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# Preparation of 1-Pyridinylethanols of High Enantiomeric Purity by Lipase Catalysed Transesterifications

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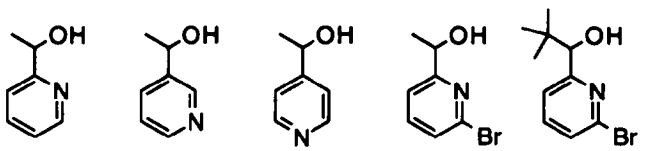
***Abstract:*** Component B lipase of the *Candida antarctica* yeast displays high enantioselectivity in catalysing transesterification reactions in non-aqeuous media with chiral secondary alcohols. This was exploited to resolve racemates of 1-(pyridinyl)-ethanols, 1-(6-bromopyridin-2-yl)ethanol, and 1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol. The lipase esterified the (*R*)-alcohols of the first four substrates in ≥99% enantiomeric excess in less than three hours with 30-40% isolated yield. Remaining (*S*)-enantiomers were isolated in similar yields and in 97-98% ee. 1-(6-Bromopyridin-2-yl)-2,2-dimethylpropanol did not form any detectable ester in one week.

**INTRODUCTION:** Enantiomerically enriched 1-pyridinylethanols (**2**, **3**, and **4**) are products of the asymmetric reduction of acetyl pyridines[1-9], and have attracted attention because of their utility as chiral ligands in metal complexes for stereoselective catalysis.[10-15] They have also been used for direct synthetic purposes.[16] 1-Pyridinylethanols of high enantiomeric purity have been prepared through catalytic biotransformations.[17-23] Here, we report such a method, applied to the racemic alcohols **2**, **3**, **4**, and racemates of two analogs of **2**, namely 1-(6-bromopyridin-2-yl)ethanol (**5**) and 1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol (**6**).



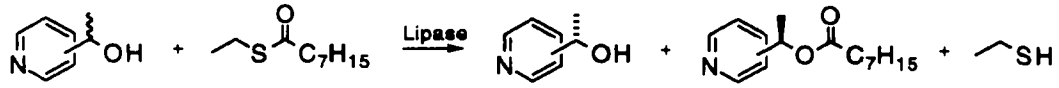
**2** **3** **4** **5** **6**

Recently published methods concerning the asymmetric reduction of these compounds can be briefly summarized as follows. In 1987, Soai *et al*[13] reported the reduction of 3-acetylpyridine with $LiBH_4$, ethanol, and (*R,R*)-N,N´-dibenzoylcystine affording (*R*)-1-(pyridin-3-yl)ethanol in 85% ee and 70 % chemical yield. Meyers and Brown[8] reduced 2-acetylpyridine with $Mg(ClO_4)_2$ and (*S*)-N-toluoyl-3-methoxy-4-methyl-1,4-dihydropyridine (88% ee) to the corresponding (*R*)-alcohol (**2**) in 87 % ee with 72% yield after 7 days. Midland *et al* [2] achieved 100% chiral transfer with Alpine-Borane (92% ee) at 6000 atm giving (*S*)-**3** (67% yield after 1.5 day). Enantiomers of **5** and **6** were previously prepared by Bolm and coworkers through asymmetric reduction ($(Ipc)_2BCl$) and recrystallization of corresponding camphanic acid esters followed by hydrolysis under basic conditions giving the alcohols in >99% ee.[24]

A key intermediate in the synthesis of the alkaloid *allo*-Heteroyohimbine[16] required enantiomerically pure (*R*)-1-(pyridin-3-yl)ethanol, which was afforded through the careful inversion of the (*S*) form (98% ee, 60% yield) from reduction of 3-acetylpyridine under anaerobic conditions by *Sporotrichum exile*.[23] Microbial reduction by *Cryptococcus macerans* provides the (*S*)-alcohols (**2**, **3**, and **4**) in 85% ee after 10 days (yield not stated).[20] Seemayer and Schneider[17] recently produced both enantiomers in the same process by kinetic

resolution (maximum theoretical yield reduced to 50%) through the hydrolysis of the corresponding acetate with a lipase from *Pseudomonas sp* (SAM II). The determination of enantiomeric purity was done using NMR, applying Mosher ester techniques (all enantiomers ≥95%). The reaction time was never less than 40 hours and yields around 40% were achieved. The pH of the aqueous solution in which the reaction was performed was kept constant through continuous addition of sodium hydroxide and work-up included continuous extraction techniques.

