

N-Nitration, ¹⁵N-Labeling, and N-to-N Linking of Hydroxyl-Silylated Pyrimidine Nucleosides

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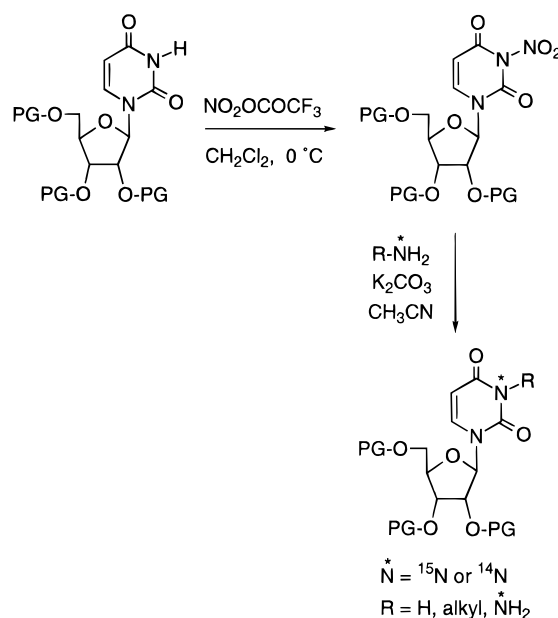
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Very recently, we reported on a novel method for the ¹⁵N-labeling, N-alkylation, and N-amination of nucleoside derivatives based on the N-nitration of appropriate precursors with nitronium trifluoroacetate followed by treatment with ¹⁵NH₃, alkylamines, or hydrazine (either unlabeled or ¹⁵N-labeled), respectively, which is shown in Scheme 1.¹ Since the hydroxy groups of the sugar rings underwent concomitant O-nitration, we protected them or most of them as acetates, benzoates, or isopropylidene acetals, but not as *tert*-butyldimethylsilyl ethers, because in preliminary experiments we noted that TBDMS groups were partially removed in the nitration medium.^{1a,c} However, the widespread use of silyl ethers in the nucleoside field,² mainly of the TBDMS and 1,1,3,3-tetraisopropylidisiloxane-1,3-diyl (TIPDS) derivatives, prompted us to restudy the performance of these protecting groups in connection with the process shown in Scheme 1. We report here that the above-mentioned limitation can be overcome by improving the N-nitration step and, furthermore, that TBDMS and TIPDS groups are stable under the conditions inherent in the second step (the ring-opening/ring-closing step¹).

