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Switching from *S*- to *R*-Selectivity in the *Candida antarctica* Lipase B-Catalyzed Ring-Opening of ω-Methylated Lactones: Tuning Polymerizations by Ring Size

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Abstract: Novozym 435-catalyzed ring-opening of a range of ω-methylated lactones demonstrates fascinating differences in rate of reaction and enantioselectivity. A switch from *S*- to *R*-selectivity was observed upon going from small (ring sizes $\leq$7) to large lactones (ring sizes $\geq$8). This was attributed to the transition from a cisoid to a transoid conformational preference of the ester bond on going from small to large lactones. The *S*-selectivity of the ring-opening of the small, cisoid lactones was low to moderate, while the *R*-selectivity of the ring-opening of the large transoid lactones was surprisingly high. The *S*-selectivity of the ring-opening of the small, cisoid lactones combined with the established *R*-selectivity of the transesterification of (aliphatic) secondary alcohols prevented polymerization from taking place. Ring-opening of the large, transoid lactones was *R*-selective with high enantioselectivity. As a result, these lactones could be polymerized, without exception, by straightforward kinetic resolution polymerization, yielding the enantiopure *R*-polyester with excellent enantiomeric excess (>99%).

Introduction

The availability of (cheap) enantiomerically pure monomers has played an important role in the development of synthetic approaches to chiral polymers. A prominent example of an optically pure monomer available from the chiral pool is L-lactide, which is industrially synthesized and employed in the synthesis of poly(L-lactide) (PLA). This polymer is well-studied as a biocompatible and biodegradable material.[1] Readily available enantiopure monomers such as D- or L-tartaric acid have also been investigated in the synthesis of chiral polyamides, poly(ester amide)s, and polyesters, and the polymers show promise as biodegradable materials with good mechanical properties.[2] Most monomers, however, are not readily available in enantiopure form. To circumvent the need for enantiopure monomers, enantioselective catalysts have been explored to prepare stereoregular polymers from racemic monomers. For example, enantioselective metal-based catalysts or organocatalysts resulted in isotactic PLA when racemic D,L-lactide was employed as the monomer.[3] In addition, racemic substituted lactones were selectively polymerized with a chiral Al-based catalyst, albeit with a significantly lower selectivity.[3k]

Catalysts from natural sources such as lipases are a valuable extension in the quest to procure enantiomerically pure polymers from optically inactive monomers. A range of chiral polyesters has been synthesized by lipase-catalyzed ring-opening polymerization of substituted racemic ϵ-caprolactones.[4−8] In most cases, commercially available Novozym 435—*Candida antarc-*

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tica lipase B (CALB) adsorbed on an acrylic resin—has been employed. Promising results were obtained, although the enantiomeric excess (ee) of the polymer is generally moderate at best (<90%), and some lactones appeared to be unreactive. The moderate ee's of the polymers obtained by Novozym 435-catalyzed ring-opening polymerizations are primarily related to the moderate selectivity of CALB for substituted ϵ-caprolactones. For example, the enantiomeric ratio E was 17.6 for the Novozym 435-catalyzed hydrolysis of 4-methyl-ϵ-caprolactone at 45 °C, and E was 12 for the transesterification of 6-methyl-ϵ-caprolactone with benzyl alcohol in toluene at 60 °C.[8,9] In both cases, the *S*-enantiomer was the more reactive monomer. In contrast, it is well-known that CALB is highly enantioselective (typically $E > 100$) in the transesterification of secondary alcohols, which is exploited in the kinetic resolution of secondary alcohols.[10] Interestingly, *R*-secondary alcohols are the faster reacting enantiomer in this case. This dramatic difference in the degree and nature of the enantioselectivity of CALB for substituted ϵ-caprolactones and secondary alcohols can be ascribed to different binding sites for the nucleophile (the alcohol) and the acyl donor (the lactone) in the active site.[11] Since the binding site for the alcohol is much more confined, the discrimination between the two enantiomers is more pronounced, resulting in high selectivities. In this respect, the *S*-enantiomer of ω-methyl-ϵ-caprolactone is a particularly fascinating substrate for Novozym 435-catalyzed ring-opening polymerizations. After ring-opening of this lactone, the *S*-secondary alcohol that is formed cannot act as a nucleophile for propagation, since only *R*-secondary alcohols are accepted as a nucleophile and, hence, act as a chain-stopper. This was indeed observed in the lipase-catalyzed ring-opening polymerization of ω-methylated δ-valerolactone (5-MeVL) and ϵ-caprolactone (6-MeCL), which did not occur on a realistic time scale.[5,6]

