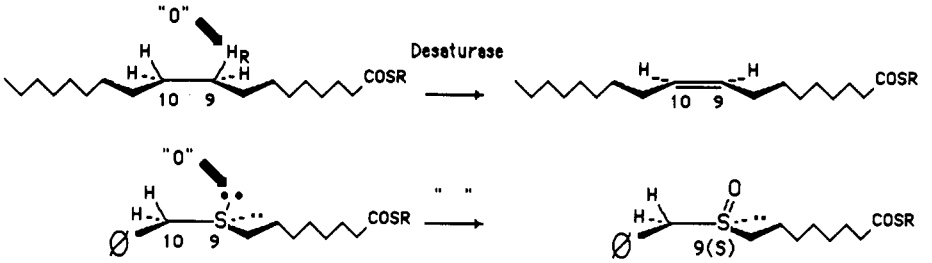
Scheme I. Relationship between Stereochemistry of Fatty Acid Desaturation and Sulfoxidation



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.

(6) (a) Yamazaki, T.; Asai, M.; Ohnogi, T.; Lin, J. T.; Kitazume, T. *J. Fluorine Chem.* **1987**, *35*, 537. (b) Crumbie, R. L.; Deol, B. S.; Nemorin, J. E.; Ridley, D. D. *Austr. J. Chem.* **1978**, *31*, 1965. (c) Madesclaire, M. *Tetrahedron* **1988**, *44*, 6537 and references contained therein.

(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.

(8) Mislow, K.; Green, M. M.; Raban, M. *J. Am. Chem. Soc.* **1965**, *87*, 2761.

(9) Rawlings, B. L.; Reese, P. B.; Ramer, S. E.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *11*, 3382 and references contained therein.

(10) Servi, S. *Synthesis* **1990**, 1.

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

Barry B. Snider* and Zhongping Shi

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254-9110

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**.

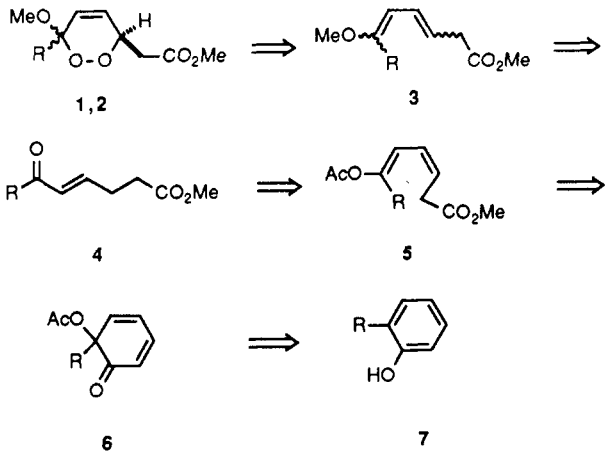
A wide variety of biologically active cyclic peroxides have been isolated from marine organisms. Chondrillin (**1a**) was isolated from a sponge of the genus *Chondrilla* by Wells.[1] More recently, xestins A (**2a**) and B (**1b**) have been isolated from a sponge of the genus *Xestospongia* by Crews,[2]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

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

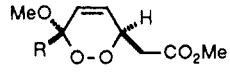
(2) Quiñoà, E.; Kho, E.; Manes, L. V.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4260.

0022-3263/90/1955-5669$02.50/0

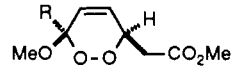
Scheme I



been isolated from *Plakortis lita* by Higa and Christophersen.[3] Peroxy ketals **2a–e** have been shown to be active against P388 mouse leukemia cells in vitro with IC_{50} of 0.05–0.3 μg/mL.[2,3] The isomers **1a–b** are approximately 1 order of magnitude less active. A variety of related cyclic peroxides, including the norsesterterpenes trunculins A and B[4] and plakortin,[5] have been shown to possess antitumor and antimicrobial activity.



1a, R = $C_{16}H_{33}$
1b, R = $C_{13}H_{26}CH{=}CHCH{=}CHCH_3$

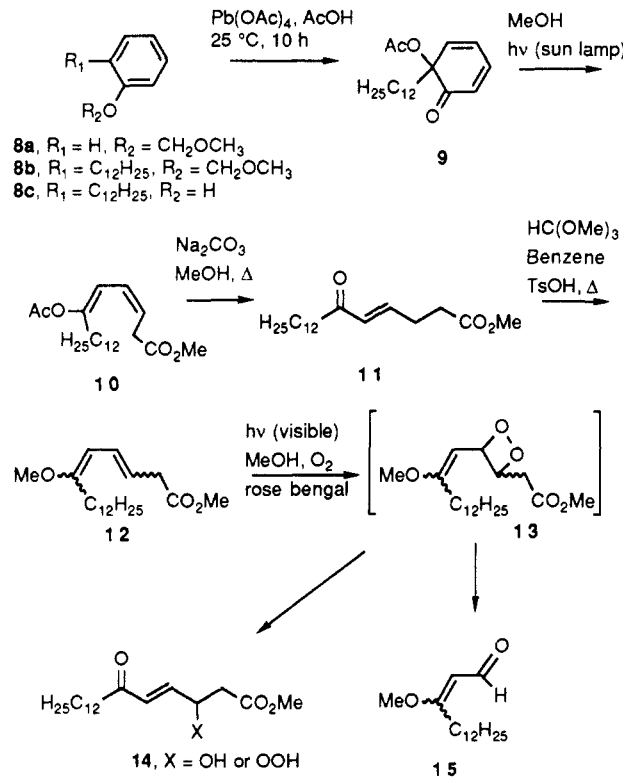


2a, R = $C_{13}H_{26}CH{=}CHCH{=}CHCH_3$
2b, R = $C_{12}H_{25}$
2c, R = $C_9H_{18}CH{=}CHCH_3$
2d, R = $C_7H_{14}CH{=}CHCH{=}CHCH_3$
2e, R = $C_9H_{18}CH{=}CHCH{=}CHCH_3$

The structural novelty and potent biological activity of peroxy ketals **1** and **2** prompted us to undertake their synthesis. Despite the biological activity and ostensible simplicity of these cyclic peroxides, no syntheses of any members of this class have been reported,[6] suggesting that the obvious approach to these compounds, the addition of singlet oxygen to the methoxy diene **3**, will not give **1** or **2**. An examination of the literature indicates that the singlet oxygen Diels–Alder reaction is most useful with endocyclic dienes and that the addition of singlet oxygen to oxygenated or highly substituted dienes gives dioxetanes and ene adducts in addition to, or instead of, Diels–Alder adducts.[7] Although the proposed singlet oxygen Diels–Alder reaction is problematic, we felt that it was necessary to investigate this obvious approach first in the absence of negative reports on this specific reaction.

Our retrosynthetic analysis is shown in Scheme I. The requisite methoxy diene **3** should be available from enone **4**. We planned to make enone **4** from phenol **7** by a procedure developed by Stork[8] for the conversion of *o*-cresol to a related enone. Wessely oxidation of phenol **7** should give the acetoxy dienone **6**.[9] Photolytic ring opening by

Scheme II



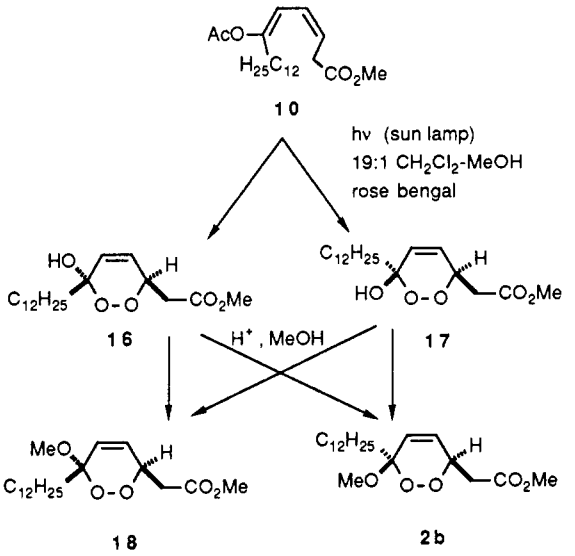
the procedure of Barton and Quinkert should provide the acetoxy diene **5**.[10,11] Hydrolysis of the acetate ester should afford enone **4**. This route is particularly attractive since it proceeds through acetoxy diene **5** which might also react with singlet oxygen to give an endo peroxide which could be converted to **1** or **2**.

Deprotonation of protected phenol **8a**[12] (*n*-BuLi in THF–TMEDA at 0 °C) followed by alkylation of the anion with 1-bromododecane (25 °C, 12 h) gives 89% of **8b**.[13] Deprotection with toluenesulfonic acid in MeOH for 30 h affords 95% of phenol **8c**. Wessely oxidation of phenol **8c** with 1.6 equiv of $Pb(OAc)_4$ in acetic acid at 25 °C for 10 h provides 76% of acetoxy dienone **9**[9b] (Scheme II). Photolysis of a solution of acetoxy dienone **9** in MeOH with a 275-W sun lamp for 4 h (the solution is heated to reflux by the sun lamp) leads to 70% of acetoxy diene **10** as a single stereoisomer.[8,10,11] Hydrolysis of the acetate ester with Na_2CO_3 in MeOH (1 h, reflux) affords 80% of enone **11**. Reaction of enone **11** with $HC(OMe)_3$ and *p*-toluenesulfonic acid in benzene (reflux, 4 h) provides 74% of methoxy diene **12** as a 3:1 mixture of trans and cis isomers at the disubstituted double bond.

Unfortunately, reaction of the methoxy diene **12** with singlet oxygen under a variety of circumstances gives none of the desired cyclic peroxide ketals. The products that are isolated appear to arise by fragmentation or cleavage of 1,2-dioxetane **13**. For instance, photolysis of a solution of **12** and rose bengal in MeOH with a visible wavelength

(3) Sakemi, S.; Higa, T.; Anthoni, U.; Christophersen, C. *Tetrahedron* **1987**, *43*, 263.
(4) Capon, R. J.; MacLeod, J. K.; Willis, A. C. *J. Org. Chem.* **1987**, *52*, 339.
(5) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454.
(6) (a) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799. (b) Steliou, K.; Milot, G.; Salama, P.; Yu., X. Presented at the 200th National Meeting of the American Chemical Society, Washington, D.C., August 1990; ORGN 119. (c) Yoshida, J.-I.; Nakatani, S.; Isoe, S. *Tetrahedron Lett.* **1990**, *31*, 2425.
(7) (a) Clennan, E. L.; Nagraba, K. *J. Am. Chem. Soc.* **1988**, *110*, 4313. (b) Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4710.
(8) Stork, G.; Sherman, D. H. *J. Am. Chem. Soc.* **1982**, *104*, 3758.
(9) (a) Wessely, F.; Sinwel, S. *Monatsh. Chem.* **1950**, *81*, 1055. (b) Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1.
(10) Barton, D. H. R.; Quinkert, G. *J. Chem. Soc.* **1960**, 1.
(11) For recent applications of this reaction in synthesis, see: Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhor, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* **1988**, *71*, 1719 and references cited therein.
(12) Yardley, J. P.; Fletcher, H., III *Synthesis* **1976**, 323.
(13) Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Dürner, G.; Zimmerman, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771.

Scheme III



flood lamp for 2 h at 20 °C provides 40% of oxygenated enone **14** and 40% of unsaturated aldehyde **15**. Apparently, singlet oxygen adds to alkoxy diene **12** to give mainly the dioxetane **13**, as reported in related systems.[7]

Fortunately, photooxygenation of the acetoxy diene **10** did lead to products that could be converted to peroxy ketals **1** and **2**. Irradiation with a sun lamp of a 3×10^{-3} M solution of acetoxy diene **10** in 19:1 CH_2Cl_2:MeOH for 8 h at 10 °C in the presence of rose bengal (10^{-4} M) and oxygen affords 45% of a 3:2 mixture of peroxy hemiketals **16** and **17**. The sensitizer is fully photobleached during the first hour of irradiation. Yet, disappearance of the starting material requires irradiation for 8 h. The bleached products from rose bengal are necessary for reaction, since **10** is stable to irradiation with a sun lamp in the absence of rose bengal. Irradiation of **10**, rose bengal, and oxygen with a visible wavelength flood lamp, the usual conditions for singlet oxygen generation, results in isomerization of the diene to the *E,E* and *Z,E* isomer, followed by slow reaction to give other products. Irradiation of these isomeric dienes, rose bengal, and oxygen with a sun lamp also gives **16** and **17**. The preparation of hemiketals **16** and **17**, which involves addition of oxygen and cleavage of the ester, may not be a singlet oxygen reaction. We are exploring the mechanism of this photooxygenation and its potential for the preparation of cyclic peroxides that cannot be prepared by classical singlet oxygen reactions. Formation of a cyclic peroxide does not occur on irradiation of methoxy diene **3** and oxygen with a sun lamp using rose bengal as a sensitizer.

Peroxy hemiketals **16** and **17** are converted quantitatively to a 1.1:1 mixture of the desired peroxy ketals **18** and **2b** by reaction with a catalytic amount of *p*-toluenesulfonic acid in MeOH for 40 h at 25 °C. Either pure hemiketal isomer gives the same 1.1:1 mixture of peroxy ketals **18** and **2b**. The success of this reaction was expected, since Wells has reported that chondrillin (**1a**) is very sensitive to base, but relatively stable to acid.[1] The peroxy ketals can be separated by flash chromatography on silica gel. The spectral data of the minor isomer **2b** are identical with those reported for the natural product.[3] The spectral data of the major isomer **18** are virtually identical with those reported for chondrillin (**1a**),[1,3] which has four additional methylene groups in the side chain.

This synthesis produces peroxy ketals **2b** and **18** in seven steps from phenol in 15% overall yield by a route which will permit us to prepare analogues. The key step in the sequence is the rose bengal sensitized photooxygenation of acetoxy diene **10** to give peroxy hemiketals **16** and **17**, which proceeds with a sun lamp, but not with a visible wavelength flood lamp. We are currently exploring the mechanism of this photooxygenation and its scope for preparing other endo peroxides not available by standard singlet oxygen reactions.

Note Added in Proof. Photolysis of enone **11** under the conditions used to convert **10** to peroxy hemiketals **16** and **17** gives 67% of peroxy hemiketals **16** and **17** and 5% of **18** and **2b**. It therefore seems likely that the first step in the conversion of acetoxy diene **10** to **16** and **17** is hydrolysis to enone **11**. Photoenolization of *o*-methylaryl ketones and aldehydes in the presence of oxygen gives peroxy hemiketals.[14] Copper sulfate sensitized photooxygenation of mesityl oxide gives 6% of the peroxy hemiketal.[15]

Supplementary Material Available: Procedures for the preparation of **9**, **10**, **16**, **17**, **18**, and **2b** with spectral data (3 pages). Ordering information is given on any current masthead page.

(14) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.
(15) Sato, T.; Tamura, K.; Maruyama, K.; Ogawa, O.; Imamura, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 779.

A New, Highly Efficient Method for Isocarbacyclin Synthesis Based on Tandem Claisen Rearrangement and Ene Reactions

Tadakatsu Mandai,* Shin-ichi Matsumoto, Makoto Kohama, Mikio Kawada, and Jiro Tsuji

Department of Applied Chemistry, Okayama University of Science, Okayama, 700 Japan

Seiki Saito* and Toshio Moriwake

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama, 700 Japan

Received July 9, 1990

Summary: A new short-step synthesis of isocarbacyclin is described which features a crucial single-pot, three-step transformation, i.e., tandem tertiary allylic vinyl ether formation, Claisen rearrangement, and ene cyclization, to lead to a bicyclo[3.3.0] framework, overcoming previous endocyclic double bond and one-carbon elongation problems.

The remarkable biological activity of prostacyclin (PGI_2) (**2**) and its very low natural abundance have promoted

0022-3263/90/1955-5671$02.50/0