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SYNTHESIS AND BIOLOGICAL EVALUATION OF THE L-ENANTIOMER OF 2'-DEOXY-5-ETHYL-4'-THIOURIDINE

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Abstract: Racemic 2'-deoxy-5-ethyl-4'-thiouridine was synthesised utilising the stereoselective iodo-lactonisation of 3-(*tert*-butyldimethylsilyl)oxy-N,N-dimethyl-4-pentenamide as the key transformation. The stereo-isomeric mixture of nucleosides was resolved using HPLC on a Chiralcel OJ column. The β-D enantiomer showed potent activity against human herpesviruses while the β-L was inactive.
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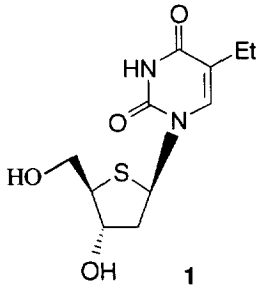
D-2'-Deoxy-5-ethyl-4'-thiouridine **1** is a potent broad spectrum anti-herpes agent[1] and we have recently published a short synthesis[2] of this material. Other 4'-thionucleosides have been reported to have potent activity against human tumour cell lines[3]. L-nucleosides such as 3'-thiacytidine[4] (3TC) and the 5-fluoro analogue[5] (FTC) have shown potent anti-human immunodeficiency virus (HIV) and anti-hepatitis B (HBV) activity. L-2',3'-didehydro-2',3'-dideoxy-4'-thiocytidine has also been shown to have significant anti-HBV and anti-HIV activity[6]. More recently β-L-dioxolane-cytidine has shown potent anti-cancer activity[7]. A trend towards greater potency for the 5'-triphosphates of L-nucleosides has been reported against woodchuck HBV DNA polymerase[8]. In addition L-FTC has been shown to be a poor substrate for cytidine deaminase whereas the D-FTC is a good substrate[5]. In view of this data we decided to synthesise the L enantiomer **2** and to evaluate its anti-viral activity. We report here a simple and efficient new racemic synthesis of 4'-thionucleosides exemplified by the 5-ethyl derivatives and the ready separation of the stereo-isomeric product mixture. This synthesis is complementary to recently described asymmetric syntheses of D and L 4'-thionucleosides of Uenishi[9] and Young[10]. We chose an approach based on the stereocontrol achievable via iodo-lactonisation of 3-O-substituted N,N-dimethylpentenamides[11]. With a 3-hydroxy or protected hydroxy group the *cis* stereoselectivity of the iodo-lactonisation is reported as > 9:1[12].



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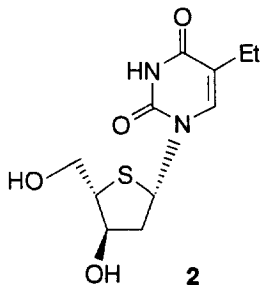
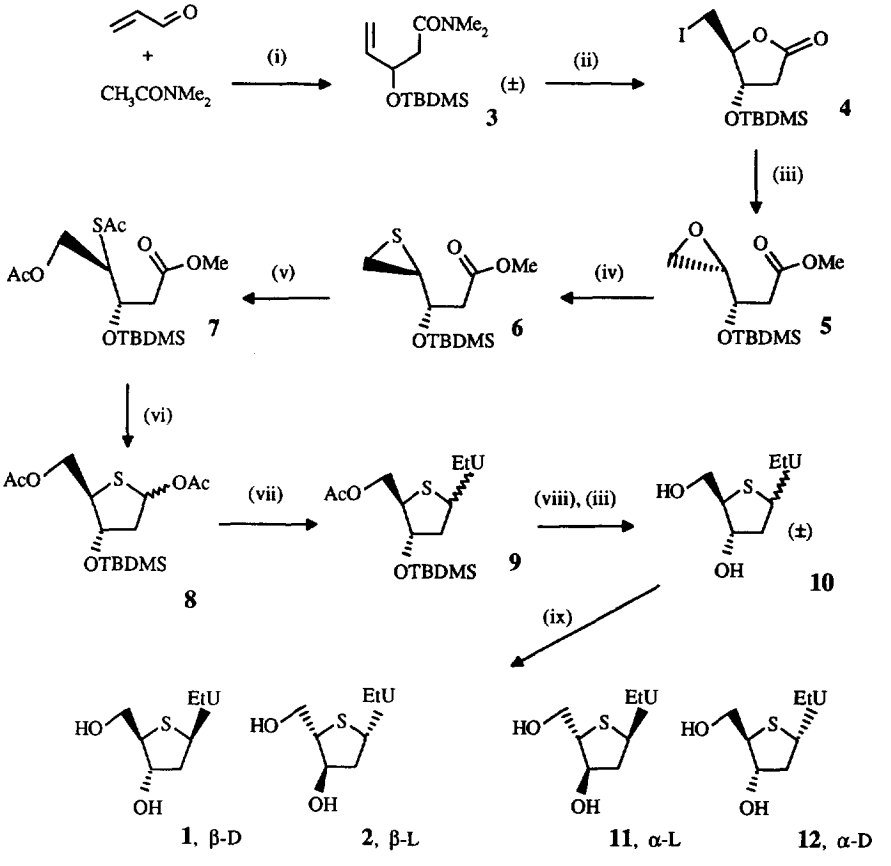