By employing iterative tandem catalysis (ITC), we recently succeeded in the complete conversion of (*S*)-6-MeCL and *rac*-6-MeCL into enantiopure poly-(*R*)-6-MeCL of high molecular weight (25 kDa) and high ee.[9] This was achieved by combining the *S*-selective ring-opening of the lactone by Novozym 435 with the Ru-catalyzed racemization of the alcohol end-groups. Since ring-opening results in the formation of an *S*-secondary alcohol, which, according to Kazlauskas's rule is the slower reacting enantiomer in enzyme-catalyzed transesterification, no further propagation takes place after initiation.[12] Ru-catalyzed racemization is, therefore, required to yield reactive *R*-terminal alcohols and to enable polymerization. As a follow-up to this work on 6-MeCL, we became interested in the activity and enantioselectivity of Novozym 435-catalyzed ring-opening of ω-methylated lactones in general. In addition, we recently observed fascinating differences in the kinetics of the lipase-catalyzed ring-opening polymerization of unsubstituted lactones with ring sizes varying from 6-membered to 16-membered.[13] Using Novozym 435 as the catalyst, we found that lactones possessing a cisoid conformation showed a lower reactivity with respect to their intrinsic chemical reactivity than large lactones possessing a transoid conformation (Figure 1). The influence of the conformation of the ester bond in lactones on the reaction rates suggests that cisoid and transoid esters represent different substrates for CALB. It can therefore be expected that the introduction of a substituent at the ω-position of lactones of varying ring sizes may lead to differences in the enantioselectivity in a CALB-catalyzed ring-opening polymerization.

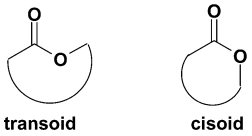
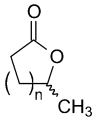


Figure 1. Cisoid and transoid conformations of the ester bond.

Table 1. ω-Methylated Lactones of Varying Ring Size



n	lactone[a]	ring size	ester conformation[b]
0	3-MePL	4	C
1	4-MeBL	5	C
2	5-MeVL	6	C
3	6-MeCL	7	C
4	7-MeHL	8	C (major) + T (minor)
5	8-MeOL	9	T (major) + C (minor)
9	12-MeDDL	13	T

[a] PL, propiolactone; BL, butyrolactone; VL, valerolactone; CL, caprolactone; HL, heptalactone; OL, octalactone; DDL, dodecalactone. [b] C represents the cisoid conformation, while T represents the transoid conformation; assignments based on data for the non-methylated lactones obtained from ref 14a, assuming that ω-methylation of the lactone does not substantially influence the conformational preference of the ester bond.

In this paper, we describe a comprehensive study of the Novozym 435-catalyzed ring-opening and ring-opening polymerization of ω-methylated lactones of ring sizes 4−13 in view of their potential for the synthesis of enantiopure polymers (Table 1). Depending on the enantioselectivity of the ring-opening of the lactone, completely different behavior in the lipase-catalyzed ring-opening polymerization can be expected. *S*-selective ring-opening requires concurrent racemization for polymerization to occur. In contrast, *R*-selective ring-opening could enable straightforward kinetic resolution polymerization (KRP) as the nucleophile that is formed upon reaction of the lactone is accepted by the lipase. To rationalize the results obtained, we take into account the conformational preference of the ester bond—transoid or cisoid—in the lactones investigated.[14] The observed differences in enantioselectivity prompted us to investigate the flexible docking of the enantiomers of the

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Table 2. CALB-Catalyzed Ring-Opening of ω-Methylated Lactones at 70 °C[a]

			k_{cat} (s^{-1})		enantioselectivity	
entry	lactone	ring size	*S*-enantiomer	*R*-enantiomer	exptl[b]	docking[c]
1	3-MePL	4	45.7	nd[d]	*S*	*S*
2[e]	5-MeVL	6	7.9	7.6	–[f]	*S*
3	6-MeCL	7	49.3	8.5	*S*	*S*
4	7-MeHL	8	0.01[g]	204.4	*R*	*R*
5	8-MeOL	9	nd[d]	10.3	*R*	*R*
6[h]	12-MeDDL	13	nd[d]	23.3	*R*	*R*

