

¹H Nuclear Magnetic Resonance Spectra and Conformations of Six Heptitols in Deuterium Oxide

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The ¹H n.m.r. spectra of six heptitols in deuterium oxide have been recorded at 400 MHz, and the shifts and coupling constants obtained by computer simulation. The shifts and ³J coupling constants were used to derive conformational data which support previous results on the heptitols.

The solution conformations of unsubstituted acyclic polyols have been interpreted using ¹H^{1,2} and ¹³C³⁻⁵ n.m.r. spectra, but there appears to be no report on the ¹H n.m.r. spectra of the heptitols, except for the partial analysis⁶ of one compound. ¹H N.m.r. spectra of alditols with free hydroxy groups are usually uninformative, but at higher fields, the spectra, though still very complex, can be analysed. This work reports on the ¹H n.m.r. spectra of six heptitols in deuterium oxide, and compares the conformational data derived with an earlier theoretical assessment⁷ and with ¹³C n.m.r. results⁵ on their likely main conformations.

Results and Discussion

Spectral Data.—The computer programs¹ for simulating the spectra are limited to seven spins, so each heptitol was analysed in two portions. The spectrum of *meso-glycero-gulo*-heptitol (5) was solved using information from its [1,1-²H₂] analogue. As previously noted¹ for the lower alditols, for each hydroxymethyl group, the proton (H') with the larger ³J value was at lower δ, and in no spectrum was a ⁴J value needed. Tables 1 and 2 list the proton chemical shifts and proton-proton coupling constants of the heptitols.

Conformational Data.—The ³J data (Table 2) were used as previously¹ to yield the conformational data in Table 3. *D-glycero-D-galacto*-Heptitol (perseitol) (1) has an essentially

planar carbon chain. In *D-glycero-D-manno*-heptitol (volemitol) (2), the C-1—C-6 part of the chain is almost as planar as that in mannitol, while the *ribo*-unit is fractionally more twisted (66%) to give O-6 extending the chain more than O-5 does in altritol¹ (63%). Possible conformers for *D-glycero-L-galacto*-heptitol (3) have (a) the C-5—C-6 bond twisted giving C-1—O-6 planar (3a), (b) the planar chain form, and (c) the C-3—C-4 and C-4—C-5 bonds twisted giving C-1—4-H and O-4—C-7 planar. Using the ³J values for 3-H—4-H, 4-H—5-H, and 5-H—6-H gives (a), 64; (b), 30 and (c), 5%. The sum (99%) was used as a check on the answer. Conformers (b) and (c) both contain a 1,3-parallel oxygen-oxygen (O//O) interaction, and the relative amounts of (b) and (c) show how unfavourable it is for a chain with this configuration to twist doubly. The *xylo*-unit is slightly more twisted, giving conformer (a), than the corresponding conformer in glucitol (Table 4). The C-1—C-6 part of the chain is of comparable planarity to that in galactitol. Since heptitols (2) and (3) only need to twist the chain once, at C-5—C-6, to relieve the O-4//O-6 interaction, it is likely that the *ribo*-unit in (2) and the *xylo*-unit in (3) display, in conformational terms, the maximum twisting of a hydroxymethyl group adjacent to an acyclic *ribo*- and *xylo*-unit respectively. *D-glycero-D-gluco*-Heptitol (β-sedoheptitol) (4) can be considered as composed of a *xylo*- and a *ribo*-unit. The *T_θ* component of the *xylo*-unit is comparable to that in glucitol, while the *ribo*-unit is conformationally identical to that in altritol. For (4) the four most likely conformers have (a) the doubly twisted chain with

