DMF). The overall yield of **8** from L-aspartic acid was ca. 50%, and the sequence could conveniently be carried out on molar scale.

Reaction of **8** with 2-lithio-2-(trimethylsilyl)-1,3-dithiane[12] (THF, -78°C) gave the substituted dithiane derivative **9** in 70-80% yield. Direct aldol condensation of the enolate derived from **9** (LDA, THF, -78 °C) with excess acetaldehyde[13] gave a 97% yield of an approximately 1:1 mixture of the desired trans-*R* isomer **10** and the trans-*S* epimer **11**. A small amount (<5%) of the cis-*R* isomer was also isolated. In order to achieve stereocontrol in the preparation of **10**, an alternate approach was examined. Direct acylation of **9** (2 equiv, of LDA, THF, -78 °C, inverse quench into 2.0 equiv of *N*-acetylimidazole, THF, -78 °C)[14] provided acetyl compound **12** in 82% yield on the basis of recovered **9**. Alternatively, the mixture of isomers produced in the aldol reaction could be oxidized to **12** (TFAA-Me_2SO/Et_3N, CH_2Cl_2, -78 °C)[15] in 88% yield. In both cases, only one isomer of **12** could be detected, and this was assigned the thermodynamically preferred trans stereochemistry on the basis of the small (2.1 Hz) coupling constant between the azetidinone ring protons. Reduction of **12** with excess K-Selectride (KI, ether, 25 °C) gave an 87% yield of a 9:1 mixture of **10** and **11**. Thus, by this method, the stereocenters at C5 and C6 are completely specific, with the C8 center 90% controlled. Compounds **10** and **11** are readily separable at this point, and the undesired hydroxyethyl isomer **11** can be recycled by reoxidation to **12**.

Compound **10** is readily converted into carboxylic acid **14** (Scheme I, intermediate B) via a two-step process. Hydrolysis of **10** ($HgCl_2$, HgO, aqueous CH_3OH, Δ)[12] provided silyl ketone **13** in 93% yield. Warming **13** with a small excess of hydrogen peroxide in aqueous methanol gave carboxylic acid **14** in 76% yield after crystallization. The required keto ester chain was homologated by using a slight modification of the method recently reported by Masamune.[16] Thus, **14** was converted to imidazolide **15** (carbonyl diimidazole, THF, room temperature), which was treated in situ with the magnesium salt of the mono *p*-nitrobenzyl ester of malonic acid (THF, room temperature) to provide keto ester **16** in 86% yield. Brief treatment of **16** with methanolic HCl effected removal of the N-silyl protecting group to give **17** in >90% yield.[17] The desired cyclization precursor **18** was prepared in 90% yield by diazo exchange with *p*-carboxybenzenesulfonyl azide (Et_3N, CH_3CN, 0-20 °C).[18]

Previous model work[19] had shown rhodium(II) acetate to be the catalyst of choice for the carbenoid-mediated cyclization of diazo azetidinones such as **18**. In the present case, thermolysis of **18** at ca. 80 °C in benzene or toluene containing a catalytic amount of rhodium(II) acetate (substrate/catalyst ca. 1000:1) smoothly produced bicyclic keto ester **19** in essentially quantitative yield. To our knowledge, this is the most efficient method yet devised to construct a highly strained and reactive bicyclic β-lactam.

The final phase of the synthesis was accomplished by activating the keto ester of **19** by conversion to vinyl phosphate **20** (ClP(O)$(OPh)_2$, catalytic DMAP, *i*-Pr_2NEt, CH_3CN, 0 °C). Although this material could be isolated and carried on in a separate step, it was more convenient to directly treat it in situ with *N*-[[(*p*-nitrobenzyl)oxy]carbonyl]cysteamine[3] (*i*-Pr_2NEt, CH_3CN, -5 °C) to provide the bis-protected thienamycin derivative **21** in 70% overall yield. Catalytic hydrogenation of **21** (H_2, 40 psi, 10% Pd/C) gave **1** identical in all respects with natural thienamycin.

The use of the above general route for the preparation of thienamycin analogues will be reported in due course.

Acknowledgment. We thank Dr. C. Shunk for the preparation of numerous starting materials; J. Smith, H. Flynn, and Dr. B. Arison for mass spectral and 300-MHz NMR measurements; J. P. Gilbert and staff for microanalytical determinations; and J. Kahan for antibacterial assays.

