Circular Dichroism Spectral and Chemical Arguments for Retention of Configuration at Sulfur in the Andersen Synthesis of Sterically Hindered Chiral Sulfoxides

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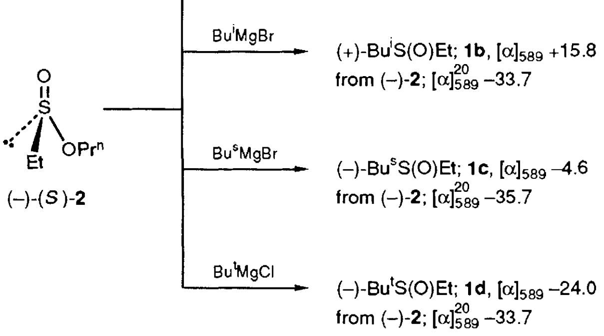
Comparison of the circular dichroism (CD) spectra of isomeric butyl ethyl sulfoxides, prepared from (−)-(*S*)-*O*-n-propyl ethanesulfinate and (−)-(*S*)-*O*-n-propyl *tert*-butanesulfinate with the appropriate organomagnesium reagents, as well as experiments on the synthesis of (−)-(*R*)-n-butyl *tert*-butyl sulfoxide strongly suggest retention of configuration in the reactions of either nonbranched alkanesulfinates with hindered organometallic reagents or sulfinates containing sterically demanding substituents at the sulfinyl sulfur atom with nonhindered organometallics.

Chiral, nonracemic sulfoxides are the most important class of chiral organosulfur compounds which have found a wide application in asymmetric synthesis.[1,2] A general and most often used method for preparing chiral sulfoxides involves treatment of chiral sulfinate esters with organometallic reagents. This method is known in the literature as the Andersen sulfoxide synthesis.[3] Andersen[4] and Mislow[5] and their coworkers showed unambiguously that nucleophilic attack by Grignard reagents on menthyl arenesulfinates is accompanied by complete inversion of configuration at the chiral sulfur atom. Since that time this stereochemical course has been generally accepted for the Grignard-sulfinate ester reactions. Moreover, the stereoinvertive conversion into sulfoxides has been applied as a convenient method for determining the optical purity and chirality of a great number of chiral sulfinates with the sulfur atom as a sole centre of chirality.[1]

Recent reports assuming either full inversion of configuration at sulfur in the reaction of *o*-(ω-hydroxy)alkyl *tert*-butanesulfinates with methyl lithium[6] or full retention of configuration at sulfur in the reaction of *o*-diacetone-D-glucose methanesulfinate with *tert*-butylmagnesium chloride[7] prompted us to disclose here our spectral and chemical observations indicating retention of configuration at sulfur in



Scheme 1

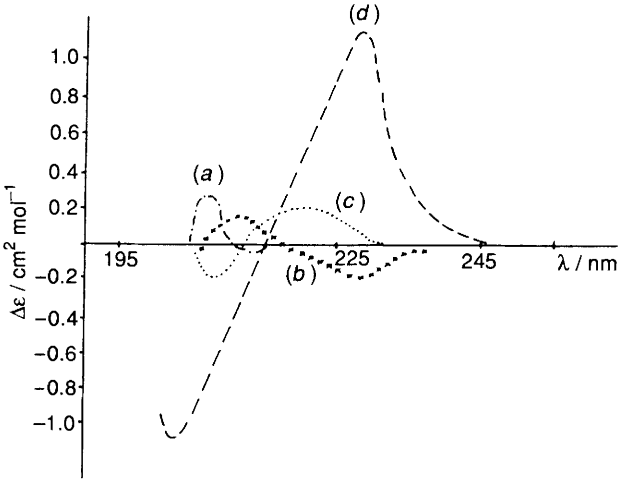


Fig. 1 CD spectra of isomeric butyl ethyl sulfoxides **1a–d** prepared from the common precursor (−)-(*S*)-EtS(O)OPr^n, **2**. (*a*) (+)-**1a**, (*b*) (+)-**1b**, (*c*) (−)-**1c** and (*d*) (−)-**1d**.

