4-methylcoumarin; MUGB, 4-methylumbelliferyl *p*-guanidinobenzoate; Tris, tris(hydroxymethyl)aminomethane; DMF, *N*,*N*-dimethylformamide; Boc-LGRpNA, Boc-lysylglycylarginyl-*p*-nitroanilide; IPTG, isopropyl β-D-thiogalactopyranoside; AFC, 7-amino-4-(trifluoromethyl)-coumarin; MOPS, 3-(*N*-morpholino)propanesulfonic acid.

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Total Synthesis of (±)-Chondrillin, (±)-Plakorin, and Related Peroxy Ketals. Development of a General Route to 3,6-Dihydro-1,2-dioxin-3-ols

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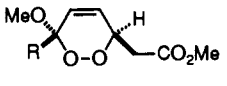
Abstract: Seven-step syntheses of the antitumor cyclic peroxy ketals **1a**, **2a**, chondrillin (**1b**), and plakorin (**2b**) from (methoxymethoxy)benzene (**8**) have been achieved in 26–28% overall yields. The key step is the photooxygenation of enone **4** with a sun lamp using rose bengal lactone or $CuSO_4$ as a sensitizer which gives a mixture of peroxy hemiketals **15** and **16** in 75–85% yields. Acetal formation in acidic methanol completes the syntheses of **1** and **2**. The mechanism of photooxygenation was ascertained using 3-nonen-2-one (**22**) as a model for **4**. Irradiation converts **22** to the *cis*-enone **23** which undergoes photoenolization to give **24**. Dienol **24** undergoes a sensitized reaction with oxygen to give **29** and **30**. The detailed mechanism of this last step is not known, although singlet oxygen is probably not involved. This reaction is general for any enone or enal which can undergo photoenolization to give a dienol. Peroxy hemiketals **33a**, **41**, and **43–46** were prepared in 30–80% yields. Peroxy ketals can be used for the synthesis of furans, diones, and pyridazines.

Introduction

A wide variety of biologically active cyclic peroxides have been isolated from marine organisms. Chondrillin (**1b**) was first isolated in 1976 from a sponge of the genus *Chondrilla* by Wells.[1] More recently, xestins A (**2c**) and B (**1c**) have been isolated from a sponge of the genus *Xestospongia* by Crews,[2] chondrillin (**1b**) and a series of related ketals (**2a,f–h**) have been isolated from *Plakortis lita* by Higa and Christophersen,[3] chondrillin (**1b**), *epi*-chondrillin (**2b**), and a series of unsaturated analogues (**1d,e**, **2d,e**) have been isolated from *P. lita* by De Guzman and Schmitz,[4] and *epi*-chondrillin (called plakorin) (**2b**) has been isolated from a *Plakortis* species by Kobayashi.[5]



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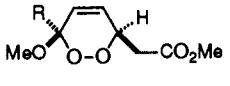


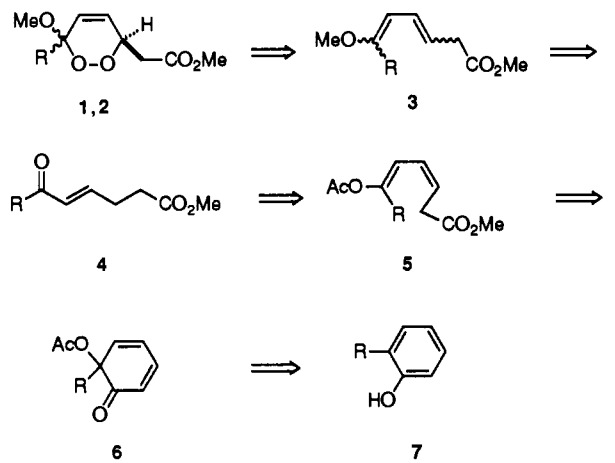
2

a, R = $C_{12}H_{25}$
b, R = $C_{16}H_{33}$
c, R = $C_{13}H_{26}CH{=}CHCH{=}CHCH_3$
d, R = $C_{13}H_{26}CH{=}CHCH_3$
e, R = $C_{11}H_{22}CH{=}CHCH{=}CHCH_3$
f, R = $C_9H_{18}CH{=}CHCH_3$
g, R = $C_7H_{14}CH{=}CHCH{=}CHCH_3$
h, R = $C_9H_{18}CH{=}CHCH{=}CHCH_3$

Peroxy ketals **2a,c,f–h** have been shown to be active against P388 mouse leukemia cells in vitro with IC_{50} values of 0.05–0.3 μg/mL.[2,3] The isomers **1b,c** are approximately 1 order of magnitude less active. Plakorin (**2b**) (10^{-5} M) activated SR Ca^{2+}-ATPase activity by 30% and exhibited antineoplastic activity against L1210 cells and KB cells in vitro with IC_{50} values of 0.85 and 1.8 μg/mL, respectively.[5] A variety of related cyclic peroxides with branched skeletons, including the norsesterterpenes trunculins A and B,[6] plakortin,[7] plakortic acid,[8] and plakinic acid B,[8] have been shown to possess antitumor and antimicrobial activity.

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

Scheme I



1,2 **3** **4** **5** **6** **7**

(1) Wells, J. R. *Tetrahedron Lett.* **1976**, 2637.
(2) Quiñoâ, E.; Kho, E.; Manes, L. V.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4260.
(3) Sakemi, S.; Higa, T.; Anthoni, U.; Christophersen, C. *Tetrahedron* **1987**, *43*, 263.
(4) De Guzman, F. S.; Schmitz, F. J. *J. Nat. Prod.* **1990**, *53*, 926.
(5) Murayama, T.; Ohizumi, Y.; Nakamura, H.; Sasaki, T.; Kobayashi, J. *Experientia* **1989**, *45*, 898.
(6) Capon, R. J.; MacLeod, J. K.; Willis, A. C. *J. Org. Chem.* **1987**, *52*, 339.
(7) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454.
(8) Phillipson, D. W.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 7735.

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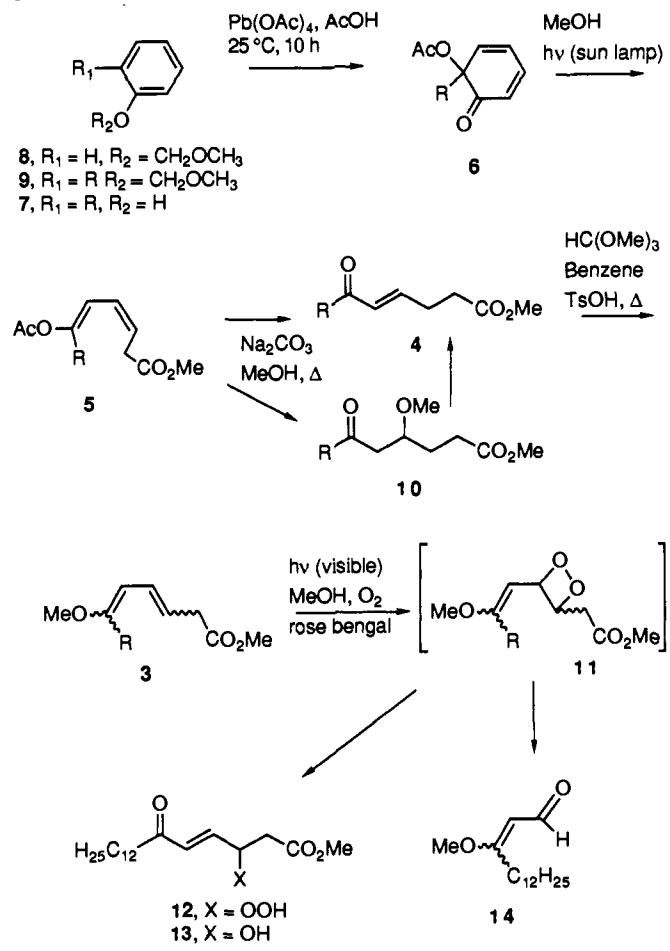
peroxides, no syntheses of any members of this class had been reported,[9] suggesting that the obvious approach to these compounds, the addition of singlet oxygen to the methoxy diene **3**, will not give **1** or **2**. An examination of the literature indicates that the singlet oxygen Diels–Alder reaction 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.[10] Although the proposed singlet oxygen Diels–Alder reaction was 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. Methoxy diene **3** should be readily available from the enone **4**. We planned to make the enone **4** by the procedure reported by Stork[11] for the conversion of *o*-cresol to an analogous enone ester and by Quinkert[12] for more complex enones analogous to **4**. Wessely oxidation of phenol **7** will give the acetoxy dienone **6**.[13] Photolytic ring opening in methanol by procedure of Barton and Quinkert[12,14] will provide the acetoxy diene **5** which can be hydrolyzed to the enone ester **4**. Although shorter routes to **3** can be envisaged, this approach is particularly attractive since it proceeds through acetoxy diene **5**, of known stereochemistry, that might also react with singlet oxygen to give an endo peroxide precursor to **1** or **2**.[15]

Results and Discussion

Synthesis of 1a and 2a. We chose **1a** and **2a** with saturated 12-carbon side chains as the initial targets since potent cytotoxicity had been demonstrated for **2a**[3] and the relatively short, saturated side chain should minimize synthetic problems.[3] Deprotonation of (methoxymethoxy)benzene (**8**)[16] with *n*-BuLi and TMEDA in THF at 0 °C followed by alkylation[17] of the ortho carbanion with 1-bromododecane gives 73–89% of **9a**. Cleavage of the MOM ether with $TsOH·H_2O$ in MeOH affords 95% of phenol **7a**. Wessely oxidation[13] of phenol **7a** with $Pb(OAc)_4$ in acetic acid provides 72% of acetoxy dienone **6a**. Photolysis of a solution of acetoxy dienone **6a** in MeOH with a 275-W sun lamp leads to 70% of acetoxy diene **5a** as a single (95%) stereoisomer.[12,13,17,18] As Quinkert has shown in a exhaustive study, hydrolysis of the dienyl acetate without concomitant Michael addition to the enone is problematic.[12] Hydrolysis of the acetate ester with Na_2CO_3 in MeOH at reflux for 1 h affords up to 81% of enone **4a**. However, this reaction is not very reproducible; variable amounts of unreacted **5a** and Michael adduct **10a** are obtained. Higher, more reproducible yields are obtained by a two-step procedure. Hydrolysis of the acetate ester with Na_2CO_3 in MeOH at reflux for 3 h affords a mixture containing mainly Michael adduct **10a** with some enone **4a**. Treatment of this mixture with $TsOH·H_2O$ and 3A molecular sieves in benzene at reflux gives 84% of **4a**. Reaction of enone **4a** with $HC(OMe)_3$ and $TsOH·H_2O$ provides 74% of methoxy diene **3a** as a mixture of stereoisomers.

Scheme II



Unfortunately, reaction of the methoxy diene **3a** with singlet oxygen under a variety of circumstances gives none of the desired cyclic peroxy ketals. The products that are isolated appear to arise by fragmentation or cleavage of 1,2-dioxetane **11a**.[10] For instance, photolysis of a solution of **3a** and rose bengal (RB) in MeOH containing O_2 with a visible wavelength flood lamp for 2 h at 20 °C provides 41% of hydroxy enone **13a** and 43% of unsaturated aldehyde **14a**. Irradiation of **3a** in 19:1 CH_2Cl_2–MeOH containing O_2 with a sun lamp for 1 h affords a mixture containing 75% of **14a** and 10% of a minor product tentatively identified as hydroperoxy enone **12a** whose ^1H NMR spectrum is similar to that of **13a** except that the methine hydrogen absorbs at δ 5.01 instead of δ 4.73. These products could all arise from cleavage of dioxetane **11a**. Hydrolysis of the vinylogous acetal will give hydroperoxy enone **12a**. Reduction during the photolysis will give **13a**. Decomposition of the dioxetane would also be expected to give **14a** and methyl 3-oxopropionate, which would be lost on workup. Since acetoxy diene **5a** was in hand, its photooxygenation was also investigated. Irradiation of **5a** and RB in 19:1 CH_2Cl_2–MeOH containing O_2 with a visible wavelength flood lamp provides a mixture containing 20% of unreacted **5a**, 60% of the *E,E* and *Z,E* isomers of **5a**, and 20% of **12a**.

To our surprise and delight, irradiation of a solution of acetoxy diene **5a**, RB, and oxygen in 19:1 CH_2Cl_2–MeOH for 8 h at 10 °C with a sun lamp affords 45% of a 3:2 mixture of peroxy hemiketals **15a** and **16a**. These peroxy hemiketals are surprisingly stable. They can be separated by chromatography on silica gel and are configurationally stable in the absence of acid, suggesting that they are not in equilibrium with the hydroperoxy *cis*-enone. The coupling constants between the olefinic protons and the adjacent methine proton in **15a** are 4.4 and 1.7 Hz. These correspond closely to the coupling constants reported for the peroxy ketals **1b** (4.3, 1.8 Hz)[3] and **1c** (4.5, 1.5 Hz).[2] To our surprise, the olefinic protons of **16a** absorb as a two-proton singlet, indicating both a coincidental equivalence of the chemical shifts and very

(9) (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, DC, Aug 1990; ORGN 119. (c) Yoshida, J.-I.; Nakatani, S.; Isoe, S. *Tetrahedron Lett.* **1990**, *31*, 2425.

(10) (a) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343. (b) Clennan, E. L.; Nagraba, K. *J. Am. Chem. Soc.* **1988**, *110*, 4312. (c) Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4710.

(11) Stork, G.; Sherman, D. H. *J. Am. Chem. Soc.* **1982**, *104*, 3758.

(12) Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhorn, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* **1988**, *71*, 1719 and references cited therein.

(13) (a) Wessely, F.; Sinwel, S. *Monatsh. Chem.* **1950**, *81*, 1055. (b) Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1.

(14) Barton, D. H. R.; Quinkert, G. *J. Chem. Soc.* **1960**, 1.

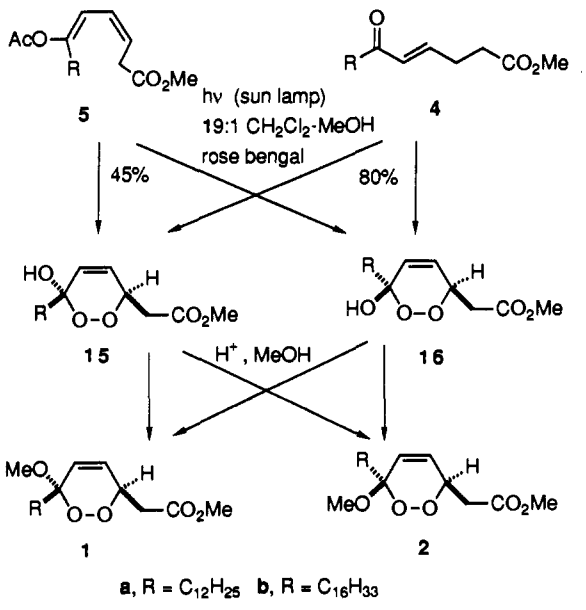
(15) For a preliminary communication see: Snider, B. B.; Shi, Z. *J. Org. Chem.* **1990**, *55*, 5669.

