Glucose-Derived 3′-(Carboxymethyl)-3′-deoxyribonucleosides and 2′,3′-Lactones as Synthetic Precursors for Amide-Linked Oligonucleotide Analogues[1]

Morris J. Robins,* Bogdan Doboszewski,[†] Victor A. Timoshchuk,[‡] and Matt A. Peterson*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

Received September 3, 1999

Treatment of a 1,2-*O*-isopropylidene-3-ketopentofuranose derivative (obtained from D-glucose) with [(ethoxycarbonyl)methylene]triphenylphosphorane and catalytic hydrogenation of the resulting alkene gave stereodefined access to 3-(carboxymethyl)-3-deoxy-D-ribofuranose derivatives. Esters of 5-*O*-acetyl- or 5-azido-5-deoxy-3-(carboxymethyl)-D-ribofuranose were coupled with nucleobases to give branched-chain nucleoside derivatives. Ester saponification and protecting group manipulation provided 2′-*O*-(*tert*-butyldimethylsilyl) ethers of 5′-azido-5′-deoxy- or 5′-*O*-(dimethoxytrityl) derivatives of 3′-(carboxymethyl)-3′-deoxyribonucleosides that are effective precursors for synthesis of amide-linked oligoribonucleosides.

Introduction

Interest in branched-chain nucleosides has been stimulated by their potential as antitumor and antiviral agents, and a number of (2′ or 3′)-branched-(2′ or 3′)-deoxy, and 2′,3′-dideoxy nucleoside analogues have been synthesized and evaluated in biological systems.[2] Additional impetus for the synthesis of 3′-branched-2′,3′-dideoxynucleosides was provided by their utility as building blocks for backbone-modified analogues of oligodeoxynucleotides for potential applications in antisense therapeutics.[3] Free radical-mediated coupling of [3′-*O*-(aryloxy)thiocarbonyl or 3′-deoxy-3′-iodo)]-2′-deoxynucleoside precursors with (allyl[4a] or styryl[4b])tributyltin/AIBN has been employed to introduce substituents at C3′ that were modified to generate internucleoside linkages for ribonucleotide-dimer mimics.[4b,5] Such radical couplings are highly stereoselective and give 3′-branched derivatives with the desired β-D-erythro configuration with 5′-O-protected 2′-deoxynucleoside substrates. However, analogous couplings with 5′-O-protected 3′-*O*-[(aryloxy)thiocarbonyl]ribonucleosides that have 2′-O-substituents gave 3′-branched derivatives with contaminating[5d] or predominant[6a] formation of the opposite (xylo) configuration, presumably resulting from the more sterically demanding effects of 2′-substituents on the α-face.

Very recently, the Novartis group[6b] and others[7] have reported adoption of our Wittig olefination/hydrogenation methodology for stereodefined synthesis of ribonucleoside amide precursors from 3′-ketonucleosides. We had described efficient syntheses of 3′-deoxy-3′-(ethoxycarbonyl)-methyl(adenosine or uridine) derivatives (80−90%) via hydrogenation of the 2′,5′-bis-*O*-TBDMS-3′-deoxy-3′-(ethoxycarbonyl)methylene(adenosine or uridine) Wittig adducts.[8a,b] Diastereoselective reduction was observed, and the 3′-(ethoxycarbonyl)methyl products had clean NMR spectra and underwent quantitative conversion into 2′,3′-lactones with the ribo configuration. This approach provides a valuable alternative to radical-coupling methods, which work well for 2′,3′-dideoxy analogues[4,5] but are not highly stereoselective for preparation of 3′-substituted-3′-deoxyribonucleosides.[5d,6] Saponification of the 3′-esters gave 3′-(carboxymethyl) analogues, which were condensed (DCC) with 5′-amino-5′-deoxynucleosides to give amide-linked ribonucleoside dimers.[8a,b]

We now report general methodology for the synthesis of 3′-(carboxymethyl)-3′-deoxyribonucleosides that includes efficient features of our work with adenosine and uridine and adds additional flexibility with other bases. Glucose is converted[8c] into derivatives of 3-deoxy-3-(carboxymethyl)-D-ribofuranose and 5-azido-3-(carboxymethyl)-3,5-dideoxy-D-ribofuranose, which undergo coupling with nucleobases to produce the protected 3′-

[†] Present address: Department of Fundamental Chemistry, Federal University of Pernambuco, Recife, Brazil.

[‡] Present address: TriLink Biotechnologies, San Diego, CA.

(1) Nucleic Acid Related Compounds. 111 (Amide-Linked Nucleosides. 3). For paper 110 (Amide-Linked Nucleosides. 2), see ref 8b.

(2) (a) Garg, N.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 5189−5202. (b) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 1368−1375. (c) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 746−754, and references therein.

(3) (a) *Oligodeoxynucleotides. Antisense Inhibitors of Gene Expression*; Cohen, J., Ed.; CRC Press: Boca Raton, 1989. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543−584. (c) Cazenave, C.; Hélène, C. In *Antisense Nucleic Acids and Proteins*; Mol, J. N. M., van der Krol, A. R., Eds.; Marcel Dekker: New York, 1991; pp 47−93. (d) *Antisense Research and Applications*; Crooke, S. T., Lebleu, B., Eds.; CRC Press: Boca Raton, 1993.

(4) (a) Chu, C. K.; Doboszewski, B.; Schmidt, W.; Ullas, G. V.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2767−2769. (b) Sanghvi, Y. S.; Bharadwaj, R.; Debart, F.; De Mesmaeker, A. *Synthesis* **1994**, 1163−1166.

(5) (a) Fiandor, J.; Tam, S. Y. *Tetrahedron Lett.* **1990**, *31*, 597−600. (b) Caulfield, T. J.; Prasad, C. V. C.; Prouty, C. P.; Saha, A. K.; Sardaro, M. P.; Schairer, W. C.; Yawman, A.; Upson, D. A.; Kruse, L. I. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2771−2776. (c) Grunder-Klotz, E.; Just, G. *Nucleosides Nucleotides* **1994**, *13*, 1829−1841. (d) Bhat, B.; Swayze, E. E.; Wheeler, P.; Dimock, S.; Perbost, M.; Sanghvi, Y. S. *J. Org. Chem.* **1996**, *61*, 8186−8199. (e) Leitzel, J. C. Ph.D. Dissertation, The University of Chicago, 1996. (f) Luo, P.; Leitzel, J. C.; Zhan, Z.-Y. J.; Lynn, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 3019−3031.

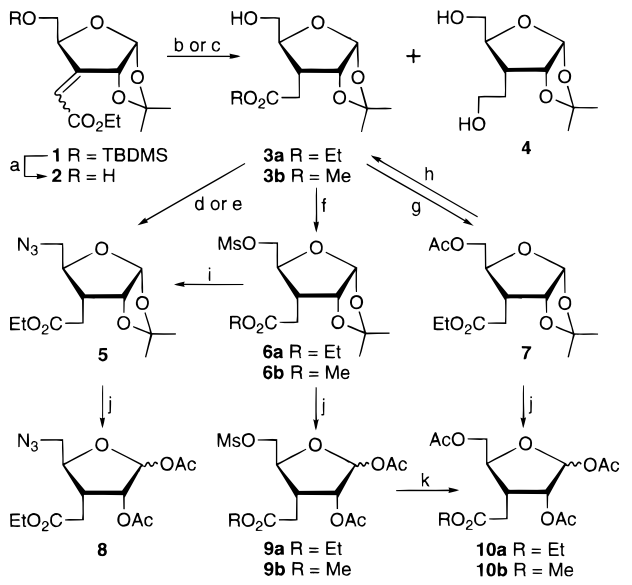
(6) (a) De Mesmaeker, A.; Lesueur, C.; Bévièrre, M.-O.; Waldner, A.; Fritsch, V.; Wolf, R. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2790−2794. (b) von Matt, P.; Lochmann, T.; Kesselring, R.; Altmann, K.-H. *Tetrahedron Lett.* **1999**, *40*, 1873−1876.

(7) Lu, D.-M.; Min, J.-M.; Zhang, L.-H. *Carbohydr. Res.* **1999**, *317*, 193−197.

(8) (a) Robins, M. J.; Sarker, S.; Xie, M.; Zhang, W.; Peterson, M. A. *Tetrahedron Lett.* **1996**, *37*, 3921−3924. (b) Peterson, M. A.; Nilsson, B. L.; Sarker, S.; Doboszewski, B.; Zhang, W.; Robins, M. J. *J. Org. Chem.* **1999**, *64*, 8183−8192. (c) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178−5179.

