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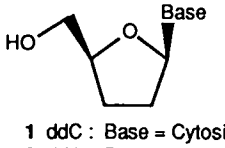
SYNTHESIS OF ISO-DDA, MEMBER OF A NOVEL CLASS OF ANTI-HIV AGENTS

Donna M. Huryn,* Barbara C. Sluboski, Steve Y. Tam, Louis J. Todaro, and Manfred Weigele

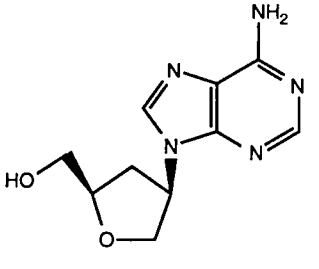
Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Summary: Iso-ddA (**3**) represents a new class of potential anti-AIDS drugs. Synthetic approaches to this compound involving nucleophilic additions to a novel carbohydrate framework are discussed.

Acquired Immune Deficiency Syndrome (AIDS) has become the most important epidemic in modern time. To date, the only proven strategy for the treatment of this disease is inhibition of viral replication, particularly, inhibition of the HIV reverse transcriptase . Recently a class of inhibitors of this enzyme, the 2',3'-dideoxynucleosides (e.g. ddC **1** and ddA **2**) has been described.[1] The therapeutic use of these compounds, particularly ddA and other dideoxypurine nucleosides, however, is limited by their rapid degradation via hydrolysis of the sugar-base linkage.[2] To overcome this deficiency we have designed a modified dideoxynucleoside (Iso-ddA, **3**) in which a more stable nucleoside linkage exists. The exchange of oxygen and carbon atoms, while maintaining an isomeric relationship with the model compounds, should impart stability at the sugar-base union. Herein we describe the synthesis, stability and x-ray structure of iso-ddA, a member of a novel class of inhibitors of HIV replication.



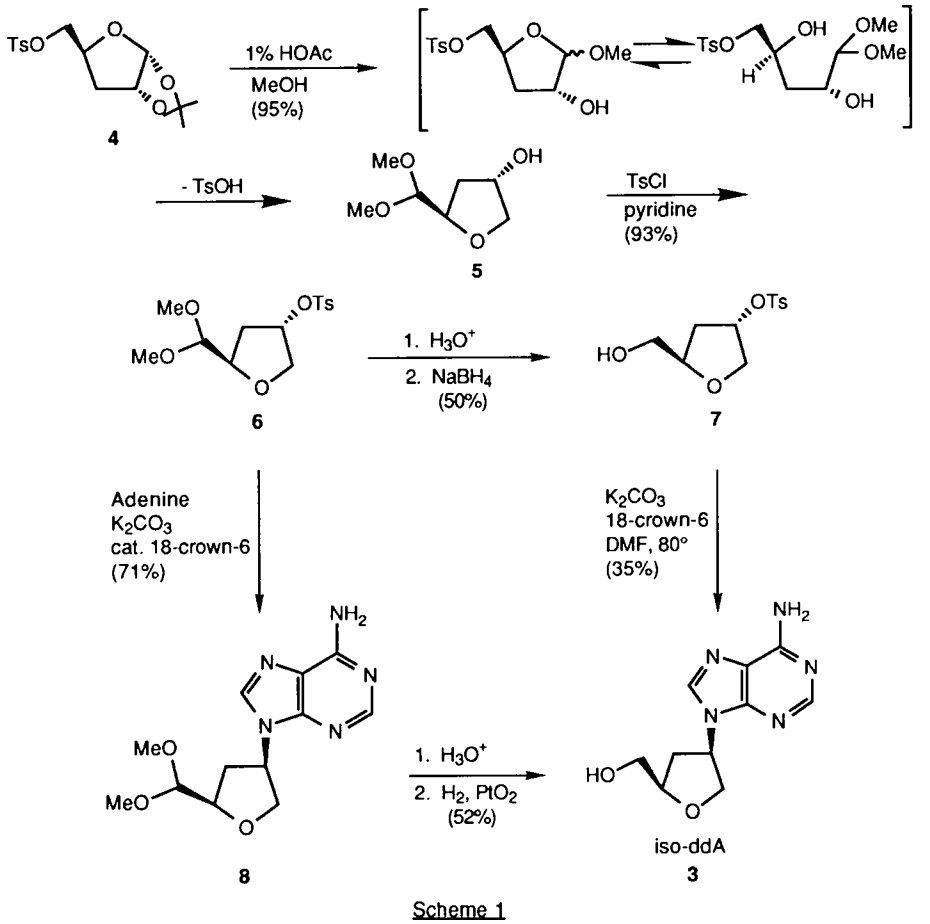
1 ddC : Base = Cytosine
2 ddA : Base = Adenine



