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LIPASE-CATALYZED IRREVERSIBLE TRANSESTERIFICATION USING ENOL ESTERS: RESOLUTION OF CYANOHYDRINS AND SYNTHESES OF ETHYL (R)-2-HYDROXY-4-PHENYLBUTYRATE AND (S)-PROPRANOLOL

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Summary: Procedures for the resolution of several cyanohydrins of synthetic value via lipase-catalyzed kinetic resolution using enol esters as irreversible transesterification reagents are developed and the syntheses of ethyl (R)-2-hydroxy-4-phenylbutyrate and (S)-propranolol from enantiomerically pure cyanohydrins are demonstrated.

Cyanohydrin compounds are versatile synthons in organic synthesis. They can be converted readily into α-hydroxycarboxylic acids,[1] α-hydroxyaldehydes[2] or ethanolamine derivatives[3]. Because most of these compounds possess unique chiral centers required for biological activity, a new synthetic strategy based on enantiomerically pure or enriched cyanohydrins is considered to be important for the preparation of many of these molecules.

Several optically active cyanohydrins have been prepared via oxynitrilase catalyzed addition of hydrogen cyanide to aldehydes in organic media,[4] but only one enantiomer can be obtained. Another method for the preparation of chiral cyanohydrins involves the use of ester hydrolases in selective hydrolysis of cyanohydrin acetates.[5] In this process, the unreacted ester was recovered for further synthesis and the cyanohydrin product was disregarded due to its rapid racemization in aqueous solution.

Our interest in the development of an enzymatic method for the resolution of cyanohydrin without product racemization led us first to examine the chiral stability of cyanohydrins in organic solvents. The enantiomerically pure cyanohydrins **1a-3a** were dissolved in dichloromethane or chloroform. After 10 days at room temperature, we found the optical purity of each cyanohydrin didn't decrease. This result revealed that not only cyanohydrins but also the esters could be obtained without racemization via resolution of the racemate in organic solvents. Here we report the resolution of several useful cyanohydrins in organic media using lipase as catalyst and enol esters as irreversible transesterification reagents. At certain degree of conversion, either the

cyanohydrin or the acetate can be prepared with high ee. This enzymatic process has proven to be more effective and more enantioselective than other transesterification processes.[6]

Substrate **1** was synthesized in 98% yield from hydrocinnamaldehyde via treatment with sodium bisulfite followed by sodium cyanide. Compounds **2** and **3** were prepared from α-naphthol and benzyl alcohol via reaction with epichlorohydrin, followed by treatment with base or acid. The diol product was then cleaved by $NaIO_4$ oxidation and the resulting aldehyde was converted to cyanohydrins **2** or **3**. The cyanohydrins **1-3** were then resolved with lipoprotein lipase from Pseudomonas species (PSL, from Amano company)[7] as shown in Scheme 1. These results are summarized in Table 1. The E values[8] for the resolution of compounds **1-3** are 24, 28 and 11.5,

Scheme 1

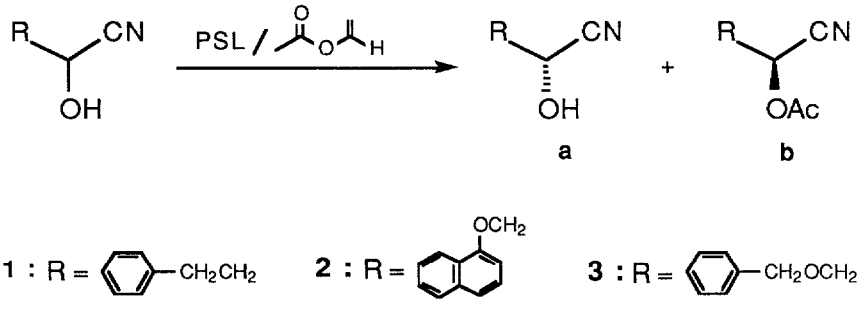


Table 1. Enantioselective transesterification of cyanohydrin compounds **1-3** catalyzed by lipoprotein lipase from Pseudomonas species

Compound	Extent of Conversion (%)	% ee & $[\alpha]_D^{23}$ [a] Acetate[b]	Alcohol[b]	Stereochemical Preference	E[c]
1	22	90, -43.8°		S	24
1	59		98, -9.93°	S	
2	25	91, -39.6°		R	28
2	56		96, +12.5°	R	
3	63	55, -29.6°	95, +5.84°	R	11.5

a: The specific rotation was measured in $CHCl_3$ with the concentration of 1.0-2.0 g/100 mL

b: The ees of acetate and alcohol were determined according to ref. 9.

c: E is the ratio of the specificity constants of the two enantiomers.[8]

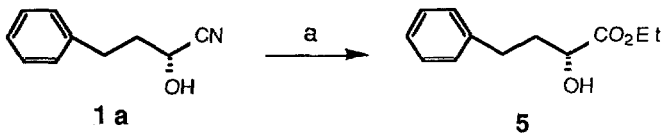
respectively. The optical purities of **1a** and **2a** isolated are 98 % and 96 % when the conversions were 59 % and 56 %, respectively.

