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Enzymatic Synthesis of (*S*)-(-)-1-(2-Thienyl)propyl Acetate

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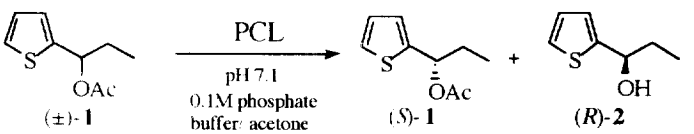
Abstract: (±)-1-(2-Thienyl)propyl acetate was resolved by PCL (*Pseudomonas cepacia* lipase) catalyzed hydrolysis to afford (*S*)-(-)-1-(2-thienyl) propyl acetate in >99% e.e.. (*S*)-(-)-1-(2-Thienyl) propyl acetate thus obtained was transformed to (*S*)-(+)-3-octanol, the alarm pheromone of ants, *Crematogaster castanea* and *liengmei*.

Enzyme-catalyzed kinetic resolution of racemic secondary alcohols to prepare enantiomerically pure secondary alcohols has become an important method in organic synthesis.[1] No enzymatic resolution of 2-thienyl alcohols or acetates has been reported although the preparation of optically active 2-thienyl alcohols by chemical resolution using Sharpless reagent was known.[2] In connection with our project on the synthesis of new chiral building blocks for the synthesis of optically active insect pheromones, we report here our results on the lipase-catalyzed preparation of (*S*)-(-)-1-(2-thienyl)propyl accetate (*S*)-(-)-**1** (Scheme 1).



(±)-**1** (*S*)-**1** (*R*)-**2**

Scheme 1

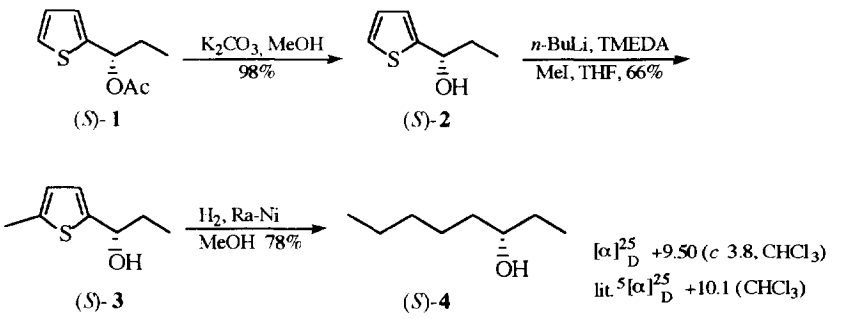
The results of enzymatic hydrolysis of (±)-**1** catalyzed by PCL are summarized in Table 1. Of the lipases tested,[3] PCL exhibited the highest enantioselectivity. A notable feature of this transformation is that the enantioselectivity is highly dependent on temperature. The system of 0.1 M acetone-phosphate buffer was the most effective for enhancing the enantioselectivity. When the reaction was run at 22 °C and stopped at 60% conversion, the % e.e. of the remaining acetate was 89% e.e. (entry 1 in Table 1). For 30% conversion at 22°C, the acetate was obtained in 82% e.e. (entry 2). The enantiomer (*S*)-(-)-**1** of >99% e.e. was obtained at 18 °C at 60% conversion (entry 3). In this conversion, the specific rotation of (*S*)-(-)-**1** was $[\alpha]^{25}_{D}$ -157.8 (*c* 0.65, $CHCl_3$). However at 14 °C for 8 h (30% conversion), the acetate with 73 % e.e. was obtained (entry 4).

The absolute configuration of (*S*)-**1** was confirmed by transformation of (*S*)-**1** to (*S*)-(+)-3-octanol (*S*)-**4**,[4,5] the alarm pheromone of ant, *Crematogaster castanea* and *liengmei* which was shown in Scheme 2. Hydrolysis of (*S*)-**1** with K_2CO_3 in MeOH at room temperature for 0.5 h provided (*S*)-**2**,[6] $[\alpha]^{25}_{D}$ -25.3 (*c* 1.6, $CHCl_3$) which was indirectly correlated to (*R*)-**2**,[5] $[\alpha]^{25}_{D}$ +25.9 (*c* 2.1, $CHCl_3$). Lithiation of (*S*)-**2** with n-BuLi followed by methylation with MeI afforded (*S*)-**3**,[5] $[\alpha]^{25}_{D}$ -29.1 (*c* 1.2, $CHCl_3$) in 66% overall yield.[7] Finally, reductive desulfurization with Ra-Ni of (*S*)-**3** provided (*S*)-**4** (Scheme 2).

