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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- β -D-GLUCOFURANOSYL)THYMINE]
A VERSATILE STARTING MATERIAL FOR HOMO - NUCLEOSIDES**

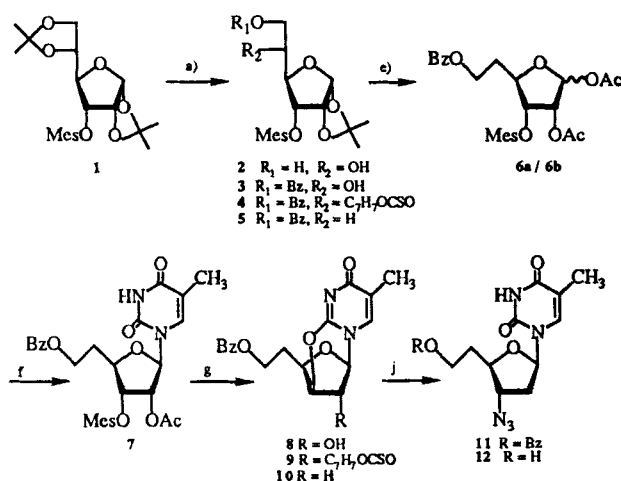
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ABSTRACT: The synthesis of 2,3'-anhydro-[1-(6'-O-benzoyl-2',5'-dideoxy- β -D-glucofuranosyl)thymine] **10**, a versatile starting material for homo-2',3'-dideoxynucleosides is described. **10** is transformed to homo-AZT.

There are only few synthetic routes¹ to nucleoside derivatives with 5'-deoxy- β -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 program 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 procedure³ of the silyl-Hilbert-Johnson method (**7**, 46%). The formation of the 2,3'-anhydro derivative **8** was performed with DBU, proofing the β -configuration of **7**. The simultaneously selective saponification of the acetyl group at 2'-position with DBU⁴ 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- β -D-glucofuranosyl)thymine] **10** is most suited for the preparation⁵ 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, $25^\circ C$; b) $BzCl$, pyridine, 16h, $-30 \rightarrow 25^\circ C$; c) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN , 16h, $25^\circ C$; d) Bu_3SnH , AIBN, toluene, 5h, $120^\circ C$; e) $Ac_2O : AcOH = 2 : 1$, H_2SO_4 cat., $CHCl_3$, 16h, $4^\circ C$; f) thymine, HMDS, $TMS-Cl$, CF_3SO_3H , CH_3CN , 5h, $80^\circ C$; g) 5 equiv. DBU, THF, 55h, $60^\circ C$; h) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN , 16h, $25^\circ C$; i) Bu_3SnH , AIBN, toluene, 5h, $120^\circ C$; j) LiN_3 , $BzOH$, DMF, 20h, $120^\circ C$; k) $NaOCH_3$, $MeOH$, 16h, $25^\circ C$.

lithium azide. Deblocking of 11 with sodium methoxide yielded 12 (homo-AZT). 12 showed no activity against HIV-I in MT-4 cells ($EC_{50} > 200 \mu g/ml$, $CC_{50} > 200 \mu g/ml$). 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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