Communication

Lipases-Catalyzed Alcoholysis for the Preparation of Chiral 1- or 2-Hydroxyalkanephosphonates†

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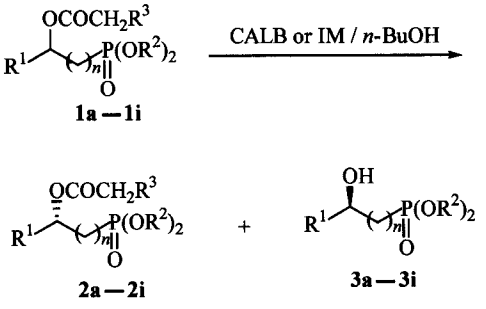
Enzymatic alcoholysis has been developed for the preparation of some chiral 1- and 2-hydroxyalkanephosphonates with high optical purity. This method ensures the convenient access to the optically pure phosphocarnitine, phosphogabob and phosphomycin.

Keywords lipase, alcoholysis, hydroxyalkanephosphonate

Chiral 1- or 2-hydroxyalkanephosphonates show intriguing properties in biology and organic chemistry.[1] The traditional synthetic route leading to such compounds sometimes has drawbacks such as harsh reaction conditions, expensive reagents and low chemical yields.[2] To explore new and convenient procedure is therefore of importance. The utility of lipases for efficient resolution of alcohols and related compounds has shown great importance in organic synthesis.[3] Hammerschmidt has exploited such hydrolases for enantioselective hydrolysis of a series of 1-acyloxyphosphonates in an organic-buffer biphase system.[4] It is known that lipase-catalyzed kinetic resolution of secondary alcohols in organic media can overcome the limitations of the conventional method, such as instability of enzymes, time consuming experimental procedures, relatively lower selectivity, *etc*. We have developed *Candida antarctica* lipase B (CALB)-catalyzed acetylation[2] and crude *Candida rugosa* lipase (CRL)-catalyzed hydrolysis[5] in isopropyl ether for preparing optically active 1- or 2-hydroxyalkanephosphonates. Continuing our study on enzymatic reactions in organic media, we herein wish to report enzymatic resolution of various functionalized acyloxyalkanephosphonates catalyzed by CALB or immobilized *Mucor miehei* lipase (IM).

The optically active 1- or 2-hydroxyalkanephosphonates bearing trifluoromethyl moiety aroused our interest. Though we have developed CALB-catalyzed enantioselective acetylation of hydroxyalkanephosphonates, the method failed to resolve the trifluoromethyl containing substrates. There was no trace of the corresponding acetate detected after one week. We ascribe the poor reactivity to the strong electron-withdrawing effect of the trifluoromethyl moiety, which greatly decreases the nucleophility of the alcohol oxygen. To circumvent this problem, we attempted enzymatic alcoholysis of acyloxyalkanephosphonates (Scheme 1).

Scheme 1



R^1 = Me, Et, vinyl, CF_3; $ClCH_2$, N_3CH_2; R^2 = Et, *n*-Pr, *i*-Pr; R^3 = $ClCH_2$, *n*-Pr; *n* = 0, 1

We have found that the acyl component has profound effect on the reactivity. As to CALB-catalyzed alcoholysis, electron-withdrawing chloroacetyl facilitated the reaction, while acetyl or butyryl group led to poor conversion. For example, some 1- and 2-chloroacetyloxyalkanephosphonates were efficiently alcoholyzed by CALB. This method also provided a convenient access to nearly optically pure hydroxyalkanephosphonates bearing a trifluoromethyl moiety. It should be noted that, however, those substrates containing another chlorine atom could not be resolved successfully by CALB, which may be due to the non-steric effect.[6] Hammerschmidt has reported the resolution of 2-azido-1-hydroxyethylphosphonates using lipase SP524 (*mucor miehei* lipase).[7] Among lipases screened, we also found that IM served as an effective biocatalyst for enantioselective alcoholysis of some 1, or 2-acyloxyalkanephosphonates including azido- or chlorine-bearing ones. It is interesting to note that IM could resolve both 1-chloroacetyloxy and 1-butyryloxyalkanephosphonates efficiently with the later giving much better enantioselectivity. When 2-hydroxyalkanephosphonates were

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used as substrates, however, only their chloroacetyl derivatives were alcoholyzed using butanol as a nucleophile .

Compound **3f** and its (*R*)-isomer underwent dealkylation with Me_3SiBr/MeOH to afford the corresponding hydroxyphosphonic acids, which could be easily converted to both isomers of phosphorus analogues of Carnitine which was prepared by Michalski's group via traditional synthetic method.[8]

Both isomers of phosphorus analogues of Gabob could also be obtained from Pd/C hydrogenation of **3n** and of its (*S*)-isomer, followed by dealkylation in the usual manner.[9]