10.1021/jo991399g CCC: $19.00 © 2000 American Chemical Society
Published on Web 04/21/2000

Scheme 1[a]



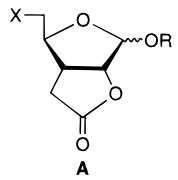
[a] Key: (a) Bu_4NF/THF; (b) H_2/Pd−C/EtOH; (c) $NaBH_4$/EtOH; (d) Ph_3P/DEAD/HN_3; (e) Ph_3P/CBr_4/LiN_3; (f) MsCl/DMAP/pyridine/CH_2Cl_2; (g) Ac_2O/DMAP/pyridine/CH_2Cl_2; (h) NaOMe/MeOH; (i) NaN_3/DMF/Δ;. (j) H_2SO_4/Ac_2O/HOAc; (k) CsOAc/DMF/Δ.

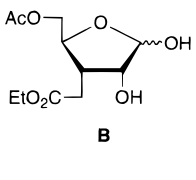
(carboxymethyl)-3′-deoxyribonucleosides. The azido function serves as a convenient "masked amino group" that can be reduced to provide 5′-amino-3′-(carboxymethyl)-3′,5′-dideoxy residues for incorporation into amide-linked oligonucleosides.

Results and Discussion

Treatment of 5-*O*-TBDMS-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose[9] with [(ethoxycarbonyl)-methylene]triphenylphosphorane gave (*E*/*Z*)-**1** (∼7:1; 90%) (Scheme 1). Desilylation of **1** gave **2**, and hydrogenation of **2** (25 psi H_2/Pd−C) gave **3a** plus trace amounts of the over-reduced diol **4**. Formation of **4** was minimized at lower hydrogen pressure (5 psi). Reduction of **2** with $NaBH_4$/EtOH gave **3a** and **4**, but the proportion of **4** was much greater. We then reexamined our prior preparation of **3a** from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Whereas "clean" reduction of the double bond was observed with the lot of $NaBH_4$ used in our original work,[8c] over-reduction of the ester function to give contaminating diol was observed with the same excess of freshly opened $NaBH_4$. A 1,2-*O*-isopropylidene group is known to direct incoming reagents to the β-face of furanosyl carbohydrate derivatives with erythro or ribo configurations,[10] and ribo diastereomers **3a** and **4** were obtained with either catalytic hydrogenation or chemical reduction.

Alcohol **3a** was converted directly into the 5-azido derivative **5** (91%) under Mitsunobu[11] (Ph_3P/DEAD/HN_3) conditions, whereas the modified Appel[12] reaction (Ph_3P/CBr_4/LiN_3)[13] with **3a** was much less efficient (**5**, 21%). The use of hydrazoic acid was avoided with larger scale preparations. Thus, alcohol **3a** was converted into its mesylate **6a** (93%), which was treated with NaN_3/DMF to give **5** (88%). Attempted removal of the isopropylidene group from **5** by various mildly acidic methods[14,15] resulted in formation of products identified spectroscopically as lactones, **A**, which is consistent with results involving similar compounds.[10b,16]





Acetolysis of **5** (H_2SO_4/Ac_2O/HOAc) gave the diacetate **8** in moderate yields (∼50%), and acetolysis of the 5-*O*-mesyl compound **6a** gave diacetate **9a** in 70% yield. In marked contrast, the 5-*O*-acetyl derivative **7** [obtained smoothly (97%) by acetylation of **3a**] gave low yields of triacetate **10a** upon parallel acetolysis, and manipulation of reaction conditions gave little improvement. Hydrolysis of the isopropylidene group from **7** gave lactone **A** (R = H, X = OAc) plus small quantities of diol **B**. However, nucleophilic displacement of mesylate from **9a** by acetate (CsOAc/DMF) proceeded without incident to give the triacetate **10a** (83%).

A large-scale preparation of **7** had been performed (in anticipation of its conversion into **10a**). Deacetylation of this **7** (NaOMe/MeOH) gave **3b** (concomitant transesterification), which was mesylated to give **6b**. Acetolysis of **6b** gave diacetate **9b** (63%), which was converted into triacetate **10b** (71%) with CsOAc/DMF.

Adenine ($SnCl_4$),[17] or trimethylsilylated derivatives of 6-*N*-benzoyladenine, thymine, or uracil (TMSOTf),[18] underwent coupling with the 5-azido diacetate **8**, or triacetates **10a** or **10b**, to give the 3′-branched nucleoside derivatives **11**−**18** (Scheme 2). Treatment of **12**, **13**, **16**, or **17** with NaOMe/MeOH effected deacetylation with accompanying transesterification and lactonization [the esters were more polar than the lactones (TLC)].

Saponification (NaOH/H_2O/MeOH) of **11** or **13** gave the 3′-(carboxymethyl) sodium salts (TLC baseline). However, neutralization, attempted purification, or other manipulation of these salts resulted in partial lactonization. This side reaction was minimized by drying and silylating the crude mixtures directly. Thus, volatiles were evaporated from the saponification solutions (without neutralization), and then dried DMF/pyridine was added and evaporated several times. The residues were dried in vacuo, and then stirred with TBDMSCl/DMF/pyridine for several days at ambient temperature to give mixtures (∼1:2) of lactones

(9) Yoshimura, Y.; Sano, T.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 162−167.

(10) (a) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 4477−4481. (b) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, 3715−3718. (c) Mazur, A.; Tropp, B. E.; Engel, R. *Tetrahedron* **1984**, *40*, 3949−3956. (d) Pudlo, J. S.; Townsend, L. B. *Tetrahedron Lett.* **1990**, *31*, 3101−3104. (e) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon: New York, 1983.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

(12) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.

(13) Castro, B. R. *Org. React.* **1983**, *29*, 1−162.

(14) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

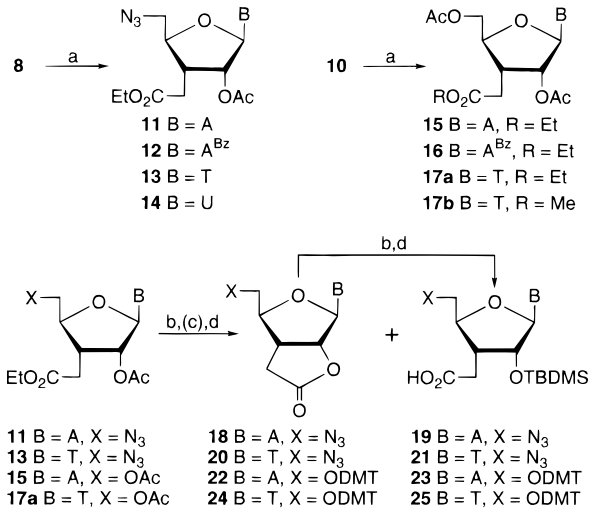
(15) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994.

(16) (a) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 3657−3660. (b) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, 3719−3722. (c) Anderson R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 3870−3871. (d) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1977**, 2865−2868.

(17) Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518−2521.

(18) Vorbrüggen, H. *Acc. Chem. Res.* **1995**, *28*, 509−520.

Scheme 2[a]



[a] Key: (a) adenine/$SnCl_4$/MeCN or $B(TMS)_n$/TMSOTf/DCE/Δ; (b) NaOH/H_2O/MeOH; (c) DMTCl/Et_3N/pyridine; (d) TBDMSCl/DMF/pyridine or TBDMS-imidazolide/CH_2Cl_2/DMF.

(**18** or **20**) and 2′-*O*-TBDMS-3′-(carboxymethyl) derivatives (**19** or **21**), respectively.

Esters **15** or **17** were saponified (NaOH/H_2O/MeOH), and the carboxylate salts were converted into their 5′-*O*-(4,4′-dimethoxytrityl)-2′,3′-lactones **22** or **24**, respectively, with DMTCl/DMF/Et_3N/pyridine. Base-promoted hydrolysis of the lactones and treatment of the resulting carboxylate salts with TBDMS-imidazolide/imidazole/DMF/CH_2Cl_2[19] gave mixtures of lactones **22** or **24** and the 3′-(carboxymethyl)-5′-*O*-DMT-2′-*O*-TBDMS derivatives **23** or **25**, respectively. The acids **19**, **21**, **23**, or **25** were readily separated from the lactone byproducts **18**, **20**, **22**, or **24**, which were recycled (hydrolysis and silylation).

Protection of the 2′-hydroxyl group to give **19**, **21**, **23**, and **25** was very slow, even with a large excess of silylating agent. TBDMSCl/pyridine was adequate for **19** and **21**, but TBDMS-imidazolide[19] was required to give reasonable yields of **23** and **25**. The TBDMS-triazolide analogue[20] was no more effective than the imidazolide, and TBDMS−OTf[21] caused cleavage of the acid-sensitive 5′-*O*-DMT group of **23** and **25**.

