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Synthesis of Oligo(spiroketal)s from Naturally Occurring *myo*-Inositol

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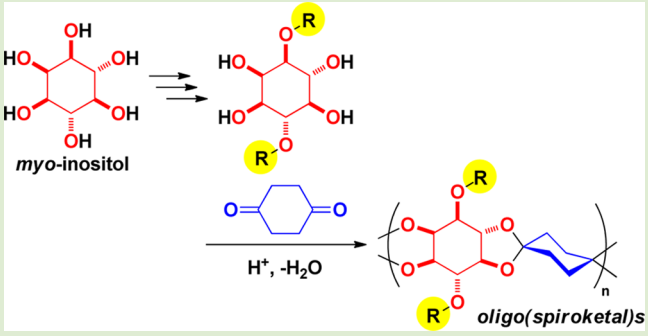
Supporting Information

ABSTRACT: Dehydrating polycondensation of tetraol-type monomers derived from naturally occurring *myo*-inositol with 1,4-cyclohexanedione formed a series of oligo(spiroketal)s. One of the spiroketals had reactive allyl pendants, which were useful for side-chain modifications via thiol−ene chemistry.

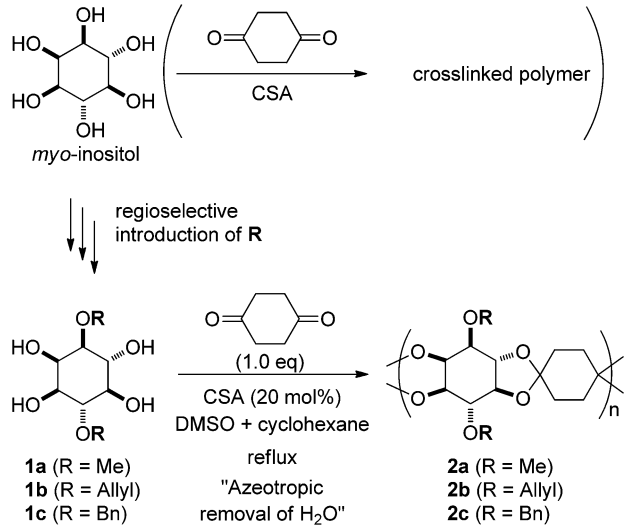


Spiropolymers and spirooligomers, whose main chains consist of spirocyclic structures,[1−6] represent a major target in polymer synthesis. They have double-stranded main chains with restricted freedom for conformational changes and, thus, are expected to exhibit a high degree of thermal stability. In addition, because of their rigid rod-like shapes, their heat resistance and mechanical strength are expected to be enhanced by their spontaneous alignment and resulting bundle-like packing. Spiropolymers and spirooligomers also exhibit potential applicability as useful linear and stiff building blocks for well-defined nanoscale architectures.[7,8]

Among the potential synthetic approaches, those based on ketalization and analogous reactions serve as straightforward and reliable methods.[1,9−14] These approaches were pioneered by Bailey and co-workers.[1] Makhseed and McKeown reported the efficient synthesis of poly(spiroketal)s by the polycondensation of cyclic diketones and pentaerythritol.[9] One of the spiroketals reported therein was highly heat-resistant, showing glass transition at 180 °C. Yaghi and co-workers reported an oligo(spiroorthocarbonate) that could be synthesized by the polycondensation of pentaerythritol and tetraethylorthocarbonate.[11] The oligo(spiroorthocarbonate) was highly crystalline because of the dense packing of the rigid nanorods, highlighting its potential applications in high-performance materials. Hino and Endo reported a cross-linking reaction of the same oligo(spiroorthocarbonate) based on the cationic ring-opening polymerization of the spiroorthocarbonate moieties in the main chain.[15]

