Synthesis of carbocyclic nucleoside analogs

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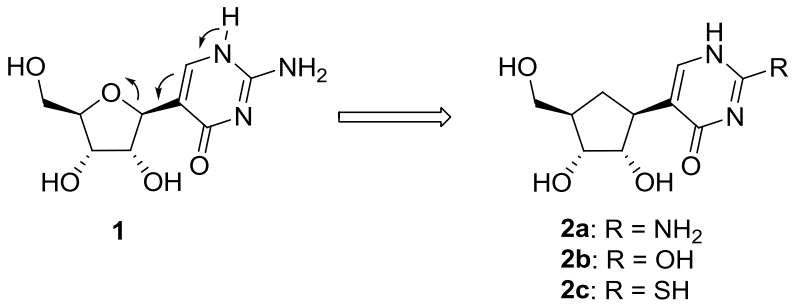
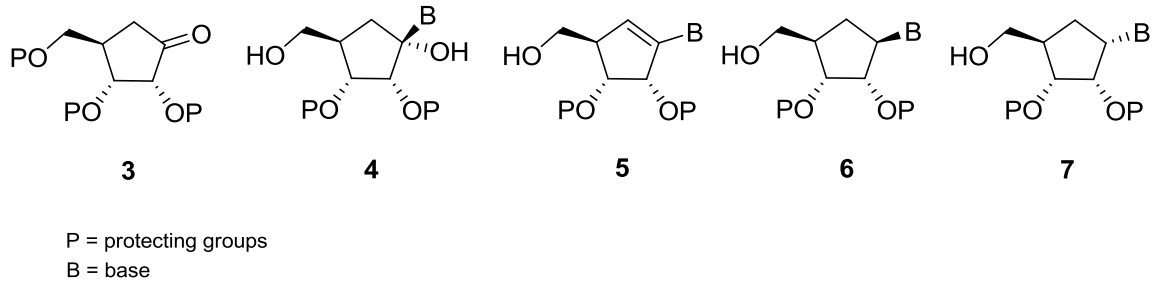
We have developed synthesis of carbocyclic analogs of pseudoisocytidine (**1**), which shows activity against cytarabine-resistant leukemias.[1] Clinical trials of **1** had to be discontinued due to observed hepatotoxicity of unknown origin.[2] Ring opening of **1** (Scheme **1**) can produce reactive and potentially toxic metabolites. On the other hand, carbocyclic analogs (**2a-c**) should be metabolically much more stable and the desired biological activity could be retained. We prepared compounds **2a-c**; each in 13 steps.[3]



Scheme **1**. Possible degradation of pseudoisocytidine and design of more stable carbocyclic analogs

Synthesis of nucleoside analogs with the cyclopentane core and the C-C connection at 1' position is not trivial. Correspondingly, there are very few known compounds and, to our best knowledge, there is no general synthetic methodology that would enable modular preparation of a sufficiently diverse series. We have thus developed a general route which enables preparation of a variety of these carbocyclic-C nucleoside analogs. We synthesized ketone **3** (8 steps from commercially available starting materials), which we then diastereoselectively transformed into heretofore unknown carbocyclic-C nucleosides (**4-7**) containing different pyrimidine and purine isosteres (Scheme **2**).[4,5]



Scheme **2**. Transformations of ketone **3** into different types of carbocyclic-C-nucleosides

The scope and limitations of our synthetic methodology will be presented.

References

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