HETEROCYCLES, Vol. 66, 2005, pp. 361 – 369. © The Japan Institute of Heterocyclic Chemistry
Received, 30th August, 2005, Accepted, 18th October, 2005, Published online, 21st October, 2005. COM-05-S(K)36

SYNTHESIS OF BASE-SELECTIVELY DEUTERIUM-LABELLED NUCLEOSIDES BY THE Pd/C-CATALYZED H-D EXCHANGE REACTION IN DEUTERIUM OXIDE

Hiroyoshi Esaki, Fumiyo Aoki, Tomohiro Maegawa, Kosaku Hirota, and Hironao Sajiki*

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502-8585, Japan, E-mail: sajiki@gifu-pu.ac.jp.

Abstract – The D_2 gas-free and base-selective H-D exchange reaction of nucleosides was developed. It discloses a convenient route to the post-synthetic incorporation of deuteriums into the base moiety of nucleic acids with high deuterium efficiency.

INTRODUCTION

Nucleoside analogues represent a significant area of drug design. In the search for potential and selective antimetabolites such as antiviral and antitumor agents, a number of nucleoside analogues have been synthesized.[1] Deuterium-labelled nucleoside analogues are quite promising tools for the study of the mechanism of the biological activity, structure-activity relationship and metabolism of biologically active nucleosides[2] and higher-order structures of DNA.[3] The catalytic and direct deuteration method of an unlabelled nucleoside is a favorable approach to the preparation of deuterated nucleosides. However, a number of reported methods are necessary to achieve laborious multi-step synthesis starting from commercially available deuterium-labelled small synthons[4] since the lability of the glycosyl bond can not tolerate the use of harsh (especially acidic) reaction conditions. Although several direct incorporation methods of deuteriums into the base-moieties of nucleosides have been reported, such conventional post-synthetic procedures are often limited to acidic positions of the nucleosides,[5a-c,e,g] leading to low levels of deuterium incorporation,[5e-f] and require a vast amount of the catalyst,[5d,f,g] addition of acidic or basic additives,[5a-c,e,f] and/or expensive deuterium atmosphere.[5d,f,g,6]

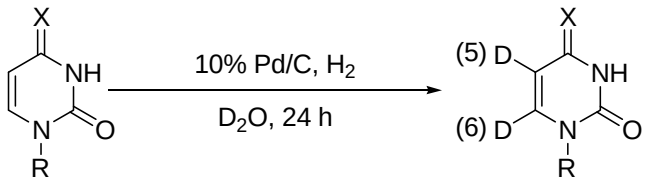
This paper is dedicated to the late Professor Kenji Koga.

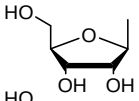
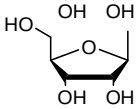
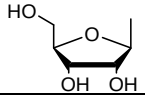
Recently, we have reported a Pd/C-catalyzed efficient and regioselective H-D exchange reaction at the benzylic position between various benzylic derivatives and deuterium oxide at room temperature under hydrogen atmosphere.[7] Under similar reaction conditions, H-D exchange reaction was achieved even on non-activated carbons by a rise in the reaction temperature.[8,9] Based upon this background, we studied application of these H-D exchange reactions to the deuteration of nucleosides.[10]

RESULTS AND DISCUSSION

In our initial investigation, we explored the scope of the deuteration method toward uracil, cytosine and their derivatives (Table 1).

Table 1. Pd/C-catalyzed deuteration of uracil, cytosine and their derivatives in D_2O

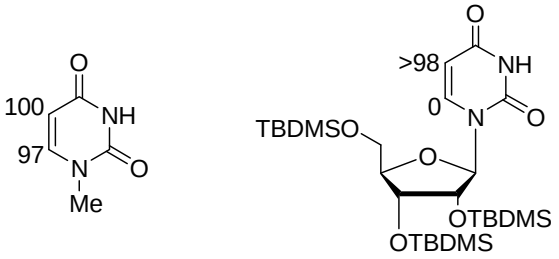


Entry	X	R	Temp (°C)	Time (h)	D content (%)[a]		Yield (%)
					5-D	6-D	
1[b]	O	H	140	48	–	–	–
2	O	H	160	24	98	97	100
3[b]	O		140	48	–	–	–
4	O		160	24	94	35	100
5[b]	NH	H	110	24	–	–	–
6	NH	H	160	48	95	96	98
7	NH		140	48	93	35	100

[a] Determined by ^{1}H NMR spectroscopy using DSS as an internal standard. [b] Partial hydrogenation of the 5,6-double bond was observed.

