

Separation of the Enantiomers of Lactide, Lactic Acid Dimer, for a Sustainable Bioplastic Management

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Abstract Despite the small difference in the steric hindrance of the substitutes of the asymmetric carbon of the lactic acid, a way for the desymmetrization of the racemic mixture was discovered. Two possibilities have arisen: the synthesis and further separation of diastereoisomers with the (S)-2-methyl-1-butanol as chiral auxiliary and the kinetic discrimination during the esterification with the (R)-(-)-Myrtenol.

Keywords: lactide, enantiomeric separation, diastereoisomers, PLA, bioplastics

1. Introduction

Lactic acid is an important molecule for chemical and food industries. Traditionally its main application is in food industry, where it plays the role of a natural acidifying agent [1,2]. However, recently another application of the lactic acid has emerged: synthesis of bioplastics [3]. Polylactic acid (PLA), bioplastic based on the lactic acid monomer and synthesized through the lactide lactic acid dimer, is foreseen to be one of the most promising substitutes of the common petrol based polymers [4,5,6]. The sustainable management of the PLA includes its recovery, de- and then re-polymerization of the lactide [7]. The major drawback of this system is the racemization occurring during the process [8,9].

Indeed, for the production of PLA, a near enantiopure biotechnologically produced (S)-lactic acid is used. During the polymerization process some racemization may occur, moreover for strengthening the heat resistance of the PLA stereocomplexes should be made [10]. These stereocomplexes are mixtures of nearly enantiopure P(L)LA and P(D)LA. Thus during the depolymerization process the (R)- and (S)-lactic acid units are recovered together, forming a racemic mixture unusable for the direct re-polymerization, racemic PLA bearing very poor mechanical properties.

The separation of the enantiomers of the lactic acid, or of its dimer, becomes then an important industrial and sustainability issue. Several attempts were made for performing this separation. Unfortunately these attempts either drove to the recovery of only 50 % of desired product, the rest being oxidized to pyruvic acid [11,12] or re-reduced to the same enantiomer of the lactic acid [13]; either were found to be unsuccessful, even using an enzyme, *Candida antarctica* lipase B (CALB), for the discrimination between the two enantiomers [14].

The synthesis and further separation of diastereoisomers is an important method for the desymmetrization of racemic mixtures. It is widely used in industry due to its ease and low cost of implementation. However, its main drawback consists on the loss of 50% of the product. In the case of the lactic acid recovery, this drawback does no longer exist, as both (S)-, (R)-lactic acid monomers are useful for the separate polymerization reactions.

Comparing to the existing synthesis of diastereoisomers, the main difficulty in the case of the lactic acid relies on that it is a bi-functional molecule, therefore standard chiral auxiliaries such as tartaric and malic acids are not good candidates for this separation. The selection of the suitable chiral auxiliary has to be based on several criteria: availability and price acceptable for industrial applications, but also chemical function compliance, that is only one function should be available at the auxiliary.

A primary screening of available chiral acids and alcohols resulted in 12 acids and 16 alcohols. The majority of them were natural products, steroids, protected amino acids and sugars etc. The most promising were found to be (S)-(-)-2-methyl-1-butanol, (R)-(-)-myrtenol and (1R,2S,5R)-(-)-menthol (Scheme 1).

