Functionalizable Stereocontrolled Cyclopolyethers by Ring-Closing Metathesis as Natural Polymer Mimics

Functionalizable Stereocontrolled Cyclopolyethers by Ring-Closing Metathesis as Natural Polymer Mimics

Mohammed Alkattan,[a,b] Joëlle Prunet*[b] and Michael P. Shaver*[a]

Abstract: While complex stereoregular cyclic architectures are commonplace in biomacromolecules, they remain rare in synthetic polymer chemistry, limiting the potential to develop synthetic mimics or advanced materials for biomedical applications. Herein we disclose the formation of a stereocontrolled 1,4-linked six-membered cyclopolyether prepared by ring-closing metathesis (RCM). Ru-mediated RCM, with careful control of catalyst, concentration and temperature, selectively affords the six-membered ring cyclopolymer. Under optimized reaction conditions, no metathetical degradation, macrocycle or crosslinking was observed. Post-polymerization modification by dihydroxylation afforded a novel polymer family encompassing a poly(ethylene glycol) backbone and sugar-like functionalities ("PEGose"). This strategy also paves the way for using RCM as an efficient method to synthesize other stereocontrolled cyclopolymers.

Control over the absolute configuration of a synthetic polymer main chain remains a significant challenge,[1,2] especially in light of the importance of this regularity in natural polymers.[3] This stereoregularity of the main chain plays a significant role in shaping the three-dimensional structure, and in-turn influencing the biological function of the natural macromolecules. In addition, rings are embedded in the backbones of many natural polymers, which restricts the bond rotation around the stereogenic centers.[4] These local conformational restrictions result in a specific compact structure along the polymer backbone: *i.e.* the six membered cyclic structures of cellulose and amylose backbones (Figure 1) form linear and helical structures, respectively. However, synthetic polymers that are made of similar 1,4-linked six-membered rings that would mimic these secondary structures, present a unique challenge to synthetic chemists, especially if conventional polymerization techniques are employed.[5]

Ring-closing metathesis (RCM) has been predominantly used to prepare cyclic small molecules, including phosphine-boranes, sulfides, amines, phenols, and oxazolines.[6] The use of RCM in polymer synthesis, however, remains rare,[7] with a few examples for the preparation of polymeric nanoparticles,[8] cyclic-[9] and cyclo-polymers.[10] We hypothesized that this underutilized post-polymerization technique could be employed for the synthesis of cyclopolyethers to mimic the topology of polysaccharides, where the configuration of all the stereogenic centers present in these polymers is controlled (Figure 1). While the broad functional group tolerance of metathesis catalysts suggests a broad reaction scope, poly(ethylene glycol) backbones are especially interesting given their role as gold standard stealth polymers in drug delivery.[11] We thus envisaged a sequence of ring-opening polymerization (ROP), ring-closing metathesis (RCM) and dihydroxylation (DH), as shown in Figure 1. ROP of 3,4-epoxy-1-butene (EB) would afford polyepoxybutene (PEB), with the chirality of the parent epoxide leading to stereogenic control in the linear polymer. Ring-closing metathesis would then give a 1,4-linked functionalizable cyclopolyether (FCPE). Further functionalization, specifically diatereoselective dihydroxylation (DH), would produce a new stereocontrolled polymer that we have called "PEGose", as it has the structural features of both sugars and PEG, replacing the glycosidic bond of amylose with a strong ether link.

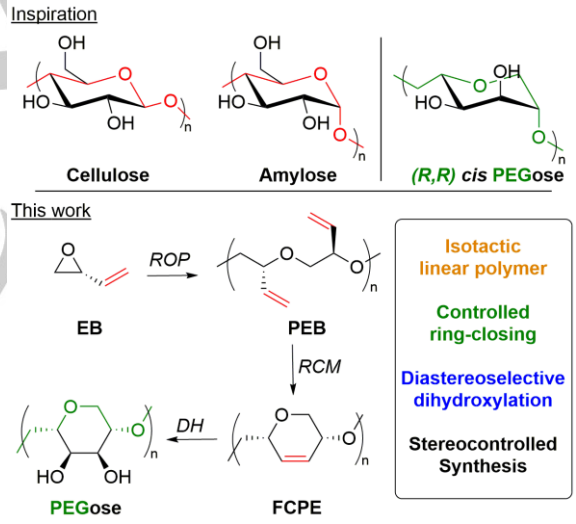

Figure 1. Biopolymers serving as inspiration for stereocontrolled polymer synthesis, and a strategy to target the desired *cis*-PEGose cyclopolymer.

