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Synthesis of Iminosugar C-Glycosides via Tandem Allylic-Azide Rearrangement – Huisgen Cycloaddition

By

Lorna Moynihan

A Thesis presented to
The National University of Ireland
For the degree of
Doctor of Philosophy

Based on the research carried out in the
School of Chemistry,
National University of Ireland, Galway

Under the supervision and direction of
Professor Paul V Murphy
National University of Ireland, Galway
Abstract

Iminosugars are naturally occurring polyhydroxylated alkaloids. These natural mimics of carbohydrates have found clinical use with their biological activity mainly attributed to their inhibition of glycoprocessing enzymes. The background to this thesis and the intramolecular tandem allylic azide rearrangement – Huisgen cycloaddition are discussed in Chapter 1.

Chapter 2 describes the synthesis of iminosugar derivatives from D-glucono-δ-lactone which is an extension of work carried out previously in the Murphy group for the preparation of 1-deoxyiminosugars. This route was particularly successful in the highly stereoselective preparation of iminosugars fused to triazoles from an intramolecular rearrangement-cycloaddition between azide and alkyne groups. However the rearrangement-cycloaddition between azide and alkene groups based on intermediates with the glucose configuration suffered from poor yields.

An alternative route using a zinc-mediated reductive fragmentation reaction from a variety of commercially available sugars to prepare allylic azide precursors was next explored. This is discussed in Chapters 3-5, which also describe the rearrangement-cycloaddition reactions of these intermediates which lead to iminosugars based on glucose, mannose and galactose. The importance of a conformational constraint to achieve the cycloaddition emerged. Again, the cycloaddition of the glucose intermediates was affected by poor yields. However, results with the mannose and galactose derivatives were more promising. The stereoselectivity was assigned using NMR coupling constants ($J_{\text{H1-H2}}$ and $J_{\text{C1-H1}}$ values), NOEs, X-ray crystallography and comparisons with analytical data for compounds already described in the literature. The stereoselectivities were rationalised with the aid of models built using molecular mechanics. The synthesis of a natural C-glycoside iminosugar was achieved.

Overall this thesis demonstrates that an allylic azide rearrangement carried out in tandem with Huisgen cycloaddition is diastereoselective in ring formation and should be useful in organic chemistry.
## Symbols and Abbreviations

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<tr>
<td>α</td>
<td>alpha</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>apt d</td>
<td>apparent doublet (spectral)</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>ASSC</td>
<td>active site specific chaperone, pharmacological chaperone</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu, nBu, tBu</td>
<td>butyl, normal (primary) butyl, tert-butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyle</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumber (IR units)</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>CFTR</td>
<td>cystic fibrosis transmembrane regulator</td>
</tr>
<tr>
<td>CMR</td>
<td>chemical molar refractivity</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>CuAAC</td>
<td>copper(I)-catalysed azide-alkyne cycloaddition</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (ppm downfield from TMS)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet doublets (spectral)</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublets of doublets (spectral)</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DHAP</td>
<td>dihydroxyacetone phosphate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropyl-N-ethylamine</td>
</tr>
<tr>
<td>DGJ</td>
<td>1-deoxygalctonojirimycin</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMJ</td>
<td>1-deoxymannojirimycin</td>
</tr>
<tr>
<td>DMP</td>
<td>2,2-dimethoxy propane</td>
</tr>
<tr>
<td>DNJ</td>
<td>1-deoxyjirimycin</td>
</tr>
<tr>
<td>D₂O</td>
<td>deuterated water</td>
</tr>
<tr>
<td>DPPA</td>
<td>diphenylphosphoryl azide</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets (spectral)</td>
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<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>eg</td>
<td>for example</td>
</tr>
<tr>
<td>eq</td>
<td>(molar) equivalents</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ER</td>
<td>endoplasmic reticulum</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>et al.</td>
<td>et alii (and others)</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>ESI-HRMS</td>
<td>Electrospray Ionization-High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier Transfer Infrared Spectroscopy</td>
</tr>
<tr>
<td>g, mg</td>
<td>gram(s), milligram(s)</td>
</tr>
<tr>
<td>Gal</td>
<td>galactose</td>
</tr>
<tr>
<td>Glc</td>
<td>glucose</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HAJ</td>
<td>Homoallonojirimycin</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HGJ</td>
<td>Homogalactonojirimycin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HNJ</td>
<td>homonojirimycin</td>
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<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation spectroscopy</td>
</tr>
<tr>
<td>HMJ</td>
<td>homomannojirimycin</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum correlation spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IC$_{50}$</td>
<td>50% inhibition concentration</td>
</tr>
<tr>
<td>Im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (Hz)</td>
</tr>
<tr>
<td>Ki</td>
<td>dissociation constant of an enzyme-inhibitor complex</td>
</tr>
<tr>
<td>L</td>
<td>litre(s)</td>
</tr>
<tr>
<td>lit.</td>
<td>literature reference</td>
</tr>
<tr>
<td>LRMS</td>
<td>Low Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>N</td>
<td>normal</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (spectral)</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m/z</td>
<td>mass over charge ratio</td>
</tr>
<tr>
<td>Man</td>
<td>mannose</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOD</td>
<td>deuterated methanol</td>
</tr>
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<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MHz</td>
<td>mega Hertz</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>ml, μl</td>
<td>millilitre(s), microlitre(s)</td>
</tr>
<tr>
<td>mol, mmol</td>
<td>mole, millimole</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxy methyl</td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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</tr>
</tbody>
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5.2.2 Synthesis and cycloaddition of \textit{cis}-isopropylidene protected intermediate  
5.2.3 Functionalization of the alkene unit  
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Chapter 1

Introduction to Iminosugars
1.1 General Overview of Iminosugars

Iminosugars are polyhydroxylated alkaloids; they are the natural mimics of carbohydrates in which the endocyclic oxygen atom has been replaced with a nitrogen atom (Fig 1.1). This simple change leads to some remarkable biological properties.

\[ \text{Fig 1.1 Glucose and its natural analogue, Nojirimycin} \]

The first syntheses of these carbohydrate analogues by Paulsen, Jones, and Hanessian and their discovery as natural products by Inouye was reported in the 1960’s.

The growing research on iminosugars is a result of their ability to inhibit glycoprocessing enzymes. Inhibitors of these enzymes are important therapeutic targets for the treatment of the associated diseases such as cancer, diabetes, lysosomal storage disorders and rare genetic disorders.

Due to their potential in medicine, a large number of synthetic approaches towards piperidines have been developed in order to generate biologically active analogues.

These small molecules are highly functionalised and stereochemically complex, making them challenging synthetic targets. This thesis is concerned with a novel stereoselective synthesis of C-glycoside iminosugars from simple carbohydrate building blocks.

1.2 Natural Occurrence

There are five main classes of iminosugars: piperidines, pyrrolidines, pyrrolizidines, indolizidines and nortropanes (Fig 1.2); of which the hydroxylated piperidines will be the focus of this work.
Most naturally occurring polyhydroxylated alkaloids have been isolated from plants, with a few isolated from bacteria and fungi.\(^{20}\) Nojirimycin (NJ) was the first iminosugar to be discovered in 1966, isolated from *Streptomyces*.\(^{21,22}\) It has antibiotic and antimicrobial properties and was also found to be a potent inhibitor of \(\alpha-\) and \(\beta-\)glucosidases\(^{23}\) as might be expected from its structural resemblance to glucose. This potent inhibition of a culture broth of *Streptomyces* also led to the isolation of mannojirimycin\(^{24}\) and galactostatin.\(^{25}\)

The isolation of other hydroxylated piperidine alkaloids from plants and microorganisms quickly followed. Fagomine was isolated from *Fagopyrum esculentum* in 1974.\(^ {26}\) 1-Deoxynojirimycin (DNJ) was isolated from *Morus* in 1976,\(^ {27}\) it had previously been synthesised by Paulsen in 1967.\(^ {28}\) It was also later found to be produced by bacteria, *Bacillus*\(^ {29}\) and *S. lavandulae*.\(^ {30}\) Swainsonine was isolated from *Swainsona canescens* in 1979.\(^ {31}\) Castanospermine was discovered in the leaves, seeds and bark of *Castanospermum austral* in 1981.\(^ {32}\)

In recent years, there has been an increase in the number of novel water-soluble alkaloids isolated, which would suggest that many more await discovery. It is not
unusual that they have been synthetically prepared before their discovery as natural products.

1.2.1 Iminosugar C-Glycosides

An exact iminosugar mimic of a glycoside structure, like nojirimycin, would result in a labile N,O-acetal function (Fig 1.3), making them unsuitable probes in biological research. Most iminosugars have to be stored as bisulfite adducts.

![Fig 1.3 Hemicetal structures of nojirimycin](image)

The 1-deoxy iminosugars lack the hemiacetal function of NJ which increases their stability. As a result, most of the synthetic targets have been based on these deoxy-iminosugars. An alternative is to replace the oxygen of the iminosugars pseudo-anomeric centre for a methylene group resulting in a stable C-glycoside mimic (Fig 1.4).^33

![Fig 1.4 Stable iminosugars](image)

Iminosugar C-glycosides provide the opportunity for the synthesis of a stable class of aza-mono and di-saccharides which may have more potent and/or specificity in comparison to the simpler 1-deoxysugars.
The first naturally occurring C-glycoside to be discovered from a plant, *Omphalea diandra*, was α-homonojirimycin (α-HNJ) (1) (Fig 1.5).\(^{41}\) It is an inhibitor of α- and β-glucosidases\(^ {41, 42}\) and a more specific α-glucosidase inhibitor than DNJ.\(^ {36}\) The alternative positioning of a substituent linked to C-1 rather than to the endocyclic N-atom, leading to a stronger influence on the piperidine ring, may explain the improved results observed with iminosugar C-glycosides. Also, more favourable interactions with the enzyme lipophilic pocket may be achieved with this alternative, perhaps improved, position of the alkyl chain.\(^ {43, 44}\)

Both α- and β-homomannojirimycin (HMJ) (3 and 4), were isolated from a member of the genus *Aglaonema* in 1997\(^ {34}\) and in 1998 from the bulbs of *Hyancinthus*.\(^ {35}\) They are inhibitors of α- and β-mannosidases respectively.\(^ {34}\)

Adenophorine (7), a naturally occurring C-glycosides bearing a lipophilic substituent at the 6-position, was isolated from the roots of *Adenophora*. It is a good α-galactosidase inhibitor and moderate α-glycosidase inhibitor.\(^ {37}\)

Homogalactostatin (HGJ) (Fig 1.6) has not yet been isolated from nature. Both anomers were prepared by Martin and co-workers.\(^ {45, 46}\) α-HGJ retains the potent activity of its parent GJ and 1-DGJ as an inhibitor of α-galactosidases, but not of β-galactosidases. β-HGJ is a weak α-galactosidase inhibitor. Derivatives of HGJ have been isolated, such as a galactostatin,\(^ {47}\) β-1-C-butyl-deoxygalactostatin (6) and batzellaside (9); it seems likely α- and β-HGJ will be discovered naturally.
Introduction to Iminosugars

Chapter 1

Fig 1.6 Homogalactonojirimycin

1.3 Biological Activity and Therapeutic Applications

Natural and synthetic piperidines inhibit oligosaccharide processing enzymes: glycosidases, glycosyltransferases, glycogen phosphorylases, nucleoside-processing enzymes, a sugar nucleotide mutase and metalloproteinases. These enzymes are involved in a whole range of essential biological transformations and inhibition of these enzymes can disrupt the biosynthesis of oligosaccharides, interfering in all of these processes. It is these biological properties that contribute to iminosugars being important therapeutic agents in the treatment of cancer, diabetes, viral diseases such as HIV, hepatitis B and C, lysosomal storage disorders including Gaucher disease and Fabry’s disease and rare disorders such as cystic fibrosis.

Their resemblance to carbohydrates allows iminosugars to be recognised by and interact with carbohydrate receptors without being processed by the pathways that they target. They can be transported by carbohydrate transporters, are normally well absorbed and can cross the blood-brain barrier, have both chemical and metabolic stability, are water-soluble (polar nature) and are normally excreted unchanged from the body.

Iminosugars have long been used as medicines, even before their discovery. Medicinal preparations of the mulberry plant in 17th century China were used for the treatment of diabetes. It is now known that some of the major components of the leaves of Morus alba (white mulberry) are iminosugars such as DNJ and its glycosides. This led to the preparation of derivatives of DNJ in modern medicine as inhibitors with increased activity against diabetes and the eventual
release of a marketed drug Miglitol (Glyset™, Bayer) in 1996 for type II diabetes (Fig 1.7).

**Fig 1.7 Marketed Iminosugar Drugs**

Also based on 1-DNJ is Miglustat (Zavesca™, Actelion), an oral administered drug approved in 2003 for Gaucher disease. It has been approved in certain countries for the treatment of Niemann Picks disease and is currently being investigated to treat Tay-Sachs disease and cystic fibrosis. There are many examples of iminosugars in various stages of clinical trials (Fig 1.8).

**Fig 1.8 Iminosugars currently undergoing clinical evaluation**

Although there are encouraging results, variability in activity and specificity/poor clinical selectivity resulting in considerable side-effects has hampered the development of iminosugars in clinical applications. There is a need to identify new targets with improved activity and selectivity and difficulties in their complexities in synthesis and purification to overcome.
1.3.1 Glycosidase Inhibition

Iminosugars are mostly recognised for their ability to inhibit glycosidases (Table 1.1). Glycosyl transferases and glycosidases are enzymes that catalyse the formation and hydrolysis of glycosidic bonds. The general mechanisms for inverting and retaining glycosidases (β-glycosidase) are shown (Fig 1.9 and 1.10).

Fig 1.9 Inverting glycosidases

Inverting glycosidases operate via a single-displacement mechanism in which water attacks the anomeric center and displaces the aglycone. This is assisted in the enzyme’s active site by two carboxylic acid residues from either aspartic or glutamic acid side chains; one of the carboxylic acids acts as a general base for the attacking water molecule and the other as an acid that protonates the glycosidic bond. Displacement of the aglycone by water produces the hemiacetal product via an oxo-carbenium-ion-like transition state.

Fig 1.10 Retaining glycosidases

Retaining glycosidases operate via a double displacement mechanism that involves a covalent enzyme-glycosyl intermediate. A narrower active site does not accommodate water initially and instead the carboxylic acid group positioned closer attacks the anomeric site to produce a covalent enzyme-glycosyl
intermediate. The aglycon diffuses out of the active site and in a second step a water molecule attacks the anomeric center under base catalysis of the remaining carboxylate.\textsuperscript{9, 66, 67}

It is thought that iminosugars can act as transition state inhibitors by mimicking their carbohydrate analogues. An iminosugar of identical or similar stereochemistry to that of a natural carbohydrate is often, but not always, a specific inhibitor for the associated processing enzymes.

<table>
<thead>
<tr>
<th>Iminosugar</th>
<th>Glycosidases Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-DNJ</td>
<td>(\alpha)-glucosidases (including isomaltase, maltase, sucrase, trehalase, invertase), (\beta)-glucosidases, (\alpha)-mannosidases, (\alpha) and (\beta)-galactosidases, (\alpha)-L-fucosidase</td>
</tr>
<tr>
<td>NJ</td>
<td>(\alpha)-glucosidases (including sucrase, maltase, isomaltase and amylase), (\beta)-glucosidases, (\beta)-galactosidases, (N)-acetyl-(\beta)-D-glucosaminidases</td>
</tr>
<tr>
<td>(\alpha)-HNJ</td>
<td>(\alpha)-glucosidases (including sucrase, maltase, trehalase), (\beta)-glucosidases, (\alpha)-galactosidases, lactase, glucosidase I and II</td>
</tr>
<tr>
<td>(\beta)-HNJ</td>
<td>(\beta)-glucosidases</td>
</tr>
<tr>
<td>1-DMJ</td>
<td>(\alpha)-mannosidases (mannosidase I), (\alpha)-fucosidase</td>
</tr>
<tr>
<td>MJ</td>
<td>(\alpha)-mannosidases</td>
</tr>
<tr>
<td>(\alpha)-HMJ</td>
<td>(\alpha)-mannosidases</td>
</tr>
<tr>
<td>(\beta)-HMJ</td>
<td>(\beta)-mannosidases</td>
</tr>
<tr>
<td>1-DGJ</td>
<td>(\alpha)-galactosidase</td>
</tr>
<tr>
<td>GJ</td>
<td>(\alpha)-galactosidases, (\beta)-galactosidases</td>
</tr>
<tr>
<td>(\alpha)-HGJ</td>
<td>(\alpha)-galactosidases</td>
</tr>
<tr>
<td>Adenophorine</td>
<td>(\alpha)-galactosidase, (\alpha)-glucosidases</td>
</tr>
<tr>
<td>DMDP</td>
<td>(\alpha)-glucosidases (including maltase, sucrase, trehalase, invertase), (\beta)-glucosidases (cellobiase), human lysosomal (\beta)-mannosidases, (\beta)-galactosidases, (\beta)-xylosidase</td>
</tr>
<tr>
<td>Fagomine</td>
<td>(\alpha)-glucosidases (including isomaltase and sucrase)</td>
</tr>
<tr>
<td>Castanospermine</td>
<td>(\alpha)-glucosidases (including amyloglucosidase, sucrase, maltase, isomaltase, trehalase, amylase), glucosidase I and II, (\beta)-glucosidases (including lactase and cellobiase), (\beta)-glucocerebrosidase, (\beta)-xylosidase</td>
</tr>
<tr>
<td>Swainsonine</td>
<td>(\alpha)-mannosidases</td>
</tr>
<tr>
<td>Alexine</td>
<td>Disaccharide-type (\alpha)-glucosidases (amiloglucosidase and trehalase), (\beta)-galactosidases</td>
</tr>
<tr>
<td>Australine</td>
<td>Disaccharide-type (\alpha)-glucosidases (amiloglucosidase sucrase, maltase), glucosidase I, (\beta)-glucosidases, (\beta)-galactosidases</td>
</tr>
<tr>
<td>Calystegine A(_3)</td>
<td>(\beta)-glucosidases, (\beta)-galactosidases</td>
</tr>
<tr>
<td>Calystegine B(_4)</td>
<td>(\alpha)-glucosidases, (\beta)-glucosidases</td>
</tr>
</tbody>
</table>

\textbf{Table 1.1 Iminosugar glycosidase inhibitors}\textsuperscript{9, 20}
It is the inhibition of these enzymes that allow iminosugars to play a pivotal role in many diseases.

1.3.1.1 Antiviral Agents and Peptidomimetics

Many viruses are enveloped; their protein capsids are contained in a membrane composed of glycoproteins, which make them susceptible to inhibitors of glucosidases. A number of iminosugars have been shown to exhibit anti-viral activities, particularly towards Human Immunodeficiency virus (HIV).\(^{68-70}\)

HIV encodes two glycosylated envelope proteins, gp120 and gp41. During infection, gp120 undergoes a conformation change upon binding to CD4, exposing gp41. This leads to fusion with the host cell and uptake of the virus into the cell. Compounds that disrupt this interaction, preventing viral-cell contact, have potential as anti-viral agents for HIV.\(^{71}\)

Treatment of HIV infected cells with \(N\)-butyldeoxynojirimycin blocked viral infectivity \textit{in vitro}. The conformational change of gp120 on binding to CD4 did not occur and this prevented fusion of the host cell with the virus.\(^{72, 73}\) However, a key challenge was to develop potency without compromising toxicity.

Mootoo and co-workers prepared \(C\)- and aza-\(C\)-glycoside analogues of \(\beta\)-galactosylceramide containing a simple \(C\)-17 hydrocarbon chain as a ceramide substitute to determine their binding to HIV gp120 (\textbf{Fig 1.11}).\(^{74}\) They reported that the aza-\(C\)-glycoside derivative below binds HIV-1 gp120 with comparable or higher affinity than \(\beta\)-galactosylceramide.

\begin{center}
\textbf{Fig 1.11} \(\beta\)-Galactosylceramide and iminosugars containing lipids
\end{center}
Previous work carried out in the Murphy group has based peptidomimetics on iminosugars such as DNJ and DMJ as ligands for somatostatin receptors and HIV protease. Peptidomimetic research has a goal of developing active compounds with improved pharmacokinetic properties. The general principle is that pharmacophoric groups are grafted onto a nonpeptide scaffold, which can orient them in the direction of their respective binding substrates (Fig 1.12).

![Fig 1.12 Peptidomimetics based on 1-DNJ](image)

Chery and Murphy designed an inhibitor based on the naturally occurring glycosidase inhibitor, 1-deoxymannojirimycin (Fig 1.13).

![Fig 1.13 Design of carbohydrate and iminosugar peptidomimetics](image)

There are advantages of using DMJ or other iminosugars, over the pyranosides, as scaffolds in peptidomimetic design. The iminosugars could be charged at
physiological pH, pharmacophoric groups can be grafted to the ring nitrogen and they can act as hydrogen bond donors. This contrasts with carbohydrate scaffolds, where the pyranose oxygen atom has hydrogen acceptor potential. Molecular modelling indicated that the protonated nitrogen could hydrogen bond with a carbonyl group of HIV-protease amide backbone.

There is potential to base scaffolds on iminosugar C-glycosides.

1.3.1.2 Anticancer Agents

Cancer is unregulated cell growth or cell migration that can be caused by mutagens, infections and viruses. Treatments include surgery, radiotherapy, chemotherapy or immunotherapy. Inhibitors of tumour metastasis and angiogenesis are important as suitable drug candidates for cancer treatment.

Iminosugars have been shown to interact with enzymes involved in the metabolic pathway of glycans responsible for tumour cell invasion and migration. Nojirimycin, swainsonine and castanospermine were all found to behave as competitive inhibitors of N-linked glycan processing in the Golgi, and reduced invasion and inhibited tumour metastasis. Swainsonine, the lowest toxicity of the three, reached phase II trials; however as a result of their inhibitory activity towards all N-linked glycan biosynthesis, the side effects were too severe.

Siastatin B is a naturally occurring 1-N-iminosugar that resembles D-glucuronic acid. Nishimura has synthesised gem-diamine 1-N-iminosugars as a new class of glycosidase inhibitors. Two gem-diamine 1-N-iminosugars have been identified as inhibitors of an enzyme in heparan sulfate synthesis, which could be of therapeutic benefit for treating tumour growth and metastasis. (Fig 1.14).
Murphy and co-workers synthesised hybrids of 1-DNJ and 5-aryl-1,2,3-triazole as bifunctional inhibitors of angiogenesis.\(^{88,89}\) One bifunctional compound was a more potent inhibitor of angiogenesis \textit{in vitro} than either 1-DNJ or 5-aryl-1,2,3-triazole alone. This compound, \(N\)-(8-(3-ethynylphenoxy) octyl-1-deoxynojirimycin (Fig 1.15), was shown to suppresses growth and migration of human lung cancer cells.\(^{90,91}\)

![Fig 1.15](image)

**Fig 1.15** \(N\)-(8-(3-Ethynylphenoxy) octyl-1-deoxynojirimycin

### 1.3.1.3 Lysosomal Storage Disorders and Pharmacological Chaperones

Lysosomal enzymes are synthesised in the ER and are responsible for the degradation of oligosaccharides, glycolipids, glycoproteins and other cell components. A mutation in a lysosomal enzyme can lead to lysosomal storage disorders, such as Gaucher disease, Fabry’s disease, Tay-Sachs disease or Pompe’s disease. These mutated enzymes, while often catalytically competent, can be unable to pass the quality control mechanisms of the ER, resulting in reduced lysosomal trafficking, substrate accumulation and cellular dysfunction.

Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of \(\beta\)-glucocerebrosidase (Gcase). It is characterised by the accumulation of glucosylceramide leading to severe symptoms such as hepatosplenomegaly, anemia and skeletal lesions in type I and neurological manifestations in type II and III. Enzyme replacement therapy (ERT) is effective for type I. Currently there is no available enzyme or substrate replacement therapy for type II and III due to the difficulty of delivering the enzyme/substrate to the CNS.\(^{92}\)

Overkleeft and co-workers synthesised a series of lipophilic \(C\)-glycoside iminosugars as glucosyltransferase inhibitors.\(^{93}\) A \(\beta\)-aza-\(C\)-glycoside analogue (Fig 1.16) showed improved inhibitory potency for glucosylceramide synthase
over the therapeutic agent \( N \)-butyl-1-DNJ currently marketed for Gaucher disease.\(^{61, 94}\)

![IC50 values for compounds](image)

**Fig 1.16 Enzyme inhibition of glucosylceramide synthase values for \( \beta \)-adamantan-1-yl-methoxy-1-DNJ and \( N \)-butyl-1-DNJ**

An alternative therapy available now is the use of hydrophilic active-site specific chaperones (ASSCs) or pharmacological chaperones (PCs). These are small molecules that bind to the active site of mutant lysosomal enzymes in the ER, stabilize and induce their proper folded conformation (Fig 1.17).\(^{95}\)

Iminosugars can be effective ASSCs; they display high affinities to the biological active site of their target proteins, they diffuse easily into the cell, they are reversible inhibitors and they can cross the blood-brain barrier.\(^{83}\)

![Diagram of protein folding and misfolding](image)

**Fig 1.17 Iminosugars as pharmacological chaperones**
Fan et al. have reported that 6-C-nonyl isofagomine is the most potent Gcase inhibitor to date ($IC_{50} = 0.6\text{ nM}$) (Fig 1.18).  

Fig 1.18 Proposed binding of 6-C-nonly isofagomine with human Gcase

Recently, a series of $O$-alkyl iminoxylitol derivatives were synthesised and compared as $\beta$-Gcase inhibitors. A structure-activity study showed a dramatic influence of the position of the alkyl chain ($\alpha$-C1, O2, O3 or O4) on human Gcase inhibition, with 2-$O$-alkyl derivatives as the most promising class of compounds for ASSC therapy (Fig 1.19).  

Fig 1.19 2-$O$-alkyl iminoxylitol compounds

1.3.1.4 Rare Disorders - Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). These mutations cause lowered expression and activity of CFTR, affecting the exocrine organs, mainly the lungs and digestive system. The most common CFTR mutation (delF805) results in improper folding in the ER and subsequent degradation. Compounds that correct the folding and trafficking defects in the CFTR are of great interest as potential therapeutic agents for this disease.  

$R_{1,3,4,5} = H, R_2 = \text{Hexyl}$$\quad IC_{50} = 9\text{ nM}$
Ireland has the highest incidence of CF in the world with 1 in every 10,000 people diagnosed with the disease and 1 in 19 classed as carriers. This is almost four times the average of every EU country and the US. There is no cure and currently life expectancy in Ireland is 25 years.\textsuperscript{100}

Becq and co-workers showed that miglustat (Fig 1.20) restored transport and activity of the CFTR in cells and temporarily relieved the effects of the disorder.\textsuperscript{101,102} Clinical trials were initiated in 2007. A study in 2009 showed that daily treatment of low concentrations of miglustat for 2 months results in progressive, stable, reversible and sustained correction of del F508 CFTR trafficking.\textsuperscript{103}

Fig 1.20 Miglustat and isoLAB

Preliminary studies show that 1,4-dideoxy-2-hydroxymethyl-1,4-imino-L-threitol (isoLAB) partially rescues the defective del F508 CFTR function and may have a role against CF.\textsuperscript{104}

1.4 Synthetic Strategies

Challenges when considering the preparation of iminosugar C-glycosides:

- the (piperidine) ring must be generated efficiently
- multiple stereogenic centres must be obtained with high stereochemical control
- protecting groups must be carefully considered due to the high density of functional groups

There are two general approaches to their preparation; through asymmetric synthesis, introducing stereocenters or chiral pool, beginning from a chiral starting material with the appropriate stereochemistry already in place. Due to their similarities and availability, carbohydrates have been a common building block for iminosugar synthesis.\textsuperscript{33,83,105-108}
General synthetic strategies reported in the literature can be divided into two main categories depending on the disconnections made in the retrosynthesis; C5-N or C1-N disconnection (Fig 1.21) and C1-CH₂R disconnection (Fig 1.22). Disconnecting at C-N, a final intramolecular cyclization is used to build the iminosugar ring. Double and single reductive amination have been the most popular method of cyclization. Activating a leaving group resulting in cyclization is an alternative method. A C-C disconnection uses an electrophilic donor; this approach has been less exploited.³³
The use of a thermally promoted intramolecular 1,3-dipolar cycloadditions in the synthesis of iminosugar C-glycosides have been reported by Fleet\textsuperscript{109} and Overkleeft\textsuperscript{110}. Cycloaddition of an azidoester and subsequent sodium cyanoborohydride reduction gave an eight carbon homologue of α-HMJ (Scheme 1.1).

Scheme 1.1 Fleet’s synthesis of an eight-membered homologue of α-HMJ
Overkleeft and co-workers prepared highly functionalised piperidines via a tandem retro-Michael-[2+3]-cycloaddition (Scheme 1.2).

Scheme 1.2 Overkleeft’s synthesis of piperidines

1.4.1 The 1,3-Dipolar Cycloaddition

The Huisgen Cycloaddition or 1,3-dipolar cycloaddition is the reaction of a 1,3-dipole with a dipolarophile to give a five membered heterocycle (Fig 1.23).

Fig 1.23 Huisgen cycloaddition between and azide and alkene

A 1,3-dipole describes a system of three atoms over which are distributed four $\pi$ electrons (Fig 1.24). There are two types of dipoles; propargyl-allenyl or allyl.

Fig 1.24 1,3-Dipole systems
The three atoms can be a variety of combinations of C, N and O (Fig 1.25). Dipolarophiles are compounds with C-C and C-N double and triple bonds, as well as many carbonyl functions.\textsuperscript{111,112}

\begin{center}
\begin{tabular}{|c|}
\hline
Propargyl - Allenyl Type & Allyl Type \\
\hline
\begin{tabular}{c}
\text{-C}^{\ddagger}\text{=N}-\text{C} \\
\text{-C}^{\ddagger}\text{=N}-\text{O} \\
\text{N}^{\ddagger}\text{=N}-\text{N} \\
\text{N}^{\ddagger}\text{=N}-\text{O}
\end{tabular} & \begin{tabular}{c}
\text{C}^{\ddagger}\text{=N}=\text{O} \\
\text{O}=\text{N}^{\ddagger}\text{=O} \\
\text{N}^{\ddagger}\text{=O}=\text{O} \\
\text{O}^{\ddagger}\text{=O}=\text{O}
\end{tabular} \\
\hline
\end{tabular}
\end{center}

**Fig 1.25 Some examples of 1,3-dipoles**

Azides are well known to behave as 1,3-dipoles in thermal cycloaddition reactions. The cycloaddition of an azide with an alkene gives an unstable triazoline. Triazoline decomposition (Fig 1.26) can proceed through a diradical or zwitterionic intermediate to form an aziridine, imine or a range of different products depending on reaction and substrate conditions.\textsuperscript{113,114}

\begin{center}
\begin{tabular}{c}
\text{R}^{2}\text{NR}^{1} \\
\text{R}^{3}\text{NR}^{1}
\end{tabular}
\end{center}

**Fig 1.26 Mechanism of 1,2,3-triazoline decomposition**

1,3-Dipoles containing a functional group that can act as a dipolarophile are extremely interesting substrates. The first example of a double bond participating in an intramolecular 1,3-dipolar cycloaddition with a suitably placed 1,3-dipole was reported by LeBel and Whang in 1959.\textsuperscript{115} Intramolecular cycloadditions\textsuperscript{116-118} are usually found in molecules large and flexible enough to accommodate the required arrangement of the azide and dipolarophile in two approximate parallel
planes, one atop the other (Fig 1.27). Substituents, therefore, have an influence on the geometry of the cycloaddition.

Fig 1.27 Overlap of 1,3-dipole and dipolarophile

One of the most attractive features of an intramolecular cycloaddition is the opportunity to control the stereochemistry of the products at multiple centers.

1.4.2 Access to 1-DNJ derivatives via azide-alkene cycloaddition

Previous research carried out in the Murphy lab by Dr Ying Zhou describes the synthesis of DNJ derivatives via intramolecular Huisgen cycloaddition between an azide and an alkene (Scheme 1.3).\textsuperscript{116}

Scheme 1.3 General scheme for Zhou’s “Access to 1-DNJ derivatives via Azide-Alkene cycloaddition”

The synthesis began from 14 which was prepared from d-glucono-δ-lactone as described previously by Fleet and co-workers.\textsuperscript{119} Regioselective mesylation of the primary hydroxyl group, followed by exchange of the mesyl group for an azide, benzylaition and regioselective acetal cleavage gave 15. Oxidative
cleavage using NaIO₄ gave the aldehyde 16. The alkene 17 was prepared using methyl triphenylphosphonium bromide and base via Wittig reaction (67%).

Scheme 1.4 Reagents and conditions: a) MsCl, 2,6-lutidine, CH₂Cl₂ 75% b) NaN₃, DMF, 85 °C c) NaH, BnBr, THF d) AcOH, e) NaIO₄, CH₂Cl₂/H₂O, 82% f) Ph₃PCH₂I, NaHMDS, THF -78 °C, 67%

The thermally promoted intramolecular cycloaddition of 17 was investigated. Heating in DMF or toluene gave, in a stereoselective manner, the 1,2,3-triazoline 18. A fraction containing the aziridine 19 was obtained after treatment of 19 with silica gel, suggesting that the acidic nature of the gel promoted loss of nitrogen. The aziridine was treated with 10% Pd-C to give an inseparable mixture of 20 and 21. The formation of 21 is explained by hydrolysis of the aziridine in the presence of adventitious water.

Scheme 1.5 Thermally promoted intramolecular cycloaddition
The stereoselectivity was rationalized by comparing the relative energy of two proposed transition states 17a and 17b (Fig 1.28). Allylic strain destabilizes the transition state conformer 17b compared with 17a and progression of the reaction through 17a gives an identical configuration to DNJ.

![Proposed transition states for Huisgen cycloaddition](image)

**Fig 1.28 Proposed transition states for Huisgen cycloaddition**

The one-pot conversion of 17 with a variety of nucleophiles was also investigated. Alkene 17 was heated in toluene for 1 h and then reagents were added and heating continued (Table 1.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70% AcOH, 110 °C, 1 h</td>
<td>Inseparable mixture</td>
</tr>
<tr>
<td>2</td>
<td>70% AcOH, rt, 15 h</td>
<td>Aziridine 19 (15%), Azepane 22 (33%), 2-O-benzyl DNJ (14%)</td>
</tr>
<tr>
<td>3</td>
<td>Toluene, 110 °C, 1 h, then NaN₃ (5.0 eq), AcOH (1.5 eq)</td>
<td>23 (R = N₃, 35%)</td>
</tr>
<tr>
<td>4</td>
<td>Toluene, 110 °C, 1 h, then MeOH 60 °C, 1 h^a</td>
<td>24 (R = OMe, 20%)</td>
</tr>
<tr>
<td>5</td>
<td>Toluene, 110 °C, 1 h, then AcOH (5.0 eq), 110 °C, 1 h^a</td>
<td>25 (R = OAc, 45%)</td>
</tr>
<tr>
<td>6</td>
<td>Toluene, 110 °C, 1 h, then PhSH rt, 15 h^a</td>
<td>26 (R = SPh, 57%)</td>
</tr>
</tbody>
</table>

^aToluene removed before addition of reagents

**Table 1.2 Summary of one-pot investigations**
This thesis describes the continuation of this work, with 1,3-dipolar cycloadditions carried out using a modified intermediate of the type below (Scheme 1.6).

**Scheme 1.6 General Intermediate towards iminosugar C-glycosides**

By introducing an aliphatic group (R) to give a secondary azide and using similar methodology as seen previously, we propose to synthesize C-glycoside iminosugar analogues. Specifically we will introduce a vinyl group at this position, creating an allylic azide, to investigate the Huisgen cycloaddition in our preparation of iminosugar C-glycosides.

### 1.4.3 The Allylic Azide Rearrangement

Azides can be valuable functional groups in organic synthesis. They are useful building blocks in the preparation of heterocycles and nitrogen-containing compounds and are inert under acidic and basic conditions. They are often used in powerful transformations including the Staudinger reaction, Schmidt reaction, Curtis rearrangement and the aza-Wittig reaction. They have a special reactivity in cycloadditions, pericyclic reactions and more recently in “Click” reactions.\(^\text{120-122}\)

\[
\begin{array}{ccc}
\text{A} & \leftrightarrow & \text{B} \\
\text{R} & \text{N} & \text{N} \\
\text{N} & \text{N} & \text{N}
\end{array}
\]

**Fig 1.29 Resonance structures and reactivities of azides**
Their unusual reactivity is due to the polar mesomeric resonance structures A-C (Fig 1.29), explaining the dual nucleophilic and electrophilic character of the proximal and distal nitrogens.

The ability of allylic azides to undergo [3,3]-sigmatropic rearrangement was first reported by Winstein and Young\textsuperscript{123} in 1960 and Heasley and VanderWerf in 1966.\textsuperscript{124} The rearrangement generally occurs at room temperature, creating an interconverting mixture of isomers (Fig 1.30).

![Fig 1.30 The allylic azide rearrangement](image)

The rearrangement has also been interpreted as a 1,3- and 1,1-intramolecular dipolar cycloaddition and cycloreversion involving a strained triazoline as an intermediate (Fig 1.31).\textsuperscript{112}

![Fig 1.31 Dipolar cycloaddition and cycloreversion](image)

Trost\textsuperscript{125} reported on the presence of intramolecular hydrogen bonding between allylic azide and free hydroxyl groups leading to a shift in the equilibrium of isomerisation. The 1,2-isomer was favoured (9:1) due to intramolecular hydrogen bonding occurring, which is not possible with the 1,4-isomer (Fig 1.32).
Sharpless and co-workers investigated the selectivity of the allylic azide rearrangement, comparing primary, secondary and tertiary aliphatic allylic azides (Fig 1.33). A trapping experiment was carried out, reacting each type of azide with phenylacetylene using a copper catalyst. Both steric and electronic effects were shown to influence the reactivity of allylic azides.\textsuperscript{126}
Excellent selectivity was shown between primary vs. tertiary and secondary vs. tertiary, with no detectable products arising from tertiary azides. Mixtures were detected when comparing primary and secondary allylic azides (~7:3, 1°:2°). On introducing a free hydroxyl adjacent to the allylic azide, evidence showed that
the H-bonding effects between the hydroxyl and the azide groups could significantly alter the equilibrium in these dynamic systems. The equilibrium between primary and secondary allylic azides changed significantly (~1:1, 1°:2°). Sluggish rearrangement rates can be due to inductive electronic effects and hydrogen bonding effects.

Aubé and co-workers demonstrated how differences in the azides reactivity patterns and the effect of substituents can prove advantageous. They combined the allylic azide rearrangement and the intramolecular Schmidt reaction to prepare substituted lactams stereoselectively (Scheme 1.7). They found that by altering substituents and their orientation, they could change the outcome of the reaction and the products.\textsuperscript{127}

\begin{equation}
\text{Scheme 1.7 Stereocontrol in a combined allylic azide rearrangement and intramolecular Schmidt reaction}^{127}
\end{equation}

Although possible to take advantage of the significant stereochemical differences between substrates; this rearrangement is generally viewed as a liability in organic synthesis and as a functional group is avoided. In this work we propose to make use of the allylic azide rearrangement in tandem with the 1,3-dipolar cycloaddition to prepare iminosugar C-glycosides (Scheme 1.8).
Scheme 1.8 Proposed route for the tandem allylic azide rearrangement – Huisgen 1,3-dipolar cycloaddition

The key reaction will not be without difficulties. The tandem rearrangement – cycloaddition will have the potential of producing two new stereogenic centers at C-1 and C-5. All four allylic azide isomers (E, Z, R and S) could exist in a dynamic equilibrium. We hypothesised that either the R- or S-isomer would be more reactive in an intramolecular cycloaddition and lead to the diastereoselective formation of piperidines via triazoline and aziridine intermediates, generating two new stereocenters (Fig 1.34).

Fig 1.34 Possible isomers of proposed intermediates
1.5 Thesis Aims and Target Compounds

In the general introduction, motivation for this project has been outlined. The main aim was to investigate the tandem allylic azide rearrangement – Huisgen cycloaddition towards the preparation of iminosugar C-glycosides. These small carbohydrate mimetics have huge medicinal potential, particularly as potent glycosidase inhibitors. Their synthesis is challenging and it is important to develop novel pathways to natural and non-natural iminosugars.

These analogues, 1-C-ethylene-deoxynojirimycin (27), 1-C-ethylene-deoxymannojirimycin (28) and 1-C-ethylene-deoxygalactostatin (29), arising from triazoline decomposition could potentially give a range of different analogues by using different nucleophiles (R = -OH, -OR, -N₃, -SR). The alkene moiety could be exploited by a range of different methods such as oxidation to give access to natural products HNJ (1) and HMJ (3). Cross metathesis or addition reactions of the terminal alkene would allow preparation of iminosugar conjugates. This thesis deals with the investigation of these possibilities.
Chapter 2

Homonojirimycin Derivatives from D-Glucono-δ-lactone
2.1 Introduction

2.1.1 Previous syntheses of homonojirimycin and analogues

Few polyhydroxylated piperidine alkaloids are commercially available; there have been many attempts to develop methods to prepare this class of compounds. α-HNJ was first prepared from the bisulfite adduct of nojirimycin in 8 steps (Scheme 2.1). \(^{128}\)

![Scheme 2.1 Synthesis of α-HNJ from NJ](image)

The first total synthesis of α-HNJ was reported in 1990 by Kibayashi and co-workers. The chiral allylic alcohol was prepared from diethyl L-tartrate in 6 steps. The cyclisation step was carried out using Et\(_3\)N in refluxing methanol and deprotection in acid gave the final product in 68% yield (Scheme 2.2). \(^{129}\)

![Scheme 2.2 First total synthesis of α-HNJ](image)

Both anomers of HNJ were prepared via a chemoenzymatic approach. The lactol synthesised from cis-but-2-ene-1,4-diol was a suitable substrate for rabbit muscle fructose 1,6-bisphosphate aldolase. Hydrogenation gave α- and β-HNJ with high selectivity (Scheme 2.3). \(^{130}\)
Martin and Saavedra prepared β-HNJ stereoselectively via a double reductive amination of a 2,6-heptodiulose using ammonium formate and NaBH$_3$CN. The diketone was prepared from tetra-$O$-benzyl-$D$-glucono-1,5-lactone (Scheme 2.4).$^{131,132}$

Blériot and co-workers showed that $N$-benzyl pentahydroxy-azepanes undergoing isomerization during mesylation of the hydroxyl group beta to the nitrogen. This is promoted by neighbouring nitrogen participation, forming an aziridine which is trapped by chlorine. The resulting chloromethyl tetrahydroxy-piperidines were converted into their corresponding homoglyconojirimycins (Scheme 2.5).$^{133}$
Compain and Martin have synthesised an eight-carbon homologue of HNJ, similar to the proposed target compounds in this thesis (Scheme 2.6), as a method of preparing glycoconjugate mimetics via cross metathesis. Intramolecular reductive amination of the amino-sorbose hemiketal liberated upon acidic hydrolysis of the isopropylidene provided the diastereomerically pure iminosugar in 66% yield.\textsuperscript{134,135}

Nicotra and co-workers carried out an intramolecular reductive amination to give the benzylated intermediate (Scheme 2.7). This intermediate was used to prepare bicyclic piperidines containing cyclic carbamate, urea and guanidine moieties.\textsuperscript{105,136}
Chapter 2

Scheme 2.7 Synthesis of homonojirimycin analogue

2.1.2 Retrosynthesis

For this work, D-glucono-δ-lactone was an obvious starting point for three reasons; a) It is a useful enantiopure scaffold from which homonojirimycin analogues could be obtained; b) Zhou and Murphy\textsuperscript{116} had used it as a starting point towards 1-DNJ derivatives and c) it is cheap and readily available. The retrosynthetic strategy to the C-glycoside derivatives was based on Zhou’s initial route, with some modifications (Scheme 2.8).

An allylic alcohol could be introduced \textit{via} a Grignard or Wittig reaction with the aldehyde derived from D-glucono-δ-lactone. The alcohol could be displaced to give the allylic azide, at which point the rearrangement would be observed. After introduction of the alkene moiety, an intramolecular Huisgen 1,3-dipolar cycloaddition could be carried out to give access to the 1,2,3-triazoline. This reaction would potentially produce two new stereogenic centres. Extrusion of nitrogen and subsequent reaction of the aziridine with nucleophiles would give access to iminosugar-C-glycoside analogues. Oxidation of the terminal alkene and deprotection would allow access to a natural product, homonojirimycin.
2.2 Results and Discussion

2.2.1 Synthesis of Allylic Azide Intermediates

The route began from **30**, which was prepared from D-glucono-δ-lactone as described previously by Fleet and co-workers.\(^\text{119}\)

![Scheme 2.8 Retrosynthesis from D-glucono-δ-lactone](image)

**Scheme 2.9 Reagents and Conditions:** a) \(p\)-TsOH, MeOH, Acetone, DMP, 73%; b) BnBr, Ag\(_2\)O, DMF, 9 – 26%

Protection of the free hydroxyl group of **30** proved troublesome. Benzyl bromide and NaH as a base were too harsh for this intermediate containing the methyl ester. Milder conditions using BnBr in the presence of silver(I)oxide in DMF provided the benzylated intermediate **31a**, however, never with full conversion of the starting material resulting in poor yield of **31a**. On one occasion, due to extended reaction times of 9 weeks, the benzylated product was isolated after difficult chromatographic separation in 40% yield. Previous publications in the
literature report 74% and 82% for this transformation. More recently a paper reported similar problems and yields to those encountered here.

Other benzylation conditions were tested including neutral conditions reported by Poon and Dudley using 2-benzyloxy-1-methylpyridinium triflate (Scheme 2.10). However, these conditions were not successful in increasing the yield or degree of reaction completion on a reasonably large scale.

![Scheme 2.10 Benzylation via benzyl trichloroacetimidate and 2-benzyloxy-1-methylpyridinium triflate](image1)

Other protecting groups were considered, though due to the chemistry required in later steps, few were considered suitable. The MOM ether was introduced using MOMCl in the presence of DIPEA to give the fully protected intermediate 31b in good yield. Although a considerable improvement in yield, this was not an ideal solution to the use of the benzyl ether, as MOMCl is highly toxic and carcinogenic and also expensive (10 eq were required for this step). Both benzylated and MOM protected intermediates were taken on.

![Scheme 2.11 MOM ether protection](image2)

Reduction of 31a-b to the primary alcohol was carried out using lithium aluminium hydride. The alcohols 32a-b were oxidised using the Dess-Martin
periodinane (prepared according to the method of Ireland and Liu\textsuperscript{141}) giving 33a-b.

Scheme 2.12 Reagents and conditions: a) LiAlH\textsubscript{4}, THF, 0 °C; b) Dess-Martin Periodinane, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C

Preparation of the allylic alcohol from the aldehyde was attempted with (2-hydroxyethyl) triphenylphosphonium bromide and n-butyllithium; however this Wittig reaction did not give the desired allylic alcohol (Scheme 2.13).  

Scheme 2.13 Wittig reaction with (2-hydroxyethyl) triphenylphosphonium bromide

The aldehydes 33a-b was reacted with a Grignard reagent, vinyl magnesium bromide, at -78 °C to give the allylic alcohol 34a-b as a mixture of syn- and anti-isomers in a ~1:1 ratio. There was no attempt to control the stereochemistry at this point as it was assumed that once the azide was introduced the allylic rearrangement would occur in a dynamic fashion regardless of stereochemistry. Mesylation of the allylic alcohol, followed by exchange of the mesyl group for an azide gave the allylic azides 36a-b and as expected, the rearrangement occurred.
There are four stereoisomers that this intermediate can potentially adopt. However, the only isomer observed by NMR was the trans-primary azide. It was not surprising that this was the most stable structure; it is known that secondary allylic azides rearrange faster than primary allylic azides and the more substituted alkene is favoured.\textsuperscript{124}

Next, the alkene moiety required for the cycloaddition was introduced. Different strength aqueous acetic acid solutions were tested; the terminal acetal group was cleaved selectively using 60\% AcOH. These acidic conditions were not strong enough to cleave the MOM protecting group on \textbf{36b} and \textbf{37b} was isolated.
Scheme 2.15 Selective cleavage of terminal acetonide group

Oxidative cleavage of the diol using NaIO₄ gave aldehyde 38a-b in good yield. Compounds 39a-b were prepared via Wittig reaction using methyl triphenylphosphonium bromide with base. The Wittig conditions were investigated; varying the base (nBuLi, NaHMDS and LiHMDS) and temperatures (-78 °C – rt). The best conditions found were treating the phosphonium salt with NaHMDS at -78 °C for 25 min, 0 °C for 15 min and rt for 25 min. Then, upon re-cooling to -78 °C, the aldehyde was introduced and the mixture was stirred for 15 min then RT for 2 h. However, the yields were found to be variable (20 – 55%).

Scheme 2.16 Reagents and conditions: a) NaIO₄, CH₂Cl₂/H₂O; b) Ph₃PCH₃Br, NaHMDS, -78 °C to rt, 20 – 55%

The two intermediates 39a and 39b were prepared from d-glucono-δ-lactone in 10 steps. A few problematic reactions, protecting the secondary hydroxyl, the Grignard and the Wittig reactions led to difficulties in scaling-up and the isolation of low quantities of the desired intermediates.
2.2.2 Thermally promoted intramolecular cycloaddition

With 39a-b to hand, the rearrangement – cycloaddition was investigated. The heating of 39 to reflux in DMF gave, in a stereoselective manner, the 1,2,3-triazoline 40 (Scheme 2.17).

Scheme 2.17 Thermally promoted intramolecular cycloaddition

The yields were significantly lower than that reported by Zhou\textsuperscript{116} (25\% vs. 50\%), due to the added complication of a tandem allylic-azide rearrangement. The cycloaddition reaction did not proceed fully to completion despite being left on for days/weeks; starting material 39a-b was always recovered.

The stereochemistry at C-5 was easily assigned using $J$ values and gave the same configuration as seen previously (Chapter 1, analogous with DNJ). Overlapping signals with the benzylated intermediate 40a made it difficult to confirm the stereochemistry at C-1. With 40b, $J_{H1-H2}$ values isolated were found to be 5.8 Hz, which fall between typical $J$ values for alpha or beta sugars (Fig 2.1). Comparisons with other $J$ values and literature reports later on help to confirm the stereochemistry.

Fig 2.1 $J$ values for 1,2,3-triazoline 40b
The optimal temperatures and solvents in which to carry out the tandem rearrangement-cycloaddition reaction were investigated (Table 2.1).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Product/Starting Material Recovered</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF, 110 °C, 6 h</td>
<td>40</td>
<td>10 - 35%</td>
</tr>
<tr>
<td>DMF, rt, 72 h</td>
<td>39</td>
<td>90%</td>
</tr>
<tr>
<td>Toluene, 110 °C, 6 h</td>
<td>40</td>
<td>15%</td>
</tr>
<tr>
<td>Neat, 80 °C, 5 min</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>DMF, 70 °C, 12 h</td>
<td>39</td>
<td>90%</td>
</tr>
<tr>
<td>EtOH, 78 °C, 12 h</td>
<td>39</td>
<td>80%</td>
</tr>
<tr>
<td>CHCl₃, 40 °C, 24 h</td>
<td>39</td>
<td>90%</td>
</tr>
<tr>
<td>Xylenes, 140 °C, 6 h</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>THF, 70 °C, 24 h</td>
<td>39</td>
<td>90%</td>
</tr>
<tr>
<td>H₂O, 100 °C, 24 h</td>
<td>39 and decomposition</td>
<td>50%</td>
</tr>
<tr>
<td>ACN, UV, 250 W, 10 min – 24 h</td>
<td>Decomposition</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2.1 Temperatures and solvents**

Raised temperatures were required for the rearrangement – cycloaddition to occur. The optimal temperature for this cycloaddition was determined to be between 90 – 110 °C. Below this, starting material was recovered exclusively or after long periods, starting material and decomposition. Above this range, complete decomposition was observed. Increasing the reaction temperature is restricted by the thermal lability of most triazolines; some triazolines decompose spontaneously at room temperature. Long reaction times gave decomposition of azide 39 and triazoline 40.

