Sonochemical and Triethylborane-Induced Tin Deuteride Reduction for the Highly Diastereoselective Synthesis of (2′*R*)-2′-Deoxy[2′-^{2}H]ribonucleoside Derivatives

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For the NMR spectroscopic conformational analysis of a sugar moiety in a DNA complex with a protein or a drug, (2′*R*)- and/or (2′*S*)-2′-deoxy[2′-^{2}H]ribonucleoside derivatives with high purity are useful. To develop a highly diastereoselective and efficient method for the synthesis of (2′*R*)-2′-deoxy[2′-^{2}H]ribonucleoside derivatives, studies of leaving groups (OPTC, Br) at the 2′ position of nucleosides, of the effects of reaction temperature on diastereoselectivity, of radical generation (ultrasound irradiation, Et_3B) at temperatures as low as −70 °C, and of protecting groups for the 3′ and 5′ hydroxyl groups (benzoate, TPDS) of nucleosides were carried out. Bu_3Sn^2H-reductive deuteration of 3′,5′-di-*O*-benzoyl-2′-bromo-2′-deoxyuridine under high-intensity ultrasound irradiation at −71 °C induced notably efficient deuterium incorporation to afford a highly diastereoselective 3′,5′-di-*O*-benzoyl-2′-deoxy[2′-^{2}H]uridine [(2′*R*):(2′*S*) = 96:4]. The use of Et_3B, as an alternative radical generator, toward 2′-bromo-2′-deoxy-3′,5′-*O*-TPDS-ribonucleosides at <−70 °C made it feasible to perform the reaction on a preparative scale, and provided excellent diastereoselectivity (2′-deoxyadenosine, thymidine, and 2′-deoxyuridine derivatives >99:1 which were converted to (2′*R*)-2′-deoxy[2′-^{2}H]cytidine derivatives, guanosine derivative = 91:9).

Introduction

The conformational diversity of the sugar moieties in DNA is considered to be important in the elucidation of sequence-specific DNA−protein or −drug recognition processes. Although NMR spectroscopy has proved to be useful for the structural analysis of DNA, the extensive signal overlap makes the spectral analysis often difficult or erroneous. In view of the spectral complexity associated with these molecules, 2′-deoxy[2′-^{2}H]ribonucleosides with higher stereoselectivity would provide enormous possibilities for enhancing the precision of NMR analyses.

Some methods to achieve the above goal have been reported. The synthesis of (2′*R*)-2′-deoxy[2′-^{2}H]cytidine starting from (2*R*)-2-deoxy-D-*erythro*-[2-^{2}H]pentose[1] was reported first by Fraser-Reid *et al.* The synthesis of (2′*R*)-2′-deoxy[2′-^{2}H]ribonucleosides was then accomplished, but it leaves much to be desired, due to the long sequence of reactions starting from methyl 2,3-anhydro-β-D-lyxofuranoside, which was converted in seven steps to (2*R*)-3,5-diaroyl-2-deoxy-D-[2-^{2}H]ribofuranosyl chloride before the coupling reaction with a nucleotide base.[2] On the other hand, a shorter, alternative approach to the nucleosides has been reported, which involves the chemical conversion of adenosine or uridine derivatives, functionalized with either chloro[3] or *O*-phenoxythiocarbonyl (*O*-PTC)[4] substituents at their 2′ position, to the corresponding deuterated compound through deuteration with tributyltin deuteride (Bu_3Sn^2H)/2,2′-azobis(isobutyronitrile) (AIBN). The deuteration, however, gives rather lower stereoselectivity (e.g., 2′*R*:2′*S* = 88:12)[4] at best. This level of stereoselectivity is unacceptable for NMR studies of complex sugar derivatives. Therefore, we searched for a method to improve the stereoselectivity up to ~100% for a (2′*R*)-diastereomer over the corresponding (2′*S*)-diastereomer.

We now report, in full, the sonochemical and triethylborane (Et_3B)-induced tin deuteride reduction of ribonucleoside derivatives functionalized at their 2′-position, at a low temperature of −60 to −70 °C, which successfully yielded high stereoselectivity, such as 2′*R*:2′*S* > 99:1.[5]

Results and Discussion

Effect of Reaction Temperature on the Diastereoselectivity (2′*R*:2′*S*). The preponderant formation of (2′*R*)-isomers under thermal conditions[3,4] is likely to reflect the steric effect of the heterocyclic moiety with the β-configuration on the Bu_3Sn^2H approaching the radical center generated at the 2′-position. Thus, the stereoselectivity favoring the (2′*R*)-isomer over the corresponding (2′*S*)-isomer could be improved further as the reaction temperature is lowered, according to predictions of kinetic law. On the basis of such an assumption, the effects of the reaction temperature on the diastereoselectivity in the deuteration reactions of 2′-functionalized ribonucleoside derivatives were examined through three categories of procedures, i.e., thermal (procedure A), sonochemical (procedure B), and Et_3B-induced reactions (procedure C),

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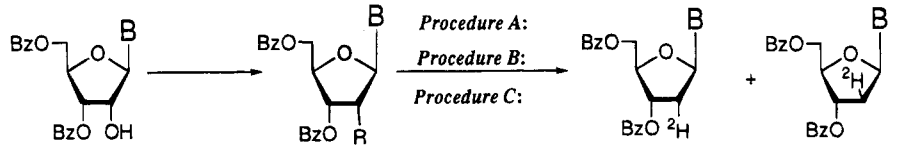
Scheme 1



Procedure A: Bu_3Sn^2H (2.0 equiv.) / AIBN (0.42 equiv.)△

Procedure B: Bu_3Sn^2H (2.0 equiv.) / AIBN (0.42 equiv.),))))

Procedure C: Bu_3Sn^2H (2.0 equiv.) / Et_3B (1.1 equiv.).

Table 1. Effects of Reaction Conditions on Diastereoselectivity[a]

entry	substrate	procedure	solvent	temp (°C)	yield (%)	ratio 2′R/2′S	$\Delta\Delta G^{\ddagger}$
1	**2b**	B	diglyme	22	55	88/12	
2	**3b**	B	diglyme	12	05	87/13	1.077
3	**3b**	B	THF	11	86	87/13	1.073
4	**3b**	B	THF	1	90	88/12	1.085
5	**3b**	B	diglyme	−32	91	92/8	1.170
6	**3b**	B	diglyme	−50	76	94/6	1.219
7	**3b**	B	THF	−71	78	96/4	1.276
8	**3b**	C	THF	10	93	84/16	
9	**3b**	C	THF	0	91	86/14	
10	**3b**	C	THF	−20	90	90/10	
11	**3b**	C	THF	−52	90	92/8	

[a] The reactions were performed in a 8.75 × 10^{-2} M solution. Yields were of the products isolated. The ratios of 2′*R*:2′*S* were determined by ^{1}H-NMR at 400 MHz. The temperature in entries 8−11 was the highest temperature observed during the dropwise addition of Et_3B.

as described below, in addition to the studies of the leaving groups (OPTC, Br) at the 2′ position of nucleosides (Scheme 1).

