residue was treated briefly with excess ethereal diazomethane, concentrated in vacuo, and chromatographed in 300 g of silica gel, eluting with 5 L of a gradient 20–70% ethyl acetate–Skellysolve B solution. Fractions were assayed by thin-layer chromatography (AIX[5] system), and the first material eluted was combined to give 1.05 g of Vb, followed by 1.343 g of a mixture of epoxides (IV and its 10β,11β isomer). Vb was characterized as follows: IR (neat) 1745, 1715, 1650, 1615, 1440, 1375, 1240, 1210, 1160, 1100, 1070, 1020, 975, 840 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (d, J = 11 Hz), 6.54 (dd, J = 14.5, 11 Hz), 5.96 (dd, J = 14.5, 6.5 Hz), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.16 (d, 2 H), 2.03 (s, 3 H), 0.89 (t, 3 H); mass spectrum, m/e 394 (M^+), 362, 352, 334, 330, 320, 302, 291, 288, 284, 281, 274, 270, 259, 251, 245, 243, 221, 199, 189, 99, 71, 55, 43. In the ^{13}C NMR spectrum, absorptions were seen at 13.9, 21.1, 22.5, 24.7 (2 carbons), 25.4, 26.7, 31.5, 33.5, 34.3, 51.4, 51.8, 74.0, 126.7, 127.6, 129,7, 131.2, 137.6, 139.5, 168.1, 170.1, and 173.9 ppm downfield from Me_4Si (Varian CFT-20 instrument at 20 MHz).

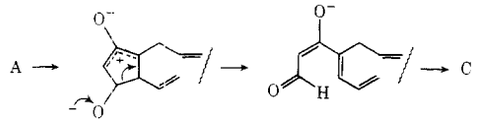
If the diazomethane treatment was omitted, the acid Va was isolated by chromatography on acid-washed silica gel, eluted with 25–50% EtOAc–Skellysolve B, followed by rechromatography of combined fractions on a reversed-phase column (C-18 Porasil B[6]), and eluted with 80% acetonitrile–20% water. The NMR spectrum was very similar to that of the diester Vb except that the 3-proton singlet at δ 3.75 was absent, and the proton which in Vb occurred at δ 7.15 was shifted downfield to δ 7.3. Esterification of this material with diazomethane gave the diester Vb, identical with that described above.

Analogous products were produced from (15S)-PGA_2 methyl ester acetate.[2]

Registry No.—III, 35730-43-9; IV, 38310-83-7; 10β,11β-IV, 38344-07-9; Va, 64200-85-7; Vb, 64200-84-6; H_2O_2, 7722-84-1.

References and Notes

(1) R. G. Salomon and M. F. Salomon, *J. Am. Chem. Soc.*, **99**, 3501 (1977).
(2) W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Am. Chem. Soc.*, **99**, 1222 (1977); compound III was first reported by A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Lett.*, 5185 (1969).
(3) A. J. Scott, "Interpretation of the UV Spectra of Natural Products", MacMillan, New York, N.Y., 1964.
(4) We are indebted to S. A. Mizsak of these laboratories for the 100-MHz NMR spectrum and decoupling data and to J. A. Woltersom for isolation of Va.
(5) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).
(6) Waters Assoc., Milford, Mass.
(7) A referee has suggested the following as an alternative mechanism:



He suggested that facile electrocyclic cyclopentenyl to pentadienyl cation rearrangement would be promoted by concomitant C=O bond formation and charge neutralization.

