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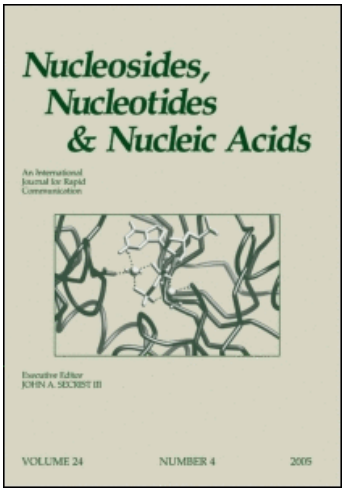

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Highly Diastereoselective Synthesis of (2'*S*)-[2'-^{2}H]-2'-Deoxyribonucleosides from the Corresponding Ribonucleosides

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HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF (2'*S*)-[2'-^{2}H]-2'-DEOXYRIBONUCLEOSIDES FROM THE CORRESPONDING RIBONUCLEOSIDES

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ABSTRACT: The four (2'*S*)-[2'-^{2}H]-2'-deoxynucleosides (>90 atom % ^{2}H), were synthesized from the corresponding ribonucleosides involving six steps of reactions, i.e., oxidation of their 2'-hydroxyl group, stereoselective reductive deuteration of the resulting 2'-ketonucleoside intermediates with NaB^2H_4 in EtOH-H_2O or EtOH, triflation, bromination with LiBr, highly stereoselective Bu_3SnH-Et_3B reduction of the resulting bromide, and, finally, unmasking.

An oligonucleotide incorporating (2'*R*) or (2'*S*)-[2'-^{2}H]-2'-deoxyribonucleosides as a stereochemical probe should be useful for elucidating subtle conformational change of their 2'-deoxy-β-D-ribofuranosyl moieties on interaction with a protein through ^{1}H NMR spectroscopy based on the distinct difference in $^3J_{1',2'}$ and $^3J_{2',3'}$ values between their $C_{2'}$ *endo* and $C_{3'}$ *endo* conformers.[1] The synthesis of (2'*R*)-[2'-^{2}H]-2'-deoxyribonucleosides[2~4] has been reported and, recently, we established a novel synthetic approach involving highly stereoselective deuteration reaction at a low temperature such as -70°C.[5] As for the (2'*S*)-[2'-^{2}H]-2'-deoxynucleosides, the synthesis of (2'*S*)-[2'-^{2}H]-2'-deoxycytidine,[4,6] -uridine,[6] and that of four (2'*R*)- and (2'*S*)-[2'-^{2}H]-2'-deoxyribonucleosides,[3] all of which involved glycosylation of a heterocycle with a 2-monodeuterated 2-deoxy-D-ribofuranose derivative, has been yielded; the glycosyl donors were derivatized through many reactions. It is, therefore, significant if it were possible to develop a more efficient and shorter way for their synthesis, e. g., starting from the corresponding ribonucleosides. Thus, we wanted to synthesize the title compounds by using the corresponding ribonucleosides.

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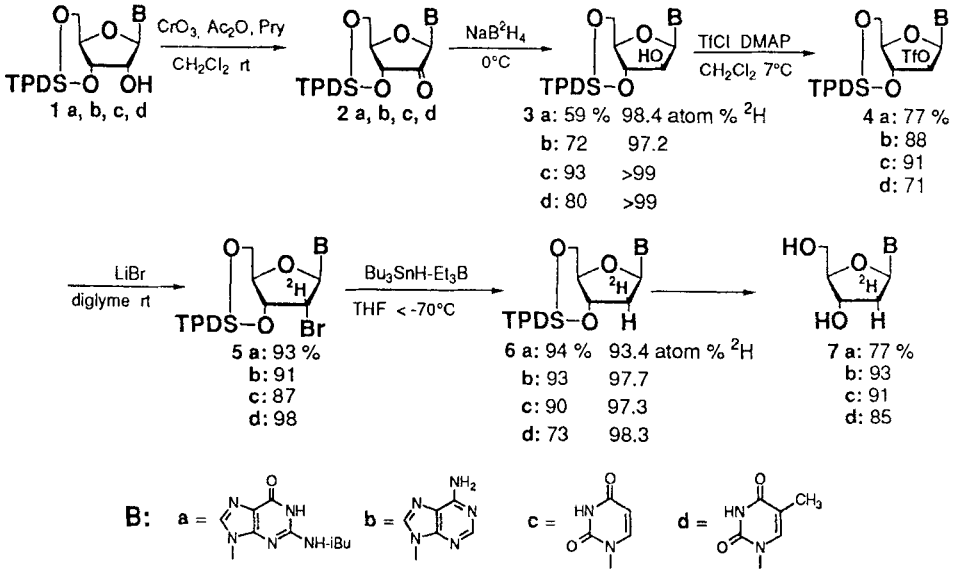

