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Short and Efficient Synthesis of (*R*)-4-Hydroxy-4-Methyl Cyclohexenone

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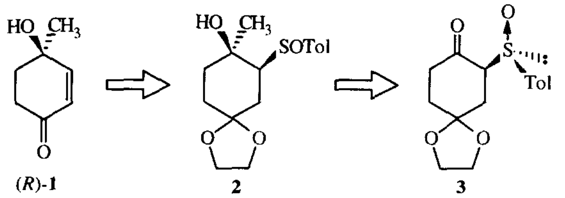
Abstract. The two steps asymmetric synthesis of the enantiomerically pure (*R*)-4-hydroxy-4-methylcyclohex-2-en-1-one is reported in a 70% overall yield. The highly stereoselective addition of $AlMe_3/ZnBr_2$ to [2*S*,(S)*R*]-4,4-ethylenedioxy-2-*p*-tolylsulfinylcyclohexanone is the key step in this synthesis.

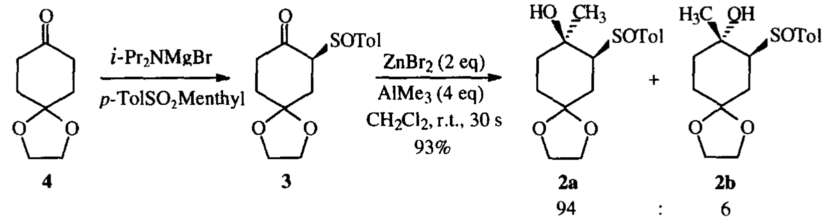
4-Hydroxy-4-methylcyclohex-2-en-1-one **1** is a volatile component of oils of some plants.[1] The racemic compound is commonly used as a component of perfumes, soaps and foods.[2] The asymmetric synthesis of the (*S*)-enantiomer has been reported by Delay and Ohloff[3] starting from limonene through a sequence involving five steps and an overall yield lower than 20%. The good results obtained by us in the addition of organoaluminium reagents to enantiomerically pure 2-*p*-tolylsulfinylcycloalkanones[4] giving rise to tertiary alkyl carbinols with excellent optical and chemical yields, prompted us to undertake the synthesis of the title compound applying this methodology. In this letter we report a short and very efficient synthesis of the (*R*)-enantiomer of **1** using the addition of $AlMe_3$ in the presence of $ZnBr_2$ to a cyclic β-ketosulfoxide as the key step. (Moreover, we show that the absolute configuration previously assigned to the (*S*)-enantiomer[3] was wrong).

The retrosynthetic scheme shown below for compound **1** suggested the use of enantiomerically pure (2*S*,(S)*R*)-4,4-ethylenedioxy-2-*p*-tolylsulfinylcyclohexanone **3** as starting material, through the intermediacy of hydroxysulfoxide **2**.



Scheme 1

Compound **3** was easily accesible following the method previously described by us[5] based on the reaction between the enolate resulting in the treatment of the commercially available 1,4-cyclohexanedione ethylene monoketal **4** with *i*-Pr_2NMgBr and (*S*)-(-)-menthyl *p*-toluenesulfinate. The (2*S*,(S)*R*)-ketosulfoxide **3** was isolated diastereoisomerically pure in a 70% yield. Compound **3** was treated with $ZnBr_2$ (2 eq.) in a CH_2Cl_2 solution and the resulting suspension was added to a solution of $AlMe_3$ (4 eq.) in CH_2Cl_2. Once the addition was finished, the mixture was hydrolyzed to give a 94:6 mixture of diastereomeric hydroxysulfoxides **2a** and **2b**[6] (93% yield) which could be easily separated by flash chromatography. It was possible to isolate **2a** in a 85% yield. The control of the reaction time was essential to obtain the addition products **2** in high yield.[7]



