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SYNTHESIS OF 2', 3'-DIDEOXY-3'-*C*-(HYDROXYMETHYL)-4'-THIOPENTOFURANOSYL NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENT

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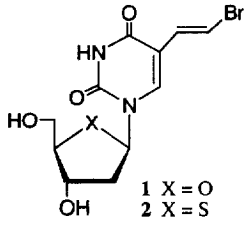
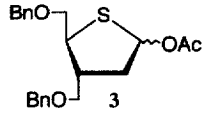
Abstract: 1-*O*-Acetyl-2,3-dideoxy-3-*C*-(hydroxymethyl)-4-thiofuranose derivative was synthesized from (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane derived from (+)-diethyl L-tartrate and the enantiomerically pure (*E*)-5-(2-bromovinyl)-1-[2', 3'-dideoxy-3'-*C*-(hydroxymethyl)-β-D-4'-thiopentofuranosyl]uracil **4** was obtained *via* coupling of silylated uracil followed by palladium-mediated coupling of methyl acrylate.

Keywords: antivirals, nucleosides.

Interest in the synthesis and biological evaluation of unusual nucleosides has continued in recent years as new structures have been found to have both anticancer and antiviral properties for clinical application. BVDU [(*E*)-5-(2-bromovinyl)-2'-deoxyuridine] **1**[1] and 4'-SBVDU **2**[2] have been shown to exhibit potent antiviral activity. In order to investigate the structure-activity relationship for this type of compound, we set ourselves toward the synthesis of compound **4** for biological evaluation. In this report we describe the syntheses of alternative new route to 2,3-dideoxy-3-*C*-(hydroxymethyl)-4-thiofuranoside **3**[3] and compound **4**.



1 X = O
2 X = S



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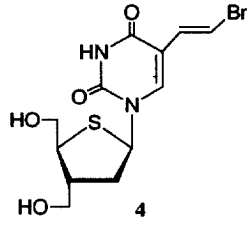

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As depicted in Scheme 1, the synthesis of 4-thiofuranoside **3** commenced with (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane **5** by a nucleophilic hydroxymethylation of oxirane ring. Reaction of **5** with (isopropoxydimethylsilyl)methyl Grignard reagent in the presence of CuI and subsequent oxidative cleavage of the silicon-carbon bond in silyl-alcohol **6** with 30 % H_2O_2 gave diol **7**.[4] Next, selective protection of the primary hydroxyl group in **7** with *tert*-butyldimethylsilyl chloride followed by mesylation with methanesulfonyl chloride afforded **8**. Then, **8** was reacted with sodium ethyl mercaptoacetate to give ester **9**. Desilylation of **9** by nBu$_4$NF and subsequent mesylation provided **10**. Intramolecular ring closure of **10** with NaH in DMF at room temperature gave tetrahydrothiophene **11** as a mixture of stereoisomers in the ratio of 2:3. Hydrolysis of **11** with LiOH followed by modified Hunsdiecker reaction of the carboxyl group of **12** using $Pb(OAc)_4$ afforded 1-*O*-acetate **3** (1:1 mixture of anomers) (31% overall yield in 10 steps from **5**). Compound **3** was then coupled in the presence of trimethylsilyl triflate with bis-silylated uracil to give the glycosylated products **13** (as 1:1 anomeric mixtures).

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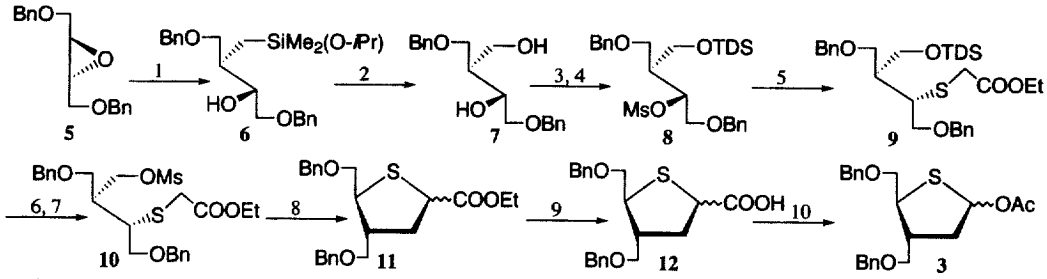
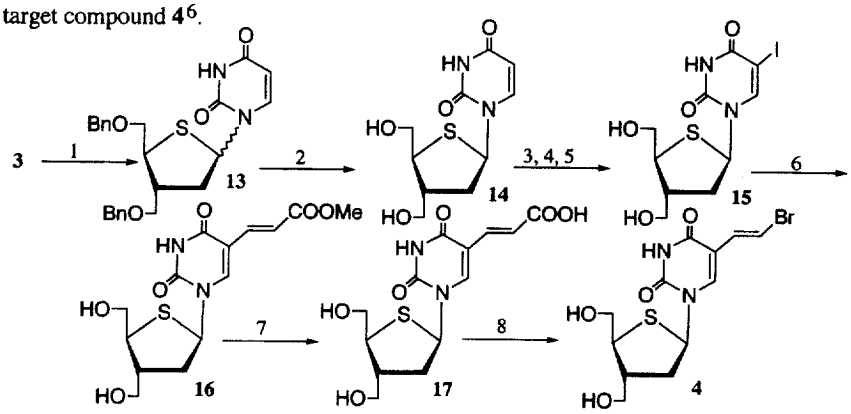