For this structural control, it is imperative to start with enantiopure EB. Atactic PEB would lead to a non-stereocontrolled cyclopolymer, where the 1,4-links would be indiscriminately *cis* (amylose-like) or *trans* (cellulose-like) (Figure 2). Furthermore, the subsequent dihydroxylation reaction would not be diastereoselective on the *trans* 1,4-disubstituted six-membered rings. On the other hand, dihydroxylation of the *cis* cyclopolymer will occur exclusively from the top face, which is not hindered by the two substituents.

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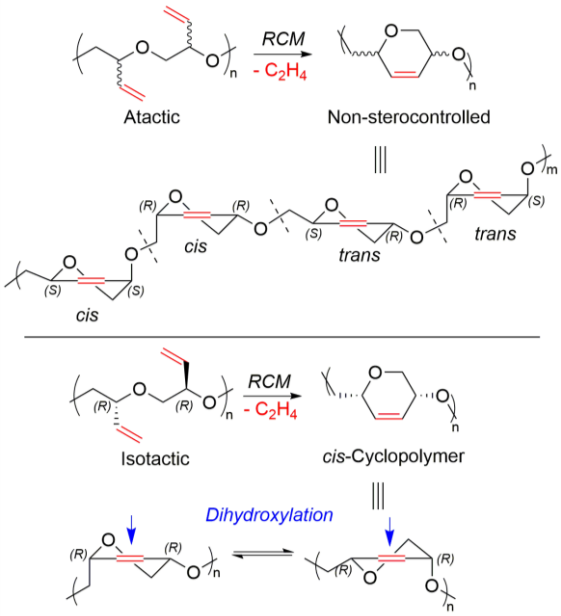
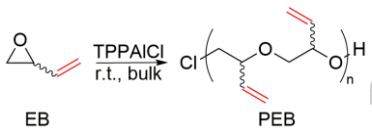


Figure 2. Influence of polymer tacticity on RCM and resultant polymer stereochemistry in *cis*- and atactic-FCPE.

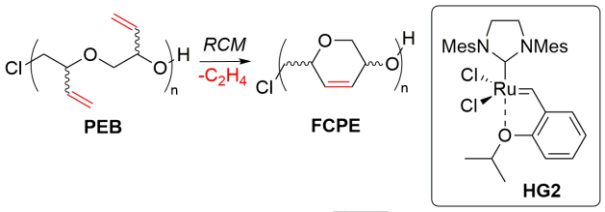
Ring-opening and ring-closing reactions were first explored with the commercially available racemic 3,4-epoxy-1-butene monomer. While PEB has been prepared via a number of routes from the EB monomer,[12,13] our optimized reaction conditions used tetraphenylporphyrin aluminium chloride [(TPP)AlCl] as an initiator[14] for the bulk polymerization of EB at ambient temperature (Equation 1, see SI-Table S1).



(1)

The ^{13}C-NMR spectrum of the resultant PEB showed two peaks for the stereogenic carbon, confirming the expected atacticity of the produced PEB (*a*-PEB), as the catalyst is not stereoselective. Low, controlled molecular weight polymers were produced, with $M_{n,GPC}$ of 2100 and 3200 respectively, and Đ < 1.2. Although RCM on *a*-PEB will not give a stereocontrolled cyclopolyether, it was used to establish optimum RCM conditions. While little difference in molecular weight was observed by gel permeation chromatography (GPC) with the lowest molecular weight PEB samples, due to overlap with eluent peaks, the higher molecular weight samples ($M_{n,GPC}$ 3200) showed a clear molecular weight loss on ring closing, correlating well with the loss of a single ethylene molecule per repeat unit (Table 1). Optimal ring-closing conditions for PEB included the use of 5 mol% of the second-generation Hoveyda-Grubbs (HG2) catalyst, at high concentrations of polymer (≥ 0.2 M respective to monomer unit) in 1,2-dichloroethane (1,2-DCE) (Table 1). Note that poor conversions were achieved with the first-generation Grubbs catalyst, likely due to lower reactivity and thermal stability (see SI-Table S2).[15]

Table 1. RCM of *a*-PEB.



