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New, highly efficient syntheses of *rac*-, (*R*)- and (*S*)-4-hydroxy-2-cyclohexenone

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Abstract

Both enantiomers of 4-hydroxy-2-cyclohexenone have been synthesised from chiral *p*-benzoquinone equivalents through very short and simple sequences in good overall yields. © 2000 Published by Elsevier Science Ltd.

1. Introduction

4-Hydroxy-2-cyclohexenone, **1**, has been used as a building block in the synthesis of several bioactive compounds such as the anti-cholesterol agents compactin and ML-236A,[1] and the immunosuppressant FK-506.[2] In these syntheses, the relative configuration of the stereogenic centres of the target molecules is induced by the stereogenic centre at C_4 of the hydroxyenone **1**.

Several preparations of racemic **1** have been published, usually embodied into wider reactivity studies.[3–6] Some reported syntheses of (*S*)-**1** (or *O*-protected derivatives of it) make use of enzymatic[6–9] or other catalytic[10] transformations as the crucial step. Alternatively, strategies based on the use of chiral auxiliaries have been employed for the preparation of both enantiomers of **1**,[11,12] and two complementary approaches starting from (–)-quinic acid, leading to (*S*)-[13] and (*R*)-**1**,[14] have also been developed. Many of these syntheses involve multi-step sequences with low overall yields or poor enantioselectivities. Moreover, there are some practical problems associated to the isolation of ketone **1**, because it is a volatile compound, highly soluble in water. As Brückner pointed out, this can be the cause for the wide dispersion of published specific rotations of (*R*)- and (*S*)-**1**.[14]

In previous reports, we have prepared a series of chiral *p*-benzoquinone derivatives, having one or both pairs of equivalent functional groups differentiated. In compound **2** (Scheme 1) one

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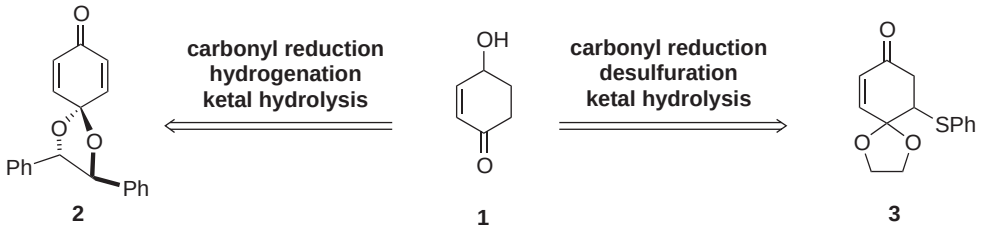
of the carbonyl groups has been protected as a ketal with a chiral C_2-symmetric diol,[15] while in the monoketal **3** one of the double bonds has been also temporarily masked by conjugate addition of thiophenol.[16] These derivatives were successfully used as chiral synthetic equivalents of *p*-benzoquinone in cycloaddition reactions.[17] (*R*,*R*)-**2** and racemic **3** are easily available in multi-gram scale from very inexpensive materials, and resolution of the racemate of **3** is effectively performed by liquid chromatography on cellulose triacetate.[16]

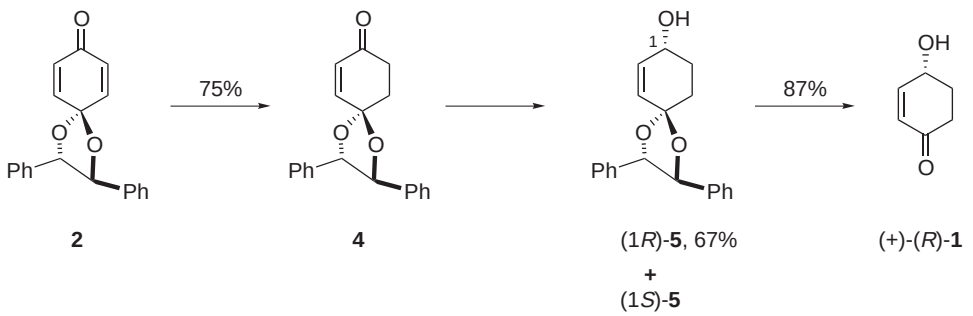


Scheme 1.

A priori, the conversion of **2** or **3** into **1** would require only a few conventional steps, namely reduction of the ketone to alcohol, selective hydrogenation of one of the double bonds (from **2**) or desulphurisation (from **3**), and hydrolysis of the ketal. We decided to explore both synthetic approaches, the results of which are described herein.

2. Results and discussion

Partial hydrogenation of **2** to give the desired α,β-unsaturated ketone **4** was accomplished working in toluene in the presence of Wilkinson's catalyst (Scheme 2). The reaction evolution was followed by ^{1}H NMR analysis of aliquot samples, and it was run until 50% conversion of **2**. In this way, **4** can be obtained in 75% yield or higher. Further conversion of **2** leads to hydrogenation of the second double bond and the dihydrogenated product contaminates recovered **2**. The use of Pd/C in several solvents afforded complex mixtures of hydrogenation products. The olefin protons of **4** show ^{1}H NMR signals at δ 6.91 and 6.11.

