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Improved Synthesis of L-1,3-Dioxolanyl and L-1,3-Oxathiolanyl Acetate from L-Gulose

Yong Can Xu[1], Joon Hee Hong[2], Jeong Ha Park[2], Ji Yeon Song[2], Joong Hyup Kim[3], Won-Keun Chung[2] and Moon Woo Chun[2]

[1]*Yanbian Medical College, Yanji City, Jilin Province, China;* [2]*College of Pharmacy, Seoul National University, San56-1, Shinlim-Dong, Kwanak-Ku, Seoul 151-742, Korea;* [3]*Korea Institute of Sciences and Technology, Seoul, Korea*

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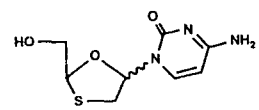
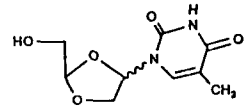
Since the discovery of AZT as a potent inhibitor of HIV, a number of other 2',3'-dideoxynucleosides such as DDI, DDC, D4T have been approved by the FDA for treating AIDS and ARC (AIDS Related Complex) patients (Goff, 1990). All of these nucleosides have various toxic side effects that make long-term administration of these drugs difficult in many cases. A number of new 2',3'-dideoxy nucleosides have been synthesized and tested against HIV in a search to find more potent and less toxic anti-HIV compounds. Among these, nucleosides with a modified sugar moiety at the C-3' position by which possess a heteroatom such as oxathiolane cytosine (**A**, (±)-BCH-189) and dioxolane-thymine (**B**, dioxolane-T) have been reported (Belleau, 1989).

Since (±) dioxolanyl thymine derivatives (I) have been reported to exhibit anti-HIV activity by Belleau (Belleau, 1989), several synthetic approaches to the sugar moiety have been reported. The first synthesis of the dioxolanyl moiety as a racemic mixture was reported by Norbeck and co-workers (Nobeck, 1989; Choi *et al.*, 1991). Chu et al. reported an asymmetric synthesis of L-dioxolane nucleosides from L-gulose in 7 steps (scheme 1)(Beach *et al.*, 1992; Jeong *et al.*, 1992; Chu *et al.*, 1991). In our on-going research efforts to develop non-classical nucleoside derivatives with anti-HIV activity, we needed large amount of L-dioxolane adnd L-oxathiolane sugars of high enantiomericurity. Although Chu's methods give enantiomerically pure sugar moieties, the over-all yield of the reactions were not high because of side-reactions. Here we report mproved asymmetric syntheses of L-dioxolane and L-oxathiolane sugars from readily available starting materials.



