Radical Contraction of 1,3,2-Dioxaphosphepanes to 1,3,2-Dioxaphosphorinanes: A Kinetic and ^{17}O NMR Spectroscopic Study

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Two diastereomeric 5-bromo-4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphepanes have been synthesized and used to study the contraction of 4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphorinan-5-yl radicals. Kinetics were determined by competition methods and demonstrate Arrhenius parameters typical of rearrangements of this kind. Isotopic labeling reveals that all rearrangements are formally of the 1,2-type with retention of configuration at phosphorus. Analysis of the stereochemistry of the rearrangements, however, reveals the two diastereomers to take different paths with respect to the geometry of the presumed alkene radical cation intermediate.

Introduction

In continuation of our investigations on the β-(phosphatoxy)alkyl rearrangement[1−8] we report here on the ring contraction of 4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphorinan-5-yl radicals and its mechanism as revealed by a combination of ^{17}O-labeling, stereochemical, and kinetic studies. The β-(acyloxy)alkyl and β-(phosphatoxy)alkyl rearrangements continue to attract the attention of computational chemists[9] and, through the trapping of intermediates, are beginning to find application in synthesis.[10,11] The present study was undertaken with the expectation that the combination of stereochemical and isotopic labeling would shed further light on the mechanism of these reactions. Earlier we had applied regioselectively mono ^{17}O-labeled lactones to pin down the first examples[12] of the largely parallel acyloxy rearrangement to take place through a pure 1,2-shift as opposed to the mixture of 1,2- and 2,3-shifts typically observed[4] with both the phosphates and carboxylates. At the outset of this study we reasoned that cyclic phosphate esters would undergo radical ring contraction analogously to the lactones. We further reasoned that the combined use of stereochemistry and regioselective mono ^{17}O-labeling, made possible by the stereogenic nature of the cyclic phosphate, would provide a powerful means by which to probe the mechanism of these rearrangements as indeed turned out to be the case.

Results and Discussion

We selected the contraction of seven- to six-membered phosphates rather than that of the six- to five-membered series because of the well-known hydrolytic instability of five-membered cyclic phosphates. Accordingly the investigation began with the synthesis of the two diastereomers of 5-bromo-4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphepane, together with their ^{17}O-labeled analogues, followed by separation and configurational assignment. To this end, *erythro*-1-phenyl-2-bromo-1,4-butanediol (**1**) was converted to the diastereomeric 2-phenoxy-1,3,2-dioxophosphepane **2** by the action of phenyl dichlorophosphite. Oxidation of **2** in situ with *tert*-butyl hydroperoxide afforded the two cyclic phosphates **3** and **4** in 18 and 21% overall yield, respectively, after chromatographic separation (Scheme 1). The minor isomer (**3**) afforded crystals suitable for X-ray crystallographic investigation (Figure 1) and, so, permitted assignment of configuration as indicated. Treatment of **2** with iodine and 10% ^{17}O-labeled water enabled the preparation of the regioselectively mono ^{17}O-labeled substrates **3*** and **4*** (Scheme 1).

Reaction of **3** with tributyltin hydride in the presence of catalytic diphenyl diselenide[13] resulted in the isolation of the reduction product **5** and a single rearrangement product ultimately assigned as the phosphorinane **8**. Under the same conditions phosphepane **4** afforded its reduction product **6** and two diastereomeric rearrangement products **7** and **8**. The reduction product **6** proved

