Tetrahedron Letters, Vol. 33, No. 12, pp. 1605-1608, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Asymmetric Synthesis of β-Hydroxyketones, Precursors of Chiral 1,3-Diols, from β, δ-Diketosulfoxides.

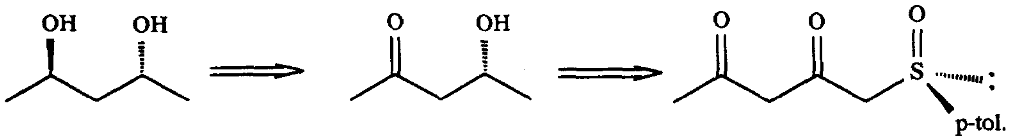
Guy Solladié* and Nasser Ghiatou

Laboratoire de Stéréochimie, associé au CNRS
Ecole Européenne des Hautes Etudes des Industries Chimiques
1 rue Blaise Pascal, F-67008-Strasbourg, France

Abstract : (R) β, δ-diketosulfoxides were reduced with DIBAL to (S_2R_S) *δ-keto β-hydroxysulfoxides (de>98%) which can be easily transformed into syn or anti chiral 1,3-diols by known procedures.*

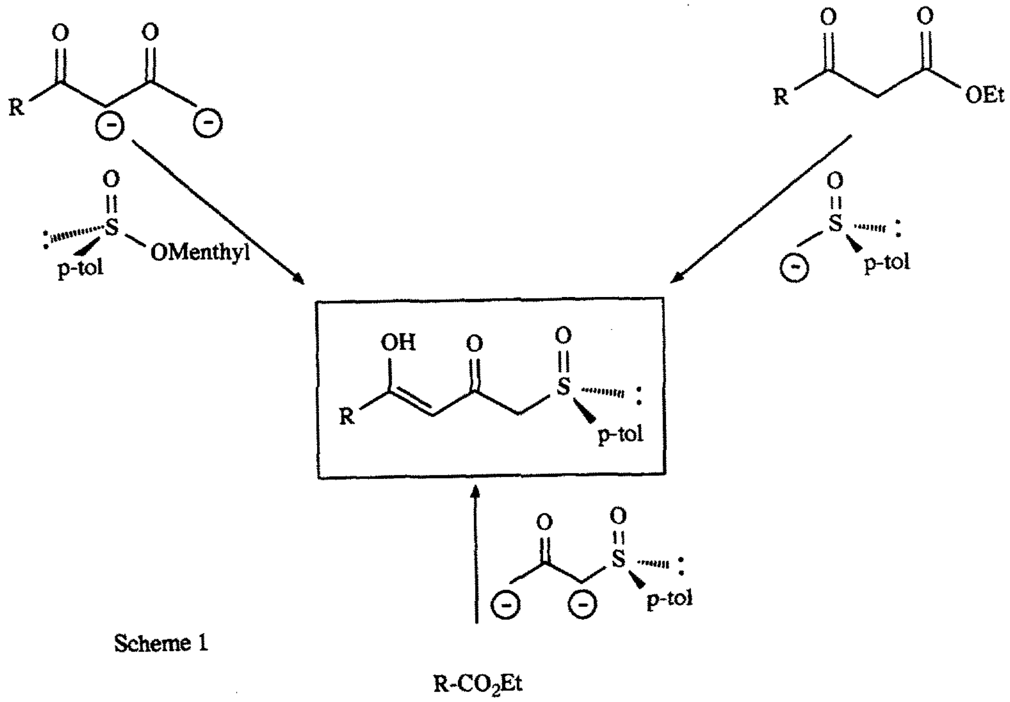
Chiral 1,3-diols are important building blocks in the synthesis of many natural products. Great efforts have been done to develop with success different routes to reduce chiral β-hydroxyketones into syn[1] or anti 1,3-diols[2]. However in most of the cases the chiral hydroxylic center present in the β-hydroxyketones was obtained from a natural chiral hydroxylated product.

We report in this paper a short asymmetric synthesis of β-hydroxyketones monitored by a chiral sulfoxide group.



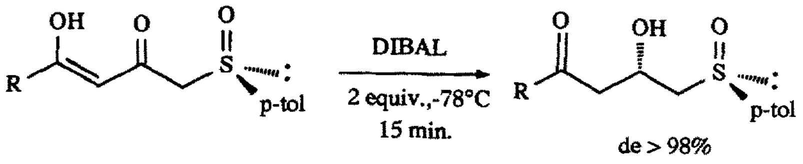
β, δ-diketosulfoxides were readily prepared in high yields either from β-diketones and (*S*) menthyl *p*-toluenesulfinate, from β-ketoesters and (*R*)-methyl *p*-tolylsulfoxide or from esters and (*R*) 1-(*p*-tolylsulfinyl) propan-2-one[3]. It was shown that the δ-carbonyl was totally enolized (scheme 1).

The reduction of these β, δ-diketosulfoxides was carried out with 2 equivalents of DIBAL in THF at -78°C in 15 minutes. As shown in the table I, the chemical yields are high. According to the structure of the β,δ-diketosulfoxides, these yields were obtained either by adding a THF solution of the product to a DIBAL solution or by reverse addition of DIBAL to the substrate solution.