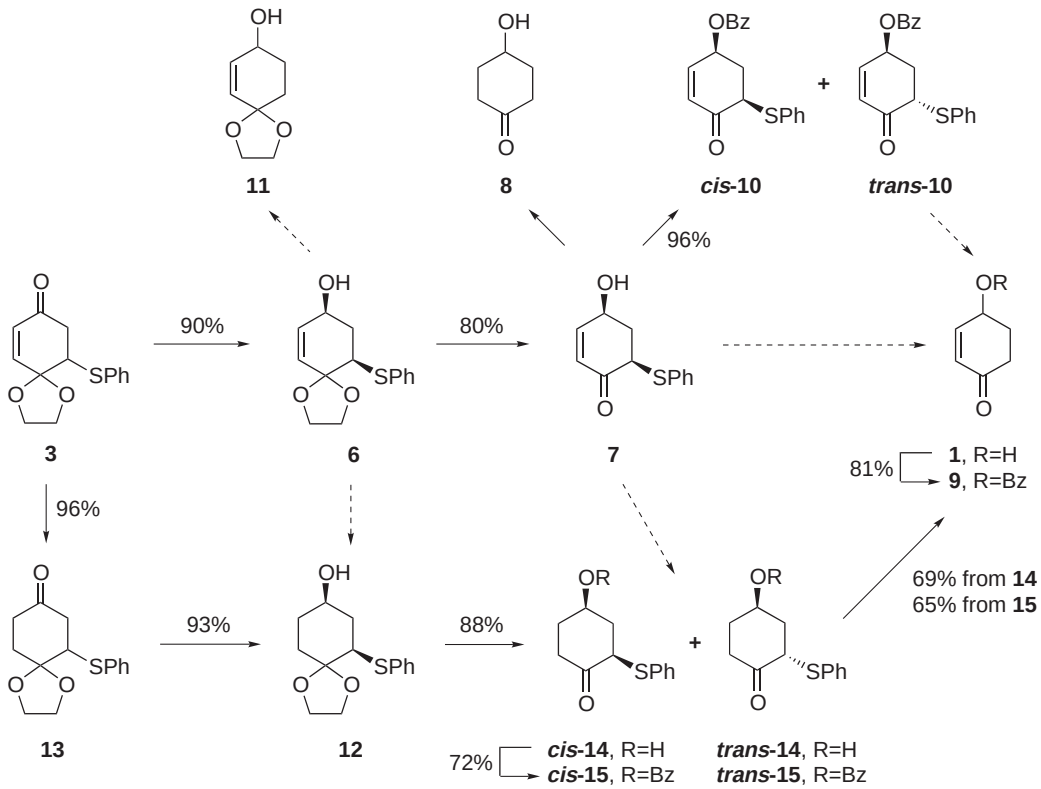


Scheme 2.

The efficiency of the asymmetric synthesis of **1** depended on the diastereoselectivity of the reduction of the carbonyl group of **4** or the ability to separate the diastereoisomeric allylic alcohols formed. Reduction of **4** with $NaBH_4$ in methanol at −78°C proceeded quantitatively to give a ca. 4:1 mixture of (1*R*)- and (1*S*)-**5**, from which the major diastereoisomer (1*R*)-**5** was isolated as a solid, $[\alpha]_D^{20}=+49.2$ (*c* 0.6, CH_2Cl_2), in 67% yield by repeated crystallisation of the mixture in ether/pentane. This crystallisation happens to be quite tedious and its efficiency can be improved if the reaction crude is previously purified by column chromatography on silica gel. The olefin proton signals of (1*R*)-**5** have shifted to δ 6.04 and 5.91 and the absorption at δ 66.6 in the ^{13}C NMR spectrum evidences the presence of the carbinol. The reduction of **4** with other hydride donors such as DIBALH, L-Selectride®, and $LiAl(^tBuO)_3H$ gave lower yields without a significant improvement of the stereoselectivity.

Removal of the ketal and retrieval of the chiral auxiliary was best performed by treatment of (1*R*)-**5** with montmorillonite K-10 in dichloromethane, according to the method described by Taylor et al.[18] Using these conditions, 91% of (1*R*,2*R*)-hydrobenzoin was recovered and the target enone (*R*)-**1**, $[\alpha]_D^{20}=+90.0$ (*c* 0.2, $CHCl_3$), was obtained in 87% yield and 97% ee determined by CGC. The configuration of **1** reveals the relative configuration of the isolated allylic alcohol (1*R*)-**5**. Hence, the conversion of **2** into (+)-(*R*)-**1** had been accomplished in 45% overall yield through a simple three-step sequence.

The synthetic pathway starting from **3** was then explored (Scheme 3). Provided that the sulphur substituent was able to exert a good asymmetric induction in the reduction of the



Scheme 3.

carbonyl group, another very simple approach could be set up to obtain both (*R*)- and (*S*)-**1**, starting from each enantiomer of **3**. In practice, the envisaged transformations were more complicated than expected and the synthetic route had to be modified accordingly.

The reduction of (±)-**3** with $NaBH_4$ gave exclusively the *cis* alcohol **6** in 90% yield. The stereochemistry of **6** was established after hydrolysis of the ketal with a DOWEX® resin, following a described methodology.[19] In both compounds **6** and **7** the α-sulphur proton (δ 3.43 in **6** and δ 3.80 in **7**) presents constant coupling values consistent with a pseudoaxial orientation (13.2 and 2.9 Hz for **6** and 13.2 and 5.1 Hz for **7**). The *cis* stereochemistry of the hydroxyketone **7** was deduced from the high NOE observed between the α-sulphur and the α-hydroxyl protons, which demonstrates their proximity, in agreement with a *cis*-1,3-diaxial relationship. Consequently, the phenylthio and the hydroxyl groups must occupy pseudoequatorial positions. Compound **7** epimerises slowly to its *trans* isomer.

