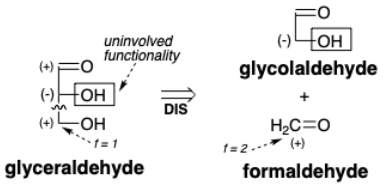
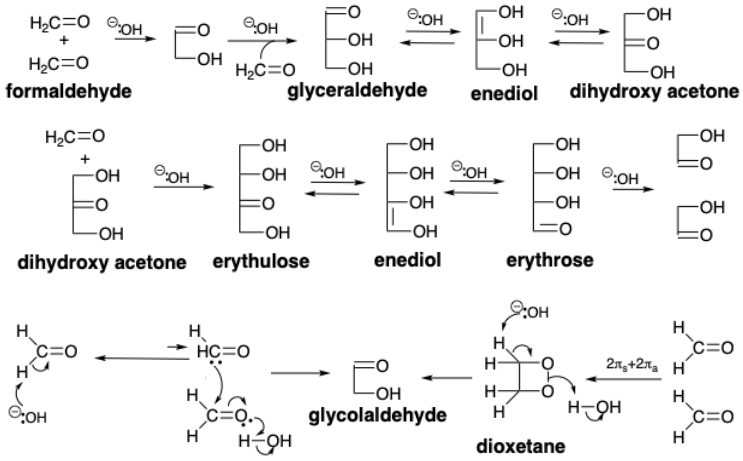
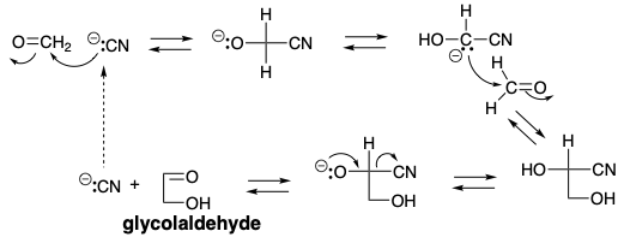
2.2: Synthesis of Sugars



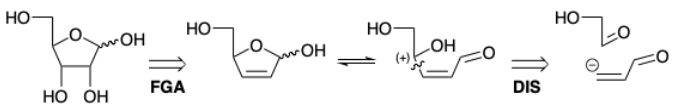
Retrosynthetic analysis reveals that a polar synthesis of glyceraldehyde can be achieved by condensation of a nucleophilic glycolaldehyde synthon with formaldehyde, a one-carbon electrophile of with f = 2. In fact, base-catalyzed aldol condensation of glycolaldehyde with formaldehyde not only generates glyceraldehyde but also dihydroxyacetone through tautomerization to an endiol and erythulose through aldol condensation with a second equivalent of formaldehyde.[1] These reactions are believed to be involved in the base-catalyzed oligomerization of formaldehyde that generates the same products. A tiny amount of glycolaldehyde is sufficient to accelerate the oligomerization that otherwise has a long induction period, but eventually proceeds with the same kinetics as the glycolaldehyde-promoted process. Under certain conditions, as much as 50% of the formaldehyde is converted to glycolaldehyde, apparently through tautomerization of erythrulose to erythrose that then undergoes retro aldol cleavage to two molecules of glycolaldehyde. Thus, the induction period in the ologomerization of formaldehyde presumably corresponds to a slow process that generates the first traces of glycolaldehyde that then catalyzes further ologomerization. One hypothesis is that the formation of glycolaldehyde from two molecules of formaldehyde involves proton abstraction to generate a tiny concentration of acylcarbanion that condenses with a second molecule of formaldehyde.[1] An alternative possibility is that a thermally allowed 2πs+2πa cycloaddition (see chapter 3, page 67) delivers a dioxetane intermediate that undergoes base catalyzed disproportionation to the hydroxyaldehyde.



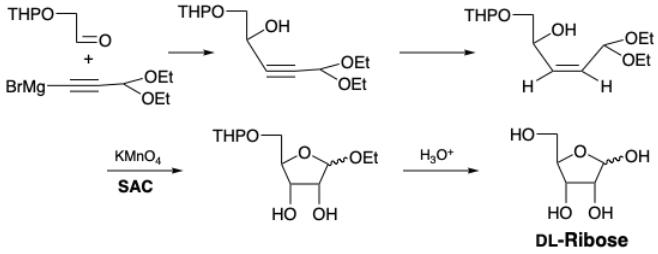
The oligomerization of formaldehyde to provide a variety of sugars is a likely (pre)biosynthetic route for the generation of these molecules in a prebiotic world. In the prebiotic world, it is likely that the formation of glycolaldehyde occurred mainly through a cyanide catalyzed condensation that involves a cyanohydrin carbanion intermediate.



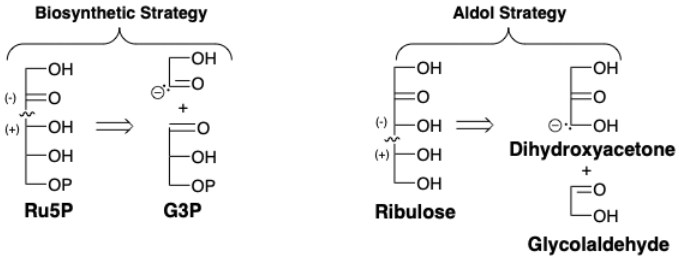
The major molecular complexity of sugars inheres in their abundance of functionality and stereochemistry. One strategy for the total synthesis of ribose exploits the prospect of stereospecific cis hydroxylation to introduce two hydroxyl groups with the requisite stereocontrol. Ribose exists predominantly in a cyclic hemiacetal form. The relatively rigid 5-membered ring can be expected to favor the appropriate stereocontrol. Disconnection of a cis alkene precursor at the carbinol carbon suggests the addition of a vinyl carbanion with glycolaldehyde.



Two refinements are required to implement this strategy. The glycolaldehyde hydroxyl must be masked to prevent protonation of the carbanion and one aldehyde group must be masked as an acetal. Rather than a vinyl carbanion, an acetylide was chosen as the nucleophile with the prospect of stereospecific cis partial hydrogenation of a disubstituted alkyne as a route to the requisite cis alkene.[2]



In the biosynthetic route to ketoses such as Ru5P from G3P, thiamine pyrophosphate serves as catalyst to provide an equivalent of a glycolaldehyde with inverted polar reactivity of the carbonyl group. An aldol condensation strategy for the C-C connective synthesis of ribulose is suggested by the latent nucleophilicity of the α-carbon enabled by the carbonyl group of dihydroxyacetone to react with a glycolaldehyde electrophile.



The biosyntesis of sugars generates single enantiomers owing to the asymmetry of the enzymes that catalyze their formation. The sugars generated by the hydroxide-catalyzed oligomerization of formaldehyde are a mixture of stereoisomers that are all racemic. However, asymmetric catalysis can be achieved in aldol C-C connective syntheses using chiral nonracemic (S)-proline as catalyst to promote the aldol condensation of dihydroxyacetone acetonide wih the benzyl ether of glyceraldehyde.[3]