A Synthesis of 5'-Amino-3',5'-dideoxyuridine

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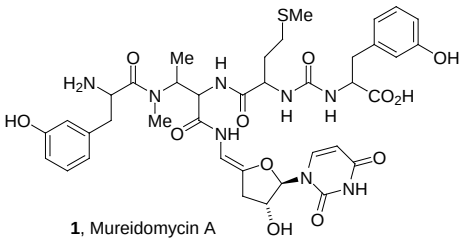
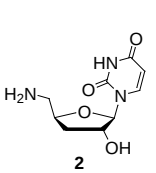
Abstract. The synthesis of 3',5'-dideoxy-5'-aminouridine starting from uridine is described.

Key words: 3',5'-dideoxy-5'-aminouridine, mureidomycin, nucleoside, deoxygenation, azidation

The synthesis of pyrimidine nucleosides containing a modified glycosyl moiety has resulted in the generation of molecules with significant biological activity. Uridine nucleosides which possess a 5'-amino group have been studied for their antiviral,[1] antibacterial[2] and antifungal[3] properties. Similarly, uridine nucleosides lacking the 3'-hydroxyl group have been found to exhibit potent antitumor[4] and antiparasitic[5] activity. A recently discovered family of antibiotics, the mureidomycins[6] (**1**), the pacidamycins,[7] and the napsamycins[8] were all found to contain an unusual pyrimidine nucleoside having both of these types of functionality. Ongoing efforts toward the synthesis of analogs of these natural products required access to synthetically useful quantities of suitably protected derivatives of 5'-amino-3',5'-dideoxyuridine (**2**). A search of the literature did not reveal any previous reports for the preparation of this compound. Described herein is an efficient procedure to synthesize an *O*-TBS-(*tert*-butyldimethylsilyl)-protected derivative of **2**.



1, Mureidomycin A



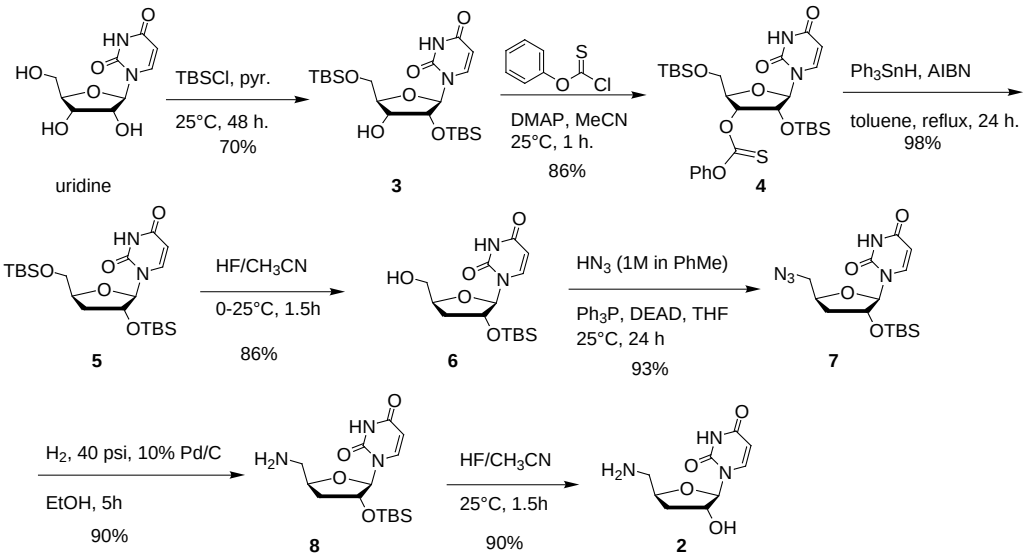
2

As shown in the Scheme, commercially available uridine was selectively protected as the 2',5'-*O*-TBS derivative **3** following the published procedure.[9] The 3'-hydroxyl group was treated with phenyl chlorothionoformate in the presence of 4-(dimethylamino)pyridine (DMAP) to give thiocarbonate **4**.[10] Using a catalytic amount of DMAP, a small quantity of the desired product was isolated after 72 hours. Increasing the amount of DMAP greatly reduced the reaction time, and when 4 equivalents were used, the reaction was complete furnishing **4** in good yield (86%) after only a few hours. Reductive deoxygenation[10,11] was carried out using tributyl or triphenyltin hydride in the presence of the radical initiator AIBN to give the corresponding 3'-deoxyuridine derivative **5** in 98% yield. Selective deprotection[12] of the 5'-*O*-silyl ether was accomplished using hydrofluoric acid in acetonitrile to give the primary alcohol **6** (86%).

