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Synthesis of enantiomerically pure (*R*)- and (*S*)-2-ethoxycarbonylmethyl-2-hydroxy-cyclohexanones

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Abstract

Sulfenylation of 2-p-tolylsulfinyl cyclohexanone can be achieved at −78°C with thiosulfonates. The in situ aldol reaction of these compounds with ethyl acetate enolate is highly stereoselective (1,2-asymmetric induction) and yields diastereomeric mixtures of β-hydroxyesters (the configuration of the major one being dependent on the sulfenylating agent) that can be readily separated and transformed into the enantiomerically pure title ketones.

1. Introduction

The α-hydroxy keto functional moieties are commonly found in natural products.[1] Consequently, efficient methods for the construction of such compounds in their enantiomerically pure form are in demand.[2] The Pummerer reaction,[3] one of the most valuable procedures for sulfinyl group exploitation, has been successfully used to obtain enantiomerically pure α-hydroxyaldehydes and 1,2-diols[4,5] from the appropriate acyclic unsubstituted β-hydroxysulfoxides. In a previous paper we have described the asymmetric aldol reaction between lithium enolates derived from esters and enantiomerically pure α-sulfinyl cyclohexanone (**1**),[6] to obtain the corresponding β-hydroxyesters (**2**) in good yields and high diastereoselectivities at the hydroxylic center. All attempts to transform these products into the corresponding α-hydroxyketones under Pummerer conditions, did not give satisfactory results (Scheme 1).[7]

The introduction of a sulfenyl group at the α position of the cyclic β-ketosulfoxide would provide a good alternative to obtain the desired ketone by hydrolysis of the resulting monothioketal S-oxide. Open-chain monothioketal S-oxides derived from α-diketones have not been reported to our knowledge,[8] probably because of the instability of these compounds which are prone to yield the corresponding

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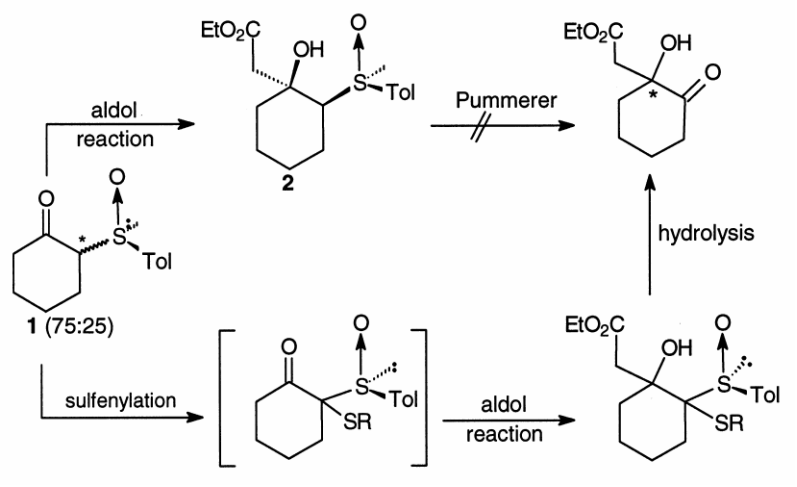


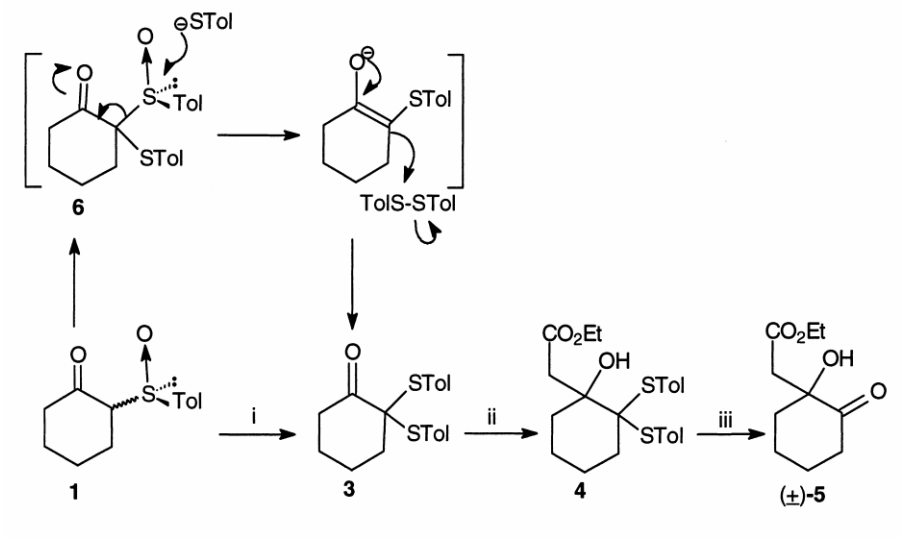
Scheme 1.

