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Chiral homoallylic and allylic sulfoxides as models for the stereochemical analysis of sulfoxide thiaoleates

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Abstract—Both enantiomers of *n*-butyl allyl sulfoxide have been synthesized and are reported as models of bio-oxidized thiafatty acid analogues. The stereochemical analysis of these aliphatic sulfoxides as well as their homoallylic counterparts, were performed by the use of chiral NMR shift reagents. We first checked the validity of the chiral solvating NMR reagents method using the α-methoxyphenylacetic acid (MPA) and the Pirkle-like alcohol 1-(9-anthryl)-2,2,2,-trifluoroethanol (TAE). We then compared the relative efficiency of these reagents in the enantiomeric discrimination of our sulfoxide models and determination of their enantiomeric excess. On the basis of experiments conducted on our real targets, optically enriched sulfoxides from the *Chlorella* incubations of 12- and 13-thiastearic acids, the versatality of these NMR reagents for the ee determination as well as the assignment of the absolute configuration at sulfur, are discussed.

1. Introduction

Chiral sulfoxides have become associated with many diverse areas of synthetic chemistry.[1] The main known methods of preparation of chiral sulfoxides follow two basic approaches: Asymmetric oxidation of nonsymmetric sulfides and nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates.[2,3] Andersen's method is currently the most widely applied strategy to access aryl sulfoxides in high enantiomeric excess.[4] This method is based on the purification of a menthylsulfinate ester from the mixture of epimeric diastereomers by repeated recrystallizations. The enantiomerically pure sulfinate is then displaced by an organomagnesium halide with complete inversion of stereochemistry at the sulfur as first demonstrated by Mislow and co-workers.[5] However the separation of alkyl menthylsulfinate diastereomers appears to be tricky and Andersen's synthesis is not efficient enough to access enantiomerically pure dialkyl sulfoxides. Other authors have developed synthetic schemes that established the enantiomeric purity at sulfur prior to addition to the organometallic reagent.[6–9] Alcudia and co-workers[8,9] reported the preparation of enantiomerically pure alkane- and arenesulfinates using diacetone D-glucose as an inducer of chirality and, by choosing the appropriate achiral base, acting as a chiral stereodirecting group.

Concerning the stereochemical analysis of the targeted chiral alkyl sulfoxides, chiral NMR shift reagents are known to be powerful tools, as first demonstrated by Pirkle and Beare.[10] It was postulated that a two point complexation model between the methyl alkyl sulfoxides and (*R*)-(−)-2,2,2-trifluorophenylethanol due to (i) hydrogen bonding between the alcohol function and the sulfinyl oxygen and to (ii) intramolecular interactions between the lone electron pair of sulfur and the carbinyl hydrogen of the alcohol reagent. This solvation model accounted for the observed enantiomeric spectral nonequivalence and appeared to be useful for direct determination of enantiomeric purities as well as the assignment of the absolute configurations of methyl alkyl sulfoxides. Pirkle et al. also demonstrated that the replacement of phenyl with α-naphthyl, 3-pyrenyl, or 9-anthryl groups of greater shielding ability, afforded powerful chiral solvents for elucidating the stereochemical data of other compounds.[11,12] Buist et al. took advantage of the known fact that carboxylic acids, such as the well known Mosher acid,[13] complex strongly with sulfoxides and have reported the use of (*S*)-α-methoxyphenylacetic acid [(*S*)-MPA] in discriminating diastereotopic hydrogens adjacent to the sulfinyl function of cyclic and acyclic sulfoxides.[14,15] (*S*)-MPA belongs to the large family of α-methoxyarylacetic acids successfully

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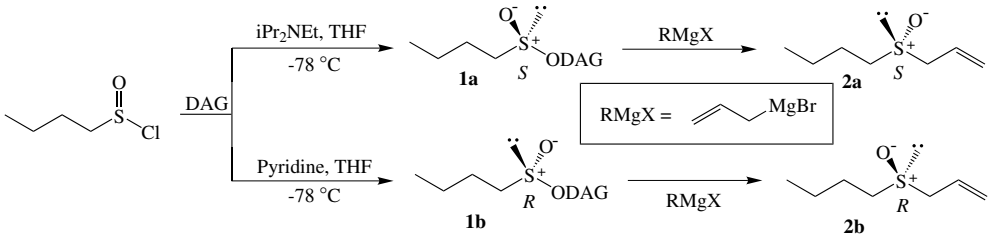


Scheme 1. Synthesis of the optically active sulfoxides model **2**.

used as NMR shift reagents to elucidate the absolute configurations of long chain aliphatic secondary alcohols,[16,17] amines[18] as well as sulfoxides.[14,15] More recently, we reported the usefulness of another member of this class of shift reagents, the (*R*)-α-methoxy-(1-naphthyl) acetic acid [(*R*)-1-NMA] obtained with high enantiomeric excess by fractional crystallization for differentiating the enantiomeric signals of quasi-symmetrical aliphatic sulfoxides.[19]

