Investigations into carbohydrate-based scaffolds for biological and synthetic applications.

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BScInternational(Hons)
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This thesis does not contain work that I have published, nor work under review for publication.

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CONTENTS

Summary iii
Acknowledgements v
Abbreviations vii

Preface 1

Chapter 1 Investigations into carbohydrate-based ligands for biologically active platinum(II) complexes.

Introduction 13
Results and Discussion 27
Experimental 65

Chapter 2 Investigations into carbohydrate-based ligands for biologically active copper(II) complexes.

Introduction 137
Results and Discussion 155
Experimental 189

Chapter 3 Efforts towards bifunctional carbohydrate-based catalysts

Introduction 211
Results and Discussion 227
Experimental 249
<table>
<thead>
<tr>
<th>Chapter 4</th>
<th>A new synthesis of 2-acetamido-1,5-imino-1,2,5-trideoxy-D-galactitol (GalNAcDNJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>265</td>
</tr>
<tr>
<td>Results and Discussion</td>
<td>277</td>
</tr>
<tr>
<td>Experimental</td>
<td>281</td>
</tr>
</tbody>
</table>

| References | 285 |
SUMMARY

Carbohydrates are a structurally diverse collection of molecules, well known for their involvement in a range of biological processes including metabolism, cell signalling, cellular regulation, and pathogenesis. Major areas of carbohydrate research focus on understanding various aspects of in vivo carbohydrate processing and recognition, with direct implications to human health.

It is thought that it is the large structural diversity of carbohydrates that enables them to be involved in so many different biological roles. Indeed, carbohydrates are a large, readily-available synthetic pool. The scope for carbohydrates outside chemical biology is vast, as their structural modularity and adaptability, as well as their inherent chirality, should make them popular synthetic scaffolds. However, it is only in recent years that carbohydrates have been increasingly used as scaffolds in applications such as the synthesis of natural products, ligands, catalysts, and chiral auxiliaries, among others.

The work in this thesis embodies the endeavour to demonstrate the expansive scope of carbohydrate scaffolds, detailing the use of two main scaffolds in several different applications.

The preface provides a general overview of carbohydrates and outlines the range of applications of carbohydrate-based scaffolds in biology, industry and synthetic organic chemistry.

The first chapter provides an account of the design and synthesis of the 1,6-anhydro scaffold 53, derivatisation of the scaffold to provide carbohydrate-based diamine ligands, and the synthesis of bidentate diamine-platinum(II) complexes. The suite of C3-functionalised complexes was assayed against HeLa and MCF-7 cell lines, in comparison to cisplatin, to ascertain their potency.

The second chapter details the design and synthesis of 1,6-anhydro-based salen ligands of the type 268 and various related metal complexes. Complexes were studied by spectroscopic and electrochemical methods before also being assayed against HeLa and MCF-7 cell lines to ascertain their potency, in comparison to cisplatin.
From the cell assays in both chapters, structure/activity relationships could be observed. Certain complexes from chapters two and three showed greater potencies than cisplatin in both cell lines, notably in the case of the MCF-7 line, as it is documented as displaying cisplatin resistance.

The third chapter also details the use of the 1,6-anhydro scaffold, but provides an account of the development of a series of thiourea/amine organocatalysts 369-373. In this work, a library of primary amine/thiourea catalysts was developed and tested in the nitro-Michael addition of acetone to β-nitrostyrene, as a catalytic proof of concept study, with promising results.

Finally, the fourth chapter outlines the use of an azido-carbohydrate scaffold 429 for the development of an efficient and simplified synthesis of GalNAcDNJ, 411, an important inhibitor of N-acetylhexosaminidases, a family of carbohydrate-processing enzymes.
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And finally, in that well-worn phrase, last but not least, my heartfelt gratitude goes to my family. To Mum and Dad, how do I thank a lifetime of selfless support, encouragement, opportunities and adventures? I have loved sharing the ups and downs of the PhD journey with you (I hope you didn’t find it too stressful) and thank you for always being there. To Ryan, thank you for your eternal patience, calmness in the face of the storm, generosity, kindness and love. I’m sorry it took so long…
ABBREVIATIONS

APCI  atmospheric pressure chemical ionisation
aq.   aqueous
atm.  atmosphere
ATR-IR attenuated total reflectance infrared spectroscopy
Boc   tert-butyloxycarbonyl
Boc₂O di-tert-butyl dicarbonate
br s  broad singlet
BzCl  benzoyl chloride
CSA   10-camphorsulfonic acid
DBU   1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL diisobutylaluminium hydride
DIPEA diisopropylethylamine
DMAP  4-N,N-dimethylaminopyridine
DMF   N,N-dimethylformamide
DMSO  dimethylsulfoxide
dppe  1,2-bis(diphenylphosphino)ethane
eq.   equivalents
ESI   electrospray ionisation
Fmoc  fluorenylmethyloxycarbonyl
h     hour(s)
HR-MS high-resolution mass spectrometry
M     mol L⁻¹
mCPBA 3-chloroperoxybenzoic acid
min   minute(s)
NMR   nuclear magnetic resonance
Pyr.  pyridine
Rf    retention factor
s     second or singlet
t-Bu  tert-butyl
THF   tetrahydrofuran
TLC   thin-layer chromatography
TMSOTf trimethylsilyl trifluoromethanesulfonate
Preface
CARBOHYDRATES

Carbohydrates in nature

Carbohydrates are ubiquitous in nature and, while the ‘sweet spice’, first exported from India, became traders’ white gold, an understanding of the true value of carbohydrates only began in the nineteenth century.

Justus von Liebig, a German chemist, was among the first scientists to posit that carbohydrates were one of the essential food groups. One of his pupils, Carl von Voit, and colleagues demonstrated that D-glucose 1 and other glucose-based carbohydrates such as D-maltose 2 were converted to glycogen 3, a glucose polymer, in the liver (Figure P.1). At this stage, it was not known that glycogen was the energy store of humans, animals, fungi and bacteria. Carl and Gerty Cori spent much of their scientific careers deducing the seminal biochemical pathway of the conversion of glucose into glycogen, for which they received a share in the 1947 Nobel Prize in Physiology or Medicine. Around the same time as the early work on glycogen, acid digestion experiments with starch, the energy stockpile of most plants, also produced 1 and 2. However, the recognition that starch was also a polymer of glucose, similar to glycogen, came about a century later.

Figure P.1 – A representation of the transformation and storage of small, glucose-based carbohydrates, such as 1 and 2, to glycogen.
As glycogen and starch are to energy storage, chitin 4 and cellulose 5 are to structural integrity (Figure P.2). Also formally discovered in the 1800s, these two carbohydrate polymers provide structural support to many living organisms; the former to arthropods and fungi, the latter to plants. Parallel to the biological investigations into carbohydrates, Emil Fischer and his colleagues were deducing the exact structure of these mono-, di- and polysaccharides, their physical characteristics and chemical reactivities. At the end of the nineteenth century, it was becoming evident that carbohydrates were chemically unique and had various, important biological roles.

![Figure P.2](image)

**Figure P.2** – Representations of the polymers chitin 4 and cellulose 5.

**Carbohydrates in biological processes**

Over the last century, collaborative efforts have revealed the scope of carbohydrate involvement in all aspects of life. Aside from their vital role as part of the backbone of DNA, carbohydrates are also incorporated into many biomolecules such as lipids and proteins. These glycoconjugates are important in cell signalling and controlling biochemical pathways. For instance, the tetrasaccharide, Sialyl-Lewis\textsuperscript{x} 6 (Figure P.3) is the terminal carbohydrate sequence of many glycoproteins that cover the outside of the human egg (oocyte). The spermatozoa contain an egg-binding protein that, when the spermatozoa reach the oocyte, binds to the Sialyl-Lewis\textsuperscript{x}-labelled glycoproteins, and initiates fertilization.
Figure P.3 – A representation of the tetrasaccharide, Sialyl-Lewis\(^x\) 6 and the blood group O disaccharide 7.

Another major cell-to-cell recognition role of 6 is to facilitate interactions between white blood cells and epithelial cells, which are important in the inflammation processes and immune response after injury.\(^{14-16}\) Other polysaccharides are also present on blood cells. The most famous of these are the terminal carbohydrate sequences on red blood cells, which define the different human blood groups.\(^{17}\) The disaccharide 7, for example, represents the sequence designating the blood group O (Figure P.3).

While these carbohydrate-mediated cell-cell interactions are vital for proper cell function, these recognition mechanisms can also be used to promote exogenous infections.\(^{12,18}\) For instance, the influenza virus uses an enzyme, neuraminidase, to cleave terminal N-acetylneuraminic acid residues from glycans as in 8 (Figure P.4), found on the surface of healthy human cells, to propagate infection.\(^{12,19}\)

Figure P.4 – Representations of a N-acetylneuraminic acid-capped glycan 8 and Thiamet-G 9.
Carbohydrate-processing enzymes, such as neuraminidase above, are responsible for either adding or removing carbohydrates from glycoconjugates. Another interesting enzyme is the human glycoside hydrolase, O-GlcNAcase, which removes 2-acetamido-2-deoxy-β-D-glucopyranose (O-GlcNAc) moieties from proteins. This post-translational modification is in a cycling mechanism with protein phosphorylation. It has been observed that the neuronal protein tau forms neurofibrillary tangles in the brains of Alzheimer’s sufferers, due to increased phosphorylation. It is the increased phosphorylation of tau that is thought to contribute to neuron death. Concomitant with the phosphorylation pathology is that the tangles also have lower than normal levels of O-GlcNAc. An inhibitor of O-GlcNAcase, 1,2-dideoxy-2’-ethylamino-a-D-glucopyranoso-[2,1-d]-Δ2’-thiazoline (Thiamet-G), has been shown to prevent the removal of O-GlcNAc from the tau protein. The use of this inhibitor has thus hindered tau phosphorylation, and consequent protein aggregation and neuron loss in mice. Thiamet-G is a key structure for the potential design of preventative treatments for neurodegenerative disorders.

Carbohydrates in industry

Owing to the origins of carbohydrate chemistry being based in the life sciences, focus is often on the in vivo roles of carbohydrates and related applications. However, carbohydrates are a renewable, economic, enantiopure chiral pool, and the structural diversity and scope of modification offered by these molecules opens the door to many and varied applications.

Cellulose is the most abundant biopolymer used in industry and its applications date back to its use in the production of papyri in Egyptian times. In modern times, it has been used to manufacture celluloid, one of the first thermoplastics, now superseded by improved synthetic plastics. The fabric viscose, also known as artificial silk, is also made from cellulose through a chemical treatment process involving sodium hydroxide, carbon disulfide and sulfuric acid. Today, is one of the most important raw materials in industry and is used in many different applications.

The food industry relies heavily on carbohydrates, not as just a main nutritional component, but as food additives to modify the texture, consistency and structure of
dishes. For example, starch is used as a thickening agent in soups, sauces and desserts. With the rise of molecular gastronomy, more carbohydrate-based additives have come to general attention. Agar (derived from agarose 10, Figure P.5) is a phycocolloid, a gelling agent derived from seaweed. It was discovered and first used by the Japanese and later, in European markets, in confectionary production and baking. The properties of agar mixtures, including the ability to hold shape at higher temperatures, have brought it fame as hydrogel beads in recipes such as el Bulli’s green ‘olives’ and at the discerning domestic dinner party. Agar is a popular vegetarian replacement for gelatine, but also finds use in microbiology, as the plates upon which bacteria and other microorganisms are often grown and in gel electrophoresis and chromatography.

Figure P.5 – A portion of the structure of agarose 10.

In biomedical material applications, chitin 4 and derivatives have found use in wound dressings to accelerate healing, and, more recently, potential use in dissolvable sutures. The biocompatibility of this polymer and derivatives is due to their carbohydrate origins, enabling indigenous enzymes to breakdown the polymers in vivo.

While polysaccharides seem to dominate the carbohydrate scope in industry, monosaccharides are also useful, being employed in the organic synthesis of fine chemicals and pharmaceuticals. This is where the modularity and inherent chirality of carbohydrates come to the fore. Chirality can be very important for drug design, as the different activities of L-DOPA, an active antipsychotic and antiparkinson drug, and its enantiomer D-DOPA, which reduces white blood cell count, illustrate well. When planning synthetic pathways to potential drugs, chiral starting materials are often sought, as introducing chirality along the way can be synthetically challenging. In addition to the multiple stereocentres of different carbohydrates, the chirality of
individual centres can be easily manipulated, relative to other methods of stereo-
induction. Furthermore, the many hydroxyl groups on a carbohydrate such as
D-glucose 1 present multiple opportunities for introducing different functional groups
or active moieties. The high structural diversity of carbohydrates, which enables them
to take on many different roles in biology, also provides an excellent scaffold for
functional molecule design.

The influenza drugs Zanamivir (11, Relenza®) and Oseltamivir (12, Tamiflu®) are
carbohydrate-based molecules designed to inhibit the action of the enzyme
neuraminidase, which promotes viral infection (Figure P.6).40 The many chiral
centres of these drugs make them challenging synthetic targets. Since the substrate of
neuraminidase is a N-acetylneuraminic acid-capped glycan moiety 8 (Figure P.4) the
carbohydrate chiral pool was used to provide starting materials with favourable
stereochemistry. The industrial synthesis of Zanamivir begins with
N-acetyleneuraminic acid 13.41 Although a carbohydrate is not used in the industrial
synthesis of Oseltamivir, several syntheses, aiming to make the pathway more
efficient and greener, have utilised carbohydrates such as D-glucal 14 and D-ribose 15
as starting materials (Figure P.6).41
Figure P.6 – Some examples of carbohydrate starting materials for the synthesis of Zanamivir 11 and Oseltamivir 12.

Carbohydrates find application not only in organic chemistry, but also inorganic chemistry. The antirheumatic drug, Auranofin 16 is a gold(I)-carbohydrate complex that is thought to suppress the immune system, preventing inflammation in rheumatoid arthritis (Figure P.7).\textsuperscript{42-43} Platinum(II) complexes such as 17 are of interest as potential anticancer chemotherapy agents.\textsuperscript{44} The inclusion of the carbohydrate moiety has been shown to reduce the toxicity and adverse side effects associated with current platinum(II) chemotherapy agents, and, in some cases, provide targeted delivery to cancer cells.\textsuperscript{45}

Figure P.7 – The structure of the carbohydrate-based complex Auranofin 16 and the platinum(II) complex 17.
Indeed, interest in carbohydrates-based ligands has recently grown, both for drug design and catalysis, where the inherent chirality of the carbohydrate moiety can be advantageous for asymmetric catalysis.\textsuperscript{46-48} The rich stereochemistry of carbohydrates also facilitates their use as chiral auxiliaries for synthetic stereo-differentiation,\textsuperscript{49} and as organocatalysts in asymmetric catalysis.\textsuperscript{49-50}

**Carbohydrates as molecular scaffolds**

From this brief overview of some of the many and varied applications of carbohydrates, it is clear that they represent a diverse, renewable, valuable resource. As new research increases the understanding of the biological roles of carbohydrates, and as new drug and material targets are presented, the pursuit of novel compounds should take chemists to the carbohydrate pool, where diversity offers countless opportunities for innovation and exploration. However, it is often avoided due to the misplaced assumption of the difficulties associated with the manipulation of carbohydrates because of the multiple hydroxyl and functional groups. As a result, the scope of carbohydrate scaffolds has been underdeveloped. However, building on the seminal work of Emil Fischer, there are now well-established methods for the chemical manipulation of carbohydrates. This body of work aims to make a contribution to the growing area of carbohydrate scaffolds through the design and synthesis of novel carbohydrate-based compounds, and a demonstration of their uses in biological and industrial applications.
Chapter 1

Investigations into carbohydrate-based ligands for biologically active platinum(II) complexes
INTRODUCTION

Cancer has become one of the most common diseases of the 21st century. When President Reagan declared his ‘War on Cancer’ in 1971 in order to boost funding for American cancer research, there was the general expectation that the disease would be speedily eradicated. However, an understanding of the many diseases that come under the umbrella term ‘cancer’ was in its early stages. The sheer scale of the number of different diseases, their individual characteristics and pathology, and the mechanisms behind initiation and progression, as well as the genetic implications were only starting to be recognised and success was perhaps overestimated. The scientific understanding of cancers has grown significantly since then, and it is now accepted that cancer treatment progress will be a marathon effort, not a sprint. As such, there continues to be a need for increased, shared research, in order to develop effective treatments against a set of disparate diseases. There is hope that cancer will become a manageable condition with time, and increased understanding and drug development.

Even though there is a long way to go until cancer becomes manageable, there are well-developed systems of treatment that can successfully control and sometimes eliminate cancer. Conventional treatments belong to three main avenues: 1) surgery to remove tumours, 2) radiotherapy to shrink or eliminate tumours, and 3) chemo- or immunotherapy to kill or arrest tumour growth. There have been some amazing advances in surgical procedures and treatments such as the ‘microscope in a needle’ used to identify tumour margins in breast tissue to ensure all the tumour is removed during surgery, genetically modified T-cells that mount an immune response against cancer antigens, cancer vaccines, proton beam therapy, and monoclonal antibody immunotherapy, as a few examples.

However, in the case of chemotherapy agents, older treatments dating back to the seventies and eighties, are still frontline treatments in many cases.

Cisplatin and related complexes

One of the most well-known and frequently used metal-based chemotherapy agents was a serendipitous discovery. Barnett Rosenberg, a biophysicist, and Loretta Van
Camp, a microbiologist, were investigating the effect of electric fields on the growth of bacteria.\textsuperscript{63} They observed that bacteria stopped dividing when an electric current was passed through the culture broth using platinum electrodes. Subsequent tests suggested that a platinum complex with a mixture of amino and chloride ligands halted cell division.\textsuperscript{64-65}

As a result, a series of platinum(II) and platinum(IV) complexes with different combinations of halide and ammine ligands were tested against bacteria and then mice with cancerous tumors.\textsuperscript{64-67} \textit{cis}-Diamminedichloro platinum(II) \textbf{18} ([\textit{cis}-\text{PtCl}_2(\text{NH}_3)_2], cisplatin) was identified as one of the more active platinum complexes tested and by 1972 it had entered Phase 1 clinical trials.\textsuperscript{66-67} Shortly after, cisplatin was approved as a single therapy, and in combinations, for testicular and ovarian tumours in the United States.\textsuperscript{68} Cisplatin has shown incredible success against testicular cancer around the world, with combination therapies resulting in around 90\% of patients entering remission.\textsuperscript{69} In addition to testicular and ovarian cancers, cisplatin is also used to treat other solid tumours including head, neck, and bladder cancers. Data on cisplatin use in Australia is less documented, though it is estimated that around 50\% of chemotherapy schedules include a platinum drug.\textsuperscript{61}

\begin{center}
\begin{tikzpicture}

\node[draw, circle, inner sep=2pt] (Pl) at (0,0) {Pt};
\node[draw, circle, inner sep=2pt] (Cl) at (-0.5,-1) {Cl};
\node[draw, circle, inner sep=2pt] (NH3) at (0,-1.5) {\texttt{H}_3\texttt{N}};
\node[draw, circle, inner sep=2pt] (NH3) at (0.5,-1.5) {\texttt{H}_3\texttt{N}};
\draw (Pl) -- (Cl); \draw (Pl) -- (NH3); \draw (Pl) -- (NH3);
\end{tikzpicture}
\end{center}

\textit{Mechanism of action}

The generally accepted mechanism of \textbf{18} activity is that cisplatin enters the cell by passive diffusion, where-upon the chloride ligands are replaced by water due to the lower chloride concentration in the cytoplasm.\textsuperscript{70-72} The mono- and diaquated species \textit{cis}-[\text{PtCl(NH}_3)_2(OH}_2)]^{\dagger} and \textit{cis}-[\text{Pt(NH}_3)_2(OH}_2)_2]^{2\dagger} are responsible for the observed activity of cisplatin.\textsuperscript{73-74} These complexes bind to DNA, with the loosely held water molecules being replaced by covalent bonds between the platinum(II) atom and a nitrogen of a purine DNA base.\textsuperscript{72,75-76} Predominantly intra-strand crosslinks form between the platinum atom and two nitrogens on different bases, which perturb the structure of the DNA duplex such that replication is either halted or disturbed.
initiating a cascade of intracellular signalling that ultimately results in apoptosis and cell death.\textsuperscript{72,77} While cisplatin is active, it has been found that the trans-diaminedichloro platinum(II) isomer is not.\textsuperscript{57}

Side effects, resistance and second-generation cisplatin derivatives

Cisplatin treatment is accompanied by severe side effects including nephrotoxicity, neurotoxicity and ototoxicity, which limit the effective dose that can be administered.\textsuperscript{78-81} Unfortunately, the given dose can be sub-lethal for tumours, allowing resistance to further drug treatment to develop. In the case of cisplatin, resistance mechanisms include increased drug efflux, enhanced DNA damage repair, detoxification of drugs by binding to intracellular molecules other than DNA, and evasion of cell death.\textsuperscript{82-84}

These treatment limits were recognised early on and a second wave of platinum-based drugs were developed to try to circumvent the drawbacks to using cisplatin. From preliminary investigations, five compounds of interest were identified; carboplatin 19, oxaliplatin 20, nedaplatin 21, lobaplatin 22, and heptaplatin 23, all with the active cis-diammine/diamine motif (Figure 1.1).\textsuperscript{61-62} Carboplatin and oxaliplatin were the two most successful derivatives, having been internationally approved as chemotherapy agents, while the others have been approved in individual countries.\textsuperscript{61-62} Carboplatin 19 contains a more stable, chelating 1,1-cyclobutanedicarboxylato moiety in place of the chloride ligands. The new bidentate ligand is more resistant to aquation, which lowers the amount of active compound transported to the kidney at any one time, mitigating nephrotoxicity.\textsuperscript{85-86} However, myelosuppression limits the dose of 19, and it also has the same mode of action as cisplatin, displaying cross-linked resistance.\textsuperscript{87-88} Oxaliplatin 20 contains an (\textit{R},\textit{R})-1,2-diaminocyclohexane ligand in place of the ammine moieties and an oxalate in place of the chloride ions and was one of the first platinum(II) complexes that showed activity in cisplatin-resistance cancers.\textsuperscript{89-90} It is thought that, due to the cyclohexane ligand, different DNA adducts are formed to those with 18 and 19, which DNA repair mechanisms take longer to overcome.\textsuperscript{91} As in 19, the dicarboxylate ligand in 20 confers stability on the molecule, reducing nephrotoxicity, though neurotoxicity is a dose-limiting factor.\textsuperscript{92-93}
Since the approval of the five cisplatin analogues mentioned above, no other new platinum compounds have successfully passed through clinical trials to market, although several platinum-based drugs are in the development pipeline. While platinum-based treatments are widely used, from the derivatives’ clinical assessments, there are clearly still side effects and resistance problems to overcome. Currently, research is centred around improving drug design and delivery, and the selection of the best treatment programmes for patients via genotyping.

The large body of research concerning cisplatin derivatives has resulted in the development of an informal set of guidelines for the design of new metal-based chemotherapy agents, with a focus on improving the therapeutic profile of potential drugs. Drug candidates should be soluble in aqueous media, have in vivo stability, be efficiently transported through blood and across membranes, bind well to DNA, but not with other proteins, have selectivity for cancerous cells over healthy ones, and be active against tumours that have acquired or intrinsic resistance to common chemotherapy regimes, which suggests that the mode of action of the drug has to be different to that of cisplatin and related compounds.
Current cisplatin-based research

With these criteria in mind, many new platinum-based compounds have been synthesised. Here, a brief overview of some of the more prominent complexes is presented, to give a sense of how these guidelines have been interpreted.

Simple derivatives

Picoplatin 24 is a cisplatin analogue currently under clinical evaluation, in which one of the ammine ligands has been replaced with a 2-methylpyridine moiety (Figure 1.2). The ligand was chosen to hinder glutathione-mediated drug detoxification that occurs with cisplatin 18.97-99 The methyl group of the pyridine-based ligand sits over the platinum(II) centre, potentially hindering attack by glutathione.100 The drug showed activity in 18 and oxaliplatin 20 resistant cell lines, even though the mode of action was thought to be the same as 18.98,101 Another analogue currently in clinical trials is satraplatin 25 hailed as the first orally available platinum drug (Figure 1.2).102-103 Satraplatin represents a class of Pt(IV) prodrugs which are presumed to be reduced in vivo to give active Pt(II) complexes.102 The extra ligands improve the solubility of the complex and this hexacoordinate Pt(IV) design is popular for synthesising drug candidates with solubility profiles, redox stability, and improved cellular uptake.104 Satraplatin showed activity in cisplatin resistant cell lines, but was also thought to form DNA adducts similar to cisplatin.103,105 Phenanthriplatin 26, with a phenanthridine ligand in place of a chloride, is under preclinical development and represents the cationic class of cisplatin derivatives (Figure 1.2).106 These compounds carry a positive charge and are thought to be good candidates for transport across the cell membrane by organic cation transporters (OCTs).107-108 The phenanthridine ligand may act similarly to the pyridine-based ligand in 24, hindering some protein-mediated detoxification pathways. Phenanthriplatin has shown unique activity when screened against a panel of cell lines.106 However, the compound, which forms only one DNA adduct per molecule, has shown signs of acquired DNA transcription repair in biological assays.109 This suggests acquired resistance may be a development limitation. Another area of interest is the phosphaplatins such as 27, which are derivatives of 20, containing a pyrophosphate ligand in place of the oxalate ligand (Figure 1.2).110 It appears that these compounds do not bind DNA and have a different
mode of action from conventional platinum(II) complexes.\textsuperscript{111} They are active against cisplatin resistant cell lines, and have also been found to be less toxic than cisplatin.\textsuperscript{110}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures.png}
\caption{Third generation cisplatin derivatives.}
\end{figure}

**Polynuclear derivatives**

As many monomeric platinum complexes appeared to have the same mode of action as cisplatin\textsuperscript{18}, forming DNA-adducts that could eventually be removed by nucleotide excision repair, the focus turned to finding new mechanisms of action. In this vein, dinuclear compounds were proposed, with some early examples being \textsuperscript{28-32}, from the work of Farrell and colleagues (Figure 1.3).\textsuperscript{112-115} It was found that these dinuclear complexes formed long-range inter-strand crosslinks, with the \textit{trans}-compound \textsuperscript{31} forming Pt-Pt inter-strand crosslinks not seen in mononuclear complexes.\textsuperscript{112} While all complexes showed activity in cisplatin-resistant cells, the potential novel mode of action of the \textit{trans}-compound prompted this scaffold to be further explored. It was found that a linker chain of five to six carbons as well as the positive charge were key characteristics of successful analogues.\textsuperscript{61,113,115} Modification of the dinuclear compound \textsuperscript{31} gave the trinuclear complex \textsuperscript{33} (BBR3464), among other analogues.\textsuperscript{116} The addition of a third, non-binding platinum(II) centre significantly increased cytotoxic activity and the compound was also active in cisplatin-resistant cell lines. Furthermore, it was found that the activity of \textsuperscript{33} was independent of p53, a tumour suppressor protein whose malfunction is implicated in the development of some cancers.\textsuperscript{117} This activity was indicative of a different mode of action from that of cisplatin and the compound was heralded as the first example of a new class of DNA-altering chemotherapy agents. It entered clinical trials, but was found to cause high levels of neutropenia and gastrointestinal toxicity, which resulted in a very low
maximum tolerable dose.$^{118}$ Two derivatives, 34 and 35, are currently being investigated as ‘non-covalent’ analogues of 33 (Figure 1.3).$^{119-120}$ The removal of the terminal chloride ligands and addition of an ammine or terminal amine results in ligand-DNA binding through electrostatic and hydrogen-bonding interactions, notably forming bidentate amine-phosphate-ammine ‘clamps’ that disrupt the phosphate backbone of DNA and contort the helical conformation.$^{121}$ These complexes showed cytotoxic activity against cancer cell lines including those resistant to cisplatin.$^{119}$

\[ \text{Figure 1.3 – Polynuclear platinum(II) complexes} \]

**Targeted delivery**

The most recent area of platinum therapy to emerge is that of chemotherapy agents that selectively target cancer cells. Although this idea of selective delivery of a ‘magic bullet’ is not a new one,$^{122}$ the increased knowledge of cancer pathologies and genetics, as well as evolving technologies, has allowed this area to rapidly expand.

Targeted delivery can be passive or active. Passive techniques may exploit the enhanced permeability of cancer cells by increasing the lipophilicity of drugs or their delivery systems. Some examples are lipoplatin and ProLindac 36 (Figure 1.4).
Lipoplatin is a formulation of cisplatin encapsulated in nanoparticle-sized liposomes. Cisplatin is held in the aqueous core, while the lipophilic exterior is thought to allow increased diffusion across the cell membrane. In addition, the nanoparticle size of the liposome may take advantage of the enhanced permeation and retention (EPR) effect. The EPR effect is the observation that tumours, as they rapidly expand their vasculature, produce endothelial cells with gaps between them that appear to naturally accumulate molecules and particles of 50-200 nm in size. Although this effect has not been confirmed for lipoplatin, preclinical and clinical trials have shown that the drug has a higher uptake than cisplatin, as well as appearing to be moderately selective for cancerous cells, and reducing side effects. It is currently under investigation as an alternative formulation of cisplatin. ProLindac 36 is a hydrophilic polymer construct of oxaliplatin. It was designed so that at physiological pH, in the blood stream, the polymer remains bound to the platinum drug, but at lower pH, in the extracellular medium around tumours, the polymer is cleaved and the active drug is released. Pre-clinical and clinical trials indicated that ProLindac has a better therapeutic index than oxaliplatin, with fewer severe side effects. Preliminary results suggest the formulation may deposit higher doses of platinum at tumour sites, with a slight selectivity of cancerous cells over normal cells, but clinical trials appear to be suspended at the present time. Dendrimers, viruses, metal nanoparticles, and carbon nanotubes among others, have also been investigated as selective passive delivery agents.

![Figure 1.4](image-url) – A representation of the polymer platinum(II) formulation, ProLindac 36.
Active targeted delivery is the incorporation into the drug structure (or carrier) of a molecule that binds directly and selectively to receptors on cancer cells. This moiety transports the drug selectively to cancer cells. Some target receptors are specific for cancer cells, others are overexpressed, in which case normal cells are still a target, albeit less significant. One of the hallmarks of cancer is the rapid growth and division of cells as tumours spread.\textsuperscript{138} With this increased growth comes an increased need for energy and essential nutrients, and cancer cells have been found to increase uptake of certain molecules vital for their continued growth.\textsuperscript{138-142} Attaching these compounds to a prodrug could lead to the delivery of drugs selectively to cancer cells. Folate,\textsuperscript{143-145} estrogen,\textsuperscript{146-148} bile acids,\textsuperscript{149-150} and short peptides\textsuperscript{151-153} have been investigated as selective transporters, among others. However, solubility issues, moderate selectivity and limited increase of drug potency when used in conjunction with platinum have prevented any formulations from progressing past preliminary testing.

\textbf{Cytotoxic carbohydrate derivatives of cisplatin}

Carbohydrates are one class of compounds that have shown success in active targeted delivery studies, with \textsuperscript{18}F 2-fluoro-2-deoxy-D-glucose being approved for use in positron emission tomography (PET) imaging of tumours.\textsuperscript{154-156} The selectively for cancer cells is due to the upregulation of D-glucose transporters (GLUTs) in the cell membrane, which facilitate the increased transport of simple carbohydrates into the cell.\textsuperscript{156} The family of GLUTs are a common target for the selective delivery of anticancer drugs incorporating a carbohydrate moiety. While many examples of carbohydrate-tethered platinum complexes such as \textsuperscript{37} and \textsuperscript{38,157} \textsuperscript{39,158} and \textsuperscript{40, 17, 41} and derivatives\textsuperscript{44,159-163} have been prepared (Figure 1.5), studies showing a direct link to GLUT-associated uptake are lacking. In the case of \textsuperscript{39, 17, and 41}, additional studies on the specific uptake mechanisms have shown that inhibition of GLUT transporters adversely affects the cellular uptake of the compounds.\textsuperscript{44,158,162}
In addition to the interest in selective delivery, carbohydrate-based molecules and conjugates are an extensive area of drug design due to the modularity, and increased solubility and dose limits conferred on these compounds by the carbohydrate moiety. As mentioned in the Preface, carbohydrates are a readily accessible, enantiopure chiral pool, that can be easily modified to prepare scaffolds with desirable properties.

Some of the first cisplatin carbohydrate analogues were dichloro(2,3-diamine-2,3-dideoxy-D-glucose-\(N,N'\)) platinum(II) 42 and dichloro(methyl 2,3-diamino-2,3-dideoxy-\(\alpha\)-D-mannopyranoside-\(N,N'\)) platinum(II) 43, reported by Tsubomura and colleagues (Figure 1.6). The diamino carbohydrate moiety was chosen for its similarity to the trans-1,2-diaminocyclohexane motif in oxaliplatin 20. The D-glucose derivative 42 almost doubled the survival time of mice with S180 sarcomas compared with cisplatin 18 and both compounds could be administered at significantly higher doses than 18 (50mg/kg vs. 8mg/kg), highlighting the decreased toxicity of the carbohydrate derivatives. A continuation of this work stressed the importance of where the pyranose ring lay in relation to the chelating motif. If it was perpendicular, the
ring was thought to inhibit DNA binding and thus activity. If it was parallel, a greater cytotoxic activity was observed, similar to that observed with 20.\textsuperscript{166} When the chloride ligands of the 42 were replaced with an oxalate or malonate, activity decreased.\textsuperscript{167}

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure16.png}
\caption{Some of the first diamino carbohydrate-based platinum(II) complexes.}
\end{figure}

Hanessian and Wag prepared L-xylose derivatives such as 44 and 45 as analogues of 20 (Figure 1.7), which showed comparable activity to 18 in \textit{in vivo} leukemia models.\textsuperscript{168} However, 20 retained superior activity in the various cell lines tested.

Sasamori and co-workers branched out from the 2,3-diamino motif, preparing the 2,4-diamino L-arabinose derivative 46 (Figure 1.7), which was found to increase survival rate by 275\% (at a 3.1mg/kg dose) in a murine leukemia model.\textsuperscript{169} Although 18 remained more active, the carbohydrate derivative had a better therapeutic profile. The cationic complex 47 (Figure 1.7) was found to have a similar 50\% inhibitory dose as 18.\textsuperscript{170}

Di- and trinuclear carbohydrate-based platinum(II) complexes such as 48 and 49 have also been synthesised, with the aim of improving the solubility of the platinum(II) complexes (Figure 1.7).\textsuperscript{171} The dinuclear compound 48 was readily soluble, whereas the trinuclear compound 49 was sparingly so. However, while both compounds had comparable activity to 18, the trinuclear complex was slightly more active. A murine study with 49 showed only recoverable weight loss as a side effect, again highlighting the reduced toxicity of carbohydrate-based complexes to healthy cells.

The carbohydrate backbone has also been further modified to give complexes such as 50, where the carbohydrate moiety forms one half of a bidentate diimine ligand (Figure 1.7). The complex was not as active as 18, but gives an idea of the scope of carbohydrate modified cisplatin analogue design.\textsuperscript{172} Additionally, known organic
Chemotherapy agents have been attached to carbohydrate-platinum(II) complexes to produce potential ‘dual-threat’ drugs.\textsuperscript{173}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.7}
\caption{Some examples of carbohydrate-based platinum(II) complexes that have been investigated as potential chemotherapy agents.}
\end{figure}

Cisplatin, \textbf{18}, remains a frontline treatment for many types of cancers and will remain relevant in future chemotherapy treatments. Research continues into ameliorating side effects and resistance whilst conserving activity. Although drug delivery and individual drug selection are important aspects of improving drug treatment, if the actual active drug is harmful, there will still be side effects and resistance to contend with. Designing drugs to circumvent these problems is concomitant with improving
other aspects of treatment. Overall, carbohydrate-based platinum(II) complexes have been shown to have the potential to be as active as current platinum(II) chemotherapy agents. Two major advantages are that the carbohydrate moiety can improve solubility and \textit{in vivo} tests show consistently lower toxic side effects. A variety of different carbohydrates with various modifications have been prepared and tested, showing the useful modularity and large scope for drug design with carbohydrates.

\textbf{A different carbohydrate scaffold}

This thesis proposes the investigation of a 1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose structure $51$ as a scaffold for the synthesis of carbohydrate-based cisplatin analogues. This scaffold is based on 1,6-anhydro-β-D-glucopyranose $52$ (levoglucosan), an important synthon in drug and natural product synthesis.\textsuperscript{174-178} The distinctive structure of $52$ offers the protection of both the C1 and C6 positions, as well as an unusual $^1\!C_4$ conformation that confers unusual reactivity on the remaining, unprotected hydroxyl groups.\textsuperscript{179} In addition, the structure is conformationally locked, giving only the \textit{cis} conformation of the C2/4 axial functional groups.

\textbf{Figure 1.8} – Representations of the structure of 1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose structure $51$ and 1,6-anhydro-β-D-glucopyranose $52$ (levoglucosan).

The general structure of $51$ differs significantly from other, previously reported carbohydrate scaffolds used for diamine platinum(II) complexes with only one previous report of this scaffold being used to prepare only a small number of platinum(II) complexes with limited data.\textsuperscript{180}
The rigid, bicyclic backbone of 51 offers a fixed, axial, bidentate diamine motif. Due to its structure, the ligand should confer stability to the related platinum(II) complexes. The axial orientation of the two amines mimics the *cis*-binding geometry of cisplatin 18 and would form a stabilising six-membered chelate ring on complexation. The 1,6-anhydro bridge offers protection of the C1 and C6 positions, which leaves only C3 open to functionalisation. This solitary site of variation offers a simplification of balancing the reactivities of multiple functional groups. In addition, this position can be functionalised with a range of moieties, offering a wide scope of drug design. Overall, this carbohydrate motif offers promising scope for drug design, but is currently underdeveloped.

**Aims of this project**

The aims of this project were to synthesise a range of cisplatin analogues based around the 1,6-anhydro scaffold 51. Both simple analogues and more complicated examples inspired by polynuclear and active targeting designs in the literature were envisioned. Novel complexes would be tested for cytotoxicity in common cancer cell lines, with cisplatin 18 acting as a positive control.
RESULTS AND DISCUSSION

**Scaffold synthesis**

In order to synthesise the proposed analogues in an efficient manner, a late-stage divergent synthesis was proposed. While the diamine 51 formed the scaffold base, it was thought that the diazide 53 could be used as a key intermediate, from which analogues could be formed in presumably three to four steps. The azide groups on 53 would act as latent amines and would also offer protection of the C2/4 positions during C3 functionalisation.

The diazide 53 has been previously synthesised by Paulsen, Koebernick and coworkers,\textsuperscript{181-182} Černý, Pacák and colleagues,\textsuperscript{183} and Bailliez, Olesker and Cleophax\textsuperscript{184} from levoglucosan 52, via a Černý epoxide 54 (Figure 1.9).

\[
\begin{align*}
\text{51} & \quad \text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{53} & \quad \text{N}_3 & \quad \text{N}_3
\end{align*}
\]

**Figure 1.9** – A representation of the general synthetic pathway to the diazide 53 from levoglucosan 52.

The stereochemistry of 52 is the same as the stereochemistry of the key intermediate 53, but multiple manipulations of the stereocentres are needed to form 53. The D-galacto diol 55 presents a C3/4 stereochemistry that is primed for the synthesis of 53 via a C4 activation/displacement tandem reaction (Scheme 1.1). The diol 55 has been efficiently synthesised from D-galactal 56 by Hawley et al. and Tailler et al. (through the iodide 57), followed by C4 activation to give the triflate 58 (Scheme 1.1).\textsuperscript{185-186} Auzanneau et al. have reported the displacement of the triflate of 58 with potassium thiocyanate, and Ogawa and Aso, among others, have demonstrated the displacement
of a similar triflate with sodium azide. Therefore, it was proposed that the key intermediate 53 could be synthesised from 58 by displacement of the triflate with sodium azide to putatively give 59, followed by removal of the benzoyl protecting group at C3 (Scheme 1.1).

Scheme 1.1 – a) i) (Bu3Sn)2O, CH3CN; ii) I2, CH2Cl2; b) NaN3, DMF, H2O; d) NaN3, DMF, H2O; e) NaOMe, MeOH.

The pathway to the diazide 53 began with the pentaacetate 60, which was treated with hydrobromic acid to produce the α-bromide 61 (Scheme 1.2). The α-bromide 61 was then subjected to reductive elimination with activated zinc and N-methylimidazole to afford presumably the per-acetylated D-galactal, which was treated with potassium carbonate to afford D-galactal 56. Activation of 56 using bis(tributyltin)oxide and further treatment of the in-situ generated stannyl ether with iodine resulted in oxidative 1,6-iodocyclisation to give the iodide 57 in good yield. Treatment with sodium azide afforded the diol 55 in good yield with a small amount of the D-ido epimer 62 formed in the reaction.
Scheme 1.2 – a) HBr, CH₂Cl₂; b) i) Zn, N-methylimidazole, EtOAc; ii) K₂CO₃, MeOH; c) i) (Bu₃Sn)₂O, CH₃CN; ii) I₂, CH₂Cl₂; d) NaN₃, DMF, H₂O.

Unfortunately, the epimer 62 could not be separated by flash chromatography from 55. However, protection, as the acetonide 63, of the diol 55, flash chromatography, and subsequent removal of the isopropylidene group with acetic acid, afforded the pure diol 55 (45% over five steps), with 62 isolated in 11% over four steps (Scheme 1.3). Following the method from Auzanneau et al., activation of O₄ by treatment with triflic anhydride, followed by in situ benzoylation of remaining hydroxyl group gave the triflate 58. Gratifyingly, treatment of the triflate with sodium azide afforded the axial diazide 59. Further treatment of 59 with sodium methoxide gave the target diazide 53 in good yield.

Scheme 1.3 – a) 2,2-dimethoxypropane, CSA, CH₃CN; b) AcOH, H₂O; c) i) Tf₂O, Pyr., CH₂Cl₂; ii) BzCl; d) NaN₃, DMF; e) NaOMe, MeOH.
With the target diazide 53 in hand, the synthesis could now diverge to produce a variety of analogues by C3 functionalisation.

**Synthesis of ester analogues**

A measured approach was taken to designing carbohydrate analogues of cisplatin 18. To begin, simple modifications were to be made at C3, to establish patterns of activity due to small structural changes.

It was first of interest to examine the effect of different functional groups at C3. An ester linkage at C3 was chosen for the first library of analogues. A range of analogues of differing alkyl chain lengths were proposed to probe the relationship between carbon-chain length and activity. Long alkyl chains were proposed as cell membrane constituent mimics, which may assist with passive diffusion of the analogues into the cell. While longer, more hydrophobic alkyl chains might decrease the solubility of the analogues in aqueous media, shorter chains derivatives should retain solubility. Some analogues were designed to incorporate phenyl rings, to hopefully enhance interaction with cellular DNA by intercalation.

It was envisioned that the ester analogues could be synthesised upon reaction of the free hydroxyl group with a variety of acyl chlorides or anhydrides, a common technique for hydroxyl protection in carbohydrate chemistry. Thus, treatment of the diazide 53 with the appropriate acyl chloride or anhydride in basic conditions gave the related esters 64-70 in excellent yields (Scheme 1.4 and Figure 1.10).

![Scheme 1.4](image)

**Scheme 1.4** – a) RC(O)Cl or (RC(O))2O, DMAP, Pyr.
Figure 1.10 – All ester diazides synthesised from 53 using an acyl chloride or anhydride.

The diazides 64-70 were then to be reduced to the diamines. There were several suitable reduction methods which could have been employed, such as the Staudinger reaction using triphenylphosphine\textsuperscript{193-194} or palladium-on-carbon in the presence of hydrogen gas.\textsuperscript{195} Phosphine salts, by-products of the Staudinger reaction, require purification of the product by flash chromatography, whereas the product can usually be purified by filtration through Celite in the case of using palladium-on-carbon. In addition, it was thought that the polarity of the diamine would be such that chromatography may prove difficult. The palladium-on-carbon method offered a more efficient reduction pathway and this was tested with the benzoate 59, which afforded the diamine 71 (Scheme 1.5). Filtration proved to be sufficient, yielding a pure product by $^1$H NMR spectroscopy.

Scheme 1.5 – a) Pd/C, H$_2$, MeOH.

The method was successfully applied to the other esters 64-70 and the parent diazide 53 to give the corresponding amines 51 and 72-78 with almost quantitative yields, except in the case of 75 (Scheme 1.6 and Figure 1.11). Unfortunately, reduction of
produced a mixture of compounds which was thought to be due to either cleavage of the acetyl group or acyl migration in methanol.\textsuperscript{196-197} Changing the solvent to THF afforded the desired diamine 75 in excellent yield (Scheme 1.6 and Figure 1.3).

Scheme 1.6 – a) Pd/C, H\textsubscript{2}, MeOH for 64-66, and 68-70 or THF for 67. The scheme for the parent diazide 53 is not shown, but is identical.

Figure 1.11 – All ester diamine ligands prepared \textit{via} the palladium-on-carbon/hydrogen reduction of the related diazides 59, and 64-70, as well as the parent diazide 53.

With the diamines 51 and 71-78 in hand, attention turned to preparing a selection of substituted halobenzoyl derivatives. It was thought that an alternate route might be needed as, under hydrogenolysis conditions, palladium-mediated dehalogenation of aromatic rings can result.\textsuperscript{198-199} It was thought that the esters could be made from the diamine 51, thus avoiding reduction after ester installation. The amino groups should
be protected to avoid potential amide formation and 9-fluorenylmethoxycarbamate (Fmoc) group was chosen as a protecting group as these moieties can be removed using piperidine. Thus, the diamine 51 was treated with 9-fluorenylmethoxycarbonyl chloride to give the dicarbamate 79. Treatment of 79 with various halogenated aromatic acyl chlorides gave the crude esters 80-83. These compounds were then treated with piperidine to give the diamines 84-87 (Scheme 1.7 and Figure 1.12).

Scheme 1.7 – a) 9-fluorenylmethoxycarbonyl chloride, NaHCO₃, THF, H₂O; b) RC(O)Cl, DMAP, Pyr.; c) C₅H₁₀NH, THF.

Figure 1.12 – All ester diamine ligands synthesised by the Fmoc-mediated route.

With the library of esters in hand, complexation methods were sought. One commonly employed complexation method is the dropwise addition of potassium tetrachloroplatinate (K₂[PtCl₄]) to a solution of a diamine in water or a mixture of water and methanol. Upon standing at room temperature, the new platinum complexes usually precipitate as powders, or crystallise out of solution. This method
was investigated with the hydroxyl analogue 51, which gave the expected complex 88 as a light brown powder upon standing overnight (Scheme 1.8).

\[
\begin{array}{c}
\text{51} \\
\text{OH} \\
\text{H}_2\text{N} \\
\text{NH}_2
\end{array}
\quad \xrightarrow{a)} \quad
\begin{array}{c}
\text{88} \\
\text{OH} \\
\text{H}_2\text{N} \\
\text{NH}_2
\end{array}
\]

\textbf{Scheme 1.8} – a) K$_2$[PtCl$_4$], H$_2$O.

$^1$H NMR spectroscopy suggested that complexation was successful, as the previously unseen amine protons were evident as pairs of signals between 5.0-6.0 ppm, one as a set of multiplets and the other as a set of doublets. The initial success of this method prompted its use for the remainder of the complexations. Complexes 89-93 were synthesised from potassium tetrachloroplatinate and the corresponding amines 72-74, 76 and 77 in fair yields (Scheme 1.9 and Figure 1.13).

\[
\begin{array}{c}
\text{71-77} \\
\text{84-87} \\
\end{array}
\quad \xrightarrow{a) \text{ or } b)} \quad
\begin{array}{c}
\text{89-99}
\end{array}
\]

\textbf{Scheme 1.9} – a) K$_2$[PtCl$_4$], H$_2$O or H$_2$O, MeOH; b) PtCl$_2$(DMSO)$_2$, CH$_3$CN.

It was found that when $^1$H NMR experiments were run in $d_6$-DMSO for 92, minor compounds were present which grew in intensity over time. This appeared to occur more slowly in complexes with larger C3 substituents. It was thought that ligand substitution was occurring, as the DMSO, through sulfur-platinum bonding, replaced the chloride ligands. When $^1$H NMR experiments were run in $d_7$-DMF, this was not observed, as the oxygen atom in DMF is a poorer coordinating atom for platinum(II). This observation would have to be taken into account during biological testing where DMSO is often used to solubilise compounds. Using DMSO would alter the nature of the complexes during testing, confounding results.
On complexation of the acetate 75 with $K_2[PtCl_4]$, two compounds were observed by $^1$H NMR spectroscopy. These were not assigned to DMSO ligand substitution, as the NMR experiment was run in $d_7$-DMF. It was thought that the pH of the reaction (pH $\approx 2$, due to \textit{in situ} HCl formation) was acidic enough to promote ester hydrolysis. Multiple products were also observed in the complexations with the benzoate 71 and the halide-substituted benzoates analogues 84-87.

Due to the low success of this more traditional complexation method, other methods with more neutral reaction mediums were sought. A platinum metal precursor of interest was the complex dichlorodi(dimethylsulfoxide)platinum(II) ($PtCl_2(DMSO)_2$), which does not produce HCl as a side product, as the DMSO ligands are substituted preferentially by the incoming diamine ligand. In addition, acetonitrile can be used as the reaction solvent. $PtCl_2(DMSO)_2$ was added to a solution of the benzoate 71 in acetonitrile, which gave the expected complex 94 in low yield (Scheme 1.9 and Figure 1.5). This method was also used for the acetate and halide-substituted benzoates to give the desired complexes 95-99 (Scheme 1.9 and Figure 1.13). Unfortunately, the complexation of the diamine 78 gave a mixture of products with both complexation methods.

![Structure images](image.png)

**Figure 1.13** – All ester platinum(II) complexes synthesised in this study using either $K_2[PtCl_4]$ for 89-93, or $PtCl_2(DMSO)_2$ for 94-99.
The suspected cleavage of some of the esters at lower pH values was a characteristic that would have to be considered when evaluating the therapeutic profile of the compounds. Initial biological testing would give the relative activities of the ester complexes compared to other analogues, allowing for insight into their comparative success. If results were promising, then further studies on the metabolism of the complexes could determine if the esters were indeed cleaved \textit{in vivo}.

**Synthesis of ether analogues**

In an effort to avoid the potential reactivity and subsequent decomposition of the ester analogues \textit{in vivo}, ether analogues were also prepared. The ether library was designed to contain similar analogues to the ester library, allowing for comparisons between the two libraries. With this in mind, the simplest ether 100, containing a methyl moiety, was synthesised from the diazide 53 using the Williamson ether method.\(^{204}\) This method was applied to synthesise a range of ethers 101-105 of different chain lengths in excellent yields from the related alkyl bromides (Scheme 1.10 and Figure 1.14).

Unfortunately, attempts to prepare the isopropyl ether 106 gave poor yields using this method. This was presumably due to β-elimination of the secondary bromide.\(^{205}\) Due to this result, another alkylation method was sought. Johnstone and Rose had reported the treatment of alcohols with potassium hydroxide (KOH) and various alkyl halides in DMSO as a mild alkylation method.\(^{205}\) Significantly, no β-elimination was observed with primary alkyl halides and only minor amounts with secondary alkyl halides, which was encouraging. This method was used to prepare the isopropyl ether 106 in an improved yield (Scheme 1.10 and Figure 1.6). Due to the success of this method with 106, it was also employed for the preparation of 107 and 108, which were both obtained in good yields (Scheme 1.10 and Figure 1.14).

![Diagram](attachment:image.png)

\textbf{Scheme 1.10} – a) NaH, RX (X = I or Br), DMF; b) KOH, RBr, DMSO.
The diamines 109-117 were synthesised using a similar methodology for the preparation of the esters 71-78 and were isolated in good to excellent yields (Scheme 1.11 and Figure 1.15).

![Diagram of Scheme 1.11](image)

**Scheme 1.11** – a) Pd/C, H₂, MeOH.

Since the ether diamines 109-117 were not acid sensitive, treatment with K₂[PtCl₄] in water gave the corresponding complexes 118-124 in good yield (Scheme 1.12 and Figure 1.16). The nonyl and hexadecanyl analogues, due to their poor water solubility,
were treated with PtCl$_2$(DMSO)$_2$ in acetonitrile to give the complexes 125 and 126 in good yields (Scheme 1.12 and Figure 1.16).

**Scheme 1.12** – a) K$_2$[PtCl$_4$], H$_2$O; b) PtCl$_2$(DMSO)$_2$, CH$_3$CN.

**Figure 1.16** – All ether platinum(II) complexes synthesised in this using either K$_2$[PtCl$_4$] (118-124) or PtCl$_2$(DMSO)$_2$ (125 and 126).

**Synthesis of amide analogues**

It was of interest to investigate the activity of a library of amide and amino acid analogues, to discover if these pendant moieties had a different effect on activity compared to the other libraries.

The diazide 53 was again chosen as an appropriate starting material. However, the C3 position required suitable activation in order to generate the amide analogues. To this end, 53 was treated with chloroacetic acid to generate the carboxylic acid 127, which was activated upon treatment with pentafluorophenyl trifluoroacetate to give the presumed pentafluorophenyl ester 128. *In situ* displacement of the ester 128 with a variety of amines gave the series of amides 129-142 (Scheme 1.13 and Figure 1.17).
Scheme 1.13 – a) NaH, ClCH₂C(O)OH, THF; b) i) DIPEA, C₆F₅OC(O)CF₃, DMF; ii) Appropriate amine.

Figure 1.17 – All amide diazides prepared in this study.
The diamines 143-156 were prepared from the corresponding diazides 129-142 in a similar fashion to the previous diamines, and were isolated in good to excellent yields (Scheme 1.14 and Figure 1.18).

Scheme 1.14 – a) Pd/C, H₂, MeOH.

Figure 1.18 – All amide diamine ligands prepared in this study.
Since amides are generally known to be less reactive than other carboxylic acid derivatives, complexation of the amines 143-152 was achieved by treatment with K₂[PtCl₄] in water (Scheme 1.15). Complexes 157-166 were isolated as pure compounds in varying yields (Figure 1.19). Complexation of the more non-polar derivative 153 with the [Pt(DMSO)₂Cl₂] platinum precursor gave the complex 167 in good yield (Scheme 1.15 and Figure 1.19).

Scheme 1.15 – a) K₂[PtCl₄], H₂O; b) [Pt(DMSO)₂Cl₂], CH₃CN.

Figure 1.19 – All amide platinum(II) complexes prepared in this study using either K₂[PtCl₄] for 157-166 and [Pt(DMSO)₂Cl₂] for 167.
Interestingly pure complexes using the diamines 154-156 could not be isolated with either complexation method. The \(^1\)H NMR spectra of these complexes showed multiple carbohydrate signal sets. Changing solvent mixtures to improve solubility was also unsuccessful. This suggested that another complexation method was required for these amines. In the interest of expanding the analogue libraries to incorporate bimetallic complexes, investigation into further methods of complexation was assigned to future work.

**Synthesis of dinuclear analogues and other derivatives**

Now the simpler carbohydrate-based cisplatin analogues were in hand, it was of interest to expand and further test the modularity of the scaffold.

Literature on the transport of charge complexes across the cell membrane by organic cation transporters and reported activity of 26 (Figure 1.2) and 47 (Figure 1.7) inspired the design of the monofunctional, cationic, triamine complex 168.\(^{107-108}\)

![complex](image)

It was thought that the pendant amine moiety could be formed from a pendant azide, installed from an azidobromide such as 169 using the established potassium hydroxide-mediated ether synthesis. The triazide 170 could then be reduced to give the triamine ligand 171. Thus, 1-azido-5-bromopentane 169 was synthesised by treatment of 1,5-bromopentane 172 with sodium azide, following the method of Caldarelli *et al.*\(^{206}\) (Scheme 1.16). Treatment of the diazide 53 with the bromide 169 in the presence of potassium hydroxide gave the triazide 170 in good yield. Reduction of 170, in the presence of palladium-on-carbon and hydrogen gas, produced the triamine 171 in moderate yield. Complexation with PtCl\(_2\)(DMSO\(_2\)) pleasingly gave the complex 168 in good yield.
Multinuclear platinum(II) complexes such as 30 (Figure 1.20) have sparked recent interest for their ability to form long-distance interstrand cross-links.\textsuperscript{112,115-116} This novel DNA binding arrangement allowed diplatinum complexes to overcome cisplatin resistance and was identified as a new mode of action for a new class of platinum(II) anticancer compounds. Three dinuclear designs 173, 174, and 175 were proposed as an initial study into the viability of using 1,6-anhydro-based bimetallic complexes for this purpose (Figure 1.20). It was envisioned that a five- to six-membered alkyl chain would separate the two metal centres, based on literature reports of these chains lengths resulting in more active compounds.\textsuperscript{113,115,207} It was also of interest to investigate the different activities of a purely carbohydrate-based dinuclear complex, such as 173 and 174, and one that contained two different metal coordination sites, such as 175. The choice of the 1,3-diaminopropyl motif as the second coordination site was inspired by recent studies into this moiety, such as the carbohydrate-linked complex 37 (Figure 1.20).\textsuperscript{157}
It was thought that the alkyl-linked carbohydrate compounds could be accessed in an efficient manner by treating the diazide 53 with a half equivalent of an α,ω-dibromoalkane. Thus, the diazide 53 were treated with a half equivalent of 1,5-dibromopentane 172 in the presence of potassium hydroxide to afford the linked carbohydrate product 176 in a very low yield (Scheme 1.17). The tetraazide 176 was only a minor product, and the other isolated material was a complex mixture, but appeared to contain a compound with an alkene moiety, presumably as a result of β-elimination. While potassium hydroxide had been used to reduce the occurrence of β-elimination, as in the ether syntheses above, it was clear that this method was not viable.