3 Iso-ddA

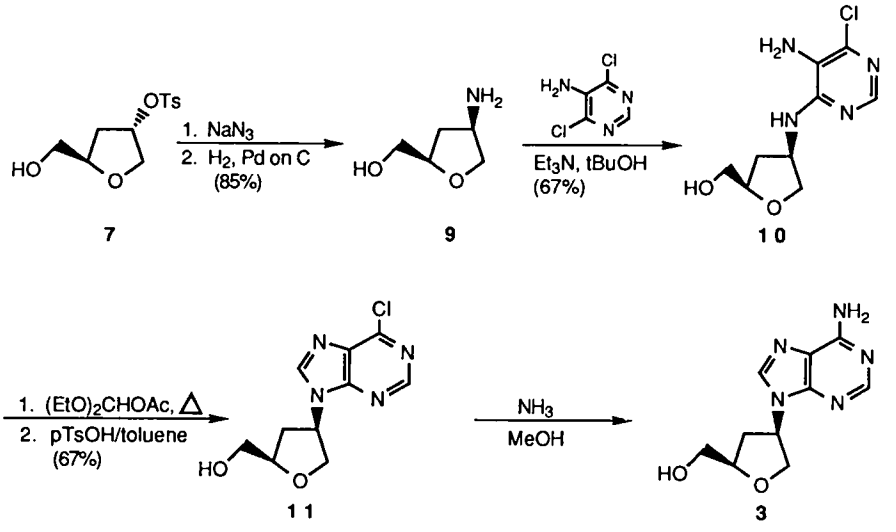
The starting material for the synthesis of **3** was the erythro-pentofuranose derivative **4**[3] (Scheme 1). This compound when treated with a 1% acetic acid/methanol solution, initially yielded a mixture of the methyl glycoside, the ring-opened dimethyl acetal, and the desired cyclized product **5**.[4] With continued stirring, complete conversion to **5** was achieved in greater than 95% isolated yield from **4**. This hydrolysis-cyclization represents an improvement over a previously reported solvolysis reaction of 1,2-0-isopropylidene-5-0-tolylsulfonyl-α, D-xylofuranose.[4] Tosylation of **5** under standard conditions provided the iso-sugar **6**.[5,6]

Conversion of **6** to iso-ddA **3** was carried out via two paths. Hydrolysis of the dimethylacetal, followed by reduction afforded tosyl-alcohol **7**.[7] This could be converted directly to iso-ddA by reaction with adenine, K_2CO_3 and 18-Crown-6.[8] An alternative synthesis involved the nucleophilic addition of adenine under similar conditions to dimethylacetal **6**. The iso-ddA acetal **8**[9] was isolated in 71% yield. Hydrolysis and reduction using standard conditions then afforded **3**.