Table 1. Proton chemical shifts^a (δ) of heptitols in D₂O

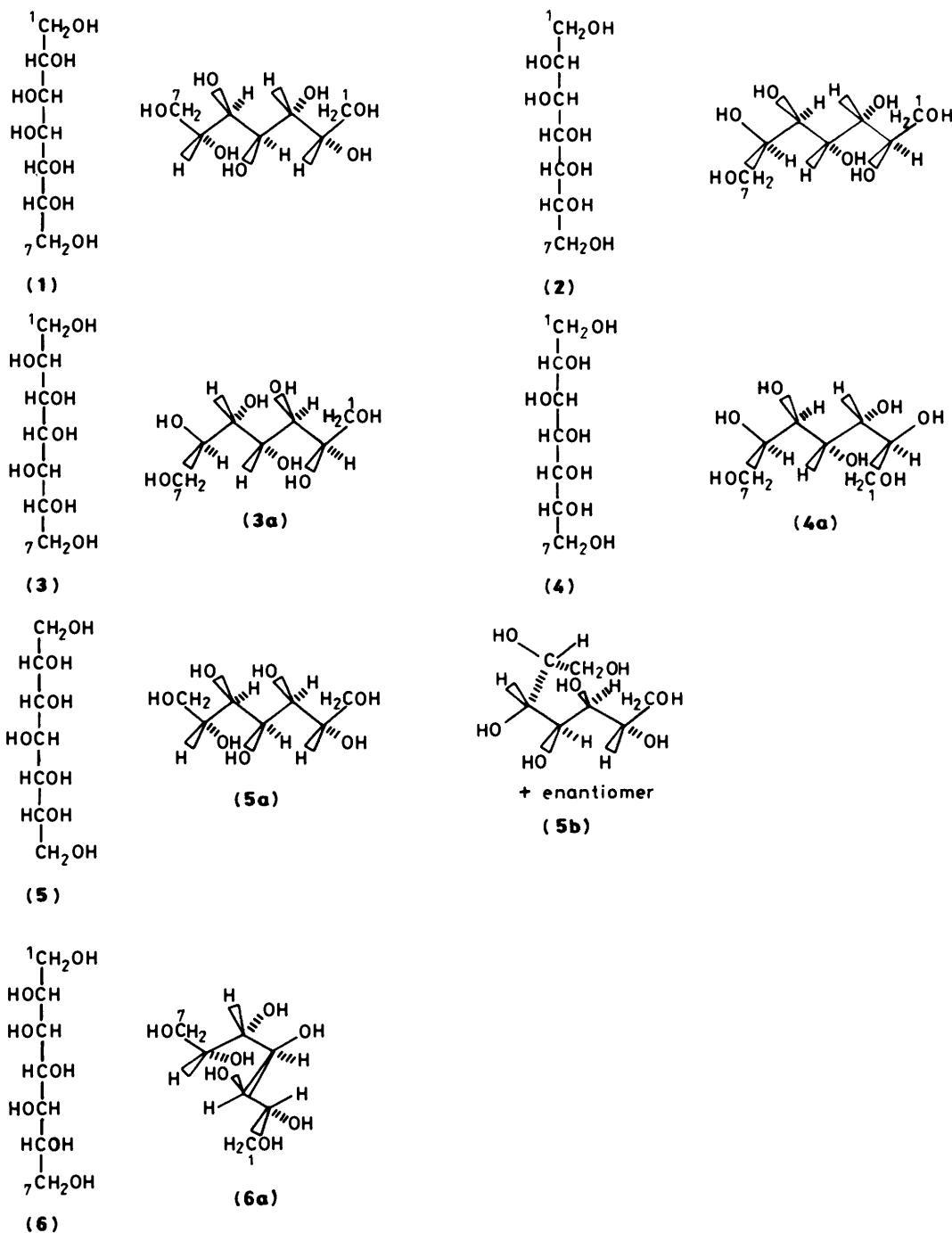
Heptitol		1-H	1'-H ^b	2-H	3-H	4-H	5-H	6-H	7-H	7'-H ^b
<i>D-glycero-D-galacto</i> -	(1)	3.69	3.69	3.98 _s	3.67	3.92	3.81	3.77	3.87	3.67
<i>D-glycero-D-manno</i> -	(2)	3.85	3.66	3.74	3.78	3.89	3.80	3.94	3.81	3.68
<i>D-glycero-L-galacto</i> -	(3)	3.67 _s	3.67	3.95	3.68	3.73	3.86	3.84 _s	3.74	3.62
<i>D-glycero-D-gluco</i> -	(4)	3.75	3.63	3.85 _s	3.87 _s	3.75 _s	3.83	3.94	3.82	3.69
<i>meso-glycero-gulo</i> -	(5)	3.82	3.67	3.79	3.75	4.02 ^c				
<i>D-glycero-L-gulo</i> -	(6)	3.83	3.65 _s	3.78	3.70	3.95	3.77	3.83	3.71	3.66

^a Compounds (1), (2), and (4) referenced to external tetramethylsilane, and the remainder to external sodium 3-(trimethylsilyl)propionate. ^b Primary geminal protons are distinguished by means of a prime for the proton having the larger coupling constant to the adjacent proton. ^c Lit.,⁶ δ 3.84.