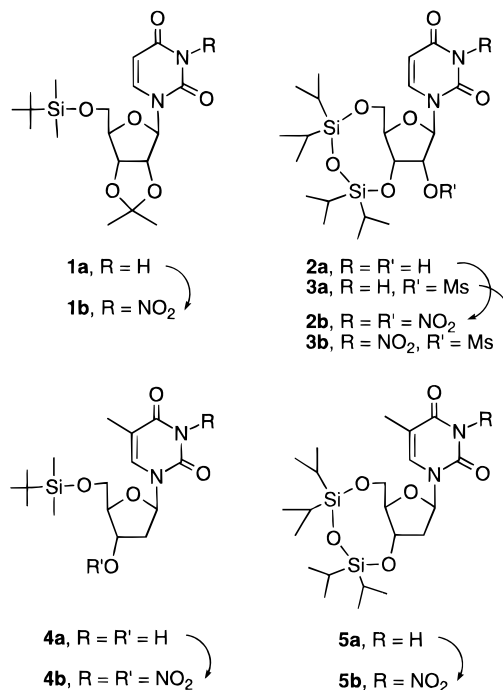
Results and Discussion

Uridine and thymidine derivatives **1a–5a** were subjected at 0 °C to the action of fresh nitrating solutions arising from mixing NH₄NO₃ (*n* mol per mol) and (CF₃CO)₂O (TFAA, 2*n* mol per mol)³ in CH₂Cl₂. Rather than using moderate excesses of reagents (*n* = 1.5–2.0) and lengthening the reaction times, the highest conversion and lowest deprotection percentages were obtained by using large excesses of the nitrating mixture (*n* = 4, in the cases of **1a**, **3a**, and **5a**, Scheme 2). Under these conditions, the isolated yields of *N*-nitro compounds **1b**, **3b**, and **5b** were always around 90% (see the Experimental Section). With the partially protected substrates **2a** and **4a**, in which the alcohol function reacted more quickly than the imide-like NH, the highest yields of *N,O*-dinitro derivatives **2b** and **4b** (88% and 85%, respectively) were obtained by employing a larger excess of nitrating

Scheme 1



Scheme 2



mixture (*n* = 6–8).⁴ The loss of *O*-silyl groups was hardly detected. Apparently, with freshly prepared nitrating mixtures, when there is an excess of mixed anhydride NO₂OCOCF₃ in the reaction medium, the silyl ether cleavage practically does not take place; on the other hand, when the nitrating mixture is almost exhausted (i.e., when most anhydrides have disappeared and the major component of the mixture is TFA)³ the chance of *O*–Si bond cleavage and nitro-exchange reactions is much higher.⁵

When **1b** was treated with ¹⁵NH₄Cl and K₂CO₃ in CH₃CN–H₂O at rt for a long time, [¹⁵N]-labeled **1a** was

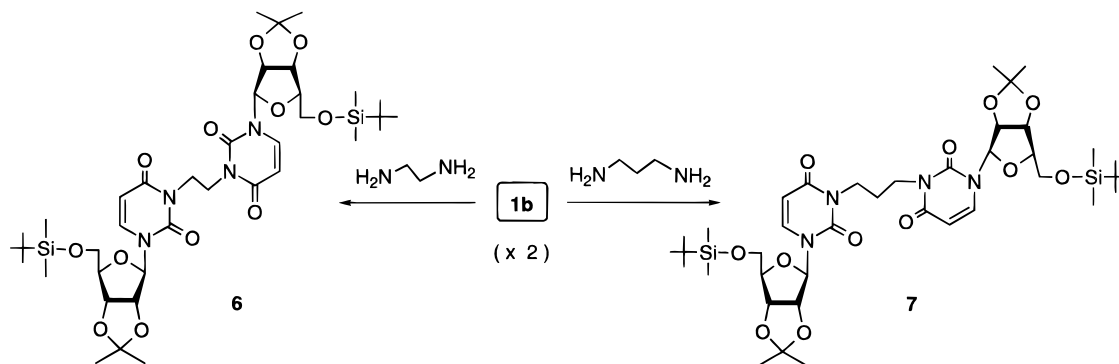
(1) Ariza, X.; Bou, V.; Vilarrasa, J. *J. Am. Chem. Soc.* **1995**, *117*, 3665. (b) For an application to the synthesis of [¹⁵N]-labeled AZT, see: Ariza, X.; Bou, V.; Vilarrasa, J.; Tereshko, V.; Campos, J. L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2454. (c) Bou, V. *Nuevas reacciones en el campo de los nucleósidos*. Ph.D. Thesis, Universitat de Barcelona, 1992.

(2) For reviews, see: (a) Ueda, T. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1988. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991. (c) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994. (d) van Look, G.; Simchen, G.; Heberle, J. *Silylating Agents*; Fluka Chemie AG: Buchs, 1995.

(3) Romea, P.; Aragonès, M.; García, J.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 7038.

(4) With smaller excesses (*n* = 2–4), uridine **2a** afforded mainly the 2'-*O*-nitro compound, while thymidine **4a** gave rise to mixtures of *O*-nitro and *N,O*-dinitro compounds (with *n* = 2, 80% of 3'-*O*-nitro derivative plus 10% of *N,O*-dinitro **4b**; with *n* = 4, 30% of *O*-nitro plus 62% of **4b**).