Scheme 1

Structural elucidation of **3**[10] was initially based on spectroscopic information, particularly NMR and UV data, which suggested attachment of the adenine ring at the N-9 position. Confirmation of this substitution pattern was provided by independent synthesis. Displacement of the tosylate of **7** with sodium azide, followed by reduction afforded the amine **9**[11] in 85% yield. Construction of the purine ring via classical methods[12] was applied to this system as shown in Scheme 2.[13, 14] The product of this sequence of reactions was identical in all respects to that isolated via the direct displacement reactions. A single-crystal X-ray analysis of **3** further confirmed its structure, and is illustrated in Figure 1.



Scheme 2

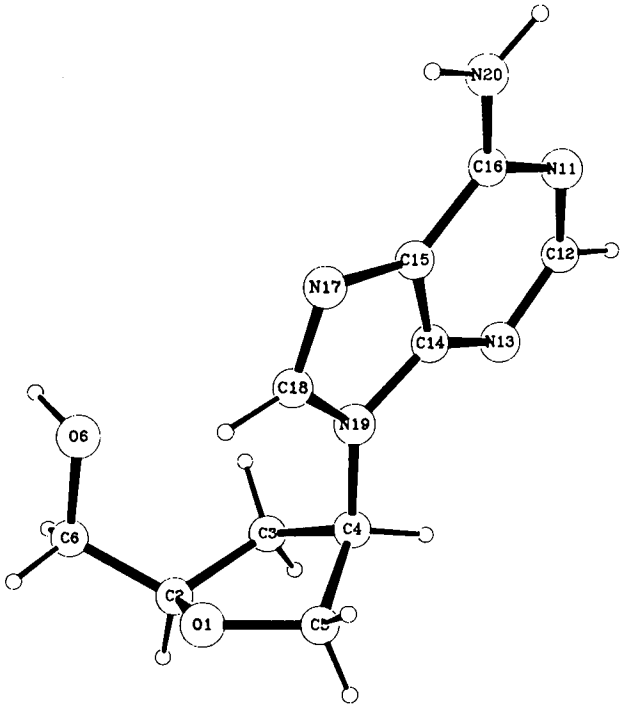


Figure 1-- X-ray structure of iso-ddA

Stability studies of iso-ddA as well as ddA were carried out at pH 3, pH 7 and pH 13. Both compounds were stable for several weeks in neutral and basic solutions. However in acid, ddA rapidly hydrolyzed to its carbohydrate and purine constituents; a half-life of less than one hour at 37 degrees was measured. In contrast, iso-ddA showed no signs of decomposition under the same conditions for the duration of the experiment (15 days).

Upon testing as an anti-viral agent in cell culture, iso-ddA was found to exhibit anti-HIV activity in the same range as that observed for ddA.[15] This compound represents a novel class of potential anti-AIDS drugs, which provides the advantage of acid stability over classical dideoxynucleosides. Further studies on the synthesis of related compounds, as well as investigations of the biological activity of iso-ddA will be reported in due course.

