# General Preparative Synthesis of 2'-*O*-Methylpyrimidine Ribonucleosides

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This manuscript is dedicated to Professor Leroy B. Townsend on the occasion of his sixtieth birthday.

A convergent and general approach to synthesizing 2'-*O*-methylpyrimidine ribonucleosides **4a-e, 6, 7** on a multigram scale is described which begins with an improved procedure for making larger quantities of 2-*O*-methyl-1,3,5-tri-*O*-benzoyl-α-D-ribose. The sugar was reacted with the desired silylated pyrimidines at room temperature under Vorbrüggen conditions. The crude products contained less than 10% of the α anomers and the desired β anomers were isolated by crystallization. The blocked nucleosides were then deprotected and isolated by standard methods.

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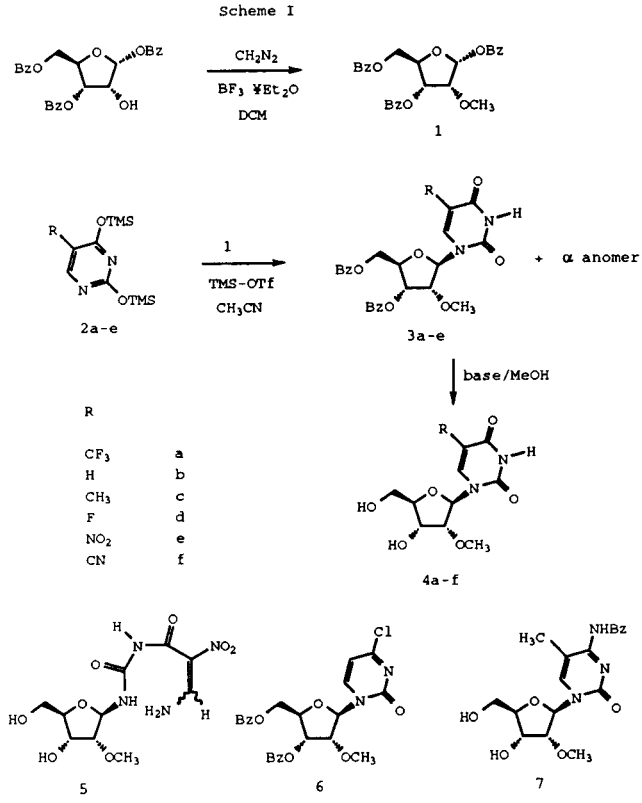
The development of antisense oligonucleotides as pharmaceutical candidates has prompted the need for multigram quantities of some key 2'-*O*-methylribonucleosides. In particular, we desired a practical and efficient route to a series of 5-substituted 2'-*O*-methyluridines. Several approaches appeared possible based on previous work with analogous 2'-deoxy and ribonucleosides. For example, the parent 2'-*O*-methyluridine could be prepared and then halogenated [1] at the C-5 position, thus allowing for further derivatization. Alternatively, novel bases could be glycosylated to their respective ribosides and these in turn could be methylated by the methods described [2-5] for uridine. The most attractive route for our purpose was reported by Imbach [6] in which silylated bases were reacted with 2-*O*-methyl-1,3,5-tri-*O*-benzoyl-α-D-ribose (**1**). Here we describe an improved procedure for making larger quantities of the sugar **1** and for reacting it under milder glycosylation conditions (Scheme I). We have demonstrated the utility and generality of this method by synthesizing multigram quantities of several 2'-*O*-methyl-β-D-ribonucleosides **4a-e, 6, 7**.

The sugar **1** was previously prepared [6] on a 5 g scale by reacting commercially available 1,3,5-tri-*O*-benzoyl-α-D-ribose [7] with a large excess of diazomethane, an explosive and extremely toxic gas. As we desired to make ten to twentyfold larger lots, we examined alternative routes. Standard alkaline conditions for alklyation invariably led to migration of the anomeric benzoyl group to the 2' position. Alkylation with methyl trifluoromethanesulfonate in the presence of 2,6-di-*tert*-butylpyridine [8] gave **1**, but in lower yields and at greater expense. Trimethylsilyl diazomethane [9] also appeared uneconomical at this scale. A closer examination of the conditions for methylation with diazomethane revealed that much of the excess reagent is quickly converted to polymethylene. If the reagent is added too fast, the resulting exotherm may trigger an explosion. To reduce this risk, we designed a mechanical device which delivered a solution of the gas under light argon pressure in a controlled and automated manner (see Diagram I). By adding the solution in a slow, constant flow, the exotherm was more easily managed and upon optimization, we found that half the amount of diazomethane could be used to obtain similar yields. By this method, we produced several hundred grams of the key intermediate **1**.