A sequential method to the linked carbohydrate was attempted with the treatment of 53 with 172 in the presence of sodium hydride and sodium iodide giving the alkylated diazide 177 in moderate yield. Further treatment of 177 with another equivalent of the diazide 53 in the presence of sodium hydride and sodium iodide afforded the linked product 176 in low yield (Scheme 1.17).
Given the multiple products for both preparations, it was clear that an \( \alpha,\omega \)-bromoalkane was potentially not an appropriate starting material. Work by Zhang, Ren and Baker reported a facile method of differentiating and functionalising \( \alpha,\omega \)-diols such as 178 by mono-protecting one alcohol as a tetrahydropyranyl ether 179 and activating the other alcohol as a tosylate 180, which could then be displaced to form an ether 181 (Scheme 1.18).

This method potentially presented an efficient way to control the installation of the alkyl chain. 1,6-Hexanediol 182 was treated with 3,4-dihydro-2\( H \)-pyran to afford the ether 183 in good yield (Scheme 1.19). This was then activated on treatment with 4-toluenesulfonyl chloride to give the tosylate 184. The diazide 53 was treated with potassium hydroxide and the tosylate 184, to give the ether 185, which was then deprotected to give the alcohol 186. This material was activated to give the tosylate.
187, which was joined to the diazide 53 using the potassium hydroxide-mediated ether synthesis to give the tetraazide 188. The tetraamine 189 was then isolated in moderate yield upon reduction in the presence of palladium-on-carbon and hydrogen gas. It was thought to test the complexation reaction with the hexyl chained ligand before synthesising any pentyl-based analogues.

Scheme 1.19 – a) TsOH, 3,4-dihydro-2H-pyran, CH₂Cl₂; b) TsCl, Pyr., CH₂Cl₂; c) 53, NaH, DMF; d) TsOH, MeOH; e) TsCl, Pyr., CH₂Cl₂; f) 53, KOH, DMSO; g) Pd/C, H₂, MeOH.

The tetraamine 189 was set aside while efforts turned to synthesising the ligand precursor to 175. It was thought that to synthesise 175 a carbohydrate moiety similar to 187 could be prepared. The terminal tosylate could then be used to form an ether bond with a moiety such as 1,3-diaminopropanol. In this case, the pentyl chain was chosen to test the THP-based chemistry in case the pentyl-based tetraamine precursor ligand of 174 was prepared later. 1,6-Pentanediol 190 was treated with 3,4-dihydro-2H-pyran to afford the ether 191 in good yield (Scheme 1.20).²¹₀ This was then activated on treatment with 4-toluenesulfonyl chloride to give the tosylate 192.²¹¹ The diazide 53 was treated with potassium hydroxide and the tosylate 192, to give the ether 193, which was then deprotected to give the alcohol 194. This material was activated to give the tosylate 195.
Scheme 1.20 – a) TsOH, 3,4-dihydro-2H-pyran, CH₂Cl₂; b) TsCl, Pyr., CH₂Cl₂; c) NaH, DMF; d) TsOH, MeOH; e) TsCl, Pyr., CH₂Cl₂.

1,3-diazidopropanol 196 was readily available from 1,3-dibromopropanol 197 upon treatment with sodium azide following literature precedent (Scheme 1.21).²¹² Treatment of the alcohol 196 with 195, via the potassium-mediated ether method, gave the tetraazide 198 in excellent yield, which was then treated with palladium-on-carbon in the presence of hydrogen gas to afford the tetraamine 199.

Scheme 1.21 – a) NaN₃, DMF; b) KOH, DMSO, CH₃C₆H₅; c) Pd/C, H₂, MeOH.

Complexation of both tetraamine ligands 189 and 199 with K₂[PtCl₄] gave highly insoluble solids. The ¹H NMR spectra gave multiple signals, and was only ~90% pure based on the H1 proton in the spectrum. Attempts at recrystallization to increase purity were unsuccessful.
Chapter 1

It was concluded that the 1,6-anhydro moiety was not an appropriate scaffold for dinuclear complexes without incorporating another moiety that increased the overall solubility of the compounds. It was decided to turn efforts towards investigating increasing the solubility of the both the simple and bimetallic complexes before returning to improve the syntheses of the dinuclear complexes.

Synthesis of an analogue with pendant pyranose motifs

One approach to addressing solubility in the literature has been the inclusion of simple pyranose moieties in platinum(II) complexes. It was proposed to attach a carbohydrate moiety to the 1,6-anhydro scaffold via an alkyl linker and investigate the effects on solubility. Using the 1,6-anhydro scaffold, the galactose-containing target complex 200 was envisioned.

Previous reports on the synthesis of alkyl chain-linked carbohydrates have used conventional glycosylation methods to link an alkyl halide or alcohol and an appropriate pyranosyl acceptor to afford the linked compounds. From the efforts towards the attempted syntheses of the dinuclear complex 174, the alcohol 186 had been synthesised. This putative glycosyl acceptor presented an opportunity to attach a carbohydrate motif.

The appropriate glycosyl donor was prepared from 60 upon treatment with aqueous methylamine to give the presumed hemiacetal intermediate 201 that was immediately converted to the α-trichloroacetimidate 202 using the method of Schmidt and Kinzy (Scheme 1.22).
Scheme 1.22 – a) aq. MeNH$_2$, THF; b) CCl$_3$CN, DBU, CH$_2$Cl$_2$.

Conventional glycosylation between 186 and 202 gave the diazide 203 in low yield (Scheme 1.23). The diazide 203 was then deacetylated using Zemplén conditions to give the tetrol 204, that was reduced to the diamine 205 in the presence of hydrogen gas and palladium-on-carbon. Complexation upon treatment with both PtCl$_2$(DMSO)$_2$ and K$_2$[PtCl$_4$] did not produce the target complex, and multiple sets of carbohydrate signals in the $^1$H NMR spectrum suggested the pendant sugar was possibly interfering with the intended complexation. While the idea of forming the complex with the acetylated carbohydrate was conceived, this was unable to be attempted within the scope of this thesis and remains an objective for future work.

Scheme 1.23 – a) 4Å sieves, BF$_3$.OEt$_2$, CH$_2$Cl$_2$; b) NaOMe, MeOH; c) Pd/C, H$_2$, MeOH.
X-ray crystallographic studies

For cisplatin 18 and related cyclohexane and pyranose analogues such as 20, 42, and 43 (Figures 1.1 and 1.6), the coordination around the Pt atom is essentially square planar with bond angles N-Pt-N ≈ 91°, N-Pt-Cl ≈ 83-90°, N-Pt-Cl ≈ 175-179° and bond distances Pt-N ≈ 2.00 Å and Pt-Cl ≈ 2.3 Å. In some cases, the crystal packing showed the formation of dimeric pairs, due to intermolecular hydrogen bonds between the amine hydrogen atoms of one molecule and the coordinated Cl atoms of the other molecule (Figure 1.21). Where dimers formed, the Pt-Pt distance ranged from 3.282 Å to 3.479 Å.

![Figure 1.21](image-url)  
Figure 1.21 – A demonstration of the formation of dimers by intermolecular hydrogen bonding.

X-Ray crystallographic analyses of suitable crystals were conducted by Dr Brian Skelton and Dr Alexandre Sobolev. Several platinum(II) complexes gave crystals suitable for single crystal X-ray analysis (92, 96, 119, 122, and 163).
Complex 92 crystallised in the trigonal space group R3, with two independent molecules in the structure, and eight molecules per unit cell (Figure 1.22 A). The two molecular structures differed only in minor conformational changes of the propanoyl chain. Packing in the unit cell was governed by hydrogen bonding, but the dimeric structures discussed above were not observed. Instead, hydrogen-bonded columns of molecules parallel to the c-axis were formed (Figure 1.22 B). A single molecule was involved in two NH…Cl and one NH…O hydrogen bond. There were also hydrogen bonds between neighbouring columns. Selected bond lengths and angles are presented for the complex as well as intermolecular hydrogen bonds (Tables 1.1 and 1.2).

Figure 1.22 – (A) A plot of a molecule of 92; (B) A plot of a molecule of 92 showing hydrogen bonding forming columns of molecules. Ellipsoids for key atoms are drawn at the 50% probability level.
Complex 96 crystallised in the triclinic space group \( P1 \) with six independent molecules in the asymmetric unit as well as four molecules of DMF and three molecules of water (Figure 1.23 A). This could be seen in the different dihedral angles between the coordination plane and the plane of the phenyl rings; 55.1(2)°, 47.0(2)°, 91.9(2)°, 70.0(2)°, 91.8(2)° and 38.0(2)° for the six unique molecules. Packing in the unit cell was governed by hydrogen bonding, with two independent molecules forming a pair of columns of molecules, arranged through hydrogen bonds between the amine hydrogen atoms and the chlorine atoms on adjacent molecules (Figure 1.23 B). The other four molecules were associated with the two columns on either side through hydrogen bonds between the amine hydrogen atoms and the chlorine atoms on adjacent molecules. In addition, hydrogen bonds were observed between carbohydrate amine hydrogen atoms and DMF solvent molecules. Selected bond lengths and angles are presented for the complex as well as intermolecular hydrogen bonds (Tables 1.1 and 1.2).

Figure 1.23 – (A) A plot of a molecule of 96; (B) A plot of a molecule of 96 showing hydrogen bonding between the six different molecules. Ellipsoids for key atoms are drawn at the 50% probability level.
Complex 119 and 163 both crystallised in the triclinic space group \( P_1 \) with four independent molecules in the unit cell (Figure 1.24 A and B). Complex 122 crystallised in the triclinic space group \( P\overline{1} \) with two independent molecules in the unit cell (Figure 1.24 C). As observed with the structures of 92 and 96, the independent molecules in the unit cells differed in minor conformational changes of the C3 functional groups for each complex. In addition, in the case of 122, one methyl group of the isopropyl unit was also modelled as being equally disordered over two sites. Packing in the unit cells was governed by hydrogen bonding. The molecules formed pseudo-centrosymmetric hydrogen-bonded dimers with hydrogen bonds formed between the amine hydrogen atoms of one molecule and the coordinated Cl atoms of the other molecule of the pair as in Figure 1.21. Selected bond lengths and angles are presented for the complexes, as well as intermolecular hydrogen bonds (Tables 1.1 and 1.2).

**Figure 1.24** – (A) A plot of a molecule of 119; (B) A plot of a molecule of 122; (C) A plot of a molecule of 163. Ellipsoids for key atoms are drawn at the 50% probability level.
Table 1.1 – Select bond lengths (Å) and angles (°) for the complexes 92, 96, 119, 122, and 163.

<table>
<thead>
<tr>
<th></th>
<th>92</th>
<th>96</th>
<th>119</th>
<th>122</th>
<th>163</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-Pt-N2</td>
<td>95.9(16)</td>
<td>95.5(2)</td>
<td>96.0(2)</td>
<td>96.3(2)</td>
<td>95.9(7)</td>
</tr>
<tr>
<td>N1-Pt-Cl4</td>
<td>86.6(12)</td>
<td>87.4(15)</td>
<td>85.4(16)</td>
<td>84.2(18)</td>
<td>85.5(5)</td>
</tr>
<tr>
<td>N1-Pt-Cl3</td>
<td>176.8(12)</td>
<td>177.8(15)</td>
<td>179.0(14)</td>
<td>178.0(18)</td>
<td>178.5(5)</td>
</tr>
<tr>
<td>Pt1-N1</td>
<td>2.073(4)</td>
<td>2.046(5)</td>
<td>2.057(5)</td>
<td>2.053(6)</td>
<td>2.072(16)</td>
</tr>
<tr>
<td>Pt1-Cl3</td>
<td>2.294(13)</td>
<td>2.296(16)</td>
<td>2.325(15)</td>
<td>2.303(18)</td>
<td>2.326(5)</td>
</tr>
<tr>
<td>Pt1-Pt2</td>
<td>-</td>
<td>-</td>
<td>3.351(3)</td>
<td>3.375(7)</td>
<td>3.449(1)</td>
</tr>
</tbody>
</table>

Table 1.2 – Select hydrogen bond lengths (Å) 92, 96, 119, 122, and 163.

<table>
<thead>
<tr>
<th></th>
<th>92</th>
<th>96</th>
<th>119</th>
<th>122</th>
<th>163</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1H…Cl3</td>
<td>2.450</td>
<td>N12H…Cl24</td>
<td>2.331</td>
<td>N1H…Cl3</td>
<td>2.519</td>
</tr>
<tr>
<td>N2H…Cl4</td>
<td>2.546</td>
<td>N21H…Cl13</td>
<td>2.442</td>
<td>N2H…Cl4</td>
<td>2.477</td>
</tr>
<tr>
<td>N2H…O5</td>
<td>2.010</td>
<td>N12H…Cl44</td>
<td>2.470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N41H…Cl63</td>
<td>2.494</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, all of the platinum complexes had comparable geometry, and bond angles and distances to similar, previously reported crystal structures.
Biological testing

The cytotoxic potentials of the complexes 88-99, 118-126, 157-167 and crude complexes 168, 174, and 175 were assessed in two human cell lines; HeLa, a human cervical cancer line, and MCF-7, a human breast cancer line, using a common colourmetric MTT-based cell viability assay. To gain a general insight into the potency of the compounds, cells were plated, and then dosed with both 200 μM and 50 μM solutions of each complex. The cells were left to incubate with the compounds before a solution of 10% 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in media was added. MTT is a positively charged, yellow compound that can cross the cell membrane of metabolically active (viable) cells. Inside the cell, the MTT is reduced to 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan (formazan), which is purple in colour. The colour change observed upon addition of MTT can be quantified and used to determine relative viabilities of cells. Upon addition of MTT, the cells were incubated, then the formazan that formed was dissolved by adding a solubilising solution. Absorbances of test wells were compared to negative (cells, no compounds) and positive (dosed with cisplatin 18) controls.
The results against HeLa showed a range of cytotoxic activities both between and within analogue families (Figure 1.25). In general, the amide series of compounds (157-167) had minimal potency, with compounds reducing viability by less than 50%, even at the higher 200 μM dose (Figure 1.25 C). Only one compound, 167, stood out as worthy of further investigation. In the ester family of compounds (88-99), compounds reduced viability between 25-50% at 200 μM (Figure 1.25 A). Compounds 94, 96, 97, 98, and 99 were especially active and compound 96, in particular, showed an activity very close to that of cisplatin. The ether family contained several compounds which reduced viability by more than 75% at 200 μM and also significantly at 50 μM (Figure 1.25 B). Compounds 120, 124, 125, and 126 stood out as compounds of interest for further examination. The crude complexes 168, 174, and 175 reduced cell viability by more than 50%, adding further importance to being able to isolate pure samples for proper biological evaluation (Figure 1.25 D).
Figure 1.26 – Platinum(II) complexes which demonstrated high activity against HeLa cells.

From the compounds highlighted as meriting further investigation, structural patterns were observed (Figure 1.26). The compounds could be grouped into two sets; those with long alkyl chains, and those with phenyl rings. It was thought that the lipophilicity of the compounds could be a characteristic associated with increased activity, and it was of interest to compare the relative lipophilicities of the complexes with their biological activities. The lipophilicities of the new platinum complexes were evaluated by calculating the partition coefficient values (log $P$) of the related ligands using the online programme ALOGSP 2.1. These values were compared to experimental octanol-water partition coefficients of some related complexes, obtained by the shake-flask method. The ascending order of lipophilicities was conserved between both methods and demonstrated that the calculated values were appropriate representations of the relative lipophilicities of the related complexes. The calculated log $P$ values were plotted against viability (Figure 1.27). There was a clear, linear relationship between increased lipophilicity and increased biological activity. At the 50 μM dose, viabilities increase, but the pattern of activity is retained and the lower dose highlights the compounds that retain activity. Interestingly, the compounds 168, 174, and 175 do
not follow this observed trend, which may be related to the different proposed mechanism of action of polynuclear complexes previously reported\textsuperscript{112,117}.

**Figure 1.27** – Plots of log $P$ against viability of HeLa cells at (A) 200 $\mu$M and (B) 50 $\mu$M of each complex. The value for cisplatin 18 is an average across all the viability assays conducted. Viabilities are calculated as a percentage of the control viability set to 100%.
Figure 1.28 – Percentage viability of; (A) esters, (B) ethers, (C) amides, and (D) miscellaneous complexes in MCF-7 cells. ‘CisPt’ represents the positive control, cisplatin 18, and ‘Control’ represents the negative control of cells with no compound added.

The results against MCF-7 also showed a range of cytotoxic activities both between and within analogue families (Figure 1.28). In general, the percentage viabilities were higher in the MCF-7 line than in the HeLa line, demonstrating the low sensitivity of MCF-7 cells to platinum compounds, particularly cisplatin 18 in clinical settings. Similar trends in potencies were also observed between the two cell lines. Again, the amide series of compounds performed poorly, with the complex 167 showing the highest cytotoxicity (Figure 1.28 C). In the ester family, 94, 96, 97, 98, 99 again showed the best activities (Figure 1.28 A). The ether family also contained several compounds that reduced viability by more than 75% at 200 μM (Figure 1.28 B). Compounds 120, 124, 125 and 126 again stood out as compounds of interest. While the ester and ether libraries contained structurally similar compounds with similar activities, the related amide derivatives were much less active against both HeLa and MCF-7 cell lines. It is not understood why this is the case, but the amide bond clearly plays a role in deactivation. It was evident that further investigations into the mode of action and metabolism of examples from each library would be needed to better understand this observation. The complexes 168, and 174 reduced cell viability by more than 50% at 200 μM, but 175 was found to be less active against the MCF-7 cell line (Figure 1.28 D).
The same lipophilicity studies were carried out for the MCF-7 cell line results, showing much the same patterns of activity (Figure 1.29). While the activities of most compounds were reduced in MCF-7 cells, there were still a few examples that retained a high level of potency, notably 96, 125 and 126.

Figure 1.29 – Plots of log P vs viability of MCF-7 cells at (A) 200 μM and (B) 50 μM of each complex. The value for cisplatin 18 is an average across all the viability assays conducted.

After both the analyses against HeLa and MCF-7 cell lines, complexes 89, 91, 94, 96, 97, 98, 99, 120, 124, 125, 126, and 167 were chosen for further investigation.
Initially, it was of interest to obtain a more accurate quantitative measure of the activities of the chosen compounds. Thus, the IC$_{50}$ values of each compound were determined. Serial dilution MTT assays with the chosen compounds gave dose-response curves from which an IC$_{50}$ values could be calculated for both cell lines (Table 1.3). The IC$_{50}$ value for cisplatin 18 against each cell line was also obtained under the same assay conditions.

**Table 1.3 – IC$_{50}$ values for select platinum(II) complexes.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>HeLa</th>
<th>MCF-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>27.0 ± 2.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>91</td>
<td>24.9 ± 6.1</td>
<td>58.5 ± 15.5</td>
</tr>
<tr>
<td>94</td>
<td>65.2 ± 17.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>96</td>
<td>3.17 ± 0.2</td>
<td>5.31 ± 1.4</td>
</tr>
<tr>
<td>97</td>
<td>43.5 ± 8.7</td>
<td>86 ± 4.6</td>
</tr>
<tr>
<td>98</td>
<td>23.9 ± 2.0</td>
<td>57.7 ± 3.9</td>
</tr>
<tr>
<td>99</td>
<td>13.5 ± 2.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>120</td>
<td>17.0 ± 1.6</td>
<td>32 ± 7.7</td>
</tr>
<tr>
<td>124</td>
<td>31 ± 2.5</td>
<td>&gt;100</td>
</tr>
<tr>
<td>125</td>
<td>8.35 ± 1.1</td>
<td>26.7 ± 2.0</td>
</tr>
<tr>
<td>126</td>
<td>3.64 ± 0.8</td>
<td>6.71 ± 0.5</td>
</tr>
<tr>
<td>167</td>
<td>4.9 ± 0.7</td>
<td>&gt;100</td>
</tr>
<tr>
<td>cisplatin</td>
<td>15.6 ± 1.6</td>
<td>50.3 ± 3.9</td>
</tr>
</tbody>
</table>

*Values and errors are calculated from interpolation of data by Grafit. Errors are standard deviations. Experiments were conducted in triplicate.*
Cisplatin 18 gave an IC$_{50}$ value of 15.6 ± 1.6 μM against HeLa cells and 50.3 ± 3.9 μM against MCF-7 cells. The higher value against MCF-7 cells highlights the cell line’s resistance to cisplatin. Complexes 89, 91, 94, 97, 98, 120, and 124 all gave higher IC$_{50}$ values than cisplatin against HeLa cells. Compounds 96, 99, 125, 126, and 167 gave values lower than 18, with 96, 126 and 167 showing potency between three to five-fold higher than cisplatin. The high potencies of 126 and 167 tie in well with the observation that longer alkyl chains and higher lipophilicity increase the activity of these carbohydrate analogues. Complex 96 is an anomaly, as it does not contain a long alkyl chain and stands out from the other benzoate halides which were not as active, including 97, which also contains the bromobenzoyl motif.

In the MCF-7 cell line, 96, 120, 125 and 126 gave IC$_{50}$ values lower than cisplatin. This was exciting, as it suggested that some of the carbohydrate analogues represented potential drugs for the treatment of cisplatin resistant cancers. It was unexpected that 167 dramatically lost activity against MCF-7 cells after performing so well against HeLa cells.

Complexes 96 and 126 were consistently the most potent complexes across the two cell lines. Presumably, the long alkyl chain of 126 might facilitate passive diffusion through the cell membrane, allowing more compound to enter the cell, and that this might contribute to its potency. Compound 96, with the 4-bromobenzoate motif, was an enigma. The best performing complex of all, it had no structural patterns or other in vitro observations to indicate why it might have been so successful. The ability of the phenyl ring to intercalate may contribute to its activity, but the other analogues with phenyl rings 89, 94, 124, and 143 were significantly less active. The other halobenzoyl analogues 97, 98 and 99 were also not as potent, and, interestingly, 97, the 3-bromobenzoate analogue, was much less active. The fact that 96 was successful, where the other halides were not, may suggest a novel mode of action linked to the specific 4-bromobenzoate motif. Without knowing the mode of action, mechanism of uptake, cellular distribution, or metabolism of these compounds in vitro, it is impossible to do more than speculate as to the reasons behind their activities.
Conclusions and future work

Generally, lipophilicity appears to govern the cytotoxicity of these 1,6-anhydro-based cisplatin analogues, with increased lipophilicity linked to increased activity. Esters and ethers appear to be equally active, but amides are less active. Further studies are needed to ascertain why this might be the case. The moderate activity of the dinuclear and cationic complexes 168, 174 and 175 was promising and future work should include trying other methods of complexation in an attempt to isolate pure products for further biological testing.

The discovery of complexes 96 and 126 as highly potent carbohydrate analogues of cisplatin, with this activity conserved in cisplatin resistant cell lines, was very promising. While the potency of 126 aligns with the general pattern of activity, complex 96 is an anomaly and its singular activity may suggest a novel mode of action. These preliminary results strongly suggest further investigations should be conducted into the mode of action, mechanism of uptake, cellular distribution, and metabolism of these compounds in vitro, before potential in vivo toxicity and activity studies.

In addition, there is also scope to expand the design of analogues to include other cationic complexes, and compounds containing intercalating ligands such as phenanthridine, as in phenanthriplatin 26. Carbohydrate-based polynuclear complexes with trans isomerism may also warrant investigation as trans polynuclear complexes developed by Farrell and co-workers have been shown to be highly active.119-120

Overall, the use of the 1,6-anhydro scaffold has successfully generated a series of platinum complexes with a range of biological activities. The scaffold has been manipulated to form simple and more intricate complexes, giving a glimpse into the range of molecules accessible from one carbohydrate skeleton.
EXPERIMENTAL

General

$^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were obtained on Bruker ARX500 (500 MHz for $^1$H and 126 MHz for $^{13}$C) or Bruker AV600 or AV600II HD (600 MHZ for $^1$H and 151 MHz for $^{13}$C) spectrometers at 298 K unless specified. Solvents used for NMR were: deuterochloroform (CDCl$_3$) with CHCl$_3$ ($^1$H, $\delta$ 7.26) or CDCl$_3$ ($^{13}$C, $\delta$ 77.16) used as an internal standard, tetradeuteromethanol (CD$_3$OD) with CD$_2$HOD ($^1$H, $\delta$ 3.31) or CD$_3$OD ($^{13}$C, $\delta$ 49.00) used as an internal standard, hexadeuterodimethyl sulfoxide (d$_6$-DMSO) with CD$_3$S(O)CD$_2$H ($^1$H, $\delta$ 2.50) or (CD$_3$)$_2$SO ($^{13}$C, $\delta$ 39.52) used as an internal standard, deuterium oxide (D$_2$O) with DHO ($^1$H, $\delta$ 4.79) or CH$_3$OH ($^{13}$C, $\delta$ 49.00) used as an internal standard, hexadeuteroacetone ((CD$_3$)$_2$CO) with CD$_3$C(O)CD$_2$H ($^1$H, $\delta$ 2.05) or (CD$_3$)$_2$CO ($^{13}$C, $\delta$ 29.84) used as an internal standard, trideuterioacetonitrile (CD$_3$CN) with CD$_2$HCN ($^1$H, $\delta$ 1.94) and CD$_3$CN ($^{13}$C, $\delta$ 1.32) used as an internal standard, and heptadeutero-N,N-dimethylformanide (d$_7$-DMF) with (CD$_3$)$_2$NC(O)H ($^1$H, $\delta$ 8.03) and (CD$_3$)$_2$NC(O)D ($^{13}$C, $\delta$ 34.89) used as an internal standard$^{225-226}$.

High resolution mass spectra (HR-MS) were recorded on a Waters LCT Premier XE spectrometer, run in W-mode, using ESI or APCI isonisation methods as indicated, with CH$_3$CN/H$_2$O (9:1) as a matrix. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One ATR-IR spectrometer as a neat sample. Elemental analyses were performed by Roberstson Microlit Laboratories, New Jersey, United States of America. Experimental partition coefficient samples were prepared according to the shake-flask method$^{191}$ UV-Visible spectra were recorded on an Agilent Technologies Cary 60 UV-Visible spectrophotometer as 20 $\mu$M or 10 $\mu$M solutions in CH$_2$Cl$_2$ or MeOH, in a quartz cell. Cyclic voltammetry was performed using Autolab PGSTAT 30, with a platinum disc working electrode, a platinum wire counter electrode and a platinum wire pseudo-reference electrode. Solutions of the analyte in CH$_2$Cl$_2$ contained 0.1 M [[N$^n$Bu$_4$]PF$_6$ as the electrolyte. Potentials are reported vs. ferrocene / ferroenium ([Fe(η$_5$-C$_5$H$_5$)$_2$] / [Fe(η$_5$-C$_5$H$_5$)$_2$]$^+ = 0$ V using a decamethylferrocene / decamethylferroenium internal standard ([Fe(η$_5$-C$_5$Me$_5$)$_2$] / [Fe(η$_5$-C$_5$Me$_5$)$_2$]$^+ = –0.48$ V)$^{227}$ Crystallographic data were collected on an Oxford Diffraction Gemini diffractometer fitted with Cu Kα or Mo Kα radiation. Following analytical absorption
corrections and solution by direct methods, the structures were refined against F\(^2\) with full-matrix least-squares using the program SHELXL-97. Anisotropic displacement parameters were employed for the non-hydrogen atoms. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those of the parent atom. Geometries of disordered atoms were restrained to ideal values.

Flash chromatography was performed on BDH silica gel with the specified solvents. Thin layer chromatography (TLC) was performed on Merk silica gel 60 F254 aluminium-backed plates that were stained by heating (>200°C) with 5% solution of sulfuric acid in EtOH.

All solvents except DMSO, DMF and CH\(_3\)CN were distilled prior to use. Dimethylsulfoxide, DMF and CH\(_3\)CN were dried over 4 Å molecular sieves before use. CH\(_2\)Cl\(_2\) and THF were dried over, and distilled from, CaH\(_2\) and Na, respectively, before use.

**General Procedures**

**Procedure 1.1**

The appropriate acyl chloride or acid anhydride (2 eq.) and DMAP (0.6 eq.) was added to a solution of the diazide (1 eq.) in pyridine (8 mL) at 0°C. The resultant solution was left to stir at room temperature until all the diazide was consumed, as judged by TLC analysis. The reaction was then quenched with MeOH and concentrated. The resultant residue was taken up in EtOAc (30 mL), washed with water (30 mL), 1M HCl (30 mL), sat. NaHCO\(_3\) (30 mL), brine (25 mL), dried (MgSO\(_4\)), filtered, and concentrated.

**Procedure 1.2**

Sodium hydride (60% mineral dispersion in oil, 2 eq.) was added to a solution of the diazide (1 eq.) in DMF (3 mL) at 0°C and the resultant mixture was left to stir (10 min.). The appropriate alkylhalide (2 eq.) was then added with stirring and the mixture was left to stir at room temperature until all the diazide was consumed, as judged by TLC analysis. The reaction was then quenched with MeOH and concentrated. The
resultant residue was taken up in water (30 mL), and extracted with CH$_3$Cl (3 x 30 mL). The organic extracts were combined, dried (MgSO$_4$), filtered, and concentrated.

Procedure 1.3

Potassium hydroxide (10 eq.) was added to a solution of the diazide (1 eq.) in DMSO (3 mL) at 0°C and the resultant mixture was left to stir (10 min.). Then the appropriate alkylhalide (2 eq.) was added with stirring and the mixture was left to stir at room temperature until all the diazide was consumed, as judged by TLC analysis. The reaction was then quenched with MeOH and concentrated. The resultant residue was taken up in water (30 mL), and extracted with CH$_3$Cl (3 x 30 mL). The organic extracts were combined, dried (MgSO$_4$), filtered, and concentrated.

Procedure 1.4

DIPEA (1.1 eq) and pentafluorophenyl trifluoroacetate (1.1 eq.) were added to a solution of the acid 127 (1 eq.) in DMF (3 mL) at 0°C, and the resultant solution was stirred at room temperature. After 1 h., the appropriate amine (2.2 eq.) was added and the resultant solution was stirred at room temperature (1 h.). The reaction was then taken up in EtOAc (30 mL), washed with water (30 mL), 1M NaOH (30 mL), water (30 mL), brine (30 mL), dried (MgSO$_4$), filtered, and concentrated.

Procedure 1.5

Palladium-on-carbon (10%, 50 mg) was added to a solution of the appropriate diazide (1 eq.) in MeOH or THF (3 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until the reaction was judged complete by TLC analysis. The mixture was filtered through Celite and concentrated.

Procedure 1.6

A solution of K$_2$[PtCl$_4$] (1 eq.) (filtered to remove any insoluble impurities) in water (1 mL) was added dropwise to a solution of the appropriate diamine (1 eq.) in water or water/methanol (1:1) (1 mL) and the resultant suspension was left to sit at room temperature (16 h.) Crystals or a precipitate were collected by filtration, washed with cold water (2 x 2 mL) and air dried.
**Procedure 1.7**

A suspension of PtCl$_2$(DMSO)$_2$ (1 eq.) in CH$_3$CN (4 mL) was added dropwise to a solution of the appropriate diamine (1 eq.) in CH$_3$CN (1 mL) and the resultant mixture was left to stand at room temperature (16 h.). Crystals or a precipitate were collected by filtration, washed with cold water (2 x 2 mL) and air dried.

1,6-Anhydro-3-\(\text{O\text{-}benzoyl}\text{-}2,4\text{-diazido}\text{-}2,4\text{-dideoxy}\text{-}\beta\text{-d-glucose} 59

Sodium azide (870 mg, 13.4 mmol) was added to a solution of the triflate (1.62 g, 3.83 mmol) in DMF (16 mL) and the resultant mixture was stirred 90°C (3 h.). The mixture was concentrated, taken up in water (30 mL) and extracted with CH$_2$Cl$_2$ (5 x 30 mL). The extracts were combined, dried (MgSO$_4$), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (1.10 g, 94%). $R_f$ 0.67 (EtOAc/petrol 2:3). IR (ATR): 2098 (N$_3$), 1717 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.03-8.01 (m, 2H), 7.63-7.61 (m, 1H), 7.50-7.47 (m, 2H), 5.59 (s, 1H), 5.19-5.18 (m, 1H), 4.72 (d, $J$ = 5.4 Hz, 1H), 4.20 (d, $J$ = 7.8 Hz, 1H), 3.93 (dd, $J$ = 5.7, 7.8 Hz, 1H), 3.59 (s, 1H), 3.54 (s, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 165.1, 134.1, 129.9, 128.9, 100.2, 74.0, 70.7, 66.2, 59.2, 59.1†

1,6-Anhydro-2,4-diazido-2,4-dideoxy-\(\beta\text{-d-glucose} 53

Sodium methoxide (10 mg) was added to a solution of the diazide (935 mg, 3.0 mmol) in MeOH (15 mL) and the resultant solution was left to stir at room temperature until judged complete by TLC analysis. The mixture was quenched with resin (Amberlite IR-120, H$^+$), filtered and concentrated. Flash chromatography

† All diazides, unless specified, were derivatised as the diamine and then characterised by mass spectrometry due to the azide materials not giving a mass spectrum signal in all ionization modes readily available.
(EtOAc/petrol 7:13) of the resultant residue yielded the title compound as a white solid (571 mg, 91%). The $^1$H spectrum was consistent with that found in the literature.\textsuperscript{184}

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-$O$-toluoyl-$\beta$-d-glucose 64

The diazide 53 (96.1 mg, 0.454 mmol) was treated with toluoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (138 mg, 92%). $R_f$ 0.79 (EtOAc/petrol 2:3). IR (ATR): 2099 (N=O), 1718 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 7.92-7.91 (m, 2H), 7.33-7.31 (m, 2H), 5.55 (s, 1H), 5.07-5.06 (m, 1H), 4.74 (d, $J = 5.5$ Hz, 1H), 4.22 (dd, $J = 0.78$, 7.9 Hz, 1H), 3.86 (dd, $J = 5.7$, 7.9 Hz, 1H), 3.73 (s, 1H), 3.53 (s, 1H), 2.42 (s, 3H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 166.5, 146.1, 130.8, 130.4, 127.8, 101.4, 75.2, 71.9, 67.2, 60.2, 60.1, 21.7.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-$O$-(3-methyl)butanoyl-$\beta$-d-glucose 65

The diazide 53 (200 mg, 0.94 mmol) was treated with 3-methylbutyric anhydride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (245 mg, 88%). $R_f$ 0.64 (EtOAc/petrol 3:7). IR (ATR): 2097 (N=O), 1737 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.51 (s, 1H), 4.92-4.91 (m, 1H), 4.67 (d, $J = 5.6$ Hz, 1H), 4.07 (dd, $J = 0.6$, 7.7 Hz, 1H), 3.86 (dd, $J = 5.6$, 7.7 Hz, 1H), 3.42 (s, 1H), 3.37 (s, 1H), 2.28-2.22 (m, 2H), 2.14-2.08 (m, 1H), 0.98 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.5, 100.1, 73.8, 70.2, 66.0, 59.3, 59.1, 43.1, 25.7, 22.4.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(4-phenyl)benzoyl-β-D-glucose 66

The diazide 53 (200 mg, 0.94 mmol) was treated with 4-phenylbenzoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (269 mg, 72%). Rf 0.60 (EtOAc/petrol 3:7). IR (ATR): 2098 (N₃), 1714 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 8.09-8.08 (m, 2H), 7.71-7.69 (m, 2H), 7.63-7.62 (m, 2H), 7.50-7.47 (m, 2H), 7.43-7.41 (m, 1H), 5.61 (s, 1H), 5.21 (s, 1H), 4.74 (d, J = 5.2 Hz, 1H), 4.22 (d, J = 7.7 Hz, 1H), 3.95 (dd, J = 5.6, 7.6 Hz, 1H), 3.62 (s, 1H), 3.57 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 164.9, 146.7, 139.6, 130.3, 129.0, 128.5, 127.4, 127.3, 100.1, 73.9, 70.6, 66.1, 59.1, 59.0.

3-O-Acetyl-1,6-anhydro-2,4-diazido-2,4-dideoxy-β-D-glucose 67

The diazide 53 (204 mg, 0.96 mmol) was treated with acetic anhydride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 3:7) of the resultant residue yielded the title compound as a colourless oil (223 mg, 91%). Rf 0.47 (EtOAc/petrol 3:7). Rf 0.37 (EtOAc/petrol 3:7). IR (ATR): 2096 (N₃), 1749 (C=O) cm⁻¹. ¹H NMR (600 MHz, CD₃OD): δ 5.48 (s, 1H), 4.83-4.82 (m, 1H), 4.69 (d, J = 5.6 Hz, 1H), 4.11 (dd, J = 1.0, 7.8 Hz, 1H), 3.79 (dd, J = 5.7, 7.8 Hz, 1H), 3.59 (s, 1H), 3.40 (s, 1H), 2.10 (s, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 171.2, 101.4, 75.2, 71.6, 67.0, 60.3, 60.2, 20.8.
The diazide 53 (200 mg, 0.94 mmol) was treated with propanoic anhydride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (241 mg, 96%). Rf 0.47 (EtOAc/petrol 3:7). IR (ATR): 2098 (N$_3$), 1739 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 5.50 (s, 1H), 4.93-4.92 (m, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.07 (dd, J = 0.6, 7.7 Hz, 1H), 3.86 (dd, J = 5.6, 7.7 Hz, 1H), 3.43 (s, 1H), 3.38 (s, 1H), 2.44-2.35 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.8, 100.1, 73.8, 70.3, 66.0, 59.3, 59.1, 27.5, 8.8.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-propanoyl-β-D-glucose 68

The diazide 53 (102 mg, 0.48 mmol) was treated with hexanoic anhydride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (137 mg, 91%). Rf 0.60 (EtOAc/petrol 3:7). Rf 0.65 (EtOAc/petrol 3:7). IR (ATR): 2098 (N$_3$), 1739 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 5.50 (s, 1H), 4.92-4.91 (m, 1H), 4.67 (d, J = 5.4 Hz, 1H), 4.07 (d, J = 7.7 Hz, 1H), 3.86 (dd, J = 5.6, 7.7 Hz, 1H), 3.42 (s, 1H), 3.37 (s, 1H), 2.40-2.32 (m, 2H), 1.67-1.62 (m, 2H), 1.35-1.30 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.2, 100.1, 73.8, 70.2, 66.0, 59.3, 59.0, 34.1, 31.2, 24.4, 22.2, 13.8.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-tetradecanoyl-β-D-glucose 70

The diazide 53 (200 mg, 0.94 mmol) was treated with tetradecanoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (245 mg, 62%). \( R_f \) 0.78 (EtOAc/petrol 3:7). IR (ATR): 2099 (N\(_3\)), 1745 (C=O) cm\(^{-1}\). \( ^1 \)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 5.48 (s, 1H), 4.92-4.91 (m, 1H), 4.70 (d, \( J = 5.6 \) Hz, 1H), 4.10 (d, \( J = 7.9 \) Hz, 1H), 3.80 (dd, \( J = 5.7, 7.7 \) Hz, 1H), 3.58 (s, 1H), 3.37 (s, 1H), 2.40-2.37 (m, 2H), 1.66-1.61 (m, 2H), 1.36-1.29 (m, 20H), 0.90 (t, \( J = 7.0 \) Hz, 3H). \( ^{13} \)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 173.8, 101.4, 75.2, 71.5, 67.1, 60.4, 60.3, 35.0, 33.1, 30.8, 30.7, 30.7, 30.5, 30.5, 30.4, 30.1, 25.8, 23.7, 14.4.

1,6-Anhydro-3-O-benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 71

The diazide 59 (190 mg, 0.60 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (148 mg, 93%). \( R_f \) 0.37 (EtOAc/petrol 3:7). IR (ATR): 1706 (C=O) cm\(^{-1}\). \( ^1 \)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 8.04-8.02 (m, 2H), 7.60-7.57 (m, 1H), 7.47-7.45 (m, 2H), 5.46 (s, 1H), 4.83-4.82 (m, 1H), 4.50 (d, \( J = 5.4 \) Hz, 1H), 4.21 (dd, \( J = 0.5, 7.3 \) Hz, 1H), 3.88 (dd, \( J = 5.7, 7.2 \) Hz, 1H), 3.02 (s, 1H.), \( \delta \) 2.99 (s, 1H.). \( ^{13} \)C NMR (151 MHz, \( d_6 \)-DMSO): \( \delta \) 164.8, 133.3, 123.0, 129.1, 128.8, 102.6, 77.2, 76.4, 65.7, 52.8, 52.2. HR-MS (ESI): \( m/z \) 287.1009; [M+Na]\(^+\) requires 287.1008.
1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 51

The diazide 53 (84 mg, 0.39 mmol) was treated according to Procedure 1.5 to give the title compound as a light brown oil (59 mg, 94%). The $^1$H spectrum was consistent with that found in the literature. 229

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-toluoyl-β-D-glucopyranose 72

The diazide 64 (97 mg, 0.29 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (76 mg, 93%). $R_f$ 0.26 (CHCl$_3$/MeOH/H$_2$O 4:4:1). IR (ATR): 1706 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, D$_2$O/CD$_3$OD): δ 7.92-7.91 (m, 2H), 7.39-7.38 (m, 2H), 5.51 (s, 1H), 4.85 (s, 1H), 4.63 (d, $J = 5.8$ Hz, 1H), 4.31 (d, $J = 7.9$ Hz, 1H), 3.92-3.90 (m, 1H), 3.07 (s, 1H), 2.94 (s, 1H), 2.43 (s, 3H). $^{13}$C NMR (151 MHz, D$_2$O/CD$_3$OD): δ 167.5, 145.6, 129.7, 129.5, 126.4, 102.3, 76.5, 76.2, 66.2, 51.9, 51.4, 20.9. HR-MS (APCI): $m/z$ 279.1347; [M+H]$^+$ requires 279.1345.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-methyl)butanoyl-β-D-glucopyranose 73

The diazide 65 (222 mg, 0.75 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (178 mg, 97%). $R_f$ 0.31 (CHCl$_3$/MeOH/H$_2$O 4:4:1). IR (ATR): 1722 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, D$_2$O): δ 5.47 (s, 1H), 4.65 (s, 1H), 4.59 (d, $J = 5.4$ Hz, 1H), 3.85 (q, $J = 5.8$, 7.7 Hz, 1H), 2.95 (s, 1H), 2.82 (s, 3H), 2.59 (s, 3H), 2.47 (s, 3H).
1H), 2.36-2.29 (m, 2H), 2.13-2.06 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H). $^{13}$C NMR (151 MHz, D$_2$O/CH$_3$OH): δ 175.6, 102.7, 77.0, 76.2, 66.6, 52.4, 51.9, 43.8, 26.1, 22.2, 22.2.

HR-MS (APCI): m/z 245.1496; [M+H]$^+$ requires 245.1501.

![Image]

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(4-phenyl)benzoyl-$\beta$-D-glucopyranose

The diazide 66 (46 mg, 0.12 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (34 mg, 86%). $R_f$ 0.33 (CHCl$_3$/MeOH/H$_2$O 4:4:1). IR (ATR): 1701 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): δ 8.11-8.10 (m, 2H), 7.77-7.76 (m, 2H), 7.69-7.68 (m, 2H), 7.49-7.46 (m, 2H), 7.41-7.39 (m, 1H), 5.40 (s, 1H), 4.87-4.86 (m, 1H), 4.51 (d, J = 5.4 Hz, 1H), 4.25 (dd, J = 0.7, 7.4 Hz, 1H), 3.84 (dd, J = 5.7, 7.4 Hz, 1H), 2.98 (s, 1H), 2.86 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): δ 166.9, 147.4, 141.1, 131.2, 130.1, 129.4, 128.3, 128.2, 104.1, 77.9, 77.8, 67.4, 54.0, 53.5. HR-MS (APCI): m/z 341.1501; [M+H]$^+$ requires 341.1501.

![Image]

3-O-Acetyl-1,6-anhydro-2,4-diamino-2,4-dideoxy-\(\beta\)-D-glucopyranose

The diazide 67 (222 mg, 0.88 mmol) was treated according to Procedure 1.5 (with THF as the solvent) to give a colourless oil (174 mg, 98%). $R_f$ 0.03 (CHCl$_3$/MeOH/H$_2$O 4:4:1). IR (ATR): 1726 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 5.37 (s, 1H), 4.54-4.53 (m, 1H), 4.44 (d, J = 5.4 Hz, 1H), 4.08 (dd, J = 0.6, 7.2 Hz, 1H), 3.80 (dd, J = 5.7, 7.1 Hz, 1H), 2.87 (s, 1H), 2.83 (s, 1H), 2.07 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 170.1, 103.0, 76.1, 76.2, 66.1, 52.7, 52.6, 21.2. HR-MS (APCI): m/z 203.1034; [M+H]$^+$ requires 203.1032.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-propanoyl-β-D-glucopyranose 76

The diazide 68 (218 mg, 0.81 mmol) was treated according to Procedure 1.5. Flash chromatography (MeOH/CH₂Cl₂ 1:9 to 3:7) of the resultant residue yielded the title compound as a colourless oil (106 mg, 60%). Rₜ 0.17 (CHCl₃/MeOH/H₂O 4:4:1). IR (ATR): 1723 (C=O) cm⁻¹. ¹H NMR (600 MHz, D₂O): δ 5.48 (s, 1H), 4.65-4.64 (m, 1H), 4.60 (d, J = 5.2 Hz, 1H), 4.22 (dd, J = 0.8, 7.8 Hz, 1H), 3.86 (dd, J = 5.8, 7.8 Hz, 1H), 2.97 (s, 1H), 2.83 (s, 1H), 2.46 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H). ¹³C NMR (151 MHz, D₂O/CH₃OH): δ 176.4, 102.2, 76.4, 75.6, 66.1, 51.8, 51.3, 27.6, 8.3. HR-MS (APCI): m/z 217.1186; [M+H]+ requires 217.1188.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-hexanoyl-β-D-glucopyranose 77

The diazide 69 (118 mg, 0.38 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (92 mg, 94%). Rₜ 0.32 (CHCl₃/MeOH/H₂O 4:4:1). IR (ATR): 1723 (C=O) cm⁻¹. ¹H NMR (600 MHz, D₂O/CD₃OD): δ 5.47 (s, 1H), 4.64 (s, 1H), 4.59 (d, J = 5.3 Hz, 1H), 4.21 (d, J = 7.6 Hz, 1H), 3.86 (dd, J = 6.1, 7.4 Hz, 1H), 2.95 (s, 1H), 2.82 (s, 1H), 2.44 (t, J = 7.4 Hz, 2H), 1.67-1.63 (m, 2H), 1.33 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H). ¹³C NMR (151 MHz, D₂O/CD₃OD): δ 176.4, 102.7, 77.0, 76.2, 66.6, 52.3, 51.9, 34.6, 31.1, 24.6, 22.2, 13.8. HR-MS (APCI): m/z 259.1660; [M+H]+ requires 259.1658.
The diazide 70 (231 mg, 0.55 mmol) was treated according to Procedure 1.5 (with THF as the solvent) to give a colourless oil (193 mg, 95%). Rf 0.54 (MeOH/CHCl₃/H₂O 4:4:1). IR (ATR): 1726 (C=O) cm⁻¹. ¹H NMR (600 MHz, CD₃OD): δ 5.31 (s, 1H), 4.58-4.57 (m, 1H), 4.43 (d, J = 5.4 Hz, 1H), 4.09 (dd, J = 0.7, 7.3 Hz, 1H), 3.74 (dd, J = 5.8, 7.2 Hz, 1H), 2.80 (s, 1H), 2.68 (s, 1H), 2.37-2.31 (m, 2H), 1.65-1.60 (m, 2H), 1.32-1.29 (m, 20H), 0.90 (t, J = 7.0 Hz, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 174.3, 103.9, 77.6, 77.3, 67.2, 53.9, 53.5, 35.2, 33.1, 30.8, 30.8, 30.7, 30.6, 30.5, 30.4, 30.2, 26.0, 23.7, 14.4. HR-MS (APCI): m/z 371.2909; [M+H]^+ requires 371.2910.

A solution of 9-fluorenlymethoxycarbonyl chloride (375 mg, 1.45 mmol) in THF (2 mL) was added dropwise to a solution of the diamine 51 (106 mg, 0.66 mmol) and sodium hydrogencarbonate (166 mg, 1.91 mmol) in water (2 mL) at 0°C. The resultant solution was stirred at room temperature until all the diamine was consumed, as judged by TLC analysis. The solution was then taken up in water (30 mL) and extracted with EtOAc (2 x 30 mL). The organic extracts were combined, washed with water (30 mL), 1 M HCl (30 mL), brine (30 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:1) of the resultant residue yielded the title compound as a white, crystalline solid (279 mg, 70%). Rf 0.18 (EtOAc/petrol 1:1). IR (ATR): 3338 (N-H), 1694 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₆-DMSO): δ 7.90-7.89 (m, 4H),
7.78 (d, $J = 9.2$ Hz, 1H), 7.73-7.70 (m, 4H), 7.58 (d, $J = 9.8$ Hz, 1H), 7.43-7.29 (m, 8H), 5.49 (s, 1H), 5.22 (s, 1H), 4.40-4.33 (m, 5H), 4.26-4.24 (m, 2H), 4.11 (d, $J = 6.4$ Hz, 1H), 3.60-3.49 (m, 3H). $^{13}$C NMR (151 MHz, $d_6$-DMSO): $\delta$ 156.0, 156.0, 143.8, 143.8, 143.8, 140.7, 140.7, 127.7, 127.6, 127.1, 127.0, 125.2, 125.1, 120.2, 120.1, 120.0, 101.1, 79.2, 75.0, 71.1, 65.7, 65.6, 54.2, 53.9, 46.8. HR-MS (APCI): $m/z$ 605.2296; [M+H]$^+$ requires 605.2288.

1,6-Anhydro-3-O-(4-bromo)benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 84

The carbamate 79 (388 mg, 0.64 mmol) was treated with 4-bromobenzoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 7:13) of the resultant residue yielded a colourless oil (405 mg). The residue was dissolved in THF (2 mL), cooled to 0°C and piperidine (0.10 mL, 1.01 mmol) was added. The resultant solution was left to stir at room temperature until the reaction was complete, as judged by TLC analysis. Concentration of the mixture followed by flash chromatography (MeOH/DCM 1:9) yielded the title compound as a colourless oil (125 mg, 57% over two steps). $R_f$ 0.17 (MeOH/EtOAc 1:9). IR (ATR): 3364 (N-H), 1712 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 7.93-7.92 (m, 2H), 7.69-7.68 (m, 2H), 5.38 (s, 1H), 4.49 (d, $J = 5.4$ Hz, 1H), 4.19 (dd, $J = 0.7$, 7.5 Hz, 1H), 3.81 (dd, $J = 5.7$, 7.4 Hz, 1H), 2.95 (s, 1H), 2.83 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 166.2, 133.1, 132.3, 130.5, 129.3, 104.0, 78.1, 77.7, 67.4, 53.9, 53.4. HR-MS (APCI): $m/z$ 343.0287; [M+H]$^+$ requires 343.0293.
1,6-Anhydro-3-\textit{O}\text{-}(3-bromo)benzoyl-2,4-diazido-2,4-dideoxy-\textgreek{\textbeta}-\texttext{D}-glucopyranose 85

The carbamate 79 (153 mg, 0.25 mmol) was treated with 3-bromobenzoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 7:13) of the resultant residue yielded a colourless oil (179 mg). The residue was dissolved in THF (2 mL), cooled to 0°C and piperidine (0.051 mL, 0.52 mmol) was added. The resultant solution was left to stir at room temperature until the reaction was complete, as judged by TLC analysis. Concentration of the mixture followed by flash chromatography (MeOH/DCM 1:9) yielded the title compound as a colourless oil (59 mg, 69% over two steps). $R_f$ 0.15 (MeOH/EtOAc 1:9). IR (ATR): 3365 (N-H), 1713 (C=O) cm\textsuperscript{-1}. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 8.13-8.13 (m, 1H), 7.99-7.98 (m, 1H), 7.79-7.77 (m, 1H), 7.44-7.42 (m, 1H), 5.39 (s, 1H), 4.85-4.84 (m, 1H), 4.49 (d, $J$ = 5.5 Hz, 1H), 4.18 (dd, $J$ = 0.7, 7.4 Hz, 1H), 3.82 (dd, $J$ = 5.7, 7.4 Hz, 1H), 2.96 (s, 1H), 2.84 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 165.5, 137.3, 133.5, 133.4, 131.6, 129.3, 123.5, 104.0, 78.3, 77.7, 67.4, 53.9, 53.3. HR-MS (ESI): $m/z$ 343.0294; [M+H]$^+$ requires 343.0293.