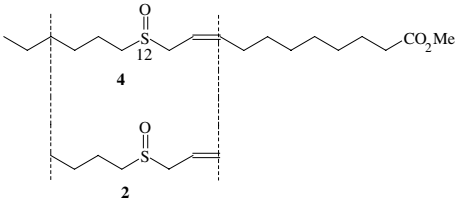
In connection with work on the mechanism of the in vivo desaturation of oleic acid,[20,21] we succeeded in synthesizing optically active sulfoxides of mono-unsaturated fatty acid analogues, by the use of the green algae *Chlorella vulgaris*.[22] We recently employed the 'DAG methodology' to synthesize, with high enantiomeric excess, both epimers of butylbutene sulfoxide **3**, which is a simple model for the homoallylic position of the sulfur in the sulfoxide 13-thiaoleate **5**.[23] Herein we report the synthesis of both epimers of the allylic model **2**, which mimics the allylic position of the sulfur in the sulfoxide 12-thiaoleate oleic acid analogue **4**. The stereochemical analysis of these models is achieved using both NMR shift reagents and chiral HPLC. We also studied the efficiency of chiral solvating NMR reagents for the stereochemical analysis of our sulfoxide models and determination of their enantiomeric excess. From these experiments, we attempted to define rules allowing the assignment of the absolute configuration of the sulfur of these dialkyl sulfoxides. The NMR methodology applied to the bio-oxidized thiafatty acids would be of great interest for elucidating the absolute configuration of these original chiral sulfoxides.

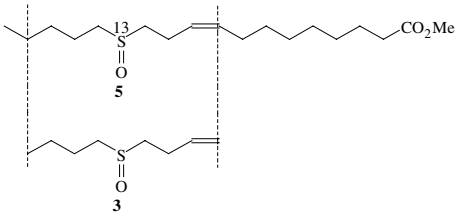
Table 1. Enantiomeric excess of sulfinates **1** and sulfoxides models **2** and **3**

Compound	Yield (%)	$[\alpha]_D^{20}$ (EtOH)	Configuration at sulfur	De or ee (%)
1a	48	−0.3 (*c* 0.5)	*S*	98[a]
1b	71	+0.1 (*c* 0.5)	*R*	98[a]
2a	66	−0.6 (*c* 0.6)	*S*	96[b]
2b	73	+0.6 (*c* 0.6)	*R*	96[b]
3a	84	+3.2 (*c* 0.5)	*S*	96[c]
3b	68	−3.7 (*c* 0.6)	*R*	96[c]

[a] Evaluated by ^{1}H NMR (only one diastereoisomer was detected).[23]
[b] Evaluated by ^{1}H NMR with MPA (only one enantiomer detected) and chiral HPLC (Chiralcel OB®).
[c] Evaluated by ^{1}H NMR with MPA (only one enantiomer detected).

are treated with freshly prepared allyl magnesium bromide in toluene at 0 °C (Scheme 1). The two epimeric sulfoxides (*S*)-**2a** and (*R*)-**2b** are then isolated after column chromatography (ethyl ether/petroleum ether 8/2, v/v then ethyl acetate) in good yield and enantiomeric excess. Table 1 summarizes the results obtained for sulfinates **1**, allylic sulfoxides **2**, and for the already reported[23] homoallylic sulfoxides **3**. The enantiomeric excess of the sulfoxides is determined by NMR shift experiments using shift reagents such as the famous α-methoxyphenyl acetic acid (MPA) previously used by Buist et al.[14,15] for analyzing the stereochemistry of dialkylsulfoxides. Moreover, allylic sulfoxides can be successfully separated by chiral HPLC using the Chiralcel OB® column with isocratic conditions of elution, whereas the homoallylic counterparts cannot be discriminated on this column. The absolute configuration





2. Results and discussion

2.1. Synthesis of optically active allylic models

According to the synthesis of homoallylic models previously described,[23] both butanesulfinates (*S*)-**1a** and (*R*)-**1b** are obtained according to the DAG methodology, and, after purification by column chromatography, of sulfur for both sulfoxides is deduced from those of the corresponding sulfinates, as the displacement step is known to occur with complete inversion of configuration at sulfur.[5,8] This inversion has recently been demonstrated by the attribution of the stereochemistry of cyclohexanesulfinate from diacetone-D-glucose and the formation of sulfoxides of already known configurations.[24]

2.2. Stereochemical analysis of homoallylic and allylic sulfoxides

2.2.1. Validation of the NMR method for the stereochemical discrimination of the sulfoxide models. The evaluation of the enantiomeric excess of the sulfoxides is first achieved by ^{1}H NMR with the use of a shift reagent to resolve the complex spin system around the sulfur. Chiral solvating agents such as the 2,2,2-trifluorophenylethanol,[10] and α-methoxyphenylacetic acid[14,25] (MPA) or the 1-(9-anthryl)-2,2,2-trifluoroethanol (TAE)[26] are commonly used to form diastereoisomeric solvation complexes with sulfoxide enantiomers *via* rapidly reversible equilibria in competition with the bulk solvent. We thus used in this study, both the MPA and Pirkle-like chiral alcohol TAE in order to compare their efficiency in the stereochemical analysis of our sulfoxide models. We first checked that the use of chiral solvating reagents could be argued in our case. As rigorously reported by Riguera and co-workers[27] and in accordance with the fundamentals of the method, the $\Delta\delta^{S,R}$ values† (identically $\Delta\delta^{R,S}$ values) must fulfill two basic conditions to be valid for configurational assignment using any of the reagents described above: (i) they should be well above the experimental error and (ii) they should take positive values on one side of the stereogenic center (R_1) and negative values on the other (R_2) as illustrated in Figure 1.

