Tetrahedron Letters 50 (2009) 3559–3563

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A concise approach to the synthesis of all twelve 5-deoxyhexoses: D-tagatose-3-epimerase—a reagent that is both specific and general

Devendar Rao [a], Daniel Best [b], Akihide Yoshihara [a], Pushpakiran Gullapalli [a], Kenji Morimoto [a], Mark R. Wormald [c], Francis X. Wilson [d], Ken Izumori [a,*], George W. J. Fleet [b,*]

[a] Rare Sugar Research Center, Faculty of Agriculture, Kagawa University, 2393 Ikenobe, Mik-choi, Kita-gun, Kagawa 761-0795, Japan
[b] Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
[c] Glycobiology Institute, Department of Biochemistry, Oxford University, South Parks Road, Oxford OX1 3QU, UK
[d] Summit PLC, 91, Milton Park, Abingdon, Oxon OX14 4RY, UK

ARTICLE INFO

Article history:
Received 13 January 2009
Revised 15 February 2009
Accepted 6 March 2009
Available online 14 March 2009

ABSTRACT

2-Deoxy-D-glucitol and 2-deoxy-D-allitol, both prepared as crystalline polyols from D-erythronolactone, are oxidized by *Gluconobacter thailandicus* NBRC 3254 to 5-deoxy-D-*threo*-hexulose [5-deoxy-D-fructose = 5-deoxy-L-sorbose] and 5-deoxy-D-*erythro*-hexulose [5-deoxy-L-psicose = 5-deoxy-D-tagatose], respectively. D-Tagatose-3-epimerase (DTE) equilibrates 5-deoxy-D-fructose to 5-deoxy-D-psicose and 5-deoxy-L-psicose to 5-deoxy-L-fructose, providing substrates for the preparation of all eight D- and L-5-deoxy aldohexoses by aldose isomerases. This combination of chemical and biotechnological methods allows a concise approach to the synthesis of all twelve 5-deoxy hexoses and further demonstrates the range of deoxy sugar substrates on which DTE is active. NMR studies show that 5-deoxy-D-fructose exists solely as the β-pyranose form whereas both pyranoses of 5-deoxy-D-fructose [α:β. 22:78] are observed. [For the sake of clarity, all ketoses in this Letter are shown in blue, alditols in red and aldoses in purple]

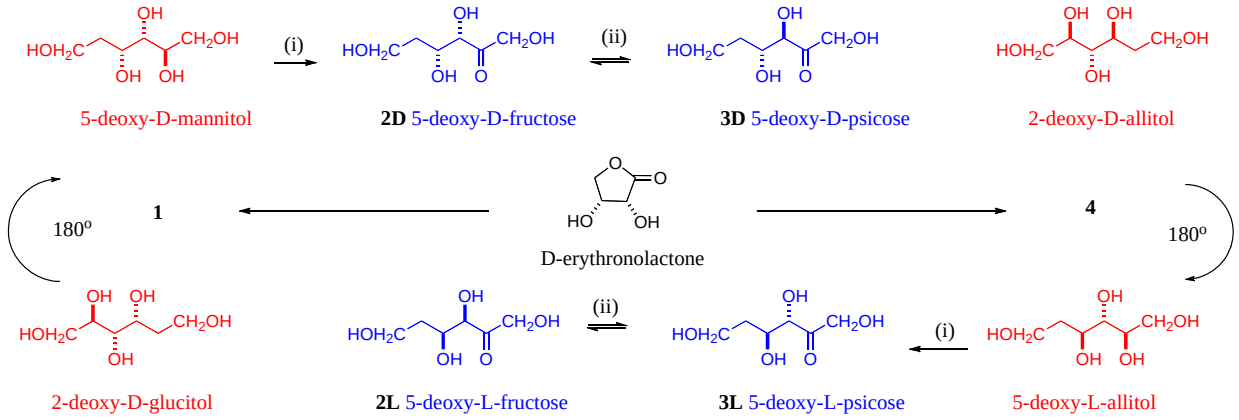
Carbohydrates are involved in a wide variety of biological processes at a cellular level.[1] Because rare and synthetic monosaccharides [including deoxysugars] possess considerable chemotherapeutic potential,[2] there is considerable effort directed towards the chemical synthesis of mostly protected derivatives.[3] An alternative more environmentally friendly approach is by the application of enzymes to organic synthesis[4] including directed evolution and the discovery of new enzymes.[5] In particular, the concept of Izumoring[6] allows the preparation, in significant quantities, of all 24 hexoses via isomerization reactions from common to rare sugars with no need for any protection; this depends on a range of microorganisms which interconvert polyols and ketoses,[7] aldose isomerases which equilibrate ketoses and aldoses, and D-tagatose-3-epimerase (DTE) which equilibrates C-3 in each of the four pairs of ketoses.[8] DTE is a highly promiscuous enzyme which accepts a very wide range of substrates, including C-branched sugars. For example, DTE equilibrates both enantiomers of 4-*C*-methyl ribulose with both enantiomers of 4-*C*-methyl xylulose,[9] and also isomerizes 5-*C*-methyl ketoses to their C-3 epimers.[10] The isomerization of L-rhamnose to 1-deoxy-L-fructose[11] and of fucose to deoxytagatose[12] indicates the technology may be extended to deoxy sugars.

