Tetrahedron Letters,Vol.28,No.17,pp 1887-1888,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CHEMOENZYMATIC APPROACH TO CARBOCYCLIC ANALOGUES OF RIBONUCLEOSIDES AND NICOTINAMIDE RIBOSE.

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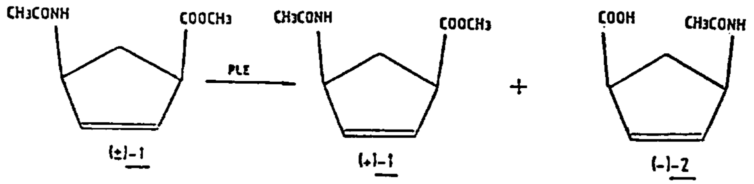
Abstract : Resolution of (±) methyl-4-*cis*-acetamido-cyclopent-2-ene carboxylate 1 was performed by enzymatic enantioselective hydrolysis using pig liver esterase with ee of 87 % and 97 %.

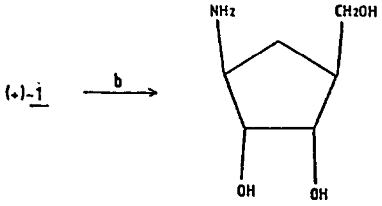
Carbocyclic analogues of ribonucleosides and nicotinamide ribose are known for their interesting biological properties in as different fields as antiviral, antimicrobial (1) and enzymatic (2) activities.

These analogues are derived from (±)-4-*cis*-amino-2,3-*trans*-dihydroxy-hydroxymethyl cyclopentane 3 (3), which is the key intermediate. Its synthesis has been the object of many efforts (4), and the preparation of the optically pure (-)-3, which is an intermediate of (-)-aristeromycin was reported (5) after an asymetric synthesis with about 80 % ee. In this work, we describe a simple access to the two enantiomers 3 based on the resolution of (±) methyl-4-*cis*-acetamido-cyclopent-2-ene carboxylate (±)-1, by selective enzymatic hydrolysis of one enantiomer.



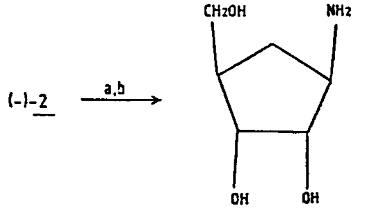
Pig liver esterase (E.C. 3.1.1.1) is known as a good stereo and enantioselective hydrolysis catalyst for a large number of esters of very different structures (6). Our substrate, a typically cyclic γ-acetamido ester, is a new example of the potentialities of PLE as an enantioselective catalyst. Furthermore, this catalyst has shown to be very efficient, and can be applied in a production scale.

In a flask containing 20 ml of distilled water (37° C), 0.5 ml of PLE (550 UI) was added and the pH of the solution adjusted at 7.5, with 1N NaOH. A solution containing 3.2 g of (±)-1 (17.5 mmoles) in 4.5 ml of water and 0.5 ml of methanol was added in the flask. The reaction, followed with a pH stat, is stopped when the half ester is hydrolyzed corresponding to a plateau with a weak slope (5 hours). Work-up of the reaction medium gives rise to 1.38 g of (+)-1 (86 % yield, $[\alpha]_D^{20}$ = +43°, C=1,MeOH) and to 1.4 g of (-)-2 (94 % yield,$[\alpha]_D^{20}$ =-39°, C=1, MeOH). The optical purity of (+)-1 and (-)-2 was determined after their transformation in 3.



(+)-(1S,2R,3S,4S) 3

$[\alpha]^{20}_{D}$ = + 9° C (c=0,5, H_2O)



(-)-(1R,2S,3R,4R) 3

$[\alpha]^{20}_{D}$ ≐ -10° (c=0,5, H_2O)

(+)-3 was obtained in a not optimized overall yield of 35 % with an ee=87 %. Its enantiomer (-)-3 was obtained in a yield of 40 % with an ee=97 %.

In conclusion, this new example of utilization of PLE in racemic resolution shows the versatility of this enzyme which could be employed with other complex substrates.

a) 1N HCl/MeOH, reflux 1h b) i : N-methylmorpholine oxide/H_2O, OsO_4/n-butanol, r.t. 16h ; ii : $LiBH(C_2H_5)_3$/THF, T=0°C, 1h ; iii : 6N HCl, reflux 5 h.

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(Received in France 9 February 1987)