The Pd/C-catalyzed reaction at 110-140 ºC yielded the desired 5,6-dideuterated products, which unfortunately accompanied by partial hydrogenation of the 5,6-double bond of the pyrimidine ring (Table 1, Entries 1, 3 and 5). But it is notable that this defect could be entirely overcome with a rise in temperature up to 160 ºC in a sealed tube (Table 1, Entries 2, 4 and 6). It is significant that the deuterium efficiency at the 6-position of pyrimidine nucleosides is lower (Table 1, Entries 4 and 7) compared to the

nearly quantitative deuterium incorporation at the 6-position of uracil and cytosine possessing no sugar moiety (Table 1, Entries 2 and 6).

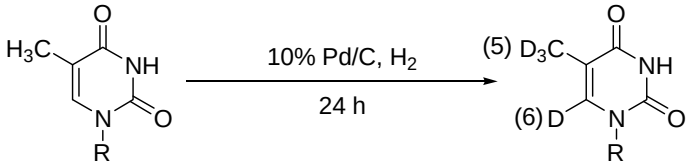


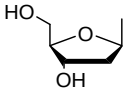
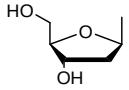
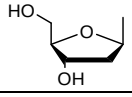
1 (100% isolated yield) **2** (93% isolated yield)

Figure 1. Deuteration efficiencies of **1** and **2** after the H-D exchange reaction at 160 ºC for 24 h.

We assumed that the lower deuterium efficiency was attributable to the lack of the acidic hydrogen at the 1-position and/or the existence of free hydroxyl groups of the sugar moiety,[8a] so we investigated the H-D exchange reaction of 1-methyluracil (**1**) and 2',3',5'-tris-*O*-TBDMS-uridine (**2**), which possesses fully protected hydroxyl groups of the furanose ring, under the reaction conditions. As a result, nearly quantitative deuterium efficiency was achieved at both the 5 and 6-positions of the uracil ring in the case of 1-methyluracil (**1**) (Figure 1). On the other hand, no deuterium incorporation into the 6-position of **2** was observed, although the 5-position was quantitatively deuterated. Therefore, it is obvious that the acidic hydrogen at the 1-position and free hydroxyl groups were not responsible for the deuterium efficiency at the 6-position of uridine derivatives while the actual reason for the lowering of the deuterium efficiency at the 6-position of uridine derivatives is not clear yet.

Table 2. Pd/C-catalyzed deuteration of thymidine derivatives in D_2O

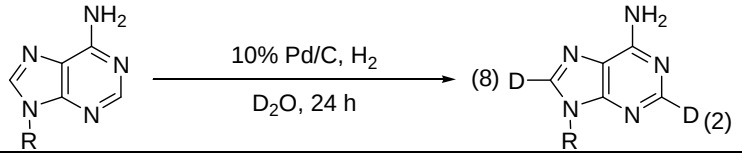


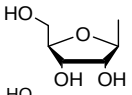
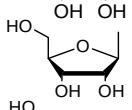
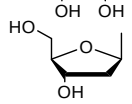
Entry	R	Solvent	Temp (°C)	D content (%)[a]		Yield (%)
				5-Me	6-D	
1	H	D_2O	110	97	96	89
2[b]		D_2O	140	71	7	53
3		CD_3OD	110	0	0	98
4		CD_3OD	160	26	0	99

[a] Determined by ^{1}H NMR spectroscopy using DSS as an internal standard. [b] Partial hydrolysis (ca. 10%) at glycosyl bond was observed.

