The Peroxide Transfer Reaction

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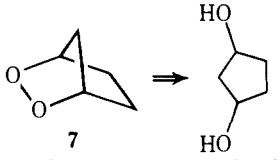
Abstract: A new method for synthesis of dialkyl peroxides is described which is based on the novel peroxide transfer reaction between germanium or tin peroxides and alkyl trifluoromethanesulfonates (triflates). Yields are generally superior to those obtainable by alkylation of hydrogen peroxide with alkyl methanesulfonates (mesylates) in the presence of base, especially for secondary alkyl peroxides. Mixed dialkyl peroxides are obtained from the reaction of tri-*n*-butyltin peralkoxide with alkyl triflates. Bis(tri-*n*-butyltin) peroxide reacts with alkyl triflates to afford symmetrical dialkyl peroxides, and with alkyl bistriflates to afford five- to eight-membered cyclic peroxides. The strained bicyclic peroxide nucleus of prostaglandin endoperoxides, 2,3-dioxabicyclo[2.2.1]heptane, is obtained in 22% yield from the bistriflate of *cis*-1,3-cyclopentanediol.

Introduction

New interest in the synthesis of dialkyl peroxides was recently sparked by the isolation of biologically important natural bicyclic peroxides, prostaglandin endoperoxides (e.g., **1**).[1] These peroxides are pivotal intermediates in the biosynthesis of prostaglandins (e.g., prostaglandin E_2 (**2**), prostaglandin $F_{2\alpha}$ (**3**), and prostaglandin D_2 (**4**)),[2] thromboxane A_2 (**5**),[3] and prostacyclin (**6**),[4] which are produced from **1** via disproportionation, reduction, or skeletal rearrangement (Scheme I). The prostaglandin endoperoxides themselves possess potent physiological activities and, together with **5** and **6**, have been implicated in the control of platelet aggregation.[3a,5]

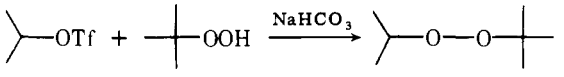
Though postulated as key biosynthetic intermediates, it was widely held that the strained bicyclic peroxide nucleus of prostaglandin endoperoxides "in all probability is not stable at room temperature."[1d] More recently, prostaglandin endoperoxides were isolated from enzymatic cyclooxygenation of polyunsaturated fatty acids. Indeed, even after purification, they are quite short lived ($t_{1/2}$ = 2.7 h at 20°C in 1:1 light petroleum–diethyl ether).[1b] Moreover, they readily rearrange on silica gel TLC plates into prostaglandins of the D and E type. This extraordinary proclivity toward disproportionation prompted us to shun alkaline conditions for construction of the 2,3-dioxabicyclo[2.2.1]heptane nucleus **7** of prostaglandin endoperoxides.

Readily available *cis*-1,3-cyclopentanediols are attractive precursors for **7**. However, existing methodology for synthesis



7

of primary and secondary alkyl peroxides from alcohols involved alkylation of hydroperoxides, hydrogen peroxide, or potassium superoxide with alkyl methanesulfonates (mesylates) under alkaline reaction conditions. Thus, mesylates do not react directly with hydroperoxides or hydrogen peroxide. Rather, base catalysis is required which generates the more nucleophilic peroxy anions. In our search for mild new synthetic methodology for preparation of secondary dialkyl peroxides starting with the corresponding alcohols, we reasoned that very reactive alkylating agents, such as alkyltrifluoromethanesulfonates (triflates),[6] might alkylate hydroperoxides directly in the absence of the strong bases normally required when less reactive alkylating agents (e.g., mesylates) are utilized. In fact, as we reported earlier,[7] primary and secondary triflates readily alkylate *tert*-butyl hydroperoxide in the



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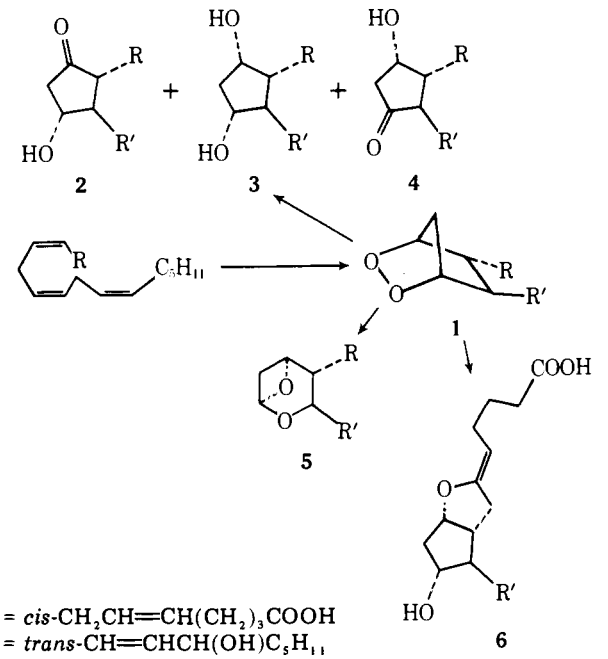
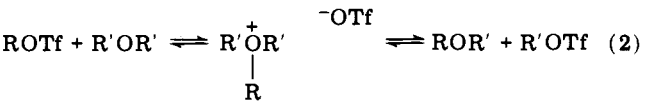
Scheme I. The Key Biosynthetic Role of Prostaglandin Endoperoxides



R = *cis*-$CH_2CH{=}CH(CH_2)_3COOH$
R′ = *trans*-$CH{=}CHCH(OH)C_5H_{11}$

presence of sodium bicarbonate (eq 1). The mechanism of these reactions probably involves initial formation of oxonium ions. Triflates are known to alkylate ethers yielding oxonium ions and giving transalkylation[8] (eq 2). An analogous transalk-



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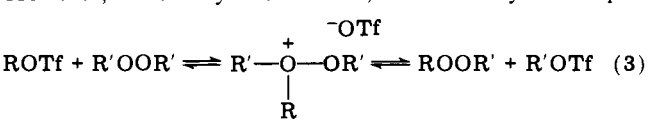
ylation of dialkyl peroxides (eq 3) would yield new peroxides. However, to be of synthetic value, the transalkylation equi-



(3)

librium must favor the desired products. This consideration led us to examine the possibility that organometallic peroxides[9]

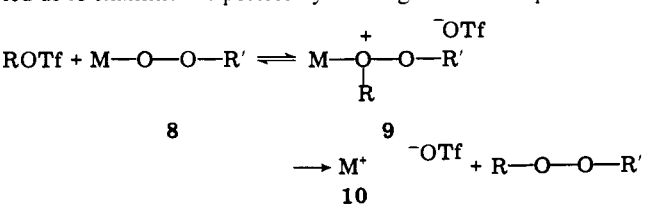


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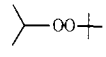
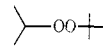
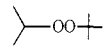
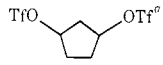
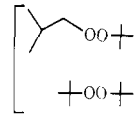
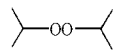
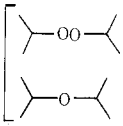
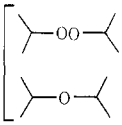
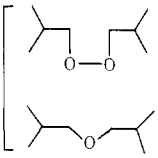
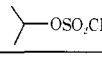
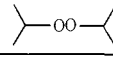
Table I. Synthesis of Mixed Alkyl *tert*-Butyl Peroxides

entry	alkylating agent	organometallic peroxide	reaction time, h (temp, °C)	products	% yield[c]
1		+OOSiMe$_3$	100 (22)		0
2		+OOGeEt$_3$	40 (22)		76
3		+OOSnBu$_3$	1.5 (22)		79 (65)[d]
4		+OOSnMe$_3$/CCl$_4$	0.5 (22)	[b]	61
5		+OOSnBu$_3$	8 (40)		45 13
6		+OOSnBu$_3$	16 (70)	no reaction	
7		+OOSnBu$_3$	200 (22)	no reaction	

[a] From cis diol. [b] Products consisted of *cis*-cyclopentane-1,3-bis-*tert*-butyl peroxide (30%), *trans*-cyclopentane-1,3-bis-*tert*-butyl peroxide (22%), and 3-*tert*-butylperoxycyclopentene (9%). [c] Yields by NMR analysis with internal standard after vacuum transfer. [d] Yield after distillation.

Table II. Synthesis of Acyclic Symmetrical Dialkyl Peroxides

entry	alkylating agent	organometallic peroxide	reaction time, h (temp, °C)	products	% yield[a]
1		Me$_3$SiOOSiMe$_3$	200 (20)		0
2		Et$_3$GeOOGeEt$_3$	3 (20)		41 9
3		Bu$_3$SnOOSnBu$_3$	0.1 (20)		79 (62%)[b] 7
4		Bu$_3$SnOOSnBu$_3$	40 (20)		62 4
5		Bu$_3$SnOOSnBu$_3$	20 (40)	no reaction	
6		Bu$_3$SnOOSnBu$_3$	24 (20)		0

[a] Yields by NMR analysis with internal standard after vacuum transfer. [b] Yield of diisopropyl peroxide after distillation (contains 8% diisopropyl ether).