This Letter shows that 5-deoxyketohexoses **2** and **3** are substrates for DTE (Scheme 1). 2-Deoxy-D-glucitol **1** and 2-deoxy-D-allitol **4** are specifically oxidized by *Gluconobacter thailandicus NBRC* 3254 at C-5 to form 5-deoxy-D-fructose **2D** and 5-deoxy-L-psicose **3L**; DTE equilibrates **3L** with **2L**, and **2D** with **3D—** allowing the easy formation of all the 5-deoxy-hexuloses. Both the deoxy alditols **1** and **4** may be synthesized from D-erythronolactone.

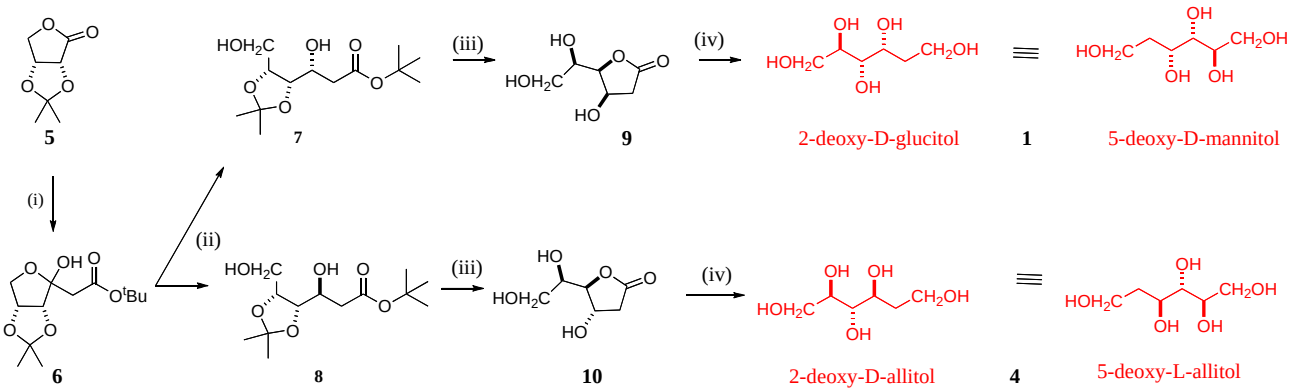
The acetonide of D-erythronolactone **5** is readily available from the oxygenation of an alkaline solution of D-arabinose[13] or by hydrogen peroxide oxidation of erythrobic acid,[14] followed by acetonation (Scheme 2). Although samarium diodide-[15] and cobalt-mediated[16] Reformatsky reactions on aldonolactones have been reported, addition of lithium *tert*-butyl acetate [generated by treatment of *tert*-butyl acetate with LDA in THF at −78 °C] to the acetonide **5** afforded the lactol **6**, mp 23–25 °C, $[\alpha]_D^{18}$ −63.7 (*c* 0.91, $CHCl_3$) in an excellent yield of 90% on a multi-gram scale. Reduction of **6** by sodium borohydride in methanol gave unselective reduction in a combined yield of 97% to afford the epimeric deoxy *glucono*- **7** (51%) and *allono*- **8** (46%) esters. The hydroxyesters **7** and **8** were separable by chromatography; the relative configuration of the gluconic ester **7** was unequivocally established by X-ray crystallographic analysis.[17] Treatment of the deoxy allono-*tert*-butyl ester **8** with trifluoroacetic acid facilitated deprotection of both the *tert*-butyl ester and isopropylidene protecting groups and subsequent cyclization to the crystalline deoxy *allono*-lactone **10** mp 66–68 °C, $[\alpha]_D^{25}$ −38.1 (*c*, 1.49 EtOH) [lit.[18]

* Corresponding authors.
E-mail addresses: izumori@ag.kagawau.ac.jp (K. Izumori), george.fleet@chem.ox.ac.uk (G.W.J. Fleet).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.061



Scheme 1. (i) *Gluconobacter thailandicus NBRC* 3254 (ii) D-tagatose-3-epimerase (DTE).

