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Silica-Catalysed and Highly Stereoselective Convergent and Nonconvergent Rearrangements of Menthone Enol Acetate Epoxides: Easy Access to the Four α-Hydroxymenthone Stereoisomers

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During a program dedicated to the biocatalytic access of structurally useful α-hydroxy ketones, we made the unexpected observation that epoxy enol acetates derived from (+)- and (–)-menthone stereoselectively rearranged on exposure to silica through a diastereoselective process, providing easy access to the complete set of α-hydroxymenthone stereoisomers. The absolute configurations of the four stereoisomers were unambiguously established by IR-VCD and X-ray diffraction, thus clarifying some literature discrepancy. Two of the four stereoisomers could also be obtained through a stereoconvergent process, thus avoiding the inherent 50 % yield limitations of such diastereoselective reactions. A solvent-free version allowing an extremely rapid reaction (< 2 h) is also described. Finally, the observed diastereoselection was investigated by DFT calculations.

Introduction

α-Hydroxy ketones (acyloins) and α-hydroxy aldehydes are very useful chiral molecules. Indeed, such functionality is found in numerous biologically active molecules and can be used for easy transformation into other extremely important systems such as *vic*-diols and α-amino alcohols or for use in chiral auxiliaries.[1] Of the numerous reported biocatalytic[1] and chemical[2] methods to afford access to such compounds, one is particularly easy and straightforward to carry out. The synthetic sequence starting from an enolisable ketone and leading to an acyloin through (i) enol ester (ether) formation, (ii) epoxidation of the enol functionality, and (iii) acidic rearrangement or ester (ether) hydrolysis (cleavage) of the formed enol ester (ether) epoxide is synthetically easy to perform and generally high-yielding.[2a,3] Furthermore, if epoxidation,[4] rearrangement[5] or hydrolysis[6] is selective, the final acyloin product can be obtained in high enantiomeric excess, thus enhancing its usefulness.

Results and Discussion

The starting point of this work was the unexpected observation that when a diastereoisomeric mixture of (–)-menthone enol acetate epoxides **1a**+**1b** (Scheme 1) was spotted on normal silica TLC plates, only one spot was visualized (*para*-anisaldehyde spray) when the TLC plate was developed immediately, but a second spot was detected if the development was delayed for at least a few minutes. Furthermore, the intensity of this second spot increased with the delay in development (up to 18–24 h) but the initial spot was never totally replaced by the second one.

These first observations were consistent with some sort of diastereoselective reaction of the initial diastereoisomeric mixture of the epoxides **1a**+**1b** on exposure to silica. In order to clarify the situation a preparative transformation of the diastereoisomeric mixture in the presence of silica (10 equiv., w/w) in dichloromethane at room temperature was set up. After approximately 48 h reaction time, the intensities of the two previously detected TLC spots looked constant, and the two corresponding products were recovered separately by flash chromatography. NMR analysis clearly established that one of the initial diastereoisomers – **1b** – had remained unaffected, whereas the second – **1a** – had been transformed into α-acetoxymenthone (**2a**, Scheme 1), probably through the well-known silica-catalysed rearrangement of enol acetate epoxides with inversion of configuration.[7,8]

At this point the absolute configurations of the more and the less reactive starting epoxides **1a** and **1b** and of the rearranged α-acetoxymenthone **2a** were unknown. This issue was first studied by infrared vibrational circular dichroism (IR-VCD) examination of the final acyloin products. Comparison of experimentally measured and calculated spectra (see the Supporting Information) allowed the unambiguous

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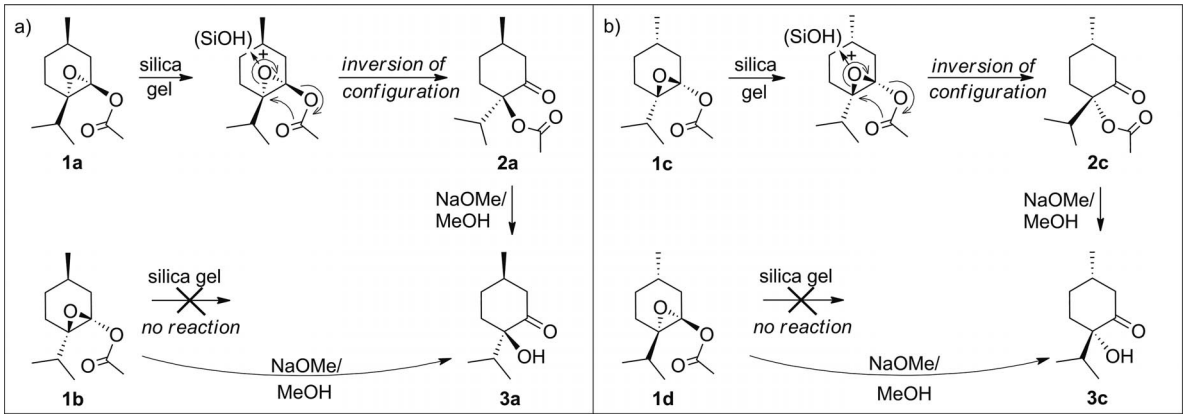


Scheme 1. Convergent transformations of diastereoisomeric mixtures of menthone enol acetate epoxides into α-hydroxymenthone isomers at moderate temperatures (0–37 °C): (a) enol acetate epoxide diastereoisomers derived from (–)-menthone; (b) enol acetate epoxide diastereoisomers derived from (+)-menthone.

assignment of the (2*R*,5*R*) absolute configuration to the obtained α-hydroxymenthone **3a** (Scheme 1), thus establishing the same absolute configuration for the rearranged α-acetoxymenthone **2a** and the (1*R*,2*S*,5*R*) absolute configuration for the more reactive diastereoisomer – **1a** – of (–)-menthone enol acetate epoxide and thus the (1*S*,2*R*,5*R*) absolute configuration for the less reactive **1b**.