Entry[a]	[Olefin]	$M_{n,st}$[b]	$Đ_{st}$[b]	Conv. %[c]	$M_{n,th}$[d]	M_n[b]	Đ[b]
1	0.2	3200	1.19	99	2540	2500	1.21
2	0.4	3200	1.19	99	2540	2900	1.3

[a] Reactions performed in 1,2-DCE at reflux with 5 mol% of HG2 catalyst for 72 h. [b] M_n and Đ determined by GPC *vs* uncorrected PS standards. [c] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration of the produced polymer. [d] $M_{n,th}$ = PEB $M_{n,GPC}$ × 0.8 due to expected loss of one C_2H_4 per monomer unit.

When concentrations were kept at 0.2 M (Table 1, entry 1), no cross-linking was observed, and polymer dispersity and viscosity remained similar. However, at higher concentrations (0.4 M), competing ring-closing and polymer cross-linking occurs, evidenced by the formation of a high molecular shoulder in GPC traces (see SI-Figure S1).[16] This new polymer represents the first synthetic cyclo-polyether prepared, yet its inherent atacticity prevents any overall topological control. Thus, *isotactic*-rich PEB (*i*-PEB) was synthesized by ROP of the *R*-enantiomer of EB (95:5 er), which was prepared from *racemic* EB by Jacobsen's hydrolytic kinetic resolution (see SI-Page 3).[17] The behavior of the isotactic polymer towards RCM was directly compared to that of its atactic derivative under the previously optimized conditions (Table 2).

Table 2. RCM of PEB with HG2 catalyst.

Entry[a]	PEB M_n[b]	Đ[b]	T_g °C[c]	Time (days)	FCPE		Đ[b]	T_g °C[c]
					$M_{n,th}$[d]	M_n[b]		
rac	4380	1.18	-56	5	3500	2700	1.22	-26
R	3940	1.15	-54	7	3150	2600	1.19	-11

[a][Olefin] = 0.2 M; the reaction conversion was monitored daily until >99% by ^{1}H-NMR spectroscopy using 1,2-DCE at reflux with 5 mol% HG2 catalyst. [b] M_n and Đ determined by GPC *vs* uncorrected PS standards. [c] Determined by differential scanning calorimetry. [d] $M_{n,th}$ = PEB $M_{n,GPC}$ × 0.8.

The kinetics of cyclization of the enantiomerically pure monomer were significantly slower than for the racemic monomer. Plotting reaction kinetics (Figure 3 and SI-Figure S2) showed that the cyclization reaction progressed quickly in the beginning, with 94% of the pendant vinyl groups forming cross-links within 30 min for both atactic and isotactic derivatives. The metathesis reaction then significantly slowed down, especially for the more conformationally rigid isotactic derivative. This profile suggests a mechanism originally proposed by Coates and Grubbs:[10] (i) a

fast stage when the catalyst randomly closes adjacent olefins until only isolated olefins remain, and (ii) a slow stage when the rings rearrange along the chain until all olefins are cyclized. This requires that the cyclized olefins can undergo further metathetic reactions, enabling a re-opening and exchange of the product rings.[18] The two-stage reactivity is showcased through the RCM optimization, with the first stage completed in a similarly short time regardless of the solvent used (1,2-DCE, DCM, THF, $CHCl_3$) or catalyst loading (2-5%) (see SI-Tables S3-S6).

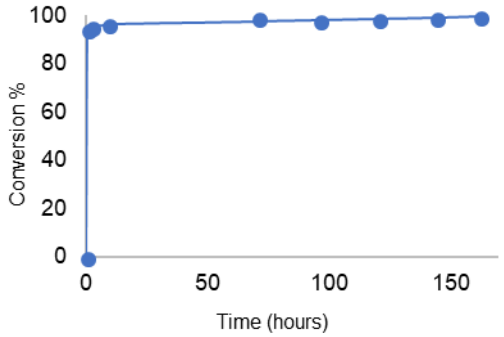


Figure 3: The RCM of iso-PEB, $M_{n,GPC}$ 3940 and Đ 1.15, kinetic profile at 0.2 M using 5% of 2nd H-G catalyst in 1,2 DCE under reflux monitored by ^{1}H-NMR spectroscopy.