Table 1 Results of the Lipase Catalyzed Hydrolysis of (±)-**1**[a]

Entry	lipase[b] (mg, mmol of substrate	Temp. °C	Time (h)	Acetate % e.e.[c](%[d]) $[\alpha]_D^{25}$[e]	Alcohol % e.e.[c](%[d]) $[\alpha]_D^{25}$[e]	E[f]
1	PCL (36.7)	22	13	89 (18.8) -144.5	69 (33.3) +19.2	15.9
2	PCL (34.8)	22	6	82 (33.4) -133.2	75 (30.7) +21.2	17.5
3	PCL (34.9)	18	20	>99 (25) -157.8	71 (57.3) +20.0	30.3
4	PCL (33.5)	14	8	73 (58) -119.1	75 (32) +20.5	15.3

[a] The compound (±)-**1** was prepared from thiophene-2-carboxaldehyde by Grignard addition of EtMgBr followed by acetylation. [b] The enzyme *Pseudomonas cepacia* lipse (PCL) used was supplied by Amano pharmaceutical Co. Ltd.. [c] % e.e. was checked by GC-MS of MTPA esters. [d] The yields are isolated yields. [e] The values in $CHCl_3$ at 25 °C. [f] See: Chen, C-S.; Fujimoto, Y.; Girdaukas, G; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.



Scheme 2

Experimental

^{1}H-NMR specra were determined in $CDCl_3$ as solvent using Gemini 200 spectrometer (^{1}H 199.98 MHz). Chemical shifts are given in ppm downfield from tetramethyl silane. IR spectra were obtained from a Nicolet Model 205 FT-IR spectrometer and are reported in cm^{-1}. Specific rotation was measured on a Rudolph Autopol polarimeter at 25°C. Mass spectra were taken on a VG Trio 2000 instrument. Elemental Analyses were performed on a EA 1108 (Carlo Erba instrument).

(*S*)-1-(2-Thienyl)propyl acetate[(*S*)-1]

To a stirred solution of (±)-**1** (301 mg, 1.64 mmol) in acetone (4 mL) at 18 °C was added 0.1 M phosphate buffer (pH 7.1, 100 mL), was added PCL (57 mg) at one portion and the reaction mixture was shaken at 18 °C for 20 h in water bath shaker and stopped at 60% conversion of (±)-**1** to (*R*)-**2**. The enzymatic hydrolysis was monitored using Varian 3700 gas chromatography (Chrom G-HP, 100/120 50 cm x 1/8") [GC conditions: injection temp 120 °C, detection temp; 160 °C; flow rate of carrier N_2 gas 20 psi. The column temperature was maintained at 50 °C for 5 min and increased at a rate of 10 °C/min to 120 °C. The retention time of the alcohol was 7.45 min and that of the acetate was 9.58 min.] The reaction mixture was extracted with ether (100 mL) for three times and then evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatograhy using ethyl acetate/hexanes (1 : 5) as eluent to afford (*S*)-**1** (76.1 mg, 25%) in >99% e.e. and (*R*)-**2** (133.6 mg, 57%) in 71% e.e.. (*S*)-**1**: TLC; SiO_2, EtOAc/hexanes 1 : 15, R_f = 0.60. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t,

3H, *J* = 8.5 Hz), 1.85-2.00 (m, 2H), 2.05 (s, 3H), 5.95 (t, 1H, *J* = 6.0 Hz), 6.95 (m, 1H), 7.05 (m, 1H), 7.25 (m, 1H). IR (film) 1745 cm^{-1}.MS(m/z) 184(M^+), 142, 123, 113(base peak), 97, 85. Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.7 ; H, 6.56 ; S, 17.4. Found: C, 58.3 ; H, 6.59 ; S, 17.1. (*R*)-**2**: TLC; SiO_2, EtOAc/hexanes 1 : 15, R_f = 0.36. ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* = 8.5 Hz), 1.90 (m, 2H), 2.05 (s, 3H), 4.89 (t, 1H, *J* = 6.0 Hz,), 7.00 (d, 1H, *J* = 3.5 Hz), 7.25 (m, 1H), 7.80 (m, 1H). IR (film) 3360, 2950, 1450 cm^{-1}

