



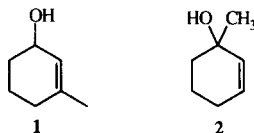
Asymmetric Synthesis of Cyclohex-2-enols: The examples of Seudenol and Analogues

Ana B. Bueno, M. Carmen Carreño,* José L. García Ruano* and Chafiq Hamdouchi

Departamento de Química Orgánica (C-I); Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

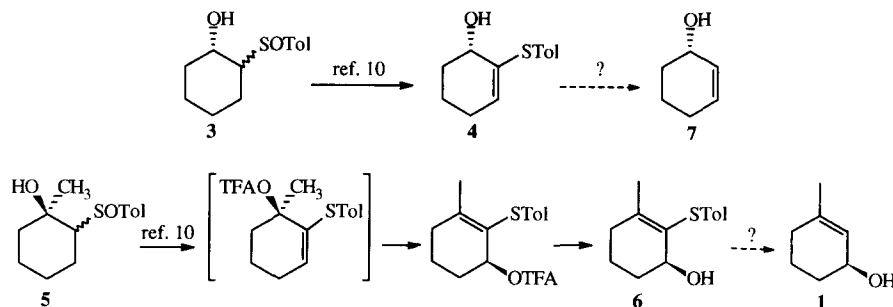
Abstract. An efficient synthesis of enantiomerically pure cyclohex-2-enols from the reaction of 2-*p*-tolylsulfinyl cyclohexanols with (CF₃CO)₂O/Py and subsequent hydrogenolysis of the C-S bond with Li/Naphthalene, is reported. This strategy has been applied to the asymmetric synthesis of seudenol and 1-methylcyclohex-2-en-1-ol. New data on the rearrangement of the trifluoroacetate group when 2-*p*-tolylsulfinyl 1-methylcyclohexenols are treated under the Pummerer reaction conditions are also reported.

Enantiomerically pure 2-cycloalkenols are not easy to obtain by conventional chemical methods.¹ Direct enzymatic resolution of 2-cyclopentanol and 2-cyclohexanol² occurred with low enantioselectivity suggesting the use of indirect enzymatic methods, such as the enantioselective transesterification of 2-halo and 2-phenylthio cycloalkanols with lipases en route to the enantiomerically pure derivatives. This solution suffered from lengthy sequences.³ Therefore, the search for a general method to obtain enantiomerically pure cyclohexenols would be particularly valuable and would allow an access to naturally occurring derivatives such as seudenol (**1**) and its isomer, 1-methylcyclohex-2-en-1-ol (**2**) which are known to be aggregation pheromones of the female Douglas-fir beetles.⁴ Seudenol (**1**) has been obtained in enantiomerically pure form both by chemical^{4,5} and enzymatic⁶ resolution as well as by enantioselective reduction of 3-methylcyclohexenone,⁷ whereas compound **2**^{4,5} has been usually prepared from the optically pure seudenol. We report herein a short entry to the cyclohex-2-enols family based on the combination of Pummerer rearrangement of homochiral β -hydroxy sulfoxides and desulfurization of the resulting vinyl thioether, that culminated into the asymmetric synthesis of compounds **1** and **2**.



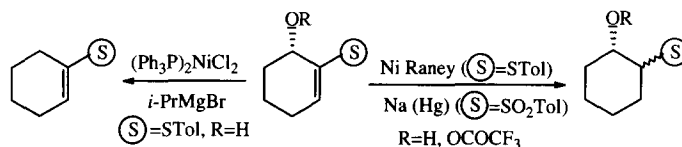
The stereoselective hydride reduction of 2-*p*-tolylsulfinylcycloalkanones with DIBAL and DIBAL/ZnCl₂ allowed the synthesis of 2-*p*-tolylsulfinylcycloalkanols with high enantiomeric purity.⁸ The reaction of the same substrates with AlMe₃ gave 2-*p*-tolylsulfinyl-1-methylcycloalkanols in their enantiomerically pure forms.⁹ When 2-*p*-tolylsulfinyl cyclohexanols **3** were treated with (CF₃CO)₂O/Py under the Pummerer reaction conditions,¹⁰ and further submitted to hydrolysis (Scheme 1), the vinylic thioether **4**, precursor of cyclohex-2-enol was formed. Under the same conditions, the tertiary alcohol **5** gave compound **6** resulting from the tandem

Pummerer reaction/sigmatropic rearrangement of the intermediate trifluoroacetate. Compound **6** is the precursor for seudenol.



