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Triphenylphosphine Reduction of Saturated Endoperoxides

Ihsan Erden,* Christian Gärtner, and M. Saeed Azimi

San Francisco State University, Department of Chemistry and Biochemistry, 1600 Holloway Avenue, San Francisco, California 94132

ierden@sfsu.edu

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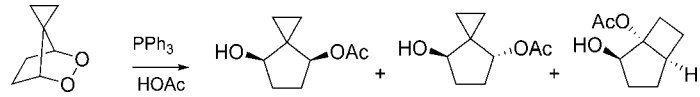
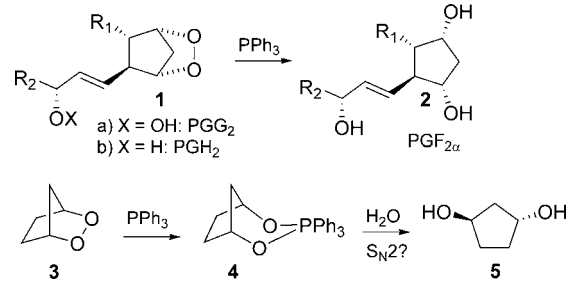
ABSTRACT



Triphenylphosphine reduction of saturated endoperoxides derived from 6,6-dimethylfulvene and spiro[2.4]hepta-4,6-diene in the presence of nucleophiles results in the formation of products that mainly stem from deoxygenation followed by carbocation formation. Nucleophilic attack by solvent proceeds by an S_N1 like mechanism; allyl shifts and cyclopropylcarbinyl-cyclobutyl rearrangements also occur. With the systems lacking carbocation-stabilizing groups, the deoxygenation step is preceded by attack of H_2O at the phosphorus.

The reduction of cyclic peroxides[1] and ozonides[2] with triphenylphosphine has been known for a long time. In the case of unsaturated endoperoxides, the reaction results in deoxygenation, leading to ene epoxides,[3] although a few exceptions have been observed.[4] In the case of 1,2-dioxetanes, the reaction with PPh_3 leads to a cyclic phosphorane that undergoes O−P cleavage followed by an intramolecular S_N2 reaction to give epoxides in a stereospecific manner.[5] With bicyclic 1,2-dioxetanes, on the other hand, where backside attack is impeded, eliminations to allylic alcohols are observed.[6] Samuelsson and co-workers reported that prostaglandin endoperoxides PGG_2 (**1a**) or PGH_2 (**1b**) upon reduction with PPh_3 give the corresponding *cis*-1,3-diol (**2**), $PGF_{2\alpha}$.[7] Clennan and Heah found that saturated bicyclic endoperoxides give with PPh_3 in the presence of H_2O *trans*-1,n-diols;[8] moreover, they were able to detect the cyclic phosphorane intermediates by NMR and postulated for their formation a biphilic insertion of PPh_3 into the O−O linkage. They also offered a mechanism for phosphorane decomposition involving heterolytic cleavage of the phosphorane to give a zwitterion that reacts with water *via* backside displacement (S_N2) to give the *trans*-diol **5** (Scheme 1). On the other hand, the studies by Westheimer and co-workers,[9] as well as McClelland and co-workers[10] have shown, with careful mechanistic work, that the hydrolysis of pentaary-

Scheme 1. PPh_3 Reductions of 2,3-Dioxabicyclo[2.2.1]heptanes[a]



[a] Previous work by Samuelsson (**1**→**2**) and Clennan and Heah (**3**→**5**).

(1) (a) Horner, L.; Jurgeleit, W. *Annalen* **1955**, *591*, 138–152. (b) Pierson, G. O.; Runquist, O. R. *J. Org. Chem.* **1969**, *34*, 3654–3655. (c) Jarvie, A. W. P.; Moore, C. G.; Skelton, D. *J. Poly. Sci. Part A: Polymer Chem* **1971**, *9*, 3105–3114.

(2) Carles, J.; Fliszar, S. *Can. J. Chem.* **1969**, *47*, 1113.

(3) Balci, M. *Chem. Rev.* **1981**, *81*, 91–108.

(4) (a) Adam, W.; Erden, I. *Tetrahedron Lett.* **1979**, *20*, 2781–2784. (b) Baldwin, J. E.; Lever, O. W., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 344–345.

