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Synthesis of Novel 4'-*C*-Methyl-Pyrimidine Nucleosides and Their Biological Activities

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Abstract: Two novel 4'-*C*-methylnucleosides, 4'-methylBVDU **9** and 4'-methylBVaraU **10**, were synthesized. The former was derived from 3',5'-di-*O*-acetyl-2'-deoxy-4'-*C*-methyluridine **12**, and the latter was produced via glycosylation between 4-*C*-methyl-D-ribose derivative **11** and a silylated bromovinyl uracil. 4'-MethylBVDU **9** exhibited particularly potent anti-varicella-zoster virus (VZV) activity in vitro.

In the search for anti-human immunodeficiency virus (HIV) agents, some 4'-*C*-substituted nucleosides have been synthesized. Among them, 4'-azido **1**,[1] 4'-cyano **2**,[2] and 4'-methyl **3**[3] derivatives have shown potent anti-HIV activities. However, they also have potent cytotoxicities. Recently, we prepared three 4'-*C*-fluoromethylnucleosides **4**, **5**, and **6** as possible anticancer agents.[4] However, their antineoplastic activity was lower than that of the lead compound **3**.

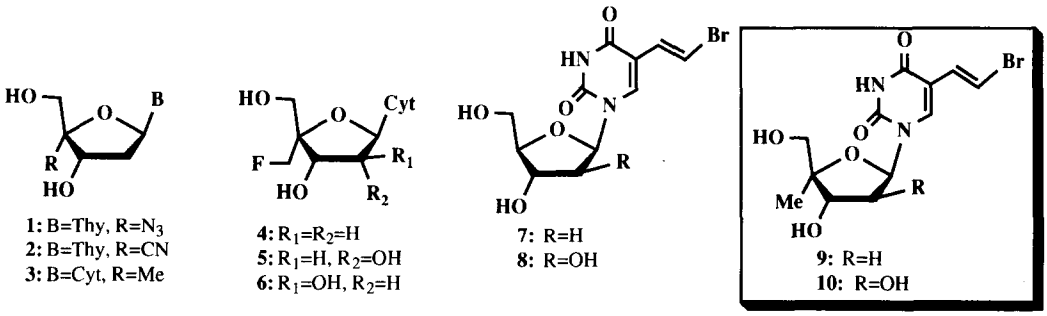

Figure 1

In the present study, we designed novel 4'-*C*-methylnucleosides, 4'-methylBVDU **9** and 4'-methylBVaraU **10**, to create more selective antiviral agents. Since BVDU **7**[5] and BVaraU **8**,[6] the lead compounds of **9** and **10**,

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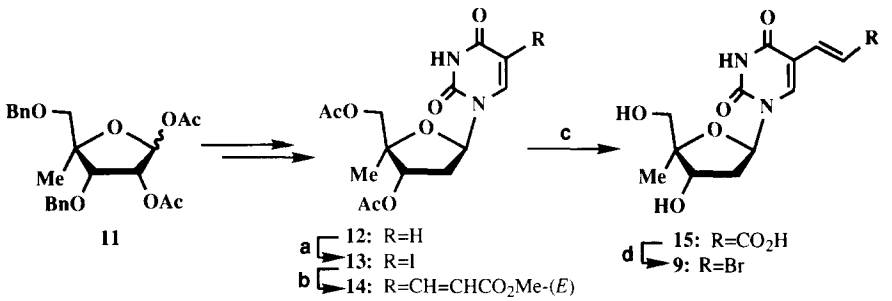
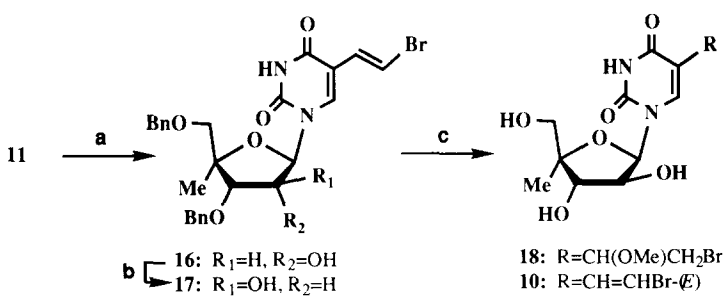
possess potent anti-herpes virus activities, particularly active against VZV,[7] the two new nucleosides are expected to have greater antiviral activities. In this communication, we describe the synthesis of 4'-*C*-methylnucleosides **9** and **10**, and present their biological activities.