8 would react with alkyl triflates to afford alkyl peroxides. Decomposition of an intermediate metallooxonium ion **9** should yield the desired alkyl peroxide by expulsion of a stable metal cation **10.**

Results

Alkylation of *tert*-butylperoxytrialkylsilanes, -germanes, and -stannanes was explored using a variety of primary and secondary alkyl triflates. Mixed dialkyl peroxides are obtained in good yields from the reactions of germyl or stannyl peroxides, but no dialkyl peroxide is produced from the reaction of *tert*-butylperoxytrimethylsilane (Table I). Also, no reaction occurs between *tert*-butylperoxytri-*n*-butylstannane and 2-methyl-1-propenyl triflate or isopropyl mesylate. Similarly, symmetrical dialkyl peroxides are produced by reaction of alkyl triflates with bis(trialkyltin) or bis(trialkylgermanium) peroxides, but not with bis(trialkylsilyl) peroxides (Table II). However, no reaction occurs between bis(tri-*n*-butyltin) peroxide and 2-methyl-1-propenyl triflate or isopropyl 2,2,2-trifluoroethanesulfonate (tresylate). These novel reactions result in net transfer of the peroxide moiety from the metal to the alkyl group:

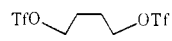
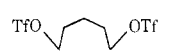
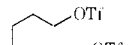
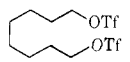
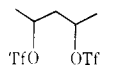
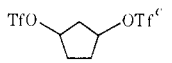
$$\text{ROTf} + \text{R'}_3\text{M-OO-}t\text{-Bu} \rightarrow \text{ROO-}t\text{-Bu} + \text{R'}_3\text{MOTf} \quad (4)$$

$$2\text{ROTf} + \text{R'}_3\text{M-OO-MR'}_3 \rightarrow \text{ROOR} + 2\text{R'}_3\text{MOTf} \quad (5)$$

$$\text{M} = \text{Sn,Ge}$$

The peroxide transfer reactions of bis(trialkyltin) and bis(trialkylgermanium) peroxides (eq 5) are accompanied by

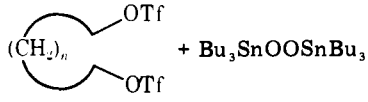
Table III. Cyclic Peroxides from Alkyl Triflates and Bis(tri-*n*-butyltin) Peroxide

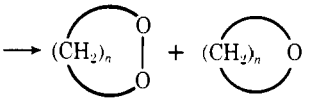
entry	starting triflate	method[a]	peroxide	yield, %[b]	ether	yield, %[b]
1		B				1.5
2		B	**11** 	68		0
		A		46		
3		A	**12** 	65		24
4		A	**13** 	37		42
5		A	**14** 	23		6
6		A		<1		
7		A		<1		
8		A	**15** 	52		
9		B		22[d]		0

[a] Method A = reaction in CH_2Cl_2 for 15 min, followed by vacuum transfer. Method B = reaction in vacuo in 1,2,4-trichlorobenzene. [b] Yields by NMR analysis with internal standard after vacuum transfer. [c] From *cis*-cyclopentane-1,3-diol. [d] 2,3-Epoxycyclopentan-1-one (6%) also formed.

side reactions which produce minor yields of the corresponding dialkyl ethers.

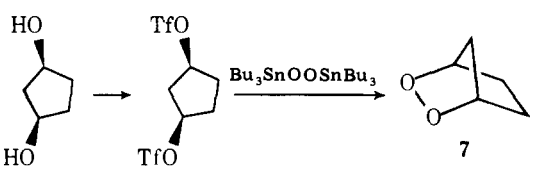
The peroxide transfer reaction between bis(tri-*n*-butyltin) peroxide and alkyl bistriflates readily affords cyclic peroxides accompanied in some cases by the corresponding cyclic ether and traces of 1-butanol (Table III). In all cases, volatile





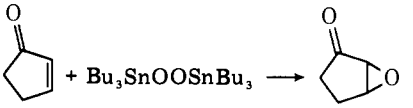
products are easily isolated by simple vacuum transfer from the nonvolatile organotin residue. All of the mixed dialkyl peroxides,[7] the acyclic symmetrical dialkyl peroxides,[10] 3,5-dimethyl-1,2-dioxolane (**15**),[11] and 1,2-dioxane (**12**)[12] are identified by comparison with authentic samples (see Experimental Section). The new compounds, 1,2-dioxolane (**11**), 1,2-dioxepane (**13**), and 1,2-dioxocane (**14**), are obtained analytically pure by preparative VPC and identified by mass spectra, ^1H and ^{13}C NMR spectra, IR spectra, and elemental analyses.

The peroxide transfer reaction is also effective for construction of the 2,3-dioxabicyclo[2.2.1]heptane nucleus **7** of prostaglandin endoperoxides from readily available *cis*-1,3-cyclopentanediol (**16**).[7] Best results are achieved with 1,2,4-trichlorobenzene as reaction solvent, and with continuous removal of the volatile peroxide **7** from the reaction mixture. Because bis(tri-*n*-butyltin) peroxide and the bistriflates are



16 **7**

not volatile, the mildly exothermic reaction can be performed in vacuo with immediate transfer of the sensitive products into a cold trap. This technique generally gives higher yields for some of the less stable peroxides, and provides 2,3-dioxabicyclo[2.2.1]heptane (**7**) in 22% yield. None of the endoperoxide **7** is obtained if the bistriflate from *cis*-cyclopentane-1,3-diol (**16**) is simply added to the tin peroxide with *subsequent* isolation of the volatile products by vacuum transfer from the nonvolatile tin residue. Instead, cyclopent-2-en-1-one (**17**) and

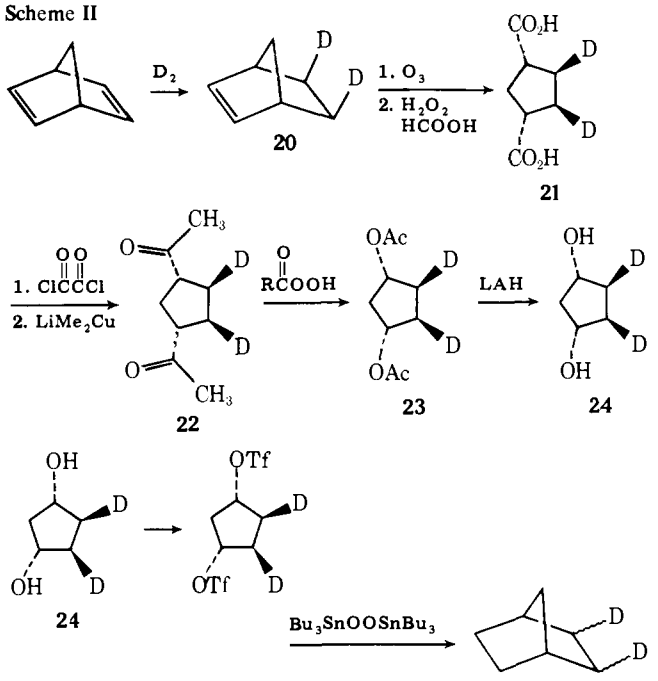


17 **18**

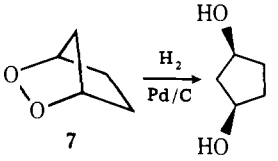
2,3-epoxycyclopentan-1-one (**18**) are obtained. The epoxy ketone **18** is also obtained (40% yield) by treatment of the unsaturated ketone **17** with the tin peroxide.

The pure prostaglandin endoperoxide nucleus, 2,3-dioxabicyclo[2.2.1]heptane (**7**), which has mp 63–65 °C,[13] is obtained by thin layer chromatography on silica gel at −20 °C followed by fractional sublimation. It gives a positive ferrous thiocyanate peroxide test.[14] The pure bicyclic dialkyl peroxide is stable toward bis(tri-*n*-butyltin) peroxide. The endoperoxide is further characterized by its proton decoupled ^{13}C NMR spectrum, which shows only three absorptions owing to the symmetry of the molecule, ^1H NMR spectrum, and elemental analysis. As shown in Figure 1, the upfield portion of the ^1H NMR spectrum of **7** in benzene-d_6 is nearly identical with the upfield portion of the 1,4-diphenyl derivative **19** reported previously,[15] except that the diphenyl compound displays its absorptions 0.8 ppm downfield from the corresponding absorptions of **7**. All of the nonequivalent hydrogens in **7** gave nonoverlapping absorptions, the exo hydrogens appearing at δ 1.05, anti at 1.34, endo at 1.64, and syn at 1.87. In addition, **7** exhibits a two-proton singlet at δ 4.2 owing to the bridgehead hydrogens. The proton coupled ^{13}C NMR spectrum of **7** exhibits a doublet at 78.7 ppm (J = 161 Hz), a triplet at 43.8 ppm (J = 136 Hz), and a triplet at 29.1 ppm (J = 136 Hz). The

Scheme II

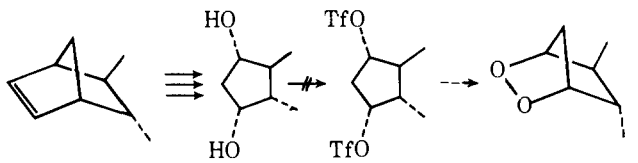


latter triplet is absent from the spectrum of 5,6-dideuterio-2,3-dioxabicyclo[2.2.1]heptane (vide infra), and is replaced by a doublet of multiplets also centered at 29.1 ppm (J = 136 Hz). As expected, peroxide **7** yields *cis*-cyclopentane-1,3-diol (**16**) stereospecifically upon catalytic hydrogenation.



