JOC Article

Synthesis of the Phosphoramidite Derivatives of 2′-Deoxy-2′-*C*-α-methylcytidine and 2′-Deoxy-2′-*C*-α-hydroxymethylcytidine: Analogues for Chemical Dissection of RNA's 2′-Hydroxyl Group

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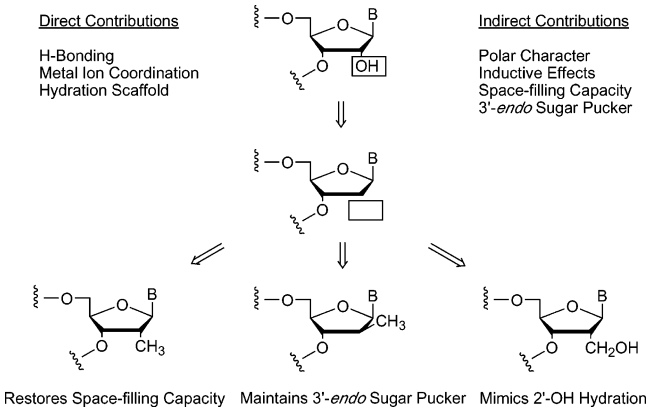
Oligonucleotides containing 2′-*C*-α-methyl and 2′-*C*-α-hydroxymethyl modifications enable strategies for delineation of the distinctive role fulfilled by the 2′-hydroxyl group in RNA structure and function. Synthetic routes to the phosphoramidite derivatives of 2′-deoxy-2′-*C*-α-methylcytidine (14%, 15 steps) and 2′-deoxy-2′-*C*-α-hydroxymethylcytidine (19%, 10 steps) from methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside are developed.

Introduction

The 2′-hydroxyl group plays a key role in RNA biology, mediating hydrogen bonds, coordinating to metal ions, and providing a scaffold for interactions with water.[1] The locations of residues bearing important 2′-hydroxyl groups therefore provide fundamental clues about RNA structure and function. Deoxynucleotide substitution reliably identifies functionally important 2′-hydroxyl groups within RNA but provides no information about the underlying chemical mechanism by which they fulfill their functional role.[2,3] Concomitant with the loss of hydrogen bonding capacity at the 2′-position, deoxynucleotides introduce a steric void (a hydrogen atom occupies less volume than a hydroxyl group), change the conformational preferences of the nucleoside, and alter hydration.[3]

To decouple these effects, we designed three new nucleoside analogues, 2′-β-CH_3, 2′-α-CH_3, and 2′-α-CH_2-OH nucleosides (Chart 1).[3] The 2′-β-CH_3 modification, in which a methyl group replaces the 2′-hydrogen atom on the β-face of the ribose, maintains the 3′-endo sugar conformation even without the 2′-hydroxyl group.[4] This modification provides a way to evaluate the effect of removing a 2′-hydroxyl group from an RNA residue without changing the inherent sugar pucker preference. The 2′-α-CH_3 modification, in which a methyl group replaces the 2′-OH, provides a means to evaluate the effect of eliminating hydrogen bonding capacity without a concomitant loss in spacing-filling capacity. The 2′-α-hydroxymethyl modification provides a strategy to determine whether a 2′-hydroxyl group interacts with a water molecule, as the $HOCH_2-$ may mimic the hydration of the 2′-hydroxyl group. Additionally, the $HOCH_2-$ analogue offers a means to test whether a 2′-hydroxyl group imparts its functional contribution through space or through the ribose σ-framework via an inductive effect. These nucleoside analogues (Chart 1), when used in combination with other analogues,[3] allow attribution of the deleterious effects observed upon 2′-deoxynucleotide to hydrogen bond removal, cavity creation, sugar pucker, inductive effects, or the hydration of the 2′-hydroxyl group and thereby permit a new level of understanding of the role that 2′-hydroxyl groups play in RNA structure and function. In addition, oligonucleotides containing these analogues merit investigation as therapeutic agents as they could engender an increased nuclease resistance compared to standard RNA. We reported previously the synthesis of the phosphoramidite derivative of 2′-deoxy-

CHART 1. Possible Mechanisms by Which RNA's 2′-Hydroxyl Group Contributes to Structure and Biological Function



(1) (a) Auffinger, P.; Westhof, E. *J. Mol. Biol.* **1997**, *274*, 54 and references therein. (b) Simons, R. W.; Grunberg-Manago, M. *RNA Structure and Function*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 1998.

(2) (a) Gesteland, R. F.; Cech, T. R.; Atkins, J. F. *The RNA World*, 2nd ed.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 1999. (b) Eckstein, F.; Lilley, D. M. J. *Catalytic RNA*; Springer-Verlag: Berlin, Germany, 1997.

(3) Gordon, P. M.; Fong, R.; Deb, S.; Li, N.-S.; Schwans, J. P.; Ye, J.-D.; Piccirilli, J. A. *Chem. Biol.* **2004**, *11*, 237 and references therein.

(4) Li, N.-S.; Piccirilli, J. A. *J. Org. Chem.* **2003**, *68*, 6799 and references therein.

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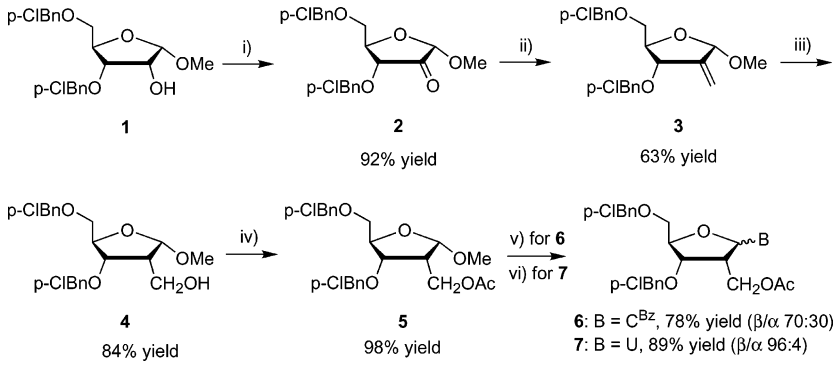
SCHEME 1[a]



[a] Key: (i) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, overnight; (ii) $Ph_3P^+CH_3Br^-$, *s*-BuLi, THF, −78 °C to rt, ovenight; (iii) (1) 9-BBN, rt, 20 h, (2) $NaBO_3$, H_2O, rt, 3 h; (iv) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 2 h; (v) N^4-benzoyl bis(trimethylsilyl)cytosine, $SnCl_4$, CH_3CN, rt, overnight, 60 °C, 30 min; (vi) bis(trimethylsilyl)uracil, $SnCl_4$, CH_3CN, rt, overnight.

2′-*C*-*β*-methylcytidine.[4] Here, we report the synthesis of the phosphoramidite derivatives of 2′-deoxy-2′-*C*-α-methylcytidine and 2′-deoxy-2′-*C*-α-hydroxymethylcytidine. We chose modified cytidine as the target because of its application to our mechanistic studies of the group II intron ribozyme.[3,5]

Results and Discussion

There exists no reported synthesis of the phosphoramidite derivative of 2′-deoxy-2′-*C*-α-hydroxymethylcytidine. In 1998, Cosstick and O'Neil reported the synthesis of the phosphoramidite derivative of 2′-deoxy-2′-*C*-α-hydroxymethyluridine from 2′-allyl-2′-deoxy-3′,5′-(TIPDS)uridine.[6] They obtained the core nucleoside via an ene reaction between the allyl nucleoside and 4-methyl-1,2,4-triazoline-3,5-dione followed by ozonolysis. Sukeda et al.[7] obtained 2′-deoxy-2′-*C*-α-hydroxylmehtylcytidine by conversion of 2′-vinyl-2′-deoxy-3′-(TBDMS)-5′-(MMTr)uridine to the corresponding cytidine derivative followed by deprotection and direct ozonolysis. Despite their elegance, we made no attempt to use these approaches to prepare the phosphoramidite derivative of 2′-deoxy-2′-*C*-α-hydroxymethylcytidine. We favored approaches based on glycosylation of a 2-α-*C*-hydroxymethyl sugar derivative so as to allow access ultimately to derivatives of A, G, C, and U in the most convergent manner.