1,6-Anhydro-3-\textit{O}\text{-}(4-chloro)benzoyl-2,4-diazido-2,4-dideoxy-\textgreek{\textbeta}-\texttext{D}-glucopyranose 86

The carbamate 79 (152 mg, 0.25 mmol) was treated with 4-chlorobenzoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 3:7) of the resultant residue yielded the title compound as a colourless oil (151 mg). The residue was dissolved in THF (2 mL), cooled to 0°C and piperidine (0.046 mL, 0.47 mmol) was added. The resultant solution was left to stir at room temperature until the reaction was complete, as judged by TLC analysis. Concentration of the mixture followed by flash chromatography (MeOH/DCM 1:9) yielded the title compound as a colourless oil (49 mg, 67% over two steps). $R_f$ 0.19 (MeOH/EtOAc 1:9). IR (ATR): 3355 (N-H), 1715
(C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 8.01\) - 7.99 (m, 2H), 7.53 - 7.51 (m, 2H), 5.38 (s, 1H), 4.85 (s, 1H), 4.49 (d, \(J = 5.1\) Hz, 1H), 4.19 (dd, \(J = 1.7, 7.5\) Hz, 1H), 3.82 - 3.80 (m, 1H), 2.95 (s, 1H), 2.83 (s, 1H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 166.0, 140.8, 132.2, 130.0, 130.0, 104.0, 78.1, 77.7, 67.4, 53.9, 53.4\). HR-MS (ESI): \(m/z \ 299.0798\); [M+H]\(^+\) requires 299.0799.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(4-fluoro)benzoyl-\(\beta\)-D-glucopyranose 87

The carbamate 79 (151 mg, 0.25 mmol) was treated with 4-fluorobenzoyl chloride according to Procedure 1.1. Flash chromatography (EtOAc/petrol 3:7 to 1:1) of the resultant residue yielded the title compound as a colourless oil (144 mg). The residue was dissolved in THF (2 mL), cooled to 0°C and piperidine (0.045 mL, 0.46 mmol) was added. The resultant solution was left to stir at room temperature until the reaction was complete, as judged by TLC analysis. Concentration of the mixture followed by flash chromatography (MeOH/DCM 1:9) yielded the title compound as a colourless oil (46 mg, 65% over two steps). \(R_t \ 0.12\) (MeOH/EtOAc 1:9). IR (ATR): 3368 (N-H), 1709 (C=O) cm\(^{-1}\). \(^1\)H NMR (500 MHz, CD\(_3\)OD): \(\delta 8.10\) - 8.07 (m, 2H), 7.25 - 7.22 (m, 2H), 5.38 (s, 1H), 4.84 - 4.82 (m, 1H), 4.49 (d, \(J = 5.6\) Hz, 1H), 4.20 (dd, \(J = 0.8, 7.5\) Hz, 1H), 3.81 (dd, \(J = 5.7, 7.4\) Hz, 1H), 2.95 (s, 1H), 2.82 (s, 1H). \(^{13}\)C NMR (125 MHz, CD\(_3\)OD): \(\delta 167.4\) (d, \(J = 253\) Hz), 166.0, 133.4 (d, \(J = 9.5\) Hz), 127.8 (d, \(J = 2.9\) Hz), 116.7 (d, \(J = 22\) Hz), 104.0, 78.0, 77.7, 67.4, 54.0, 53.4. HR-MS (ESI): \(m/z \ 283.1093\); [M+H]\(^+\) requires 283.1094.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-\(\beta\)-D-glucopyranose-\(N,N'\)) platinum(II) 88
Chapter 1

The diamine 51 (55 mg, 0.34 mmol) was treated with according to Procedure 1.6 to give a light brown solid (43 mg, 29%). IR (ATR): 3420, 3208, 3122 (N-H) cm$^{-1}$. $^1$H NMR (600 MHz, $d_7$-DMF): $\delta$ 5.69-5.66 (m, 3H), 5.55 (br s, 1H), 4.99 (d, $J = 12.3$ Hz, 1H), 4.89 (d, $J = 12.3$ Hz, 1H), 4.84-4.86 (m, 1H), 4.36 (d, $J = 6.7$ Hz, 1H), 3.65 (s, 1H), 3.59-3.57 (m, 1H), 2.57 (s, 1H), 2.48 (d, $J = 4.5$ Hz, 1H). $^{13}$C NMR (151 MHz, $d_7$-DMF): $\delta$ 100.0, 73.7, 72.1, 65.2, 51.3, 51.0. HR-MS (ESI): $m/z$ 467.0284; [M+DMSO-Cl]$^+$ requires 467.0303.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-toluoyl-$\beta$-D-glucopyranose-$N,N'$) Platinum(II) 89

The diamine 72 (61 mg, 0.22 mmol) was treated with according to Procedure 1.6 to give the title compound as a cream solid (47 mg, 39%). IR (ATR): 1715 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, $d_6$-DMSO): $\delta$ 7.86-7.84 (m, 2H), 7.38-7.36 (m, 2H), 5.87-5.84 (m, 1H), 5.77-5.74 (m, 1H), 5.56 (s, 1H), 5.23 (d, $J = 11.8$ Hz, 1H), 5.05 (d, $J = 11.8$ Hz, 1H), 4.78 (d, $J = 4.7$ Hz, 1H), 4.73 (s, 1H), 4.17 (d, $J = 7.5$ Hz, 1H), 3.59 (dd, $J = 5.8$, 7.4 Hz, 1H), 3.16 (d, $J = 2.6$ Hz, 1H), 2.39 (s, 3H), 2.25 (d, $J = 5.1$ Hz, 1H). $^{13}$C NMR (151 MHz, $d_7$-DMF): $\delta$ 164.8, 144.8, 129.9, 129.8, 127.2, 99.8, 73.8, 72.6, 65.6, 49.4, 48.8, 21.1. HR-MS (ESI): $m/z$ 606.0430; [M+CH$_3$CN+Na]$^+$ requires 606.0434.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-methyl)butanoyl-$\beta$-D-glucopyranose-$N,N'$) Platinum(II) 90

The diamine 73 (161 mg, 0.66 mmol) was treated with according to Procedure 1.6 to give the title compound as a light brown solid (227 mg, 68%). IR (ATR): 1728 (C=O)
\[ \text{Chapter 1} \]

\[ \text{H NMR (600 MHz, } d_6\text{-DMSO): } \delta 5.79-5.76 (m, 1H), 5.71-5.68 (m, 1H), 5.49 (s, 1H), 5.14 (d, } J = 12 \text{ Hz, 1H}), 4.97 (d, } J = 12 \text{ Hz, 1H}), 4.71 (d, } J = 4.5 \text{ Hz, 1H}), 4.51 (s, 1H), 4.02 (d, } J = 7.8 \text{ Hz, 1H}), 3.50 (dd, } J = 6.0, 7.1 \text{ Hz, 1H}), 2.30 (d, } J = 5.0 \text{ Hz, 1H}), 2.20 (dd, } J = 5.7, 7.0 \text{ Hz, 2H}), 2.10 (d, } J = 5.3 \text{ Hz, 1H}), 0.90 (d, } J = 6.7 \text{ Hz, 6H}). \]

\[ \text{13C NMR (151 MHz, } d_6\text{-DMSO): } \delta 170.5, 98.5, 72.6, 71.2, 64.6, 48.1, 47.7, 42.6, 25.2, 22.1, 22.0. \]

\[ \text{HR-MS (ESI): } m/z 572.0595; [\text{M+CH}_3\text{CN+Na}]^+ \text{ requires } 572.0590. \]

\[ \text{Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-(4-phenyl)benzoyl-}\beta\text{-D-glucopyranose-}\text{-}N,N') \text{ Platinum(II) 91} \]

The diamine 74 (170 mg, 0.50 mmol) was treated with according to Procedure 1.6 to give the title compound as a cream solid (237 mg, 79%). IR (ATR): 1709 (C=O) cm\(^{-1}\). \[ \text{1H NMR (600 MHz, } d_6\text{-DMSO): } \delta 8.06-8.05 (m, 2H), 7.90-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.54-7.52 (m, 2H), 7.47-7.45 (m, 1H), 5.92-5.90 (m, 1H), 5.81-5.78 (m, 1H), 5.60 (s, 1H), 5.27 (d, } J = 11.8 \text{ Hz, 1H}), 5.09 (d, } J = 11.8 \text{ Hz, 1H}), 4.82 (d, } J = 4.3 \text{ Hz, 1H}), 4.79 (s, 1H), 4.24 (d, } J = 7.5 \text{ Hz, 1H}), 3.63 (dd, } J = 5.3, 7.5 \text{ Hz, 1H}), 2.56 (s, 1H), 2.31 (s, 1H)). \]

\[ \text{13C NMR (151 MHz, } d_6\text{-DMSO): } \delta 163.9, 145.2, 138.7, 130.0, 129.2, 127.9, 127.2, 127.1, 98.7, 72.8, 71.9, 64.9, 48.3, 47.5. \]

\[ \text{HR-MS (ESI): } m/z 643.0065; [\text{M+K}]^+ \text{ requires } 643.0064. \]
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-propanoyl-β-D-glucopyranose-N,N') Platinum(II) 92

The diamine 76 (92 mg, 0.43 mmol) was treated with according to Procedure 1.6 to give the title compound as bright yellow crystals (46 mg, 22%). IR (ATR): 1732 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 5.83-5.80 (m, 1H), 5.74-5.71 (m, 2H), 5.27 (d, J = 12.1 Hz, 1H), 5.14 (d, J = 12.1 Hz, 1H), 4.93 (d, J = 5.4 Hz, 1H), 4.71 (s, 1H), 4.25 (d, J = 7.5 Hz, 1H), 3.66 (dd, J = 5.6, 7.4 Hz, 1H), 2.71 (d, J = 5.1 Hz, 1H), 2.50 (d, J = 5.1 Hz, 1H), 2.44-2.37 (m, 2H), 1.09 (t, J = 7.5 Hz, 3H). ¹³C NMR (151 MHz, d₇-DMF): δ 172.4, 99.6, 73.6, 71.9, 65.3, 49.1, 48.6, 27.3, 8.7. HR-MS (ESI): m/z 544.0281; [M+CH₃CN+Na]⁺ requires 544.0277.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-hexanoyl-β-D-glucopyranose-N,N') Platinum(II) 93

The diamine 77 (77 mg, 0.29 mmol) was treated with according to Procedure 1.6 to give the title compound as a pale yellow solid (120 mg, 79%). IR (ATR): 1718 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₆-DMSO): δ 5.79-5.76 (m, 1H), 5.70-5.67 (m, 1H), 5.49 (s, 1H), 5.13 (d, J = 12 Hz, 1H), 4.96 (d, J = 12 Hz, 1H), 4.71 (d, J = 4.8 Hz, 1H), 4.49 (s, 1H), 4.03 (d, J = 7.8 Hz, 1H), 3.50 (dd, J = 6.6, 6.6 Hz, 1H), 2.34-2.29 (m, 3H), 2.10 (d, J = 4.5 Hz, 1H), 1.55-1.50 (m, 2H), 1.29-1.23 (m, 4H), 0.85 (t, J = 6.8 Hz, 3H). ¹³C NMR (151 MHz, d₆-DMSO): δ 171.2, 98.5, 72.6, 71.2, 64.6, 48.1, 47.6, 33.5, 30.5, 23.9, 21.7, 13.8. HR-MS (ESI): m/z 586.0750; [M+CH₃CN+Na]⁺ requires 586.0747.
Dichloro-(1,6-anhydro-3-O-benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 94

The diamine 71 (54 mg, 0.20 mmol) was treated with according to Procedure 1.7 to give the title compound as a cream solid (41 mg, 38%). IR (ATR): 1716 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, d$_7$-DMF): $\delta$ 8.06-8.05 (m, 2H), 7.75-7.72 (m, 1H), 7.63-7.60 (m, 2H), 5.94-5.91 (m, 1H), 5.84-5.82 (m, 1H), 5.80 (s, 1H), 5.37 (d, $J = 12.0$ Hz, 1H), 5.22 (d, $J = 12.0$ Hz, 1H), 5.02 (d, $J = 5.4$ Hz, 1H), 4.98 (s, 1H), 4.41 (d, $J = 7.7$ Hz, 1H), 3.76 (dd, $J = 5.6$, 7.6 Hz, 1H), 2.69 (d, $J = 5.2$ Hz, 1H). $^{13}$C NMR (151 MHz, d$_7$-DMF): $\delta$ 164.8, 134.1, 129.9, 129.8, 129.3, 99.8, 73.8, 72.7, 65.7, 49.4, 48.7. HR-MS (ESI): $m/z$ 567.9772; [M+K]$^+$ requires 567.9772.

![Dichloro-(1,6-anhydro-3-O-benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II)](image)

Dichloro-(3-O-acetyl-1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 95

The diamine 75 (100 mg, 0.49 mmol) was treated with according to Procedure 1.7 to give the title compound as a cream solid (88 mg, 38%). IR (ATR): 3552, 3217, 3177, 3118 (N-H), 1713 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, d$_7$-DMF): $\delta$ 5.83-5.82 (m, 1H), 5.73-5.72 (m, 1H), 5.71 (s, 1H), 5.26 (d, $J = 11.9$ Hz, 1H), 5.13 (d, $J = 11.9$ Hz, 1H), 4.93 (d, $J = 5.0$ Hz, 1H), 4.69 (s, 1H), 4.26 (d, $J = 7.6$ Hz, 1H), 3.65 (dd, $J 5.6$, 7.5 Hz, 1H), 2.70 (d, $J = 6.0$ Hz, 1H), 2.51 (d, $J = 5.4$ Hz, 1H), 2.10 (s, 3H). $^{13}$C NMR (151 MHz, d$_7$-DMF): $\delta$ 169.2, 99.5, 73.6, 72.0, 65.3, 49.1, 48.6, 20.4. HR-MS (ESI): $m/z$ 542.0587; [M+H+DMF]$^+$ requires 542.0586.
Dichloro-(1,6-anhydro-3-O-(4-bromo)benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 96

The diamine 84 (117 mg, 0.34 mmol) was treated with according to Procedure 1.7 to give the title compound as a bright yellow solid (180 mg, 87%). IR (ATR): 1732 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 7.99-7.97 (m, 2H), 7.86-7.84 (m, 2H), 5.95-5.92 (m, 1H), 5.84-5.82 (m, 1H), 5.80 (s, 1H), 5.38 (d, J = 12.1 Hz, 1H), 5.24 (d, J = 12.1 Hz, 1H), 5.01 (d, J = 5.1 Hz, 1H), 4.97 (s, 1H), 4.40 (d, J = 7.7 Hz, 1H), 3.74 (dd, J = 5.5, 7.7 Hz, 1H), 2.94 (s, 1H), 2.69 (d, J = 5.2 Hz, 1H). ¹³C NMR (151 MHz, d₇-DMF): δ 164.1, 132.5, 131.7, 129.1, 128.4, 99.7, 73.8, 72.9, 65.6, 49.3, 48.6. HRMS (ESI): m/z 644.8867; [M+K]+ requires 644.8856.

Dichloro-(1,6-anhydro-3-O-(3-bromo)benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 97

The diamine 85 (101 mg, 0.29 mmol) was treated with according to Procedure 1.7 to give the title compound as a bright yellow solid (139 mg, 79%). IR (ATR): 1717 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 8.15-8.14 (m, 1H), 8.06-8.03 (m, 1H), 7.97-7.95 (m, 1H), 7.62-7.60 (m, 1H), 5.97-5.94 (m, 1H), 5.86-5.83 (m, 1H), 5.80 (s, 1H), 5.40 (d, J = 12.1 Hz, 1H), 5.25 (d, J = 12.1 Hz, 1H), 5.03 (d, J = 5.3 Hz, 1H), 4.99 (s, 1H), 4.41 (d, J = 7.7 Hz, 1H), 3.76 (dd, J = 5.5, 7.6 Hz, 1H), 2.98 (d, J = 5.4 Hz, 1H), 2.72 (d, J = 5.4 Hz, 1H). ¹³C NMR (151 MHz, d₇-DMF): δ 163.5, 136.9, 132.3, 132.1, 131.5, 128.8, 122.5, 99.7, 73.8, 73.1, 65.6, 49.3, 48.5. HRMS (ESI): m/z 608.9221; [M+H]+ requires 608.9222.
Dichloro-(1,6-anhydro-3-O-(4-chloro)benzoyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-\(N,N'\)) Platinum(II) \(\text{98}\)

The diamine \(86\) (45 mg, 0.15 mmol) was treated with according to Procedure 1.7 to give the title compound as a bright yellow solid (59 mg, 69%). IR (ATR): 1725 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 8.07-8.05 (m, 2H), 7.71-7.70 (m, 2H), 5.95-5.93 (m, 1H), 5.85-5.83 (m, 1H), 5.80 (s, 1H), 5.39 (d, \(J = 11.4\) Hz, 1H), 5.24 (d, \(J = 11.4\) Hz, 1H), 5.02 (s, 1H), 4.98 (s, 1H), 4.40 (d, \(J = 7.9\) Hz, 1H), 3.75 (d, \(J = 5.5, 7.6\) Hz, 1H), 2.94 (s, 1H), 2.69 (d, \(J = 3.9\) Hz, 1H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 164.0, 139.5, 131.7, 129.5, 128.7, 99.8, 73.8, 72.9, 65.6, 49.3, 48.6. HR-MS (ESI): \(m/z\) 562.9708; [M+H]\(^+\) requires 562.9716.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy3-O-(4-fluoro)benzoyl-β-D-glucopyranose-\(N,N'\)) Platinum(II) \(\text{99}\)

The diamine \(87\) (87 mg, 0.31 mmol) was treated with according to Procedure 1.7 to give the title compound as a bright yellow solid (2.2 mg, 1.3%). IR (ATR): 1714 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 8.14-8.12 (m, 2H), 7.46-7.43 (m, 2H), 5.95-7.92 (m, 1H), 5.85-7.83 (m, 1H), 5.80 (s, 1H), 5.39-5.37 (d, \(J = 12.0\) Hz, 1H), 5.24 (d, \(J = 12.0\) Hz, 1H), 5.02 (d, \(J = 5.1\) Hz, 1H), 4.97 (s, 1H), 4.40 (d, \(J = 7.8\) Hz, 1H), 3.75 (dd, \(J = 5.5, 7.7\) Hz, 1H), 2.94 (s, 1H), 2.69 (d, \(J = 5.5\) Hz, 1H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 166.2 (d, \(J = 253\) Hz), 163.9, 132.8 (d, \(J = 9.8\) Hz), 126.5 (d, \(J = 2.5\) Hz) 116.4 (d, \(J = 22\) Hz), 99.8, 73.8, 72.9, 65.6, 49.4, 48.7. HR-MS (ESI): \(m/z\) 549.0022; [M+H]\(^+\) requires 549.0023.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-methyl-\(\beta\)-d-glucose 100

The diazide 53 (209 mg, 0.98 mmol) was treated with methyl iodide according to Procedure 1.2. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (184 mg, 89%). \(R_f\) 0.27 (EtOAc/petrol 3:17). IR (ATR): 2092 (\(N_3\)) cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.50 (s, 1H), 4.62 (d, \(J = 4.9\) Hz, 1H), 4.06 (ddd, \(J = 0.30, 1.0, 7.5\) Hz, 1H), 3.79 (ddd, \(J = 0.44, 5.6, 7.4\) Hz, 1H), 3.47 (s, 3H), 3.43 (s, 1H), 3.37 (s, 1H), 3.36-3.34 (m, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 100.5, 79.7, 74.1, 66.3, 60.1, 59.7, 58.5

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-propyl-\(\beta\)-d-glucose 101

The diazide 53 (207 mg, 0.98 mmol) was treated with 1-bromopropane according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (215 mg, 86%). \(R_f\) 0.61 (EtOAc/petrol 1:4). IR (ATR): 2094 (\(N_3\)) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 5.45 (s, 1H), 4.64 (dd, \(J = 1.3, 5.8\) Hz, 1H), 4.09 (dd, \(J = 1.0, 7.4\) Hz, 1H), 3.73 (dd, \(J = 5.8, 7.4\) Hz, 1H), 3.56 (s, 1H), 3.54 (t, \(J = 6.4\) Hz, 2H), 3.41-3.39 (m, 1H), 3.38 (s, 1H), 1.63-1.57 (m, 2H), 0.95 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \(\delta\) 101.9, 79.3, 75.5, 73.5, 67.3, 61.5, 61.5, 24.1, 10.9.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-hexyl-β-D-glucose 102

The diazide 53 (202 mg, 0.95 mmol) was treated with 1-bromohexane according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (302 mg, 94%). Rf 0.64 (EtOAc/petrol 1:4). IR (ATR): 2095 (N\textsubscript{3}) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}OD): δ 5.45 (s, 1H), 4.64 (dd, J = 1.2, 5.7 Hz, 1H), 4.08 (dd, J = 1.0, 7.4 Hz, 1H), 3.73 (dd, J = 5.8, 7.4 Hz, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.56 (s, 1H), 3.40-3.39 (m, 1H), 3.37 (s, 1H), 1.61-1.56 (m, 2H), 1.41-1.31 (m, 6H), 0.91 (t, J = 7.0 Hz, 3H). \textsuperscript{13}C NMR (151 MHz, CD\textsubscript{3}OD): δ 101.9, 79.3, 75.5, 71.9, 67.4, 61.6, 61.5, 32.8, 30.9, 26.9, 23.7, 14.3.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(3-methyl)butyl-β-D-glucose 103

The diazide 53 (200 mg, 0.94 mmol) was treated with 3-methylbutyl bromide according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (231 mg, 87%). Rf 0.77 (EtOAc/petrol 3:7). IR (ATR): 2095 (N\textsubscript{3}) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD): δ 5.47 (s, 1H), 4.66 (dd, J = 1.1, 5.7 Hz, 1H), 4.08 (dd, J = 1.0, 7.4 Hz, 1H), 3.72 (dd, J = 5.8, 7.2 Hz, 1H), 3.61-3.58 (m, 3H), 3.40-3.38 (m, 2H), 1.77-1.69 (m, 1H), 1.49-1.45 (m, 2H), 0.93 (d, J = 6.7 Hz, 6H). \textsuperscript{13}C NMR (126 MHz, CD\textsubscript{3}OD): δ 101.8, 79.2, 75.4, 70.0, 67.2, 61.1, 60.9, 39.7, 26.1, 23.0, 23.0.
The diazide 53 (210 mg, 0.99 mmol) was treated with 1-bromononane according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (311 mg, 72%). \( R_f \) 0.44 (EtOAc/petrol 1:9). IR (ATR): 2097 (N\(_3\)) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \( \delta \) 5.44 (s, 1H), 4.65-4.63 (m, 1H), 4.08 (dd, \( J = 1.0, 7.5 \) Hz, 1H), 3.73 (dd, \( J = 5.7, 7.4 \) Hz, 1H), 3.58-3.55 (m, 3H), 3.40-3.39 (m, 1H), 3.37 (s, 1H), 1.60-1.56 (m, 2H), 1.40-1.28 (m, 12H), 0.90 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \( \delta \) 101.9, 79.3, 75.5, 71.9, 67.4, 61.6, 61.5, 33.0, 30.9, 30.7, 30.5, 30.4, 27.2, 23.7, 14.4.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-hexadecanyl-\( \beta \)-D-glucose 105

The diazide 53 (202 mg, 0.95 mmol) was treated with hexadecanyl bromide according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a white solid (384 mg, 92%). \( R_f \) 0.68 (EtOAc/petrol 1:4). IR (ATR): 2095 (N\(_3\)) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \( \delta \) 5.44 (s, 1H), 4.64 (dd, \( J = 1.4, 5.8 \) Hz, 1H), 4.08 (dd, \( J = 1.0, 7.5 \) Hz, 1H), 3.73 (dd, \( J = 5.7, 7.4 \) Hz, 1H), 3.58-3.56 (m, 3H), 3.40-3.39 (m, 1H), 3.37 (s, 1H), 1.60-1.56 (m, 2H), 1.40-1.29 (m, 26 H), 0.90 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \( \delta \) 101.9, 79.3, 75.5, 71.9, 67.4, 61.6, 61.5, 33.1, 30.9, 30.8, 30.8, 30.7, 30.7, 30.5, 27.2, 23.7, 14.4.
Chapter 1

1,6-anhydro-2,4-diazido-2,4-dideoxy-3-O-isopropyl-β-D-glucose 106

Method A: The diazide 53 (200 mg, 0.94 mmol) was treated with 2-methylethyl bromide according to Procedure 1.2. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (48 mg, 20%). $R_f$ 0.61 (EtOAc/petrol 1:4). IR (ATR): 2094 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.45 (s, 1H), 4.65 (dd, $J = 1.3$, 5.8 Hz, 1H), 4.12 (dd, $J = 0.9$, 7.4 Hz, 1H), 3.78 (septet, $J = 6.0$ Hz, 1H), 3.73 (ddd, $J = 0.3$, 5.8, 7.0 Hz, 1H), 3.49-3.48 (m, 2H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.18 (d, $J = 6.0$ Hz, 3H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 101.9, 76.3, 75.5, 73.1, 67.3, 62.4, 62.3, 22.5, 22.5.

Method B: The diazide 53 (128 mg, 0.60 mmol) was treated with 2-methylethyl bromide according to Procedure 1.3. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (113 mg, 74%). The $^1$H and $^{13}$C NMR spectra were consistent with that found above.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(3-methyl)propyl-β-D-glucose 107

The diazide 53 (200 mg, 0.94 mmol) was treated with 3-methylpropyl bromide according to Procedure 1.3. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (185 mg, 74%). $R_f$ 0.67 (EtOAc/petrol 1:4). IR (ATR): 2094 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.46 (s, 1H), 4.65 (dd, $J = 1.1$, 5.7 Hz, 1H), 4.10 (dd, $J = 1.1$, 7.4 Hz, 1H), 3.73 (dd, $J = 5.7$, 7.4 Hz, 1H), 3.57 (s, 1H), 3.39-3.38 (m, 2H), 3.35 (d, $J = 1.3$ Hz, 1H), 3.34 (d, $J = 1.3$ Hz, 1H), 1.89-1.80 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 101.9, 79.3, 78.5, 75.5, 67.3, 61.4, 61.1, 29.9, 19.6.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(3-phenyl)propyl-\(\beta\)-D-glucose 108

The diazide 53 (205 mg, 0.94 mmol) was treated with 3-phenylpropyl bromide according to Procedure 1.3. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded the title compound as a colourless oil (266 mg, 86%). \(R_f\) 0.75 (EtOAc/petrol 1:4). IR (ATR): 2095 (\(N_3\)) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 7.27-7.25 (m, 2H), 7.20-7.19 (m, 2H), 7.16-7.14 (m, 1H), 5.46 (s, 1H), 4.65 (dd, \(J = 1.2, 5.8\) Hz, 1H), 4.11 (dd, \(J = 1.0, 7.4\) Hz, 1H), 3.75 (dd, \(J = 5.8, 7.4\) Hz, 1H), 3.57 (t, \(J = 6.2\) Hz, 2H), 3.55 (s, 1H), 3.39-3.37 (m, 1H), 3.36 (s, 1H), 2.71-2.29 (m, 2H), 1.92-1.87 (m, 2H). \(^13\)C NMR (151 MHz, CD\(_3\)OD): \(\delta\) 143.0, 129.5, 129.4, 126.9, 101.9, 79.3, 75.5, 70.9, 67.3, 61.5, 61.2, 33.2, 32.7.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-methyl-\(\beta\)-D-glucopyranose 109

The diazide 100 (177 mg, 0.78 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (127 mg, 93%). \(R_f\) 0.05 (MeOH/CH\(_2\)Cl\(_2\) 1:9). IR (ATR): 3352 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 5.29 (s, 1H), 4.40 (d, \(J = 5.3\) Hz, 1H), 4.07 (d, \(J = 6.8\) Hz, 1H), 3.68 (dd, \(J = 6.4\) Hz, 1H), 3.37 (s, 3H), 3.13 (s, 1H), 2.90 (s, 1H), 2.79 (s, 1H). \(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 103.5, 85.4, 66.0, 57.8, 52.1, 51.7, 50.8. HR-MS (ESI): \(m/z\) 175.1083; [M+H]\(^+\) requires 175.1083.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-\(\text{-propyl}\)-\(\beta\)-D-glucopyranose 110

The diazide 101 (202 mg, 0.79 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (136 mg, 85%). \(R_f\) 0.06 (MeOH/CH\(_2\)Cl\(_2\) 1:9). IR (ATR): 3359 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 5.28 (s, 1H), 4.38 (d, \(J = 5.2\) Hz, 1H), 4.13 (dd, \(J = 0.9, 6.9\) Hz, 1H), 3.69-3.66 (m, 1H), 3.45 (t, \(J = 6.5\) Hz, 2H), 3.20-3.20 (m, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.60-1.54 (m, 2H), 0.93 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \(\delta\) 104.3, 83.9, 77.9, 72.5, 66.9, 53.5, 53.3, 24.2, 11.1. HR-MS (ESI): \(m/z\) 203.1398; [M+H\(^+\)] requires 203.1396.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-\(\text{-hexyl}\)-\(\beta\)-D-glucopyranose 111

The diazide 102 (247 mg, 0.83 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (145 mg, 71%). \(R_f\) 0.12 (MeOH/CH\(_2\)Cl\(_2\) 1:9). IR (ATR): 3359 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 5.28 (s, 1H), 4.38 (d, \(J = 5.6\) Hz, 1H), 4.12 (dd, \(J = 0.9, 6.8\) Hz, 1H), 3.68 (dd, \(J = 6.3, 6.3\) Hz, 1H), 3.51-3.45 (m, 2H), 3.20-3.19 (m, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.58-1.53 (m, 2H), 1.40-1.29 (m, 6H), 0.91 (t, \(J = 6.9\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \(\delta\) 104.3, 83.9, 77.9, 70.9, 66.9, 53.5, 53.3, 32.8, 31.0, 27.0, 23.7, 14.4. HR-MS (ESI): \(m/z\) 245.1865; [M+H\(^+\)] requires 245.1865.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-methyl)butyl-β-D-glucopyranose

The diazide 103 (225 mg, 0.80 mmol) was treated according to Procedure 1.5. Flash chromatography (MeOH/CH₂Cl₂ 1:9) of the resultant residue yielded the title compound as a colourless oil (160 mg, 87%). Rf 0.11 (MeOH/CH₂Cl₂ 1:9). IR (ATR): 3357 (N-H) cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ 5.28 (s, 1H), 4.38 (d, J = 5.2 Hz, 1H), 4.11 (dd, J = 0.9, 6.9 Hz, 1H), 3.67 (dd, J = 6.4, 6.4 Hz, 1H), 3.55-3.48 (m, 2H), 3.20-3.19 (m, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.76-1.68 (m, 1H), 1.47-1.43 (m, 2H), 0.92 (d, J = 6.7 Hz, 6H). ¹³C NMR (126 MHz, CD₃OD): δ 104.3, 84.0, 77.9, 69.2, 66.9, 53.4, 53.4, 40.0, 26.2, 23.0. HR-MS (ESI): m/z 272.1975; [M+H]⁺ requires 272.1974.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-nonyl-β-D-glucopyranose

The diazide 104 (293 mg, 0.87 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (208 mg, 84%). Rf 0.30 (MeOH/CH₂Cl₂ 1:9). IR (ATR): 3358 (N-H) cm⁻¹. ¹H NMR (600 MHz, CD₃OD): δ 5.28 (s, 1H), 4.38 (d, J = 5.5 Hz, 1H), 4.12 (dd, J = 0.8, 6.8 Hz, 1H), 3.68 (dd, J = 6.4, 6.4 Hz, 1H), 3.50-3.46 (m, 2H), 3.19 (s, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.58-1.53 (m, 2H), 1.38-1.31 (m, 12H), 0.90 (t, J = 7.0 Hz, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 104.3, 83.9, 77.9, 70.9, 66.9, 53.4, 53.3, 33.1, 31.0, 30.7, 30.6, 30.4, 27.4, 23.7, 14.4. HR-MS (ESI): m/z 287.2329 [M+H]⁺ requires 287.2335.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-hexadecanyl-β-D-glucopyranose 114

The diazide 105 (367 mg, 0.84 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (258 mg, 80%). \( R_f 0.26 \) (MeOH/CH\(_2\)Cl\(_2\) 1:9). IR (ATR): 3357 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): δ 5.28 (s, 1H), 4.38 (d, \( J = 5.5 \) Hz, 1H), 4.12 (dd, \( J = 0.9, 6.8 \) Hz, 1H), 3.68 (dd, \( J = 6.3, 6.3 \) Hz, 1H), 3.50-3.46 (m, 2H), 3.19 (s, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.57-1.53 (m, 2H), 1.34-1.29 (m, 26H), 0.90 (t, \( J = 7.0 \) Hz, 3H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): δ 104.3, 83.9, 77.9, 70.9, 66.9, 53.4, 53.3, 33.1, 31.0, 30.8, 30.8, 30.8, 30.7, 30.6, 30.5, 27.4, 23.8, 14.4. HR-MS (ESI): \( m/z \) 385.3436; [M+H]+ requires 385.3430.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-isoproyl-β-D-glucopyranose 115

The diazide 106 (183 mg, 0.72 mmol) was treated according to Procedure 1.5. Flash chromatography (MeOH/CH\(_2\)Cl\(_2\) 3:7) of the resultant residue yielded the title compound as a colourless oil (120 mg, 83%). \( R_f 0.10 \) (MeOH/CH\(_2\)Cl\(_2\) 1:9). IR (ATR): 3362 (N-H) cm\(^{-1}\). \(^1\)H NMR (500 MHz, CD\(_3\)OD): δ 5.27 (s, 1H), 4.39-4.37 (m, 1H), 4.17 (dd, \( J = 1.0, 6.9 \) Hz, 1H), 3.72-3.66 (m, 2H), 3.30-3.29 (m, 1H), 2.77 (s, 1H), 2.68 (s, 1H), 1.15 (d, \( J = 2.7 \) Hz, 3H), 1.14 (d, \( J = 2.7 \) Hz, 3H). \(^{13}\)C NMR (126 MHz, CD\(_3\)OD): δ 104.3, 81.0, 78.0, 71.5, 66.9, 54.6, 54.0, 22.8, 22.6. HR-MS (ESI): \( m/z \) 203.1395; [M+H]+ requires 203.1396.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-methyl)propyl-β-D-glucopyranose

The diazide 107 (173 mg, 0.64 mmol) was treated according to Procedure 1.5. Flash chromatography (MeOH/CH$_2$Cl$_2$ 1:9) of the resultant residue yielded the title compound as a colourless oil (123 mg, 88%). $R_f$ 0.18 (MeOH/CH$_2$Cl$_2$ 1:9). IR (ATR): 3328 (N-H) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.28 (s, 1H), 4.39 (d, $J = 5.7$ Hz, 1H), 4.14 (dd, $J = 1.0$, 6.8 Hz, 1H), 3.68 (dd, $J = 6.4$, 6.4 Hz, 1H), 3.27 (d, $J = 0.9$ Hz, 1H), 3.26 (d, $J = 0.8$ Hz, 1H), 3.19-3.18 (m, 1H), 2.85 (s, 1H), 2.77 (s, 1H), 1.85-1.78 (m, 1H), 0.92 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 104.3, 84.0, 77.9, 77.8, 66.9, 53.3, 53.2, 29.9, 19.8, 19.7. HR-MS (ESI): $m/z$ 217.1552; [M+H]$^+$ requires 217.1552.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-phenyl)propyl-β-D-glucopyranose

The diazide 108 (254 mg, 0.76 mmol) was treated according to Procedure 1.5. Flash chromatography (MeOH/CH$_2$Cl$_2$ 1:4) of the resultant residue yielded the title compound as a colourless oil (191 mg, 89%). $R_f$ 0.15 (MeOH/CH$_2$Cl$_2$ 1:4). IR (ATR): 3360 (N-H) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 7.26-7.23 (m, 2H), 7.20-7.19 (m, 2H), 7.15-7.13 (m, 1H), 5.29 (s, 1H), 4.39 (d, $J = 5.6$ Hz, 1H), 4.16 (dd, $J = 1.0$, 6.9 Hz, 1H), 3.70 (dd, $J = 6.4$, 6.4 Hz, 1H), 3.50-3.47 (m, 2H), 3.19-3.18 (m, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 2.69 (dd, $J = 7.6$ Hz, 2H), 1.89-1.84 (m, 2H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 143.3, 129.5, 129.3, 126.8, 104.3, 84.0, 77.9, 69.9, 67.0, 53.4, 53.3, 33.4, 32.8. HR-MS (ESI): $m/z$ 279.1708; [M+H]$^+$ requires 279.1709.
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-methyl-β-D-glucopyranose-\(N,N'\)) Platinum(II) 118

The diamine 109 (117 mg, 0.67 mmol) was treated with according to Procedure 1.6 to give the title compound as a yellow solid (147 mg, 50\%). IR (ATR): 3187, 3119 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 5.60-5.57 (m, 1H), 5.55-5.48 (m, 1H), 5.44 (s, 1H), 5.01 (d, \(J = 11.4\) Hz, 1H), 4.86 (d, \(J = 11.4\) Hz, 1H), 4.64 (d, \(J = 5.4\) Hz, 1H), 3.93 (d, \(J = 7.0\) Hz, 1H), 3.43 (dd, \(J = 6.4\) Hz, 1H), 3.24 (s, 3H), 2.95 (s, 1H), 2.33 (d, \(J = 5.0\) Hz, 1H), 2.15 (d, \(J = 5.0\) Hz, 1H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 98.6, 80.5, 72.4, 64.4, 57.1, 47.3, 46.8. HR-MS (ESI): \(m/z\) 502.0179; [M+CH\(_3\)CN+Na]\(^+\) requires 502.0171.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-propyl-β-D-glucopyranose-\(N,N'\)) Platinum(II) 119

The diamine 110 (128 mg, 0.63 mmol) was treated with according to Procedure 1.6 to give the title compound as bright yellow crystals (248 mg, 84\%). IR (ATR): 3216, 3119 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 5.63-5.60 (m, 1H), 5.54-5.51 (m, 1H), 5.45 (s, 1H), 5.00 (d, \(J = 12.1\) Hz, 1H), 4.84 (d, \(J = 12.1\) Hz, 1H), 4.66 (d, \(J = 5.6\) Hz, 1H), 4.00 (d, \(J = 6.9\) Hz, 1H), 3.45 (dd, \(J = 6.0\) Hz, 1H), 3.40-3.33 (m, 2H), 3.04 (s, 1H), 2.30 (d, \(J = 5.4\) Hz, 1H), 2.14 (d, \(J = 5.0\) Hz, 1H), 1.51-1.46 (m, 2H), 0.86 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 98.6, 78.6, 72.4, 70.5, 64.4, 47.7, 47.4, 22.4, 10.5. HR-MS (ESI): \(m/z\) 530.0474; [M+CH\(_3\)CN+Na]\(^+\) requires 530.0484.
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-hexyl-β-D-glucopyranose-N,N') Platinum(II) 120

The diamine 111 (134 mg, 0.55 mmol) was treated with according to Procedure 1.6 to give the title compound as a pale yellow solid (248 mg, 89%). IR (ATR): 3218, 3118 (N-H) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 5.62-5.59 (m, 1H), 5.53-5.50 (m, 1H), 5.44 (s, 1H), 4.98 (d, J = 11.8 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.64 (d, J = 5.4 Hz, 1H), 3.98 (d, J = 7.0 Hz, 1H), 4.43 (dd, J = 5.9 Hz, 1H), 3.40-3.34 (m, 2H), 3.02 (s, 1H), 2.27 (d, J = 5.2 Hz, 1H), 2.12 (d, J = 5.2 Hz, 1H), 1.47-1.43 (m, 2H), 1.29-1.24 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H). ¹³C NMR (151 MHz, d₇-DMF): δ 98.6, 78.7, 72.4, 68.9, 64.4, 47.7, 47.4, 31.0, 29.0, 25.2, 22.0, 13.9. HR-MS (ESI): m/z 572.0956; [M+CH₃CN+Na]⁺ requires 572.0954.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-methyl)butyl-β-D-glucopyranose-N,N') Platinum(II) 121

The diamine 112 (150 mg, 0.65 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (282 mg, 88%). IR (ATR): 3235, 3180, 3116 (N-H) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 5.88-5.87 (m, 1H), 5.83 (s, 1H), 5.78-5.76 (m, 1H), 5.26 (d, J = 12.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.02 (d, J = 5.1 Hz, 1H), 4.37 (d, J = 7.0 Hz, 1H), 3.76-3.71 (m, 3H), 3.53 (s, 1H), 2.86 (d, J = 5.0 Hz, 1H), 2.72 (d, J = 5.0 Hz, 1H), 1.86-1.84 (m, 1H), 1.63-1.55 (m, 2H), 1.06 (dd, J = 0.71, 6.7 Hz, 6H). ¹³C NMR (151 MHz, d₇-DMF): δ 99.8, 79.8, 73.6, 68.3, 65.2, 48.9, 48.8, 38.7, 25.2, 22.5, 22.4. HR-MS (ESI): m/z 558.0790; [M+CH₃CN+Na]⁺ requires 558.0797.
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-0-isoproyl-γ-D-glucopyranose-N,N') Platinum(II) 122

The diamine 115 (111 mg, 0.55 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow crystals (199 mg, 77%). IR (ATR): 3221, 3116 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta \) 5.76-5.75 (m, 1H), 5.70-5.68 (m, 1H), 5.65 (s, 1H), 5.05 (d, \(J = 11.6\) Hz, 1H), 4.92 (d, \(J = 11.6\) Hz, 1H), 4.84 (d, \(J = 5.4\) Hz, 1H), 4.27 (d, \(J = 7.0\) Hz, 1H), 3.88 (septet, \(J = 6.1\) Hz, 1H), 3.57 (dd, \(J = 5.9, 5.9\) Hz, 1H), 3.42 (s, 1H), 2.60 (d, \(J = 5.2\) Hz, 1H), 2.45 (d, \(J = 5.2\) Hz, 1H), 1.14 (d, \(J = 6.1\) Hz, 3H), 1.12 (d, \(J = 6.1\) Hz, 3H). \(^1^3\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta \) 99.9, 76.9, 73.7, 70.4, 65.2, 49.9, 49.4, 22.2, 21.9. HR-MS (ESI): \(m/z \) 530.0479; [M+CH\(_3\)CN+Na]\(^+\) requires 530.0484.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-0-(2-methyl)propyl-β-D-glucopyranose-N,N') Platinum(II) 123

The diamine 116 (111 mg, 0.52 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (212 mg, 85%). IR (ATR): 3217, 3116 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta \) 5.71-5.68 (m, 1H), 5.66 (s, 1H), 5.61-5.59 (m, 1H), 5.09 (d, \(J = 12.0\) Hz, 1H), 4.97 (d, \(J = 12.0\) Hz, 1H), 4.86 (d, \(J = 5.4\) Hz, 1H), 4.21 (d, \(J = 7.0\) Hz 1H), 3.59 (d, \(J = 6.0\) Hz, 1H), 3.35 (s, 1H), 3.232-3.26 (m, 2H), 2.69 (d, \(J = 5.2\) Hz, 1H), 2.55 (d, \(J = 5.2\) Hz, 1H), 1.81 (app. septet, \(J = 6.6\) Hz, 1H), 0.88 (d, \(J = 6.7\) Hz, 6H). \(^1^3\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta \) 99.9, 79.8, 76.6, 73.6, 65.2, 48.8, 48.7, 28.6, 19.1. HR-MS (ESI): \(m/z \) 544.0643; [M+CH\(_3\)CN+Na]\(^+\) requires 544.0641.
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(3-phenyl)propyl-β-D-glucopyranose-N,N') Platinum(II) **124**

The diamine **117** (180 mg, 0.65 mmol) was treated with according to *Procedure 1.6* to give the title compound as a cream solid (301 mg, 86%). IR (ATR): 3211, 3117 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): δ 7.32-7.31 (m, 2H), 7.26-7.25 (m, 2H), 7.22-7.19 (m, 1H), 5.73-5.70 (m, 1H), 5.63 (s, 1H), 5.62-5.59 (m, 1H), 5.10 (d, \(J = 12.0\) Hz, 1H), 4.98 (d, \(J = 12.0\) Hz, 1H), 4.87 (d, \(J = 5.3\) Hz, 1H), 4.26 (d, \(J = 7.0\) Hz, 1H), 3.61 (dd, \(J = 5.9, 5.9\) Hz, 1H), 3.56-3.54 (m, 2H), 3.39 (s, 1H), 2.72-2.67 (m, 3H), 2.57 (d, \(J = 5.3\) Hz, 1H), 1.88-1.83 (m, 2H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): δ 142.4, 128.8, 128.7, 126.1, 99.9, 79.6, 73.6, 69.0, 65.3, 48.9, 48.8, 32.3, 31.7. HR-MS (ESI): \(m/z\) 616.1236; [M+H+DMF]\(^+\) requires 616.1240.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-nonyl-β-D-glucopyranose-N,N') Platinum(II) **125**

The diamine **113** (41 mg, 0.55 mmol) was treated with according to *Procedure 1.7* to give the title compound as a cream solid (29 mg, 36%). IR (ATR): 3217, 3120 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): δ 5.73-5.70 (m, 1H), 5.66 (s, 1H), 5.62-5.59 (m, 1H), 5.12 (d, \(J = 11.9\) Hz, 1H), 5.00 (d, \(J = 11.9\) Hz, 1H), 4.86 (d, \(J = 5.3\) Hz, 1H), 4.21 (d, \(J = 7.0\) Hz, 1H), 3.58 (dd, \(J = 6.0\) Hz, 1H), 3.35 (s, 1H), 2.69 (d, \(J = 5.1\) Hz, 1H), 2.54 (d, \(J = 5.1\) Hz, 1H), 1.56-1.51 (m, 2H), 1.35-1.27 (m, 12H), 0.89-0.86 (m, 3H). \(^{13}\)C NMR (151 MHz, \(d_7\)-DMF): δ 99.8, 79.7, 73.6, 69.8, 65.2, 65.2, 48.9, 48.7, 32.0, 29.9, 29.5, 29.5 26.3, 22.8, 13.9. HR-MS (ESI): \(m/z\) 626.1887; [M+H+DMF]\(^+\) requires 626.1889.
Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-hexadecanyl-β-D-glucopyranose-\(N,N'\)) Platinum(II) 126

The diamine 114 (25 mg, 0.07 mmol) was treated with according to Procedure 1.7 to give the title compound as a cream solid (42 mg, 66%). IR (ATR): 3217, 3119 (N-H) cm\(^{-1}\). \(^1\)H NMR (500 MHz, \(d_7\)-DMF): \(\delta\) 5.73-5.69 (m, 1H), 5.66 (s, 1H), 5.62-5.58 (m, 1H), 5.08 (d, \(J = 12.0\) Hz, 1H), 4.97 (d, \(J = 12.0\) Hz, 1H), 4.85 (d, \(J = 5.4\) Hz, 1H), 4.22 (d, \(J = 7.0\) Hz, 1H), 3.58 (dd, \(J = 5.8, 6.8\) Hz, 1H), 3.36 (s, 1H), 2.69 (d, \(J = 5.4\) Hz, 1H), 2.55 (d, \(J = 5.4\) Hz, 1H), 1.56-1.51 (m, 2H), 1.35-1.28 (m, 26H), 0.88 (t, \(J = 7.0\) Hz, 3H). \(^{13}\)C NMR (126 MHz, \(d_7\)-DMF): \(\delta\) 99.8, 79.6, 73.6, 69.8, 65.2, 48.9, 48.7, 32.0, 30.0, 30.0, 26.3, 22.8, 13.9. HR-MS (ESI): \(m/z\) 724.2979; [M+H+DMF]\(^+\) requires 724.2984.

1,6-Anhydro-3-O-(carboxymethyl)-2,4-diazido-2,4-dideoxy-β-D-glucose 127

Sodium hydride (60% mineral dispersion in oil, 380 mg, 9.5 mmol) was added to a solution of the diazide 53 (400 mg, 1.89 mmol) in THF (4 mL) at 0°C and the resultant mixture was stirred. After 10 min., chloroacetic acid (357 mg, 3.78 mmol) was added and the mixture was refluxed (1 h.). The mixture was then diluted with water (5 mL), acidified (1 M HCl, pH = 4), and extracted with EtOAc (2 x 10 mL). The organic extracts were combined, dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:4) of the resultant oil yielded the title compound as a colourless oil (441 mg, 87%). \(R_f\) 0.11 (EtOAc/petrol 2:3), IR (ATR): 2910 (O-H), 2096 (N\(_3\)), 1728 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.54 (s, 1H), 4.66 (d, \(J = 5.0\) Hz, 1H), 4.31 (A part of ABq, \(J = 17.2\) Hz, 1H), 4.27 (B part of ABq, \(J = 17.2\) Hz, 1H), 4.15 (dd, \(J = 0.70, 7.6\) Hz, 1H), 3.82 (dd, \(J = 5.6, 7.6\) Hz, 1H), 3.61 (s, 1H),
3.56-3.54 (m, 1H), 3.49 (s, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 173.8, 100.6, 79.5, 74.3, 67.9, 66.5, 60.6, 60.2. HR-MS (APCI): $m/z$ 243.0721; [M+H-N$_2$]$^+$ requires 243.0729.

1,6-Anhydro-3-O-(2-(benzylamino)-2-oxoethyl)-2,4-diazido-2,4-dideoxy-β-D-glucose 129

The diazide 127 (83 mg, 0.31 mmol) was treated with benzylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3) of the resultant residue yielded the title compound as a colourless oil (93 mg, 85%). $R_f$ 0.42 (EtOAc/petrol 2:3). IR (ATR): 3340 (N-H), 2093 (N$_3$), 1665 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 7.37-7.34 (m, 2H), 7.31-7.29 (m, 3H), 7.09 (s, 1H), 5.45 (s, 1H), 4.65 (d, $J$ = 5.2 Hz, 1H), 4.53-4.45 (m, 2H), 4.32 (A part of ABq, $J$ = 15.4 Hz, 1H), 4.04 (B part of ABq, $J$ = 15.4 Hz, 1H), 4.00 (d, $J$ = 7.6 Hz, 1H), 3.77 (dd, $J$ = 5.5, 7.6 Hz, 1H), 3.50 (s, 1H), 3.47 (s, 1H), 3.30 (s, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 168.5, 137.9, 128.9, 128.0, 127.9, 100.5, 79.4, 74.3, 70.6, 66.6, 60.5, 59.1, 43.2.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-((1-((S)-methyl-2-oxo-2-amino)ethyl)amino)-2-oxoethyl)-β-D-glucose 130

The diazide 127 (173 mg, 0.64 mmol) was treated with (S)-2-aminopropanamide according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3) of the resultant residue yielded the title compound as a white crystalline solid (108 mg, 50%). $R_f$ 0.25 (EtOAc). IR (ATR): 3383, 3212 (N-H), 2100 (N$_3$), 1704, 1667 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): δ 5.53 (s, 1H), 4.72 (d, $J$ = 5.4 Hz, 1H), 4.44 (q, $J$ = 7.1 Hz, 1H), 4.21 (d, $J$ = 7.6 Hz, 1H), 4.19 (A part of ABq, $J$ = 15.2 Hz, 1H), 4.12 (B part of ABq,
$J = 15.2 \text{ Hz, } 1\text{H}), 3.78 \text{ (dd, } J = 5.7, 7.7 \text{ Hz, } 1\text{H}), 3.73 \text{ (s, } 1\text{H}), 3.57 \text{ (s, } 1\text{H}), 3.53 \text{ (s, } 1\text{H}), 1.40 \text{ (d, } J = 7.1 \text{ Hz, } 3\text{H}). ^{13}\text{C NMR (151 MHz, CD}_{3}\text{OD): } \delta 177.1, 171.2, 101.7, 80.0, 75.5, 70.5, 67.4, 60.9, 60.1, 49.3, 18.8.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(2-(((2-oxo-2-amino)ethyl)amino)-2-oxoethyl)-β-D-glucose 131

The diazide 127 (192 mg, 0.71 mmol) was treated with 2-aminoacetamide according to Procedure 1.4. Flash chromatography (EtOAc to MeOH/EtOAc 1:9) of the resultant residue yielded the title compound as a pale yellow crystalline solid (170 mg, 73%). $R_f$ 0.33 (MeOH/EtOAc 1:9) IR (ATR): 3336 (N-H), 2099 (N=O), 1660 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 5.53 (s, 1H), 4.71 (d, $J = 5.4$ Hz, 1H), 4.21 (A part of ABq, $J = 15.2$ Hz, 1H), 4.18 (d, $J = 7.8$ Hz, 1H), 4.14 (B part of ABq, $J = 15.2$ Hz, 1H), 3.93 (s, 2H), 3.77 (dd, $J = 5.7, 7.6$ Hz, 1H), 3.73 (s, 1H), 3.60 (s, 2H). $^{13}$C NMR (126 MHz, CD$_3$OD): $\delta$ 173.8, 172.2, 101.7, 80.2, 75.4, 70.6, 67.3, 60.7, 60.1, 42.5.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(2-(pyrrolidino)-2-oxoethyl)-β-D-glucose 132

The diazide 127 (124 mg, 0.46 mmol) was treated with pyrrolidine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 1:1 to 3:1) of the resultant residue yielded the title compound as a colourless oil (112 mg, 76%). $R_f$ 0.39 (EtOAc). IR (ATR): 2102 (N=O), 1637 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.52 (s, 1H), 4.64 (d, $J = 5.2$ Hz, 1H), 4.32 (A part of ABq, $J = 15.0$ Hz, 1H), 4.28 (dd, $J = 0.72, 7.4$ Hz, 1H), 4.12 (B part of ABq, $J = 15.0$ Hz, 1H), 3.83 (s, 1H), 3.81 (dd, $J = 5.7, 7.4$ Hz, 1H), 3.59-3.57 (m, 1H), 3.52 (s, 1H), 3.51 (t, $J = 7.0$ Hz, 2H), 3.32 (t, $J = 6.9$ Hz, 2H), 3.17 (t, $J = 7.4$ Hz, 2H), 3.12 (t, $J = 7.4$ Hz, 2H), 2.86 (d, $J = 7.4$ Hz, 2H), 2.78 (d, $J = 7.0$ Hz, 2H), 2.72 (d, $J = 7.0$ Hz, 2H), 2.62 (d, $J = 7.4$ Hz, 2H), 2.59 (d, $J = 7.4$ Hz, 2H), 2.54 (d, $J = 7.0$ Hz, 2H), 2.49 (d, $J = 7.0$ Hz, 2H), 2.42 (d, $J = 7.4$ Hz, 2H), 2.38 (d, $J = 7.4$ Hz, 2H), 2.30 (d, $J = 7.0$ Hz, 2H), 2.25 (d, $J = 7.0$ Hz, 2H), 2.16 (d, $J = 7.4$ Hz, 2H), 2.12 (d, $J = 7.4$ Hz, 2H), 1.98 (d, $J = 7.0$ Hz, 2H), 1.94 (d, $J = 7.0$ Hz, 2H), 1.86 (d, $J = 7.4$ Hz, 2H), 1.82 (d, $J = 7.4$ Hz, 2H), 1.77 (d, $J = 7.0$ Hz, 2H), 1.73 (d, $J = 7.0$ Hz, 2H), 1.67 (d, $J = 7.4$ Hz, 2H), 1.63 (d, $J = 7.4$ Hz, 2H), 1.58 (d, $J = 7.0$ Hz, 2H), 1.54 (d, $J = 7.0$ Hz, 2H), 1.49 (d, $J = 7.4$ Hz, 2H), 1.45 (d, $J = 7.4$ Hz, 2H), 1.39 (d, $J = 7.0$ Hz, 2H), 1.35 (d, $J = 7.0$ Hz, 2H), 1.30 (d, $J = 7.4$ Hz, 2H), 1.26 (d, $J = 7.4$ Hz, 2H), 1.21 (d, $J = 7.0$ Hz, 2H), 1.17 (d, $J = 7.0$ Hz, 2H), 1.12 (d, $J = 7.4$ Hz, 2H), 1.08 (d, $J = 7.4$ Hz, 2H), 1.03 (d, $J = 7.0$ Hz, 2H), 0.99 (d, $J = 7.0$ Hz, 2H), 0.95 (d, $J = 7.4$ Hz, 2H), 0.91 (d, $J = 7.4$ Hz, 2H), 0.86 (d, $J = 7.0$ Hz, 2H), 0.82 (d, $J = 7.0$ Hz, 2H), 0.78 (d, $J = 7.4$ Hz, 2H), 0.74 (d, $J = 7.4$ Hz, 2H), 0.69 (d, $J = 7.0$ Hz, 2H), 0.65 (d, $J = 7.0$ Hz, 2H), 0.61 (d, $J = 7.4$ Hz, 2H), 0.57 (d, $J = 7.4$ Hz, 2H), 0.53 (d, $J = 7.0$ Hz, 2H), 0.49 (d, $J = 7.0$ Hz, 2H), 0.44 (d, $J = 7.4$ Hz, 2H), 0.40 (d, $J = 7.4$ Hz, 2H), 0.36 (d, $J = 7.0$ Hz, 2H), 0.32 (d, $J = 7.0$ Hz, 2H), 0.28 (d, $J = 7.4$ Hz, 2H), 0.24 (d, $J = 7.4$ Hz, 2H), 0.2 (d, $J = 7.0$ Hz, 2H), 0.16 (d, $J = 7.0$ Hz, 2H), 0.12 (d, $J = 7.4$ Hz, 2H), 0.08 (d, $J = 7.4$ Hz, 2H), 0.04 (d, $J = 7.0$ Hz, 2H), 0.0 (d, $J = 7.0$ Hz, 2H).
Hz, 2H), 1.99 (m, 2H), 1.89-1.84 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 167.1, 100.5, 79.3, 74.2, 69.9, 66.2, 60.2, 60.1, 46.1, 45.4, 26.4, 24.0.

![Structure](image)

3-O-(2-((2-amino-1-(S)-(2-methyl)propyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diazido-2,4-dideoxy-β-D-glucose 133

The diazide 127 (146 mg, 0.54 mmol) was treated with (S)-2-amino-4-methylpentanamide according to Procedure 1.4. Flash chromatography (EtOAc to MeOH/EtOAc 1:9) of the resultant residue yielded the title compound as a colourless oil (150 mg, 72%). $R_f$ 0.38 (EtOAc) IR (ATR): 3327 (N-H), 2098 (N$_3$), 1661 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.16 (d, $J = 8.2$ Hz, 1H), 6.15 (s, 1H), 5.55 (s, 1H), 4.69 (d, $J = 5.3$ Hz, 1H), 4.53-4.49 (m, 1H), 4.25 (A part of ABq, $J = 15.4$ Hz, 1H), 4.13 (d, $J = 7.3$ Hz, 1H), 4.05 (B part of ABq, $J = 15.4$ Hz, 1H), 3.86 (dd, $J = 5.5$, 7.8 Hz, 1H), 3.55 (s, 1H), 3.52-3.51 (m, 1H), 3.35 (s, 1H), 1.73-1.57 (m, 3H), 0.96 (t, $J = 6.2$ Hz, 6H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.8, 169.0, 100.6, 79.3, 74.4, 70.2, 66.8, 60.7, 59.3, 50.9, 41.0, 25.1, 23.0, 22.3.

![Structure](image)

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(2-(hexylamino)-2-oxoethyl)-β-D-glucose 134

The diazide 127 (104 mg, 0.38 mmol) was treated with hexylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 3:7 to 3:2) of the resultant residue yielded the title compound as a colourless oil (120 mg, 89%). $R_f$ 0.43 (EtOAc/petrol 1:1) IR (ATR): 3348 (N-H), 2097 (N$_3$), 1662 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.75 (br s, 1H), 5.57 (s, 1H), 4.69 (d, $J = 5.3$ Hz, 1H), 4.26 (A part of ABq, $J = 15.3$ Hz, 1H), 4.09 (d, $J = 7.5$ Hz, 1H), 3.96 (B part of ABq, $J = 15.3$ Hz, 1H), 3.85 (dd, $J = 5.6$, 7.4 Hz, 1H), 3.52-3.51 (m, 2H), 3.36 (s, 1H), 3.30-3.26 (m,
2H), 1.54-1.49 (m, 2H), 1.35-1.25 (m, 6H), 0.90-0.88 (m, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 168.5, 100.6, 79.2, 74.3, 70.5, 66.6, 60.4, 59.1, 39.2, 31.6, 29.5, 26.7, 22.7, 14.1.