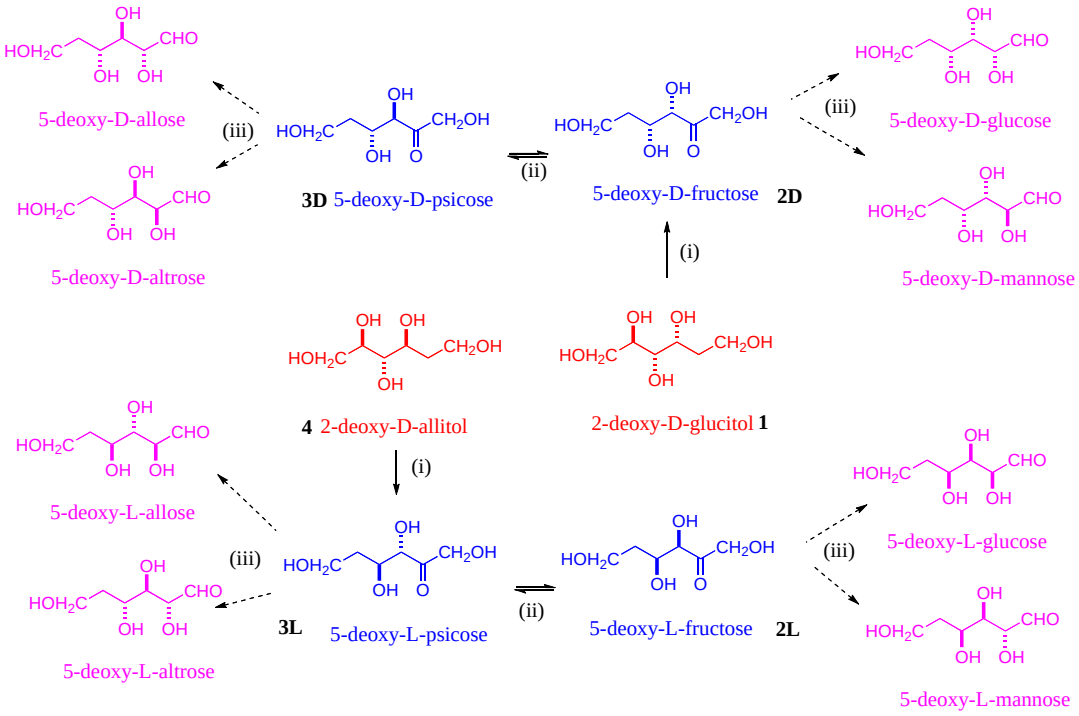


Scheme 2. Reagent and conditions: (i) $MeCO_2{}^tBu$, LDA, −78 °C, 90%; (ii) $NaBH_4$, MeOH; (iii) CF_3CO_2H, H_2O, dioxane, 1:6:3; (iv) $NaBH_4$, *tert*-BuOH, MeOH.

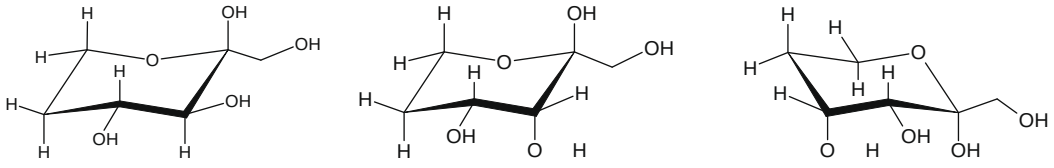
71–73 °C, $[\alpha]_D$ −42 (EtOH)] in quantitative yield. Reduction of the lactone **10** in *tert*-butanol by sodium borohydride with addition of methanol gave 2-deoxy-D-allitol **4**[19] in 78% yield; the mixed solvent-sodium borohydride method gave much cleaner products in higher yields than other hydride reductions.[20] Similarly, treatment of **7** with trifluoroacetic acid gave the deoxy gluconolactone **9**, mp 92–94 °C, $[\alpha]_D^{25}$ +70.4 (*c* 0.49, H_2O) [lit.[21] 95–96 °C, $[\alpha]_D^{25}$ +73 (*c*, 0.5 H_2O)], which was then reduced to give the deoxy glucitol **1** in 70% yield.[22]