(16) Yardley, J. P.; Fletcher, H., III. *Synthesis* **1976**, 244.

(17) 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.

(18) Waring, A. J.; Morris, M. R.; Islam, M. M. *J. Chem. Soc. C* **1971**, 3274.

Scheme III



small coupling to the adjacent methine proton. The peroxy ketals **2b** (2.1, 1.5 Hz) and **2c** (2.1, 1.2 Hz) also have small coupling constants. The stereochemical assignments of **1** and **2** are based on conformational analysis and confirmed by NOE studies. The methoxy group prefers to be axial due to the anomeric effect. Therefore, the methine hydrogen is pseudoequatorial and strongly coupled to the adjacent olefinic proton in **1** and pseduoaxial and weakly coupled to the adjacent olefinic proton in **2**.[2,3,5]

The syntheses of **1a** and **2a** are easily completed by reaction with acidic methanol. The mixture of peroxy hemiketals **15a** and **16a** is converted quantitatively to a 1.1:1 mixture of the desired peroxy ketals **1a** and **2a** by reaction with a catalytic amount of TsOH in MeOH for 40 h at 25 °C. Pure **15a** or **16a** also gives 1.1:1 mixtures of **1a** and **2a**. The spectral data for **2a** are identical to those previously described.[3] The spectral data for **1a** are analogous to those reported for **1b** and **1c**.[1-5]

The key step in the sequence is the mechanistically novel, sensitized photooxygenation of acetoxy diene **5a** to give peroxy hemiketals **15a** and **16a**, which proceeds with a sun lamp but not with a visible wavelength flood lamp. The sensitizer is fully bleached[19] during the first 1 h of irradiation. However, disappearance of the starting material requires irradiation for 8 h. The bleached products from RB are necessary for the formation of **15a** and **16a** since irradiation of **5a** in the absence of RB gives only the double-bond stereoisomers of **5a**.

The key observation that allowed us to sort out the sequence of steps leading from acetoxy diene **5a** to peroxy hemiketals **15a** and **16a** was that photolysis of enone **4a**, under the conditions used to convert acetoxy diene **5a** to peroxy hemiketals **15a** and **16a**, gives 75–85% of peroxy hemiketals **15a** and **16a**. It therefore seems likely that the first step in the conversion of acetoxy diene **5a** to the peroxy hemiketals is the sensitized photohydrolysis[20] to enone **4a**, which presumably proceeds in modest yield, since the yield of peroxy hemiketals from **4a** (75–85%) is much higher than from **5a** (45%). We did not concern ourselves with the details of this photohydrolysis since direct oxygenation of enone **4a** is much more efficient. Discussion of the details of the conversion of enone **4a** to **15a** and **16a** is deferred until additional mechanistic experiments using model enones are presented.

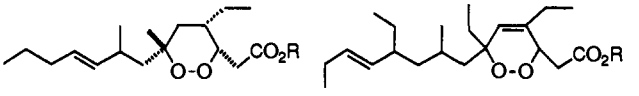
The conversion of (methoxymethoxy)benzene (**8**) to **1a** and **2a** proceeds in 28% overall yield through a simple seven-step sequence making these peroxy ketals readily available.

(19) Lindern, S. M.; Neckers, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 1257. Neckers, D. C. *J. Photochem. Photobiol. A.* **1989**, *47*, 1.

(20) Yogev, A.; Gorodetsky, M.; Mazur, Y. *J. Am. Chem. Soc.* **1964**, *86*, 5208.

Synthesis of Chondrillin (1b) and Plakorin (2b). Syntheses of chondrillin and plakorin were carried out analogously by alkylating **8** with 1-bromohexadecane instead of 1-bromododecane. Intermediates **9b** (91%), **7b** (98%), **6b** (70%), **5b** (70%), **4b** (82%), and **15b** and **16b** (73%) were obtained as described above for the shorter side chain. Reaction of a mixture of **15b** and **16b** with TsOH in MeOH for 80 h at room temperature affords 98% of an easily separable 1.1:1 mixture of chondrillin (**1b**) and plakorin (**2b**) whose ^1H and ^{13}C NMR spectral data are identical to those previously described.[1,3-5] The overall yield for the seven-step conversion of (methoxymethoxy)benzene (**8**) to **1b** and **2b** is 26%.

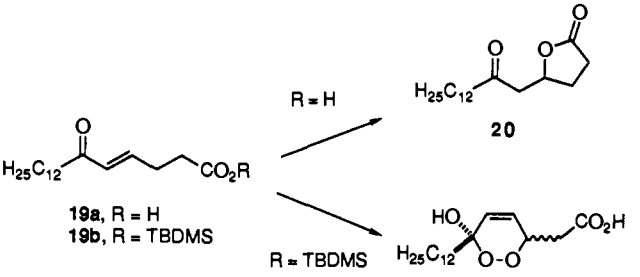
Synthesis of Hydroxy Acids 21a and 21b. Plakortic acid (**17a**) is a potent antifungal and antibacterial agent, while the methyl ester plakortin (**17b**) is inactive.[8] Similar observations have been made with the related unsaturated peroxides **18a** and **18b**.[21] The acid **18a** inhibits P-388 cells with an IC_{50} of 0.3 μg/mL and inhibits the growth of the fungus *Candida albicans* with an MIC of 1.6 μg/mL. The ester **18b** is a slightly weaker antitumor agent but has no antifungal activity. These observations suggested that the free acids corresponding to **1** and **2** might be more biologically active than the naturally occurring methyl esters.



17a, R = H
17b, R = CH_3

18a, R = H
18b, R = CH_3

The peroxy ketals **1** and **2** are moderately acid stable but are known to be very sensitive to base.[1] The methyl ester of **4a** therefore had to be hydrolyzed prior to photooxygenation. Hydrolysis of **4a** with NaOH in 1:1 THF–H_2O affords 95% of a 6:1 mixture of **19a** and 4-hydroxy-6-oxooctadecanoic acid. Attempted photooxygenation of **19a** under the conditions used successfully for the preparation of **15a** and **16a** gives only lactone **20**, indicating that a free acid is not compatible with the photooxygenation. The



19a, R = H
19b, R = TBDMS

6:1 mixture containing **19a** was treated with (TBDMS)Cl and imidazole in DMF to provide 84% of **19b**.[22] Photooxygenation of **19b** followed by chromatography on silica gel affords 32% of **20** and 52% of a 1:1.1 mixture of **21a** and **21b**. Hydrolysis of the silyl ester occurs during photolysis at a rate somewhat slower than that of photooxygenation. Lactone **20** is derived from **19a** obtained by hydrolysis of **19b** before photooxygenation while **21a** and **21b** are derived from hydrolysis after photooxygenation. Only 5–10% of peroxy hemiketals could be obtained from the THP ester of **19a**. Mixtures of the naturally occurring ketal esters **1a** and **2a** (0.33 μg/mL), the hemiketal esters **15a** and **16a** (0.25 μg/mL), and hydroxy acids **21a** and **21b** (0.50 μg/mL) all have similar IC_{50} against P-388.[23]

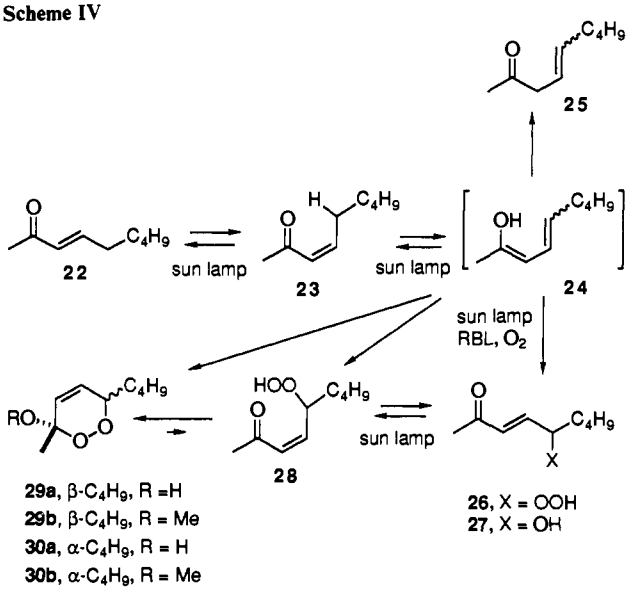
Mechanism of Peroxy Hemiketal Formation. The more readily available, simpler ketones 3(*E*)-nonen-2-one (**22**) and pulegone (**32**) were used to investigate the mechanism of peroxy hemiketal formation. As expected, irradiation of a solution of **22** with RB in 19:1 CH_2Cl_2–MeOH affords 72–83% of a 1.7:1 mixture of **29a**

(21) Gunasekera, S. P.; Gunasakera, M.; Gunawardana, G. P.; McCarthy, P.; Burres, N. *J. Nat. Prod.* **1990**, *53*, 669.

(22) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.

(23) We thank Dr. Ross E. Longley, Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, Fort Pierce, FL 34946, for carrying out these analyses.

Scheme IV



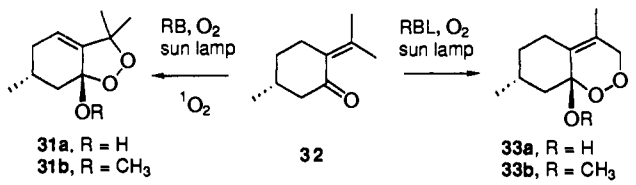
and **30a**. The spectral data are analogous to those of **15a** and **16a**, respectively. We believe that the conversion of enone **22** to peroxy hemiketals **29a** and **30a** occurs as outlined in Scheme IV. The first step is the facile cis–trans photoisomerization of *trans*-enone **22** to *cis*-enone **23** initiated by absorption of light in the n → π* absorption band.[24] Photochemical enolization[24] will give dienol **24**. Photoenolization is facile for enones which can adopt an s-cis conformation and either have a cis γ-hydrogen or can undergo cis–trans isomerization to generate an isomer with a cis γ-hydrogen. Dienol **24** is rapidly reconverted to *cis*-enone **23** by a thermal sigmatropic hydride 1,5-shift and can be converted to the photostable unconjugated ketone **25** by a formal hydrogen 1,3-shift.[24] Irradiation of **22** under oxygen with a sun lamp in the absence of RB gives only **25**, establishing that dienol **24** is a competent intermediate in the oxygenation reaction and that a sensitizer is needed for the conversion of **22** to peroxy hemiketals.

RB cannot be the sensitizer since the solution is fully bleached long before the starting material has been consumed. Colorless rose bengal lactone (RBL), which is claimed to be the bleaching product of RB under both oxidative or reductive conditions, can be prepared by acidification of RB.[19] Use of RBL as a sensitizer in the photooxygenation of either **4a**, **4b**, **19b**, or **22** gives yields of peroxy hemiketals comparable to those obtained with RB. Use of pulegone as a substrate confirms that RBL and not RB is the sensitizer. Pulegone (**32**) is converted very efficiently (70%) to the singlet oxygen ene adduct **31a**[25] by irradiation with a sun lamp and oxygen with RB as a sensitizer. Peroxy ketal **31b** is the major product at longer reaction times in solvent mixtures containing methanol. With RBL as the sensitizer, only 20% of **31a** is obtained. The major product (50%) is the previously unknown peroxy hemiketal **33a** which is formed by a pathway analogous to that outlined above for the formation of **29a** and **30a**. If the RBL is preirradiated for 1.5 h before addition of pulegone to bleach any residual RB, 5% of **31a** and 62% of **33a** are isolated. RBL, and not RB, must be the sensitizer in the formation of **33a**, since **31a** is formed selectively by addition of singlet oxygen to pulegone when RB is used as sensitizer.

Dienol **24**, generated photolytically in the presence of both RBL and oxygen, is converted to peroxy hemiketals **29a** and **30a** more rapidly than it undergoes a hydrogen 1,3-shift to give **25**. The hydroperoxy enones **26** and **28** may be the initial product of sensitized photooxygenation of **24**. Hydroperoxy *trans*-enone **26** is isolated in 5% yield from one oxygenation reaction and can be detected by NMR as a minor product in early aliquots. Photoisomerization of **26** should give hydroperoxy *cis*-enone **28** which should close spontaneously to the more stable peroxy hemiketals **29a** and **30a**. Photolysis with λ > 347 nm of hydroperoxy *trans*-enones obtained by singlet oxygen addition to β,γ-unsaturated enones has been reported to give peroxy hemiketals.[26,27] Irradiation of **26** with a sun lamp in 9:1 CH_2Cl_2–MeOH under N_2 without a sensitizer for 4 h provides 90% of a mixture of **29a** and **30a**, indicating that the sensitizer is needed only for the conversion of **24** to **26** and **28**. Hydroxy *trans*-enone **27** is isolated as a minor product from some photolyses. This compound probably arises from reduction or hydrolysis of **26**. Partial conversion (5%) of **26** to **27** occurs on flash chromatography.

The novel step in this sequence is the sensitized photooxygenation of dienol **24** to give **29a** and **30a**, possibly by the intermediacy of **26** and **28**. RBL is necessary as a sensitizer in the conversion of **22** to the peroxy hemiketals. The sensitizer could serve to convert oxygen to singlet oxygen, or to superoxide,[28-30] which would react with the ground state of dienol **24**. Alternatively the sensitizer could excite the dienol to an excited state which will react with triplet oxygen. Finally, the sensitizer could serve simply to initiate a radical-chain process.

Addition of singlet oxygen to the ground state of **24** appears unlikely in view of the following evidence. The formation of **29a** and **30a** is not inhibited by 0.002 M DABCO, a very efficient singlet oxygen quencher, but is inhibited by 0.001 M BHT, a free-radical inhibitor.[25,31] Pulegone (**32**) reacts very rapidly with singlet oxygen to give the ene adduct **31**.[25] Although this product is obtained in high yield with sun lamp irradiation and RB as a sensitizer, use of RBL as the sensitizer leads mainly to peroxy hemiketal **33a**. Therefore singlet oxygen is not involved in the formation of **33a**.