While uracil, cytosine and their derivatives were hydrogenated at the 5,6-double bond at 110-140 ºC, thymine possessing a methyl group at the 5-position of the pyrimidine ring was entirely deuterated at 110 ºC without the partial hydrogenation of the 5,6-double bond (Table 2, Entry 1). Partial hydrolysis of the glycosyl bond was unfortunately observed when thymidine, a 2'-deoxy-pyrimidine nucleoside, was used as the substrate[10,11] (Table 2, Entry 2), and hence purification using column chromatography was required. When CD_3OD was used as a solvent and D source instead of D_2O in order to prevent the hydrolysis, the D content at both the 5-methyl group and the 6-position of the thymine ring was strongly depressed although there was no hydrolysis of the glycosyl bond (Table 2, Entries 3 and 4).

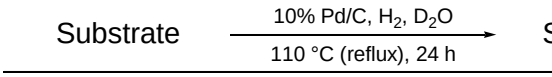
Table 3. Pd/C-catalyzed deuteration of adenine derivatives in D_2O

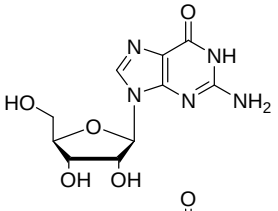
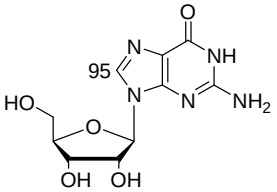
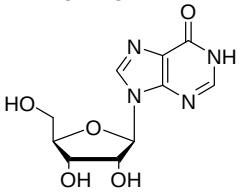
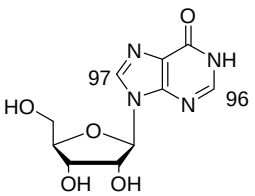
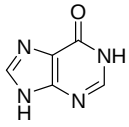
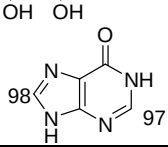


Entry	R	Temp (°C)	D content (%)[a] 2-D	D content (%)[a] 8-D	Yield (%)
1	H	110	95[b]	95[b]	99
2		110	95	92	99
3		160	95	96	98
4		110	96	96	81

[a] Determined by ^{1}H NMR spectroscopy using 3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS) as an internal standard. [b] Indicates the average D content.

Table 4. Pd/C-catalyzed deuteration of guanosine, inosine, and hypoxantine in D_2O

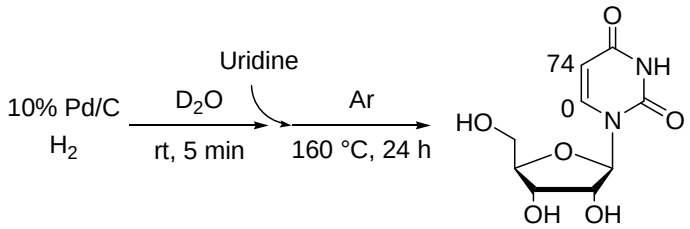


Entry	Substrate	D content (%)[a]	Yield (%)
1			92
2			100
3			92

[a] Determined by ^{1}H NMR spectroscopy using DSS as an internal standard.

In contrast, the H-D exchange reaction of purine derivatives including nucleosides such as adenosine, guanosine and inosine gave excellent deuterium efficiencies at the 2 and 8-positions of the purine rings with high isolated yields even at 110 ºC (Table 3 and Table 4). No significant differences in the D content and the isolated yield were observed at 160 ºC (Table 3, Entry 3). It is noteworthy that nearly quantitative deuteration was achieved in the case of 2'-deoxyadenosine without hydrolysis of the glycosyl bond (Table 3, Entry 4).

In the presented deuteration method using the Pd/C-H_2-D_2O system, no H-D exchange proceeded in the absence of hydrogen gas.[7,8a] To investigate the role of hydrogen gas, we examined the following reaction. 10% Pd/C (10 wt% of the substrate) was suspended in 1 mL of D_2O in a test tube (10 mL) and pre-stirred under H_2 atmosphere for 5 minutes at room temperature. After two vacuum/Ar cycles to remove hydrogen gas from the reaction tube, uridine was added and stirred at 160 ºC in a sealed tube under Ar atmosphere for 24 h. Consequently, the H-D exchange reaction at the 5-position of uridine progressed while the deuterium efficiencies at the 5 and 6-positions were rather depressed compared with the deuterium efficiencies in Table 1, entry 4 (Scheme 1). It is obvious that the existence of a small amount of hydrogen gas for the activation of the palladium surface is essential for the H-D exchange reaction. It is likely that hydrogen gas acts as a so-called ligand of the Pd metal in this reaction.