Referring to experiments carried out by Zhou, a series of one-pot investigations were carried with little success. It was thought that by eliminating the isolation of the unstable intermediate, the triazoline, the iminosugar derivatives could be prepared directly from 39, however, due to the small amounts of the triazoline being generated, this was difficult.
Table 2.2 Attempts to react triazoline in situ with nucleophiles

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF, then AcOH, 100 °C, 24 h</td>
<td>41a Nu = OAc</td>
<td>11%</td>
</tr>
<tr>
<td>DMF, AcOH, NaN₃, 110 °C,</td>
<td>41b Nu = NaN₃, 41a Nu = OAc</td>
<td>9%</td>
</tr>
<tr>
<td>Tol, 110 °C, then H₂O at rt</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>Tol, 110 °C, then PhSH at rt</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>Tol, 110 °C, then NaN₃ at rt</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>Tol, 110 °C, then MeOH at rt</td>
<td>Decomposition</td>
<td>-</td>
</tr>
</tbody>
</table>

Heating in DMF first and then adding AcOH led to the isolation of one product which was characterised as the 6-O-acetylated sugar 41a. The $J_{H1-H2}$ value for 41a was determined as 8.9 Hz (appendix 1). This indicated the beta anomer had formed.

Using NaN₃ as a nucleophile, in the presence of AcOH, led to a mixture of products obtained, containing the 6-azido product as confirmed by infrared spectroscopy (strong peak at 2103 cm⁻¹). When the cycloaddition was carried out using only NaN₃, (no acid present), starting material 39 was recovered exclusively.

We attempted to open the triazoline ring using stronger acidic conditions, HCl or H₂SO₄, hoping to generate the 6-OH or 6-Me products. These conditions appeared too harsh for the triazoline. Due to the presence of acid-labile protecting groups on 40b, complex mixtures were observed. It was clear that although the strength of the acid and its addition to the reaction needed to be controlled, the use of acid was necessary for the breakdown of the triazoline ring into desired products.

There are a few reasons that could account for the poor yielding cycloadditions:
2.2.2.1 Di-substituted Alkene Intermediates

In an attempt to optimise the cycloaddition reaction, we considered using di-substituted alkenes. Strained alkenes have been reported to react faster in these types of cycloadditions.\textsuperscript{111} It was thought that by introducing substituted alkenes this would have an effect on the reactivity of the alkene; altering the cycloaddition reactivity.

From intermediate 38, a number of Wittig reagents were investigated in order to access di-substituted alkenes with varying degrees of success. Yields were quite poor (Scheme 2.18).

![Scheme 2.18 Synthesis of di-substituted alkenes](image)

Upon heating 42a-c in DMF, no desired products were isolated. Starting material was usually recovered in good yield. Conjugated dipolarophiles are generally reported to be more reactive than unconjugated dipolarophiles, however in the
case of 42c, the bulky phenyl substituent possibly hinders the approach of the reactant groups and consequently decreases/blocks the rate of cycloaddition.\textsuperscript{142}

2.2.3 Considering the Stereochemistry

Although there were difficulties optimizing the low-yielding rearrangement – cycloaddition of 39a-b; it was proceeding selectively. In every case, the triazoline was isolated as one stereoisomer (by NMR analysis). With $J$ values obtained so far in the $^1$H NMR spectra (Fig 2.1), it was difficult to determine the structure as the alpha or beta-anomer.

Minimization of the allylic strain in the transition state would account for the axial substituent forming at C-6. However, at the anomeric position, it was unclear why one stereoisomer would form preferentially (Fig 2.2).

![Fig 2.2 Proposed transition states](image_url)
It is possible that the allylic azide rearrangement mechanism favours one isomer exclusively. Or, there could be a significant energy difference between the $S$- and $R$-isomers, due to more attainable alignment of the azide and alkene in the transition state. A molecular mechanics study was carried out on the four isomers of intermediate 39b to try to rationalise the stereoselectivity of the tandem cycloaddition.

Structures were generated by Monte Carlo conformational search method and minimized by Macromodel 6.0. An MMFF94s force field was used due to the presence of an azide in the structures. The total energy was calculated, which include parameters such as stretch, bend, torsion, improper torsion, Van der Waals and electrostatic energies. The lowest relative energies of the different conformers were compared as an explanation for the preference of one conformer over another. Molecular mechanics is empirical and approximate, it is, however, a useful technique which is able to tackle many of the important questions in chemistry.\textsuperscript{143}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.3.png}
\caption{Lowest energy conformers of trans- and cis-isomers 39b ($E$ and $Z$ isomers and $E$ values from Macromodel)}
\end{figure}
Azide 39b exists at room temperature in the \textit{trans}-configuration as the major isomer observed by NMR. This correlates with the lowest total energy value 106.4201 kJ/mol obtained for the $E$-configuration. The huge jump in energy required from the $1^\circ$ azide to the $2^\circ$ azide could explain the low yield of the cycloaddition.

Additional conformational searches were carried out constraining the bond distances of the $2^\circ$ allylic azides up to $1.0 \pm 0.5 \, \text{Å}$ and setting the dihedral angle (between the azide and alkene defined below) to zero to help provide a more accurate picture of the type of conformer that would undergo the cycloaddition (Fig 2.5 and 2.6). The allylic strain was minimised during the conformational search to account for the stereochemistry at C-6.\textsuperscript{144,145}
$S$ (243.7666 kJ/mol) $R$ (297.3574 kJ/mol)

**Fig 2.5** Lowest energy conformers of constrained isomers 39b ($S$ and $R$ isomers with dihedral angle defined set to zero and distances $1.5 \pm 1$ Å

From these models, the $S$-isomer looks to be approaching a chair conformer and was calculated to have a lower total energy value. The $R$-isomer looked to be approaching a boat-type transition state. Newman projections below show possible gauche interactions (**Fig 2.6**). Alignment of the alkene in the $S$ configuration shows one possible gauche interaction *versus* two gauche interactions for the alkene in the $R$-isomer configuration.

**Fig 2.6** Possible transition states and Newman projections of $S$- and $R$-isomers for 39b

These factors could account for the stereoselectivity observed with the rearrangement-cycloaddition reaction and would predict favourable formation of the beta anomer.
2.3 Alternative Dipolarophiles

A major advantage of the route described in this chapter is the preparation of intermediate 38 (Fig 2.7). This aldehyde can be exploited in a number of reactions.

![Fig 2.7 Aldehyde intermediate](image1)

### 2.3.1 Schmidt/Boyer Reaction

The Schmidt reaction (Scheme 2.19) is an acid-catalysed reaction of hydrogen azide with electrophiles such as carbonyls, tertiary alcohols or alkenes, followed by a rearrangement and extrusion of N₂ to produce amines, nitriles, amides or imines. An extension of the Schmidt reaction using alkyl azides is the Boyer reaction.  

![Scheme 2.19 Schmidt/Boyer reaction mechanism](image2)
Acidic conditions/Lewis acids (TFA, BF$_3$.Et$_2$O, TiCl$_4$) are generally used to promote lactam formation. Zhou isolated the lactam derivative of DNJ after treating the aldehyde with TFA at rt (Scheme 2.20).

Scheme 2.20 Zhou’s lactam

With the allylic azide intermediate 38, there was no trace of the lactam isolated after treatment with TFA at rt. The use of TiCl$_4$ led to decomposition of the starting material after 5 min. Heat has been necessary in all previous experiments to promote rearrangement to the secondary allylic azide and allow cyclisation. Heating the aldehyde in the presence of TFA/AcOH did not give the desired lactam, just the deprotected intermediate.

Scheme 2.21 Schmidt/Boyer reaction with allylic azide

2.3.2 Huisgen Cycloaddition with nitrile dipolarophile

Bicyclic systems with a piperidine ring fused to a tetrazole ring, often with enhanced glycosidase inhibitory activity, have been reported (Fig 2.8). This
has been attributed to their greater rigidity, locking their conformation favouring inhibition.\textsuperscript{67}

Fig 2.8 Bicyclic iminosugar-tetrazoles as inhibitors\textsuperscript{9}

Tetrazoles have uses as bioisosteric replacements for carboxylic acids in drug design; they have similar pKa and cLogP (Fig 2.9).\textsuperscript{151}

Fig 2.9 Tetrazoles as bioisoteric replacement for carboxylic acids

Aldehyde 38 was reacted with iodine in a mixture of aq ammonia and THF at rt to give the nitrile 43 in good yield.\textsuperscript{152} Upon heating to reflux for 3 days only starting material was recovered. The reaction was also tested using the MW reactor and only starting material recovered.

Scheme 2.22 Synthesis of nitrile dipolarophile

The reactivity of dipolarophiles decreases with the introduction of a heteroatom (alkynes>alkenes>heteroatoms).\textsuperscript{111} Demko and Sharpless demonstrated that a
heteroatom (N, O, S) adjacent to the nitrile dipolarophile increases its reactivity in inter- and intra-molecular cycloadditions with azides,\textsuperscript{153,154} however it was not possible to easily introduce a heteroatom to the intermediates prepared here.

### 2.3.3 Huisgen Cycloaddition with alkyne dipolarophile

A 1,3 dipolar cycloaddition reaction between an azide and a terminal alkyne with elevated temperatures can give rise to a mixture of regioisomers 1,4- and 1,5-triazoles (Scheme 2.23).

\[
R\text{-}N_3 + \overset{\equiv}{R'} \xrightarrow{\Delta} R'N=NR + \overset{\equiv}{R'N=NR}
\]

**Scheme 2.23 Azide-alkyne 1,3-dipolar cycloaddition**

Meldal\textsuperscript{155} and Sharpless\textsuperscript{156} working independently, introduced the copper catalysed variant, which gives rise to the 1,4-regioisomer exclusively via a different mechanism (Fig 2.10).\textsuperscript{157} More recently, a ruthenium based cycloaddition has also been introduced which gives 1,5-disubstituted regioisomers exclusively.\textsuperscript{158}

**Fig 2.10 CuAAC mechanism**
There is interest in triazoles and triazole-fused compounds as targets for medicinal purposes.\textsuperscript{159, 160} Examples of triazole-fused iminosugars as inhibitors are shown (Fig 2.11).

![Fig 2.11 Reported iminosugar-fused triazole glycosidase inhibitors\textsuperscript{83}](image)

Zhou carried out an intramolecular 1,3-dipolar cycloaddition with an azide and an alkyne to give the 1-DNJ derivative.\textsuperscript{161}

![Scheme 2.24 Zhou’s synthesis of a 1-DNJ triazole derivative](image)

To prepare an allylic-azide intermediate with the alkyne dipolarophile, the aldehyde 38 was reacted with the Ohira-Bestmann reagent and base in MeOH. The Ohira-Bestmann reagent, (Dimethyl 1-diazo-2-oxopropyl phosphonate) was prepared by the reaction of dimethyl-2-oxopropylphosphonate and p-acetamido-benzenesulfonyl azide (Scheme 2.25).\textsuperscript{162}
Scheme 2.25 Synthesis and reaction of Ohira-Bestmann reagent

The mechanism of the Ohira-Bestmann is shown (Scheme 2.26). The phosphonate adds to the carbonyl compound forming an alkoxide to give an oxaphosphetane. A cycloelimination gives a dimethyl phosphate anion and a diazo-alkene (comparable to the Wittig reaction mechanism). Upon loss of nitrogen a vinylidene carbene is formed that undergoes a 1,2-migration of the hydrogen substituent to give the desired alkyne.

Scheme 2.26 Ohira-Bestmann mechanism

The alkyne 44 was heated in DMF to give the iminosugar fused triazole 45 observed in good yield (60 – 73%); this was much higher than the azide-alkene
cycloaddition and comparable with Zhou’s experiment. Alkynes are generally the most reactive partners for azides in these types of cycloadditions.\textsuperscript{111}

![Scheme 2.26 Preparation of triazole](image)

Again, one stereoisomer was formed exclusively. The $J_{\text{H1-H2}}$ value of 45 were larger than seen previously (6.6 Hz vs. 5.8 Hz), but still not typical of $\beta$. Upon deprotection, the $J_{\text{H1-H2}}$ value (8.3 Hz) seemed to indicate an equatorial orientated alkene (Scheme 2.27).

![Scheme 2.27 Deprotection of triazole and $J$ values](image)

1D $^1$H NOE experiments carried out also indicated the beta structure (Fig 2.12).

![Fig 2.12 NOE couplings for 45](image)
A coupled $^{13}\text{C}$ NMR was carried out, determining $J_{\text{C1-H1}}$ values for 45 to be 142.4 Hz (Fig 2.13). The other $J$ values observed can be due to $^2J_{\text{C1-H1}}$ and $^3J_{\text{C1-H1}}$ couplings. While, there are no reported $J_{\text{H1-C1}}$ values for iminosugars in the literature, there are values for carbohydrates. A series of $J_{\text{H1-C1}}$ values for iminosugars could show a trend and indicate the formation of $\alpha$ or $\beta$ products (see appendix 1). A crystal structure of the protected triazole 45 confirmed the $\beta$-product (Fig 2.14).

**Fig 2.13 Coupled $^{13}\text{C}$ NMR spectrum of protected triazole 45**
The S-configuration in the triazole intermediate could be preferred, leading to the β-anomer. Models of the two isomers are shown below (Fig 2.15). The distance between the azide and alkyne were set to 1.5 ± 1 Å and the dihedral angle set to zero (defined as before in Fig 2.5). There could be a steric interaction of the alkene group in the axial position of the R-isomer destabilising this conformer. A lower energy transition state could allow for the favourable formation of the beta anomer. As discussed previously (Fig 2.6), unfavourable gauche interactions with the alkene in the R-isomer could allow for the stereoselective formation of the beta-anomer.
HNJ Derivatives from d-Glucono-δ-Lactone

Chapter 2

Fig 2.15 Proposed transition state of azide-alkyne cycloaddition

While the yields were much improved on using the alkyne in the cycloaddition, it was thought that by using either the ruthenium or copper catalyst, the yields would improve further. However, the observed yields were slightly lower than with no catalyst (Table 2.3).

Table 2.3 Catalysed azide-alkyne cycloadditions

<table>
<thead>
<tr>
<th>Exp</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF, 100 °C</td>
<td>60 - 73</td>
</tr>
<tr>
<td>2</td>
<td>Cul, Na ascorbate, H&lt;sub&gt;2&lt;/sub&gt;O/tBuOH, rt, then heat</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Cp*RuCl(cod), DMF rt, then heat</td>
<td>30</td>
</tr>
</tbody>
</table>
Although the difficulties associated with reacting and handling the 1,2,3-triazolines, their advantage is that there are more options for functionalization. Triazoles are stable and generally do not break down. Attempts were made to functionalize the alkynes before carrying out the cycloaddition; alkylation reactions of the alkynes were carried out using acid chlorides like methyl chloroformate in the presence of base (nBuLi) to no success.\textsuperscript{163} Introducing a halide using \(N\)-iodosuccinimide and AgNO\(_3\) also proved futile.\textsuperscript{164}

### 2.3.3.1 Oxidation of alkene moiety

Yu\textsuperscript{165} describes a procedure for the oxidative cleavage of olefins by OsO\(_4\), NaIO\(_4\) and 2,6-lutidine. Oxidation of the alkene 45 to the diol was carried out using catalytic OsO\(_4\), followed by addition of NaIO\(_4\) for oxidative cleavage. The aldehyde was not isolated to prevent epimerisation at the anomeric center occurring. NaBH\(_4\) was added to the crude aldehyde to give the hydroxyl 47. The oxidation proceeded very slowly with low conversion of starting material.

![Scheme 2.28 Reagents and conditions](image)

**Scheme 2.28 Reagents and conditions:** a) OsO\(_4\), 2,6-lutidine, NaIO\(_4\), Dioxane/H\(_2\)O b) NaBH\(_4\), EtOH

Ozone is often preferred for these oxidations (\textbf{Scheme 2.30}). An A2Z MP-8000 Corona Discharge Ozone Generator was used to carry out this step.

An exothermic cycloaddition of ozone with an alkene generates a primary ozonide, which has limited stability and undergoes cycloreversion to a carbonyl oxide and a carbonyl. These species readily undergo another cycloaddition to give an ozonide or other products. The ozonide reacts with reducing agents to product the aldehyde.
Dussault and co-workers have carried out the ozonolysis of alkenes in a solvent/water mixture to aldehydes and ketones. A mixture of O$_2$/O$_3$ was bubbled through a solution of the protected triazole in acetone/H$_2$O. Sudan Red 7B indicator was used to visually determine conversion of the alkene and prevent over oxidation of the compound. The crude aldehyde was reduced using NaBH$_4$ in EtOH (Scheme 2.30) to give compound 47 in 56% over two steps.

**Scheme 2.30 Reagents and conditions:** a) O$_2$/O$_3$, Acetone/H$_2$O, 0 °C b) NaBH$_4$, EtOH, 56% over two steps

The $J_{H1-H2}$ values of 47 were determined as 6.2 Hz, which were comparable to previous triazole intermediates. A coupled $^{13}$C NMR experiment was carried out to determine $J_{H1-C1}$ values ($J = 145.7$ Hz) (Fig 2.16), which correlated with previous values.
Deprotection of 47 in methanolic acid gave the final product, a new compound, 48 in 88% yield (Scheme 2.31). The $J_{H1-H2}$ values were determined as 9.3 Hz. A coupled $^{13}$C NMR experiment was carried out to determine $J_{H1-C1}$ value ($J = 145.1$ Hz) (Fig 2.17).

Scheme 2.31 Deprotection of 47
Fig 2.17 Coupled $^{13}$C NMR spectrum of unprotected triazole 48

All of the $J_{H1-C1}$ values determined have been in close agreement with each other.

2.4 Conclusions

A route was devised based upon previous chemistry carried out by Dr Ying Zhou. Overall this route provided allylic azide intermediates in 10 steps from d-glucono-δ-lactone. The benzylation step, Grignard and Wittig reactions led to isolation of intermediates in poor overall yields. Upon investigation of the key step, it was noted that the cycloadditions seemed more complicated than seen previously with the primary azide. It was however, a stereoselective cycloaddition leading to a beta-configuration. The one-pot experiments were mostly unsuccessful due to low yields of the triazoline.

Molecular mechanics was used to rationalise the stereochemistry of the key reaction. All constrained stereoisomers show a lower relative energy in the transition state for the $S$-isomer. There are fewer gauche interactions for the alkene in the $S$-configuration. These reasons perhaps indicate why the beta-product is observed exclusively over the alpha.
A valuable intermediate, aldehyde 38, gave scope for other dipolarophiles to be introduced. The alkyne dipolarophile was a successful precursor to 1,2,3-triazole products, stereoselectively giving the β-product (confirmed by NMR and X-ray crystallography).

In summary, this route showed some encouraging results, particularly the stereoselectivity of the tandem rearrangement – cycloaddition. However, the various problems with this route hampered a full investigation. Alternative routes were considered towards the synthesis of the allylic azide intermediates and are discussed in the next chapters.
Chapter 3

Homonojirimycin Derivatives from Methyl $\alpha$-D-Glucopyranoside
3.1 Introduction

3.1.1 A new route from methyl α-D-glucopyranoside

Although the route discussed in Chapter 2 did allow for the stereoselective preparation of iminosugar analogues, it did suffer from a number of drawbacks. An alternative route from commercially available sugars, such as methyl α-D-glucopyranoside, was explored. A reductive fragmentation reaction was used to prepare the intermediates (Fig 3.1).

Bernet and Vasella described the zinc-mediated reductive fragmentation of methyl 6-deoxy-6-halo-hexopyranosides.\(^\text{167}\) The activated zinc reacts with alkyl iodides in an iodine-zinc exchange followed by elimination to give the aldehyde (Scheme 3.1). Harsh conditions and high temperatures can lead to experimental difficulties. Madsen optimised the fragmentation of 6-iodo-6-deoxysugars using sonication.\(^\text{168, 169}\)
There were many advantages to this synthetic route. It is shorter than the previous route; the alkene moiety is easily introduced and there is the potential to begin with any commercially available sugar to give access to the corresponding iminosugar C-glycosides.

3.2 Results and Discussion

3.2.1 Synthesis of mono-protected intermediates

Using Garegg’s conditions, methyl α-D-glucopyranoside was heated in THF with triphenylphosphine, iodine and imidazole to give the 6-deoxy-6-iodo sugar 49. The 6-iodo sugar was protected as benzyl, methyl and triethyl silyl ethers; protecting groups used had to be stable under the zinc reduction conditions and the chemistry of later steps. The fully protected intermediates 50a-c were sonicated in a mixture of THF and H₂O with pre-activated zinc dust for 2 - 4 h at 40 °C to give 51a-c. Aldehyde 51a was reacted immediately to prevent epimerization using Grignard conditions to give the allylic alcohol 52a as a mixture of syn- and anti-isomers (~1:1 ratio) (Scheme 3.2).
Scheme 3.2 Reagents and conditions: a) I₂, Im, PPh₃, THF, reflux, 79%; b) BnBr, NaH, DMF, 60%; c) IMe, KOH, DMF, 78%; d) TESCl, Im, CH₂Cl₂; e) Zn (()), THF/H₂O (9:1), 40 °C; f) Vinyl MgBr, THF, 67%

Introducing the secondary azide to 52a proved difficult. A range of different conditions were tested (Table 3.1). The preparation of the mesylate, tosylate and triflate (entries 1, 2 and 9), were investigated and observed by NMR. However, after chromatography, decomposition was observed and when brought on directly, no azido products were isolated.
Exp | Conditions |
--- | --- |
1 | MsCl, Et$_3$N, CH$_2$Cl$_2$, rt and -78 °C, then NaN$_3$, DMF, reflux |
2 | TsCl, Et$_3$N, CH$_2$Cl$_2$, rt, then NaN$_3$, DMF, reflux |
3 | PPh$_3$, DIAD, DPPA, THF, 0 °C to rt |
4 | PPh$_3$, DIAD, Me$_3$SiN$_3$, TBAF, THF, 0 °C to rt |
5 | DPPA, DBU, 0 °C to rt |
6 | DPPA, DBU, NaN$_3$, 0 °C to rt |
7 | pNO$_2$DPPA, DBU, rt |
8 | pNO$_2$DPPA, DIAD, 0 °C to rt |
9 | Py, Tf$_2$O, CH$_2$Cl$_2$, 0 °C to rt, then NaN$_3$, DMF, rt |

**Table 3.1 Azidation reactions**

An alternative route via the Wittig reaction involved heating 51a-c with (carbethoxymethylene)triphenylphosphorane in toluene to give the α,β-unsaturated esters 53a-c in good yields. Compounds 53a-c were reduced using DIBAL-H at -78 °C to give 54a-c. The azide was introduced using Mitsunobu type conditions to give 55a-c. The fully protected allylic azides were all observed as 1° trans-allylic azide by $^1$H NMR (and as seen previously in Chapter 2).
Scheme 3.3 Reagents and conditions: a) Ph₃PCHCO₂Et, Tol, reflux; b) DIBAL-H, CH₂Cl₂, -78 °C; c) PPh₃, DIAD, DPPA, THF

3.2.2 Cycloaddition Investigations

Next, the thermally promoted intramolecular cycloaddition of the above allylic azides were investigated. However, in the case of these intermediates, heating 55a-c in DMF for approx. 8 h did not lead to any cyclized products being isolated.

Scheme 3.4 Tandem rearrangement – cycloaddition

A wide range of conditions, in attempts to optimise the rearrangement-cycloaddition, were carried out. Varying temperatures and solvents (as described in Chapter 2, Table 2.1), using additives (Table 3.2), carrying out one-pot
investigations and experimenting with a microwave reactor, did not lead to any of the desired products to be observed.

Some Lewis acid catalysts are reported to co-ordinate to alkenes and/or nitrogen functionalities\textsuperscript{173, 174} and many reactions are reported to be improved in their presence.\textsuperscript{118, 175, 176} A range of catalysts were chosen due to the co-ordination abilities and availability. However, when conditions were too mild; starting material was recovered from the reaction and under harsher conditions; decomposition was observed.

![55a-c](image_url)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis Acids: AlCl(_3), TiCl(_4), FeCl(_3), ZnI(_2), ZnCl(_2), BF(_3), Et(_2)O, TfOH, CH(_3)CH(_2)CN</td>
<td>55a-c and decomposition</td>
<td>-</td>
</tr>
<tr>
<td>DMF, NEt(_3)/TFA, rt, 24 hr</td>
<td>Decomposition</td>
<td>-</td>
</tr>
<tr>
<td>DMF, I(_2), 100°C</td>
<td>55a-c</td>
<td>60%</td>
</tr>
<tr>
<td>Pd(OAc)(_2)</td>
<td>Decomposition</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 3.2 Use of additives to promote cycloaddition**

The fully deprotected intermediate was also prepared. Compound 55c was reacted with tetrabutylammonium fluoride to cleave the TES ethers\textsuperscript{177} and give the fully deprotected intermediate 56. This triol was observed as a ~1:1 mixture of 1° cis- and trans-allylic azides, most likely due to intramolecular hydrogen bonding.\textsuperscript{125} Again heating in DMF, the fully deprotected intermediate did not lead to any cycloaddition products (Scheme 3.5).
Scheme 3.5 Reagents and conditions: a) TBAF, THF, 76% b) Ac\textsubscript{2}O, Py c) DMF, 100 °C

Acetyl groups were introduced to 56 as electron withdrawing groups (compared with benzyl and methoxy protecting groups) to possibly alter the reactivity. Exact equivalents of Ac\textsubscript{2}O were necessary to stop acetylation of the azide functionality. Heating of 57 in DMF, gave recovered starting material in 88%.

A new route had been developed and a range of allylic azide intermediates prepared, however, the rearrangement-cycloaddition had not occurred upon heating any of the intermediates.

3.3.3 Synthesis of ‘conformationally constrained’ intermediates

For 1,3-dipolar cycloadditions to occur, a highly organised transition state is required to allow sufficient overlap of the HOMO and LUMO orbitals. If overlap is not sufficient, the reaction can be quite slow and sluggish or not occur at all.

Fig 3.2 HOMO and LUMO overlap of azide-alkene cycloaddition

Previously, the 1,2,3-triazoline was successfully isolated from intermediate 39 (Chapter 2); while only starting material or decomposition had been observed from intermediates 55a-c, 56 and 57 (Chapter 3). Considering the two general structures of the allylic azide intermediates (Fig 3.3), it could be that the diol isopropylidene protecting group is acting as a conformational constraint,
allowing sufficient overlap of the azide and alkene for the cycloaddition to proceed upon heating, which is not occurring on the intermediates discussed so far in this chapter.

Fig 3.3 Structures of intermediates from Chapter 2 vs. Chapter 3

To test this theory, an isopropylidene group was introduced selectively to the C-4 and C-5 hydroxyls of the triol 56. Acetonide 58 was observed as a mixture of 1° cis- and trans-isomers.

Scheme 3.6 Introduction of diol scaffold

Acetylation of the free 6-OH to give 59 was used to verify that the acetonide had been introduced at C-4 and C-5. There was significant downfield shift (~1 ppm) of the ¹H NMR signal for the C-6 proton; this shift is commonly observed for a CH proton after acetylation of an adjacent hydroxyl group. The use of 2D-heteronuclear multiple bond correlation spectroscopy (HMBC) of 59 showed the required three bond correlation between the carbonyl of the acetyl group with H-6 (Table 3.3, Fig 3.4 and 3.5).
Scheme 3.7 Acetylation of free hydroxyl

Table 3.3 $^1$H NMR data for H-6

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H NMR (500 MHz, CDCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>$\delta$ 4.09 (t, $J = 4.8$ Hz, 1H, H-6), 4.05 (t, $J = 5.1$ Hz, 1H, H-6b);</td>
</tr>
<tr>
<td>59</td>
<td>$\delta$ 5.38 – 5.33 (m, 2H, H-6a, H-6b)</td>
</tr>
</tbody>
</table>

Fig 3.4 $^1$H NMR downfield shift comparison for 58 and 59
Heating 58 in DMF allowed the cycloaddition to occur and gave the 1,2,3-triazoline 60 as the major product in yields similar to those seen previously (~30%). Again the stereochemistry at C-6 was easily assigned using $J$ values and gave the same configuration as before. $J$ values isolated for the anomeric carbon were $J_{H1-H2}$ 6.4 Hz. This value, as before (5.8 Hz), falls between typical alpha and beta ranges. However, based on experimental and modelling data carried out as described in Chapter 2, it is most likely the beta anomer forming.

Scheme 3.8 Cycloaddition reaction

On one occasion, the migration product of the 1,2-dioxolane 58 to the 1,3-dioxane 61 was isolated. The dioxane was heated in DMF for 24 h which
resulted in full recovery of 61. From this experiment, it was concluded that protection of the 1,3-diol does not allow the intramolecular cycloaddition to occur (Scheme 3.9).

Scheme 3.9 Cycloaddition of dioxolane-protected azide 61

The free hydroxyl on compound 58 was also protected using benzyl bromide, to provide a direct comparison with compound 39a (Chapter 2). Intermediate 62 was more stable than 58 and existed exclusively as the 1° trans-allylic azide (by $^1$H NMR). Heating compound 62 in DMF gave the triazoline 63 in 15 - 23% with recovered starting material 45%. This compared with yields obtained from the intramolecular cycloaddition of 39b. Nucleophilic attack of AcOH on the triazoline gave the 6-acetylated iminosugar 64.

Scheme 3.10 Reagents and conditions: a) BnBr, NaH, DMF, 82%  b) DMF, 100 °C, 23%  c) DMF, AcOH, 100 °C, 40%
It was not possible to isolate $J_{H_1-H_2}$ values for triazoline 63. $J_{H_2}$ values for 64 were resolved and determined $J_{H_2-H_1}$ to be 5.8 Hz. This value correlates with values isolated previously and is most likely beta.

3.3.3.1 Optimisation of rearrangement-cycloaddition reaction

The rearrangement-cycloaddition was proceeding, however still at low yields. We looked at ways in which to improve this.

The thermally promoted cycloaddition of 58 carried out in HPLC grade DMF (by chance) led to the isolation of trace amounts of a side product. This was determined to be the 6-OH iminosugar 65, perhaps due to adventitious water present in the lower grade DMF. The $J_{H_1-H_2}$ value in 65 was 7.8 Hz (apt triplet), which would be more indicative of the beta anomer than previous values isolated. Deprotection of 65 in acid gave 66 (signals were overlapping; $J$ values were not isolated).

![Scheme 3.11](image)

**Scheme 3.11 Reagents and conditions:** a) HPLC grade DMF, 100 °C; b) aq AcOH, 24%

It was thought that by perhaps varying the ratio of DMF to H$_2$O, optimal conditions could be determined for the synthesis of 66. An experiment carried out with 0.5 to 5 eq of H$_2$O in DMF gave the starting material 12 - 15% and the
triazoline 10 – 20%, however, no improvement on increasing the yield of the 6-hydroxyl sugar was made. Often, difficulties were encountered in isolating compound 65 as a product, even in trace amounts.

Many cycloaddition reactions have been reported to be improved by the use of a MW reactor. At the appropriate power and temperature, the cycloaddition proceeds in a shorter time period than in the oil bath. However, this appears to be the only advantage. Above the higher threshold, complete decomposition of the azide occurs in less than 5 min (Table 3.4).

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>58</th>
<th>60</th>
<th>Decomposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF, 80 °C, 200 W, 1 h</td>
<td>18%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>DMF, 150 °C, 200 W, 5 min</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>HPLC DMF, 80 °C, 150 W, 1 h</td>
<td>40%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>HPLC DMF, 150 °C, 300 W, 1 h</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Table 3.4 MW studies**

3.3.3.2 Alternative diol protecting groups

It had been determined that a constraint in the form of a diol scaffold is necessary for the cycloaddition to occur. There are a number of options for the protection of diol functional groups (Table 3.5).
Table 3.5 Diol protecting groups

Selected examples were investigated. The use of a p-methoxybenzyl group led to complex mixture of inseparable isomers due to lack of selectivity and additional chiral centers within the protecting group (Scheme 3.12). Heating the mixture did not lead to any cyclized products being isolated.

Scheme 3.12 Reagents and conditions: a) p-Anisaldehyde dimethylacetal, pyridinium p-toluenesulfonate, DMF; b) DMF, 100 °C

Protection of the triol 56 with a cyclohexyldiene group gave, as with the isopropylidene, the 4,5-intermediate 67. Upon heating in DMF, the triazoline 68 was observed, however in very poor yield. Isolated J values for H-1 to H-2 were 6.5 Hz, which correlates with values for previous triazoline products.
Scheme 3.13 Reagents and conditions: a) Cyclohexanone, H$_2$SO$_4$, dioxane, 73%; b) DMF, 100 °C, 5 – 7%

A 7-membered disiloxane protecting group was also investigated. From the triol 56, a complex mixture was formed. Heating in solvent did not lead to any desired products.

Scheme 3.14 Reagents and conditions: a) TiPDSiCl$_2$, Im, DMF; b) DMF, 100 °C

3.3.3.3 Secondary allylic azides

So far, we had looked at varying the reaction conditions (temperature, solvent additives etc.), different protecting groups and substituting the alkene dipolarophile, with little success in optimisation. Modifying the azide moiety had not yet been considered (Fig 3.6). Possibly, two secondary azides competing would allow for a shift in equilibrium towards the azide we wanted to react and result in higher yields.

Fig 3.6 Possible equilibrium of two 2° azides competing
To prepare the substituted azide, a methyl group was introduced (Scheme 3.15). Intermediate 54c was reacted with the Dess-Martin reagent to give the aldehyde 69 in good yield. Methyl magnesium chloride was used in the Grignard reaction to give the 2° allylic alcohol 70 as a mixture of isomers. Under Mitsunobu conditions with DIAD and DPPA, the azide was introduced and deprotection with TBAF gave azido-alcohol 72. The isopropylidene group was selectively introduced at the C-4 and C-5 position as before to give 73. Compounds 72 and 73 were observed as complex mixtures of isomers.

Scheme 3.15 Reagents and conditions: Dess-Martin Periodinane, CH₂Cl₂, 85%; b) MeMgCl, THF, 86%; c) PPh₃, DIAD, DPPA, THF, 72%; d) TBAF, THF, 71%; e) Acetone, H₂SO₄, 74%; f) DMF, 100 °C

Azide 73 was heated in DMF for up to 24 h. However, mostly starting material was recovered (15 – 55%).

3.2.4 Consideration of the stereochemistry using molecular mechanics

Some simple molecular mechanics studies were attempted in order to try to rationalise the results. Models of the R and S-allylic azides for both the fully deprotected compound 56 and the isopropylidene protected intermediate 58 were built and calculations were performed using the Maestro MacroModel molecular mechanics program as in Chapter 2. The lowest energy conformations generated
by conformational searches are shown below (Fig 3.7 and 3.8). The azide and alkene functionalities are in closer proximity for the protected compound 58, but still does not seem that they could be easily aligned for the cycloaddition to proceed.

Fig 3.7 Lowest energy conformers of 56 (R and S isomers and E values from MacroModel)

Fig 3.8 Lowest energy conformers of 58

We carried out calculations limiting the distances between the proximal and distal atoms of the azide and alkene up to $1.5 \pm 1.0 \text{ Å}$. The dihedral angle, defined below (Fig 3.9), was set to zero in order to generate a planar arrangement.
between the azide and the alkene.\textsuperscript{180-182} The allylic strain was minimised to account for the stereochemistry forming at C-6. We hoped that this would generate a conformer perhaps representative of the transition state. Below are pictures of the lowest energy conformers generated within these parameters (Fig 3.9 and 3.10).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig3_9.png}
\caption{Fig 3.9 Lowest energy conformers of 56 with dihedral angle (defined by 1-2-3-4 set to 0) and distances (1.5±1 Å)}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig3_10.png}
\caption{Fig 3.10 Lowest energy conformers of 58 with dihedral angle (as before and set to 0) and distances (1.5±1 Å)}
\end{figure}

There was a huge jump in energy upon constraining the distances and forcing the azide and alkene into a closer proximity and also a significant difference in
energy between compounds 56 and 58, indicating the importance of the diol constraint. The \( S \) isomer was found to be lower in energy in 58.

Rotating these images, lining up the azide and alkene as we imagine they would in a transition state; it looks like both conformers are in a half-chair formation (Fig 3.10).

![Fig 3.10 Possible transition states of 58 (S and R) and Newman projections](image)

Newman projections show two gauche interactions for the alkene in the \( R \) isomer and only one gauche interaction in the \( S \) isomer, perhaps a factor in why we observed stereoselectivity in the tandem allylic azide rearrangement – Huisgen cycloaddition of these intermediates.

### 3.3 Conclusions

An alternative route to substances for the rearrangement-cycloaddition was developed. This route was shorter and had better scope, although the observed yields were still poor. The importance of the effect of different protecting groups was emerging and the requirement of the 1,2-diol constraint in promoting the cycloaddition was discovered. The isopropylidene was the best scaffold investigated so far.

\( J \) values isolated compared with values discussed in chapter 2 and it would seem that the beta sugars were forming exclusively. Models build for both \( R \) and \( S \) intermediates showed that the allylic azide intermediate could be going through a
half chair transition state. Minimisation of gauche interactions in the S-isomer could allow for favourable formation of the beta-anomer.

Despite alternative routes and various attempts at optimisation, this rearrangement-cycloaddition was not observed to proceed very successfully from these glucose derivatives. This route was also used in the preparation of mannose and galactose derivatives which are discussed in the following chapters.
Chapter 4

Homomannojirimycin Derivatives from Methyl α-D-Mannopyranoside
4.1 Introduction

4.1.1 Previous syntheses of homomannojirimycin and analogues

Fleet and co-workers prepared α- and β-HMJ via a key intermediate bicyclic amino-lactone bearing a D-mannose configuration. The unstable lactone underwent nucleophilic attack to give the α-amino ester which epimerised to the β-amino ester. Separation and deprotection afforded both α- and β-HMJ, as well as other isomers such as 6-epi-homomannojirimycin (Scheme 4.1).

\[
\begin{align*}
\text{Scheme 4.1 Fleet's synthesis of } & \alpha- \text{ and } \beta-\text{HNJ} \\
\end{align*}
\]

The first reported synthesis of β-HMJ was a chemoenzymatic approach for the synthesis of iminosugars, using an aldolase (D-fructose diphosphate (FDP) aldolase) to catalyse the key asymmetric aldol addition reaction (Scheme 4.2).

\[
\begin{align*}
\text{Scheme 4.2 Wong's chemoenzymatic synthesis of } & \beta-\text{HMJ} \\
\end{align*}
\]

Another chemoenzymatic approach towards the synthesis of β-HMJ was using fructose 1,6-bisphosphate (FBP) aldolase (Scheme 4.3). The lactol was stereoselectively synthesised via Sharpless epoxidation, treated with rabbit muscle fructose 1,6-bisphosphate aldolase and phosphatase and hydrogenated to give β-HMJ.
Fernández-Mayoralas et al. describe the synthesis of β-HMJ and isomers from d- and l-diethyl tartrate. The key step involves a proline-catalyzed aldol condensation, in which both enantiomers of proline have been used as a catalyst, affording complementary anti-aldol products (Scheme 4.4).  

Fleet and co-workers prepared β-methyl, ethyl and phenyl-derivatives of deoxymannojirimycin. Some of which have been isolated as natural products since by Kato and co-workers.  

These compounds (Fig 4.1) were assayed as inhibitors of human liver glycosidases. All compounds tested were potent and specific competitive inhibitors of human liver α-L-fucosidase. Introduction of a bulkier aromatic group gave a more potent inhibitor than 1-DMJ. However, only 1-DMJ was an inhibitor of α-mannosidase.
This chapter presents a route allowing access to iminosugar C-glycoside based on mannose. The same chemistry employed from glucose (Chapter 3) was used to prepare these derivatives.

### 4.2 Results and Discussion

#### 4.2.1 Synthesis and cycloaddition of trans-isopropylidene protected intermediate

The route starts from methyl α-D-methyl mannopyranoside. The fully deprotected azide 80 was prepared via intermediates 74-79 as seen previously in chapter 3. The acetonide was introduced to 80 using 2,2-dimethoxypropane in the presence of H$_2$SO$_4$ in dry acetone to give 81 (Scheme 4.6).
Scheme 4.6 Reagents and conditions: a) I₂, PPh₃, Im, THF, reflux, 75%; b) TESCl, Im, CH₂Cl₂, 70%; c) Zn (()), THF/H₂O, 40 ºC, 84%; d) Ph₃PCHCO₂Et, Tol, reflux, 82%; e) DIBAL-H, CH₂Cl₂, -78 ºC, 84%; f) PPh₃, DIAD, DPPA, THF, 77%; h) TBAF, THF, 73%; i) p-TsO₂H, 2,2-DMP, Acetone, 71%

Acetylation of the free 4-OH of 81 verified the acetonide had been introduced at C-5 and C-6. This regioselectivity is different to the glucose derivatives in chapter 3, where the isopropylidene was regioselectively introduced at the C-4 and C-5 position.

Scheme 4.7 Acetylation of free hydroxyl
The $^1$H NMR spectra below shows the significant downfield shift of the H-4 signal upon acetylation (Table 4.1) (Fig 4.2). The HMBC shows the correlation between the carbonyl of the acetyl group to H-6 (Fig 4.3).

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H (500 MHz, CDCl$_3$)</th>
<th>$^{13}$C (126 MHz, CDCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>δ 4.39 - 4.35 (2H, H-4, H-6)</td>
<td>δ 70.4 (d, C-4)</td>
</tr>
<tr>
<td>82</td>
<td>δ 5.42 (t, $J = 5.0$ Hz, 1H, H-4)</td>
<td>δ 72.4 (d, C-4)</td>
</tr>
</tbody>
</table>

**Table 4.1 Chemical shifts of H-4 and C-4**

**Fig 4.2 $^1$H NMR spectra of 81 and 82**
The isopropylidene protected intermediate 81 was heated in anhydrous DMF for 6 h and gave the 1,2,3-triazoline 83, stereoselectively, in 50 - 60% and recovered starting material 81 in trace amounts up to 10%. This yield is significantly better than the experiments carried out with the glucose derivatives.

![Fig 4.3 HMBC Spectra of 82](image)

Scheme 4.8 Thermally promoted cycloaddition

The $J_{H1-H2}$ value for the anomeric proton of 83 was 2.2 Hz. In the case of mannose, $J_{H1-H2}$ values alone are not sufficient to confirm the stereochemistry at the anomeric centre. A coupled $^{13}$C NMR experiment was carried out and determined $J_{H1-C1}$ to be 142.2 Hz (Fig 4.4). This compares to the values obtained in Chapter 2 for the $\beta$-triazoles (142-145 Hz) and could indicate the triazoline as
the beta anomer. The other values obtained below are most likely due to $2J_{C1-H1}$ and $3J_{C1-H1}$ coupling.

**Fig 4.4 Coupled $^{13}$C NMR spectrum for 83**

For mannopyranoside, a value of 170 Hz for $^1J_{C1-H1}$ indicates an equatorial proton at C-1 and a $^1J_{C1-H1}$ of 160 Hz indicates an axial proton (Fig 4.5). While the $^1J_{C1-H1}$ values observed here differs from these values, we hope that by comparing a series of $^1J_{C1-H1}$ values, a trend will emerge (see appendix 1).

**Fig 4.5 $^1J_{C1-H1}$ values for $\alpha$- and $\beta$-mannopyranoside**

Following the success of the rearrangement-cycloaddition of 81, we tested the one-pot reaction. Intermediate 81 was heated in DMF or toluene for 6 h, then cooled to approx. 50 °C and AcOH was charged. The main product was the 6-acetylated iminosugar 84 in 35% yield from 81. When acid (pH>2) was charged
to the pot, the main product isolated after ion exchange chromatography was the fully deprotected intermediate 85 (Scheme 4.9). Although, this procedure led to the desired products, it was not a completely clean reaction and there were some undetermined side products remaining. The $J_{H_1,H_2}$ value of 84 was 2.3 Hz.

![Scheme 4.9 Reagents and conditions: a) DMF, 100 °C, 6 h; b) AcOH, 50 °C, 8 h, 35%; c) aq HCl, 80%](image)

4.2.2 Synthesis and cycloaddition of trans-butane diacetal protected intermediate

Some work was described in Chapter 3 detailing results using different diol protecting groups. We decided to investigate further the influence of the diol protecting group on the cycloaddition reaction using the more successful mannose based derivatives. It was thought a 6- or 7-membered diol protecting group would allow more flexibility, while still introducing sufficient constraint for the cycloaddition (Fig 4.6). We investigated introducing alternative diol protecting groups directly from the triol intermediate (Chapter 3), however, this led to mixtures. We looked at introducing these groups at the beginning, eliminating the need for deprotection/re-protection steps later on in the scheme.

![Fig 4.6 5- vs. 6- vs. 7-membered diol protecting groups](image)
The dispiroketalts (dispoke), cyclohexane-1,2-diacelets (CDA) and butane-2,3-diacelets (BDA)\textsuperscript{190} are specifically designed for the protection of vicinal \textit{trans}-diols. BDA was investigated as a 6-membered diol protecting group as it was easy to prepare and yields are usually superior to the corresponding cyclohexane-1,2-diacelet protecting group.\textsuperscript{191}

The BDA group was introduced from reaction of methyl \(\alpha\)-\(\text{d}-\)mannopyranoside and butane-2,3-dione in methanol with trimethyl orthoformate and CSA as a catalyst.\textsuperscript{192} The route proceeded smoothly to give the allylic azide \textbf{93} via \textbf{86-92} in good yield as a white solid. This is the first allylic azide that was isolated as a solid (\textbf{Scheme 4.10}).

\textbf{Scheme 4.10 Reagents and conditions:} a) 2,3-Butanedione, CSA, CH(OCH\(_3\))\(_3\), DMF, reflux, 72%; b) I\(_2\), PPh\(_3\), Im, THF, reflux, 88%; c) TESCl, imidazole, CH\(_2\)Cl\(_2\), 70%; d) Zn \textit{)), THF/H\(_2\)O, 40 °C, 90%; e) Ph\(_3\)PCHCO\(_2\)Et, Tol, reflux, 83%; f) DIBAL-H, CH\(_2\)Cl\(_2\), -78 °C, 79%; g) PPh\(_3\), DIAD, DPPA, THF, 74%; h) TBAF, THF, 63%
Heating 93 in DMF proceeded to give the 1,2,3-triazoline 94 in poorer yield than the isopropylidene intermediate. However, the triazoline 94 was isolated as a white solid. It was possible to grow crystals and obtain a crystal structure (Fig 4.7).

![Scheme 4.11 Thermally promoted cycloaddition of 93](image)

The structure shows the stereochemistry at the anomeric carbon to be alpha, which is the opposite to what has been observed so far. This is the first reported
crystal structure of a triazoline fused iminosugar. There are very few reports of triazoline crystal structures in the literature.\textsuperscript{193} A coupled $^{13}$C NMR was carried and determined the $J_{C1-H1}$ value of 94 to be 149.6 Hz (Fig 4.8), which is larger than any $J_{C1-H1}$ values isolated previously, perhaps being indicative of the different anomer configuration in this case.

Fig 4.8 $^{13}$C NMR spectrum showing $J_{H1-C1}$ values for 94
Unfortunately due to the lower yield, any one-pot conditions tested did not lead to the isolation of iminosugar products from 93.

The dispoke 93 was benzylated to observe if the free hydroxyl had an effect on the cycloaddition (Scheme 4.12).

Scheme 4.12 Reagents and conditions: a) BnBr, NaH, DMF 0 °C 52%; b) DMF, 100 °C, 52%

The benzylated intermediate 95 was reacted as in every other cycloaddition experiment. Monitoring by TLC, the reaction proceeded similarly to others. Upon chromatography, the major product was determined to be the reduced imine product 96.

It has been shown throughout this work that the protecting groups have a major influence over the results of the tandem rearrangement – cycloaddition. A change in reactivity occurred on introducing the benzyl protecting group. It is likely the triazoline formed during the reaction but was more unstable than its unprotected analogue and broke down to form an imine (Scheme 4.13).

Scheme 4.13 Mechanism of imine formation

The presence of hydrogen bonding can stabilise certain conformations over others that, in the absence of hydrogen bonding, would be favoured. On
examination of the crystal structure (Fig 4.7), it is possible that intramolecular hydrogen-bonding is stabilising the triazoline. On introducing the protecting group, there is no H-bonding, N₂ is a good leaving group and the imine is formed. It is not clear why the imine would be preferred over the aziridine.

### 4.2.3 Synthesis and cycloaddition of trans-disiloxane protected intermediate

To investigate a 7-membered diol scaffold a TIPDS group was introduced using the difunctional reagent 1,3-dichloro-1,1,3,3-tetraisopropylsilyleneoxane in the presence of imidazole in DMF (or pyridine). In the case of hexopyranoses, these conditions give the kinetic product 97, an 8-membered ring product, which is formed by rapid reaction first at the least hindered primary hydroxyl group followed by a second intramolecular silylation with the next proximate hydroxyl at C-4. The 8-membered disiloxane ring rearranges under acidic conditions to give the more stable 7-membered ring derivative 98.

![Scheme 4.14](image)

**Scheme 4.14 Reagents and conditions:** a) TIPDSiCl₂, Im, DMF, 79%; b) p-TsOH, DMF, 91%; c) I₂, PPh₃, Im, THF, reflux, 70%; d) MOMCl, DIPEA, DMAP, DMF, 89%

The triethylsilyl ether protecting group could not be used at C-2, as it would not be selectively cleaved in the presence of the disiloxane group. A MOM ether was introduced therefore to give 100. From here, the same chemistry was used as previously described to prepare the allylic azide 104 via intermediates 101-103 (Scheme 4.15).
Scheme 4.15 Reagents and conditions: a) Zn, THF/H$_2$O, 40 °C, 89%; b) Ph$_3$PCHCO$_2$Et, Tol, reflux, 83%; c) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 74%; d) PPh$_3$, DIAD, DPPA, THF, 60%; e) see text

It was difficult to deprotect the MOM ether of 104 selectively. Acidic conditions, including catalytic $p$-TsOH in MeOH gave the fully deprotected triol. Neutral conditions, using P$_2$I$_4$ in CH$_2$Cl$_2$ also gave the triol. The thermally promoted cycloaddition was carried out with the MOM protected azide 104. However, there was no triazoline product isolated.

4.2.4 Synthesis and cycloaddition of cis-isopropylidene protected intermediate

We observed that the 5-membered isopropylidene diol protecting group yielded the best results. So far, only trans-isopropylidene intermediates, with glucose and mannose had been investigated. In the case of the manno-derivatives, there was the option for introducing a cis-isopropylidene (Fig 4.9). It was thought that this might exert less strain on the ring-closed product than the trans-isopropylidene and improve yields.
Fig 4.9 Trans- and cis-isopropylidene protected iminosugars

The cis-protected intermediate 111 was prepared via 105-110 in good yield (Scheme 4.16). 197

Scheme 4.16 Reagents and conditions: a) PPh₃, Im, I₂, THF, reflux then p-TsOH, 2,2-DMP, Acetone rt, 71%; b) TESCl, Im, CH₂Cl₂, 70%; c) Zn), THF/H₂O, 40 °C, 79%; d) Ph₃PCHCO₂Et, Tol, reflux, 83%; e) DIBAL-H, CH₂Cl₂, -78 °C, 84%; f) PPh₃, DIAD, DPPA, THF, 77%; g) TBAF, THF, 73%

The thermally promoted cycloaddition of 111 was carried out. Full conversion of starting material was observed after 2 h. By TLC it appeared that the triazoline product was forming; however in this case the triazoline could not be isolated and appeared to decompose on work up and chromatography.
Scheme 4.17 Thermally promoted cycloaddition of 111

Heating of 111 in DMF for 2 h and subsequent addition of AcOH led to the isolation of the 6-O-acetylated product 112 as a single diastereoisomer in a cleaner reaction and in higher yields compared with the trans-isopropylidene intermediate. Reaction with aq HCl gave the deprotected compound 85 as before.

Scheme 4.18 Reagents and conditions: a) DMF, 100 °C, then AcOH, 45%; b) aq HCl, 82%

A coupled $^{13}$C NMR experiment carried out on compound 112 gave an approximate $J_{C1-H1}$ value of 137.8 Hz. (Fig 4.10). This is slightly lower than values isolated previously for beta sugars (~142 Hz) and much lower than a value isolated for an alpha iminosugar (149 Hz).
A one-pot reaction of heating 111 in DMF and using NaN₃ as the nucleophile in the presence of an acid catalyst gave 113 (Scheme 4.19). The major product, assumed to be beta, was isolated along with a fraction of what looked like the alpha anomer. This was the first case that both anomers were isolated from the same reaction. ¹H NMR shifts and J values are below (Table 4.2). Mass spectrometry measurements of both isomers of 113 and also a mixture of 113 gave one major peak of 215 m/z [M+H]⁺.