Imbach [6] reported that the glycosylation was catalyzed by stannic chloride in refluxing 1,2-dichloroethane. We desired the mildest conditions possible to accomodate our most sensitive bases. We found that Vorbrüggen [10] conditions employing trimethylsilyl trifluoromethanesulfonate in acetonitrile at room temperature effected a complete reaction in fifteeen to sixty minutes for all bases tested. After an aqueous workup, the crude products were analyzed by $^1$H nmr to determine their anomeric ratio. The β/α values ranged from 9:1 to 15:1. The pure β anomers were isolated directly by crystallization from methanol. Assignments of anomeric configuration were made based on a combination of comparing literature values of the known dibenzoyl product **3b** [6], the H-1' and H-4' crosspeaks in the NOESY spectra of **3a** and **3e** and the consistent observation in the series that the α anomers exhibited the downfield anomeric signals with larger coupling constants than those of the β anomers.

Removal of the benzoyl protecting groups using standard methods was easily accomplished with the exception of **3a** and **3e**. Electron withdrawing substituents on the C-5 position enhance the electrophilicity of the heterocycle.




As a consequence of this reactivity, treatment [11] of 5-trifluoromethyl-2'-deoxyuridine with dilute sodium hydroxide gave the 5-carboxylic acid whereas sodium methoxide [12] gave the methyl carboxylate. A recent paper [13] reported successful incorporation of the same deoxynucleoside into an oligonucleotide under standard conditions which we presume included the use of ammonium hydroxide. However, treatment of **3a** with ammonium hydroxide in a sealed tube at 55° gave a new product which we tentatively assigned as the 5-nitrile analog **4f** based on its elemental analysis and IR spectrum. The desired product **4a** could be obtained using one equivalent of sodium methoxide in methanol at room temperature overnight. The nitro analog **3e** was even more sensitive. Methanolic ammonia treatment at room temperature gave a product in which, as judged by elemental analysis, ammonia had added to the ring. Based on its spectral data, we have assigned its structure as the ring opened product **5** which results from attack on the C-6 carbon [14]. Again, sodium methoxide gave the desired product **4e**, although this proved too unstable for further derivatization.

The deprotected residues were triturated with ether or purified by simple chromatography to remove the benzoyl by-products followed by crystallization from methanol to afford pure products in 40-67% yields for the two steps.

