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A NEW ACCESS TO CHIRAL 2-FURYLCARBINOLS BY ENANTIOSELECTIVE HYDROLYSIS WITH PENICILLIN ACYLASE

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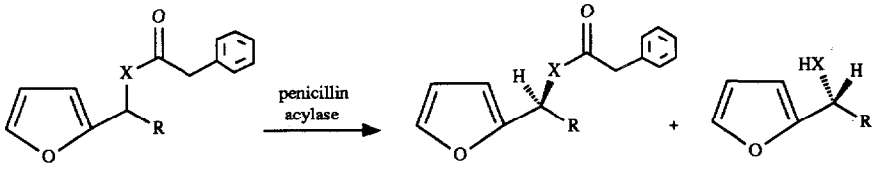
Abstract: The phenylacetic acid esters of 2-furylcarbinols were enantioselectively hydrolyzed with the aid of penicillin acylase.

2-Furylcarbinols and -amines have proven to be versatile starting materials for the construction of various natural products, e.g. carbohydrates,[1] macrolides and related compounds,[2] pheromones[3] and alkaloids.[4,7] Previously devised methods for their preparation in optically active form have focused on conventional resolution processes,[5] chiral auxiliary-based asymmetric syntheses,[2,6] enzyme-catalyzed reductions and enantioselective saponifications with lipases and esterases.[7] The enzymatic resolutions, however, only furnished the desired furan derivatives with preparatively useful ee's if a double resolution strategy (13% yield) or hydrolysis with low conversion (20% yield) was applied. The purpose of this paper is to report that enantiomerically enriched 2-furylcarbinol derivatives can be obtained in preparative amounts and with useful ee's by kinetic resolution of the respective phenylacetic acid esters with commercially available penicillin G acylase (EC 3.5.1.11), immobilized on Eupergit C.[8] The enzyme-catalyzed hydrolyses of the phenylacetates **1** proceeded rapidly at 25°C and pH=5.6-7.5 in 0.05 M Na_3PO_4-buffer in the presence of 10 vol% acetone as cosolvent. The course of the reactions was monitored by the consumption of 0.1 N NaOH and the unhydrolyzed esters **2** were isolated at 60% conversion in gram amounts and in yields of 35-40%.

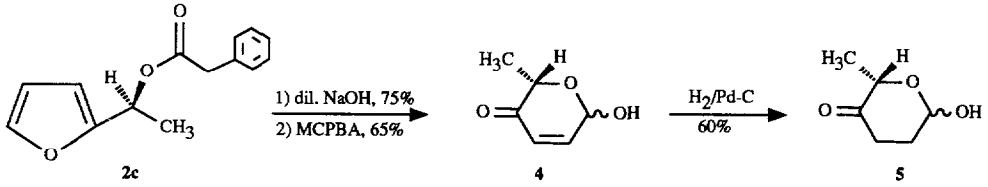


1a-d **2a-d** **3a-d**

compound	R	X	pH	relative velocity [%]*	enantiomer ratio of **2**	$[\alpha]_D^{22}$ c=0.5 CH_2Cl_2	configuration of faster attacked enantiomer of **1**
1a	COOMe	O	7.5	3.4	*91 : 9*	-52.8	*S*
1b	CN	O	5.6	6.2	86 : 14	-15.5	*R*
1c	CH_3	O	7.5	2.7	90 : 10	-40.4	*R*
1d	CN	NH	7.5	39	55 : 45	-1.2	not determined

* 100% = hydrolysis of benzylpenicillin at pH=7.5. The substrates (3g) were incubated with 200 units of penicillin acylase in 600 ml 0.05 M Na_3PO_4-buffer/acetone 9:1 (v/v).

Their enantiomeric excess was determined by recording the ^{1}H-NMR-spectra in the presence of the chiral shift reagent Eu(hfc)$_3$. As is evident, the enzyme tolerates the presence of different functional groups adjacent to the ester moiety and makes the desired furan derivatives available with useful ee's. Surprisingly, the hydrolysis of the acylated aminonitrile **1d** furnished nearly racemic product. To prove the absolute configurations of the products, **2b** was independently synthesized from (*S*)-furan-2-aldehyde cyanohydrine (ee 98%), obtained by enantioselective cyanohydrin formation with mandelonitrile lyase.[9] From this cyanohydrin also **3a** was synthesized by treatment with HCl/methanol and subsequent hydrolysis of the imidoester hydrochloride formed. Comparison of the specific rotations of these reference compounds (**2b**: $[\alpha]_D^{22}$=-29.4° (c=0.9, $CHCl_3$; **3a**: $[\alpha]_D^{22}$=-128.5° (c=1, $CHCl_3$)) with the values for the products of the enzymatic hydrolysis (**2b**: see table; **3a**: $[\alpha]_D^{22}$=+71° (c=0.2, $CHCl_3$)) indicated that in both cases the enantiomer which corresponds to a phenylacetylated L-amino acid was preferably attacked. The stereochemistry of **2c** was assured by saponification of the ester and comparison of the specific rotation of the alcohol obtained ($[\alpha]_D^{22}$=-14.2° (c=0.6, CH_2Cl_2) with literature data ($[\alpha]_D^{22}$=+20.8° (c=1.27, $CHCl_3$) for the (*R*)-enantiomer).[5,6] Again the stereochemical course of the enzyme-mediated reacion was in accordance with the abovementioned observation. The potential synthetic utility of the chiral furan derivatives was demonstrated by the conversion of the 2-furyl-methylcarbinol obtained from **2c** to enantiomerically enriched L-aculose **4** and L-cinerulose A **5** by oxidation with m-chloroperbenzoic acid (MCPMA)[10] (→**4**) and subsequent hydrogenolysis of the double bond (→**5**). These unstable ketosugars are important constituents of naturally occurring antitumor, macrolide and anthracycline antibiotics.[11]



2c **4** **5**

The results presented in this paper further illustrate the usefulness of penicillin acylase for organic syntheses.[12]

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