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Sonochemical and Triethylborane-induced Tin Deuteride Reduction for the Highly Stereoselective Synthesis of (2'*R*)-[2'-^{2}H]-2'-Deoxyribonucleosides from 2'-Functionalized Ribonucleosides

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ABSTRACT: Bu_3Sn^2H-reduction of a 2'-bromo-2'-deoxyuridine benzoate under high-intensity ultrasound irradiation at -71 °C resulted in highly efficient deuterium incorporation to afford a 96:4 mixture of (2'*R*)- and (2'*S*)-[2'-^{2}H]-2'-deoxyuridine. The use of both Et_3B, as an alternative radical generator, and 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-ribonucleosides made it feasible to perform the reaction in a preparative scale in addition to an excellent stereoselectivity (>99:1).

It should be essential to establish an efficient approach to the chemical synthesis of (2'*R*)-[2'-^{2}H]-2'-deoxyribonucleosides for the investigation on intermolecular interaction of a DNA with a protein. Such achievement should completely exclude the complexity in the region of H-2' signals, i.e., the analysis of the subtle conformational change of 2'-deoxy-D-ribofuranosyl moieties in an oligodeoxyribonucleotide, taking place on the intermolecular events, should be feasible through ^{1}H-NMR spectroscopy. In addition, $J_{1',2'}$-value difference between their $C_{2'}$-*exo* - $C_{3'}$-*endo* and $C_{2'}$-*endo* - $C_{3'}$-*exo* conformations is more distinct in the (2'*R*)-isomers than in the corresponding (2'*S*)-isomers.[1]

Two methods have been reported to achieve the above goal. The first one involves Bu_3Sn^2H-AIBN reduction of 2'-chloro-2'-deoxy derivatives of adenosine or uridine,[2] and of 2'-*O*-phenoxythiocarbonyl (PTC) derivative of adenosine.[3] The reduction under the conventional thermal conditions gave (2'*R*)-isomers only in 76-88% stereoselectivity, favoring over the corresponding (2'*S*)-isomers. Such stereoselectivity is not acceptable for the NMR studies. The second involves 7 steps of reactions from methyl 2,3-anhydro-β-D-lyxofuranoside by way of (2*R*)-[2-^{2}H]-2-deoxy-D-ribofuranosyl chloride intermediate;[4] this one suffers from low overall yield in spite of its unambiguousness.

One of us recently demonstrated the remarkable utility of the "nonhomogeneous" environment created by ultrasound irradiation of a homogeneous solution at a low temperature (e.g., -64°C) for generating the radical from $Bu_2Sn^2H_2$ as a chain carrier to induce radical chain reaction.[5] It has also been shown that cyclization reaction of allyl 1-phenyl-2-iodoethyl ether induced sonochemically at -55°C, giving 2-phenyl-4-methyltetrahydrofuran, gave rise to improvement of cis-trans stereoselectivity from 21:79 (at 70°C) to 6:94.[5] It was thus logically expected that application of the low-temperature sonochemistry to the reduction of 2'-

functionalized ribonucleoside derivatives would provide a new tool for more highly stereoselective deuteration. The preponderant (2'*R*)-isomer formation[2,3] may reflect the steric hindrance that is caused by the heterocyclic moiety toward the approach of Bu_3Sn^2H from the β-face of the sugar moiety to the radical center at the 2' position, and may be further improved as the reaction temperature is lowered, according to what a kinetic law would predict.

3',5'-Di-*O*-benzoyl-2'-*O*-PTC- (**1**) and -2'-bromo-2'-deoxyuridine (**2**) were chosen as the substrates and feasibility of the sonochemical stereoselective deuteration was elucidated in comparison with that under the thermal conditions. The results are summarized in Table 1 (entries 1- 13). Conventional thermal conditions were first examined for **1** (entries 1 and 2), by treating a solution of **1** (8.75×10^{-2} M) in diglyme with Bu_3Sn^2H (2 mol. equiv.) and AIBN (0.42 mol. equiv.) at 100 °C for 30 min afforded [2'-^{2}H]-3',5'-di-*O*-benzoyl-2'-deoxyuridine (**3**) (mp 227-228 °C, 3:1 EtOH-$CHCl_3$; 2'*R*:2'*S* = 79:21[6]) in 90% yield. A lower reaction temperature (65 °C) improved the ratio of 2'*R*:2'*S* to 82:18. Further lowered temperatures were not feasible for **1**, which is rather unreactive, we next examined the reaction of the bromide **2**. Not unexpectedly, the reactions at 100 °C and at 65 °C (entries 3 and 4) gave a similar trend in the improvement of diastereomer ratios obtained for **1**. These results strongly suggeted that the selectivity is not controlled by the property of nucleofuges, but by the reactivities of incipient carbon radical. As for the solvent, no difference was observed between diglyme and THF (entry 4 versus 5). Attempts at carrying out the reduction at 0 °C brought about only a trace amount of **3** (entry 6).