Scheme 3



obtained in 78% yield. As this yield is similar to those achieved in related experiments with other standard protecting groups,¹ it appears that the corresponding O–Si bond is reasonably stable under these conditions, i.e., the TBDMS group can be reliably used in ^{15}N labeling experiments.

Nevertheless, these conditions are milder than those often required for reactions with other N-nucleophiles, where substrates and reagents are heated in the presence of K_2CO_3 to accelerate the rate-limiting and nonquantitative ring-closing step.¹ Thus, we first checked the stability of the TBDMS and TIPDS groups of **1a** and **5a**, respectively, in refluxing CH_3CN or $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ for 7 h, in the presence of an excess of K_2CO_3 and/or an alkylamine (ethylenediamine).⁶ Since in all experiments >97% of the starting material was recovered, it was concluded that the basic media in which the second step of Scheme 1 is usually carried out are not strong enough for the cleavage of the above-mentioned O–Si bonds. Moreover, the reaction of **1b** with ethylenediamine (in the 2:1 molar ratio) and likewise with 1,3-propanediamine, envisaged as a preliminary approach to a new cross-linking procedure⁷ for N-nitro-containing oligonucleotide chains, afforded the desired N-to-N “dimers” **6** and **7** (see Scheme 3) in 55% and 57% yields, respectively, after purification by flash chromatography. These figures mean a yield of ca. 70–80% per each ring closing, which agree with the best yields found for the reaction of N-nitropyrimidine nucleosides with simple alkylamines.^{1a}

In summary, both TBDMS and TIPDS ethers do survive to the action of the excess of nitrating mixture utilized in the first step (from N–H to N– NO_2) and to the basic media required in the second step (from N– NO_2 to N–R) of our N-exchange procedure.¹ Contrary to our former suggestion,^{1a} these common protecting groups are

a good choice for the ^{15}N labeling of nucleosides and related reactions.

Experimental Section

For the general section, see ref 1a. Compounds **1a–5a** were prepared according to standard procedures.² Coupling constants (J) are reported in Hz.

5'-O-(tert-Butyldimethylsilyl)-2',3'-O-isopropylidene-3-nitrouridine (1b). TFAA (1.12 mL, 8.0 mmol) was added to a suspension of finely powdered NH_4NO_3 (320 mg, 4.00 mmol) in anhydrous CH_2Cl_2 (10 mL), at 0 °C. The mixture was vigorously stirred at rt until the solid was dissolved (45 min) and then cooled again. Compound **1a**⁸ (399 mg, 1.00 mmol) in CH_2Cl_2 (0.5 mL) was added, the syringe was rinsed with an additional volume of CH_2Cl_2 (1.5 mL), and the resulting solution was stirred for 15 min. Addition of more solvent, washing with cold phosphate buffer, drying, and filtration through a pad of silica gel afforded chromatographically pure **1b** (400 mg, 90% yield) as a viscous oil: $[\alpha]_D = -22.28$ (c 0.61, CHCl_3); ^1H NMR (CDCl_3) δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.91 (s, 9 H), 1.37 (s, 3 H), 1.59 (s, 3 H), 3.80 (dd, $J = 11.8$, 2.6, 1 H), 3.94 (dd, $J = 11.8$, 1.8, 1 H), 4.44 (m, 1 H), 4.65–4.80 (m, 2 H), 5.81 (d, $J = 8.4$, 1 H), 5.95 (d, $J = 2.2$, 1 H), 7.82 (d, $J = 8.4$, 1 H); ^{13}C NMR (CDCl_3) δ -5.6, -5.5, 18.3, 25.2, 25.8, 27.2, 63.4, 80.5, 85.6, 87.2, 93.4, 100.8, 114.2, 139.9, 145.3, 155.2; FABMS m/z 444 ($M + 1$).

