

## Racemization-free Monomer: $\alpha$ -Hydroxyisobutyric Acid from Bio-based Lactic Acid

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In order to solve the important problem of the racemization of poly(L-lactic acid), a high yield of racemization-free monomer:  $\alpha$ -hydroxyisobutyric acid (HIBA) was synthesized from bio-based lactic acid by methylation using specific bases with bulky side groups. Obtained HIBA can be converted into poly(tetramethylglycolide), which is racemization-free and has higher melting and glass transition points than poly(L-lactic acid).

Poly(L-lactic acid) (PLLA), a biomass-based biodegradable polyester capable of synthesis from renewable resources, is already well known for its excellent attributes of thermoplasticity, transparency, crystallinity, and high melting point ( $T_m = 170\text{ }^\circ\text{C}$ ).<sup>1</sup> Recently, however, PLLA has been attracting much interest from researchers as a superior recyclable polymer capable of conversion into the cyclic monomer L,L-lactide under heating.<sup>2</sup> This reversible conversion results from the equilibrium between PLLA and lactide.<sup>3</sup> However, one important issue affecting monomer recovery is racemization,<sup>4</sup> thereby resulting in the recovery of diastereoisomers, meso and D,D-lactide causing decrease in the crystallinity and melting point of the reproduced PLLA.<sup>5</sup>

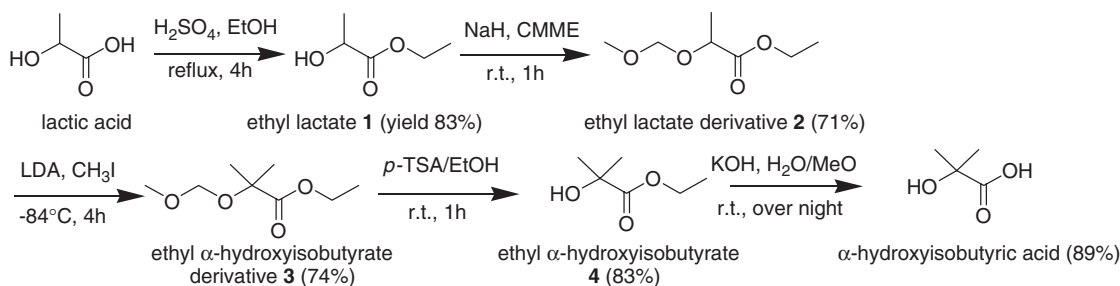
This racemization of PLLA, reported as resulting from ester-semiacetal tautomerization,<sup>6</sup> suggests the reactivity of  $\alpha$ -hydrogen on a chiral carbon. However, by substituting the active  $\alpha$ -hydrogen with a methyl group, lactic acid can be changed into the racemization-free  $\alpha$ -hydroxyisobutyric acid (HIBA), which has been synthesized from petroleum via many processes using HCN.<sup>7</sup> Poly( $\alpha$ -hydroxyisobutyric acid) [poly(tetramethylglycolide): PTMG], which has been prepared by the ring-opening polymerization of a cyclic diester of HIBA: tetramethylglycolide (TMG),<sup>8</sup> is known as an optically nonactive polymer and has a higher  $T_m$  value ( $>190\text{ }^\circ\text{C}$ ) than PLLA.<sup>9</sup>

Previously, the methylation of lactic acid was also attempted by using hindered lithium dialkylamides, but a very low conversion of less than 10% was reported.<sup>10</sup> In the present study, in order to solve the important issue of the racemization of