Supplementary Material Available: Physical constants, optical rotations, infrared and proton magnetic resonance spectra for compounds **4**, **8**, **10**, **12**, **14**, **18**, **19**, and **21** (2 pages). Ordering information is given on any current masthead page.

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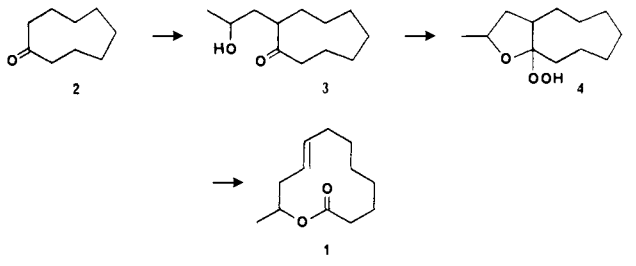
Received April 14, 1980

Fragmentation Reactions of α-Alkoxy Hydroperoxides and Application to the Synthesis of the Macrolide (±)-Recifeiolide

Sir:

As part of an investigation into the generation and synthetic usefulness of α-alkoxy hydroperoxides, we have studied new applications of the metal ion catalyzed fragmentation reactions of peroxides. Although a great deal is known about the mechanism of these reactions due to the elegant work of Kochi,[1] very few synthetic applications have been reported. We report our initial efforts which have led to a very short and efficient synthesis of (±)-recifeiolide (**1**), a naturally occurring macrolide isolated from the fungus *Cephalosporium recifei*.[2,3]

We have found that monoalkylation of the lithium enolate of cyclononanone with propylene oxide could be cleanly effected at -78 °C by the addition of 2.4 equiv of $AlMe_3$ to give the keto alcohol **3**[4-6] (80% yield, 96% based on recovered **2**). Treatment



2 3 4

1

(12) (a) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Am. Chem. Soc.*, **89**, 431 (1968); (b) E. J. Corey, D. Seebach, and R. Freedman, *ibid.*, **89**, 434 (1968).

(13) The procedure used for this reaction was analogous to that reported in ref 3. The configurations of the various hydroxyethyl isomers were established by comparison of spectra to those of related compounds of unambiguous structure. See: F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, **45**, 1130 (1980).

(14) For a related example, see: S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, 2757 (1976).

(15) S. L. Huang, K. Omura, and D. Swern, *Synthesis*, 297 (1978); K. Omura and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).

(16) D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, **18**, 72 (1979).

(17) The Merck Process Research Department has prepared compound **17** in racemic form via an alternate synthetic route which is potentially amenable to the production of thienamycin on a commercial scale; see: D. G. Melillo, I. Shinkai, K. M. Ryan, T. M. H. Liu, and M. Sletzinger, *Tetrahedron Lett.*, **21**, 2783 (1980). Both approaches employ similar strategy for the ultimate conversion of **17** to thienamycin.

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(19) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 31 (1980).

(1) For a review, see: J. K. Kochi, "Free Radicals", Wiley-Interscience, New York, 1973, Vol. 1, Chapter 11, Vol. 2, Chapter 23.

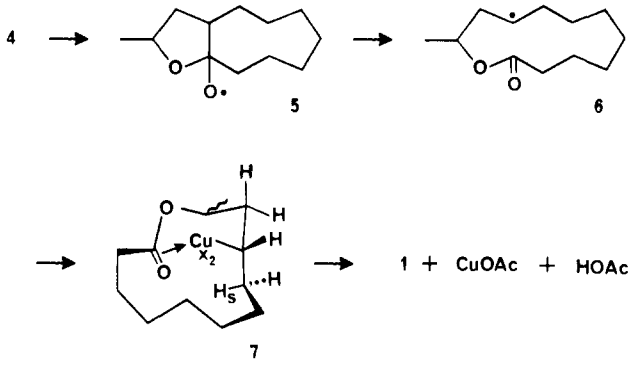
(2) (a) R. F. Vesonder, F. H. Stodola, L. J. Wickerham, J. J. Ellis, and W. K. Rohwedder, *Can. J. Chem.*, **49**, 2029 (1971); (b) R. F. Vesonder, F. H. Stodola, and W. K. Rohwedder, *Can. J. Biochem.*, **50**, 363 (1972).