**Diagram 1**

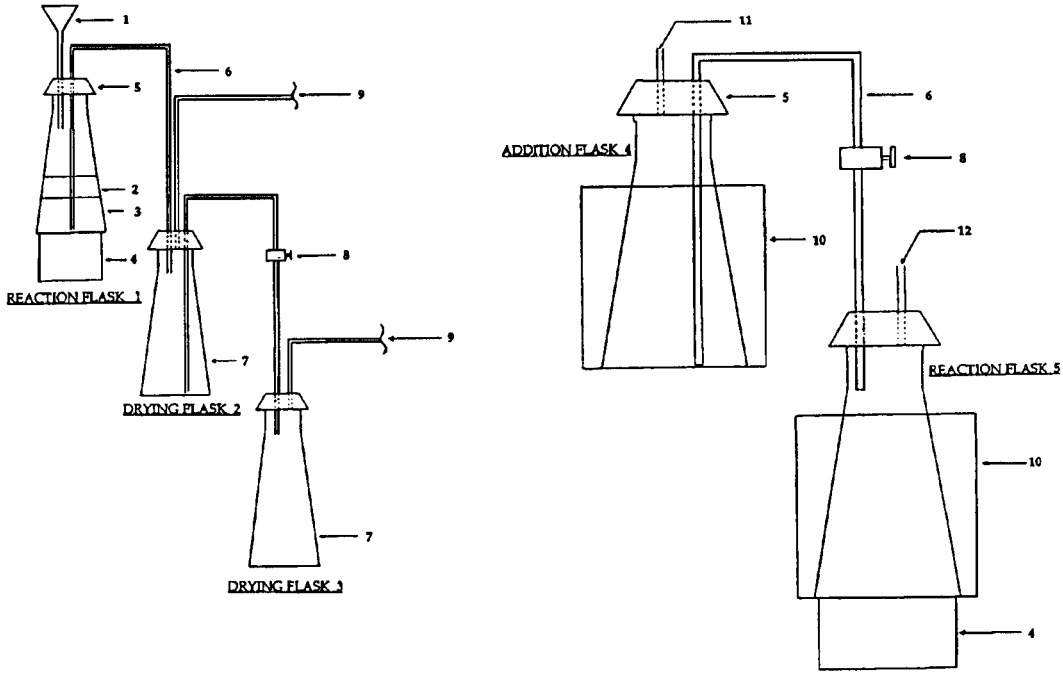



Diagram 1. Glassware consists of flame-dried four liter Erlenmeyer flasks. **1**: wide bore plastic funnel. **2**: aqueous potassium hydroxide. **3**: dichloromethane solution of diazomethane. **4**: magnetic stirrer. **5**: rubber stopper. **6**: transfer apparatus, Teflon tubing (1/8 inch ID, heavy wall). **7**: potassium hydroxide pellets. **8**: Hamilton two-way low pressure valve. **9**: water aspirator. **10**: ice bath. **11**: Argon pressure (3-5 psi). **12**: vent. Transfer of diazomethane solution from Drying Flask 3 to Addition Flask 4 was accomplished by the use of **6**.

The method employs little or no chromatography and thus may be easily scaled up further. We have included, as an example, a transformation of **3c** to $N^4$-benzoyl-2'-*O*-methyl-5-methylcytidine (**7**). Although we were most interested in uridines, we see no reason why other pyrimidine bases could not be glycosylated using this method.

## EXPERIMENTAL

The $^1H$ nmr spectra were recorded on a Varian Gemini 200 MHz Fourier-transform spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. Infrared specta were taken in potassium bromide pellets with a Perkin Elmer Fourier-transform IR-16 spectrophotometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed at Quantitative Technologies Incorporated, P. O. Box 470, Whitehouse, NJ 08888.

2-*O*-Methyl-1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**1**).

Diazomethane is generated by the slow (60 minutes) addition of 1-methyl-3-nitro-1-nitrosoguanidine (125 g, 0.85 mole) powder to a rapidly stirred biphasic solution of 40% potassium hydroxide (400 ml) over methylene chloride (800 ml) at 4°. When the addition is complete, the cold biphasic solution is allowed to fully separate into layers. The organic layer (bottom) is transferred to a clean Erlenmeyer flask containing 20 g of potassium pellets with the use of a Teflon transfer apparatus. All solid precipitants remain suspended in the water layer. After 15 minutes at 4°, the organic solution is again transferred into a second flask containing potassium hydroxide pellets using the Teflon transfer apparatus. The second flask is kept at 4° for 10 minutes and then the diazomethane solution is transferred into a clean and dry Erlenmeyer flask. This solution is then transferred dropwise into a cold, rapidly stirred solution of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (Pfanshtiehl, 50 g, 0.11 mole) and boron trifluoride etherate (0.8 ml, 0.007 mole) in dichloromethane (300 ml) using an argon controlled pressure feed (see Diagram 1) while maintaining the temperature of both flasks at 4°.

After addition of the diazomethane, the Erlenmeyer reaction flask is kept in an ice bath for an additional 30 minutes, then filtered with suction. The clear yellow filtrate is washed with cold, saturated sodium bicarbonate (3 x 200 ml), dried over sodium sulfate, filtered and evaporated to yield 53 g of a light yellow sirup, $R_f$ = 0.80, chloroform/acetone 19:1. This sirup is flash-chromatographed on a silica gel column (500 g) using methylene chloride (2 l) and then dichloromethane-acetone (98:2, 2 l) to afford 36.6 g (71%) of clear sirup; $^1H$ nmr (deuteriochloroform): δ 3.46 (s, 3H, $OCH_3$), 4.21 (dd, $J_{2,3}$ = 6.3 Hz, 1H, H-2), 4.65 (m, 2H, H-5,5'), 4.80 (m, 1H, H-4), 5.71 (dd, $J_{3,4}$ = 2.3 Hz, 1H, H-3), 6.76 (d, $J_{1,2}$ = 4.3 Hz, 1H, H-1), 7.20-8.30 (m, 15H, aromatic).

