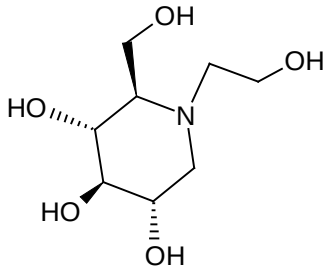
‘Design and Divergent Synthesis of Aza Nucleosides from a Chiral Imino Sugar’

Martinez-Monero, S.; Fernandez, S.; Sanghvi, Y.; Chattopadhyaya, J.; Ganesan, M.; Ramesh, N.; Gotor, V.; Ferrero, M. *J. Org. Chem* **77** (2012) 4671-4678

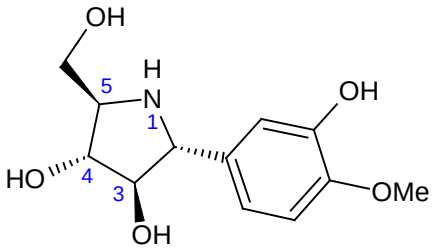
Selected items from the Chemical Literature

Reviewed by the Gaylord Chemical Literature Club

Azasugars as glycodase inhibitors



Miglitol



Radicamine A

- Glycodases are enzymes which catalyze the metabolic cleavage of glycosidic bonds
- Compounds capable of inhibiting these enzymes are good medicinal chemistry targets for the glycobiologic mitigation of cancer, diabetes, and viral infection.

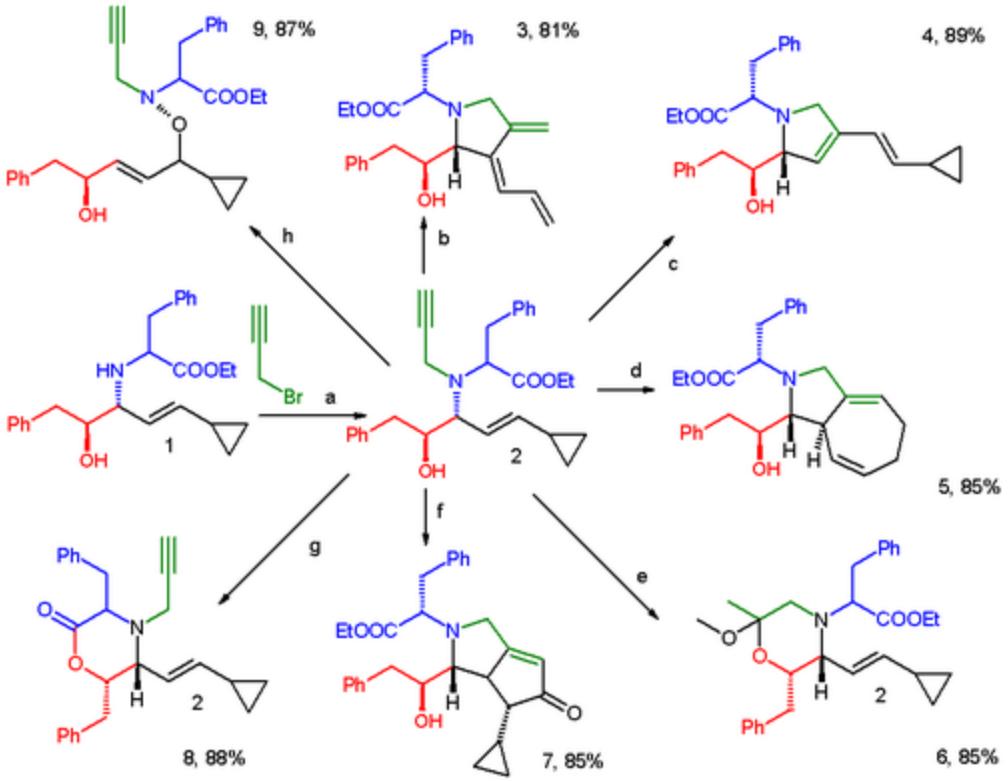
- Aza sugars (or imino sugars) are a promising class of glycosidase inhibitor
- They are 'carbohydrate mimics'

The Authors describe the synthesis of a versatile imino sugar precursor useful as a building block in the Diversity Oriented Synthesis (DOS) of many medicinally interesting target compounds.