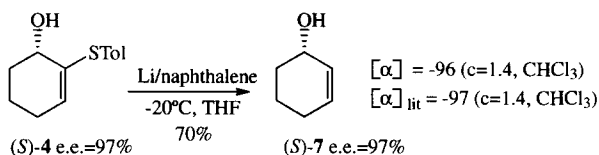
Scheme 1

Desulfurization of vinylthioethers¹¹ with Raney Ni and vinylsulfones¹² with Na(Hg) is well documented. However, when either the vinyl thioether **4** or the sulfonyl derivative (as well as their corresponding trifluoroacetates)¹³ were subjected to these classical conditions, the reaction did not give rise to the desired compounds, instead a net reduction of the double bond occurred. Also other known methods such as the use of the Grignard reagents-Ni-phosphine complexes¹⁴ failed to break the C-S bond without cleaving the hydroxyl group (Scheme 2).



Scheme 2

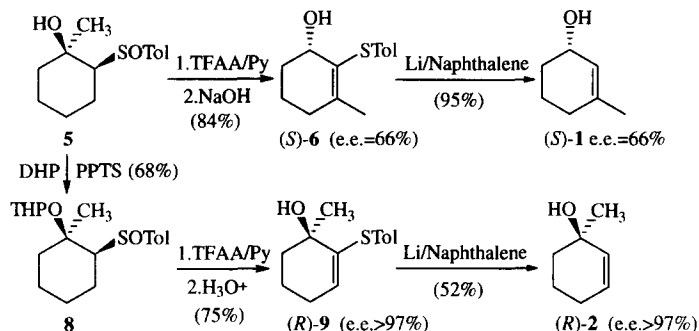
Li-aromatic anion radicals have been successfully employed as electron transfer reagents for the C-S bond breaking in the series of cycloalkenyl thioethers.¹⁷ The treatment of **4** with Li/Naphthalene in THF at -20°C for 2 hours afforded the (*S*)-2-cyclohexenol **7** in 70% yield.¹⁸ The enantiomeric excess of **7** was deduced from the value of its specific rotation (see Scheme 3). Comparison with the reported value demonstrated that the process of desulfurization does not imply any significant loss of the enantiomeric purity at the hydroxylic center.



Scheme 3

The synthesis of the seudenol **1** was achieved in 95% yield, by reaction of compound (*S*)-**6**,¹⁰ with Li/Naphthalene (Scheme 4). Comparison of the specific rotation with the available data, showed that this compound was formed with 66% *ee*. This was also confirmed by the ¹H-NMR study that was carried out on its

MTPA ester derivative. Taking into account that the starting hydroxysulfoxide **5** was diastereomerically pure (Scheme 4) and the desulfurization process proceeds with complete retention of the configuration at the hydroxylic carbon, the result indicated that the rearrangement of the OCOCF_3 group was not completely stereoselective (see Scheme 1). Therefore, the enantiomeric purity we advanced previously¹⁰ which assumed a complete stereoselectivity of this rearrangement was wrong.¹⁹ We have then made new studies to shed light onto this reaction. These studies showed that the stereoselectivity of the rearrangement step (TFAA/Py treatment) is concentration dependent: increasing the concentration of **5** resulted in an increase of the *ee* with the highest stereoselectivity (85%) being observed at $c=0.2 \text{ mol.l}^{-1}$, which suggests that this rearrangement does not take place in a fully concerted manner.



Scheme 4

The synthesis of compound **2** was thus achieved after protecting the alcohol **5** with DHP. Subsequent Pummerer reaction on **8** and then Li/Naphthalene reduction of the resulting vinylic thioether **9** ($[\alpha]_D^{25} = 22$, $c=1$, CHCl_3) yielded compound (*R*)-**2** in 52% yield.²⁰ The specific rotation of **2** has been again compared to the reported value⁴, indicating that it had been formed with an *ee*>97%.

