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Solid-phase synthesis of enantio-controlled lactic acid oligomers

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ABSTRACT

A synthetic method for lactic acid oligomers *via* solid-phase synthesis under mild reaction conditions with up to 99% yield is presented. The fine control of the chirality on each lactic acid unit of the oligomers was easily achieved by the substitution of (*R*)-THP-protected lactic acid (*R*)-**2** by (*S*)-**2** without alternating the procedure. The overall synthesis of the trimer and tetramer was completed in one and two days, respectively. Intramolecular cyclizations of enantio-controlled lactic acids were also attempted through the Yamaguchi macrolactonization or the Mitsunobu reaction. However, we were unable to isolate single cyclic oligomers but always obtained a mixture of cyclic oligomers.

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1. Introduction

Biodegradable and biocompatible polymers have gained much attention in the field of the bio-application of polymers[1] because biodegradability and biocompatibility of polymers play a key role in drug delivery and in tissue engineering.[2] Poly-lactic acid is one of the most promising biodegradable polymers and has been employed in a variety of bio-applications including drug delivery systems, sutures, and stents.[3] In addition to their biodegradability, their hydrophilicity makes lactic acid oligomers suitable as a component of amphiphilic block copolymers in drug delivery systems.[4] For example, pluronic/poly-lactic acid block copolymers can form vesicles to be used as a delivery system of insulin.[5]

Although racemic or homo-enantiomeric poly-lactic acids have been used efficiently for the delivery of various drugs and peptides, enantio-controlled poly-lactic acids are potentially important for the cellular delivery of drugs because the cell membranes possess an asymmetric environment. In fact, Piwnica-Worms et al. reported that altering the configuration of each amino acid of a cell permeable peptide from L to D increases the uptake value by up to 13-fold.[6]

While numerous preparation methods of poly-lactic acid from cyclic lactide dimers have been reported,[7] only a few synthetic procedures for enantio-controlled lactic acid oligomers have been established. For examples, Hawker and coworkers designed elegant synthetic routes to (*S*)-lactic acid oligomers from a dimer to a 64mer by orthogonal protecting groups.[8] In addition, lipase-catalyzed oligomerization of alkyl lactate has been reported to produce a mixture of (*R*)-lactic acid oligomers from a dimer to a heptamer.[9] Meanwhile, various cyclic lactic acid oligomers have also been synthesized through the ring-opening oligomerization of lactide.[10] These studies have helped facilitate access to lactic acid oligomers, but the synthetic process to enantio-controlled lactic acid oligomers including hetero-enantiomeric as well as homo-enantiomeric oligomers remains limited. Thus, we began to develop a simple and efficient process to synthesize enantio-controlled lactic acid oligomers.

Initially, we attempted to couple acid- and hydroxyl-protected (*R*)-lactic acids (*R*)-**1** and (*R*)-**2** in solution to develop a synthetic process of enantio-controlled lactic acid oligomers (Eq. 1). Although the esterification between the two different lactic acids was facile, a significant loss of the product (*R*,*R*)-**3** occurred during the multi-step purification. Furthermore, the purification in the next coupling reaction after the deprotection step was even more problematic and provided a negligible isolated yield. Thus, an alternative strategy was necessary to solve this problem.

Herein, we report a facile solid-phase synthesis of a series of enantio-controlled lactic acid oligomers. To date, a detailed solid-phase synthesis for lactic acid oligomers has not been described. Recently, Riguera coworkers reported a general procedure in a solid-phase synthesis with several hydroxyl carboxylic acids,[11] which seems to be a suitable approach to avoid a multi-step purification in the synthesis of lactic acid oligomers. The Riguera method mainly focused on the synthesis of homo-chiral oligomers of lactic acid. We have developed a synthetic process of enantio-controlled lactic acid oligomers including hetero-enantiomeric as well as homo-enantiomeric oligomers.

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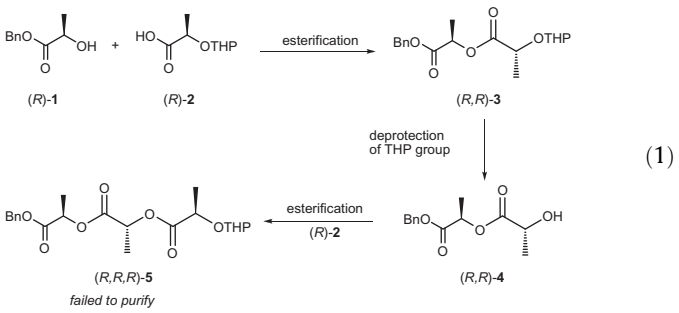


(1)