An illustration of this mechanism can be observed in ^{13}C-NMR spectra of both atactic and isotactic FCPE and PEB (Figure 4), which demonstrate that greater than 99% of the olefins of PEB are cyclized (Figure 4, B and E). In the atactic FCPE (Figure 4, B), the new olefin peaks appear as broad, overlapping resonances (δ 125-132), reflecting the different ring configurations along the polymer backbone. On the other hand, *i*-FCPE showed only two sharp olefin resonances (Figure 4, E), confirming the stereocontrolled structure of the polymer (Figure 2, *cis*-cyclopolymer). However, the spectrum of *i*-FCPE after 94% conversion (Figure 4, D), which was taken after 30 min, showed the 6% of uncyclized isolated olefin peaks (δ 118.3 and 135.6) and several cyclic olefin peaks (δ 125-132).

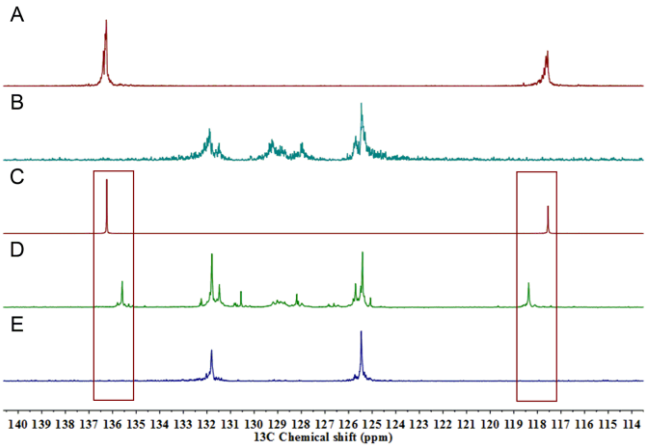


Figure 4: ^{13}C-NMR of olefin region in *CDCl*$_3$ of: (A) *a*-PEB, (B) *a*-FCPE, (C) *i*-PEB, (D) metathesis product of *i*-PEB after 30 min (94% conversion) and (E) metathesis product of *i*-PEB after 7 days (>99% conversion).

Most of these cyclic olefin peaks were not observed at the end of the reaction (after 7 days), which purports that in the initial metathesis stage when the catalyst randomly closes olefins, different ring sizes were formed (Figure 5). In the subsequent slow stage, rings rearrange along the chain until only the most thermodynamically stable 6-membered rings are present.

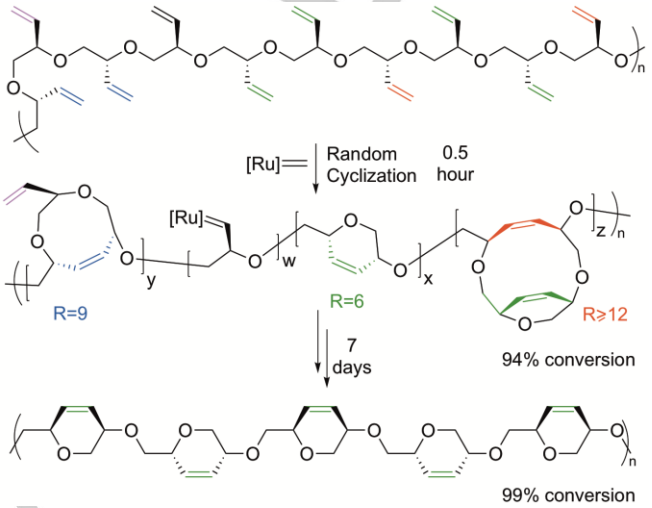


Figure 5: Proposed kinetic mechanism of RCM of *i*-PEB.

Fixing the free rotation of the pendent olefins through RCM impacts the glass transition temperature (T_g) in both *a*- and *i*-PEB. The organized structure of *i*-FCPE has a significantly higher T_g vs. *a*-FCPE (-11 °C from -26 °C). This is consistent with the presence of cycles hindering segmental chain mobility in both structures.

