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Enantiomerically Pure Cyclopropyl Hemiacetals: Lipase-Catalyzed Synthesis of Chiral, Nonracemic Ester Homoenolate Equivalents

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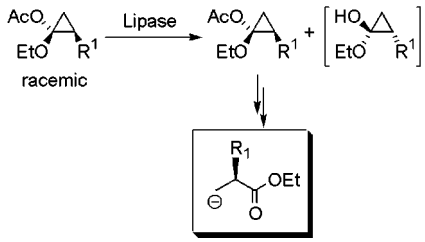
ABSTRACT



Enantiomerically pure cyclopropyl hemiacetals can be obtained by lipase-catalyzed kinetic resolution of their acylated congeners. It is demonstrated that lipases from *Candida antarctica* and *Pseudomonas cepacia* show enantiodivergent behavior toward these substrates. Subsequent ring opening of these building blocks can be achieved with $ZnCl_2$ leading to chiral, nonracemic α-substituted homoenolate anions.

The exploration of aldol reactions has been the cornerstone of asymmetric synthesis. In particular, the use of chiral enolates has been surveyed thoroughly.[1] In contrast, chiral nonracemic homoenolate anions, which are versatile d^3 building blocks, have found less abundant applications in asymmetric synthesis.[2] Among the approaches used to obtain these umpoled reagents, two main strategies have evolved in recent years: (i) metalation of a heterovinyl group (offensive strategy) and (ii) metalation of protected and suitably substituted carbonyl compounds (defensive strategy), respectively.[3,4]

A third approach called the direct strategy, however, has been utilized only to a minor extent, mainly due to the limited availability of appropriate precursors. In studies by Kuwajima and Nakamura, it has been demonstrated that cyclopropanols or cyclopropanone hemiacetals can be ring-opened regioselectively to afford keto and ester homoenolates, respectively.[5] No racemization was observed when the reaction was carried out from enantiomerically pure starting compounds **1a** as exemplified in Scheme 1.[6] In our recent studies to synthesize non-natural amino acids of type **4**, we became interested in these building blocks in enantiomerically pure form (**1b**−**e**).[7] For this purpose, we envisaged a lipase-catalyzed kinetic resolution of acylated cyclopropanone hemiacetals (±)-**5b**−**e**. Lipases are well-known for their high degree of stereodifferentiation of secondary alcohols (Kazlauskas rule), but only a few cases have been reported where tertiary alcohols have been successfully resolved.[8−10] In these cases, one of

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(2) Hoppe, D. *Angew. Chem.* **1984**, *96*, 930; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2377; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

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(4) Ahlbrecht, H. *Synthesis* **1999**, 365.

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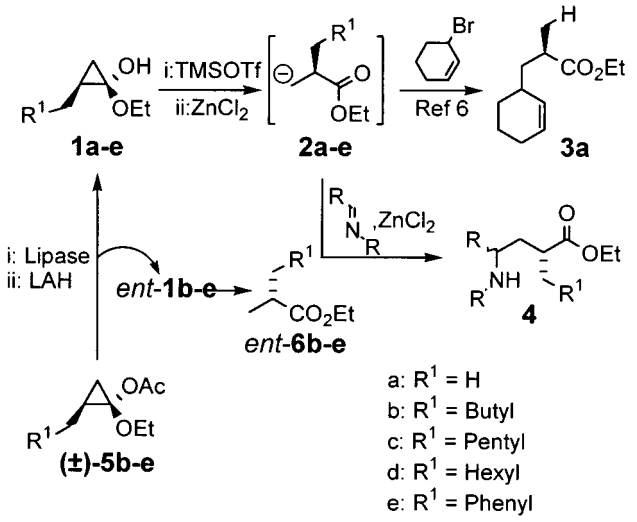
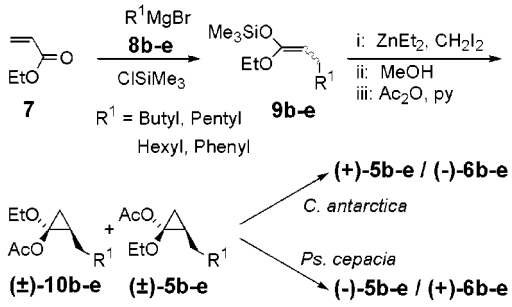
Scheme 1



the substituents was a minor steric hindrance, namely nitrile or alkine residues. Therefore, we thought it might be possible to subject cyclopropanone hemiacetals **(±)-5** to lipase-catalyzed kinetic resolution with the methylen group exhibiting insignificant steric hindrance, too.[11] Another striking feature in these substrates is that the hydroxy group to be attacted by the enzyme is part of a hemiacetal. In pioneering reports, Feringa and Kellogg demonstrated that pyranes which form stable hemiacetals (from aldehydes) can be transformed by lipases.[12] However, the use of ketone hemiacetals has been precedentless as we encountered the stereoselective transformation of **(±)-5** by lipases. Here we want to present our results concerning the lipase-catalyzed resolutions of **(±)-5b−e** and their transformation into chiral-nonracemic homoenolates **2** as outlined in Scheme 1.

The cyclopropanone hemiacetals **5b−e** and their *cis*-configured congeners **10b−e** are readily prepared via cyclopropanation of silyl ketene acetals **9b−e** and diiodomethane as outlined in Scheme 2.[13,14] Methanolysis of

Scheme 2



the silyl acetal and acetylation with acetic anhydride in pyridine gave the cyclopropanone hemiacetals **5** and **10** as a diastereomeric mixture of *cis/trans* isomers (**5**:**10** ≅ 1:1) in high yields. They can be separated easily by chromatography; in general the difference of R_f values is greater than 0.4. We have chosen this approach despite its low *cis/trans*-selectivity, but at this stage of our studies we wanted to have easy access to both diastereomers.