Procedure A: Bu_3Sn^2H/AIBN System. In order to investigate the effects of the reaction temperature on the diastereoselectivity (2′*R*:2′*S*), the conventional thermal conditions were first examined for 3′,5′-di-*O*-benzoyl-2′-*O*-(phenoxythiocarbonyl)adenosine (**2a**) with Bu_3Sn^2H and AIBN at 100 °C, 80 °C, 60 °C, and 0 °C; 3′,5′-di-*O*-benzoyl-2′-*O*-(phenoxythiocarbonyl)uridine (**2b**) at 100 °C, 65 °C, and 0 °C, and 3′,5′-di-*O*-benzoyl-2′-bromo-2′-deoxyuridine (**3b**) at 100 °C and 65 °C.[5] The results from these experiments suggested that the stereoselectivity is not controlled by the properties of the group introduced at the 2′-position, and that a lower reaction temperature tends to improve the diastereomer ratio 2′*R*/2′*S*.

Procedure B: Sonochemical Bu_3Sn^2H Reduction (entries 1 and 7). Since procedure A is not feasible for the reaction at any lower temperature, in place of the conventional thermal conditions, the reactions at low temperatures were next examined using sonochemical conditions [under an argon atmosphere with 20 KHz ultrasound (50 W) irradiation[6]], which have been strikingly efficient for generating the tin radical from Bu_3Sn^2H, even at around −60 °C.[7]

In the first place, a comparative study on the reactivities of **2b** and **3b** under sonochemical conditions was undertaken (entries 1 and 2) and revealed the significant

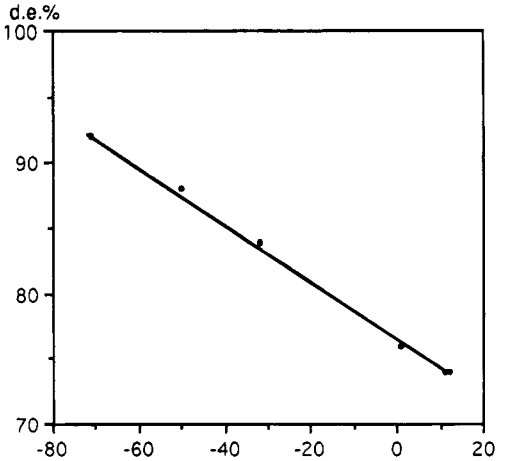


Figure 1. Cross-correlation of entries 2−7 in Table 1 between de% of (2′*R*)- and (2′*S*)-2′-deoxy[2′-^{2}H]uridine and the reaction temperature.

superiority of **3b** [yield of (2′*R*)- and (2′*S*)-3′,5′-di-*O*-benzoyl-2′-deoxy[2′-^{2}H]uridine (**4b**) at 12 °C: 95%] to **2b** (yield of **4b** at 22 °C: 55%), although the diastereoselectivity obtained was almost the same. Therefore, experiments at a lower temperature were performed with **3b,** by examining the reaction at temperatures starting from 11 °C, 1 °C, −32 °C, −50 °C, and finally −71 °C in the reaction system. It was of great interest to find the significant improvement in the diastereoselectivity, given by 2′*R*:2′*S* as 87:13, 88:12, 92:8, 94:6, and 96:4, respectively. The diastereomer excess (de) amounts observed in the temperature range of −71 °C (entry 7) to 12 °C (entry 2) were plotted against the reaction temperature to give the profile shown in Figure 1. With the viewpoint from the activation energy, the isomeric ratios observed in the temperature range of −71 to 12 °C correspond to a 1.0−1.3 kcal/mol [$\Delta\Delta G^{\ddagger}$] energy difference between the α- and β-face approaches of Bu_3Sn^2H to the free radical generated at the 2′ position (entries 2−7). Thus, the diastereoselectivity is controlled mainly by the reaction temperature.

The present approach through ultrasound irradiation is significant as a basic study, but is impractical for the synthesis of (2′*R*)-2′-deoxy[2′-^{2}H]ribonucleosides on a preparative scale, due to the irradiation apparatus, and, thus, it is inadequate to ensure a sufficient supply for us to construct an objective oligodeoxyribonucleotide for NMR analysis.

Procedure C: Bu_3Sn^2H/Et_3B System (entries 8−11). In place of the sonochemical conditions, the Bu_3Sn^2H reductive deuteration of **3b** induced by Et_3B was examined based on the reduction using Et_3B, which was