To prepare the PEGose polymer, *i*-FCPE was dihydroxylated under mild conditions using N-methylmorpholine N-oxide (NMO) and OsO_4 as catalyst. This second post-polymerization functionalization was diastereoselective, as OsO_4 attacks on the less hindered side of the ring (Figure 2), as demonstrated by ^{13}C-NMR spectroscopy (Figure 6). The dihydroxylation produces a unique stereocontrolled polymer structure, with a hydrophilic surface (*cis*-diols) opposite of a hydrophobic backbone. This distinctive structure could have potential applications in biomaterials, blood storage or drug delivery, with face polarity shaping surface chemistry and self-assembly.[19,20] While amylose, $(C_6H_{10}O_5)_n$, and PEGose, $(C_6H_{10}O_4)_n$, have similar monomer units, PEGose is connected with an additional methylene bridge, giving more flexibility to the polymer backbone. Circular dichroism (CD) was used to determine the influence of this CH_2 unit on the secondary structure of PEGose. Indeed, PEGose and amylose have the same prominent negative bands at 182 nm (SI Figure S25), showing that this new PEGose has an extended pseudo-helical structure similar to amylose.[21] Efforts to gain complementary X-ray characterization of this self-assembly is ongoing.

While excess NMO affords complete dihydroxylation of the double bonds, the reaction also offers the ability to adjust polymer polarity by limiting this co-oxidizing reagent. Reducing the NMO loading from 1.1- 0.8 equivalents dramatically alters

the polarity and solubility of the resultant polymer (Table 3), offering a secondary tuning for biomedical applications and leaving sites remaining for further functionalization or drug conjugation.[22] While the parent polymer is soluble in organic solvents and the fully dihydroxylated polymer is freely soluble in water and DMSO, this strategy allows for a broad range of polymer polarities to be accessed.

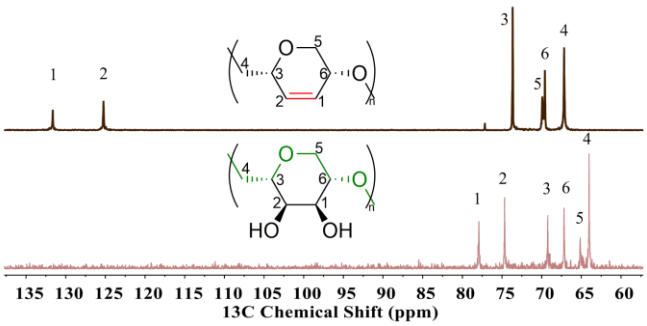
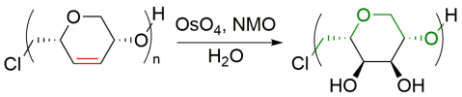


Figure 6. ^{13}C-NMR spectra of *i*-FCPE (top) and *cis*-PEGose (bottom) in $CDCl_3$ and D_2O respectively.

Table 3. Controlled dihydroxylation to form *cis*-PEGose.



***i*-FCPE** ***cis* PEGose**

Entry	[Olefin]: [NMO]	Con. (%)[a]	Soluble in	Insoluble in
1	1:1.1	>99	H_2O, DMSO	DMF
2	1:0.9	91	DMF, MeOH	Acetone
3	1:0.8	80	Acetone	EtOAc, CH_2Cl_2

[a]Determined by ^{1}H-NMR spectroscopy of olefin peaks integration to the polymer peaks.

In conclusion, we have shown that RCM of linear, stereoregular polymers with pendent olefins can be used to prepare cyclopolymers with excellent control of the ring size. Further functionalization of the latent olefin groups by dihydroxylation provides sugar-like structures with a poly(ethylene glycol) backbone, leading to a new PEGose architecture. The *isotactic* linear PEB leads, after RCM, to a cyclic polymer with well defined *cis* substitution patterns. By taking advantage of the diastereoselectivity of the subsequent dihydroxylation reaction, we were able to create a cyclopolymer where the configuration of all the stereogenic centers is controlled, and which mimics the natural amylose. This new platform offers significant potential for future functionalization, drug conjugation and biomedical mimicry, and is a significant focus of our future work, as is expanding this idea to other polymer backbones.

