

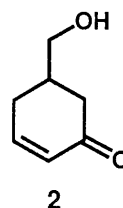
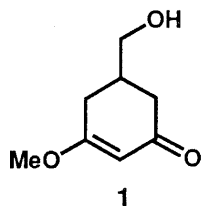
EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXENONES

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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 obtained by lipase-catalyzed esterification.



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 PS⁷⁾ 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

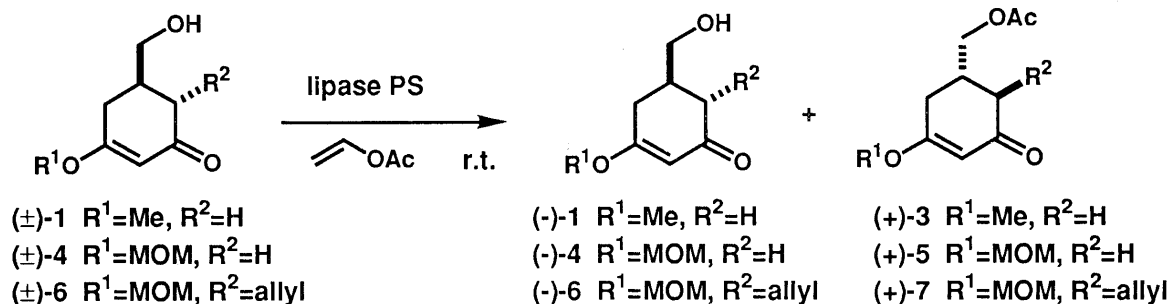


Chart 1

Table I. Lipase-Catalyzed Enantioselective Esterification

Entry	Substrate	Vinyl acetate	Reaction time (h)	Product Yield % ^{c)} (optical purity % ee)	
1 ^{a)}	(\pm)-1	1.0 eq	3.5	(-)-1 48% (46% ee) ^{d)}	(+)-3 48% (80% ee) ^{e)}
2 ^{a)}	(\pm)-1	0.6 eq	4.0	(-)-1 43% (80% ee) ^{d)}	(+)-3 47% (69% ee) ^{e)}
3 ^{b)}	(\pm)-4	1.0 eq	3.5	(-)-4 31% (77% ee) ^{f)}	(+)-5 31% (74% ee) ^{f)}
4 ^{b)}	(\pm)-4	0.6 eq	4.0	(-)-4 42% (99% ee) ^{f)}	(+)-5 43% (95% ee) ^{f)}
5 ^{b)}	(\pm)-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 ¹H-NMR analysis of its (s)-MTPA ester.e) Determined by ¹H-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, $[\alpha]_D +42.3^\circ$ ($c=0.10$, 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 $[\alpha]_D -80.8^\circ$ ($c=0.25$, 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⁾ $[\alpha]_D +80.8^\circ$ ($c=0.24$, 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.

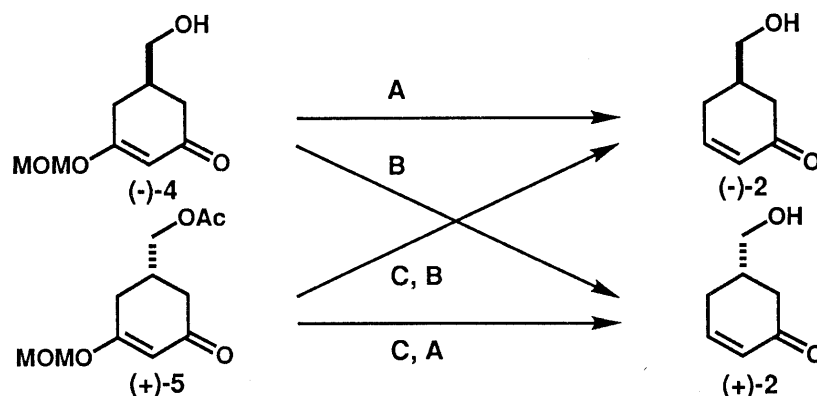
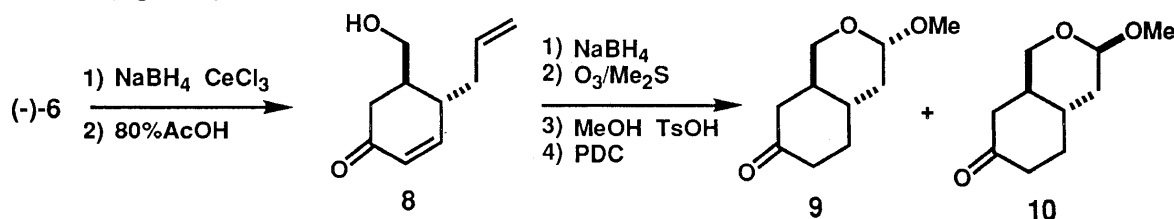


Chart 2 Reagents: A. i) H_2 , 5% Pd-C, MeOH, r.t.; ii) DBU, benzene, 70°C ; B. i) NaBH_4 , CeCl_3 , MeOH, 0°C ; ii) 80% AcOH, r.t.; C. 1N LiOH, DME, 0°C .

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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 , 1N HCl, and $\text{MOMCl-Et}_3\text{N}$ 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**: $^1\text{H-NMR}$ (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**: $[\alpha]_D -94.2^\circ(c=0.34, \text{CHCl}_3)$. HRMS. Found 186.0878, Calcd for $\text{C}_9\text{H}_{14}\text{O}_4$ (M^+) 186.0892. IR (neat): 3401, 2943, 1637, 1604 cm^{-1} . $^1\text{H-NMR}$ (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**: $[\alpha]_D +74.2^\circ(c=0.53, \text{CHCl}_3)$. HRMS. Found 229.1084, Calcd for $\text{C}_{11}\text{H}_{17}\text{O}_5$ (M^+) 229.1076. IR (neat): 2953, 1740, 1658, 1610 cm^{-1} . $^1\text{H-NMR}$ (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**: $[\alpha]_D -44.8^\circ(c=0.12, \text{CHCl}_3)$. HRMS. Found 226.1232, Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_4$ (M^+) 226.1205. IR(neat): 3415, 2927, 1637, 1613 cm^{-1} . $^1\text{H-NMR}$ (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**: $[\alpha]_D +44.3^\circ(c=0.11, \text{CHCl}_3)$. HRMS. Found 268.1307, Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_5$ (M^+) 268.1311. IR(neat): 2945, 1716, 1643, 1605 cm^{-1} . $^1\text{H-NMR}$ (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 ($\Delta\epsilon -5.1$).



- 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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