Gluconobacter strains attack polyols and sugar alcohols according to the Bertrand and Hudson rule[23] which states that polyols with a *syn*-arrangement of two secondary hydroxyl groups in D-configuration to the adjacent primary alcohol group (D-*erythro* configuration) are oxidized regioselectively to the corresponding ketoses. The size and structure of the remaining part of the polyol molecule have little or no effect on the oxidation capability of Gluconobacter. Thus, polyols with different carbon chain lengths ranging from glycerol to heptitols and octitols, and chemically modified pentitols and hexitols are oxidized to the corresponding ketoses. *G. thailandicus* NBRC 3254 oxidizes D-glucitol at C-2 and C-5 to give D-fructose and L-sorbose, respectively; the efficient synthesis of 4-*C*-methyl ketopentoses and 5-*C*-methyl ketohexoses from the corresponding alditols has been described.[9,10] Under similar conditions [Scheme 3], 2-deoxy-D-glucitol **1** (10 g) [related to 5-deoxy-D-mannitol by a 180° rotation] was oxidized by *G. thailandicus* NBRC 3254 to afford crystalline 5-deoxy-D-fructose **2D** (8 g, 80%), mp 101–103 °C, $[\alpha]_D^{20}$ −58.3 (*c* 1.0, H_2O) [lit.[24] mp 109–111 °C, $[\alpha]_D^{20}$ −67.3 (*c* 0.7, H_2O)]. *G. thailandicus* NBRC 3254 also oxidizes allitol to L-psicose with no oxidation to the enantiomer D-psicose;[25] likewise, 2-deoxy-D-allitol **4** [equivalent to 5-deoxy-L-allitol] gave pure 5-deoxy-L-psicose **3L** (80%), as an oil, $[\alpha]_D^{20}$ +19.2 (*c* 1.0, H_2O). The oxidation of 2-deoxy-D-glucitol **1** to 5-deoxy-D-fructose **2D** by *Gluconobacter oxydans* has been previously reported.[24]

DTE epimerizes the C-3 position of many ketoses and, in particular, equilibrates D-fructose with D-psicose and L-fructose with L-psicose.[26] Equilibration of 5-deoxy-D-fructose **2D** to 5-deoxy-D-psicose **3D** was carried out under similar conditions. A solution of 5-deoxy-D-fructose **2D** (final concentration: 10% w/v) and manganese(II) chloride (final concentration: 1 mM) in 30 mL of 50 mM Tris–HCl buffer (pH 7.5), was shaken at 42 °C in a 100 mL Erlenmeyer flask containing 2 g of immobilized DTE (200 U) prepared as described previously.[6c,26] Ketoses **2D** and **3D** reached an equilibrium state after 8 h with a ratio of 80% substrate and 20% product. The accumulation of product was analyzed by HPLC. The reaction mixture was concentrated and applied to a column of Dowex 50W-X2 (Ca^{2+} form). The column was eluted with deionized water and 3 mL fractions were collected. The fractions containing only 5-deoxy-D-psicose **3D** were pooled and concentrated under vacuum at 39 °C to give pure 5-deoxy-D-psicose (0.45 g, 15%), as an oil, $[\alpha]_D^{20}$ −18.5 (*c* 1.0, H_2O). The epimerization of 5-deoxy-L-psciose **3L** with 5-deoxy-L-fructose **2L** was carried out under similar conditions to attain an equilibrium state after 6 h with ratios of 20% substrate **3L** and 80% product **2L**. Pure 5-deoxy-L-fructose (0.2 g, 50%), was isolated as an oil, $[\alpha]_D^{20}$ +59.5 (*c* 1.0, H_2O). Thus DTE is active on all the 5-deoxyketohexoses. The purity of the deoxyketoses was established by HPLC.



Scheme 3. (i) *G. thailandicus* NBRC 3254, H_2O; (ii) DTE, H_2O, ratio of 68:32; (iii) aldose isomerases.



2Dβ 5-deoxy-β-D-fructopyranose

3Dβ 5-deoxy-β-D-psicopyranose

3Dα 5-deoxy-α-D-psicopyranose

Figure 1. Pyranose forms of 5-deoxy-D-fructose **2** and of 5-deoxy-D-psicose **3**.