What is Diversity Oriented Synthesis (DOS)?

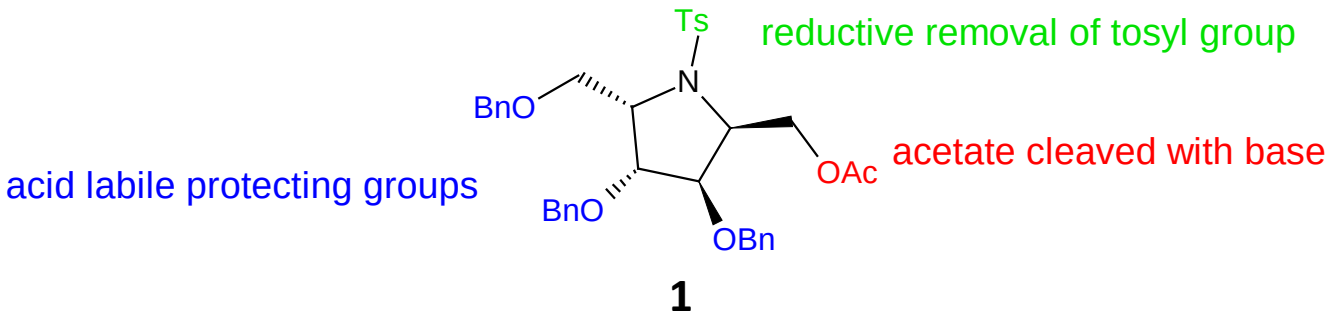
DOS is a strategy which employs a 'starting point' molecule which has a high degree of skeletal diversity.

A large library of target compounds can be made in one synthetic 'generation'.