a) I_2, CAN/MeCN, b) methyl acrylate, $Pd(OAc)_2$, Ph_3P, Et_3N/dioxane, c) 1N NaOH/MeOH, d) NBS, $KHCO_3$/DMF

Scheme 1

Following the synthetic method reported by Meguro,[3] we prepared 3',5'-di-*O*-acetyl-2'-deoxy-4'-*C*-methyluridine **12** from 4-*C*-methyl-D-ribose derivative **11**.[8] Iodination of the 5-position of **12** using iodine and ceric ammonium nitrate (CAN),[9] followed by a Heck reaction with methyl acrylate,[10] gave the 5-methyl acrylate **14** in 56% yield from **12**. Hydrolysis of **14** was conducted under alkaline conditions, followed by acidification with HCl to afford the carboxylic acid **15** as crystals. Since the yield of the collected crystals was low (20%), we tried recovering **15** from the filtrate. Neutralization with NaOH was followed by purification using ODS reversed-phase column chromatography and ion exchange resin to gave **15**, the total yield of which was 68%. Finally, decarboxylative bromination of **15** with anhydrous $KHCO_3$ and *N*-bromosuccinimide (NBS) in DMF[10] produced the desired compound **9**[11] in 84% yield (Scheme 1).



a) silylated BVUr, TMSOTf/MeCN, then K_2CO_3/MeOH, b) MsCl/pyridine, then 1N NaOH/EtOH-H_2O(3:1), c) BBr_3/CH_2Cl_2

Scheme 2

On the other hand, 4'-methylBVaraU **10** was easily obtained from **11**. Glycosylation between **11** and a silylated bromovinyl uracil in the presence of TMSOTf, followed by deacetylation with anhydrous K_2CO_3 in MeOH, gave the di-*O*-benzylated nucleoside **16** in 73% yield. Next, **16** was converted to its mesylate, which was treated with NaOH in EtOH-H_2O[12] to afford **17** in 58% yield. Debenzylation of **17** was conducted with

BBr_3 in CH_2Cl_2 at -78 °C. When the reaction was quenched with MeOH according to our general practice, an unexpected compound **18**[13] was obtained, the diastereomer ratio of which was 1.1/1, in 57% yield. Assuming that **18** was produced due to the catalytic effect of HBr which originated from MeOH and BBr_3, we carried out the quenching with saturated $NaHCO_3$ solution. As expected, only the debenzylation proceeded in this case, and we were able to obtain the target compound **10**[14] in 60% yield (Scheme 2).

The results of the biological evaluation of the synthesized 4'-*C*-methylnucleosides are summarized in Table 1. 4'-MethylBVDU **9** showed potent antiviral activity superior to that of the lead compound **7**. However, it also possessed cytotoxicity against human T-cell leukemia, CCRF-HSB-2, which was 4 times less potent than that of **3**. Although 4'-methylBVaraU **10** exhibited no cytotoxicity, its antiviral activity was weaker than that of the lead compound **8**. We compared resistance of 2'-deoxynucleosides, arabinofuranosylnucleosides and a 4'-*C*-methylnucleoside to pyrimidine phosphorylase by incubation with enterobacteria cells using *Klebsiella pneumoniae*.[15] BVDU **7** was very rapidly deglycosylated. After incubation for 4 hours at 37 °C, BVaraU **8** and 1-(β-D-arabinofuranosyl)-5-ethyluracil were degraded 32% and 53%, respectively, while 4'-*C*-methyl-5-ethyldeoxyuridine was deglycosylated only 6% under the same conditions (unpublished data). Thus, the introduction of a methyl group into the 4'-position resulted in marked resistance to biological deglycosylation including degradation by enterobacteria.

Table 1. Antiviral Activities and Cytotoxicity of 4'-*C*-Methylnucleosides

compound	Antiviral Activities ED_{50} (μg/mL)			Cytotoxicity IC_{50} (μg/mL)
	HSV-1[a,d]	HSV-2[b,d]	VZV[c,d]	CCRF-HSB-2[e]
9	0.0053	0.26	0.00077	0.45
10	24.4	63.5	0.18	>100
3	0.071	0.27	0.094	0.12
7	0.052	>100	0.013	>100
8	0.048	62	0.00083	>100

[a]HSV-1 VR-3 strain, [b]HSV-2 MS strain, [c]VZV Oka strain,
[d]plaque reduction assay, [e]MTT assay

In summary, we prepared two novel 4'-*C*-methylnucleosides **9** and **10** from 4-*C*-methyl-D-ribose derivative **11**, which is known to be an intermediate of other 4'-*C*-methylnucleosides. We then found that **9** had significant anti-HSV-1 and anti-VZV activities. Further synthesis of 4'-*C*-methylnucleosides with different groups at the 5-positions of their uracil moieties is underway.