2

The full synthesis is shown in scheme 1. A simple aldol condensation of the enolate of N,N-dimethylacetamide with acreolin and treatment *in situ* with TBDMSCl gave the protected pentenamide **3** (50%). Iodo-lactonisation of this material with iodine in THF gave the key iodo-lactone **4** (70%) in a 16:1 ratio of *cis : trans* isomers. The mixture was treated with NaOMe/ MeOH to give the oxirane **5** (63%). This intermediate has also been prepared by Mukaiyama[13]. Thiirane formation with thiourea[14] proceeded uneventfully to give the intermediate **6** (70%) with inversion of configuration. Ring opening of the thiirane proved problematic and the best conditions (KOAc, Ac_2O)[15] only gave a 33% yield of the diacetate **7**. With the 4-thio-acetate intact we were now able to apply a DiBALH reduction[6] and acetylation to provide **8** in 79% overall yield. Nucleoside formation[2] using TMSOTf and silylated 5-ethyluracil gave a 60:40 ratio of the α:β protected nucleosides **9**. Deprotection using TBAF followed by NaOMe gave the racemic thiouridine **10** (50%).

Scheme 1



EtU = 5-ethyluracil

Note: All compounds to **10** are racemic.

Reagents (i) LDA / TBDMSCl/ THF, (ii) I_2 / THF / H_2O, (iii) NaOMe / MeOH, (iv) $(H_2N)_2C=S$/ MeOH, (v) KOAc / Ac_2O/ 140°, (vi) DiBALH/ THF, (vii) TMSOTf / CH_2Cl_2/ di-TMS-5-ethyluracil, (viii) TBAF / THF, (ix) HPLC separation.

The racemic α/β mixture was readily separated[16] by HPLC using a chiral phase Chiralcel OJ column (see figure 1). A near baseline separation of the four components was achieved. Thus we have established a novel stereocontrolled synthesis of the 2'-deoxy-4'-thionucleosides. We could have employed chiral enolate methodology in a modified synthesis of **3** in order to provide a homochiral synthetic route, but in our case the production of the four stereoisomers, coupled with the ease of the HPLC separation, was advantageous as the D isomers could be compared with material made by other synthetic routes[1,2].

Figure 1: Typical HPLC Trace Showing Separation of α/β Racemic Mixture

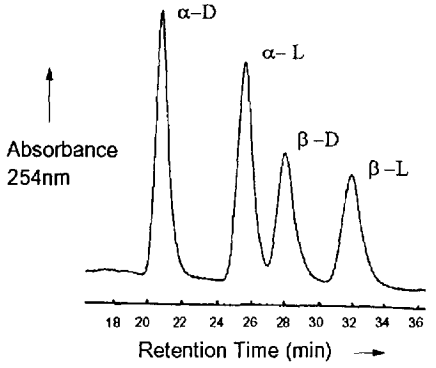


Table 1: Antiviral Activity of the D and L 2'-Deoxy-5-Ethyl-4'-Thiouridine

VIRUS	1, (β - D)	2, (β - L)
HSV-2	2.3	>50
VZV	0.76	>40
HCMV	>100	>100
HIV-1	>100	>50

Figures are IC_{50}'s, μM. > indicates no significant activity at the concentration given

The antiviral activity of the two β-enantiomers is shown in table 1. In contrast to the potent activity of the β-D enantiomer **1** the β-L-enantiomer **2** was shown to be inactive against herpes simplex virus 2 (HSV-2) and varicella zoster virus (VZV). Both enantiomers were inactive against human cytomegalovirus (HCMV) and against HIV-1[17]. Similarily both α anomers **11** and **12** were found to be inactive against all the viruses examined.

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16 Separation of the racemic α/β anomer mixture was achieved on a Chiralcel OJ analytical column (J.T. Baker Ltd.) using hexane / EtOH as eluent. The identity of the components was established by co-injection with authentic D isomers and analysis of the nmr spectra. Analytical data were as reported for compound 1 (ref 2).

17 see ref 1 for details of the anti-viral assays employed

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