(3) For previous syntheses, see: E. J. Corey, P. Ulrich, and J. M. Fitzpatrick, *J. Am. Chem. Soc.*, **98**, 222 (1976); H. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, **59**, 755 (1976); K. Narasaka, M. Yamaguchi, and T. Mukaiyama, *Chem. Lett.*, 959 (1977); K. Utimoto, K. Uchida, M. Yamaya, and H. Nozaki, *Tetrahedron. Lett.*, 3641 (1977); B. M. Trost and T. R. Verhoeven, *ibid.*, 2775 (1978).

(4) Satisfactory spectroscopic data [^1H NMR, IR, mass spectrum (MS)] were obtained for all compounds. All experimental procedures and spectral data are included in the supplementary material.

0002-7863/80/1502-6163$01.00/0

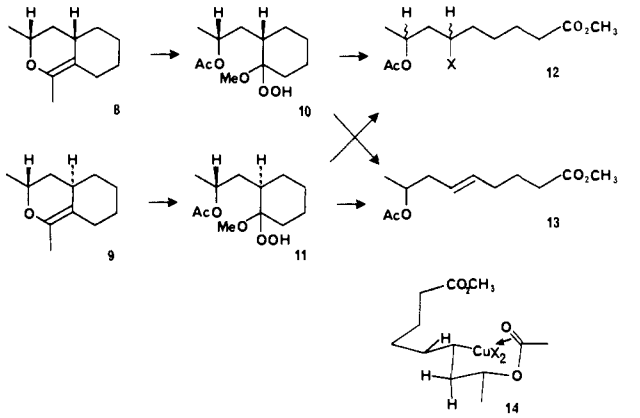
Scheme I



of **3** with 30% H_2O_2 in AcOH gave the alkoxy hydroperoxide **4** isolated as a mixture of stereoisomers (99% based on 57% conversion). The addition of $FeSO_4$ to a solution of **4** in MeOH saturated with $Cu(OAc)_2$ resulted in fragmentation to give the lactone recifeiolide (**1**) in 96% yield.[7] Inspection of the crude NMR data indicated this was a highly regio- and stereoselective process, as no isomeric olefins could be detected.

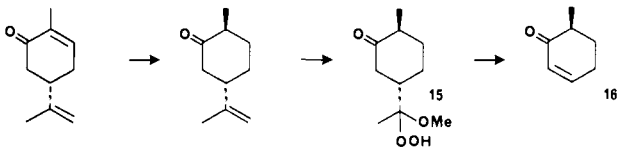
The mechanism outlined in Scheme I is analogous to what has been proposed for other metal ion promoted reactions of peroxides.[1] Transfer of an electron from Fe^{2+} to the peroxide produces the oxy radical **5**. Weakening of the central C–C bond by antiperiplanar overlap with the lone pair on the tetrahydrofuran oxygen leads to cleavage of that bond and formation of the carbon radical **6**. Oxidative coupling with $Cu(OAc)_2$ yields a well-precedented[1] alkyl copper intermediate (**7**). If we invoke that the alkyl copper intermediate **7** should exist (a) as a *Z* ester, stabilized by n (ether O) → σ^* (C=O) overlap (anomeric effect),[8] and (b) be internally coordinated by the ester to form a pseudo-six-membered ring, then only one of the four β hydrogens is available for a syn-β-elimination process (H_s, Scheme I).[1,9] β-Elimination of this hydrogen would then lead specifically to the trans olefin with the observed regiochemistry. Similar directive effects have been reported in the literature.[9]

Results obtained from a study of isomeric peroxides **10** and **11** are consistent with the proposed carbon radical intermediate which can be oxidatively intercepted by cupric salts to yield products of substitution and elimination. Peroxides **10** and **11** are obtained from the dihydrofurans **8** and **9**,[10] respectively, by ozonolysis in methanol. Whereas acid-catalyzed addition of H_2O_2 to an enol



ether generates an α-alkoxy hydroperoxide at the α carbon of the enol ether, ozonolysis in an alcoholic solvent produces an α-alkoxy hydroperoxide at the β carbon.[11] Treatment of either pure **10** or **11** with cupric halides CuX_2 (X = Cl,Br,I) under a variety of conditions gave the same approximately 1:1 mixture of isomeric alkyl halides **12**, in 60–80% yield. The isomeric alkyl halides presumably derive by a nonselective ligand-transfer process from the cupric salt to a carbon radical. Treatment of **10** or **11** with $Cu(OAc)_2/FeSO_4$ led to a mixture of olefin isomers (75% yield) of which the major isomer (70%) was the trans homoallylic olefin **13**.[12] A similar directive effect as was observed with **4**, via the alkyl copper intermediate **14**, could be operative in this case.