Scheme 1

The reduced products were purified by chromatography on silicagel free of metallic impurities[4] (eluent : ethylacetate-hexane gradient). The diastereoselectivity was very high : only one diastereomer was detected by ^{1}H NMR of the crude product. This diastereomer is characterized mainly by the AB pattern displayed by the methylene group α to the sulfoxide. The S_2R_S configuration was predicted according to our previous studies on the reduction of β-ketosulfoxides[5] and was confirmed by chemical correlation to the known 2,4-pentanediol (R=CH_3), (scheme 3).



Scheme 2

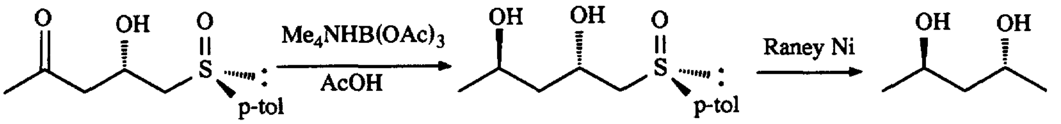
TABLE I

DIBAL reduction of β, δ-diketosulfoxides

R	Yld%[a]	mp	$[\alpha]_D(c)^b$	de %
CH_3	85	98-100	+243(2)	>95
EtO_2CCH_2	80	86-8	+169(2.3)	>98
C_6H_5	80[c]	84-6	+160(2.04)	>98
$CH_3CH{=}CH$	70[c]	72-3	+162(1.3)	>98

a) yields in isolated products ; b) in $CHCl_3$; c) reverse addition.

(+) 1-(*p*-tolylsulfinyl) 2-hydroxypentan-4-one ($R{=}CH_3$) was reduced by Evan's reagent[2a], tetramethylammonium triacetoxyborohydride, in modified experimental conditions[6], into the corresponding anti diol in 90% yield. The diastereoselectivity was 88%, determined by ^1H NMR from the terminal methyl group signal. Desulfurization with Raney Nickel afforded in quantitative yield (-)-(*R,R*)-2,4-pentanediol, $[\alpha]_D$ -39 (c=1.12, $CHCl_3$), (lit.[7] -40).



Scheme 3

90% yld , 88% de
mp 125-130°C
$[\alpha]_D$ + 248 (c=1,$CHCl_3$)

(-) (*RR*)
$[\alpha]_D$ = -39 (c=1,$CHCl_3$)

References:

1) a) Hanamoto, T.; Hiyama, T., Tetrahedron Lett. 1988, **29**, 6467. b) Chen, K.M.; Hardtmann, G.E.; Prasad, K.; Repic, O.; Shapiro, M.J., Chem. Lett. 1987, 1923. c) Bonadies, F.; Difabio, R.; Gubioti, A.; Mecozzi, S.; Bonini, C., Tetrahedron Lett. 1987, **28**, 703. d) Kiyooka, S.; Kuroda, H.; Shimasaki, Y., Tetrahedron Lett. 1986, **27**, 3009. e) Kathawala, F.G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M.J.; Stabler, R.S.; Widler, L., Helv. Chim. Acta 1986, **69**, 803. f) Narasaka, K.; Pai, F.C., Tetrahedron 1984, **40**, 2233. g) Narasaka, K; Pai F.C., Chem. Lett. 1980, 1415. h) Evans, D.A.; Hoveyda, A.H., J. Org. Chem. 1990, **55**, 5190.

2) a) Evans, D.A.; Chapman, K.T.; Carreira, E.M.J., J. Am. Chem. Soc. 1988, **110**, 3560. b) Anwer, S.; Davis, A.P., Tetrahedron 1988, **44**, 3761. c) Evans, D.A.; Hoveyda, A.H., J. Am. Chem. Soc. 1990, **112**, 6447.

3) Solladié, G.; Ghiatou, N., Tetrahedron Asymmetry, in Press.

4) Hubbard, J.S.; Harris, T.M., J. Org. Chem. 1981, 46, 2566.

5) a) Solladié, G., Demailly, G., Greck, C., Tetrahedron Lett. 1985, 26, 435. b) Solladié, G., Demailly, G., Greck, C., J. Org. Chem. 1985, 50, 1552. c) Solladié, G., Fréchou, C., Demailly, G., Greck, C., J. Org. Chem. 1986, 51, 1912. d) Carreno, M.C., Garcia Ruano, J.L., Martin, A., Pedregal, C., Rodriguez, J.H., Rubio, A., Sanchez, J., Solladié, G., J. Org. Chem. 1990, 55, 2120.

6) Tetramethylammonium triacetoxyborohydride (5 equiv.) was dissolved in anhydrous acetic acid (17 mL) and cooled with an ice bath till solidification. Then a solution of the δ-keto β-hydroxysulfoxide (2 mmol.) in acetic acid (34 mL) was added dropwise and the reaction mixture stirred at room temperature for 2h. A sodium tartrate solution (20 mL) was then added and the resulting solution poured on ice and neutralized with $NaHCO_3$. After extraction with CH_2Cl_2 (3x100 mL), addition of NaCl to the aqueous solution, and extraction again with ethylacetate (3x100 mL), the organic phases were dried (Na_2SO_4), evaporated and the crude product purified by chromatography on silicagel free of metallic impurities[4] (ethyl acetate : hexane gradient).

7) a) Fry, A.J.; Britton W.E., J. Org. Chem. 1973, 38, 4016. b) Ito, K.; Harada, T.; Tai, A., Bull. Chem. Soc. Jpn 1980, 53, 3367.

(Received in France 29 November 1991)