Carbohydrates as chiral starting compounds in synthetic organic chemistry
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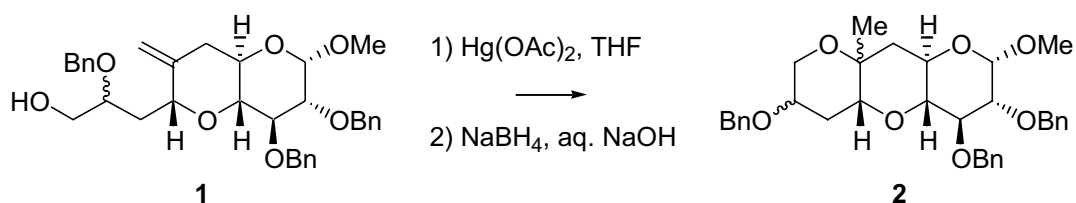
Chapter 6

Summary and Future Prospects

The focus of the research described in this Thesis entails the conversion of monosaccharides into polycyclic ethers, novel sugar amino acids and spiroketals. A common theme in this research, besides protective group manipulations and functional group transformations, comprises the cyclisation methods employed throughout the syntheses. These include radical cyclisations, selenocyclisations, Ferrier rearrangements and spiroketalisations. **Chapter 1** gives a selective overview concerning the use of carbohydrates as starting material in the construction of natural products and biologically relevant compounds. Examples discussed involve the synthesis of oligosaccharides, fused polycyclic ethers, alkaloids, sugar amino acids and spiroketals.

The synthesis of *trans*-fused tricyclic ethers containing a methyl group located at a bridgehead position was investigated in **Chapter 2**. Radical cyclisation of carbohydrate-derived ene-yne intermediates proceeded smoothly to furnish two pyrano-pyran ring systems. In the next ring-closing event, it was anticipated to take full advantage of the exocyclic vinylstannane moiety thereby simultaneously installing the methyl group. Attempts to obtain a tricyclic ether composed of three pyran rings were

inefficacious, but the synthesis of an analogous 8,6,6-tricyclic ether was accomplished successfully.
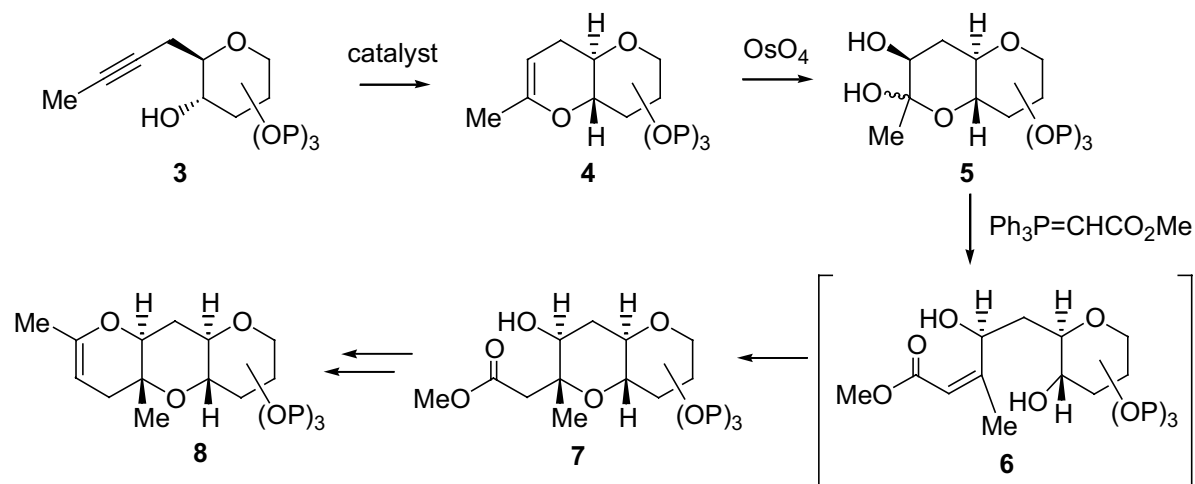
In a pilot experiment to assemble a 6,6,6-tricyclic ether, cyclisation and concomitant release of the methyl group could be effected (Scheme 1). By means of an oxymercuration,[1] ring-closure of compound **1** proceeded to give **2**, but the absolute stereochemistry could not be determined at this stage.