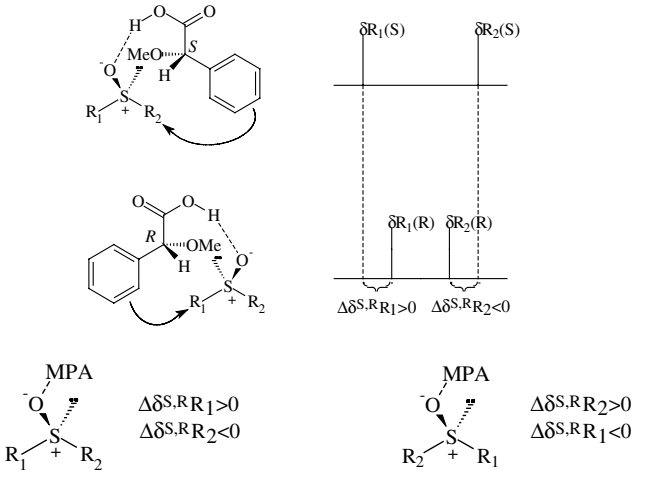


Figure 1. Configurational models for diastereoisomeric aggregates of alkyl sulfoxides with MPA according to the Buist's model.[14,15] Arrows indicate the predominant shielding effect caused by the phenyl group in their NMR spectra.

In our two sulfoxides **2** and **3**, the expected opposite signs of $\Delta\delta^{R,S}$ are obtained at both sides of the asymmetric center, confirming the applicability of the NMR method in that case. Table 2 shows the alternation of signs of the $\Delta\delta^{R,S}$ concerning the homoallylic sulfoxide **3** with MPA as well as with TAE.

Table 2. $\Delta\delta^{R,S}$ for the chiral sulfoxide **3b** with TAE and for the chiral sulfoxide **3a** with MPA in $CDCl_3$

Position	TAE		MPA	
	$\Delta\delta^{R,S}$ ^{1}H NMR	$\Delta\delta^{R,S}$ ^{13}C NMR	$\Delta\delta^{R,S}$ ^{1}H NMR	$\Delta\delta^{R,S}$ ^{13}C NMR
1	−0.081	nm	−0.227	−0.017
2	−0.107	nm	−0.032	−0.025
3	−0.132	−0.120	−0.039	−0.041
4	nm	−0.016	−0.050	−0.041
	nm		−0.012	
5	nm	+0.016	+0.028	+0.031
	+0.086		+0.008	
6	+0.137	+0.064	+0.031	+0.023
7	+0.123	+0.104	+0.029	+0.023
8	+0.085	+0.056	+0.020	+0.015

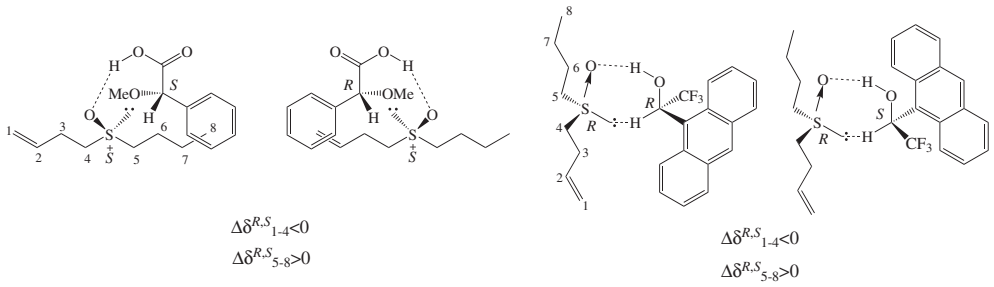
nm: not measured.

The different complexation models for both NMR shift reagents, initially proposed by Buist et al. (MPA)[14,15] and Pirkle and Hoover (TAE),[26] are presented in Scheme 2 and appear to be consistent with the measured values. It is noteworthy that the signs of $\Delta\delta^{R,S}$ are opposite for both NMR reagents. Indeed the $\Delta\delta^{R,S}$ data mentioned above (Table 2) have the same signs but in one case (MPA), for the (*S*)-enantiomer **3a** and in the other (TAE), for the (*R*)-enantiomer **3b**. Moreover, we checked that one enantiomer of the chiral models **2** and **3** in the presence of one of the enantiomeric forms of an NMR reagent gave the same spectrum as the one obtained with the respective enantiomers [i.e., the spectrum of **2a** with (*R*)-MPA is the same as the one obtained with **2b** and (*S*)-MPA]. Lastly, the larger splitting effect of TAE over MPA was seen to extend on the overall aliphatic chain and both the ^{13}C and ^{1}H NMR spectra.

From these experiments, the assignment of the absolute configuration at the sulfur for these dialkyl sulfoxides **2** and **3** as well as the real targets **4** and **5**, could notably be deduced on the basis of the sign of the $\Delta\delta^{R,S}$ for the unsaturated and the saturated parts of the alkyl chain as reported in Table 3.

