Synthesis of Carbasugar Derivatives as Potential Inhibitors of Glycogen Phosphorylase

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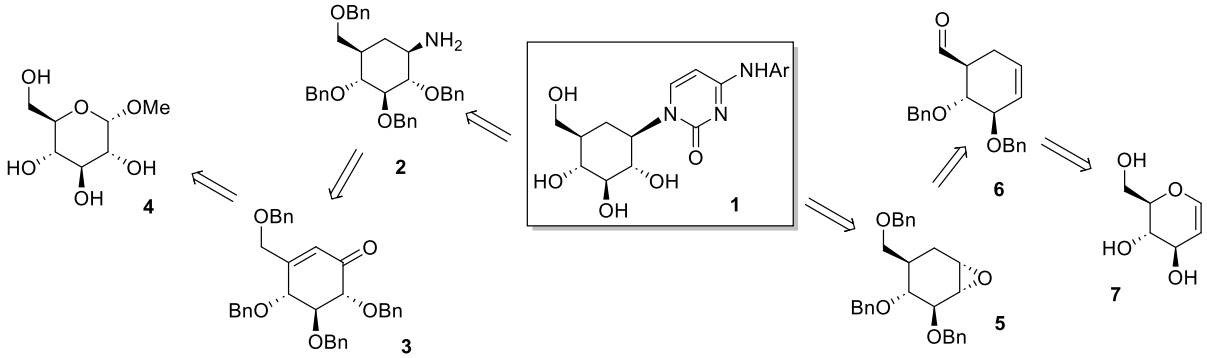
Glycogen phosphorylase (GP) is a key regulatory enzyme involved in maintaining glucose homeostasis by catalyzing the breakdown of stored glycogen in the body. Inhibition of GP presents a promising therapeutic strategy for the treatment of type II diabetes mellitus, as well as other pathological conditions, including cancer. In our laboratory, several N^4-aryl-N^1-(β-D-glucopyranosyl)cytidines, potent nM inhibitors of GP have been synthesized and studied in recent years.[1] The primary objective of the current study is to synthesize 5a-carbasugar analogs (**1, Scheme**) of the above strong inhibitors, that target specifically the enzyme's catalytic center, with desirable pharmacokinetic profiles, including smooth transport across the cell membrane, that would enhance inhibitory potency *in vivo.*

Initially, 1-*O*-methoxy-glucose (**4**) served as the starting material, which after a series of transformations and a Swern-Horner-Wadsworth-Emmons reaction,[2] in the key step, led to **2**. The carbocyclic compound **3** was subsequently converted stereoselectively into amine **2**, through multiple steps, and was then coupled with uracil to yield, after a final three-step sequence, the desired inhibitors **1**. To enhance the synthetic process, we also explored an alternative route that involves fewer steps and a simplified intermediate handling. The process begins with D-glucal (**7**) and features a Claisen reaction,[3] as the pivotal step, converting the sugar into carbocyclic compound **6**. Later epoxidation to **5** followed by subsequent substitution with uracil is under study, in order to produce the same inhibitors in fewer steps and enhanced yields.



Scheme: The two retrosynthetic routes for the synthesis of carbocyclic GP inhibitors (**1**).

References

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