Double Arbuzov Reaction of in Situ Generated Bis(trimethylsiloxy)phosphine with Dielectrophiles: Methodology for the Synthesis of Cyclic Phosphinic Acids

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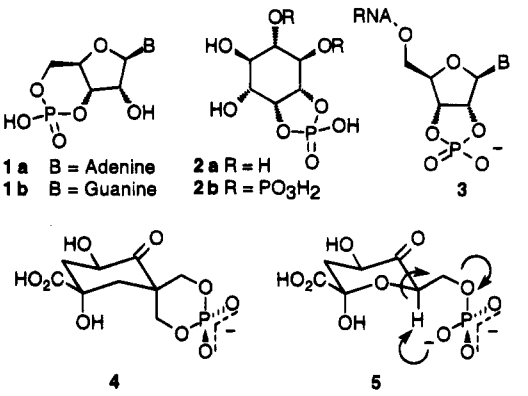
Received March 21, 1995 (Revised Manuscript Received July 5, 1995®)

Phosphetanic, phospholanic, phosphorinanic, phosphepanic, and phosphocanic acid derivatives have been prepared in a single step by the double Arbuzov reaction of bis(trimethylsiloxy)phosphine (BTSP) with dielectrophiles. Mild, thermal reaction conditions are employed during reaction of BTSP with 1,*n*-dihaloalkanes ($n = 3-7$), a ditriflate, and ω-bromo 1,2-epoxides possessing varying levels of steric congestion and functionalization. Isolation and manipulation of pyrophoric BTSP is avoided with in situ generation of the reagent from ammonium hypophosphite and hexamethyldisilazane. Monocyclic, bicyclic, and spirocyclic phosphinic acids are obtained after purification in moderate to good isolated yields. The developed methodology is of particular interest for synthesis of nonhydrolyzable analogues of cyclic phosphodiesters.

Many cyclic phosphodiesters that play critical metabolic and regulatory roles are enzymatically or hydrolytically labile. Examples include cyclic adenosine monophosphate (cAMP, **1a**), its guanosine counterpart (cGMP, **1b**), inositol-1,2-cyclic monophosphates (cIPs, **2**), and the 2′,3′-cyclic intermediate **3** formed during ribonuclease A-catalyzed RNA hydrolysis (Chart 1). Replacement of the ring oxygens with methylene carbons would afford cyclic phosphinic acids that are nonhydrolyzable, isosteric analogues of the naturally-occurring cyclic phosphodiesters. Such analogues could be employed to study and potentially alter regulation of important metabolic processes. A different use of cyclic phosphodiesters can be found in a transition state analogue (**4**, Chart 1) designed to inhibit 3-dehydroquinate (DHQ) synthase.[1] The cyclic phosphodiester structurally mimics the six-centered transition state involved in the elimination of phosphate from a reactive intermediate (**5**, Chart 1). A number of enzymes are mechanistically[2] similar to DHQ synthase in their recruitment of a phosphate group attached to an enzyme-bound substrate or reactive intermediate to effect intramolecular proton transfer. Cyclic phosphodiester mimics of these various transition states could conceivably result in potent enzyme inhibition. However, cyclic phosphodiester hydrolytic stability would be difficult to predict and could preclude use of the synthesized transition state analogue as an inhibitor. Neither in vitro or in vivo hydrolytic stability would be a concern for cyclic phosphinic acids with methylene carbons substituted for the ring oxygens of cyclic phosphodiester transition state mimics.

Despite their potential utility as antimetabolites and enzyme inhibitors, such uses of cyclic phosphinic acids are rare.[3] This partially reflects the limitations attendant with current synthetic routes to cyclic phosphinic acids.[4] Reported cyclic phosphinate syntheses suffer from either lack of generality, low yield, or use of reaction conditions that are incompatible with the presence of various functional groups. A route to cyclic phosphinic acids has now been developed which involves the double Arbuzov reaction of bis(trimethylsiloxy)phosphine (BTSP) with dielectrophiles. Five-membered-ring phospholanic acids and a six-membered-ring phosphorinanic acid are easily obtained by reaction of BTSP with the appropriate dielectrophile. BTSP is also sufficiently reactive to allow synthesis of strained, four-membered-ring phosphetanic acids as well as difficult-to-assemble seven-membered- and eight-membered-ring phosphepanic and phosphocanic acids. The array of different dielectrophiles that react with BTSP and the mild, thermal reaction conditions that are employed should ultimately allow access to a wide spectrum of cyclic phosphinic acids potentially possessing unique biological activities.

