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Enantioselectivity and Diastereoselectivity in the Hydrolysis of Acylals and Structurally Related Esters of Secondary Alcohols with *Candida Rugosa* Lipase.

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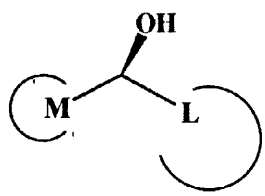
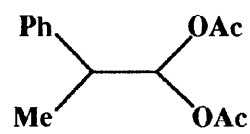
Abstract: Comparative studies of enantioselectivities and diastereoselectivities in the hydrolysis reactions of acylals and 50:50 threo-erythro mixtures of the esters of related secondary alcohols with *Candida rugosa* lipase gave significant information about the reactivity order in the enzymatic hydrolysis of acylals.

Biotransformations of organic substrates are one of the most powerful and popular methods for the synthesis of optically pure chemicals.[1] Enzymes, due to their great catalytic activities and their unique stereoselectivities, have been used in many reactions with excellent stereochemical results. Hydrolytic enzymes especially play an important role in the optical resolution of various substrates, through hydrolysis, esterification and transesterification reactions.

In order to explain the enantiopreference of lipases toward secondary alcohols, Kazlauskas and coworkers proposed[2] an empirical rule that is based on the relative sizes of the substituents at the stereocenter. This rule, which is shown below, is in good agreement with the observed enantioselectivities of most lipases. In the case of *Candida rugosa* lipase (CRL) it has been strongly supported by crystallographic results of menthol transition state analogs.[3]





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We have recently reported[4] the optical resolution of 2-phenylpropionaldehyde, in one step, by enzymatic deprotection of the corresponding acylal **1**, with *Candida rugosa* lipase, in aqueous medium, at pH 7. After 25% conversion, the enantioselectivity (%ee) was 72% and 25% after 50% conversion. As we noted there[4], the acetoxy groups of substrate **1** are prochiral, and the enzyme is expected to distinguish them by showing α-selectivity[5], if we are to use Kazlauskas' convention for secondary alcohols.[6a] Due to the difficulty in observing the proR-, and proS- selectivity of this particular reaction- loss of stereochemistry from the product hemiacylal to the aldehyde-, we determined the enantiomeric composition of the product among the four possible transition states, which represent the β-selectivity.[5] As we observed[4], the R enantiopreference of the enzyme remained constant up to 50% conversion, with a gradual decrease of enantioselectivity from 25% to 50% conversion.

We report here the results of a comparative study between enantioselectivity and diastereoselectivity of the hydrolysis of acylals and 50:50 threo-erythro esters of related secondary

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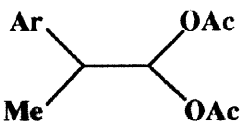
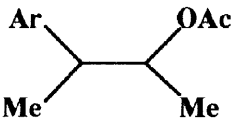
alcohols with *Candida rugosa* lipase. For this study we synthesized[7] acylals **2** and **3**, which bear an aryl susbstituent of increased size,[6] compared to the phenyl of **1**, on the β carbon stereocenter. We also synthesized[8] the 50:50 threo-erythro mixtures of the acetate of 3-phenylbutanol-2, **4**, and 3-m-tolyl butanol-2, **5**, and studied their enzymatic hydrolyses. The results of all the enzymatic hydrolyses are summarized in Table 1.