General Method for Glycosylation. Preparation of 3',5'-di-*O*-benzoyl-2'-*O*-methyl-5trifluoromethyluridine (**3a**).

5-Trifluoromethyluracil (7.6 g, 42 mmoles) and ammonium sulfate (0.1 g) were suspended in hexamethyldisilazane (40 ml). The mixture was heated to reflux under an argon atmosphere for 16 hours. The resulting solution was concentrated (50°, 1 mm) to a colorless, clear oil. While maintaining the inert atmosphere, the oil was dissolved in dry acetonitrile (100 ml) and transferred *via* cannula to a reaction vessel containing 2-*O*-methyl-1,3,5-tri-*O*-benzoyl-α-D-ribose (20.0 g, 42 mmoles). The stirred solution was treated with trimethylsilyl trifluoromethanesulfonate (7.2 ml, 37 mmoles) in one portion at room temperature. The reaction was monitored by tlc. If the reaction was not complete after 30 minutes, 0.2 equivalents additional catalyst was added. After 30 minutes, the reaction was diluted with dichloromethane (200 ml) and washed with saturated aqueous sodium bicarbonate (100 ml). The aqueous layer was back-extracted with dichloromethane (150 ml). The organic layers were combined, dried (sodium sulfate), filtered and concentrated under reduced pressure to afford 23.0 g of off-white foam as a 9:1 β/α anomeric mixture of products based on the H-1' resonances (α at 6.43 ppm). The pure β product **3a** crystallized from methanol (100 ml) to give 13.9 g (62%), white crystals, mp 156-158°; $^1H$ nmr (DMSO-$d_6$): δ 3.38 (s, 3H, $OCH_3$), 4.5-4.7 (m, 4H, H-2',4',5'), 5.63 (m, 1H, H-3'), 5.92 (d, J = 3.9 Hz, 1H, H-1'), 7.5-8.1 (m, 10H, Bz), 8.35 (s, 1H, H-6) and 12.05 (br s, 1H, NH).

*Anal.* Calcd. for $C_{25}H_{21}F_3N_2O_8$ (466.44): C, 56.28; H, 3.93; N, 5 24. Found: C, 56.42; H, 3.93; N, 5.19.

2'-*O*-Methyl-5-trifluoromethyluridine (**4a**).

Compound **3a** (10.6 g, 20 mmoles) was dissolved in dry methanol (250 ml). Sodium metal (0.7 g, 30 mmoles) was added and the resulting solution was stirred at room temperature for 17 hours. Ammonium chloride (1.6 g, 31 mmoles) was added and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel (100 g) column eluting with a gradient of 0 to 10% methanol in dichloromethane to afford 6.1 g (94%) of **4a** as a white solid, mp 192-194°; $^1H$ nmr (DMSO-$d_6$): δ 3.43 (s, 3H, $OCH_3$), 3.5-3.8 (m, 2H, H-5'), 3.8-4.0 (m, 2H, H-3',4'), 4.12 (m, 1H, H-2'), 5.18 (d, J = 7 Hz, 1H, 3'-OH), 5.40 (br t, 1H, 5'-OH), 5.78 (d, J = 2.5 Hz, 1H, H-1'), 8.92 (s, 1H, H-6), 11.80 (br s, 1H, N-H).

*Anal.* Calcd. for $C_{11}H_{13}F_3N_2O_6$ (326.23): C, 40.49; H, 3.99; N, 8.59. Found: C, 40.42; H, 4.17; N, 8.32.