The stereochemistry of the dialkyl peroxide forming reaction was investigated using *trans,trans*-4,5-dideuterio-*cis*-1,3-cyclopentanediol (**24**). As shown in Scheme II, the labeled diol is prepared from *exo*-5,6-dideuteriobicyclo[2.2.1]hept-2-ene (**20**)[16] via ozonolysis to the diacid **21** which gives the 1,3-diacetylcyclopentane (**22**) by reaction of the derived diacid chloride with methyl Gilman reagent. Baeyer–Villiger oxidation of **22** affords diacetate **23** which provides the diol **24** by treatment with lithium aluminum hydride. The labeled diol **24** is converted to a bistriflate with triflic anhydride and pyridine, and the bistriflate treated with bis(tri-*n*-butyltin) peroxide in vacuo. Meticulous purification followed by detailed 100-MHz ^{1}H NMR analysis reveals that the product 5,6-dideuterio-2,3-dioxabicyclo[2.2.1]heptane contains 1.55 deuterium in the 5 and 6-endo positions and 0.42 deuterium in the 5 and 6-exo positions.

trans-5,6-Dimethyl-2,3-dioxabicyclo[2.2.1]heptane might be a useful model for assessing the effect on endoperoxide stability of prostaglandin-like alkyl substitution on the ethano bridge. A synthesis of this endoperoxide was explored briefly. *exo,endo*-5,6-Dimethylbicyclo[2.2.1]hept-2-ene was converted stereospecifically in good overall yield into *trans*-4,5-dimethyl-*cis*-cyclopentane-1,3-diol by a reaction sequence paralleling the **20** → **24** conversion outlined above. We have



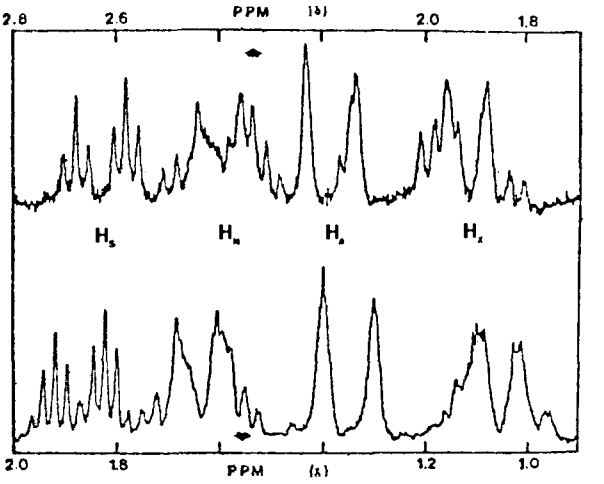
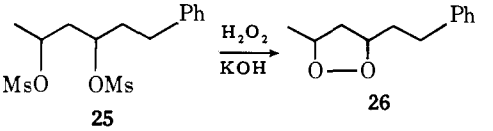


Figure 1. Upfield region of 100-MHz ^{1}H NMR spectra of **7** and **19** (top) in benzene-d_6 (note different scales).

not yet succeeded in converting this diol into the requisite bistriflate for a peroxide transfer synthesis of the desired endoperoxide.

Discussion

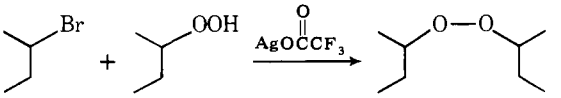
Synthesis of dialkyl peroxides from alcohols generally involves nucleophilic substitution with peroxy nucleophiles.[17] For tertiary alkyl peroxides, substitution is achieved under acidic conditions by an S_N1 process. Until recently, secondary and primary alkyl peroxides were only available by S_N2 processes involving base-catalyzed alkylations with active esters, such as sulfates or mesylates, or, less directly, with alkyl halides.[17] Alkaline reaction conditions are employed to promote these S_N2 reactions by converting hydroperoxide into more nucleophilic peroxy anions. However, disproportionation of alkyl peroxides to alcohol and carbonyl compounds is also subject to catalysis by base.[18] Moreover, base can promote elimination reactions of alkyl halides and sulfonates. Therefore, yields tend to be low (10–50%), especially for secondary alkyl peroxides. Even under optimum conditions, bisalkylation of hydrogen peroxide with bismesylate **25** affords dioxolane **26**



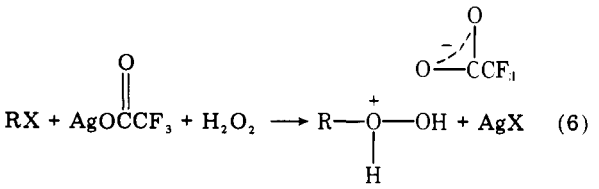
in only 13% yield.[19] More recently, the reaction of potassium superoxide with alkyl bromides, mesylates, or tosylates was found to give dialkyl peroxides in yields generally superior to those attainable by base-catalyzed alkylation of hydrogen peroxide.[20] Although side reactions involving formation of olefin or alcohol occur, the method was successfully applied to synthesis of the dioxolane **26** in 35% yield.[20b]

We recently developed an alternative approach for synthesis of primary and secondary alkyl peroxides from alcohols which exploits the extreme electrophilicity of the derived triflate esters.[7] Alkyl hydroperoxides are alkylated under nonalkaline conditions by reaction with alkyl triflates in the presence of sodium bicarbonate. These reactions apparently involve direct alkylation of hydroperoxides via presumed oxonium ion intermediates.

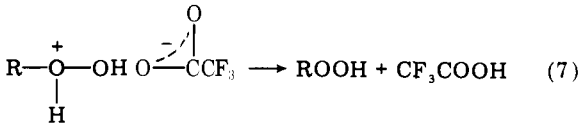
Silver acetate assisted intramolecular alkylation of bromo hydroperoxides is also a mild nonalkaline method which is



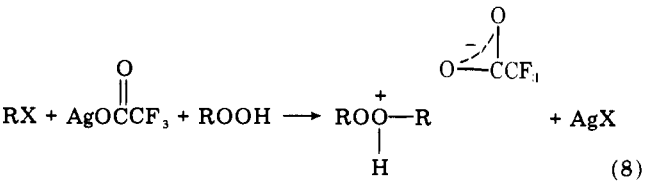
applicable to synthesis of 1,2-dioxetanes.[21] With silver trifluoroacetate, this reaction becomes highly effective for preparation of primary, secondary, or tertiary hydroperoxides or dialkyl peroxides.[22] The method is readily applicable to preparation of unsymmetrical or symmetrical dialkyl peroxides in generally good yields, but the reported yield of the secondary 2-butyl peroxide is low (27%). These alkylations probably also involve oxonium ion intermediates (eq 6-9).



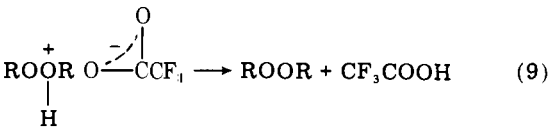
(6)



(7)

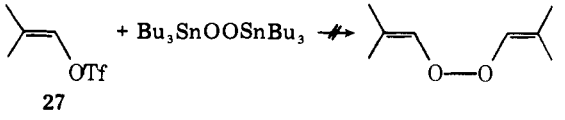


(8)



(9)

The novel peroxide transfer reactions reported herein between germanium or tin peroxides and alkyl triflates are achieved under notably mild conditions. Although a harsh alkaline catalyst is not present, the dialkyl peroxide syntheses proceed smoothly usually at room temperature. For these syntheses bis(tributyltin) peroxide (**32**), prepared by reaction of tributylin methoxide with anhydrous hydrogen peroxide, is the favored peroxide reagent since it is inexpensive and relatively stable. Reaction of bistriflates is complete in less than 10 min at room temperature. Secondary monotriflates take somewhat longer and primary triflates require a modest amount of heat to make the reaction proceed conveniently. In contrast, the vinyl triflate **27** does not react with bis(tri-*n*-

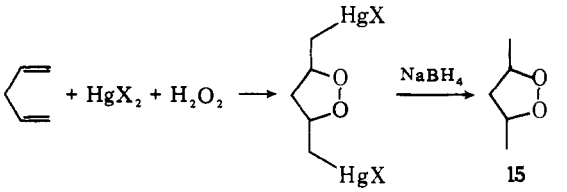


27

butyltin) peroxide. Thus, the peroxide transfer reaction is not applicable to preparation of alkenyl peroxides, an almost unknown type of compound.[23] Vinyl triflates are relatively weak electrophilic reagents, apparently incapable of alkylating organometallic peroxides. Similarly, isopropyl mesylate and isopropyl tresylate, which are less electrophilic than triflates, also do not undergo peroxide transfer reactions with organometallic peroxides.

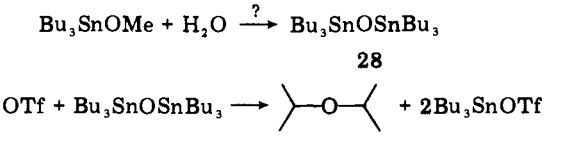
As shown in Tables I and II, several different organometallic peroxides were tested for reactivity toward alkyl triflates. Neither bis(trimethylsilyl) peroxide[24] nor *tert*-butyl trimethylsilyl peroxide[25] gives any organic peroxide products by reaction with isopropyl triflate. Good peroxide yields are obtained using either bis(triethylgermyl) peroxide or *tert*-butyl triethylgermyl peroxide,[26] but even better yields are obtained with the corresponding tributyltin derivatives, which have the added advantage of being very inexpensive to prepare. Utilization of *tert*-butyl trimethyltin peroxide[26] (Table I, entry 4) permits facile preparation of nonvolatile mixed peroxides, since the trimethyltin-containing byproducts are water soluble and easily washed away from the organic peroxide.