Scheme 4.19 Reagents and conditions: a) DMF, 100 °C, then NaN₃, AcOH, 80 °C, 25% overall, 10% mixture (1:0.6 β:α); b) aq HCl, 50% mixture (1:0.2 β:α)
\[
\begin{array}{|c|c|c|c|c|}
\hline
^1H & \text{Compound 113 Major Isomer} & \text{Compound 113 Minor Isomer} \\
\hline
\text{Shift} & \text{J values} & \text{Shift} & \text{J values} \\
\hline
H-8' & 5.30 & \text{dt, 17.3, 1.5 Hz} & 5.33 & \text{dt, 17.4, 1.4 Hz} \\
H-8 & 5.21 & \text{dt, 10.4, 1.4 Hz} & 5.27 & \text{dt, 10.6, 1.4 Hz} \\
H-7 & 5.91 & \text{ddd, 17.0, 10.4, 6.4 Hz} & 5.87 & \text{ddd, 17.4, 10.6, 5.4 Hz} \\
H-1 & 3.84 & \text{dq, 6.4, 1.4 Hz} & 3.73-3.71 & \text{m (overlapping)} \\
H-2 & 4.28-4.24 & \text{m (overlapping)} & 4.14 & \text{dd, 5.6, 4.1 Hz} \\
H-3 & 4.28-4.24 & \text{m (overlapping)} & 4.10 & \text{dd, 6.9, 5.7 Hz} \\
H-4 & 3.94 & \text{apt t, 3.1 Hz} & 3.64 & \text{dd, 9.0, 6.9 Hz} \\
H-5 & 3.39 & \text{apt td, 6.4, 3.2 Hz} & 2.86 & \text{ddd, 8.9, 6.4, 3.7 Hz} \\
H-6 & 3.51-3.44 & \text{m (overlapping)} & 3.63-3.58 & \text{m (overlapping)} \\
H-6' & 3.51-3.44 & \text{m (overlapping)} & 3.57 & \text{dd, 12.3, 3.7 Hz} \\
\hline
\end{array}
\]

**Table 4.2 J values for 113 isomers**

Some J values did not correlate well (H-4). It was considered that an isomerisation of the isopropylidene could have occurred to give two isomers. However, deprotection of a mixture of 113 gave a mixture of two isomers 114 by NMR. The J\textsubscript{H1-H2} values for the major anomer of 114 were 3.3 Hz. It is not clear why both anomers would form during these conditions.

### 4.2.5 Functionalization of the alkene

The majority of the mannose products forming seemed to be the beta anomer, apart from the 6-membered butane diacetal protected triazoline verified by X-ray crystallography, which gave the alpha anomer. We set about modifying the alkene unit with a view to obtaining greater evidence for the stereochemical assignment. Natural and non-natural products in Fig 4.11 are in the literature for comparison.
Oxidative cleavage of the terminal alkene unit followed by reduction would potentially allow access to the natural product HMJ (either alpha or beta). Reaction of the fully deprotected sugar 85 with O₃ was used in an attempt to oxidise the alkene. However, this reaction did not proceed, perhaps due to the presence of the free amine. Wong and co-workers demonstrated the ozonolysis of free amines using perchloric acid. However, even after 4 hours of bubbling ozone through a solution containing the alkene and acid, starting material 85 was recovered untouched.

Scheme 4.21 Reagents and conditions: O₃, HClO₄, 2,6-lutidine, MeOH

We also tried the ozonolysis of the fully protected sugar. The amine was protected using di-tert-butyl dicarbonate to give 115. After exposure of 115 to ozone for up to 6 h, only starting material 115 was recovered (20%).

Scheme 4.22 Reagents and conditions: a) Boc₂O, Et₃N, DMAP, CH₂Cl₂ 70%; O₃, Acetone/H₂O
Epoxidation of the alkene using $m$-chloroperoxybenzoic acid at rt for up to 5 days only resulted in starting material recovered (up to 50%).

A coupled $^{13}$C NMR experiment was carried out for compound 115 (Fig 4.12). A value of 137.7 Hz was determined for $J_{C1-H1}$. This correlates with previous values for beta anomers.

![NMR spectrum](image)

**Fig 4.12 $J_{C1-H1}$ values for 115**

We also looked at the reduction of the terminal alkene. Reaction of 85 with $H_2$ in the presence of Pd/C and acid gave access to the ethyl derivative 8 in good yield (Scheme 4.23).

![Scheme 4.23 Hydrogenation of 85](image)
All NMR data corresponded well to the natural product isolated by Kato et al. in 2007 and synthesised previously by Fleet in 1989 and was reported in both cases as the beta anomer (Table 4.3 and 4.4). This would confirm the stereochemistry as beta.

<table>
<thead>
<tr>
<th></th>
<th>Compound 8</th>
<th>Kato</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D₂O, 500 MHz</td>
<td>D₂O, 500 MHz</td>
</tr>
<tr>
<td>H-1</td>
<td>2.93 (2.4, 7.6)</td>
<td>2.98</td>
</tr>
<tr>
<td>H-2</td>
<td>3.97 (2.8)</td>
<td>3.98 (2.5)</td>
</tr>
<tr>
<td>H-3</td>
<td>3.76 (3.2, 9.5)</td>
<td>3.76 (3.1, 9.5)</td>
</tr>
<tr>
<td>H-4</td>
<td>3.64 (9.7)</td>
<td>3.66 (9.5)</td>
</tr>
<tr>
<td>H-5</td>
<td>2.74 (4.0, 9.9)</td>
<td>2.79</td>
</tr>
<tr>
<td>H-6</td>
<td>3.79 (4.0)</td>
<td>3.79 (3.5)</td>
</tr>
<tr>
<td>H-6'</td>
<td>1.59 (7.5)</td>
<td>1.6</td>
</tr>
<tr>
<td>CH2</td>
<td>0.97 (7.5)</td>
<td>0.97 (7.6 Hz)</td>
</tr>
</tbody>
</table>

Table 4.3 ¹H NMR spectra comparison data

<table>
<thead>
<tr>
<th></th>
<th>Fleet</th>
<th>Compound 8</th>
<th>Kato</th>
<th>Compound 8 (corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D₂O</td>
<td>D₂O, 500 MHz</td>
<td>D₂O, 500 MHz</td>
<td>D₂O, 500 MHz</td>
</tr>
<tr>
<td>C-1</td>
<td>60.95 or 59.17</td>
<td>59.0</td>
<td>62.1</td>
<td>62.0</td>
</tr>
<tr>
<td>C-2</td>
<td>76.21</td>
<td>71.1</td>
<td>73.1</td>
<td>74.1</td>
</tr>
<tr>
<td>C-3</td>
<td>70.42</td>
<td>71.4</td>
<td>74.1</td>
<td>74.4</td>
</tr>
<tr>
<td>C-4</td>
<td>69.14</td>
<td>68.6</td>
<td>71.2</td>
<td>71.6</td>
</tr>
<tr>
<td>C-5</td>
<td>60.95 or 59.17</td>
<td>54.8</td>
<td>57.8</td>
<td>57.8</td>
</tr>
<tr>
<td>C-6</td>
<td>61.61</td>
<td>60.8</td>
<td>63.4</td>
<td>63.8</td>
</tr>
<tr>
<td>CH2</td>
<td>24.19</td>
<td>21.5</td>
<td>24.3</td>
<td>24.5</td>
</tr>
<tr>
<td>CH3</td>
<td>10.66</td>
<td>10.5</td>
<td>13.4</td>
<td>13.5</td>
</tr>
<tr>
<td>[α]D</td>
<td>-6.5 (1.07, D₂O)</td>
<td>-2.2 (0.29, H₂O)</td>
<td>+5.0 (0.19, H₂O)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4 ¹³C NMR spectra and optical rotation comparison data

1D NOE experiments were carried out on 8. However, conflicting results were obtained (Fig 4.13). We observed a correlation for H-1 to H-2 and H-7, but not to H-3 or H-5. We did see a correlation between H-7 to H-2 and H-3. Based on these correlations, the NOE would indicate the alpha anomer. Further research is ongoing in the Murphy lab to resolve these contradictions.
4.2.6 Molecular mechanics models

As in chapter 2 and 3, simple molecular mechanics calculations were attempted. We used models of both R- and S-allylic azide isomers of the cis- and trans-isopropylidene protected intermediates 81 and 111 to discuss the stereochemical outcome of the rearrangement-cycloaddition reaction.

The structures were minimised and a conformational search was carried out to give the lowest energy S and R-conformers for compound 81 below (Fig 4.14). The total energy values are the same, however the azide and alkene are in much closer proximity in the S-conformer.

\[ S \ (242.5066 \text{ kJ/mol}) \text{ and } R \ (242.0758 \text{ kJ/mol}) \]

Fig 4.14 Lowest energy conformers for compound 81(S and R isomers and E values from MacroModel)

The distance between the proximal and terminal atoms of the azide and alkene were limited to \(1.5 \pm 1 \text{ Å}\) and the dihedral angle defined below (Fig 4.15) was set to zero. Perhaps the energy difference observed with these conformers is enough to favour the beta isomer.
**Fig 4.15** Lowest energy conformers for compound 81 with dihedral angle (defined by 1-2-3-4, set to 0) and distances (1.5±1 Å)

The 5,6-\textit{O}-isopropylidene intermediate 81 above was compared with the 4,5-\textit{O}-isopropylidene intermediate 111 below (**Fig 4.16**). Total energy values are slightly lower for compound 111. However, in this case, the \textit{R} isomer was found to be lower in energy.

**Fig 4.16** Lowest energy conformers for compound 111
Fig 4.17 Lowest energy conformers for constrained compound 111 with dihedral angle (defined by 1-2-3-4, set to 0) and distances (1.5±1 Å)

Possible models of both the R- and S-isomers approaching a chair transition state are below (Fig 4.17). In the case of the mannose derivatives, there could be less gauche interactions in the R-isomer conformation compared with the glucose derivatives. It is difficult to determine why beta would be selective over alpha with these mannose derivatives.

We can compare the above models to the butane diacetal compound 93 which was confirmed by x-ray crystallography to form the alpha anomer. Below are models of the possible conformers (Fig 4.18). The total energy values are much higher than observed with the isopropylidene protected intermediates 81 and 111.
which could account for the lower yields. In this case, the $S$-isomer was calculated to have a lower energy; however the $R$-isomer reacted to give the alpha iminosugar as confirmed by x-ray crystallography. The use of a 6-membered diol constraint could allow for a different configuration in the transition state leading to the different stereochemistry. The gauche interactions as drawn above for compound 111 (Fig 4.17) could help explain why it was possible to obtain the opposite selectivity with the mannose derivatives.

$S$ (650.0477 kJ/mol) and $R$ (672.0818 kJ/mol)

**Fig 4.18 Lowest energy conformers for compound 93**

### 4.3 Summary and Conclusions

A route from methyl $\alpha$-D-mannopyranoside was used to prepare suitable intermediates that underwent an intramolecular 1,3-dipolar cycloaddition. A table below summaries the various rearrangement-cycloadditions carried out (Table 4.5) and the effects of the different protecting groups on the outcome of the product and yields.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Product</th>
<th>Yield$^*$</th>
<th>Recovered SM$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>ND</td>
<td>ND</td>
<td><strong>79</strong> 50 – 90%</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td><strong>79</strong> $R$ = TES, $E$ only</td>
<td></td>
<td><strong>80</strong> 80 – 85%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><strong>79</strong> $R$ = H, $E:Z$ (1:1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fig 4.17 The lowest energy conformers for compound 93.*
| 81 | 83 | 50 – 60% | 81 10% |
| 81 | 83 | 50 – 60% | 81 10% |
| 93 | 94 | 20 - 35% | 93 trace |
| 93 | 94 | 20 - 35% | 93 trace |
| 95 | 96 | 55% | 95 ND |
| 95 | 96 | 55% | 95 ND |
| ND | ND | ND | 104 14% |
| ND | ND | ND | 104 14% |
| 111 | 112 | 45% | 111 ND |

Table 4.5 Summary of cycloaddition results

*Triazoline isolated after 2-8 h reflux in anhydrous DMF; †Starting material recovered depended on reaction time; ND; none determined
The observed yields were higher than seen previously for the glucose derivatives. A study on the effect of protecting groups on the cycloaddition showed the 5-membered cis-acetonide group to give the cleanest reaction and best yields. A crystalline BDA-protected 1,2,3-triazoline was isolated upon heating which gave the first example of a iminosugar-fused-triazoline crystal structure. While this confirmed the α-configuration of the 6-membered protected compound, it would seem that the 5-membered isopropylidene protecting group favoured formation of the β-sugar due to comparisons with literature data.
Chapter 5

Homogalactostatin Derivatives from Methyl \( \alpha \)-D-Galactopyranoside
5.1 Introduction

5.1.1 Previous syntheses of homogalactonojirimycin and analogues

Martin and co-workers reported the first synthesis of α- and β-HGJ, from a common intermediate, tetra-O-benzyl-D-galacto-heptenitol (Scheme 5.1). A stereoselective sequence included a Wittig chain extension and internal amidomercuration to give the α-anomer and a double reductive amination leading to the β-anomer.

Scheme 5.1 Martin’s route to α- and β-HGJ

Fleet and co-workers described the synthesis of DGJ, α- and β-HGJ and other 2,6-imino-heptitols via nucleophilic addition of a hydroxymethyl anion to 5-azido-1,4-lactones to afford 6-azido-lactols. Hydrogenation induces intramolecular reductive amination to produce the desired piperidine ring systems (Scheme 5.2).

Scheme 5.2 Syntheses of DGJ, HGJ and derivatives

Using the chemistry from chapters 3 and 4, a slightly modified route was used to prepare galacto-iminosugar derivatives and the results are discussed here.
5.2 Results and Discussion

5.2.1 Synthesis and cycloaddition of trans-isopropylidene protected intermediate

The route began from the commercially available 1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside which was converted to 116. Reaction of 116 with acetyl chloride in methanol gave the 6-deoxy 6-iodo methyl-α-D-galactopyranoside 117 in good yield. From here on, the chemistry used previously with glucose and mannose was applied to prepare the allylic azide intermediate 124 via 118-123 (Scheme 5.3). Allylic azide 124 was observed as a mixture of E and Z isomers.

Scheme 5.3 Reagents and conditions: a) I₂, imidazole, PPh₃, THF, reflux, 85%; b) AcCl, MeOH, 92%; c) TESCl, imidazole, CH₂Cl₂, 80%; d) Zn)), THF/H₂O, 40 °C, 88%; e) Ph₃PCH₂CO₂Et, Tol, reflux, 83%; f) DIBAL-H, CH₂Cl₂, -78 °C, 89%; g) PPh₃, DIAD, DPPA, THF, 67%; h) TBAF, THF, 78%; i) Acetone, H₂SO₄, 82%
Compounds 122 and 123 were heated in DMF, but did not lead to any of the desired cyclised products.

Upon introducing the isopropylidene to 123, formation of 124 occurred and the 4,5-acetonide was favoured. When the iminosugar forms, the protecting group on this position will give the trans-dioxolane, which is more strained than the cis-dioxolane (Fig 5.1). As with the mannose derivatives, there is the option of preparing both cis- and trans-isopropylidene protected intermediates.

![cis- vs. trans- dioxolanes](image)

**Fig 5.1 Vicinal cis- and trans-dioxolanes**

The 4,5-acetonide 124 was heated in DMF to yield the triazoline 125 (~20%), as one stereoisomer. The $J$ values for the protons at C-6 were easily assigned and indicated the same configuration as the glucose and mannose derivatives. The $J_{H1-H2}$ value isolated for 125 was 5.6 Hz. This falls between typical $J$ values for either the alpha or beta stereoisomer but it compares to those isolated for the glucose derivative and were determined to be beta.

![Scheme 5.4 Thermally promoted cycloaddition](image)

**Scheme 5.4 Thermally promoted cycloaddition**

The formation of 125 was a lower yielding cycloaddition compared with the manno-derivatives (Chapter 4), but similar to the yields obtained with the gluco-derivatives (Chapter 2 and 3).
Due to the poor yields of the trans-protected intermediate and the success of the thermally promoted cycloaddition of the cis-isopropylidene protected mannose-derivatives, we decided to investigate this approach with galactose.

5.2.2 Synthesis and cycloaddition of cis-isopropylidene protected intermediate

Starting from methyl α-D-galactopyranoside, the acetonide was selectively introduced at the 3,4-position. The primary hydroxyl group was displaced with iodine to give 127 and the remaining free hydroxyl at C-2 was protected as the TES ether 128. The route, as before, provided 133 via 129-132 (Scheme 5.6).

Scheme 5.6 Reagents and conditions: a) 2,2-DMP, CSA, Acetone, 70%; b) I₂, imidazole, PPh₃, THF, reflux, 86%; c) TESCl, imidazole, CH₂Cl₂, 78%; d) Zn (n)), THF/H₂O, 40 °C, 90%; e) Ph₃PCHCO₂Et, Tol, reflux 91%; f) DIBAL-H, CH₂Cl₂, -78 °C, 90%; g) PPh₃, DIAD, DPPA, THF, 76%; h) TBAF, THF, 71%

Intermediate 133 was heated in DMF. This cis-isopropylidene intermediate 133 proved more reactive than the mannose cis-isopropylidene derivative. After 1 h at 100 °C, there was no starting material remaining. This cycloaddition was also observed to proceed slowly at rt. Again, the cis-isopropylidene triazoline from 133 was not stable enough to be isolated.

A one-pot cycloaddition was carried out, heating 133 in DMF and after 1 h charging AcOH at 100 °C and stirring at rt for 6 h. The major product isolated
was the 6-\textit{O}-acyetylated product 134, this time in similar yields to the mannose derivative. The $J_{\text{H1-H2}}$ value for iminosugar 134 was 7.1 Hz. This value is larger than the $J_{\text{H1-H2}}$ value for the triazoline 125 and would seem more indicative of the beta anomer.

Scheme 5.8 One-pot cycloaddition

Compound 134 was deprotected under acidic conditions to give the HGJ derivative 135. The $J_{\text{H1-H2}}$ value isolated was 9.1 Hz, which again would indicate the beta anomer had been generated. A coupled $^{13}$C NMR experiment was carried out to determine $J_{\text{C1-H1}}$ values. C-1, C-5 and C-6 signals were overlapping so a value of 138.1 Hz was estimated (Fig 5.2). This values correlates well with values isolated previously (Chapter 2 and 4) for other beta iminosugars.

Scheme 5.9 HGJ derivative
Chapter 5

5.2.3 Functionalization of the alkene unit

Ozonolysis of the alkene was attempted using the free amine directly according to the procedure of Wong. Ozone was bubbled through a solution containing perchloric acid and 2,6-lutidine, however, the aldehyde was not isolated.

Scheme 5.10 Reagents and conditions: a) O₃, HClO₄, 2,6-lutidine, CH₂Cl₂, -78 °C; b) NaBH₄, EtOH

Again, with the N-Boc protected amine 136, the ozonolysis/reduction procedure did not proceed.
Scheme 5.11 Reagents and conditions: a) Boc₂O, DMAP, Et₃N, CH₂Cl₂, 70%;
b) O₃, Acetone/H₂O; c) NaBH₄, EtOH

The alkene 135 was reduced using H₂ and palladium on charcoal in the presence of HCl in good yield to give 137. The $J_{\text{H1-H2}}$ value was 8.8 Hz which again indicates beta. This value is in agreement with similar compounds found in the literature (Fig 5.3).

Scheme 5.12 Reduction reaction of 135

A coupled $^{13}$C NMR experiment was carried out. The $J_{\text{C1-H1}}$ value for 137 was 136.1 Hz (Fig 5.4), which is in agreement with values obtained previously for other beta iminosugars.
It is assumed that there is a significant difference between the transition states of the \(S\) and \(R\)-isomers of 133 to allow for the stereoselective preparation of 134. We hypothesize that the transition states could go through a chair formation (Fig 5.5), with the lower energy structure \((S)\) generating the beta anomer. Looking at the Newman projections of the anomeric carbon (Fig 5.6), it is possible that in order to minimise unwanted gauche interactions, that the beta transition state is a lower energy.

**Fig 5.4 Coupled \(^{13}\)C NMR spectrum for 137**

**Fig 5.5 Possible transition states of \(S\) and \(R\)-isomers of 133**
5.3 Summary and Conclusions

The route discussed in previous chapters was successfully applied to galactose (Scheme 5.12). Experiments carried out with these derivatives further confirmed the importance of the dioxolane acting as a conformational constraint. As with mannose, the *cis*-isopropylidene dioxolane 124 was observed to be more reactive than the *trans*-isopropylidene dioxolane derivative 133 and gave higher yields. The rearrangement-cycloaddition favoured the formation of the beta anomer again, most likely due to a lower energy transition state in the reaction of the *S*-isomer.

Scheme 5.12 Summary of rearrangement-cycloaddition with galactose derivatives
5.4 Conclusions and Future Work

Iminosugars are polyhydroxylated piperidines that can mimic naturally occurring saccharides and have found clinical use or are in clinical trials.

It has been established that the stereoselective allylic rearrangement-cycloaddition reactions generating two stereocenters occur from intermediates containing a 5- or 6-membered diol protecting group acting as a conformational constraint, yielding α- and β-C-iminosugars. This route was successfully applied toward the preparation of glucose, galactose and mannose iminosugar derivatives. This is the first application of this strategy to ring formation.

A diol protecting group seemed necessary for this reaction to proceed. The most effective constraint was the use of the isopropylidene protecting group. Specifically, a cis-isopropylidene protection yielded better results compared to a trans-isopropylidene protecting group, as seen in the cases of mannose and galactose. It was sometimes found to be more effective to convert the triazoline in situ to a more stable product.

The alkene which acts as the dipolarophile adopts a conformation to minimize allylic strain. We believe this is a factor in controlling the configuration of the stereocenter forming at the C-5 atom, which always took the (R)-configuration.

It is assumed that the secondary azides are in dynamic equilibrium with the primary azide. It appears that there is a higher energy barrier for one of these stereoisomers to cyclise, resulting in a stereoselective reaction. In most cases, the cycloaddition proceeded stereoselectively to give the β-anomer confirmed by NMR experiments (see appendices 1 and 2 for NMR tables and spectra) and of final product comparisons with related compounds in the literature. The β-anomer in the case of the triazoles was confirmed by NMR spectroscopy and X-ray crystallography.

An exception, as confirmed by NMR spectroscopy and x-ray crystallography, was the triazoline formed upon cyclization of the butane diacetal protected mannose intermediate. The six-membered protecting group ring facilitates the formation of the alpha-anomer. Due to a configuration based on mannose,
minimising gauche interactions would favour the formation of the alpha anomer in this case.

5.4.1 Future work

Future work could include the application of other sugars to this route, particularly sugars that present the opportunity to introduce a cis-protecting group.

Quaternary centers are generally difficult to prepare. It is possible that this tandem allylic-azide rearrangement – Huisgen cycloaddition would allow the stereoselective preparation of quaternary centers (Scheme 5.13).

![Scheme 5.13 Preparation of quaternary centers](image)

There is interest in carboxylic acid analogues of homogalactonojirimycin as potential polygalacturonase inhibitors (Fig 5.5).

![Fig 5.5 Carboxylic derivatives of HGJ](image)

There is potential of iminosugar C-glycosides as scaffolds in peptidomimetics, expanding on the work already carried out in the Murphy group with 1-deoxyiminosugars such as 1-DMJ.
Chapter 6

Experimental Data
General Experimental Section

NMR spectra were recorded with a Varian 500 MHz spectrometer. Chemical shifts are reported relative to internal Me₄Si in CDCl₃ (δ 0.0), HOD for D₂O (δ 4.79) and CD₂HOD (δ 3.31) for ¹H and CDCl₃ (δ 77.16) and CD₂OD (δ 49.0) for ¹³C. NMR spectra were analysed using MestReNova (v8) software. ¹H-NMR signals were assigned with the aid of COSY. ¹³C signals were assigned with the aid of DEPT-135, HSQC and HMBC. Coupling constants are reported in Hertz. All J values were reported uncorrected. Low and high resolution mass spectra were measured on a Waters LCT Premier XE Spectrometer and were measured in positive and/or negative mode as indicated using ACN, H₂O and/or MeOH as solvent. FT-IR spectra were recorded with a Perkin Elmer Spectrum 100 FTIR Spectrometer with a polarized UATR (Universal Attenuated Total Reflectance) Accessory. Optical rotations were determined with Schmidt & Haensch Unipol L 1000 polarimeter at the sodium D line at 23 °C using CHCl₃ or D₂O as indicated. TLC was performed on aluminium sheets pre-coated with Silica Gel 60 (HF₂₅₄, E. Merck) and spots visualized by UV and charring with cerium (IV) molybdate solution or ninhydrin stains. Flash column chromatography was generally employed and was carried out using Silica Gel 60 (0.040-0.630 mm, E. Merck or Aldrich) using a stepwise solvent polarity gradient correlated with TLC mobility. Chromatography solvents used were Petroleum Ether (40-60 °C, Fisher Scientific), EtOAc, CH₂Cl₂ and MeOH (Sigma Aldrich). Ion exchange chromatography was carried out using DOWEX-50WX8 (200-400 mesh) resin. Anhydrous pyridine was used as purchased from Sigma-Aldrich. THF, Tol, CH₂Cl₂, Et₂O, DMF and methanol were used as obtained from a Pure-Solv™ solvent purification system.
Experimental Data for Chapter 2

Methyl 3,4:5,6-di-O-isopropylidene-ᴅ-gluconate 30

ᴅ-Glucono-ᴅ-lactone (20 g, 0.11 mol) was dissolved in a mixture of acetone (12 mL), ethanol (4 mL) and dimethoxypropane (40 mL). p-TsOH (300 mg, 1.57 mmol) was added and the reaction was stirred at rt for 2 days. Satd NaHCO₃ (4 mL) was added and the reaction was stirred for 1 h. The white suspension was concentrated to remove the solvents. The residue was re-dissolved in CH₂Cl₂ (100 mL) and washed with brine (50 mL). The aq layer was extracted with CH₂Cl₂ (3 x 50 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give 30 (23.8 g, 73%) as a colourless oil, which was used directly in the next step. All analytical data corresponded well to the literature. [α]D -5.3 (c 6.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.34 (1H, dd, J = 9.0, 1.2 Hz, H-2), 4.23 (dd, J=7.6, 1.4 Hz, 1H, H-3), 4.15 (dd, J = 8.4, 5.8 Hz, 1H, H-6), 4.08 - 4.12 (m, 1H, H-5), 4.06 (dd, J = 14.4, 6.7 Hz, 1H, H-4), 3.99 (dd, J = 8.5, 3.9 Hz, 1H, H-6'), 3.84 (s, 3H, -OCH₃), 3.02 (d, 1H, -OH), 1.35, 1.36, 1.39, 1.43 (4 x s, 12H, 2 x -C(CH₃)₂); ¹³C NMR (128 MHz, CDCl₃) δ 172.9 (C-1), 110.0, 109.8 (-C(CH₃)₂), 80.9 (C-3), 77.3 (C-5), 76.5 (C-4), 69.4 (C-2), 67.9 (C-6), 52.6 (-OCH₃), 27.1, 26.6, 26.5, 25.2 (-C(CH₃)₂); FTIR 3485, 2988, 2937, 1744, 1457, 1440, 1372, 1247, 1210, 1129, 1064, 981, 928, 896, 843, 791, 715 cm⁻¹; HRMS (ESI) m/z calc for C₁₃H₂₅O₇Na: 313.1263, found: 313.1157 [M+Na]⁺.
Methyl 2-O-benzyl-3,4:5,6-di-O-isopropylidene-α-gluconate 31a

Compound 30 (10 g, 0.03 mol) was dissolved in CH₂Cl₂ (100 mL) was added silver(I)oxide (16.0 g, 0.07 mol). The black suspension was cooled to 0 °C and benzyl bromide (4.5 mL, 0.04 mol) was added slowly and the reaction was left to stir at rt for 48 - 72 h. The suspension was filtered through a pad of celite, washed with CH₂Cl₂ (100 mL) and concentrated. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 31a (1.31 g, 10%) as white crystals with starting material recovered (4.0 g, 40%). (1:4 EtOAc:Hexane, Rₚ 0.3); [α]D +65.5 (c 2.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.23 – 7.41 (m, 5H, Ar H), 4.87 (d, J = 11.5 Hz, 1H, -OCH₂Ph), 4.43 (d J = 11.5 Hz, 1H, -OCH₂Ph), 4.35 (dd, J = 2.6, 6.6 Hz, 1H, H-6), 4.15 (d, J =2.6 Hz, 1H, H-3), 4.08 - 4.13 (m, 1H, H-5), 4.04 - 4.08 (m, 2H, H-4), 3.87 (dd, J = 4.5, 8.3 Hz, 1H, H-6'), 3.80 (s, 3H, -OCH₃), 1.30, 1.32, 1.36, 1.39 (s, 12H, 2 x -C(CH₃)₂); ¹³C NMR (128 MHz, CDCl₃) δ 170.7 (C-1), 137.3 (Ar C), 127.8 – 128.3 (Ar CH), 109.6 (-C(CH₃)₂), 110.3 (-C(CH₃)₂), 80.7 (C-7), 73.1, 76.8, 77.3, 77.4 (C-2, C-3, C-4, C-5), 67.7 (C-6), 52.1 (-OCH₃), 27.3, 26.5, 25.2 (-C(CH₃)₂); FTIR 2988, 2937, 1750, 1431, 1455, 1371, 1210, 1130, 1060, 1023, 979, 910, 850, 754, 702 cm⁻¹; HRMS (ESI) m/z calc for C₂₀H₂₈O₇Na: 403.1733, found: 403.1742 [M+Na]⁺.
(2S,3R,4R,5R)-2-O-Benzyl-3,4:5,6-di-O-isopropylidene-hexan-1-ol 32a

A suspension of LiAlH₄ (1.5 g, 0.04 mol) in THF (100 mL) was cooled to 0 °C. A solution of 31a (10 g, 0.03 mol) in THF (100 mL) was added and the reaction was stirred at rt for 2 h. The suspension was carefully quenched with aq Na₂SO₄ solution. The salts were filtered through a pad of celite and washed with Et₂O (200 mL). The combined org layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo to give 32a (8.0 g, 85%) as a colourless oil. (TLC 1:4 EtOAc:Hexane, Rf 0.15); [α]D +17.6 (c 4.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.18 (m, 5H, Ar H), 4.76 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.68 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.17 – 4.01 (m, 4H, H-1, H-2, H-3, H-4, overlapping signals), 3.91 (dd, J = 8.5, 5.6 Hz, 1H, H-1'), 3.87 (s, 1H, H-6), 3.79 (dd, J = 12.0, 4.1 Hz, 1H, H-6'), 3.63 (q, J = 4.2 Hz, 1H, H-5), 2.52 (s, 1H, -OH), 1.41, 1.39, 1.35 (s, 12H, 4 x -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 138.4 (Ar C), 128.3 – 127.6 (Ar CH), 109.7, 109.7 (-C(CH₃)₂), 81.7, 78.0, 77.3, 77.2 (C-2, C-3, C-4, C-5), 72.6 (-OCH₂Ph), 67.8 (C-1), 62.2 (C-6), 27.2, 26.7, 26.4, 25.2 (-C(CH₃)₂); FTIR 3471, 2987, 2935, 1729, 1455, 1371, 1248, 1212, 1122, 1062, 921, 846, 734, 679 cm⁻¹; HRMS (ESI) m/z calc for C₁₉H₂₈O₆Na: 375.1874, found: 375.1739 [M+Na]⁺.
(2R,3S,4R,5R)-2-O-Benzyl-3,4:5,6-di-O-isopropylidene-hexan-1-al 33a  To a stirred solution of the Dess-Martin periodinane (14.3 g, 0.03 mol, prepared in situ) in CH₂Cl₂ (50 mL) at 0 °C was added a solution of the alcohol 32a (7.9 g, 0.02 mol) in CH₂Cl₂ (40 mL). The suspension was stirred for 30 min and raised to rt for 1 h. The reaction mixture was diluted with Et₂O (150 mL) and poured into cold satd aq NaHCO₃ containing Na₂S₂O₃ and stirred for 30 minutes, until clear. The org layer was washed with aq NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated to give 33a (6.5 g, 83%) as a colourless oil. (TLC 1:4 EtOAc: Hexane, streak); [α]D +43.8 (c 0.63, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.73 (d, J = 1.9 Hz, 1H, H-1), 7.39 – 7.29 (m, 5H, Ar H), 4.77 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.62 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.30 (dd, J = 7.12, 2.67 Hz, 1H, H-4), 4.15 – 4.12 (m, 1H, H-6), 4.07 – 4.03 (m, 2H, H-3, H-5, overlapping signals), 3.99 (t, J = 2.25 Hz, 1H, H-2), 3.91 – 3.88 (m, 1H, H-6’), 1.41, 1.35, 1.33, 1.32 (s, 12H, -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 202.6 (C-1), 137.0 (Ar C), 128.6 – 128.0 (Ar CH), 110.4, 109.8 (-C(CH₃)₂), 82.6 (C-2), 80.1 (C-4), 77.1, 76.6 (C-3, C-5), 73.5 (-OCH₂Ph), 67.9 (C-6), 27.1, 26.6, 26.5, 25.1 (-C(CH₃)₂); FTIR 2928, 2917, 1713, 1453, 1317, 1060, 1026, 999, 784, 699 cm⁻¹; LRMS (ESI) m/z calc for C₁₉H₂₇O₆Na₂: 395.1441, found: 395.1301 [M+2Na-H]⁺.
(4S,5R,6R,7R)-4-O-Benzyl-3-O-hydroxy-5,6,7,8-di-O-isopropylidene-1-octene 34a To a stirred solution of the aldehyde (6.5 g, 0.02 mol) in THF (80 mL) was added vinyl magnesium bromide (28 mL, 0.028 mol, 1.0 M in THF) at 0 °C. The reaction was allowed to reach rt and left to stir for 6 h. The reaction was quenched at 0 °C with satd aq NH₄Cl. The org layer was separated and the aq layer was extracted with Et₂O (3 x 30 mL). The combined org layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (1:6 EtOAc:Hexane) to give 34a (3.8 g, 54%), a mixture of syn- and anti-isomers (~1:1) as a colourless oil. (TLC 1:4 EtOAc:Hexane, Rf 0.5); ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.27 (m, 10H, Ar H), 6.02 – 5.93 (m, 2H, H-2a, H-2b), 5.47 – 5.40 (m, 2H, H-1a, H-1b), 5.26 – 5.21 (m, 2H, H-1’a, H-1’b), 4.80 – 4.76 (m, 3H, -OCH₂Bn), 4.56 (d, J = 11.5 Hz, 1H, -OCH₂Bn), 4.22 – 3.53 (m, 14H, -CH, -CH₂), 1.44 – 1.30 (m, 24H, 4 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) Major Isomer δ 138.04 (Ar C), 137.83 (C-2), 128.40 – 127.68 (Ar CH), 116.07 (C-1), 109.88, 109.69, (-C(CH₃)₂), 80.31, 78.61, 77.13, 77.11 (CH), 72.24 (-OCH₂Ph), 72.02 (CH), 67.88 (C-8), 27.24, 26.59, 26.58, 25.20 (-C(CH₃)₂); Minor Isomer δ 138.20 (Ar C), 137.55 (C-2), 128.40 – 127.68 (Ar CH), 116.60 (C-1), 109.83, 109.57 (-C(CH₃)₂), 81.55, 80.95, 77.67, 77.13 (CH), 74.92 (-OCH₂Ph), 73.67 (CH), 67.97 (C-8), 27.07, 26.82, 26.48, 25.20 (-C(CH₃)₂); FTIR 3478, 2987, 2934, 1739, 1455, 1371, 1212, 1063, 921, 846, 733, 697 cm⁻¹; HRMS (ESI) m/z calc for C₂₁H₃₀O₆Na: 401.1940, found: 401.1931 [M+Na]⁺.
(4R,5R,6R,7R)-4-O-Benzyl-5,6,7,8-di-O-isopropylidene-3-O-methanesulfonyl-1-octene 35a Compound 34a (3.8 g, 9.92 mmol) was dissolved in CH₂Cl₂ (60 mL) and cooled to -78 °C. Et₃N (1.7 mL, 11.90 mmol) and MsCl (0.9 mL, 11.90 mmol) were added slowly and the mixture was left to stir for 3 h at -78 °C. The mixture was diluted with CH₂Cl₂ (40 mL), washed with aq NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:8 EtOAc:Hexane) to give 35a (2.76 g, 61%), a colourless oil as a mixture of syn- and anti-isomers (~1:1). (TLC 1:4 EtOAc:Hexane, Rf 0.65); ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.26 (m, 10H, Ar H), 6.08 – 5.96 (m, 2H, H-2a, H-2b), 5.62 – 5.57 (m, 2H, H-1a, H-1b), 5.47 – 5.42 (m, 2H, H-1’a, H-1’b), 5.33 (t, J = 6.6 Hz, 1H, -CH), 5.25 (t, J = 8.0 Hz, 1H, -CH), 4.86 (d, J = 11.3 Hz, 1H, -OCH₂Ph), 4.75 (d, J = 11.2 Hz, 1H, -OCH₂Ph), 4.70 (d, J = 11.3 Hz, 1H, -OCH₂Ph), 4.63 (d, J = 11.2 Hz, 1H, -OCH₂Ph), 4.18 – 3.72 (m, 14H, -CH, -CH₂), 3.02 (s, 3H, -OSO₂CH₃), 2.88 (s, 3H, -OSO₂CH₃), 1.40 – 1.33 (s, 24H, 4 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) Major Isomer: δ 137.54 (Ar C), 132.6 (C-2), 128.45 – 127.39 (Ar CH), 120.72 (C-1), 109.84 (-C(CH₃)₂), 82.06, 79.75, 79.15, 77.78, 77.02 (CH), 74.31 (-OCH₂Ph), 68.22 (C-8), 38.92 (-OSO₂CH₃), 27.15, 26.70, 26.56, 25.18 (-C(CH₃)₂); Minor Isomer: δ 137.77 (Ar C), 132.11 (C-2), 128.45 – 127.39 (Ar CH), 121.58 (C-1), 109.84 (-C(CH₃)₂), 84.98, 79.65, 78.71, 77.78, 77.02 (CH), 74.95 (-OCH₂Ph), 68.22 (C-8), 38.66 (-OSO₂CH₃), 27.03, 26.64, 26.55, 25.08 (-C(CH₃)₂); FTIR 2987, 2935, 2601, 2496, 1736, 1456, 1358, 1245, 1213, 1171, 1067, 908, 845, 793, 749, 699 cm⁻¹; HRMS (ESI) m/z calc for C₂₂H₃₂O₈SNa: 479.1716, found: 479.1725 [M+Na]+.
(2E,4S,5R,6R,7R)-1-Azido-4-O-benzyl-5,6:7,8-di-O-isopropylidene-oct-2-ene 36a Sodium azide (0.5 g, 7.84 mmol) was added to 35a (2.8 g, 6.03 mmol) in DMF (50 mL) and stirred at 100 °C for 3 h. The reaction mixture was cooled to rt, diluted with EtOAc (80 mL) and washed with water (30 mL). The aq layer was extracted with EtOAc (3 x 50 mL) and the combined org layers were dried over Na2SO4 and concentrated in vacuo to give the trans-primary azide 36a (2.0 g, 83%), a pale yellow oil as the major isomer observed by NMR. (TLC 1:2 EtOAc:Hexanes, Rf 0.75); [α]D +49.2 (c 1.0, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.32 – 7.23 (m, 5H, Ar H), 5.89 – 5.77 (m, 2H, H-2, H-3), 4.67 (d, J = 12.0 Hz, 1H, -OCH2Ph), 4.39 (d, J = 12.0 Hz, 1H, -OCH2Ph), 4.09 – 4.04 (m, 3H, H-5, H-6, H-8 overlapping signals), 4.01 – 3.96 (m, 2H, H-4, H-7, overlapping signals), 3.92 – 3.89 (m, 1H, H-8'), 3.80 (qd, J = 14.1, 5.8 Hz, 2H, H-1, H-1'), 1.39, 1.37, 1.32 (s, 12H, 2 x -C(CH3)2); 13C NMR (126 MHz, CDCl3) δ 138.0 (Ar C), 132.6 (C-2), 128.3 – 127.7 (Ar CH), 127.6 (C-3), 109.9, 109.5 (2 x -C(CH3)2), 82.5, 78.2, 77.2, 77.1 (C-4, C-5, C-6, C-7), 70.5 (-OCH2Ph), 67.3 (C-8), 52.2 (C-1), 27.5, 26.9, 26.5, 25.3 (-C(CH3)2); FTIR 2987, 2935, 2098 (-N3), 1455, 1380, 1371, 1212, 1116, 1060, 977, 917, 844, 736, 697 cm⁻¹; HRMS (ESI) m/z calc for C21H29O5N3Na: 426.2005, found: 426.1993 [M+Na]+.
(2E,4S,5R,6R,7R)-1-Azido-4-O-benzyl-7,8-hydroxy-5,6-O-isopropylidene-oct-2-ene 37a Compound 36a (2.0 g, 4.96 mmol) was reacted with 60 % AcOH (40 mL) at rt for 15 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:2 EtOAc:Hexane) gave 37a (1.3 g, 70%) as a pale yellow oil. (TLC 1:4 EtOAc:Hexane, Rf 0.3); [α]D +44.4 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.29 (m, 5H, Ar H), 5.88 – 5.81 (m, 2H, =CH, H-6, H-7, overlapping signals), 4.72 (d, J = 11.7 Hz, 1H, -OCH₂Ph), 4.46 (d, J = 11.7 Hz, 1H, -OCH₃Ph), 4.21 – 4.20 (m, 1H, H-5), 4.06 (dd, J = 7.7, 4.0 Hz, 1H, H-4), 3.94 (t, J = 7.4 Hz, 1H, H-3), 3.89 – 3.81 (m, 2H, H-8, H-8'), 3.74 (dd, J = 13.2, 5.4 Hz, 1H, H-1), 3.66 – 3.62 (m, 2H, -CH, -CH₂, H-2, H-1', overlapping signals), 1.36, 1.35 (2 x s, 6H, 2 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 136.8 (Ar C), 130.5, 128.7 (C-2, C-3), 128.6 – 128.1 (Ar CH), 109.5 (-C(CH₃)₂), 81.0 (C-5), 77.3 (C-4), 76.8 (C-6), 72.7 (C-7), 71.4 (-OCH₃Ph), 63.8 (C-8), 52.1 (C-1), 27.0, 26.8 (-C(CH₃)₂); FTIR 3425, 2987, 2932, 2098 (-N₃), 1736, 1371, 1214, 1071, 978, 871, 698 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₂₅O₅N₃Na: 386.1692: Found: 386.1676 [M+Na]⁺.
(2E,4S,5R,6S)-1-Azido-4-O-benzyl-5,6-O-isopropylidene-hept-2-en-7-al 38a

Compound 37a (1.3 g, mmol) was dissolved in a mixture of CH₂Cl₂ and H₂O (40 mL, 1:1). The reaction mixture was cooled to 0 °C and NaIO₄ (1.0 g, 4.51 mmol) was added. The solution was slowly allowed to reach rt and stirred for 4 h. H₂O (15 mL) was added, the org layer was separated and the aq layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined org layers were dried over Na₂SO₄ and concentrated to give 38a (0.9 g, 74%) as a colourless oil. (TLC, 1:4 EtOAc:Hexane, streak); [α]D +29.9 (c 4.8, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.73 (s, 1H, H-7), 7.36 – 7.26 (m, 5H, Ar H), 5.88 – 5.75 (m, 2H, H-2, H-3, overlapping signals), 4.69 (d, J = 12.0 Hz, 1H, -OCH₂Ph), 4.48 (d, J = 11.9 Hz, 1H, -OCH₂Ph), 4.32 (d, J = 6.7 Hz, 1H, H-6), 4.24 (dd, J = 6.7, 5.0 Hz, 1H, H-5), 4.04 (dd, J = 7.0, 5.1 Hz, 1H, H-4), 3.82 (h, J = 8.4, 7.5 Hz, 2H, H-1, H-1’), 1.47, 1.38 (s, 6H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 200.7 (C-1), 137.6 (Ar C), 130.7, 128.9 (C-2, C-3), 128.4 – 127.7 (Ar CH), 111.8 (-C(CH₃)₂), 81.2 (C-6), 78.5 (C-5), 78.0 (C-4), 70.8 (-OCH₂Ph), 52.1 (C-1), 26.6, 26.2 (-C(CH₃)₂); FTIR 2987, 2930, 2869, 2098 (-N₃), 1735, 1497, 1455, 1371, 1245, 1215, 1165, 1070, 1054, 1028, 977, 868, 810, 736, 697 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₂₆O₅N₃: 364.1872; Found: 364.1867 [M+CH₃OH+H]⁺.
To a cooled solution of methyl triphenylphosphonium bromide (1.2 g, 3.34 mmol) in THF (30 mL) at -78 °C was added NaHMDS (3.9 mL, 3.85 mmol, 1.0 M solution) dropwise and stirring was continued for 25 min at -78 °C followed by 15 min at 0 °C and a further 30 min at rt. The yellow mixture was cooled to -78 °C and a solution of 38a (0.9 g, 2.57 mmol) in THF (15 mL) was added dropwise. The reaction was stirred for 10 min and then at rt for 2 h. The reaction was quenched by addition of H₂O (20 mL). The aq layer was extracted with EtOAc (3 x 20 mL) and the combined org layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:20 EtOAc:Hexane) gave 39a (0.4 g, 45%) as a colourless oil. (TLC 1:4 EtOAc:Hexane, Rₜ 0.85); ¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.26 (m, 5H, Ar H), 5.81 – 5.74 (m, 3H, H-2, H-3, H-7), 5.21 – 5.17 (m, 2H, H-8, H-8'), 4.70 (d, J = 12.24 Hz, 1H, -OCH₂Ph), 4.45 (d, J = 12.25 Hz, 1H, -OCH₂Ph), 4.35 (dd, J = 8.00, 7.13 Hz, 1H, H-6), 3.91 (dd, J = 6.1, 5.0 Hz, 1H, H-4), 3.87 – 3.76 (m, 3H, H-1, H-1', H-5), 1.43 (s, 6H, 2 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 137.9 (Ar C), 135.7 (C-7), 131.7 (C-2), 128.4 - 127.7 (Ar CH), 128.0 (C-3), 118.6 (C-8), 109.5 (-C(CH₃)₂), 82.6 (C-6), 78.4 (C-5), 77.4 (C-4), 70.4 (-OCH₂Ph), 52.2 (C-1), 27.0, 26.8 (-C(CH₃)₂); FTIR 2988, 2930, 2873, 2099 (-N₃), 1671, 1596, 1496, 1455, 1371, 1251, 1217, 1167, 1116, 1056, 980, 930, 874, 817, 737, 698 cm⁻¹; HRMS (ESI) m/z calc for C₂₀H₂₆O₃N₃Na: 393.1903: Found: 393.1890 [M+ACN+Na]^+. 
Experimental

Chapter 6

2-O-Benzyl-1,5-dideoxy-3,4-O-isopropylidene-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-d-glucitol 40a

Compound 39a (35 mg, 0.105 mmol) in DMF (4 mL) was stirred at 110 °C for 8 h. The mixture was cooled to rt. H₂O (5 mL) was added and the layers were separated. The aq layer was extracted with EtOAc (3 x 10 mL) and the combined org layers were dried over Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography of the residue (1:9 EtOAc:Hexane) gave 40a (7 mg, 20%) as a colourless oil. (TLC, 1:4 EtOAc:Hexane, Rf 0.5); ¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.29 (m, 5H, Ar H), 6.27 (ddd, J = 17.2, 10.7, 3.7 Hz, 1H, H-7), 5.43 – 5.35 (m, 3H, H-1, H-8, H-8’), 4.83 (d, J = 12.0 Hz, 1H, -OCH₂Ph), 4.70 (d, J = 11.9 Hz, 1H, -OCH₂Ph), 4.51 (dd, J = 16.2, 2.6 Hz, 1H, H-6), 4.01 (dd, J = 16.2, 9.8 Hz, 1H, H-6’), 3.72 (dd, J = 10.2, 2.7 Hz, 1H, H-5), 3.71 (apt dd, J = 10.0, 4.0 Hz, 1H, H-2), 3.59 (dd, J = 10.2, 9.1 Hz, 1H, H-3), 2.84 (dd, J = 10.4, 9.1 Hz, 1H, H-4), 1.41 (s, 3H, -C(CH₃)₂), 1.40 (s, 4H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 137.7 (Ar C), 131.8 (C-7), 128.5, 127.9, 127.8 (Ar CH), 117.4 (C-8), 111.3 (-C(CH₃)₂), 77.8 (C-2), 77.7 (C-3), 75.0 (C-4), 72.2 (-OCH₂Ph), 67.5 (C-6), 58.7 (C-1), 54.6 (C-5), 26.9, 26.7 (-C(CH₃)₂); HRMS (ESI) m/z calc for C₁₈H₂₄O₃N₃: 330.1818, found: 330.1836 [M+H]⁺.
Methyl 3,4:5,6-di-O-isopropylidene-2-O-methoxymethyl-d-gluconate \(31b\)

Compound \(30\) (8.0 g, 0.028 mol) in \(\text{CH}_2\text{Cl}_2\) (150 mL) was cooled to 0 °C. \(N,N\)-Diisopropylethylamine (49.2 mL, 0.28 mol) and DMAP (1.68 g, 0.014 mol) were charged. MOMCl (20.9 mL, 0.28 mol) was charged over 2 h. The reaction was allowed to reach rt and stirred for 48 h. The reaction was diluted with \(\text{CH}_2\text{Cl}_2\) (100 mL), washed with 2% HCl (50 mL), NaHCO\(_3\) (50 mL), brine (50 mL), dried over Na\(_2\)SO\(_4\) and concentrated to give \(31b\) as a yellow solid (7.5 g, 75%).

(TLC 1:2 EtOAc:Hexane, \(R_f\) 0.8); \([\alpha]_D^\text{+} 58.6 (c 1.4, \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.78 (d, \(J = 6.8\) Hz, 1H, -OCH\(_3\)O-), 4.74 (d, \(J = 6.8\) Hz, 1H, -OCH\(_3\)O-), 4.38 (dd, \(J = 7.1, 2.7\) Hz, 1H, H-4), 4.35 (d, \(J = 2.6\) Hz, 1H, H-2), 4.18 (dd, \(J = 8.5, 6.2\) Hz, 1H, H-6), 4.08 (dt, \(J = 8.4, 6.0\) Hz, 1H, H-5), 4.03 – 3.98 (m, 1H, H-3), 3.92 (dd, \(J = 8.5, 5.6\) Hz, 1H, H-6’), 3.80 (s, 3H, -COOCH\(_3\)), 3.44 (s, 3H, -OCH\(_2\)OCH\(_3\)), 1.43 (s, 3H, -C(CH\(_3\))\(_2\)), 1.41 (s, 3H, -C(CH\(_3\))\(_2\)), 1.37 (s, 3H, -C(CH\(_3\))\(_2\)), 1.35 (s, 3H, -C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.5 (C-1), 110.3 (-C(CH\(_3\))\(_2\)), 109.8 (-C(CH\(_3\))\(_2\)), 96.7 (-OCH\(_2\)O-), 80.7 (C-4), 77.1, 77.1 (C-3, C-5), 74.6 (C-2), 67.9 (C-6), 56.6 (-OCH\(_2\)OCH\(_3\)), 52.2 (-COOCH\(_3\)), 27.2 (-C(CH\(_3\))\(_2\)), 26.6 (-C(CH\(_3\))\(_2\)), 26.4 (-C(CH\(_3\))\(_2\)), 25.1 (-C(CH\(_3\))\(_2\)); FTIR 2986, 2960, 2935, 1750, 1433, 1383, 1372, 1252, 1210, 1149, 1061, 1022, 981, 920, 845, 797 cm\(^{-1}\); HRMS (ESI) \(m/z\) calc C\(_{15}\)H\(_{26}\)O\(_8\)Na: 357.1525, found: 357.1532 [M+Na]\(^+\).
A 1.0 M soln of LiAlH$_4$ (2.05 g, 0.05 mol) in THF (50 mL) was cooled to 0 °C. A soln of 31b (12.0 g, 0.04 mol) in THF (100 mL) was added dropwise, maintaining the temperature at 0 °C. The reaction was stirred at rt for 3 h. The reaction was quenched at 0 °C with aq Na$_2$SO$_4$, filtered and washed with EtOAc (3 x 50 mL). The org layer was washed with brine (50 mL), dried over Na$_2$SO$_4$ and concentrated to give 32b as a clear oil (10.99 g, 87%). (TLC 1:2 EtOAc:Hexane, R$_f$ 0.25); [α]$_D$ -10.2 (c 1.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 4.82 (d, $J = 6.7$ Hz, 1H, -OCH$_2$O-), 4.74 (d, $J = 6.8$ Hz, 1H, -OCH$_2$O-), 4.18 (dd, $J = 8.5$, 6.2 Hz, 1H, H-6), 4.14 – 4.03 (m, 2H, H-3, H-4), 3.96 – 3.92 (m, 2H, H-5, H-6'), 3.80 – 3.78 (m, 2H, -CH$_2$OH), 3.74 – 3.71 (m, 1H, H-2), 3.46 (s, 3H, -OCH$_3$), 1.41 (s, 6H, -C(CH$_3$)$_2$), 1.38 (s, 3H, -C(CH$_3$)$_2$), 1.35 (s, 3H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 109.8, 109.8 (-C(CH$_3$)$_2$), 97.2 (-OCH$_2$O-), 81.4 (C-4), 79.9 (C-2), 77.5, 77.4 (C-3, C-5), 68.0 (C-6), 63.5 (C-1), 55.9 (-OCH$_3$), 27.2 (-C(CH$_3$)$_2$), 26.7 (-C(CH$_3$)$_2$), 26.4 (-C(CH$_3$)$_2$), 25.2 (-C(CH$_3$)$_2$); FTIR 3467, 2987, 2937, 2896, 1704, 1457, 1371, 1249, 1212, 1151, 1060, 1022, 917, 878, 845 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{14}$H$_{28}$O$_7$Na: 329.1576, found: 329.1591 [M+Na]$^+$. 

