

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–Et₃N–D₂O.

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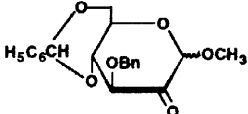
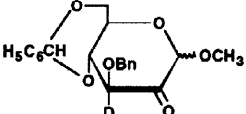
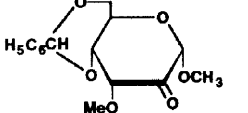
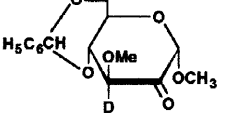
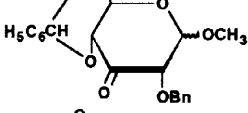
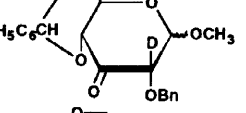
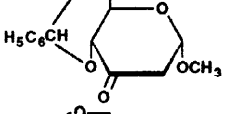
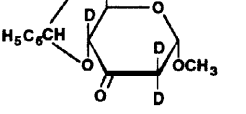
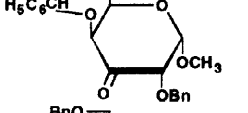
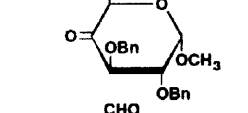
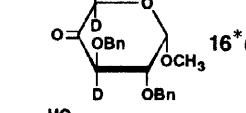
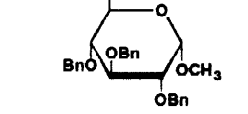
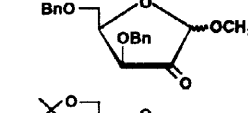
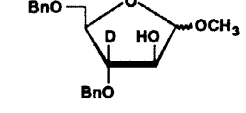
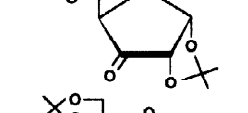
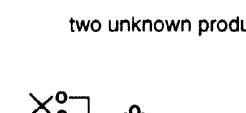
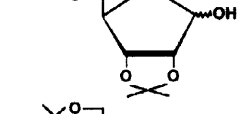
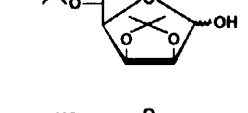
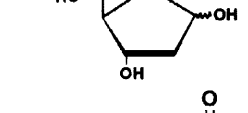
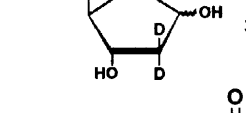
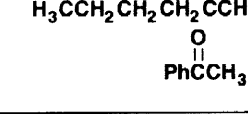
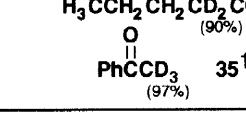
In the study of mechanism¹ of chemical² and biochemical¹ transformations, partially deuterated carbohydrates¹⁻⁶ have been widely used in combination with NMR spectroscopy.³ These compounds also play an important role in conformational analysis of oligo⁴ and polysaccharides as well as nucleoside(tide)s⁶ 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 D₂O), 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–Et₃N–D₂O (in this solvent, all compounds described later dissolved readily), gave the corresponding [2-²H] derivative (8) together with the [2-²H]-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 compound⁸ (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 (1⁹ and 3¹⁰) afforded the [3-²H] compounds (2 and 4) in high yields without contamination of the [1-²H] or 3-epimerized compounds. In the case of 3-*O*-methyl-2-oxo-D-ribo compound¹¹ (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 compound¹² 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 NaBH₄ gave the corresponding [3-²H]-*ribo*- (22, major)

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 ⁸	A 5d	 13* (75%, ch)
 14* ^e (82%, dr)	A 5d	a mixture of unknown products
 15 ^{2a}	A 6d	 16* (79%, ch)
 17* (19%, 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%)
 22* (73%)		
 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)

a) General procedure: a solution of a carbonyl compound (1 eq) in a 4:4:2:3 mixture of 1,4-dioxane–THF–Et₃N–D₂O (~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 H₂O 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 NaBH₄. e) Obtained by oxidation of the precursor¹⁹ with oxalyl chloride–Me₂SO. f) The deuterated product obtained was treated with NaBH₄ (1.5 eq) for 1h in MeOH, CO₂ 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-xylofuranosides²⁰ with oxalyl chloride–Me₂SO 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 BnOCH₂-5 groups. 1,2;5,6-Di-*O*-isopropylidene 3-oxo compound¹³ (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–D₂O (5 : 1) [incidentally, 7 showed insufficient and nonselective (at C-2 and 4) deuterated products in hot pyridine–D₂O]. Two protected free sugars (26¹⁴ and 28¹⁵) 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 derivative¹⁶ (33) and acetophenone (34) gave the 1,1,1-trideuterio derivative¹⁷ (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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22. **2**: mp 146–148°C, $[\alpha]_D^{22} +11^\circ$ (c 1, CHCl₃), m/z [fab-ms(+) in NBA] 372.19 (M+H)⁺, ¹H NMR (only important signals are shown in all compounds; all in CDCl₃): 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, CH₂Ph), 5.56 (s, 1H, CHPh); *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, $[\alpha]_D^{22} -76^\circ$ (c 1, CHCl₃), 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, $[\alpha]_D^{18} +49^\circ$ (c 0.7, CHCl₃), 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, $[\alpha]_D^{22} -94^\circ$ (c 1, CHCl₃), 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), $[\alpha]_D^{23} +152^\circ$ (c 1, EtOAc) [unlabeled⁸, $[\alpha]_D^{22} +150^\circ$ (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, CHPh)]. **14**: mp 110–112°C, $[\alpha]_D^{18} +19^\circ$ (c 1.7, CHCl₃), ¹H NMR: δ 4.46 (d, 1H, *J*_{4,5} 1.5 Hz, H-4). **16**: syrup, $[\alpha]_D^{22} +27^\circ$ (c 1, CHCl₃), 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, CH₂Ph ×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, $[\alpha]_D^{22} +2^\circ$ (c 1, CHCl₃), 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, PhCH₂-3,6), 6.20 (d, 1H, *J*_{1,2} 2.5 Hz, H-2). ¹³C NMR (CDCl₃): δ 59.06 (OCH₃), 71.30 (C-6), 71.80 (C-1) 73.69 and 82.41 (each PhCH₂), 77.07 (t, *J*_{C,D} 25 Hz, C-5), 123.69 (C-2), 154.85 (C-3), 198.16 (C=O). **19**: syrup, $[\alpha]_D^{23} +21^\circ$ (c 1, CHCl₃) [unlabeled, $+20^\circ$ (CHCl₃)], 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, $[\alpha]_D^{22} +78^\circ$ (c 1, CHCl₃), 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, $[\alpha]_D^{23} +65^\circ$ (c 1, CHCl₃) [unlabeled²¹, $[\alpha]_D^{23} +67^\circ$ (CHCl₃)], 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, $[\alpha]_D^{21} -43^\circ$ (c 2, CHCl₃), 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), $[\alpha]_D^{23} -26^\circ$ (c 1, CHCl₃) [**26**: -27.4° (CHCl₃)], 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, Me₂C ×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, Me₂C ×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 (D₂O): 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, CHD₂-1), 2.40 (tt, 0.19H, *J*_{H,D} 2, *J*_{3,4} 7 Hz, CH₂CHDCO). **35**: ¹H NMR: δ 2.57 (quintet, 0.28H, CHD₂-1).