[a] Reaction conditions: lactone (4 mmol), BA (1 mmol), Novozym 435 (27 mg), and 1,3,5-tri-*tert*-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C. [b] Enantioselectivity experimentally determined by chiral GC. [c] Enantioselectivity predicted from docking experiments. [d] Could not be determined. [e] Experiment performed with 1-octanol (8 mmol) as initiator; enzyme dried overnight at 50 °C over P_2O_5. [f] No significant enantioselectivity was observed for the reaction. [g] Determined in a separate experiment using 2 mmol of isolated (*S*)-7-MeHL. [h] 2 mmol of 12-MeDDL.

various lactones in the active site of CALB by computer-aided molecular modeling. Finally, we describe the polymerization of the larger racemic lactones (ring sizes ≥8) to enantiopure polyesters.

Results and Discussion

CALB-Catalyzed Ring-Opening of ω-Methylated Lactones with Increasing Ring Sizes. We first evaluated the enantioselectivity of the Novozym 435-catalyzed ring-opening of a range of ω-methylated lactones (Table 1). The ω-methylated lactones that were not commercially available were synthesized by methylation of the suitable cycloketone, followed by Baeyer–Villiger oxidation employing *m*-CPBA (see Experimental Section in the Supporting Information). The racemic lactones were obtained in moderate to good purity. The non-methylated lactone was present as an impurity in the large lactones (ring sizes ≥8), but this did not affect the enantioselectivity of the ring-opening experiments. Experiments were performed with benzyl alcohol (BA) as the nucleophile and the appropriate lactone as the acyl donor. We will refer to BA as the initiator (I) and to the lactone as the monomer (M), even if conditions are selected in which polymerization cannot take place. For the ring-opening experiments, an M/I ratio of 4 was selected in order to prevent possible polymerization from taking place. In all cases, Novozym 435 was dried overnight *in vacuo* over P_2O_5 at 50 °C prior to use (see Experimental Section in the Supporting Information) to limit the amount of water.[15] The results are summarized in Table 2. The turnover frequency (TOF) for the ring-opening of the enantiomers of the lactones was determined, and under the applied conditions the TOF equals k_{cat} (see Experimental Section in the Supporting Information). Table 2 also shows the experimentally determined enantioselectivities (chiral GC) as well as the enantioselectivities that were predicted by docking experiments (*vide infra*).

Ring-opening of 3-methylpropiolactone (3-MePL) was *S*-selective, with $k_{cat} = 45.7\ s^{-1}$ for the *S*-enantiomer. No significant conversion of the *R*-lactone was observed on the time scale of the reaction (Table 2, entry 1).[5a,16] Only one molar equivalent of (*S*)-3-MePL is consumed with respect to BA. Ring-opening of the 5-membered ring, 4-methyl-γ-butyrolactone (4-MeBL), does not occur at all, which is related to its thermodynamic stability. As a result of a highly unfavorable ring-chain equilibrium for the 6-membered lactone, ring-opening of 5-methyl-δ-valerolactone (5-MeVL) with M/I = 4 and BA as the initiator did not produce meaningful results.[17] The reaction was, therefore, repeated with 1-octanol as the initiator and M/I = 0.5. 1-Octanol is a stronger nucleophile and a weaker leaving group than benzyl alcohol. As a result, the ring-chain equilibrium is more favorable with 1-octanol than with benzyl alcohol. In order to push the equilibrium to a high lactone conversion, an excess of 1-octanol was employed. Comparable k_{cat} values were observed for the *R*- and *S*-enantiomers, 7.6 and 7.9 s^{-1}, respectively, indicative of a virtually aselective reaction (Table 2, entry 2). Conversion of both enantiomers reached equilibrium at approximately 65%. Apparently, CALB is unable to discriminate between the enantiomers of this particular lactone. Ring-opening of 6-MeCL was *S*-selective with a moderate enantioselectivity, as was previously reported (Figure 2a).[9] The k_{cat} was 49.3 s^{-1} for the *S*-enantiomer and 8.5 s^{-1} for the *R*-enantiomer.