N³,O^{2'}-Dinitro-3',5'-O-(tetraisopropylidisiloxane-1,3-diyl)-uridine (2b). From **2a** plus NH_4NO_3 (6 mol/mol) and TFAA (12 mol/mol); reaction time = 40 min; 88% yield; white gum; $[\alpha]_D = +28.74$ (c 0.43, CHCl_3); ^1H NMR (CDCl_3) δ 1.0–1.1 (m, 28 H), 4.00 (dd, $J = 13.3$, 2.7, 1 H), 4.09 (dd, $J = 9.5$, 2.7, 1 H), 4.26 (d, $J = 13.3$, 1 H), 4.49 (dd, $J = 9.5$, 4.6, 1 H), 5.59 (d, $J = 4.4$, 1 H), 5.80 (s, 1 H), 5.87 (d, $J = 8.4$, 1 H), 7.67 (d, $J = 8.4$, 1 H); ^{13}C NMR (CDCl_3) δ 12.5, 12.8, 12.9, 13.4, 16.7, 16.8, 17.2,

(5) When a sample of **1a** was added to an excess of nitrating mixture that had been left for 18 h under N_2 , N-nitro compound **1b** was not obtained; only starting material (**1a**) and deprotected product (desilylated **1a**) were present in similar amounts. While the nitration of **1a** with an excess of freshly prepared nitrating mixture for 15–30 min always gives yields above 90% of **1b** (deprotected product being not observed), when the reaction was left overnight the yield of **1b** decreased to 31% and the crude mixture contained, in addition to 16% of **1a**, 18% of 2',3'-O-isopropylideneuridine (desilylated **1a**) and 33% of N³,O^{2'}-dinitro derivative.

(6) (a) The TIPDS group is known to be sensitive to aqueous basic media: Markiewicz, W. T. *J. Chem. Res., Synop.* **1979**, 24. (b) There are also examples of the moderate stability of TBDMS protecting groups under certain basic conditions: Reddy, M. P.; Farooqui, F.; Hanna, N. B. *Tetrahedron Lett.* **1995**, 36, 8929 and references 1–3 therein. (c) Also see: Fallois, L. L. H.; Décout, J.-L.; Fontecave, M. *Tetrahedron Lett.* **1995**, 36, 9479.

(7) For illustrative reports regarding formation of bridges among nucleosides through their pyrimidine or purine rings and/or of inter-strand covalent cross-links in oligonucleotide and DNA duplexes, see the following papers (and references cited therein): (a) Wang, H.; Zuiderweg, E. R. P.; Glick, G. D. *J. Am. Chem. Soc.* **1995**, 117, 2981 (T-to-T disulfide bridges, from N3– $\text{CH}_2\text{CH}_2\text{SH}$). (b) Milton, J.; Connolly, B. A.; Nikiforov, T. T.; Cosstick, R. *J. Chem. Soc., Chem. Commun.* **1993**, 779 (T-to-T disulfide bridges through 4-thiothymine and 6-mercaptopurine bases). (c) Agathocleous, D. C.; Page, P. C. B.; Cosstick, R.; Galpin, I. J.; McLennan, A. G.; Prescott, M. *Tetrahedron* **1990**, 46, 2047 (dinucleosides bridged by a carbon chain through the amino groups). (d) Asseline, U.; Thuong, N. T. *Tetrahedron Lett.* **1994**, 35, 5221 (dC-dC derivative linked through the amino groups). (e) Kirchner, J. J.; Sigurdsson, S. T.; Hopkins, P. B. *J. Am. Chem. Soc.* **1992**, 114, 4021 (HNO_2 -promoted G-to-G links, C2–NH–C2). (f) Rink, S. M.; Solomon, M. S.; Taylor, M. J.; Rajur, S. B.; McLaughlin, L. W.; Hopkins, P. B. *J. Am. Chem. Soc.* **1993**, 115, 2551 (nitrogen mustard-promoted G-to-G links through N7). (g) Armstrong, R. W.; Salvati, M. E.; Nguyen, M. *J. Am. Chem. Soc.* **1992**, 114, 3144 (G-to-G and G-to-A links through N7 caused by carzinophilin). (h) Bose, D. S.; Thompson, A. S.; Ching, J.; Hartley, J. A.; Berardini, M. D.; Jenkins, T. C.; Neidle, S.; Hurley, L. H.; Thurston, D. E. *J. Am. Chem. Soc.* **1992**, 114, 4939 (pyrrolobenzodiazepine derivative, G-to-G links through the amino groups).

