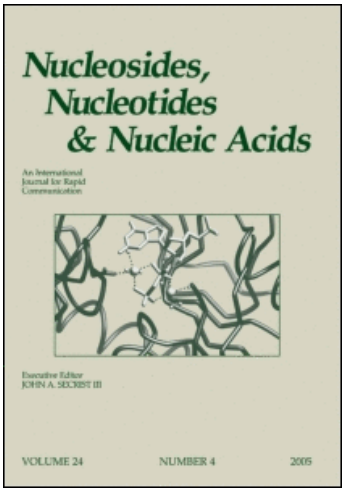

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2,3'-Anhydro-[l- (6'- O-benzoyl-2',5'- dideoxy-β-D-glucofuranosyl)thymine], a Versatile Starting Material for Homo - Nucleosides

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2,3′-ANHYDRO-[1-(6′-O-BENZOYL-2′,5′-DIDEOXY-ß-D-GLUCOFURANOSYL)THYMINE] A VERSATILE STARTING MATERIAL FOR HOMO - NUCLEOSIDES

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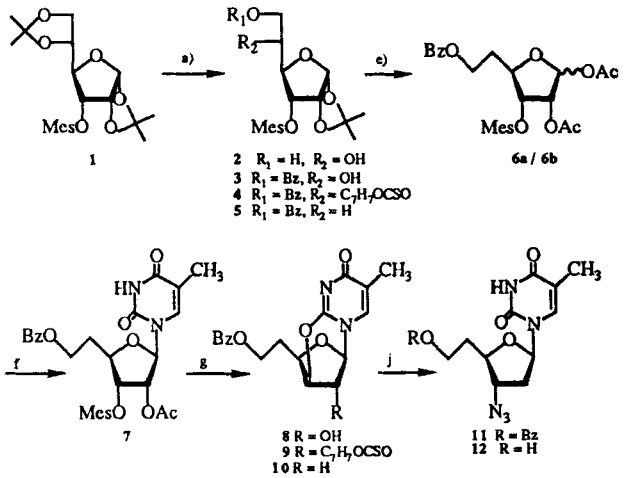
ABSTRACT: The synthesis of 2,3′-anhydro-[1-(6′-O-benzoyl-2′,5′-dideoxy-ß-D-glucofuranosyl)thymine] **10**, a versatile starting material for homo-2′, 3′-dideoxynucleosides is described. **10** is transformed to homo-AZT.

There are only few synthetic routes[1] to nucleoside derivatives with 5′-deoxy-ß-D-allofuranose as sugar moiety (homo-nucleosides). These derivatives are of interest because of their enhanced lipophilicity compared to their parent compounds. As part of our programm preparing new nucleoside derivatives with more selective activity we developed a general strategy for the preparation of side-chain derivatives of biological active 2′,3′-dideoxy nucleoside derivatives. The synthesis of the requisite carbohydrate unit began with 1,2;5,6-di-O-isopropylidene-3-O-mesyl-α-D-allofuranose **1** [2], from which 1,2-O-isopropylidene-α-D-allofuranose **2** was transformed to the anomeric mixture of 6-O-benzoyl-1,2-di-O-acetyl-3-O-mesyl-D-allofuranoses **6a/6b** (Scheme 1). These sugar derivatives were coupled with thymine using the one-pot procedure[3] of the silyl-Hilbert-Johnson method (**7**, 46%). The formation of the 2,3′-anhydro derivative **8** was performed with DBU, proofing the ß-configuration of **7**. The simultaneously selective saponification of the acetyl group at 2′-position with DBU[4] is noticeable. The 2′-O-(4-methylphenyloxy)thiocarbonyl derivative **9** was deoxygenated with tributyltin hydride to yield the title compound **10**.

2,3′-Anhydro-[1-(6′-O-benzoyl-2′,5′-dideoxy-ß-D-glucofuranosyl)thymine] **10** is most suited for the preparation[5] of 2′,3′-dideoxy-side chain-homologues of biological active nucleoside derivatives. This is demonstrated by opening the 2,3′-anhydro-bridge of **10** with



Scheme 1: a) AcOH : H_2O = 4 : 1, 16h, 25°C; b) BzCl, pyridine, 16h, -30 ->25°C; c) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN, 16h, 25°C; d) Bu_3SnH, AIBN, toluene, 5h, 120°C; e) Ac_2O : AcOH = 2 : 1, H_2SO_4 cat.,$CHCl_3$, 16h, 4°C; f) thymine, HMDS, TMS-Cl, CF_3SO_3H, CH_3CN, 5h, 80°C; g) 5 equiv. DBU, THF, 55h, 60°C; h) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN, 16h, 25°C; i) Bu_3SnH, AIBN, toluene, 5h, 120°C; j) LiN_3, BzOH, DMF, 20h, 120°C; k) $NaOCH_3$, MeOH, 16h, 25°C.

lithium azide. Deblocking of **11** with sodium methoxide yielded **12** (homo-AZT). **12** showed no activity against HIV-I in MT-4 cells(EC_{50}>200µg/ml, CC_{50}> 200µg/ml). The synthesis of side-chain homologues of biological active 2′, 3′- dideoxynucleoside derivatives, using this new and general strategy is in progress.

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