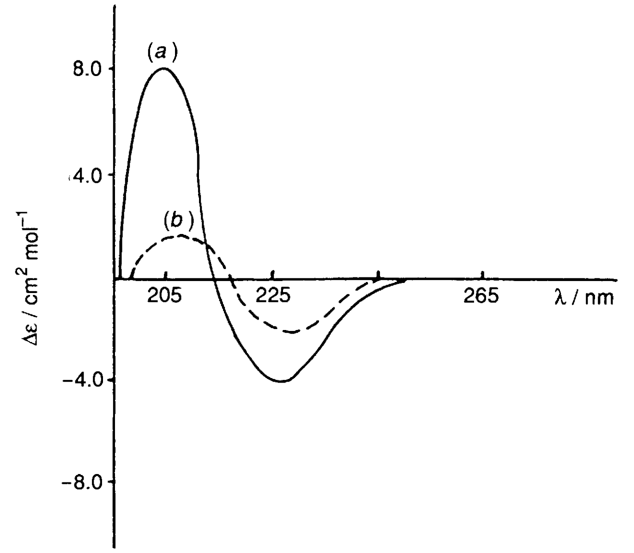
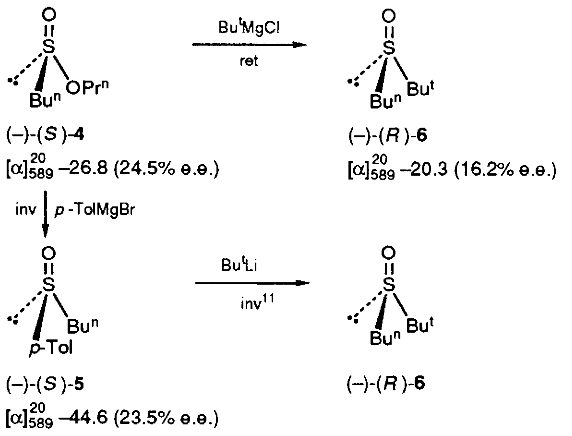


Fig. 2 CD spectra of (*a*) (−)-(*S*)-Bu^{t}S(O)OPr^n **3** and (*b*) (+)-(*S*)-Bu^{t}S(O)Et **1d**

the reaction of some sulfinic esters with selected organometallic reagents.

First, it was found that the reaction of optically active (−)-(*S*)-*O*-n-propyl ethanesulfinate **2**[8] with isomeric butylmagnesium halides, RMgX (R = Bu^n, Bu^i, Bu^s, Bu^t), produced the corresponding butyl ethyl sulfoxides **1a–d**, the first two of which, Bu^{n}S(O)Et **1a** and Bu^{i}S(O)Et **1b**, exhibited opposite optical rotations in the 365–589 nm region compared with those of Bu^{s}S(O)Et **1c** and Bu^{t}S(O)Et **1d** (Scheme 1).

All of these sulfoxides, just as a series of methyl alkyl sulfoxides,[5] exhibit in the far-UV region well-defined maxima at *ca.* 210–230 nm.† These absorptions are optically active, what is manifested by the presence of the Cotton effects in their CD spectra‡ (see Fig. 1). If the spectrum of the (+)-**1b** is compared with the spectrum of (−)-**1d**, one can easily see that the signs of these Cotton effects are inverted. Such a relationship clearly indicates the opposite chiralty at sulfur and consequently opposite stereochemical course of the reaction of the sulfinate (*S*)-**2** with the appropriate Grignard reagents. From this comparison, however, it is not evident which conversion is taking place with inversion of configuration and which affords the product with retained configuration with respect to the starting sulfinate **2**. To solve this question we compared the CD spectra of (−)-(*S*)-*O*-n-propyl *tert*-butanesulfinate **3**,[9] $[\alpha]^{20}_{589}$ −37.9 (EtOH) and (+)-**1d** $[\alpha]^{20}_{589}$ +23.7 (EtOH), obtained by the reaction of **3** with ethylmagnesium bromide (see Fig. 2). Homochiral character of these curves may be taken as evidence that this conversion occurs with retention of configuration§ at the sulfinyl sulfur atom and the sulfoxide (+)-**1d** should have the absolute configuration *S*. In the light of these observations one can conclude that both the reaction of *O*-n-propyl ethanesulfinate **2** with sterically demanding Grignard reagents such as *tert*-butylmagnesium chloride and the reaction of *O*-n-propyl *tert*-butanesulfinate **3** with ethylmagnesium bromide occur with retention of configuration at the reaction centre. Consequently, the reaction of sterically less demanding Grignard reagents such as the primary and secondary butylmagnesium halides with the sulfinate **2** should afford the appropriate butyl ethyl sulfoxides **1a** and **1d** with inverted configuration at the sulfur atom.