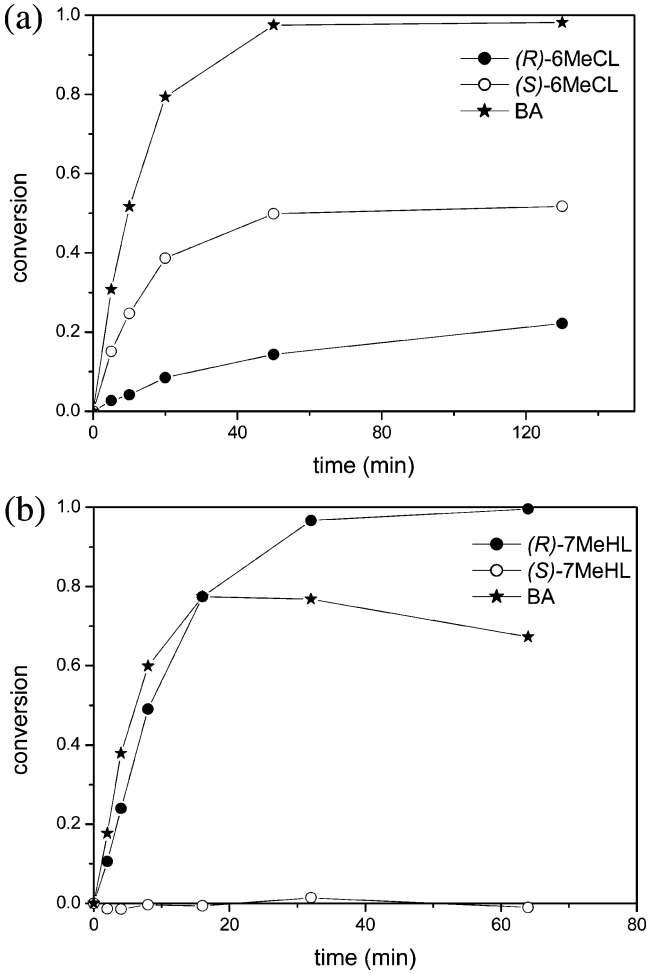

Figure 2. Conversion–time history for CALB-catalyzed ring-opening of (a) 6-MeCL and (b) 7-MeHL. Reaction conditions: lactone (4 mmol), BA (1 mmol), Novozym 435 (25 mg), and 1,3,5-tri-*tert*-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C; conversions were determined with chiral GC.

Ring-opening of an *S*-lactone furnishes an *S*-secondary alcohol, which is not accepted as a nucleophile by CALB (*vide supra*). In the cases of 3-MePL and 6-MeCL, BA reacts with

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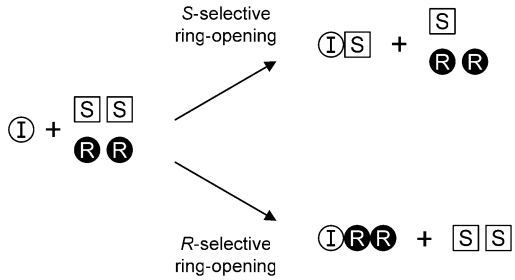
Scheme 1. Ring-Opening of ω-Methylated Lactones with M/I = 4[a]



[a] Basic scenarios on short time scales for *S*- and *R*-selective ring-opening of ω-methylated lactones with M/I = 4 (I represents the initiator): *S*-selective ring-opening furnishes a nonreactive *S*-terminal alcohol, and, therefore, the reaction essentially stops after 1 equiv of *S*-lactone is consumed; (highly selective) *R*-selective ring-opening results in both equivalents of *R*-lactone being consumed, while the *S*-lactone remains unreacted.

one molar equivalent of the *S*-lactone (corresponding to 50% conversion), and no further consumption is observed. In these cases, the *R*-lactone is virtually unreactive (3-MePL) or reacts only slowly (6-MeCL). For the small lactones, the spatial orientation of the methyl substituent is highly dependent on the ring size, which can explain the differences in selectivity for the lactones with ring sizes ≤ 7.

In contrast to the ring-opening of the lactones with ring sizes ≤ 7, ring-opening of the larger lactones with ring sizes between 8 and 13 was *R*-selective. This resulted in the formation of a reactive *R*-secondary alcohol, and both molar equivalents of the *R*-lactone (with respect to BA, M/I = 4) were quickly consumed (entries 4−6, Figure 2b). No consumption of the *S*-lactone could be observed in these cases. For (*R*)-7-methylheptalactone (7-MeHL), a k_{cat} value of 204.4 s^{-1} was calculated (Table 2, entry 4, Figure 2b). The *S*-enantiomer was isolated after reaction, and in a separate experiment a k_{cat} value of only 0.01 s^{-1} was calculated for (*S*)-7-MeHL, indicative of a very high enantiomeric ratio *E* for the ring-opening of 7-MeHL. Similar behavior was observed for 8-methyloctalactone (8-MeOL) and 12-methyldodecalactone (12-MeDDL). The basic scenarios on short time scales for *S*- and *R*-selective ring-opening of ω-methylated lactones with M/I = 4 are visualized in Scheme 1.