Desulphuration of **7** with different reagents in a variety of conditions was unsuccessful. Raney nickel in ethanol without previous deactivation gave 4-hydroxycyclohexanone,[20] **8**, as the only identifiable product. Under milder conditions, the starting compound **7** was recovered, along with its *trans* epimer, traces of the saturated hydroxyketone **8**, the target compound **1** and other unidentified products. Other reductive systems such as catalytic hydrogenation, Bu_3SnH, Zn, Al/Hg and SmI_2 proved ineffective as well. Considering the problems associated with the isolation of **1** and that its benzoyl derivative **9** was already known,[7] we decided to protect the hydroxyl group of **7** as a benzoate and to test the desulphuration reactions on the benzoate. Treatment of **7** with benzoyl chloride in pyridine, not surprisingly, gave a mixture of *cis*- and *trans*-**10** in 96% yield. In the ^1H NMR spectrum of the more stable *trans* isomer, the α-sulphur proton H_5 absorbs at δ 4.02 as a false triplet with $J \approx 4.8$ Hz, in agreement with a pseudoequatorial disposition of this proton; therefore the phenylthio group must be in a pseudoaxial orientation. The ^1H NMR spectrum of the less stable epimer *cis*-**10** is very similar to that of *cis*-**7**, H_5 presenting a double doublet at δ 3.93 with J values of 11.3 and 4.8 Hz, in agreement with an axial orientation. This isomer epimerises too fast to be fully characterised, but this process would not be detrimental to the synthesis, since the configurationally unstable stereogenic α-carbonyl centre should disappear in the desulphuration step. Unfortunately, the conventional procedures to remove the sulphur residue were also ineffective for the benzoate **10**, and again either unchanged starting material or unidentified products were obtained. We also intended the desulphuration of the ketal **6** with the same variety of reagents. The expected hydroxyketal **11** could only be detected as a minor component in the reaction mixtures of reductions with Bu_3SnH/AIBN in toluene. All the other reducing agents let **6** unchanged.

In view of the difficulty of performing the desulphuration of these substrates, we decided to attempt an alternative strategy. If the hydrogenation of the carbon–carbon double bond of **6** or **7** could be efficiently performed, later on the double bond could be regenerated at the enantiotopic position by elimination of thiophenol, and the overall process would be equivalent to the impossible desulphuration. The hydrogenation of **6** was tried with Pd, $Pd(OH)_2$ and Pt as catalysts in MeOH or EtOH, at room temperature. In all cases the conversion was low and the desired hydroxyketal **12** was contaminated by other unidentified products. Under similar hydrogenation conditions, compound **7** remained unchanged, except for occasional epimerisation of the α-carbonyl centre.

At this point, the only remaining option was to perform the hydrogenation of the carbon–carbon double bond of **3** in the first place, followed by reduction of the ketone to alcohol, and then elimination of thiophenol. After different trials, the hydrogenation of **3** was effectively

performed using Pearlman's catalyst in methanol at room temperature. The new ketone **13** was isolated in 96% yield. Treatment of **13** with $NaBH_4$ gave the alcohol **12** in 93% yield, as the only reaction product. The α-sulphur proton H_3 of **12** presents *J* values of 12.4 and 4.4 Hz, according to a preference for the axial orientation and it shows a positive NOE with the α-hydroxyl proton H_1, proving the *cis* stereochemistry of **12**. As in the enone **3**, the phenylthio group directs the *anti* approach of the hydride. Ketal **12** was recovered unchanged after treatment with DOWEX® under the same conditions used to hydrolyse **6**, but heating **12** in a mixture of THF–H_2O with a trace of *p*-toluenesulphonic acid gave ketone **14** in 88% yield, as a 1:2.5 mixture of the *cis* and *trans* epimers. The *cis* stereochemistry of the minor isomer was determined by a positive NOE between the α-hydroxyl and the α-sulphur protons. ^{1}H NMR analysis of aliquot samples showed that *cis*-**14** is the only isomer present at the beginning of the hydrolysis, but it evolves to the more stable *trans*-**14**. The mixture **14** was oxidised with *m*-CPBA in CH_2Cl_2 at 0°C to the corresponding sulphoxides, which were submitted to pyrolysis by heating them in chloroform at reflux temperature without previous purification. After column chromatography, the hydroxyenone **1** was isolated in 69% yield. Complementarily, the mixture of *cis*- and *trans*-**14** was converted into the corresponding benzoates *cis*- and *trans*-**15** in 72% yield, which were oxidised to the sulphoxides with *m*-CPBA; subsequent pyrolysis furnished the benzoyloxyenone **9**[7] in 65% yield. Compound **9** was also obtained through benzoylation of **1** in 81% yield. The two epimers of **15** equilibrated rapidly and we could only isolate a pure analytical sample of the more stable *trans* isomer, the ^{1}H NMR spectrum of which resembles closely that of *trans*-**14**. The *cis* stereochemistry of the minor isomer was again confirmed by the positive NOE between H_1 and H_3. In spite of the problems associated with the isolation of **1**, the oxidation–pyrolysis step of **15** works similar to that of **14** and we were unable to improve the yield of the benzoylation of **14**; therefore, passing through the benzoyl derivative is not advantageous for the overall synthesis.

The new synthesis of (±)-**1** starting from the precursor (±)-**3** had been completed in only four steps and 54% overall yield. Then the same sequence was repeated starting with each enantiomer of **3**. From (−)-**3**, we arrived at (+)-**1**, $[\alpha]_D^{20} = +92.0$ (*c* 0.96, $CHCl_3$), corresponding to (*R*)-**1**, and from (+)-**3** we obtained (−)-**1**, $[\alpha]_D^{20} = -92.3$ (*c* 1.30, $CHCl_3$), according to (*S*)-**1**. The enantiomeric purity of both antipodes was determined by CGC to be 98%. This correlation establishes the configuration of (−)-**3**, (−)-**13** and (−)-**12** as (5*R*), (3*R*) and (1*R*,3*R*), and that of (+)-**3**, (+)-**13** and (+)-**12** as (5*S*), (3*S*) and (1*S*,3*S*), respectively.

