Tetrahedron Vol. 42, No 11, pp. 2945 to 2950, 1986
Printed in Great Britain.

0040–4020/86 $3.00 + .00
Pergamon Journals Ltd.

IRON/COPPER PROMOTED FRAGMENTATION REACTIONS OF α-ALKOXY HYDROPEROXIDES

REGIO- AND STEREOCONTROLLED FORMATION OF OLEFIN-CONTAINING MACROLIDES

STUART L. SCHREIBER,* BERNARD HULIN and WAI-FONG LIEW
Sterling Chemistry Laboratory, Yale University, Department of Chemistry, New Haven, CT 06511, U.S.A.

(*Received in U.S.A.* 5 *June* 1985)

Abstract—Several new examples of iron/copper mediated fragmentation reactions of hydroperoxides are reported. The regio- and stereochemistry of olefin formation is in accord with a model that takes into account the preferred conformations of the radical intermediate and potential olefin products. In combination with group selective peroxyketalization reactions, several stereocontrolled syntheses of olefin containing macrolides have been achieved.

The homolytic cleavage of the peroxide bond mediated by ferrous ions provides an efficient means for the production of an alkoxy radical.[1] The effect of this substituent on the dissociation energy of a neighboring carbon–carbon bond is dramatic. As part of their studies on the bond-weakening properties of an oxido substituent, Evans and Baillargeon compiled the data listed in Table 1.[2] The anionic oxido group lowers the bond dissociation energy of an adjacent carbon–carbon bond by *ca* 13–17 kcal mol^{-1}, an effect that has been demonstrated to have relevance to a variety of reaction processes.[3] The alkoxy radical results in a more substantial bond weakening (*ca* 70 kcal mol^{-1}); indeed, the homolytic cleavage to produce an allyl radical is expected to be near thermoneutral.

Accordingly, the ferrous ion promoted fragmentation reaction of hydroperoxides results in the formation of carbon radicals via concomitant oxygen–oxygen and carbon–carbon bond cleavage. The generation of the carbon radical by this procedure,[4] as well as others,[5] in the presence of cupric acetate gives rise to olefin-containing products by the net removal of a beta-hydrogen atom. We have been interested in the application of these methods to regio- and stereocontrolled formation of olefin-containing macrolides, and wish to report several new examples of this reaction process that have implications for stereocontrolled organic synthesis.[6]

Recently, we described several spiroketalization reactions that proceed with group selectivity at prostereogenic carbon centers equipped with diastereotopic hydroxymethyl groups.[7] These reactions provide added flexibility to synthetic operations, since either of two possible stereoisomers can be obtained after the hydroxymethyl groups have been differentiated.[7d] Expression of the diastereotopic group selectivity via the spiroketalization reaction provides a method for remote internal asymmetric induction, and applications to the synthesis of both spiroketal[7a–c] and non-spiroketal products[7d] have followed. In order to extend this method, we have developed several peroxyketalization reactions that proceed with group selectivity at prostereogenic carbon centers. In combination with the iron/copper promoted fragmentation reaction, a new method for stereocontrolled macrolide synthesis has been developed.

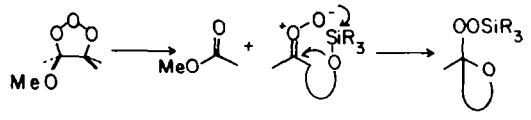
Table 1. Bond dissociation energies (kcal mol^{-1})

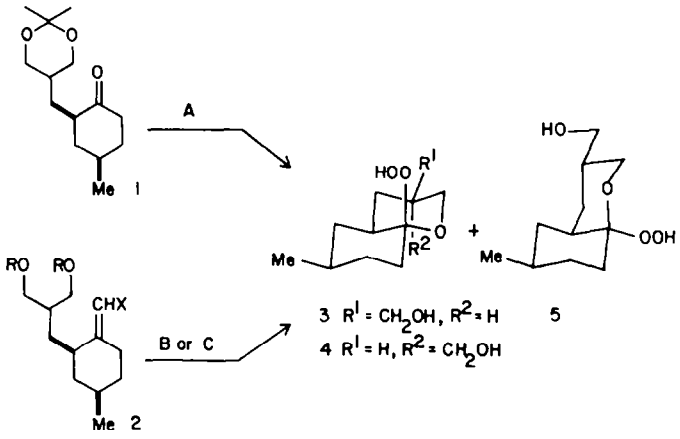
$$X{-}CH_2{-}R \rightarrow X{-}CH_2^{\cdot} + R^{\cdot}$$

R	X = OH	X = O$^-$	X = O$^{\cdot}$
H	93	76	22
CH_3	83	68	13
$CH_2CH{=}CH_2$	71	58	−1

The preparation of cyclononenolide **6** began with the alkylation of 4-methylcyclohexanone with 2,2-dimethyl-5-trifluoromethanesulfonyloxymethyl-1,3-dioxane. Thermodynamic equilibration of the disubstituted cyclohexanone **1** (NaOMe, MeOH) was best carried out at 0° (*cis*/*trans* = 20:1 at 0°, 12:1 at 25°). The direct acid-catalyzed peroxyketalization (Scheme 1) resulted in the formation of three peroxyketals in an 8:1:1 ratio. Since these conditions result in modest group selectivity, and are complicated by the formation of *cis*- and *trans*-fused oxadecalin products, other conditions were examined. In particular, we sought to preclude internal hydrogen bonding, a development that would be expected to favor isomer **3** at the expense of isomer **4**.