Reaction of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate with Aqueous Hydroxide. Axial vs. Equatorial Displacement of Methoxide

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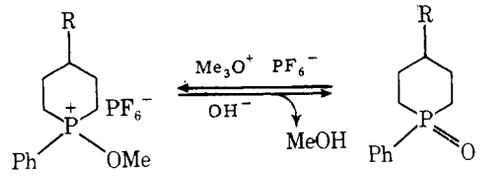
Nucleophilic displacement of methoxide by aqueous hydroxide on phosphorus in cis and trans isomers of 4-methyl-1-methoxy-1-phenylphosphorinanium hexafluorophosphate (**1a**)[1] was observed to occur with 100% inversion of configuration at the phosphorus atom (eq 1).[2] Labeled oxygen studies showed 8–9% retention of configuration due to attack at carbon.[2] We have recently synthesized *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinane 1-oxide (**2b**),[3a] and wished to investigate the rates at which axially vs. equatorially P-bonded alkoxide was hydrolyzed from **1b** in these conformationally biased systems derived from **2b**. We were also interested in determining ratios of stereoisomeric phosphine oxide products obtained by base cleavage. Configurational assignments for *cis*- and *trans*-**1b** and -**2b** were previously made[3a] and were based upon proton NMR spectra. These assignments have been subsequently verified through an x-ray structure analysis of *cis*-**2b**.[4]

Table I. Some Results of Heterogeneous Cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate at 24 °C

Wt of salt, g	Solvent	% retention Cis salt	% retention Trans salt
0.284	9 mL of 0.50 N NaOH	11.3	4.0
0.140	4.5 mL of 0.50 N NaOH[a]		2.7
0.284	30 mL of 0.50 N NaOH[b]	5.8	
0.284	32 mL of 1.00 N NaOH in 25% dioxane	13.7	12.9

[a] Solution was refluxed. [b] 15 mL of 1.00 N NaOH added to a suspension of **1b** in 15 mL of water.



1a, R = Me
b, R = *t*-Bu

2a, R = Me
b, R = *t*-Bu

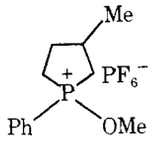
(1)

The configurationally pure 4-*tert*-butyl oxides were converted by a previous procedure[2] into their alkoxy salts (eq 1) with complete retention of configuration. The salts were characterized by proton NMR spectroscopy and elemental analysis.

Unlike the 4-methyl analogues (**1a**), these salts were ideally suited to careful isomeric oxide product studies by proton NMR spectroscopy because of the presence of separated *tert*-butyl proton signals for the isomeric phosphorinane derivatives. Initially, cleavage of *cis*- and *trans*-**1b** was carried out under heterogeneous conditions because of the sparing solubility of the hexafluorophosphate salts in water. Inability to reproduce product ratios led to the belief that nucleophilic attack by hydroxide on methoxy carbon, as previously demonstrated with **1a**,[2] was influenced in some way by the heterogeneous nature of the reaction. Some results are shown in Table I.

However, when the reaction was conducted homogeneously by dissolving the salts in 50% aqueous dioxane and then adding aqueous sodium hydroxide, *no* retention was detected either by NMR or oxygen-18 labeling experiments.

Previous work on the phosphorinanium system, **1a**, and the cis and trans phospholanium salts (**3**) was conducted under



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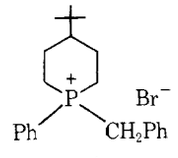

4

heterogeneous conditions and retention of configuration at phosphorus due to attack at methoxy carbon was found to be 9 and 11%, respectively.[2] We are now convinced that attack at carbon could have been obviated by homogeneous treatment with base. From the results in Table I it seems very reasonable that attack of hydroxide at carbon is the result of a phase phenomenon and not a solvent effect.

Luckenback has reported different stereochemical results with homogeneous vs. heterogeneous reaction conditions in base-promoted cleavage reactions at chiral phosphorus in

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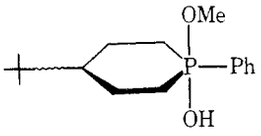
Table II. Phosphine Oxide Formation upon Hydroxide Cleavage of *cis*- and *trans*-4

	trans-4	*cis*-4
Heterogeneous results	23.4 trans	65.0 trans
(% *cis*- or *trans*-**2b**)	76.6 cis	35.0 cis
Homogeneous results	20.6 trans	65.6 trans
(% *cis*- or *trans*-**2b**)	79.4 cis	34.4 cis

acyclic phosphonium salts,[5] although attack at carbon is obviously not occurring in these salts. This work promoted us to reexamine homogeneous vs. heterogeneous cleavage of isomeric benzylphosphorinanium salts[2,3a] (**4**) with aqueous NaOH. In this case we observed no significant differences in the distribution of isomeric oxides (**2b**) formed as seen in Table II.