(8) Hayakawa, H.; Tanaka, H.; Maruyama, Y.; Miyasaka, T. *Chem. Lett.* **1985**, 1401. Hayakawa, H.; Tanaka, H.; Maruyama, Y.; Obi, K.; Miyasaka, T. *Nucleic Acids Symp. Ser.* **1985**, 16, 109.

17.4, 59.0, 67.8, 82.3, 82.5, 87.6, 101.4, 138.6, 144.9, 155.0; CIMS (NH_4^+) m/z 594 ($M + 18$).

2'-O-(Methanesulfonyl)-3-nitro-3',5'-O-(tetraisopropyl-disiloxane-1,3-diyl)uridine (3b). From **3a** plus NH_4NO_3 (4 mol/mol) and TFAA (8 mol/mol): reaction time = 20 min; 90% yield; white gum; $[\alpha]_D = +34.25$ (c 0.36, CH_2Cl_2); ^1H NMR (CDCl_3) δ 1.0–1.3 (m, 28 H), 3.22 (s, 3 H); 4.00 (dd, $J = 13.5$, 2.4, 1 H), 4.13 (dd, $J = 9.6$, 2.4, 1 H), 4.27 (d, $J = 13.5$, 1 H), 4.34 (dd, $J = 9.6$, 4.5, 1 H), 5.08 (d, $J = 4.5$, 1 H), 5.82 (s, 1 H), 5.84 (d, $J = 8.4$, 1 H), 7.85 (d, $J = 8.4$, 1 H); ^{13}C NMR (CDCl_3) δ 12.5, 12.7, 12.8, 13.4, 16.7, 16.8, 17.1, 17.3, 39.1, 58.8, 66.6, 82.1, 82.2, 89.4, 101.1, 138.5, 145.1, 154.9; CIMS (NH_4^+) m/z 627 ($M + 18$).

5'-O-(tert-Butyldimethylsilyl)-N³,O^{3'}-dinitrothymidine (4b). From **4a** plus NH_4NO_3 (6 mol/mol) and TFAA (12 mol/mol): reaction time = 20 min; 85% yield; white solid; mp 89.0–90.5 °C; ^1H NMR (CDCl_3) δ 0.16 (s, 6 H), 0.94 (s, 9 H), 2.01 (d, $J = 1.2$, 3 H), 2.28 (ddd, $J = 14.7$, 9.2, 6.4, 1 H), 2.64 (dd, $J = 14.7$, 5.7, 1 H), 3.93 (dd, $J = 11.5$, 1.9, 1 H), 4.01 (dd, $J = 11.5$, 2.0, 1 H), 4.30 (m, 1 H), 5.47 (d, $J = 6.4$, 1 H), 6.27 (dd, $J = 9.2$, 5.7, 1 H), 7.54 (d, $J = 1.2$, 1 H); ^{13}C NMR (CDCl_3) δ -5.5, -5.4, 12.8, 18.3, 25.8, 36.7, 63.5, 83.4, 84.1, 85.5, 110.9, 134.1, 145.2, 156.4; CIMS (NH_4^+) m/z 464 ($M + 18$). Anal. Calcd for $\text{C}_{16}\text{H}_{26}\text{N}_4\text{O}_9\text{Si}$: C, 43.04; H, 5.87; N, 12.55. Found: C, 42.90; H, 6.18; N, 12.30.