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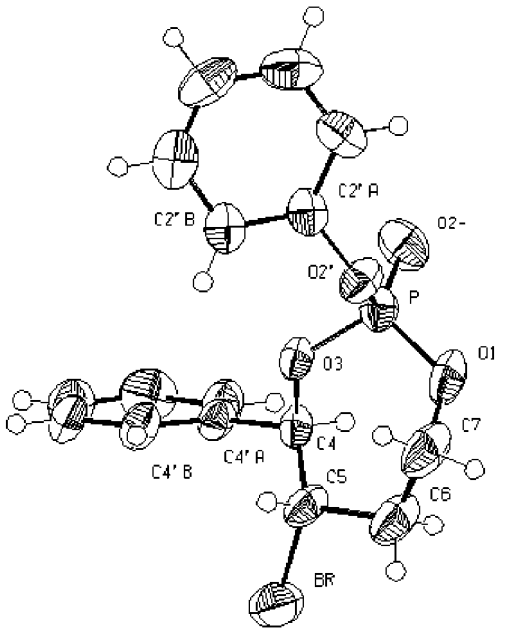
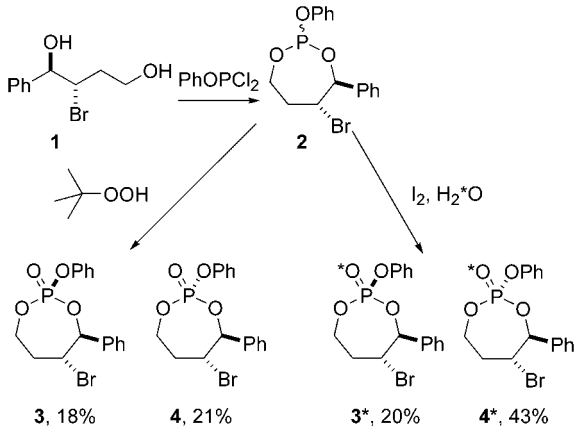
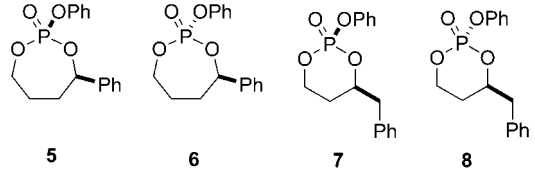


Figure 1. X-ray crystallographic structure of **3**.

Scheme 1



amenable for X-ray analysis (Figure 2) leading to the conclusion that no change of configuration at phosphorus takes place in the straight reduction process. It is noteworthy that both **4** and **6** adopt twist conformations in the crystal so as to place the 4-phenyl and, in the case of **4**, the 5-bromo groups pseudoequatorial. The twist conformation also minimizes repulsion between the lone pairs of the ring oxygens and enables the 2-phenoxy group to adopt a pseudoaxial position, which is considered to be the preferred site in the lower homologues, the 1,3,2-dioxaphosphorinanes.[14,15] Previous crystallographic studies of 1,3,2-dioxaphosphepanes have indicated that both chair and twist conformations are possible depending on the substitution pattern within the ring.[16]



Unfortunately neither **7** nor **8** were crystalline; stereochemistry was therefore assigned by NMR methods

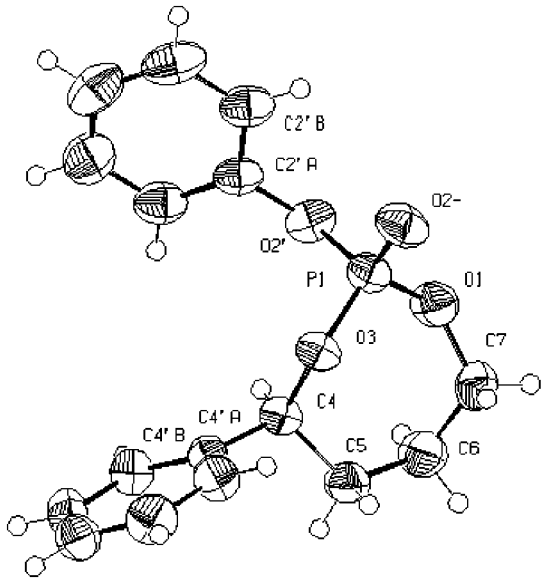


Figure 2. X-ray crystallographic structure of **6**.