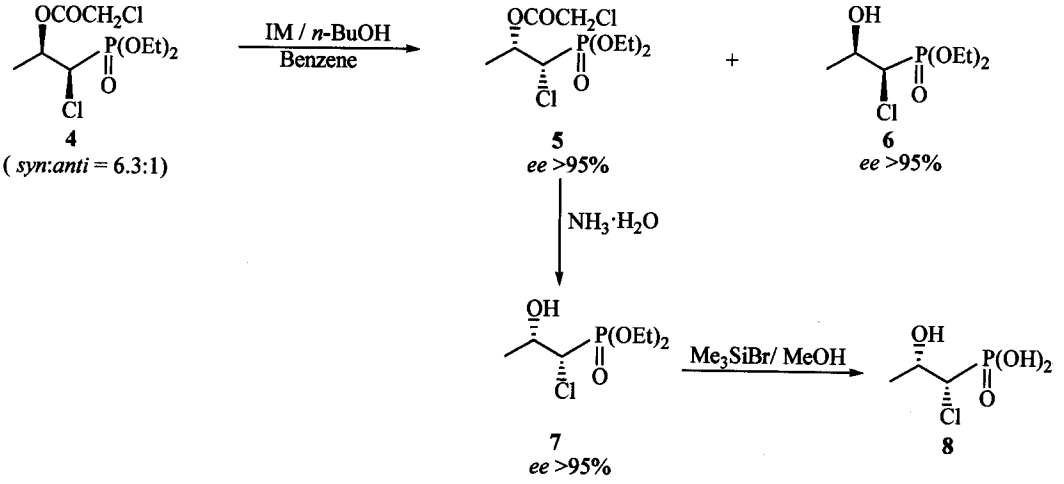
Additionally, this methodology also ensured the preparation of optically pure *syn*-1-chloro-2-hydroxypropanephosphonates (**7**), which underwent dealkylation to afford the key precursor **8** of phosphomycin (Scheme 2).[10]

Table 1 CALB and IM catalyzed enantioselective alcoholysis of 1- and 2-acyloxyalkanephosphonates [a,b]

Entry	Sub	*n*	R^1	R^2	R^3	Lipase	Time (h)	Yield of **2** (%)	*ee* of **2** (%)[d]	Yield of **3** (%)	*ee* of **3** (%)[c]	*E*[e]
1	**1a**	0	Me	*i*-Pr	$ClCH_2$	CALB	40	41	> 95	42	> 95	> 100
2	**1b**	0	Et	Et	$ClCH_2$	CALB	42	42	> 95	41	> 95	> 100
3	**1c**	0	Et	*i*-Pr	$ClCH_2$	CALB	40	43	> 95	41	> 95	> 100
4	**1d**	0	vinyl	Et	$ClCH_2$	CALB	55	42	> 95	41	91	> 100
5[f]	**1e**	0	$ClCH_2$	Et	$ClCH_2$	CALB	58	—	—	—	28	< 10
6	**1f**	0	$ClCH_2$	*n*-Pr	*n*-Pr	IM	49	43	> 95	42	> 95	> 100
7	**1g**	0	CF_3	Et	$ClCH_2$	CALB	33	38	94	44	79	30
8	**1h**	0	CF_3	*n*-Pr	$ClCH_2$	CALB	49	39	> 95	43	82	> 37
9[g]	**1i**	0	CF_3	*n*-Pr	*n*-Pr	IM	30	41	—	40	> 95	—
11	**1j**	1	Me	*i*-Pr	$ClCH_2$	IM	42	43	> 95	44	> 95	> 100
12	**1k**	1	Et	Et	$ClCH_2$	IM	78	36	> 95	45	> 95	> 100
13	**1l**	1	vinyl	Et	$ClCH_2$	CALB	40	43	> 95	44	> 95	> 100
14	**1m**	1	$ClCH_2$	Et	$ClCH_2$	IM	50	45	90	44	94	100
15	**1n**	1	N_3CH_2	Et	$ClCH_2$	CALB	55	44	> 95	48	92	> 89
16	**1n**	1	N_3CH_2	Et	$ClCH_2$	IM	29	45	70	38	94	67
17	**1o**	1	CF_3	Et	$ClCH_2$	CALB	40	43	93	44	> 95	> 100
18	**1p**	1	CF_3	*i*-Pr	$ClCH_2$	IM	43	44	75	40	> 95	> 88
19	**1q**	1	CF_3	*n*-Pr	$ClCH_2$	CALB	35	44	94	39	> 95	> 100

[a] Reactions were generally performed on 1 mmol of scale, 1.5—2 mL of solvent, 0.3—0.5 mL of *n*-BuOH, 100 mg of lipase, 30 ℃. [b] The configurations of **2** and **3**, determinded by refined Mosher's method, are depicted in Scheme 1. [c] *ee* value was determined by ^{19}F NMR or ^1H NMR of its Mosher's ester; some of them were confirmed by ^{19}F NMR or ^{31}P NMR using quinine as the chiral solvating agent. [d] The *ee* value of ester was determined after its chemical conversion to alcohols. [e] The enantiomeric ratio, $E = \ln[(1-c)(1-ees)] / \ln[(1-c)(1+ees)] = \ln[1-c(1+eep)]/\ln[1-c(1-eep)]$, $c = ees/(ees+eep)$.[11] [f] *E* was calculated according to the conversion and the *ee* of **3e** based on the ^{31}P NMR (adding quinine) of reaction mixture. [g] *ee* value of **3i** was not determined.

Scheme 2



4 (*syn*:*anti* = 6.3:1)

5 *ee* >95%

6 *ee* >95%

7 *ee* >95%

8

In summary, we have developed a convenient enzymatic route to some optically active 1- and 2-hydroxyalkanephosphonates. The scope and limitations of this method are under investigation.

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