2'-*O*-Methyl-5-cyanouridine (**4f**) was the major product under the following deprotection conditions: Compound **3a** (1.0 g, 2.1 mmoles) was dissolved in concentrated ammonium hydroxide (60 ml) and heated in a sealed tube at 55° for 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (30 g) using a gradient of 0-5% methanol in dichloromethane to give 0.3 g (50% crude yield) of oil. A small portion of **4f** crystallized from methanol as slightly impure white solid, mp 208-211°; ir (potassium bromide): 2240 $cm^{-1}$ (sharp, -CN); $^1H$ nmr (DMSO-$d_6$): δ 3.45 (s, 3H, $OCH_3$), 3.5-3.6 (m, 1H, H-5'), 3.7-3.9 (m, 3H, H-3',4',5'), 4.13 (m, 1H, H-2'), 5.17 (d, J = 6 Hz, 1H, 3'-OH), 5.48 (br t, 1H, 5'-OH), 5.75 (br s, 1H, H-1'), 8.99 (d, J = 1.5 Hz, 1H, H-6), 12.08 (br s, 1H, N-H).

*Anal.* Calcd. for $C_{11}H_{13}N_3O_6$ (283.24): C, 46.64; H, 4.63; N, 14.83. Found: C, 45.98; H, 4.63; N, 14.35, (F, O).

3',5'-Di-*O*-benzoyl-2'-*O*-methyluridine (**3b**).

Uracil (1.1 g, 9.7 mmoles) was glycosylated as described in the General Method to afford 5.1 g of off-white foam as a 13:1 β/α anomeric mixture of the dibenzoyl intermediate based on the H-1' resonances (α at 6.36 ppm). The pure β product **3b** crystallized from methanol to give 3.4 g (75%), white crystals, mp 132-134° (lit [6] mp 132-133°); $^1H$ nmr (DMSO-$d_6$): δ 3.36

(s, 3H, $OCH_3$), 4.42 (m, 1H, H-2'), 4.5-4.7 (m, 3H, H-4',5'), 5.60 (m, 1H, H-3'), 5.64 (d, J = 8 Hz, 1H, H-5), 5.92 (d, J = 3 Hz, 1H, H-1'), 7.5-8.1 (m, 11H, Bz-H, H-6), 11.45 (s, 1H, NH). The filtrate was chromatographed on silica gel (30 g) with hexanes-ethyl acetate to give 0.5 g (11%) more crystalline product.

2'-*O*-Methyluridine (**4b**).

A sample of **3b** (0.80 g, 17 mmoles) was deprotected in a mixture of methanol (65 ml) and concentrated ammonium hydroxide (35 ml) overnight at room temperature. The solution was allowed to evaporate to an oil in the fume hood. The residue was triturated with ether (100 ml). The resulting solid was collected, rinsed with ether and dried to afford 0.38 g (86%) of **4b** as a white solid, mp 158-159° (lit [6] mp 156-159°); $^1$H nmr (DMSO-$d_6$) δ 3.34 (s, 3H, $OCH_3$), 3.5-3.7 (m, 2H, H-5'), 3.7-3.9 (m, 2H, H-3',4'), 4.14 (m, 1H, H-2'), 5.19 (m, 2H, 3',5'-OH), 5.66 (d, J = 8 Hz, 1H, H-5), 5.87 (d, J = 5 Hz, 1H, H-1'), 7.95 (d, J = 8 Hz, 1H, H-6), 11.35 (br s, 1H, N-H).

*Anal.* Calcd. for $C_{10}H_{14}N_2O_6$ (258.23): C, 46.51; H, 5.46; N, 10.85. Found: C, 46.57; H, 5.49; N, 10.82.

3',5'-Di-*O*-benzoyl-2'-*O*-methyl-5-methyluridine (**3c**).

Thymine (8.0 g, 63 mmoles) was glycosylated as described in the General Method. The crude dibenzoyl product containing a β/α ratio of 16:1 (α H-1' at 6.41 ppm) was chromatographed on silica gel (600 g) using a gradient of ethyl acetate in hexanes (40-60%) to give 23.2 g of foam which contained 3.5% of the α anomer. The pure β product crystallized from methanol to give 16.1 g (55%) of first crop of **3c** as white crystals, mp 128-130°. Subsequent crops were contaminated with the α anomer; $^1$H nmr (DMSO-$d_6$): δ 1.68 (s, 3H, 5-$CH_3$), 3.34 (s, 3H, $OCH_3$), 4.41 (m, 1H, H-2'), 4.5-4.7 (m, 3H, H-4',5'), 5.67 (m, 1H, H-3'), 5.98 (d, J = 5 Hz, 1H, H-1'), 7.5-8.1 (m, 11H, Bz-H, H-6), 11.49 (s, 1H, NH).

