

# Summer Scholar Report

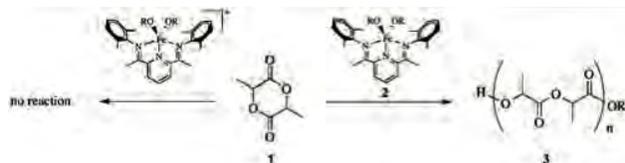
## *Synthesis of Epoxide Functionalized Cyclic Diesters for the use in Redox-Triggered Cross-Linked Polymers*

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### Introduction:

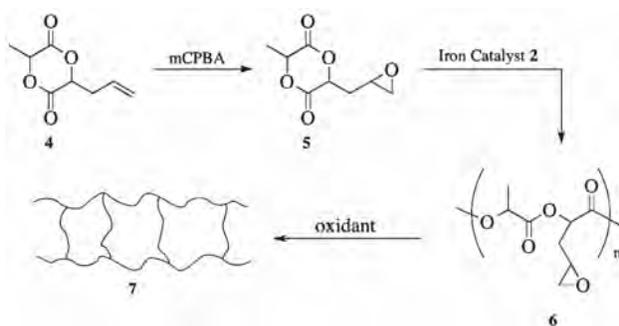
There is a high demand for polymers in the United States today. One commonly used polymer is poly(ethylene), owing to its desirable properties. However, one of the limitations of poly(ethylene) and many other commercial polymers is that they are synthesized from nonrenewable resources.<sup>1</sup> In attempts to find better polymers, researchers have been investigating degradable polymers derived from renewable resources such as polylactic acid (PLA).<sup>2</sup> PLA is the polymer of lactide, the cyclic dimer of lactic acid, which can be obtained from corn. Unlike polymers such as poly-ethylene and polypropylene, when PLA is exposed to heat and air, it decomposes into lactic acid, which is then further broken down into carbon dioxide and water.<sup>1</sup> Because of these properties, PLA has a wide variety of uses, including disposable cups and packaging, and is a promising material for use in drug delivery devices, implants, and screws.<sup>1,3,4</sup>

PLA is best synthesized through the ring-opening polymerization of lactide. There are a wide variety of complexes that will catalyze the polymerization. Many of these complexes are non-redox active metals, such as tin,<sup>5</sup> aluminum,<sup>6</sup> and yttrium.<sup>7</sup> Organocatalysts that have also been developed include N-heterocyclic carbenes,<sup>8</sup> 4-dimethylaminopyridine (DMAP),<sup>9</sup> and phosphines.<sup>10</sup> In order to increase the versatility of lactide polymerization catalysts, the Byers' Group has been exploring new strategies to synthesize copolymers of poly(lactic acid) and a comonomer. To aid with this goal, the group has been exploring the reactivity of the bis(imino)pyridine iron bis(alkoxide) complex **2** for lactide polymerization reactions.<sup>11</sup> It was reasoned that this catalyst would be capable of incorporating a wide variety of functionalized monomers because similar iron complexes are known to catalyze a variety of reactions, including [2 + 2] cycloadditions,<sup>12</sup> ethylene polymerization,<sup>13</sup> and hydrogenation reactions.<sup>14</sup> The (bis)imino(pyridine) ligands are also known to be redox active.<sup>15</sup> During initial investigations it was discovered that **2** is a competent catalyst for the polymerization of lactide (Scheme 1).