Table 2. Proton-proton coupling constants (Hz) of heptitols in D₂O

Heptitol		<i>J</i> _{1,1'}	<i>J</i> _{1,2}	<i>J</i> _{1',2}	<i>J</i> _{2,3}	<i>J</i> _{3,4}	<i>J</i> _{4,5}	<i>J</i> _{5,6}	<i>J</i> _{6,7}	<i>J</i> _{6,7'}	<i>J</i> _{7,7'}
<i>D-glycero-D-galacto</i> -	(1)	-11.7 _s	5.4	7.4 _s	1.5	9.4 _s	1.2	8.8 _s	2.9	6.3 _s	-11.7 _s
<i>D-glycero-D-manno</i> -	(2)	-11.8 _s	2.9 _s	6.4	8.8	1.1	8.6	4.7 _s	3.1	7.6	-11.8
<i>D-glycero-L-galacto</i> -	(3)	-11.5	5.5	7.5	1.3	9.2 _s	0.9 _s	6.3 _s	3.5 _s	6.2	-11.9
<i>D-glycero-D-gluco</i> -	(4)	-11.9	3.5	6.4	5.7 _s	1.9	8.1 _s	5.0	3.0 _s	7.4	-11.9
<i>meso-glycero-gulo</i> ^a	(5)	-11.9	3.1	6.4	7.6	3.2 _s					
<i>D-glycero-L-gulo</i> -	(6)	-12.0	3.0	6.2 _s	8.3	2.0	6.3 _s	3.1 _s	4.7 _s	7.5	-11.6 _s

^a Lit.,⁶ *J*_{1,1'} -12, *J*_{1,2} 2, *J*_{1',2} 6, *J*_{2,3} 6.5, and *J*_{3,4} ca. 3 Hz.



O-2-O-6 planar (4a), (b) the C-2-C-3 bond as the T_g rotamer giving O-2-C-7 planar. (c) the C-5-C-6 bond twisted giving C-1-O-6 planar, and (d) the planar chain form. Assuming that the twisting of the *xylo*- and *ribo*-units is independent of each other, then using the 3J (2-H, 3-H) and 3J (5-H, 6-H) values, and the fact that the four conformers add to 100, gives the populations of conformers (a)–(d) as 36, 22, 27, and 15%, respectively. Thus although the major conformer is (4a), it only occurs to about a third of the total. To calculate the conformers of *meso-glycero-gulo*-heptitol (5) the chain was assumed to be planar (5a) or to be doubly twisted (5b) so that either O-2-O-4 or O-4-O-6 is planar. This gives (5a) as 42 and the enantiomers (5b) as 30% each (sum, 102%). These results are consistent with

the prediction that the planar chain form will be >29%.² If it is assumed that *D-glycero-L-gulo*-heptitol (6) has only the following four conformers: (a) C-4-C-5 twisted giving C-1-O-5 planar (6a), (b) C-5-C-6 twisted giving O-6-C-1 planar, *i.e.*, leaving the O-3/O-5 interaction, (c) C-2-C-3 and C-3-C-4 both twisted giving C-1-3-H planar and O-3-C-7 planar, *i.e.*, leaving the O-4/O-6 interaction, and (d) C-2-C-3, C-3-C-4, and C-5-C-6 all twisted giving O-3-O-6 planar, then using the 3J values (Table 2) for 2-H-3-H, 3-H-4-H, 4-H-5-H, and 5-H-6-H gives the values (sum, 99%) in Table 4. Conformer (a) is as predicted to be by far the main form present. Since the smaller group prefers to be *exo*-planar,² conformer (b) would be expected to be populated more than conformer (c). So far as