Acknowledgements

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Keywords: Polyethylene glycol • Ring-closing metathesis • Post-polymerization modification • Cyclopolymers • Stereocontrolled synthesis

[1] G. Bounos, S. Ghosh, A. K. Lee, K. N. Plunkett, K. Dubay, J. C. Bolinger, R. Zhang, R. A. Friesner, C. Nuckolls, D. R. Reichman, P. F. Barbara, *J. Am. Chem. Soc.* **2011**, *133*, 10155-10160.
[2] J. Kim , T. M. Swager, *Nature* **2001**, *411*, 1030-1034.
[3] M. Wathier, S. S. Stoddart, M. J. Sheehy, M. W. Grinstaff, *J. Am. Chem. Soc.* **2010**, *132*, 15887-15889.
[4] N. Kanbayashi, S. Miyamoto, Y. Ishido, T. Okamura, K.Onitsuka, *Polym. Chem.* **2017**, *8*, 985-994.
[5] [a] T. Kakuchi, T. Satoh, S. Umeda, H. Hashimoto, K. Yokota, *Macromolecules* **1995**, *28*, 5643-5648; [b] L. Guo, S. Dai, X. Sui, C. Chen, *ACS Catal.* **2016**, *6*, 428-441; [c] L. Resconi, G. W. Coates, A. Mogstad, R. M. Waymouth, *J. Macromol. Sci. A* **1991**, *28*, 1225-1234.
[6] F. D. Toste, A. K. Chatterjee, R. H. Grubbs, *Pure Appl. Chem.* **2002**, *74*, 7-10.
[7] F. Sinclair, M. Alkattan, J. Prunet, M. P. Shaver, *Polym. Chem.* **2017**, *8*, 3385-3398.
[8] N. G. Lemcoff, A. T. Spurlin, A. A. Gewirth, C. S. Zimmerman, B. J. Beil, L. S. Elmer, G. H. Vandeveer, *J. Am. Chem. Soc.* **2004**, *126*, 11420-11421.
[9] P. G. Clark, E. N. Guidry, W. Y. Chan, W. Steinmetz, R. H. Grubbs, *J. Am. Chem. Soc.* **2010**, *51*, 3405-3412.
[10] G. W. Coates, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 229-230.
[11] J. Herzberger, K. Niederer, H. Pohlit, J. Seiwert, M. Worm, F. R. Wurm, H. Frey, *Chem. Rev.* **2015**, *116*, 2170-2243.
[12] R. M. Thomas, P. C. B. Widger, S. M. Ahmed, R. C. Jeske, W. Hirahata, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* **2010**, *132*, 16520-16525.
[13] P. C. B. Widger, S. M. Ahmed, W. Hirahata, R. M. Thomas, E. B. Lobkovsky, G. W. Coates, *Chem. Comm.* **2010**, *4*, 2935-2937.
[14] S. Asano, T. Aida, S. Inoue, *Macromolecules* **1985**, *18*, 2057-2061.
[15] G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746-1787.
[16] A. E. Cherian, F. C. Sun, S. S. Sheiko, G. W. Coates, *J. Am. Chem. Soc.* **2007**, *129*, 11350-11351.
[17] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.
[18] For classification of olefins reflecting their reactivity towards metathesis, see: K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
[19] T. Mirfakhrai, D. W. J. Madden, R. H. Baughman, *Mater. Today* **2007**, *10*, 30-38.
[20] P. F. Nicoletta, D. Cupelli ; P. Formoso, D. G. Filpo, V. Colella, A. Gugliuzza, *Membranes* **2012**, *2*, 134-197.
[21] D. G. Lewis, W. C. Johnson Jr, *Biopolymers*, **1978**, 17, 1439-1449.
[22] M. Hruby, Č. Konák, K. Ulbrich, *J. Control. Release* **2005**, *103*, 137-148.

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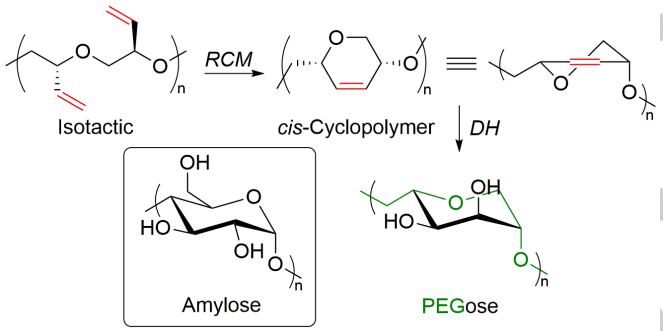

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Page No. – Page No.

Title: Functionalizable Stereocontrolled Cyclopolyethers *via* Ring-Closing Metathesis as Natural Polymer Mimics

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Page No. – Page No.

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Text for Table of Contents