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Candida rugosa lipase-catalyzed enantioselective hydrolysis in organic solvents. Convenient preparation of optically pure 2-hydroxy-2-arylethanephosphonates†

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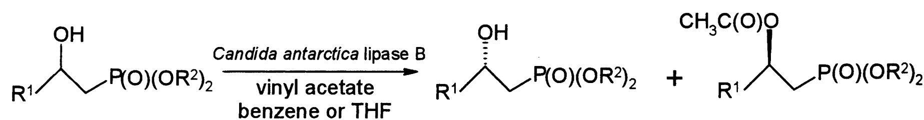
Abstract—A convenient enzymatic method is presented for the preparation of optically pure 2-hydroxy-2-arylethanephosphonates. It is proved that 2-butyryloxy-2-arylethanephosphonates can be enantioselectively hydrolyzed in diisopropyl ether equilibrated with water to give both isomers in high yield and excellent enantiomeric excess. © 2002 Elsevier Science Ltd. All rights reserved.

Undoubtedly, lipase-catalyzed kinetic resolution of enantiomers has become an important tool in organic chemistry to obtain optically pure compounds.[1] The commonly used method for lipase-catalyzed resolution is hydrolysis of esters in the aqueous phase. Enzymatic activity in non-aqueous media did not become a major field of research until Klibanov's first report on the special activity of enzymes in organic solvents.[2] Nowadays, however, one can carry out reactions such as esterification and transesterification which are difficult to conduct in the aqueous phase. This methodology can overcome the limitations of traditional hydrolysis methodology, such as poor substrate solubilities, time consuming work-up procedures and the reuse of enzymes. The selectivity can be modulated by 'solvent engineering'.[3] Lipase-catalyzed esterification is, however, especially effective for primary alcohols; secondary alcohols often required the use of "activated esters" such as vinyl acetates, 1-ethoxyvinyl acetate etc.[4] More sterically hindered secondary alcohols, and those bearing electron withdrawing groups, usually do not react in this manner in many cases. Enzymatic alcoholysis of esters of secondary alcohols in organic solvents seems an attractive alternative.[5] However, poor activity is demonstrated in some cases, probably due to the weak nucleophility of alcohols. Taking into account the intensive nucleophility of water, the combination of hydrolysis and the advantages of enzymatic reactions in organic media, i.e. hydrolysis in organic solvents, seems an intriguing solution. One possibility is to perform the hydrolysis reaction in a water-saturated organic solvent.[6] The enzyme can be recovered and recycled easily. Additionally, the partial loss of specificity due to high concentration of water in aqueous solutions may be eliminated, and thus the enantioselectivity may be higher due to the effect of the organic solvent. Herein we wish to report this approach for the preparation of optically pure 2-hydroxy-2-arylethanephosphonates. Hydroxyalkanephosphonates have received much attention due to their potential biological activities as well as their ability to mimic their carboxylic counterparts.[7] Moreover, they also serve as useful precursors for a variety of substituted phosphonates.[8] There are several chemical methods for the preparation of optically enriched 2-hydroxy-2-arylethanephosphonates.[7d,9] Although Hammerschmidt has exploited lipases for the



Scheme 1.

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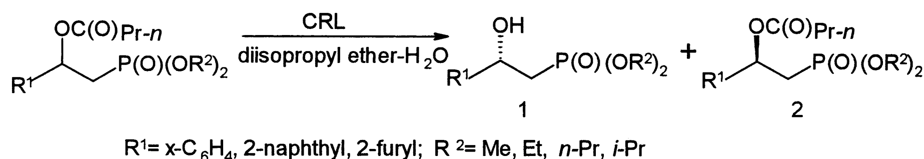
enantioselective hydrolysis of a series of 1-acyloxyphosphonates in an organic-buffer biphase system at pH 7.0 using an autotitrater,[10] few enzymatic methods have been adopted for the resolution of 2-hydroxyalkanephosphonates. We have already developed *Candida antarctica* lipase B-catalyzed acetylation for the preparation of such compounds (Scheme 1).[11]