Herein, we describe a new series of partially biobased oligo(spiroketal)s (Scheme 1). The monomers used in the present work are based on tetraols **1** derived from naturally occurring *myo*-inositol. *myo*-Inositol is a cyclic hexaol; its phosphorylated derivatives such as phytic acid are abundantly distributed in animals and plants (e.g., rice bran). Recently, we reported a few polymer syntheses using *myo*-inositol as a renewable source,[16,17] in an effort to contribute to the progress of biobased polymers.[18−21] To date, *neo*-inositol, a stereoisomer of *myo*-inositol, has been used as the core of a highly rigid oligo(spiroketal).[12] However, to the best of our knowledge, there has been no report regarding the synthesis of oligo(spiroketal)s from *myo*-inositol. A partially biobased poly(spiroacetal) synthesized from trehalose has been reported.[22,23] The use of *myo*-inositol as a starting material for the synthesis of oligo(spiroketal)s has a distinct advantage, as *myo*-inositol has six hydroxyl groups, two of which can be used for

Scheme 1. Synthesis of Oligo(spiroketal)s from *myo*-Inositol



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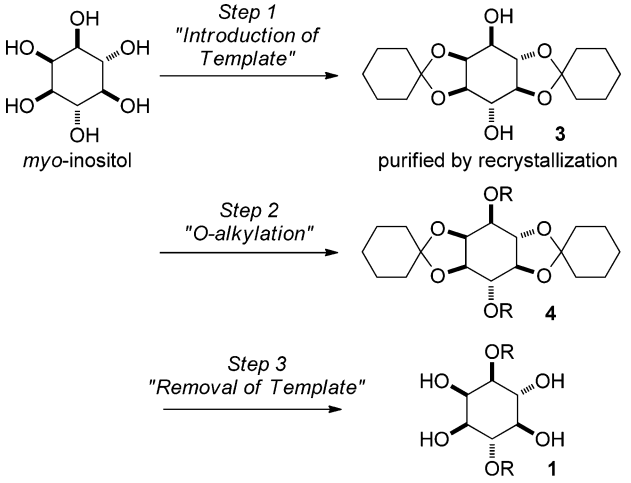
functionalization such as the introduction of alkyl groups (R in Scheme 1), thus, facilitating the design of diverse tetraol monomers. By utilizing tetraol monomers with different R groups, a series of oligo(spiroketal)s with different physical properties can be synthesized. Such structural diversity from one starting material has been not reported thus far.

Initially, we attempted to use pristine *myo*-inositol in the polycondensation with 1,4-cyclohexanedione (CHD; Scheme 1). This reaction yielded an insoluble solid, implying that the poor regioselectivity in the ketalization led to cross-linking. To overcome this problem, we envisaged the derivation of *myo*-inositol into tetraols **1** and their use as monomers for the synthesis of oligo(spiroketal)s. The synthetic route consists of the three following steps (Scheme 2): (1) introduction of

Scheme 2. Synthesis of Tetraol Monomers from *myo*-Inositol[a]



[a]Step 1: 1,1-Dimethoxycyclohexane, *p*-TsOH; Step 2: NaH, DMF, then RX; Step 3: TFA, H_2O.

templates, that is, ketalization of *myo*-inositol into the corresponding bisketal **3**, (2) *O*-alkylation of **3** to obtain bisether **4** to mask the unnecessary hydroxyl groups for the polycondensation, and (3) removal of the template from **4** to obtain **1**. Potential advantages of this derivation involve (1) knowing the specific reaction sites to be ketalized in the chain growth of the oligo(spiroketal)s and (2) the opportunity to introduce functional groups onto the tetraol monomers during the *O*-alkylation step. In the first step, the bisketalization of *myo*-inositol was carried out using 1,1-dimethoxycyclohexane according to a reported procedure.[24] The reaction afforded a mixture of isomers with **3** as the major isomer. Recrystallization of the mixture from hexane/ethyl acetate allowed for the isolation of pure **3**.[16] In the second step, *O*-alkylation was performed according to a reported procedure to obtain corresponding bisethers **4**.[24−28] The ^{1}H NMR spectrum of **4a** is shown in Figure 1. ^{1}H NMR spectra of **4b** and **4c** are shown in the Supporting Information as Figures S1 and S2, respectively. The ^{13}C NMR spectra of **4** are shown in Figures S3−S5. In the third step, the ketals were hydrolyzed under acidic conditions. The resulting tetraols **1** were isolated by recrystallization. The NMR spectroscopic data of **1** agreed with the reported data.[26,27,29−31] The spectra are shown in the Supporting Information as Figures S6−S8.