2.2.2. Influence of the shift reagent and of the solvent on the discrimination of the sulfoxide enantiomers. The main drawback of the method using chiral solvating agents is that $\Delta\delta$ values tend to be rather small. Nonpolar solvents ($CDCl_3$, C_6D_6, ...) tend to maximize the observed anisochrony between the diastereoisomeric complexes.[26] We previously observed the very efficient effect of C_6D_6 as an NMR solvent over $CDCl_3$ causing a much larger splitting of the signals for the discrimination of the enantiomers of **3**.[23] As expected, this effect coupled with the use of (*S*)-MPA allows us to resolve most of the methylene signals. Figure 2 shows the shielding and deshielding effects of the solvent used ($CDCl_3$ and C_6D_6)

† $\Delta\delta^{S,R}$ for R_1 (or R_2) represents the difference between the chemical shift of the substituent R_1 (or R_2) of the chiral substrate when it is derivatized with the (*S*)-chiral auxiliary reagent [i.e., (*S*)-MPA] and the chemical shift when the substrate is derivatized with the (*R*)-chiral auxiliary reagent [i.e., (*R*)-MPA]. Obviously, considering $\Delta\delta^{R,S}$ instead of $\Delta\delta^{S,R}$ involves a permutation of the signs concerning R_1 and R_2.



Scheme 2. $\Delta\delta^{R,S}$ at both sides of the stereogenic center for the complexation models **3** with MPA and TAE.

Table 3. Attribution of the absolute configuration of the alkyl alkenyl sulfoxides according to the respective signs of the $\Delta\delta^{R,S}$ at both sides of the stereogenic center

NMR reagent	Sign of the $\Delta\delta^{R,S}$		Absolute configuration
	Unsaturated part	Saturated part	
MPA	+	–	*R*
	–	+	*S*
TAE	+	–	*S*
	–	+	*R*

as well as the splitting effect of the NMR reagent (MPA or TAE) on the overall ^{1}H NMR spectra of the racemic sulfoxide **2**. The use of C_6D_6 causes a better splitting effect of the H_3 and $H_{3'}$ signals without any shift reagent (Fig. 2a and b) as well as with a shift reagent, TAE in particular (Fig. 2e and f). It is noteworthy that all the NMR experiments are realized with 3 mol equiv of the shift reagent, according to our previous work.[19,23] Indeed, Buist et al.[28] recorded the NMR signals due to the α-sulfinyl hydrogens of various racemic sulfoxide and demonstrated that 3 equiv of MPA is necessary to cause these resonances to shift downfield and split into doublets. Moreover, Pirkle et al.[29] who first described a solvation model, which accounts for this observed nonequivalence for many sulfoxides forming solvates with its famous 'Pirkle alcohol', demonstrated that these nonequivalence values are dependent on the relative concentration of the shift reagent. In particular, he showed that a two to threefold excess of its alcohol shift reagent ensures that all the sulfoxide is hydrogen bonded and that little additional nonequivalence is obtained beyond a threefold excess of NMR reagent.

In order to evaluate the enantiomeric excess of an enantiomerically enriched chiral compound, the chemical shifts' difference of identical groups of the two enantiomeric forms of this compound, in the presence of an enantiomerically pure NMR shift reagent, noted $\Delta\delta$, could be of valuable interest. The evaluation of these values for the proton and the carbons chemical shifts of sulfoxide **2** in the presence of MPA are reported in the Table 4. According to these data, it appears that some of the $\Delta\delta$ are not measurable, especially using deuterated

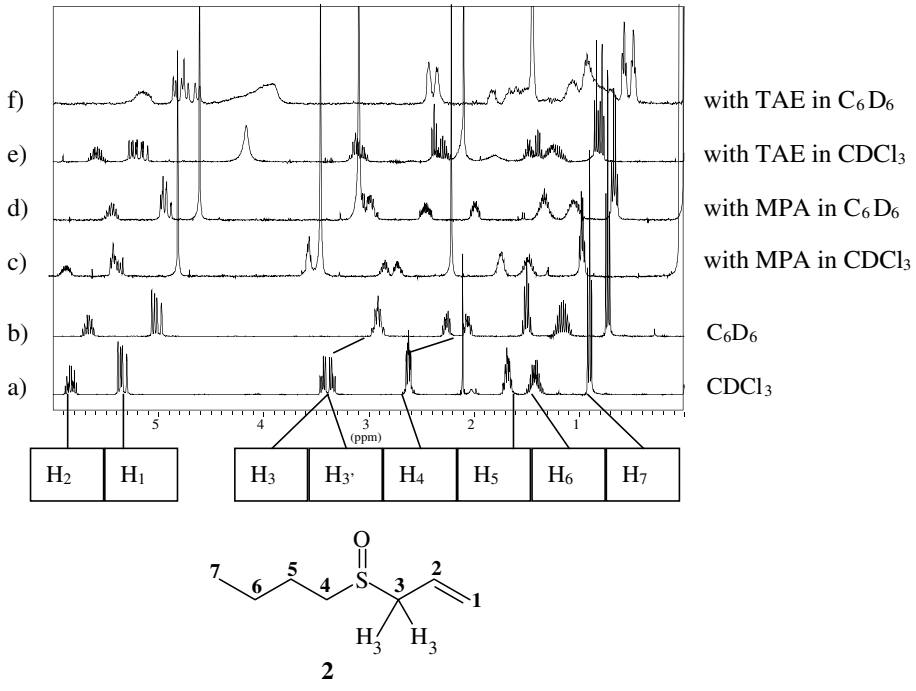


Figure 2. Influence of the solvent and the NMR reagent on the splitting and position of the signals of the racemic sulfoxide **2**.