Influence of the Conformation of the Ester Function on the Ring-Opening of the Lactone. It is reasonable to assume that ω-methylation does not substantially influence the conformational preference of the ester bond in the lactone. In analogy to the non-methylated lactones (*vide supra*), 6-MeCL will be almost exclusively in the cisoid conformation, and starting from 7-MeHL the transoid conformation appears (Table 1).[13,14] Reactivities that were obtained for the Novozym 435-catalyzed ring-opening of ω-methylated lactones are roughly in line with those previously obtained for the unsubstituted lactones (Table 2).[13] Notably, ring-opening of 7-MeHL was fastest, while reactivity of the small lactones (ring size 4−7) was relatively low. The appearance of the transoid conformer of the ester bond coincides with the remarkably sharp transition that is observed in the enantioselectivity of the ring-opening of the lactones: lactones of ring sizes ≤ 7 show limited selectivity for the *S*-enantiomer (3-MePL and 6-MeCL) or no selectivity at all (5-MeVL), while lactones of ring sizes ≥ 8 exhibit very high selectivity for ring-opening of the *R*-enantiomer.

As a substrate for the lipase, the large, transoid lactones are structurally similar to linear aliphatic (transoid) esters. Transesterification of the latter substrates represents the reverse reaction of the well-known *R*-selective esterification of secondary alcohols and, therefore, necessarily exhibits the same (*R*-) enantioselectivity.[11,18] Surprisingly, the significant population of the cisoid conformers in 7-MeHL and (to a lesser extent) 8-MeOL does not appear to influence the enantioselectivity of ring-opening, while it is reasonable to assume that—analogous to the smaller lactones—the selectivity of ring-opening of the cisoid conformer of the lactone will be limited and possibly even *S*-selective. Presumably, the transoid conformer reacts much faster than the cisoid conformer, which is also in agreement with the observation that ring-opening of the small, cisoid-only lactones is relatively slow, despite their high ring strain.[13] The enantioselectivity of the 8-membered lactone 7-MeHL is unexpectedly high, with k_{cat} for the *R*-enantiomer of 7-MeHL several orders of magnitude higher than that of the *S*-enantiomer.

Computer-Aided Molecular Modeling of Docking of ω-Methylated Lactones in CALB. In order to verify our hypothesis regarding the opposite enantioselectivity for the ring-opening of the small cisoid lactones and the larger transoid lactones, computer-aided molecular modeling was performed. The molecular structure of the enantiomers of each lactone was docked flexibly into the active site cavity of CALB, specifically mimicking the interactions between the lactones and the catalytic triad (Ser105, His224, Asp187) before acylation. Furthermore, several expected stabilizing interactions between protein and ligand were investigated by additional docking runs. While this is a very rough approximation, the difference between the calculated average free energies of binding of the complex for both enantiomers ($\Delta\Delta G$) can give an indication for the enantioselectivity of the protein.

The predicted enantiopreferences resulting from the docking study are given in Table 2. The predicted ΔG values for the lactone enantiomers are listed in the Supporting Information. Docking of the *S*-enantiomer of the small cisoid-only lactones was energetically favored over that of the *R*-enantiomer, implying *S*-selectivity. However, differences in free energy between the enantiomers are small and in most cases within the margin of error of the calculation. For 7-MeHL, docking of the transoid conformation was lower in free energy than that of the cisoid conformation, and for both conformations the calculated average free energy of binding suggests *R*-selectivity (see Supporting Information). *R*-enantioselectivity was also predicted for 8-MeOL and 12-MeDDL. For these larger lactones the differences in free energy are, in every case, significant.