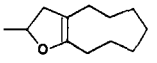
As an example of the use of this process in a degradative sense, a very facile synthesis of (+)-6-methylcyclohex-2-enone (**16**) has been developed starting from (−)-carvone. Reduction[13] of



(−)-carvone, separation of the major (3:1) trans isomer, and ozonolysis in methanol led to the formation of the methoxy hydroperoxide **15**. Treatment of **15** with $Cu(OAc)_2/FeSO_4$ led to **16**, $[\alpha]^{20}_D$ +66.5°, in 76% yield, under essentially neutral conditions. In this case, the ketone functionality appears to direct elimination of the presumed β-copper intermediate to form the α,β-unsaturated enone. This methodology should be readily applicable to the synthesis of (−)-6-methylcyclohex-2-enone by the use of *cis*-dihydrocarvone derived from (−)-carvone or *trans*-dihydrocarvone derived from (+)-carvone. As far as we know, this is the first reported synthesis of this potentially useful chiral substrate.

The simple substrates chosen for this study illustrate some of the basic reactions of peroxides with metal ions and the directive effects operative in the oxidative elimination reactions. More suitably substituted substrates are being studied which could direct the cupric reagents stereoselectively in the ligand-transfer reactions. The application of this methodology to the synthesis of ionophore

(5) The dihydrofuran **17** was obtained quantitatively upon distillation and was fully characterized (^{1}H NMR, IR, MS, combustion analysis).



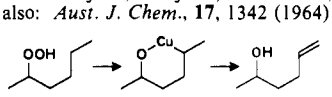
17

(6) Work is in progress to study the generality of this enolate anion epoxide opening reaction.

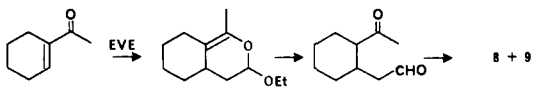
(7) The macrolide obtained in this manner is identical (^{1}H NMR, IR, MS) with natural recifeiolide. We are grateful to Professor E. J. Corey for supplying the spectral data.

(8) P. Deslongchamps, *Heterocycles*, **7**, 1271 (1977). The author cites Professor A. Eshenmoser as the first to explain the relative stability of *Z* and *E* esters by application of the anomeric effect.

(9) An alkyl copper intermediate was invoked to explain the preponderance of terminal olefin formation in the remote oxidation of aliphatic hydroperoxides: Z. Cerovic, J. Dimitrijevic, G. Djokic, and T. Srnic, *Tetrahedron*, **35**, 2021 (1979). See also: *Aust. J. Chem.*, **17**, 1342 (1964).



(10) The synthesis of **8** and **9** utilized an inverse-demand heterodiene Diels–Alder reaction, the details of which will be reported shortly. We have studied the analogous reaction with propyl propenyl ether followed by hydrolysis which results in the net overall Michael addition of a CH_3CH_2CHO unit with control of stereochemistry. While this work was in progress, similar results were reported in a related system: B. B. Snider, *Tetrahedron Lett.* **21**, 1133 (1980).



(11) Philip S. Bailey, "Ozonation in Organic Chemistry", Academic Press, New York, 1978, Vol. 1, Chapter 7.

(12) NMR analysis of the reaction mixture with the shift reagent $Eu(fod)_3$ indicated a 70:15:10:5 mixture of four olefin isomers which could not be separated by chromatography (VPC, high-pressure liquid chromatography). The structure of the minor isomers could not be conclusively identified. The structure of the major product (**9**) was concluded on the basis of the following spectral evidence: ^{1}H NMR ($CDCl_3$, Me_4Si standard) δ 5.40 (2 H, m), 4.90 (1 H, sextet, J = 7 Hz), 3.67 (3 H, s), 2.25 (6 H, m), 2.01 (3 H, s), 1.6 (2 H, m), 1.26 (3 H, d, J = 7 Hz); irradiation at δ 1.26 collapsed the sextet at δ 4.90 to a triplet. The addition of 0.35 M equiv of $Eu(fod)_3$ resolves the 2 H olefin multiplet at δ 5.4 to two 1 H signals: δ 6.48 (1 H, d of t, J = 15.4, 7 Hz, respectively), 6.09 (1 H, d of t, J = 15.4, 7 Hz). IR: 3025, 1725, 895 cm^{-1}; mass spectrum, *m/e* 197, 168, 137.