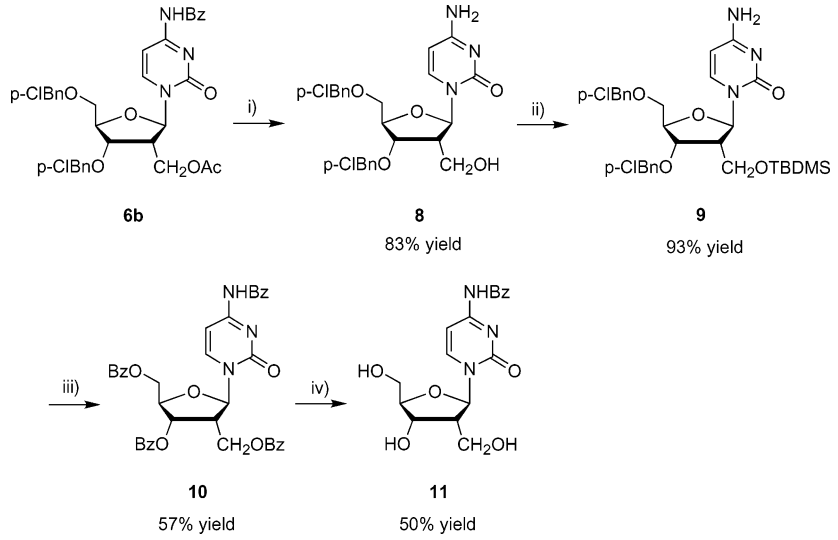
In 1994, Schmit reported the synthesis of the phosphoramidite derivative of 2′-deoxy-2′-*C*-α-hydroxymethylthymidine (5% overall yield) via stereoselective glycosylation with methyl 2-α-acetoxymethyl-3,5-di-*O*-(dichlorobenzyl)-2-deoxy-α-D-ribofuranoside.[8] This approach appeared attractive for accessing our target molecules because the starting material, methyl 3,5-di-*O*-(dichlorobenzyl)-α-D-ribofuranoside, was prepared easily from D-ribose in three steps[9] and because the subsequent glycosylation reaction proceeded stereoselectively to give the *β*-nucleoside. In adopting Schmit's approach for our synthesis of 2′-deoxy-2′-*C*-α-hydroxymethylcytidine, we explored alternative reagents and conditions to improve yields. We protected the glycosylating agent **5** as the 4-chlorobenzyl ether rather than as Schmit's 2,4-dichlorobenzyl ether[10] (Scheme 1). Methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (**1**) was prepared according to the method of Martin et al.[9] and converted to methyl 2-α-acetoxymethyl-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-α-D-ribofuranoside (**5**) essentially via the same sequence of reactions used by Schmit to prepare the dichlorobenzyl derivative. The major difference was that our procedures allow more efficient access to a 2′-*C*-α-hydroxymethyl ribofuranosylating agent than reported previously (48% vs 31%[8]). Glycosylation of persilylated N^4-benzoylcytosine[11] with **5** in the presence of tin(IV) chloride gave the cytidine derivative (**6**) in 78% yield with 70:30 *β*/α selectivity. Under similar conditions, **5** glycosylated bis-(trimethylsilyl)uracil to give the uridine derivative (**7**) in greater yield (89%) with greater selectivity (*β*/α 96:4) (Scheme 1).

Conversion of **6** to a phosphoramidite suitable for solid-phase oligonucleotide synthesis requires removal of the benzyl groups. Attempts to debenzylate **6b** (the *β*-isomer of **6**) directly, using hydrogen in the presence of Pd/C or $Pd(OH)_2$/C, resulted in deamination of cytosine nucleobase.[12] To render the nucleobase less susceptible to reduction, we removed the benzoyl group from **6b** by treatment with ammonia in methanol to give 2′-hydroxymethylcytidine derivative (**8**)[13] in 83% yield (Scheme 2). The 2′-hydroxymethyl group was then protected as the 2′-TBDMS ether (**9**) in 93% yield using TBDMS

(5) Gordon, P. M.; Sontheimer, E. J.; Piccirilli, J. A. *Biochemistry* **2000**, *39*, 12939.
(6) Pavey, J. B. J.; Lawrence, A. J.; Potter, A. J.; Cosstick, R.; O'Neil, I. A. *Tetrahedron Lett*. **1988**, *39*, 6967.
(7) Sukeda, M.; Shuto, S.; Sugimoto, I.; Ichikawa, S.; Matsuda, A. *J. Org. Chem*. **2000**, *65*, 8988.
(8) Schmit, C. *Synlett* **1994**, 238.
(9) Martin, O. R.; Kurz, K. G.; Rao, S. P. *J. Org. Chem*. **1987**, *52*, 2922.

(10) We used the less expensive 4-chlorobenzyl chloride [Aldrich (03−04): $55.00/500 g] rather than dichlorobenzyl chloride [Aldrich (03−04): $59.90/100 g] as reported in ref 8.
(11) (a) Tang, X.-Q.; Liao, X.-M.; Piccirilli, J. A. *J. Org. Chem*. **1999**, *64*, 747. (b) Li, N.-S.; Tang, X.-Q.; Piccirilli, J. A. *Org. Lett*. **2001**, *3*, 1025.
(12) Benzoylamide was formed during catalytic hydrogen debenzylation.
(13) NOESY experiments of compound **8** indirectly confirmed the 1′-*β*- and 2′-α-configuration of compound **6b**. We observed a stronger NOE between 2′-H (*δ*: 2.47) and 6-H (*δ*: 7.68) than between 2′-H (*δ*: 2.47) and 1′-H (*δ*: 6.18); a stronger NOE between 1′-H (*δ*: 6.18) and 2′-CH_2 (*δ*: 3.89) than between 1′-H (*δ*: 6.18) and 2′-H (*δ*: 2.47); a stronger NOE between 2′-H (*δ*: 2.47) and 3′-H (*δ*: 4.12) than between 1′-H (*δ*: 6.18) and 2′-H (*δ*: 2.47). These results suggest that the 2′-, 3′-, and 6-hydrogen atoms reside on one side of the ribose ring, and the 1′-H and 2′-CH_2 reside on the other side of the ribose ring.

SCHEME 2[a]



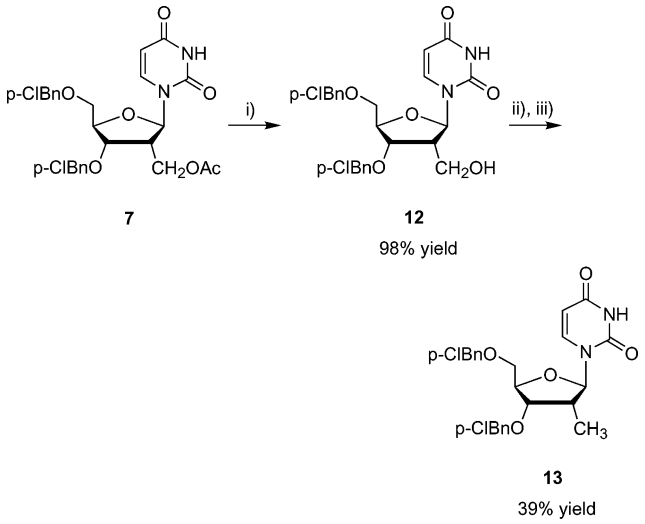
[a] Key: (i) NH_3, CH_3OH, 0−4 °C, 2 days; (ii) TBDMSOTf, pyridine, rt, 24 h; (iii) (1) H_2, Pd/C 10%, CH_3OH, rt, 7 h, (2) BzCl, DMAP, Et_3N, DMF, rt, overnight; (iv) 2 N NaOH, pyridine, CH_3OH, −20 to 0 °C, 1−2 h.

triflate. Debenzylation of **9** with hydrogen in the presence of 10% Pd/C followed by acylation with benzoyl chloride gave perbenzoylated hydroxymethylcytidine (**10**) in 57% yield. Reduction of the nucleobase still occurred to some extent, accounting for the relatively low yield. However, the loss of the TBDMS group proved even more problematic, as we could not differentially protect the primary hydroxyl groups following selective hydrolysis of the benzoyl esters. No further attempt was made to convert **11** to the phosphoramidite derivative of 2′-*C*-α-hydroxymethylcytidine. Before developing an alternative synthesis (see below), we turned our attention to the phosphoramidite derivative of 2′-*C*-α-methylcytidine, envisioning the hydroxymethyluridine derivative (**7**) as a possible precursor.

Schmit reported the synthesis of the phosphoramidite derivatives of 2′-deoxy-2′-*C*-α-methylcytidine and 2′-deoxy-2′-*C*-α-methylthymidine from the glycosylating agent 3-*O*-benzoyl-5-*O*-TBDMS-2-deoxy-2-α-methylribose (26% and 21% overall yield, respectively).[8] The glycosylation reactions in these syntheses gave product with good *β*/α selectivity (6.7:1−9:1), but the preparation of the glycosylating agent required a special chiral organotitanium reagent. No experimental details for the synthesis and use of this reagent have been published, however.[14]

As an alternative approach to access 2′-deoxy-2′-α-methylpyrimidine nucleosides, we explored strategies to deoxygenate the hydroxymethyluridine derivative (**7**) (Schemes 3 and 4). The acetyl group was removed from **7** to give the corresponding 2′-deoxy-2′-α-hydroxymethyluridine derivative (**12**) in 98% yield (Scheme 3). Deoxygenation via radical chemistry[15] gave the corresponding 2′-*C*-α-methyluridine (**13**) in only 39% yield (Scheme 3). Iodination followed by hydrogenation proved to be significantly more efficient (Scheme 4). Reaction of **12** with

SCHEME 3[a]



[a] Key: (i) 2 N NaOH, MeOH, rt, 1 h; (ii) PhOCSCl, DMAP, CH_3CN, rt, 2 h; (iii) *n*-Bu_3SnH/AIBN, toluene, reflux, 2 h.

iodine/triphenylphosphine[16] gave the corresponding 2′-α-iodomethyluridine (**14**) in quantitative yield. Hydrogen in the presence of Pd/C and $Pd(OH)_2$/C reduced the benzyl ether and the iodomethyl group to give 2′-deoxy-2′-*C*-α-methyluridine (**15**)[17,18] in 82% yield over the two steps. To obtain the corresponding cytidine derivative, we protected the 3′- and 5′-hydroxyl groups as TBDMS

(14) Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Rothe-Streit, P.; Rihs, G. *Pure Appl. Chem.* **1992**, *64*, 1897.