2. Results

2.1. Synthesis of (*R*)- and (*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)propanoic acid: (*R*)- and (*S*)-2

To synthesize each enantiomer of **2**, the hydroxyl group of the (*R*)-lactic acid methyl ester was first protected by dihydropyran. The protection was performed by using 3 equiv of dihydropyran with 2 mol % of pyridinium *p*-toluene sulfonate to give (*R*)-methyl-2-(tetrahydro-2*H*-pyran-2-yloxy)propanoate (*R*)-**6** in 66% yield. After protection, hydrolysis of the ester was carried out under weak basic conditions (LiOH) to provide (*R*)-2-(tetrahydro-2*H*-pyran-2-yloxy)propanoic acid (*R*)-**2** in 50% yield. The other enantiomer (*S*)-**2** was similarly synthesized from (*S*)-lactic acid methyl ester in 81% yield (Scheme 1).

2.2. Coupling of (*R*)-2 to Wang resins and deprotection of the THP group from (*R*)-7 to give (*R*)-8

The coupling of (*R*)-**2** to Wang resins was accomplished by diisopropylcarbodiimide (DIC) with 4-dimethylaminopyridine (DMAP) in THF to afford (*R*)-**7**. First, 3 equiv of (*R*)-**2** were added to Wang resins, DIC (3 equiv), and DMAP (0.1 equiv) in THF. After being shaken for 2 h at 40 °C, the resulting resins were washed with THF, acetone, and CH_2Cl_2, consecutively, and the THP protecting group of (*R*)-**7** was removed by *p*-TsOH in CH_2Cl_2/MeOH. The resulting (*R*)-**8** resins were also washed by the same washing conditions (THF, acetone, and CH_2Cl_2), and used for further expansion of the lactic acid without determining a yield.

2.3. Extension of (*R*)-lactic acid from (*R*)-8 to (*R,R*)-9′-OH: the first cycle

The second lactic acid was coupled to the hydroxyl groups of (*R*)-**8** by following the same procedures of the coupling of (*R*)-**2** to Wang resins. Three equivalents of (*R*)-**2** were added with (*R*)-**8**, DIC (3 equiv), and DMAP (0.1 equiv) in THF. After being shaken for 2 h at 40 °C, the resulting resins were washed with THF, acetone, and CH_2Cl_2, and the THP protection group was eliminated by *p*-TsOH in CH_2Cl_2/MeOH to afford an (*R,R*)-**9**′-OH, which was used for further expansion of lactic acid without determining a yield.

2.4. Synthesis of (*R*)-lactic acid trimer (*R,R,R*)-10-OH: the second cycle

The coupling of (*R*)-**2** to (*R,R*)-**9**′-OH and the deprotection of the THP group from the hydroxyl group in the resins were conducted by following the first cycle procedures to give (*R,R,R*)-**10**′-OH. The cleavage of the (*R*)-lactic acid trimer from (*R,R,R*)-**10**′-OH was then performed with trifluoroacetic acid (TFA) in CH_2Cl_2. The remaining resins were removed by filtration, and the filtrate was concentrated under reduced pressure to afford the (*R*)-lactic acid trimer (*R,R,R*)-**10**-OH in 99% yield.

2.5. Synthesis of enantio-controlled lactic acid trimers: (*R,R,S*)-10-OH and (*R,S,S*)-10-OH

By switching (*R*)-**2** with (*S*)-**2** when the second cycle procedure was carried out with (*R,R*)-**9**′-OH, lactic acid trimer, (*R,R,S*)-**10**-OH was obtained in 88% yield. When switching (*R*)-**2** with (*S*)-**2**, respectively, in the first and second cycle procedures, (*R,S,S*)-**10**-OH was obtained in 99% yield.

2.6. Synthesis of (*R*)-lactic acid tetramer (*R,R,R,R*)-11-OH: the third cycle

The (*R*)-lactic acid tetramer (*R,R,R,R*)-**11**-OH, was obtained in 95% yield through coupling of (*R*)-**2** to (*R,R,R*)-**10**′-OH, the deprotection of the THP group from the hydroxyl group on the resins, and the cleavage of the (*R*)-lactic acid tetramer from the resins.

