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RESOLUTION OF SOLKETAL BY ENZYMATIC HYDROLYSIS OF ITS DECANOYL ESTER

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Abstract : (S) and (R)-solketal useful synthetic intermediates were prepared from the corresponding racemic decanoyl ester by an enantioselective hydrolysis mediated by porcine pancreas lipase in presence of acetonitrile.

(S) and (R)-solketal 1 or their derivatives are valuable building blocks for the synthesis of a variety of molecules[1,2] (S)-solketal is advantageously prepared from D-mannitol[3] whereas L-serine or ascorbic acid may be converted into (R)-solketal[4]. These chiral molecules can also be obtained from racemic solketal or derivatives, by a simple resolution procedure and experiments using either enzymes[5,6,7] or microbial strains[8,9] have already been described. If hydrolysis often occurred in good yield the selectivity is limited and in any case incompatible with a preparative resolution procedure.

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We describe herein the results we obtained by treating benzoyl solketal and cyclohexane carboxylic acid solketal ester and decanoyl solketal with a phosphate buffered water solution of porcine pancreatic lipase (PPL)[10] as well as other enzymatic preparations. As the substrates are insoluble in water, an organic solvent was added to the medium : acetonitrile or cyclohexane. The enzymatic reaction is monitored with a pH-stat[11] at 25°C and its velocity is a direct function of the amount of 0.1M NaOH solution added. To stop the reaction at the chosen degree of conversion, ethyl ether and sodium sulfate were added. The mixture thus obtained is well stirred, filtered and solvent is then removed by vacuum evaporation. The recovered mixture (90%) is chromatographed on silicic acid (gradient of pentane and ethyl acetate). The alcohol and the ester thus isolated are finally distilled and their enantiomeric purity measured by capillary gas chromatography. Before derivatization according to Mosher's method[12] the isolated ester is saponified and both alcohols are reacted with R(+) MTPA in the conventional way[13].

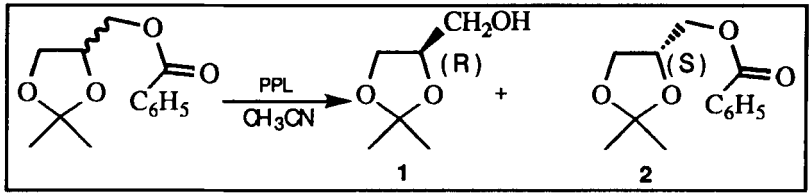
From our experiments it is possible to sum up the results indicated below (see tables).

It is clear that a low degree of conversion would lead to the best enantioselectivity for solketal released and a poor enantiomeric purity for solketal ester present at the end of the reaction and vice versa.

Both enantiomers of benzoyl solketal as well as the cyclohexyl carbonyl derivative are poorly specifically recognized by PPL (see tables 1 and 2). This is probably due to the fact that the recognition part of the molecule is at the level of solketal moiety rather than at the level of the acyl residue.

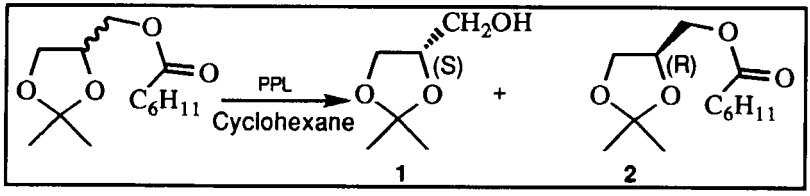
When decanoyl solketal is treated under the same experimental conditions (table 3), the results are much more encourageous probably because of the flexibility of the aliphatic chain. After 20% of hydrolysis, (S)-solketal with a 40%

Table 1. PPL Mediated Hydrolytic Resolution of Racemic Benzoyl Solketal



	(R)-1		(S)-2	
conversion[a] (%)	yield (%)	ee[b] (%)	yield (%)	ee[c] (%)
20	20	11	80	2
60	60	2	60	5