In summary, we have developed two new, stereoselective, very short and simple synthetic approaches to (*R*)- and (*S*)-4-hydroxy-2-cyclohexenone from easily available chiral synthetic equivalents of *p*-benzoquinone. The access in multi-gram quantities to compound **1** in both enantiomeric forms encouraged us to use it in the syntheses of more complex molecules, which are currently investigated.

3. Experimental

Reaction mixtures were stirred magnetically. TLC was performed using 0.25 mm Alugram Sil plates, Machery–Nagel. Flash column chromatography was performed using SDS 230–400 mesh or Baker 40 μm silica gel. CGC were performed with an FS-Lipodex B 20 m×0.25 mm column. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de*

Barcelona on Bruker AC-250-WB or AM-400-WB instruments. Mass spectra were performed at *Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona (SAQ-UAB)* on an Hewlett–Packard 5985B instrument. Elemental analyses were performed at *Centre d'Investigació i Desenvolupament de Barcelona CSIC* or at *SAQ-UAB*.

*3.1. 4,4-[(1*R*,2*R*)-(1,2-Diphenylethylene)dioxy]-2-cyclohexenone*, ***4***

A solution of **2** (892 mg, 2.93 mmol) and $RhCl(PPh_3)_3$ (65 mg, 0.07 mmol) in toluene (36 mL) was stirred under a hydrogen atmosphere at room temperature. The evolution of the reaction mixture was followed by ^1H NMR analysis of aliquot samples. After 5 h, when the spectrum showed around 50% conversion, the hydrogen was evacuated and the solvent was removed under vacuum, giving 900 mg of crude material. Purification of this residue by flash chromatography (hexane/CH_2Cl_2, 3/7) gave 439 mg (1.44 mmol, 49%) of starting material and 343 mg (1.12 mmol, 38%) of **4**. Considering the recovered **2** the yield is 75%. **4**: white solid, mp 73–75°C (ether/pentane); IR (KBr): 3065, 3037, 2959, 2924, 2864, 1687, 1455, 1223, 1124, 1019 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.40–7.25 (m, 6H: $6H_{Ar}$), 7.25–7.10 (m, 4H: $4H_{Ar}$), 6.91 (d, $J_{3,2}=10.2$ Hz, 1H: H_3), 6.11 (d, $J_{2,3}=10.2$ Hz, 1H: H_2), 4.86 (d, $J_{1',2'}=8.4$ Hz, 1H: $H_{1'}/H_{2'}$), 4.79 (d, $J_{1',2'}=8.4$ Hz, 1H: $H_{1'}/H_{2'}$), 2.81 (ddd, $J=16.8$ Hz, $J'=9.3$ Hz, $J''=6.4$ Hz, 1H: H_5/H_6), 2.68 (dt, $J=16.8$ Hz, $J'=J''=5.5$ Hz, 1H: H_5/H_6), 2.60–2.40 (complex absorption, 2H: H_5, H_6); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 198.6, 146.7, 135.6, 135.4, 130.8, 128.7, 128.6, 126.6, 104.5, 85.8, 85.2, 35.2, 34.0; MS (CI/NH_3) (m/z) 324 (M^++18, 13), 307 (M^++1, 22), 214 (100), 200 (46), 197 (68). Anal. calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.23; H, 5.96. $[\alpha]_D^{20}=+48.0$ (c 1.0, $CHCl_3$).

*3.2. (1*R*)-4,4-[(1*R*,2*R*)-(1,2-Diphenylethylene)dioxy]-2-cyclohexenol, (1*R*)-****5***

To a solution of **4** (620 mg, 2.02 mmol) in 20 mL of MeOH at −78°C, $NaBH_4$ (48 mg, 1.27 mmol) was added in small portions and the mixture was stirred at the same temperature, following the reaction evolution by TLC (hexane/EtOAc, 2/1). After 5 h of reaction, the solvent was removed under vacuum, water (6 mL) was added, the solution was acidified with 3% HCl, and the aqueous phase extracted with CH_2Cl_2. Evaporation of the solvent gave 616 mg (2.00 mmol, 99%) of a ca. 4:1 mixture of (1*R*)- and (1*S*)-**5**. Repeated crystallisation from ether/pentane yielded 67% of pure (1*R*)-**5**. The crystallisation is more efficient if the reaction crude is previously purified by flash chromatography on silica gel (hexane/EtOAc, 2/1). (1*R*)-**5**: white solid, mp 117–119°C (ether/pentane); IR (KBr): 3255, 3037, 2952, 2875, 1602, 1455, 1384, 1258, 1159, 1110, 1012 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.35–7.25 (m, 6H: $6H_{Ar}$), 7.23–7.10 (m, 4H: $4H_{Ar}$), 6.04 (d, $J_{2,3}=10.0$ Hz, 1H: H_2/H_3), 5.91 (d, $J_{2,3}=10.0$ Hz, 1H: H_2/H_3), 4.78 (d, $J_{1',2'}=8.5$ Hz, 1H: $H_{1'}/H_{2'}$), 4.68 (d, $J_{1',2'}=8.5$ Hz, 1H: $H_{1'}/H_{2'}$), 4.28 (br s, 1H: H_1), 2.25 (m, 2H), 2.07 (m, 1H), 1.87 (m, 1H), 1.55 (m, 1H: OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 136.3, 136.2, 135.7, 129.5, 128.5, 128.40, 128.36, 126.83, 126.6, 105.72, 85.5, 85.1, 66.6, 32.8, 31.0; MS (CI/NH_3) (m/z) 309 (M^++1, 22), 214 (100), 202 (31). Anal. calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.98; H, 6.40. $[\alpha]_D^{20}=+49.2$ (c 0.6, CH_2Cl_2). (1*S*)-**5**: ^1H NMR (250 MHz, $CDCl_3$, observable signals): δ 6.06 (d, $J_{2,3}=10.0$ Hz, 1H: H_2/H_3), 5.96 (d, $J_{2,3}=10.0$ Hz, 1H: H_2/H_3), 4.81 (d, $J_{1',2'}=8.5$ Hz, 1H: $H_{1'}/H_{2'}$), 4.74 (d, $J_{1',2'}=8.5$ Hz, 1H: $H_{1'}/H_{2'}$), 2.35 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$, observable signals): δ 136.43, 136.39, 134.4, 130.4, 126.76, 105.67, 65.3, 31.7, 30.0.