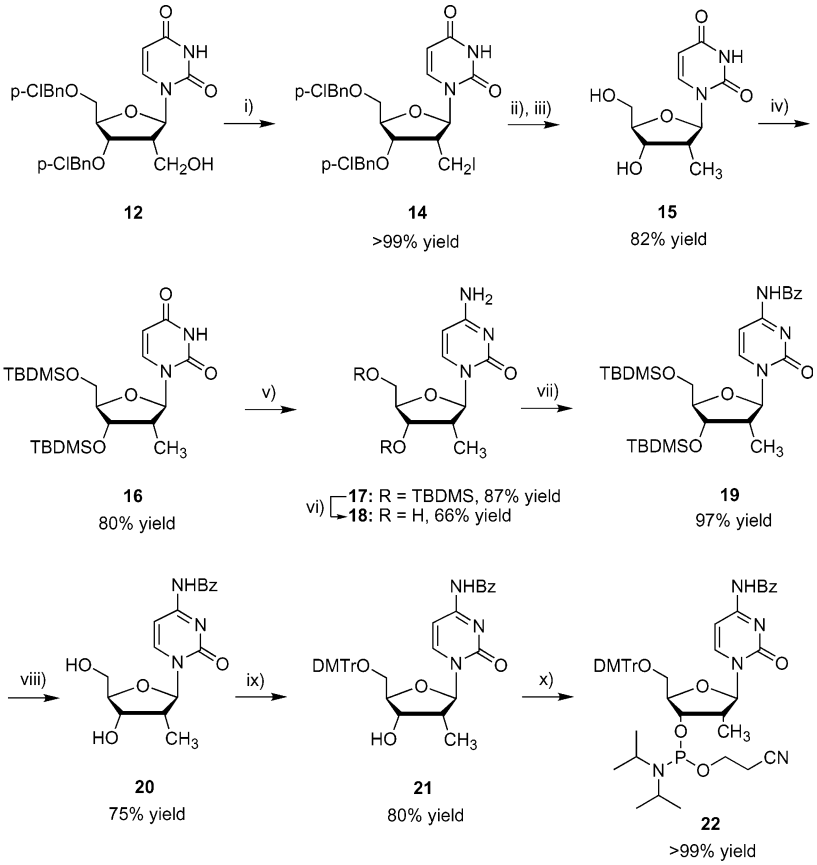
(15) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

(16) Corey, E. J.; Nagata, R. *Tetrahedron Lett.* **1987**, *28*, 5391.

(17) The 1′-*β*- and 2′-α-configuration of 2′-deoxy-2′-*C*-α-methyluridine (**15**) was confirmed by the NOESY experiments. We observed strong NOEs between the 2′-H (*δ*: 2.39) and 6-H (*δ*: 7.78); between the 5′-H (*δ*: 3.70) and 6-H (*δ*: 7.78); a stronger NOE between 1′-H (*δ*: 5.88) and 2′-CH_3 (*δ*: 1.00) than between 1′-H (*δ*: 5.88) and 2′-H (*δ*: 2.39); we observed no NOE between 2′-CH_3 (*δ*: 1.00) and 6-H (*δ*: 7.78). These results suggest that the 2′-, 6-, and 5′- hydrogen atoms reside on one side of the ribose ring and that the 1′-H and 2′-CH_2 reside on other side of the ribose ring.

(18) Cicero et al. described the synthesis of 2′-deoxy-2′-*C*-*β*-methyluridine and obtained **15** as a minor product. The yield was not reported. See: Cicero, D. O.; Neuner, P. J. S.; Franzese, O.; D'Onofrio, C.; Iribarren, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 861.

SCHEME 4[a]



[a] Key: (i) I_2, PPh_3, imidazole, C_6H_6/CH_3CN (4:1), 0 °C to rt, 4.5 h; (ii) H_2, Pd/C 10%, Et_3N, CH_3CO_2Et, rt, 24 h; (iii) H_2, $Pd(OH)_2$/C 20%, CH_3OH/CH_3CO_2Et (1:1), rt, 24 h; (iv) TBDMSCl, DMF, imidazole, rt, ovrnight; 60 °C, 4 h; (v) (1) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, CH_3CN, rt, 24 h, (2) NH_4OH, rt, 3 h; (vi) TBAF, THF, rt, overnight, reflux, 2 h; (vii) BzCl, DMAP, CH_2Cl_2, rt, overnight; (viii) $Et_3N{-}3HF$, Et_3N, THF, 60 °C, overnight; (ix) DMTrCl, pyridine, DMAP, rt, overnight; (x) $(i\text{-}Pr)_2NP(Cl)OCH_2CH_2CN$, $i\text{-}Pr_2NEt$, 1-methylimidazole, CH_2Cl_2, 0 °C to rt, 2 h.

ethers (**16**, 80% yield) and transformed the uracil heterocycle to cytosine via a two step reaction sequence (2,4,6-triisopropylbenzenesulfonyl chloride and ammonia)[19] giving **17** in 87% yield. The parent nucleoside was obtained by TBAF desilylation to give 2′-deoxy-2′-*C*-α-methylcytidine (**18**)[20] in 66% yield. Continuing with the synthesis, we converted **17** efficiently to a suitably protected phosphoramidite **22** using consecutive benzoylation, desilylation, 5′-dimethoxytritylation, and phosphitylation reactions (Scheme 4).

Returning to the hydroxymethylcytidine analogue, we developed a direct and efficient route by removing the benzyl groups from the glycosylating agent **5** before installation of the nucleobase, thereby avoiding cytosine side reactions (Scheme 5). Debenzylation of **5** with hydrogen catalyzed by $Pd(OH)_2$/C in the presence of triethylamine gave methyl 2-acetoxymethyl-2-deoxy-α-D-ribofuranoside (**23**) in 92% yield. Reprotection of the hydroxyl groups with TBDMSCl gave the new glycosylating agent, methyl 2-α-acetoxymethyl-3,5-di-*O*-(TBDMS)-D-ribofuranoside (**24**), in 97% yield as a mixture of anomers (α/β ratio ∼ 85:15 based on ^1H NMR).[21] Glycosylation of persilylated N^4-acetylcytosine in the presence of tin(IV) chloride gave the cytidine nucleoside **25** in 63% yield with 9:1 β/α selectivity. Glycosylation of bis(trimethylsilyl)uracil under similar conditions gave the uridine nucleoside **26** in 57% yield with 94:6 β/α selectivity. Cytidine analogue **25** was converted efficiently to phosphoramidite **29** via consecutive desilylation, 5′-dimethyoxytritylation,[22] and 3′-phosphitylation reactions.[23]

Conclusion

We modified the approach of Schmit[8] to develop an effective synthesis of methyl 2-α-acetoxymethyl-3, 5-di-

(19) Iino, T.; Yoshimura, Y.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10397.

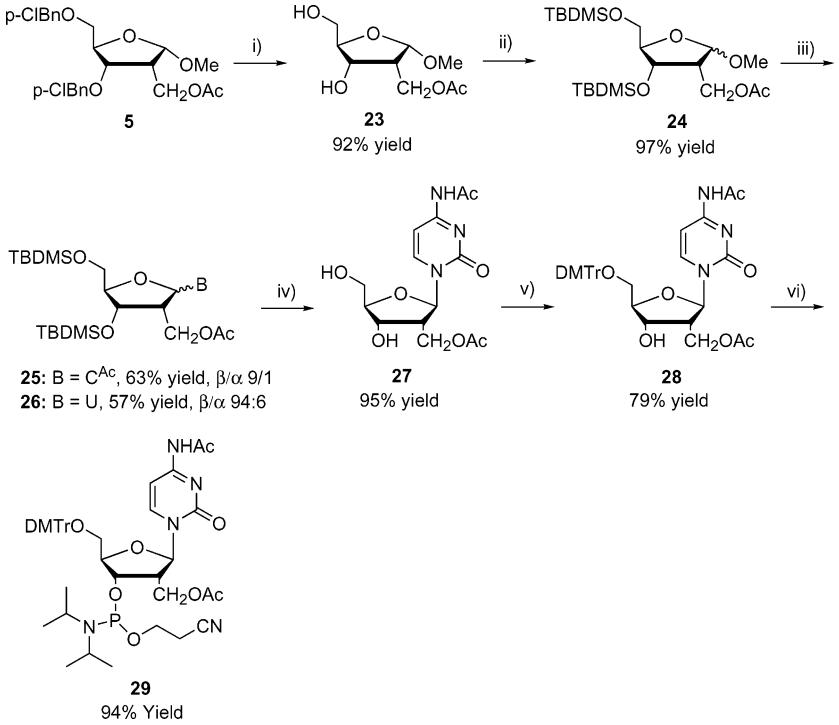
(20) Matsuda et al. obtained **18** as a minor product in a lengthy synthesis starting from uridine (12 steps, 6% overall yield). See: (a) Matsuda, A.; Takenuki, K.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 234. (b) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945.