The pseudo-first-order rate constants for the cleavage of *cis*- and *trans*-**1b** were determined in 50% dioxane/standard pH 7 buffer at 25 °C and calculated to be as shown in Chart I.

That the rate constants are nearly identical indicates virtually no influence on reaction velocity by the *tert*-butyl group or the orientation of the methoxy substituents at phosphorus (axial or equatorial). This supposes the unlikelihood of compensating effects on reaction rate by interaction of the *tert*-butyl group and methoxy substituent for the two isomers. The transition states probably do not resemble products because the oxides are known to differ in thermodynamic stability.[3a] Evidently the ground-state energies of the two disastereomeric salts are comparable, since stabilities of the presumed diastereomeric pentacovalent intermediates (**5**) would be expected to be very similar. Where the leaving group is benzyl (**4**), in an otherwise identical system, the rate constants for inversion of the two isomers were also found to be nearly equal,[3b] probably for the same reasons.



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Alkaline cleavage of alkoxyphosphorinanium salts under homogeneous conditions provides an excellent synthetic method for complete stereospecific transformations of cis or trans phosphorinane 1-oxides, via their alkoxy salts, into opposite configuration.

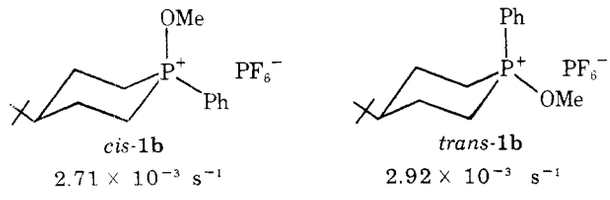
Experimental Section[7]

Melting points are uncorrected and were determined in sealed tubes in a Thomas Hoover melting point apparatus. NMR spectra were obtained by use of a Perkin-Elmer R12-B spectrometer. Oxygen-18 analyses were performed by West Coast Technical Service, Inc., Cerritos, Calif.

***cis*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate (*cis*-1b).** *cis*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinane 1-oxide (*cis*-**2b**) (0.50 g, 0.0020 mol) dissolved in 5 mL of dry methylene chloride was added in a dry atmosphere to a suspension of 0.439 g (0.00213 mol) of trimethyloxonium hexafluorophosphate in 10 mL of dry methylene chloride. The mixture was magnetically stirred overnight at room temperature and any insoluble residue was removed by centrifugation and decantation. After removal of the solvent in vacuo the resulting white residue was extracted with five 10-mL portions of dry ether, and the solid residue was dried overnight in vacuo to give a 64% yield of *cis*-**1b**. Recrystallization was accomplished by dissolving the dried material in dry methylene chloride, removal of insoluble material by centrifugation, and addition of petroleum ether to the decantate to the cloud point. The resulting solution was cooled and the crystals were removed by filtration in a dry atmosphere: mp 140–142 °C; NMR ($CDCl_3$) δ 0.93 (s, 9, *t*-Bu), 3.83 (d, OCH_3), 7.85 (m, C_6H_5).

Anal. Calcd for $C_{16}H_{26}OP_2F_6$: C, 46.84; H 6.39. Found: C, 46.79; H, 6.65.

Chart I



***trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate (*trans*-1b).** The preparative procedure was the same in all respects as for the cis salt: mp 158.3–159.8 °C; NMR ($CDCl_3$) δ 0.83 (s, *t*-Bu), 3.81 (d, OCH_3), 8.70 (m, C_6H_5).

