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# Novel Synthesis of 2'-Deoxy[5'-$^2$H]ribonucleoside Derivatives from 5'-*O*-Ac-2'-deoxy-5'-PhSe-ribonucleoside Derivatives

**Etsuko Kawashima, Keizo Toyama, Kenshiro Ohshima, Masatsune Kainosho,¶ Yoshimasa Kyogoku,§ Yoshiharu Ishido***

Laboratory of Pharmaceutical Chemistry, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

¶Department of Chemistry, Faculty of Science, Tokyo Metropolitan University,1-1 Minamiosawa, Hachioji, Tokyo 192-03, Japan

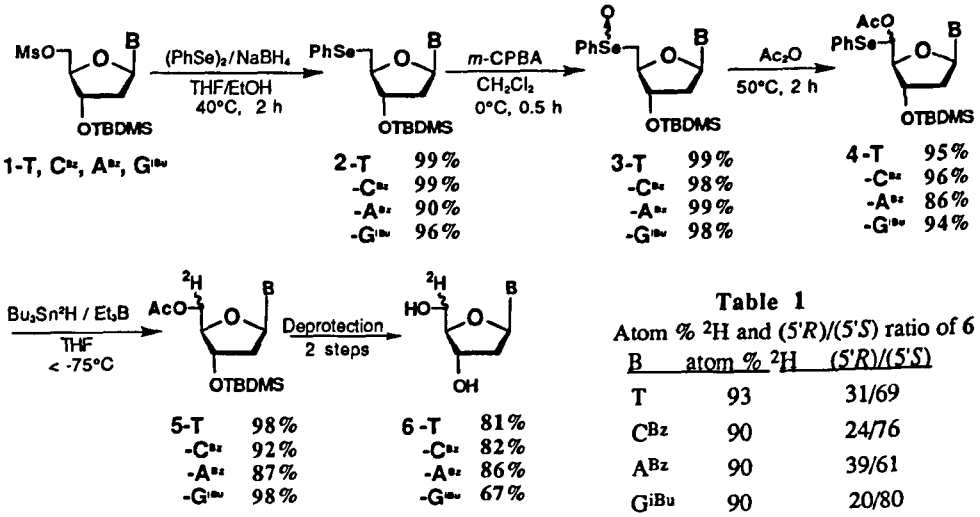
§Institute for Protein Research, Osaka University, 3-2 Yamadagaoka, Suita-shi, Osaka 565, Japan

*Abstract:* An excellent approach to the synthesis of [5'-$^2$H]thymidine (**6-T**), -$N^4$-benzoyl-2'-deoxycytidine (**6-C$^{Bz}$**), -$N^6$-benzoyl-2'-deoxyadenosine (**6-A$^{Bz}$**), and -2'-deoxy-$N^2$-isobutylylguanosine (**6-G$^{iBu}$**) was accomplished by treating the corresponding 5'-*O*-Ac-3'-*O*-TBDMS-2'-deoxy-5'-PhSe-ribonucleosides (**4**) with $Bu_3Sn^2H$ - $Et_3B$ at < -70°C, followed by removal of the TBDMS and Ac groups in the usual manner, in 79-66% yields. Compounds **4** were synthesized in a three-step reaction from the corresponding 3'-*O*-TBDMS-2'-deoxy-5'-*O*-Ms-ribonucleosides (**1**) (93-77% overall yields).