2. Ar=m-tolyl-
3. Ar=1-naphthyl-



4. Ar=Ph-
5. Ar=m-tolyl-

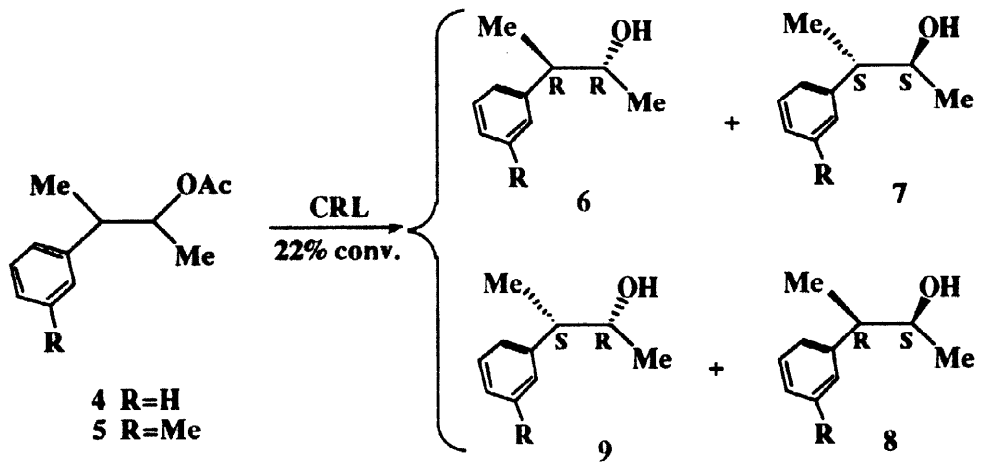
Table 1. Asymmetric Enzymatic Hydrolysis of Substrates **2**, **3**, **4** and **5** with **CRL.**

entry	Substrate	Time/ h	Conversion %[a]	de %[a,b]	ee %	Configuration
1	2	0.5	25	-	>95[c]	R[d]
2	2	1.5	50	-	85[c]	R[d]
3	3	0.5	25	-	90[c]	R[9]
4	3	2.0	50	-	60[c]	R[9]
5	4	8	22	66	62[e]	RR[f]
6	4	8			59[e]	RS[f]
7	5	10	23	65	35[g]	RR[10]
8	5	10			43[g]	RS[10]

[a]By ^{1}H NMR (500MHz). [b]By GC analysis. [c]By ^{1}H NMR in the presence of Eu(hfc)$_3$. The error was ±5%. [d]From the correlation of the pattern of the aldehydic proton signals relative to that of 2-phenyl-propanal and 2-(1-naphthyl) propanal of known configuration, in the presence of Eu(hfc)$_3$. [e]By GC analysis of MTPA derivatives. [f]By optical rotation of tosylate derivative.[11] [g]By ^{1}H NMR of MTPA esters in DMSO-d6. The error was ±5%.

Acylals **2** and **3**, (entries 1 and 3, Table 1), proved to be excellent substrates for *Candida rugosa* Lipase, as shown by their high enantioselectivities . CRL hydrolyzed them faster than it did the acetates of the corresponding secondary alcohols. As can been seen from Table 1, the substituted phenyl ring improved the ee's of the products from 72% in acylal **1**[4] to 95% in acylal **2** and 90% in acylal **3**. It is interesting to note that the 1-naphthyl-substituted acylal **3**, gives higher ee than substrate **1**, but lower ee than the m-tolyl-substituted acylal **2**. These results are in agreement and confirm further those we reported recently[4]. For example, the enzyme shows R enantiopreference in 25% and 50% conversion of acylals , but different enantioselectivity.

Comparing the present results, relative reactivity and enantioselectivity, with those reported previously[12] for the enzymatic resolution of diastereomeric mixtures of open chain secondary alcohols, and drawing meaningful conclusions, is somewhat difficult because of the significant differences in substitution at the carbinol stereocenter. However replacement of one acetoxy group by a methyl group in substrates **1** and **2**, produces the corresponding substrates **4** and **5** which are structurally similar to each other. So, comparison of the enzymatic hydrolyses[6a] of 50:50 threo:erythro mixtures of the acetates of 3-



phenylbutanol-2 (**4**) and 3-m-tolylbutanol-2 (**5**)[8], with the corresponding hydrolyses of acylals **1** and **2**, may clarify the reactivity order and the high enantioselectivities observed for acylals.

