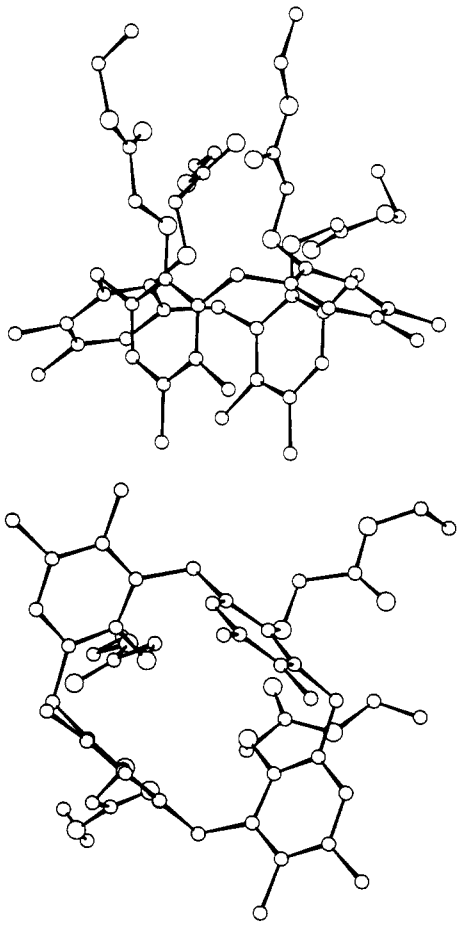

Figure 2. Molecular structure of **5a** seen from two different directions. Two enantiomeric molecules of **5a** are correlated in the crystal lattice via a symmetry center.

Figure 1, are doubled on addition of Pirkles reagent ((*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, **6**).[12] Surprisingly this doubling is found neither for the tetraester **5a** nor for the calixarene **2a** (at low temperature). Presumably hydroxyl groups not already involved in intramolecular hydrogen bonds are needed for an effective interaction with **6**.

The X-ray analysis of **5a** shows[13] the molecule in a strongly distorted cone conformation (Figure 2). A similar deformation of the calixarene part, obviously due in part to the steric requirements of the residues attached to the phenolic oxygens, was also observed for tetraester or tetraamide derivatives of calix[4]arenes substituted exclusively in the para position.[14] A comparison of the angles formed between the phenyl rings and the plane of the methylene carbons demonstrates that the distortion of **5a** is more pronounced. These angles are 150°, 94°, 147°, and 83° in **5a**, while 139°, 94°, 136°, and 92° were found for the corresponding tetraester derivative of *tert*-butylcalix[4]arene.[14]

The dissymmetric calix[4]arenes described have some important advantages in comparison to asymmetric compounds. As shown for two examples, derivatives in a well-defined conformation, including also mono and 1,2 derivatives,[15] will be easily accessible. Furthermore, it should be possible to obtain similar compounds with different substituents.

Acknowledgment. This investigation was supported by the Deutsche Forschungsgemeinschaft and the Commission of the European Communities (grant no. ST2J-0215-2-D). We are indebted to A. Vierengel for recording the ^{1}H NMR spectra. We are grateful to Prof. R. M. Coates who kindly arranged an attempt by Prof. W. Pirkle to separate the enantiomers of **5b**. Meanwhile he could show that a separation of these enantiomers is possible, using a (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine column and methanol as eluent, the dextrorotatory enantiomer emerging first. We are very glad to acknowledge this valuable help.

(12) The same set of signals and the analogous doubling on the addition of a chiral reagent would be observed for a nonchiral molecule with C_i symmetry. However, since all 1,3 derivatives prepared up to now by direct derivatization of calix[4]arenes were obtained in the cone conformation, it seems unreasonable to assume a 1,2 alternate conformation for **5b**.

(13) **5a**: triclinic, space group $P\bar{1}$, a = 15.519 (4), b = 12.060 (4), and c = 14.640 (4) Å, α = 109.01 (3), β = 75.24 (3), and γ = 111.31 (3)°, V = 2384 (1) Å^3, Z = 2, ρ_{ber} = 1.227 g·cm^{-3}; Ni-filtered Cu Kα radiation, λ = 1.5418 Å; Siemens AED diffractometer, $\theta/2\theta$ scan; total number of collected reflections 10437 (9057 unique reflections, internal R = 0.02); the structure was solved by direct methods and refined with 6329 reflections (6051 unique reflections, internal R = 0.015) with $I_{hkl} \geq 3\sigma(I_{hkl})$ by a blocked full-matrix least-squares method to R = 0.067 and R_w = 0.076 (weighting formula $W = 2.8132/(\sigma^2(F_o) + 0.001168F_o^2)$).