(5) Bartlett, P. D.; Landis, M. E.; Shapiro, M. J. *J. Org. Chem.* **1977**, *42*, 1661–1662.

(6) Kopecky, K. R.; Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J.-Y. *Can. J. Chem.* **1975**, *53*, 1103–1122.

(7) (a) Hamberg, M.; Svensson, J.; Wakabayashi, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345–349. (b) Samuelsson, B. *Nobel Lectures in Physiology or Medicine 1981−1990*; Lindtsen, J., Ed.; World Scientific Publishing: Stockholm, Sweden, 1982; pp 117−138.

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loxyphosphoranes occurs by an "inner sphere" mechanism (attack at phosphorus).

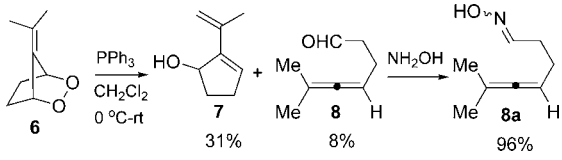
The base hydrolysis appears to be an associative process proceeding through a hexacoordinated phosphoroxanide ion, whereas the acid-catalyzed reaction is a dissociative pathway resembling the acetal or orthoester hydrolysis. Also contrary to the "outer sphere" mechanism, Taylor and Greatrex reported that a *cis*-1,4-diphenyl substituted 4,5-epoxy-1,2-dioxine resulted in the hydrolysis of the phosphorane intermediate at phosphorus rather than at the carbon center to give a *meso*-1,4-diol, in addition to deoxygenation products.[11]

Herein we disclose our results from PPh_3 reductions of saturated endoperoxides derived from 6,6-dimethylfulvene and spiro[2.4]hepta-4,6-diene that have unraveled new pathways involving carbocation intermediates and rearrangements. We also report that the origin of the above-mentioned discrepancy regarding the stereochemistry of the diols **2** and **5**, and hence the mechanism of phosphorane decomposition during PPh_3 reductions of saturated endoperoxides in the [2.2.1] and [2.2.2] series in the presence of H_2O is likely just due to a misassignment of the 1,n-diol stereochemistry.

In the course of our studies on peroxides derived from fulvenes and fulvene analogs,[12] we investigated the triphenylphosphine reductions of 6,6-dimethylfulvene and [2.4]spirohepta-4,6-diene since our systems promised some unusual behavior due to the presence of the vinyl and cyclopropyl groups adjacent to the peroxo carbons, respectively.

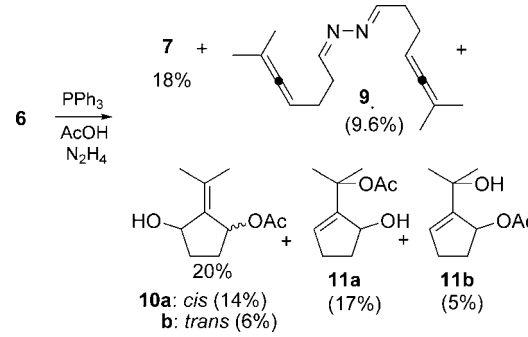
After singlet oxygenation of 6,6-dimethylfulvene at −78 °C in CH_2Cl_2, and subsequent diazene reduction at low temperature, as described previously,[13] the saturated endoperoxide **6** was treated with 1.2 equivalents PPh_3 at 0 °C, and the mixture was stirred at room temperature for 10 h. The product mixture was chromatographed on silica gel to give one major product, **7**, and a minor product, **8**, a known aldehyde.[14] For characterization purposes the latter was converted to its oxime **8a** (*syn* and *anti* isomers in ca. 1:1 ratio) (Scheme 2).

Scheme 2. PPh_3 Reduction of the Saturated Fulvene Endoperoxide **6** without H_2O



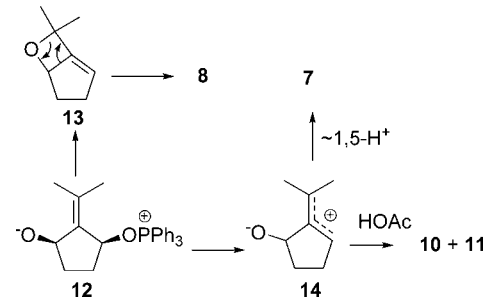
We then decided to carry out the PPh_3 reduction in the presence of a nucleophile, and for reasons of easier purification/isolation of products we chose acetic acid instead of water. The reaction was conducted in CH_2Cl_2 at 0 °C in the presence of a slight excess of acetic acid. Under these conditions, a mixture of six products was formed, four carrying the acetoxy group. They were separated by silica gel chromatography (after treating the mixture with cold ether/petroleum ether and removing most of the $Ph_3P{=}O$ by filtration) and identified as the products shown in Scheme 3.