The lowest energy conformations of (cisoid) (*S*)-6-MeCL and both enantiomers of cisoid and transoid 7-MeHL docked in the active site pocket of CALB are depicted in Figure 3. Clearly, there is a good agreement between the lowest energy conformations of (*S*)-6-MeCL—the fastest reacting enantiomer of the 7-membered lactone—and transoid (*R*)-7-MeHL (with respect to the ring itself, the carbonyl, and the methyl group). For transoid (*S*)-7-MeHL, the carbonyl and methyl groups point in completely different directions (Figure 3a). This is in agreement with the lower calculated free energy of docking for the

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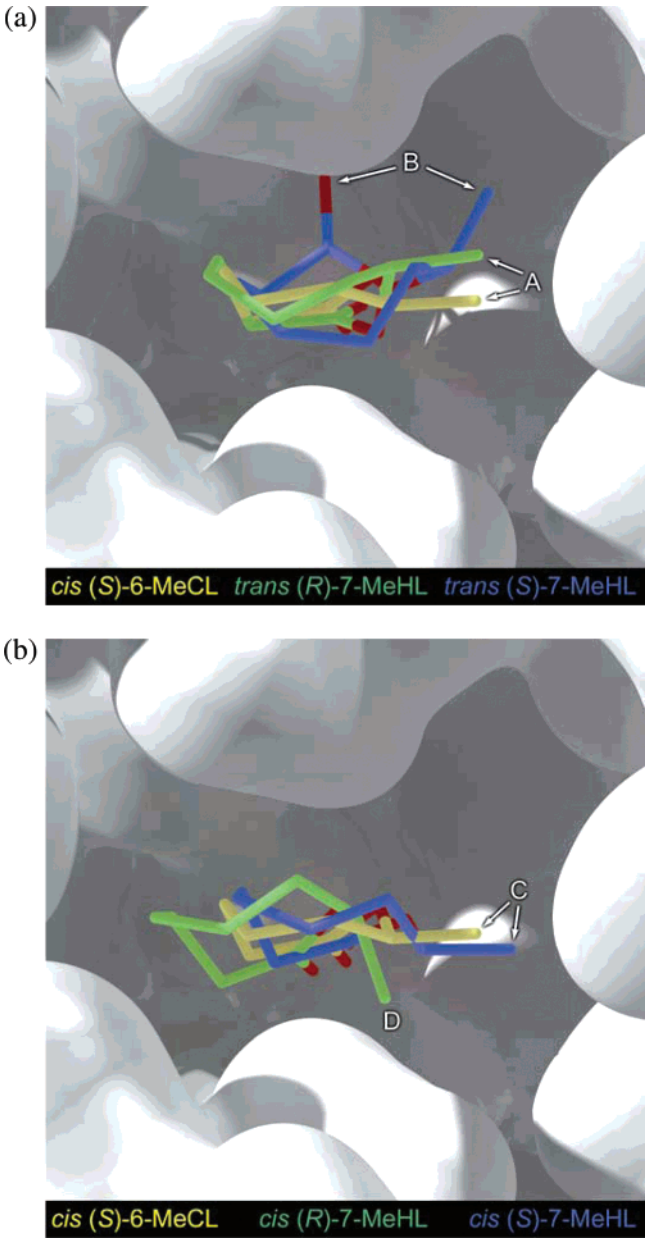
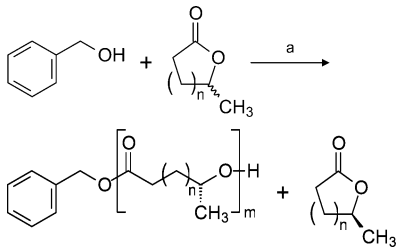


Figure 3. (a) Lowest energy conformations of (cisoid) (*S*)-6-MeCL (yellow), transoid (*R*)-7-MeHL (green), and transoid (*S*)-7-MeHL (blue) docked in the active-site pocket of CALB (oxygen atoms are colored red). The methyl groups of (*S*)-6-MeCL and transoid (*R*)-7-MeHL point approximately in the same direction (indicated with **A**, right side of the figure), while their rings nearly overlap; the carbonyl groups point deeper into the active site. For transoid (*S*)-7-MeHL, both the carbonyl and the methyl groups (both indicated with **B**) are directed into a different part of the active-site pocket than in the case of (*S*)-6-MeCL. (b) Lowest energy conformations of (cisoid) (*S*)-6-MeCL (yellow), cisoid (*R*)-7-MeHL (green), and cisoid (*S*)-7-MeHL (blue) docked in the active-site pocket of CALB (oxygen atoms are colored red). The methyl groups of (*S*)-6-MeCL and cisoid (*S*)-7-MeHL point approximately in the same direction (indicated with **C**, right side of the figure), while their rings nearly overlap; the carbonyl groups point deeper into the active site. For cisoid (*R*)-7-MeHL, the methyl group points in a different direction (downward, indicated with **D**) and there is almost no overlap of the ring with that of (*S*)-6-MeCL.