(21) The β-isomer of **24** might be formed by partial anomerization of the α-isomer under the TBDMS protection conditions.

(22) The 1′-β- and 2′-α-configuration of tritylnucleoside **28** was confirmed by the NOESY experiments. We observed stronger NOEs between 2′-H (δ: 2.63) and 6-H (δ: 8.15) than between 2′-H (δ: 2.63) and 1′-H (δ: 6.33); NOE between 5′-H (δ: 3.48) and 6-H (δ: 8.15). We observed no NOE between 2′-CH_2 (δ: 4.50, 4.40) and 6-H (δ: 8.15). These results suggest that 2′-, 6-, and 5′- hydrogen atoms reside on one side of the ribose ring.

(23) A phosphoramidte derivative of 2′-deoxy-2′-C-α-hydroxymethylcytidine might be accessed by ozonolysis of 2′,5′-*O*-(MMTr)-2′-deoxy-2′-C-α-vinyl-3′-*O*-(TBDMS)cytidine, prepared by the approach of Sukeda et al.[7] This possible synthetic route would involve more than 10 steps starting from 2,2′-*O*-anhydrouridine.

SCHEME 5[a]



[a] Key: (i) H_2, $Pd(OH)_2$/C 20%, CH_3CO_2Et, Et_3N, rt, overnight; (ii) TBDMSCl, imidazole, DMF, rt, overnight; (iii) N^4-acetylbis(trimethylsilyl)cytosine or bis(trimethylsilyl)uracil, $SnCl_4$, CH_3CN, rt, 14 h; (iv) Et_3N-3HF, Et_3N, THF, 60 °C, 14 h; (v) DMTrCl, pyridine, DMAP, rt, overnight; (vi) (*i*-Pr)$_2$NP(Cl)OCH$_2$CH$_2$CN, *i*-Pr$_2$NEt,1-methylimidazole, CH_2Cl_2, 0 °C to rt, 1 h.

O-(4-chlorobenzyl)-α-D-ribofuranoside (**5**). This glycosylating agent allows efficient access to protected hydroxymethyluridine and, following conversion to methyl 2-α-acetoxymethyl-3,5-di-*O*-(TBDMS)-α-D-ribofuranoside (**24**), allows direct and efficient access to hydroxymethylcytidine and the corresponding phosphoramidite (**29**, Scheme 5). We further demonstrated that hydroxymethyluridine offers robust and convergent synthetic entry into the 2′-deoxy-2′-methylnucleoside manifold via an iodination/hydrogenation sequence. 2′-*C*-α-Hydroxymethylnucleosides and 2′-*C*-α-methylnucleosides serve as valuable analogues with which to explore the role of RNA's 2′-hydroxyl group.[3]

Experimental Section

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-keto-α-D-ribofuranoside (2). Under argon, methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (**1**) (5.762 g, 14.0 mmol) was added to a solution of Dess−Martin periodinane (8.91 g, 21.0 mmol) in dry dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. The solvent was removed, and the residue was triturated with diethyl ether (100 mL). Following filtration through a pad of silica gel and anhydrous magnesium sulfate (w/w = 1:1), the ether solution was washed with saturated aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ and dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was dried under vacuum to give **2** as a colorless oil (5.283 g, 92% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.32−7.17 (m, 8H), 4.91 (d, 1H, J = 11.6 Hz), 4.83 (s, 1H), 4.63 (d, 1H, J = 11.6 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.45 (d, 1H, J = 12.0 Hz), 4.30 (m, 1H), 4.09 (d, 1H, J = 8.4 Hz), 3.80 (dd, 1H, J = 11.2, 2.4 Hz), 3.64 (dd, 1H, J = 11.2, 3.6 Hz), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.6, 135.9, 135.4, 133.8, 133.5, 129.4, 129.2, 128.9, 128.5, 98.6, 77.6, 75.3, 72.7, 71.6, 68.1, 55.8; HRMS calcd for $C_{18}H_{20}Cl_2NO_5$ [MNH_4^+] 428.1032, found 428.1031.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-methylene-α-D-ribofuranoside (3). Under an argon atmosphere, *s*-BuLi in cyclohexane (38.5 mL, 1.3 M, 50.0 mmol) was added to a suspension of triphenylmethylphosphonium bromide (19.65 g, 55.0 mmol) in THF (100 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, a solution of **2** (10.28 g, 25.0 mmol) in THF (50 mL) was transferred slowly into the reaction mixture. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solid was filtered away and rinsed with ether. The filtrate was washed sequentially with saturated ammonium chloride and brine and dried over anhydrous $MgSO_4$. After solvent was removed, the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 4:1) to give **3** (6.40 g, 63% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.30−7.20 (m, 8H), 5.45 (s, 1H), 5.39 (s, 1H), 5.24 (s, 1H), 4.59 (d, 1H, J = 12.2 Hz), 4.54−4.45 (m, 3H), 4.27 (m, 2H), 3.56 (m, 2H), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.6, 136.4, 136.3, 133.31, 133.27, 128.93, 128.86, 128.4, 114.3, 104.1, 80.9, 78.5, 72.5, 69.8, 69.7, 54.8; HRMS calcd for $C_{21}H_{26}Cl_2NO_4$ [MNH_4^+] 426.1239, found 426.1251.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-deoxy-2-α-hydroxymethyl-α-D-ribofuranoside (4). Under argon, the 9-BBN dimer (3.05 g, 12.5 mmol) was added to the solution of **3** (7.524 g, 18.4 mmol) in THF (50 mL) at room temperature. After the reaction mixture was stirred at room temperature for 20 h, oxidizing agent sodium perborate tetrahydrate (11.5 g, 75.0 mmol) and water (25 mL) were added and the mixture was stirred at room temperature for an additional 3 h. The organic layer was separated, and the aqueous was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed, and the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 6:4) to give **4** (6.60 g, 84% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.31−7.15 (m, 8H), 5.02 (d, 1H, J = 5.0 Hz), 4.55−4.40 (m, 4H), 4.26 (m, 1H), 3.95−3.85 (m, 3H), 3.44−3.35 (m, 2H), 3.40 (s, 3H), 2.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 136.3, 136.0, 133.2, 129.0, 128.8, 128.3, 105.1, 82.7, 78.6, 72.4,

71.0, 70.2, 57.3, 55.3, 48.9; HRMS calcd for $C_{21}H_{24}Cl_2NaO_5$ [MNa^+] 449.0898, found 449.0912.

Methyl 2-α-Acetoxymethyl-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-α-D-ribofuranoside (5). To a mixture of **4** (4.246 g, 9.94 mmol) in dry CH_2Cl_2 (50 mL), pyridine (7.92 mL, 98 mmol), and DMAP (1.22 g, 10.0 mmol) at 0 °C was added acetyl anhydride (2.76 mL, 29.45 mmol). After the reaction mixture was stirred at room temperature for 2 h, the mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (20 mL), 1 N HCl (100 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 4:1) to give **5** (4.557 g, 98% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.35−7.15 (m, 8H), 4.99 (d, 1H, J = 4.8 Hz), 4.60−4.25 (m, 7H), 3.88 (dd, 1H, J = 2.0, 7.2 Hz), 3.41 (s, 3H), 3.45−3.30 (m, 2H), 2.44 (m, 1H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 136.4, 136.2, 133.5, 133.4, 129.2, 128.9, 128.5, 128.4, 105.0, 83.3, 78.3, 72.7, 71.1, 70.4, 59.3, 55.6, 46.4, 20.9; HRMS calcd for $C_{23}H_{30}Cl_2NO_6$ [MNH_4^+] 486.1450, found 446.1448.

2′-α-Acetoxymethyl-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-*N*^{4}-benzoylcytidine (6). Persilylated N^4-benzoylcytosine was prepared by the reaction of N^4-benzoylcytosine (1.18 g, 5.5 mmol) with TMS_2NH (30 mL) and $(NH_4)_2SO_4$ (15 mg) at reflux under an argon atmosphere. After 1 h, the reaction mixture became clear. The excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum for 1 h. Under argon, the persilylated base was dissolved into acetonitrile (40 mL), and the solution was transferred into the flask containing compound **5** (1.245 g, 2.65 mmol). $SnCl_4$ (0.65 mL, 5.5 mmol) was added in one portion with vigorous stirring and exclusion of moisture. The homogeneous pale yellow solution was stirred at room temperature overnight and heated to 60 °C for 30 min. After it was cooled, the reaction mixture was quenched carefully by addition of 10% aqueous $NaHCO_3$ (40 mL) and stirred for 15 min. The mixture was extracted with methylene chloride, and the organic phase was washed with brine. The organic layer was dried over $MgSO_4$. After evaporation of solvent, ^{1}H NMR showed that the crude product contained both the β- and α-anomers (β/α = 70:30). The product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 1:1) to give β-anomer **6b** (0.948 g, 55% yield, R_f = 0.51 in ethyl acetate) and α-anomer **6a** (0.406 g, 23% yield, R_f = 0.38 in ethyl acetate). **6b**: ^{1}H NMR ($CDCl_3$/TMS) δ 9.40 (br s, 1H), 8.24 (d, 1H, J = 7.6 Hz), 7.93 (d, 2H, J = 8.0 Hz), 7.50−7.15 (m, 12H), 6.26 (d, 1H, J = 6.0 Hz), 4.65−4.40 (m, 6H), 4.35−4.25 (m, 2H), 4.19 (m, 1H), 3.80 (m, 1H), 3.57 (m, 1H), 2.77 (m, 1H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 166.8, 162.1, 154.5, 144.4, 135.44, 135.41, 133.8, 133.6, 132.9, 129.0, 128.9, 128.5, 128.3, 128.2, 128.0, 127.6, 96.7, 88.4, 82.7, 77.7, 72.6, 71.1, 69.2, 60.1, 47.9, 20.7. **6a**: ^{1}H NMR ($CDCl_3$/TMS) δ 8.89 (br s, 1H), 8.02 (d, 1H, J = 7.6 Hz), 7.90 (d, 2H, J = 7.2 Hz), 7.60 (m, 1H), 7.53−7.15 (m, 11H), 6.55 (d, 1H, J = 7.2 Hz), 4.65−4.40 (m, 5H), 4.21 (m, 1H), 4.14−4.09 (m, 2H), 3.50 (m, 2H), 3.22 (m, 1H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 166.8, 162.1, 155.0, 145.7, 136.1, 135.8, 134.0, 133.7, 133.1, 129.5, 129.2, 129.0, 128.7, 128.6, 128.5, 127.5, 96.1, 87.5, 84.0, 78.8, 72.7, 71.3, 70.1, 58.3, 45.4, 20.7.

