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A Convenient Method for Deuteration at the Alpha Position of an Oxo Group in Carbohydrates

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Abstract: CH-Hydrogens at the alpha position of an oxo group in carbohydrates are readily exchanged in 4:4:2:3 1,4-dioxane–THF–Et_3N–D_2O.

In the study of mechanism[1] of chemical[2] and biochemical[1] transformations, partially deuterated carbohydrates[1-6] have been widely used in combination with NMR spectroscopy.[3] These compounds also play an important role in conformational analysis of oligo[4] and polysaccharides as well as nucleoside(tide)s[6] in alleviating the overcrowding of resonances. To introduce deuterium, base-catalyzed hydrogen-deuterium exchange at the carbon atom alpha to a carbonyl group is a well-known method; commonly used bases are NaOAc, NaOD, alkylamines (all in D_2O), and NaOMe/MeOD. However, only a few applications of the procedure to carbohydrates have been reported.[7]

Recently, we have found[2b] that methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**7**), on dissolving in a mixture of 4:4:2:3 1,4-dioxane–THF–Et_3N–D_2O (in this solvent, all compounds described later dissolved readily), gave the corresponding [2-^{2}H] derivative (**8**) together with the [2-^{2}H]-D-*arabino* isomer (**9**), without any contamination of the 4-deuterated compound. This easy deuteration stimulated us to apply the procedure to other simple sugars having a carbonyl group (Table 1). Similar treatment of the β-anomer[2c] (**10**) of **7** gave **11** as the major product, and 2-deoxy-3-oxo compound[8] (**12**) gave the 2,2,4-trideuterated compound **13**; the latter suggests that the 3(4)-enolization of **12** occurs possibly by the absence of a BnO-2 group. The same treatment of **14**, however, gave several unidentified products.

Likewise, 2-oxo compounds (**1**[9] and **3**[10]) afforded the [3-^{2}H] compounds (**2** and **4**) in high yields without contamination of the [1-^{2}H] or 3-epimerized compounds. In the case of 3-*O*-methyl-2-oxo-D-*ribo* compound[11] (**5**), D-*arabino* derivative (**6**) was exclusively formed under inversion. This indicates that the MeO-3-axial structure is thermodynamically unstable. Monocyclic 4-oxo-compound[2a] **15** gave the 3,5-dideuterated compound **16** along with the 5-deuterated-2-eno derivative **17**. A 6-aldehyde compound[12] gave the 5-deuterio derivative as expected.

Some furanosides were also examined. Similar treatment of methyl 3,5-di-*O*-benzyl-α-D-*threo*-pentofuranosid-2-ulose (**20**) followed by reduction with $NaBH_4$ gave the corresponding [3-^{2}H]-*ribo*- (**22**, major)

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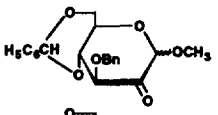
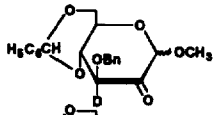
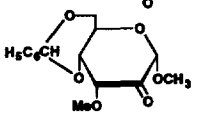
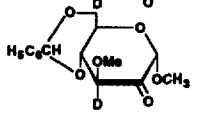
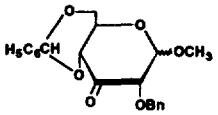
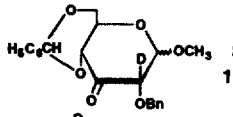
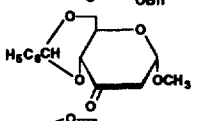
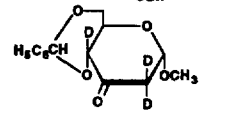
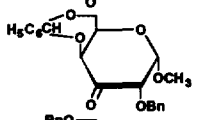
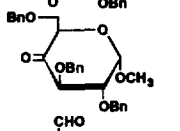
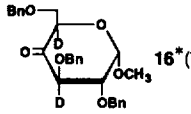
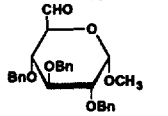
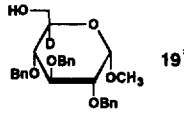
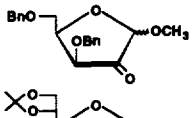
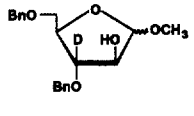
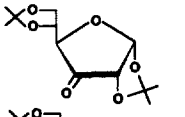
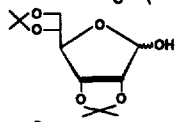
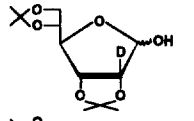
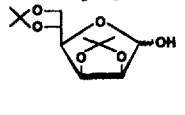
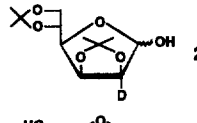
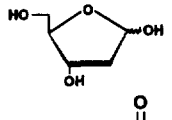
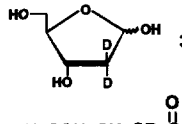
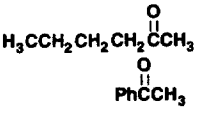
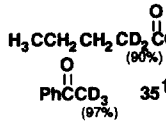
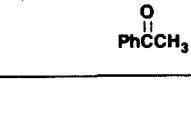
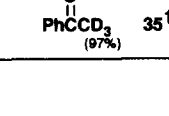
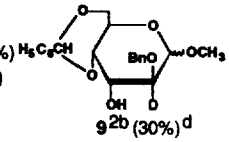
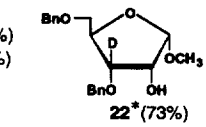
Table 1 Hydrogen–Deuterium Exchange in Oxo Compounds