Scheme 1

Tungsten- or ruthenium-catalysed cyclisomerisation of terminal alkyne alcohols have been found to form 5-, 6- and 7-membered cyclic enol ethers.[2] However, application of 2-alkynes as substrates for this transformation, such as **3** (Scheme 2), have not been reported. *Endo*-cyclisation of 2-alkynes can be effected under the agency of mercury or palladium catalysts.[3] Based on these findings, carbohydrate-derived alkynol **3** could in
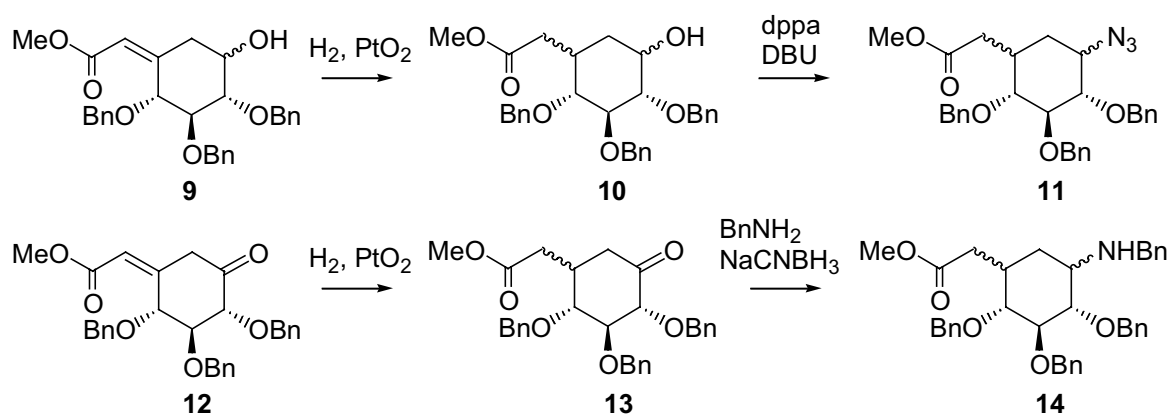
Scheme 2

potential be used in an iterative procedure, as follows. Cyclisation of **3** under the influence of one of the above catalytic systems should give enol ether **4**. Further elaboration of **4**, with the angular methyl already installed, to construct a third pyran ring would proceed as follows: 1) dihydroxylation of the double bond (**4** to **5**), 2) Wittig olefination of the resulting ketal functionality (**5** to **6**), 3) ring-closure through Michael addition (**6** to **7**) followed by 4) transformation of the methylester into an alkyne. After transformation of the methylester into a 2-alkyne, the same sequence of events may provide tricyclic system **8**.

Chapter 3 describes the application of the radical cyclisation strategy towards the synthesis of conformationally constrained γ-sugar amino acids. Obtaining the requisite alkynol proved to be the crucial step throughout the course of operations. For instance, nucleophilic opening of a cyclic sulfate was accompanied by side-reactions. Instead, opening of an oxetane in the presence of a Lewis acid, served as a suitable alternative to furnish an appropriate Michael acceptor.

