

Carbohydrate analogue polymers by ring opening metathesis polymerisation (ROMP) and subsequent catalytic dihydroxylation

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Ring opening metathesis polymerisation (ROMP) followed by catalytic dihydroxylation affords macromolecules with 1,2-diol structures. These new macromolecular compositions represent C-glycoside analogues of ribofuranose polymers that are thermally and hydrolytically stable.

Carbohydrate–protein interactions play an important role in many biological processes. Polysulfates derived from carbohydrates were recognized as potent and selective inhibitors of the *in vitro* replication of HIV and other enveloped viruses. In the case of sulfated dextrans the activity strongly depended on the molar mass of the oligosaccharides.^{1,2} The design of new carbohydrate-analogue polymers is of special interest in polymer chemistry and life sciences—applications range from drug systems to novel biocompatible materials and surface coatings. Ring-opening metathesis polymerisation (ROMP) offers attractive potential for the synthesis of well defined carbohydrate analogue polymers. The modern catalyst generations, developed by Schrock and Grubbs, tolerate polar groups and afford living polymerisation which is the key to molar mass control. Novel families of ROMP glycopolymers were prepared by Kiessling, Schrock, Grubbs and co-workers^{3–7} using sugar-substituted derivatives of norbornene and 7-oxanorbornenes as monomers. Since conventional polysaccharides are prone to metabolic degradation by glycosidases due to their glycosidic linkages,² hydrolytically stable carbohydrate-analogue compounds without glycoside linkages in the backbone represent interesting candidates for biomedical applications (Fig. 1).

Here we present a versatile synthetic method for the preparation of novel polyribofuranose analogue polymers which do not contain glycoside linkages between the monomeric units in the polymer backbone that are prone to metabolic degradation by glycosidases. This should provide an oligosaccharide analogue structure with improved biocompatibility and longer half-life times. Initial research on related oligosaccharide-analogue polymers was reported by Clark and Lee⁸ who used ROMP of 7-oxanorbornene diol derivatives. Since the double bonds of the polymer backbone were hydrogenated, the resulting saccharide-analogue polymers contained only two

hydroxy groups per repeating unit. The objective of our research was the synthesis of polymers containing fully hydroxylated repeating units. These are pseudo-polyribofuranoses, with structures very similar to those of natural carbohydrates. The synthetic strategy displayed in Scheme 1 employs ROMP of dihydroxy-substituted bicyclic olefin monomers and subsequent dihydroxylation of the double bonds in the polymer backbone.

Both pure 2-*exo*, 3-*exo*-7-oxanorbornene diol **1a** and the corresponding *endo* isomer **1b** were synthesized according to a literature procedure.⁹ Unfortunately, all attempts to perform ring-opening metathesis polymerisation in water, employing the water soluble Grubbs catalyst RuCl₂(=CHPh)-[Cy₂PCH₂CH₂N(CH₃)₃⁺Cl⁻]₂ **7** failed. Therefore, compounds **1a** and **1b** were transformed into their corresponding ketals **2a** and **2b** as reported by Schrock and co-workers.¹⁰ ROMP in THF gave high yields (80–90%) using the well known Grubbs catalyst **6**. The monomer to catalyst ratio was varied in order to obtain polymers with different molecular masses. Properties of the obtained polymers are listed in Table 1. The resulting polymers **3a,b** were soluble in THF, acetone, CHCl₃ and CH₂Cl₂ but not in water or methanol. A polydispersity index *M_w/M_n* of 1.5, determined by size exclusion chromatography (SEC), reflects a relatively narrow molecular mass distribution (*cf.* Table 1). A significant difference was observed with respect to the *cis/trans* double bond ratio in **3a** and **3b**, respectively. The *cis* double bond content of **3a** was 30% compared to 80% for **3b**.