Superoxide can be generated photolytically.[28] It usually does not react with electron-rich alkenes,[30] although it has been reported to react with certain classes of enols.[29a] Superoxide is probably not involved in these reactions since substrates which are known to react with superoxide, such as bromohexadecane[28] and 4-cholesten-3-one,[29b] react very slowly under these conditions.

Photoenolization of *o*-methylaryl ketones and aldehydes, such as **34**, in the presence of oxygen to give peroxy hemiketals, such as **36**, is well-known.[32,33] The reaction of dienol **35** with oxygen does not require a sensitizer but may occur by a spin-allowed triple-triplet Diels–Alder reaction between an excited state of the enol and oxygen.[33] This reaction should be more facile for **35** than for dienol **24** since aromaticity is restored in the product **36**. Stable dienols such as **38** which can be generated by tautomerization of alkylidene dione **37** react spontaneously with oxygen to give **39**, a plant growth regulator from *Eucalyptus grandis*.[34]

In conclusion, the mechanism for the oxygenation of dienol **24** to give hydroperoxy enones **26** and **28** probably does not involve

(24) For leading references see: (a) Ricard, R.; Sauvage. P.; Wan, C. S. K.; Weedon, A. C.; Wong, D. F. *J. Org. Chem.* **1986**, *51*, 62. (b) Piva, O.; Pete, J.-P. *Tetrahedron Lett.* **1990**, *31*, 5157.

(25) Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2836.

(26) Nishio, T.; Mathies, P.; Job, K.; Frei, B.; Jeger, O. *Helv. Chim. Acta* **1989**, *72*, 943.

(27) Appendino, G.; Gariboldi, P.; Nano, G. M.; Têtênyi, P. *Phytochemistry* **1984**, *23*, 2545.

(28) Frimer, A. A. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; pp 429–462.

(29) (a) Frimer, A. A.; Gilinsky-Sharon, P.; Aljadeff, G. *Tetrahedron Lett.* **1982**, *23*, 1301. (b) Frimer, A. A.; Gilinsky-Sharon, P.; Hameiri, J.; Aljadeff, G. *J. Org. Chem.* **1982**, *47*, 2818.

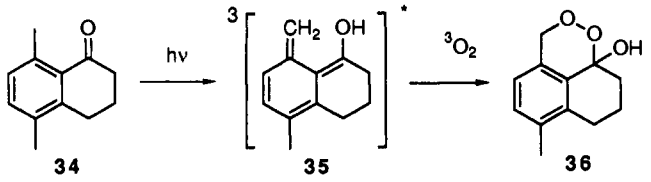
(30) Meskina, M. Ya.; Baider, L. M.; Skibida, I. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 733; *Bull. Acad. Sci. USSR, Chem. Ser.* **1990**, 646.

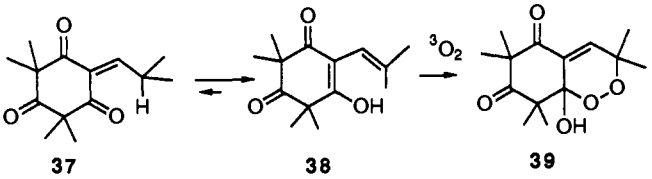
(31) Frimer, A. A. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; pp 208–209.

(32) For a review see: Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.

(33) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595.

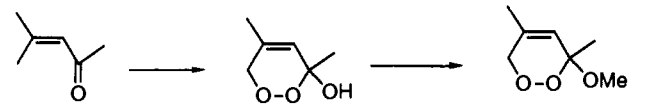
(34) For leading references see: Kalsi, P. S.; Singh, J.; Crow, W. D.; Chhabra, B. R. *Phytochemistry* **1987**, *26*, 3367.





singlet oxygen. It could involve superoxide addition to the dienol **24**, addition of an excited state of the dienol to ground-state oxygen, or a radical-chain process.

Use of Cu(II) as a Sensitizer. The only related example of the conversion of a simple enone to a peroxy hemiketal that we are aware of is the copper sulfate sensitized photooxygenation of mesityl oxide (**40**) in methanol which gives 3.5% of the peroxy hemiketal **41** and 1.8% of peroxy ketal **42**.[35] Under the conditions reported by these workers (0.5 M **40**), we obtain similarly low yields of **41** and **42**. However, when the concentration of **40** was reduced to 0.02 M, 10% of **41** and 50% of **42** are obtained. Irradiation of **40** with RBL in CH_2Cl_2 for 8 h provides 50% of **41**. In 19:1 CH_2Cl_2–MeOH 5% of **41** and 60% of **42** are obtained. We therefore decided to compare RBL and $CuSO_4$ as sensitizers in this photooxygenation.

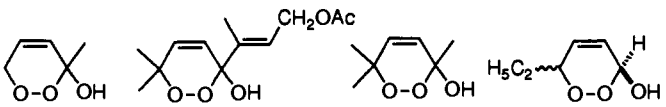


Irradiation of **22** with $CuSO_4$ in 9:1 MeOH–CH_2Cl_2 affords mixtures of hemiketals **29a** and **30a** and methyl ketals **29b** and **30b**. Enone **22** is converted to the hemiketals which undergo a $CuSO_4$-catalyzed ketalization. After 4.5 h, 25% of **22**, 65% of the hemiketals, and 5% of the ketals are present. After 16 h, no **22**, 2% of the hemiketals, and 80% of the ketals are present. Use of $CuSO_4$ as a sensitizer provides a one-pot route to methylperoxy ketals. Ketal formation is much slower with RBL. Irradiation of **22** for 11.5 h gives 2% of **22**, 85% of the hemiketals, and only 5% of the ketals. Hemiketals (83%) are obtained exclusively using RBL in CH_2Cl_2 as solvent. Mixed solvents were used initially since RB and $CuSO_4$ are not sufficiently soluble in pure CH_2Cl_2. Similar results are obtained with pulegone. In 9:1 CH_2Cl_2–MeOH, 62% of **33a** and 5% of **33b** are obtained with RBL and 75% of **33b** is obtained with $CuSO_4$.

A large-scale reaction with RBL as the sensitizer was cooled by cold water passed through copper tubing submerged in the solution. The solution slowly turned light blue, indicating that the copper tube was reacting. We therefore investigated the use of copper tubing as a sensitizer. Photooxygenation of pulegone in 9:1 CH_2Cl_2–MeOH containing copper tubing affords 76% of **33a** and 3% of **33b**. Similar results are obtained with copper powder (1 μm) in 19:1 CH_2Cl_2–MeOH.

We briefly investigated other sensitizers and solvents for this reaction. With RBL as sensitizer enone **22** is converted into hemiketals **29a** and **30a** in good yield in CH_2Cl_2 (85%), $CHCl_3$ (80%), benzene (75%), and MeOH (85%) and in poor yield in EtOAc (20%) and acetone (<5%). In 9:1 CH_2Cl_2–MeOH, $NiSO_4$ (80%) is also a good sensitizer. Eosin Y (30%), 1,10-phenanthroline (30%), naphthalene (5%), phenanthrene (10%), anthracene (0%), benzophenone (0%), and methylene blue (15%) are much less effective. The remaining material is a mixture of unreacted enone **22** and unconjugated enone **25**.

Scope and Limitations. If the mechanism proposed in Scheme IV is correct, any enone or enal which can undergo photoenolization to give a dienol should give peroxy hemiketals. Photooxygenation of 3-penten-2-one with RBL provides 56% of **43**. A variety of terpenoid peroxy hemiketals such as **44** have been isolated.[27,36] This class of compounds should be readily available since photooxygenation of 5-methyl-3-hexen-2-one with RBL affords 77% of **45**. Enals are also suitable substrates. Photooxygenation of 2-hexenal with RBL affords 30% of a 3:2 mixture of peroxy hemiacetals **46a** and **46b**. The same mixture is obtained in 52% yield with $CuSO_4$. The hemiacetal protons of both isomers are coupled to the adjacent olefinic protons with J = 3.4 and 3.6 Hz, respectively, indicating that methine protons are equatorial and the hydroxyl groups are axial as predicted by the anomeric effect. The other methine proton of the cis isomer **46a** is coupled to the adjacent olefinic proton with J = 1.1 Hz, indicating that the methine proton is axial and the ethyl group is equatorial. The other methine proton of the trans isomer **46b** is coupled to the adjacent olefinic proton with J = 4.2 Hz, indicating that the methine proton is equatorial and the ethyl group is axial. As predicted, no reaction occurs on irradiation of 3-methyl-2-cyclohexenone, 4-cholesten-3-one, or 1-acetylcyclohexene since these ketones cannot form dienols on irradiation.



Reactivity of Peroxy Ketals. We briefly examined the synthetic utility of peroxy ketals and peroxy hemiketals. Formation of methyl ketals from hemiketals with TsOH in methanol is a general reaction. Reaction of a mixture of **29a** and **30a** in MeOH containing a trace of TsOH for 30 h affords 97% of a 1:1 mixture of **29b** and **30b**. Similar treatment of **33a** in 4:1 hexane–MeOH for 2.5 h affords 99% of methyl ketal **33b**.

More complex reactions occur in stronger acid. Treatment of **33a** with concentrated HCl in methanol yields 93% of **49** and 6% of **48b**. This type of reaction was first observed by Wells in the structure determination of chondrillin.[1] As reported by Wells for **1b**, treatment of **15a** with HCl in aqueous THF gives 91% of *trans*-1-chloro-1-tetradecen-3-one. Protonation of **33a**, loss of water, and reaction with a nucleophile (MeOH or Cl^-) at the other end of the allylic cation will give **47**. A facile retro-Diels–Alder reaction driven by cleavage of a weak oxygen–oxygen bond will give **48**. Chloride **48b** is isolated while enol ether **48a** is hydrolyzed to **49**. Reaction of **33a** with TsOH in methanol gives 60% of **33b** and 40% of **49**. Reaction of **33a** with concentrated HCl in ether gives 91% of **48b** as a single stereoisomer. The data for **48b** (δ 2.40 br s, 3; 1690, 1600 cm^{-1}) correspond closely to those reported for the *E* isomer of the analogue lacking the methyl group (δ 2.41 br s, 3; 1695, 1605 cm^{-1}) and differ significantly from those of the *Z* isomer (δ 2.19 br s, 3; 1705, 1635 cm^{-1}).[37]

Reduction of **33a** with Zn in AcOH affords 90% of menthofuran (**50**).[38] Although menthofuran has been synthesized many times,[39] this two-step route from pulegone proceeding in 68% overall yield is one of the most efficient.

Diimide has been successfully used for the reduction of double bonds in the presence of the peroxide linkage.[40] The base sen-

(35) Sato, T.; Tamura, K.; Maruyama, K.; Ogawa, O.; Imamura, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 779.

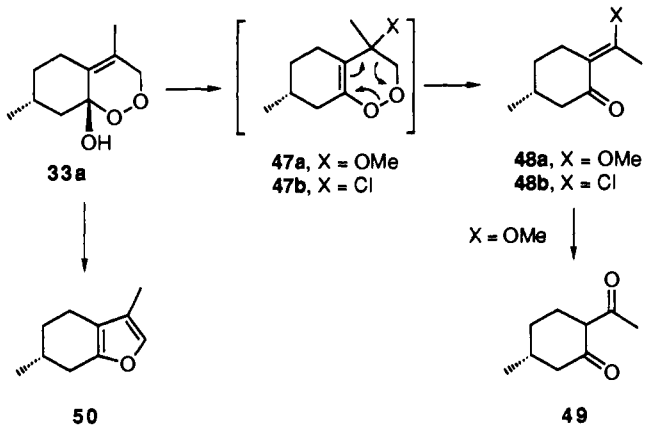
(36) Rustaiyan, A.; Bamonieri, A.; Raffatrad, M.; Jakupovic, J.; Bohlmann, F. *Phytochemistry* **1987**, *26*, 2307.

(37) Blanco, L.; Mansouri, A. *Tetrahedron Lett.* **1988**, *29*, 3239.

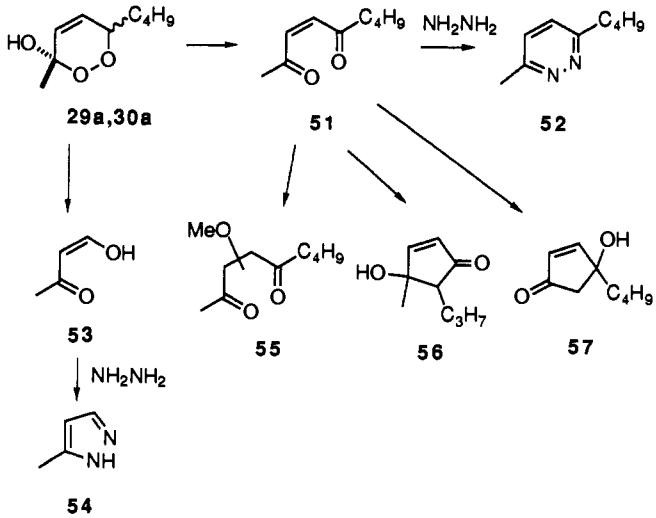
(38) Swigar, A. A.; Silverstein, R. M. *Monoterpenes*; Aldrich: Milwaukee, WI, 1981; p 65.

(39) Ho, T.-L.; Din, Z. U. *Synth. Commun.* **1989**, *19*, 813 and references cited therein.

(40) Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 1533.



sitivity of these peroxy hemiketals restricts the procedures that can be used to generate diimide. Reaction of a mixture of **29a** and **30a** with hydrazine, acetic acid, oxygen, and $CuSO_4$ in methanol[41] provides 65% of the pyridazine **52**[42] which is probably formed by condensation of hydrazine with the ene dione **51** obtained by loss of water from the peroxy hemiketals. Diimide is not involved in the reaction. Reaction of **29a** and **30a** with hydrazine and acetic acid in methanol affords 19% of **52** and 72% of 3-methylpyrazole (**54**). Presumably this solution is more acidic so that **53** and pentanal are formed by the same mechanism as **49**. Condensation of **53** with hydrazine will give **54**.



Although peroxy ketals are known to be very base sensitive, the decomposition products are not known. We therefore examined the reactions of **29a** and **30a** with NEt_3 in MeOH. Dehydration gives *cis*-ene dione **51**. Michael addition affords 47% of **55** as a mixture of regioisomers and 23% of a 5:1 mixture of aldol products **56** and **57**.