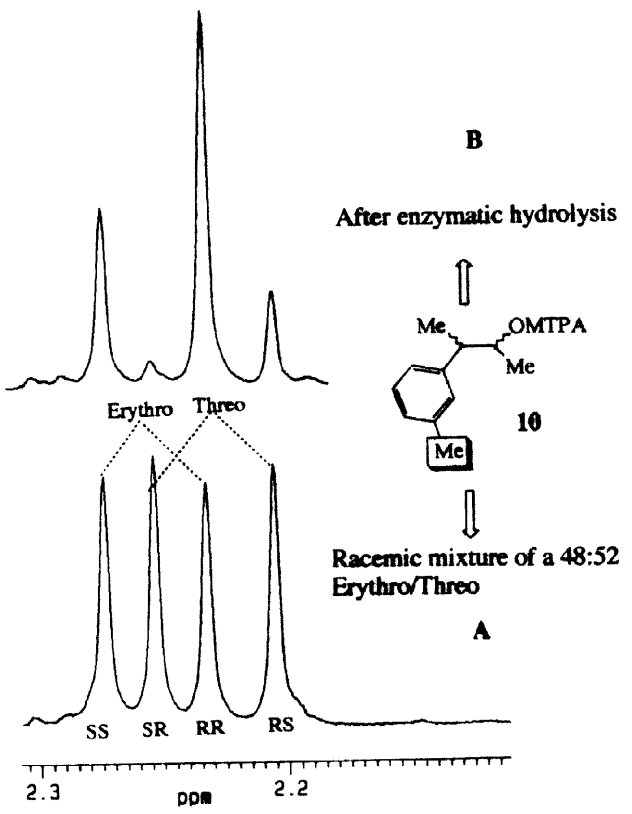


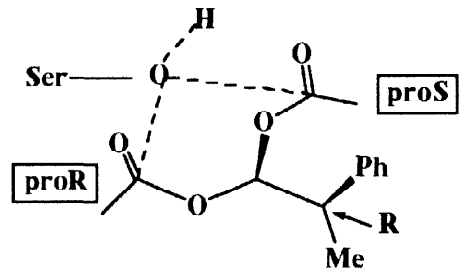
Figure 1. Spectrum A shows the ^{1}H NMR (500MHz) signals of the four diastereotopic aryl-methyl groups of the MTPA esters **10**, in DMSO-d_6. Spectrum B determines the diastereoselectivity and enantioselectivity of the enzymatic reaction by integration of the proper aryl-methyl groups of the corresponding MTPA esters.

As shown in Table 1, the acetates of alcohols, **4** and **5** (entries 5 and 7), hydrolyzed substantially slower than acylal **1** [4], (8 hours for 22% conversion and 26 hours for 45% conversion). From the diastereoselectivities and the enantioselectivities obtained in the hydrolyses of the acetates, of the four stereoisomers the RR hydrolyzes first, followed by the SS and RS -which show small differences in reactivity- and finally by the SR isomer. Substrate **5** shows the same reactivity pattern with no change in diastereoselectivity but a small decrease in enantioselectivity.

The observed R stereoselectivity for each indivi--dual diastereoisomer in the carbinol stereocenter is in accordance with the proposed[2] model for CRL. However, unlike the PFL[6a], in which the small diastereoselectivity for the same substrate showed that the factor governing the order of reactivity is the R stereochemistry in the stereocenter bearing the acetoxy group, CRL reacts with the SS stereo-isomer faster than with the RS. This shows a clear difference in enzyme reactivity between CRL and PFL.

To facilitate the discussion, we wish to point out that due to the change in the priority order of methyl versus acetoxy, according to the Cahn-Ingold-Prelog rules, the RR and SS configurations of the alcohol mixture represent the proS-R and proR-S

transition states of the acylals, respectively. Unlike the finding with acylals, the β stereocenter does not dictate the observed enantioselectivity in the hydrolysis of secondary alcohols. In the case of acylals, a proS-R and proR-R selectivity was shown. In fact the SR stereoisomer which represents the proR-R transition state of the corresponding acylal, is the least reactive among the four stereoisomers.



Although this reversal of reactivity may be attributed to differences in the stereoelectronic nature of the methyl versus the acetoxy group, we would like to propose the following explanation: Both enantiomers of the acylals can bind at the active site of CRL, which, as a non specific enzyme, can hydrolyze readily the proS and proR acetoxy group of each individual enantiomer, as shown in the following scheme. Hense, only the first two configurations of the secondary alcohols RR and SS, represent the order of reactivity of acylals which are the proS-R and proR-R.

Acknowledgements We thank Prof. G. J. Karabatsos for valuable comments.

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