Summary

Conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose into a 5-*O*-TBDMS-3-ketone, Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane, removal of TBDMS protection, and catalytic hydrogenation of the *E*/*Z* adducts gave the 3-deoxy-3-[(ethoxycarbonyl)methyl] sugar **3a**. Its 5-*O*-mesyl derivative **6a** was transformed into 1,2-di-*O*-acetyl-5-azido, **8**, and 1,2,5-tri-*O*-acetyl, **10a**, intermediates that were coupled with nucleobases. Base-promoted hydrolysis followed by silylation gave 2′-*O*-TBDMS-3′-(carboxymethyl)-3′-deoxyribonucleosides. The 5′-azido group provides a "masked" primary amine for condensation with activated 3′-(carboxymethyl)nucleosides for synthesis of amide-linked oligomers. Catalytic hydrogenation of Wittig adduct **2** gave **3a** much more readily than parallel reductions of analogous unsaturated nucleosides. The present approach is more convenient and versatile than such parallel syntheses.[6b,7,8a,b]

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. NMR spectra were determined with solutions in $Me_4Si/CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C) unless otherwise noted. Protons labeled "ex" were exchanged with D_2O, but exchange was not performed with all NMR samples. Observed ("apparent") multiplicities are noted with quotation marks for ^1H NMR peaks that should exhibit more complex splitting. High-resolution mass spectra (MS) were determined under FAB conditions (NaOAc/thioglycerol matrix) unless otherwise noted (CH_4 was used for CI). Reagent chemicals were used, and solvents were dried by distillation from standard drying agents (under N_2). TLC was performed with Merck kieselgel 60-F_{254} sheets with visualization under 254-nm light, or by spraying (5% H_2SO_4/EtOH) and then heating the sheet.

5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-[(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (1). Oxidation[9] of 5-*O*-TBDMS-1,2-*O*-isopropylidene-α-D-xylofuranose (22.0 g, 72.3 mmol), treatment of the resulting 3-ulose with [(ethoxycarbonyl)methylene]triphenylphosphorane [30.4 g (95%), 83.1 mmol] in CH_2Cl_2 (350 mL) overnight at ambient temperature, evaporation of volatiles, filtration of a solution of the residue in CH_2Cl_2 through silica gel (CH_2Cl_2 followed by MeOH/CH_2Cl_2, 0.1:20), and evaporation of volatiles gave an *E*/*Z* mixture (~7:1) of **1** (24.3 g, 90%) as an oil: ^1H NMR (major isomer) δ 6.01 (t, J = 1.7 Hz, 1H), 5.91 (d, J = 4.3 Hz, 1H), 5.68−5.62 (m, 1H), 4.85 (hept, J = 1.9 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.81 (dd, J = 4.2, 10.0 Hz, 1H), 3.73 (dd, J = 3.4, 10.0 Hz, 1H), 1.48, 1.43 (2 × s, 2 × 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.052, 0.045 (2 × s, 2 × 3H); ^{13}C NMR δ 164.9, 156.8, 116.4, 112.7, 105.3, 81.0, 78.8, 65.3, 60.5, 27.4, 27.2, 25.7, 18.1, 14.1, −5.5, −5.6; MS *m*/*z* 395.1873 (MNa^+ [$C_{18}H_{32}O_6NaSi$] = 395.1866).

3-Deoxy-3-[(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (2). Bu_4NF/THF (1 M, 22 mL, 22 mmol) was added to a cold solution of **1** (6.8 g, 18 mmol) in THF (150 mL), and stirring was continued at 4 °C for 5 h and then ambient temperature for 2 h. Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 0.4:20) to give **2** (4.47 g, 95%) as a syrup: ^1H NMR (Me_2SO-d_6) δ 6.04 (t, J = 1.7 Hz, 1H), 5.90 (d, J = 4.0 Hz, 1H), 5.58−5.52 (m, 1H), 4.95 (t, J = 5.5 Hz, 1H, ex), 4.77 (heptet, J = 1.8 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.64 (dd, J = 4.5, 11.0 Hz, 1H), 3.53 (dd, J = 5.5, 12.0 Hz, 1H), 1.38, 1.35 (2 × s, 2 × 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (major isomer) δ 164.8, 154.8, 116.7, 112.7, 104.8, 80.4, 78.3, 62.9, 60.6, 27.1, 26.9, 13.9; MS (CI) *m*/*z* 259.1190 (MH^+ [$C_{12}H_{19}O_6$] = 259.1182).

3-Deoxy-3-[(ethoxycarbonyl)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (3a) and 3-Deoxy-3-(2-hydroxyethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (4). Method A. Hydrogenation of **2** (4.1 g, 16 mmol) in EtOH (30 mL) [H_2/25 psi, 5% Pd−C (0.3 g), Parr apparatus] for 4 h gave **3a** and **4**. TLC (MeOH/CH_2Cl_2, 0.8:20) showed that **2** and **3a** had identical mobilities, but **3a** was UV transparent. The catalyst was filtered (with Celite), the filtrate was evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 0.2:10) to give **3a**[8c] (3.0 g, 73%). Further elution of the column (MeOH/CH_2Cl_2, 1:20) gave **4** (120 mg, 3.5%).

Method B. Hydrogenation of **2** (30 mg, 0.12 mmol) in EtOH (5 mL) [H_2/5 psi, 10% Pd−C (3 mg), Parr apparatus] for 12 h gave **3a** (no **4** detected by TLC). The catalyst was filtered (with Celite), the filtrate was evaporated, and the residue was chromatographed (PTLC, EtOAc/hexanes, 1:1) to give **3a** (26 mg, 86%).

(19) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686−1695.
(20) Fabrega, C.; Eritja, R.; Sinha, N. D.; Dosanjh, M. K.; Singer, B. *Bioorg. Med. Chem.* **1995**, *3*, 101−108.
(21) (a) LaLonde, M.; Chan, T. H. *Synthesis* **1985**, 817−845. (b) Jones, D. M.; Nilsson, B.; Szelke, M.; *J. Org. Chem.* **1993**, *58*, 2286−2290.

Method C. Treatment of **2** (4.47 g, 17.3 mmol) with "freshly opened" $NaBH_4$ (0.96 g, 25 mmol) in dried EtOH (100 mL) overnight also gave **3a** (1.95 g, 43%), plus the alcohol **4** (1.29 g, 34%): ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 5.68 (d, J = 3.6 Hz, 1H), 4.77 (t, J = 5.9 Hz, 1H, ex), 4.64 (t, J = 5.1 Hz, 1H, ex), 4.61 (t, J = 4.2 Hz, 1H), 3.68 (ddd, J = 2.7, 4.6, 10.3 Hz, 1H), 3.61−3.57 (m, 1H; overlap with H_2O peak), 3.52 (ddd, J = 5.1, 7.6, 10.5 Hz, 1H), 3.46−3.41 (m, 1H), 3.38 (dd, J = 4.9, 12.2 Hz, 1H), 1.91 (dddd, J = 5.0, 5.0, 10.1, 10.1 Hz, 1H), 1.64−1.57, 1.52−1.44 (2 × m, 2 × 1H), 1.35, 1.22 (2 × s, 2 × 3H); ^{13}C NMR (Me_2SO-d_6) δ 110.5, 104.6, 82.6, 80.9, 61.1, 59.3, 41.0, 28.0, 26.8, 26.5; MS (CI) m/z 219.1238 (MH^+ [$C_{10}H_{19}O_5$] = 219.1232).

5-Azido-3,5-dideoxy-3-[(ethoxycarbonyl)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (5). Method A. Ph_3P (2.0 g, 7.6 mmol), DEAD (1.2 mL, 1.3 g, 7.6 mmol), and HN_3/toluene [8 mL; stock solution prepared from NaN_3 (3.0 g) and H_2SO_4 (1.1 mL) in 30 mL of toluene[22]] were added to a solution of **3a** (500 mg, 1.92 mmol) in dioxane (40 mL), and stirring was continued (under Ar) for 30 min (TLC showed conversion of **3a** into a less polar product). Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 0.1:20, or EtOAc/hexanes, 1:9) to give **5** (500 mg, 91%) as an oil.

Method B. Ph_3P (1.3 g, 5.0 mmol), CBr_4 (1.9 g, 5.7 mmol), and LiN_3 (0.56 g, 11 mmol) were added to a solution of **3a** (1.0 g, 3.8 mmol) in dioxane (40 mL), and stirring (under Ar) was continued for 96 h (the major amount of **3a** remained unreacted). Volatiles were evaporated, and the residue was chromatographed to give **5** (230 mg, 21%).