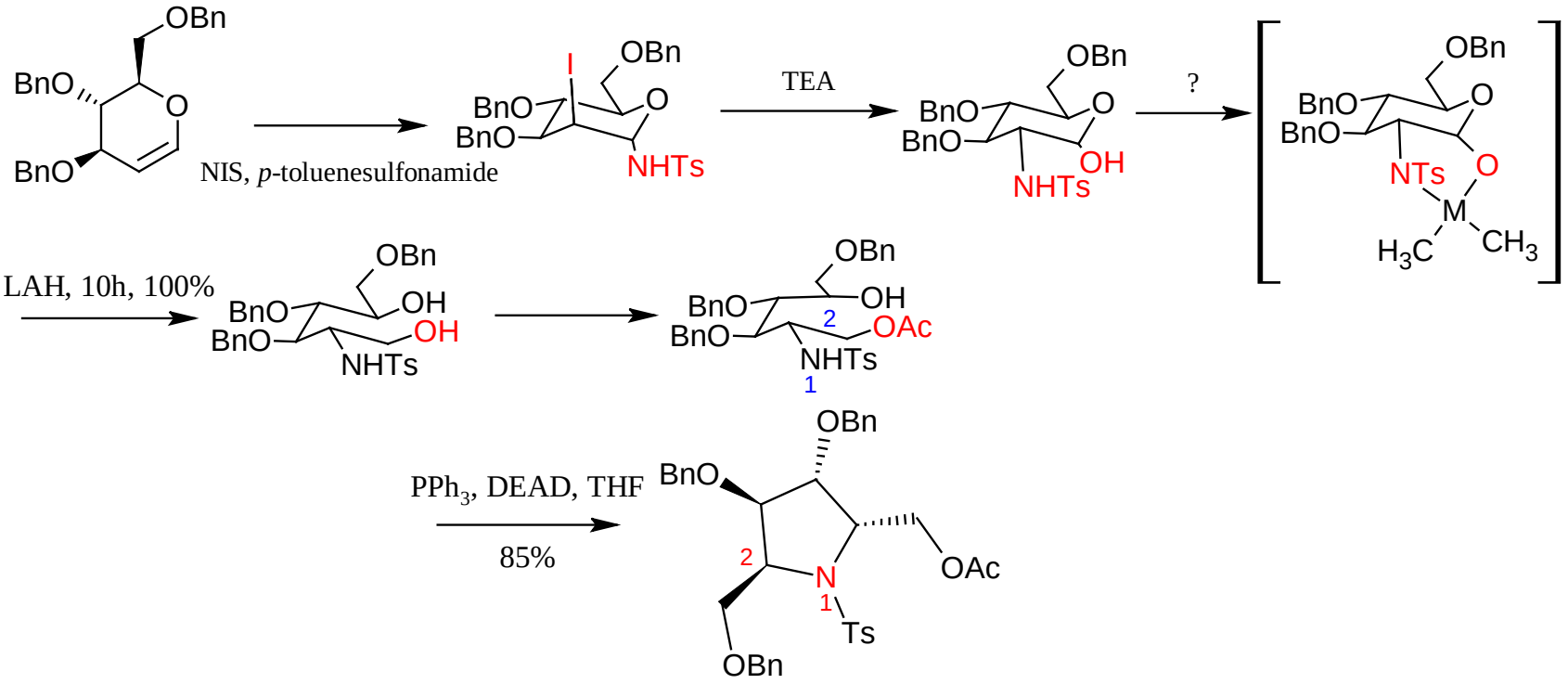
Wikipedia: Diversity-Oriented Synthesis

The starting point



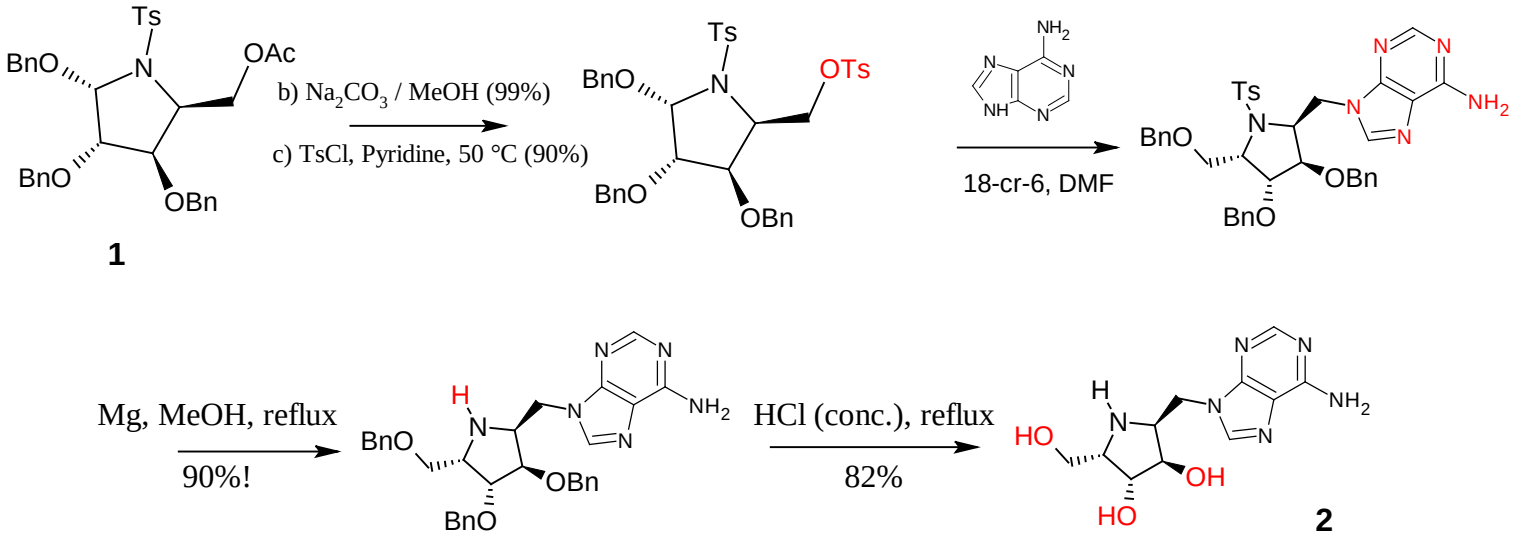
- The authors have further developed the use of a protected polyhydroxypyrollidone published by *V. Kumar and N.G. Ramesh*
- Protection logic: Orthogonal PGs can be selectively removed for adenosine functionalization
- Elucidation of 1 C-Linked and N-Linked Nucleosides
- They reported an unusual bicyclic ‘Locked’ Nucleoside