The yields of peroxides are usually significantly higher than yields reported previously for other methods of synthesis. Thus, isopropyl *tert*-butyl peroxide, synthesized by peroxide transfer from (*tert*-butylperoxy)tri-*n*-butyltin in 65% yield, has been prepared by a variety of different methods in yields ranging from 25 to 40%.[27] Our earlier method of mixed peroxide synthesis, reaction of isopropyl triflate with *tert*-butyl hydroperoxide in the presence of bicarbonate, gave only 56%.[7] The yield of 3,5-dimethyldioxolane (Table III, entry 8) is about the same as the synthesis reported previously which utilized peroxymercuration-demercuration of 1,4-pentadiene with hydrogen peroxide.[11]



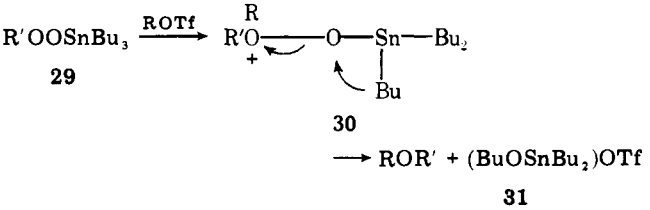
15

The formation of symmetrical peroxides by peroxide transfer is often accompanied by smaller amounts of ether formation (Tables II and III). Thus, diisopropyl peroxide prepared by peroxide transfer from bis(tri-*n*-butyltin) peroxide to isopropyl triflate in 62% yield was not separated by distillation from byproduct diisopropyl ether (8% of the mixture). Ether-free, analytically pure peroxides were obtained by preparative VPC (see Experimental Section). Furthermore, if an ether impurity can be tolerated, the peroxide transfer approach is superior to base-catalyzed alkylation of hydrogen peroxide with isopropyl mesylate, which gives only 16-26% yield.[10a] We considered that ether formation might be due to the presence of bis(tributyltin)oxide (**28**) which could be formed during preparation of bis(tributyltin) peroxide if any water were present. Indeed, the presence of small amounts of water did lead to increased quantities of ethers. Independent treatment of bis(tributyltin) oxide (**28**) with isopropyl triflate did give diisopropyl ether



28

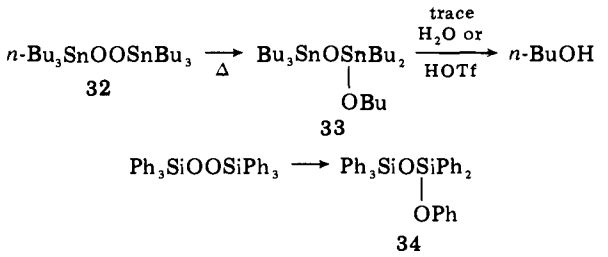
(28%), but the reaction was very much slower (18 h, room temperature) than the peroxide-forming reaction. Thus, a different source of ether formation is likely. The formation of the ether and 1-butanol products might alternatively arise by alkylation of the alkyl tributyltin peroxide intermediate **29** β to tin to give oxonium ion intermediate **30** which could de-



31

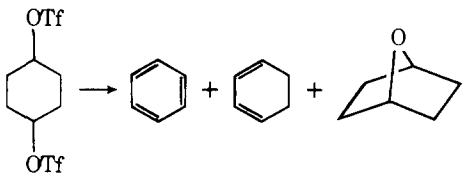
compose to **31** with migration of butyl from tin to oxygen. Similar, 1,2-alkyl migrations from germanium or tin to oxygen in peroxides are well-known.[9b] Further study is necessary to establish a mechanism. The formation of 1-butanol might also result from thermal decomposition of the excess bis(tributyltin) peroxide (**32**) to form **33** during the heating involved in bulb to bulb transfer of the product peroxides. In fact, as heating is prolonged, more and more butanol is formed. In thermal

decomposition of triphenylsilyl peroxides, aryl migration from silicon to oxygen occurs to give a similar intermediate **34**.[28]

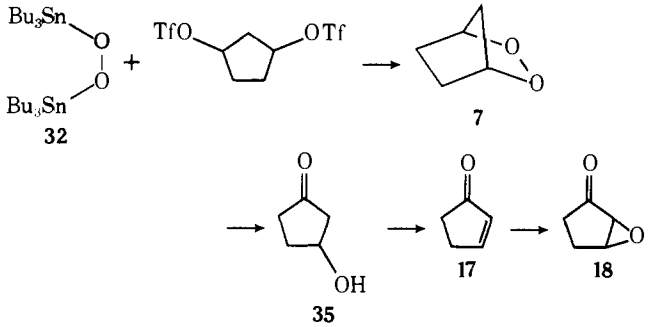


With the synthesis of the new cyclic peroxides, 1,2-dioxolane (**11**), 1,2-dioxepane (**13**), and 1,2-dioxocane (**14**), a homologous series of monocyclic peroxides is now available. This may prove useful in studies of the effect of geometrical constraints on properties of the oxygen–oxygen bond and on peroxide chemistry. The yields of these cyclic peroxides decrease considerably as ring size increases, apparently due to formation of polymeric peroxides. Thus, examination of the NMR in the reaction of hexane 1,6-bistriflate with bis(tri-*n*-butyltin) peroxide reveals an 85% yield of peroxide (based on ^{1}H NMR absorption at δ 3.9) before bulb to bulb transfer, but only a 23% yield of volatile 1,2-dioxocane is obtained. Similarly, in attempts to prepare the nine- and ten-membered ring peroxides, considerable amounts of alkyl peroxide are formed (75–77%), but no volatile peroxides could be isolated. At the other end of the scale, we were unable to isolate the four-membered ring cyclic peroxide 1,2-dioxetane. Under vacuum conditions, along with ethylene oxide, several very unstable products ($t_{1/2}$ = ca. 10 min at 35 °C) were formed possessing singlets in the ^{1}H NMR (δ 3.41 and 4.72). No formaldehyde, a possible decomposition product of 1,2-dioxetane, was detected.

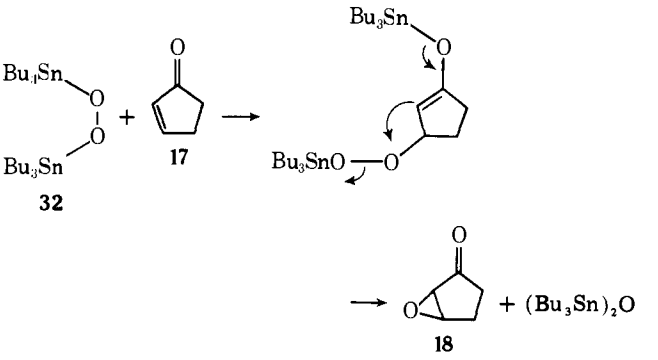
Decomposition also occurs upon reaction of cyclohexane 1,4-bistriflate with tin peroxide. The products consist of a mixture of benzene, cyclohexa-1,3-diene, and 7-oxabicyclo[2.2.1]heptane (relative amounts 1:2.1:1.4).



The efficacy of the peroxide transfer reaction for synthesis of sensitive dialkyl peroxides is demonstrated by the successful synthesis of the strained bicyclic peroxide nucleus **7** of prostaglandin endoperoxides in 22% yield. Simple mixing of *cis*-cyclopentane 1,3-bistriflate with bis(tri-*n*-butyltin) peroxide (**32**) gives the desired bicyclic peroxide **7**. However, unless this sensitive peroxide is removed immediately from the reaction mixture, it undergoes disproportionation to give cyclopent-2-en-1-one (**17**) via 3-hydroxycyclopentan-1-one (**35**) which eliminates water. These transformations are analogous to the formation of the E and A prostaglandins from the prostaglandin endoperoxide (see Scheme 1). The disproportionation

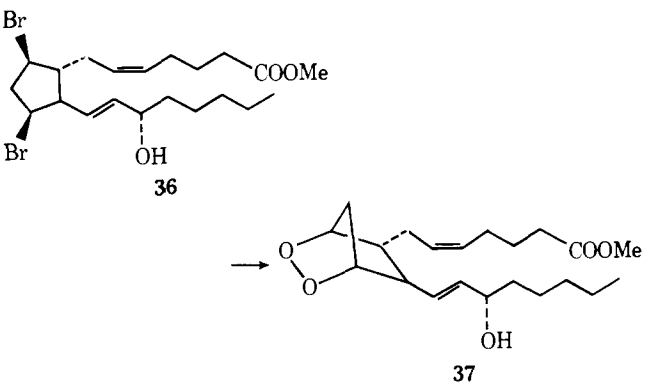


of **7** which occurs upon prolonged exposure to the reaction product mixture is not catalyzed by bis(tri-*n*-butyltin) peroxide (**32**). The pure bicyclic peroxide **7** is stable toward the tin peroxide which is apparently a covalent nonalkaline reagent. 2,3-Epoxycyclopentan-1-one (**18**) is a secondary reaction product formed from cyclopentenone and excess tin peroxide. Thus, treatment of cyclopentanone **17** with **32** cleanly produces



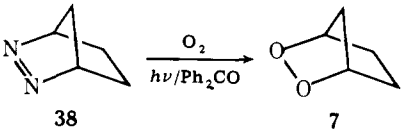
the epoxide (43% yield). This novel aprotic epoxidation probably occurs via Michael addition to the unsaturated ketone followed by intramolecular nucleophilic displacement of tributyltin oxide. The bistin peroxide **32** is necessary in this epoxidation, as *tert*-butyl tributyltin peroxide fails to give any epoxide. A similar epoxidation occurs in the reaction of unsaturated ketones with the sodium salt of *tert*-butyl hydroperoxide.[29]

Although derivatives of **7** have been prepared with a strongly alkaline reagent, the most effective methods employ neutral or acidic reaction conditions. Thus, prostaglandin H_2 methyl ester (**37**) is obtained in 3% yield by reaction of dibromide **36**



with potassium superoxide.[30] The endoperoxide **37** is unstable toward this strongly alkaline reagent. In comparison, **37** is obtained in 21% yield from **36** by reaction with hydrogen peroxide and silver trifluoroacetate.[31] The long sequence of reactions and low yield[32] reported for preparation of **36** from prostaglandin $F_{2\alpha}$ detract from the effectiveness of this approach.

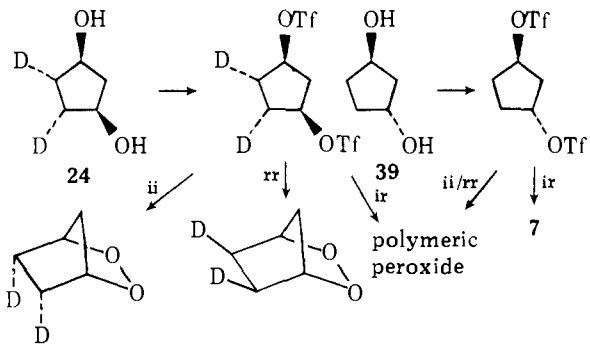
A novel strategy for synthesis of the nucleus **7** of prostaglandin endoperoxides under neutral reaction conditions involves sensitized photolysis of 2,3-diazabicyclo[2.2.1]hept-2-enes under 150 psi of oxygen.[33] Thus, **38** affords **7** in 79%



yield after 21% conversion. However, sensitized decomposition of **7** becomes increasingly important as the reaction proceeds, giving 43% yield if the photolysis is run to 54% completion.

