Chapter 1

General Introduction

A wide array of natural products are characterised by the presence of carbohydrate entities. Apart from oligo- and polysaccharides, these include glycolipids and glycoproteins. Together, these glycoconjugates play a role in many different biological processes. Organic chemists are faced with the challenge to prepare suitable quantities of specific glycoconjugates, and their synthetic analogues, in order to unravel these processes. Fortunately, the monosaccharide building blocks, of which glycoconjugates are assembled, are in most cases available in large quantities and glycoconjugate synthetic studies are largely devoted to the development of efficient strategies to interconvert and oligomerise these monosaccharides. The accessibility of monosaccharides as cheap chiral starting materials that are endowed with multiple functional groups has inspired organic chemists to use them as starting material in the total synthesis of a wide range of complex natural products, compounds that, other than glycoconjugates, do not necessarily contain carbohydrate entities in their structure. As such, carbohydrates are important components of the chiral pool from which organic
chemists may choose their starting point. Moreover, many synthetic studies have appeared over the decades in which monosaccharides have been transformed into compounds that resemble the structure and/or function of natural carbohydrates and glycoconjugates. These carbohydrate mimics include compounds that find application as glycosidase and glycosyltransferase inhibitors in the study of the biosynthesis and processing of glycoconjugates. Another fruitful line of research is the design of compounds that emulate secondary structural features of glycoconjugates. In this introductionary chapter, selected examples of the individual research aims outlined above are presented. Further, a brief outline of the contents of the research chapters in this thesis is given.

The potential of organic chemistry in the preparation of both naturally occurring oligosaccharides and synthetic analogues is well illustrated by synthetic studies involving heptasaccharide 1a (Figure 1), isolated from the mycelial cell walls of *Phytophtora megasperma*. This so-called phytoalexin elicitor, the terminal glucose of which is reduced to the corresponding glucitol moiety, is found to be a key intermediate in the interaction between the host plant and guest bacteria and fungi. Starting from readily available 1,2-anhydroglucose 2 (Scheme 1), Timmers *et al.* prepared both methyl heptaglucoside 1b and mimetic 1c, in which the interglycosidic linkages in the backbone pentasaccharide are replaced by amide bonds (Figure 1).

![Figure 1](image-url)
Key step in both synthetic sequences is the efficient and selective ring-opening of epoxide 2 in the presence of zinc chloride either by an aglycon glucoside (route A, Scheme 1) or by acetonitrile (route B). Biological evaluation revealed that methyl heptasaccharide 1b is as effective as glucitol 1a in inducing phytoalexin accumulation in soybean, whereas the conformationally constrained sugar amino acid analogue 1c has virtually no activity at all.

Scheme 1

In the field of oligosaccharide and glycoconjugate synthesis many efficient strategies have been developed. Key in this research area is the ability to install the proper interglycosidic linkages with respect to regio- and stereospecificity. The majority of glycosylation procedures involve activation of the anomeric position of a suitable protected donor glycoside. The acetal is formed by displacement of the anomeric leaving group by the free hydroxyl of the acceptor. With the aim to synthesise biologically relevant trisaccharides Codée et al. recently described a novel sequential glycosylation procedure combining the use of 1-hydroxyl- and thiodonors (Figure 2). The method is based on Ph2SO/Tf2O-mediated dehydrative condensation (I) of 1-hydroxyl donors (7) with thioglycosides (8) to afford thiodisaccharides. In the next glycosylation event (II), this thiodisaccharide can be activated with the same sulfonium triflate activator system to furnish a trisaccharide.
The scope of this sequential glycosylation strategy was nicely illustrated by the efficient assembly of a hyaluronan trisaccharide \((14)\) in a stepwise procedure (Scheme 2). First glucuronic acid building block \((10)\) was pre-activated and chemoselectively coupled to thio glucosamine \((11)\) resulting in disaccharide \((12)\). Successive coupling with another glucuronic acid building block \((13)\) afforded protected hyaluronan trisaccharide \((14)\). Key to the above studies was the accessibility of (partially) protected donor- and acceptor uronic acid derivatives. Van den Bos et al.\(^\text{11}\) presented an elegant strategy in which the primary alcohol function in a series of carbohydrate-derived diols, including thioglycosides \((15, 18\) and \(21\) (Scheme 3), is selectively oxidised to the corresponding uronic acids \((16, 19\) and \(22\) through the action of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) and [bis-(acetoxy)-iodo]benzene (BAIB). Treatment with diazomethane furnishes thioglycosides \((17, 20\) and \(23\), suited for further elaboration in oligosaccharide synthesis.
Carbohydrates are often used as chiral precursors in the synthesis of natural products. The class of polycyclic ether marine natural products presents an interesting and challenging synthetic target due to their structural complexity, biological activities and scarcity. \(^\text{12}^\) After its isolation and structural elucidation in 1981, the potent neurotoxin brevetoxin B (24, Figure 3) was reported as the first example of a marine polycyclic ether. \(^\text{13}^\) The first total synthesis of brevetoxin B was accomplished by the group of Nicoloau in 1995. \(^\text{14}^\) In a convergent approach they made use of several carbohydrates to construct parts of the polycyclic ether framework.

