Efficient Synthesis of a Conformationally Rigid Polymer Based on *myo*-Inositol Carbonate

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Compounds having three syn-axial hydroxyl groups on a six membered ring draw an interest due to their ability to form complexes with many cations.[1,2] The steric requirements of the cyclohexane polyols to form complexes with cations are, however, rather strict and only a few such compounds with three syn-axial hydroxyls, including *cis*-inositol, were known.[3-8] Moreover, none of these compounds is readily available, especially in large scales. Recently, synthesis of the readily available *myo*-inositol 4,6-carbonate **1** with three hydroxyl groups at the axial position on a cyclohexane was reported.[9] To our knowledge, this was the first example of the conformationally rigid cyclohexane polyols using the readily available *myo*-inositol. Here, the carbonate group was introduced as a short bridge between O-4 and O-6 of *myo*-inositol, holding the conformation of the cyclohexane that has three axial hydroxyl groups. Other bridges, including a methylene group, were known to have difficulties to be placed between the two axial hydroxyl groups.[10]


1   **2**
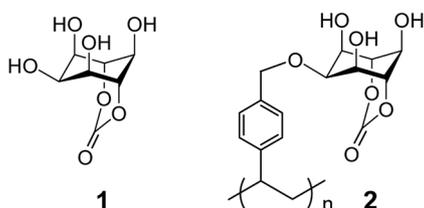
We were interested in developing a novel inositol-based polymer with an organized backbone and oriented functional groups. It was expected that the oriented functional groups, originated from the structurally rigid inositol structure, would be responsible for the desired interaction with the substrate, cations in this case, whereas the polymer backbone provide a structural framework and mechanical stability.[11-16] Polymeric analogues of inositol should, therefore, be useful as a metal chelating ligand since polymers are generally valued as chelating agents due to their advantages of easy use and removal after chelation.

We report herein an efficient synthesis of a conformationally rigid inositol carbonate-based polymer **2** to deliver such features. Although the reported procedure by Angyal,[9] was efficient to prepare the inositol carbonate itself (Scheme 1), it seemed difficult to functionalize for further derivatization (*vide infra*). We have, therefore, developed an alternative synthetic route to *myo*-inositol 4,6-carbonate with a polymerizable group at the equatorial position and successfully polymerized to afford a conformationally rigid polymer as a novel metal-chelating ligand.

Following the literature procedure,[9,17] the silylated inositol carbonate **5** was first prepared (Scheme 1). Deprotection of the silyl group, however, in order to introduce a polymerizable group at the equatorial hydroxyl group of the cyclohexane, using a standard basic fluoride ion (*e.g.* TBAF) also cleaved the carbonate group. None of the silyl deprotection methods attempted proved to be effective. Although the desired inositol carbonate with a free equatorial hydroxyl group **6** was obtained by a partial cleavage of the silyl group during the strongly acidic deprotection of the orthoformate group, the yield was rather too low.[18] The poor solubility of **6** also made further derivatization of this compound difficult.