Anal. Calcd for $C_{16}H_{26}OP_2F_6$: C, 46.84; H, 6.39. Found: C, 47.10; H, 6.44.

Heterogeneous Base Cleavage of *cis*-1b and *trans*-1b in Aqueous Base. The cis or trans hexafluorophosphate salt (**1b**) (0.284 g) was added to 9.0 mL of 0.50 N NaOH and the mixture was stirred for 3 h at room temperature. The resulting reaction mixture was extracted with five 25-mL portions of methylene chloride and the combined extracts were flash evaporated. A Kugelrohr distillation was performed on the residue: bp 205 °C (0.15 mm); overall yields, 88.2% from *cis*-**1b** and 83.6% from *trans*-**1b**. Compositions of product mixtures are given in Table I. Other reactions listed in Table I followed essentially the same procedure. NMR analysis of the residue prior to distillation yielded the same oxide composition as the distillate in every case.

Homogeneous Base Cleavage of *cis*-1b and *trans*-1b. The cis or trans hexafluorophosphate salt (**1b**) (0.149 g) was dissolved in 10 mL of dioxane in a 50-mL round-bottom flask with the aid of magnetic stirring. Water (10 mL) was then added with stirring until the salt dissolved. This was followed by the addition of 20 mL of 1.00 N NaOH, and the mixture was stirred for 3 h at room temperature. The reaction mixture was extracted with five 25-mL portions of methylene chloride, the combined extracts were evaporated, and an NMR spectrum was recorded on the residue dissolved in $CDCl_3$. Only the oxide isomer corresponding to inversion of configuration could be detected in each case. NMR analysis of the distillate resulting from distillation of the residue gave the same results.

Preparation of Isotopically Labeled *cis*-1b and *trans*-1b. A mixture of *cis*- and *trans*-**2b** (1 g; 9.7% trans/90.3% cis) was placed in an ampule with 5 mL of 10% $D_2{}^{18}O$ which had had hydrogen chloride gas introduced to a pH of 2. The ampule was sealed and the contents were heated to 125 °C in an oil bath for 24 h. The $D_2{}^{18}O$ was then removed by distillation and the residue was vacuum distilled to afford an 82% recovery of the oxide (24.5% trans/74.5% cis). The labeled oxides were separated by preparative thin-layer chromatography[3a] and each was alkylated with trimethyloxonium hexafluorophosphate as described above. [Two separate runs with $D_2{}^{18}O$ (under nonidentical conditions) were necessary in order to obtain sufficient amounts of labeled *trans*-**2b**.] Mass spectral analysis of the labeled salts (**1b**) gave the following results: *trans*-**1b**, 1.173 atom % ^{18}O; *cis*-**1b**, 0.220 atom % ^{18}O.

Homogeneous Base Cleavage of Oxygen-18 Labeled *cis*- and *trans*-1b. The same procedure was followed as detailed above for homogeneous cleavage of nonlabeled **1b**. Mass spectral analysis of product oxides showed: *trans*-**2b**, 0.204 atom % ^{18}O; *cis*-**2b**, 0.202 atom % ^{18}O; natural abundance, 0.204 atom %.

Heterogeneous Cleavage of *cis*- and *trans*-4. A published procedure was followed.[6]

Homogeneous Clevage of *cis*- and *trans*-4. The *cis*- or *trans*-4 salt (0.250 g) was dissolved in 4.5 mL of 1.00 N NaOH and the solution was heated under reflux for 9 h. The remainder of the procedure was identical with literature instructions (see ref 6). Results are given in Table II. Isomer composition is unaffected by distillation.

Pseudo-First-Order Rate Constant Determinations for Cleavage of *cis*- and *trans*-1b. The rate constants for the hydrolysis of these salts were determined at 275.0 nm and 25 °C in a standard pH 7 buffer in 50% water–50% dioxane (v/v). Under conditions of the stereochemical experiment the reaction was too rapid for rate constant determination.

