Enantioconvergent Access to the Enantiomerically Pure Building Blocks (+)- or (–)-4-Hydroxy-3-methyl-2-cyclohexenone Using a Chemoenzymatic Process

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Abstract: A convenient chemoenzymatic enantioconvergent access to enantiomerically pure (+)- or (–)-4-hydroxy-3-methyl-2-cyclohexenone is described using a one-pot two-step kinetic resolution–stereoinversion protocol followed by hydrolysis. The key step of the sequence is the spontaneous elimination of an undesired stereocenter. The choice between enzymatic acyl transfer or ester alcoholysis of the corresponding racemic starting material, together with the selectivity of a lipase, determines the absolute configuration of the desired single enantiomer.

Key words: enantioconvergence, biocatalysis, kinetic resolution, stereoinversion, chiral building blocks

A great variety of natural products contain structural units related to 4-hydroxy-3-methyl-2-cyclohexenone (**1**, Figure 1). Some examples are chapinolin,[1] elegansidiol,[2] cordiaquinone C[3] or pouosides.[4]

In the course of our work directed towards the enantioselective synthesis of natural products or their intermediates containing such a scaffold,[5] we described the enzymatic kinetic resolution of racemic **1**,[5a] which was the key building block of our approaches (Scheme 1).

In spite of its efficiency, the most striking limitations of this procedure were the maximum theorical yield of 50% of each enantiomer and chromatographic separation of the intermediate resolution products. Moreover, in kinetic resolutions,[6,7] half of the starting material has the wrong absolute configuration for certain purposes. In order to circumvent these drawbacks, approaches have been developed which render an enantioconvergent process delivering a single enantiomeric product in 100% theoretical yield.[8] Among them, one of the widely employed is the in situ selective inversion of one enantiomer via a chemoenzymatic protocol.[8b,e,g,9] Using this technique, both derivatives must be obtained at a maximum of enantiomeric excess and the point to stop the kinetic resolution has to be carefully chosen. Depending on the enantioselectivity, the latter is usually close to or slightly beyond 50%.[10] We therefore decided to reinvestigate our resolution procedure to determine if a more efficient kinetic resolution followed by a stereoinversion could be employed in order to obtain 100% of the desired isomer. Lipases distinguish between enantiomeric secondary alcohols primarily by comparing the size of the two substituents,[6,11] so we intended to increase the enantioselectivity of the lipase-catalyzed deracemization described in Scheme 1 by modifying the substrate to increase the size of one substituent.

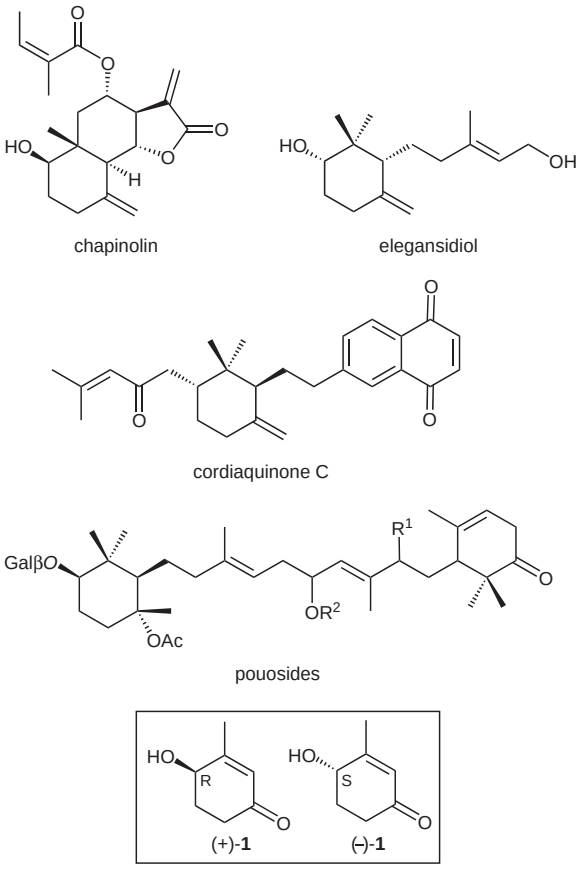

Figure 1

For this purpose, the starting material was (±)-*cis*-3,4-dihydroxy-3-methyl-cyclohexanone (**2**) obtained in 80% yield by standard osmylation (cat. OsO_4, NMO, *t*-BuOH–H_2O, 9:2) of readily available 3-methyl-3-cyclohexenone (*m*-methylanisole, Birch reduction).[12]

Our strategy is described in Scheme 2. A one-pot reaction sequence could be envisaged wherein a highly enantioselective kinetic resolution of racemic diol **2** (or monoacetate **3** for the final reverse enantioselectivity) would be followed by an efficient $MsCl/Et_3N$-mediated in situ mesylation–spontaneous elimination of the tertiary hydroxyl group to afford **4** and **5** with opposite configurations.

