

## 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)- $\beta$ -D-4'-thiopentofuranosyl]uracil **4** was obtained *via* coupling of silylated uracil followed by palladium-mediated coupling of methyl acrylate. © 1999 Elsevier Science Ltd. All rights reserved.

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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<sup>1</sup> and 4'-SBVDU 2<sup>2</sup> 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<sup>3</sup> and compound 4.



As depicted in Scheme 1, the synthesis of 4-thiofuranoside 3 commenced with (S, S)-1,4-bis(benzyloxy)-2,3epoxybutane 5 by a nucleophilic hydroxymethylation of oxirane ring. Reaction of 5 with (isopropoxydimethylsilyl)methyl Grignard reagent in the presence of Cul and subsequent oxidative cleavage of the silicon-carbon bond in silyl-alcohol 6 with 30 % H<sub>2</sub>O<sub>2</sub> gave diol 7.<sup>4</sup> 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  $nBu_4NF$ 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)<sub>4</sub> 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).



Scheme 1 Reagents and Conditions: 1) (iPrO)Me<sub>2</sub>SiCH<sub>2</sub>MgBr, CuI, THF-Et<sub>2</sub>O (4:1), -25 °C, 3.5 h; 2) 30 % H<sub>2</sub>O<sub>2</sub>, MeOH, THF, NaHCO<sub>3</sub>, 65 °C, 8h, 73 % in 2 steps; 3) TBDMSiCl, imidazole, DMF, rt, 7 h, 92 %; 4) MsCl, Et<sub>3</sub>N, rt, 3 h, 95 %; 5) HSCH<sub>2</sub>COOEt, NaH, THF, reflux, 2 h, 97%; 6) *n*Bu<sub>4</sub>NF, THF, rt, 3 h, 87%; 7)MsCl, Et<sub>3</sub>N, rt, 3 h, 86 %; 8) NaH, DMF, rt, 4 h, 90 %; 9) LiOH, H<sub>2</sub>O, rt, 12 h, 84%; 10) Pb(OAc)<sub>4</sub>, 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, jodination with LiI and subsequent hydrolysis to provide 5-iodouracil 15. Reaction of 15 with methyl acrylate under Heck conditions<sup>5</sup> 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<sub>2</sub>Cl<sub>2</sub>, -20 °C to rt, 3 h, 61 %; 2) BCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 3 h, 49 %; 3) Ac<sub>2</sub>O, pyridine, rt, 5 h, 92 %; 4) Lil, CAN, MeCN, 80 °C, 30 min, 71 %; 5) NaOMe, MeOH, rt, 1.5 h, then 1N aq.HCl, 86 %; 6) PPh<sub>3</sub>, Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>=CHCOOMe, dioxane, 100 °C, 1 h, 29 %; 7) 1N aq.NaOH, rt, 1.5 h, then 1N aq.HCl, 74 %; 8) NBS, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 30 min, 32 %.

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

## **References and Notes:**

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- 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.