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Chemoenzymatic Synthesis of Both Enantiomers of 3-Hydroxy-2,2-dimethylcyclohexanone

Robert Chênevert,* Carine Lévesque, and Pierre Morin

Département de Chimie, CREFSIP, Faculté des Sciences et de Génie, Université Laval, Québec (QC), Canada G1K 7P4

robert.chenevert@chm.ulaval.ca

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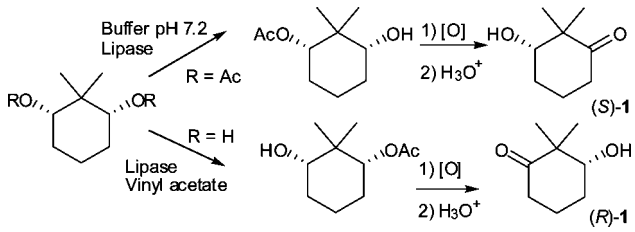


The stereoselective acetylation of *meso*-2,2-dimethyl-1,3-cyclohexanediol by vinyl acetate in the presence of three lipases gave the (1*R*,3*S*)-monoester in high enantiomeric excess (ee ≥ 98%). The hydrolysis of the corresponding *meso*-diacetate in the presence of *Candida antarctica* lipase in phosphate buffer provided the opposite enantiomer. Optically active monoacetates were converted to both enantiomers of 3-hydroxy-2,2-dimethylcyclohexanone, a versatile chiral building block.

Optically active 3-hydroxy-2,2-dimethylcyclohexanone (**1**) has been used as a chiral building block for the synthesis of a large number of natural products or biologically active compounds.[1,2] The (*S*)-enantiomer is usually prepared by baker's yeast (*Saccharomyces cerevisiae*) reduction of 2,2-dimethylcyclohexane-1,3-dione (**2**).[2] Recently, Corey et al. reported the enantioselective preparation of **1** by a modified CBS reduction of **2**, giving access to both enantiomers.[3] This three-component reduction is carried out by the addition of the hydride donor catecholborane (1.8 equiv) to a cold (−60 °C) toluene solution of diketone **2**, an oxazaborolidine catalyst (0.1 equiv), and *N*,*N*-diethylaniline (0.5 equiv) to give **1** (yield = 69%, ee = 92%). Herein, we report the synthesis of both enantiomers of **1** via the enzymatic desymmetrization of *meso*-*cis*-2,2-dimethylcyclohexane-1,3-diol (**3**) and the corresponding *meso*-diacetate **4**.

SCHEME 1

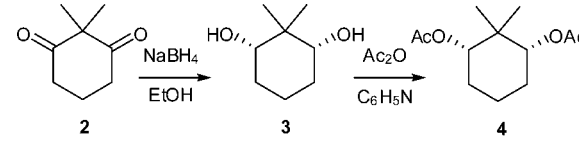
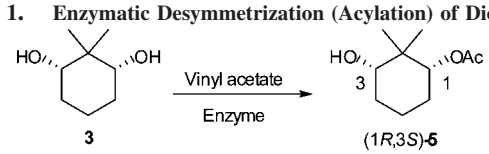


TABLE 1. Enzymatic Desymmetrization (Acylation) of Diol 3



entry	enzyme[a]	time (h)	yield[b] (%)	ee[c] (%)	abs conf
1	CAL-B	7	94	≥98	(1*R*,3*S*)
2	CRL	20	95	≥98	(1*R*,3*S*)
3	BCL	28	88	≥98	(1*R*,3*S*)
4	ANL	144			
5	PPL	144			
6	PLE	144			

[a] CAL-B = *Candida antarctica* lipase B, CRL = *Candida rugosa* lipase, BCL = *Burkholderia cepacia* lipase, ANL = *Aspergillus niger* lipase, PPL = porcine pancreatic lipase, PLE = pig liver esterase. For reaction conditions, see Experimental Section. [b] Isolated yield. [c] Determined by GC on chiral phase.

2,2-Dimethylcyclohexane-1,3-dione (**2**), which was prepared by methylation of commercially available 2-methylcyclohexane-1,3-dione or cyclohexane-1,3-dione,[2,4,5] was reduced with $NaBH_4$ in ethanol to yield a mixture of *cis*-*trans* diastereomeric 2,2-dimethylcyclohexane-1,3-diols. The major *cis* isomer, *meso*-**3**, was easily purified by recrystallization[5] (Scheme 1). Diacetate **4** was prepared by the acylation of **3** with acetic anhydride in pyridine.