Conformational analysis of the sugar backbone structure of an oligodeoxyribonucleotide should be attained through $^1$H-NMR spectroscopy by the use of a sample which uniformly consists of 2'-deoxyribonucleotide units monodeuterated at their 5'-position. The synthesis of completely stereoselective (5'*R*)- and (5'*S*)-2'-deoxy[5'-$^2$H]cytidine has been reported by Townsend *et al.*[1] The completely stereoselectively labeled 2'-deoxy[5'-$^2$H]ribonucleosides make possible explicit stereospecific assignments and exact determination of the coupling constants, $^3J_{5'pro\text{-}S,\,4'}$ and /or $^3J_{5'pro\text{-}R,\,4'}$; thus, the precise conformation of the sugar-phosphate backbone could be elucidated. The data of NOESY was, however, only one-sided, therefore, two DNA-oligomer introduced (5'-*R*)-2'-deoxy[5'-$^2$H]ribonucleotide and the counter parts should be always synthesized. If we can get a difference ratio (60:40 ~ 70:30) of stereoselective (5'-*R*)- and 2'-deoxy[5'-$^2$H]ribonucleotide, in the short DNA-oligomer, it would not only give both NOESY spectra with one sample, but also enable easy assignment of the chirality (*pro-R* and *pro-S* 5'-protons). Drobny *et al*[2] and Ried *et al.*[3] have reported the synthesis of [5'-$^2$H]thymidine, but this approach gave no stereoselectivity: 1:1 mixture of (5'*R*)- and (5'*S*)-[5'-$^2$H]thymidine. In our laboratory, recently, synthesis of (2'*R*)-2'-deoxy[2'-$^2$H]ribonucleosides by the reduction of 2'-bromo-2'-deoxyribonucleoside derivatives with $Bu_3Sn^2H$-$Et_3B$ at a low temperature has been attained.[4] Subsequent to the investigations previously described, therefore, the authors set out to establish an approach to the synthesis of a difference ratio of (5'-*R*)- and (5'-*S*)-2'-deoxy[5'-$^2$H]ribonucleosides. This novel method is characterized by the reduction of 5'-*O*-Ac-3'-*O*-TBDMS-2'-deoxy-5'-PhSe-ribonucleoside derivatives with $Bu_3Sn^2H$-$Et_3B$ at < -70°C. We now communicate the results herein.

A PhSe group was chosen as the leaving group for the radical deuteration reaction since it is easily susceptible to the reaction. An efficient approach to the synthesis of an acyloxyselenide was established by modification of the report of Miyasaka *et al.*[5] First, synthesis of [5'-$^2$H]thimidine was tried as follows: introduction of the PhSe group with $(PhSe)_2$ and $NaBH_4$ into **1-T**, oxidation with *m*-CPBA of **2-T** to give **3-T**, then derivation of **3-T** into **4-T** by Pummerer rearrangement using $Ac_2O$, followed by reductive deuteration[4] using $Bu_3Sn^2H$ - $Et_3B$ at < -70 °C of **4-T** to give **5-T**. Compound **5-T** was synthesized in 91% overall yield from **1-T** in the four steps and converted to **6-T** in 82% overall yield by removal of both the TBDMS and Ac

protecting groups. Compound 6-T was confirmed to have 93 atom % $^2H$ and the proportion of (5'*R*)- vs. (5'*S*)-diastereomers was 31 vs. 69 according to the method reported by Serianni *et al.*[6] after introducing the TPDS protection to 3'- and 5'-OH. Since the synthesis of 6-T gave good results, the syntheses of 6-$C^{Bz}$, -$A^{Bz}$, and -$G^{iBu}$ were performed similarly as above described. The results obtained are summarized in Scheme 1 and Table 1.




Scheme 1

**Table 1**

Atom % $^2H$ and (5'*R*)/(5'*S*) ratio of 6

| B | atom % $^2H$ | (5'*R*)/(5'*S*) |
|---|---|---|
| T | 93 | 31/69 |
| $C^{Bz}$ | 90 | 24/76 |
| $A^{Bz}$ | 90 | 39/61 |
| $G^{iBu}$ | 90 | 20/80 |

It is concluded, therefore, that a novel and stereoselective method has been established from the present study for the synthesis of 2'-deoxy[5'-$^2H$]ribonucleosides (90 atom % $^2H$). In terms of the ratio of (5'*R*)/(5'*S*) on 2'-deoxy[5'-$^2H$]guanosine, however, more examination of this aspect is necessary to get the selectivity.

In Fig. 1, the regions of $^1H$ NMR spectra giving the corresponding proton signals of the sugar moieties are also exemplified by that of 3',5'-*O*-TPDS-[5'-$^2H$]thymidine together with that of 3',5'-*O*-TPDS-thymidine.

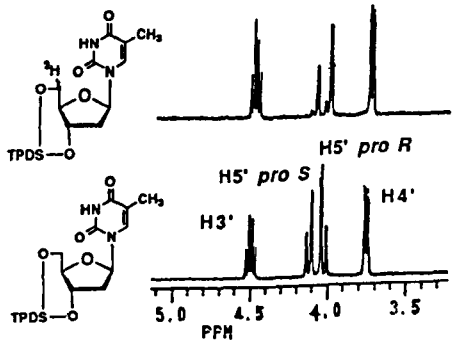



Fig. 1

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