Scheme 1. Investigation of the role of H_2 in this deuterating method

In summary, an efficient base selective H-D exchange reaction can be achieved with the Pd/C-H_2-D_2O system under heating conditions.[12] This deuteration method does not require the use of D_2 gas and special apparatus, and is applicable to a variety of nucleic acids under neutral reaction conditions. The reactions are very clean and the products were obtained in excellent yields without chromatographic purification. This chemoselective deuterating method should contribute to extensive studies of nucleic acids chemistry.

EXPERIMENTAL

General

^1H, ^2H, and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (^1H NMR: 400 MHz, ^2H NMR: 61 MHz, ^{13}C NMR: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or 3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS) as

an internal standard. EI and FAB MS spectra were taken on a JEOL JMS-SX102A machine. Optical rotations were measured using a JASCO DIP-360 Digital Polarimeter.

10 % Pd/C was purchased from Aldrich Chemical Co. and deuterium oxide (99.7% isotopic purity) was purchased from Cambridge Isotope Laboratories. All of the substrates were used without further purification.

Typical procedure for deuteration of adenosine (Table 3, Entry 3): After two vacuum/H_2 cycle to remove air from the reaction tube, adenosine (66.8 mg, 0.25 mmol) and 10% Pd/C (6.7 mg, 10 wt% of the substrate) in D_2O (1 mL) was stirred at 160 ºC in a sealed tube for 24 h. After cooling, the reaction mixture was filtered using a membrane filter (Millipore Millex®-LG, 0.20 μm). The filtered catalyst was washed with boiling water (50 mL) and the combined filtrates were concentrated in vacuo to give adenosine-d_2 as a white powder (66.3 mg, 98%). The deuterium content (%) was determined by ^{1}H NMR spectroscopy and confirmed by ^{2}H NMR spectroscopy and MS spectrum. $[\alpha]_D^{20}$ -55° (c 0.38, H_2O) [adenosine[13] $[\alpha]_D^{11}$ -62° (c 0.71, H_2O)]. MS (EI): *m/z* (%) = 269 (3) [M+2] (21% d_1, 56% d_2, 23% d_3). ^{1}H NMR (DMSO-d_6): 8.37 (s, 0.05H), 8.12 (s, 0.04H), 7.34-7.30 (br s, 2H), 5.90 (d, *J* = 6.4 Hz, 1H), 5.45-5.41 (m, 2H), 5.20 (d, *J* = 4.9 Hz, 1H), 4.63 (dd, *J* = 4.9, 6.4 Hz, 1H), 4.16 (dd, *J* = 3.4, 4.4 Hz, 1H), 3.99 (dd, *J* = 3.4, 3.4 Hz, 1H), 3.72-3.67 (m, 1H), 3.60-3.54 (m, 1H). ^{13}C NMR (DMSO-d_6): 156.2, 152.3 (small multiplet), 149.0, 139.9 (small mutiplet), 119.3, 87.9, 85.9, 73.4, 70.6, 61.6. ^{2}H NMR (DMSO): 8.02 (br).

[^{2}H]-Uracil (Table 1, Entry 2): MS (EI): *m/z* (%) = 114 (100) [M+2] (4% d_1, 88% d_2, 7% d_3, 1% d_4). ^{1}H NMR (DMSO-d_6): 10.91 (br, 2H), 7.41 (s, 0.03H), 5.47 (s, 0.02H), ^{2}H NMR (DMSO): 7.40 (br s), 5.46 (br s).