Method C. A solution of mesylate **6a** (700 mg, 2.10 mmol) and NaN_3 (960 mg, 14.8 mmol) in DMF (30 mL) was stirred at 90 °C for 4 h. The solution was cooled, CH_2Cl_2 and H_2O were added, and the aqueous layer was extracted (CH_2Cl_2). The combined organic phase was evaporated, xylene was added and evaporated several times, and the brown oil was dried in vacuo. Filtration through a short bed of silica gel (CH_2Cl_2) gave **5** (520 mg, 88%): ^{1}H NMR δ 5.85 (d, J = 3.7 Hz, 1H), 4.80 (t, J = 3.9 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.97 (dt, J = 3.7, 9.9 Hz, 1H), 3.61 (dd, J = 3.1, 13.5 Hz, 1H), 3.26 (dd, J = 4.4, 13.5 Hz, 1H), 2.79−2.59 (m, 1H), 2.49−2.28 (m, 2H), 1.50, 1.33 (2 × s, 2 × 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 171.1, 110.9, 104.4, 80.5, 79.2, 60.1, 50.9, 40.9, 29.0, 26.5, 26.3, 14.0; MS (CI) m/z 270.1102 (M − CH_3 [$C_{11}H_{16}N_3O_5$] = 270.1090).

Methyl 5-Azido-3-(carboxymethyl)-3,5-dideoxy-D-ribofuranoside 2,3-lactone (A; R = CH_3, X = N_3). A suspension of **5** (147 mg, 0.515 mmol) and Dowex 50W-X8 (H^+) resin (400 mg) in H_2O/MeOH (1:10, 11 mL) was refluxed overnight (TLC, $MeOH/CH_2Cl_2$, 0.2:20, showed conversion of **5** into a more polar product). The resin was filtered, volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 0.2:20) to give an anomeric mixture (~6:1) of the title compound (100 mg, 91%): ^{1}H NMR (Me_2SO-d_6, major anomer) δ 5.11 (s, 1H), 4.91 (d, J = 5.4 Hz, 1H), 4.19 (ddd, J = 4.2, 4.3, 6.4 Hz, 1H), 3.39−3.32 (m, 5H), 2.99−2.83 (m, 2H), 2.68−2.58 (m, 1H); ^{13}C NMR (Me_2SO-d_6, major anomer*) δ 175.8, 107.0*, 101.3, 86.3*, 85.6*, 81.5, 80.6, 55.0*, 54.5*, 54.3, 52.5, 38.3, 33.1*, 32.4; MS (CI) m/z 214.0830 (MH^+ [$C_8H_{12}N_3O_4$] = 214.0828).

3-Deoxy-3-[(ethoxycarbonyl)methyl]-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-ribofuranose (6a). A solution of **3a** (8.06 g, 31.0 mmol), mesyl chloride (6.0 mL, 8.9 g, 78 mmol), pyridine (12.5 mL), and DMAP (trace) in CH_2Cl_2 (200 mL) was stirred overnight at ambient temperature (TLC, $MeOH/CH_2Cl_2$, 0.4:20, showed conversion of **3a** to a less polar product). The solution was cooled in an ice bath, H_2O was added, and stirring was continued for 3 h. Extraction workup, chromatography (EtOAc/hexanes 4:6), and recrystallization (hexanes/EtOAc) gave **6a** (9.75 g, 93%): mp 60−62 °C; ^{1}H NMR δ 5.81 (d, J = 3.4 Hz, 1H), 4.82 (t, J = 4.0 Hz, 1H), 4.45 (dd, J = 2.2, 11.7 Hz, 1H), 4.25 (dd, J = 4.2, 12.0 Hz, 1H), 4.17 (q, J = 7.4 Hz, 2H), 4.06 (ddd, J = 2.6, 4.4, 9.9 Hz, 1H), 3.07 (s, 3H), 2.72 (dd, J = 10.4, 18.0 Hz, 1H), 2.50−2.31 (m, 2H), 1.58, 1.33 (2 × s, 2 × 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 171.5, 112.1, 104.8, 81.1, 78.5, 68.4, 60.9, 40.8, 37.7, 29.7, 26.7, 26.3, 14.1; MS m/z 361.0916 (MNa^+ [$C_{13}H_{22}O_8NaS$] = 361.0933). The extract of **6a** (without chromatography) could be used for the preparation of azide **5** or diacetate **9a**.

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-3-[(methoxycarbonyl)methyl]-α-D-ribofuranose (6b). Treatment of **7** (5.5 g, 18 mmol) with NaOMe/MeOH [Na (chips) in MeOH (300 mL)] overnight, neutralization (CO_2), evaporation of volatiles, and addition of toluene and evaporation gave a light yellow oil. This oil was dissolved in CH_2Cl_2 (250 mL), pyridine (15 mL), MsCl (7.30 mL, 10.8 g, 94.3 mmol), and DMAP (trace) were added, and stirring was continued overnight. H_2O (3 mL) was added, and stirring was continued for 3 h. Extraction workup and chromatography ($MeOH/CH_2Cl_2$, 0.15:20) gave **6b** (3.7 g, 63%), which crystallized spontaneously: mp 77−78 °C; ^{1}H NMR (500 MHz) δ 5.83 (d, J = 3.4 Hz, 1H), 4.81 (t, J = 3.9 Hz, 1H), 4.43 (dd, J = 2.4, 11.7 Hz, 1H), 4.26 (dd, J = 4.4, 11.7 Hz, 1H), 4.05 (ddd, J = 2.2, 4.9, 10.0 Hz, 1H), 3.72, 3.07 (2 × s, 2 × 3H), 2.73 (dd, J = 10.3, 18.1 Hz, 1H), 2.44−2.39 (m, 2H), 1.50, 1.33 (2 × s, 2 × 3H); ^{13}C NMR δ 171.9, 112.0, 104.8, 81.0, 78.3, 68.2, 52.0, 40.8, 37.6, 29.4, 26.7, 26.3; MS (thioglycerol) m/z 325.0942 (MH^+ [$C_{12}H_{21}O_8S$] = 325.0957).

5-*O*-Acetyl-3-deoxy-3-[(ethoxycarbonyl)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (7). Acetylation (Ac_2O/pyridine) of **3a** (8.10 g, 31.1 mmol) and extraction workup gave **7** (9.15 g, 97%): ^{1}H NMR (Me_2SO-d_6) δ 5.79 (d, J = 3.6 Hz, 1H), 4.72 (t, J = 4.1 Hz, 1H), 4.22 (dd, J = 1.8, 12.2 Hz, 1H), 4.12−3.85 (m, 4H), 2.51 (d, J = 7.2 Hz, 2H; partial overlap with solvent peaks), 2.28−2.05 (m, 1H), 2.03, 1.40, 1.24 (3 × s, 3 × 3H), 1.19 (t, J = 7.0 Hz, 3H); ^{1}H NMR δ 5.82 (d, J = 3.2 Hz, 1H), 4.78 (t, J = 4.1 Hz, 1H), 4.27 (dd, J = 2.5, 12.1 Hz, 1H), 4.20−4.07 (m, 3H), 3.96 (ddd, J = 2.7, 5.3, 10.1 Hz, 1H), 2.69 (dd, J = 9.7, 16.9 Hz, 1H), 2.38 (dd, J = 4.2, 16.6 Hz, 1H), 2.35−2.19 (m, 1H), 2.07, 1.48, 1.30 (3 × s, 3 × 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C δ 171.9, 170.9, 111.8, 104.9, 80.9, 78.5, 63.4, 60.7, 41.2, 29.5, 26.5, 26.2, 20.7, 14.0; MS (thioglycerol) m/z 303.1461 (MH^+ [$C_{14}H_{23}O_7$] = 303.1444.

5-*O*-Acetyl-3-(carboxymethyl)-3-deoxy-D-ribofuranose 2,3-lactone (A; R = H, X = OAc) and 5-*O*-Acetyl-3-deoxy-3-[(ethoxycarbonyl)methyl]-D-ribofuranose (B). A solution of **7** (150 mg, 0.496 mmol) in AcOH/H_2O (8:2, 14 mL) was refluxed for 40 min [TLC showed lactone **A** (R = H, X = OAc) (major) plus diol **B** (minor)]. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:20) to give **A** (R = H, X = OAc) (70 mg, 65%): ^{1}H NMR (Me_2SO-d_6) δ 6.89 (d, J = 4.6 Hz, 0.75H, ex), 6.79 (d, J = 4.8 Hz, 0.25H, ex), 5.40 (d, J = 4.6 Hz, 0.25H), 5.33 (d, J = 4.8 Hz, 0.75H), 4.84 (dd, J = 4.0, 8.9 Hz, 0.25H), 4.77 (d, J = 5.4 Hz, 0.75H), 4.16−4.03, 3.05−2.57 (2 × m, 2 × 3H), 2.03 (s, 3H); ^{13}C NMR (major anomer) δ 175.4, 171.2, 101.2, 87.6, 85.4, 66.7, 39.5, 33.9, 20.8; MS (CI) m/z 217.0728 (MH^+ [$C_9H_{13}O_6$] = 217.0712).