α-sulfenyl α,β-unsaturated ketones by pyrolytic elimination of the sulfinyl group.[9] In this paper we report the successful preparation of monothioketal S-oxides of 1,2-cyclohexanedione, taking advantage of the restrictions imposed by the cyclic ketone structure to the pyrolytic elimination, their use in situ as substrates of asymmetric aldol reactions with lithium ethyl acetate enolate, and the deprotection of the obtained adducts into the enantiomerically pure title compounds.

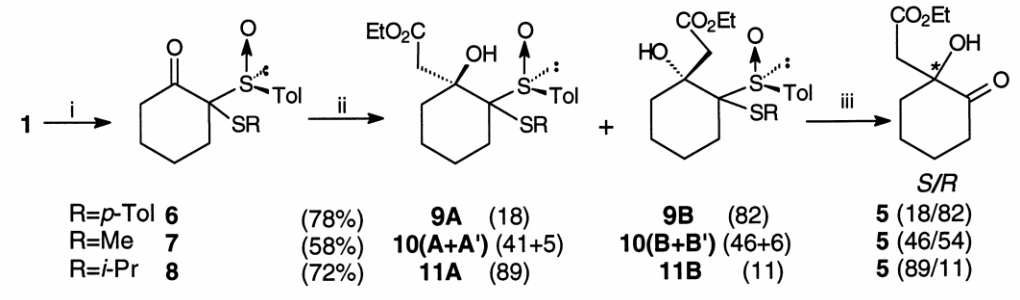
2. Results and discussion

The first step of the proposed strategy consists of the asymmetric introduction of a sulfenyl group at the α position of the β-ketosulfoxide (**1**) (as a 75:25 diastereomeric mixture at C-2), in order to generate a non-epimerizable stereogenic center. Among the usual sulfenylating reagents, such as disulfides, sulfenyl chlorides or thiosulfonates,[10,11] the first attempts were carried out with p-tolyldisulfide under the conditions previously reported for acyclic α-alkyl β-ketosulfoxides (NaH, DMF, 0°C).[12,13] The reaction of the resulting compound **3** with the lithium ethyl acetate enolate yielded hydroxyester **4**, which was transformed into the racemic ketone **5** by reaction with NBS.[14] This result indicates that a thioketal (but not a thioketal S-oxide) structure must be assumed for compounds **3** and **4** (Scheme 2).[15] We presumed that this evolution was a result of the strong nucleophilic character of the p-tolylthiolate group[16] and hence we decided to use thiosulfonates as the sulfenylating agents, because they do not liberate nucleophilic species, thus precluding the undesired nucleophilic attack with sulfinyl group removal (see Scheme 2). Additionally, their enhanced reactivity would allow a decrease in the reaction temperature and therefore open the possibility to perform the aldol step in situ, and to prevent the easy elimination of the sulfinyl group from **6**.

Three different acyl thioketal S-oxides (**6**–**8**) (R=p-Tol, Me, i-Pr) were synthesized starting from the corresponding thiosulfonates and the lithium enolate of the β-ketosulfoxide (**1**).[17] As compounds **6**–**8** could not be isolated and characterized because of their easy decomposition, they were treated in situ with 4 equiv. of the ethyl acetate enolate, affording the corresponding hydroxy esters derivatives **9**–**11**, as a mixture of diastereoisomers. As can be seen, only two diastereoisomers, easily separable by column chromatography, are obtained starting from **6** and **8**. The composition and the yields for the two-steps sequence (**1**→**9**–**11**) of the diastereoisomeric mixtures are indicated in Scheme 3.



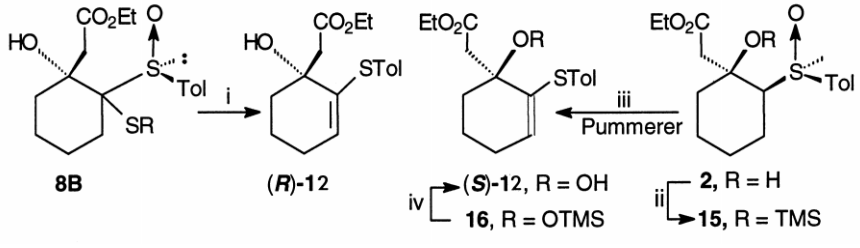
Scheme 2. Reagents: (i) NaH, DMF, p-TolS_2, 88%; (ii) $LiCH_2CO_2Et$, 86%; (iii) NBS, 90%