[^{2}H]-Uridine (Table 1, Entry 4): $[\alpha]_D^{21}$ +5° (c 0.27, H_2O) [uridine[13] $[\alpha]_D^{20}$ +4° (c 2)]. MS (EI): *m/z* (%) = 245 (4) [M+1], 246 (3) [M+2] (27% d_0, 36% d_1, 24% d_2, 13% d_3). ^{1}H NMR (DMSO-d_6): 11.09 (br, 1H), 7.91 (s, 0.65H), 5.81 (d, *J* = 5.3 Hz, 1H), 5.68-5.65 (m, 0.06H), 5.41 (br s, 1H), 5.13 (br s, 2H), 4.04 (s, 1H), 3.98 (s, 1H), 3.86 (d, *J* = 3.4 Hz, 1H), 3.65-3.55 (m, 2H). ^{13}C NMR (DMSO-d_6): 163.2, 150.8, 140.7, 101.8 (small mutiplet), 87.7, 84.9, 73.6, 69.9, 60.9. ^{2}H NMR (DMSO): 7.90 (br), 5.58 (br).

[^{2}H]-Cytosine (Table 1, Entry 6): MS (EI): *m/z* (%) = 113 (100) [M+2] (2% d_0, 9% d_1, 79% d_2, 9% d_3, 1% d_4). ^{1}H NMR (DMSO-d_6): 10.32 (br s, 1H), 7.35 (s, 0.04H), 7.09 (br s, 2H), 5.61 (s, 0.04H).^{13}C NMR (DMSO-d_6): 166.9, 157.3, 142.8 (small multiplet), 92.4 (small multiplet). ^{2}H NMR (DMSO): 7.32 (br s), 5.58 (br s).

[^{2}H]-Cytidine (Table 1, Entry 7): $[\alpha]_D^{21}$ +25° (c 0.26, H_2O) [cytidine[13] $[\alpha]_D^{25}$ +31° (c 0.7, H_2O)]. MS (EI): *m/z* (%) = 244 (1) [M+1], 245 (1) [M+2] (26% d_0, 32% d_1, 29% d_2, 13% d_3). ^{1}H NMR (DMSO-d_6):

7.87 (s, 0.65H), 7.21 (br s, 2H), 5.79 (d, *J* = 3.4, 1H), 5.20 (s, 0.07H), 5.32 (br, 1H), 5.09 (br, 2H), 3.95 (br s, 2H), 3.84 (br s, 1H), 3.69-3.42 (m, 2H). ^{2}H NMR (DMSO): 7.87 (br), 5.79 (br s).

[^{2}H]-1-Methyluracil (1): MS (EI): *m/z* (%) = 128 (2) [M+2] (4% d_1, 82% d_2, 14% d_3). ^{1}H NMR (DMSO-d_6): 11.2 (br s, 1H), 7.65 (s, 0.03H), 5.55 (s, 0.004H). ^{2}H NMR (DMSO): 7.40 (br s), 5.46 (br s).

[^{2}H]-2',3',5'-Tris-*O*-TBDMS-uridine (2): $[\alpha]_D^{21}$ +18° (c 0.74, CH_3Cl) [2',3',5'-tris-*O*-TBDMS-uridine $[\alpha]_D^{22}$ +22° (c 0.83, CH_3Cl)]. MS (FAB+): *m/z* (%) = 588 (17) [M+1] (4% d_0, 58% d_1, 31% d_2). ^{1}H NMR ($CDCl_3$): 7.94 (s, 1H), 5.80 (d, *J* = 3.38 Hz, 1H), 5.60 (small multiplet, 0.01H), 4.10-3.99 (m, 3H), 3.91 (d, *J* = 11.6 Hz, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 0.87 (s, 9H), 0.83 (s, 9H), 0.81 (s, 9H), 0.15-0.00 (m, 18H). ^{2}H NMR (DMSO): 5.63 (br s).

[^{2}H]-Thymine (Table 2, Entry 1): MS (EI): *m/z* (%) = 130 (100) [M+4] (1% d_2, 12% d_3, 80% d_4, 6% d_5, 1% d_6). ^{1}H NMR (DMSO-d_6): 11.0 (br, 1H), 10.6 (br, 1H), 7.23 (s, 0.04H), 1.68 (s, 0.10H). ^{2}H NMR (DMSO): 7.23 (br s), 1.66 (br s).

