The Synthesis and Antiviral Properties of *E*-5-(2-Bromovinyl)-4′-thio-2′-deoxyuridine

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A practical 7 step synthesis of benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside from 2-deoxy-D-ribose is described and the product has been used in the synthesis of some 4′-thio-2′-deoxynucleosides which have potentially useful biological activity.

E-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU), a potent and selective inhibitor of Herpes Simplex Virus Type-1 (HSV-1) and Varicella Zoster Virus (VZV), was first synthesized in this laboratory several years ago.[1] Its high therapeutic index (*ca.* 10000)[2] is due to a combination of its efficacy and its low toxicity because it is only phosphorylated to the 5′-mono- and 5′-di-phosphates by the thymidine (and thymidylate) kinases of HSV-1 and VZV. Despite many subsequent attempts to synthesise other analogues,[3] no significant improvement in therapeutic index has been achieved. However, BVDU is a good substrate for pyrimidine phosphorylase[4] and is thus rapidly degraded *in vivo* into *E*-5-(2-bromovinyl)uracil (BVU) and 2-deoxyribose-1 phosphate. We here describe the synthesis of the 4′-thio-analogue of BVDU **1** which retains the antiviral activity, is not rapidly degraded by phosphorylases and is bioavailable.

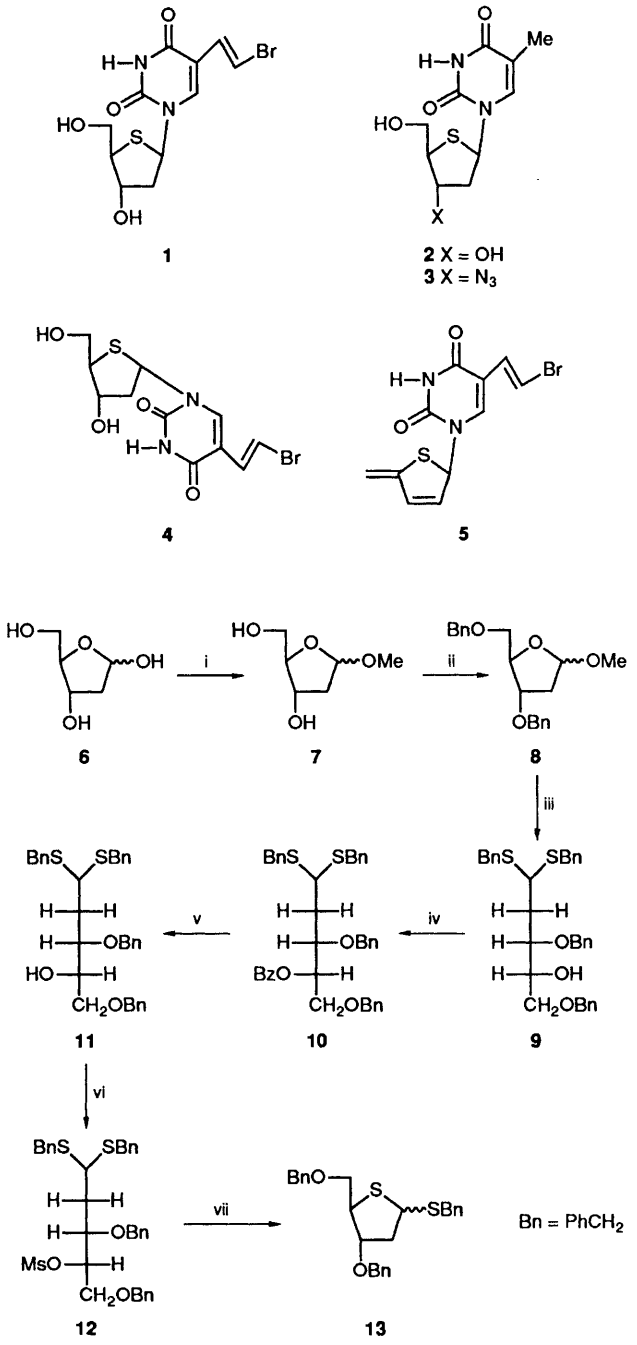
The only previous synthesis of a 4-thio-2-deoxyribose derivative suitable for nuceloside synthesis involved 14 steps[5] and only one 4′-thio-2′-deoxy nucleoside has been reported.[6] The synthesis of a suitable sugar derivative reported here contains 7 steps and has a non-optimized overall yield of 26%.

Starting from 2-deoxy-D-ribose, the synthesis of the necessary sugar analogue is shown in Scheme 1. All new compounds had satisfactory analyses, mass spectrometric data and NMR spectra. In most cases the products were purified by column chromatography on silica prior to the next step. A detailed description of this synthesis will be published elsewhere but the two key steps are inversion of the hydroxy

Table 1 Antiviral results

Compound	Concentration (μmol dm^{-3}) required					
	To inhibit virus-induced CPE[a] by 50%				To reduce cell viability by 50%	
	HSV-1	HSV-2	VZV	HIV-1	VERO	MT4
4	>100	>100	>100	—[b]	>100	>100
2	0.37	2.3	ND	—[b]	7.1	1
3	>100	>100	ND	>100	ND	>100
1	0.6	~10	0.08	ND	>500	ND
BVDU	0.03	12	0.02	ND	>100	>100

[a] CPE = cytopathic effect. [b] No activity above toxic level, 100 μmol dm^{-3}.



Scheme 1 *Reagents and conditions*: i, MeOH–HCl (the small amount of pyranoside formed is separated at the dibenzylthioacetal stage; ii, NaH, tetrabutylammonium iodide, benzyl bromide in tetrahydrofuran (THF); iii, HCl (conc.), BnSH; iv, triphenylphosphine, benzoic acid, diethyl azodicarboxylate, THF; v, NaOMe, MeOH; vi, $MeSO_2Cl$, pyridine; vii, NaI, $BaCO_3$, acetone

group at C-4 using a Mitsunobu reaction and ring closure of the resulting dibenzyl dithioacetal using conditions described by Harness and Hughes.[7]

Thus for the first time a 4-thio-deoxyribose analogue suitable for use in nucleoside synthesis is available from readily available starting materials and can be made in substantial (>100 g) quantities in the laboratory.

Using the method of Horton and Markovs,[8] we synthesised 4′-thiothymidine **2** which as an α:β mixture in the ratio of 2.8:1, could be separated as the 3′,5′-di-*O*-benzyl ethers and subsequently deblocked. The 4′-thio derivative of AZT **3** was synthesised from 4′-thiothymidine using the method of Glinski with the Yarovenko reagent.[9] The yield was low (9%) because a substantial quantity of O^2,5′-anhydro-4′-thiothymidine is produced, which is not the case in the normal thymidine series.

Condensation of the bis-trimethylsilyl ether of BVU with the 4′-thiosugar gave (after deblocking) a low yield (30%) of a complex mixture of nucleosides. Among the products identified were the expected α- and β-anomers, (**4** and **1**) and the eliminated product **5** in the ratio 1:1:2.4 of which only the β-anomer showed any biological activity.

Table 1 shows the antiviral results for compounds **1**–**4** and BVDU. These results suggest that compound **2** is a substrate for cellular and viral kinases and is hence active and toxic; compound **3** is not a substrate for either kinase and compound **1** is a substrate for the viral kinase only and is active and non-toxic. Preliminary mouse bioavailability studies have revealed that at 40 mg kg^{-1}, plasma levels in excess of 50 μmol dm^{-3} are obtained with compound **1** with a half-life of 2–3 hours.

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