The intramolecular 1,3-addition of alcohols to carbonyl oxides represents an alternative method for the preparation of α-alkoxy hydroperoxides and was expected to proceed without equilibration of initially formed products (kinetic control). Accordingly, the methylene cyclohexane derivative **2** (R = X = H) was prepared from **1** and ozonolyzed in acetone to provide, somewhat surprisingly, only *trans*-fused oxadecalin peroxyketals. However, the ratio of **3** and **4** was diminished (**3**/**4** = 4:1).[8] To prevent internal hydrogen bonding of the hydroxymethyl group, a stabilizing property that was available to isomer **4**, the silicon version of the 1,3-addition reaction was examined (Eq. 1). To this end, vinyl ether **2** (R = TMS, X = OMe) was





	Conditions	3/4/5	Yield (%)
A.	1 N HCl, THF, then TFA, H_2O_2/ether, 1 h, −78°	8:1:1	85
B.	O_3, acetone, Na_2CO_3 (R = H, X = H)	4:1:0	85
C.	O_3, CH_2Cl_2, Na_2CO_3 (R = TMS, X = OMe)	20:1:0	40

Scheme 1.

prepared as a 20:1 mixture of olefin isomers (stereochemistry undetermined) via the lithium salt free Wittig olefination (KHMDS, $Ph_3P^+CH_2OMe\ Br^-$) of the bis-silyl ether derivative of **1**. The choice of the vinyl ether as a carbonyl oxide precursor was based on two considerations. The methoxyl substituent is known to direct breakdown of the primary ozonide formed upon oxidation with ozone to provide an ester and the carbonyl oxide at the beta carbon of the vinyl ether.[9] Furthermore, the ester was expected to serve as a poor dipolarophile towards the carbonyl oxide, a reaction process that could compete with internal 1,3-addition of the alcohol.[10]

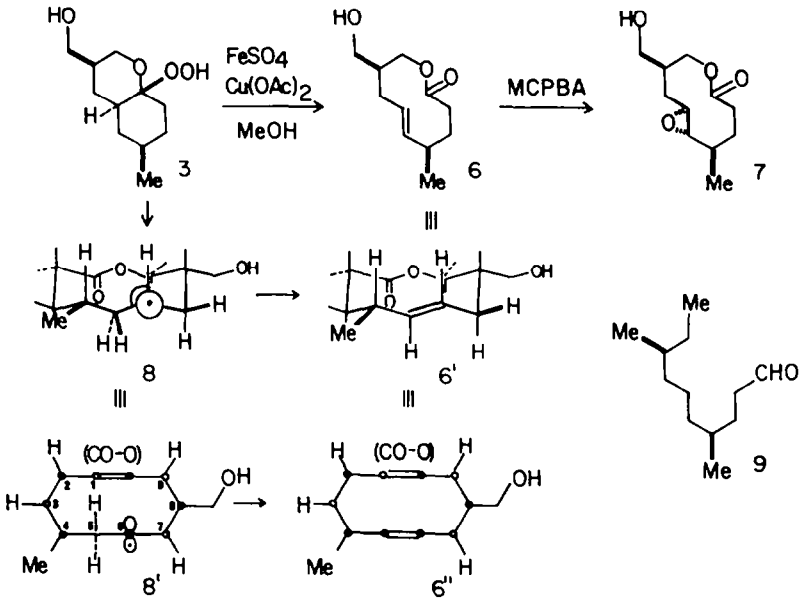
Ozonolysis (O_3, CH_2Cl_2, Na_2CO_3, −78°) of **2** (R = $SiMe_3$, X = OMe) resulted in peroxyketalization with high stereocontrol (**3**/**4** = 20:1), and concomitant desilylation (room temperature, CH_2Cl_2, Na_2CO_3) but in diminished yield (40%). Attempts to effect this reaction on the methylene-cyclohexane (**2**, R = TMS, X = H) resulted in a 25% yield of **3** along with a 50% yield of the "normal" 1,2,4-trioxolane (ozonide) product.[10]

Treatment of the hydroperoxide **3**, obtained from the ozonolysis of the bis-silyl ether **2** (R = TMS, X = OMe), with ferrous sulfate and cupric acetate in methanol provided a single *trans*-$\Delta^{5,6}$-cyclononenolide **6** in 76% yield (Scheme 2). The regio- and stereochemistry of the olefin could be assigned through a combination of 490 MHz 1D and COSY 2D NMR experiments. These experiments also provided evidence that the macrolide adopts the chair–chair–chair (CCC) conformation **6'**, as expected on the basis of the torsional constraints imposed on the ring system by the olefin and ester moieties,[11] and as suggested by molecular modelling.

