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

Azasugars as glycodase inhibitors

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 polyhydroxypyrololidone 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

Synthetic scheme: C-Linked nucleosides

1. Nucleoside synthesis:
   - a) OAc, Ts, BnO
   - b) Na$_2$CO$_3$, MeOH (99%)
   - c) TsCl, Pyridine, 50 °C (90%)

2. Nucleoside modification:
   - 18-crown-6, DMF (90%)
   - Mg, MeOH, reflux (90%)
   - HCl (conc.), reflux (82%)

Diagram showing the steps of nucleoside synthesis and modification.
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 hydroxypyrrolidine:

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

BnO

\[ \text{adenine} \]

HCl, 66%

Ts

BnO

\[ \text{adenine} \]

pTSA, DMF / THF

99%

MeO

\[ \text{adenine} \]

TfCl, DMF, pyridine

53%

Mg, MeOH

reflux, 79%

Ts

\[ \text{adenine} \]
Miscellany

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

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