References and Footnotes

1. Mitsuya, H.; Broder, S. *Proc. Nat'l. Acad. Sci. USA*, **1986**, *83*, 1911.
2. Marquez, V. E.; Tseng, C. K.-H.; Kelley, J. A.; Mitsuya, H.; Broder, S.; Roth, J. S.; Driscoll, J. S. *Biochem. Pharmacology*, **1987**, *36*, 2719.
3. Synthesized in analogy to the method of: DeBernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.*, **1985**, *50*, 3457.
4. DeFaye, J.; Horton, D.; Muesser, M. *Carb. Res.*, **1971**, *20*, 305.
5. All spectral data for new compounds are in accordance with the assigned structure.
6. **6**: ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.10 (m, 2H), 2.46 (s, 3H), 3.41 (s, 6H), 3.92 (m, 2H), 4.20 (m, 2H), 5.13 (m, 1H), 7.35 (d, 2H, J=8Hz), 7.80 (d, 2H, J=8Hz).
7. **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 - 2.14 (m, 3H), 2.52 (s, 3H), 3.52, 3.82 (AB of ABX, 2H, J_{AB}=12Hz, J_{AX}=6Hz, J_{BX}=3Hz), 3.93, 4.04 (AB of ABX, 2H, J_{AB}=11Hz, J_{AX}=1Hz, J_{BX}=4Hz), 4.25 (m, 1H), 5.10 (m, 1H), 7.40 (d, 2H, J=9Hz), 7.84 (d, 2H, J=9Hz).
8. Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.*, **1987**, *28*, 4131.
9. **8**: ^{1}H NMR (400 MHz, Me_2SO-d_6) δ 2.20 (ddd, 1H, J=13, 8, 7Hz), 2.59 (ddd, 1H, J=13, 8, 8Hz), 3.35 (s, 6H) 4.07 - 4.01 (m, 3H), 4.45 (d, 1H, J=5.5Hz), 5.14 (m, 1H), 7.23 (br s, 2H), 8.15 (s, 1H), 8.18 (s, 1H).
10. **3**: mp 183-185°; $[\alpha]_D$ + 47.91 (c 0.67, MeOH); UV λ_{max} (methanol) 260 nm (ε 13990); UV λ_{max} (pH 1) 210 nm (ε 19700), 259 nm (ε 13600); ^{1}H NMR (400 MHz, Me_2SO-d_6) δ 2.09 (ddd, 1H, J=13, 8, 5Hz), 2.55 (m, 1H), 3.53 (m, 1H), 3.61 (m, 1H), 4.01 (m, 3H), 4.93 (dd, 1H, J=5, 5Hz), 5.16 (m, 1H), 7.21 (br s, 2H), 8.14 (s, 1H), 8.25 (s, 1H); IR (KBr) 3450-3200, 3115, 1645, 1605 cm^{-1}; MS 235 (M^+); Anal. Calcd. for $C_{10}H_{13}N_5O_2$ (235.24): C, 51.06; H, 5.57; N, 29.77. Found: C, 50.97; H, 5.38; N, 29.82.
11. **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (ddd, 1H, J=13, 4, 2Hz), 2.26 (ddd, 1H, J=13, 9, 6Hz), 2.76 (br s, 3H), 3.53, 3.82 (AB of ABX, 2H, J_{AB}=12Hz, J_{AX}=3Hz, J_{BX}=2Hz), 3.71 - 3.78 (m, 3H), 4.27 (m, 1H).
12. Madhavan, G. V.; Martin, J. C. *J. Org. Chem.*, **1986**, *51*, 1287; Shealy, Y. F.; Clayton, J. D. *J. Amer. Chem. Soc.*, **1969**, *91*, 3075.
13. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (br dd, 1H, J=14, 4Hz), 2.48 (ddd, 1H, J=14, 10, 7Hz), 2.89 (br s, 1H), 3.50 (br s, 2H), 3.62, 3.94 (br AB, 2H, J=12Hz) 3.84, 3.93 (AB of ABX, 2H, J_{AB}=9.5Hz, J_{AX}=4Hz, J_{BX}=1Hz), 4.21 (m, 1H), 4.27 (m, 1H), 6.24 (br d, 1H, J=7Hz), 8.03 (s, 1H).
14. **11**: ^{1}H NMR (400 MHz, Me_2SO-d_6) δ 2.15 (ddd, 1H, J=13, 8, 4Hz), 2.64 (ddd, 1H, J=13, 8, 6Hz), 3.54, 3.66 (AB of ABMX, 2H, J_{AB}=12Hz, J_{AM}=5Hz, J_{AX}=5Hz, J_{BM}=5Hz, J_{BX}=4Hz), 3.98, 4.15 (AB of ABX, 2H, J_{AB}=10Hz, J_{AX}=6Hz, J_{BX}=2Hz), 4.03 (m, 1H), 4.97 (dd, 1H, J=5, 5Hz), 5.34 (m, 1H), 8.80 (s,1H), 8.82 (s, 1H).
15. Results of H. Mitsuya and S. Broder, Clinical Oncology Program, National Cancer Institute.

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