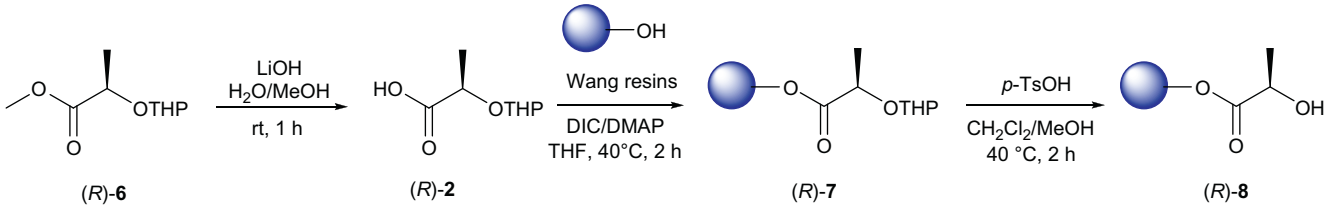
2.7. Synthesis of (*R,R,R,S*)-11-OH

The other enantio-controlled lactic acid tetramer (*R,R,R,S*)-**11**-OH was produced by coupling (*S*)-**2**, instead of (*R*)-**2**, with (*R,R,R*)-**10**′-OH during the third cycle. The resulting tetramer was obtained in 99% yield after cleavage from (*R,R,R,S*)-**11**′-OH.

2.8. Attempt to synthesize the cyclized (*R*)-lactic acid trimer and tetramer

Two approaches were applied to the synthesis of the cyclized (*R*)-lactic acid trimer: the Yamaguchi macrolactonization[12] and the Mitsunobu coupling.[13] In the Yamaguchi macrolactonization, (*R,R,R*)-**10**-OH was reacted with 2,4,6-trichlorobenzoyl chloride for 24 h and then the resulting ester was cyclized in the presence of DMAP in a diluted concentration (2 mM) for another 24 h (Eq. 2). Alternatively, (*R,R,S*)-**10**-OH was cyclized in the presence of diethyl azodicarboxylate (DEAD) and PPh_3 in a diluted concentration (2 mM) (the Mitsunobu coupling) (Eq. 3). When the products formed in both approaches, they were analyzed by LC/MS-MS spectroscopy (data not shown). A mixture of cyclic lactic acid oligomers, sequentially increased lactones started from the cyclic trimer containing trace amounts of the cyclic dimer was characterized.

The same approach was also applied to the synthesis of the cyclized tetramers of (*R,R,R,R*)-**11**-OH and (*R,R,R,S*)-**11**-OH. However, a mixture of cyclic lactic acid oligomers was again obtained.



Scheme 1. Synthesis of (*R*)-lactic acid-coupled resins.

(*R,R,R*)-**10**-OH or (*R,R,R,R*)-**11**-OH → Cyclic lactic acid oligomers
1) 2,4,6-trichlorobenzoyl chloride/DIPEA benzene, rt, 24 h
2) DMAP benzene, rt, 24 h (2)

(*R,R,S*)-**10**-OH or (*R,R,R,S*)-**11**-OH → Cyclic lactic acid oligomers
DEAD/PPh_3 toluene, rt, 24 h (3)

3. Discussion

The solid phase synthesis of the lactic acid oligomers was straightforward and afforded high yields (88–99%) compared to the synthesis in a solution. The initial conjugation of THP-protected (*R*)-lactic acid (*R*)-**2** to Wang resins was conducted by using DIC and the lactic acid-coupled resins were utilized for the next coupling reactions after the THP deprotection. Expansion of the lactic acid oligomers was achieved by sequential conjugation of (*R*)-**2** to the lactic acid-coupled resins through the conventional ester coupling and deprotection of the THP groups. This procedure of the lactic acid expansion successfully generated enantio-controlled lactic acid oligomers (Schemes 1 and 2).

The key intermediate in the current process was to properly protect (*R*)-**2** or (*S*)-**2**, which is utilized as a basic unit for increasing the length of oligomers. Several compounds can be utilized as protection reagents for the hydroxyl group of lactic acid. Among them, benzyl or methoxymethyl ether (MOM) protecting reagents for the hydroxyl group of (*R*)-lactic acid methyl ester require strong basic conditions in the protection reaction and could cause epimerization of the lactic acid as well as hydrolysis of the ester. Thus, we discarded these protection reagents in the current investigation.

Initially, we examined trimethylsilyl (TMS) chloride and *t*-butyldimethylsilyl (TBDMS) chloride as protecting reagents for the hydroxyl group of lactic acid methyl ester. Although TMS- and TBDMS-protected lactic acid methyl esters were obtained with moderate yields (~70%), both compounds were not suitable for the further experiments. TMS-protected lactic acid methyl esters possess high volatility and thus proved difficult to handle. Furthermore, the hydrolysis of TMS- and TBDMS-protected lactic acid methyl esters resulted in decomposition and produced complex reaction mixtures. In addition, when the solution-phase coupling reaction between the TMS- or TBDMS-protected (*R*)-lactic acid and (*R*)-lactic acid benzyl ester (*R*)-**1** was performed, the isolation of the resulting dimer was unsuccessful during the multiple column chromatographic purification.

