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# Kinetic Enzymatic Resolution of β-Tetralols[1]

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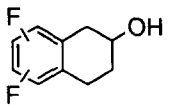
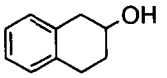
*Key Words:* kinetic esterification; enzymatic resolution; β-tetralol; porcine pancreatin; lauric acid

**Abstract:** Several substituted β-tetralols **1a-c** and β-tetralol **2** were successfully resolved using porcine pancreatin in hydrocarbon solvents. All attempts to resolve the substituted β-tetralols by diasteromeric derivatization have failed. The absolute configuration of the products was established by literature precedence.

In onging studies of dopamine β-hydroxylase inhibitors, substrates possessing substitution at the beta position of a tetralin, a prochiral center, presented itself as a synthetic problem. While several methods exist for enantioselective reduction[3] of benzylic ketones, several of these methods gave poor results when applied to substituted β-tetralones. Secondly, these ketones had unpleasant physical and stability properties. It was to our advantage to use the substituted β-tetralols as intermediates for future syntheses. The challenge was to find a method which would allow easy preparation of each enantiomer in both stoichemetric and enantiomeric purity.




**1a** 5,7-Difluoro
**1b** 6,8-Difluoro
**1c** 6,7-Difluoro




**2**

There exists literature[4] precedence for resolving prochiral alcohols using enzymes in anhydrous organic solvents. Whereas yeast reductions of prochiral ketones give mainly one resolved center in high enantiomeric yields, this method is limited to finding another yeast or mold that can afford the antipode. Triantaphylides[4c] has demonstrated that both enantiomers are available *via* lipase-catalyzed esterification in anhydrous organic solvents. Tetralols **1a-c** and lauric acid as a solution in heptane, benzene or toluene were enzymatically esterified to a corresponding mixture of laurate, lauric acid and unesterified alcohol when stirred at 40-45 °C as a suspension with porcine pancreatin for 48-72 h. Tetralol **2** required 7.25 d, while the corresponding *seco*-analog, 2-phenylpropan-2-ol, was only a 68.7:31.3 mixture of undetermined enantiomers after 13.25 d under the same conditions. The absolute configuration of the enantiomers produced utilizing pancreatin under Triantaphylides' conditions were determined by using β–tetralone as a substrate. The absolute configuration at the carbinol center in the β-tetralol series for the kinetic alcohol was established as (*S*) based upon prior work.[5] The absolute configuration for the alcohol derived from the saponified laurate is therefore (*R*).

Progress of the esterification was followed either by TLC or chiral HPLC.[6] The unesterified kinetic

alcohol was easily separated from the laurate and lauric acid mixture by flash chromatography. Saponification of the isolated laurate (10 N NaOH, EtOH, $H_2O$; 18 h) afforded the antipode. Table 1 lists the physical properties of **1a-c** and **2**, while the yields were near quantitative.

A representative procedure is outlined as follows; 5,7-difluorotetralol **1a** (5.00 g, 29.7 mmol) and lauric acid (12.1 g, 60.2 mmol) were weighed into a round-bottom flask. Pancreatin (7.35 g) was added to a vigorously stirred homogeneous heptane (250 mL) solution at 45 °C. The reaction flask was fitted with a drying tube, filled with Dri-Rite®, and stirred for 72 h. After cooling the suspension to ambient temperature, the mixture was filtered and washed with EtOAc through a Celite® filter pad. The filtrate was evaporated under reduced pressure and the remaining mixture loaded onto a column of silica gel (230-400 mesh) eluting, under medium pressure chromatography, with a mixture of EtOAc, hexane and $Et_3N$ (2.5:96.5:1) until the elution of the laurate (5.24 g, 14.3 mmol) was complete. Further elution with a mixture (25:74:1) of the above solvents afforded the alcohol (2.41 g, 14.3 mmol). The laurate (5.15 g, 14.1 mmol) was dissolved in EtOH (150 mL), 10 N NaOH (2 mL) was added and the solution was stirred for 18 h. The solvent was removed under reduced pressure, and the remaining solid was triturated with $Et_2O$ and filtered. The collected solid was quickly chromatographed on silica eluting with $CH_2Cl_2$ to afford the antipodal alcohol (2.35 g, 14.1 mmol).

Table 1. Physical Properties of Alcohols[a]

| Entry[b] | Kinetic Alcohol $[\alpha]_D^{25}$ | ep[c] | mp[d] | Laurate $[\alpha]_D^{25}$ | mp | Saponified Laurate $[\alpha]_D^{25}$ | ep | mp |
|---|---|---|---|---|---|---|---|---|
| **1a** | –37.7° c = 0.55 | 96.0 | 84-86° | +19.9 c = 0.35 | oil | +34.2 c = 0.50 | 91.4 | 83-85° |
| **1b** | –40.0° c = 0.54 | 97.9 | 56-58° | +15.0 c = 0.45 | 47-48° | +43.7 c = 1.00 | 98.6 | 80-82° |
| **1c** | –41.3° c = 0.54 | 98.5 | 81-82° | +19.3 c = 0.32 | oil | +41.1 c = 0.47 | 95.8 | 52-55° |
| **2** | –55.4° c = 0.70 | 95.5 | oil | +25.6 c = 1.04 | 28-29° | +59.2 c = 2.71 | 94.5 | 38-42° |