The significance of the stereocontrolled olefin formation is underscored by the epoxidation of **6** to provide a single epoxide **7** in 90% yield. The stereochemical outcome of this reaction is in accord with the Vedejs model of local conformer control,[12,13] and is presumed to result from peripheral attack[14] of the peracid on the CCC conformation **6'** of the macrolide. In addition, the capability of converting differentiated alkoxymethyl groups, such as those present in **6**, into alkyl groups with stereochemical flexibility[7d] suggests applications to problems associated with 1,5-stereocontrol. The structure of the aggregation pheromone of the red flour beetle, *syn*-dimethyldecanal **9**,[15] is representative of compounds with this stereochemical feature.

Consideration of this reaction and others that we have described[6b,d] leads us to propose a conformational model that can be used to predict the regio- and stereochemical outcome of olefin formation. Ferrous ion promoted homolytic cleavage of the peroxide bond in **6** gives rise to the alkoxy radical that fragments to provide the carbon radical **8**. The macrolide radical is expected to exist largely in the CCC conformation **8** (**8'**) which can accommodate a planar *Z*-ester. Removal of a beta hydrogen by the d^9 radicaloid copper acetate reagent could proceed to give four possible olefin isomers. Elimination could take place through direct hydrogen atom abstraction or through prior carbon–copper bond formation[4] and subsequent beta-hydrogen elimination. Although hydrogen atom loss is suggested to occur via the CCC conformation **8**(**8'**), subsequent arguments are equally valid with related boat–chair–chair (BCC) or BCB conformers (*Z*-ester located along the starboard).

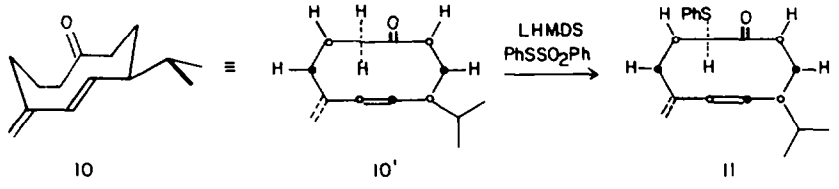
Loss of hydrogen from C_5 of **8'** removes an eclipsed ethane and a transannular hydrogen interaction and is expected to be favored over elimination at the corner carbon, C_7. Formation of the *trans*-$\Delta^{5,6}$ olefin results from elimination along the C_4–C_7 local conformer that contains a C_4–C_5–C_6–C_7 dihedral angle of 180°, whereas the *trans*-$\Delta^{6,7}$ olefin results from elimination



Scheme 2.

along the C_5–C_8 local conformer that contains a C_5–C_6–C_7–C_8 dihedral angle of 120°. In the transition state for the latter possibility major conformational reorganization must occur with a concomitant increase in strain throughout the molecule, in order to avoid the formation of a twisted olefin (see **8'**). There is evidence that the preference for 1,6- over 1,5-cyclodecadienes (note relationship to *trans*-$\Delta^{5,6}$- and *trans*-$\Delta^{6,7}$-cyclononenolides) can also be manifested in other reaction processes. For example, a pivotal observation in studies that resulted in a synthesis of periplanone-B is expressed in Eq. (2). Enolization of the ten-membered ring ketone **10** with lithium hexamethyldisilazide resulted in a 16:1 mixture of 1,6- and 1,5-cyclodecadiene enolates, as reflected by the ratio of sulfenylated products.[16] The BCC solution conformation depicted for **10** is in accord with the results of COSY 2D NMR and NOE difference experiments.[17]