[^{2}H]-Thymidine (Table 2, Entry 2): $[\alpha]_D^{25}$ +28° (c 0.27, CH_3OH) [thymidine[13] $[\alpha]_D^{20}$ +31° (c 1.03)]. MS (EI): *m/z* (%) = 243 (5) [M+1], 244 (5) [M+2] (31% d_0, 37% d_1, 23% d_2, 9% d_3). ^{1}H NMR (DMSO-d_6): 11.3 (br s, 1H), 7.72 (s, 1H), 6.19 (t, 1H), 5.25 (d, *J* = 3.9 Hz, 1H), 5.04 (t, 1H), 4.26 (br s, 1H), 3.78 (m, 1H), 3.64-3.53 (m, 2H), 2.15-2.07 (m, 2H), 1.80-1.76 (m, 0.88H). ^{2}H NMR (DMSO): 1.67 (br s).

[^{2}H]-Thymidine (Table 2, Entry 4): MS (EI): *m/z* (%) = 243 (4) [M+1], 244 (3) [M+2], 245 (1) [M+3] (33% d_0, 36% d_1, 22% d_2, 9% d_3). ^{1}H NMR (DMSO-d_6): 11.3 (br s, 1H), 7.72 (s, 1H), 6.19 (t, 1H), 5.24 (d, *J* = 3.9 Hz, 1H), 5.04 (t, 1H), 4.26 (br s, 1H), 3.78 (d, *J* = 2.9 Hz, 1H), 3.64-3.55 (m, 2H), 2.15-2.07 (m, 2H), 1.80-1.78 (m, 2.23H). ^{2}H NMR (DMSO): 1.76 (br s).

[^{2}H]-Adenine (Table 3, Entry 1): MS (EI): *m/z* (%) = 137 (100) [M+2] (2% d_0, 6% d_1, 78% d_2, 13% d_3, 1% d_4). ^{1}H NMR (DMSO-d_6): 12.79 (br 1H), 8.14 (s, 0.05H), 8.11 (s, 0.05H), 7.10 (br s, 2H). ^{2}H NMR (DMSO): 8.11 (br s).

[^{2}H]-Adenosine (Table 3, Entry 2): $[\alpha]_D^{19}$ -60° (c 0.38, H_2O) [adenosine[13] $[\alpha]_D^{11}$ -62° (c 0.71, H_2O)]. MS (EI): *m/z* (%) = 269 (2) [M+2] (5% d_0, 20% d_1, 50% d_2, 25% d_3). ^{1}H NMR (DMSO-d_6): 8.37 (s, 0.08H), 8.17 (s, 0.05H), 7.35 (br s, 2H), 5.90 (d, *J* = 6.3 Hz, 1H), 5.45-5.43 (m, 2H), 5.20 (d, *J* = 4.8 Hz, 1H), 4.63 (dd, *J* = 2.9, 5.8 Hz, 1H), 4.17 (dd, *J* = 2.1, 4.2 Hz, 1H), 3.99 (dd, *J* = 1.4, 2.9 Hz, 1H), 3.71-3.67 (m, 1H), 3.60-3.58 (m, 1H). ^{2}H NMR (DMSO): 8.02 (br s).

[^{2}H]-Deoxyadenosine (Table 3, Entry 4): $[\alpha]_D^{20}$ -19° (c 0.36, CH_3OH) [deoxyadenosine $[\alpha]_D^{20}$ -20° (c 0.36, CH_3OH)]. MS (EI): *m/z* (%) = 253 (5) [M+2] (24% d_1, 51% d_2, 25% d_3). ^{1}H NMR (DMSO-d_6): 8.35 (s, 0.04H), 8.15 (s, 0.04H), 7.30 (br s, 2H), 6.36 (t, 1H), 5.32 (d, *J* = 3.9 Hz, 1H), 5.25 (t, 1H), 4.43 (dd, *J*

= 2.9, 2.9 Hz, 1H), 3.91 (dd, *J* = 2.4, 4.4 Hz, 1H), 3.99 (dd, *J* = 3.4, 3.4 Hz, 1H), 3.67-3.62 (m, 1H), 3.57-3.51 (m, 1H), 2.77-2.71 (m, 1H), 2.30-2.25 (m, 1H).^{2}H NMR (H_2O): 8.10 (br).