Conclusion. Seven-step synthesis of the antitumor cyclic peroxy ketals **1a**, **2a**, chondrillin (**1b**), and plakorin (**2b**) from (methoxymethoxy)benzene (**8**) have been achieved in 26–28% overall yields. The key step is the photooxygenation of enone **4** with a sun lamp using rose bengal lactone or $CuSO_4$ as a sensitizer which gives a mixture of peroxy hemiketals **15** and **16** in 75–85% yields. Acetal formation in acidic methanol completes the syntheses of **1** and **2**. The mechanism of photooxygenation was ascertained using 3-nonen-2-one (**22**) as a model for **4**. Irradiation converts **22** to the *cis*-enone **23** which undergoes photoenolization to give **24**. Dienol **24** undergoes a sensitized reaction with oxygen to give **29** and **30**. The detailed mechanism of this last step is not known, although singlet oxygen is probably not involved. This reaction is general for any enone or enal which can undergo photoenolization to give a dienol permitting a wide variety of peroxy hemiketals to be easily prepared. An initial examination of their reactivity suggests that peroxy hemiketals are versatile synthetic intermediates.

Experimental Section

General Procedures. NMR spectra were recorded at 300 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants are reported in hertz. Rose bengal (RB) and rose bengal lactone (RBL) were purchased from Aldrich. A 275-W GE sun lamp was used for irradiations. Oxygen was introduced through a fritted filter stick. Copper powder (1 μm) was purchased from Alfa.

2-Dodecyl(methoxymethoxy)benzene (9a). To a stirred solution of **8** (29.6 g, 215 mmol) and TMEDA (25 g, 215 mmol) in 360 mL of dry THF under N_2 at 0 °C was added dropwise a solution of *n*-BuLi (86.0 mL, 2.5 M in hexane, 215 mmol). The mixture was stirred at 0 °C for 1.5 h, and 1-bromododecane (57.5 g, 230 mmol) was added dropwise. The mixture was stirred at 0 °C for 1.5 h and at room temperature (rt) for 12 h, treated with water (200 mL), and extracted with ether (3 × 150 mL). The combined ether layers were washed with saturated NH_4Cl (50 mL), brine (50 mL), and H_2O (50 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave 79.86 g of crude **9a**. Flash chromatography of 5.53 g on silica gel (19:1 hexane–EtOAc) gave 3.42 g (73%) of **9a** as a colorless oil. A similar reaction on a 2-mmol scale gave 89% of **4a**: ^{1}H NMR 7.13 (m, 2), 7.05 (dd, 1, J = 8.5, 1.2), 6.93 (ddd, 1, J = 7.6, 7.0, 1.3), 5.20 (s, 2), 3.48 (s, 3), 2.62 (t, 2, J = 7.8), 1.58 (m, 2), 1.23–1.40 (m, 18), 0.88 (t, 3, J = 6.4); ^{13}C NMR 155.1, 132.0, 129.9, 126.8, 121.5, 113.9, 94.4, 55.9, 31.9, 30.3, 30.1, 29.70 (3 C), 29.63, 29.61, 29.56, 29.4, 22.7, 14.1; IR (neat) 3060, 3030, 2960, 2925, 1605, 1495, 1465 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_2$: C, 76.55; H, 10.71. Found: C, 76.54; H, 10.77.

2-Hexadecyl(methoxymethoxy)benzene (9b). Reaction of **8** (1.38 g, 10 mmol) with *n*-BuLi (2.5 M in hexane, 4.5 mL, 11.3 mmol) in 20 mL of THF and then with *n*-hexadecyl bromide (3.2 g, 10.5 mmol) as described above followed by flash chromatography on silica gel (19:1 hexane–EtOAc) gave 1.82 g (91%, based on recovered **8**) of **9b** as a colorless oil: ^{1}H NMR 7.13 (m, 2), 7.05 (dd, 1, J = 8.4, 1.2), 6.94 (ddd, 1, J = 7.3, 7.3, 1.2), 5.20 (s, 2), 3.48 (s, 3), 2.62 (t, 2, J = 7.7), 1.56 (m, 2), 1.12–1.40 (m, 26), 0.88 (t, 3, J = 6.7); ^{13}C NMR 155.0, 132.0, 129.9, 126.8, 121.5, 113.8, 94.4, 56.0, 31.9, 30.27, 30.16, 30.09, 29.70 (5 C), 29.66, 29.63, 29.60, 29.56, 29.36, 22.7, 14.1; IR (neat) 3050, 3030, 2960, 1600, 1590, 1470, 1230, 1180, 1125, 1050 cm^{-1}. Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.42; H, 11.73.

2-Dodecylphenol (7a). A solution of crude **9a** (39.96 g) and 10 M HCl solution (20 mL) in 200 mL of 1:1 THF–*i*-PrOH was stirred at rt for 16 h. The mixture was treated with water (300 mL) and extracted with ether (3 × 150 mL). The combined ether layers were washed with brine (80 mL) and water (80 mL), and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave 32.3 g of crude **7a** as a yellow oil. Vacuum distillation of crude **7a** (160–175 °C, 1.0 Torr) gave 16.6 g (58% from **8**) of **7a**.

A solution of pure **9a** (42.0 mg, 0.137 mmol) and $TsOH·H_2O$ (5.0 mg, 0.026 mmol) in 20 mL of methanol was heated at reflux for 30 h. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (14:1 hexane–EtOAc) gave 34.0 mg (95%) of phenol **7a**: mp 43.0–44.0 °C (lit.[43] mp 43–44 °C); ^{1}H NMR 7.09 (m, 2), 6.87 (ddd, 1, J = 7.6, 7.4, 1.2), 6.78 (dd, 1, J = 7.9, 1.2), 4.66 (s, 1, OH), 2.59 (t, 2, J = 7.8), 1.61 (m, 2), 1.20–1.40 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 153.4; 130.1, 128.5, 127.0, 120.7, 115.2, 31.9, 29.9, 29.8, 29.67(3 C), 29.64, 29.61, 29.55, 29.35, 22.7, 14.1; IR (KBr) 3450, 2960, 1595, 1490, 1470, 1380 cm^{-1}.

2-Hexadecylphenol (7b). A solution of ether **9b** (1.72 g) and $TsOH·H_2O$ (10 mg) in 100 mL of MeOH was heated at reflux as described above for 10 h followed by flash column chromatography on silica gel (14:1 hexane–EtOAc) to give 1.49 g (98%) of phenol **7b** as a white solid: mp 57.6–58.2 °C (lit.[44a] mp 59–60 °C; lit.[44b] mp 54–55 °C); ^{1}H NMR 7.08 (m, 2), 6.86 (ddd, 1, J = 8.0, 1.2), 4.78 (s, 1, OH), 2.59 (t, 2, J = 7.7), 1.6 (m, 2), 1.05–1.40 (m, 26), 0.88 (t, 3, J = 6.7); ^{13}C NMR 153.3, 130.1, 128.6, 127.0, 120.7, 115.2, 31.9, 29.93; 29.85, 29.77, 29.68 (6 C), 29.61, 29.56, 29.54, 29.36, 22.7, 14.1; IR (KBr) 3450, 2960, 1600, 1490, 1470, 1380, 1250, 1080 cm^{-1}.

6-Dodecyl-6-acetoxy-2,4-cyclohexadienone (6a). A solution of phenol **7a** (5.24 g, 20 mmol) in 40 mL of acetic acid was added to a solution of $Pb(OAc)_4$ (14.2 g, 32 mmol) in 200 mL of acetic acid, keeping the

(41) Ohno, M.; Okamoto, M. In *Organic Syntheses Collective Vol. 5*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; p 281.
(42) Hirsch, J. A.; Szur, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 523.
(43) Cooper, J. E.; Paul, J. M. *J. Chem. Eng. Data* **1970**, 586.
(44) (a) Rothschild, H. *Anais. Assoc. Brasil. Quim.* **1951**, *10*, 254. (b) Wissner, A.; Sum, P.-E.; Schaub, R. E.; Kohler, C. A.; Goldstein, B. M. *J. Med. Chem.* **1984**, *27*, 1174.

temperature under 30 °C. The solution was stirred at 25 °C for 10 h, treated with 300 mL of saturated $NaHCO_3$ solution, and extracted with ether (3 × 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), and water (100 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 4.58 g (72%) of dienone **6a** as yellow crystals: mp 40.0–41.0 °C; ^{1}H NMR 6.98 (ddd, 1, J = 9.9, 5.5, 2.0), 6.23–6.34 (m, 2), 6.17 (dd, 1, J = 9.9, 1.0), 2.10 (s, 3), 1.62–1.86 (m, 2), 1.15–1.50 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 199.0, 169.5, 141.5, 140.4, 126.9, 122.7, 81.6, 38.3, 31.9, 29.76, 29.59 (2 C), 29.55, 29.46, 29.31, 29.25, 22.7, 22.4, 20.5, 14.1; IR (KBr) 3080, 3060, 3030, 1745, 1670, 1640 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.07. Found: C, 74.84; H, 10.06.

6-Hexadecyl-6-acetoxy-2,4-cyclohexadienone (6b). Reaction of phenol **7b** (1.40 g, 4.4 mmol) with $Pb(OAc)_4$ (2.92 g, 6.6 mmol) in 20 mL of AcOH as described above followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 1.13 g (70%) of dienone **6b** as a light yellow solid: mp 54.0–55.0 °C; ^{1}H NMR 6.98 (ddd, 1, J = 9.8, 5.5, 2.0), 6.31 (ddd, 1, J = 9.6, 5.5, 0.9), 6.25 (ddd, 1, J = 9.6, 2.0, 0.9), 6.17 (d, 1, J = 9.8), 2.10 (s, 3), 1.6–1.9 (m, 2), 1.42 (m, 2), 1.00–1.35 (m, 26), 0.88 (t, 3, J = 6.7); ^{13}C NMR 199.0, 169.5, 141.5, 140.4, 126.9, 122.7, 81.6, 38.3, 31.9, 29.76, 29.66 (4 C), 29.64, 29.59, 29.56, 29.47, 29.33, 29.26, 22.7, 22.4, 20.5, 14.1; IR (KBr) 3830, 3030, 2960, 1745, 1675, 1630, 1375 cm^{-1}. Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.54; H, 10.77.

Methyl 6-Acetoxyoctadeca-3(Z),5(E)-dienoate (5a). A solution of dienone **6a** (1.81 g, 5.66 mmol) in 300 mL of MeOH in a 500-mL Pyrex flask equipped with a condenser was irradiated for 3 h with a 275-W sun lamp placed 10 cm from the flask, which heated the solution at gentle reflux. Removal of the MeOH at reduced pressure followed by flash chromatography on silica gel (14:1 hexane–EtOAc) gave 1.645 g (70%) of acetoxy diene **5a**: ^{1}H NMR 6.22 (ddt, 1, J = 11.4, 10.8, 1.6), 5.96 (dd, 1, J = 11.4, 0.9), 5.64 (ddt, 1, J = 10.8, 0.9, 7.4), 3.69 (s, 3), 3.18 (dd, 2, J = 7.4, 1.6), 2.37 (t, 2, J = 7.5), 2.16 (s, 3), 1.20–1.35 (m, 20), 0.88 (t, 3, J = 6.6); ^{13}C NMR 171.8, 169.4, 153.1, 124.8, 122.7, 113.3, 51.9, 33.1, 31.9, 29.63, 29.61 (2 C), 29.50, 29.46, 29.35, 29.33, 29.11, 26.9, 22.7, 21.0, 14.1; IR (neat) 3035, 2955, 1740, 1710, 1660, 1615 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.55; H, 10.29. Found: C, 71.34; H, 10.30.

Methyl 6-Acetoxydocosa-3(Z),5(E)-dienoate (5b). A solution of acetoxy dienone **6b** (1.07 g) in 200 mL of MeOH was irradiated for 2 h as described above for **5a**. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (12:1 hexane–EtOAc) gave 0.814 g (70%) of acetoxy diene **5b** as a yellow oil: ^{1}H NMR 6.22 (ddt, 1, J = 11.7, 10.8, 1.7), 5.96 (dd, 1, J = 11.7, 0.9), 5.64 (dtd, 1, J = 10.8, 7.4, 0.9), 3.69 (s, 3), 1.45 (m, 2), 1.05–1.40 (m, 26), 0.88 (t, 3, J = 6.7); ^{13}C NMR 171.8, 169.4, 153.0, 124.7, 122.7, 113.3, 51.9, 33.1, 31.9, 29.67 (6 C), 29.63, 29.60, 29.49, 29.45, 29.33, 29.10, 26.9, 22.7, 21.0, 14.1; IR (neat) 3030, 2960, 1740, 1710, 1655, 1620, 1470, 1380 cm^{-1}. Anal. Calcd for $C_{25}H_{44}O_4$: C, 73.48; H, 10.85. Found: C, 73.39; H, 10.62.

Methyl 6-Oxo-4(E)-octadecenoate (4a). Method A. A suspension of acetoxy diene **5a** (120 mg, 0.34 mmol) and Na_2CO_3 (30 mg, 0.28 mmol) in 20 mL of methanol was stirred at reflux for 1 h. The mixture was treated with 1 N HCl (1 mL) and H_2O (15 mL) and extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and H_2O (10 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 86.0 mg (81%) of enone **5a**.

Method B. A suspension of acetoxy diene **5a** (300 mg, 0.85 mmol) and Na_2CO_3 (65 mg, 0.60 mmol) in 30 mL of MeOH was stirred at reflux for 3 h. The mixture was cooled and treated with 2 mL of 3 M HCl. Removal of the solvent at reduced pressure gave crude **10a**. A solution of crude **10a** and $TsOH·H_2O$ (10 mg) in 50 mL of benzene was refluxed for 4 h in a 100-mL flask fitted with a Soxhlet extractor containing 10 g of 3A molecular sieves. Removal of the solvent at reduced pressure follow by flash chromatography gave 227 mg (84%, from **5a**) of enone **4a** as white crystals: mp 35.0–36.0 °C; ^{1}H NMR 6.81 (dt, 1, J = 15.9, 6.3), 6.12 (dt, 1, J = 15.9, 1.4), 3.70 (s, 3), 2.40–2.60 (m, 6), 1.58 (m, 2), 1.16–1.35 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 200.6, 172.7, 144.2, 130.9, 51.8, 40.3, 32.3, 31.9, 29.65, 29.62 (2 C), 29.48, 29.43, 29.34, 29.29, 27.4, 24.2, 22.7, 14.1; IR (KBr) 3025, 1745, 1680, 1635, 1370 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.55; H, 11.06.

