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Enzyme catalysed resolution of aminophosphonic acids - I - Serin and Isoserin analogues

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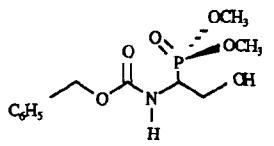
***Abstract** : Lipase PS (Pseudomonas- Amano) was proved to to be the catalyst of choice for the transesterification reaction of N-benzyloxycarbonyl derivatives of the phosphonic analogues of isoserin and serin. A very high enantiomeric excess was obtained for the former while the lipase showed a very poor selectivity for the latter.*

Aminophosphonic acids are a very important class of compounds because of their structural similarity with the natural carboxylic aminoacids. The tetrahedral phosphorus can mimic the transition state of the hydrolysis reaction of esters and amides and thus they can act as inhibitors of hydrolases[1-4]. As a consequence, they have found a lot of industrial applications as pharmaceuticals and agrochemicals[5-8]. The bioactivity of these compounds is known to be strongly dependent on their enantiomeric structure, but up to now only a few methods are available to synthesize optically pure aminophosphonic acids, including diastereoisomeric resolutions[9,10] and asymmetric synthesis[11-19]. Furthermore, chemoenzymatic methodology has not been widely used for this purpose[20,21,22]. In our effort to provide efficient resolutions by means of enzymes, we have undertaken the investigation of several reactions with protected aminophosphonic acids.

In this paper, we describe the resolution of N-benzyloxycarbonyl esters of the phosphonic analogues of serine (SER-P) and isoserine (isoSER-P) using lipases.

Results and discussion

The two protected compounds N-Cbz-SER-P(OMe)$_2$ 1 and N-Cbz-isoSER-P(OEt)$_2$ 2 used in this work were prepared as racemic mixtures according to well known methods[23,24].



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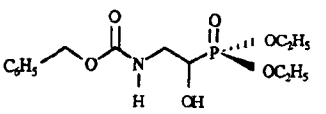

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At the start of our research, we investigated the vinyl acetate transesterification mediated by five classical enzyme preparations, namely *Candida Cylindracea* (AY 30 Amano), *Porcine pancreatic* (PPL Sigma), *Pseudomonas* (PS Amano), *Rhizopus* (lipase N Amano) and *Mucor* (M-AP10 Amano) lipases. The screening

showed that all these lipases apart from PPL were very good catalysts for the transesterification of the compound 1, as after three days of incubation 100 % of the substrate was consumed. At this point, PPL produced 34% conversion (^{1}H NMR) and we hoped in that case, the exhibition of an enantioselectivity. Disappointingly, the optical rotations of the synthesized ester and of the remaining alcohol 1 were very low, showing a very poor enantioselectivity. In contrast, the catalytic activity of the enzymes cited above towards the secondary alcoholic function of N-Cbz-isoSER-P(OEt)$_2$ 2 in the transesterification reaction was shown to produce slow but very enantioselective reactions. Thus, *Pseudomonas lipase* produced 33% conversion (^{1}H-NMR) of 2 within 7 days of incubation. After a silica gel separation (eluent CH_2Cl_2/acetone 4:1 for the ester and 0:1 for the alcohol) the two compounds were hydrolysed (HCl 6N) separately. The optical rotation of the unprotected aminophosphonic acid obtained from the product (overall yield=85%) was $[\alpha]_D^{22}$=+32.5, (c=1 in water) lit.[24]:$[\alpha]_D^{22}$=+31.8 (c=0.525 in water) for the S configuration showing an ee value very close to 100% and from the remaining substrate (overall yield =78%) , $[\alpha]_D^{22}$= -11 (lit.[24]: -31,4 for the R configuration.). The optical rotation of the pure (S) diethyl 1-acetoxy-2-benzyloxycarbonylaminoethanephosphonate was found to be $[\alpha]_D^{22}$= +12,5(c=1 in $CHCl_3$). According to C.J. Sih's equations[25], an E value of 1000 can be estimated for this reaction. Work is in progress in the threonin and isothreonin phosphonate analogues as well as a comparative study of the use of lipases and proteases for the resolution of those compounds.

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