Methods for Shortening and Extending the Carbon Chain in Carbohydrates

Carbohydrates play a central role in a variety of physiological and pathological processes such as HIV, cancer and diabetes. The understanding of these processes and the development of specific therapeutic agents is relying on the ability to chemically synthesize unnatural sugars, glycoconjugates and carbohydrate mimetics. Such polyhydroxylated compounds are conveniently synthesized from carbohydrates, however, due to the scarcity of many sugars from nature, efficient methods for transformation of readily available carbohydrates into valuable chiral building blocks are required.

The work presented in this thesis focuses on the development and application of transition metal mediated methods for shortening and extending the carbon chain in carbohydrates thereby providing access to lower and higher sugars. A new catalytic procedure for shortening unprotected sugars by one carbon atom has been developed. By means of a rhodium-catalyzed decarbonylation of the aldehyde functionality, aldoses are converted into their corresponding lower alditols in yields around 70%. The reaction is performed with 8% of the catalyst Rh(dppp)2Cl in the presence of small amounts of pyridine to facilitate mutarotation. The procedure has been employed as the key step in a short five-step synthesis of the unnatural sugar L-threose in 74% overall yield from D-glucose. A zinc-mediated one-pot fragmentation-allylation reaction has been used to elongate D-glucose and D-ribose by three carbon atoms thereby producing carbohydrate-derived α,ω-diienes, which have been converted into the natural products calystegine A3 and gabosine A. The glycosidase inhibitor calystegine A3 was produced by two similar routes from commercially available methyl α-D-glucopyranoside in 13 and 14 steps with 8.3 and 5.3% overall yield, respectively. The present work thereby constitutes the shortest synthesis of enantiomerically pure calystegine A3, and furthermore, it enables the absolute configuration of the natural product to be determined. Gabosine A has been prepared in nine steps and 13.9% overall yield from D-ribose, and this synthesis provides the first route to gabosine A from an abundant carbohydrate precursor.

During an external stay at University of Oxford, the metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs) has been investigated. It was found that known acyl glucuronide metabolites of ibuprofen and several analogues modify human plasma protein under conditions encountered in therapy. Two different kinds of protein modification occur depending on the structure of the parent drug. The obtained results strongly suggest that irreversible modification of human proteins takes place during treatment with carboxylic acid containing drugs such as NSAIDs. Furthermore, the observed reactivity of these metabolites with respect to protein modification may provide an explanation for the severe toxicity that has led to the withdrawal of certain carboxylate drugs.