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Synthesis of Novel Nucleoside Analog (3R)-2,3-Dideoxy-3- (N-hydroxy-N-methylamino)-L-arabinofuranosyl Uracil

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Abstract: The synthesis of novel nucleoside analog (3R)-2,3-dideoxy-3-(N-hydroxy-N- methylamino)-L-arabinofuranosyl uracil was studied. A twelve-step synthetic route, started from L-ascorbic acid, was designed, and the final product was obtained in 20.8% yield.

Keywords: L-Nucleoside, Wittig reaction, Michael addition, uracil analog.

Nucleoside analogs are currently served as promising anti-HIV agents. Although much attention has been devoted to synthesis and activity assay of D-nucleoside, the biological activity of L-nucleosides has recently been recognized to be effective reverse transcriptase inhibitors[1]. In particular, the anti-HIV and anti-HBV activity of (-)-(2R, 5S)-1-[(2-hydroxymethyl)-oxathiolan-5-yl] cytosine (3TC) inspires active research in the field of L-nucleoside analogs[2]. Based on our previous work on designing and synthesizing a series of D-isomer of 2′-hydroxylamino nucleoside analogs[3], a novel L-isomer (3R)-2,3-dideoxy-3-(N-hydroxy-N-methylamino)-L-arabinofuranosyl uracil **10** was prepared for its antiviral studies.

L-Ascorbic acid **1**, which has the desired configuration for the target molecule, was converted to an aqueous solution of aldehyde **2** according to the reported procedure[4]. Due to the fact that **2** is soluble in water, the aqueous solution was directly used for the Wittig reaction to give a mixture of isomers **3*E*** and **3*Z*** in a ratio of 1/4, which was determined after the purification of the products from the next step. Without separation of two isomers, the mixture was subjected to the deprotection procedure using concentrated hydrochloric acid in methanol. Furanone **4** and diol **5** were separated by column chromatography. Lactone **4** was treated with *tert*-butyldiphenylsilylchloride (TBDPSCl)[5] in the presence of triethylamine to give **6**. The Michael addition[6] of N-methylhydroxyamine to **6** was carried out in DMF at room temperature to produce hydroxylamine **7** in 95% yield. Compound **7** was converted into **8** *via* a three-step procedure: (a) protection the *N*-hydroxyl group of **7** with *tert*-

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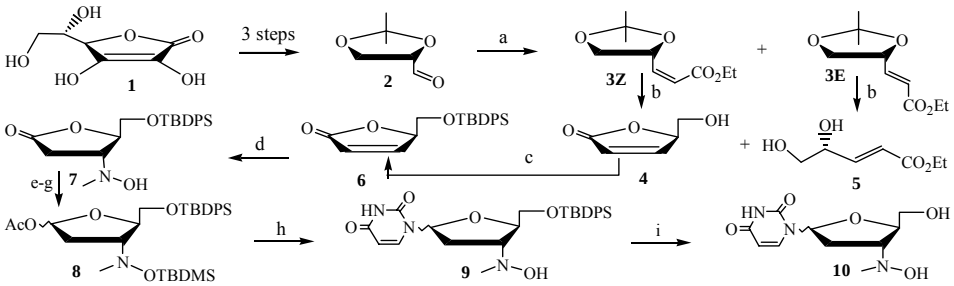
butyldimethylsilylchloride(TBDMSCl)[7] in the presence of imidazole, (b) reduction to a

Scheme 1



(a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2/H_2O, 0℃; (b) HCl/MeOH, 2 h; (c) TBDPCl, Et_3N, CH_2Cl_2, 2 h; (d) MeNHOH•HCl, Et_3N, DMF; (e) TBDMSCl, Imidazole, DMAP, CH_2Cl_2; (f) $NaAlH(OCH_2CH_2OMe)_2$ OEt, PhMe, -78℃, 1.5 h; (g) AcCl, Et_3N, 0℃, CH_2Cl_2, 2 h. (h) Silylated uracil, Me_3SiOTf, MeCN; (i) conc. HCl/MeOH, 30 min.

lactol in 43% yield[7], and (c) acetylation with acetyl chloride in 83% yield. Acetate **8** reacted with silylated uracil in acetonitrile catalyzed with trimethylsilyl trifluoromethanesulfonate to give protected nucleoside analog **9**[8]. Compound **9** was hydrolyzed with concentrated hydrochloric acid in methanol to give the final nucleoside analog **10**[9].

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9. Data of compound **10**: ^{1}H NMR (DMSO-d_6), δ11.08 (s, 1H, -NH), 8.09 (s, 1/3H, -NOH), 7.99 (s, 2/3H, -NOH), 7.89 (d, 2/3H, J=8 Hz, CH=CHN), 7.80 (d, 1/3H, J=8 Hz, CH=CHN), 6.11 (dd, 1/3H, J=4.4, 7.2 Hz, -OCHN-), 6.06 (t, 2/3H, J=6.8 Hz, -OCHN-), 5.65 (d, 2/3H, J=5.6 Hz, -CH=CHN-), 5.57 (d, 1/3H, J=5.6 Hz, -CH=CHN-), 4.95 (s, 2/3H, -CH_2OH), 4.77 (s, 1/3H, -CH_2OH), 4.31 (m, 1/3H, -OCHCH$_2$O-), 4.04 (m, 2/3H, -OCHCH$_2$O-), 3.64-3.10 (3H, -OCHCH$_2$O-, -CHN-), 2.49 (s, 3H, -NCH_3), 2.39 (m, 1H, -NCHCH$_2$CHN-), 2.03 (m, 1/3H, -NCHCH$_2$CHN-), 1.89 (m, 2/3H, -NCHCH$_2$CHN-).

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