2′-α-Acetoxymethyl-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-β-uridine (7): Bis(trimethylsilyl)uracil was prepared under an argon atmosphere by the reaction of uracil (1.26 g, 11.2 mmol) with refluxing TMS_2NH (35 mL) in the presence of $(NH_4)_2SO_4$ (15 mg). After the reaction mixture became clear, the excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum for 1 h. Under argon, the persilylated base was dissolved into acetonitrile (50 mL), and the solution was transferred into the flask containing compound **5** (2.10 g, 4.48 mmol). $SnCl_4$ (1.31 mL, 11.2 mmol) was added in one portion with vigorous stirring and exclusion of moisture. The homogeneous pale yellow solution was stirred at room temperature overnight. TLC showed that no starting material remained. The reaction mixture was quenched carefully by addition of 10% aqueous $NaHCO_3$ (75 mL) and stirred for 15 min. The mixture was extracted with methylene chloride, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 4:6) to give compound **7** (2.19 g, 89% yield). The β/α selectivity is 96:4 based on the ^{1}H NMR spectra of **7**. β-anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 9.39 (br s, 1H), 7.65 (d, 1H, J = 8.0 Hz), 7.37−7.30 (m, 4H), 7.21 (m, 4H), 6.23 (d, 1H, J = 8.0 Hz), 5.56 (d, 1H, J = 8.0 Hz), 4.55−4.40 (m, 5H), 4.26−4.20 (m, 2H), 4.13 (m, 1H), 3.74 (m, 1H), 3.54 (m, 1H), 2.65 (m, 1H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 163.1, 150.3, 139.9, 135.43, 135.39, 134.1, 133.9, 129.2, 129.0, 128.8, 128.7, 102.6, 87.3, 82.5, 79.1, 72.9, 71.0, 70.3, 60.1, 47.9, 20.7; HRMS calcd for $C_{26}H_{27}Cl_2N_2O_7$ [MH^+] 549.1195, found 549.1194.

3′,5′-Di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-hydroxymethyl-β-cytidine (8). Compound **6b** (0.844 g, 1.29 mmol) in methanol (50 mL) was saturated with ammonia gas at 0 °C for 30 min. The mixture was kept in the refrigerator (4 °C) for 2 days. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with 10% methanol in chloroform to give **8** (0.543 g, 83% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.97 (br s, 1H), 7.68 (d, 1H, J = 7.4 Hz, 6-H), 7.32−7.15 (m, 8H), 6.48 (br s, 1H), 6.18 (d, 1H, J = 6.4 Hz, 1′-H), 5.69 (d, 1H, J = 7.4 Hz, 5-H), 4.55−4.40 (m, 4H), 4.18 (m, 1H), 4.12 (dd, 1H, J = 3.6, 6.0 Hz, 3′-H), 3.89 (d, 2H, J = 6.4 Hz, 2′-CH_2), 3.68 (m, 1H, 5′-H), 3.52 (m, 1H, 5′-H), 2.47 (m, 1H, 2′-H); ^{13}C NMR ($CDCl_3$) δ 165.7, 156.6, 140.4, 135.9, 133.6, 133.5, 129.1, 128.9, 128.6, 128.5, 95.6, 89.0, 82.3, 79.3, 72.6, 71.1, 69.8, 58.7, 51.1.

2′-α-(*tert*-Butyldimethylsiloxymethyl)-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-β-cytidine (9). TBDMSOTf (0.53 g, 0.46 mL, 2.0 mmol) was added to a solution of **8** (0.478 g, 0.94 mmol) in dry pyridine (10 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed, and the residue was diluted with chloroform. The solution was washed with brine and dried over anhydrous magnesium sulfate. After solvent was removed, the residue was purified by silica gel chromatography, eluting with 8% methanol in chloroform to give **9** (0.544 g, 93% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 8.40 (br s, 1H), 7.68 (d, 1H, J = 8.0 Hz), 7.34−7.19 (m, 8H), 6.70 (br s, 1H), 6.18 (d, 1H, J = 8.0 Hz), 5.76 (d, 1H, J = 8.0 Hz), 4.55−4.40 (m, 4H), 4.23 (m, 1H), 4.13 (m, 1H), 4.02 (m, 1H), 3.69 (m, 2H), 3.50 (m, 1H), 2.46 (m, 1H), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.5, 156.0, 140.5, 136.3, 135.9, 133.4, 133.1, 128.9, 128.53, 128.47, 128.3, 95.3, 86.8, 82.5, 79.0, 72.4, 71.0, 70.2, 58.0, 51.3, 25.6, 17.8, −5.68, −5.73.

2′-α-(Benzoxylmethyl)-3′,5′-di-*O*-benzoyl-2′-deoxy-*N*^{4}-benzoyl-β-cytidine (10). The mixture of compound **9** (0.544 g, 0.88 mmol) and Pd/C 10% (0.10 g) in methanol (10 mL) was stirred under hydrogen atmosphere (hydrogen balloon) at room temperature for 7 h. The catalyst was filtered off and rinsed with methanol. The filtrate was concentrated, and the residue was dried under vacuum for 1 h. The crude hydrogenation product was then dissolved into anhydrous DMF (15 mL), and DMAP (122 mg, 1.0 mmol), triethylamine (1.4 mL, 10.0 mmol) and benzoyl chloride (0.703 g, 0.58 mL, 5.0 mmol) were added. The reaction mixture was stirred at room temperature overnight. TLC showed the reaction was complete. The solvent was removed, and the residue was extracted with ether and washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. After the solvent was removed, the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 1:1) to give compound **10** (0.335 g, 57% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 8.15−7.95 (m, 8H), 7.87 (d, 2H, J = 8.0 Hz), 7.60−7.20 (m, 13H), 6.64 (d, 1H, J = 8.0 Hz), 5.82 (dd, 1H, J = 2.4, 6.0 Hz), 4.87 (m, 1H), 4.80−4.73 (m, 3H), 4.67 (m, 1H), 3.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.8, 166.0, 165.8, 165.6, 162.7, 154.6, 143.6, 133.8, 133.6, 133.1, 133.0, 129.9, 129.7, 129.45, 129.40, 129.1, 129.0, 128.6, 128.5, 128.2, 128.1, 128.0, 126.9, 97.6, 88.0, 82.5, 74.2, 64.0, 60.3, 47.9.

2′-Deoxy-2′-α-(hydroxymethyl)-*N*^{4}-benzoyl-β-cytidine (11). To the solution of compound **10** (300 mg, 0.446 mmol) in

pyridine (5 mL) and methanol (1 mL) at −20 °C was added 2 N NaOH (0.67 mL, 1.34 mmol). The mixture was stirred below 0 °C until TLC showed the reaction was complete (1−2 h). The reaction mixture was neutralized to pH = 7 with DOWEX 50WX 8-200 resin. The resin was filtered off and washed with a mixture of H_2O/pyridine (v/v = 4:1, 25 mL). The filtrate was evaporated to dryness, and the residue was purified by silica gel chromatography, eluting with 10% methanol in chloroform to give compound **11** (81 mg, 50% yield): ^{1}H NMR (CD_3OD/$CDCl_3$/TMS) δ 8.54 (d, 1H, J = 7.5 Hz), 7.99 (d, 2H, J = 7.2 Hz), 7.70−7.60 (m, 2H), 7.60−7.50 (m, 2H), 6.18 (d, 1H, J = 6.6 Hz), 4.49 (dd, 1H, J = 3.9, 6.4 Hz), 4.12 (m, 1H), 4.00 (m, 1H), 3.95−3.85 (m, 2H), 3.82 (m, 1H), 2.53 (m, 1H); ^{13}C NMR (CD_3OD/$CDCl_3$) δ 168.4, 163.7, 157.4, 146.1, 133.6, 132.2, 129.3, 128.5, 98.5, 89.8, 88.1, 72.1, 61.9, 58.8, 53.0.