(2S,3R,4R,5R)-3,4:5,6-di-O-isopropylidene-2-O-methoxymethyl-hexan-1-ol

32b
To a stirred solution of the Dess-Martin periodinane (22.8 g, 0.05 mol, prepared in situ) in CH$_2$Cl$_2$ (50 mL) at 0 °C was added a solution of the alcohol 32b (11.0 g, 0.04 mol) in CH$_2$Cl$_2$ (0.35 M solution). The suspension was stirred for 30 min and raised to room temp for 1 h. The reaction mixture was diluted with Et$_2$O (200 mL) and poured into cold sat aq NaHCO$_3$ (100 mL) containing Na$_2$S$_2$O$_3$ and stirred for 30 min. The org layer was washed with sat aq NaHCO$_3$ (50 mL) and brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated n vacuo to give 33b (9.1 g, 83%) as a colourless oil. [α]$_D$ +15.9 (c 4.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.73 (d, $J$ = 1.5 Hz, 1H, H-1), 4.82 (d, $J$ = 6.8 Hz, 1H, -OCH$_2$O-), 4.76 (d, $J$ = 6.8 Hz, 1H, -OCH$_2$O-), 4.33 (dd, $J$ = 7.7, 2.5 Hz, 1H, H-4), 4.18 (dd, $J$ = 8.6, 6.2 Hz, 1H, H-6), 4.10 (t, $J$ = 2.0 Hz, 1H, H-2), 4.06 (dt, $J$ = 8.7, 5.7 Hz, 1H, H-5), 3.98 (m, 1H, H-3), 3.93 (dd, $J$ = 8.6, 5.4 Hz, 1H, H-6'), 3.46 (s, 3H, -C(CH$_3$)$_2$), 1.43 (s, 3H, -C(CH$_3$)$_2$), 1.40 (s, 3H, -C(CH$_3$)$_2$), 1.36 (s, 3H, -C(CH$_3$)$_2$), 1.34 (s, 3H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.7 (C-1), 110.3, 109.8 (-C(CH$_3$)$_2$), 97.6 (-OCH$_2$O-), 81.7 (C-2), 79.9 (C-4), 77.1, 76.7 (C-3, C-5), 68.0 (C-6), 56.4 (-OCH$_3$), 27.0 (-C(CH$_3$)$_2$), 26.5 (-C(CH$_3$)$_2$), 26.4 (-C(CH$_3$)$_2$), 25.0 (-C(CH$_3$)$_2$); FTIR 2988, 2940, 2901, 1736, 1706, 1457, 1372, 1245, 1213, 1151, 1062, 1029, 918, 844 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{14}$H$_{24}$O$_7$Na: 327.1420, found: 327.1418 [M+Na]$^+$. 

(2R,3S,4R,5R)-3,4:5,6-di-O-isopropylidene-2-O-methoxymethoxy-hexan-1-al
Experimental

(4S,5R,6R,7R)-5,6:7,8-di-O-isopropylidene-3-hydroxy-4-O-methoxymethyl-1-octene 34b: Compound 33b (9.1 g, 0.03 mol) was dissolved in THF (100 mL) and cooled to -78 °C. Vinyl Magnesium Bromide (44 mL, 0.04 mol, 1.0 M in THF) was charged slowly. The reaction was stirred for 6 h. The reaction was warmed to rt and quenched with NH₄Cl solution. The org layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc:Hexane 1:1) to give 34b as a mixture of isomers (~1:1, 5.5 g, 56%). (TLC 1:2 EtOAc:Hexane, Rf 0.55); ¹H NMR (500 MHz, CDCl₃) δ 6.03 (ddd, J = 17.2, 10.5, 4.8 Hz, 1H, C-2), 5.94 (ddd, J = 16.9, 10.6, 5.9 Hz, 1H, C-2), 5.44 (ddt, J = 17.3, 8.3, 1.8 Hz, 2H, C-1'), 5.23 (dt, J = 10.4, 1.8 Hz, 2H, C-1'), 4.80 (apt t, J = 6.9 Hz, 2H, -OCH₂O-), 4.76 (d, J = 6.7 Hz, 1H, -OCH₂O-), 4.71 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.42 – 3.45 (m, 14H, 12 x -CH, 2 x -CH₂), 3.45 (s, 3H, -OCH₃), 3.43 (s, 3H, -OCH₃), 2.03 (s, 1H, -OH), 1.43 – 1.31 (s, 24H, 4 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) Major isomer δ 137.51 (C-2), 115.89 (C-1), 109.92, 109.77 (-C(CH₃)₂), 97.18 (-OCH₂O-), 80.24, 79.33, 77.59, 77.06 (C-4, C-5, C-6, C-7), 73.17 (C-3), 67.99 (C-8), 56.23 (-OCH₃), 27.18, 26.66, 26.42, 25.11 (-C(CH₃)₂); Minor isomer δ 136.61 (C-2), 117.07 (C-1), 109.79, 109.46 (-C(CH₃)₂), 98.51 (-OCH₂O-), 82.82, 80.79, 77.45, 77.12 (C-4, C-5, C-6, C-7), 73.21 (C-3), 68.03 (C-8), 56.21 (-OCH₃), 26.93, 26.72, 26.40, 25.11 (-C(CH₃)₂); FTIR 3466, 2987, 2936, 2886, 1456, 1371, 1212, 1150, 1063, 1027, 919, 845 cm⁻¹; HRMS (ESI) m/z calc for C₆H₁₆O₇Na: 355.1733, found: 355.1746 [M+Na⁺].
Compound 34b (5.5 g, 16.56 mmol) was dissolved in CH₂Cl₂ (80 mL) and cooled to -78 °C. Et₃N (2.77 mL, 19.87 mmol) and MsCl (1.54 mL, 19.87 mmol) were added slowly and the mixture was left to stir for 3 h at -78 °C. Upon completion (TLC 1:4 EtOAc: Hexane, Rf 0.3), the mixture was diluted with CH₂Cl₂ (50 mL), washed with sat NaHCO₃ (40 mL) and brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give a mixture of syn- and anti-isomers (~1:1) 35b as a colourless oil (4.1 g, 61%).

**1H NMR (500 MHz, CDCl₃)** δ 6.06 – 5.95 (m, 2H, =CH), 5.59 (dd, J = 17.3, 10.0 Hz, 2H, =CH₂), 5.46 (dd, J = 15.2, 10.5 Hz, 2H, =CH₂), 5.32 – 5.29 (m, 1H, -CH), 5.21 (t, J = 8.0 Hz, 1H, -CH), 4.80 (apt t, J = 7.5 Hz, 2H, -OCH₂O-), 4.76 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.72 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.18 – 3.89 (m, 11H, -CH₂, overlapping signals), 3.76 (dd, J = 8.1, 1.5 Hz, 1H, -CH), 3.44 (s, 3H, -OCH₃), 3.42 (s, 3H, -OCH₃), 3.05 (s, 3H, -SCH₃), 3.02 (s, 3H, -SCH₃), 1.43 – 1.33 (5 x s, 24H, -C(CH₃)₂); **13C NMR (126 MHz, CDCl₃)**

**Major Isomer** δ 132.25 (C-2), 121.16 (C-1), 109.94 (-C(CH₃)₂), 97.77 (-OCH₂O-), 81.93 (C-3), 79.41, 78.17, 77.10 (C-4, C-5, C-6, C-7), 68.14 (C-8), 56.35 (-OCH₃), 39.06 (-SCH₃), 27.14, 26.78, 26.28, 25.22 (-C(CH₃)₂); **Minor Isomer** δ 132.01 (C-2), 122.10 (C-1), 109.79, 109.78 (-C(CH₃)₂), 98.62 (-OCH₂O-), 84.62 (C-3), 78.83, 78.11, 77.35, 77.13 (C-4, C-5, C-6, C-7), 67.90 (C-8), 56.49 (-OCH₃), 39.17 (-SCH₃), 27.17, 26.70, 26.24, 25.11 (-C(CH₃)₂); **FTIR** 2988, 2937, 2901, 1457, 1415, 1359, 1250, 1213, 1175, 1152, 1065, 1024, 907, 842, 768, 736, 683 cm⁻¹; **HRMS (ESI)** m/z calc for C₁₇H₃₀O₉Na⁺: 433.1508, found: 433.1500 [M+Na⁺].
**Experimental**

**Chapter 6**

(2E,4S,5R,6R,7R)-1-Azido-5,6:7,8-di-O-isopropyldiene-4-O-methoxymethyl-oct-2-ene 36b Compound 35b (4.1 g, 10.04 mmol) was dissolved in anhydrous DMF (50 mL) and NaN₃ (0.9 g, 13.06 mmol) was added. The mixture was heated to 100 °C for 3 h. The mixture was cooled to rt, diluted with EtOAc (50 mL) and washed with H₂O (20 mL). The aq layer was extracted with EtOAc (3 x 20 mL), dried over Na₂SO₄ and concentrated to give a yellow syrup. Flash column chromatography of the residue (1:6 EtOAc:Hexane) gave 36b as a colourless oil (2.40 g, 67%). (TLC 1:4 EtOAc:Hexane, Rₚ 0.5); [α]D +67.0 (c 1.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.87 – 5.77 (m, 2H, C-2, C-3, overlapping signals), 4.74 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.62 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.23 (dd, J = 7.0, 3.7 Hz, 1H, H-4), 4.14 (dd, J = 8.2, 6.1 Hz, 1H, H-8), 4.10 – 3.98 (m, 3H, H-5, H-6, H-7, overlapping signals), 3.94 (dd, J = 8.4, 5.5 Hz, 1H, H-8’), 3.86 – 3.78 (m, 2H, H-1, H-1’), 3.40 (s, 3H, -OCH₃), 1.44, 1.42, 1.39, 1.35 (s, 12H, 2 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 131.8 (C-2), 128.0 (C-3), 110.0 (-C(CH₃)₂), 109.6 (-C(CH₃)₂), 94.0 (-OCH₂O), 82.4, 77.5, 77.1 (C-5, C-6, C-7), 75.4 (C-4), 67.4 (C-8), 55.8 (-OCH₃), 52.1 (C-1), 27.4, 27.0, 26.4, 25.2 (-C(CH₃)₂); FTIR 2988, 2935, 2886, 2100 (-N₃), 1456, 1381, 1371, 1212, 1151, 1064, 1022, 979, 919, 845 cm⁻¹; HRMS (ESI) m/z calc for C₁₆H₂₇O₆N₃Na: 380.1798, found: 380.1811 [M+Na]⁺.
Experimental

Chapter 6

(2E,4S,5R,6R,7R)-1-Azido-7,8-hydroxy-5,6-O-isopropylidene-4-O-methoxymethyl-oct-2-ene 37b Compound 36b (2.4 g, 6.72 mmol) was suspended in 60 % AcOH (40 mL) and stirred at rt for 12 h. The mixture was concentrated and purified by flash column chromatography (1:1 EtOAc:Hexane) to give 37b as a clear oil (1.6 g, 73%). (TLC 1:1 EtOAc:Hexane, Rf 0.1); [α]D +65.7 (c 1.6, CHCl3); ¹H NMR (500 MHz, CDCl3) δ 5.88 – 5.77 (m, 2H, H-2, H-3, overlapping signals), 4.75 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.65 (d, J = 6.6 Hz, 1H, -OCH₂O-), 4.43 (dd, J = 6.7, 4.3 Hz, 1H, H-4), 4.08 (dd, J = 7.5, 4.2 Hz, 1H, H-5), 3.98 (t, J = 7.4 Hz, 1H, H-6), 3.85 – 3.79 (m, 3H, H-1, H-1’, H-8, overlapping signals), 3.74 – 3.69 (m, 2H, H-7, H-8’, overlapping signals), 3.41 (s, 3H, -OCH₃), 1.40 (s, 6H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl3) δ 130.3 (C-3), 128.5 (C-2), 109.6 (-C(CH₃)₂), 94.5 (-OCH₂O-), 81.1 (C-5), 77.0 (C-6), 75.1 (C-4), 72.7 (C-7), 63.9 (C-8), 56.0 (-OCH₃), 52.1 (C-1), 27.1 (-C(CH₃)₂), 26.9 (-C(CH₃)₂); FTIR 3423, 2988, 2935, 2891, 2100 (-N₃), 1456, 1371, 1237, 1213, 1151, 1068, 1022, 980, 919, 864 cm⁻¹; HRMS (ESI) m/z calc for C₁₃H₂₃O₄N₃Na: 340.1509, found: 340.1498 [M+Na]⁺.
Compound 37b (1.6 g, 4.92 mmol) was dissolved in CH$_2$Cl$_2$:H$_2$O (1:1, 40 mL) and cooled to 0 °C. NaIO$_4$ (1.4 g, 6.39 mmol) was added and the mixture was allowed to reach rt. The mixture was diluted with H$_2$O (20 mL) and the layers separated. The aq layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined org layers were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give 38b as a clear oil (1.1 g, 79%). (TLC 1:1 EtOAc:Hexane, R$_f$ 0.35); [α]$_D$ +36.7 (c 1.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.69 (d, $J$ = 1.4 Hz, 1H, H-1), 5.82 (dt, $J$ = 15.5, 6.0 Hz, 1H, H-2), 5.67 (dd, $J$ = 15.6, 7.4 Hz, 1H, H-3), 4.66 (d, $J$ = 6.6 Hz, 1H, -OCH$_2$O-), 4.57 (d, $J$ = 6.8 Hz, 1H, -OCH$_2$O-), 4.24 – 4.21 (m, 2H, H-4, H-6, overlapping signals), 4.17 (dd, $J$ = 6.6, 5.3 Hz, 1H, H-5), 3.80 – 3.73 (m, 2H, H-1, H-1’), 3.33 (s, 3H, -OCH$_3$), 1.44, 1.33 (s, 6H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 199.7 (C-1), 129.0 (C-3), 128.2 (C-2), 110.9 (-C(CH$_3$)$_2$), 93.1 (-OCH$_2$O-), 80.3 (C-6), 77.5 (C-5), 74.4 (C-4), 54.7 (-OCH$_3$), 51.0 (C-1), 25.6, 25.2 (-C(CH$_3$)$_2$); FTIR 2989, 2937, 2897, 2099 (-N$_3$), 1734 (C=O), 1456, 1383, 1373, 1255, 1212, 1152, 1071, 1023, 979, 918, 858, 736, 702 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{12}$H$_{23}$O$_5$N$_4$: 303.1668, found: 303.1661 [M+NH$_4$]$^+$. 
A solution of methyl triphenylphosphonium bromide (2.5 g, 7.11 mmol) in THF (30 mL) was cooled to -78 °C. NaHMDS (7.1 mL, 7.11 mmol, 1.0 M in THF) was added dropwise and the solution was stirred at -78 °C for 25 min, 0 °C for 15 min and rt for 30 min. The yellow solution was re-cooled to -78 °C and 38b (1.6 g, 5.47 mmol) in THF (30 mL) was added dropwise. After 10 min the reaction was raised to rt and stirred for 2 h. The reaction was diluted with H₂O (40 mL) and the layers were separated. The aq layer was extracted with EtOAc (3 x 30 mL), dried over Na₂SO₄, and concentrated in vacuo. Flash column chromatography of the residue (1:1 EtOAc:Hexane) gave 39b as a clear oil (1.3 g, 50%). (TLC 1:2 EtOAc:Hexane, R₅ 0.8); [α]D +62.7 (c 0.37, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.86 – 5.79 (m, 2H, H-2, H-7, overlapping signals), 5.73 – 5.68 (m, 1H, H-3), 5.35 (dt, J = 17.1, 1.0 Hz, 1H, H-8), 5.26 (dt, J = 10.5, 1.2 Hz, 1H, H-8'), 4.73 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.63 (d, J = 6.7 Hz, 1H, -OCH₂O-), 4.35 (dd, J = 7.9, 7.2 Hz, 1H, H-6), 4.20 (dd, J = 7.7, 5.4 Hz, 1H, H-4), 3.89 – 3.75 (m, 3H, H-1, H-1', H-5, overlapping signals), 3.41 (s, 3H, -OCH₃), 1.45, 1.44 (s, 6H, -C(CH₂)₃); ¹³C NMR (126 MHz, CDCl₃) δ 135.6 (C-7), 130.9 (C-3), 128.4 (C-6), 118.8 (C-8), 109.5 (-C(CH₂)₃), 93.8 (-OCH₂O-), 82.5 (C-5), 78.6 (C-6), 75.2 (C-4), 55.6 (-OCH₃), 52.1 (C-1), 27.0, 26.9 (-C(CH₂)₃); FTIR 2988, 2935, 2891, 2099 (-N₃), 1647, 1455, 1371, 1213, 1151, 1099, 1024, 983, 920, 875, 812 cm⁻¹; HRMS (ESI) m/z calc for C₂₆H₄₅N₅O₈: 567.3137, found: 567.3148 [2M+H]+.
1.5-Dideoxy-3,4-\(O\)-isopropylidene-2-\(O\)-methoxymethyl-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-d-glucitol 40b

Compound 26 (36 mg, 0.13 mmol) was heated to 100 °C in anhydrous DMF (5 mL) for 8 h. The mixture was cooled to rt. H\(_2\)O (5 mL) was added and the layers were separated. The aq layer was extracted with EtOAc (3 x 10 mL) and the combined org layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. Flash column chromatography of the residue (1:4 EtOAc:Hexane) gave 27 as a clear oil (10.8 mg, 30%). (TLC 1:4 EtOAc:Hexane, R\(_f\) 0.3); [\(\alpha\)]\(_D\) -34.9 (c 4.9 in CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.25 (ddd, \(J = 17.3, 10.7, 3.4\) Hz, 1H, H-7), 5.46 (dq, \(J = 5.9, 3.1\) Hz, 1H, H-1), 5.43 – 5.38 (m, 2H, H-8, H-8’, overlapping signals), 4.87 (d, \(J = 6.7\) Hz, 1H, -OCH\(_2\)O-), 4.76 (d, \(J = 6.7\) Hz, 1H, -OCH\(_2\)O-), 4.52 (dd, \(J = 16.2, 2.7\) Hz, 1H, H-6), 4.02 (dd, \(J = 16.2, 9.8\) Hz, 1H, H-6’), 3.87 (dd, \(J = 10.4, 6.2\) Hz, 1H, H-2), 3.71 (td, \(J = 10.1, 2.6\) Hz, 1H, H-5), 3.56 (dd, \(J = 10.4, 9.1\) Hz, 1H, H-3), 3.43 (s, 3H, -OCH\(_3\)), 2.87 (dd, \(J = 10.4, 9.2\) Hz, 1H, H-4), 1.40 (s, 3H, -C(CH\(_3\))\(_2\)), 1.38 (s, 3H, -C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 131.8 (C-7), 117.6 (C-8), 111.3 (-C(CH\(_3\))\(_2\)), 96.6 (-OCH\(_2\)O-), 76.9 (C-3), 76.2 (C-2), 75.1 (C-4), 67.4 (C-6), 59.3 (C-1), 56.0 (-OCH\(_3\)), 54.5 (C-5), 26.8, 26.6 (2 x -C(CH\(_3\))\(_2\)); FTIR 2986, 2935, 2893, 1640, 1494, 1455, 1403, 1373, 1329, 1280, 1231, 1146, 1106, 1079, 1021, 993, 918, 837, 788, 757, 706 cm\(^{-1}\); HRMS (ESI) \(m/\)z calc for C\(_{13}\)H\(_{22}\)O\(_3\)N\(_3\): 284.1610, found: 284.1642 [M+H]+.
6-O-Acetyl-1,5-Dideoxy-2,3-O-isopropylidene-2-O-methoxymethyl-1-(R)-ethenyl-1,5-imino-D-mannitol 41a Compound 39b (88 mg, 0.311 mmol) was dissolved in anhydrous DMF (10 mL). NaN₃ (101 mg, 1.557 mmol) and AcOH (26 μl, 0.466 mmol) were charged and the mixture was heated to 80 °C for 16 h and then cooled to rt. The solution was diluted with H₂O (5 mL) and extracted with EtOAc until no product remained (as observed by TLC 1:1 EtOAc:Hexane), dried over Na₂SO₄ and concentrated. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 41a (8 mg, 9%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.92 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H, H-7), 5.36 (apt d, J = 17.2 Hz, 1H, H-8), 5.25 (apt d, J = 10.4 Hz, 1H, H-8’), 4.93 (d, J = 6.6 Hz, 1H, -OCH₂O-), 4.62 (d, J = 6.6 Hz, 1H, -OCH₂O-), 4.41 (dd, J = 11.3, 2.9 Hz, 1H, H-6), 4.01 (dd, J = 11.4, 7.4 Hz, 1H, H-6’), 3.57 (t, J = 9.1 Hz, 1H, H-2), 3.48 (t, J = 9.1 Hz, 1H, H-3), 3.38 (s, 3H, -OCH₃), 3.19 (t, J = 9.2 Hz, 1H, H-4), 3.16 (apt t, J = 8.9 Hz 1H, H-1), 3.07 (ddd, J = 9.8, 7.3, 2.9 Hz, 1H, H-5), 1.25 (s, 6H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 206.9 (C=O), 136.9 (C-7), 118.0 (C-8), 110.0 (-C(CH₃)₂), 95.7 (-OCH₂O-), 83.3 (C-3), 76.7 (C-2), 76.2 (C-4), 65.2 (C-6), 61.9 (C-1), 56.0 (C-5), 55.9 (-OCH₃), 29.6 (-C(CH₃)₂).
(2E,7E,4S,5R,6R) Ethyl 1-azido-4-O-benzyl-5,6-O-isopropylidene-none-2,7-diene-9-oate 42a Compound 38a (72 mg, 0.22 mmol) was dissolved in toluene (5 mL) and (carbethoxy) triphenylphosphorane (99 mg, 0.28 mmol) was charged. The reaction was stirred at rt for 2 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:6 EtOAc:Hexane) gave isomers 42a (E(a):Z(b), 1:0.7) as a colourless oil (33 g, 38%). 1H NMR (500 MHz, CDCl3) δ 7.37 – 7.27 (m, 10H, Ar H), 6.82 (dd, J = 15.7, 5.4 Hz, 1H, H-7a), 6.13 (dd, J = 11.6, 9.0 Hz, 1H, H-8b), 5.97 (dd, J = 15.7, 1.5 Hz, 1H, 8a), 5.94 (dd, J = 11.6, 1.0 Hz, 1H, 6b), 5.87 – 5.76 (m, 4H, H-2a,b, H-3a,b, overlapping signals), 5.65 (ddd, J = 9.0, 7.8, 1.0 Hz, 1H, H-6b), 4.71 (d, J = 12.2 Hz, 1H, -OCH2Ph), 4.64 (d, J = 11.8 Hz, 1H, -OCH2Ph), 4.53 (d, J = 12.2 Hz, 1H, -OCH2Ph), 4.53 – 4.50 (m, 1H, H-6a, overlapping signals), 4.45 (d, J = 12.2 Hz, 1H, -OCH2Ph), 4.21 – 4.11 (m, 4H, 2 x Et), 4.04 (t, J = 5.6 Hz, 1H, H-4b), 4.00 (ddd, J = 6.3, 4.6 Hz, 1H, H-4a), 3.89 – 3.73 (m, 6H, H-1a,b, H-1’a,b, H-5a, H-5b, overlapping signals), 1.45 – 1.42 (s, 12H, 2 x -C(CH3)2), 1.30 – 1.25 (m, 6H, 2 x Me); 13C NMR (126 MHz, CDCl3) Major Isomer (E) δ 165.98 (C=O), 144.47 (C-7), 138.23 (Ar C), 131.00 (C-2), 128.44 – 127.40 (Ar CH, C-3), 122.53 (C-8), 110.27 (C(CH3)2), 81.88 (C-4), 77.00 (C-5), 76.08 (C-6), 70.65 (-OCH2Ph), 60.52 (-OCH2), 52.09 (C-1), 26.81, 26.80 (-C(CH3)2), 14.19 (-CH3); Minor Isomer (Z) δ 165.26 (C=O), 145.04 (C-7), 137.60 (Ar C), 131.33 (C), 128.44 – 127.40 (Ar CH, C-3), 123.34 (C-8), 110.30 (-C(CH3)2), 83.36 (C-4), 78.51 (C-5), 72.29 (C-6), 70.67 (-OCH2Ph), 60.39 (-OCH2), 52.17 (C-1), 27.33, 26.76 (-C(CH3)2), 14.16 (-CH3); FTIR 2986, 2935, 2872, 2099 (-N3), 1718 (C=O), 1661, 1455, 1371, 1163, 1028, 978, 875, 697 cm⁻¹; HRMS (ESI) m/z calc for C21H26O5N3: 402.2029; Found: 402.2025 [M+H]+.
Experimental

(2E,7E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-8-C-phenyl-octa-2,7-diene 42c Triphenyl phosphate (1.5 g, 5.72 mmol) and benzyl bromide (0.7 mL, 5.72 mmol) were dissolved in toluene (30 mL) and heated to reflux for 20 h. A white solid precipitated out of solution, was filtered, washed with Et₂O (80 mL) and dried to give the phosphonium salt (2.2 g, 89 %). The phosphonium salt (0.3 g, 0.58 mmol) was suspended in THF (10 mL) and cooled to -78 °C. KHMDS (0.5 mL, 1 M in THF) was added dropwise to give a yellow solution which was stirred at -78 °C for 30 min and then raised to rt for 1 hr. The red solution containing the ylide was re-cooled to -78 °C. The aldehyde 38b (0.2 g, 0.53 mmol) in THF (10 mL) was charged to the mixture, raised to rt and stirred for 1 hr. The reaction was quenched by addition of H₂O (10 mL), extracted with EtOAc (3 x 10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (1:4 EtOAc:Hexane) to give the alkene 42c (0.1 g, 72%) as a clear oil. (TLC 1:1 EtOAc:Hexane, Rf 0.95); [α]D +99.1° (c 0.54, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, Ar H), 6.77 (d, J = 11.4 Hz, 1H, H-1), 5.67 – 5.50 (m, 3H, H₂, H-6, H-7, overlapping signals), 4.70 (apt t, J = 8.77 Hz, 1H, H-3), 4.61 (d, J = 6.7 Hz, 1H, -OCH₂O), 4.49 (d, J = 6.8 Hz, 1H, -OCH₂O), 4.04 (apt t, J = 6.5 Hz, 1H, H-5), 3.85 (dd, J = 7.9, 5.7 Hz, 1H, H-4), 3.59 (qd, J = 14.4, 5.5 Hz, 2H, H-8, H-8'), 3.15 (s, 3H, -OCH₃), 1.50 (s, 3H, -C(CH₃)₂), 1.48 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 136.0 (C-1), 130.3 – 127.7 (Ar C, Ar CH, C-2, C-6, C-7), 109.6 (-C(CH₃)₂), 93.7 (-OCH₂O), 83.7 (C-4), 75.4 (C-5), 73.5 (C-3), 55.3 (-OCH₃), 51.9 (C-8), 27.3 (-C(CH₃)₂), 26.8 (-C(CH₃)₂); FTIR 2987, 2932, 2893, 2100 (-N₃), 1726, 1495, 1451, 1381, 1371, 1213, 1151, 1100, 1063, 1025, 979, 919, 875, 810, 774, 739, 699 cm⁻¹; HRMS (ESI) m/z calc for C₁₉H₂₅O₄N₃Na: 382.1743, found 382.1739 m/z [M+Na]⁺.
Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).

(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-7-nitrile-hept-2-ene 43

Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).

(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-7-nitrile-hept-2-ene 43

Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).

(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-7-nitrile-hept-2-ene 43

Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).

(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-7-nitrile-hept-2-ene 43

Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).

(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-7-nitrile-hept-2-ene 43

Compound 38b (138 mg, 0.48 mmol) was suspended in a mixture of aq NH₃ (5 mL of 28 % soln) and THF (0.5 mL). Iodine (135 mg, 0.53 mmol) was charged and the mixture was stirred at rt and the colour changed from dark to yellow. Aq Na₂S₂O₃ (5 mL of 5 % soln) was added. The aq layer was extracted with Et₂O (3 x 10 mL), the combined org layers were dried over Na₂SO₄ and concentrated to give the nitrile 43 as a yellow oil (105 mg, 77%).
(2E,4S,5R,6R)-1-Azido-5,6-O-isopropylidene-4-O-methoxymethyl-oct-2-en-7-yln 44 Compound 38b (162 mg, 0.57 mmol) was dissolved in MeOH (20 mL). K₂CO₃ (23.6 mg, 1.70 mmol) and the Ohira-Bestmann reagent (0.12 mL, 0.74 mmol, prepared in situ) were added. The mixture was stirred at rt overnight. The solvent was removed under diminished pressure. The crude product was re-dissolved in CH₂Cl₂ (20 mL), washed with H₂O (10 mL), dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:4 EtOAc:Hexane, Rₚ 0.8) gave 44 as a clear oil (125 mg, 78%). (TLC 1:1 EtOAc:Hexane, Rₚ 0.8); [α]ᵦ +98.6 (c 0.98, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.89 (dt, J = 15.5, 6.0 Hz, 1H, H-2), 5.75 (ddt, J = 15.4, 7.3, 1.4 Hz, 1H, H-3), 4.73 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.64 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.52 (dd, J = 6.8, 2.2 Hz, 1H, H-6), 4.23 (dd, J = 7.2, 5.8 Hz, 1H, H-4), 4.20 (dd, J = 6.9, 5.6 Hz, 1H, H-5), 3.83 (apt t, J = 4.8 Hz, 1H, H-1, H-1’), 3.40 (s, 3H, -OCH₃), 2.54 (d, J = 2.1 Hz, 1H, H-8), 1.51, 1.44 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 130.1 (C-3), 129.0 (C-2), 111.3 (-C(CH₃)₂), 94.0 (-OCH₂O-), 83.2 (C-5), 81.2 (C-7), 75.1 (C-4), 74.8 (C-8), 66.8 (C-6), 55.6 (-OCH₃), 52.1 (C-1), 26.7, 26.0 (-C(CH₃)₂); FTIR 3419, 2988, 2936, 2100 (-N₃), 1747, 1371, 1213, 1068, 1025, 980, 917, 879 cm⁻¹; HRMS (ESI) m/z calc for C₁₃H₂₀N₃O₄: 282.1454: found 282.1445 [M+H]⁺.
1,5-Dideoxy-3,4-O-isopropylidene-2-O-methoxymethyl-1,5-[1,2,3]-triazole-1-\((S)\)-ethenyl-1,5-imino-\(\delta\)-glucitol 45 \textit{Compound 44 (47 mg, 0.17 mmol) was dissolved in anhydrous DMF (5 mL) and heated to 100 °C for 8 h. The mixture was cooled to rt. H\textsubscript{2}O (5 mL) was added and the layers were separated. The aq layer was extracted with EtOAc (3 x 10 mL) and the combined org layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated in vacuo. Flash column chromatography of the residue (1:4 EtOAc:Hexane) gave 45 (26 mg, 63%) as a white solid. The white solid was recrystallized by dissolving in a minimum volume of CH\textsubscript{2}Cl\textsubscript{2} and adding a few drops of hexane. The solvent was evaporated off slowly to allow the crystals to form. (TLC 1:1 EtOAc:Hexane, R\textsubscript{f} 0.7); [\(\alpha\)]\textsubscript{D} -64.3 (c 1.2, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.69 (d, \(J = 1.0\) Hz, 1H, H-6), 6.04 (ddd, \(J = 17.0, 10.3, 6.9\) Hz, 1H, H-7), 5.42 (dd, \(J = 10.3, 1.1\) Hz, 1H, H-8), 5.25 (dd, \(J = 16.9, 1.2\) Hz, 1H, H-8\'), 5.06 (t, \(J = 6.6\) Hz, 1H, H-1), 5.02 (d, \(J = 6.8\) Hz, 1H, -OCH\textsubscript{2}O-), 4.72 (d, \(J = 6.8\) Hz, 1H, -OCH\textsubscript{2}O-), 4.60 (d, \(J = 9.2\) Hz, 1H, H-4), 4.30 (dd, \(J = 9.9, 6.3\) Hz, 1H, H-2), 3.81 (t, \(J = 9.6\) Hz, 1H, H-3), 3.44 (s, 3H, -OCH\textsubscript{3}), 1.55 (s, 3H, -C(CH\textsubscript{3})\textsubscript{2}), 1.50 (s, 3H, -C(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 133.8 (C-7), 133.2 (C-5), 128.3 (C-6), 119.7 (C-8), 114.6 (-C(CH\textsubscript{3})\textsubscript{2}), 96.0 (-OCH\textsubscript{2}O-), 80.7 (C-3), 75.4 (C-2), 70.1 (C-4), 65.8 (C-1), 56.1 (-OCH\textsubscript{3}), 26.8 (-C(CH\textsubscript{3})\textsubscript{2}), 26.6 (-C(CH\textsubscript{3})\textsubscript{2}); FTIR 2998, 2951, 2885, 1646, 1421, 1381, 1296, 1228, 1195, 1152, 1102, 1067, 1048, 1019, 984, 964, 947, 912, 881, 847, 810, 775, 679 cm\textsuperscript{-1}; HRMS (ESI) \textit{m/z} calc for C\textsubscript{13}H\textsubscript{20}N\textsubscript{3}O\textsubscript{4}: 282.1454; found 282.1441 [M+H]\textsuperscript{+}. \textbf{Crystal Structure}.}
**1,5-Dideoxy-1,5-[1,2,3]-triazole-1-(S)-ethenyl-1,5-imino-ᴅ-glucitol**

Compound 45 (26 mg, 0.09 mmol) was dissolved in aqueous HCl (5 mL) and stirred at rt overnight. The solvent was removed under diminished pressure to give 46 was obtained as a pale yellow foam (18 mg, quantitative yield). \([\alpha]_D^+23.6 (c \ 3.9, D_2O); \ ^1H\ NMR (500 MHz, CD_3OD) \delta 8.39 (s, 1H, H-6), 5.92 (ddd, \(J = 17.0, 10.1, 8.3\ Hz, 1H, H-7), 5.54 (d, \(J = 17.0\ Hz, 1H, H-8), 5.50 (d, \(J = 10.0\ Hz, 1H, H-8'), 4.83 (t, \(J = 8.3\ Hz, 1H, H-1), 4.71 (d, \(J = 7.9\ Hz, 1H, H-4), 3.82 (dd, \(J = 9.3, 8.4\ Hz, 1H, H-2), 3.75 (dd, \(J = 9.3, 7.9\ Hz, 1H, H-3); \ ^{13}C\ NMR (126 MHz, CD_3OD) \delta 141.4 (C-5), 131.4 (C-7), 127.4 (C-6), 122.6 (C-8), 74.2 (C-3), 70.8 (C-2), 67.7 (C-1), 65.9 (C-4); FTIR 3266, 2451, 1914, 1679, 1578, 1422, 1378, 1306, 1276, 1209, 1088, 1060, 1009, 933, 835, 794, 673 cm^{-1}; HRMS (ESI) \textit{m/z} \textit{calc for C}_{8}H_{12}N_{3}O_{3}: 198.0879; \textit{found 198.0878 [M+H]^+}.\)
1,5-Dideoxy-3,4-O-isopropylidene-2-O-methoxymethyl-1,5-[1,2,3]-triazole-1-(S)-ethanol-1,5-imino-α-glucitol 47

Compound 45 (13.3 mg, 0.047 mmol) was dissolved in THF/H₂O (2:1, 4 mL). OsO₄ (15 μl, cat. 2.5% in tBuOH) and N-methylmorpholine N-oxide (11 mg, 0.095 mmol) were charged. The mixture was diluted with H₂O (5 mL) and extracted with Et₂O (3 x 5 mL). The combined org layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo. The diol (7 mg, 0.021 mmol) was dissolved in CH₂Cl₂/H₂O (1:1, 4 mL) and cooled to 0 °C. NaIO₄ (6 mg, 0.028 mmol) was added, the reaction was raised to rt. The reaction was diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄ and concentrated in vacuo. The aldehyde (5 mg, 0.018 mmol) was dissolved in EtOH (3 mL). NaBH₄ (1 mg, 0.021 mmol) was charged and the reaction was stirred at rt for 12 h. The solution was removed under diminished pressure. The residue was re-dissolved in EtOAc (5 mL), washed with H₂O (5 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude alcohol was purified using flash column chromatography to give 47 (1.1 mg, 9% over 3 steps) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 1H, H-6), 4.99 (d, J = 6.9 Hz, 1H, -OCH₂O-), 4.66 (d, J = 6.8 Hz, 1H, -OCH₂O-), 4.56 (d, J = 9.2 Hz, 1H, H-4), 4.53 – 4.46 (m, 2H, H-1, H-2), 4.37 (dd, J = 11.8, 1,8 Hz, 1H, H-7), 4.01 (m, 1H, H-7'), 3.75 (dd, J = 9.9, 9.1 Hz, 1H, H-3), 3.41 (s, 3H, -OCH₃), 1.49 (s, 3H, -C(CH₃)₂), 1.43 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 127.8 (C-6), 95.5 (-OCH₂O-), 79.5 (C-3), 71.2 (C-2), 69.1 (C-4), 64.4 (C-1), 61.6 (C-7), 55.2 (-OCH₃), 25.8 (-C(CH₃)₂), 25.6 (-C(CH₃)₂).
Experimental

Chapter 6

1,5-Dideoxy-3,4-O-isopropylidene-2-O-methoxymethyl-1,5-[1,2,3]-triazole-1-(S)-ethanol-1,5-imino-β-glucitol 47 Compound 45 (42.3 mg, mmol) was dissolved in a mixture of acetone/H$_2$O (95/5, 0.15 M) and cooled to 0 °C. A solution of Sudan Red 7B in acetone was added to the reaction. O$_2$/O$_3$ (generated via a MP-8000 Corona Discharge Ozone generator) was bubbled through the solution confirmed by colour change from red to clear. The mixture was sparged with O$_2$ for 2 min. The solution was diluted with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined org layers were washed with brine (5 mL), dried over Na$_2$SO$_4$ and concentrated to give a yellow oil. The crude aldehyde was diluted in EtOH (10 mL) and cooled to 0 °C. NaBH$_4$ (excess) was added slowly and the reaction was stirred for 1 h. The reaction was quenched by addition of HCl, diluted with H$_2$O (mL) and extracted with EtOAc (3 x mL). The combined org layers were washed with 10 % NH$_4$Cl solution; dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give 47 (23.9 mg, 56% over 2 steps) as a pale yellow solid.\textsuperscript{166} (TLC 1:1 EtOAc:Hexane, R$_f$ 0.3); [α]$_D$ -88.6 (c 0.53, CHCl$_3$); \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 (s, 1H, H-6), 5.04 (d, J = 6.8 Hz, 1H, -OCH$_2$O-), 4.73 (d, J = 6.8 Hz, 1H, -OCH$_2$O-), 4.65 (d, J = 9.2 Hz, 1H, H-4), 4.61 (dd, J = 9.8, 6.4 Hz, 1H, H-2), 4.56 (apt d, J = 6.2 Hz, 1H, H-1), 4.48 (dd, J = 11.9, 4.3 Hz, 1H, H-7), 4.08 (m, 1H, H-7'), 3.83 (t, J = 6.0 Hz, 1H, -OH), 3.78 (t, J = 9.5 Hz, 1H, H-3), 3.47 (s, 3H, -OCH$_3$), 1.55 (s, 3H, -C(CH$_3$)$_2$), 1.48 (s, 3H, -C(CH$_3$)$_2$); \textsuperscript{13}C NMR (126 MHz, CDCl$_3$) δ 134.5 (C-5), 127.7 (C-6), 114.5 (-C(CH$_3$)$_2$), 96.5 (-OCH$_2$O-), 80.5 (C-3), 72.2 (C-1), 70.0 (C-4), 65.8 (C-2), 62.4 (C-7), 56.1 (-OCH$_3$), 26.9 (-C(CH$_3$)$_2$), 26.6 (-C(CH$_3$)$_2$); FTIR 3327, 2991, 2934, 2883, 1471, 1438, 1383, 1375, 1314, 1233, 1194, 1158, 1103, 1090, 1039, 1023, 962, 918, 882, 822, 782, 732, 699, 662 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{12}$H$_{20}$N$_3$O$_4$: 286.1403; found 286.1414 [M+H]$^+$. 

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1,5-Dideoxy-1,5-[1,2,3]-triazole-1-(S)-ethanol-1,5-imino-β-glucitol 48

Compound 47 (20 mg, 0.07 mmol) was dissolved in aqueous HCl in MeOH (5 mL) and stirred at rt overnight. The solvent was removed and the unprotected product 48 was obtained as a white foam (14 mg, quantitative yield). [α]D +129.8 (c 0.81, D2O); 1H NMR (500 MHz, D2O) δ 7.78 (s, 1H, H-6), 4.66 (apt s, 1H, H-4, overlapping signals), 4.43 (dd, J = 12.7, 2.5 Hz, 1H, H-7), 4.28 (dt, J = 9.3, 1.9 Hz, 1H, H-1), 4.07 (dd, J = 12.7, 2.1 Hz, 1H, H-7'), 3.95 (dd, J = 10.1, 9.3 Hz, 1H, H-2), 3.69 (dd, J = 10.1, 8.9 Hz, 1H, H-3); 13C NMR (126 MHz, D2O) δ 138.7 (C-5), 131.2 (C-6), 74.2 (C-3), 66.8 (C-2), 65.7 (C-4), 63.4 (C-1), 57.8 (C-7); FTIR 3221, 3136, 2923, 1571, 1455, 1371, 1328, 1307, 1267, 1201, 1123, 1085, 1066, 1016, 986, 974, 904, 851, 822, 779 682 cm⁻¹; HRMS (ESI) m/z calc for C7H12N3O4: 202.0828; found 202.0823 [M+H]+.
Experimental Data for Chapter 3

Methyl 6-deoxy-6-iodo-α-D-glucopyranoside 49 Methyl α-D-glucopyranoside (3.0 g, 9.87 mmol) was dissolved in THF (30 ml). Triphenyl phosphine (3.2 g, 12.14 mmol) and imidazole (2.42 g, 35.53 mmol) were added and the mixture was heated to 60 °C. Iodine (3.08 g, 12.14 mmol) in a solution of THF was added portionwise and the colour changed from brown to yellow. The reaction mixture was heated to reflux for 2 h. The reaction was cooled to rt and the salts filtered. The solvent was removed under diminished pressure and the residue was purified by flash column chromatography (CH$_2$Cl$_2$ followed by 1:9 MeOH:CH$_2$Cl$_2$) to give 49 (3.3 g, 79%). All analytical data corresponded well to the literature.$^{169}$ (1:9 MeOH:CH$_2$Cl$_2$, R$_f$ 0.2); [α]$_D$ +83.6 ($c$ 1.2, MeOH); $^1$H NMR (500 MHz, CD$_3$OD) δ 4.66 (d, $J$ = 3.7 Hz, 1H, H-1), 3.63 (d, $J$ = 9.3 Hz, 1H, H-3), 3.59 (dd, $J$ = 10.5, 2.2 Hz, 1H, H-6), 3.44 (s, 3H, OCH$_3$), 3.41 (dd, $J$ = 9.7, 3.8 Hz, 1H, H-2), 3.37 (ddd, $J$ = 9.5, 7.7, 2.1 Hz, 1H, H-5), 3.27 (dd, $J$ = 10.5, 7.5 Hz, 1H, H-6'), 3.13 (t, $J$ = 9.14 Hz, 1H, H-4); $^{13}$C NMR (126 MHz, CD$_3$OD) δ 101.9 (C-1), 76.0 (C-4), 75.0 (C-3), 73.7 (C-2), 72.7 (C-5), 57.9 (-OCH$_3$), 9.2 (C-6); FTIR 3114, 2838, 1985, 1578, 1527, 1415, 1327, 1256, 1188, 1144, 1085, 1039, 934, 828, 748, 657 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_7$H$_{13}$O$_5$I$^+$Na: 326.9700, found: 326.9711 [M+Na]$^+$.
Methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside 50a

Compound 49 (3.0 g, 9.87 mmol) and benzyl trichloroacetimidate (10.7 ml, 0.06 mol) were dissolved in 1,4-dioxane (40 ml). Trifluoromethanesulfonic acid was added dropwise until the soln was strongly acidic (dark red). The soln was diluted with Et₂O (100 ml) and the org layer was washed with NaHCO₃ (50 ml), water (50 ml) and brine (50 ml), dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:10 EtOAc:Hexane) to provide 50a (4.1 g, 73%) as a white solid. All analytical data corresponded well to the literature.¹⁶⁹ [α]D +35 (c 2.9, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.26 (m, 15H, Ar H), 4.99 (d, J = 10.8 Hz, 1H, -OCH₂Ph), 4.93 (d, J = 11.0 Hz, 1H, -OCH₂Ph), 4.80 (d, J = 10.8 Hz, 1H, -OCH₂Ph), 4.79 (d, J = 12.1 Hz, 1H, -OCH₂Ph), 4.68 (d, J = 12.2 Hz, 1H, -OCH₂Ph), 4.65 (d, J = 12.3 Hz, 1H, -OCH₂Ph), 4.61 (d, J = 3.5 Hz, 1H, α-CH, H-1), 4.01 (t, J = 9.2, 1H, H-3), 3.53 (dd, J = 9.6, 3.6 Hz, 1H, H-2), 3.48 – 3.43 (m, 2H, H-5, H-6, overlapping signals), 3.41 (s, 3H, -OCH₃), 3.33 (t, J = 9.1 Hz, 1H, H-4), 3.28 (dd, J = 10.8, 6.5 Hz, 1H, H-6’); ¹³C NMR (126 MHz, CDCl₃) δ 138.5, 138.0, 138.0 (Ar C), 128.5 – 127.7 (Ar CH), 98.1 (C-1), 81.6 (C-3), 81.5 (C-4), 80.1 (C-2), 75.8, 75.4, 73.4 (-OCH₂Ph), 69.3 (C-5), 55.5 (-OCH₃), 7.7 (C-6); FTIR 3030, 2908, 1721, 1497, 1454, 1359, 1196, 1045, 1028, 950, 910, 734, 698 cm⁻¹; HRMS (ESI) m/z calc for C₂₈H₂₉O₅Na: 597.1114, found: 597.1095 [M+Na]⁺.
(2R,3S,4R)-2,3,4-Tri-O-benzyl-5,6-dideoxy-hex-5-en-1-ol 51a Compound 50a (0.7 g, 1.26 mmol) was dissolved in a mixture of THF/H₂O (9:1, 20 ml). Pre-activated Zn dust* (0.8 g, 12.6 mmol) was charged and the mixture was sonicated at 40 °C for 2–4 h. The mixture was filtered and washed with Et₂O (20 ml). The org layer was washed with H₂O (10 ml), sat aq NaHCO₃ (10 ml) and brine (10 ml), dried over Na₂SO₄ and concentrated in vacuo to give 51a (0.4 g, 77%) as a clear oil. The crude product was used immediately to prevent epimerization. [α]D +10.1 (c 3.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 9.65 (d, J = 1.0 Hz, 1H, H-1), 7.35 – 7.24 (m, 15H, Ar H), 5.83 (ddd, J = 17.1, 10.7, 7.7 Hz, 1H, H-5), 5.27 (m, 2H, H-6, H-6'), 4.72 (d, J = 11.7 Hz, 1H, -OCH₂Ph), 4.71 (d, J = 12 Hz, 1H, -OCH₂Ph), 4.59 – 4.48 (3 x d, J = 12 Hz, 3H, -OCH₂Ph), 4.36 (d, J = 11.5 Hz, 1H, -OCH₂Ph), 4.15 (dd, J = 7.5, 5.1 Hz, 1H, H-4), 3.88 (dd, J = 4.3, 1.0 Hz, 1H, H-2), 3.80 (t, J = 4.7 Hz, 1H, H-3); ¹³C NMR (126 MHz, CDCl₃) δ 201.6 (C-1), 137.8 – 137.2 (Ar C), 134.8 (C-5), 128.5 - 127.6 (Ar CH), 119.4 (C-6), 82.4, 81.7, 79.9 (CH), 74.5, 73.2, 70.9 (-OCH₂Ph); FTIR 3067, 3031, 2867, 1730, 1497, 1454, 1353, 1243, 1208, 1070, 1048, 1027, 933, 847, 733, 696 cm⁻¹; HRMS (ESI) m/z calc for C₂₇H₂₆O₄Na: 439.1885; found: 439.1903 [M+Na]⁺.

