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Synthesis of Cyclopropane-fused Dideoxycarbocyclic Nucleosides Structurally Related to Neplanocin C

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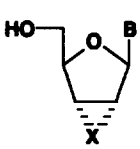
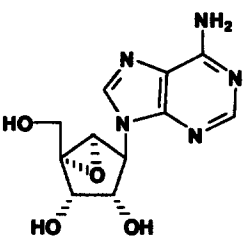
Abstract. The syntheses of five novel carbocyclic dideoxynucleosides with a bicyclo[3.1.0]hexane skeleton was accomplished via a Mitsunobu-type coupling reaction with various heterocyclic bases. These compounds appear to prefer a typical nucleoside northern conformation.

The conformation of the sugar moiety in dideoxynucleosides is believed to play a critical role in modulating anti-HIV activity.[1-3] However, the problem in attempting to correlate a specific type of sugar conformation to biological activity is that the dideoxyribose ring is quite flexible and its conformation in solution can differ sharply from that determined in the solid state.[4,5] Consequently, any structure-activity study based exclusively on solid state conformational parameters would be flawed unless it is substantiated that both solution and solid-state conformations are the same.

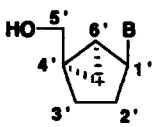
Some [3.1.0]-fused 2',3'-modified dideoxynucleosides (i.e., **1**,[6] **2**[7,8] and **3**[9]), which were devoid of anti-HIV activity, appear to be quite rigid and their altered sugar moiety shows the same conformational preference in solution as in the solid state.[10] Unfortunately, the conformation of the furanose ring in these compounds falls well outside the typical range of northern (N-geometry)[11] or southern (S-geometry)[11] conformations that are characteristic of nucleosides.[10] On the other hand, an alternative type of [3.1.0]-fusion found in the carbocyclic nucleoside neplanocin C (**4**) forces the cyclopentane ring to adopt a typical N-geometry.[12] Therefore, since the bicyclo[3.1.0] systems appear to provide a rigid scaffolding, we reasoned that compounds **5-9**, having a cyclopropane ring fused in the same manner as the epoxide ring of neplanocin C should engender rigid N-geometry conformers. These compounds were selected as synthetic targets to study the relationship between ring puckering and anti-HIV activity.



1, B = uracil, X = CH_2
2, B = cytosine, X = CH_2
3, B = adenine, X = O



4, neplanocin C



5, B = adenine
6, B = guanine
7, B = thymine
8, B = uracil
9, B = cytosine

The synthetic plan envisioned a convergent approach to incorporate the heterocyclic base onto the carbocyclic moiety in one step. Hence, Mitsunobu-type condensations[13] with the appropriate bases were performed using the common intermediate carbocyclic alcohol, (±)-5-[(benzyloxy)methyl]-2-hydroxy-*cis*-bicyclo[3.1.0]hexane (**11**, Schemes 1 and 2). This requisite carbocyclic alcohol was obtained in excellent yield by a "hydroxyl-directed" cyclopropanation reaction performed on the allylic alcohol **10**[14] via a samarium(2+) carbenoid intermediate.[15] Results from the NOE difference spectra for the acetate **12** (Figure 1) agreed well with the disposition of the bicyclic system as inferred by the mode of cyclopropanation.

Condensation of **11** with 6-chloropurine gave a 28% yield of a separable 3:1 mixture of N-9/N-7 isomers (**13** and **15**). When 2-amino-6-chloropurine was used, the yield was better (38%) and only the desired N-9 isomer **14** appeared to have been formed. The low yield of these condensations is probably a reflection of the instability of the starting carbocyclic alcohol **11** under the reaction conditions. Compound **13** was transformed into the adenosine derivative **5** after treatment with methanolic ammonia in a sealed tube, followed by BCl_3 removal of the benzyl group. Compound **14** was converted into the guanosine analogue **6** via the intermediate 6-O-benzyl ether derivative **17** which was deblocked in a similar manner.