Scheme 2

The absolute configuration of the hydroxysulfoxides **2a** and **2b** was deduced from their ^1H-NMR data, assuming that the configuration at both C-2 and sulfur stereogenic centers was not affected by the experimental conditions used in the methyl addition. The presumably most stable conformations of the two possible carbinols resulting in the addition of $AlMe_3$ to the precursor (2*S*,(S)*R*)-**3** are depicted in Figure 1. Compound exhibiting the OH group in axial position can be intramolecularly associated by hydrogen bonding with the sulfinyl oxygen, whereas this is not possible for the diastereomer with the OH in equatorial position due to the presence in the later of a highly destabilizing $(Tol/Me)_{1,3\text{-parallel}}$ interaction. The multiplicity (dd) and coupling constants of H-2a (J=13.1 and 3.6 Hz for **2a** and J=13.3 and 4.0 Hz for **2b**) are consistent with the equatorial arrangement of the sulfinyl group in both hydroxysulfoxides. The hydroxylic proton appears as a doublet in **2a** (δ 4.09 ppm, $^4J_{OH,H\text{-}6a}$=1.9 Hz) and as a broad singlet (δ 2.90 ppm) in **2b**. The long range coupling constant observed between the OH and H-6a requires a W planar arrangement of the coupled protons. This situation, which is only possible for the axial arrangement of the hydroxy group, allowed us to assign the configuration (1*R*,2*S*,(S)*R*) for compound **2a** as indicated in fig. 1. This assignment was the expected considering the stereochemical model already proposed by us from the alkylation studies carried out on the simplest 2-*p*-tolylsulfinyl cyclohexanone.[4,8] The absolute configuration of the minor epimer **2b** must be (1*S*,2*S*,(S)*R*).

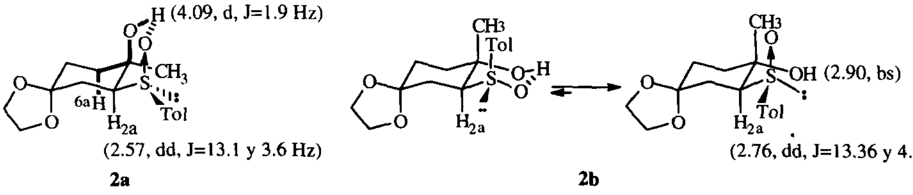
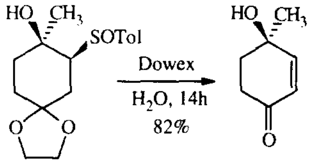


Figure 1

The use of classical methods to hydrolyze the ketal group (*p*-TsOH, PPTS, oxalic acid, silica gel/H_2SO_4) afforded poor results, either recovering the starting material or obtaining products resulting from the evolution of the enone, like *p*-cresol. Only the treatment of **2a** with a Dowex resin[9] in water gave the desired reaction. In these conditions, compound **1**, resulting from the hydrolysis of the ketal group and instantaneous pyrolytic elimination of sulfenic acid was isolated in a 82% yield. According with the configurational assignment established above and assuming that the hydrolytic conditions used must not affect the configuration of the tertiary carbinol, the absolute configuration of **1** was assigned as (*R*).



2a (*R*)-**1**

$[\alpha]_D$= +43° (0.82% in ethanol)

$[\alpha]_{D}\text{lit.}^{3}$ = +40° (1% in ethanol for (*S*)-enantiomer)

Scheme 3

The comparison of the specific rotations of the enantiomer (*R*)-**1** synthesized by us ($[\alpha]_D$=+43°, EtOH, c=0.82) with that described in the literature for (*S*)-**1** ($[\alpha]_D$=+40°, EtOH, c=1) surprisingly showed that both of them had the same sign, which indicated that one of the two assignments was wrong.

In order to firmly stablish the stereochemistry of **1** we made a single crystal X-ray structure determination of **2a**, making use of Kα Cu radiation in order to establish its absolute configuration. [10] The ORTEP diagram obtained is shown in Fig. 2. Taking into account that the absolute configuration of the sulfoxide was (*R*), the hydroxylic carbon presents the (*R*) absolute configuration. As can be seen in figure 2, the preferred conformation around the C-S bond is similar to that depicted for compound **2a** in Fig.1 As the hydrolysis of the ketal group and the subsequent pyrolysis of the sulfinyl group has not any influence on the configuration of the hydroxylic carbon, we can conclude that the enantiomer obtained by us showing a $[\alpha]_D$=+43° is (*R*)-**1**, and that the (*S*) configuration assigned in the literature[3] to the compound having an $[\alpha]_D$=+40° was wrong.

