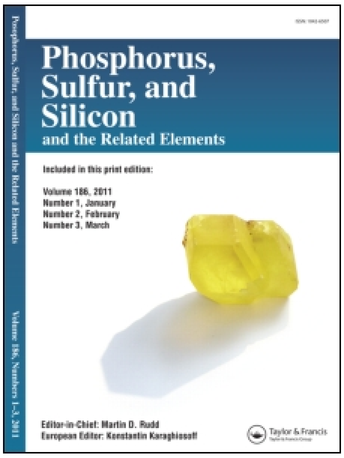

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Synthesis, Characterization, and Reactions of Mono and Bicyclic Phostones

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SYNTHESIS, CHARACTERIZATION, AND REACTIONS OF MONO AND BICYCLIC PHOSTONES

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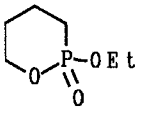
ABSTRACT Improved methods for the synthesis of 5- and 6-membered ring phostones **2** and **1** as well as original preparations of bicyclic phostones **4** (n=1,2) have been successfully executed. The preparation of the 4-membered ring **3** was more elusive, but the observed products indicated its presence as an intermediate which underwent further transformations. Reaction of **1** with 2,2,6,6-tetramethylpiperidide at low temperature, followed by treatment with a variety of alkyl halides gave the expected alkylation products whose cis/trans stereochemistry was dependent on the reaction conditions. Subsequent ring closure of the cis or trans alkylated product **10**, gave only the cis fused bicyclic product **4**. In fact, other synthetic routes to **4** produced only the cis isomer. The mechanisms and stereochemistry of these various conversions will be discussed.

INTRODUCTION

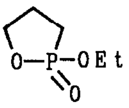
The purpose of this investigation was to explore efficient synthetic pathways to the mono and bicyclic phostones **1-4**. The second phase of the investigation was concerned with stereochemical studies of these materials, including conformational preferences, establishing the **cis/trans** nature of fusion in the bicyclic systems, and controlling the stereochemistry upon alkylation of the ylide **8** **(scheme 3)**. Our basic interest in exploring optimized synthesis of these materials was guided by the observation of rapid hydrolysis rates of 5-membered ring phosphate esters and associated stereoelectronic effects[1] which account for unique structure/reactivity behavior in this and related molecular systems.

SYNTHESIS OF MONOCYCLIC PHOSTONES

The following phostone derivatives were targeted for improved synthesis and characterization:



1



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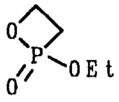

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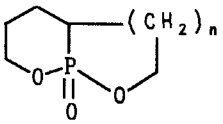


4 (n = 1 , 2)

Previous syntheses of the parent 5- and 6-membered ring phostones have been described[2], but several suffer from low yields. We have prepared **2** through the reaction sequence in **scheme 1**. The final step (93% yield) was best carried out in the presence of LiH in benzene at reflux. Ring closure occurred in the absence of base, but was slower and required 72 hours at reflux in xylene.[3] The 6-membered ring phostone **1** was also obtained in 68% yield using the homologue of alcohol **5**. Alternative preparations of the precursor ω-hydroxyphosphonate esters originated from hydroboration of $CH_2{=}CH(CH_2)_nPO(OEt)_2$ (n=1,2). The alkenyl esters were in turn prepared from reaction of the appropriate alkenylbromide with $(EtO)_3P$ or $(EtO)_2PO^-$.

scheme 1

$$OH(CH_2)_3Br \xrightarrow{a,b} THPO(CH_2)_3I \xrightarrow{c} THPO(CH_2)_3PO(OEt)_2$$

$$\xrightarrow{d} \underset{5}{OH(CH_2)_3PO(OEt)_2} \xrightarrow{e} 2$$

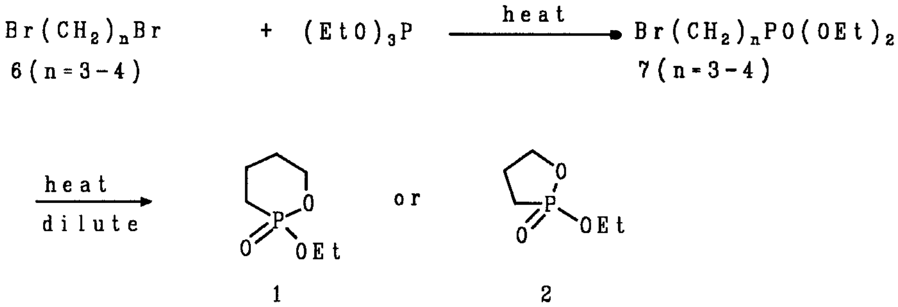
a) dihydropyran/ether/TsOH; b)NaI/acet./heat

c) NaH/$(EtO)_2$POH/THF; d)MeOH/TsOH; e)LiH/benz./heat

Another synthesis of **1** or **2** is shown in **scheme 2**. By using an excess of the dibromoalkane **6**, the intermediate bromophosphonate ester **7** was made in good yield.