*Anal.* Calcd. for $C_{25}H_{24}N_2O_8$ (480.46): C, 62.49; H, 5.04; N, 5.83. Found: C, 62.49; H, 4.92; N, 5.75.

2'-*O*-Methyl-5-methyluridine (2'-*O*-Methylribothymidine) (**4c**).

The dibenzoyl intermediate **3c** (14.3 g, 30 mmoles) was dissolved in methanol (130 ml) and concentrated ammonium hydroxide (65 ml) for 24 hours. The solvent was evaporated under reduced pressure and the residue was triturated with ether to give 6.5 g (80%) of white solid. An analytical sample was crystallized from absolute ethanol to afford **4c** as white needles, mp 192-193° (lit [15] mp 197-198°); $^1$H nmr (DMSO-$d_6$): δ 1.79 (s, 3H, 5-$CH_3$), 3.35 (s, 3H, $OCH_3$), 3.5-3.7 (m, 2H, H-5'), 3.7-3.9 (m, 2H, H-3',4'), 4.15 (m, 1H, H-2'), 5.17 (m, 2H, 3',5'-OH), 5.87 (d, J = 5 Hz, 1H, H-1'), 7.80 (s, 1H, H-6), 11.37 (br s, 1H, N-H).

*Anal.* Calcd. for $C_{11}H_{16}N_2O_6$ (272.26): C, 48.52; H, 5.92; N, 10.29. Found: C, 48.56; H, 5.88; N, 10.22.

3',5'-Di-*O*-benzoyl-2'-*O*-methyl-5-fluorouridine (**3d**).

5-Fluorouracil (4.1 g, 32 mmoles) was glycosylated as described in the General Method to give 15.1 g of crude dibenzoyl product containing a β/α ratio of 15:1 (α H-1' at 6.41 ppm). The pure β product crystallized from methanol in two crops for a total of 10.4 g (68%) of **3d** as white needles, mp 182-184°; $^1$H nmr (DMSO-$d_6$): δ 3.35 (s, 3H, $OCH_3$), 4.44 (m, 1H, H-2'), 4.5-4.7 (m, 3H, H-4',5'), 5.60 (m, 1H, H-3'), 5.93 (d, J = 4 Hz, 1H, H-1'), 7.5-8.0 (m, 10H, Bz-H), 8.06 (d, J = 7 Hz, 1H, H-6), 12.02 (s, 1H, NH).

2'-*O*-Methyl-5-fluorouridine (**4d**).

The dibenzoyl intermediate **3d** (9.6 g, 20 mmoles) was dissolved in methanol (350 ml) which had been previously saturated with ammonia at -20°. The solution was sealed in a stainless steel bomb at room temperature for 17 hours and then concentrated to an oil under reduced pressure. The oil was chromatographed on silica gel (200 g) using ethyl acetate to give 5.4 g (98%) of **4d** as white solid. A portion (0.5 g) was crystallized from ethyl acetate-toluene to yield 0.4 g of white needles as the analytical sample, mp 151-152° (lit [16] mp 144-147°); $^1$H nmr (DMSO-$d_6$): δ 3.39 (s, 3H, $OCH_3$), 3.5-3.7 (m, 2H, H-5'), 3.7-3.9 (m, 2H, H-3',4'), 4.13 (m, 1H, H-2'), 5.18 (d, J = 6 Hz, 1H, 3'-OH), 5.35 (br t, 1H, 5'-OH), 5.81 (dd, 1H, H-1'), 8.35 (d, J = 7 Hz, 1H, H-6), 11.40 (br d, 1H, N-H).

*Anal.* Calcd. for $C_{10}H_{13}FN_2O_6$ (276.22): C, 43.48; H, 4.74; N, 10.14. Found: C, 43.56; H, 4.63; N, 10.02.

3',5'-Di-*O*-benzoyl-2'-*O*-methyl-5-nitrouridine (**3e**).

