Expedient Approaches to Bicyclic Nucleosides:
Precursors to nucleic acid modifications for antisense-based therapeutics

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The human race is afflicted by countless diseases, many of which have genetic origins. Small molecule therapeutics, the traditional mode of treatment for genetic diseases, has focused on targeting the pathogenic protein when it may be more effective to target the messenger RNA (mRNA) strand that codes for the protein. This can be accomplished using a complementary DNA-based sequence known as an antisense strand, which binds to the mRNA before it is translated into a protein. This binding event prevents the mRNA from undergoing translation, thus inhibiting protein synthesis.

Incorporating chemically modified nucleosides in antisense strands has been shown to result in a stronger binding interaction between the antisense strand and the mRNA, which translates to a more effective drug. The modifications we are interested in are tricyclic nucleic acids (TriNAs), so named because the modified ribose sugar contains three rings. Antisense strands that contain TriNAs show a higher thermal stability when bound to mRNA compared to antisense strands containing other reported modifications. However, a major drawback to the use of TriNAs as potential drug candidates is the length of the synthesis used for their preparation.

The first and only reported synthesis involves 29 synthetic steps,[1] which is uneconomical in terms of both time and money. In order to solve this problem, our research is focused on the development of short, streamlined synthetic approaches to TriNAs.

The inexpensive ($0.40/gram) and commercially available nucleoside 5-methyluridine **(1)** was selected as the starting material for our synthesis (**Figure 1**). Following protection with cyclohexanone dimethyl ketal to obtain the protected cyclohexylidene acetal **(2)** and oxidation with Dess-Martin

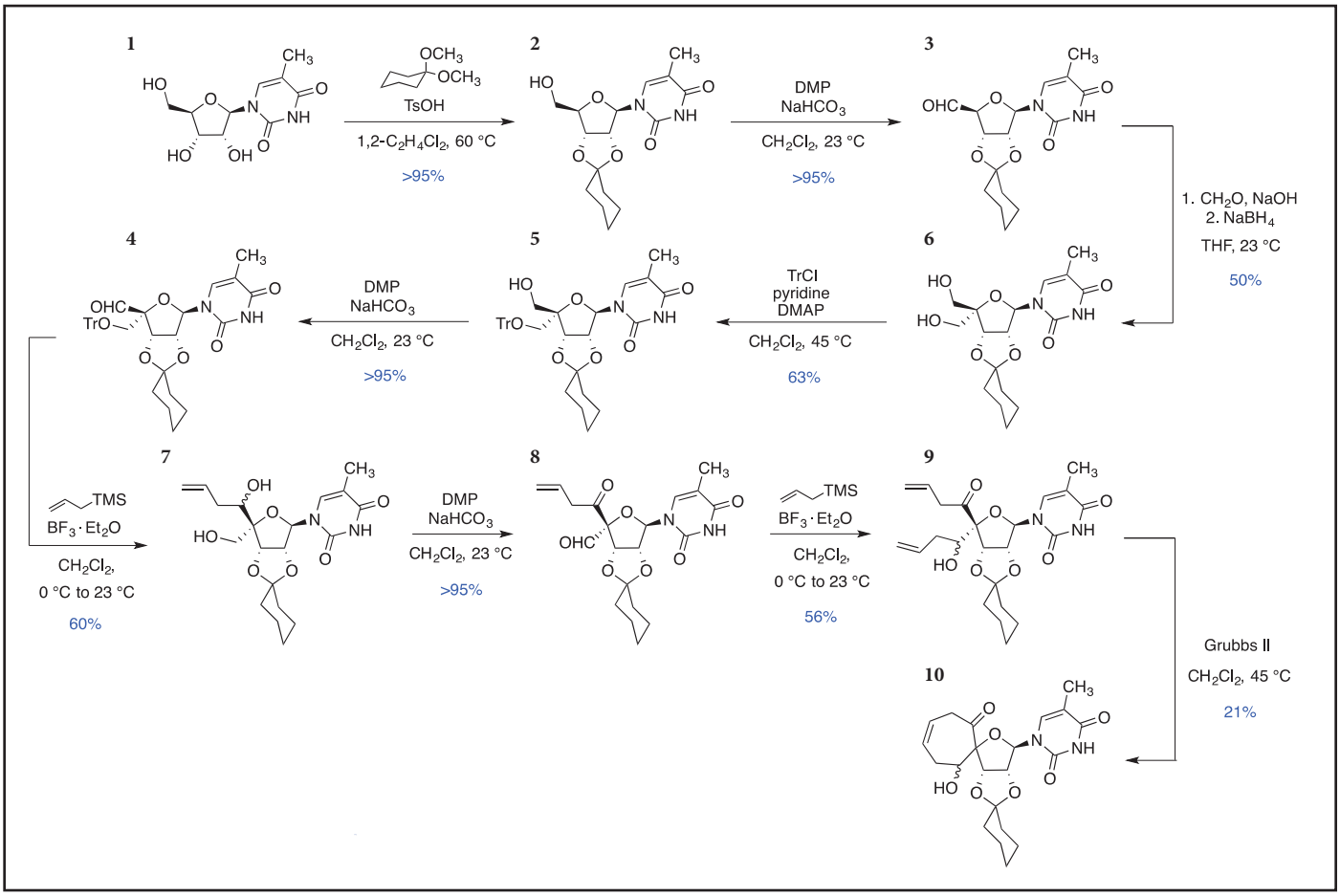

Figure 1, *Narayanan*. Synthesis of bicyclic nucleoside precursor.

periodinane, the resulting aldehyde **(3)** was subjected to aldol reaction conditions to afford diol **(4)**. A protection reaction using trityl chloride yielded a mixture of separable diastereomers, and the trityl-protected compound **(5)** was subjected to Dess-Martin oxidation conditions to furnish aldehyde **(6)**. Upon treatment with allyltrimethylsilane and boron trifluoride diethyl etherate (conditions that cleave the trityl protecting group) in a Hosomi-Sakurai allylation, compound **(7)** was obtained and oxidized to afford aldehyde **(8)**. Following a second Hosomi-Sakurai allylation, diene **(9)** was treated with Grubbs second generation catalyst in a ring-closing metathesis reaction to furnish bicyclic nucleoside **(10)**, which contains all of the carbon atoms and two of the three rings present in the TriNA targets. All reactions were monitored by thin layer chromatography, and synthesized compounds were purified by flash chromatography and analyzed using NMR spectroscopy and mass spectrometry. This project has yielded a nine-step synthesis to a key bicyclic nucleoside intermediate that can be used as a precursor in the synthesis of TriNA analogues. Several different synthetic approaches to other bicyclic nucleosides are currently being investigated.

The development of a more efficient synthesis of TriNAs will save time and money, reduce chemical waste, and ideally improve the overall yield of the desired compounds. Ultimately, we hope to use our optimized synthesis to build up large quantities of TriNA analogues to be tested as potential drug candidates in antisense strands.

Statement of Research Advisor:

Natasha has developed a short, efficient synthesis of a bicyclic nucleoside intermediate that can serve as a precursor molecule to the tricyclic nucleoside modifications that we hope to synthesize in my lab. All of the compounds that Natasha has prepared are novel and have not been reported in the primary literature.
- *Bradley L. Merner, Department of Chemistry and Biochemistry*

References:

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