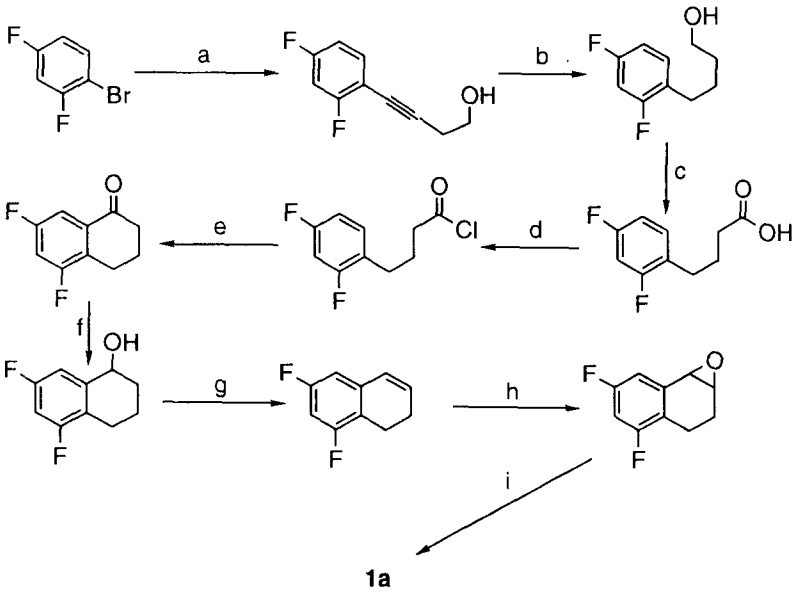
[a] All rotations were measured in $CHCl_3$; [b] Each entry was spectrophotometrically consistent with the proposed structure and the elemental analysis is within ± 0.4% of theoretical value; [c] ep = enantiometric purity; [d] mp = uncorrected melting point in °C.

One notices that this method of resolving a secondary alcohol seems to be limited to planar secondary alcohols, especially substituted β-tetralols. Aromatic substitution was limited only to fluorine, but it can be seen that the affect of this substitution relative to simply β-tetralol increased the rate of this method. In the same manner, it can be seen that breaking a bond of β-tetralol to give 2-phenylpropan-2-ol worsens the rate of this method possibly due to an entropic increase of this molecule.

Whereas this method works well on a 5-10 g scale, a problem does arise when run on a larger scale. When the resolution is attempted on a larger scale (40-50 g) the amount of water generated becomes a problem since the porcine pancreatin in essence becomes its own drying agent. The water generated becomes intercalated within the enzyme and it therefore slows the rate of the esterification to the point that it becomes cumbersome to filter the reaction and recharge with a fresh lot of enzyme repeatedly. Experiments using predried molecular sieves, anhydrous magnesium sulfate or vinyl acetate as a drying agent were tried but to no avail.

Although this method may seem limited, it is an easy and expeditious way of preparing the two antipodes of β-tetralols in 5-10 g quantities.

Scheme: Preparation of Tetralol **1a**




*Reagents and Conditions:* a) butyn-3-ol, $(Ph)_2PCl_2$, $Et_3N$, DMF, 85 °C, 6 h; b) EtOAc, $H_2$ , 10% Pd/C, 60 psi; c) 6N $H_2CrO_4$, acetone, 20 °C; d) oxayl chloride, $CH_2Cl_2$, trace DMF, 20 °C; e) $AlCl_3$, $CS_2$, 40 °C; f) $NaBH_4$, MeOH, 0 °C ; g) 10% *p*-TsOH, benzene (-$H_2O$), 80 °C; h) *m*-chloroperbenzoic acid, $CHCl_3$, 0-20 °C; i) $LiAlH_4$, THF, -78 °C.

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## References and Notes

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3. Singh, V. K. Practical and Useful Methods for the Enantoselective Reduction of Unsymmetrical Ketones. *Synthesis* **1992,** *7,* 605-617.
4. a) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. USA* Enzyme-catalyzed Processes in Organic Solvents. **1985,** *82,* 3192-3196. b) Oberhauser, T.; Faber, K.; Grieng, H. A Substrate Model for the Enzymatic Resolution of Esters of Bicyclic Alcohols by *Candida Cylindracea* Lipase. *Tetrahedron* **1989,** *45,* 1679-1682. c) Langrand, G; Baratti, J.; Triantaphylides, C. Lipase Catalyzed Reactions and Stategy for Alcohol Resolution. *Tetrahedron Lett.* **1986,** *27,* 29-32.
5. a) Arakawa, H.; Torimoto, N.; Masui,Y. Die Absolute Konfiguration des (–)-Tetralols und des Agromonolides. *Tetrahedron Lett.* **1968,** 4115-4117. b) Kawasaki, M.; Suzuki, Y.; Terashima, S.

Asymmetric Reduction of Prochiral Cyclic Ketones with Lithium Aluminum Hydride Partially Decomposed by (1*R*,2*S*)-(–)-*N*-Methylephedrine and 2-Alkylaminopyridine. *Chem. Lett.* **1984,** 239-242.

6. The HPLC conditions for **1b** were 97:3 hexane:isoprpanol (IPA) at 0.8mL/min on a Chiralcel OJ column; the conditions for **1c** were 98:2 hexane/IPA at 0.8 mL/min on a Chiralcel OJ column; for **1a** and **2** the conditions were 97:3 hexane:IPA at 0.8 mL/min on a Chiralpak AD column; the conditions for 2-phenylpropan-2-ol were 98:2 hexane:IPA at 0.8 mL/min on a Chiralpak AD column. All measurements were based upon comparative areas under the curve relative to the racemate in each case.

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