Synthesis of Racemic Ribose from D-Glucose

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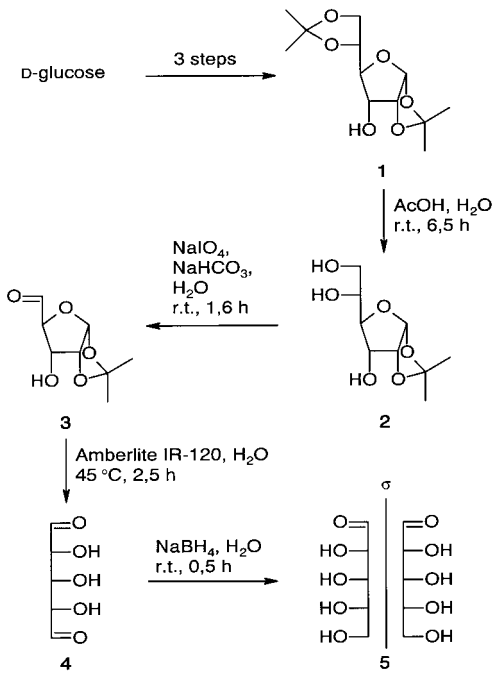
Abstract: Racemic ribose is a valuable starting material for investigations of the origins of biomolecular homochirality. It can be synthesized in seven steps starting from D-glucose.

Key words: biomolecular homochirality, cleavage, *ribo*-pentodialdose, partial reduction, racemic ribose

D-Ribose is the central sugar unit of oligonucleotides: In natural RNA it occurs in its furanosyl constitution, in Eschenmoser's p-RNA in its pyranosyl constitution.[2] In our studies of the pairing between homochiral oligonucleotide strands of opposite sense of chirality in the p-RNA series[3] and relating to the question of the origin of biomolecular homochirality[4] racemic ribose was synthesized in preparative amounts.

So far, *rac*-ribose has been synthesized only in minute amounts by treatment of formaldehyde with NaOH,[5] CaOH,[6] NH_4SCN and light,[7] from glyceraldehyde and glycolic aldehyde with CaOH,[8] or as ribose diphosphate from glycolic aldehyde phosphate and formaldehyde under basic conditions.[9] Mixing of equal amounts of both available enantiomers of ribose[10] did not seem appropriate for the intended pairing and crystallization experiments.

Our concept for the synthesis of racemic ribose was the partial reduction of the *meso*-configurated 2,3,4-trihydroxypentandial **4** (Scheme 1).



Scheme 1

This concept is of preparative interest since the necessary *meso*-dialdehyde can be synthesized from readily available diacetone glucose (Scheme 1) via regioselective glycol cleavage of a D-allose derivative **2** of corresponding relative configuration. Recently a modified approach has been described by Pitsch[11] for the synthesis of an L-ribose derivative from D-glucose. Surprisingly, *ribo*-pentodialdose **4** has so far only been detected by GC-MS as a by-product of γ-radiation of aqueous solutions of D-ribose[12] and D-ribose-5-phosphate[13] and has been described as its 2,4-dimethylether[14] in the context of a natural product structure elucidation.

The conversion of diacetone glucose (synthesized from D-glucose) to diacetone allose **1** by oxidation with pyridinium dichromate followed by stereoselective reduction with $NaBH_4$ is well known.[15] Selective cleavage of the 5-/6-hydroxyl protecting group of 1,2:5,6-bis-*O*-(1-methylethylidene)-α-D-*allo*-furanose **1** was performed with 50% aqueous acetic acid following Paulsen's procedure[16] and furnished **2**. Treatment of 1,2-*O*-(1-methylethylidene)-α−D-*allo*-furanose **2** with sodium periodate in water[17] instead of lead tetraacetate[18] gave 1,2-*O*-(1-methylethylidene)-α-D-*ribo*-pentodialdo-1,4-furanose **3** in quantitative yield. In aqueous solution **3** exclusively existed as aldehyde hydrate as shown by ^1H NMR spectra. As expected, the dialdehyde **4** was obtained in quantitative yield by cleavage of **3** with strong acidic ion-exchange resin and gentle heating for 2.5 h. *Ribo*-pentodialdose **4** is stable at room temperature for months and shows only a single spot on the TLC in spite of five possible isomers. At room temperature it is only soluble in water, but not in methanol.

The structure of *ribo*-pentodialdose **4** was investigated by $^1H,^1H$- and $^1H,^{13}C$- correlated NMR spectra in D_2O. Formation of the hemiacetal and hydration of **4** can lead to five isomers, two of them being furanoses, three of them pyranoses (Figure 1). An assumption on the distribution of individual pyranose isomers was made based on conformational analysis: Lack of 1,3-*syn*-positioned axial hydroxy groups should favor ***meso*-β-p** (β-*allo*-pentodialdopyranose) over the two other isomers. Antiperiplanar position of the electronegative substituent at C1 relative to the non-bonding electron pair of the endocyclic oxygen atom (anomeric effect) should make **rac-p** (α-*allo*-pentodialdo-pyranose) the preferred isomer compared to the $_4C^1$-conformer of ***meso*-α-p** (β-*talo*-pentodialdo-pyranose). The $^4C_1$-conformer of ***meso*-α-p** is sterically highly disfavored due to three axial hydroxy groups.