In a representative procedure, a solution of **1** (644 mg, 4 mmol) and vinyl acetate (1.6 mL, 16 mmol) in 16 mL of dichloromethane was mixed with 80 mg of PSL and stirred for 6.5 days at 28 ° C. The enzyme was filtered off and washed with dichloromethane. The combined filtrates were evaporated to give a residue which was separated by silica gel column chromatography to give 455 mg (56 %) of acetate **1b**, $[\alpha]_D^{23}$ - 32.7° (c= 1.5; $CHCl_3$), ee=69 %[9] and 251 mg (39 %) of **1a**, $[\alpha]_D^{23}$ -9.93° , (c=1.5; $CHCl_3$); ee=98 %. [9]

To determine the absolute stereochemistry of **3a**, it was converted to 1-aminopropane-2,3-diol,[10] which has the **S** configuration based on the optical rotation. This indicated that compound **3a** has the **S** configuration.

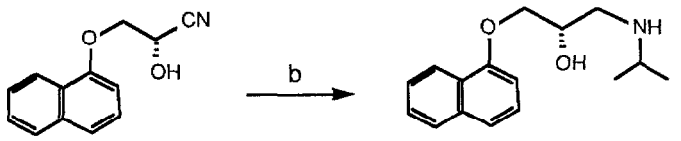
The chiral cyanohydrin **1a** has the appropriate stereochemistry for the synthesis of **5**, which is an important intermediate for the synthesis of Angiotensin-Converting enzyme inhibitors.[11] To prepare **5**, compound **1a** ($[\alpha]_D^{23}$ -9.93°, c=1.0; $CHCl_3$) was treated with dihydropyran (DHP) in the presence of pyridinium p-toluenesulfonate (PPTS) to give its THP derivative (Scheme 2).

Scheme 2



1 a **5**

a : 1) DHP/PPTS; 2) OH^-; 3) cat. conc-H_2SO_4/EtOH



2 a **6**

b : 1) $LiAlH_4$; 2) acetone/$NaBH_4$

The nitrile group was then hydrolyzed with 1N NaOH and the resulting acid was treated with anhydrous ethyl alcohol in the presence of catalytic amount of conc-sulfuric acid. The desired compound **5** ($[\alpha]_D^{23}$ - 21.6° , (c= 1.2, $CHCl_3$) [Lit.[11a] $[\alpha]_D^{20}$ - 22.1° , (c=1.0, $CHCl_3$)] was obtained in 78 % yield based on **1a**.

On the other hand, **2a** was an obvious substrate for the synthesis of (S)-(-)-propranolol (**6**), a typical β-adrenergic blocking agent.[12] Reduction of **2a** ($[\alpha]_D^{23}$ +12.5° , c=1.5; $CHCl_3$) with $LiAlH_4$ gave its corresponding (S)-aminoalcohol[13] which was further converted by known procedures[5a]

(acetone/$NaBH_4$) to compound **6** (Scheme 2). The crude product was recrystallized from petroleum ether to give optically pure (S)-propranolol: mp 72 °C; [α]$_D^{23}$ -9.95°, (c=1.0, EtOH) [Lit.[11a] [α]$_D^{21}$ -10.2°, (c=1.02, EtOH)].

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7. After screening with **1** as a substrate, the PSL enzyme was chosen because it gave the best enantioselectivity.
8. E is the ratio of the specificity constants of the two enantiomers. See: C.-S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, J. Am. Chem. Soc., **104**, 7294 (1982).
9. The ee of acetate, **1b-3b,** was determined by ^{1}H-NMR spectroscopy in the presence of Tris[3-heptafluoropropylhydroxymethylene]-(+)camphorato]-europium(III). The alcohols, **1a-3a**, were treated with (+)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA chloride] and the resulting (+)-MTPA esters were analyzed by ^{1}H-NMR spectroscopy.
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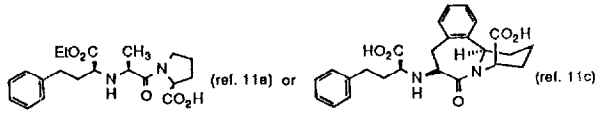
11. 5 ⇒  (ref. 11a) or (ref. 11c)

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13. The ester products can also be reduced by $LiAlH_4$ to its corresponding aminoalcohol. See ref. 5.

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