Scheme 3. Reaction **6** with PPh_3 in the Presence of AcOH



The results presented above deserve some comment: Oxetane **13** is most likely formed from **12** by an S_N2' reaction. Under the conditions, **13** undergoes oxetane cleavage to give the allenic aldehyde **8** (Scheme 4). Compound **7**

Scheme 4. Mechanisms for the Formation of Compounds **7**, **8**, **10** and **11**



is formed from **14** by proton loss. Azine **9** in Scheme 3 is formed from **8** with hydrazine, a disproportionation product of diazene,[15] in a serendipitous manner: the latter was present in the mixture in large excess since after reduction and

(8) (a) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1981**, *46*, 4105–4107. (b) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1982**, *47*, 3329–3331. (c) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1984**, *49*, 2284–2286.

(9) William, W. C. A., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1973**, *95*, 5955–5959.

(10) McClelland, R. A.; Patel, G.; Cirinna, C. *J. Am. Chem. Soc.* **1981**, *103*, 6432–6436.

(11) Greatrex, B. W.; Taylor, D. K. *J. Org. Chem.* **2004**, *69*, 2577–2579.

(12) Erden, I.; Ocal, N.; Song, J.; Gleason, C.; Gaertner, C. *Tetrahedron* **2006**, *62*, 10676–10682, and references cited therein.

(13) Adam, W.; Erden, I. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 210–211.

(14) (a) Bertrand, M.; Cavallin, B.; Roumestant, M. L.; Sylvestre-Panthet, P. *Isrl. J. Chem.* **1985**, *26*, 95–100. (b) Crandall, J. K.; Mualla, M. *Tetrahedron Lett.* **1986**, *27*, 2243–2246.

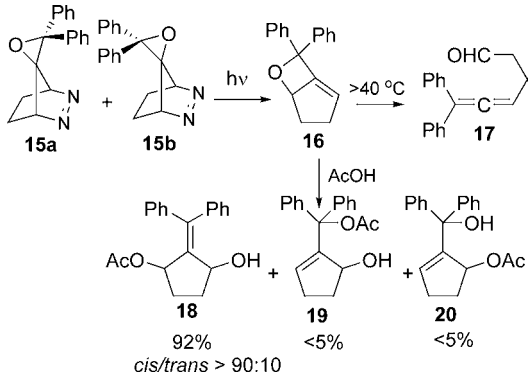
(15) Wiberg, N.; Bachhuber, H.; Fischer, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 830–831.

filtration of KOAc, the solution was treated with PPh_3 without aqueous workup.

The hydroxyacetates **10a** and **b** (*cis* and *trans*) were isolated as mixtures, whereas **11a** was obtained in pure form. Through repeated chromatography the major isomer **10a** could be isolated free of **10b**. An attractive mechanism for the formation of **7**, **8** as well as **10** and **11** would feature oxetane **13** as the key intermediate (Scheme 4). The assignment of the *cis* and *trans* isomers of **10** is based on independent synthesis of an authentic sample of **10a** from **6** by $NaBH_4$ reduction in MeOH at 0 °C followed by monoacetylation of the resulting *cis*-1,3-diol with acetyl chloride in CH_2Cl_2 in the presence of NEt_3.

