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Synthesis of L-Enantiomers of 4'-Thioarabinofuranosyl Pyrimidine Nucleosides

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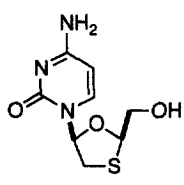
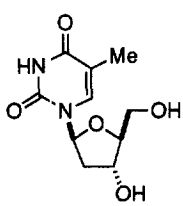
Abstract: L-Enantiomers of 4'-thioarabinofuranosyl pyrimidine nucleosides were synthesized from D-xylose. Methyl 2,3,5-tri-*O*-benzyl-D-xylofuranoside **6** was converted to the corresponding xylitol **7**, which was treated with MsCl and then Na_2S to give 1,4-anhydro-L-4-thioarabitol **8**. As previously reported, Pummerer rearrangement of **8** followed by glycosylation with a silylated thymine and *N*4-acetylcytosine derivative and deprotection gave the corresponding α- and β-L-4'-thioarabinofuranosyl pyrimidine nucleosides.

Nucleoside antimetabolites are known to inhibit the synthesis of DNA or RNA after conversion to the corresponding triphosphate analogues, and thus have antiviral and antineoplastic activities.[1] Until 1992, the biologically active analogues, which should be phosphorylated by kinases, were believed to be the D-enantiomers, as with naturally occurring nucleosides. However, this preconception changed with the discovery of the potent anti-human immunodeficiency virus type 1 activity of L-(-)-3TC **1**, which exhibited less cytotoxicity than its D-enantiomer.[2] It was also reported that L-thymidine **2** was a substrate of thymidine kinase that was coded by herpes viruses and had weak anti-herpes simplex virus type 1 (HSV-1) activity.[3] Therefore, L-nucleosides have been considered as potential selective antiviral agents.[4]



1 (3TC)



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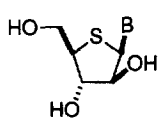

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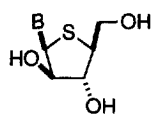

4 : B = thymin-1-yl
5 : B = cytosin-1-yl

We focused on the L-enantiomers of 4'-thioarabinonucleosides as potential antiviral agents. We recently exploited a facile synthesis of D-4'-thioarabinonucleosides **3** and reported their potent antiherpes viral

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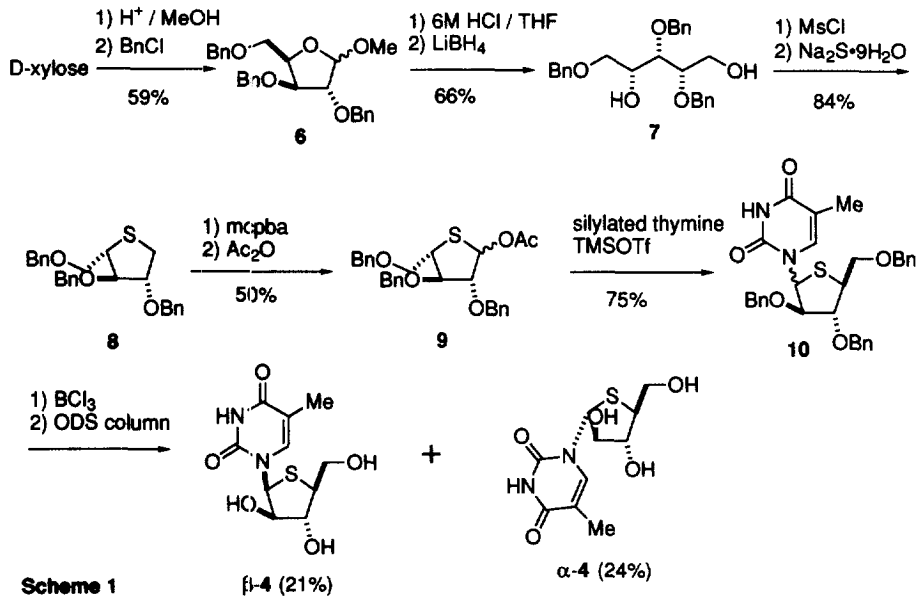
activities.[5] Although many other syntheses of D-4'-thionucleosides have been reported,[6] the synthesis of their L-enantiomers has been limited.[7] To the best of our knowledge, there has been no report concerning the synthesis of L-4'-thioarabinonucleosides. Thus, we describe here a novel and convenient synthesis of L-4'-thioarabinonucleosides from D-xylose.