taking into account the well-known axial preference of alkoxy and aryloxy groups in 2-alkoxy or aryloxy 2-oxo-1,3,2-dioxaphoshorinanes.[14,15] In particular the $^4J_{PH}$ coupling of 2.8 Hz to one of the benzylic hydrogens in **8** was indicative of an equatorial benzyl group. The absence of a similar coupling in **7**, on the other hand, suggests an axial benzyl group. Compound **8** therefore has a chair conformation with the 2-phenoxy and 4-benzyl groups occupying their preferred sites, respectively axial and equatorial. Compound **7**, however, is likely to be a somewhat distorted chair in order to relieve the 1,3-diaxial interactions between the axial benzyl and axial phenoxy groups. This analysis of the stereochemistry of **7** and **8** follows directly from that of *cis*- and *trans*-4-methyl-2-phenoxy-2-oxophosphorinane by Majoral and Navech.[15] Analysis of the more common $^3J_{PH}$ couplings between phosphorus and H-4 and H-6, for which there is a well-established stereochemical relationship,[14,17] was not possible owing to insufficient resolution.

The kinetics of rearrangement were determined by competition kinetic methods, using our pseudo-first-order benzeneselenol-catalyzed variant of the standard tin hydride protocol.[3,12,18−20] In the case of **3** the reduction product (**5**) was formed along with a single rearrangement product (**8**) whose formation is described by the Arrhenius parameters in eq 1. The rate constant $k_{3,8}$ for the rearrangement of **3** to **8** at 80 °C is 1.8×10^6 s^{-1}.

$$\log (k_{3,8}) = 11.4 \pm 1.7 - 8.3 \pm 2.7/\theta \qquad (1)$$

Isomer **4**, on the other hand, provided the two rearrangement products **7** and **8**, with the parameters shown

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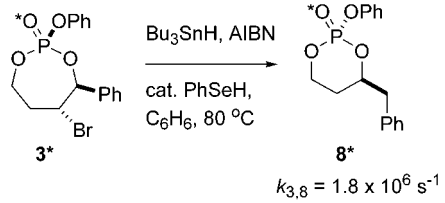
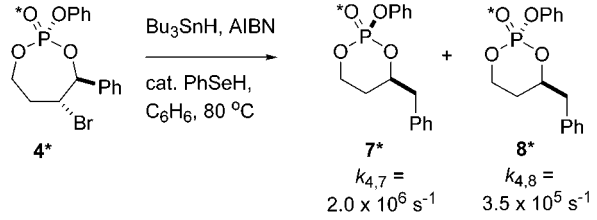
Scheme 2



Scheme 3

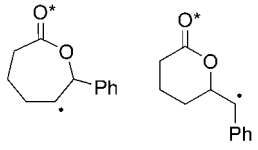


in eqs 2 and 3, together with the reduction product **6**. The rate constants for the rearrangement of **4** to **7** and **8** are $k_{4,7}$ and $k_{4,8}$ of 2.0×10^6 and 3.5×10^5 s^{-1}, respectively, at 80 °C.

$$\log (k_{4,7}) = 10.4 \pm 0.8 - 6.6 \pm 1.4/\theta \qquad (2)$$

$$\log (k_{4,8}) = 14.1 \pm 0.8 - 13.8 \pm 1.3/\theta \qquad (3)$$

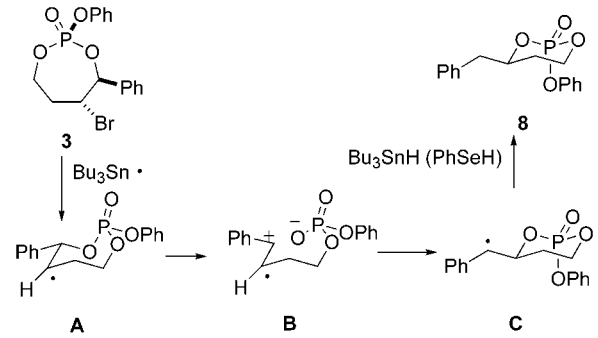
These numbers, particularly the preexponential factors, fall within the range normally observed for β-(phosphatoxy)alkyl and β-(acyloxy)alkyl rearrangements and fragmentations and imply a commonality of mechanism with those reactions.[4,5,7,8,22−24] They also compare well with the preexponential factor determined for the contraction of the related lactone radical **9** to **10**.[12]