(14) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. R.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. H.; Schwing-Weill, M.-J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 388. Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Incl. Phenom.* **1988**, *6*, 119.

(15) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407.

Enantioselective Sulfoxidation of a Fatty Acid Analogue by Bakers' Yeast

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Received June 28, 1990

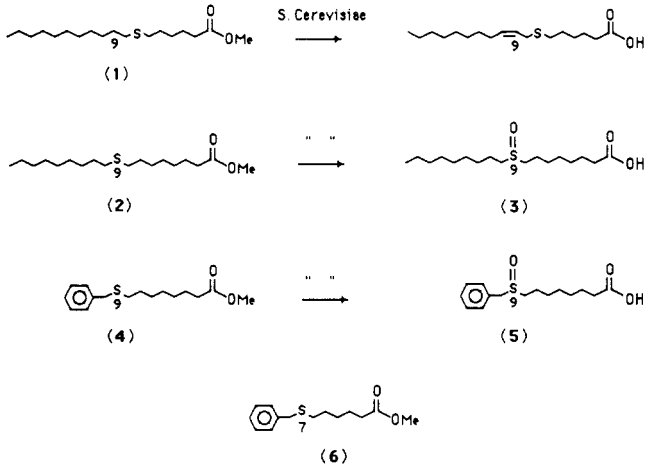
Summary: *S*-Benzyl-8-mercaptooctanoic acid methyl ester is converted by bakers' yeast to the corresponding sulfoxide with an enantiomeric excess of ca. 70% as determined by the Kagan chiral shift reagent.

We have shown previously that while sulfur analogues of stearic acid such as **1** are dehydrogenated by the desaturase system of *Saccharomyces cerevisiae* NRC 2335 (bakers' yeast), methyl 9-thiastearate (**2**) is sulfoxidized to give **3**.[1] Due to the pseudosymmetrical nature of **3**, we have been unable to determine the optical purity of this sulfoxide. In light of the current interest in the enantioselective oxidation of sulfides using chemical and mi-

(1) Buist, P. H.; Dallmann, H. G.; Rymerson, R. R.; Seigel, P. M.; Skala, P. *Tetrahedron Lett.* **1988**, *29*, 435.

0022-3263/90/1955-5667$02.50/0

crobiological oxidants,[2] we decided to probe the stereochemistry of this unusual sulfoxidation using a less symmetrical substrate. We thus elected to test a substrate in which the pendant nonyl group of **3** has been replaced by a benzyl group. We now report that not only is **4** is a good substrate but that it is oxygenated with high enantioselectivity.



S-Benzyl-8-mercaptooctanoic acid was prepared by alkylation of 8-mercaptooctanoic acid with benzyl bromide in the manner previously described.[3] The corresponding methyl ester (**4**) was purified to homogeneity by flash chromatography (silica gel, 10% EtOAc/hexane), and all spectral data (^{1}H NMR, MS) was in accord with our structural assignment.

4 (50 mg, 5% solution in absolute ethanol), was administered to each of five 1-L Erlenmeyer flasks containing 300 mL of sterile media[4] which was freshly innoculated with *S. cerevisiae* NRC 2335 (1.5×10^9 cells). The cultures were allowed to grow out to a cell density of 1.1×10^8/mL at 30 °C in a rotary shaker operating at 150 rpm for 35 h. The cells were centrifuged at 1600*g* for 10 min at 4 °C, and the resultant supernatant was acidified to a pH of 1.5 with 50% sulfuric acid and extracted with five 80-mL portions of CH_2Cl_2. Emulsions were broken by evaporation of partially separated organic layer on a rotary evaporator; 150 mg of an oily residue was obtained after evaporation of the combined organic extracts at 30–40 °C under reduced pressure.

Examination of this residue by TLC (silica gel, 10% MeOH/CH_2Cl_2, visualization by UV) revealed that neither starting material (**4**) nor the corresponding sulfoxide (authentic reference material synthesized by treatment of **4** with 1 equiv of MCPBA[1]) was present. Suspecting that ester hydrolysis had occurred, the extract was treated with an ethereal solution of diazomethane. TLC analysis (silica gel, 60% EtOAc/hexane) of the methylated extract showed that along with a considerable amount of starting material, a new UV-active spot corresponding to sulfoxide methyl ester (**5**) could be observed.

A 41.2-mg portion of crystalline **5** (mp 66–67 °C) was isolated by flash chromatography (silica gel, 10% hexane/EtOAc) of the mixture. All spectral data of this material (IR, ^{1}H NMR, MS) was identical with that of authentic reference material.