A (±)-BCH-189

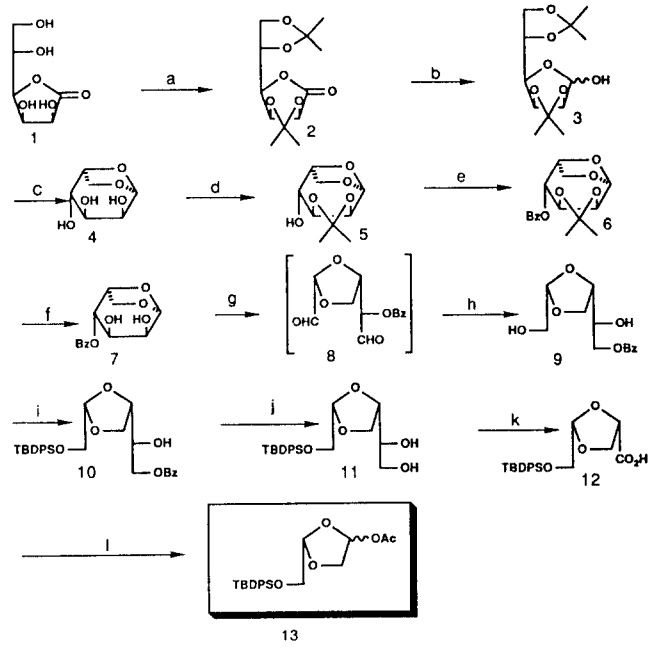


B (±)-Dioxolane-T

Our synthesis begins with commercially available L-gulono-6,3-lactone (**1**), which has the same absolute configuration as L-gulose (scheme 1). After protection of both vicinal diols as the isopropylidenes, the lactone was reduced to hemiacetal (**3**) in quantitative yield. L-1,6-anhydro gulopyranose was obtained from the *in situ* cyclization of L-gulose that was formed by heating (**3**) in acid overnight. In order to avoid the yield-lowering side reactions in the direct 2,3-diol cleavage reaction of (**4**) the 2,3-*cis*-diol was protected as the isopropylidene (**5**), followed by benzoylation of the 4-hydroxy group. After selective deprotection of the 2,3-diol (**6**) under acidic conditions, $NaIO_4$ treatment gave the di-aldehyde intermediate (**8**). Direct reduction of (**8**) with $NaBH_4$ without isolation gave (**9**) in which the benzoyl group migrated from the secondary to the primary position. Since our final target molecules were dioxolane nucleosides, the 4-hydroxy group was protected as a TBDPS-ether (**10**) before the oxidative cleavage of the diol (**11**) to carboxylic acid (**12**) using RuO_2 and $NaIO_4$ (Akagi *et al.*, 1963). Decarboxylative acetylation was achieved by $Pb(OAc)_4$ (Whistler and Seib, 1966) to obtain L-1,3-dioxolanyl acetate (**13**) in 12 steps (over-all-yield of 8.1%).

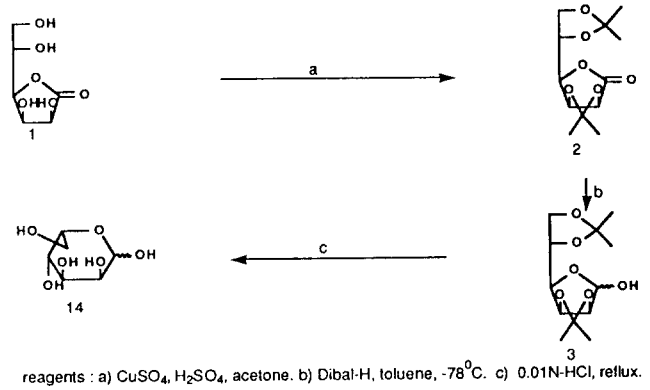
L-Oxathiolanyl acetate (**29**) was synthesized from the same starting material, L-gulo-lactone. L-gulose was prepared in quantitative yield by treating the protected hemiacetal (**3**) with a mild acid (Scheme 2). All of the secondary hydroxy groups were protected as acetates (**16**) in good yield after the selective protection of the primary hydroxy group with tosyl chloride. Selective bromination at the anomeric position (**17**) was achieved by treating this protected sugar with a 30% HBr solution. 1,6-thioanhydro-2-gulose triacetate (**18**) was obtained by reaction with potassium O-ethylxanthate (Akagi *et al.*, 1963; Whistler and Seib, 1966). After

Correspondence to: Moon Woo Chun, College of Pharmacy, Seoul National University, Seoul 151-742, Korea



reagents : a) $CuSO_4$, H_2SO_4, acetone. b) Dibal-H, toluene. c)0.5-HCl, reflux. d) DMP, acetone, p-TSA, RT. e) BzCl, pyridine, 0°C. f) H_2SO_4, dioxane, H_2O, 70~80°C. g) $NaIO_4$, H_2O, EtOH. h) $NaBH_4$, H_2O, 0°C, RT. i) TBDPS-Cl, imidazole, DMF, RT. j) NaOMe, MeOH, 0°C. k) RuO_2, $NaIO_4$, H_2O, CCl_4, CH_3CN, RT. l) $Pb(OAc)_4$, pyridine, THF, 0°C.