3-Nitro-3',5'-O-(tetraisopropyl-disiloxane-1,3-diyl)thymidine (5b). From **5a** plus NH_4NO_3 (4 mol/mol) and TFAA (8 mol/mol): reaction time = 20 min; 92% yield; white solid; mp 106.5–107.5 °C; ^1H NMR (CDCl_3) δ 0.99–1.10 (m, 24 H), 1.99 (d, $J = 1.2$, 3 H), 2.33 (ddd, $J = 13.8$, 7.6, 1.8, 1 H), 2.55 (ddd, $J = 13.8$, 10.3, 7.2, 1 H), 3.79 (ddd, $J = 8.4$, 2.8, 2.2, 1 H), 4.02 (dd, $J = 13.4$, 2.8, 1 H), 4.16 (dd, $J = 13.4$, 2.2, 1 H), 4.48 (ddd, $J = 10.3$, 8.4, 7.6, 1 H), 6.02 (dd, $J = 7.2$, 1.8, 1 H), 7.52 (q, $J = 1.2$, 1 H); ^{13}C NMR (CDCl_3) δ 12.4, 12.7, 12.8, 12.9, 13.5, 16.8, 16.9, 17.3, 17.4, 39.8, 59.7, 66.8, 85.1, 85.4, 109.8, 134.6, 145.0, 156.3; CIMS (NH_4^+) m/z 547 ($M + 18$); FABMS m/z 530 ($M + 1$). Anal. Calcd for $\text{C}_{22}\text{H}_{39}\text{N}_3\text{O}_8\text{Si}_2$: C, 49.88; H, 7.42; N, 7.93. Found: C, 49.69; H, 7.70; N, 7.81.

Reaction of 1b with $^{15}\text{NH}_3$. To a solution of $^{15}\text{NH}_4\text{Cl}$ (22 mg, 0.4 mmol) and K_2CO_3 (111 mg, 0.80 mmol) in water (1 mL), in a septum-closed vial, was added a solution of **1b** (178 mg, 0.40 mmol) in CH_3CN (1 mL; plus 2 mL to rinse the syringe). The mixture was either shaken or vigorously stirred for 6 days at rt. Afterwards, it was poured into a phosphate buffer solution and extracted with CH_2Cl_2 . The organic layer was dried with Na_2SO_4 , and the solvent was removed under vacuum. Purification of the residue by column chromatography over silica gel, with CH_2Cl_2 –MeOH 99:1 to 98:2 as the eluents, gave a pure product (chromatographically identical to **1a**), the NMR spectra of which showed the splittings expected for $^{15}\text{N}_3$ -labeled **1a**: 300-MHz ^1H NMR (CDCl_3) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 1.36 (s, 3 H), 1.59 (s, 3 H), 3.80 (dd, $J = 11.6$, 3.0, 1 H), 3.94 (dd, $J = 11.6$, 2.4, 1 H), 4.33 (m, 1 H), 4.68 (dd, $J = 6.0$, 3.0, 1 H), 4.78 (dd, $J = 6.4$, 2.7, 1 H), 5.70 (ddd, $J = 8.0$, $J_{\text{H5-N}} = 2.8$, $J_{\text{H5-NH}} = 2.2$, 1 H), 5.98 (d, $J = 2.7$, 1 H), 7.71 (d, $J = 8.0$, 1 H), 8.1 (concentration-dependent value, $J_{\text{HN}} = 90.8$, $J = 2.2$, 1 H); ^{13}C NMR (CDCl_3) δ -5.6, -5.5, 18.3, 25.3, 25.8, 27.2, 63.3, 80.2, 85.3, 86.6, 91.8, 102.1 (d, $J_{\text{CN}} = 7.3$, C5), 114.0, 140.6, 150.2 (d, $J_{\text{CN}} = 18.2$, C2), 163.4 (d, $J_{\text{CN}} = 9.1$, C4); CIMS (NH_4^+) m/z 417 ($M + 18$, 100), 400 ($M + 1$, 53) [$M(\text{C}_{18}\text{H}_{30}\text{N}_4^{15}\text{NO}_9\text{Si}) = 399$].

