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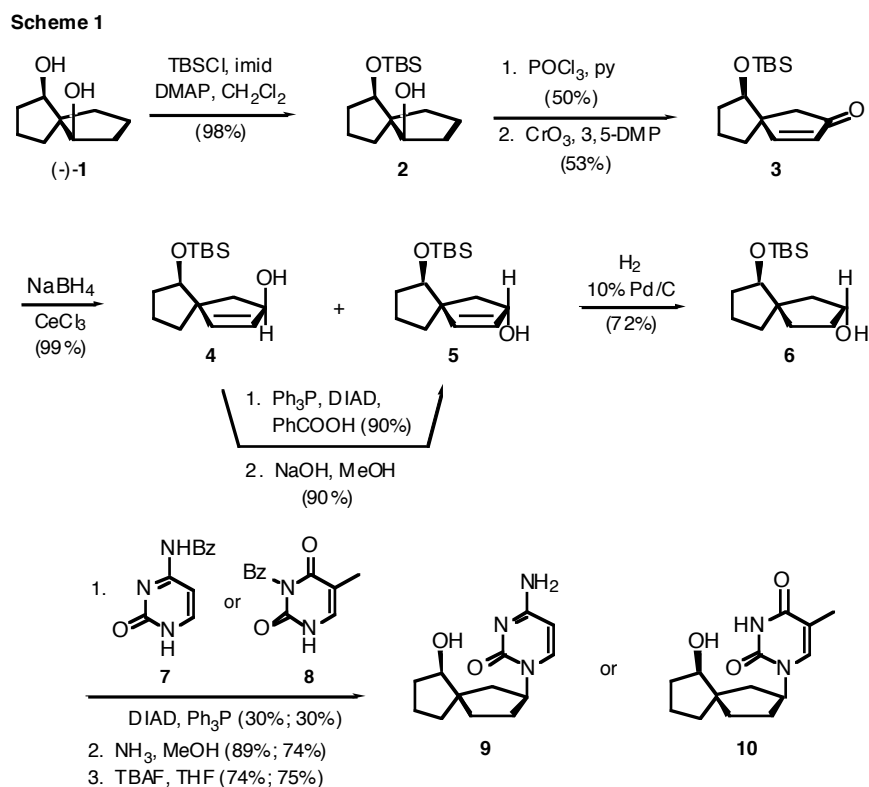
## DIRECT COMPARISON OF S<sub>N</sub>2 MESYLATE DISPLACEMENT *VERSUS* THE MITSUNOBU PROTOCOL FOR 2',3'-DIDEOXYSPIROCARBANUCLEOSIDE CONSTRUCTION<sup>‡</sup>

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**Abstract** – The two title reactions have been evaluated in order to maximize the efficiency with which pyrimidine and purine nucleobases can be introduced into 2',3'-dideoxyspirocarbanucleosides.

Recently, we described a synthesis of the structurally novel cytidine and thymidine carbanucleosides (**9**) and (**10**).<sup>2</sup> Among the issues that had to be addressed was that of incorporating the nucleobases with high stereoselectivity. Our approach began with the known levorotatory diol (**1**),<sup>3</sup> and took ultimate advantage