Selective reduction with diimide of the adduct of singlet oxygen with cyclopentadiene is presently the method of choice

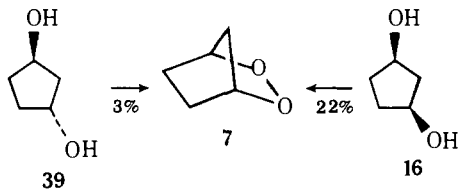
Scheme III



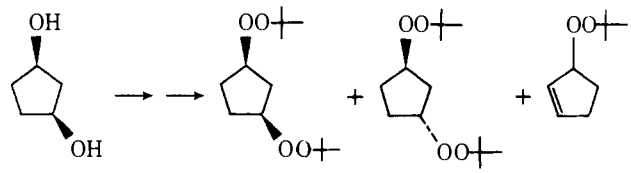
ii = double inversion, rr = double retention
ir = inversion + retention

for preparation of the nucleus **7** of prostaglandin endoperoxides.[15,34] Several grams are readily prepared in 1 day in about 50% yield. However, this synthetic approach cannot be extended to synthesis of trans-5,6-disubstituted derivatives such as **37** since addition of hydrogen occurs stereospecifically cis.

Transformation of *cis*-cyclopentane-1,3-diol (**16**) into 2,3-dioxabicyclo[2.2.1]heptane (**7**) via the peroxide transfer reaction occurs with net, but incomplete, inversion stereochemistry. Thus, stereospecifically deuterium labeled *trans,trans*-4,5-dideuterio-*cis*-1,3-cyclopentanediol (**24**) gives endo and exo deuterated peroxide corresponding to a substitution with double inversion favored over double retention by about 4:1. Complete loss of stereochemical integrity does not occur during triflate formation, since *trans*-cyclopentane-1,3-diol gives at most 3% endoperoxide **7** under conditions where cis diol **16** gives 22% of **7**. Likewise, the reaction of the



bistriflate from *cis*-cyclopentane-1,3-diol with *tert*-butylperoxytributyltin is not stereospecific, the ratio of cis to trans bisperoxide being 1.4:1.



Similar findings, predominant but not exclusive inversion, have been reported in the solvolyses of reactive secondary triflates.[35] Thus, our results can be rationalized as shown in Scheme III. Triflates are formed from **24** or **39** with retention of configuration followed by reaction with predominant inversion of configuration to form the endoperoxide. The trans diol **39** gives decreased amounts of endoperoxide **7** since the major pathway, double inversion, would lead to polymeric peroxides.

Conclusions

A completely new method of peroxide synthesis applicable to a wide variety of peroxides is reported. Thus, reaction of *tert*-butyltrialkyltin peroxide with primary or secondary alkyl trifluoromethanesulfonates (triflates) produces mixed *tert*-butyl alkyl peroxides in good to excellent yields. Symmetrical primary or secondary peroxides are also easily formed, in yields far higher than previously reported for other methods, by reaction of the symmetrical tin peroxide, bis(tributyltin) peroxide (**32**), with primary or secondary triflates. The method is easily extended to the synthesis of new primary or secondary cyclic peroxides through utilization of bistriflates. The reaction proceeds with overall inversion from alcohol to peroxide as the primary stereochemical pathway.

The only potential drawbacks to this new synthetic method are the production of some ether along with peroxide and the requirement for very potent alkylating agents, alkyl triflates, which are unstable for tertiary and some secondary alkyl groups. The new method is particularly attractive because of the mildness of conditions (room temperature, short reaction times), the absence of base which can lead to peroxide decomposition, the low cost of the new peroxide organometallic reagent, and the unprecedented high yields of peroxides. An added advantage of the method is the low volatility of the organotin reagent, permitting the reaction to be carried out in vacuo to produce extremely sensitive volatile peroxides.

Experimental Section

General. Microanalyses were performed by Chemalytics, Tempe, Ariz. ^{1}H NMR spectra were recorded on Varian A60 or HA-100 spectrometers. Mass spectra were taken on a 21-490 Du Pont GC/mass spectrometer, using a 3 ft × 1/8 in. column 10% DC 710 packing on Chromosorb W (AW, DMCS treated) at 40 °C. Preparative gas chromatography was done on a Varian Aerograph chromatograph unless otherwise noted with detector and injector 100 °C using a 3 ft × 1/4 in. 10% DC 710 on 60/80 Chromosorb W (acid washed, DMCS treated) column at less than 70 °C. Infrared spectra were measured as neat films on a Perkin-Elmer Infracord spectrometer.

Methylene chloride was dried by stirring over phosphorus pentoxide followed by distillation. Tetrahydrofuran and benzene were dried by distillation from the blue potassium ketyl of benzophenone. Pyridine was dried by standing over KOH for several days followed by distillation and storage over molecular sieves. Literature procedures were followed for the preparation of isopropyl triflate,[36] isopropyl mesylate,[37] isobutyl triflate,[7] cyclopentane 1,3-bistriflate,[7] butane 1,4-bistriflate,[36] and isobutenyl triflate.[38] The known organometallic peroxide reagents *tert*-butyl trimethylsilyl peroxide,[25] *tert*-butyl triethylgermyl peroxide,[26] *tert*-butyl tributyltin peroxide,[26] *tert*-butyl trimethyltin peroxide,[26] bis(trimethylsilyl) peroxide,[24] and bis(triethylgermyl) peroxide[26] were all prepared by the published methods.

Caution: All reactions involving peroxides and especially anhydrous hydrogen peroxide should be performed behind a safety shield.

Alkyl Trifluoromethanesulfonate Preparation. General Procedure.[37] A mixture of dry alcohol (distilled from sodium, 10 mmol if monoalcohol, 5 mmol if diol) and anhydrous pyridine (10 mmol) in dry methylene chloride (3 mL) was added dropwise over 20 min to an ice-cooled, stirred solution of trifluoromethanesulfonic anhydride (10 mmol) in methylene chloride (7 mL) under nitrogen. The solution was stirred for an additional 10 min, then washed with water (10 mL) and dried ($MgSO_4$). The primary bistriflates were not purified further and were stable at −20 °C for several months.

(1) Ethane 1,2-bistriflate was prepared in 81% yield: ^{1}H NMR ($CDCl_3$) δ 4.75 (s).

(2) Propane 1,3-bistriflate was prepared in 80% yield: ^{1}H NMR ($CDCl_3$) δ 2.33 (2 H, quintet, J = 6 Hz), 4.63 (4 H, t, J = 6 Hz).

(3) Pentane 1,5-bistriflate was prepared in 80% yield: ^{1}H NMR ($CDCl_3$) δ 1.36–2.17 (6 H, m), 4.55 (4 H, t, J = 6 Hz).

(4) Hexane 1,6-bistriflate was prepared in 79% yield: ^{1}H NMR ($CDCl_3$) δ 1.16–2.12 (8 H, m), 4.53 (4 H, t, J = 6 Hz).

(5) Heptane 1,7-bistriflate was prepared in 90% yield: ^{1}H NMR ($CDCl_3$) δ 1.16–2.16 (10 H, m), 4.55 (4 H, t, J = 6 Hz).

(6) Octane 1,8-bistriflate was prepared in 96% yield: ^{1}H NMR ($CDCl_3$) δ 1.20–2.17 (12 H, m), 4.53 (4 H, t, J = 6 Hz).

(7) Pentane 2,4-bistriflate was prepared in 68% yield and used immediately after preparation: ^{1}H NMR (CCl_4) δ 1.51 (6 H, d, J = 6.5 Hz), 2.13 (2 H, t, J = 6.5 Hz), 5.10 (2 H, br quintet, J = 6 Hz).

(8) Cyclohexane 1,4-bistriflate was prepared in 77% yield and used

immediately after preparation: ^{1}H NMR ($CDCl_3$) δ 1.83–2.47 (8 H, m), 4.95–5.37 (2 H, m).

(9) The preparation of cyclooctane 1,5-bistriflate was attempted. The bistriflate abruptly decomposed when the solvent was removed.

(10) The preparation of *trans*-2,3-dimethylcyclopentane *cis*-1,4-ditriflate was attempted using the standard procedure. By NMR, the product was very impure, containing less than 10% of possible triflate. Increasing the reaction time gave even poorer yields.

Isopropyl 2,2,2-trifluoroethanesulfonate was prepared from anhydrous 2-propanol, 2,2,2-trifluoroethanesulfonyl chloride, and triethylamine following the general procedure of Crossland, Wells, and Shiner.[39] The product could be stored neat at −20 °C for several days: ^{1}H NMR ($CDCl_3$) δ 1.38 (6 H, d, J = 6 Hz), 3.81 (2 H, q, J = 9 Hz), 4.90 (1 H, heptet, J = 6 Hz).

***trans*-2,3-Dimethylcyclopentane-*cis*-1,4-diol.** *exo,endo*-5,6-Dimethylbicylo[2.2.1]hept-2-ene[40] was ozonolyzed in methanol at −75 °C and treated with 30% hydrogen peroxide in formic acid according to the published method[41] to give *trans*-2,3-dimethylcyclopentane-*cis*-1,4-dicarboxylic acid: ^{1}H NMR ($CDCl_3$) δ 0.66–1.53 (6 H, m, CH_3), 1.53–3.33 (6 H, m), 11.73 (2 H, br s).