3.3. Conversion of (1R)-**5** into (R)-4-hydroxy-2-cyclohexenone, (R)-**1**

A mixture of (1*R*)-**5** (92 mg, 0.30 mmol) and montmorillonite K-10 (420 mg) in CH_2Cl_2 (8 mL) was stirred at room temperature for 29 h. The montmorillonite was filtered off and the solvent was removed under vacuum. Flash chromatography (hexane/EtOAc, 1/1) of the residue (115 mg) afforded (1*R*,2*R*)-hydrobenzoin (58 mg, 0.27 mmol, 91%) and (+)-**1** (58 mg, 0.27 mmol, 87%), $[\alpha]_D^{20} = +90.0$ (*c* 0.2, $CHCl_3$).

3.4. cis-4,4-Ethylenedioxy-5-phenylthio-2-cyclohexenol, **6**

To a stirred solution of 4,4-ethylenedioxy-5-phenylthio-2-cyclohexenone, **3**, (765 mg, 2.9 mmol) in a mixture of CH_2Cl_2 (8 mL) and MeOH (8 mL) at 0°C was added $NaBH_4$ (31 mg, 0.82 mmol) in small portions. The mixture was stirred at 0°C for 1 h and then at room temperature until TLC (CH_2Cl_2/ether, 9/1) showed complete conversion of **3**. The solvent was removed under vacuum, water (10 mL) was added, the solution was acidified with 4% HCl and then extracted with CH_2Cl_2 (4×10 mL). The organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated, giving 730 mg of an oily residue. This oil was purified by flash chromatography (CH_2Cl_2/ether, 9/1), yielding 680 mg (2.6 mmol, 90%) of **6**: white solid, mp 62–64°C (CH_2Cl_2/pentane); IR (KBr): 3395, 3055, 2945, 2882, 1680, 1581, 1476, 1441, 1230, 1152, 1061, 1005 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.30 (m, 3H), 5.91 (dt, $J = 10.2$ Hz, $J_{2,1} \approx J_{2,6} \approx 1.8$ Hz, 1H: H_2), 5.66 (dd, $J_{3,2} = 10.2$ Hz, $J_{3,1} = 2.2$ Hz, 1H: H_3), 4.15 (m, 5H: OCH_2CH_2O, H_1), 3.43 (dd, $^{trans}J_{5,6} = 13.2$ Hz, $^{cis}J_{5,6} = 2.9$ Hz, 1H: H_5), 2.46 (m, 1H: H_6), 2.00 (td, $^{trans}J_{6,5} \approx J_{6,6} \approx 12.8$ Hz, $J_{6,1} = 9.5$ Hz, 1H: H_6), 1.80 (br d, $J = 7.3$ Hz, 1H: OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 135.3, 134.3, 131.6, 128.8, 128.7, 126.8, 105.7, 67.0, 66.2, 65.9, 52.4, 38.7; MS (*m*/*z*) 264 (M^+, 1), 128 (100). Anal. calcd for $C_{14}H_{16}O_3S$: C, 63.62; H, 6.11; S, 12.11. Found: C, 63.55; H, 6.06; S, 12.01.

3.5. cis-6-Phenylthio-4-hydroxy-2-cyclohexenone, **7**

To a stirred suspension of **6** (135 mg, 0.51 mmol) in water (7 mL) and EtOAc (200 μL) were added 150 mg of resin DOWEX®-50WX8-400 (previously washed with 2% HCl and then water) and the mixture was stirred at room temperature for 2.5 h. The resin was filtered off and washed with EtOAc (4×4 mL). The organic phase was separated, dried with anhydrous $MgSO_4$ and the solvent evaporated under vacuum. The residue (108 mg) was purified by flash chromatography (CH_2Cl_2/ether, 9/1), yielding 90 mg (0.41 mmol, 80%) of **7**: oil; IR (film): 3423, 2931, 2957, 2868, 1743, 1680, 1588, 1476, 1441, 1378, 1251, 1223, 1061 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.35 (m, 2H), 7.20 (m, 3H), 6.84 (br d, $J_{3,2} = 10.2$ Hz, 1H: H_3), 5.92 (dd, $J_{2,3} = 10.2$ Hz, $J_{2,4} = 2.2$ Hz, 1H: H_2), 4.48 (m, 1H: H_4), 3.80 (dd, $^{trans}J_{5,6} = 13.2$ Hz, $^{cis}J_{5,6} = 5.1$ Hz, 1H: H_6), 2.47 (m, 1H: H_5), 1.98 (m, 1H: H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 195.1, 153.2, 132.8, 132.5, 128.9, 127.7, 127.6, 66.2, 51.9, 39.1; MS (*m*/*z*) 220 (M^+, 27), 202 ($M^+ - H_2O$, 6), 137 (30), 136 (48), 135 (62), 110 (100), 84 (89), 55 (42). Anal. calcd for $C_{12}H_{12}O_2S$: C, 65.44; H, 5.50; S, 14.53. Found: C, 65.40; H, 5.56; S, 14.53. Compound **7** epimerises slowly to the *trans* isomer: ^1H NMR (250 MHz, $CDCl_3$, significant signals): δ 6.82 (m, H_3), 5.91 (br d, $J = 10.2$ Hz, H_2), 4.78 (m, H_4), 3.89 (br t, $J \approx 4.8$ Hz, H_6).

