DRUG DEVELOPMENT

Unifying the synthesis of nucleoside analogs

A short, versatile synthetic pathway transforms achiral reactants into nucleoside analogs

By **Gavin J. Miller**

Nucleosides, the building blocks of DNA and RNA, typically contain a ribose sugar attached to a nucleobase. Structurally modified nucleoside analogs can disrupt the biological processes that mediate nucleoside assembly into DNA and RNA. Nucleoside analogs that target viral and cell replication have delivered generations of drugs combatting cancer, herpes simplex virus, human immunodeficiency virus, and hepatitis C virus (*1*–*4*). Despite these successes, considerable challenges remain in chemically synthesizing nucleoside analogs, especially the development of short and general synthetic routes. On page 725 of this issue, Meanwell *et al.* (*5*) report a rapid and scalable de novo synthesis of a diverse range of nucleoside analogs from simple achiral starting materials. Their approach builds on previous work by Peifer *et al.* (*6*), who introduced a facile and enantioselective synthetic approach to pentose sugars.

The molecular assembly of nucleosides requires consideration of the complex stereochemical environment within the sugar ring and must also enable any modification from the native metabolite to be included in the final analog structure. In many cases, a "chiral pool" of available carbohydrate starting materials has been used effectively, because the majority of the stereochemical information required is already in place. However, this strategy often requires lengthy and costly synthetic processes and is not usually amenable to rapid diversification, that is, accessing many different structures within one synthetic pathway. Asserting control of stereochemistry at the position where the nucleobase (or an unnatural variant thereof) is incorporated is crucial to avoid difficult and inefficient separation of diastereomeric mixtures. Finally, stereochemically defined modifications must be installed at key positions around the sugar ring. For example, the antiviral drug sofosbuvir has modifications at the 2′-position carbon atom of the ribose ring where the native hydrogen and hydroxyl groups are replaced with methyl and fluoride, respectively.

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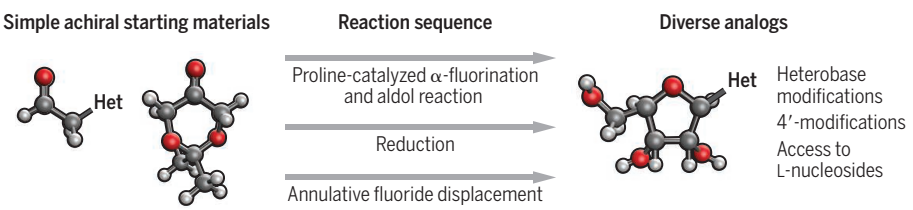
Starting from a simple ketone and heteroaryl aldehyde, Meanwell *et al.* used a proline-mediated organocatalytic α-fluorination, followed by an aldol reaction, to furnish a fluorohydrin intermediate. This material was converted through to the nucleoside analog scaffold by using an annulative fluoride displacement strategy that enabled formation of the sugar ring product (see the figure). The process used simple, commercially available chemicals, and the reaction sequence installed the correct spatial orientation of atoms at all ring positions in high yield and with excellent stereochemical purity.

Versatile nucleoside synthesis

Nucleosides are often synthesized by modifying natural chiral compounds. Meanwell *et al.* present a scalable three-step synthesis from simple achiral molecules. Het, heteroaromatic group.



Having established this method to access the nucleoside core structure, the utility of this short synthetic approach was explored and shown to be amenable in accessing an exciting range of derivatives, including nucleosides containing different nucleobases (endogenous and exogenous), partially protected species, enantiomeric L-nucleosides, locked nucleosides, and iminonucleosides. The protocol also enabled products from these reactions to undergo further functionalization—for example, to 2′-modified analogs—drastically improving their ease of synthetic access. The pivotal annulative fluoride displacement method was also adapted to enable direct access to 4′-position–modified derivatives of α-linked D- and L-nucleosides, providing a contemporary structural motif for future exploration in nucleoside-analog medicinal chemistry. Finally, in an examination of scalability, the α-fluorination-aldol reaction was completed on a 380-g scale with a 72% yield and afforded a rapid, two-step entry to a precursor of MK-3682 (uprifosbuvir), a hepatitis C RNA polymerase inhibitor developed by Merck (*7*).

Nucleoside analogs are a historically accomplished class of drug with highly diversified scaffolds and proven potential to treat a wide range of diseases (*1*–*4*). Their complexity requires that efficient and adaptable synthetic methodologies are developed to enable entry to new classes of analogs and to support current requirements to produce quantities that can satisfy pharmaceutical demand. In this context, the de novo synthetic approach developed by Meanwell *et al.* has unified access to a wide range of nucleosides and will serve as a blueprint for future developments, such as rapidly accessing 4′-modified–β-D-linked analogs.

Alongside this new synthetic methodology, examples describing the enzymatic synthesis of nucleoside derivatives are increasing (*8*). Combining these two powerful synthetic approaches is an exciting prospect for the field, yet challenges lie ahead. For example, allied to these achievements is the requirement for phosphorylated forms of nucleosides (*9*) and broadening scaffold access to include sugar-heterocycle substitution (*10*). Finally, the repurposing of the nucleoside analog remdesivir to target the viral replication machinery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*11*) further highlights the critical need for nucleoside-analog therapeutic development and the underpinning importance of synthetic organic chemistry. ■

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