1,6-Anhydro-3-O-(2-(cyclopropylamino)-2-oxyethyl)-2,4-diazido-2,4-dideoxy-β-D-glucose 135

The diazide 127 (137 mg, 0.51 mmol) was treated with cyclopropylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 7:3) of the resultant residue yielded the title compound as a colourless oil (102 mg, 65%). $R_t$ 0.16 (EtOAc/petrol 1:1) IR (ATR): 3333 (N-H), 2096 (N$_3$), 1662 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 6.82 (s, 1H), 5.57 (s, 1H), 4.68 (d, $J = 5.1$ Hz, 1H), 4.25 (A part of ABq, $J = 15.4$ Hz, 1H), 4.06 (d, $J = 7.6$ Hz, 1H), 3.95 (B part of ABq, $J = 15.4$ Hz, 1H), 3.84 (dd, $J = 5.5$, 7.5 Hz, 1H), 3.50 (br s, 2H), 3.32 (s, 1H), 2.80-2.76 (m, 1H), 0.82-0.80 (m, 2H), 0.55-0.52 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 170.0, 100.6, 79.3, 74.4, 70.6, 66.7, 60.5, 59.1, 22.3, 6.6, 6.5.

1,6-Anhydro-3-O-(2-(cyclopentylamino)-2-oxyethyl)-2,4-diazido-2,4-dideoxy-β-D-glucose 136

The diazide 127 (141 mg, 0.66 mmol) was treated with cyclopentylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 7:3) of the resultant residue yielded the title compound as a colourless oil (144 mg, 64%). $R_t$ 0.43 (EtOAc/petrol 1:1) IR (ATR): 3342 (N-H), 2097 (N$_3$), 1660 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 6.76 (d, $J = 4.8$ Hz, 1H), 5.58 (s, 1H), 4.70 (d, $J = 5.2$ Hz, 1H), 4.27-4.21 (m, 2H), 4.09 (d, $J = 7.6$ Hz, 1H), 3.93 (A part of ABq, $J = 15.3$ Hz, 1H), 3.85 (dd, $J = 5.5$, 7.5 Hz, 1H), 3.52 (s, 2H), 3.34 (s, 1H), 2.01-1.96 (m, 2H), 1.72-1.61
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(2-(morpholino)-2-oxyethyl)-\(\beta\)-D-glucose 137

The diazide 127 (138 mg, 0.65 mmol) was treated with morpholine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 7:3) of the resultant residue yielded the title compound as a colourless oil (127 mg, 58%). \(R_f\) 0.35 (EtOAc/petrol 1:1) IR (ATR): 2095 (N\(\equiv\)N), 1651 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.52 (s, 1H), 4.65 (d, \(J = 5.1\) Hz, 1H), 4.38 (A part of ABq, \(J = 14.3\) Hz, 1H), 4.22 (B part of ABq, \(J = 14.3\) Hz, 1H), 4.17 (dd, \(J = 0.8\), 7.5 Hz, 1H), 3.81 (dd, \(J = 5.7\), 7.4 Hz, 1H), 3.71-3.69 (m, 5H), 3.63-3.62 (m, 2H), 3.55-3.54 (m, 1H), 3.48 (s, 1H), 3.38 (br s, 2H). \(^1\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 167.0, 100.5, 79.2, 74.2, 69.4, 66.9, 66.5, 66.3, 60.5, 60.0, 45.3, 42.2.

1,6-Anhydro-3-O-(2-(butylamino)-2-oxyethyl)-2,4-diazido-2,4-dideoxy-\(\beta\)-D-glucose 138

The diazide 127 (129 mg, 0.61 mmol) was treated with butylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 3:2) of the resultant residue yielded the title compound as a colourless oil (142 mg, 72%). \(R_f\) 0.40 (EtOAc/petrol 2:3) IR (ATR): 3349 (N-H), 2097 (N\(\equiv\)N), 1661 (C=O) cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.75 (br s, 1H), 5.58 (s, 1H), 4.70 (d, \(J = 5.3\) Hz, 1H), 4.26 (A part of ABq, \(J = 15.3\) Hz, 1H), 4.09 (dd, \(J = 0.6\), 7.6 Hz, 1H), 3.97 (B part of ABq, \(J = 15.3\) Hz, 1H), 3.85 (dd, \(J = 5.5\), 7.5 Hz, 1H), 3.53-3.51 (m, 2H), 3.36 (s, 1H), 3.32-3.27 (m, 2H), 1.54-1.48 (m, 2H), 1.40-1.32 (m, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H). \(^1\)C NMR
The diazide 127 (255 mg, 0.94 mmol) was treated with dodecylamine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 3:2) of the resultant residue yielded the title compound as a colourless oil (371 mg, 90%). $R_f$ 0.50 (EtOAc/petrol 3:2) IR (ATR): 3408 (N-H), 2106 (N₃), 1673 (C=O) cm⁻¹. $^1$H NMR (600 MHz, CDCl₃): δ 6.75 (br s, 1H), 5.58 (s, 1H), 4.70 (d, $J = 5.2$ Hz, 1H), 4.26 (A part of ABq, $J = 15.3$ Hz, 1H), 4.09 (dd, $J = 0.7$, 7.6 Hz, 1H), 3.96 (B part of ABq, $J = 15.3$ Hz, 1H), 3.85 (dd, $J = 5.4$, 7.6 Hz, 1H), 3.53-3.51 (m, 2H), 3.36 (s, 1H), 3.32-3.24 (m, 2H), 1.54-1.50 (m, 2H), 1.31-1.26 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl₃): δ 168.5, 100.6, 79.2, 74.3, 70.6, 66.6, 60.4, 59.1, 39.3, 32.1, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 27.1, 22.8, 14.3.

The diazide 127 (114 mg, 0.42 mmol) was treated with (S)-2-amino-4-(methylthio)butanamide according to Procedure 1.4. Flash chromatography (EtOAc to MeOH/EtOAc 1:9) of the resultant residue yielded the title compound as a colourless oil (141 mg, 83%). $R_f$ 0.19 (EtOAc/petrol 1:1) IR (ATR): 3333 (N-H), 2098 (N₃), 1661 (C=O) cm⁻¹. $^1$H NMR (600 MHz, CDCl₃): δ 7.39 (d, $J = 8.0$ Hz, 1H), 6.26 (br s, 1H), 5.56 (br s, 2H), 4.69-4.65 (m, 2H), 4.23 (A part of ABq, $J = 15.4$ Hz, 1H), 4.14 (dd, $J = 0.7$, 7.8 Hz, 1H), 4.08 (B part of ABq, $J = 15.4$ Hz, 1H), 3.81 (dd, $J =$...
5.4, 7.8 Hz, 1H), 3.55 (br s, 1H), 3.52-3.51 (m, 1H), 3.38 (br s, 1H), 2.65-2.53 (m, 2H), 2.17-2.12 (m, 4H), 2.04-1.98 (m, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.7, 168.9, 100.6, 79.3, 74.4, 70.2, 66.8, 60.8, 59.5, 51.3, 31.3, 30.3, 15.5.

The diazide 127 (130 mg, 0.61 mmol) was treated with piperidine according to Procedure 1.4. Flash chromatography (EtOAc/petrol 2:3 to 7:3) of the resultant residue yielded the title compound as a colourless oil (160 mg, 78%). $R_t$ 0.29 (EtOAc/petrol 1:1) IR (ATR): 2095 (N$_3$), 1644 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$CN): δ 5.46 (s, 1H), 4.65 (d, $J$ = 6.0 Hz, 1H), 4.30 (A part of ABq, $J$ = 14.8 Hz, 1H), 4.25 (B part of ABq, $J$ = 14.8 Hz, 1H), 4.14 (dd, $J$ = 1.0, 7.6 Hz, 1H), 3.73 (br s, 1H), 3.71 (dd, $J$ = 5.9, 7.5 Hz, 1H), 3.57 (br s, 1H), 3.53-3.52 (m, 1H), 3.4-3.43 (m, 2H), 3.28-3.26 (m, 2H), 1.63-1.60 (m, 2H), 1.55-1.48 (m, 4H). $^{13}$C NMR (151 MHz, CD$_3$CN): δ 167.7, 101.0, 78.6, 74.7, 69.6, 66.5, 60.2, 60.1, 46.2, 43.3, 27.0, 26.3, 25.1.

3-O-(2-((2-Amino-1-(S)-benzyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diazido-2,4-dideoxy-$\beta$-D-glucose 142

The diazide 127 (108 mg, 0.40 mmol) was treated with (S)-2-amino-3-phenylpropanamide according to Procedure 1.4. Flash chromatography (EtOAc/petrol 1:1 to MeOH/EtOAc 1:9) of the resultant residue yielded the title compound as a colourless oil (160 mg, 96%). $R_t$ 0.53 EtOAc. IR (ATR): 3331 (N-H), 2098 (N$_3$), 1661 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 7.38 (d, $J$ = 7.6 Hz, 1H), 7.35-7.32 (m, 2H), 7.29-7.27 (m, 1H), 7.25-7.24 (m, 2H), 5.81 (br s, 1H), 5.37 (s, 1H), 5.31 (s, 1H), 106
4.82 (dd, $J = 7.8, 15.0$ Hz, 1H), 4.65 (d, $J = 5.2$ Hz, 1H), 4.26 (A part of ABq, $J = 15.7$ Hz, 1H), 4.08 (d, $J = 7.8$ Hz, 1H), 3.91 (B part of ABq, $J = 15.7$ Hz, 1H), 3.83 (dd, $J = 5.5, 7.8$ Hz, 1H), 3.45 (s, 1H), 3.43-3.41 (m, 1H), 3.20-3.13 (m, 2H), 2.97 (s, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.6, 169.2, 136.5, 129.1, 128.9, 127.4, 100.3, 79.4, 74.3, 70.3, 66.5, 60.3, 58.3, 52.9, 37.4.

1,6-Anhydro-3-O-(2-(benzylamino)-2-oxoethyl)-2,4-diamino-2,4-dideoxy-$\beta$-D-glucopyranose 143

The diazide 129 (164 mg, 0.46 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (110 mg, 79%). $R_f$ 0.13 (MeOH/EtOAc 1:9). IR (ATR): 3342 (N–H), 1652 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, CD$_3$OD): δ 7.34-7.29 (m, 4H), 7.26-7.25 (m, 1H), 5.35 (s, 1H), 4.48 (d, $J = 5.4$ Hz, 1H), 4.44 (s, 2H), 4.20 (A part of ABq, $J = 15.5$ Hz, 1H), 4.15 (d, $J = 7.3$ Hz, 1H), 4.06 (B part of ABq, $J = 15.5$ Hz, 1H), 3.70 (dd, $J = 5.9, 7.1$ Hz, 1H), 3.38 (s, 1H), 3.11 (s, 1H), 2.92 (s, 1H). $^{13}$C NMR (126 MHz, CD$_3$OD): δ 172.3, 139.7, 129.6, 128.6, 128.4, 103.6, 83.3, 77.1, 70.4, 67.1, 52.9, 52.3, 43.7. HR-MS (ESI): $m/z$ 308.1609; [M+H]$^+$ requires 308.1610.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(((1-(S)-methyl-2-oxo-2-amino)ethyl)amino)-2-oxoethyl)-$\beta$-D-glucopyranose 144

The diazide 130 (108 mg, 0.32 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (90 mg, 98%). $R_f$ 0.05 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3297 (N–H), 1652 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): δ 5.36 (s, 1H), 4.45-4.42 (m, 2H), 4.23 (d, $J = 7.3$ Hz, 1H), 4.16 (A part of ABq, $J = 15.7$ Hz, 1H), 4.00 (B part of ABq, $J = 15.7$ Hz, 1H), 3.74 (dd, $J = 5.8, 7.3$ Hz, 1H),
3.35-3.34 (m, 1H), 2.97 (s, 1H), 2.80 (s, 1H), 1.40 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 177.2, 172.3, 104.1, 85.0, 78.0, 70.2, 67.2, 53.6, 52.4, 49.5, 18.7. HR-MS (ESI): $m/z$ 289.1510; [M+H]$^+$ requires 289.1512.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-oxo-2-((2-oxo-2-amino)ethyl)amino)ethyl)-$\beta$-D-glucopyranose 145

The diazide 131 (163 mg, 0.50 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (129 mg, 94%). $R_f$ 0.03 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3298 (N-H), 1660 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.35 (s, 1H), 4.44 (d, $J = 5.4$ Hz, 1H), 4.21 (dd, $J = 0.6, 7.2$ Hz, 1H), 4.18 (A part of ABq, $J = 15.4$ Hz, 1H), 4.06 (B part of ABq, $J = 15.4$ Hz, 1H), 3.94 (s, 2H), 3.72 (dd, $J = 5.8, 7.1$ Hz, 1H), 3.37 (s, 1H), 3.00 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 173.8, 173.1, 104.1, 84.8, 77.8, 70.2, 67.2, 53.3, 52.6, 42.4. HR-MS (ESI): $m/z$ 275.1355; [M+H]$^+$ requires 275.1355.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(pyrrolidino)-2-oxoethyl)-$\beta$-D-glucopyranose 146

The diazide 132 (104 mg, 0.31 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (82 mg, 94%). $R_f$ 0.06 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3357 (N-H), 1628 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.30 (s, 1H), 4.41 (d, $J = 5.3$ Hz, 1H), 4.25 (A part of ABq, $J = 14.6$ Hz, 1H), 4.17-4.15 (m, 2H), 3.68 (dd, $J = 6.0, 6.8$ Hz, 1H), 3.48-3.43 (m, 4H), 3.27-3.26 (m, 1H), 2.97 (s, 1H), 2.86 (d, $J = 1.2$ Hz, 1H), 2.00-1.96 (m, 2H), 1.90-1.85 (m, 2H). $^{13}$C NMR...
(151 MHz, CD\textsubscript{3}OD): δ 170.3, 104.1, 84.9, 77.8, 69.7, 67.1, 53.5, 53.4, 47.1, 46.7, 27.0, 24.9. HR-MS (ESI): m/z 272.1609; [M+H]\textsuperscript{+} requires 272.1610.

\[
\text{H}_2\text{N} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{H}_2\text{N} \quad \text{NH}_2
\]

3-O-(2-((2-Amino-1-(S)-(2-methyl)propyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 147

The diazide 133 (163 mg, 0.50 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (129 mg, 94%). R\textsubscript{f} 0.05 (MeOH/CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{3}N 1:4:0.5). IR (ATR): 3301 (N-H), 1660 (C=O) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}OD): δ 5.40 (s, 1H), 4.51-4.48 (m, 2H), 4.27 (dd, J = 0.5, 7.5 Hz, 1H), 4.19 (A part of ABq, J = 15.7 Hz, 1H), 4.04 (B part of ABq, J = 15.7 Hz, 1H), 3.77 (dd, J = 5.7, 7.4 Hz, 1H), 3.39-3.38 (m, 1H), 3.11 (d, J = 1.0 Hz, 1H), 2.88 (d, J = 1.1 Hz, 1H), 1.69-1.59 (m, 3H), 0.97 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.3 Hz, 3H). \textsuperscript{13}C NMR (151 MHz, CD\textsubscript{3}OD): δ 177.3, 172.5, 103.7, 83.1, 77.2, 70.2, 67.2, 53.2, 52.4, 52.1, 42.4, 26.1, 23.5, 21.9. HR-MS (ESI): m/z 331.1985; [M+H]\textsuperscript{+} requires 331.1981.

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\text{H}_2\text{N} \quad \text{N} \quad \text{O} \\
\text{H}_2\text{N} \quad \text{NH}_2
\]

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(hexylamino)-2-oxoethyl)-β-D-glucopyranose 148

The diazide 134 (100 mg, 0.28 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (77 mg, 89%). R\textsubscript{f} 0.07 (MeOH/CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{3}N 1:4:0.5). IR (ATR): 3333 (N-H), 1653 (C=O) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}OD): δ 5.37 (s, 1H), 4.45 (d, J = 5.5 Hz, 1H), 4.15-4.12 (m, 2H), 3.95 (A part of ABq, J = 15.6 Hz, 1H), 3.73 (dd, J = 6.0, 6.8 Hz, 1H), 3.34 (s, 1H), 3.25-3.23 (m, 2H), 2.97 (s, 1H), 2.81 (s, 1H), 1.56-1.51 (m, 2H), 1.37-1.33 (m, 6H), 0.92 (t, J = 6.8 Hz, 3H). \textsuperscript{13}C NMR (151 MHz, CD\textsubscript{3}OD): δ 172.6, 104.1, 84.9, 77.9, 70.3, 67.2, 53.3, 52.4, 40.0, 32.6, 30.3, 27.7, 23.6, 14.4. HR-MS (ESI): m/z 302.2086; [M+H]\textsuperscript{+} requires 302.2080.
Chapter 1

1,6-Anhydro-3-\(O\)-(2-(cyclopropylamino)-2-oxoethyl)-2,4-diamino-2,4-dideoxy-\(\beta\)-D-glucopyranose 149

The diazide 135 (93 mg, 0.30 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (70 mg, 90%). \(R_f\) 0.05 (MeOH/CH\(_2\)Cl\(_2\)/Et\(_3\)N 1:4:0.5). IR (ATR): 3292 (N-H), 1651 (C=O) \(\text{cm}^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)CN): \(\delta\) 7.42 (s, 1H), 5.27 (s, 1H), 4.36 (d, \(J = 4.8\) Hz, 1H), 4.05-4.02 (m, 2H), 3.81 (A part of ABq, \(J = 15.7\) Hz, 1H), 3.63 (dd, \(J = 6.1, 6.1\) Hz, 1H), 3.21 (s, 1H), 2.90 (s, 1H), 2.75 (s, 1H), 2.71-2.67 (m, 1H), 0.68-0.67 (m, 2H), 0.52-0.47 (m, 2H). \(^{13}\)C NMR (151 MHz, CD\(_3\)CN): \(\delta\) 172.2, 104.3, 85.1, 77.9, 70.6, 66.9, 53.9, 52.2, 22.8, 6.4, 6.3. HR-MS (ESI): \(m/z\) 258.1452; [M+H]^+ requires 258.1454.

1,6-Anhydro-3-\(O\)-(2-(cyclopentylamino)-2-oxoethyl)-2,4-diamino-2,4-dideoxy-\(\beta\)-D-glucopyranose 150

The diazide 136 (93 mg, 0.30 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (70 mg, 90%). \(R_f\) 0.04 (MeOH/CH\(_2\)Cl\(_2\)/Et\(_3\)N 1:4:0.5). IR (ATR): 3313 (N-H), 1651 (C=O) \(\text{cm}^{-1}\). \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 5.43 (s, 1H), 4.51 (d, \(J = 5.2\) Hz, 1H), 4.20-4.17 (m, 3H), 3.95 (A part of ABq, \(J = 15.7\) Hz, 1H), 3.77 (dd, \(J = 5.7, 7.0\) Hz, 1H), 3.38 (s, 1H), 3.06 (s, 1H), 2.87 (s, 1H), 1.99-1.93 (m, 2H), 1.77-1.75 (m, 2H), 1.66-1.63 (m, 2H), 1.57-1.49 (m, 2H). \(^{13}\)C NMR (151 MHz, CD\(_3\)OD): \(\delta\) 172.2, 103.9, 84.0, 77.5, 70.5, 67.1, 53.4, 53.1, 52.0, 33.6, 33.5, 24.7, 24.7. HR-MS (ESI): \(m/z\) 286.1769; [M+H]^+ requires 286.1767.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(morpholino)-2-oxyethyl)-β-D-glucopyranose 151

The diazide 137 (113 mg, 0.33 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (82 mg, 86%). Rf 0.04 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3354 (N-H), 1635 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): δ 5.33 (s, 1H), 4.45 (d, $J$ = 5.3 Hz, 1H), 4.36 (A part of ABq, $J$ = 14.1 Hz, 1H), 4.24 (B part of ABq, $J$ = 14.1 Hz, 1H), 4.22 (d, $J$ = 7.1 Hz, 1H), 3.71-3.66 (m, 5H), 3.62-3.46 (m, 4H), 3.29-3.28 (m, 1H), 3.05 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): δ 170.2, 103.8, 83.6, 77.3, 69.5, 67.7, 67.1, 53.5, 53.1, 46.6, 43.3. HR-MS (ESI): m/z 288.1566; [M+H]$^+$ requires 288.1559.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(butylamino)-2-oxyethyl)-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 152

The diazide 138 (130 mg, 0.40 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (105 mg, 96%). Rf 0.04 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3328 (N-H), 1652 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): δ 5.41 (s, 1H), 4.50 (d, $J$ = 5.2 Hz, 1H), 4.18 (d, $J$ = 7.1 Hz, 1H), 4.14 (A part of ABq, $J$ = 15.5 Hz, 1H), 3.97 (B part of ABq, $J$ = 15.5 Hz, 1H), 3.75 (dd, $J$ = 5.8, 7.1 Hz, 1H), 3.37 (s, 1H), 3.26-3.24 (m, 2H), 3.08 (s, 1H), 2.90 (s, 1H), 1.55-1.50 (m, 2H), 1.40-1.34 (m, 2H), 0.95 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, CD$_3$OD): δ 172.4, 103.8, 83.6, 77.3, 70.4, 67.1, 53.0, 52.2, 39.7, 32.5, 21.1, 14.1. HR-MS (ESI): m/z 274.1768; [M+H]$^+$ requires 274.1767.
1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(dodecanlamino)-2-oxyethyl)-β-D-glucopyranose 153

The diazide 139 (175 mg, 0.40 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (140 mg, 91%). $R_f$ 0.11 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3325 (N-H), 1652 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.47 (s, 1H), 4.59 (d, $J = 5.3$ Hz, 1H), 4.25 (d, $J = 7.5$ Hz, 1H), 4.16 (A part of ABq, $J = 15.3$ Hz, 1H), 4.02 (B part of ABq, $J = 15.3$ Hz, 1H), 3.79 (dd, $J = 5.7$, 7.4 Hz, 1H), 3.44-3.43 (m, 1H), 3.29 (d, $J = 1.3$ Hz, 1H), 3.25-3.23 (m, 2H), 3.06 (d, $J = 1.3$ Hz, 1H), 1.56-1.51 (m, 2H), 1.34-1.29 (m, 18H), 0.90 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 170.1, 103.1, 83.3, 78.7, 70.2, 66.2, 52.7, 50.9, 39.2, 32.1, 29.8, 29.8, 29.8, 29.5, 29.5, 29.5, 27.1, 22.8, 14.3. HR-MS (ESI): m/z 386.3017; [M+H]$^+$ requires 386.3019.

3-O-((2-(2-Amino-1-(S)-(2-methylthio)ethyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 154

The diazide 140 (138 mg, 0.34 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (103 mg, 86%). $R_f$ 0.04 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3299 (N-H), 1660 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.45 (s, 1H), 4.58 (d, $J = 4.7$ Hz, 1H), 4.55 (dd, $J = 4.7$, 8.8 Hz, 1H), 4.30 (d, $J = 7.4$ Hz, 1H), 4.21 (A part of ABq, $J = 15.6$ Hz, 1H), 4.12 (B part of ABq, $J = 15.6$ Hz, 1H), 3.79 (dd, $J = 5.8$, 7.3 Hz, 1H), 3.49 (s, 1H), 3.23 (s, 1H), 2.99 (s, 1H), 2.59-2.50 (m, 2H), 2.13-2.10 (m, 4H), 2.03-1.97 (m, 1H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 176.1, 172.5, 103.4, 82.1, 76.7, 70.2, 67.2, 53.2, 53.0, 52.0, 33.0, 31.1, 15.3. HR-MS (APCI): m/z 349.1545; [M+H]$^+$ requires 349.1546.
3-O-(2-((2-Amino-1-(S)-benzyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose 156

The diazide 142 (148 mg, 0.36 mmol) was treated according to Procedure 1.5 to give the title compound as a colourless oil (93 mg, 71%). Rf 0.03 (MeOH/CH2Cl2/Et3N 1:4:0.5). IR (ATR): 3314 (N-H), 1661 (C=O) cm⁻¹. ¹H NMR (600 MHz, CD3OD): δ 7.31-7.21 (m, 5H), 5.44 (s, 1H), 4.75 (dd, J = 5.4, 9.0 Hz, 1H), 4.64 (d, J = 5.2 Hz, 1H), 4.26 (d, J = 7.8 Hz, 1H), 4.12 (A part of ABq, J = 15.4 Hz, 1H), 4.02 (B part of ABq, J = 15.4 Hz, 1H), 3.81 (dd, J = 5.7, 7.8 Hz, 1H), 3.44 (s, 1H), 3.41 (s, 1H), 3.22-3.19 (m, 1H), 2.99-2.96 (m, 2H). ¹³C NMR (151 MHz, CD3OD): δ 175.7, 171.6, 138.1, 130.3, 129.5, 127.9, 102.5, 79.0, 75.2, 70.3, 67.3, 54.8, 52.6, 51.7, 39.1. HR-MS (ESI): m/z 365.1827; [M+H]+ requires 365.1825.
Dichloro-(1,6-anhydro-3-O-(2-(benzylamino)-2-oxoethyl)-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 157

The diamine 143 (49 mg, 0.16 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (46 mg, 49%). IR (ATR): 3424, 3364, 3191, 3122 (N-H), 1671 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 8.23-8.21 (m, 1H), 7.35-7.34 (m, 4H), 7.29-7.26 (m, 1H), 5.69 (s, 1H), 5.66-5.64 (m, 1H), 5.53-5.51 (m, 1H), 5.20 (d, J = 12.2 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 4.89 (d, J = 5.2 Hz, 1H), 4.48-4.42 (m, 2H), 4.32 (d, J = 7.3 Hz, 1H), 4.17 (s, 2H), 3.59 (dd, J = 5.8, 7.0 Hz, 1H), 3.54 (s, 1H), 2.89 (d, J = 5.0 Hz, 1H), 2.71 (d, J = 5.0 Hz, 1H). ¹³C NMR (151 MHz, d₇-DMF): δ 169.4, 140.0, 128.7, 127.7, 127.2, 99.7, 73.6, 69.8, 65.3, 48.7, 48.1, 42.4. HR-MS (ESI): m/z 616.0498; [M+HC(O)O]⁻ requires 616.0512.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-((1-(S)-methyl-2-oxo-2-amino)ethyl)amino)-2-oxoethyl)-β-D-glucopyranose-N,N') Platinum(II) 158

The diamine 144 (76 mg, 0.27 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow crystals (77 mg, 51%). IR (ATR): 3410, 3378, 3185, 3122 (N-H), 1659 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 7.79 (d, J = 7.7 Hz, 1H), 7.62 (s, 1H), 7.18 (s, 1H), 5.72 (s, 1H), 5.62-5.55 (m, 2H), 5.22 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.92 (d, J = 5.1 Hz, 1H), 4.50-4.45 (m, 1H), 4.34 (d, J = 7.4 Hz, 1H), 4.11 (s, 2H), 3.64 (dd, J = 5.9, 7.2 Hz, 1H), 3.50 (s, 1H), 2.87 (d, J = 5.0 Hz, 1H), 2.66 (d, J = 5.0 Hz, 1H), 1.36 (d, J = 7.1 Hz, 3H). ¹³C NMR (151
MHz, $d_7$-DMF): δ 174.6, 168.9, 99.7, 80.6, 73.6, 69.8, 65.3, 49.0, 48.2, 48.1, 18.8.

HR-MS (ESI): $m/z$ 597.0325; [M+HC(O)O$^-$] requires 597.0328.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-oxo-2-((2-oxo-2-amino)ethyl)amino)ethyl)-β-D-glucopyranose-$N,N'$) Platinum(II) 159

The diamine 145 (117 mg, 0.43 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (122 mg, 53%). IR (ATR): 3476, 3344, 3195, 3121 (N-H), 1662 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, $d_7$-DMF): δ 7.90 (dd, $J = 5.4, 5.4$ Hz, 1H), 7.57 (s, 1H), 7.18 (s, 1H), 5.70 (s, 1H), 5.65-5.62 (m, 1H), 5.53-5.50 (m, 1H), 5.20 (d, $J = 11.9$ Hz, 1H), 5.10 (d, $J = 11.9$ Hz, 1H), 4.90 (d, $J = 5.2$ Hz, 1H), 4.31 (d, $J = 7.3$ Hz, 1H), 4.14 (A part of ABq, $J = 15.3$ Hz, 1H), 4.11 (B part of ABq, $J = 15.3$ Hz, 1H), 3.92 (d, $J = 5.9$ Hz, 2H), 3.62 (dd, $J = 5.8, 7.2$ Hz, 1H), 3.48 (s, 1H), 2.87 (d, $J = 4.9$ Hz, 1H), 2.74 (s, 1H). $^{13}$C NMR (151 MHz, $d_7$-DMF): δ 171.3, 169.8, 99.7, 80.6, 73.5, 69.7, 65.3, 48.7, 48.4, 41.7. HR-MS (APCI): $m/z$ 614.0868; [M+DMF+H]$^+$ requires 614.0857.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(pyrrolidino)-2-oxoethyl)-β-D-glucopyranose-$N,N'$) Platinum(II) 160

The diamine 146 (75 mg, 0.28 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow crystals (83 mg, 55%). IR (ATR): 3439, 3191, 3122 (N-H), 1628 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, $d_7$-DMF): δ 5.67 (s, 1H), 5.61-5.58 (m, 1H), 5.54-5.51 (m, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 5.04 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 5.3$ Hz, 1H), 4.44 (d, $J = 7.1$ Hz, 1H), 4.30 (A part of ABq, $J = 14.3$
Dichloro-(3-O-(2-((2-amino-1-(S)-(2-methyl)propyl-2-oxoethyl)amino)-2-oxoethyl)-1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 161

The diamine 147 (110 mg, 0.33 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (110 mg, 55%). IR (ATR): 3352, 3191, 3122 (N-H), 1660 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 7.89 (d, J = 8.9 Hz, 1H), 7.85 (s, 1H), 7.33 (s, 1H), 5.92 (s, 1H), 5.79-7.76 (m, 1H), 5.72-5.69 (m, 1H), 5.42 (d, J = 12.0 Hz, 1H), 5.33 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 5.2 Hz, 1H), 4.75-4.71 (m, 1H), 4.54 (d, J = 7.3 Hz, 1H), 4.32 (s, 2H), 3.84 (dd, J = 5.7, 7.3 Hz, 1H), 3.07 (d, J = 5.3 Hz, 1H), 2.82 (d, J = 5.3 Hz, 1H), 1.86-1.78 (m, 3H), 1.10 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.3 Hz, 3H). ¹³C NMR (151 MHz, d₇-DMF): δ 174.6, 169.3, 99.8, 80.7, 73.6, 69.8, 65.3, 50.9, 49.2, 48.0, 42.1, 25.1, 23.1, 21.5. HR-MS (ESI): m/z 639.0826; [M+HC(O)O⁻] requires 639.0838.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(hexylamino)-2-oxoethyl)-β-D-glucopyranose-N,N') Platinum(II) 162

The diamine 148 (71 mg, 0.24 mmol) was treated with according to Procedure 1.6 to give the title compound as a pale yellow solid (110 mg, 83%). IR (ATR): 3370, 3190, 3122 (N-H), 1670, 1660 (C=O) cm⁻¹. ¹H NMR (600 MHz, d₇-DMF): δ 7.67-7.65 (m,
Chapter 1

1H, 5.73 (s, 1H), 5.68-5.65 (m, 1H), 5.55-5.52 (m, 1H), 5.22 (d, J = 11.9 Hz, 1H), 5.12 (d, J = 11.9 Hz, 1H), 4.92 (d, J = 5.2 Hz, 1H), 4.32 (d, J = 7.5 Hz, 1H), 4.11 (A part of ABq, J = 15.2 Hz, 1H), 4.07 (B part of ABq, J = 15.2 Hz, 1H) 3.63 (dd, J = 5.8, 7.1 Hz, 1H), 3.52 (s, 1H), 3.25-3.16 (m, 2H), 2.86 (d, J = 5.1 Hz, 1H), 2.68 (d, J = 5.1 Hz, 1H), 1.50-1.46 (m, 2H), 1.33-1.28 (6H), 0.89-0.86 (m, 3H). 13C NMR (151 MHz, d7-DMF): δ 169.1, 99.8, 80.8, 73.6, 69.9, 65.3, 48.9, 48.0, 38.8, 31.7, 26.8, 22.7, 13.9. HR-MS (ESI): m/z 612.1035; [M+HC(O)O]− requires 612.1005.

Dichloro-(1,6-anhydro-3-O-(2-(cyclopropylamino)-2-oxyethyl)-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 163

The diamine 149 (59 mg, 0.23 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow crystals (75 mg, 62%). IR (ATR): 3185, 3119 (N-H), 1670, 1657 (C=O) cm⁻¹. 1H NMR (600 MHz, d7-DMF): δ 7.67 (s, 1H), 5.71 (s, 1H), 5.67-5.64 (m, 1H), 5.54-5.51 (m, 1H), 5.20 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.90 (d, J = 5.2 Hz, 1H), 4.29 (d, J = 7.3 Hz, 1H), 4.08 (A part of ABq, J = 15.3 Hz, 1H), 4.05 (B part of ABq, J = 15.3 Hz, 1H), 3.62 (dd, J = 5.8, 7.1 Hz, 1H) 2.83 (d, J = 5.2 Hz, 1H), 2.79-2.76 (m, 1H), 2.65 (d, J = 5.2 Hz, 1H), 0.70-0.66 (m, 2H), 0.53-0.51 (m, 2H). 13C NMR (151 MHz, d7-DMF): δ 170.5, 99.8, 80.9, 73.6, 69.8, 65.3, 48.8, 47.9, 22.4, 5.8, 5.7. HR-MS (ESI): m/z 568.0393; [M+HC(O)O]− requires 568.0379.
Dichloro-(1,6-anhydro-3-O-(2-(cyclopentylamino)-2-oxyethyl)-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 164

The diamine 150 (100 mg, 0.35 mmol) was treated with according to Procedure 1.6 to give the title compound as a yellow solid (132 mg, 68%). IR (ATR): 3187, 3120 (N-H), 1651 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 7.75 (d, \(J = 7.5\) Hz, 1H), 5.94 (s, 1H), 5.86-5.83 (m, 1H), 5.74-5.71 (m, 1H), 5.41 (d, \(J = 12.0\) Hz, 1H), 5.28 (d, \(J = 12.0\) Hz, 1H), 5.11 (d, \(J = 5.1\) Hz, 1H), 4.50 (d, \(J = 7.2\) Hz, 1H), 4.36-4.19 (m, 3H), 3.84 (dd, \(J = 5.9, 7.0\) Hz, 1H), 3.70 (m, 1H), 3.01 (d, \(J = 4.9\) Hz, 1H), 2.84 (d, \(J = 4.9\) Hz, 1H), 2.07-2.03 (m, 2H), 1.90-1.83 (m, 2H), 1.76-1.64 (m, 4H). \(^13\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 168.9, 99.9, 80.9, 73.7, 70.1, 65.3, 50.7, 49.1, 47.8, 32.8, 32.8, 23.8. HR-MS (ESI): \(m/z\) 598.0731; [M+HC(O)O]\(^-\) requires 598.0721.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(piperidino)2-oxyethyl)-β-D-glucopyranose-N,N') Platinum(II) 165

The diamine 151 (73 mg, 0.25 mmol) was treated with according to Procedure 1.6 to give the title compound as a bright yellow solid (49 mg, 34%). IR (ATR): 3507, 3199, 3121 (N-H), 1631 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, \(d_7\)-DMF): \(\delta\) 5.68 (s, 1H), 5.64-5.61 (m, 1H), 5.56-5.53 (m, 1H), 5.18 (d, \(J = 11.9\) Hz, 1H), 5.07 (d, \(J = 11.9\) Hz, 1H), 4.88 (d, \(J = 5.3\) Hz, 1H), 4.43 (A part of ABq, \(J = 13.4\) Hz, 1H), 4.33 (d, \(J = 7.1\) Hz, 1H), 4.26 (B part of ABq, \(J = 13.4\) Hz, 1H), 3.63-3.58 (m, 6H), 3.54-3.45 (m, 4H), 2.82 (d, \(J = 5.2\) Hz, 1H), 2.68 (d, \(J = 5.2\) Hz, 1H). \(^13\)C NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 167.5, 99.7, 80.8, 73.6, 69.5, 66.8, 65.2, 48.6, 48.6, 45.7, 42.1. HR-MS (ESI): \(m/z\) 602.0508; [M+HC(O)O]\(^-\) requires 602.0484.
Dichloro-(1,6-anhydro-3-O-(2-(butylamino)-2-oxyethyl)-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N,N') Platinum(II) 166

The diamine 152 (92 mg, 0.34 mmol) was treated with according to Procedure 1.6 to give the title compound as a pale yellow solid (120 mg, 64%). IR (ATR): 3370, 3189, 3120 (N-H), 1655 (C=O) cm⁻¹. ¹H NMR (600 MHz, d⁷-DMF): δ 7.66 (s, 1H), 5.72 (s, 1H), 5.67-5.65 (m, 1H), 5.54-5.52 (m, 1H), 5.2 (d, J = 11.9 Hz, 1H), 5.10 (d, J = 11.9 Hz, 1H), 4.91 (d, J = 5.1 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.10 (A part of ABq, J = 15.1 Hz, 1H), 4.06 (B part of ABq, J = 15.1 Hz, 1H), 3.63 (dd, J = 5.8, 7.0 Hz, 1H), 3.51 (s, 1H), 3.25-3.18 (m, 2H), 2.85 (d, J = 5.1 Hz, 1H), 2.68 (d, J = 5.1 Hz, 1H), 1.49-1.45 (m, 2H), 1.35-1.29 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ¹³C NMR (151 MHz, d⁷-DMF): δ 169.1, 99.8, 80.8, 73.6, 69.9, 65.3, 48.8, 48.0, 38.5, 31.9, 20.1, 13.6. HR-MS (ESI): m/z 588.0621; [M+HC(O)O]⁻ requires 588.0633.

Dichloro-(1,6-anhydro-2,4-diamino-2,4-dideoxy-3-O-(2-(dodecylamino)-2-oxyethyl)-β-D-glucopyranose-N,N') Platinum(II) 167

The diamine 153 (70 mg, 0.18 mmol) was treated with according to Procedure 1.7 to give the title compound as a bright yellow solid (92 mg, 78%). IR (ATR): 3366, 3189, 3122 (N-H), 1671, 1661 (C=O) cm⁻¹. ¹H NMR (600 MHz, d⁷-DMF): δ 7.68-7.66 (m, 1H), 5.73 (s, 1H), 5.69-5.66 (m, 1H), 5.56-5.53 (m, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 4.91 (d, J = 5.3 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.10 (A part of ABq, J = 15.2 Hz, 1H), 4.07 (B part of ABq, J = 15.2 Hz, 1H), 3.63 (dd, J = 5.7, 7.2 Hz, 1H), 3.51 (s, 1H), 3.22-3.19 (m, 2H), 2.85 (d, J = 5.5 Hz, 1H), 2.68 (d, J = 5.2 Hz, 1H), 1.52-1.47 (m, 2H), 1.29-1.28 (m, 18H), 0.88 (t, J = 7.1 Hz, 3H). ¹³C
Chapter 1

NMR (151 MHz, \(d_7\)-DMF): \(\delta\) 169.1, 99.8, 80.8, 73.6, 69.9, 65.3, 48.9, 48.0, 38.8, 32.0, 27.1, 22.8, 13.9. HR-MS (ESI): \(m/z\) 725.2568; [M+H+DMF]⁺ requires 725.2573.

1-Azido-5-bromopentane 171

Sodium azide (183 mg, 2.8 mmol) was added over 1 h. to a solution of 1,5-dibromopentane (969 mg, 4.21 mmol) in DMF (10 mL) at 55°C. The resultant mixture was stirred at 55°C (16 h.) then concentrated. The resultant residue was taken up in \(\text{CH}_2\text{Cl}_2\) (20 mL), washed with water (20 mL), dried (\(\text{MgSO}_4\)), filtered and concentrated. Flash chromatography (petrol) of the resultant residue yielded the title compound as a colourless oil (258 mg, 52%). The \(^1\)H NMR spectrum was consistent with that found in the literature.\(^{206}\)

1,6-Anhydro-3-\(O\)-(5-azido)pentyl-2,4-diazido-2,4-dideoxy-\(\beta\)-D-glucose 169

The diazide 53 (101 mg, 0.50 mmol) and bromide 171 (115 mg, 0.60 mmol) were added to a solution of KOH (122 mg, 2.2 mmol) in DMSO (5 mL) and the resultant mixture was stirred for 2 h. at room temperature. The mixture was then diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL), the organic extracts combined, washed with water (3 x 20 mL), dried (\(\text{MgSO}_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (125 mg, 78%). \(R_f\) 0.45 (EtOAc/petrol 1:4). IR (ATR): 2093 (N\(\equiv\)N) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.48 (s, 1H), 4.61 (d, \(J = 5.5\) Hz, 1H), 4.05 (dd, \(J = 0.8, 7.4\) Hz, 1H), 3.79 (dd, \(J = 5.7, 7.4\) Hz, 1H), 3.62-3.54 (m, 2H), 3.43-3.42 (m, 2H), 3.35 (s, 1H), 3.229-3.27 (m, 2H), 1.65-1.60 (m, 4H), 1.47-1.44 (m, 2H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 100.8, 78.3, 74.4, 71.0, 66.6, 61.1, 60.6, 51.4, 29.4, 28.7, 23.5.
Palladium-on-carbon (10%, 50 mg) was added to a solution of the triazide 169 (113 mg, 0.35 mmol) in MeOH (5 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until judged complete by TLC. The mixture was filtered through Celite and concentrated. Flash chromatography (CHCl₃/MeOH/NH₃(aq) 5:5:1) yielded the title compound as a colourless oil (58 mg, 67%).

IR (ATR): 3351 (N-H) cm⁻¹. ¹H NMR (600 MHz, CD3OD): δ 5.28 (s, 1H), 4.38 (d, J = 5.5 Hz, 1H), 4.11 (d, J = 6.8 Hz, 1H), 3.68 (dd, J = 6.4 Hz, 1H), 3.51-3.49 (m, 2H), 3.20 (s, 1H), 2.84 (s, 1H), 2.75 (s, 1H), 2.72-2.70 (m, 2H), 1.61-1.52 (m, 4H), 1.45-1.40 (m, 2H). ¹³C NMR (151 MHz, CD3OD): δ 104.3, 84.0, 77.9, 70.6, 66.9, 53.4, 53.3, 42.0, 32.1, 30.7, 24.6. HR-MS (APCI): m/z 246.1813; [M+H]+ requires 246.1818.

Chloro-(1,6-anhydro-3-O-5-aminopentyl-2,4-diamino-2,4-dideoxy-β-D-glucopyranose-N, N',N'') platinum(II) 168

A suspension of PtCl₂DMSO₂ (39 mg, 0.9 mmol) in CH₃CN (1 mL) was added dropwise to a solution of the triamine 170 (23 mg, 0.09 mmol) in a mixture of CH₃CN (6 mL) and MeOH (1 mL). The resultant mixture was left to stand at room temperature. After 16 h., a white solid was collected by filtration, washed with cold water (3 x 2 mL) and air dried to give the title compound as a white solid (27 mg, 70%). IR (ATR): 3429, 3063 (N-H) cm⁻¹. ¹H NMR (600 MHz, D₂O): δ 5.67-5.57 (m, 1H), 4.76 (s, 1H), 4.36-4.30 (m, 1H), 3.81 (s, 1H), 3.66-3.57 (m, 4H), 3.29-3.25 (m, 1H), 2.72 (s, 2H), 1.74-1.64 (m, 4H), 1.46-1.44 (m, 2H). ¹³C NMR (151 MHz, D₂O): δ 99.8, 78.9, 74.2,
Chapter 1

71.2, 71.2, 66.3, 47.1, 44.7, 31.1, 29.2, 23.7. HR-MS (ESI): \( m/z \) 558.1196; [M+DMSO]\(^+\) requires 558.1217.

![Chemical structure](image)

1,6-Anhydro-3-\(O\)-(5-(1,6-anhydro-2,4-diazido-2,4-dideoxy-3-\(O\)-oxy-\(\beta\)-D-glucosyl))pentyl-2,4-diazido-2,4-dideoxy-\(\beta\)-D-glucose 176

Method A: Potassium hydroxide (5.6 mg, 0.1 mmol) was added to a stirred solution of the diazide 53 (8.5 mg, 0.04 mmol) in a mixture of DMSO (0.02 mL) and toluene (0.8 mL) at 0°C, followed by 1,5-dibromopentane (0.004 mL, 0.03 mmol) and the resultant mixture was stirred at room temperature (4 d.). The reaction was then quenched with water (2 mL), extracted with EtOAc (2 x 5 mL), dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:19 to 1:9) of the resultant residue yielded the title compound as a waxy white solid (1.4 mg, 9\%). \( R_f \) 0.6 (EtOAc/petrol 2:3). IR (ATR): 2097 (N\(_3\)) cm\(^{-1}\). \( ^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 5.48 (s, 2H), 4.60 (d, \( J = 5.7 \) Hz, 2H), 4.05 (d, \( J = 7.4 \) Hz, 2H), 3.78 (dd, \( J = 5.6, 7.3 \) Hz, 2H), 3.62-3.54 (m, 4H), 3.42 (s, 4H), 3.36 (s, 2H), 1.64-1.59 (m, 4H), 1.45-1.40 (m, 2H). \( ^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 100.8, 78.3, 74.4, 71.2, 66.7, 61.2, 60.7, 29.6, 22.9.

Method B: Sodium hydride (60% mineral dispersion in oil, 2.4 mg, 0.06 mmol) was added to a stirred solution of the diazide 53 (16 mg, 0.08 mmol) and sodium iodide (8.9 mg, 0.06 mmol) in DMF (1 mL) at 0°C. After 10 min., the diazide 177 (18 mg, 0.05 mmol) was added dropwise and the resultant solution was stirred at room temperature (16 h.). The reaction was then quenched with MeOH, diluted with water (5 mL), extracted with EtOAc (2 x 10 mL), dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:19 to 1:9) of the resultant residue yielded the title compound as a waxy solid (7.5 mg, 30\%). \( ^1\)H and \( ^{13}\)C NMR spectra were consistent with that found above.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(5-bromo)pentyl-β-D-glucose

Sodium hydride (60% mineral dispersion in oil, 4.9 mg, 0.129 mmol) was added to a stirred solution of the diazide 53 (21 mg, 0.1 mmol) and sodium iodide (16 mg, 0.11 mmol) in DMF (1 mL) at 0°C. After 10 min., 1,5-dibromopentane (0.04 mL, 0.30 mmol) was added dropwise and the resultant solution was stirred at room temperature. After 5 h., further 1,5-dibromopentane (0.04 mL, 0.30 mmol) was added and the resultant solution was stirred at room temperature (16 h.). The reaction was then quenched with MeOH, diluted with water (5 mL), extracted with EtOAc (2 x 5 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/Hex 1:19) of the resultant residue yielded the title compound as a pale yellow oil (21 mg, 60%). R<sub>f</sub> 0.28 (EtOAc/petrol 1:9). IR (ATR): 2095 (N<sub>3</sub>) cm⁻¹. <sup>1</sup>H NMR (600 MHz, CDCl₃): δ 5.49 (s, 1H), 4.61 (d, J = 5.8 Hz, 1H), 4.07 (dd, J = 0.80, 7.4 Hz, 1H), 3.79 (dd, J = 5.6, 7.4 Hz, 1H), 3.63-3.54 (m, 2H), 3.43-3.41 (m, 4H), 3.36 (s, 1H), 1.91-1.86 (m, 2H), 1.65-1.60 (m, 2H), 1.55-1.50 (m, 2H). <sup>13</sup>C NMR (151 MHz, CDCl₃): δ 100.8, 78.3, 74.4, 71.0, 66.63, 61.1, 60.5, 33.7, 32.5, 29.0, 24.9.

6-((2-Tetrahydropyranyl)oxy)-1-hexanol

4-Toluenesulfonic acid (12.4 mg, 0.07 mmol) was added to a solution of 1,6-hexanediol (1.55 g, 13.1 mmol) and 3,4-dihydro-2H-pyran (547 mg, 6.5 mmol) in CH₂Cl₂ (12 mL) at 0°C and the resultant solution was left to stir at room temperature (16 h.). The reaction was then quenched with a solution of sat. NaHCO₃ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:4 to 1:1) of the resultant residue yielded the title compound as a colourless oil (921 g, 70%). The <sup>1</sup>H and <sup>13</sup>C NMR spectra were consistent with that found in the literature. 209
6-((2-Tetrahydropyranyl)oxy)-1-hexyl 4-toluenesulfonate 184

4-Toluenesulfonyl chloride (564 mg, 2.96 mmol) was added to a solution of the alcohol 183 (460 mg, 2.27 mmol) in a mixture of CH₂Cl₂ (6 mL) and pyridine (4 mL) and the resultant solution was left to stir at room temperature (16 h.). The reaction was then concentrated and the residue was taken up in CH₂Cl₂ (25 mL), washed with water (3 x 25 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (490 g, 60%). The ¹H and ¹³C NMR spectra were consistent with that found in the literature. ²⁰⁸

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-((2-tetrahydropyranyl)oxy)hexyl-β-D-glucose 185

Sodium hydride (60% mineral dispersion in oil, 30 mg, 0.69 mmol) was added to a stirred solution of the diazide 53 (100 mg, 0.47 mmol) in DMF (5 mL) at 0°C. After 10 min., the tosylate 184 (252 mg, 0.7 mmol) was then added and the resultant mixture was stirred at room temperature (16 h.). The reaction was then quenched with MeOH and concentrated. The resultant residue was taken up in water (15 mL), extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (2 x 15 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (155 g, 83%). Rf 0.53 (EtOAc/toluene 1:9). IR (ATR): 2096 (N₃) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.48 (s, 1H), 4.61 (d, J = 5.3 Hz, 1H), 4.57-4.56 (m, 1H), 4.07 (d, J = 7.4 Hz, 1H), 3.88-3.84 (m, 1H), 3.78 (dd, J = 5.8, 7.3 Hz, 1H), 3.75-3.71 (m, 1H), 3.58-3.48 (m, 3H), 3.41-3.40 (m, 4H), 1.84-1.82 (m, 1H), 1.74-1.69 (m, 1H), 1.60-1.52 (m, 8H), 1.41-1.38 (m, 4H). ¹³C NMR (151 MHz, CDCl₃): δ 100.8, 99.1, 78.1, 74.3, 71.3, 67.6, 66.5, 62.6, 60.9, 60.4, 30.9, 29.8, 29.8, 26.1, 26.1, 25.6, 19.9.
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(6-hydroxy)hexyl-β-D-glucose 186

4-toluenesulfonic acid (8.8 mg, 0.05 mmol) was added to a solution of the diazide 185 (204 mg, 0.51 mmol) in MeOH (5 mL) and the resultant solution was stirred at room temperature until judged complete by TLC. The reaction was then quenched with a solution of sat. NaHCO₃ (5 mL), diluted with water (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 2:3) of the resultant residue yielded the title compound as a colourless oil (132 g, 83%). Rf 0.32 (EtOAc/petrol 2:3). IR (ATR): 3341 (O-H), 2095 (N₃) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.48 (s, 1H), 4.61 (d, J = 5.4 Hz, 1H), 4.07 (d, J = 7.4 Hz, 1H), 3.79 (dd, J = 5.8, 7.1 Hz, 1H), 3.65-3.64 (m, 2H), 3.66-3.52 (m, 2H), 3.42 (s, 2H), 3.36 (s, 1H), 1.62-1.56 (m, 4H), 1.40-1.38 (m, 4H), 1.30 (br s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 100.8, 78.1, 74.4, 71.3, 66.6, 63.0, 61.0, 60.5, 32.7, 29.8, 26.0, 25.6.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(6-(4-toluenesulfonyloxy)hexyl-β-D-glucose 187

4-Toluenesulfonyl chloride (89 mg, 0.47 mmol) was added to a solution of the diazide 186 (312 mg, 0.23 mmol) in a mixture of CH₂Cl₂ (3 mL) and pyridine (2 mL) and the resultant solution was stirred at room temperature until judged complete by TLC. The reaction was then concentrated, taken up in EtOAc (20 mL), and washed with water (20 mL), 1M HCl (20 mL), water (20 mL), sat. NaHCO₃ (20 mL), brine (20 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:4) of the resultant residue yielded the title compound as a colourless oil (86 mg, 80%). Rf 0.61 (EtOAc/petrol 2:3). IR (ATR): 2097 (N₃) cm⁻¹. ¹H NMR (500 MHz, (CD₃)₂CO): δ 7.81-7.80 (m, 2H), 7.50-7.48 (m, 2H), 5.48 (s, 1H), 4.72 (d, J = 5.7 Hz, 1H), 4.13-4.11
(m, 1H), 4.06-4.03 (m, 2H), 3.74-3.72 (m, 1H), 3.67 (s, 1H), 3.60-3.57 (m, 2H), 3.44-3.42 (m, 2H), 2.47 (s, 3H), 1.66-1.61 (m, 2H), 1.56-1.51 (m, 2H), 1.34-1.32 (m, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 144.8, 133.3, 130.0, 128.0, 100.8, 78.2, 74.4, 71.1, 70.6, 66.6, 61.0, 60.6, 29.6, 28.9, 25.6, 25.3, 21.8.

1,6-Anhydro-3-O-(6-(1,6-anhydro-2,4-diazido-2,4-dideoxy-3-O-oxy-β-D-glucosyl)hexyl)-2,4-diazido-2,4-dideoxy-β-D-glucose 188

Potassium hydroxide (28 mg, 0.5 mmol) was added to a solution of the diazide 53 (53 mg, 0.25 mmol) in a mixture of DMSO (1.6 mL) and toluene (2.4 mL) and the resultant mixture was stirred at room temperature (1 h.). Then, the tosylate 187 (82 mg, 0.18 mmol) was added and the resultant mixture was left to stir at room temperature (16 h.). The reaction was diluted with EtOAc (20 mL) and washed with water (2 x 20 mL), brine (20 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:4) of the resultant residue yielded the title compound as a colourless oil (74 mg, 83%). $R_f$ 0.35 (EtOAc/petrol 1:4). IR (ATR): 2093 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 5.48 (s, 2H), 4.61 (d, $J = 5.8$ Hz, 2H), 4.06 (d, $J = 7.3$ Hz, 2H), 3.79 (dd, $J = 5.6, 7.4$ Hz, 2H), 3.61-3.52 (m, 4H), 3.43-3.42 (m, 4H), 3.36 (s, 2H), 1.61-1.57 (m, 4H), 1.39-1.36 (m, 4H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 100.8, 78.2, 74.4, 71.2, 66.6, 61.1, 60.6, 29.8, 26.0.

1,6-Anhydro-3-O-(6-(1,6-anhydro-2,4-diazido-2,4-dideoxy-3-O-oxy-β-D-glucosyl)hexyl)-2,4-diamino-2,4-dideoxy-β-D-glucose 189

Palladium-on-carbon (10%, 50 mg) was added to a solution of the tetraazide 188 (93 mg, 0.18 mmol) in MeOH (8 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until judged
complete by TLC. The mixture was filtered through Celite and concentrated to give the title compound as a colourless oil (59 mg, 80%). \( R_t 0.04 \) (EtOAc/MeOH/water 5:4:1). IR (ATR): 3352 (N-H) cm\(^{-1}\). \(^1\)H NMR (600 MHz, D\(_2\)O): \( \delta \) 5.42 (s, 2H), 4.56 (d, \( J = 5.5 \) Hz, 2H), 4.15 (d, \( J = 7.4 \) Hz, 2H), 3.79-3.77 (m, 2H), 3.62-3.53 (m, 4H), 3.30 (s, 2H), 3.06 (s, 2H), 2.88 (s, 2H), 1.62-1.56 (m, 4H), 1.38-1.36 (m, 4H). \(^{13}\)C NMR (151 MHz, D\(_2\)O): \( \delta \) 103.2, 82.3, 77.2, 71.0, 66.8, 53.1, 51.3, 29.7, 26.2. HR-MS (APCI): \( m/z \) 403.2554; [M+H\(^+\)] requires 403.2557.