R-enantiomer compared to the *S*-enantiomer ($\Delta\Delta G = -7.5$ kJ/mol), implying *R*-selectivity; moreover, this matches the experimentally observed selectivity. For the cisoid conformation of 7-MeHL, a different picture is obtained (Figure 3b): the lowest energy conformation of cisoid (*S*)-7-MeHL appears to be in good agreement with that of (*S*)-6-MeCL, while a significantly different orientation is observed for that of cisoid (*R*)-7-MeHL. However, a lower free energy is calculated for cisoid (*R*)-7-MeHL than for the *S*-enantiomer, indicating that more subtle interactions, not evident from this (2D) figure, play an important role ($\Delta\Delta G = -14$ kJ/mol).

Scheme 2. Polymerization of ω-Methylated Lactones with Ring Sizes ≥8[a]



[a] Reagents and conditions: (a) Novozym 435, toluene, 70 °C.

The combination of (1) the good agreement between the lowest energy conformations of transoid (*R*)-7-MeHL and the reactive (*S*)-6-MeCL in contrast to the (visually) significantly different orientation of cisoid (*R*)-7-MeHL with (2) the very high enantioselectivity that was observed experimentally for the ring-opening (while a limited enantioselectivity can be expected for ring-opening of the cisoid lactone, *vide supra*) suggests that the transoid conformer of 7-MeHL is the reactive one in CALB-catalyzed ring-opening. More detailed (quantum mechanical) molecular modeling studies are in progress to support this tentative conclusion.

Polymerization of ω-Methylated Lactones. Novozym 435-catalyzed ring-opening of the small cisoid-only lactones is *S*-selective (3-MePL and 6-MeCL) or virtually aselective (5-MeVL). As a result, *S*-secondary alcohols are formed as end-groups which, according to Kazlauskas's rule, are the slower reacting enantiomers in the highly enantioselective enzyme-catalyzed transesterification.[12] Therefore, no further propagation takes place on a realistic time scale, and polymerization is impossible.

The highly *R*-selective ring-opening of ω-methylated lactones with ring sizes ≥8 enables straightforward KRP of these substrates (Scheme 2). 7-MeHL, 8-MeOL, and 12-MeDDL were successfully polymerized with M/I = 100 (Table 3). The highest activity was observed for the polymerization of 7-MeHL ($k_{cat} = 270$ s^{-1}), followed closely by that of 12-MeDDL ($k_{cat} = 223$ s^{-1}) (see Supporting Information for the conversion plots). The polymerization of 8-MeOL was around 3 times slower ($k_{cat} = 44$ s^{-1}) than the polymerization of 7-MeHL and 12-MeDDL. The small amount of non-methylated lactone that is present as an impurity in the monomer (*vide supra*) is also polymerized. The amount of non-methylated monomeric units in the polymer was determined by ^{1}H NMR and varied from 11 to 22% (Table 3). In all cases, good molecular weights were obtained for the chiral polymers (14−16 kDa) after precipitation. These are higher than the calculated values, which can be rationalized by the loss of low-molecular-weight species during precipitation. The polydispersities vary between 1.23 and 2.25 (after precipitation). As an example, the gel permeation chromatography (GPC) traces of poly-(*R*)-7-MeHL obtained by KRP of *rac*-7-MeHL (entry 1) before and after precipitation in methanol are presented in Figure 4.

To enable the isolation of the unreacted lactones and unambiguously determine the enantioselectivity of CALB for

Table 3. Kinetic Resolution Polymerization of ω-Methylated Lactones Using Novozym 435 at 70 °C[a]

entry	lactone	M/I	time (h)	conv (%)[b]	k_{cat} (s^{-1})[b]	ee_m (%)[c]	ee_p (%)[d]	% non-methylated (mol/mol)[e]	$M_{n,th}$ (kDa)[f]	M_n (kDa)[g]	PDI
1	7-MeHL	102	4	>99	270	99	>99	16	7.2	16.7	1.23
2	8-MeOL	101	24	>99	44	99	>99	11	7.9	14.4	1.29
3	12-MeDDL	99	7	>99	223	>99	>99	22	10.7	14.2	2.25

[a] Reaction conditions: lactone (5 mmol), BA (0.05 mmol), Novozym 435 (50 mg), and 1,3,5-tri-*tert*-butylbenzene (0.25 mmol, internal standard) in toluene (2.5 mL); reaction at 70 °C under an argon atmosphere. Conversions were determined with chiral GC. [b] Results for the *R*-lactone; the *S*-lactone is practically unreactive. [c] Determined by chiral GC. [d] Determined by chiral GC after acid-catalyzed methanolysis of the polymer. [e] Determined by ^{1}H NMR after precipitation of the polymer in methanol. [f] Calculated molecular weight: $M_{n,th} = M_{BA} + 100 \times M_{lactone} \times 0.50$. [g] Determined by GPC (relative to polystyrene standards) after precipitation of the polymer in methanol.