Methyl 6-Oxo-4(E)-docosenoate (4b). Acetoxy diene **7b** (100 mg, 0.25 mmol) was converted to **4b** by method B as described above. Flash chromatography on silica gel (12:1 hexane–EtOAc) gave 71.0 mg (82%) of enone **4b** as a white solid: mp 54.0–55.0 °C; ^{1}H NMR 6.81 (dt, 1, J = 15.9, 6.4), 6.12 (dt, 1, J = 15.9, 1.4), 3.70 (s, 3), 2.40–2.60 (m, 6), 1.58 (m, 2), 1.10–1.40 (m, 26), 0.88 (t, 3, J = 6.7); ^{13}C NMR 200.6, 172.7, 144.2, 130.9, 51.8, 40.4, 32.3, 31.9, 29.69 (5 C), 29.65, 29.61, 29.48, 29.43, 29.35, 29.29, 27.4, 24.2, 22.7, 14.1; IR (KBr) 3025, 2960, 1745, 1700, 1640, 1475, 1440, 1380 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_3$: C, 75.36; H, 11.55. Found: C, 75.46; H, 11.46.

Methyl 6-Methoxy-3,5-octadecadienoate (3a). A solution of enone **4a** (180 mg, 0.59 mmol), trimethyl orthoformate (424 mg, 4 mmol), and $TsOH·H_2O$ (30 mg, 0.16 mmol) in benzene (3 mL) was heated at reflux for 3.5 h. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 138.0 mg (74%) of methoxy diene **3a** as a 3:1 mixture of trans and cis isomers at the disubstituted double bond.

The data for the 3E isomer were determined from the mixture: ^{1}H NMR 6.21 (ddt, 1, J = 15.0, 10.7, 1.3), 5.52 (ddt, 1, J = 15.0, 7.3, 0.6), 5.24 (d, 1, J = 10.7), 3.69 (s, 3), 3.54 (s, 3), 3.12 (dd, 2, J = 7.3, 1.3), 2.23 (t, 2, J = 7.6), 1.47 (m, 2), 1.20–1.40 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 172.6, 160.9, 129.7, 118.2, 98.5, 54.4, 51.8, 38.3, 31.9, 30.7, 29.64, 29.58, 29.55, 29.46, 29.43, 29.35, 29.33, 27.8, 22.7, 14.1.

The data for the 3Z isomer were determined from the mixture: ^{1}H NMR 6.24 (ddt, 1, J = 11.0, 10.7, 1.7), 5.33 (ddt, 1, J = 10.7, 7.4, 1.0), 5.30 (d, 1, J = 11.0), 3.70 (s, 3), 3.58 (s, 3), 3.20 (dd, 2, J = 7.4, 1.7), 2.25 (t, 2, J = 8.4), 1.47 (m, 2), 1.20–1.40 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 171.5, 162.5, 127.0, 115.8, 93.9, 54.4, 51.8, 38.4, 31.9, 30.7, 29.64, 29.58, 29.55, 29.46, 29.43, 29.35, 29.33, 27.8, 22.7, 14.1.

3-Methoxy-2-pentadecenal (14a) and Methyl 6-Oxo-3-hydroxy-4-(E)-octadecenoate (13a). Oxygen was bubbled into a solution of methoxy diene **3a** (20.0 mg, 0.062 mmol) and RB (1.5 mg, 0.0015 mmol) in 25 mL of MeOH which was irradiated for 2 h with a visible wavelength flood lamp (150 W) placed 10 cm from the mixture. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (12:1 and then 6:1 hexane–EtOAc) gave 6.8 mg (43%) of **14a** followed by 8.4 mg (41%) of enone **13a**. Irradiation of **3a** for 1 h with a sun lamp in 19:1 CH_2Cl_2–MeOH gave a mixture containing 75% of **14a** and 10% of **12a** as determined by ^{1}H NMR.

The data for **12a** were determined from the mixture: ^{1}H NMR 6.75 (dd, 1, J = 16.1, 6.1), 6.36 (dd, 1, J = 16.1, 1.3), 5.01 (dddd, 1, J = 8.0, 6.1, 5.2, 1.3), 3.72 (s, 3), 2.79 (dd, 1, J = 15.8, 8.0), 2.64 (dd, 1, J = 15.8, 5.2), 2.57 (t, 2, J = 7.2), 1.61 (m, 2), 1.10–1.36 (m, 18), 0.88 (t, 3, J = 6.7).

The data for **13a**: mp 49.0–50.0 °C; ^{1}H NMR 6.75 (dd, 1, J = 15.9, 4.3), 6.42 (dd, 1, J = 15.9, 2.5), 4.73 (dddd, 1, J = 8.6, 4.3, 4.2, 2.5), 3.75 (s, 3), 2.68 (dd, 1, J = 16.2, 4.2), 2.54 (dd, 1, J = 16.2, 8.6), 2.55 (t, 2, J = 7.5), 1.61 (m, 2), 1.12–1.40 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 200.5, 172.3, 144.5, 128.7, 67.3, 52.1, 41.3, 40.1, 31.9, 29.64, 29.62 (2 C), 29.47, 29.41, 29.33, 29.24, 24.0, 22.7, 14.1; IR (KBr) 3450, 2920, 2840, 1745, 1710, 1680, 1635, 1470, 1440, 1410, 1250, 1170, 1115, 1070, 1035, 990 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.84; H, 10.48.

The data for **14a**: ^{1}H NMR 9.81 (d, 1, J = 8.0), 5.39 (d, 1, J = 8.0), 3.68 (s, 3), 2.59 (t, 2, J = 7.2), 1.60 (m, 2), 1.05–1.40 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 190.2, 180.6, 104.3, 55.8, 31.9, 31.3, 29.60 (2 C), 29.57, 29.45, 29.33, 29.27, 29.1, 28.2, 22.7, 14.1.

Methyl (3R*,6S*)- and (3R*,6R*)-6-Dodecyl-3,6-dihydro-6-hydroxy-1,2-dioxine-3-acetate (15a and 16a). Method A. Oxygen was bubbled through a solution of acetoxy diene **5a** (20 mg, 0.06 mmol) and RB (2 mg, 0.002 mmol) in 20 mL of 19:1 CH_2Cl_2–MeOH in a Pyrex tube cooled in an ice–water bath. The solution was irradiated for 8 h with a 275-W sun lamp placed 10 cm from the mixture. The red solution became light yellow during the first 1 h of irradiation. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 8.7 mg (45%) of a 3:2 mixture of **15a** and **16a** which was used for further reactions. ^{1}H NMR spectra of aliquots taken after irradiation with the sun lamp for 2 h showed the presence of about 5% of hydroperoxy enone **12a** and some 3E double-bond isomer of **5a**. Irradiation of a solution of acetoxy diene **5a** and RB in 19:1 CH_2Cl_2–MeOH with a flood lamp (150 W) for 20 h gave a mixture containing 60% of double-bond isomers of **5a** (mainly 3E,5E), and 20% of **12a** as determined by ^{1}H NMR. When $CuSO_4$ or RBL was used as sensitizer for the irradiation reaction, only double-bond isomers, mainly 3E, of **5a** were obtained after irradiation for 40 h.

Method B. Oxygen was bubbled through a solution of enone **4a** (14.8 mg, 0.045 mmol) and RBL (0.8 mg) in 25 mL of 19:1 CH_2Cl_2–MeOH in a Pyrex reaction tube cooled in a water bath, which was irradiated for 10 h with a 275-W sun lamp placed 5–10 cm from the mixture. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 12.8 mg (78%) of a 3:2 mixture of **15a** and **16a**. Careful flash chromatography on silica gel (19:1 hexane–EtOAc) gave 4.5 mg of pure **16a** followed by 4.5 mg of a mixture rich in **15a** and 3 mg of pure **15a**. The same mixture was obtained in similar yields when RB (1.0 mg, 70%) or $CuSO_4$ (3.0 mg, 85%) was used in place of RBL.

Data for **15a**: mp 75.0–76.0 °C; ^{1}H NMR 6.10 (dd, 1, J = 10.2, 4.4), 5.95 (dd, 1, J = 10.2, 1.7), 4.73–4.79 (m, 1), 3.73 (s, 3), 3.26 (br s, 1, OH), 2.98 (dd, 1, J = 16.3, 7.8), 2.65 (dd, 1, J = 16.3, 5.4), 1.64–1.72 (m, 2), 1.20–1.44 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.9, 128.5, 128.2, 97.7, 73.9, 52.0, 37.1, 36.4, 31.9, 29.7, 29.63 (3 C), 29.52, 29.38, 29.34, 23.0, 22.7, 14.1; IR (KBr) 3540, 3460, 3010, 1740, 1730, 1725, 1655, 1635 cm^{-1}.

Data for **16a**: mp 74.2–75.0 °C; ^{1}H NMR 5.97 (br s, 2), 5.05 (ddd, 1, J = 6.7, 6.3, 0.5), 3.72 (s, 3), 3.48 (br s, 1, OH), 2.61 (dd, 1, J = 16.2, 6.7), 2.54 (dd, 1, J = 16.2, 6.3), 1.64–1.72 (m, 2), 1.20–1.45 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.1, 129.1, 128.7, 98.0, 73.6, 52.1, 36.3, 36.1, 31.9, 29.71, 29.62 (2 C), 29.49, 29.40, 29.34, 22.85, 22.67, 22.65, 14.1; IR (KBr) 3540, 3460, 3010, 1740, 1730, 1725, 1655, 1636 cm^{-1}.

Anal. (**15a** and **16a**) Calcd for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.56; H, 9.78.

Methyl (3*R,6*S**)- and (3*R**,6*R**)-6-Hexadecyl-3,6-dihydro-6-hydroxy-1,2-dioxine-3-acetate (15b and 16b). Method A.** Irradiation of a solution of acetoxy diene **5b** (96 mg, 0.23 mmol) and RB (2.5 mg, 0.0025 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH as described above followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 39.5 mg (42%) of a 3:2 mixture of **15b** and **16b**. Careful flash chromatography on silica gel (20:1 hexane–EtOAc) gave 5.5 mg of pure **16b** followed by 29.0 mg of a mixture rich in **15b** and 4.5 mg of pure **15b**.

Method B. Irradiation of a solution of **4b** (14.8 mg, 0.048 mmol) and RBL (1.0 mg, 0.001 mmol) in 25 mL of 9:1 CH_2Cl_2–MeOH for 12 h as described above for **4a** followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 12.8 mg (73%) of a 3:2 mixture of **15b** and **16b**.

Data for **15b**: mp 75.0–76.0 °C; ^{1}H NMR 6.10 (dd, 1, J = 10.1 4.3), 5.95 (dd, 1, J = 10.1, 1.7), 4.72–4.80 (m, 1), 3.73 (s, 3), 2.98 (dd, 1, J = 16.1, 7.8), 2.65 (dd, 1, J = 16.1, 5.6), 1.70 (m, 2), 1.60 (br s, 1, OH), 1.10–1.45 (m, 28), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.9, 128.5, 128.2, 97.7, 73.9, 52.0, 37.1, 36.4, 31.9, 29.80, 29.69 (4 C), 29.65, 29.62, 29.53, 29.39, 29.36, 29.29, 23.1, 22.7, 14.1.

Data for **16b**: mp 84.0–85.0 °C; ^{1}H NMR 5.97 (br s, 2), 5.05 (ddd, 1, J = 6.7, 6.5, 0.5), 3.72 (s, 3), 2.61 (dd, 1, J = 16.1, 6.7), 2.54 (dd, 1, J = 16.1, 6.5), 1.70 (m, 2), 1.60 (br s, OH), 1.15–1.50 (m, 28), 0.88 (t, 3, J = 6.7); ^{13}C NMR 169.8, 129.1, 128.7, 98.0, 73.6, 52.1, 36.3, 36.1, 31.9, 29.74, 20.68 (4 C), 29.65, 29.62, 29.50, 29.45, 29.40, 29.35, 22.9, 22.7, 14.1.

IR (KBr) 3500, 3450, 3020, 1740, 1720, 1650, 1630, 1470, 1380 cm^{-1}. Anal. (**15b** and **16b**) Calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62. Found: C, 69.41; H, 10.52.

Methyl (3*R,6*S**)- and (3*R**,6*R**)-6-Dodecyl-3,6-dihydro-6-methoxy-1,2-dioxine-3-acetate (1a and 2a). Method A.** A solution of **15a** and **16a** (10 mg, 0.03 mmol) and *p*-TsOH monohydrate (1 mg) in MeOH (6 mL) was stirred for 40 h at 25 °C. Removal of most of the solvent at reduced pressure followed by filtration through silica gel (6:1 hexane–EtOAc) to remove the acid catalyst gave 10.4 mg (100%) of a 1.1:1 mixture of **1a** and **2a**. Careful flash chromatography on silica gel (25:1 hexane–EtOAc) gave 4 mg of pure **2a**, followed by 4 mg of a mixture rich in **1a** and 2 mg of pure **1a**.

Method B. Oxygen was bubbled into a suspension of $CuSO_4$ (3.0 mg) and enone **4a** (20 mg, 0.065 mmol) in 25 mL of 9:1 CH_2Cl_2–CH_3OH in a Pyrex reaction tube cooled in a water bath which was irradiated for 12 h with a 275-W sun lamp placed 5–10 cm from the mixture. Removal of the solvent at reduced pressure gave a mixture **15a**, **16a**, **1a**, and **2a**. A solution of this mixture and TsOH·H_2O (1.0 mg) in 5 mL of MeOH was stirred at rt for 30 h, treated with 10 mL of H_2O, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (12:1 hexane–EtOAc) gave 17.4 mg (76%) of a 1.1:1 mixture of **1a** and **2a**.

Data for **1a**: ^{1}H NMR 6.19 (dd, 1, J = 10.2, 4.4), 5.88 (dd, 1, J = 10.2, 1.7), 4.76–4.83 (m, 1), 3.73 (s, 3), 3.40 (s, 3), 2.93 (dd, 1, J = 16.2, 7.9), 2.62 (dd, 1, J = 16.2, 5.2), 1.60–1.68 (m, 2), 1.20–1.36 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.8, 129.2, 126.4, 100.5, 73.7, 52.0, 50.9, 37.2, 34.2, 31.9, 29.76, 29.63, 29.53, 29.45, 29.40, 29.34, 23.4, 22.68, 22.65, 14.1.