2. Results and Discussion

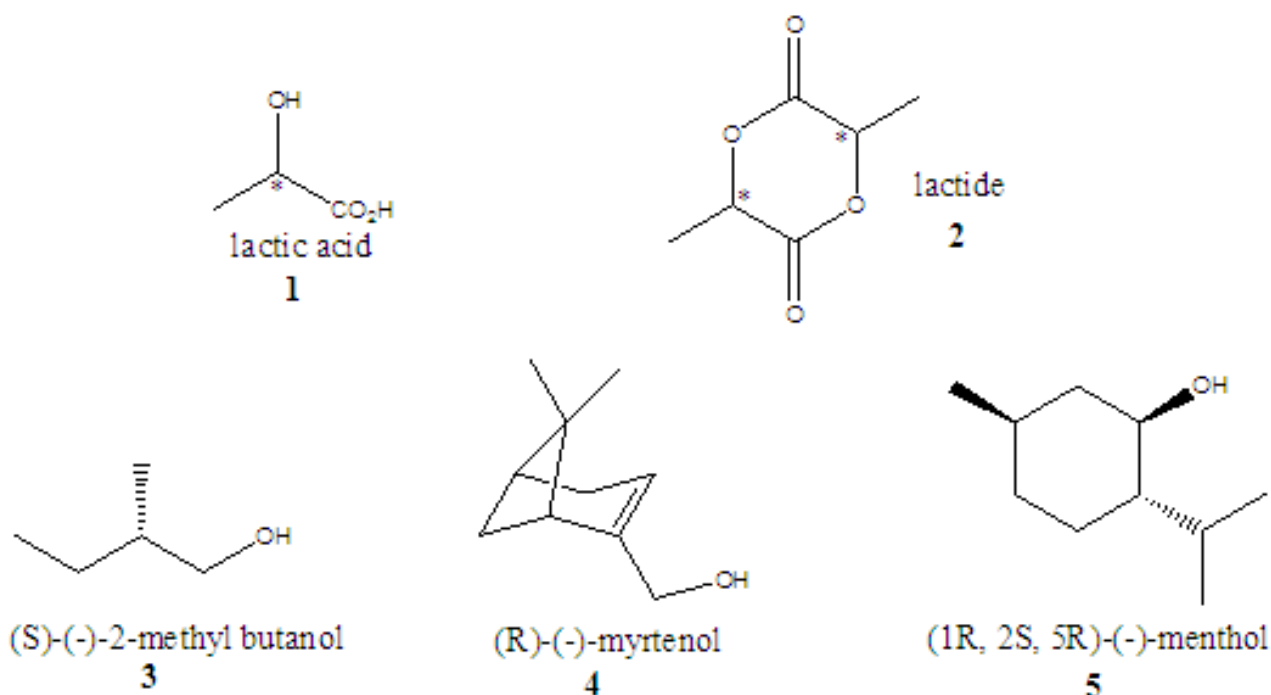
Table 1 Products and yields of the reactions of chiral auxiliaries with (S)- and (R)-lactides

Reaction parameters	(S)-2-methyl butanol	(R)-myrtenol	(-)-menthol			
Reflux	reaction time	3h	7h			
	yield (%)	77-78 %	destruction of the auxiliary	56.4		
	by-products	n. d. ^a		yes		
	enantiomers	S and R		S and R		
80 °C	reaction time	5h	7h	7h		
	yield (%)	n. d. ^a	35.3	5.3	9.3	14.5
	by-products		n. d. ^a		yes	
	enantiomers		S	R	S	R

^a not determined

The lactide, in two enantiomeric forms (S,S) and (R,R), was used in this study as a test substrate. The main results of these experiments are summarized Table 1. An important conversion (77-78%) of both enantiomers in only 3 hours of refluxed reaction was observed with the (S)-2-methyl-1-butanol whereas in these conditions the

(R)-myrtenol was destroyed. And the (-)-menthol have afforded only 56.4% of yield in desired substrate and presented at least 2 by-products (most probably corresponding to the esters of lactoyl lactates following GC-MS analyses).



Scheme 1. Molecular structure of studied substrate

Therefore, the reaction was also performed at lower temperature, 80 °C, with myrtenol and menthol. Menthol did not show any improvement under these conditions, the synthesis was only slowed (only 9-14% of conversion after 7 hours), but the by-products remained. Different attempts of varying the proportion of the auxiliary *versus* the substrate etc. were also tempted, unfortunately the by-products problem persisted. Thus, menthol definitely is not a suitable chiral auxiliary for the separation of the lactic acid' enantiomers.