(*S*)-1-(2-Thienyl)propanol [(*S*)-2]

To a stirred solution of (*S*)-**1** (300 mg, 1.64 mmol) in dry MeOH (5 mL) was added anhydrous K_2CO_3 (0.23 g, 1.63 mmol) in one portion. The reaction mixture was stirred for 0.5 h and then MeOH was evaporated and extracted with ether (30 mL). The ether layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was separated by SiO_2 chromatograhy using EtOAc/hexanes (1 : 30) as eluent to afford (*S*)-**2** (228 mg, 98%). (*S*)-**2**: TLC; SiO_2, EtOAc/hexanes 1 : 15, R_f = 0.36. ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* = 8.5 Hz), 1.90 (m, 2H), 2.05 (s, 3H), 4.89 (t, 1H, *J* = 6.0 Hz,), 7.00 (d, 1H, *J* = 3.5 Hz), 7.25 (m, 1H), 7.80 (m, 1H). IR (film) 3360, 2950, 1450 cm^{-1}. MS(m/z) 142(M^+), 113(base peak), 85. The value of % e.e. was checked by GC-MS analysis (Hewlett-Packard 5890 GC-MS) of (*R*)-MTPA ester (column: HP-1, 25 m x 0.32 mm x 0.52 mm, carrier gas: N_2, injection temperature: 250 °C, ion source temperature 180 °C) The column temperature was maintained at 180 °C for 5 min and increased at a rate of 5 °C/min to 280 °C. The values of retention times for the MTPA esters were 8.51 min for the (*S*)-isomer and 8.38 min for the (*R*)-isomer.

(*S*)-(-)-1-(5-Methyl-2-Thienyl)propanol [(*S*)-3]

To a stirred solution of n-BuLi (2.5 M in hexanes, 0.74 mL, 1.9 mmol) and TMEDA (0.28 mL, 1.9 mmol) was added (*S*)-**2** (125 mg, 0.89 mmol) in dry THF (2 mL) at -78 °C. The reaction mixture was stirred for 1 h and warmed to room temperature and then MeI (380 mg, 2.60 mmol) was added slowly and stirred for additional 2 h. The reaction mixture was poured into ice water and extracted with ether. The ether layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was separated by SiO_2 chromatograhy using EtOAc/hexanes (1 : 15, R_f = 0.36) as eluent to afford (*S*)-**3** (92 mg, 66%). $[\alpha]^{25}_D$ -29.1 (*c* 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 8.3 Hz), 1.70-1.95 (m, 2H), 2.15 (bs, 1H), 2.50 (s, 3H), 4.75 (t, 1H), 6.60 (d, 1H, *J* = 2.8 Hz),6.95 (d, 1H, *J* = 2.8 Hz). IR (film) 3400 cm^{-1}. MS(m/z) 156(M^+) 127(base peak), 99, 65. Anal. Calcd. for $C_8H_{12}OS$: C, 61.5 ; H, 7.74 ; S, 20.5. Found: C, 61.2 ; H, 7.79 ; S, 20.4.

(*S*)-3-Octanol [(*S*)-4]

To a stirred solution of (*S*)-**3** (120 mg, 0.77 mmol) in MeOH (5 mL) was added Ra-Ni (50% w/w in H_2O solution) under 1 atm of H_2 atmosphere. The reaction mixture was stirred at room temperature for 1 h and then stirred at room temperature for 1 h and then filtered through silica gel pad. The filtrate was evaporated *in vacuo*. The crude product was separated by SiO_2 chromatograhy using EtOAc/hexanes (1 : 6, R_f = 0.68) as eluent to afford (*S*)-**4** (77.2 mg, 78%). ^1H NMR (200MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.5Hz), 1.20-1.70 (m, 11H), 3.50 (m, 1H). IR(film) 3400, 1450, 1370 cm^{-1}.

Acknowledgments

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