5-((2-Tetrahydropyranyl)oxy)-1-pentanol 191

4-Toluenesulfonic acid (36 mg, 0.10 mmol) was added to a solution of 1,6-hexanediol (2.0 g, 19.0 mmol) and 3,4-dihydro-2H-pyran (800 mg, 9.5 mmol) in CH\(_2\)Cl\(_2\) (11 mL) at 0°C and the resultant solution was left to stir at room temperature (16 h.). The reaction was then quenched with a solution of sat. NaHCO\(_3\) (20 mL) and extracted with EtOAc (2 x 60 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 3:7) of the resultant residue yielded the title compound as a colourless oil (1.2 g, 64%). The \(^1\)H NMR spectrum was consistent with that found in the literature.\(^{210}\)

6-((2-Tetrahydropyranyl)oxy)-1-pentyl 4-toluenesulfonate 192

4-Toluenesulfonyl chloride (1.4 g, 7.3 mmol) was added to a solution of the alcohol 191 (1.1 g, 5.84 mmol) in a mixture of CH\(_2\)Cl\(_2\) (12 mL) and pyridine (1 mL) and the resultant solution was left to stir at room temperature (16 h.). The reaction was then concentrated and the residue was taken up in CH\(_2\)Cl\(_2\) (30 mL), washed with water (30 mL), 1M HCl (30 mL), water (30 mL), sat. NaHCO\(_3\) (30 mL), brine (30 mL), dried (MgSO\(_4\)), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:4) of the resultant residue yielded the title compound as a colourless oil (1.8 g, 92%). \( R_t 0.30 \) (EtOAc/petrol 1:4). The \(^1\)H and \(^{13}\)C NMR spectra were consistent with that found in the literature.\(^{211}\)
1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-\(O\)-(5-(2-tetrahydropyranyl)oxy)pentyl-\(\beta\)-D-glucose 193

Potassium hydroxide (106 mg, 1.88 mmol) was added to a solution of the diazide 53 (200 mg, 0.94 mmol) in a mixture of DMSO (1.2 mL) and toluene (1.8 mL) and the resultant mixture was stirred (1 h.). Then the tosylate 192 (226 mg, 0.66 mmol) was added and the resultant mixture was stirred at room temperature (16 h.). The reaction was then diluted with water (15 mL), and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (40 mL), brine (40 mL), dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (226 g, 90\%). \(R_f\) 0.35 (EtOAc/toluene 1:4). IR (ATR): 2096 (N\(_3\)) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.48 (s, 1H), 4.61 (d, \(J = 5.3\) Hz, 1H), 4.57-4.56 (m, 1H), 4.07 (d, \(J = 7.4\) Hz, 1H), 3.88-3.84 (m, 1H), 3.78 (dd, \(J = 5.7, 7.2\) Hz, 1H), 3.76-3.72 (m, 1H), 3.61-3.48 (m, 3H), 3.42-3.36 (m, 4H), 1.85-1.81 (m, 1H), 1.74-1.71 (m, 1H), 1.65-1.51 (m, 8H), 1.46-1.42 (m, 2H). \(^1^3\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 100.8, 99.1, 78.1, 74.3, 71.2, 67.5, 66.5, 62.6, 60.9, 60.4, 30.9, 29.7, 29.6, 25.6, 23.0, 19.9.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-\(O\)-(5-hydroxy)pentyl-\(\beta\)-D-glucose 194

4-Toluenesulfonic acid (9.7 mg, 0.06 mmol) was added to a solution of the diazide 193 (216 mg, 0.57 mmol) in MeOH (5 mL) and the resultant solution was stirred at room temperature until judged complete by TLC. The reaction was then quenched with a solution of sat. NaHCO\(_3\) (5 mL), diluted with water (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated. Flash chromatography (EtOAc/petrol 2:3) of the resultant residue
yielded the title compound as a colourless oil (156 g, 93%). $R_t$ 0.24 (EtOAc/petrol 2:3). IR (ATR): 3338 (O-H), 2095 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.48 (s, 1H), 4.61 (d, $J = 5.7$ Hz, 1H), 4.07 (dd, $J = 0.6, 7.4$ Hz, 1H), 3.79 (dd, $J = 5.7, 7.4$ Hz, 1H), 3.67-3.64 (m, 2H), 3.62-3.54 (m, 2H), 3.42 (s, 2H), 3.36 (s, 1H), 1.65-1.57 (m, 4H), 1.47-1.42 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 100.8, 78.1, 74.4, 71.2, 66.6, 62.8, 61.0, 60.4, 32.5, 29.6, 22.5.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(5-(4-toluenesulfonyl)oxy)pentyl-$\beta$-D-glucose 195

4-Toluenesulfonyl chloride (189 mg, 0.99 mmol) was added to a solution of the diazide 194 (148 mg, 0.49 mmol) in a mixture of CH$_2$Cl$_2$ (3 mL) and pyridine (2 mL) and the resultant solution was stirred at room temperature until judged complete by TLC. The reaction was then concentrated, taken up in EtOAc (20 mL), and washed with water (20 mL), 1M HCl (20 mL), water (20 mL), sat. NaHCO$_3$ (20 mL), brine (20 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:3) of the resultant residue yielded the title compound as a colourless oil (132 mg, 59%). $R_t$ 0.6 (EtOAc/petrol 2:3). IR (ATR): 2096 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.79-7.78 (m, 2H), 7.35-7.34 (m, 2H), 5.47 (s, 1H), 4.60 (d, $J = 5.7$ Hz, 1H), 4.04-4.02 (m, 3H), 3.78 (dd, $J = 5.7, 7.5$ Hz, 1H), 3.55-3.51 (m, 2H), 3.40-3.39 (m, 2H), 3.33 (s, 1H), 2.45 (s, 3H), 1.70-1.65 (m, 2H), 1.59-1.54 (m, 2H), 1.43-1.38 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 144.9, 133.3, 130.0, 128.0, 100.8, 78.3, 74.4, 70.8, 70.4, 66.6, 61.0, 60.5, 29.2, 28.7, 22.2, 21.8.

1,3-Diazido-2-propanol 196

Sodium azide (287 mg, 4.4 mmol) was added to a solution of 1,3-dibromopropanol (0.22 mL, 2.1 mmol) in DMF and the resultant mixture was stirred at 90°C (16 h). The
mixture was diluted with water (30 mL), extracted with EtOAc (3 x 30 mL) and the organic extracts were combined, dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:4) of the resultant residue yielded the title compound as a colourless oil (290 mg, 95%). The ¹H and ¹³C NMR spectra were consistent with that found in the literature.²¹²

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(5-(1,3-diazidoprop-2-yl)oxy)pentyl-β-D-glucose 198

Potassium hydroxide (845 mg, 0.80 mmol) was added to a solution of the diazide 196 (47 mg, 0.33 mmol) in a mixture of DMSO (2 mL) and toluene (3 mL) and the resultant mixture was stirred at room temperature (1 h.). Then, the tosylate 195 (130 mg, 0.29 mmol) was added and the resultant mixture was left to stir at room temperature (3 h.). The reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The organic extracts were combined, washed with brine (20 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (98 mg, 82%). Rᵣ 0.37 (EtOAc/petrol 1:4). IR (ATR): 2091 (N₃) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.48 (s, 1H), 4.60 (d, J = 5.5 Hz, 1H), 4.07 (d, J = 7.4 Hz, 1H), 3.79-3.77 (m, 1H), 3.61-3.53 (m, 5H), 3.42 (s, 2H), 3.36-3.34 (m, 5H), 1.66-1.60 (m, 4H), 1.49-1.43 (m, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 100.8, 78.2, 78.1, 74.3, 71.2, 70.6, 66.5, 60.9, 60.5, 51.8, 29.8, 29.6, 22.8.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(5-(1,3-diaminoprop-2-yl)oxy)pentyl-β-D-glucopyranose 199

Palladium-on-carbon (10%, 50 mg) was added to a solution of the tetraazide 198 (250 mg, 0.59 mmol) in MeOH (5 mL) and the resulting mixture was stirred under an
atmosphere of hydrogen at ambient pressure and room temperature until judged complete by TLC. The mixture was filtered through Celite and concentrated to give the title compound as a colourless oil (167 mg, 88%). Rf 0.03 (MeOH/CH2Cl2/Et3N 1:4:0.5). IR (ATR): 3364 (N-H) cm⁻¹. ¹H NMR (600 MHz, D₂O): δ 5.39 (s, 1H), 4.52 (d, J = 5.4 Hz, 1H), 4.13 (d, J = 7.4 Hz, 1H), 3.77 (dd, J = 6.6, 6.6 Hz, 1H), 3.65-3.54 (m, 4H), 3.43-3.39 (m, 1H), 3.29 (s, 1H), 2.99 (s, 1H), 2.84 (s, 1H), 2.77-2.66 (m, 4H), 1.66-1.58 (m, 4H), 1.45-1.39 (m, 2H). ¹³C NMR (151 MHz, D₂O): δ 103.4, 83.1, 82.7, 77.7, 71.0, 70.8, 66.9, 53.2, 51.4, 42.8, 29.9, 29.7, 23.1. HR-MS (ESI): m/z 319.2343; [M+H]+ requires 319.2345.

O-(2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl) 2,2,2-trichloroacetimidate 202

Methylamine solution (11.57 M, 0.29 mL, 3.32 mmol) was added to a solution of penta-O-acetyl-β-D-galactopyranose (1.0 g, 2.56 mmol) in THF (10 mL) and the resultant solution was stirred (30 min.) The solution was then concentrated and the residue taken up in EtOAc, washed with water (30 mL), 1 M HCl (30 mL), sat. NaHCO₃ (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:1) of the resultant yellow oil yielded 2,3,4,6-tetra-O-acetyl-β-D-galactopyranose (201) as a colourless oil (795 mg) which was used without further purification. To a solution of 201 (790 mg, 2.27 mmol) in CH₂Cl₂ (10 mL) was added trichloroacetonitrile (0.46 mL, 4.6 mmol) and DBU (10 μL, 0.07 mmol). The resultant solution was stirred at room temperature (2 h.) and then concentrated to 25% of the original volume, applied to a short flash chromatography column and eluted (EtOAc/petrol 3:7) to give the title compound as a cream solid (814 mg, 74%). The ¹H NMR spectrum was consistent with that found in the literature.
1,6-Anhydro-3-O-(6-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxy)hexyl-2,4-
diazido-2,4-dideoxy-β-D-glucose 203

4 Å molecular sieves (350 mg) were added to a stirred solution of the alcohol 186 (79 mg, 0.25 mmol) and the trichloroacetimidate 202 (151 mg, 0.31 mmol) in CH₂Cl₂ (5 mL). After 0.5 h., BF₃.OEt₂ (0.002 mL, 0.16 mmol) was added to the resultant suspension at -30°C. The suspension was then stirred at 0°C (0.5 h.), then neutralised with Et₃N, filtered through Celite, and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil. (37 mg, 22%). Rₐ 0.28 (EtOAc/petrol 1:1). IR (ATR): 2099 (N₃), 1747 (C=O) cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.48 (s, 1H), 5.39 (d, J = 3.4 Hz, 1H), 5.20 (dd, J = 8.0, 10.4 Hz, 1H), 5.02 (dd, J = 3.5, 10.5 Hz, 1H), 4.61 (d, J = 5.6 Hz, 1H), 4.45 (d, J = 8.0 Hz, 1H), 4.21-4.17 (m, 1H), 4.14-4.10 (m, 1H), 4.06 (d, J = 7.4 Hz, 1H), 3.91-3.87 (m, 2H), 3.79 (dd, J = 5.8, 7.2 Hz, 1H), 3.60-3.45 (m, 3H), 3.41 (s, 2H), 3.36 (s, 1H), 2.15 (s, 3H), 2.05 (s, 6H), 1.99 (s, 3H), 1.61-1.56 (m, 4H), 1.35 (br s, 4H). ¹³C NMR (151 MHz, CDCl₃): δ 170.6, 170.4, 170.4, 169.5, 101.5, 100.8, 78.2, 74.4, 71.2, 71.1, 70.7, 70.2, 69.1, 67.2, 66.6, 61.4, 61.0, 60.6, 29.8, 29.5, 25.9, 25.7, 20.9, 20.8, 20.8, 20.8.

1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-O-(6-(β-D-galactopyranosyl)oxy)hexyl-β-D-
glucose 204

Sodium methoxide (10 mg) was added to a solution of the diazide 203 (123 mg, 0.19 mmol) in MeOH (3 mL) and the mixture was stirred until judged complete by TLC. The solution was quenched with resin (Amberlite IR-120, H⁺), filtered, and concentrated. Flash chromatography (EtOAc) of the resultant residue yielded the title
compound as a colourless oil. (75 mg, 82\%). $R_f$ 0.63 (MeOH/EtOAc 1:9). IR (ATR): 3391, 2514 (O-H), 2097 (N-O) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.45 (s, 1H), 4.65 (dd, $J = 1.0$, 5.7 Hz, 1H), 4.20 (d, $J = 7.6$ Hz, 1H), 4.09 (dd, $J = 0.90$, 7.5 Hz, 1H), 3.92-3.88 (m, 1H), 3.83 (dd, $J = 0.80$, 3.3 Hz, 1H), 3.76-3.71 (m, 3H), 3.59-3.44 (m, 7H), 3.40-3.39 (m, 1H), 3.38 (s, 1H), 1.65-1.59 (m, 4H), 1.42-1.41 (m, 4H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 105.0, 101.9, 79.3, 76.6, 75.5, 75.1, 72.6, 71.8, 70.7, 70.3, 67.3, 62.5 61.4, 61.3, 30.8, 30.7, 27.1, 26.9.

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-(6-(β-D-galactopyranosyl)oxy)hexyl-β-D-glucose 205

Palladium-on-carbon (10%, 50 mg) was added to a solution of the diazide 204 (65 mg, 0.14 mmol) in MeOH (2 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until judged complete by TLC. The mixture was filtered through Celite and concentrated to give the title compound as a colourless oil (38 mg, 67\%). $R_f$ 0.03 (MeOH/CH$_2$Cl$_2$/Et$_3$N 1:4:0.5). IR (ATR): 3350 (N-H) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 5.28 (s, 1H), 4.39 (d, $J = 5.4$ Hz, 1H), 4.20 (d, $J = 7.6$ Hz, 1H), 4.12 (dd, $J = 1.0$, 6.9 Hz, 1H), 3.92-3.88 (m, 1H), 3.83 (dd, $J = 1.0$, 3.3 Hz, 1H), 3.76-3.71 (m, 2H), 3.68 (dd, $J = 6.4$, 6.4 Hz, 1H), 3.56-3.43 (m, 6H), 3.20 (s, 1H), 2.84 (s, 1H), 2.76 (s, 1H), 1.64-1.62 (m, 2H), 1.558-1.56 (m, 2H), 1.44-1.37 (m, 4H). $^{13}$C NMR (151 MHz, CD$_3$OD): $\delta$ 105.0, 104.3, 87.0, 77.9, 76.6, 75.1, 72.6, 70.8, 70.7, 70.3, 67.0, 62.5, 53.5, 53.3, 30.9, 30.7, 27.1, 26.8. HR-MS (ESI): $m/z$ 423.2353; [M+4H]$^+$ requires 423.2343.

Cytotoxicity in cancer cell lines

Cisplatin, used as a reference compound, was obtained from Sigma Aldrich. The human HeLa cervix and oestrogen receptor-positive MCF-7 breast cancer cell lines were obtained from Sigma Aldrich. The cells were grown as monolayer cultures in
Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1% glutamine, and 0.5% penicillin/streptomycin. The cultures were grown in T25 flasks at 37°C and 5% CO₂ in air, and 95% relative humidity.

Cytotoxicity was determined using a colorimetric metabolism microculture assay (MTT assay, MTT = 3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyl-2H-tetrazolium bromide). HeLa and MCF-7 cells were harvested from culture flasks by trypsinisation and seeded into 96-well microculture plates (plates from where) in cell densities of 7.5 x 10³ and 10 x 10³ cells/well, respectively, to ensure exponential growth throughout drug exposure. After 24 hours of pre-incubation, cells were exposed to various concentrations of the test compounds in 100 μL/well complete DMEM culture medium for 72 hours. Cells were exposed to 50 and 200 μM concentrations of compounds in triplicate for screening assays and concentrations ranging from 1mM to 0.78 μM and 200 μM to 0.20 μM in triplicate for IC₅₀ assays. At the end of exposure, drug solutions were replaced by 100 μL/well phenol-free DMEM (supplemented with 10% FBS and X mM glutamine) plus 10 μL MTT as a solution in phosphate-buffered saline (5 mg mL⁻¹). After incubation for 3 hours. 100 μL of detergent solution (40% vol/vol DMSO in 2% vol/vol glacial acetic acid with 16% wt/vol SDS, at pH 4.7) was added to each well and left to stand for 16 hours. Absorbances were then measured at 570 nm using a SpectraMax 190 plate reader and absorbance values standardised to the drug-free control wells and plotted as [Pt] against % viability for screening assays. IC₅₀ values were calculated by interpolating dilution curves using Grafit.
Chapter 2

Investigations into carbohydrate-based ligands for biologically active copper(II) complexes
INTRODUCTION

Schiff bases

The German chemist, Hugo Schiff, gave his name to a class of compounds entitled Schiff bases: imines formed from the condensation of a primary amine and an aldehyde or ketone which have the general structure $\text{R}_2\text{C}=\text{NR'} (\text{R'}\neq\text{H})$ 206 (Figure 2.1).\textsuperscript{231-232} One of the best-known Schiff bases is $N,N'$-bis(salicylidine)ethylenediamine 207 (salen) (Figure 2.1), synthesised from the condensation of 1,2-diaminoethane and two equivalents of salicylaldehyde.

![Figure 2.1](image)

Figure 2.1 – The general structure of a Schiff base and the popular salen ligand 207.

Salen and its derivatives

Pfieffer and colleagues first described the production of 207 and some associated metal complexes in 1933.\textsuperscript{233} The $N,N',O,O'$ motif usually results in tetradeinate coordination to a range of transition and main group metals.\textsuperscript{234} The term ‘salen’ largely represents a class of salen derivatives containing the original $N,N',O,O'$ diimine/phenolate ligand motif with a variety of backbones and phenyl substitutions such as 208 and 209 (Figure 2.2).\textsuperscript{235-236} Even more broadly, any ligand with a diimine motif and various O donor atom motifs (e.g. 210)\textsuperscript{237} or even amino-salen-type complexes (e.g. 211)\textsuperscript{238} can be referred to as a salen-type ligand (Figure 2.2.).

Salen ligands form relatively stable complexes with a wide range of metals with different oxidation states, in a variety of coordination geometries.\textsuperscript{239} The versatility of coordination geometry and the ability to fine tune complexes by altering the bridge between the two diimines, differing the substituents on the phenyl ring, or removing the phenyl ring entirely gives the resultant complexes broad applicability. Metal-salen complexes are generally found to be active asymmetric catalysts in many different
reactions, useful enzyme mimics, and potential therapeutics, as a small example of their scope.\textsuperscript{239-240} As a result of the wide spread applicability, the salen ligand family is often referred to as a privileged ligand class.\textsuperscript{241}

![Figure 2.2 - Some examples of the diverse variations of the salen ligand.](image)

This introduction gives a brief overview of the varied applications of metal salen complexes. The focus is on the traditional definition of a salen complex, such as \textbf{208} and \textbf{209}. Demi- and reduced-salen ligands, such as \textbf{210}, \textbf{211}, and related complexes, are only mentioned if they are relevant to the synthetic work presented herein.

**Enzyme mimics**

One of the applications of metal-salen complexes is as enzyme mimics. The enzyme class of superoxide dismutases (SOD) act as antioxidants, protecting cells by catalysing the dismutation of the superoxide radical (\(O_2^-\)) into hydrogen peroxide (\(H_2O_2\)) (which is further broken down) and molecular oxygen (\(O_2\)). There are several types of SODs, classified according to the different metals centres; the dual copper and zinc class (CuZn-SODs) as well as manganese (Mn-SODs), iron (Fe-SODs) and nickel (Ni-SODs) classes, of which humans have CuZn- and Mn-SODs. Dysfunction
of these enzymes and build-up of toxic superoxide radicals have been implicated in several disease states including motor neurone disease, cancer, and cardiovascular disease.\textsuperscript{242-243}

![Figure 2.3 – Representations of the active sites of the human Cu,Zn and Mn superoxide dismutases 212 and 213.](image)

The active site of the Mn-SOD, 213 (Figure 2.3), contains the manganese atom surrounded by one aspartate and three histidine residues, and a OH/H\textsubscript{2}O residue in a trigonal bipyramidal geometry.\textsuperscript{244} The Cu,Zn-SOD active site, 212 (Figure 2.3), contains a copper atom surrounded by four histidines and one solvent molecule in a distorted square pyramidal geometry.\textsuperscript{244-245} One of the histidine residues links the copper to the zinc centre which is in a tetrahedral geometry with two other histidines and one aspartate residue. In order to understand the mechanism of cation of the enzymes, simple synthetic mimics of the active site were prepared. The numerous N and O donor atoms enclosing the active site resulted in the first SOD mimics being porphyrin based, but salen complexes soon featured as well.\textsuperscript{246-247} Research has focussed on Mn-type mimics, possibly due to the lower toxicity of manganese compared to iron and copper, whose redox activity can lead to dangerous oxidative stress \textit{in vivo}.\textsuperscript{247-248} Malfroy, Jacobsen, and colleagues reported one of the first examples of an Mn(III)-salen complex having SOD mimetic properties such as 214 (Figure 2.4).\textsuperscript{249} Since then, variations on the Mn(III)-salen theme such as 215 and 216 (Figure 2.4) have aimed at improving the \textit{in vivo} stability and SOD activity for eventual use as therapeutics (discussed further below).\textsuperscript{250}
Another enzyme, galactose oxidase (GAO), found in fungi, catalyses the oxidation of D-galactose. The active site of the enzyme contains a copper atom coordinated to two histidine residues and two tyrosine residues, one of which is a radical tyrosyl species (217, Figure 2.5). The fifth coordination site is taken up with the carbohydrate substrate. The radical form allows for the two-electron alcohol oxidation to occur, as the copper is limited to the single electron redox process Cu(I)/Cu(II).

This radical-based metal/ligand redox cooperativity was intriguing and simple enzyme mimics were sought to better understand the mechanism of oxidation. Knowledge that
ligand radicals also occurred upon oxidation of salen complexes promoted the adoption of the salen framework as a model for GAO. Early examples of Cu(II)-salen complex models included work by Kitajima and colleagues 218, 256 Wang and Stack 219, 253 Pratt and Stack 220, 257 and Orio and co-workers 221 (Figure 2.5)258. Investigations into the electronic and structural characteristics of the models revealed that the substituents on the phenolates had to be ortho- and para- to the hydroxyl moiety for stabilisation of the phenoxy radical. 253, 259 In addition, some flexibility was required in the salen backbone to accommodate geometrical rearrangement from distorted square planar to tetrahedral on reduction of Cu(II) to Cu(I). 251, 260 Without this flexibility, the model could not exhibit all the oxidation states observed in the natural enzyme. A new methodology by Campbell and Nguyen allowed for the preparation of salen-type molecules with non-symmetrically substituted phenolates. 261 The subsequent design of salen models with one phenolate containing a thioether moiety increased model fidelity with the GAO active site, as Pratt and colleagues have shown with 222 (Figure 2.5).262
Figure 2.5 – Examples of salen-based ligands for GAO mimics.

Several other enzymes have been successfully modelled with salen complexes, which a recent review by Erxleben describes.\textsuperscript{239} The modularity of salen ligands has made them excellent simple enzyme mimics. However, salens lack the ability to mimic the steric bulk of the protein structure that shields the active site in enzymes which limits their usefulness. Complex deactivation often occurs during analysis. In terms of future use as therapeutics, if the salen complex decomposes \textit{in vivo}, redox active metals may be released into cells, potentially disrupting the reactive oxygen species homeostasis. In addition, the phenyl rings incorporated into the ligand are potentially prime DNA intercalators, and,
indeed, the cytotoxicity of salen complexes has been well researched and is discussed below.\textsuperscript{239,263-267} These factors limit the use of salen complexes as enzyme models, but their use in biocatalysis has inspired their application to synthetic catalysis.

**Salen ligands as synthetic catalysts**

Kochi and colleagues designed some of the first salen-based complexes, \textbf{223} and \textbf{224}, for catalysis (Figure 2.6).\textsuperscript{268-269} Jacobsen and colleagues,\textsuperscript{270-271} and Katsuki and co-workers\textsuperscript{272} also produced similar examples around the same time (\textbf{225} and \textbf{226}, and \textbf{227} respectively, Figure 2.6). These first seminal complexes were investigated as catalysts in epoxidations, with the chirality of compounds \textbf{225-227} providing stereoselective outcomes.

![Diagram of metal-salen complexes](image)

**Figure 2.6** – A generalised scheme of the epoxidation of alkenes and some examples of metal-salen complexes used in this type of epoxidation.
The scope of metal-salen catalysts expanded to include aziridinations, asymmetric epoxide ring opening reactions, conjugate additions, and Diels-Alder cycloadditions, among other reactions. Once the reaction scope of salen catalysts was established, focus shifted to improving recovery and recyclability of the catalysts.

Carbohydrate-based salen ligands for catalysis

The modularity, ability to fine-tune structures, and inherent chirality of carbohydrates presents an ideal scaffold for chiral catalyst design. However, of the many examples of salen-based catalysts, those containing carbohydrates are not common. The few examples are mainly of Mn(III)-salen complexes used in epoxidations.

Yan and Klemm produced an β-L-idofuranose-based Mn(III)-salen complex (Figure 2.7) that catalysed the epoxidation of alkenes in moderate yields, in a manner similar to Jacobsen’s catalyst (Figure 2.6). It was noted that the attachment of a single stereogenic centre (C5) to the salen backbone was enough to induce weak enantioselectivity. Lin and RajanBabu synthesised an α-D-glucopyranose salen derivative (Figure 2.7). This formed a complex with yttrium which could be used to kinetically resolve the acyl transfer products of racemic alcohols.

![Figure 2.7 – Examples of an early salen complex 228 and ligand 229, incorporating a carbohydrate moiety.](image-url)
Borriello and colleagues produced a suite of salen ligands with α-D-glucose and α-D-mannose derivatives as the backbone.\textsuperscript{290} The related manganese complexes of the type 230 were tested in the epoxidation of substituted styrenes and it was found that glucose-based complexes gave the best diastereomeric and enantioselectivity (Figure 2.8). This was thought to be due to the preservation of C2 symmetry in the glucose-based molecules.

![Image of Mn(III)-salen complex](230)

**Figure 2.8** – An example of the Mn(III)-salen complexes synthesised by Borriello et al.

Zhao and colleagues synthesised a set of Mn(III)-salen complexes with a pendant α-D-glucofuranose derivative on the phenyl rings of the salen ligand.\textsuperscript{291} Compounds contained either an achiral backbones, ethylenediamine, or a chiral backbone; racemic 1,2-diaminocyclohexane, or (R,R)-1,2-diaminocyclohexane. Compound 231 (Figure 2.9) was the most active catalyst in the epoxidation of styrene and related alkenes. They extended their original ligand set to include pendant derivatives of α-D-mannofuranose and α-D-galactopyranose, as well as α-D-glucofuranose, di-substituted at the 3- or 5-positions of the phenyl rings (232-238, Figure 2.9).\textsuperscript{292} It was observed that of the manganese complexes evaluated in the epoxidation of styrene and related alkenes, C3-substituted complexes were of lower activity. This was thought to be due to the increase in steric hindrance around the metal centre, restricting substrate binding. Pendant carbohydrates with achiral or racemic salen bridges were less enantioselective than those with chiral bridges, indicating that the combination of a pure chiral backbone and chiral carbohydrate motif improves enantioselectivity.
Finally, Ruffo and co-workers prepared the complexes 239-243 (Figure 2.10), pseudo-enantiomers of the complexes reported by Borriello and colleagues (Figure 2.8). The coordinating nitrogen atoms were shifted around the glucopyranose ring from C2/C3 to C1/C2, changing the relative stereochemistry of the ligand as a whole. The Mn(III) complexes were evaluated for activity in the epoxidation of styrenes and the pseudo-enantiomers gave the opposite enantio-induction. Removing the tert-butyl groups at 3' eliminated any enantioselection.

From the examples of carbohydrate scaffolds for salen ligands and complexes, it is clear that carbohydrate-based complexes have interesting activities. Their chirality can induce stereoselection and a facile modification of ligand attachment can be used to prepare pseudo-enantiomeric catalysts. However, carbohydrate-based metal-salen complexes do not currently challenge the established salen catalysts, which generally show better activity.
Medical applications

The use of salen complexes as enzyme mimics inspired research into their potential as therapeutics.

From superoxide dismutase mimics, the compounds 214-216 (Figure 2.4) were investigated for their reactive oxygen species (ROS) scavenging abilities. While certain levels of ROS, such as superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hypochlorite (OCl$^-$) and peroxynitrite (ONOO$^-$), are needed for proper biological function, imbalance in their levels has been implicated in a range of neurodegenerative and cardiovascular diseases, as well as cancer and associated radiation injury. The ability to scavenge ROS and control levels of ROS in vivo is a potential preventative treatment for neurological and cardiovascular disease, as well as mitigation for radiation-associated injury to healthy cells. In addition to 214-216, a variety of other Mn(III)-salen complexes have also been studied for their antioxidant abilities.

In a somewhat of a contradiction to the previous use of metal-salen complexes as ROS scavengers, similar compounds have been investigated as ROS inducers for cancer treatment. Elevated levels of ROS have been associated with the initiation and
growth of tumours.\textsuperscript{302-303} However, if cancer cells already operate under high levels of ROS, further increase may place cancerous cells under lethal levels of oxidative stress, while the ROS levels in normal cells remain below the toxicity threshold after treatment. To this end, interest in redox active metal complexes that generate ROS has increased, and salen complexes of metals such as Cu(II) 244 and 246,\textsuperscript{304-305} Ni(II) 245,\textsuperscript{304} Co(II) 247-250,\textsuperscript{306-307} and Fe(II/III) 251-253\textsuperscript{236,308} have been studied for their ROS generating activity and potential chemotherapeutic application (Figure 2.11). However, the majority of these studies did not implicate intrinsic ROS generation as the main mode of action. Often external oxidants/reductants were required for redox activity and, in one case, a non-redox active compound was more cytotoxic.\textsuperscript{306} It was thought that the mode of action was multimodal and nearly always included some form of metal-salen complex-DNA interaction.

Interest in the cytotoxicity of metal-salen complexes through direct interaction with DNA opened up another avenue of metal-salen research. In addition to the types of metal-salen complexes shown in Figure 2.11, the addition of pendant DNA groove-binding moieties to salen ligands facilitated the binding of complexes such as 254-257 to DNA resulting in DNA cleavage (Figure 2.12).\textsuperscript{263} The cationic Cu(II) complexes 258 and 259 were shown to bind DNA, changing from intercalating to groove-binding on changing the salen bridge from a phenyl to an ethylene motif (Figure 2.12).\textsuperscript{264} Interestingly, the Ni(II)-salen complexes 260 and 261 have been shown to be excellent quadruplex DNA binders (Figure 2.12).\textsuperscript{265} Other metals, including Cu(II) and Zn(II), have also been identified as binding to G-quadruplex DNA, but Ni(II) appears to provide the most stability to the DNA structure.\textsuperscript{239,266,309} A subset of salen complexes, such as 262, coordinating a demi-salen ligand and a DNA intercalating ligands such as 1,10-phenanthroline or 2,2-bipyridine, have shown activity against cancer cell lines (Figure 2.13).\textsuperscript{267}

Ultimately, the overall mode of action of salen complexes comprises many different aspects, and differs from metal to metal and ligand to ligand.\textsuperscript{239} One significant, repeated finding is that salen complexes are active against cisplatin-resistance cell lines. This suggests that these compounds have different modes of action to that of cisplatin and other platinum-based chemotherapeutics. Current efforts are focussed on developing novel salen complexes as new chemotherapy agents for cancer treatments that circumvent existing chemo-resistance.
Figure 2.11 – Examples of cytotoxic salen complexes with activity potentially due to ROS generation.
Figure 2.12 – Examples of metal-salen complexes investigated for DNA-binding abilities.
Figure 2.13 – The demi-salen complex 262, demonstrated to have activity against a range of cancerous cell lines.

In addition to the focus on cancer and neurodegenerative diseases, salen complexes have also been studied for their antibacterial activity and as a potential treatment for diabetes.\textsuperscript{310-314}

Carbohydrate-based salen ligands for therapeutics

Currently there are limited salen-based ligands with incorporated carbohydrates that have been synthesised for biological applications. The tetrahydrosalen ligands 263 and 264 were functionalised with pendant glucose molecules as a potential treatment of Alzheimer’s disease (Figure 2.14).\textsuperscript{315-316} The ligands were proposed to act as metal chelators, binding to and reducing the concentration of Zn(II) and Cu(II) \textit{in vivo}. Metal-ion chelation therapy is seen as a promising neurodegeneration preventative treatment.\textsuperscript{317} These metals have been associated with promoting amyloid-β plaque formation and increasing oxidative stress in the brain, which are pathologies of some neurodegenerative diseases. In the examples of 263 and 264, carbohydrate moieties were included to facilitate transport of the active ligand across the blood-brain barrier (BBB), as hexose transporters (GLUTs) are highly prevalent at the BBB.\textsuperscript{318} In addition, carbohydrates may increase drug solubility. \textit{In vivo} testing demonstrated that the ligands did reduce metal-promoted Aβ aggregation.\textsuperscript{315}
Salen ligands are a privileged ligand class and the resulting complexers find use in many areas of chemistry. The 1,6-anhydro scaffold 51 from Chapter 1 incorporates a diamine moiety, separated by a 1,3-carbon bridge. Following on from examples presented in this introduction, it was thought to be of interest to examine the scope of this diamine scaffold as a salen backbone. The 1,6-anhydro scaffold provides a novel material, structurally different from the previous scaffolds used to prepare salen-type ligands. In addition to the 1,6-anhydro backbone, different substituents at C3 and on the phenyl ring can be explored for their effect on the properties of the ligands and metal complexes (Figure 2.15). Once prepared, the spectroscopic and electronic properties of the complexes will be investigated, as well as their biological activity. Although there are a limited number of carbohydrate-based salen ligands synthesised for biological applications, metal-salen complexes, in general, have shown interesting biological activity. Therefore, it is of interest to evaluate the activity of the complexes against various cancer cell lines.
Figure 2.15 – Proposed structure of 1,6-anhydro-based metal-salen complexes from 51.
RESULTS AND DISCUSSION

Synthesis of carbohydrate-based salen ligands and copper(II) complexes

The first step in exploring the potential of the 1,6-anhydro scaffold as a salen backbone was to build upon the diamine 51, synthesised in Chapter 1. It provided the amino moieties primed for imine formation on treatment with a salicylaldehyde derivative. In addition, as also discussed in Chapter 1, simple modifications were to be made to C3, to establish patterns of activity due to small structural changes. Since ester moieties had proven to be reactive and amide derivatives might provide alternative donor atoms for complexation, an ether linkage was chosen as a relatively inert functional group. Two salicylaldehyde derivatives, salicylaldehyde and 3,5-di-tert-butylsalicylaldehyde, were chosen for imine formation.

![Diagram of 1,6-anhydro-based salen ligands](image)

**Figure 2.16** – General design of 1,6-anhydro-based salen ligands.

Starting from the diazide 53, treatment with sodium hydride and an appropriate alkyl bromide afforded the related ether 100, 101, or 265 *(Scheme 2.1)*. Reduction of the azides 53, 100, 101 and 265 with palladium-on-carbon and hydrogen gas gave the diamines 51, 109, 110, and 266, which, on treatment with the appropriate aldehyde, formed the target salen ligands 267-271. Imine formation was tracked by the formation of a strong signal at around 1630 cm\(^{-1}\) in the infrared spectrum, which is due to C=N stretching.
Scheme 2.1 – a) NaH, RX (X = I or Br), DMF; b) Pd/C, H$_2$, MeOH; c) salicylaldehyde or 3,5-di-tert-butylsalicylaldehyde, MeOH.

The proximity and relative stereochemistry of the two Schiff base motifs was also of interest and, fortuitously, the pathway to the azide 55 in Chapter 1 also gave the diol 62 in the D-idose form (Scheme 1.2). The stereochemistry of 62 was such that it could be used to produce a 2/3- or 3/4-diazide 272 or 273 following the methods described in Chapter 1, namely activation, protection and displacement (Figure 2.17). These diazides could then be used to prepare the salen ligands 274 and 275. However, the relative reactivities of the hydroxyl groups at C2 and C4 were undetermined and it was unknown if both or only one of the diazide configurations could be prepared.
In order to determine the relative reactivities at C2 and C4, it was proposed to treat the diol 62 with benzoyl chloride to give the dibenzoate 276, followed by controlled deprotection, would allow for both alcohols 277 and 278 to be formed. From the amount of each alcohol formed, an understanding of the relative reactivities at the C2 and C4 positions could be determined. The diol 62 was treated with benzoyl chloride to give the presumed dibenzoate 276, which was then treated with catalytic sodium methoxide in methanol to give mainly the fully deprotected alcohol 62, and a small amount of the mono-benzoylated products 277 (Scheme 2.2). Interestingly the 4-O-benzoyl derivative 278 was not observed in the 1D and 2D $^1$H NMR experiments of isolated fractions.

**Figure 2.17** – Proposed pathways to C2/3 or C3/4 salens.
The deprotection reaction demonstrated that the hydroxyl group at C4 was marginally more susceptible to deprotection than that at C2. It was thought that selective protection of C2 in the diol 62 would give the benzoate 277 as the major product. With careful management of reactant equivalents and temperature, the benzoate 277 was prepared from the diol 62 (Scheme 2.3). Activation of the hydroxyl group on 277 as a triflate gave 279, followed by displacement with sodium azide gave the diazide 280 in excellent yield. With the diazide 280 in hand, treatment with sodium methoxide gave the alcohol 272, followed by potassium hydroxide and bromopropane gave the propyl ether 281. Reduction in the presence of palladium-on-carbon and hydrogen gas, followed by addition of 3,5-di-tert-butylsalicylaldehyde gave the C3/4 Schiff base ligand 274 in good yield.
Scheme 2.3 – a) BzCl, CH₂Cl₂, Pyr.; b) Tf₂O, CH₂Cl₂, Pyr. c) NaN₃, DMF; d) NaOMe, MeOH; e) KOH, CH₃CH₂CH₂Br, DMSO; f) i) Pd/C, H₂, MeOH; ii) 3,5-di-tert-butylsalicylaldehyde, MeOH.

Finally, based on the knowledge that carbohydrates are used to aid in the solubility of salen ligands (Compounds 263 and 264, Figure 2.14) and it is possible that monosaccharides such as glucose and galactose may act as ‘directing motifs’, targeting cancer cells over normal cells, it was thought useful to explore the effect of having a free pendant carbohydrate attached to a salen ligand, such as 282 and 283 (Figure 2.18).
The two chosen ligands, 282 and 283, were thought to be able to be made from the bromoalcohol 284 (Scheme 2.4). Protection of 284 with 3,4-dihydro-2$H$-pyran gave the ether 285 in good yield. The alcohol 196 was treated with NaH and then the bromide 285 to give the diazide 286 in good yield. This diazide was the precursor to the salen ligand and was chosen for the 1,3-diamine bridge being similar to that of the 1,6-anhydro carbohydrate scaffold previously used.

Removal of the tetrahydropyranyl group under acidic conditions gave the alcohol 287, which was combined with the $\alpha$-trichloroacetimidate 202 to give, after deacetylation, the diazide 288 (Scheme 2.4). The diazide 288 was reduced, in the presence of palladium-on-carbon and hydrogen gas, to give the presumed diamine 289 in good yield, which was then treated with either salicylaldehyde or 3,5-di-$\text{tert}$-butylsalicylaldehyde, to give the desired salen ligands 282 and 283.
Scheme 2.4 – a) 3,4-dihydro-2H-pyran, TsOH, CH₂Cl₂; b) NaH, DMF; c) PhMeSO₂OH, MeOH; d) i) 4 Å sieves, TMSOTf, CH₂Cl₂; ii) NaOMe, MeOH; e) Pd/C, H₂, MeOH; f) salicylaldehyde or 3,5-di-tert-butylsalicylaldehyde, MeOH.

Inspired by the recent literature concerning Cu(II)-salen chemotherapy agents\textsuperscript{322-323}, the library of salen ligands \textbf{267-271}, \textbf{274}, \textbf{282} and \textbf{283} were treated with copper(II) acetate monohydrate to afford the copper complexes \textbf{290-297} in moderate to excellent yields (Scheme 2.5).
Scheme 2.5 – a) Cu(OAc)$_2$·H$_2$O, MeOH or EtOH.

The inclusion of DNA-intercalators, such as 1,10-phenanthroline and 2,2'-bipyridine, in metal complexes has been shown to increase the biological activity.$^{322,324-326}$
complexes with an intercalating ligand may bind to the DNA via the metal atom, DNA-intercalator or both. It is also thought that square planar complexes with intercalating ligands can insert further into a DNA strand and may display a higher affinity for DNA than tetrahedral or octahedral complexes. Copper(II) complexes, such as 262 and 298, with the addition of an intercalating ligand, have shown biological activity against cancer cell lines (Figure 2.19). Therefore, it was of interest to investigate the synthesis of a mixed salen/phenanthroline copper complex. It was thought that a carbohydrate-based demi-salen ligand such as 299 (Scheme 2.6) could be combined with phenanthroline to produce a tetra- or penta-coordinated copper complex such as 300 (Figure 2.19).

![Figure 2.19](image)

**Figure 2.19** – Literature copper(II)-salen complexes 262 and 298 with intercalating ligands and the proposed carbohydrate-based complex, 300.

In an attempt to synthesise a demi-salen/phenanthroline Cu(II) complex, the amine 301 was treated with salicylaldehyde, followed by the addition of a solution of phenanthroline in methanol, then a solution of aqueous copper(II) acetate monohydrate (Scheme 2.6). The resultant grey-green precipitate was recrystallised from MeOH/CH2Cl2 to give crystals which were subject to X-ray crystallographic analysis. Unfortunately, the desired compound 300 was not obtained, but the unexpected copper(II) dimer, 302, containing only the demi-salen ligand 299 (presumably formed in situ), was observed. Dimers of this nature have been previously observed. It is thought that the square planar dimer is more stable than the proposed square pyramidal geometry of the complex incorporating the phenanthroline
ligand. Despite varying the reaction conditions, using different amounts of each ligand and the order in which they were added, the target compound could not be synthesised.

![Scheme 2.6](image)

**Scheme 2.6** – a) Salicylaldehyde, MeOH; b) 1,10-phenanthroline, then Cu(OAc)$_2$·H$_2$O, MeOH, H$_2$O.

**Characterisation of the carbohydrate-based salen ligands and related Cu(II) complexes**

The physical and chemical properties of salen ligands and complexes have been widely studied and are well documented in the literature. It was of interest to see if the addition of the 1,6-anhydro carbohydrate scaffold significantly affected the properties of the ligands and related Cu(II) complexes, compared to similar literature examples.

**Electronic absorption spectra of the carbohydrate-based salen ligands and related Cu(II) complexes**

The UV-Visible spectra of the archetypal salen ligand, $N,N'$-bis(salicylidene)ethylenediamine 207, and its Cu(II)-salen complex 303, and the related 1,3-bridged ligand 304, as well as their tert-butyl derivatives 305, 306, and 307 have been previously studied (Figure 2.20).$^{334-342}$
Figure 2.20 – The parent salen ligand 207, the related copper complex 303, the tert-butyl ligand and Cu(II) complex 305 and 306 and the 1,3-bridged ligands 304 and 307.

The salen ligand 207 and Cu(II) complex 303 were synthesised using literature methods. The UV-Visible spectra was obtained for 207 and 303 and agreed with previous literature reports (Figure 2.21). The ligand 207 has been previously reported to show absorbances around 230 nm, 260 nm and 320 nm in CH$_2$Cl$_2$. The two higher energy bands were generally assigned to π→π* transitions of the phenoxy chromophore and the lower energy band was assigned to the imine group.

The Cu(II) complex 303 was reported to show absorbances around 240 nm, 280 nm, 370-380 nm and 560 nm. The lowest energy band was assigned to d-d transitions of the metal centre. The assignment of the next band between 370-380 nm varies in the literature. Some report this band as a π→π* transition, red-shifted on complexation to a metal centre. This band has also been reported as only a charge transfer (CT) band and as an amalgamation of several overlapping bands due to π→π* transitions and CTs. The CT band is influenced by the solvent, and solvatochromic effects can be used to ascertain if bands in this area are due to CTs. The higher energy bands were still attributed to π→π* transitions of the phenoxy chromophore, red-shifted on complexation.

Since the carbohydrate-based ligands contained a 1,3-diamine bridge, as opposed to the 1,2-diamine bridge in 207, literature spectra of the salen ligand derivative N,N'-bis(salicylidene)propylenediamine 304 were also used as a comparison.
was reported to show absorbances at 256 nm, and 316 nm in CH$_2$Cl$_2$. These bands do not differ greatly from 207, and it was inferred that the addition of one carbon in the diamine bridge does not significantly alter the electronic properties of the ligand and complex.

**Figure 2.21** – UV-Vis absorption spectra for the salen ligand 207 and the related Cu(II) complex 303 as 20 μM solutions in CH$_2$Cl$_2$.

UV-Visible spectra were obtained for the ligands 267-271, 274, and 282 and 283, as well as the related Cu(II) complexes 290-297 and 302, as CH$_2$Cl$_2$ solutions (20 μM).

The spectra of the carbohydrate salen derivatives 267-269 and 282 all exhibited three main absorption bands at approximately 230 nm, 255 nm, and 320 nm, very similar to the prototype salen ligand. These signals were attributed to π→π* transitions due to the conjugated phenyl rings (230 nm and 255 nm) and to a π→π* transition of the imine group (320 nm) (**Figure 2.22 A**).

For complexes 290-292 and 296, there was a red shift of the ligand-based absorption bands to approximately 249 nm, 275 nm, and 366 nm, observed presumably due to metal complexation (**Figure 2.22 B**). However, the band around 366 nm appears to have a shoulder on the right side, which may be indicative of an overlapping of ligand-based bands and CT bands, as described above. The spectra of the complexes were also conducted in methanol. Comparison between the spectra revealed a slight solvatochromic effect which suggests that the band may be an amalgamation of both CT and ligand-based bands (**Figure 2.24**). Again, the band absorbance values were similar to those reported for the Cu(II)-salen complex and derivatives. In addition,
a broad, weak absorbance at around 570 nm was observed in the case of Cu(II)-salen, which was attributed to a d-d transition (Figure 2.23). This band was much weaker and harder to observe in the spectra of the carbohydrate-based complexes, but appeared to be slightly red-shifted in comparison to the parent Cu(II)-salen complex.

**Figure 2.22** – UV-Visible spectra of (A) salen ligands 267-269 and 282; (B) Cu(II) complexes 290-292 and 296, and 302 as 20 μM CH₂Cl₂ solutions.
Figure 2.23 - UV-Visible spectra of Cu(II) complexes 290 and 292, and the parent Cu(II)-salen complex as 20 μM CH₂Cl₂ solutions showing the d-d transition absorbances.

![UV-Visible spectra](image)

Figure 2.24 - UV-Visible spectra of Cu(II) complexes 291 and 294, as both 20 μM CH₂Cl₂ and MeOH solutions, as examples of the solvatochromic shift of the mixed CT/ligand-based band around 375 nm with change of solvent.

The UV-Visible spectra of \( N,N' \)-bis(3,5-di-tert-butylsalicylidene)ethylenediamine 305, and the related Cu(II) complex 306 have been also previously studied. The ligand was reported to show absorbances around 220 nm, 260 nm, and 320-330 nm in both CHCl₃ and CH₂Cl₂.\(^{34,345-346}\) The two higher energy bands were generally assigned to \( \pi \rightarrow \pi^* \) transitions of the phenoxy chromophore and the lower energy band was assigned to the imine group. The Cu(II) complex was reported to show absorbances at 306 nm, 405 nm, and 500 nm in CH₂Cl₂.\(^{347}\) The lowest energy bands (500 nm) were assigned to d-d transitions of the metal centre. The assignment of the next band between 405 nm was reported as a CT band.\(^{347-348}\) The higher energy bands were not assigned, but can be attributed to \( \pi \rightarrow \pi^* \) transitions of the phenoxy chromophore.

In addition, the UV-Visible spectra of 307 has also been reported, with absorbances at 222 nm, 262 nm and 328 nm in EtOH.\(^{346}\) The similarity to the 1,2-bridged ligand again suggests that the addition of one carbon in the diamine bridge does not significantly alter the electronic properties of the ligand and complex.

The tert-butyl salen ligands 270, 271, 274 and 283 all displayed three main absorption bands at approx. 230 nm, 264 nm, and 334 nm (Figure 2.25 A), compared to literature
values. It has been observed that strongly electron donating/accepting phenoxy substituents (-OMe, -NO$_2$) as well as extended $\pi$-systems (-naphthyl) result in an obvious red shift of absorption bands.\textsuperscript{334} However, alkyl substituents usually have little effect on the absorption spectra. Here, it can be seen that the two lower energy bands showed a small red shift compared to the unsubstituted carbohydrate-based ligands 267-269 and 282. For the corresponding complexes 293-295 and 297, there was again a red shift of the ligand-based absorption bands to 238 nm, 283 nm, and 387 nm (Figure 2.25 B). The strong absorbance at $\approx$387 nm, based on the literature, should be attributed to a CT band. However, it was probably a case of overlapping bands, as clarified above for the unsubstituted carbohydrate complexes 290-292 and 296. The shape of the band, showing a shoulder on the right-hand side, suggests it comprises several bands including the red-shifted ligand band and a CT band. Comparison between spectra in MeOH and CH$_2$Cl$_2$ revealed a slight solvatochromic effect which suggests that this is the case (Figure 2.24).

The spectra of complexes 294 and 296 also displayed a broad, weak absorbance at about 650 nm and 297 showed a band at about 620 nm, which were attributed to a d-d transition (Figure 2.26). The complex 295 showed a broad, weak absorbance at 570 nm due to d-d transitions, similar to 303. This slight difference in d-d transition absorbances can be attributed to the length of the diamine bridge. The Cu(II) complexes 303 and 295 have a two-carbon bridge, whereas 293, 294, and 297 have a three-carbon bridge. This pattern was also observed in 1,2- and 1,3-bridged salen complexes found in the literature.\textsuperscript{349-350} It is thought that the 6-membered chelate, formed due to the 1,3-diamine bridge, distorts the coordination sphere and changes the ligand field strength. This also explains the same observed absorption red shift in the simpler Cu(II) salen complexes 290 and 292.
Figure 2.25 - UV-Vis spectra of (A) tert-butyl salen ligands 270, 271, 274, and 283 and (B) related complexes 293-295, and 297 as 20 μM CH₂Cl₂ solutions.

Figure 2.26 - UV-Vis spectra of copper(II) complexes 293-295 and 297 as 20 μM CH₂Cl₂ solutions showing the d-d transition absorbances.

Overall, the UV-Vis spectra of the carbohydrate-salen derivatives were very similar to the model Cu(II)-salen compound and ligand, and similar tert-butyl derivatives
from literature. This suggests that the inclusion of the carbohydrate backbone does not greatly influence the electronic characteristics of the ligand and complex.

Cyclic Voltammetry studies

The electrochemical properties of Cu(II)-salen complexes have been widely studied, due to the interest in these compounds as galactose oxidase (GAO) mimics. The groups of Stack, Storr, Thomas, and Shimazaki have devoted particular interest to the (redox) non-innocent role of salen ligands in the oxidation of Cu(II)-salen complexes, among other transition metals.\textsuperscript{251,257-258,262,350-353}

There is a distinction made between a non-innocent ligand and a redox-active moiety,\textsuperscript{354} where redox-active ligands may participate in the redox event, but the formal charge of the metal complex can be experimentally determined. A single oxidation of a metal complex with redox-active ligands can produce (in broad terms) either a metal-ligand radical, \((M^{n+}(L^\cdot))\), where the ligand is oxidized preferentially to the metal center, or a high-valent metal complex, \((M^{(n+1)^+}(L^\cdot))\), where the metal is oxidised. For a non-innocent ligand, there is uncertainty as to where the oxidation occurred and this makes it difficult to determine the formal oxidation state of the complex. Until the formal charge of the complex can be experimentally proven, the ligand remains non-innocent. A more in-depth description and investigation of redox-active and non-innocent ligands can be found in the seminal paper by Jørgensen,\textsuperscript{355} as well as other essays and reviews.\textsuperscript{251,354-357}

Previous studies on the oxidation of Cu(II) complexes \textbf{308-312} (Figure 2.27) revealed a pattern of metal/ligand oxidation dependent on the length of the diamine bridge and the substituents on the phenyl ring (Table 2.1).\textsuperscript{258,262,350-353} For complexes with simple 1,2- and 1,3-bridged \textit{tert}-butyl-substituted salen ligands \textbf{308} and \textbf{309}, the redox values varied by only 0.03 V.\textsuperscript{350} However, the speciation of the oxidised complexes was found to be subtly different. The 1,2-salen ligand \textbf{309} was experimentally determined to exist as an oxidised Cu(III) species, \([\text{Cu(III)Sal}]^{+}\), in the solid state, but, in solution, the speciation was an equilibrium between the \([\text{Cu(III)Sal}]^{+}\) state and a ligand-radical species, \([\text{Cu(II)Sal}^\cdot]^{+}\).\textsuperscript{355} As the electron-donating ability of the substituents increased in \textbf{311-312}, the speciation of the oxidised complexes was found to be the ligand-
radical species in all conditions. As the electron-accepting ability of the substituents increased as in 310, the oxidised complex was determined to be a [Cu(III)Sal]+ species. When the diimine moieties are separated by a 1,3-bridge as in 308, the oxidation occurs preferentially at the ligand, and the Cu(II)-phenoxy radical species is observed.

![Figure 2.27](image)

**Figure 2.27** – The structures of Cu(II)-salen complexes previously studied by cyclic voltammetry, referred to in this study.

**Table 2.1** – Electrochemical data for Cu(II) complexes 308-312, in a 0.1 M [N^8Bu_4]PF_6 CH_2Cl_2 solution, quoted against [Fe(η^5-C_5H_5)_2]/ [Fe(η^5-C_5H_5)_2]^+ at 0.00 V.

<table>
<thead>
<tr>
<th>Complex</th>
<th>E_{1/2} (1) (V)</th>
<th>E_{1/2} (2) (V)</th>
<th>ΔE (mV)</th>
</tr>
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<tr>
<td>308</td>
<td>0.48</td>
<td>0.63</td>
<td>150</td>
</tr>
<tr>
<td>309</td>
<td>0.45</td>
<td>0.65</td>
<td>200</td>
</tr>
<tr>
<td>310</td>
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<td>1.28</td>
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<td>160</td>
</tr>
<tr>
<td>312</td>
<td>0.34</td>
<td>0.44</td>
<td>110</td>
</tr>
</tbody>
</table>

The electrochemical responses of complexes 290-295 were examined by cyclic voltammetry (CV) in 0.1 M tetra-butylammonium hexafluorophosphate ([N^8Bu_4]PF_6) CH_2Cl_2 solutions. Potentials are quoted against an internal...
decamethylferrocene/decamethylferroenium reference ([Fe(η⁵-C₅Me₅)₂]/ [Fe(η⁵-
C₅Me₅)]⁺ = -0.55 V relative to external [Fe(η⁵-C₅H₅)₂]/ [Fe(η⁵-C₅H₅)]⁺ at 0.00 V). (Figure 6). The internal standard is standardised to an external ferrocene standard, as used in the studies discussed above. Therefore, direct comparisons can be made between literature data and the data presented here-in.

Complexes 290, 291 and 292 all showed irreversible electrochemical behaviour, with cyclic voltammograms suggesting decomposition of the complexes and plating occurring at the electrode. This may be due to the lack of substituents on the phenyl ring, since substituents are known to contribute to stabilising oxidation states. The inability of the complexes to undergo geometric adjustment to accommodate any structural changes upon oxidation, due to the rigid 1,6-anhydro scaffold, may also contribute to decomposition.

The complexes 293, 294 and 295 displayed a reversible first oxidation process, with ΔE (Eₚc – Eₚa) values being close to the internal standard (94 mV at 298 K) at all scan rates, and being independent of scan rate (Figure 2.28, Table 2.2). The complexes also exhibited a quasi-reversible secondary oxidation event, with ΔE increasing with scan rate. Decomposition and plating on the electrode occurred for all compounds after several redox cycles, indicating the relative instabilities of the complexes under redox conditions.

The E½(1) values of the novel complexes were comparable with those in the literature, as discussed above. The E½(2) values were slightly higher, possibly due to the quasi-reversibility of the novel complexes. Although the speciation of the oxidized complexes of 293-295 were not determined, the similar CV characteristics to other 1,3-salen copper(II) complexes suggest that the oxidation would likely take place at the ligand, [Cu(II)Sal⁺]. It would be interesting to see if the 1,2-bridge derivative 295 also displayed the same speciation, or if, like 309, it existed in equilibrium between the [Cu(III)Sal]⁺ and [Cu(II)Sal⁺]⁺ species in solution.
Figure 2.28 – Cyclic voltammograms of the three copper(II) complexes with tert-butyl derivatives, 293, 294, and 295, showing both oxidations. Scans were recorded in 0.1 M [NnBu4]PF6 CH2Cl2 solutions at rates of 100 mVs⁻¹.

