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OPTICALLY ACTIVE α-SULFINYL EPOXIDES : PRECURSORS OF CHIRAL FUNCTIONALIZED HOMOALLYLIC ALCOHOLS

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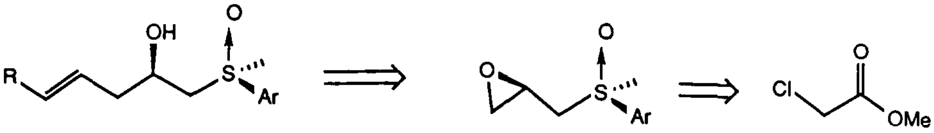
Abstract : An asymmetric synthesis of chiral functionalized homoallylic alcohols in both configurations is described from the corresponding optically active α-sulfinyl epoxides.

Optically active functionalized homoallylic alcohols are very often involved in total synthesis of natural products ; the leukotriene family is one example of such compounds.

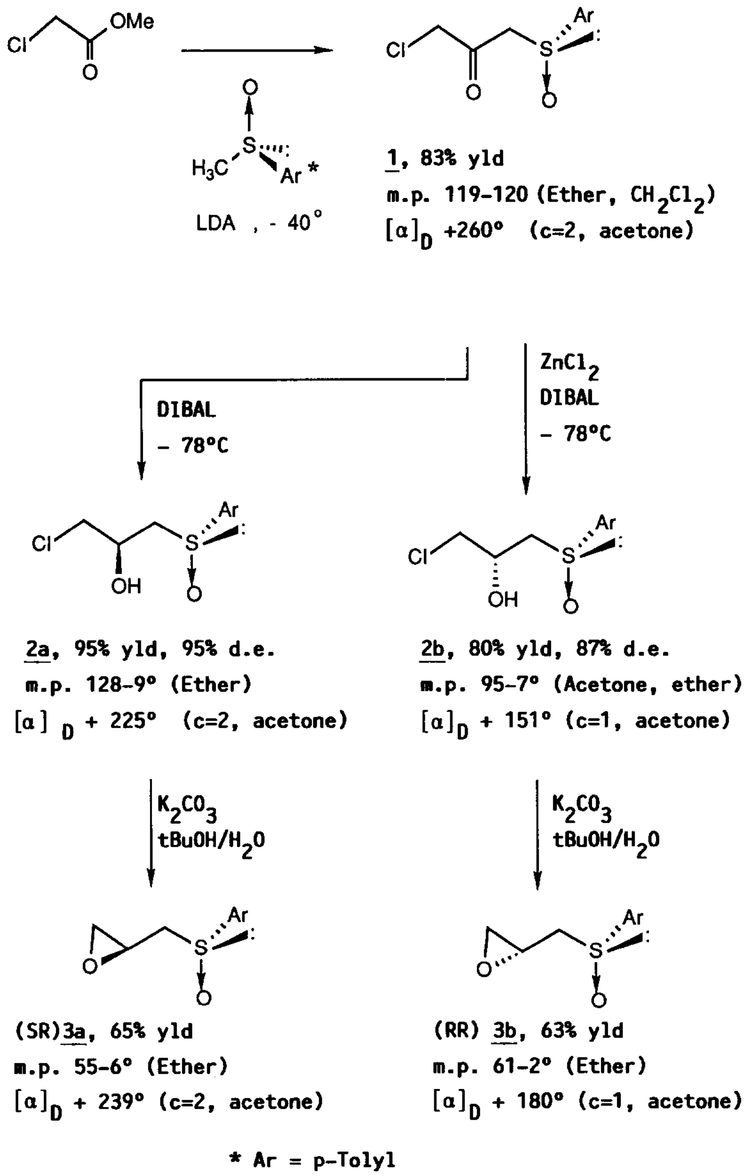
We describe in this paper the asymmetric synthesis of such homoallylic alcohols from α-sulfinyl epoxides which are readily obtained from methyl chloroacetate.



The γ-chloro β-ketosulfoxide 1 was prepared in one step from methyl chloroacetate and the carbanion of (R)(+)methyl p-tolylsulfoxide in 83% yield according the usual procedure (1,2).

We have already reported that the reduction of β-ketosulfoxides to the corresponding β-hydroxysulfoxides was highly stereoselective, the (RR) or (SR) absolute configuration depending on the reduction conditions : the use of $ZnCl_2$ and DIBAL gives the (RR) diastereoisomer whereas DIBAL alone leads only to the (SR) diastereoisomer, as a result of a different conformation of the β-ketosulfoxide in the reaction mixture (3).