It is a pity that 2-hydroxy-2-arylethanephosphonates are not ideal substrates for enzymatic acylation systems. Although several lipases (*Candida cylindracea*, *Candida rugosa*, *Geotrium*, *Mucor miehei*, *PS-30*, *PPL*, *Lipozyme*, *IM-60* etc.) were screened for acetylation, none proved to be fruitful. We deduced that the ineffectiveness may be ascribed to the bulkiness of the molecular structure. Alcoholysis of the esters did not give satisfactory results either. Among the lipases tested, however, *Candida rugosa* lipase (CRL)-catalyzed hydrolysis in buffer system proved effective ($E=65$). Unfortunately, the yield was low due to loss in the unavoidable extraction work-up, and the enzyme could not be recycled. We then turned our attention to CRL-catalyzed hydrolysis in water saturated solvents. The aggregation of lipase is serious in water saturated diisopropyl ether and this, consequently, resulted in low conversion, and also necessitated a large excess of lipase to perform the hydrolysis. After several trials, we chose diisopropyl ether equilibrated with 0.5% 1.2 M $MgCl_2$ solution, which resulted in greatly diminished lipase aggregation (Scheme 2).

The choice of the acyl component seemed important for practical purposes since the acetyl group led to lower reaction rates under our experimental conditions. Butyryloxyarylethanephosphonates can be hydrolyzed easily. Indeed, *C. rugosa* lipase-catalyzed enantioselective hydrolysis of 2-butyryloxy- 2-arylethanephosphonates showed even higher enantioselectivity than that performed in buffer system. The work-up procedure is quite simple and the yield is also satisfactory since no extraction is needed (see Table 1).

In conclusion, the high enantioselectivity and the simplicity of the experimental procedure make *C. rugosa* lipase-catalyzed enantioselective hydrolysis in diisopropyl ether quite a convenient procedure for the preparation of optically pure 2-hydroxyarylethanephosphonates.



Scheme 2.

Table 1. *C. rugosa* lipase-catalyzed enantioselective hydrolysis of 1-butyryloxylarylethylphosphonates[a]

Entry	R^1	R^2	Time (h)	1		2		E[e]
				Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[d]	
1	C_6H_5	Me	30	41	>95	42	>95	>100
2	C_6H_5	Et	40	44	>95	45	>95	>100
3	C_6H_5	*n*-Pr	40	43	>95	44	>95	>100
4	C_6H_5	*i*-Pr	48	41	>95	42	>95	>100
5	2-ClC_6H_4	Et	38	44	>95	40	>95	>100
6	4-FC_6H_4	Et	39	41	>95	42	>95	>100
7	$4\text{-NO}_2C_6H_4$	Et	44	43	>95	44	>95	>100
8	4-EtC_6H_4	Et	30	45	>95	40	>95	>100
9	4-BrC_6H_4	Et	30	41	>95	42	>95	>100
10	2-BrC_6H_4	Et	28	42	>95	42	>95	>100
11	$2,4\text{-Cl}_2C_6H_3$	Et	15	42	>95	45	>95	>100
12	3-ClC_6H_4	Et	27	41	>95	44	>95	>100
13	4-MeOC_6H_4	Et	33	41	>95	42	>95	>100
14	$2\text{-CF}_3C_6H_4$	Et	40	44	>95	42	>95	>100
15	2-Furyl	Et	20	45	88.7	40	93.8	93
16	2-Naphthyl	Et	35	41	>95	39	>95	>100

[a] All reactions were performed on 1 mmol scale with 100 mg crude lipase and 4 ml diisopropyl ether, at 30°C.
[b] Isolated yield after column chromatography.
[c] Ee value was determined by ^{31}P NMR with quinine as the solvating agent, a single peak was judged as >95% ee; the configuration of the alcohol was assigned as (*S*) by comparing the optical rotation value with the literature.[7d,9g,h,i]
[d] Determined by ^{31}P NMR with quinine as the solvating agent after chemical conversion into alcohols using K_2CO_3/MeOH.
[e] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.

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