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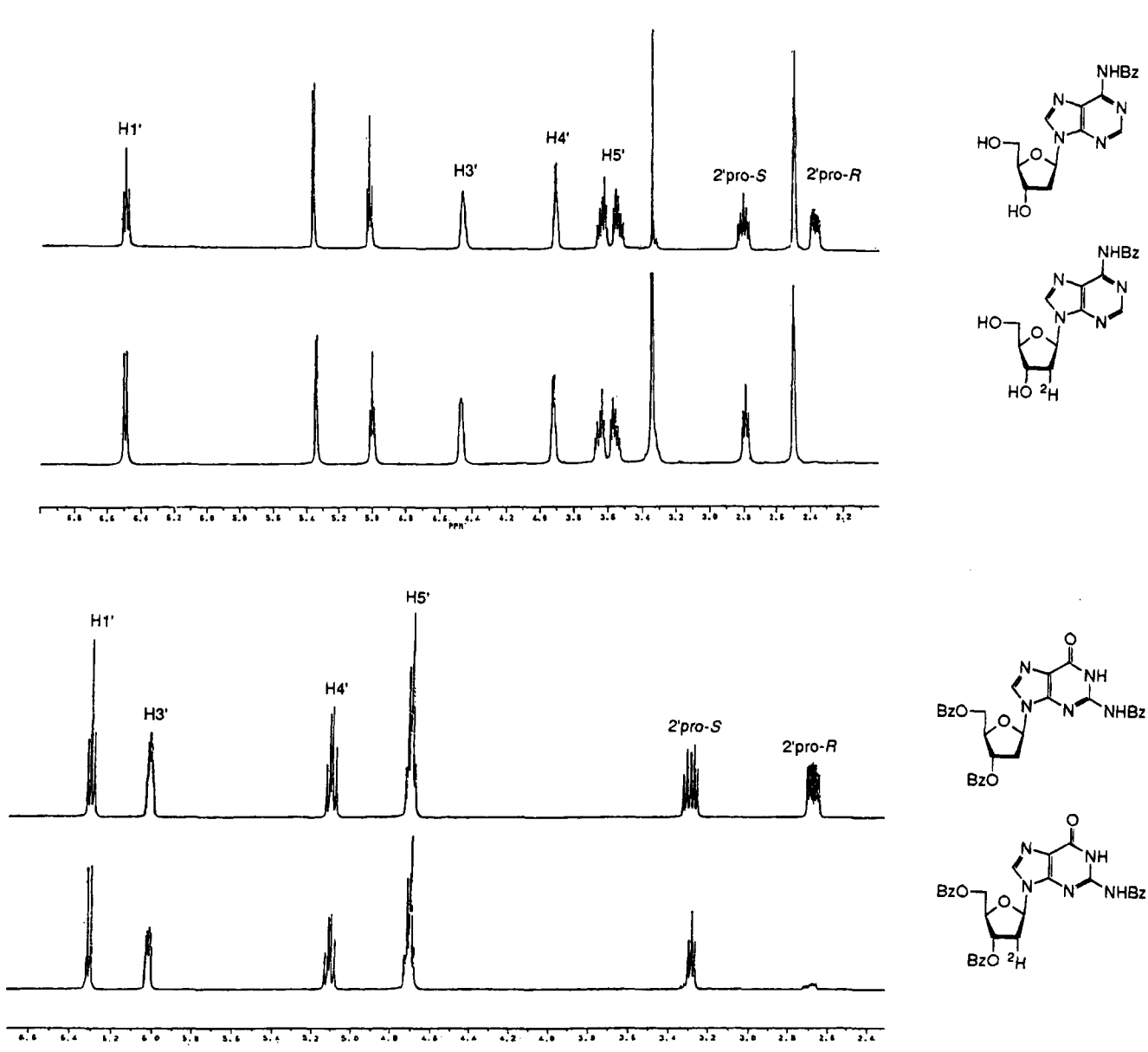

Figure 2. ^{1}H-NMR spectra (400 Mhz) of (2′*R*)-2′-deoxy[2′-^{2}H]nucleosides and corresponding nondeuterated 2′-deoxynucleosides. These spectra clearly show the absence of both of the H-2′*pro-R* proton signal and of the *J* network through H-1′- and H-2′*pro-R* in the ribose ring. A comparison of these spectra illustrates the diastereoselective labeling achieved in present work.

confirmed to yield an ethyl free radical in the presence of a trace amount of oxygen at a very low temperature, such as −70 °C.[8] The present system was thus proven to be remarkably significant as a preparative method, giving excellent yields without regard to the reaction temperature, and higher (2′*R*)-diastereoselectivity with temperature: down to −52 °C, i.e., 84:16 at 10 °C, 86:14 at 0 °C, 90:10 at −20 °C, and finally 92:8 at −52 °C.

Effect of Protecting Groups on the Diastereoselectivity (2′*R*:2′*S*). Our experience in benzoyl groups for ribonucleosides[9] led us to use them for the present work. On the other hand, Robins and his co-workers used a bidentate 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TPDS) group for the protection of the hydroxyl groups at the 3′ and 5′ positions and obtained diastereoselectivity such as ~88:12,[4] which seems better than that of 74:26 for the reduction of **2a** under the thermal conditions at 100 °C we obtained herein. Therefore, a comparative study on the diastereoselectivity in the Bu_3Sn^2H−AIBN reduction of 3′,5′-*O*-TPDS-2′-*O*-PTC- and 3′,5′-di-*O*-benzoyl-2′-*O*-PTC-adenosine (**2a**) was undertaken in toluene at 100 °C in the same way, which gave 85:15 (87% yield) and 74:26 (93% yield), respectively. These results prompted us to assume that the 3′,5′-*O*-TPDS protection for the D-ribofuranosyl moiety of the ribonucleosides, as compared to 3′,5′-di-*O*-benzoyl protection, probably forces it to occupy the $C_{2'exo}$−$C_{3'endo}$ conformation; i.e., the heterocyclic moiety is forced to shift to the more rectangular disposition, which might then exert its steric effect more efficiently on the Bu_3Sn^2H molecule to hinder its β-face attack on the free radical generated at the 2′ position. Alternatively, the protection might favor the attack of the Bu_3Sn^2H molecule from the α-face on the free radical.

Consequently, the 3′,5′-*O*-TPDS protection[4,10] was applied to all the nucleoside substrates functionalized with the bromo substituent at their 2′ position, and these were