3′,5′-Di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-hydroxymethyl-β-uridine (12). NaOH (2 N, 1.0 mL, 2.0 mmol) was added to the solution of 2′-α-acetoxymethyl-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-β-uridine (659 mg, 1.2 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed, and the residue was dissolved into methylene chloride (20 mL), washed with brine, and dried over magnesium sulfate. After the solvent was removed, the residue was purified by silica gel chromatography, eluting with ethyl acetate to give **12** as a white foam (0.597 g, 98% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 9.77 (br s, 1H), 7.68 (d, 1H, J = 8.1 Hz), 7.35−7.29 (m, 4H), 7.20 (m, 4H), 6.21 (d, 1H, J = 7.4 Hz), 5.52 (d, 1H, J = 8.1 Hz), 4.55−4.42 (m, 4H), 4.24 (m, 1H), 4.19 (dd, 1H, J = 6.4, 2.8 Hz), 3.93 (m, 2H), 3.73 (m, 1H), 3.53 (dd, 1H, J = 10.4, 2.5 Hz), 3.03 (br s, 1H), 2.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.5, 150.9, 140.1, 135.63, 135.59, 134.0, 133.8, 129.2, 129.0, 128.8, 128.7, 102.5, 88.1, 82.8, 79.7, 72.9 71.3, 70.1, 58.7, 50.3; HRMS calcd for $C_{24}H_{25}Cl_2N_2O_6$ [MH^+] 507.1090, found 507.1071.

3′,5′-Di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-methyl-β-uridine (13). To the solution of **12** (157 mg, 0.31 mmol) in dry acetonitrile (20 mL) was added DMAP (122 mg, 1.0 mmol) followed by the addition of phenyl chlorothionoformate (69 μL, 0.5 mmol). The mixture was stirred at room temperature for 2 h, but TLC showed that the reaction was not yet complete. Additional phenyl chlorothionoformate (17 μL, 0.12 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed, and the residue was dissolved into ethyl acetate (50 mL), washed with 0.1 N HCl (10 mL), water (10 mL), and brine (10 mL), and dried over magnesium sulfate. After the solvent was removed, the residue was dried under vacuum overnight. To the vacuum-dried crude thioformate ester were added toluene (10 mL), n-Bu_3SnH (133 μL, 0.5 mmol), and AIBN (10 mg) under an argon atmosphere. After the reaction mixture was stirred at reflux for 2 h, the solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 1:1) to give **13** (59 mg, 39% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 9.17 (br s, 1H), 7.68 (d, 1H, J = 8.0 Hz), 7.36−7.19 (m, 8H), 5.98 (d, 1H, J = 7.6 Hz), 5.53 (d, 1H, J = 8.1 Hz), 4.55−4.43 (m, 4H), 4.22 (m, 1H), 3.98 (dd, 1H, J = 6.0, 2.8 Hz), 3.74 (dd, 1H, J = 10.4, 3.2 Hz), 3.56 (dd, 1H, J = 10.4, 2.4 Hz), 2.34 (m, 1H), 1.13 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 163.0, 150.5, 140.0, 136.0, 135.7, 134.1, 133.7, 129.2, 128.8, 128.7, 102.4, 90.1, 82.4, 80.2, 73.0, 71.0, 70.4, 43.0, 9.4.

3′,5′-Di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-iodomethyl-β-uridine (14). Iodine (1.27 g, 5.0 mmol) was added to the mixture of 3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-hydroxymethyl-β-uridine (**12**) (483 mg, 0.95 mmol), PPh_3 (1.31 g, 5.0 mmol), and imidazole (0.34 g, 5.0 mmol) in dry benzene/CH_3CN (v/v = 4:1, 25 mL) at 0 °C. After the mixture was stirred at room temperature for 4.5 h, TLC showed that the reaction was complete. The reaction mixture was diluted with ether, and the solid was filtered off. The filtrate was washed with saturated $Na_2S_2O_3$ and brine and dried over magnesium sulfate. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 1:1) to give compound **14** (0.586 g, 100% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 9.44 (br s, 1H), 7.61 (d, 1H, J = 8.1 Hz), 7.38−7.23 (m, 8H), 6.07 (d, 1H, J = 9.1 Hz), 5.60 (d, 1H, J = 8.1 Hz), 4.60−4.48 (m, 4H), 4.29 (m, 1H), 4.11 (m, 1H), 3.73 (dd, 1H, J = 10.3, 2.8 Hz), 3.49 (dd, 1H, J = 8.5, 1.8 Hz), 3.39 (m, 1H), 3.10 (dd, 1H, J = 9.9, 4.9 Hz), 2.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.0, 150.7, 139.5, 135.4, 134.1, 133.9, 129.4, 129.2, 128.9, 128.6, 103.1, 86.8, 82.0, 81.8, 72.8 71.7, 70.7, 52.5, 29.6; HRMS calcd for $C_{24}H_{24}Cl_2IN_2O_5$ [MH^+] 617.0107, found 617.0100.

2′-Deoxy-2′-α-methyl-β-uridine (15). To the solution of 3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-iodomethyl-β-uridine (**14**) (458 mg, 0.74 mmol) in ethyl acetate (15 mL) were added 10% Pd/C (78 mg, 0.074 mmol) and triethylamine (0.52 mL, 3.7 mmol). The mixture was stirred at room temperature under hydrogen atmosphere (hydrogen balloon) for 24 h. TLC showed that no starting material (**14**) remained and compound (**13**) had formed. The catalyst was filtered off and rinsed with ethyl acetate. The filtrate was washed sequentially with 1 N HCl (5 mL), water (5 mL), saturated $NaHCO_3$, and brine and dried over magnesium sulfate. After solvent was removed, the residue was dissolved into a mixed solvent of methanol (10 mL) and ethyl acetate (10 mL). $Pd(OH)_2$/C 20% (208 mg, 0.3 mmol) was added. The reaction mixture was stirred under hydrogen atmosphere for 24 h. TLC showed that the reaction was complete. The catalyst was filtered off and rinsed with methanol. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with 7.5% methanol in ethyl acetate to give compound **15**[18](147 mg, 82% yield): ^{1}H NMR (D_2O) δ 7.78 (d, 1H, J = 8.1 Hz, 6-H), 5.88 (d, 1H, J = 8.9 Hz, 1′-H), 5.85 (d, 1H, J = 8.1 Hz, 5-H), 4.21 (dd, 1H, J = 5.7, 2.1 Hz, 3′-H), 4.03 (m, 1H, 4′-H), 3.75 (dd, 1H, J = 12.5, 4.1 Hz, 5′-H), 3.70 (dd, 1H, J = 12.5, 5.1 Hz, 5′-H), 2.39 (m, 1H, 2′-H), 1.00 (d, 3H, J = 7.0 Hz, 2′-CH_3); ^{13}C NMR (D_2O) δ 166.0, 151.9, 141.6, 102.6, 89.4, 86.3, 72.9, 61.6, 42.3, 7.7; HRMS calcd for $C_{10}H_{15}N_2O_5$ [MH^+] 243.0981, found 243.0981.

3′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2′-α-methyl-β-uridine (16). To the solution of 2′-deoxy-2′-α-methyl-β-uridine (**15**) (100 mg, 0.41 mmol) in dry DMF (10 mL) were added imidazole (338 mg, 4.96 mmol) and TBDMSCl (374 mg, 2.48 mmol). The reaction mixture was stirred at room temperature overnight. TLC showed that the reaction was not yet complete. The reaction mixture was then heated to 60 °C for 2 h. The solvent was removed, and the residue was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, and dried over magnesium sulfate. After solvent was removed, the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 3:1) to give compound **16** (154 mg, 80% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 9.72 (br s, 1H), 7.83 (d, 1H, J = 8.1 Hz), 5.96 (d, 1H, J = 7.7 Hz), 5.69 (dd, 1H, J = 1.9, 8.1 Hz), 4.19 (dd, 1H, J = 5.6, 2.1 Hz), 3.95 (m, 1H), 3.84 (dd, 1H, J = 11.4, 2.8 Hz), 3.72 (dd, 1H, J = 11.4, 1.9 Hz), 2.16 (m, 1H), 1.04 (d, 3H, J = 6.9 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.083 (s, 3H), 0.081 (s, 3H), 0.054 (s, 3H), 0.044 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.6, 150.8, 140.2, 102.4, 89.7, 87.2, 74.1, 63.2, 44.7, 25.8, 25.6, 18.3, 18.0, 9.4, −4.8, −4.9, −5.6, −5.7; HRMS calcd for $C_{22}H_{43}N_2O_5Si_2$ [MH^+] 471.27106, found 471.27108.