Scheme 3. Reagents: (i) LHMDS, HMPA, $RSSO_2R$; (ii) $LiCH_2CO_2Et$; (iii) NBS diastereomers A and A′ (and B and B′) are epimers at the thioketal S-oxide stereogenic center

The reaction of diastereoisomeric mixtures of **9**–**11** with NBS yielded ketone **5**, the enantiomeric excess of which was established by the use of chiral lanthanide shift reagents.[18] As can be seen, the enantiomeric ratios of **5** are identical to those of the starting diastereoisomers, which suggests that **9A** and **9B** (as well as **11A** and **11B**) must exhibit the opposite configuration at the hydroxylic center.

In order to confirm the configurational assignment of these compounds, **9B** was correlated with compound **2**, of known absolute configuration,[6] by transformation of both into the enantiomers of compound **12** (Scheme 4). Such a correlation allowed us to assign the *R* configuration to the hydroxylic center of **9B** and therefore the *S* configuration to that of **11A** (Scheme 3).

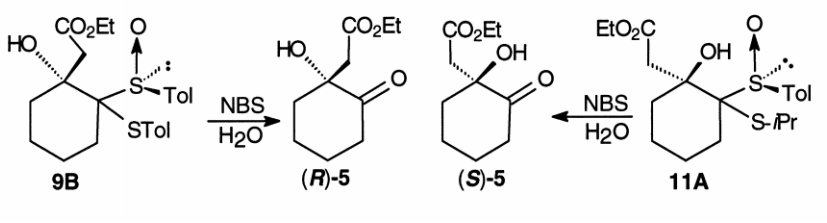


Scheme 4. Reagents: (i) toluene, $NaHCO_3$ (40 equiv.), 100°C, 85%; (ii) TMSOTf, 85%; (iii) TFAA, 45%; (iv) HF, CH_3CN

The described compound (1*S*,2*S*,R_S)-**2**, was protected as its trimethylsilyl derivative and submitted to Pummerer conditions to afford the corresponding O-TMS protected vinyl thioether **16**, which was easily desilylated to pure (*S*)-**12**. In parallel, adduct **9B** was transformed, by pyrolytic elimination of the sulfinyl group, in the same hydroxy thioether **12**, but of opposite configuration.

Similarly to **9B**, and in order to complete the characterization of aldolic adducts, **10A** and **11A** were transformed into the more stable enantiomerically pure methylthioether (*S*)-**13** and isopropylthioether (*S*)-**14**, respectively.

As we can see from Scheme 3, the major configuration induced at the hydroxylic center is the opposite, starting from compounds **6** (R=p-Tol) and **8** (R=i-Pr). Taking into account that configuration at sulfinylic sulfur is identical at both substrates, we proposed that these aldol reactions are 1,2-asymmetric induction processes, controlled by the configuration of the thioketal S-oxide carbon, which must be different in compounds **5** and **7**. Despite this dependence being crucial from a synthetic perspective, the reasons of this configurational change, associated to the starting thiosulfonate, are not clear. Separation of diastereoisomeric mixtures **9A**+**9B** and **11A**+**11B** allows pure diastereomers **9B** and **11A** to be obtained, which were further transformed into enantiomerically pure (*R*)-**5** and (*S*)-**5**, respectively, by hydrolysis in the presence of NBS (Scheme 5).



Scheme 5.

In conclusion, we have described a two step synthesis of the enantiomerically pure (*R*)- and (*S*)-α-substituted α-hydroxy cyclohexanones (**5**) from sulfinylcyclohexanone (**1**) (as a 75:25 diastereomeric mixture at C-2), by sulfenylation and in situ aldol reaction followed by hydrolysis of the resulting thioketal S-oxide. The configuration of the obtained hydroxy ketone (**5**) can be selected by the proper choice of the introduced sulfenyl moiety. The absence of the strongly acidic proton in the sulfenylated β-ketosulfoxides, which avoids the enolization of the substrates, has allowed us to extend this methodology to the addition of other nucleophiles. The results of this research will be published in due course.

3. Experimental

Diastereoisomeric aldol ratios were established by integration (^{1}H NMR) of well separated signals of the diastereoisomers in the crude reaction mixtures. Mass spectra were obtained in the electron impact mode (EI) at 70 eV unless stated otherwise. All reactions were monitored by TLC, that was performed on precoated sheets of silica gel 60 (F_{254}), and flash chromatography was effected with silica gel 60 (230–400 mesh). The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. THF was distilled from sodium/benzophenone under argon. Diisopropylamine and diisopropylethyl amine were distilled from potassium hydroxide. HMPA was distilled from calcium hydride. LHMDS, 1 M solution in THF and n-butyl lithium 2.5 M solution in hexanes were purchased from Aldrich.