3.6. Reaction of **7** with Raney nickel

Compound **7** (20 mg, 0.09 mmol) was added to a suspension of aqueous Raney nickel (W-2, Aldrich) in ethanol (1.5 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite, the filtrate was dried with anhydrous Mg_2SO_4 and the solvent was evaporated under vacuum. ^{1}H NMR analysis of the oily residue (16 mg) showed the presence of 4-hydroxycyclohexanone,[20] **8**, as the major compound.

3.7. 4-Oxo-5-phenylthiocyclohex-2-enyl benzoate, ***10***

To a stirred solution of **7** (235 mg, 1.10 mmol) in pyridine (6 mL) under nitrogen at 0°C, benzoyl chloride (250 μL, 2.14 mmol) was added and the mixture was stirred for 75 min. Then CH_2Cl_2 (10 mL) and water (10 mL) were added and stirring was continued for 30 min. The organic layer was separated, washed with water (2×10 mL), dried over anhydrous $MgSO_4$ and the solvent removed. The residue (400 mg) was purified by flash chromatography (hexane/EtOAc, 9/1), giving 139 mg (0.43 mmol, 40%) of *trans*-4-oxo-5-phenylthiocyclohex-2-enyl benzoate, *trans*-**10**, and 193 mg (0.59 mmol, 56%) of *cis*-**10**. The last isomer epimerised on standing and therefore it could not be fully characterised. *trans*-**10**: yellowish solid, mp 93–96°C (hexane/EtOAc); IR (KBr): 3058, 2931, 1792, 1715, 1673, 1609, 1588, 1482, 1448, 1314, 1272, 1240, 1216, 1110, 1068, 1026 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.02 (d, $J=7.3$ Hz, 2H), 7.50 (m, 5H), 7.25 (m, 3H), 6.91 (br d, $J_{2,3}=9.5$ Hz, 1H: H_2), 6.09 (d, $J_{3,2}=9.5$ Hz, 1H: H_3), 6.05 (m, 1H: H_1), 4.02 (t, $^{trans}J_{5,6}\approx{}^{cis}J_{5,6}\approx4.8$ Hz, 1H: H_5), 2.59 (m, 2H: $2H_6$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.1, 165.5, 146.4, 133.7, 133.4, 129.7, 129.3, 129.1, 128.5, 128.4, 66.6, 50.6, 34.6; MS (m/z) 218 (M^+–PhCHO, 5), 202 (M^+–$PhCO_2H$, 13), 122 (67), 105 (100), 77 (72), 51 (39). Anal. calcd for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.98; S, 9.87. Found: C, 70.26; H, 4.96; S, 9.67. *cis*-**10**: yellowish solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.07 (m, 4H), 7.56–7.25 (complex absorption, 6H), 7.02 (d, $J_{2,3}=8.9$ Hz, 1H: H_2), 6.15 (d, $J_{3,2}=8.9$ Hz, 1H: H_3), 5.83 (m, 1H: H_1), 3.93 (dd, $^{trans}J_{5,6}=11.3$ Hz, $^{cis}J_{5,6}=4.8$ Hz, 1H: H_5), 2.70 (dt, $J_{6,6}=12.0$ Hz, $J_{6,5}\approx J_{6,1}\approx4.3$ Hz, 1H: H_6); 2.31 (dt, $J_{6,6}=12.0$ Hz, $J_{6,5}\approx J_{6,1}\approx8.9$ Hz, 1H: H_6); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.6, 171.5, 146.7, 133.5, 133.3–127.8 (several signals), 67.6, 51.6, 35.6; MS (m/z) 218 (M^+–PhCHO, 1), 202 (M^+–$PhCO_2H$, 24), 122 (75), 105 (100), 77 (75), 51 (39).

3.8. 4,4-Ethylenedioxy-3-phenylthiocyclohexanone, ***13***

Palladium hydroxide on carbon (20%, 756 mg) was added to a solution of **3** (5.16 g, 19.7 mmol) in methanol (250 mL) and the mixture was stirred under a hydrogen atmosphere at room temperature for 15 h. After this time, ^{1}H NMR analysis of an aliquot sample still showed a residual amount of starting material. Therefore, 100 mg of catalyst was added and the mixture stirred again under hydrogen for 2 h. Then the hydrogen was evacuated and the mixture was filtered through Celite. Evaporation of the solvent under vacuum furnished 5.09 g of an oily residue. Purification of this material by flash chromatography (CH_2Cl_2/ether, 9/1) gave 5.00 g (18.9 mmol, 96%) of **13**: white solid, mp 47–50°C (ether–pentane); IR (KBr): 3058, 2966, 2896, 1722, 1581, 1476, 1441, 1265, 1202, 1145, 1117, 1033 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40 (m, 2H), 7.20 (m, 3H), 4.08 (m, 4H: OCH_2CH_2O), 3.53 (dd, $^{trans}J_{3,2}=9.9$ Hz, $^{cis}J_{3,2}=5.1$ Hz, 1H: H_3), 2.78–2.45 (complex absorption, 3H), 2.38 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 207.4, 133.9, 132.4, 128.9, 127.4, 108.1, 65.8, 53.8, 45.5, 38.0, 32.4; MS