Table 3. Conformer distributions (%) in the heptitols in D₂O

Heptitol	Hydroxymethyl group			Planar carbon chain, except where stated ^a
	O _e	O _p	O _i	
(1) C-1	54	15	31	C-1—C-4 > 71 < 89; C-2—C-5 97;
C-7	56	45	(-1)	C-3—C-6 > 80 < 95; C-4—C-7 90
(2) C-1	56	44	0	C-1—C-4 89; C-2—C-5 > 84 < 94; C-3—C-6 85;
C-7	68	31	1	C-4—C-7 34 (i.e. O-6—C-4 planar 66)
(3) C-1	54	14	32	C-1—C-4 > 77 < 91; C-2—C-5 94;
C-7	51	42	8	C-3—C-6 > 87 < 95; C-4—C-7 < 36, C-5—C-6 T _p > 42 < 64 (3a)
(4) C-1	53	40	7	C-1—C-4 < 42, C-2—C-3 T _p > 31 < 58;
C-7	67	33	0	C-2—C-5 > 60 < 85, C-3—C-4 T _p < 15, T _i < 40; C-3—C-6 79; C-4—C-7 37 (i.e. O-6—C-4 planar 63) (4a)
(5)	55	43	2	C-1—C-7 (5a) 42; O-2—O-4 planar (5b) 30; O-4—O-6 planar (5b) 30
(6) C-1	54	46	0	C-1—C-4 82; C-2—C-5 > 57 < 84;
C-7	58	20	22	C-3—C-6 < 37, C-4—C-5 T _p > 41 < 64 (6a); C-4—C-7 > 24 < 71, C-5—C-6 T _p < 29

^a For nomenclature, see ref. 1.**Table 4.** Conformers (%) for (6), L-glucitol, and D-iditol

Conformer	(6)	L-Glucitol	D-Iditol
(a) Single twist at C-ω-2—C-ω-3	64		49
(b) Single twist at C-ω-1—C-ω-2	19	61	24
(c) Double twist at C-ω'-1—C-ω'-2 and C-ω'-2—C-ω'-3	6	13	
(d) Other	10 ^a	22 ^b	26 ^c

^a Trebly twisted chain conformer (d). ^b Planar chain, ref. 2. ^c Doubly twisted chain, ref. 1.

the C-4—C-6 *xylo*-unit is concerned, conformers (c) and (d) approximate to planar chain (3) and (3a), respectively, and since the latter pair occur in the ratio 30:64, we predict that conformer (d) will be more populated than conformer (c). Concerning the C-3—C-5 *xylo*-unit, conformer (b) corresponds to planar chain glucitol and (d) to glucitol with the doubly twisted chain. In glucitol (Table 4) the former occurs more than the latter, and thus conformer (b) should be populated more than (d). The predicted sequence is (a) ≫ (b) > (d) > (c), as observed. Comparing (6) with iditol (Table 4), the main conformer in each has a singly twisted chain at C-ω-2—C-ω-3, but for (6) all other conformers are relatively unfavoured, whereas in iditol there can also exist two other significantly populated conformers. Hence conformer (a) occurs to a larger extent in (6) than its analogue in iditol. Interestingly, the amount (22–25%) of conformers with an O//O interaction for each of the three compounds is about the same. In summary, the results for the six heptitols support the previous conformational analysis and ¹³C n.m.r. results on these alditols.

Considering the O_e, O_p, and O_i hydroxymethyl ratios, galactitol (53:16:31) and mannitol (54:46:0) have been taken as limiting examples for planar *lyxo*- and *arabino*-configurations, respectively. The value (54:15:31) for the C-1 group of (1) confirms the planar C-1—C-4 chain. At the C-7 group (56:45:–1) the O_i rotamer is under-populated and adjusting the ratio as previously² gives an essentially planar *arabino*-type chain. The C-1 ratio for (2) confirms the planar nature of the C-1—C-4 chain, while the C-7 group ratio (68:31:1) is typical¹ for a hydroxymethyl group adjacent to a *ribo*-unit. In (3), C-1 has a ratio for a planar *lyxo*-configuration while C-7 has a ratio similar to C-1 in glucitol, i.e., twisting of a *xylo*-unit at the C-ω-1—C-ω-2 bond from the hydroxymethyl group. In (4) the C-1