In contrast, the THP protecting group was quantitatively removed in mild acidic conditions without any decomposition and provided the most promising results compared to the other protecting groups in the model solution reactions. Therefore, the THP group assigned as the hydroxyl protecting group in the current solid-phase synthesis, although the preparation of THP-protected lactic acid from the corresponding lactic acid methyl ester requires a two-step process and gave a moderate overall yield (33–81%).

For the next coupling reaction of (*R*)-**2** to Wang resins, we investigated various activating reagents, such as DIC, DCC (*N,N′*-dicyclohexylcarbodiimide), CDI (carbonyldiimidazole), and EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). In the reagents, DIC or DCC provided the highest yields (data not shown). However, DCC was discarded in the further experiments because the removal of dicyclohexylurea, which is formed during the coupling reaction, was difficult due to its poor solubility in washing solvents (THF, acetone, and CH_2Cl_2), whereas diisopropylurea from the coupling reaction by DIC was easy to wash out. The amount of conjugated (*R*)-**2** to Wang resins by DIC was verified by investigating the amount of the detached (*R*)-**2** (>99%) from (*R*)-**7** in acidic conditions.

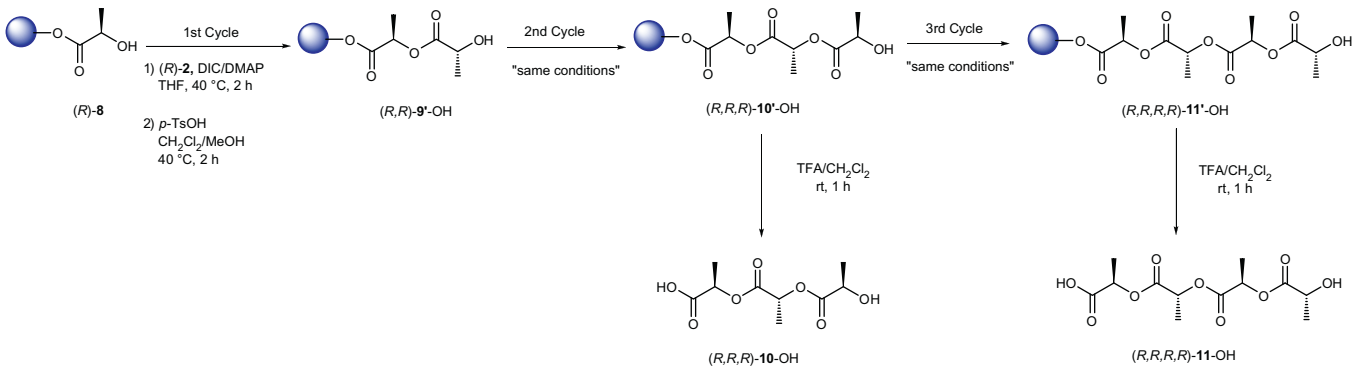
(*R*)-Lactic-acid-coupled resins (*R*)-**8** were generated by the deprotection of the THP group from (*R*)-**7** and utilized for the next coupling with (*R*)-**2** to provide the dimeric-lactic-acid-coupled resins (*R,R*)-**9′**-OH. The sequential attachments of (*R*)-**2** to (*R,R*)-**9′**-OH by repetitive deprotecting and coupling reactions generated lactic acid trimer (*R,R,R*)-**10**-OH and tetramer (*R,R,R,R*)-**11**-OH with 99% and 95% yields after the resin cleavages (Table 1).

The fine control of the configuration on each lactic acid unit of the oligomers was accomplished by the substitution of (*R*)-**2** by (*S*)-**2** without altering the above procedure. Through the routes described in Figure 1, various enantio-controlled lactic acid oligomers were efficiently synthesized with high yields (88–99%) (Figs. 1 and 2). The overall synthesis of the trimer or tetramer was completed in one or two days, respectively.

In addition, we attempted to synthesize the intramolecular cyclization of lactic acid oligomers. We employed the Yamaguchi macrolactonization and the Mitsunobu coupling to the cyclization of the trimers (*R,R,R*)-**10**-OH and (*R,R,S*)-**10**-OH and tetramers (*R,R,R,R*)-**11**-OH and (*R,R,R,S*)-**11**-OH. However, we were unable to isolate single cyclic oligomers but instead obtained a mixture of cyclic oligomers. Presumably, the additional coupling reaction, which causes to form a mixture of oligomers, was faster enough to compete with the cyclization.