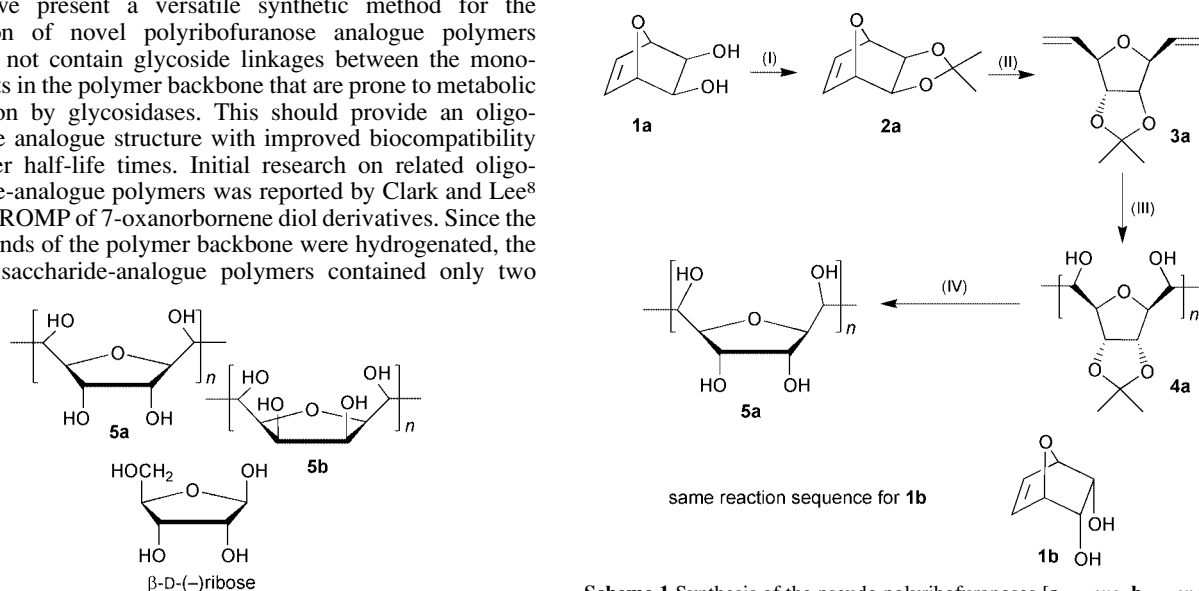


Fig. 1 Comparison between β -D-(-)ribose and the novel carbohydrate analogue polymers **5a,b**.

Scheme 1 Synthesis of the pseudo polyribofuranoses [**a** = *exo*, **b** = *endo*; (I), *cf.* ref. 10; (II), RuCl₂(=CHPh)(PCy₃)₂ (**6**), THF; (III), cat. OsO₄, NMO, acetone, H₂O, MeOH; (IV), CF₃CO₂H–H₂O (9:1 vol. ratio)].

Table 1 Properties of **3a,b** and **4a,b**

	[M]/ [[Ru] ^a	M _n / g mol ^{-1b}	PDI	T _g /°C ^c	σ _c /mol% ^d	σ _E /mol% ^e
<i>endo</i>	25	7 100	1.50	n.d.	80	71
	50	12 200	1.50	155	82	71
	75	14 800	1.47	156	82	69
<i>exo</i>	50	19 300	1.42	85	33	n.d.
	75	33 900	1.42	86	34	n.d.
	100	36 600	1.51	86	30	n.d.

^a Monomer to catalyst ratio. ^b Determined for **3a,b** in CHCl₃ against PS standard. ^c Obtained for **3a,b**. ^d Content of *cis* double bonds in **3a,b**. ^e Content of *erythro* diols in **4a,b**.

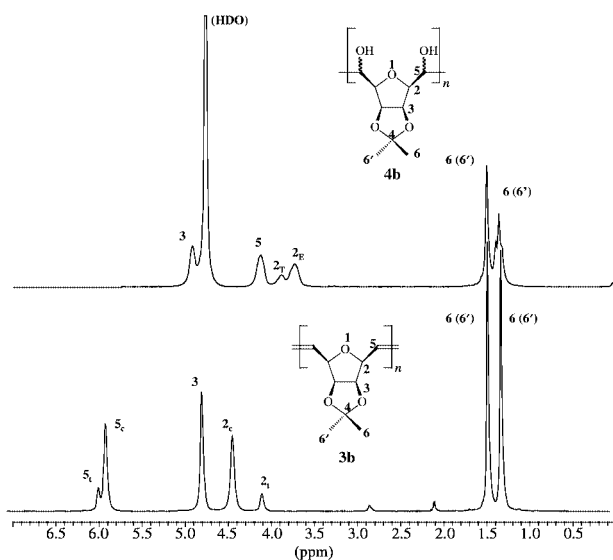


Fig. 2 ¹H NMR spectrum of **3b** (acetone-d₆, 300 MHz) in comparison to **4b** (D₂O, 300 MHz).

The NMR-peaks were assigned based on COSY and DEPT-NMR techniques and by comparison with chemical shifts of related structures.¹¹ It is noteworthy that the *exo* and *endo* polymers also differ strongly in their glass transition temperatures (*T_g*) (**3a** *T_g* = 85 °C, **3b** *T_g* = 155 °C).