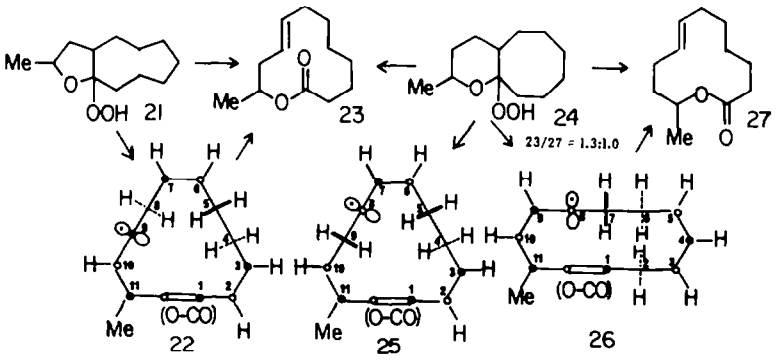
The conformational analysis discussed in the copper acetate provided the lactone **23** (recifeiolide) with near complete regio- and stereocontrol.[6b] The intermediate macrolide radical is expected to adopt the crown-like conformation **22** with the more stable *Z*-ester configuration (Scheme 3). Hydrogen atom abstraction to provide the observed *trans*-homoallylic alkanoate **23** is again expected to be favored along the zig-zag portion of the paraffin chain. As in the previous example (**3** → **6**), abstraction of hydrogen from a corner carbon should be disfavored. The situation is somewhat more complex with the peroxyketal **24**.† Treatment of **24** with conditions identical to those employed in the fragmentation of **21** produced a 1.3:1 ratio of two *trans*-olefins, recifeiolide **23** and the positional isomer **27**, respectively. The location and geometry of the olefin present in **27** could be determined by 490 MHz 1D and 2D (COSY) NMR experiments. The C_8 macrolide radical derived from **24** can react with cupric acetate from the crown-like conformation



reaction resulting in the formation of *trans*-$\Delta^{5,6}$-cyclononenolide **6** can be extended to other systems. For example, several years ago we reported that treatment of peroxide **21** with ferrous sulfate and **25** to produce **23** selectively. Unlike the radical that resulted from fragmentation of **21**, the radical derived from **24** can assume a second low-energy conformation **26** that favors the formation of a positonal isomer of **23**. The reaction of **26** with cupric acetate is expected to provide the isomeric macrolide **27**. In each instance (**25** → **23**, **26** → **27**) the abstraction of hydrogen from a corner carbon (C_7 in **25** and C_9 in **26**) is expected to be disfavored.

Conformation **26** of the C_8 radical is free of torsional strain about each sp^2–sp^3 and sp^3–sp^3 bond (neglecting the carbon radical), whereas **25** contains three eclipsed

† Prepared by the reaction sequence: (a) N,N-dimethylhydrazone of cyclooctanone, LDA, 1-bromo-3-tetrahydropyranyloxybutane; THF, 0°; (b) 6 N HCl, HOAc, room temperature, 3 h; (c) 30% H_2O_2, HOAc, room temperature, 5 min.



Scheme 3.

ethane fragments as well as the bisected propionate conformation.[11a] This is compensated for by the increased van der Waals strain in **26** (e.g. five *gauche* butane-like interactions vs two in **25**). Computational modelling (MM2) of the macrolide radicals was hindered by the unavailability of accurate parameters for carbon radicals, therefore calculations were performed on the unsaturated macrolide products.† The lowest energy conformations of the three possible *E*-olefin-*Z*-ester macrolide products from **21** and **24** that we could obtain are illustrated in Fig. 1. If the factors involved in determining the strain energies of the olefin products are present in the transition states for their formation, the values illustrated may have relevance to the product distribution from **21** and **24**. Whereas the low-energy conformations for the two products obtained from **24** contain a similar enthalpy, the allylic alkanoate **28** that was not observed in the fragmentation of **21** is seen to be more strained than **23**, albeit by only 1.3 kcal mol^{-1}.

For reactions that involve secondary macrolide radicals, this kind of analysis could be useful for making decisions concerning the .choice of alternative peroxyketal precursors to macrolides (e.g. **21** vs **24** for recifeiolide synthesis). Given the constraint that only (radical containing) local conformers with dihedral angles close to 180° (→*trans*) or 0° (→*cis*) will result in olefin formation, a protocol for assessing the fate of macrolide radicals in their reactions with cupric acetate can be followed. The low-energy molecular conformations that give rise to each olefin isomer should be constructed and their energies compared. The distribution of olefin products should be reflected by the difference in total strain energy of the olefin products and of the conformations of their corresponding radical precursors.[14]

In addition to the role of conformation, other influences on olefin selectivity are being considered. In previous work, the possibility of chelated organocopper(III) intermediates in these reactions was discussed.[4,6] We are presently designing experiments that serve to delineate the relative contributions of these and other factors that may influence the selectivity in olefin formation.

† Conformational analyses were performed with Professor W. Clark Still's molecular mechanics program MODEL.

In conclusion, the ferrous ion promoted fragmentation of certain α-alkoxy hydroperoxides provides an efficient means of producing macrolide radicals. The interception of these radicals with cupric acetate can result in the formation of olefin products with regio- and stereocontrol and often in a predictable manner. In combination with stereocontrolled methods for peroxyketal formation, this reaction process can provide access to valuable macrolide products.