In order to provide information about the selectivity of the observed process, the two products were treated separately with sodium methoxide in methanol, leading to the corresponding α-hydroxymenthones (Scheme 1). The acyloins thus formed were then analysed by chiral gas chromatography and compared to those obtained after application of the same sodium methoxide treatment to the initial diastereoisomeric mixture of the epoxides **1a**+**1b**. Whereas in the latter case the obtained α-hydroxymenthone resolved into two peaks (two diastereoisomers), application of the same procedure to each of the two isolated products obtained after silica treatment led mainly to the same peak in both cases (with 97:3 to 100:0 ratios for each compound depending on the reaction time). These results were consistent with a highly diastereoselective process leaving one of the enol acetate epoxide diastereoisomers unaffected, whereas the other rearranged with inversion of configuration at the epoxide carbon atom attacked by the acetoxy group[7,8] (Scheme 1).

The stereochemical outcome of the reaction having been established, its stereoselectivity was next investigated. The reaction was first conducted in dichloromethane at different temperatures, and the progress of the reaction was monitored by chiral GC analysis after sodium methoxide treatment of regularly withdrawn aliquots. The diastereoselectivity was not affected by the temperature used (over the 9–37 °C range studied), with maxima of 97:3 to 98:2 diastereoisomeric ratios being obtained in all cases for acyloins resulting from sodium methoxide treatment (Figure 1).

In order to mimic the initial rearrangement observed on TLC plates more closely, a solvent-free version of the process was developed, with the silica used either as received from the supplier or after activation (3 h treatment at 250 °C and under vacuum). The selectivity of the reaction was not significantly affected neither by the reaction temperature (over the 0–37 °C range studied) nor by the status of the silica used (Figure 1); the only noteworthy differences were that the rate of the reaction was enhanced by a factor of 5 with use of untreated silica without solvent and by a further factor of 1.5 when activated silica was used, leading to a very quick solvent-free rearrangement (Figure 1).

Essentially the same results were obtained when starting from a mixture of (+)-menthone enol acetate epoxides (**1c**+**1d**).

The known inversion of configuration[7,8] associated with the described diastereoselective process offered the opportunity to treat both the unchanged enol acetate epoxide and the rearranged α-acetoxymenthone together with sodium methoxide. In that case, mainly one acyloin diastereoisomer should be formed, thus making this process convergent. This procedure effectively led to the synthesis of (2*R*,5*R*)-α-hydroxymenthone (**3a**) in a 98.6% yield and with a diastereoisomeric excess (*de*) of 95.1% and also to (2*S*,5*S*)-α-hydroxymenthone (**3c**) with a 98.5% yield and a 95.3% *de* by starting from (–)-menthone derivatives **1a**+**1b** [Scheme 1(a)] and (+)-menthone derivatives **1c**+**1d** [Scheme 1(b)], respectively.

In order to gain access to the other two possible diastereoisomers, both (–)- and (+)-menthone enol acetate epoxide stereoisomers were treated with silica in the same way and the thus obtained rearranged α-acetoxy-(–)- and -(+)-menthone stereoisomers (**2a** and **2c**) and the unaffected (–)- and (+)-menthone enol acetate epoxide stereoisomers (**1b** and **1d**) were separated by silica gel chromatography. Isomers **1b** and **1d** were then rearranged by silica treatment, but at a higher temperature (80 °C), leading to the two corresponding inverted stereoisomers of α-acetoxy-(–)- and -(+)-menthone **2b** and **2d** (Scheme 2). All four obtained stereoisomers of α-acetoxy-menthone (**2a**, **2b**, **2c**, **2d**) were then transformed into the corresponding acyloins (**3a**, **3b**, **3c**, **3d**) in high diastereoisomeric excess with sodium methoxide (Schemes 1 and 2).

