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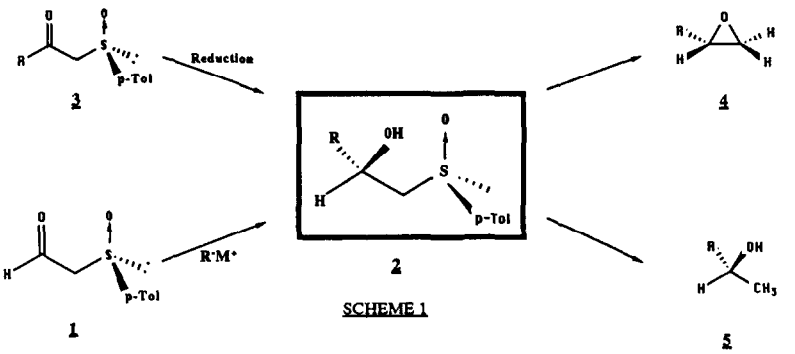
SYNTHESIS OF OPTICALLY ACTIVE α-SULFINYLACETALDEHYDE

P. PFLIEGER [a], C. MIOSKOWSKI [a]*,
J.P. SALAUN [b], D. WEISSBART [b] and F. DURST [b]

[a] Laboratoire de Chimie Bio-organique, Université Louis Pasteur-CNRS UA 31
Faculté de Pharmacie, 74, Route du Rhin F-67401 Strasbourg Cedex, France.
[b] Laboratoire d'Enzymologie Cellulaire et Moléculaire, Université Louis Pasteur-CNRS UA 1182,
28, rue Goethe, F-67083 Strasbourg Cedex, France.

Abstract: *Optically active α-sulfinylacetaldehyde is prepared by formylation of the (R)-methyl p-tolylsulfoxide anion with N-formylpiperidine .*

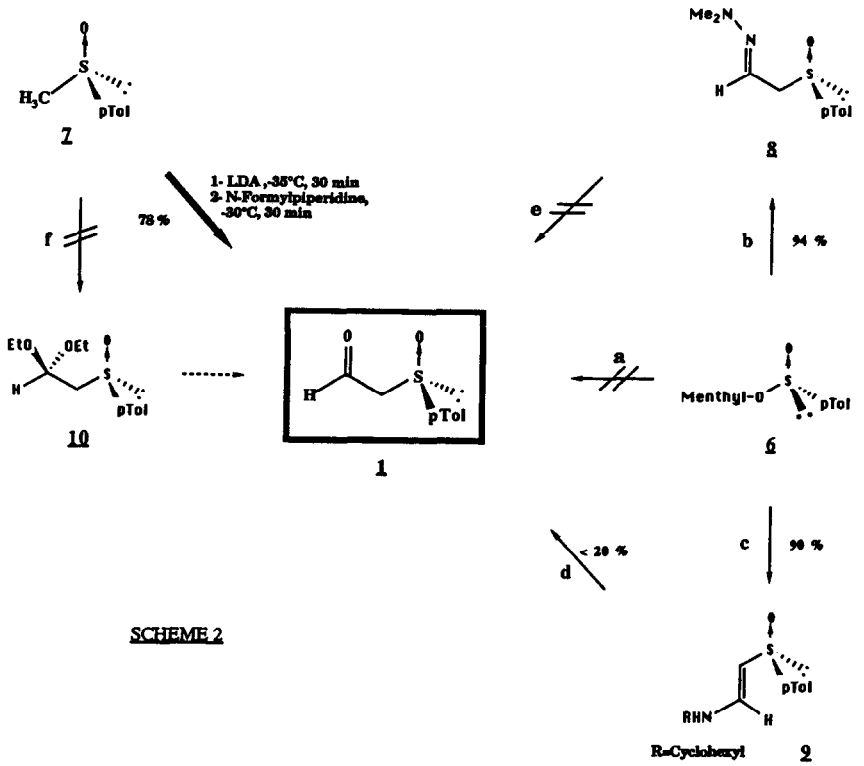
Recently several groups have utilized chiral β-hydroxysulfoxides 2 [1-4], via the corresponding β-ketosulfoxides 3, for the synthesis of optically active epoxides 4 and secondary alcohols 5. Both antipodes of the epoxide and alcohol are accessible from the same β-ketosulfoxide 3 by stereoselective reduction of the keto fonctionality (scheme 1).



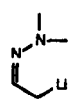
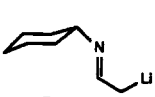
SCHEME 1

Unfortunately, to vary the substituent R, it is necessary to synthesize the starting β-ketosulfoxide 3 in each case. We felt it would be advantageous to prepare α-sulfinylacetaldehyde 1 as a versatile reagent to which a wide range of nucleophiles could be added selectively to either face depending on the organometallic used, thus providing direct access to a variety of β-hydroxysulfoxides 2.

Although it was reported that α-sulfinylacetaldehyde 1 could not be prepared due to its instability [5], we studied several different approaches to overcome this problem (scheme 2).



SCHEME 2

a) /THF/-78°C to R.T.[6]; b) 2 eq  /THF/-78°C, 1 h[5]; c) 3 eq  /THF/-78°C, 0.5 h[9,10]; d) HCl/H_2O/THF at R.T. [10]; e) $CuCl_2$/THF/phosphate buffer pH 7[7]or MeI/95% EtOH, heated under reflux[8]; f) After metallation with 1 eq of LDA at -30°C, followed by addition of $HC(OPh)(OEt)_2$ [11] (-30°C to +20°C) no reaction was observed.