Scheme 1

Methyl 2,3,5-tri-*O*-benzyl-D-xylofuranoside **6**, which was easily obtained from D-xylose in 2 steps, was hydrolyzed under acidic conditions and reduced by $LiBH_4$ in THF to give xylitol **7** in 66% yield from **6**. As originally reported in the synthesis of 4'-thioDMDC and 4'-thiogemcitabine,[8] xylitol **7** was converted to its dimesylate, which was treated with sodium sulfide in DMF at 100 °C for 3 h to give 1,4-anhydro-4-thio-L-arabitol **8** in 84% yield. Following the synthesis of D-4'-thioarabinonucleosides,[5] oxidation of **8** with *m*-chloroperbenzoic acid (mcpba) at -78 °C in CH_2Cl_2 gave a diastereo mixture of the sulfoxides, which was subjected to Pummerer rearrangement with acetic anhydride to give an anomeric mixture of L-4-thioarabinose **9** in 50% yield from **8** (Scheme 1).

Table 1: Optical Rotations of D- and L-Enantiomers of **8** and **9**[a]

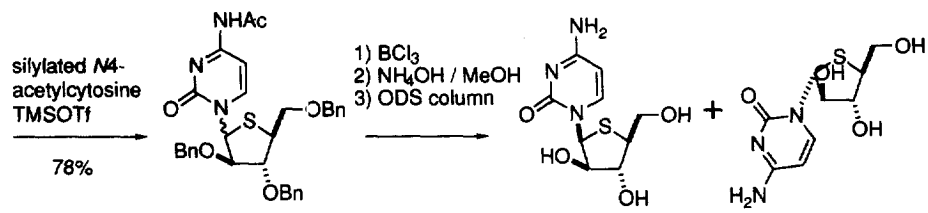
	D-**8**[b]	L-**8**	D-**9**[b]	L-**9**
$[\alpha]_D^{25}$	+0.32° (c = 2.5)	-0.38° (c = 2.5)	-30.6° (c = 2.0)	+29.8° (c = 2.0)

[a]All of the optical rotations were measured in $CHCl_3$ at 25 °C. [b]Yoshimura, unpublished data

To confirm the stereochemistry of the resulting compounds, the optical rotations of **8** and **9** were compared with those of their D-enantiomers, which were synthesized previously.[5] Although 4-thioarabinose **9** was an anomeric mixture, separation of the mixture was unsuccessful. However, the ratio of the anomers was identical for the D- and L-enantiomers ($\alpha : \beta = 1 : 2$), thus, the optical rotations of D- and L-**9** were measured as

they were. The results, summarized in Table 1, clearly supported the L-stereochemistry of **8** and **9**, as we expected. Previous synthesis of the D-enantiomers **8** and **9** was also started from a D-xylofuranoside derivative.[5] It is noteworthy that both D- and L-4-thioarabinose moiety could be synthesized from the same starting material by shifting the corresponding chiral carbons to use.

The glycosylation reaction between L-4-thioarabinose **9** and a persilylated thymine derivative in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave an anomeric mixture of benzylated L-4'-thioarabinosylthymine **10** in 75% yield. Debenzylation of **10** by treatment with BCl_3 in CH_2Cl_2 at -20 °C, followed by separation of the anomers using ODS reversed-phase column chromatography gave α- and β-4'-thioarabinosylthymine **4** in yields of 24% and 21%, respectively.[9] The determination of the α- and β stereochemistry was made by ^1H NMR and other instrumental analyses in comparison with α- and β-D-**4**. In a similar manner, glycosylation using persilylated *N*4-acetylcytosine with **9** gave 4'-thionucleoside **11**, which was deprotected (2 steps) to give α- and β-L-4'-thioarabinosylcytosine **5**[10] (Scheme 2).



Scheme 2 **11** β-**5** (19%) α-**5** (34%)

The antiviral activities of α-**4**, β-**4**, and β-**5** were evaluated against HSV-1 and herpes simplex virus type 2 (HSV-2). However, they did not show any activities up to 100 μg/mL. These compounds were not cytotoxic against human T-cell leukemia, CCRF-HSB-2, up to 100 μg/mL. Only α-**5** showed moderate anti-HSV-1 activity (ED_{50} = 10 μg/mL) without cytotoxicity against CCRF-HSB-2 (IC_{50} >100 μg/mL). α-**5** was also active against HSV-2 (ED_{50} = 10 μg/mL). Only the α-L-cytidine derivative, and not the β-L-cytidine derivative, showed antiviral activity. These results are contrasted with those of D-4'-thioarabinonucleosides: β-D-isomers possess potent anti-herpesvirus activities, while α-D-isomers are inactive.[5]

In summary, we developed a novel and convenient synthesis of L-enantiomers of 4'-thioarabinofuranosyl pyrimidine nucleosides from D-xylose. Further synthesis of L-4'-thioarabinonucleoside derivatives are underway.

