Synthesis of Ara-Neplanocin A Analogues at Sub-Ambient Temperatures Using Microwave Irradiation

Neplanocin A (NPA, **1**), a cyclopentenyl analog of adenosine, is a natural occurring antiviral agent and antibiotic which exhibits anti-tumor activity both *in vitro* and *in vivo*.[1] However, neplanocin A is toxic to healthy cells – a major drawback if it were to be used for medicinal reasons. Neplanocin A derivatives would be of great interest if they possessed the therapeutic properties without the cytotoxicity, but little research has been done on this group of analogs. Ara-neplanocin A (ara-NPA, **2**) was found to be less toxic while retaining antiviral activity and ara-neplanocin C (ara-NPC, **3**) has shown anti-tumor activity. Due to the potential of these analogs as useful anti-microbial drugs and in the treatment of cancers, Professor Chung Chu at the University of Georgia, College of Pharmacy developed a convergent synthetic strategy to obtain a host of base modified ara-neplanocins whose biological activities have yet to be explored.[2]

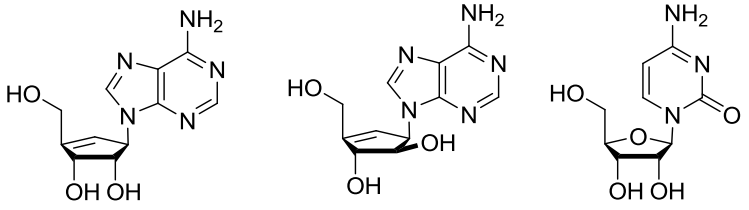

Figure 1. NPA and known analogs ara-NPA and ara-NPC

The key intermediate, **4**, was converted under Mitsunobu conditions (Scheme 1) to an array of ara-neplanocin analogues using the CEM Discover® microwave synthesizer with CoolMate® accessory, Figure 2. The CoolMate accessory allows for sub-ambient microwave assisted conditions which increase the reaction rate while minimizing by-product formation.[3] At room temperature without microwave irradiation the Mitsunobu reaction takes up to 16 hours with poor yields around 35 %. In the CoolMate the reaction time was only 5 min with yields ranging from 40 – 67 %. The last step, deprotection or amination, afforded the ara-neplanocin derivatives **5** – **8.**

Scheme 1. Subzero microwave assisted synthesis of ara-NPC analogues.

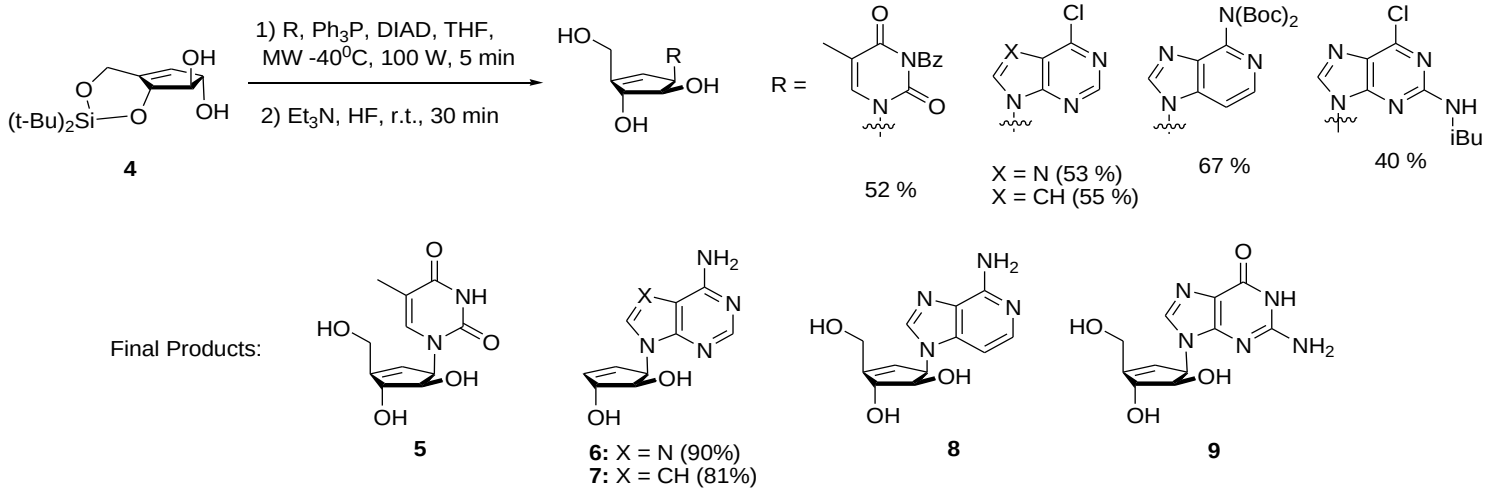

Figure 2. CEM Discover microwave unit with CoolMate accessory.

References

1) Hoshi, A.; Yoshida, M.; go, M.; Tokuzen, R.; Fukukawwa, K.; Ueda, T. *J. Pharmacobio-Dyn.* **1986**, 9, 202–206.
2) Radi, M.; Rao, J. R.; Jha, A. K.; Chu. C. K. *Nucleosides Nucleotides and Nucleic Acids* **2009**, *28*, 504 – 518. DOI: 10.1080/15257770903044143
3) http://www.cem.com/coolmate.html