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SYNTHESIS OF CHIRAL 1-ARYLALKAN-1-OLS USING CRUDE ENZYMES

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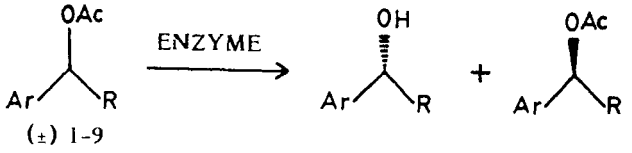
Abstract: Enantioselective hydrolysis of racemic 1-acetoxy-1-arylalkanes has been examined by two selected enzymes, crude pig liver acetone powder and crude goat liver acetone powder, providing 1-arylalkan-1-ols in high optical purities.

Synthesis of enantiomerically pure molecules is one of the most challenging and fascinating areas in Organic Chemistry.[1-4] In recent years, chemico-enzymatic methodology has been extensively utilized for the preparation of optically active molecules.[5-8] In continuation of our research programme[9,10] in chemico-enzymatic methods, we herein report enantioselective hydrolysis of 1-acetoxy-1-arylalkanes using two selected enzymes, crude pig liver acetone powder (PLAP) and crude goat liver acetone powder (GLAP) to provide the corresponding chiral 1-arylalkan-1-ols.

We recently reported a convenient enantioselective hydrolysis of trans-1-acetoxy-2-aryloxycyclohexanes using crude PLAP in two phase medium (ether:aqueous phosphate buffer) producing chiral trans-2-

aryloxycyclohexan-1-ols in high optical purities.[9] With a view to expand the applicability of crude enzymes in organic synthesis we have investigated the enantioselective hydrolysis of 1-acetoxy-1-arylalkanes in two phase medium, using two selected enzymes, namely, pig liver acetone powder (PLAP)[11] and goat liver acetone powder (GLAP)[11] and found that the corresponding alcohols are obtained in 50-95% optical purities (Table 1).



(±) 1-9

(1) Ar = Phenyl, R = Ethyl, (2) Ar = Phenyl, R = n-Propyl, (3) Ar = Phenyl, R = n-Butyl, (4) Ar = Phenyl, R = i-Propyl, (5) Ar = Phenyl, R = i-Butyl, (6) Ar = p-Chlorophenyl, R = Methyl, (7) Ar = p-Bromophenyl, R = Methyl, (8) Ar = p-Chlorophenyl, R = i-Propyl (9) Ar =α-Naphthyl, R = Methyl.

In a typical experimental procedure, to 80 mL of 0.5M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer, 10 mM of racemic 1-acetoxy-1-arylalkane in 15 mL of ether was added with rapid stirring at room temperature. After 15 min. 2 g of the curde enzyme was added. The reactions are monitored by HPLC (Table 1). Usual work-up followed by silica gel column chromatography (ethyl acetate/hexane: 10/90) afforded optically active alcohols.

Table 1. Enzymatic hydrolysis of the racemic acetates of 1-arylalkan-1-ols with crude enzymes.[a]

Substrate	Enzyme	Hydrolysis time(h)	Conversion ratio[b] alcohol:acetate	(+) alcohol obtained				Recovered acetate	
				Yield[c] %	e.e. %	Abs Conf	Optical rotation $[\alpha]_D^{20}$	Yield[c] %	e.e.[d] %
1	PALP	12	45:55	91	50[e]	R	+ 22.85 (c2.5, $CHCl_3$)	89	39
	GLAP	60	40:60	70	75[e]	R	+ 33.97 (c2.3, $CHCl_3$)	90	46
2	PLAP	48	46:54	83	55[f]	R	+ 24.80 (c4.7, C_6H_6)	87	29
	GLAP	92	45:55	67	76[f]	R	+ 34.20 (c2.1, C_6H_6)	82	55
3	PLAP	48	46:54	84	52[g]	R	+ 16.33 (c3.0, C_6H_6)	87	40
	GLAP	80	35:65	77	84[g]	R	+ 26.41 (c2.6, C_6H_6)	84	39
4	PLAP	36	30:70	85	62[h]	R	+ 29.47 (c3.8, Et_2O)	86	49
5	PLAP	65	41:59	82	80[i]	R	+ 25.86 (c5.0 C_7H_{16})	81	69
6	PLAP	10	37:63	90	87[j]	R	+ 43.97 (c1.5, Et_2O)	86	39
	GLAP	22	38:62	86	90[j]	R	+ 45.61 (c1.5, Et_2O)	88	66
7	PLAP	15	36:64	85	90[k,l]	R	+ 37.71 (c5.4, $CHCl_3$)	87	61
	GLAP	36	42:58	90	85	R	+ 35.69 (c8.0, $CHCl_3$)	86	65
8	PLAP	96	37:63	87	70[m]	R[n]	+ 24.40 (c5.6, $CHCl_3$)	81	54
9	PLAP	9	40:60	87	81[o]	R	+ 66.31 (c1.8, Et_2O)	85	60
	GLAP	24	42:58	84	95[k,o]	R	+ 78.09 (c1.1, Et_2O)	83	65

(a) All reactions were carried out in 10 mM scale with 2 g of crude enzyme. (b) Percentage of hydrolysis (conversion ratio) was determined by HPLC analysis. (c) Yields of pure, isolated products after column purification and are based on percentage of hydrolysis. (d) Determined by hydrolyzing the acetate and comparing the specific rotation of alcohol obtained with literature value. (e) Based on the maximum rotation reported[12] $[\alpha]_D^{20}$ -45.45 (c5.15, $CHCl_3$). (f) Based on the maximum rotation reported[13] $[\alpha]_D^{20}$ -45.2 (c4.81, C_6H_6). (g) Based on the maximum rotation reported[14] $[\alpha]_D^{20}$ + 31.3 (c3, C_6H_6). (h) Based on the maximum rotation reported[15] $[\alpha]_D^{20}$ -47.7 (c7, ether). (i) Based on the maximum rotation reported[15] $[\alpha]_D^{20}$ -32.3 (c16.6, heptane). (j) Based on the literature value[16] $[\alpha]_D^{21}$ +46.1 (c1, ether) 91% e.e. and also determined by ^1H NMR (100 MHz) analysis of the corresponding acetate in the presence of shift reagent Eu(hfc)$_3$. (k) Optical purity was determined by ^1H NMR (100 MHz) analysis of the corresponding MTPA derivative. (l) Reported[17] rotation $[\alpha]_D^{25}$ +16.5 (c7.22, $CHCl_3$) for 36 ±4% e.e. (m) Optical purity was determined by g.l.c. analysis (capillary column) of the corresponding MTPA derivative. (n) Tentatively assigned as R. (o) Based on the literature value[18] $[\alpha]_D^{25}$ + 82.1 (c1, ether).

This study demonstrates the applicability of crude enzymes for the preparation of chiral 1-aryl-1-alkanols. Work towards the resolution of biologically active molecules using crude enzymes is in progress in our laboratory.

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