5-Nitrouracil (5.5 g, 35 mmoles) was glycosylated as described in the General Method to give 17.9 g of crude product containing a β/α ratio of 9:1 (α H-1' at 6.46 ppm). The pure β product crystallized from methanol to afford 10.0 g (56%) of **3e** as white needles, mp 187-189°. Further concentration of the the mother liquor gave only inseparable, contaminated product; $^1$H nmr (DMSO-$d_6$): δ 3.41 (s, 3H, $OCH_3$), 4.5-4.8 (m, 4H, H-2',4',5'), 5.62 (m, 1H, H-3'), 5.97 (d, J = 3 Hz, 1H, H-1'), 7.5-8.1 (m, 10H, Bz-H), 9.16 (s, 1H, H-6), 12.23 (br s, 1H, NH).

2'-*O*-Methyl-5-nitrouridine (**4e**).

A sample of the dibenzoyl intermediate **3e** (2.0 g, 4 mmoles) was dissolved in methanol (50 ml). Sodium metal (0.1 g, 4 mmoles) was added and the solution was stirred at room temperature for 17 hours. The sodium salt of **4e** precipitated. The solid was collected, triturated with ether (50 ml) and dried under reduced pressure at 100° overnight to 1.1 g (88%) of white powder, mp 237° (dec. with efflorescence). A portion was neutralized by dissolving into 10% aqueous methanol and passing through an Amberlite IRC-50 weak acid resin column. The solution was concentrated and dried under reduced pressure to **4e** as a tan paste; $^1$H nmr (DMSO-$d_6$): δ 3.47 (s, 3H, $OCH_3$), 3.5-3.7 (m, 1H, H-5'), 3.7-3.9 (m, 3H, H-3',4',5'), 4.15 (m, 1H, H-2'), 5.17 (d, J = 7 Hz, 1H, 3'-OH), 5.44 (br t, 1H, 5'-OH), 5.79 (br s, 1H, H-1'), 9.72 (s, 1H, H-6), 12.05 (br s, 1H, N-H). Attempts to crystallize out an analytical sample of the neutral product failed due to the unstable nature of **4e**. The crude sodium salt of **4e** analyzed as follows:

*Anal.* Calcd. for $C_{10}H_{12}N_3NaO_8$ (325.22): C, 36.93; H, 3.72; N, 12.92. Found: C, 36.57; H, 3.71; N, 12.44.

The ring-opened side product **5** was produced as follows: Dibenzoyl intermediate **3e** (16.0 g, 31 mmoles) was dissolved in methanol (350 ml) previously saturated with ammonia at -20°. The solution was sealed in a stainless steel bomb for 17 hours at room temperature. The solvent was removed under reduced pressure. The product precipitated from methanol to give 7.9 g (80%), white solid, mp 182-183° (dec. with efflorescence); $^1$H nmr (DMSO-$d_6$): δ 3.41 (s, 3H, $OCH_3$), 3.45 (br s, 2H, H-5', 5'), 3.59 (m, 1H, H-4'), 3.76 (m, 1H, H-3'), 4.09 (m, 1H, H-2'), 4.88 (t, J = 5 Hz, 1H, 5'-OH), 4.99 (d, J = 6 Hz, 1H, 3'-OH), 5.42 (dd, J = 6 Hz and J = 9 Hz, 1H, H-1'), 8.35 (br s, 1H, H-2), 8.83 (d, J = 9 Hz, 1H, 1-NH), 10.00 (br s, 2H, $NH_2$), 10.55 (br s, 1H, 5-NH). Upon deuterium oxide exhange, H-1' collapses to a doublet

(J = 6 Hz) and the H-2 singlet sharpens.

*Anal.* Calcd. for $C_{10}H_{16}N_4O_8$ (320.27): C, 37.50; H, 5.04; N, 17.50. Found: C, 37.48; H, 5.03; N, 17.31.

4-Chloro-1-(2-*O*-methyl-3,5-di-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**6**).