Starting material	Conditions[a]	Product[b]
	1 (α)[9] 3 (β)[10]	A		2*[c] (α, 96%, dr) 4*[c] (β, 91%, dr)
	5[11]	A 5d		6* (84%, re)
	7 (α) 10 (β)[2c]	A		8[2b] (α, 60%) 11* (β, 83%)
	12[13]	A 5d		13* (75%, ch)
	14*[e] (82%, dr)	A 5d	a mixture of unknown products	
	15[12a]	A 6d		16* (79%, ch)
	18[12]	A, $NaBH_4$[f]		19* (91%)
	20*[g] (α) 23*[g] (β)	A 5d, $NaBH_4$[f]		21* (α, 12%) 24* (β, 83%)
	25[13]	A	two unknown products (ch)	
	26[14]	B		27* (quant, dr)
	28[15]	B		29* (quant, dr)
	30	A 5d		31*[18] (quant, dr)
	32	A 5d × 2[h]		33[16] (71%, dr)
	34	A 5d × 2[h]		35[17] (92%, dr)


9[2b] (30%)[d]


22* (73%)

a) General procedure: a solution of a carbonyl compound (1 eq) in a 4:4:2:3 mixture of 1,4-dioxane–THF–Et_3N–D_2O (~20 v/w) was kept for 3 days (unless otherwise stated) at room temperature (condition A), or refluxed for 4 days (condition B). After concentration, the residue was dried thoroughly (dr) (for the 1-OH sugars, pretreatment with H_2O was necessary), or recrystallized (re) from hexane–EtOAc, or subjected to chromatography (ch) on silica gel with 2:1 hexane–EtOAc. b) New compounds prepared are marked by * and characterized.[22] c) Initially obtained as a mixture of oxo and the hydrate forms, which was converted into the oxo form by drying for 8h at 80°C. d) Estimated[2b] after reduction with $NaBH_4$. e) Obtained by oxidation of the precursor[19] with oxalyl chloride–Me_2SO. f) The deuterated product obtained was treated with $NaBH_4$ (1.5 eq) for 1h in MeOH, CO_2 was introduced, and the crude product was chromatographed (2:1 hexane–EtOAc). g) Obtained by oxidation of methyl 3,5-di-*O*-benzyl-α- and -β-D-xylofuranosides[20] with oxalyl chloride–Me_2SO as syrups (88 and 94%, respectively). h) The procedure A 5d was repeated.

and -*arabino*-furanosides (**21**), and the β-D-anomer (**23**) gave the *arabino* compound (**24**). It is noteworthy that the BnO-3 group was inverted, possibly by steric repulsion between the BnO-3 and $BnOCH_2$-5 groups. 1,2;5,6-Di-*O*-isopropylidene 3-oxo compound[13] (**25**), however, did not give the expected 4-deuterio compound, although Russel and Liu[7b] obtained it (>95% purity) by repetitive incubation of **25** in pyridine–D_2O (5 : 1) [incidentally, **7** showed insfficient and nonselective (at C-2 and 4) deuterated products in hot pyridine–D_2O]. Two protected free sugars (**26**[14] and **28**[15]) were also examined. In these cases, refluxing for 4 days was necessary to achieve deuteration. As D-ribofuranose, D-xylopyranose as well as D-glucose, D-mannose, and D-galactose gave no deuterated product under the refluxing, the hemiacetal structure of **26** and **28** would be slightly labile compared with hexoses and pentoses. Surprisingly, 2-deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) (**30**) gave the corresponding 2,2-dideuterio derivative (**31**) at room temperature.