The interesting properties of polycyclic ethers have inspired many scientists. However, general and modular approaches towards the synthesis of polycyclic ethers are so far still lacking. This is mainly caused by the range of variations in ring size and substitution pattern of the individual ether rings. Leeuwenburgh \textit{et al.} \(^\text{15}^\) disclosed an elegant procedure to construct fused cyclic ethers via a radical cyclisation approach of
Figure 3

sugar-derived β-(alkynyloxy)-acrylates (Scheme 4). Accordingly, functionalised bicyclic ethers of various ring sizes (31, n = 0-3) were prepared. The synthesis commenced with a hetero Michael addition of suitably protected carbohydrate-derived alkynols (28) to ethyl propiolate. Next, the resulting ene-yne intermediates (29) were subjected to a tributyltin radical mediated cyclisation followed by acidic destannylation to furnish the set of bicyclic ethers.

Scheme 4

The efficiency of this methodology was nicely demonstrated in the construction of a trans-fused tricyclic ether in an iterative fashion. Thus, ozonolysis of the exocyclic
alkene (31, n =1) followed by reduction of the resulting ketone afforded alcohol 32 (Scheme 5). In a five step procedure, ester 32 was transformed into the requisite acetylene. Now alkynol 33 was subjected to the three step hetero Michael addition/radical cyclisation/reductive destannylation protocol as discussed above to yield tricyclic system 34.

Scheme 5

Another class of compounds widely distributed in nature are the polyhydroxylated alkaloids. These imino- or azasugars, in which the ring oxygen in pyranoses or furanoses is replaced by a nitrogen atom, are carbohydrate analogues which closely resemble the parent natural sugar. They can be classified into five structural categories: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes which are presented in Figure 4. Representative examples of each of these classes respectively are nojirimycin (35), 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP, 36), castanospermine (37), alexine (38) and calystegine B2 (39). The first alkaloid isolated from nature, nojirimycin, was found to be a potent inhibitor of α- and β-glucosidases as might be expected from its close structural resemblance with glucose. Since the discovery of nojirimycin in 1966, many naturally occurring iminosugars have been identified and found to possess glycosidase inhibitor activity.
In many of the numerous reported synthetic strategies towards iminosugars, the key step concerns incorporation of the nitrogen atom into a monosaccharide derivative as is exemplified by the first synthesis of nojirimycin, reported by Inouye and co-workers. Starting with glucose (40) the amine function was incorporated with overall retention of configuration at the C-5 position as key in the total synthesis (Scheme 6).

**Scheme 6**

DMDP 36 and many of its analogues show very interesting biological activities in different glycosidase mediated processes. In 1985 the first synthesis of 36 was reported.
starting from L-sorbose (45, Scheme 7), which contains the desired stereochemistry at the C-3 and C-4 positions. Bisacetate 46 was obtained in three steps from L-sorbose. Introduction of an azide function, subsequent removal of the protective groups followed by hydrogenation to liberate the amine resulted in the formation of DMDP.