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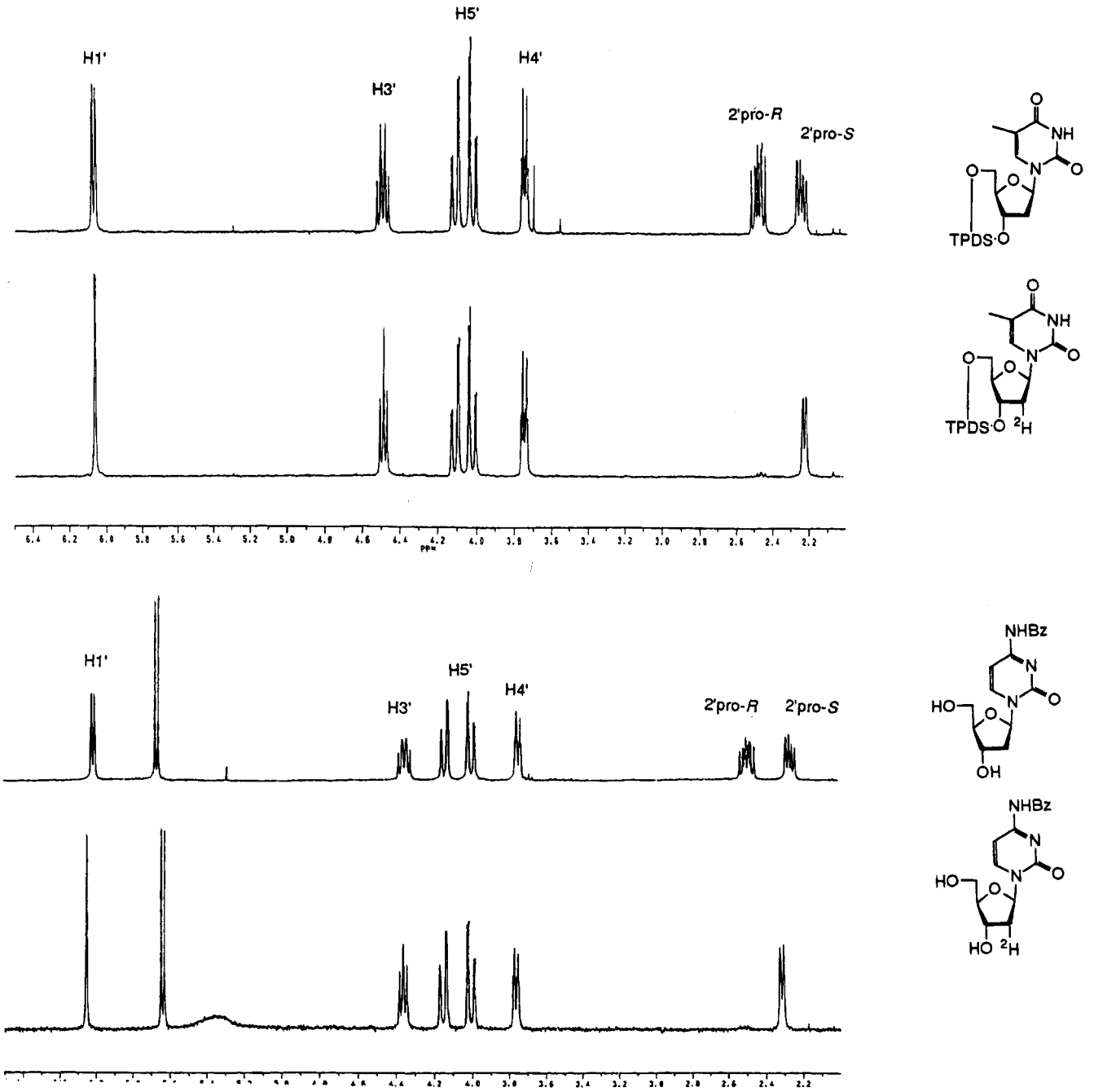

Figure 2. (continued)

subjected to the $Bu_3Sn^2H-Et_3B$ reductive deuteration (procedure C).

Highly Diastereoselective Synthesis of (2′*R*)-2′-Deoxy[2′-^{2}H]ribonucleoside Derivatives. In addition to the 3′,5′-*O*-TPDS protection, the exocyclic amino groups of the corresponding nucleosides were protected by either a benzoyl or an isobutyryl group, in anticipation of their utility in the synthesis of an oligonucleotide. N^6-benzoyl-9-(2-bromo-2-deoxy-3,5-*O*-TPDS-β-D-arabinofuranosyl)adenine (**5a**) was derived from N^6-benzoyl-3′,5′-*O*-TPDS-adenosine[11] via N^6-benzoyl-3′,5′-*O*-TPDS-2′-*O*-trifluoromethanesulfonyl (Tf) adenosine by a sequence of reactions with trifluoromethanesulfonyl chloride (TfCl) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (94% yield) and with lithium bromide (LiBr) (94% yield).[12] Compound **5a** was then applied to the reductive deuteration to give N^6-benzoyl-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]-adenosine (**6a**) (94% yield), followed by the unmasking of the TPDS group with ammonium fluoride (NH_4F) in MeOH,[13] to give a >99:1 mixture (85% yield) of (2′*R*)- and (2′*S*)-N^6-benzoyl-2′-deoxy[2′-^{2}H]adenosine (**7a**). 9-(2-bromo-2-deoxy-3,5-*O*-TPDS-β-D-arabinofuranosyl)-N^2-isobutyrylguanine (**5c**) (91% yield) was also derived from N^2-isobutyryl-3′,5′-*O*-TPDS-guanosine[14] via N^2-isobutyryl-3′,5′-*O*-TPDS-2′-*O*-Tf-guanosine (62% yield). Compound **5c** was then similarly subjected to the reaction through procedure C to give 2′-deoxy-N^2-isobutyryl-3′,5′-*O*-TPDS-

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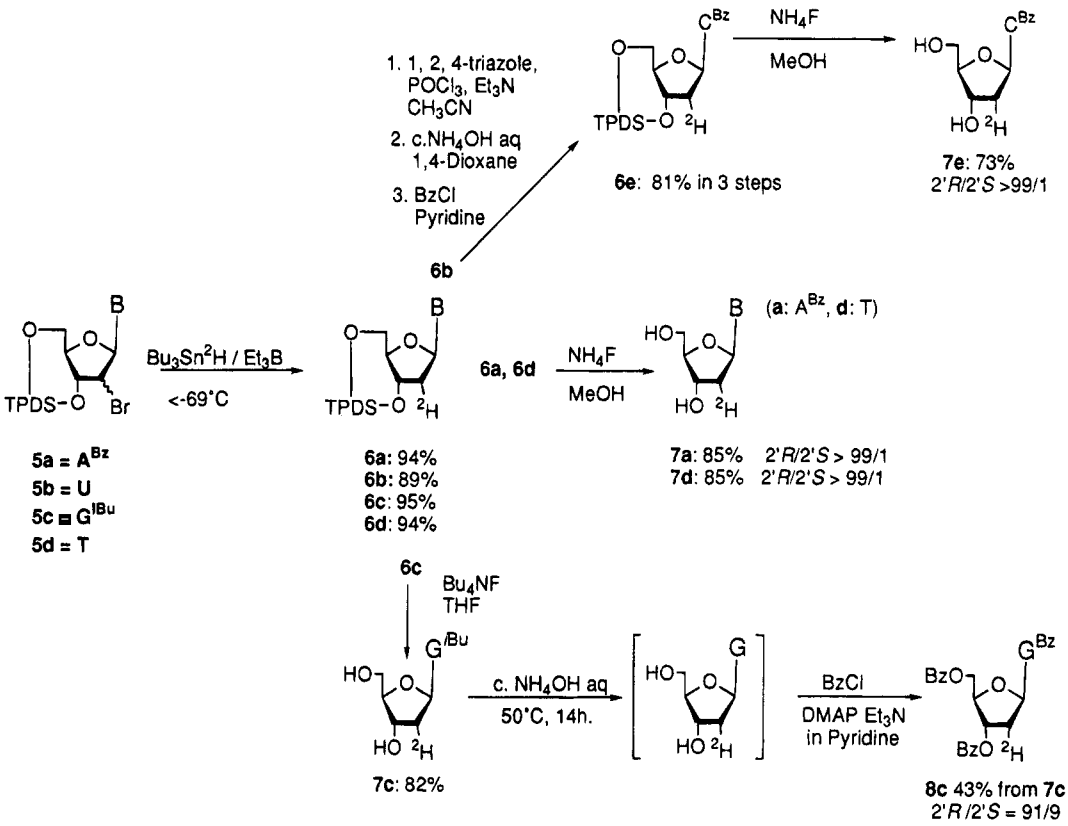
Scheme 2