Further elution gave **B** (6 mg, 5%): ^{1}H NMR (Me_2SO-d_6) δ 6.24 (d, J = 4.6 Hz, 1H, ex), 5.14 (d, J = 4.8 Hz, 1H, ex), 4.98 (d, J = 4.6 Hz, 1H), 4.19 (dd, J = 2.2, 11.0 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.96−3.78, 2.57−2.33 (2 × m, 2 × 3H), 2.01 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 172.2, 170.6, 102.5, 79.6, 75.7, 66.9, 60.1, 30.0, 20.8, 14.2; MS (CI) m/z 263.1115 (MH^+ [$C_{11}H_{19}O_7$] = 263.1131).

1,2-Di-*O*-acetyl-5-azido-3,5-dideoxy-3-[(ethoxycarbonyl)methyl]-D-ribofuranose (8). A solution of **5** (500 mg, 1.75 mmol) in HOAc (10 mL)/Ac_2O (1 mL)/H_2SO_4 (0.55 mL) was stirred overnight (TLC, $MeOH/CH_2Cl_2$, 0.1:20, developed twice, showed conversion of **5** to a slightly more polar product). Extraction workup and chromatography ($MeOH/CH_2Cl_2$, 0.1:20) gave an anomeric mixture (~8:1) of **8** (290 mg, 50%) as a syrup: ^{1}H NMR (major anomer) δ 6.10 (s, 1H), 5.33 (d, J = 4.8 Hz, 1H), 4.16 ("q", J = 7.1 Hz, 3H), 3.65 (dd, J = 3.2, 13.4 Hz, 1H), 3.24 (dd, J = 4.1, 13.5 Hz, 1H), 3.05−2.87 (m, 1H), 2.55 (dd, J = 8.5, 16.4 Hz, 1H), 2.39 (dd, J = 6.4, 16.4 Hz, 1H), 2.12 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (major anomer*) δ 170.9, 169.5, 169.1, 98.5*, 95.0, 83.4*, 83.2, 77.6*,

(22) Wolff, H. *Org. React.* **1947**, *III*, 307−336.

72.0, 61.0*, 60.9, 53.0, 52.6*, 37.8*, 36.2, 33.3, 30.3*, 21.0*, 20.5*, 14.1*; MS *m/z* 352.1104 (MNa^+ [$C_{13}H_{19}N_3O_7Na$] = 352.1121].

1,2-Di-*O*-acetyl-3-deoxy-3-[(ethoxycarbonyl)methyl]-5-*O*-methanesulfonyl-D-ribofuranose (9a). A solution of **6a** (930 mg, 2.75 mmol) in HOAc (20 mL)/Ac_2O (2 mL)/H_2SO_4 (1.1 mL) was stirred overnight (TLC, MeOH/CH_2Cl_2, 0.25:20, showed conversion of **6a** to a more polar product). Extraction workup and chromatography (MeOH/CH_2Cl_2, 0.25:20) gave **9a** (740 mg, 70%): ^{1}H NMR δ 6.08 (s, 1H), 5.32 (d, J = 4.8 Hz, 1H), 4.41 (dd, J = 2.2, 10.6 Hz, 1H), 4.39−4.24 (m, 3H), 4.16 (q, J = 7.2 Hz, 1H), 3.07 (s, 3H), 2.93−2.80 (m, 1H), 2.62 (dd, J = 6.8, 16.6 Hz, 1H), 2.48 (dd, J = 7.0, 16.6 Hz, 1H), 2.12 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (major anomer*) δ 170.9, 169.5, 169.2, 98.5*, 94.9, 82.1*, 82.0, 77.2*, 71.8, 70.4*, 70.0, 61.1*, 37.6*, 37.5*, 35.9, 33.1, 21.0, 20.5, 14.0; MS *m/z* 405.0816 (MNa^+ [$C_{14}H_{22}O_{10}NaS$] = 405.0831).

1,2-Di-*O*-acetyl-3-deoxy-5-*O*-methanesulfonyl-3-[(methoxycarbonyl)methyl]-α-D-ribofuranose (9b). A solution of **6b** (3.0 g, 9.3 mmol) in HOAc (40 mL)/Ac_2O (4 mL)/H_2SO_4 (2.2 mL) was stirred for 7 h (TLC, MeOH/CH_2Cl_2, 0.25:20, developed twice, showed conversion of **6b** to a slightly more polar product). Extraction workup gave clean **9b** (2.16 g, 63%): ^{1}H NMR δ 6.42 (d, J = 4.0 Hz, 0.15H), 6.09 (s, 0.85H), 5.32 (d, J = 5.0 Hz, 1H), 4.42−4.19 (m, 3H), 3.73, 3.07 (2 × s, 2 × 3H), 2.94−2.80 (m, 1H), 2.63 (dd, J = 7.3, 16.7 Hz, 1H), 2.48 (dd, J = 7.0, 16.7 Hz, 1H), 2.12, 2.11 (2 × s, 2 × 3H); ^{13}C NMR δ 171.3, 169.6, 169.3, 98.5, 82.1, 70.4, 52.2, 37.8, 37.6, 30.4, 21.0, 20.6; MS *m/z* 391.0680 (MNa^+ [$C_{13}H_{20}O_{10}NaS$] = 391.0675).

1,2,5-Tri-*O*-acetyl-3-deoxy-3-[(ethoxycarbonyl)methyl]-D-ribofuranose (10a). Method A. A solution of **7** (141 mg, 0.466 mmol) in HOAc (10 mL)/Ac_2O (1 mL)/H_2SO_4 (0.5 mL) was stirred for 3 h [TLC, EtOAc/hexanes, 1:3, showed conversion of **7** to a more polar product (major) and a less polar byproduct (trace)]. Extraction workup and chromatography (EtOAc/hexanes 1:4) gave **10a** (41 mg, 25%).

Method B. A suspension of CsOAc (6.03 g, 31.4 mmol) in DMF (200 mL) was stirred at reflux for 3 h, and the oil bath was cooled to 120 °C. A solution of **9a** (4.00 g, 10.5 mmol) in DMF (30 mL) was added, stirring was continued for 20 min (TLC, EtOAc/hexanes, 1:2, showed conversion of **9a** into a less polar product), and volatiles were evaporated. Extraction workup and chromatography (EtOAc/hexanes, 1:2) of the brown residue gave **10a** (2.99 g, 83%): ^{1}H NMR δ 6.11 (s, 1H), 5.30 (d, J = 4.8 Hz, 1H), 4.29−4.06 (m, 5H), 2.88−2.72 (m, 1H), 2.56 (dd, J = 8.6, 16.6 Hz, 1H), 2.44 (dd, J = 6.5, 16.7 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.1, 170.7, 169.7, 169.2, 98.7, 82.1, 77.1, 65.2, 61.0, 37.9, 30.3, 21.0, 20.7, 20.5, 14.0; MS (CI) *m/z* 347.1339 (MH^+ [$C_{15}H_{23}O_9$] = 347.1342).

1,2,5-Tri-*O*-acetyl-3-deoxy-3-[(methoxycarbonyl)methyl]-D-ribofuranose (10b). A suspension of CsOAc (3.16 g, 16.5 mmol) in DMF (40 mL) was stirred at reflux for 1 h, and the oil bath was cooled to ∼120 °C. A solution of **9b** (1.82 g, 4.94 mmol) in DMF (40 mL) was added, stirring was continued for 80 min (TLC, EtOAc/hexanes, 1:1, showed conversion of **9b** to a less polar product), and volatiles were evaporated. Extraction workup, chromatography (EtOAc/hexanes 1:2), and recrystallization (hexanes/EtOAc) gave **10b** (1.17 g, 71%) with mp 85−88 °C: ^{1}H NMR δ 6.41 (d, J = 4.2 Hz, 0.15H), 6.10 (s, 0.85H), 5.31 (d, J = 4.4 Hz, 1H), 4.35−4.08 (m, 3H), 3.70 (s, 3H), 2.88−2.74 (m, 1H), 2.59 (dd, J = 8.6, 16.4 Hz, 1H), 2.47 (dd, J = 5.8, 16.4 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (major anomer*) δ 171.4, 170.6, 169.6, 169.1, 98.7*, 95.0, 82.1*, 82.0, 77.2*, 72.0, 65.2*, 65.1, 52.1*, 38.1*, 36.3, 33.0, 30.2*, 21.1, 20.8, 20.6; MS *m/z* 355.1020 (MNa^+ [$C_{14}H_{20}O_9Na$] = 355.1005).

Procedure A (Coupling Adenine with 8 or 10a). Adenine was added to a solution of the carbohydrate derivative in dried MeCN, and $SnCl_4$ (2 equiv) in dried MeCN was added to the suspension. Stirring was continued for 24 h, and the mixture was neutralized with saturated $NaHCO_3/H_2O$. Extraction workup (CH_2Cl_2) and chromatography gave **11** or **15**.