and C-7 ratios agree with the *xylo*- and *ribo*-arrangements. In (5) a given hydroxymethyl group will either be in a planar *arabino*-configuration (42 + 30%) or at the end of a doubly twisted chain (30%). In the latter case, the hydroxymethyl group seems to be in approximately the same environment as a hydroxymethyl group adjacent to a *ribo*-unit twisted to give O-ω-1 extending the chain, e.g., C-7 in (2). Thus the hydroxymethyl group conformer ratio should resemble that from an *arabino*-type configuration with a slightly enhanced O_e and reduced O_p contribution arising from the 30% *ribo*-type arrangement, but the observed ratio (55:43:2) is in fact *arabino*-type. This is puzzling, but in keeping with the ratios found for similar doubly twisted chains, e.g. 1-deoxy-D-glycero-D-gulo-heptitol.² In (6), C-1 is a typically *arabino*-type ratio while C-7 has a ratio similar² to that given by C-5 in 1-deoxy-D-xylitol, i.e., twisting of the *xylo*-unit at the C-ω-2—C-ω-3 bond from the hydroxymethyl group. The reason for the slightly enhanced O_e component, which also occurs in iditol, is unclear.

The separation (Δ, Hz at 400 MHz) of the shifts of the primary protons provides useful conformational data. Thus C-1 in (1) 0.3, and C-1 in (3) 1.75, are similar to that of the methylene protons in galactitol (1.0), whereas C-7 in (1) 80.0, and C-1 in (2) 77.0 are similar to that of the methylene protons in mannitol (77.5). When an O//O interaction in a *ribo*-unit can only be relieved by rotation of the C-ω-1—C-ω-2 bond from the hydroxymethyl group, then Δ is ca. 51 Hz [C-7 in (2) 51.9_s, C-7 in (4) 51.0_s, and C-6 in altritol 50.7_s], but when the C-ω-2—C-ω-3 bond can also rotate, as it does progressively in ribitol and 1-deoxyribitol, then Δ increases (62.0_s and 71.9 respectively). In the *xylo*-series, C-7 of (6) 18.9_s mainly twists at the C-ω-2—C-ω-3 bond from the hydroxymethyl group, but as twisting of the C-ω-1—C-ω-2 bond increasingly occurs in 1-deoxy-D-xylitol (23.0), xylitol (28.8_s), 6-deoxy-D-glucitol (39.7_s), D-glucitol (45.5), C-1 in (4) (45.8_s), and C-7 in (3) (49.0), so Δ increases. There is a parallel increase in the O_p rotamer through the series from C-7 in (6) (20) to C-7 in (3), (42%). In (5) the hydroxymethyl conformer ratio fails to detect any doubly twisted chain. However, there is a gradual decrease in Δ from mannitol, 1-deoxyglucitol 74.4_s, glucitol C-6 70.1_s, 1-deoxy-D-glycero-D-gulo-heptitol 68.5 to (5), 60.3 as the doubly twisted chain component rises. The relation¹ established for the lower alditols between Δ and ³J (ω-H, ω-1-H) also holds for the heptitols.

Turning now to the shifts of the protons, just as the carbon shifts in ¹³C n.m.r. spectra correlated with the analogous carbon shifts in the hexitols when the conformations are similar so too do the proton shifts, except for 4-H which has no hexitol analogue. In (1) 4-H (δ 3.92) suffers two H//O interactions, whereas in (2) and (3) it has an H//O and an H//C interaction so that it might be expected to be more shielded in (2) and (3). This is true for (3) (δ 3.73) but in (2) (δ 3.89) it is only marginally so. In (4) 4-H (δ 3.75_s) experiences H//H and H//C interactions, so it seems anomalously deshielded relative to 4-H in (3). Comparing (5) and (2) in the twisted form of (2) (66%), 4-H seems to resemble 4-H in (5b) (60%) in that both have similar interactions. In (5a) (42%) a deshielding H//O and an *anti*-oxygen replace H//z and a *gauche*-oxygen in planar (2) (34%). Thus 4-H (δ 4.02) in (5) should be more deshielded than δ 3.89. In the main conformer of (6) 4-H experiences similar interactions to 4-H in (1), and the shifts of both are similar.

It was predicted⁷ that it is easier for a *xylo*-unit to twist and relieve an O//O interaction than it is for a *ribo*-unit, and some of the ¹³C n.m.r. data on the heptitols used this idea. Thus twisting of a *threo*-diol unit T_p → T_i favourably converts the O//O and 2 C//O interactions into a C//C and O//O interactions, whereas in an *erythro*-diol E_p → E_i unfavourably converts 2 C//O interactions into C//C, C//O, and O//O interactions (Figure).