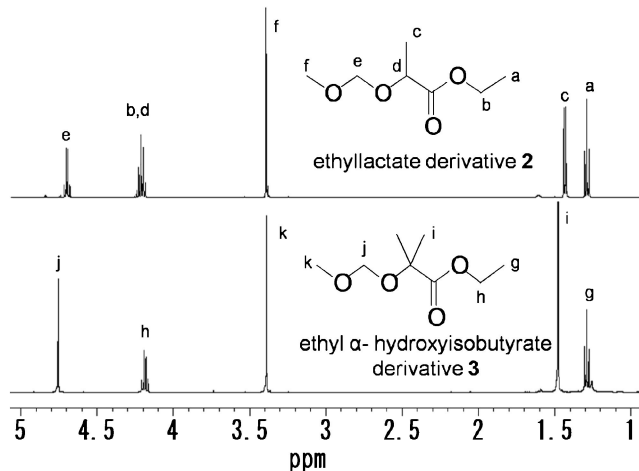
poly(L-lactic acid), synthesis<sup>11</sup> of the racemization-free monomer HIBA was achieved using D,L-lactic acid as a starting material to prepare the biomass-based PTMG.

Before the substitution of a methine proton by a methyl group, more reactive groups hydroxy and carboxyl groups were protected with methoxymethoxy<sup>12</sup> and ethyl ester groups, resulting in the preparation of an ethyl lactate derivative **2** in high yield (Scheme 1).<sup>13</sup> The methoxymethoxy group was chosen as a specific protection group because of its stability under basic conditions of methylation. Protected derivative **2** was reacted with various kinds of basic reagents and methyl iodide ( $\text{CH}_3\text{I}$ ) to substitute the methine proton by a methyl group. General basic reagents, such as  $\text{K}_2\text{CO}_3$ ,  $\text{NaOH}$ ,  $\text{NaH}$ , and DBU gave no methylated product, because of preferential reactions of the reagents with ester groups and  $\text{CH}_3\text{I}$ . In order to control the nucleophilicity of the counter anions of basic reagents, bulky side groups, such as isopropyl and trimethylsilyl groups, were introduced plurally in the anions. These bulky side groups may allow a center anion to abstract a proton from the methine group, but prevent attacks on the carbonyl carbon. Typical bases with bulky side groups are lithium diisopropylamide (LDA),<sup>14</sup> hexamethyldisilazane lithium (LHMDS) and sodium (NHMDS) salts.<sup>15</sup> These are strong bases as demonstrated by the  $\text{p}K_a$ 's values for the conjugate acids of LDA and LHMDS are 35.7 and 25.8, respectively.<sup>16</sup>

When LDA and  $\text{CH}_3\text{I}$  were reacted with the protected derivative **2** at  $-84\text{ }^\circ\text{C}$ , the methylation proceeded smoothly to give an ethyl  $\alpha$ -hydroxyisobutyrate derivative **3** in 83% conversion. The derivative **3** was isolated in 74% yield. In Figure 1, <sup>1</sup>H NMR spectra of the derivatives **2** and **3** clearly show a doublet peak at 1.43 ppm and a singlet peak at 1.47 ppm, respectively.<sup>17</sup> In the same manner, LHMDS and NHMDS also gave the derivative **3** with moderate conversions of 45 and 23% as listed in Table 1, respectively. When another lithium amide having compact side groups, for example  $\text{LiNH}_2$ , was used, no methylation proceeded, indicating the steric hindrance effect of bulky side groups.



Scheme 1. Synthesis of  $\alpha$ -hydroxyisobutyric acid from lactic acid.



**Figure 1.**  $^1\text{H}$ NMR spectra of ethyl lactate derivative **2** and ethyl  $\alpha$ -hydroxyisobutyrate derivative **3**.

**Table 1.** Synthesis of ethyl  $\alpha$ -hydroxyisobutyrate derivative **3** from ethyl lactate derivative **2**

Run	Base (equiv)	Temp/ $^{\circ}\text{C}$	Time/h	Conv./% <sup>a</sup>
1	LDA (1.3)	-84	4	83
2	LHMDS (1.1)	-84 – r.t.	24	45
3	NHMDS (1.1)	-84 – r.t.	24	23
4	$\text{LiNH}_2$ (1.1)	-84 – r.t.	24	0

<sup>a</sup>Calcd from GC.

