Challenge 4: Designing a biosynthetic pathway to a non-natural nucleoside

Background: My research group studies using synthetic nucleotides in a variety of synthetic biology applications. These nucleotides are not found in nature, and as such no natural pathway exists to biosynthesize them. Given how humans are clever creatures, maybe we can design biosynthetic pathways to access these building blocks.

Goal: In this open ended problem, your goal is to use a retro-biosynthetic tool to design a biosynthetic pathway that could be used to access a pair of non-natural nucleotide (i.e., no natural pathway exists). You can pick one sugar (either ribose or deoxy ribose) with one of the 6 nucleobases shown as your target. Since these building blocks are unnatural, it is very likely your pathway will have gaps that will require enzyme evolution, enzyme discovery, or enzyme design to bridge. Alternatively, you might find that we can access some of these biosynthetic building blocks if we feed our organisms other small, synthetic molecules. For all enzymes, provide a source (enzyme accession) that can be looked up. For all substrates, provide a possible vendor + catalogue number. Include all cofactors.

Starting materials you can use: Ribose, deoxy ribose, and any other molecule. The nucleobases themselves (P, Z, S) cannot be used as possible reagents in your design (i.e., they need to be made through enzymatic synthesis in one of your steps).

Approach: Use RetroBioCat or other retrobiosynthesis tools available on github or other sources. All programs are fair game. Solution is open ended, just provide a brief justification for your design choices. Explain any gaps in the biosynthesis that might need to be bridged, and include a possible enzyme candidate + strategy that can be used for bridging that gap. Synthetic chemicals **<u>are</u>** allowed to be used as reagents and might be necessary to access some of the nucleobases below.

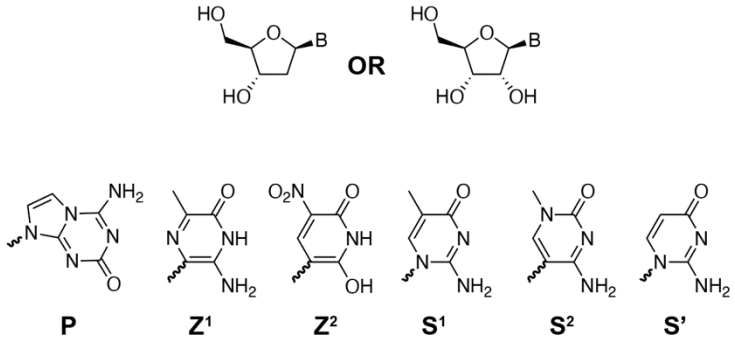

Figure: (Top) Nucleosides are a sugar (ribose or deoxyribose) attached to a base (B). Options of possible bases are shown in the bottom.