To a suspension of the diacid (1.44 g, 7.7 mmol) in dry benzene (3 mL) under nitrogen was added oxalyl chloride (2.02 g, 16 mmol). After heating under reflux for 15 min, the solvent and excess oxalyl chloride were removed under aspirator vacuum and the product was distilled, bp 90–95 °C (0.2 mm), yielding 1.67 g (97%) of *trans*-2,3-dimethylcyclopentane-*cis*-1,4-diacid chloride: ^{1}H NMR (CCl_4) δ 0.93–1.42 (6 H, m), 1.63–3.25 (6 H, m).

An ethereal solution of methyllithium (18 mmol) was added to a suspension of cuprous iodide (1.9 g, 10 mmol) in dry ether (30 mL) under nitrogen at 0 °C. The mixture was stirred at 0 °C until the solution was nearly homogeneous (5–10 min, gray solution). After cooling to −78 °C, the diacid chloride (615 mg, 2.76 mmol) was added. The resulting mixture was stirred at −78 °C for 15 min and then quenched with MeOH at −78 °C. The mixture was washed with saturated aqueous ammonium chloride (50 mL), dried, and filtered, the solvent was removed by rotary evaporation, and the product was distilled, bp 86–88 °C (0.1 mm) (78% yield): ^{1}H NMR (CCl_4) δ 0.88 (3 H, d, J = 6.5 Hz), 1.00 (3 H, d, J = 6.5 Hz), 2.11 (6 H, s), 1.63–3.35 (6 H, m).

The diketone (5.5 g, 30 mmol) and 85% *m*-chloroperbenzoic acid (24.4 g, 120 mmol) in ethylene dichloride (120 mL) were heated under reflux for 20 h. After cooling, methylene chloride (75 mL) was added, the mixture was filtered, and the solid was washed with methylene chloride (25 mL). The combined filtrates were washed with saturated $NaHCO_3$ (2 × 100 mL), water (100 mL), and saturated NaCl (100 mL). The washings were reextracted in succession with methylene chloride (100 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation. Distillation afforded 5.1 g (78%) of *trans*-2,3-dimethyl-*cis*-1,4-diacetoxycyclopentane: bp 95–99 °C (0.4 mm); ^{1}H NMR (CCl_4) δ 0.97 (3 H, d, J = 6 Hz), 1.05 (3 H, d, J = 6 Hz), 1.25–1.83 (3 H, m), 2.05 (6 H, s, OAc), 2.27–2.88 (1 H, m), 4.50–4.95 (1 H, m), 4.95–5.37 (1 H, m). This spectrum corresponds well with the detailed published spectrum of the known diacetate and differs from the spectra of all the other isomeric diacetates.[42]

The diacetate (5.4 g, 25 mmol) was added dropwise to lithium aluminum hydride (2.85 g, 75 mmol) in anhydrous tetrahydrofuran (250 mL) under nitrogen. After completion of addition, the mixture was heated under reflux for 30 min and cooled, and water (2.75 mL), 15% NaOH (2.75 mL), and water (8.75 mL) were added dropwise in succession. The solution was filtered, the solid washed with additional THF (25 mL), and the combined filtrates concentrated by rotary evaporation. Distillation afforded *trans*-2,3-dimethylcyclopentane-*cis*-1,4-diol:[43] bp 85–88 °C (0.03 mm) (78%); ^{1}H NMR ($CDCl_3$) δ 1.05 (6 H, d, J = 6 Hz), 1.16–1.97 (3 H, m), 2.30 (1 H, ddd, J = 6, 8, 15 Hz), 3.62–3.98 (1 H, m), 3.98–4.33 (1 H, m), 4.26 (2 H, br s, OH).

***trans,trans*-4,5-Dideuterio-*cis*-1,3-cyclopentanediol (24).** 5,6-*exo*-Dideuteriobicyclo[2.2.1]heptene[16] was converted to the corresponding diacid **21** (95%) by ozonolysis. The *trans,trans*-dideuterio-*cis*-diacid chloride, bp 92–93 °C (0.4 mm) (98%), was prepared from the diacid with oxalyl chloride as in the dimethylcyclopentane diacid chloride preparation above: ^{1}H NMR ($CDCl_3$) δ 2.00–2.4 (3 H, m), 2.50 (1 H, d, J = 8 Hz), 3.12–3.6 (2 H, m).

cis-1,3-Diacetyl-*trans,trans*-4,5-dideuteriocyclopentane (**22**), bp 74–75 °C (0.2 mm), was prepared in 55% yield by treatment of the diacid chloride with lithium dimethylcuprate as in the dimethyl case above: ^{1}H NMR (CCl_4) δ 1.71–2.17 (4 H, m), 2.10 (6 H, s), 2.58–3.12 (2 H, m).

The diacetyl derivative was treated with *m*-chloroperbenzoic acid in ethylene dichloride as in the dimethyl case above, yielding *cis*-1,3-diacetoxy-*trans,trans*-4,5-dideuteriocyclopentane (**23**): bp 75 °C (0.1 mm) (84%); ^{1}H NMR ($CDCl_3$) δ 1.5–2.0 (3 H, m), 2.03 (6 H, s), 2–2.67 (1 H, m), 4.97–5.32 (2 H, m).

The diacetate was reduced with lithium aluminum hydride as in the dimethyl case above to yield *trans,trans*-4,5-dideuterio-*cis*-1,3-cyclopentanediol (**24**) (85%): ^{1}H NMR (MeOH-d_4) δ 1.06–1.91 (3 H, m), 2.03 (1 H, heptet, J = 6 Hz), 3.98–4.37 (2 H, m), 4.80 (2 H, s, OH).

Bis(tri-*n*-butyltin) Peroxide (32). Tri-*n*-butyltin methoxide was synthesized by the method of Davies and Alleston[20] except that, after preparation of the sodium methoxide, anhydrous ether was added so that the solvent consisted of 80% ether and 20% methanol. Anhydrous hydrogen peroxide was prepared in ca. 2 M concentration by adding 90% H_2O_2 to the proper amount of ether and a large excess of magnesium sulfate dropwise at 0 °C under nitrogen. The solution was dried at 0 °C for 1 h, and the hydrogen peroxide concentration was determined by titration with $KMnO_4$.[43] The solution was kept at 0 °C and was transferred via syringe. The bistin peroxide was then prepared by mixing 2n mmol of n-Bu_3SnOMe with n mmol of anhydrous ethereal hydrogen peroxide under nitrogen at 0 °C. The product was stirred for 1 h at 0 °C and then the ether and methanol were removed at 0 °C at 20 mm, the last traces being removed at 0.5 mm. The product is hygroscopic and thermally unstable, but can be stored for 1 day neat at −20 °C. Attempted purification by rapid column chromatography on silica gel or Florisil led to decomposition.

Preparation of Organic Peroxides. General Procedures. A. The peroxide reagent (10% excess) was added to anhydrous CH_2Cl_2 (1 mL) in a dry 5-mL flask under N_2. The triflate (1 mmol) in CH_2Cl_2 (1 mL) was added with magnetic stirring and the reaction progress was monitored by NMR. When NMR indicated that the reaction was complete, an NMR standard (normally chloroform) was added, and the reaction mixture was bulb to bulb distilled into a dry ice/acetone cooled receiver at 20 mm, removing the last traces of product at 0.5 mm. As noted below in the individual instances, heat is sometimes required in the bulb to bulb distillation.

Isopropyl *tert*-butyl and diisopropyl peroxides were also prepared on a larger scale. *tert*-Butylperoxy(tri-*n*-butyl)tin (10 g) was added over 5 min at 20 °C to freshly distilled isopropyl triflate (27 mmol) in CH_2Cl_2 (80 mL). After stirring at 20 °C for 1.5 h, solvent and volatile reaction products were transferred into a cold trap (−78 °C) with gentle heating (35 °C) under reduced pressure (15 Torr). This solution was then shaken with aqueous 5% KOH (100 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and distilled to afford pure isopropyl *tert*-butyl peroxide: bp 45–48 °C (90 mm) (2.3 g, 65%).

Bis(tri-*n*-butyltin) peroxide (10 mL, 19 mmol) was added to dry CH_2Cl_2 under a blanket of dry nitrogen. To this solution was added over 5 min a 1.18 M solution of freshly distilled isopropyl triflate in CH_2Cl_2 (30.6 mL). After stirring for an additional 10 min at 20 °C, solvent and volatile reaction products were transferred under reduced pressure (15 Torr) into a cold receiver (−78 °C). Fractional distillation of the solution of crude peroxide afforded 1.42 g of a mixture of diisopropyl peroxide and diisopropyl ether (92:8 by NMR), bp 49–53 °C (150 mm). The yield of peroxide was 62%.

B. In Vacuo. In a dry three-neck 50-mL round-bottom flask under nitrogen fitted with a thermometer and a serum cap were placed dry 1,2,4-trichlorobenzene (10 mL, distilled from Na) and the bistriflate (6 mmol). The flask was connected by means of a bent adapter to a receiver (10 mL) with a side arm connected to a vacuum pump. The entire system was placed under vacuum (0.5 mm) and the receiver was cooled with a dry ice/acetone bath. Bis(tributyltin) peroxide (9 mmol, 4.7 mL) obtained by concentration of a methylene chloride solution of the peroxide at 0 °C was added via syringe over ca. 1 min. The addition is exothermic, and an ice bath may be needed briefly to maintain the reaction temperature at 40–50 °C. Along with products, some solvent also is condensed in the receiver.