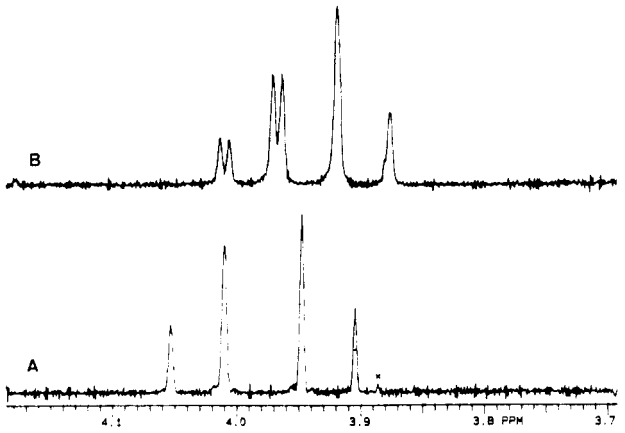


Figure 1. Effect of addition of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine on ^{1}H NMR resonances due to the benzylic protons of racemic sulfoxide **5**: (a) AB quartet of benzylic protons before addition of shift reagent; (b) splitting of lower field doublet after addition of 2 equiv of shift reagent.

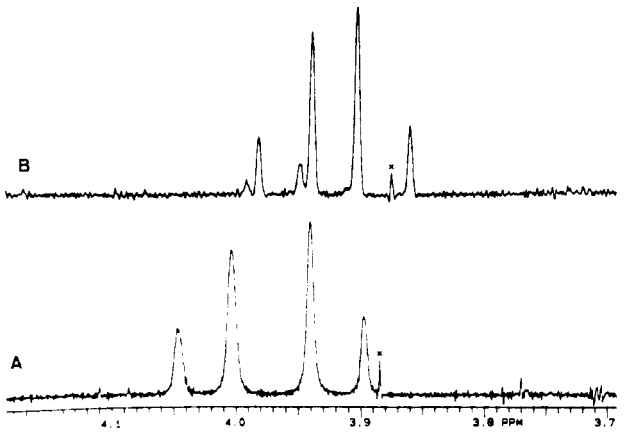


Figure 2. Effect of addition of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine on ^{1}H NMR resonances due to the benzylic protons of optically active sulfoxide **5**: (a) AB quartet of benzylic protons before addition of shift reagent; (b) splitting of lower field doublet after addition of 4 equiv of shift reagent.

The optical purity of our biologically produced sulfoxide ($[\alpha]_D$ −70.8° ($CHCl_3$, *c* 2), $[\alpha]_D$ +5.2° (ethanol, *c*2)) was assessed by ^{1}H NMR (300 MHz, in $CDCl_3$) with the assistance of the Kagan chiral shift reagent: (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine.[5] Addition of this shift reagent to **5**, caused one of the diastereomeric benzylic hydrogens to split as shown in Figures 1 and 2. We were thus able to estimate the ratio of sulfoxide enantiomers to be 84:16 (68% ee).

We have also carried out this feeding experiment on a smaller scale with another strain of *S. cerevisiae*: ATTC 12341. Once again, we were able to isolate sulfoxide **5** (9.4 mg) by flash chromatography. This material when combined with the Kagan chiral shift reagent was shown to possess an ee of 70%—very similar to that measured previously.

In both feeding experiments, we were unable to detect any other oxidized products such as sulfone. A considerable amount of starting material (20.5 mg) was isolated from the large scale feeding along with some β-oxidized sulfide (**6**, 2 mg), which we isolated by flash chromatography and identified by direct probe MS (molecular ion:

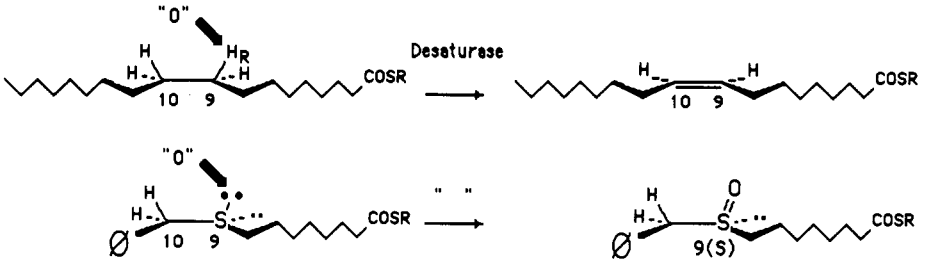
(2) (a) Holland, H. L. *Chem. Rev.* **1988**, *88*, 473. (b) Katopodis, A. G.; Smith, H. A., Jr.; May, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 897. (c) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. (d) Ohta, H.; Matsumoto, S.; Okamoto, Y.; Sugai, T. *Chem. Lett.* **1989**, 625.