Two straight-chain ketones were also examined. 2-Hexanone (**32**) gave the 1,1,1,3,3-pentadeuterio derivative[16] (**33**) and acetophenone (**34**) gave the 1,1,1-trideuterio derivative[17] (**35**).

The structures of the deuterated compounds were confirmed by mass and ^1H NMR spectra; the latter showed identical ^1H shift-values with those for nondeuterated compounds, respectively (see Note 22).

In summary, CH-hydrogens at the alpha position of a carbonyl group are exchanged readily and cleanly with deuterium under the conditions described in most cases. As methyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid)uronate was not deuterated, it is concluded that an oxo group is requisite for the exchange.

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21. T-L. Su, R.S. Klein, J.J. Fox, *J. Org. Chem.*, **1982**, *47*, 1506 – 1509.
22. **2**: mp 146–148°C, $[\alpha]_D^{22}$ +11° (*c* 1, $CHCl_3$), m/z [fab-ms(+) in NBA] 372.19 $(M+H)^+$, ^1H NMR (only important signals are shown in all compounds; all in $CDCl_3$): δ 3.46 (s, 3H, OMe), 3.81 (t, 1H, H-6), 3.86 (d, 1H, H-4), 4.19 (dt, 1H, H-5), 4.38 (dd, 1H, H-6'), 4.74 (s, 1H, H-1), 4.81 (ABq, 2H, *J* 12 Hz, C*H*$_2$Ph), 5.56 (s, 1H, C*H*Ph); $J_{4,5}$ 9.5, $J_{5,6} = J_{6,6'}$ 10.5, $J_{5,6'}$ 5 Hz [*cf* **1**: 3.87 (dd, 1H, $J_{3,4}$ 10, $J_{4,5}$ 9.5 Hz, H-4), 4.53 (d, 1H, $J_{3,4}$ 10 Hz, H-3)]. **4**: mp 179–180°C, $[\alpha]_D^{22}$ –76° (*c* 1, $CHCl_3$), m/z 371.98 $(M+H)^+$, ^1H NMR: δ 3.60 (s, 3H, OMe), 3.76 (dt, 1H, H-5), 3.86 (t, 1H, H-6), 3.94 (d, 1H, H-4), 4.45 (dd, 1H, H-6'), 4.77 (s, 1H, H-1); $J_{4,5}$ 9.0 $J_{5,6} = J_{6,6'}$ 10, $J_{5,6'}$ 4.5 Hz [*cf* **3**: 3.94 (dd, 1H, $J_{3,4}$ 10, $J_{4,5}$ 9.0 Hz, H-4), 4.23 (dd, 1H, $J_{1,3}$ 1, $J_{3,4}$ 10 Hz, H-3), 4.76 (d, 1H, $J_{1,3}$ 1 Hz, H-1)]. **6**: mp 137–138°C, $[\alpha]_D^{18}$ +49° (*c* 0.7, $CHCl_3$), ^1H NMR: δ 3.50 and 3.61 (each s of 3H, MeO-1,3), 3.79 (d, 1H, H-4), 3.81 (t, 1H, H-6), 4.22 (dt, 1H, H-5), 4.39 (dd, 1H, H-6'), 4.74 (s, 1H, H-1) [*cf* **5**: 3.42 and 3.50 (each s of 3H, MeO-1,3), 3.74 (t, 1H, H-6), 3.77 (dd, 1H, $J_{3,4}$ 2.5, $J_{4,5}$ 9.5 Hz, H-4), 4.02 (d, 1H, H-3), 4.46 (dd, 1H, H-6'), 4.56 (dt, 1H, H-5), 4.66 (s, 1H, H-1)]. **11**: mp 175–177°C, $[\alpha]_D^{22}$ –94° (*c* 1, $CHCl_3$), m/z 372.03 $(M+H)^+$, ^1H NMR: δ 3.59 (dt, 1H, H-5), 