EXPERIMENTAL

IR spectra were recorded on a Nicolet 5 SX FT-IR spectrometer (ν_{max} in cm^{-1}). Bands are characterized as strong (s), medium (m) and weak (w). ^{1}H-NMR were recorded on Bruker WM-250 (250 MHz), WM-500 (500 MHz) or 490 MHz NMR instruments, and are reported in ppm using $CDCl_3$ as standard on a δ-scale. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants (Hz) and integration. ^{13}C-NMR were recorded on a Bruker WM-250 (62.9 MHz) and are reported in ppm using $CDCl_3$ as standard on a δ-scale. A Hewlett–Packard 5985-GC/MS system equipped with a 2% OV-101 column (3 ft × ¼ × 2 mm) on Chromosorb WHP 100/120 was used to obtain mass spectra. Diastereomer ratios were determined by (a) weight measurements of isolated materials, (b) NMR integration, or (c) integration of HPLC traces (assuming equal response factors for diastereomers), or a combination of these methods.

All reactions were carried out under N_2 and were monitored by analytical TLC using E. Merck silica gel 60F-24 glass plates (0.25 mm). Flash chromatography was carried out using E. Merck silica gel 60 (230–400 mesh). O_3 was produced by a Welsbach Corporation Ozonator, style T-709, with the voltage set at 100 V and oxygen pressure at 7 psi to give approximately 2% O_3 concentration. All distillations were performed under N_2. Iron(II) sulfate was recrystallized from an EtOH–H_2O bilayer, washed with Et_2O and dried under high vacuum overnight.

Acid-catalyzed peroxyketalization of cis-2-[5-(2,2-*dimethyl*-1,3-*dioxanyl*)]*methyl*-4-*methylcyclohexan*-1-*one*, **1**

The diol function of **1** was deprotected by a standard procedure using 1 N HCl–THF in quantitative yield. The resulting tricyclic ketal (15 mg, 0.082 mmol) was dissolved in dry Et_2O soln of H_2O_2[18] (2 ml) at −78° and treated with trifluoroacetic acid (2 ml) for 1 h. The reaction was quenched with Et_3N (3 ml), diluted with Et_2O (5 ml) and warmed to room temp. The soln was washed with 5% $NaHCO_3$ aq (5 ml), H_2O (5 ml) and brine (5 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (hexanes–EtOAc, 1:1) provided the mixture of hydroperoxides. HPLC (5 μm Porasil,

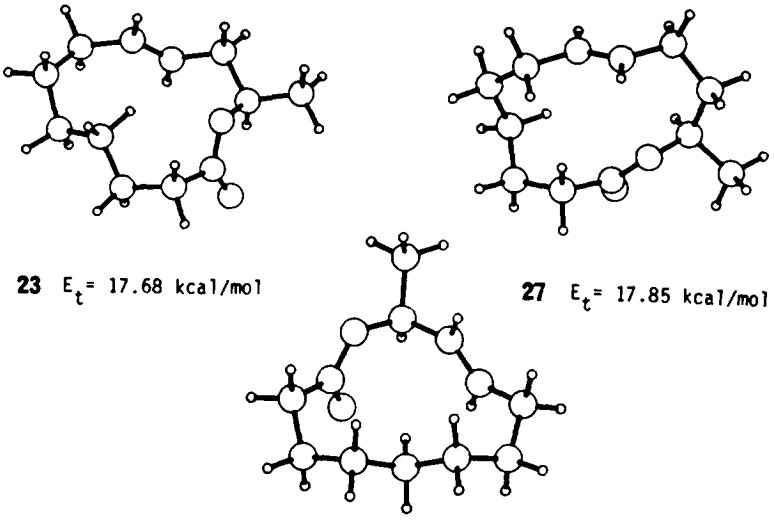


Fig. 1.

1:1 hexanes–EtOAc) allowed the isolation of **5** (1.5 mg, 8%) and an approximately 8:1 mixture of **3** and **4** (13 mg, 73%).

Compound **5**. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.90 (d, J = 5.7 Hz, 3H), 0.90–1.80 (m, 9H), 2.14 (m, 1H), 2.29 (m, 1H), 3.37–3.50 (m, 2H), 3.61 (dd, J = 11.4 Hz, 1H), 3.88 (ddd, J = 11.0, 5.0, 1.7 Hz, 1H), 7.31 (br, 1H). IR ($CHCl_3$) 3300 (br), 2922 (s), 2908 (s), 1598 (w), 1337 (w), 1081 (m) cm^{-1}. MS (EI, 20 eV) *m/z* 182 ($M^+ - H_2O_2$, 5) 137(39), 112(38), 109(22), 101(30), 97(22), 95(23), 85(26), 83(100), 82(28), 69(37), 68(23), 67(25), 56(24), 55(59).