Several methods for the conversion of the uridine 5'-hydroxyl group to the corresponding amine have been reported in the literature. The classical method involves formation of the mesylate or tosylate derivative followed by S_N2 displacement with azide and subsequent reduction to produce the corresponding amine.[13] More recently, Yamamoto[14] reported the one-pot synthesis of azido derivatives of nucleosides by reaction of the primary alcohol with a mixture of $LiN_3/Ph_3P/CBr_4$. When alcohol **6** was subjected to either of these conditions, only starting materials were recovered. The Mitsunobu reaction[15] is an effective method for the conversion of alcohols to a variety of different functional groups and this protocol was extended to generate the desired 5'-azido intermediate. Alcohol **6** was subjected to standard Mitsunobu conditions (DEAD/Ph_3P) in the presence of a freshly prepared toluene solution of HN_3 to give an excellent yield (93%) of azide **7**. Catalytic hydrogenation with 10% Pd/C produced the 2'-*O*-TBS-protected amine **8** in 90% yield. This intermediate should be useful as a template for the synthesis of saturated analogs of Mureidomycin A (**1**), which could be obtained via peptide coupling reactions with the free 5'-amino group. A small amount of **8** was deprotected using HF to give the title compound **2** in an overall yield of 38% from uridine.

5'-Amino-3',5'-dideoxyuridine (**2**) was prepared from uridine in a straightforward and efficient manner. This procedure also represents a useful application of the Mitsunobu reaction as a means to introduce nitrogen functionality in the pentose moiety of nucleosides. This reaction sequence should be applicable to the synthesis of similarly functionalized analogs of other pyrimidine as well as purine nucleosides.

^{1}H NMR spectra were obtained on a Bruker AC 300 MHz spectrometer and chemical shifts were reported in parts per million relative to TMS (0.00), $CDCl_3$ (7.24), DMSO-d_6 (2.54), or D_2O (4.80). The numbers in parentheses were specified by Cambridge Isotope Labs, Andover, MA. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR as KBr pellets or thin films from CH_2Cl_2 on NaCl plates. Optical rotations were determined on a Rudolph Research Autopol III automatic polarimeter at a wavelength of 589 nm (sodium D line) with a 1.0 dm cell and a volume of 1 mL. Specific rotations are reported in degrees per decimeter at 25 °C and



Scheme

concentration of grams per 100 mL. Melting points were obtained using a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories in Phoenix, AZ and are accurate to within ±0.4%. Mass spectra were obtained on a Fisons VG Autospec at the Chemistry Department at Colorado State University. Column chromatography was performed with Merck silica gel grade 60, 230−400 mesh, 60 Å. Analytical preparatory TLC was performed with Merck Kieselgel 60 F_{254} plates. Reagents and solvents were all commercial grade and used without further purification with the exception of THF (distilled over sodium, benzophenone), CH_2Cl_2 (distilled over CaH_2), Et_2O (distilled over sodium, benzophenone), and DMF and HMPA (dried over 4Å molecular sieves). All air-sensitive reactions were run under an atmosphere of nitrogen or argon. All glassware was oven or flame-dried prior to use.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)uridine (3)

Uridine (20.0 g, 81.9 mmol) was dissolved in anhyd pyridine (160 mL) and stirred at r.t. for 10 min. *tert*-Butyldimethylsilyl chloride (30.86 g, 204.8 mmol) was added in a single portion and the mixture was stirred at r.t. for 48 h. The mixture was concentrated under vacuum and the resulting crude material was dissolved in CH_2Cl_2 (500 mL), washed with aq 5% $NaHCO_3$ solution (2 × 100 mL), dried ($MgSO_4$), and concentrated to a white foam. The product was purified by silica gel (800 g) column chromatography (Et_2O/hexane, 2:1 v/v) to yield 26.3 g (70%) of **3** as a white solid; mp 122 °C (Lit.[9] mp 122 °C); $[\alpha]_D$ +20.6 (*c* = 0.5, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (12 H, m), 0.88 (9 H, s), 0.90 (9 H, s), 2.61 (1 H, d, *J* = 4.8 Hz, D_2O exchangeable), 3.79 (1 H, 1/2Abx, *J* = 1.1, 11.7 Hz), 3.96 (1 H, 1/2Abx, *J* = 1.5, 11.7 Hz), 4.05−4.18 (3 H, m), 5.66 (1 H, dd, *J* = 2.2, 8.1 Hz), 5.94 (1 H, d, *J* = 4.1 Hz), 7.96 (1 H, d, *J* = 8.1 Hz), 9.41 (1 H, s, D_2O exchangeable).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.5, −5.4, −5.2, −4.7, 18.0, 18.4, 25.7, 25.9, 62.5, 70.3, 76.5, 84.7, 88.5, 102.3, 140.0, 150.2, 163.3.