Synthetic scheme of Kumar and Ramesh

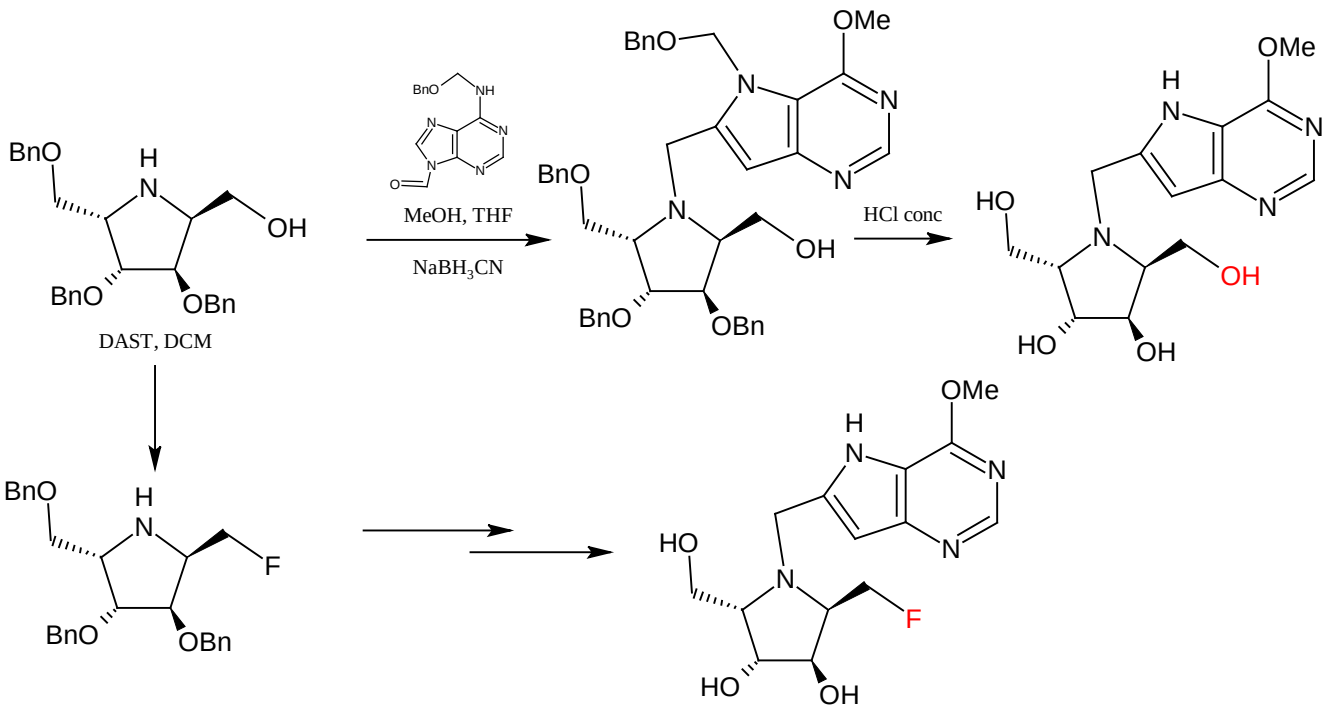


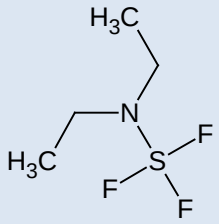
Tetrahedron **2006,** *62*, 1877-1885.