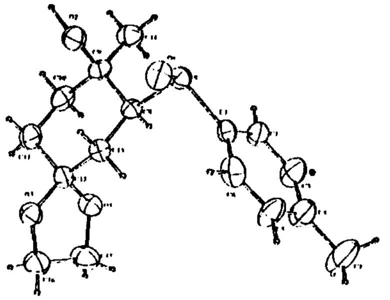


Figure 2.- ORTEP plot of (1*R*,2*S*,(S)*R*)-**2a**

In conclusion we have carried out the synthesis of the natural (*R*) enantiomer of 4-hydroxy-4-methylcyclohexenone in two steps and 70% overall yield from a readily available optically active cyclic β-ketosulfoxide. The key step allowing the creation of the tertiary carbinol group was the highly stereoselective addition of $AlMe_3$ to cyclic β-ketosulfoxides. Moreover we have brought ligth on the absolute configuration of this compound that had been mistakenly assigned in the literature.

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References and Notes

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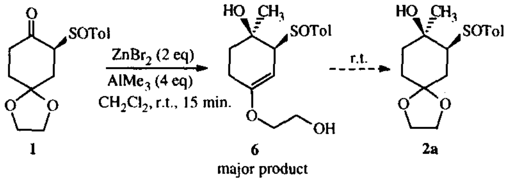
6. The new compounds gave satisfactory analysis and spectral data. As representative we indicate the rotatory power and NMR data. Compound **2a**: $[\alpha]_D^{20}$= +211° (c=0.5, chloroform); m.p. 100°-102°C (ether); ^{1}**H-NMR** ($CDCl_3$, 200MHz): 7.33 (AA'BB' system, 4H, Tol), 4.09 (d, 1H, J=1.9 Hz, OH), 3.90-3.50 [m, 4H, $O(CH_2)_2O$], 2.57 (dd, 1H, J=13.1 and 3.6 Hz, CHSO), 2.40 (s, 3H, CH_3), 2.40-1.20 (m, 5H), 1.72 (s, 3H, CH_3), 1.0 (dc, 1H, J=12.8 and 2.7 Hz, H-3eq); ^{13}**C-NMR** ($CDCl_3$, 50MHz): 141.1, 136.2, 129.8 (2C), 123.9 (2C), 108.8, 70.8, 64.7, 64.1, 63.7, 37.5, 29.6, 28.7, 25.8, 21.2. Compound **2b**: $[\alpha]_D^{20}$= +126° (c=0.48, chloroform); m.p. 177°-178°C (acetone-hexane); ^{1}**H-NMR** ($CDCl_3$): 7.45 y 7.29 (AA'BB' system, 4H, Tol), 4.0-3.50 [m, 4H, $O(CH_2)_2O$], 2.90 (bs, 1H, OH), 2.76 (dd, 1H, J=13.3 and 4.0 Hz, CHSO), 2.40 (s, 3H, CH_3), 1.92 (t, 1H, J=13.3 Hz, H-3ax), 1.92-1.40 (m, 5H), 1.59 (s, 3H, CH_3); ^{13}**C-NMR** ($CDCl_3$, 50MHz): 140.6, 139.3, 129.7 (2C), 124.2 (2C), 108.6, 72.1, 71.1, 64.5, 64.0, 39.0, 32.3, 27.4, 22.6, 21.3.
7. Reaction times longer than 30 seconds gave rise to compound **6** (Scheme 4), resulting from the opening of the ethylenedioxy group after the addition of the methyl group to the ketone. This compound, which was the major reaction product when the reaction mixture was allowed to stand more than 15 minutes, evolved on standing at room temperature into **2a**.



Scheme 4

8. The comparison of the spectroscopic data for **2a** with those of the related compound previously described by us in reference 4b showed to be very similar, which is in accordance with the assignment proposed.
9. *Experimental procedure to transform 2a into 1*: To a suspension of 112 mg (0.36 mmol) of **2a** in 5 ml of water 267 mg of washed Dowex were added. The mixture was stirred at room temperature for 24 h. The resin was filtered off and washed with EtOAc. After separation, the organic layer was dried over $MgSO_4$ and the solvent was evaporated under *vacuo*. Flash chromatography of the residue (EtOAc/hexane 1:1) gave pure **1** in 82% yield.
10. Crystals of 2a belong to the orthorhombic space group P212121, and accurate lattice constants of a=10.730(3), b=16.890(5) and c=9.020(3) Å. All unique diffraction maxima [θ min/max (deg) 3/52] were collected using 2θ:θ scans and CuKα radiation at -100°C. Of the 1084 reflections measured, 944 (87%) were judged observed [I>3σ(I)] and used in subsequent calculations. The structure, solved by the heavy atom method using Enraf-Nonius SDP/VAX package was refined to R=0.036. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary materials) are available on request from the Cambridge Crystallographic Data Center.

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