Chart 1



Results and Discussion

Some generalizations can be made about the hydrolytic stability of phosphodiesters and their analogues.[5] For

® Abstract published in *Advance ACS Abstracts,* August 15, 1995.

(1) Montchamp, J.-L.; Frost, J. W. *J. Org. Chem.* **1994**, *59*, 7596.

(2) These enzymes include the following. (a) Triose phosphate isomerase: Richard, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4926. (b) Aldolase: Periana, R. A.; Motiu-DeGrood, R.; Chiang, Y.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3923. (c) Aspartate carbamoyl transferase: Gouaux, J. E.; Krause, K. L.; Lipscomb, W. N. *Biochem. Biophys. Res. Commun.* **1987**, *142*, 893.

(3) See, for example: (a) Hewitt, D. G.; Teese, M. W. *Aust. J. Chem.* **1984**, *37*, 205. (b) Campbell, M. M.; Carruthers, N. I.; Mickel, S. J.; Winton, P. M. *J. Chem. Soc., Chem. Commun.* **1984**, 200.

(4) Reviews on phosphorus heterocycles: (a) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley: New York, 1981. (b) Mann, F. G. *The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth*; Wiley: New York, 1970; Part I. (c) Berlin, K. D.; Hellwege, D. M. *Top. Phosphorus Chem.* **1969**, *6*, 1. (d) Venkatamaru, S. D.; McDonell, G. D.; Purdum, W. R.; El-Deek, M.; Berlin, K. D. *Chem. Rev.* **1977**, *77*, 121.

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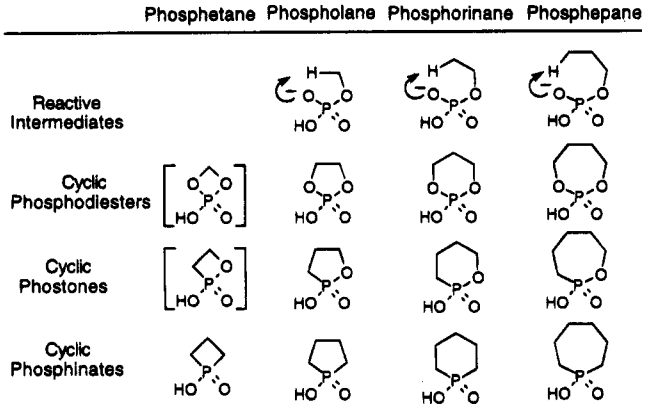
Table 1. Isosteric and Nonisosteric Cyclic Phostone and Cyclic Phosphinate Analogues of Cyclic Phosphodiesters and Phosphate-Mediated Proton Transfers