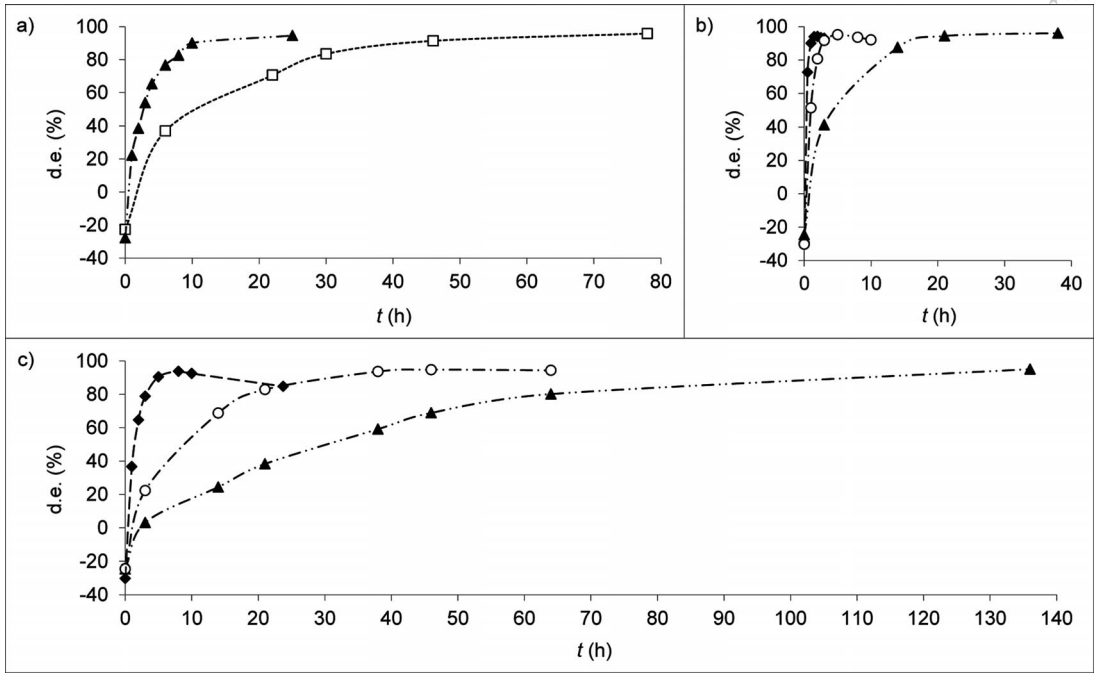
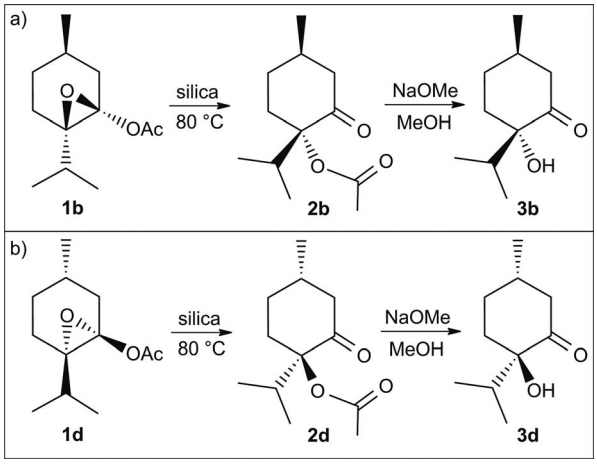


Figure 1. Kinetic analysis of silica-catalysed rearrangement of diastereoisomeric mixtures of (–)-menthone enol acetate epoxides (**1a**+**1b**) under various conditions. The *de* is the diastereoisomeric excess of the α-hydroxy-(–)-menthone **3a** after methoxide treatment. Open squares: 0 °C; triangles: 9 °C; open circles: 23–26 °C; diamonds: 37 °C. (a) Activated silica gel, no solvent; (b) untreated silica gel, no solvent; (c) untreated silica gel, CH_2Cl_2.



Scheme 2. Silica-catalysed rearrangement of the less reactive menthone enol acetate epoxides. (a) Enol acetate epoxide **1b** derived from (–)-menthone; (b) enol acetate epoxide **1d** derived from (+)-menthone.

It should be noted that the two α-acetoxy-(–)- and -(+)-menthone isomers **2b** and **2d** were solid compounds and that the previously attributed absolute configuration of the former was fully confirmed by X-ray diffraction analysis (see the Supporting Information). Isolation of the four stereoisomeric α-acetoxy-(–)- and -(+)-menthones **2a**, **2b**, **2c** and **2d** and of the four α-hydroxy-(–)- and -(+)-menthones **3a**, **3b**, **3c** and **3d** allowed the determination of their optical rotations and comparison with those reported in the literature (Table 1). Curiously, the optical rotation of (2*R*,5*R*)-α-acetoxymenthone **2a** obtained in this work and that reported in the literature[9] have opposite signs. In both cases the starting material used to obtain access to **2a** has the carbon atom bearing the methyl substituent in an (*R*) absolute configuration [(–)-menthone and (+)-menth-3-ene, respectively]. In each work this carbon atom is believed to be unaffected during the reported transformations, so the observed difference could tentatively be assigned to contamination of **2a** by (2*S*,5*R*)-α-acetoxymenthone **2b** in the previously reported work.[9] Indeed, because **2b** possesses a positive and much larger optical rotation than (2*R*,5*R*)-α-acetoxymenthone (**2a**, Table 1) the diastereoisomeric excess of the reported (2*R*,5*R*)-α-acetoxymenthone should be around 40%, if it is assumed that this compound is the only contaminant. Such an assumption is in line with the facts that no diastereoisomeric determination was carried out during the reported work and that recrystallization was believed to be sufficient to afford diastereoisomerically pure

Table 1. Optical rotations of the α-acetoxymenthone and α-hydroxymenthone stereoisomers derived from (–)-menthone obtained in this work and comparison with literature data.

Acetoxymenthone	**2a**	**2b**
This work, $[\alpha]_D^{25}$	–17.6 (*c*=0.39, MeOH)	+121.6 (*c*=0.44, MeOH)
Ref.[9] $[\alpha]_D^{25}$	+24.4 (*c*=0.4, MeOH)	+127.1 (*c*=0.39, MeOH)
Hydroxymenthone	**3a**	**3b**
This work, $[\alpha]_D^{25}$	–122.3 (*c*=2.8, $CHCl_3$)	+132.5 (*c*=2.0, $CHCl_3$)
Ref.[9] $[\alpha]_D^{25}$	–32.5 (neat)	+72.5 (neat)
Ref.[10] $[\alpha]_D^{25}$	–30.9 (*c*=0.1, EtOH)	+72 (*c*=0.1, EtOH)
Ref.[11] $[\alpha]_D^{25}$	–128.2 (neat)	+114.2 (neat)
Ref.[12] $[\alpha]_D^{25}$	–96.7 (neat)	