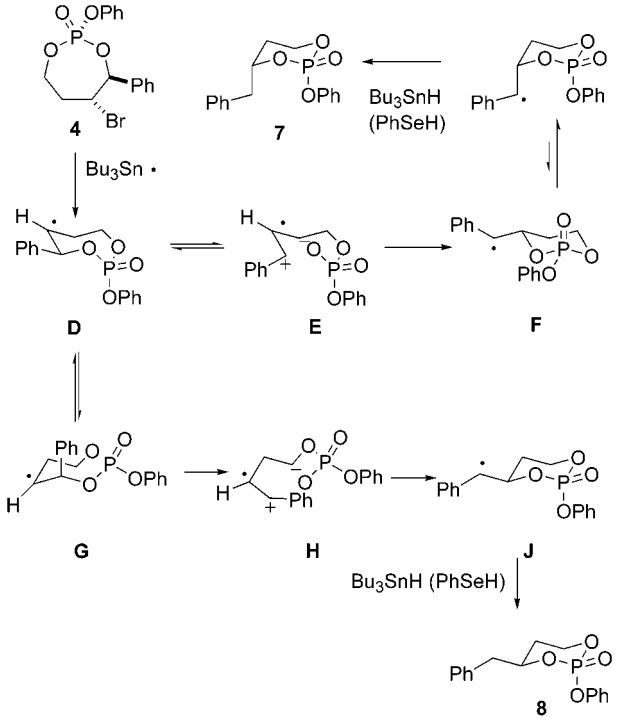
Rearrangement of the mono ^{17}O-labeled **3*** at 80 °C under the conditions employed for the kinetic runs, i.e., with catalytic benzeneselenol as reductant,[13] provided the contraction product **8*** whose ^{17}O NMR spectrum indicated complete retention of configuration at phosphorus (Scheme 2). Parallel rearrangement of **4*** afforded both contraction products **7*** and **8***, both with complete retention of configuration at phosphorus as determined by ^{17}O NMR spectroscopy (Scheme 3).

The rearrangement of **3** to **8** is readily explained by fragmentation of the derived radical **A** from a conformation approximating that of the bromide itself, leading to a zwitterionic species **B**, which then undergoes immediate collapse to the product radical **C** and, after chain transfer, the product **8** (Scheme 4). This process gives radical **C** and product **8** both directly in the preferred

Scheme 4



Scheme 5



chair conformation with the axial phenoxy and equatorial phenyl groups, respectively. The situation with **4** is somewhat more complicated because of the formation of two rearranged products **7** and **8**. The major product **7** is readily explained by fragmentation of the derived radical **D**, from conformation not unlike that obtained crystallographically for the reduction product **6**, to a zwitterion **E** with recombination to **F** and trapping to give **7** (Scheme 5). The closure of **E** to **F**, however, provides **F** either in a chairlike conformation with a disfavored equatorial phenoxy group or in an alternative boat or twist boat conformation that must subsequently invert or relax to the final conformation. The closure of **E** to **F** is therefore less favorable than that of **B** to **C**, and through partitioning of **E** between **D** and **F**, enables the population of radical **G**, *cisoid* radical cation **H**, and the formation of product **8** (Scheme 5).[25] In such a scheme the equilibrium between conformers **D** and **G** is an integral part of the rate equation for the formation of **8**, and this is reflected in the kinetic parameters of eq 3

(21) Rate constants have units of s^{-1}; θ is $2.3RT$ kcal/mol; errors are at 2σ.

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(25) An alternative explanation in which zwitterions **E** and **H** are in direct equilibrium, rather than via radicals **D** and **G**, is considered unlikely, as is any other conformational equilibrium of the zwitterions, as this would retard the collapse to the product radicals and so lead to scrambling of the ^{17}O-label.

and in $k_{4,8}$. Recent work from our laboratory with α-alkoxy-β-(phosphatoxy)alkyl radicals has shown, through labeling and internal trapping experiments, that any recollapse of radical cation/phosphate anion contact ion pairs to the initial radical occurs so rapidly as to preclude scrambling of the label at phosphorus.[26] This is all the more likely in the present series when the covalent tethering of the phosphate anion to the radical cation necessarily facilitates recombination in both the forward and backward directions. The formation of **7** and **8** without scrambling at phosphorus is entirely in agreement with this picture of the very rapid collapse of the contact ion pairs.