4-Chloro-2-trimethylsilylethoxypyrimidine was prepared in the following way. A solution of trimethylsilylethanol (10.0 g, 85 mmoles) in anhydrous tetrahydrofuran was cooled to -68° in an 2-propanol-dry ice bath and then treated with *n*-butyllithium (33.8 ml of a 2.5 *M* solution) dropwise over 30 minutes. This mixture was warmed to -25° and then added *via* cannula to a solution of 2,4-dichloropyrimidine (12.6 g, 85 mmoles) at -68° while maintaining anhydrous conditions. After addition, the mixture was allowed to warm to room temperature over 30 minutes and stirred at this temperature for 1 hour. The clear yellow solution was diluted with diethyl ether (200 ml) and then washed with cold water and cold, saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and evaporated to yield a thick amber oil. This oil was kept under vacuum overnight and then flash chromatographed over a silica gel column (7.5 x 8.5 cm) using chloroform as eluent. The solvent was thoroughly evaporated and the resulting yellowish oil was crystallized at -68° from a minimum volume of hexane to give 20.3 g (91%)of silylated base as white waxy plates; $^1$H nmr (DMSO-$d_6$): δ 0.10 (s, 9H, $SiCH_3$), 1.08 (t, 2H, $SiCH_2$), 4.40 (t, 2H, $OCH_2$), 7.27 (d, 1H, H-5), 8.55 (d, $J_{6,5}$ = 4.5 Hz, 1H, H-6).

A portion of the 4-chloro-2-trimethylsilylethoxypyrimidine (6.0 g, 26 mmoles) was glycosylated as described in the General Method to give 12.1 g (96%) of crude dibenzoyl product **6** containing a β/α ratio of 14:1 (α H-1' at 6.39 ppm). Due to its reactivity, the product was used as is for further derivatization; $^1$H nmr (deuteriochloroform): δ 3.64 (s, 3H, $OCH_3$), 4.33 (m, 1H, H-2'), 4.6-4.9 (m, 3H, H-4',5',5"), 5.20 (m, 1H, H-3'), 6.03 (br s, 1H, H-1'), 6.15 (d, $J_{6,5}$ = 5.8 Hz, 1H, H-6), 7.4 -8.2 (m, 11H, aromatic and H-5).

$N^4$-Benzoyl-2'-*O*-methyl-5-methylcytidine (**7**).

A solution of **3c** (15.3 g, 32 mmoles) in dry pyridine (350 ml) was stirred at 3-5° under argon. Phosphorus oxychloride (6.8 ml, 73 mmoles) was added dropwise over 1 hour. After stirring for an additional 1 hour, a solution of 1,2,4-triazole (15.3 g, 221 mmoles) in dry pyridine (100 ml) was added in one portion. The reaction was allowed to warm to room temperature and to stir for 24 hours. The reaction was diluted with dichloromethane (500 ml) and washed with water (4 x 400 ml). The organic layer was dried (magnesium sulfate), and concentrated under reduced pressure to a foam. In a separate flask, benzamide [17] (34 g, 281 mmoles) and sodium hydride (60% in oil, 10.4 g, 260 mmoles) were suspended in dioxane (350 ml) and heated to 65° for 1 hour. The resulting solution was cooled to room temperature and added to the nucleoside. The mixture was stirred for 2 hours, then treated with methanol (175 ml) to cleave the benzoyl esters. After 5 hours, the reaction was neutralized with glacial acetic acid (14.7 ml). The solvent was removed under reduced pressure. The residue was extracted with ether to separate the product from solid by-products. The ether layer was filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (300 g) using ethyl acetate-hexanes (4:1). The product **7** (*ca* 4 g, 33% crude yield) was slightly contaminated with benzamide and was used as such for further derivatization. An analytical sample (0.25 g) crystallized from ethyl acetate as white needles, mp 222-224°; $^1$H nmr (DMSO-$d_6$): δ 2.03 (s, 3H, 5-$CH_3$), 3.42 (s, 3H, $OCH_3$), 3.5-4.0 (m, 4H, H-3',4',5'), 4.17 (m, 1H, H-2'), 5.20 (d, J = 6 Hz, 1H, 3'-OH), 5.32 (br t, 1H, 5'-OH), 5.89 (d, J = 4 Hz, 1H, H-1'), 7.5-7.6 (m, 3H, *m* and *p* Bz-H), 9.72 (s, 1H, H-6), 8.21 (m, 3H, *o* Bz-H and H-6), 12.95 (br s, 1H, N-H).

*Anal.* Calcd. for $C_{18}H_{21}N_3O_6$ (375.38): C, 57.58; H, 5.64; N, 11.20. Found: C, 57.61; H, 5.63; N, 11.15.

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