**Scheme 1:** Lactide Polymerization

Further investigations demonstrated that the catalyst is active for lactide polymerization when it is in the iron(II) oxidation state but not when it is in the iron(III) oxidation state.<sup>11</sup> What this means is that the catalyst can be oxidized *in situ* to the iron(III) oxidation state, thereby halting the polymerization reaction. If a reductant is subsequently added to the reaction mixture, the iron(III) catalyst is reduced to iron(II) and lactide polymerization resumes. As an extension of this research, it was recently discovered that epoxides demonstrate complementary reactivity and are polymerized by the catalyst in the iron(III) oxidation state but not in the iron(II) oxidation state. This discovery led to the ability to make block copolymers starting with a mixture of lactide and epoxides and switching between iron(II) and iron(III) oxidation states to polymerize the lactide and epoxide sequentially.<sup>16</sup> Another way to take advantage of the redox-switching capabilities of the catalysts is to make crosslinked polymers. In order to carry out a redox-triggered crosslinking reaction, a monomer with both a cyclic diester and an epoxide is required. In this case, the diester will do this through ring-opening polymerization when the catalyst is in the iron(II) oxidation state. Then an oxidant can be added to generate the catalyst in the iron(III) oxidation state, which would allow for the epoxide substituent to be polymerized, causing crosslinking to occur (Scheme 2).

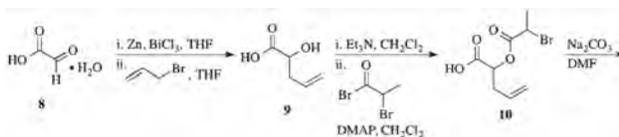


**Scheme 2:** Cross-linked Polymers

This approach is a new method for forming crosslinked polymers, which will allow access to novel crosslinked polymers. This summer research was focused on synthesizing the monomers needed for the crosslinked polymerization reaction.

## Results and Discussion:

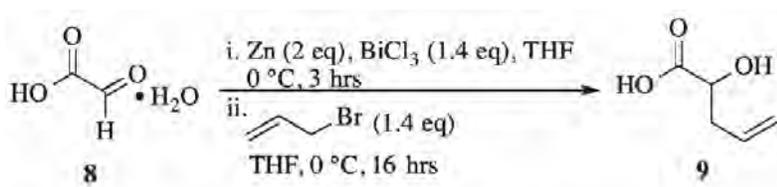
The first targeted monomer was 3-allyl-6-methyl-1,4-dioxane-2,5-dione (**4**).<sup>17</sup> The synthesis involves the allylation of glyoxylic acid (**8**) followed by a two-step condensation and ring-closing sequence (Scheme 3).



**Scheme 3:** General procedure for the Synthesis of 4

The first step of the synthesis was carried out several times in order to optimize the conditions. From earlier results, it was determined that the reaction was air sensitive and transferring the zinc and bismuth trichloride was difficult due to their insolubility in tetrahydrofuran (THF). For these reasons, the reaction was carried out in an inert atmosphere glovebox. This resulted in clean product (Table 1, entry 1).

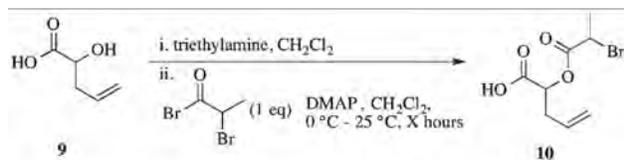
Since, the synthesis needed to be carried out on a large scale to ensure a large amount of monomer is synthesized, and since it can be cumbersome to set up the reaction in the glovebox, the reaction was run open to the air (Table 1, entry 2). As anticipated, this procedure resulted in impure product. However, the impurities in the reaction could be avoided if the zinc and bismuth trichloride were added as solids at 0 °C to a solution of **8** in THF in round bottom flask under a strong purge of nitrogen (Table 1, entry 3)



Entry	Scale	Location	Yield
1	10 g	glovebox	78 %
2	250 mg	air	not isolated
3	20 g	glovebox/N <sub>2</sub>	66%