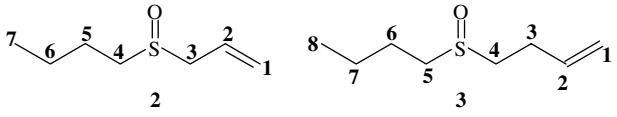
Table 4. Effect of MPA on the $|\Delta\delta|$ of sulfoxide **2**

Position	^{1}H NMR		^{13}C NMR	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1	0.043	nm	0	0
	0.025	nm		
2	0.012	0.024	0.032	0.056
3	0.001	0.003	0.024	0.048
	0.012	0.046		
4	0.014	nm	0	0
	0.015	nm		
5	nm	nm	0.016	0.024
6	nm	nm	0	0
7	0.016	0.020	0	0

nm: not measured.

benzene as solvent, because of the overlapping of the multiplets or because of the masking effect by the NMR reagent's signals. Moreover, the effect of MPA on the magnitude of the nonequivalence of the carbon signals are low or sometimes almost zero, especially in the deuterated chloroform. However, TAE appears to be more efficient in the enantiomer differentiation of most carbons signals of sulfoxide **2** when compared to MPA (Table 5). Surprisingly, the carbons adjacent to the sulfinyl function cannot successfully be differentiated with TAE (Table 5). This phenomenon could probably be explained by the conformation of the solvation complex between the sulfoxides and TAE (Scheme 2), as well as by the likely weaker π-stacking (π-acid π-base) interactions[30] involved in this complex when compared to the greater π-stacking interactions of the MPA complexes due to the acidity function of the MPA.

Table 5. Effect of TAE on the $|\Delta\delta|$ of sulfoxides **2** and **3** in the ^{13}C NMR spectra



2 **3**

Position	Sulfoxide **2**		Sulfoxide **3**	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1	nm	nm	0.056	0.080
2	nm	nm	0.048	0.088
3	0	0	0.080	0.112
4	0	0	0.024	0
5	0.048	0.056	0	0
6	0.072	0.104	0.048	0.064
7	0.04	0.056	0.072	0.088
8	—	—	0.032	0.048

nm: not measured.

The very large nonequivalence $\Delta\delta$ for the diastereotopic protons, observed with TAE, is responsible for the overlapping of some multiplets signals, limiting the efficiency of this reagent. However, the TAE is able to differentiate between the diastereotopic protons of the terminal methyl group to such an extent that chiral discrimination can be detected and ee evaluated. In order to better appreciate the larger splitting effect of TAE when compared to the one caused by MPA, Figure 3 illustrates the splitting of the methyl signal in the ^{1}H NMR spectra of the racemic sulfoxide **2** in C_6D_6. The discrimination of the enantiomeric triplets is very well achieved with TAE $\{|\Delta\delta| = 0.0852$ for **2**, $|\Delta\delta| = 0.0852$ for **3** in $C_6D_6\}$ in order to allow the determination of the enantiomeric excess of enantiomerically enriched sulfoxides **2** and **3**.

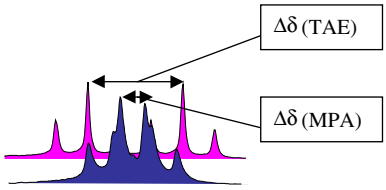


Figure 3. Splitting of the ^{1}H NMR CH_3 signal of racemic **2** with added shift reagent (pink: TAE; blue: MPA).

2.2.3. Stereochemical analysis of the bio-oxidized thiaoleates. We recently reported[19] the efficient splitting effect of the enantiomerically pure α-methoxy-(1-naphthyl) acetic acid (1-NMA) for differentiating the enantiomeric signals of the methyl of our target **5**, obtained from the bioconversion experiments.[22] Due to its extended effect on the alkyl chain reported above on the sulfoxide models, TAE could be a reagent of valuable interest for the discrimination of enantiomers of **4** and **5** in ^{1}H NMR spectra. However, the extrapolation to the case of the sulfoxide thiaoleates must be done very carefully as their alkyl chains are much longer than the models' chains, leading to an excessive amount of protons multiplets. This is likely to cause numerous overlappings and thus make difficult the interpretation of the spectrum. The analysis should consequently be done on isolated signals such as the (homo)allylic system as well as the terminal methyl. In fact, it appears that, because of a very bulky ^{1}H NMR spectrum, the methyl signal is the only one split sufficiently in order to discriminate both enantiomers of the sulfoxide. TAE is shown to be more efficient than our synthetic reagent 1-NMA for the discrimination of the enantiomeric triplets of our targets **4** and **5** (Fig. 4 illustrates this effect on the methyl triplets of **5**).