Addition of the lithium enolate of acetaldehyde, prepared from THF and n-butyllithium [6], to (-)-menthyl (S)-*p*-tolylsulfinate 6, did not lead to 1. Metallated acetaldehyde hydrazone adds to (-)-menthyl (S)-*p*-tolylsulfinate giving the α-sulfinylhydrazone 8 in high yields but all attemps to hydrolyse the hydrazone to the corresponding aldehyde were unsuccessfull [7,8]. However, α-sulfinylacetaldehyde 1 could be obtained in lower yields after acid hydrolysis of a mixture of α-sulfinylcyclohexylacetaldimine and the corresponding enamine 9, prepared by condensation of metallated cyclohexylacetaldimine [9,10] and (-)-menthyl (S)-*p*-tolylsulfinate 6.

Finally we changed strategy and tried to formylate the anion of methyl p-tolyl sulfoxide: condensation with diethyl-phenyl-orthoformate [11] did not afford the diethylacetal 10, but with N-formylpiperidine [12], after 30 min at -30°C, the desired product 1 was obtained in 78% yield.

Preliminary results of condensations with organometallic reagents showed that α-sulfinylacetaldehyde 1 enolises easily. Trialkynylaluminium reagents, under the conditions used by H. Kosugi [4] give β-hydroxysulfoxides 2 in poor yields (20-30%) with a 75/25 diastereoisomeric ratio. Further studies to improve upon these results will be reported in due course.

Preparation of the α-sulfinylacetaldehyde 1:

(R)-(+)-methyl p-tolylsulfoxide (600 mg, 3.89 mmol, 1 eq) , obtained by condensation of methylmagnesium iodide with (-)-menthyl-(S) *p*-tolylsulfinate, was metallated using 14.3 ml of LDA (0.3 M in THF, 4.28 mmol, 1.1 eq) at -35°C during 30 min. Freshly distilled N-formylpiperidine (480 mg, 4.24 mmol , 1.1 eq) in 1 ml of THF was then added slowly and the temperature was maintained 30 min at -30°C. The reaction mixture was poured into 40 ml of an ice-cooled 5 % aqueous HCl solution and extracted with ethylacetate (3x150 ml). The organic layers were washed with cold brine (3x100 ml) and dried over Na_2SO_4. After evaporation of the solvent under vacuo, α-sulfinylacetaldehyde was obtained in 78% yield (554 mg). The crude material could neither be purified by silica gel chromatography nor by distillation. Fortunatly the ^{1}H-NMR (200 MHz, $CDCl_3$)[13] spectrum indicated a purity greater than 95% and thus the crude material can be used without further purification or stored in dry THF (10ml) under N_2 at -30°C without decomposition for several months. The 2,4-DNPH derivative of the α-sulfinylacetaldehyde was prepared and fully characterized [14].

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References and notes

1- G. Solladié, C. Greck, G. Demailly, A. Solladié-Cavallo, Tetrahedron Lett., 23, 5047-5050 (1982)

2- G. Solladié and J. Hutt, Tetrahedron Lett., 28, 797-800 (1987)

3- H.J. Altenbach, Nachr. Chem. Tech. Lab., 36, 33-36 (1988)

4- H. Kosugi, J. Synth. Org. Chem. Jap., 45, 472-480 (1987)

5- L. Banfi, L. Colombo, C. Gennari, Synthesis, 829-831 (1982)

6- R.B. Bates, L.M. Kroposki and D.E. Potter, J. Org. Chem., 37, 560-562 (1972)

7- E.J. Corey , S. Knapp, Tetrahedron Lett., 3667-3668 (1976)

8- M. Avaro, J. Levisalles and H. Rudler, J. Chem. Soc., Chem. Commun., 445-446 (1969)

9- R. Tiollais , Bull. Soc. Chim. Fr. , 708 (1947)

10- J. F. Le Borgne , J. Organomet. Chem. , 122 , 123-143 (1976)

11- F. Barbot, L. Poncini, B. Radrianoelina and P. Miginiac, J. Chem. Research (M), 4016-4035 (1981)

12- G. A. Olah and M. Arvanaghi, Angew. Chem. Int. Ed. Engl., 20, 878-879 (1981)

13- α-sulfinylacetaldehyde 1: oil. ^{1}H NMR ($CDCl_3$) 200 MHz: δ 2.43 (s, 3H), 3.82 (splitted AB system, 2 H, J=2.5 Hz, ν_A=3.78, ν_B=3.86, J_{AB}=14 Hz), 7.47 (AB system, 4H, ν_A=7.38, ν_B=7.56, J_{AB}=8.5 Hz), 9.71 (t , 1H, J=2.5 Hz)

14- 2,4-DNPH derivative: Solid, m.p. 160°C. ^{1}H NMR ($CDCl_3$) 200 MHz: δ 2.43 (s, 3H), 3.87 (splitted AB system, 2H, J=6.0 Hz, ν_A=3.77, ν_B=3.97, J_{AB}=13.5 Hz), 7.43 (t, 1H, J=6 Hz), 7.46 (AB system, 4H, ν_A=7.38, ν_B=7.54, J_{AB} = 9.0 Hz), 7.79 (d,1H, J=9.5 Hz), 8.28 (dd, 1H, J_1=9.5 Hz, J_2=2.5 Hz), 9.11 (d, 1H, J=2.5 Hz), 11.18 (s, 1H). IR ($CHCl_3$): 3280 cm^{-1} . Anal. $C_{15}H_{14}N_4O_5S$: Calculated C 49.72; H 3.89; N 15.46. Found: C 49.79; H 3.89; N 15.41. $[\alpha]_D$ (c=0.373, acetone) = + 214°

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