3′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2′-α-methyl-β-cytidine (17). Triethylamine (0.14 mL, 1.0 mmol) was added to a mixture of **16** (148 mg, 0.315 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (303 mg, 1.0 mmol), and DMAP (122 mg, 1.0 mmol) in CH_3CN (10 mL). After the mixture was stirred at room temperature for 24 h, concentrated ammonium hydroxide (28%, 15 mL) was added, and the reaction mixture was stirred at room temperature for 3 h. The organic solvent was removed, and the product was extracted with chloroform, washed with brine, and dried over magnesium sulfate. After solvent was removed, the residue was purified by silica gel chromatography, eluting with 5% methanol in chloroform to give compound **17** (128 mg, 87% yield):

^{1}H NMR ($CDCl_3$/TMS) δ 9.72 (br s, 1H), 7.83 (d, 1H, J = 8.0 Hz), 6.01 (d, 1H, J = 8.0 Hz), 5.72 (d, 1H, J = 8.0 Hz), 4.21 (dd, 1H, J = 8.0, 4.0 Hz), 3.92 (m, 1H), 3.86 (dd, 1H, J = 12.0, 4.0 Hz), 3.73 (dd, 1H, J = 12.0, 4.0 Hz), 2.15 (m, 1H), 1.07 (d, 3H, J = 8.0 Hz), 0.94 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.7, 156.3, 141.0, 94.6, 90.3, 86.2, 73.3, 62.8, 45.0, 25.9, 25.7, 18.3, 18.0, 9.9, −4.8, −5.5, −5.6; HRMS calcd for $C_{22}H_{44}N_3O_4Si_2$ [MH^+] 470.2870, found 470.2872.

2′-Deoxy-2′-α-methyl-β-cytidine (18). To the solution of **17** (57 mg, 0.12 mmol) in THF (5 mL) was added TBAF (1.0 M solution in THF, 0.35 mL, 0.35 mmol). The mixture was stirred at room temperature overnight, but TLC showed that the reaction was not yet complete. The reaction mixture was then heated to reflux for 2 h. After the solvent was removed, the residue was purified by silica gel chromatography, eluting with 20% methanol in chloroform to give compound **18**[20] (19 mg, 66% yield): ^{1}H NMR (CD_3OD/TMS) δ 7.96 (d, 1H, J = 7.5 Hz), 6.00 (d, 1H, J = 8.2 Hz), 5.91 (d, 1H, J = 7.5 Hz), 4.19 (dd, 1H, J = 5.7, 2.5 Hz), 3.96 (m, 1H), 3.77−3.73 (m, 2H), 2.28 (m, 1H), 1.07 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4, 158.7, 142.9, 96.3, 91.7, 88.1, 74.4, 63.3, 45.5, 9.4.

3′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-2′-α-methyl-*N*^{4}-benzoyl-β-cytidine (19). A mixture of **17** (100 mg, 0.213 mmol), DMAP (52 mg, 0.426 mmol), and benzoyl chloride (45 mg, 0.32 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. TLC showed that the reaction was complete. Methanol (1.0 mL) was added into the mixture. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 7:3) to give compound **19** (119 mg, 97% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 8.88 (br s, 1H), 8.35 (d, 1H, J = 8.0 Hz), 7.88 (d, 2H, J = 8.0 Hz), 7.55 (t, 1H, J = 8.0 Hz), 7.47−7.39 (m, 3H), 5.99 (d, 1H, J = 4.0 Hz), 4.23 (m, 1H), 3.96−3.91 (m, 2H), 3.74 (dd, 1H, J = 12.0, 4.0 Hz), 2.22 (m, 1H), 1.12 (d, 3H, J = 8.0 Hz), 0.91 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 161.9, 158.0, 144.7, 133.2, 133.0, 128.9, 127.6, 96.6, 91.2, 86.4, 72.5, 62.4, 45.7, 25.9, 25.6, 18.4, 18.0, 10.2, −4.6, −4.8, −5.5; HRMS calcd for $C_{29}H_{48}N_3O_5Si_2$ [MH^+] 574.3133, found 574.3138.

2′-Deoxy-2′-α-methyl-*N*^{4}-benzoyl-β-cytidine (20). To the solution of **19** (117 mg, 0.204 mmol) in THF (10 mL) was added triethylamine trihydrofluoride (258 mg, 0.26 mL, 1.6 mmol). After the mixture was stirred at room temperature for 40 h, TLC showed that the reaction was not yet complete. Triethylamine (28 μL, 0.204 mmol) was then added into the mixture, and the reaction was continued at 60 °C overnight. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 2% methanol in ethyl acetate to give compound **20**[8] (53 mg, 75% yield): ^{1}H NMR (CD_3OD/TMS) δ 8.52 (d, 1H, J = 8.0 Hz), 7.96 (d, 2H, J = 8.0 Hz), 7.64−7.51 (m, 4H), 6.02 (d, 1H, J = 8.0 Hz), 4.25 (m, 1H), 4.04 (m, 1H), 3.86 (dd, 1H, J = 8.0, 4.0 Hz), 3.78 (dd, 1H, J = 8.0, 4.0 Hz), 2.37 (m, 1H), 1.14 (d, 3H, J = 8.0 Hz); ^{13}C NMR (CD_3OD) δ 164.6, 158.3, 146.7, 134.6, 134.1, 129.8, 129.1, 98.7, 92.7, 88.3, 73.7, 62.8, 46.5, 9.8; HRMS calcd for $C_{17}H_{20}N_3O_5$ [MH^+] 346.1403, found 346.1387.

5′-*O*-(Dimethoxytrityl)-2′-deoxy-2′-α-methyl-*N*^{4}-benzoyl-β-cytidine (21). Compound **20** (53 mg, 0.154 mmol) was coevaporated with pyridine (2 mL) and dissolved into pyridine (5 mL) again. DMTrCl (171 mg, 0.51 mmol) and DMAP (42 mg, 0.34 mmol) were added to the pyridine solution of **20** under argon. After the mixture was stirred at room temperature overnight, methanol (1.0 mL) was added to the reaction mixture. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 3% methanol in chloroform to give compound **21**[8] (80 mg, 80% yield). Some starting material (**20**) (11 mg, 20%) was also recovered by silica gel chromatography, eluting with 8% methanol in chloroform. **21**: ^{1}H NMR ($CDCl_3$/TMS) δ 9.10 (br s, 1H), 8.33 (d, 1H, J = 7.4 Hz), 7.81 (d, 2H, J = 7.6 Hz), 7.60−7.10 (m, 12H), 6.85 (m, 5H), 6.05 (d, 1H, J = 5.0 Hz), 4.44 (m, 1H), 4.19 (m, 1H), 3.79 (s, 6H), 3.53 (dd, 1H, J = 10.9, 2.7 Hz), 3.48 (dd, 1H, J = 10.9, 3.2 Hz), 2.44 (m, 1H), 1.26 (d, 3H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 162.6, 162.1, 158.6, 144.9, 144.2, 135.6, 135.4, 132.9, 130.0, 129.9, 129.1, 128.8, 128.1, 128.0, 127.7, 127.5, 127.0, 113.2, 96.8, 91.4, 86.9, 84.5, 71.7, 62.7, 55.2, 45.3, 10.0; HRMS calcd for $C_{38}H_{38}N_3O_7$ [MH^+] 648.2710, found 648.2730.

5′-*O*-(Dimethoxytrityl)-2′-deoxy-2′-α-methyl-*N*^{4}-benzoyl-β-cytidine 3′-*N*,*N*-Diisopropyl(cyanoethyl)phosphoramidite (22). *N*,*N*-Diisopropylethylamine (69 μL, 0.4 mmol), 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (67 μL, 0.3 mmol), and 1-methylimidazole (8.0 μL, 0.1 mmol) were quickly added to a solution of compound **21** (80 mg, 0.124 mmol) in dry dichloromethane (10 mL) at 0 °C under argon. The reaction mixture was then warmed to room temperature and stirred until TLC indicated that the reaction was complete (2 h). The reaction mixture was cooled to 0 °C, quenched with methanol (0.5 mL), and stirred for an additional 5 min. After the solvent was removed, the residue was purified by silica gel chromatography, eluting with 4% acetone in dichloromethane with 0.2% triethylamine to give the corresponding phosphoramidite (**22**)[8] (105 mg, 100% yield): ^{31}P NMR ($CDCl_3$) δ 153.8, 151.8; MS (*m*/*z*) 848.3 [MH^+], 303 (DMtr, 100).

Methyl 2-Acetoxymethyl-2-deoxy-α-D-ribofuranoside (23). A mixture of compound **5** (2.103 g, 4.48 mmol), 20% Pd-$(OH)_2$/C (754 mg, 1.07 mmol), and triethylamine (0.93 mL, 6.7 mmol) in ethyl acetate (30 mL) was stirred under a hydrogen atmosphere (hydrogen balloon) at room temperature overnight. TLC showed that the reaction was complete. The catalyst was filtered off and rinsed with ethyl acetate. The filtrate was concentrated, and the residue was isolated by silica gel chromatography, eluting with ethyl acetate to give compound **23** (0.906 g, 92% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 5.04 (d, 1H, J = 4.2 Hz), 4.41 (dd, 1H, J = 11.5, 7.9 Hz), 4.27 (dd, 1H, J = 11.5, 6.4 Hz), 4.19−4.12 (m, 2H), 3.73−3.66 (m, 2H), 3.41 (s, 3H), 2.37 (m, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 105.0, 87.8, 72.4, 62.8, 59.2, 55.1, 47.5, 20.8; HRMS calcd for $C_9H_{16}O_6Na$ [MNa^+] 243.0845, found 243.0848.