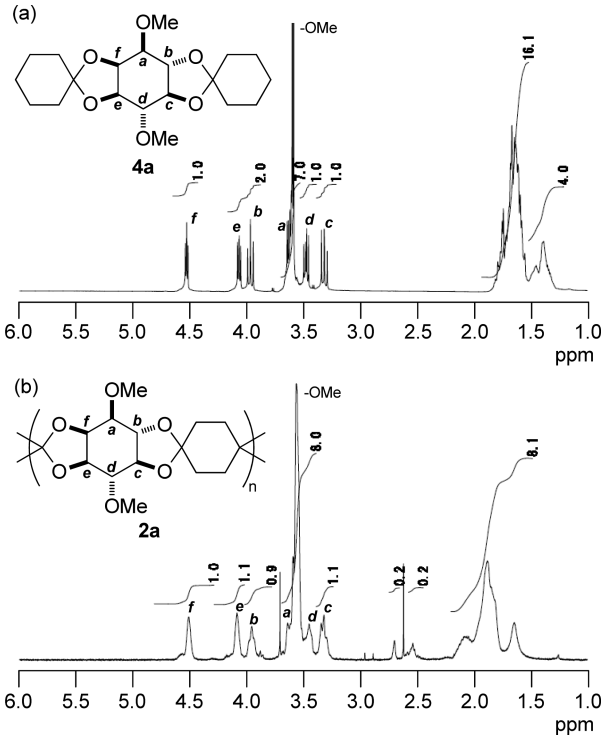


Figure 1. ^{1}H NMR spectra (in $CDCl_3$) of (a) model compound **4a** and (b) oligo(spiroketal) **2a**.

The polycondensation of tetraols **1** and CHD was performed using camphorsulfonic acid (CSA) as the acid catalyst (Scheme 1). Cyclohexane was added to a solution of **1**, CHD, and CSA in DMSO to azeotropically remove the water formed by ketalization. The resultant biphasic mixture was stirred vigorously by heating it to above 100 °C to reflux the cyclohexane. For the experiments, an apparatus equipped with a condenser and water receiver was used (Figure S9 in the Supporting Information). After 48 h, the cyclohexane layer was removed by decantation, and the DMSO layer was poured into a solution of 5% aqueous sodium bicarbonate in order to precipitate the target oligo(spiroketal)s **2**. The yields of the oligo(spiroketal)s, their number-average molecular weights (M_n), and their weight-average molecular weights (M_w), as estimated by size exclusion chromatography (SEC), are shown in Table 1. The number of the repeating units in **2a**, which was

Table 1. Synthesis of Oligo(spiroketal)s 2 and Their Properties

run	2	R	yield[a] (%)	M_n[b]	M_w[b]	T_{d5}[c] (°C)
1	**2a**	Me	67	2100	4000	334
2	**2b**	allyl	94	1400	2600	319
3	**2c**	benzyl	93	1400	2400	321

[a]Insoluble parts in 5% $NaHCO_3$ aq. [b]Estimated by size exclusion chromatography (SEC; polystyrene standards, eluent = DMF containing 1 wt % LiBr). [c]Determined by TGA.

roughly estimated by dividing M_n by the molecular weight of the repeating unit, was 7.4. The estimated values for **2b** and **2c** were 4.2 and 3.2, respectively.

The chemical structures of oligo(spiroketal)s **2** were analyzed using ^{1}H NMR. The ^{1}H NMR spectrum of **2a** is shown in Figure 1, along with that of bisketal **4a**, a low-

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molecular-weight model of **2a**. The spectra clarified the structural similarities between the repeating unit of **2a** and **4a**.