(13) S. K. Malhorta, D. F. Moakley, F. Johnson, *J. Am. Chem. Soc.*, **89**, 2794 (1967).

and macrolide antibiotics will be reported in the future.

Acknowledgment. I am indebted to the late Professor R. B. Woodward for his generous support (National Science Foundation Grant CHE-7825699) and guidance and to Professor Yoshito Kishi for his guidance and encouragement. Additional financial assistance provided by an NIH Training Grant and a John Parker Fellowship is gratefully acknowledged.

Supplementary Material Available: Experimental procedures and spectroscopic data (NMR, IR, mass spectroscopy) (12 pages). Ordering information is given on any current masthead page.

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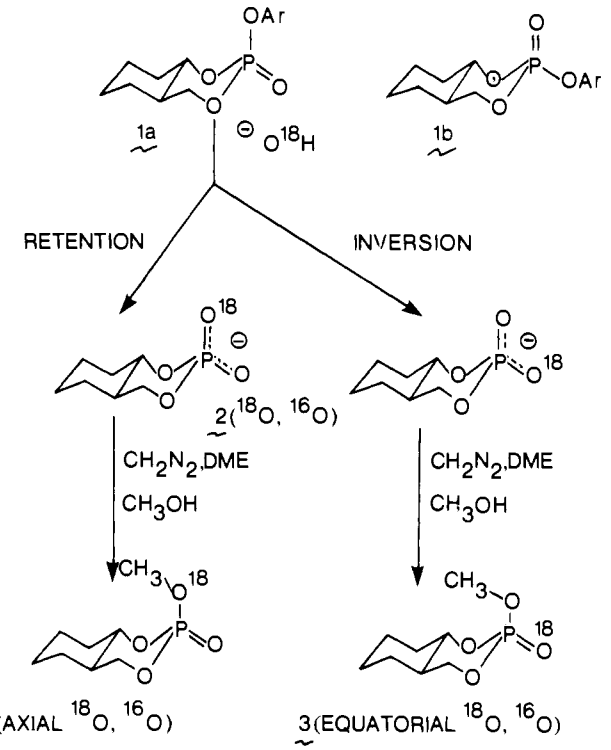
Received April 10, 1980

Isotopic Oxygen-18 Shifts in Phosphorus-31 NMR as a Probe of Stereochemistry of Hydrolysis in Phosphate Triesters

Sir:

Recent demonstration of an ^{18}O isotope shift in ^{31}P NMR chemical shifts has provided a convenient new probe for study of the stereochemistry of the hydrolysis of phosphate esters.[1-3] Previous work on the stereochemistry of nucleophilic displacement reactions in cyclic phosphate esters has been based upon the determination of the ratios of geometrical isomers that are formed.[4-6] Thus, we have previously established that the methoxide reaction of the 2,4-dinitrophenyl ester of 1,3,2-dioxaphosphorinane (**1**) proceeds with 100% inversion for the equatorial epimer and 83% inversion for the axial epimer[6a] (Scheme I). Product stereochemistry was determined by ^{31}P NMR analysis of the methyl esters of **1** since axial isomers of chair six-membered ring phosphorinanes resonate 4-6 ppm upfield from equatorial isomers.[5,6] This method, however, cannot be used for hydroxide or water attack on **1** since the product, cyclic diester **2**, has a prochiral phosphorus center. In this communication, we demonstrate a new, general technique for resolution of this problem by application of an ^{18}O isotope shift on the ^{31}P chemical shift of an ^{18}O isotopically substituted phosphate ester.

Scheme I



Base-catalyzed hydrolysis in $H_2{}^{18}O$/dioxane of the aryl dioxaphosphorinane **1** yielded the monooxygen-18 labeled cyclic diester **2**. The ^{18}O incorporation into the phosphate diester was determined by ^{31}P NMR analysis as shown in Figure 1A. In D_2O, the ^{31}P chemical shift of the $^{16}O,^{16}O$ cyclic diester (exocyclic oxygens only are designated) is -2.53 ppm. The $^{16}O,^{18}O$ cyclic diester is shifted 0.026 ppm upfield. This ^{18}O-induced upfield shift is expected from earlier studies.[1-3] Integration of the two signals confirms that ^{18}O hydroxide attack produces 100 ± 5% P-O aryl cleavage, based upon the calculated atom percent of ^{18}O in the hydroxide solution. No ^{18}O was incorporated into the 2,4-dinitrophenol product (analyzed via mass spectra) as expected for complete P-O aryl cleavage.

