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BOVINE LIVER ACETONE POWDER (BLAP): A CRUDE ENZYME FOR SYNTHESIS OF OPTICALLY ACTIVE 1-ARYL-1-ALKANOLS#

D.Basavaiah* and S.Bhaskar Raju
School of Chemistry, University of Hyderabad
Hyderabad - 500 134, INDIA.

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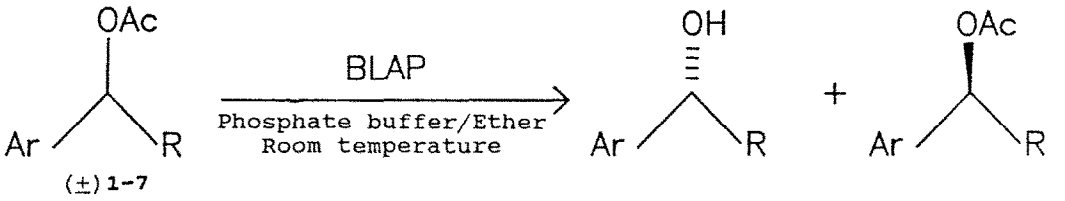
Abstract: 1-Acetoxy-1-arylalkanes have been enantioselectively hydrolyzed by crude bovine liver acetone powder (BLAP) to provide the corresponding 1-aryl-1-alkanols in high (90 - >99%) optical purities.

In recent years there has been an increasing interest for obtaining enantiomerically pure organic molecules and several synthetic strategies have been developed[1-4]. Chemico-enzymatic methodology for this purpose has seen a rapid development over the past few years[5-11]. Recent work of Klibanov on asymmetric transformations catalyzed by enzymes in organic solvents has made enzymes more popular among organic chemists[6,11]. In continuation of our research programme in the applications of crude enzymes for enantioselective synthesis[12-14], we herein report enantioselective hydrolysis of 1-acetoxy-1-arylalkanes with crude bovine liver acetone powder (BLAP) to provide 1-aryl-1-alkanols in high optical purities.

We have recently utilized crude enzymes namely pig liver acetone powder (PLAP) and goat liver acetone powder (GLAP) in two phase medium (ether:aqueous phosphate buffer) for enantioselective hydrolysis of representative classes of racemic acetates[12-14]. With a view to examine the applications of bovine liver acetone powder in organic synthesis, we have prepared BLAP in our laboratory[15] and carried out the enantioselective hydrolysis of 1-acetoxy-1-arylalkanes. It is found that desired (R)-(+)-1-aryl-1-alkanols are obtained in high optical purities (90 - >99%). The results are summarized in Table 1.

The following procedure for hydrolysis of (±)-1-(α-naphthyl)ethanol acetate is representative. To 80mL of 0.5M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer, 2.14g (10mM) of racemic 1-acetoxy-1-(α-naphthyl)ethane in 15mL of ether was added with rapid stirring at room temperature. To it 2g of BLAP was added. The reaction was monitored by HPLC. After 65 hours (40% conversion by HPLC analysis) the reaction mixture was quenched with 2N HCl. The usual workup followed by the column chromatography on silica gel [ethyl acetate-hexane (1:9)] and crystallization from petroleum ether (60-80° fraction) gave 0.530g (77%) of (+)-1-(α-naphthyl)ethanol mp 46-47° in >99% optical purity, $[\alpha]_D^{20}$ +82.06 (c 1.2, ether) [lit[16] $[\alpha]_D^{25}$ +82.1 (c1, ether)]. Optically active 1-(α-naphthyl)ethanol (7) is an important reagent for enantioselective opening of prochiral anhydrides leading to chiral acids[16].



1: Ar = Phenyl, R = Ethyl; 2: Ar = p-Methylphenyl, R = Methyl;
3: Ar = p-Isopropylphenyl, R = Methyl; 4: Ar = p-Chlorophenyl, R = Methyl
5: Ar = p-Bromophenyl; R = Methyl; 6: Ar = β-Naphthyl, R = Methyl;
7: Ar = α-Naphthyl, R = Methyl.

This methodology represents a simple and economical (Bovine liver is cheap and BLAP can be eiasly prepared in large quantities) synthesis of 1-aryl-1-alkanols in high optical purities. Work towards possible applications of BLAP for a variety of asymmetric transformations is in progress in our laboratory.