The above experiments do not conclusively rule out the possibility that the rearrangements are concerted and take place through three center-three electron cyclic transitions states. The ^{17}O-labeling studies do, however, exclude any possibility of five center−five electron transition states. The recent direct observation of styrene radical cations,[7,8,23] and the indirect observation of enol ether radical cations,[8,24] together with the strong linear correlation of preexponential factors across a very wide range of solvent polarities[7,23] combine to provide a compelling argument that all reactions of β-(phosphatoxy)-alkyl are dissociative in nature. The present results therefore are best interpreted in terms of the mechanisms of Schemes 4 and 5. The implication is that the same is true for the contraction of radical **9*** to **10*** and for related lactones.[12]

Experimental Section[27]

***erythro*-1-Phenyl-2-bromo-1,4-butanediol (1) and *trans*-1-Phenyl-2-bromotetrahydrofuran.** To a solution of *trans*-1-phenyl-1-buten-4-ol[28] (0.210 g, 1.4 mmol) in DMSO (20 mL) and water (0.5 mL) at 10 °C was added NBS (0.5 g, 2.8 mmol). After the mixture was stirred for 1 h at 10 °C, water was added and the mixture was extracted with ether. The extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on silica gel (eluent: hexane/AcOEt 5:1) to give **1** (0.10 g, 44%) as a colorless oil and *trans*-1-phenyl-2-bromo-tetrahydrofuran (0.18 g, 58%). **1:** ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H), 5.01 (d, 1H, J = 4.7 Hz), 4.51 (m, 1H), 3.82 (m, 1H), 3.69 (m, 1H), 2.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 139.9, 128.3, 128.0, 126.5, 77.1, 60.0, 58.9, 34.4. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 49.16; H, 5.43. ***trans*-1-Phenyl-2-bromo-tetrahydrofuran:**[29] ^1H NMR ($CDCl_3$) δ 7.40 (m, 5H), 5.10 (d, 1H, J = 3.2 Hz), 4.24 (td, 1H J = 8.4, 4.0 Hz), 4.18 (m, 2H), 2.52 (m, 1H), 2.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 140.1, 129.1, 128.7, 128.5, 128.2, 125.8, 88.5, 67.6, 53.0, 36.2.

5-Bromo-4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphepanes (3 and 4). To a solution of **1** (190 mg, 0.775 mmol) in THF (15 mL) was added triethylamine (0.23 mL, 1.6 mmol). The mixture was cooled to −10 °C and phenyl dichlorophosphite (0.12 mL, 0.83 mmol) was added dropwise. After the mixture was stirred for 4 h, *tert*-butyl hydroperoxide (0.16 mL, 0.8 mmol, 5−6 M in decane) was added. The mixture was stirred for a further 2 h and then concentrated under vacuum and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 2:1) to give **3** (50 mg, 18%) and **4** (60 mg, 21%). Isomer **3**: mp 114 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 10H), 5.56 (dd, 1H, J = 10.3, 8.4 Hz), 4.28 (m, 3H), 2.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 136.1, 129.9, 129.5, 128.6, 127.5, 120.1, 81.9, 67.7, 50.5, 40.9; ^{31}P NMR ($CDCl_3$) δ −5.3. Anal. Calcd for $C_{16}H_{16}BrO_4P$: C, 50.15; H, 4.21. Found: C, 50.40; H, 4.25. Isomer **4**: mp 148 °C; ^1H NMR ($CDCl_3$) δ 7.29 (m, 10H), 5.24 (dd, 1H, J = 9.9, 8.8 Hz), 4.52 (dddd, 1H, J = 13.5, 9.9, 7.6, 1.8 Hz), 4.34 (m, 2H), 2.84 (dddd, 1H, J = 15.8, 5.8, 4.0, 1.5 Hz), 2.57 (dddd, 1H, J = 15.8, 9.9, 7.7, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 141.1, 137.4, 132.2, 129.9, 128.5, 127.9, 127.4, 127.0, 126.3, 120.7, 120.0, 84.2, 73.6, 65.7, 28.2; ^{31}P NMR ($CDCl_3$) δ −6.38. Anal. Calcd for $C_{16}H_{16}BrO_4P$: C, 50.15; H, 4.21. Found: C, 49.94, H, 4.32.