In **Chapter 4**, the synthesis of a novel carbasugar amino acid (CSAA) is presented. Methodologies to assemble this class of hybrid molecules remain relatively unexplored to date. The carbocyclic core was readily accessible by converting a carbohydrate-derived enol acetate into a cyclitol via a Ferrier rearrangement. Installation of the carboxylate and amine functionalities was shown to be rather cumbersome, often due to the occurrence of β-eliminations and subsequent aromatisations. After exploring several conditions, introduction of the carboxylate functionality was achieved using a Lewis acid mediated Mukaiyama-Michael addition. Ensuing reductive amination afforded a novel conformationally restricted CSAA which can be regarded as a dipeptide isoster. In view of the β-eliminations during the syntheses, saturation of the double bonds in either **9** or **12** (Scheme 3) should prevent eliminations to occur. Thus, selective hydrogenation of **9** and **12** should allow installation of amine functionalities under basic conditions at the right hand side of the cyclohexane core in **10** and **13**.
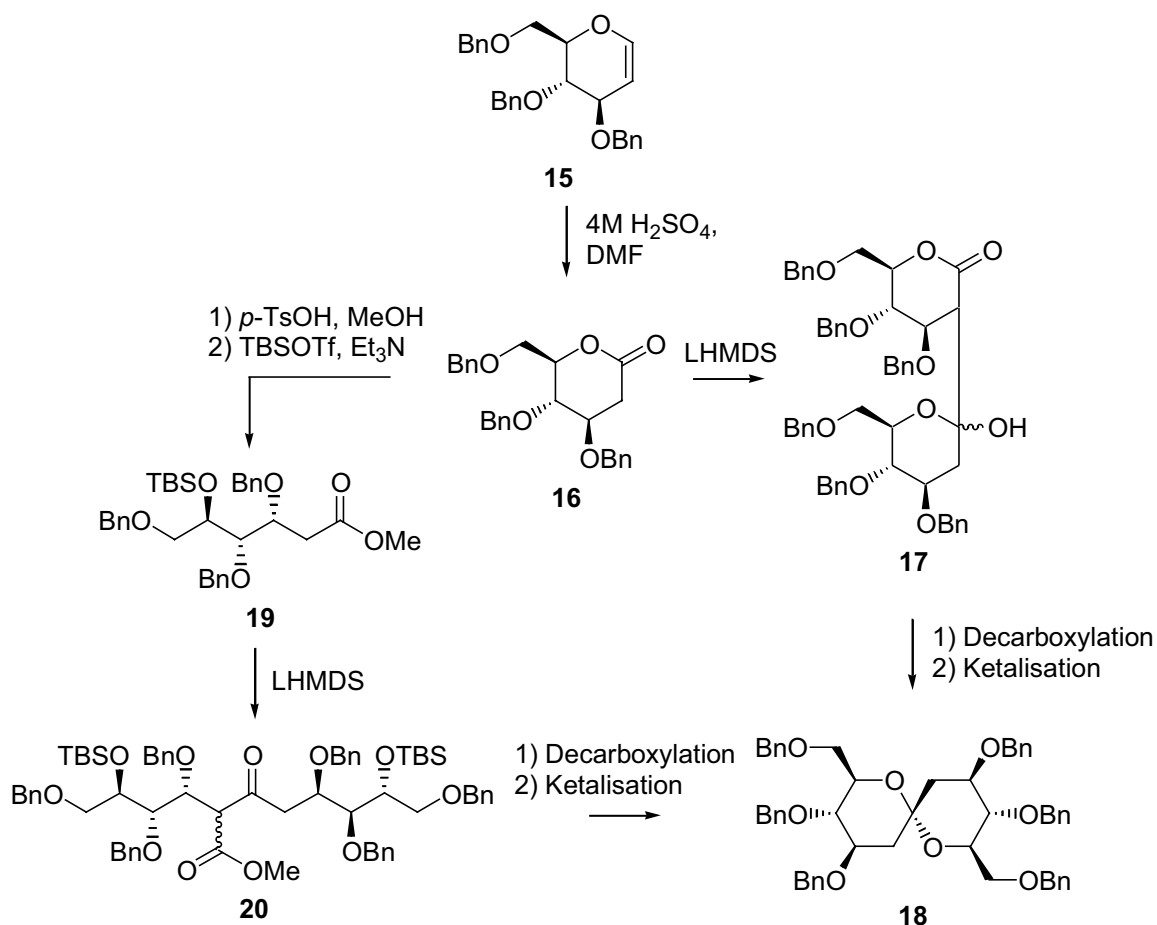
Scheme 3