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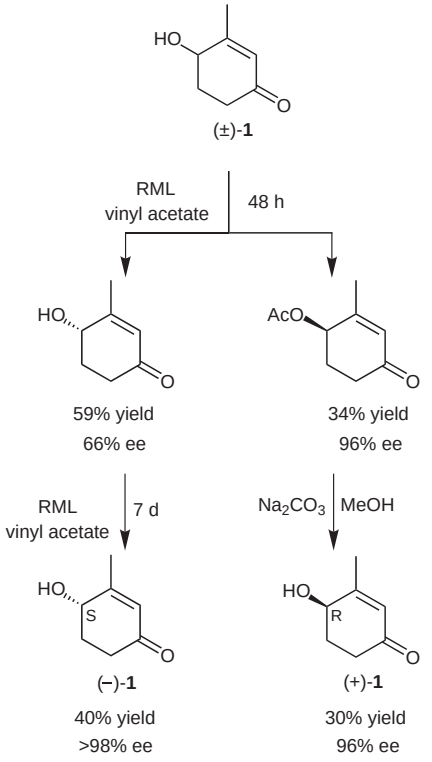
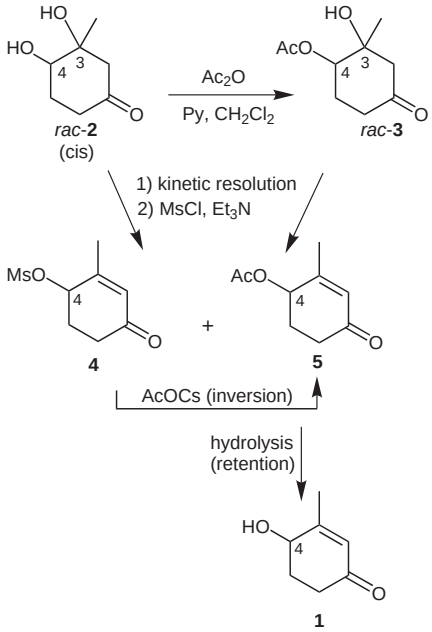


Scheme 1 Kinetic resolution of racemic **1**



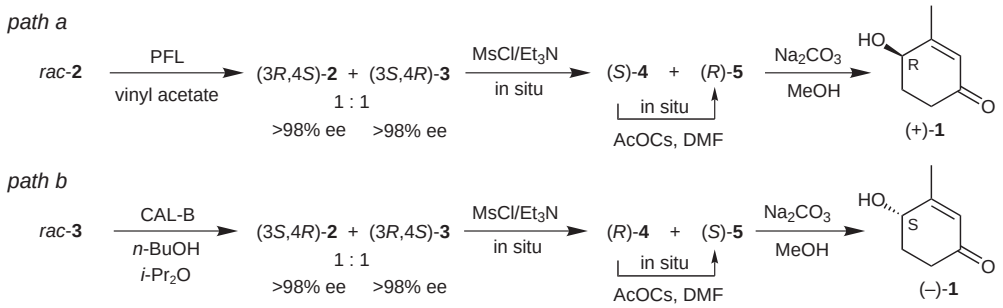
Scheme 2 Strategic plan for the synthesis of **1**

Following this methodology, the undesired stereocenter C-3 would be discarded. Treating the mixture with AcOCs would convert the mesylate to the acetate[13] while inverting the configuration to give **5**.[14] As a consequence, a single enantiomeric *sec*-alcohol **1** would be formed as the sole product after hydrolysis.

Proof-of-principle was provided through treatment of racemic **2** (1 g) with vinyl acetate as acyl donor and solvent (30 mL) in the presence of PFL (Amano AK lipase, 250 mg),[15] which gave the excellent results outlined in Scheme 3 (path a). The reaction ended by itself after 96 hours to bring about clear-cut enantiotopical discrimination giving rise to the alcohol **2** and the acetate **3** as a 1:1 mixture with >98% ee each. Both the progress of the reaction and the enantiomeric excess (ee) were determined by the ratio of the peak areas obtained by GC separation using the same chiral MEGADEX DETTBSβ fused silica column. The enantiomers of the remaining alcohol and those of the produced acetate were perfectly separated. After the biocatalytic deracemization protocol was terminated at 50% conversion, the active enzyme was recovered for reuse by filtration. The mixture of remaining unreacted (3*R*,4*S*)-diol **2** and formed (3*S*,4*R*)-hydroxy acetate **3** was concentrated under reduced pressure and treated with MsCl/Et_3N (3.0/4.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C to effect one-pot two-step mesylation with retention of configuration and elimination to afford (*S*)-**4** and (*R*)-**5**, respectively. The solvent was evaporated and the reaction mixture extracted with Et_2O. Concentration under reduced pressure and stirring with AcOCs (2 equiv) in DMF (30 mL) at room temperature effected the S_N2 reaction on (*S*)-**4** with the desired inversion of configuration to yield (*R*)-**5** in >98% ee and 85% overall yield from the racemic starting diol. Hydrolysis of (*R*)-**5** with Na_2CO_3/MeOH afforded the target molecule (+)-**1** in 88% yield.[5a,16]