Mixed Peroxides. A summary of reaction conditions and product yields appears in Table I. Method A was used throughout. Yields were determined by NMR with internal standard chloroform. Isopropyl *tert*-butyl peroxide[7] and isobutyl *tert*-butyl peroxide[7] were identified

by comparison with authentic samples. The reaction of cyclopentane bistriflate (derived from *cis*-cyclopentane-1,3-diol) was carried out in CCl_4 instead of methylene chloride, and bis(trimethyltin) peroxide was used since the water-soluble methyltin-containing byproducts of the reaction can be easily washed away from the relatively nonvolatile bisperoxide. The product composition in the reaction from cyclopentane 1,3-bistriflate was determined by reduction and acetylation as described previously.[7]

Acyclic Symmetrical Dialkyl Peroxides. A summary of reaction conditions and products yields appears in Table II. Method A was used throughout. Yields were determined by NMR with internal standard chloroform. Diisopropyl peroxide,[10a] diisopropyl ether, diisobutyl peroxide,[10b] and diisobutyl ether were identified by NMR and VPC comparison with authentic samples. An authentic sample of diisobutyl ether was prepared by the reaction of isobutyl mesylate with sodium isobutoxide in the presence of hexamethylphosphoramide.

Cyclic Peroxides. A summary of reaction conditions and product yields appears in Table III. Yields were determined by NMR with internal standard chloroform. For analytical purposes, the peroxides could be detected by thin layer chromatography using a ferrous thiocyanate visualizing reagent.[14]

(1) Attempted reaction of ethane-1,2-bistriflate was carried out by method B, with a small amount of CCl_4 in the distillation receiver from the start. The product was kept at −78 °C until examined by ^1H NMR. The NMR indicated the presence of ethylene oxide at δ 2.60 (s, 1.5%) and unstable unknown products with singlets at δ 3.41 (3%, disappears after 10 min at 35 °C) and 4.72 (1.5%, nearly disappeared after 10 min at 35 °C). No formaldehyde is found by NMR.

(2) Propane 1,3-bistriflate: 1,2-dioxolane **11** was prepared by both method A (46%) and method B (68%). By NMR, no trimethylene oxide was formed. Preparative VPC at 35 °C gave pure 1,2-dioxolane: ^1H NMR (CCl_4) δ 2.53 (2 H, quintet, J = 7 Hz), 3.92 (4 H, t, J = 7 Hz); IR (cm^{-1}) 1150 (s), 1110 (s), 987 (m), 925 (m), 780 (w); mass spectrum (70 eV) *m/e* (rel intensity) 26 (28), 27 (48), 28 (64), 29 (100), 30 (25), 31 (39), 42 (41), 43 (47), 44 (26), 46 (20), 74 (44).

Anal. Calcd for $C_3H_6O_2$: C, 48.64; H, 8.16. Found: C, 48.75; H, 8.41.

(3) Butane-1,4-bistriflate was reacted using method A. Preparative VPC at 35 °C gave tetrahydrofuran and 1,2-dioxane **12**,[12] identified by NMR and GC/mass spectral comparison with authentic samples. ^1H NMR (1,2-dioxane) δ 1.67–1.95 (4 H, m), 4.03–4.25 (4 H, m); IR (cm^{-1}) 1447 (m), 1200 (m), 1150 (s), 1105 (s), 1060 (m), 1022 (m), 965 (s), 916 (m), 763 (m); mass spectrum (70 eV) *m/e* (rel intensity) 26 (25), 27 (64), 28 (85), 29 (100), 30 (25), 31 (53), 39 (51), 40 (22), 41 (61), 42 (80), 43 (34), 55 (29), 57 (26), 70 (23), 71 (21) 88 (70).

(4) Pentane 1,5-bistriflate was reacted using method A. The crude product was bulb to bulb distilled at 80 °C (0.05 mm) for 0.5 h. Preparative VPC at 45 °C gave tetrahydropyran and 1,2-dioxepane **13**. 1,2-Dioxepane: ^1H NMR (CCl_4) δ 1.80 (6 H, m), 4.00 (4 H, m); IR (cm^{-1}) 1443 (s), 1360 (m), 1260 (m), 1130 (m), 1060 (s), 1000 (s), 977 (m), 918 (m), 863 (m), 791 (m); mass spectrum (70 eV) *m/e* (rel intensity) 27 (79), 28 (89), 29 (94), 31 (42), 39 (62), 41 (100), 42 (69), 43 (60), 44 (40), 55 (67), 56 (69), 102 (50).

Anal. Calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.69; H, 9.98.

(5) Hexane 1,6-bistriflate was reacted using method A. The crude product was bulb to bulb distilled at 100 °C (0.2 mm). Oxepane and 1,2-dioxocane **14** were obtained by preparative VPC at 45 °C. 1,2-Dioxocane: ^1H NMR (CCl_4) δ 1.70 (8, H, m), 3.87 (4 H, m); IR (cm^{-1}) 1445 (s), 1370 (m), 1190 (m), 1150 (m), 1105 (m), 1070 (s), 1020 (s), 1005 (s), 947 (s), 845 (w), 816 (w), 770 (w), 733 (w); mass spectrum (70 eV) *m/e* (rel intensity) 27 (69), 28 (63), 29 (100), 31 (57), 39 (59), 41 (95), 42 (59), 43 (51), 44 (40), 55 (68), 56 (23), 57 (51), 67 (37), 68 (35), 69 (32), 70 (45), 98 (20), 116 (27).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.08; H, 10.35.

(6) Heptane 1,7-bistriflate was reacted using method A. NMR analysis after 10 min reaction indicated that reaction was complete and the product consisted of 77% peroxide material (δ 3.8) and less than 10% ethereal material (δ 3.3). However, these products were apparently polymeric since less than 1% peroxide or ether were obtained after bulb to bulb distillation at 110 °C (0.1 mm).

(7) Octane 1,8-bistriflate was reacted by method A. NMR analysis after 10 min reaction indicated that reaction was complete and the product consisted of 75% peroxidic material (δ 3.8) and less than 5% ethereal material. Again, these products were apparently polymeric since less than 1% peroxide or ether were obtained after bulb to bulb distillation at 110 °C (0.1 mm).

(8) Pentane 2,4-bistriflate was reacted by method A. After bulb to bulb distillation at 50 °C (0.2 mm), the 3,5-dimethyl-1,2-dioxolane **15** was purified by preparative VPC at 40 °C. Approximately equal amounts of cis and trans isomers were obtained by NMR. The NMR of the mixture corresponded exactly with the NMR of 3,5-dimethyl-1,2-dioxolane kindly furnished by Dr. A. J. Bloodworth. ^1H NMR (CCl_4): δ 1.23 (3 H, d, J = 7 Hz), 1.26 (3 H, d, J = 7 Hz), 1.43–2.0 (0.5 H, m), 2.0–2.37 (1 H, m), 2.37–3.03 (0.5 H, m), 4.23 (1 H, sextet, J = 7 Hz), 4.27 (1 H, sextet, J = 7 Hz); IR (cm^{-1}) 1450 (s), 1380 (s), 1260 (m), 1150 (s), 1020 (m), 970 (w), 920 (w), 810 (m); mass spectrum (70 eV) *m/e* (rel intensity) 27 (38), 28 (45), 29 (64), 39 (25), 41 (41), 42 (38), 43 (100), 45 (29), 55 (20), 69 (34), 102 (48).

(9) Cyclohexane 1,4-bistriflate was reacted according to method B using tetrabromoethane as the solvent. No yield was determined, but the products obtained were benzene, 1,3-cyclohexadiene, 1-butanol, and 7-oxabicyclo[2.2.1]heptane in relative amounts of 1:2.9:3.7:1.4, respectively. No 2,3-dioxabicyclo[2.2.2]octane formed.

(10) Cyclooctane 1,5-bistriflate was prepared and used immediately, because of its instability, after aqueous workup and drying without removal of solvent. After reaction by method A, the products were removed by bulb to bulb distillation at 95 °C (0.1 mm). The presence of a large quantity of 1-butanol hampered interpretation of the NMR. The mixture was purified by preparative thin layer chromatography (0.25 mm, silica gel, $CHCl_3$), but no 9-oxabicyclo[3.3.1]nonane or 9,10-dioxabicyclo[3.3.2]decane was obtained by NMR.

Preparation of 2,3-Dioxabicyclo[2.2.1]heptane (7). The bistriflate derived from *cis*-cyclopentane-1,3-diol (**16**) was reacted with bis(tri-*n*-butyltin) peroxide (**32**) by method B (diffusion vacuum pump). NMR analysis indicated the presence of 2,3-dioxabicyclo[2.2.1]-heptane (**7**, 22%), 1-butanol (3%), and 2,3-epoxycyclopentan-1-one (**18**, 6%; for preparation see below). The crude product was purified further by bulb to bulb distillation at room temperature (0.05 mm) for 15 min, collecting the peroxide, alcohol, and epoxide in a dry ice cooled receiver and leaving most of the trichlorobenzene solvent in the distillation flask. The distillate was purified by preparative thin layer chromatography (silica gel, 0.5 mm, three developments with methylene chloride) at −20 °C. The peroxide (R_f 0.48–0.55) was eluted at 5 °C with methylene chloride, and the solvent was carefully removed at room temperature (150 mm). The epoxy ketone **16** shows an R_f of 0.3–0.48 under these conditions. NMR analysis indicates that the peroxide is pure: ^1H NMR (benzene-d_6) δ 0.91–1.20 (2 H, m), 1.35 (1 H, d, J = 10 Hz), 1.51–1.76 (2 H, m), 1.87 (1 H, d of quintets, J = 10, 2 Hz), 4.20 (2 H, br, s); IR (cm^{-1}) 1460 (w), 1430 (m), 1300 (w), 1210 (s), 1120–1170 (s), 1030 (s), 975 (w), 950 (m), 908 (s), 886 (s), 820 (m), 780 (w), 700 (m).

Hydrogenation of the endoperoxide (10 mg) in ethanol (3 mL) with 5% Pd/C (30 mg) gave cyclopentane-1,3-diol (11 mg) after filtration and solvent removal by rotary evaporation. VPC analysis (3 ft × 1/8 in. 10% Carbowax 20M on AW, DMCS-treated Chromosorb W, 130 °C) indicated that the product consisted of more than 98% *cis*-cyclopentane-1,3-diol (**16**)[7] (retention time 1.4 min) and less than 2% *trans*-cyclopentane-1,3-diol (**39**)[7] (retention time 2.0 min).