Methyl 2-Acetoxymethyl-3,5-di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-D-ribofuranoside (24). A mixture of compound **23** (220 mg, 1.0 mmol), TBDMSCl (904 mg, 6.0 mmol), and imidazole (816 mg, 12 mmol) in DMF (30 mL) was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved into CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was isolated by 5% ethyl acetate in pentane to give compound **24** (436 mg, 97% yield), a mixture of anomers α/β ~85:15 from ^{1}H NMR spectra. α-Anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 4.93 (d, 1H, J = 4.0 Hz), 4.25 (m, 3H), 4.00 (m, 1H), 3.66 (m, 1H), 3.55 (m, 1H), 3.31 (s, 3H), 2.34 (m, 1H), 2.01 (s, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.05−0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 170.9, 105.1, 87.6, 72.2, 63.6, 59.8, 55.0, 47.2, 25.9, 25.7, 21.0, 18.3, 17.9, −4.4, −5.2, −5.3, −5.5; HRMS calcd for $C_{21}H_{44}O_6Si_2Na$ [MNa^+] 471.2574, found 471.2583.

2′-Acetoxymethyl-3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-*N*^{4}-acetyl-β-cytidine (25). Persilylated N^4-acetylcytosine was prepared by the reaction of N^4-acetylcytosine (0.80 g, 5.2 mmol) with TMS_2NH (20 mL) in the presence of $(NH_4)_2SO_4$ (10 mg), as described for the synthesis of **6**. Under argon, the persilylated base was dissolved in acetonitrile (50 mL), and the solution was transferred into the flask containing compound **24** (938 mg, 2.09 mmol). $SnCl_4$ (0.61 mL, 5.2 mmol) was added in one portion with vigorous stirring and exclusion of moisture. The homogeneous pale yellow solution was stirred at room temperature overnight. TLC showed that no starting material remained. The reaction was quenched carefully by addition of 10% aqueous $NaHCO_3$ (50 mL) and stirred for 15 min. The mixture was extracted with methylene chloride, and the organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 3:7) to give compound **25** (748 mg, 63% yield). The β/α selectivity is 9:1 based on the ^{1}H NMR spectra of **25**. β-Ano-

mer: ^{1}H NMR ($CDCl_3$/TMS) δ 10.45 (br s, 1H), 8.22 (d, 1H, J = 7.6 Hz), 7.38 (d, 1H, J = 7.6 Hz), 6.22 (d, 1H, J = 7.1 Hz), 4.40−4.20 (m, 3H), 4.02 (m, 1H), 3.88 (m, 1H), 3.75 (m, 1H), 2.48 (m, 1H), 2.26 (s, 3H), 1.93 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.4, 170.3, 163.0, 155.1, 144.5, 97.1, 87.6, 87.5, 72.2, 62.8, 59.8, 50.6, 25.8, 25.6, 24.8, 20.7, 18.3, 17.9, −4.8, −5.1, −5.5, −5.6; HRMS calcd for $C_{26}H_{47}N_3O_7Si_2Na$ [MNa^+] 592.2850, found 592.2828.

2′-Acetoxymethyl-3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-β-uridine (26). Bis(trimethylsilyl)uracil was prepared by the reaction of uracil (0.168 g, 1.5 mmol) with TMS_2NH (5 mL) in the presence of $(NH_4)_2SO_4$ (5 mg) as described for the synthesis of **7**. Under argon, bis(trimethylsilyl)uracil was dissolved into acetonitrile (10 mL), and the solution was transferred into the flask containing compound **24** (188 mg, 0.42 mmol). $SnCl_4$ (0.18 mL, 1.5 mmol) was added in one-portion with vigorous stirring and exclusion of moisture. The homogeneous pale yellow solution was stirred at room temperature overnight (14 h). TLC showed that no starting material remained. The reaction was quenched carefully by addition of 10% aqueous $NaHCO_3$ (10 mL) and stirred for 15 min. The mixture was extracted with methylene chloride, and the organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v = 6:4) to give compound **26** (126 mg, 57% yield). The β/α selectivity is 94:6 based on the ^{1}H NMR spectra of **26**. β-Anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 9.65 (br s, 1H), 7.79 (d, 1H, J = 8.0 Hz), 6.17 (d, 1H, J = 8.0 Hz), 5.69 (d, 1H, J = 8.0 Hz), 4.35 (m, 1H), 4.28 (m, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.83 (m, 1H), 3.72 (dd, 1H, J = 12.0, 4.0 Hz), 2.50 (m, 1H), 1.94 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 163.4, 150.4, 139.9, 102.6, 87.6, 86.5, 73.1, 63.3, 59.9, 50.0, 25.7, 25.6, 20.6, 18.2, 17.9, −4.8, −5.2, −5.6, −5.8; HRMS calcd for $C_{24}H_{45}N_2O_7Si_2$ [MH^+] 529.2765, found 529.2765.

2′-Acetoxymethyl-2′-deoxy-*N*^{4}-acetyl-β-cytidine (27). Triethylamine trihydrofluoride (670 mg, 0.68 mL, 4.16 mmol) and triethylamine (72 μL, 0.52 mmol) were added to the solution of **25** (294 mg, 0.52 mmol) in dry THF (15 mL). The mixture was heated to 60 °C and stirred for 14 h. TLC showed that the reaction was complete. The reaction mixture was diluted with pyridine (2 mL). Water (50 mL) and CH_2Cl_2 (20 mL) were added, and the aqueous layer was collected. After evaporation of water, the residue was purified by silica gel chromatography, eluting with 10% methanol in chloroform to give compound **27** (168 mg, 95% yield): ^{1}H NMR (CD_3OD/TMS) δ 8.17 (d, 1H, J = 7.6 Hz), 7.27 (d, 2H, J = 7.6 Hz), 6.14 (d, 1H, J = 7.6 Hz), 4.40−4.34 (m, 2H), 4.22 (dd, 1H, J = 11.4, 7.5 Hz), 4.09 (m, 1H), 3.78 (dd, 1H, J = 12.4, 3.5 Hz), 3.73 (dd, 1H, J = 12.4, 4.7 Hz), 2.68 (m, 1H), 2.14 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (CD_3OD) δ 174.0, 173.8, 162.7, 157.0, 145.6, 98.5, 88.6, 86.9, 71.0, 61.2, 61.0, 47.8, 23.9, 20.0.

2′-α-Acetoxymethyl-5′-*O*-(dimethoxytrityl)-2′-deoxy-*N*^{4}-acetyl-β-cytidine (28). Compound **27** (176 mg, 0.516 mmol) was coevaporated with pyridine (5 mL) and dissolved into pyridine (10 mL) again. To the solution of **27** in pyridine were added DMTrCl (372 mg, 1.1 mmol) and DMAP (126 mg, 1.03 mmol). After the mixture was stirred at room temperature overnight, methanol (5.0 mL) was added into the reaction mixture. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 3% methanol in chloroform to give compound **28** (263 mg, 79% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 9.83 (br s, 1H), 8.15 (d, 1H, J = 7.5 Hz, 6-H), 7.40 (d, 2H, J = 7.7 Hz), 7.30 (d, 6H, J = 8.3 Hz), 7.24 (m, 1H), 7.21 (d, 1H, J = 7.5 Hz, 5-H), 6.85 (d, 4H, J = 8.6 Hz), 6.33 (d, 1H, J = 6.6 Hz, 1′-H), 4.65 (m, 1H, 3′-H), 4.50 (m, 1H, 2′-CH_2), 4.45 (br s, 1H), 4.40 (m, 1H, 2′-CH_2), 4.25 (m, 1H, 4′-H), 3.78 (s, 6H, MeO), 3.48 (m, 2H, 5′-H), 2.63 (m, 1H, 2′-H), 2.20 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 170.8, 162.6, 158.6, 155.6, 144.6, 144.2, 135.3, 135.2, 130.0, 128.0, 127.9, 127.0, 113.3, 97.0, 87.7, 86.9, 85.7, 71.4, 63.1, 60.4, 55.2, 50.9, 24.7, 20.8; HRMS calcd for $C_{35}H_{38}N_3O_9$ [MH^+] 644.2608, found 644.2609.

2′-α-Acetoxymethyl-5′-*O*-(dimethoxytrityl)-2′-deoxy-*N*^{4}-acetyl-β-cytidine 3′-*N*,*N*-Diisopropyl(cyanoethyl)phosphoramidite (29). To a solution of compound **28** (53 mg, 0.082 mmol) in dry dichloromethane (10 mL) at 0 °C under argon were added *N*,*N*-diisopropylethylamine (50 μL, 0.29 mmol), 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (45 μL, 0.20 mmol), and 1-methylimidazole (4.0 μL, 0.05 mmol). The reaction mixture was stirred at room temperature until all starting material was consumed (1 h). The reaction mixture was cooled to 0 °C, quenched with methanol (0.5 mL), and stirred for 5 min. After the solvent was removed, the residue was purified by silica gel chromatography, eluting with 4% acetone in dichloromethane with 0.5% triethylamine to give the corresponding phosphoramidite (**29**) (65 mg, 94% yield): ^{31}P NMR ($CDCl_3$) δ: 151.14, 151.07. MS (*m*/*z*) 842.3 [M − 1, 100], 843.3, 844.3.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **2**−**21** and **23**−**28**. ^{1}H NMR and ^{31}P NMR spectra of compounds **22** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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