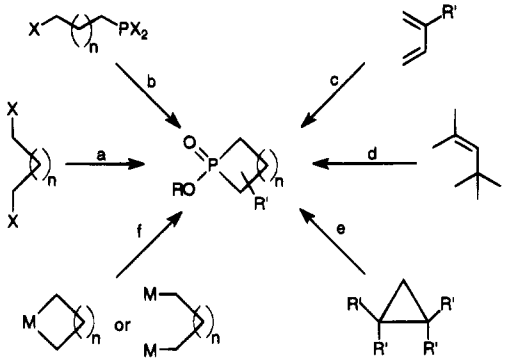


instance, stability toward hydrolysis typically improves with increasing ring size. 1,3,2-Dioxaphosphorinanes (Table 1) are substantially more stable than rapidly hydrolyzed 1,3,2-dioxaphospholanes. A similar correlation is observed for cyclic phosphonic acid monoesters (phostones) where one ring oxygen of the cyclic phosphodiester is replaced with a methylene carbon. 1,2-Oxaphosphepanes (Table 1) are more resistant to hydrolysis than 1,2-oxaphosphorinanes which, in turn, are substantially more stable than 1,2-oxaphospholanes. Cyclic phosphonic acid monoesters are generally more stable than the corresponding cyclic phosphodiesters as indicated by the slower rate of ring opening observed for 1,2-oxaphosphorinanes (Table 1) relative to 1,3,2-dioxaphosphorinanes. While rates of hydrolysis for 1,2-oxaphospholanes (Table 1) are likewise slower than those for 1,3,2-dioxaphospholanes, 1,2-oxaphospholanes are still rapidly hydrolyzed. This indicates that cyclic phosphonic acid esters, despite their improved stability, can be relatively reactive molecules.

The best way to eliminate problems with hydrolysis is to utilize a cyclic phosphinic acid (Table 1). Irrespective of ring size, cyclic phosphinic acids are stable. Conceptually, cyclic phosphinic acids result from replacement of both phosphodiester oxygen atoms with methylene carbons, removal of one ring oxygen atom, and substitution of methylene carbon for the other ring oxygen atom or removal of both ring oxygen atoms. Cyclic phosphinic acids thus provide access to a number of isosteric and uniquely nonisosteric structural relationships. For example, phospholanic acid is an isosteric analogue of a 1,3,2-dioxaphospholane as well as a five-centered transition state involving a phosphate monoester. Phosphetanic acid is a nonisosteric analogue of this same cyclic phosphodiester and five-centered transition state. Because the corresponding phosphodiester and 1,2-oxaphosphetanic acid are unknown chemical species (see bracketed structures in Table 1), phosphetanic acid is the only molecule capable of providing this structural relationship.

Cyclic Phosphinate Syntheses. The preferred method for the synthesis of cyclic phosphinic acids varies depending on the ring size and the substitution pattern desired. Scheme 1 summarizes some of the approaches

Scheme 1[a]



[a] Key: (a) (i) $P(OR)_3$, △, (ii) HBr, (iii) PCl_5, (iv) Mg, (v) H_3O^+; (b) (i) ROH, pyridine, (ii) △; (c) (i) $ROPCl_2$, or PX_3, (ii) H_2; (d) (i) PCl_3·$AlCl_3$, (ii) H_2O; (e) (i) i-Pr_2NPCl_2·$AlCl_3$, (ii) HCl, H_2O, △; (f) $ROP(O)Cl_2$ or (i) $ROPCl_2$, (ii) [O].

that have been used. Each method has its own set of restrictions such as the ring size of the synthesized cyclic phosphinate, the availability of the starting materials, or the compatibility of the reaction conditions to various functional groups. Intramolecular, nucleophilic attack on a phosphonyl dichloride (Scheme 1, reaction a) was one of the early syntheses of a cyclic phosphinic acid, but this strategy requires several steps and the overall yields are low.[6] A variation on this same theme is the intramolecular Arbuzov reaction of a suitable ω-halo phosphonite (Scheme 1, reaction b).[7]

The McCormack cycloaddition reaction between a 1,3-diene and a P(III) reagent (Scheme 1, reaction c) allows access to a variety of different phospholanic acids after hydrogenation but is limited to synthesis of five-membered cyclic phosphinic acids.[8] Availability of the diene starting material can be a problem, and depending on the diene structure, lengthy reaction times and forcing reaction conditions are sometimes required. The mechanistically related reaction of a phosphenium ion with a substituted olefin (Scheme 1, reaction d) developed by McBride provides access to phosphetanic acids.[9] This approach is limited to alkylated four-membered cyclic phosphinic acids due to the requirement for a carbocationic rearrangement. These same limitations also characterize the recently reported insertion of a phosphenium ion into a cyclopropane ring (Scheme 1, reaction e).[10] An approach providing more flexibility in the ring size of the synthesized cyclic phosphinic acid is based on the reaction of dimetallic or metallacyclic species with dichlorophosphates or dichlorophosphites (Scheme 1, reaction f).[11] However, a number of functional groups are not compatible with the strongly nucleophilic and/or basic organometallics that are used in this type of cyclization. Certain 1,n-dimetallic reagents are also difficult to prepare. For example, 1,3-dihaloalkanes do not give good yields of di-

(5) (a) Aksnes, G.; Bergesen, K. *Acta Chem. Scand.* **1966**, *20*, 2508. (b) Westheimer, F. H. In *Rearrangements in Ground and Excited States*; DeMayo, P., Ed.; Academic: New York, 1980; Chapter 10, p 229. (c) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

(6) Kosolapoff, G. M.; Struck, R. F. *J. Chem. Soc.* **1957**, 3739.

