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DIASTEREOSELECTIVE AND REGIOSELECTIVE REACTIONS ON D-ALDOPENTOSE MIXTURES: A POSSIBLE REASON FOR NATURE'S CHOICE OF D-RIBOFURANOSE BASED NUCLEIC ACIDS?

Jesper Wengel*[1] and Claus Scheuer-Larsen

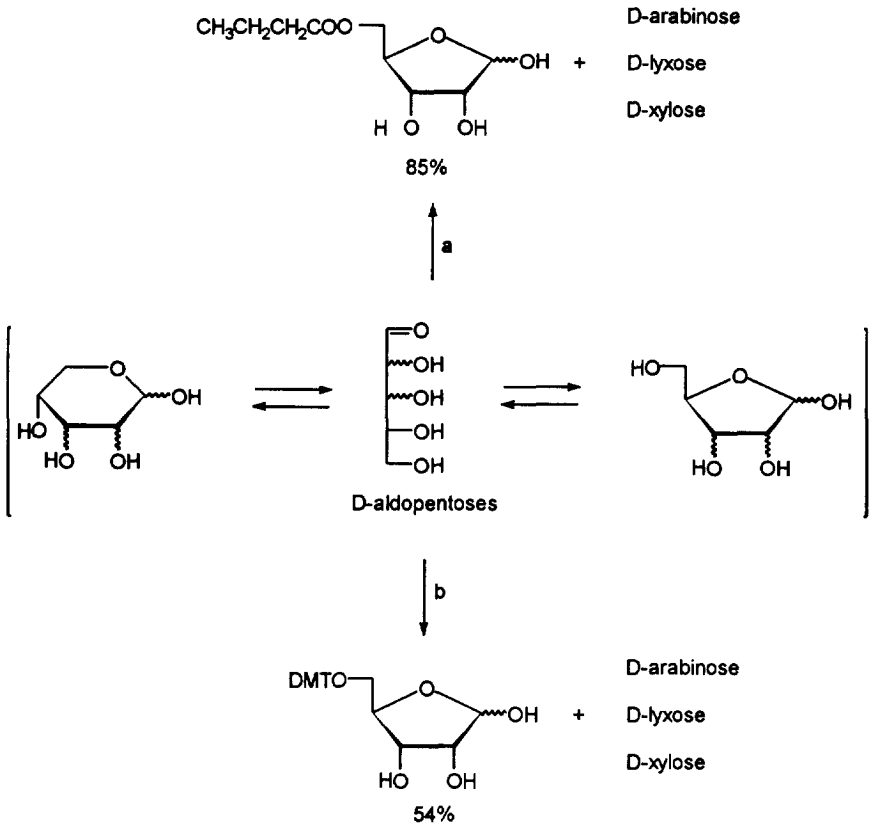
Department of Chemistry, Chemical Laboratory II, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

Abstract: Remarkably diastereoselective and regioselective reactions on an equimolar mixture of D-ribose, D-arabinose, D-xylose and D-lyxose are reported to give 5-*O*-functionalised D-ribofuranose derivatives.

Recently, we have reported[1] synthesis of a 1,2,3,5-tetra-*O*-acyl D-ribofuranose derivative and 2-deoxy-1,3,5-tri-*O*-acyl D-ribofuranose derivatives using the lipase Novozym® 435 from *Candida antarctica* for selective 5-*O*-acylations of the parent D-riboses. Our attempts on extending this selective enzymatic acylation to other D-pentoses[2] failed which has been one motivation for the research described herein. Another has been the recent work and reflections of Eschenmoser and his coworkers on the structure and chemistry of potentially prebiological nucleic acids.[3] Following the discovery of ribozymes,[4,5] the hypothesis of an early "RNA-world", in which RNA functioned both as a carrier of information and as a non-enzymatic catalyst, has appeared.[6] In this context, the problem of identifying a plausible prebiological route to substantial amounts of oligonucleotides is of considerable interest.[7] Especially, the low amount of ribose in the putative prebiological formose reaction[7,8] leading to a mixture of trioses, tetroses, pentoses, hexoses and heptoses, poses a dilemma for the RNA-world hypothesis. This leads to many questions, *e.g.* why has nature chosen a pentose and not a hexose?[7] and why has nature chosen ribofuranose and not ribopyranose or one of the other diastereomeric pentoses?[7]

Puzzled by these questions, we have examined the outcome of reactions on D-aldopentose mixtures. In one experiment (Scheme), an equimolar mixture of D-ribose, D-arabinose, D-xylose and D-lyxose (1 mmol of each) in anhydrous THF (25 mL) was mixed with butyric anhydride (1 mmol) and the lipase Novozym® 435 from *Candida antarctica*,[9] and the mixture was stirred at 50 °C for 5 h. Isolation of the fraction containing acylated product by silica gel flash chromatography yielded 5-*O*-butyryl-D-ribofuranose in 85% yield (α:β~3:2) as the only acylated product.[10]

[1]E-mail address: wengel@kiku.dk, fax no. +45 35 32 02 12



Scheme: a) Butyric anhydride, Novozym® 435, THF; b) 4,4'-dimethoxytrityl chloride (DMTCl), pyridine.

