Pseudopolysaccharides from the Ring-Opening Metathesis Polymerization (ROMP) of Derivatives of 7-Oxanorbornene

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Introduction

Polysulfates are potent and selective inhibitors of the *in vitro* replication of HIV and other enveloped viruses.[1] These properties were known as early as the 1960s when heparin sulfate was found to inhibit replication of the herpes simplex virus.[2] More recently, sulfated polymers were shown to exhibit varying degrees of inhibition with changing molecular weight and degree of sulfation. Dextran, for example, with molecular weights ranging from 1,000 to 500,000 were sulfated with one to two sulfate groups per glucose unit, and the anti-HIV activity against both HIV-1 and HIV-2 were found to vary with molecular weight: the higher M_W dextran sulfates showed greater inhibition of HIV-1, while the lower M_w fractions showed greater inhibition of HIV-2.[3]

The sulfated polymers in Figure 1 are known to be selective inhibitors of enveloped viruses.[1] Their selectivity and efficacy, however, varies with changes in structure. While the first three polymers are highly effective inhibitors in studies *in vitro*, they are likely to suffer from a lack of biocompatibility when employed in true biological systems. Indeed, the design of effective polymeric antiviral therapies must confront the issues of biocompatibility if concrete advances are to be made.

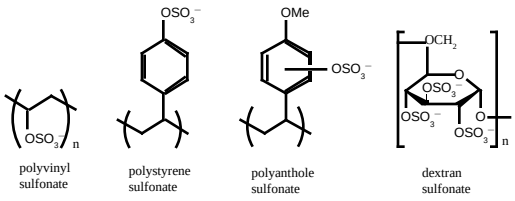


Figure 1. Examples of sulfonated polymers that inhibit HIV and other enveloped viruses.

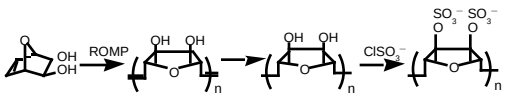
While the use of sulfated polysaccharides circumvents many of the problems of biocompatibility,[4] these sulfated polymers suffer from a different type of problem: the metabolic half-life of the sulfated polysaccharides is remarkably short. Dextran sulfate, for example, has an *in vivo* half-life of only 30 min due to facile degradation by glycosidases.[1] Short metabolic half-lives limit the therapeutic potential of any drug due to poor bioavailability and/or a high frequency of administration.

This paper describes a new class of psuedopolysaccharides designed to provide convenient solutions to both of these problems. We are targeting a new class of anionic pseudopolyribofuranoses that should exhibit biocompatibility and sufficiently long half-lives for therapeutic application.

Results and Discussion

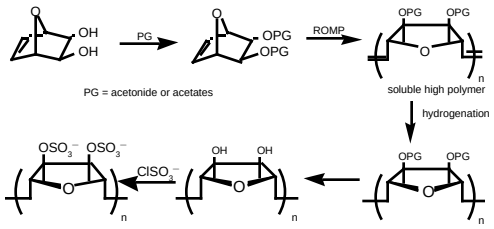
Scheme 1 shows our initial strategy for generating anionic pseudopolyribofuranoses. We explored the direct ring-opening metathesis polymerization (ROMP) of the *exo*- and *endo*-2,3-dihydroxy-7-oxanorbornenes initiated by $(Cy_3P)_2Cl_2Ru{=}CHPh$.[5] The catalyst to monomer ratio was varied, and the polymerizations were followed by ^1H NMR spectroscopy in CD_2Cl_2, THF-d_8 and C_6D_6. Unfortunately, the best results produced only oligomers, which readily precipitated from solution.

Scheme I. Synthesis of Anionic Pseudopolyribofuranoses.



To circumvent precipitation during the polymerization, we protected the diol derivatives as acetonides or acetates.[6] The revised strategy for generating the anionic pseudopolyribofuranoses is shown in Scheme II. The protected oxanorbornene derivatives were polymerized using the metal alkylidenes $Mo(NAr)(CH\text{-}t\text{-}Bu)(O\text{-}t\text{-}Bu)_2$ and $(Cy_3P)_2Cl_2Ru{=}CHPh$. In both THF-d_8 and C_6D_6, soluble polymers were produced.

Scheme II. Alternative Functionalization Strategy.



To examine the degree of control over the molecular weight during the polymerizations, the monomer to catalyst ratio was varied in a series of polymerizations of *endo-cis*-(isopropylidenedioxy)-7-oxabicyclo[2.2.1] hept-5-ene using the Mo-based initiator. Figure 2 shows that a moderate degree of control can be achieved. The PDIs of the polymers ranged from 1.3 to 1.8.

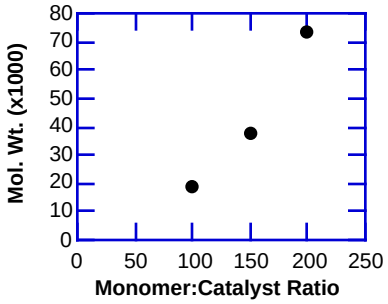


Figure 2. Plot of M_W versus Ratio of Monomer:Catalyst.

Conclusions

A successful route to the targeted pseudopolysaccharides via the ROMP of acetonide- and acetate-protected derivatives of *exo*- and *endo*-2,3-dihydroxy-7-oxanorbornenes has been demonstrated.

Experimental Section

Materials. Furan (99+%) and vinylene carbonate (97%) were purchased from Aldrich Chemical Company. The 7-oxanorbornene derivatives were prepared from literature procedures.[3,7,8] The Mo-based catalyst was purchased from Strem Chemicals, and the Ru-based catalyst was synthesized via a literature method.[9] Polymerizations were terminated by the addition of benzaldehyde or ethyl vinyl ether purchased from Aldrich Chemical Company. Polymers were precipitated into pentane, hexane or methanol.

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