Compound **3**. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.903 (d, J = 6.5 Hz, 3H), 1.100 (ddd, J = 12.6 Hz, 1H), 1.248 (ddd, J = 12.6 Hz, 1H), 1.22–1.30 (m, 2H), 1.30–1.40 (m, 2H), 1.527 (m, 1H), 1.737 (dddd, J = 13.0, 13.0, 4.0, 4.0 Hz, 1H), 1.985 (m, 1H), 2.265 (m, 1H), 3.449 (dd, J = 10.7, 5.4 Hz, 1H), 3.509 (dd, J = 10.7, 5.4 Hz, 1H), 3.623 (dd, J = 11.4 Hz, 1H), 3.845 (ddd, J = 11.0, 4.9, 1.6 Hz, 1H), 7.46 (br, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 21.81, 27.74, 31.21, 31.73, 32.49, 37.83, 38.97, 42.60, 64.02, 64.62, 103.21. IR (neat) 3365 (br s), 2943 (s), 2863 (s), 1585 (w), 1450 (s), 1374 (m), 1251 (m), 1211 (m), 1140 (m), 1088 (m), 970 (m), 948 (m), 904 (m), 860 (m), 756 (s), 725 (m), 666 (m) cm^{-1}. MS (EI, 20 eV) *m/z* 182 ($M^+ - H_2O_2$, 100) 109(60), 108(100), 59(77), 55(54), 45(57).

Ozonolysis of cis-2-[2,2-*bis*(*hydroxymethyl*)]*ethyl*-4-*methyl*-1-*methylenecyclohexane* **2** (R = H, X = H)

A soln of **2** (50 mg, 0.25 mmol) in Me_2CO (2 ml) was treated with O_3 at −78° then purged with N_2, warmed to room temp and concentrated *in vacuo*. Flash chromatography (1:2 hexanes–EtOAc) afforded a 4:1 mixture of **3** and **4** (40 mg, 85%).

Ozonolysis of cis-2-[2,2-*bis*(*trimethylsilyloxymethyl*)]*ethyl*-4-*methyl*-1-*methoxymethylenecyclohexane* **2** (R = $SiMe_3$, X = OMe)

A soln of **2** (52 mg, 0.14 mmol) in dry CH_2Cl_2 (28 ml) containing Na_2CO_3 (22 mg, 0.21 mmol) was treated with O_3 at −78° than purged with N_2, warmed to room temp and stirred overnight. The soln was filtered and concentrated *in vacuo* and the product was isolated by flash chromatography (1:2 hexanes–EtOAc) followed by HPLC (5 μm Porasil, hexanes–EtOAc to afford a 20:1 mixture of **3** and **4** (12 mg, 40%).

Fragmentation of (6*S*,*R*)-11*S*,*R*-*hydroperoxy*-4*S*,*R*-*hydroxymethyl*-8*R*,*S*-*methyl*-2-*oxabicyclo*[4.4.0]*cyclodecane* **3**

A cupric acetate-staturated soln of the hydroperoxide (10 mg, 0.05 mmol) in MeOH (1 ml) was treated with a ferrous sulfate-saturated MeOH soln (1 ml). After 1 h the soln was diluted with EtOAc, washed with 1% aq HCl, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product **6** was purified by flash chromatography (1:2 hexanes–EtOAc) (7 mg, 76%).

The ^{1}H-NMR assignments and spin connectivities in **6** were determined by 2D homonuclear correlation spectroscopy ($CDCl_3$, 490 MHz, 2K × 512 data set). ^{1}H-NMR ($CDCl_3$, 490 MHz) δ 0.955 (CH_3, d, J = 6.6 Hz), 1.283 (O—H, br t, J = 5.0 Hz), 1.67 (H_{3eq}, m), 1.715 (H_{3ax}, dddd, $^3J_{3ax-4ax}$ = 11.5, $^2J_{3ax-3eq}$ = 11.5, $^3J_{3ax-2ax}$ = 11.5, $^3J_{3ax-2eq}$ = 2 Hz), 1.831 (H_{7ax}, dddd, $^3J_{7ax-6}$ = 11.9, $^2J_{7ax-7eq}$ = 11.9, $^3J_{7ax-8}$ = 11.9, $^4J_{7ax-5}$ = 1.5 Hz), 2.06–2.15 (H_{2ax}, H_4, H_8, m), 2.24–2.31 (H_{2eq}, H_{7eq}, m), 3.467 ($H_{9'}$, m), 3.513 ($H_{9''}$, m), 3.774 (H_{3eq}, ddd, $^2J_{9eq-9ax}$ = 11.2, $^3J_{9eq-8}$ = 2.1, $^4J_{9eq-7eq}$ = 2.1 Hz), 4.866 (H_{9ax}, dd, $^3J_{9ax-8}$ = 11.3, $^2J_{9ax-9eq}$ = 11.3 Hz), 4.993 (H_5, ddd, $^3J_{5-6}$ = 15.2, $^3J_{5-4}$ = 9.9, $^4J_{5-7ax}$ = 1.8 Hz), 5.477 (H_6, ddd, $^3J_{6-5}$ = 15.1, $^3J_{6-7ax}$ = 11.3 Hz, $^3J_{6-7eq}$ = 3.4 Hz). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 20.80, 34.37, 34.46, 35.21, 40.51, 40.98, 64.62, 65.89, 129.84, 134.58, 175.78. IR ($CHCl_3$) 3925 (br), 2957 (m), 2928 (m), 1726 (s), 1457 (w), 1179 (w), 1161 (w), 1108 (w), 977 (w) cm^{-1}. MS (EI, 20 eV) 198 (M^+, 2), 137(30), 101(100), 83(57), 81(30), 55(86). HRMS calc 198.1256; obtained 198.1258.