Reaction of 1b with Ethylenediamine. To a solution of **1b** (89 mg, 0.2 mmol) in anhyd CH_3CN (4 mL) was added finely powdered anhyd K_2CO_3 (21 mg, 0.15 mmol). To the resulting suspension was added a solution of ethylenediamine (1,2-ethanediamine, 7 μL , 0.1 mmol) in anhyd CH_3CN (1 mL) dropwise (over 1 h). After vigorous stirring for 2 days at rt, slow warming to 80 °C, and then refluxing for 7 h, the mixture was poured into an excess of phosphate buffer solution and extracted with CH_2Cl_2 . Drying of the organic phase, removal of the solvent under vacuum, and separation of the desired compound from polar byproducts by column chromatography (SiO_2 , CH_2Cl_2 –MeOH 98:2) gave 1,2-bis(5'-O-(tert-butyldimethylsilyl)-2',3'-O-isopropylideneuridin-3-yl)ethane, **6** (45 mg, 55%), as a white gum: ^1H NMR (CDCl_3) δ 0.08 (s, 2×6 H), 0.88 (s, 2×9 H), 1.36 (s, 2×3 H), 1.57 (s, 2×3 H), 3.75 (dd, $J = 11.6$, 3.5, 2×1 H), 3.91 (dd, $J = 11.6$, 2.4, 2×1 H), 4.2–4.4 (m, 6 H), 4.6–4.8 (m, 4 H), 5.58 (d, $J = 8.2$, 2×1 H), 5.89 (d, $J = 1.0$, 2×1 H), 7.64 (d, $J = 8.2$, 2×1 H); ^{13}C NMR (CDCl_3) δ -5.6, -5.5, 18.3, 25.4, 25.8, 27.2, 38.8, 63.1, 79.9, 85.9, 87.2, 92.9, 100.9, 113.7, 138.3, 150.9, 163.1; HRMS (FAB) calcd for $\text{C}_{38}\text{H}_{63}\text{N}_4\text{O}_{12}\text{Si}_2$ ($M + \text{H}^+$) m/z 823.3981, found 823.3906.

Reaction of 1b with 1,3-Propanediamine. To a solution of **1b** (222 mg, 0.50 mmol) in anhyd CH_3CN (5 mL) was added finely powdered anhyd K_2CO_3 (55 mg, 0.4 mmol). To the resulting suspension was added a solution of 1,3-propanediamine (21 μL , 0.25 mmol) in anhyd CH_3CN (3 mL) dropwise, over 1 h. After vigorous stirring for 2 days at rt, slow warming to 80 °C, and then refluxing for ca. 2 h, the solvent was removed and the residue was purified by column chromatography (SiO_2 , CH_2Cl_2 –MeOH 98:2) to afford 1,3-bis[5'-O-(tert-butyldimethylsilyl)-2',3'-O-isopropylideneuridin-3-yl]propane, **7** (120 mg, 57%), as a white gum: 300-MHz ^1H NMR (CDCl_3) δ 0.08 (s, 2×6 H), 0.89 (s, 2×9 H), 1.37 (s, 2×3 H), 1.59 (s, 2×3 H), 2.00 (m, 2 H), 3.80 (dd, $J = 11.5$, 3.1, 2×1 H), 3.92 (dd, $J = 11.5$, 2.5, 2×1 H), 4.02 (m, 4 H), 4.36 (m, 2×1 H), 4.73 (m, 2×2 H), 5.68 (d, $J = 8.1$, 2×1 H), 5.92 (d, $J = 2.1$, 2×1 H), 7.64 (d, $J = 8.1$, 2×1 H); ^{13}C NMR (CDCl_3) δ -5.6, -5.5, 18.2, 25.3, 25.8, 26.1, 27.2, 38.9, 63.3, 80.3, 85.9, 87.0, 93.2, 101.3, 113.8, 138.1, 150.7, 162.6. HRMS (FAB) calcd for $\text{C}_{39}\text{H}_{65}\text{N}_4\text{O}_{12}\text{Si}_2$ ($M + \text{H}^+$) m/z 837.4138, found 837.4098.

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Supporting Information Available: ^1H NMR spectra of compounds **1b**, **2b**, **3b**, **1a***, **6**, and **7** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.