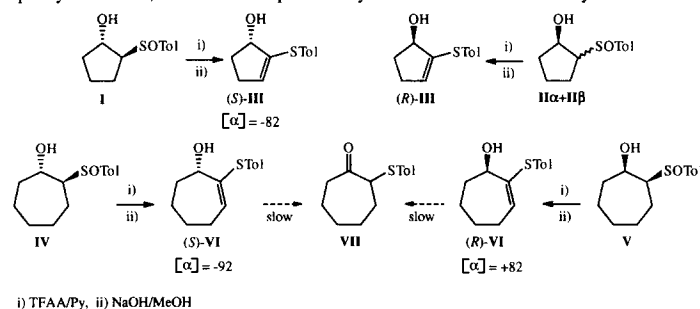
In summary, we have reported a convenient approach to the synthesis of cyclohex-2-enols in high *ee*. The method resides in the Pummerer rearrangement of 2-sulfinylcycloalkanols and subsequent reductive cleavage of the C-S bond.

Acknowledgements: We thank DGICYT (Grant PB92-0162) for financial support.

References and Notes

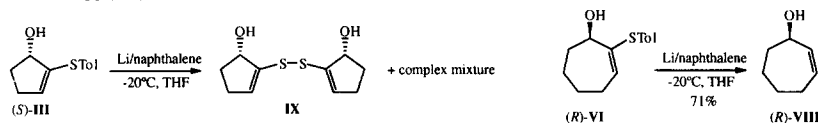
1. S. Takano, O. Yamada, H. Iida, K. Okasawara, *Synthesis*, **1994**, 592 and references cited therein.
2. a) M. Kasai, H. Ziffer, *J. Org. Chem.*, **1983**, *48*, 712. b) M. Kasai, H. Ziffer, J.V. Silverton, *Can. J. Chem.*, **1987**, *65*, 574.
3. T. Fukazaga, T. Hashimoto, *Tetrahedron:Asymmetry*, **1993**, *4*, 2323.
4. K. Mori, B.G. Hazra, R.J. Pfeiffer, A.K. Gupta, B.S. Lindgren, *Tetrahedron*, **1987**, *43*, 2249.
5. V.S. Martín, S.W. Woodwad, T. Katsuki, J. Yamada, M. Ikeda, K.B. Sharpless, *J. Am. Chem. Soc.*, **1981**, *103*, 6237.
6. B.D. Johnston, B. Morgan, C. Oehlchalager, S. Ramaswamy, *Tetrahedron:Asymmetry*, **1991**, *2*, 377 and references cited therein.
7. a) K.-M. Wu, W.H. Okamura, *J. Org. Chem.*, **1990**, *55*, 4025. b) M.H. Kress, B.F. Kaller, Y. Kishi, *Tetrahedron Lett.*, **1993**, *34*, 8047.
8. a) M. C. Carreño, J.L. García Ruano, B. Peña, A. Rubio, *Tetrahedron Lett.*, **1987**, *28*, 4861. b) A.B. Bueno, M. C. Carreño, J.L. García Ruano, B. Peña, A. Rubio, M.A. Hoyos, *Tetrahedron*, **1994**, *50*, 9355.