IR (neat): ν = 3452, 3190, 1683 cm^{-1}.

Phenyl Chlorothionoformate

Phenol (10.0 g, 106.3 mmol) was dissolved in $CHCl_3$ (64 mL) and aq 5% NaOH solution (95 mL) and cooled to 0 °C in an ice bath. Thiophosgene (8.1 mL, 106.3 mmol) was added dropwise and the reaction was warmed to 25 °C and stirred for 2 h. The layers were separated and the organic phase was washed with 0.1 M HCl and H_2O, dried ($MgSO_4$) and concentrated to a yellow oil. Kugelrhor distillation (bp 78−81 °C/8 Torr, Lit.[16,17] bp 81−83 °C/6 Torr) gave 15.6 g (85%) of phenoxythiocarbonyl chloride (phenyl chlorothionoformate) as a bright yellow oil.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*O*-(phenoxythiocarbonyl)uridine (4)

To a stirred solution of **3** (24.84 g, 53.97 mmol) and 4-(dimethylamino)pyridine (24.90 g, 204.0 mmol) in anhyd MeCN (250 mL) was added dropwise phenyl chlorothionoformate (7.90 mL, 57.10 mmol) under N_2 at r.t.. After 1 h, all starting material had been consumed. The solvent was removed under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (400 mL) and extracted with cold 1.0 M HCl (2 × 100 mL), aq sat. $NaHCO_3$ (2 × 100 mL), and brine (2 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil which was purified by silica gel (500 g) column chromatography (4:1 to 1:2 hexanes/EtOAc) to yield 27.00 g (86%) of **4** as a light yellow crystalline solid; mp 54−56 °C (dec.); $[\alpha]_D$ +46.2 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12 (12 H, m), 0.91 (18 H, d, *J* = 9.52 Hz), 3.81 (1 H, 1/2ABq, *J* = 15.3 Hz), 3.97 (1 H, 1/2 ABq, *J* = 12.8 Hz), 4.36 (1 H, m), 4.42 (1 H, t, *J* = 4.48 Hz), 5.49 (1 H, t, *J* = 4.76 Hz), 5.61 (1 H, d, *J* = 8.1 Hz), 5.92 (1 H, d, *J* = 3.8 Hz), 6.92−7.39 (5 H, m), 7.88 (1 H, d, *J* = 8.1 Hz), 8.78 (1 H, s, D_2O exchangeable).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.4, −5.1, −4.8, 18.0, 18.4, 25.6, 25.9, 62.1, 74.2, 77.5, 79.6, 81.9, 89.0, 102.4, 121.6, 126.7, 129.6, 139.6, 150.3, 153.2, 162.5, 189.2.

IR (neat): ν = 3413, 1682 cm^{-1}.

HRMS (FAB): *m/z* calcd for $C_{28}H_{45}N_2O_7SSi_2$ (MH^+): 609.2503. Found: 609.2487.

Anal. calcd for $C_{28}H_{44}N_2O_7SSi_2$: C, 55.23; H, 7.28; N, 4.60. Found: C, 55.47; H, 7.06; N, 4.57.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-deoxyuridine (5)

Compound **4** (7.51 g, 12.90 mmol) was dissolved in anhyd toluene (180 mL) and 2,2'-azobis(2-methylpropionitrile) (AIBN, 2.78 g, 16.93 mmol) was added and the solution was degassed with N_2 for