Obtained ethyl  $\alpha$ -hydroxyisobutyrate derivative **3** was hydrolyzed via conversion into ethyl  $\alpha$ -hydroxyisobutyrate **4** under acidic conditions and then under basic conditions into  $\alpha$ -hydroxyisobutyric acid (HIBA) in 83 and 89% yields, respectively (Scheme 1).<sup>18</sup>

The synthesized HIBA was converted into tetramethylglycolide to prepare poly(tetramethylglycolide) by ring-opening polymerization (see Supporting Information). This polymer showed higher thermal properties and recyclability than poly(lactic acid). These results will be reported elsewhere in the near future.

In conclusion, racemization-free monomer HIBA was synthesized from bio-based lactic acid by the substitution of a methine proton by a methyl group using specific bases LDA, LHMDS, and NHMDS with bulky side groups. Obtained bio-based HIBA allowed us to prepare a bio-based, racemization-free, and thermally stable polymer: poly(tetramethylglycolide).

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- Ethyl lactate derivative **2** was isolated as a liquid product in a 71% yield.  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (3H, t,  $J = 7.13$  Hz,  $\text{CH}_3\text{CH}_2$ ), 1.43 (3H, d,  $J = 6.85$  Hz,  $\text{CH}_3\text{CH}$ ), 3.39 (3H, s,  $\text{CH}_3\text{O}$ ), 4.18–4.25 (3H,  $\text{CH}_3\text{CH}_2 + \text{CH}_3\text{CH}$ , m), 4.70 (2H, dd,  $J = 11.5, 6.85$  Hz,  $\text{CH}_3\text{OCH}_2\text{O}$ );  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  14.2, 18.6, 55.8, 60.9, 71.5, 95.8, 173; FTIR (neat,  $\text{cm}^{-1}$ ): 2980 ( $\nu_{\text{C-H}}$ ), 2925 ( $\nu_{\text{C-H}}$ ), 1745 ( $\nu_{\text{C=O}}$ ), 1446, 1375, 1267, 1190, 1156, 1106, 1077, 1017, 918, 860, 753.
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- Ethyl  $\alpha$ -hydroxyisobutyrate derivative **3** was isolated as a pale yellow liquid product in a 74% yield.  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (3H, t,  $J = 7.1$  Hz,  $\text{CH}_3\text{CH}_2$ ), 1.47 (6H, s,  $(\text{CH}_3)_2\text{CH}$ ), 3.39 (3H, s,  $\text{CH}_3\text{O}$ ), 4.19 (2H, q,  $J = 7.0$  Hz,  $\text{CH}_3\text{CH}_2$ ), 4.76 (2H, s,  $\text{CH}_3\text{OCH}_2\text{O}$ );  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  14.1, 25.1, 55.8, 61.0, 77.1, 92.8, 174.5; FTIR (neat,  $\text{cm}^{-1}$ ): 2979 ( $\nu_{\text{C-H}}$ ), 2925 ( $\nu_{\text{C-H}}$ ), 1731 ( $\nu_{\text{C=O}}$ ), 1463, 1364, 1274, 1228, 1137, 1086, 1032, 918, 857, 763, 599.
- $\alpha$ -Hydroxyisobutyric acid (HIBA) was isolated as a white crystalline in an 89% yield.  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (6H, s,  $(\text{CH}_3)_2\text{C}$ );  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  27.1, 72.1, 181.9; FTIR (ATR,  $\text{cm}^{-1}$ ): 3417 ( $\nu_{\text{O-H}}$ ), 2918 ( $\nu_{\text{C-H}}$ ), 1716 ( $\nu_{\text{C=O}}$ ), 1363, 1270, 1228, 1136, 973, 889, 796, 761, 601, 544; FAB MS  $m/z$ : [ $\text{C}_4\text{H}_7\text{O}_3^- + 2\text{Na}^+$ ], 148.94.  $T_m = 76\text{--}81$   $^{\circ}\text{C}$ .