Table 2.2 – Selected electrochemical data (V) of complexes, 293, 294, and 295, where: $E_{1/2}$ = half wave oxidation potential, $\Delta E$ = potential difference between the forward and reverse peaks in each oxidation event, $I_a/I_c$ = the ratio of the anodic peak current to cathodic peak current.

<table>
<thead>
<tr>
<th>Complex</th>
<th>1st Oxidation</th>
<th>2nd Oxidation</th>
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<td></td>
<td>$E_{1/2}$ (V)</td>
<td>$\Delta E$ (mV)</td>
</tr>
<tr>
<td>293</td>
<td>0.498</td>
<td>92</td>
</tr>
<tr>
<td>294</td>
<td>0.51</td>
<td>87</td>
</tr>
<tr>
<td>295</td>
<td>0.499</td>
<td>81</td>
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</table>
X-Ray crystallographic studies

X-ray crystallographic analyses were conducted by Dr Brian Skelton.

Only one ligand, 274, gave crystals suitable for single crystal X-ray diffraction (Figure 2.29). The compound crystallised in the monoclinic space group P2₁. There were two molecules per asymmetric unit, whose differences were only slight variations in the orientation of the pendant groups on the carbohydrate ring. As a metal atom was not present to impose a constrained geometry, the only interactions of interest were intramolecular hydrogen bonds between the phenol hydrogens and the nitrogen atoms (O-H…N) (Table 2.3). The rigid 1,6-anhydro scaffold did not seem to perturb the crystal structure, as the observed hydrogen bond interactions and bond lengths were in agreement with the previously reported structure of \( N,N^-\text{bis}(3,6\text{-}\text{di}\text{-}\text{tert}\text{-}\text{butylsalicylidene})\text{ethylenediamine} \).³⁵⁸ Packing of the molecules in the unit cell appeared to be to minimise steric hindrance.

![Figure 2.29 – A plot of a molecule of 274. Ellipsoids for key atoms are drawn at the 50% probability level.](image)

<table>
<thead>
<tr>
<th></th>
<th>O-H…N</th>
<th>d(O-H)</th>
<th>d(H…N)</th>
<th>d(O…N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(4)-H(4)…N(1)</td>
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<td>1.82(4)</td>
<td>2.575(3)</td>
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<tr>
<td>O(3)-H(3)…N(2)</td>
<td>0.82(3)</td>
<td>1.79(3)</td>
<td>2.565(3)</td>
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</table>
The structures of the complexes 290, 291 and 302 were also elucidated by single crystal X-ray diffraction studies (Figures 2.30 and 2.32). Complexes 290 and 291 crystallised in the monoclinic space group $P2_1$, and orthorhombic space group $P2_12_12_1$, respectively. The bond angles N1-Cu1-N2 ($\approx 98^\circ$), O3-Cu1-O4 ($\approx 81^\circ$), N1-Cu-O4 ($\approx 90^\circ$), and N1-Cu-O3 ($\approx 170^\circ$) indicate the approximate square planar geometry about the copper centres. Previously reported structures of Cu(II)-salen complexes with a three-carbon bridge separating the diimines display a larger deviation from normal square planar geometry towards a tetrahedral geometry, with the two phenoxy rings lying in different planes.\textsuperscript{349,359-360} When the 1,3-bridge is part of a 1,3-diaminocyclohexane backbone, similar to the six-membered carbohydrate ring, this tetrahedral distortion is also reduced.\textsuperscript{350} Therefore, due to the rigid structure of the 1,6-anhydro ring as well as the axial geometry of the two imines, the ligating motifs are held in the same plane. This imposes a fixed square planar geometry on the complexes.

Additionally, in both complexes, two molecules in the asymmetric unit form a pseudo-centrosymmetric dimer with intermolecular contacts between the copper atom and oxygen atoms on the facing molecule (Figure 2.31). Cu-Cu distances are about 3.102(4) Å for 290 and 3.7790(4) Å for 291. This dimerization phenomenon has been previously reported for 1,2-bridged Cu(II)-salen complexes.\textsuperscript{359-360} The 1,3- and 1,4-bridges were reported as being too distorted to form sufficient interactions for the stacked dimer. However, a 1,4-bridged example synthesised from \textit{cis}-2,5-diaminobicyclo[2.2.2]octane was reported as forming a dimer.\textsuperscript{286} The cyclic structure appears to prevent tetrahedral distortion of the coordination centre. The retained square planar geometry facilitates the molecular stacking \textit{via} intermolecular interactions, without steric hindrance or electronic repulsion from out-of-plane phenoxy rings.
**Figure 2.30** – (A) A plot of a molecule of 290; (B) A plot of molecule 291. Ellipsoids for key atoms are drawn at the 50% probability level.

**Figure 2.31** – A plot of the pseudo-centrosymmetric dimer formation of 291, with ellipsoids for key atoms drawn at the 50% probability level.
Table 2.4 – Select bond lengths (Å) and angles (°) for the complexes 290 and 291.

<table>
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</tbody>
</table>

The complex 302 was hypothesised to contain a phenanthroline motif. However, single X-ray diffraction studies revealed a bimetallic structure, with two demi-salen molecules 299 coordinating both copper centres, the C3 hydroxyl groups bridging both metal centres, Cu-O-Cu (Figure 2.32). The complex crystallised in the monoclinic space group C2 and contained 2.5 molecules of methanol and 1.75 molecules of water per dimer. The bond angles O3-Cu1-N4 (≈ 99°), N4-Cu1-O5 (≈ 95°), O3-Cu1-O6 (≈ 78°), and N4-Cu1-O6 (≈ 171°) indicate the approximate square planar geometry about the copper centre, similar to the monometallic complexes above. This bimetallic structure is in agreement with previously reported similar structures.332-333 In addition, the bimetallic complex forms pseudo-centrosymmetric dimeric pairs in the unit cell, as in the examples of 290 and 291 above, with close contacts being O5…O12, Cu1…CX, Cu1…Cu3 and Cu2…Cu4 (Table 2.5).
Figure 2.32 – a) A plot of a molecule of 302; with ellipsoids for key atoms drawn at the 50% probability level.

Table 2.5 – Select bond lengths (Å) and angles (°) for the complex 302.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O3-Cu1-N4</td>
<td>98.8(3)</td>
<td>O6-Cu2-N7</td>
<td>96.6(3)</td>
</tr>
<tr>
<td>N4-Cu1-O5</td>
<td>94.5(3)</td>
<td>N7-Cu2-O8</td>
<td>94.3(4)</td>
</tr>
<tr>
<td>O3-Cu1-O6</td>
<td>77.9(3)</td>
<td>O3-Cu2-O6</td>
<td>77.9(3)</td>
</tr>
<tr>
<td>N4-Cu1-O6</td>
<td>171.1(3)</td>
<td>O3-Cu2-N7</td>
<td>172.5(4)</td>
</tr>
<tr>
<td>Cu1-O3</td>
<td>1.949(7)</td>
<td>Cu2-O3</td>
<td>1.944(7)</td>
</tr>
<tr>
<td>Cu1-N4</td>
<td>1.960(8)</td>
<td>Cu2-N7</td>
<td>1.955(9)</td>
</tr>
<tr>
<td>Cu1-O6</td>
<td>1.933(7)</td>
<td>Cu2-O6</td>
<td>1.933(7)</td>
</tr>
<tr>
<td>Cu1...Cu2</td>
<td>3.011(19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, analysis of the crystal structures highlighted similarities between the complexes synthesised here-in, and similar literature complexes with an open alkyl chain 1,2-bridge or a cyclic 1,3-bridge backbone. The carbohydrate scaffold imposed a fixed, square planar geometry on the complexes, preventing tetrahedral distortion. This allowed for intermolecular interactions which lead to stacked dimers in the solid
crystal structures. Aside from some geometric constraint, the carbohydrate scaffold appeared to have little effect on the molecular structure of the complexes.

**Biological testing**

The antiproliferative activities of the complexes 290-297 and 302 were assessed in two human cancer cell lines; HeLa, a human cervical cancer line, and MCF-7, a human breast cancer line, similarly to that described in Chapter 1. Initially, the complexes were all screened for activity against the standard, cisplatin 18 (Figure 2.33). The general trend in cytotoxicity was found to be conserved between both cell lines. Compounds 290, 291, 293, and 297 performed best when compared to their respective cisplatin controls. Compounds 290 and 291 showed decreased activity against MFC-7 cells, but the cytotoxicity of 293 and 297 appeared to be retained. Interestingly, the copper substrate, Cu(II) acetate was of low activity compared to the Cu(II)-salen compounds. This suggests that the activity of the novel complexes is due to their distinct copper-salen structure.

**Figure 2.33** – Activity assays of Cu(II) complexes against (A) HeLa and (B) MCF-7 cell lines. Data are the result of experiments run in triplicate, standardised to the
positive control of untreated cells. Errors are the mean standard error of the triplicate values. There were insufficient amounts of 292 at the time of testing, and this compound was not assayed.

The log $P$ values of the free ligands were calculated using the VCC labs’ online applet ALOGSP 2.1, as representative of lipophilicity of the complexes (Table 2.6).\textsuperscript{191,222-223} Patterns of lipophilicity were analysed alongside the activities of the complexes (as in Chapter 1). However, there was no apparent connection between lipophilicity and activity, except in the case of the pendant carbohydrate compounds 296 and 297, where the increased lipophilicity of 297, due to the tert-butyl groups, may have resulted in increased cytotoxicity. However, overall, the tert-butyl groups themselves do not appear to confer increased activity, likewise the pendant carbohydrate moiety. The absence of any obvious structure/activity relationships suggests that the mode of actions of these copper complexes may be multifaceted and diverse. Knowledge of the stability of the complexes \textit{in vivo}, and their respective membrane permeabilities, interactions with DNA and cellular distribution would help in understanding their uptake and potential modes of action.
Table 2.6 – Computed ligand log $P$ values of Cu(II) complexes 290-297

<table>
<thead>
<tr>
<th>Ligand</th>
<th>log $P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>2.06 ± 0.62</td>
</tr>
<tr>
<td>291</td>
<td>2.83 ± 0.70</td>
</tr>
<tr>
<td>292</td>
<td>3.72 ± 0.90</td>
</tr>
<tr>
<td>293</td>
<td>7.01 ± 0.66</td>
</tr>
<tr>
<td>294</td>
<td>8.75 ± 3.68</td>
</tr>
<tr>
<td>295</td>
<td>8.10 ± 1.59</td>
</tr>
<tr>
<td>296</td>
<td>0.17 ± 0.66</td>
</tr>
<tr>
<td>297</td>
<td>5.57 ± 1.60</td>
</tr>
</tbody>
</table>

$^a$Calculated from VCC labs ALOGPS 2.1 applet. Errors are the standard deviations from seven different computational algorithms. $^c$Errors are the standard deviations from five different computational algorithms.
As complexes 290, 291, 293, and 297 showed activities similar to or better than cisplatin, these were selected for further IC$_{50}$ value determinations. IC$_{50}$ values were calculated and compared to those of cisplatin under the same conditions (Table 2.7).

**Table 2.7** – IC$_{50}$ values of 290-293 and 297 and Cisplatin in Hela and MCF-7 cell lines.

<table>
<thead>
<tr>
<th>Compound</th>
<th>HeLa (μM)</th>
<th>MCF-7 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>15.9 ± 0.8</td>
<td>58.2 ± 6.2</td>
</tr>
<tr>
<td>291</td>
<td>16.1 ± 0.8</td>
<td>30.4 ± 1.7</td>
</tr>
<tr>
<td>293</td>
<td>5.2 ± 0.0</td>
<td>7.0 ± 0.8</td>
</tr>
<tr>
<td>297</td>
<td>4.7 ± 0.4</td>
<td>5.3 ± 0.2</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15.6 ± 1.6</td>
<td>50.3 ± 3.9</td>
</tr>
</tbody>
</table>

*Errors incorporate the standard deviations of triplicate experiments and are determined in the calculation of the IC$_{50}$ values.

The general trend of cytotoxicity is 290 ≈ 291 < 293 ≈ 297. Complexes 290 and 291 showed similar activities to cisplatin in both HeLa and MCF-7 cell lines. Most gratifyingly, compounds 293 and 297 showed a 3-fold greater activity than cisplatin in HeLa cells and a 10-fold increase in potency in MCF-7 cells. This significantly higher cytotoxicity warrants further investigation into the *in vivo* molecular and cellular modes of action, especially due to the activity in the cisplatin-resistant MFC-7 cell line.
Carbohydrate-salen ligands with other transition metals

Given the positive results from the Cu(II) salen ligands, several new complexes were synthesised from the ligand 291 (Scheme 2.7). Complexation with the appropriate metal(II) acetate salts (Pd(II), Ni(II) or Co(II)) gave the complexes 313-315 in moderate to good yields.

Crystals of X-ray quality were obtained for complexes 313 and 314. The structure of the Pd(II)-salen complex 313 agreed with those of the previous Cu(II) complexes. The Ni(II) complex 314 was isolated as a trinuclear complex, which was unexpected but similar structures have been previously reported.361-362 The elemental analysis of the Co(II) complex 315 suggested it had a structure similar to the Pd(II) and Cu(II) complexes.
Scheme 2.7 – a) Pd(OAc)$_2$, MeOH; b) Ni(OAc)$_2$·4H$_2$O, MeOH; c) Co(OAc)$_2$·4H$_2$O, MeOH, CH$_3$C$_6$H$_5$

X-Ray crystallographic studies

The structures of the complexes 313 and 314 were elucidated by single crystal X-ray diffraction studies conducted by Dr Brian Skelton (Figure 2.34 and 2.35 respectively). The Pd(II) complex 313 crystallised in the monoclinic space group $P2_1$ and the Ni(II) complex 314 in the triclinic space group $P1$. The bond angles N1-Pd1-N2 ($\approx 97^\circ$), O3-Pd1-O4 ($\approx 80^\circ$), N1-Pd1-O4 ($\approx 92^\circ$), and N1-Pd1-O3 ($\approx 172^\circ$) indicate the approximate square planar geometry about the palladium centre (Table 2.8). The observed bond
lengths and angles were in agreement with previously reported similar structures.\textsuperscript{349,363-364} In addition, two molecules formed pseudo-centrosymmetric pairs, as in the Cu(II) examples above, with the distance between metal centres Pd1…Pd being 2 3.624(3) Å (Table 2.8).

**Figure 2.34** - A plot of a molecule of 313, with ellipsoids for key atoms drawn at the 50% probability level.

**Table 2.8** – Select bond lengths (Å) and angles (°) for the complex 313.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-Pd1-N2</td>
<td>96.6(13)</td>
</tr>
<tr>
<td>O3-Pd1-O4</td>
<td>80.3(12)</td>
</tr>
<tr>
<td>N1-Pd1-O4</td>
<td>91.9(13)</td>
</tr>
<tr>
<td>N1-Pd1-O3</td>
<td>171.7(13)</td>
</tr>
<tr>
<td>Pd1-N1</td>
<td>2.032(3)</td>
</tr>
<tr>
<td>Pd1-O3</td>
<td>1.997(3)</td>
</tr>
<tr>
<td>Pd1-O7</td>
<td>3.831(3)</td>
</tr>
<tr>
<td>Pd2-O3</td>
<td>3.822(3)</td>
</tr>
<tr>
<td>Pd1-Pd2</td>
<td>3.624(3)</td>
</tr>
</tbody>
</table>

The bond angles N1-Ni1-N2 (≈97°), O3-Ni1-O4 (≈90°), N1-Ni1-O14 (≈91°), and N1-Ni1-O4 (≈172°) indicate the approximate octahedral geometry about the nickel centre (Table 2.9). This is conserved for the two other nickel centres. The trinuclear structure was unexpected. However, this configuration has been observed before, and bond lengths and angles were in agreement with previously reported similar structures.\textsuperscript{361-362} In the synthesis of this nickel complex, a slight excess of Ni(II) acetate was used.
which may have resulted in the trinuclear structure. In order to synthesise a mononuclear complex, the nickel(II) salt should be the limiting reagent.

**Figure 2.35** - A plot of a molecule of 314, with ellipsoids for key atoms drawn at the 50% probability level.

**Table 2.9** – Select bond lengths (Å) and angles (°) for the complex 314.

<table>
<thead>
<tr>
<th>Bond Description</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-Ni1-N2</td>
<td>96.7(4)</td>
</tr>
<tr>
<td>O3-Ni1-O4</td>
<td>91.9(3)</td>
</tr>
<tr>
<td>N1-Ni1-O14</td>
<td>91.9(4)</td>
</tr>
<tr>
<td>N1-Ni1-O4</td>
<td>172.4(4)</td>
</tr>
<tr>
<td>Ni1-N1</td>
<td>2.07(1)</td>
</tr>
<tr>
<td>Ni1-O3</td>
<td>2.102(9)</td>
</tr>
<tr>
<td>Ni1-O4</td>
<td>2.02(1)</td>
</tr>
<tr>
<td>Ni1-O14</td>
<td>2.12(1)</td>
</tr>
<tr>
<td>Ni1-Ni2</td>
<td>3.176(3)</td>
</tr>
<tr>
<td>O4-Ni2-O13</td>
<td>74.4(3)</td>
</tr>
<tr>
<td>O5-Ni2-O6</td>
<td>91.6(3)</td>
</tr>
<tr>
<td>O13-Ni2-O12</td>
<td>91.8(3)</td>
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<tr>
<td>O13-Ni2-O6</td>
<td>174.8(3)</td>
</tr>
<tr>
<td>Ni2-O13</td>
<td>2.19(1)</td>
</tr>
<tr>
<td>Ni2-O5</td>
<td>2.16(1)</td>
</tr>
<tr>
<td>Ni2-O6</td>
<td>2.18(9)</td>
</tr>
<tr>
<td>Ni2-O12</td>
<td>2.22(1)</td>
</tr>
<tr>
<td>Ni2-Ni3</td>
<td>3.157(3)</td>
</tr>
</tbody>
</table>
Conclusions and future work

A series of Cu(II)-salen complexes 290-297 and 302, based on two carbohydrate scaffolds, were successfully synthesised and characterised.

Their UV-Visible properties were similar to other Cu(II)-salen complexes, indicating that the carbohydrate scaffolds do not greatly change the electronic properties of the complexes. Cyclic voltammetry studies indicated that these complexes probably undergo oxidation at the phenol hydroxyl site of the ligand, similar to that observed in the literature. Oxidation destabilised the molecules and decomposition occurred on the first oxidation or soon after, even at low scan rates. It is possible that the rigidity of the 1,6-anhydro scaffold contributes to the instability of the complexes. The electrochemistry of complexes 296 and 297 was not investigated in this study. It would be worthwhile investigating the redox activity of these compounds, and comparing the results from these more flexible complexes against the 1,6-anhydro structures.

Biological testing against two cancer cell lines gave a variety of results, with no obvious associations between complex structure and cytotoxicity. However, the compounds 293 and 297 were significantly more active than cisplatin in the tested cell lines. This positive result opens an avenue for further investigations into their mode of action and scope of activity against other cell lines, especially those which demonstrate resistance to cisplatin.

Of interest would be to test the copper complexes as catalysts in synthetic reactions (e.g. epoxidations) and to determine their ROS generating ability, as further measures of redox activity. In addition, the Pd(II), Ni(II) and Co(II)-salen compounds 313-315 should be subjected to the same biological and catalytic tests, to explore the changes in activity due to the metal centre. Finally, to further explore the scope of these ligands, it would be worthwhile expanding the range of coordinating metals.
EXPERIMENTAL

1,6-Anhydro-2,4-diamino-2,4-dideoxy-3-O-pentyl-β-D-glucopyranose 266

The diazide 53 (150 mg, 0.71 mmol) was treated with 1-bromopentane according to Procedure 1.3. Flash chromatography (EtOAc/petrol 1:19) of the resultant residue yielded a colourless oily residue (185 mg) which was used without further purification. The residue (182 mg) was treated according to Procedure 1.5 to give the title compound as a colourless oil (144 mg, 88% over two steps). Rf 0.15 (MeOH/CH₂Cl₂ 1:9). IR (ATR): 3358 (N-H) cm⁻¹. ¹H NMR (600 MHz, CD₃OD): δ 5.27 (s, 1H), 4.38 (d, J = 5.6 Hz, 1H), 4.12 (dd, J = 1.0, 6.9 Hz, 1H), 3.67 (dd, J = 6.4 Hz, 1H), 3.49-3.47 (m, 2H), 3.20-3.19 (m, 1H), 2.84 (s, 1H), 2.75 (s, 1H), 1.58-1.54 (m, 2H), 1.37-1.34 (m, 4H), 0.93-0.91 (m, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 104.3, 84.0, 77.9, 70.9, 66.9, 53.5, 53.3, 30.7, 29.6, 23.5, 14.4. HR-MS (APCI): m/z 231.1703; [M+H]⁺ requires 231.1709

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-methyl-β-D-glucose 267

Salicylaldehyde (0.043 mL, 0.40 mmol) was added dropwise to a solution of the diamine 100 (35 mg, 0.2 mmol) in MeOH (5 mL) and the resultant solution refluxed (1 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19 to 3:7) yielded the title compound as a bright yellow, crystalline solid (57 mg, 75%). Rf 0.41 (EtOAc/petrol 2:3). IR (ATR): 1632 (C=N) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 12.82 (s, 1H), 12.73 (s, 1H), 8.45 (s, 1H), 8.44 (s, 1H), 7.36-7.32 (m, 2H), 7.31-7.29 (m, 2H), 7.02-6.99 (m, 2H), 6.92-6.89 (m, 2H), 5.47 (s, 1H), 4.68-4.67 (m, 1H), 3.97 (d, J = 7.2 Hz, 1H), 3.82 (dd, J = 5.0, 7.2 Hz, 1H), 3.49 (dd, J = 6.5 Hz, 1H), 1.34 (m, 2H), 0.93-0.91 (m, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 104.3, 84.0, 77.9, 70.9, 66.9, 53.5, 53.3, 30.7, 29.6, 23.5, 14.4. HR-MS (APCI): m/z 231.1703; [M+H]⁺ requires 231.1709
3.36 (d, $J = 6.4$ Hz, 1H), 3.35-3.34 (m, 1H), 3.26 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 167.4, 166.5, 161.1, 161.1, 133.1, 133.1, 132.0, 132.0, 119.1, 119.0, 118.7, 118.6, 117.4, 117.4, 103.6, 81.9, 77.4, 75.2, 74.1, 68.6, 60.9. HR-MS (APCI): $m/z$ 383.1603; [M+H]$^+$ requires 383.1607. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 319 [0.98], 259 [2.86], 229 [3.37].

[Chemical structure image]

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-propyl-β-D-glucose 268

Salicylaldehyde (0.173 mL, 1.63 mmol) was added dropwise to a solution of the diamine 101 (164 mg, 0.813 mmol) in MeOH (5 mL) and the resultant solution refluxed (1 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:9 to 2:3) yielded the title compound as a bright yellow, crystalline solid (207 mg, 62%). $R_f$ 0.28 (EtOAc/petrol 3:7). IR (ATR): 2820 (O-H), 1628 (C=N) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 12.82 (s, 1H), 12.74 (s, 1H), 8.43 (s, 1H), 8.42 (s, 1H), 7.36-7.32 (m, 2H), 7.29-7.27 (m, 2H), 7.01-6.98 (m, 2H), 6.92-6.89 (m, 2H), 5.48 (s, 1H), 4.70-4.69 (m, 1H), 3.95 (d, $J = 7.1$ Hz, 1H), 3.82 (dd, $J = 4.9$, 7.3 Hz, 1H), 3.57 (dd, $J = 7.0$, 7.0 Hz, 1H), 3.35 (d, $J = 6.9$ Hz, 1H), 3.33 (dd, $J = 1.0$, 7.2 Hz, 1H), 3.29-3.25 (m, 2H), 1.35-1.29 (m, 2H), 0.69 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 167.4, 166.5, 161.1, 161.1, 133.0, 133.0, 133.0, 131.9, 131.9, 119.1, 119.0, 118.6, 118.5, 117.4, 117.3, 103.8, 80.0, 76.0, 75.0, 68.8, 23.4, 10.7. HR-MS (APCI): $m/z$ 411.1928; [M+H]$^+$ requires 411.1920. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 318 [0.92], 259 [2.73], 229 [3.21].
Salicylaldehyde (0.034 mL, 0.323 mmol) was added dropwise to a solution of the diamine 266 (35.4 mg, 0.154 mmol) in MeOH (5 mL) and the resultant solution refluxed (1 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19 to 1:5) yielded the title compound as a bright yellow, crystalline solid (54.7 mg, 81%). Rf 0.62 (EtOAc/petrol 2:3). IR (ATR): 1626 (C=N) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 12.83 (s, 1H), 12.76 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 7.36-7.34 (m, 2H), 7.29-7.27 (m, 2H), 7.01-6.98 (m, 1H), 6.92-6.89 (m, 2H), 5.49 (s, 1H), 4.70 (d, \(J = 5.0\) Hz, 1H), 3.94 (d, \(J = 7.1\) Hz, 1H), 3.81 (dd, \(J = 5.0, 7.3\) Hz, 1H), 3.57 (dd, \(J = 7.3\) Hz, 1H), 3.33 (d, \(J = 7.0\) Hz, 1H), 3.31-3.28 (m, 3H), 1.30-1.25 (m, 2H), 1.05-1.03 (m, 4H), 0.66 (t, \(J = 6.0\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 167.4, 166.5, 161.1, 161.1, 133.0, 133.0, 131.9, 131.9, 119.1, 119.0, 118.6, 118.5, 117.3, 117.3, 103.8, 80.0, 76.2, 75.0, 73.5, 68.8, 30.0, 28.4, 22.4, 14.0. HR-MS (APCI): \(m/z\) 439.2227; [M+H]\(^+\) requires 439.2233. UV-Visible (CH\(_2\)Cl\(_2\)) \(\lambda\) (nm) [\(\varepsilon \times 10^4\) M\(^{-1}\) cm\(^{-1}\)]: 319 [0.92], 260 [2.65], 228 [3.10].

3,5- Di-tert-butyldisalicylaldehyde (290.3 mg, 1.24 mmol) was added to a solution of the diamine 51 (99.2 mg, 0.619 mmol) in MeOH (4 mL) and the resultant solution was refluxed (1h). Concentration of the mixture followed by flash chromatography
(EtOAc/petrol 1:9) yielded the title compound as a pale yellow solid (255 mg, 69%). Rf 0.72 (EtOAc/petrol 2:3). IR (ATR): 3486 (O-H), 1625 (C=O) cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 13.19 (s, 1H), 13.14 (s, 1H), 8.47 (s, 1H), 8.45 (s, 1H), 7.44-7.43 (m, 2H), 7.15 (s, 2H), 5.56 (s, 1H), 4.76 (d, J = 4.7 Hz, 1H), 3.96-3.91 (m, 2H), 3.84 (dd, J = 4.9, 7.5 Hz, 1H), 3.67 (dd, J = 7.0, 7.0 Hz, 1H), 3.41-3.33 (m, 4H), 1.46 (s, 9H), 1.44 (s, 9H), 1.33-1.32 (m, 20H), 1.12-1.03 (m, 4H), 0.65 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 168.3, 167.4, 158.2, 158.1, 140.4, 140.4, 137.0, 137.0, 127.7, 127.7, 126.4, 126.4, 117.8, 117.7, 103.9, 80.3, 77.4, 75.8, 74.6, 73.2, 68.8, 35.2, 35.2, 34.3, 31.6, 30.0, 29.6, 29.6, 28.4, 22.4, 14.0. HR-MS (APCI): m/z 663.4735; [M+H]^+ requires 663.4735.

1,6-Anhydro-2,4-bis(3,5-di-tert-butylsalicylidene)amino-2,4-dideoxy-3-O-pentyl-β-D-glucose 271

3,5-Di-tert-butylsalicylaldehyde (156.5 mg, 0.67 mmol) was added to a solution of the diamine 266 (69.9 mg, 0.30 mmol) in MeOH (4 mL) and the resultant solution was refluxed (1h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19 to 1:9) yielded the title compound as a bright yellow, crystalline solid (155 mg, 78%). Rf 0.22 (EtOAc/petrol 1:9). IR (ATR): 1624 (C=N) cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 13.30 (s, 1H), 13.21 (s, 1H), 8.46 (s, 1H), 8.46 (s, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.13-7.12 (m, 2H), 5.50 (s, 1H), 4.72 (d, J = 5.3 Hz, 1H), 3.97 (d, J = 7.3 Hz, 1H), 3.83 (dd, J = 5.1, 7.2 Hz, 1H), 3.67 (dd, J = 7.0, 7.0 Hz, 1H), 3.41-3.33 (m, 4H), 1.46 (s, 9H), 1.44 (s, 9H), 1.33-1.32 (m, 20H), 1.12-1.03 (m, 4H), 0.65 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 168.3, 167.4, 158.2, 158.1, 140.4, 140.4, 137.0, 137.0, 127.7, 127.7, 126.4, 126.4, 117.8, 117.7, 103.9, 80.3, 77.4, 75.8, 74.6, 73.2, 68.8, 35.2, 35.2, 34.3, 31.6, 30.0, 29.6, 29.6, 28.4, 22.4, 14.0. HR-MS (APCI): m/z 663.4735; [M+H]^+ requires
663.4737. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 334 [0.90], 266 [2.77], 230 [3.62].

1,6-Anhydro-3-azido-2-O-benzoyl-3-deoxy-\(\beta\)-D-idose 277

Method A: Benzoyl chloride (1.7 mL, 14.7 mmol) was added to a solution of the azide 62 (1.25 g, 6.68 mmol) in a mixture of CH$_2$Cl$_2$ (10 mL) and pyridine (5 mL) and the resultant solution was stirred at room temperature (20 min). The solution was quenched with MeOH (5 mL) and concentrated. The resultant residue was dissolved in EtOAc (30 mL), washed with water (30 mL), 1 M HCl (30 mL), sat. NaHCO$_3$ (30 mL), brine (30 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:19 to 1:4) of the resultant residue yielded the presumed dibenzoate 276 as a colourless oil (2 g) which was used without further purification. A portion of this oil (100 mg) was dissolved in MeOH (10 mL), sodium methoxide (10 mg) was added, and the resultant mixture was stirred at room temperature until the reaction was judged complete by TLC analysis. The solution was quenched with resin (Amberlite IR-120, H$^+$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 3:7) of the resultant residue yielded the title compound as a colourless oil (11.5 mg, 15% over two steps). $R_f$ 0.22 (EtOAc/petrol 2:3). IR (ATR): 3462 (O-H), 2110 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.09-8.07 (m, 2H), 7.61-7.60 (m, 1H), 7.48-7.46 (m, 2H), 5.59 (d, $J$ = 1.4 Hz, 1H), 4.92 (dd, $J$ = 1.5, 9.0 Hz, 1H), 4.53 (dd, $J$ = 4.5, 4.5 Hz, 1H), 4.24 (d, $J$ = 8.0 Hz, 1H) 3.90 (dd, $J$ = 4.0, 8.8 Hz, 1H), 3.86 -3.81 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 165.8, 133.6, 129.9, 128.9, 128.5, 99.0, 75.4, 75.0, 70.2, 65.3, 64.2. HR-MS (APCI): $m/z$ 333.1194; [M+H+CH$_3$CN]$^+$ requires 333.1199.

Method B: Benzoyl chloride (0.26 mL, 2.25 mmol) were added to a solution of the azide 62 (420 mg, 2.25 mmol) in a mixture of CH$_2$Cl$_2$ (5 mL) and pyridine (2.5 mL) at -10°C and the resultant solution was left to stir at -10°C (2 h). The solution was quenched with MeOH (5 mL) and concentrated. The resultant residue was dissolved in EtOAc (30 mL), washed with water (30 mL), 1 M HCl (30 mL), sat. NaHCO$_3$ (30 mL), brine (30 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography
(EtOAc/petrol 1:4) of the resultant residue yielded the title compound as a colourless oil (530 mg, 81%). $^1$H and $^{13}$C NMR spectra were consistent with that found above.

1,6-Anhydro-3-azido-2-O-benzoyl-3-deoxy-4-O-trifluoromethanesulfonyl-β-D-idose 279

Trifluoromethanesulfonic anhydride (0.33 mL, 1.98 mmol) was added to a solution of the benzoate 276 in a mixture of CH$_2$Cl$_2$ (20 mL) and pyridine (4 mL) at -10°C and the resultant solution was left to stir at -10°C until the reaction was judged complete by TLC analysis. The solution was quenched with MeOH and concentrated. The resultant residue was dissolved in EtOAc (30 mL), washed with water (30 mL), 1 M HCl (30 mL), sat. NaHCO$_3$ (30 mL), brine (30 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:16 to 1:6) of the resultant residue yielded the title compound as a colourless oil (625 mg, 66% over two steps). Rf 0.53 (EtOAc/petrol 2:8). IR (ATR): 2114 (N$_3$), 1728 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 8.07-8.06 (m, 2H), 7.64-7.61 (m, 1H), 7.50-7.47 (m, 2H), 5.67 (d, $J$ = 1.5 Hz, 1H), 4.99 (dd, $J$ = 1.6, 8.9 Hz, 1H), 4.81-4.80 (m, 2H), 4.27 (d, $J$ = 8.7 Hz, 1H), 4.13-4.10 (m, 1H), 3.96 (ddd, $J$ = 1.5, 4.4, 8.8 Hz, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 165.5, 134.1, 130.1, 128.8, 128.6, 118.6 (q, $J$ = 320 Hz, CF$_3$), 99.2, 81.6, 75.8, 73.2, 65.7, 60.9. HR-MS (APCI): m/z 396.0362; [M+H−N$_2$]$^+$ requires 396.0365.

1,6-Anhydro-2-O-benzoyl-3,4-diazido-3,4-dideoxy-β-D-altrose 280

Sodium azide (314 mg, 4.84 mmol) was added to a solution of 279 (585 mg, 1.38 mmol) in DMF (6 mL) and the resultant mixture was heated at 90°C until the reaction was judged complete by TLC analysis. The mixture was concentrated and the residue was taken up in EtOAc (30 mL), washed with water (3 x 30 mL), brine (30 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:6) of the
resultant residue yielded the title compound as a colourless oil (347.3 mg, 80%). Rf 0.16 (EtOAc/petrol 1:5). IR (ATR): 2104 (N3), 1709 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 8.08-8.07 (m, 2H), 7.61-7.59 (m, 1H), 7.48-7.46 (m, 2H), 5.66 (d, J = 1.3 Hz, 1H), 5.22 (dd, J = 1.4, 9.7 Hz, 1H), 4.73-4.71 (m, 1H), 4.13 (dd, J = 4.9, 9.7 Hz, 1H), 3.93-3.89 (m, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 165.7, 133.9, 130.1, 129.0, 128.7, 99.6, 75.5, 73.7, 66.8, 62.2, 59.1. HR-MS (APCI): m/z 317.1001; [M+H]+ requires 317.0998.

1,6-Anhydro-3,4-diazido-3,4-dideoxy-β-D-altrrose 272

Sodium methoxide (10 mg) was added dropwise to a solution of 279 (153.1 mg, 0.48 mmol) in MeOH (5 mL) and the resultant solution was left to stir until the reaction was judged complete by TLC analysis. The solution was quenched with resin (Amberlite IR-120, H⁺), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:2) of the resultant residue yielded the title compound X as a colourless oil (92 mg, 90%). Rf 0.25 (EtOAc/petrol 1:2). IR (ATR): 3412 (O-H), 2115, 2095 (N₃) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.41 (d, J = 1.3 Hz, 1H), 4.66 (dd, J = 2.0, 5.3 Hz, 1H), 3.89-3.84 (m, 2H), 3.80 (d, J = 8.4 Hz, 1H), 3.74 (dd, J = 2.1, 5.0 Hz, 1H), 3.70 (dd, J = 5.0, 8.9 Hz, 1H), 2.07 (d, J = 8.6 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 101.8, 75.5, 72.1, 66.6, 62.4, 61.7.

1,6-Anhydro-3,4-diazido-3,4-dideoxy-2-O-propyl-β-D-altrose 281

A suspension of KOH (223 mg, 3.98 mmol) in DMSO (4 mL) was stirred (10 min). After this time, a solution of 272 (84.4 mg, 0.398 mmol) in DMSO (2 mL) was added to this suspension, followed by addition of 1-bromopropane (0.18 mL, 1.99 mmol), and the resultant mixture was left to stir until the reaction was judged complete by TLC analysis. The reaction mixture was diluted with water (30 mL) and extracted with
EtOAc (3 x 25 mL). The organic extracts were combined, washed with water (2 x 50 mL), brine (50 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the resultant residue yielded the title compound as a colourless oil (89 mg, 88%). R$_f$ 0.29 (EtOAc/petrol 1:4). IR (ATR): 2105 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.50 (s, 1H), 4.60 (dd, $J = 2.0, 5.2$ Hz, 1H), 3.86-3.84 (m, 2H), 3.80 (d, $J = 8.3$ Hz, 1H), 3.72 (dd, $J = 2.1, 5.0$ Hz, 1H), 3.69-3.66 (m, 1H), 3.58-3.53 (m, 2H), 1.69-1.63 (m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 99.7, 79.7, 75.4, 72.9, 66.7, 61.8, 60.5, 23.3, 10.5. HR-MS (APCI): m/z 227.1138; [M+H]$^+$ requires 227.1144.

1,6-Anhydro-2,4-bis(3,5-di-tert-butylsalicylidene)amin-2,4-dideoxy-3-$O$-propyl-$\beta$-D-altrose 274

Palladium-on-carbon (10%, 50 mg) was added to a solution of 281 (85 mg, 0.32 mmol) in MeOH (3 mL) and the resultant mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until the reaction was judged complete by TLC analysis (1 atm.). The mixture was filtered through Celite and concentrated to give a colourless residue (61 mg). The residue was dissolved in MeOH (5 mL), 3,5-di-tert-butylsalicylaldehyde (126.5 mg, 0.54 mmol) was added dropwise, and the resultant solution was refluxed (1h). Concentration of the solution followed by flash chromatography (EtOAc/petrol 1:9 to 1:4) yielded the title compound as a bright yellow, crystalline solid (116 mg, 67% over two steps). R$_f$ 0.8 (EtOAc/petrol 1:2). IR (ATR): 1627 (N=C) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 13.54 (s, 1H), 13.23 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 7.40 (d, $J = 2.4$ Hz, 1H), 7.32 (d, $J = 2.4$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 5.69 (s, 1H), 4.62 (dd, $J = 1.7, 4.9$ Hz, 1H), 4.06 (d, $J = 7.8$ Hz, 1H), 3.98 (dd, $J = 5.3, 7.8$ Hz, 1H), 3.77 (dd, $J = 5.0, 8.9$ Hz, 1H), 3.71 (dd, $J = 1.1, 9.0$ Hz, 1H), 3.59 (dt, $J = 6.4, 9.2$ Hz, 1H), 3.55 (dd, $J = 1.8, 5.0$ Hz, 1H), 3.37 (dt, $J = 6.8, 9.3$ Hz, 1H), 1.54-1.49 (m, 2H), 1.48 (s, 9H), 1.28
(s, 9H), 1.27 (s, 9H), 1.22 (s, 9H), 0.83 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 168.1, 168.1, 158.4, 158.4, 140.0, 137.0, 136.8, 127.6, 127.4, 126.3, 126.2, 117.8, 117.7, 100.5, 79.1, 72.9, 71.5, 67.4, 67.2, 35.2, 35.1, 34.2, 34.2, 31.6, 31.6, 29.7, 29.4, 23.3, 10.6. HR-MS (APCI): m/z 635.4420; [M+H]$^+$ requires 635.4424. UV-Visible (CH$_2$Cl$_2$) λ (nm) [ε × 10$^4$ M$^{-1}$ cm$^{-1}$]: 333 [0.81], 263 [2.31], 229 [3.62].

2-(2-bromoethoxy)tetrahydro-$2H$-pyran 285

Dihydropyran (0.8 mL, 8.8 mmol) and pyridinium tosylate (140 mg, 0.56 mmol) were added to a solution of 2-bromoethanol (1 g, 8.0 mmol) in CH$_2$Cl$_2$ (2 mL) at 0°C and the resultant solution was stirred at room temperature. The reaction was quenched with a solution of NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:49 to 1:9) of the resultant residue yielded the title compound as a colourless oil (1.51 g, 91%). The $^1$H NMR data was consistent with those presented in the literature.$^{321}$

2-(2-((1,3-diazidopropan-2-yl)oxy)ethoxy)tetrahydro-$2H$-pyran 286

Sodium hydride (60% dispersion in oil, 233 mg, 5.82 mmol) was added to a solution of the alcohol 196 (276 mg, 1.94 mmol) in DMF (3 mL) at 0°C. The resultant mixture stirred at 0°C (0.5 h), then a solution of the bromide 285 (608 mg, 2.91 mmol) in DMF (4 mL) was added dropwise and the resultant mixture was stirred at room temperature (1 h). The reaction was quenched with MeOH, concentrated and the resultant residue was taken up in EtOAc (25 mL), washed with water (25 mL), brine (25 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol 1:19 to 1:9) of the resultant residue yielded the title compound as a colourless oil (307.1 mg, 58%). R$_f$ 0.28 (EtOAc/petrol 1:5.7). IR (ATR): 2101 (N$_3$) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 4.64-4.63 (m, 1H), 3.90-3.85 (m, 2H), 3.83-3.77 (m, 2H), 3.70-3.66 (m, 1H), 3.64-3.60 (m, 1H), 3.53-3.50 (m, 1H), 3.39-3.37 (m, 4H), 1.84-1.82 (m, 1H), 1.76-1.70 (m, 1H), 1.63-1.51 (m, 4H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 99.3, 78.7, 70.2, 67.1, 62.5,
51.9, 51.9, 30.7, 25.5, 19.6. HR-MS (APCI): \( m/z \) 243.1453; [M+H−N₂]^+ requires 243.1457.

2-((1,3-Diazidopropan-2-yl)oxy)ethanol 287

4-Toluenesulfonic acid (25.4 mg, 0.148 mmol) was added to a solution of 286 (399 mg, 1.48 mmol) in MeOH and the resultant solution was stirred until the reaction was judged complete by TLC analysis. The reaction was quenched with a solution of NaHCO₃, diluted with water (20 mL), and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with water (2 x 20 mL), brine (20 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (EtOAc/petrol 1:1.5) of the resultant residue yielded the title compound as a colourless oil (242 mg, 88%). Rᵣ 0.25 (EtOAc/petrol 1:2). IR (ATR): 3370 (O-H), 2092 (N₃) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 3.78-3.77 (m, 2H), 3.75-3.73 (m, 2H), 3.67 (quin, \( J = 5.2 \) Hz, 1H), 3.40 (d, \( J = 5.2 \) Hz, 4H). ¹³C NMR (151 MHz, CDCl₃): δ 78.5, 71.9, 62.0, 51.8.

(2-((1,3-Diazidopropan-2-yl)oxy)ethoxy)-β-D-galactopyranoside 288

4 Å molecular sieves (2 g) were added to a stirred solution of 287 (226 mg, 1.22 mmol) and 202 (720 mg, 1.46 mmol) in CH₂Cl₂ (10 mL). After cooling to -30°C, TMSOTf (10 μL) was added dropwise to the resultant suspension. The suspension was stirred at 0°C (0.5h), then neutralised with Et₃N, filtered through Celite, and concentrated. Flash chromatography (EtOAc/petrol 1:3 to 1:1) of the resultant residue yielded a colourless residue. The residue was then dissolved in MeOH (4 mL), and sodium methoxide (10 mg) was added, and the resultant solution was left to stand at room temperature until the reaction was judged complete by TLC analysis. The solution was quenched with resin (Amberlite IR-120, H⁺), filtered, and concentrated to give the title compound as a colourless oil. (127 mg, 96% over two steps). Rᵣ 0.41 (CH₃OH/EtOAc 1:9). IR (ATR): 3390 (O-H), 2097 (N₃) cm⁻¹. ¹H NMR (600 MHz, CD₃OD): δ 4.28 (d, \( J = 7.6 \) Hz, 1H).
Hz, 1H), 4.03-4.00 (m, 1H), 3.85-3.83 (m, 3H), 3.79-3.71 (m, 4H), 3.55-3.50 (m, 2H), 3.48-3.48 (m, 1H), 3.47-3.43 (m, 2H), 3.40-3.36 (m, 2H). $^{13}$C NMR (151 MHz, CD$_3$OD): δ 105.2, 79.6, 76.7, 75.0, 72.6, 70.8, 70.3, 70.1, 62.5, 52.8. HR-MS (APCI): $m/z$ 321.1400; [M+H−N$_2$]$^+$ requires 321.1410.

(2-((1,3-Bis(salicylideneamino)propan-2-yl)oxy)-β-D-galactopyranoside 282)

Palladium-on-carbon (10%, 50 mg) was added to a solution of the azide 288 (122 mg, 0.35 mmol) in MeOH (5 mL) and the resultant mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until the reaction was judged complete by TLC analysis (1 atm.). The mixture was filtered through Celite and concentrated to give, presumably, the crude amine 289, as a colourless oil (101 mg). A portion of the 289 (45 mg) was then dissolved in MeOH (5 mL) and salicylaldehyde (0.035 mL, 0.33 mmol) was added dropwise and the resultant solution was refluxed (1 h). Concentration of the mixture followed by flash chromatography (EtOAc to MeOH/EtOAc 1:9) yielded the title compound as a yellow solid (38.3 mg, 50 % over two steps). R$_f$ 0.69 (MeOH/EtOAc 1:9). IR (ATR): 3371 (O-H), 1630 (C=N) cm$^{-1}$. $^1$H NMR (500 MHz, CD$_3$OD): δ 8.51 (s, 1H), 8.50 (s, 1H), 7.39-7.36 (m, 2H), 7.33-7.30 (m, 2H), 6.87-6.82 (m, 4H), 4.19 (d, $J = 7.7$ Hz, 1H), 4.04-4.01 (m, 1H), 3.98-3.90 (m, 3H), 3.84-3.77 (m, 5H), 3.75-3.67 (m, 3H), 3.53-3.50 (m, 1H), 3.45-3.40 (m, 2H). $^{13}$C NMR (126 MHz, CD$_3$OD): δ 169.0, 164.6, 164.2, 134.2, 134.1, 133.3, 133.3, 119.9, 119.8, 119.3, 119.2, 118.6, 118.4, 105.2, 80.2, 76.7, 74.9, 72.5, 71.1, 70.3, 70.1, 62.5, 60.1, 60.5. HR-MS (APCI): $m/z$ 505.2193; [M+H]$^+$ requires 505.2186. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 316 [1.04], 257 [3.25], 229 [4.12].
(2-((1,3-Bis-(3,5-di-tert-butylsalicylideneamino)propan-2-yl)oxy)ethoxy)-β-D-galactopyranoside 283

3,5-Di-tert-butylsalicylaldehyde (76.5 mg, 0.327 mmol) was added to a solution of crude amine 289 (44 mg) in MeOH (4 mL) and the resultant solution was refluxed (1 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 4:1 to EtOAc to MeOH/EtOAc 1:19) yielded the title compound as a yellow solid (58 mg, 54%). Rf 0.33 (EtOAc/petrol 4:1). IR (ATR): 3406 (O-H), 1630 (C=N) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 8.40 (s, 2H), 7.39 (s, 2H), 7.11-7.10 (m, 2H), 4.25 (d, J = 7.7 Hz, 1H), 4.01-3.99 (m, 2H), 3.95 (d, J = 2.9 Hz, 1H), 3.89-3.71 (m, 9H), 3.65 (t, J = 8.6 Hz, 1H), 3.49 (dd, J = 3.31, 9.6 Hz, 1H), 3.42 (t, J = 5.3 Hz, 1H), 1.44 (s, 18H), 1.30 (s, 18H). ¹³C NMR (151 MHz, CDCl₃): δ 168.4, 168.3, 158.4, 158.2, 140.4, 136.9, 136.9, 127.5, 127.4, 126.3, 118.0, 117.9, 103.6, 79.5, 74.3, 71.6, 69.8, 69.5, 69.2, 62.6, 61.0, 60.8, 35.2, 34.3, 31.6, 29.6. HR-MS (APCI): m/z 729.4694; [M+H]+ requires 729.4690. UV-Visible (CH₂Cl₂) λ (nm) [ε × 10⁴ M⁻¹ cm⁻¹]: 327 [0.72], 265 [2.02], 229 [3.30].

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-methyl-β-D-glucose

Copper(II) 290

A suspension of copper(II) acetate monohydrate (36.6 mg, 0.2 mmol) in EtOH (1 mL) was added to a solution of the imine 267 (70 mg, 0.183 mmol) in EtOH (3 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and
concentrated. The resultant solid was dissolved in CH$_2$Cl$_2$, filtered through Celite, and concentrated to give the title compound as a green powder (81.5 mg, 98%). $R_f$ 0.38 (EtOAc). IR (ATR): 1606 (C=N) cm$^{-1}$. HR-MS (APCI): $m/z$ 444.0746; [M+H]$^+$ requires 444.0746. Anal. Found: C, 57.03; H, 4.51; N, 6.04. Calc. for C$_{21}$H$_{20}$N$_2$O$_5$Cu: C, 56.82; H, 4.54; N, 6.31. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 374 [1.08], 273 [2.20], 249 [3.20], 600 [0.02].

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dIDEOXY-3-O-propyl-\textbeta-D-glucose Copper(II) 291

A suspension of copper(II) acetate monohydrate (17.2 mg, 0.095 mmol) in EtOH (1 mL) was added to a solution of the imine 268 (35.3 mg, 0.086 mmol) in EtOH (1 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene, and concentrated. The resultant solid was dissolved in CH$_2$Cl$_2$, filtered through Celite, and concentrated. The resultant solid was recrystallised from a CH$_2$Cl$_2$/petrol layer diffusion to give the title compound as a green powder (27 mg, 77 %). $R_f$ 0.44 (EtOAc). IR (ATR): 1605 (C=N) cm$^{-1}$. HR-MS (APCI): $m/z$ 472.1062; [M+H]$^+$ requires 472.1059. Anal. Found: C, 58.75; H, 5.41; N, 5.80. Calc. for C$_{23}$H$_{24}$N$_2$O$_5$Cu: C, 58.53; H, 5.13; N, 5.94. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 374 [1.30], 273 [2.96], 249 [4.06].
1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-pentyl-β-D-glucose
Copper(II) 292

A suspension of copper(II) acetate monohydrate (16.4 mg, 0.09 mmol) in EtOH (1 mL) was added to a solution of the imine 269 (36.1 mg, 0.08 mmol) in EtOH (3 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant solid was dissolved in CH$_2$Cl$_2$, filtered through Celite, and concentrated to give the title compound as a green powder (40 mg, 97%). R$_f$ 0.48 (EtOAc). IR (ATR): 1606 (C=N) cm$^{-1}$. HR-MS (APCI): m/z 500.1370; [M+H]$^+$ requires 500.1372. Anal. Found: C, 59.88; H, 5.44; N, 5.42. Calc. for C$_{25}$H$_{28}$N$_2$O$_5$Cu: C, 60.05; H, 5.64; N, 5.60. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [$\varepsilon \times 10^4$ M$^{-1}$ cm$^{-1}$]: 374 [1.12], 273 [2.29], 249 [3.27], 600 [0.01].

1,6-Anhydro-2,4-bis(3,5-di-tert-butyrsalicylidene)amino-2,4-dideoxy-β-D-glucose
Copper(II) 293

A suspension of copper(II) acetate monohydrate (24.0 mg, 0.13 mmol) in EtOH (4 mL) was added to a solution of the imine 270 (60 mg, 0.102 mmol) in CHCl$_3$ (1 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant solid was dissolved in CH$_2$Cl$_2$ and filtered through Celite. Addition of Et$_2$O to the solution resulted in precipitation of the title compound as a green powder (65.7 mg, 98%). R$_f$ 0.22 (EtOAc/petrol 1:4). IR (ATR): 1598 (C=N) cm$^{-1}$. HR-MS (APCI): m/z 654.3099; [M+H]$^+$ requires 654.3094. Anal. Found: C, 202
66.09; H, 7.53; N, 4.19. Calc. for C_{36}H_{50}N_{2}O_{5}Cu: C, 66.08; H, 7.70; N, 4.28. UV-Visible (CH_{2}Cl_{2}) \lambda (nm) [\varepsilon \times 10^{4} M^{-1} \text{cm}^{-1}]: 236 [4.10], 282 [2.73], 389 [1.16], 651 [0.03]

1,6-Anhydro-2,4-bis(3,5-di-tert-butylsalicylidene)amino-2,4-dideoxy-3-O-propyl-\beta-D-altrose Copper(II) 294

A suspension of copper(II) acetate monohydrate (17.8 mg, 0.098 mmol) in EtOH (4 mL) was added to a solution of the imine 271 (56.7 mg, 0.089 mmol) in CHCl_{3} (1 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant solid was dissolved in CH_{2}Cl_{2}, filtered through Celite, concentrated to give the title compound as a green powder (54 mg, 87%). R_{f} 0.35 (EtOAc/petrol 1:9). IR (ATR): 1610 (C=N) cm^{-1}. HR-MS (APCI): m/z 696.3563; [M+H]+ requires 696.3562. Anal. Found: C, 67.31; H, 7.87; N, 3.82. Calc. for C_{39}H_{56}N_{2}O_{5}Cu: C, 67.26; H, 8.10; N, 4.02. UV-Visible (CH_{2}Cl_{2}) \lambda (nm) [\varepsilon \times 10^{4} M^{-1} \text{cm}^{-1}]: 239 [3.59], 284 [2.35], 384 [1.06], 567 [0.05].

1,6-Anhydro-2,4-bis(3,5-di-tert-butylsalicylidene)amino-2,4-dideoxy-3-O-pentyl-\beta-D-glucose Copper(II) 295

A suspension of copper(II) acetate monohydrate (18.7 mg, 0.103 mmol) in EtOH (4 mL) was added to a solution of the imine 271 (61.2 mg, 0.092 mmol) in CHCl_{3} (1 mL)
and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant solid was dissolved in CH$_2$Cl$_2$, and filtered through Celite. Addition of Et$_2$O to the solution resulted in precipitation of the title compound as a green powder (24.7 mg, 37%). R$_f$ 0.59 (EtOAc/petrol 1:9). IR (ATR): 1598 (C=N) cm$^{-1}$. HR-MS (APCI): m/z 724.3880; [M+H]$^+$ requires 724.3876. Anal. Found: C, 67.79; H, 8.22; N, 3.70. Calc. for C$_{41}$H$_{60}$N$_2$O$_5$Cu: C, 67.97; H, 8.35; N, 3.87. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [\(\varepsilon \times 10^4\) M$^{-1}$ cm$^{-1}$]: 238 [3.81], 282 [2.49], 388 [1.09], 650 [0.03].

(2-((1,3-Bis(salicylideneamino)propan-2-yl)oxy)ethoxy)-\(\beta\)-D-galactopyranoside Copper(II) 296

A suspension of copper(II) acetate monohydrate (13.9 mg, 0.077 mmol) in EtOH (3 mL) was added to a solution of the imine 282 (35 mg, 0.07 mmol) in CHCl$_3$ (1.6 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant residue was dissolved in a mixture of MeOH/DCM and precipitated with petrol to give the title compound as a green powder (19 mg, 48%). R$_f$ 0.06 (MeOH/EtOAc 1:9). IR (ATR): 3354 (O-H), 1615 (C=N) cm$^{-1}$. HR-MS (APCI): m/z 566.1315; [M+H]$^+$ requires 566.1326. Anal. Found: C, 53.00; H, 5.08; N, 4.74. Calc. for C$_{23}$H$_{30}$N$_2$O$_9$Cu: C, 53.05; H, 5.34; N, 4.95. UV-Visible (CH$_2$Cl$_2$) $\lambda$ (nm) [\(\varepsilon \times 10^4\) M$^{-1}$ cm$^{-1}$]: 369 [0.72], 274 [1.71], 245 [2.80].
(2-((1,3-Bis(3,5-di-tert-butylsalicylideneamino)propan-2-yl)oxy)ethoxy)-β-D-galactopyranoside Copper(II) 297

A suspension of copper(II) acetate monohydrate (13.5 mg, 0.074 mmol) in EtOH (2 mL) was added to the imine 283 (49.1 mg, 0.067 mmol) dissolved in CHCl₃ (2.5 mL) and the resultant solution was refluxed (1 h). The solution was diluted with toluene and concentrated. The resultant residue was dissolved in a mixture of MeOH/DCM and precipitated with petrol to give the title compound as a green powder (30.4 mg, 57 %). Rₚ 0.19 (EtOAc). IR (ATR): 3410 (O-H), 1611 (C=N), 1068 (C-O) cm⁻¹. HR-MS (APCI): m/z 790.3848; [M+H]⁺ requires 790.3830. Anal. Found: C, 62.44; H, 7.70; N, 3.53. Calc. for C₄₁H₆₂N₂O₉Cu: C, 62.30; H, 7.91; N, 3.54. UV-Visible (CH₂Cl₂) λ (nm) [ε × 10⁻⁴ M⁻¹ cm⁻¹]: 612 [0.04]

Di-(μ-4-O-1,6-anhydro-2-deoxy-2-salicylideneamino-β-D-glucose) Dicopper(II) 302

Salicyaldehyde (136 mg, 1.11 mmol) was added to a solution of 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose¹⁸⁵ (179 mg, 1.1 mmol) in MeOH (8 mL) and the resultant solution was heated at reflux (10 min). A solution of phenanthroline (200 mg, 1.70 mmol) in MeOH (2 mL) then a solution of copper(II) acetate monohydrate (202 mg, 1.11 mmol) in water (4 mL) were added and the resultant mixture was heated at reflux (10 min). A grey-green precipitate formed on cooling and was collected by
filtration, washed with MeOH (2 x 3 mL) and Et₂O (2 x 3 mL), and dried. Recrystallisation of the resultant solid in a mixture of MeOH/CH₂Cl₂ gave the title compound (102.2 mg, 14%). Rₚ 0.63 (EtOAc). IR (ATR): 3518, 3352 (O-H), 1617 (C=N) cm⁻¹. HR-MS (APCI): m/z; 653.0264 [M+H]⁺ requires 653.0258. Anal. Found: C, 47.81; H, 4.04; N, 4.23. Calc. for C₂₆H₂₆N₂O₁₀Cu₂: C, 47.78; H, 4.01; N, 4.29. UV-Visible (CH₂Cl₂) λ (nm) [ε × 10⁴ M⁻¹ cm⁻¹]: 372 [1.34], 274 [2.35], 246 [4.09].