![Scheme 7]

Dondoni and co-workers\textsuperscript{25} devised a general procedure towards functionalised pyrrolidine iminosugars starting from furanoses (Scheme 8). This strategy commences with a nitrene addition followed by thiazole addition and ring-closure with inversion of stereochemistry. To attain DMDP, protected L-xylofuranose (49) was transformed into 50 using N-benzylhydroxylamine at elevated temperature. Treatment of 50 with 2-lithiothiazole (51) gave, after separation of the isomers, the open chain derivative 52. Reduction of the hydroxylamine function in 52 was achieved using a Zn-Cu couple. Next, ring-closure of amine 53 proceeded with inversion of configuration upon activation of the free hydroxyl with triflic anhydride, providing pyrrolidine 54. Cleavage of the thiazole ring, followed by reduction of the resulting aldehyde intermediate 55 and removal of the benzyl ethers eventually afforded 36.

An elegant synthesis of castanospermine (37) was reported by Mootoo and co-workers\textsuperscript{26} who made use of a triple reductive amination strategy to incorporate the
tertiary amine function (Scheme 9). The requisite tricarbonyl intermediate (60) was obtained from glucose-derived aldehyde 56 by the following sequence of events: tin-mediated addition of an allyl anion, followed by benzylation of the major product, then

Scheme 8

Scheme 9
iodocyclisation under the agency of iodonium dicollidine perchlorate (IDCP) in CH$_2$Cl$_2$/MeOH and reductive elimination with zinc furnished dimethylacetal 59. Swern oxidation, ozonolysis and liberation of the aldehyde gave dialdehydo ketone 60 which upon treatment with ammonium formate and sodium cyanoborohydride yielded perbenzylated castanospermine 61. Hydrogenolysis of the benzyl ethers in 61 provided castanospermine 37.

Madsen and Skaanderup devised a short and efficient general strategy to prepare polyhydroxylated nortropanes (calystegines B$_2$, B$_3$ and B$_4$, Figure 5).$^{27}$ They took full advantage of the predisposed arrangement of the hydroxyl functions of the corresponding carbohydrate starting materials.

![Figure 5](image)

Key steps in the synthesis of the polyhydroxylated seven-membered carbocyclic cores include a zinc mediated domino reaction followed by olefin ring-closing metathesis (RCM), as is exemplified for calystegine B$_2$ (Scheme 10).$^{28}$

The naturally occurring trihydroxy piperolic acid (73a), isolated from the seeds of Baphia racemose,$^{29}$ was shown to be a glucuronidase and iduronidase inhibitor. Fleet and co-workers$^{30}$ synthesised amino acid 73a starting from D-glucuronolactone 69 with overall retention of configuration at the C5-position (Scheme 11). Thus, 69 was converted into a triflate followed by treatment with sodium trifluoroacetate to give L-idose derivative 70.
Scheme 10

Again installation of a triflate followed by nucleophilic displacement with sodium azide afforded gluco-azide 71. Reduction of the azide and subsequent protective group manipulations furnished 73a. With a single inversion of configuration, the 2R-isomer (73b) of the naturally occurring polyhydroxy pipecolic acid was prepared starting from 69 in an analogy to the sequence of reactions described going from 70 to 73a.

Scheme 11
Recently Timmer et al.\textsuperscript{31} developed a new and efficient multicomponent reaction giving access to polyhydroxylated pipecolic acid amides starting from ribose-derived azido hemiacetal (75, Scheme 12). In a one-pot process imine 76 is generated via a Staudinger/aza-Wittig sequence of events, after which an Ugi three-component reaction with a series of isocyanates and carboxylic acids provided a small library of trihydroxypipecolic acids 77 in yields varying between 22\% and 78\%.