The solution structures of both **2** and **3** were established by NMR analysis (Fig. 1). The ^{13}C and ^{1}H chemical shifts and $^{2/3}J_{HH}$ coupling constants, and the proportions of each form, for **2D** and **3D** are given in Tables 1–3. The 1D ^{1}H NMR spectra are shown in Figure 2.

For 5-deoxy-D-fructose **2D**, there is only one major spin-system observed at ~90% (Fig. 1). The large and small $^{3}J_{HH}$ couplings observed for H6/H6′ are only consistent with a pyranose ring structure of fixed geometry. From the large $^{3}J_{HH}$ couplings, H3, H4, H5′ and H6 are all axial, hence H5 and H6′ are both equatorial. This confirms the relative stereochemistry at C3 and C4 and is consistent with the $^{2}C_5$ ring conformation of 5-deoxy-D-fructose. From 500 ms NOESY, there is no evidence of NOEs from H1/H1′ to any other protons, although the severe overlap between H1 and H6′ makes this difficult to assess. From the absence of NOEs from H1, it is most likely to be the β-anomer **2Dβ**. This is fully consistent with the previous NMR studies of **2D**.[27]

For 5-deoxy-D-psicose **3D**, there are two components, with relative intensities 0.78:0.22. There are several other minor components at less than 4%. The two major components are consistent with the two pyranose anomers of 5-deoxy-psicose. In the major isomer, the large $^{3}J_{HH}$ couplings indicate that H4, H5 and H6 are all axial, whilst H3, H5′ and H6′ must be equatorial. This is in agreement with the $^{2}C_5$ ring conformation of 5-deoxy-D-psicose. In the minor isomer, both H5 and H6 must be axial, with H4, H5′ and H6′ being equatorial. There is a very weak H3/H5 NOE at 300 ms mixing time, which suggests that H3 is also axial. This is consistent with the $^{5}C_2$ ring conformation of 5-deoxy-D-psicose. There are no significant NOEs from either H1/H1′ for either anomer, suggesting that C1 is equatorial in both, that is, the major isomer is β and the minor isomer is α.

In summary, this Letter describes efficient syntheses of both the deoxy alditols **1** and **4** from D-erythronolactone. Although the isomerization of the ketoses to all the corresponding aldoses [in purple in Scheme 3] by aldose isomerases has yet to be confirmed, this work indicates that the technique of Izumoring may be applied to provide deoxy hexoses in amounts sufficient for exploitation of

Table 1
^{13}C chemical shifts of 5-deoxy-D-ketoses (referenced to acetone at 30.90 ppm)

	%age	^{13}C chemical shift (ppm)					
		C1	C2	C3	C4	C5	C6
5-Deoxy-D-fructose **2D**							
β-Pyranose	100	64.39	98.83	72.93	68.97	33.45	59.39
5-Deoxy-D-psicose **3D**							
α-Pyranose	22	63.97	99.11	67.09	68.70	31.34	55.92
β-Pyranose	78	65.05	98.83	68.89	66.11	27.80	59.82

%ages were estimated from peak area in the ^{1}H 1D spectrum.

Table 2
^{1}H chemical shifts of 5-deoxy-D-ketoses (referenced to acetone at 2.220 ppm)

	%age	^{1}H chemical shift (ppm)							
		H1	H1′	H3	H4	H5	H5′	H6	H6′
5-Deoxy-D-fructose **2D**									
β-Pyranose	100	3.698	3.481	3.436	*3.903*	1.976	1.646	*3.886*	*3.705*
5-Deoxy-D-psicose **3D**									
α-Pyranose	22	3.689	3.412	*3.703*	4.200	1.949	*1.849*	4.066	3.639
β-Pyranose	78	3.705	3.485	*3.760*	4.102	1.840	1.676	3.905	*3.741*

%ages were estimated from peak area in the ^{1}H 1D spectrum. Values in *italics* were determined from simulation of the 1D ^{1}H spectrum and traces through the gHSCQ spectrum.

Table 3
Two and three-bond J_{HH} values of 5-deoxy-D-ketoses

	%age	J_{HH} (Hz)									
		H1–H1′	H3–H4	H4–H5	H4–H5′	H5–H5′	H5–H6	H5–H6′	H5′–H6	H5′–H6′	H6–H6′
5-Deoxy-D-fructose **2D**											
β-Pyranose	100	−11.7	9.7	5.2	*11.5*	−13.2	*2.0*	*2.0*	*13.0*	5.3	*−12.0*
5-Deoxy-D-psicose **3D**											
α-Pyranose	22	−11.8	3.2	3.1	3.2	−13.2	12.1	5.8	2.7	2.1	−12.2
β-Pyranose	78	−11.8	3.2	11.9	4.7	−13.0	11.9	5.3	2.7	*1.5*	−12.7

%ages were estimated from peak area in the ^{1}H 1D spectrum. Values *in italics* determined from simulation of the 1D ^{1}H spectrum and traces through the gHSCQ spectrum.