In the spectrum of **2a**, signals attributed to the chain ends were observed; a signal at 2.6 ppm was attributed to the methylene groups adjacent to the ketone carbonyl on the chain ends, while the signal at 2.7 ppm was attributed to the OH groups on the chain ends. The spectra of **2b** and **2c** are shown in Figures S1 and S2, respectively. The successful formation of the oligo(spiroketal)s was confirmed by comparing their spectra with those of relevant model compounds **4b** and **4c**. The presence of ketone moieties on the chain ends was also confirmed by IR spectroscopy. An absorption attributed to the ketone carbonyl was observed at 1716 cm^{-1} (Figure S9 in the Supporting Information).

For the ^{13}C NMR analysis of **2**, solid-state spectroscopy with cross-polarization magic angle spinning (CP-MAS) was used, because the solubility of **2** in $CDCl_3$ and DMSO-d_6 was limited, and it was rather difficult to obtain solution NMR spectra with high S/N ratios. In the spectrum of **2a** (Figure S3 in the Supporting Information), signals attributable to the quaternary carbons formed by the ketalization were clearly observed. Similarly, the presence of quaternary carbons in the main chains of **2b** and **2c** was clearly confirmed as well (Figures S4 and S5, respectively).

In addition, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass analysis of the oligo(spiroketal)s provided detailed information regarding their structures. The MALDI-TOF MS spectrum of **2a** is shown in Figure 2. The m/z numbers of the signals are shown in Table S1 in the Supporting Information. M_n and M_w (calculated from the data) were 2600 and 3400, respectively. The spectrum confirmed the presence of three series of oligo(spiroketal)s sharing a common main chain with different terminal structures. Specifically, series A contained a diol and ketone moiety on each of the chain ends, series B bore ketone moieties on both chain ends, and series C exhibited diol moieties on both chain ends. The signals attributed to each series differed by 284 Da, which corresponded to the molecular weight of the repeating unit of **2a**.

The MALDI-TOF MS spectrum of **2b** is shown in Figure S11 in the Supporting Information. The m/z values of the peaks are listed in Table S2 in the Supporting Information. M_n and M_w of **2b** were calculated as 2700 and 3800, respectively. Moreover, three major series of signals were observed, similar to the spectrum of **2a**. Besides the three major series, there were also three minor series, namely, series A′, B′, and C′, of which the m/z values were smaller than those of series A, B, and C, respectively, by 40 Da. The decrease in the m/z value was attributed to the loss of one allyl group from one polymer chain and the addition of one proton. The MALDI-TOF-MS spectrum of **2c** is shown in Figure S12 in the Supporting Information. The m/z values of the peaks are listed in Table S3 in the Supporting Information. M_n and M_w of **2c** were calculated to be 2100 and 3100, respectively. Three major series of signals (series A, B, and C) and a minor series (series C′) were observed. The m/z values of the peaks corresponding to series C′ were smaller than those of series C by 91 Da, owing to the loss of one benzyl group from one polymer chain and the addition of one proton.

The defect-free main chain structures clarified by MALDI-TOF mass analysis implied that the low molecular weights were not caused by side reactions. Therefore, as the reaction was conducted under equilibrium conditions, hydrolysis could not