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Table 1. Enzymatic hydrolysis of the racemic acetates of 1-arylalkan-1-ols with crude BLAP[a] and a comparison with PLAP.

sub-strate	Hydro-lysis time (hours)	Conver-sion ratio[b] -OH:-OAc	(+) Alcohol obtained Yield[c] %	e.e % (config)	Optical rotation $[\alpha]_D^{20}$	Recovered acetate Yield[c] %	e.e[d] %	% e.e of (+)Alcohol obtained with PLAP
1	35	45:55	75	95[e] (R)	+43.17(c2.59, $CHCl_3$)	85	84	50[f]
2	12	35:65	79	93[g] (R)	+50.98(c1.78, $CHCl_3$)	90	52	33[h]
3	48	37:63	83	90[i] (R)[j]	+40.28(c4.16, $CHCl_3$)	83	62	72[k]
4	30	37:63	89	94[l] (R)	+47.61(c2.5, Et_2O)	91	58	87[f]
5	36	35:65	87	92[m] (R)	+38.10(c3.4, $CHCl_3$)	89	55	90[f]
6	12	33:67	81	93[n] (R)	+38.48(c1.5, EtOH)	85	58	57[o]
7	65	40:60	77	>99[p] (R)	+82.06(c1.2, Et_2O)	90	75	81[f]

a) All reactions were carried out in 10mM scale with 2g 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 maximum rotation reported[17] $[\alpha]_D^{20}$ -45.45 (c5.15, $CHCl_3$), conf. S. f) From ref. 14. g) Based on literature value[18] $[\alpha]_D^{25}$ +51.6 (c1, $CHCl_3$) 94% e.e, conf. R. h) Optical purity of the (+) alcohol for 37% conversion. i) Determined by ^1H NMR (100 MHz) analysis of the corresponding MTPA derivative. j) Tentatively assigned as R. k) Optical purity of the (+) alcohol for 36% conversion. l) Based on literature value[18] $[\alpha]_D^{20}$ +46.1 (c1, ether) 91% e.e, conf. R. m) Determined by ^1H NMR (100 MHz) analysis of the corresponding MTPA derivative, literature value[19] $[\alpha]_D^{25}$ +16.5 (c7.22, $CHCl_3$) for 36 ± 4% e.e, conf. R. n) Based on maximum rotation reported[20] $[\alpha]_D$ +41.3 (EtOH), conf. R. o) Optical purity of (+) alcohol for 42% conversion. p) Determined by ^1H NMR (200 MHz) analysis of the corresponding MTPA derivative, literature value[16] $[\alpha]_D^{25}$ +82.1 (c1, ether). conf. R.

References and Notes:

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1. Brown,J.M.; Nature **1991**, 350, 191.
2. Schmidt,B.; Seebach,D.; Angew. Chem. Int. Ed. Engl., **1991**, 30, 99-101
3. Evans,D.A.; Science, **1988**, 240, 420-426.
4. Morrison,J.D.; (Editor) Asymmetric synthesis vol 1-5, Academic press, New York **1985**.
5. Jones,J.B.; Tetrahedron, **1986**, 42, 3351-3403.
6. Klibanov,A.M.; Acc. Chem. Res., **1990**, 23, 114-120.
7. Chen,C.S.; Sih,C.J.; Angew. Chem. Int. Ed. Engl., **1989**, 28, 695-707.
8. Laumen,K.; Breitgoff,D.; Seemayer,R.; Schneider,M.P.; J. Chem. Soc., Chem. Commun., **1989**, 148-150.
9. Matsumoto,K.; Tsutsumi,S.; Ihori,T.; Ohta,H.; J. Am. Chem. Soc., **1990**, 112, 9614-9619.
10. Burgess,K.; Jennings,L.D.; J. Am. Chem. Soc., **1990**, 112, 7434-7436.
11. Kirchner,G.; Scollar,M.P.; Klibanov,A.M.; J. Am. Chem. Sco., **1985**, 107, 7072-7076.
12. Basavaiah,D.; Rama Krishna,P.; Bharathi,T.K.; Tetrahedron Lett., **1990**, 31, 4347-4348.
13. Basavaiah,D.; Dharma Rao,P.; Syn. Commun., **1990**, 20, 2945-2949.
14. Basavaiah,D.; Bhaskar Raju,S.; Syn. Commun., **1991**, 21, 1859-1863.
15. Freshly purchased bovine liver (500g) is homogenized in cold acetone using kitchen juicer. The brown mash is filtered and mixed again with cold acetone in juicer. The mass obtained after filteration, is air dried at room temperature and powdered in a juicer. Fine powder (70-80g) was finally obtained after sieving. This powder can be stored in refregerator for 2-3 months without any significant loss in activity.
16. Theisen,P.D.; Heathcock,C.H.; J. Org. Chem., **1988**, 53, 2374-2378.
17. Pickard,R.H.; Kenyon,J.; J. Chem. Soc., **1914**, 105, 1115-1131.
18. Hayashi,T.; Matsumoto,Y.; Ito,Y.; J. Am. Chem. Soc., **1989**, 111, 3426-3428.
19. Peyronel,J.F.; Fiaud,J.C.; Kagan,H.B.; J. Chem. Research (M), **1980**, 4057-4080.
20. Collyer,T.A.; Kenyon,J.; J. Chem. Soc., **1940**, 676-679.