EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXENONES

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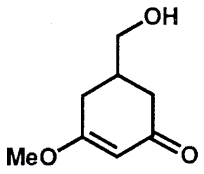
Optically active 5-hydroxymethylcyclohexenones and 5-acetoxymethylcyclohexenones were efficiently obtained by enzymatic enantioselective esterification and chemical conversion.

KEYWORDS enantioselective esterification; lipase PS; 5-hydroxymethylcyclohexenone; 5-acetoxymethylcyclohexenone; CD

Cyclohexenone derivatives are useful for the synthesis of natural products as starting material. Sesquiterpenoid eriolanin was synthesized from (±)-5-hydroxymethyl-3-methoxycyclohexenone (**1**) by Schlessinger's group,[2] and sesquiterpenoid paniculide B was synthesized from (±)-5-hydroxymethylcyclohexenone (**2**) by Smith III 's group.[3] However, no optically active compound of **1** has been obtained to date, and methods for the synthesis of optically active **2** are very few.[4] This paper presents a method for the efficient synthesis of optically active 5-hydroxymethylcyclohexenone derivatives by enantioselective esterification using lipase and by the chemical conversion of 5-hydroxymethylcyclohexenone derivatives obtaind by lipase-catalyzed esterification.



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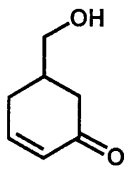

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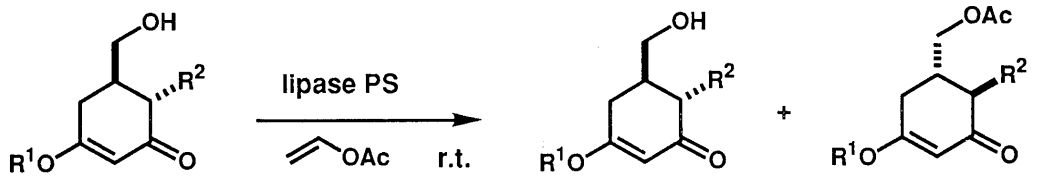
The lipase-catalyzed enantioselective esterification of alcohols (±)-**1**,[2] (±)-**4**[5] and (±)-**6**[6] was conducted first. The alcohol (±)-**1** possessing a methoxy group was treated with vinyl acetate in the presence of immobilized lipase PS[7] in benzene and tetrahydrofuran (THF) (2:1) at room temperature, to give (-)-**1** and (+)-**3**, as shown in Table I (entries 1 and 2). However, enantiomeric excess of (-)-**1** and (+)-**3**[8] was not adequately achieved, possibly owing to the low solubility of (±)-**1** in the solvent used. Esterification of alcohol (±)-**4** possessing a methoxymethyl group using 1.0 equivalent of vinyl acetate also gave an unsatisfactory enantiomeric excess (entry 3). Satisfactory results were obtained by reducing the amount of vinyl acetate (entry 4) : treatment of (±)-**4** with 0.6 equivalent of vinyl acetate in the presence of immobilized lipase PS in benzene at room temperature gave (-)-**4**[9] and (+)-**5**[9] with 99% and 95% enantiomeric excesses, respectively. The absolute structures of (-)-**1**, (-)-**4** and (+)-**5** were determined by the chemical conversion of these compounds to (+)-**2** as described below. The absolute structure of (+)-**3** was determined by alkaline hydrolysis of (+)-**3** to (+)-**1**. Esterification of (±)-**6** under conditions similar to those for entry 4 gave (-)-**6**[10] (99% ee) in 47% yield and (+)-**7**[10] (92% ee) in 52% yield (entry 5). The absolute structure of (-)-**6** was



(±)-1 R^1=Me, R^2=H
(±)-4 R^1=MOM, R^2=H
(±)-6 R^1=MOM, R^2=allyl

(-)-1 R^1=Me, R^2=H
(-)-4 R^1=MOM, R^2=H
(-)-6 R^1=MOM, R^2=allyl

(+)-3 R^1=Me, R^2=H
(+)-5 R^1=MOM, R^2=H
(+)-7 R^1=MOM, R^2=allyl

Chart 1

Table I. Lipase-Catalyzed Enantioselective Esterification

Entry	Substrate	Vinyl acetate	Reaction time (h)	Product Yield %[c] (optical purity % ee)	
1 [a]	(±)-**1**	1.0 eq	3.5	(-)-**1** 48% (46% ee) [d]	(+)-**3** 48% (80% ee) [e]
2 [a]	(±)-**1**	0.6 eq	4.0	(-)-**1** 43% (80% ee) [d]	(+)-**3** 47% (69% ee) [e]
3 [b]	(±)-**4**	1.0 eq	3.5	(-)-**4** 31% (77% ee) [f]	(+)-**5** 31% (74% ee) [f]
4 [b]	(±)-**4**	0.6 eq	4.0	(-)-**4** 42% (99% ee) [f]	(+)-**5** 43% (95% ee) [f]
5 [b]	(±)-**6**	0.6 eq	2.0	(-)-**6** 47% (99% ee) [d]	(+)-**7** 52% (92% ee) [e]

