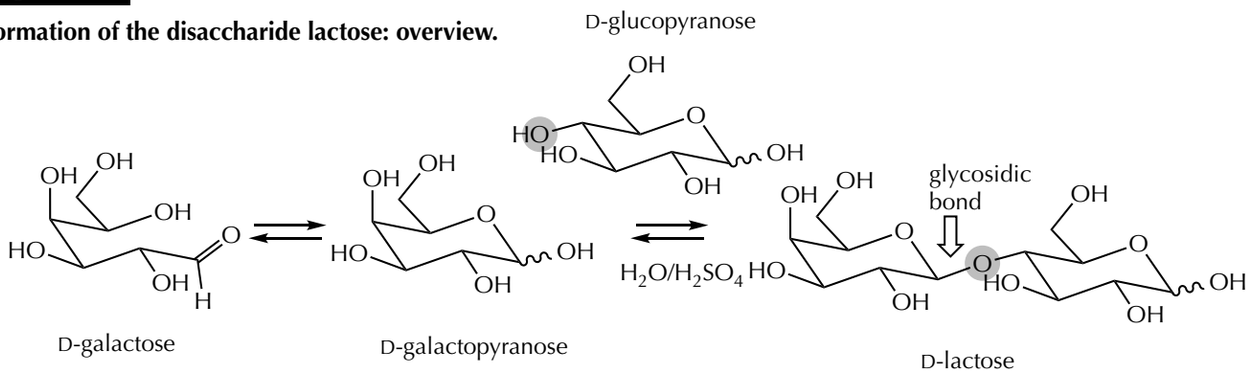
Figure 1644

Formation of the disaccharide lactose: overview.



You should naturally wonder about the selectivity in the reaction shown in Figure 1644. The hydroxyl at carbon-4 of the glucopyranose is not the only nucleophile present, both of the monosaccharides have hemiacetal electrophiles, and the new glycosidic bond could be formed with either the α- and β-stereochemistry. Simply mixing these two monosaccharides together with some catalytic acid would create a complex mixture of products.

The selectivity for building this disaccharide would have to come from one of two places. Using laboratory chemical methods, every functional group that might interfere with the desired bond formation would need to be protected. Then the desired reaction would be carried out, followed by the deprotection and restoration of the original functional groups (Figure 1645).

Three goals need to be achieved: (1) the carbon-**4** hydroxyl group from glucose is the only one available to act as a nucleophile, (2) the anomeric site from the galactose is the only one available to act as an electrophile, and (3) the reaction results in the new glycosidic bond with the β-stereochemistry. You are not expected to be able to create the strategies to achieve these goals, but you should be able to follow the logic of the strategy. All of the reactions are familiar.

(1) The carbon-4 hydroxyl group from glucose is the only one available to act as a nucleophile: The double ketal derivative of glucose shown in Figure 1638 left the carbon-3 hydroxyl open, but that does not help. The other information on that figure can be used. First, forming the acetal at the anomeric center allows for the formation of the 6-membered ring acetal with the hydroxyl groups on carbons 4 and 6. The hydroxyl groups at carbons 2 and 3 can be protected at their benzyl ethers. Removing the acetal from carbons 4 and 6 leaves the primary alcohol at carbon-6, which can be selectively acylated, leaving only the hydroxyl group at carbon-4 open.

(2) The anomeric site from the galactose is the only one available to act as an electrophile: The strategy for galactose is comparable and takes fewer steps. If all of the hydroxyl groups in galactose are transformed into benzyl ethers, the acetal group that forms at carbon-1 can be hydrolyzed back to the hemiacetal without removing any of the ethers. This leaves the anomeric position available for reaction.

(3) The reaction results in the new glycosidic bond with the β-stereochemistry: The direct S_N1 reaction of the protected glucose derivative, with its free carbon-3 hydroxyl group, with the protected galactose derivative will give a mixture of α- and β-glycosidic bonds, likely favoring the β-stereochemistry thanks to the anomeric effect. High selectivity in substitution reactions comes from S_N2 reactions, not S_N1 reactions. If the galactose derivative is treated with HCl, the anomeric effect is predicted to strongly favor the axial α-stereochemistry in that S_N1 reaction product, which sets up the anomeric center for being able to undergo an S_N2 reaction resulting in the β-stereochemistry as the outcome.