4. Conclusion

In conclusion, we have developed a synthetic method for lactic acid oligomers via solid-phased synthesis under mild condi-



Scheme 2. Synthesis of (*R*)-lactic acid trimer (*R,R,R*)-**10**-OH, and tetramer (*R,R,R,R*)-**11**-OH.

Table 1
The yields and optical rotations of oligo-lactic acids generated by the current solid-phase syntheses

Lactic acid oligomers	Yield (%)	$[\alpha]_D$[a]
(*R*,*R*,*R*)-**6**-OH	>99	+0.2
(*R*,*R*,*S*)-**6**-OH	88	+0.1
(*R*,*S*,*S*)-**6**-OH	99	+0.05
(*R*,*R*,*R*,*R*)-**7**-OH	95	+0.1
(*R*,*R*,*R*,*S*)-**7**-OH	99[b] (61)[c]	+0.1

[a] $[\alpha]_D$ (*c* 2.0, $CHCl_3$).
[b] 95% purity. Unknown impurity was contained.
[c] >99% purity. The yield decreased after purification by column chromatography.

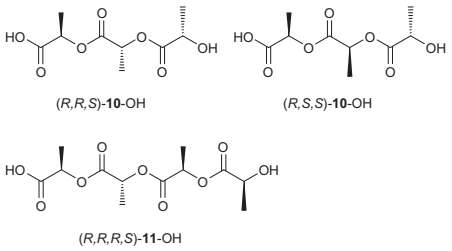


Figure 2. Enantio-controlled lactic acid oligomers: (*R*,*R*,*S*)-**10**-OH, (*R*,*S*,*S*)-**10**-OH, and (*R*,*R*,*R*,*S*)-**11**-OH.

tions with up to 99% yield. The control of the configuration of the lactic acid oligomers was easily carried out by switching the order of linear oligomers without serious side reactions. In addition, the current method can save significant effort and time for the synthesis.

5. Experimental

5.1. General

All Chemicals were purchased from Aldrich, Fluka, TCI, and Alfa-Aesar and used without further purification. All solvents used for the solid-phase reaction are synthesis grade, and were dried in the appropriate manner.[14] Wang resins were purchased from TCI (100–200 mesh, loading capacity 1.0 mmol/g). ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in ppm (δ) on a Varian Gemini 300 using $CDCl_3$ as a solvent. Coupling constants (*J*) were reported in Hz. IR spectra and LC/MS-MS spectra were obtained on a Shimadzu IR-435 spectrometer and Thermo LXQ mass spectrometer (ESI-MS) with Thermo ACCELA LC. For all solid-phase reactions, yields are referred to the purified materials and based upon the loading of the starting resin. All solid-phase reactions were performed by *Synthesis 1* (Heidolph).

5.2. Synthesis of THP-protected (*R*)- and (*S*)-lactic acid

5.2.1. Preparation of (*R*)-methyl-2-(tetrahydro-2*H*-pyran-2-yloxy)propanoate (*R*)-6

In a 100 mL round-bottomed flask, pyridinium *p*-toluene sulfonate (158 mg, 0.63 mmol, 2 mol %) and (*R*)-(+)-lactic acid methyl ester (3.27 g, 31.5 mmol) were dissolved in $CHCl_3$ (60 mL) at 0 °C. Into the solution, dihydropyran (3.71 g, 44.1 mmol) was added dropwise at 0 °C. After addition, the mixture was allowed to warm to rt. After 1 day, the reaction mixture was extracted with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography with hexane/EtOAc afforded (*R*)-**6** as a colorless oil in a 66% yield (3.92 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.82–4.69 (1H, m), δ 4.43 (q, *J* = 7.0 Hz) and 4.21 (q, *J* = 6.8 Hz) (1H), δ 3.97–3.80 (1H, m), δ 3.74 (3H, s), δ 3.53–3.44 (1H, m), δ 1.87–1.38 (9H, m).