Synthetic scheme: C-Linked nucleosides



Synthetic scheme: N-Linked nucleosides

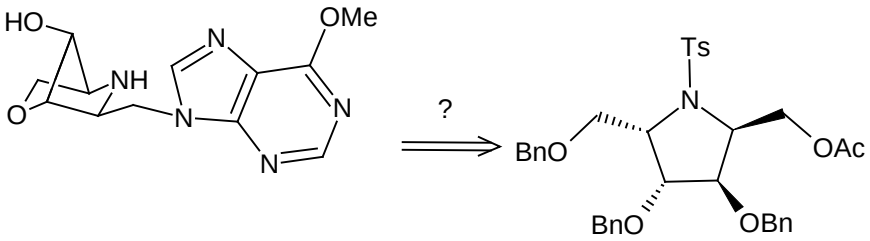




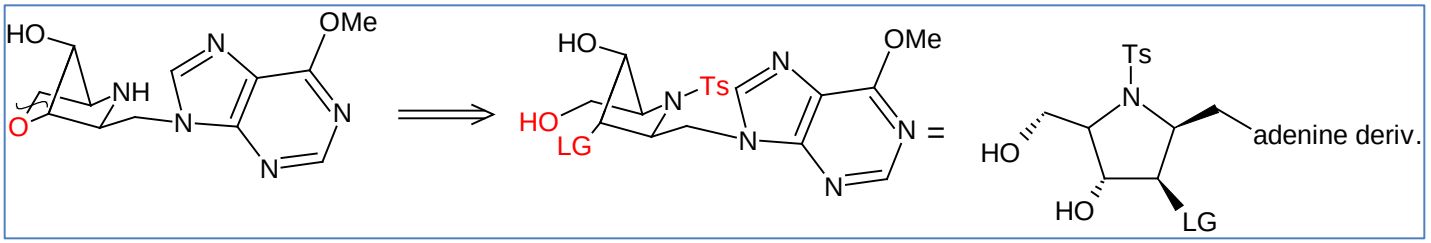
DAST: Diethylamino sulfur trifluoride

A novel bicyclic nucleoside

The authors reported an unusual bicyclic nucleoside based on the Kumar / Ramesh hydroxypyrollidine:

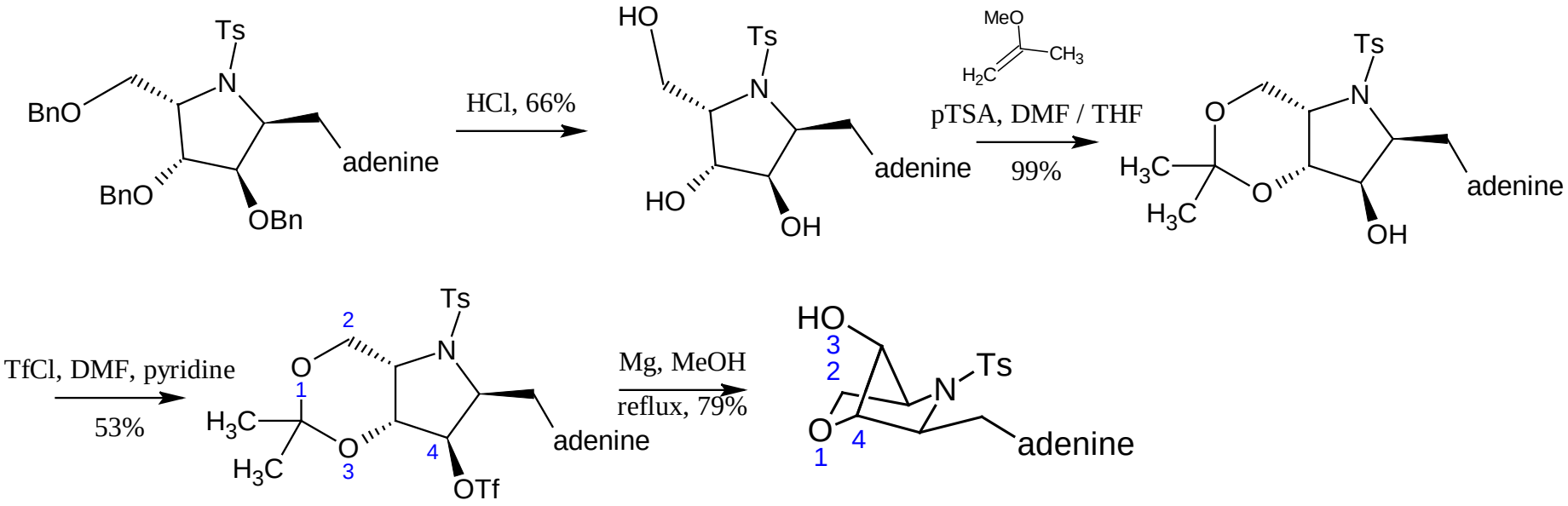


How would you design this synthesis?



A disconnection in the ring is required …..an inversion is required relative to the starting material, which drives this decision… deprotection of the tosylamide is needed…a n OH-protection scheme is required to produce the leaving group selectively.

Published Synthesis



Miscellany

- HMBC / NOESY correlations used to establish the stereochemistry of key C, H atoms in bicyclic nucleosides

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There are almost certainly errors contained in these slides which are the fault of the reviewer (A.S. McKim) and not the responsibility of the publishing scientists.