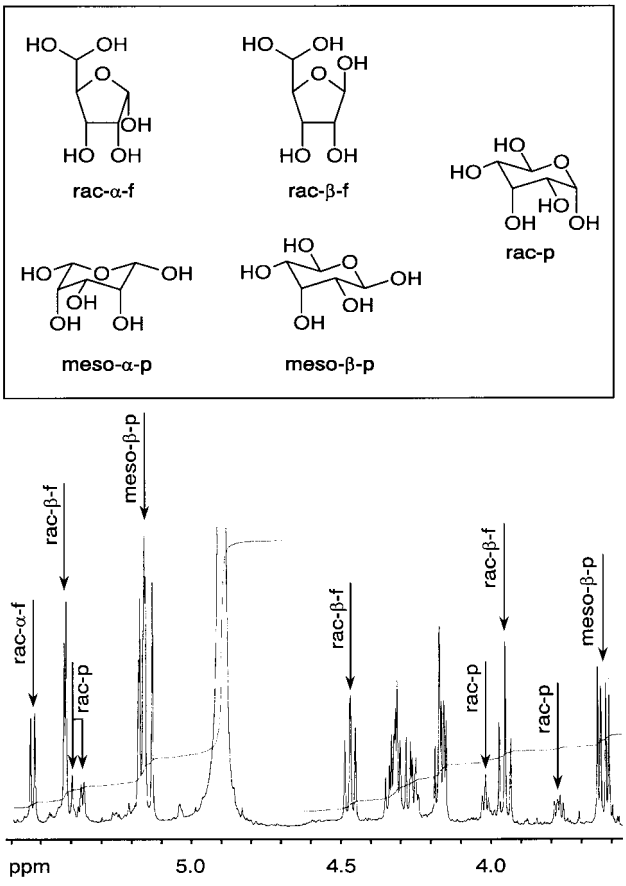


Figure 1

Four of the five isomers were present in sufficient amounts to be detected by NMR: The furanoses ***rac*-α-f** and ***rac*-β-f** (α− and β-*ribo*-pentodialdo-1,4-furanose) could be identified by their characteristic doublets at 5,53 (α) and 5,42 ppm (β). The third major doublet in the anomeric proton area was at 5,15 ppm (J = 8,2 Hz) and showed a cross-peak with the *dd*-peaks at 3,63 ppm, which correlated with H-(C3) at 4,31 ppm. Since no further correlation was found this major pyranose had to be one of the *meso*-forms. The coupling constants of 8,2 and 3,1 Hz of H-(C2) unambiguously assigned these signals to ***meso*-β-p** (Figure 2). The last (minor) isomer present was confirmed to be **rac-p** based on its correlation pattern and the coupling constants ($^3J_{4,5} < {}^3J_{1,2}$).

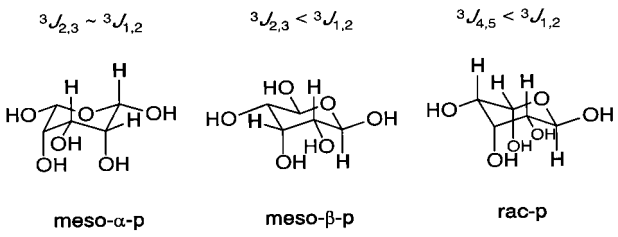


Figure 2

The ratio between the two anomeric *ribo*-pentodialdose furanoses was almost the same as between the two anomeric *ribo*-furanoses, whereas the ratio of *ribo*-pentodialdose furanoses compared to *ribo*-pentodialdose pyranoses was higher than in ribose (Table 1). In addition, this pyranose isomer ratio correlated well with the predictions based on conformational analysis.

Table 1. **^{1}H-, ^{13}C-NMR data (δ in ppm, J in Hz) and distribution of isomers**

	H-(C1) C1	H-(C2) C2	H-(C3) C3	H-(C4) C4	H-(C5) C5
***rac*-α-f**	5.53	4.27	4.34	~4.17	~5.17
22 %	*d*, 4.2	*dd*, 5.8, 4.1	*dd*, 5.9, 3.8	*dd*, 4.1, 4.1	*d*, ~4.5
	98.96	73.50	72.53	87.89	91.93
***rac*-β-f**	5.42	4.16	4.47	3.96	5.16
39 %	*d*, 2.1	*dd*, 4.9, 2.2	*dd*, 5.4, 5.3	*dd*, 5.8, 5.7	*d*, 5.6
	103.57	77.89	73.79	86.80	93.46
***meso*-β-p**	5.15	3.63	4.31	= H-(C2)	= H-(C1)
25 %	*d*, 8.2	*dd*, 8.2, 3.1	*t*, 3.1		
	94.56	73.94	73.17	= C2	= C1
***rac*-p**	~5.4	3.78	~4.25	4.02	5.36
14 %	*d*, ~5.8	*dd*, 5.6, 2.9	*dd*, ~3, n/d	*dd*, 3.0, 2.9	*d*, 3.0
	93.46	73.11	~71.6	71.65	94.46

