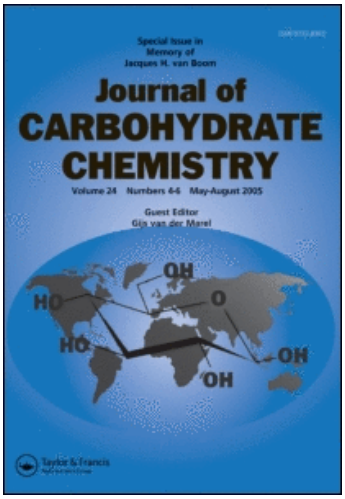

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Asymmetric Oxidation Of D-Glyceraldehyde Diethyl Dithioacetal With A Sharpless Reagent

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ABSTRACT

The asymmetric oxidation reaction of D-glyceraldehyde diethyl dithioacetal **1** and its di-*O*-acetyl derivative with a Sharpless reagent to produce the corresponding D-glyceraldehyde diethyl dithioacetal *S*-oxide derivatives takes place with high stereoselectivity. The configuration of the two new chiral centres formed is deduced.

INTRODUCTION

The most immediate and usual method for the synthesis of optically active sulfoxides is the oxidation of sulfides with different Sharpless reagents. This procedure has been widely investigated by Kagan and coworkers,[1] and by Modena and coworkers,[2] using, in both cases, the mixture [$Ti(OiPr)_4$/(+)DET/H_2O/*t*-BuOOH] but, in proportions of 1:2:1:1 and 1:4:0:1, respectively. A great variety of sulfides has been oxidized by both procedures, the best results being obtained with substrates such as arylmethylsulfides,[1] 1,3-dithianes,[3,4] and 2-substituted-1,3-dithiolanes.[2] However, when dialkyl sulfides were oxidized, only moderate enantiomeric excesses were found.

We are interested in the preparation of optically active dialkyl dithioacetal mono S-oxides. These compounds represent a special class of chiral sulfoxides because their anions are the synthetic equivalents of acyl anions. In addition, the stability of these anions makes them very useful as nucleophiles, as has been proved in the synthesis of interesting compounds having notable biological activity.[4]

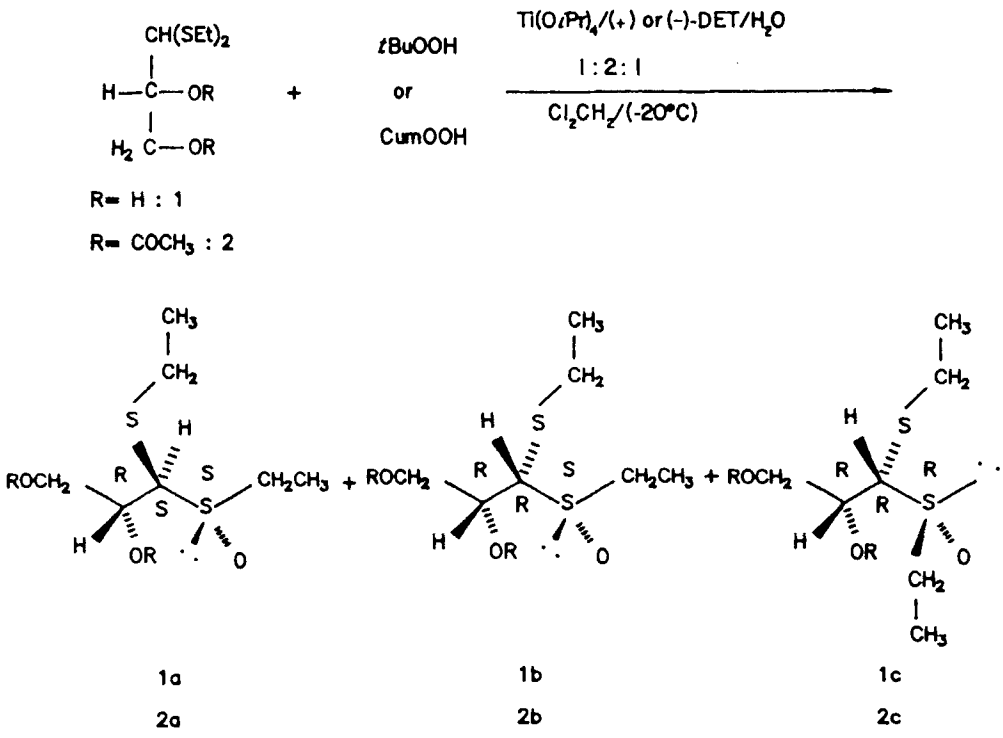
In an earlier paper,[5] we described the asymmetric oxidation of formaldehyde dimethyl and diethyl dithioacetals with a Sharpless reagent, obtaining an enantiomeric excess of up to 75% when Kagan's reaction was used, but strangely only 25% with Modena's procedure. The resulting optically active dialkyl dithioacetals mono S-oxides were used to react with *aldehydo*-sugars to obtain higher sugar derivatives[6,7] and to study the stereochemistry of the reaction.[8]

In a continuation of this research and to generalize the earlier results, the asymmetric oxidation of some dithioacetals, **1** and **2**, derived from D-glyceraldehyde, with a Sharpless reagent is described in the present paper (see **Scheme**).

RESULTS AND DISCUSSION

D-glyceraldehyde diethyl dithioacetal **1** was obtained by treatment of 2,3-*O*-isopropylidene-D-glyceraldehyde[9] with ethanethiol.[10] Acetylation of **1** with acetic anhydride and pyridine yields 2,3-di-*O*-acetyl-D-glyceraldehyde diethyl dithioacetal **2** quantitatively.

Initial oxidation experiments on **1** and **2** were carried out with the mixture $Ti(OiPr)_4/(+)$-DET/H_2O/*t*BuOOH in a 1:2:1:1 proportion at -20 °C. Oxidations of both compunds gave good yields and good product diastereoselectivity. Three of the four theoretically possible diastereoisomers were obtained, and, in both reactions, isomers **c** were formed in much higher proportion than isomers **a** and **b** (Table 1, entries 1 and 2). In order to improve the diastereomeric excess of **c**, the influences of temperature, oxidant and chiral ligand on the diastereoselectivity of oxidation of dithioacetal **2**, were studied. At -78 °C, no significant oxidation occurred, and when the temperature was increased (reaction above -20 °C), diastereoselectivity of the process decreased. Furthermore, the presence of the disulfoxides as secondary products was detected (entries 3 and 4). Oxidation of **2** with cumene hydroperoxide[11]



Scheme

Table 1. Asymmetric oxidation of dithioacetals **1** and **2** into monosulfoxides **a-c**.

Entry	D	T(°C)	Y(%)	a:b:c R	Oxidant	Ligand
1	1	-20	70	14:10:76	*t*-BuOOH	(+)-DET
2	2	-20	76	12: 8:80	*t*-BuOOH	(+)-DET
3	2	-10	60	23:23:54	*t*-BuOOH	(+)-DET
4	2	0	63	31:22:47	*t*-BuOOH	(+)-DET
5	2	-20	78	10: 5:85	CumOOH	(+)-DET
6	2	-20	80	42:28:30	*t*-BuOOH	(-)-DET
7	2	-78	no react.	-	-	-

D: dithioacetal. Y: total yield of isolated products. R: ratio of isolated products **a**:**b**:**c**.

(CumOOH), resulted in the formation of the monosulfoxide **2c** as the main product (entry 5). When (-)-DET was used as the chiral ligand (entry 6), a remarkable decrease in the yield of **2c** was observed, as well as an increase of that of **2a** and **2b**, **2a** being now the major isomer.

The absolute configurations of **1a**, **1b** and **1c** have been previously established[12] by X-ray crystallography and that of **2a**, **2b** and **2c**[13] can be established as well, because they are produced by acetylation of the former compounds[12] (Table 2). So, it can be concluded that when oxidations are carried out using (+)-DET, monosulfoxides **1c** and **2c** having *R* configurations at the sulfoxide centres[3] are the main products. In addition, compounds **1c** and **2c** both have an *R* configuration at the new chiral centre formed at C-1. When (-)-DET was used as the chiral ligand, the proportion of **2a** and **2b**, having an *S* configuration at the sulfoxide centre increases. Compound **2a**, having the *S* configuration at C-1, now becames the major product of the reaction.

These results indicate that the asymmetric induction of (+)-DET can justify the fact that the total amount of the diastereoisomers **b** and **c**, with an *R* configuration at C-1, is higher than that of **a**, bearing an *S* configuration at C-1. These differences among the relative yields of the three products are smaller in the last experiment, when (-)-DET is used. The most characteristic physical constants of **1a-c** and **2a-c** are indicated in the experimental section.

EXPERIMENTAL

Solvents used were dried over anhydrous sodium or magnesium sulfate, and solutions were concentrated under reduced pressure at a temperature below 40 °C. Methylene chloride was distilled over calcium hydride before being used. Commercial *t*-butyl hydroperoxide (Merck) and cumene hydroperoxide (Fluka) were used as supplied. Titanium isopropoxide [$Ti(OiPr)_4$], (+)-(*R,R*)-diethyl tartrate [(+)-DET] and (-)-(*S,S*)-diethyl tartrate [(-)-DET] (Fluka) were distilled and stored under argon. TLC was performed on glass plates coated with Silica Gel G (Merck), spots being detected with iodine vapors or by charring with sulfuric acid in ethanol (10%). Column chromatography was performed using Silica Gel Merck 60 (70-230 mesh).

Table 2. C-1 and S*O configuration in compunds **a**, **b** and **c**.

	a	**b**	**c**
C-1	*S*	*R*	*R*
S*O	*S*	*S*	*R*

Melting points were determined with a Gallenkamp MFB-595 apparatus, and optical rotations were measured at room temperature (20 °C) with a Perkin-Elmer 141 or an Atago "POLAX" polarimeters.

^{1}H NMR spectra for solutions in $CDCl_3$ were measured using Bruker WP-80-SY or an AM-300 spectrometers. Chemical shift values are expressed in ppm (δ) relative to TMS as an internal reference; signal multiplicities are noted as s, singlet; d, doublet; t, triplet; dd, double doublet; q, quartet and m, multiplet. Labile active hydrogens of some compounds were exchanged with deuterium oxide.

IR spectra were measured using a Perkin-Elmer 782, a Shimadzu 408 or a Nicolet FTIR-20-SX spectrometers. Mass spectra were recorded by the direct insertion technique, using an HP-5988-A spectrometer at 230 eV with a temperature source of 200 °C.

Elemental analyses were determined with a Carlo Erba Elemental Analyzer 1106.

Asymmetric Oxidation of D-Glyceraldehyde Diethyl Dithioacetal (1). Titanium isopropoxide [Ti(O*i*Pr)$_4$] (8 mmol, 2.4 mL) and (+)-(R,R)-DET (16 mmol, 2.75 mL) were dissolved in methylene chloride (80 mL) under an argon atmosphere at 25 °C. Water (0.14 mL, 8 mmol) was added, and the mixture was stirred until it became homogeneous. Then compound **1** (8 mmol) was added, the mixture cooled to -20 °C and a solution of *t*-butyl hydroperoxide (1M, 4 mL) in methylene chloride added. After 100 h at -20 °C, water (2.5 mL) was added to the cooled solution. The gelatinous mixture was stirred for one h while the temperature was allowed to rise to 20 °C. After filtration, the filtrate was extracted with methylene chloride, the organic

extracts were combined, dried, concentrated and the residue chromatographed (methylene chloride : diethyl ether, 50:1). Three of the possible diastereoisomers of (2*R*)-1-ethylsulfinyl-1-ethylthio-2,3-dihydroxy-propane were isolated as follows:

(1*S*,2*R*)-1-[(*S*)-Ethylsulfinyl]-1-ethylthio-2,3-dihydroxypropane (1a). Compound **1a** was a solid (166 mg, 10 %) : mp 68-69 °C (acetone-diethyl ether); R_f 0,4 (acetone : diethyl ether 3:1), as reported.[12]

(1*R*,2*R*)-1-[(*S*)-Ethylsulfinyl]-1-ethylthio-2,3-dihydroxypropane (1b). Compound **1b** was a solid (119 mg, 7 %); R_f 0.37 (acetone : diethyl ether 3:1), mp 74-75 °C (acetone-diethyl ether), $[\alpha]_D$ -24.2° (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$): 1.22-1.31 (m, 3H, $\underline{CH_3}$-CH_2-S), 1.38-1.46 [m, 3H, $\underline{CH_3}$-CH_2-S(O)], 2.62-3.00 (m, 2H, CH_2-S), 3.0-3.21 [m, 2H, CH_2-S(O)], 3.68-3.99 (m, 3H, H-C1 and 2H-C3), 4.23-4.39 (m, 1H, H-C2); IR (KBr) 3500-3150, 1445, 1380, 1270, 1000, 965 cm^{-1}; MS (m/z, CH_4 chemical ionization, relative intensity): 241 [(M+ +29), 0.3], 213 [(M+1)+, 4.6], 197 [(M+1)+-(O), 0.5], 195 [(M+1)+-H2O, 4], 177 [(M+1)$^+$-2H_2O, 4.7], 163 [(M+1)$^+$-H_2O-S, 3.2], 149 [(M+1)$^+$-H_2O-C_2H_4, 2], 135 [(M+1)$^+$-EtSOH, 100], 117 [(M+1)$^+$-EtSOH-H_2O, 63].

Anal. Calcd for $C_7H_{16}O_3S_2$: C, 39.59; H, 7.60. Found: C, 39.55; H, 7.67.

(1*R*,2*R*)-1-[(*R*)-Ethylsulfinyl]-1-ethylthio-2,3-dihydroxypropane (1c). Compound **1c** was a solid (904 mg, 54 %): R_f 0.31 (acetone : diethyl ether 3:1), mp 83-84 °C (acetone-diethyl ether); $[\alpha]_D$ +54.0° (*c* 0.5, chloroform), as reported.[12]

Asymmetric Oxidation of 2,3-Di-*O*-Acetyl-D-glyceraldehyde Diethyl Dithioacetal, 2. The procedure used was identical to that applied to compound **1**, except that two equiv of cumene hydroperoxide (20 mmol, 3.8 g) were employed as oxidant. The residue was chromatographed (methylene chloride : diethyl ether, 20:1), to give three products isolated in order of their elution as follows:

(1*R*,2*R*)-2,3-Diacetoxy-1-[(*S*)-ethylsulfinyl]-1-ethylthiopropane (2b). Compound **2b** was a colorless syrup (162 mg, 7 %): R_f 0.79 (acetone : diethyl ether 1:6); $[\alpha]_D$ -15.6° (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$): 1.3 (t, 3H, J = 7.5 Hz, $\underline{CH_3}$-CH_2S), 1.42 [t, 3H, J = 7,5 Hz, $\underline{CH_3}$-CH_2SO], 2.01 and 2.08 [2s, 6H, CH_3COO), 2.66-2.99 (m, 4H, CH_2-S and CH_2-SO), 3.82 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 4.31 (dd, 1H, $J_{3,3'}$ = 11.6 Hz, $J_{3,2}$ = 6.3 Hz, H-3), 4.54 (dd, 1H, $J_{3',3}$ = 11.6 Hz, $J_{3',2}$ = 4.8 Hz, H-3'), 5.63 (m (ABX), 1H, $J_{2,1}$ = 4 Hz, $J_{2,3'}$ = 4.8 Hz, $J_{2,3}$ = 6.3 Hz, H-2); IR (KBr, liquid film)), 1740,

1450, 1375, 1230 and 1055, 970 cm^{-1}; MS (m/z, CH_4 chemical ionization, relative intensity): 325 [M^++29, 0.7], 297 [(M+1)$^+$, 2.8], 237 [(M+1)$^+$-AcOH, 10.3], 219 [(M+1)$^+$-EtSOH, 100], 159 [(M+1)$^+$-EtSOH-AcOH, 67], 117 [(M+1)$^+$-EtSOH-$C4H_6O_3$, 15.6].

Anal. Calcd for $C_{11}H_{20}O_5S_2$: C, 44.57; H, 6.80. Found C, 44.45; H, 6.82.

(1*S*,2*R*)-2,3-Diacetoxy-1-[(*S*)-ethylsulfinyl]-1-ethylthiopropane (2a). Compound **2a** was a transparent syrup (81 mg, 3.5): R_f 0.74 (acetone : diethyl ether 1:6); $[\alpha]_D$ +23° (*c* 0.7, chloroform); ^1H NMR ($CDCl_3$): 1.37 (t, 3H, J = 7.5 Hz, $\underline{CH_3}$-CH_2S), 1.45 (t, 3H, J = 7.5 Hz, $\underline{CH_3}$-CH_2SO), 2.07 and 2.11 (2s, 6H, CH_3COO), 2.75-2.94 (m, 4H, CH_2-S and CH_2-SO), 4.05 (1H, d, $J_{1,2}$ = 7 Hz, H-1) 4.37 (dd, 1H, $J_{3,3'}$ = 12 Hz, $J_{3,2}$ = 5.8 Hz, H-3), 4.59 (dd, 1H, $J_{3',3}$ = 12 Hz, $J_{3',2}$ = 3.7 Hz, H-3'), 5.31-5.51 (m, 1H, $J_{2,1}$ = 7 Hz, $J_{2,3'}$ = 3.7 Hz, $J_{2,3}$ = 5.8 Hz, H-2); IR (KBr, liquid film), 1740, 1455,1375, 1230 and 1050, 970 cm^{-1}; MS (m/z, CH_4 chemical ionization, relative intensity): 325 [M^++29, 0.7], 297 [(M+1)$^+$, 4], 281 [(M+1)$^+$-(O), 0.3], 253 [(M+1)$^+$-C_2H_4O, 5], 237 [(M+1)$^+$-AcOH, 12.6], 219 [(M+1)$^+$-EtSOH, 100], 177 [(M+1)$^+$-2AcOH, 7.8], 159 [(M+1)$^+$-EtSOH-AcOH, 82.5], 117 [(M+1)$^+$-EtSOH-$C_4H_6O_3$, 20].

Anal. Calcd for $C_{11}H_{20}O_5S_2$: C, 44.57; H, 6.80. Found: C, 44.55; H, 6.85.

(1*R*,2*R*)-2,3-Diacetoxy-1-[(*R*)-ethylsulfinyl]-1-ethylthiopropane (2c). Compound **2c** was a solid (1.38 g, 58 %): R_f 0,65 (acetone : diethyl ether 1:6); mp 57-58 °C; $[\alpha]_D$ +58.2° (*c* 1.1, chloroform); ^1H NMR ($CDCl_3$): 1.29 (t, 3H, J = 7.3 Hz, $\underline{CH_3}$-CH_2S), 1.42 (t, 3H, J = 7.4 Hz, $\underline{CH_3}$-CH_2SO), 2.07 and 2.10 (2s, 6H, CH_3-COO), 2.63-3.18 (m, 4H, CH_2-S and CH_2-SO), 3.76 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.36 and 4.45 (2dd, 2H, $J_{3,3'}$ = 11 Hz, $J_{3,2}$ = $J_{3',2}$ = 6.2 Hz, 2H-3), 5.70 (t, 1H, $J_{2,1}$ = 3.2 Hz, $J_{2,3}$ = $J_{2,3'}$ = 6.2 Hz, H-2); IR (KBr) 1740, 1460, 1375, 1230 and 1050, 1215, 975 cm^{-1}; MS (m/z, CH_4 chemical ionization, relative intensity): 235 [M^++29, 0.3], 297 [(M+1)$^+$, 1], 281 [(M+1)$^+$-(O), 1.1], 253 [(M+1)$^+$-C2H_4O, 2], 237 [(M+1)$^+$-AcOH, 7], 219 [(M+1)$^+$-EtSOH, 61], 193 [(M+1)$^+$-C_2H_4O-AcOH, 1.1], 159 [(M+1)$^+$-EtSOH-AcOH, 100], 117 [(M+1)$^+$-EtSOH-$C_4H_6O_3$, 29].

Anal. Calcd for $C_{11}H_{20}O_5S_2$: C, 44.57; H, 6.80. Found: C, 44.50; H, 6.88.

Asymmetric Oxidations of 2 under different conditions. Oxidations of **2** under different conditions, varying the oxidant and the chiral ligand, were performed following the procedure for the previous oxidation. Experimental conditions used are indicated in Table 1, as well as total and partial yields of oxidation compounds.

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13. Treatment of **1a**, **1b** and **1c** with acetic anhydride and pyridine, yields **2b**, **2a** and **2c** respectively, exactly the same products as were obtained by asymmetric oxidation of **2**.