3.1. Sulfenylation reagents

3.1.1. p-Tolyl p-toluenethiosulfonate

This was obtained following the previously described procedure.[9] The crude product was purified by crystallization ($CHCl_3$). Yield 86%. Mp 75°C. ^{1}H NMR δ 7.5 (2H, m), 7.3–7.0 (6H, m), 2,43 (3H, s), 2.39 (3H, s); ^{13}C NMR δ 144.6, 142.0, 140.7, 136.3, 130.1, 129.3, 127.4, 124.3, 21.5, 21.4. Anal. calcd for $C_{14}H_{14}S_2O_2$: C, 60.42; H, 5.07; S, 23.0. Found C, 60.63; H, 5.40; S, 23.16.

3.2. Isopropylthio isopropanethiosulfonate

This was obtained following the previously described procedure.[9] The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to yield pure compound as a colorless liquid. ^{1}H NMR δ 3.69 (1H, m, *J*=7.2 Hz), 3.35 (1H, m, *J*=7.2 Hz), 1.50 (6H, d), 1.49 (6H, d); ^{13}C NMR δ 63.5, 43.0, 24.3 (2C), 16.3 (2C).

3.3. 2,2-Bis-(p-tolylthio)cyclohexanone ***3***

To a DMF (5 ml) suspension of NaH (1.1 mmol, 26 mg) cooled in an ice–salt bath (−15°C), a DMF solution of 2-(p-tolylsulfinyl)-cyclohexanone (**1**) (1.0 mmol, 236 mg) was added dropwise. After 30 min at the same temperature, a solution of p-tolyl disulfide (292 mg, 1.05 mmol) was added to the above sodium enolate. After 10 min, the reaction was quenched with a NH_4Cl saturated solution (20 ml) and the mixture was extracted with ethyl ether (2×40 ml). The organic extracts were washed with brine (2×15 ml) and dried ($MgSO_4$). The solvent was removed under vacuum and the product was isolated by flash chromatography (hexane:acetate=4:1). Yield 88%. The product was further purified by crystallization from ether:hexane. ^{1}H NMR δ 7.6–7.15 (8H, m), 2.68 (2H, m), 2.38 (3H, s), 2.12 (3H, s), 2.0–0.9 (4H, m); ^{13}C NMR δ 202.1, 139.0 (2C), 135.6 (2C), 129.2, 126.8 (2C), 72.1, 40.0, 37.8, 26.1, 21.6, 20.9 (2C).

3.4. Sulfenylation of β-ketosulfoxides and condensation with lithium ethyl acetate enolate. General procedure

A THF solution of β-ketosulfoxide **1** (1 mmol) was added dropwise to a 0.3 M THF solution of LHMDS (3.33 ml, 1 mmol) cooled at −78°C. After 30 min at the same temperature, 3 ml of HMPA was added and the temperature was raised to 0°C in a 15 min period. The reaction mixture was introduced to a bath at −78°C and a THF solution of the corresponding thiosulfonate was added dropwise at the same temperature. Once the addition has finished, the reaction was kept at the appropriate temperature (−78°C for compound **6**, R=p-Tol and **7**, R=Me and −20°C for **8**, R=i-Pr) until the complete disappearance of **1** (TLC). Then, the reaction mixture containing the thioketal S-oxide was added dropwise at −78°C, via cannula over a THF solution (−78°C) of lithium ethyl acetate enolate, prepared from LHMDS (3.5 mmol) and ethyl acetate (341 μl, 3.5 mmol). After 5 min at −78°C, the reaction was quenched with a NH_4Cl saturated solution (40 ml) and the mixture was extracted with ethyl ether (2×40 ml). The organic extracts were washed with water (2×20 ml) and dried ($MgSO_4$). The solvent was removed under vacuum without heating, and the crude product purified by flash chromatography or recrystallization to afford the corresponding hydroxyester.