a) Reaction conducted in benzene -THF (2:1).
b) Reaction conducted in benzene.
c) Isolated yield.
d) Determined by ^{1}H-NMR analysis of its (s)-MTPA ester.
e) Determined by ^{1}H-NMR analysis of the (s)-MTPA ester of the alcohol obtained by alkaline hydrolysis.
f) Determined from optical rotation.

determined by CD measurement of its derivative,[11] and that of (+)-7 was determined by hydrolysis of (+)-**7** to (+)-**6**, $[\alpha]_D$ +42.3° (c=0.10, $CHCl_3$).

The alcohol (-)-**4** was converted to (-)-**2** and (+)-**2**, respectively, as shown in Chart 2.[12] Hydrogenation of (-)-**4** over 5% palladium on carbon followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave (-)-**2** $[\alpha]_D$ -80.8°(c=0.25, $CHCl_3$) in 64% overall yield. On the other hand, reduction of (-)-**4** with sodium borohydride in the presence of cerium(III) chloride followed by treatment with 80% acetic acid gave (+)-**2**,[4] $[\alpha]_D$ +80.8°(c=0.24, $CHCl_3$) in 79% overall yield. Similarly, the acetate (+)-**5** was also converted to (-)-**2** and (+)-**2**, respectively. Treatment of (+)-**5** with lithium hydroxide in dimethoxyethane (DME) gave alcohol (+)-**4** in 99% yield, which was converted to (-)-**2** in 63% overall yield by reactions similar to those for the conversion of (-)-**4** to (+)-**2**. Hydrogenation of (+)-**4** followed by treatment with DBU gave (+)-**2** in 78% overall yield.

The present method of enantioselective esterification can be easily conducted under mild conditions even in a large-scale experiment.[13] The cyclohexenone derivatives synthesized in this study are useful as chiral building blocks for the synthesis of natural products.

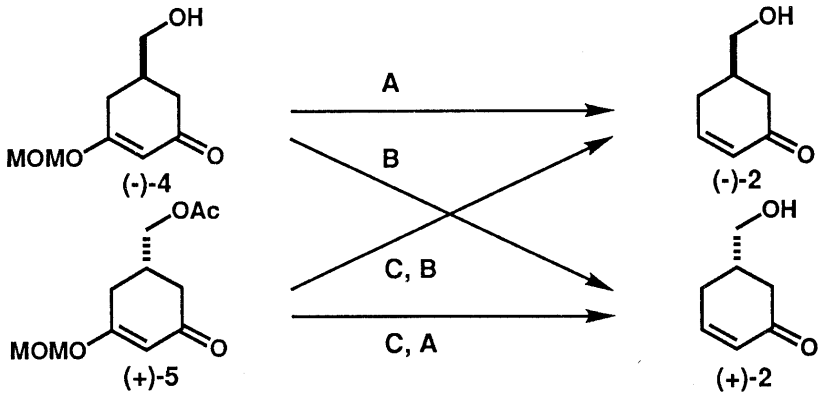


Chart 2 *Reagents*: **A**. i) H_2, 5% Pd-C, MeOH, r.t.; ii) DBU, benzene, 70°C; **B**. i) $NaBH_4$, $CeCl_3$, MeOH, 0°C; ii) 80% AcOH, r.t.; C. 1*N* LiOH, DME, 0°C.