The intermediacy of oxetane **13** and its role as a precursor of **8** as well as **11a/b** has precedent. The diphenyl analog of **13** has been prepared by Abe and Adam et al.[16] and also by Abe et al.[17] (Scheme 5). The latter group observed that **16**

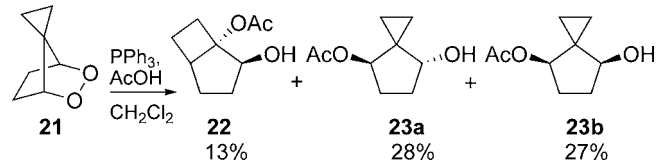
Scheme 5. Abe et al.'s Pathway to a 6-Oxabicyclo[3.2.0]hept-1-ene (**16**) and its Decomposition Products



undergoes rearrangement to form **17**, the corresponding allene aldehyde of type **8**. On the other hand, with CH_3CO_2H the same oxetane was reported to give mostly the *cis*-acetoxy alcohol **18** with traces of the hydroxyacetates **19** and **20**. In our case, products **10a, b** and **11a, b** do not have to stem from **13** and can directly be formed from **12** by loss of $Ph_3P{=}O$, followed by capture of the allyl cation **14** by the acetate ion. We believe that **11b** is a secondary product stemming from **11a** by an intramolecular acyl transfer.[18]

Next, we studied the triphenylphosphine reduction of the saturated endoperoxide **21** derived from [2.4]-spiro-4,6-heptadiene **21**.[19] Considering the significant stabilizing effect of a cyclopropyl group on adjacent carbocations when the three-membered ring and the carbocation are fixed in a

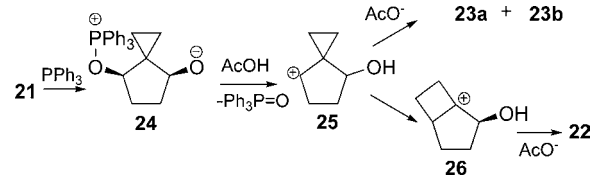
Scheme 6. PPh_3 Reduction of **21** in the Presence of AcOH



bisected conformation,[20] we expected a similar mechanism as with **6** with possible carbocation rearrangement involving the cyclopropyl group. These expectations were borne out by the following experiments. The saturated endoperoxide **21** derived from spiro[2.4]hepta-4,6-diene, prepared as previously described,[19] reacted with PPh_3 in the presence of acetic acid at room temperature to give a mixture of three products all of which contained an acetoxy group and which were separated from one another by silica gel chromatography. They were identified as **22**, **23a** and **23b** (in order of their R_f values with 1:1 pet.ether/EtOAc, respectively) by means of their spectral and accurate HRMS data. The formation of the hydroxy acetates **23a** and **23b** is analogous to that of **10a** and **10b** from **6**, and is indicative of a carbocation intermediate derived from the initial bicyclic phosphorane by way of $Ph_3P{=}O$ extrusion. In particular the formation of the 1-acetoxybicyclo[3.2.0^{1,5}]heptan-2-ol (**22,** a single stereoisomer) constitutes clear-cut evidence for the intervention of a carbocation intermediate of the type **26**, undergoing a cyclopropylcarbinyl-cyclobutyl rearrangement,[21] followed by capture of the cyclobutyl cation by the acetate ion.

Both **23a** and **23b** were stable toward AcOH under the reaction conditions applied to **21** and did not undergo rearrangement to **22**. The mechanism outlined in Scheme 7 satisfactorily accounts for all three products.

Scheme 7. Mechanism for the PPh_3 Reduction of **21**



The question remained whether the parent 2,3-dioxabicyclo[2.2.1]heptyl system **3** and its [2.2.2]octyl homologue **27** lacking carbocation stabilizing groups indeed undergo PPh_3 reduction by an S_N2-like attack of the nucleophile (e.g., H_2O) at the bridgehead carbon. Our results, as presented above,

(16) (a) Abe, M.; Adam, W.; Nau, W. M. *J. Am. Chem. Soc.* **1998**, *120*, 11304–11310, 15. (b) Abe, M.; Ino, S.; Nojima, M. *J. Am. Chem. Soc.* **2000**, *122*, 6508–6509.

(17) Abe, M.; Minamoto, T.; Ino, Y.; Kawakami, T.; Nojima, M. *Tetrahedron* **2002**, *58*, 7043–7047.