Then, we examined both the acylation (transesterification) of *meso*-diol **3** and the hydrolysis of *meso*-diacetate **4** in the presence of commercially available hydrolases under various conditions. The reactions were monitored by TLC and terminated when all of the starting material (diol or diacetate) was consumed (conversion = 100%). The enantiomeric excess (ee) of monoacetate **5** was measured by gas chromatography on a chiral phase column. The absolute configuration of monoester **5** was determined by chemical correlation with compound **1** of known absolute configuration.

The results of the hydrolase-mediated acylation of substrate **3** using vinyl acetate in ether as acyl donor are summarized in Table 1. *Candida antarctica* lipase B (CAL-B) not only showed the best performance in the analytical runs but also gave

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(4) Hoffmann, J.; Holst, H.; Volz, W.; Voss, J. *J. Chem. Res. (S)* **1989**, 40–41.

(5) Jacobsen, B. M.; Soteropoulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247–3255.

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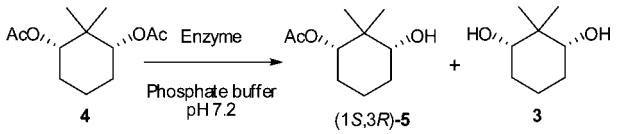
TABLE 2. Enzymatic Desymmetrization (Hydrolysis) of Diacetate 4



			monoester **5**			diol **3**
entry	enzyme[a]	time (h)	yield[b] (%)	ee[c] (%)	abs conf	yield[b] (%)
1	CAL-B	30	94	≥98	(1*S*,3*R*)	
2	BCL	39	99	≥98	(1*R*,3*S*)	
3	PPL	6	93	71	(1*S*,3*R*)	
4	PLE	4	57	53	(1*R*,3*S*)	38
5	CRL	6	53	56	(1*S*,3*R*)	40
6	ANL	110				

[a] CAL-B = *Candida antarctica* lipase B, CRL = *Candida rugosa* lipase, BCL = *Burkholderia cepacia* lipase, ANL = *Aspergillus niger* lipase, PPL = porcine pancreatic lipase, PLE = pig liver esterase. For reactions conditions, see Experimental Section. [b] Isolated yield. [c] Determined by GC on chiral phase.

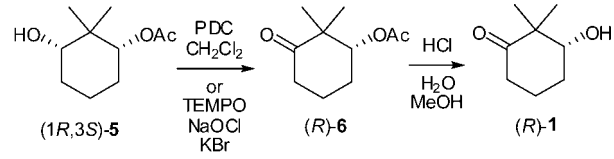
excellent results (yield = 94%, ee ≥ 98%) for the acylation of **3** on a preparative scale (entry 1). This highly (*R*)-selective acylation was also observed for *Candida rugosa* lipase (CRL) and *Burkholderia cepacia* lipase (BCL, formerly named *Pseudomonas cepacia*), although in the latter cases the reaction was slower (entries 2 and 3). The reaction stopped after one acylation, and overacylation to diacetate **4** was negligeable. *Aspergillus niger* lipase (ANL), porcine pancreatic lipase (PPL), and pig liver esterase (PLE) were not active (entries 4−6).

The enzymatic hydrolysis of diacetate **4** was performed in phosphate buffer−hexanes in the presence of various hydrolases (Table 2). The addition of a secondary solvent (hexanes) is to assist the solubility of the diacetate in the two-phase reaction medium. CAL-B showed good activity, and (*S*)-monoacetate (1*S*,3*R*)-**5** was obtained in high yield and excellent enantioselectivity (ee ≥ 98%, entry 1). Unexpectedly, hydrolysis and acylation with BCL afforded the same enantiomer (entry 2). When both the alcohol and the corresponding ester are substrate for a hydrolase, acylation and hydrolysis are usually complementary and give opposite enantiomers. Although acylation and hydrolysis represent reactions in opposite directions, the hydrolase favors the same enantiomer or the same prochiral group in both cases. This empirical rule applies to kinetic resolutions and desymmetrizations, but exceptions have been reported.[6] PPL was very active but moderately enantioselective (entry 3). With both PLE and CRL, extensive overhydrolysis to achiral diol **3** occurred, and monoester **5** was obtained in poor yield and low ee (entry 4 and 5). Compound **4** was not a substrate for ANL (entry 6).

