Enantioselective Acylation of Amino Alcohols by Porcine Pancreatic Lipase

Vicente Gotor,* Rosario Brieva, and Francisca Rebolledo

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

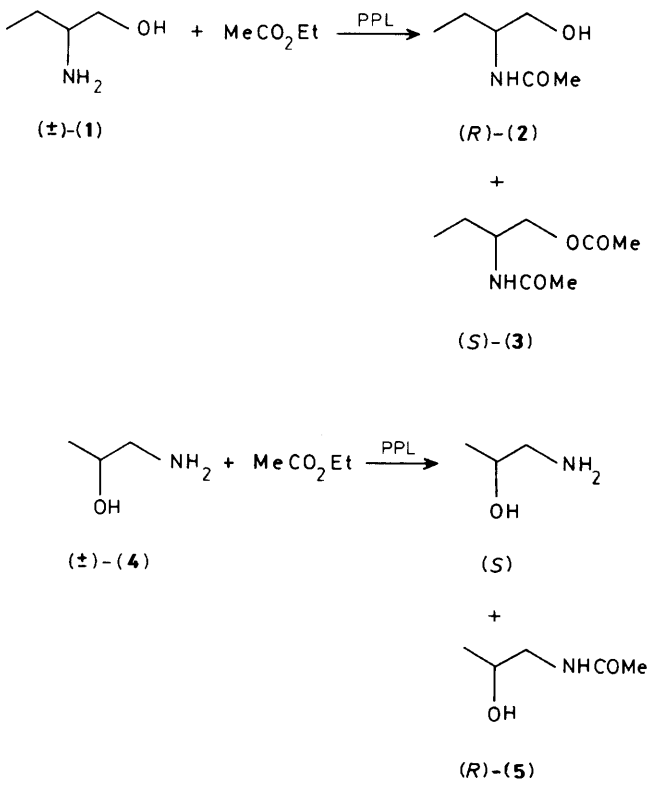
Porcine pancreatic lipase catalysed the enantioselective acylation of the amino group of 1-aminopropan-2-ol and the *N*- and *O*-acylation of 2-aminobutan-1-ol.

During the last decade, interest in the use of enzymes for the resolution of racemic mixtures has been growing continuously and their utilization in organic synthesis to prepare chiral compounds of synthetic value is well documented.[1] This recent increase in the number of applications of enzymes has been largely due to the development of new purification methods which have led to commercially available and relatively inexpensive enzymes. Moreover, the fact that some enzymes can work in organic solvents offers new catalytic perspectives in synthetic organic chemistry.[2]

Lipases are the most common enzymes acting as catalysts in anhydrous organic solvents,[3] and have been widely used for the resolution of racemic alcohols, carboxylic acids, and esters *via* enzymatic transesterification.[4] However, aminolysis reactions have been less widely reported, and in principle, lipases should also be able to catalyse this type of process. In view of previous results obtained using lipases, we have studied the use of these enzymes with different amino-compounds.

Chiral amino-alcohols are of pharmaceutical interest. Recently, Francalanci *et al.*[5] have described the resolution of chiral 2-amino-alcohols with lipases, *via* the *N*-alkoxycarbonyl derivative of the amino-alcohol. We now report that the inexpensive porcine pancreatic lipase (PPL)† can catalyse enantioselective amide formation and esterification of 2-aminobutan-1-ol and amide formation from 1-aminopropan-2-ol.

When (**1**) (10 mmol) was treated with PPL (7.5 g) in ethyl acetate (20 ml), the amide (**2**) and the amido-ester (**3**) were obtained with >95% enantioselectivity.‡ Other solvents (CCl_4, benzene, tetrahydrofuran) did not give satisfactory



† The porcine pancreatic lipase (E.C. 3.1.1.3) used was as purchased from Sigma, Type II crude.

‡ Reactions were carried out at 25 °C and for 20 h. Compound (**1**) gave 37% of (**2**) ($[\alpha]_D^{20}$ −22.1°, *c* 1.3, EtOH) and 37.6% of (**3**) ($[\alpha]_D^{20}$ +36.3°, *c* 0.4, EtOH) as determined by g.c. Compound (**4**) gave 38.3% of the amide (**5**) ($[\alpha]_D^{20}$ −4.0°, *c* 0.5, EtOH). The e.e.s. were determined by ^{1}H n.m.r. spectroscopy (300 MHz) in the presence of tris-3-(2,2,2-trifluoro-1-hydroxyethylidene)-(+)-camphoratoeuropium, $Eu(tfc)_3$.The configuration of the products was assigned by comparation with literature data[5] for the corresponding starting chiral amino-alcohols.

results. In contrast to PPL, yeast lipase (*Candida cylindracea*) showed a very low catalytic activity.

The reaction of 1-aminopropan-2-ol (**4**) in ethyl acetate (20 ml) with PPL (5 g) led to stereoselective acylation of the amino group. This reaction could be stopped at the amide (**5**) stage, yielding only traces of the corresponding amido-ester (<1%). The amide (**5**) was obtained with >95% enantiomerc excess.‡ As for (**1**), the use of other organic solvents or *Candida cylindracea* yielded much poorer results.

In conclusion, PPL can be an excellent catalyst for the enantioselctive transformations of amino-compounds.

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