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Note

Lipase catalyzed asymmetric synthesis of (*R*)-melonol

Sujata Syam[a], Monica D Rane[b] & Sujata V Bhat*[a,b]

[a]Department of Chemistry, Indian Institute of Technology, Powai, Mumbai, 400 076, India

[b]Laboratory for Advanced Research in Natural and Synthetic Chemistry, V. G. Vaze College, University of Mumbai, Mithagar Road, Mulund East, Mumbai 400 081, India

E-mail: sujata8b@gmail.com

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Synthesis of optically pure 2,6-dimethyl-5-hepten-1-ol (melonol) has been attempted using lipases. Among three different lipases tested, pig pancreatic lipase (PPL) is found to be suitable for transesterification of (±)-melonol to afford (*R*)-(+)-melonol with an enantiomeric excess of 94%.

Keywords: Asymmetric synthesis, melonol, lipases, transesterification, hydrolysis

(*R*)-(+)- Melonol (2,6-dimethyl-5-hepten-1-ol) is an alarm pheromone of ants of genus *Crematogaster* and *Acanthomyops*[1]. The male ants of genus *Mymecocystus* also secrete this compound through their mandibular glands[2]. Moreover, melonol is also a constituent of several essential oils[3] and melon fruit. In addition, (*S*)- (-)- melonol has been used as chiral synthon for the asymmetric synthesis of (+)-cassiol[4], dendrobatid alkaloids[5] and insect juvenile hormones[6]. Melonal under Lewis acid catalysis afforded 2-isopropenyl-5-methyl-cyclopentanol through carbonyl-Ene reaction[7]. Melonal was also used for the synthesis of fluoro-dihydromyrcene[8].

Two approaches towards asymmetric synthesis of melonol have been reported[1,5]. In the first approach, (-)-(*S*)-melonol was obtained from geraniol through Sharpless asymmetric epoxidation, reduction of the epoxide, periodate oxidation of the resulting diol and sodium borohydride reduction of (-)-(*S*)-melonal thus formed. In the second approach, dihydro-myrcene was converted to the title compound through a series of steps. Thus, both these routes involve multistep conversions.

The use of lipases for the enantioselective hydrolysis of esters as well as for transesterification of alcohols has been well documented in the literature[9-11]. Therefore, the use of lipases has been evaluated for the synthesis of enantiomers of melonol **1**. Herein is reported the studies on asymmetric hydrolysis of (±)-melonol acetate **2** and transesterification of commercially available (±)-melonol.

Results and Discussion

Transacetylation of racemic melonol was achieved in anhydrous conditions using three different lipases: porcine pancreatic lipase (PPL), *Candida cylindrica* lipase (CCL) and *Aspergillus niger* lipase (ANL). The (±)-melonol was treated with vinyl acetate in the presence of these lipases at the temperature and for the period mentioned in **Table I** (**Scheme I**). It was observed that CCL and ANL are non-specific for this conversion. However, PPL exhibits a high degree of specificity at 25°C yielding 92.5% enantiomeric excess of (*R*)-melonol **1**. Further improvement in the resolution to *ee* 94% was obtained by lowering the temperature to -10°C (Ref. 12).

Hydrolysis of (±)-melonol acetate was also attempted using above mentioned lipases. The results are given in **Table II**. The resolution obtained by lipase catalyzed hydrolysis was found to be much inferior to transesterification. The maximum enantiomeric excess obtained by hydrolysis at 33°C was found to be 63.4%, which was enhanced to 74%, when the reaction was performed at 0-5°C. Interestingly, lipase-catalyzed hydrolysis of (±)-melonol acetate gave (*S*)-melonol **1** (Ref. 13).

