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New Chiral Synthon from the PLE Catalyzed Enantiomeric Separation of 6-Acetoxy-3-MethylCyclohex -2-en-1-one

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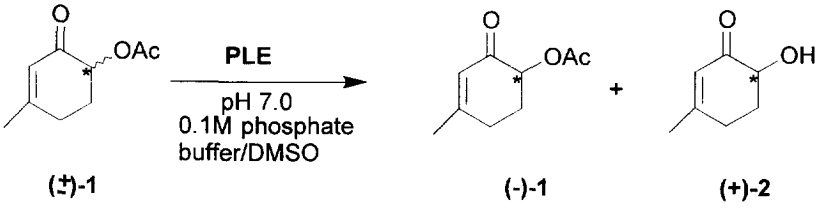
Abstract : (±)-6-Acetoxy-3-methylcyclohex-2-en-1-one was resolved by PLE catalyzed hydrolysis to afford (+)-6-hydroxy-3-methylcyclohex-2-en-1-one in >95% e.e. (+)-6-Hydroxy-3-methylcyclohex-2-en-1-one was transformed to its (*S*)-O-acetyllactyl ester derivative to determine the e.e. %. Copyright © 1996 Elsevier Science Ltd

α′-Hydroxy-α,β-unsaturated cyclic ketones occupy a central position in the synthesis of complex natural products[1]. No enzymatic resolution of α′-hydroxy-α,β-unsaturated ketones has been reported. In connection with our work on the development of new chiral building blocks for the synthesis of optically active natural products, we report here our results on the PLE-catalyzed preparation of (+)-6-hydroxy-3-methylcyclohex-2-en-1-one **2** (Scheme 1).



Scheme 1

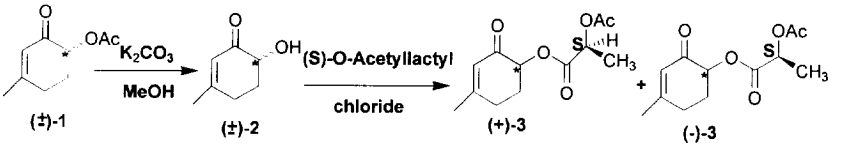
The results of enzymatic hydrolysis of (±)-**1** catalyzed by PLE are summarized in Table 1. Lipases isolated from porcine pancrease (PPL) and from the yeast *Candida cylindracea* (CCL) show low selectivity (< 20% e.e.). PLE exhibited the highest enantioselectivity among the other lipases tested. The broad substrate specificity and high stereoselectivity of pig liver esterase (PLE) is well documented. Many examples of the use of PLE in the stereoselective hydrolysis of racemic monoesters have been reported[2,3]. The important feature of this transformation is that the enantioselectivity is highly dependent on the co-solvent and the temperature. Dimethylsulphoxide-phosphate buffer system was the most effective for enhancing the enantioselectivity.

Table 1 Results of the PLE catalyzed Hydrolysis of (±)-**1**

Entry	Conv(%)	Temp	Solv	Time	Alcohol			Acetate		
		°C		(h)	ee(%)	Yield(%)	$[\alpha]^{20}_D$	ee(%)	Yield(%)	$[\alpha]^{20}_D$
1	0	15	none	36	-	-	-	-	-	-
2	39	30	DMSO	18	32	38.6	+49.8	30	25.7	-47.8
3	43	15	DMSO	29	≥95	43.0	+155.5	≤88	40.0	-142.0
4	37	30	none	28	23	37	+37.6	-	-	-

We improved the literature procedure for the synthesis of (±)-6-acetoxy-3-methylcyclohex-2-en-1-one **1**[4]. Enzymatic hydrolsis of (±)-**1** was done according to the following procedure. To a stirred solution of (±)-**1** (700 mg, 4.2 mmol) in dimethylsulphoxide (2 mL) at 15°C was added 0.1 M phosphate buffer (pH 7.00, 75 mL), was added PLE (100 μL) at one portion and the reaction mixture was stirred at 15 °C for 29 h in pH-stat unit and stopped at 43% conversion of (±)-**1** to (+)-**2** in > 95% e.e.

(*S*)-O-Acetyllactyl chloride[5] was used to assess enantiomeric excess of chiral alcohols by the formation of diastereomeric esters, which can be differentiated by ^{1}H-NMR spectroscopy. Racemic mixture of (±)-6-acetoxy-3-methylcyclohex-2-en-1-one **1** was treated with K_2CO_3 according to the standard procedure to afford (±)-**2**[6]. Subsequent hydrolysis of (-)-**1** with K_2CO_3 yielded (-)-**2**. (±)-**2**, (+)-**2** and (-)-**2** were treated with (*S*)-O-acetyllactyl chloride to afford (*S*)-O-acetyllactyl derivative of the corresponding diastereomeric esters (±)-**3**, (+)-**3** and (-)-**3** (Scheme 2). The ^{1}H-NMR spectrum of the methyl protons arising from the (*S*)-O-acetyllactyl moiety of the diastereomeric esters give signals as doublet in the range 1.55-1.62 ppm. We determined the enantiomeric excess of the (+)-**2** and (-)-**2** by resolving these signals mentioned above.