*3.4.1. 1-[(Ethoxycarbonyl)methyl]-2,2-bis-(p-tolylthio)cyclohexanol **4***

This was obtained from **3** (342 mg, 1 mmol) and lithium acetate enolate (3.5 mmol equiv.), following the general procedure for the aldol reaction. The crude product was purified by flash chromatography (hexane:acetate=4:1). Yield 86%. Recrystallized from hexane, mp 145°C. ^{1}H NMR δ 7.62 and 7.21 (4H, AA′BB′ system), 7.28 and 6.99 (4H, AA′BB′ system), 4.22 (2H, q, *J*=7.0 Hz), 3.9 (1H, s, OH), 3.42 and 2.66 (2H, AB system, J_{AB}=14.5 Hz, Δν=153 Hz), 2.40 (3H, s), 2.29 (3H, s), 2.30–1.10 (8H, m), 1.32 (3H, t, *J*=7.0 Hz). ^{13}C NMR δ 173.0, 139.5, 139.0, 137.5 (2C), 129.3, 129.1, 127.3 (2C), 76.6, 75.6, 60.7, 42.3, 33.9, 31.7, 21.9, 21.3, 21.2, 20.6, 14.19. Anal. calcd for $C_{24}H_{30}S_2O_3$: C, 66.95; H, 7.03; S, 14.87. Found C, 67.34; H, 7.15; S, 14.42.

*3.4.2. 1-[(Ethoxycarbonyl)methyl]-2-(p-tolylthio)-2-(p-tolylsulfinyl)cyclohexanol **9***

This was obtained following the general procedure starting from **1** and p-tolyl p-toluenethiosulfonate, as an 18:82 mixture of diastereomers **9A**:**9B** (global yield 78%). Column chromatography on silica gel (hexane:ethyl acetate=3:1) affords pure **9B** (45%). Isolation of isomer **9A** has not been accomplished and is described from an enriched mixture. **9A**: ^{1}H NMR δ 7.89–6.80 (8H, m), 4.22 (2H, q, *J*=7.1 Hz), 4.0 (1H, s, OH), 3.42 and 3.13 (2H, AB system, J_{AB}=14.5 Hz, Δν=58 Hz), 2.45 (3H, s), 2.27 (3H, s), 2.5–1.7 (8H, m), 1.29 (3H, t, *J*=7.1 Hz). **9B**: ^{1}H NMR δ 7.72 and 6.90 (4H, AA′BB′ system), 7.38 and 6.75 (4H, AA′BB′ system), 5.20 (1H, s, OH), 4.18 (2H, q, *J*=7.1 Hz), 3.78 and 2.87 (2H, AB system, J_{AB}=16 Hz, Δν=182 Hz), 2.48 (3H, s), 2.30 (3H, s), 2.3–0.7 (8H, m), 1.27 (3H, t, *J*=7.1 Hz). ^{13}C NMR δ 173.6, 141.8, 139.2, 137.5 (2C), 129.5, 129.3, 129.0 (2C), 83.1, 72.1, 60.9, 40.0, 35.2, 34.1, 21.6, 21.4, 21.2, 19.7, 14.1.

*3.4.3. 1-[(Ethoxycarbonyl)methyl]-2-(methylthio)-2-(p-tolylsulfinyl)cyclohexanol **10***

This was obtained following the general procedure starting from **1** and methyl methanethiosulfonate, as a 41:5:46:6 mixture of diastereomers **10A**:**10A′**:**10B**:**10B′** (global yield 58%). Column chromatography on silica gel (hexane:ethyl acetate:acetone=3:1:0.1) affords pure **10A**: ^{1}H NMR δ 7.69 and 7.30 (4H, AA′BB′ system), 4.34 (1H, s, OH), 4.17 (2H, q, *J*=7.1 Hz), 3.39 and 3.16 (2H, AB system, J_{AB}=13 Hz, Δν=46 Hz), 2.41 (3H, s), 2.5–1.4 (8H, m), 1.27 (3H, t, *J*=7.0 Hz), 1.1 (3H, s). ^{13}C NMR δ 172.8, 142.8, 134.5, 129.1, 127.1, 80.6, 78.1, 60.7, 40.6, 33.7, 26.7, 21.8, 21.6, 21.5, 14.2, 11.3. Isolation of the other isomers has not been accomplished, and their ^{1}H NMR data are obtained from enriched mixtures. **10A′**: ^{1}H NMR δ 7.62 and 7.33 (4H, AA′BB′ system), 5.34 (1H, s, OH), 4.05 (2H, q, *J*=7.0 Hz), 3.18 and 2.73 (2H, AB system, J_{AB}=13.5 Hz, Δν=90 Hz), 2.38 (3H, s), 2.5–1.2 (8H, m), 1.26 (3H, s), 1.23 (3H, t, *J*=7.0 Hz). **10B**: ^{1}H NMR δ 7.79 and 7.26 (4H, AA′BB′ system), 4.94 (1H, s, OH), 4.20 (2H, q, *J*=7.1 Hz), 3.38 and 2.90 (2H, AB system, J_{AB}=16 Hz, Δν=120 Hz), 2.41 (3H, s), 2.5–1.2 (8H, m), 1.28 (3H, t, *J*=7.1 Hz), 1.0 (3H, s). **10B′**: ^{1}H NMR δ 7.62 and 7.30 (4H, AA′BB′ system), 5.12 (1H, s, OH), 4.15 (2H, q, *J*=6.9 Hz), 3.39 and 3.16 (2H, AB system, J_{AB}=16 Hz, Δν=272 Hz), 2.41 (3H, s), 2.5–1.4 (8H, m), 1.24 (3H, s), 1.27 (3H, t, *J*=6.9 Hz).