Procedure B (Coupling 6-*N*-Benzoyladenine, Uracil, or Thymine with 8, 10a, or 10b). A suspension of nucleobase and $(NH_4)_2SO_4$ (trace) in HMDS was stirred at reflux (with exclusion of moisture) until a clear solution was formed. Volatiles were evaporated, and xylene was added and coevaporated several times. The residue was dried in vacuo, and a solution of the carbohydrate derivative in 1,2-dichloroethane (under Ar) was added. TMSOTf (trace) was added, and the solution was stirred overnight (oil bath temperature 55−70 °C). Extraction workup and chromatography gave **12**−**14**, **16**−**18**.

2′-*O*-Acetyl-5′-azido-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]adenosine (11). Procedure A [**8** (580 mg, 1.76 mmol), adenine (260 mg, 1.92 mmol), $SnCl_4$ (0.4 mL, 890 mg, 3.42 mmol), MeCN (25 mL), chromatography (MeOH/CH_2Cl_2, 0.6:20)] gave **11** (680 mg, 96%): ^{1}H NMR δ 8.36, 8.01 (2 × s, 2 × 1H), 6.04 (d, J = 1.6 Hz, 1H), 5.86 (br s, 2H), 5.84 (dd, J = 1.6, 6.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.21−4.10 (m, 1H), 3.71 (dd, J = 3.3, 13.4 Hz, 1H), 3.60 (dd, J = 4.9, 13.4 Hz, 1H), 3.50−3.40 (m, 1H), 2.64 (dd, J = 8.2, 16.5 Hz, 1H), 2.47 (dd, J = 6.6, 16.7 Hz, 1H), 2.15 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 170.9, 169.8, 155.6, 153.3, 149.5, 139.1, 120.1, 88.9, 82.9, 78.1, 61.1, 52.2, 38.8, 30.4, 20.5, 14.0; MS (thioglycerol) *m/z* 405.1634 (MH^+ [$C_{16}H_{21}N_8O_5$] = 405.1635).

2′-*O*-Acetyl-5′-azido-6-*N*-benzoyl-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]adenosine (12). Procedure B [**8** (292 mg, 0.887 mmol), 6-*N*-benzoyladenine (480 mg, 2.01 mmol), TMSOTf (0.18 mL, 221 mg, 0.99 mmol), chromatography (MeOH/CH_2Cl_2, 0.5:20)] gave **12** (350 mg, 77%): ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 11.20 (br s, 1H, ex), 8.77, 8.62 (2 × s, 2 × 1H), 8.04 (d, J = 7.0 Hz, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 6.24 (d, J = 2.0 Hz, 1H), 5.85 (dd, J = 2.0, 7.0 Hz, 1H), 4.19 (ddd, J = 2.9, 5.9, 9.3 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.75 (dd, J = 2.8, 13.7 Hz, 1H), 3.56 (dd, J = 6.0, 13.5 Hz, 1H), 3.38 (m, 1H), 2.68 (dd, J = 5.8, 16.8 Hz, 1H), 2.60 (dd, J = 9.0, 17.0 Hz, 1H), 2.09 (s, 3H), 1.18 (t, J = 7.3 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 171.0, 169.7, 165.9, 151.8, 150.5, 143.3, 133.6, 132.4, 128.4, 125.9, 88.3, 82.5, 76.8, 60.2, 51.4, 38.4, 29.8, 20.4, 14.0; MS *m/z* 531.1713 (MNa^+ [$C_{23}H_{24}N_8O_6$-Na] = 531.1717).

2′-*O*-Acetyl-5′-azido-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]-5-methyluridine (13). Procedure B [**8** (320 mg, 0.972 mmol), thymine (250 mg, 2.00 mmol), TMSOTf (0.20 mL, 245 mg, 1.1 mmol), chromatography (MeOH/CH_2Cl_2, 0.4:20)] gave **13** (320 mg, 81%): ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 11.41 (s, 1H, ex), 7.55 ("q", J = 1.0 Hz, 1H), 5.68 (d, J = 3.0 Hz, 1H), 5.39 (dd, J = 2.9, 7.8 Hz, 1H), 4.05 (q, J = 7.3 Hz, 2H), 3.99−3.97 (m, 1H), 3.72 (dd, J = 2.7, 13.4 Hz, 1H), 3.50 (dd, J = 5.9, 13.7 Hz, 1H), 2.95−2.85 (m, 1H), 2.57 (dd, J = 5.6, 16.8 Hz, 1H), 2.48 (dd, J = 9.3, 17.1 Hz, 1H), 2.03 (s, 3H), 1.79 (d, J = 1.0 Hz, 3H), 1.16 (t, J = 7.3 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 171.1, 169.5, 163.7, 150.0, 137.3, 109.7, 90.3, 81.3, 76.0, 60.1, 51.4, 38.0, 30.0, 20.3, 14.0, 11.9; MS (thioglycerol) *m/z* 396.1517 (MH^+ [$C_{16}H_{22}N_5O_7$] = 396.1519).

2′-*O*-Acetyl-5′-azido-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]uridine (14). Procedure B [**8** (330 mg, 1.00 mmol), uracil (260 mg, 2.32 mmol), TMSOTf (0.20 mL, 245 mg, 1.1 mmol), chromatography (MeOH/CH_2Cl_2, 0.4:20)] gave **14** (295 mg, 77%): ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 11.91 (s, 1H, ex), 7.67 (d, J = 8.3 Hz, 1H), 5.66 (d, J = 2.0 Hz, 1H), 5.65 (d, J = 7.8 Hz, 1H), 5.37 (dd, J = 2.7, 7.1 Hz, 1H), 4.02 (q, J = 7.0 Hz, 2H), 3.99−3.97 (m, 1H), 3.69 (dd, J = 2.4, 13.7 Hz, 1H), 3.48 (dd, J = 5.9, 13.7 Hz, 1H), 2.89−2.82 (m, 1H), 2.54 (dd, J = 5.4, 17.2 Hz, 1H), 2.45 (dd, J = 9.3, 17.0 Hz, 1H), 2.00 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 171.1, 169.5, 163.0, 150.0, 142.0, 102.0, 90.8, 81.4, 76.2, 60.1, 51.3, 38.0, 29.9, 20.3, 14.0; MS (thioglycerol) *m/z* 382.1356 (MH^+ [$C_{15}H_{20}N_5O_7$] = 382.1363).

2′,5′-Di-*O*-acetyl-3′-deoxy-3′-[(ethoxycarbonyl)methyl]-adenosine (15). Procedure A [**10a** (1.09 g, 3.15 mmol), adenine (470 mg, 3.45 mmol), $SnCl_4$ (0.74 mL, 1.65 g, 6.33 mmol), MeCN (50 mL), chromatography (MeOH/CH_2Cl_2, 0.6:20)] gave **15** (1.0 g, 75%): ^{1}H NMR δ 8.36, 7.98 (2 × s, 2 × 1H), 6.03 (d, J = 1.2 Hz, 1H), 5.90 (br s, 2H), 5.84 (dd, J = 1.3, 5.7 Hz, 1H), 4.47−4.40 (m, 1H), 4.35−4.20 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.48−3.32 (m, 1H), 2.63 (dd, J = 8.5, 16.6 Hz, 1H), 2.50 (dd, J = 6.2, 16.7 Hz, 1H), 2.15, 2.06 (2 × s, 2 × 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 170.9, 170.6, 169.8,

155.6, 153.2, 149.4, 139.0, 120.1, 89.3, 82.1, 78.0, 63.4, 61.0, 38.1, 30.2, 20.6, 20.5, 14.0; MS (thioglycerol) *m/z* 422.1667 (MH^+ [$C_{18}H_{24}N_5O_7$] = 422.1676).

2′,5′-Di-*O*-acetyl-6-*N*-(benzoyl)-3′-deoxy-3′-[(ethoxycarbonyl)methyl]adenosine (16). Procedure B [**10a** (1.50 g, 4.33 mmol), 6-*N*-benzoyladenine (2.07 g, 8.65 mmol), TMSOTf (0.87 mL, 1.1 g, 4.8 mmol), chromatography ($MeOH/CH_2Cl_2$, 0.65:20)] gave **16** (1.51 g, 66%): ^{1}H NMR δ 8.99 (s, 1H, ex), 8.83, 8.20 (2 × s, 2 × 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.66−7.50 (m, 3H), 6.10 (s, 1H), 5.87 (d, J = 5.6 Hz, 1H), 4.50−4.29 (m, 3H), 4.16 (q, J = 7.2 Hz, 2H), 3.50−3.31 (m, 1H), 2.66 (dd, J = 8.4, 16.6 Hz, 1H), 2.54 (dd, J = 6.0, 16.6 Hz, 1H), 2.18, 2.08 (2 × s, 2 × 3H), 1.26 (t, J = 7.2 Hz, 3H); MS *m/z* 548.1760 (MNa^+ [$C_{25}H_{27}N_5O_8Na$] = 548.1757).