*Zn powder (8 g) was activated by stirring with 2M HCl (150 ml) for 10 min. The suspension was filtered and washed sequentially with H₂O (75 ml), MeOH (75 ml) and Et₂O (75 ml) and dried under vacuum.
(4S,5S,6R)-4,5,6-Tri-O-benzyl-3-hydroxy-octa-1,7-diene 52a Compound 51a (0.4 g, 0.96 mmol) was dissolved in THF (10 ml) under argon and cooled to -78 °C. Vinyl magnesium bromide (1.4 ml, 1.44 mmol, 1.0 M in THF) was added dropwise. The yellow solution was stirred at -78 °C. The mixture was quenched by the addition of H2O (5 ml) followed by 1.0 M HCl. The org layer was separated and washed with H2O (5 ml), brine (5 ml), and then dried with Na2SO4 and concentrated. Flash column chromatography of the residue (1:5 EtOAc:Hexane) gave 52a (0.2 g, 54%) as a mixture of syn- and anti-isomers (~1:1). (TLC 1:5 EtOAc:Hexane, Rf 0.25); 1H NMR (500 MHz, CDCl3): δ 7.32 – 7.28 (m, 5H, Ar H), 5.97 – 5.77 (m, 1H), 5.35 – 5.18 (m, 1H), 5.14 (dt, J = 10.56, 1.46 Hz, 1H), 4.84 (d, J = 11.1 Hz, 1H, -OCH2Ph), 4.74 – 4.60 (m, 4H, -OCH2Ph), 4.54 (d, J = 11.5 Hz, 1H, -OCH2Ph), 4.37 (dd, J = 15.6, 11.8 Hz, 2H), 4.20 – 4.17 (m, H), 4.10 (apt s, 1H), 4.06 (dd, J = 7.4, 3.6 Hz, 1H), 3.74 – 3.69 (m, 1H), 3.57 (dd, J = 4.9, 4.0 Hz, 1H), 3.13 (d, J = 7.0 Hz, 1H); 13C NMR (126 MHz, CDCl3) Major isomer δ 138.68 – 137.86 (Ar C), 135.39 (=CH), 135.32 (=CH), 128.49 - 127.68 (Ar CH), 119.02 (=CH2), 115.56 (=CH2), 82.13, 82.01, 80.02, 75.22, 75.04, 72.05, 70.52 (CH, CH2); Minor isomer δ 138.68 – 137.86 (Ar C), 135.39 (=CH), 135.32 (=CH), 128.49 - 127.68 (Ar CH), 119.20 (=CH2), 116.27 (=CH2), 81.76, 81.38, 80.21, 74.73, 72.71, 71.96, 70.73 (CH, CH2); FTIR 3467, 3065, 3031, 2871, 1724, 1497, 1454, 1349, 1207, 1063, 1027, 993, 928, 733, 696 cm⁻¹; HRMS (ESI) m/z calc for C29H32O4Na: 467.2198; found: 467.2188 [M+Na]⁺.
Experimental

Chapter 6

**Compound 51a** (1.2 g, 2.8 mmol) was dissolved in toluene (30 ml). (Carbethoxy methylene) triphenylphosphorane (1.3 g, 3.66 mmol) was charged and the reaction was heated to reflux for 12 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (Hexane followed by 1:6 EtOAc:Hexane) to give **53a** (1.2 g, 88%) as a clear oil. (TLC 1:4 EtOAc:Hexane, Rf 0.6); [α]D +4.5 (c 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.22 (m, 15H, Ar H), 6.91 (dd, J = 15.8, 6.3 Hz, 1H, H-2), 6.01 (dd, J = 15.8, 1.3 Hz, 1H, H-3), 5.82 (ddd, J = 18.0, 10.7, 7.5 Hz, 1H, H-7), 5.23 (apt d, J = 17.6 Hz, 1H, H-8), 5.22 (apt d, J = 10.5 Hz, 1H, H-8’), 4.72 (d, J = 11.5 Hz, 1H, -OCH₂Ph), 4.70 (d, J = 11.5 Hz, 1H, -OCH₂Ph), 4.56 (d, J = 12.0 Hz, 1H, -OCH₂Ph), 4.54 (d, J = 11.9 Hz, 1H, -OCH₂Ph), 4.33 (d, J = 11.6 Hz, 1H, -OCH₂Ph), 4.31 (d, J = 11.6 Hz, 1H, -OCH₂Ph), 4.21 (ddd, J = 6.5, 5.2, 1.4 Hz, 1H, H-4), 4.16 (qd, J = 7.2, 2.4 Hz, 2H, -OCH₂-), 4.00 (dd, J = 7.5, 5.1 Hz, 1H, H-6), 3.48 (t, J = 5.1 Hz, 1H, H-5), 1.26 (t, J = 7.2 Hz, 3H, -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 166.0 (C-1), 145.2 (C-2), 138.2 – 137.8 (Ar C), 135.3 (C-7), 128.3 – 128.2 (Ar CH), 123.3 (C-3), 118.9 (C-8), 83.5 (C-5), 80.8 (C-6), 79.1 (C-4), 75.3 (-OCH₂Ph), 71.8 (-OCH₂Ph), 70.7 (-OCH₂Ph), 60.4 (-OCH₂-), 14.3 (-CH₃); FTIR 3031, 2987, 2867, 1717, 1656, 1497, 1454, 1367, 1300, 1268, 1174, 1066, 1027, 984, 930, 733, 696 cm⁻¹; HRMS (ESI) m/z calc for C₃₁H₃₄O₅Na: 509.2304, found: 509.2286 [M+Na]^+. 

**Ethyl 4,5,6-tri-O-benzyl-2,3,7,8-tetra-deoxy-octa-2,7-dienoate (2E,4S,5S,6R)**
Compound 53a (1.15 g, 2.37 mmol) was dissolved in CH₂Cl₂ (30 ml) and cooled to -78 °C. DIBAL-H (7.1 ml, 7.1 mmol, 1.0 M in CH₂Cl₂) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H₂O (15 ml), dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:4 EtOAc:Hexane) gave 54a (0.8 g, 75%) as a clear oil.  

(2E,4S,5S,6R)-4,5,6-Tri-O-benzyl-2,3,7,8-tetraeoxo-octa-2,7-dien-1-ol  

54a  

Compound 54a (0.8 g, 75%) as a clear oil.  

(1:4 EtOAc:Hexane, Rf 0.2); [α]D +7.0 (c 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.25 (m, 15H, Ar H), 5.80 (ddd, J = 17.4, 10.3, 7.4, 1H, H-7), 5.70 (dt, J = 15.7, 5.2 Hz, 1H, H-3), 5.56 (dd, J = 15.7, 7.6 Hz, 1H, H-2), 5.25 – 5.22 (m, 2H, H-8, H-8′, overlapping signals), 4.78 (d, J = 11.6 Hz, 1H, -OCH₂Ph), 4.74 (d, J = 11.6 Hz, 1H, -OCH₂Ph), 4.60 (d, J = 11.7 Hz, 1H, -OCH₂Ph), 4.55 (d, J = 11.7 Hz, 1H, -OCH₂Ph), 4.35 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.32 (d, J = 11.8 Hz, 1H, -OCH₂Ph), 4.09 – 3.98 (m, 2H, H-4, H-6), 3.97 (d, J = 5.0 Hz, 2H, H-8, H-8′), 3.41 (t, J = 5.2 Hz, 1H, H-5'); ¹³C NMR (126 MHz, CDCl₃) δ 137.7, 137.4, 137.4 (Ar C), 134.6 (C-7), 132.0 (C-3), 127.7 (C-2), 127.7 – 126.4 (Ar CH), 117.6 (C-8), 83.1 (C-5), 80.0 (C-4), 79.0 (C-6), 74.2, 69.8, 69.5 (-OCH₂Ph), 61.8 (C-1); FTIR 3403, 3063, 3030, 2868, 1720, 1703, 1497, 1454, 1391, 1346, 1272, 1207, 1087, 1060, 1027, 999, 930, 820, 733, 696 cm⁻¹; HRMS (ESI) m/z calc for C₂⁹H₃₁O₄Na: 467.2198, Found: 467.2185 [M+Na]⁺.
(2E,4S,5S,6R)-1-Azido-4,5,6-tri-O-benzyl-2,3,7,8-tetrahydroxy-octa-2,7-diene

Compound 54a (0.8 g, 1.68 mmol) was dissolved in THF (20 ml). Triphenylphosphine (0.8 g, 2.87 mmol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (0.6 ml, 2.87 mmol) and diphenylphosphoryl azide (0.6 ml, 2.87 mmol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 55a (0.5 g, 65%) as a pale yellow oil. (TLC 1:4 EtOAc:Hexane, Rf 0.75); [α]_D +2.3 (c 1.5, CHCl_3); ^1^H NMR (500 MHz, CDCl_3) δ 7.32 – 7.21 (m, 15H, Ar H), 5.83 (ddd, J = 17.8, 10.4, 7.7 Hz, 1H, H-7), 5.63 – 5.56 (m, 2H, H-2, H-3, overlapping signals), 5.25 – 5.21 (m, 2H, H-8, H-8’, overlapping signals), 4.76 (d, J = 11.9 Hz, 1H, -OCH_2Ph), 4.74 (d, J = 11.8 Hz, 1H, -OCH_2Ph), 4.59 (d, J = 11.8 Hz, 1H, -OCH_2Ph), 4.55 (d, J = 11.6 Hz, 1H, -OCH_2Ph), 4.32 (d, J = 11.6 Hz, 1H, -OCH_2Ph), 4.31 (d, J = 11.8 Hz, 1H, -OCH_2Ph), 4.08 – 4.06 (m, 1H, H-4), 4.02 (dd, J = 7.5, 5.1 Hz, 1H, H-6), 3.60 – 3.52 (m, 2H, H-1, H-1’), 3.40 (t, J = 5.2 Hz, 1H, H-5); ^13^C NMR (126 MHz, CDCl_3) δ 138.7, 138.4, 138.3 (Ar C), 135.7 (C-7), 133.1 (C-3), 128.6 – 127.7 (Ar CH), 126.7 (C-2), 118.9 (C-8), 84.4 (C-5), 80.8 (C-6), 80.0 (C-4), 75.5 (-OCH_2Ph), 71.1 (-OCH_2Ph), 70.5 (-OCH_2Ph), 52.3 (C-1); FTIR 2925, 2855, 2101 (-N_3), 1678, 1590, 1487, 1456, 1316, 1267, 1189, 1162, 1071, 1000, 918, 778, 753, 689 cm^{-1}; HRMS (ESI) m/z calc for C_{29}H_{31}O_{3}N_{3}Na: 492.2263, found: 492.2281 [M+Na]^+. 
Methyl 6-deoxy-6-iodo-2,3,4-tri-O-triethylsilyl-α-D-mannopyranoside 50c

Compound 49 (4.7 g, 0.02 mol) was suspended in CH$_2$Cl$_2$ (50 ml). Imidazole (6.3 g, 0.09 mol) and chlorotriethylsilane (15.6 ml, 0.09 mol) were charged and the reaction was stirred at rt overnight. The reaction was diluted with H$_2$O (20 ml) and stirred for 15 min. The layers were separated and the org layer was washed with H$_2$O (20 ml), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (Hexane followed by 1:30 EtOAc:Hexane) to give 50c as a clear oil (7.3 g, 70%). All analytical data corresponded well to literature data.$^{169}$ (1:20 EtOAc:Hexane, R$_f$ 0.8); [α]$^D$ +58.9 ($c$ 1.8, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 4.65 (d, $J = 3.7$ Hz, 1H, H-1), 3.80 (dd, $J = 8.9$, 8.2 Hz, 1H, H-3), 3.55 (dd, $J = 10.4$, 2.5 Hz, 1H, H-6), 3.49 (dd, $J = 9.0$, 3.4 Hz, 1H, H-2), 3.45 (dt, $J = 8.6$, 2.7, 1H, H-5), 3.41 (s, 3H, -OCH$_3$), 3.24 (dd, $J = 9.1$, 8.0 Hz, 1H, H-4), 3.15 (dd, $J = 10.2$, 8.3 Hz, 1H, H-6’), 1.00 – 0.95 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.73 – 0.58 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 99.9 (C-1), 76.7 (C-4), 75.0 (C-3), 74.4 (C-2), 71.3 (C-5), 55.1 (C-6), 8.1 (C-5), 7.2 – 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.6 – 5.2 (Si(CH$_2$CH$_3$)$_3$); FTIR 2954, 2912, 2877, 1458, 1413, 1377, 1238, 1198, 1145, 1085, 1054, 1003, 956, 907, 853, 831, 794, 721, 679 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{25}$H$_{55}$IO$_5$Si$_3$Na: 669.2300, found: 669.2283 [M+Na]$^+$. 

$^{169}$
(4R,5S,6R)-5,6-Dideoxy-2,3,4-tri-O-triethylsilyl-hex-5-en-1-al 51a Compound 50c (20.0 g, 0.03 mol) was dissolved in a mixture of THF/H$_2$O (9:1, 100 ml). Pre-activated Zn dust (20.2 g, 0.03 mol) was charged and the mixture was sonicated at 40 °C for 2-4 h. The mixture was filtered and washed with Et$_2$O (100 ml). The org layer was washed with H$_2$O (30 ml), sat aq NaHCO$_3$ (30 ml) and brine (30 ml), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 51c (12.9 g, 85%) as a clear oil. The crude product was used immediately to prevent epimerization. [α]$_D$ +2.3 (c 6.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.61 (d, $J$ = 0.9 Hz, 1H, H-1), 5.93 (ddd, $J$ = 17.4, 10.4, 7.0 Hz, 1H, H-5), 5.13 (dt, $J$ = 17.4, 1.5 Hz, 1H, H-6), 5.07 (dt, $J$ = 10.4, 1.4 Hz, 1H, H-6'), 3.86 (dd, $J$ = 6.1, 0.9 Hz, 1H, H-2), 3.74 (dd, $J$ = 6.1, 2.9 Hz, 1H, H-3), 0.92 – 0.83 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.58 – 0.48 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 199.6 (C-1), 138.6 (C-5), 115.8 (C-6), 78.7 (C-3), 78.3 (C-2), 73.7 (C-4), 6.8 – 6.7 (CH$_3$, -Si(CH$_2$CH$_3$)$_3$), 5.0 – 4.8 (CH$_2$, -Si(CH$_2$CH$_3$)$_3$); FTIR 2954, 2911, 2877, 1736, 1458, 1414, 1378, 1238, 1136, 1071, 1003, 970, 920, 897, 866, 800, 725 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{24}$H$_{53}$O$_4$Si$_3$: 489.3252; found: 489.3241 [M+H]$^+$.
(2E,4S,5S,6R) Ethyl 2,3,7,8-tetradeoxy-4,5,6-tri-O-triethylsilyl-octa-2,7-dienoate 53c Compound 51c (12.5 g, 0.03 mol) was dissolved in toluene (100 ml). (Carbethoxy methylene) triphenylphosphorane (13.4 g, 0.04 mol) was charged and the reaction was heated to reflux for 8 h. The solvent was removed under diminished pressure. The residue was purified by column chromatography (1:20 EtOAc:Hexane) to give 53c (12.6 g, 88%) as a clear oil. (TLC 1:20 EtOAc:Hexane, Rf 0.65); [α]D +24.1 (c 0.89, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.16 (dd, J = 15.7, 4.5 Hz, 1H, H-3), 6.01 (ddd, J = 16.8, 10.4, 5.7 Hz, 1H, H-7), 5.93 (dd, J = 15.6, 2.4 Hz, 1H, H-2), 5.22 (dt, J = 17.2, 1.9 Hz, 1H, H-8), 5.10 (dt, J = 11.0, 1.7 Hz, 1H, H-8'), 4.26 (ddd, J = 6.2, 4.7, 1.7 Hz, 1H, H-4), 4.24 – 4.14 (m, 3H, H-6, -OCH2, overlapping signals), 3.52 (dd, J = 6.2, 4.3 Hz, 1H, H-5), 1.29 (t, J = 7.1 Hz, 3H, -CH3), 1.03 – 0.87 (m, 27H, -Si(CH2CH3)3), 0.74 – 0.49 (m, 18H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 166.8 (C-1), 149.1 (C-3), 138.3 (C-7), 119.5 (C-2), 114.7 (C-8), 78.9 (C-5), 74.2 (C-6), 73.2 (C-4), 60.1 (-OCH2), 14.3 (-CH3), 6.9 – 6.8 (CH3, -Si(CH2CH3)3), 5.1 – 4.9 (CH2, -Si(CH2CH3)3); FTIR 2954, 2912, 2877, 1724, 1489, 1415, 1266, 1238, 1125, 1081 1003, 973, 918, 886, 798, 723 cm-1; HRMS (ESI) m/z calc for C28H58O5Si3H: 559.3670; found: 559.3603 [M+H]+.
Compound 53c (12.0 g, 0.021 mol) was dissolved in CH$_2$Cl$_2$ (100 ml) and cooled to -78 °C. DIBAL-H (0.06 ml, 0.06 mol, 3.0 M in CH$_2$Cl$_2$) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and brought to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H$_2$O (40 ml), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (Hexane followed by 1:30 EtOAc:Hexane) to give 53c (8.9 g, 80%) as a clear oil. (TLC 1:20 EtOAc:Hexane, R$_f$ 0.2); [$\alpha$]$_D$ +18.9 (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.01 (ddt, $J$ = 17.4, 10.3, 6.5 Hz, 1H, H-7), 5.85 (td, $J$ = 15.4, 6.2 Hz, 1H, H-3), 5.74 (dt, $J$ = 15.6, 5.7 Hz, 1H, H-2), 5.17 (dd, $J$ = 17.2, 9.5 Hz, 1H, H-8), 5.04 (dd, $J$ = 18.7, 10.5 Hz, 1H, H-8’), 4.21 – 4.11 (m, 4H, H-4, H-6, H-1, H-1’), overlapping signals), 3.45 (dt, $J$ = 13.3, 5.3 Hz, 1H, H-5), 0.99 – 0.92 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.65 – 0.55 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.6 (C-7), 132.8 (C-3), 128.8 (C-2), 114.4 (C-8), 79.1 (C-5), 74.8 (C-6), 74.0 (C-4), 63.5 (C-1), 7.0 – 6.8 (CH$_3$, -Si(CH$_2$CH$_3$)$_3$), 5.2 – 5.0 (CH$_2$, -Si(CH$_2$CH$_3$)$_3$); FTIR 3352, 2954, 2912, 2877, 1549, 1415, 1238, 1079, 1003, 971 919, 879, 721 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{26}$H$_{56}$O$_4$Si$_3$Na: 539.3384; found: 539.3367 [M+Na]$^+$. 

(2E,4S,5S,6R)-2,3,7,8-Tetradexoxy-4,5,6-tri-O-triethylsilyl-octa-2,7-dien-1-ol
Compound 54c (8.0 g, 0.015 mol) was dissolved in THF (80 ml). Triphenyl phosphine (6.9 g, 0.026 mol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (5.2 ml, 0.026 mol) and diphenylphosphoryl azide (5.7 ml, 0.026 mol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure and the residue was purified by flash column chromatography (Hexane followed by 1:20 EtOAc:Hexane) to give 55c (5.6 g, 67%) as a pale yellow oil. (TLC 1:20 EtOAc:Hexane, Rf 0.85); [α]D +13.6 (c 0.5, CHCl3); 1H NMR (500 MHz, CDCl3) δ 6.04 – 5.95 (m, 2H, H-3, H-7, overlapping signals), 5.66 (dt, J = 14.0, 6.0 Hz, 1H, H-2), 5.19 (d, J = 17.2 Hz, 1H, H-8), 5.07 (d, J = 10.5 Hz, 1H, H-8'), 4.20 – 4.12 (m, 2H, H-4, H-6, overlapping signals), 3.75 (d, J = 6.5 Hz, 2H, H-1, H-1'), 3.45 (t, J = 5.4 Hz, 1H, H-5), 0.99 – 0.91 (m, 27H, -Si(CH2CH3)3), 0.65 – 0.49 (m, 18H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 138.5 (C-7), 136.4 (C-3), 122.5 (C-2), 114.4 (C-8), 79.0 (C-5), 74.7, 73.6 (C-4, C-6), 52.7 (C-1), 7.0 – 6.8 (CH3, -Si(CH2CH3)3), 5.2 – 5.0 (CH2, -Si(CH2CH3)3); FTIR 2954, 2912, 2877, 2097 (-N3), 1458, 1414, 1378, 1238, 1120, 1070, 1004, 974, 923, 834, 776, 723 cm⁻¹; HRMS (ESI) m/z calc for C26H56O3N3Si3: 542.3630, found: 542.3645 [M+H]^+. 

(2E,4S,5S,6R)-1-Azido-2,3,7,8-tetrae oxy-4,5,6-tri-O-triethylsilyl-octa-2,7-diene 55c
Experimental

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(4S,5S,6R)-1-Azido-2,3,7,8-tetradeoxy-4,5,6-hydroxy-octa-2,7-diene  56

Compound 55c (5.6 g, 0.01 mol) was dissolved in THF (60 ml). TBAF (0.03 ml, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The solution was stirred with CaCO$_3$, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated. The residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give 56 (1.6 g, 76%), a mixture of cis- and trans-isomers as a clear oil.$^{177}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.87 (ddd, $J = 16.9, 10.5, 6.1$ Hz, 1H, H-7), 5.81 (m, 2H, H-2, H-3, overlapping signals), 5.32 (dt, $J = 17.2, 1.3$ Hz, 1H, H-8), 5.21 (dt, $J = 10.5, 1.3$ Hz, 1H, H-8'), 4.25 (t, $J = 3.6$ Hz, 1H, H-4), 4.20 (ddt, $J = 5.7, 4.1, 1.4$ Hz, 1H, H-6), 3.79 – 3.73 (m, 2H, H-1, H-1', overlapping signals), 3.38 (t, $J = 4.1$ Hz, 1H, H-5), 2.93 (s, -OH); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 137.2 (C-7), 134.2 (C-3), 126.0 (C-2), 117.5 (C-8), 75.8 (C-5), 73.5 (C-6), 72.4 (C-4), 52.1 (C-1);

$^1$H NMR (500 MHz, D$_2$O) $\delta$ 5.88 – 5.80 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.26 (dt, $J = 17.3, 1.4$ Hz, 1H, H-8), 5.19 (dt, $J = 10.5, 1.4$ Hz, 1H, H-8'), 4.21 – 4.19 (m, 1H, H-4), 4.16 – 4.13 (m, 1H, H-6), 3.81 – 3.74 (m, 2H, H-1, H-1'), 3.41 (t, $J = 5.1$ Hz, 1H, H-5); $^{13}$C NMR (126 MHz, D$_2$O) $\delta$ 136.9 (C-2), 133.7 (C-3), 126.5 (C-7, 117.2 (C-8), 76.0 (C-5), 72.7 (C-6), 71.8 (C-4), 51.7 (C-1); FTIR 3329, 2920, 2851, 2101 (-N$_3$), 1644, 1504, 1408, 1345, 1253, 1056, 991, 930, 868 cm$^{-1}$; HRMS (ESI) m/z calc for C$_8$H$_{12}$N$_3$O$_3$: 198.0879, found: 198.0881 [M-H].
Compound 56 (48 mg, 0.24 mmol) was dissolved in Py/\text{Ac}_2\text{O} (2/1, 3 ml) and stirred for 6 h at rt. Upon completion (TLC 1:2 EtOAc:Hexane, R_f 0.3) the mixture was concentrated. The crude product was purified by flash column chromatography (1:4 to 1:2 EtOAc:Hexane) to give 57 as a clear oil (34 g, 44%).

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.79 (dt, \(J = 15.1, 5.6\) Hz, 1H, H-2), 5.73 (ddd, \(J = 17.0, 10.5, 6.3\) Hz, 1H, H-7), 5.67 (dd, \(J = 15.5, 6.5\) Hz, 1H, H-3), 5.45 (dt, \(J = 12.1, 5.8\) Hz, 2H, H-4, H-6, overlapping signals), 5.32 (d, \(J = 11.6\) Hz, 1H, H-8), 5.29 (d, \(J = 5.0\) Hz, 1H, H-8’), 5.22 (t, \(J = Hz\), 1H, H-5) 3.83 – 3.75 (m, 2H, H-1, H-1’), 2.10 (s, 6H, 2 x -CH\textsubscript{3}), 2.09 (s, 3H, -CH\textsubscript{3}); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 170.0, 169.6, 169.6 (C=O), 131.6 (C-7), 128.8 (C-2), 128.0 (C-3), 119.8 (C-8), 73.2 (C-5), 72.6, 71.6 (C-4, C-6), 51.7 (C-1), 20.9, 20.6 (3 x -CH\textsubscript{3}); HRMS (ESI) m/z calc for C\textsubscript{14}H\textsubscript{19}O\textsubscript{6}N\textsubscript{3}Na: 348.1172, found: 348.1183 [M+Na]\textsuperscript{+}.

**Note:** Excess Ac\textsubscript{2}O gave the per-acetylated compound (acetylated amine).
**Experimental**

(4S,5S,6R)-1-Azido-6-hydroxy-4,5-O-isopropylidene-2,3,7,8-tetraol-oxy-2,7-diene 58 Compound 56 (0.7 g, 3.46 mmol) was dissolved in dry acetone (10 ml, over 4Å sieves). H₂SO₄ (34 µl, cat.) were charged and the reaction stirred at rt for 12 h. The reaction was neutralised with aq NaHCO₃ and the acetone was removed under diminished pressure. The residue was re-dissolved in CH₂Cl₂ (20 ml) and washed with H₂O (10 ml), dried over Na₂SO₄ and concentrated in vacuo. The crude oil was purified by flash column chromatography (1:4 EtOAc:Hexane) to give 58 (0.7 g, 78%) as a mixture of cis- and trans-isomers (~0.8:1). (TLC 1:1 EtOAc:Hexane, Rₖ 0.7) ¹H NMR (500 MHz, CDCl₃) δ 5.84 – 5.68 (m, 6H, H-2a,b, H-3a,b, H-7a,b, overlapping signals), 5.34 – 5.30 (m, 2H, H-8a, H-8b, overlapping signals), 5.21 (dt, J = 10.3, 1.1 Hz, 1H, H-8’a), 5.18 (dt, J = 10.5, 1.4 Hz, 1H, H-8’b), 4.35 (t, J = 7.5 Hz, 1H, H-4a), 4.29 (dd, J = 8.2, 7.3 Hz, 1H, H-4b), 4.09 (t, J = 4.8 Hz, 1H, H-6a), 4.05 (t, J = 5.1 Hz, 1H, H-6b), 3.78 – 3.70 (m, 4H, H-1a,b, H-1’a,b, overlapping signals), 3.66 (dd, J = 8.1, 4.0 Hz, 1H, H-5a), 3.64 (d, J = 8.1, 4.0 Hz, 1H, H-5b), 2.47 (s, 1H, -OH), 2.38 (s, 1H, -OH), 1.38 (s, 3H, -C(CH₃)₂), 1.37 (s, 3H, -C(CH₃)₂), 1.37 (s, 3H, -C(CH₃)₂), 1.37 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) Major Isomer δ 135.08 (C-7), 133.77, 125.79 (C-2, C-3), 119.56 (C-8), 109.68 (-C(CH₃)₂), 83.04 (C-5), 78.93 (C-4), 70.28 (C-6), 52.07 (C-1), 27.08 (-C(CH₃)₂), 26.93 (-C(CH₃)₂); Minor Isomer δ 136.96 (C-7), 131.97, 127.87 (C-2, C-3), 117.12 (C-8), 109.75 (-C(CH₃)₂), 83.25 (C-5), 77.52 (C-4), 71.46 (C-6), 51.89 (C-1), 27.05 (-C(CH₃)₂), 26.92 (-C(CH₃)₂); FTIR 3450, 2988, 2919, 2100 (-N₃), 1719, 1662, 1456, 1372, 1216, 1165, 1054, 974, 929, 871, 819, 742, 701 cm⁻¹; HRMS (ESI) m/z calc for C₁₁H₁₆O₃N₃: 238.1197, found: 238.1163 [M-H]⁻.
(2E,4S,5S,6R)-6-O-Acetyl-1-azido-4,5-O-isopropylidene-2,3,7,8-tetradeoxy-octa-2,7-diene 59 Compound 58 (129 mg, 0.54 mmol) was dissolved in dry pyridine (5 ml). Ac₂O (60 µl, 0.59 mmol) and DMAP (cat.) were added and the reaction was stirred at rt for 12 h. The solvent was removed under diminished pressure. The crude residue was purified by flash column chromatography (1:4 EtOAc:Hexane) to give 59, a mixture of cis- and trans-isomers (~1:1) as a clear oil (132 mg, 87%). (TLC 1:2 EtOAc:Hexane, Rₜ 0.8); ¹H NMR (500 MHz, CDCl₃) δ 5.82 – 5.67 (m, 6H, H-2a,b, H-3a,b, H-7a,b), 5.38 – 5.33 (m, 2H, H-6a, H-6b), 5.31 (dt, J = 17.3, 1.3, 1H, H-8a), 5.29 (dt, J = 17.2, 1.2, 1H, H-8b), 5.24 (dt, J = 10.6, 1.2 Hz, 1H, H-8a’), 5.20 (dt, J = 10.3, 1.2 Hz, 1H, H-8b’), 4.22 (t, J = 7.3 Hz, 1H, H-5a), 4.16 (dd, J = 8.1, 7.0, Hz, 1H, H-5b), 3.79 (m, 2H, H-4a, H-4b, overlapping signals), 3.74 – 3.73 (m, 4H, H-1a,b, H-1a,b’), 2.05 (s, 3H, -OCH₃), 2.04 (s, 3H, -OCH₃), 1.36 (s, 12H, 2 x -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) Major Isomer δ 169.75 (C=O), 135.03, 128.92, 128.30 (C-2, C-3, C-7), 119.18 (C-8), 109.76 (-C(CH₃)₂), 81.08, 78.52, 71.90 (C-4, C-5, C-6), 51.84 (C-1), 27.00 (-C(CH₃)₂), 26.62 (-C(CH₃)₂), 20.98 (-OCH₃); Minor Isomer δ 169.80 (C=O), 132.37, 131.78, 127.61 (C-2, C-3, C-7), 119.19 (=CH₂), 109.82 (-C(CH₃)₂), 81.40, 77.18, 72.99 (C-4, C-5, C-6), 51.82 (C-1), 26.96 (-C(CH₃)₂), 26.62 (-C(CH₃)₂), 20.97 (-OCH₃); FTIR 2990, 2936, 2877, 2100 (-N₃), 1740, 1429, 1372, 1229, 1169, 1111, 1064, 1024, 975, 933, 867, 810 cm⁻¹; HRMS (ESI) m/z calc for C₂₆H₃₉O₈N₆: 563.2829, found: 563.2808 [2M+H]⁺.
1.5-Dideoxy-2,3-O-isopropylidene-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-D-glucitol 60 Compound 58 (741 mg, mmol) was dissolved in DMF (30 ml) and heated to 120 °C for 6 h. The reaction was cooled to rt and diluted with H₂O (20 mL). The aq layer was extracted with Et₂O until no product remained (as observed by TLC 1:1 EtOAc:Hexane, UV and stain, Rf 0.5). The combined org layers were dried over Na₂SO₄ and concentrate in vacuo. Flash column chromatography of the residue (gradient EtOAc:Hexane) to give 60 (143 mg, 15%) and 61 (267 mg, 36%). 

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \delta 6.24 - 6.18 (m, 1H, H-7), 5.45 - 5.41 (m, H-8, H-8', overlapping signals), 5.38 (dd, J = 6.4, 4.2, 2.1 Hz, 1H, H-1), 4.53 (dd, J = 16.1, 2.7 Hz, 1H, H-6), 4.02 (dd, J = 16.2, 9.8 Hz, 1H, H-6'), 3.98 (apt t, J = 7.9 Hz, 1H, H-2), 3.87 (dd, J = 10.3, 9.2 Hz, 1H, H-3), 3.74 (td, J = 10.3, 9.1 Hz, 1H, H-4), 1.42 (s, 3H, -C(CH₃)₂), 1.38 (s, 3H, -C(CH₃)₂); } \]

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3 \delta 131.0 (C-7), 118.4 (C-8), 111.6 (-C(CH₃)₂), 78.1 (C-3), 74.7 (C-4), 71.4 (C-2), 67.5 (C-6), 60.5 (C-1), 54.8 (C-5), 26.8 (-C(CH₃)₂), 26.6 (-C(CH₃)₂); LRMS (ESI) m/z calc for C₁₁H₂₀O₃N₃: 240.1348, found: 240.1354 [M+H]^+ \].

\[(2E,4S,5S,6S)-1-Azido-5-hydroxy-4,6-O-isopropylidene-octa-2,7-diene 61 \text{ } ^1H \text{NMR (500 MHz, CDCl}_3 \delta 5.97 - 5.85 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.38 (dt, J = 17.4, 1.5 Hz, 1H, H-8), 5.29 (dt, J = 10.7, 1.4 Hz, 1H, H-8'), 4.46 (dd, J = 4.2, 1.4 Hz, 1H, H-4), 4.42 (dd, J = 5.4, 1.4 Hz, 1H, H-6), 3.83 (apt d, J = 4.7 Hz, 2H, H-1, H-1'), 3.40 - 3.33 (m, 1H, H-5), 1.53 (s, 3H, -C(CH₃)₂), 1.51 (s, 3H, -C(CH₃)₂); } \]

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3 \delta 134.8 (C-7), 131.9, 126.1 (C-2, C-3), 117.4 (C-8), 99.6 (-C(CH₃)₂), 73.7 (C-6), 72.8 (C-4), 67.8 (C-5), 52.3 (C-1), 29.7 (-C(CH₃)₂), 19.1 (-C(CH₃)₂); LRMS (ESI) m/z calc for calc for C₁₁H₁₆O₃N₃: 238.1197, found: 238.8911 [M-H]^-. \]
Experimental

Chapter 6

Compound 58 (97.5 mg, 0.408 mmol) was dissolved in DMF (10 ml) and cooled to 0 °C. NaH (2.1 mg, 0.53 mmol) was added slowly and the mixture was stirred for 1 h at rt. The reaction was cooled again to 0 °C and benzyl bromide (60 μl, 0.53 mmol) was added slowly. The reaction was slowly allowed to reach rt and stirred for 16 h. The reaction was diluted with H₂O (10 ml) and extracted with EtOAc until no product remained in the aq layer (as observed by TLC). The combined org layers were dried over Na₂SO₄, and concentrated. The brown oil was purified by flash column chromatography (1:8 EtOAc:Hexane) to give 62 (110 mg, 82%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.27 – 7.19 (m, 5H, Ar H), 5.76 – 5.67 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.12 (t, J = 17.2, 1.0 Hz, 1H, H-8), 5.11 (dd, J = 10.3, 1.1 Hz, 1H, H-8’), 4.63 (d, J = 12.3 Hz, 1H, -OCH₂Ph), 4.38 (d, J = 12.4 Hz, 1H, -OCH₂Ph), 4.28 (dd, J = 8.0, 7.0 Hz, 1H, H-6), 3.87 – 3.81 (dd, J = 6.3, 4.8 Hz, 1H, H-4), 3.79 – 3.70 (m, 3H, H-1, H-1’, H-5, overlapping signals), 1.40 (s, 3H, -C(CH₃)₂), 1.32 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 137.9 (Ar C), 135.7 (C-7), 131.7 – 127.7 (Ar CH, C-2, C-3), 118.6 (C-8), 109.5 (-C(CH₃)₂), 82.6 (C-5), 78.4 (C-6), 77.4 (C-4), 70.4 (-OCH₂Ph), 52.2 (C-1), 27.0 (-C(CH₃)₂), 26.8 (-C(CH₃)₂);
4-O-Benzyl-1.5-dideoxy-2,3-O-isopropylidene-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-D-glucitol 63 Compound 62 (270 mg, 0.82 mmol) was dissolved in DMF (10 ml) and heated to 100 °C for 8 h. The reaction was cooled and diluted with H₂O (10 ml). The aq layer was extracted with EtOAc until no product remained in the aq layer (as observed by TLC 1:4 EtOAc:Hexane, Rₜ 0.45). The combined org layers were dried over Na₂SO₄, and concentrated. Purification by flash column chromatography (gradient EtOAc:Hexane) gave 63 (48 mg, 18%) and starting material (59 mg, 22%) as the two products.¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H, Ar H), 6.30 – 6.23 (m, 1H, H-7), 5.42 – 5.36 (m, 3H, H-8, H-8’, H-1, overlapping signals), 4.83 (d, J = 11.9 Hz, 1H, -OCH₂Ph), 4.71 (d, J = 11.9 Hz, 1H, -OCH₂Ph), 4.52 (apt d, J = 16.2 Hz, 1H, H-6), 4.01 (ddd, J = 16.2, 9.8, 1.6 Hz, 1H, H-6’), 3.72 (apt t, J = 8.6 Hz, 2H, H-2, H-5, overlapping signals), 3.62 – 3.58 (m, 1H, H-3), 2.86 – 2.82 (m, 1H, H-4), 1.41 (s, 3H, -C(CH₃)₂), 1.40 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 137.6 (s, Ar C), 131.8 (d, C-7), 128.5 – 127.7 (d, 5 x Ar CH), 117.4 (t, C-8), 111.3 (q, -C(CH₃)₂), 77.8 (d, C-2), 77.7 (d, C-3), 75.0 (d, C-4), 72.1 (t, -OCH₂Ph), 67.5 (t, C-6), 58.7 (d, C-1), 54.6 (d, C-5), 26.9 (q, -C(CH₃)₂), 26.7 (q, -C(CH₃)₂); FTIR 2987, 2871, 2098, 1455, 1371, 1215, 1030, 980, 929, 873, 735, 678 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₂₄N₃O₃: 330.1818, found 330.1810 [M+H]⁺.
**6-O-Acetyl-4-O-benzyl-1,5-dideoxy-2,3-O-isopropyldene-1-ethenyl-1,5-imino-ᴅ-glucitol 64**

Compound 63 (10 mg, 0.03 mmol) was dissolved in anhydrous DMF (3 ml). AcOH (1.7 μl, 0.03 mmol) was charged and the reaction was heated to 100 °C for 24 h. The reaction was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography to give 64 (2.8 mg, 25%) as a pale yellow oil. 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 – 7.21 (m, 5H, Ar H), 6.13 (ddd, $J = 17.5, 10.7, 4.5$ Hz, 1H, H-7), 5.26 (dt, $J = 17.6, 1.9$ Hz, 1H, H-8), 5.22 (dt, $J = 10.8, 2.0$ Hz, 1H, H-8'), 4.72 (d, $J = 12.1$ Hz, 1H, -OCH$_2$Ph), 4.61 (d, $J = 12.1$ Hz, 1H, -OCH$_2$Ph), 4.29 (dd, $J = 11.3, 2.9$ Hz, 1H, H-6), 3.96 (dd, $J = 11.3, 6.8$ Hz, 1H, H-6'), 3.85 – 3.82 (m, 1H, H-1), 3.71 (dd, $J = 10.2, 5.8$ Hz, 1H, H-2), 3.52 (dd, $J = 10.2, 8.8$ Hz, 1H, H-3), 3.18 (dd, $J = 9.7, 6.7, 2.9$ Hz, 1H, H-5), 3.09 (apt t, $J = 9.3, 1H, H-4$), 2.01 (s, 3H, -COCH$_3$), 1.50 (broad s, 1H, -NH), 1.36 (s, 3H, -C(CH$_3$)$_2$), 1.35 (s, 3H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.8 (C=O), 138.2 (Ar C), 134.3 (C-7), 128.3 – 127.7 (Ar CH), 116.4 (C-8), 110.4 (-C(CH$_3$)$_2$), 79.4 (C-3), 78.7 (C-2), 77.2 (C-4), 71.6 (-OCH$_2$Ph), 64.7 (C-6) 56.1 (C-1), 51.8 (C-5), 27.0 (-C(CH$_3$)$_2$), 26.7 (-C(CH$_3$)$_2$), 20.8 (-COCH$_3$); HRMS (ESI) m/z calc for C$_{20}$H$_{27}$NO$_5$H 362.1967, found 362.1979 [M+H]$^+$.
1,5-Dideoxy-2,3-O-isopropylidene-1-ethenyl-1,5-imino-D-glucitol

Compound 58 (33 mg, 0.01 mmol) was dissolved in HPLC grade DMF (30 ml) and heated to 85 °C for 3 days. The reaction was cooled to rt and diluted with H2O (10 ml). The aq layer was extracted with EtOAc until no product remained in the aq layer (as observed by TLC 1:1 EtOAc:Hexane, Rf 0.15). The combined org layers were dried over Na2SO4, and concentrated. Purification by flash column chromatography (1:1 EtOAc:Hexane) gave 65. 1H NMR (500 MHz, CDCl3) δ 5.77 (ddd, J = 17.6, 10.3, 7.5 Hz, 1H, H-7), 5.32 (dt, J = 17.2, 1.2 Hz, 1H, H-8), 5.27 – 5.24 (m, 1H, H-8’), 4.44 (ddd, J = 11.4, 2.9, 1.0 Hz, 1H, H-6), 4.07 (ddd, J = 11.4, 7.2, 0.9 Hz, 1H, H-6’), 3.47 – 3.40 (m, 2H, H-2, H-4, overlapping signals), 3.19 (dd, J = 9.5, 8.4 Hz, 1H, H-3), 3.08 (ddd, J = 9.8, 7.2, 2.9 Hz, 1H, H-5), 3.01 (apt t, J = 7.8 Hz, 1H, H-1), 1.39 (s, 3H, -C(CH3)2), 1.37 (s, 3H, -C(CH3)2); 13C NMR (126 MHz, CDCl3) δ 136.1 (C-7), 119.4 (C-8), 111.4 (-C(CH3)2), 82.8 (C-4), 75.8 (C-3), 72.9 (C-2), 64.5 (C-6), 64.0 (C-1), 56.1 (C-5), 26.8 (-C(CH3)2), 26.6 (-C(CH3)2); HRMS (ESI) m/z cale for C11H20NO4 230.1392, found 230.1389 [M+H]+.
1,5-Dideoxy-1-ethyl-1,5-imino-D-glucitol 66 The crude sugar 65 (10 mg, 0.087 mmol) was dissolved in aq AcOH (80%, 5 ml) and stirred at rt overnight. The solvent was removed under diminished pressure and the residue was purified by ion exchange chromatography (DOWEX 50WX8, washed with MeOH, H₂O and NH₄OH) to give 66 (2 mg, 24%) as a clear oil. ¹H NMR (500 MHz, D₂O) δ 5.68 (ddd, J = 17.0, 10.5, 8.3 Hz, 1H, H-7), 5.45 (d, J = 10.3 Hz, 1H, H-8), 5.43 (d, J = 17.1 Hz, 1H, H-8’), 3.80 – 3.73 (m, 2H, H-6, H-6’), 3.55 – 3.48 (m, 2H, H-1, H-4, overlapping signals), 3.45 – 3.39 (m, 2H, H-2, H-3, overlapping signals), 3.09 (dt, J = 10.6, 3.9 Hz, 1H, H-5); ¹³C NMR (126 MHz, D₂O) δ 129.3 (C-7), 124.8 (C-8), 75.8, 70.6 (C-2, C-3), 67.6 (C-4), 61.2 (C-1), 59.5 (C-5), 57.7 (C-6); HRMS (ESI) m/z calc for C₈H₁₆NO₄ 190.1079, found 190.1036 [M+H]⁺.
(4S,5S,6R)-1-Azido-4,5-O-cyclohexane-6-hydroxy-octa-2,7-diene

Compound 58 (129 mg, 0.65 mmol) was dissolved in dioxane (10 ml). Cyclohexanone (0.13 ml, 0.06 mmol) and H$_2$SO$_4$ (cat.) were added, and the reaction was stirred at rt for 10 h. The reaction was diluted with CH$_2$Cl$_2$ (20 ml), washed with H$_2$O (5 ml), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:Hexane) to give 67 (132 mg, 73%), a mixture of isomers as a clear oil. (TLC 1:1 EtOAc:Hexane, R$_f$ 0.8); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.84 – 5.674 (m, 6H, H-2a,b, H-3a,b, H-6a,b, overlapping signals), 5.34 – 5.29 (m, 2H, H-8a,b), 5.25 – 5.09 (m, 1H, H-8’a,b), 4.34 (apt t, $J = 7.7$ Hz, 1H, H-4a), 4.29 (apt t, $J = 7.7$ Hz, 1H, H-4b), 4.08 – 4.02 (m, 2H, H-6a,b, overlapping signals), 3.77 – 3.73 (m, 4H, H-1a,b, H-1’a,b, overlapping signals), 3.64 (ddd, $J = 10.8, 8.0, 4.2$ Hz, 2H, H-5a,b), 1.58 – 1.55 (m, 20H, cyclohexane); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 137.0 – 125.7 (C-2, C-3, C-7), 119.25, 117.13 (C-8), 110.33, 110.25 (C), 82.9, 82.6 (C-5), 78.6, 77.2 (C-4), 71.8, 70.5 (C-6), 52.1, 51.9 (C-1), 36.6 – 23.7 (ring CH).
2,3-O-cyclohexane-1,5-dideoxy-4-hydroxy-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-ᴅ-glucitol 68 Compound 67 (127 mg, 0.45 mmol) was heated in DMF (10 ml) to 100 °C. The reaction was cooled to rt and diluted with H₂O (10 mL). The aq layer was extracted with Et₂O until no more product remained (as observed by TLC 1:1 EtOAc:Hexane, Rf 0.45, UV and stain). The residue was purified by flash column chromatography (gradient EtOAc:Hexane) to give 68 (3.4 mg, 3%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.14 (ddd, J = 17.0, 10.8, 4.5 Hz, 1H, H-7), 5.37 − 5.32 (m, 2H, H-8, H-8’, overlapping signals), 5.31 (td, J = 4.5, 2.3 Hz, 1H, H-1), 4.48 (dd, J = 16.2, 2.6 Hz, 1H, H-6), 3.96 (dd, J = 16.3, 9.8 Hz, 1H, H-6’), 3.89 (dd, J = 10.4, 6.5 Hz, 1H, H-2), 3.67 (td, J = 10.1, 2.6 Hz, 1H, H-5), 3.41 (dd, J = 10.3, 9.1 Hz, 1H, H-3), 2.79 (dd, J = 10.4, 9.2 Hz, 1H, H-4), 1.55 − 1.52 (s, 20H, cyclohexane); ¹³C NMR (126 MHz, CDCl₃) δ 131.0 (C-7), 118.2 (C-8), 110.2 (C), 77.7 (C-3), 74.4 (C-4), 71.4 (C-2), 67.6 (C-6), 60.4 (C-1), 54.9 (C-5), 36.2 − 23.6 (ring CH).
(2E,4S,5S,6R)-4,5,6-tri-O-triethylsilyl-octa-2,7-dien-1-al 69  

Dess-Martin periodinane (4.7 g, 11.16 mmol, prepared in situ) was dissolved in CH$_2$Cl$_2$ (0.35 M) and cooled to 0 °C. Compound 54c (3.8 g, 7.43 mmol) was added to the reaction. The mixture was warmed to rt and stirred for 1 h. The mixture was warmed to rt and stirred for 1 h. The mixture was diluted with Et$_2$O (50 ml) and stirred with a solution of Na$_2$S$_2$O$_3$ (100 g/L) containing NaHCO$_3$ (100 g/L) until clear. The org layer was separated and washed with H$_2$O (20 ml) and brine (20 ml), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 69 (3.18 g, 83%) as a clear oil. (TLC 1:20 EtOAc:Hexane, R$_f$ 0.60); [α]$_D$ +20.3 (c 3.7, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.56 (dd, $J = 8.1, 1.2$ Hz, 1H, H-1), 7.17 (dd, $J = 15.6, 3.9$ Hz, 1H, H-3), 6.23 (dd, $J = 15.6, 8.2$ Hz, 1H, H-2), 6.00 (ddd, $J = 16.9, 10.4, 6.0$ Hz, 1H, H-7), 5.21 (d, $J = 17.3$ Hz, 1H, H-8), 5.12 (d, $J = 10.5$ Hz, 1H, H-8'), 4.35 – 4.33 (m, 1H, H-4), 4.25 – 4.24 (m, 1H, H-6), 3.57 (dd, $J = 6.4, 3.6$ Hz, 1H, H-5), 0.99 – 0.88 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.65 – 0.57 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 194.1 (C-1), 159.1 (C-3), 138.3 (C-7), 129.7 (C-2), 115.0 (C-8), 79.0 (C-5), 73.9 (C-6), 73.5 (C-4), 6.9, 6.8, 6.7 (CH$_3$, -Si(CH$_2$CH$_3$)$_3$), 5.1, 4.9, 4.9 (CH$_2$, -Si(CH$_2$CH$_3$)$_3$); FTIR 2955, 2912, 2878, 1694, 1459, 1415, 1379, 1238, 1106, 1003, 972, 921, 880, 845, 795 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{26}$H$_{54}$O$_3$Si$_3$Na: 537.3228, found: 537.3253 [M+Na]$^+$. 