(3) Buist, P. H.; Dallmann, H. G.; Rymerson, R. R.; Seigel, P. M. *Tetrahedron Lett.* **1987**, *28*, 857.

(4) Bloomfield, D. K.; Bloch, K. *J. Biol. Chem.* **1960**, *235*, 337.

(5) Deshmukh, M. N.; Duñach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 3467.

Scheme I. Relationship between Stereochemistry of Fatty Acid Desaturation and Sulfoxidation



252). Interestingly, **6** does not appear to undergo sulfoxidation—an observation which is in accord with our earlier finding that oxygenation is optimal when the sulfur atom is at the "C-9" position of a fatty acid. We are currently examining these regiochemical questions more closely.

Although it is known[6a,b] that simple β-keto sulfoxides are reduced selectively by bakers' yeast at the carbonyl group without reducing the sulfoxide function, nevertheless cases of sulfoxide reduction by this microorganism have been reported.[6c] We were thus concerned that the observed ee of our benzyl sulfoxide was simply a result of enantioselective reduction of the corresponding sulfone or selective reduction of one sulfoxide enantiomer. We thus carried out two small-scale (60-mL) incubations with 11 mg of racemic **5** and 11 mg of the corresponding sulfone (synthesized[1] by treatment of **4** with 2 equiv of MCPBA). These compounds were administered to *S. cerevisiae* NRC 2335 under the conditions outlined above for the sulfide feedings. In neither case were we able to detect significant quantities of reduction product. In the case of the sulfone feeding we recovered only sulfone from the culture medium as shown by TLC. In the case of the sulfoxide feeding, we carried out a standard hydrolysis/extraction/methylation sequence[1] on the cells to look for sulfide (**4**), which might possibly be incorporated into nonpolar cellular lipids. No sulfide was found by TLC. The medium was also extracted and again no appreciable amounts of sulfide (**4**) were detected by TLC. However, since no starting sulfoxide could be isolated from this extract, we are repeating this experiment on a larger scale in order to obtain more conclusive results.

Finally, we can only speculate as to the absolute configuration of the predominant sulfoxide enantiomer produced in this system since no reference standards are available[7] and since the Kagan shift reagent has been nearly exclusively used for methyl sufoxides.[2b,c] On the basis of the optical data alone, we would assign the *S* configuration to the more abundant enantiomer since it is known that in all cases examined benzyl *n*-alkyl sulfoxides of *S* configuration exhibit negative optical rotations in $CHCl_3$ and positive optical rotations in EtOH.[8] Synthetic work is underway to place our assignment of absolute configuration on a firmer basis.

In conclusion, it is interesting to note that if our biological sulfoxidation is in fact desaturase-mediated as we presume, we would predict that the stereochemistry of sulfide oxygenation should match the stereochemistry of hydrogen removal. All desaturases studied to date remove the *pro-R* hydrogens.[9] This would predict the production of (*S*)-benzyl sulfoxides. (See Scheme I).

In summary, we have shown for the first time[10] that baker's yeast is capable of enantioselective sulfoxidation. Thus this organism joins the growing list[2] of other microbial oxidants capable of performing this important task.

Acknowledgment. We wish to thank N.S.E.R.C. and Carleton University for financial support of this work. The technical assistance of Dr. Heather Dettmann and Raj Capoor is greatly appreciated.

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(7) Benzyl decyl sulfoxide has been prepared in enantiomerically pure form, but the optical rotation of this material was unfortunately not reported: Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Agric. Biol. Chem.* **1985**, *49*, 2229.

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Synthesis of Antitumor Cyclic Peroxy Ketals Related to Chondrillin and Xestins A and B

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Received August 7, 1990

Summary: A seven-step synthesis of the antitumor cyclic peroxy ketals **2b** and **18** from phenol has been carried out in 15% overall yield. The key step is the photooxygenation of acetoxy diene **10** using rose bengal as a sensitizer and a sun lamp to give peroxy hemiketals **16** and **17**.

A wide variety of biologically active cyclic peroxides have been isolated from marine organisms. Chondrillin (**1a**) was isolated from a sponge of the genus *Chondrilla* by Wells.[1] More recently, xestins A (**2a**) and B (**1b**) have been isolated from a sponge of the genus *Xestospongia* by Crews,[2] and chondrillin (**1a**) and a series of related ketals (**2b–e**) have

(1) Wells, J. R. *Tetrahedron Lett.* **1976**, 2637.

(2) Quiñoà, E.; Kho, E.; Manes, L. V.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4260.

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