Confronting these results, the ultrasound-driven reaction was examined under irradiation of 20 KHz ultrasound (50 W) and argon atmosphere by the use of immersion titanium horn in a vessel similar to the one previously described.[7] Compound **1** gave the objective **3** (55% yield, 2'*R*:2'*S* = 88:12) on treating at 22 °C. This substrate was, however, too unreactive to be examined at further lower temperatures, and our attention turned to the more reactive **2**. This substrate was found to be reactive enough at 11°C, 1°C, and even at -71 °C in THF (entries 9, 10, and 13), and showed consistent improvement in the diastereomer ratio, which reached as high as 96:4 — a level practically useful for conformational analysis of sugar moieties invovled in DNA by ^{1}H-NMR spectroscopy. The reactions in diglyme (entries 8, 11, and 12) also gave a similar tendency in terms of the diastereoselectivity and the product yield. No indication of deleterious effects of ultrasound on the nucleoside skeleton itself was detected. The isomeric ratios observed in the temperature range of -71 to 100 °C correspond to 1.0-1.3 Kcal/mol energy difference between the α- and β-face approach of the tin deuteride to the 2'-radical.

The above approach is, however, impractical for the synthesis of (2'*R*)-[2'-^{2}H]-2'-deoxyribonucleosides in a preparative scale due to the entity of the reactions mediated by ultrasound irradiation, and, thus, inadequate to ensure their sufficient supply for us in oder to construct an objective oligonucleotide.

Trialkylborane was, incidentally, reported as an efficient reagent for generating trialkyltin free radical from trialkyltin hydrides even at a very low temperature.[7] The Bu_3Sn^2H - Et_3B system might thus be an alternative expecting candidate for performing the highly stereoselective deuteration reaction in a preparative scale. The feasibility of this system was then elucidated by the use of **2**, and the results are summarized in

Scheme 1

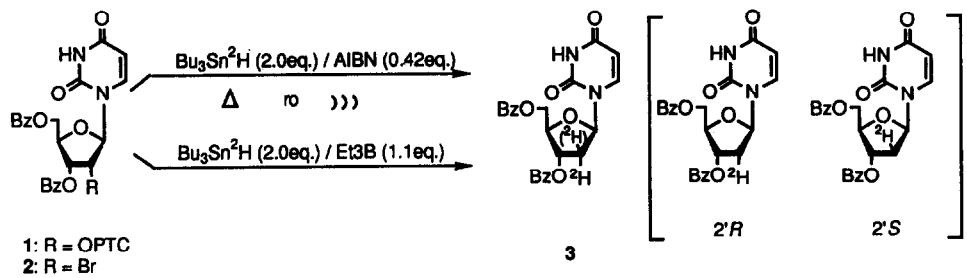


Table 1 (entries 14 - 17). Utility of this approach was proved, and significant improvement in the diastereoselectivity was observed on lowering the reaction temperature. A typical procedure is exemplified by the synthesis of [2'-^{2}H]-2'-deoxyuridine: To a solution of 2 (0.35 mmol) and Bu_3Sn^2H (2.0 mol. equiv.) in THF (4 mL) at -52°C, was dropwise added Et_3B (1.1 mol. equiv. which is necessary for inducing efficient reaction) and recrystallization from 3:1 MeOH - $CHCl_3$, after quenching the reaction by the addition of a solution of iodine in THF and the subsequent work-up, gave a 92:8 mixture of (2'*R*)- and (2'*S*)-[2-^{2}H]-2'-deoxyuridine (mp 227 - 228°C) in 90% yield.

Table 1

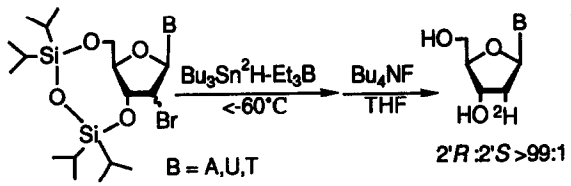
entry	R	method	solvent	temp.(℃)	time (min.)	3 (% yield)	2'R / 2'S
1	OPTC	AIBN / thermolysis	diglyme	100	30	90	79 / 21
2	OPTC	AIBN / thermolysis	diglyme	65	30	80	82 / 18
3	Br	AIBN / thermolysis	diglyme	100	30	93	79 / 21
4	Br	AIBN / thermolysis	diglyme	65	30	91	81 / 19
5	Br	AIBN / thermolysis	THF	65	60	93	82 / 18
6	Br	AIBN / thermolysis	THF	0	60	trace	
7	OPTC	AIBN / U. S.	diglyme	22	180	55	88 / 12
8	Br	AIBN / U. S.	diglyme	12	30	95	87 / 13
9	Br	AIBN / U. S.	THF	11	23	86	87 / 13
10	Br	AIBN / U. S.	THF	1	30	90	88 / 12
11	Br	AIBN / U. S.	diglyme	-32	360	91	92 / 8
12	Br	AIBN / U. S.	diglyme	-50	360	76	94 / 6
13	Br	AIBN / U. S.	THF	-71	360	78	96 / 4
14	Br	Et_3B	THF	10	25	93	84 / 16
15	Br	Et3B	THF	0	45	91	86 / 14
16	Br	Et_3B	THF	-20	60	90	90 / 10
17	Br	Et_3B	THF	-52	90	90	92 / 8