![Chemical Structure](image)
Experimental

(4S,5S,6R)-1-C-methyl-4,5,6-tri-O-triethylsilyl-octa-2,7-dien-1-ol

Compound 69 (3.2 g, 6.18 mmol) was dissolved in THF (150 ml) and cooled to 0 °C. MeMgCl (3.1 ml, 9.27 mmol, 3.0 M in THF) was charged dropwise. The mixture was warmed to rt and stirred for 12 h. The reaction was quenched with aq NH₄Cl, extracted with EtOAc (3 x 30 ml), dried over Na₂SO₄ and concentrated in vacuo. After flash column chromatography (100 % Hexane to 1:20 EtOAc:Hexane) 70 (2.26 g, 69%) was isolated as a clear oil observed as a mixture of syn- and anti-isomers (~1:1). (TLC 1:20 EtOAc:Hexane, Rf 0.4); ⁱH NMR (500 MHz, CDCl₃) δ 6.01 (ddd, J = 17.2, 10.5, 5.7 Hz, 1H, H-7), 5.78 (dddd, J = 15.6, 6.7, 3.3, 1.0 Hz, 1H, H-3), 5.62 (dddd, J = 15.7, 9.5, 6.5, 1.1 Hz, 1H, H-2), 5.17 (dt, J = 17.3, 1.8 Hz, 1H, H-8), 5.06 (ddt, J = 10.5, 3.3, 1.7 Hz, 1H, H-8'), 4.32 – 4.26 (m, 1H, H-1), 4.19 – 4.16 (m, 1H, H-6), 4.12 (t, J = 6.1 Hz, 1H, H-4), 3.45 (td, J = 5.2, 2.7 Hz, 1H, H-5), 1.26 (d, J = 6.3 Hz, 3H, -CH₃), 0.99 – 0.92 (q, 27H, -Si(CH₂CH₃)₃), (t, 18H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) Major Isomer δ 138.4 (C-7), 134.0 (C-2), 131.0 (C-3), 114.4 (C-8), 79.1 (C-5), 74.9 (C-6), 74.1 (C-4), 68.7 (C-1), 22.8 (-CH₃), 7.0 – 6.8 (CH₃, -Si(CH₂CH₃)₃), 5.2 – 5.0 (CH₂, -Si(CH₂CH₃)₃); Minor Isomer δ 138.5 (C-7), 134.0 (C-2), 130.9 (C-3), 114.3 (C-8), 79.1 (C-5), 74.9 (C-6), 74.1 (C-4), 68.6 (C-1), 22.9 (-CH₃), 7.0 – 6.9 (CH₃, -Si(CH₂CH₃)₃), 5.2 – 5.0 (CH₂, -Si(CH₂CH₃)₃); FTIR 3385, 2954, 2912, 2877, 1459, 1415, 1378, 1238, 1120, 1088, 1004, 972, 920, 883, 859, 804, 723 cm⁻¹; HRMS (ESI) m/z calc for C₂₇H₅₅O₄Si₃: 529.3565, found: 529.3580 [M-H]⁻.
(4S,5S,6R)-1-Azido-1-C-methyl-4,5,6-tri-O-triethyldisilyl-octa-2,7-diene 71

Compound 70 (2.2 g, 4.14 mmol) was dissolved in THF (100 ml). Triphenylphosphine (1.9 g, 7.05 mmol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (1.4 ml, 7.05 mmol) and diphenylphosphoryl azide (1.5 ml, 7.05 mmol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure and the residue was purified by flash column chromatography (1:20 EtOAc:Hexane) to give 71 (1.5 g, 68%) as a pale yellow oil. The mixture was observed by NMR as a mixture of cis- and trans-allylic azides (~1:1). (TLC 1:20 EtOAc:Hexane, Rf 0.5); 1H NMR (500 MHz, CDCl3) δ 6.00 (ddt, J = 17.2, 10.6, 5.4 Hz, 1H, H-7), 5.90 (dddd, J = 15.6, 9.9, 5.9, 1.1 Hz, 1H, H-3), 5.57 (ddd, J = 15.5, 7.4, 1.4 Hz, 1H, H-2), 5.21 – 5.16 (m, 1H, H-8), 5.06 (dddd, J = 10.5, 3.4, 2.1, 1.4 Hz, 1H, H-8'), 4.20 – 4.15 (m, 2H, H-4, H-6, overlapping signals), 3.98 (p, J = 6.7 Hz, 1H, H-1), 3.45 (td, J = 5.3, 1.9 Hz, 1H, H-5), 1.27 (dd, J = 6.8, 1.8 Hz, 3H, -CH3) 0.99 – 0.93 (m, 27H, -Si(CH2CH3)3), 0.65 – 0.55 (m, 18H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) Major Isomer δ 138.46 (C-7), 133.69 (C-3), 128.82 (C-2), 114.32 (C-8), 79.05 (C-5), 74.82 (C-6), 73.86 (C-4), 59.20 (C-1), 19.92 (-CH3), 6.96 – 6.86 (CH3, -Si(CH2CH3)3), 5.19 – 5.03 (CH2, -Si(CH2CH3)3); Minor Isomer δ 138.38 (C-7), 133.84 (C-3), 128.56 (C-2), 114.36 (C-8), 79.03 (C-5), 74.80 (C-6), 73.57 (C-4), 59.26 (C-1), 19.95 (-CH3), 6.96 – 6.86 (CH3, -Si(CH2CH3)3), 5.19 – 5.03 (CH2, -Si(CH2CH3)3); FTIR 2955, 2912, 2877, 2101 (-N3), 1459, 1414, 1377, 1238, 1124, 1088, 1003, 971, 923, 880, 847, 796, 725 cm⁻¹; HRMS (ESI) m/z calc for C27H58O3Si3N3: 556.3786, found: 555.3762 [M+H]+.
Compound 71 (1.5 g, 2.77 mmol) was dissolved in THF (50 ml). TBAF (16.6 ml, 16.63 mmol, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The solution was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give 72 (0.42 g, 70%), a clear oil as a mixture of isomers. (TLC 1:1 EtOAc:Hexane Rf 0.15); ¹H NMR (500 MHz, CDCl₃) δ 5.98 – 5.76 (m, C-2, C-3, C-7), 5.42 – 5.28 (m, C-8, C-8’), 4.32 – 3.41 (m, 6H, C-4, C-5, C-6), 1.82 (dd, J = 6.6, 1.7 Hz, 1H, H-1a), 1.79 (dd, J = 6.6, 1.7 Hz, 1H, H-1b), 1.31 – 1.30 (s, -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 137.2 – 124.4 (C-2, C-3, C-7), 118.0 – 117.5 (C-8), 75.7 – 58.6 (C-4, C-5, C-6), 19.9 – 19.8 (-CH₃), 17.9 – 17.9 (C-1); FTIR 3373, 2981, 2918, 2099 (-N₃), 1644, 1379, 1239, 1044, 992, 970, 926, 866, 738 cm⁻¹; HRMS (ESI) m/z calc for C₉H₁₄O₃N₃: 212.1035, found: 212.1037 [M+H]⁺.
Experimental

Chapter 6

(4S,5S,6R)-1-Azido-4,5-O-isopropylidene-1-C-methyl-6-hydroxy-octa-2,7-diene 71 Compound 70 (400 mg, 1.88 mmol) was dissolved in acetone (50 ml, dried over 4 Å molecular sieves). H₂SO₄ (cat.) was charged and the mixture was stirred at rt overnight. The reaction was neutralised with aq NaHCO₃ and the acetone was removed under diminished pressure. The crude residue was re-dissolved in CH₂Cl₂ (40 ml), washed with water (20 ml) and brine (20 ml), dried over Na₂SO₄ and concentrated in vacuo to give 71 (347 mg, 73%), a complex mixture of isomers as a clear oil. (TLC 1:1 EtOAc:Hexane, Rf 0.8); ¹H NMR (500 MHz, CDCl₃) δ 5.88 – 5.65 (m, =CH), 5.39 – 5.21 (m, =CH₂), 4.39 – 3.28 (m, -CH), 1.44 – 1.39 (m, -C(CH₃)₂), 1.28 – 1.24 (m, -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 137.0 – 129.5 (=CH), 119.75 – 117.1 (=CH₂), 109.7 – 109.6 (-C(CH₃)₂), 83.4 – 58.2 (-CH), 27.0 – 26.9 (-C(CH₃)₂), 19.9 – 19.6 (-CH₃); FTIR 3447, 2987, 2940, 2888, 2103 (-N₃), 1646, 1454, 1373, 1237, 1216, 1168, 1120, 1057, 971, 928, 875, 817 cm⁻¹; HRMS (ESI) m/z calc for C₁₂H₂₀O₃N₃: 254.1505, found: 254.1507 [M+H]⁺.
Experimental Data for Chapter 4

Methyl 6-deoxy-6-iodo-α-d-mannopyranoside 74

Methyl α-d-mannopyranoside (10.0 g, 0.051 mol) was dissolved in THF (100 mL). Triphenyl phosphine (20.3 g, 0.077 mol) and imidazole (7.0 g, 0.103 mol) were added and the mixture was heated to approx. 60 °C. Iodine (19.6 g, 0.077 mol) in THF was added portionwise and the colour changed from brown to yellow. The reaction was stirred while heating at reflux for 4 h. The salts were then filtered and solvent was removed under diminished pressure. Flash column chromatography of the residue (CH₂Cl₂ followed by 1:9 MeOH:CH₂Cl₂, Rf 0.15) gave 74 (11.7 g, 75%) as a white solid. All analytical data provided below for 74 corresponded well to literature data. \[ \alpha \]D +19.0 (c 7.9, D₂O); \(^1\)H NMR (500 MHz, D₂O) \( \delta 4.53 \) (d, \( J = 1.7 \) Hz, 1H, H-1), 3.74 (dd, \( J = 3.5, 1.7 \) Hz, 1H, H-2), 3.58 (dd, \( J = 9.6, 3.5 \) Hz, 1H, H-3), 3.43 – 3.35 (m, 2H, H-4, H-6, overlapping signals), 3.27 – 3.23 (m, 1H, H-5), 3.22 (s, 3H, -OCH₃), 3.15 (dd, \( J = 11.0, 7.2 \) Hz, 1H, H-6); \(^1^3\)C NMR (126 MHz, D₂O) \( \delta 101.0 \) (C-1), 71.4 (C-5), 70.6 (C-4), 70.1 (C-3), 69.8 (C-2), 55.0 (-OCH₃), 6.5 (C-6); FTIR 3113, 2976, 2937, 1988, 1576, 1525, 1412, 1327, 1256, 1187, 1130, 1085, 1041, 962, 917, 748, 657 cm\(^{-1}\); LRMS (ESI) \( m/z \) calc for C₇H₁₇O₅IN: 322.0146, Found: 322.1298 [M+NH₄]⁺.
Methyl 6-deoxy-6-iodo-2,3,4-tri-O-triethylsilyl-α-D-mannopyranoside 75

Compound 74 (16.0 g, 0.053 mol) was suspended in CH₂Cl₂ (200 mL). Imidazole (21.5 g, 0.317 mol) and chlorotriethylsilane (53.0 mL, 0.317 mol) were charged and the reaction was stirred at rt overnight. The reaction was diluted with H₂O (100 mL) and stirred for 15 min. The layers were separated and the org layer was washed with H₂O (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the crude residue (Hexane followed by 1:20 EtOAc:Hexane, Rf 0.6) gave 75 as a clear oil (23.8 g, 70%). All analytical data provided below for 75 corresponded well to literature data.¹⁶⁹ [α]D +35.4 (c 0.81, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.51 (apt s, 1H, H-1), 3.83 – 3.78 (m, 3H, H-2, H-3, H-4), 3.56 (dd, J = 10.0, 3.5 Hz, 1H, H-6), 3.41 (s, 3H, -OCH₃), 3.32 – 3.25 (m, 2H, H-5, H-6'), 1.00 – 0.94 (m, 27H, -Si(CH₂CH₃)₃), 0.69 – 0.59 (m, 18H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 101.7 (C-1), 73.6 – 72.5 (CH, C-2, C-3, C-4, C-5), 55.2 (-OCH₃), 8.3 (C-6), 7.1 – 6.8 (-Si(CH₂CH₃)₃), 5.2 – 5.1 (-Si(CH₂CH₃)₃); FTIR 2954, 2911, 2877, 1459, 1413, 1378, 1238, 1135, 1102, 1062, 1003, 967, 919, 880, 837, 803, 782, 721 cm⁻¹; HRMS (ESI) m/z calc for C₂₇H₅₈O₅Si₃INa: 710.2565, Found: 710.2569 [M+ACN+Na]⁺.

Note: Although sample was purified numerous times and determined to be clean by TLC, MS and NMR, resolution of signals by NMR was always poor.
Compound 75 (3.1 g, 4.81 mmol) was dissolved in a mixture of THF/H$_2$O (9:1, 50 mL). Pre-activated Zn dust* (3.2 g, 48.1 mmol) was charged and the mixture was sonicated at 40 °C for 2 - 4 h. The mixture was filtered and washed with Et$_2$O (50 mL). The org layer was washed with H$_2$O (30 mL), sat aq NaHCO$_3$ (30 mL) and brine (30 mL), dried over Na$_2$SO$_4$ and concentrated to give 76 (1.97 g, 84%) as a clear oil. The crude product was used immediately to prevent epimerization. [α]$_D$ +33.4 (c 3.4, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.52 (d, $J = 1.3$ Hz, 1H, H-1), 5.97 (ddd, $J = 17.0$, 10.4, 6.3 Hz, 1H, H-5), 5.23 (dt, $J = 17.4$, 1.6 Hz, 1H, H-6), 5.14 (dt, $J = 10.5$, 1.5 Hz, 1H, H-6'), 5.14 (tt, $J = 6.3$, 1.4 Hz, 1H, H-4), 4.13 (t, $J = 1.4$ Hz, 1H, H-2), 3.93 (dd, $J = 6.2$, 1.5 Hz, 1H, H-3), 1.00 – 0.90 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.66 – 0.53 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.4 (C-1), 137.9 (C-5), 116.2 (C-6), 79.9 (C-3), 79.2 (C-2), 75.0 (C-4), 6.8 – 6.7 (-Si(CH$_2$CH$_3$)$_3$), 4.8 – 4.7 (-Si(CH$_2$CH$_3$)$_3$); FTIR 2955, 2912, 2878, 1734, 1459, 1414, 1379, 1239, 1135, 1110, 1079, 1003, 974, 924, 813, 725 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{24}$H$_{52}$O$_4$Si$_3$Na: 511.3071, Found: 511.3095 [M+Na]$^+$. 

(2S,3S,4R)-5,6-Dideoxy-2,3,4-tri-O-triethysilyl-hex-5-en-1-al 76
(2E,2R,3S,4R) Ethyl 2,3,7,8-tetradeoxy-4,5,6-tri-O-triethylsilyl-octa-2,7-dienoate 77 Compound 76 (2.4 g, 0.049 mol) was dissolved in toluene (50 mL). (Carbethoxy methylene) triphenylphosphorane (2.5 g, 0.073 mol) was charged and the reaction was heated to reflux for 12 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (Hexane followed by 1:40 EtOAc:Hexane, Rf 0.5) gave 77 (2.2 g, 80%) as a clear oil. [α]D +40.8 (c 0.31, CHCl3); 1H NMR (500 MHz, CDCl3) δ 6.98 (dd, J = 15.6, 5.1 Hz, 1H, H-3), 5.97 – 5.88 (m, 2H, H-2, H-7, overlapping signals), 5.25 (dt, J = 17.4, 1.8 Hz, 1H, H-8), 5.14 (dt, J = 10.6, 1.8 Hz, 1H, H-8'), 4.48 (dt, J = 5.1, 1.6 Hz, 1H, H-4), 4.18 (q, J = 7.1 Hz, 2H, -OCH2), 4.13 (q, J = 5.4, 4.7 Hz, 1H, H-6), 3.80 – 3.78 (m, 1H, H-5), 1.27 (t, J = 7.1 Hz, 3H, -CH3), 1.00 – 0.91 (m, 27H, -Si(CH2CH3)3), 0.63 – 0.57 (m, 18H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 166.7 (C-1), 148.8 (C-3), 137.8 (C-2), 121.2 (C-7), 115.3 (C-8), 80.8 (C-5), 74.9 (C-6), 72.0 (C-4), 60.0 (-OCH2), 4.2 (-CH3), 6.83 – 6.82 (-Si(CH2CH3)3), 4.9 – 4.8 (-Si(CH2CH3)3); FTIR 2955, 2912, 2878, 1724, 1660, 1459, 1414, 1367, 1262, 1239, 1113, 1064, 1004, 975, 923, 856, 798, 723 cm⁻¹; HRMS (ESI) m/z calc for C28H58O5Si3Na: 581.3490, Found: 581.3477 [M+Na]⁺.
Compound 77 (2.2 g, 3.87 mmol) was dissolved in CH$_2$Cl$_2$ (70 mL) and cooled to -78 °C. DIBAL-H (12 mL, 11.61 mmol, 1.0 M in CH$_2$Cl$_2$) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H$_2$O (40 mL), dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (1:20 EtOAc:Hexane, R$_f$ 0.2) to give 78 (1.4 g, 73%) as a clear oil. [$\alpha$]$_D$ +22.9 (c 0.87, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.88 (ddd, $J$ = 17.3, 10.5, 5.8 Hz, 1H, H-7), 5.78 – 5.66 (m, 2H, H-2, H-3, overlapping signals), 5.17 (dt, $J$ = 17.3, 1.8 Hz, 1H, H-8), 5.07 (dt, $J$ = 10.5, 1.7 Hz, 1H, H-8’), 4.30 (dd, $J$ = 6.3, 1.3 Hz, 1H, H-4), 4.10 (t, $J$ = 5.8 Hz, 2H, H-1, H-1’), 4.05 (tt, $J$ = 6.0, 1.4 Hz, 1H, H-6), 3.73 (dd, $J$ = 6.1, 1.8 Hz, 1H, H-5), 1.06 – 0.84 (m, 27H, -Si(CH$_2$CH$_3$)$_3$), 0.71 – 0.42 (m, 18H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.5 (C-7), 132.2 (C-3), 130.5 (C-2), 115.0 (C-8), 80.4 (C-5), 75.2 (C-6), 72.6 (C-4), 63.6 (C-1), 6.9 – 6.9 (-Si(CH$_2$CH$_3$)$_3$), 5.2 – 4.3 (-Si(CH$_2$CH$_3$)$_3$); FTIR 3326 (-OH), 2954, 2912, 2877, 1458, 1414, 1379, 1238, 1120, 1083, 1050, 1003, 972, 921, 835, 788, 719, 672 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{26}$H$_{55}$O$_4$Si$_3$: 515.3408, Found: 515.3430 [M-H].
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(2E,4R,5S,6R)-1-Azido-2,3,7,8-tetradeoxygen-4,5,6-tri-O-triethylsilylocta-2,7-diene 79 Compound 78 (1.4 g, 2.77 mmol) was dissolved in THF (40 mL). Triphenyl phosphine (1.24 g, 4.71 mmol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (0.9 mL, 4.71 mmol) and diphenylphosphoryl azide (1.0 mL, 4.71 mmol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was evaporated and the residue was purified by flash column chromatography (1:20 EtOAc:Hexane, Rf 0.8) to give 79 (1.2 g, 77%) as a pale yellow oil. [α]D +23.5 (c 1.2, CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.92 – 5.81 (m, 2H, H-3, H-7, overlapping signals), 5.59 (dtd, J = 15.5, 6.6, 1.1 Hz, 1H, H-2), 5.19 (dt, J = 17.3, 1.8 Hz, 1H, H-8), 5.09 (dt, J = 10.5, 1.8 Hz, 1H, H-8”), 4.33 (apt d, J = 6.6 Hz, 1H, H-4), 4.06 (tt, J = 5.9, 1.6 Hz, 1H, H-6), 3.74 (dd, J = 6.2, 1.7 Hz, 1H, H-5), 3.73 – 3.68 (m, 2H, H-1, H-1’, overlapping signals), 0.98 – 0.93 (m, 27H, -Si(CH2CH3)3), 0.65 – 0.56 (m, 18H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 138.2 (C-7), 135.7 (C-3), 124.5 (C-2), 115.1 (C-8), 80.4 (C-5), 75.2 (C-6), 72.3 (C-4), 52.7 (C-1), 6.9 – 6.8 (-Si(CH2CH3)3), 5.0 – 4.9 (-Si(CH2CH3)3); FTIR 2955, 2912, 2877, 2097 (-N3), 1458, 1414, 1379, 1237, 1119, 1081, 1051, 1004, 971, 921, 884, 860, 834, 788, 725 cm⁻¹; HRMS (ESI) m/z calc for C26H55O3N3Si3Na: 564.3449, Found: 564.3439 [M+Na]⁺.
Compound 79 (1.1 g, 1.98 mmol) was dissolved in THF (30 mL). TBAF (12 mL, 11.86 mmol, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The solution was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo. Flash column chromatography of the residue (1:1 EtOAc:Hexane, Rᵣ 0.15) gave 80 (0.28 g, 72%), a mixture of isomers (cis:trans, ~1:1) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 5.95 – 5.87 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.38 (dt, J = 17.2, 1.4 Hz, 1H, H-8), 5.28 (dt, J = 10.5, 1.4 Hz, 1H, H-8’), 4.37 (t, J = 4.3 Hz, 1H, H-4), 4.34 (ddt, J = 5.9, 3.6, 1.3 Hz, 1H, H-6), 3.88 – 3.81 (m, 2H, H-1, H-1’), 3.56 (dd, J = 4.5, 3.7 Hz, 1H, H-5), 2.83 (s, -OH); ¹³C NMR (126 MHz, CDCl₃) δ 136.9 (C-7), 133.4 (C-3), 126.0 (C-2), 117.4 (C-8), 75.0 (C-5), 73.5 (C-4), 72.4 (C-6), 52.1 (C-1); FTIR 3387 (-OH), 3219, 2100 (-N₃), 1749, 1438, 1371, 1219, 1037, 980, 930 cm⁻¹; HRMS (ESI) m/z calc for C₈H₁₂O₃N₃: 198.0879, Found: 198.0886 [M-H]⁻.
(4R,5R,6R)-1-Azido-4-hydroxy-5,6-O-isopropylidene-2,3,7,8-tetraoxy-oct-2,7-diene

Compound 80 (0.7 g, 3.72 mmol) was dissolved in dry acetone (50 mL, dried over 4 Å sieves). H₂SO₄ (cat.) was charged and the reaction stirred at rt for 12 h. The reaction was neutralised with aq NaHCO₃ and evaporated to remove the acetone. The residue was re-dissolved in CH₂Cl₂ (40 mL) and washed with H₂O (20 mL), dried over Na₂SO₄ and concentrated to give 81 (0.89 g, 78%) as a clear oil. (1:1 EtOAc:Hexane, Rf 0.8); [α]D -1.5 (c 2.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.87 – 5.67 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.33 (dt, J = 17.1, 1.3 Hz, 1H, H-8), 5.21 (dt, J = 10.3, 1.2 Hz, 1H, H-8'), 4.39 – 4.35 (m, 2H, H-4, H-6), 3.79 – 3.74 (m, 3H, H-5, H-1, H-1', overlapping signals), 2.59 (s, 1H, -OH), 1.41 (s, 3H, -C(CH₃)₂), 1.39 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 136.0 (C-7), 132.1, 125.7 (C-2, C-3), 118.7 (C-8), 109.3 (C, -C(CH₃)₂), 82.7 (C-5), 77.7 (C-6), 70.4 (C-4), 52.1 (t, C-1), 26.9 (CH₃, -C(CH₃)₂), 26.9 (CH₃, -C(CH₃)₂); FTIR 3460, 2988, 2937, 2887, 2099 (-N₃), 1645, 1457, 1373, 1216, 1168, 1121, 1055, 976, 910, 873, 814, 727 cm⁻¹; HRMS (ESI) m/z calc for C₈H₁₈O₃N₃: 240.1348, Found: 240.1349 [M+H]⁺.
(4R,5S,6R)-4-O-Acetyl-1-azido-5,6-O-isopropylidene-2,3,7,8-tetradeoxy-octa-2,7-diene 82 Compound 81 (50 mg, 0.21 mmol) was dissolved in pyridine (5 mL, excess). Ac₂O (20 μl, 0.23 mmol) and DMAP (2 mg, cat.) were charged and stirred at rt for 6 h. The reaction was removed under diminished pressure. Flash column chromatography of the residue (1:4 EtOAc:Hexane, Rᵢ 0.5) gave 82 (47 mg, 81%) as a pale yellow oil. [α]D -13.8 (c 0.78, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.85 – 5.78 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.42 (t, J = 5.0 Hz, 1H, H-4), 5.36 (apat d, J = 17.1 Hz, 1H, H-8), 5.27 (apat d, J = 10.2 Hz, 1H, H-8’), 4.25 (t, J = 7.8 Hz, 1H, H-6), 3.84 (dd, J = 8.3, 4.6 Hz, 1H, H-5), 3.81 – 3.80 (m, 2H, H-1, H-1’, overlapping signals), 2.07 (s, 3H, -OCH₃), 1.42 (s, 3H, -C(CH₃)₂), 1.40 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 169.7 (C-1), 135.1 (C-7), 128.7, 128.5 (C-2, C-3), 119.3 (C-8), 109.8 (C, -C(CH₃)₂), 81.1 (C-5), 79.4 (C-6), 72.4 (C-4), 51.9 (C-1), 27.0 (CH₃, -C(CH₃)₂), 26.7 (CH₃, -C(CH₃)₂), 21.0 (-OCH₃); FTIR 2989, 2931, 2857, 2101 (-N₃), 1743, 1713, 1431, 1372, 1223, 1172, 1065, 1021, 984, 934, 872, 811, 715 cm⁻¹; HRMS (ESI) m/z calc for C₂₆H₃₉O₈N₆: 563.2829, Found: 563.2857 [2M+H]⁺.
1.5-Dideoxy-3,4-\textit{O}-isopropylidene-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-\textit{a}-mannitol 83 Compound 81 (150 mg, 0.63 mmol) was dissolved in DMF (30 mL) and heated to 100 °C for 6 h. The mixture cooled to rt and diluted with H$_2$O (30 mL). The aq layer was extracted with Et$_2$O until no product remained in the aq layer (as observed by TLC, 1:1 EtOAc:Hexane, R$_f$ 0.5, visualised by UV and stain). The combined org layers were dried over Na$_2$SO$_3$ and concentrated. The crude residue was purified by flash column chromatography (1:4 to 1:2 EtOAc:Hexane) to give 83 (90.1 mg, 60%) as a clear oil. [\textalpha]$_D$ -64.8 (c 1.8, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.84 (ddd, $J = 17.2$, 10.6, 3.7 Hz, 1H, H-7), 5.35 (apt dd, $J = 17.2$, 1.5 Hz, 1H, H-8), 5.30 (apt dd, $J = 10.6$, 1.6 Hz, 1H, H-8’), 5.25 (dq, $J = 4.1$, 2.2 Hz, 1H, H-1), 4.54 (dd, $J = 16.1$, 2.7 Hz, 1H, H-6), 4.42 (apt s, 1H, H-2), 4.01 (dd, $J = 16.1$, 10.0 Hz, 1H, H-6’), 3.75 (td, $J = 9.7$, 2.7 Hz, 1H, H-5), 3.53 - 3.47 (m, 2H, H-3, H-4, overlapping signals), 2.84 (s, 1H, -OH), 1.39 (s, 3H, -C(CH$_3$)$_2$), 1.37 (s, 3H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 133.7 (C-7), 117.4 (C-8), 110.4 (C, -C(CH$_3$)$_2$), 77.1 (C-3), 70.2 (C-2), 69.1 (C-4), 67.6 (C-6), 63.3 (C-1), 56.3 (C-5), 26.8 (CH$_3$, -C(CH$_3$)$_2$), 26.6 (CH$_3$, -C(CH$_3$)$_2$); FTIR 3402, 2986, 2934, 1592, 1560, 1491, 1372, 1228, 1141, 1084, 1062, 1034, 924, 834, 778, 730, 715, 662 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{11}$H$_{18}$O$_3$N$_3$: 240.1348, Found: 240.1344 [M+H]$^+$.
**Experimental**

**Chapter 6**

6-\textit{O}-Acetyl-1,5-dideoxy-2,3-\textit{O}-isopropylidene-1-ethenyl-1,5-imino-\textit{d}-mannitol \textbf{84}

Compound \textbf{83} (80 mg, 0.209 mmol) was dissolved in DMF (10 mL) and heated to 100 °C. AcOH (60 μL, 1.04 mmol) was charged slowly. The reaction was cooled to rt and diluted with H₂O (30 mL). The aq layer was extracted with Et₂O until no product remained (as observed by TLC, EtOAc, R₉ 0.4). The combined org layers were dried over Na₂SO₃ and concentrated \textit{in vacuo}. Flash column chromatography of the residue (2:1 EtOAc:Hexane) gave \textbf{84} as a yellow oil (25 mg, 35 %). $^1$H NMR (500 MHz, CDCl₃) δ 5.79 (ddd, $J = 17.4$, 10.7, 4.1 Hz, 1H, H-7), 5.36 (ddd, $J = 17.4$, 2.3, 1.3 Hz, 1H, H-8’), 5.24 (ddd, $J = 10.7$, 2.5, 1.3 Hz, 1H, H-8’), 4.34 – 4.28 (m, 2H, H-2, H-6, overlapping signals), 4.15 (dd, $J = 11.5$, 5.7 Hz, 1H, H-6’), 3.78 (dq, $J = 4.4$, 2.3 Hz, 1H, H-1), 3.70 (t, $J = 9.7$ Hz, 1H, H-4), 3.49 (dd, $J = 9.3$, 2.3 Hz, 1H, H-3), 3.20 (ddd, $J = 10.2$, 5.8, 3.2 Hz, 1H, H-5), 2.09 (s, 3H, -COOCH₃), 1.42 (s, 3H, -C(CH₃)₂), 1.40 (s, 3H, -C(CH₃)₂); $^{13}$C NMR (126 MHz, CDCl₃) δ 170.8 (C=O), 135.3 (C-7), 116.8 (C-8), 109.3 (C, -C(CH₃)₂), 78.3 (C-3), 71.8 (C-4), 70.9 (C-2), 64.6 (C-6), 59.8 (C-1), 53.4 (C-5), 26.8, 26.6 (CH₃, -C(CH₃)₂), 20.8 (CH₃, -C(CH₃)₂);

HRMS (ESI) m/z calc for C$_{13}$H$_{22}$O$_{5}$N: 272.1498, Found: 272.1504 [M+H]$^+$;

HRMS (ESI) m/z calc for C$_{13}$H$_{20}$O$_{5}$N: 270.1341 Found: 270.1340 [M-H]$^-$.
6-O-Acetyl-1,5-dideoxy-2,3-O-isopropylidene-1-ethenyl-1,5-imino-d-mannitol 84 Compound 81 (220 mg, 0.92 mmol) was dissolved in toluene (20 mL) and heated to reflux for 6 h. The reaction was cooled to 50 °C. AcOH (0.3 mL, 4.6 mmol) was charged slowly, evolution of gas was observed along with a colour change of yellow to orange. After 5 min the reaction was complete by TLC and concentrated to remove the toluene. Flash column chromatography of the residue (2:1 EtOAc:Hexane) gave 84 as a yellow oil (8.7 mg, 35%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.79 (ddd, \(J = 17.4, 10.7, 4.1\) Hz, 1H, H-7), 5.36 (ddd, \(J = 17.4, 2.3, 1.3\) Hz, 1H, H-8’), 5.24 (ddd, \(J = 10.7, 2.5, 1.3\) Hz, 1H, H-8’), 4.34 – 4.28 (m, 2H, H-2, H-6, overlapping signals), 4.15 (dd, \(J = 11.5, 5.7\) Hz, 1H, H-6’), 3.78 (dq, \(J = 4.4, 2.3\) Hz, 1H, H-1), 3.70 (t, \(J = 9.7\) Hz, 1H, H-4), 3.49 (dd, \(J = 9.3, 2.3\) Hz, 1H, H-3), 3.20 (ddd, \(J = 10.2, 5.8, 3.2\) Hz, 1H, H-5), 2.09 (s, 3H, -COOCH\(_3\)), 1.42 (s, 3H, -C(CH\(_3\))\(_2\)), 1.40 (s, 3H, -C(CH\(_3\))\(_2\)); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.8 (C=O), 135.3 (C-7), 116.8 (C-8), 109.3 (C, -C(CH\(_3\))\(_2\)), 78.3 (C-3), 71.8 (C-4), 70.9 (C-2), 64.6 (C-6), 59.8 (C-1), 53.4 (C-5), 26.8, 26.6 (CH\(_3\), -C(CH\(_3\))\(_2\)), 20.8 (CH\(_3\), -C(CH\(_3\))\(_2\)); HRMS (ESI) \(m/z\) calc for C\(_{13}\)H\(_{22}\)O\(_5\)N: 272.1498, Found: 272.1504 [M+H]\(^+\); HRMS (ESI) \(m/z\) calc for C\(_{13}\)H\(_{20}\)O\(_5\)N: 270.1341 Found: 270.1340 [M-H].
**1,5-Dideoxy-1-ethenyl-1,5-imino-D-mannitol 85** Compound 84 (8.7 mg, 0.032 mmol) was dissolved in aq HCl (5 mL) and stirred at rt for 4 h. The solvent was evaporated and the residue was purified using ion-exchange chromatography (Dowex 50WX8 (200-400 mesh). The column was washed thoroughly with MeOH (25 mL) and water (25 mL) followed by 1 N NH₄OH (40 mL) to give the product 85 (4.3 mg, 70%) as a yellow foam. (1:9 MeOH:EtOH containing 1% NH₄OH, Rf 0.35) 

**1H NMR** (500 MHz, D₂O) δ 5.81 (ddd, J = 17.8, 10.6, 5.7 Hz, 1H, H-7), 5.23 (apt d, J = 11.8 Hz, IH, H-8), 5.23 (apt d, J = 16.6 Hz, 1H, H-8’), 3.92 (t, J = 2.6 Hz, 1H, H-2), 3.69 – 3.66 (m, 2H, H-6, H-6’, overlapping signals), 3.60 (dd, J = 5.5, 2.7 Hz, 1H, H-1), 3.58 – 3.57 (m, 2H, H-3, H-4, overlapping signals), 2.74 (ddt, J = 7.8, 5.1, 3.0 Hz, 1H, H-5); 

**13C NMR** (126 MHz, D₂O) δ 133.3 (C-7), 118.5 (C-8), 71.9 (C-2), 71.2 (C-3), 68.1 (C-4), 60.3 (C-6), 59.0 (C-1), 55.6 (C-5).
Methyl 3,4-\textit{O-}(2',3'-dimethoxybutane-2'-3'-diyl)-\textit{α-d-mannopyranoside} 86

Methyl-\textit{α-d-mannopyranoside} (10.0 g, 0.051 mol), trimethyl orthoformate (34 mL, 0.309 mol) and 2,3-butanedione (5.9 mL, 0.07 mol) were suspended in MeOH (150 mL, 5 mL/mmol of sugar). CSA (1.2 g, 5 mmol) was added and the mixture was refluxed under Ar for 12 - 18 h. The reaction mixture was cooled to rt and treated with powdered NaHCO$_3$ and the solvents were removed under diminished pressure. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 86 (11.4 g, 72%) as a white foam. All analytical data provided below for 86 corresponded well to literature data.$^{202}$ (TLC 3:1 EtOAc:Hexane, R$_f$ 0.2); [$\alpha$]$_D$ +160.3 (c 0.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.70 (d, $J = 1.5$ Hz, 1H, H-1), 4.06 (apt t, $J = 10.1$ Hz, 1H, H-4), 3.95 (dd, $J = 10.3, 3.1$ Hz, 1H, H-3), 3.88 (dd, $J = 3.1, 1.5$ Hz, 1H, H-2), 3.79 (dd, $J = 11.9, 2.8$ Hz, 1H, H-6), 3.73 (dd, $J = 11.8, 4.2$ Hz, 1H, H-6’), 3.69 (dt, $J = 9.9, 3.3$ Hz, 1H, H-5), 3.32 (s, 3H, -OCH$_3$), 3.22 (s, 3H, -OCH$_3$), 3.22 (s, 3H, -OCH$_3$), 1.28 (s, 3H, -CCH$_3$), 1.24 (s, 3H, -CCH$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 101.1 (C-1), 100.3 (C), 99.8 (C), 70.6 (C-5), 69.5 (C-2), 68.1 (C-3), 62.7 (C-4), 61.1 (C-6), 54.8 (-OCH$_3$), 48.0, 47.8 (-OCH$_3$), 17.7, 17.6 (-CCH$_3$); FTIR 3420, 2992, 2949, 2835, 2246, 1454, 1377, 1329, 1207, 1114, 1078, 1031, 972, 928, 883, 848, 808, 730, 664 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{13}$H$_{23}$O$_8$: 307.1393, Found: 307.1408 [M-H].
Methyl 6-deoxy-3,4-O-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-iodo-α-d-mannoside 87 To a stirred solution of compound 86 (11.4 g, 0.037 mol), Triphenyl phosphine (11.6 g, 0.044 mol), and imidazole (4.03 g, 0.059 mol) in THF (150 mL) was added a solution of iodine (11.3 g, 0.044 mol) in THF (60 mL) dropwise under reflux over 15 min. After the addition was complete, the brown solution was refluxed for an additional 2 h. The mixture was diluted with EtOAc (150 mL). The org layer was washed with a 0.5 N Na2S2O3 aqueous solution (30 mL) followed by brine (50 mL), dried over Na2SO4, filtered, and concentrated. Flash column chromatography of the residue (gradient EtOAc:Hexane 1:5 to 1:3) gave 87 (13.61 g, 88%) as a white foam (EtOAc:Hexane 1:3, Rf 0.26). All analytical data provided below for 87 corresponded well to literature data.192 [α]D +120.3 (c 6.0, CHCl3); 1H NMR (500 MHz, CDCl3) δ 4.71 (apt s, 1H, H-1), 3.94 (dd, J = 10.1, 3.1 Hz, 1H, H-3), 3.88 (dd, J = 3.1, 1.5 Hz, 1H, H-2), 3.83 (apt t, J = 9.9 Hz, 1H, H-4), 3.62 (m, 1H, H-5), 3.51 (dd, J = 10.6, 2.3 Hz, 1H, H-6), 3.40 (s, 3H, -OCH3), 3.24 – 3.21 (m, 1H, H-6, overlapping signals), 3.24 (s, 3H, -OCH3), 3.23 (s, 3H, -OCH3), 1.28 (s, 3H, -CCH3), 1.25 (s, 3H, -CCH3); 13C NMR (126 MHz, CDCl3) δ 101.1 (C-1), 100.3, 100.0 (C), 70.0 (C-5), 69.6 (C-2), 67.9 (C-3), 67.1 (C-4), 55.1 (-OCH3), 48.2, 48.1 (-OCH3), 17.7, 17.6 (-CCH3), 5.0 (C-6); FTIR 3444, 2993, 2936, 2834, 2247, 1736, 1452, 1378, 1331, 1214, 1144, 1127, 1111, 1074, 1041, 989, 966, 908, 882, 848, 811, 774, 729, 677, 664 cm⁻¹; HRMS (ESI) m/z calc for C15H26O7INaN: 482.0652, Found: 482.0648 [M+ACN+Na]+.
Methyl 6-deoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-6-iodo-2-O-triethoxysilyl-α-ᴅ-mannoside 88

Compound 87 (13.6 g, 0.032 mol) was dissolved in CH₂Cl₂ (200 mL). Chlorotriethylsilane (10.9 mL, 0.065 mol) and imidazole (4.4 g, 0.065 mol) were charged and the reaction was stirred at rt for 12 h. The reaction was quenched with H₂O (100 mL). The org layer was washed with H₂O (3 x 50 mL), dried over Na₂SO₄ and concentrated. Flash column chromatography (1:4 EtOAc:Hexane, Rf 0.8) gave 88 (12.21 g, 70%) as a clear oil. [α]D +95.6 (c 7.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.58 (d, J = 1.3 Hz, 1H, H-1), 3.87 – 3.83 (m, 3H, H-2, H-3, H-4, overlapping signals), 3.64 – 3.60 (m, 1H, H-5), 3.55 (dd, J = 10.5, 2.3 Hz, 1H, H-6), 3.40 (s, 3H, -OCH₃), 3.26 – 3.24 (m, 1H, H-6’, overlapping signals), 3.23 (s, 3H, -OCH₃), 3.22 (s, 3H, -OCH₃), 1.26 (s, 3H, -CCH₃), 1.25 (s, 3H, -CCH₃), 0.98 – 0.94 (m, 9H, -Si(CH₂CH₃)₃), 0.63 – 0.56 (m, 6H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 102.6 (C-1), 99.8, 99.5 (C), 70.6 (C-5), 70.4, 67.7, 67.1 (C-2, C-3, C-4), 54.8 (-OCH₃), 47.9, 47.9 (-OCH₃), 17.7, 17.5 (-CCH₃), 6.7 (-Si(CH₂CH₃)₃), 5.8 (C-6), 4.8 (-Si(CH₂CH₃)₃); FTIR 2953, 2911, 2876, 1605, 1458, 1414, 1377, 1238, 1172, 1146, 1128, 1117, 1050, 1003, 962, 902, 883, 951, 832, 777, 725, 678 cm⁻¹; HRMS (ESI) m/z calc for C₁₉H₃₇O₇SiNa: 555.1241, Found: 555.1251 [M+Na]⁺.
(4S,5S,6R)-5,6-Dideoxy-3,4-O-(2’,3’-dimethoxybutane-2’,3’-diyl)-2-O-triethylsilyl-hex-5-en-1-ose 89 Compound 88 (7.6 g, 0.014 mol) was dissolved in a mixture of THF/H₂O (9:1, 100 mL). Pre-activated Zn dust (9.3 g, 0.142 mol) was charged and the mixture was sonicated at 40 °C for 2-4 h. The mixture was filtered and washed with Et₂O (100 mL). The org layer was washed with H₂O (50 mL), sat aq NaHCO₃ (50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo to give 90 (5.85 g, 90%) as a clear oil. The crude product was used immediately to prevent epimerization. \[\alpha\]D +13.6 (c 10.6, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.47 (d, J = 1.1 Hz, 1H, C-1), 5.61 (dd, J = 17.1, 10.3, 8.1 Hz, 1H, C-5), 5.38 (dd, J = 17.2, 0.9 Hz, 1H, H-6), 5.24 (dd, J = 10.3, 1.8 Hz, 1H, H-6’), 4.28 (apt t, J = 9.0, 1H, H-4), 3.99 (apt s, 1H, H-2), 3.85 (dd, J = 9.9, 1.9 Hz, 1H, H-3), 3.22 (s, 3H, -OCH₃), 3.16 (s, 3H, -OCH₃), 1.22 (s, 6H, 2 x -C(CH₃)₃), 0.95 – 0.90 (m, 9H, -Si(CH₂CH₃)₃), 0.63 – 0.58 (m, 6H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 203.4 (C-1), 133.8 (C-5), 120.9 (C-6), 98.9, 98.4 (C), 78.1 (C-2), 74.4 (C-3), 69.8 (C-4), 47.8, 47.6 (-OCH₃), 17.5, 17.2 (-C(CH₃)₃), 6.5 (-Si(CH₂CH₃)₃), 4.6 (-Si(CH₂CH₃)₃); FTIR 2956, 2917, 2878, 2248, 1733, 1459, 1376, 1241, 1138, 1120, 1039, 1003, 906, 848, 815, 727 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₃₄O₆SiNa: 397.2022, Found: 397.2030 [M+Na]+.
(2E,4R,5S,6R) Ethyl 5,6-O-(2',3'-dimethoxybutane-2',3'-diyl)-2,3,7,8-tetradeoxy-4-O-triethylsilyl-octa-2,7-dienoate 90 Compound 89 (5.8 g, 0.015 mol) was dissolved in toluene (100 mL). (Carbethoxy methylene) triphenylphosphorane (8.1 g, 0.023 mol) was charged and the reaction was heated to reflux for 12 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 90 (5.6 g, 83%) as a clear oil. (TLC 1:4 EtOAc:Hexane, Rf 0.75); [α]D +78.5 (c 4.7, CHCl3); 1H NMR (500 MHz, CDCl3) δ 6.93 (dd, J = 15.6, 5.2 Hz, 1H, H-6), 5.95 (dd, J = 15.6, 1.7 Hz, 1H, H-7), 5.76 (ddd, J = 17.5, 10.4, 7.5 Hz, 1H, H-2), 5.37 (apt d, J = 17.2 Hz, 1H, H-8), 5.23 (dd, J = 10.4, 1.6 Hz, 1H, H-8'), 4.36 (dt, J = 4.6, 2.1 Hz, 1H, H-5), 4.20 (q, J = 7.1 Hz, 2H, -CH2), 4.14 (dd, J = 9.5, 7.8 Hz, 1H, H-3), 3.65 (dd, J = 9.8, 2.6 Hz, 1H, H-4), 3.24 (s, 3H, -OCH3), 3.21 (s, 3H, -OCH3), 1.29 (t, J = 7.1 Hz, 3H, -CH2CH3), 1.27 (s, 6H, 2 x -CH2), 0.95 (t, J = 7.9 Hz, 9H, -Si(CH2CH3)3), 0.64 – 0.59 (m, 6H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 166.4 (C-1), 147.6 (C-6), 134.1 (C-2), 121.5 (C-7), 119.6 (C-8), 98.9, 98.4 (C), 74.5 (C-4), 72.6 (C-5), 70.3 (C-3), 60.3 (-CH2CH3), 47.8, 47.7 (-OCH3), 17.6, 17.4 (-CCH3), 14.2 (-CH2CH3), 6.8 (-Si(CH2CH3)3), 4.8 (-Si(CH2CH3)3); FTIR 2954, 2911, 2877, 2833, 1721, 1660, 1558, 1512, 1464, 1412, 1372, 1284, 1122, 1036, 1005, 975, 931, 850, 823, 726 cm⁻¹; HRMS (ESI) m/z calc for C22H40O7SiNa: 467.2441, Found: 467.2432 [M+Na]+.
Compound 90 (5.6 g, 0.013 mol) was dissolved in CH$_2$Cl$_2$ (150 mL) and cooled to -78 °C. DIBAL-H (40 mL, 0.039 mol, 1.0 M in CH$_2$Cl$_2$) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H$_2$O (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography of the residue (1:4 EtOAc:Hexane, R$_f$ 0.3) gave 91 (3.7 g, 74%) as a clear oil. $[\alpha]_D$ +94.7 (c 4.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.85 – 5.71 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.34 (dd, $J = 17.0$, 0.5 Hz, 1H, H-8), 5.25 (dd, $J = 10.5$, 1.0 Hz, 1H, H-8'), 4.16 (dd, $J = 7.0$, 2.0 Hz, 1H, H-4), 4.13 (apt t, $J = 5.0$ Hz, 2H, H-1, H-1'), 3.99 (dd, $J = 9.7$, 7.9 Hz, 1H, H-6), 3.63 (dd, $J = 9.9$, 2.5 Hz, 1H, H-5), 3.25 (s, 3H, -OCH$_3$), 3.20 (s, 3H, -OCH$_3$), 1.26 (s, 3H, -CCH$_3$)$_2$, 1.26 (s, 3H, -CCH$_3$)$_2$, 0.92 (t, $J = 7.9$ Hz, 9H, -Si(CH$_2$CH$_3$)$_3$), 0.57 (q, $J = 7.9$ Hz, 6H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 134.4 (C-7), 131.2 (C-2), 130.7 (C-3), 119.5 (C-8), 98.7, 98.5 (C), 74.9 (C-5), 72.6 (C-4), 70.9 (C-6), 63.0 (C-1), 47.7, 47.7 (-OCH$_3$), 17.7, 17.5 (-CCH$_3$), 6.8 (-Si(CH$_2$CH$_3$)$_3$), 4.9 (-Si(CH$_2$CH$_3$)$_3$); FTIR 3428, 2996, 2953, 2911, 2877, 2833, 1459, 1413, 1374, 1238, 1209, 1120, 1012, 973, 928, 899, 887, 850, 727, 670 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{20}$H$_{38}$O$_6$SiNa: 425.2335, Found: 425.2332 [M+Na]$^+$. 

(2E,4R,5S,6R)-5,6-O-(2',3'-dimethoxybutane-2',3'-diyl)-2,3,7,8-tetraeoxy-4-O-triethylsilyl-octa-2,7-dien-1-ol
(2E,4R,5S,6R)-1-Azido-5,6-O-(2',3'-dimethoxybutane-2',3'-diyl)-2,3,7,8-tetrahydroxy-4-O-triethylsilyl-octa-2,7-diene 92 Compound 91 (3.7 g, 9.22 mmol) was dissolved in THF (100 mL). Triphenyl phosphine (4.1 g, 15.68 mol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (3.1 mL, 15.68 mol) and diphenylphosphoryl azide (3.4 mL, 15.68 mol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 92 (3.1 g, 79%) as a pale yellow oil. (TLC 1:20 EtOAc:Hexane, Rf 0.8); [α]D +95.6 (c 2.8, CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.90 (dd, J = 15.5, 7.1 Hz, 1H, H-3), 5.78 (ddd, J = 17.9, 10.3, 7.8 Hz, 1H, H-7), 5.67 – 5.61 (m, 1H, H-2), 5.34 (dd, J = 17.3, 0.8 Hz, 1H, H-8), 5.23 (dd, J = 10.3, 1.3 Hz, 1H, H-8’), 4.16 (dd, J = 7.0, 2.0 Hz, 1H, H-4), 4.02 (dd, J = 9.8, 7.9 Hz, 1H, H-6), 3.73 (dd, J = 33.1, 13.6, 6.4 Hz, 2H, H-1, H-1’), 3.62 (dd, J = 9.9, 2.6 Hz, 1H, H-5), 3.24 (s, 3H, -OCH3), 3.18 (s, 3H, -OCH3), 1.26 (s, 3H, -CCH3), 1.24 (s, 3H, -CCH3), 0.92 (t, J = 7.9 Hz, 9H, -Si(CH2CH3)3), 0.57 (q, J = 7.8 Hz, 6H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 135.0 (C-3), 134.4 (C-7), 125.1 (C-2), 119.5 (C-8), 98.7, 98.4 (C), 74.5 (C-5), 72.6 (C-4), 70.8 (C-6), 52.3 (C-1), 47.7, 4.47 (-OCH3), 17.6, 17.4 (-CCH3), 6.7 (-Si(CH2CH3)3), 4.8 (-Si(CH2CH3)3); FTIR 2954, 2913, 2877, 2832, 2097 (-N3), 1458, 1412, 1374, 1235, 1210, 1120, 1036, 1015, 975, 930, 886, 851, 741, 727 cm⁻¹; HRMS (ESI) m/z calc for C20H38O5SiN3: 428.2581, Found: 428.2567 [M+H]+.
Compound 92 (3.1 g, 7.28 mmol) was dissolved in THF (80 mL). TBAF (20 mL, 18.26 mmol, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The reaction was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo.