9. a) A.B. Bueno, M. C. Carreño, J. Fischer, J.L. García Ruano, B. Peña, L. Peñas, A. Rubio, *Tetrahedron Lett.*, **1991**, 32, 3191. b) A.B. Bueno, M. C. Carreño, J.L. García Ruano, *An. Quim.*, (submitted).
10. A.B. Bueno, M. C. Carreño, J.L. García Ruano, A. Rubio, *Tetrahedron: Asymmetry*, **1992**, 3, 251.
11. a) R.B. Boar, D.W. Hawkins, J.F. McGhie, D.H. Barton, *J. Chem. Soc., Perkin I*, **1973**, 654. b) E.J. Corey, G. Schmidth, *Tetrahedron Lett.*, **1979**, 20, 2317. c) Y. Tominaga, A. Ushirogoshi, Y. Matsuda, *J. Heterocycl. Chem.*, **1987**, 24, 1557.
12. J.L. Aceña, O. Arjona, R. Fernandez de la Pradilla, J. Plumet, A. Viso, *J. Org. Chem.*, **1992**, 57, 1945.
13. Desulfurization of the sulfoxides with Al(Hg) was also tried with the same negative results.
14. H. Okamura, M. Miura, H. Takei, *Tetrahedron Lett.*, **1979**, 20, 43. b) B.M. Trost, P.L. Ornstein, *Tetrahedron Lett.*, **1981**, 22, 3463.
15. a) S. Kamata, S. Uyeo, N. Haga, W. Nagata, *Synth. Commun.*, **1973**, 3, 265. b) M. Ramaiah, *Tetrahedron*, **1987**, 43, 3541. c) E. Block, M. Aslam, *Tetrahedron*, **1988**, 44, 281. d) C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.*, **1978**, 43, 1064. e) *ibid.*, **1979**, 44, 713.
16. a) W. Oppolzer, I. Rodriguez, *Hel. Chim. Acta*, **1993**, 76, 1275. b) J. Yu, H-S. Cho, J.R. Falk, *J. Org. Chem.*, **1993**, 58, 5892.
17. T. Cohen, M.D. Doubleday, *J. Org. Chem.*, **1990**, 55, 4784.
18. This result suggested the use of the same procedure to the synthesis of enantiomerically pure 2-cyclopentenol and 2-cycloheptenol from the corresponding vinyl thioethers. The latter were obtained from the reaction of sulfinylcycloalkanols^{8b} with TFAA/Py and subsequent hydrolysis of the trifluoroacetate group with NaOH/MeOH¹⁰ (Scheme 5). The ¹H-NMR analysis showed a *ee* higher than 97% for both enantiomers of **III**. The chemical instability of **VI** did not allow the determination of their enantiomeric purity. However, this was made possible by their conversion to the vinyl alcohol.



Scheme 5

When freshly prepared (*R*)-**VI** was treated with Li/Naphthalene, the isolated (*R*)-2-cycloheptenol was shown to maintain the enantiomeric purity of the starting hydroxysulfonate **V**. In contrast, the reaction of (*S*)-**III** with Li/Naphthalene did not give rise to the desired cyclopentenol, instead a complex mixture of products was formed with disulfide **IX** being identified. The failure encountered while applying this procedure to the five membered rings had been previously reported.¹⁷



Scheme 6

19. The use of 0.4 equivalents of Eu(tfc)₃ to determine the enantiomeric purity of **6** was necessary to observe the two enantiomers in the racemate. The failure in the determination was possibly due to a mistake in the weight of the Eu(tfc)₃.
20. **Experimental procedure to transform 5 into 2:** To a solution of 1.44 g (5.7 mmol) of **5** in 50 ml of dry CH₂Cl₂, 1.04 ml (11.4 mmol) of dihydropyran and 25 mg (0.1 mmol) of PPTS were added. After 12 h. of stirring at rt, 1 ml of dihydropyran was added. This operation was repeated twice. After 48 h. the solution was diluted with CH₂Cl₂, washed with NaHCO₃ sat. (2x30 ml), dried over MgSO₄ and evaporated under *vacuo*. Flash chromatography of the residue (hexane/OEtAc 5:1) gave **8** in 68% yield along with a 32% of the starting material. To a solution of 1.15 g (4.9 mmol) of **8** in 50 ml of dry CH₂Cl₂ were added successively 2.3 ml (20.8 mmol) of pyridine and 1.5 ml (10.4 mmol) of TFAA. After stirring for 3-4 h., 20 ml of H₂SO₄ (5%) were added and the mixture was stirred for 2 h. Layers were separated and washed with H₂SO₄ (5%), then with NaHCO₃ sat., dried over MgSO₄. Removal of the solvents followed by a flash chromatography (hexane/OEtAc 5:1) gave **9** (75% yield). A green solution of lithium naphthalenide was prepared from lithium (34 mg, 4.8 mmol) and naphthalene (1.02 g, 4.8 mmol) in 7 ml of THF under dry atmosphere. 5 ml of the resulting solution of Li-radical anion were injected to a solution of 100 mg of **9** (0.40 mmol) in 2 ml of dry THF at -20°C. After stirring at -20°C for 3-4 h., water was added and the mixture was extracted with ether. The organic layer was washed with NaCl sat., dried over MgSO₄ and evaporated under *vacuo*. Flash chromatography (hexane:ether 3:1) gave **2** in 51% yield.

(Received in UK 12 April 1995)