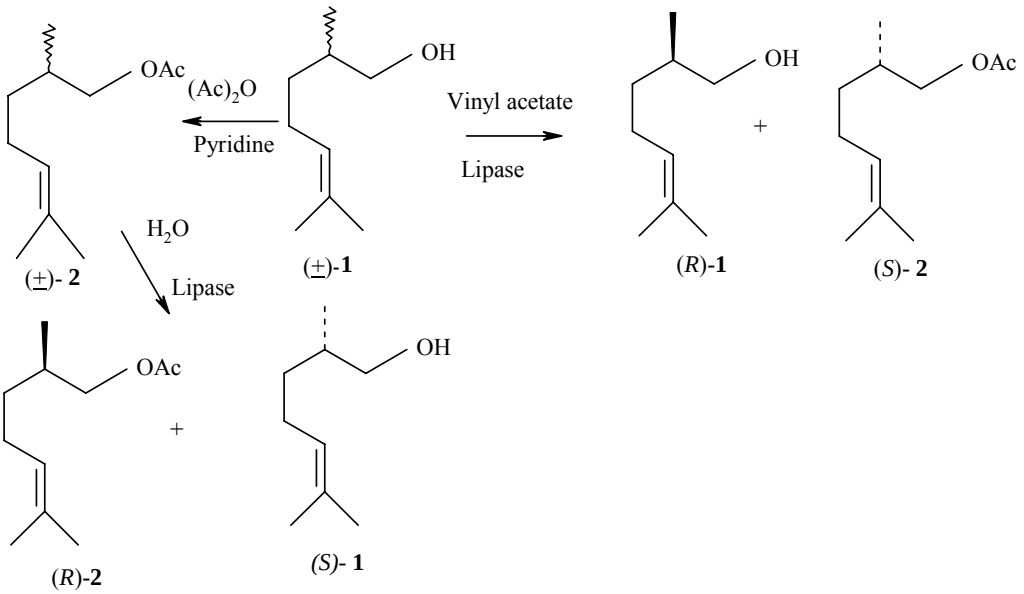
Experimental Section

IR spectra (Neat) were recorded on a Perkin-Elmer model 681 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded respectively on 400 MHz and 75 MHz spectrometers in $CDCl_3$ with TMS as internal standard. Optical rotations were measured using a Jasco DIP-370 digital polarimeter. Enantiomeric excess of (*S*)- and (*R*) melonol was determined using enantioselective gas chromatographic separations on a capillary column coated with 60% heptakis (2,3-di-O-acetyl-6-O-TBDMS)-β-cyclodextrin in polysiloxane. Silica gel (100-200 mesh) used for column chromatography was activated by heating at 120°C for 4 hr.

Table I — Transacetylation of (±)-melonol **1** catalyzed by three different lipases

Entry	Enzyme	Temp°C	Time (hr)	Conv %[a]	$[\alpha]_D^{20}$ of (*R*)-**1**	*ee* (%) of (*R*)-**1**
1	PPL	25	01.5	51	8.68	92.5
2	PPL	-10	20.5	49	8.83	94
3	CCL	25	30	51	1.40	14.95
4	ANL	25	16	49	1.57	16.74

[a] As observed in the GC of reaction product mixture.



Scheme I — Lipase catalysed kinetic resolution of (±)-melonol and its acetate

Table II — Hydrolysis of (±)-melonol acetate **2** catalyzed by three different lipases

Entry	Enzyme	Temp°C	Time (hr)	Conv %[a]	$[\alpha]_D^{20}$ of (*S*)-**1**	*ee* (%) of (*S*)-**1**
1	PPL	33	3.0	51	-5.96	63.44
2	PPL	0-5	8.0	51	-6.96	74.09
3	CCL	33	16.5	50	-2.82	29.98
4	ANL	33	50	49	0.00	0.00

[a] As observed in the GC of reaction product mixture.

Lipases were dried *in vacuo* (2 mm) for 48 hr and were used in transesterification.

General procedure for transesterification

To a stirred mixture of (±)-melonol **1** (0.142 mg, 1 mmol), vinyl acetate (0.5 mL), molecular sieve 4A (50 mg), in dry hexane (4 mL), dry lipase (80 mg) was added and stirring was continued for the period and at the temperature mentioned in **Table I**. The reaction was monitored by gas chromatography. The reaction mixture was subjected to the usual work-up and column chromatography over silica gel. The yield, optical rotation and enantiomeric excess of (*R*)-melonol thus obtained are mentioned in **Table I**.

Spectal data:

(*R*)-Melonol

IR (Neat): 3348, 2963, 2915, 1454, 1410, 1377, 1041, 828 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.1 (1H, bt, *J*=7.1), 3.51 (1H, dd, *J*= 5.6, 10.4), 3.42 (1H, dd, *J*= 6.4, 10.4), 1.80-2.10 (2H, m), 1.69 (3H, s), 1.60 (3H, s), 1.15-1.40 (2H, m), 0.96 (3H, d, *J*= 6.8); ^{13}C NMR ($CDCl_3$): δ 16.5, 17.7, 25.4, 25.7, 33.2, 35.3,

68.2, 124.6, 131.4; MS: *m/z* (%) 142 (M^+), 110,109, 96, 95, 85, 82, 71, 69; HRMS: Calcd. for $C_9H_{18}O$: *m/z* 142.1358; Found 142.1356.

(*S*)-Melonol acetate

IR (Neat): 2964, 2921, 1741, 1455, 1371, 1238, 1036, 984, 825 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.09 (1H, t, *J*=7.1), 3.95 (1H, dd, *J*= 6.4, 11.2), 3.85 (1H, dd, 6.8, 11.2), 2.05 (3H, s), 1.82-2.10 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.15-1.40 (2H, m), 0.93 (3H, d, *J*= 6.8); ^{13}C NMR ($CDCl_3$): δ 16.7, 17.6, 20.9, 25.2, 25.7, 32.1, 33.4, 69.3, 124.3, 131.6, 171.2; HRMS: Calcd. for $C_{11}H_{20}O_2$: *m/z* 184.1726; Found 184.1723.

General procedure for hydrolysis

Melonol acetate **2** (0.184 g, 1 mmol) was dispersed in 0.02 *M* phosphate buffer (*p*H 7, 12 mL) and lipase (100 mg) was added and the reaction mixture was stirred at RT (33°C) while the *p*H kept constant by addition of 1*N* NaOH and stirring was continued for the period mentioned in **Table II**. The reaction mixture was subjected to the usual work-up and column chromatography over silica gel. The yield, optical rotation and enantiomeric excess of (*S*)-melonol thus obtained are mentioned in **Table II**.

Conclusion

Thus, the present study has yielded the convenient synthesis of (*R*)-melonol using PPL with *ee* 94% through lipase catalyzed transesterification. Melonol enantiomers, thus obtained can be used for the asymmetric synthesis of natural products through chiron approach[14] and for flavour and pheromone applications.

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13 Spectral properties of the (*S*)-melonol thus prepared were identical with those of reported values (Ref. 5).

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