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11. **9**: ^{1}H NMR (DMSO-d_6) δ 1.06 (3H, S, Me), 2.24 (2H, t, *J* = 5.9 Hz, 2'-H), 3.42 (1H, dd, *J* = 11.7, 4.9 Hz, 5-*H*H'), 3.48 (1H, dd, *J* = 11.2, 5.4 Hz, 5'-H*H'*), 4.23 (1H, q, *J* = 5.4 Hz, 3'-H), 5.15 (1H, d, *J* = 4.9 Hz, OH), 5.20 (1H, t, *J* = 5.4 Hz, OH), 6.05 (1H, t, *J* = 6.4 Hz, 1'-H), 6.83 (1H, d, *J* = 13.7 Hz, vinyl *H*H'), 7.22 (1H, d, *J* = 13.7 Hz, vinyl H*H'*), 8.19 (1H, s, 6-H), 11.52 (1H, br s, NH); FAB MS *m/z* 347, 349 (M+H$^+$). Anal. Calcd for $C_{12}H_{15}BrN_2O_5.0.25H_2O$: C, 40.99; H, 4.44; N, 7.97. Found: C, 40.95; H, 4.38; N, 7.91.
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13. The diastereomer ratio was determined based on the ^{1}H NMR spectrum. **18**: ^{1}H NMR (DMSO-d_6) δ 1.07 (3H, S, Me), 3.23 (1.44H, s, OMe), 3.24 (1.56H, s, OMe), 3.37-3.60 (3H, m, 2 x 5-H, C*H*H'Br), 3.65 (0.48H, dd, *J* = 10.3, 3.4 Hz, CH*H'*Br), 3.71 (0.52H, dd, *J* = 10.8, 3.9 Hz, CH*H'*Br), 3.94-4.00 (1H, m, 3'-H), 4.16 (1H, q, *J* = 5.4 Hz, 2'-H), 4.27 (0.52H, dd, *J* = 7.3, 3.9 Hz, C*H*OMe), 4.34 (0.48H, dd, *J* = 7.8, 3.4 Hz, C*H*OMe), 5.11 (0.48H, t, *J* = 4.9 Hz, OH), 5.14 (0.52H, t, *J* = 5.4 Hz, OH), 5.37 (0.52H, d, *J* = 5.4 Hz, OH), 5.39 (0.48H, d, *J* = 4.9 Hz, OH), 5.57 (0.52H, d, *J* = 5.4 Hz, OH), 5.62 (0.48H, d, *J* = 5.4 Hz, OH), 6.02 (0.52H, d, *J* = 5.9 Hz, 1'-H), 6.04 (0.48H, d, *J* = 5.4 Hz, 1'-H), 7.76 (0.48H, s, 6-H), 7.83 (0.52H, s, 6-H), 11.38 (0.52H, s, NH), 11.38 (0.48H, s, NH); FAB MS *m/z* 395, 397 (M+H$^+$).
14. **10**: ^{1}H NMR (DMSO-d_6) δ 1.07 (3H, S, Me), 3.46 (1H, dd, *J* = 10.8, 5.4 Hz, 5-*H*H'), 3.50 (1H, dd, *J* = 11.2, 5.4 Hz, 5'-H*H'*), 3.95 (1H, t, *J* = 5.4 Hz, 3'-H), 4.16 (1H, q, *J* = 5.9 Hz, 2'-H), 5.23 (1H, t, *J* = 5.4 Hz, OH), 5.38 (1H, d, *J* = 5.4 Hz, OH), 5.59 (1H, d, *J* = 5.4 Hz, OH), 5.99 (1H, d, *J* = 5.4 Hz, 1'-H), 6.81 (1H, d, *J* = 13.7 Hz, vinyl *H*H'), 7.20 (1H, d, *J* = 13.7 Hz, vinyl H*H'*), 8.06 (1H, s, 6-H), 11.50 (1H, br s, NH); FAB MS *m/z* 363, 365 (M+H$^+$). Anal. Calcd for $C_{12}H_{15}BrN_2O_6$: C, 39.69; H, 4.16; N, 7.71. Found: C, 39.71; H, 4.31; N, 7.53.
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