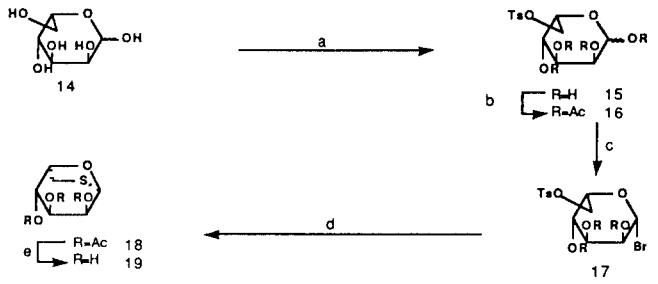
Scheme 1. Synthesis of L-1,3-dioxolanyl acetate.



reagents : a) $CuSO_4$, H_2SO_4, acetone. b) Dibal-H, toluene, -78°C. c) 0.01N-HCl, reflux.

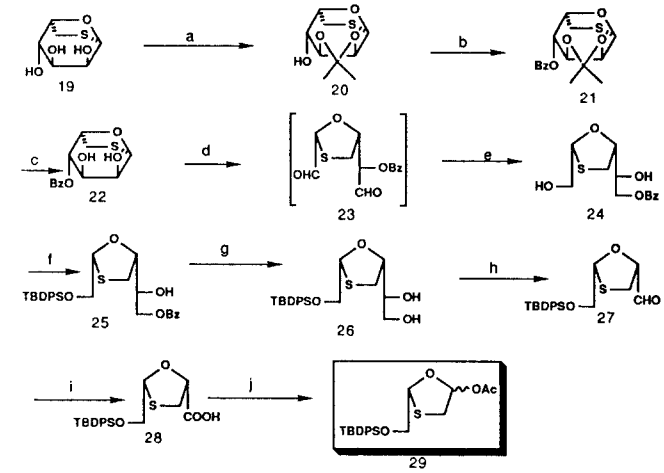
Scheme 2. Synthesis of L-gulose.

the selective protection of the primary alcohol, the vicinal diol was cleaved with lead tetraacetate instead of $NaIO_4$. Using $Pb(OAc)_4$ gives improved solubility and more importantly (**23**) and (**24**) in which the benzoyle group was migrated to the primary position. After the selective protectin of the 4'-OH group, we used a step-wise oxidative cleavage of the diol instead of one step cleavage using $NaIO_4/RuO_2$ to prevent sulfur oxidation. The diol (**26**) was first converted to aldehyde (**27**) by $Pb(OAc)_4$, then to carboxylic acid (**28**) using PDC. Decarboxylative acetylation was achieved by $Pb(OAc)_4$ to pbtained L-1,3-oxathiolanyl acetate (**29**) in steps (over-all-yield of 17.7%) (Scheme 2, 3, 4).



reagents : a) TsCl, pyridine. b) Ac_2O, pyridine. c) HBr/AcOH, 0°C, RT. d) potassium O-ethyl xanthate, acetone, reflux. e) NH_4OH/MeOH (1:4)

Scheme 3. Synthesis of 1,6-thioanhydro L-gulopyranose.



reagents : a) p-TSA, DMP, acetone. b) BzCl, pyridine. c) 2% aqueous H_2SO_4, dioxane,70°C. d) $Pb(OAc)_4$, THF, 0°C. e) $NaBH_4$, EtOH. f) TBDPS-Cl, imidazole, DMF. j) $Pb(OAc)_4$, pyridine, THF.

Scheme 4. Synthesis of L-oxathiolane acetate.

In summary, the enantiomerically pure L-dioxolane and L-oxathiolane have been synthesized in improved yields by modifying Chu's procedure. These sugar moieties were conjugated with various pyrimidine bases to synthesize L-1,3-dioxolananyl and L-1,3-oxathiolanyl pyrimidine nucleosides.

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