**Table 1:** Synthesis of 2-hydroxypent-4-enoic acid (**9**)

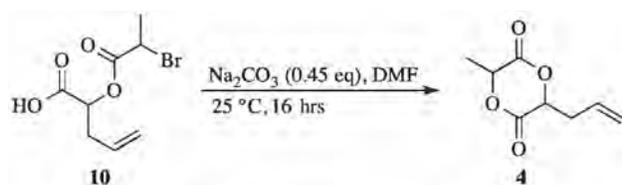
With compound **8** in hand, the next step in the synthesis of cyclic diester **4** was the addition of 2-bromopropionyl bromide to **9**. When this reaction was performed it gave a product that contained an impurity (Table 2, entry 1). Based on analysis of the <sup>1</sup>H NMR spectrum of the product mixture, it was reasoned that HBr being formed in the reaction was causing hydrobromination of the alkene.<sup>18</sup> In an attempt to prevent this side product from forming, three equivalents of triethylamine was used, however this was not productive (Table 2, entry 2). Since adding excess triethyl amine was unsuccessful, a different method was attempted to eliminate the formation of the presumed hydrobromination side product. It was believed that **9** and 2-bromopropionyl bromide reacts quickly to form an anhydride intermediate, which then undergoes a DMAP-catalyzed esterification to form the desired product. Since any HBr formed should be made when the anhydride is formed, the DMAP was left out of the reaction mixture so that the anhydride could be isolated, and the HBr could be removed from the reaction. However, somewhat surprisingly, when the condensation reaction was carried out without DMAP, the desired product was isolated cleanly within three hours (Table 2, entry 3). The methodology was reproducible and scalable thereby providing access to compound **10** on a gram scale. In order to gain some insight into the function of DMAP, the pure product isolated from the reaction without DMAP, was subjected to DMAP. Monitoring this reaction by <sup>1</sup>H NMR spectroscopy revealed that the side product that was originally observed was a result of the desired product **10** reacting with DMAP.



Entry	Scale	Eq. Et <sub>3</sub> N	mol % DMAP	X hours	Yield
1	1.5 g	1	10	66	20 %
2	0.6 g	3	10	66	19 %
3	0.5 g	1	0	3	30 %
4	1.5 g	1	0	16	94 %

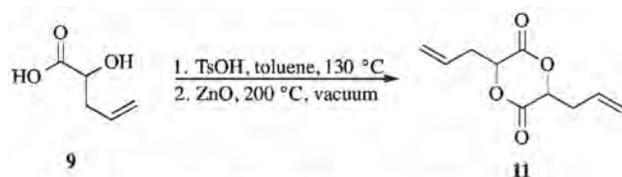
**Table 2:** Synthesis of 10

The final step in the synthesis was the ring closing reaction. It was previously found that adding the starting material relatively quickly to sodium carbonate in DMF gave two products (Table 3, entry 1). Analysis of the product mixture by <sup>1</sup>H NMR spectroscopy and gel-permeation chromatography was most consistent with the side product being oligomers. Attempts to purify the cyclic diester from its oligomers by column chromatography, extraction, and distillation were unsuccessful. In order to limit the amount of oligomerization in the reaction, the addition of **10** in DMF to the solution of sodium carbonate in DMF was done over



Entry	Scale	Time of Addition	Yield
1	0.5 g	1 min	not isolated
2	0.3 g	8 hrs	67 %

**Table 3:** Synthesis of diester (4)



Entry	Scale	mol % TsOH	Time	Yield
1	0.5 g	0.7	9 days	2.4 %
2	1.5 g	1.4	9 days	11 %

**Table 4:** Alternative Procedure for the Synthesis of diester (4)

the course of 8 hours. This led to product that contained only a small amount of the oligomers (Table 3, entry 2).

In parallel with efforts towards the synthesis of cyclic diester **4**, an alternate monomer was pursued: bis-allyl cyclic diester **11**. This molecule could be obtained in one step starting with the previously synthesized  $\alpha$ -hydroxy acid **9** (Table 4).<sup>19</sup> In this reaction *para*-toluenesulfonic acid (TsOH) and **9** were refluxed in toluene with a Dean-Stark trap to drive the reaction towards the product by removing water. When the reaction reached equilibrium as determined by <sup>1</sup>H NMR spectroscopy, the organic phase was washed with saturated sodium bicarbonate, concentrated and distilled over ZnO at 200 °C at 0.05 torr. affording the product diester **11**, albeit in low isolated yields.

### Conclusions:

Using the two routes outlined above, we were able to synthesis the two allyl substituted monomers. The routes are efficient and straightforward ways of making the desired compounds. In the future, we plan to scale up the reactions and work on the epoxidation reactions.

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