Although, the presence of the halogen in compound 1 could interfere and modify the conformation of the β-ketosulfoxide during the reduction process, mainly in presence of a chelated species such as $ZnCl_2$, we observed that the DIBAL and the $ZnCl_2$/DIBAL gave the corresponding γ-chloro β-hydroxysulfoxides diastereoisomers 2a and 2b with a high stereoselectivity (95% d.e. and 87% d.e.). Diastereoisomeric excesses were determined by NMR from the signals corresponding to CH_2 α to sulfur (4,5).



1, 83% yld
m.p. 119-120 (Ether, CH_2Cl_2)
$[\alpha]_D$ +260° (c=2, acetone)

2a, 95% yld, 95% d.e.
m.p. 128-9° (Ether)
$[\alpha]_D$ + 225° (c=2, acetone)

2b, 80% yld, 87% d.e.
m.p. 95-7° (Acetone, ether)
$[\alpha]_D$ + 151° (c=1, acetone)

(SR)3a, 65% yld
m.p. 55-6° (Ether)
$[\alpha]_D$ + 239° (c=2, acetone)

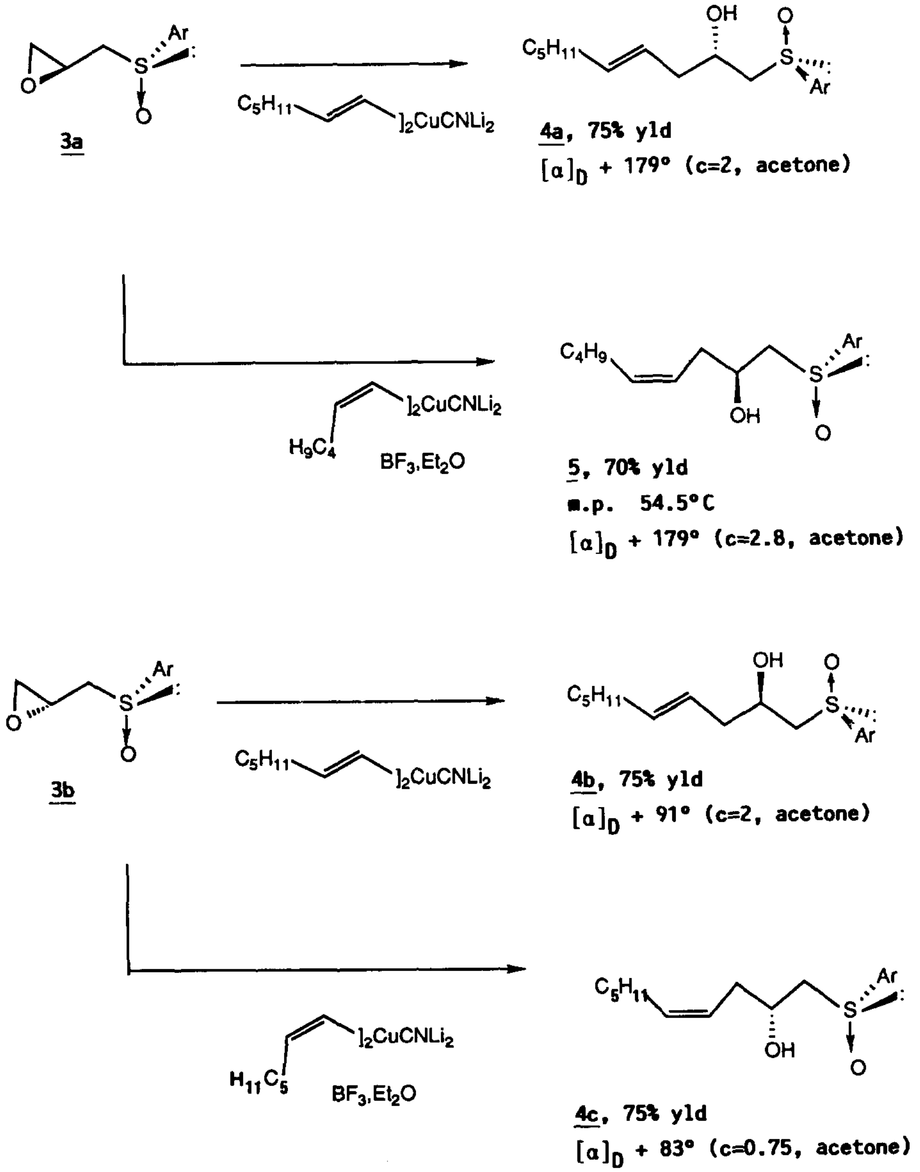
(RR) 3b, 63% yld
m.p. 61-2° (Ether)
$[\alpha]_D$ + 180° (c=1, acetone)

*** Ar = p-Tolyl**

Finally, treatment of compounds 2a and 2b with potassium carbonate in a mixture tBuOH/H_2O (5/95) gave the corresponding α-sulfinyl epoxides (SR)-3a and (RR)-3b which are solid and easily purified (6).