(7) Helferich, B.; Aufderhaar, E. *Ann.* **1962**, *658*, 100.

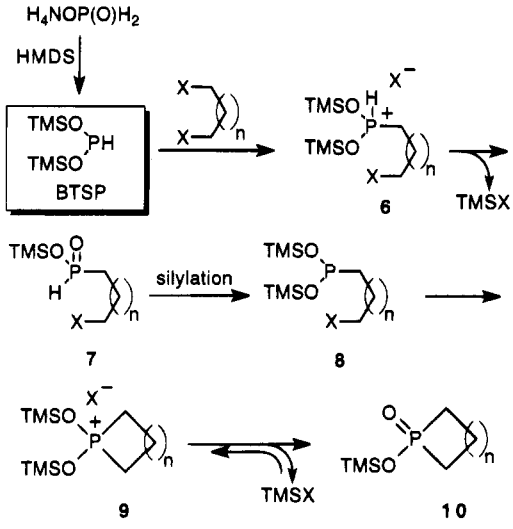
(8) (a) McCormack, W. B. U. S. Patents 2 663 736 and 2 663 737, 1953; *Chem. Abstr.* **1955**, *49*, 7601. (b) Quin, L. D. In *1,4-Cycloaddition Reactions*; Hamer, J. D., Ed; Academic: New York, 1967; Chapter 3.

(9) (a) McBride, J. J., Jr.; Jungerman, E.; Killheffer, J. V.; Clutter, R. J. *J. Org. Chem.* **1962**, *27*, 1833. (b) Jungerman, E.; McBride J. J., Jr.; Clutter, R. J.; Mais, A. *J. Org. Chem.* **1962**, *27*, 606.

(10) Weissman, S. A.; Baxter, S. G. *Tetrahedron Lett.* **1988**, *29*, 1219.

(11) (a) Wong, S.-C.; Carruthers, N. I.; Chan, T.-M. *J. Chem. Res., Synop.* **1993**, 268. (b) Polniaszek, R. P.; Foster, A. L. *J. Org. Chem.* **1991**, *56*, 3137. (c) Doxsee, K. M.; Shen, G. S.; Knobler, C. B. *J. Am. Chem. Soc.* **1989**, *111*, 9129. (d) For an early example using dialkyl phosphite as the electrophile: Kosolapoff, G. M. *J. Am. Chem. Soc.* **1955**, *77*, 6658.

Scheme 2



Grignard reagents due to competing intramolecular cyclization or β-elimination.[12]

BTSP Reactivity. Synthesis of symmetrical dialkylphosphinic acids by sequential, intermolecular Arbuzov-type reactions between bis(trimethylsiloxy)phosphine (BTSP)[13] and alkyl halides has been examined in two recent reports.[14] One report[14a] details reaction of preformed BTSP in refluxing benzene solution containing highly reactive alkyl halides, chlorotrimethylsilane, and triethylamine. A second report[14b] uses the same general reaction but relies on in situ generation of BTSP, thereby avoiding manipulation of this pyrophoric reagent. Subsequent reaction of the BTSP under neat reaction conditions at 80–120 °C allows the preparation of dialkylphosphinic acids from less reactive bromoalkanes. This last report provided a starting point for developing a synthetic route to cyclic phosphinic acids. In addition, synthesis of dialkylphosphinic acids from BTSP allows a likely reaction path (Scheme 2) to be formulated for cyclic phosphinic acid synthesis from BTSP condensation with dielectrophiles. Consideration of this mechanism was particularly helpful for optimization of the reaction parameters associated with cyclic phosphinic acid synthesis.