Data for **2a**: ^{1}H NMR 6.11 (dd, 1, J = 10.3, 1.5), 5.85 (dd, 1, J = 10.3, 2.2), 4.98–5.04 (m, 1), 3.72 (s, 3), 3.39 (s, 3), 2.62 (dd, 1, J = 16.0, 7.6), 2.51 (dd, 1, J = 16.0, 7.5), 1.60–1.69 (m, 2), 1.20–1.36 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.0, 130.3, 126.9, 101.1, 73.5, 52.1, 51.3, 36.3, 34.8, 31.9, 29.74, 29.63 (3 C), 29.52, 29.43, 29.34, 23.3, 22.7, 14.1. The ^{1}H NMR spectra data are identical to those previously described.[3]

Plakorin (2b) and Chondrillin (1b). A solution of **15b** and **16b** (29.0 mg) and TsOH·H_2O (4.0 mg) in 8 mL of MeOH was stirred at rt for 80 h and worked up as described above. Flash chromatography on silica gel (12:1 hexane–EtOAc) gave 29.5 mg (98%) of a 1.1:1 mixture of **1b** and **2b**. Careful flash chromatography on silica gel (25:1 hexane–EtOAc) gave 6.0 mg of pure **2b**, followed by 19.4 mg of a mixture rich in **1b** and 4.0 mg of pure **1b**.

Data for **1b**: ^{1}H NMR 6.19 (dd, 1, J = 10.2, 4.4), 5.88 (dd, 1, J = 10.2, 1.8), 4.80 (m, 1), 3.73 (s, 3), 3.40 (s, 3), 2.94 (dd, 1, J = 16.1, 8.0), 2.63 (dd, 1, J = 16.1, 5.4), 1.65 (m, 2), 1.10–1.40 (m, 28), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.9, 129.2, 126.4, 100.5, 73.7, 52.0, 50.9, 37.2, 34.2, 31.9, 29.78, 29.69 (5 C), 29.66, 29.62, 29.55, 29.41, 29.36, 23.5, 22.7, 14.1; IR (neat) 2955, 1740, 1465, 1430, 1250, 1160, 1125, 1060 cm^{-1}. The data was identical to those previously described.[1,3,4]

Data for **2b**: ^{1}H NMR 6.12 (dd, 1, J = 10.2, 1.6), 5.86 (dd, 1, J = 10.2, 2.1), 4.98–5.05 (m, 1), 3.72 (s, 3), 3.39 (s, 3), 2.62 (dd, 1, J = 16.2, 7.6), 2.51 (dd, 1, J = 16.2, 6.6), 1.65 (m, 2), 1.05–1.40 (m, 28), 0.88 (t, 3, J = 6.7); ^{13}C NMR 170.0, 130.3, 126.9, 101.1, 73.5, 52.1, 51.3, 36.3, 34.7, 31.9, 29.74, 29.68 (5 C), 29.65, 29.61, 29.52, 29.43, 29.35, 23.3, 22.7, 14.1; IR (neat) 2960, 2930, 1740, 1465, 1270, 1165, 1120 cm^{-1}. The data are identical to those previously described.[4,5]

6-Oxo-4(*E*)-octadecenoic Acid (19a). A mixture of enone **4a** (100.0 mg, 0.33 mmol) and 10% NaOH solution (2 mL) in 25 mL of 1:1 THF–H_2O was stirred at 50 °C for 1 h and cooled to rt. The THF was removed under reduced pressure, and the solution was treated with 2.5 M HCl solution (3 mL) to precipitate **19a**. Acid **19a** was isolated by suction filtration and washed with H_2O and 10:1 hexane–EtOAc to give 92.8 mg (95%) of a 6:1 mixture of **19a** and 6-oxo-4-hydroxyoctadecanoic acid, which was used for the preparation of **19b**.

An analytical sample of **19a** was prepared by recrystallization from MeOH: mp 83.0–84.0 °C; ^{1}H NMR 6.82 (m, 1), 6.14 (d, 1, J = 15.8), 2.50–2.56 (m, 6), 1.59 (m, 2), 1.20–1.36 (m, 18), 0.88 (t, 3, J = 6.7); ^{13}C NMR 200.7, 177.5, 143.9, 131.0, 40.4, 32.2, 31.9, 29.63 (2 C), 29.61, 29.48, 29.43, 29.34, 29.28, 27.1, 24.2, 22.7, 14.1; IR 3300–2800, 1720, 1700, 1630, 1470, 1285, 1270, 1210 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.76; H, 10.59.

***tert*-Butyldimethylsilyl 6-Oxo-4(*E*)-octadecenoate (19b).** A solution of the 6:1 mixture containing **19a** (34.6 mg, 0.11 mmol), *tert*-butyldimethylsilyl chloride (55.4 mg, 0.36 mmol), and imidazole (50.0 mg, 0.73 mmol) in 2 mL of DMF was stirred at rt for 12 h under N_2. The solution was treated with saturated brine (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine (10 mL) and H_2O (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 34.2 mg (84%) of **19b** as a colorless oil: ^{1}H NMR 6.82 (m, 1), 6.12 (dd, 1, J = 16.1, 1.3), 2.48–2.55 (m, 6), 1.60 (m, 2), 1.22–1.37 (m, 18), 0.93 (s, 9), 0.88 (t, 3, J = 6.7), 0.28 (s, 6); ^{13}C NMR 200.6, 172.6, 144.5, 130.8, 40.3, 34.2, 31.9, 29.65 (2 C), 29.62, 29.48, 29.42, 29.33, 29.30, 27.6, 25.5 (3 C), 24.2, 22.7, 17.6, 14.1, 0.0 (2 C).

(3*R,6*S**)- and (3*R**,6*R**)-6-Dodecyl-3,6-dihydro-6-hydroxy-1,2-dioxine-3-acetic Acid (21a and 21b).** A solution of enone **19b** (30.0 mg, 0.075 mmol) and RBL (0.7 mg, 0.0007 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated with a sun lamp (275 W) for 12 h as described above. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 7.2 mg (32%) of 6-oxo-4-octadecanoic lactone (**20**) as a white solid. Elution with 2:1 EtOAc–hexane gave 13.0 mg (52%) of a 1.2:1 mixture of acids **21a** and **21b** as a white solid. Irradiation of acid **19a** and RBL in 19:1 CH_2Cl_2–MeOH for 6 h gave 90% of **20** which can be converted to a 6:1 mixture of **19a** and 6-oxo-4-hydroxyoctadecanoic acid in 95% yield by treatment with NaOH and then HCl.

Data for **20**: mp 57.0–58.0 °C; ^{1}H NMR 4.85–4.97 (m, 1), 2.98 (dd, 1, J = 17.1, 6.2), 2.68 (dd, 1, J = 17.1, 6.5), 2.35–2.60 (m, 5), 1.91 (m, 1), 1.58 (m, 2), 1.10–1.37 (m, 18), 0.88 (t, 3, J = 6.6); ^{13}C NMR 207.3, 176.6, 76.3, 47.6, 43.6, 31.9, 29.60, 29.55, 29.40, 29.33, 29.30 (2 C), 29.1, 28.6, 28.1, 23.5, 22.7, 14.1. IR (KBr) 2920, 1770, 1710, 1470, 1410, 1390, 1190, 1015, 980, 915 cm^{-1}.

Data for **21a** and **21b**: mp 108.0–110.0 °C; IR (KBr) 3450, 3300, 3030, 1735, 1470, 1410, 1255, 1190, 1145, 1040 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.56; H, 9.75.

Data for **21a** were determined from the mixture: ^{1}H NMR 6.11 (dd, 1, J = 10.1, 4.2), 5.96 (dd, 1, J = 10.1, 1.5), 4.76 (m, 1), 3.02 (dd, 1, J = 16.4, 8.0), 2.70 (dd, 1, J = 16.4, 5.4), 1.69 (m, 2), 1.15–1.40 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 174.1, 128.6, 128.0, 97.8, 73.6, 36.7, 36.4, 31.9, 29.7, 29.63 (2 C), 29.53, 29.42, 29.39, 29.35, 23.1, 22.7, 14.1.

Data for **21b** were determined from the mixture: ^{1}H NMR 6.00 (br d, 1, J = 10.2), 5.96 (br d, 1, J = 10.2), 5.03 (m, 1), 2.66 (dd, 1, J = 16.2, 1.9), 2.57 (dd, 1, J = 16.2, 1.6), 1.69 (m, 2), 1.15–1.40 (m, 20), 0.88 (t, 3, J = 6.7); ^{13}C NMR 173.4, 129.0, 128.6, 98.0, 73.5, 36.45, 36.42, 31.9, 29.7, 29.63 (2 C), 29.53, 29.42, 29.39, 29.35, 22.9, 22.7, 14.1.

(3*R,6*S**)- and (3*R**,6*R**)-3-Methyl-6-butyl-3,6-dihydro-1,2-dioxin-3-ol (29a and 30a). Method A.** Oxygen was bubbled into a solution of **22** (3.0 g, 21.4 mmol) and RBL (30 mg, 0.03 mmol) in 300 mL of 19:1 CH_2Cl_2–MeOH in a Pyrex beaker. The solution was cooled by cold

water through a glass coil and irradiated with a sun lamp (275 W) placed 5–10 cm from the mixture for 30 h. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 2.70 g (72%) of a 1.7:1 mixture of hemiketals **29a** and **30a**. Elution with 6:1 hexane–EtOAc gave 0.20 g (6%) of **27**. On a small scale (31 mg of **22**), 83% of a similar mixture was obtained. Less than 10% of this mixture was obtained when 2,6-di-*tert*-butyl-4-methylphenol (0.001 M) was present during irradiation. The mixture was obtained in good yield (65–80%) when DABCO (0.002 M) was present during irradiation.

Method B. A suspension of **22** (40.0 mg, 0.29 mmol) and $CuSO_4$ (3.2 mg, 0.02 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated for 5 h as described above. The solution was washed with H_2O (5.0 mL) and dried (Na_2SO_4). Removal of solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 5.3 mg (10%) of methyl ketals **29b** and **30b**. Elution with 6:1 hexane–EtOAc gave 38.9 mg (79%) of a 1.7:1 mixture of **29a** and **30a**. Careful flash chromatography on silica gel (20:1 hexane–EtOAc) gave 5.6 mg of pure **30a**, followed by 26.6 mg of a mixture rich in **29a** and 6.4 mg of pure **29a**.

^1H NMR spectra of an aliquot taken after 1 h of irradiation with RBL indicated the presence of about 5% of *trans*-5-hydroperoxy-3-nonen-2-one (**26**). Less than 1% of **26** was present during irradiation with $CuSO_4$. Irradiation of a solution of 3-nonen-2-one with a sun lamp without sensitizer gave a 1:1 mixture of *trans*- and *cis*-4-nonen-2-one (**25**). No reaction occurred on irradiation for 12 h of **22** with either RB, RBL, or $CuSO_4$ and a visible wavelength flood lamp.

Data for **25**: ^1H NMR 5.45–5.65 (m, 2), 3.17 (d, 0.5 × 2, J = 6.0), 3.10 (d, 0.5 × 2, J = 5.4), 2.17 (s, 0.5 × 3), 2.15 (s, 0.5 × 3), 1.96–2.08 (m, 2), 1.20–1.40 (m, 4), 0.89 (t, 3, J = 7.0). The NMR data are identical to those previously described.[45]

Data for **29a**: ^1H NMR 6.00 (dd, 1, J = 10.1, 4.0), 5.90 (dd, 1, J = 10.1, 1.6), 4.20 (m, 1), 1.63 (m, 2), 1.41 (s, 3), 1.20–1.50 (m, 4), 0.92 (t, 3, J = 7.1); ^{13}C NMR 129.3, 128.0, 96.0, 77.9, 31.7, 28.1, 22.9, 22.5, 14.0; IR (neat) 3500, 3050, 3000, 1690, 1470, 1130, 1020 cm^{-1}.

Data for **30a**: ^1H NMR 5.92 (br s, 2), 4.66 (td, 1, J = 6.6, 1.1), 1.62 (m, 2), 1.42 (s, 3), 1.20–1.50 (m, 4), 0.90 (t, 3, J = 7.1); ^{13}C NMR 130.0, 128.8, 96.3, 77.1, 31.5, 26.9, 22.8, 22.6, 13.8; IR (neat) 3500, 3050, 3000, 1690, 1470, 1130, 1020 cm^{-1}.

Anal. (**29a** and **30a**) Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.78; H, 9.17.

5-Hydroperoxy-3-nonen-2-one (26) and 5-Hydroxy-3-nonen-2-one (27). Oxygen was bubbled into a solution of **22** (1.20 g, 8.6 mmol) and RBL (15 mg, 0.015 mmol) in 50 mL of 9:1 CH_2Cl_2–MeOH while the solution was irradiated with a sun lamp (275 W) at 20 °C for 20 h. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (12:1 to 4:1 hexane–EtOAc) gave 820 mg (68%) of recovered **22**, followed by 196 mg (16%) of **29a** and **30a**, 60 mg (5%) of **26**, and 16.4 mg (1.3%) of **27**.

Data for **26**: ^1H NMR 6.72 (dd, 1, J = 16.2, 6.8), 6.27 (dd, 1, J = 16.2, 1.0), 4.53 (dtd, 1, J = 6.8, 6.8, 1.0), 2.31 (s, 3), 1.50–1.75 (m, 2), 1.30–1.50 (m, 4), 0.90 (t, 3, J = 7.0); ^{13}C NMR 198.5, 145.3, 131.9, 84.9, 31.9, 27.31, 27.24, 22.5, 13.8; IR (neat) 3350, 2965, 2940, 2875, 1680, 1640, 1465, 1365, 1260, 980 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.94; H, 9.16.

Data for **27**: ^1H NMR 6.77 (dd, 1, J = 16.0, 5.1), 6.27 (dd, 1, J = 16.0, 1.5), 4.33 (dtd, 1, J = 5.1, 5.9, 1.5), 2.29 (s, 3), 1.60 (m, 2), 1.27–1.44 (m, 4), 0.91 (t, 3, J = 7.0); ^{13}C NMR 198.6, 148.9, 129.0, 71.2, 36.4, 27.44, 27.35, 22.5, 13.9; IR (neat) 3450, 2960, 2935, 2870, 1675, 1630, 1470, 1425, 1360, 1255, 975 cm^{-1}. The NMR data are identical to those previously described.[46]

The structures of **26** and **27** were confirmed by the following experiments. An authentic sample of **27** was prepared in 65% yield from **25** by epoxidation of **25** (prepared in 95% yield by photoenolization of **22**) with MCPBA in CH_2Cl_2 and treatment of the epoxide with K_2CO_3 in *tert*-butyl alcohol for 16 h at rt. Reduction of **26** with $NaHSO_3$ in 5:1 MeOH–H_2O afforded **27**. Irradiation of a solution of **26** (8.0 mg) in 25 mL of 9:1 CH_2Cl_2–MeOH under N_2 with a sun lamp for 4 h at rt followed by removal of the solvent gave 7.9 mg of 90% pure **29a** and **30a** as determined by ^1H NMR analysis. The differing effects of the hydroxy and hydroperoxy groups on the ^1H and ^{13}C NMR spectra of **26** and **27** are consistent with those observed in related systems.[47]

(3*R,6*S**)- and (3*R**,6*R**)-3-Methoxy-3-methyl-6-butyl-3,6-dihydro-1,2-dioxine (29b and 30b). Method A.** A solution of **29a** and **30a** (300.0 mg) and $TsOH·H_2O$ (3.0 mg) in 20 mL of MeOH was stirred at rt for 30 h. The mixture was treated with water (40 mL) and extracted with 1:1 ether–hexane (3 × 40 mL). The combined organic layer was dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 314.0 mg (97%) of a 1.1:1 mixture of **29b** and **30b**.