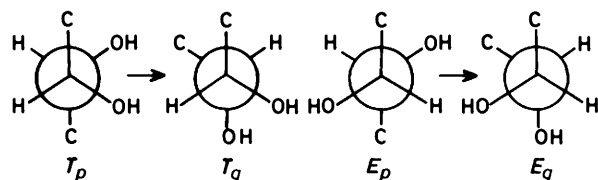


Figure. Interactions for a *threo*-(*T*) and *erythro*-(*E*) diol when the carbon chain is planar (*p*) and *gauche* (*g*)

However, glucitol and (3) with a *xylo*-unit have similar (61–64%) amounts of twist about the C- ω -1-C- ω -2 bond as have altritol and (2) with a *ribo*-unit. Also, the attractive *gauche*-effect in propane-1,2-diol between the primary and secondary oxygens was worth² 0.5 kcal mol⁻¹ assuming additivity of interaction energies. If this effect also operates between two secondary adjacent oxygens as in the *T_p* rotamer, then the conversion *T_p* \rightarrow *T_g* could indeed be comparable in energy to that of *E_p* \rightarrow *E_g*. It could be however that sometimes simple additivity schemes for estimating interaction energies in acyclic molecules breakdown when there is multiple substitution of the carbon atoms. Thus, in liquid 2,3-dimethylbutane at -180 °C the conformer with 2-H and 3-H *anti* (*T_g* or *E_p* with OH replaced by Me) is as stable⁸ as the conformer with 2-H and 3-H *gauche* (*T_p*, *E_g*), yet a simple additivity scheme gives the *anti*-conformer more stable by a C//C, *i.e.*, a H//C, interaction than the *gauche*-conformer.

Experimental

Spectra were recorded² and computed¹ as previously cited.

Materials.—*D-glycero-D-galacto*-Heptitol (1) was a commercial sample. Borohydride reduction of commercial *D-glycero-D-gulo*-heptono-1,4-lactone in the presence⁹ of a cation-exchange resin or of commercial *D-glycero-D-gulo*-heptose yielded *meso-glycero-gulo*-heptitol (5) (76 and 82%, respectively), m.p. 127–128 °C (lit.,¹⁰ 129 °C). It gave a *heptabenzoate* (84%), m.p. 122–125 °C (Found: C, 71.6, H, 4.7. C₅₆H₄₄O₁₄ requires C, 71.5, H, 4.7%) from 50 parts ethanol. Similarly sodium borodeuteride reduction of the 1,4-lactone yielded [1,1-²H₂]-*D-glycero-D-gulo*-heptitol (80%), m.p. 128–129.5 °C, mixed m.p. with non-deuteriated compound was not depressed; ν_{\max} (KBr disc) 2 235 and 2 110 cm⁻¹ (C-D). 2,7-Anhydro- β -*D-altro*-heptulopyranose hydrate¹¹ was converted¹² into mixed heptitols, part (4.9 g) of which after five fractional crystallisations from aqueous ethanol gave *D-glycero-D-manno*-heptitol (2) (1.32 g), m.p. 154–156 °C (lit.,¹³ 152–153 °C). Part (1.55 g, m.p. *ca.* 121–130 °C) of the liquors was sequentially¹³ benzylidenated and hydrolysed, yielding *D-glycero-D-gluco*-heptitol (4) (0.51 g), m.p. 128–129 °C (lit.,¹³ 128–129 °C).

Crude *D-glycero-D-ido*-heptono-1,4-lactone¹⁴ (in our hands, the cadmium bromide double salt could not be prepared; 1.04 g) was reduced with borohydride⁹ in the presence of a cation-exchange resin to yield *D-glycero-L-gulo*-heptitol (6) (0.18 g), m.p. 126–127 °C (lit.,¹⁰ 128–129 °C), from methanol. *D-Galactose* was treated with cyanide as described for *D-glucose*.¹⁴ Part (5.2 g) of the partially lactonised mixture was reduced by borohydride in the presence of sulphuric acid, as described⁹ for *D-glycero-D-gulo*-heptono-1,4-lactone, to yield *D-glycero-L-gluco*-heptose (0.28 g), m.p. 194–196 °C (lit.,¹⁵ 198–199 °C), from ethanol–water (1:1). Borohydride reduction of the heptose give *D-glycero-L-galacto*-heptitol (3) (60%), m.p. 139–140 °C (lit.,¹⁰ 141 °C), from ethanol–water (4:1).

Acknowledgements

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