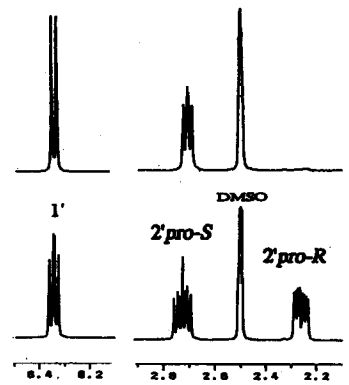
Furthermore, we compared the proportion of (2'*R*)- and (2'*S*)-isomers resulting from the deuteration reactions of 3', 5'-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)- (TPDS)[3] and -di-*O*-Bz-2'-*O*-PTC-adenosine with Bu_3Sn^2H - AIBN in toluene at 100°C by ourselves. The proportion in the former was 85 : 15 and that in the latter was 76 : 24. These results led us to an assumption that it is expectingly potential to use TPDS protection for both hydroxyl groups at 3' and 5' positions of the 2'-bromo derivatives of nucleosides. The TPDS group might be assumed to force the furanosyl moieties to occupy $C_{2'}$-*exo* - $C_{3'}$-*endo* conformation, i.e., the steric hindrance of a heterocyclic moiety has been more efficiently exerted against Bu_3Sn^2H molecule on attacking on the planar free radical generated at the 2' position. Therefore, Bu_3Sn^2H might be expected to predominantly attack the radical from the α-face of the furanosyl ring to bring about a further improved diastereoselectivity. Consequently, the deuteration reaction through Bu_3Sn^2H - Et_3B system was performed with respect to 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-uridine (1.05 mmol) in a similar manner to give a >99:1 mixture of (2'*R*)- and (2'*S*)-[2'-^{2}H]-2'-deoxyuridine (67% yield), expectedly. Similarly, adenosine and ribothymidine were, after the introduction of 3',5'-*O*-TPDS group and functionalization with the bromo group at 2' position, subjected to the deuteration reaction conditions, followed by unmasking of TPDS group and, in the latter case, benzoylation as usual, to give a >99:1 mixture of (2'*R*)- and (2'*S*)-[2'-^{2}H]-2'-deoxyadenosine[9] (60% overall yield from the bromo derivative) and a

>99:1 mixture of (2'*R*:)- and (2'*S*)-[2'-^{2}H]-3',5'-di-*O*-benzoylthymidine (52% overall yield from the bromo derivative), respectively. The anomeric and 2' proton regions of ^{1}H-NMR spectrum of the resulting (2'*R*)-[2'-^{2}H]-2'-deoxyadenosine is demonstrated in Panel B as an example in comparison with that of 2'-deoxyadenosine in Panel A. In addition, the 2'-deoxyuridine derivative was efficiently converted to the corresponding cytidine derivatives by the known method.[10]

^{1}H-NMR of [2'-^{2}H]-2'-deoxyadenosine (Panel B) and 2'-deoxyadenosine (Panel A)

Scheme of deuteration of 2'-Br-2'-deoxy-3',5'-TPDS-nucleosides





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6. The 2'*R* : 2'*S* ratio was calculated from the relative area of the 2'-proton signals of (2'*R*)- and (2'*S*)-isomers appearing at δ 2.32 (t) and at δ 2.72-2.79 (dd), respectively.
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9. ^{1}H-NMR data of a >99:1 mixture of (2'*R*:)- and (2'*S*)-[2'-^{2}H]-2'-deoxyadenosine at 400 MHz in DMSO-d_6: δ 2.71 (1H, dd, $J_{2',1'}$ 7.58 Hz, $J_{2',3'}$ 5.93 Hz, H-2'), 3.57 (1H, dd, $J_{5',4'}$ 4.23 Hz, $J_{5',5''}$ 2.01 Hz, H-5'), 3.68 (1H, dd, $J_{5',4'}$ 4.02 Hz, $J_{5',5''}$ 12.01 Hz, H-5'), 3.94 (1H, m, H-4'), 4.46 (1H, dd, $J_{3',2'}$ 5.93 Hz, $J_{3',4'}$ 2.69 Hz, H-3'), 5.20 (1H, dd, H-5'OH), 5.27 (1H, d, $J_{3'OH,3'}$ 3.88 Hz, H-3'OH), 6.34(1H, d, $J_{1',2'}$ 7.58 Hz, H-1'), 7.26 (2H, bs, N^6H_2), 8.13 (1H, s, H-2), 8.32 (1H, s, H-8)
10. The derivatization was attained by treating the 4-triazolyl derivative with aqueous ammonia in 1,4-dioxane [*cf.* Hodge, R. P., Brush, C. K., Harris, C. M., Harris, T. M., *J. Org. Chem.*, **1991**, *56*, 1553 - 1564]

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