Scheme 1 *Reagents and Conditions*: 1) (*i*PrO)Me_2SiCH_2MgBr, CuI, THF-Et_2O (4:1), -25 °C, 3.5 h; 2) 30 % H_2O_2, MeOH, THF, $NaHCO_3$, 65 °C, 8h, 73 % in 2 steps; 3) TBDMSiCl, imidazole, DMF, rt, 7 h, 92 %; 4) MsCl, Et_3N, rt, 3 h, 95 %; 5) $HSCH_2COOEt$, NaH, THF, reflux, 2 h, 97%; 6) *n*Bu_4NF, THF, rt, 3 h, 87%; 7)MsCl, Et_3N, rt, 3 h, 86 %; 8) NaH, DMF, rt, 4 h, 90 %; 9) LiOH, H_2O, rt, 12 h, 84%; 10) $Pb(OAc)_4$, pyridine, THF, rt, 0.5 h, 88%.

Debenzylation of **13** (mixture of anomers) with boron trichloride afforded **14**[3]after purification by preparative reversed-phase HPLC (C-18 column), which was subjected to acetylation, iodination with LiI and subsequent hydrolysis to provide 5-iodouracil **15**. Reaction of **15** with methyl acrylate under Heck conditions[5] resulted in isolation of ester **16** in 29 % yield, together with deiodinated product in 22 % yield. Hydrolysis of **16** with aqueous NaOH followed by acidification gave acid **17**, which on treatment with N-bromosuccinimide in DMF gave the target compound **4**[6].



Scheme 2 *Reagents and Conditions*: 1) bis-silylated uracil, TMSOTf, CH_2Cl_2, -20 °C to rt, 3 h, 61 %; 2) BCl_3, CH_2Cl_2, -78 °C, 3 h, 49 %; 3) Ac_2O, pyridine, rt, 5 h, 92 %; 4) LiI, CAN, MeCN, 80 °C, 30 min, 71 %; 5) NaOMe, MeOH, rt, 1.5 h, then 1N aq.HCl, 86 %; 6) PPh_3, $Pd(OAc)_2$, Et_3N, CH_2=CHCOOMe, dioxane, 100 °C, 1 h, 29 %; 7) 1N aq.NaOH, rt, 1.5 h, then 1N aq.HCl, 74 %; 8) NBS, K_2CO_3, DMF, rt, 30 min, 32 %.

In summary, we have developed the syntheses of a new route to 2,3-dideoxy-3-*C*-(hydroxymethyl)-4-thiofuranoside and (*E*)-5-(2-bromovinyl)-1-[2', 3'-dideoxy-3'-*C*-(hydroxymethyl)-β-D-4'-thiopentofuranosyl] uracil.

References and Notes:

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2. Michael, R. D.; Paul. L. C.; Richard, T. W. *J. Med. Chem.* **1991**, *34*, 2782-2786.
3. Two groups have reported the synthesis of the same type of compound **3** that we have prepared, though their routes to these compounds are different from ours. Brånalt, J.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 1783-1788. Brånalt, J.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 4430-4432. Mann, J.; Tench, A.; J.; Weymouth-Wilson, A. C.; Shaw-Ponter, S.; Young, R. J. *J. Chem. Soc. Perkin Trans 1.* **1995**, 677-681.
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6. Evaluation of compound **4** against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay at concentrations up to 10 μg/ml, and HIV-1 in MT-4 cells by an indirect immunofluorescence assay at concentrations up to 100 μg/ml revealed this compound to be devoid of antiviral activity and cytotoxicity.