Alternatively, the *myo*-inositol orthoformate **3** was first diallylated to give the 4,6-diallyl inositol derivative **7** (Scheme 2). The preferential allylation of the axial hydroxyls, in the presence of the less hindered 2-hydroxyl group, was possible due to the stabilizing effect from the neighboring axial group in **3** as the Na$^+$ counterion is chelated by the second axial OH group.[19] Although the yield for the direct diallylation of the axial hydroxyl groups was rather low (36%), it innecessitated the tedious protection and deprotection of the more reactive equatorial hydroxyl group, using TBDMSCl, a typically used expensive protecting agent for this system. The diallyl groups in **7** were then isomerized to the enol ethers **8** using Wilkinson's catalyst.[20] Introduction of the styrenyl moiety as a polymerizable group to the free alcohol, followed by hydrolysis of the enol ethers using mercury(II) acetate[21] produced the diol **9** in 84% yield
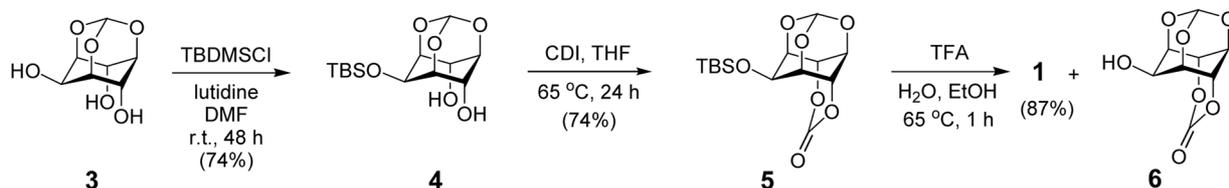
Scheme 1. Synthetic route to *myo*-inositol 4,6-carbonate.
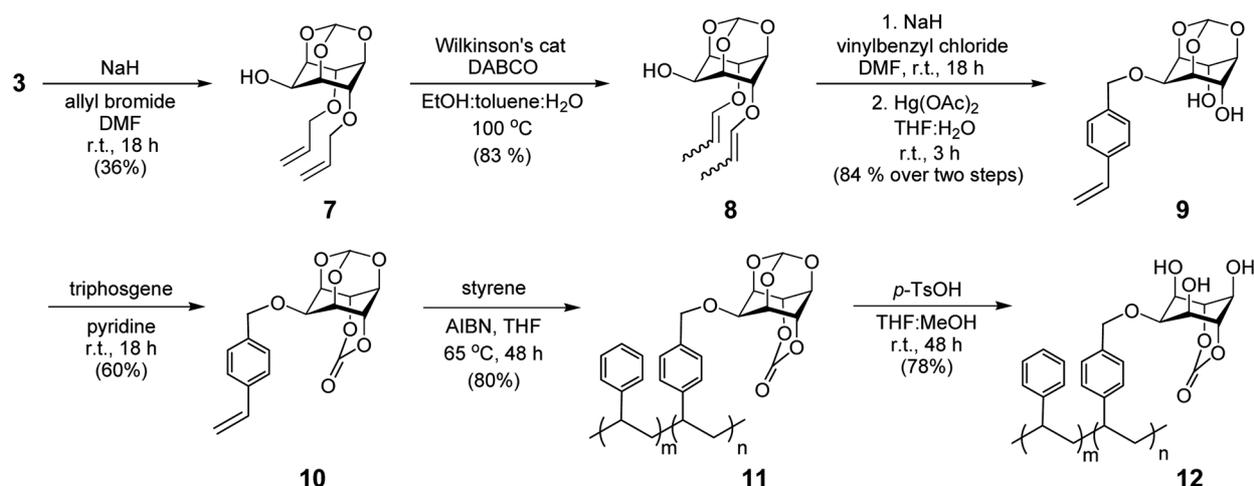
Scheme 2. Synthesis of *myo*-inositol 4,6-carbonate-based polymer[†]

over two steps. Treatment of **9** with triphosgene in the presence of pyridine afforded the carbonate **10** in a moderate yield (60%). Formation of the carbonate using CDI, as used the literature,[9] was not very effective for our system. The monomer **10** was expected to fit the need for the preparation of well-defined synthetic polymers, arranging functional groups in a predetermined fashion, and it can be prepared in a multigram scale. Copolymerization of the *myo*-inositol carbonate **10** with styrene was carried out at 65 °C in THF with AIBN as a radical initiator to give the inositol polymer **11** in 80% yield and molecular weight of 11,000 (M_n).[22]

Finally, removal of the orthoformate group in polymer **11** was accomplished in the presence of *p*-TsOH in 78% yield (Scheme 2). The structure determination of the deprotected polymer **12** was carried out by the ^{13}C NMR spectrum, and showed disappearance of the signal corresponding to the orthoformate carbon ($\delta = 102$), whilst preserving the carbonate signal ($\delta = 145$). The IR spectrum of **12** also showed the maintenance of the carbonate group at 1750 cm^{-1}, and a strong signal due to the free hydroxyls appeared at 3440 cm^{-1}.[23] In addition, the spectroscopic properties of the inositol ring atoms in **12** were very similar to those of other precursors, indicating that the conformation of the inositol ring was maintained.[23] The preliminary metal binding studies using polymer **12** were carried out by comparing the IR spectra of **12** with polychelate (**12** with CaCl$_2$). The region assigned to the hydroxyl groups of the polychelate, compared with the parent polymer ligand **12**, exhibited broadness toward lower wavenumbers, which is ascribed to the involvement of the hydroxyl groups in metal-chelation.[24]

In conclusion, we have successfully synthesized the polystyrene carrying a conformationally rigid *myo*-inositol substituent as a possible metal-chelating ligand. We are further investigating the metal binding properties of this polymer and its applicability to the practical use such as molecular imprinting.

References

[†]All new compounds exhibited satisfactory analytical data, which included IR, ^{1}H and ^{13}C NMR spectra, and high-resolution mass spectra.

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