10 min. Triphenyltin hydride (7.90 g, 22.51 mmol) was added in a single portion and the solution was heated at reflux temperature for 23 h. The solvent was removed under reduced pressure and the crude material was purified by silica gel (250 g) column chromatography (hexanes to 1:2 hexanes/EtOAc) to give 5.77 g (98%) of **5** as a white foam; $[\alpha]_D$ +9.7 (*c* = 1.3, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (12 H, m), 0.92 (18 H, m), 1.69−1.76 (1 H, m), 2.01−2.09 (1 H, m), 3.72 (1 H, 1/2 ABq, *J* = 12.1 Hz), 4.18 (1 H, 1/2 ABq, *J* = 12.0 Hz), 4.35 (1 H, d, *J* = 3.9 Hz), 4.47−4.53 (1 H, m), 5.62 (1 H, d, *J* = 8.1 Hz), 5.73 (1 H, s), 8.16 (1 H, d, *J* = 8.1 Hz), 8.50 (1 H, s, D_2O exchangeable).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.6, −5.5, −5.2, −4.7, 17.8, 18.4, 23.3, 32.7, 39.3, 62.7, 81.6, 92.3, 100.9, 136.3, 140.3, 150.1, 163.7.

IR (neat): ν = 3171, 1682 cm^{-1}.

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{41}N_2O_5Si_2$ (MH^+): 457.2554. Found: 457.2561.

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxyuridine (6)

Compound **5** (2.01 g, 4.40 mmol) was dissolved in MeCN (220 mL) and cooled to 0 °C with an ice/water bath. The mixture was treated with a 5% solution of HF in MeCN (17.0 mL) and stirred at 0 °C for 30 min. The mixture was allowed to warm to r.t. and stirred for another hour. The mixture was quenched with solid $NaHCO_3$, filtered, concentrated under reduced pressure and the residue was chromatographed over silica gel (100 g) (15:1 CH_2Cl_2/MeOH) to yield 1.30 g (86%) of **6** as a white foam; mp 58−60 °C (dec.); $[\alpha]_D$ −9.8 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (3 H, s), 0.11 (3 H, s), 0.86 (9 H, s), 1.79 (1 H, ddd, *J* = 2.6, 5.9, 12.8 Hz), 2.02−2.11 (1 H, m), 2.82 (1 H, br s, D_2O exchangeable), 3.71 (1 H, 1/2 ABx, *J* = 2.6, 12.1 Hz), 4.07 (1 H, 1/2 ABx, *J* = 1.8, 12.1 Hz), 4.43−4.51 (2 H, m), 5.60 (1 H, d, *J* = 1.8 Hz), 5.67 (1 H, d, *J* = 8.1 Hz), 7.82 (1 H, d, *J* = 8.0 Hz), 9.36 (1 H, br s, D_2O exchangeable).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.7, 17.9, 25.7, 33.6, 62.6, 76.5, 81.2, 94.0, 101.3, 141.0, 150.1, 163.6.

IR (neat): ν = 3399, 1684 cm^{-1}.

HRMS (FAB): *m*/*z* calcd for $C_{15}H_{27}N_2O_5Si$ (MH^+):343.1689. Found 343.1697.

Anal. Calcd for $C_{15}H_{26}N_2O_5Si$: C, 52.61; H, 7.65; N, 8.18. Found: C, 52.73; H, 7.70, N; 8.23.

Preparation of Hydrazoic Acid Solution

A slurry of NaN_3 (5.0 g, 0.08 mmol) in H_2O (5 mL) was covered with anhyd toluene (50 mL) and cooled to 0 °C while stirring under N_2. Conc. H_2SO_4 (2.2 mL, 0.04 mmol) was added dropwise over 10 min. Upon completion of the addition, the flask was placed in a −78 °C bath and the toluene was decanted off and dried ($MgSO_4$). A small aliquot of the toluene solution was diluted with H_2O and titrated with aq 1 M NaOH solution using phenolphthalein indicator. Typical concentrations of HN_3 ranged from 0.6 to 1.5 M. These solutions were generally used immediately, but could be stored at 0 °C for several days if necessary.