Attempted preparation of the endoperoxide by method A gave only 2-cyclopenten-1-one (**17**) and 2,3-epoxycyclopentan-1-one (**18**) in relative amounts of 1:2, respectively. All triflate was reacted after 5 s. Attempted purification of the endoperoxide by column chromatography on silica gel or Florisil led to total loss of peroxide. Purification by preparative VPC at 35 °C gave endoperoxide contaminated by considerable (ca. 40%) unknown impurities.

Using the same procedure starting from bistriflate prepared from *trans*-cyclopentane-1,3-diol (**39**)[7] the yield of endoperoxide was consistently lower, never more than 3%.

5,6-Dideuterio-2,3-bicyclo[2.2.1]heptane. The bistriflate was prepared from *trans,trans*-4,5-dideuterio-*cis*-1,3-cyclopentanediol (**24**) in the usual manner. The bistriflate was immediately reacted with bis(tri-*n*-butyltin) peroxide (**32**) as in the endoperoxide preparation above. After two careful thin layer chromatographies at −20 °C, the pure endoperoxide was analyzed by HA100 NMR in benzene-d_6, indicating the presence of 1.55 endo deuterium and 0.42 exo deuterium.

2,3-Epoxycyclopentan-1-one (18). Cyclopent-2-en-1-one (**17**, 10

mmol), bis(tri-*n*-butyltin) peroxide (**32**, 10 mmol, 5.25 mL), and chloroform (5 mmol, NMR standard) were heated at 42 °C, and the reaction was monitored by NMR. After 50 min, 43% epoxide was present along with 10% of starting olefin. (Longer reaction times led to loss of epoxide.) The volatile starting material and epoxide were removed from the tin-containing residue by bulb to bulb distillation at 42 °C (0.1 mm). The epoxide can be easily purified by column chromatography with a pentane/methylene chloride gradient, the epoxide being eluted before the olefin. An analytical sample of the epoxide was obtained by preparative VPC (40 °C): ^{1}H NMR (CCl_4) δ 1.8–2.5 (4 H, m), 3.17 (1 H, d, J = 2.3 Hz), 3.81 (1 H, br d, J = 2.3 Hz).

Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 61.26; H, 6.02.

Attempted reaction of cyclopent-2-en-1-one with *tert*-butyl tributyltin peroxide (2 h, 100 °C) gave no 2,3-epoxycyclopentan-1-one.

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References and Notes

(1) (a) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 89 (1973); (b) D. H. Nugteren and E. Hazelhof, *Biochim. Biophys. Acta*, **326**, 448 (1973); (c) C. Pace-Asciak and M. Nashat, *ibid.*, **388**, 243 (1975); (d) D. H. Nugteren, R. K. Beerthius, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **85**, 405 (1966).

(2) Recent reviews of prostaglandin biosynthesis: (a) B. Samuelsson, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **31**, 1442 (1972); (b) J. W. Hinman, *Annu. Rev. Biochem.*, **41**, 161 (1972); (c) M. P. L. Caton, *Prog. Med. Chem.*, **8**, 317 (1971); (d) T. O. Oesterling, W. Morazowich, and T. J. Roseman, *J. Pharm. Sci.*, **61**, 1861 (1972).

(3) (a) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975); (b) G. B. Kolata, *Science*, **190**, 770 (1975).

(4) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976); *Prostaglandins*, **12**, 715 (1976); S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, *Ibid.*, **12**, 897 (1976); R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. McGuire, F. Sun, N. Whittaker, S. Bunting, J. Salomon, S. Moncada, and J. R. Vane, *Ibid.*, **12**, 916 (1976).

(5) Review: R. R. Gorman, *J. Cyclic Nucleotide Res.*, **1**, 1 (1975).

(6) Review: R. D. Howells and J. D. McCown, *Chem. Rev.*, **77**, 69 (1977).

(7) M. F. Salomon, R. G. Salomon, and R. D. Gleim, *J. Org. Chem.*, **41**, 3983 (1976).

(8) (a) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957); (b) H. A. Brown, Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1955, No. 29M.

(9) Reviews on organometallic peroxides: (a) D. Brandes and A. Blaschette, *J. Organomet. Chem.*, **78**, 1 (1974); (b) G. Sosnovsky and J. H. Brown, *Chem. Rev.*, **66**, 529 (1966).

(10) (a) W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.*, **86**, 4237 (1964); (b) F. Welch, H. R. Williams, and H. S. Mosher, *Ibid.*, **77**, 551 (1955).

(11) A. J. Bloodworth and M. E. Loveitt, *J. Chem. Soc., Chem. Commun.*, 94 (1976).

(12) R. Criegee and G. Muller, *Ber.*, **89**, 238 (1956).

(13) We cannot account for the lower melting points (≃41–43 °C) reported previously for 7: (a) W. Adam and H. J. Eggelte, *J. Org. Chem.*, **42**, 3987 (1977); (b) N. A. Porter and D. W. Gilmore, *J. Am. Chem. Soc.*, **99**, 3503 (1977).

(14) M. H. Abraham, A. G. Davies, D. R. Llewellyn, and E. M. Thain, *Anal. Chim. Acta*, **17**, 499 (1957).

(15) D. J. Coughlin and R. G. Salomon, *J. Am. Chem. Soc.*, **99**, 655 (1977).

(16) B. Franzus, W. C. Baird, and J. H. Surridge, *J. Org. Chem.*, **33**, 1288 (1968).

(17) R. Hiatt in "Organic Peroxides", Vol. 3, D. Swern, Ed., Wiley, New York, 1972, p 1 ff.

(18) (a) F. Welch, H. R. Williams, and H. S. Mosher, *J. Am. Chem. Soc.*, **77**, 551 (1955); (b) O. L. Magelli and C. S. Sheppard, *Org. Peroxides*, **1**, 54 (1970).

(19) P. M. Jacobs and A. H. Soloway, *J. Org. Chem.*, **39**, 3427 (1974).

(20) (a) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975); (b) E. J. Corey, K. C. Nicolaou, M. Shibasaki, T. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).

(21) (a) K. R. Kopecky, J. H. van de Sande, and C. Mumford, *Can. J. Chem.*, **46**, 25 (1968); (b) K. R. Kopecky, J. E. Filby, C. Mumford, P. A. Lockwood, and J. Y. Ding, *ibid.*, **53**, 1103 (1975).

(22) P. G. Cookson, A. G. Davies, and B. P. Roberts, *J. Chem. Soc., Chem. Commun.*, 1022 (1976).

(23) A naturally occurring vinyl peroxide, rhodophytin, is known: W. Fenical, *J. Am. Chem. Soc.*, **96**, 5580 (1974).

(24) A. Simon and H. Arnold, *J. Prakt. Chem.*, **8**, 241 (1959).

(25) E. Buncel and A. G. Davies, *J. Chem. Soc.*, 1550 (1958).

(26) A. Rieche and J. Dahlmann, *Justus Liebigs Ann. Chem.*, **675**, 19 (1964).

(27) (a) F. F. Rust, F. H. Seubold, and W. E. Vaughn, *J. Am. Chem. Soc.*, **72**, 338 (1950); (b) F. H. Dickey and E. R. Bell, U.S. Patent 2 403 709; *Chem. Abstr.*, **40**, 6495 (1946); (c) G. A. Razuvaev, V. A. Dodonov, and S. N. Zaburdyaeva, *J. Org. Chem. USSR (Engl. Transl.)*, 659 (1970); (d) A. J. Bloodworth and I. M. Griffin, *J. Chem. Soc., Perkin Trans.* **1**, 195 (1975); D. H. Ballard, A. J. Bloodworth, and R. J. Bunce, *Chem. Commun.*, 815 (1969).

(28) A. K. Shubber and R. L. Dannley, *J. Org. Chem.*, **36**, 3784 (1971).

(29) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).

(30) R. A. Johnson, E. G. Nidy, L. Baczynskyj, and R. R. Gorman, *J. Am. Chem. Soc.*, **99**, 7738 (1977).

(31) N. A. Porter, J. D. Byers, R. C. Mebane, D. W. Gilmore, and J. R. Nixon, *J. Org. Chem.*, **43**, 2088 (1978).

(32) A mixture of epimeric dibromides which is difficult to separate is formed owing to Finkelstein reactions of the desired isomer.

(33) R. M. Wilson and F. Geiser, *J. Am. Chem. Soc.*, **100**, 2225 (1978).

(34) (a) D. J. Coughlin, R. S. Brown, and R. G. Salomon, *J. Am. Chem. Soc.*, **101**, 1533 (1979); (b) W. Adam and H. J. Eggelte, *J. Org. Chem.*, **42**, 3987 (1977).

(35) J. G. Traynhan and S. D. Elakovich, *Tetrahedron Lett.*, 155 (1973).

(36) C. D. Beard, K. Baum, and V. Grakauskas, *J. Org. Chem.*, **38**, 3673 (1973).

(37) H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76**, 2987 (1954).

(38) P. J. Stang, M. G. Mangum, D. P. Fox, and P. Haak, *J. Am. Chem. Soc.*, **96**, 4562 (1974).

(39) R. K. Crossland, W. E. Wells, and V. J. Shiner, *J. Am. Chem. Soc.*, **93**, 4217 (1971).

(40) V. S. Beckmann and R. Bamberger, *Justus Liebigs Ann. Chem.*, **574**, 76 (1951).

(41) P. S. Bailey, R. H. Perry, C. A. Cohen, and L. K. Beach, British Patent 844 825; *Chem. Abstr.*, **55**, 5379*f* (1961).

(42) D. Van Hauer, D. Tavernier, M. Anteunis, and M. Vandewalle, *Tetrahedron*, **30**, 105 (1974).

(43) W. C. Schumb, C. N. Satterfield, and W. L. Wentworth, "Hydrogen Peroxide", Reinhold, New York, 1955, p 553.