Scheme 12

Carbohydrate derivatives which contain an amine and a carboxylate function can be classified as sugar amino acids (SAAs).\textsuperscript{5} SAAs, such as neuraminic acid\textsuperscript{32} and muramic acid,\textsuperscript{33} are largely found in nature as structural elements but they also play an important role as constituents of certain complex nucleoside antibiotics,\textsuperscript{34} which exhibit inhibitory activity against fungi and/or bacteria. Heyns and Paulsen reported\textsuperscript{35} in 1955 the first synthesis of an unnatural SAA (80) in three steps starting from a glucosamine building block (78, Scheme 13).
Scheme 13

In 1975 Fuchs and Lehmann\textsuperscript{36} reported the synthesis of a novel set of SAAs (e.g. 82, Scheme 14) and were the first to recognise that these compounds combine both carbohydrate and amino acid properties. They proposed the use of SAAs as monomers to construct polysaccharide analogues through amide bonds. However, it was not until 1996 that the first structure of an oligosaccharide mimic in which glycosidic linkages were replaced by amide bonds (84) was analysed in depth with respect to its structural behaviour.\textsuperscript{37} Kessler \textit{et al.}\textsuperscript{38} reported the synthesis of SAA 85, the enantiomer of 82 which was previously prepared by Fuchs and Lehmann.

Scheme 14

In recent years, many examples of synthetic SAAs have appeared in the literature. These SAAs are used in various areas of research, in the creation of both peptide and carbohydrate mimics. Some relevant examples of synthetic SAAs and their routes of
preparation are listed in Schemes 15-19. SAAs, like carbohydrates, often exist as an equilibrium between a mixture of several specific conformers depending on the substitution pattern of the carbohydrate framework. Recently, research in the field of glyco- and peptidomimetics have focussed on the design and synthesis of unnatural rigidified SAAs to urge a conformational bias. These so-called locked SAAs can be obtained through annulation of a second ring. These compounds have found application as glyco-or peptidomimetics, inducing secondary structures in linear or cyclic oligomers.

Nicotra et al.\textsuperscript{39} devised an elegant approach for the construction of spiro- and fused bicyclic furanoid SAAs. Arabinofuranose 86 was converted into C-glycoside 87 by Lewis acid mediated allylation of the anomeric acetate (Scheme 15). Upon treatment of perbenzylated 87 with iodine in DCM iodocyclisation took place providing a mixture of fused bicyclic ethers (88). Displacement of the iodide with an azide group followed by regioselective debenzylation of the primary hydroxyl group by acetolysis gave acetate 89. Hydrolysis of the acetate function and Jones oxidation afforded the corresponding bicyclic azido acids 90.

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_15.png}
\end{figure}
\end{center}

\textbf{Scheme 15}

In an analogous approach making use of the iodoetherification, an epimeric mixture of two oxaspirobicyclic SAAs or spiroazidoacids (93) were obtained starting from fructo-C-furanoside 91 (Scheme 16).
Scheme 16

Grotenbreg et al.\(^{40}\) described the synthesis of two pyranopyran SAAs. The synthesis commenced with the formation of C-glycoside 94, which is readily available in a two step sequence starting from 1,2-anhydroglucitol (2, Scheme 17). Thus, zinc-mediated ring-opening of the epoxide with lithium phenylacetylide and partial reduction
of the acetylene group gave alkene 94. Alkylation of the free hydroxyl in compound 94 with methylbromoacetate and sodium hydride followed by olefination of methyl ester 95, using Petasis reagent, furnished enol ether 96. Olefin RCM of 96 afforded pyranopyran 97. TFA-assisted hydrolysis of the enol ether 97 and subsequent reduction of the resulting ketone under the agency of L-selectride gave an epimeric mixture of alcohols (98). Treatment of 98 with methylsulfonyl chloride in pyridine, separation of the isomers and hydrogenolysis of the benzylethers, eventually led to the assembly of mesylates 99a and 99b. Nucleophilic displacement of the mesylate functions with sodium azide and selective oxidation of the primary alcohol finally furnished two constrained SAAs (100a and 100b).