Convenient methods utilizing the catalytic power and stereospecificity of *Candida antarctica* lipase (component B) in transesterification reactions are available.[25-26] Here, we report the selectivity of the lipase catalysed transesterification[25] of S-ethyl thiooctanoate with racemic 1-pyridinylethanols.




**RESULTS:** The rate difference of slow and fast reacting enantiomer was sufficiently large to virtually stop the reaction at 50% conversion of alcohol, hence conversion did not need to be carefully monitored. In an open system, used to achieve equilibrium displacement (through the evaporation of the leaving group) of the acyl-enzyme forming reaction, the conversion of the acyl-donor can increase due to hydrolytic side-reactions caused by water present. However, under the applied conditions, total consumption of the fast reacting (*R*)-enantiomer was afforded in less than three hours, thus avoiding the formation of octanoic acid.

The results, presented in Table 1, illustrate the high selectivity of the catalyst with 1-pyridinyl ethanols. With **2** and **5**, only the (*R*)-enantiomer of the alcohols obtained from hydrolyses of product esters could be detected. In the resolution of **4**, the (*S*)-enantiomer was detected, but the enantiomeric excess was still well above 99%. Consistently, the (*R*)-alcohol was the fast reacting enantiomer indicating an "(*R*)-specificity" of the enzyme.

**Table 1.** Enantiomeric Purities and Yields of Resolved *sec*-Alcohol Racemates

| Substrate | Conversion[a] | Products | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| racemate of | % | Remaining alcohol | | | | Reacted alcohol | | | |
| | | ee | rot. | conf. | yield[b] | ee | rot. | conf. | yield[b] |
| **2** | 49(50) | 97 | (-) | *S* | 45 | >99 | (+) | *R* | 39 |
| **3** | 50(50) | 98 | (-) | *S* | 44 | 99 | (+) | *R* | 35 |
| **4** | 49(50) | 97 | (-) | *S* | 38 | >99 | (+) | *R* | 33 |
| **5** | 49(49) | 98 | (-) | *S* | 46 | >99 | (+) | *R* | 31 |
| **6** | n.r. | | | | | | | | |

[a] Value calculated from ee of remaining and reacted alcohol, within brackets value of GC determination.
[b] Isolated.

**DISCUSSION:** The corresponding transesterification of 1-phenyl ethanol is almost equally selective (98% ee of remaining enantiomer and >99% ee of produced, but (*S*) detected, at 50% conversion) compared to **2** and **5**. The failure of **6** to give any detectable product over a period of one week is interesting information in view of substrate-structure requirements of the *Candida antarctica* B lipase. Such data enable an initial evaluation of potentially successful kinetic resolutions, thus significantly reducing the process of trial and error. Apparently, the *t*-butyl substituent introduces a steric incompatibility with the active-site of the enzyme. However, efficiency and selectivity are maintained with secondary allylic alcohols[27], indicating a crucial substituent size limit in this α–position. Present work at our laboratory, combined with computer-aided dynamics calculations, aim at more precisely defining these substrate-structure limitations of this lipase.

**CONCLUSION:** The described method resolves the racemates of **2**, **3**, **4**, and **5** in a one-step process requiring less than three hours with, to our knowledge, unmatched stereoselectivity. Reaction conditions are most convenient and larger scale reactions feasible.[25] Recycling the catalyst twice did not affect either activity or selectivity.