5.2.2. Preparation of (*R*)-2-(tetrahydro-2*H*-pyran-2-yloxy)propanoic acid (*R*)-2

In a 500 mL round-bottomed flask, (*R*)-**1** (19.7 g, 105 mmol) and $LiOH{\cdot}H_2O$ (5.27 g, 125 mmol) were dissolved in H_2O (125 mL) and MeOH (210 mL), and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to remove MeOH, and extracted with $CHCl_3$. The combined aqueous layers were acidified with 3 M HCl to pH 6–7, and extracted with $CHCl_3$. Again the combined aqueous layers were acidified with 3 M HCl to pH 4, and extracted with $CHCl_3$/*i*-PrOH (3:1). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (*R*)-**2** as a colorless oil (9.08 mg) in a 50% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.75 (br, 0.33H), 4.64–4.62 (m, 0.67H), 4.46 (q, *J* = 6.3 Hz 0.33H), 4.28 (q, *J* = 6.3 Hz 0.67H), 4.07–3.97 (m, 0.67H), 3.93–3.84 (m, 0.33H), 3.61–3.50 (m, 1H), 1.95–1.73 (m, 2H), 1.74–1.44 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.3, 176.0, 100.2, 98.1, 73.6, 70.1, 64.3, 62.7, 30.9, 30.4, 25.4, 25.1, 20.2, 19.2, 18.8, 18.0; IR (NaCl) ν_{max} 2945, 2873, 1798, 1740, 1454, 1377, 1206, 1129, 1076,

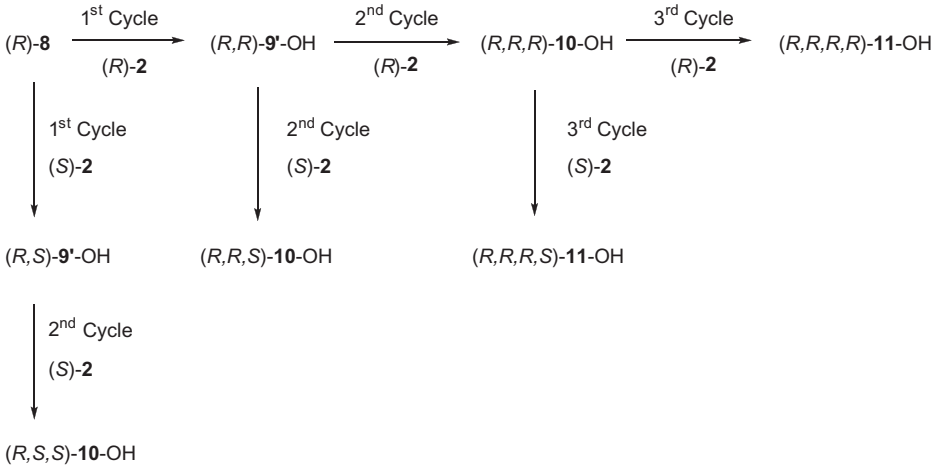


Figure 1. The synthetic routes to diverse enantio-controlled lactic acid oligomers.

1034 cm^{-1}; HRMS (EI) calcd for $C_8H_{14}O_4$: m/z 174.0892, found 174.0884.

5.2.3. (*S*)-2-(Tetrahydro-2*H*-pyran-2-yloxy)propanoic acid (*S*)-2

Compound (*S*)-**2** was prepared from (*S*)-(−)-lactic acid methyl ester (3.27 g, 31.5 mmol) by following the same procedure of the preparation of (*R*)-**2** without the isolation of (*S*)-**6** to give a yellow oil (4.3 g) in 81% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.76–4.73 (m, 0.43H), 4.64–4.62 (m, 0.57H), 4.46 (q, J = 7.1 Hz 0.43H), 4.28 (q, J = 6.9 Hz, 0.57H), 4.03–3.97 (m, 0.57H), 3.91–3.84 (m, 0.43H), 3.59–3.49 (m, 1H), 1.88–1.81 (m, 2H), 1.62–1.46 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.2, 175.8, 100.4, 98.1, 73.7, 70.2, 64.5, 62.8, 30.9, 30.5, 25.4, 25.0, 20.3, 19.3, 18.8, 18.0. IR (NaCl) ν_{max} 2945, 2874, 1798, 1742, 1454, 1378, 1205, 1129, 1076, 1034 cm^{-1}; HRMS (EI) calcd for $C_8H_{14}O_4$: m/z 174.0892, found 174.0880.

5.3. Solid-phase synthesis

5.3.1. Coupling with (*R*)-2 to Wang resins: (*R*)-7

In a reaction vessel, Wang resins (100–200 mesh) (2.0 g, 1.0 mmol/g) and (*R*)-**2** (1.05 g, 6.0 mmol) were dissolved in THF (20 mL). Into the reaction mixture, 4-dimethylaminopyridine (DMAP) (24 mg, 0.2 mmol) and *N*,*N*′-diisopropylcarbodiimide (DIC) (758 mg, 6.0 mmol) were added. The reaction mixture was shaken at 40 °C, 800 rpm for 2 h, cannular-filtered, and washed with THF (3 × 20 mL), acetone (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL) to give (*R*)-**7**, which was used for next reaction without further purification.