[2'-^{2}H]guanosine (**6c**) (95% yield), followed by the unmasking of the TPDS group with tetrabutylammonium fluoride (Bu_4NF) in THF to give a diastereomeric mixture of 2'-deoxy-N^2-isobutyryl[2'-^{2}H]guanosine (**7c**) (82% yield). The ratio of the (2'*R*)- and (2'*S*)-diastereoisomers of **7c** were confirmed to be 91: 9 after conversion into the corresponding N^2,$O^{3'}$,$O^{5'}$-tribenzoyl-2'-deoxy[2'-^{2}H]guanosine (**8c**) (43% overall yield in two steps) via 2'-deoxy-[2'-^{2}H]guanosine. (2'*R*)-2'-Bromo-3',5'-*O*-TPDS-thymidine (**5d**)[15] was similarly treated through procedure C to give a >99:1 mixture (94% yield) of (2'*R*)- and (2'*S*)-3',5'-*O*-TPDS-[2'-^{2}H]thymidine (**6d**). The deprotection of the 3',5'-*O*-TPDS group of **6d** was also easily performed by the use of NH_4F in MeOH[13] to give (2'*R* > 99%)-[2'-^{2}H]thymidine (**7d**) (85% yield).

The synthesis of (2'*R*)-N^4-benzoyl-2'-deoxy[2'-^{2}H]cytidine (**7e**) could not be performed via 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-cytidine, because 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-cytidine is unstable and immediately equilibrates with O^2,2'-anhydro-(3,5-*O*-TPDS-β-D-arabinofuranosyl)-cytosine hydrobromide.[16] Therefore, (2'*R*)-2'-deoxy-3',5'-*O*-TPDS-[2'-^{2}H]cytidine was synthesized from (2'*R* >99%)-2'-deoxy-3',5'-*O*-TPDS-[2'-^{2}H]uridine in two steps (Scheme 2). 2'-Bromo-2'-deoxy-3',5'-*O*-TPDS-uridine (**5b**)[15] was similarly treated through procedure C to give a >99:1 mixture (89% yield) of (2'*R*)- and (2'*S*)-2'-deoxy-3',5'-*O*-TPDS-[2'-^{2}H]uridine (**6b**). The resulting **6b** was efficiently converted into (2'*R* >99%)-2'-deoxy-3',5'-*O*-TPDS-[2'-^{2}H]cytidine via 1-{(2*R* >99%)-3,5-*O*-TPDS-2-deoxy-β-D-[2-^{2}H]ribofuranosyl}-4-(1,2,4-)-1*H*-pyrimidin-2-one by a sequence of reactions with 1,2,4-triazole/phosphorus oxychloride/Et_3N in CH_3CN, with ammoniacal 1,4-dioxane.[17]

After protection of the N^4-amino group with a benzoyl group, (2'*R* >99%)-N^4-benzoyl-2'-deoxy-3',5'-*O*-TPDS-[2'-^{2}H]cytidine (**6e**) was also treated with NH_4F in dry MeOH[13] to give (2'*R*)-N^4-benzoyl-2'-deoxy[2'-^{2}H]cytidine (**7e**) (73% yield).

The sugar moiety regions of ^{1}H-NMR spectral data of these products are shown in Figure 2, together with those of the corresponding 2'-deoxyribonucleosides, for comparison. These spectra in Figure 2 clearly show the absence of both the H-2'*pro-R* proton signal and the *J* network through H-1' and H-2'-*pro-R* and H-3' and H-2'*pro-R* in the ribose ring. The results described here demonstrate the promising utility of the present approach in terms of procedure C for their preparation.

Experimental Section

General Procedures. Melting points were uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 400 and 300 MHz and at 100 and 75 MHz, respectively. Chemical shifts were recorded in the δ scale relative to an internal reference of CH_3Cl (7.26 ppm for ^{1}H-NMR and 77.0 ppm for ^{13}C-NMR spectra), unless otherwise noted. Dimethyl sulfoxide-d_6 (DMSO-d_6) (2.50 ppm for ^{1}H spectra) was occasionally used as an internal reference. The signal peaks of the ^{13}C-NMR spectra were assigned by the DEPT experiment. Mass spectra (MS), high resolution mass spectra, and elemental analyses were recorded at The Tokyo University of Pharmacy and Life Science Chemical Instrumentation Center. Irradiation with high-intensity ultrasound (20 KHz, 50 W) was performed under an argon atmosphere by the use of an immersion-type titanium horn in a glass vessel equipped with a thermocouple.[6] TLC was performed on aluminum plates precoated with Merck silica gel 60 F_{254}, and spots were detected with a UV lamp (253.7 nm). Column chromatography was performed using Wakogel C-300 (Wako Pure Chemicals Co., Ltd.) and Kieselgel

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60 (Merck Co., Ltd.). Solvents were reagent grade and in many cases were dried before use.

3′,5′-Di-*O*-benzoyl-2′-deoxy[2′-^{2}H]uridine (4b). Through Procedure A (from 3b). A solution of 3′,5′-di-*O*-benzoyl-2′-bromouridine (**3b**) (180.37 mg, 0.35 mmol) and AIBN (24.3 mg, 0.15 mmol) in diglyme (4 mL) was heated up at 100 °C under an argon atmosphere. To the heated solution was added Bu_3Sn^2H (0.19 mL, 0.7 mmol). After continuing to stir at 100 °C for 1 h, the resulting solution was quenched with 0.1 M iodine solution in THF, which was added until the pale color of iodine remained, and the mixture was concentrated *in vacuo* to dryness. The residue was extracted with MeCN (50 mL), and the solution was washed with hexane (25 mL × 3). The MeCN solution was evaporated to dryness and subjected to chromatography on a column of silica gel employing $CHCl_3$–MeOH system to give a colorless crystals of **4b** (142.81 mg, 93% yield): mp 227–228 °C (from 3:1 EtOH–$CHCl_3$) (lit.[3] 225–227 °C); ^{1}H-NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.4–8.1 (m, H-6, 11H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.6–5.66 (dd, *J* = 2.5, 6.7 Hz, 1H), 5.59 (dd, *J*= 8.2, 2.0 Hz, 1H), 4.65–4.8 (m, 2H), 4.5–4.6 (m, 1H), 2.72–2.79 (m, 0.04H), 2.32 (dd, *J* = 8.3, 6.8 Hz, 0.96H); HRMS calcd for $C_{23}H_{19}{}^2HN_2O_7$ (M^+) 437.1333, found 437.1305.

