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CHEMOENZYMATIC SYNTHESIS OF MACROCYCLIC POLYAMINES

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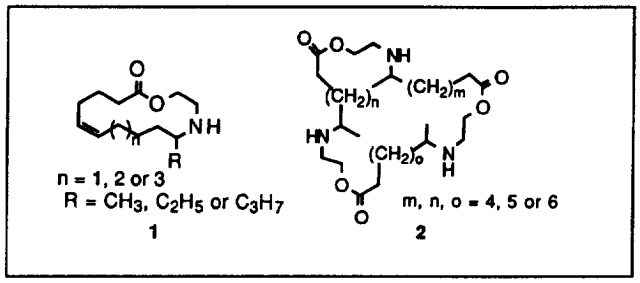
ABSTRACT: (±)-Azamacrolides were synthesized via lipase-catalyzed intramolecular cyclization of (±)-hydroxy-azaesters. Further, the size of the macrocyclic lactones formed could be altered by the substituent on the nitrogen atom. This allows one to prepare a combinatorial library of azamacrolides from a small number of hydroxy-azaesters using this biocatalytic approach.

The azamacrolides, **1**, are a family of 13- to 16-membered *cis*-unsaturated cyclic lactones with a nitrogen atom incorporated into the ring.[1] They are produced by the pupae of *Epilachna varivestis* (the Mexican bean beetle) as a defensive secretion against ants. More recently, Meinwald and coworkers[2] reported that the pupal defensive secretion of *Epilachna borealis* (squash beetle) consisted of a combinatorial library of polyazamacrolides (**2**) derived from a small set of (2-hydroxyethylamino)alkanoic acids. The combinatorial assembly of these building blocks generated a vast array of macrocyclic polyamines and provided an unique example of combinatorial chemistry operating in a living system. As the biosynthetic enzyme(s) has yet to be identified, we became interested in determining whether it would be possible to duplicate this pattern of combinatorial biocatalysis using commercially available enzymes. Herein we report the results of our preliminary studies on the use of lipases for the synthesis of azamacrolides.



Lipases (triacylglycerol hydrolases EC 3.1.1.3) have been widely used for the preparative synthesis of macrocyclic lactones via the intramolecular lactonization of hydroxy acids and esters or via the intermolecular condensation of diacids with diols in anhydrous organic media.[3] From our previous studies,[3h] we have found that the lipases AK, K-10, PPL and Novozym 435 were most suitable for catalyzing macrocyclic lactone formation in anhydrous solvents but the yield of product(s) depended heavily on reaction conditions. Hence, we selected these four lipases for our investigations of their capabilities in catalyzing azamacrolide synthesis.

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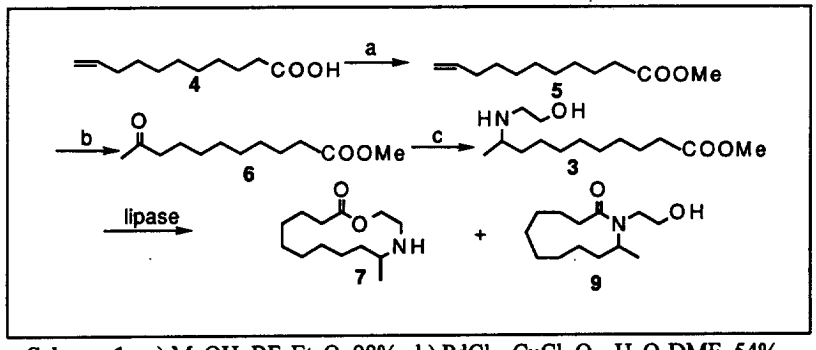
The requisite substrate, (±)-(2'-hydroxyethyl) amino ester, **3** was readily prepared from the commercially available, 10-undecenoic acid, **4**. After methylation, the resulting ester, **5** was subjected to Wacker oxidation[4] in DMF to yield the keto ester, **6**. Reduction amination of **6** afforded (±)-**3** in 37% overall yield from **4** (Scheme 1).



Scheme 1: a) MeOH, BF_3Et_2O, 98%. b) $PdCl_2$, CuCl, O_2, H_2O-DMF, 54%. c) PtO_2, H_2, $HOCH_2CH_2NH_2$, 71%.

At 25°C, lipases K-10 and Novozym 435 reacted very slowly with (±)-**3** in isooctane although a trace of monolactone was detectable in the K-10 incubation mixture. While virtually all of the starting material disappeared in incubations with PPL and AK lipases, no macrocyclic lactones was detected, presumably because of the extensive oligomerization of (±)-**3** occurred resulting in the formation of polymers. However, by inclusion of molecular sieves (4A) in the reaction medium, Novozym 435 converted (±)-**3** into the monolactone **5** as the major product in 46% yield, accompanied by a mixture of dilactone, **8** and the monolactam, **9** (rearranged product, 10%), which was not separable from each other by silica gel column chromatography. In contrast, Lipase K-10 afforded **7** in only 6% yield; the major products were the diester (25%) and triester (7%), products of head to tail condensation.