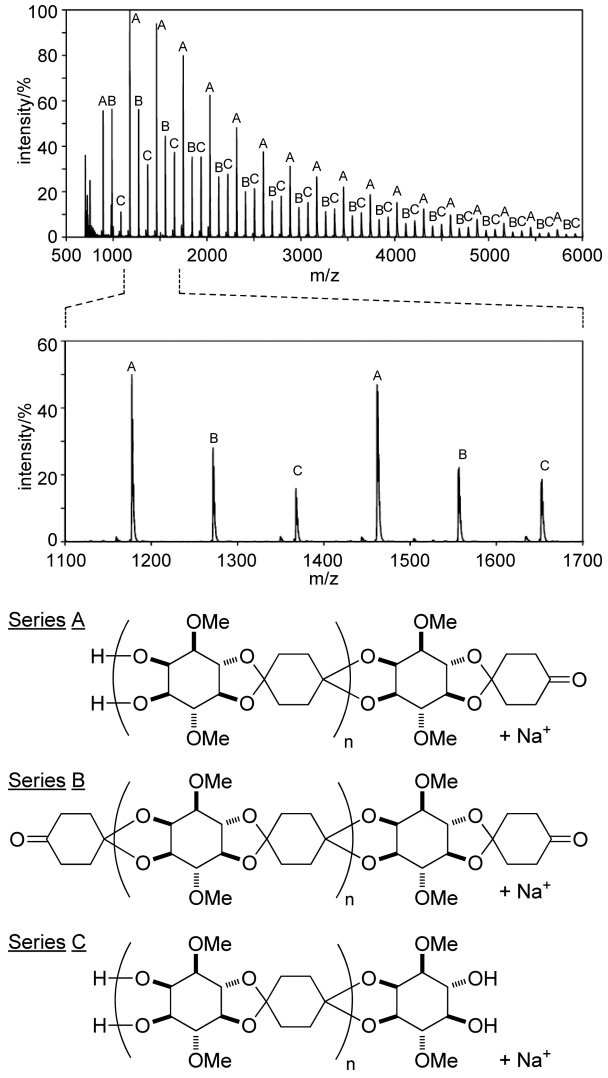

Figure 2. MALDI-TOF MS spectrum of **2a**.

be prevented, owing to the insufficient azeotropic removal of water from DMSO, which led to the low molecular weights.

Oligo(spiroketal)s **2** were subjected to thermogravimetric analysis (TGA) in order to evaluate their thermal degradation. The resulting TGA profiles are shown in Figures S13−S15 in the Supporting Information. Accordingly, 5% weight loss temperatures (T_{d5}) were extracted and are listed in Table 1. The T_{d5} values of **2** were greater than 300 °C. The TGA profile of **2a** did not show any noticeable weight loss below 310 °C. Oligo(spiroketal)s **2b** and **2c** were less thermally stable than **2a** and began degrading at 270 and 230 °C, respectively. The decreased thermal stability of **2b** and **2c** compared to **2a**, as judged from the onset temperatures, could be related to their low degree of polymerization and consequential larger number of terminals bearing hydroxyl groups, from which H_2O molecules can be eliminated at relatively low temperatures. On the other hand, the residual wt % values at 500 °C of **2a**, **2b**, and **2c** increased in this order, suggesting that the allyl side chains of **2b** and the benzyl side chains of **2c** were capable of undergoing thermally induced cross-linking at sufficiently high temperatures.

In addition, oligo(spiroketal)s **2** were analyzed by DSC. The resulting profiles are shown in Figures S13−S15 in the Supporting Information. Although the profiles were of

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somewhat poor quality because of the decreased baselines and low signal-to-noise ratios, the glass transition temperatures (T_gs) of **2** were detected. The T_gs of **2a**, **2b**, and **2c** were 130, 90, and 123 °C, respectively. The low T_g of **2b** was in good accordance with the high flexibility of the allyl group, as compared to the two other side chains in the oligo(spiroketal)s. The DSC profile of oligo(spiroketal) **2a** showed not only glass transition, but also an endothermic peak around 250 °C, which was attributed to the melting of crystalline domains in bulk **2a**. This suggested that the compact methyl side chains did not hinder the alignment of the chains in **2a** to result in a densely packed structure.

Next, molecular mechanics (MM) calculations were carried out to obtain an insight into the conformation of oligo(spiroketal)s **2**. The oligo(spiroketal)s synthesized in this work were not well-defined in terms of stereochemistry and sequential regulation. Tetraols **1** used herein were racemic, and thus, the corresponding oligomers can be randomly composed of two enantiomeric repeating units. In addition, because the conditions for the polycondensation might be harsher than those that would allow for the differing reactivities of the *cis*-diol and *trans*-diol moieties in the monomers, the oligo(spiroketal)s can be randomly composed of head-to-head and head-to-tail sequences. In contrast, for the MM calculations, a much simpler model composed of homochiral inositol-derived units was used in order to avoid complexity in the molecular modeling. In the model, the inositol-derived units were connected to the CHD-derived cyclohexane components in alternating head-to-head and tail-to-tail manners, but not in a head-to-tail manner. Figure S16 shows the resulting structure in the global minimum energy and implies that oligo(spiroketal)s **2** would become rigid rod-like molecules if enantiomerically pure tetraols **1** were used and if sequence regulation in the polycondensation was achieved.

