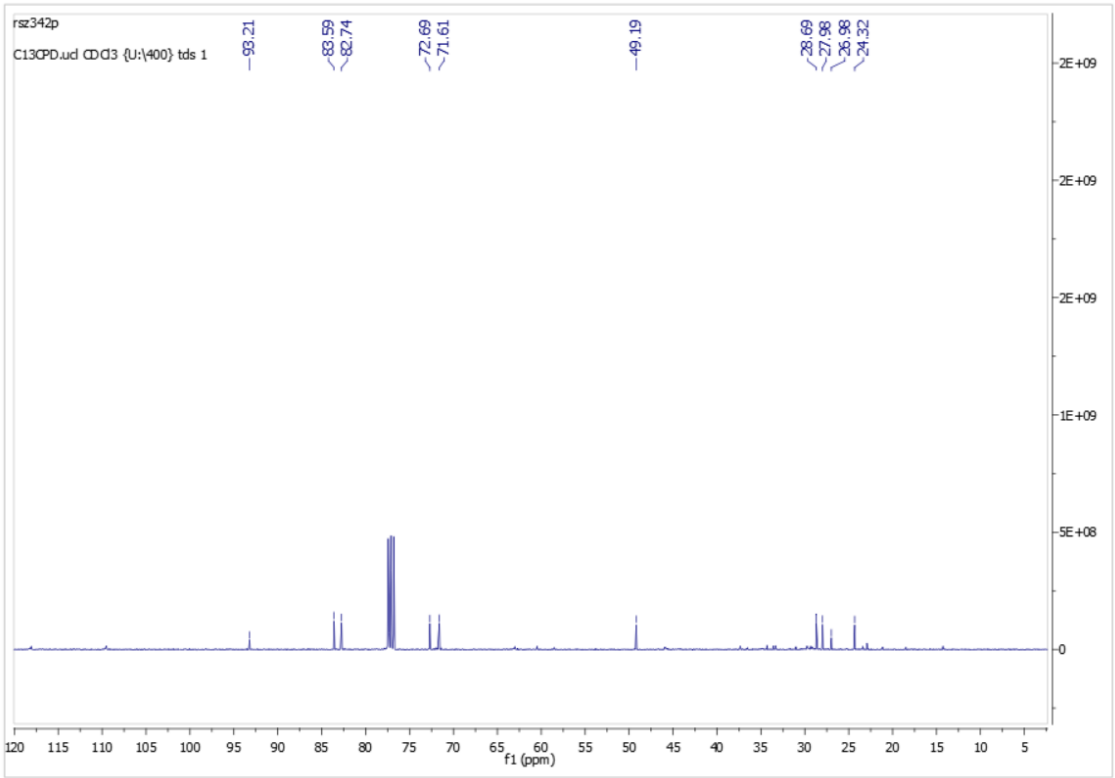
L-Arabinose 1,3-dithiane alkene, (*R*,*E*)-4-(1,3-dithian-2-yl)but-3-ene-1,2-diol [**122**]:



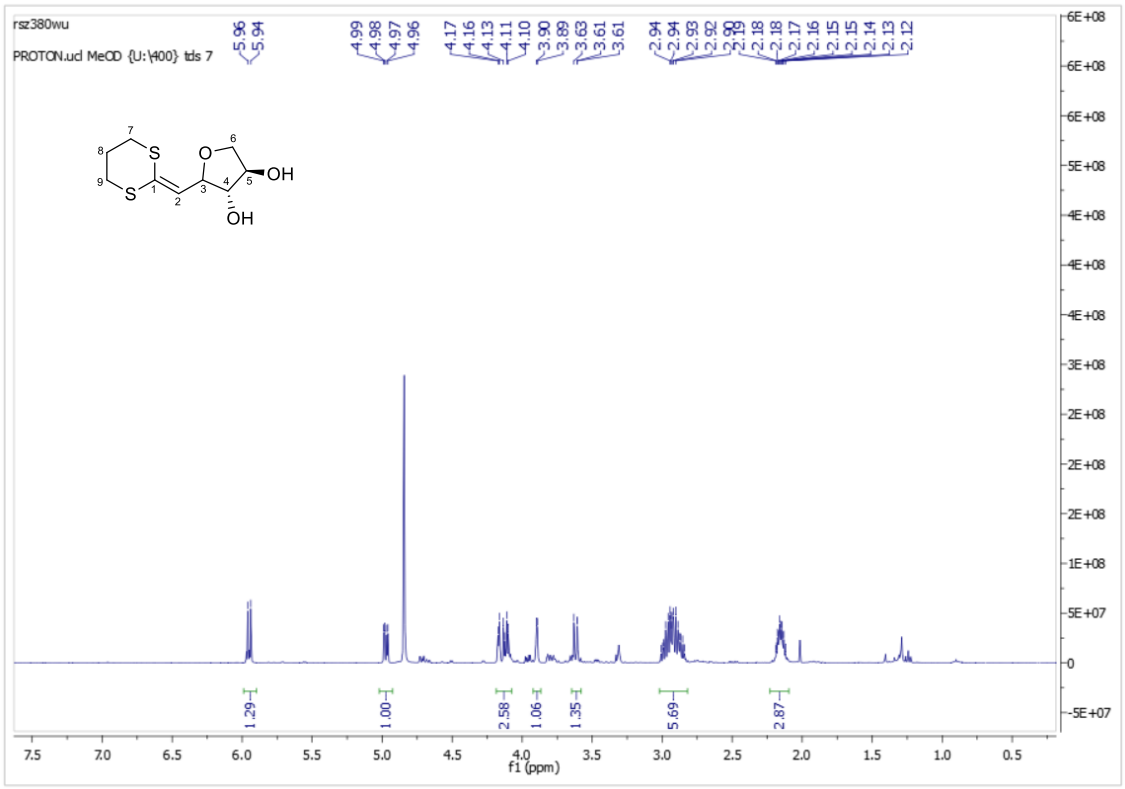



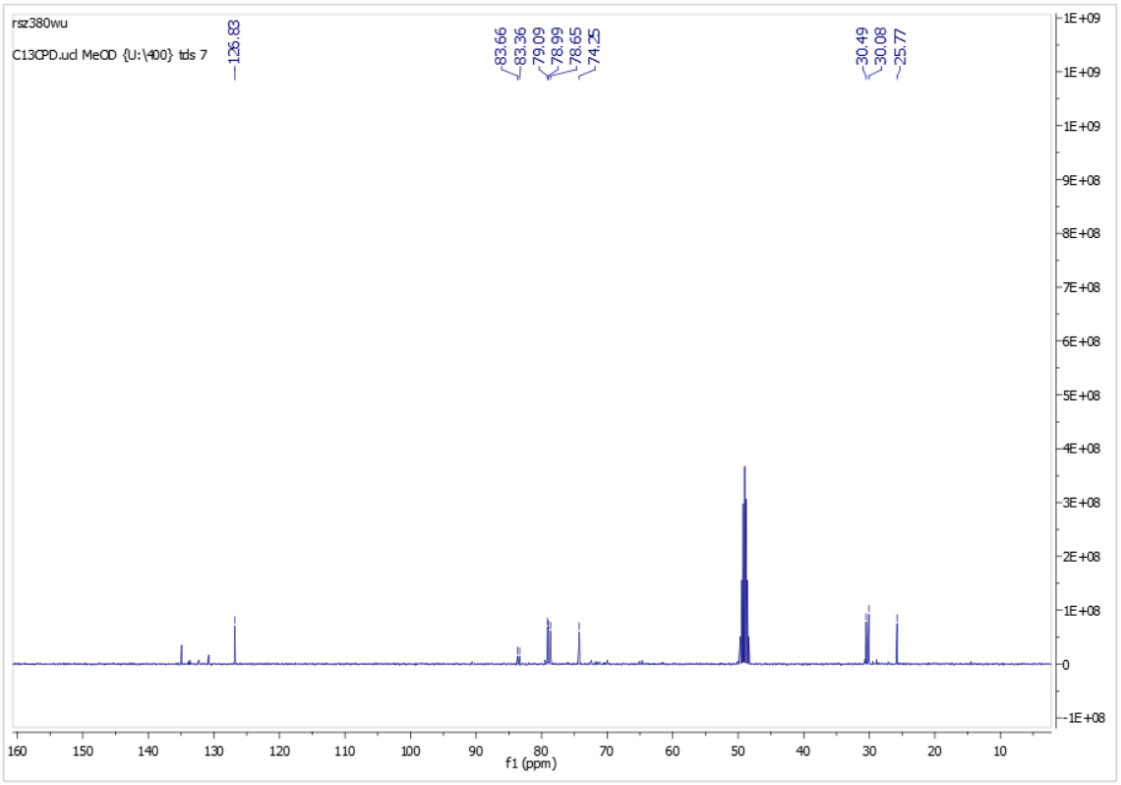
8-(Hydroxymethyl)-7-oxa-1,5-dithiaspiro[5.5]undecane-9,10-diol [**123**]:



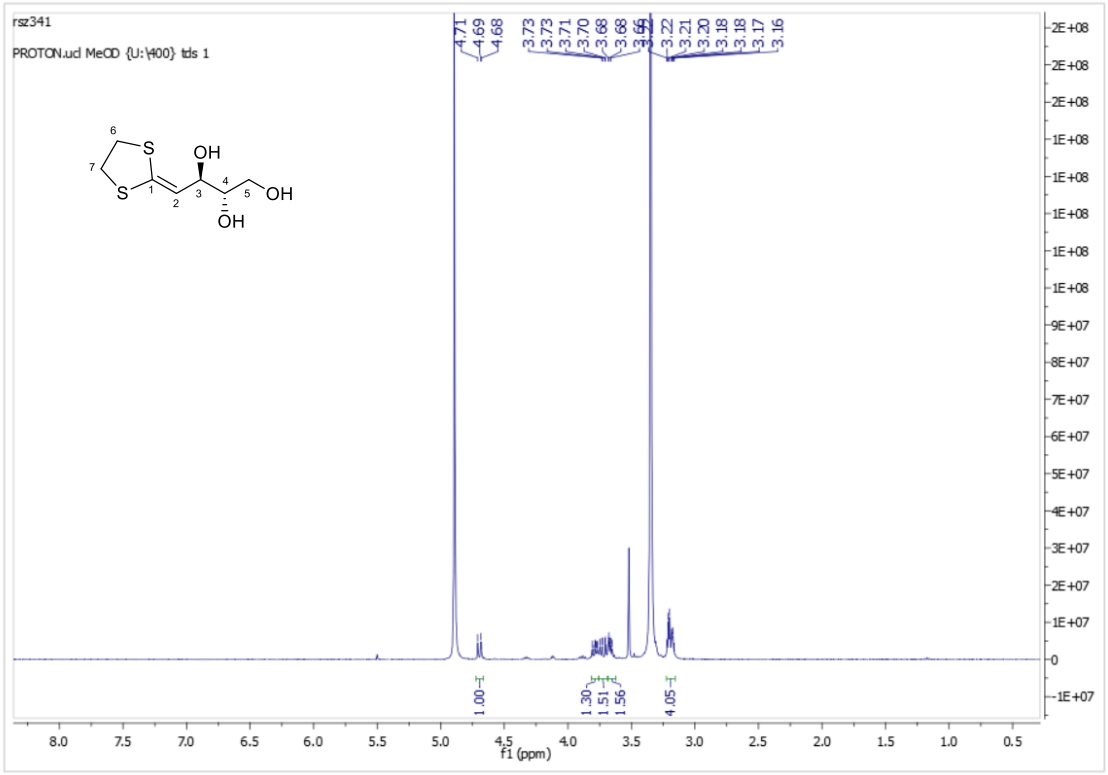



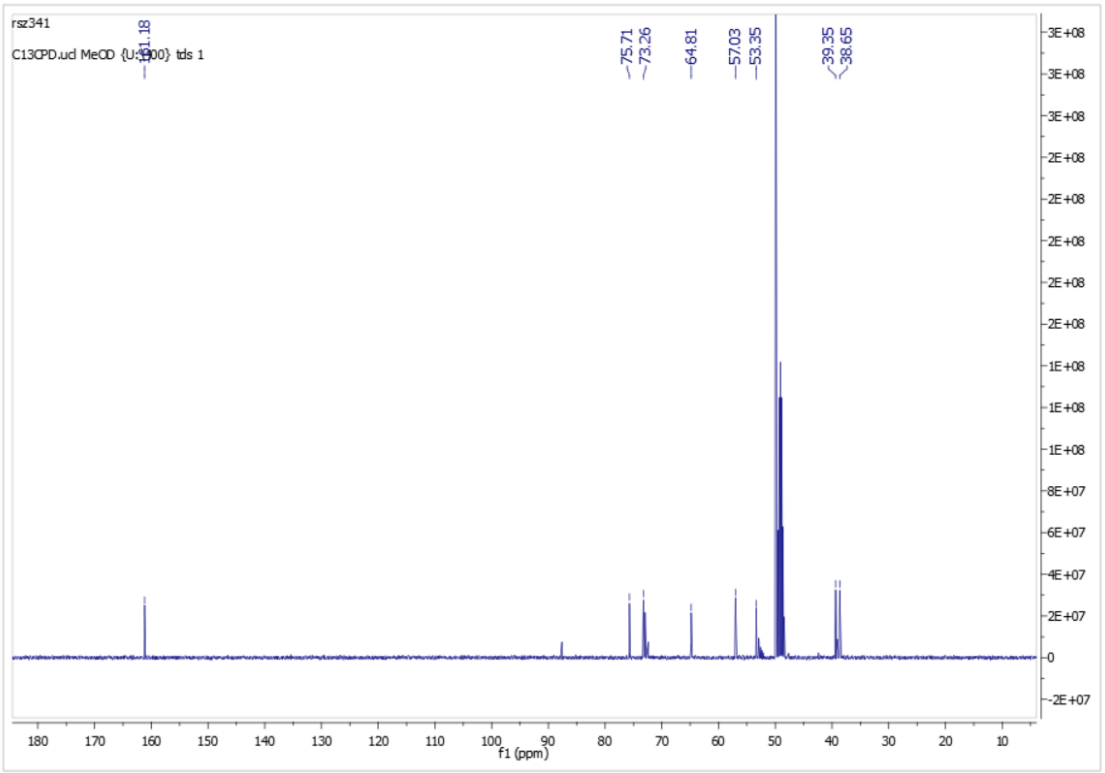
(3*S*,4*R*)-2-((1,3-Dithian-2-ylidene)methyl)tetrahydrofuran-3,4-diol [**128**]:



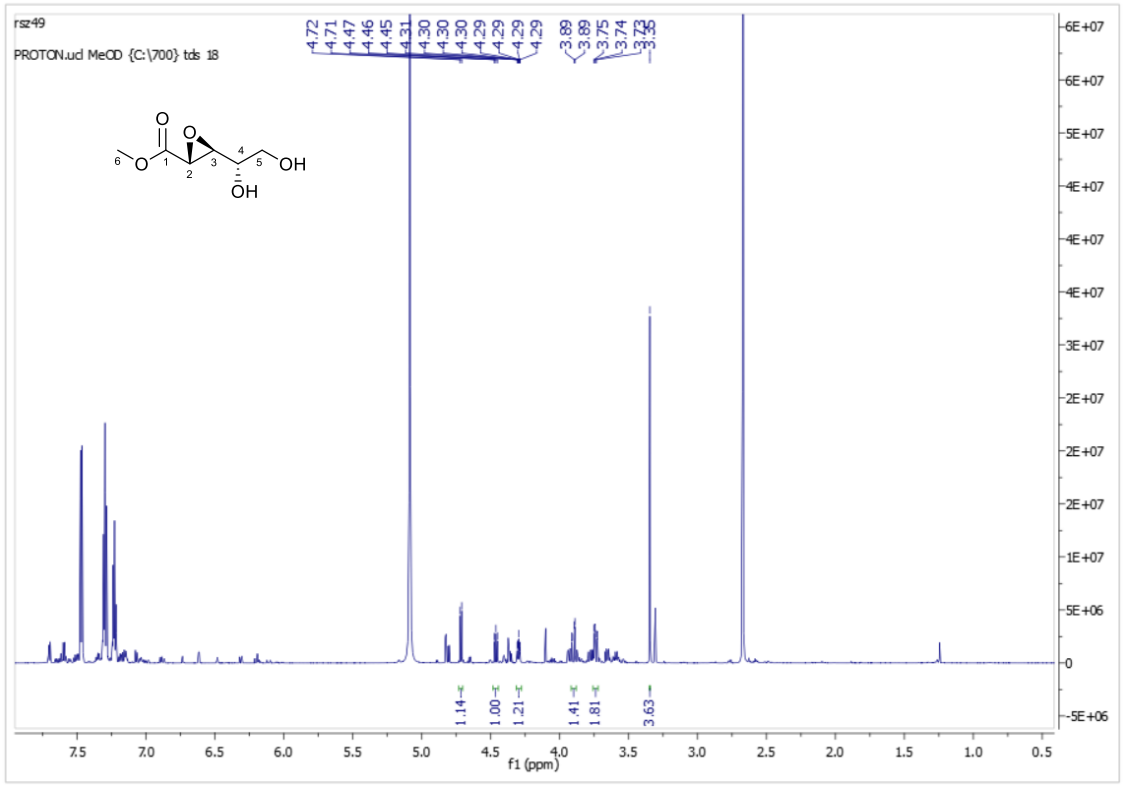



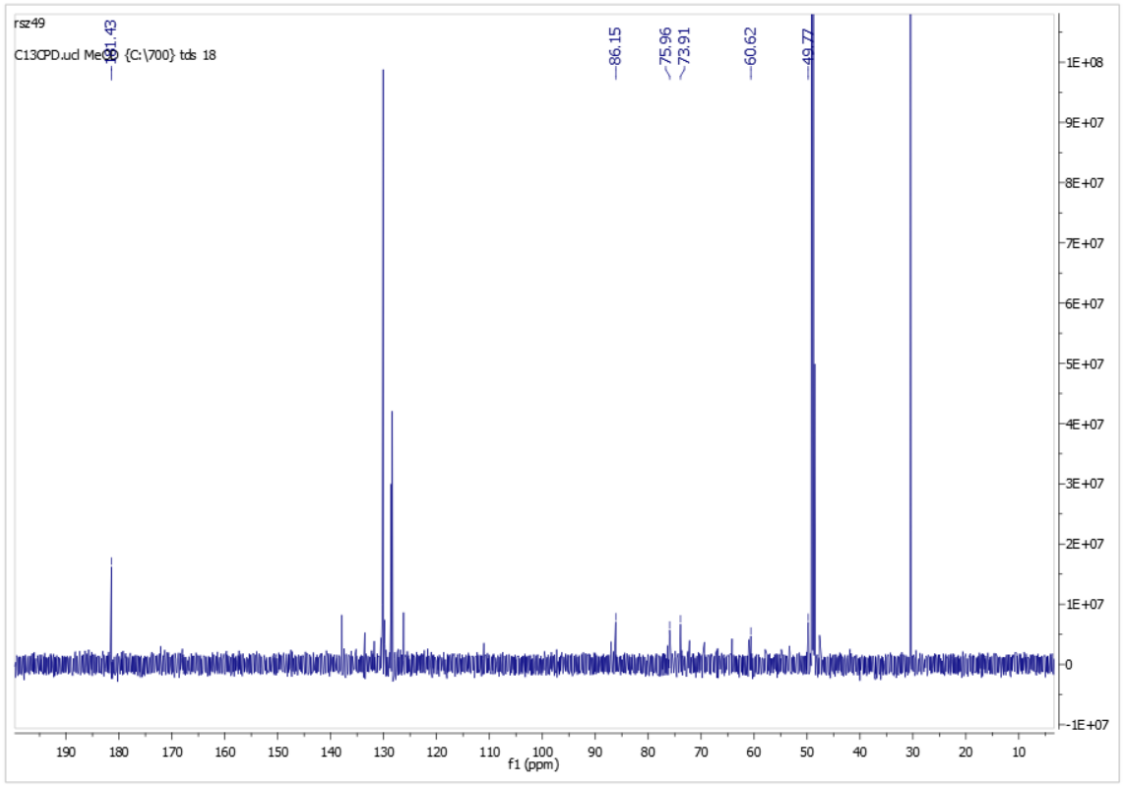
(2*S*,3*R*)-4-(1,3-Dithiolan-2-ylidene)butane-1,2,3-triol [**129**]:



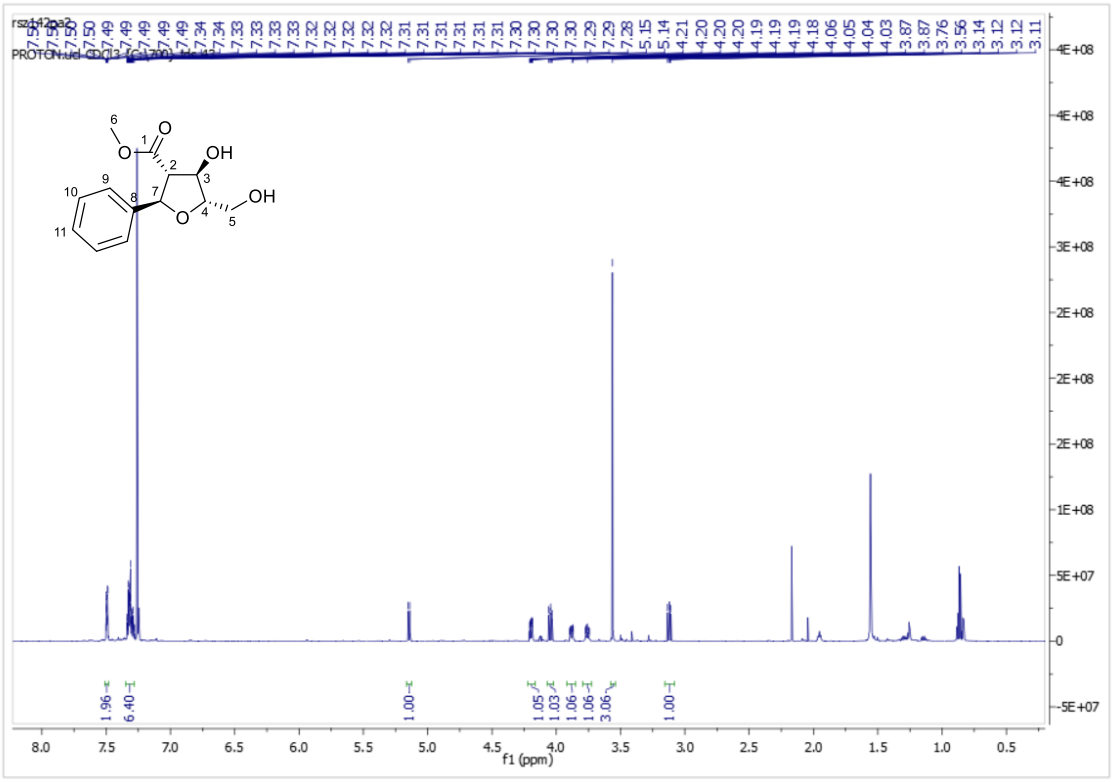



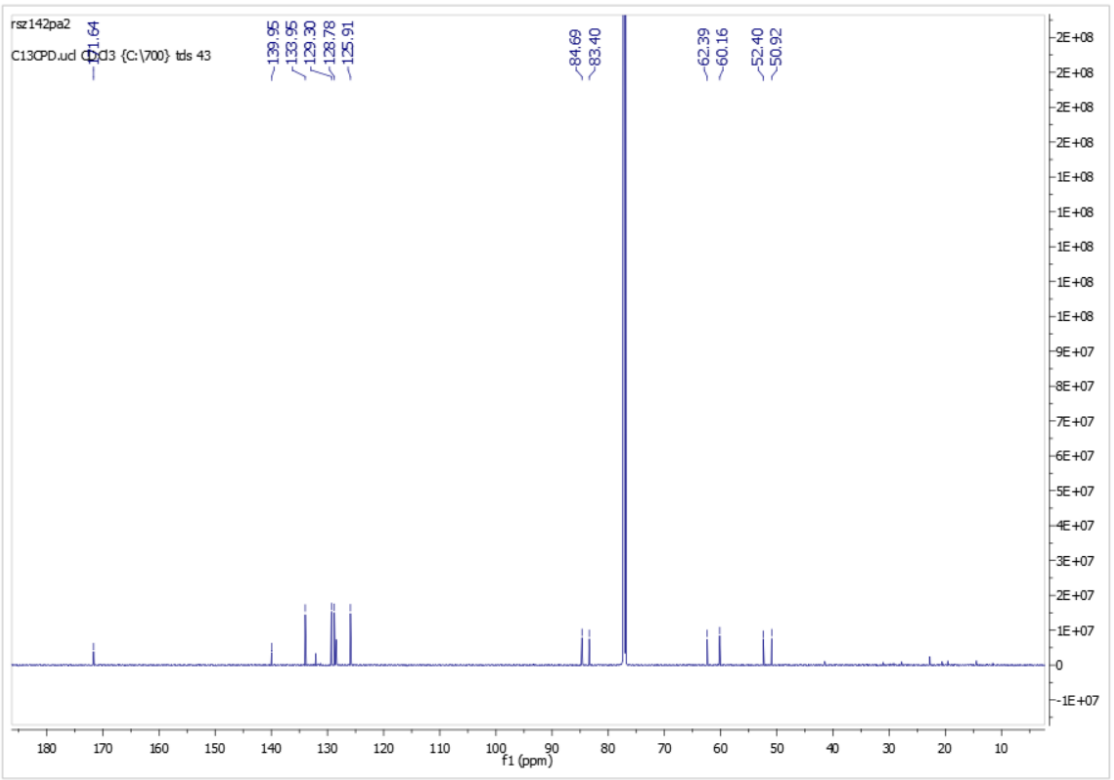
Methyl (2*R*,3*R*)-3-((*S*)-1,2-dihydroxyethyl)oxirane-2-carboxylate [**138**]:



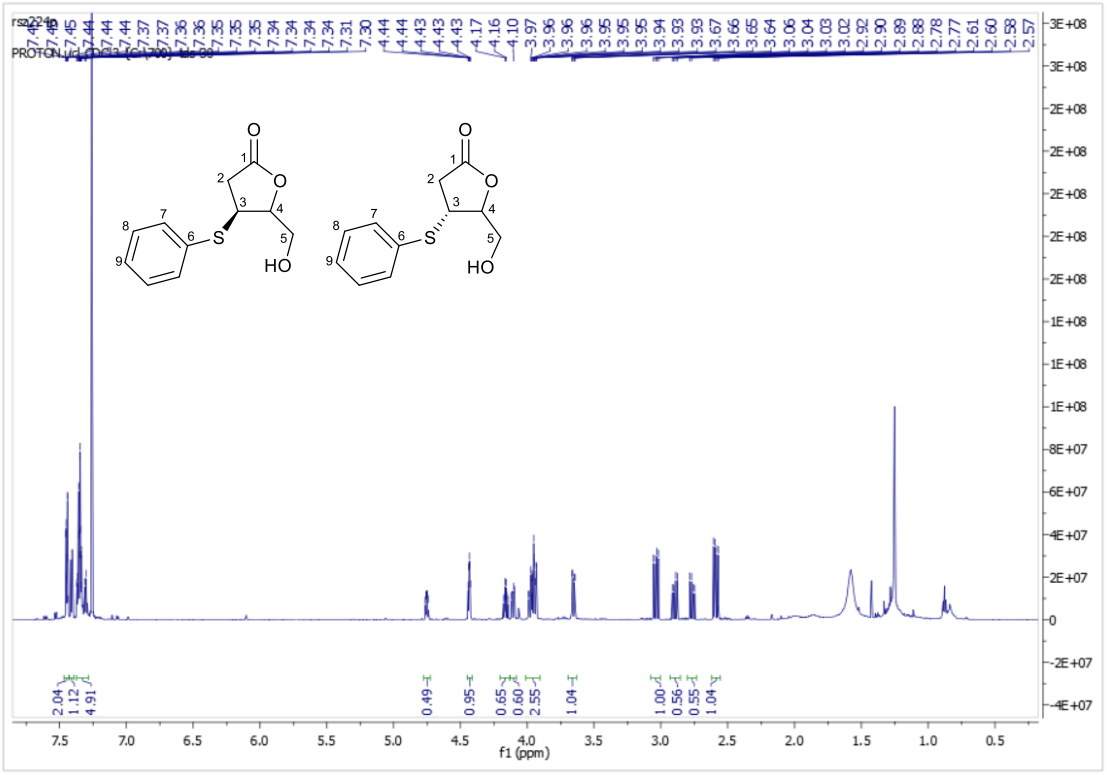



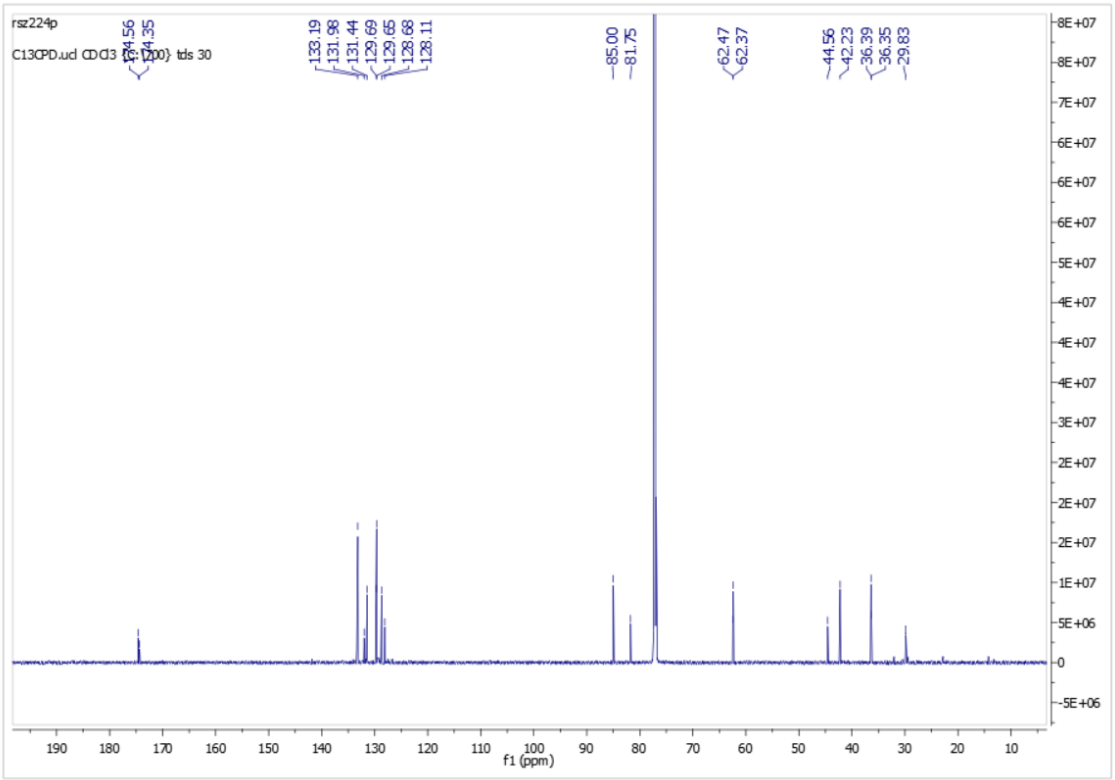
Methyl-(2*R*,3*R*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)-2-phenyltetrahydro furan-3-carboxylate [**141**]:



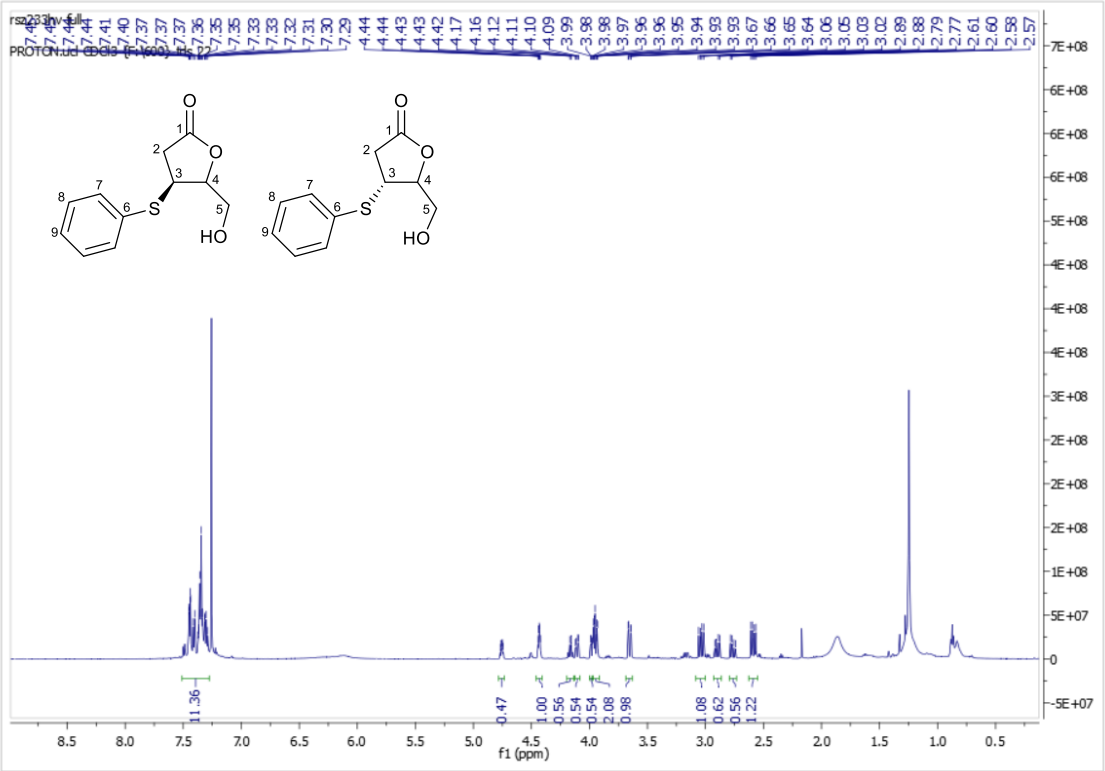



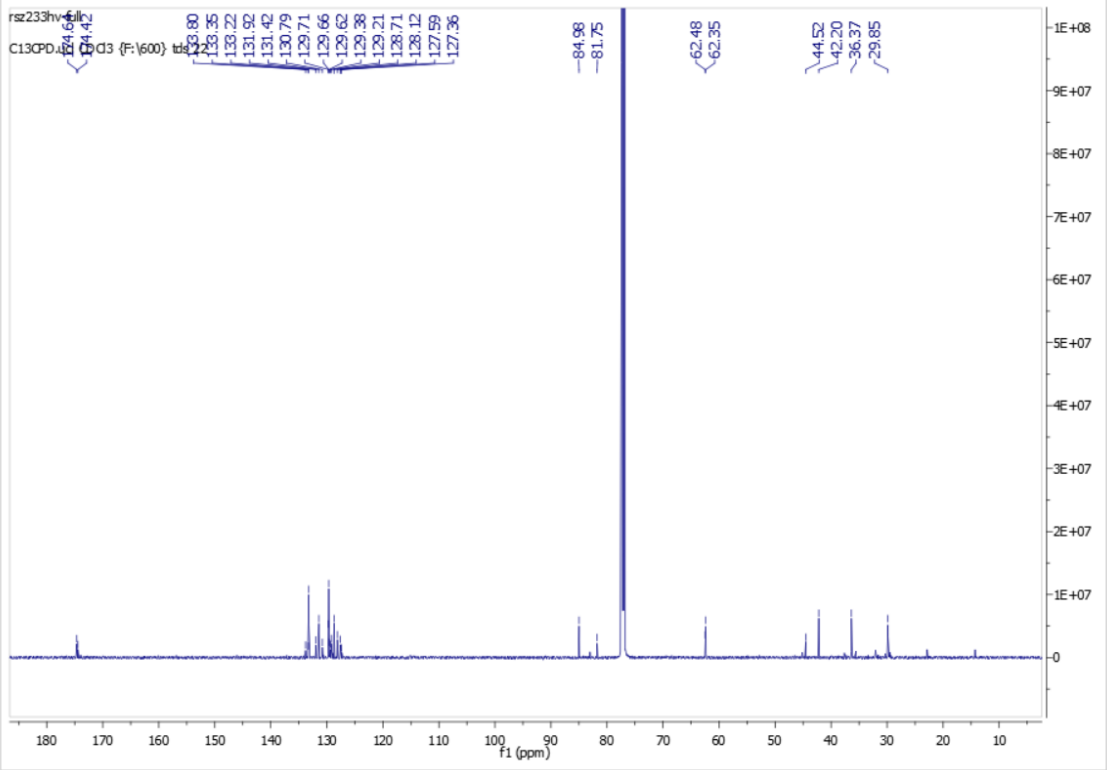
(4*S*)-5-(Hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one, (4*R*)-5-(hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one via $Et_3SiH$ [**145**, **146**]:



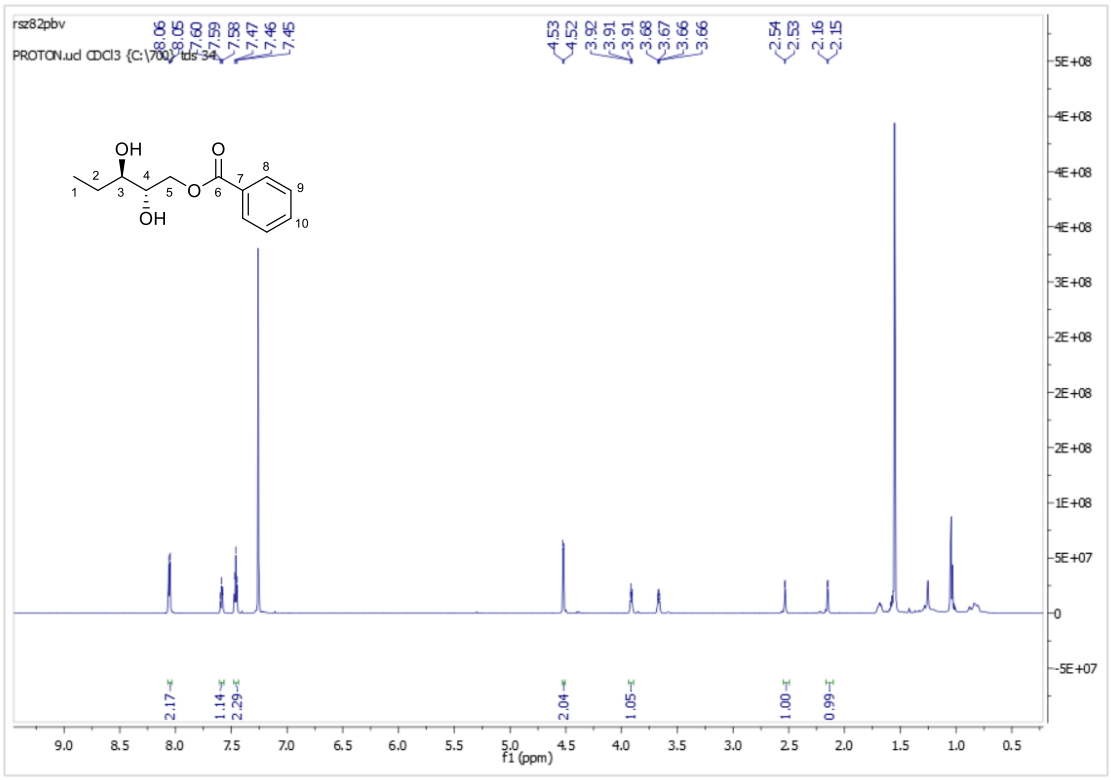



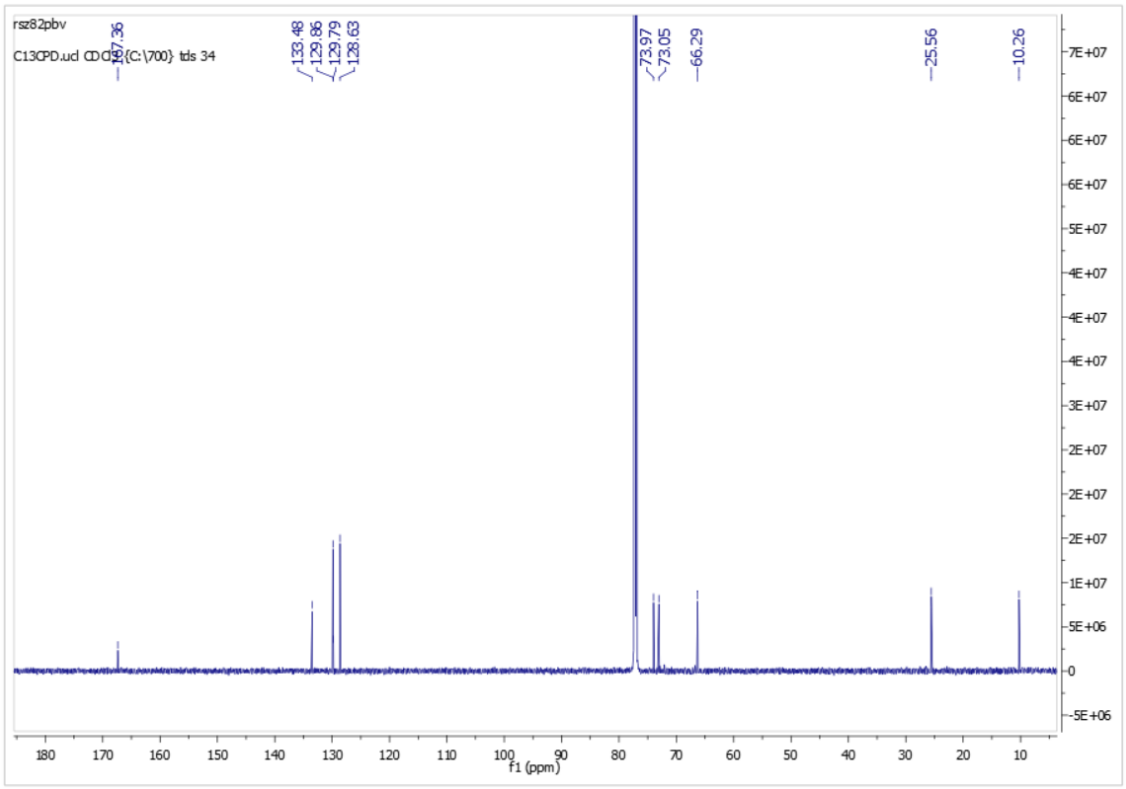
(4*S*)-5-(Hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one, (4*R*)-5-(hydroxymethyl)-4-(phenylthio)dihydrofuran-2(3H)-one via $In(OTf)_3$ [**145**, **146**]:



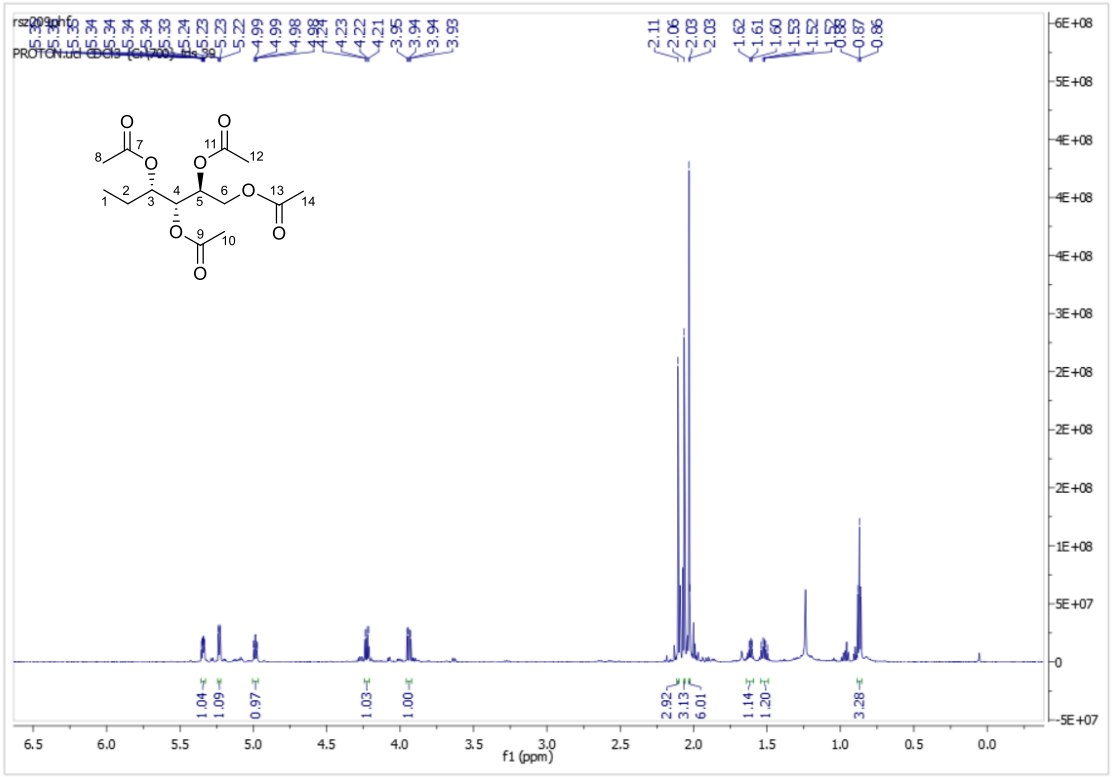



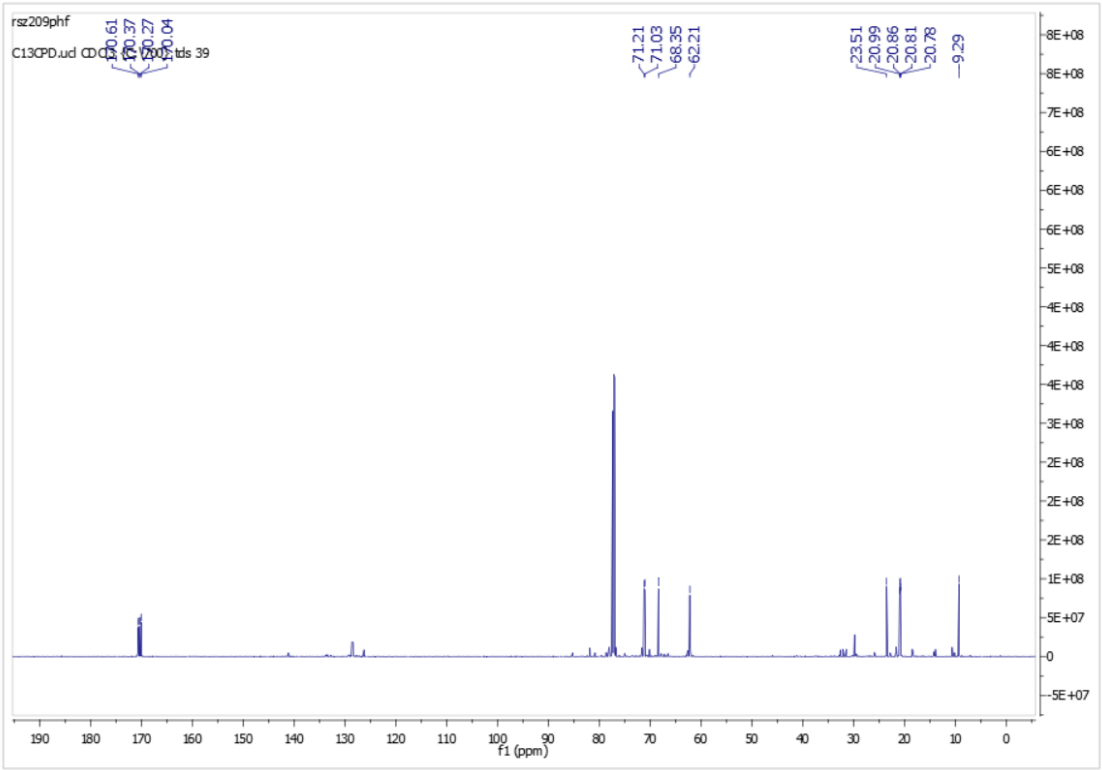
(2*S*,3*R*)-2,3-Dihydroxypentyl benzoate [**161**]:



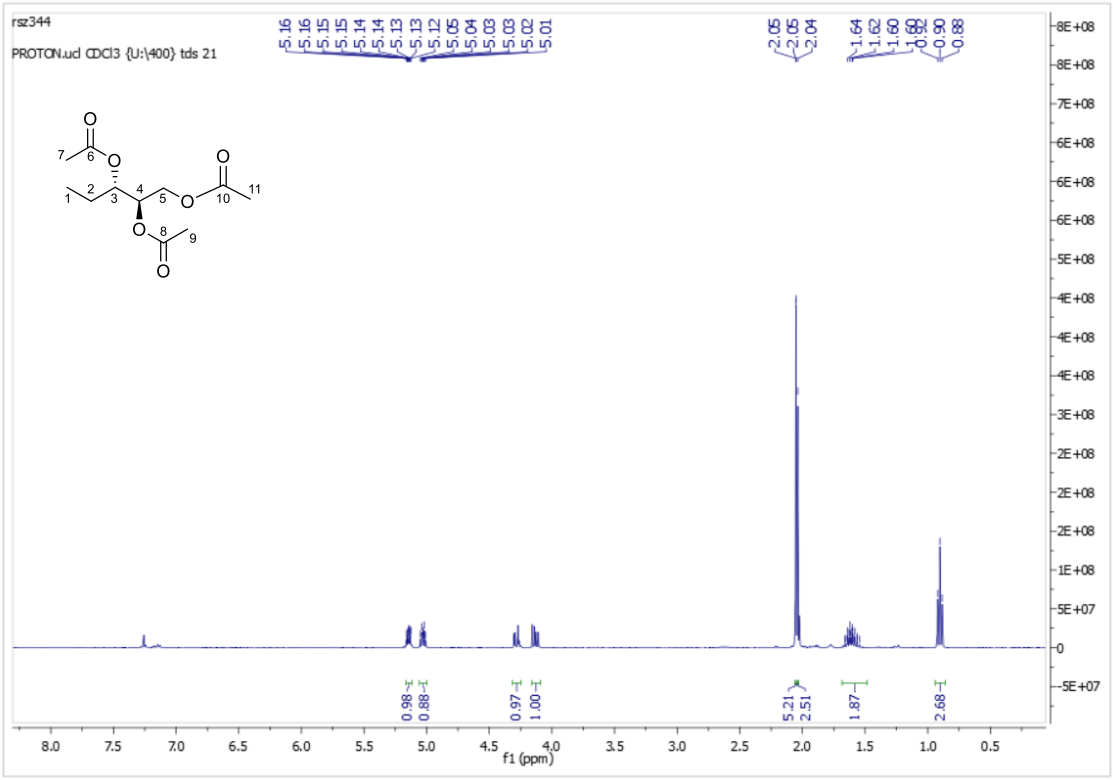



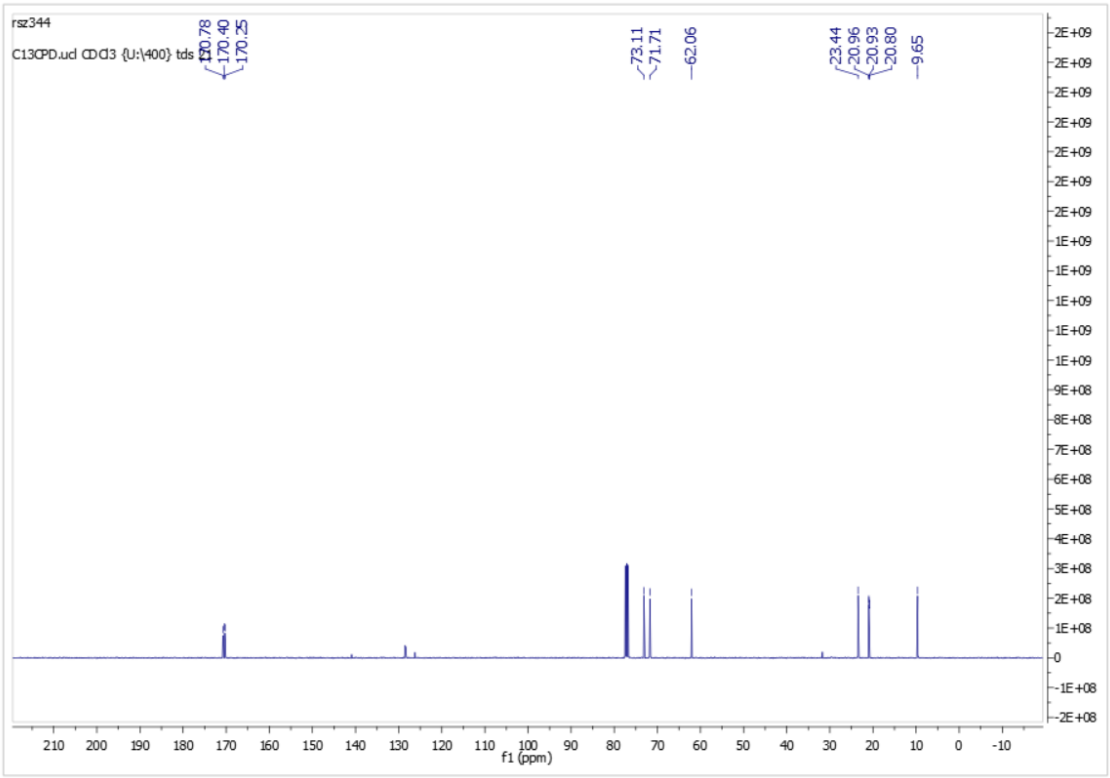
(2*R*,3*R*,4*R*)-Hexane-1,2,3,4-tetrayl tetraacetate [**164**]:



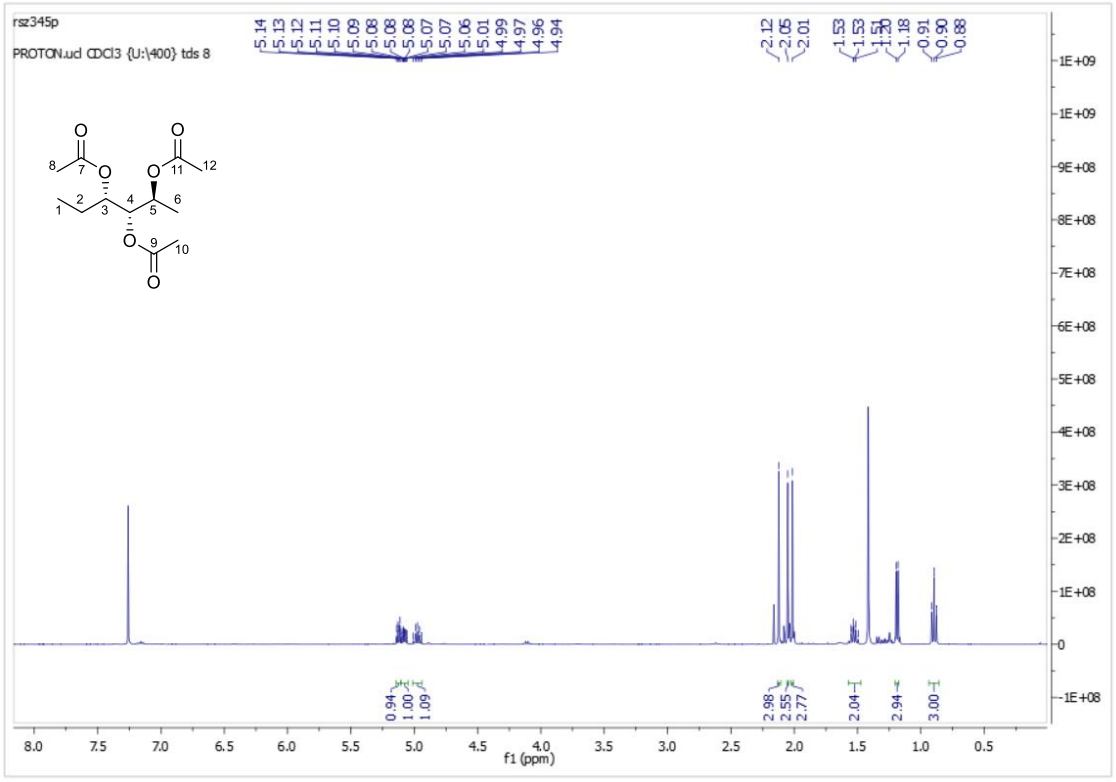



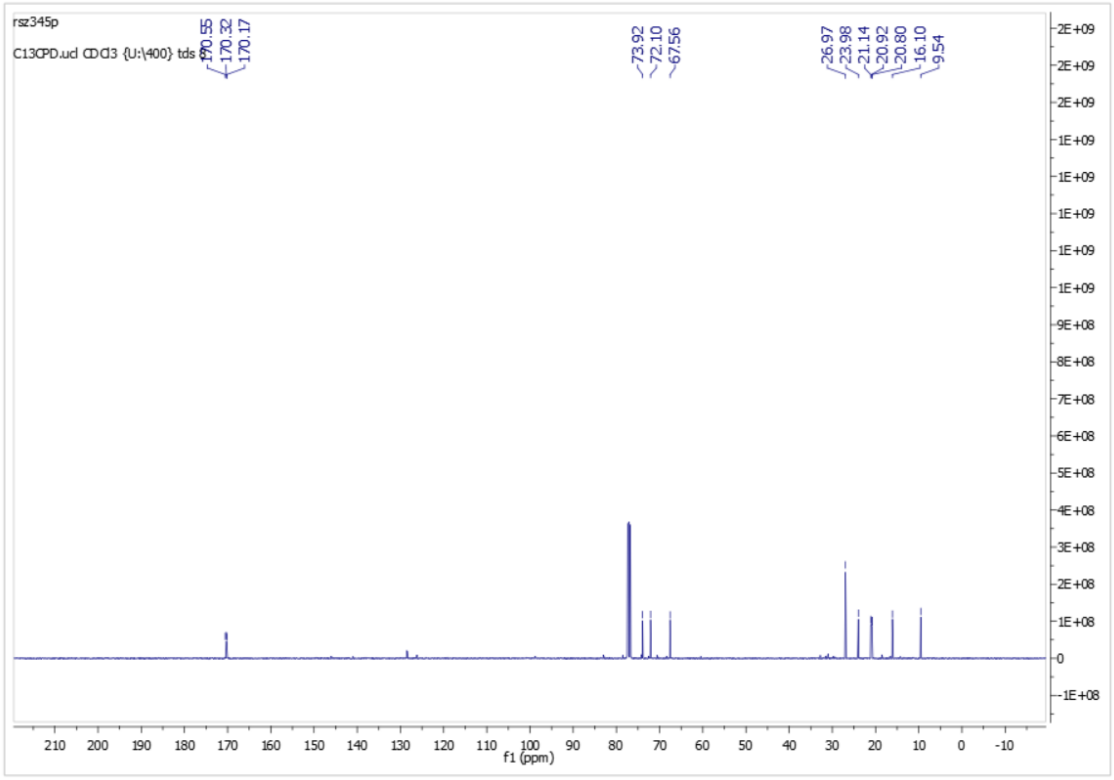
(2*R*,3*S*)-Pentane-1,2,3-triyl triacetate [**165**]:



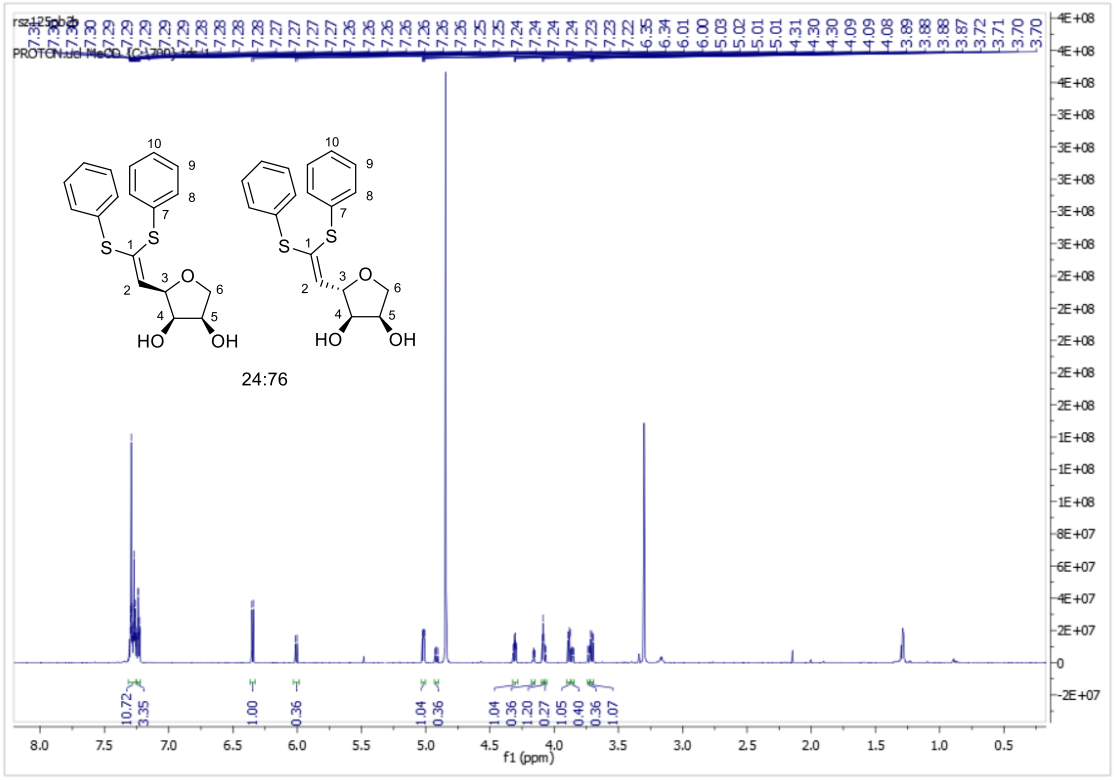



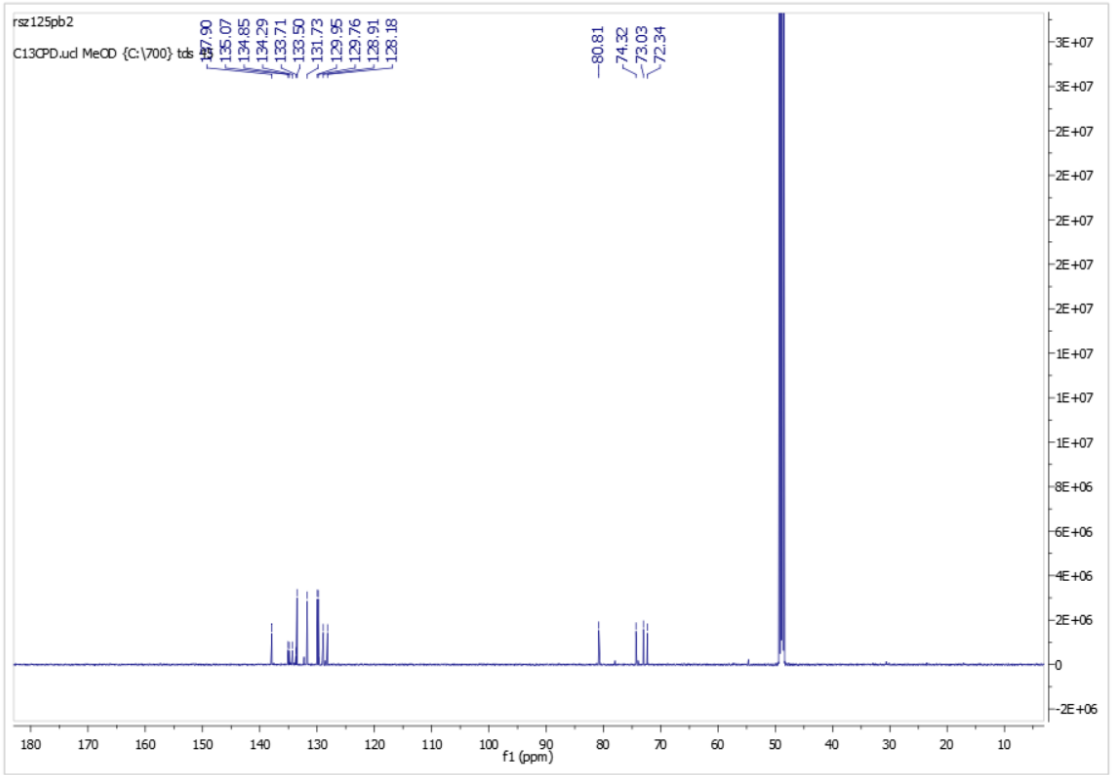
(2*S*,3*S*,4*S*)-Hexane-2,3,4-triyl triacetate [**166**]:



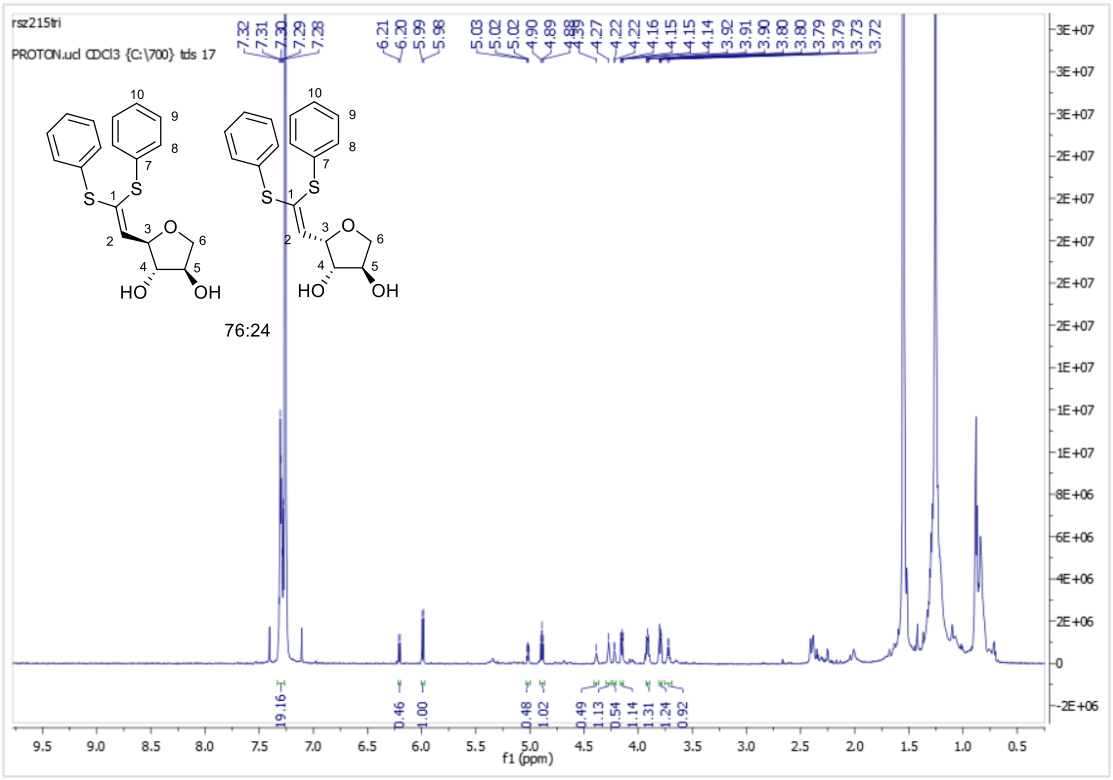



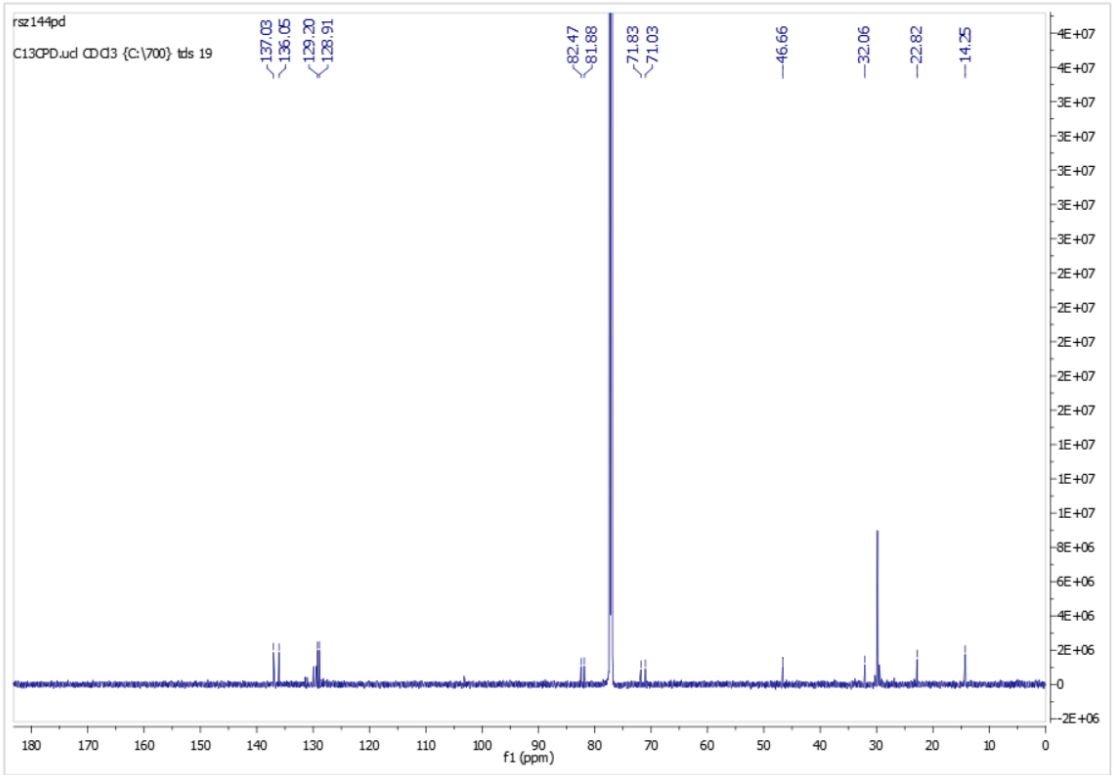
D-Glucose dithioacetal alkenyl THF, ((3*R*,4*R*)-2-(2,2,-bis(phenylthiol)vinyl) tetrahydrofuran-3,4-diol) [**127**]:



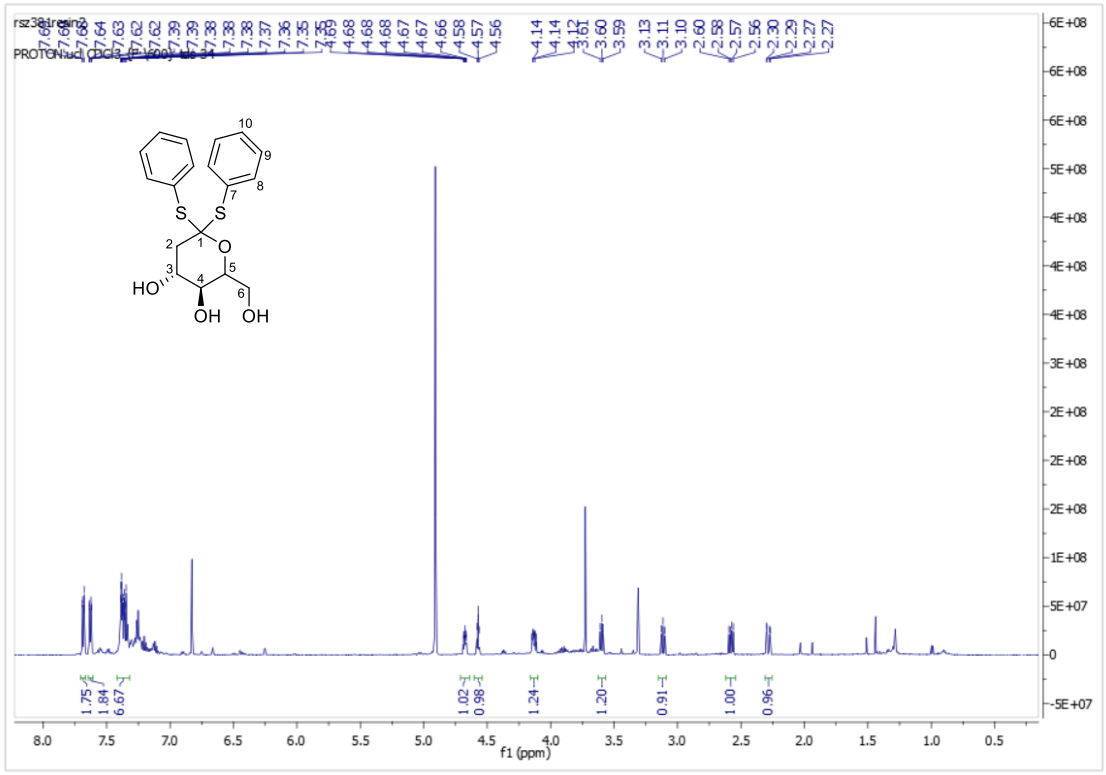



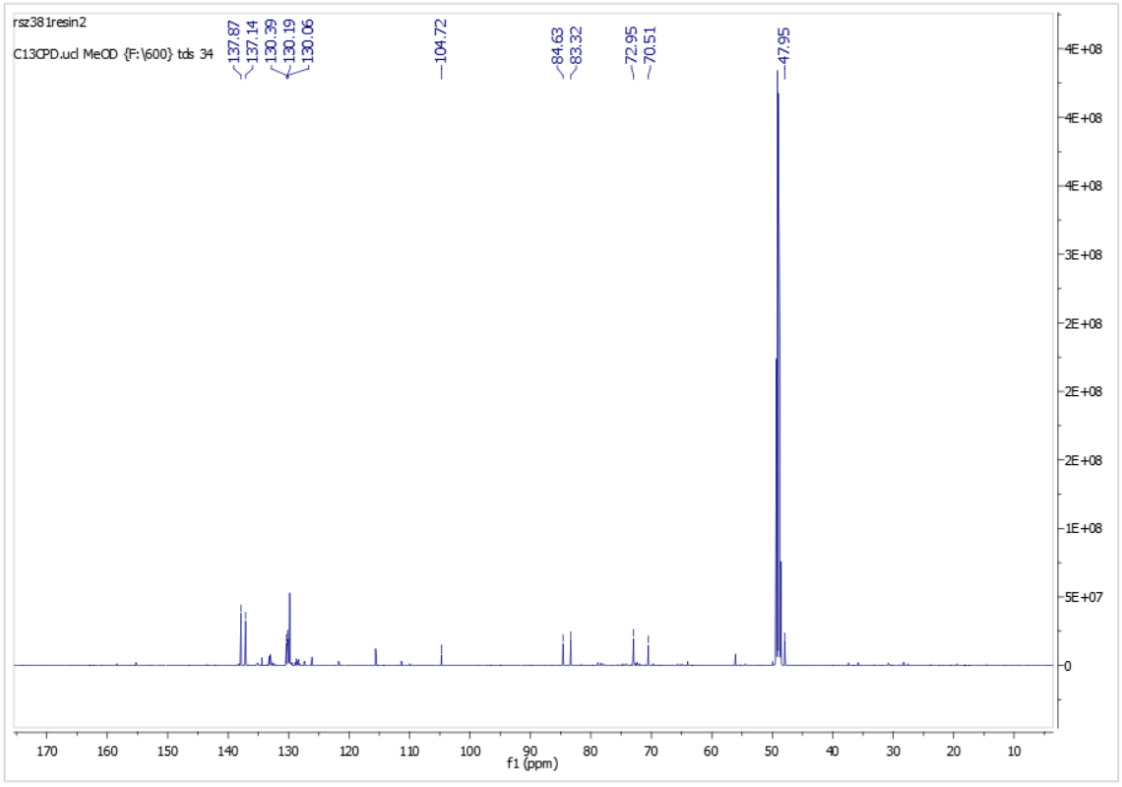
D-Glucose dithioacetal alkenyl THF, ((3*R*,4*R*)-2-(2,2,-bis(phenylthiol)vinyl) tetrahydrofuran-3,4-diol) via borate catalyst [**127**]:



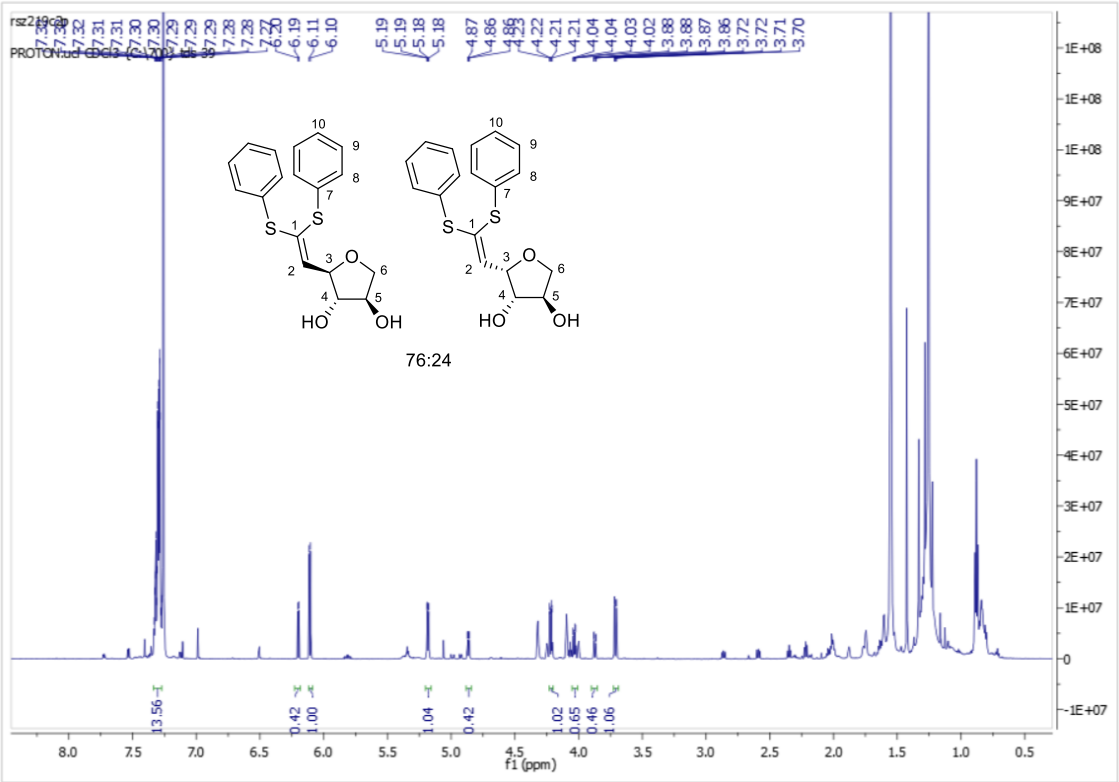



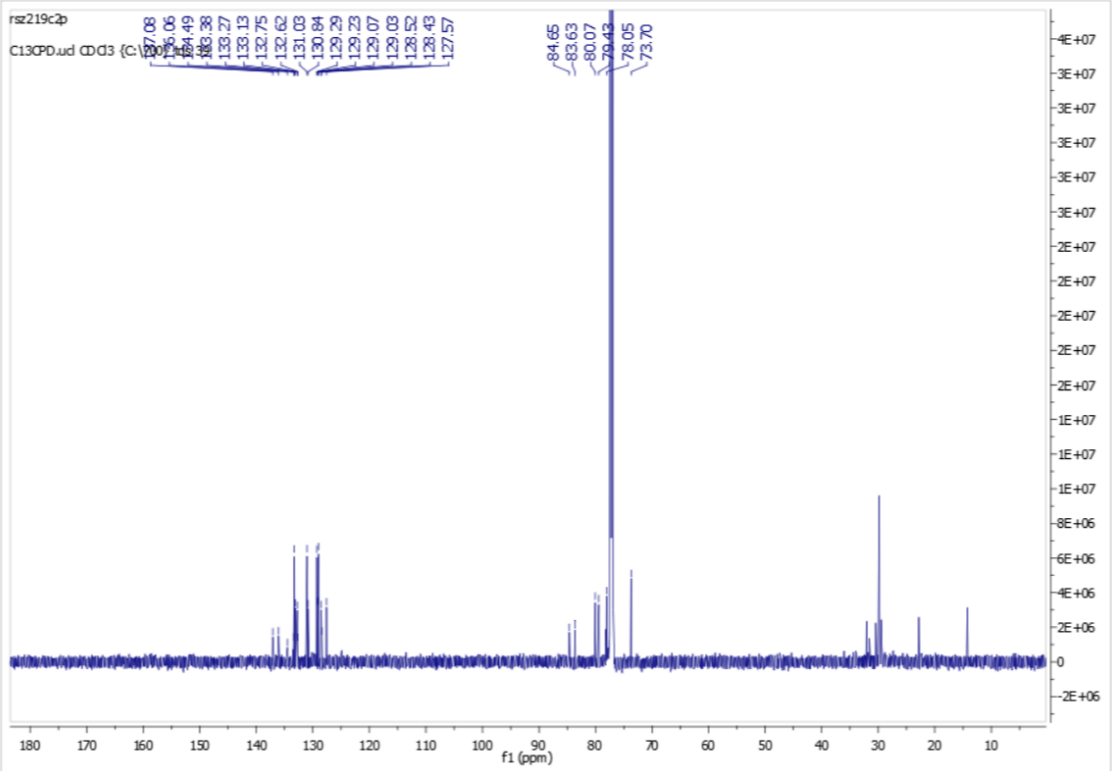
(3*S*,4*R*)-2-(Hydroxymethyl)-6,6-bis(phenylthio)tetrahydro-2H-pyran-3,4-diol [**171**]:



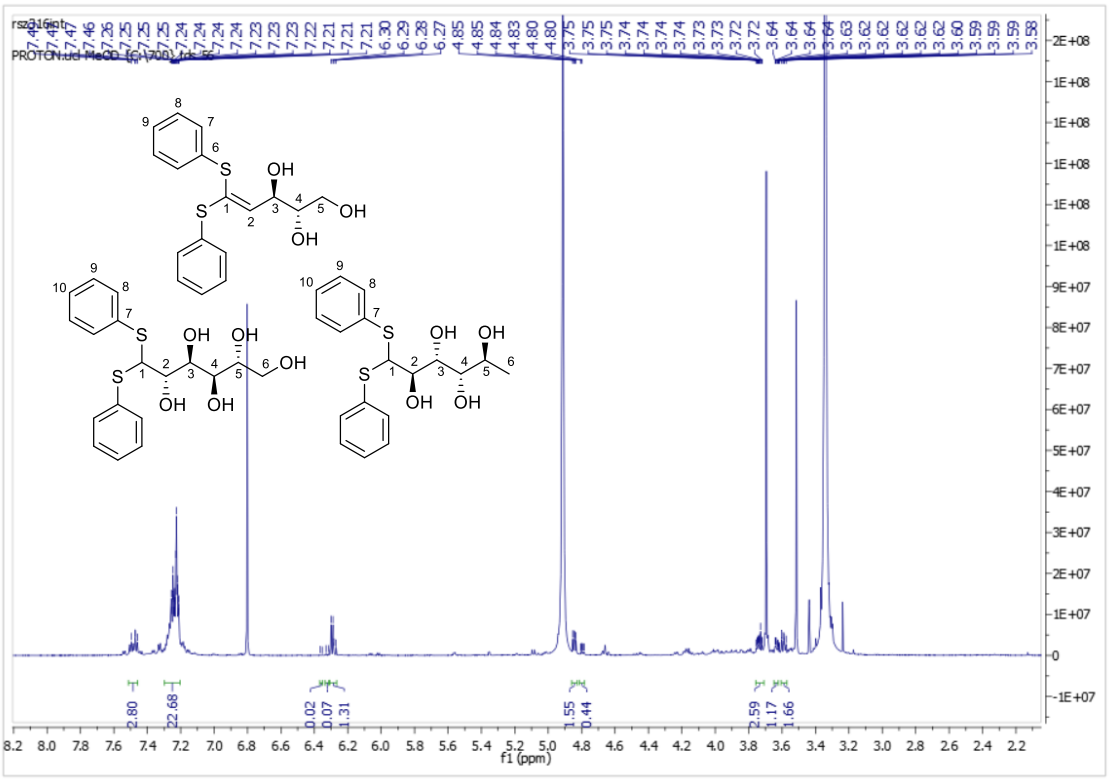



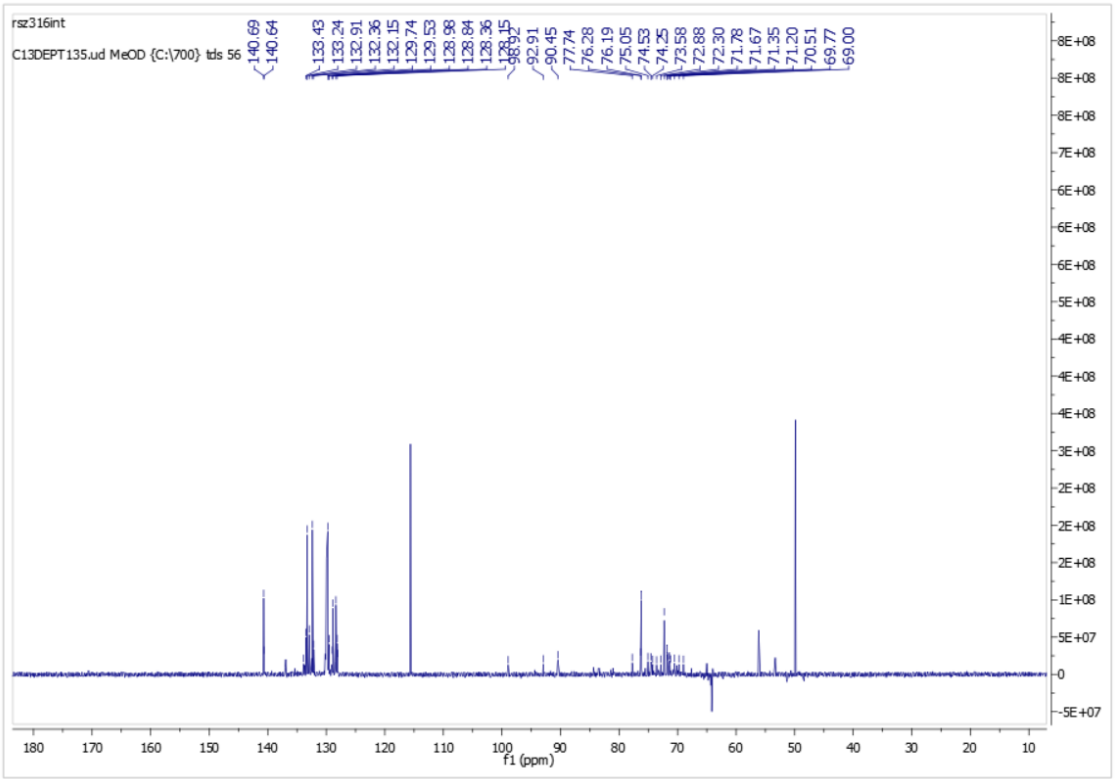
D-Galactose dithioacetal alkenyl THF, (2*R*,3*S*,4*R*)-2-(2,2-bis(phenylthio)vinyl)tetrahydrofuran-3,4-diol, (2*S*,3*S*,4*R*)-2-(2,2-bis(phenylthio)vinyl)tetrahydrofuran-3,4-diol [**172**]:



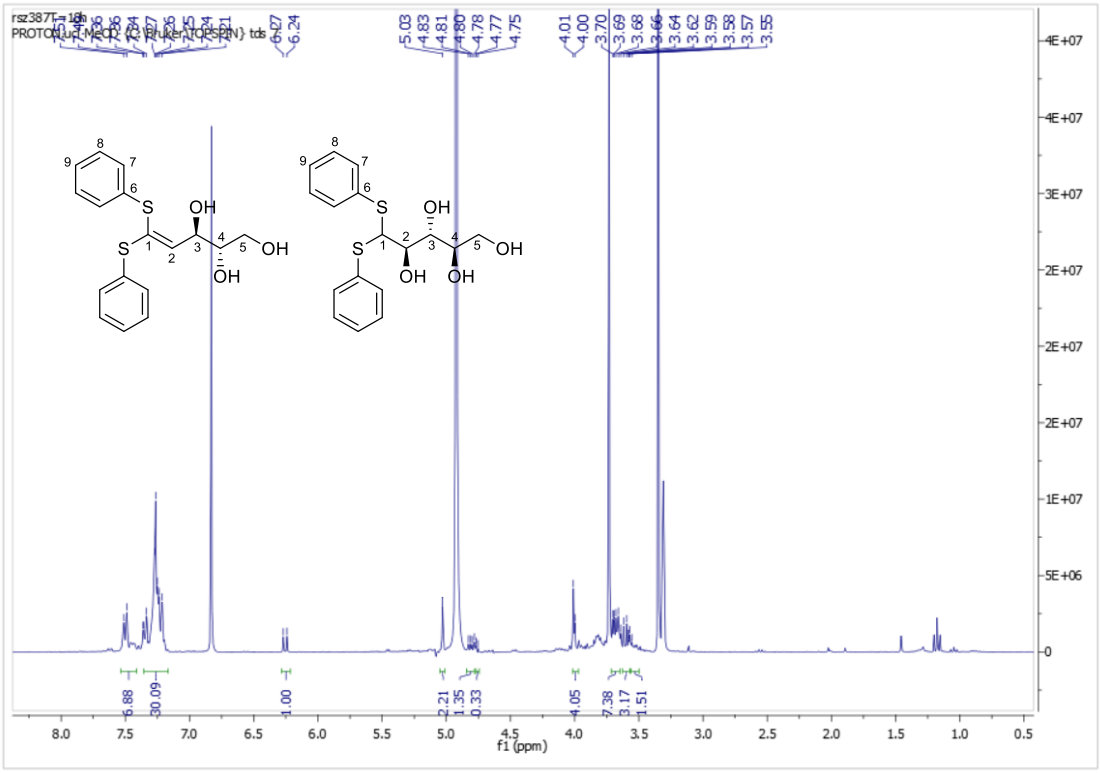



(2*S*,3*R*)-5,5-Bis(phenylthio)pent-4-ene-1,2,3-triol, (2*R*,3*R*,4*S*,5*S*)-6,6-bis(phenylthio)hexane-1,2,3,4,5-pentaol, (2*R*,3*R*,4*S*,5*S*)-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol [**Scheme 70**]:

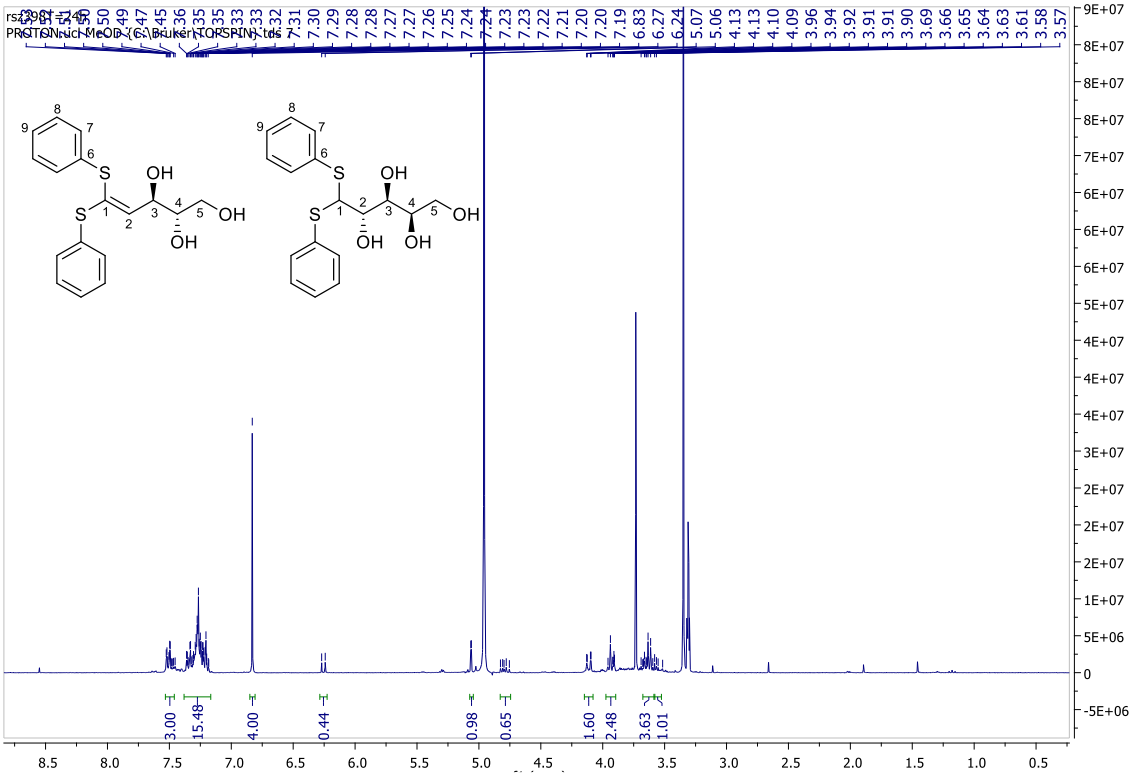


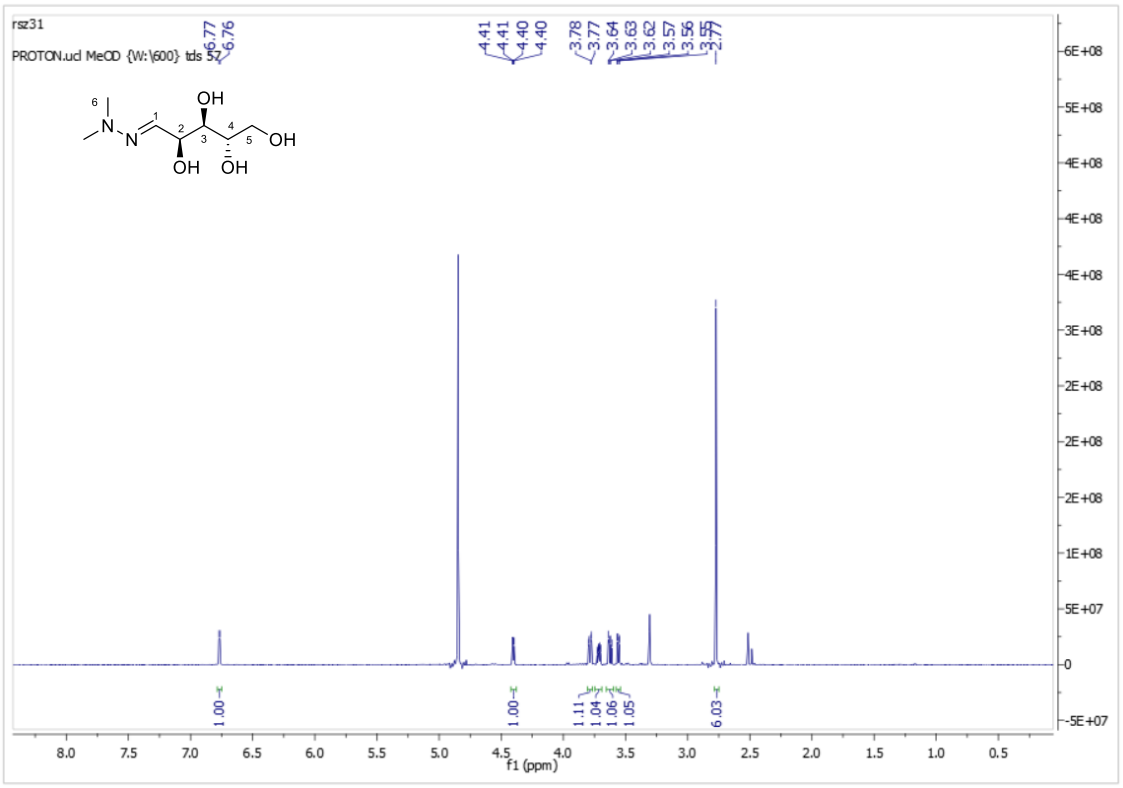
(*2*S,3*R*)-5,5-Bis(phenylthio)pent-4-ene-1,2,3-triol, (2*R*,3*R*,4*R*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**Scheme 71**]:

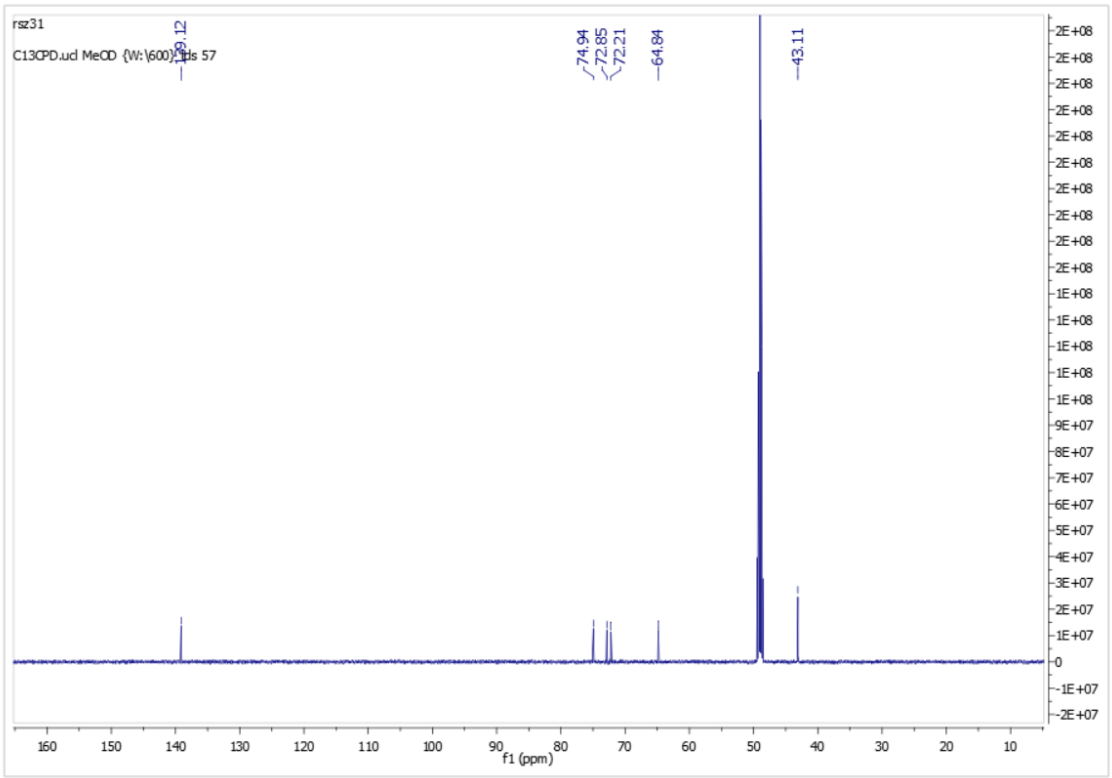


(2*S*,3*R*)-5,5-Bis(phenylthio)pent-4-ene-1,2,3-triol, (2*R*,3*S*,4*S*)-5,5-bis(phenylthio)pentane-1,2,3,4-tetraol [**Scheme 72**]:

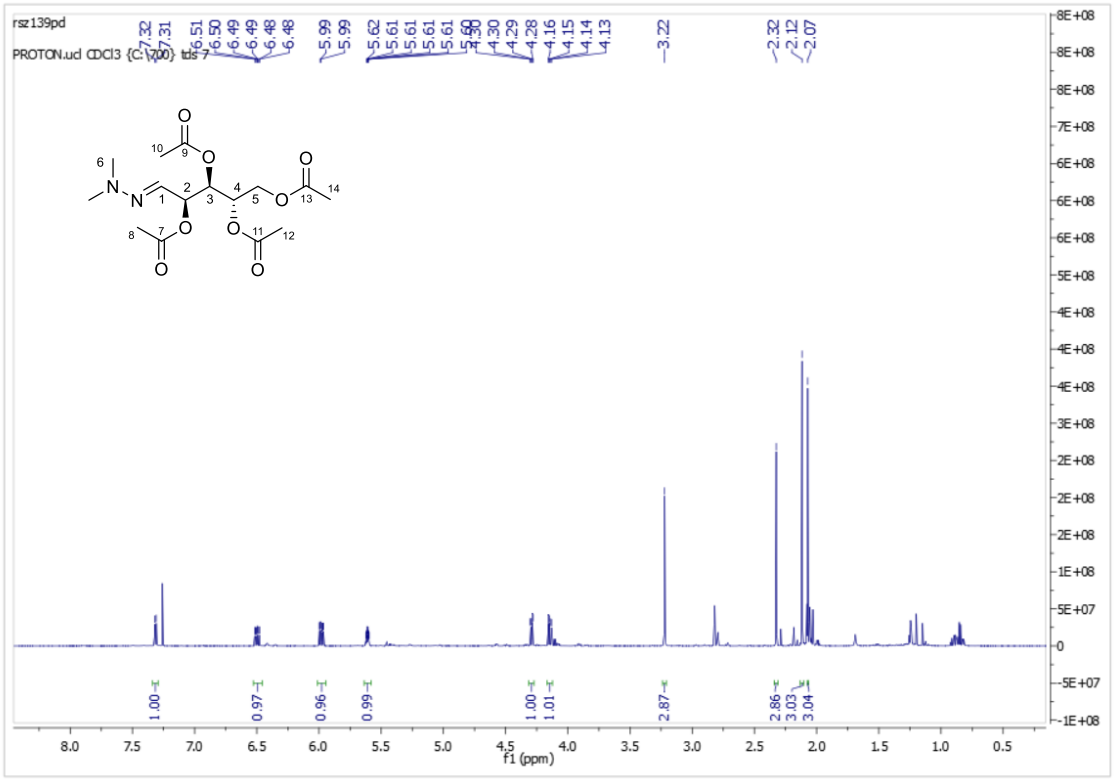


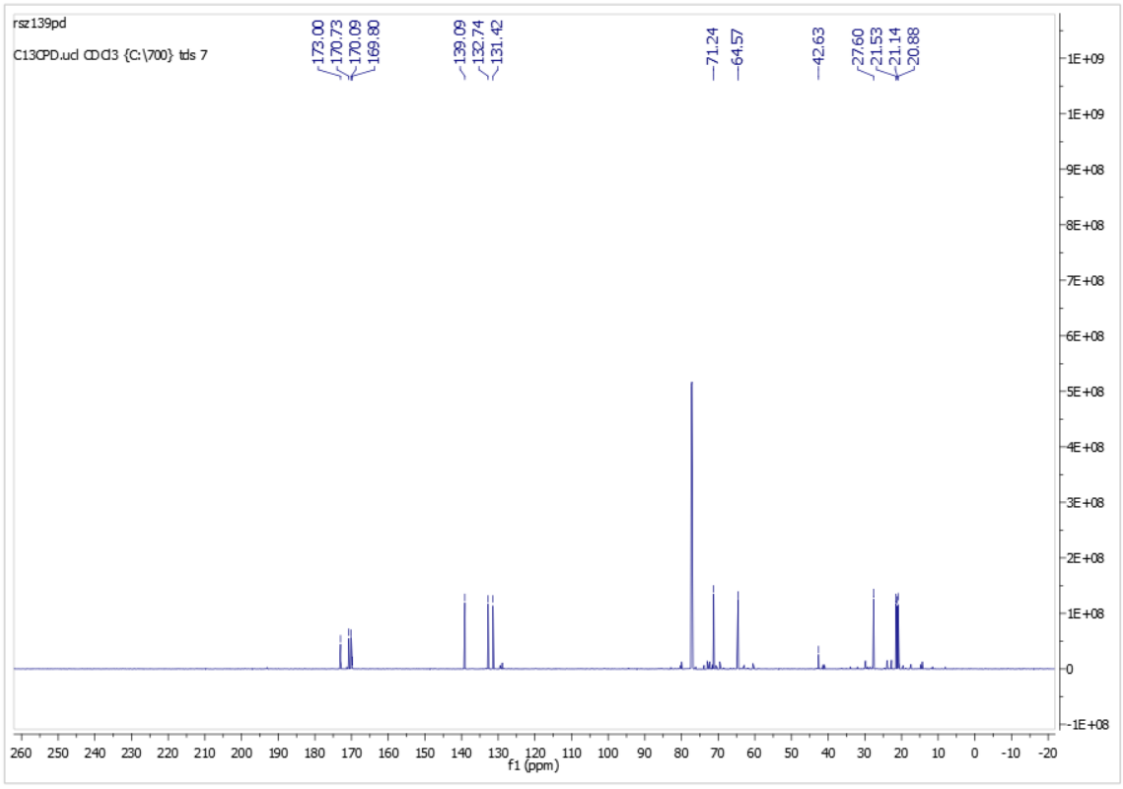
L-Arabinose dimethylhydrazone, (2*S*,3*R*,4*S*,*E*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetraol [**40**]:



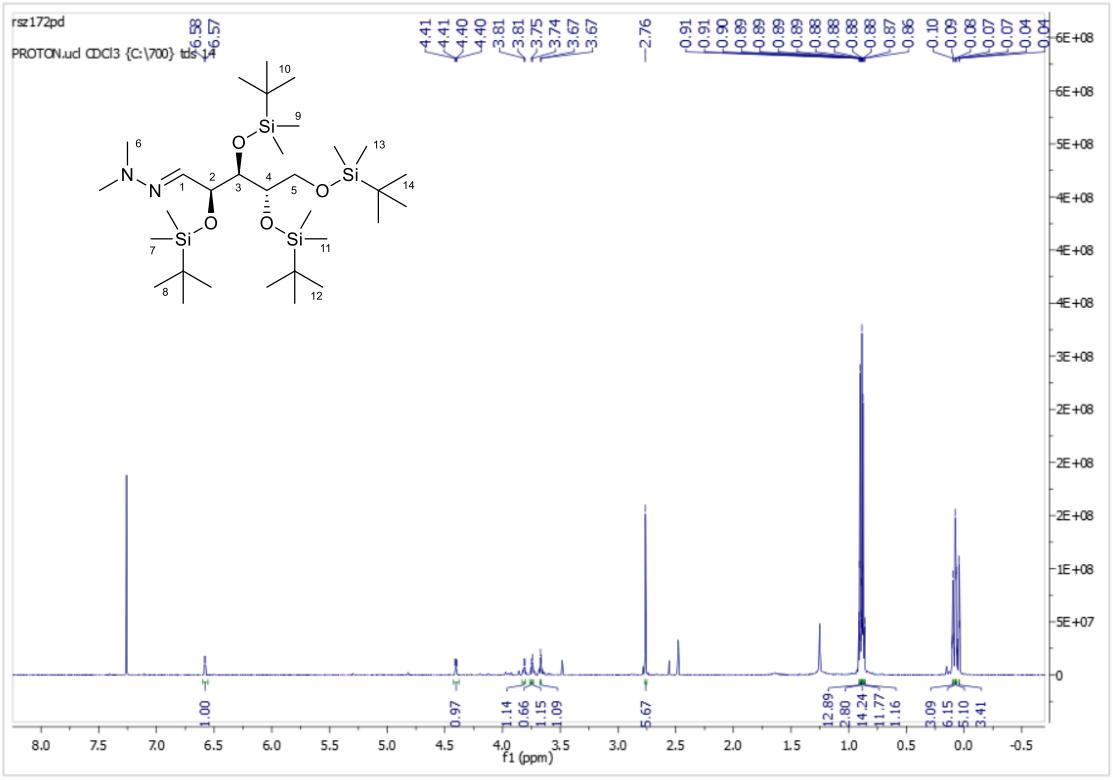



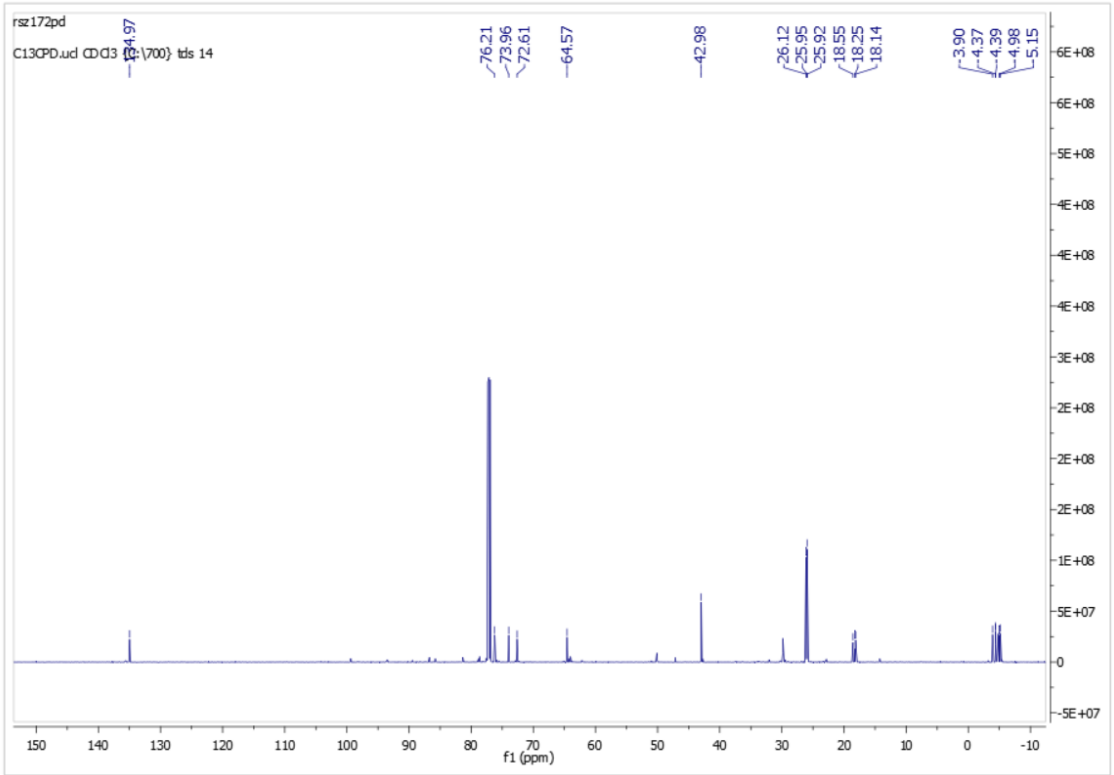
L-Arabinose dimethylhydrazone tetraacetate, (2*S*,3*R*,4*S*,*E*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetrayl tetraacetate [**176**]:



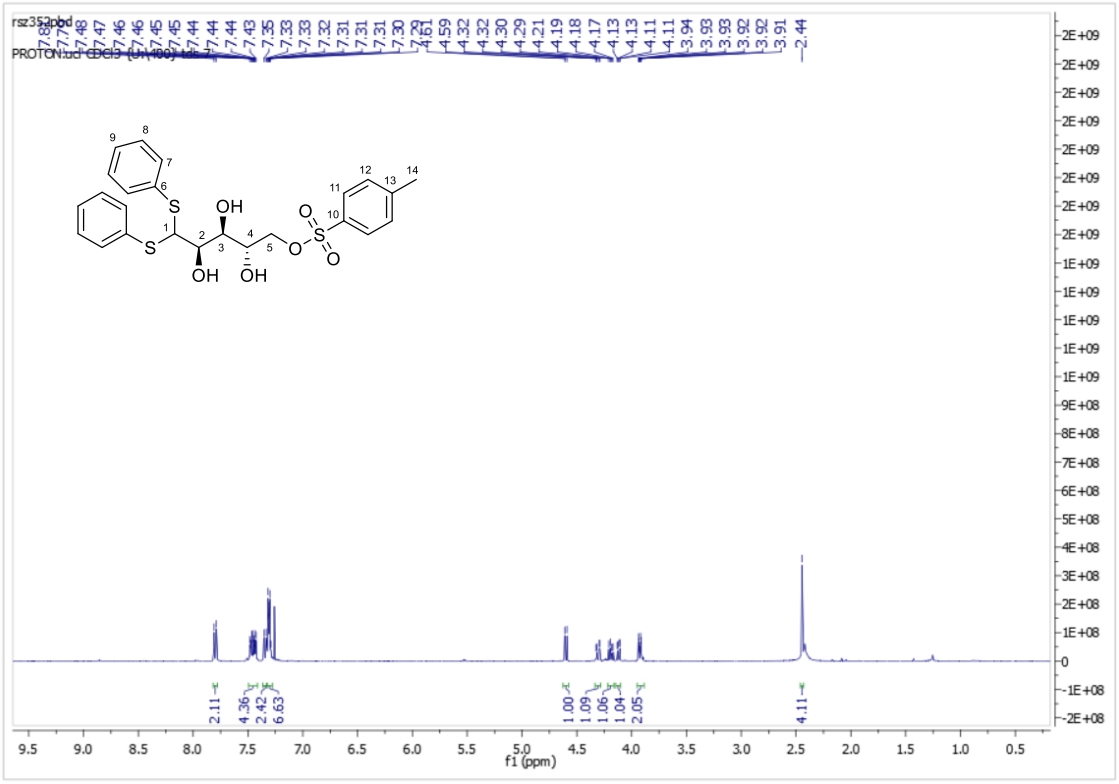



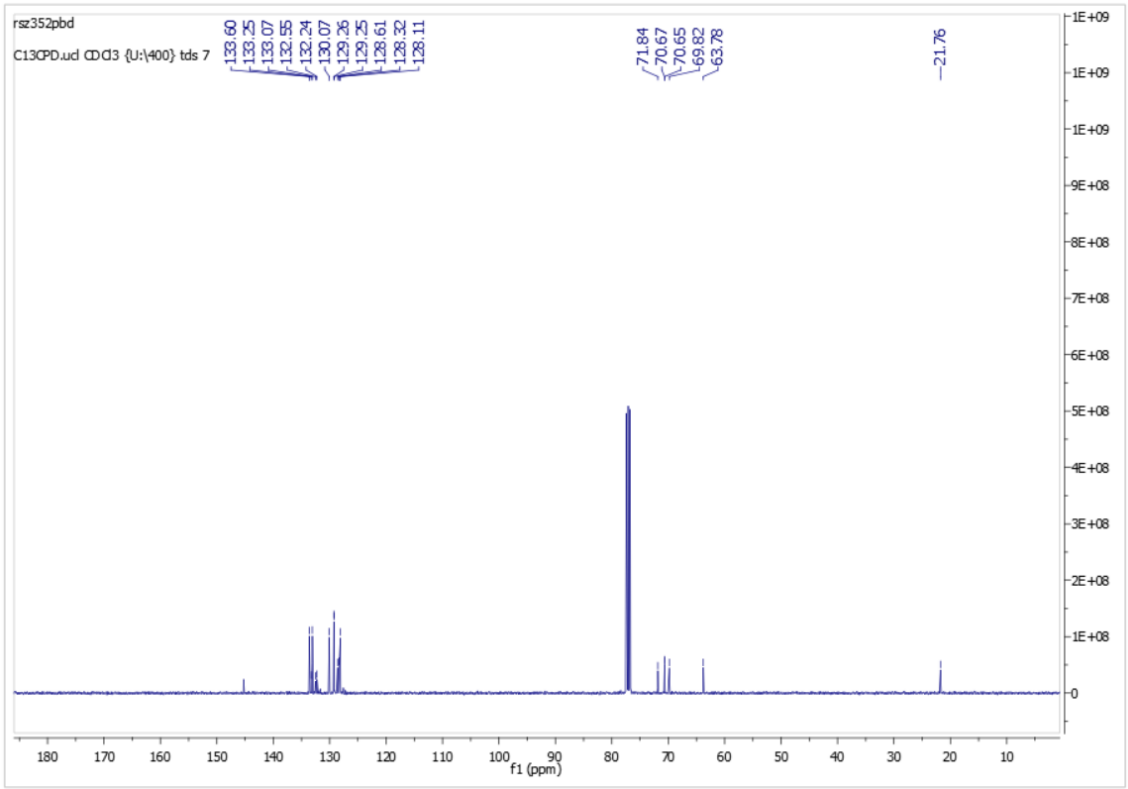
(*E*)-1,1-Dimethyl-2-((2*S*,3*R*,4*S*)-2,3,4,5-tetrakis ((tert-butyldimethylsilyl)oxy)pentylidene)hydrazine [**180**]:



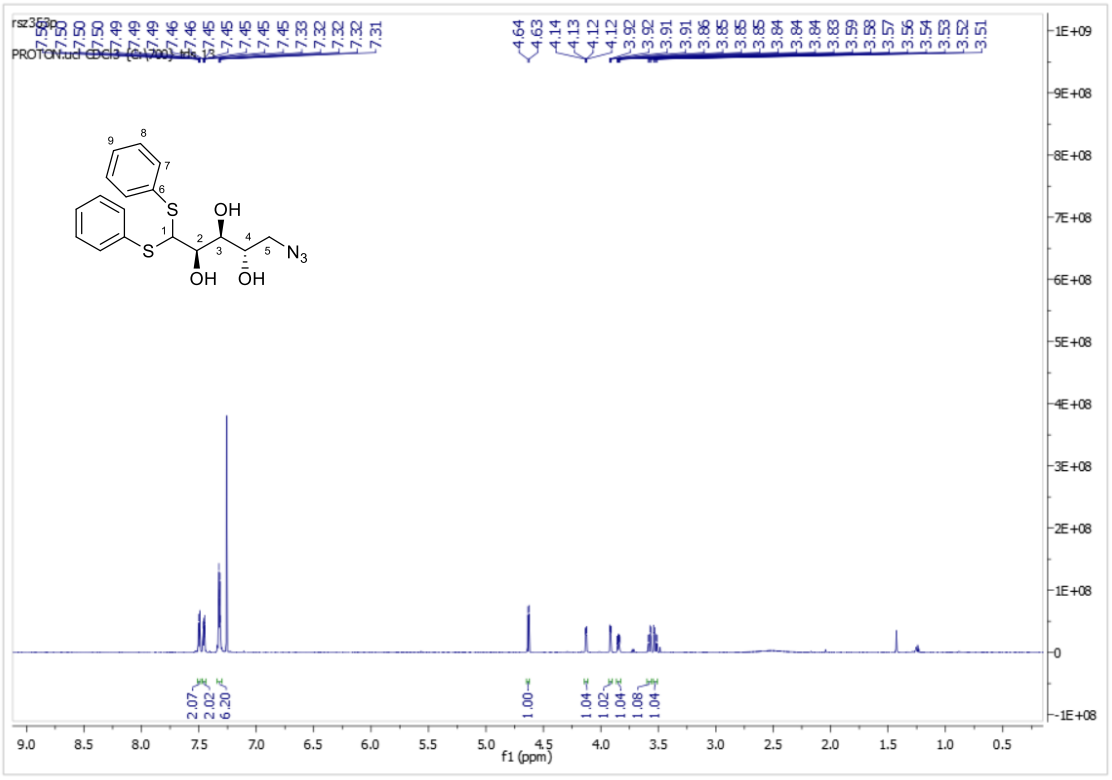



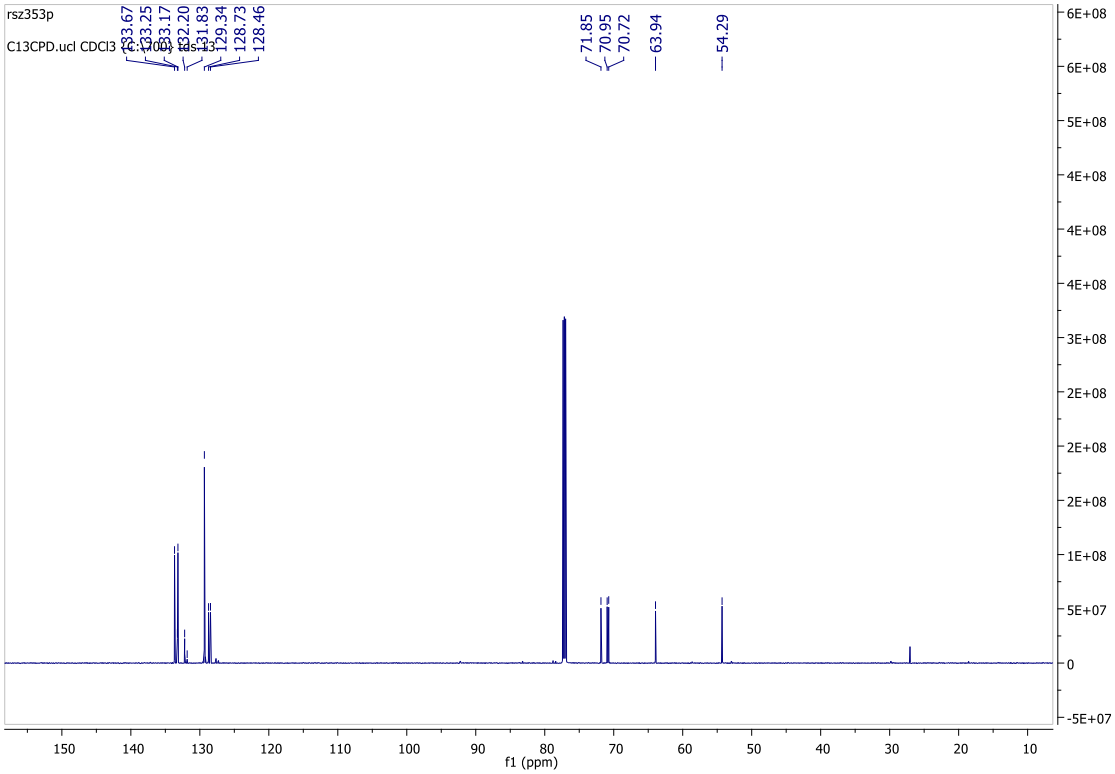
(2*S*,3*S*,4*R*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl 4-methylbenzenesulfonate [**190**]:



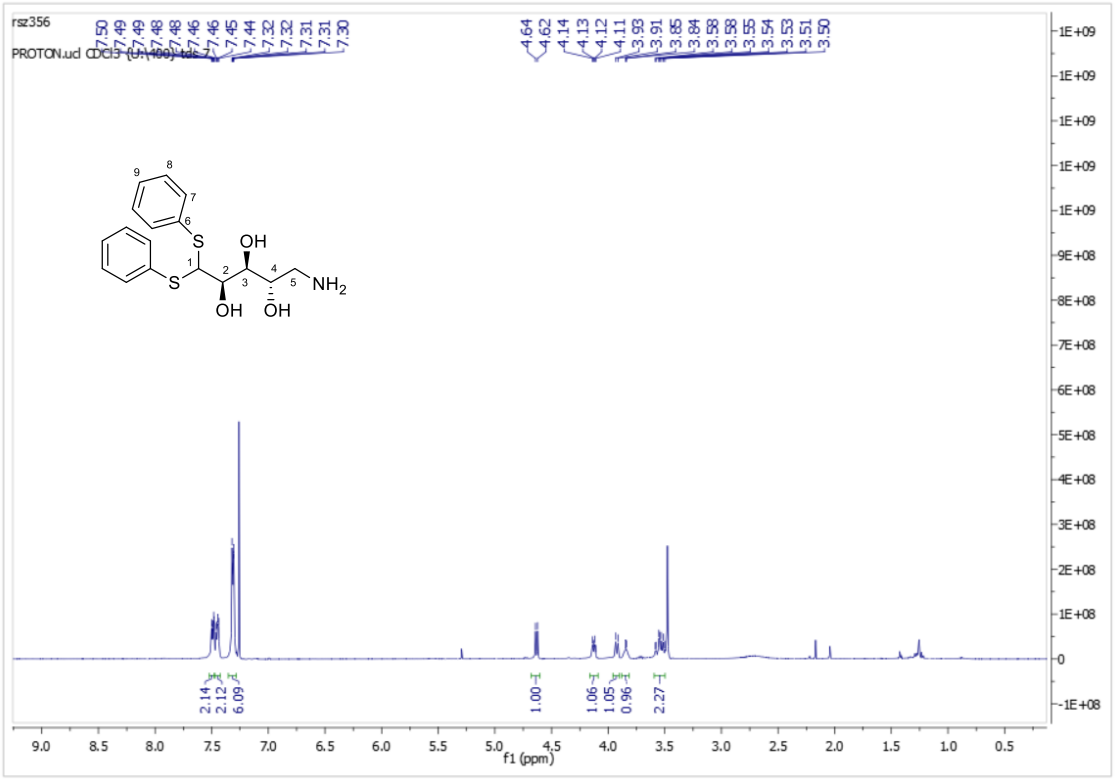



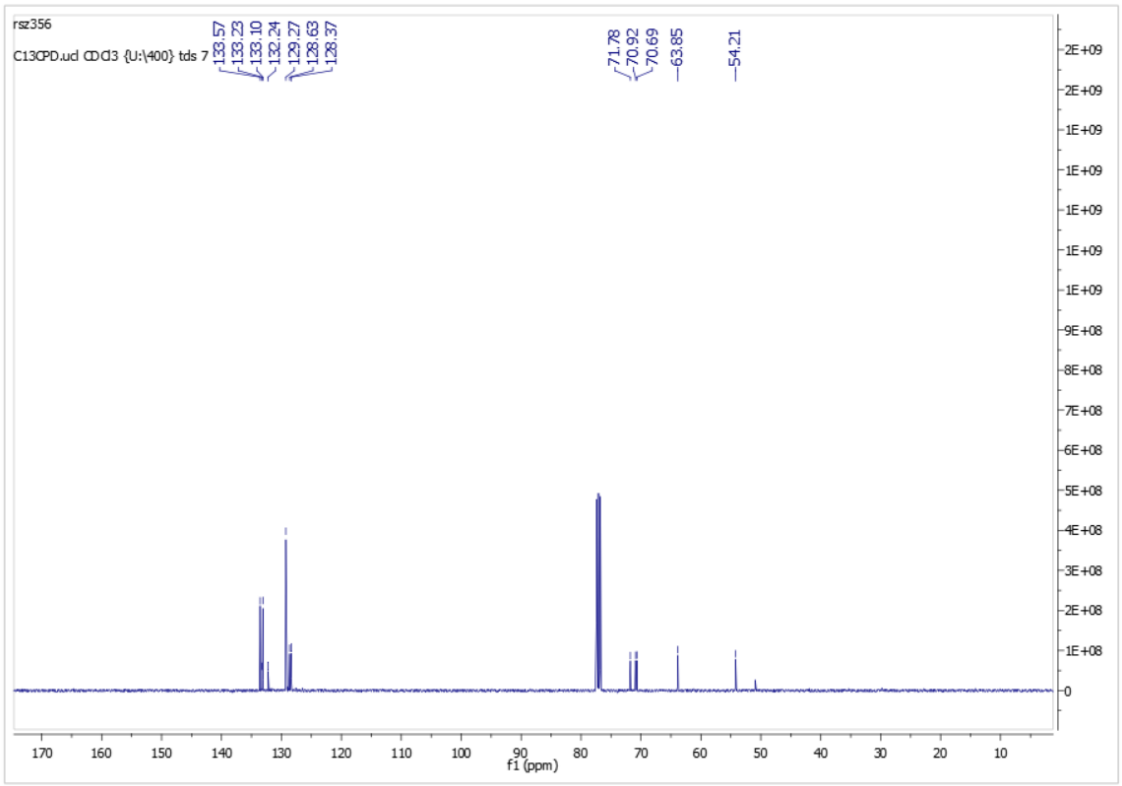
(2*R*,3*S*,4*S*)-5-Azido-1,1-bis(phenylthio)pentane-2,3,4-triol [**191**]:



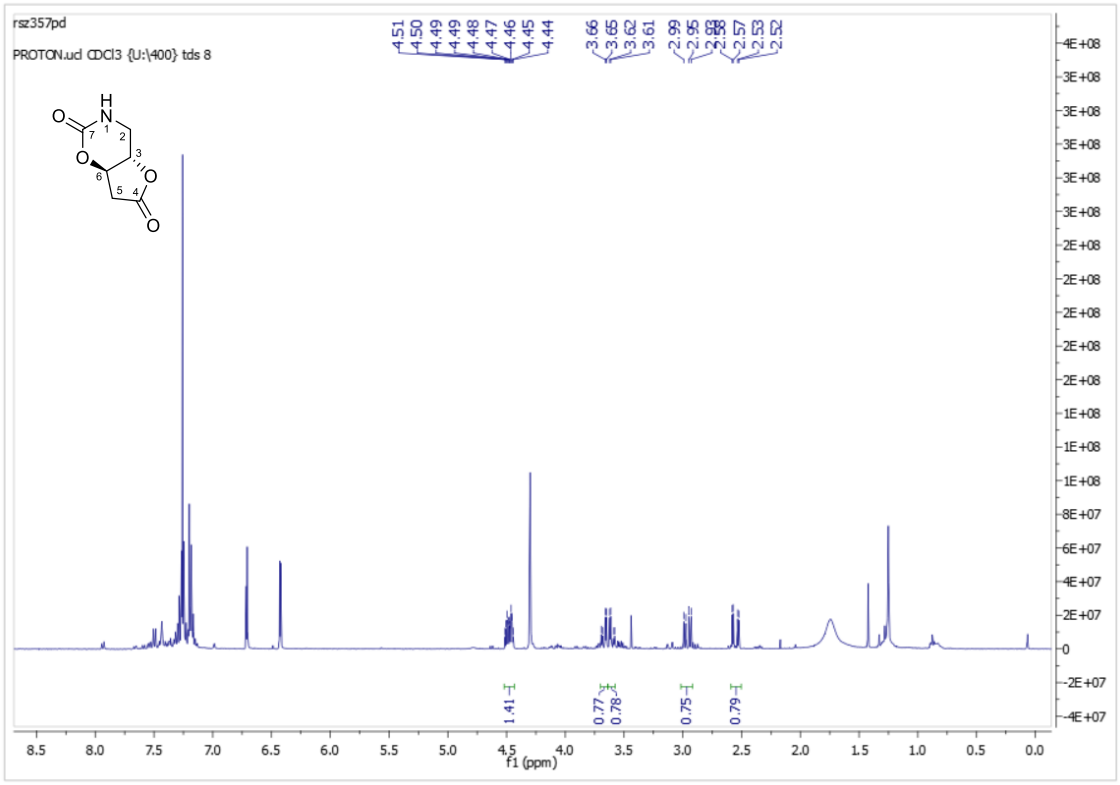



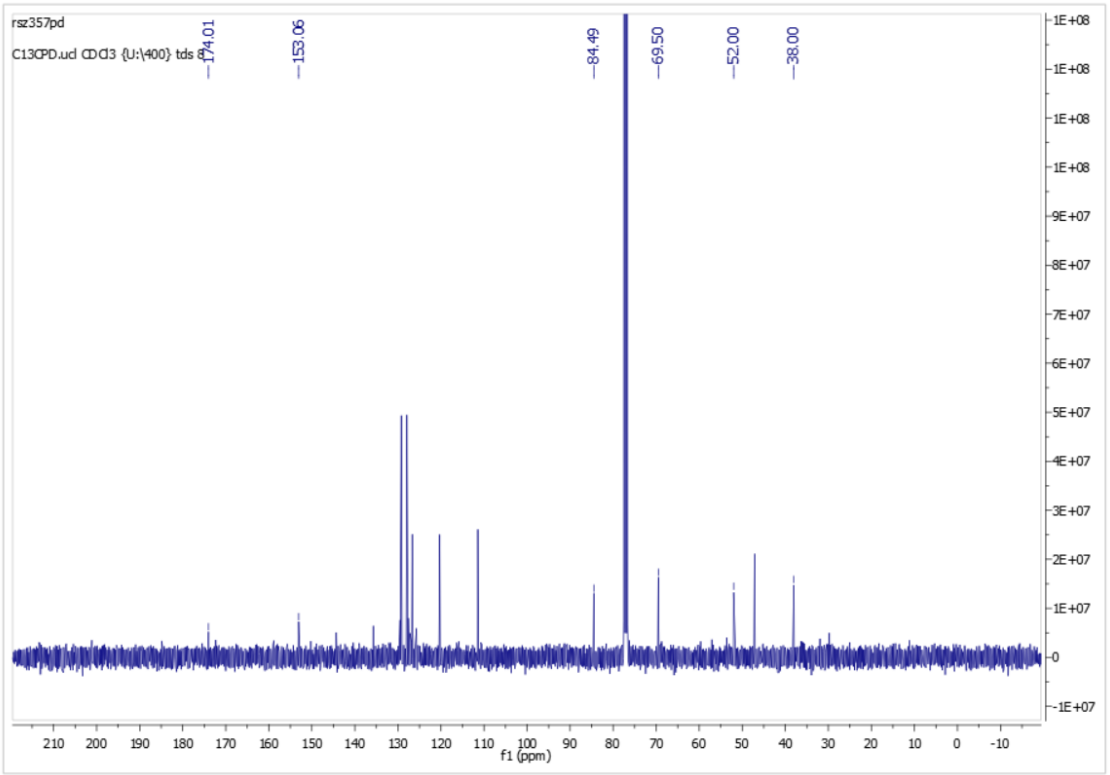
(2*R*,3*S*,4*S*)-5-Amino-1,1-bis(phenylthio)pentane-2,3,4-triol [**192**]:



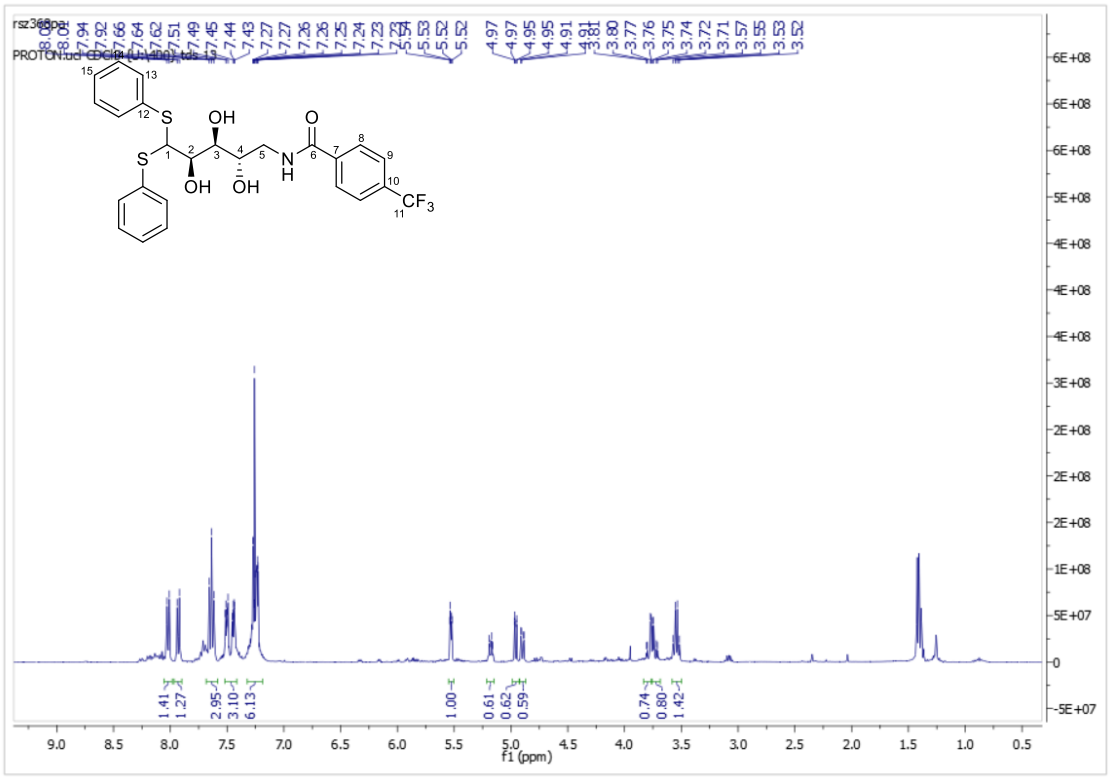



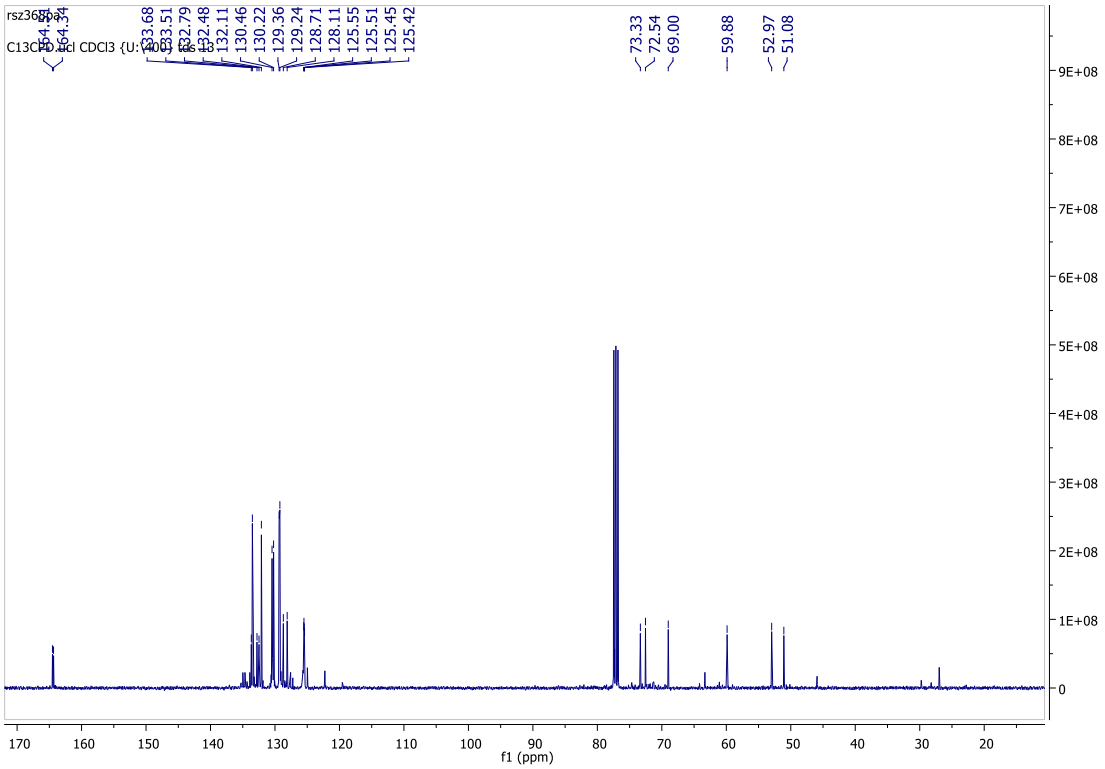
Tetrahydro-2H-furo[2,3-e][1,3]oxazine-2,6(3H)-dione [**194**]:



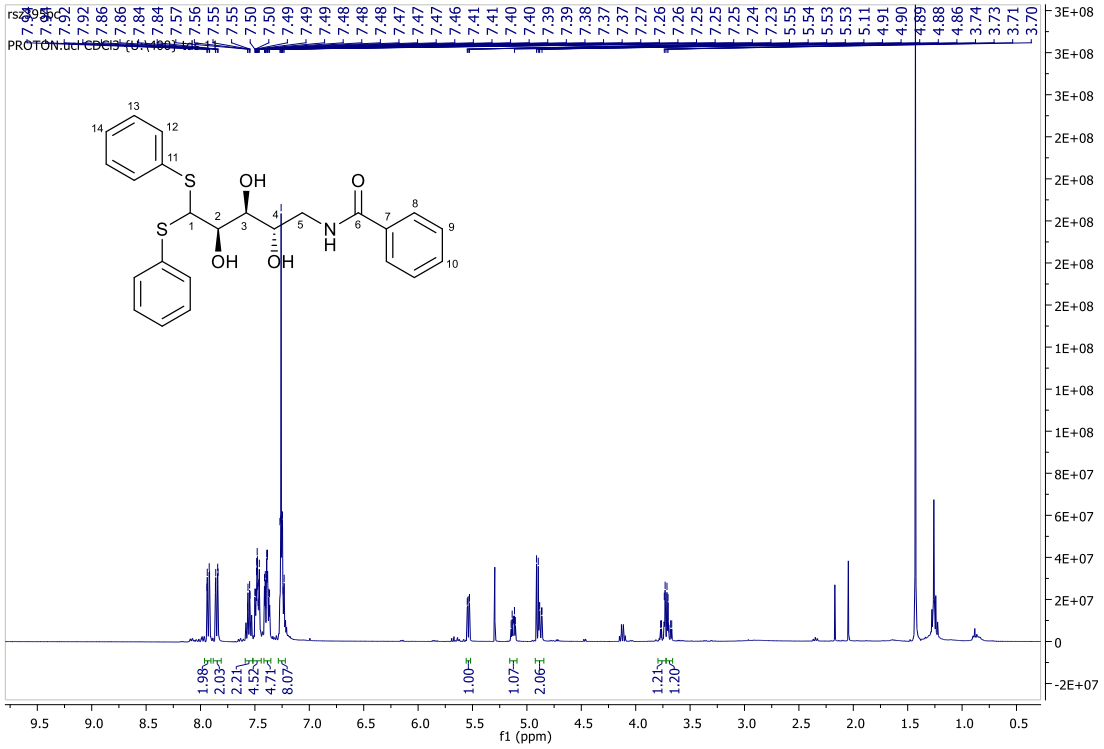



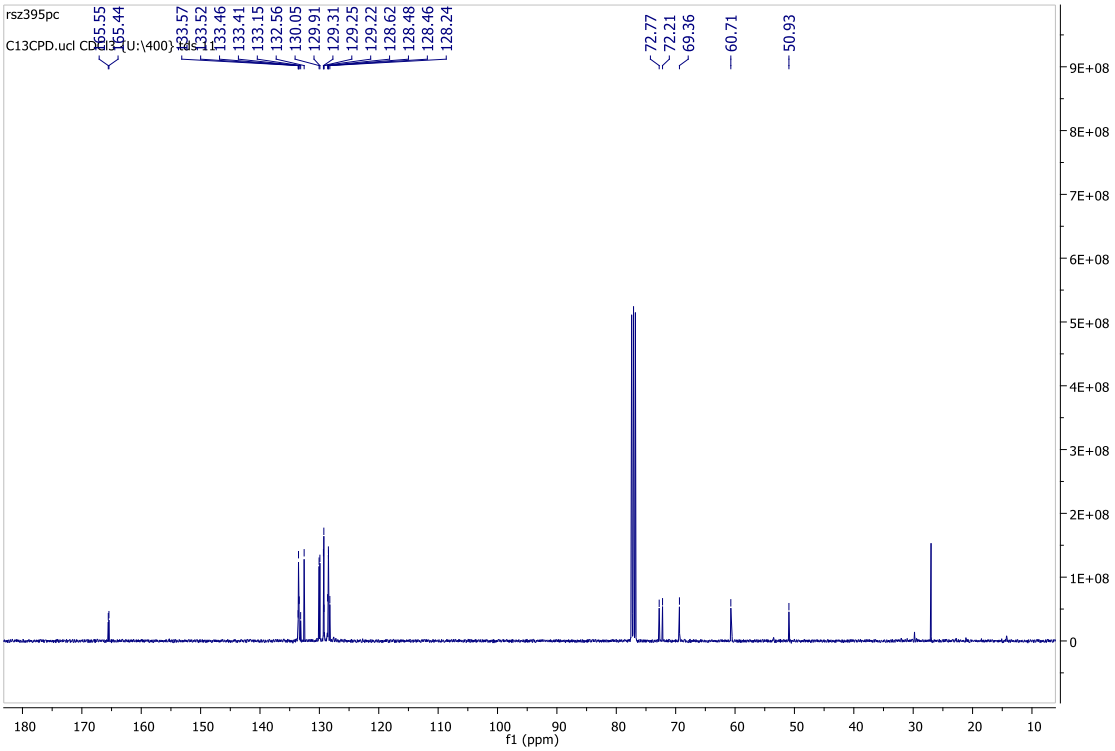
4-(Trifluoromethyl)- *N*-((2*S*,3*S*,4*R*)-2,3,4-trihydroxy-5,5-bis(phenylthio)pentyl)benzamide [**197**]:



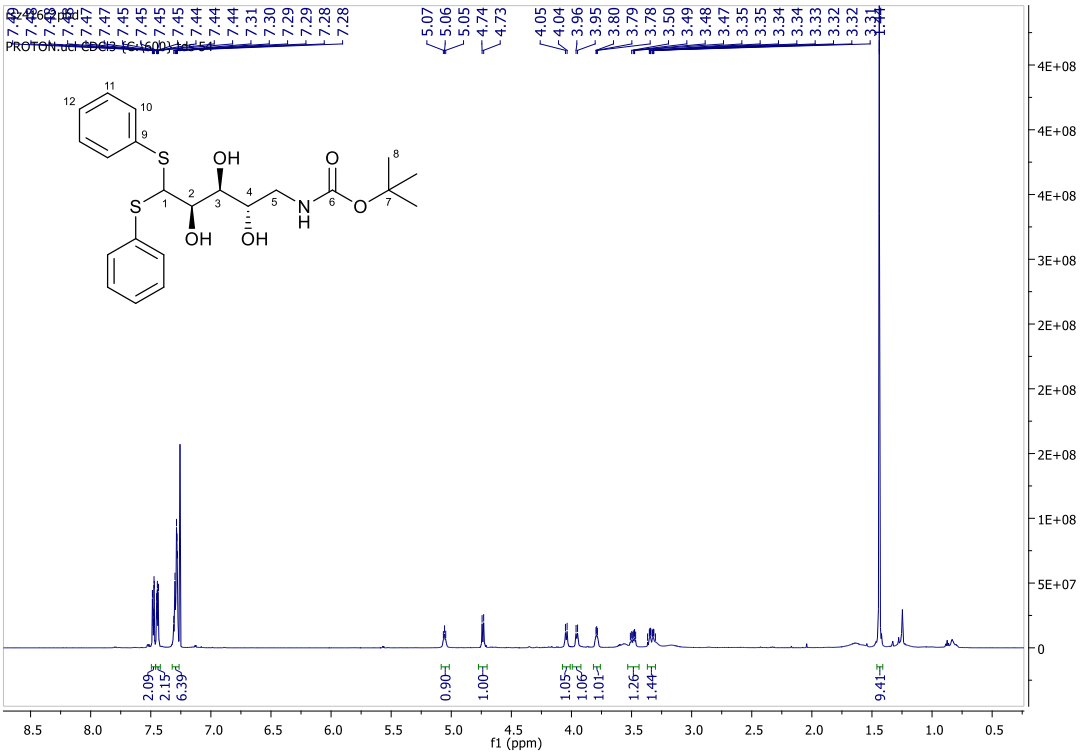



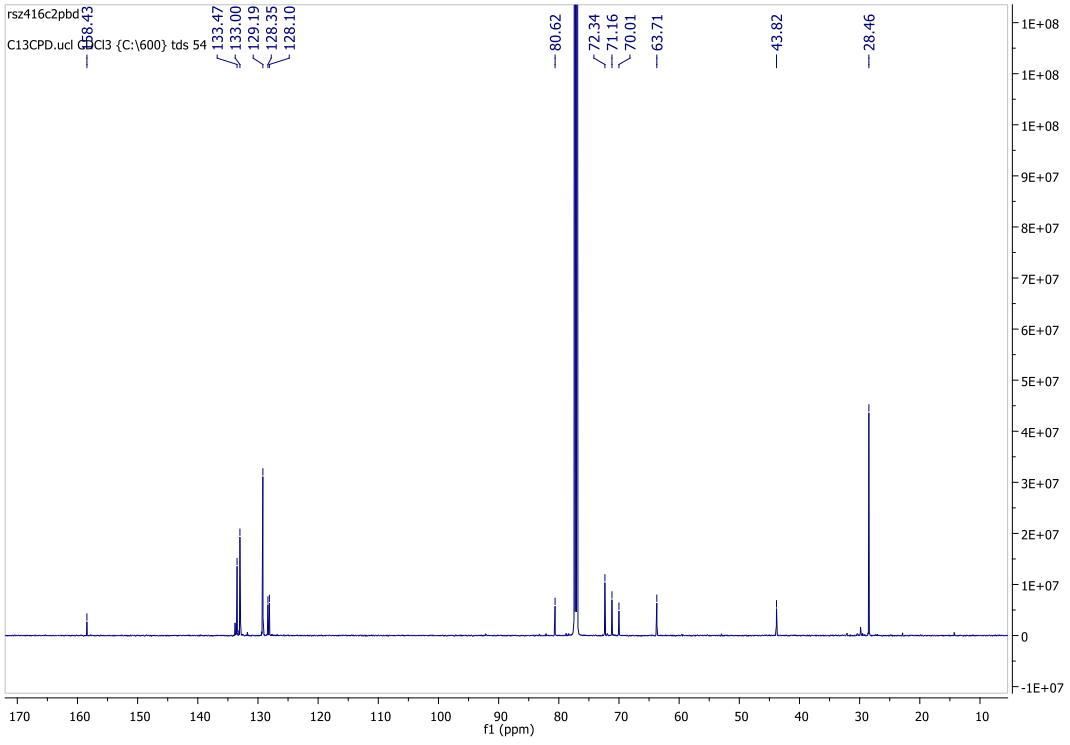
*N*-((2*S*,3*S*,4*R*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl)benzamide [**198**]:



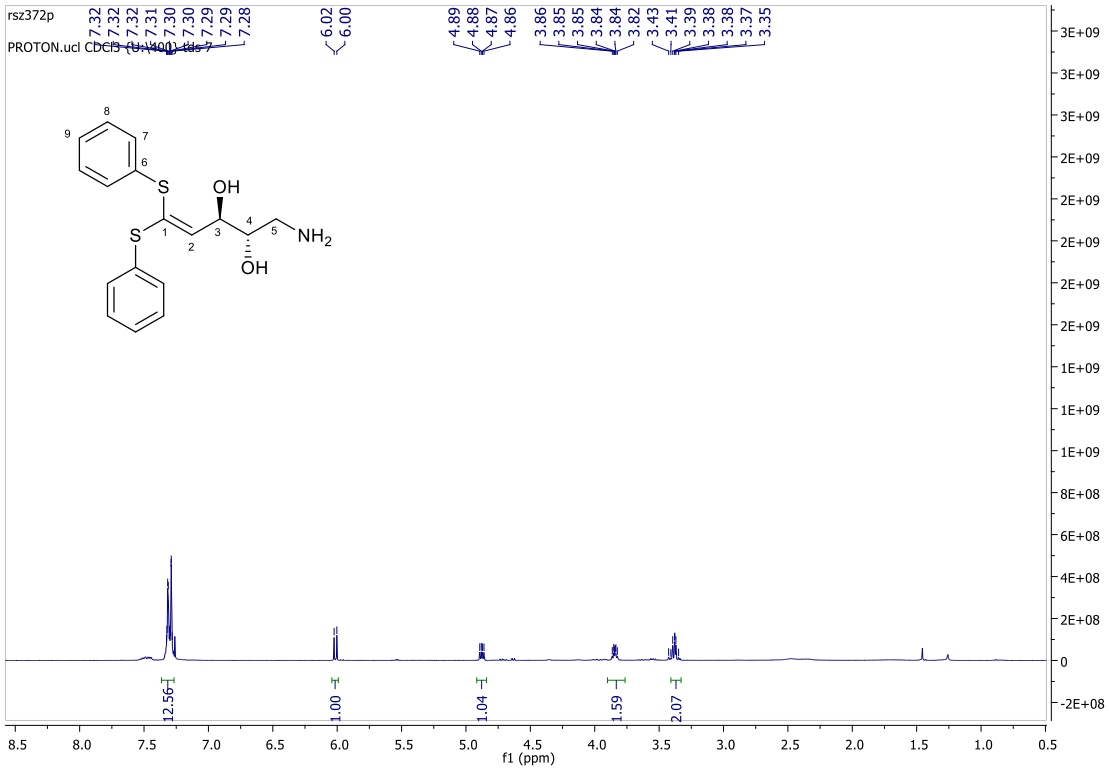



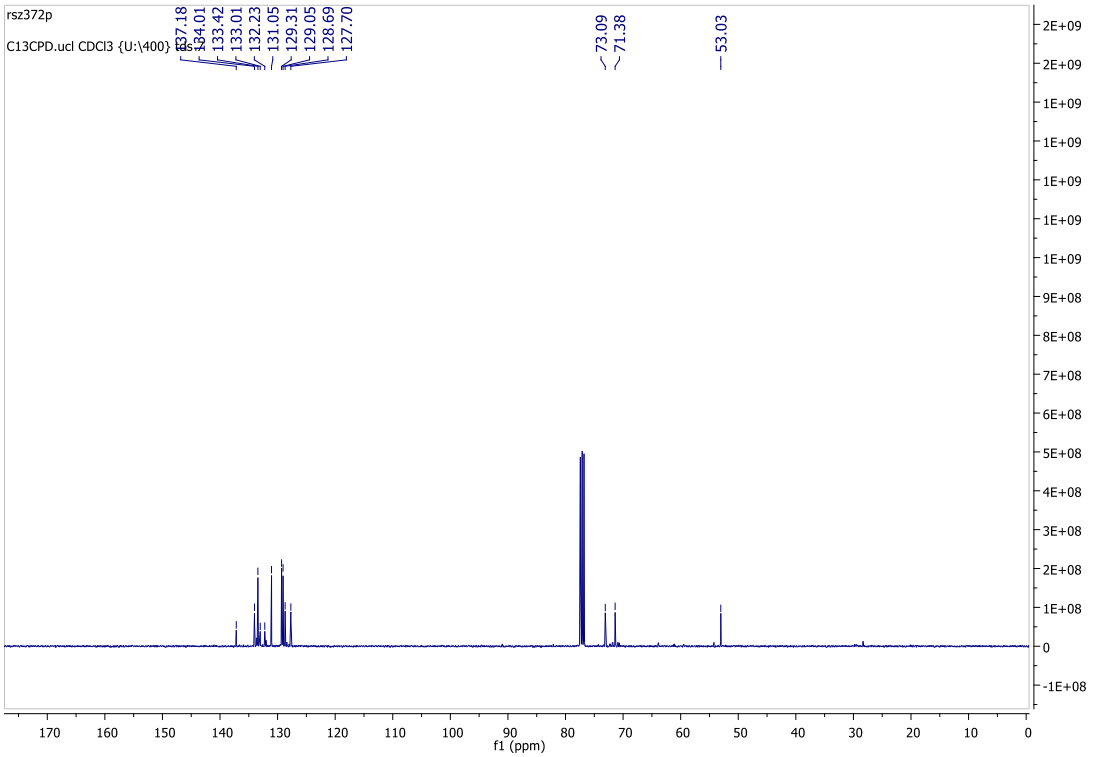
*tert*-Butyl ((2*S*,3*S*,4*R*)-2,3,4-trihydroxy-5,5-bis(phenylthio)pentyl)carbamate [**199**]:



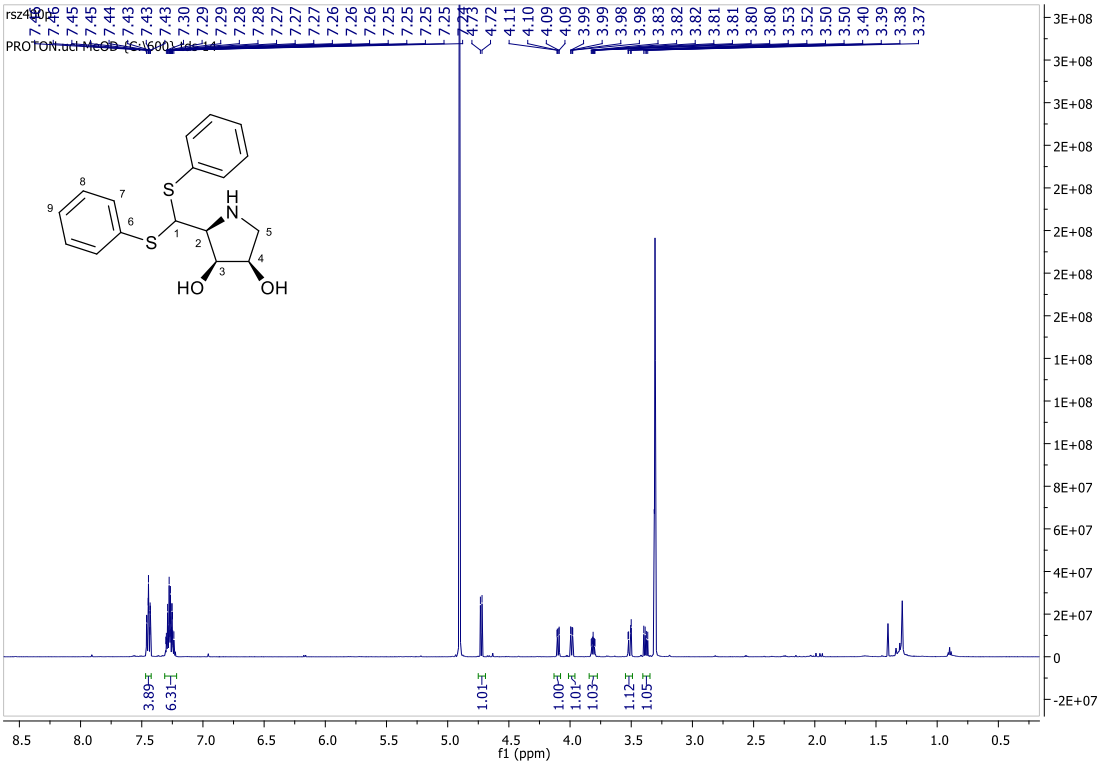



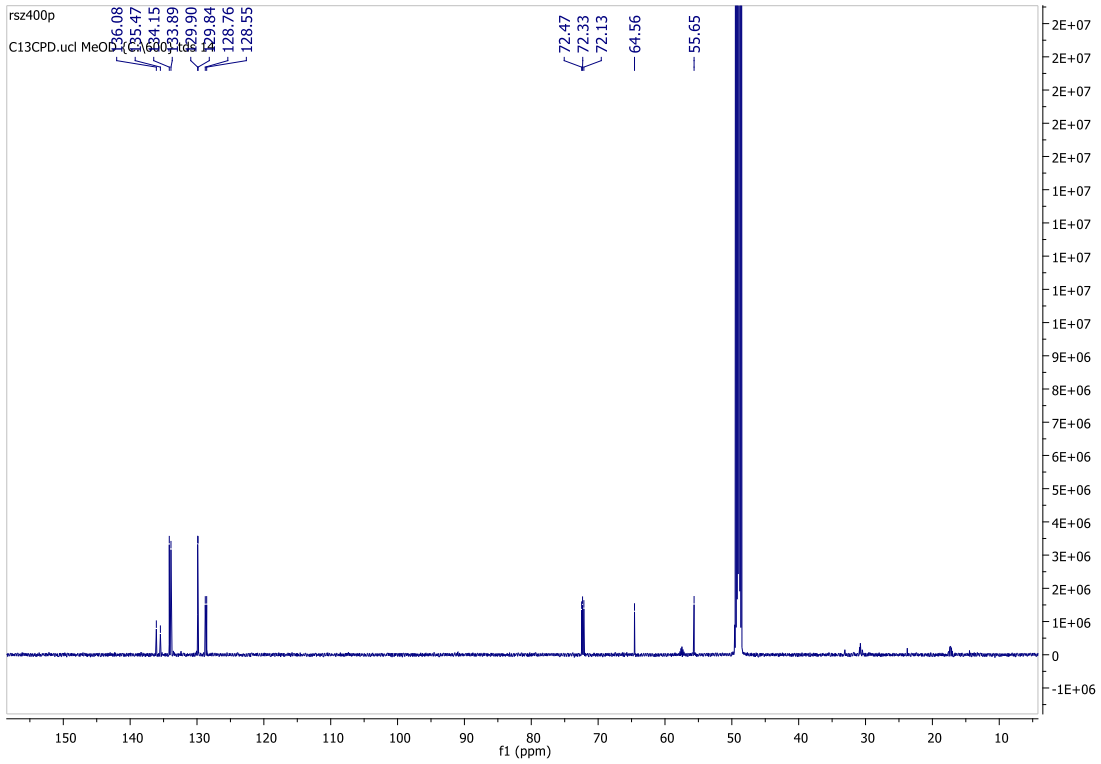
(2*S*,3*R*)-1-Amino-5,5-bis(phenylthio)pent-4-ene-2,3-diol [**200**]:



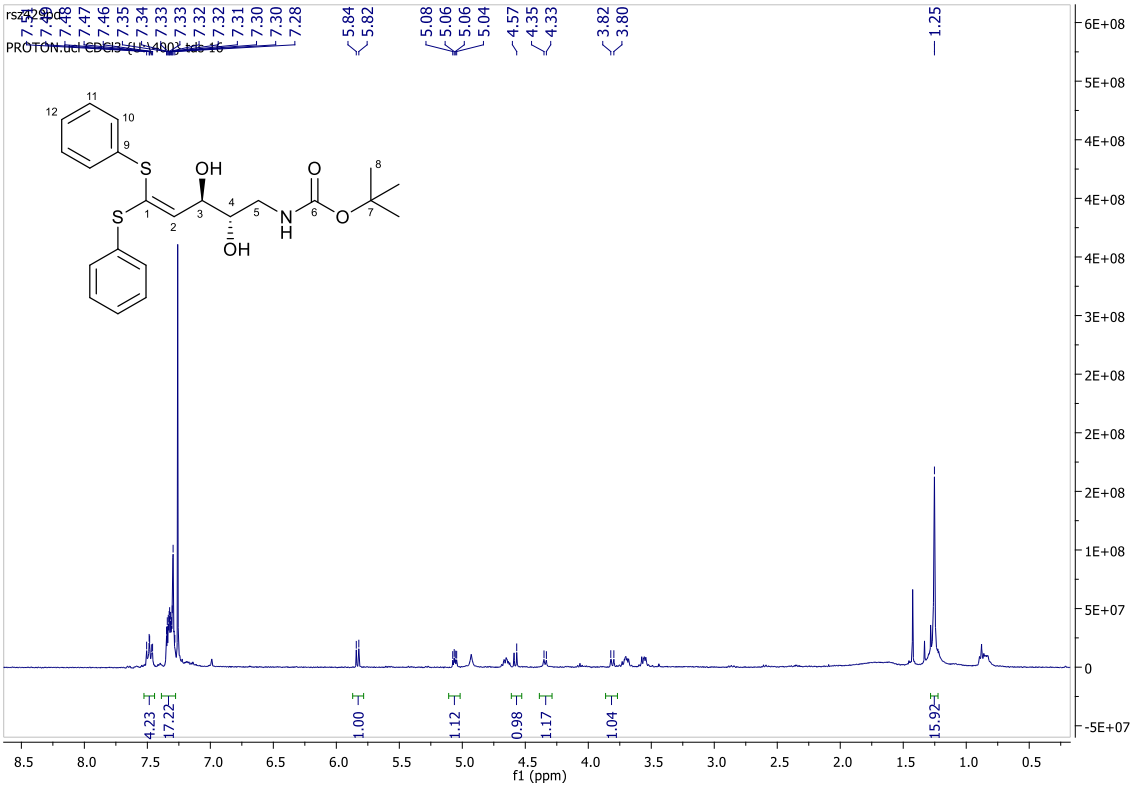



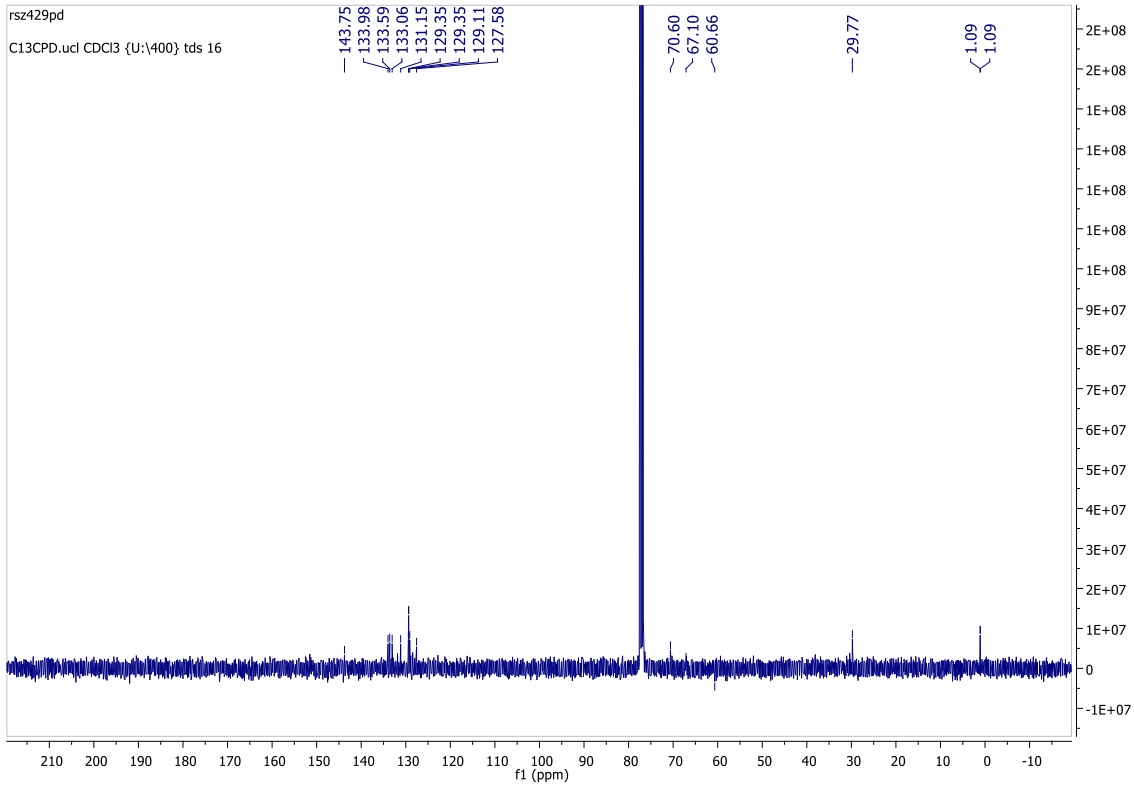
(2*S*,3*S*,4*R*)-2-(Bis(phenylthio)methyl)pyrrolidine-3,4-diol [**201**]:



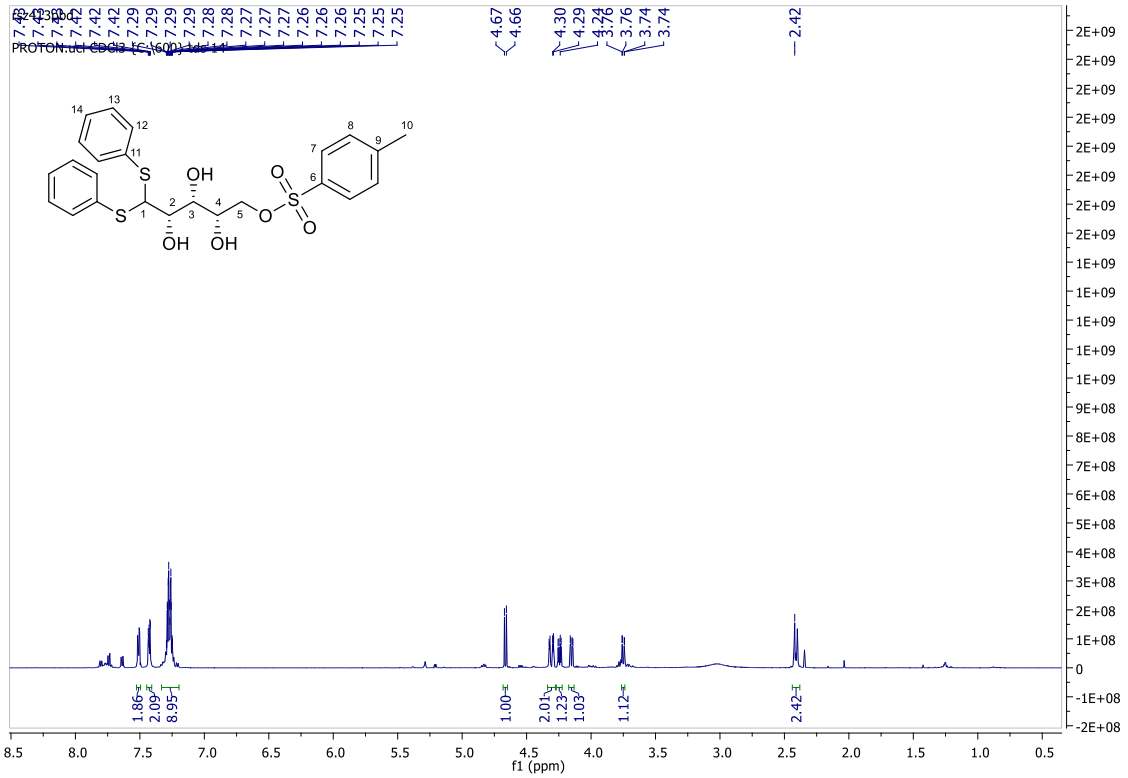



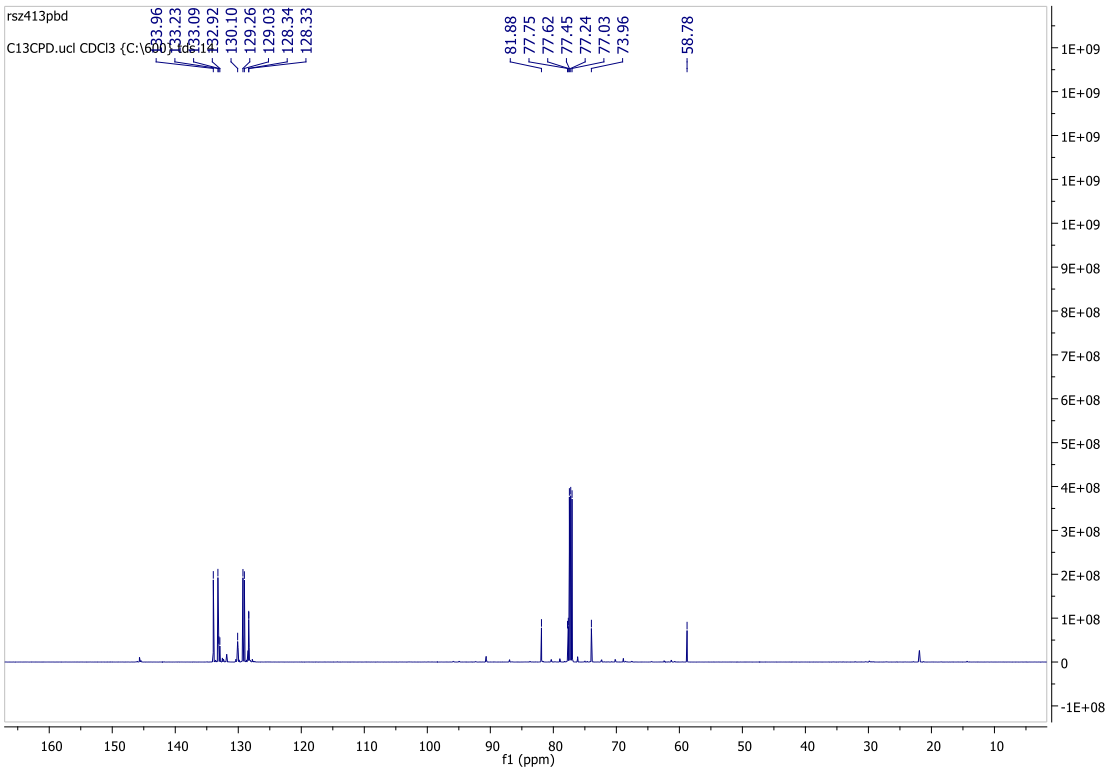
*tert*-Butyl ((2*S*,3*R*)-2,3-dihydroxy-5,5-bis(phenylthio)pent-4-en-1-yl)carbamate [**202**]:



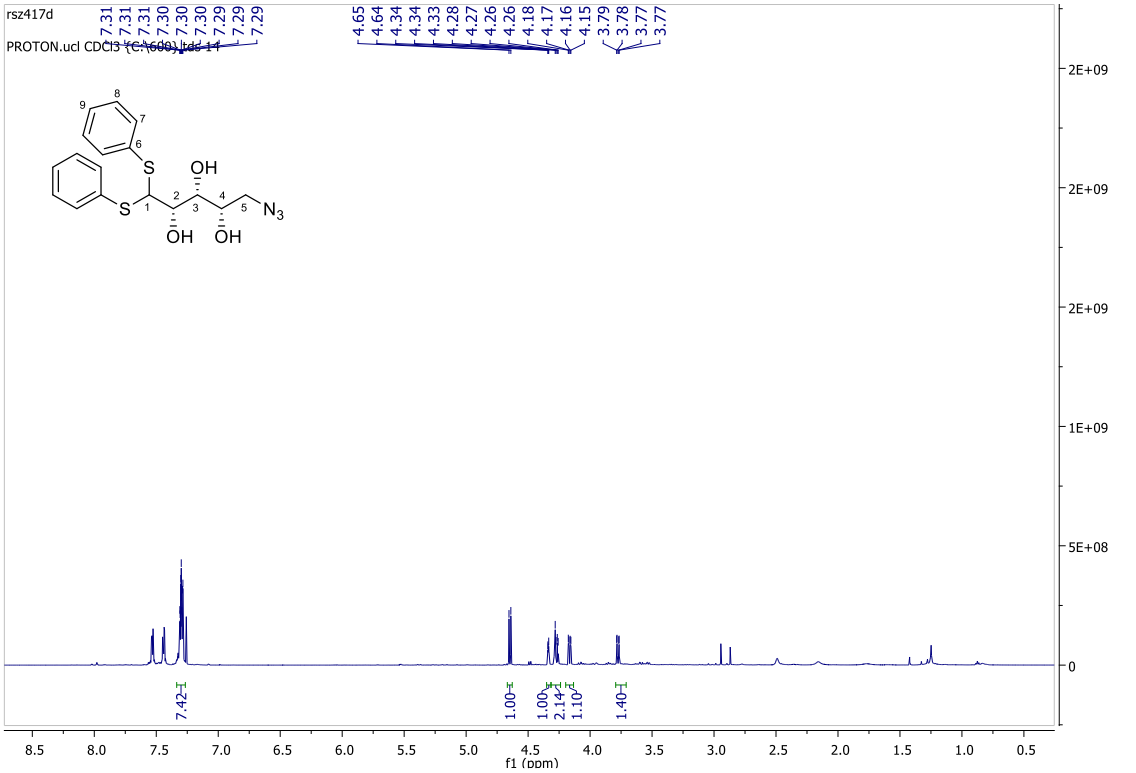



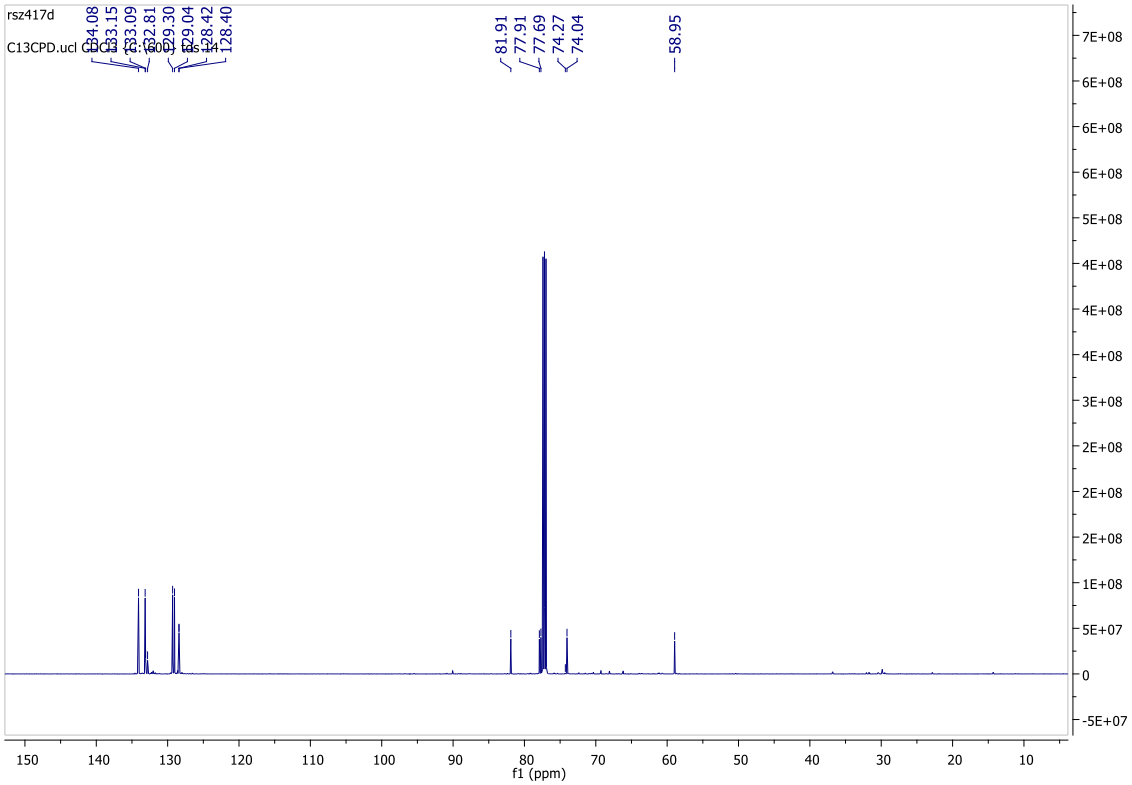
(2*S*,3*R*,4*S*)-2,3,4-Trihydroxy-5,5-bis(phenylthio)pentyl 4-methylbenzenesulfonate [**203**]:



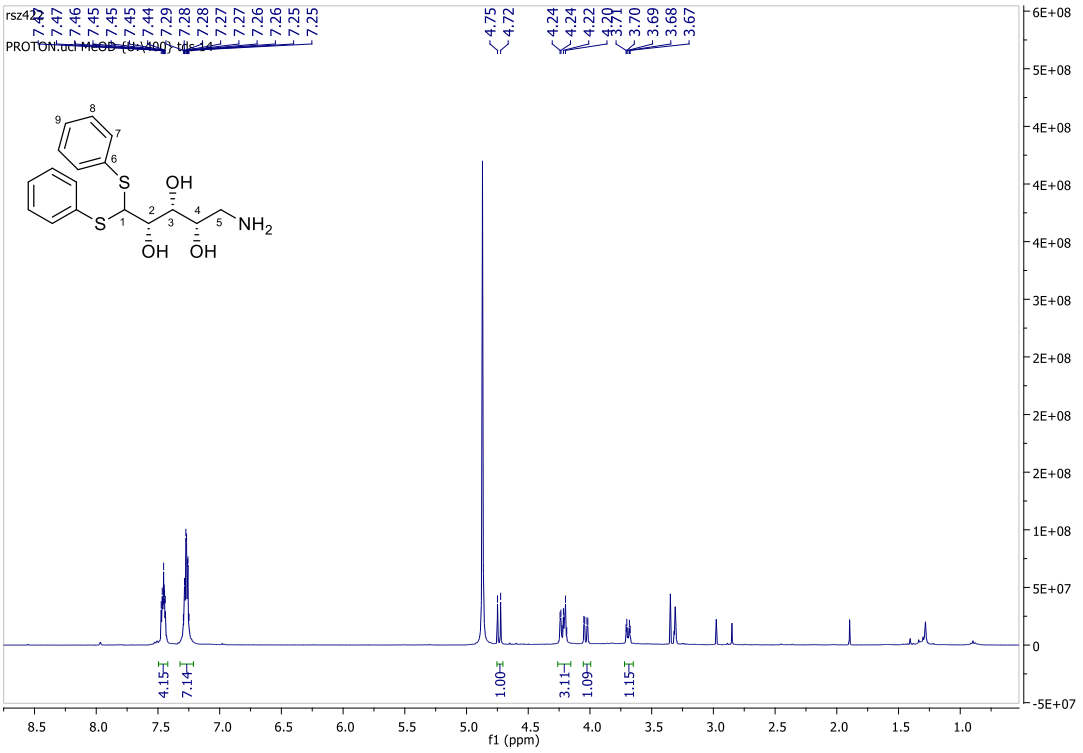



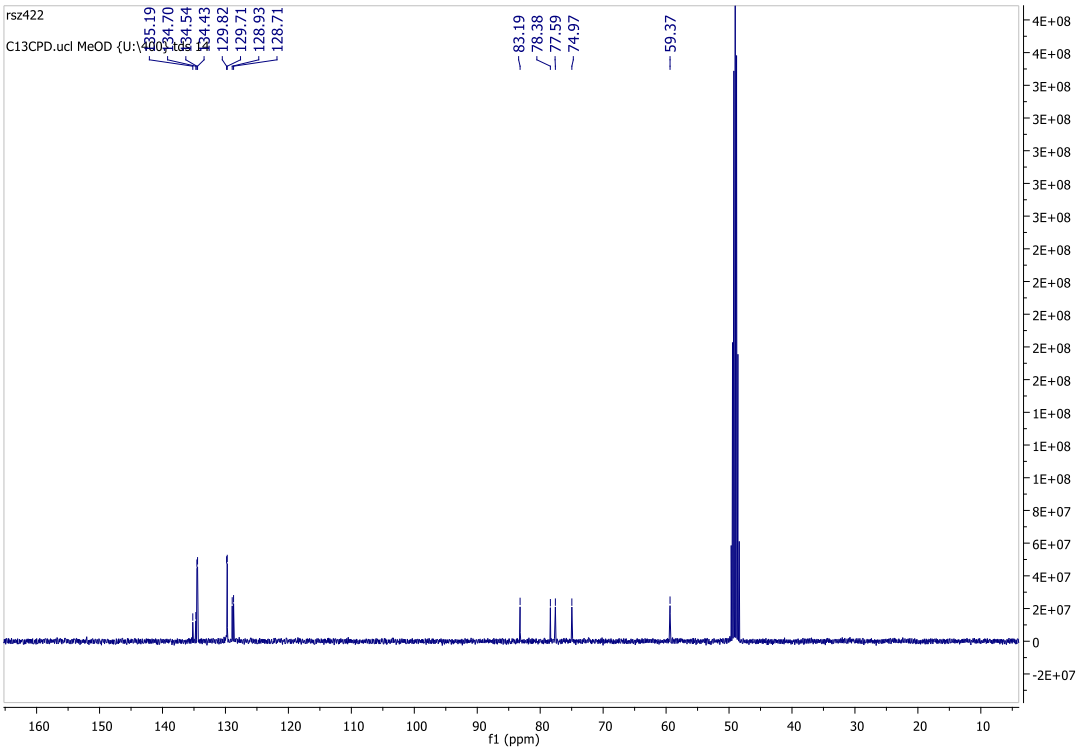
(2*S*,3*R*,4*S*)-5-Azido-1,1-bis(phenylthio)pentane-2,3,4-triol [**204**]:



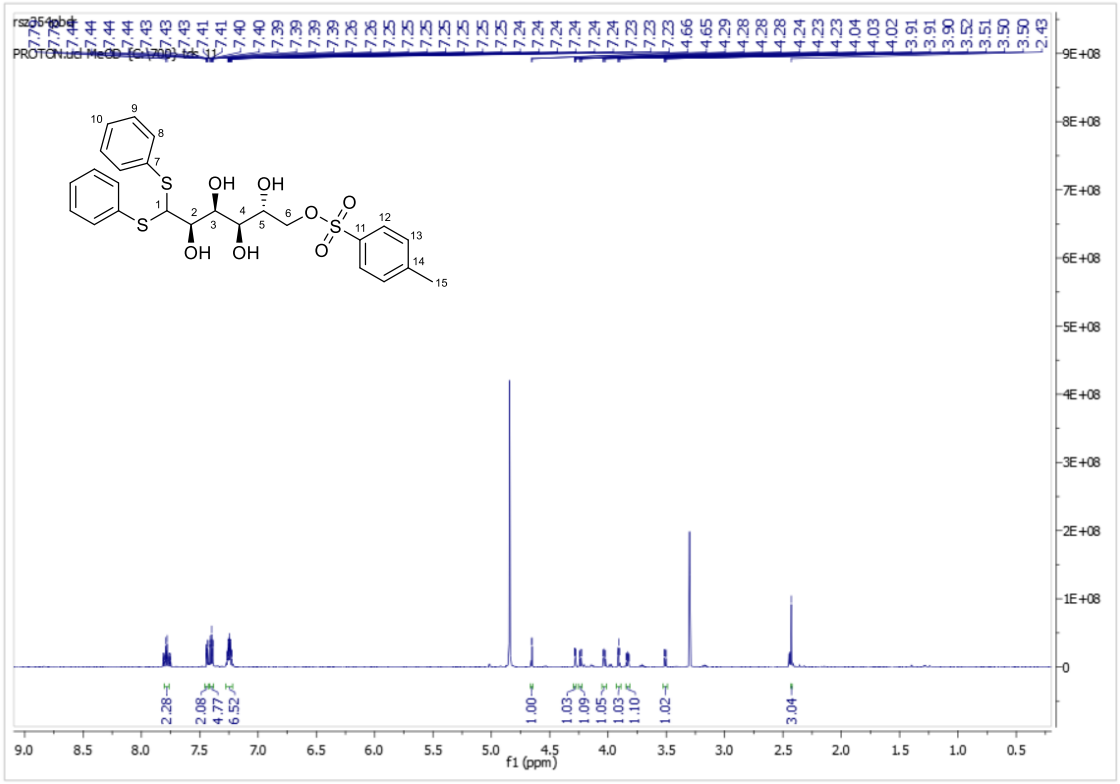



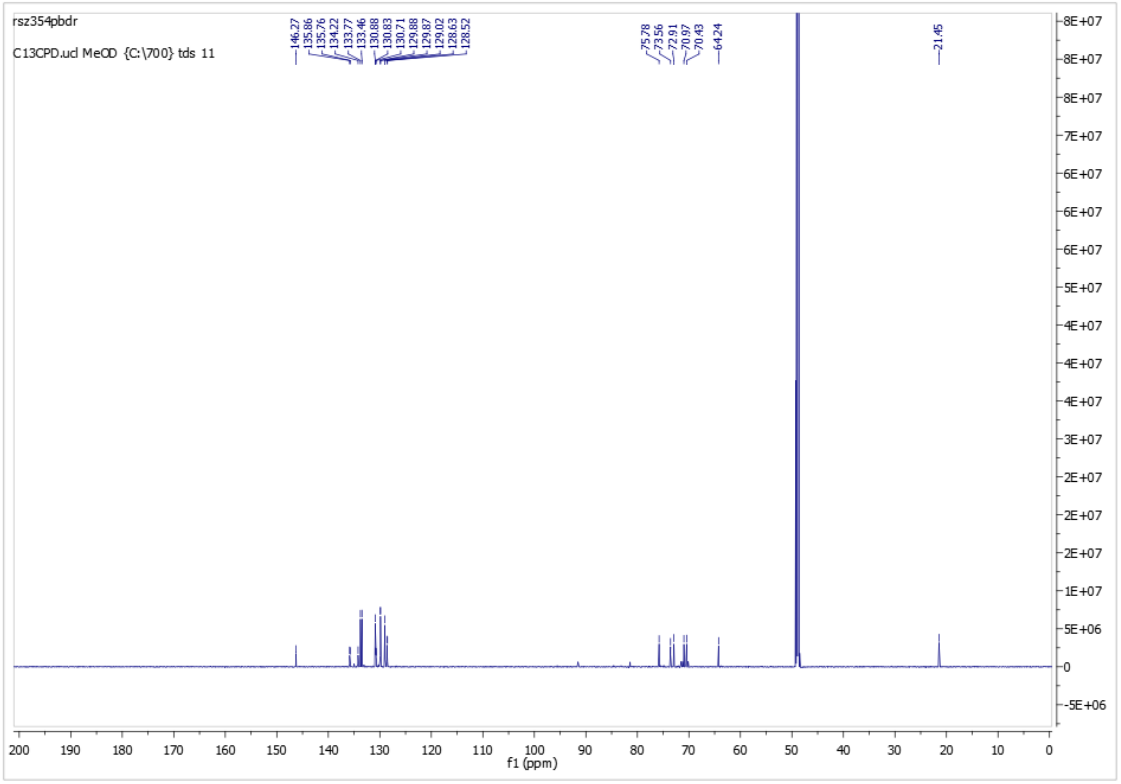
(2*S*,3*R*,4*S*)-5-Amino-1,1-bis(phenylthio)pentane-2,3,4-triol [**205**]:



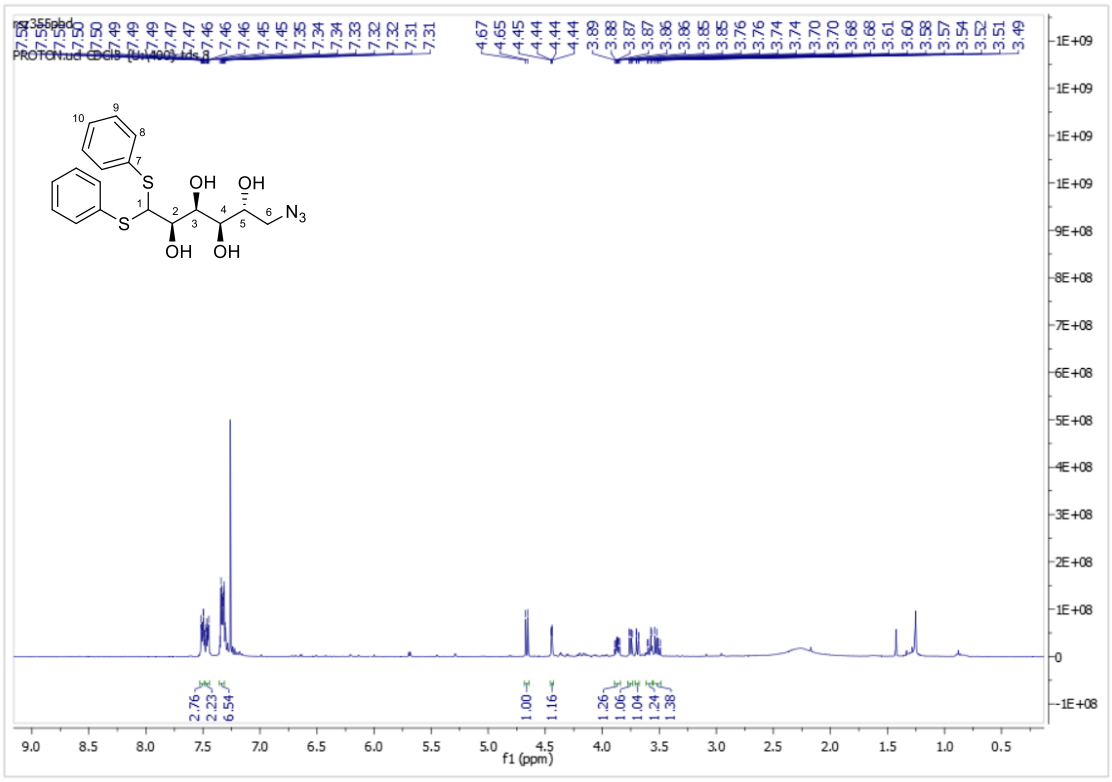



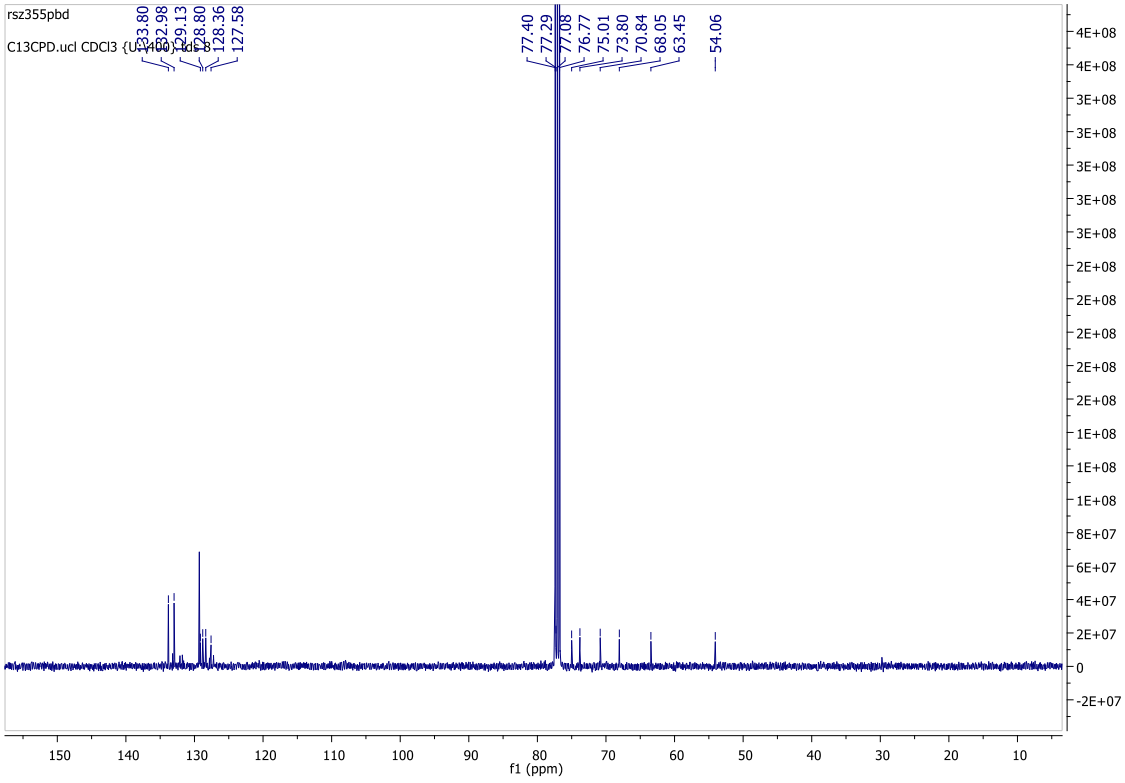
(2*R*,3*R*,4*S*,5*R*)-2,3,4,5-Tetrahydroxy-6,6-bis(phenylthio)hexyl 4-methylbenzenesulfonate [**208**]:



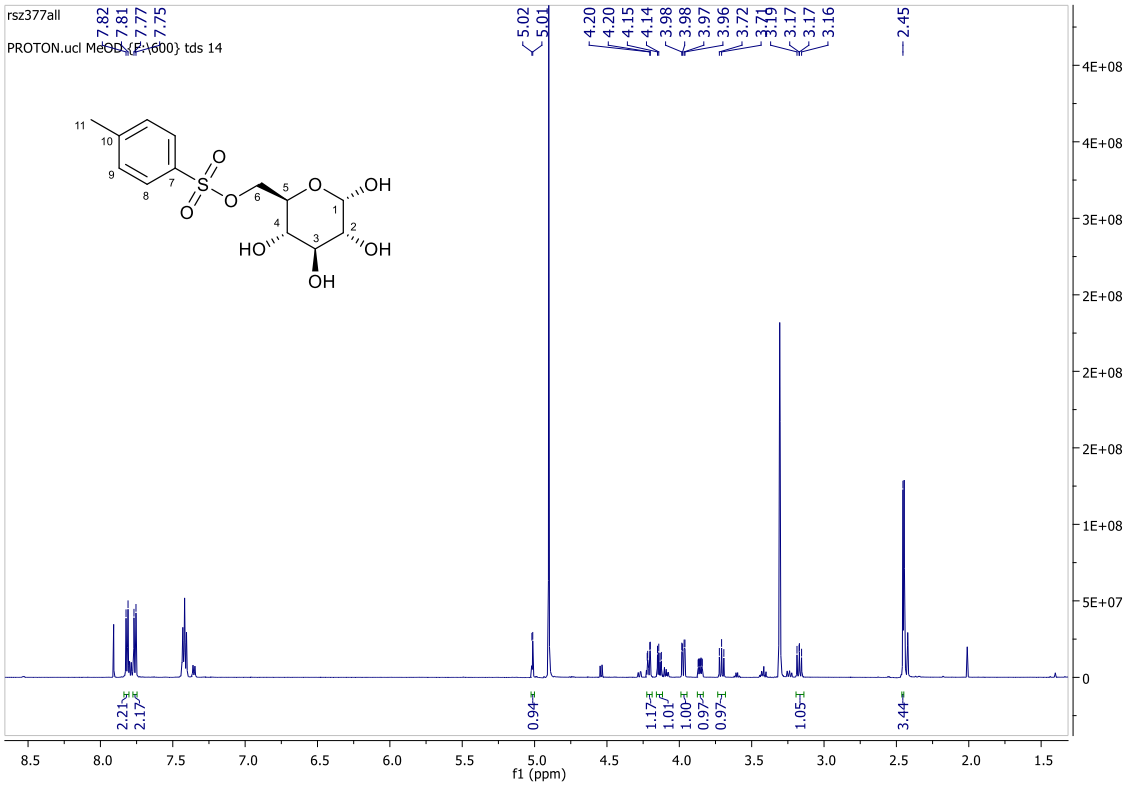



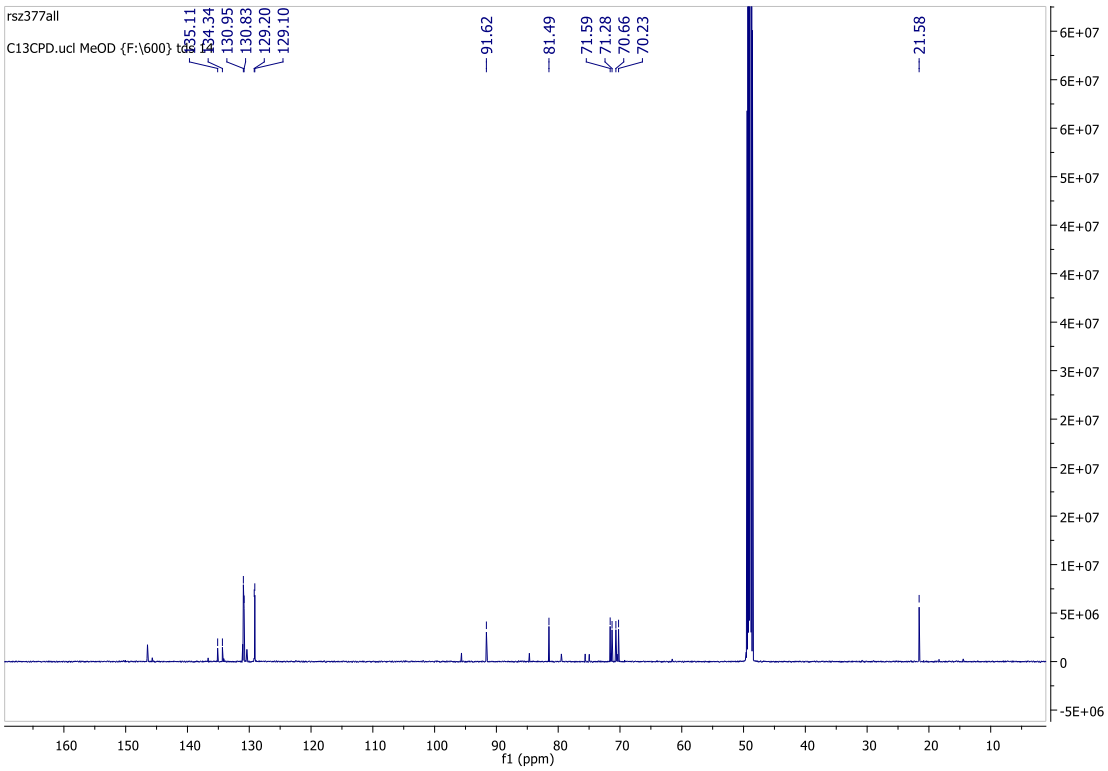
(2*R*,3*S*,4*R*,5*R*)-6-Azido-1,1-bis(phenylthio)hexane-2,3,4,5-tetraol [**209**]:



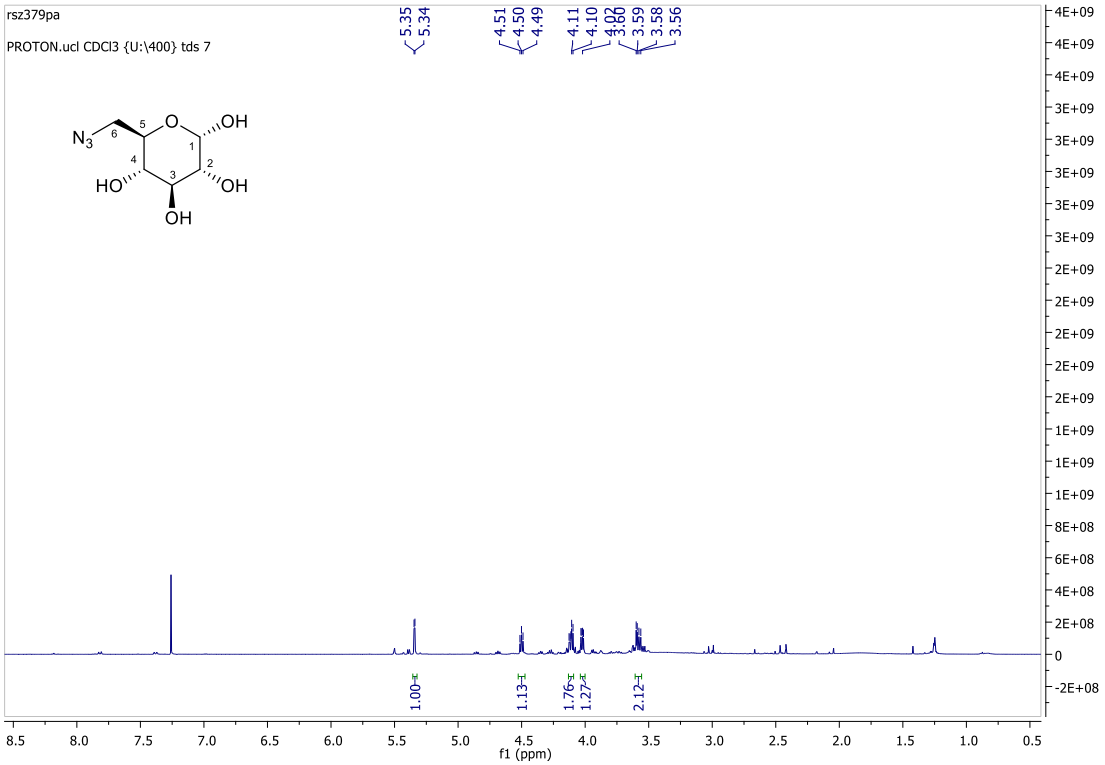



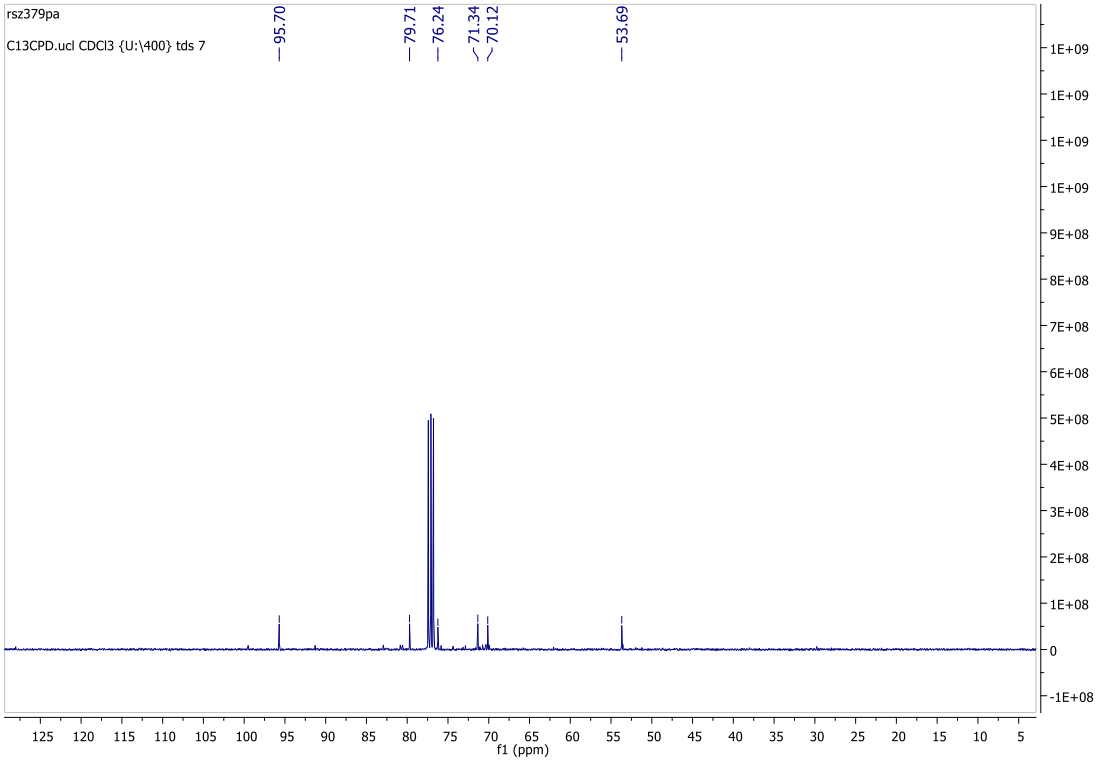
((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5,6-Tetrahydroxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate [**213**]:



(2*S*,3*R*,4*S*,5*S*,6*R*)-6-(Azidomethyl)tetrahydro-2H-pyran-2,3,4,5-tetraol [**214**]:



Supporting Information: Computational

Conformational searches on tetraols *ent*-**5a** and **5c**, and on cyclic carbonates *ent*-**7a** and **7c**, were carried out using the MMFF force field and the SCAN function in Tinker.[1] All structures within 10.0 kJ $mol^{-1}$ of the lowest-energy structure for each compound were then optimised in the gas phase using Gaussian 09,[2] with the M06-2X functional and 6-31G(d,p) basis set. All structures were confirmed as minima by the absence of imaginary vibrational frequencies. Duplicate structures were removed, then solvation energies for each of the unique minima was determined by a single-point solution-phase energy calculation (IEFPCM, methanol). Free energies were corrected for low-frequency vibrations using *GoodVibes*.[3]

The lowest-energy conformation of each compound is depicted overleaf.[4] Coordinates are provided in xyz format in an accompanying zip file.

| Compound | $E_{gas}$/Hartree | $G_{gas}$/Hartree | $E_{MeOH}$/Hartree | $G_{MeOH}$/Hartree[a] | $G_{rel}$/kJ $mol^{-1}$ [b] |
|---|---|---|---|---|---|
| *ent*-**5a** | –1756.661759 | –1756.366811 | –1756.676496 | –1756.381547 | 12.3 |
| **5b** | –1756.670599 | –1756.373674 | –1756.683212 | –1756.386287 | 0.0 |
| *ent*-**7a** | –1868.772929 | –1868.492095 | –1868.791090 | –1868.510257 | 0.0 |
| **7b** | –1868.768289 | –1868.487270 | –1868.788221 | –1868.507202 | 9.0 |

All calculations at the M06-2X/6-31G(d,p) level.

[a]Calculated as $G_{MeOH} = E_{MeOH} + (G_{gas} - E_{gas})$.