2′,5′-Di-*O*-acetyl-3′-deoxy-3′-[(ethoxycarbonyl)methyl]-5-methyluridine (17a). Procedure B [**10a** (1.45 g, 4.19 mmol), thymine (1.10 g, 8.72 mmol), TMSOTf (0.88 mL, 1.1 g, 4.9 mmol), chromatography ($MeOH/CH_2Cl_2$, 0.6:20)] gave **17a** (1.73 g, quant.): ^{1}H NMR (Me_2SO-d_6) δ 11.38 (s, 1H, ex), 7.51 (s, 1H), 5.67 (d, J = 2.6 Hz, 1H), 5.34 (dd, J = 2.7, 7.3 Hz, 1H), 4.30 (dd, J = 2.5, 12.1 Hz, 1H), 4.16 (dd, J = 5.6, 12.2 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 4.08−3.97, 2.94−2.78 (2 × m, 2 × 1H), 2.57 (dd, J = 5.8, 17.2 Hz, 1H), 2.46 (dd, J = 9.0, 16.6 Hz, 1H), 2.02 (s, 6H), 1.78 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 171.4, 170.4, 169.7, 164.0, 150.3, 137.2, 109.9, 90.2, 80.5, 76.4, 63.7, 60.3, 37.6, 30.2, 20.6, 20.3, 14.0, 12.1; MS *m/z* 435.1370 (MNa^+ [$C_{18}H_{24}N_2O_9Na$] = 435.1380).

2′,5′-Di-*O*-acetyl-3′-deoxy-3′-[(methoxycarbonyl)methyl]-5-methyluridine (17b). Procedure B [**10b** (166 mg, 0.500 mmol), thymine (126 mg, 1.00 mmol), TMSOTf (100 μL, 123 mg, 0.553 mmol), chromatography ($MeOH/CH_2Cl_2$, 0.6:20)] gave **17b** (155 mg, 78%): ^{1}H NMR δ 8.63 (s, 1H, ex), 7.23 (s, 1H), 5.76 (d, J = 1.8 Hz, 1H), 5.48 (dd, J = 1.8, 6.6 Hz, 1H), 4.40 (dd, J = 2.9, 12.9 Hz, 1H), 4.31 (dd, J = 4.6, 13.2 Hz, 1H), 4.14 (dt, J = 3.1, 9.5 Hz, 1H), 3.70 (s, 3H), 2.95−2.84 (m, 1H), 2.57 (dd, J = 8.1, 16.0 Hz, 1H), 2.43 (dd, J = 6.3, 16.0 Hz, 1H), 2.14, 2.12, 1.94 (3 × s, 3 × 3H); ^{13}C NMR δ 171.3, 170.4, 169.5, 163.3, 149.8, 135.6, 111.2, 90.7, 81.4, 77.1, 63.2, 52.2, 38.1, 30.2, 20.8, 20.5, 12.6; MS *m/z* 421.1223 (MNa^+ [$C_{17}H_{22}N_2O_9Na$] = 421.1223).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-(carboxymethyl)-3′,5′-dideoxyadenosine (19). A solution of **11** (65 mg, 0.16 mmol) in MeOH (0.3 mL) and NaOH/H_2O (6 M, 0.17 mL) was stirred overnight at ambient temperature. Volatiles were evaporated, and dried DMF/pyridine (1:1) were added and evaporated several times. The residue was dried in vacuo (40 °C, 24 h), TBDMSCl (300 mg, 2.0 mmol) and dried DMF/pyridine (1:2, 1.5 mL) were added, and stirring was continued for 5 days at ambient temperature (while protected from moisture). MeOH (1−2 mL) was added, and volatiles were evaporated (≤40 °C). Chromatography of the residue (5 → 15% $MeOH/CH_2Cl_2$) gave **18** (21 mg, 41%) [^{1}H NMR δ 8.33, 7.91 (2 × s, 2 × 1H), 6.20 (s, 1H), 5.69 (s, 2H), 5.67 (d, J = 6.2 Hz, 1H), 4.14−4.10, 3.88−3.76 (2 × m, 2 × 1H), 3.60−3.52 (m, 2H), 2.96 (dd, J = 8.3, 18 Hz, 1H), 2.54 (d, J = 18 Hz, 1H); MS *m/z* 317.1114 (MH^+ [$C_{12}H_{13}N_8O_3$] = 317.1111]] and **19** (34 mg, 47%).

Lactone **18** was subjected to the same saponification and protection sequence [TBDMSCl (100 mg, 0.664 mmol) in dried DMF/pyridine (1:2, 0.75 mL)] to give additional **19** (15 mg, 21%; combined yield, 68%): ^{1}H NMR δ 8.30, 8.25 (2 × s, 2 × 1H), 7.15 (br s, 2H), 6.02 (s, 1H), 4.77 (d, J = 4.0 Hz, 1H), 4.25 ("d", J = 9.0 Hz, 1H), 3.87 ("d", J = 14.0 Hz, 1H), 3.62 (dd, J = 3.9, 13.7 Hz, 1H), 2.81 (m, 1H), 2.71 (dd, J = 8.2, 15.7 Hz, 1H), 2.40 (dd, J = 4.5, 15.7 Hz, 1H), 0.93 (br s, 9H), 0.20, 0.09 (2 × s, 2 × 3H); ^{13}C NMR δ 176.1, 155.6, 152.1, 149.1, 138.9, 119.1, 91.2, 82.6, 78.0, 52.0, 40.0, 29.7, 25.8, 18.0, −4.5, −5.4; MS *m/z* 449.2074 (MH^+ [$C_{18}H_{29}N_8O_4Si$] = 449.2081).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-(carboxymethyl)-3′,5′-dideoxy-5-methyluridine (21). NaOH/H_2O (6 M, 0.1 mL) was added to a solution of **13** (50 mg, 0.13 mmol) in MeOH (0.4 mL), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, dried DMF/pyridine (1:1) was added and evaporated several times, and the residue was dried in vacuo (≤40 °C, 24 h). TBDMSCl (180 mg, 1.19 mmol) and dried DMF/pyridine (1:1, 3 mL) were added, and stirring was continued for 5 days at ambient temperature (while protected from moisture). MeOH (1−2 mL) was added, volatiles were evaporated (≤40 °C), and the residue was chromatographed (5 → 7% $MeOH/CH_2Cl_2$) to give **20** (16 mg, 40%) [^{1}H NMR δ 9.48 (br s, 1H, ex), 7.09, 5.57 (2 × s, 2 × 1H), 5.33 (d, J = 6.8 Hz, 1H), 4.03−3.94 (m, 1H), 3.65 (dd, J = 4.2, 13.2 Hz, 1H), 3.54 (dd, J = 5.4, 13.0 Hz, 1H), 3.41 ("q", J = 7.8 Hz, 1H), 2.84 (dd, J = 8.6, 18.4 Hz, 1H), 2.42 (d, J = 18.2 Hz, 1H), 1.93 (s, 3H); MS *m/z* 352.0620 ([MNa_2 − H]$^+$ [$C_{12}H_{12}N_5O_5Na_2$] = 352.0634)] and **21** (30 mg, 52%).

Lactone **20** was saponified and treated with TBDMSCl (60 mg, 0.40 mmol) and dried DMF/pyridine (1:1, 1.5 mL) as described to give additional **21** (12 mg, 21%; combined yield, 73%): ^{1}H NMR δ 9.53 (br s, 1H, ex), 7.63, 5.68 (2 × s, 2 × 1H), 4.45 (d, J = 4.2 Hz, 1H), 4.10 (d, J = 10.0 Hz, 1H), 3.89 (dd, J = 1.5, 13.7 Hz, 1H), 3.58 (dd, J = 2.8, 13.6 Hz, 1H), 2.75−2.63 (m, 1H), 2.51−2.30 (m, 2H), 1.94 (s, 3H), 0.89 (br s, 9H), 0.18, 0.06 (2 × s, 2 × 3H); ^{13}C NMR δ 164.5, 150.4, 136.0, 110.5, 92.0, 81.7, 77.3, 51.5, 39.2, 29.6, 25.7, 17.9, 12.6, −4.6, −5.7; MS *m/z* 440.1971 (MH^+ [$C_{18}H_{30}N_5O_6Si$] = 440.1965).

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)adenosine Triethylammonium Salt (23). A solution of **15** (100 mg, 0.237 mmol) in MeOH (0.45 mL) and NaOH/H_2O (3.5 M, 0.45 mL) was stirred overnight at ambient temperature and neutralized (dropwise addition of 3% HCl/H_2O), and volatiles were evaporated. Dried DMF/pyridine (1:1) was added and evaporated several times, and the residue was dried in vacuo (40 °C, 48 h). DMTCl (100 mg, 0.296 mmol) and dried Et_3N/pyridine (1:1, 1.5 mL) were added, and stirring was continued for 24 h at ambient temperature. TLC (5% $MeOH/CH_2Cl_2$) showed conversion of the "baseline" intermediate into a product (R_f 0.4) assumed to be 3′-(carboxymethyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)adenosine 2′,3′-lactone (**22**) (orange color developed with 5% H_2SO_4/EtOH).