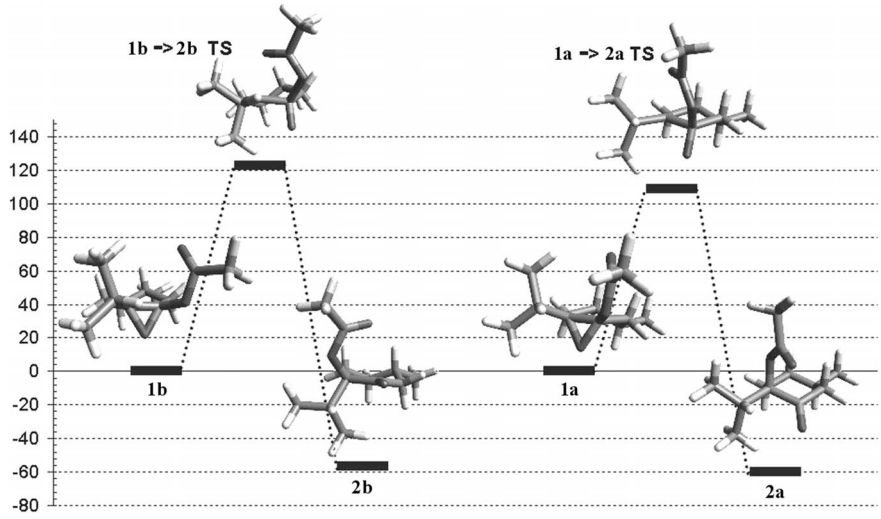


Figure 2. Relative Gibbs free energies during the silica-catalysed rearrangement of the less (**1b**) and the more reactive (**1a**) (–)-menthone enol acetate epoxide (at the B3LYP/def2-TZVP level, gas phase; see the Supporting Information for details on thermodynamic calculations) in kJ mol^{-1}, the obtained products being α-acetoxy-(–)-menthone isomers **2b** and **2a**, respectively (TS: transition state, characterized by frequency calculations).

compound, although this latter point is not clearly stated.[9] We thus found in this work that the pure or nearly pure (2*R*,5*R*)-α-acetoxymenthone diastereoisomer had a negative optical rotation sign rather than the previously reported positive one (Table 1).

Finally, we were interested in the reasons for such a stereoselective rearrangement. Silica could be ruled out as a chiral auxiliary, so we investigated the energetics of the reaction by computational DFT calculations. On the assumption that the studied reactions occurred through acetoxy group carbonyl oxygen atom attack on the distal epoxide carbon atom with inversion of configuration,[7,8] the energies of the various conformers allowing such an attack were first calculated for both **1a** and **1b** (–)-menthone enol acetate epoxide stereoisomers (see the Supporting Information).

As expected, the conformation of lowest energy for each diastereoisomer was that bearing the methyl group in a (pseudo)equatorial position. Starting from these two conformations, the optimized structures for transition state and products were determined (Figure 2). Frequency calculations allowed us access to kinetic and thermodynamic parameters of the reaction (see the Supporting Information).

First of all, the reaction was clearly exergonic and of the same order for the two diastereoisomers. Secondly, a quite important difference in $\Delta G^{\#}$ was observed for the two different diastereoisomers, in line with the observed experimental data and, a priori, ruling out silica surface discrimination between the two diastereoisomers **1a** and **1b** (see the Supporting Information). Indeed, the calculated nearly 14 kJ mol^{-1} $\Delta\Delta G^{\#}$ value was sufficient to explain the observed stereoselection of the reaction, the thermodynamics establishing a rate constant (at 25 °C) for the more reactive stereoisomer **1a** 300 times higher than that for **1b**.

This result suggested that the observed diastereoselection depended only on the intrinsic energies of each stereoisomer around the transition state.

The ultimate reason for such an important difference in activation energy could be the existence of a steric clash between the approaching acetoxy group carbonyl oxygen atom and the exposed pseudoaxial hydrogen atom at C-3just before the creation of the new carbon–oxygen bond (Figure 3). Indeed, in the case of the more reactive diastereoisomer **1a**, this hydrogen atom is less likely to interfere with the attacking oxygen atom than in the case of the less reactive **1b**, thus lowering the activation energy of the rearrangement.

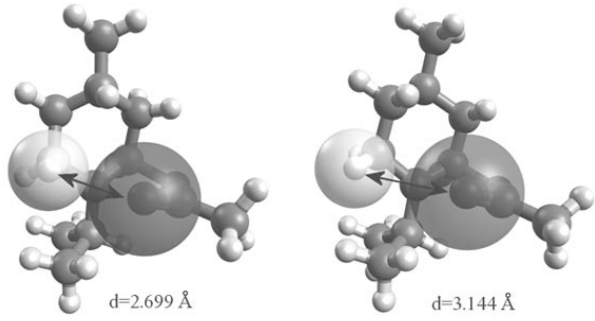


Figure 3. Representative van der Waals radii of the approaching acetoxy group carbonyl oxygen atom and the exposed pseudoaxial hydrogen atom at C-3 at the start of the reaction for the less reactive (left, **1b**) and the more reactive (right, **1a**) (–)-menthone enol acetate epoxides.