5.3.2. Deprotection of THP group from (*R*)-7: (*R*)-8

In a reaction vessel, (*R*)-**7** and *p*-TsOH (100 mg) were dissolved in CH_2Cl_2/MeOH (97:3) and shaken at 40 °C, 800 rpm for 2 h. The reaction mixture was shaken at 40 °C, 800 rpm for 2 h, cannular-filtered, and washed with THF (3 × 20 mL), acetone (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The resulting (*R*)-lactic acid couple resins, (*R*)-**8** were used for the next coupling reaction without further purification.

5.3.3. The first cycle: from (*R*)-8 to (*R*,*R*)-9′-OH

In a reaction vessel, (*R*)-lactic acid conjugated resins (*R*)-**8** produced from the above procedures and (*R*)-**2** (1.05 g, 6.0 mmol) were dissolved in THF (20 mL), and then DMAP (24 mg, 0.20 mmol) and DIC (758 mg, 6.00 mmol) were added. The reaction mixture was shaken at 40 °C, 800 rpm for 2 h, cannular-filtered, and washed with THF (3 × 20 mL), acetone (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The THP deprotection was performed through the same procedure as in the deprotection of the THP group from (*R*)-**7**.

5.3.4. The second cycle: from (*R*,*R*)-9′-OH to (*R*,*R*,*R*)-10′-OH

(*R*,*R*,*R*)-**10**′-OH was obtained by following the first cycle except for using (*R*,*R*)-**9**′-OH instead of (*R*)-**8**.

5.3.5. Resin cleavage from (*R*,*R*,*R*)-10′-OH: (*R*,*R*,*R*)-10-OH

In a reaction vessel, (*R*,*R*,*R*)-**10**′-OH was dissolved in trifluoroacetic acid/CH_2Cl_2 (1:1) (20 mL). The reaction mixture was shaken at rt. After 1 h, the reaction mixture was filtered and concentrated under reduced pressure to afford (*R*,*R*,*R*)-**10**-OH as a yellowish oil in a >99% yield. $[\alpha]_D$ = +0.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.50–5.50 (br, 1H), 5.21–5.15 (m, 2H), 4.38 (q, J = 6.9 Hz, 1H), 1.61–1.55(m, 6H), 1.49 (dd, J = 6.9 Hz, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1, 169.8, 169.6, 69.19, 69.16, 66.9, 20.3, 16.7, 16.6; IR (NaCl) ν_{max} 3486, 2994, 1753, 1445, 1381, 1196, 1131, 1098, 1047 cm^{-1}; HRMS (EI) calcd for $C_9H_{14}O_7$: m/z 234.0740, found 234.0754.

5.3.6. Synthesis of (*R*,*R*,*S*)-10-OH

The second cycle with (*R*,*R*)-**9**′-OH and (*S*)-**2**, instead of (*R*)-**2**, and resin cleavage from the resulting (*R*,*R*,*S*)-**10**′-OH provided (*R*,*R*,*S*)-**10**-OH as a brownish oil in 88% yield: $[\alpha]_D$ = +0.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.24–5.16 (m, 2H), 4.41 (q, J = 6.9 Hz, 1H), 1.61–1.56(m, 6H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1, 169.9, 169.7, 69.4, 69.3, 66.9, 20.1, 16.9, 16.8; IR (NaCl) ν_{max} 3450, 2992, 2924, 1746, 1456, 1377, 1203, 1130, 1097, 1046 cm^{-1}; HRMS (EI) calcd for $C_9H_{14}O_7$: m/z 234.0740, found 234.0737.

5.3.7. Synthesis of (*R*,*S*,*S*)-10-OH

By switching (*R*)-**2** with (*S*)-**2** in the first cycle, (*R*,*S*)-**9**′-OH was obtained from (*R*)-**8**. Then the second cycle with (*R*,*S*)-**9**′-OH and (*S*)-**2**, and cleavage of resins from the resulting (*R*,*S*,*S*)-**10**′-OH provided an (*R*,*S*,*S*)-**10**-OH as a brownish oil in 99% yield: $[\alpha]_D$ = +0.05 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.27–5.13 (m, 2H), 4.37 (q, J = 6.9 Hz, 1H), 1.61–1.54(m, 6H), 1.47 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 170.1, 169.9, 69.34, 69.27, 66.9, 19.9, 16.8, 16.7; IR (NaCl) ν_{max} 3479, 2945, 1749, 1456, 1377, 1202, 1130, 1097, 1047 cm^{-1}; HRMS (EI) calcd for $C_9H_{14}O_7$: m/z 234.0740, found 234.0747.