[^{2}H]-Guanosine (Table 4, Entry 1): $[\alpha]_D^{20}$ -59° (c 0.25, 0.02 *N* NaOH) [guanosine $[\alpha]_D^{20}$ -61° (c 0.30, 0.02 *N* NaOH)]. MS (ES+): *m/z* (%) = 284 (1) [M+1] (43% d_1, 38% d_2, 19% d_3). ^{1}H NMR (DMSO-d_6): 10.65 (br s, 1H), 7.95 (s, 0.03H), 6.50 (br s, 2H), 5.72 (d, *J* = 6.3 Hz, 1H), 5.41 (d, *J* = 5.8 Hz, 1H), 5.14 (d, *J* = 3.9 Hz, 1H), 5.05 (t, 1H), 4.42 (dd, *J* = 2.8, 5.6 Hz, 1H), 4.11 (dd, *J* = 2.2, 4.4 Hz, 1H), 3,90 (dd, *J* = 1.7, 3.4 Hz, 1H), 3.67-3.52 (m, 1H). ^{2}H NMR (DMSO): 7.96 (br).

[^{2}H]-Inosine (Table 4, Entry 2): $[\alpha]_D^{21}$ -46° (c 0.34, H_2O) [Inosine[13] $[\alpha]_D^{18}$ -49° (c 0.9, H_2O)]. MS (EI): *m/z* (%) = 270 (1) [M+2] (30% d_1, 40% d_2, 30% d_3). ^{1}H NMR (DMSO-d_6): 12.45 (br s, 1H), 8.37 (s, 0.04H), 8.11 (s, 0.03H), 5.90 (d, *J* = 5.9 Hz, 1H), 5.54 (br s, 1H), 5.26 (br s, 1H), 5.12 (br s, 1H), 4.51 (br s, 1H), 4.15 (br s, 1H), 3,96 (d, *J* = 3.9 Hz, 1H), 3.74-3.62 (m, 1H), 3.60-3.56 (m, 1H). ^{2}H NMR (DMSO): 8.06 (br).

[^{2}H]-Hypoxantine (Table 4, Entry 3): MS (EI): *m/z* (%) = 138 (100) [M+2] (3% d_0, 8% d_1, 76% d_2, 12% d_3, 1% d_4). ^{1}H NMR (DMSO-d_6): 13.3 (br, 1H), 12.3 (br, 1H), 8.14 (s, 0.02H), 8.01 (s, 0.03H). ^{2}H NMR (DMSO): 7.99 (br d).

ACKNOWLEDGEMENTS

The authors are grateful for the financial supports from Research Foundation of Gifu Pharmaceutical University and JSPS Research Fellowships for Young Scientists (176469).

REFERENCES AND NOTES

1. For examples, see: (a) 'Chemistry of Nucleosides and Nucleotides,' ed. by L. B. Townsend, Plenum Press, New York, 1988; (b) C. Perigaud, G. Gosselin, and J. L. Imbach, *Nucleosides and Nucleotides*, 1992, **11**, 903; (c) 'Nucleosides and Nucleotides as Antitumor and Antiviral Agents,' ed. by C. K. Chu and D. C. Baker, Plenum Press, New York, 1993; (d) K. Haraguchi, Y, Itoh, and H. Tanaka, *J. Synth. Org. Chem., Jpn.,* 2003, **61**, 974; (e) A. Matsuda and T. Sasaki, *Cancer Sci.,* 2004, **95**, 105.
2. (a) T. Junk and W. J. Catallo, *Chem. Soc. Rev.*, 1997, **26**, 401; (b) N. Elander, J. R. Jones, S. –Y. Lu, and S. Stone-Elander, *Chem. Soc. Rev.*, 2000, **29**, 239; (c) A. Durazo and M. M. Abu-Omar, *Chem. Commun.*, 2002, 66; (d) D. Gani and D. W. Young, *J. Chem, Soc., Chem. Commun.,* 1983, 576; (e) D. Gani, P. B. Hitchcock, and D. W. Young, *J. Chem, Soc., Chem. Commun.,* 1983, 898.
3. (a) E. Kawashima, Y. Aoyama, T. Sekine, M. Miyahara, M. F. Radwan, E. Nakamura, M. Kainosho, Y. Kyogoku, and Y. Ishido, *J. Org. Chem.,* 1995, **60**, 6980; (b) A. Földesi, A. Trifonova, Z. Dinya, and J.