Conclusions

We have discovered a very unexpected, easy to conduct and highly diastereoselective silica-catalysed rearrangement

of (–)- and (+)-menthone enol acetate epoxides (**1a+1b** and **1c+1d**). This diastereoselective process could be used in a convergent manner leading to (2*R*,5*R*)-α-hydroxymenthone (**3a**) or (2*S*,5*S*)-α-hydroxymenthone (**3c**), respectively, in high yields and with high diastereoisomeric excesses. This process could also be used in a more classical way, allowing the synthesis of all four α-hydroxymenthone stereoisomers, two by two, depending on the starting material, once again with very high diastereoisomeric excesses. It should be noted that the formed acyloins each contain a newly formed tertiary alcohol stereocentre α to a ketone, a motif of substantial interest. The unambiguous absolute configuration assignment of all four α-hydroxymenthone stereoisomers and their corresponding acetoxy derivatives (through VCD and X-ray diffraction studies) allowed clarification of some literature inconsistency about the latter. Furthermore, this silica-catalysed rearrangement could be conducted with or without solvent; in the latter case the reaction could take place in as little as 2 h and is thus particularly ecofriendly. Finally, computational energetic calculations (DFT) have shown that with diastereoisomeric mixtures of either (–)- or (+)-menthone enol acetate epoxides, one of the diastereoisomers (the one found to be experimentally more reactive – **1a** and **1c**, respectively) is energetically favoured during this rearrangement.

Experimental Section

Caution: Numerous products described below are extremely volatile, especially the acetates.

General: Commercially available reagents were used without further purification except for *n*-pentane, which was freshly distilled before use. (–)-Menthone, (+)-menthone, *p*-toluenesulfonic acid and $NaHCO_3$ were purchased from Sigma–Aldrich, *m*-chloroperbenzoic acid and acetic anhydride were purchased from Acros Organics, and sodium thiosulfate was purchased from Prolabo. Flash chromatography (FC) was performed with silica gel 60 from Merck (230–400 mesh). When specifically stated, the silica gel 60 was activated by heating under vacuum (5 mbar) at 250 °C for 3 h. NMR spectra were recorded in $CDCl_3$, with Bruker spectrometers at operating frequencies of 300 MHz (^1H) or 75 MHz (^{13}C) as indicated in the individual spectra. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (*J*) in Hz. Multiplicities are tabulated as s for singlet, d for doublet, t for triplet, sept for septuplet, and m for multiplet. Optical rotations were measured with a Perkin–Elmer 241 polarimeter with use of the yellow sodium D line at 589 nm in a 1 dm pathlength cuvette. Diastereoisomeric excesses were determined by GC analysis with a GC2010 Shimadzu system and a CyclosilB column (Agilent technology, length 60 m, internal diameter 0.25 mm, film 0.25 μm) at the following temperatures: $t_{injector}$ = 180 °C; t_{column} = 150 °C; t_{FID} = 220 °C. The differences in FID detection for all four α-hydroxymenthone diastereoisomers (**3a**, **3b**, **3c**, **3d**) were checked and found to be less than 1%.

Menthone Enol Acetate Formation: In a 10 mL round-bottomed flask, (–)-menthone (459.4 mg, 2.98 mmol), acetic anhydride (2 mL, 21.18 mmol, 7 equiv.) and *p*-toluenesulfonic acid (200 mg, 1.16 mmol, 0.4 equiv.) were stirred at 110 °C for 1 h. The reaction mixture was allowed to cool to room temp. and purified by FC [diethyl ether in *n*-pentane (5%)] to afford the (–)-menthone enol acetate [(5*R*)-5-methyl-2-(propan-2-yl)cyclohex-1-en-1-yl acetate] as a colourless oil (495.8 mg, 2.53 mmol, yield 86%). $[\alpha]_D^{25}$ = +76.9 (*c* = 2.8, $CHCl_3$). ^1H NMR (300 MHz): δ = 0.92 (d, *J* = 7.0 Hz, 6 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 1.15–1.28 (m, 1 H), 1.66–1.89 (m, 3 H), 1.99–2.11 (m, 3 H), 2.12 (s, 3 H), 2.71 (sept, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.0, 20.4, 20.9, 21.3, 22.0, 26.9, 29.2, 30.6, 35.5, 128.6, 139.9, 169.4 ppm. HRMS (ESI-MS): calcd. for $C_{12}H_{20}O_2$ $[M + H]^+$ 197.1536; found 197.1536.

The same procedure was used with (+)-menthone (440.2 mg, 2.86 mmol), giving the corresponding (+)-menthone enol acetate [(5*S*)-5-methyl-2-(propan-2-yl)cyclohex-1-en-1-yl acetate] as a colourless oil (473.5 mg, 2.42 mmol, yield 84.5%). $[\alpha]_D^{25}$ = –79.5 (*c* = 2.2, $CHCl_3$).

Menthone Enol Acetate Epoxidation: In a 100 mL round-bottomed flask, (–)-menthone enol acetate (468.9 mg, 2.39 mmol) was dissolved in dichloromethane (20 mL). The solution was stirred and cooled in an ice/water bath, and a solution of *m*-chloroperbenzoic acid (1.0662 g, 6.18 mmol, 2.6 equiv.) in dichloromethane (30 mL) was then added dropwise from a separating funnel (the last mL, containing the hydration water of the *m*-chloroperbenzoic acid, was retained). The reaction mixture was then stirred at room temp. for 1 h. A sodium thiosulfate solution (10 mL, 10%, w/v) was added, and the mixture was stirred vigorously for another 20 min. The reaction mixture was washed with a hydrogencarbonate solution (3 × 50 mL, 10%, w/v), and the combined water phases were back-extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by FC [diethyl ether in *n*-pentane (10%)] to afford a mixture of (–)-menthone enol acetate epoxide diastereoisomers [**1a+1b**, **1a** = (1*S*,2*R*,5*R*)-1,2-epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl acetate, **1b** = (1*R*,2*S*,5*R*)-1,2-epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl acetate] as a colourless oil (443.2 mg, 2.09 mmol, yield 87.4%, diastereoisomeric excess of **1a** 26.5%).