5.3.8. The third cycle to (*R*,*R*,*R*,*R*)-11′-OH and resin cleavage to (*R*,*R*,*R*,*R*)-11-OH

Compound (*R*,*R*,*R*,*R*)-**11**′-OH was obtained by following the first cycle except for using (*R*,*R*,*R*)-**10**′-OH instead of (*R*)-**8**. Then resin cleavage of (*R*,*R*,*R*,*R*)-**11**′-OH was performed through the same procedure in the resin cleavage from (*R*,*R*,*R*)-**10**′-OH to give (*R*,*R*,*R*,*R*)-**11**-OH as a brownish oil in 95% yield. $[\alpha]_D$ = +0.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.70–5.70 (br, 1H), 5.23–5.16 (m, 3H), 4.38 (q, J = 6.8 Hz, 1H), 1.61–1.55(m, 9H), 1.50 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, 169.7, 169.6, 169.5, 69.1, 69.0, 68.8, 66.7, 20.4, 16.7, 16.7, 16.6; IR (NaCl) ν_{max} 3489, 2995, 2945, 1754, 1455, 1382, 1194, 1131, 1097, 1046 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_9$: m/z 306.0951, found 306.0920.

5.3.9. Synthesis of (*R*,*R*,*R*,*S*)-11-OH

The third cycle with (*R*,*R*,*R*)-**10**′-OH and (*S*)-**2**, and the following resin cleavage of (*R*,*R*,*R*,*S*)-**11**′-OH provided (*R*,*R*,*R*,*S*)-**11**-OH as a brownish oil in 99% yield. $[\alpha]_D$ = +0.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.23–5.13 (m, 3H), 4.70 (br, 1H), 4.43–4.38 (m, 1H), 1.71–1.55(m, 9H), 1.51–1.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 170.0, 169.9, 169.7, 69.42, 69.37, 69.31, 66.9, 20.0, 16.83, 16.78, 16.72; IR (NaCl) ν_{max} 3481, 2994, 2945, 1750, 1455, 1380, 1198, 1130, 1097, 1046 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_9$: m/z 306.0951, found 306.0934.

5.4. Attempt to synthesize cyclic (*R*)-lactic acid oligomers

5.4.1. Intramolecular cyclization of (*R*,*R*,*R*)-10-OH through Yamaguchi macrolactonization

In an 1 L round bottomed flask, (*R*,*R*,*R*)-**10**-OH (217 mg, 0.927 mmol), DIPEA (240 mg, 1.86 mmol), and 2,4,6-trichlorobenzoyl chloride (314 mg, 1.40 mmol) were dissolved in benzene (40 mL). The reaction mixture was stirred at rt for 24 h. Next, DMAP (341 mg, 2.79 mmol) dissolved in benzene (400 mL) was added dropwise into the reaction mixture at rt. After another 24 h, the reaction mixture was evaporated and dissolved in ethyl acetate (EtOAc). The organic layer was washed with 2 M NaOH (aq) and 1 M HCl (aq), respectively. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography with hexane/EtOAc (9:1) provided a mixture of cyclic lactic acid oligomers as a white solid (82 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.23–5.15 (m, 1H), 1.57–1.48 (m, 3H).

5.4.2. Yamaguchi macrolactonization of (*R*,*R*,*R*,*R*)-11-OH

The Yamaguchi macrolactonization of (*R*,*R*,*R*,*R*)-**11**-OH (224 mg, 0.731 mmol) was conducted under the same conditions of (*R*,*R*,*R*)-**10**-OH. However, a mixture of cyclic lactic acid oligomers was again obtained as a white solid (82 mg). And the same spectroscopy data of (*R*,*R*,*R*)-**10**-OH were obtained from ^{1}H NMR and LC/MS-MS.

5.4.3. Intramolecular cyclization of (*R*,*R*,*S*)-10-OH through Mitsunobu reaction

In a 1 L round bottomed flask, (*R*,*R*,*S*)-**10**-OH (230 mg, 0.982 mmol) and PPh_3 (336 mg, 1.28 mmol) were dissolved in toluene (500 mL). Next, DEAD (223 mg, 1.28 mmol) was added dropwise at 0 °C for 15 min. Then the reaction mixture was stirred at rt for 24 h, evaporated under reduced pressure, and dissolved in EtOAc. The organic layer was washed with 1 M NaOH (aq) and 3 M HCl (aq), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide trace amounts of a mixture of cyclic lactic acid oligomers.

5.4.4. Intramolecular Mitsunobu reaction of (*R*,*R*,*R*,*S*)-11-OH

The intramolecular Mitsunobu reaction of (*R*,*R*,*R*,*S*)-**11**-OH (186 mg, 0.607 mmol) was conducted under the same conditions of (*R*,*R*,*S*)-**10**-OH. However, trace amounts of a mixture of cyclic lactic acid oligomers were again obtained.

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