(m/z) 264 (M^+, 15), 126 (35), 99 (100). Anal. calcd for $C_{14}H_{16}O_3S$: C, 63.62; H, 6.11; S, 12.11. Found: C, 63.64; H, 6.10; S, 11.95. (*R*)-**13**: oil, $[\alpha]_D^{20}=-48.7$ (*c* 5.3, $CHCl_3$). (*S*)-**13**: oil, $[\alpha]_D^{20}=+44.7$ (*c* 6.4, $CHCl_3$).

3.9. cis-*4,4-Ethylenedioxy-3-phenylthiocyclohexanol*, ***12***

To a stirred solution of **13** (506 mg, 1.9 mmol) in a mixture of CH_2Cl_2 (6 mL) and MeOH (6 mL) at 0°C was added $NaBH_4$ (22 mg, 0.58 mmol) in small portions and the mixture was stirred at 0°C for 1 h and then at room temperature until total conversion of **13** (TLC, CH_2Cl_2/ether, 9/1). The solvent was removed under vacuum, water (8 mL) was added, the solution was acidified with 4% HCl and then extracted with CH_2Cl_2. The organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated, giving 600 mg of an oily residue. This oil was purified by flash chromatography (CH_2Cl_2/ether, 9/1), yielding 473 mg (1.78 mmol, 93%) of **12**: white solid, mp 88–91°C (EtOAc/pentane); IR (KBr): 3381 (br), 3100, 2959, 2889, 1581, 1476, 1441, 1363, 1328, 1265, 1209, 1166, 1131, 1082, 1054 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.37 (m, 2H), 7.14 (m, 3H), 3.98 (m, 4H: OCH_2CH_2O), 3.59 (m, 1H: H_1), 3.18 (dd, $^{trans}J_{3,2}=12.4$ Hz, $^{cis}J_{3,2}=4.4$ Hz, 1H: H_3), 2.17 (m, 1H: H_2), 1.82 (m, 3H: H_2, H_5, H_6), 1.47 (m, 3H: H_5, H_6, OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 135.8, 131.5, 128.7, 126.6, 108.6, 69.1, 65.6, 53.6, 40.8, 32.6, 32.1; MS (m/z) 266 (M^+, 14), 99 (100). Anal. calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.82; S, 12.02. Found: C, 63.06; H, 6.93; S, 11.97. (1*R*,3*R*)-**12**: oil, $[\alpha]_D^{20}=-3.4$ (*c* 4.6, $CHCl_3$). (1*S*,3*S*)-**12**: oil, $[\alpha]_D^{20}=+2.9$ (*c* 5.6, $CHCl_3$).

3.10. *2-Phenylthio-4-hydroxycyclohexanone*, ***14***

A stirred mixture of **12** (879 mg, 3.3 mmol), *p*-TsOH (135 mg, 0.71 mmol), water (118 mL) and THF (9 mL) was heated at 80°C for 22 h. Then it was neutralised with saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over anhydrous $MgSO_4$ and evaporation of the solvent furnished 650 mg of an oily residue. Purification of this material by flash chromatography (CH_2Cl_2/ether, 9/1) gave 640 mg (2.9 mmol, 88%) of a 1:2.5 mixture of *cis*- and *trans*-**14**, respectively: IR (KBr): 3338, 2931, 1715, 1588, 1469, 1434, 1258, 1202, 1068 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.41 (m), 7.22 (m), 4.32 (m, H_4 of *trans*-**14**), 4.16 (m, H_4 of *cis*-**14**), 4.10 (ddd, $J_{2,3}=7.6$ Hz, $J_{2,3}=5.1$ Hz, $J_{2,6}=1.4$ Hz, H_2 of *trans*-**14**), 3.83 (ddd, $J_{2,3}=7.6$ Hz, $J_{2,3}=5.8$ Hz, $J=1.5$ Hz, H_2 of *cis*-**14**), 2.96 (ddd, $J_{6,6}=14.6$ Hz, $J_{6,5}=7.3$ Hz, $J_{6,5}=5.1$ Hz, $1H_6$ of *cis*-**14**), 2.79 (ddd, $J_{6,6}=14.4$ Hz, $J_{6,5}=8.0$ Hz, $J_{6,5}=5.8$ Hz, $1H_6$ of *trans*-**14**), 2.60 (dddd, $J_{6,6}=14.4$ Hz, $J_{6,5}=8.5$ Hz, $J_{6,5}=5.6$ Hz, $J_{6,2}=1.4$ Hz, $1H_6$ of *trans*-**14**), 2.45 (dddd, $J_{3,3}=13.9$ Hz, $J_{3,2}=5.8$ Hz, $J_{3,4}=3.6$ Hz, $J_{3,5}=1.5$ Hz, $1H_3$ of *cis*-**14**), 2.40–1.90 (complex absorption), 1.72 (br d, $J=2.9$ Hz, 1H: OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 206.5, 206.1, 133.7, 133.3, 132.1, 131.7, 131.3, 128.9, 128.6, 127.5, 127.3, 66.5, 64.8, 53.6, 52.8, 40.8, 40.7, 35.2, 34.1, 34.0; MS (m/z) 222 (M^+, 26), 218 (28), 110 (100), 109 (36). Anal. calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35; S, 14.42. Found: C, 64.41; H, 6.18; S, 13.91.