Application of the same procedure to (+)-menthone enol acetate (392.7 mg, 1.78 mmol) afforded a mixture of diastereoisomers [**1c+1d**, **1c** = (1*R*,2*S*,5*S*)-1,2-epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl acetate, **1d** = (1*S*,2*R*,5*S*)-1,2-epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl acetate] as a colourless oil [378.2 mg, 1.78 mmol, yield 89.2%, *de* of **1c** (1*S*,2*R*,5*S*)-1,2-epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl acetate 26.4%].

General Procedure for the Kinetic Study of the Rearrangement of the Mixture of (–)-Menthone Enol Acetate Epoxide Diastereoisomers on Silica Gel: A mixture of (–)-menthone enol acetate epoxide diastereoisomers **1a+1b** (30 mg, 0.28 mmol) was dissolved in dichloromethane (2 mL) in a 10 mL round-bottomed flask. Silica gel (activated or not) was added (300 mg, 10 mass equiv.), and the suspension was stirred at the required temperature. For the experiments without solvent, the dichloromethane was removed under vacuum, and the flask was maintained at the desired temperature. To monitor the reaction, suspension (100 μL, or ca. 20 mg of silica gel for experiments without solvent) was withdrawn and placed in a Pasteur pipette plugged with cotton. The liquid was drained, and the silica gel was eluted with methanol (3 × 100 μL). The liquid phases were pooled, and sodium methoxide (30% in methanol, 50 μL) was added. The reaction mixture was incubated at room temp. for 1 h, diluted with water (400 μL) and extracted with diethyl ether (400 μL). The organic phase was analysed by GC to determine the diastereoisomeric excess of formed α-hydroxymenthones **3a** and **3b**.

Specific Rearrangement of Menthone Enol Acetate Epoxide on Silica Gel: A mixture of (–)-menthone enol acetate epoxide diastereoisomers **1a+1b** (604.2 mg, 2.85 mmol) was dissolved in dichlorometh-

ane (40 mL) in a 100 mL round-bottomed flask. Activated silica gel (6 g, 10 mass eq.) was suspended in this solution, and the dichloromethane was removed under vacuum to adsorb the products on the silica gel. The reaction mixture was then incubated at 9 °C for 15 h. The silica gel was placed in a flash column, and the products were eluted with diethyl ether (60 mL). The solvent was removed under vacuum, and the mixture was purified by FC (sequential elution with *n*-pentane/diethyl ether 95:5, 90:10 and 80:20 mixtures) to afford **1b** (213.7 mg, 1.01 mmol, yield 35.4%) and **2a** (334.2 mg, 1.58 mmol, yield 55.3%).

(1*S*,2*R*,5*R*)-1,2-Epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl Acetate (1b): Colourless oil, *de* > 99%. $[a]_D^{25}$ = +86.5 (*c* = 2.9, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.07 (td, *J* = 12.4, 4.6 Hz, 1 H), 1.30–1.41 (m, 1 H), 1.49–1.95 (m, 5 H), 2.07 (s, 3 H), 2.19 (ddd, *J* = 1.6, 6.2, 14.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 17.6, 18.8, 21.1, 21.5, 22.2, 27.0, 28.1, 29.5, 38.3, 69.3, 88.7, 169.7 ppm. GC: t_R = 7.9 min. HRMS (ESI-MS): calcd. for $C_{12}H_{20}O_3$ $[M + H]^+$ 213.1485; found 213.1487.

(2*R*,5*R*)-5-Methyl-1-oxo-2-(propan-2-yl)cyclohexyl Acetate (2a): Colourless oil, *de* > 99%. $[a]_D^{25}$ = –20.1 (*c* = 2.9, $CHCl_3$) and –18.5 (*c* = 5, MeOH). ^{1}H NMR (300 MHz): δ = 0.83 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.49–1.77 (m, 3 H), 1.86–2.03 (m, 1 H), 2.10 (s, 3 H), 2.14–2.40 (m, 3 H), 2.58 (sept, *J* = 6.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 17.0, 17.8, 21.1, 21.6, 28.9, 29.6, 30.4, 34.7, 47.5, 86.9, 170.0, 206.9 ppm. $C_{12}H_{20}O_3$ (212.29): calcd. C 67.89, H 9.50; found C 67.69, H 9.53. GC t_R = 12.5 min.

The same procedure was applied to the mixture of (+)-menthone enol acetate epoxide diastereoisomers **1c**+**1d** (605.1 mg, 2.85 mmol) to afford **1d** (202.3 mg, 0.95 mmol, yield 33.4%) and **2c** (341.2 mg, 1.61 mmol, yield 56.4%), both as colourless oils.

(1*R*,2*S*,5*S*)-1,2-Epoxy-5-methyl-2-(propan-2-yl)cyclohex-1-yl Acetate (1d): *de* > 99%. $[a]_D^{25}$ = –101.8 (*c* = 2.4, $CHCl_3$). GC: t_R = 8.6 min.

(2*S*,5*S*)-5-Methyl-1-oxo-2-(propan-2-yl)cyclohex-2-yl Acetate (2c): *de* > 99%. $[a]_D^{25}$ = +23.9 (*c* = 2.7, $CHCl_3$). GC: t_R = 12.6 min.