Reaction of the cyclic diester anion with diazomethane in methanol yields the axial methyl ester while reaction in water yields the equatorial ester. Epimers were identified by comparison with authentic methyl esters by GPC and ^{31}P NMR spectroscopy (axial methyl ester in $CDCl_3$, -5.96 ppm; equatorial methyl ester in $CDCl_3$, -3.97 ppm).[6] Verkade[9] has previously noted that the stereochemistry of methylation of phosphate anions by diazomethane is quite sensitive to the experimental conditions, although a 100% change in epimer distribution has not previously been observed.

The high-resolution ^{31}P NMR spectrum of the axial methyldioxaphosphorinanes produced by methylation of the cyclic diester product from the ^{18}O hydroxide catalyzed hydrolysis of the axial epimer of 2,4-dinitrophenyldioxaphosphorinane (**1**) is shown in Figure 1B. Signals at -5.833, -5.848, and -5.873 ppm integrate for 43.5, 10.3, and 46.3% of the total signal, respectively. Mass spectral analysis of this ^{18}O-enriched triester indicates 61 ± 5% $^{16}O,^{18}O$ methyl ester. No $^{18}O,^{18}O$ triester peak is seen in the mass spectrum. Addition of authentic $^{16}O,^{16}O$ methyl ester **3** to the NMR sample of Figure 1B increased the intensity of the downfield signal at -5.833 ppm and confirms that the two upfield signals at -5.848 and -5.873 ppm both represent $^{16}O,^{18}O$ stereoisomers **3**. NMR integration of the two upfield signals shows 56.6 ± 5% ^{18}O enrichment and is within experimental error of the mass spectral value.

(1) Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 200.
(2) Lowe, G.; Sproat, B. S. *J. Chem. Soc., Chem. Commun.* **1978**, 565.
(3) Lutz, O.; Nolle, A.; Staschewski, D. *Z. Naturforsch., A* **1978**, *33A*, 380.
(4) Wadsworth, W. S., Jr.; Larsen, S.; Horten, H. L. *J. Org. Chem.* **1973**, *38*, 256. Hudson, R. F.; Verkade, J. G. *Tetrahedron Lett.* **1975**, *37*, 3271. Cooper, D. B.; Inch, T. D.; Lewis, G. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1043.
(5) Majoral, J. P.; Pujol, P.; Navech, J. *Bull. Soc. Chim. Fr.* **1972**, 606. Marsi, K. L. *J. Org. Chem.* **1975**, *40*, 1179.
(6) (a) Gorenstein, D. G.; Rowell, R. *J. Am. Chem. Soc.* **1980**, *102*, 5077. (b) *Ibid.* **1979**, *101*, 4925, and references therein.
(7) Typical analysis of the stereochemistry of hydrolysis proceeded as follows: epimeric pairs of 2-(2,4-dinitrophenoxy)-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane (**1**) were prepared as previously described in ref 6. To a solution of 42 mg (0.12 mmol) of the axial 2,4-dinitrophenyl ester in 0.9 mL of dioxane is added 0.3 mL of 95% $H_2{}^{18}O$ and 19 mg (0.47 mmol) of NaOH. The mixture was tightly stoppered, stirred, and reacted at 60 °C for 14 h. The dioxane/$H_2{}^{18}O$ was recovered by sublimation. An aliquot of 4 mL of water was added to the residue. The solution was acidified to pH 2, and the 2,4-dinitrophenol was extracted three times with methylene chloride. The water was then removed from the diester, **2**, by sublimation.
(8) The ^{18}O-labeled diester (**2**) was dissolved in methanol and reacted with diazomethane in 1,2-dimethoxyethane as in ref 9. The solvent was removed on a rotary evaporator, and the methyl triester (**3**) was partitioned between 15 mL of chloroform and 5 mL of water. The chloroform layer was extracted with 10 mL of 10 mM EDTA in water. From this point, all glassware used had been soaked in concentrated nitric acid to remove metal ions. The chloroform was removed on a rotary evaporator. The residue was dissolved in $CDCl_3$ (Norell) and centrifuged. In the other preparation, the chloroform was dried with $MgSO_4$ then removed in vacuo. The residue was dissolved in 30% dioxane/70% D_2O containing 10 mM EDTA, and Chelex-100 was added. After the mixture stood for 30 min, the Chelex was centrifuged down and the solution pipetted into an NMR tube.
(9) Hong, A. P.; Lee, J. B.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 6547.

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