Thus, both enantiomers of monoester **5** have been obtained in high yield and excellent ee. Chiral 1,3-diols and derivatives such as **5** are important building blocks in asymmetric synthesis.[7] Several examples of desymmetrization of *meso*- cyclohexanediols using enzymatic reactions have been previously reported. [8]

Monoester (1*R*,3*S*)-**5** underwent smooth oxidation with pyridinium dichromate (PDC) affording ketoester (*R*)-**6** (Scheme 2). The reaction took also place with TEMPO and sodium hypochlorite as terminal oxidant, but the yield was lower. Hydrolysis of the acetate group with aqueous HCl−methanol provided the title compound (*R*)-**1**. In the same manner, (1*S*,3*R*)-**5** was transformed into (*S*)-**1**.

SCHEME 2



The present procedure complements the two other methods for the preparation of **1**. Although it involves more steps, it provides both enantiomers in high ee, requires inexpensive reagents, and may prove to be a more practical method for large-scale preparations. The oxazaborolidine-mediated reduction requires substantial quantities of expensive catalyst (0.1 equiv) and reagent catecholborane (1.8 equiv) at low temperature (−60 °C). The bioreduction with baker's yeast provide only the (*S*)-enantiomer and has several drawbacks: high ratio of biomass and source of carbon (saccharose) to substrate, low yield due to side reactions, and tedious workup due to large volumes and foaming. In summary, we have developed syntheses of (*R*)- and (*S*)-3-hydroxy-2,2-dimethylcyclohexanone **1** from cyclohexane-1,3-dione **2**. The key step is the enzymatic desymmetrization of *meso-cis*-2,2-dimethylcyclohexane-1,3-diol and the corresponding *meso*-diacetate. The title compound **1** and intermediates **5** and **6**, obtained in both enantiomeric forms with high ee, are valuable synthons in asymmetric synthesis.

Experimental Section

Enzymatic Desymmetrization (Acylation) of Diol 3. Typical Procedure. To a solution of **3** (1.5 g, 10.4 mmol) in diethyl ether (75 mL) were added vinyl acetate (15 mL) and CAL-B (4000 units). The mixture was stirred at room temperature. The reaction was monitored by TLC and quenched by filtration of the enzyme when all starting material was consumed (14 h). Evaporation of the solvents gave (1*R*,3*S*)-3-hydroxy-2,2-dimethylcyclohexyl acetate **5** (1.88 g, 96%) as a colorless oil, which was further processed without purification. For analytical purposes a sample was purified by flash column chromatography (hexanes−ethyl acetate, 4:1): $[\alpha]^{23}_{D}$ −9.5 (*c* 0.92, $CHCl_3$), (ee ≥ 98%); ^{1}H NMR ($CDCl_3$) δ 4.53 (dd, J = 9.9 and 3.4 Hz, 1H), 3.33 (dd, J = 9.7 and 3.2 Hz, 1H), 2.05 (s, 3H), 1.60−1.80 (m, 3H), 1.30−1.55 (m, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 78.0, 75.9, 40.1, 29.5, 26.3, 24.4, 21.1, 19.3, 13.8; HRMS (CI, NH_3) *m*/*z* calcd for $C_{10}H_{19}O_3$ $(M + H)^+$ 187.1334, found 187.1341.

***cis*-3-(Acetoxy)-2,2-dimethylcyclohexyl Acetate 4.** To a solution of diol **3** (250 mg, 1.75 mmol) in pyridine (25 mL) were added DMAP (5 mg, 0.2 mmol) and acetic anhydride (1.5 mL). The solution was stirred overnight at room temperature. The mixture was diluted with methylene chloride (100 mL), and the organic phase was washed with water (3 × 20 mL), dried ($MgSO_4$), and

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evaporated to give diacetate **4** (369 mg, 95%) as a solid: mp 63−65 °C, ^{1}H NMR ($CDCl_3$) δ 4.55 (dd, J = 9.9 and 3.4 Hz, 2H), 2.05 (s, 6H), 1.70−1.77 (m, 3H), 1.40−1.47 (m, 3H), 0.97 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 77.3, 39.3, 26.4, 24.3, 21.1, 19.7, 14.0; HRMS (ES) *m*/*z* calcd for $C_{12}H_{20}O_4Na$ $(M + Na)^+$ 251.1259, found 251.1254.