Examination of the ^{13}C NMR spectrum of **5** in the presence of TAE reveals splitting on carbons 8, 9, 10, 11, 15, and 18 whereas the carbons adjacent to the sulfinyl function as well as the carbons remote from the sulfur are not affected by TAE. Table 5 presents the $\Delta\delta$ values obtained on these carbon signals of **5** with different NMR reagents. Once again, TAE appears to be the more efficient NMR reagent for the differentiation of the carbons signals of both enantiomers of **5**, with a particularly high effect on C11, as previously reported by Buist et al. during the *S. cerevisiae* oxidation experiments on methyl 9-thiastearate. Therefore, the determination of the absolute configuration at the sulfur of these chiral sulfoxides, according to the respective signs of the $\Delta\delta^{R,S}$ at both sides of the stereogenic center (Table 3), is only supported by the $\Delta\delta^{R,S}$ data obtained for a few positions and thus appears to be more hazardous.

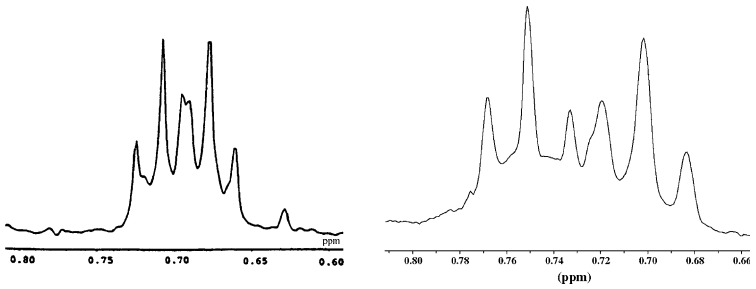


Figure 4. Splitting of the ^{1}H NMR CH_3 signal of racemic **5** with added shift reagent (left: 1-NMA; right: TAE).

Moreover, the rather tiny amount of bio-oxidized sulfoxides isolated from the cellular bulk has not yet allowed the evaluation of the ee by this method because of a bad resolution of the NMR spectrum. This thiafatty acids incubation process must be scaled-up in order to achieve the stereochemical analysis by the NMR methodology of the isolated optically active sulfoxides (ee >90% determined by chiral HPLC).[22]

3. Conclusion

The synthesis of enantiomerically pure dialkyl sulfoxides as models for the complicated stereochemical analysis of the bio-oxidized thiafatty acids, has been achieved successfully by the use of the DAG methodology. The use of MPA and TAE, as chiral solvating agents in NMR, allows the validation of this method for the stereochemical analysis of these types of compounds. Moreoever, TAE appears to be very efficient in discriminating between both enantiomers of the sulfoxide models and to evaluate the ee of enantiomerically enriched samples. Lastly, experiments conducted on our real targets, enantiomerically enriched sulfoxides from the *Chlorella* incubations of 12- and 13-thiastearic acids[22] (ee >90% determined by chiral HPLC) demonstrate the interesting behavior of TAE in the measurement of ee as well as the limitation of the method compared to the HPLC analysis, as more considerable amounts of isolated material is needed. Indeed, 5–10-fold increased incubation experiments should allow the stereochemical analysis of the bio-oxidized sulfoxides by this method. The determination of the absolute configuration at the sulfur might be attempted on the basis of the $\Delta\delta^{R,S}$ data but only if TAE effect could at last be extended in order to successfully decouple most of the carbon atoms of S-oxide thiaoleic acids. However, the methodology presented herein will be of great interest for the stereochemical analysis of the sulfoxides obtained from our *C. vulgaris* oxidation experiments currently conducted on alkyl alkenyl sulfurs.

4. Experimental

4.1. General methods

Tetrahydrofuran (THF) and toluene were dried with sodium/benzophenone before distilling. Chemicals were commercially available and used as received. Thin layer chromatography (TLC) analysis was carried out on precoated plates of silica gel 60 F_{254} (Merck) with detection by UV absorption (254 nm) when applicable, and charring with 5% H_2SO_4 in EtOH or spraying with 60 g/L phosphomolybdic acid in EtOH. Preparative chromatography was performed by elution from columns of silica gel 60 H (5–40 μm). Enantiomeric excesses were determined on a Chiralcel OB® column (Daicel Chemical Industries Ltd 250×4.6 mm). Optical rotations were determined with a Perkin–Elmer 341 polarimeter at 20 °C using a 1-dm cell. ^{1}H NMR and ^{13}C NMR spectra were recorded with an ARX-400 Bruker spectrometer at 400 and 100 MHz, respectively. Chemical shifts are given in ppm (δ) and coupling constants (J) in hertz (Hz). The abbreviations br, m, s, d, t, q, qt, and st stand for broad, multiplet, singlet, doublet, triplet, quadruplet, quintuplet, and sextuplet, respectively. Glucose carbons of sulfinates **1a** and **1b** are designated as C_1, C_2, C_3, C_4, C_5, and C_6. Carbons and hydrogens of sulfoxides **2** and **3** are designated as numbered in the text. Tetramethylsilane (TMS) is used as the internal standard. The correct assigments are established using routine COSY and HMQC (HETCOR) experiments. For the assays with NMR shift reagent, all the samples were prepared as follows: to 1 mg of the sulfoxide in 0.5 mL of solvent, were added 3 equiv of the desired NMR shift reagent. All the spectra were recorded in $CDCl_3$, at 298 K, after thermal stabilization of the samples. Mass spectra were realized and recorded by the C.R.M.P.O (Rennes Beaulieu, France) using a high resolution mass spectrometer MAT 311. Microanalyses were performed by the Service de Microanalyses de l'ICSN (Gif-sur-Yvette, France).

4.2. *n*-Butylsulfinyl chloride

n-Butyl disulfide (9.7 mL, 50 mmol) was dissolved in acetic acid (5.7 mL, 100 mmol). The mixture was cooled at −20 °C while stirring under a nitrogen atmosphere. Sulfuryl chloride was then added slowly (15 min). The reaction mixture was next warmed up to room temperature for 2 h then heated at 35 °C for 1 h. After distillation under reduced pressure, *n*-butylsulfinyl chloride was obtained (12.4 g, 79%), Eb (1 mbar) = 44–46 °C; ^{1}H NMR: δ 3.46 (m, 2H, CH_2SO), 1.97 (qt, 2H, $J = 7.64$ Hz, CH_2CH_2S), 1.64 (st, 2H, $J = 7.64$ Hz, CH_2CH_3), 1.06 (t, 3H, $J = 7.12$ Hz, CH_3); ^{13}C NMR: δ 64.8 (CH_2SO), 24.79, 22.23 (2C), 14.27 (CH_3).

4.3. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranosyl-(*S*)-butyl-sulfinate 1a

To a solution of diacetone-D-glucose (DAG) (3.98 g, 15 mmol) and iPr$_2$NEt (6.7 mL, 37.5 mmol) in anhydrous THF, cooled to −78 °C and placed under nitrogen atmosphere, *n*-butylsulfinyl chloride (5.28 g, 37.5 mmol) was added while the reaction mixture was being vigorously stirred. After stirring at −78 °C for 4 h and warming to room temperature, H_2O (40 mL) and CH_2Cl_2 (80 mL) were added and the organic layer successively washed with HCl, $NaHCO_3$ (2%) and a saturated solution of aqueous NaCl. After drying on $MgSO_4$ and removal of the solvent, chromatographic purification (Et_2O/petroleum 3/7) gave the compound **1a** as a colorless oil (2.62 g, 48%); TLC: $R_f = 0.35$ (Et_2O/petroleum ether 2/1); $[\alpha]_D = -0.3$ (c 0.5 EtOH); de = 98%; ^{1}H NMR: δ 5.91 (d, 1H, $J = 3.56$ Hz, H_1), 4.74 (d, 1H, $J = 2.60$ Hz, H_3), 4.60 (d, 1H, $J = 3.60$ Hz, H_2), 4.33–4.26 (m, 2H, H_4 and H_5), 4.10 (dd,1H, $J_{H5,H6} = 5.62$ Hz, $J_{H6,H6'} = 8.64$ Hz, H_6), 4.01 (dd, 1H, $J_{H5,H6'} = 4.84$ Hz, $J_{H6,H6'} = 8.64$ Hz, $H_{6'}$), 2.80 (m, 2H, CH_2S), 1.67 (qt, 2H, $J = 7.12$ Hz, CH_2CH$_2$S), 1.51, 1.43, 1.34, 1.31 (4s, 12H, C(CH$_3$)$_2$), 1.45 (q, 2H, $J = 7.64$ Hz, CH_2CH$_2$CH$_2$S), 0.96 (t, 3H, $J = 7.12$ Hz, CH_3); ^{13}C NMR: δ 113.09 (C(CH$_3$)$_2$), 109.86 (C(CH$_3$)$_2$), 105.64 (C_1), 84.28 (C_2), 81.05 (C_4), 79.81 (C_3), 73.07 (C_5), 67.36 (C_6), 57.80 (CH_2S), 27.40, 27.38, 26.94, 25.84 (C(CH$_3$)$_2$), 23.94 (CH$_2$CH$_2$S), 22.64 (CH$_2$CH$_2$CH$_2$S), 14.34 (CH_3). Anal. Calcd for $C_{16}H_{28}O_7S$: C, 52.73; H, 7.74. Found: C, 52.87; H, 7.82.

4.4. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranosyl-(*R*)-butyl-sulfinate 1b

Compound **1b** was obtained as described previously for **1a**, except that iPr$_2$NEt was replaced by pyridine (3.1 mL, 37.5 mmol) and gave **1b** as a colorless oil (3.88 g, 71%); TLC: $R_f = 0.5$ (Et_2O/petroleum ether 2/1); $[\alpha]_D = +0.1$ (c 0.5 EtOH); de = 98%; ^{1}H NMR: δ 5.90 (d, 1H, $J = 3.56$ Hz, H_1), 4.79 (d, 1H, $J = 3.60$ Hz, H_3), 4.72 (br s, 1H, H_2), 4.16–4.11 (m, 3H, H_4, H_5, and H_6), 4.00–3.97 (m, 1H, $H_{6'}$), 2.81 (2dt, 2H, $J = 13.30$ Hz, $J = 7.70$ Hz, CH_2S), 1.71 (qt, 2H, $J = 7.64$ Hz, CH_2CH$_2$S), 1.49, 1.41, 1.32, 1.29 (4s, 12H, C(CH$_3$)$_2$), 1.45 (q, 2H, $J = 7.64$ Hz, CH_2CH$_2$CH$_2$S), 0.95 (t, 3H, $J = 7.64$ Hz, CH_3); ^{13}C NMR: δ 113.03 (C(CH$_3$)$_2$), 110.06 (C(CH$_3$)$_2$), 106.00 (C_1), 84.48 (C_2), 83.70 (C_4), 81.61 (C_3), 72.76 (C_5), 68.37 (C_6), 58.37 (CH_2S), 27.50, 27.39, 26.84, 25.91 (C(CH$_3$)$_2$), 23.75 (CH$_2$CH$_2$S), 22.62 (CH$_2$CH$_2$CH$_2$S), 14.35 (CH_3).

4.5. (*S*)- and (*R*)-Allylbutyl-sulfoxides 2a and 2b

Butyl-sulfinate (0.6 g, 1.65 mmol) was dissolved in anhydrous toluene (33 mL). After cooling to 0 °C, allyl magnesium bromide (3.3 mL, 1 mol/L in Et_2O, 3.3 mmol) was added with stirring maintained for 1 h at room temperature. Neutralization was then carried out with a saturated solution of aqueous NH_4Cl (30 mL). The aqueous layer was extracted with CH_2Cl_2 and the resulting organic layers combined, washed with a saturated solution of aqueous NaCl, dried on $MgSO_4$ and concentrated. Chromatography of the residue was done successively with Et_2O/petroleum ether 8/2 and ethyl acetate giving allylbutyl sulfoxide as a colorless liquid; TLC: $R_f = 0.1$ (ethyl acetate); **2a** ($m = 0.16$ g, 66%); $[\alpha]_D = -0.6$ (c 0.6 EtOH); ee 96%; **2b** ($m = 0.18$ g, 73%); $[\alpha]_D = +0.6$ (c 0.6 EtOH); ee 96%; ^{1}H NMR: δ 5.86 (m, 1H, H_2), 5.40 (d, 1H,$J_{H1-H2} = 9.9$ Hz, H_1), 5.35 (dd, 1H, $J_{H1'-H2} = 17.0$ Hz, $J_{H1-H1'} = 1$ Hz, $H_{1'}$), 3.49–3.35 (m, 2H, H_3), 2.71–2.59 (m, 2H, H_4), 1.75–1.66 (m, 2H, H_5), 1.54–1.35 (m, 2H, H_6), 0.93 (t, 3H, $J = 7.4$ Hz, H_7); ^{13}C NMR: δ 126.4 (C_2), 124.0 (C_1), 56.3 (C_3), 51.2 (C_4), 25.0 (C_5), 22.6 (C_6), 14.3 (C_7). HRMS for $C_7H_{14}OS$: m/z [M]$^+$: calcd 146.0765; found 146.077; [M−OH]$^+$: calcd 129.0738; found 129.074.

4.6. (*S*)- and (*R*)-Butenylbutyl-sulfoxides 3a and 3b

Previously worn off magnesium turnings (0.18 g, 7.13 mmol) were covered with the minimal amount of anhydrous THF under nitrogen flux. The Grignard reagent was prepared by the slow addition of 4-bromobut-1-ene (0.57 mL, 5.49 mmol) diluted in anhydrous THF (11 mL). After 1 h at reflux, the Grignard reagent was transferred to a solution of butyl-sulfinate (1 g, 2.74 mmol) in anhydrous toluene (55 mL) at 0 °C. As soon as the sulfinate had disappeared, the reaction mixture was neutralized with a saturated solution of aqueous NH_4Cl (30 mL). The aqueous layer was extracted twice with CH_2Cl_2, the resulting organic layers are combined, washed with a saturated solution of aqueous NaCl, dried over $MgSO_4$, and concentrated. Chromatography of the residue was done successively with Et_2O/petroleum ether 8/2 and ethyl acetate giving the expected butenylbutyl sulfoxide as a colorless liquid; TLC: $R_f = 0.14$ (Et_2O); **3a** ($m = 0.37$ g, 84%); $[\alpha]_D = +3.2$ (c 0.51 EtOH); ee 96% ; **3b** ($m = 0.3$ g, 68%) ; $[\alpha]_D = -3.7$ (c 0.62 EtOH); ee 96%; ^{1}H NMR: δ 5.86 (m, 1H, H_2), 5.10 (d, 1H, $J_{H1-H2} = 17.29$ Hz, H_1), 5.04 (d, 1H, $J_{H1'-H2} = 10.16$ Hz, $H_{1'}$), 2.83–2.61 (m, 4H, H_4 and H_5), 2.56 (dt, 2H, $J_{H2-H3} = 7.12$ Hz, $J_{H3-H4} = 6.60$ Hz, H_3), 1.76 (q, 2H, $J = 7.64$ Hz, H_6), 1.66–1.41 (m, 2H, H_7), 0.96 (t, 3H, $J = 7.60$ Hz, H_8); ^{13}C NMR: δ 135.95 (C_1), 117.52 (C_2), 56.66, 51.02 (C_4 and C_5), 27.62 (C_3), 25.39 (C_6), 22.68 (C_7), 14.31 (C_8). HRMS for $C_8H_{16}OS$: m/z [M−C_3H_7]$^+$: calcd 117.0375; found 117.037.

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