In a recent study to obtain highly constrained SAAs as dipeptide isosters, Van Well et al.41 described the synthesis of novel bicyclic furanoid SAAs locked with an oxetane ring (Scheme 18). The synthesis started with carbonyl-insertion, in the presence

![Scheme 18](attachment:image.png)
of diethylmethylsilane (DEMS) and CO-gas, on fully protected ribofuranose 101. Acidic removal of the silyl group, followed by mesylation and treatment with sodium azide gave compound 105. Removal of the benzoyl protecting groups, and ensuing installation of an isopropylidene of the cis-diol followed by Dess-Martin oxidation of the primary hydroxyl function afforded aldehyde 106. Treatment of 106 with formaldehyde in the presence of NaOH followed by a Cannizzaro reaction of the intermediate β-hydroxy aldehyde furnished diol 107. Transformation of the two primary alcohol functions into mesylate groups followed by acidic removal of the acetonide afforded 108. Ring-closure to the oxetane (109) was accomplished under basic conditions. Liberation of the primary alcohol with sodium hydroxide at elevated temperature provided locked furan 110. The azide was transformed into a protected amine using a modified Staudinger reaction in the presence of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON). Finally oxidation of the primary alcohol into a carboxylic acid furnished locked SAA 111.

The synthesis of pyrrolizidine SAA 120 (Scheme 19), starting from a protected D-arabinofuranose, was accomplished by Dondoni et al.42 D-Arabinose 112 was converted to pyrrolidine 116 using their thiazole based aminohomologation procedure previously described in Scheme 8. Next, Horner-Wadsworth-Emmons olefination of aldehyde 116 followed by saturation of the double bond and protective group manipulations provided amino acid 118. The conformationally constrained dipeptide 120 was obtained by the following sequence of reactions. First formation of the cyclic amide was achieved under basic conditions. Next, two acetate functions were installed (119) followed by removal of the p-methoxyphenyl group and subsequent oxidation of the primary alcohol to give 120.
Spiroketals are often found as structural constituents in many biologically active compounds. Spiroketals are found as simple structures in insect pheromones and are present as part of more complex compounds such as polyether marine toxins, steroids or plant metabolites. The vast majority of the spiroketal frameworks are composed of spiro[5.5], spiro[4.5] and spiro[4.4] ring systems. Talaromycins A and B (129, 130, Scheme 20) are toxic metabolites isolated from the fungus Talaromyces Stripitatas. An enantiospecific synthesis of 129 and 130 was realised by Cubero et al. starting from diisopropylidene-D-fructopyranose 121. In a five-step procedure chain elongation led to 122, which after treatment with aqueous TFA furnished two spiroketals 123. Acetonation of the cis-diol followed by Barton deoxygenation of the remaining hydroxyl gave compound 124. Removal of the isopropylidene ketal, installation of a dibutylstannylidene
and regioselective opening of intermediate 125 with benzyl bromide followed by PCC oxidation furnished ketone 126. Next, Wittig olefination of 126, hydroboration of the resulting exocyclic alkene in 127 followed by hydrogenolysis of 128 afforded talaromycin A. An acid catalysed isomerisation of 129 led to the formation of talaromycin B.

Scheme 20

An interesting class of spiroketals, not identified in nature, are the perhydroxylated 1,7-dioxaspiro[5.5]undecanes. Redlich et al.\textsuperscript{46} reported a general
approach towards the synthesis of a set of hexopyranoses linked together by a spiroketal center. According to the Corey-Seebach procedure, the synthesis commenced with the coupling of a dithioacetal with an open chain aldopentose as follows (Scheme 21). Reaction of the dianion of glucose-derived dithiane 131, prepared under the agency of n-butyl lithium in THF, with an aldehyde, protected D-arabinose 132, furnished thioketal 133. The desired diol 135 was obtained after systematic manipulation of protective groups. Liberation of the masked ketone in 135, upon treatment of the dithiane with HgCl$_2$/HgO, followed by cyclisation and subsequent hydrogenation afforded polyhydroxy spiroketal 136.