Scheme 1

The details of our results is exemplified by the synthesis of (2'*S*)-[2'-^{2}H]-2'-deoxyguanosine derivative from guanosine: oxidation of 3',5'-*O*-TPDS-guanosine with the CrO_3-Ac_2O-pyridine complex[7] followed by reduction with NaB^2H_4 gave a complex mixture of products which we were unable to characterize.[8] We protected the 2-amino group and used N^2-isobutyryl-3',5'-*O*-TPDS-guanosine (**1a**) as substrate of the oxidation. Oxidation of **1a** with the complex at room temperature, followed by reduction with NaB^2H_4 in absolute EtOH -THF at 0 °C, gave [2'-^{2}H]-N^2-isobutyryl-9-(3, 5-*O*-TPDS-β-D-arabinofuranosyl)guanine (**3a**) in an overall yield of 58% in two steps via 2'-oxo-3',5'-*O*-TPDS-guanosine (**2a**). Deuterium content (atom % ^{2}H) at the 2' position of **3a** was unexpectedly estimated to be 86% based on ^{1}H NMR; the content was 12% less than that of NaB^2H_4 (98 atom % ^{2}H) used for the reduction. Such a deuterium content reduction in the deuteration was assumed to be brought about potentially by radical reaction mechanism as has been known in the $NaBH_4$ reduction.[9] Therefore, the reduciton was performed in an aqueous solvent system, making the reaction system more polar, which might induce the ionic reaction mechanism preferentially; 2:1 EtOH - H_2O used for the reduction of **2a** with NaB^2H_4 expectedly gave **3a** with 98.4 atom % ^{2}H in an overall yield of 59% from **1a**. Compound 3a was converted to [2'-^{2}H]-2'-bromo-N^2-isobutyryl-3',5'-*O*-TPDS-2'-deoxyguanosine (**5a**) (93% yield from **4a**), via the

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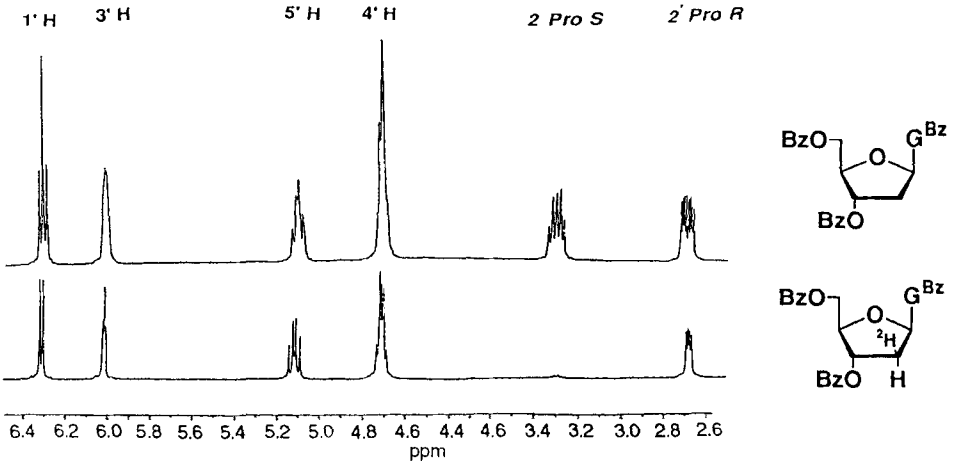

Fig. 1

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corresponding 2'-*O*-Tf-derivative (**4a**) (77% yield from **3a**). The resulting **5a** was then subjected to the highly stereoselective reduction using Bu_3SnH - Et_3B system[4] at < -70 °C to give (2'*S*)-[2'-^{2}H]-N^2-isobutyryl-2'-deoxy-3',5'-*O*-TPDS-guanosine (**6a**) (94% yield), which was confirmed to have 93.4 atom % ^{2}H after removing both TPDS and isobutyryl groups, followed by tribenzoylation.

Similarly, the synthesis of 3',5'-*O*-TPDS-(2'*S*)-[2'-^{2}H (97.7 atom % ^{2}H)]-2'-deoxyadenosine (**6b**), -[2'-^{2}H (97.3 atom % ^{2}H)]-2'-deoxyuridine (**6c**), and -[2'-^{2}H (98.3 atom % ^{2}H)]-thymidine (**6d**) was also achieved. Treatment of **6b**, **6c** and **6d** with NH_4F in MeOH at 60°C for 3 h[10] gave (2'*S*)-[2'-^{2}H]-2'-deoxyadenosine (**7b**), -2'-deoxyuridine (**7c**), and -thymidine (**7d**) in 93%, 91%, and 85% yield, respectively. The results obtained are summarized in SCHEME 1. Compound **6c** was, incidentally, converted to (2'*S*)-[2'-^{2}H]-3',5'-*O*-TPDS-2'-deoxycytidine (**6e**) (92% yield from 4-triazolyl derivative; 93.8 atom % ^{2}H) through 4-(1,2,4-triazolyl)ation (98% yield) and subsequent ammonolysis.[11]

The spectral region corresponding to the signals of the sugar moieties in ^{1}H NMR spectra was illustrated by that of (2'*S*)-[2'-^{2}H]-N^2, $O^{3'}$, $O^{5'}$-tribenzoyl-2'-deoxy-guanosine[12] together with corresponding tribenzoyl-2'-deoxyguanosine (Figure 1).

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12 ^{1}H-NMR data of (2'*S*)-[2'-^{2}H]-N^{2},O^{3},$O^{5'}$-tribenzoyl-2'-deoxyguanosine ($CDCl_3$): δ 2.6 (1H, dd, $J_{1',2''}$= 6.5 Hz, $J_{2'',3'}$ = 3.1 Hz, H-1'), 4.7 (2H, m, H-5'x 2), 5.1 (1H, m, H-4'), 6.0 (1H, t, $J_{3',2''}$ =3.1 Hz, H3'), 6.3 (1H, d, $J_{1',2''}$ = 6.5 Hz, H1'), 7.3 -8.1 (15H, m, phenyl protons), 7.7 (1H, s, H-8), 9.5 (1H, s, 2-NH), 12.1 (1H, s, 1-NH).

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