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The Synthesis of Modified D- and L-Anhydrohexitol Nucleosides

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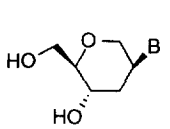
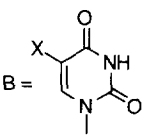
Abstract: The synthesis and antiviral activities of novel L-isomers **9-13** and modified D-guanine analogs **1d,e** of recently reported anhydrohexitol nucleosides **1** are described. An efficient approach to known anhydrohexitol nucleoside precursor **2** from diacetone-D-glucose **3** is also reported. Copyright © 1996 Elsevier Science Ltd

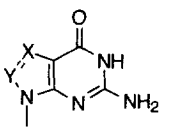
The synthesis and anti-herpes activity of novel 6-membered nucleoside analogs **1** were recently reported.[1] Although nucleoside analogs bearing diverse sugars have been a rich source of antiviral agents, this was the first time that a 6-membered congener exhibited potent antiviral activity. Of the original series, the 5-iodo- and 5-ethyluracil analogs, **1a, b**, displayed activity comparable to acyclovir against herpes simplex virus (HSV-1 and HSV-2) with no evidence of cytotoxicity to a variety of cells. The corresponding guanine, 2,6-diaminopurine, cytosine, and 5-fluorocytosine analogs of **1** were also potent inhibitors of human cytomegalovirus (HCMV) in vitro, but were more toxic to human bone marrow progenitors than ganciclovir. In order to more fully examine this novel class of nucleosides and to identify more selective anti-HCMV agents, we synthesized additional nucleoside analogs with modified pyranoses and heterocyclic bases. Modified guanines (e.g. **1d,e**) were synthesized in an attempt to improve antiviral selectivity using approaches which have been successful with certain carbocyclic nucleosides.[2] Additionally, recent interest in L-nucleosides[3] led us to synthesize the enantiomers of **1**.



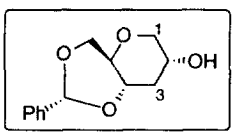
1, B= Heterocyle



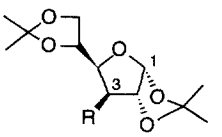
1a, X=I
1b, X=Et



1c, X=N; Y=CH
1d, X=Y=N
1e, X=Y=CH

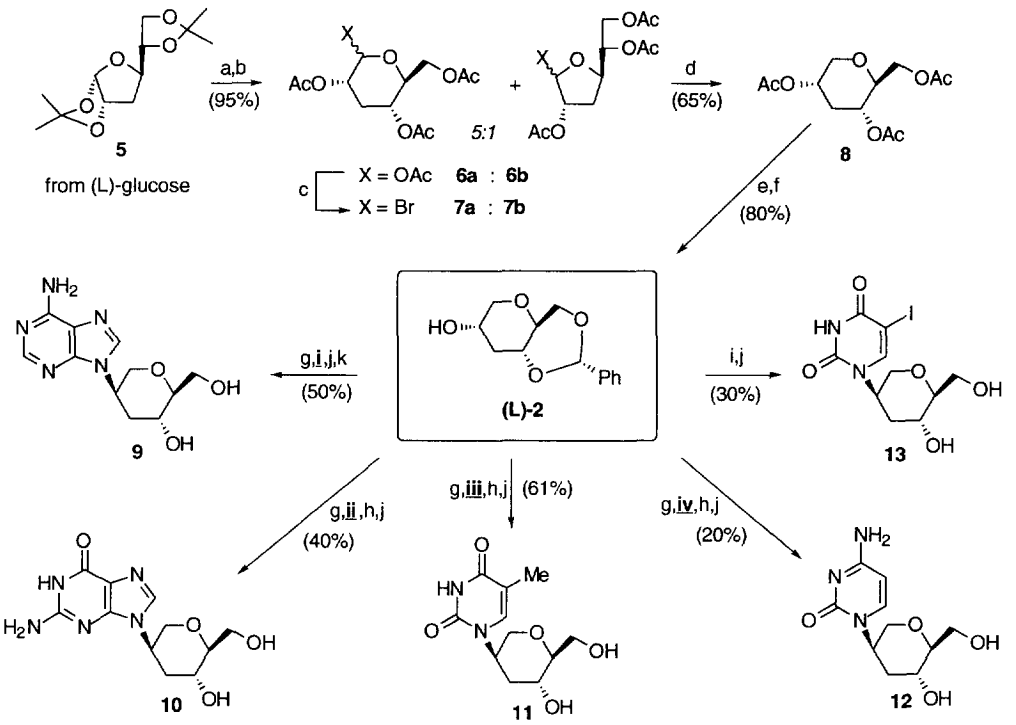


2, *Key Intermediate*



3, R=OH
4, R=H

The reported route to anhydrohexitol nucleosides **1** requires 9 steps (20% overall yield) to arrive at key intermediate **2**.[1a] We developed a shorter route to **2** starting from commercially available diacetone D-glucose **3**. The known Barton deoxygenation of **3** proved scalable and was utilized to prepare multigram quantities of distillable 3-deoxy-diacetone-D-glucose **4**.[4a] Conversion of **4** to **2** proceeded as shown for the synthesis of the L-isomers **9-13** (scheme 1).