Analogously, if the equimolar D-aldopentose mixture was reacted with 4,4'-dimethoxytrityl chloride in anhydrous pyridine (40 mL) and stirred for 24 h at room temperature, reaction of D-ribose was exclusively observed and 5-*O*-(4,4'-dimethoxytrityl)-D-ribofuranose was isolated in 54% yield (α:β~2:1) (Scheme).[11]

In both reactions, remarkable regio- and diastereoselectivities were observed. In the lipase-catalysed reaction, a possible explanation could be structural information from the diastereomerically pure active site of the enzyme. However, as the second reaction employing the achiral reagent 4,4'-dimethoxytrityl chloride proceeded with analogous selectivity it is clear that instruction for the observed regio- and diastereoselectivity relies in the D-aldopentose molecules. The regioselectivity towards the 5-OH group was expected from earlier results on preferential protections of primary hydroxy groups using Novozym® 435[1,12] or 4,4'-dimethoxytrityl chloride,[13] and can be explained by steric considerations.

NMR experiments on the four D-aldopentoses under the reaction conditions (THF, 50 °C; pyridine, room temperature) showed approximately 30% furanose form for D-ribose, approximately 25% furanose form for

D-arabinose and virtually exclusively pyranose form for D-xylose and D-lyxose.[14] Therefore, as the reagents selectively react on primary hydroxy groups, the diastereoselectivities observed can be explained in part by the furanose/pyranose equilibria,[15] but an additional explanation is needed for the selectivity between D-ribose and D-arabinose.

In connection with the ribose problem and the putative RNA-world, the properties of different nucleic acid alternatives have been experimentally evaluated.[7] Especially "Ribopyranosyl-RNA", the structural isomer of RNA with the ribose in pyranose form (Figure), has shown interesting properties like stronger and more selective Watson-Crick base paring than in natural DNA or RNA duplexes, and the ability to replicate non-enzymatically.[16] But why did nature then choose/shift to "Ribofuranosyl-RNA"? Based on the model experiments described herein, we suggest that 5-*O*-selective reactions (*e.g.* phosphorylations[17]) of D-ribose in mixtures of sugars could have played a major role for nature's choice of D-ribofuranose based nucleic acids (Figure).

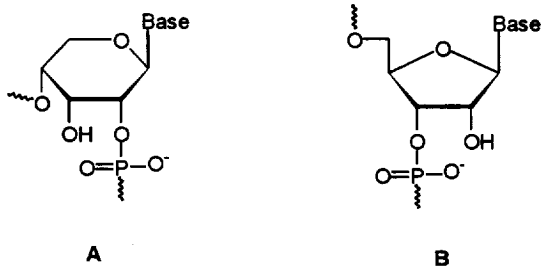


Figure: "Ribopyranosyl-RNA"[16] **(A)** and nature's choice: "Ribofuranosyl-RNA" **(B)**

Summarising, remarkably regio- and diastereoselective reactions on equimolar mixtures of the four D-aldopentoses have been accomplished. Thus, out of the many hydroxy groups present in the substrates only one, namely the primary hydroxy group of D-ribose, reacted to give 5-*O*-derivatised D-ribofuranoses. A possible implication of this selectivity to nature's selection of D-ribofuranose based nucleic acids has been suggested.

Acknowledgement

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9. This lipase is commercially available from Novo-Nordisk A/S, Bagsværd, Denmark.
10. Selected ^{13}C NMR data ($CDCl_3$): δ 63.5, 64.9, 70.5, 70.6, 71.0, 74.9, 79.7, 80.1, 96.0, 101.2, 173.4, 173.7. Calcd. C: 49.08; H: 7.32; Found C: 48.89; H: 7.02%.
11. Selected ^{13}C NMR data ($(CD_3)_2SO$): δ 55.1, 64.3, 65.9, 70.6, 70.8, 71.3, 75.4, 80.6, 81.1, 85.3, 96.5, 101.7. Calcd. C: 69.01; H: 6.24; Found C: 69.37; H: 6.22%.
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13. See, *e.g.*: von Büren, M.; Petersen, G. V.; Rasmussen, K.; Brandenburg, G.; Wengel, J. *Tetrahedron* **1995**, *51*, 8491.
14. Similar ratios were found when recording the spectra in D_2O.
15. The selectivity obtained here during 4,4'-dimethoxytritylation could not be repeated during tritylations. See also an earlier report describing selective 5-*O*-tritylations of D-ribose, D-arabinose, D-xylose and D-lyxose in separate reactions using trityl chloride in anhydrous pyridine at room temperature: Kam, B. L.; Oppenheimer, N. J. *Carbohydr. Res.* **1979**, *69*, 308. Synthesis of 2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-D-ribofuranose from 2-deoxy-D-ribose using a similar procedure has been reported: Groebke, K.; Leumann, C. *Helv. Chim. Acta.* **1990**, *73*, 608.
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