*3.4.4. 1-[(Ethoxycarbonyl)methyl]-2-(isopropylthio)-2-(p-tolylsulfinyl)cyclohexanol **11***

This was obtained following the general procedure from **1** and isopropyl isopropanethiosulfonate, as an 89:11 mixture of diastereoisomers **11A**:**11B** (global yield 72%). Column chromatography on silica gel (hexane:ethyl acetate=3:1) affords diastereomerically pure isomers. **11A** (64%): $[\alpha]_D^{25}$ +112 (*c* 1; $CHCl_3$); ^{1}H NMR δ 7.70 and 7.22 (4H, AA′BB′ system), 4.06 (2H, q, *J*=6.9 Hz), 3.52 (1H, s, OH), 3.14 and 2.89 (2H, AB system, J_{AB}=14.5 Hz, Δν=50 Hz), 2.33 (3H, s), 2.5–1.6 (9H, m), 1.17 (3H, t, *J*=6.9 Hz), 1.17 (3H, d, *J*=6.7 Hz), 1.03 (3H, d, *J*=6.9 Hz); ^{13}C NMR δ 171.7, 141.8, 137.1, 128.8, 128.5, 78.9, 75.3, 60.7, 41.8, 34.4, 34.3, 27.3, 26.3, 24.2, 22.2, 21.3, 20.8, 14.1. **11B**: $[\alpha]_D^{25}$ −25 (*c* 1.2; $CHCl_3$); ^{1}H

NMR δ 7.70 and 7.22 (4H, AA′BB′ system), 4.06 (2H, q, *J*=6.9 Hz), 3.52 (1H, s, OH), 3.14 and 2.89 (2H, AB system, J_{AB}=14.5 Hz, Δν=50 Hz), 2.33 (3H, s), 2.5–1.6 (9H, m), 1.17 (3H, t, *J*=6.9 Hz), 1.17 (3H, d, *J*=6.7 Hz), 1.03 (3H, d, *J*=6.9 Hz); ^{13}C NMR δ 171.4, 142.0, 136.7, 128.7, 127.2, 84.2, 82.7, 60.3, 41.4, 33.7, 33.3, 28.9, 25.9, 24.8, 21.9, 21.1 (2C), 14.2.

3.5. Thioketal and thioketal-S-oxide hydrolysis in the presence of NBS

*3.5.1. 2-[(Ethoxycarbonyl)methyl]-2-hydroxycyclohexanone **5***

To a solution of NBS (9 mmol equiv.) in an acetone:water (90:10) mixture at 0°C, an acetone solution of thioketal or thioketal-S-oxide was slowly added. The mixture turned orange and after 5 min was poured into a separation funnel containing 20 ml of hexane, 20 ml of dichloromethane and 20 ml of saturated Na_2SO_3 solution. The organic layer was succesively washed with saturated $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$), concentrated and purified by flash chromatography (hexane:ethyl acetate:acetone=4:1:0.1) to yield **5** as colorless oil. Racemic **5** was obtained from **4**. Yield: 90%. ^{1}H NMR δ 5.58 (1H, s), 4.23 (2H, q, *J*=7.1 Hz), 2.93 and 2.47 (2H, AB system, J_{AB}=16 Hz), 2.8–1.5 (8H, m) 1.24 (3H, t, *J*=7.1 Hz). ^{13}C NMR δ 211.78, 171.5, 77.4, 60.8, 41.5, 41.4, 37.8, 28.3, 21.7, 14.0. Anal. calcd for $C_{10}H_{16}O_3$: C, 65.14; H, 8.75. Found C, 64.76; H, 9.10. From pure **9B**, (*R*)-**5** was obtained in 78% yield: $[\alpha]_D^{25}$ −28 (*c* 1; $CHCl_3$), and from pure **11A**, (*S*)-**5** was prepared in 75% yield: $[\alpha]_D^{25}$ +28 (*c* 1; $CHCl_3$).