**EXPERIMENTAL: General Procedure.** In an open reaction vessel, alcohols **2**, **3**, or **4** (4.0 mmol or 0.492 g) were added to a mixture of S-ethyl thiooctanoate (4.0 mmol, 0.75 g) and enzyme preparation (50 mg). The reaction proceeded at 39 °C and was quenched through removal of enzyme by filtration. Most of the remaining enantiomers of **3** and **4** can be conveniently retrieved as crystals (**4**) or insolubles (**3**) after filtration (diethyl ether washing, 25 ml), volume reduction, and resuspension in cold hexane. Work-up by liquid column chromatography[28] with deactivated silica-gel ($NH_3$) afforded separation of reactants and products.

**Enzyme.** The lipase (component B) derived from *Candida antarctica* is a product of NOVO-Nordisk A/S, Denmark. The enzyme used was an immobilized preparation on a macroporous polypropylic resin, containing 1% (w/w) enzyme, with a catalytic activity of approximately 43 000 LU/g preparation.

**Gas Chromatography.** Instrumentation: Varian 3500 and 3300 equipped with DB1 (15 m,widebore 0.32 mm i.d., 0.25 μm film) and Chrompack Cp-cyclodextrin-B-2,3,6-M-19 (50 m, 0.25 mm i.d., 0.25 μm film)/Astec Chiraldex™ G-TA (10 m, 0.25 mm i.d., 0.25 μm film) were used in the monitoring of conversion (hexadecane as internal standard) and enantiomeric excess determinations, respectively. Alcohols or alcohol derivatives of 1,1,1,3,3,3-hexamethyl silazan were injected on the latter column.

**Absolute configuration.** Assignment of absolute configuration was done by optical rotation measurements (Perkin Elmer 241 Polarimeter) and literature data comparisons.

**Hydrolysis of ester products, general procedure.** Ester was added to a solution of 0.5 g KOH in methanol (20 ml, HPLC grade) and stirred overnight. Formic acid (1 ml) neutralized the reaction mixture and the solvent was evaporated under reduced pressure. Ethyl acetate (100 ml) was used in the filtration and washing of solid residue. The product-containing solvent was evaporated in the presence of Silica gel and liquid chromatography (hexane/ethyl acetate/ethanol gradient) isolated the alcohol. Alternatively (**2**), the hydrolysis mixture was evaporated and the alcohol retrieved by extraction with dichloromethane (100 ml, dist.). The organic layer was washed with water (3x50 ml).

**S-Ethyl thiooctanoate.** Ethanethiol (49.7 g, 0.80 mol) and pyridine (77.6 ml, 0.96 mol) were dissolved in dry diethyl ether (295 ml) at 0 °C. A solution of octanoyl acid chloride (65.1 g, 0.40 mol) in diethyl ether (95 ml) was added dropwise. Following the addition, the reaction mixture was stirred at room temperature for 24 hours. After filtration, the reaction mixture was washed with water twice and subsequently dried over $MgSO_4$. Distillation (b.p 65 °C at 2 mm Hg) yielded the crude product (75 g). Pure product (74.4 g, GC purity of 99.5%) was obtained after flash chromatography on silica gel 60 (Merck; hexane/ethyl acetate, 90:10, v/v). $^1$H-NMR ($CDCl_3$), Bruker 250 MHz: 0.88 (t, 3H), 1.21-1.4 (m, 8H), 1.25 (t, 3H), 1.59-1.68 (m, 2H), 2.49-2.55 (t, 2H), 2.72-2.91 (m, 2H).

**1-(Pyridinyl)ethanols (2), (3), and (4).** Reduction at room temperature of corresponding acetyl pyridin (8.25 mmol, 1.0 g) in methanol (50 ml, HPLC grade) with sodium borohydride (10.0 mmol, 0.378 g) overnight was followed by addition of ammonium chloride (2.0 mmol, 0.11 g) and filtration. Methanol was evaporated under reduced pressure and replaced by dichloromethane (50 ml), which was washed with water (3x50 ml). Subsequent evaporation of solvent afforded oils of **2** and **3**, and crystals of **4**.

**1-(6-Bromopyridin-2-yl)ethanol (5) and 1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol (6).** The compounds were synthesized according to Bolm and coworkers as described in reference[26].

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