Abstract

As they make up DNA and RNA, nucleosides are considered the key to life. Synthetic nucleosides also constitute many drugs that treat viral infections and cancer. As a result, more efficient methods to access these crucial molecules would have implications that extend beyond a synthetic chemist's benchtop and into medicinal chemistry and medical research. One of the most challenging steps in the synthesis of nucleosides is the glycosylation step between the acceptor heterocycle (nucleobase) and the saccharide-based donor. Often to obtain satisfactory yield of this step with good regio- and stereochemical control the extensive use of protecting groups must be employed to squelch reactivity at unwanted reactive groups. Consequently, this process of protection–glycosylation–deprotection is laborious, inefficient, and often requires the use of toxic reagents. It would be, therefore, highly welcomed if new methodology to effect this glycosylation step was designed that reduces or removes the need to use protecting groups, but would still provide nucleosides in good yield, regio- and stereoselectively. Herein, this thesis presents my efforts into achieving this end. By employing modified Mitsunobu conditions, I determined that it is possible to directly glycosylate a nucleobase with D-ribose to afford stereoselectively β-ribopyranosyl nucleosides in the complete absence of protecting groups. By then employing a 5-*O*-monoprotected ribosyl unit, I could use a two-step one-pot process to provide the more medicinally and physiologically relevant β-ribofuranosyl nucleosides, but with some shortcomings to be discussed. In our second study, I improved the reaction conditions and elucidated a plausible mechanism that proceeds through an *in situ*-formed α-1,2-anhydrosugar (termed "anhydrose") that is then opened nucleophilically by the nucleobase stereoselectively at gram scale. This key anhydrose intermediate is stable indefinitely *in situ* and can be formed using other *C*5-modified ribosyl monomers as well. It can also be opened by other non-nucleobase-based substrates still perfectly stereoselectively for the β-anomer. We demonstrate that this anhydrose is a powerful electrophilic intermediate that can glycosylate a wide range of nucleobases and other nucleophiles to provide a host of β-ribosyl glycosides. This research provides the foundation for a new stereoselective reaction for medicinal chemists to add to their toolbox of reactions to aid in the design of novel drugs and therapeutics.