![Scheme 21]

Recently Van Hooft et al. described the asymmetric synthesis of carbohydrate-derived spiroketals following a three step procedure (Scheme 22). Grignard addition of allylmagnesium bromide to perbenzylated gluconolactone 137, condensation of hemiketal 138 with a second terminal alkenol (n = 1-3) and subsequent ring-closure of 139 by olefin RCM led to the assembly of pyranose spiroketals 140. The scope of this procedure was
further demonstrated by variation of the Grignard reagent (allyl- or vinylmagnesium bromide) followed by the addition to different pyrano- as well as a furanolactones, in combination with changing the chain length of the alkenol. In this manner several pyranose- and furanose-derived lactones were transformed into spiroketals.\textsuperscript{49}

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle,minimum size=1cm] (137) at (0,0) {137};
  \node[draw,shape=circle,minimum size=1cm] (138) at (2,0) {138};
  \node[draw,shape=circle,minimum size=1cm] (140) at (0,-2) {140};
  \node[draw,shape=circle,minimum size=1cm] (139) at (2,-2) {139};
  \draw[->,thick] (137) -- (138);
  \draw[->,thick] (140) -- (139);
\end{tikzpicture}
\end{center}

Scheme 22

Aim and outline of the Thesis

The research described in this Thesis is directed to the implementation of monosaccharides in the construction of a variety of functionalised cyclic and oligocyclic systems. \textbf{Chapter 2} describes the construction of two trans-fused tricyclic ethers (144, \(n=1\) or 3, Scheme 23) with a methyl group positioned at a bridgehead position. Such structural entities are often found as motif in naturally occurring polycyclic ethers. According to the tributyltin mediated radical cyclisation procedure developed by Leeuwenburgh \textit{et al.}, two glucose-derived pyranopyrans (143) were efficiently obtained. Next, the emphasis was directed towards cyclisation of the third ether ring and simultaneous installation of the methyl group at the bridgehead position taking advantage of the exocyclic alkene resulting from the radical cyclisation.
The assembly of carbohydrate-based γ-amino acids using the radical cyclisation approach as key step is the subject of Chapter 3. Glucose-derived alkynol 145 is condensed with a propiolate and subsequently converted into enyne 146 (Scheme 24). The tributyltin mediated ring-closure of 146 proceeded smoothly to give cyclic ether 147. Introduction of the amine functionality proved feasible by exploiting the exocyclic vinylstannane moiety, resulting from the radical cyclisation, leading to the formation of two protected γ-SAAs 148.

Scheme 24
The transformation of D-glucose into a carbasugar amino acid (CSAA), a novel class of conformationally restricted SAAs, is described in Chapter 4. The Ferrier-rearrangement proved to be a convenient method to convert glucose-derived enopyranoside 149 into cyclitol 150 (Scheme 25). At this stage, several synthetic pathways were explored to install the amine and carboxylate functionalities. β-Elimination of the hydroxy group in 150 afforded an enone which was subjected in the next step to a Mukaiyama-Michael addition to give ester 151. Hydrolysis of the silyl enol ether in 151 followed by installation of the amino function at the resulting ketone 152 gave protected CSAA 153.

Scheme 25

Chapter 5 reports a convenient method for the synthesis of functionalised C2-symmetrical 1,7-dioxaspiro[5,5]undecanes, such as 158 and 160, using acid-catalysed spiroketalisations of substituted dihydroxyketones (Scheme 26). A two step Claisen self-condensation and decarboxylation procedure are the key steps in this synthetic route. The synthesis of spiroketal 158 commenced with the conversion of (S)-malic acid (154) into suitably protected ester 155. Claisen self-condensation, upon treatment of ester 155 with lithium hexamethyldisilazane (LHMDS), readily afforded β-ketoesters 156. Decarboxylation of the methyl esters under Krapcho conditions then smoothly furnished the requisite dihydroxyketone (157), which, upon acidic removal of the isopropylidene
moieties followed by cyclisation, led to the formation of C₂-symmetrical spiroketalts 158. In a similar approach, partially protected glutamic acid 159 was converted into spiroketal 160, containing protected amine functions

![Chemical structures](image)

Scheme 26

**Chapter 6** summarises the results described in this Thesis. In addition several future prospects concerning its contents will be discussed.

**References and notes:**


28. Hanna and co-worker were the first to report only the synthesis of calystegine B₂, also starting from D-glucose using the same sequence of reactions described by Madsen. Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2001**, *42*, 1275-1277.