The epoxide opening was not a straightforward reaction because of the acidity of the methylene hydrogens α to sulfur, organolithium reagents leading mainly to the elimination product. However, Z and E cyanocuprates (7,8) opened clearly the epoxides 3a and 3b giving the expected homoallylic β-hydroxysulfoxides 4 and 5 in high yields.

Such homoallylic β-hydroxysulfoxides can be easily transformed by a Pummerer rearrangement into homoallylic α-hydroxyaldehydes which are useful chirons for total synthesis.



3a

4a, 75% yld
[α]$_D$ + 179° (c=2, acetone)

5, 70% yld
m.p. 54.5°C
[α]$_D$ + 179° (c=2.8, acetone)

3b

4b, 75% yld
[α]$_D$ + 91° (c=2, acetone)

4c, 75% yld
[α]$_D$ + 83° (c=0.75, acetone)

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References and notes

a) On leave from the University of Valladolid (Spain).

b) UA du CNRS n° 466

1) G. Solladié, J. Hutt and A. Girardin, Synthesis, 173 (1987).

2) It is interesting to remark that methyl bromoacetate reacts also with methyl p-tolylsulfoxide giving mainly the α-sulfinylester by bromine displacement.

3) G. Solladié, G. Demailly and C. Greck, Tetrahedron Lett., 26, 435 (1985).

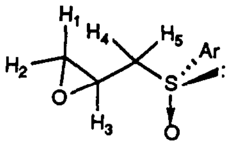
4) 200MHz NMR : **2a**, δ: 2.44 (s, 3H, CH_3), 2.90 (AB part of ABX, 2H, J_{AB}=13.6Hz, J_{AX}=10Hz, J_{BX}=2.1Hz, $\Delta\nu$=71Hz, CH_2 α to S), 3.56 (AB part of ABX, 2H, J_{AB}=10Hz, J_{AX}=5.1Hz, J_{BX}=5.1Hz, $\Delta\nu$=12.1Hz, CH_2Cl), 4.22 (d, 1H, J=3Hz, OH), 4.37 (X part of $(AB)_2X$, m, 1H, CHOH), 7.46 (AB, 4H, J_{AB}=8.3Hz, $\Delta\nu$=32Hz, Arom. H).

2b, δ : 2.43 (s, 3H, CH_3), 3.04 (d, 2H, J=6.0Hz, CH_2S), 3.64 (AB part of ABX, 2H, J_{AB}=11.8Hz, J_{AX}=5.0Hz, J_{BX}=5.60Hz, $\Delta\nu$=19Hz, CH_2Cl), 4.16 (d, 1H, J=3.3Hz, OH), 4.41 (1H, X part of ABX, m, CHOH), 7.47 (AB, 4H, J_{AB}=8.4Hz, $\Delta\nu$=38.8Hz, Arom. H).

5) Dr. Bravo, University of Milano, informed us that he recently obtained very similar results for the reduction of compound 1.

6) 200MHz NMR : **3a**, δ : 2.4 (s, 3H, CH_3), 2.6 (dd, 1H, H_2, ^2J=4.5Hz, $^3J_{trans}$=2.5Hz), 2.9 (dd, 1H, H_1, ^2J=4.5Hz, $^3J_{cis}$=4Hz), 2.95 (2H, H_4-H_5, AB part of ABX, J_{AB}=13Hz, J_{AX}=5Hz, J_{BX}=7Hz, $\Delta\nu$=21Hz), 3-4 (1H, H_3, X part of an ABXAM), 7.4 (AB, 4H, J=8.0Hz, $\Delta\nu$=40Hz, Arom. H).

3b, δ , 2.4 (s, 3H, CH_3), 2.67 (1H, H_1, dd, ^2J=4.5Hz, $^3J_{trans}$=2.Hz), 2.83 (1H, H_2, dd, ^2J=4.5Hz, $^3J_{cis}$=4.Hz), 3.05 (broad m, 3H, ABX system, H_3, H_4, H_5), 7.4 (AB, 4H, J=8Hz, $\Delta\nu$=42Hz, Arom. H).



7) a) J.F. Normant, Synthesis 63 (1972). b) A. Alexakis, G. Cahiez and J.F. Normant, J. Organometal. Chem., 177, 293 (1979). c) B.H. Lipshutz, R.S. Wilhem, J. Org. Chem., 49, 3928 (1984). d) A. Alexakis, G. Cahiez, J.F. Normant, Org. Synth., 62, 1 (1984).

8) The low reactivity of E-cyanocuprates required a BF_3 catalysis for the epoxide opening. See A. Alexakis, D. Jachiet and J.F. Normant, Tetrahedron, 42, 5607 (1986).

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