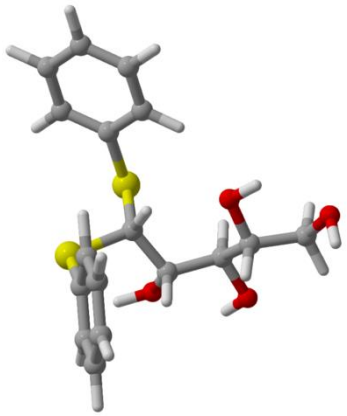
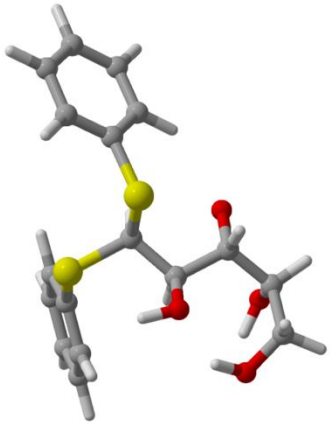
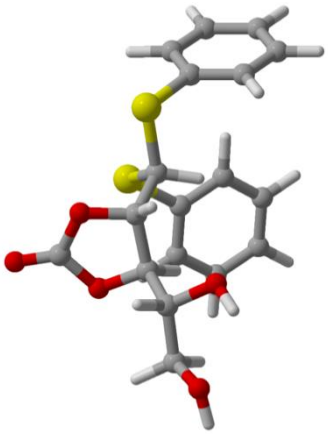
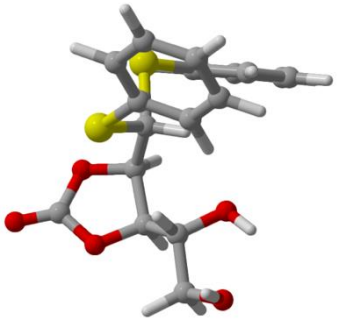
[b]Free energy relative to the lower of the two stereoisomers considered.

[1] Ponder, J. W., *Tinker 7.1*, **2015**, http://dasher.wustl.edu/tinker.

[2] *Gaussian 09, Revision D.01*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian, Inc.,* Wallingford CT, **2013**.

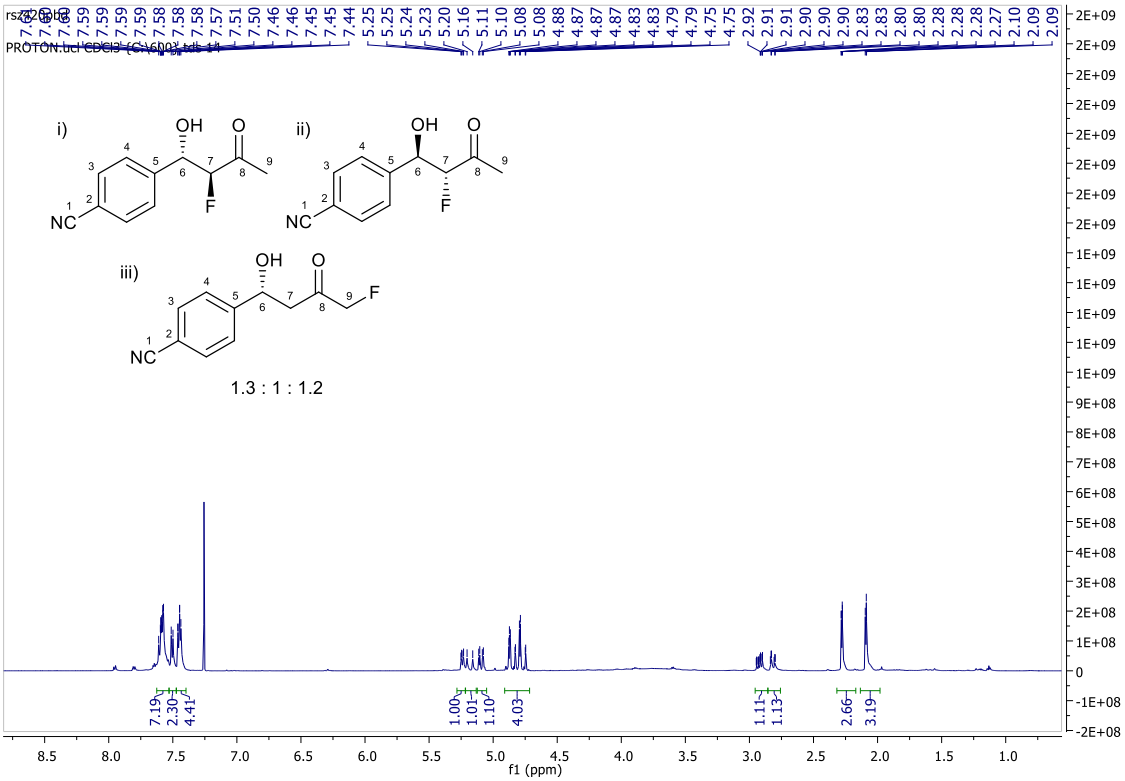
[3] Funes-Ardoiz, I.; Paton, R.S., *GoodVibes v1.0.2*, **2017**, https://zenodo.org/record/841362.

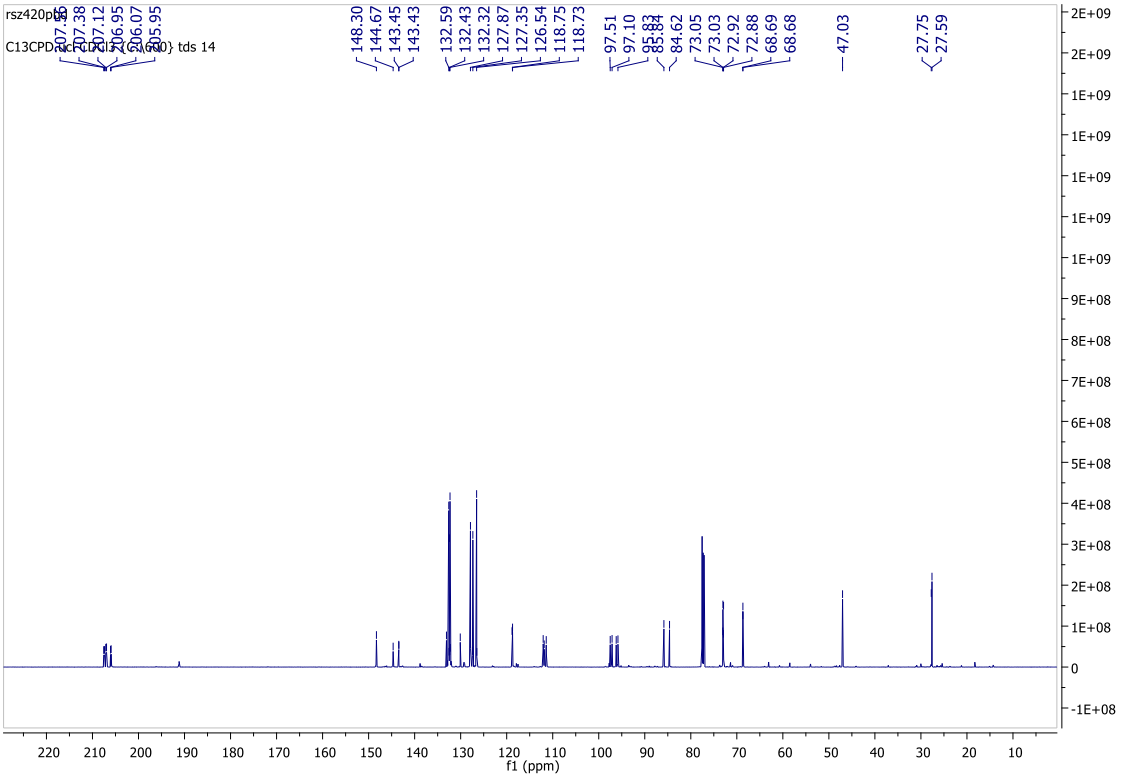
[4] Images generated using *Cylview 20*; Legault, C.Y., Université de Sherbrooke, **2020**, www.cylview.org.

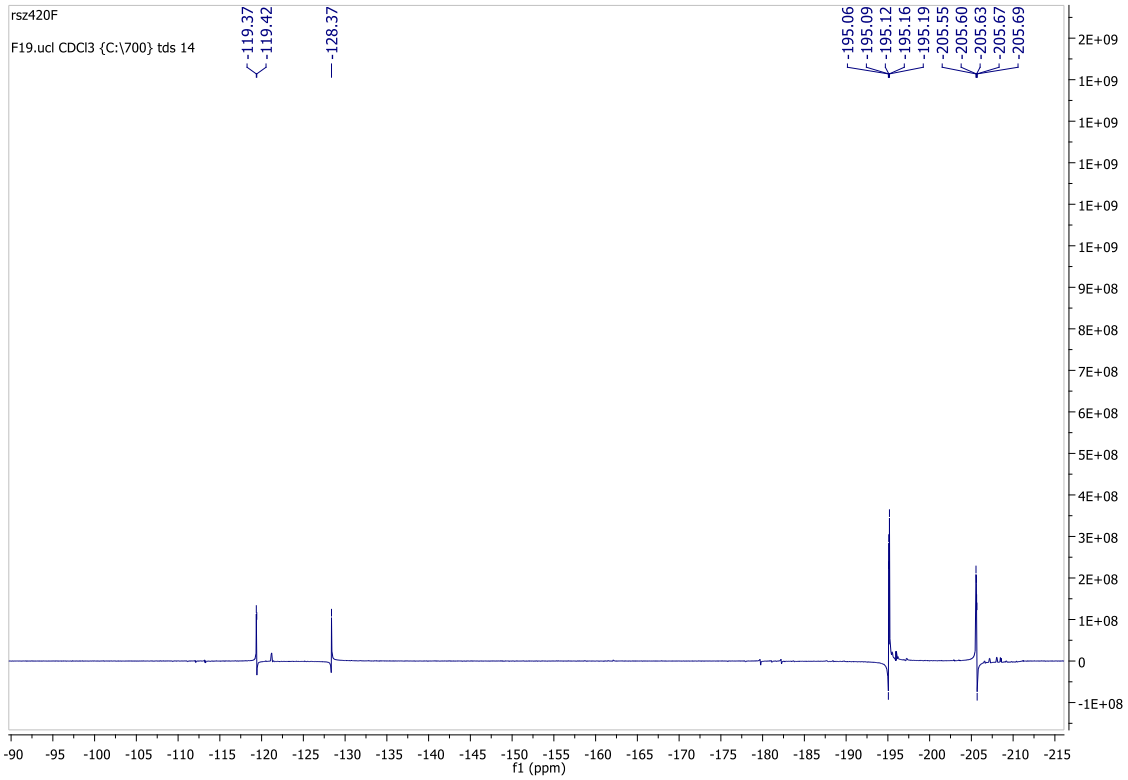
| | |
|---|---|
|  L-ara thioacetal |  D-rib thioacetal |
|  L-ara derived DMC TS |  D-rib derived DMC TS |

Supporting Information: $^{1}H$, $^{13}C$ & $^{19}F$ NMR

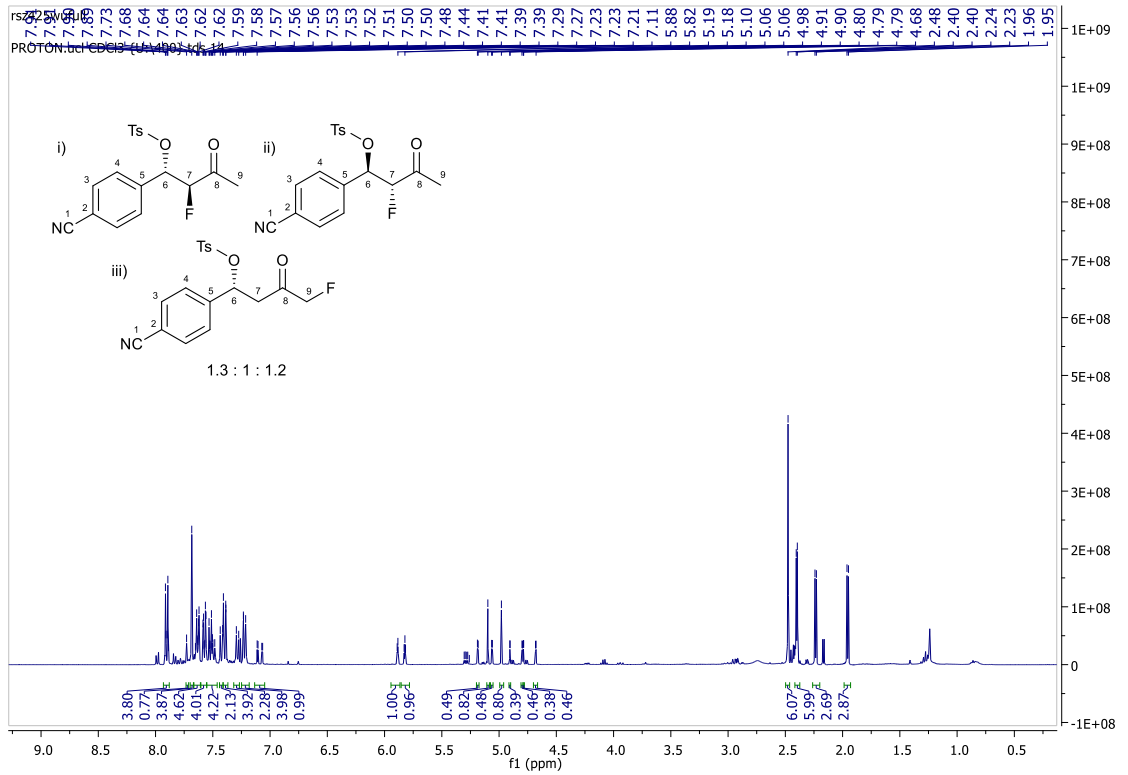
4-(2-Fluoro-1-hydroxy-3-oxobutyl)benzonitrile [**235**]:

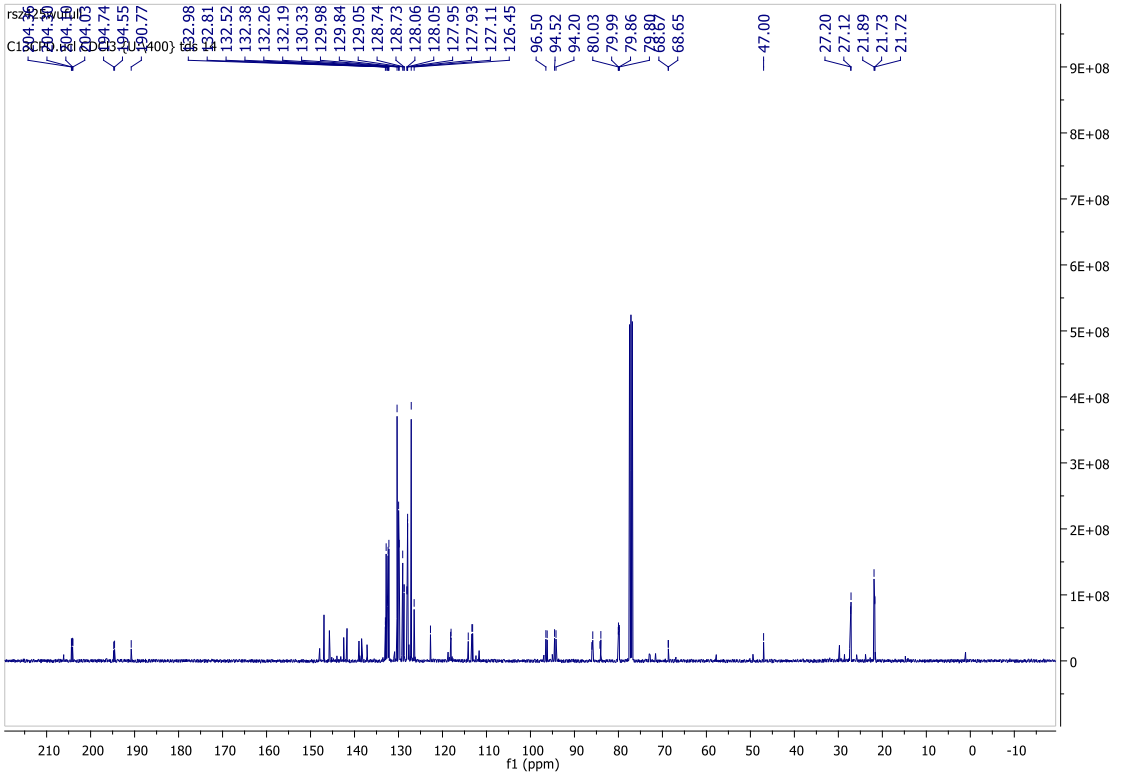


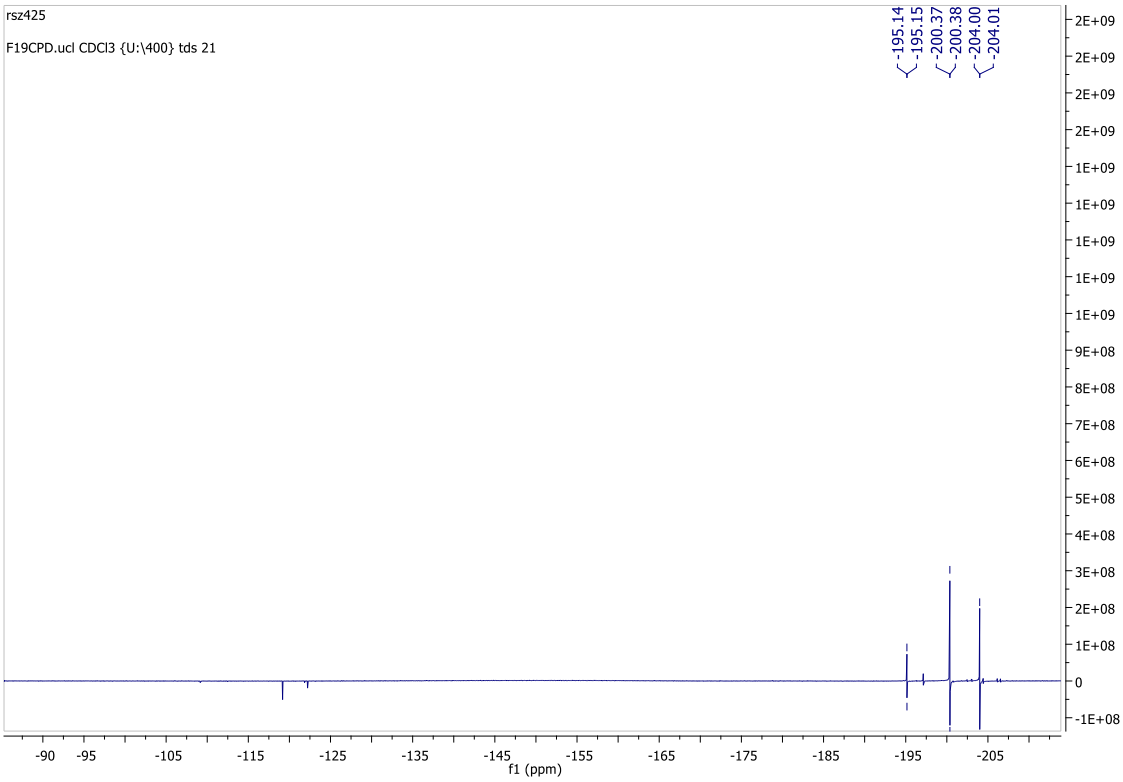





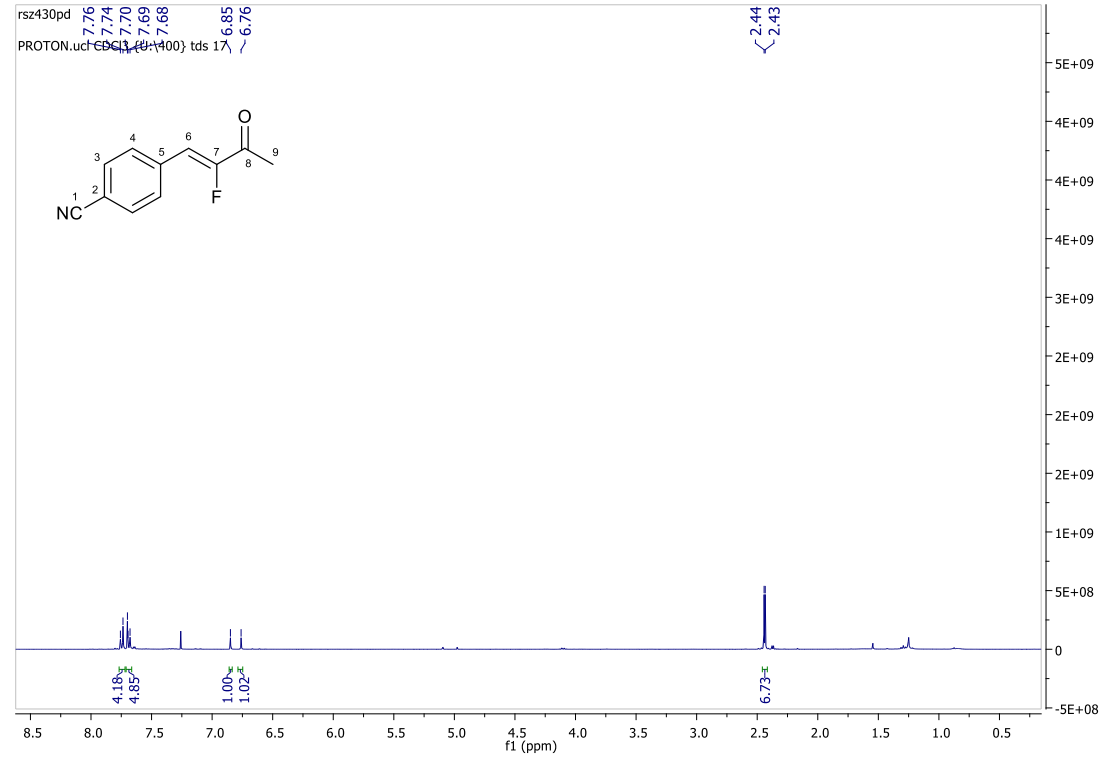

(2*S*)-1-(4-Cyanophenyl)-2-fluoro-3-oxobutyl 4-methylbenzenesulfonate, (*R*)-1-(4-cyanophenyl)-4-fluoro-3-oxobutyl 4-methylbenzenesulfonate425 [**236**]:

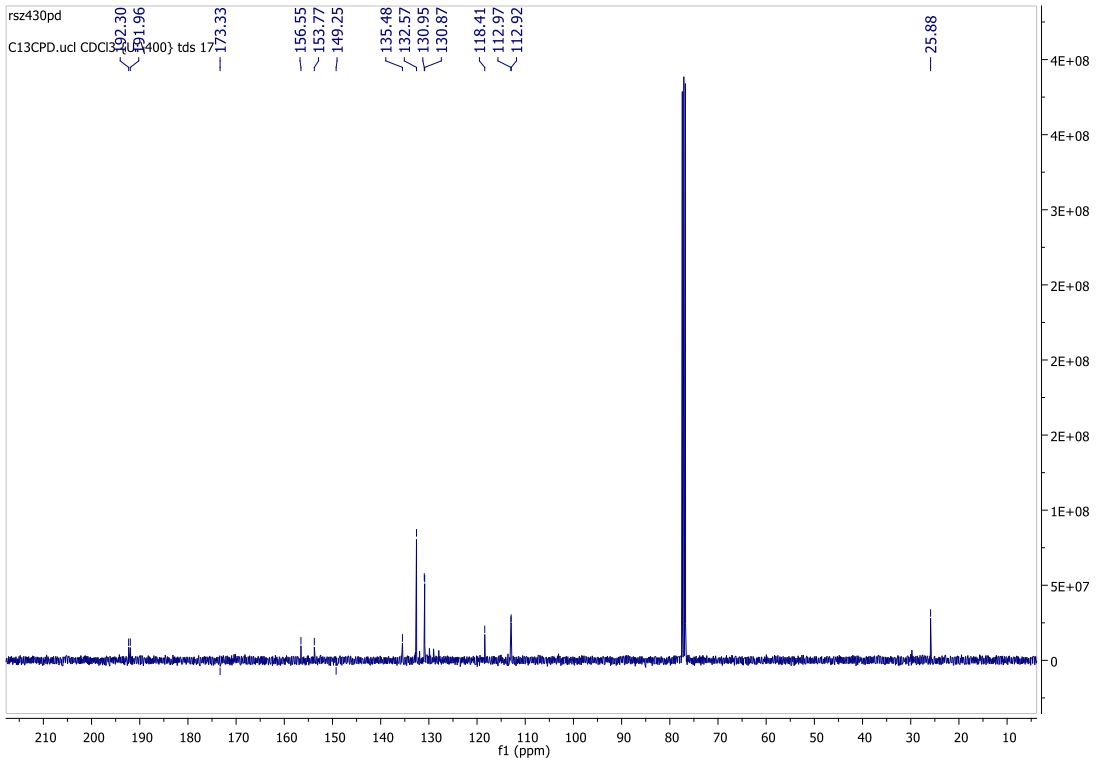


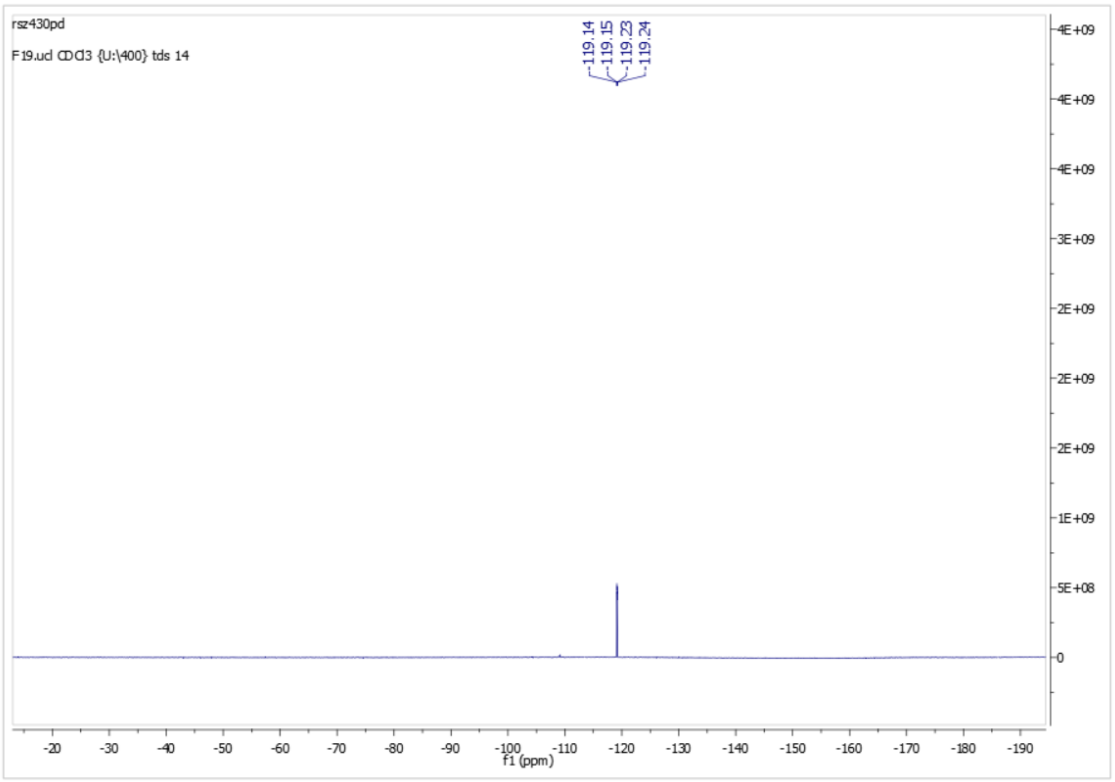

rsz425
C13CPD.ucl CDCl3 {U:\400} tds 14
204.55
204.03
194.74
194.55
190.77
132.98
132.81
132.52
132.38
132.26
132.19
130.33
129.98
129.84
129.05
128.74
128.73
128.06
128.05
127.95
127.93
127.11
126.45
96.50
94.52
94.20
80.03
79.99
79.86
79.80
68.87
68.65
47.00
27.20
27.12
21.89
21.73
21.72
f1 (ppm)


rsz425
F19CPD.ucl CDCl3 {U:\400} tds 21
-195.14
-195.15
-200.37
-200.38
-204.00
-204.01
f1 (ppm)

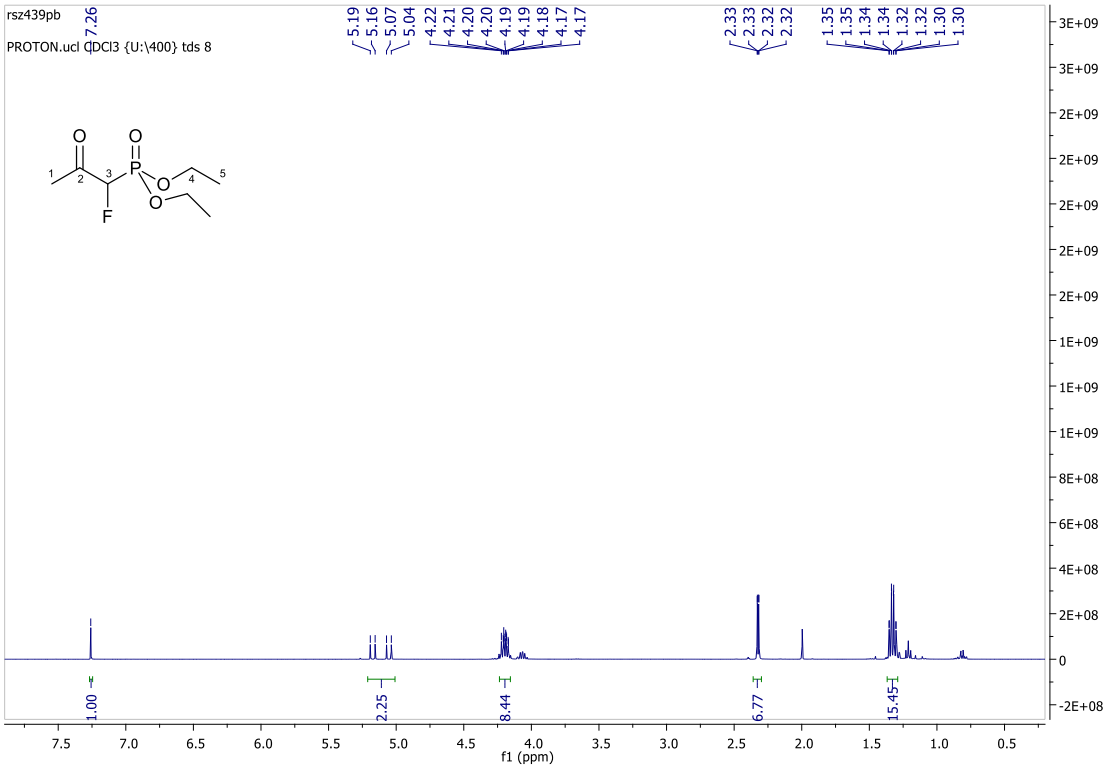
(*Z*)-4-(2-Fluoro-3-oxobut-1-en-1-yl)benzonitrile [**237**]:

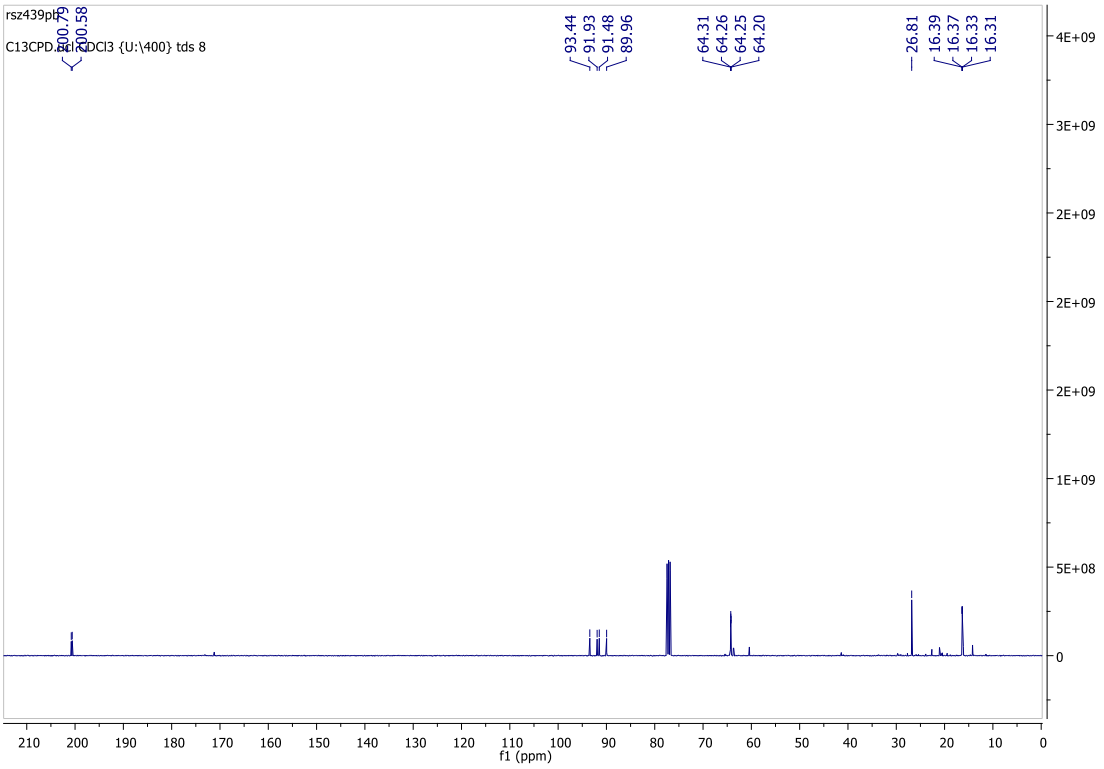


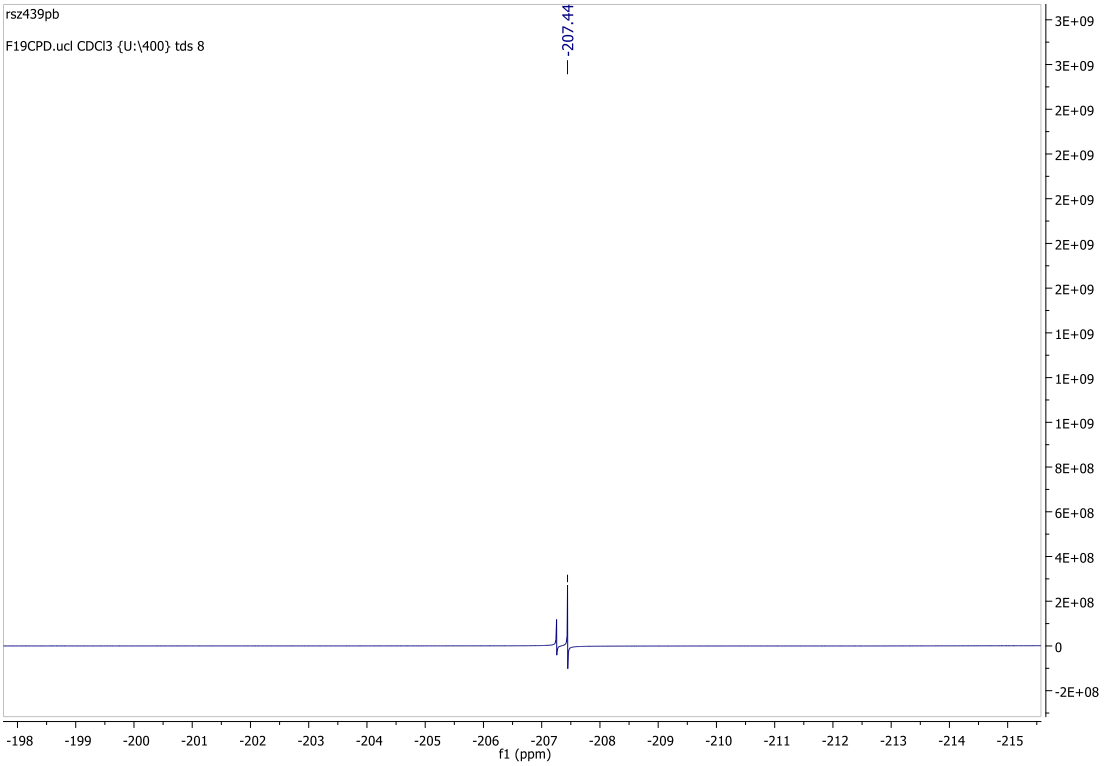



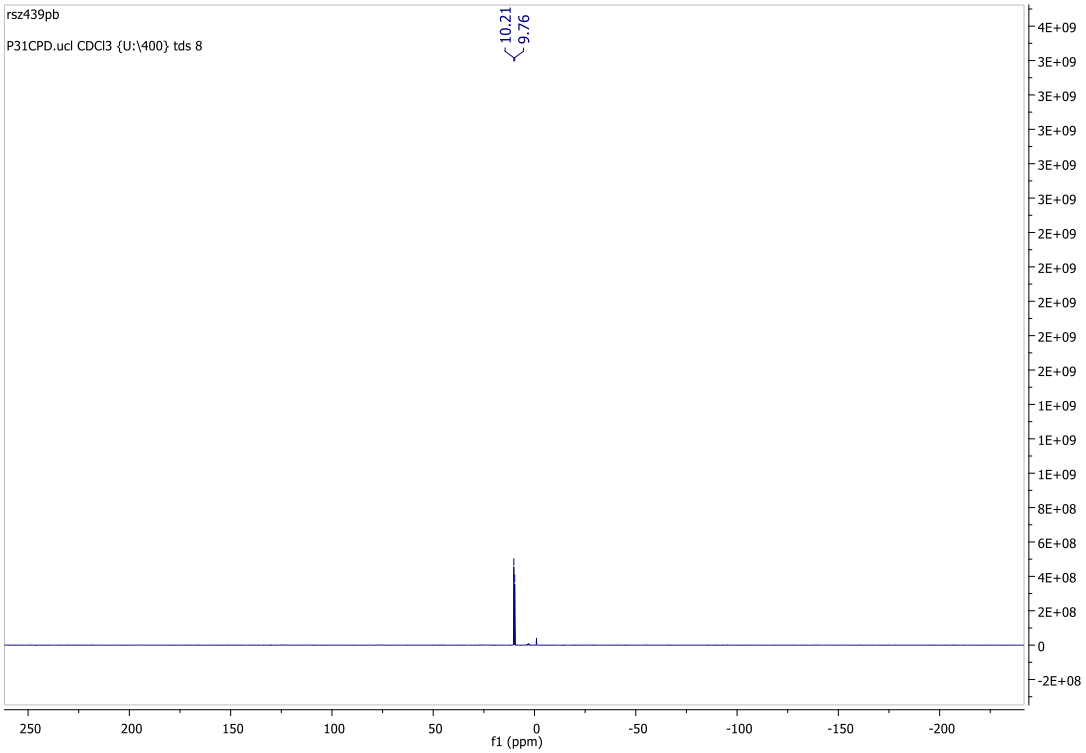



Diethyl (1-fluoro-2-oxopropyl)phosphonate [**241**]:

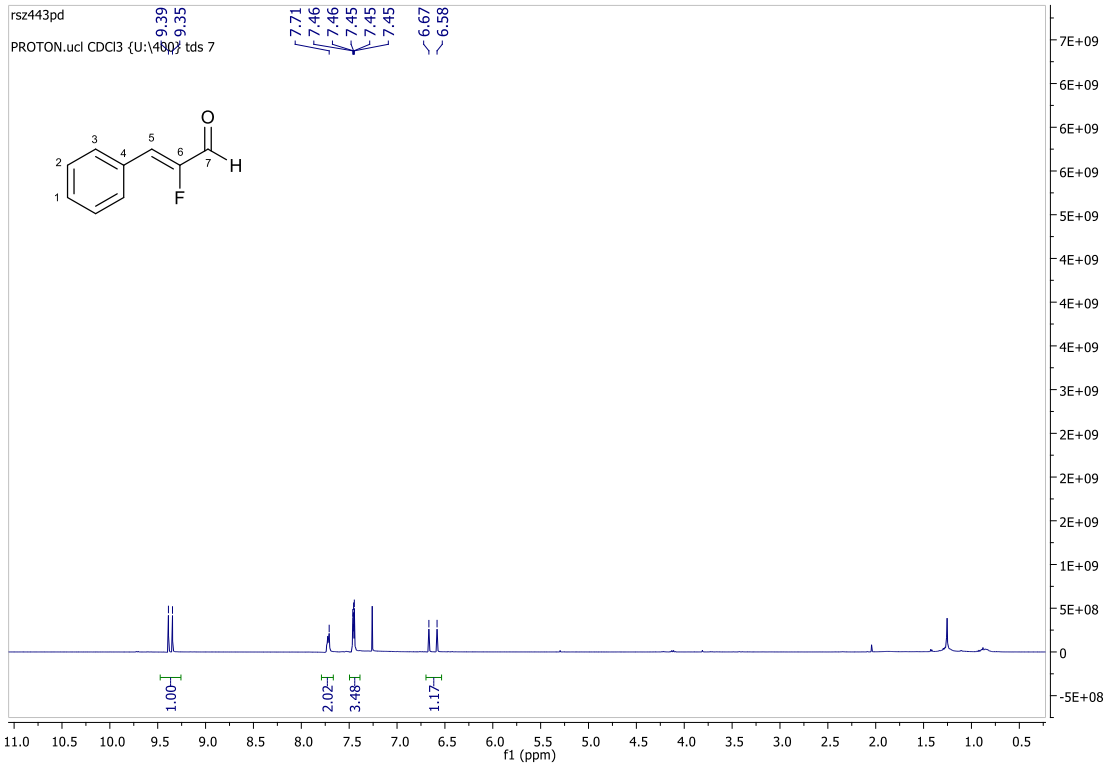


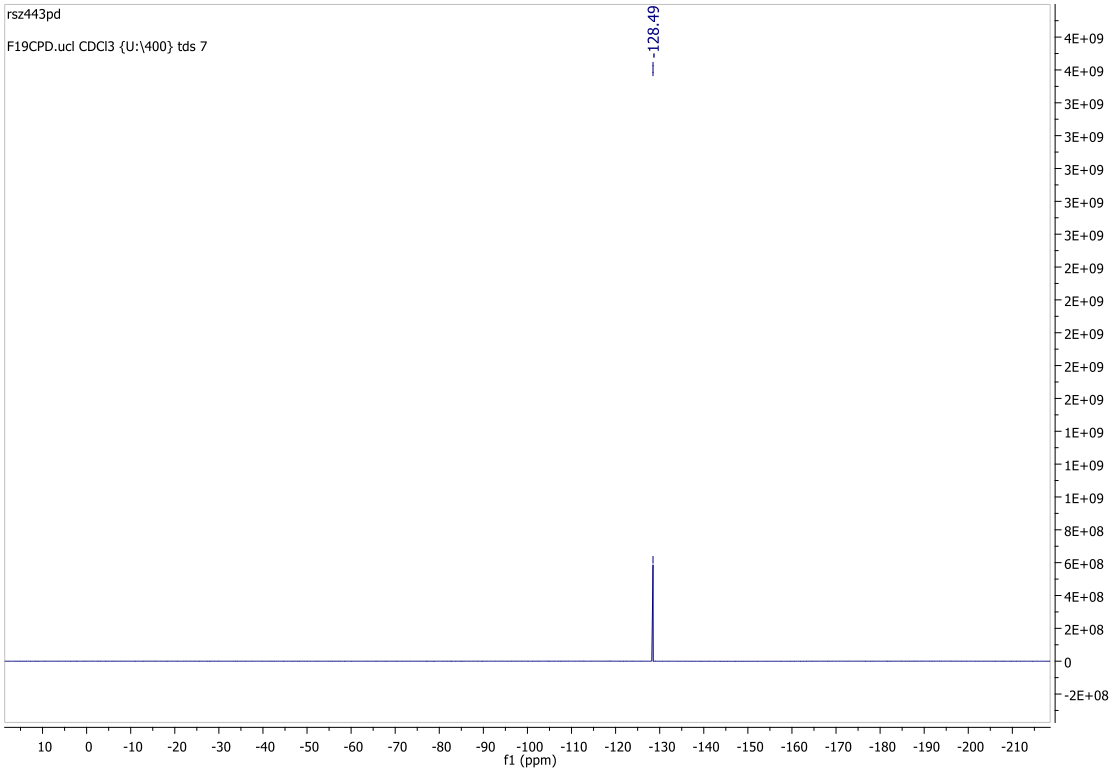

rsz439pb
C13CPD.ucl CDCl3 {U:\400} tds 8
200.79
200.58
93.44
91.93
91.48
89.96
64.31
64.26
64.25
64.20
26.81
16.39
16.37
16.33
16.31
4E+09
3E+09
2E+09
2E+09
2E+09
1E+09
5E+08
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

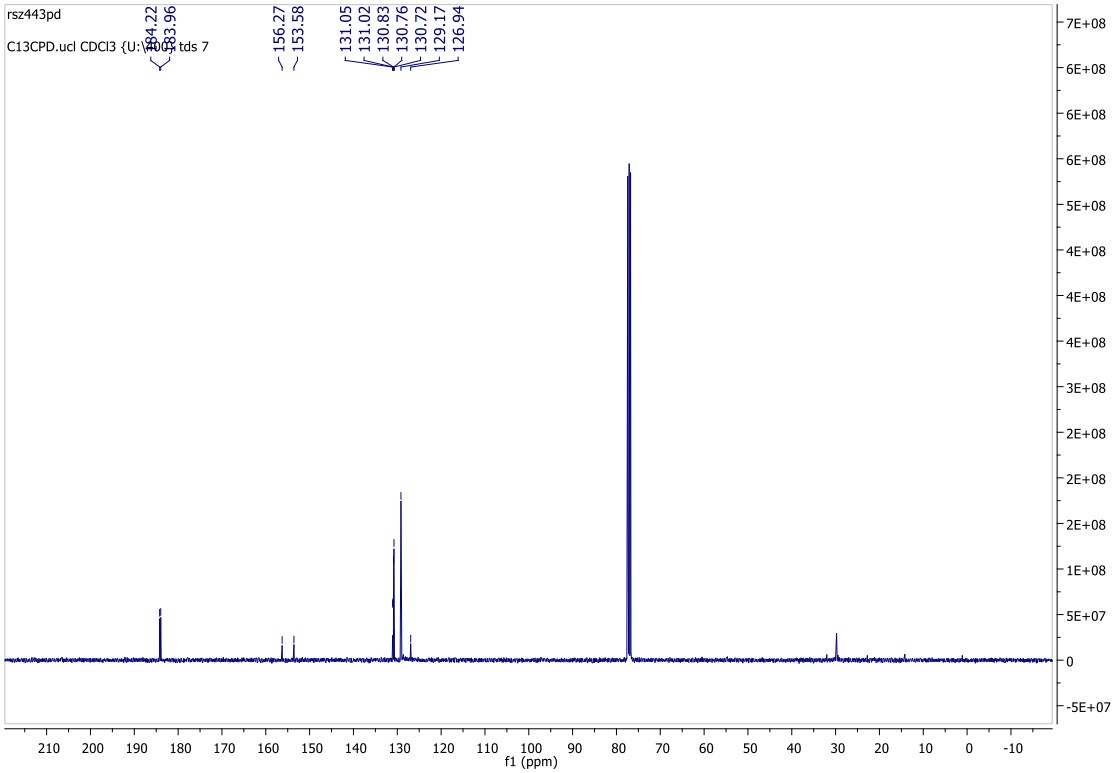

rsz439pb
F19CPD.ucl CDCl3 {U:\400} tds 8
-207.44
3E+09
3E+09
2E+09
2E+09
2E+09
2E+09
2E+09
2E+09
1E+09
1E+09
1E+09
8E+08
6E+08
4E+08
2E+08
0
-2E+08
-198 -199 -200 -201 -202 -203 -204 -205 -206 -207 -208 -209 -210 -211 -212 -213 -214 -215
f1 (ppm)



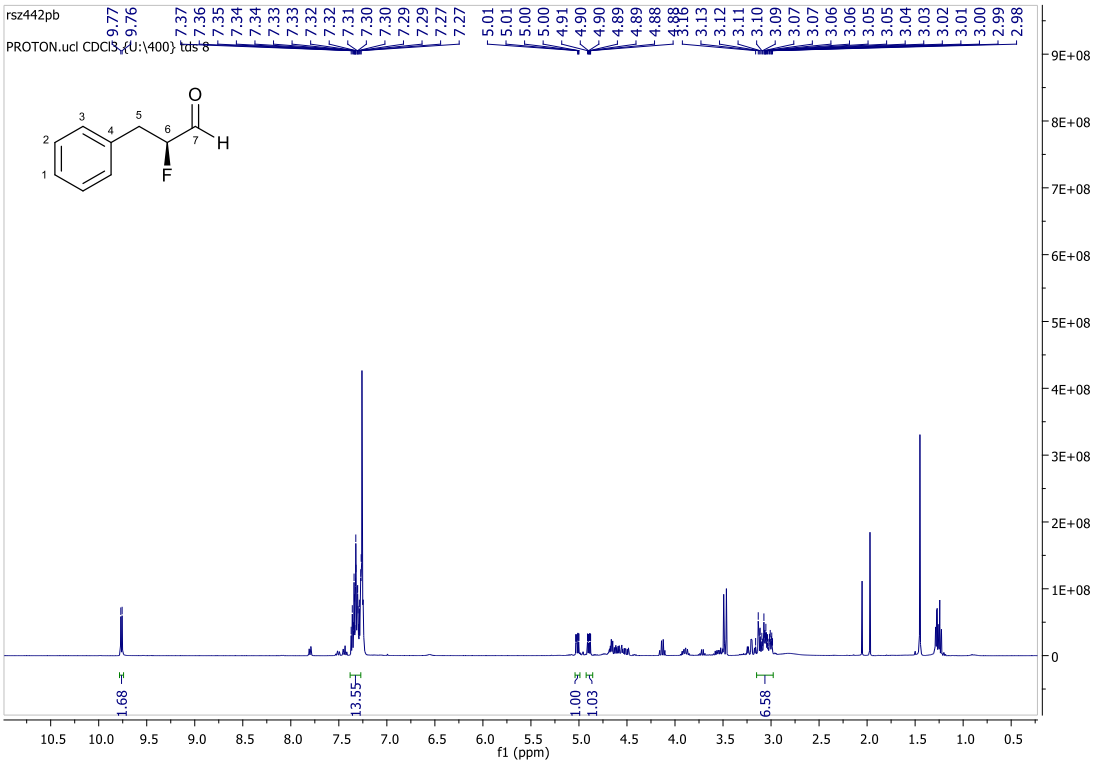

*Z*-2-Fluoro-3-phenylacrylaldehyde [**247**]:

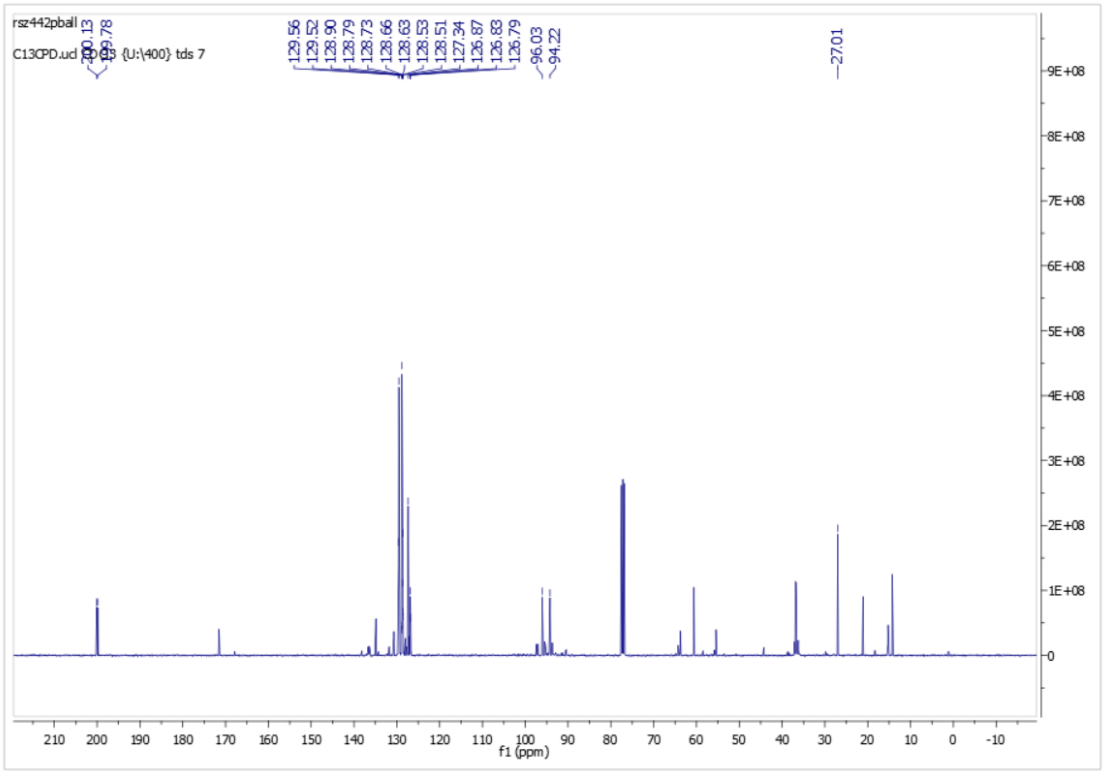


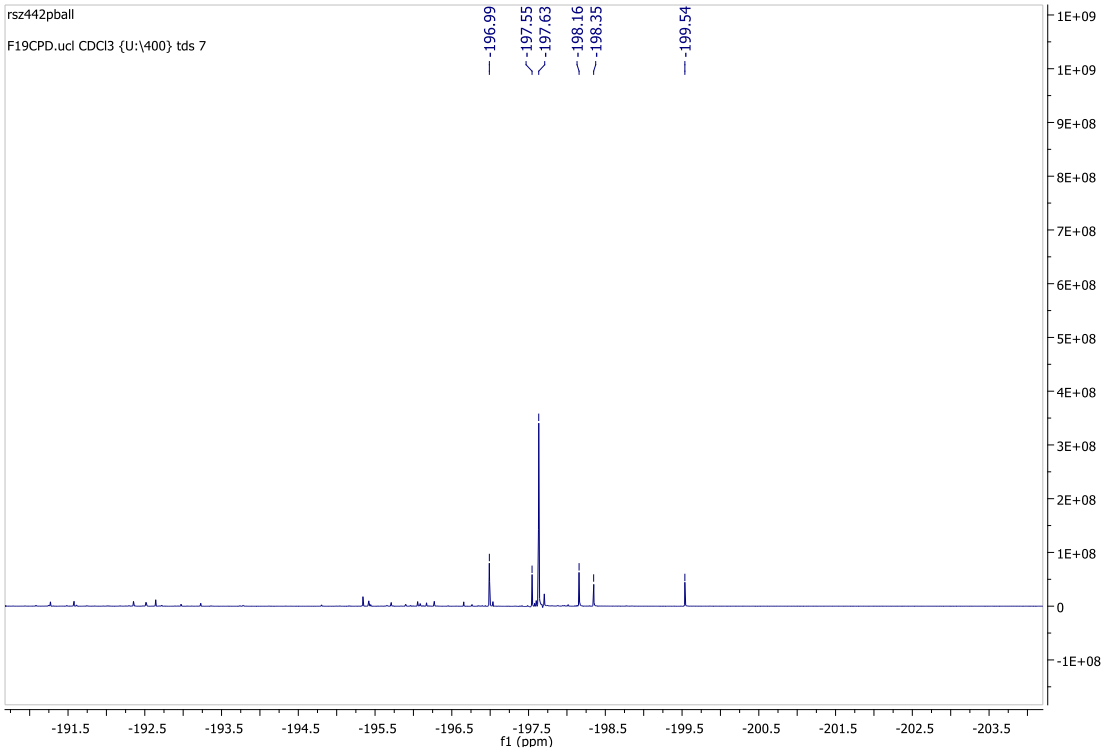

rsz443pd
F19CPD.ucl CDCl3 {U:\400} tds 7
-128.49
f1 (ppm)


rsz443pd
C13CPD.ucl CDCl3 {U:\400} tds 7
184.22
183.96
156.27
153.58
131.05
131.02
130.83
130.76
130.72
129.17
126.94
f1 (ppm)

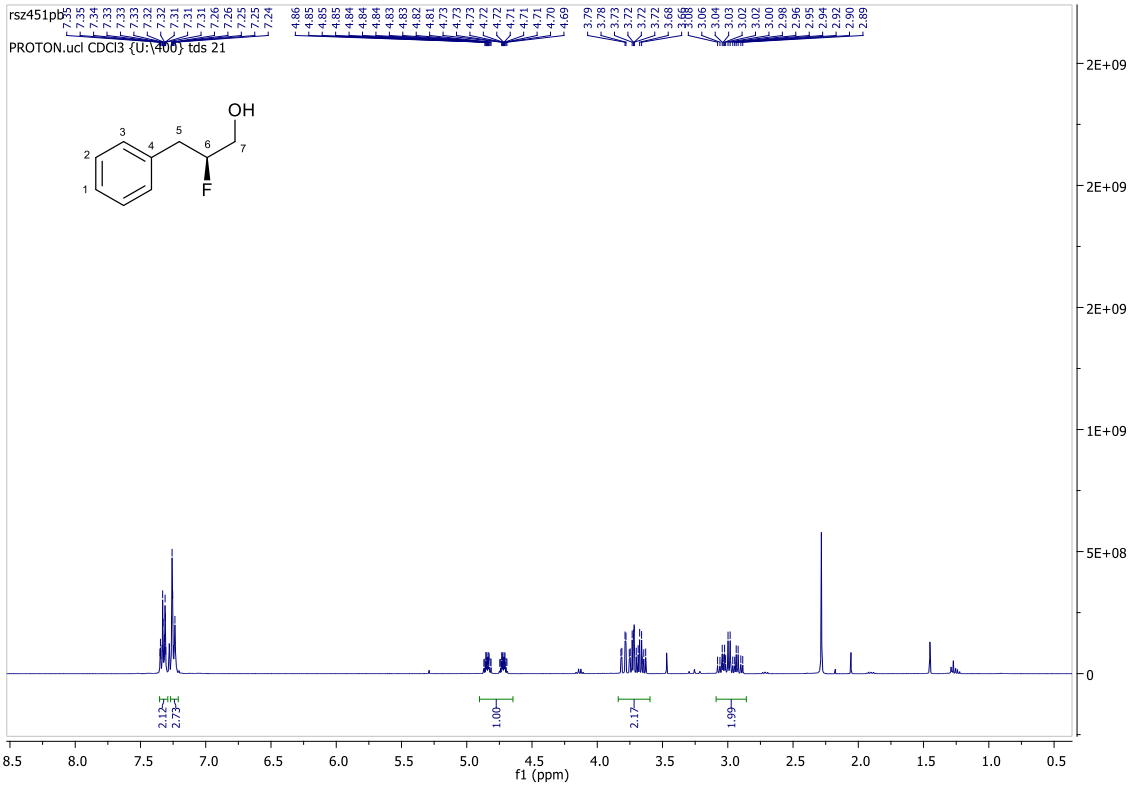
2-Fluoro-3-phenylpropanal [**250**]:

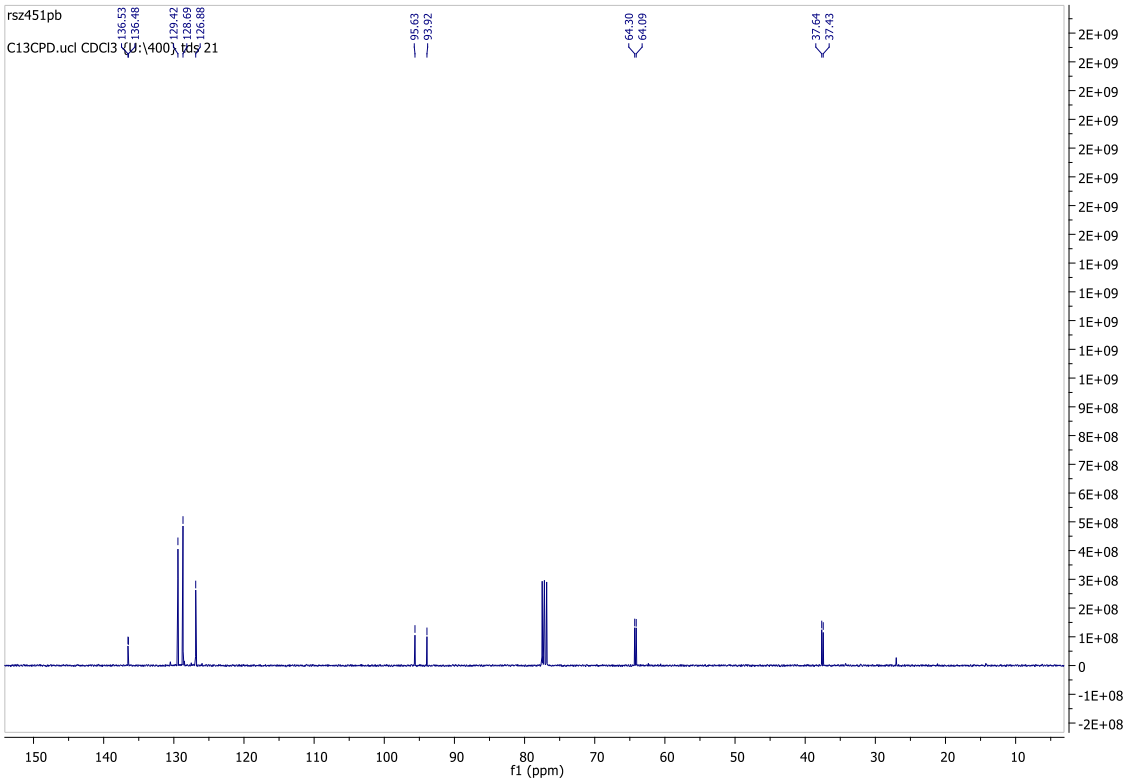


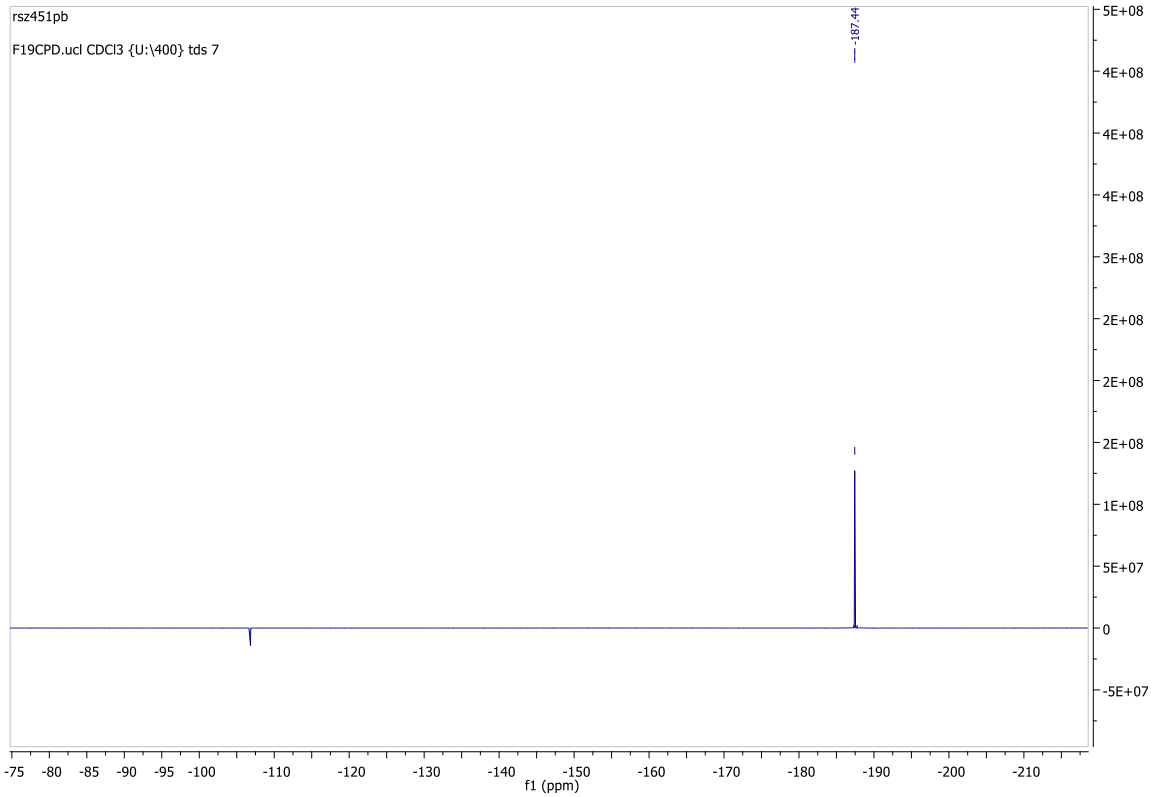





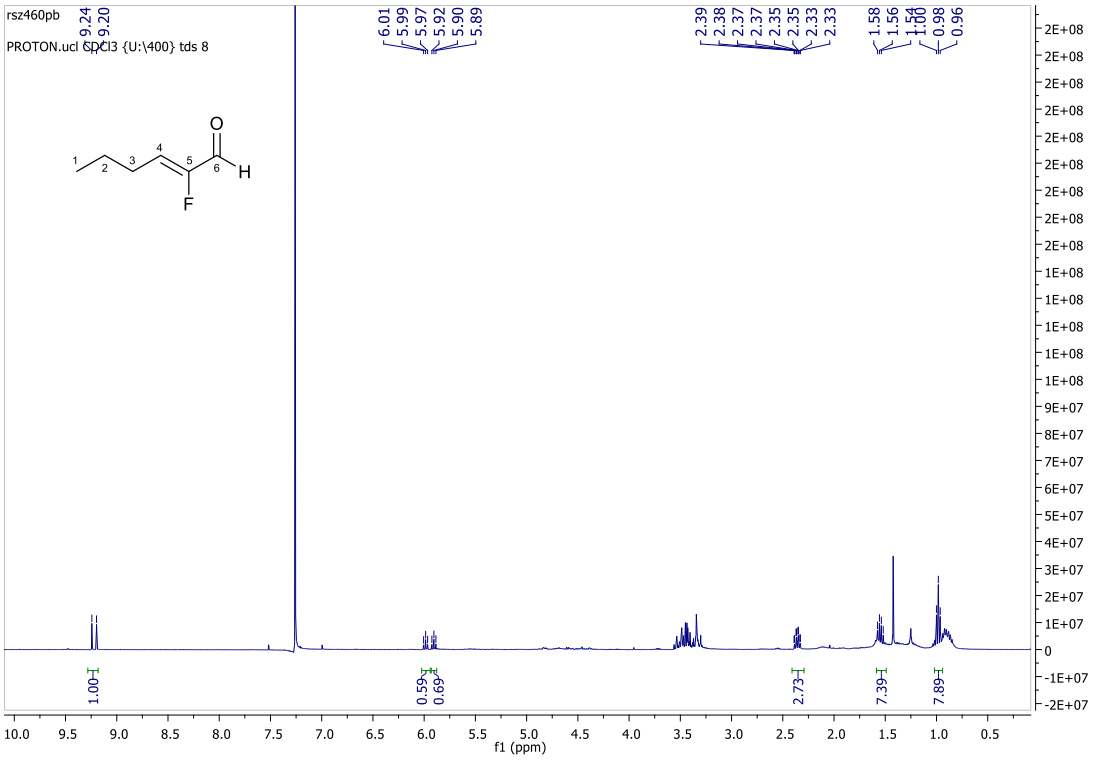

(*S*)-2-Fluoro-3-phenylpropan-1-ol [**251**]:

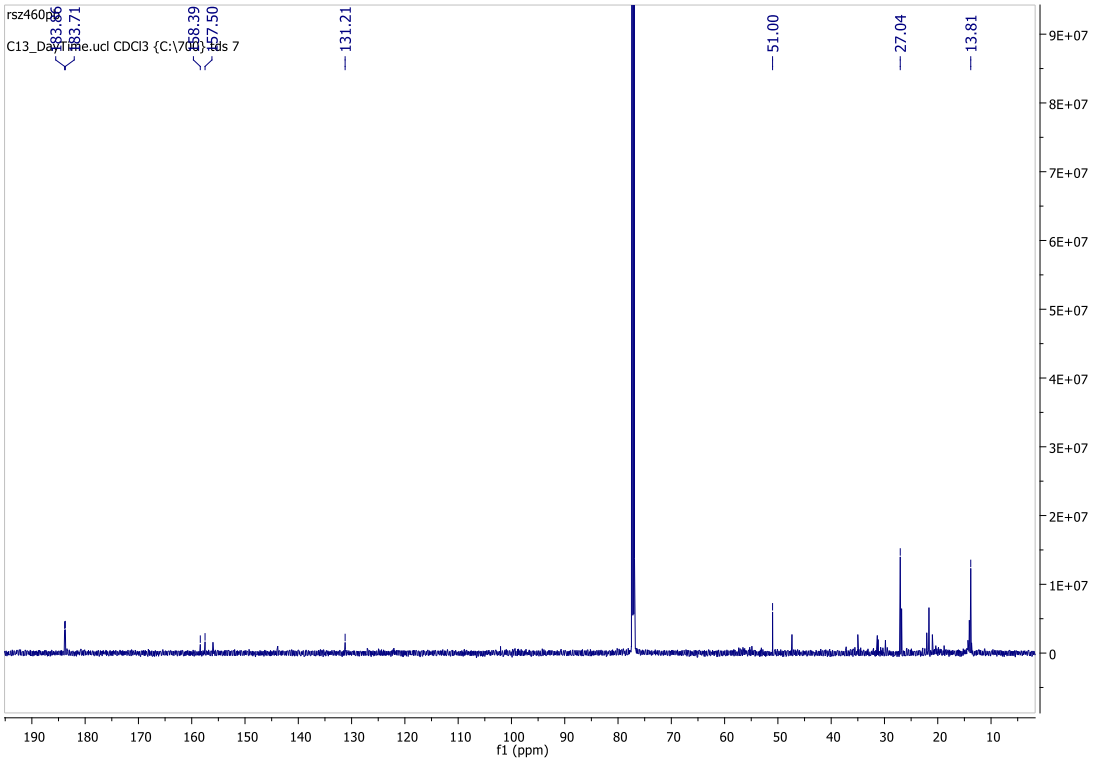


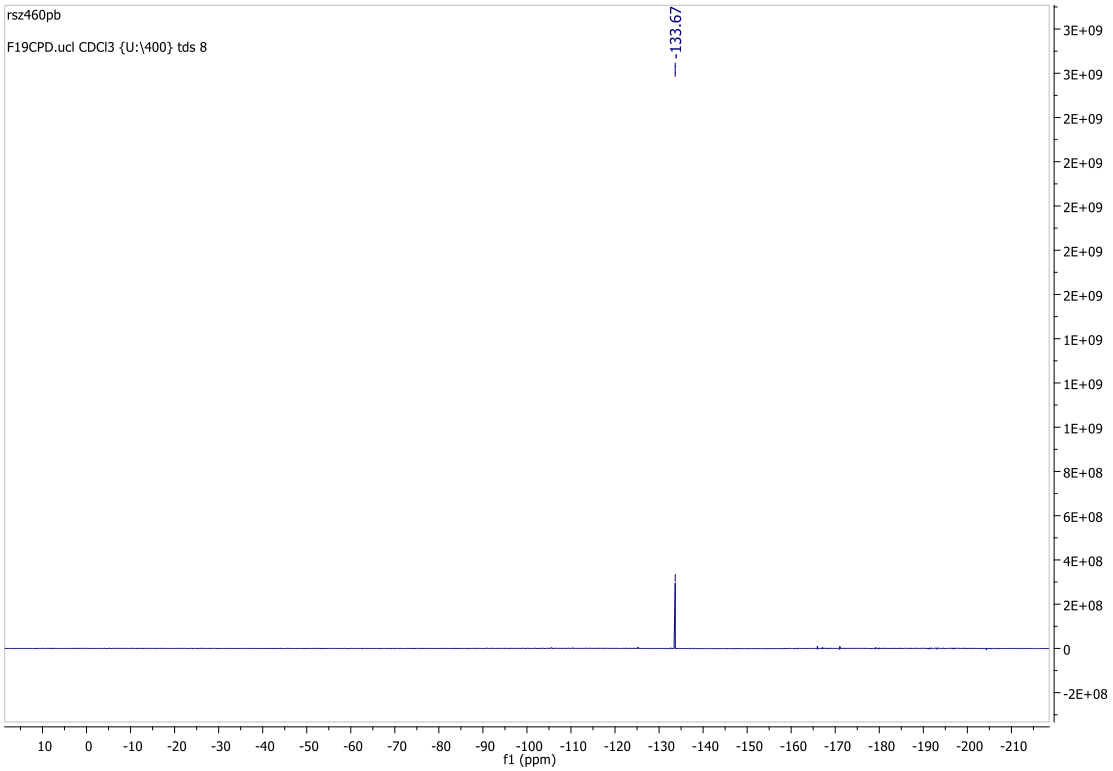

rsz451pb
C13CPD.ucl CDCl3 {U:\400} tds 21
136.53
136.48
129.42
128.69
126.88
95.63
93.92
64.30
64.09
37.64
37.43
f1 (ppm)


rsz451pb
F19CPD.ucl CDCl3 {U:\400} tds 7
-187.44
f1 (ppm)

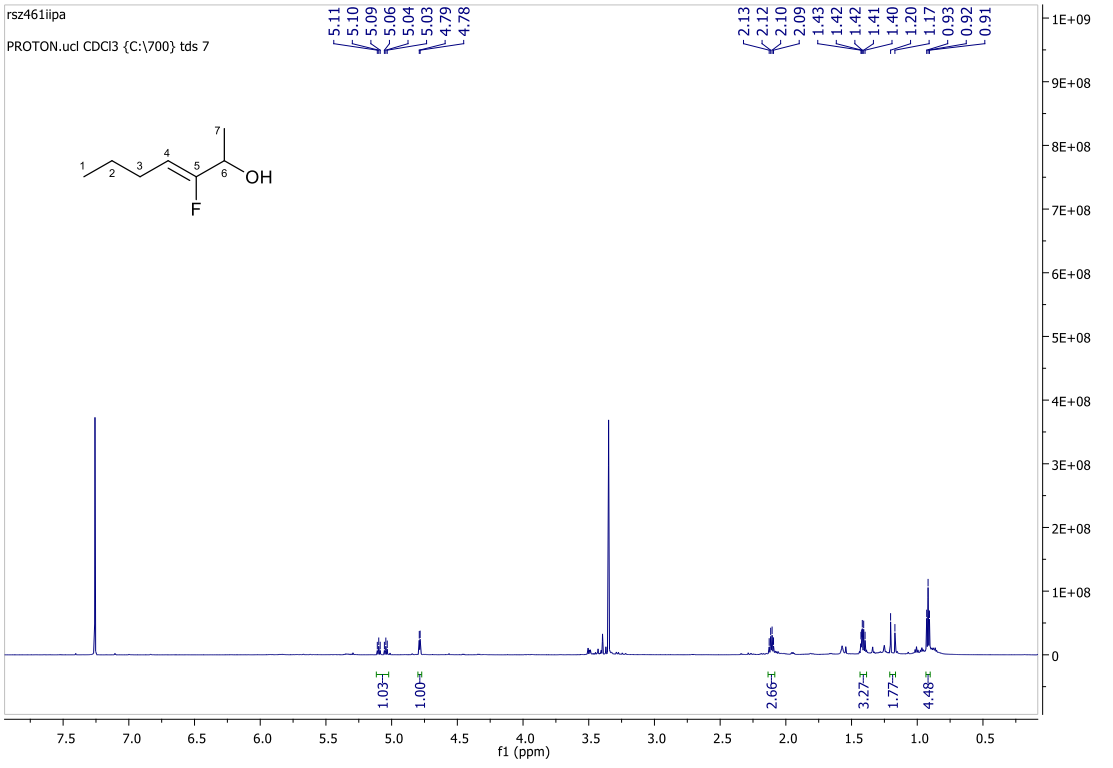
(*Z*)-2-Fluorohex-2-enal [**252**]:

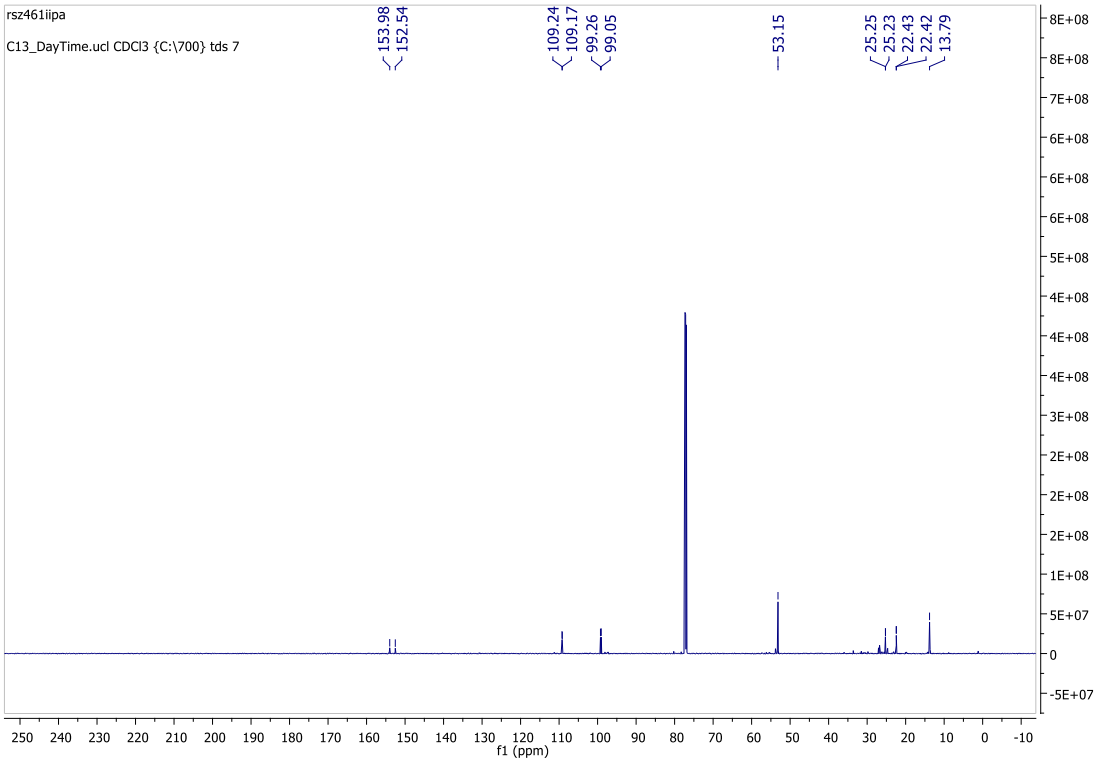


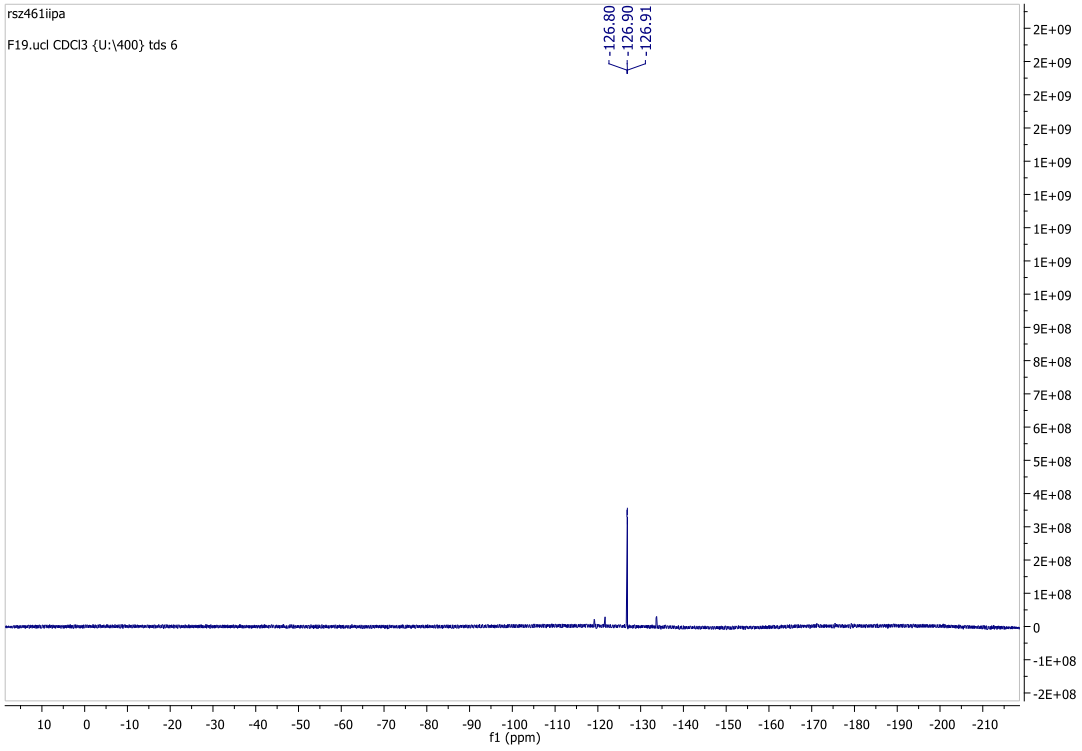





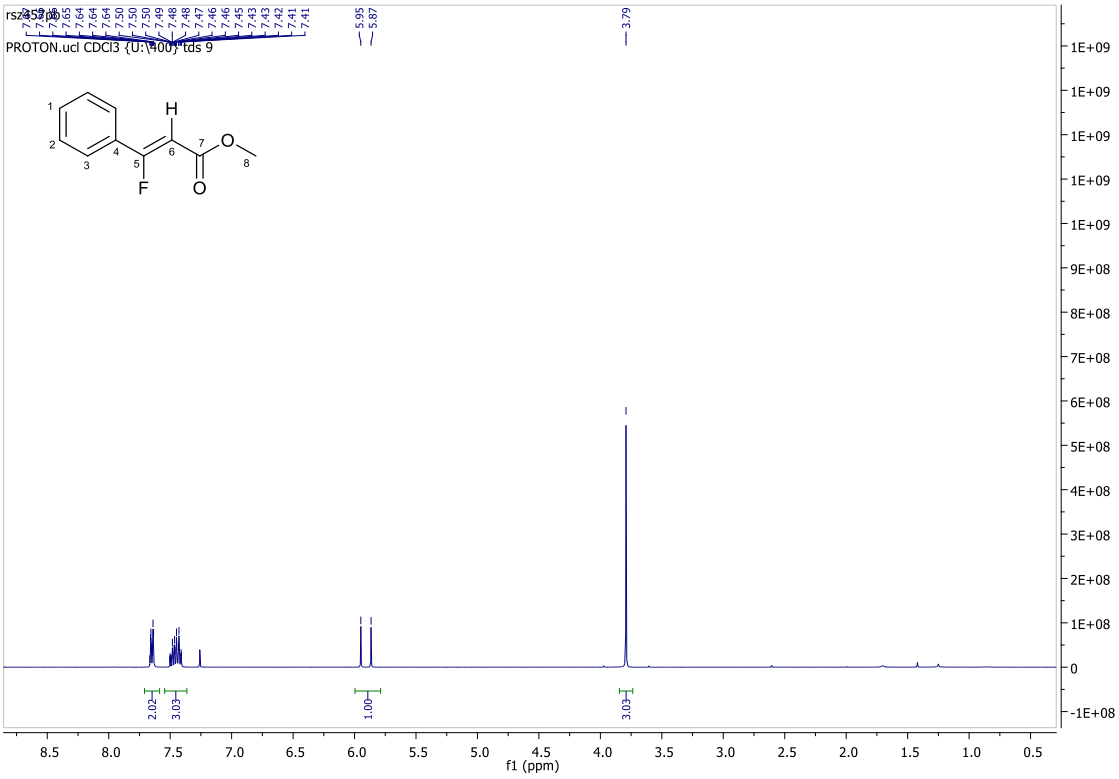

(*Z*)-3-Fluorohept-3-en-2-ol [**253**]:

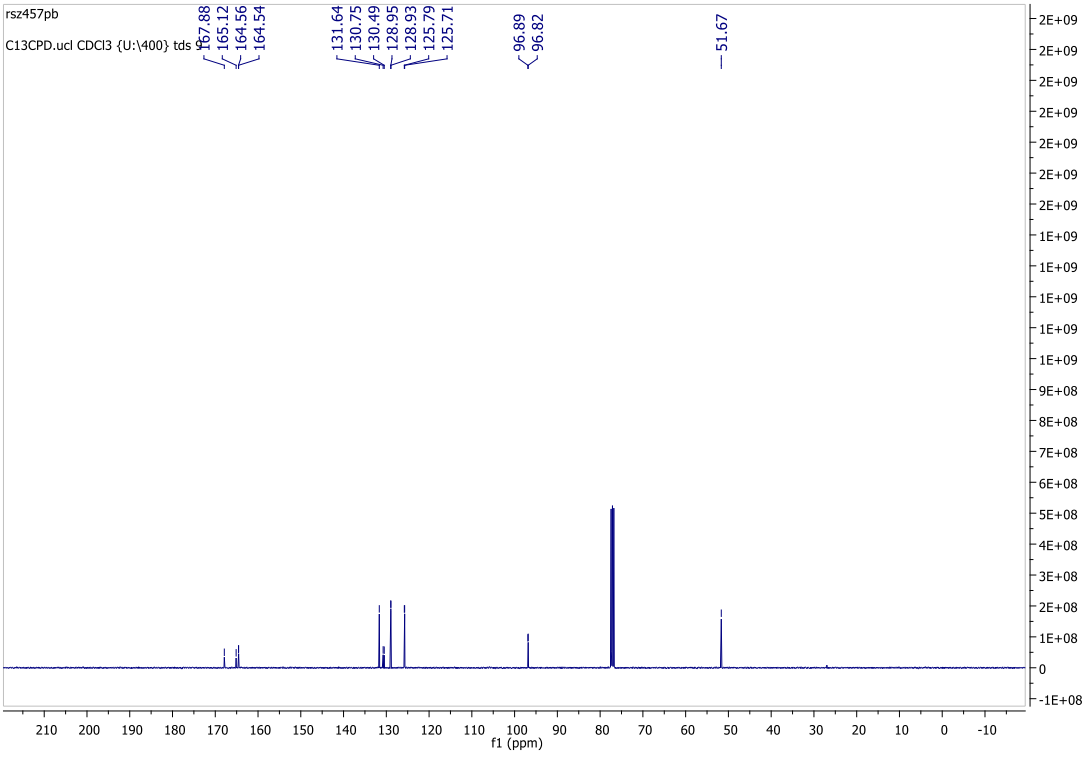


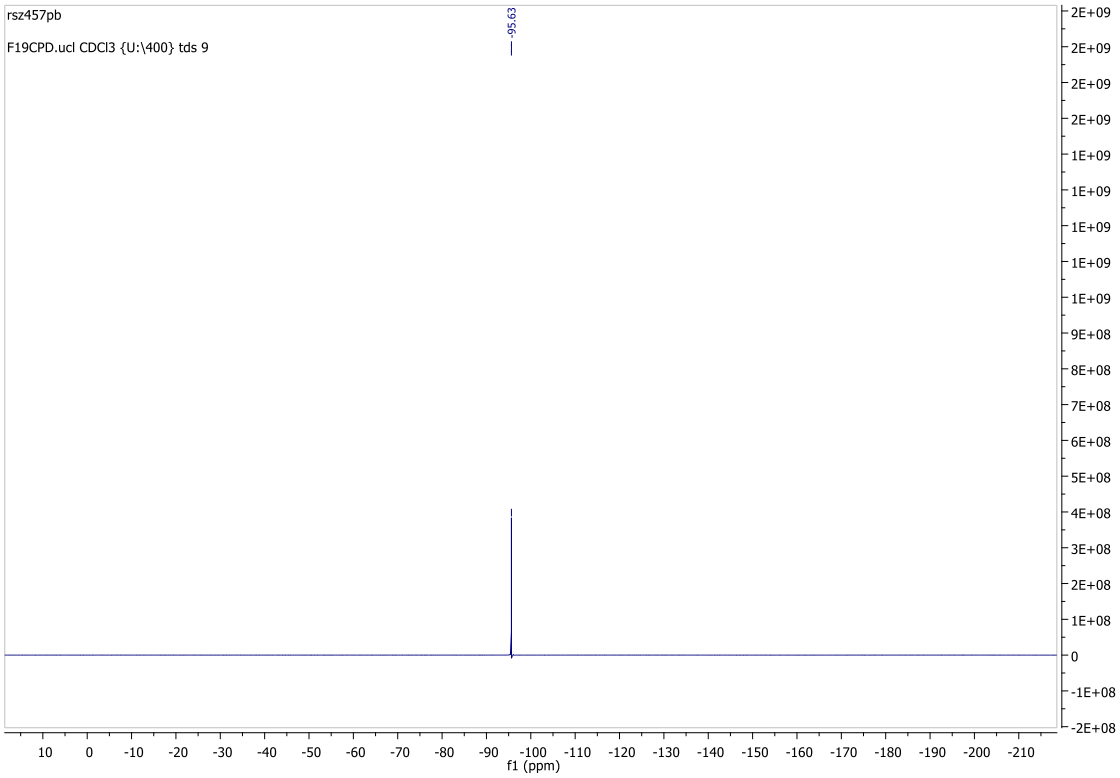

rsz461iipa
C13_DayTime.ucl CDCl3 {C:\700} tds 7
153.98
152.54
109.24
109.17
99.26
99.05
53.15
25.25
25.23
22.43
22.42
13.79
f1 (ppm)


rsz461iipa
F19.ucl CDCl3 {U:\400} tds 6
-126.80
-126.90
-126.91
f1 (ppm)

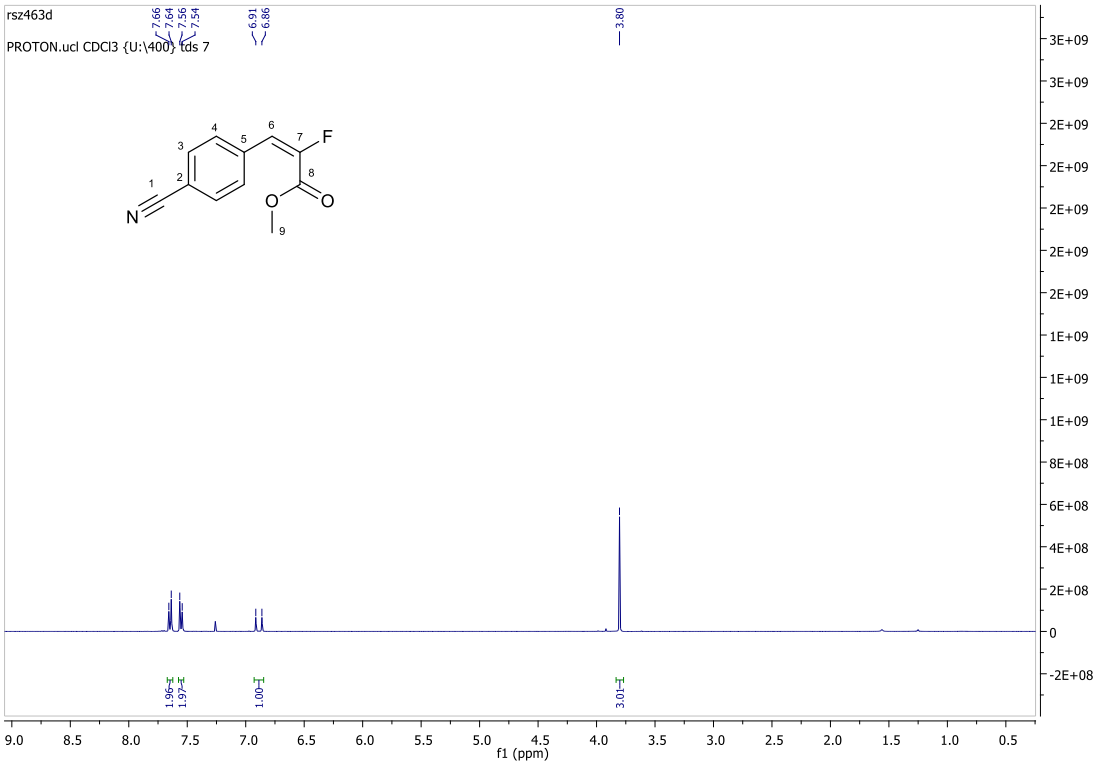
Methyl (*Z*)-3-fluoro-3-phenylacrylate [**256**]:

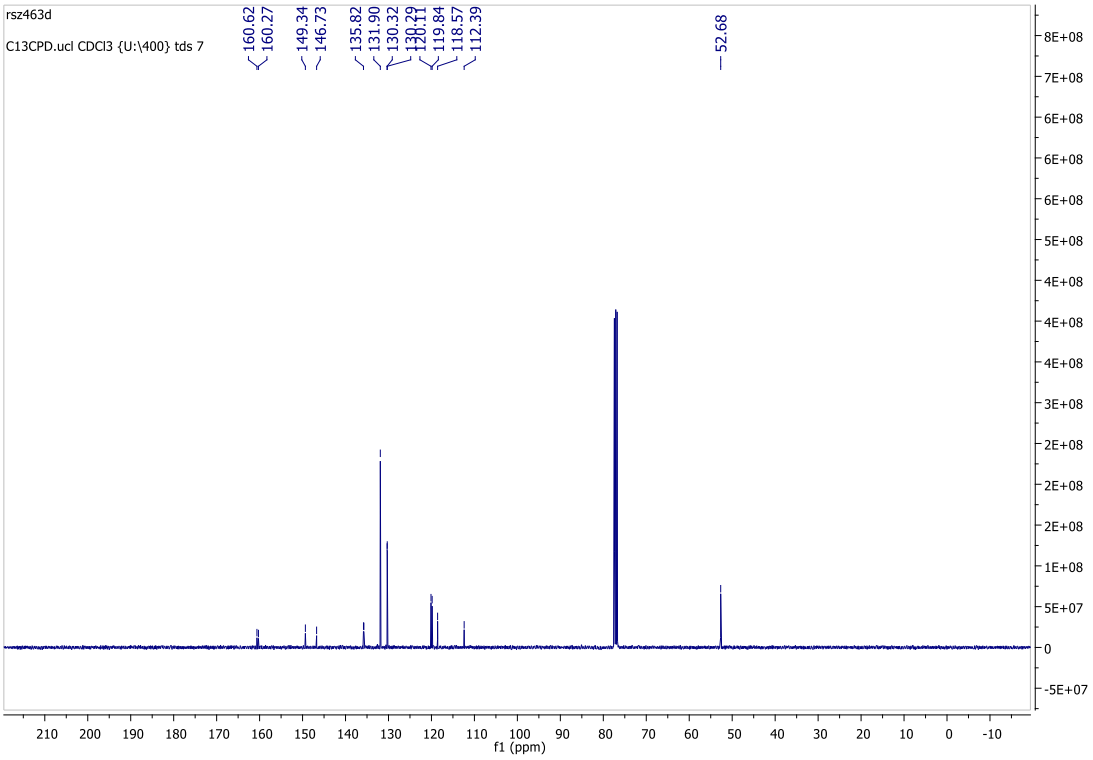


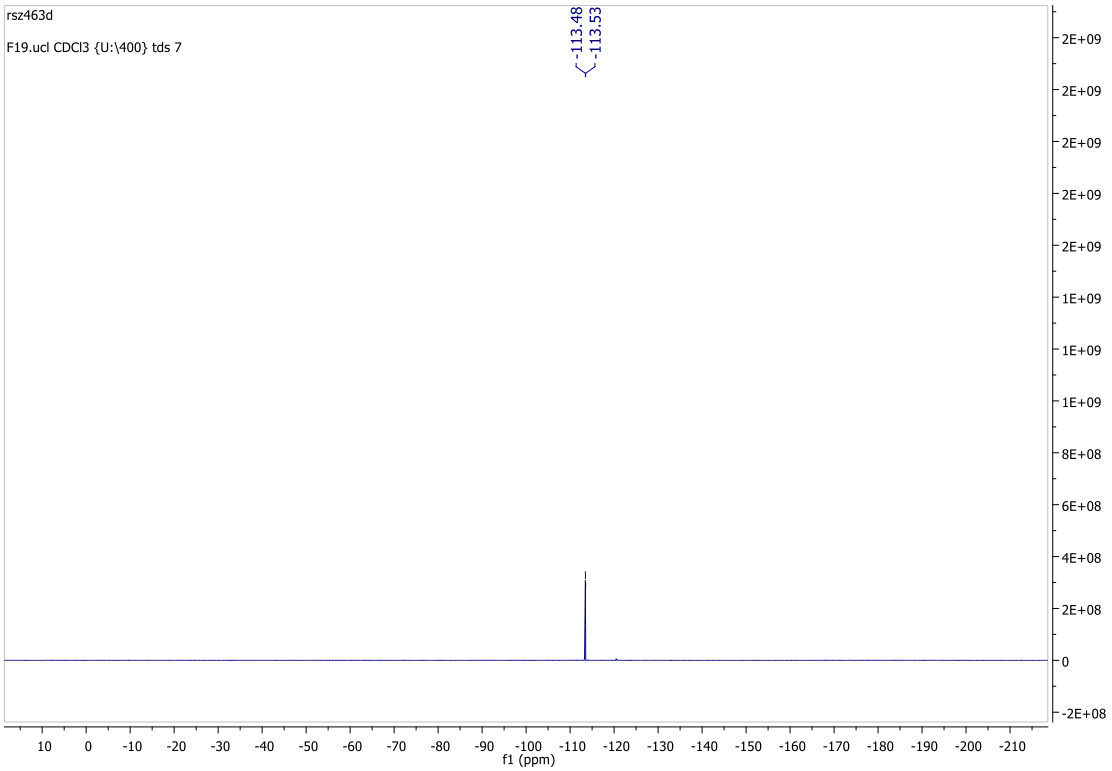






Methyl (*E*)-3-(4-cyanophenyl)-2-fluoroacrylate [**265**]:

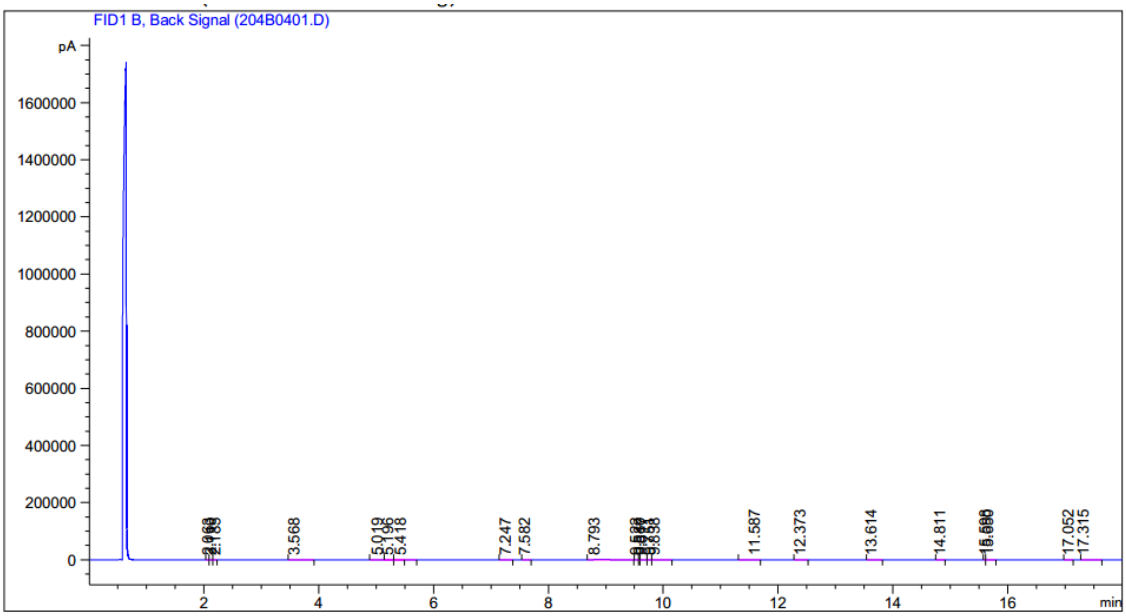



rsz463d
C13CPD.ucl CDCl3 {U:\400} tds 7
160.62
160.27
149.34
146.73
135.82
131.90
130.32
130.29
130.11
120.11
119.84
118.57
112.39
52.68
f1 (ppm)

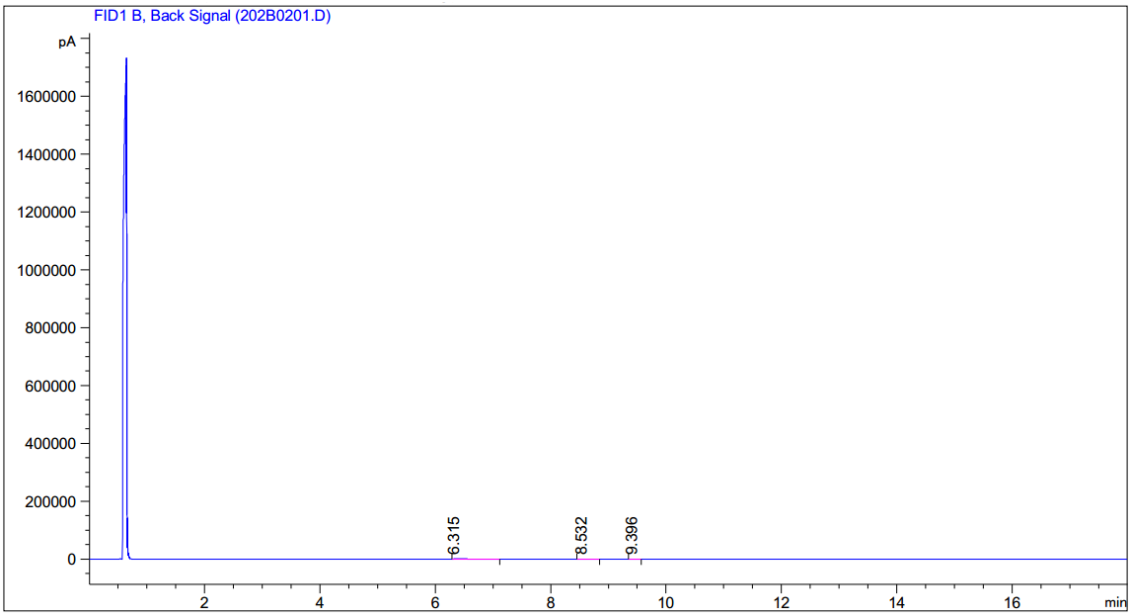

rsz463d
F19.ucl CDCl3 {U:\400} tds 7
-113.48
-113.53
f1 (ppm)

Chromatography:

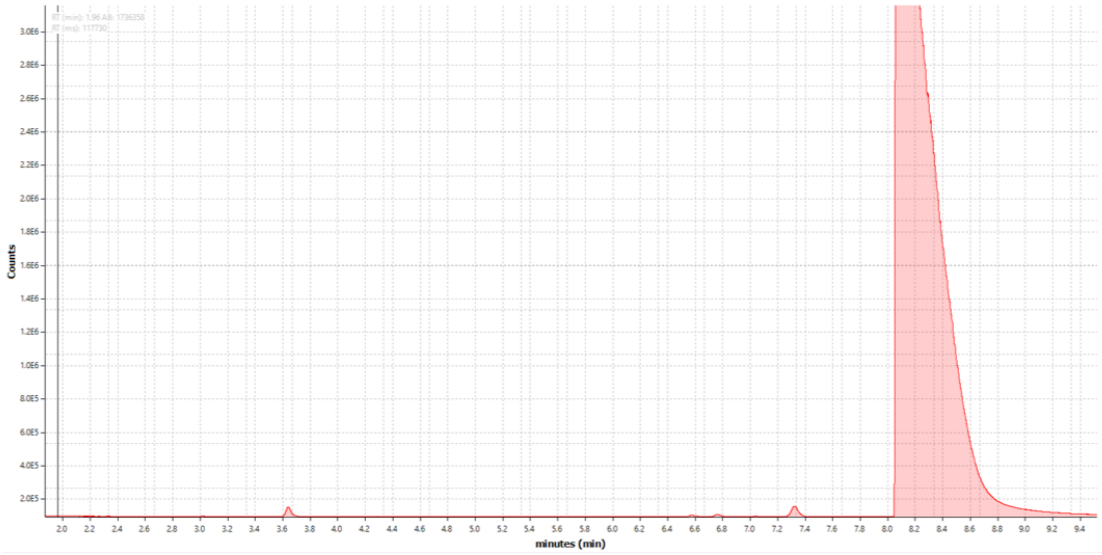
Reference compound **248** GC trace, retention time 8.79 mins:



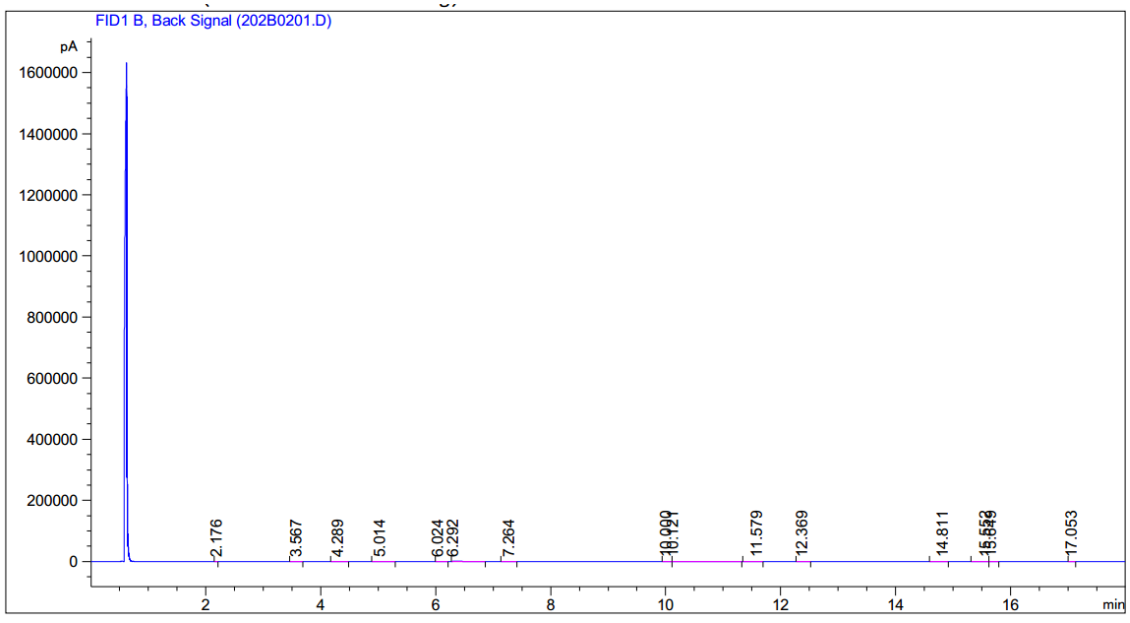

Reference compound **249** GC trace, retention time 6.32 mins:



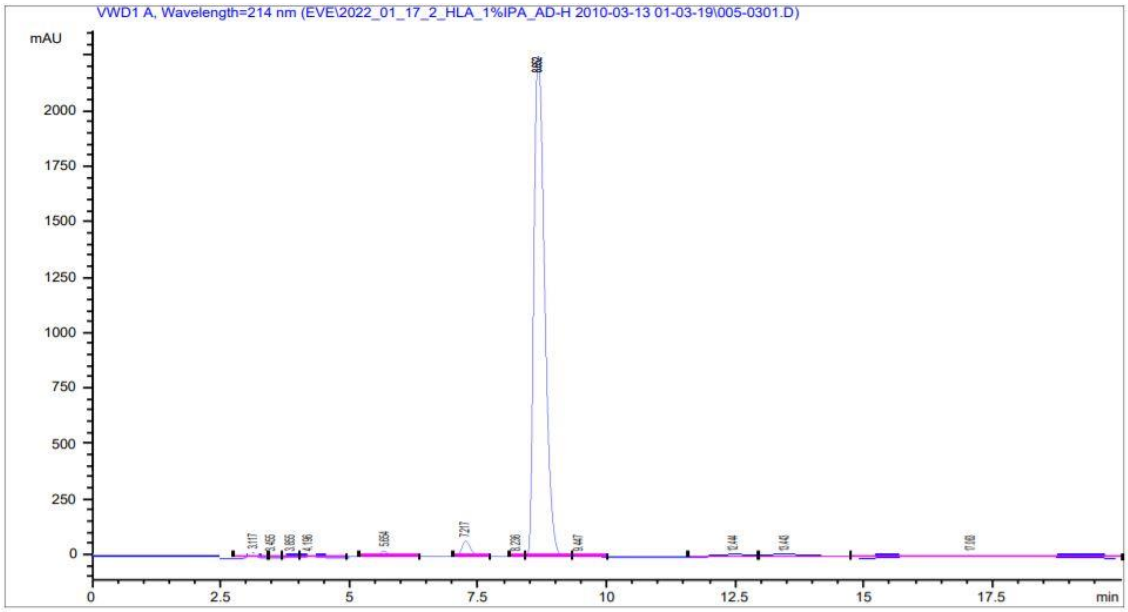
Reference compound **257** GC trace, retention time 8.21 mins:



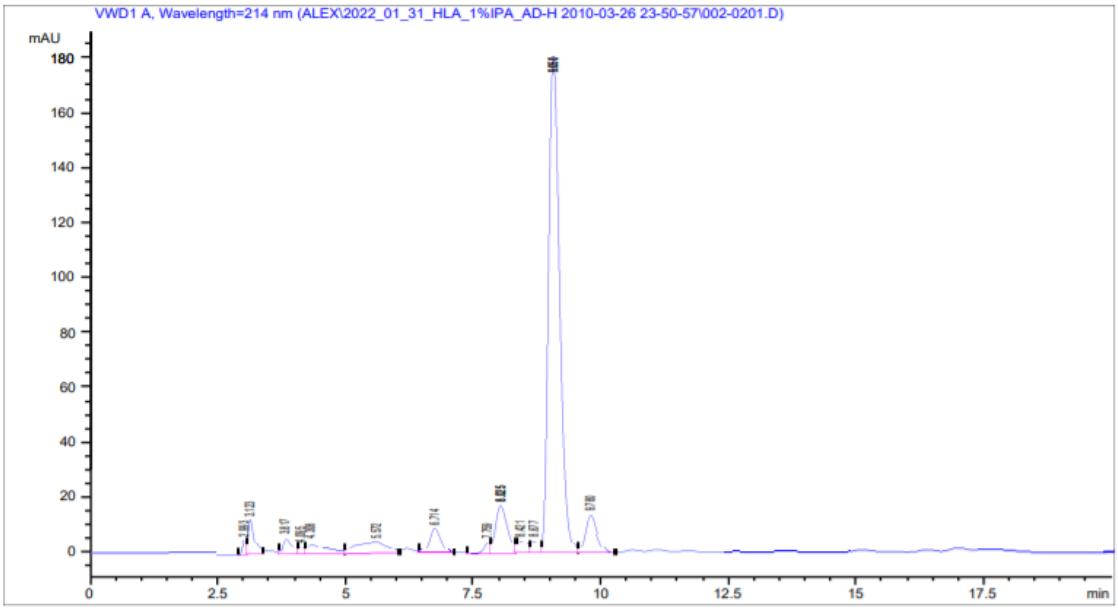

Biotransformation of **248** GC trace:



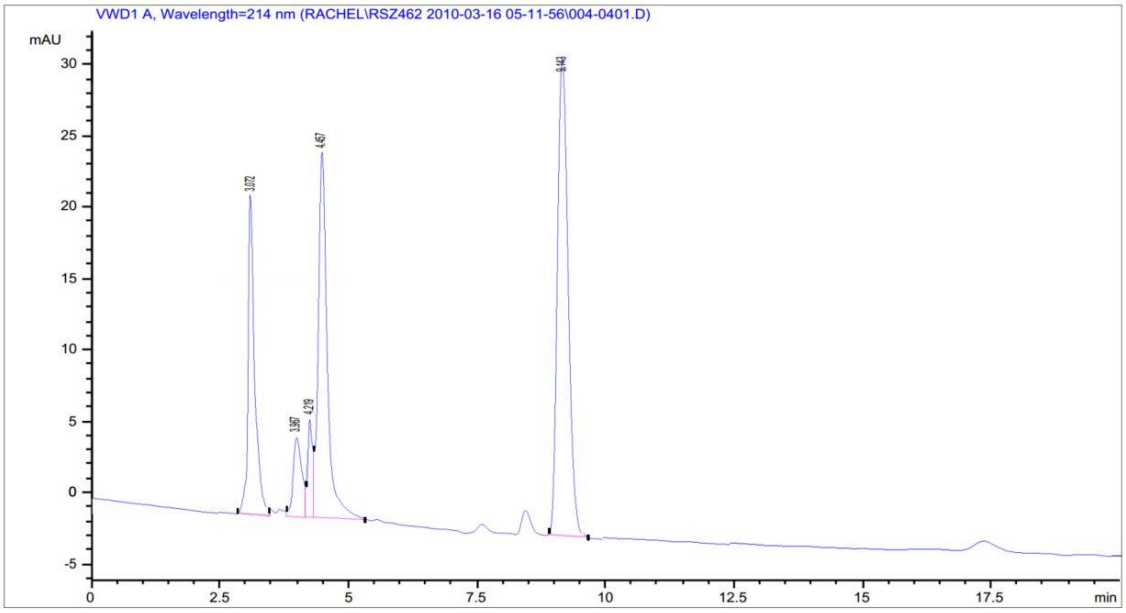
Compound **258** HPLC trace**:**



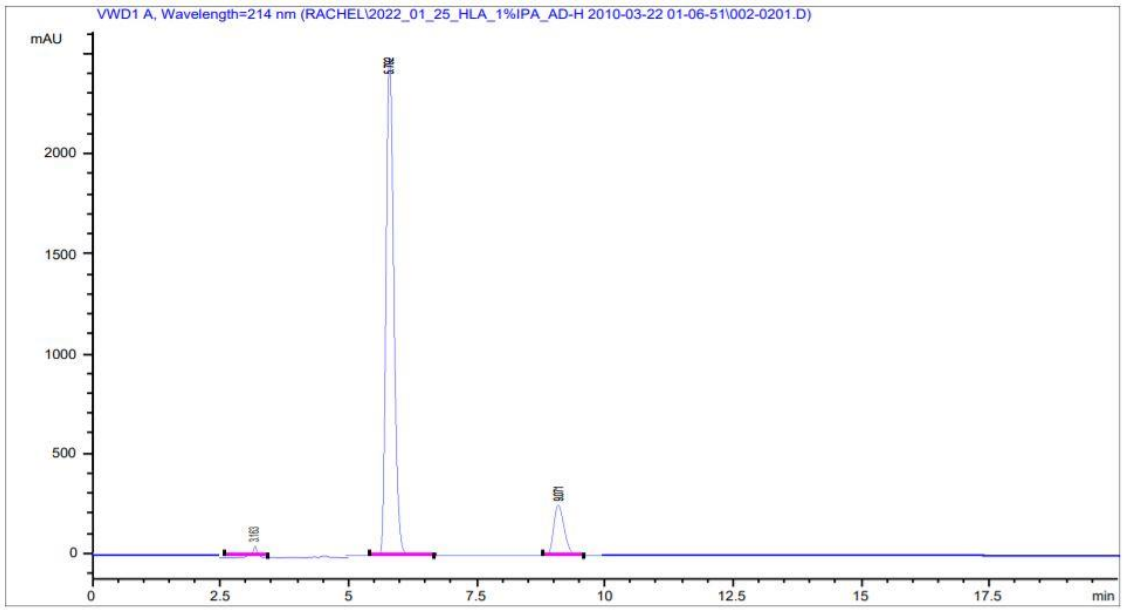

Synthesised standard, compound **260** HPLC trace:



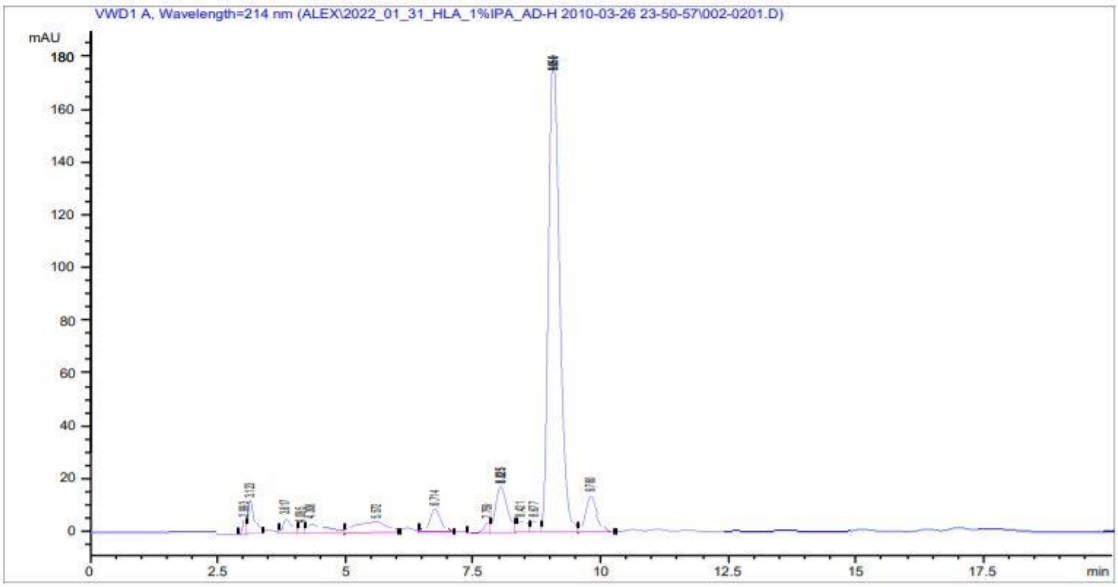
Biotransformation of **258** HPLC trace:



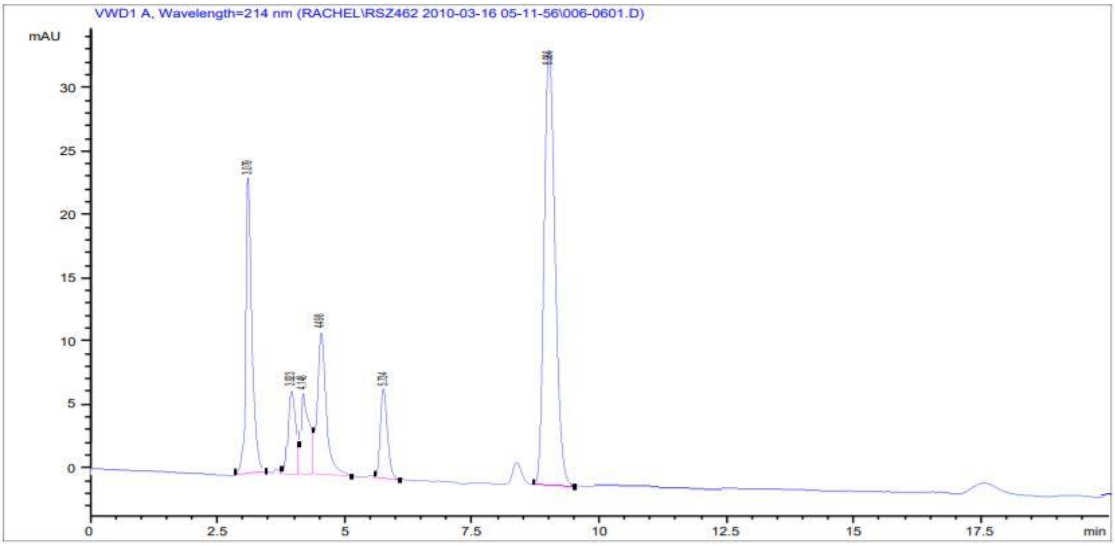

Compound **259** HPLC trace**:**



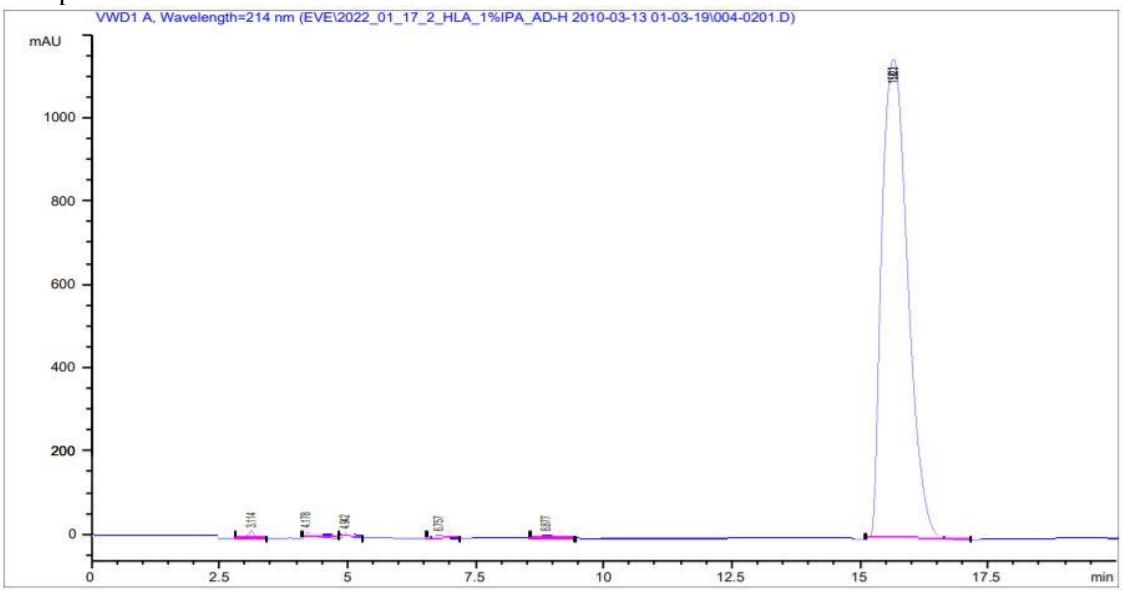
Synthesised standard, compound **260** HPLC trace:



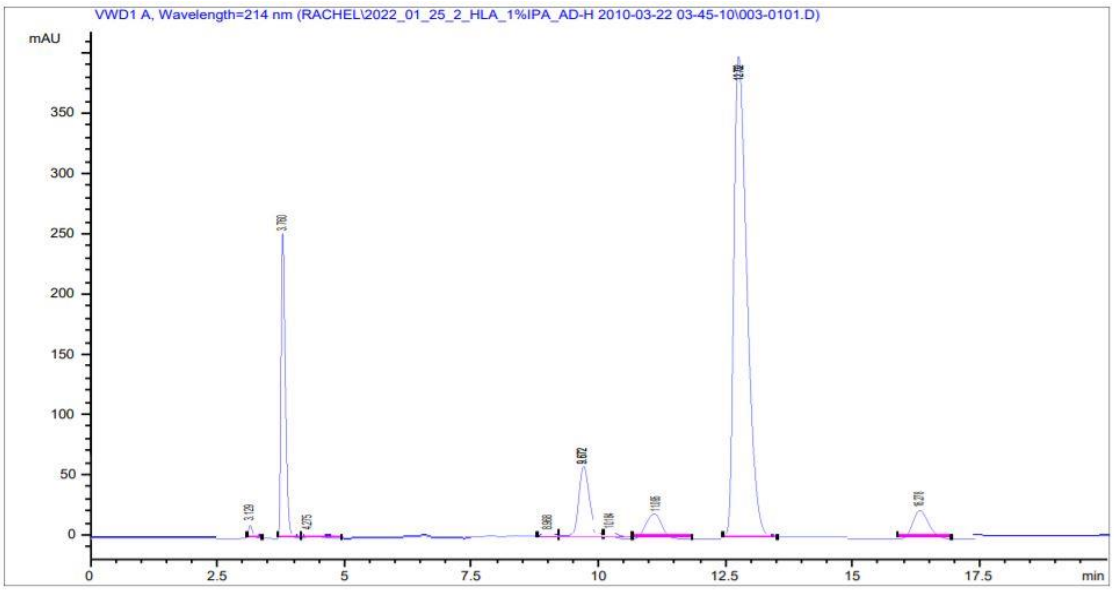

Biotransformation of **259** HPLC trace:



Compound **256** HPLC trace:




Synthesised standard, compound **261** HPLC trace:



Biotransformation of **256** HPLC trace: