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Carbohydrates as chiral starting compounds in synthetic organic chemistry

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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.¹ 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.² 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.³ 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.^{4,5} 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 introductory 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 *Phytophthora megasperma*.⁶ 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 heptagluco-side **1b**⁷ and mimetic **1c**,⁸ in which the interglycosidic linkages in the backbone pentasaccharide are replaced by amide bonds (Figure 1).

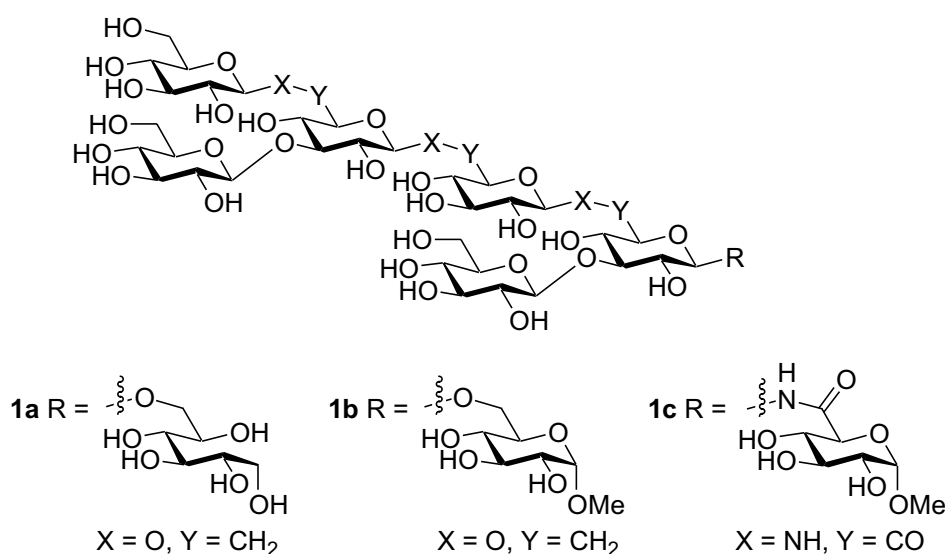
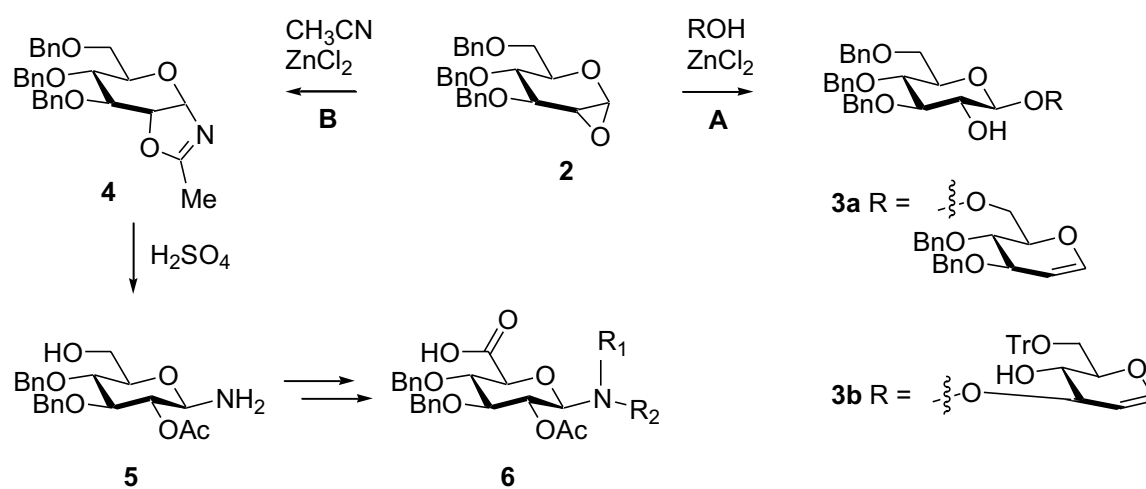


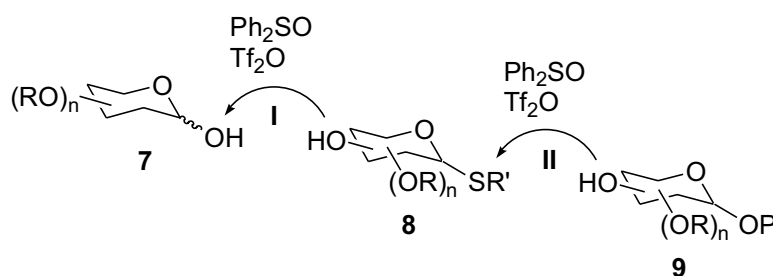
Figure 1

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).⁹ 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.

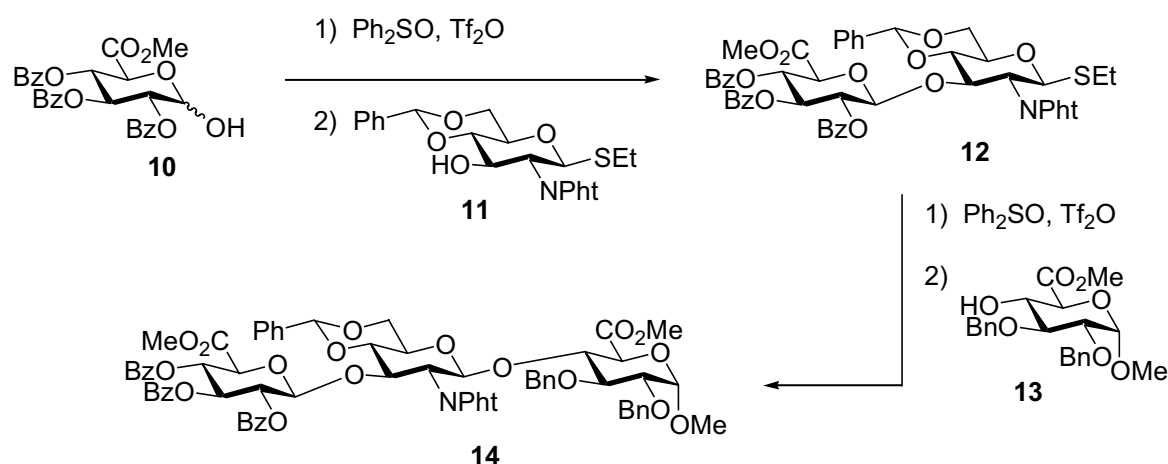


Scheme 1

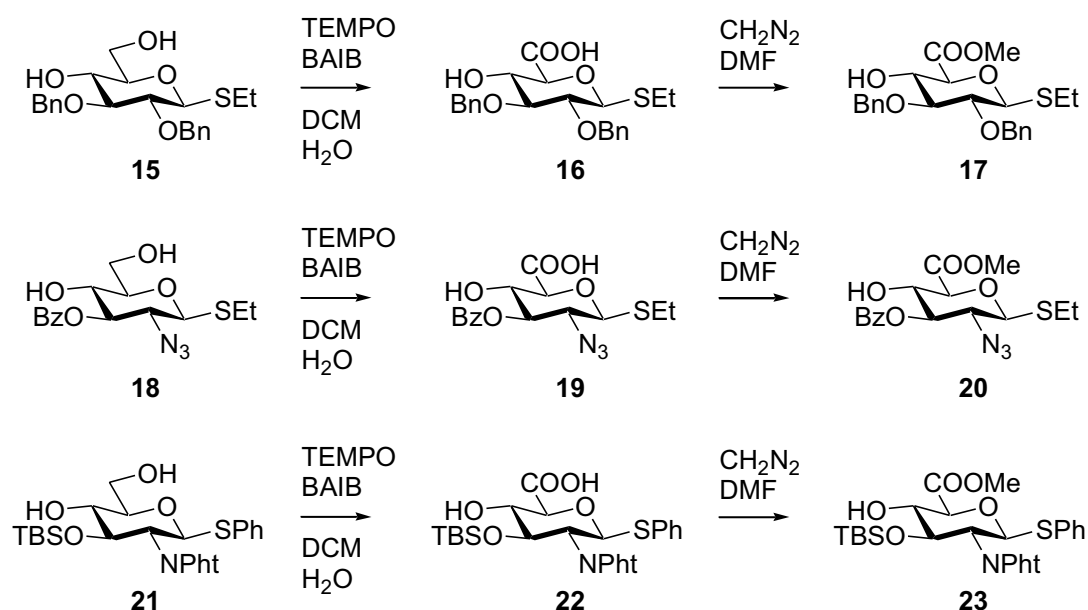
In the field of oligosaccharide and glycoconjugate synthesis many efficient strategies have been developed.^{1,2} Key in this research area is the ability to install the proper interglycosidic linkages with respect to regio- and stereospecificity. The majority of glycosylation procedures involve activation 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.*¹⁰ 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.

**Figure 2**

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

**Scheme 2**

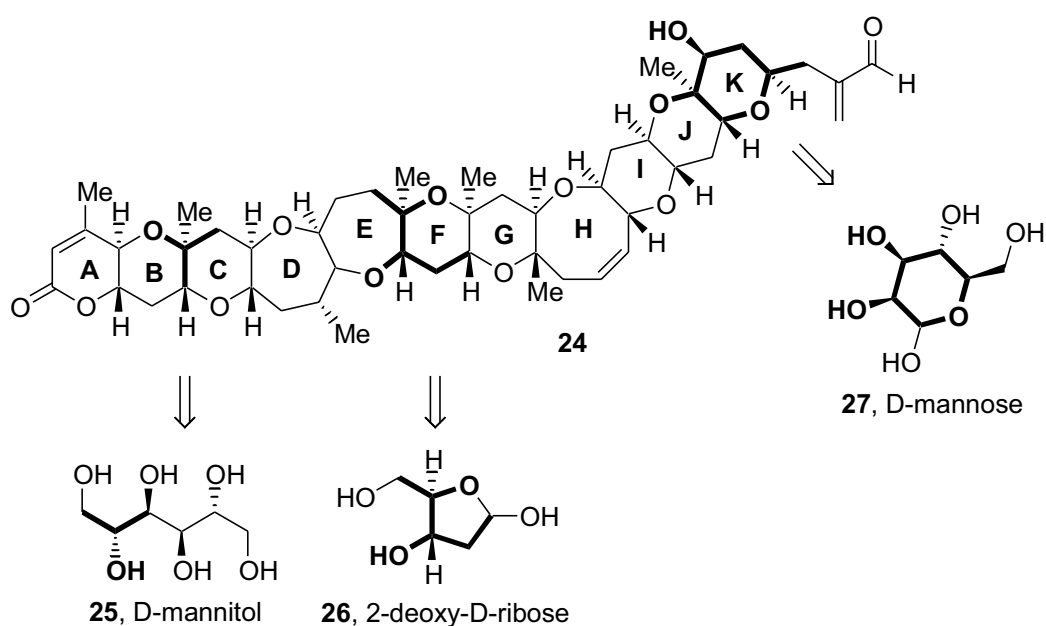
glucuronic acid building block (**13**) afforded protected hyaluronan trisaccharide **14**. Key to the above studies was the accessibility of (partially) protected donor- and acceptor uronic acid derivatives. Van den Bos *et al.*¹¹ presented an elegant strategy in which the primary alcohol function in 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.



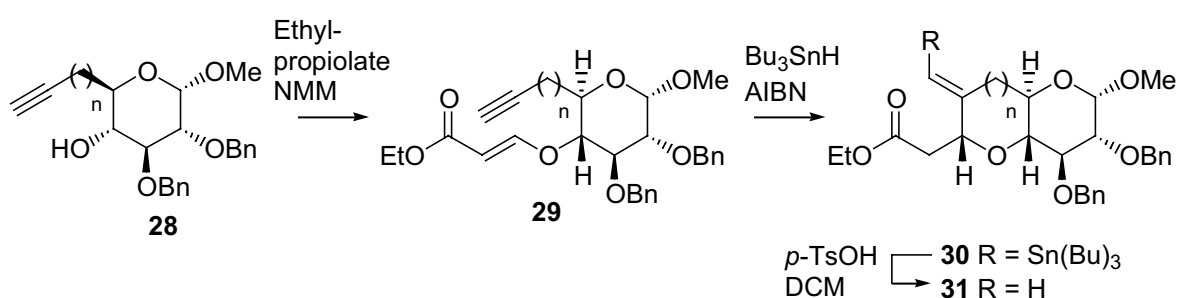
Scheme 3

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.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.¹³ The first total synthesis of brevetoxin B was accomplished by the group of Nicolaou in 1995.¹⁴ 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 *et al.*¹⁵ disclosed an elegant procedure to construct fused cyclic ethers via a radical cyclisation approach of

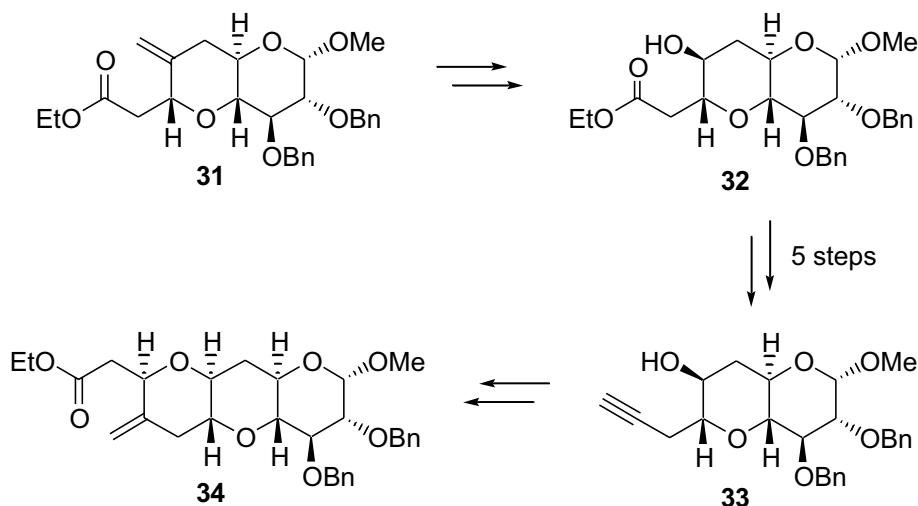
**Figure 3**

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**

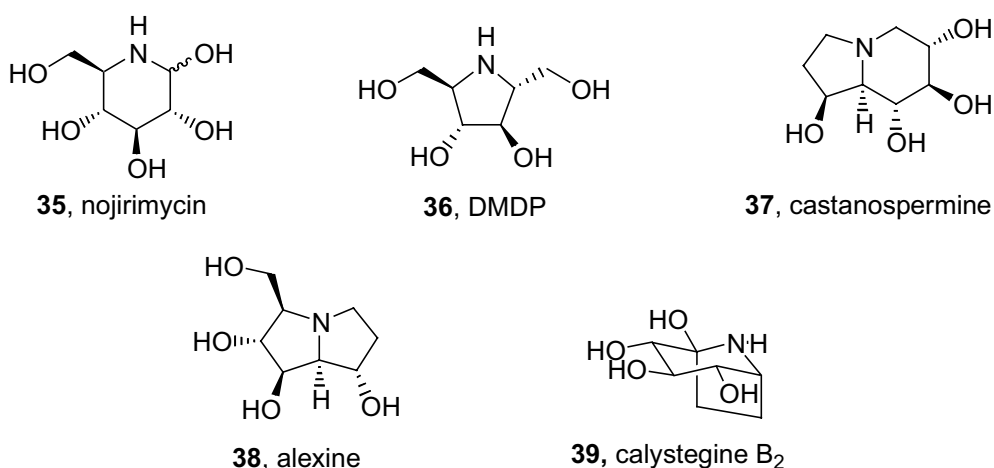
The efficiency of this methodology was nicely demonstrated in the construction of a *trans*-fused tricyclic ether in an iterative fashion. Thus, ozonolysis of the exocyclic

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**.

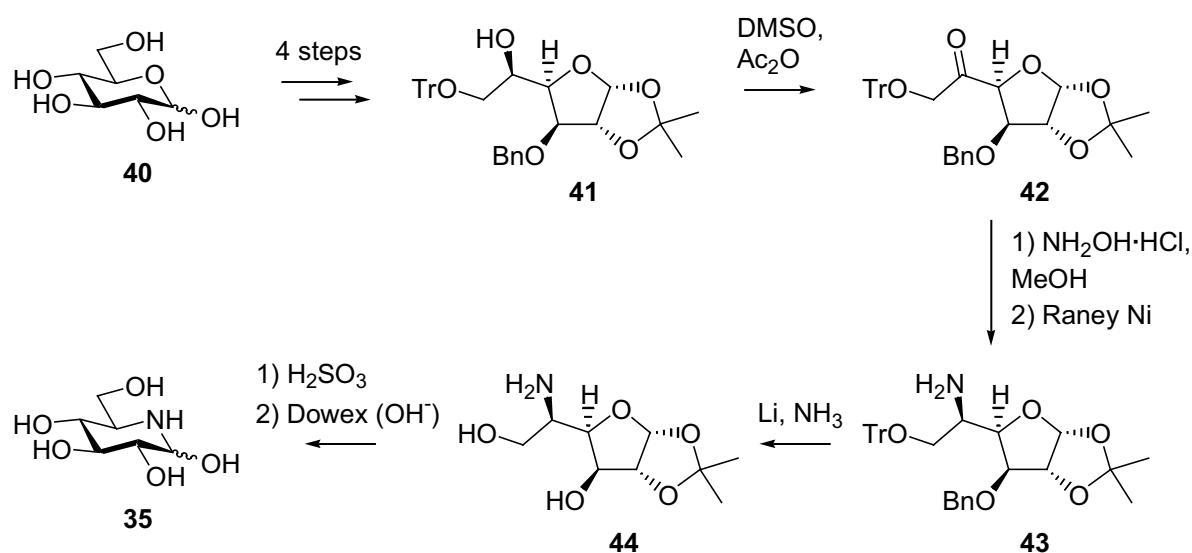


Scheme 5

Another class of compounds widely distributed in nature are the polyhydroxylated alkaloids.¹⁶ 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**),¹⁷ 2,5-dihydroxymethyl-3,4-dihydropyrrolidine (DMDP, **36**),¹⁸ castanospermine (**37**),¹⁹ alexine (**38**)²⁰ and calystegine B₂ (**39**).²¹ The first alkaloid isolated from nature, nojirimycin,^{17a} 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.²²

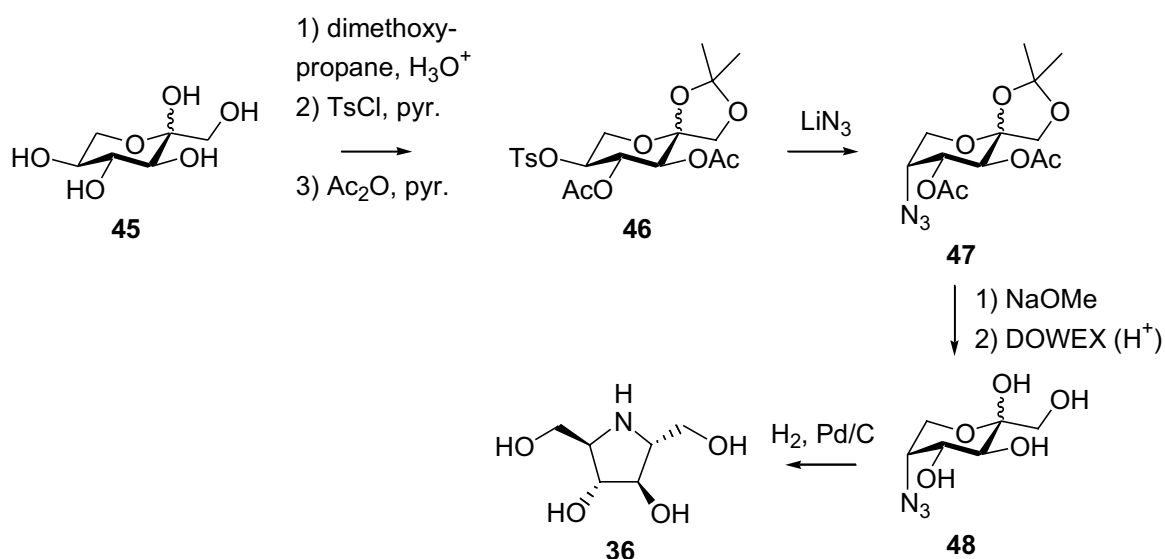
**Figure 4**

In many of the numerous reported synthetic strategies towards iminosugars,²³ 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.^{17b} 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.¹⁸ In 1985 the first synthesis of **36** was reported

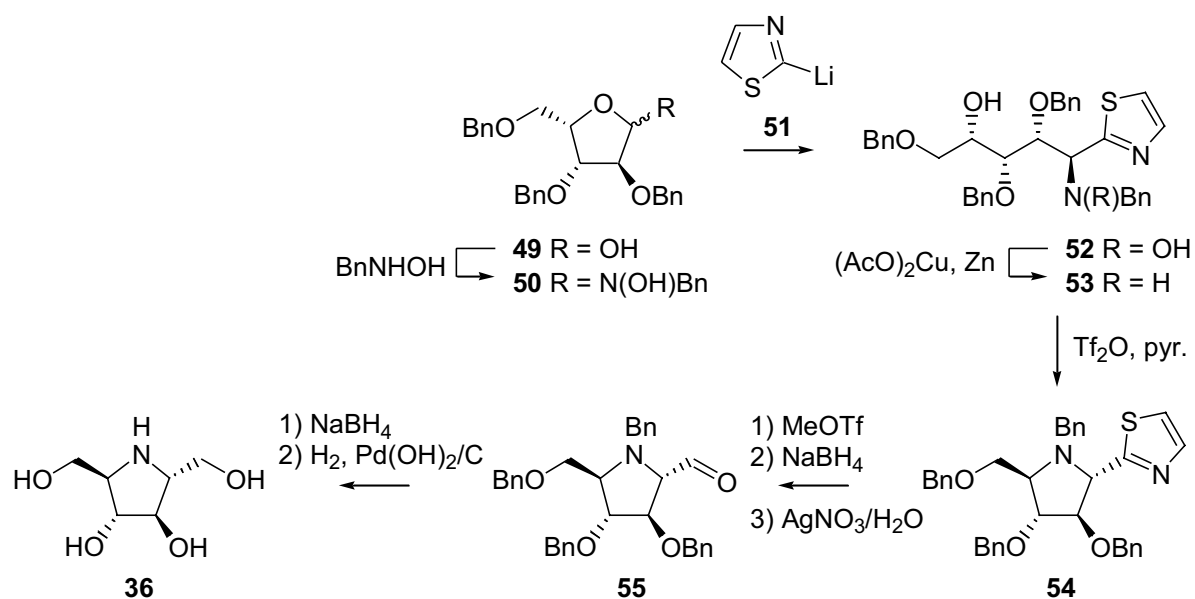
starting from L-sorbose (**45**, Scheme 7),²⁴ which contains the desired stereochemistry at the C-3 and C-4 positions. Bisacetate **46** was obtained in three steps from L-sorbose. Introduction of an azide function, subsequent removal of the protective groups followed by hydrogenation to liberate the amine resulted in the formation of DMDP.



Scheme 7

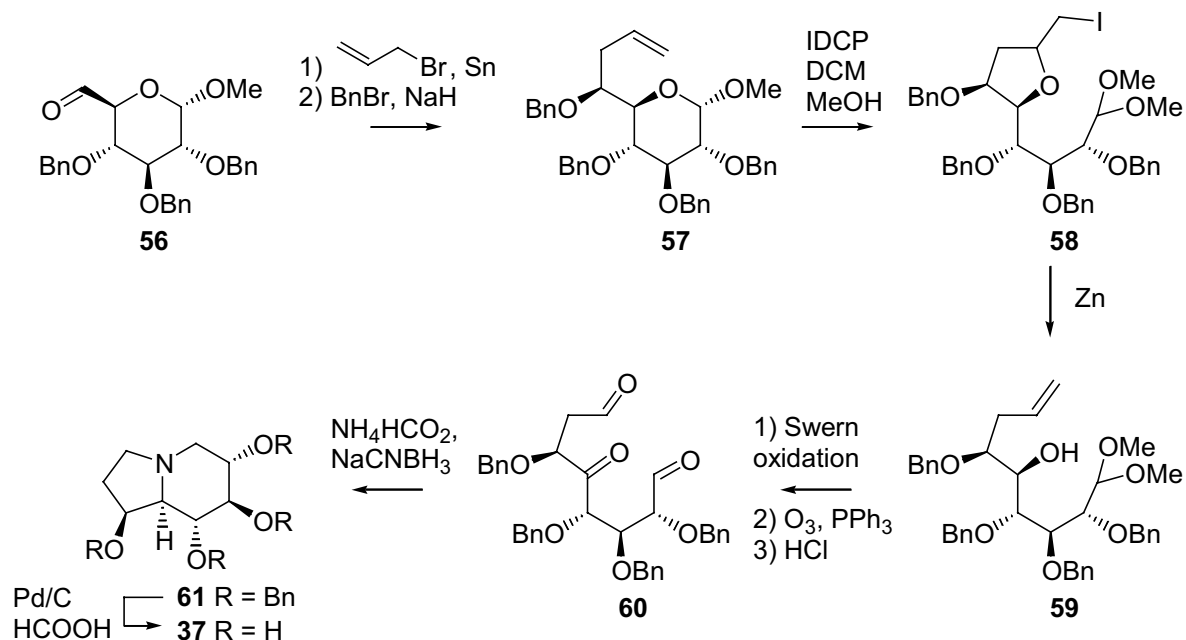
Dondoni and co-workers²⁵ devised a general procedure towards functionalised pyrrolidine iminosugars starting from furanoses (Scheme 8). This strategy commences with a nitron addition followed by thiazole addition and ring-closure with inversion of stereochemistry. To attain DMDP, protected L-xylofuranose (**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-workers²⁶ who made use of a triple reductive amination strategy to incorporate the



Scheme 8

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 9

iodocyclisation under the agency of iodonium dicollidine perchlorate (IDCP) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ and reductive elimination with zinc furnished dimethylacetal **59**. Swern oxidation, ozonolysis and liberation of the aldehyde gave dialdehyde 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 nortropenes (calystegines B₂, B₃ and B₄, Figure 5).²⁷ They took full advantage of the predisposed arrangement of the hydroxyl functions of the corresponding carbohydrate starting materials.

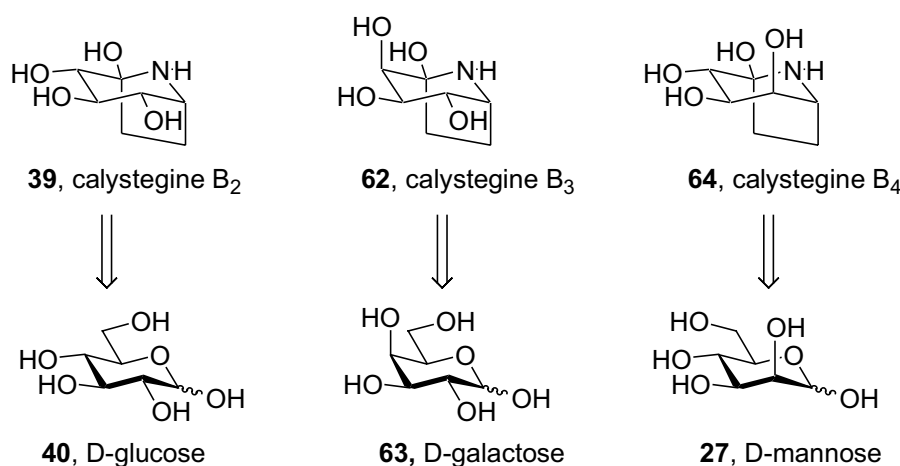
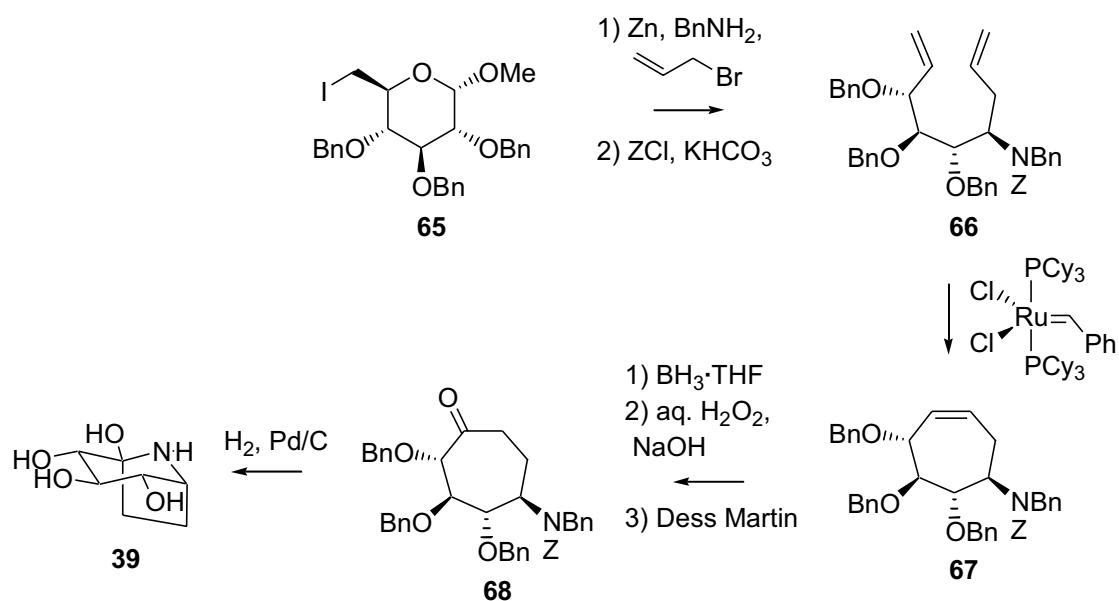


Figure 5

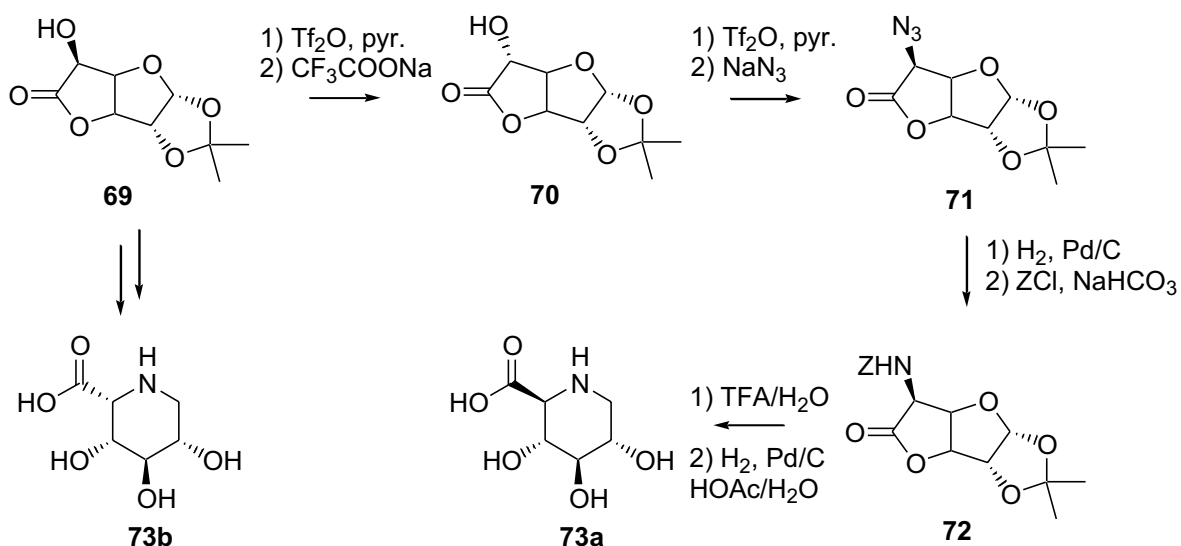
Key steps in the synthesis of the polyhydroxylated seven-membered carbocyclic cores include a zinc mediated domino reaction followed by olefin ring-closing metathesis (RCM), as is exemplified for calystegine B₂ (Scheme 10).²⁸

The naturally occurring trihydroxy pipecolic acid (**73a**), isolated from the seeds of *Baphia racemose*,²⁹ was shown to be a glucuronidase and iduronidase inhibitor. Fleet and co-workers³⁰ 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**.



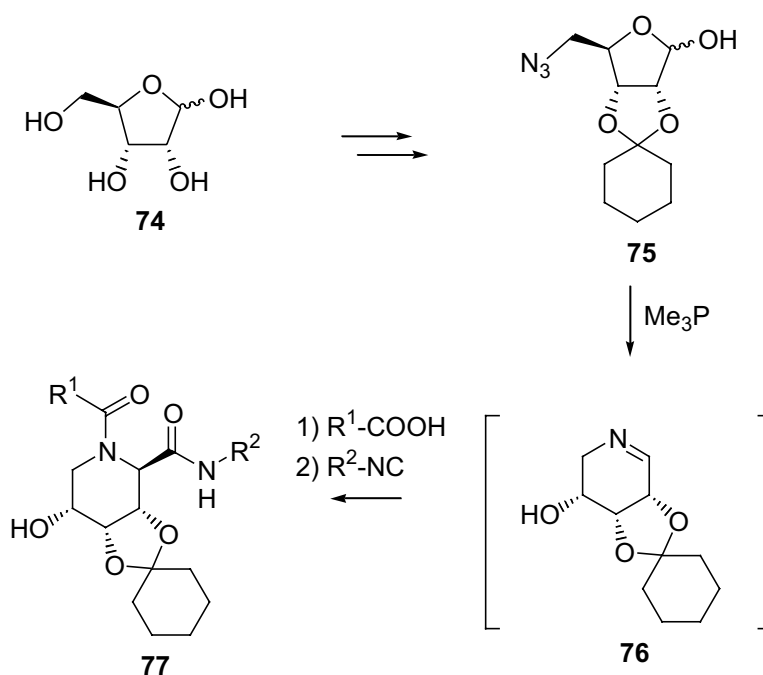
Scheme 10

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 2*R*-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**.



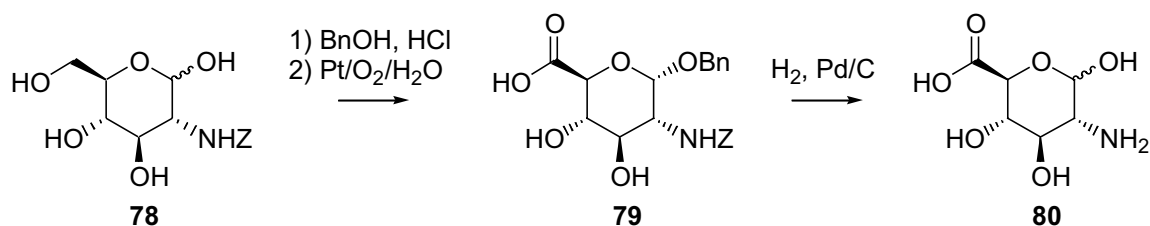
Scheme 11

Recently Timmer *et al.*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%.



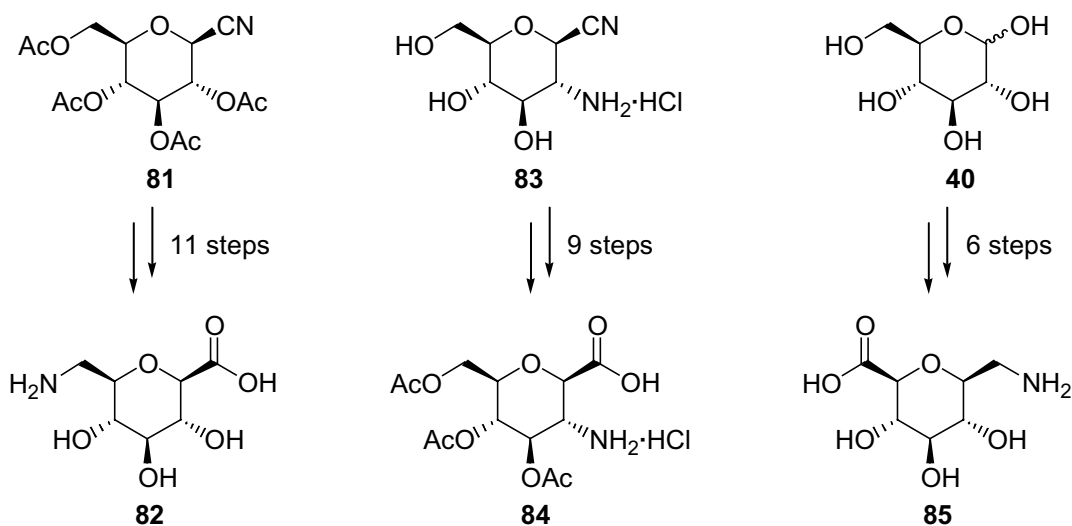
Scheme 12

Carbohydrate derivatives which contain an amine and a carboxylate function can be classified as sugar amino acids (SAAs).⁵ SAAs, such as neuraminic acid³² and muramic acid,³³ are largely found in nature as structural elements but they also play an important role as constituents of certain complex nucleoside antibiotics,³⁴ which exhibit inhibitory activity against fungi and/or bacteria. Heyns and Paulsen reported³⁵ 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 Lehmann³⁶ 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.³⁷ Kessler *et al.*³⁸ reported the synthesis of SAA **85**, the enantiomer of **82** which was previously prepared by Fuchs and Lehmann.

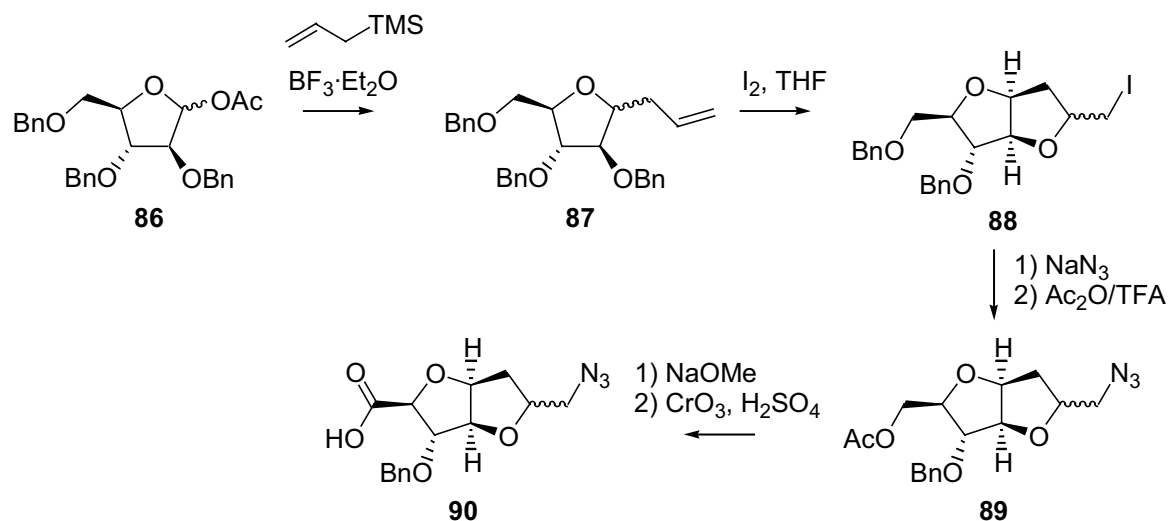


Scheme 14

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

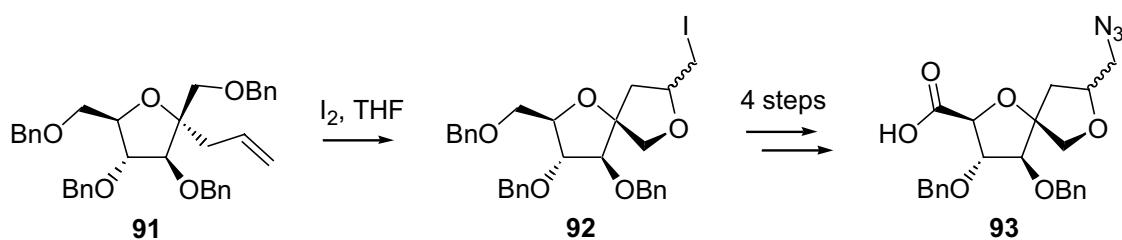
preparation are listed in Schemes 15-19. SAAs, like carbohydrates, often exist as an equilibrium between a mixture of several specific conformers depending on the substitution pattern of the carbohydrate framework. Recently, research in the field of glyco- and peptidomimetics have focussed on the design 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.*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**.



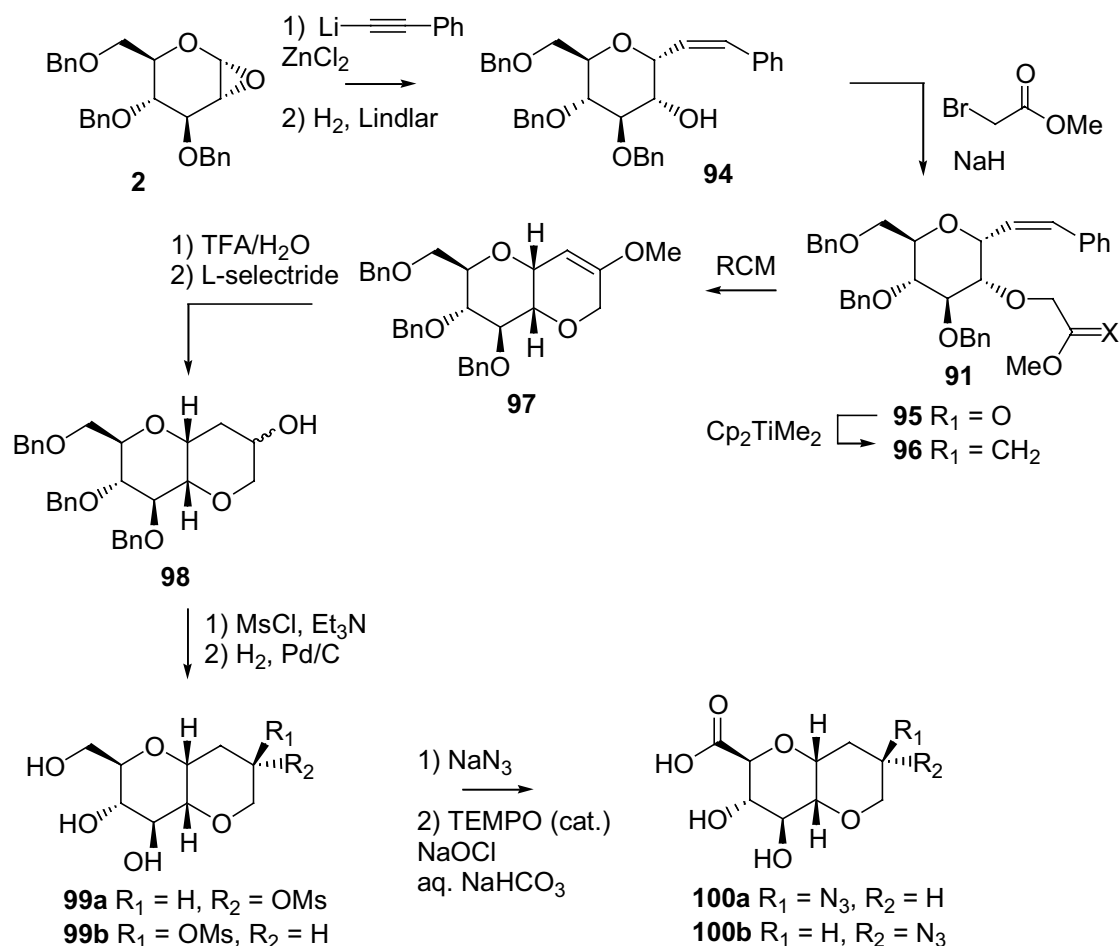
Scheme 15

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

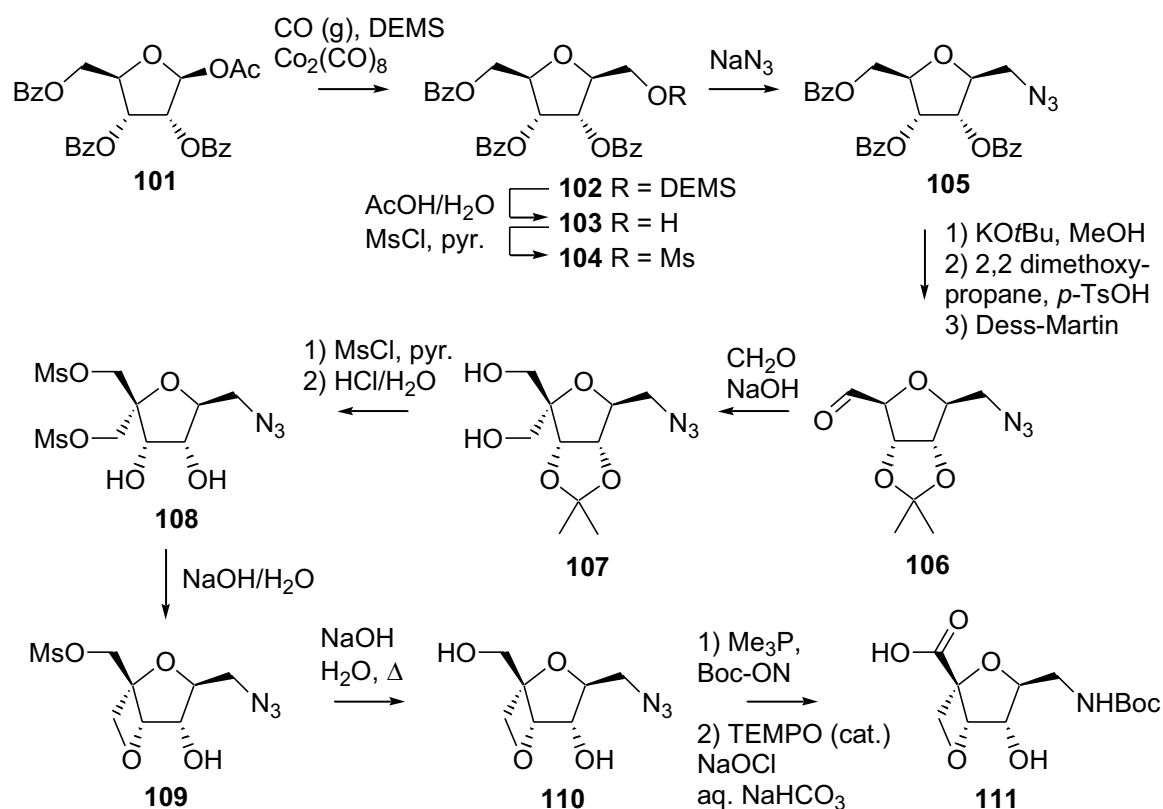
Grottenbreg *et al.*⁴⁰ described the synthesis of two pyranopyran SAAs. The synthesis commenced with the formation of C-glycoside **94**, which is readily available in a two step sequence starting from 1,2-anhydroglucitol (**2**, Scheme 17). Thus, zinc-mediated ring-opening of the epoxide with lithium phenylacetylide and partial reduction



Scheme 17

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**).

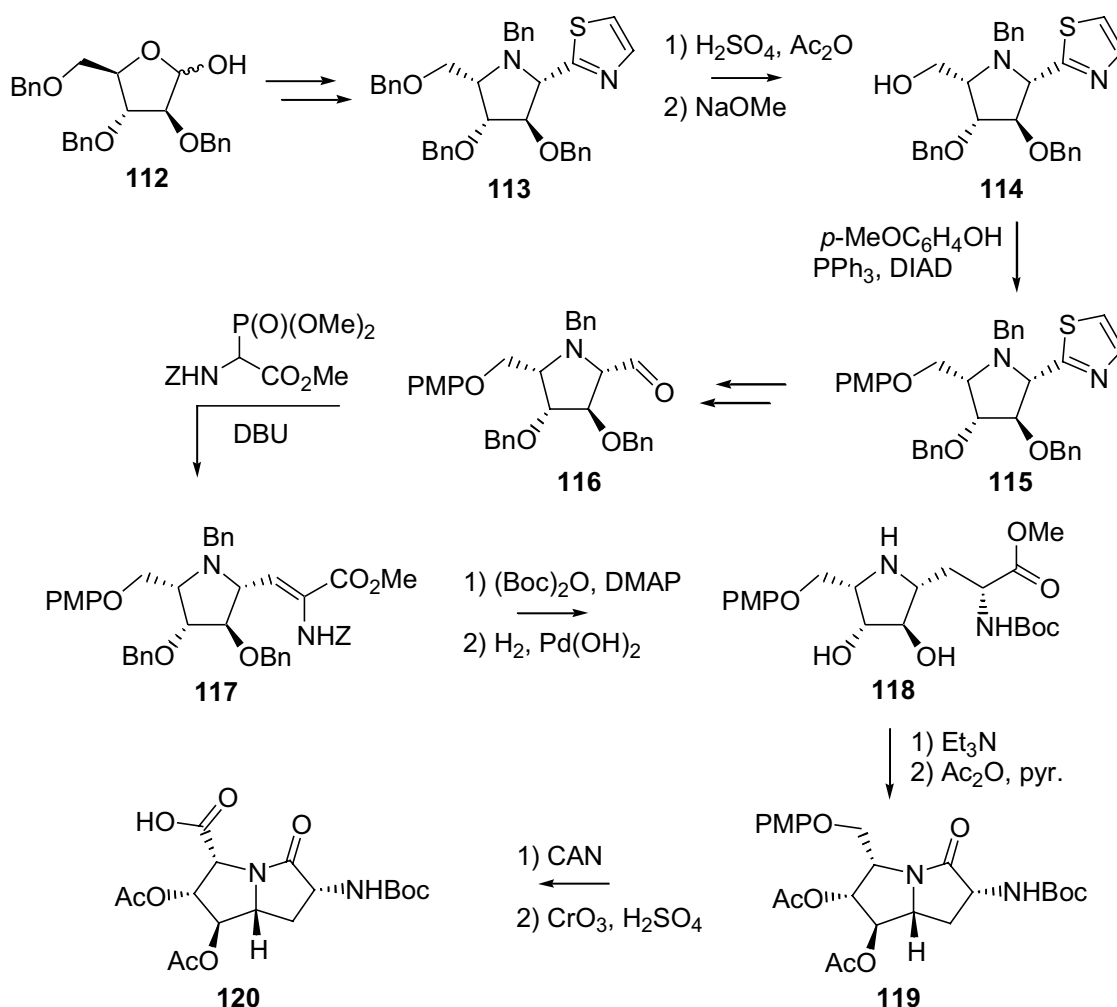
In a recent study to obtain highly constrained SAAs as dipeptide isosters, Van Well *et al.*⁴¹ described the synthesis of novel bicyclic furanoid SAAs locked with an oxetane ring (Scheme 18). The synthesis started with carbonyl-insertion, in the presence



Scheme 18

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**.

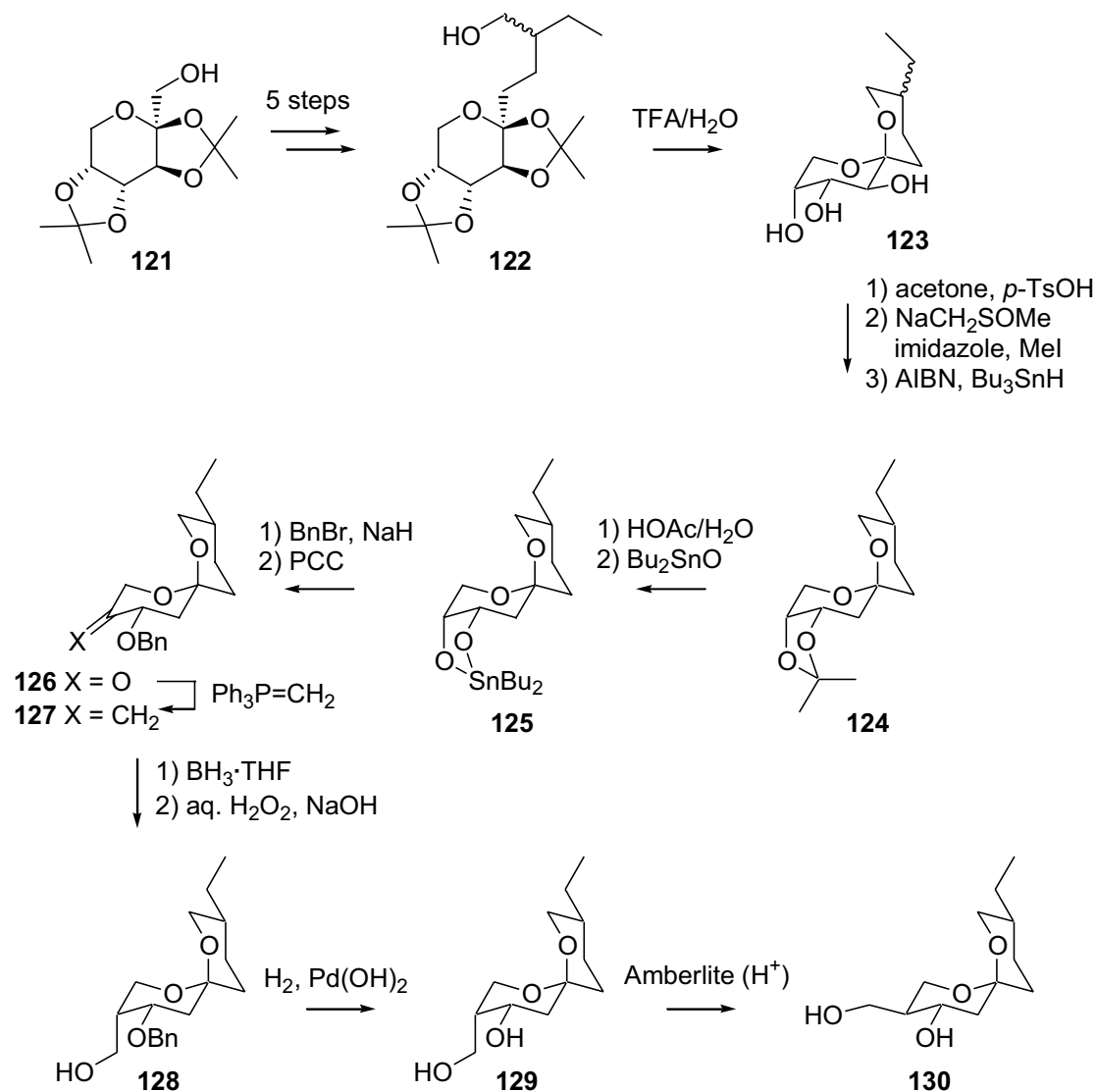
The synthesis of pyrrolizidine SAA **120** (Scheme 19), starting from a protected D-arabinofuranose, was accomplished by Dondoni *et al.*⁴² D-Arabinose **112** was converted to pyrrolidine **116** using their thiazole based aminohomologation procedure previously described in Scheme 8. Next, Horner-Wadsworth-Emmons 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**.



Scheme 19

Spiroketal are often found as structural constituents in many biologically active compounds.⁴³ Spiroketal 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*.⁴⁴ An enantiospecific synthesis of **129** and **130** was realised by Cubero *et al.*⁴⁵ 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

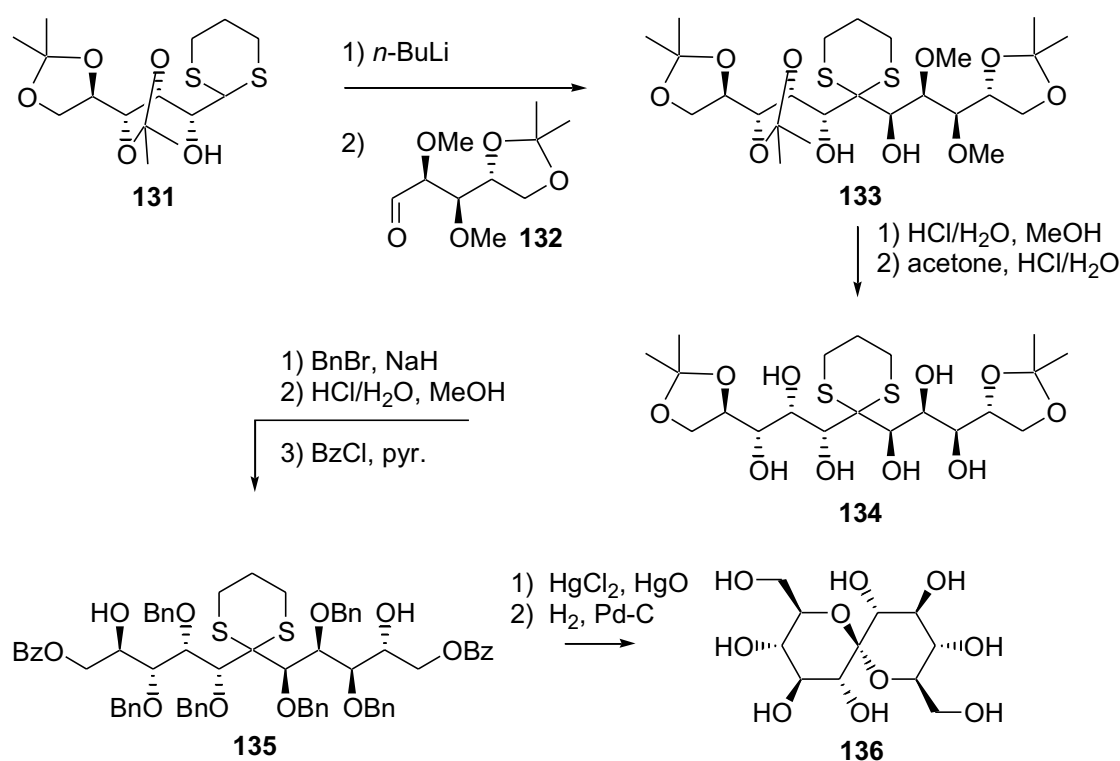
and regioselective opening of intermediate **125** with benzyl bromide followed by PCC oxidation furnished ketone **126**. Next, Wittig olefination of **126**, hydroboration of the resulting exocyclic alkene in **127** followed by hydrogenolysis of **128** afforded talaromycin A. An acid catalysed isomerisation 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.*⁴⁶ reported a general

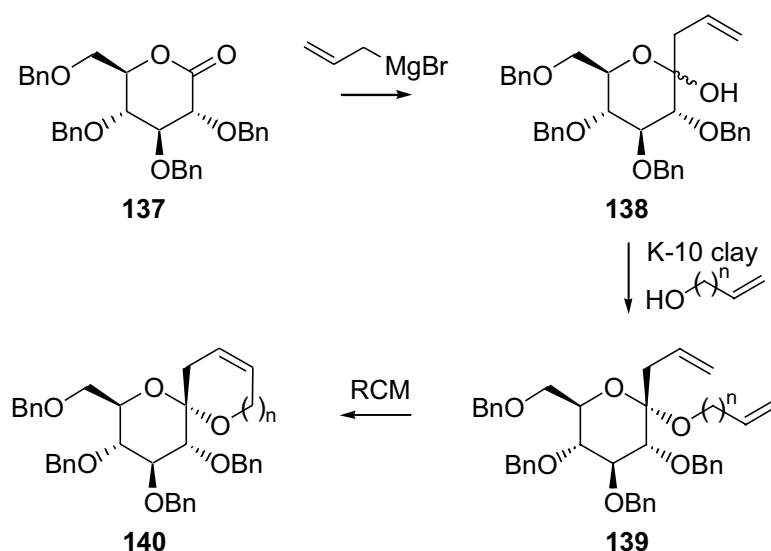
approach towards the synthesis of a set of hexopyranoses linked together by a spiroketal center. According to the Corey-Seebach procedure,⁴⁷ the synthesis commenced with the coupling of a dithioacetal with an open chain aldopentose as follows (Scheme 21). Reaction of the dianion of glucose-derived dithiane **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.*⁴⁸ 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

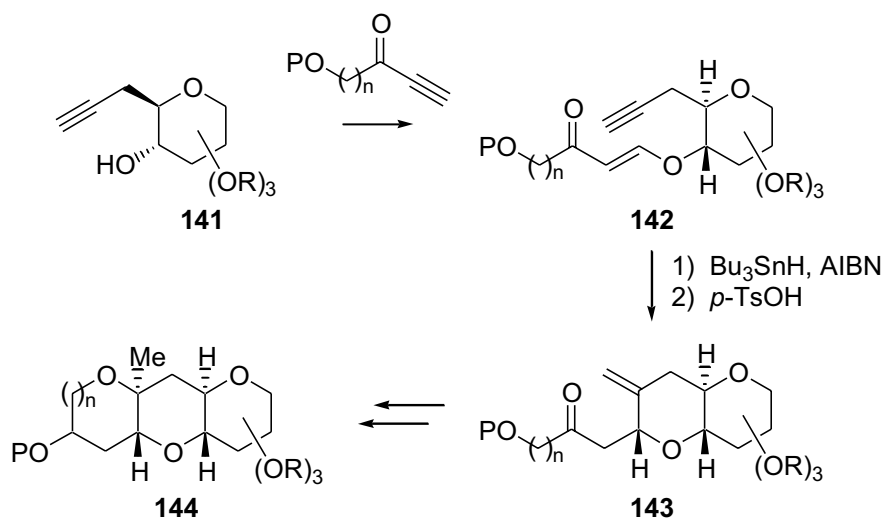
further demonstrated by variation of the Grignard reagent (allyl- or vinylmagnesium bromide) followed by the addition to different pyrano- as well as a furanolactones, in combination with changing the chain length of the alkenol. In this manner several pyranose- and furanose-derived lactones were transformed into spiroketals.⁴⁹



Scheme 22

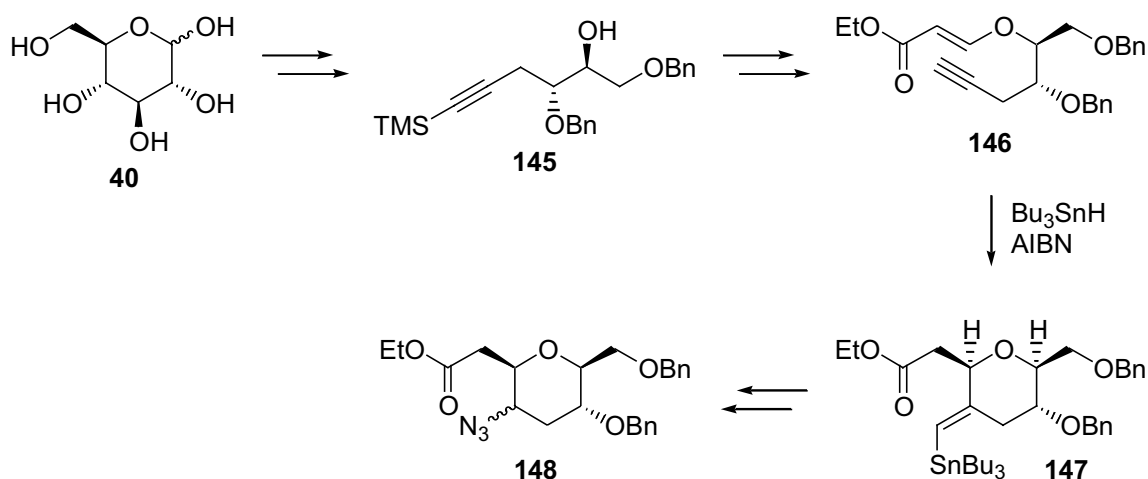
Aim and outline of the Thesis

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. **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 *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.



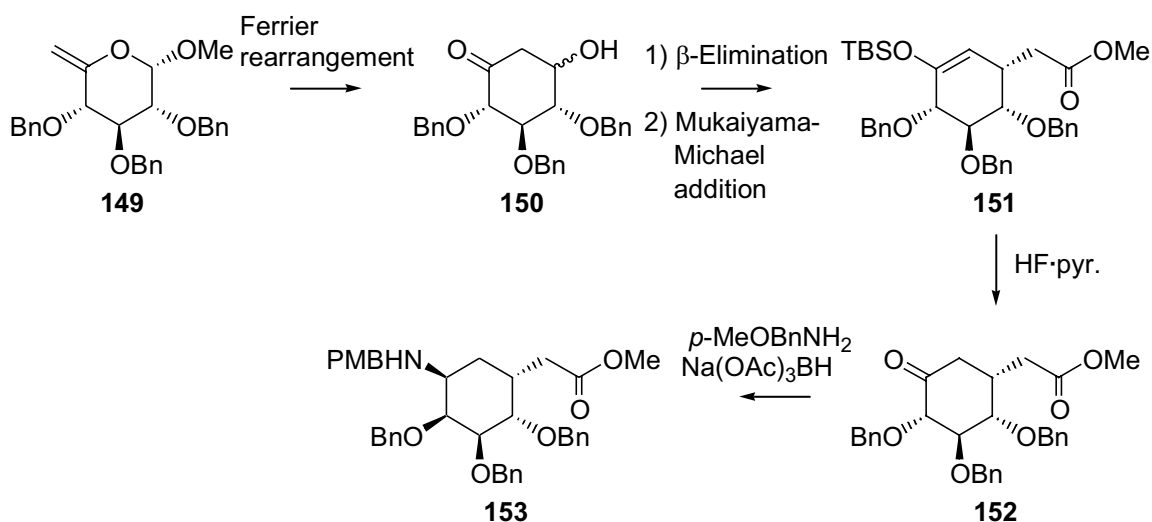
Scheme 23

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

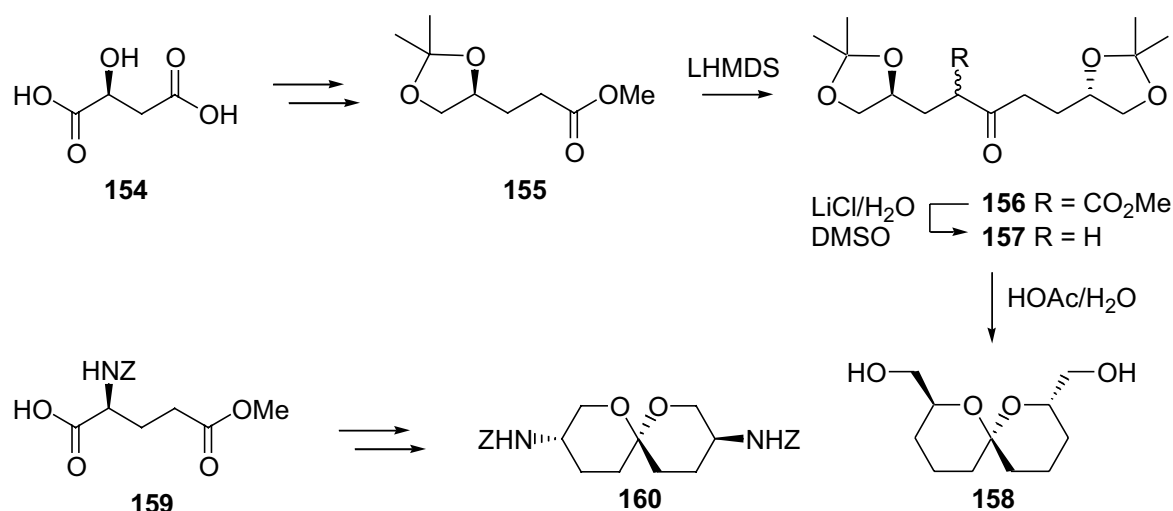
The transformation of D-glucose into a carbasugar amino acid (CSAA), a novel class of conformationally restricted SAAs, is described in **Chapter 4**. The Ferrier-rearrangement proved to be a convenient method to convert glucose-derived enopyranoside **149** into cyclitol **150** (Scheme 25). At this 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 spiroketals **158**. In a similar approach, partially protected glutamic acid **159** was converted into spiroketal **160**, containing protected amine functions



Scheme 26

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

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