The Selective Protection of Uridine with a *p*-Methoxybenzyl Chloride: A Synthesis of 2′-*O*-Methyluridine

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Synopsis. 2′-*O*-Methyluridine was prepared through 5 steps from uridine by use of *p*-methoxybenzyl group (PMB) as an N^3-protecting group of uridine. A chemoselective protection method has been developed by use of DBU as a base and deprotection was effected by $AlCl_3$–anisole system.

Protection of the N^3-imide function in uridine moiety has attracted considerable attention and many protecting groups have been reported.[1] We reported that *p*-methoxybenzyl (PMB) was an effective protecting group for the N^3-imide group of 5-fluorouridine (FUR) and utilized it in a facile synthesis of 5′-*O*-acryloyl-5-fluorouridine.[2] PMB group was selectively introduced in the presence of OH group by use of *N*,*N*-diisopropylethylamine as a base and removed by treatment with $AlCl_3$ and anisole under mild conditions. In this paper we applied this protecting group to uridine moiety[3] and found that it is also useful as a protecting group for the N^3-imide group of uridine, thus demonstrating in a short step synthesis of 2′-*O*-methyluridine (**5**).[1b,4]

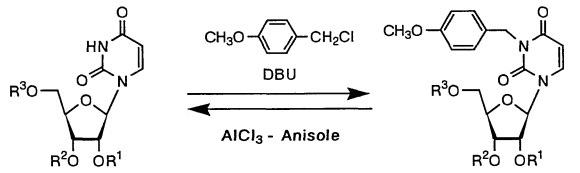

Fig. 1.

Following scheme shows the present method for the synthesis of 2′-*O*-methyluridine. In the first place, 3′,5′-protected uridine **1**[5] was allowed to react with *p*-methoxybenzyl bromide and *N*,*N*-diisopropylethylamine, according to the procedure described before,[2] but no N^3-alkylated product **2** was obtained. When the reaction was carried out in DMF, with K_2CO_3 as a base, inseparable mixture of **2** and 2′-*O*,*N*-dialkylated compound were obtained. After screening of bases, it was found that 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) was effective in the selective alkylation of uracil moiety. Treatment of **1** with *p*-methoxybenzyl bromide (2.6 equiv) in the presence of DBU (2.2 equiv) in CH_3CN at room temperature for 1.5 h gave selectively **2** in 80% yield, the structure of which was clearly confirmed on the basis of the chemical shift of C5 of ^{13}C NMR to be N^3-alkylated product, not O^4-alkylated compound.[1d,6] The use of *p*-methoxybenzyl chloride as an alkylating agent increased the yield of **2** to 92%. 2′-*O*-Methylation, followed by HF catalyzed hydrolysis of tetraisopropyldisiloxane-1,3-diyl group afforded a diol **4**. A mixture of **4** and $AlCl_3$ in anisole was heated at 65 °C for 2 h to give **5** in 81% yield. The overall yield of **5** from uridine was 67% in 5 steps.

In conclusion, PMB group was found to be an efficient protecting group of uridine moiety, with following features; 1) N^3-imide function of uridine is protected selectively in the presence of OH group by use of DBU as a base, 2) it is deprotected by the combined use of $AlCl_3$ and anisole without affecting N-glycosidic bond under mild conditions. Since PMB-protected uridine derivatives are stable to acid and alkali, they can be used for the synthesis of *O*-alkyl-substituted uridine derivatives.

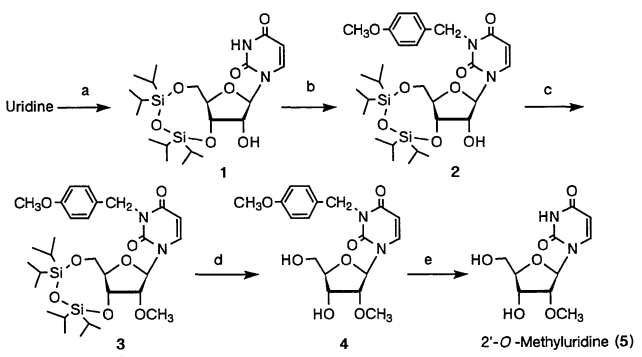

Fig. 2. Reagents and conditions: a. Ref. 1b). b. *p*-Methoxybenzyl chloride (1.8 equiv), DBU (2.0 equiv), CH_3CN, 45 °C, 6 h, 92%. c. CH_3I, Ag_2O, reflux, 5 h, 100%. d. aq HF, CH_3CN, r.t., 94%. e. $AlCl_3$ (8 equiv), anisole, 65 °C, 2 h, 81%.