In the final step *ribo*-pentodialdose **4** was reduced with $NaBH_4$ to give the desired racemic ribose **5**. No further reduction to ribit could be detected by TLC. A chromatographic purification step could be avoided by work-up of the reaction first with strong acidic and then with strong basic ion-exchange resin. The synthetic *rac*-ribose was analyzed by ^{1}H NMR spectra and capillary electrophoresis and was found to be sufficiently pure for further synthetic steps. The enantiomeric ratio of **5** was determined by Freissmuth's method.[19] A sample was converted to the diastereomeric Schiff bases with *(S)*-(-)-1-phenylethylamine, which were reduced with $NaBH_3CN$ and then directly subjected to capillary electrophoresis: Thus, the synthetic product **5** was proven to be racemic.

Racemic ribose was synthesized in 7 steps in 50% yield from D-glucose by the procedure described here.[20] The use of *rac*-ribose for the synthesis of 9-(β-DL-*ribo*-pyranosyl)-adenine and further results obtained will be published elsewhere.[21]

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References and Notes

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(20) Experimental:
1,2-O-(1-methylethylidene)-α-D-ribo-*pentodialdo-1,4-furanose **3**:* 15.0 g (70.13 mmol) $NaIO_4$ was added to a solution of 6.60 g (30.0 mmol) of **2** and 3 g $NaHCO_3$ in 300 ml H_2O within 10 min. After stirring at r. t. for 100 min, the reaction mixture was concentrated (< 40 °C), the residue extracted four times with 200 ml EtOAc, filtered, and the combined filtrates concentrated. The residue was treated with 5 ml CCl_4 and evaporated to dryness: 5.58 g (98%) **3**. Colorless foam. TLC (silica gel, EtOAc/MeOH 4:1): R_f 0.55. ^{1}H NMR (200 MHz, D_2O):1.32, 1.5 (2*s*, Me); 3.82 (*dd*, *J* = 3.8, 8.9, H-C(4)); 4.04 (*dd*, *J* = 4.6, 9.0, H-C(3)); 4.66 (*dd*, *J* = 4, H-C(2)); 5.01 (*d*, *J* = 3.8, H-C(5)); 5.80 (*d*, *J* = 3.5, H-C(1)).
*Ribo-pentodialdose **4**:* 40 ml ion-exchange resin *Amberlite IR-120* (H^+form) was added to a solution of 5.0 g (26.2 mmol) **3** in 50 ml of H_2O and stirred at 45 °C for 2.5 h. The reaction mixture was filtered and evaporated:3.83 g (98%) **4** as mixture of isomers. Colorless foam. TLC (silica gel, $CHCl_3$/MeOH/H_2O 85:30:2): R_f 0.28. 1H NMRand 13C NMRsee Table 1. IR (KBr):3401*s* (br.), 2973*m*, 1656*m*, 1465*s*, 1420*m*, 1347*m*, 1264*m*, 1054*s* (br.), 566*m* (br.). FAB-MS:167 (2, MH_2O^+), 149 (13, MH^+), 31 (100). Elem. anal.: calc: $C_5H_8O_5 \cdot 0.6\ H_2O$: C 37.79, H, 5.84; found: C 38.01, H 6.15.
*DL-Ribose **5**:* 95 mg (2.51 mmol; 0.28 eq.) $NaBH_4$ in 5 ml H_2O was added to 1.33 g (8.98 mmol) **4** in 30 ml H_2O. After 30 min at r. t. 15 ml ion-exchange resin *Amberlite IR-120* (H^+form) was added. The reaction mixture was stirred for 10 min and filtered. 10 ml ion-exchange resin *Amberlite IRA-400* (OH^- form) was added to the filtrate, stirred for 10 min, filtered and evaporated: 0.86 g (64%) **5**. Colorless foam. TLC (silica gel, $CHCl_3$/MeOH/H_2O 85:30:2): R_f 0.17 (identical to natural D-ribose).
Determination of enantiomeric ratio:20 µl of an 0.1M aqueous solution of **5** was treated with 10 µl of a 1M aqueous solution of *(S)*-(-)-1-phenylethylamine (pH 6.3 adjusted with hydrochloric acid in advance) in an *Eppendorf* cap, which was sealed and heated to 90 °C for 10 min. 90 mg of $NaBH_3CN$ were dissolved in 300 µl of H_2O and 4.5 µl of that solution added to the reaction mixture. It was kept at 90 °C for 60 min, diluted with 60 µl of H_2O and injected for capillary electrophoresis analysis (capillary: 77 cm, ID = 50 µm; injection time: 2 sec; buffer: 50mM borate pH 10.3/23% MeCN; 30 kV).
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