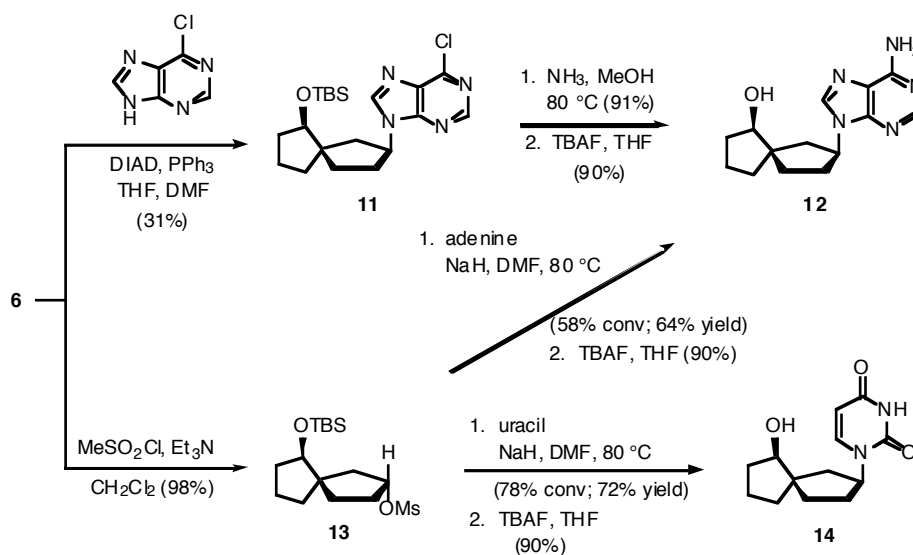


<sup>‡</sup>This paper is dedicated to Professor Barry Trost as we celebrate his 65<sup>th</sup> birthday and his many substantive contributions to the field of synthetic organic chemistry.

of the Mitsunobu reaction<sup>4</sup> for proper installation of each C-N bond (Scheme 1). Advance in this direction required penultimate debenzoylation with ammonia in methanol in advance of silyl deprotection.

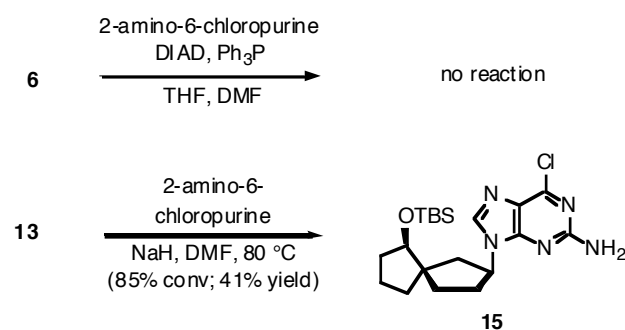
Although the general outline of Scheme 1 was successfully realized, only pyrimidine nucleoside analogs were prepared at that time. To evaluate the effectiveness with which purine bases would enter into reaction, the sequence of steps was repeated with 6-chloropurine (Scheme 2). The conversion to **11** proceeded in a parallel fashion and with comparable efficiency (31%). Disappointingly, no unconsumed

Scheme 2



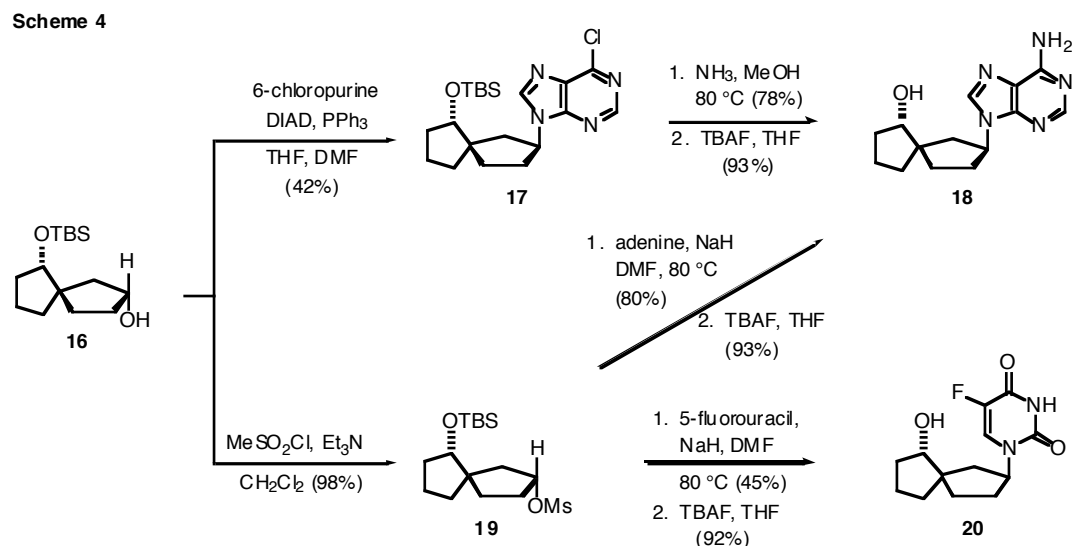
**6** could be recovered subsequent to workup. These factors prompted exploration of the S<sub>N</sub>2 displacement option that would capitalize on the ready availability of mesylate (**13**). In practice, the reactions leading from **13** to both **12** and **14** could be accomplished directly with the natural forms of adenine and uracil.<sup>5</sup> For the Mitsunobu process, the insolubility of these reagents in the reaction medium can be a complication.<sup>4b</sup> The backside attack on **13** is, in contrast, effected with sodium hydride in DMF at 80 °C where solubility is much less an issue. The direct recourse to free nucleoside bases skirts the need to prepare masked forms thereof and eliminates the accompaniment of a deprotection step.