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-propyl-β-D-glucose

Palladium(II) 313

A solution of palladium(II) acetate (22 mg, 0.097 mmol) in MeOH (1 mL) was added to the imine 268 (40 mg, 0.097 mmol) dissolved in MeOH (2 mL) and the resulting solution was refluxed (2 h). The resultant mixture was concentrated and the crude powder was washed with MeOH (3 x 3 mL). The title compound was recrystallised from CH₂Cl₂/Hexanes to give yellow needles (36 mg, 72 %). Rₚ 0.25 (EtOAc). IR (ATR): 1604 (C=N) cm⁻¹. HR-MS (APCI): m/z 515.0806; [M+H]⁺ requires 515.0798. Anal. Found: C, 53.46; H, 5.00; N, 5.15. Calc. for C₂₃H₂₄N₂O₃Pd: C, 53.65; H, 4.70; N, 5.44.
Di(1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-propyl-β-D-glucose)diaquadi-µ-acetato Trinickel(II) 314

Nickel(II) acetate tetrahydrate (12.9 mg, 0.052 mmol) was added to a solution of the imine 268 (20 mg, 0.049 mmol) in MeOH (3 mL) and the resulting solution was refluxed (0.5 h). The resultant mixture was concentrated and the crude powder was washed with ice cold CH₂Cl₂ (2 mL) to give the title compound as a pale green powder (20 mg, 87 %). Rf 0.11 (EtOAc/petrol 3:7). IR (ATR): 1618 (C=\(\text{N}\)) cm\(^{-1}\). HR-MS (APCI): \(m/z\) 471.1071; [M]+ requires 471.1080. Anal. Found: C, 52.60; H, 5.21; N, 5.03. Calc. for C\(_{50}\)H\(_{58}\)N\(_4\)O\(_{16}\)Ni\(_3\): C, 52.35; H, 5.10; N, 4.88.

1,6-Anhydro-2,4-bis(salicylidene)amino-2,4-dideoxy-3-O-propyl-β-D-glucose Cobalt(II) 315

Cobalt(II) acetate tetrahydrate (29.0 mg, 0.116 mmol) was added to a solution of the imine 268 (40.0 mg, 0.097 mmol) in a mixture of toluene (1.5 mL) and MeOH (1.5 mL) and the resulting solution was heated at 40 °C (10 min) then stirred at room temperature (16 h). The resultant mixture was concentrated and flash chromatography (EtOAc/petrol 9:1 to MeOH/EtOAc 1:9) of the residue gave the title compound as a dark red glassy solid (20 mg, 44 %). Rf 0.57 (EtOAc). IR (ATR): 1610 (C=\(\text{N}\)) cm\(^{-1}\). HR-MS (APCI): \(m/z\) 468.1086; [M+H]+ requires 468.1095. Anal. Found: C, 59.23; H, 5.40; N, 5.88. Calc. for C\(_{23}\)H\(_{24}\)N\(_2\)O\(_5\)Co: C, 59.11; H, 5.18; N, 5.99.
Cytotoxicity in cancer cell lines

Assays were performed with compounds 290-297, and 302 using the same details as described in Chapter 1.
Chapter 3

Efforts towards bifunctional carbohydrate-based catalysts
INTRODUCTION

The hydrogen bond

The hydrogen bond (H-bond) underpins the very existence of life and yet its chemical history only dates back a hundred years or so.\textsuperscript{365-367} In the early 1920s, Huggins, Langmuir, Sidgwick, and Pauling published papers expounding the general concept of the hydrogen bond.\textsuperscript{368-373} Hydrogen bonding was publicly recognised at a meeting of the Faraday Society in 1936, but it took until 2011 for the governing chemical body, IUPAC, to publish an official definition of the infamous bond which reads thus: \textsuperscript{367,374}

“The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.”

While the report goes on to further clarify a hydrogen bond, and describes how to experimentally identify one and some of the characteristics of hydrogen bonding, the article misses the excitement and true worth of hydrogen bonding.

Hydrogen bonds and their importance are ubiquitous. These intramolecular forces are crucial for maintaining the genetic code, in keeping the double strands of DNA and RNA intact.\textsuperscript{375} It has been surmised that hydrogen bonding in RNA could have been a contributing factor to the origins of life.\textsuperscript{376} In some other biological aspects, hydrogen bonds are the source of the unique and life-sustaining properties of water, aid in the folding of proteins, and control the activity of many enzymes.\textsuperscript{365,375,377}

From a synthetic chemistry perspective, research has focused on exploring the use of hydrogen bonding interactions in mediating enantioselective reaction outcomes. The interest in the ability of hydrogen bonding to activate substrates during enzymatic catalysis has inspired a new class of asymmetric organocatalysts.\textsuperscript{365} These organocatalysts contain H-bond donor motifs, which act as electrophile activators similar to Brönsted-acid catalysts.
Hydrogen bonding and asymmetric organocatalysts

Organocatalysts, as the name suggests, are comprised of non-metal elements such as carbon, hydrogen, oxygen, nitrogen, sulfur and phosphorus. The general advantages of organocatalysts compared to metal catalysts is that they are usually stable in air and water. Reactions do not require Schlenk techniques, inert gases, or dry solvents. In addition, there are no toxic metal by-products, the organocatalysts are usually non-toxic, and ‘greener’ and safer than most metal catalysts. These catalysts can be chiral or achiral, as both are reported as capable of inducing enantioselectivity during reactions. This chapter will focus on chiral catalysts for asymmetric catalysis.

There are 3 broad classifications of small molecule hydrogen bonding organocatalysts: (1) Single H-bond donors, (2) Double H-bond donors, and (3) Bifunctional H-bond donors

Research into single H-bond donor catalysts is relatively recent. This type of H-bonding is less popular because the disadvantage of a single hydrogen bond is that it often lacks the strength and directionality of a double H-bond donor. The electrophile is less tightly held and the catalyst is often not rigid enough to induce asymmetry in the reaction. (R)-(+)1,1'-Bi-2-naphthol and (4R,5R)-2,2-Dimethyl-α,α,α',α'-tetraphenylidioxolane-4,5-dimethanol, and derivatives have been cited as single H-bond donors. However, for complete clarification, the mode of activation should be determined on a case-by-case basis.

![Figure 3.1](image-url) – Some examples of single hydrogen bond donors.
Double H-bond donors contain two hydrogen bonds quite close together, mimicking successful biocatalysts of Nature such as aldolases.\textsuperscript{365,383-386} The double hydrogen bond offers the advantage of a stronger, more directional substrate interaction than a single hydrogen bond.\textsuperscript{365} This removes flexibility and confers a more rigid conformational binding of the substrate, favourable for an enantioselective outcome. Double H-bond catalysts include ureas,\textsuperscript{387-388} thioureas,\textsuperscript{379,389} and guanidinium,\textsuperscript{390-391} and amidinium\textsuperscript{392-393} ion derivatives (Figure 3.2).

![Figure 3.2](image)

**Figure 3.2** – The general structures of the main four classes of double H-bond catalysts.

Specifically, some examples of ureas and thioureas include 318 and 319, 320, and 321 from the groups of Curran,\textsuperscript{387-388} Schreiner,\textsuperscript{379} and Jacobsen,\textsuperscript{389} respectively, which have been used as organocatalysts in Claisen rearrangements, Strecker and Diels-Alder reactions (Figure 3.3).

![Figure 3.3](image)

**Figure 3.3** – Some examples of urea and thiourea double hydrogen bond donors.
Bifunctional catalysts contain two catalytic motifs attached to a chiral scaffold; a H-bond donor and another acidic or basic functional group. It is thought that chiral bifunctional catalysts are able to bind electrophiles and nucleophiles in a close, selective, three-dimensional spatial arrangement amenable to asymmetric catalysis.\(^3\)\(^9\)\(^4\)

L-Proline 322 and cinchona alkaloids such as 323 were popular chiral scaffolds among the first bifunctional catalysts reported, combining an amino group and a carboxylic acid or acidic alcohol, respectively, on a chiral core (Figure 3.4).\(^3\)\(^6\)\(^5\)-\(^3\)\(^9\)\(^6\)

![Figure 3.4](image)

**Figure 3.4** – Some examples of bifunctional hydrogen bond donors.

Based on the success of proline and cinchona-based catalysts, studies have also been conducted using bifunctional thiourea derivatives, such as thiourea/amine combinations of the type 324, inspired by knowledge of thio/urea moieties acting as double H-bond donors (Figure 3.4).\(^3\)\(^8\)\(^8\)-\(^3\)\(^9\)\(^8\)

**Pioneering studies in bifunctional thiourea/amine organocatalysis**

Jacobsen,\(^3\)\(^8\)\(^9\) and Schreiner and Wittkopp\(^3\)\(^7\)\(^9\)-\(^3\)\(^9\)\(^9\) prepared some of the first examples of thiourea derivatives which were used to catalyse important C-C bond formations, namely 320 and 321 (Figure 3.3).\(^3\)\(^7\)\(^9\)-\(^3\)\(^8\)\(^9\)-\(^3\)\(^9\)\(^9\) Takemoto and colleagues followed close behind with the development of the chiral bifunctional thiourea/amine system 325 (Figure 3.5).\(^4\)\(^0\)
Takemoto’s catalyst 325, incorporating a thiourea moiety and tertiary dimethylamino group around a 1,2-diaminocyclohexane scaffold, successfully catalysed the addition of malonates to nitroolefins with high enantioselectivities. Other early examples of thiourea/amine catalysts include 326 by Tsogovera and colleagues, 327 by Jacobsen and Huang, and 328 by Tang and co-workers (Figure 3.6).

From the early thiourea/amine catalysts grew three subclasses; thiourea motifs with either a tertiary, secondary, or primary amine moiety. All catalysts were based on the design of a chiral backbone separating the thiourea and amine moieties (Figure 3.7). For catalysts with secondary or tertiary amines, the simultaneous activation of both electrophile and nucleophile (or pre-nucleophile) is proposed to occur through one of two pathways (Figure 3.7).
Figure 3.7 – The general design for a bifunctional thiourea/amine catalyst and two possible mechanistic pathways for a conjugate addition reaction with a thiourea/amine catalyst.

In pathway A, the electrophile is activated by the double hydrogen bonding of the thiourea, while the amino group deprotonates the nucleophile. In pathway B, the thiourea binds the deprotonated nucleophile, while the amine activates the electrophile by single hydrogen bonding. Computational chemistry and reaction intermediate characterisation enable the determination of the most thermodynamically probable
mechanism. In the case of primary amines, the commonly proposed mechanism is that of enamine formation between the primary amine and the nucleophile, and electrophile activation through H-bonding with the thiourea moiety (Figure 3.8).\cite{386,405}

Investigation into the mechanism of bifunctional thiourea catalysts serves to reinforce the advantage of simultaneous coordination and activation of both substrates in a controlled orientation that leads to high stereoinductions in products. Thiourea/amine catalysts have been successfully employed in a wide range of organic reaction such as conjugate additions, aldol reactions and variations, domino reactions, and reductions.\cite{365,386,406-411}

![Figure 3.8](image.png)

**Figure 3.8** – The commonly proposed enamine mechanism for thiourea/primary amines in an example of a nitro-Michael additions with acetone as the pre-nucleophile and β-nitrostyrene as the nucleophile.

**Carbohydrate-based thiourea/amine catalysts**

The inherent chirality of carbohydrates could make them good scaffolds for asymmetric catalysis, with fine tuning of the catalyst being possible due to the many stereochemical and functional permutations accessible from one monosaccharide.\cite{50,412-413}

In 2007, Ma and colleagues reported preparing catalysts that incorporated per-acetylated D-glucose 329 and 330, D-lactose 331 and D-maltose 332 moieties as secondary chiral backbones; 1,2-diaminocyclohexane being the primary backbone (Figure 3.9).\cite{414} these were the first examples of carbohydrate-containing bifunctional thiourea/amine catalysts. The most active catalyst 329 efficiently catalysed the addition of various aromatic ketones to nitroolefins, with the S-enantiomeric products
being favoured. It was hypothesised that \((R,R)\)-diaminocyclohexane ‘matched’ the \(\beta\)-D-glucopyranose chirality, as catalyst 329 resulted in the highest yield and stereoselectivity. However, the exact role of the chirality of the carbohydrate in determining the stereochemical outcome was unclear and has not been further elucidated. Interestingly, 330, which was the \((S,S)\)-diaminocyclohexane enantiomer, promoted the opposite enantioinduction in the same reaction. This demonstrates that a simple stereochemical change on the scaffold is enough to fine-tune the catalyst to produce the opposite enantiomer and that any chiral effects due to the carbohydrate motifs are minor.

**Figure 3.9** – Ma and colleagues’ thiourea/amine catalysts, incorporating carbohydrate motifs.

Other contributions which give an idea of the scope of design of thiourea/amine bifunctional catalysts incorporating carbohydrates include work by; Wu et al. investigating epimer variations of D-glucose, D-galactose and D-mannose on scaffolds such as 333-336. Ma et al. investigating the primary chiral scaffolds 337-339 with secondary scaffolds encompassing D-glucose with different protecting groups, and the
disaccharides lactose and maltose, and Shao et al. investigating catalysts derived from carbohydrates and amino acids such as permutations with (Figure 3.10). In most cases, a combination of D-glucose with the (R,R)-configuration of the primary chiral scaffold gave the most active catalyst. In addition, the overall catalyst structure and reaction type dictated whether including a primary or tertiary amine moiety would be most successful.

Figure 3.10 – Further carbohydrate-incorporating thiourea/amine catalysts.
Several of the catalysts above have been compared with non-carbohydrate analogues such as Takemoto’s catalyst 325. Carbohydrate-based catalysts with stereochemistry that ‘matched’ that of the primary scaffold gave superior enantioselectivity compared to non-carbohydrate catalysts. This suggests that the carbohydrate motif, when matched, benefits the enantioselective outcome of the reaction. This effect could be described as secondary-sphere chirality, enhancing the primary chiral scaffold and outcome of the reaction from a distance. Secondary sphere effects are usually discussed in relation to enzyme and metal-based catalysis. These effects including inducing a degree of order in the structuring of solvent lattices around the primary active site, confining non-participating sections of larger substrates to limited configurations, or creating reaction channels which pre-orient substrates before they reach the active site or metal centre. These methods all serve to enhance stereoinduction by providing a larger, controlled chiral zone. In the case of carbohydrate-based thiourea/amine catalysts, these catalysts function without the sugar moiety, but show increased enantioselectivity when a matched carbohydrate is included. This suggests that the carbohydrate moiety exerts some control over the extend chiral zone, to the benefit of the catalytic outcome.

Carbohydrate-based primary scaffolds

In many of the cases discussed above, the catalysts contain a carbohydrate moiety in conjunction with another chiral scaffold, usually the popular 1,2-diaminocyclohexane motif. As discussed above, the latter is thought to be the main driver of enantioselectivity. From using carbohydrates as a secondary chiral sphere, the logical progression was to use them as primary chiral scaffold.

Some of the first carbohydrate-based thiourea/amine catalysts 341-346 were reported by Puglisi and colleagues, catalysing nucleophilic additions to nitroolefins and imines (Figure 3.11). The scaffold had trans-C2,3 symmetry between the two catalytic motifs, similar to the prototypical Takemoto’s catalyst 325. It was found that silyl-protecting groups afforded better catalytic results. Based on these results, it was hypothesised that free hydroxyl and acetyl groups could also form hydrogen bonds with the reagents and interrupt the stereospecific activation of the bifunctional catalyst.
In 2014, Fügedi and Ágoston described a range of bifunctional thiourea/amine catalysts 347-355 based on carbohydrate cores (Figure 3.12).\textsuperscript{426} D-Gluco, as well as D-galaco and D-manno, were used as scaffolds and the catalytic groups were placed at different positions around the pyranose ring. Selected catalysts were tested in the reaction of the addition of acetylacetone to β-nitrostyrene. Only, 347, 348, and 349, containing a secondary amine, were active, and, unfortunately, gave only low enantioselectivity. The limited catalytic results prevented any in-depth comparisons of the effect of different epimers and scaffold modifications. However, notably, cis-geometry between the thiourea and amine resulted in an active catalyst.

Narula and co-workers produced a series of catalysts 356-365 with a furanose core, also for use in nitro-Michael additions (Figure 3.13).\textsuperscript{427} They used both a two- and three-bridged carbon chain between the two catalytic centres to examine the effects of rigidity on activity. In addition, they attached the catalytic centres to the furanose ring.
in both cis and trans configurations and varied the substituents on the amine nitrogen. It was found that C3/4-trans-geometry was the best arrangement of the catalytic centres, with 365 giving enantioselectivities above 90% in the addition of cyclohexanone to trans-β-styrene derivatives. Secondary amines were better than tertiary amines and a benzyl motif worked best as the amine substituent, providing facial hindrance for stereoselectivity without bringing steric bulk close to the nitrogen atom.

![Chemical structures](image)

**Figure 3.13** – Carbohydrate-based thiourea/amine catalysts by Narula et al.

In recent years, there have been many reports of bifunctional thiourea catalysts with basic moieties other than amines, as well as acidic groups. Where knowledge of these catalysts has complemented the studies here-in, they are discussed in the Results and Discussion section. While interesting, many are beyond the scope of this thesis. However, reviews and articles by Kotke and Schreiner,394 Limnios and Kokotos,406 and Phillips50 give good overviews of the wider topic of bifunctional thiourea catalysts.
1,2- and 1,3-diamine bridges

In designing bifunctional thiourea/amine catalysts, a convention of placing the two catalytic centres within two carbons of each other seems to have become established. This is probably due to the archetypal Takemoto catalyst 325, as the 1,2-diaminocyclohexane core is almost always cited as the inspiration behind most designs. Although the examples of 1,3-diamine and larger bridged bifunctional catalysts in the literature are fewer in number, the design boundaries are expanding and longer bridges are being incorporated into potential catalysts, with positive results.

Some examples of 1,3-diamine bridged catalysts have reported excellent enantiomeric selectivity. These all contain chiral scaffolds other than a carbohydrate core. The guanidine/bis-thiourea 366 was used in 1,4-type Friedel-Crafts alkylations of phenols and phospha-Michael reactions with enantioselectivities above 90%. The ferrocene-based thiourea/amine 367 and the thiourea/amine co-catalyst 368 (used with L-proline) both successfully catalysed Michael addition reactions (Figure 3.14).

![Figure 3.14](image-url)  

**Figure 3.14** – Examples of 1,3-diamine bridged thiourea/amine catalysts in the literature.

Narula and co-workers prepared the 1,3-diamine bridged compounds 358-363 in addition to 1,2-diamines (Figure 3.13). In that instance, however, the 1,2-diamine
bridged catalysts performed better, which was explained as being due to the increased rigidity of the 1,2-bridge. Fügedi and Ágoston have also prepared the 1,3-diamine bridged compounds 347-350 and 355 (Figure 3.12). In that instance, both the diamine bridge and substitution of the amine moiety were altered together, so the results cannot be compared for the sole effect of the diamine bridge modification on catalytic activity.

**Utilising a 1,6-anhydro scaffold as a 1,3-diamine bridge**

It is evident that a carbohydrate core can be a useful chiral scaffold to complement the more frequently used 1,2-diaminocyclohexane, cinchona alkaloids, or amino acids as a primary scaffold. Carbohydrates have been proven to be active, versatile scaffolds for the preparation of bifunctional thiourea/amine catalysts.

While carbohydrates have been successfully incorporated into bifunctional thiourea/amine catalysts, the extensive scope for modification and functionalisation of the carbohydrate core has not been rigorously investigated.

Typically, the carbohydrate has been used to take advantage of *cis/trans*-geometry and placement of the catalytic motifs around the ring. Also, little interest has been reserved for the conformation of the pyranose ring itself. In addition, almost all the examples have the catalytic motif in a 1,2-diamine arrangement.

Given the small number of 1,3-diamine bifunctional thiourea/amine catalysts and the lack of diversity of the carbohydrate core in the literature, it is of particular interest to explore the use of the 1,6-anhydropyranose frame as a viable chiral carbohydrate scaffold. This chapter is devoted to synthesising a small library of 1,6-anhydro-based thiourea/primary amine-type compounds 369-373 and investigating their potential as catalysts for nitro-Michael additions (Figure 3.15).
Figure 3.15 – Proposed library of 1,6-anhydro-β-D-glucose-based thiourea/amine catalysts.
RESULTS AND DISCUSSION

Catalyst design strategy

The five proposed catalytic targets 369-373 (Figure 3.15) were designed to investigate four main points of interest being: (1) the effect on activity of a rigid carbohydrate core, (2) the effect on enantioselectivity of the position of each catalytic moiety (C2 or C4), (3) the effect on activity of a 1,3-diamine bridge, and (4) the effect on hydrogen donating ability of the thiourea motif with different substituents.

In their 2003 review, Wittkopp and Schreiner outlined the makings of a successful (thio)urea catalyst including the need for the catalytic structure to be paradoxically rigid to restrict the degrees of freedom of substrate binding, but flexible enough to adapt to changes in conformation as the reaction proceeds through the transition state to the final product. This ‘Goldilock’s principle’ is often referred to in catalysis. In combination, the rigid 1,6-anhydro backbone of the catalyst with the pendant, flexible catalytic motifs on C2/4 may provide a successful mix of flexible and inflexible.

In considering the positioning of the catalytic motifs, the literature examples presented in the Introduction demonstrated that the position of the catalytic centres relative to each other affected the facial positioning of the bound substrates. The terms matched and mismatched were used to describe the placement of two chiral units which resulted in substrates binding with minimal steric repulsion, giving maximum catalytic activity. In the 1,6-anhydro model there may be an enantioselective advantage of the placement of the two catalytic motifs (either 4-amino-2-thioureido or 2-amino-4-thioureido). In addition, in the examples of Ágoston and Fügedi (Figure 3.12), and Narula and co-workers (Figure 3.13), the configuration of the two catalytic centres cis or trans to each other had a marked effect on catalytic activity. In this pilot study, to control the number of variables studied, it was chosen to fix the two catalytic moieties cis to each other.

The bridge between the catalytic motifs would be a 1,3-diamine bridge, a variation on the common 1,2-diamine bridge often used. However, as previously discussed, 1,3- and 1,4-bridges have also seen success. At the time of writing, based on
the literature, the fixed \textit{cis}-1,3-diamine geometry of the 1,6-anhydro scaffold has not yet appeared in a catalyst structure.

Thioureas are incorporated into catalysts more often than ureas, as it is generally proposed that they enhance catalytic activity over ureas.\textsuperscript{379,435} The substitution of oxygen for sulfur makes the thiourea motif more acidic thus increasing hydrogen bond donor abilities.\textsuperscript{436} Consequently, the p$K_a$ values of ureas are greater than thioureas, (Table 3.1).\textsuperscript{436-437} In addition, thioureas show a lower tendency to self-aggregate through H-bonding, which increases the amount of active catalyst present in a reaction.

Concerning substitution on a thiourea motif, Jakab and co-workers evaluated the effect of substitution on thiourea H-bond donor strength by measuring the p$K_a$ of a variety of substituted thioureas and thiourea/amines.\textsuperscript{436} In simple scaffolds, they observed that N-aryl groups significantly increased the acidity of the thiourea and electron-withdrawing trifluoromethyl (CF$_3$) groups on the phenyl ring further increased acidity and activity of catalysts incorporating this moiety (Table 3.1).

\textbf{Table 3.1} – p$K_a$ Values of unsubstituted and substituted thioureas\textsuperscript{436}

\begin{tabular}{c cc c}
\hline
 & \multicolumn{3}{c}{p$K_a$} \\
 & H$_2$N & S & H$_2$N \\
\hline
O & 26.9 ± 0.1 & 21.1 ± 0.1 & 13.4 ± 0.1 \\
\hline
S & & & \\
\hline
 & CF$_3$ & CF$_3$ & CF$_3$ \\
N & 10.9 ± 0.1 & 8.5 ± 0.1 & \\
\hline
F$_3$C
\end{tabular}

The study assumed, therefore, that N-alkyl groups would show decreased acidity. It did note, however, that some literature N-alkyl examples such as the Jacobsen-like thiourea derivative \textsuperscript{374} (Figure 3.16), were successful catalysts.\textsuperscript{436,438} In this study, the effect on the hydrogen donating ability of the thiourea motif was investigated using three different N-substituents; ethyl, phenyl and \textit{bis}-3,5-(trifluoromethyl)phenyl.
In choosing a 1,6-anhydro scaffold as the chiral core, there were a few design areas that could not be explored, such as the polyfunctionalization of the carbohydrate ring. Recent studies by Puglisi et al. and Ma et al. have shown that different substituents on non-participating hydroxyl groups can affect the catalytic outcome (Figures 3.10 and 3.11). With most of the hydroxyl groups incorporated into the bicyclic ring system on this 1,6-anhydro scaffold, it was not a major area of interest. The C3 oxygen would be protected as a methyl ether, with potential to expand to other protecting groups after the pilot study. A methyl ether is a relatively innocuous motif, due to its small size and stability in a majority of conditions.

**Synthesis of the 1,6-anhydro-based organocatalysts**

Thioureas are often prepared through the addition of a free amine to an isothiocyanate.

The synthetic route to the bifunctional thiourea/amine compounds was designed to potentially afford both the 4-amino-2-thioureido and the 2-amino-4-thioureido derivatives from the same starting material. This required a method that differentiated between an amine prepared at C2 or C4. Therefore, a divergent pathway, where the activities at C2 and C4 could be manipulated discretely, was sought. It was envisioned that this divergence should take place as late as possible in the synthetic pathway, for an atom economical synthesis.

Starting from the diol **55**, it was proposed that the azide could be reduced to an amine and suitably protected as in **375** (Figure 3.17). Then the established triflate route from Chapter 1 could be used to prepare the C4 axial azide **376**. This could allow for
manipulation of the two amine sites. Deprotection with sodium methoxide would leave the free C3 hydroxyl group that could be converted to an ether as in 377, masking the hydroxyl group.

Figure 3.17 – The proposed synthetic route to carbohydrate-based thiourea/amines highlighting the important divergent intermediate 377.

From 377, the synthesis could then diverge with a C4-thiourea 378 being potentially prepared by reduction the azide to give the amine 379, followed by formation of the thiourea and removal of the protecting group. Conversely, the C2-thiourea 380 could be prepared by removal of the protecting group to give the amine 381, followed by formation of the thiourea and reduction of the azide (Figure 3.17).

Starting from the diol 55, reduction in the presence of palladium-on-carbon and hydrogen gas, followed by treatment with di-tert-butyl dicarbonate gave the N-Boc protected diol 382 (Scheme 3.1). N-Boc protection was chosen as the carbamate can be readily removed under mild acidic conditions.192
From this material, it was thought that the triflate 383 could be prepared in a fashion similar to that of 58 (as discussed in Chapter 1). Unfortunately, after reaction of 382 with triflic anhydride then benzoyl chloride, two compounds by NMR were formed, with identical polarity by TLC. It is known that N-Boc protected amino acids present as rotamers in solution-based NMR. It was thought that the Boc groups could give rise to rotamers in this instance, but variable temperature $^1$H NMR experiments showed no resolution of signals. Overall, these experiments do not rule out rotamers, but strongly suggest that there are two separate compounds.

Another possibility worth considering was that the Boc-protecting group was interfering in the protection and activation at C3 and C4 respectively. Preparation of the triflate 58 (as described in Chapter 1), followed by a one pot reduction/in situ protection adapted from Henry et al. gave one product, 383, on isolation (Scheme 3.2). This then suggests that there were two compounds in the first attempt at the preparation of 383.

With 383 in hand, attention could be given to the preparation of the desired azide of the type 377. Displacement of the triflate of 383 with NaN$_3$ gave 384, followed by deprotection with sodium methoxide gave the alcohol 385 (Scheme 3.3). Installation
of the desired methyl ether at C3 using MeI and NaH gave two compounds by $^1$H NMR, one presumably being the desired compound 386, with both having the same $R_f$ by TLC. Variable temperature $^1$H NMR experiments ruled out rotamers existing, so it was thought that $N$-methylation could be occurring.\(^{444}\)

![Diagram](image)

**Scheme 3.3** – a) NaN$_3$, DMF; b) NaOMe, MeOH; c) NaH, MeI, DMF.

The Boc group was proving to be synthetically challenging and another approach to amine protection was sought. Although the Boc group could still be useful for the divergent synthesis, the first set of reactions to prepare the azide 385 could also proceed with an acetamido protecting group. In fact, the acetyl group may also deactivate the amine towards alkylation.\(^{444}\) Henry and co-workers successfully applied a method from Burk and Allan for converting amides to carbamates.\(^{444,445}\) The acetamide 387 was protected with a Boc group, to give the dual protected amide 388, followed by treatment with hydrazine to give the Boc carbamate 389 (Scheme 3.4).

![Diagram](image)

**Scheme 3.4** – a) Boc$_2$O, DMAP, THF; b) NH$_2$NH$_2$, H$_2$O, MeOH.

This method presented a facile pathway to the important intermediate 386, as none of the other functional groups were hydrazine sensitive. From the triflate 58, one-pot
hydrogenation and acetylation, via the Henry method, gave the acetamide 390 in good yield (Scheme 3.5). Subsequent displacement of the triflate with sodium azide gave 391. The alcohol 392 was obtained in good yield following treatment with sodium methoxide.

![Scheme 3.5](image)

Scheme 3.5 – a) Pd/C, H₂, Ac₂O, EtOAc; b) NaN₃, DMF; c) NaOMe, MeOH.

Treatment of the azide 392 with sodium hydride followed by methyl iodide again resulted in two or more compounds by ¹H NMR analysis, but with identical polarity by TLC (Scheme 3.6). However, the use of the acetyl group made deciphering the NMR spectrum much easier. It was thought that the compound of interest 393 had been prepared, and that potential amide methylation had also occurred. Although an amide should be deactivated towards alkylation, the conditions were harsh enough to force N-methylation. N-methylation was evident from two singlets between 2.90-3.13 ppm. There was also evidence of O-methylation, with three singlets observed between 3.40-3.50 ppm. The multiple signals in the regions for both N- and O-methylation suggested multiple side products had been formed in addition to the target compound 393. If the side products included the hypothesised methylated acetamide 394, then further reaction with di-tert-butyldicarbonate would give both the N-AcBoc azide 395 and leave the N-AcMe azide 394 untouched. While the methyl group does not significantly change the polarity of the side-product, it was hoped that the Boc-group would allow for isolation of the target compound.
Scheme 3.6 – a) NaH, MeI, DMF; b) Boc₂O, DMAP, THF; c) NH₂NH₂·H₂O, MeOH.

On treatment of the mixture with di-tert-butyl dicarbonate, a new spot was observed by TLC. On separation, the product of interest 395 with both the acetyl and Boc groups was obtained. Further treatment of 395 with hydrazine afforded the N-Boc protected compound 386 (Scheme 3.6).

The remaining mixture of compounds, presumably mostly 394, from the Boc-protection eluted as one spot during purification. ¹H NMR experiments showed two sets of signals, with two signals for N-methylation (2.77 and 2.97 ppm), signals for two O-methyl groups (3.30 and 3.34 ppm), an acetamide signal, and no evidence of the Boc-methyl groups.

Of interest is that, due to the partial double bond character of amides preventing free rotation around the amide bond, these two signal sets may have arisen due to conformational isomers on the NMR timescale (Figure 3.18). Similar phenomena are observed in other unsymmetrically N,N-disubstituted acetamides and amino acids, where the two methyl groups are either arranged cis or trans to each other.
Figure 3.18 – A representation of the potential conformational isomers of 394, due to the methylated C2 acetamide.

Variable temperature NMR experiments suggested the two observed signal sets were due to rotamers, as increasing temperatures resulted in coalescence of signals (Figure 3.19).
Figure 3.19 – 600 MHz $^1$H NMR data sets of putative compound 394 at various temperatures showing coalescence of signals as the temperature increased.
In order to identify the region of the molecule undergoing conformational change, exchange spectroscopy (EXSY) NMR experiments were conducted. EXSY experiments are modified nuclear Overhauser effect spectroscopy (NOESY) experiments. NOESY experiments use NMR spin-lattice cross-relaxation to investigate intramolecular structural and exchange events. In an NOESY experiment two phenomena can be observed; signals belonging to two resonances from a single nucleus in conformational or chemical exchange on the NMR timescale, or two different nuclei close in conformational space. The former is the focus of EXSY and the latter provides structural information about molecular conformation. Both processes can be observed in a single suite of NOESY experiments. Fortuitously, in the case of small molecules, EXSY cross peaks are of opposite sign to conformation ‘through-space’ NOESY peaks in the spectrum, due to the switch in spin states during exchange. Thus, the positive off-diagonal peaks in the spectrum link two conformational signals belonging to one proton and pinpoint the area of conformational change. In addition, the NOE signals of opposite phase provide supporting information to identify molecular structures. These experiments are also useful for quantitative analysis of the exchange process and rate constants and activation parameters of the conformational exchanges can be calculated from the data.

In collaboration with Dr. Mark Howard and Dr. Gareth Nealon, EXSY experiments were conducted with mixing times of 300, 500, 800, 1000, 1500 and 2000 ms. Positive cross peaks between H1, H2 and the N-methyl group in each signal set were observed (x, y, and z respectively), indicating that magnetisation transfer between these signals is due to a chemical or conformational change and not a through-space relationship (NOE) (Figure 3.20). This finding compliments the VT NMR experiments and suggests the two signals sets may be due to the partial double bond character of the amide.
Figure 3.20 – 600 MHz $^1$H EXSY/NOESY NMR spectrum of putative 394, with a mixing time of 1000s. The off-diagonal, blue signals indicate magnetisation transfer due to chemical or conformational exchange (EXSY), the off-diagonal, red signals indicate through-space interactions.

In order to confirm the signal sets as due to rotamers about the amide bond, the NOE signals in the EXSY spectrum at 1000 ms were analysed.

For the major conformer (conformer a), H$_{1a}$ showed strong through-space interactions with N-CH$_{3a}$ (a, Figure 3.20), as H$_{3a}$ did with N-CH$_{3a}$ (b) and N-CH$_{3a}$ with the acetyl
CH$_{3a}$ (c) (Figure 3.20). For the minor conformer (conformer b), H$_{1b}$ showed weaker through-space interactions with N-CH$_{3b}$ (d), H$_{2b}$ showed a strong interaction with the acetyl CH$_{3b}$ (e), H$_{3b}$ showed a similar magnitude interaction with N-CH$_{3b}$ as in conformer a (f) and N-CH$_{3b}$ showed a weaker interaction with the acetyl CH$_{3b}$ than in conformer a (g). These results strongly suggest that the two signal sets are due to conformers occurring due to the slow chemical exchange between the two amide forms (the acetyl CH$_3$ being cis or trans to the N-CH$_3$). The postulated structures of the two conformers show the major form with the N-CH$_3$ and acetyl CH$_3$ cis to each other, which agrees with the stronger through space interactions observed in the EXSY spectrum (b and c, Figure 3.20). Conversely, the minor form shows stronger through-space interaction of the H$_{2b}$ with the acetyl CH$_{3b}$ (e, Figure 3.20), expected for a trans configuration.

From the experiments, exchange rate constant approximates were calculated by Dr. Mark Howard, using the method published by Bodenhausen and Ernst. The exchange rate constants were found to be $k_{ab} = 0.13 \pm 0.02$ s$^{-1}$ and $k_{ba} = 0.32 \pm 0.03$ s$^{-1}$, showing that the a form is indeed the major species. These rate constants agreed with the relative ratios of the conformational isomers in the $^1$H NMR spectrum (1:2.5).

With evidence that 394 was one compound, removal of the acetamide under basic conditions gave the azide 396 (Scheme 3.7). Crystals suitable for single crystal X-ray diffraction were obtained and diffraction studies were carried out by Dr Alexandre Sobolev indeed showed the postulated N-methylation (Figure 3.21).

Scheme 3.7 – a) KOH, MeOH, H$_2$O.
Figure 3.21 – X-ray crystal structure of the azide 396, showing N-methylation. Ellipsoids for key atoms are drawn at the 50% probability level.

With the mono-protected amine 386 in hand, the synthesis could now diverge to prepare the desired thiourea/amine isomers.

For the C2 thiourea, the Boc group was removed with trifluoracetic acid to give the amine 397 as a salt (Scheme 3.8). Treatment of the amine with the appropriate isothiocyanate gave the desired thioureas 398-400. With the thiourea motifs installed, the azide could then be reduced. Using the N'-ethyl derivative 398, reducing conditions of palladium on carbon in the presence of hydrogen gas gave the amine 369 in moderate yield. As this yield was not ideal, a different reduction procedure was attempted for 399 and 400. Literature precedents have used triphenylphosphine to reduce amines in the presence of such thiourea substituents.427,452-453

Scheme 3.8 – a) CF₃COOH, CH₂Cl₂; b) RNCS, Et₃N, CH₂Cl₂; c) Pd/C, H₂, MeOH or Me₃P, THF, H₂O.
Deprotection of the bis-3,5-(trifluoromethyl)phenyl derivative 400 using Staudinger conditions with triphenylphosphine appeared to afford only the iminophosphorane intermediate, as observed by TLC.\textsuperscript{193-194} Exchanging triphenylphosphine for the more reactive trimethylphosphine, afforded the target thiourea 372 in moderate yield (Scheme 3.8). The same reaction conditions with 398 also gave thiourea 371 in moderate yield.

Attention was now focussed on preparing the C4-thiourea molecules 370 and 373. Reduction of the azide 386 gave the amine 401 which was followed by treatment with the appropriate isothiocyanate to give the target thioureas 402 and 403 in good yields. The Boc group was removed using trifluoroacetic acid with the target thiourea 370 isolated as the trifluoroacetate salt 404, but, interestingly, 373 was isolated as the free amine (Scheme 3.9).

\textbf{Scheme 3.9} – a) Pd/C, H\textsubscript{2}, MeOH; b) RNCS, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}; c) CF\textsubscript{3}COOH, CH\textsubscript{2}Cl\textsubscript{2}.

\textbf{Catalytic studies}

Catalytic activity was evaluated using a nitro-Michael addition of acetone to β-nitrostyrene (Figure 3.22).

\textbf{Figure 3.22} – The nitro-Michael reaction.
This model reaction was chosen due to the simplicity of the reagents and the enantiomeric outcome of the products; a single pair of enantiomers. The test method, adapted from Yalalov et al., used 1 mmol β-nitrostyrene, 20 eq. acetone, and 15 mol% catalyst in 0.25 mL of solvent, which was stirred for 72 h. A range of solvents were tested; methanol, dichloromethane, tetrahydrofuran, acetone, acetonitrile, and toluene. As acid additives have been shown improve yields in some cases, a second set of screen reactions were conducted with the addition of a combination of 0.15 eq. acetic acid and 2 eq. water. The enantiomeric excess was determined by HPLC in comparison with the literature.

Compound 373, with the activating bis-3,5-(trifluoromethyl)phenyl substituent, was the first compound to be evaluated (Table 3.2). Importantly, no conversion was observed when no catalyst was present in the reaction over the same time period.

**Table 3.2 – Catalyst 373 initial screening in the nitro-Michael addition of acetone to β-nitrostyrene.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>17</td>
<td>12 S</td>
<td>7*</td>
<td>MeOH</td>
<td>52</td>
<td>r.</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>39</td>
<td>77 R</td>
<td>8*</td>
<td>CH₂Cl₂</td>
<td>13</td>
<td>65 R</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>19</td>
<td>65 R</td>
<td>9*</td>
<td>THF</td>
<td>18</td>
<td>57 R</td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>29</td>
<td>52 R</td>
<td>10*</td>
<td>Acetone</td>
<td>10</td>
<td>52 R</td>
</tr>
<tr>
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<td>CH₃CN</td>
<td>30</td>
<td>51 R</td>
<td>11*</td>
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<tr>
<td>6*</td>
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<td>32</td>
<td>84 R</td>
<td>12*</td>
<td>Toluene</td>
<td>24</td>
<td>78 R</td>
</tr>
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</table>

* With the addition of CH₃COOH/H₂O 0.15 eq.:2 eq. a Determined by ¹H NMR. b Determined by chiral HPLC. r. = racemic.

The best result for the combination of conversion and enantiomeric excess was found to be in toluene, without additives, giving a yield of 32% and an enantiomeric excess of 84% R (Entry 6, Table 3.2). Toluene was found to be the best solvent for catalyst 373, followed by dichloromethane (Entries 2, 6, 8 and 12, Table 3.2), mirroring
similar results in the literature. While methanol provided the highest conversion, the product was isolated as a racemate (Entry 7, Table 3.2). The chosen additive combination only improved conversion in the case of methanol (Entry 7, Table 3.2), and decreased the enantiomeric excess in most examples.

The remaining catalysts 369, 371, 372, and 404 were also screened against all solvents, both with and without the additives, to construct an overall picture of the conditions required for optimal conversion and enantiomeric excess. For efficiency, and due to the numerous low yields, enantiomeric excess was only determined for those entries of 20% conversion and above (Table 3.3).
Table 3.3 – Catalytic activities of 369, 371, and 372 in the addition of acetone to β-nitrostyrene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]^a</th>
<th>ee [%]^b</th>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]^a</th>
<th>ee [%]^b</th>
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<tr>
<td></td>
<td></td>
<td>Catalyst 369</td>
<td></td>
<td></td>
<td></td>
<td>Catalyst 371</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>0</td>
<td></td>
<td>7*</td>
<td>MeOH</td>
<td>91</td>
<td>32 R</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>21</td>
<td>r. c</td>
<td>8*</td>
<td>CH₂Cl₂</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>15</td>
<td>30 R</td>
<td>9*</td>
<td>THF</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>17</td>
<td></td>
<td>10*</td>
<td>Acetone</td>
<td>48</td>
<td>16 R</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN</td>
<td>15</td>
<td></td>
<td>11*</td>
<td>CH₃CN</td>
<td>20</td>
<td>r.</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>22</td>
<td>14 S</td>
<td>12*</td>
<td>Toluene</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

* With the addition of CH₃COOH/H₂O 0.15 eq.: 2 eq. ^a Determined by ¹H NMR. ^b Determined by chiral HPLC. ‘r.’ = racemic.
Overall, catalysts 369 and 372 were of moderate activity compared to catalyst 373. Toluene and dichloromethane without the additive were the best combinations in the case of the bis-3,5-(trifluoromethyl)phenyl substituted catalyst 372, similar to that observed for catalyst 373 (Entries 26, 30, Table 3.3). As mentioned above, the bis-

3,5-(trifluoromethyl)phenyl substituent increases the acidity of the thiourea, increasing activation of the β-nitrostyrene.436 Catalysts 369 and 372 certainly showed more activity than 371, with the unsubstituted phenyl group. From the reports by Bordwell and Ji, and Schreiner and colleagues, an aryl group has been shown to make the thiourea more acidic than an alkyl group.436-437 However, the results here-in suggest that the ethyl thiourea 369 is a more active catalyst than 371 and has better activity in methanol over toluene or dichloromethane (Entries 7, 10 for 369, and 19, 22 for 371, Table 1.2). However, this unexpected result may also be due to factors other than the acidity of the thiourea moiety.

The polar, aprotic solvents tetrahydrofuran and acetonitrile gave low conversions and lower enantioselectivities overall for catalysts 369, 371, and 372. Generally, methanol, acetone and acetonitrile showed improved yields on addition of the additive, whereas the additive lowered yields in the other solvents. The use of acid additives in Michael-type addition reactions is purported to accelerate the condensation and/or hydrolysis of the enamine intermediate.455,457 Acetic acid, benzoic acid, and other common acids have been used to increase catalytic yields.454 Often there is no explanation for why one acid works over another and appropriate additives are found on a case-by-case basis. The addition of water is thought to prevent catalyst degradation.457 The poor yields in solvents other than methanol, acetone, and acetonitrile suggest that the acetic acid/water mix may not be an appropriate additive in the case of these catalysts. Other acid additives could be explored in reactions with catalysts 373 and 372 in toluene or dichloromethane, to investigate increasing yields without affecting enantiomeric excess.

Gratifyingly, catalyst 372 gave the reverse enantiomer to 373, indicating that the interchange of catalytic motifs on the carbohydrate ring may be sufficient to produce a pseudo-enantiomeric catalytic environment.459-460 The higher yields and good enantiomeric excess with 373 suggests it is perhaps a ‘matched’ catalyst, in that the substitution pattern of the two catalytic centres compliments the chirality of the
carbohydrate scaffold, leading to optimal three-dimensional spatial binding of the substrates.

For compound 404, very low activity was shown, giving no conversions over 5%, both with and without the acetic acid/water additive (Table 3.4). As catalyst 404 was the only compound isolated as the trifluoroacetic acid salt, it was thought that the additional trifluoroacetic acid (TFA) in the reaction was inhibiting conversion. To investigate the role of the acid further, 0.15 eq. TFA and 2 eq. water were added to test reactions with catalysts 369 and 373 and 2 eq. of water was added to the reaction with 404 (Table 3.5). These combinations provided identical reaction environments, so the effect of the catalyst with equal amounts of TFA could be examined. For the ethyl substituted catalysts, the entries showed low conversions, which suggested that TFA was a hindering factor in these reactions. Further mechanistic studies would be required to determine if TFA hinders substrate activation (enamine formation), hydrolysis, or affects another aspect of the catalytic cycle. Surprisingly, the addition of TFA to reactions with catalyst 373 in acetone increased the yields without affecting the enantiomeric excess, and this would be interesting to investigate in further reaction optimisation studies.

Table 3.4 – Catalyst 404 screening in the nitro-Michael addition of acetone to β-nitrostyrene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]^a</th>
<th>ee [%]^b</th>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%]^a</th>
<th>ee [%]^b</th>
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<td>-</td>
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<td>CH₂Cl₂</td>
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<td>-</td>
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<td>THF</td>
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<td>Acetone</td>
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<tr>
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<td>CH₃CN</td>
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<td>CH₃CN</td>
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<td>Toluene</td>
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<td>-</td>
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<td>Toluene</td>
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^a With the addition of CH₃COOH/H₂O 0.15 eq.:2 eq. ^b Determined by ¹H NMR. "Determined by chiral HPLC."
Table 3.5 – The effect of TFA on catalysis

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<td>404†</td>
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<td>-</td>
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</tbody>
</table>

* With the addition of CF₃COOH/H₂O 0.15 eq.:2 eq. † With the addition of 2 eq. H₂O. a Determined by ¹H NMR. b Determined by chiral HPLC. c r. = racemic

In order to confirm the importance of the thiourea moiety, the diamine 51 was also tested in the model reaction (Table 3.6).

Table 3.6 – Catalytic activity of the diamine 51.

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Conversion [%] a</th>
<th>ee [%] b</th>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [%] a</th>
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<td>r.</td>
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<tr>
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<td>r.</td>
<td>9</td>
<td>THF</td>
<td>97</td>
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<tr>
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<td>Acetone</td>
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<td>r.</td>
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<tr>
<td>5</td>
<td>CH₃CN</td>
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<td>r.</td>
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<tr>
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<td>r.</td>
<td>12</td>
<td>Toluene</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

* With the addition of CH₃COOH/H₂O 0.15 eq.:2 eq. a Determined by ¹H NMR. b Determined by chiral HPLC. c r. = racemic.
The diamine 51 produced only racemic products, leading to the conclusion that the thiourea moiety is indeed an integral part of the carbohydrate-based catalyst for asymmetric catalysis.

**Conclusions and future work**

Catalyst 373 was found to be the best bifunctional thiourea/primary amine from this pilot study. It was found to catalyse the addition of acetone to β-nitrostyrene in 32% yield and 84% ee in toluene at room temperature, without any additives. This activity was thought to be due to the increase in thiourea acidity afforded by the bis-3,5-(trifluoromethyl)phenyl substituent on the aryl ring, the matching of the thiourea/amine substitution on the carbohydrate ring with the chirality of the scaffold, and the lack of competition for substrate activation in a non-polar solvent.

The next step in catalyst development would be to improve the yield of the reaction. Increasing the equivalents of β-nitrostyrene, increasing the catalyst loading, and investigating temperature scope, in addition to the use of acidic or basic additives in varying molar equivalents, would allow for a deeper insight into the results obtained here-in.

Once the conditions have been optimised, the substrate scope of the reaction could be explored with the use of various aryl and alkyl nitroalkenes, and cyclic, branched, alkyl or aryl ketones or aldehydes as some examples.

In addition, there is also possibility, due to synthetic methodology, to improve the catalyst design. Different secondary or tertiary amines could be investigated, as well as changing the stereochemistry at C2/4, and moving the catalytic groups closer to each other on a 1,2-diamine bridge (C2/3 or C3/4). Bulkier groups at C3 could be used to explore the steric space around the scaffold and the effect on enantioselectivity.
EXPERIMENTAL

1,6-Anhydro-2-(tert-butoxycarbonyl)amino-2-deoxy-β-D-glucopyranose 382

Palladium-on-carbon (10%, 75 mg) was added to a solution of the diol 57 (204 mg, 1.09 mmol) in MeOH (5 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure (1 atm.) and room temperature until judged complete by TLC analysis. The mixture was then filtered through Celite and concentrated. The residue was dissolved in MeOH (5 mL) and Boc₂O (294 mg, 1.35 mmol) then triethylamine (0.167 mL, 1.2 mmol) were added. The mixture was stirred at room temperature (2.5 h), then concentrated. The residue was taken up in CHCl₃ (20 mL), washed with water (20 mL), brine (25 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography of the residue (EtOAc/petrol 3:2) yielded the title compound as a colourless oil (168 mg, 59%). Rf 0.68 (MeOH/EtOAc 1:9). IR (ATR): 3409 (O-H), 1662 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.37 (s, 1H), 4.89 (d, J = 9.0 Hz, 1H), 4.41 (s, 1H), 4.28 (d, J = 7.7 Hz, 1H), 3.94 (d, J = 9.2 Hz, 1H), 3.89 (s, 2H), 3.65 (dd, J = 4.9, 7.7 Hz, 1H), 3.62 (br s, 1H), 3.38 (br s, 1H), 1.43 (s, 9H). ¹³C NMR (151 MHz, CDCl₃): δ 155.1, 100.8, 80.7, 75.0, 70.1, 64.5, 64.1, 54.8, 28.4. HR-MS (APCI): m/z 247.0931; [M+2H-Boc+CH₃CN]+ requires 247.0930.

1,6-Anhydro-3-O-benzoyl-2-(tert-butoxycarbonyl)amino-2,4-deoxy-4-O-trifluoromethanesulfonyl-β-D-glucose 383

Palladium-on-carbon (10%, 50 mg) and Boc₂O (68.9 mg, 0.32 mmol) were added to a solution of the azide 382 (150 mg, 0.354 mmol) in EtOAc (2 mL) and the resultant mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature (1 atm., 16 h). The reaction mixture was filtered through Celite and concentrated. Flash chromatography of the residue (EtOAc/petrol 3:17) yielded the
title compound as a white solid (93.2 mg, 93%). Rf 0.47 (EtOAc/petrol 1:4). IR (ATR): 3314 (N-H), 1724 (C=O), 1678 (C=O) cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 8.06-8.04 (m, 2H), 7.63-7.60 (m, 1H), 7.50-7.47 (m, 2H), 5.63 (br s, 1H), 5.46 (s, 1H), 5.18 (dd, J = 4.2 Hz, 1H), 4.86 (s, 1H), 4.66 (dd, J = 3.9 Hz, 1H), 4.58 (d, J = 8.1 Hz, 1H), 4.16 (d, J = 7.3 Hz, 1H), 3.92 (dd, J = 7.7, 4.9 Hz, 1H), 1.47 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 164.9, 154.2, 133.8, 130.0, 129.1, 128.8, 118.2 (q, J = 319 Hz), 101.2, 81.2, 77.2, 72.6, 69.0, 64.8, 54.7, 28.4. HR-MS (APCI): \(m/z\) 498.1052; [M+H]\(^+\) requires 498.1046.

1,6-Anhydro-4-azido-3-O-benzoyl-2-(tert-butoxycarbonyl)amino-2,4-dideoxy-β-D-glucose 384

Sodium azide (47.5 mg, 0.73 mmol) was added to a solution of the triflate 383 (149 mg, 0.31 mmol) in DMF (3 mL) and the resultant mixture was heated at 90°C (2 h). The mixture was then concentrated and the residue taken up in EtOAc (25 mL), washed with water (2 x 25 mL), brine (25 mL), dried (MgSO\(_4\)), filtered, and concentrated. Flash chromatography of the residue (EtOAc/petrol 1:9) yielded the title compound X as a white solid (112 mg, 92%). Rf 0.23 (EtOAc/petrol 1:4). IR (ATR): 3361 (N-H), 2102 (N\(_3\)), 1704 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 8.06-8.05 (m, 2H), 7.62-7.59 (m, 1H), 7.49-7.46 (m, 2H), 5.48 (s, 1H), 5.16 (d, J = 9.8 Hz, 1H), 5.02 (s, 1H), 4.57 (d, J = 4.8 Hz, 1H), 4.15 (d, J = 7.7 Hz, 1H), 3.96 (d, J = 10.0 Hz, 1H), 3.89 (dd, J = 5.8, 7.5 Hz, 1H), 3.74 (s, 1H), 1.46 (s, 3H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 165.4, 154.9, 133.9, 130.0, 129.2, 128.8, 101.3, 80.6, 73.6, 71.24, 66.1, 59.6, 50.5, 28.5. HR-MS (APCI): \(m/z\) 391.1606; [M+H]\(^+\) requires 391.1618.
1,6-Anhydro-4-azido-2-(tert-butoxycarbonyl)amino-2,4-dideoxy-β-D-glucose 385

Sodium methoxide (10 mg) was added to a solution of the azide 384 (96 mg, 0.25 mmol) in MeOH (3 mL) and the resultant solution was left to stir until judged complete by TLC analysis. The solution was quenched with resin (Amberlite IR-120, H+), filtered, and concentrated. Flash chromatography of the residue (EtOAc/petrol 1:4) yielded the title compound as a colourless oil (65 mg, 92%). Rf 0.33 (EtOAc/petrol 2:3). IR (ATR): 3342 (N-H), 2100 (N_3), 1690 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.44 (s, 1H), 5.07 (d, J = 9.3Hz, 1H), 4.6 (d, J = 5.2 Hz, 1H), 4.28 (d, J = 7.6 Hz, 1H), 3.82 (dd, J = 5.4, 7.6 Hz, 1H), 3.78 (d, J = 5.3 Hz, 1H), 3.74 (d, J = 9.5 Hz, 1H), 3.66 (s, 1H), 3.10 (d, J = 6.0 Hz, 1H), 1.45 (s, 9H). ¹³C NMR (151 MHz, CDCl₃): δ 155.2, 101.5, 80.4, 73.9, 70.7, 66.1, 61.7, 52.5, 28.3. HR-MS (APCI): m/z 272.0987; [M−t-Bu+CH₃CN+H]^+ requires 272.0995.

