Advancements in the Synthesis of 2′ and 4′ Modified Nucleoside Analogues

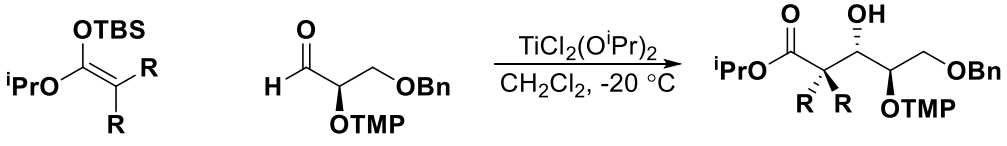
Reported by Wesley Wang October 13, 2020

Introduction

There are more than thirty nucleoside based small molecules on the market today.[1] Nucleoside based small molecules are used in various treatments such as chemotherapeutics, liver diseases, antivirals, and fungal infections. There are three main components of a nucleoside: the sugar backbone, the glycosidic bond, and the nucleobase[1]. Nucleoside analogs are potent small molecule drugs because they can insert themselves into the DNA of cancer cells and viruses and disrupt their functionality.[2] While many modifications of nucleosides have been performed, specific modification to the 2′ and 4′ sites of a nucleoside are lacking. Recent advances in the *de novo* synthesis of such nucleosides demonstrate a promising future for the field of nucleoside synthesis.

Synthesis of 2′ Modified Nucleosides

A longstanding challenge in the synthesis of 2′ modified nucleosides included differentiating between the 2′-and the 3′- and 5′-hydroxy group. In 2014, the Macmillan group sought to devise a *de novo* synthesis of the sugar backbone, which involved preinstalled groups in the starting material, followed by a Mukaiyama aldol reaction to provide enantioenriched sugar backbones (**Scheme 1**).[3] This allowed for the quick and straightforward synthesis of a large variety of different sugar backbones, with yields ranging 62-89% and excellent enantiomeric ratios. Macmillan′s synthesis marked the first example of a generalized, stereoselective synthesis of 2′ modified nucleosides.



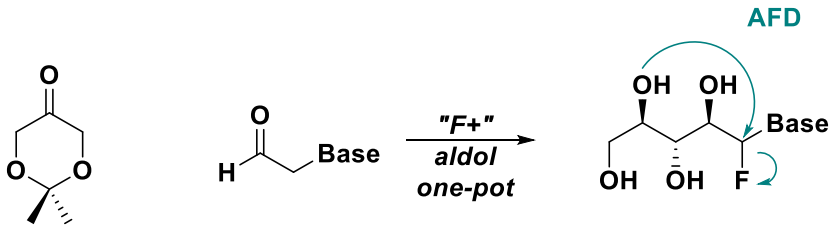
Scheme 1. Mukaiyama aldol reaction involving starting material with preinstalled R groups and enantioenriched OTMP group

Synthesis of 4′ Modified Nucleosides

Like 2′ modified nucleosides, 4′ modified nucleosides suffered from similar challenges, such as selective protection of alcohols. In 2019, scientists at Merck developed the synthesis of Islatravir via a biocatalytic cascade. With the aid of five evolved enzymes and four auxiliary enzymes, Islatravir could be synthesized in three steps with a 51% overall yield using achiral building blocks and without the use of protecting groups.[4] Even more remarkably, by utilizing solid-state support enzymes, purification became practical.

A Short *de Novo* Synthesis of Nucleoside Analogs

In 2020, Meanwell and coworkers truly streamlined the process of synthesizing nucleoside analogs. By doing a one-pot α-fluorination and aldol reaction (**Scheme 2**),[5] followed by annulative fluoride displacement, a variety of nucleoside analogs could be synthesized in 2-3 steps ranging from 47-94% yields. Because the base is preinstalled, the late-stage installation of the nucleobase, which usually leads to a mixture of anomers, and thus, a huge decrease in yield, was no longer necessary. Simple modifications (such as removing the acid workup step or adding a Grignard reagent instead of reduction) allowed for access to a variety of 2′ and 4′ modified nucleosides.



Scheme 2. One pot alpha fluorination and aldol reaction followed by annulative fluoride displacement

Conclusion and Outlook

In the past 10 years, there′s been a tremendous improvement in the synthesis of 2′ and 4′ nucleoside analogs. Nevertheless, general methods for synthesizing such moieties are still few and far between. With the introduction of the short de novo synthesis to make nucleoside analogs, new nucleoside based small molecules may emerge within the next couple of years.

References

1. K. L. Seley-Radtke *et al. Antivir. Res.* **2019**, *162*, 5-21.
2. L. P. Jordheim *et al. Nature Rev.* **2013**, *12*, 447-464.
3. M. Peifer *et al. J. Am. Chem. Soc.*., **2014**, *136*, 5900-5903.
4. M. A. Huffman *et al. Science* **2019**, *366*, 1255-1259.
5. M. Meanwell *et al. Science* **2020**, *369*, 725-730.