3.61 (s, 3H, OMe), 3.86 (t, 1H, H-6), 4.23 (d, 1H, H-4), 4.47 (dd, 1H, H-6'), 4.59 (s, 1H, H-1); $J_{4,5}$ 10, $J_{5,6} = J_{6,6'}$ 10.5, $J_{5,6'}$ 5.0 Hz [*cf* **10**: 3.98 (dd, 1H, $J_{1,2}$ 7.5, $J_{2,4}$ 1.5 Hz, H-2), 4.23 (dd, 1H, H-4)]. **13**: mp 169–171°C (needles), $[\alpha]_D^{23}$ +152° (*c* 1, EtOAc) [unlabeled[8], $[\alpha]_D^{22}$ +150° (EtOAc)], m/z 268.37 $(M+H)^+$, ^1H NMR: δ 3.38 (s, 3H, OMe), 3.92 (t, 1H, H-6), 4.15 (dd, 1H, H-5), 4.38 (dd, 1H, H-6'), 5.14 (s, 1H, H-1), 5.59 (s, 1H, CHPh); $J_{5,6} = J_{6,6'}$ 10, $J_{5,6'}$ 5 Hz [*cf* **12**: 2.68 (dd, 1H, $J_{1,2}$ 1, $J_{2,2'}$ 15 Hz, H-2), 2.83 (ddd, 1H, $J_{1,2'}$ 5, $J_{2',4}$ 1.2 Hz, H-2'), 4.15 (dt, 1H, $J_{4,5} = J_{5,6}$ 10, $J_{5,6'}$ 5 Hz, H-5), 4.31 (dd, 1H, H-4), 5.14 (sl br d, $J_{1,2'}$ 5 Hz, H-1), 5.59 (s, 1H, C*H*Ph]. **14**: mp 110–112°C, $[\alpha]_D^{18}$ +19° (*c* 1.7, $CHCl_3$), ^1H NMR: δ 4.46 (d, 1H, $J_{4,5}$ 1.5 Hz, H-4). **16**: syrup, $[\alpha]_D^{22}$ +27° (*c* 1, $CHCl_3$), m/z 463.24 $(M-H)^+$, 487.22 $(M+Na)^+$ (NBA+NaCl), ^1H NMR: δ 3.48 (s, 3H, OMe); 3.67 and 3.90 (each d of 1H forming ABq, $J_{6,6'}$ 11 Hz, H-6,6'), 3.79 (d, 1H, $J_{1,2}$ 3.5 Hz, H-2); 4.57, 4.75, and 4.81 (each ABq of 2H, *J* 12 Hz, C*H*$_2$Ph ×3), 4.80 (d, 1H, H-1) [*cf* **15**: 3.67 (dd, 1H, H-6), 3.80 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, H-2), 3.90 (dd, 1H, H-6'), 4.27 (dd, $J_{5,6}$ 6.0, $J_{5,6'}$ 3.5 Hz, H-5), 4.42 (d, 1H, H-3), 4.80 (d, 1H, H-1)]. **17**: syrup, $[\alpha]_D^{22}$ +2° (*c* 1, $CHCl_3$), m/z 354.15 $(M-H)^+$, 355.15 (M^+); 377.10, 378.10 $(M+Na)^+$ (+NaCl), ^1H NMR: δ 3.49 (s, 3H, OMe); 3.54 and 3.70 (each d of 1H, H-6,6'), 4.26 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.54 and 5.97 (each ABq of 2H, PhC*H*$_2$-3,6), 6.20 (d, 1H, $J_{1,2}$ 2.5 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ 59.06 (O*C*H$_3$), 71.30 (C-6), 71.80 (C-1) 73.69 and 82.41 (each Ph*C*H$_2$), 77.07 (t, $J_{C,D}$ 25 Hz, C-5), 123.69 (C-2), 154.85 (C-3), 198.16 (C=O). **19**: syrup, $[\alpha]_D^{23}$ +21° (*c* 1, $CHCl_3$) [unlabeled, +20° ($CHCl_3$)], m/z 464.03 $(M-H)^+$, 488.02 $(M+Na)^+$ (+NaCl), ^1H NMR: δ 1.63 (m, 1H, OH), 3.36 (s, 3H, OMe), 3.69 (dd, 1H, $J_{6,6'}$ 11, $J_{6,OH}$ 7 Hz, H-6), 3.76 (dd, 1H, $J_{6',OH}$ 5 Hz, H-6'), no peak corresponding to H-5 was observed. **20** and **23**: used without purification. **21**: syrup, $[\alpha]_D^{22}$ +78° (*c* 1, $CHCl_3$), m/z 346.18 $(M+H)^+$, ^1H NMR: δ 3.33 (s, 3H, OMe), 3.61 (dd, 1H, $J_{4,5}$ 2.5, $J_{5,5'}$ 10.5 Hz, H-5), 3.66 (dd, 1H, $J_{4,5'}$ 3.2 Hz, H-5'), 4.04 and 4.31 (each d of 1H, *J* 10 Hz, H-2,OH), 4.29 (sl br t, 1H, H-4), 4.85 (s, 1H, H-1). **22**: syrup, $[\alpha]_D^{23}$ +65° (*c* 1, $CHCl_3$) [unlabeled[21] $[\alpha]_D^{23}$ +67° ($CHCl_3$)], m/z 344.18 $(M-H)^+$, 368.14 $(M+Na)^+$ (+NaCl), ^1H NMR: δ 2.95 (d, 1H, $J_{2,OH}$ 11 Hz, OH), 3.36 and 3.43 (each dd of 1H, $J_{4,5} = J_{4,5'}$ 4, $J_{5,5'}$ 10.5 Hz, H-5,5'), 3.47 (s, 3H, OMe), 4.12 (dd, 1H, $J_{1,2}$ 4.5, $J_{2,OH}$ 11 Hz, H-2), 4.15 (t, 1H, H-4), 4.89 (d, 1H, H-1). **24**: syrup, $[\alpha]_D^{21}$ –43° (*c* 2, $CHCl_3$), m/z 344.16 $(M-H)^+$, 368.12 $(M+Na)^+$ (+NaCl), ^1H NMR: δ 2.57 (d, 1H, OH), 3.41 (s, 3H, OMe), 3.53 (d, 2H, $J_{4,5} = J_{4,5'}$ 5.5 Hz, H-5,5'), 4.03 (t, 1H, H-4), 4.25 (dd, 1H, $J_{1,2}$ 5, $J_{2,OH}$ 10 Hz, H-2), 4.86 (d, 1H, H-1). **27**: mp 65–67°C (**26**: 66–67°C), $[\alpha]_D^{23}$ –26° (*c* 1, $CHCl_3$)] [**26**: –27.4° ($CHCl_3$)], m/z 260.14 $(M-H)^+$, 284.15 $(M+Na)^+$ (+NaCl), ^1H NMR: δ (β-isomer was only shown: δ 1.33, 1.36 and 1.48 (each s of 3, 3 and 6H, Me_2C ×2), 3.86 (dd, 1H, H-6), 4.16 (dd, 1H, H-6'), 4.19 (dd, 1H, $J_{3,4}$ <1, $J_{4,5}$ 4 Hz, H-4), 4.31 (ddd, 1H, H-5), 4.79 (sl br s, 1H, H-3), 5.33 (s, 1H, H-1) [*cf* **26**: 4.56 (dd, 1H, $J_{2,3}$ 6 Hz, H-2), 4.79 (sl br d, 1H, H-3)]. **29**: mp 121–122°C (**28**: 122–123°C), m/z 260.20 $(M+H)^+$, ^1H NMR (α-anomer was only shown): δ 1.33, 1.38, 1.46, and 1.47 (each s of 3H, Me_2C ×2), 4.05 (dd, 1H, H-6), 4.08 (dd, 1H, H-6'), 4.19 (dd, 1H, $J_{3,4}$ 3.5, $J_{4,5}$ 7 Hz, H-4), 4.40 (m, 1H, H-5), 4.81 (d, 1H, H-3), 5.38 (s, 1H, H-1) [*cf* **28**: 4.62 (d, 1H, $J_{1,2}$ 6 Hz, H-2), 4.81 (dd, 1H, H-3)]. **31**: ^1H NMR (D_2O): all δ-values were identical with those for **30**, and the peaks for H-2,2' (δ 1.65–2.05) were missing; 3.40 and 4.10 [each sl br d (by small $J_{H,D}$) of $J_{3,4}$ 3.5 Hz, 1H in total, H-3], 4.78 and 5.28 (each s, 1H in total, H-1). **33**: ^1H NMR: δ 0.91 (t, 3H, Me-6), 2.10 (quintet, 0.11H, $J_{H,D}$ 2 Hz, C*H*D$_2$-1), 2.40 (tt, 0.19H, $J_{H,D}$ 2, $J_{3,4}$ 7 Hz, CH$_2$C*H*DCO). **35**: ^1H NMR: δ 2.57 (quintet, 0.28H, CHD$_2$-1).