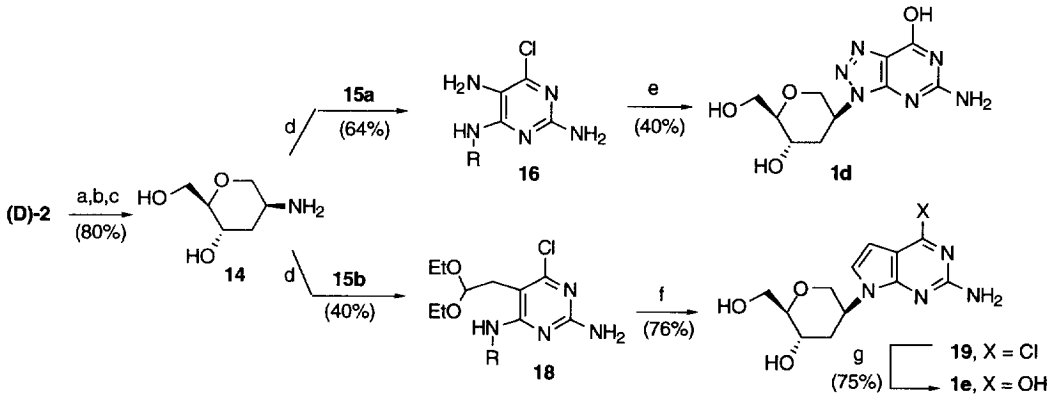


Scheme 1. a) IRA-120 (H+) resins, EtOH, H_2O, rflx. b) Pyr, Ac_2O. c) HBr, HOAc. d) $HSnBu_3$, Et_2O, RT. e) NaOMe, MeOH. f) 1.2 eq. $PhCH(OMe)_2$, dioxane, RT, 24 h. g) PPh_3, DEAD, then Blocked Heterocycles i-iv: i: 6-chloropurine, ii: N^2-acetyl-6-O-diphenylcarbamoylguanine, iii: N^3-benzoylthymine, iv: N^4-benzoylcytosine. h) NH_3, MeOH. i) NaH; TsCl then the sodium salt of 5-iodo-uracil, DMF, 90 °C, 12 h. j) 80% HOAc, rflx. 1 h. k) NH_3, Parr bomb, 60 °C, 12 h.

Acid deprotection of 3-deoxy-L-glucose **5**[4b] and peracetylation as previously reported for the D-isomer[5a,b] gave the expected 2:1 α/β anomeric mixture of **6a** along with 15-20% of the α/β furanoses **6b**. Treatment of this mixture with HBr/AcOH and reduction of the crude glycosyl bromides **7a,b** with Bu_3SnH in Et_2O[6a] gave 65-74% isolated yields of the desired pyranose **8** after chromatography. Other hydride reagents examined for the reduction of labile anomeric bromides **7** or acetates **6** were less efficient affording mostly glucal products of elimination.[6b] Deacetylation of **8** and benzylidene formation then provided **2** in 30-40% overall yield from diacetone-(D or L)-glucose.

Conversion of alcohol **2** to L-nucleoside analogs **9-12** was carried out under Mitsunobu conditions with appropriately blocked purines and pyrimidines as described for the analogous D-series.[1a] Yields varied widely depending on the blocked heterocycle used. 6-Chloropurine alkylated cleanly at N-9, affording good yields of the adenine diol **9** after acid-deprotection and ammonolysis. N^2-Acetyl-6-O-diphenylcarbamoylguanine[7] provided guanine **10** in high yield after deblocking. Yields for the thymine **11**, cytosine **12**, and 5-iodo-uracil **13** analogs were consistent with those reported for the enantiomeric D-series.[1a] We also obtained low yields in the Mitsunobu coupling using N^4-benzoylcytosine due to competing O-alkylation.

The syntheses of 8-azaguanine **1d**, and 7-deazaguanine **1e** utilized amine **14**, which was prepared in good overall yield via azide displacement of the mesylate of **(D)-2**, catalytic hydrogenation (Pd/C), and acid deprotection (scheme 2). Reaction of amine **14** with 2,5-diamino-4,6-dichloropyrimidine **15a**[8] gave chloropyrimidine **16**. Nitrosation with $NaNO_3$ in dilute acid provided 8-azaguanine **1d** in moderate yield after hydrolysis of the intermediate chloropurine.[9]



Scheme 2. a) MsCl, TEA. b) NaN_3, DMF, 70 °C, 3 h. c) H_2, Pd/C, EtOH; aq. HCl. d) EtOH, TEA, rfx, 12-48 h. e) $NaNO_3$, aq. HCl, RT, then 60 °C, 1 h. f) 0.1 N HCl, dioxane, RT, 3 d. g) 1 N HCl, 80 °C, 12 h.

Coupling of amine **14** with 2-(2-amino-4,6-dichloropyrimidin-5-yl) acetaldehyde diethyl acetal **15b**[10], afforded intermediate **18** which was directly cyclized to the 6-chloropurine **19** by treatment with acid. Subsequent acidic hydrolysis then gave 7-deaza guanine **1e**.

Compounds **9-13** and **1d,e** were found inactive at 200 μM against HIV-1 (strain IIIB in MT4 cells), HCMV (strain AD169 in MRC5 cells) and HSV-1 (Vero cells).

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