Acknowledgments. We are grateful for financial support from the National Science Foundation (Grant GP 38756X) and for helpful suggestions from Dr. James L. Jensen.

Registry No.—*cis*-**1b**, 64457-45-0; *trans*-**1b**, 64457-47-2; *cis*-**2b**, 61332-82-9; *trans*-**2b**, 61332-81-8; *cis*-**4**, 61332-79-4; *trans*-**4**, 61332-80-7; trimethyloxonium hexafluorophosphate, 12116-05-1.

References and Notes

(1) Cis and trans designations are in accordance with *Chemical Abstracts* usage by which, for example, the cis isomer has the senior groups (as defined by the sequence rule) on the same side of the reference plane of the ring: cf. *Chem. Abstr.*, **76**, 85 I (1972); *J. Chem. Inf. Comput. Sci.*, **15**, 67 (1975).
(2) K. L. Marsi, *J. Org. Chem.*, **40**, 1779 (1975).
(3) (a) K. L. Marsi, J. L. Jasperse, F. M. Llort, and D. B. Kanne, *J. Org. Chem.*, **42**, 1306 (1977). (b) The pseudo-first-order rate constants for *cis*- and *trans*-**4** for the inversion component of benzyl cleavage at phosphorus are, respectively, 0.96×10^{-3} and 1.16×10^{-3} s^{-1} at 80.0 °C in 1.28 N NaOH (50% aqueous ethanol) (ref 3a).
(4) Personal communication from K. D. Berlin and D. van der Helm.
(5) R. Luckenbach, *Z. Naturforsch. B*, **31**, 1127 (1976); R. Luckenbach, *Phosphorus*, **3**, 117 (1973), and references contained therein.
(6) K. L. Marsi and R. T. Clark, *J. Am. Chem. Soc.*, **92**, 3791 (1970); K. L. Marsi, *J. Org. Chem.*, **40**, 1779 (1975); ref 3a.
(7) Stereochemical relationships among 4-*tert*-butylphosphorinane derivatives mentioned in this paper were established previously (see ref 3a).

Atomic Oxygen. 8. Reactions of Methylenecycloalkanes with Oxygen (^3P) Atoms

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The reactions of atomic oxygen with unsaturated organic compounds have demonstrated that the primary reactive intermediates can undergo extensive rearrangement before forming isolable oxygenated products. The examination of the product mixture allows one to determine two important factors of the reaction: the orientation of the oxygen atom addition to the molecule and the relative migratory aptitudes of substituents on the molecule's unsaturated site. The reactions of methylenecycloalkanes with $O(^3P)$ illustrate the effects of ring size and strain on the former of these two factors.

In this study, conditions for the gas-phase production and reaction of atomic oxygen were derived from the pioneering work of Cvetanovic and co-workers.[2] Ground-state (^3P) oxygen atoms were produced by the mercury photosensitized decomposition of nitrous oxide.[3] The reaction apparatus and conditions have been described previously.[4] The total pressure before photolysis was 0.9 atm, and the reaction temperature was 25–30 °C.

The products of the reactions of methylenecycloalkanes (**1**) with atomic oxygen consisted of spiro epoxides (**2**), cycloalkanecarboxaldehydes (**3**), cycloalkanones (**4**), and alken-2-ones (**5**). Product yields are listed in Table I. A probable mechanism for the formation of these products is shown in Scheme I.