Through Procedure B (entry 7). A solution of **3b** (268 mg, 0.52 mmol) and AIBN (36.4 mg, 0.22 mmol) in THF (6 mL) in a glass vessel equipped with a thermocouple was cooled in a dry ice–acetone bath under an argon atmosphere and was irradiated with ultrasound (20 KHz, 50 W) by the sonicator.[6] When the temperature of the solution could be maintained at −71 °C, Bu_3Sn^2H (0.28 mL, 1.04 mmol) was injected into the solution, and the irradiation was continued until no further reaction was observed by monitoring through TLC (6 h). After quenching the reaction by the addition of a 0.1 M iodine solution in THF, the solvent was evaporated, and the residue was extracted with MeCN (100 mL). The extract was washed with hexane (50 mL × 3), and then, concentrated *in vacuo*. The residue was recrystallized to give colorless crystals of **4b** (176.6 mg, 78% yield), mp 227–228 °C (from 3:1 EtOH–$CHCl_3$) (lit [3] 225–227 °C); ^{1}H-NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.4–8.1 (m, H-6, 11H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.6–5.66 (dd, *J* = 2.5, 6.7 Hz, 1H), 5.59 (dd, *J*= 8.2, 2.0 Hz, 1H), 4.65–4.8 (m, 2H), 4.5–4.6 (m, 1H), 2.72–2.79 (m, 0.04H), 2.32 (dd, *J* = 8.3, 6.8 Hz, 0.96H); HRMS calcd for $C_{23}H_{19}{}^2HN_2O_7$ (M^+) 437.1333, found 437.1305.

Through Procedure C. To a solution of **3b** (180.4 mg, 0.35 mmol) in THF (4 mL), cooled down to −60 °C under an argon atmosphere, were successively added Bu_3Sn^2H (0.19 mL, 0.7 mmol) and a 1.0 M Et_3B solution in hexane (0.385 mL, 0.385 mmol, 1.1 mol equiv was necessary for inducing efficient reaction). The reaction mixture was similarly quenched with a 0.1 M iodine solution in THF after stirring for 1.5 h at −52 °C (which was the highest temperature observed during the dropwise addition of Et_3B). The resulting solution was concentrated in vacuo, and the residue was dissolved in MeCN (100 mL). The extract was washed with hexane (50 mL × 2), and the MeCN layer was concentrated *in vacuo*. The residue was recrystallized to give colorless crystals of **4b** (138.0 mg, 90% yield), mp 227–228 °C (from 3:1 EtOH–$CHCl_3$) (lit.[3] 225–227 °C); ^{1}H-NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.4–8.1 (m, H-6, 11H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.6–5.66 (dd, *J* = 2.5, 6.7 Hz, 1H), 5.59 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.65–4.8 (m, 2H), 4.5–4.6 (m, 1H), 2.72–2.79 (m, 0.08H), 2.32 (dd, *J* = 8.3, 6.8 Hz, 0.92H); HRMS calcd for $C_{23}H_{19}{}^2HN_2O_7$ (M^+) 437.1333, found 437.1316.

(2′*R*)-*N*^{6}-Benzoyl-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]adenosine (6a). To a solution of *N*^{6}-benzoyl-2′-bromo-2′-deoxy-3′,5′-*O*-TPDS-adenosine (**5a**) (1.35 g, 2.0 mmol) in THF (20 mL) under an argon atmosphere at −70 °C were successively added Bu_3Sn^2H (1.13 mL, 4.2 mmol) and a 1.0 M solution of Et_3B in THF (2.2 mL, 2.2 mmol). After stirring the solution at −78 °C for 1 h, the resulting mixture was worked up similarly as described above, and the residue thus obtained was chromatographed on a column of silica gel, employing a toluene–EtOAc system, to give a foam of **6a** (1.13 g, 94%): ^{1}H-NMR ($CDCl_3$) δ 9.07 (br s, 1H), 8.77 (s, 1H), 8.21 (s, 1H), 7.5–8.1 (m, 5H), 6.48 (d, *J* = 2.3 Hz, 1H), 4.99 (t, *J* = 7.4, 7.4 Hz, 1H), 4.05 (m, 1H), 3.8–4.0 (m, 2H), 2.77 (t, *J* = 2.1, 7.4 Hz, 1H). 1.2–1.0 (m, 28H); ^{13}C-NMR ($CDCl_3$) 164.61, 152.53, 150.88, 149.53, 141.49, 133.71, 132.68, 128.79, 127.83, 85.28, 83.38, 69.89, 60.47, 61.79, , 39.64 (t, J_{CD} = 18.7), 17.45, 17.29, 17.13, 16.99, 16.94, 16.85, 13.34, 13.08, 12.84, 12.52; HRMS calcd for $C_{29}H_{42}{}^2HN_5O_5Si_2$ (M^+) 598.2865, found 598.2872.

(2′*R*)-2′-Deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]uridine (6b). 2′-Bromo-2′-deoxy-3′,5′-*O*-TPDS-uridine (**5b**)[15] (1.02 g, 1.86 mmol) was subjected to procedure C to give a foam of **6b** (0.78 g, 89% yield): ^{1}H-NMR ($CDCl_3$) δ 8.08 (br s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 1.5 Hz, 1H), 5.68 (dd, *J* = 2.3, 8.1 Hz, 1H), 4.44 (q, *J* = 7.8, 7.7 Hz, 1H), 4.13 (dd, *J* = 2.1, 13.2 Hz, 1H), 4.01 (dd, *J* = 2.9 , 13.3 Hz, 1H), 3.76 (ddd, *J* = 8.4, 2.4, 2.5 Hz, 1H), 2.24 (d, *J* = 6.6 Hz, 1H), 0.90–1.2 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 163.77, 150.18, 139.33, 128.65, 127.65, 101.51, 84.76, 84.00, 67.13, 60.01, 39.29 (t, $J_{C,D}$ = 19.42 Hz), 17.18, 17.08, 17.01, 16.95, 16.76, 16.64, 16.53, 13.12, 12.71, 12.69, 12.56, 12.32, 12.18 (lit.[18] for the protio compound); HRMS calcd for $C_{21}H_{38}{}^2HN_2O_6Si_2$ (M^+ + 1) 472.24249, found 472.24329.