2*S,4*R**-2-Phenoxy-4-phenyl-2-oxo-1,3,2-dioxaphosphepane (5)**: mp 104−105 °C; ^1H NMR ($CDCl_3$) δ 7.26 (m, 10H), 5.54 (m, 1H), 4.27 (m, 2H), 2.1 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 140.1, 129.8, 128.6, 128.4, 125.7, 125.2, 120.2, 79.7, 68.8, 37.4, 29.3; ^{31}P NMR ($CDCl_3$) δ −3.8; HRMS M^+ Calcd for $C_{16}H_{17}0_4P$: 304.08645, found: 304.08687.

2*R,4*R**-2-Phenoxy-4-phenyl-2-oxo-1,3,2-dioxaphosphepane (6):** mp 141 °C; ^1H NMR ($CDCl_3$) δ 7.35 (m, 10H), 5.31 (dd, 1H, J = 9.8, 7.8 Hz), 4.53 (m, 1H), 4.37 (ddd, 1H, J = 24.3, 11.9, 3.0 Hz), 2.18 (m, 3H), 2.03 (m, 1H).; ^{13}C NMR ($CDCl_3$) δ 150.8, 140.6, 130.1, 129.0, 128.7, 125.9, 125.5, 120.5, 81.9, 67.8, 37.9, 29.6; ^{31}P NMR ($CDCl_3$) δ −4.21; HRMS M^+ Calcd for $C_{16}H_{17}0_4P$: 304.08645, found: 304.08589.

2*S,4*R**-4-Benzyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (7):** ^1H NMR ($CDCl_3$) δ 7.30 (m, 10H), 4.97 (m, 1H), 4.48 (m, 2H), 3.17 (dd, 1H, J = 13.8, 5.9 Hz), 2.94 (dd, 1H, J = 13.8, 7.5 Hz), 1.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 135.5, 129.8, 129.6, 128.5, 127.2, 125.3, 120.3, 120.2, 80.8, 67.2, 42.1, 30.0; ^{31}P NMR ($CDCl_3$) δ −11.01; HRMS M^+ Calcd for $C_{16}H_{17}0_4P$: 304.08645, found: 304.08619.

2*R,4*R**-4-Benzyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (8):** ^1H NMR ($CDCl_3$) δ 7.22 (m, 10H), 4.72 (m, 1H), 4.44 (m, 2H), 3.01 (dd, 1H, J = 14.0, 7.0 Hz), 2.90 (ddd, 1H, J = 14.0, 6.0, 2.8 Hz), 2.14 (m, 1H), 1.82 (dm, 1H, J = 14.7 Hz); ^{13}C NMR ($CDCl_3$) δ 135.8, 129.9, 129.6, 128.8, 127.2, 125.1, 119.6, 81.7, 68.5, 42.6, 31.1; ^{31}P NMR ($CDCl_3$) δ − 12.72; HRMS M^+ Calcd for $C_{16}H_{17}0_4P$: 304.08645, found: 304.08546.