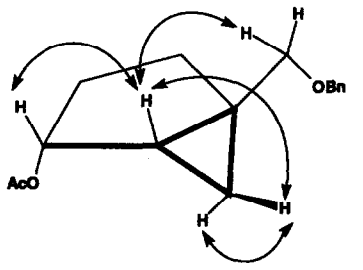
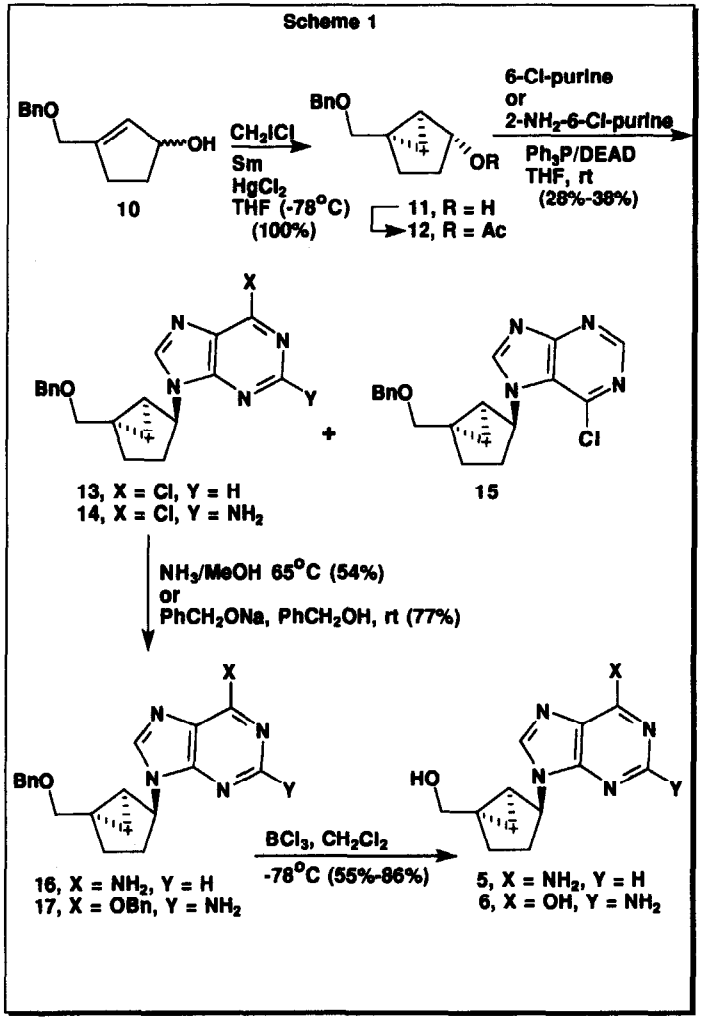
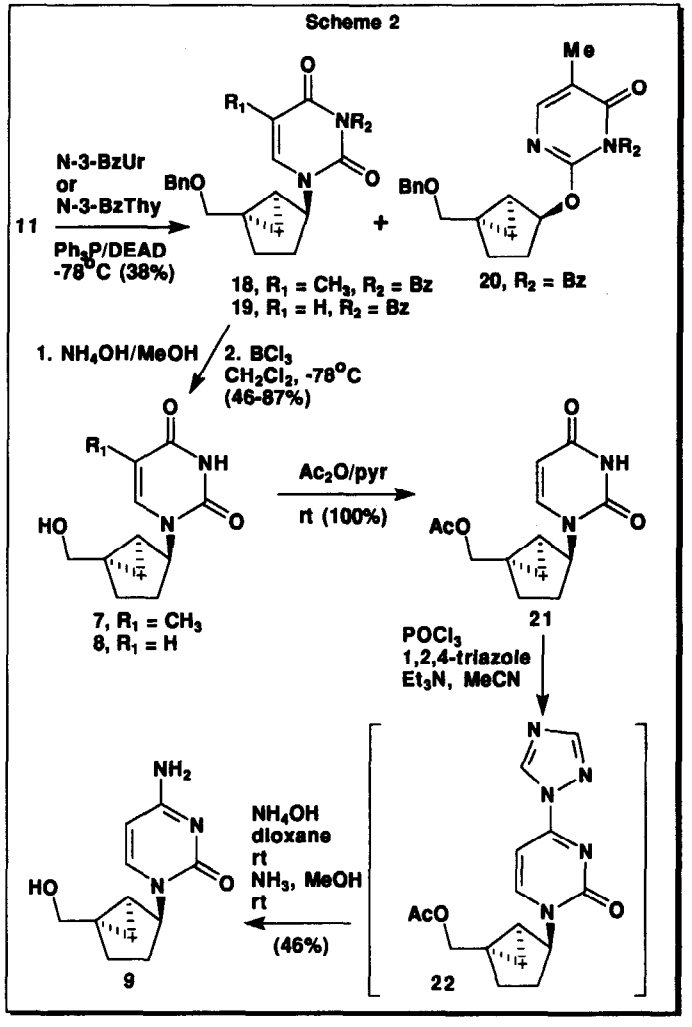


Figure 1. Conformation of compound **12** as deduced by ^{1}H NMR. The double arrows represent reciprocal positive enhancements in a 1-D NOE difference experiment.