Scheme 3

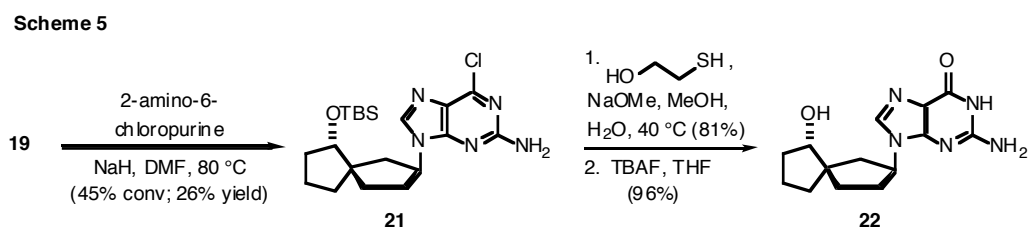


When **6** was found not to undergo coupling to 2-amino-6-chloropurine in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine, we proceeded to examine the  $S_N2$  displacement option involving (**13**) (Scheme 3). Under the prescribed conditions, this experiment gave **15** in 41% yield at 85% conversion. Thus, heterocyclic bases long known to enter only sluggishly into nucleoside production as in this instance, fare respectably when a mesylate is the co-reactant.

Comparably sharp improvements in yield have been noted when the OTBS substituent is projected  $\alpha$  as in **16** and **19** (Scheme 4). Under circumstances that closely paralleled the Mitsunobu conditions employed above, **17** was produced without the benefit of recovering unreacted **16**. Otherwise, the passage *via* mesylate (**19**) to both **18** and **20** underscores the benefits of facile purification and the possible recycling of unconsumed **19**. The series of steps depicted in Scheme 5 further accentuated the synthetic potential offered by this mesylate.



In summary, the unique chemical reactivity offered by **13** and **19** and their proclivity for high-fidelity inversion of configuration during C-N bond formation offer notably useful advantages for the preparation of a variety of 2',3'-dideoxyspirocarbanucleosides. These stereocontrolled bond heterolyses proceed as well under conditions which allow for recycling of unconsumed mesylate, thereby bypassing problems that often beset the Mitsunobu protocol.



## ACKNOWLEDGMENT

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## REFERENCES

1. Lubrizol Graduate Fellow, 2004-2005.
2. L. A. Paquette, R. E. Hartung, and D. J. France, *Org. Lett.*, 2003, **5**, 869.
3. (a) J. A. Nieman, B. A. Keay, M. Kubicki, D. Yang, A. Rauk, D. Tsankov, and H. Wieser, *J. Org. Chem.*, 1995, **60**, 1918. (b) J. A. Nieman and B. A. Keay, *Tetrahedron: Asymmetry*, 1993, **4**, 1973. (c) J. A. Nieman and B. A. Keay, *Synth. Commun.*, 1999, **29**, 3829.
4. (a) O. Mitsunobu, *Synthesis*, 1981, 1. (b) T. F. Jenny, N. Previsani, and S. A. Benner, *Tetrahedron Lett.*, 1991, **32**, 7029. (c) P. Wang, B. Gullen, M. G. Newton, Y.-C. Cheng, R. F. Schinazi, and C. K. Chu, *J. Med. Chem.*, 1999, **42**, 3390. (d) G. Wang, *Tetrahedron Lett.*, 2000, **41**, 7139. (e) M. Ono, K. Nishimura, H. Tsubouchi, Y. Nagaoka, and K. Tomioka, *J. Org. Chem.*, 2001, **66**, 8199.
5. (a) Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, *J. Am. Chem. Soc.*, 1984, **106**, 6379. (b) K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts, and P. Youds, *J. Chem. Soc., Chem. Commun.*, 1987, 1083. (c) Q. Chao and V. Nair, *Tetrahedron*, 1957, **53**, 1957. (d) X.-F. Zhu, F. Nydegger, and A. Gossauer, *Helv. Chim. Acta*, 2004, **87**, 2245.