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A NOVEL AND EFFICIENT SYNTHESIS OF (+)- AND (-)-*TRANS*-2-AMINOCYCLOHEXANOL BY ENZYMATIC HYDROLYSIS

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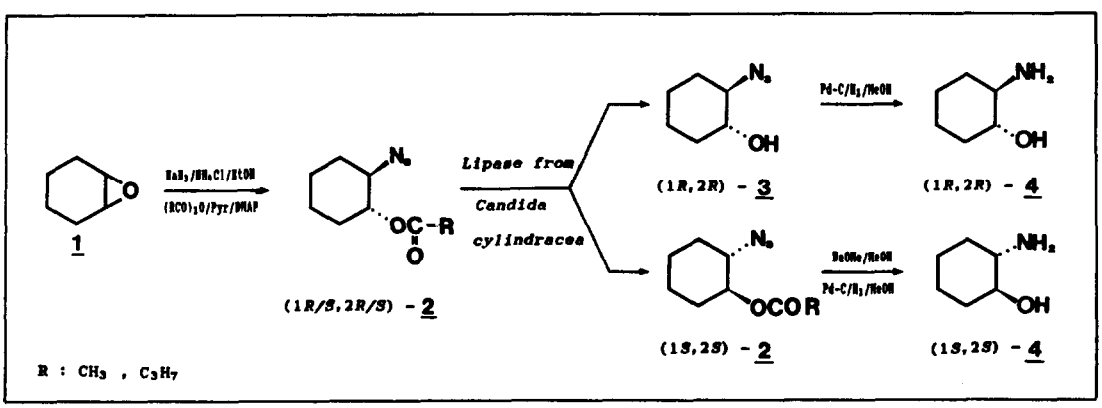
Abstract: Both enantiomers of *trans*-2-aminocyclohexanol were obtained by enzymatic hydrolysis of (±)-2-azidocyclohexanoates using lipases and subsequent hydrogenation.

Enantiomers of *trans*-2-aminocyclohexanol 4 have been obtained very early by fractional crystallisation of their respective tartaric acid salts[1]. They were used later on as model compounds for amino cyclitols and glucosamines[2,3,4]. Very recently various approaches to optically active isomers of 4 and related substances appeared in the literature. Thus, Fujisawa et al.[5] enantioselectively reduced α-nitro- and α-phthalimidoketones with baker's yeast. Besides the frequently encountered difficulties in working up such reactions, only one isomer can be obtained by this method. Yamashita[6] asymmetrically opened oxiranes with the aid of chiral auxiliaries like optically active metal tartrates with 20 - 40% e.e.. Francalanci et al.[7] used enzymatic hydrolysis of α-O-acyl-N-alkoxycarbonyl derivatives for the preparation of some chiral acyclic aminoalcohols.

We want to report on a very simple and efficient preparation of both enantiomers of 4 using enzymatic resolution[8] of *trans*-(±)-2-azidocyclohexanoates 2 and subsequent hydrogenation thereof. Esters (±)-2 can easily be obtained by ring opening of 1 with sodium azide[9] (82 %, mp 25.5-26.5° C, $bp^{0.5}$ 68° C; ref. 9: 70-75 %, mp 28.5-29.5° C, $bp^{0.05}$ 62-64° C) and subsequent esterification according to the general procedure of Steglich[10] (acetate[9]: 85 %, n_D^{20} 1.4715; butyrate: 78 %, n_D^{20} 1.4673; after column chromatography).



The rate of enzymatic hydrolysis of the esters 2 was investigated using the following enzymes[11]: *Candida cylindracea lipase* (CC), *Lipase Amano P* (LIP P), *Lipase Amano AP6, Porcine pancreas lipase* (PPL), *Lipase Amano N, Lipase Amano AY, Lipase Amano A, Pig liver esterase* (PLE) (20 mg substrate, 2 ml phosphate buffer 0.02 N, pH 7.5, 20 mg enzyme, tlc as monitoring aid, 0 to 60 hrs). With the butyrate as substrate, all of these enzymes showed considerable activities, CC and LIP AY exhibiting the fastest rate of hydrolysis. PLE, PPL and LIP A required considerable prolongation of reaction time. Hydrolysis of the acetate in general proceeds much slower, LIP AP6 being the enzyme with highest activity.

Considering these results, a multigram preparation was performed with CC (10g butyrate, 150 ml phosphate buffer, pH 7.2, 500 mg enzyme, pH 7.2, 3 hrs). Hydrolysis, monitored by the consumption of 1 N NaOH with the aid of an autoburette was performed until 40% conversion was reached. Extraction (CH_2Cl_2), evaporation, column chromatography (Cy/EE: 4/1) and Kugelrohr-distillation yielded 35 % of (1*R*,2*R*)-3 (87 % based on the 40 % consumption of starting ester 2) with $[\alpha]_D^{20}$ -66.9° (c 1.5, CH_2Cl_2), 92 % e.e.[12]. The remaining mixture, containing mainly (1*S*,2*S*)-2 was subjected to further 20 % of enzymatic hydrolysis[7]. CC showes a strong enantiodifferentiation, thus slowing down hydrolysis significantly at around 50 %. After workup as above, (1*S*,2*S*)-2 (34 %, 85 % based on 40 % remaining substrate, $[\alpha]_D^{20}$ -6.5° (c 2.4, CH_2Cl_2)) was subjected to chemical hydrolysis with MeOH/NaOMe furnishing 24 % of (1*S*,2*S*)-3 ($[\alpha]_D^{20}$ +66.3° (c 1.6, CH_2Cl_2), 91 % e.e.). Both enantiomers can be hydrogenated with the aid of 10 % Pd on charcoal in practically quantitative yield, giving the respective amino alcohols 4 (1*R*,2*R*: $[\alpha]_D^{20}$ -36.0° (c 1.2, H_2O), 96 % e.e.; 1*S*,2*S*: $[\alpha]_D^{20}$ +37.7°, (c 1.2, H_2O), 98 % e.e.; both after trituration with petroleum ether). A comparative run with acetate 2 and LIP AP6 furnished (1*R*,2*R*)-3 with an e.e. of only 24 %.

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12. e.e. and absolute configuration were determined according to the optical rotations given in the literature[1,3,6] and independently checked by ^{1}H-nmr of the respective MTPA-esters[14]. All products were identified by their ^{1}H-(300 MHz) and ^{13}C-(75 MHz) nmr spectra.
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