Finally, a preliminary investigation regarding the utilization of allyl-functionalized oligo(spiroketal) **2b** as a precursor for the synthesis of diverse oligo(spiroketal)s through chemical modification of its C−C double bonds was carried out. The thiol−ene reaction was chosen because of its high reliability and versatility.[32−36] Scheme 3 shows the radically induced thiol−ene reaction at the side chains. By employing AIBN as a radical source, the reaction of **2b** with an excess of octanethiol was conducted in 1,4-dioxane at 65 °C. The resulting oligo(spiroketal) **5** was isolated as the methanol-insoluble fraction. Its M_n and M_w, as estimated by SEC analysis (calibrated with polystyrene standards; eluent = DMF containing 1 wt % LiBr), were 3400 and 4700, respectively, and were larger than those of precursor **2b**.

Scheme 3. Side Chain Modification of Oligo(spiroketal) by Thiol−Ene Reaction

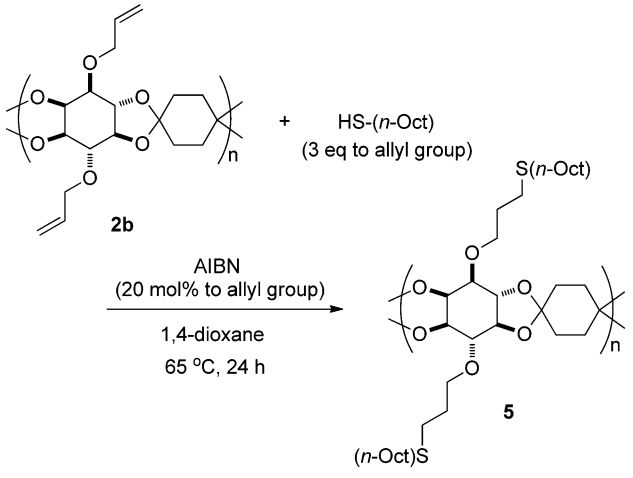

Figure S17 in the Supporting Information shows the ^{1}H NMR spectrum of **5**, which confirmed the complete consumption of the allyl groups. Figure S17 also shows the ^{13}C NMR spectrum, which confirmed the presence of quaternary carbons in the ketal moieties. Additional confirmation of the successful side-chain modification was obtained by MALDI-TOF MS analysis of **5**. Figure S18 in the Supporting Information shows the resulting spectrum, which consisted of seven series of peaks. In each series, the signals appeared in intervals of 629 Da, which was in good accord with the formula weight of the repeating unit of **5**. The peaks attributed to series A were attributed to the chains with a diol moiety at one end and a ketone moiety at the other end. The peaks corresponding to series B were attributed to the chains with ketone moieties on both chain ends, while those in series C were attributed to the chains with diol moieties on both chain ends. Additionally, series A′ and series C′ were also observed, and the signal intensities were much lower than those of series A and series C. The signals in series A′ were shifted from those in series A to a smaller m/z value by 186 Da. A similar shift by 186 Da from series C to series C′ was observed as well. The m/z value of 186 Da was in good accord with the formula $C_{11}H_{22}S$, suggesting some of the chains of oligo(spiroketal) **5** lost an octylthio group and were protonated during the ionization process. The remaining series were series A″ and series C″. Compared with series A and series C, the m/z values of the signals corresponding to series A″ and series C″ were larger by 16 Da, owing to the oxidation of one sulfide in each of the chains to the corresponding sulfoxide.

In summary, a novel series of oligo(spiroketal)s were developed based on naturally occurring *myo*-inositol as a starting material, and its regioselective *O*-alkylation into the corresponding tetraol-type monomers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, ^{1}H and ^{13}C NMR spectra, MALDI-TOF MS spectra and data, TGA profiles, DSC profiles, and MM2 modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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