Experimental

The melting points were recorded on a Yamato melting point apparatus and are uncorrected. NMR spectra were observed with a JEOL GSX-270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on Hitachi EPI G-3 spectrometer.

3-(4-Methoxyphenylmethyl)-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (2): To a mixture of 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (68.1 mg, 0.14 mmol) and 4-methoxybenzyl chloride (34 μl, 0.25 mmol) in CH_3CN (1 ml) was added DBU (42 μl, 0.28 mmol) and the mixture was heated at 60 °C for 30 min. After cooling to 0 °C, the mixture was diluted with 5% $KHSO_4$ solution. The organic phase was separated, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After the solvent had been removed in vacuo, the residue was purified by column chromatography on silica gel (hexane:AcOEt=3:1) to give **2** as a foam in 92% yield. ^1H NMR ($CDCl_3$) δ=0.9—1.15 (28H, m), 3.23 (1H, brs, OH), 3.79 (3H, s, OCH_3), 3.98 (1H, dd, $J_{4',5'}$=2.7 Hz, $J_{5',5''}$=13.1 Hz, H-5′), 4.05—4.16 (2H, m, H-2′, H-4′), 4.19 (1H, dd, $J_{4',5''}$=1.0 Hz, H-5″), 4.35 (1H, dd, J=4.9 Hz, 8.9 Hz, H-3′), 4.97, 5.07 (2H, AB q, J=13.4 Hz, CH_2), 5.72 (1H, d, $J_{5,6}$=8.2 Hz, H-5), 5.72

(1H, s, H-1′), 6.80 (2H, d, J=8.9 Hz, aromatic), 7.45 (2H, d, J=8.9 Hz, aromatic), and 7.63 (1H, d, H-6); IR ($CHCl_3$) 3500, 2980, 1645, 1425, and 1025 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=12.16, 12.63, 13.08, 16.53, 16.63, 16.67, 16.73, 16.96, 17.00, 17.11, 17.17, 43.16, ($ArCH_2$), 54.78 (OCH_3), 59.88 (C-5′), 68.60 (C-3′), 74.96 (C-2′), 81.48 (C-4′), 91.12 (C-1′), 101.11 (C-5), 113.31 (aromatic C-3″, 5″), 128.59 (aromatic C-1″), 130.57 (aromatic C-2″, 6″), 137.47 (C-6), 150.33 (C-2), 158.78 (aromatic C-4″), and 162.38 (C-4). Found: C, 57.03; H, 7.64; N, 4.27%. Calcd for $C_{29}H_{46}N_2O_8Si_2$: C, 57.39; H, 7.64; N, 4.62%.

3-(4-Methoxyphenylmethyl)-2′-*O*-methyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (3): A mixture of **2** (267 mg, 0.44 mmol), Ag_2O (837 mg, 3.61 mmol), and MeI (3.0 ml) was refluxed for 5 h. The mixture was diluted with Et_2O and filtrated over Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane:AcOEt=4:1) to give **3** as a foam in quantitative yield. ^1H NMR ($CDCl_3$) δ=0.90—1.17 (28H, m), 3.66 (1H, d, $J_{2',3'}$=4.8 Hz, H-2′), 3.68 (3H, s, OCH_3), 3.78 (3H, s, $ArOCH_3$), 3.95 (1H, dd, $J_{4',5'}$=2.1 Hz, $J_{5',5''}$=13.7 Hz, H-5′), 4.10 (1H, dd, $J_{3',4'}$=9.7 Hz, H-4′), 4.16 (1H, dd, H-3′), 4.23 (1H, d, H-5″), 4.79, 5.12 (2H, AB q, J=13.7 Hz, CH_2), 5.72 (1H, d, $J_{5,6}$=8.2 Hz, H-5), 5.75 (1H, s, H-1′), 6.83 (2H, d, J=8.9 Hz, aromatic), 7.46 (2H, d, J=8.9 Hz, aromatic), and 7.84 (1H, d, H6); IR ($CHCl_3$) 3010, 1645, 1440, 1200, 1025, and 720 cm^{-1}. Found: C, 58.10; H, 7.80; N, 4.20%. Calcd for $C_{30}H_{48}N_2O_8Si_2$: C, 58.03; H, 7.79; N, 4.51%.