An improvement in the last step was effected by carrying out the reaction under higher dilution than previous work.[2a] Ring closure of **7** gave **1** and **2** in 94% and 77% yields, respectively.

scheme 2

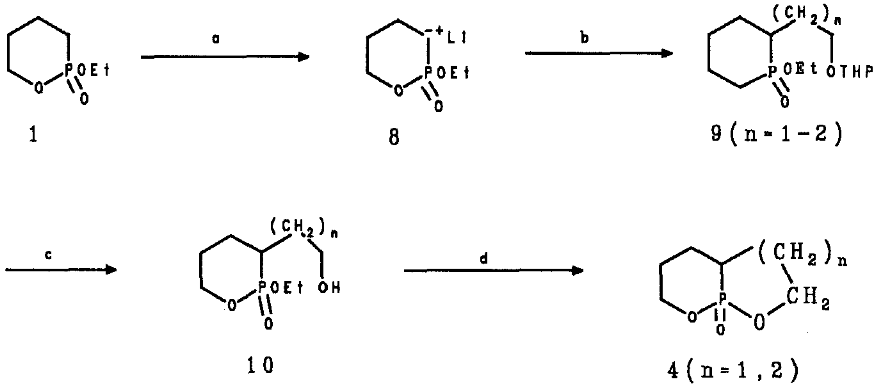


Several reports of the synthesis of substituted 4-membered ring phostones have appeared.[4] An attempt to close $HOC(CH_3)_2C(CH_3)_2PO(OEt)_2$ via the methodology in scheme 1, produced 2,3-dimethyl-2-butene, $(EtO)_2PO_2H$, and the terminal alkene, $CH_2{=}CCH_3C(CH_3)_2PO(OEt)_2$ .The first two products may arise from a 4-ring phostone which fragments to the alkene and metaphosphate derivative. The origin of the terminal alkene may be from direct elimination of water, or a more complex pathway.

SYNTHESIS OF THE BICYCLIC COMPOUNDS-4

The syntheses of the bicyclic materials **4** (n=1,2) were effected using three different procedures, one of which is illustrated in **scheme 3**. Treatment of **1** with lithium tetramethylpiperidide at low temperature was followed by reaction with a THP protected ω-haloalcohol. The cis/trans stereochemistry of the intermediate products **9** and **10** was dependent on the reaction conditions, including the use of additives such as HMPA. Rationalization of the stereochemical outcome followed the earlier arguments of Polniaszek.[5] Subsequent ring closure of *either* the cis or trans intermediate **10** (n=2) led only to cis fused **4** (n=2). In fact, all synthetic approaches, including one by G. Whitham[6,7] led to this same stereoisomer. Attempts to isomerize **4** to the trans isomer have not yet been successful. In contrast, it is noteworthy that the analogous parent acetal, 2,10-dioxabicyclo[3.3.0]decane, is a 55:45% (cis:trans) mixture at equilibrium.[7] Molecular mechanics calculations[8] favor the cis isomer in both the parent acetal and **4**(n=2), but the error limits are too large to be relevant.

scheme 3



a)LiTMP/THF-78°;b)Br$(CH_2)_x$OTHP (x=2-3);
c)MeOH/TsOH;d)LiH/benzene/heat

REFERENCES

1. For a recent leading reference see D. G. Gorenstein, Chem. Rev., 87, 1047, (**1987**). See also, A. J. Kirby, "**Reactivity and Structure Concepts in Organic Chemistry,**" Vol. 15, Springer-Verlag, N.Y., 1983.
2. a) A.Y. Garner, Chem. Abstr., 55, 5346, (**1961**); US Pat. 2,953,591 (1960);b) K. Bergesen, Acta.Chem. Scand., 21, 578, (**1967**) and 26, 2975, (**1972**) c) J.Songstad, *ibid.*, 21,1681, (**1967**); d) F. H. Westheimer, J. Am. Chem. Soc., 87, 253, (**1965**).
3. Recently, Taylor and Kluger J. Am. Chem. Soc., 114, 5714, (**1991**) prepared methyl propylphostonate in 70% yield by heating dimethyl γ-hydroxypropyl phosphonate at 100 °C under nitrogen for one hour.
4. a) H. Tomioka, M. Watanabe, N. Kobayashi, and K. Hirai, Tetrahedron Lett., 31, 5061, (**1990**); b) M. Regitz and H. Eckes, Tetrahedron Lett., 447, (**1975**).
5. R. P. Polniaszek and A. L. Foster, J. Org. Chem, 56, 3137, (**1991**).
6. We thank Prof. G. H. Whitham for providing us with his synthetic scheme and spectra.
7. An x-ray crystal structure has been reported by S. Bellard, S. Postle, and G.M. Sheldrick, Acta Cryst., B34, 1032, (**1978**).
8. We thank Profs. M. Steinmetz (M.U.) and P.M.Lahti (Univ. Mass.-Amherst) for these calculations.