Method B. A solution of **22** (60.0 mg, 0.43 mmol) and $CuSO_4$ (3.0 mg, 0.02 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated for 16 h as described above. The solution was washed with 5 mL of water and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 66.8 mg (83%) of a 1.2:1 mixture of peroxy ketals **29b** and **30b** as a colorless oil. Careful flash chromatography on silica gel (25:1 hexane–EtOAc) gave 14.2 mg of pure **30b**, followed by 43.8 mg of a mxiture rich in **29b** and 8.4 mg of pure **29b**.

Data for **29b**: ^1H NMR 6.09 (dd, 1, J = 10.2, 4.1), 5.80 (dd, 1, J = 10.2, 1.8), 4.25 (m, 1), 3.41 (s, 3), 1.20–1.90 (m, 6), 1.37 (s, 3), 0.92 (t, 3, J = 7.1); ^{13}C NMR 130.1, 126.4, 98.6, 77.5, 50.6, 31.8, 28.0, 22.5, 21.0, 13.9; IR (neat) 3060, 3000, 1760, 1745, 1705, 1680, 1635, 1470, 1245, 1190, 1100, 1050 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.57; H, 9.64.

Data for **30b**: ^1H NMR 6.00 (dd, 1, J = 10.1, 1.3), 5.81 (dd, 1, J = 10.1, 2.2), 4.59 (m, 1), 3.42 (s, 3), 1.56 (m, 2), 1.20–1.50 (m, 4), 1.36 (s, 3), 0.90 (t, 3, J = 7.1); ^{13}C NMR 130.9, 127.1, 98.9, 76.7, 51.1, 31.5, 27.1, 22.6, 21.3, 13.8; IR (neat) 3060, 3000, 1760, 1745, 1705, 1680, 1635, 1470, 1245, 1190, 1100, 1050 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.36; H, 9.77.

(7*R*,8a*R*)-3,5,6,7,8,8a-Hexahydro-4,7-dimethyl-1,2-benzodioxin-8a-ol (33a). Method A. Oxygen was bubbled into a solution of (+)-pulegone (**32**) (1.0 g, 85% pure, 10.6 mmol) in 300 mL of 9:1 CH_2Cl_2–MeOH containing five 3-in.-long pieces of $^1/_4$-in. copper tubing. The mixture was irradiated with two sun lamps (275W) placed 5–10 cm from the mixture for 17 h giving a light yellow-blue solution. The solution was cooled by cold water circulating through a glass coil inserted into the solution. The copper tubing was removed, and the mixture was washed with water (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by chromatography on silica gel (15:1 hexane–EtOAc) gave 3% of **33b**. Elution with 6:1 hexane–EtOAc gave 0.74 g (76%) of **33a** as a white solid.

Method B. Oxygen was bubbled into a solution of RBL (45 mg, 0.045 mmol) and $CuSO_4$ (3.2 mg, 0.02 mmol) in 900 mL of 9:1 CH_2Cl_2–MeOH which was irradiated for 1.5 h with two sun lamps (275 W) placed 5–10 cm from the mixture to bleach any RB present. The solution was cooled by cold water passed through a glass coil in the solution. (+)-Pulegone (2.4 g, 80%, 13 mmol) was then added to the solution which was irradiated for 24 h, washed with 50 mL of water, and dried (Na_2SO_4). Removal of the solvent at reduced pressure, followed by flash chromatography on silica gel (15:1 hexane–EtOAc), gave 5% of **33b**. Elution with 6:1 hexane–EtOAc gave 1.42 g (62%) of peroxy hemiketal **33a** as a white solid. On a smaller scale, 80% of **33a** was obtained. When a flood visible lamp (150 W) was used as light source, <3% of **33a**, <5% of **31a**, and 80% of unreacted **32** were obtained.

Data for **33a**: mp 96.0–97.0 °C; ^1H NMR 4.71 (ddd, 1, J = 15.9, 2.6, 1.1), 4.04 (dd, 1, J = 15.9, 3.0), 3.10 (br s, 1, OH), 2.61 (ddd, 1, J = 14.3, 4.0, 2.6), 1.75–2.14 (m, 4), 1.65 (s, 3), 0.94 (d, 3, J = 6.5), 0.80–1.08 (m, 2); ^{13}C NMR 129.5, 124.3, 97.4, 73.0, 41.8, 34.9, 29.0, 24.9, 21.8, 13.6; IR (KBr) 3460, 2960, 1700, 1460, 1435, 1345, 1260, 1160, 1095 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: H, 65.22; H, 8.69.

(7*R*,8a*R*)-4,7-Dimethyl-8a-methoxy-3,5,6,7,8,8a-hexahydro-1,2-benzodioxine (33b). Method A. Oxygen was bubbled into a suspension of (+)-pulegone (2.0 g, 80%, 10.5 mmol) and $CuSO_4$ (25 mg, 0.16 mmol) in 800 mL of 9:1 CH_2Cl_2–MeOH which was irradiated with two sun lamps for 24 h at cold water temperature. The solution was washed with water (100 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 1.58 g (75%) of peroxy ketal **33b** as a colorless oil. The yield was 65% when only 300 mL of solvent used. The yield was 82% in a small-scale reaction (60 mg in 25 mL of solvent). When a flood visible lamp (150 W) was used as light source, no reaction took place after 12-h of irradiation.

Method B. A mixture of peroxy hemiketal **33a** (21.0 mg, 0.11 mmol) and $TsOH·H_2O$ (1.0 mg, 0.006 mmol) in 10 mL of 4:1 hexane–MeOH was stirred at room temperature for 2.5 h. The mixture was treated with

(45) Gardrat, C.; Montaudon, E.; Lalande, R. *Bull. Soc. Chim. Belg.* **1980**, *89*, 1039.

(46) Nokami, J.; Nishimura, A.; Sunami, M.; Wakabayashi, S. *Tetrahedron Lett.* **1987**, *28*, 649.

(47) Dang, H.-S.; Davies, A. G.; Davison, I. G. E.; Schiesser, C. H. *J. Org. Chem.* **1990**, *55*, 1432.

water (1 mL), and the aqueous layer was separated and extracted with hexane (2 × 4 mL). The combined hexane layers were dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 22.6 mg (99%) of peroxy ketal **33b**: ^{1}H NMR 4.66 (ddd, 1, J = 15.9, 2.6, 1.2), 4.08 (dd, 1, J = 15.9, 2.8), 3.36 (s, 3), 2.62 (ddd, 1, J = 14.0, 4.2, 2.4), 1.92–2.08 (m, 2), 1.73–1.88 (m, 2), 1.67 (s, 3), 0.93 (d, 3, J = 6.4), 0.85–1.05 (m, 2); ^{13}C NMR 128.1, 125.0, 99.8, 72.9, 49.9, 38.7, 34.9, 28.7, 24.9, 21.7, 13.7; IR (neat) 2960, 1720, 1630, 1460, 1330, 1190, 1100, 1060, 1020 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.27.

(1*R*,8*R*)-1-Hydroxy- and (1*R*,8*R*)-1-Methoxy-4,4,8-trimethyl-2,3-dioxabicyclo[4.3.0]-5(*Z*)-nonene (31a and 31b). A solution of (+)-pulegone (30.4 mg, 0.2 mmol) and RB (1.5 mg, 0.0015 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated with a sun lamp for 4 h as described above. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 2.0 mg (5%) of **31b**. Elution with 8:1 hexane–EtOAc gave 25.8 mg (70%) of **31a** as a colorless oil. Irradiation for 10 h followed by flash chromatography on silica gel (15:1 hexane–EtOAc) gave 72% of **31b**. Irradiation for 14 h with a visible wavelength flood lamp (150 W) gave 80% of **31b** as a colorless oil. Irradiation with a visible wavelength flood lamp with RBL or $CuSO_4$ as the sensitizer gave <3% of **31a** and **31b** and 90% of unreacted **32**.

Data for **31a**: ^{1}H NMR 5.52 (t, 1, J = 3.5), 3.06 (br s, 1, OH), 2.36 (ddd, 1, J = 18.5, 5.8, 3.5), 2.15 (m, 1), 2.03 (dd, 1, J = 12.4, 3.2), 1.68 (ddd, 1, J = 18.5, 10.2, 3.5), 1.46 (s, 3), 1.38 (s, 3), 1.24 (dd, 1, J = 12.4, 12.4), 1.08 (d, 3, J = 6.7); ^{13}C NMR 149.9, 119.7, 102.4, 82.3, 38.6, 33.7, 28.3, 25.8, 25.7, 21.3; IR (neat) 3450, 2960, 1750, 1670, 1460, 1380, 1360, 1270, 1200, 1175, 1110, 1045, 1020, 980 cm^{-1}. The data are identical to those previously described.[25]

Data for **31b**: ^{1}H NMR 5.52 (t, 1, J = 3.5), 3.33 (s, 3), 2.36 (ddd, 1, J = 18.5, 6.0, 3.5), 2.19 (dd, 1, J = 12.7, 3.2), 1.99 (m, 1), 1.66 (ddd, 1, J = 18.5, 10.2, 3.5), 1.44 (s, 3), 1.37 (s, 3), 1.07 (d, 3, J = 6.7), 1.03 (dd, 1, J = 12.7, 12.7); ^{13}C NMR 150.3, 119.4, 104.5, 82.1, 48.8, 33.7, 33.5, 28.4, 25.4, 25.1, 21.4; IR (neat) 2960, 1735, 1720, 1685, 1460, 1380, 1360, 1285, 1200, 1165, 1105, 1060, 1005, 965 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.44; H, 9.07.

3,5-Dimethyl-3,6-dihydro-1,2-dioxin-3-ol (41) and 3-Methoxy-3,5-dimethyl-3,6-dihydro-1,2-dioxine (42). A solution of 4-methyl-3-penten-2-one (**40**) (21.0 mg, 0.21 mmol) and RBL (0.6 mg, 0.0006 mmol) in 25 mL of CH_2Cl_2 was irradiated for 8 h as described above. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 13.7 mg (50%) of **41** as a colorless oil. Irradiation of **40** in 25 mL of 9:1 CH_2Cl_2–MeOH gave a crude product which contained 5% of **41** and 60% of **42**. Flash chromatography on silica gel (pentane) gave 58% of **42**. Irradiation of a solution of **40** (1.50 g, 15.3 mmol) and $CuSO_4$ (15.0 mg) in 25 mL of MeOH for 40 h gave less than 1% of **41** and **42**. Irradiation of a solution of **40** (50 mg) and $CuSO_4$ (5.0 mg) in 25 mL of MeOH gave 10% of **41** and 50% of **42**.

Data for **41**: ^{1}H NMR 5.67 (m, 1), 4.63 (ddd, 1, J = 16.1, 2.1, 1.1), 4.08 (br d, 1, J = 16.1), 3.25 (br s, 1, OH), 1.74 (d, 3, J = 0.7), 1.41 (s, 3); ^{13}C NMR 134.1, 123.0, 96.5, 71.8, 23.2, 17.7. IR (neat) 3500, 3300, 2940, 1775, 1725, 1690, 1630, 1450, 1205, 1130, 905 cm^{-1}. The data are identical to those previously described.[35]

Data for **42**: ^{1}H NMR 5.58 (m, 1), 4.58 (br d, 1, J = 16.1), 4.12 (br d, 1, J = 16.1), 3.38 (s, 3), 1.75 (br s, 3), 1.33 (s, 3); ^{13}C NMR 134.6, 121.5, 99.0, 71.7, 50.5, 20.8, 17.9. IR (neat) 3000, 2950, 1730, 1700, 1625, 1450, 1370, 1325, 1260, 1190, 1125, 1050, 895 cm^{-1}. The data are identical to those previously described.[35]

3-Methyl-3,6-dihydro-1,2-dioxin-3-ol (43). A solution of 3-penten-2-one (20.0 mg, 0.24 mmol) and RBL (0.8 mg, 0.0008 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated for 20 h as described above. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 13.8 mg (56%) of **43**: ^{1}H NMR 6.06 (ddd, 1, J = 10.0, 4.2, 1.4), 5.97 (ddd, 1, J = 10.0, 2.2, 1.5), 4.77 (ddd, 1, J = 16.7, 2.2, 1.4), 4.28 (ddd, 1, J = 16.7, 4.2, 1.5), 3.30 (br s, 1, OH), 1.43 (s, 3); ^{13}C NMR 128.7, 125.7, 96.6, 68.6, 22.8; IR (neat) 3450, 3060, 3000, 1765, 1720, 1630, 1450, 1375, 1210, 1165, 1100, 1035 cm^{-1}. Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.95. Found: C, 51.62; H, 7.04.

3,6,6-Trimethyl-3,6-dihydro-1,2-dioxin-3-ol (45). A solution of 5-methyl-3-hexen-2-one (19.8 mg, 0.18 mmol) and RBL (0.8 mg, 0.0008 mmol) in 25 mL of 19:1 CH_2Cl_2–MeOH was irradiated for 6 h as described above. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 19.6 mg (77%) of **45**: ^{1}H NMR 5.87 (d, 1, J = 10.0), 5.79 (d, 1, J = 10.0), 3.25 (br s, 1, OH), 1.42 (s, 3), 1.40 (s, 3), 1.25 (s, 3); ^{13}C NMR 134.4, 126.9, 95.6, 77.1, 24.5, 23.9, 22.9; IR (neat) 3450, 3050, 2990, 1730, 1650, 1450, 1375, 1360, 1250, 1140 cm^{-1}. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.27; H, 8.38.