Fragmentation of 1-*hydroperoxy*-11-*methyl*-12-*oxabicyclo*-[6.4.0]*dodecane* **24**

Copper(II) acetate monohydrate (280 mg, 1.40 mmol) was added to a soln of 1-hydroperoxy-11-methyl-12-oxabicyclo[6.4.0]dodecane (200 mg, 0.93 mmol) in abs MeOH (22 ml). When all of the Cu salt was solvated, iron(II) sulfate heptahydrate (390 mg, 1.40 mmol) was then added. TLC of the mixture and staining with KI–starch soln indicated the immediate consumption of peroxidic material. MeOH was removed *in vacuo*. The remaining suspension was taken up in EtOAc (2 × 50 ml) and washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography followed by HPLC (10 μm Porasil, 100:1 hexanes–EtOAc) provided **23** [2-methyl-oxacyclododeca-4(*E*)-ene-12-one] and the positional isomer **27** [2-methyl-oxacyclododeca-5(*E*)-ene-12-one] in a ratio of 1.3:1 (94% yield).

Compound **23**. ^{1}H-NMR ($CDCl_3$, 490 MHz) δ 1.22 (2H, m), 1.23 (3H, d, J = 6.3 Hz), 1.43 (2H, m), 1.52 (3H, m), 1.78 (1H, m), 1.88 (1H, m), 2.1–2.4 (5H, m), 5.16 (1H, ddq, J = 14.2, 2.9, 6.3 Hz), 5.25 (1H, dddd, J = 15.0, 10.0, 3.3, 1.7 Hz), 5.30 (1H, dddd, J = 15.0, 10.3, 3.1, 1.5 Hz). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ

20.54, 23.43, 24.21, 24.83, 25.01, 30.37, 33.04, 40.96, 68.52, 127.05, 133.51, 173.34. IR (CH_2Cl_2) 2977 (m), 2933 (s), 2855 (m), 1718 (s), 1457 (m), 1363 (m), 978 (m) cm^{-1}. MS (EI, 70 eV) (rel. int.) 196 (M^+, 100). HRMS calc 196.1464; obtained 196.1471.

Compound **23** prepared in this manner is contaminated with *ca* 15% of a second compound, presumed to be *cis*-recifeiolide,[19] which could not be separated by chromatography: 1.25 (d, J = 6.2 Hz).

Compound **27**. ^{1}H-NMR ($CDCl_3$, 490 MHz), δ 1.21 (1H, m), 1.22 (3H, d, J = 6.3 Hz), 1.38 (3H, m), 1.50 (1H, m), 1.78 (3H, m), 2.10 (4H, m), 2.30 (1H, br s), 2.40 (1H, ddd, J = 13.9, 6.0, 3.5 Hz), 4.83 (1H, ddq, J = 9.6, 3.8, 6.3 Hz), 5.15 (1H, ddd, J = 14.9, 7.2, 7.2 Hz), 5.44 (1H, ddd, J = 14.9, 4.6, 4.4 Hz). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 20.27, 20.86, 24.48, 24.87, 29.57, 30.15, 34.88, 35.71, 72.56, 126.86, 133.27, 173.24. IR (CH_2Cl_2) 2975 (m), 2933 (s), 2855 (m), 1717 (s), 1457 (m), 974 (m) cm^{-1}. MS (EI, 70 eV) *m/z* (rel. int.) 196 (M^+, 100). HRMS calc 196.1464; obtained 196.1468.

Acknowledgements—This investigation was supported by the Institute for General Medical Sciences of the National Institutes of Health (GM-30738) to whom we are grateful. We thank the Camille and Henry Dreyfus Foundation, Inc. (Teacher–Scholar Award to S.L.S.), NSF (Presidential Young Investigator Award to S.L.S.), Merck, Inc., Eli Lilly and Co., Pfizer, Inc., The Upjohn Co., American Cyanamid, and Hoffmann–LaRoche, Inc. for additional support. We thank Professor David A. Evans for providing us with additional information relevant to Ref. 2 and for stimulating discussions on this topic. The assistance of Peter C. Demou with the 2D NMR experiments is gratefully acknowledged.