Flash column chromatography of the residue (1:1 EtOAc:Hexane) gave 93 (1.4 g, 63%) as a white solid. (TLC, 1:3 EtOAc:Hexane Rf 0.5); [α]D +125.0 (c 2.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.92 (dd, J = 15.5, 7.4 Hz, 1H, H-3), 5.80 – 5.70 (m, 2H, H-2, H-7), 5.36 (apt d, J = 17.1 Hz, 1H, H-8), 5.27 (dd, J = 10.3, 1.3 Hz, 1H, H-8’), 4.10 (td, J = 7.6, 3.4 Hz, 1H, H-4), 4.01 (dd, J = 10.0, 7.9 Hz, 1H, H-6), 3.79 (dd, J = 14.0, 7.0 Hz, 1H, H-1), 3.74 – 3.69 (m, 2H, H-1’, H-5, overlapping signals), 3.24 (s, 3H, -OCH₃), 3.19 (s, 3H, -OCH₃), 2.51 (d, J = 7.8 Hz, 1H, -OH), 1.28 (s, 3H, -CCH₃), 1.26 (s, 3H, -CCH₃); ¹³C NMR (126 MHz, CDCl₃) δ 133.9 (C-7), 133.3 (C-3), 126.7 (C-2), 120.5 (C-8), 99.0, 98.8 (C), 73.1 (C-5), 71.5 (C-4), 71.0 (C-6), 52.4 (C-1), 48.1, 48.1 (OCH₃), 17.8, 17.6 (-CCH₃); FTIR 3506, 2994, 2967, 2950, 2907, 2832, 2117, 2083 (-N₃), 1462, 1428, 1396, 1376, 1256, 1208, 1114, 1068, 1054, 1036, 1007, 981, 879, 852, 686 cm⁻¹; HRMS (ESI) m/z calc for C₁₄H₂₄O₅N₃: 314.1716, Found: 314.1708 [M+H]⁺.
1.5-Dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-5-[1,2,3]-triazoline-1-(R)-ethenyl-1,5-imidazoleino-α-mannitol 93 Compound 94 (485 mg, 1.55 mmol) was refluxed in DMF (20 mL) for 8 h. The reaction was cooled to rt and diluted with H₂O (20 mL). The aq layer was extracted with Et₂O until no product remained (as observed by TLC, 1:2 EtOAc:Hexane, Rf 0.4, UV and stain) and concentrated in vacuo. Flash column chromatography of the residue (1:6 EtOAc:Hexane) gave 94 as a white solid (86 mg, 17%). [α]D +85.6 (c 3.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddd, J = 17.3, 10.6, 3.9 Hz, 1H, H-7), 5.36 (dd, J = 17.7, 2.4 Hz, 1H, H-8), 5.32 (dd, J = 11.1, 2.6 Hz, 1H, H-8’), 5.23 (dd, J = 4.1, 2.1 Hz, 1H, H-1), 4.43 (dd, J = 16.1, 2.7 Hz, 1H, H-6), 4.07 (t, J = 2.0 Hz, 1H, H-2), 4.01 (dd, J = 16.2, 9.7 Hz, 1H, H-6’), 3.69 (dd, J = 10.1, 2.3 Hz, 1H, H-3), 3.64 (t, J = 9.9 Hz, 1H, H-4), 3.58 (td, J = 9.7, 2.6 Hz, 1H, H-5), 3.23 (s, 3H, -OCH₃), 3.21 (s, 3H, -OCH₃), 2.47 (s, 1H, -OH), 1.27 (s, 3H, -CCH₃), 1.27 (s, 3H, -CCH₃); ¹³C NMR (126 MHz, CDCl₃) δ 133.3 (C-7), 117.8 (C-8), 100.0, 99.7 (C), 71.2 (C-2), 68.1 (C-6), 67.8 (C-3), 62.7 (C-4), 62.1 (C-1), 53.6 (C-5), 48.1, 47.9 (-OCH₃), 17.6, 17.6 (-CCH₃); FTIR 3364, 2996, 2950, 2834, 2246, 1643, 1490, 1378, 1335, 1195, 1131, 1114, 1074, 1034, 1006, 922, 883, 867, 787, 728, 708 cm⁻¹; HRMS (ESI) m/z calc for C₁₄H₂₄O₅N₃: 314.1716, Found: 314.1702 [M+H]⁺; Crystal Structure.
(2E,4R,5R,6R)-1-Azido-5,6-O-(2',3'-dimethoxybutane-2',3'-diyl)-2,3,7,8-tetradeoxy-octa-2,7-diene 95 Compound 93 (132 mg, 0.422 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. NaN (22 mg, 0.55 mmol) was added slowly and the reaction was warmed to rt for 30 min. The mixture was re-cooled to 0 °C and BnBr (70 μl, 0.55 mmol) was added dropwise. The reaction was warmed to rt and stirred for 12 h. The reaction was quenched slowly with H2O. The aq layer was extracted with EtOAc (3 x 10 mL), dried over Na2SO4 and concentrated. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 95 as a pale yellow oil (91 mg, 52%). (TLC 1:4 EtOAc:Hexane, Rf 0.6); [α]D +82.8 (c 2.0 in CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.34 – 7.27 (m, 5H, Ar H), 5.95 (apt dd, J = 14.9, 8.7 Hz, 1H, H-2), 5.79 (ddd, J = 17.1, 10.3, 8.0 Hz, 1H, H-7), 5.71 (dt, J = 15.4, 6.6 Hz, 1H, H-3), 5.33 (apt d, J = 17.1 Hz, 1H, H-8), 5.22 (dd, J = 10.4, 1.5 Hz, 1H, H-8'), 4.59 (d, J = 12.1 Hz, 1H, -OCH2Ph), 4.40 (d, J = 12.1 Hz, 1H, -OCH2Ph), 4.02 (dd, J = 9.8, 8.0 Hz, 1H, H-6), 3.86 (dd, J = 9.9, 3.7 Hz, 1H, H-5), 3.83 – 3.80 (m, 3H, H-1, H-1', H-4, overlapping signals), 3.30 (s, 3H, -OCH3), 3.23 (s, 3H, -OCH3), 1.31 (s, 3H, -CCH3), 1.30 (s, 3H, -CCH3); 13C NMR (126 MHz, CDCl3) δ 138.3 (Ar C), 134.4 (C-7), 132.1 (C-2), 128.1 (C-3), 128.5 – 127.7 (Ar CH), 119.9 (C-8), 99.0, 98.9 (C), 78.4 (C-4), 72.8 (C-5), 71.8 (C-6), 70.4 (-OCH2Ph), 52.5 (C-1), 48.1, 48.1 (-OCH3), 17.9, 17.8 (-CCH3); FTIR 2992, 2949, 2905, 2833, 2097 cm⁻¹; HRMS (ESI) m/z calc for C21H29O3N3Na: 426.2005, Found: 426.2002 [M+Na]+.
2-O-Benzyl-1,5-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-5-[1,2,3]-triazoline-1-(R)-ethenyl-1,5-imine-D-mannitol 96

Compound 95 (42 mg, 0.1 mmol) was heated to reflux in DMF (5 mL) for 6 h. The reaction was cooled to rt and diluted with H2O (10 mL). The aq layer was extracted with Et2O until no product remained (as observed by TLC 1:4 EtOAc: Hexane, Rf 0.2, UV and stain) and concentrated in vacuo. Flash column chromatography of the residue (1:8 to 1:4 EtOAc: Hexane) gave 96 (20 mg, 52%), a clear oil as the major product. [α]D +178.2 (c 0.9, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.43–7.27 (m, 5H, Ar H), 5.81 (ddd, J = 17.1, 10.5, 5.7 Hz, 1H, H-7), 5.15 (dt, J = 10.5, 1.5 Hz, 1H, H-8), 5.11 (dt, J = 17.2, 1.6 Hz, 1H, H-8’), 4.97 (d, J = 11.7 Hz, 1H, -OCH2Ph), 4.67 (d, J = 11.7 Hz, 1H, -OCH2Ph), 4.58 (d, J = 10.4 Hz, 1H, H-4), 4.51 (ddd, J = 5.5, 2.8, 1.4 Hz, 1H, H-1), 3.80 (dd, J = 10.4, 2.1 Hz, 1H, H-3), 3.75 (dd, J = 2.2, 1.1 Hz, 1H, H-2), 3.33 (s, 3H, -OCH3), 3.22 (s, 3H, -OCH3), 2.11 (dd, J = 1.4, 0.6 Hz, 3H, -CH3), 1.37 (s, 3H, -CCH3), 1.34 (s, 3H, -CCH3); 13C NMR (126 MHz, CDCl3) δ 167.6 (C-5), 138.7 (Ar C), 136.6 (C-7), 128.3–127.5 (Ar CH), 116.8 (C-8), 100.6, 99.8 (-C), 77.2 (C-2), 72.9 (-OCH2Ph), 67.1 (C-1), 67.0 (C-4), 66.6 (C-3), 47.9, 47.9 (-OCH3), 21.1 (C-6) 17.9, 17.8 (-CCH3); FTIR 2993, 2950, 2833, 1728, 1660 (R2C=N-R stretch), 1455, 1432, 1378, 1210, 1136, 1114, 1072, 1037, 992, 927, 884, 849, 795, 748, 699 cm⁻¹; HRMS (ESI) m/z calc for C21H30O5N: 376.2124, Found: 376.2133 [M+H]+.
Methyl \(4,6-O-(1,1,3,3\text{-tetraisopropyldisiloxane-1,3-diyl})-\alpha\text{-d-mannopyranoside}\) 97 Methyl α-\(\text{d}\)-glucopyranoside (5.0 g, 0.026 mol) was dissolved in DMF (70 mL). 1,3-Dichloro tetraisopropyl disiloxane (8.9 mL, 0.028 mmol) and imidazole (3.5 g, 0.052 mol) were charged and the mixture was stirred at rt for 16 h. The reaction was quenched with \(\text{H}_2\text{O}\) (30 mL) and extracted with EtOAc (3 x 50 mL). The combined org layers were dried over Na\(\text{2SO}_4\) and concentrated \textit{in vacuo}. Flash column chromatography of the residue (1:8 EtOAc:Hexane) gave 97 as a white solid (8.87 g, 79%). (TLC 1:4 EtOAc:Hexane, \(R_f\) 0.75); \(\left[\alpha\right]_D \pm 49.5\) (c 2.0, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.76 (d, \(J = 1.8\) Hz, 1H, H-1), 4.12 (dd, \(J = 12.6, 1.9\) Hz, 1H, H-6), 4.08 (t, \(J = 9.4\) Hz, 1H, H-4), 3.95 (m, 1H, H-2), 3.90 (dd, \(J = 12.6, 1.6\) Hz, 1H, H-6'), 3.84 (ddd, \(J = 9.1, 5.4, 3.4\) Hz, 1H, H-3), 3.47 (apt d, \(J = 9.5\) Hz, 1H, H-5), 3.34 (s, 3H, -OCH\(_3\)), 2.39 (d, \(J = 5.4\) Hz, 1H, -OH), 2.28 (d, \(J = 4.5\) Hz, 1H, -OH), 1.14 – 1.01 (m, 24H, 8 x -SiCH(Pr\(_5\))\(_2\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 101.3 (C-1), 72.6 (C-5), 72.1 (C-3), 71.4 (C-2), 67.4 (C-4), 61.1 (C-6), 55.2 (-OCH\(_3\)), 17.7 – 17.3 (CH\(_3\), -SiCH(Pr\(_5\))\(_2\)), 14.0 – 12.7 (CH, -SiCH(Pr\(_5\))\(_2\)); FTIR 3364, 2944, 2925, 2867, 1464, 1387, 1325, 1248, 1196, 1126, 1094, 1065, 1040, 981, 931, 884, 861, 834, 767, 697, 663 cm\(^{-1}\); HRMS (ESI) \(m/z\) calc for C\(_{18}\)H\(_{38}\)O\(_7\)Si\(_2\): 481.2289, Found: 481.2284 [M+H]\(^+\).
Methyl 3,4-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diy)-α-D-mannopyranoside 98 Compound 97 (8.8 g, 0.02 mol) was dissolved in DMF (50 mL). p-TsOH (cat.) was charged and the reaction stirred at rt for 14 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:8 EtOAc:Hexane) gave 98 (8.0 g, 91%) as a white solid. [α]D +57.7 (c 5.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.78 (d, J = 1.4 Hz, 1H, H-1), 3.92 – 3.91 (m, 2H, H-3, H-4, overlapping signals), 3.89 – 3.86 (m, 2H, H-2, H-6, overlapping signals), 3.78 (dd, J = 11.6, 5.2 Hz, 1H, H-6’), 3.58 (ddd, J = 8.9, 5.4, 3.3 Hz, 1H, H-5), 3.38 (s, 3H, -OCH₃), 1.08 – 0.97 (m, 28H, 4 x -SiCH(Pr’₂); ¹³C NMR (126 MHz, CDCl₃) δ 100.0 (C-1), 74.4 (C-3), 71.7 (C-5), 71.3 (C-2), 70.5 (C-4), 62.3 (C-6), 54.9 (-OCH₃), 17.5 – 17.1 (CH₃, -SiCH(Pr’₂), 12.9 – 12.1 (CH, -SiCH(Pr’₂)); FTIR 3362, 2944, 2929, 2867, 1464, 1387, 1247, 1127, 1094, 1065, 1041, 983, 920, 884, 961, 834, 788, 767, 696 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₃₈O₇Si₂: 481.2289, Found: 481.2278 [M+H]⁺.
Methyl 6-deoxy-6-iodo-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-mannopyranoside 99

Compound 98 (2.4 g, 5.39 mmol) was dissolved in THF (50 mL). Triphenyl phosphine (1.7 g, 6.23 mmol) and imidazole (1.3 g, 19.39 mmol) were added and the mixture was heated to 60 °C. Iodine (1.7 g, 6.23 mmol) in THF was added portionwise and the solution colour changed from brown to yellow. The reaction was stirred at reflux for 4 h. The solution was cooled to rt and diluted with EtOAc (30 mL). The org layer was washed with Na$_2$S$_2$O$_3$ solution (30 mL). The aq layer was extracted with EtOAc (3 x 30 mL). The combined org layers were dried over Na$_2$SO$_4$ and concentrated in vacuo.

Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 99 (2.1 g, 70%) as a clear oil. (TLC 1:4 EtOAc:Hexane, R$_f$ 0.8); [α]$_D$ +28.9 (c 1.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 4.79 (d, $J$ = 1.3 Hz, 1H, H-1), 3.90 (dd, $J$ = 8.2, 3.6 Hz, 1H, H-3), 3.88 (dt, $J$ = 3.6, 1.2 Hz, 1H, H-2), 3.73 (dd, $J$ = 9.2, 8.2 Hz, 1H, H-4), 3.63 (dd, $J$ = 10.3, 2.4 Hz, 1H, H-6), 3.53 (td, $J$ = 8.8, 2.4 Hz, 1H, H-5), 3.46 (s, 3H, -OCH$_3$), 3.27 (dd, $J$ = 10.3, 8.5 Hz, 1H, H-6'), 2.64 (d, $J$ = 1.1 Hz, 1H, -OH), 1.09 – 1.00 (m, 28H, -Si(CH$_3$)$_2$)$_2$; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 100.1 (C-1), 74.3 (C-4), 74.1 (C-3), 71.7 (C-5), 71.45 (C-2), 55.3 (-OCH$_3$), 17.6 – 17.1 (CH$_3$, -SiCH(Pr$_i$)$_2$), 13.2 – 12.1 (CH, -SiCH(Pr$_i$)$_2$), 6.4 (C-6); FTIR 3439, 2945, 2867, 1743, 1721, 1463, 1386, 1370, 1326, 1273, 1243, 1232, 1196, 1126, 1088, 1054, 979, 920, 884, 846, 761, 695 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{19}$H$_{38}$O$_6$Si$_2$: 545.1252, Found: 545.1279 [M-H]$^-$.
Methyl 6-deoxy-6-ido-2-O-methoxymethyl-3,4-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-α-D-mannopyranoside 100

Compound 99 (1.0 g, 1.83 mmol) was dissolved in DMF (20 mL) and cooled to 0 °C. *N*,*N*-Diisopropylethylamine (3.2 mL, 0.018 mmol) and DMAP (111 mg, cat.) were charged. MOMCl (1.4 mL, 0.018 mmol) was added dropwise. The reaction was brought to rt and stirred for 24 h. The reaction was diluted with CH$_2$Cl$_2$ (50 mL) and washed with 2 % HCl (15 mL), sat aq NaHCO$_3$ (15 mL) and brine (15 mL). The org layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography of the residue (1:8 EtOAc:Hexane) gave 100 (85 mg, 89%) as a clear oil. (TLC 1:4 EtOAc:Hexane, R$_f$ 0.9); [α]$_D$ +55.7 (c 2.2, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 4.91 (d, J = 7.4 Hz, 1H, -OCH$_2$O-), 4.71 (apt s, 1H, H-1), 4.67 (d, J = 7.0 Hz, 1H, -OCH$_2$O-), 3.96 (d, J = 8.8 Hz, 1H, H-3), 3.87 (apt s, 1H, H-2), 3.76 (t, J = 8.9 Hz, 1H, H-4), 3.65 (d, J = 10.2 Hz, 1H, H-6), 3.55 (m, 1H, H-5), 3.44 (s, 3H, -OCH$_3$), 3.39 (s, 3H, -OCH$_3$), 3.26 (t, J = 9.5 Hz, 1H, H-6'), 1.07 – 1.01 (m, 28H, -SiCH(Pr$_i$)$_2$)$_2$; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 100.5 (C-1), 97.4 (-OCH$_2$O-), 76.0 (C-2), 74.6 (C-4), 74.0 (C-3), 72.6 (C-5), 55.6 (-OCH$_3$), 55.1 (-OCH$_3$), 17.6 – 17.1 (CH$_3$, -SiCH(Pr$_i$)$_2$), 13.1 – 12.2 (CH, -SiCH(Pr$_i$)$_2$), 6.3 (C-6); FTIR 2944, 2897, 2868, 1744, 1464, 1386, 1247, 1199, 1127, 1104, 1064, 1032, 987, 920, 884, 845, 763, 698 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{21}$H$_{43}$O$_7$Si$_2$Na: 613.1490, Found: 613.1478 [M+Na]$^+$. 

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(4S,5S,6R)-5,6-Dideoxy-2-O-methoxymethyl-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-hex-5-en-1-ose 101 Compound 100 (0.9 g, 1.49 mmol) was dissolved in a mixture of THF/H₂O (9:1, 20 mL). Pre-activated Zn dust (1.0 g, 14.91 mmol) was charged and the mixture was sonicated at 40 °C for 2 h. The mixture was filtered and washed with Et₂O (20 mL). The org layer was washed with H₂O (10 mL), sat aq NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo to give 101 (0.57 g, 89%) as a clear oil. The crude product was used immediately to prevent epimerization. [α]D +30.5 (c 11.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.63 (apt s, 1H, H-1), 5.80 (ddd, J = 16.8, 10.4, 6.2 Hz, 1H, H-5), 5.44 (dt, J = 17.1, 1.6 Hz, 1H, H-6), 5.21 (dt, J = 10.5, 1.4 Hz, 1H, H-6'), 4.77 (d, J = 6.7 Hz, 1H, OCH₂O-), 4.72 (d, J = 6.7 Hz, 1H, OCH₂O-), 4.36 (dd, J = 8.0, 6.5 Hz, 1H, H-4), 4.02 – 4.00 (m, 2H, H-2, H-3, overlapping signals), 3.40 (s, 3H, OCH₃), 1.09 – 1.00 (m, 28H, 2 x SiCH(Prᵢ)₂); ¹³C NMR (126 MHz, CDCl₃) δ 202.3 (C-1), 135.8 (C-5), 117.7 (t, C-6), 96.8 (OCH₂O-), 83.1, 80.9 (C-2, C-3), 76.8 (C-4), 55.8 (OCH₃), 17.4 – 17.1 (CH₃, SiCH(Prᵢ)₂), 13.1 – 12.0 (CH, SiCH(Prᵢ)₂); FTIR 2945, 2897, 2868, 1750, 1682, 1605, 1483, 1457, 1419, 1367, 1294, 1257, 1218, 1185, 1135, 1093, 1035, 1012, 988, 917, 884, 839, 803, 754, 703, 667 cm⁻¹; HRMS (ESI) m/z calc for C₂₀H₃₀O₆Si₂: 431.2285, Found: 431.2305 [M-H]⁻.
(2,4\text{R},5\text{R},6\text{R}) Ethyl 4-O-methoxymethyl-2,3,7,8-tetraedioxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-octa-2,7-dienoate 102

Compound 101 (0.6 g, 1.30 mmol) was dissolved in toluene (50 mL). (Carbethoxy methylene) triphenylphosphorane (0.7 g, 1.94 mmol) was charged and the reaction was heated to reflux for 12 h. The reaction was concentrated to a brown solid. The residue was purified by column chromatography (1:10 EtOAc:Hexane) to give 102 (0.5 g, 83%) as a clear oil. (TLC 1:8 EtOAc:Hexane, Rf 0.8); $[\alpha]_D +24.9$ (c 2.1, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.92 (dd, $J = 15.8, 6.9$ Hz, 1H, H-3), 6.00 (dd, $J = 15.9, 1.2$ Hz, 1H, H-2), 5.84 (ddd, $J = 16.8, 10.4, 6.2$ Hz, 1H, H-7), 5.37 (dt, $J = 17.0, 1.6$ Hz, 1H, H-8), 5.20 (ddd, $J = 10.4, 1.9, 1.1$ Hz, 1H, H-8'), 4.60 (d, $J = 2.1$ Hz, 2H, -OCH$_2$O-), 4.26 (ddd, $J = 7.0, 2.4, 1.3$ Hz, 1H, H-4), 4.21 (t, $J = 7.2$ Hz, 2H, -OCH$_2$), 4.06 (ddt, $J = 7.7, 6.3, 1.2$ Hz, 1H, H-6), 3.84 (dd, $J = 8.2, 2.3$ Hz, 1H, H-5), 3.35 (s, 3H, -OCH$_3$), 1.29 (t, $J = 7.1$ Hz, 3H, -CH$_3$), 1.12 – 0.93 (m, 28H, 2 x -SiCH(Pr$_i^\text{t}$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 166.0 (C=O), 143.5 (C-3), 135.8 (C-7), 124.0 (C-2), 117.0 (C-8), 94.4 (-OCH$_2$O-), 80.7 (C-5), 77.5 (C-6), 75.8 (C-4), 60.4 (-OCH$_2$), 55.6 (-OCH$_3$), 17.4 – 17.1 (CH$_3$, -SiCH(Pr$_i^\text{t}$)$_2$), 14.2 (-CH$_3$), 12.8 – 12.1 (CH, -SiCH(Pr$_i^\text{t}$)$_2$); FTIR 2945, 2894, 2868, 1725 (C=O), 1660, 1464, 1387, 1368, 1368, 1263, 1246, 1143, 1065, 1032, 977, 921, 884, 847, 764, 699 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{24}$H$_{40}$O$_7$Si$_2$Na: 525.2680, Found: 525.2681 [M+Na$^+$].
(2,E,4R,5R,6R)-2-O-Methoxymethyl-2,3,7,8-tetrahydroxy-5,6-O-(1,1,3,3-
tetraisopropylsiloxane-1,3-diyl)-octa-2,7-dien-1-ol 103 Compound 102 (0.5 g, 1.07 mol) was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to -78 °C. DIBAL-H (3.2 mL, 3.23 mol, 1.0 M in CH$_2$Cl$_2$) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H$_2$O (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 103 (36.6 mg, 74%) as a clear oil. (TLC 1:4 EtOAc:Hexane, R$_f$ 0.4); [α]$_D$ -10.8 (c 6.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.87 – 5.80 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.35 (dt, J = 17.0, 1.7 Hz, 1H, H-8), 5.17 (ddd, J = 10.4, 2.0, 1.2 Hz, 1H, H-8'), 4.64 (d, J = 6.7 Hz, 1H, -OCH$_2$O-), 4.54 (d, J = 6.7 Hz, 1H, -OCH$_2$O-), 4.18 (apt s, 2H, H-1, H-1', overlapping signals), 4.09 (dd, J = 7.2, 2.1 Hz, 1H, H-5), 4.03 (ddt, J = 8.3, 6.0, 1.3 Hz, 1H, H-3), 3.80 (dd, J = 8.1, 2.1 Hz, 1H, H-4), 3.33 (s, 3H, -OCH$_3$), 1.10 – 0.98 (m, 28H, 2 x -SiCH(Pr$_i$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 135.9 (C-2), 134.5 (C-3), 126.5 (C-7), 116.5 (C-8), 93.3 (-OCH$_2$O-), 80.7 (C-4), 77.4 (C-3), 76.4 (C-5), 63.1 (C-1), 55.3 (-OCH$_3$), 17.5 – 17.0 (CH$_3$, -SiCH(Pr$_i$)$_2$), 12.8 – 12.1 (CH, -SiCH(Pr$_i$)$_2$); FTIR 3407, 2945, 2893, 2867, 1464, 1387, 1248, 1146, 1088, 1033, 975, 920, 884, 855, 818, 744, 699 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{22}$H$_{43}$O$_6$Si$_2$: 459.2598, Found: 459.2609 [M-H].
(2,E,4R,5R,6R)-1-Azido-2-methoxymethyl-2,3,7,8-tetradeoxy-5,6-O-(1,1,3,3-tetraisopropyl disiloxane-1,3-diyl)-octa-2,7-diene

**Compound 103** (180 mg, 0.39 mmol) and triphenyl phosphine (170 g, 0.67 mmol) were dissolved in THF (20 mL) and cooled to 0 °C. DIAD (0.13 mL, 0.67 mmol) and DPPA (0.1 mL, 0.67 mmol) were added dropwise. The reaction was stirred at rt for 6 h. The mixture was concentrated. The residue was purified by column chromatography (Hexane followed by 1:50 EtOAc:Hexane) to give **104** (114 mg, 60%) as a clear oil. (1:4 EtOAc:Hexane, Rf 0.9); [α]D -45.2 (c 0.88, CHCl3); 

**1H NMR (500 MHz, CDCl3)** δ 5.87 (ddt, J = 15.6, 8.3, 1.2 Hz, 1H, H-3), 5.82 (ddd, J = 16.8, 10.4, 6.3 Hz, 1H, H-7), 5.73 (dt, J = 15.7, 6.4 Hz, 1H, H-2), 5.35 (ddd, J = 17.0, 1.9, 1.2 Hz, 1H, H-8), 5.19 (ddd, J = 10.4, 2.0, 1.1 Hz, 1H, H-8'), 4.64 (d, J = 6.8 Hz, 1H, H-1), 4.54 (d, J = 6.8 Hz, 1H, -OCH2O-), 4.54 (d, J = 10.4, 2.0, 1.1 Hz, 1H, H-8), 5.19 (ddd, J = 10.4, 2.0, 1.1 Hz, 1H, H-8'), 4.64 (d, J = 6.8 Hz, 1H, H-1), 4.54 (d, J = 6.8 Hz, 1H, -OCH2O-), 4.10 (dd, J = 8.3, 2.0 Hz, 1H, H-5), 3.79 – 3.77 (m, 2H, H-1, H-1', overlapping signals), 3.34 (s, 3H, -OCH3), 1.14 – 0.93 (m, 28H, 2 x -SiCH(Pr)i2); 

**13C NMR (126 MHz, CDCl3)** δ 135.8 (C-7), 130.8 (C-3), 128.2 (C-2), 116.9 (C-8), 93.2 (C-2), 80.4 (C-5), 77.5 (C-6), 75.9 (C-4), 55.38 (OCH3), 52.4 (C-1), 17.5 – 17.0 (CH3, -SiCH(Pr)i2), 12.8 – 12.0 (CH3, -SiCH(Pr)i2); 

**FTIR** 2945, 2893, 2868, 2169, 2099 (-N3), 1464, 1386, 1248, 1147, 1096, 1063, 973, 920, 885, 856, 824, 700 cm⁻¹; 

Methyl 6-deoxy-6-iodo-2,3-O-isopropylidene-α-d-mannopyranoside 105

Methyl α-d-mannopyranoside (10.0 g, 0.051 mol), imidazole (7.0 g, 0.103 mol) and Triphenyl phosphine (20.3 g, 0.077 mol) were dissolved in THF (150 mL) and heated to 60 °C. Iodine (19.7 g, 0.077 mol) was added portionwise and the reaction was refluxed for 2 h. The reaction was cooled to rt and the solvent was removed under diminished pressure. The residue was re-dissolved in a mixture of acetone (300 mL) and 2,2-DMP (30 mL) and cooled to 0 °C. p-TsOH (5.3 g, 0.031 mol) was added and the mixture was stirred at rt for 2 h. Et₃N (30 mL) was added and the solvent was removed under diminished pressure. The crude residue was re-dissolved in CH₂Cl₂ (50 mL), washed with NaHCO₃ (40 mL), dried over Na₂SO₄ and concentrated. Flash column chromatography of the residue (1:4 EtOAc:Hexane) gave 105 (12.6 g, 71%) as a white solid. All analytical data provide below for 105 corresponded well to literature data.

(TLC 1:4 EtOAc:Hexane, Rf 0.35); [α]D +32.9 (c 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.92 (apt s, 1H, H-1), 4.16 – 4.09 (m, 2H, H-3, H-4, overlapping signals), 3.59 (dd, J = 10.6, 2.7 Hz, 1H, H-6), 3.54 (m, 1H, H-2), 3.50 – 3.47 (m, 4H, H-4, -OCH₃, overlapping signals), 3.31 (dd, J = 10.6, 7.2 Hz, 1H, H-6’), 1.52 (s, 3H, -C(CH₃)₂), 1.35 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 109.8 (-C(CH₃)₂), 98.5 (C-1), 78.2, 75.7 (C-3, C-4), 73.2 (C-2), 69.3 (C-5), 55.6 (-OCH₃), 28.0 (-C(CH₃)₂), 26.1 (-C(CH₃)₂), 6.6 (C-6); FTIR 3442, 2985, 2937, 2910, 1456, 1444, 1402, 1383, 1308, 1269, 1238, 1221, 1202, 1169, 1133, 1080, 1061, 1027, 988, 967, 956, 919, 848, 815, 781, 735 cm⁻¹; HRMS (ESI) m/z calc for C₁₀H₁₈O₅I: 345.0199, Found: 345.0188 [M+H]⁺.
Methyl 6-deoxy-6-iodo-2,3-O-isopropylidene-4-O-triethylsilyl-α-D-mannopyranoside 106 Compound 105 (12.6 g, 3.66 mol) was dissolved in CH₂Cl₂ (200 mL). Imidazole (4.99 g, 7.33 mol) and chlorotriethylsilane (15.4 mL, 7.33 mol) were charged and the mixture was stirred at rt. H₂O (100 mL) was charged. The layers were separated and the org layer was dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 106 (11.8 g, 70%) as a clear oil. (TLC 1:4 EtOAc:Hexane, Rf 0.9); [α]D +36.8 (c 3.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.91 (apt s, 1H, H-1), 4.09 (dd, J = 5.7, 0.8 Hz, 1H, H-2), 4.00 (t, J = 6.0 Hz, 1H, H-3), 3.56 (dd, J = 10.4, 2.0 Hz, 1H, H-6), 3.48 (s, 3H, -OCH₃), 3.44 – 3.41 (m, 2H, H-4, H-5, overlapping signals), 3.23 (dd, J = 10.4, 7.3 Hz, 1H, H-6’), 1.51 (s, 3H, -C(CH₃)₂), 1.33 (s, 3H, -C(CH₃)₂), 0.96 (t, J = 7.9 Hz, 9H, -Si(CH₂CH₃)₃), 0.71 – 0.63 (m, 6H, -Si(CH₂CH₃)₃);¹³C NMR (126 MHz, CDCl₃) δ 109.3 (-C(CH₃)₂), 98.4 (C-1), 78.9 (C-3), 75.9 (C-2), 74.7 (C-4), 69.5 (C-5), 55.5 (-OCH₃), 28.0 (-C(CH₃)₂), 26.3 (-C(CH₃)₂), 7.20 (C-6), 6.8 (CH₃, -Si(CH₂CH₃)₃), 4.9 (CH₂, -Si(CH₂CH₃)₃); FTIR 2954, 2911, 2877, 1742, 1458, 1414, 1381, 1372, 1243, 1219, 1168, 1122, 1090, 1026, 974, 960, 853, 776, 743, 727, 677 cm⁻¹; HRMS (ESI) m/z calc for C₁₆H₃₅O₃SiN: 476.1329, Found: 476.1340 [M+NH₄]⁺.
(4S,5R,6R)-5,6-Dideoxy-2,3-O-isopropyldene-4-O-triethylsilyl-hex-5-en-1-ose 107 Compound 106 (11.5 g, 0.025 mol) was dissolved in a mixture of THF/H₂O (9:1, 110 mL). Pre-activated Zn dust (16.4 g, 0.25 mol) was charged and the mixture was sonicated at 40 °C for 2 h. The mixture was filtered and washed with Et₂O (100 mL). The org layer was washed with H₂O (80 mL), sat aq NaHCO₃ (80 mL) and brine (80 mL), dried over Na₂SO₄ and concentrated to give 107 (5.95 g, 79%) as a clear oil. [α]D -3.1 (c 10.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.69 (t, J = 1.7 Hz, 1H, H-1), 5.95 (ddd, J = 7.4, 10.3, 17.8 Hz, 1H, H-5), 5.26 (dd, J = 17.4, 1.3 Hz, 1H, H-6), 5.18 (dq, J = 10.3, 0.7 Hz, 1H, H-6'), 4.38 (dt, J = 7.8, 1.7 Hz, 1H, H-2), 4.34 (ddd, J = 7.8, 3.4, 1.4 Hz, 1H, H-3), 4.24 - 2.21 (m, 1H, H-4), 1.56 (s, 3H, -C(CH₃)₂), 1.35 (s, 3H, -C(CH₃)₂), 0.92 (t, J = 8.0 Hz, 9H, -Si(CH₂CH₃)₃), 0.56 (q, J = 7.9 Hz, 6H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 200.5 (C-1), 137.1 (C-5), 117.5 (C-6), 110.8 (-C(CH₃)₂), 83.5 (C-3), 81.1 (C-2), 72.5 (C-4), 26.6 (-C(CH₃)₂), 25.2 (-C(CH₃)₂), 6.7 (CH₃, -Si(CH₂CH₃)₃), 5.1 (CH₂, -Si(CH₂CH₃)₃); FTIR 2955, 2913, 2878, 1732, 1458, 1416, 1381, 1372, 1241, 1215, 1126, 1066, 1003, 928, 831, 727, 972 cm⁻¹; HRMS (ESI) m/z calc for C₁₅H₂₈O₄SiNa: 323.1655, Found: 323.1664 [M+Na]⁺.
(2E,4R,5R,6R) Ethyl 4,5-O-isopropylidene-2,3,7,8-tetraol-2,7-dien-1-oate 108 Compound 107 (6.0 g, 0.020 mol) was dissolved in toluene (100 mL). (Carbethoxy methylene) triphenylphosphorane (10.4 g, 0.030 mol) was charged and the reaction was heated to reflux for 12 h. The reaction was concentrated to a yellow solid. The residue was purified by column chromatography (1:10 EtOAc:Hexane) to give 108 (6.1 g, 83%) as a clear oil. (TLC 1:9 EtOAc:Hexane, Rf 0.7); [α]D +15.3 (c 4.9, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.02 (dd, J = 15.7, 6.2 Hz, 1H, H-3), 6.02 (dd, J = 15.7, 1.5 Hz, 1H, H-2), 5.84 (dddd, J = 16.8, 10.4, 4.1, 2.1 Hz, 1H, H-7), 5.28 (d, J = 17.2 Hz, 1H, H-8'), 5.17 (dd, J = 10.4, 1.7 Hz, 1H, H-8'), 4.65 (td, J = 6.4, 1.5 Hz, 1H, H-4), 4.20 (q, J = 7.1 Hz, 2H, -CO2Et), 4.16 – 4.13 (m, 2H, H-5, H-6, overlapping signals), 1.51 (s, 3H, -C(CH3)2), 1.36 (s, 3H, -C(CH3)2), 1.28 (t, J = 7.1 Hz, 3H, -CO2Et), 0.94 (t, J = 7.9 Hz, 9H, -Si(CH2CH3)3), 0.59 (qd, J = 7.9, 1.2 Hz, 6H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 165.9 (C-1), 143.7 (C-3), 136.7 (C-7), 122.8 (C-2), 117.4 (C-8), 109.3 (-C(CH3)2), 81.6 (C-5), 76.5 (C-4), 72.9 (C-6), 60.4 (-CO2Et), 27.3 (-C(CH3)2), 25.3 (-C(CH3)2), 14.2 (-CO2Et), 6.7 (CH3, -Si(CH2CH3)3), 4.9 (CH2, -Si(CH2CH3)3); FTIR 2956, 2909, 2877, 1722, 1659, 1459, 1416, 1369, 1303, 1250, 1216, 1159, 1063, 1034, 1005, 979, 931, 884, 837, 802, 727 cm⁻¹; HRMS (ESI) m/z calc for C19H34O5SiNa: 393.2073, Found: 393.2060 [M+Na]+.
(2E,4R,5R,6R)-4,5-O-isopropylidene-2,3,7,8-tetradeoxy-6-O-triethylsilyl-octa-2,7-dien-1-ol 109 Compound 108 (6.0 g, 0.016 mol) was dissolved in CH₂Cl₂ (80 mL) and cooled to -78 °C. DIBAL-H (49 mL, 0.049 mol, 1.0 M in CH₂Cl₂) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H₂O (40 mL), dried over Na₂SO₄ and concentrated to give 109 (4.41 g, 84%) as a clear oil. (1:9 EtOAc:Hexane, Rf 0.2); [α]D +20.6 (c 1.0 in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.89 – 5.82 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.30 (dt, J = 17.2, 1.7 Hz, 1H, H-8), 5.14 (dt, J = 10.5, 1.6 Hz, 1H, H-8’), 4.50 (t, J = 6.8 Hz, 1H, H-4), 4.16 – 4.14 (m, 3H, H-1, H-1’, H-6, overlapping signals), 3.98 (t, J = 6.5 Hz, 1H, H-5), 1.48 (s, 3H, -C(CH₃)₂), 1.34 (s, 3H, -C(CH₃)₂), 0.94 (t, J = 7.9 Hz, 9H, -Si(CH₂CH₃)₃), 0.60 (qd, J = 7.9, 2.8 Hz, 6H, -Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 137.0 (C-7), 133.7 (C-2), 127.3 (C-3), 116.6 (C-8), 108.6 (-C(CH₃)₂), 81.7 (C-5), 78.1 (C-4), 72.6 (C-6), 62.8 (C-1), 27.7 (-C(CH₃)₂), 25.5 (-C(CH₃)₂), 6.8 (CH₃, -Si(CH₂CH₃)₃), 5.0 (CH₂, -Si(CH₂CH₃)₃); FTIR 3423, 2954, 2913, 2877, 1742, 1458, 1415, 1370, 1239, 1218, 1145, 1126, 1093, 1059, 1003, 974, 928, 868, 845, 741, 725 cm⁻¹; HRMS (ESI) m/z calc for C₃₄H₆₃O₈SiO: 655.4062, Found: 655.4061 [2M-H]⁺.
Experimental

Chapter 6

(2E,4R,5R,6R)-1-Azido-4,5-O-isopropylidene-2,3,7,8-tetrahydroxy-6-O-
trithylsilyl-octa-2,7-diene 110

Compound 109 (4.4 g, 0.013 mol) was dissolved in THF (80 mL). Triphenyl phosphine (6.0 g, 0.023 mol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (4.5 mL, 0.023 mol) and diphenylphosphoryl azide (4.9 mL, 0.023 mol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (1:6 EtOAc:Hexane) gave 110 (3.46 g, 73%) as a clear oil. (TLC 1:9 EtOAc:Hexane, Rf 0.7); [α]D +18.2 (c 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.94 – 5.84 (m, 2H, H-3, H-7, overlapping signals), 5.77 (dt, J = 15.4, 6.1 Hz, 1H, H-2), 5.32 (d, J = 18.3 Hz, 1H, H-1), 5.17 (d, J = 10.4 Hz, 1H, H-1’), 4.53 (t, J = 7.0 Hz, 1H, H-4), 4.17 (t, J = 6.4 Hz, 1H, H-6), 4.02 (t, J = 6.5 Hz, 1H, H-5), 3.80 (apt d, J = 6.0 Hz, 2H, H-1, H-1’), 1.50 (s, 3H, -C(CH₃)₂), 1.36 (s, 3H, -C(CH₃)₂), 0.96 (t, J = 7.9 Hz, 9H, -Si(CH₂CH₂CH₃)), 0.62 (qd, J = 7.9, 2.1 Hz, 6H, -Si(CH₂CH₂CH₃)); ¹³C NMR (126 MHz, CDCl₃) δ 136.8 (C-7), 131.2 (C-3), 127.2 (C-2), 116.9 (C-8), 108.8 (C(1)), 81.6 (C-5), 77.6 (C-4), 72.6 (C-6), 52.1 (C-1), 27.7 (C(1)C₂), 25.5 (C(1)C₂), 6.8 (CH₃, -Si(CH₂CH₂CH₃)), 5.0 (CH₂, -Si(CH₂CH₂CH₃)); FTIR 2935, 2913, 2877, 2099 (-N₃), 1741, 1458, 1415, 1380, 1370, 1240, 1218, 1144, 1125, 1092, 1060, 1006, 974, 930, 866, 844, 915, 777, 741, 725 cm⁻¹; HRMS (ESI) m/z calc for C₁₇H₃₂O₃N₃Si: 354.2213, Found: 354.2201 [M+H]⁺.
(4R,5S,6R)-1-Azido-6-hydroxy-4,5-O-isopropylidene-2,3,7,8-tetraedoxy-octa-2,7-diene 111 Compound 110 (3.5 g, 9.77 mmol) was dissolved in THF (80 mL). TBAF (29 mL, 0.029 mol, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The solution was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo. Flash column chromatography of the residue (1:1 EtOAc:Hexane) gave 111 (1.7 g, 73%), a mixture of isomers as a clear oil. (1:4 EtOAc:Hexane Rf 0.1); ¹H NMR (500 MHz, CDCl₃) δ 5.97 (ddt, J = 15.4, 7.7, 1.3 Hz, 1H, H-3), 5.87 – 5.81 (m, 2H, H-2, H-7, overlapping signals), 5.37 (apt d, J = 17.2 Hz, 1H, H-8), 5.25 (apt d, J = 10.5 Hz, 1H, H-8’), 4.66 (apt t, J = 6.8 Hz, 1H, H-4), 4.14 – 4.10 (m, 2H, H-5, H-6, overlapping signals), 3.83 – 3.82 (m, 2H, H-1, H-1’, overlapping signals), 1.54 (s, 3H, -C(CH₃)₂), 1.40 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 136.7 (C-7), 130.7 (C-3), 128.2 (C-2), 117.4 (C-8), 109.0 (-C(CH₃)₂), 80.5 (C-5), 77.6 (C-4), 70.7 (C-6), 52.0 (C-1), 27.3 (-C(CH₃)₂), 24.9 (-C(CH₃)₂); FTIR 3449, 2988, 2935, 2909, 2099 (-N₃), 1738, 1643, 1455, 1372, 1218, 1165, 1139, 1085, 1048, 974, 931, 859, 789 cm⁻¹; HRMS (ESI) m/z calc for C₂₂H₃₄O₈N₆Na: 501.2438, Found: 501.2421 [2M+Na]⁺.
6-O-Acetyl-1,5-dideoxy-2,3-O-isopropylidene-1-(S)-ethenyl-1,5-imino-D-mannitol 112 Compound 111 (400 mg, 1.67 mmol) was dissolved in DMF (20 mL) and heated to 100 °C for 1 h. The reaction was cooled to 80 °C. AcOH (480 μl, 8.36 mmol) was charged and the solution was stirred at rt for 8 h. The mixture was diluted with H₂O (15 mL) and extracted with EtOAc until no product remained in the aq layer (as observed by TLC EtOAc, Rf 0.3). The combined org layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:1 EtOAc:Hexane) gave 112 as a pale yellow foam (205.4 mg, 45%). [α]D -17.6 (c 0.47, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddd, J = 17.4, 10.6, 5.5 Hz, 1H, H-7), 5.31 (ddd, J = 17.4, 1.7, 1.1 Hz, 1H, H-8), 5.26 (dt, J = 10.6, 1.4 Hz, 1H, H-8'), 4.46 (dd, J = 11.4, 5.8 Hz, 1H, H-6), 4.18 (dd, J = 11.4, 3.3 Hz, 1H, H-6'), 4.14 (dd, J = 5.6, 4.1 Hz, 1H, H-2), 4.05 (dd, J = 6.7, 5.6 Hz, 1H, H-3), 3.72 (ddt, J = 5.7, 3.9, 1.7 Hz, 1H, H-1), 3.59 (dd, J = 8.9, 6.7 Hz, 1H, H-4), 2.91 (ddd, J = 9.0, 5.8, 3.3 Hz, 1H, H-5), 2.10 (s, 3H, -COCH₃), 1.53 (s, 3H, -C(CH₃)₂), 1.38 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 171.3 (C=O), 136.8 (C-7), 117.2 (C-8), 109.1 (-C(CH₃)₂), 78.6 (C-3), 76.8 (C-2), 70.4 (C-4), 64.0 (C-6), 55.1 (C-1), 53.2 (C-5), 28.1 (-C(CH₃)₂), 26.1 (-C(CH₃)₂), 20.8 (-COCH₃); FTIR 3323, 2986, 2935, 1737, 1644, 1457, 1370, 1238, 1219, 1164, 1056, 924, 842, 786, 738 cm⁻¹; HRMS (ESI) m/z calc for C₁₃H₂₂O₅N: 272.1498, Found: 272.1507 [M+H]⁺.
1,5-Dideoxy-1-(S)-ethenyl-1,5-imino-ᴅ-mannitol 85 Compound 112 (40.2 mg, 0.15 mmol) was dissolved in aq HCl (5 mL) and stirred at rt for 4 h. The solvent was removed under diminished pressure and the residue was purified using ion-exchange chromatography (Dowex 50WX8 (200-400 mesh). The resin was washed thoroughly with MeOH (25 mL), water (25 mL) followed by 1 N NH₄OH (40 mL) to give 85 (25.4 mg, 91%) as a yellow foam. (TLC 1:9 MeOH:EtOH w/NH₄OH, Rₜ 0.35); [α]D +18.7 (c 0.44, MeOH); ¹H NMR (500 MHz, D₂O) δ 5.98 (ddd, J = 17.7, 10.5, 6.0 Hz, 1H, H-7), 5.44 (apt d, J = 10.6 Hz, 1H, H-8), 5.44 (apt d, J = 17.8 Hz, 1H, H-8’), 4.11 (t, J = 2.8 Hz, 1H, H-2), 3.890 – 3.83 (m, 3H, H-1, H-6, H-6’, overlapping signals), 3.81 – 3.76 (m, 2H, H-3, H-4, overlapping signals), 3.01 (m, 1H H-5); ¹³C NMR (126 MHz, D₂O) δ 131.9 (C-7), 119.8 (C-8), 71.3 (C-2), 70.8 (C-3), 67.6 (C-4), 59.7 (C-6), 59.2 (C-1), 55.8 (C-5); FTIR 3302, 2929, 2887, 2460, 1654, 1560, 1410, 1387, 1338, 1254, 1058, 928, 804 cm⁻¹; HRMS (ESI) m/z calc for C₈H₁₆O₄N: 190.1079, Found: 190.1084 [M+H]⁺.
6-Azido-1,5-dideoxy-2,3-O-isopropylidene-1-ethenyl-1,5-imino-d-mannitol

Compound 111 (50 mg, 0.21 mmol) was dissolved in DMF (5 mL) and heated to 100 °C for 1 h. The reaction was cooled to 80 °C. NaN₃ (68 mg, 1.05 mmol) and AcOH (6 μL, 0.10 mmol) were charged and the solution was stirred at 80 °C for 8 h. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc until no product remained in the aq layer (as observed by TLC EtOAc, Rf 0.4). The combined org layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (gradient EtOAc:Hexane) gave 113 as a pale yellow foam (13.3 mg, 25% overall, 10% mixture β:α, 1:0.6).

**Major isomer:** [α]_D -5.7 (c 1.8, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.91 (ddd, J = 17.0, 10.4, 6.4 Hz, 1H, H-7), 5.30 (dt, J = 17.3, 1.5 Hz, 1H, H-8), 5.21 (dt, J = 10.4, 1.4 Hz, 1H, H-8'), 4.28 – 4.24 (m, 2H, H-2, H-3, overlapping signals), 3.94 (apt t, J = 3.1 Hz, 1H, H-4), 3.84 (dq, J = 6.4, 1.4 Hz, 1H, H-1), 3.51 – 3.44 (m, 2H, H-6, H-6', overlapping signals), 3.39 (td, J = 6.4, 3.2 Hz, 1H, H-5), 1.49 (s, 3H, -C(CH₃)₂), 1.35 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 136.9 (C-7), 116.6 (C-8), 109.1 (-C(CH₃)₂), 75.6, 75.0 (C-2, C-3), 68.7 (C-4), 53.0 (C-6), 52.7 (C-1), 50.3 (C-5), 26.8 (-C(CH₃)₂), 24.3 (-C(CH₃)₂); FTIR 3317, 2984, 2960, 2930, 2873, 2103 (-N₃), 1721, 1645, 1554, 1456, 1377, 1261, 1243, 1212, 1161, 1082, 1056, 991, 925, 873, 723 cm⁻¹; HRMS (ESI) m/z calc for C₁₁H₁₉O₄N₄: 255.1457, Found: 255.1447 [M+H]^+.

**Minor isomer:** ¹H NMR (500 MHz, CDCl₃) δ 5.87 (ddd, J = 17.4, 10.6, 5.4 Hz, 1H, H-7), 5.33 (dt, J = 17.4, 1.4 Hz, 1H, H-8), 5.27 (dt, J 10.6, 1.4 Hz, 1H, H-8'), 4.14 (dd, J = 5.7, 4.1 Hz, 1H, H-2), 4.01 (dd, J = 6.9, 5.7 Hz, 1H, H-3), 3.73 – 3.71 (m, 1H, H-1), 3.64 (dd, J = 9.0, 6.9 Hz, 1H, H-4), 3.63 – 3.58 (m, 1H, H-6, overlapping signals), 3.57 (dd, J = 12.3, 3.7 Hz, 1H, H-6'), 2.86 (ddd, J = 8.9, 6.4, 3.7 Hz, 1H, H-5), 1.54 (s, 3H, -C(CH₃)₂), 1.38 (s, 3H, -C(CH₃)₂); HRMS (ESI) m/z calc for C₁₁H₁₉O₄N₄: 255.1457, Found: 255.1450 [M+H]^+.
6-Azido-1,5-dideoxy-1-ethenyl-1,5-imino-d-mannitol 114 Compound 113 (5 mg, 0.2 mmol) was dissolved in aq HCl (5 mL) and stirred at rt for 4 h. The solvent was removed under diminished pressure and the residue was purified using ion-exchange chromatography (Dowex 50WX8 (200-400 mesh). The resin was washed thoroughly with MeOH and H₂O followed by 1 N NH₄OH to give 114 (2.1 mg, 50% (1:0.2 β:α)) as an oil. (TLC 1:9 MeOH:EtOH w/NH₄OH, Rᵣ 0.4); ¹H NMR (500 MHz, D₂O) δ 5.82 (ddd, J = 17.6, 11.9, 6.6 Hz, 1H, H-7), 5.15 (apt d, J = 17.5 Hz, 1H, H-8’), 5.14 (apt d, J = 10.6 Hz, 1H, H-8’), 3.85 (dd, J = 9.5, 5.5 Hz, 1H, H-4), 3.82 (t, J = 2.9 Hz, 1H, H-2), 3.64 (dd, J = 9.4, 3.3 Hz, 1H, H-3), 3.54 – 3.46 (m, 2H, H-6, H-6’, overlapping signals), 3.47 (dd, J = 5.8, 3.3 Hz, 1H, H-1), 3.25 – 3.21 (m, 1H, H-5); ¹³C NMR (126 MHz, D₂O) δ 135.2 (C-7), 117.0 (C-8), 71.3 (C-2), 70.6 (C-3), 68.4 (C-4), 54.7 (C-1), 54.0 (C-5), 47.5 (C-6); HRMS (ESI) m/z calc for C₈H₁₆O₃N₄: 215.1144, Found: 215.1148 [M+H]⁺.
6-O-Acetyl-N-tert-butoxycarbonyl-1,5-dideoxy-2,3-O-isopropylidene-1-(S)-ethenyl-1,5-imino-D-mannitol 115 Compound 112 (80 mg, 0.30 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL). Et$_3$N (49 µl, 0.35 mmol), Boc$_2$O (167 mg, 0.77 mmol) and DMAP (26.3 mg, 0.30 mmol) were added and the reaction was stirred at rt for 24 h. The solvent was removed under diminished pressure and flash column chromatography of the residue (1:1 EtOAc:Hexane) gave 115 as a pale yellow foam (82 mg, 75%). (TLC EtOAc, R$_f$ 0.8); $[\alpha]_D$ -25.0 (c 1.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.85 (ddd, $J$ = 17.4, 10.7, 5.0 Hz, 1H, H-7), 5.31 (ddd, $J$ = 17.5, 1.9, 1.1 Hz, 1H, H-8), 5.27 (ddd, $J$ = 10.7, 1.9, 1.1 Hz, 1H, H-8’), 4.79 (dd, $J$ = 9.1, 6.7 Hz, 1H, H-4), 4.28 (dd, $J$ = 11.5, 5.5 Hz, 1H, H-6), 4.18 (dd, $J$ = 5.1, 3.2 Hz, 1H, H-2), 4.14 (dd, $J$ = 6.7, 5.1 Hz, 1H, H-3), 4.02 (dd, $J$ = 11.5, 3.4 Hz, 1H, H-6’), 3.80 (ddt, $J$ = 5.1, 3.5, 1.9 Hz, 1H, H-1), 3.02 (ddd, $J$ = 9.0, 5.5, 3.4 Hz, 1H, H-5), 2.08 (s, 3H, -COCH$_3$), 1.59 (s, 3H, -C(CH$_3$)$_3$), 1.47 (s, 9H, -C(CH$_3$)$_3$), 1.38 (s, 3H, -C(CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.7 (C=O), 152.7 (C=O), 136.2 (C-7), 117.4 (C-8), 109.2 (-C(CH$_3$)$_2$), 82.7 (-C(CH$_3$)$_3$), 76.8 (C-2), 76.0 (C-3), 74.0 (C-4), 63.1 (C-6), 54.5 (C-1), 51.1 (C-5), 27.9 (-C(CH$_3$)$_2$), 27.7 (-C(CH$_3$)$_3$), 26.5 (-C(CH$_3$)$_2$), 20.8 (-COCH$_3$); FTIR 3341, 2984, 2936, 1742, 1478, 1369, 1274, 1253, 1219, 1158, 1094, 1060, 982, 927, 865, 787, 737 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{18}$H$_{29}$O$_7$N: 372.2022, Found: 372.2024 [M+H]$^+$. 