In order to provide access to the mirror image enantiomer (–)-**1**, kinetic resolution in the reverse direction via butanolysis of *rac*-**3** (synthesized in 91% yield by standard monoacylation of *rac*-**2**)[12] was performed. In this case, the enantioselectivity of PFL was considerably lower (Table 1, entry 1) and screening experiments were made. The resolution procedure was as follows: a mixture of (±)-**3** (50 mg), lipase (50 mg) and *n*-BuOH (245 μL, 10 equiv) in *i*-Pr_2O (3 mL) was stirred at room temperature. The reaction progress was monitored as before by direct chiral GC (see supra) and the reaction was stopped at the conversion rate indicated in Table 1. The outcome of the screening test indicated that with CAL-B (entry 4) the lipase-mediated butanolysis reached 50% conversion in 24 hours with a molecular recognition of >98% ee both for the remaining acetate and the produced alcohol. Consequently, a large-scale enzymatic resolution of (±)-**3** (1 g) was performed using a mixture of that lipase (250 mg), *n*-BuOH (5 mL), *i*-Pr_2O (40 mL) and gave the results outlined in Scheme 3 (path b). After 96 hours (50% conversion) the active enzyme was recovered for reuse by filtration and the reaction mixture was treated exactly like previously (see above) except that complete removal of *n*-BuOH under reduced pressure had to be ensured carefully. Hydrolysis of (*S*)-**5** afforded the target molecule (–)-**1** with 71% overall yield.[5a]

In conclusion, the presented methodology provides a very simple and practical tool for synthesizing the enantiomers of the versatile building block 4-hydroxy-3-methyl-2-cyclohexenone (**1**) in enantiomerically pure form and a theorical 100% yield. The efficiency of our approach



Scheme 3 Synthesis of building blocks (+)-**1** and (–)-**1** involving biocatalytic deracemization combined with in situ inversion

Table 1 Kinetic Resolution of Racemic **3** via Butanolysis

Entry	Lipase[a]	Reaction time (d)	Conversion (%)[b]	Remaining acetate (3*R*,4*S*)-**3** ee (%)[b]	Produced alcohol (3*S*,4*R*)-**2** ee (%)[b]
1	PFL	7	14	35	>98
2	PCL	7	0	–	–
3	RML	7	27	69	>98
4	CAL-B	1	50	>98	>98

[a] PFL (*Pseudomonas fluorescens*, Amano AK); PCL (*Pseudomonas cepacia*, Amano PS); RML (*Mucor miehei*, Lipozyme RM IM, Novo Nordisk A/S); CAL-B (*Candida antarctica* B, Novozyme 435, Novo Nordisk A/S).
[b] Measured by GC on a MEGADEX DETTBSβ fused silica column (30 m × 0.25 mm i.d.; N_2 carrier gas: 70 kPa).

leans on the 'ideal' kinetic resolution of the racemic substrate, as the enzymatic reaction stopped spontaneously at 50% conversion when one enantiomer was completely consummated, both in the acyl-transfer or ester butanolysis pathways.

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(12) **Characterization of Compound 2**: white solid; mp 62 °C. IR (KBr): ν = 3412, 1728, 1211, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (dd, *J* = 7.2, 3.6 Hz, 1 H), 3.07 (s, 2 OH), 2.66 and 2.35 (ABX, *J* = 14.0, 1.5 Hz, 2 H), 2.49 (dddd, *J* = 14.2, 7.9, 6.2, 1.7 Hz, 1 H), 2.25 (dddd, *J* = 14.2, 7.2, 6.0, 1.1 Hz, 1 H), 2.05 (dtd, *J* = 13.6, 7.2, 6.2 Hz, 1 H), 1.93 (dddd, *J* = 13.6, 7.9, 6.0, 3.6 Hz, 1 H), 1.24 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8 (C), 75.0 (C), 72.8 (CH), 51.3 (CH_2), 36.8 (CH_2), 28.1 (CH_2), 26.1 (CH_3). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.21; H, 8.43. **Characterization of Compound 3**: white solid; mp 106 °C. IR (KBr): ν = 3391, 1757, 1723, 1148 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.00 (dd, *J* = 8.8, 4.1 Hz, 1 H), 2.54 and 2.40 (ABX, *J* = 14.6, 1.7 Hz, 2 H), 2.36 (m, 2 H), 2.18–2.05 (partially overlapped m, 1 H), 2.08 (s, 3 H), 1.97 (m, 1 H), 1.20 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7 (C), 170.4 (C), 75.0 (CH), 73.7 (C), 51.7 (CH_2), 37.4 (CH_2), 26.3 (CH_3), 25.3 (CH_2), 20.9 (CH_3). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.89; H, 7.60.

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(16) Using commercially available AD-mix-α or AD-mix-β, the Sharpless AD reaction applied to 3-methyl-3-cyclohexenone, also afforded directly the target molecule **1** by an in situ elimination of the tertiary hydroxyl group in **2** (64% yield), but in the racemic form, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.