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxyuridine (7)[18]

2'-*O*-(*tert*-butyldimethylsilyl)-3'-deoxyuridine (**6**; 500 mg, 1.46 mmol) was dissolved in freshly distilled THF (10 mL) and stirred at r.t. under Ar. Ph_3P (422 mg, 1.61 mmol) was added followed by HN_3 (1.52 mL of a 1.06 M solution in toluene, 1.61 mmol) and DEAD (254 mL, 1.61 mmol). The mixture was stirred at r.t. under argon for 24 h. The solvent was removed and the residue was chromatographed over silica gel (20:1 CH_2Cl_2/MeOH) to yield 498 mg (93%) of **7** as a colorless oil; $[\alpha]_D$ −38.6 (*c* = 0.3, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (3 H, s), 0.12 (3 H, s), 0.88 (9 H, s), 1.69−2.01 (2 H, m), 3.55 (1 H, 1/2ABx, *J* = 3.9, 13.5 Hz), 3.82 (1 H, 1/2ABx, *J* = 3.3, 13.5 Hz), 4.39 (1 H, m), 4.55 (1 H, m), 5.70 (1 H, s), 5.74 (1 H, d, *J* = 8.1 Hz), 7.69 (1 H, d, *J* = 8.1 Hz), 8.62 (1 H, s, D_2O exchangeable).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.2, −4.8, 14.4, 17.8, 25.6, 35.3, 53.0, 62.1, 78.7, 93.2, 101.7, 139.6, 150.1, 163.6.

IR (neat): ν = 3211, 2102, 1713 cm^{-1}.

HRMS (FAB): *m*/*z* calcd for $C_{15}H_{26}N_5O_4Si$ (MH^+): 368.1754. Found: 368.1739.

5'-Amino-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxyuridine (8)

The azidouridine **7** (0.30 g, 0.82 mmol) was combined with 10% Pd/C in absolute EtOH and hydrogenated under 40 psi of H_2 for 8 h. The mixture was concentrated to a clear oil under reduced pressure. The product crystallized upon the addition of Et_2O to afford 245 mg (88%) of **8**; mp 89−91 °C (dec.); $[\alpha]_D$ −26.3 (*c* = 0.3, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (3 H, s), 0.12 (3 H, d), 0.89 (9 H, s), 1.65 (2 H, s, D_2O exchangeable), 1.80−1.87 (1 H, m), 2.06−2.16 (1 H, m), 3.75 (1 H, d, *J* = 12.0 Hz), 4.10 (1 H, d, *J* = 11.7 Hz), 4.48 (2 H, m), 5.63 (1 H, d, *J* = 0.9 Hz), 5.69 (1 H, d, *J* = 8.1 Hz), 7.87 (1 H, d, *J* = 8.1 Hz), 8.62 (1 H, s, D_2O exchangeable).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.1, −4.7, 14.4, 17.9, 25.6, 35.7, 62.1, 93.4, 101.5, 140.0, 150.1, 156.7, 163.6.

IR (CH_2Cl_2): ν = 3853, 3744, 3196, 1694 cm^{-1}.

HRMS (FAB): *m*/*z* calcd for $C_{15}H_{28}N_3O_4Si$ (MH^+): 342.1849. Found: 342.1853.

5'-Amino-3',5'-dideoxyuridine (2)

The aminouridine **8** (8.4 mg, 0.025 mmol) was dissolved in anhyd MeCN (1.0 mL) and treated with a solution of HF (5%) in MeCN (1.0 mL). The mixture was stirred at r.t. for 1.5 h at which time the starting material was consumed (TLC monitoring). The solvent was removed under reduced pressure giving a white solid which was triturated with cold EtOH to give 5.0 mg (90%) of **2** as a white solid; $[\alpha]_D$ +7.1 (*c* = 0.6, 1 N HCl).

^{1}H NMR (300 MHz, D_2O): δ = 2.02−2.08 (1 H, m), 2.13−2.21 (1 H, m), 3.21−3.29 (1 H, dd, *J* = 9.3, 13.6 Hz), 3.41 (1 H, dd, *J* = 2.6, 13.6 Hz), 4.59−4.64 (2 H, m), 5.75 (1 H, d, *J* = 1.8 Hz), 5.84 (1 H, d, *J* = 8.1 Hz), 7.62 (1 H, d, *J* = 8.0 Hz).

^{13}C NMR (75 MHz, D_2O): δ = 35.5, 42.7, 74.9, 76.7, 94.3, 101.7, 142.2, 151.4, 166.3.

HRMS (FAB): *m*/*z* calcd for $C_9H_{14}N_3O_4$ (MH^+): 228.0984. Found: 228.0991.

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(18) Due to potential safety considerations of handling the azide, smaller scale reactions were conducted from this point forward. Although no safety problems were encountered with this substrate, conservative reaction scales seemed the most prudent approach.

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