REFERENCES

[1a]G. Sosnovsky and D. J. Rawlinson, *Organic Peroxides* (Edited by D. Swern), Vol. 2, Chap. 2. Wiley–Interscience, New York (1971); [b]J. K. Kochi, *Free Radicals*, Vol. 1, Chap. 11. Wiley–Interscience, New York (1973); [c]R. A. Sheldon, *The Chemistry of Functional Groups, Peroxides* (Edited by S. Patai), Chap. 6. Wiley–Interscience, New York (1983). [d]Other metal ions capable of undergoing one-electron redox processes such as manganese(II) and cobalt(II) are frequently employed.

[2a]D. J. Baillargeon, Ph.D. Thesis, Chap. 2. California Institute of Technology (1979); [b]D. A. Evans and D. J. Baillargeon, *Tetrahedron Lett.* 3315 (1978); [c]D. A. Evans and D. J. Baillargeon, *Ibid.* 3319 (1978).

[3]D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.* **97**, 4765 (1975).

[4a]Z. Cekovic and M. M. Green, *J. Am. Chem. Soc.* **96**, 3000 (1974); [b]Z. Cekovic, Lj. Dimitrijevic, G. Djokic and T. Srnic, *Tetrahedron* **35**, 2021 (1979).

[5]$Mn(OAc)_3/Cu(OAc)_2$: [a]E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.* **93**, 524 (1971); [b]E. I. Heiba and R. M. Dessau, *J. Org. Chem.* **39**, 3456 (1974); [c]F. J. McQuillin and M. Wood, *J. Chem. Soc. Perkin Trans. I* 1762 (1976); [d]D. Uguen and P. Breuilles, *Tetrahedron Lett.* **25**, 5759 (1984). $Pb(OAc)_4/Cu(OAc)_2$: [e]R. A. Sheldon and J. K. Kochi, *Organic Reactions*, Vol. 19, Chap. 2. Wiley–Interscience, New York (1972).

[6a]J. v. Becker and G. Ohloff, *Helv. Chim. Acta* **54**, 2889 (1971); [b]S. L. Schreiber, *J. Am. Chem. Soc.* **102**, 6163 (1980); [c]S. L. Schreiber, R. E. Claus and J. Reagan, *Tetrahedron Lett.* **23**, 3867 (1982); [d]S. L. Schreiber and W.-F. Liew, *Tetrahedron Lett.* **24**, 2363 (1983); [e]S. L. Schrieber and W.-F. Liew, *J. Am. Chem. Soc.* **107**, 2980 (1985).

[7a]M. Shibuya, F. Jaisli and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **18**, 636 (1979); S. L. Schreiber and T. J. Sommer, *Tetrahedron Lett.* **24**, 4781 (1983); [b]A. P. Kozikowski and J. G. Scripko, *J. Am. Chem. Soc.* **106**, 353 (1984); [c]S. L. Schreiber, T. J. Sommer and K. Satake, *Tetrahedron Lett.* **26**, 17 (1985); [d]S. L. Schreiber and Z. Wang, *J. Am. Chem. Soc.* **107**, 5303 (1985). Enantiotopic hydroxymethyl groups: T. Fukuyama, C.-L. Wang and Y. Kishi, *J. Am. Chem. Soc.* **101**, 261 (1979).

[8]R. M. Carman and D. E. Cowley, *Tetrahedron Lett.* 2723 (1968).

[9]P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. 1, Chap. 7. Academic Press, New York (1978).

[10]H. Keul and R. L. Kuczkowski, *J. Am. Chem. Soc.* **106**, 3383 (1984).

[11a]G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.* **5**, 167 (1970); [b]N. D. Epiotis, W. R. Cherry, S. Shaik, R. L. Yates and F. Bernardi, *Top. Curr. Chem.* **70**, 1 (1977).

[12]E. Vedejs and D. M. Gapinski, *J. Am. Chem. Soc.* **105**, 5058 (1983).

[13]For a related result, see: S. L. Schreiber, Ph.D. Thesis, Chap. 2. Harvard University (1981).

[14]W. C. Still and I. Galynker, *Tetrahedron* **37**, 3981 (1981).

[15]K. Mori, S. Kuwahara and H. Ueda, *Tetrahedron* **39**, 2439 (1983).

[16]S. L. Schreiber and C. Santini, *J. Am. Chem. Soc.* **106**, 4038 (1984).

[17]Personal communication with Professor David Lynn, University of Chicago; D. W. Graden and D. G. Lynn, *J. Am. Chem. Soc.* **106**, 1119 (1984).

[18]I. Saito, R. Nagata, K. Yuba and T. Matsuura, *Tetrahedron Lett.* **24**, 1737 (1983).

[19]B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* **102**, 4743 (1980).