Scheme 2

Retention of configuration in the Andersen synthesis of optically active sulfoxides may also be deduced from the chemical correlation shown in Scheme 2 concerning the synthesis of (−)-n-butyl *tert*-butyl sulfoxide **6**.

To this end we have prepared *O*-n-propyl n-butanesulfinate **4** $[\alpha]^{20}_{569}$ −26.8 by the asymmetric condensation of n-butanesulfinyl chloride with n-propanol in the presence of (+)-*N*,*N*-dimethyl-α-phenylethylamine.[8] Its absolute configuration has been established as *S* based on the conversion into the corresponding (−)-(*S*)-n-butyl *p*-tolyl sulfoxide **5**[5] assuming inversion of configuration in this process.¶ When the sulfinate (−)-**4** was allowed to react with *tert*-butylmagnesium chloride, the corresponding (−)-n-butyl *tert*-butyl sulfoxide **6** was isolated. The same sulfoxide should be obtained from (−)-(*S*)-**5** on treatment with *tert*-butyllithium according to the procedure of Johnson.[11] If one assumes, as Johnson did,[11] that

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† All UV spectra were recorded on a Perkin-Elmer Lambda 5 UV–VIS spectrometer in hexane solutions.

‡ CD spectra were obtained on a Dichrograph Mark III (ISA-Jobin-Yvon) in quartz cells of lengths 0.02–1.00 cm, in hexane solutions, at concentrations of *ca.* 1 mg cm^{-3}.

§ Homochiral character of optical rotatory dispersion curves of methyl steroidal sulfinates and methyl steroidal sulfoxides derived from them of equivalent configuration at sulfur has already been observed. [see: D. N. Jones, D. Mundy and R. D. Whitehouse, *J. Chem. Soc.* (*C*), 1969, 1668]. This observation strongly supports our assumption that the chiroptical properties of *O*-alkyl alkenesulfinates parallel that of dialkyl sulfoxides. We would like to thank the referee for bringing this fact to our attention.

¶ This assignment has additionally been supported by the conversion of (−)-**4** into the corresponding (−)-n-butyl methyl sulfoxide; $[\alpha]^{20}_{589}$ −24.0 (acetone), 21.6% enantiomeric excess (e.e.), having *R* absolute configuration.[5]

this exchange reaction proceeds with inversion of configuration at sulfur, the absolute configuration *R* may be assigned to the sulfoxide (−)-**6**. This assignment is in accord with the shape of its CD spectrum (negative and positive Cotton effect at 202 and 226 nm, respectively). Since (−)-(*R*)-sulfoxide **6** was obtained from (−)-(*S*)-**4** and *tert*-butylmagnesium chloride, it should be assumed that this reaction occurs with retention of configuration at sulfur.[12]

These results call for more detailed studies on the stereochemical aspects of the reactions either nonbranched alkanesulfinates with hindered organometallic reagents as well as sulfinates containing sterically demanding substituents at the sulfinyl sulfur atom with nonhindered organometallics.

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11 J. P. Lockard, C. W. Schroeck and C. R. Johnson, *Synthesis*, 1973, 485; according to the procedure described in this paper treatment of (+)-(*R*)-**5**; $[\alpha]_{589}$ + 198.0 (acetone) with *tert*-butyllithium at −78 °C gave (+)-(*S*)-**6**; $[\alpha]_{589}$ +125.4 (acetone). In our hands this conversion was much less stereoselective. Thus, starting from the sulfoxide (+)-(*R*)-**5**; $[\alpha]_{589}$ +209.0 (acetone) the sulfoxide (+)-**6**; $[\alpha]^{20}_{589}$ +29.5 (acetone) was obtained.

12 Recently it has also been reported on retention of configuration at sulfur in the Andersen-type reaction of optically active monosubstituted sulfinamides with lithium acetates; S. Collona, G. Germinario, A. Manfredi and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1965.