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REFERENCES AND NOTES

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3) A. B. Smith, III, R. E. Richmond, *J. Am. Chem. Soc.*, **105**, 575 (1983).
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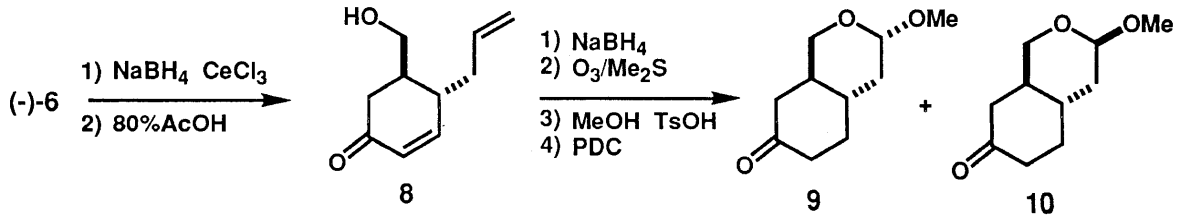
5) (±)-**4** was prepared from 3, 5-dimethoxybenzoic acid by Li-liq. NH_3 reduction followed by sequential reaction with $LiAlH_4$, 1*N* HCl, and MOMCl-Et_3N in 50% overall yield.
6) (±)-**6** was prepared from (±)-**4** by treatment with TBDMSCl-imidazole followed by treatment with LDA-allyl bromide and then Bu_4NF in 71% overall yield.
7) D. Bianchi, P. Cesti, E. Battistel, *J. Org. Chem.*, **53**, 5531 (1988).
8) (+)-**3**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.05 (3H, s), 2.15 (1H, m), 2.31 (1H, m), 2.43-2.50 (3H, m), 3.69 (3H, s), 4.03 (2H, d, *J*=5.8 Hz), 5.37 (1H, d, *J*=1.1 Hz).
9) (-)-**4**: $[\alpha]_D$ -94.2°(*c*=0.34, $CHCl_3$). HRMS. Found 186.0878, Calcd for $C_9H_{14}O_4$ (M^+) 186.0892. IR (neat): 3401, 2943, 1637, 1604 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.19 (1H, m), 2.32-2.53 (4H, m), 3.46 (3H, s), 3.63 (2H, m), 5.04 (1H, d, *J*=6.1 Hz), 5.07 (1H, d, *J*=6.1 Hz), 5.48 (d, *J*=1.0 Hz).
(+)-**5**: $[\alpha]_D$ +74.2°(*c*=0.53, $CHCl_3$). HRMS. Found 229.1084, Calcd for $C_{11}H_{17}O_5$ (M^++1) 229.1076. IR (neat): 2953, 1740, 1658, 1610 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.06 (3H, s), 2.15 (1H, m), 2.32 (1H, m), 2.42-2.51 (3H, m), 3.45 (3H, s), 4.04 (2H, d, *J*=5.8 Hz), 5.04 (1H, d, *J*=6.1 Hz), 5.06 (1H, d, *J*=6.1 Hz), 5.49 (1H, d, *J*=1.4 Hz).
10) (-)-**6**: $[\alpha]_D$ -44.8°(*c*=0.12, $CHCl_3$). HRMS. Found 226.1232, Calcd for $C_{12}H_{18}O_4$ (M^+) 226.1205. IR(neat): 3415, 2927, 1637, 1613 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (1H, m), 2.34 (1H, m), 2.42 (1H, m), 2.52-2.64 (3H, m), 3.47 (3H, s), 3.69 (2H, brd, *J*=5.5 Hz), 5.04-5.08 (3H, m), 5.10 (1H, dq, *J*=17.0, 1.7 Hz), 5.46 (1H, s). 5.77 (1H, m).
(+)-**7**: $[\alpha]_D$ +44.3°(*c*=0.11, $CHCl_3$). HRMS. Found 268.1307, Calcd for $C_{14}H_{20}O_5$ (M^+) 268.1311. R(neat): 2945, 1716, 1643, 1605 cm^{-1}. ^{1}H-NMR(300 MHz, $CDCl_3$) δ ppm: 2.06 (3H, s), 2.26-2.47 (4H, m), 2.52-2.68 (2H, m), 3.45 (3H, s), 4.10 (2H, m), 5.02-5.06 (3H, m), 5.09 (1H, dd, *J*=17.1, 1.1 Hz), 5.48 (1H, s), 5.70 (1H, m).
11) The absolute configuration of (-)-**6** was determined by analysis of the CD spectrum of **10** prepared from (-)-**6** as shown in the following. The CD spectrum of **10** showed negative Cotton effect; λ_{ext} (EtOH) 290.5 nm ($\Delta\varepsilon$ −5.1).



12) (-)-**1** was converted to (+)-**2** by a similar procedure.
13) Applying this method, (±)-**6** (30g) gave (-)-**6** (14.1g) and (+)-**7**(20.8g).

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