3.6. Sulfinyl group pyrolysis. General procedure

To a flame-dried flask equipped with a reflux condenser containing sodium bicarbonate (3.5 g, 40.6 mmol) was added via cannula a solution of the hydroxythioketal S-oxide (1.06 mmol). The mixture was heated in an oil bath under vigorous stirring at the temperature and in the solvent indicated in each case. The reaction progress was monitored by TLC (CH_2Cl_2:hexane=3:1). The mixture was cooled to room temperature, and the crude product was filtered and washed with a saturated NH_4Cl solution (20 ml). The organic layer was separated, and the aqueous layer was extracted with ethyl ether (2×30 ml). The combined organic extracts were finally washed with brine and dried ($MgSO_4$). The ethyl ether was evaporated under vacuum.

*3.6.1. (1*R*)-1-[(Ethoxycarbonyl)methyl]-2-(p-tolylthio)-cyclohex-2-en-1-ol **12***

This was obtained from **9B** following the general procedure, by heating 2 h at 100°C in toluene. The crude product was extracted as above, the ether was removed under vacuum and the crude toluene solution was directly chromatographed using sucessively as eluents, hexane (to remove toluene) and CH_2Cl_2:hexane (3:1). $[\alpha]_D^{25}$ −12 (*c* 1; $CHCl_3$); ^{1}H NMR δ 7.29 and 7.09 (4H, AA′BB′ system), 5.80 (1H, 7, *J*=4Hz), 4.16 (2H, q, *J*=7.0 Hz), 3.80 (1H, s, OH), 3.07 and 2.56 (2H, AB system, J_{AB}=15.2 Hz, Δν=10 Hz), 2.31 (3H, s), 2.2–1.6 (6H, m), 1.26 (3H, t, *J*=7.0 Hz); ^{13}C NMR δ 172.4, 137.7, 136.9, 134.8, 131.7, 131.4, 129.8, 72.1, 60.7, 43.6, 36.2, 21.0, 18.9, 14.1; MS *m/z*; 306 (20) M^+, 288 (9), 218 (37), 124 (100). HRMS calcd for $C_{17}H_{22}SO_3$ 306.12896; found 306.12766.

*3.6.2. (1*S*)-1-[Ethoxycarbonyl)methyl]-2-(methylthio)-cyclohex-2-en-1-ol **13***

This was obtained from **10A** by heating for 2 h in refluxing $CHCl_3$. The reaction mixture was filtered and the solvent evaporated at reduced pressure. Purification was effected by flash chromatography (CH_2Cl_2:hexane=3:1). Yield 90%: $[\alpha]_D^{25}$ +7 (*c* 0.75; $CHCl_3$); ^{1}H NMR δ 5.54 (1H, t, *J*=4.0 Hz), 4.17 (2H, q, *J*=7.2 Hz), 3.89 (1H, s, OH), 3.04 and 2.56 (2H, AB system, J_{AB}=15.4 Hz, Δν=95 Hz), 2.22 (3H,

s), 2.2–1.5 (6H, m), 1.27 (3H, t, *J*=7.2 Hz); ^{13}C NMR δ 172.6, 135.8, 128.5, 71.9, 60.7, 43.6, 36.3, 26.5, 19.1, 15.9, 14.2. MS *m/z*; 230 (20) M^+, 212 (48), 185 (5), 165 (34), 143 (41), 91 (100). HRMS calcd for $C_{11}H_{18}SO_3$ 230.09766; found 230.09784.

3.6.3. (1S)-1-[(Ethoxycarbonyl)methyl]-2-(isopropylthio)-cyclohex-2-en-1-ol ***14***

14 was obtained from **11A** by heating for 2 h in refluxing $CHCl_3$. The reaction mixture was filtered and the solvent evaporated at reduced pressure. Purification was effected by flash chromatography. (CH_2Cl_2:hexane=3:1). Yield 95%. $[\alpha]_D^{25}$ +11 (*c* 1; $CHCl_3$). ^{1}H NMR δ 5.97 (1H, t, *J*=4.0 Hz), 4.16 (2H, q, *J*=6.9 Hz), 3.78 (1H, s, OH), 3.22 (1H, sept, *J*=6.6 Hz), 3.03 and 2.49 (2H, AB system, J_{AB}=15.2 Hz, Δν=160 Hz), 2.3–0.7 (6H, m), 1.27 (3H, t, *J*=7.2 Hz), 1.25 (6H, two d, *J*=6.6 Hz); ^{13}C NMR δ 172.6, 136.5, 134.1, 72.1, 60.7, 43.9, 37.3, 36.1, 27.0, 23.1, 22.8, 18.9, 14.1; MS *m/z*; 258 (4) M^+, 240 (17), 151 (86), 124, 91 (100). HRMS calcd for $C_{13}H_{22}SO_3$ 258.12896; found 258.12936.