The pyrimidine derivatives were also obtained under Mitsunobu conditions in comparable yields using protected N-3-benzoyl thymine[16] or N-3-benzoyl uracil[16] (Scheme 2). The thymine precursor produced a separable 1:1 mixture of N- and O-alkylated products (**18** and **20**), and removal of both N-benzoyl and O-benzyl groups from **18** afforded the thymidine analogue **7**. When N-3-benzoyl uracil was used, no O-alkylation was observed and after using a similar deprotection protocol the corresponding uridine analogue **8** was obtained. The cytosine analogue **9** was prepared via the triazole intermediate **22** according to published methods.[17]

With the exception of signals corresponding to the individual aglycons, the ^{1}H NMR spectra of compounds **5-9** were nearly identical and no apparent changes in the coupling constants were observed from 25 °C to 80 °C. This indicated that all these compounds have a highly similar rigid conformation. Taking compound **5** as a prototype, the pseudoanomeric signal appeared as a doublet (J = 6.0 Hz) centered at δ 4.90. In order to understand the origin of the multiplicity of this signal, models of N- and S-conformers of **5** were constructed using the QUANTA program.[18] The structures were minimized by systematic conformational search and the implicated torsion angles were measured for both conformers. For the N-conformer the values were: H6'—C6'—C1'—H1' (–86.1°), H1'—C1'—C2'—H2'β (91.3°), and H1'—C1'—C2'—H2'α (–23.9°). Although the Karplus equation might not apply perfectly due to the distortion produced by the fused cyclopropane ring, these values suggest that two of the three coupling constants should be zero, or inordinately small. On the other hand, none of the same torsion angles


Scheme 1
BnO
OH
10
CH2ICl
Sm
HgCl2
THF (-78°C)
(100%)
BnO
OR
11, R = H
12, R = Ac
6-Cl-purine
or
2-NH2-6-Cl-purine
Ph3P/DEAD
THF, rt
(28%-38%)
X
N
N
N
N
Y
BnO
13, X = Cl, Y = H
14, X = Cl, Y = NH2
+
N
N
N
N
BnO
Cl
15
NH3/MeOH 65°C (54%)
or
PhCH2ONa, PhCH2OH, rt (77%)
BnO
16, X = NH2, Y = H
17, X = OBn, Y = NH2
BCl3, CH2Cl2
-78°C (55%-86%)
HO
5, X = NH2, Y = H
6, X = OH, Y = NH2


Scheme 2
11
N-3-BzUr
or
N-3-BzThy
Ph3P/DEAD
-78°C (38%)
R1
NR2
O
N
BnO
18, R1 = CH3, R2 = Bz
19, R1 = H, R2 = Bz
+
Me
N
NR2
O
BnO
20, R2 = Bz
1. NH4OH/MeOH
2. BCl3
CH2Cl2, -78°C
(46-87%)
R1
NH
HO
7, R1 = CH3
8, R1 = H
Ac2O/pyr
rt (100%)
AcO
21
POCl3
1,2,4-triazole
Et3N, MeCN
NH2
HO
9
NH4OH
dioxane
rt
NH3, MeOH
rt
(46%)
AcO
22

measured for the S-conformer approached 90° (-134.7°, 175.7° and 60.9°). Therefore, the torsion angles measured for the N-geometry agree better with the multiplicity observed for the pseudoanomeric signal of **5** in the ^{1}H NMR spectrum. These torsion angles are also quite similar to those measured from the crystal structure of neplanocin C, thus suggesting that structures **5-9** have equivalent N-geometries in solution. The N-geometry in compounds **5-9** can only be achieved if the bicyclo[3.1.0]hexane system exists as a pseudoboat, since a pseudochair conformation would correspond to the S-geometry. A search for compounds containing unrestricted bicyclo[3.1.0]hexanes in the Cambridge Structural Data Base[19] revealed that in the seven examples found the pseudoboat was the only form of puckering observed. Why there is a preference for the pseudoboat conformation in these systems is not clear. For example, the energy difference between both conformers of **5** as calculated by QUANTA was only 0.6 Kcal/mol.

Compounds **5-9** were evaluated against HIV-1 in ATH8 cells, but only compound **5** displayed a dose-dependent activity in the 0.5 -50 μM range. The level of protection to the infected cells, however, was opposed by an equally dose-dependent toxicity in the same range.[20]

These compounds represent the first examples of carbocyclic dideoxynucleosides that appear to exist rigidly in a defined N-geometry conformation typical of conventional nucleosides. Future crystallographic analysis of these compounds and biological evaluation of the two optical antipodes of **5** will permit us to offer some important conclusions regarding structure-activity relationships.

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20. The biological evaluation of these compounds was performed by Dr. Hiroaki Mitsuya, COP, NCI, NIH.

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