3-(4-Methoxyphenylmethyl)-2′-*O*-methyluridine (4): To a solution of **3** (132 mg, 0.213 mmol) in CH_3CN (2 ml) was added 60% aqueous HF solution and the mixture was stirred at room temperature for 4 h. An aqueous $NaHCO_3$ solution (5%) was added to the mixture and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2:AcOEt=1:1) to afford **4** (76 mg, 0.20 mmol) as an amorphous in 94% yield. ^1H NMR ($CDCl_3$:CD_3OD (v/v)=5:1) δ=2.59 (2H, s, OH), 3.59 (3H, s, OCH_3), 3.78 (3H, s, $ArOCH_3$), 3.75—3.83 (1H, m, H-5′), 3.85 (1H, dd, $J_{1',2'}$=2.7 Hz, $J_{2',3'}$=5.2 Hz, H-2′), 3.92—4.02 (2H, m, H-4′, H-5″), 4.26 (1H, dd, $J_{3',4'}$=6.7 Hz, H-3′), 5.00, 5.08 (2H, AB q, J=14 Hz, CH_2), 5.77 (1H, d, $J_{5,6}$=8.2 Hz, H-6), 5.87 (1H, d, H-1′), 6.80—6.88 (2H, m, aromatic), 7.38—7.50 (2H, m, aromatic), 7.90 (1H, d, H5); IR (Nujol) 3350, 1680, 1640, 1600, 1240, and 1105 cm^{-1}. Found: C, 57.12; H, 5.97; N, 7.00%. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.14; H, 5.86; N, 7.40%.

2′-*O*-Methyluridine (5): A solution of $AlCl_3$ (282 mg, 2.1 mmol) in anisole (1.0 ml) was added to **4** (100 mg, 0.26 mmol) under N_2 atmosphere, and the mixture heated to 65 °C for 2 h. Hydrochloric acid (1 mol dm^{-3}) was added to the reaction mixture. Aqueous layer was washed with ether and concentrated in vacuo to leave an oil, which was purified by thin-layer chromatography (SiO_2, ethyl acetate–methanol, 10:1) to afford **5** as crystals in 81% yield.; mp 159.5—160.5 °C. (lit, 159—161 °C).[4b] ^1H NMR (D_2O, internal standard of HDO as 4.64) δ=3.35 (3H, s, CH_3), 3.64 (1H, dd, $J_{4',5'}$=4.3 Hz, $J_{5',5''}$=12.8 Hz, H-5′), 3.76 (1H, dd, $J_{4',5''}$=2.7 Hz, H-5″), 3.89 (1H, dd, $J_{1',2'}$=4.0 Hz, $J_{2',3'}$=5.8 Hz, H-2′), 3.92—3.97 (1H, m, H-4′), 4.17 (1H, t, $J_{3',4'}$=5.8 Hz, H-3′), 4.64 (2H, s, OH), 5.73 (1H, d, $J_{5',6'}$=8.2 Hz, H-5), and 7.74 (1H, d, H-6).

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3) Independent from our work, Danishefsky already employed PMB group as a protecting group for the N^3-imide function of uridine in a synthesis of tunicamycin subunit, whereby the protecting group was deprotected by use of ammonium cerium (IV) nitrate. See, S. J. Danishefsky, S. L. DeNimno, S. Chen, L. Boisvert, and M. Barbachyn, *J. Am. Chem. Soc.*, **111**, 5810 (1989).

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5) **1** was prepared from uridine in 95% yield according to the method shown in Ref. 1b).

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