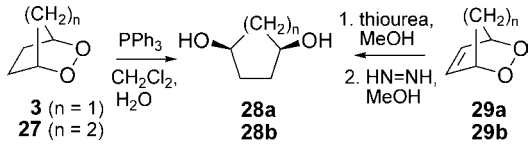
(18) (a) Yue, L.; Zhang, C.; Zhang, G. *Lipids* **2006**, *41*, 301–303. (b) Hasegwa, H.; Akira, K.; Shinohara, Y.; Kasuya, Y.; Hashimoto, T. *Biol. Pharm. Bull.* **2001**, *24*, 852–855. (c) Chu, L.; Davin, L. B.; Zajicek, J.; Lewis, N. G.; Croteau, R. *Phytochem.* **1993**, *34*, 473–476.

(19) Adam, W.; Erden, I. *J. Org. Chem.* **1978**, *43*, 2737–2738.

(20) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809–886, and references cited therein. (b) Schleyer, P. v. R.; van Dine, G. W. *J. Am. Chem. Soc.* **1966**, *88*, 2321–2322.

(21) (a) Closson, W. D.; Kwiatkowski, G. T. *Tetrahedron* **1965**, *21*, 2779–2789. (b) Hanack, M.; Schneider, H.-J. *Ann.* **1965**, *686*, 8–18. (c) Wiberg, K. B.; Hiatt, J. E.; Hseih, K. *J. Am. Chem. Soc.* **1970**, *92*, 544–553.

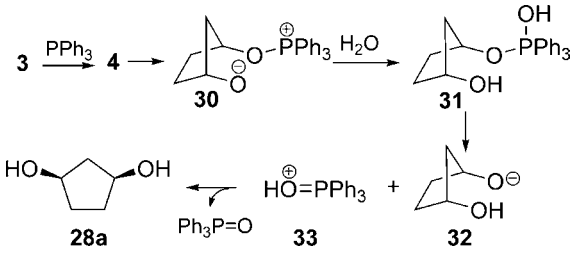
Scheme 8. Ph_3P Reduction of 2,3-Dioxabicyclo[2.2.1]heptane- and [2.2.2]octane and Independent Syntheses of the *cis*-Diols



do not support the S_N2 mechanism, though it is clear that carbocation-stabilizing groups at the α-position would dramatically influence the mechanistic pathway in the deoxygenation step. We therefore subjected the saturated endoperoxide derived from cyclopentadiene as well as 1,3-cyclohexadiene to PPh_3 reduction in the presence of water.

In our hands, the sole products formed from both reactions were exclusively the *cis*-diols **28a** and **28b** (in 92 and 79% yields, respectively, from the corresponding dienes) with no traces of the *trans* isomers. These results confirm Samuelsson's earlier report on the isolation of the *cis*-diol **2** from prostaglandin endoperoxide **1** with PPh_3 and render the S_N2 pathway less likely. We propose the mechanism shown in Scheme 9 for PPh_3 reduction of endoperoxides of the type **3**

Scheme 9. Ph_3 Reduction of **3** in the Presence of H_2O



and **27** lacking carbocation- stabilizing groups adjacent to the peroxo carbons in the presence of H_2O.

Authentic samples of **28a** and **28b** were independently synthesized by thiourea reduction of the respective unsaturated endoperoxides **3** and **27**, followed by diazene reduction of the resulting unsaturated *cis*-diols in methanol (diazene generated in situ from potassium azodicarboxylate with AcOH in MeOH at 0 °C).

In conclusion, we have shown that PPh_3 reductions of saturated endoperoxides such as **6** and **21** containing vinyl or cyclopropyl groups α to the peroxo carbon facilitate direct deoxygenation and carbocation formation. The initial biphilic insertion of PPh_3 into the peroxo bridge had elegantly been demonstrated by Clennan and Heah.[8] However, it is quite likely that the deoxygenation step in the case of **28a** or **28b** proceeds by heterolytic O−P cleavage of the cyclic phosphorane intermediate of the type **4** followed by attack of water at the phosphonium ion before **31** collapses to $Ph_3P{=}O$ and the *cis*-diol (Scheme 9). With a vinyl or cyclopropyl group present at the carbon adjacent to the bridgehead position (as in **12** and **24**), facile $Ph_3P{=}O$ loss from intermediate **30** occurs leading to an allyl or cyclopropylcarbinyl cation that undergoes S_N1 substitution either directly or after allyl shift (both *cis* and *trans* hydroxyacetates are formed in each case), or cyclopropylcarbinyl-cyclobutyl rearrangement, respectively.

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Supporting Information Available: Experimental procedures and spectral characterization data as well as ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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