Synthetic Strategies Towards Rare Monosaccharides

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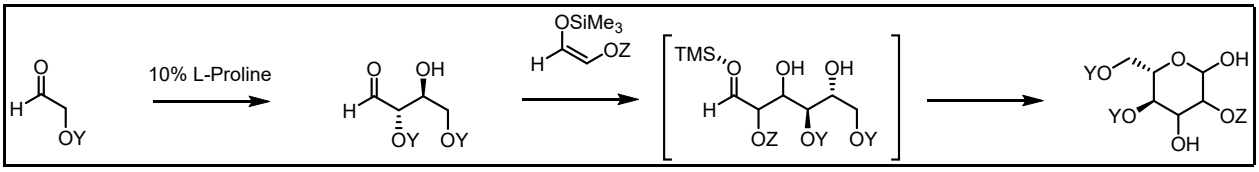
Introduction

Rare monosaccharides can broadly be defined as carbohydrates not readily accessible from biomass processing. Often, these sugars are deoxygenated, stereoisomers of commonly accessed biomass products that may also include amino or alkyl groups. Many natural products are glycosylated, but structure-activity relationships are difficult to conduct given the synthetic challenges of accessing rare monosaccharides. Current strategies include *de novo* syntheses, chemoenzymatic approaches, and site-selective radical functionalizations.

De novo Approaches to Monosaccharides

Exotic monosaccharides are most commonly prepared *de novo*. Given their dense stereochemistry and numerous functional groups, pathways from the both the chiral pool and achiral starting materials have been developed, yet remain inefficient for on-demand, affordable, rare monosaccharides. Landmark linear and divergent carbohydrate syntheses have been developed since Fischer's synthesis of glucose such as Masamune's synthesis of hexoses, Brown's syntheses of 2,6-dieoxyhexoses, and McMillan's divergent two-step syntheses. However, these pathways often remain less efficient than hydrolysis of monosaccharides from their most accessible glycosylated natural products. Recent examples have improved past routes, yet often remain relatively long and customized for each monosaccharide – a barrier to easily accessible monosaccharides on the industrial scale.

Figure 1. MacMillan's two-step carbohydrate synthesis.[3]



Chemoenzymatic Approaches

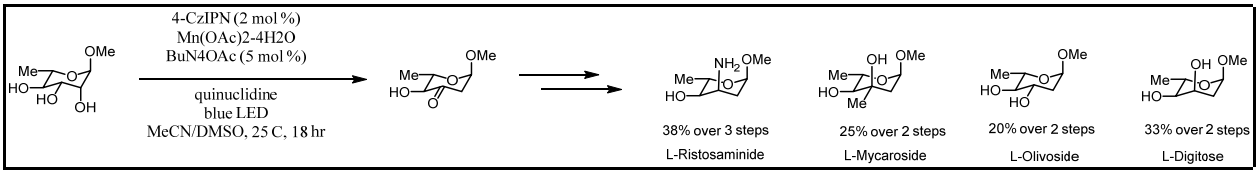
Enzymatic tools are used for D-fructose and D-ribose's respective one-step industrial processing from D-glucose. Leveraging multi-step enzymatic sequences has been implemented in the chemoenzymatic syntheses of various rare monosaccharide. However, these multistep

sequences are relatively low-yielding and often require customized enzymes for each target. D-allose had been made across three enzymatic steps in 2.5% yield.[4] More robust examples include the 20% yield, one-step, chemoenzymatic synthesis of D-psicose from D-fructose and the 20% yield, one-step synthesis of L-tagatose from L-sorbose.[4]

Site-Selective Radical Functionalization

Older methods of rare monosaccharides from biomass materials were limited due to a lack of site-selective methods. Hence, long sequences of protecting group manipulations were required. Development of a method capable of site-selective deoxygenation and oxidation of unprotected monosaccharides was identified as being highly strategic. This tandem isomerization generates a point of deoxygenation and creates a ketone moiety ready for further functionalization such as reduction to an alcohol, reductive amination, or *C*-alkylation with a carbon nucleophile. Biomimetic methods have been developed using photoredox-HAT methodology to site selectively form carbon-centered radicals at the C3 position. Lewis-acids, intramolecular acyl groups, redox-active metals, and HAT donors have been utilized for differentially functionalizing the generated radical.[5-8] However, improved methods to access variability in site-selectivity and expansion of the scope of deoxygenation sites needs to be completed for radical functionalizations to become commonplace in industry.

Figure 3. Photoredox-HAT/manganese catalyzed C2-3 redox isomerization and derivatization.[7]



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