3.7. [1S,2S,R$_S$]-1-[(Ethoxycarbonyl)methyl]-2-(p-tolylsulfinyl)-1-trimethylsilyloxycyclohexane ***15***

To a flame dried flask containing a cooled solution (−10°C) of **2** (485 mg, 1.5 mmol), in dry dichloromethane (5 ml) and diisopropyl ethylamine (697 μl, 6 mmol) a dichloromethane solution of TMSOTf (879 μl, 4.5 mmol) was added dropwise. The reaction mixture turned to red and after 30 min, the reaction was quenched by addition of 10 ml of saturated NaCl. The organic layer was separated and the aqueous layer was extracted with hexane (3×50 ml). The combined organic extracts were finally washed with brine and dried ($MgSO_4$). The solvent was removed and the crude product purified by flash chromatography (hexane:ethyl acetate=3:1 with 5% of NEt_3). Yield 90%. $[\alpha]_D^{25}$ +107 (*c* 0.42; $CHCl_3$). ^{1}H NMR δ 7.54 and 7.28 (4H, AA′BB′ system), 4.16 (2H, q, *J*=7.0 Hz), 3.42 and 2.73 (2H, AB system, J_{AB}=14 Hz, Δν=131 Hz), 2.34 (3H, s), 2.2–1.3 (8H, m), 1.28 (3H, t, *J*=7.0 Hz), 0.23 (9H, m); ^{13}C NMR δ 170.5, 141.5, 140.0, 129.5, 124.3, 75.8, 68.7, 60.7, 53.4, 45.9, 37.8, 24.2, 21.3 (2C), 17.0, 14.3, 2.4; MS *m/z*; 397 (3) M^+, 381 (11), 257 (94), 212 (49), 183 (49), 139 (84), 73 (100). HRMS calcd for $C_{20}H_{32}SO_4Si$ 396.17906; found 396.17758.

3.8. [1S]-1-[(Ethoxycarbonyl)methyl]-2-(p-tolylthio)-1-trimethylsilyloxy-2-cyclohexene ***16***

To a solution of **15** (204 mg, 0.5 mmol) and 2,6-lutidine (235 μl, 2 mmol) in CH_3CN (5 ml) at −78°C was added dropwise a cooled CH_3CN solution of TFAA (143 μl, 1 mmol). The mixture was gradually warmed to −20°C. After 1 h, the mixture was quenched with 10 ml of water and extracted with hexane (3×20 ml). The combined organic extracts were finally washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (CH_2Cl_2:hexane=1:1) yielded pure **16** as a colorless oil (90 mg, 48%). $[\alpha]_D^{25}$ −40 (*c* 1; $CHCl_3$). ^{1}H NMR δ 7.32 and 7.10 (4H, AA′BB′ system), 5.38 (1H, 7, *J*=4Hz), 4.13 (2H, m), 3.0 and 2.74 (2H, AB system, J_{AB}=13.5 Hz, Δν=52 Hz), 2.33 (3H, s), 2.5–1.6 (6H, m), 1.27 (3H, t, *J*=6.9 Hz), 0.18 (9H, m); ^{13}C NMR δ 170.7, 136.1, 134.8, 133.2, 131.2, 129.8, 128.3, 75.5, 60.1, 45.2, 36.0, 26.6, 19.7, 14.3, 2.1; MS *m/z*; 378 (11) M^+, 291 (37), 201 (12), 124 (100), 73 (66). HRMS calcd for $C_{20}H_{30}SO_3Si$ 378.16849; found 378.16800.

3.9. (1S)-1-[(Ethoxycarbonyl)methyl]-2-(p-tolylthio)-cyclohex-2-en-1-ol ***12***

This was prepared by treatment of a CH_3CN solution of **16** with HF (48% in water) at 0°C for 20 min. The mixture was treated with saturated $NaHCO_3$ solution (10 ml). The crude was extracted with ethyl ether (2×30 ml). The organic extracts were finally washed with brine and dried ($MgSO_4$). The solvent

was evaporated under vacuum, and chromatographed (CH_2Cl_2:hexane=3:1) to yield pure (*S*)-**12** (92%): $[\alpha]_D^{25}$ +10 (*c* 0.7; $CHCl_3$).

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18. 0.25 equiv. Eu $(tfc)_3$ was necessary to observe completely separated signals of the ester ethoxy group.