Enzymatic Desymmetrization (Hydrolysis) of Diacetate 4. Typical Procedure. A mixture of diacetate **4** (200 mg, 0.80 mmol), CAL-B (700 units), phosphate buffer (30 mL, pH 7.2), and hexane (5 mL) was stirred at room temperature. The reaction was monitored by TLC (hexanes−ethyl acetate, 4:1) and terminated when the substrate had disappeared. The mixture was filtrated through a Celite pad, diluted with CH_2Cl_2 (20 mL), and washed with brine (2 × 5 mL) and water (10 mL). The organic phase was dried and evaporated to yield (1*S*,3*R*)-**5** (136 mg, 91%) as a colorless oil, which was further processed without further purification. For analytical purposes a sample was purified by flash column chromatography (hexanes−ethyl acetate, 4:1): $[\alpha]^{23}_D$ +9.13 (*c* 0.9, $CHCl_3$); spectral data as above.

2,2-Dimethyl-3-oxocyclohexylacetate (6). Method 1. To a solution of (1*R*,3*S*)-**5** (500 mg, 2.66 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added pyridinium dichromate (1.20 g, 3.2 mmol). The mixture was stirred at room temperature overnight. Silica gel (500 mg) was added to the mixture, and stirring was continued for 1 h. The mixture was filtered through a Celite pad, and the solvent was evaporated. The crude product was purified by flash chromatography (hexanes−ethyl acetate, 4:1) to give (*R*)-**6** (396 mg, 81%) as an oil: $[\alpha]^{23}_D$ −9.36 (*c* 1.45, $CHCl_3$), lit.[9] $[\alpha]^{20}_D$ +8.62 (*c* 0.58, $CHCl_3$) for the (*S*)-enantiomer. ^{1}H NMR ($CDCl_3$) δ 4.92 (dd, J = 6.2 and 2.4 Hz, 1H), 2.35−2.50 (m, 2H), 2.03 (s, 3H), 1.72−2.00 (m, 4H), 1.16 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.5, 170.5, 79.4, 49.5, 37.4, 26.0, 23.5, 21.2, 20.9, 20.4. The (*S*)-enantiomer showed identical physical and spectroscopic data except for the sign of the optical rotation.

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Method 2. To a solution of (1*R*,3*S*)-**5** (1.00 g, 5.32 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added an aqueous solution of KBr (3 N, 5 mL) followed by addition of TEMPO (80 mg, 0.52 mmol). The mixture was stirred at 0 °C during the addition of aqueous sodium hypochlorite (10−15%, 50 mL). The mixture was stirred at room temperature for 20 h and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with brine (3 × 50 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (hexanes−ethyl acetate, 4:1) to give (*R*)-**6** (600 mg, 61%): $[\alpha]^{23}_D$ −9.21 (*c* 1.5, $CHCl_3$); spectral data as above.

3-Hydroxy-2,2-dimethylcyclohexanone (1). To a solution of (*R*)-**6** (700 mg, 3.80 mmol) in methanol−water (1:1, 50 mL) was added concentrated HCl (2 mL). The solution was stirred overnight at room temperature. The solution was neutralized (pH < 8) with a saturated aqueous solution of $NaHCO_3$. The solution was evaporated with addition of methanol to form an azeotrope. The residue was dissolved in CH_2Cl_2 and filtered, and the solvent was evaporated to give (*R*)-**1** (512 mg, 92%) as a colorless oil: $[\alpha]^{25}_D$ −23.7 (*c* 1.5, $CHCl_3$); lit.[3] $[\alpha]^{25}_D$ −22.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.71 (dd, J = 7.5 and 2.2 Hz, 1H), 2.38−2.42 (m, 2H), 1.99−2.04 (m, 2H), 1.93 (br s, 1H), 1.79−1.90 (m, 2H), 1.60−1.70 (m, 1H), 1.16 (s, 3H), 1.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 215.1, 77.9, 51.4, 37.4, 29.1, 22.9, 20.8, 19.7. The (*S*)-enantiomer showed identical physical and spectroscopic data except for the sign of the optical rotation.

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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