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9. β-**4**: $[\alpha]_D^{25}$ -28.3° (*c* 0.13, H_2O) [*cf.* β-D-**4**: $[\alpha]_D^{25}$ +24.7° (*c* 0.18, H_2O)]; ^1H NMR (DMSO-d_6) δ 11.25 (1H, s, D_2O exchangeable), 7.93 (1H, d, *J* = 1.0 Hz), 6.07 (1H, d, *J* = 5.9 Hz), 5.69 (1H, d, *J* = 5.4 Hz, D_2O exchangeable), 5.40 (1H, d, *J* = 4.9 Hz, D_2O exchangeable), 5.21 (1H, t, *J* = 5.1 Hz, D_2O exchangeable), 4.00 (1H, q, *J* = 5.9 Hz), 3.94 (1H, q, *J* = 5.4 Hz), 3.75 (1H, dt, *J* = 4.9, 11.2 Hz), 3.66 (1H, dt, *J* = 5.9, 11.2 Hz), 3.13 (1H, q, *J* = 5.4 Hz), 1.77 (3H, s); FAB MS *m/z* 275 ($M+H^+$). Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.79; H, 5.14; N, 10.21. Found: C, 43.64; H, 5.31; N, 10.20. α-**4**: $[\alpha]_D^{25}$ -122.2° (*c* 0.13, H_2O) [*cf.* α-D-**4**: $[\alpha]_D^{25}$ +116.8° (*c* 0.15, H_2O)]; ^1H NMR (DMSO-d_6) δ 11.27 (1H, s, D_2O exchangeable), 7.84 (1H, s), 5.74 (1H, d, *J* = 7.8 Hz), 5.67 (1H, d, *J* = 5.7 Hz, D_2O exchangeable), 5.52 (1H, d, *J* = 4.9 Hz, D_2O exchangeable), 4.89 (1H, t, *J* = 5.1 Hz, D_2O exchangeable), 3.99 (1H, dt, *J* = 5.7, 7.8 Hz), 3.87-3.82 (1H, m), 3.60 (1H, dt, *J* = 4.9, 8.3 Hz), 3.52 (1H, dt, *J* = 3.4, 8.3 Hz), 3.40-3.35 (1H, m), 1.81 (3H, s); FAB MS *m/z* 275 ($M+H^+$). Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.79; H, 5.14; N, 10.21. Found: C, 43.50; H, 5.10; N, 9.82.
10. β-**5**: $[\alpha]_D^{25}$ -74.0° (*c* 0.12, H_2O) [*cf.* β-D-**5**: *lit.* $[\alpha]_D^{25}$ +72.8°; Ototani, N.; Whistler, R. L. *J. Med. Chem.* **1974**, *17*, 535-537.]; ^1H NMR (DMSO-d_6) δ 7.96 (1H, d, *J* = 7.8 Hz), 7.10, 7.01 (total 2H, brs, D_2O exchangeable), 6.33 (1H, d, *J* = 4.9 Hz), 5.69, (1H, d, *J* = 7.8 Hz), 5.56 (1H, d, *J* = 4.9 Hz, D_2O exchangeable), 5.35 (1H, d, *J* = 3.9 Hz, D_2O exchangeable), 5.05 (1H, t, *J* = 5.4 Hz, D_2O exchangeable), 3.98-3.92 (2H, m), 3.78 (1H, dt, *J* = 5.4, 11.2 Hz), 3.58 (1H, dt, *J* = 5.9, 11.2 Hz), 3.18-3.13 (1H, m); FAB MS *m/z* 260 ($M+H^+$). Anal. Calcd for $C_9H_{13}N_3O_4S \cdot 0.5H_2O$: C, 40.29; H, 5.26; N, 15.66. Found: C, 40.22; H, 5.06; N, 15.38. α-**5**: $[\alpha]_D^{25}$ -136.3° (*c* 0.10, H_2O); ^1H NMR (DMSO-d_6) δ 7.89 (1H, d, *J* = 7.3 Hz), 7.14, 7.08 (total 2H, brs, D_2O exchangeable), 5.85 (1H, d, *J* = 7.3 Hz), 5.76 (1H, d, *J* = 7.3 Hz), 5.57 (1H, d, *J* = 5.9 Hz, D_2O exchangeable), 5.44 (1H, d, *J* = 4.9 Hz, D_2O exchangeable), 4.87 (1H, t, *J* = 5.4 Hz, D_2O exchangeable), 3.93 (1H, q, *J* = 6.8 Hz), 3.82 (1H, dt, *J* = 4.4, 10.7 Hz), 3.64 (1H, dt, *J* = 4.9, 7.3 Hz), 3.45 (1H, dt, *J* = 3.9, 7.8 Hz), 3.36 (1H, ddd, *J* = 5.9, 8.3, 10.7 Hz); FAB MS *m/z* 260 ($M+H^+$). Anal. Calcd for $C_9H_{13}N_3O_4S \cdot 0.25H_2O$: C, 40.98; H, 5.16; N, 15.93. Found: C, 41.01; H, 5.04; N, 15.82.