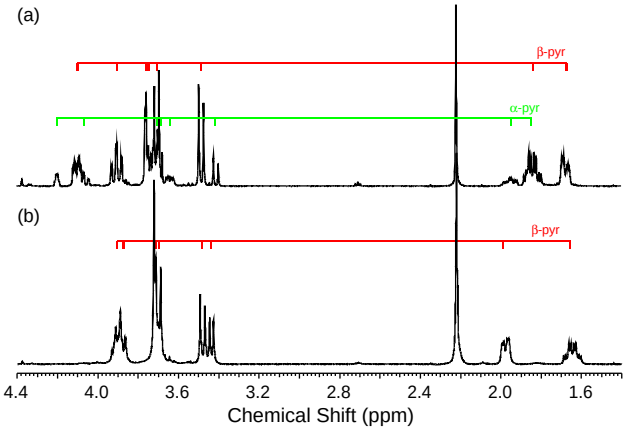


Figure 2. 1D ^{1}H NMR spectra of (a) 5-deoxy-D-psicose **3D** and (b) 5-deoxy-D-fructose **2D**, showing the spin-systems for the pyranose forms.

their biological and chemical properties; the isomerization of some 5-deoxyaldoses with glucose isomerase has been reported.[28] This Letter further illustrates the synergistic potential of the combination of chemistry with biotechnology in providing access to novel monosaccharides and rare sugars with a minimum use of protecting groups, and further extends the range of substrates recognized by DTE.

Acknowledgements

This work was supported in part by the Program for Promotion of Basic Research Activities for Innovative Biosciences (PROBRAIN) and by Summit PLC.

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19. Selected data for 2-deoxy-D-allitol **4**: mp 82–84 °C [lit.[29] 84–85 °C]; $[\alpha]_D^{25}$ −17.8 (*c* 1.62, MeOH) [lit.[29] $[\alpha]_D^{26}$ −20.4 (*c* 1.6, MeOH)]; δ_H (CD_3OD, 400 MHz): 1.69 (1H, ddt, H2a, J_{gem} 14.1, $J_{2a,1}$ 5.6, $J_{2a,3}$ 9.3), 1.91 (1H, ddt, H2b, J_{gem} 14.1, $J_{2b,1}$ 7.0, $J_{2b,3}$ 2.8), 3.50 (1H, dd, H4, $J_{4,3}$ 5.8, $J_{4,5}$ 6.8), 3.59-3.80 (5H, m, H1, H5, H6), 3.87 (1H, ddd, H3, $J_{3,2a}$ 9.3, $J_{3,2b}$ 2.8, $J_{3,4}$ 5.8). δ_C (CD_3OD, 100 MHz): 35.6 (C2), 60.2 (C1), 64.7 (C6), 71.4 (C3), 74.2 (C5), 76.0 (C4).
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22. Selected data for 2-deoxy-D-glucitol **1**: mp 100–102 °C [lit.[30] 103.5–105 °C]; $[\alpha]_D^{25}$ +17.2 (*c* 1.02, H_2O) [lit.[30] $[\alpha]_D^{20}$ +17.5 (*c* 1, H_2O)]; δ_H (CD_3OD, 400 MHz): 1.64–1.72 (1H, m, H2a), 1.78–1.86 (1H, m, H2b), 3.32 (1H, dd, H4, $J_{4,3}$ 1.8, $J_{4,5}$ 8.1), 3.58 (1H, dd, H6a, J_{gem} 11.0, $J_{6a,5}$ 5.9), 3.63–3.78 (3H, m, H1, H5), 3.76 (1H, dd, H6b, J_{gem} 11.0, $J_{6b,5}$ 3.4), 3.99 (1H, ddd, H3, $J_{3,2}$ 9.1, 6.1, $J_{3,4}$ 1.8). δ_C (CD_3OD, 100 MHz): 36.5 (C2), 59.2 (C1), 64.1 (C6), 67.8 (C3), 72.1 (C5), 73.8 (C4).
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