We have previously shown that at high reaction temperatures, intramolecular macrolactonization (k_{intra}) was favored at the expense of intermolecular esterification (k_{inter}).[3h] Indeed at 65°C, the yield of monolactone, **7**, formed ranged from 24 % for AK lipase to 74% for Novozym 435. In all cases, the mixture of dilactone, **8**, and monolactam, **9**, obtained were in the order of 10-15% (Table 1).

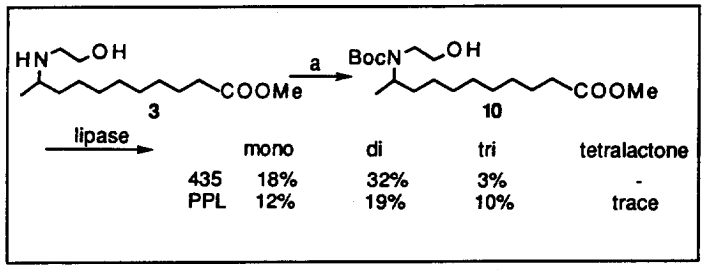
Having defined the reaction conditions for monolactone formation, we next turned our

Table 1: Lipase-catalyzed lactonization of **3**

Entry	Lipase	MS 4A	Temp. (°C)	Monolactone (7)
1	K10	-	25	trace
2	PPL	-	25	0
3	Novo 435	-	25	0
4	AK	-	25	0
5	K10	+	25	6%
6	PPL	+	25	trace
7	Novo 435	+	25	46.2%
8	AK	+	25	0
9	K10	+	65	38%
10	PPL	+	65	28%
11	Novo 435	+	65	74%
12	AK	+	65	24%

The reaction mixtures contained: ester 3 (5 mmol/L), lipase (4 g/L), and MS 4A (10 g/L when used) in anhydrous isooctane. The mixture was incubated for 24 h on a rotary shaker and then analyzed.

attention to the synthesis of macrocyclic lactones of varying sizes. We envisaged that to obtain a combinatorial library of macrocylic lactones, it is imperative that the relative rates for k_{intra} versus k_{inter} of the open chain precursors at different stages should be of the same magnitude. Large differences between these two rates would either terminate the reaction at the monolactone stage or result in the formation of oligomeric esters. Since the conformational properties of a given bifunctional substrate can influence the reaction outcome of an intramolecular process such as macrocyclization. Techniques such as protecting group tuning[6] have been used to alter the conformation of substrates. We reasoned that aside from steric factors, substitution of protecting groups could result in a favorable entropy factor stemming from reduction of the rotational motion in the open chain precursors to favor cyclization although this entropy effect diminishes as the chain length increases. We therefore protected the amino group in (±)-**3** as the *tert*-BOC ester, (±)-**10**, and subjected it to the same transesterification conditions (molecular sieve 4A; 65°C). Of the four lipases examined, Novozym 435 and PPL afforded an array of macrocyclic lactones in the amounts indicated (Scheme 2).



Scheme 2: a) THF, $(BOC)_2O$, 88%.

In summary we have shown for the first time that (±)-azamacrolides could be conveniently prepared by lipase-catalyzed intramolecular cyclization of the corresponding (±)-hydroxy-azaesters. Moreover, the size of the macrocyclic lactones formed could be altered by the substituent on the nitrogen atom. Thus, it should now be possible to synthesize a combinatorial library of azamacrolides from a small series of hydroxy-azaesters using this biocatalytic methodology. The stereoselectivity of this macrocyclic lactonization reaction is currently under investigation and the results of these studies will be reported at a later time.

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5. The data of **1**: ^{1}H NMR (300 MHZ, $CDCl_3$): 4.50 (1H, ddd, J=2.5, 5.6, 11.4 Hz), 4.07 (1H, ddd, J=2.4, 8.5, 11.3 Hz), 2.96 (1H, ddd, J=2.4, 5.6, 13.1 Hz), 2.79 (1H, ddd, J=2.5, 8.5, 13.0 Hz), 2.75 (1H, m), 2.42 (2H, m), 1.68 (2H, m) 1.19-1.47 (12H, m), 1.03 (3H, d, J=6.3 Hz). ^{13}C NMR (75 MHZ, $CDCl_3$): 173.69, 63.32, 49.74, 45.70, 35.26, 33.74, 26.44, 25.53, 25.29, 24.63, 24.52, 22.35, 20.75. ESI (m/z): 228 (M+1).

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8. All lactones gave (M^{+}+Na) peaks (ESI mass spectrometry).