A general and efficient strategy to construct functionalised 1,7-dioxaspiro[5.5]undecane ring systems is presented in **Chapter 5**. This procedure is based on an acid catalysed spiroketalisation of C_2-symmetrical dihydroxyketones. Accordingly, Claisen self-condensation of suitably protected hydroxyesters afforded the corresponding β-keto esters. Hydrolysis of the ester functions followed by decarboxylation of the resulting β-keto acids smoothly furnished the requisite dihydroxyketones. Acidic removal of the protective groups and subsequent ring-closure effectively transformed the hydroxyketones into the spiroketals. The absolute stereochemistry and conformational preference of the spiroketals entirely hinges on the chirality present in the starting material. This chirality induces a double anomeric effect of the ketal center and forces substituents to adopt equatorial positions resulting in the formation of the thermodynamically most favorable isomer.
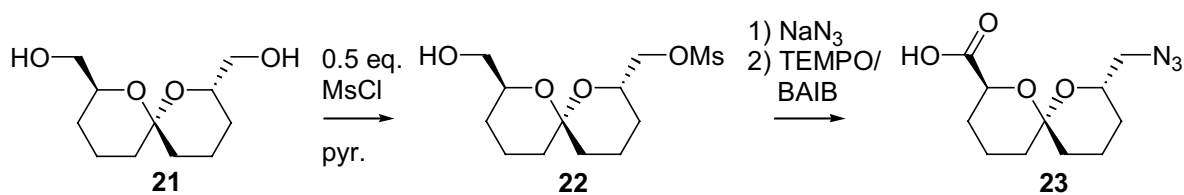
It would be of interest to establish the viability of the Claisen condensation/decarboxylation procedure in the synthesis of more densely functionalised spiroketals, starting from more complex precursors. For instance, starting from 2-deoxy gluconolactone **16**, easily accessible from D-glucal **15** (Scheme 4) and application of the two-step condensation/decarboxylation procedure, the synthesis of polyhydroxylated spiroketal **18** may be feasible. In case Claisen self-condensation of lactone **16** proves to be troublesome, transformation of **16** into protected hydroxyester **19** and ensuing Claisen self-condensation/decarboxylation provides an alternative entry to assemble spiroketal **18**.
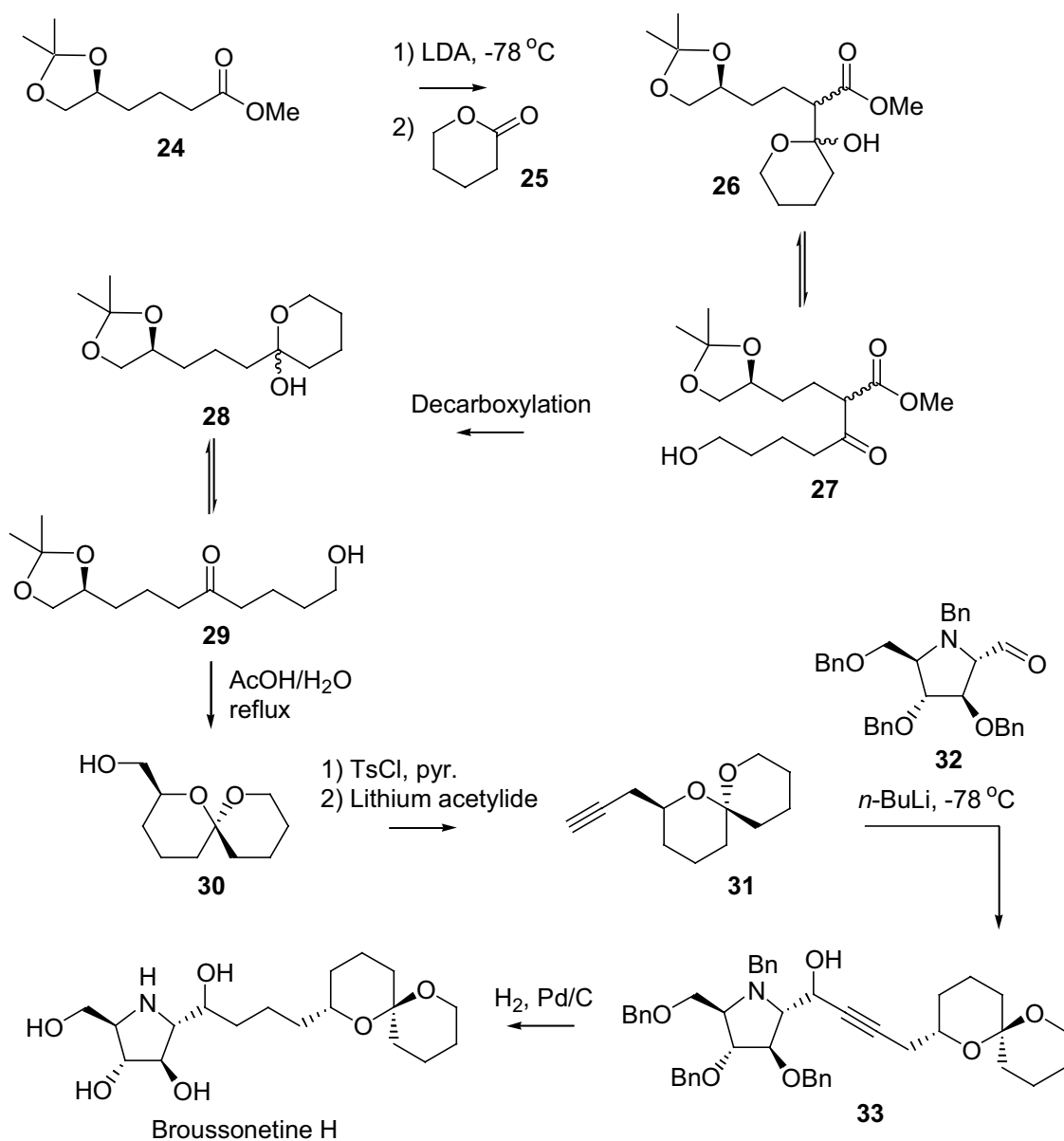
Scheme 4

A second interesting follow-up of the research described in **Chapter 5** is to investigate whether dihydroxy spiroketal **21** can be transformed into a novel conformationally restricted amino acid **23** (Scheme 5). Installation of a mesylate function (**22**), subsequently followed by nucleophilic displacement with an azide and oxidation of the primary alcohol may furnish spiroketal **23**.

Scheme 5

A variety of natural products, such as broussonetine H[4] (Scheme 6), contain spiroketal entities. The construction of the spiroketal can in potential be achieved starting from protected hydroxy ester **24** and δ-valerolactone (**25**). Enolate formation of **24** under the agency of LDA[5] followed by addition of **25** would result in either β-substituted ester **26** or **27**. Decarboxylation and acidic ketalisation then furnishes spiroketal **30**.

Scheme 6

Installation of an acetylene would facilitate coupling of **31** with pyrrolidine **32**.[6] Removal of the protective groups along with saturation of the triple bond in **33** completes the synthesis of broussonetine H.

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