Several features of this mechanism are of interest. Previous research has shown that triplet oxygen atoms add to olefins to produce carbon–oxygen 1,3-biradicals. In the case of an unsymmetrical olefin, the orientation of addition parallels that obtained when a monoradical adds to the olefin. The direction of addition is controlled by radical stability. In the reactions of methylenecycloalkanes, the orientation of addition is approximately indicated by the ratio of aldehydic product **3** to ketonic products **4** and **5**. These ratios in the series of methylenecyclobutane (2.9), methylenecyclopentane (4.6), and methylenecyclohexane (21) demonstrate that increasing the ring size increases the stability of the cycloalkyl radical site (intermediate **6**) relative to the stability of the methylene radical (intermediate **7**).[5]

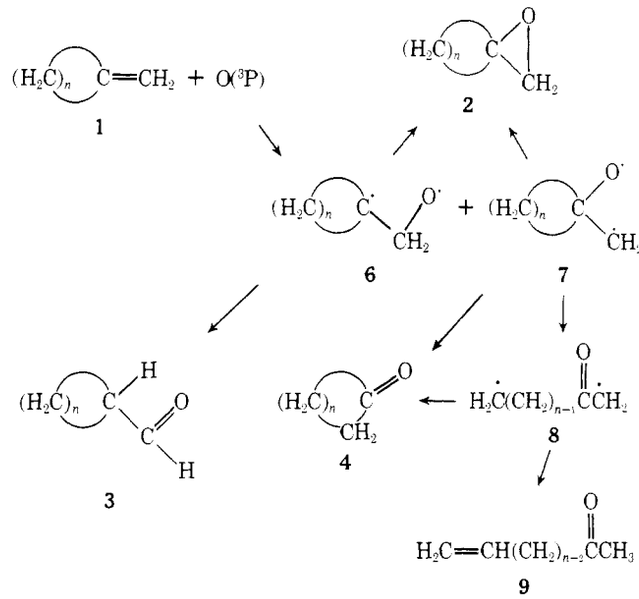
Another aspect of the proposed mechanism is the ring opening of 1,3-biradical **7** to yield the 1,ω-biradical **8**. It has been noted in previous atomic oxygen studies[6,7] that the rearrangement of alkyl radicals is partially accomplished by detachment of the migrating radical from the remainder of the molecule. In acyclic olefins, these detached alkyl radicals can be scavenged by added molecular oxygen. The formation of biradical **8** is analogous to this process.

Table I. Product Yields[a] from Reactions of $O(^3P)$ with Methylenecycloalkanes

Reactant	Product yield, % 2	3	4	5
1a (n = 3)	35	29	7.1	2.9
1b (n = 4)	57	19	2.6	1.5
1c (n = 5)	56	26	0.81	0.40

[a] Product yields are based on the measured amounts of nitrogen produced by the mercury photosensitized decomposition of nitrous oxide. Reproducibility among reactions was ±10% of the stated yields.

Scheme I



Relative rate constants for the reactions of the methylenecycloalkanes were also determined. These rates (relative to 2-methylpropene as 1.00) were: methylenecyclobutane, 1.05; methylenecyclopentane, 1.81; and methylenecyclohexane, 0.99. The same reactivity pattern has been observed for the addition of dichlorocarbene to these olefins,[8] but the origin of the enhanced reactivity of methylenecyclopentane is not clear.

Experimental Section

Reaction Technique. Procedures for the reaction of atomic oxygen with organic substrates have been described previously.[4] The olefins used were obtained from Chemical Samples Co. and were determined to be of >99% purity. Analyses of unreacted olefins recovered after photolysis showed that the reactant was not isomerized under the reaction and workup conditions used. The reaction of methylenecyclopropane with $O(^3P)$ was attempted several times, but this substrate polymerized rapidly under the reaction conditions.

Relative rate constants of the methylenecycloalkanes vs. cyclopentene were determined by the method of Cvetanovic[2] and converted to the usual standard, 2-methylpropene, using the figure $k_{cyclopentene}/k_{2\text{-methylpropene}} = 1.19$. Reaction temperature during these studies was controlled at 24 ± 2 °C.

Product Analysis. Products of the reaction of **1a** were analyzed by VPC on a dinonyl phthalate column at 99 °C. Product mixtures from **1b** and **1c** were analyzed on an XE-60 column at 132 and 155 °C, respectively.

Authentic samples of all products were available for comparative VPC retention times and, where possible, comparative NMR, IR, and

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