![Diagram of compounds 112 and 115]
6-O-Acetyl-N-tert-butoxycarbonyl-1,5-dideoxy-2,3-O-isopropylidene-1-(S)-ethynyl-1,5-imino-β-mannitol Compound 115 (40 mg, mmol) was dissolved in MeOH (10 mL). Pd/C (10 mol %) was added. A H₂ balloon was attached and the reaction was stirred at rt for 4 h. The reaction was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give the product as a clear oil (34.2 mg, 86%). [α]₀ -21.8 (c 1.16, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.76 (dd, J = 8.9, 6.8 Hz, 1H, H-4), 4.26 (dd, J = 11.4, 5.8 Hz, 1H, H-6), 4.14 (dd, J = 6.8, 5.3 Hz, 1H, H-3), 4.01 (dd, J = 11.4, 3.3 Hz, 1H, H-6'), 3.97 (dd, J = 5.2, 3.3 Hz, 1H, H-2), 3.00 (ddd, J = 9.2, 5.6, 3.5 Hz, 1H, H-1), 2.94 (ddd, J = 9.1, 5.8, 3.5 Hz, 1H, H-5), 2.07 (s, 3H, -COCH₃), 1.59 – 1.55 (m, 1H, -CH₂, overlapping signals), 1.55 (s, 3H, -C(CH₃)₂), 1.47 (s, 9H, -C(CH₃)₃), 1.44 – 1.41 (m, 1H, -CH₂, overlapping signals), 1.35 (s, 3H, -C(CH₃)₂), 0.98 (t, J = 7.4 Hz, 3H, -CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 170.7 (C=O), 152.7 (C=O), 109.2 (-C(CH₃)₂), 82.6 (-C(CH₃)₃), 77.6 (C-2), 76.0 (C-3), 74.2 (C-4), 63.3 (C-6), 54.0 (C-1), 50.7 (C-5), 27.9 (-C(CH₃)₂), 27.7 (-C(CH₃)₃), 26.4 (-C(CH₃)₂), 24.8 (-CH₂-), 20.8 (-COCH₃), 10.9 (-CH₃); FTIR 2980, 2960, 2934, 2873, 1743, 1459, 1370, 1274, 1253, 1221, 1160, 1094, 1052, 1040, 979, 929, 866, 787, 744 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₃₂O₇N: 374.2179, Found: 374.2202 [M+H]^+. 
1,5-Dideoxy-1-(S)-ethynl-1,5-imino-D-mannitol 8 Compound 85 (20 mg, 0.11 mmol) was dissolved in MeOH (10 mL). Pd/C (10 mol %) and HCl (3.6 μL, 0.12 mmol) were charged. A H₂ balloon was attached and the reaction was stirred at rt for 4 h. The reaction was filtered and concentrated in vacuo. The residue was purified by ion exchange chromatography (MeOH, H₂O, 1.0 M NH₄OH) to give 8 (16.2 mg, 80%) as a clear oil. [α]D -2.2 (c 0.29, D₂O); ¹H NMR (500 MHz, D₂O) δ 3.97 (t, J = 2.8 Hz, 1H, H-2), 3.79 (apt d, J = 4.0 Hz, 2H, H-6, H-6’), 3.76 (dd, J = 9.5, 3.2 Hz, 1H, H-3), 3.64 (t, J = 9.7 Hz, 1H, H-4), 2.93 (td, J = 7.6, 2.4 Hz, 1H, H-1), 2.74 (dt, J = 9.9, 4.0 Hz, 1H, H-5), 1.59 (p, J = 7.5 Hz, 2H, -CH₂), 0.97 (t, J = 7.5 Hz, 3H, -CH₃); ¹³C NMR (126 MHz, D₂O) δ 71.4 (C-3), 71.1 (C-2), 68.6 (C-4), 60.8 (C-6), 59.0 (C-1), 54.8 (C-5), 21.5 (-CH₂), 10.5 (-CH₃); FTIR 3301, 2964, 2934, 2881, 1664, 1613, 1572, 1461, 1404, 1344, 1250, 1150, 1054, 952, 891, 812, 749 cm⁻¹; HRMS (ESI) m/z calc for C₆H₁₆O₄N: 190.1079, Found: 190.1080 [M-H].
Experimental Data for Chapter 5

6-Deoxy-1,2:3,4-di-O-isopropylidene-6-iodo-α-D-galactopyranoside  116

1,2:3,4-di-O-isopropyl-α-D-galactopyranoside (20.0 g, 0.077 mol), triphenyl phosphine (30.3 g, 0.115 mol) and imidazole (10.5 g, 0.154 mol) were dissolved in THF (100 mL). Iodine (29.27 g, 0.115 mol) in THF was added portionwise. The reaction mixture was stirred at reflux for 4 h. The reaction was cooled to rt and quenched with 10% aq Na2S2O3. The product was extracted with EtOAc (3 x 100 mL), the combined org layers were washed with brine (80 mL), dried over Na2SO4 and concentrated in vacuo. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 116 as a pale yellow solid (24.5 g, 86%). (1:4 EtOAc:Hexane, Rf 0.7); [α]D -49.4 (c 0.86, CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.54 (d, J = 5.0 Hz, 1H, H-1), 4.62 (dd, J = 7.9, 2.5 Hz, 1H, H-3), 4.41 (dd, J = 7.9, 1.9 Hz, 1H, H-4), 4.30 (dd, J = 5.0, 2.5 Hz, 1H, H-2), 3.95 (td, J = 7.0, 1.9 Hz, 1H, H-5), 3.32 (dd, J = 10.0, 6.8 Hz, 1H, H-6), 3.21 (dd, J = 9.9, 7.1 Hz, 1H, H-6'), 1.54 (s, 3H, -C(CH3)2), 1.45 (s, 3H, -C(CH3)2), 1.36 (s, 3H, -C(CH3)2), 1.34 (s, 3H, -C(CH3)2); 13C NMR (126 MHz, CDCl3) δ 109.74 (-C(CH3)2), 109.06 (-C(CH3)2), 96.90 (C-1), 71.78 (C-3), 71.33 (C-4), 70.78 (C-2), 69.15 (C-5), 26.23 (-C(CH3)2), 26.16 (-C(CH3)2), 25.08 (-C(CH3)2), 24.64 (-C(CH3)2), 2.51 (C-6); FTIR 2974, 2916, 2904, 1460, 1390, 1369, 1257, 1203, 1166, 1109, 1060, 1023, 996, 902, 865, 811, 760 cm⁻1.
Methyl 6-deoxy-6-iodo-\(\alpha\)-\(\delta\)-galactopyranoside 117 AcCl (14.2 mL, 0.199 mol) was added dropwise to 1 (24.54 g, 0.066 mol) in MeOH (350 mL). After stirring for 2 days at rt, the mixture was concentrated \textit{in vacuo} and the residue was crystallised from MeOH to give 117 (14.72 g, 73%) as white crystals. All analytical data given for 117 corresponded well with the literature.\(^{169}\) \([\alpha]_D \) -54.7 (c 2.0 in CHCl\(_3\); \(^1\)H NMR (500 MHz, D\(_2\)O) \(\delta\) 4.69 (d, \(J = 1.8\) Hz, 1H, H-1), 3.97 (d, \(J = 1.3\) Hz, 1H, H-4), 3.93 (dd, \(J = 9.2, 4.7\) Hz, 1H, H-5), 3.70 – 3.66 (m, 2H, H-2, H-3, overlapping signals), 3.35 (s, 3H, -OCH\(_3\)), 3.27 – 3.18 (m, 2H, H-6, H-6', overlapping signals); \(^{13}\)C NMR (126 MHz, D\(_2\)O) \(\delta\) 99.5 (C-1), 71.4 (C-5), 70.1 (C-4), 69.3 (C-2), 67.8 (C-3), 55.5 (-OCH\(_3\)), 2.3 (C-6); FTIR 3354, 3234, 2954, 2936, 2906, 2487, 2422, 1648, 1451, 1415, 1360, 1298, 1200, 1146, 1133, 1099, 1076, 1025, 999, 934, 883, 853, 788, 687 cm\(^{-1}\); HRMS (ESI) \(m/z\) calc for C\(_7\)H\(_{13}\)I\(_5\)O\(_5\): 338.9496, found: 338.9500 [M+Cl\(^{-}\)].
Methyl 6-deoxy-6-iodo-2,3,4-tris-O-triethylsilyl-α-D-galactopyranoside 118

Compound 117 (12.9 g, 0.042 mol) was suspended in CH₂Cl₂ (200 mL). Imidazole (17.27 g, 0.25 mol) and chlorotriethylsilane (42.6 mL, 0.25 mol) were charged and the reaction was stirred at rt for 12 h. The reaction was diluted with H₂O (100 mL) and stirred for 15 min. The layers were separated and the org layer was washed with H₂O (80 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (Hexane followed by 1:30 EtOAc:Hexane) to give 118 as a clear oil (21.9 g, 80%). All analytical data given for 118 corresponded well with the literature.[^69] [α]₀ +60.2 (c 3.0 in CHCl₃); [¹H NMR (500 MHz, CDCl₃) δ 4.69 (d, J = 3.4 Hz, 1H, H-1), 4.05 (apt s, 1H, H-4), 3.98 (dd, J = 9.4, 3.4 Hz, 1H, H-2), 3.90 – 3.87 (m, 2H, H-3, H-5, overlapping signals), 3.46 (s, 3H, CH₃), 3.33 (apt t, J = 8.6 Hz, 1H, H-6), 3.24 (dd, J = 9.8, 5.7 Hz, 1H, H-6), 0.92 – 0.85 (m, 27 H, -Si(CH₂CH₃)₃), 0.95 – 0.52 (m, 18H, -Si(CH₂CH₃)₃); [¹³C NMR (126 MHz, CDCl₃) δ 100.5 (C-1), 73.7 (C-4), 72.2 (C-3), 71.5 (C-5), 69.5 (C-2), 55.5 (-OCH₃), 7.1 – 6.7 (CH₃, -Si(CH₂CH₃)₃), 5.8 – 5.2 (CH₂, -Si(CH₂CH₃)₃), 4.9 (C-6); FTIR 2953, 2911, 2877, 1458, 1414, 1379, 1355, 1238, 1199, 1145, 1102, 1070, 1037, 1003, 979, 924, 895, 850, 789, 721 cm⁻¹; HRMS (ESI) m/z calc for C₂₇H₅₈IO₅Si₃Na: 710.2565, found: 710.2551 [M+ACN+Na]^+.
Compound 118 (10.2 g, 0.016 mol) was dissolved in a mixture of THF/H$_2$O (9:1, 150 mL). Zn powder (pre-activated, 10.3 g, 0.16 mol) was added and the suspension was sonicated at 40 °C for 5 h. The reaction was filtered through a pad of celite and washed with Et$_2$O (150 mL). The combined org layers were washed with NaHCO$_3$ (50 mL), brine (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 119 as a clear oil (5.93 g, 77%). [α]$_D$ -36.2 (c 1.7, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.66 (s, 1H, H-1), 5.89 – 5.82 (m, 1H, H-5, 5.04 – 5.00 (m, 2H, H-6, H-6’, overlapping signals), 4.21 (apt d, $J = 8.1$ Hz, 1H, H-4), 3.93 (apt d, $J = 0.9$ Hz, 2H, H-2, H-3, overlapping signals), 0.93 – 0.84 (m, 27H, -SiCH$_3$CH$_2$), 0.59 – 0.49 (m, 18H, -SiCH$_3$CH$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.0 (C-1), 138.2 (C-5), 117.0 (C-6), 79.3, 79.2 (C-2, C-3), 76.2 (C-4), 6.8 – 6.4 (CH$_3$, -SiCH$_3$CH$_2$), 5.8 – 4.8 (CH$_2$, -SiCH$_3$CH$_2$); FTIR 2955, 2912, 2877, 1736, 1459, 1415, 1378, 1238, 1167, 1132, 1089, 1004, 973, 930, 884, 845, 821, 787 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{24}$H$_{52}$O$_4$Si$_3$Na: 511.3071, found: 511.3059 [M+Na]$^+$. 

(2R,3S,4S)-5,6-Dideoxy-2,3,4-tri-O-triethylsilyl-hex-5-en-1-ol 119
(2E,4S,5S,6S) Ethyl 2,3,7,8-Tetrahydroxy-4,5,6-O-triethylsilyl-octa-2,7-dienoate 120 Compound 119 (5.9 g, 0.012 mol) was dissolved in toluene (80 mL). (Carbethoxymethylene) triphenylphosphorane (6.4 g, 0.018 mol) was charged and the mixture was heated to reflux for 12 h. The solvent was removed under diminished pressure and flash column chromatography of the residue (Hexane followed by 1:30 EtOAc:Hexane) gave 120 as a clear oil (5.6 g, 83%). (TLC 1:20 EtOAc:Hexane, Rf 0.65); \([\alpha]_D ^{20} = -0.6 (c 1.3, \text{CHCl}_3)\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta 6.97 (dd, J = 15.7, 4.3 \text{ Hz}, 1\text{H}, H-3), 5.86 (dd, J = 15.7, 1.9 \text{ Hz}, 1\text{H}, H-2), 5.74 (ddd, J = 17.5, 10.4, 7.2 \text{ Hz}, 1\text{H}, H-7), 4.99 (ddd, J = 10.3, 2.0, 0.9 \text{ Hz}, 1\text{H}, H-8), 4.97 (ddd, J = 17.2, 2.0, 1.0 \text{ Hz}, 1\text{H}, H-8'), 4.19 (ddd, J = 6.0, 4.3, 2.0 \text{ Hz}, 1\text{H}, H-4), 4.16 – 4.10 (m, 3\text{H}, H-3, -OCH\(_2\)), 3.73 (dd, J = 5.9, 1.8 \text{ Hz}, 1\text{H}, H-5), 1.22 (t, J = 7.1 \text{ Hz}, 3\text{H}, -CH\(_3\)), 0.91 – 0.84 (m, 27\text{H}, -SiCH\(_2\)CH\(_3\)), 0.59 – 0.47 (m, 18\text{H}, -SiCH\(_2\)CH\(_3\)); \(^{13}^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta 166.5 (\text{C-1}), 148.9 (\text{C-3}), 137.9, 120.1 (\text{C-2, C-7}), 116.8 (\text{C-8}), 80.1 (\text{C-5}), 74.2 (\text{C-6}), 73.8 (\text{C-4}), 60.1 (-OCH\(_2\)), 14.3 (-CH\(_3\)), 6.9 – 6.8 (CH\(_3\), -SiCH\(_2\)CH\(_3\)), 4.9 – 4.8 (CH\(_2\), -SiCH\(_2\)CH\(_3\)); FTIR 2955, 2877, 1724, 1356, 1459, 1369, 1258, 1239, 1203, 1164, 1110, 1063, 1019, 900, 925, 903, 836, 723 cm\(^{-1}\); HRMS (ESI) \(m/z\) calc for C\(_{28}\)H\(_{59}\)O\(_5\)Si\(_3\): 559.3670, found 559.3674 [M+H].
Compound 120 (5.6 g, 0.010 mol) was dissolved in CH$_2$Cl$_2$ (100 mL) and cooled to -78 °C. DIBAL-H (30.25 mL, 0.030 mol, 1.0 M in THF) was charged slowly. The reaction was stirred at -78 °C for 8 h. The reaction was quenched with MeOH at -78 °C. The solution was warmed to rt and stirred with aq potassium sodium tartrate solution for 1 h. The layers were separated and the org layer washed with H$_2$O (30 mL) and brine (30 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography of the residue (Hexane followed by 1:30 EtOAc:Hexane) gave 121 as a colourless oil (6.1 g, 90%).

(TLC 1:20 EtOAc:Hexane, R$_f$ 0.4); [α]$_D$ -9.3 (c 0.42, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.81 (ddd, $J$ = 16.9, 10.9, 7.1 Hz, 1H, H-7), 5.72 – 5.65 (m, 2H, H-2, H-3, overlapping signals), 5.00 (d, $J$ = 16.9 Hz, 1H, H-8), 5.00 (d, $J$ = 10.9 Hz, 1H, H-8’), 4.18 (dd, $J$ = 7.0, 0.5 Hz, 1H, H-6), 4.05 (d, $J$ = 2.3 Hz, 2H, H-1, H-1’, overlapping signals), 4.03 (dt, $J$ = 5.1, 2.3 Hz, 1H, H-4), 3.65 (dd, $J$ = 6.0, 1.8 Hz, 1H, H-5), 0.91 – 0.85 (m, 27H, -SiCH$_2$CH$_3$), 0.58 – 0.48 (m, 18H, -SiCH$_2$SiCH$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.7 (C-7), 132.1, 129.3 (C-2, C-3), 115.9 (C-8), 80.5 (C-5), 74.2 (C-4), 74.0 (C-6), 63.4 (C-1), 6.9 – 6.9 (CH$_3$, -SiCH$_2$CH$_3$), 5.0 – 4.9 (CH$_2$, -SiCH$_2$CH$_3$); FTIR 3363, 2954, 2912, 2877, 1458, 1414, 1378, 1238, 1118, 1073, 1003, 973, 916, 833, 719 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{26}$H$_{55}$O$_4$Si$_3$: 515.3408, found 515.3422 m/z [M-H]$^-$. 

(2$E$,4$S$,5$S$,6$S$)-2,3,7,8-Tetra-O-triethyldimethylsilyl-octa-2,7-dien-1-ol

121 Compound 120 (5.6 g, 0.010 mol) was dissolved in CH$_2$Cl$_2$ (100 mL) and cooled to -78 °C. DIBAL-H (30.25 mL, 0.030 mol, 1.0 M in THF) was charged slowly. The reaction was stirred at -78 °C for 8 h. The reaction was quenched with MeOH at -78 °C. The solution was warmed to rt and stirred with aq potassium sodium tartrate solution for 1 h. The layers were separated and the org layer washed with H$_2$O (30 mL) and brine (30 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatography of the residue (Hexane followed by 1:30 EtOAc:Hexane) gave 121 as a colourless oil (6.1 g, 90%).
(2E,4S,5S,6S)-1-Azido-2,3,7,8-tetradeoxy-4,5,6-tri-O-triethylsilyl-octa-2,7-diene 122 Compound 121 (6.12 g, 0.012 mol) and triphenyl phosphine (5.29 g, 0.02 mol) in THF (100 mL) was cooled to 0 °C. Diisopropyl azodicarboxylate (3.97 mL, 0.02 mol) and diphenylphosphoryl azide (4.35 mL, 0.02 mol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was evaporated and the residue was purified by flash column chromatography (Hexane followed by 1:30 EtOAc:Hexane) to give 122 as a colourless oil (5.5 g, 85%). (1:20 EtOAc:Hexane, Rf 0.8); [α]_D -6.6 (c 0.51, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.83 – 5.75 (m, 2H, H-3, H-7, overlapping signals), 5.58 (dtd, J = 15.4, 6.4, 1.5 Hz, 1H, H-2), 5.00 (d, J = 16.0 Hz, 1H, H-8), 5.00 (d, J = 12.1 Hz, 1H, H-8’), 4.18 (d, J = 7.1 Hz, 1H, H-6), 4.05 (t, J = 5.7 Hz, 1H, H-4), 3.70 – 3.62 (m, 3H, H-5, H-1, H-1’, overlapping signals), 0.91 – 0.85 (m, 27H, -SiCH₂CH₃), 0.59 – 0.48 (m, 18H, -SiCH₂CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 138.4 (C-7), 135.8 (C-3), 123.5 (C-2), 116.1 (C-8), 80.3 (C-5), 74.1 (C-4), 74.0 (C-6), 52.5 (C-1), 6.9 – 6.8 (CH₃, -SiCH₂CH₃), 5.0 – 4.9 (CH₂, -SiCH₂CH₃); FTIR 2955, 2912, 2877, 2097 (-N₃), 1732, 1459, 1414, 1238, 1083, 1003, 972, 879, 844, 800, 721 cm⁻¹; HRMS (ESI) m/z calc for C₂₆H₅₆O₃N₃Si₃: 542.3630, found: 542.3618 [M+H]+.
Experimental

Compound 122 (5.5 g, 0.01 mol) was dissolved in THF (80 mL). TBAF (60 mL, 0.06 mol, 1.0 M in THF) was charged and the reaction was stirred at rt overnight. The solution was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo. Flash column chromatography (1:1 EtOAc:Hexane, Rᵣ 0.15) of the residue gave 123 (1.5 g, 76%), a clear oil as a mixture of isomers (cis:trans, ~1:1). (1:1 EtOAc:Hexane, Rᵣ 0.15); ¹H NMR (500 MHz, CDCl₃) δ 5.96 (ddd, J = 17.3, 10.6, 5.9 Hz, 1H, H-7), 5.87 – 5.86 (m, 2H, H-2, H-3, overlapping signals), 5.41 (dt, J = 17.3, 1.5 Hz, 1H, H-8), 5.32 (dt, J = 10.6, 1.4 Hz, 1H, H-8'), 4.41 (td, J = 3.2, 1.4 Hz, 1H, H-4), 4.34 (ddt, J = 5.9, 4.5, 1.5 Hz, 1H, H-6), 3.85 – 3.79 (m, 2H, H-1, H-1'), 3.54 (dd, J = 4.5, 3.4 Hz, 1H, H-5), 2.78 (s, 1H, -OH); ¹³C NMR (126 MHz, CDCl₃) δ 136.4 (C-7), 134.0 (C-3), 125.8 (C-2), 117.6 (C-8), 74.9 (C-6), 74.8 (C-5), 71.1 (C-4), 52.1 (C-1); ¹H NMR (500 MHz, D₂O) δ 5.81 (ddd, J = 17.5, 10.5, 7.0 Hz, 1H, H-7), 5.76 – 5.69 (m, 2H, H-2, H-3, overlapping signals), 5.19 (d, J = 17.5 Hz, 1H, H-8), 5.16 (s, J = 10.7 Hz, 1H, H-8'), 4.10 (t, J = 5.1 Hz, 1H, H-4), 4.02 (t, J = 6.4 Hz, 1H, H-6), 3.76 – 3.70 (m, 2H, H-1, H-1', overlapping signals), 3.40 (t, J = 5.5 Hz, 1H, H-5); ¹³C NMR (126 MHz, D₂O) δ 136.0 (C-7), 133.7, 126.4 (C-2, C-3), 118.1 (C-8), 76.0 (C-5), 72.4 (C-6), 71.4 (C-4), 51.7 (C-1); FTIR 3353, 2920, 2846, 2096 (-N₃), 1644, 1421, 1345, 1246, 1079, 1040, 975, 930, 884 cm⁻¹; HRMS (ESI) m/z calc for C₈H₁₂N₃O₃: 198.0879, found: 198.0877 [M-H]⁻.

(4S,5S,6S)-1-Azido-2,3,7,8-tetrahydroxy-4,5,6-hydroxy-octa-2,7-diene 123
(4S,5S,6S)-1-Azido-6-hydroxy-4,5-O-isopropylidene-2,3,7,8-tetrahydroxy-oct-2,7-diene 124 Compound 123 (800 mg, 4.02 mmol) was dissolved in dry acetone (10 mL, stored over sieves for 24 h). H$_2$SO$_4$ (4 μL, cat.) was added and the reaction was stirred at rt overnight. The mixture was neutralised with aq NaHCO$_3$. The solvent was removed under diminished pressure. The crude mixture was re-dissolved in CH$_2$Cl$_2$ (20 mL), washed with H$_2$O (5 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 124 (800 mg, 80%) as a clear oil. (TLC 1:1 EtOAc:Hexane, R$_f$ 0.9) $^1$H NMR (500 MHz, CDCl$_3$) δ 5.82 – 5.68 (m, 3H, H-2, H-3, H-7, overlapping signals), 5.34 (dt, $J = 17.2$, 1.6 Hz, 1H, H-8), 5.19 (dt, $J = 10.6$, 1.5 Hz, 1H, H-8'), 4.42 – 4.39 (m, 1H, H-4), 4.33 (td, $J = 3.9$, 2.0 Hz, 1H, H-6), 3.75 (dd, $J = 8.1$, 3.9 Hz, 1H, H-5), 3.73 – 3.68 (m, 2H, H-1, H-1', overlapping signals), 1.39 (s, 3H, -C(CH$_3$)$_2$), 1.37 (s, 3H, -C(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 134.2 (C-7), 132.1 (C-3), 126.0 (C-2), 116.2 (C-8), 108.4 (-C(CH$_3$)$_2$), 82.0 (C-5), 75.3 (C-4), 70.4 (C-6), 51.0 (C-1), 25.9 (-C(CH$_3$)$_2$), 25.9 (-C(CH$_3$)$_2$); FTIR 3451, 2963, 2925, 2100 (-N$_3$), 1644, 1456, 1373, 1258, 1166, 1080, 1010, 931, 864, 789, 701, 661 cm$^{-1}$; HRMS (ESI) m/z calc for C$_{11}$H$_{18}$N$_3$O$_3$: 240.1348, found: 240.1336 [M-H].
1.5-Dideoxy-2,3-O-isopropylidene-5-[1,2,3]-triazoline-1-ethenyl-1,5-imino-ᴅ-galactitol 125 Compound 124 (80 mg, 0.33 mmol) was heated to 100 °C in HPLC grade DMF (10 mL) for 12 h. The mixture cooled to rt and diluted with H₂O (10 mL). The aq layer was extracted with Et₂O until no product remained in the aq layer (as observed by TLC, 1:1 EtOAc:Hexane, Rₚ 0.5, visualised by UV and stain). The combined org layers were dried over Na₂SO₃ and concentrated. The crude residue was purified by flash column chromatography (1:2 to 1:1 EtOAc:Hexane) to give the triazoline 125 (16 mg, 20%) as a pale yellow oil and recovered starting material 124 (13 mg, 16%). ^1H NMR (500 MHz, CDCl₃) δ 6.01 – 5.95 (m, 1H, H-7), 5.54 (dq, J = 5.6, 2.6 Hz, 1H, H-1), 5.32 – 5.28 (m, 2H, H-8, H-8’), 4.65 (dd, J = 16.2, 4.2 Hz, 1H, H-6), 4.06 (dd, J = 16.2, 11.8 Hz, 1H, H-6’), 3.97 – 3.94 (m, 2H, H-2, H-4, overlapping signals), 3.55 – 3.52 (m, 2H, H-3, H-5, overlapping signals), 1.37 (s, 3H, -C(CH₃)₂), 1.37 (s, 3H, -C(CH₃)₂); ^13C NMR (126 MHz, CDCl₃) δ 130.5 (C-7), 117.6 (C-8), 110.0 (-C(CH₃)₂), 75.1, 70.5, 68.5 (C-2, C-3, C-4), 65.7 (C-6), 58.7 (C-1), 53.4 (C-5), 26.7 (-C(CH₃)₂), 26.7 (-C(CH₃)₂); LRMS (ESI) m/z calc for C₁₁H₁₈N₃O₃: 240.1343; found: 240.1288 [M+H]^+; LRMS (ESI) m/z calc for C₁₁H₁₆N₃O₃: 238.1197; found: 238.8880 [M-H]^-. 
Methyl 3,4-O-isopropylidene-α-D-galactopyranoside 126  Methyl α-D-galactopyranoside (6.0 g, 0.031 mol) was suspended in acetone (100 mL). 2,2-DMP (9.5 mL, 0.077 mol) and CSA (0.4 g, 1.54 mmol) were charged. The suspension cleared after 10 min and the solution was stirred at rt for 1.5 h. The reaction was quenched with NEt₃ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (10 % MeOH: EtOAc) to give the major product, the 3,4-O-isopropylidene protected sugar 126 (5.0 g, 70%) as a white solid and the minor product, the 4,6-O-isopropylidene protected sugar (0.7 g, 10%) as a white solid. (TLC EtOAc, Rₜ 0.24); [α]D +102.5 (c 1.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.77 (d, J = 3.8 Hz, 1H, H-1), 4.24 – 4.21 (m, 2H, H-3, H-4), 4.05 – 4.02 (m, 1H, H-5), 3.91 (ddd, J = 11.6, 6.4, 2.9 Hz, 1H, H-6), 3.80 (m, 2H, H-2, H-6, overlapping signals), 3.44 (s, 3H, -OCH₃), 2.53 (d, J = 6.6 Hz, 1H, -OH), 1.49 (s, 3H, -C(CH₃)₂), 1.33 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 109.8 (s, -C(CH₃)₂), 98.6 (d, C-1), 76.3 (d, C-3), 73.9 (d, C-4), 69.6 (d, C-2), 68.0 (d, C-5), 62.7 (t, C-6), 55.5 (q, -OCH₃), 27.7 (q, -C(CH₃)₂), 25.9 (q, -C(CH₃)₂); Minor isomer δ 4.83 (d, J = 3.6 Hz, 1H, H-1), 4.17 (dd, J = 3.7, 1.3 Hz, 1H), 4.04 (dd, J = 13.0, 1.8 Hz, 1H, H-6), 3.86 – 3.77 (m, 3H, H-2, H-6’, overlapping signals), 3.52 – 3.51 (m, 1H), 3.38 (s, 3H, -OCH₃), 1.43 (s, 3H, -C(CH₃)₂), 1.41 (d, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 100.1 (C-1), 98.9 (-C(CH₃)₂), 69.4 (C-2), 69.4, 68.6 (C-3, C-4), 62.6 (C-6), 62.4 (C-5), 55.6 (-OCH₃), 29.3 (-C(CH₃)₂), 18.4 (-C(CH₃)₂); FTIR 3391, 2987, 2937, 1695, 1644, 1456, 1371, 1240, 1219, 1195, 1155, 1104, 1068, 1026, 986, 898, 871, 828, 798, 775 cm⁻¹; HRMS (ESI) m/z calc for C₁₀H₁₇O₆: 233.1025 Found: 233.1035 [M-H]⁻.
Experimental

Chapter 6

**Methyl 6-deoxy-6-ido-3,4-isopropylidene-α-D-galactopyranoside 127**

Compound 126 (2.6 g, 0.01 mol), triphenyl phosphine (3.9 g, 0.015 mol) and imidazole (1.4 g, 0.02 mol) were dissolved in THF (100 mL) and heated to 50 °C. A solution of iodine (3.8 g, 0.015 mol) in THF (20 mL) was added portionwise. The reaction mixture was stirred at reflux for 4 h. The reaction was cooled to rt and quenched with 10% aq Na₂S₂O₃. The product was extracted with EtOAc (3 x 50 mL), the combined org layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the residue (1:10 EtOAc:Hexane) gave 127 as a pale yellow solid (3.28 g, 86%).

(1:4 EtOAc:Hexane, Rₖ 0.7); [α]D +105.0 (c 2.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.68 (d, J = 3.9 Hz, 1H, H-1), 4.25 (dd, J = 6.2, 2.2 Hz, 1H, H-4), 4.21 (t, J = 6.1 Hz, 1H, H-3), 4.05 (ddd, J = 9.0, 6.2, 2.7 Hz, 1H, H-5), 3.77 (q, J = 4.3 Hz, 1H, H-2), 3.44 (s, 3H, -OCH₃), 3.32 – 3.19 (m, 2H, H-6, H-6′, overlapping signals), 2.86 (s, 1H, -OH), 1.41 (s, 3H, -C(CH₃)₂), 1.28 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 109.6 (-C(CH₃)₂), 98.4 (C-1), 75.8 (C-3), 73.5 (C-4), 69.2 (C-5), 68.6 (C-2), 55.5 (-OCH₃), 27.4 (-C(CH₃)₂), 25.7 (-C(CH₃)₂), 2.8 (C-6); FTIR 3461, 2986, 2934, 2906, 2837, 1453, 1418, 1371, 1339, 1243, 1217, 1146, 1128, 1039, 1002, 904, 886, 865, 831, 797, 731, 696 cm⁻¹; HRMS (ESI) m/z calc for C₁₁H₁₈O₇I: 389.0097 Found: 389.0101 [M+FA-H]⁻.
Methyl 6-deoxy-6-ido-3,4-O-isopropylidene-2-O-triethylsilyl-α-D-galactopyranoside 128 Compound 127 (3.5 g, 10.29 mmol) was dissolved in CH₂Cl₂ (50 mL). Chlorotriethylsilane (2.1 mL, 12.35 mmol) and imidazole (1.8 g, 12.35 mmol) were charged and the reaction stirred at rt for 10 h. The reaction was quenched by addition of H₂O (30 mL). The layers were separated and the org layer washed with H₂O (3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (Hexane followed by 1:10 EtOAc:Hexane) to give 128 (3.7 g, 78%) as a white solid. (1:4 EtOAc:Hexane, Rf 0.8); [α]D +92.1 (c 1.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.59 (d, J = 3.6 Hz, 1H, H-1), 4.28 (dd, J = 5.7, 2.5 Hz, 1H, H-4), 4.15 (dd, J = 7.3, 5.7 Hz, 1H, H-3), 4.11 (ddd, J = 8.3, 5.7, 2.5 Hz, 1H, H-5), 3.71 (dd, J = 7.3, 3.6 Hz, 1H, H-2), 3.44 (s, 3H, -OCH₃), 3.39 – 3.32 (m, 2H, H-6, H-6’), 1.48 (s, 3H, -C(CH₃)₂), 1.33 (s, 3H, -C(CH₃)₂), 0.94 (dt, J = 17.1, 8.0 Hz, 9H, Si(CH₂CH₃)₃), 0.62 (qd, J = 7.9, 3.5 Hz, 6H, Si(CH₂CH₃)₃); ¹³C NMR (126 MHz CDCl₃) δ 109.1 (-C(CH₃)₂), 100.2 (C-1), 76.9 (C-3), 74.0 (C-4), 71.2 (C-2), 68.3 (C-5), 55.7 (-OCH₃), 28.1 (-C(CH₃)₂), 26.2 (-C(CH₃)₂), 6.6 (CH₃, -Si(CH₂CH₃)₃), 4.7 (CH₂, -Si(CH₂CH₃)₃), 2.8 (C-6); FTIR 2953, 2910, 2877, 1626, 1552, 1458, 1380, 1314, 1241, 1208, 1124, 1039, 1015, 968, 916, 871, 842, 800, 725 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₃₄O₅SiINa: 522.1149, Found: 522.1139 [M+ACN+Na]⁺.
Compound 128 (5.1 g, 11.1 mmol) was dissolved in a mixture of THF/H$_2$O (9:1, 100 mL). Pre-activated Zn dust (7.3 g, 0.11 mol) was charged and the mixture was sonicated at 40 °C for 2-4 h. The mixture was filtered and washed with Et$_2$O (100 mL). The org layer was washed with H$_2$O (40 mL), sat aq NaHCO$_3$ (40 mL) and brine (40 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 129 (3.0 g, 90%) as a clear oil. The crude product was used immediately to prevent epimerization. 

$[\alpha]_D$ +31.8 (c 0.77, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.65 (d, $J = 0.9$ Hz, 1H, C-1), 5.92 (ddd, $J = 17.3, 10.4, 6.9$ Hz, 1H, H-5), 5.35 (dt, $J = 17.2, 1.4$ Hz, 1H, H-6), 5.22 (dt, $J = 10.5, 1.4$ Hz, 1H, H-6'), 4.72 (t, $J = 6.8$ Hz, 1H, H-4), 4.32 (dd, $J = 6.7, 5.2$ Hz, 1H, H-3), 4.07 (dd, $J = 5.2, 0.9$ Hz, 1H, H-2), 1.50 (s, 3H, -C(CH$_3$)$_2$), 1.35 (s, 3H, -C(CH$_3$)$_2$), 0.96 (t, $J = 7.9$ Hz, 9H, -Si(CH$_2$CH$_3$)$_3$), 0.64 (q, $J = 7.8$ Hz, 6H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.7 (C-1), 133.6 (C-5), 118.8 (C-6), 109.2 (-C(CH$_3$)$_2$), 78.9 (C-3), 78.4 (C-4), 77.2 (C-2), 26.8 (-C(CH$_3$)$_2$), 25.2 (-C(CH$_3$)$_2$), 6.7 (CH$_3$, -Si(CH$_2$CH$_3$)$_3$), 4.9 (CH$_2$, -Si(CH$_2$CH$_3$)$_3$); FTIR 2955, 2913, 2878, 1736, 1458, 1414, 1370, 1241, 1216, 1149, 1074, 1040, 1005, 928, 872, 789, 724 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{17}$H$_{31}$O$_5$SiNa: 364.1920, Found: 364.1905 [M+ACN+Na]$^+$. 

(4R,5S,6S)-5,6-Dideoxy-3,4-O-isopropylidene-2-O-triethylsilyl-hex-5-en-1-al
(2E,4S,5S,6S) Ethyl 5,6-isopropylidene-2,3,7,8-tetraoxo-4-O-
triethylsilyl-octa-2,7-dien-1-oate 130 Compound 129 (3.4 g, 0.011 mol) was
dissolved in toluene (70 mL). (Carbethoxy methylene) triphenylphosphorane (5.9
mol) was charged and the reaction was heated to reflux for 12 h. The
solvent was removed under diminished pressure. Flash column chromatography
of the residue (1:10 EtOAc:Hexane) gave 130 (3.8 g, 91 %) as a clear oil. (TLC
1:4 EtOAc:Hexane, Rf 0.7); [α]D -4.2 (c 5.1, CHCl3); 1H NMR (500 MHz,
CDCl3) δ 6.96 (dd, J = 15.5, 4.5 Hz, 1H, H-3), 6.10 (dd, J = 15.6, 1.8 Hz, 1H, H-2), 5.94 (ddd, J = 17.1, 10.2, 8.2 Hz, 1H, H-7), 5.35 (dt, J = 17.1, 1.2 Hz, 1H, H-8), 5.27 (apt d, J = 10.3, Hz, 1H, H-8'), 4.50 (dd, J = 8.1, 6.3 Hz, 1H, H-6), 4.35 (ddd, J = 7.1, 4.5, 1.8 Hz, 1H, H-4), 4.19 (q, J = 7.1 Hz, 2H, -OCH2), 4.01 (dd, J = 7.1, 6.1 Hz, 1H, H-5), 1.51 (s, 3H, -C(CH3)2), 1.35 (d, 3H, -C(CH3)2), 1.29 (t, J = 7.2 Hz, 3H, -CH3), 0.96 (t, J = 7.9 Hz, 9H, -Si(CH2CH3)3), 0.62 (qd, J = 7.9, 3.5 Hz, 6H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 166.3 (C-1), 146.2
(C-3), 134.0 (C-7), 122.3 (C-2), 119.2 (C-8), 108.9 (-C(CH3)2), 81.0 (C-5), 78.9
(C-6), 71.1 (C-4), 60.4 (-OCH2), 27.6, 25.4 (-C(CH3)2), 14.2 (-CH3), 6.8 (CH3, -
Si(CH2CH3)3), 4.9 (CH2, -Si(CH2CH3)3); FTIR 2983, 2956, 2920, 2877, 1722,
1660, 1458, 1413, 1380, 1368, 1279, 1216, 1163, 1131, 1073, 1038, 1003, 931,
839, 796, 739, 727 cm⁻¹; HRMS (ESI) m/z calc for C19H34O5SiNa: 393.2073, Found: 393.2089 [M+Na]+.
Compound 130 (3.6 g, 9.78 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL) and cooled to -78 °C. DIBAL-H (30 mL, 29.35 mmol, 1.0 M in CH$_2$Cl$_2$) was added dropwise. The reaction was stirred at -78 °C for 4 h. The mixture was quenched with MeOH at -78 °C and warmed to rt. The mixture was stirred with aq sodium potassium tartrate solution until clear. The layers were separated and the org layer was washed with H$_2$O (50 mL), dried over Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography (1:4 EtOAc: Hexane) to give 131 (2.9 g, 90%) as a clear oil. (1:4 EtOAc:Hexane, R$_f$ 0.45); [α]$_D$ $-$4.5 (c 2.7, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.94 (ddd, $J$ = 17.2, 10.3, 8.1 Hz, 1H, H-7), 5.87 (dt, $J$ = 15.5, 5.3, 1.3 Hz, 1H, H-2), 5.71 (ddt, $J$ = 15.4, 5.8, 1.5 Hz, 1H, H-3), 5.27 (apt d, $J$ = 17.2 Hz, 1H, H-8), 5.21 (apt d, $J$ = 10.2 Hz, 1H, H-8'), 4.46 – 4.43 (apt t, $J$ = 7.0 Hz, 1H, H-6), 4.18 – 4.15 (m, 1H, H-4), 4.10 (d, $J$ = 5.2 Hz, 2H, H-1, H-1'), 3.97 (t, $J$ = 6.5 Hz, 1H, H-5), 1.47 (s, 3H, -Si(CH$_2$CH$_3$)$_3$), 1.33 (s, 3H, -C(CH$_3$)$_2$), 0.93 (t, $J$ = 8.0 Hz, 9H, -Si(CH$_2$CH$_3$)$_3$), 0.59 (qd, $J$ = 7.9, 3.4 Hz, 6H, -Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 134.5 (C-7), 131.4 (C-2), 129.8 (C-3), 118.6 (C-8), 108.7 (-C(CH$_3$)$_2$), 81.8 (C-5), 79.0 (C-6), 71.6 (C-4), 62.8 (C-1), 27.6, 25.5 (-C(CH$_3$)$_2$), 6.8 (CH$_3$, -Si(CH$_2$CH$_3$)$_3$), 5.0 (CH$_2$, -Si(CH$_2$CH$_3$)$_3$); FTIR 3391, 2954, 2909, 2877, 1458, 1414, 1379, 1369, 1238, 1217, 1132, 1090, 1061, 1037, 1002, 975, 927, 873, 847, 739, 725 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{17}$H$_{32}$O$_4$SiNa: 351.1968, Found: 351.1975 [M+Na]$^+$. 

(2E,4S,5S,6S)-5,6-O-Isopropylidene-2,3,7,8-tetradexy-4-O-triethysilyl-octa-2,7-dien-1-ol 131
Compound 131 (2.5 g, 7.50 mmol) was dissolved in THF (50 mL). Triphenyl phosphine (3.3 g, 12.74 mol) was charged and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (2.5 mL, 12.74 mmol) and diphenylphosphoryl azide (2.8 mL, 12.74 mmol) were added dropwise. The mixture was warmed to rt and stirred for 8 h. The solvent was removed under diminished pressure. Flash column chromatography of the residue (100 % Hexane) gave 132 (2.0 g, 76%) as a pale yellow oil. (TLC 1:20 EtOAc:Hexane, Rf 0.8); [α]D -4.0 (c 6.0 in CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.95 (ddd, J = 17.1, 10.3, 8.1 Hz, 1H, H-7), 5.86 – 5.78 (m, 2H, H-2, H-2, overlapping signals), 5.30 (apt d, J = 17.2 Hz, 1H, H-8), 5.25 (apt d, J = 10.1 Hz, 1H, H-8’), 4.46 (dd, J = 8.2, 6.2 Hz, 1H, H-6), 4.21 (dd, J = 6.9, 3.1 Hz, 1H, H-4), 3.98 (t, J = 6.5 Hz, 1H, H-5), 3.75 (apt d, J = 4.1 Hz, 2H, H-1, H-1’ overlapping signals), 1.49 (s, 3H, -C(CH3)2), 1.35 (s, 3H, -C(CH3)2), 0.96 (t, J = 8.0 Hz, 9H, -Si(CH2CH3)3), 0.62 (qd, J = 7.8, 3.8 Hz, 6H, -Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 134.5 (d, C-7), 134.0 (d, C-2), 125.3 (d, C-3), 118.8 (t, C-8), 108.7 (s, -C(CH3)2), 81.8 (d, C-5), 79.0 (d, C-6), 71.4 (d, C-4), 52.2 (t, C-1), 27.7 (q, -C(CH3)2), 25.5 (q, -C(CH3)2), 6.8 (q, -Si(CH2CH3)3), 5.0 (t, -Si(CH2CH3)3); FTIR 2988, 2955, 2913, 2877, 2098 (-N3), 1458, 1414, 1380, 1370, 1238, 1215, 1133, 1068, 1038, 1003, 975, 930, 871, 848, 739, 725 cm−1; HRMS (ESI) m/z calc for C17H32O3N3Si: 354.2213, Found: 354.2225 [M+H]⁺.
(2E,4S,5S,6S)-1-Azido-4-hydroxy-5,6-O-isopropylidene-2,3,7,8-tetradecoxy-octa-2,7-diene 133 Compound 132 (2.0 g, 5.66 mmol) was dissolved in THF 70 (mL). TBAF (12 mL, 11.32 mmol, 1.0 M in THF) was added slowly and the reaction was stirred at rt for 12 h. The solution was stirred with CaCO₃, DOWEX-50X8 and MeOH for 1 h. The slurry was filtered through a pad of celite and washed thoroughly with MeOH and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give 133 (1.0 g, 71%) as a clear oil. (1:4 EtOAc:Hexane Rf 0.3); [α]D +6.8 (c 6.0 in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.01 (ddd, J = 17.1, 10.3, 7.8 Hz, 1H, H-7), 5.88 (dt, J = 15.5, 6.1, 1.2 Hz, 1H, H-2), 5.78 (dt, J = 15.4, 5.6 Hz, 1H, H-3), 5.40 (dt, J = 17.0 Hz, 1H, H-8), 5.33 (dt, J = 10.3 Hz, 1H, H-8'), 4.64 (t, J = 7.2 Hz, 1H, H-6), 4.18 – 4.17 (m, 1H, H-4), 4.08 (dd, J = 6.8, 5.5 Hz, 1H, H-5), 3.80 (dt, J = 6.0 Hz, 2H, H-1, H-1’), 2.41 (s, 1H, -OH), 1.55 (s, 3H, -C(CH₃)₂), 1.41 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 133.6 (C-7), 133.5 (C-3), 126.0 (C-2), 119.7 (C-8), 108.9 (-C(CH₃)₂), 80.6 (C-5), 78.9 (C-6), 69.7 (C-4), 52.1 (C-1), 27.4, 25.0 (-C(CH₃)₂); FTIR 3470, 2987, 2936, 2893, 2097 (-N₃), 1734, 1644, 1429, 1381, 1243, 1213, 1164, 1038, 993, 975, 869, 813, 664 cm⁻¹; HRMS (ESI) m/z calc for C₁₁H₁₄O₃N₃: 240.1348, Found: 240.1351 [M+H]⁺.
6-O-Acetyl-1,5-dideoxy-3,4-O-isopropylidene-1-ethenyl-1,5-imino-D-galactitol 134

Compound 133 (200 mg, 0.84 mmol) was dissolved in DMF (40 mL) and heated to 100 °C for 1 h. AcOH (24 μl, 4.18 mmol) was charged and the reaction was stirred at rt. The reaction was diluted with H2O (20 mL) and extracted with Et2O until no product remained in the aq layer (as observed by TLC 1:1 EtOAc:Hexane, Rf 0.4). The combined org layers were dried over Na2SO4 and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:Hexane) to give 134 (102 mg, 45%) as a clear oil. [α]D +4.5 (c 1.5, CHCl3); 1H NMR (500 MHz, CDCl3) δ 5.98 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H, H-7), 5.29 (dt, J = 17.2, 1.3 Hz, 1H, H-8), 5.24 (dt, J = 10.3, 1.2 Hz, 1H, H-8’), 4.27 (dd, J = 11.2, 4.0 Hz, 1H, H-6), 4.13 (t, J = 6.1 Hz, 1H, H-3), 4.09 (dd, J = 11.2, 7.4 Hz, 1H, H-6’), 4.04 (t, J = 6.0 Hz, 1H, H-4), 3.69 (dd, J = 7.4, 6.3 Hz, 1H, H-2), 3.35 – 3.28 (m, 2H, H-1, H-5, overlapping signals), 2.09 (s, 3H, -OCH3), 1.50 (s, 3H, -C(CH3)2), 1.36 (s, 3H, -C(CH3)2); 13C NMR (126 MHz, CDCl3) δ 170.8 (sC=O), 136.9 (C-7), 117.6 (C-8), 109.5 (-C(CH3)2), 78.1 (C-3), 73.7 (C-4), 72.2 (C-2), 65.2 (C-6), 58.2 (C-1), 51.9 (C-5), 27.9 (C(CH3)2), 25.8 (-C(CH3)2), 20.9 (-OCH3); FTIR 3335, 2986, 2936, 1740, 1663, 1456, 1372, 1217, 1163, 1062, 1040, 922, 858, 787, 734, 701 cm⁻¹; HRMS (ESI) m/z calc for C13H22O5N: 272.1498, Found: 272.1511 [M+H]+.
1,5-Dideoxy-1-ethenyl-1,5-imino-ᴅ-galactitol 135 Compound 134 (97.1 mg, 0.36 mmol) was dissolved in aq HCl (5 mL) and stirred at rt. The reaction was concentrated to a brown foam. The crude residue was purified by ion exchange chromatography (MeOH, H₂O followed by 1 M NH₄OH) to give 135 (56 mg, 82%) as a pale yellow foam. (TLC 1:9 MeOH:EtOH w/NH₄OH, Rₚ 0.5); [α]₀ +13.1 (c 2.2, D₂O); ¹H NMR (500 MHz, D₂O) δ 5.72 (ddd, J = 17.1, 10.4, 7.7 Hz, 1H, H-7), 5.23 (d, J = 17.3 Hz, 1H, H-8), 5.20 (d, J = 10.7 Hz, 1H, H-8'), 3.92 (t, J = 3.1 Hz, 1H, H-4), 3.65 (dd, J = 11.8, 7.9 Hz, 1H, H-6), 3.60 (dd, J = 11.8, 6.4 Hz, 1H, H-6'), 3.57 (dd, J = 9.2, 3.3 Hz, 1H, H-3), 3.48 (t, J = 9.1 Hz, 1H, H-2), 3.15 (apt t, J = 8.4 Hz, 1H, H-1), 3.09 (ddd, J = 7.8, 6.4, 2.9 Hz, 1H, H-5); ¹³C NMR (126 MHz, D₂O) δ 134.9 (C-7), 119.6 (C-8), 71.1 (C-3), 70.9 (C-2), 68.5 (C-4), 58.8 (C-6), 58.7 (C-5), 58.0 (C-1); FTIR 3295, 2902, 2457, 1645, 1561, 1416, 1342, 1255, 1043, 925, 843, 777 cm⁻¹; HRMS (ESI) m/z calc for C₈H₁₄O₄N: 188.0923, Found: 188.0919 [M-H]⁻.
Experimental

Chapter 6

**6-O-Acetyl-N-tert-butyloxycarbonyl-1,5-dideoxy-3,4-O-isopropylidene-1-ethenyl-1,5-imino-ᴅ-galactitol 136**

Compound 134 (60 mg, 0.22 mmol) was dissolved in CH₂Cl₂ (20 mL). Et₃N (40 μl, 0.29 mmol), Boc₂O (174 mg, 0.80 mmol) and DMAP (27 mg, 0.22 mmol) were added and the reaction was stirred at rt for 24 h. The solvent was removed under diminished pressure and flash column chromatography of the residue (1:1 EtOAc:Hexane) to give 136 as a pale yellow foam (59.1 mg, 72%). (TLC 100 % EtOAc, Rₜ 0.8); [α]D +19.8 (c 2.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H, H-7), 5.28 (dt, J = 17.2, 1.4 Hz, 1H, H-8), 5.17 (dt, J = 10.4, 1.3 Hz, 1H, H-8’), 4.77 (dd, J = 7.2, 6.1 Hz, 1H, H-2), 4.21 – 4.13 (m, 3H, H-3, H-6, H-6’, overlapping signals), 4.05 (t, J = 5.5 Hz, 1H, H-4), 3.41 (tt, J = 7.1, 1.2 Hz, 1H, H-1), 3.34 (ddd, J = 6.7, 5.5, 4.5 Hz, 1H, H-5), 2.08 (s, 3H, -CH₃), 1.51 (s, 3H, -C(CH₃)₂), 1.46 (s, 9H, -C(CH₃)₃), 1.34 (s, 3H, -C(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 170.7 (C=O), 152.7 (C=O), 135.7 (C-7), 117.7 (C-8), 109.4 (-C(CH₃)₂), 82.6 (-C(CH₃)₃), 75.9 (C-2), 75.5 (C-3), 73.5 (C-4), 65.0 (C-6), 56.4 (C-1), 51.4 (C-5), 27.8 (-C(CH₃)₂), 27.7 (-C(CH₃)₃), 26.2 (-C(CH₃)₂), 20.9 (-CH₃); FTIR 2983, 2937, 1741, 1659, 1457, 1370, 1273, 1251, 1157, 1090, 1069, 1040, 984, 925, 867, 788, 732 cm⁻¹; HRMS (ESI) m/z calc for C₁₈H₃₀O₇N: 372.2022, Found: 372.2020 [M+H]⁺.
1,5-Dideoxy-1-(S)-ethyl-1,5-imino-d-galactitol 137 Compound 136 (10 mg, 0.06 mmol) was dissolved in MeOH (5 mL). Pd/C (10 mol %) and HCl (1.8 μL, 0.06 mmol) were charged. A H₂ balloon was attached and the reaction was stirred at rt for 4 h. The reaction was filtered and concentrated in vacuo. The residue was purified by ion exchange chromatography (MeOH, H₂O, 1.0 M NH₄OH) to give 8 (8.1 mg, 80%) as a clear oil. [α]D -17.5 (c 0.63, MeOH); ¹H NMR (500 MHz, D₂O) δ 3.90 (t, J = 3.1 Hz, 1H, H-4), 3.65 – 3.57 (m, 2H, H-6, H-6’, overlapping signals), 3.54 (dd, J = 9.1, 3.3 Hz, 1H, H-3), 3.43 (t, J = 9.1 Hz, 1H, H-2), 3.10 – 3.06 (m, 1H, H-5), 2.55 (td, J = 8.5, 3.8 Hz, 1H, H-1), 1.73 (dqd, J = 15.2, 7.8, 4.1 Hz, 1H, H-7), 1.36 (dp, J = 14.8, 7.5 Hz, 1H, H-7’), 0.83 (t, J = 7.6 Hz, 3H, -CH₃); ¹³C NMR (126 MHz, D₂O) δ 71.4 (C-3), 70.8 (C-2), 68.4 (C-4), 58.7 (C-5), 58.6 (C-6), 55.7 (C-1), 23.1 (C-7), 8.9 (C-8); HRMS (ESI) m/z calc for C₈H₁₈O₄N: 192.1236, Found: 192.1232 [M+H]+.
References

10. Asano, N., Glycobiology 2003, 13 (10), 93R-104R.
References

References

References

References

References

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## NMR tables

Chapter 2 and Chapter 3: $^1$H NMR shifts, $J$ values and $^{13}$C NMR shifts

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Chapter 4: $^1$H NMR shifts, $J$ values and $^{13}$C NMR shifts

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## Chapter 5: $^1$H NMR shifts, $J$ values and $^{13}$C NMR shifts

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<td>$J_{7,7}$</td>
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### Chapters 2, 3, 4 and 5: $J_{C1-H1}$ values

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<tr>
<th>Compound</th>
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<th>$J_{C1-H1}$</th>
<th>Anomer</th>
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<td>136.1</td>
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</table>
NMR Spectra for Selected Compounds

Compound 40a (CDCl₃, 500 Hz)
Compound 40b (CDCl₃, 500 Hz)
Compound 41a (CDCl₃, 500 Hz)
NMR Spectra

Appendix 2

(CDCl₃, 500 Hz)
Compound 45 (CDCl₃, 500 Hz)
Compound 46 (MeOD, 500 Hz)
Compound 47 (CDCl₃, 500 Hz)
Compounds 48 (D$_2$O, 500 Hz)
Compound 65 (CDCl₃, 500 Hz)
Compound 63 (CDCl₃, 500 Hz)
Compound 64 (CDCl$_3$, 500 Hz)
Compound 83 (CDCl$_3$, 500 Hz)
Compound 94 (CDCl₃, 500 Hz)
Compound 96 (CDCl₃, 500 Hz)
Compound112 (CDCl₃, 500 Hz)
Compound 113 (CDCl₃, 500 Hz)
Compound 113 (CDCl₃, 500 Hz)
Compound 85 (D$_2$O, 500 Hz)
Compound 8 (D$_2$O, 500 Hz)
Compound 125 (CDCl₃, 500 Hz)
Compound 134 (CDCl₃, 500 Hz)
Compound 135 (D₂O, 500 Hz)
Compound 136 (CDCl₃, 500 Hz)
Compound 137 (D$_2$O, 500 Hz)