3.11. *4-Oxo-3-phenylthiocyclohexyl benzoate*, ***15***

To a stirred solution of **14** (655 mg, 2.9 mmol) and pyridine (315 μL, 3.9 mmol) in CH_2Cl_2 (5 mL) under nitrogen at 0°C, benzoyl chloride (690 μL, 5.9 mmol) was added and the mixture was stirred at 0°C for 1.5 h and at room temperature for 30 min. Then CH_2Cl_2 (4 mL) and water

(8 mL) were added and stirring was continued for 30 min. The organic layer was separated, washed with water (3×10 mL), dried over anhydrous $MgSO_4$ and the solvent removed. The residue (1.16 g) was purified by flash chromatography (hexane/EtOAc, 9/1), giving 700 mg (2.1 mmol, 72%) of a 2:1 mixture of *trans*- and *cis*-4-oxo-3-phenylthiocyclohexyl benzoate, *trans*- and *cis*-**15**. The two isomers equilibrate rapidly. An analytical sample of *trans*-**15** could be obtained by crystallisation (ether/pentane) of an enriched fraction: mp 81–85°C (ether/pentane); IR (KBr): 3058, 2966, 2945, 2910, 1708, 1602, 1581, 1441, 1321, 1279, 1202, 1173, 1117, 1068, 1026 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.98 (d, $J=8.1$ Hz, 2H), 7.55 (t, $J=5.1$ Hz, 1H), 7.25 (m, 4H), 7.20 (m, 3H), 5.51 (m, 1H: H_1), 4.07 (m, 1H: H_3), 2.86 (m, 1H), 2.54 (m, 2H), 2.30 (m, 1H), 2.18 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 205.4, 165.7, 134.0, 133.1, 132.2, 129.8, 129.4, 129.0, 128.4, 127.8, 68.1, 53.3, 37.2, 34.1, 30.9; MS (*m*/*z*) 326 (M^+, 8), 204 (M^+–$PhCO_2H$, 68), 105 (100), 77 (48). Anal. calcd for $C_{19}H_{18}O_3S$: C, 69.92; H, 5.56; S, 9.80. Found: C, 70.02; H, 5.66; S, 9.54. *cis*-**15**: ^1H NMR (250 MHz, $CDCl_3$): δ 8.10 (d, $J=8.1$ Hz, 2H), 7.60–7.18 (complex absorption, 8H), 5.37 (m, 1H: H_1), 3.79 (m, 1H: H_3), 3.14 (m, 1H); 2.56 (m, 1H), 2.33 (m, 2H), 2.15 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 205.1, 165.4, 133.2–127.7 (several signals), 68.2, 53.0, 37.5, 35.5, 30.9.

*3.12. Conversion of **14** into 4-hydroxy-2-cyclohexenone, **1***

To a solution of **14** (202 mg, 0.91 mmol) in CH_2Cl_2 (6 mL) at 0°C was added 54% *m*-CPBA (289 mg, 0.89 mmol) and the mixture was stirred at 0°C for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2 (5×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed under vacuum to give 255 mg of a residue. This residue was solved in $CHCl_3$ (7 mL) and heated at reflux temperature for 25 h. During this time, the reaction evolution was monitored by TLC (hexane/EtOAc, 7/3). Removal of the solvent under vacuum furnished 209 mg of a residue. Purification of this material by flash chromatography (hexane/EtOAc, 7/3) gave 71 mg (0.63 mmol, 69%) of **1**.[3–6] The same procedure applied to a mixture of *trans*- and *cis*-**14** prepared from (1*R*,3*R*)-**12** gave (*R*)-**1**,[11,12,14] $[\alpha]_D^{20}=+94.7$ (*c* 1.1, $CHCl_3$), and from (1*S*,3*S*)-**12** gave (*S*)-**1**,[11–13] $[\alpha]_D^{20}=-92.3$ (*c* 1.3, $CHCl_3$).

*3.13. Conversion of **15** into 4-oxocyclohexen-2-yl benzoate, **9***

To a solution of **15** (564 mg, 1.7 mmol) in $CHCl_3$ (5 mL) at 0°C was added 41% *m*-CPBA (716 mg, 1.7 mmol) and the mixture was stirred at 0°C until TLC analysis (hexane/ether, 2/1) showed total conversion of **15**. The reaction mixture was washed with saturated aqueous $NaHCO_3$, the aqueous phase was extracted with $CHCl_3$ (5×5 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed, giving 841 mg of a residue, which was solved in $CHCl_3$ (10 mL) and heated at reflux temperature for 19 h. Removal of the solvent under vacuum furnished 796 mg of crude material. Purification by flash chromatography (hexane/EtOAc, 7/3) gave 241 mg (1.1 mmol, 65%) of **9**.[7]

*3.14. Benzoylation of **1***

To a stirred solution of **1** (278 mg, 1.29 mmol) in pyridine (500 μL) and CH_2Cl_2 (800 μL) at 0°C, benzoyl chloride (270 μL, 2.32 mmol) was added and the mixture was stirred at 0°C for 30

min and at room temperature for 20 h. Then CH_2Cl_2 (5 mL) and water (5 mL) were added and stirring was continued for 30 min. The organic layer was separated, washed with water (2×5 mL), dried over anhydrous $MgSO_4$ and the solvent removed. Purification of the residue (481 mg) by flash chromatography (hexane/ether, 9/1) gave 291 mg (1.35 mmol, 81%) of **9**.[7]

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