Volatiles were evaporated, the residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$), and the combined organic phase was evaporated. The residue was dissolved in MeOH (0.4 mL) and NaOH/H_2O (2.5 M, 0.4 mL), and conversion of this material into TLC-baseline product was monitored. When saponification was complete, the solution was neutralized carefully (pH ∼8, dropwise addition of 5% AcOH/H_2O at 0 °C). Volatiles were evaporated, dried DMF was added and evaporated (2 × 30 mL), and the residue was dried in vacuo (overnight, 40 °C). Dried DMF (11 mL), imidazole (720 mg, 10.6 mmol), and TBDMS-imidazolide/CH_2Cl_2 (1 M, 5 mL, 5 mmol) were added, and stirring was continued for 3 days at ambient temperature. Volatiles were evaporated, and the residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The combined organic phase was dried (Na_2SO_4), evaporated, and chromatographed (5 → 10% $MeOH/CH_2Cl_2$ containing 0.2% Et_3N) to give **22** and **23** (102 mg, 52% from **15**): ^{1}H NMR (Me_2SO-d_6) δ 8.21, 8.13 (2 × s, 2 × 1H), 7.40−7.23 (m, 9H), 6.87−6.82 (m, 4H), 5.89 (d, J = 1.0 Hz, 1H), 4.80 (d, J = 4.8 Hz, 1H), 4.05−3.93 (m, 1H), 3.73 (s, 6H), 3.41−3.36 (m, 1H), 3.29 (dd, J = 5.0, 11.2 Hz, 1H), 2.77 (q, J = 7.2 Hz, ∼6H), 2.40 (dd, J = 9.2, 16.8 Hz, 1H), 2.04 (dd, J = 4.3, 17.1 Hz, 1H), 1.06 (t, J = 7.2 Hz, ∼9H), 0.84 (s, 9H), 0.51, 0.00 (2 × s, 2 × 3H); ^{13}C NMR (Me_2SO-d_6) δ 173.6, 158.2, 156.2, 152.8, 149.0, 144.9, 138.4, 135.6, 129.8, 127.9, 127.8, 126.8, 119.3, 113.3, 90.0, 85.8, 82.5, 76.7, 63.6, 55.0, 45.4, 30.2, 25.6, 17.6, 9.8, −4.8, −5.6; ^{1}H NMR δ 8.28, 8.07 (2 × s, 2 × 1H), 7.49−7.12 (m, 9H), 6.80 (d, J = 8.0 Hz, 4H), 6.04 (s, 1H), 5.82 (br s, 2H), 4.79 (d, J = 3.8 Hz, 1H), 4.27−4.17 (m, 1H), 3.76 (s, 6H), 3.48−3.40 (m, 1H), 3.33 (dd, J = 5.4, 10.8 Hz, 1H), 2.76 (q, J = 7.2 Hz, ∼6H), 2.62−2.42, 2.16−2.04 (2 × m, 2 × 1H), 1.11 (t, J = 7.3 Hz, ∼9H), 0.92 (s, 9H), 0.26, 0.10 (2 × s, 2 × 3H); ^{13}C NMR δ 177.0, 158.5, 155.3, 152.6, 144.7, 138.8, 136.1, 135.8, 130.2, 130.1, 128.3, 127.9, 126.8, 113.2, 91.5, 86.4, 83.5, 77.8, 64.2, 55.1, 45.1, 40.3, 31.2, 25.8, 18.0, 9.5, −4.5, −5.5; MS *m/z* 748.3160 (MNa^+ [$C_{39}H_{47}N_5O_7SiNa$] = 748.3142).

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-5-methyluridine (25). A

solution of **17a** (100 mg, 0.242 mmol) in MeOH (0.40 mL) and NaOH/H_2O (5 M, 0.40 mL) was stirred overnight at ambient temperature and then neutralized by dropwise addition of HCl/dioxane (4 M). Volatiles were evaporated, MeOH was added and evaporated (3×), and the residue was dried in vacuo (40 °C, 48 h). DMTCl (164 mg, 0.48 mmol) and dried Et_3N/pyridine (1:1, 1.5 mL) were added, and stirring was continued for 24 h at ambient temperature. TLC (5% MeOH/CH_2Cl_2) showed conversion of the "baseline" intermediate into a single product (R_f 0.5, orange color developed with 5% H_2SO_4/EtOH). Volatiles were evaporated, the residue was partitioned ($NaHCO_3$/H_2O//CH_2Cl_2), and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (5% MeOH/CH_2Cl_2 containing 0.2% Et_3N) to give amorphous 3′-(carboxymethyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-5-methyluridine 2′,3′-lactone (**24**): ^{1}H NMR δ 7.42−7.22 (m, 9H), 6.82 (dd, J = 1.4, 9 Hz, 4H), 5.75 (s, 1H), 5.16 (dd, J = 1.2, 6.8 Hz, 1H), 3.95−3.86 (m, 1H), 3.78 (s, 6H), 3.45 ("d", J = 4.6 Hz, 2H), 3.32−3.19 (m, 1H), 2.74 (dd, J = 8.2, 18.0 Hz, 1H), 2.33 (d, J = 18.4 Hz, 1H), 1.76 (d, J = 1.0 Hz, 3H); MS m/z 584.2163 (M^+ [$C_{33}H_{32}N_2O_8$] = 584.2159).

This material was dissolved in MeOH (0.4 mL) and NaOH/H_2O (2.5 M, 0.4 mL) and stirred at ambient temperature until saponification was complete (TLC). The solution was neutralized *carefully* (pH ∼8, 5% AcOH/H_2O at 0 °C), and volatiles were evaporated. Dried DMF was added and evaporated (2 × 30 mL), and the residue was dried in vacuo (overnight, 40 °C). DMF (11 mL), imidazole (720 mg, 10.6 mmol), and TBDMS-imidazolide/CH_2Cl_2 (1 M, 5 mL, 5 mmol) were added, and stirring was continued for 3 days at ambient temperature. TLC showed formation of two major products [MS (FAB) m/z 853.3909 (MNa^+ [$C_{45}H_{62}N_2O_9Si_2Na$] = 853.3892) indicated bis-silylation of the less polar compound]. Volatiles were evaporated, the residue was partitioned ($NaHCO_3$/H_2O//CH_2Cl_2), and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated, and the residue was stirred in acetone (10 mL)/H_2O (10 drops)/Et_3N (10 drops) for 3 days at ambient temperature (TLC showed conversion of the less to more polar product). Volatiles were evaporated, and the residue was chromatographed (5 → 10% MeOH/CH_2Cl_2 containing 0.2% Et_3N) to give **25** (106 mg, 61% from **17**): ^{1}H NMR (500 MHz) δ 9.58 (s, 1H), 7.83 (d, J = 1.0 Hz, 1H), 7.42 ("d", J = 7.5 Hz, 2H), 7.31−7.26 (m, 7H), 6.85−6.82 (m, 4H), 5.71 (s, 1H), 4.53 (d, J = 3.5 Hz, 1 H), 4.10 (dt, J = 2.3, 9.5 Hz, 1H), 3.80−3.74 (m, 1H), 3.78 (s, 6H), 3.67 (dd, J = 1.5, 11.5 Hz, 1H), 3.23 (dd, J = 3.3, 11.3 Hz, 1H), 2.69−2.56 (m, 2H), 2.10 (dd, J = 3.0, 16.5 Hz, 1H), 1.40 (d, J = 1.0 Hz, 3H), 0.88 (br s, 9H), 0.22, 0.07 (2 × s, 2 × 3H); ^{13}C NMR (75 MHz) δ 176.3, 164.6, 158.7, 150.5, 144.1, 136.0, 135.2, 135.1, 130.1, 128.1, 128.0, 127.2, 126.2, 115.6, 113.3, 110.3, 92.0, 86.8, 83.1, 77.3, 61.8, 55.2, 38.4, 28.8, 25.8, 18.0, 12.0, −4.4, −5.7; MS m/z 761.2858 {(MNa_2 − H)$^+$ [$C_{39}H_{47}N_2O_9SiNa_2$] = 761.2846}.

Acknowledgment. We thank Brigham Young University and Isis Pharmaceuticals for financial support and Mrs. Jeanny K. Gordon for assistance with the manuscript.

Supporting Information Available: Copies of ^{1}H NMR spectra for **1**, **2**, **4**−**19**, **21**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991399G