On the contrary, myrtenol has shown an outstanding discrimination of the kinetics of the reaction at 80 °C. The S enantiomer was transformed much faster, at least 35.3% of the diastereoisomer was formed after 5 hours, whereas the R one was transformed much slower, only 5.3% of the diastereoisomer was recovered after 7 hours of reaction time (Figure 1). Thus, this chiral auxiliary shows a very interesting property, most likely due to its own steric hindrance. The important difference of the chemical structure of the residual (R,R)-lactide and the obtained (R,S)-myrtenyl lactate induces significant gap between boiling points, 142 °C at 10.4mbar and 185 °C at 12mbar, respectively. Thus an easy separation of these products by distillation becomes possible.

Concerning the (S)-2-methyl butanol, the situation is more classical. The diastereoisomers are synthesized with similar kinetics. The (S)-2-methyl butanol is, as lactic acid, a rather small molecule, thus differences of the physical properties of the two diastereoisomers are modest (Table 2). The attempts of separation of diastereoisomeric mixtures of 2-methyl butyl lactates have, however, induced diastereoisomeric enrichment: 80.9% by

crystallization and 65.2% by distillation. The crystallization appears thus to be a more efficient technique than the distillation even if the melting points of the two diastereoisomers were found to be closer than their boiling points. Thus, the efficacy of the crystallization is mostly due to the difference in the kinetics of the crystallization process among the 2 diastereoisomers. Indeed, the crystallization of the (S,R)-2-methyl butyl lactate occurred within 3 days at -40 °C and within 4 days at -28 °C (Figure 2), whereas the (S,S)-2-methyl butyl lactate remained liquid at these temperatures for several weeks.

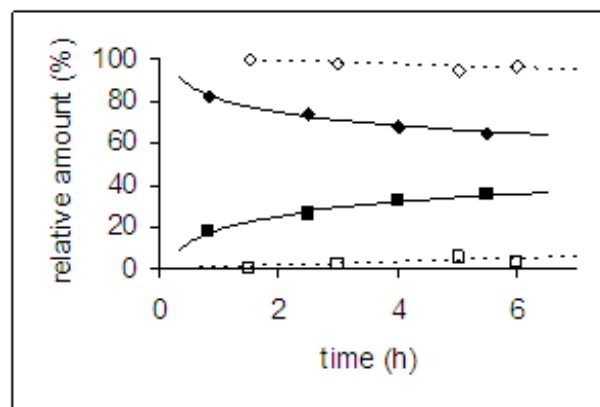


Figure 1. Kinetics of the esterification of (R,R)- and (S,S)-lactides with (R)-myrtenol. Filled symbols stand for the reaction with the (S,S)-lactide, empty symbols – for the reaction with the (R,R)- lactide, squares stand for the diastereoisomers formation, diamonds – for the (R)-myrtenol consumption

Table 2. Chemical and physical characterizations of the diastereoisomers of 2-methyl butyl lactate

Constants		(S,S)-2-methyl butyl lactate	(S,R)-2-methyl butyl lactate
Boiling point		51 °C at 6mbar 93 °C at 200mbar	62 °C at 7mbar 98 °C at 300mbar
Melting point ^a		- 25.5 °C	- 25.8 °C
Crystallisation temperature ^a		- 58.6 °C	- 58.4 °C
NMR ^b	¹ H	4.25-4.32 1H q J=11.4 Hz -CH-CO; 4.01-4.04 2H dd J=2.3 Hz J=10 Hz -CH ₂ -O; 1.69-1.81 1H m CH ₂ -CH-CH ₂ ; 1.41-1.43 3H d J=11.2 Hz CH ₃ -CH; 1.16-1.26 & 1.36-1.48 2x1H 2m -CH-CH ₂ -CH ₃ ; 0.89-0.95 6H m 2 CH ₃	4.25-4.32 1H q J=11.4 Hz -CH-CO; 3.93-3.98 1H dd J=9.6 Hz J=16.7 Hz & 4.05-4.13 1H dd J=9.6 Hz J=19.2 Hz -CH ₂ -O; 1.69-1.81 1H m CH ₂ -CH-CH ₂ ; 1.41-1.43 3H d J=11.2 Hz CH ₃ -CH; 1.16-1.26 & 1.36-1.48 2x1H 2m -CH-CH ₂ -CH ₃ ; 0.89-0.95 6H m 2 CH ₃
	¹³ C	175.9 -O-CO-; 70 -CH ₂ -O; 66.9 -CH-OH; 34 -CH-CH ₃ ; 25.5 CH ₂ -CH ₃ ; 20.6 CH ₃ -CHOH-; 16.5 CH ₃ -CH-; 11.3 CH ₃ -CH ₂ -	
Specific rotation ^c	[α] _D ²⁰	- 1.4	+ 28.1
	[α] ₅₄₆ ²⁰	- 3.3	+ 22.3

