

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 antimicrobial 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

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**.

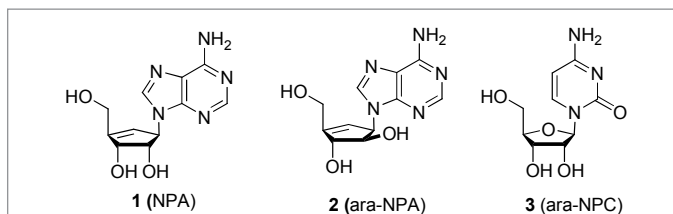
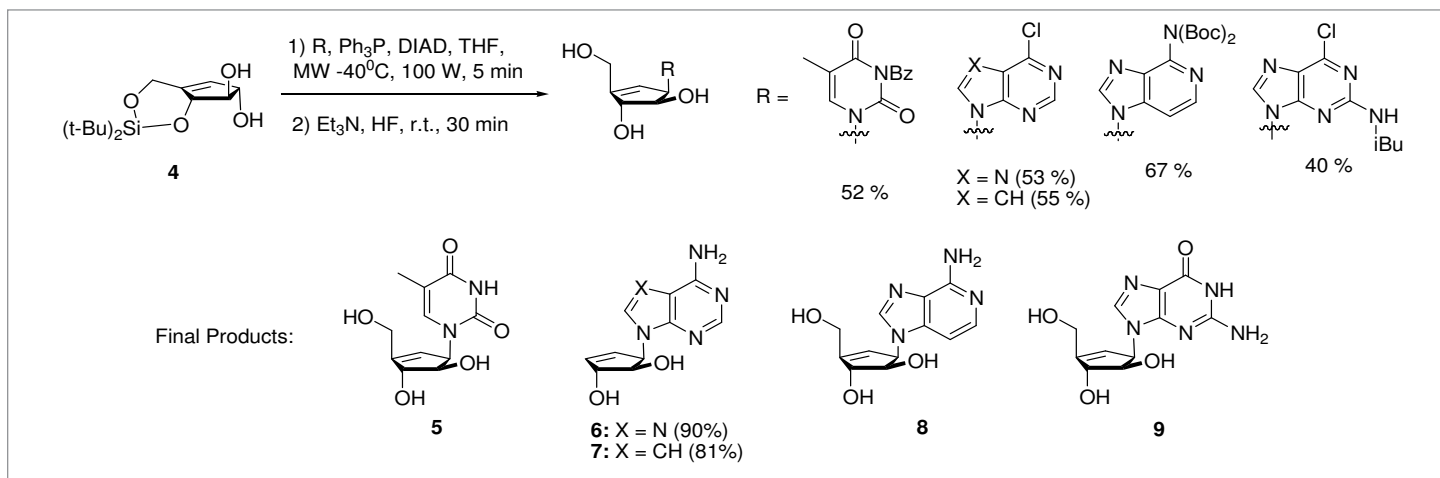


Figure 1. NPA and known analogs ara-NPA and ara-NPC



Scheme 1. Sub-ambient microwave assisted synthesis of ara-NPC analogues.



Figure 2. CEM CoolMate and Discover

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.

³ <http://www.cem.com/coolmate.html>

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