2-Acetamido-1,6-anhydro-3-O-benzoyl-2-deoxy-4-O-trifluoromethanesulfonyl-β-D-glucose 390

Palladium-on-carbon (10%, 70 mg) and Ac₂O (0.18 mL, 1.9 mmol) were added to a solution of the triflate 58 (150 mg, 0.354 mmol) in EtOAc (4 mL), and the resultant mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature (1 atm., 16 h). The reaction mixture was filtered through Celite and concentrated. Flash chromatography of the residue (EtOAc/petrol 2:3 to 3:2) yielded the title compound as a white solid (144 mg, 93%). Rf 0.30 (EtOAc/petrol 3:2). IR (ATR): 3312 (N-H), 1736 (C=O), 1644 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 8.07-8.05 (m, 2H), 7.63-7.60 (m, 1H), 7.49-7.47 (m, 2H), 5.77 (d, J = 8.7 Hz, 1H), 5.60-5.59 (m, 1H), 5.44 (s, 1H), 5.17 (dd, J = 4.6 Hz, 1H), 4.68 (dd, J = 4.5 Hz, 1H), 4.59 (d, J = 8.2 Hz, 1H), 4.49 (dt, J = 1.6, 9.2 Hz, 1H), 3.94 (dd, J = 5.1, 7.7 Hz, 1H), 2.15 (s, 3H), 1.88 (d, J = 7.2 Hz, 3H).
2.08 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$169.3, 164.8, 133.8, 130.1, 129.0, 128.8, 118.4 (q, $J = 321.2$ Hz), 101.1, 77.9, 72.7, 68.4, 64.8, 53.4, 23.4. HR-MS (APCI): $m/z$ 440.0621; [M+H]$^+$ requires 440.0627.

2-Acetamido-1,6-anhydro-4-azido-3-O-benzoyl-2,4-dideoxy-β-D-glucose 391

Sodium azide (75.6 mg, 1.16 mmol) was added to a solution of the triflate 390 (143 mg, 0.325 mmol) in DMF (3 mL) and the resultant mixture was heated at 90°C (2 h). The mixture was then concentrated and the residue was taken up in EtOAc (25 mL), washed with water (2 x 25 mL), brine (25 mL), dried (MgSO$_4$), filtered, and concentrated. Flash chromatography of the residue (EtOAc/petrol 4:1) yielded the title compound as a white solid (83 mg, 77%). $R_f$ 0.30 (EtOAc/petrol 3:2). IR (ATR): 3296 (N−H), 2105 (N$_3$), 1721 (C=O), 1667 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.06-8.05 (m, 2H), 7.63-7.60 (m, 1H), 7.49-7.46 (m, 2H), 6.04 (d, $J = 9.6$ Hz, 1H), 5.45 (s, 1H), 4.97-4.96 (m, 1H), 4.60 (d, $J = 5.3$ Hz, 1H), 4.30 (dd, $J = 0.7$, 9.7 Hz, 1H), 4.17 (d, $J = 7.8$ Hz, 1H), 3.91 (dd, $J = 5.6$, 7.8 Hz, 1H), 3.75 (s, 1H), 2.07 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 169.5, 165.3, 133.9, 130.0, 129.1, 128.8, 101.0, 73.7, 71.0, 66.2, 59.8, 49.1, 23.4. HR-MS (APCI): $m/z$ 333.1196; [M+H]$^+$ requires 333.1199.

2-Acetamido-1,6-anhydro-4-azido-2,4-dideoxy-β-D-glucose 392

Sodium methoxide (50 mg) was added to the azide 391 (805 mg, 2.42 mmol) in MeOH (15 mL) and the resultant solution was left to stir until judged complete by TLC analysis. The solution was quenched with resin (Amberlite IR-120, H$^+$), filtered, and concentrated. Flash chromatography of the residue (EtOAc/petrol 4:1 to EtOAc then MeOH/EtOAc 1:9) yielded the title compound as a colourless oil (521 mg, 94%). $R_f$ 0.13 (EtOAc/petrol 3:2). IR (ATR): 3324 (N-H), 2099 (N$_3$), 1652 (C=O) cm$^{-1}$. $^1$H
NMR (600 MHz, CDCl₃): δ 6.00 (d, J = 8.9 Hz, 1H), 5.41 (s, 1H), 4.60 (d, J = 5.3 Hz, 1H), 4.33 (d, J = 7.5 Hz, 1H), 4.11 (d, J = 9.4 Hz, 1H), 3.83 (dd, J = 5.5, 7.5 Hz, 1H), 3.75 (s, 2H), 3.67 (s, 1H), 2.04 (s, 3H). ¹³C NMR (151 MHz, CDCl₃): δ 170.1, 101.3, 74.0, 70.6, 66.2, 62.0, 51.4, 23.4. HR-MS (APCI): m/z 229.0932; [M+H]⁺ requires 229.0937.

1,6-Anhydro-4-azido-2-(N-[tert-butoxycarbonyl]acetamido)-2,4-dideoxy-3-O-methyl-β-D-glucose 395

and

1,6-Anhydro-4-azido-2-(N-[methyl]acetamido)-2,4-dideoxy-3-O-methyl-β-D-glucose 394

Sodium hydride (60% mineral dispersion in oil, 244 mg, 6.10 mmol) was added to a solution of the alcohol 392 (819 mg, 3.59 mmol) in DMF (20 mL) at 0°C. The resultant mixture was kept at 0°C and stirred (0.5 h), then methyl iodide (0.24 ml, 3.95 mmol) was added dropwise. The resultant mixture was stirred at room temperature (1 h), then quenched with MeOH, and concentrated. The residue was taken up in EtOAc (25 mL) and washed with water (25 mL). The water was thoroughly extracted with EtOAc (3 x 25 mL), the organic extracts were combined, washed with brine (25 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 13:7) of the residue yielded a mixture of two compounds (436 mg). The mixture of compounds was then dissolved in THF (35 mL), and DMAP (40 mg) and Boc₂O (1.20 mL, 5.22 mmol) were added. The resulting solution was stirred at room temperature (16 h), then concentrated. The residue was taken up in CH₂Cl₂ (25 mL), washed with water (25 mL), brine (25 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 3:17) of the residue yielded the title compound 395 as a pale yellow solid (319 mg, 45% over two steps). Rf 0.41 (EtOAc/petrol 1:4). IR (ATR): 2988 (C-H), 2102 (N₃), 1735 (C=O), 1701 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.39 (s, 1H), 4.58 (d, J = 10.1 Hz, 1H), 4.42 (d, J = 5.8 Hz, 1H), 3.85 (dd, J = 5.9, 7.9 Hz, 1H), 3.67 (s, 1H), 2.04 (s, 3H).
3.78 (dd, J = 1.2, 7.9 Hz, 1H), 3.72 (dd, J = 10.1, 7.8 Hz, 1H), 3.43 (s, 3H), 3.35 (d, J = 7.8 Hz, 1H), 2.50 (s, 3H), 1.58 (s, 9H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.0, 152.9, 103.8, 84.9, 78.5, 75.8, 68.7, 68.5, 60.7, 59.9, 28.1, 27.0. HR-MS (APCI): $m/z$ 243.1093; [M+H-BOC]$^+$ requires 243.1093.

Next to elute was 394 as a white, crystalline solid (183 mg, 35% over two steps). $R_f$ 0.22 (EtOAc/petrol 1:1). IR (ATR): 2098 (N$_3$), 1643 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, $d_6$-DMSO, 383 K): $\delta$ 5.31 (br s, 1H), 4.58 (d, $J = 5.6$ Hz, 1H), 4.38 (br s, 1H), 3.91 (d, $J = 7.5$ Hz, 1H), 3.75 (dd, $J = 1.1, 5.2$ Hz, 1H), 3.65 (dd, $J = 5.7, 8.0$ Hz, 1H), 3.37 (br s, 3H), 3.30 (dd, $J = 5.5, 5.5$ Hz, 1H), 2.99 (s, 3H), 2.06 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.4, 171.3, 102.9, 102.4, 79.5, 79.2, 75.8, 74.0, 68.8, 66.4, 65.8, 64.8, 63.1, 60.3, 58.2, 55.1, 33.3, 29.2, 22.4, 22.0. HR-MS (APCI): $m/z$ 257.1245; [M+H]$^+$ requires 257.1250.

1,6-Anhydro-4-azido-2-(tert-butoxycarbonyl)amino-2,4-dideoxy-3-O-methyl-$\beta$-D-glucose 386

Hydrazine hydrate (99% aq. solution, 204 mg, 4.08 mmol) was added to a solution of the azide 395 (466 mg, 1.36 mmol) in MeOH (20 mL), and the resulting solution was stirred until judged complete by TLC. The solution was diluted with toluene, and concentrated. Flash chromatography (EtOAc/petrol 1:9) of the residue yielded the title compound as a colourless oil (402 mg, 98%). $R_f$ 0.59 (EtOAc/petrol 2:3). IR (ATR): 3346 (N-H), 2099 (N$_3$), 1705 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.38 (s, 1H), 5.02 (d, $J = 9.5$ Hz, 1H), 4.53 (d, $J = 5.4$ Hz, 1H), 4.18 (d, $J = 7.4$ Hz, 1H), 3.82 (d, $J = 9.7$ Hz, 1H), 3.78 (dd, $J = 5.8, 7.3$ Hz, 1H), 3.59 (s, 1H), 3.46 (s, 3H), 3.27 (s, 1H), 1.45 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 155.1, 101.3, 80.3, 79.5, 73.5, 65.8, 60.3, 58.1, 48.6, 28.5. HR-MS (APCI): $m/z$ 201.985; [M+2H-Boc]$^+$ requires 201.0988.
1,6-Anhydro-4-azido-2-(methylamino)-2,4-dideoxy-3-O-methyl-β-D-glucose **396**

Potassium hydroxide (109 mg, 1.95 mmol) was added to a solution of the azide **394** (50 mg, 0.195 mmol) in MeOH (2 mL) and water (1 mL). The resultant mixture was then heated at 80 °C (4 d.). After this time, the mixture was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (5 x 10 mL). The organic extracts were combined and concentrated. Flash chromatography (EtOAc/petrol 2:3 to 3:2) of the resultant residue gave the title compound as a white crystalline solid (41 mg, 98%). R$_f$ 0.33 (EtOAc/petrol 2:3). IR (ATR): 3335 (N-H), 2095 (N$_3$) cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.51 (s, 1H), 4.54 (d, $J = 5.7$ Hz, 1H), 4.12 (dd, $J = 0.85$, 7.3 Hz, 1H), 3.78 (dd, $J = 5.7$, 7.2 Hz, 1H), 3.56 (s, 1H), 3.42 (s, 3H), 3.35 (quin, $J = 1.5$ Hz, 1H), 2.59 (s, 1H), 2.53 (s, 3H), 2.52 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 101.6, 78.0, 73.7, 65.7, 60.2, 59.0, 58.0, 34.3. HR-MS (APCI): $m/z$ 215.1141; [M+H]$^+$ requires 215.11444.

2-Amino-1,6-anhydro-4-azido-2,4-dideoxy-3-O-methyl-β-D-glucose trifluoroacetate **397**

Trifluoroacetic acid (0.31 mL, 4.06 mmol) was added to a solution of the carbamate **386** (143 mg, 0.475 mmol) in CH$_2$Cl$_2$ at 0°C and the resulting solution was stirred at room temperature (16 h). The solution was then diluted with toluene and concentrated. Flash chromatography (EtOAc then MeOH/EtOAc 1:49 to 1:19) of the residue yielded the title compound as a colourless oil (138 mg, 92%). R$_f$ 0.30 (EtOAc). IR (ATR): 3389 (N-H), 2108 (N$_3$), 1673 (C=O) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.71 (s, 1H), 4.69 (d, $J = 5.4$ Hz, 1H), 4.27 (d, $J = 7.5$ Hz, 1H), 3.87 (dd, $J = 5.7$, 7.5 Hz, 1H), 3.74 (s, 1H), 3.59 (s, 1H), 3.43 (s, 3H), 3.38 (s, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 162.8
(q, J = 36 Hz), 116.7 (q, J = 290 Hz), 99.0, 76.8, 73.7, 65.9, 59.7, 58.4, 48.9. HR-MS (APCI): m/z 201.0986; [M]^+ requires 201.0988.

1,6-Anhydro-4-azido-2,4-dideoxy-2-(3-ethylthioureido)-3-O-methyl-β-D-glucose

Ethyl isothiocyanate (0.11 mL, 1.22 mmol) was added to a solution of the amine 397 (81.3 mg, 0.41 mmol) and triethylamine (0.14 mL, 1.0 mmol) in CH$_2$Cl$_2$ at 0°C and the resulting solution was stirred (16 h), then concentrated. Flash chromatography (EtOAc/petrol 1:3) of the residue gave the title compound as a colourless oil (106 mg, 91%). R$_f$ 0.48 (EtOAc/petrol 1:1). IR (ATR): 3329 (N-H), 2098 (N$_3$), 1533 (NC(S)N) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 6.01 (br s, 1H), 5.87 (dd, J = 8.7 Hz, 1H), 5.45 (s, 1H), 4.79 (d, J = 8.9 Hz, 1H), 4.57 (d, J = 5.5 Hz, 1H), 4.25 (d, J = 7.5 Hz, 1H), 3.81 (dd, J = 5.8, 7.2 Hz, 1H), 3.64 (s, 1H), 3.54 (s, 3H), 3.40 (s, 1H), 3.36 (br s, 2H), 1.26 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 181.0, 101.0, 78.8, 73.6, 65.9, 61.1, 58.4, 52.1, 38.5, 14.0. HR-MS (APCI): m/z 288.1126; [M+H]^+ requires 288.1130.

Phenyl isothiocyanate (0.055 mL, 0.462 mmol) was added to a solution of the amine 397 (131. mg, 0.42 mmol) and triethylamine (0.12 mL, 0.84 mmol) in CH$_2$Cl$_2$ at 0°C, and the resulting solution was stirred at room temperature (1 h) then concentrated. Flash chromatography (EtOAc/petrol 1:3 to 7:19) of the residue gave the title compound as a colourless oil (136.5 mg, 97%). R$_f$ 0.25 (EtOAc/petrol 3:7). IR (ATR): 3357 (N-H), 2098 (N$_3$), 1520 (NC(S)N) cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$): δ 7.76 (s, 1H), 7.47 (m, 2H), 7.34 (m, 1H), 7.25 (m, 2H), 6.49 (d, J = 9.1 Hz, 1H), 5.41 (s, 1H), 256
4.79 (d, J = 9.3 Hz, 1H), 4.48 (d, J = 5.5 Hz, 1H), 4.23 (d, J = 7.4 Hz, 1H), 3.77 (dd, J = 5.8, 7.3 Hz, 1H), 3.61 (s, 1H), 3.53 (s, 3H), 3.32 (m, 1H). $^1$H NMR (151 MHz, CDCl$_3$): $\delta$ 180.1, 135.6, 130.4, 128.0, 125.4, 100.6, 78.7, 73.2, 65.8, 60.3, 58.4, 52.4. 13C NMR (151 MHz, CDCl$_3$): δ 180.1, 135.6, 130.4, 128.0, 125.4, 100.6, 78.7, 73.2, 65.8, 60.3, 58.4, 52.4. HR-MS (APCI): m/z 336.1128; [M+H]$^+$ requires 336.1130.

1,6-Anhydro-4-azido-2,4-dideoxy-3-O-methyl-2-(3-(3,5-bis(trifluoromethyl))phenylthiourea)-\(\beta\)-D-glucose 400

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.096 mL, 0.52 mmol) was added to a solution of the amine 397 (150 mg, 0.48 mmol) and triethylamine (0.13 mL, 0.96 mmol) in CH$_2$Cl$_2$ at 0°C and the resulting solution was stirred at room temperature (0.5 h) then concentrated. Flash chromatography (EtOAc/petrol 3:17 to 1:3) of the residue gave the title compound as a white crystalline solid (192.8 mg, 86%). R$_f$ 0.52 (EtOAc/petrol 2:3). IR (ATR): 3328 (N-H), 2106 (N$_3$), 1523 (NC(S)N) cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.35 (d, J = 14.6 Hz, 1H), 7.83 (s, 2H), 7.76 (s, 1H), 6.57 (d, J = 8.6 Hz, 1H), 5.44 (s, 1H), 4.79 (d, J = 8.8 Hz, 1H), 4.56 (d, J = 5.4 Hz, 1H), 4.26 (d, J = 7.4 Hz, 1H), 3.81 (dd, J = 6.0, 7.0 Hz, 1H), 3.66 (s, 1H), 3.53 (s, 3H), 3.39 (s, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 179.8, 138.2, 133.5 (q, J = 34 Hz), 124.1, 122.9 (q, J = 274), 120.1, 100.4, 78.7, 73.5, 65.9, 61.0, 58.4, 52.4. HR-MS (APCI): m/z 472.0872; [M+H]$^+$ requires 472.0875.

4-Amino-1,6-anhydro-2,4-dideoxy-2-(3-ethylthiourea)-3-O-methyl-\(\beta\)-D-glucopyranose 369

Palladium-on-carbon (10%, 100 mg) was added to a solution of the azide 398 (91 mg, 0.32 mmol) in MeOH (5 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until judged complete by TLC. Analysis (1 atm.). The mixture was filtered through Celite and
concentrated. Flash chromatography (CH$_2$Cl$_2$ then MeOH/CH$_2$Cl$_2$ 1:49 to 1:9) of the residue gave the title compound as a glassy white solid (54.8 mg, 66%). R$_f$ 0.55 (CH$_2$Cl$_2$). IR (ATR): 3287 (N-H), 1538 (NC(S)N) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$CN): δ 6.96 (s, 1H), 6.66 (s, 1H), 5.29 (s, 1H), 4.43 (br s, 1H), 4.37 (d, $J = 5.3$ Hz, 1H), 4.08 (d, $J = 6.8$ Hz, 1H), 3.62 (dd, $J = 6.1, 6.1$ Hz, 1H), 3.36 (br s, 5H), 3.07 (s, 1H), 3.01 (br s, 1H), 1.13 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (151 MHz, CD$_3$CN): δ 182.5, 101.3, 82.7, 77.1, 66.8, 53.8, 52.2, 39.6, 14.4. HR-MS (APCI): $m/z$ 262.1216; [M+H]$^+$ requires 262.1225.

![4-Amino-1,6-anhydro-2,4-dideoxy-3-O-methyl-2-(3-phenylthioureido)-β-D-glucopyranose 371](image)

Trimethylphosphine (1 M solution in toluene, 0.23 mL, 0.23 mmol) was added to a solution of the azide 399 (62.1 mg, 0.186 mmol) in a mixture of THF (2.5 mL) and water (0.05 mL) at 0°C and the resulting mixture was stirred at room temperature (2 h) then concentrated. Flash chromatography (MeOH/CHCl$_3$ 1:49) of the residue gave the title compound as a colourless oil (47.5 mg, 82%). R$_f$ 0.34 (MeOH/CH$_2$Cl$_2$ 1:9). IR (ATR): 3272 (N-H), 1520 (NC(S)N) cm$^{-1}$. $^1$H NMR (600 MHz, CD$_3$CN): δ 8.47 (br s, 1H), 7.62 (br s, 1H), 7.41-7.38 (m, 2H), 7.34-7.32 (m, 2H), 7.24-7.22 (m, 1H), 5.33 (s, 1H), 4.55 (s, 1H), 4.31 (d, $J = 5.5$ Hz, 1H), 4.09 (dd, $J = 0.7, 6.9$ Hz, 1H), 3.60 (dd, $J = 5.8, 6.8$ Hz, 1H), 3.36 (s, 3H), 3.09-3.08 (m, 1H), 3.02 (s, 1H). $^{13}$C NMR (151 MHz, CD$_3$CN): δ 180.5, 138.3, 130.4, 126.9, 125.4, 100.8, 82.0, 76.8, 66.8, 57.9, 54.2, 51.7. HR-MS (APCI): $m/z$ 310.1222; [M+H]$^+$ requires 310.1225.
4-Amino-1,6-anhydro-2,4-dideoxy-3-O-methyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-β-D-glucopyranose 372

Trimethylphosphine (1 M solution in toluene, 0.48 mL, 0.48 mmol) was added to a solution of the azide 400 (181 mg, 0.385 mmol) in a mixture of THF (4.9 mL) and water (0.1 mL) at 0°C and the resulting mixture was stirred at room temperature (2 h) then concentrated. Flash chromatography (CHCl₃ to MeOH/CHCl₃ 1:49) of the residue gave the title compound as a glassy solid (97 mg, 56%). Rf 0.61 (MeOH/CH₂Cl₂ 1:9). IR (ATR): 3281 (N-H), 1521 (NC(S)N) cm⁻¹. ¹H NMR (500 MHz, CD₃CN): δ 8.10 (s, 2H), 7.75 (s, 1H), 5.38 (s, 1H), 4.56 (s, 1H), 4.38 (d, J = 5.5 Hz, 1H), 4.12 (dd, J = 0.7, 7.0 Hz, 1H), 3.65 (dd, J = 5.8, 6.8 Hz, 1H), 3.38 (s, 3H), 3.15 – 3.13 (m, 1H), 3.06 (s, 1H). ¹³C NMR (126 MHz, CD₃CN): δ 180.9, 141.5, 132.4 (q, J = 33 Hz), 124.4 (q, J = 271 Hz), 124.4, 118.9, 100.7, 82.0, 77.0, 66.9, 58.0, 54.0, 51.9. HR-MS (APCI): m/z 446.0979; [M+H]⁺ requires 446.0973.

4-Amino-1,6-anhydro-2-(tert-butoxycarbonyl)amino-2,4-dideoxy-3-O-methyl-β-D-glucopyranose 401

Palladium-on-carbon (10%, 50 mg) was added to a solution of the azide 386 (103 mg, 0.34 mmol) in MeOH (4 mL) and the resulting mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature until judged complete by TLC analysis (1 atm.). The mixture was filtered through Celite and concentrated. Flash chromatography (EtOAc then MeOH/EtOAc 3:97) of the residue gave the title compound as a colourless oil, which was used without further purification.
1,6-Anhydro-2,4-dideoxy-2-(tert-butoxycarbonyl)amino-4-(3-ethylthioureido)-3-O-methyl-β-D-glucose **402**

Ethyl isothiocyanate (0.1 mL, 1.14 mmol) was added to a solution of the amine **401** (98 mg, 0.36 mmol) and triethylamine (0.1 mL, 0.72 mmol) in CH₂Cl₂ at 0°C and the resulting solution was stirred at room temperature (16 h) then concentrated. Flash chromatography (EtOAc/petrol 2:3) of the residue gave the title compound as a colourless oil (127 mg, 98%). Rᵣ 0.69 (EtOAc). IR (ATR): 3335 (N-H), 1694 (C=O), 1537 (NC(S)N) cm⁻¹. ¹H NMR (600 MHz, DMSO-d₆): δ 7.67 (s, 1H), 7.33 (s, 1H), 6.44 (s, 1H), 5.27 (s, 1H), 4.47 (d, J = 5.4 Hz, 1H), 4.36 (s, 1H), 4.02 (d, J = 7.3 Hz, 1H), 3.59 (dd, J = 6.2, 6.9 Hz, 1H), 3.47-3.41 (m, 3H), 3.36 (s, 3H), 3.07 (s, 1H), 1.39 (s, 9H), 1.09 (t, J = 7.2 Hz, 3H). ¹³C NMR (151 MHz, DMSO-d₆): δ 181.7, 154.9, 100.5, 79.9, 74.6, 65.5, 57.3, 52.6, 51.0, 40.1, 38.5, 28.1, 14.4. HR-MS (APCI): m/z 362.1752; [M+H]⁺ requires 362.1750.

![Chemical structure](image)

1,6-Anhydro-2-(tert-butoxycarbonyl)amino-2,4-dideoxy-3-O-methyl-4-(3-(3,5-bis(trifluoromethyl))phenylthioureido)-β-D-glucose **403**

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.07 mL, 0.37 mmol) was added to a solution of the amine **401** (92.0 mg, 0.34 mmol) and triethylamine (0.09 mL, 0.68 mmol) in CH₂Cl₂ at 0°C and the resulting solution was stirred at room temperature (4.5 h), the concentrated. Flash chromatography (EtOAc/petrol 3:7) of the residue gave the title compound as a white crystalline solid (87.1 mg, 47%). Rᵣ 0.48 (EtOAc /petrol 4:1). IR (ATR): 3329 (N-H), 1679 (C=O) cm⁻¹. ¹H NMR (600 MHz, DMSO-d₆): δ 10.09 (s, 1H), 8.47 (s, 1H), 8.29 (s, 1H), 7.78 (s, 1H), 6.66 (s, 1H), 5.35 (s, 1H), 4.59 (d, J = 5.5 Hz, 1H), 4.40 (d, J = 7.0 Hz, 1H), 4.09 (d, J = 7.3 Hz, 1H), 3.65 (dd, J = 6.6 Hz, 1H), 3.50 (d, J = 9.0 Hz, 1H), 3.40 (s, 3H), 3.24 (s, 1H), 1.35 (s,
2-Ammonium-1,6-anhydro-2,4-dideoxy-4-(3-ethylthioureido)-3-O-methyl-β-D-glucose trifluoroacetate 404

Trifluoroacetic acid (0.12 mL, 1.59 mmol) was added to a solution of the carbamate 402 (115 mg, 0.319 mmol) in CH$_2$Cl$_2$ at 0°C and the resulting solution was stirred at room temperature (5 h) then concentrated. Flash chromatography (MeOH/CH$_2$Cl$_2$ 1:19 to 1:9) of the residue yielded the title compound as a white solid (99.5 mg, 83%). R$_f$ 0.17 (EtOAc/petrol 7:3). IR (ATR): 3329 (N-H), 1668 (C=O), 1548 (NC(S)N) cm$^{-1}$. $^1$H NMR (600 MHz, d$_6$-DMSO): δ 8.04 (br s, 3H), 7.42 (br s, 1H), 5.49 (s, 1H), 4.60 (d, $J$ = 5.5 Hz, 1H), 4.34 (br s, 1H), 4.07 (d, $J$ = 7.4 Hz, 1H), 3.67 (dd, $J$ = 5.9, 7.4 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 2H), 3.17-3.16 (m, 2H), 1.09 (t, $J$ = 7.01 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 181.8, 163.0 (q, $J$ = 38 Hz), 116.5 (q, $J$ = 290 Hz), 98.3, 77.5, 75.6, 66.4, 58.9, 52.0, 51.5, 39.8, 14.1. HR-MS (APCI): $m/z$ 262.1216; [M+H]$^+$ requires 262.1225.

2-Amino-1,6-anhydro-2,4-dideoxy-3-O-methyl-4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-β-D-glucose 373

Trifluoroacetic acid (0.09 mL, 1.18 mmol) was added to a solution of the carbamate 403 (81.0 mg, 0.148 mmol) in CH$_2$Cl$_2$ at 0°C and the resulting solution was stirred at room temperature (4 h) then concentrated. Flash chromatography of the residue (MeOH/CH$_2$Cl$_2$ 1:99 to 1:24) of the residue yielded the title compound as a white solid (50 mg, 76%). R$_f$ 0.47 (MeOH/CH$_2$Cl$_2$ 1:19). IR (ATR): 3311 (N-H) cm$^{-1}$. $^1$H NMR (500 MHz, CD$_3$CN): δ 8.14 (s, 2H), 7.75 (s, 1H), 5.27 (s, 1H), 4.60 (s, 1H), 4.55 (d, $J$
= 5.5 Hz, 1H), 4.18 (d, J = 7.3 Hz, 1H), 3.65 (dd, J = 6.2, 6.9 Hz, 1H), 3.41 (s, 3H),
3.18 (s, 1H), 2.94 (s, 1H). $^{13}$C NMR (126 MHz, CD$_3$CN): $\delta$ 181.2, 142.2, 132.9 (q, J
= 33 Hz), 124.9 (q, J = 272 Hz), 124.9, 119.4, 104.1, 82.7, 75.7, 66.7, 58.7, 54.5, 53.5.
HR-MS (APCI): $m/z$ 446.0975; [M+H]$^+$ requires 446.0973.

Catalytic studies general method

$\beta$-nitrostyrene (7.2 mg, 0.048 mmol) was dissolved in the appropriate solvent (0.25
mL). Acetone (20 eq.), catalyst (0.15 eq.), and water (2 eq.) and acetic acid (0.15 eq.),
where applicable, were added and the resultant mixture was stirred at room
temperature (72 h). The mixture was then concentrated and flash chromatography
(EtOAc/petrol 3:17) of the residue gave the desired product. The $^1$H NMR spectrum
was consistent with that found in the literature.$^{461}$ The enantiomeric excess of the
product was determined by chiral HPLC analysis (Daicel Chiralpak AS-H,
isopropanol/petrol 3:7, 1 mL/min) in comparison with racemic material and using
literature retention times when using the same column and parameters.$^{401}$
Chapter 4

A new synthesis of 2-acetamido-1,5-imino-1,2,5-trideoxy-D-galactitol (GalNAcDNJ)
INTRODUCTION

Carbohydrate-processing enzymes

As touched upon in the Preface, carbohydrates play important roles in biological processes such as cell-to-cell recognition and cell signalling. In order to fully understand their biological roles, there must first be an understanding of the basic mechanisms of carbohydrate processing; how they are added to and removed from biomolecules. In Nature, carbohydrates are usually joined to other carbohydrates or biomolecules through a glycosidic bond. This is a bond formed between the anomeric C1 of the carbohydrate of interest and another carbohydrate or non-carbohydrate (e.g. lipid, protein). The formation and cleavage of the glycosidic bond are both carried out by carbohydrate-processing enzymes; glycoside transferases and glycoside hydrolases (glycosidases) respectively (Figure 4.1). This chapter will focus on glycosidases.

In general, a glycosidase is termed an exo-glycosidase if it cleaves terminal carbohydrates from a polysaccharide chain or biomolecule. Excision at an internal glycosidic link in a polysaccharide chain is carried out by an endo-glycosidase. Glycosidases are also identified by the stereochemistry of the glycosidic linkage that they cleave; α- or β-glycosidases (Figure 4.2).
The mechanisms by which glycosidases cleave carbohydrates are governed mainly by the form of the active site of the enzyme; the type of exposed amino acid residues and the shape of the catalytic pocket. The two most prevalent catalytic mechanisms of glycosidases are the retaining and inverting mechanisms. There are other glycosidase mechanisms, but these will not be discussed further as they are beyond the scope of this chapter. For further information on these other mechanisms, reviews by Yip et al., Jongkees and Withers, and Rye and Withers give good overviews of the topic.

The inverting mechanism is the simplest of all the mechanisms, being a concerted, one-step reaction first proposed by Koshland in 1953. An amino acid residue acts as a general acid to deprotonate a water molecule present in the active site. In concert, the oxygen atom of the water attacks the anomeric carbon while the aglycon is protonated by a basic amino acid residue and is cleaved. The simultaneous nature of the mechanism results in inversion of the stereochemistry at the anomeric carbon of the sugar (Figure 4.3).
Figure 4.3 – The single step inverting catalytic mechanism utilizing a β-glucosidase as an example.

Koshland also first proposed the retaining mechanism, which is a two-step, double displacement process, involving a glycosyl-enzyme intermediate (Figure 4.4). In the first step, the aglycon is protonated by an acidic amino acid residue. Concurrently, a nucleophilic amino acid residue attacks the glycoside at C1, displacing the aglycon. This generates a covalently bound glycosyl-enzyme intermediate with an inversion of stereochemistry at the anomeric carbon. In the second step, a water molecule fills the space left by the removal of the aglycon and is deprotonated by the conjugate basic amino acid residue. The new nucleophile attacks the glycosyl-enzyme intermediate to release the carbohydrate with a retention of anomeric configuration and regenerates the active site. A subclass of the retaining catalytic mechanism is the substrate-assisted catalytic mechanism where the carbonyl oxygen of an acetamido group at C2 acts as the nucleophile to generate an oxazoline intermediate (Figure 4.5).
Figure 4.4 – The retaining catalytic mechanism utilising a β-glucosidase as an example.

Figure 4.5 – The putative transition state of the substrate-assisted mechanism, showing the formation of the oxazoline-type intermediate.

In both of these types of catalytic mechanisms, the transition state molecule is thought to be an oxocarbenium ion, with the positive charge shared between C1 and the endocyclic oxygen atom. The carbohydrate ring is thought to take a half-chair or half-boat conformation along the reaction pathway. X-ray crystallographic studies have been used to identify the active amino acid residues and to determine the average diameter of the active site pocket in different enzymes. Retaining glycosidases have an average pocket size of 5.5 Å. Inverting glycosidases have a pocket size of
around 10 Å, larger, presumably, in order to accommodate the water molecule alongside the aglycon.\textsuperscript{462}

**Tools to investigate carbohydrate-processing enzymes**

A variety of chemical tools are used to facilitate understanding the roles and mechanisms of carbohydrate-processing enzymes. These include X-ray crystallography, affinity labelling probes, substrate-based visualisation probes, and small molecule inhibitors.\textsuperscript{472-475} Small molecule inhibitors are of particular interest for their wide range of applications. Not only can they be used to understand the catalytic mechanism of the enzyme but they also have potential as future therapeutics such as treating enzymological dysfunction disorders or exogenous pathogenic infections.\textsuperscript{476-477}

These inhibitors can be broadly categorised as reversible and irreversible inhibitors. Irreversible inhibitors typically form covalent bonds with the enzyme or enzyme-substrate complex and this chemical change deactivates the enzyme. Reversible inhibitors form non-covalent interactions with the enzyme. One class of reversible inhibitors that has received considerable attention in the literature is competitive inhibitors. As their name suggest, these compounds compete with the substrate for access to the active site of the enzyme and the formation of the enzyme-inhibitor complex is reversible. They inhibit the enzyme by mimicking either the molecular geometry or charge distribution of the substrate, transition state or an intermediate along the reaction pathway, but in a chemical form that cannot be processed by the enzyme.\textsuperscript{478-479} The reversibility and active site target of these inhibitors allow for complex kinetic studies to be undertaken, elucidating enzyme catalytic mechanisms and overall potency of the inhibitor.\textsuperscript{473,478,480}

**Iminosugars**

One class of important competitive inhibitors is iminosugars which are classified by the endocyclic oxygen being replaced with a nitrogen atom (Figure 4.6).\textsuperscript{481} This class of compounds has been investigated since the 1960s. Jones and colleagues published
the synthesis of the iminosugar, 5-acetamido-5-deoxy-L-arabinopyranose \( \text{405} \), in 1962, as a reference compound in order to study the oxidation products of some alcohols in the bacteria *Acetobacter suboxydans* (**Figure 4.6**).\(^{482}\) Their synthesis was closely followed by the synthesis of 5-acetamido-5-deoxy-D-xylpyranose \( \text{406} \) by both Paulsen, and Hanessian and Heskell.\(^{483-484}\) These syntheses were followed by the discovery of iminosugars in Nature with the isolation of 5-amino-5-deoxy-D-glucopyranose (norjirimycin, \( \text{407} \)) from fermentation broths of several strains of *Streptomyces* in 1966.\(^{485-486}\) In the same year, Paulsen published the first synthesis of \( \text{408} \) (1-deoxynojirimycin, DNJ), the 1-deoxy analogue of \( \text{407} \).\(^{487}\) Investigations into DNJ by Schmidt and co-workers at Bayer showed that it was a potent inhibitor of \( \alpha \)-glucosidases and this sparked the widespread interest in DNJ and iminosugars that continues today.\(^{488}\)

**Figure 4.6** – Some of the first iminosugars discovered.

Iminosugars are inhibitors of a variety of glycosidases, with the endocyclic nitrogen thought to mimic the charged formed of the putative transition state of the glycosidase-catalysed reaction (**Figure 4.7**).\(^{488}\) The initial success of DNJ has ensured it has remained an archetypal iminosugar inhibitor scaffold for investigations into carbohydrate-processing enzymes.

**Figure 4.7** – Demonstration of the premise of how an iminosugar, such as \( \text{408} \) (in its protonated form), is thought to be an inhibitor of glycosidases by mimicking the transition state of the enzyme-catalysed reaction.
Two prominent examples of successfully commercialised iminosugars based on DNJ are Miglitol (Glyset® 409) and Miglustat (Zavesca®, 410) (Figure 4.8). Miglitol is an N-2-hydroxyethyl derivative of 408 and is used as a treatment for Type II diabetes mellitus. Miglustat is an N-butyl derivative of 408 and is used as a substrate reduction treatment for Type I Gaucher’s disease, a serious lysosomal storage disorder.

![Figure 4.8](image)

**Figure 4.8 – Some examples of iminosugar therapeutics.**

DNJ analogues have also been investigated as therapeutics against HIV, Hepatitis B and C, Dengue virus, Influenza A, as enzyme-folding chaperones, and chemotherapeutic agents among a multitude of other potential applications.493-501

**N-Acetyl-iminosugars**

From 408 came the family of N-acetyl-iminosugars, such as 411, with an acetamido group at C2. These molecules are inherent inhibitors of N-acetylhexoaminidases, enzymes which process N-acetylgalactosamine residues. Some well-known examples of these enzymes are the human β-hexosaminidases HexA and HexB, and NagZ, a bacterial β-glucosaminidase.502-505 2-Acetamido-1,5-imino-1,2,5-trideoxy-D-galactitol, (GalNAcDNJ, 411) is an N-acetylhexosaminidase inhibitor of particular interest.

![411](image)

In 2010, 411 was found to be the most potent inhibitor of N-acetylhexosaminidases, which process N-acetylgalactosamine residues, to date.503 Despite the importance of the synthesis of iminosugars in understanding the role of enzymes in biological settings, the synthesis of 411 has had only minor attention.
Synthesis of GalNAcDNJ

There are many synthetic avenues to iminosugars; chemo-enzymatic routes, via asymmetric synthesis, and using readily available carbohydrate- and non-carbohydrate-based chiral pools. Employing the carbohydrate chiral pool is a popular strategy as most of the specific chirality required is already installed. Regardless of the starting material, the overarching aim in iminosugar synthesis is to introduce an amino or amino-based precursor into an open carbohydrate structure containing a carbonyl or leaving group, allowing for the required iminosugar to be formed (Figure 4.9).

![Figure 4.9 - Some common synthetic routes to iminosugars from carbohydrates showing iminosugar formation. Adapted from Ferla et al.](image)

Of the aforementioned routes, asymmetric synthesis and carbohydrate-based pathways have been used to synthesise GalNAcDNJ, 411.

Schueller and Heiker reported the synthesis of 411 by modifying 408 directly, with Hasegawa et al. also using 408 as the starting material. The overall yields were 10% over 13 steps and 1.5% over 12 steps, respectively. Using 408 as the starting
material has the advantage that the endocyclic nitrogen is already installed. However, 408 is not an economically prudent choice and is also time consuming to synthesise.

Riera et al. used an asymmetric route, starting with a nitrogen-containing bicyclic precursor 412, which also side-stepped the need to introduce the endocyclic nitrogen (Scheme 4.1).510 Over six steps, they obtained 411 in 16% yield. While this method provides a shorter pathway to 411 than the methods above, formation of the acetamido precursor 413 required an air-sensitive Pd-catalysed allylic substitution. Organometallic, air-sensitive reactions may not be possible in all laboratory settings and a more widely-applicable synthetic route to 411 would be one without the requirement for Schlenk conditions.

Scheme 4.1 - a) [Pd(μ3-C3H5)Cl]2, dppe, phthalimide, THF.

Best et al. currently present the most efficient and simple synthesis of 411, modifying glucuronolactone 414 to reach 411 in 20% overall yield (Scheme 4.2).503 A key step in the procedure is the formation of a 2,6-ditriflate 415. In a tandem substitution/ring closure, benzylamine displaces the triflates to afford ring closure with an inversion of stereochemistry at C2 giving the D-galacto epimer 416.
While Best and co-workers have produced a robust synthesis of 411, another recent method used to access iminosugars by a ulososide precursor presents an appealing potential route to 411.

**Improving the synthesis of GalNAcDNJ**

Stütz and colleagues demonstrated that the utilisation of a ulososide 417 was an effective way to access iminosugars, using it to generate a library of NHAcDNJ-lysine derivatives (Scheme 4.3). Although ulososides had been previously investigated as iminosugar intermediates, the modified method from Stütz et al. simplified access to the required compound. The pathway to the iminosugar requires a 5,6-alkene 418, which upon epoxidation in the presence of an alcohol, in this specific case benzyl alcohol, produced the ulososide 417. Deacetylation under Zemplén conditions, followed by catalytic hydrogenation, gave a 1,5-dicarbonyl compound 419, that, with the appropriate amine, undergoes a double reductive amination reaction to give iminosugars of the type 420 (Scheme 4.3).
Scheme 4.3 – The conversion of a 5,6 alkene 418 through the uloside 417 and 1,5-dicarbonyl compound 419 to give the desired iminosugar 420.

The method from Stütz et al. was applied by Gandy and co-workers to the synthesis of 408 and a variety of epimers of 408 (Scheme 4.4).\textsuperscript{513} They chose to access the 5,6-alkene 421 from the iodide 422 via elimination of hydrogen iodide across the 5,6-bond.

Scheme 4.4 – a) i) I$_2$, Ph$_3$P, imidazole, C$_6$H$_5$CH$_3$, ii) Ac$_2$O, Pyr.; b) DBU, THF; c) i) mCPBA, CH$_2$Cl$_2$, BnOH; ii) NaOMe, MeOH; e) NH$_4$OC(O)CH$_3$, Pd(OH)$_2$/C, H$_2$, MeOH, H$_2$O.

Using the uloside route to generate derivatives of 408 has the advantage of starting from simple, easily accessible methyl glycosides. Recently, Stubbs and colleagues reported the convenient and efficient synthesis of NHAcDNJ 423 and derivatives starting from the methyl glycoside 424 via the uloside intermediate 425 (Scheme 4.5).\textsuperscript{502}
Starting from 424, the iodide 426 was prepared in a one pot by treatment of 424 with 4-toluenesulfonyl chloride, displacement of the presumed tosylate with sodium iodide, followed by acetylation. Elimination with DBU gave the 5,6-alkene 427. From here, the synthesis could diverge to form any amide at C2, such as 428, using a suitable anhydride or acyl chloride. Oxidation of the amide 428 with mCPBA, in the presence of benzyl alcohol, followed by deprotection with sodium methoxide gave the isolated ulososide triol 425. Finally, in the presence of palladium hydroxide and ammonium acetate under an atmosphere of hydrogen gas, the triol 425 gave the target compound 423.

Scheme 4.5 – a) i) PhMeSO₂Cl, Pyr., CH₂Cl₂; ii) NaI, DMF; iii) Ac₂O, Pyr.; b) DBU, THF; c) i) PBU₃, THF, H₂O; ii) (RCO)₂O; d) i) mCPBA, CH₂Cl₂, BnOH; ii) NaOMe, MeOH; e) NH₄OAc, Pd(OH)₂/C, H₂, MeOH, H₂O.

Adaption of the ulososide method presents a much more efficient synthesis to GalNAcDNJ 411 than previous syntheses, as many of the steps can be performed sequentially and without the need for purification.

This chapter investigates the translation of the ulososide method into an efficient synthesis of GalNAcDNJ.
**RESULTS AND DISCUSSION**

The methods of Stubbs and Gandy were chosen to form the basis of the synthesis of 411. However, glucose-based synthetic methods are not automatically translatable to other pyranose epimers. Frequently, epimers have markedly different reactivities and unforeseen, proximity-induced reactivity is observed when following an established synthetic pathway for another epimer. In adapting the syntheses of Stubbs and Gandy, it was important to avoid any of these pitfalls.

The pathway to 411 could start from methyl 2-azido-2-deoxy-β-D-galactopyranoside 429, which is commercially available or can be synthesised from literature procedures. Although this synthesis was being explored specifically for the preparation of 411, it was envisioned that the pathway could be used to generate N-acylamide analogues. As such, a divergent synthesis similar to the Stubbs method was sought and the azido group would allow divergence to occur further down the synthetic pathway as previously described.

From the azide 429, there were several possible pathways to the iodide 430, which is a critical intermediate to the potential synthesis of 411 (Scheme 4.6).

Starting from the azide 429, adapting the Gandy method, triphenylphosphine and iodine would install the iodide. However, triphenylphosphine would also reduce the azide, making this method unsuitable for our purpose. Utilisation of the Stubbs method would involve the preparation of the 6-O-tosylate 431 from the azide 429, which could then be displaced with sodium iodide to give the iodide 432. However, there is literature precedent of a D-galacto C6 mesylate forming a 3,6-anhydro ring on treatment with sodium azide. If this occurred with sodium iodide, the undesired azide 433 could be formed. The 3,6-anhydro formation could also occur in the Gandy method.
While the Stubbs method can work in principle, it would first require the protection of the C3 hydroxyl group to prevent 3,6-anhydro ring formation. Therefore, the azide 429 was acetylated at C3, over 3 steps, to give the diol 434 (Scheme 4.7). Activation of O6 through the use of a tosylate and subsequent displacement with sodium iodide, in conjunction with acetylation of the remaining hydroxyl groups gave the iodide 430.

Elimination across the 5,6-bond using DBU in THF gave the 5,6-alkene 435 in excellent yield (Scheme 4.8). With the alkene in hand, the azide was then converted to the acetamide 436 by reduction with trimethylphosphine, followed by treatment
with acetic anhydride. As discussed earlier, other amide analogues could be prepared using a variety of acyl anhydrides.

The alkene 436 was then treated with 3-chloroperbenzoic acid in the presence of benzyl alcohol and then deprotection with sodium methoxide in a one pot method to give the presumed triol 437 as a mixture of isomers (Scheme 4.8). Treatment of the presumed triol 437 with ammonium formate in the presence of palladium hydroxide on carbon and hydrogen gas afforded GalNAcDNJ 411 in 30% overall yield. As expected based on previous work, only the D-galacto configuration was observed on cyclisation.502

![Scheme 4.8](image)

Scheme 4.8 – a) DBU, THF; b) i) Me3P, Ac2O, H2O, THF; ii) Ac2O, Pyr.; c) i) mCPBA, BnOH, CH2Cl2; ii) NaOMe, MeOH; iii) NH4HCOO, Pd(OH)2/C, MeOH, H2O.

The adaptation of Stubbs and coworkers’ NHAcDNJ synthesis was ultimately successful, producing 411 in good yield. This opens the door to an efficient method for preparing analogues of 411 through either modification of the acetamido moiety or by using different amines in the reductive amination step. The success of this synthesis suggests that this method could be generally used to efficiently generate amide analogues of other epimers of DNJ as well.
Applications in studying carbohydrate-processing enzymes

While 411 has been previously studied with β-hexoaminidases, a recent collaboration with Professor Shinya Fushinobu at the University of Tokyo has provided the opportunity to investigate the potency of 411 as an inhibitor of NagBb, an α-GalNAcase from the probiotic bacterium Bifidobacterium bifidum.

*Bifidobacterium* is a bacterium found in the lower intestine of humans, most prevalent in new born infants who have been breast-fed. Reported probiotic properties include prevention of exogenous infections and down-regulation of allergy responses. The bacteria live in a symbiotic relationship with the human host, harvesting carbohydrates from oligosaccharides and glycoconjugates leftover from food consumption, as well as glycoproteins attached to the lining of the intestine (mucin glycans) to meet their energy requirements. Part of understanding the role *Bifidobacteria* play in infant health is understanding the symbiotic relationship between the human host and the bacterium. This includes understanding the mechanisms for energy production in the bacteria, including the roles of the many carbohydrate-processing enzymes involved.

The α-GalNAcase, NagBb, is a glycosidase which cleaves 2-acetamido-D-galactopyranose (GalNAc) from mucin glycoproteins. Through kinetic studies and genome sequence comparisons with similar enzymes, it is known that NagBb is an exo-type retaining glycosidase. However, the structure of NagBb was until recently. As part of the study, the potency of 411 as an inhibitor was evaluated and found to be a potent inhibitor with a $K_i$ value of 51 nM.

**Conclusion and future work**

Competitive inhibitors are important tools for gaining an understanding of the role of glycosidases play in a biological context. Here, a short, efficient synthesis of GalNAcDNJ 411 is presented, which could be useful for developing further analogues of this potent inhibitor for use in biological studies.
EXPERIMENTAL

Methyl 3-O-acetyl-2-azido-2-deoxy-β-D-galactopyranoside 434

10-Camphorsulfonic acid (128.9 mg, 0.55 mmol) was added to a stirred suspension of methyl 2-azido-2-deoxy-β-D-galactopyranoside \(^{189,505,514-515}\) (1.23 g, 5.6 mmol) and benzaldehyde dimethylacetal (1.3 mL, 8.9 mmol) in CH\(_3\)CN (20 mL), and the resultant solution was stirred at room temperature (2.5 h). The reaction mixture was then quenched with Et\(_3\)N and concentrated. The resultant white solid was washed thoroughly with hexanes (8 x 20 mL) and then dissolved in a mixture of CH\(_2\)Cl\(_2\) (5 mL) and pyridine (5 mL). Ac\(_2\)O (1.4 mL, 14.8 mmol) was then added to the mixture and the resultant solution left to stir at room temperature (16 h). The mixture was quenched with MeOH and concentrated. The resultant residue was dissolved in a mixture of AcOH (12 mL) and water (3 mL), and heated at 80 °C (3 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 7:2 to 4:1) yielded the title compound as a colourless oil (1.19 g, 80 % over three steps). R\(_f\) 0.08 (EtOAc/petrol 7:3). IR (ATR): 3517 (N-H), 3339 (O-H), 2120 (N\(_3\)), 1713 (C=O) cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 4.70 (dd, \(J = 3.1, 11\) Hz, 1H), 4.27 (d, \(J = 8.0\) Hz, 1H), 4.15 (d, \(J = 2.6\) Hz, 1H), 3.96-3.90 (m, 2H), 3.78 (dd, \(J = 8.0, 11\) Hz, 1H), 3.61 (s, 3H), 3.53 (dt, \(J = 0.8, 4.7\) Hz, 1H), 3.11 (br s, 1H), 2.44 (br s, 1H), 2.17 (s, 3H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 170.3, 103.6, 73.7, 73.6, 68.0, 63.0, 60.8, 57.6, 21.1. HR-MS (APCI): \(m/z\) 244.0941; [M-H\(_2\)O] requires 244.0933.

Methyl 3,4-di-O-acetyl-2-azido-2-deoxy-6-iodo-β-D-galactoside 430

4-Toluenesulfonyl chloride (862 mg, 4.5 mmol) was added to a solution of the azide 434 (1.0 g, 3.8 mmol) in a mixture of CH\(_2\)Cl\(_2\) (10 mL) and pyridine (4.5 mL) and the resultant solution was stirred at room temperature (4 h). The reaction mixture was quenched with water and the resultant mixture was stirred (1 h). The organic layer was
then collected and washed with water (30 mL), 1M HCl (30 mL), water (30 mL), sat. NaHCO₃ (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated. The residue was then dissolved in DMF (12 mL), and NaI (2.5 g, 16.7 mmol) added, with the resultant mixture heated at 90 °C (16 h). The mixture was then concentrated and the resultant residue was diluted with EtOAc (100 mL) and washed with water (30 mL), sat. NaHCO₃ (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated. The residue was then dissolved in a mixture of CH₂Cl₂ (6 mL) and pyridine (4 mL), and to the resultant mixture Ac₂O (1.03 mL, 10.9 mmol) was added, and the resultant solution was stirred at room temperature (16 h). The mixture was quenched with MeOH and concentrated. The resultant residue was dissolved in CH₂Cl₂ (60 mL) and washed with water (30 mL), 1M HCl (30 mL), water (30 mL), sat. NaHCO₃ (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 3:17) of the resultant residue yielded the title compound as a colourless oil (1.21 g, 77 % over three steps). Rᵣ 0.74 (EtOAc/petrol 3:7). IR (ATR): 2114 (N₃), 1742 (C=O) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.48 (dd, J = 0.8, 3.3 Hz, 1H), 4.79 (dd, J = 3.4, 11 Hz, 1H), 4.27 (d, J = 8.0 Hz, 1H), 3.79-3.77 (m, 1H), 3.65-3.62 (m, 4H), 3.22 (dd, J = 7.9, 11 Hz, 1H), 3.15 (dd, J = 6.0, 11 Hz, 1H), 2.16 (s, 3H), 2.05 (s, 3H). ¹³C NMR (151 MHz, CDCl₃): δ 170.2, 169.9, 103.1, 73.8, 71.4, 67.9, 60.7, 57.7, 20.7, 20.7, 0.0. HR-MS (APCI): m/z 414.0164; [M+H]⁺ requires 414.0162.

Methyl 3,4-di-O-acetyl-2-azido-2,6-dideoxy-α-L-arabino-hex-5-enoside 435

1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1 mL, 7.4 mmol) was added to a solution of the iodide 430 (1.1 g, 2.7 mmol) dissolved in THF (10 mL) and the resultant solution refluxed (5 h). The mixture was then concentrated and the resultant residue was dissolved in EtOAc (50 mL) and washed with water (2 x 20 mL), ice-cold 1M HCl (20 mL), water (20 mL), sat. NaHCO₃ (20 mL), brine (20 mL), dried (MgSO₄), filtered, and concentrated. Flash chromatography (EtOAc/petrol 3:22 to 3:17) of the resultant residue yielded the title compound as a colourless oil (718 mg, 94 %). Rᵣ 0.71 (EtOAc/petrol 3:7). IR (ATR): 2112 (N₃), 1744 (C=O), 1666 (C=C) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.62 (d, J = 3.5 Hz, 1H), 4.90 (d, J = 0.7 Hz, 1H), 4.83 (dd, J =
4.34 (d, J = 7.8 Hz, 1H), 3.86 (dd, J = 7.8, 11 Hz, 1H), 3.65 (s, 1H), 2.13 (s, 3H), 2.09 (s, 3H). 13C NMR (151 MHz, CDCl3): δ 169.9, 169.9, 150.0, 103.9, 103.5, 70.1, 68.4, 60.6, 57.7, 21.1, 20.8. HR-MS (APCI): m/z 286.1033; [M+H]+ requires 286.1039.

Methyl 2-acetaamido-3,4-di-O-acetyl-2,6-dideoxy-α-L-arabino-hex-5-enoside 436

Trimethylphosphine (1M solution in toluene, 0.57 mL, 0.57 mmol), water (0.15 mL) and Ac2O (0.13 mL) was added to a solution of the alkene 435 (135 mg, 0.47 mmol) in THF (3.5 mL) at 0 °C. The resultant solution was stirred at room temperature (2 h) and then concentrated. The residue was then dissolved in pyidine (2 mL) and Ac2O (0.15 mL), and the resultant mixture was stirred (1 h). The mixture was concentrated and the resultant residue was dissolved in CH2Cl2 (20 mL) and washed with water (20 mL), sat. NaHCO3 (20 mL), brine (20 mL), dried (MgSO4), filtered, and concentrated. Flash chromatography (EtOAc/petrol 7:3 to 4:1) of the residue yielded the title compound as a colourless oil (103 mg, 72 %). Rf 0.19 (EtOAc/petrol 3:7). IR (ATR): 3283 (N-H), 1743 (C=O), 1661 (C=O) cm⁻¹. 1H NMR (600 MHz, CDCl3): δ 5.62 (d, J = 3.5 Hz, 1H), 5.59 (d, J = 8.8 Hz, 1H), 5.16 (dd, J = 3.5, 10 Hz, 1H), 4.89 (d, J = 1.2 Hz, 1H), 4.73 (d, J = 1.2 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 4.37-4.33 (m, 1H), 3.54 (s, 3H), 2.12 (s, 3H), 2.05 (s, 1H). 13C NMR (151 MHz, CDCl3): δ 170.8, 170.3, 170.1, 150.5, 103.2, 101.9, 69.2, 68.2, 56.8, 50.8, 23.5, 21.1, 20.9. HR-MS (APCI): m/z 302.1237; [M+H]+ requires 302.1240.

2-Acetamido-1,5-imino-1,2,5-trideoxy-D-galactitol 411

3-chloroperbenzoic acid (70%, 245 mg 1.0 mmol) was added to a solution of 436 (250 mg, 0.83 mmol) in a mixture of CH2Cl2 (5 mL) and benzyl alcohol (5 mL). The resultant mixture was stirred at room temperature (2 h) and then diluted with CH2Cl2 (20 mL) and washed with saturated NaHCO3 solution (50 mL), dried (MgSO4), filtered.
and concentrated. Flash chromatography (EtOAc) yielded a residue that was dissolved in MeOH and treated with sodium methoxide (10 mg) and the solution stirred at room temperature (30 min). The mixture was quenched with resin (Amberlite IR-120, H\(^+\)), filtered and concentrated. Flash chromatography (MeOH/CHCl\(_3\) 1:9) of the resultant residue yielded a colourless residue (200 mg), presumably 437. The residue was then dissolved in a mixture of MeOH and H\(_2\)O (0.03 M, 15:1, v/v), and NH\(_4\)HCOO (40 mg, 0.64 mmol) and Pd(OH)\(_2\)/C (20%, 40 mg) added, and the resultant mixture stirred under an atmosphere of hydrogen at ambient pressure and room temperature (1 atm., 48 h). The mixture was filtered and concentrated. Flash chromatography (CHCl\(_3\)/MeOH/conc. NH\(_3\), 12:8:1) of the resultant solution yielded the title compound as a colourless oil (110 mg, 65%, over three steps). The \(^1\)H and \(^{13}\)C NMR spectra were consistent with that reported.\(^{503}\)
REFERENCES

References

References


References

References


References

References


[222] VCCLAB, Virtual Computational Chemistry Laboratory.
http://www.vcclab.org


References

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References

References