(3*R,6*R**)- and (3*R**,6*S**)-6-Ethyl-3,6-dihydro-1,2-dioxin-3-ol (46a and 46b).** A suspension of *trans*-2-hexenal (36.0 mg, 0.36 mmol) and $CuSO_4$ (3.2 mg, 0.02 mmol) in 25 mL of 9:1 CH_2Cl_2–MeOH was irradiated for 24 h as described above. The mixture was washed with 5 mL of water and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 24.0 mg (52%) of a 3:2 mixture of peroxy hemiketals **46a** and **46b**. A 30% yield of **46a** and **46b** was obtained when RBL was used instead of $CuSO_4$: IR (neat) 3500, 3050, 2970, 1730, 1660, 1460, 1250, 1020 cm^{-1}. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.16; H, 7.63.

Data for **46a** were determined from the mixture: ^{1}H NMR 6.08 (ddd, 1, J = 10.1, 1.1, 1.1), 5.99 (ddd, 1, J = 10.1, 3.4, 2.1), 5.35 (ddd, 1, J = 3.4, 1.2, 1.1), 4.65 (m, 1), 1.60 (dq, 2, J = 7.2, 7.2), 1.01 (t, 3, J = 7.2); ^{13}C NMR 132.2, 124.4, 91.9, 78.5, 24.9, 9.2.

Data for **46b** were determined from the mixture: ^{1}H NMR 6.17 (ddd, 1, J = 10.1, 4.2, 1.1), 5.96 (ddd, 1, J = 10.1, 3.6, 1.7), 5.35 (ddd, 1, J = 3.6, 1.1, 0.9), 4.15 (m, 1), 1.83 (ddq, 1, J = 14.8, 7.4, 5.4), 1.68 (ddq, 1, J = 14.8, 7.4, 4.9), 1.05 (t, 3, J = 7.4); ^{13}C NMR 131.4, 123.5, 91.6, 79.7, 25.1, 10.4.

(5*R)-2-Acetyl-5-methylcyclohexanone (49).** A solution of hemiketal **33a** (35.0 mg, 0.19 mmol) and 12 M HCl (0.3 mL) in 2 mL of MeOH was stirred at room temperature for 4 h. The mixture was treated with water (2 mL) and extracted with hexane (3 × 6 mL). The combined hexane layers were dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (32:1 hexane–EtOAc) gave 27.3 mg (93%) of **49** as a colorless oil and 2.8 mg (6%) of **48b**. Use of $TsOH·H_2O$ (2.0 mg) instead of HCl gave 40% of **49** and 60% of **33b**. Dione **49** exists predominantly in the enol form.[48]

Data for **49**: ^{1}H NMR 2.25–2.44 (m, 3), 2.13 (s, 3), 1.72–2.10 (m, 3), 1.18–1.32 (m, 1), 1.01 (d, 3, J = 6.4); ^{13}C NMR 198.9, 181.6, 106.5, 39.2, 30.9, 28.0, 25.1, 23.8, 21.2; IR (neat) 2960, 1710, 1610, 1420, 1240, 950 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.03.

(*E*)-(5*R)-5-Methyl-2-(1-chloroethylidene)cyclohexanone (48b).** A solution of hemiketal **33a** (20.0 mg, 0.11 mmol) and 12 N HCl (2 mL) in 4 mL of ether was stirred at room temperature for 1.5 h. The mixture was extracted with hexane (3 × 6 mL). The combined hexane layers were dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (hexane) gave 16.8 mg (91%) of **48b**: ^{1}H NMR 2.96–3.04 (m, 1), 2.54 (dd, 1, J = 11.4, 2.2), 2.40 (s, 3), 2.32–2.48 (m, 1), 1.75–2.10 (m, 3), 1.30–1.42 (m, 1), 1.02 (d, 3, J = 6.2); ^{13}C NMR 201.2, 142.2, 133.2, 50.5, 32.0, 31.3, 30.1, 25.1, 21.5; IR (neat) 2960, 1690, 1600, 1440, 1270, 1210, 1080, 1005 cm^{-1}. Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.58; Cl, 20.53. Found: C, 62.74; H, 7.68; Cl, 20.65.

***trans*-1-Chloro-1-tetradecen-3-one.** A solution of peroxy hemiketal **15a** (3.0 mg) and 1.5 M HCl solution (1 mL) in 4 mL of 2:1 THF–H_2O was stirred at rt for 60 h. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (10:1 hexane–EtOAc) gave 2.1 mg (91%) of *trans*-1-chloro-1-tetradecen-3-one: ^{1}H NMR 7.29 (d, 1, J = 14.0), 6.53 (d, 1, J = 14.0), 2.52 (t, 2, J = 7.0), 1.62 (m, 2), 1.16–1.40 (m, 18), 0.88 (t, 3, J = 6.7). The data are identical to those previously reported.[49]

Menthofuran (50). A suspension of peroxy hemiketal **33a** (25.0 mg, 0.14 mmol) and zinc (26.2 mg, 0.4 mmol) in 2 mL of acetic acid was stirred at 40 °C for 2 min. The mixture was treated with 2 mL of H_2O and extracted with hexane (4 × 3 mL). The combined hexane layers were dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (pentane) gave 18.4 mg (90%) of **50** as a colorless oil: ^{1}H NMR 7.03 (br s, 1), 2.64 (dd, 1, J = 16.1, 5.2), 2.23–2.43 (m, 2), 2.15 (dd, 1, J = 16.1, 9.4), 1.92 (d, 3, J = 1.2), 1.76–2.00 (m, 2), 1.35 (m, 1), 1.07 (d, 3, J = 6.6); ^{13}C NMR 150.6, 136.7, 119.6, 117.4, 31.4, 31.3, 29.6, 21.5, 19.8, 8.1; IR (neat) 2940, 1650, 1560, 1460, 1420, 1260, 1170, 1100 cm^{-1}. The data are identical to those previously reported.[38]

3-Methyl-5-*n*-butylpyridazine (52). Oxygen was bubbled into a solution of hemiketals **29a** and **30a** (35 mg, 0.2 mmol), $CuSO_4$ (1.0 mg, 0.006 mmol), hydrazine (100 mg, 3.1 mmol), and acetic acid (200 mg, 3.1 mmol) in 15 mL of MeOH at room temperature for 10 h. The mixture was treated with water (10 mL) and extracted with hexane (3 × 15 mL). The combined hexane layers were dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (6:1 hexane–EtOAc) gave 18.8 mg (65%) of **52** as a colorless oil.

(48) Descotes, G.; Querou, Y. *Bull. Soc. Chim. Fr.* **1968**, 3395.
(49) Kaufmann, H. P.; Stamm, W. *Fette, Seifen, Anstrichmittel* **1957**, *59*, 946; *Chem. Abstr.* **1960**, *54*, 1288h.

A solution of hemiketals **29a** and **29b** (60.0 mg, 0.34 mmol), hydrazine (14.0 mg, 0.44 mmol), and acetic acid (14.0 mg, 0.22 mmol) in 10 mL of MeOH was stirred at room temperature for 48 h. The mixture was treated with water (10 mL) and extracted with ether (3 × 20 mL). The ether solution was dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 20.9 mg (72%) of 3-methylpyrazole (**54**) and 10.3 mg (19%) of **52**.

Data for **52**: ^{1}H NMR 7.23 (d, 1, J = 8.6), 7.20 (d, 1, J = 8.6), 2.94 (t, 2, J = 7.8), 2.67 (s, 3), 1.68–1.79 (m, 2), 1.40 (tq, 2, J = 7.4, 7.3), 0.95 (t, 3, J = 7.3); ^{13}C NMR 161.5, 157.7, 126.8, 126.2, 35.6, 31.8, 22.3, 22.0, 13.8; IR (neat) 2960, 1590, 1505, 1440, 1380 cm^{-1}; MS m/z 150 (M^+, 6.3), 108 (100). The data are similar to those of other 3,6-dialkylpyridazines.[42]

Data for **54**: ^{1}H NMR 7.49 (d, 1, J = 1.2), 6.09 (d, 1, J = 1.2), 2.34 (s, 3); IR (neat) 3250, 1580, 1450, 1100, 1045, 930 cm^{-1}. The ^{1}H NMR data are identical to those previously described.[50]

3- and/or 4-Methoxy-2,5-nonanedione (55), 4-Hydroxy-4-methyl-5-*n*-propyl-2-cyclopentenone (56), and 4-Hydroxy-4-*n*-butyl-2-cyclopentenone (57). A solution of hemiketals **29a** and **30a** (80.0 mg, 0.45 mmol) and Et_3N (300 mg, 3.0 mmol) in 15 mL of MeOH was stirred at room temperature for 48 h. The mixture was treated with water (20 mL) and extracted with ether (3 × 20 mL). The combined ether layers were dried with Na_2SO_4. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 40.8 mg (47%) of **55** as a colorless oil followed by 18.4 mg (23%) of a 5:1 mixture of **56** and **57**.

Data for **55**: ^{1}H NMR 4.32 (dd, 1, J = 5.7, 1.1), 3.39 (s, 3), 2.62 (dd, 1, J = 18.2, 5.7), 2.29 (dd, 1, J = 18.2, 1.1), 2.17 (t, 2, J = 7.5), 2.06 (s, 3), 1.30–1.50 (m, 4), 0.89 (t, 3, J = 7.4).

(50) Pouchert, C. J. *The Aldrich Library of NMR Spectra Edition II*; Aldrich: Milwaukee, WI, 1983; Vol. 2, p 480-D.

Data for **56** were determined from the mixture: ^{1}H NMR 7.40 (d, 1, J = 5.8), 6.09 (d, 1, J = 5.8), 2.37 (dd, 1, J = 8.6, 5.4), 1.30–1.82 (m, 4), 1.37 (s, 3), 0.99 (t, 3, J = 7.2); ^{13}C NMR 200.6, 165.5, 131.4, 79.5, 58.8, 27.4, 24.1, 21.5, 14.2.

Data for **57** were determined from the mixture: ^{1}H NMR 7.42 (d, 1, J = 5.8), 6.13 (d, 1, J = 5.8), 2.57 (d, 1, J = 17.9), 2.45 (d, 1, J = 17.9), 1.30–1.83 (m, 6), 0.92 (t, 3, J = 7.2).

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Registry No. (±)-**1a**, 130296-76-3; (±)-**1b**, 138380-85-5; (±)-**2a**, 130296-77-4; (±)-**2b**, 138380-86-6; (3*E*,5*E*)-**3a**, 138286-30-3; (3*E*,5*Z*)-**3a**, 138286-31-4; (3*Z*,5*E*)-**3a**, 138286-57-4; (3*Z*,5*Z*)-**3a**, 138286-58-5; **4a**, 130296-70-7; **4b**, 138286-29-0; **5a**, 130296-69-4; **5b**, 138286-28-9; (±)-**6a**, 138286-26-7; (±)-**6b**, 138286-27-8; **7a**, 5284-29-7; **7b**, 25401-86-9; **8**, 824-91-9; **9a**, 130296-78-5; **9b**, 138286-25-6; (±)-**12a**, 130296-80-9; (±)-**13a**, 130296-72-9; **14a**, 138286-32-5; (±)-**15a**, 130296-74-1; (±)-**15b**, 138286-33-6; (±)-**16a**, 130296-75-2; (±)-**16b**, 138286-34-7; **19a**, 138286-35-8; **19b**, 138286-37-0; (±)-**20**, 138286-38-1; (±)-**21a**, 138286-39-2; (±)-**21b**, 138286-40-5; **22**, 18402-83-0; (*E*)-**25**, 59637-34-2; (*Z*)-**25**, 138286-47-2; (±)-**26**, 138286-46-1; (±)-**27**, 138286-42-7; (±)-**29a**, 138286-41-6; (±)-**29b**, 138286-44-9; (±)-**30a**, 138286-43-8; (±)-**30b**, 138286-45-0; **31a**, 138380-87-7; **31b**, 138286-50-7; (+)-**32**, 89-82-7; **33a**, 138286-48-3; **33b**, 138286-49-4; **40**, 141-79-7; **41**, 60026-75-7; **42**, 60026-74-6; **43**, 138286-51-8; **45**, 138286-52-9; (±)-**46a**, 138286-53-0; (±)-**46b**, 138286-54-1; (±)-**48b**, 138286-55-2; **49**, 14698-76-1; **50**, 17957-94-7; **52**, 23990-19-4; **54**, 88054-14-2; **55**, 138286-56-3; **56**, 79547-21-0; **57**, 104248-54-6; 1-bromododecane, 143-15-7; *n*-hexadecyl bromide, 1127-15-7; 6-oxo-4-hydroxyoctadecanoic acid, 138286-36-9; 3-penten-2-one, 625-33-2; 5-methyl-3-hexen-2-one, 5166-53-0; *trans*-2-hexenal, 6728-26-3; *trans*-1-chloro-1-tetradecen-3-one, 80037-06-5.

Enantiomerically Pure Dihydropyrimidinones as Reagents and Auxiliaries for Asymmetric Synthesis

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Abstract: We report herein full experimental details of the synthesis, structure, and reactivity of (*R*)- and (*S*)-2-*tert*-butyl-1-carbomethoxy-2,3-dihydropyrimidin-4(1*H*)-one (**1**). The synthesis employs asparagine as the starting material and provides **1** in 55% yield without the need for chromatographic purification. The structure of **1**, as determined by X-ray crystallographic analysis, demonstrates significant pyramidalization at the C4 (carbonyl) and N1 centers, with little evidence of conjugation of N1 with the α,β-unsaturated (vinylogous urea) system. In contrast, compound **11** [2-*tert*-butyl-3-((*S*)-*O*-methylmandeloyl)-2,3-dihydropyrimidin-4(1*H*)-one] shows strong coupling of N1 to the α,β-unsaturated system, as evidenced by changes in bond lengths and torsional angles. Compound **1** has proven useful as a *reagent* for the synthesis of enantiomerically pure β-aryl-β-amino acids. The key step in this protocol is the palladium-catalyzed conjugate addition of aryl iodides to **1**. Evidence is presented to support a mechanism for this reaction that involves an unprecedented transannular hydride transfer into the palladium coordination sphere. In additional experiments, **1** has been employed as an *auxiliary* for the synthesis of enantiomerically pure α-substituted carboxylic acids. The crystalline properties of **1** and many of its derivatives allow for simplified purification procedures to be utilized.

In two recent papers,[4,5] we disclosed preliminary results concerning the synthesis and reactivity of (*R*)- and (*S*)-2-*tert*-butyl-1-carbomethoxy-2,3-dihydropyrimidin-4(1*H*)-one (**1**). Herein we report, in full detail, our work on this compound and its derivatives.

Synthesis

As part of our total synthesis of the marine depsipeptide (+)-jasplakinolide (**2**),[6] we sought a new route to the requisite

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(4) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355–7.

(5) Negrete, G. R.; Konopelski, J. P. *Tetrahedron: Asymmetry* **1991**, *2*, 105–8.

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