Chattopadhyaya, *J. Org. Chem.,* 2001, **66**, 6560.

4. (a) R. K. Hill, N. D. Ledford, and L. A. Renbaum, *J. Labelled. Compds. Radiopharm,* 1985, **22**, 143; (b) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.,* 1991, **39**, 301; (b) M. Sako, T. Hayashi, K. Hirota, and Y. Maki, *Chem. Pharm. Bull.,* 1992, **40**, 1656.
5. (a) G. Guroff, C. A. Reifsnyder, and J. Daly, *Biochem. Biophys. Res. Commun.,* 1996, **24**, 720; (b) D. V. Santi and C. F. Brewer, *J. Am. Chem. Soc.,* 1968, **90**, 6236; (c) M. Maeda, M. Saneyoshi, and Y. Kawazoe, *Chem. Pharm. Bull.,* 1971, **19**, 1641; (d) M. Maeda and Y. Kawazoe, *Tetrahedron Lett.,* 1975, **19**, 1643; (e) J. L. Wong and J. H. Keck, Jr., *J. Chem, Soc., Chem. Commun.,* 1975, 125; (f) R. Kiritani, T. Asano, S. Fujita, T. Dohmaru, and T. Kawanishi, *J. Labelled. Compds. Radiopharm,* 1986, **23**, 207; (g) J. Roček, V. Sváta, and L. Lešetický, *Coll. Czech, Chem. Commun.,* 1985, **50**, 1244.
6. D_2 gas [$96.40/10 L of D_2 gas (Aldrich 36,186-0) in lecture bottle] is also purchased as a lecture bottle or cylinder charged by high-pressure.
7. H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, and K. Hirota, *Synlett*, 2002, 1149.
8. (a) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, and K. Hirota, *Org. Lett.,* 2004, **6**, 1485; (b) T. Maegawa, A. Akashi, H. Esaki, F. Aoki, H. Sajiki, and K. Hirota, *Synlett,* 2005, 845.
9. Matsubara *et al*. also reported interesting H-D exchange reactions under hydrothermal conditions, see: (a) S. Matsubara, Y. Yokota, and K. Oshima, *Chem. Lett.,* 2004, **33**, 294. (b) S. Matsubara, Y. Yokota, and K. Oshima, *Org. Lett.*, 2004, **6**, 2071; (c) M. Yamamoto, Y. Yokota, K. Oshima, and S. Matsubara, *Chem. Commun.,* 2004, 1714. (c) M. Yamamoto, K. Oshima, and S. Matsubara, *Org. Lett.,* 2004, **6**, 5015.
10. H. Sajiki, H. Esaki, F. Aoki, T. Maegawa, and K. Hirota, *Synlett,* 2005, 1385.
11. Although we previously reported[10] that the glycosyl bond of thymidine completely was hydrolyzed under the same reaction conditions, we could obtain the deuterated thymidine at the 5-methyl group (71% deuterium efficiency) accompanied by the partial hydrolysis of thymidine.
12. No deuterium incorporation into the sugar moieties was found in all cases although Matsubara *et al*. recently reported quiet interesting H-D exchange reaction of primary alcohols at the α-position using $RuCl_2(PPh_3)_2$ as a catalyst, see: M. Takahashi, K. Oshima, and S. Matsubara, *Chem. Lett.,* 2005, **34**, 192.
13. The Merck Index 13th Ed., Merck & CO., Inc., Whitehouse Station, 2001.