Convergent Synthesis of (2*R*,5*R*)- and (2*S*,5*S*)-2-Hydroxymenthone (3a and 3c) by Starting from Mixtures of (–)- and (+)-Menthone Enol Acetate Epoxide Diastereoisomers: A mixture of (–)-menthone enol acetate epoxide diastereoisomers **1a**+**1b** (313.9 mg, 1.48 mmol) was dissolved in dichloromethane (20 mL) in a 50 mL round-bottomed flask. Silica gel (3 g, 10 mass-equiv.) was suspended in this solution, and the reaction mixture was stirred at 23 °C for 44 h. The mixture was placed in a flash column, the dichloromethane was drained, and the silica was washed with diethyl ether (60 mL) to recover all the products. The organic phases were pooled, and the solvent was removed under vacuum. The products were dissolved in methanol (15 mL), and sodium methoxide (30% in methanol, 3 mL) was added. The reaction mixture was stirred at room temp. for 1 h, diluted with water (150 mL) and extracted with diethyl ether (3 × 50 mL). The organic phases were pooled, the solvent was removed under vacuum, and the reaction mixture was purified by FC [diethyl ether in *n*-pentane (20%)] to afford **3a** as a colourless oil (247.6 mg, 1.46 mmol, yield 98.6%) with a *de* of 95.1%.

Application of the same procedure to the (+)-menthone enol acetate diastereoisomers **1c**+**1d** (306.4 mg, 1.45 mmol) afforded **3c** as a colourless oil (241.9 mg, 1.42 mmol, yield 98.5%) with a *de* of 95.3%.

Rearrangement of 1b and 1d on Silica Gel: Compound **1b** (199.3 mg, 0.94 mmol) was dissolved in dichloromethane in a 50 mL round-bottomed flask. Silica gel (2 g, 10 mass-equiv.) was suspended in the mixture, and the solvent was removed under vacuum. The reaction mixture was heated at 80 °C for 6 h, allowed to cool to room temp. and placed on a flash column. The product was eluted with diethyl ether (60 mL), concentrated and purified by FC [diethyl ether in *n*-pentane (20%)] to afford **2b** = (2*S*,5*R*)-5-methyl-1-oxo-2-(propan-2-yl)cyclohexyl acetate as a white solid (172.8 mg, 0.82 mmol, yield 86.7%), m.p. 78 °C, *de* > 99%. $[a]_D^{25}$ = +137.4 (*c* = 2.2, $CHCl_3$) and +122.4 (*c* = 3.0, MeOH). ^{1}H NMR (300 MHz): δ = 0.83 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.4 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 1.32–1.49 (m, 1 H), 1.76–1.88 (m, 1 H), 1.92–2.18 (m, 3 H), 2.06 (s, 3 H), 2.22 (sept, *J* = 6.8 Hz, 1 H), 2.50–2.68 (m, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 16.3, 16.4, 21.5, 21.7, 30.3, 31.0, 31.2, 32.4, 48.5, 87.1, 169.9, 205.2 ppm. $C_{12}H_{20}O_3$ (212.29): calcd. C 67.89, H 9.50; found C 67.99, H 9.70. GC: t_R = 12.1 min.

CCDC-860415 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Application of the same procedure to the (+)-menthone-derived compound **1d** (141.2 mg, 0.67 mmol) afforded **2d** [= (2*R*,5*S*)-5-methyl-1-oxo-2-(propan-2-yl)cyclohex-2-yl acetate] as a white solid (116.7 mg, 0.55 mmol, yield 82.1%), m.p. 77.5 °C, *de* = 97.8%. $[a]_D^{25}$ = –133.2 (*c* = 1.5, $CHCl_3$). GC: t_R = 12.2 min.

Representative Procedure for the Acetate Methanolysis: Compound **2a** (162.6 mg, 0.77 mmol) was dissolved in methanol (10 mL) and sodium methoxide (2 mL, 30% in methanol) in a 50 mL round-bottomed flask. The solution was stirred at room temp. for 1 h. The reaction mixture was diluted with water (50 mL), extracted with diethyl ether (3 × 50 mL), dried, concentrated and purified by FC [diethyl ether in *n*-pentane (20%)] to afford **3a** [= (2*R*,5*R*)-2-hydroxymenthone] as a colourless oil (107.8 mg, 0.63 mmol, yield 82.7%), *de* > 99%. $[a]_D^{25}$ = –122.3 (*c* = 2.8, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.70 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.46–1.57 (m, 1 H), 1.67 (td, *J* = 13.9, 4.0 Hz, 1 H), 1.97 (tt, *J* = 13.9, 4.3 Hz, 1 H), 2.14–2.30 (m, 3 H), 2.41–2.56 (m, 1 H), 2.72 (dd, *J* = 13.2, 6.4 Hz, 1 H), 3.78 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 15.5, 16.2, 18.8, 27.9, 30.9, 32.3, 33.0, 44.4, 80.7, 215.0 ppm. GC t_R = 7.0 min. HRMS (ESI-MS): calcd. for $C_{10}H_{18}O_2$ $[M + H]^+$ 171.1380; found 171.1386. The spectroscopic data are in agreement with those in ref.[10]

Application of the same procedure to the (+)-menthone-derived compound **2c** (162.6 mg, 0.77 mmol) afforded **3c** [= (2*S*,5*S*)-2-hydroxymenthone] as a colourless oil (107.8 mg, 0.63 mmol, yield 81.8%), *de* = 97.8%. $[a]_D^{25}$ = –133.2 (*c* = 2.2, $CHCl_3$). GC: t_R = 7.1 min.