(2′*R*)-2′-Deoxy-*N*^{2}-isobutyryl-3′,5′-*O*-TPDS-[2′-^{2}H]guanosine (6c). Procedure C was applied to 2′-bromo-*N*^{2}-Isobutyryl-2′-deoxy-3′,5′-*O*-TPDS-guanosine (**5c**) (340 mg, 0.52 mmol) to give **6c** (287 mg, 95% yield): ^{1}H-NMR ($CDCl_3$) δ 11.96 (br s, 1H), 8.23 (br s, 1H), 7.88 (s, 1H), 6.10 (d, *J* = 2.6 Hz, 1H), 4.71 (t, *J* = 7.3, 7.3 Hz, 1H), 4.04 (dd, *J* = 3.3, 12.6 Hz, 1H), 3.97 (dd, *J* = 4.7, 12.6 Hz, 1H), 3.84–3.87 (m, 1H), 2.54–2.65 (m, 1.09H), 2.53 (dd, *J* = 2.6, 7.3 Hz, 0.91H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.00–1.11 (m, 28H); ^{13}C-NMR ($CDCl_3$) 178.73, 155.61, 147.60, 147.54, 136.47, 121.50, 85.07, 82.24, 69.53, 61.55, 39.73 (br), 36.37, 18.97, 18.91, 17.43, 17.32, 17.26, 17.14, 16.99, 16.91, 16.82, 13.37, 13.04, 12.91, 12.48; HRMS calcd for $C_{26}H_{45}{}^2HN_5O_6Si_2$ (M^+ + 1): 581.3065, found 581.3071.

(2′*R*)-3′,5′-*O*-TPDS-[2′-^{2}H]thymidine (6d). Procedure C was applied to (2′*R*)-2′-bromo-3′,5′-*O*-TPDS-thymidine (**5d**)[15] (1.13 g, 2.0 mmol) to give a foam of **6d** (921 mg, 94% yield): ^{1}H-NMR ($CDCl_3$) δ 8.31 (br s, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 4.49 (dd, *J* =7.8, 7.8 Hz, 1H), 4.11 (dd, *J* = 2.6, 13.1 Hz, 1H), 4.02 (dd, *J* = 3.0, 13.1 Hz, 1H), 3.75 (ddd, *J* = 8.0, 2.8, 2.8 Hz, 1H), 2.24 (dd, *J* = 1.9, 7.4 Hz, 1H), 1.92 (d, *J* = 1.1 Hz,3H), 0.58–1.3 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 164.05, 1644.04, 150.29, 135.11, 10.53, 84.91, 83.72, 67.71, 60.31, 39.47 (t, J_{CD} = 19.42 Hz), 17.40, 17.36, 17.27, 17.23, 17.06, 16.94, 16.92, 16.81, 13.44, 12.99, 12.76, 12.54, 12.47; HRMS calcd for $C_{22}H_{40}{}^2HN_2O_6Si_2$ (M^+ + 1) 486.2581, found 486.2574.

(2′*R*)-*N*^{6}-Benzoyl-2′-deoxy[2′-^{2}H]adenosine (7a). Compound **6a** (1.13 g, 1.89 mmol) was deprotected according to the method of Robins[13] to give a foam of **7a** (570 mg, 85% yield): ^{1}H-NMR (DMSO-d_6) δ 11.16 (br s, 1H), 8.75 (s, 1H), 8.68 (s, 1H), 7.5–8.1 (m, 5H), 6.48 (d, *J* = 7.3 Hz, 1H), 5.34 (d, *J* = 4.2 Hz, 1H), 5.00 (t, *J* = 5.5 Hz, 1H), 4.4–4.5 (m, 1H), 3.8–4.0 (m, 1H), 3.5–3.7 (m, 2H), 2.78 (t, *J* = 6.7 Hz, 1H); ^{13}C-NMR (DMSO-d_6) 166.61, 151.84, 151.41, 150.28, 142.98, 133.38, 132.36, 128.40, 125.82, 87.95, 83.68, 70.61, 61.57, 3.97; HRMS calcd for $C_{17}H_{16}{}^2HN_5O_4$ (M^+) 356.1343, found 356.1342.

(2′*R*)-2′-Deoxy-*N*^{2}-isobutyryl[2′-^{2}H]guanosine (7c). Compound **6c** (275 mg, 0.47 mmol) in THF (4.7 mL) was treated with 1 M Bu_4NF in THF (2.07 mL, 2.07 mmol) at 40 °C under an argon atmosphere. After stirring for 40 h at 40 °C, the solvent was evaporated and the residue was chromatographed on a column of silica gel employing a $CHCl_3$–MeOH (50:1–9:1) system to give a foam of **7c** (130 mg, 82% yield), which was recrystalized from H_2O to give colorless crystals (94 mg, 59%). mp > 300 °C (softens at 133 °C, does not melt below 300 °C) (lit.[19] softens at 133 °C, darkens at 235 °C, does not melt below 300 °C for the protio compound): ^{1}H-NMR (DMSO-d_6): δ 12.06 (br s, 1H), 11.66 (br s, 1H), 8.23 (s, 1H), 6.20 (d, *J* = 7.4 Hz, 1H), 5.30 (d, *J* = 3.8 Hz, 1H), 4.95 (t, *J* = 5.4 Hz, 1H), 4.35–4.38 (m, 1H), 3.82–3.85 (m, 1H), 3.48–3.60 (m, 2H), 2.73–2.80 (m, 1H), 2.54 (dd, *J* = 7.4, 6.0 Hz, 0.91H), 2.24–2.29 (m,

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0.09H), 1.12 (d, J = 6.8 Hz, 6H). Anal. Calcd for $C_{14}H_{18}{}^2HN_5O_5$: C, 49.70 H, 5.96 N, 20.70. Found: C, 49.68; H, 5.76; N, 20.63.

(2′*R*)-*N*^{2},*O*$^{3'}$,*O*$^{5'}$-Tribenzoyl-2′-deoxy[2′-^{2}H]guanosin(8c). Compound **7c** (130 mg, 0.38 mmol) in MeOH (1 mL) was treated with a 29% aqueous NH_3 solution (8 mL) in a flask equipped with a tight stopper and was stirred at 50 °C. After stirring for 14 h at 50 °C, the solution was concentrated *in vacuo* and dried *in vacuo*. The resulting residue was dissolved in distilled pyridine (4.7 mL) under an argon atmosphere. After the addition of DMAP (31 mg, 0.25 mmol) and Et_3N (0.35 mL, 1.74 mmol), the solution was cooled to 0 °C and stirred for 10 min. Benzoyl chloride (0.26 mL, 1.58 mmol) was then added, and the solution was stirred at 40 °C for 17 h. The solvent was then evaporated to dryness, and the resulting mixture was extracted with CH_2Cl_2 (20 mL × 3) and then washed successively with a saturated $NaHCO_3$ solution in H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to dryness. The residue was then chromatographed on a column of silica gel employing a $CHCl_3$–MeOH (100:1) system to give a foam of **8c** (117 mg, 43%): ^{1}H-NMR ($CDCl_3$) δ 12.20 (br s, 1H), 9.51 (br s, 1H), 7.75 (s, 1H), 7.35–8.16 (m, 15H), 6.32 (d, J = 6.5 Hz, 1H), 5.97 (dd, J = 6.5, 2.6 Hz, 1H), 5.02–5.07 (m, 1H), 4.66–4.70 (m, 2H), 3.25 (t, J = 6.5 Hz, 0.91H), 2.54–2.65 (m, 0.09H). HRMS calcd for $C_{31}H_{25}{}^2HN_5O_7$ (M^+ + 1): 581.1910, found 581.1925. (lit.[20] for the protio compound).