Scheme 2

EXPERIMENTAL:

^{1}H-NMR spectra were determined in $CDCl_3$ as solvent using Bruker Avance DPX 400 and Bruker 80 AC spectrometers. Chemical shifts are given in ppm downfield from tetramethyl silane. IR spectra were obtained from a Perkin Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Optical rotation was measured on a Bellingham & Stanley P20 Polarimeter at 25 °C. Elemental Analyses were performed on a LECO 932.

(±)-6-Acetoxy-3-methylcyclohex-2-en-1-one (±)-1

A mixture of $Mn(OAc)_3$ (4.64 g,10.0 mmol) in benzene (200 mL) was refluxed for 45 min. Then, the mixture was cooled down to 25 °C and 3-methylcyclohex-2-en-1-one (1.65 g, 15.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown color disappeared. The reaction mixture was diluted with equal amount of ethyl acetate and the organic phase was washed with 1N HCl (3x100 ml) followed by saturated $NaHCO_3$ (3x100 ml) and with brine (3x50 ml). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was separated by flash column chromatography using ethyl acetate/hexane (1:4) as eluent to afford (±)-**1** (2.03 g, 80.4%). ^{1}H-NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.18 (s, 3H, $OCOCH_3$), 2.30 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 5.32 (dd, 1H, C**H**($OCOCH_3$), J= 7.4 and 13

Hz), 5.90-5.98 (m, vinylic H, 1H). IR (neat) 3025, 1735, 1685 cm^{-1}. Anal. calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found : C, 64.26; H, 7.21.

(+)-6-Hydroxy-3-methylcyclohex-2-en-1-one (+)-2

To a stirred solution of (±)-**1**.(700 mg, 4.2 mmol) in dimethylsulphoxide (2 mL) at 15°C was added 0.1 M phosphate buffer (pH 7.00, 75 mL), was added PLE (100 μL) at one portion and the reaction mixture was stirred at 15 °C for 29 h in pH-stat unit and stopped at 43% conversion of (±)-**1** to (+)-**2**. The reaction mixture was extracted with ethyl acetate (50 mL) for three times and then evaporated *in vacuo* . The crude product was separated by flash column chromatography using ethyl acetate/hexane (1:4) as eluent to afford (+)-**2** (220 mg, 43%) in >95% e.e. $[\alpha]_D^{25}$= +155.5 (c 1.1, $CHCl_3$).^{1}H-NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 3.80 (s, -OH), 4.15 (dd, 1H, C**H**OH, J= 8 and 13.4 Hz), 5.90-5.98 (m, vinylic H, 1H). IR (neat) 3024, 1680,1630 cm^{-1}. Anal. calcd. for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found : C, 66.63; H, 7.97.

Hydrolysis of (±)-1 and (-)-1 with K_2CO_3 (Typical Procedure)

To K_2CO_3 (1.03 g., 7.5 mmol) in 25 ml methanol and 0.5 ml H_2O was added (±)-**1** (1.20 g., 7.1mmol). The mixture was stirred for 1 h at 25° C. The mixture was diluted with ethyl acetate, washed with 1 N HCl, brine and dried over $MgSO_4$. The crude product was separated by flash column chromatography using ethyl acetate/hexane (1:4) as eluent to afford (±)-**2** (0.63 g., 68%).

(*S*)-O-Acetyllactyl ester of (+)-6-hydroxy-3-methylcyclohex-2-en-1-one (+)-3

(+)-6-hydroxy-3-methylcyclohex-2-en-1-one **2** (200 mg 1.60 mmol) was mixed with dry pyridine (134 mg 1.70 mmol) in 25 ml CH_2Cl_2 at 0° C, for 1/2 h. Then (*S*)-O-acetyllactyl chloride (240 mg 1.60 mmol)was added. The mixture was stirred for 6 h at room temperature. The organic phase was washed with water (3x50 ml), dried over $MgSO_4$ and evaporated *in vacuo* to yield (+)-**3** (317 mg, 83%). $[\alpha]^{25}_D$ +200 (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, 3H, CH_3, J= 7.1 Hz), 1.99 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 5.11 (q, 1H, C**H**(CH_3)($OCOCH_3$), J= 7.1 Hz), 5.34 (dd, 1H,C**H**(OCO) J= 5.4 and J= 13.4 Hz), 5.90 (s, vinylic 1H). IR (neat) 1740, 1686 cm^{-1}. TLC; SiO_2, EtOAc/Hexane 1:2, R_f= 0.63. Anal. calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found : C, 59.88; H, 6.64.

(S)-O-Acetyllactyl ester of (-)-6-hydroxy-3-methylcyclohex-2-en-1-one (-)-3

278 mg, 72.2%. $[\alpha]^{25}_D$ -138 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, 3H, CH_3 , J= 7.1 Hz), 1.98 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.27 (m, 2H, CH_2), 2.41 (m, 2H, CH_2), 5.21 (q, 1H, C**H**(CH_3)($OCOCH_3$), J= 7.1 Hz), 5.28 (dd, 1H, C**H**(OCO), J= 5.4 and J= 13.0 Hz), 5.91 (s, olefinic 1H). IR (neat) 1740, 1686 cm^{-1}. TLC ; SiO_2, EtOAc/Hexane 1:2, R_f= 0.60.

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