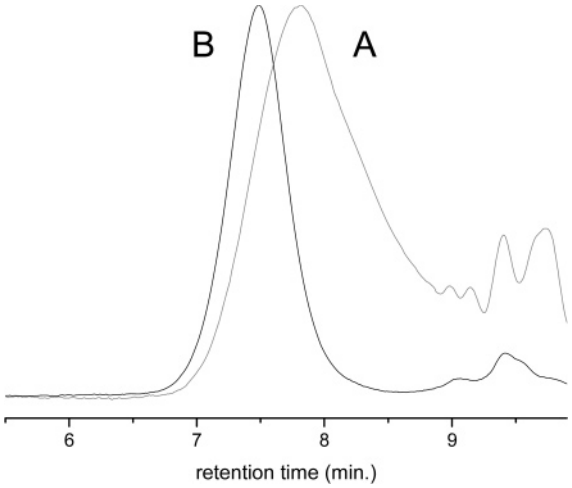


Figure 4. GPC traces of polymer obtained by KRP of *rac*-7-MeHL (Table 3, entry 1) before (A) and after (B) precipitation in methanol (M_n = 16.7 kDa, PDI = 1.23).

the larger ω-methylated lactones, KRP of 7-MeHL and 8-MeOL was performed at a larger scale and the unreacted lactones were isolated by (vacuum) distillation. Isolated (*S*)-7-MeHL (ee >99%) displayed an optical rotation of +58°, while (*S*)-8-MeOL (ee >99%) displayed a value of +50°. The latter value is in agreement with the optical rotation of −41° previously reported for (*R*)-8-MeOL of 91% ee.[19] These data further confirm the enantioselectivity of the present polymerizations. Finally, the polyesters resulting from the experiments described in Table 3 were degraded by acid-catalyzed methanolysis.[9a] Subsequent chiral GC analysis enabled determination of the ee_p (Table 3). In all cases, an excellent ee_p >99% was obtained.

Conclusions

Novozym 435-catalyzed ring-opening of ω-methylated lactones exhibits fascinating variations in reactivity and enantioselectivity. Ring-opening of the small, cisoid lactones is *S*-selective (3-MePL and 6-MeCL) or aselective (5-MeVL). Ring-opening of the larger lactones, for which the ester bond can adopt a transoid conformation, is *R*-selective with a very high enantioselectivity. For the intermediate ring sizes—7-MeHL (8-membered) and 8-MeOL (9-membered)—the significant presence of cisoid conformers does not appear to affect the enantioselectivity of the ring-opening. Molecular modeling studies supported the reversal of selectivity observed upon going from the small, cisoid-only lactones to the larger lactones which can adopt a transoid conformation. The *R*-selectivity for the transoid lactones was related to the *R*-selectivity of the transesterification of (transoid) linear, aliphatic esters. Importantly, this selectivity enables the Novozym 435-catalyzed kinetic resolution polymerization of these lactones. Poly-(*R*)-7-MeHL, poly-(*R*)-8-MeOL, and poly-(*R*)-12-MeDDL were all obtained with good molecular weight and excellent ee (>99%). To the best of our knowledge, this ee represents by far the highest value obtained for CALB-catalyzed ring-opening polymerization of racemic lactones.

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Supporting Information Available: Experimental details for the synthesis of the methylated lactones, their ring-opening and ring-opening polymerizations, and the molecular modeling studies; conversion−time history of CALB-catalyzed ring-opening of 3-MePL, 5-MeVL, and isolated (*S*)-7-MeHL; calculated average free energy of binding of the protein−ligand complex for the different lactones; and conversion−time history of kinetic resolution polymerization of 7-MeHL, 8-MeOL, and 12-MeDDL. This material is available free of charge via the Internet at http://pubs.acs.org.

JA071241A

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