(2′*R*)-[2′-^{2}H]thymidine (7d). Compound **6d** (838 mg, 1.46 mmol) was treated similarly to **6a** to give colorless crystals of **7d** (331 mg, 85% yield): mp 187–189 °C (from MeOH) (lit.[21] 187 °C for the protio compound), ^{1}H-NMR (DMSO-d_6) δ 11.25 (br s, 1H), 7.69 (d, J = 1.1 Hz, 1H), 6.16 (d, J = 7.8 Hz, 1H), 5.20 (d, J = 4.3 Hz, 1H), 4.99 (dd, J = 5.2 Hz, 1H), 4.2–4.25 (m, 1H), 3.76 (dd, J = 3.76, 6.89 Hz, 1H), 3.5–3.7 (m, 2H), 2.07 (dd, J = 6.3, 7.5 Hz, 1H), 1.77 (d, J = 1.1 Hz, 3H); ^{13}C NMR (MeOH-d_4) δ 166.37, 152.36, 138.16, 111.51, 88.81, 86.26, 72.14, 62.84, 40.85 (t, $J_{C,D}$ = 20.4 Hz), 12.39; HRMS calcd for $C_{10}H_{13}{}^2HN_2O_5$ (M^+) 243.0965, found 243.0977.

(2′*R*)-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]cytidine was synthesized according to the method of Reese[17] from (2′*R*)-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]uridine: ^{1}H-NMR (DMSO-d_6) δ 7.63 (d, J = 7.4 Hz, 1H), 7.18 (br d, J = 34.1 Hz, 2H), 5.96 (d, J = 3.1 Hz, 1H), 5.70 (d, J = 7.4 Hz, 1H), 4.46 (q, J = 7.5, 7.4 Hz, 1H), 4.03 (dd, J = 4.6, 12.5 Hz, 1H), 3.92 (dd, J = 2.9, 12.5 Hz, 1H), 3.72 (ddd, J = 7.3, 4.4, 3.0 Hz, 1H), 2.20 (dd, J = 3.0, 7.6 Hz, 1H), 0.98–1.1(28H, m, *i*Pr × 4); ^{13}C NMR ($CDCl_3$) δ 166.00, 155.79, 140.61, 93.88, 84.87, 84.75, 67.17, 60.29, 39.71 (br), 17.45, 17.40, 17.29, 17.02, 16.92, 16.81, 13.38, 12.99, 12.94, 12.44; HRMS calcd for $C_{21}H_{38}{}^2HN_3O_5Si_2$ (M^+) 470.2491, found 470.2486.

(2′*R*)-*N*^{4}-Benzoyl-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]cytidine (6e): ^{1}H-NMR ($CDCl_3$) δ 8.66 (br s, 1H), 8.32 (d, J =7.2 Hz, 1H), 7.5–7.9 (m, H-5, 6H), 6.09 (s, 1H), 4.40 (dd, J = 7.0, 8.4 Hz, 1H), 4.22 (d, J = 13.7 Hz, 1H), 4.04 (dd, J = 2.7, 13.4 Hz, 1H), 3.84 (ddd, J = 8.5, 1.6, 2.5 Hz, 1H), 2.37 (dd, J = 6.8 Hz, 1H), 0.9–1.1(m, 28H); ^{13}C NMR ($CDCl_3$) δ 166.67, 162.43, 154.74, 144.38, 133.00, 129.28, 128.85, 128.72, 127.78, 127.62, 96.14, 85.59, 85.52, 85.17, 66.20, 59.63, 39.34 (t, $J_{C,D}$ = 13.53 Hz), 17.43, 17.36, 17.23, 16.94, 16.88, 16.85, 16.75, 16.60, 13.32, 12.95, 12.87, 12.431; HRMS calcd for $C_{28}H_{42}{}^2HN_3O_6Si_2$ (M^+) 574.2753, found 574.2752.

(2′*R*)-*N*^{4}-Benzoyl-2′-deoxy[2′-^{2}H]cytidine (7e). Compound **6e** (761 mg, 1.33 mmol) was treated similarly to **6a** to give a colorless crystals of **7e** (323 mg, 73% yield): mp 207–208 °C (from EtOH) (lit[22], 203–205 °C for the protio compound); ^{1}H-NMR (DMSO-d_6) δ 11.21(br s, 1H), 8.40 (d, J =7.3 Hz, 1H), 7.5–8.0 (m, 5H), 7.36 (d, J = 7.4 Hz, 1H), 6.14 (d, J = 6.5 Hz, 1H), 5.27 (d, J = 4.3 Hz, 1H), 5.06 (t, J = 5.2 Hz, 1H), 4.24 (q, J = 5.8 Hz, J = 3.9 Hz, 1H), 3.88 (dd, J = 3.7, 7.3 Hz, 1H), 3.5–3.7 (m, 2H), 2.04 (dd, J = 6.2, 6.2 Hz,1H); ^{13}C NMR (DMSO-d_6) δ 167.27, 162.91, 154.38, 144.90, 136.89, 133.17, 132.64, 128.39, 102.17, 96.02, 87.93, 86.16, 69.86, 60.93, 40.76 (t, $J_{C,D}$ = 13.4 Hz); HRMS calcd for $C_{16}H_{16}{}^2HN_3O_5$ (M^+) 332.1231, found 332.1201.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **6a–e**, **7a,d,e** and procedure, analytical data, and ^{1}H and ^{13}C NMR data of **2a, 2b, 3b, 4a** (from **2a** through procedure A), **4b** (from **2b** through procedure A), **5a, 5c**, and **6e** via (2′*R*)-*N*^{4}-benzoyl-2′-deoxy-3′,5′-*O*-TPDS-[2′-^{2}H]cytidine (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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