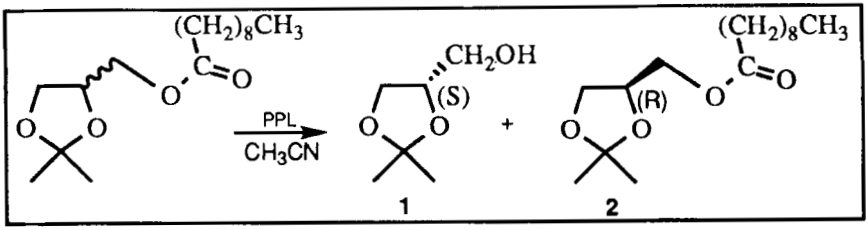
Table 2. PPL Mediated Hydrolytic Resolution of Racemic Cyclohexane Carboxylic Acid Solketal Ester



	(S)-1	
conversion[a] (%)	yield (%)	ee[b] (%)
20	20	1,5
60	60	2,7

enantiomeric excess is produced and after 80% of conversion, (R)-decanoyl solketal with a 90% ee remains in the medium. Therefore by this kinetic resolution procedure (R)-solketal can be prepared with a high degree of enantiomeric purity but the yield of the reaction is too low to be of significant preparative interest.

Table 3. PPL Mediated Hydrolytic Resolution of Racemic Decanoyl Solketal



	(S)-**1**		(R)-**2**	
conversion[a] (%)	yield (%)	ee[b] (%)	yield (%)	ee[c] (%)
20	20	40	70	10
30	27	30	70	25
80	46	6	20	90

with an enantiomeric ratio E≈3

Table 4. Lipase My Mediated Hydrolytic Resolution of Racemic Benzoyl Solketal

	(S)-**1**		(R)-**1**	
conversion [a] (%)	yield (%)	ee[b] (%)	yield (%)	ee[c] (%)
35	35	20	65	10
80	80	3	20	10

In order to improve these results we assayed other commercially available enzymatic preparations such as lipase My, esterase 30 000 and Rhizopus lipase[14] with cyclohexane as co-solvent. In all cases the kinetics measured for the three esters with esterase 30 000 and Rhizopus lipase are of two types : they are too fast so that the enantiospecificity is low or too slow as compared to our previous results. We indicate in table 4, the results we got for the hydrolysis of the benzoyl ester with the

lipase My. Here also the enantiomeric recognition of benzoyl solketal remains poor.

From our results, it clearly appears that different solketal esters are in general poorly recognized by the enzymatic preparations. However when hydrolyzed by PPL, decanoyl solketal undergoes (R)-solketal decanoyl ester in a fairly good enantiomeric purity (90%) but with a poor overall yield, indicating that the recognition step of the process is not important enough.

Therefore additional experiments need to be undertaken in order to verify what part of the molecule is essential for the specific enzymatic recognition to occur and to select the residue to introduce in the molecule instead of the 2,2 dimethyl moiety.

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10. Lipase from porcine pancreas was purchased from Sigma [typeII crude (Steapsina) cat.no. L3126] EC 3.1.1.3

11. The hydrolysis conditions : the substrate (3g) is dissolved in 3ml of acetonitrile and 12ml of 0.1M sodium phosphate buffer (pH=7.5).
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13. The analysis were made on a capillary CP SIL 5CB with a gradient of temperature. The pics were identified from the enantiomeric pure samples. The retention times of the diastereoisomers are for the (R)-solketal 24 min. and for the (S)-solketal 24.3 min.
14. lipase My from Meito Sangyo CO.L1602
    esterase 30 000 from Gist Brocades
    lipase Rhizopus from Sigma

a. determined by the titration of acid released :

$$\% = CV100/(1000m/M)$$

C, concentration of NaOH solution; V, volume of titration; m, weight of substrate (g); M, molar weight

b. determined by gas chromatographic analysis of the Mosher's esters from alcohol
c. determined by gas chromatographic analysis of the Mosher's esters after saponification with KOH in methanol of the unreacted ester

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