^a determination made by DSC

^b analysis performed in CDCl₃, δ is given in ppm

^c analysis performed in CHCl₃ with the concentration of 10 g/L

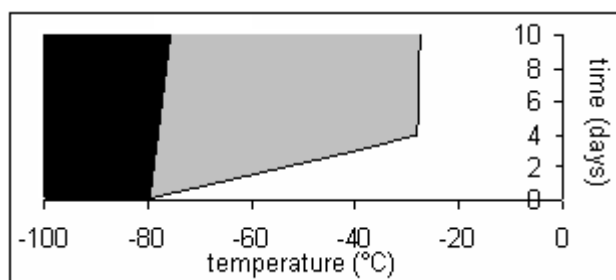


Figure 2. Crystallization of the diastereoisomers of 2-methyl butyl lactate. White surface represents the conditions where both diastereoisomers are liquid, grey – where the (S,S) is liquid and the (S,R) is solid and black – where both diastereoisomers are solid

3. Materials and Methods

3.1. General

The (S,S)- and (R,R)-lactides were from Galactic SA (Escanaffles, Belgium), all other chemicals were from Sigma-Aldrich (Belgium). The NMR analyses were performed in CDCl₃ on a Bruker 500MHz instrument. Melting and crystallization temperatures were measured with the differential scanning calorimetry (DSC) Q1000 TA instrument. The specific rotation angles were measured with the Propol Anton Paar instrument. Kinetic monitoring of the reaction was performed with the QP 2010 GC-MS Shimadzu instrument.

3.2. Synthesis of Diastereoisomers

A round-bottom double-necked flask equipped with a reflux condenser was filled with the (S,S)- or (R,R)-lactide, the chiral auxiliary (3equivalents as standard procedure, 1

to 3 equivalents were tested for the menthol) and the tin octanoate (0.001equivalent) as the transesterification agent. The reaction mixture was heated at reflux (or 80 °C, cf. Table 1) under magnetic stirring. The samples were regularly taken for the kinetic monitoring of the reaction.

After the reaction completion, the mixture was rinsed with saturated Na₂CO₃ solution and distilled under reduced pressure using Hempel distillation system filled with the Raschig's stainless steel rings.

4. Conclusion

Two different ways for the desymmetrization of the enantiomers of the lactic acid dimer, lactide, were found. The first route is based on a synthesis of the diastereoisomers with the (S)-2-methyl-1-butanol and further separation by either distillation or crystallization (more efficient for these substrates). The second route is based on the kinetic discrimination between the enantiomers of the lactide towards the transesterification with the (R)-myrtenol. In this case the separation is even easier, as the residual (R,R)-lactide has to be separated from the diastereoisomeric (R,S)-myrtenyl lactate. The separation of the racemic mixture of lactides described here allows recovery of monomers and thus improves the efficiency of the repetitive chemical recycling of PLA, hence reducing its production costs and promoting the widespread usage of this bioplastic.

Acknowledgements

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