ABSTRACT

This thesis deals with the synthesis of higher sugars using two methodologies, namely, 1) Wadsworth-Emmons reaction and 2) tetra-hydroxylation of sugar derived dienes. The thesis consists of three sections, namely, introduction, results and discussion and experimental. The results and discussion is divided into two parts. Part-I deals with preparation of sugar derived p-keto phosphonates and their use in the synthesis of higher sugars. Part-II deals with synthesis of higher sugars by bis-dihydroxylation of sugar dienes.

The introduction briefly presents various available methods for the synthesis of higher sugars. Different approaches, which are commonly used are discussed under six major headings, namely, 1) Wittig reaction, 2) Aldol condensation, 3) Radical reactions, 4) Nucleophilic additions, 5) (3+2) Cycloaddition and 6) Ab-initio synthesis.

Synthesis of higher sugars has been a target of interest to the organic chemist since the time of Fischer. This is due to the fact that higher sugars are, a) complex carbohydrates, which are not available in nature, b) components of some natural products like hikizimycin and tunicamycin and c) chiral, highly functionalized synthons for the preparation of macrolide antibiotics like erythromycin and streptovaricin.
Synthesis of higher sugars using Wadsworth-Emmons reaction.

One of the earliest methods for the synthesis of higher sugars is the Kiliani-Fischer reaction, which is used to extend the aldose chain by one carbon from the reducing end. More recently, the Wittig reaction has been used in all possible combinations. Still, due to its limitations, the need for a new methodology for this purpose was felt. The advantage of the Wadsworth-Emmons reaction over the classical Wittig reaction is well known to bear repetition.

The required p-keto phosphonates 87, 97, 98, and 99 were obtained in quantitative yields by the acylation of lithium dimethyl methylphosphonate with the readily available methyl glycuronates or glyconate. A systematic study of the reaction of the phosphonate 87 with p-anisaldehyde in the presence of various bases like DBU, NaH, K$_2$CO$_3$, and Cs$_2$CO$_3$ showed Cs$_2$CO$_3$ to be the most suitable base for the purpose and the corresponding enone was obtained in high yield. Subsequently, phosphonates 87, 97, 98 and 99 were condensed with various sugar aldehydes derived from aldoses at C-1, C-5, and C-6 to give rise to the expected higher sugar enones, in high yields.

Similarly, to facilitate the extension of carbon chain from both ends, C-2 symmetric bis-phosphonate 113 was prepared from diethyl-2,3-O-isopropylidene-L-tartarate (112) and was treated with various sugar aldehydes to provide the corresponding C-2 symmetric bis-enones in moderate yields.

In order to highlight the synthesis of higher sugars from higher sugar enones, enone 103 was hydroxylated using osmium tetroxide/N-methylmorpholine N-oxide to
obtain 124 and 125 in 90% yield. While this work was in progress, Jarosz reported the preparation of 124 and 125 by the same method.

Synthesis of higher sugars using tetra-hydroxylation of sugar derived dienes.

Kishi, in his paper on stereochemistry of osmium tetroxide oxidation of allylic alcohol and ether systems, showed that the relative stereochemistry between the existing hydroxyl or alkoxy group and the adjacent newly introduced hydroxyl group of the major product is erythro in all cases. Recently, Sharpless observed that on hydroxylation of achiral dienes and trienes, the major product has erythro relationship between the hydroxyl groups formed between two double bonds and selective asymmetric dihydroxylation of unsymmetrical dienes occurs at the more substituted double bond. At this stage, it was of interest to make a model in which both Kishi’s and Sharpless’s observations would be operative (i.e., a diene attached to a chiral centre). Dienes 137 and 140 were chosen for this purpose and their advantage can be understood by analyzing the structures of all possible hydroxylated products, 151-154 and 155-158, respectively. 1) Both dienes 137 and 140 on hydroxylation provide one meso and one C-2 symmetric diastereomer each, 2) one of the diastereomers obtainable from both 137 and 140 form an enantiomeric pair and 3) one of the diastereomers obtainable from 137 is identical to one of those derivable from 140. These features allow for easy and unambiguous product identification.

Dienes 137 and 140 were synthesized by the Wittig reaction of the known enals 136 and 139, respectively. Dienes 137 and 140 were hydroxylated using osmium tetroxide/N-methylmorpholine N-oxide, and the resulting hydroxylated products were converted to their peracetylated octitol mixtures 148 and 150, respectively, using
conventional protection and deprotection methods. Analysis of the mixture 148 revealed that 151-OAc, 152-OAc and 153-OAc were formed in a ratio of 1.15:6.6:1. The diastereomeric peracetylated octitol mixture 150 obtained from 140 showed that 155-OAc, 156-OAc and 158-OAc were present in a 1.33:1:1 ratio, respectively.

Results of the diastereoselective hydroxylation of dienes 137 and 140 indicate that the major isomer formed is the one in which both the relations between the existing hydroxyl group and the adjacent newly introduced hydroxyl group, as well as the hydroxyl groups formed between two double bonds are erythro. It is also interesting to note that stereo isomers 154-OAc and 157-OAc are not formed at all, since in them both stereochemical relationships are threo.

Conclusion

The above results show that the methodology developed here provides a simple and convenient procedure for the preparation of higher sugars. Higher sugars of any combination of lower constituent sugars can be synthesized easily. A study on the diastereoselectivity of complex diene hydroxylation was performed for the first time. Results of these experiments show that the major isomer formed is the one which is in accordance with Kishi's and Sharpless's observations.