Determination of Arrhenius Function for Rearrangement of 3. A stock solution of **3** (150 mg) in toluene (30 mL) was prepared and 4 mL (0.052 mmol) transferred to each of five 50-mL round-bottomed flasks. A stock solution of PhSeSePh (98.4 mg) in toluene (12 mL) was made up and 2 mL (0.013 mmol) added to each flask, followed by Bu_3SnH (2 mL of a 0.013 M solution in toluene, 0.015 mmol). Each flask was made up to 12 mL with toluene and purged with Ar for 30 min. Each flask was then equilibrated at the required temperature and Bu_3SnH and AIBN in toluene (1 mL of stock solution containing 180 mg and 6 mg of AIBN in a total of 10 mL) was added dropwise over 1 h. After the addition was complete, the reaction mixture was stirred for 4 h before the solvent was removed under reduced pressure, and the product ratios determined by ^1H NMR and/or ^{31}P NMR. The experiment was conducted in duplicate.

Determination of Arrhenius Function for Rearrangement of 4. A stock solution of **4** (170 mg) in toluene (30 mL) was prepared and 5 mL (0.074 mmol) transferred to each of five 50-mL round-bottomed flasks. A stock solution of PhSeSePh (100 mg) in toluene (40 mL) was made up and 0.92 mL (0.00736 mmol) added to each flask, followed by Bu_3SnH (3.08 mL of a 0.0028 M solution in toluene, 0.00883 mmol). Each flask was made up to 14 mL with toluene and purged with Ar for 30 min. Each flask was then equilibrated at the required temperature and Bu_3SnH and AIBN in toluene (1.3 mL of stock solution containing 200 mg and 6 mg of AIBN in a total of 10 mL) was added dropwise over 1 h. After addition was complete, the reaction mixture was stirred for 4 h before the solvent was removed under reduced pressure, and the product ratios determined by ^1H NMR and/or ^{31}P NMR. The experiment was conducted in duplicate.

Preparation of Regioselectively Mono ^{17}O-Labeled Phosphepanes 3 and 4. Phenyl dichlorophosphite (0.116 mL, 0.8 mmol) was added dropwise to a stirred solution of **1** (200 mg, 0.8 mmol) and anhydrous pyridine (0.13 mL, 1.6 mmol) in THF (5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 4 h before I_2 (0.13 g) dissolved in a 5/1/1 mixture of THF/Py/10% ^{17}O enriched water[30] (1 mL) was added. When

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the addition was complete, the reaction mixture was warmed to room temperature and a saturated solution $Na_2S_2O_3$ (5 mL) was added, followed by extraction with CH_2Cl_2, drying ($MgSO_4$), and concentration under vacuum. Chromatography over silica gel then gave **3*** (32 mg, 20%) and **4*** (67 mg, 43%). **3*** ^{31}P NMR ($CDCl_3$) δ −5.35, − 5.39 (2.1/5.2 relative intensity); ^{17}O NMR ($CDCl_3$) δ 81.1 (broad singlet). **4*** ^{31}P NMR ($CDCl_3$) δ −6.41, −6.45 (2.1/5.2 relative intensity); ^{17}O NMR ($CDCl_3$) δ 81.1 (d, J = 83.8 Hz). Note that the observance of two signals in the ^{31}P NMR spectra of **3*** and **4*** arises from the labeled water employed being enriched in ^{17}O and ^{18}O to the extent of ∼10 and ∼57%, respectively. Thus, in each case one ^{31}P resonance arises from the ^{16}O isotopomer and the other from the ^{18}O isotopomer with that from the ^{17}O isotopomer being lost in the noise owing to coupling with the quadrupolar ^{17}O nucleus.[31,32]

Rearrangement of Regioselectively Mono ^{17}O-Labeled Phosphepanes 3 and 4. Phosphate **3*** was rearranged at 80 °C under the conditions of the kinetic experiment (Table 1, Supporting Information), providing the contraction product **8*** with ^{17}O NMR ($CDCl_3$) δ 80.8. Phosphate **4*** was similarly rearranged and afforded **7*** with ^{17}O NMR ($CDCl_3$) δ 87.6 (d, J = 110.8 Hz) and **8*** with ^{17}O NMR ($CDCl_3$) δ 80.8.

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Supporting Information Available: Tables of kinetic data for the rearrangement of **3** and **4**, copies of the ^{1}H and ^{13}C NMR spectra of **5**−**8** (pdf), and full crystallographic details of **3** and **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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