So far, typical polymer analogue reactions for the derivatisation of the double bonds produced by ROMP have employed sulfonation, hydrogenation, the formation of carbonamide¹² and epoxidation.^{12,13} In order to produce the desired pseudo-polyribofuranose structures we decided to dihydroxylate the double bonds in the backbone of the ROMP polymers **3a,b**. To the best of our knowledge this is the first time that successful catalytic dihydroxylation of ROMP polymer has been achieved. While catalytic dihydroxylation is well known for many low molecular weight oligoalkenes^{14a} it has rarely been successfully applied in polymer functionalisation.^{14b}

It is even more surprising that for the ROMP polymer **3a/b** a quantitative conversion of all double bonds into 1,2-diol structures could be achieved. SEC measurements confirmed that polymer degradation did not occur during dihydroxylation. In the ¹H NMR spectra displayed in Fig. 2 the signals at δ = 5.86 ppm and 5.94 ppm, which are assigned to the *cis* and *trans* double bonds of **3b**, completely disappeared after the dihydroxylation step. The signal for the protons in the 5 position

was shifted to δ = 4.1 ppm. The signal for the proton in the allylic position to the *cis* and *trans* double bonds 2c, 2t were shifted from δ = 4.38 ppm and 4.04 ppm to 3.8 ppm and 3.6 ppm respectively. In accordance with the dihydroxylation of double bonds of low molecular weight compounds, the *cis* double bonds are converted selectively to *erythro* diols and the *trans* double bonds to the corresponding *threo* diols.¹⁵ In the case of **3b** the dihydroxylation method described for oligoalkenes^{14a} and polyalkenes^{14b} was well suited to obtain the fully hydroxylated pseudo-polyribofuranose **4b** which was completely water and methanol soluble. However, it was not soluble in THF, acetone and other organic solvents. In the case of **3a** the fully dihydroxylated polymer **4a** was only partially soluble in water but fully soluble in methanol. Therefore methanol was added instead of water as medium for the dihydroxylation in order to achieve a quantitative conversion. After deprotection of the ketal groups of **4b** by means of CF₃COOH–H₂O (9:1 vol. ratio) a water insoluble polymer **5b** was obtained which formed fine needles after precipitation from solution. These needles were only soluble in DMF or DMSO. ¹H-NMR data showed that the polymer was fully deprotected, which was indicated by the lack of peaks in the region of δ = 1.0–1.7 ppm. The hydrolytic stability of this carbohydrate analogue polymer towards acidic media (see above) is much better with respect to that of natural carbohydrates containing acetal linkages in the backbone. The solubility behaviour of these new pseudo-polyribofuranose derivatives is very similar to that of e.g. cellulose (cellulose is water insoluble, methyl cellulose with up to 45% ether bonds is water soluble), thus indicating that the pseudo-polyribofuranoses are likely to exhibit superstructures via intermolecular hydrogen bonding. The structure–property relationships of these new polyribofuranose analogue compounds will be investigated in more detail.

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Notes and references

- Y. C. Lee and R. T. Lee, *Acc. Chem. Res.*, 1995, **28**, 321.
- M. Witvrouw, J. Desmyter and E. DeClercq, *Antiviral Chem. Chemother.*, 1994, **5**, 345.
- K. H. Mortell, M. Gingras and L. L. Kiessling, *J. Am. Chem. Soc.*, 1994, **116**, 12 053.
- M. C. Schuster, K. H. Mortell, A. D. Hegeman and L. L. Kiessling, *J. Mol. Catal. A*, 1997, **116**, 209.
- D. D. Manning, X. Hu, P. Beck and L. L. Kiessling, *J. Am. Chem. Soc.*, 1997, **119**, 3162.
- K. Nomura and R. R. Schrock, *Macromolecules*, 1996, **29**, 540.
- C. Fraser and R. H. Grubbs, *Macromolecules*, 1995, **28**, 7248.
- M. B. Clark and T. R. Lee, *Polym. Prepr.*, 1998, **39**(1), 416.
- H. Prinzbach, H. Bringmann, J. Markert, G. Fischer and L. Knothe, *Chem. Ber.*, 1986, **119**, 589.
- G. C. Bazan, J. H. Oskam, H.-N. Cho, L. Y. Park and R. R. Schrock, *J. Am. Chem. Soc.*, 1991, **113**, 6899.
- B. M. Novak and R. H. Grubbs, *J. Am. Chem. Soc.*, 1988, **110**, 960.
- T. J. Boyd and R. R. Schrock, *Macromolecules*, 1999, **32**, 6608.
- M. Lautens, A. S. Abd-El-Azis and G. Schmidt, *Macromolecules*, 1990, **23**, 2819.
- (a) R. Haag, R. Zuber, S. Donon, C.-H. Lee, M. Noltemeyer, K. Johnson and A. de Meijere, *J. Org. Chem.*, 1998, **63**, 2544; (b) R. Haag, A. Sunder and J. F. Stumbé, *J. Am. Chem. Soc.*, 2000, **122**, 2954.
- P. Hadwiger and A. E. Stütz, *Synlett*, 1999, **11**, 1787.