Methanolysis of compound **2b** (69 mg, 0.33 mmol) afforded **3b** [= (2*S*,5*R*)-2-hydroxymenthone] as a colourless oil (48.6 mg, 0.29 mmol, yield 88%), *de* > 99%. $[a]_D^{25}$ = +132.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.69 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.4 Hz, 3 H), 1.38–1.52 (m, 2 H), 1.64–1.78 (m, 1 H), 1.81–1.99 (m, 1 H), 2.12–2.37 (m, 3 H), 2.46 (ddd, *J* = 13.1, 4.3, 2.2 Hz, 1 H), 3.77 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 15.3, 16.0, 22.2, 30.7, 30.9, 36.2, 37.1, 46.1, 80.3, 214.6 ppm. GC: t_R = 6.4 min. The spectroscopic data are in agreement with those in ref.[10]

Application of the same procedure to the (+)-menthone-derived compound **2d** (76.8 mg, 0.36 mmol) afforded **3d** [= (2*R*,5*S*)-2-hydroxymenthone] as a colourless oil (48.7 mg, 0.29 mmol, yield

80.6%), *de* = 96.8%. $[\alpha]_D^{25}$ = –121.5 (*c* = 1.3, $CHCl_3$). GC: t_R = 6.2 min.

IR/VCD Analysis[13]

IR and VCD Measurements: Infrared (IR) and vibrational circular dichroism (VCD) spectra were recorded with a Bruker PMA 50 accessory coupled to a Vertex70 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light at 50 kHz. Demodulation was performed with a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) before the photoelastic modulator was used to enhance the signal/noise ratio. A transmission cell with CaF_2 windows and a 210 μm spacer were used. A solution of **3a** was prepared by dilution of the sample in CD_2Cl_2 to a concentration of 0.5 mol L^{-1}. The VCD spectra of the cell filled with CD_2Cl_2 was used for baseline correction of the spectra of **3a**. For each individual VCD spectrum, about 12000 scans were averaged at 4 cm^{-1} resolution (corresponding to 3 h measurement time). For the infrared spectrum the cell filled with CD_2Cl_2 served as reference. The spectra are presented without smoothing and further data processing in the Supporting Information.

Conformational Analysis: Calculations were performed on the (2*S*,5*R*)-**3b** (= A) and (2*R*,5*R*)-**3a** (= B) diastereomers. The conformational analysis and the calculation of Boltzmann populations were performed with Density Functional Theory (DFT) and the BLYP functional combined with the 6-31G(d) basis set (see the Supporting Information).

Spectra Calculation: The geometry optimizations, vibrational frequencies, IR absorption and VCD intensities were calculated with Density Functional Theory (DFT) and the B3LYP functional combined with the 6-31+G(d,p) basis set. Frequencies were scaled by a factor of 0.98 with B3LYP. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths with the assumption of Lorentzian band shape with a half-width at half maximum of 6 cm^{-1} (Figure SI1 in the Supporting Information). All calculations were performed with Gaussian 09.[14]

Computational Details:[15] All calculations were performed with use of the TURBOMOLE program package. They are based on density-functional theory (DFT) with the gradient-corrected exchange-correlation functional BP (B-P86) in combination with the resolution-of-the-identity (RI) technique in a first exploratory step. A standard basis step implemented in Turbomole def2-SV(P) was used, in combination with the corresponding auxiliary basis set for the RI. In a second step, hybrid functional B3LYP with a standard polarized triple-zeta split-valence basis set def2-TZVP was used. All geometries were optimized with a threshold of 10^{-6} a.u. The m3 grid option of the Turbomole suite was used as a default.

Frequency calculations [for BP/def2-SV(P) and B3LYP/def2-TZVP] allowed stationary points to be characterized as energy minima or transition states. Furthermore, under the assumption that the reaction proceeded in the gas phase with ideal gas behaviour, frequency calculations allowed us to determine the thermodynamic quantities such as zero-point vibrational energy (ZPVE), temperature corrections for the energy [*E*(*T*)] and the absolute entropies [*S*(*T*)] for all reactants/products and transition states by standard methods. No scaling factor was used for frequencies. The Gibbs energy change between the reactant and the transition state ($\Delta G^{\ddagger}$) was estimated at given temperature *T* as follows:

$$\Delta G^{\ddagger} = \Delta E_{elect} + \Delta ZPVE + \Delta E(T)$$

ΔE_{elect} is the difference between the calculated electronic energy extracted from the DFT calculation for TS and reactant, whereas ΔZPVE and Δ*E*(*T*) are the differences in the zero point vibrational energy (ZPVE) and in the temperature corrections for the energy [*E*(*T*)], respectively.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

where $\Delta S^{\ddagger}$ is the difference in the absolute entropies for the TS and the reactant.

The first-order rate coefficient *k*(*T*) was then calculated by transition state theory (TST) under the assumption that the transmission coefficient is equal to 1:

$$k(T) = (k_B T/h) \exp(-\Delta G^{\ddagger}/RT)$$

where k_B and *h* are the common Boltzmann and Planck constants.

Supporting Information (see footnote on the first page of this article): Analytical data, IR/VCD analysis and computational details.

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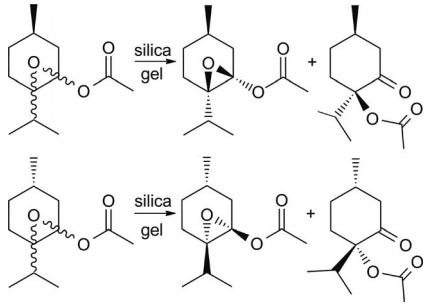
Selective Epoxide Opening

Epoxy enol acetates derived from menthone unexpectedly rearranged diastereoselectively on exposure to silica, giving easy access to the complete set of α-hydroxymenthone stereoisomers. Two of the four stereoisomers were also available through a diastereoconvergent process. Finally, the observed stereoselection was investigated by DFT calculations.



Keywords: Rearrangement / Chiral resolution / Diastereoselectivity / Acyloins / Menthone