At the same time we developed a suitable method to monitor the kinetic resolution by GLC employing cyclodextrin-modified capillary columns.[15] All substrates could be baseline separated.

Upon screening of various lipases and esterases, *Candida antarctica* lipase B (CALB) and *Pseudomonas cepacia* lipase (PCL) proved to be suitable for enzymic resolution of *trans* derivatives (±)-**5b**−**e**.[16,17] Unfortunately, the saponified cyclopropanone hemiacetals **1b**−**e** turned out to be of limited stability during the lipase-catalyzed reaction; as a consequence, the ring-opened esters **6b**−**e** could be isolated. However, the desired isolation of both enantiomers of **5b**−**e** could still be accomplished, because the lipases CALB and PCL showed enantiodivergent behavior toward (±)-**5b**−**e** (Figure 1). In the case of the CALB-catalyzed resolutions,

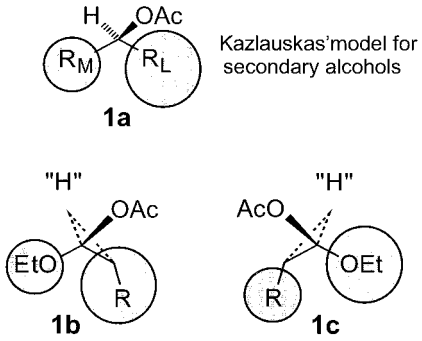


Figure 1. Productive vs nonproductive binding of acylated cyclopropanone hemiacetals: (**1b**) enantiopreference of *P. cepacia* lipase, (**1c**) enantiopreference of *C. antarctica* lipase B toward substrates (±)-**5b**−**e**.

the reaction proceeded faster, leading to products in high yields and high enantiomeric excesses (Table 1). The optical purity was determined by GLC as stated above and was

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(14) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315.

(15) We used a 6-TBDMS-3-butyrate-2-methyl-β-cyclodextrin-modified GLC column.

(16) CALB has been provided by Novo Nordisk; PCL has been purchased from Sigma. The bacterial species PC has been renamed recently (*Burkholderia cepacia*), but we contiunue to use the traditional name.

(17) We screened 11 different lipases and 3 different estereases (from Altus, Amano, Novo, and Fluka).

Table 1. Results of the Enantiodivergent Kinetic Resolution of Cyclopropanone Hemiacetals **5b−e**

	C. antarctica **(+)-5**[a]			*P. cepacia* **(−)-5**[a]		
R^1	$[\alpha]_D$[c]	% ee[b]	yield [%]/time [d]	$[\alpha]_D$[c]	ee[b]	yield [%]/time [d]
butyl	+29.5	>99	84/11	−28.6	98	70/18
pentyl	+25.9	>99	64/7	−23.2	95	34/16
hexyl	+22.7	>99	86/4	−21.9	97	75/36
phenyl	+55.2	>99	98/3	−52.0	96	52/7

[a] Absolute configuration determined after reaction to **6**. [b] Determined via GLC (6-TBDMS-3-butyrate-2-methyl-β-cyclodextrin). [c] In $CHCl_3$.

proven to be >99% ee. In the case of PCL-catalyzed resolutions, the reaction time was prolonged; however almost no decrease in isolated yields and optical purities, respectively, was observed.

The configuration of the products has been determined via comparison of known compounds **6**; therefore, for (+)-**5b−e** a (1*S*,2*S*)-configuration and for (−)-**5b−e** a (1*R*,2*R*)-configuration was established.[18]

Cis-configured cyclopropanone hemiacetals **10b−e**, however, could not saponified using lipase CALB and PCL, respectively. Other screened lipases failed, too.[15] These substrates behave in a manner similar to tertiary alcohols, which have a remote reactivity toward enzyme-catalyzed saponifications.

To predetermine the stereoselectivity of lipase-catalyzed reactions of secondary alcohols, the Kazlauskas model has been endorsed as the most valuable.[19] In Figure 1a, the substrate alignment of a secondary alcohol in the active site of lipase CALB is shown. To superimpose the experimentally determined configuration of tertiary alcohols (+) and (−)-**5**, respectively, and the active site model, the arrangements presented in Figures 1b (for CALB) and 1c (for PCL) may account for the observed enantiodivergent stereoselectivity.

In the context of generating chiral, nonracemic homoenolates **2b−e**, **5b−e** needed to be reduced first. We chose this approach due to the instability of the cyclopropanone hemiacetals (Scheme 1). By reduction with LAH at 0 °C and a quick workup, **1b−e** could be obtained in almost quantitative yields. Treatment with TMS-triflate gave the silylated cyclopropanone hemiacetal derivatives without any racemization. Therefore, we proved that the configuration of **1b−e** is stable.

By stirring silylated hemiacetals in the presence of $ZnCl_2$ and subsequent hydrolysis of intermediary formed homoenolates **2b−e**, the ring-opened esters **6b−e** could be isolated enantiomerically pure. These experiments demonstrate that the homoenolate is formed regioselectively without racemization.

The scope and limitations of this lipase-catalyzed reaction will be disclosed in due course. In ongoing studies we are currently exploring conditions to add these nucleophiles to imines, a reaction which could be termed a "homo-Mannich reaction".

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Supporting Information Available: Characterization data for compounds **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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