Reaction (Scheme 2) of ammonium hypophosphite and hexamethyldisilazane (HMDS) was well precedented to produce BTSP in excellent yield with generation of ammonia as the only byproduct.[13] Intermolecular reaction of one electrophilic center with the in situ generated BTSP was anticipated to lead to phosphonium ion **6** formation. The rates for dielectrophile reaction with BTSP needed to be rapid since alkyl halide-catalyzed disproportionation of BTSP into bis(trimethylsiloxy)-phosphine oxide, hexamethyldisiloxane, phosphine, and elemental phosphorus is a competing reaction.[15] After BTSP, trimethylsilyl alkylphosphinate **7** was likely to be the next problematic intermediate. Alkylphosphinate esters like intermediate **7**, which is formed from the collapse of phosphonium **6**, are known to disproportionate to primary phosphine and phosphonate diesters unless a silylating reagent is present.[16] Apparently, trimethylsilylation of **7** with HMDS or trimethylsilyl halide in the presence of base generates bis(trimethylsilyl) phosphonite **8** at a more rapid rate than the disproportionation of **7**. Intramolecular attack by phosphorus on the second electrophilic center in phosphonite **8** and collapse of the resulting phosphonium ion **9** were the expected final steps required for cyclic phosphinic acid formation.

Phosphetanic Acid Synthesis. The synthesis of phosphetanic acid was the initial test for using the reaction of BTSP with dielectrophiles as a synthetic route to cyclic phosphinic acids. Prior to this work, unsubstituted phosphetanic acid had been synthesized only twice.[6,11a] In 1957, a circuitous synthesis (Scheme 1, reaction a) was reported that began with Arbuzov reaction of 1,3-dibromopropane with triethyl phosphite.[6] The resulting diethyl (3-bromopropyl)phosphonate was converted to (3-bromopropyl)phosphonic dichloride. Treatment of this intermediate with Mg to form a Grignard reagent was followed by cyclization. Subsequent hydrolysis and product purification afforded phosphetanic acid in an estimated yield of only 0.01%.[6] A recently reported reaction of trimethylenedimagnesium dibromide with ethyl dichlorophosphate (Scheme 1, reaction f) afforded phosphetanic acid in 6% yield after hydrolysis of the ethyl phosphetanate intermediate.[11a] In contrast to these earlier approaches, reaction of BTSP with 1,3-dibromopropane using the reaction parameters outlined below resulted in a 36% isolated yield of phosphetanic acid.

Initial attempts at cyclization of 1,3-dibromopropane under previously reported neat reaction conditions[14b] failed to afford the desired product. Instead, some of the starting material remained unreacted and a large amount of an unidentified solid formed. The reaction was then conducted in refluxing toluene solution since dilution of the reagents was anticipated (Scheme 2) to favor intramolecular pathways (cyclization) over intermolecular pathways (polymerization, disproportionation). Under these conditions, a small amount of cyclized material was detected in the ^{13}C NMR spectrum of the crude reaction mixture. Increasing the reaction temperature to 140 °C (refluxing xylenes) or 163 °C (refluxing mesitylene, Table 2, entry 1) resulted in cleaner reaction and higher conversion. Mesitylene was subsequently used for the synthesis of the remaining phosphinic acids. An arbitrarily set concentration of 1 mmol of dielectrophile per 10 mL of solvent was used throughout the study. These relatively dilute conditions were not necessary for successful cyclization, and similar yields of phosphetanic acid could be obtained using a larger scale and more concentrated conditions. Increasing the number of equivalents of BTSP-forming reagents did not significantly improve the yields.

Reaction of BTSP with Dielectrophiles. A variety of 1,*n*-dibromides reacted with BTSP to afford cyclic phosphinic acids under the conditions utilized for synthesis of phosphetanic acid from BTSP and 1,3-dibromopropane. In most cases, inspection of the crude trimethylsilylated cyclic phosphinate (Scheme 2, **10**) by ^1H NMR and ^{13}C NMR revealed a clean conversion of the dielectrophile to the cyclized product with little or no

(12) (a) Seetz, J. W. F. L.; Hartog, F. A.; Böhm, H. P.; Blomberg, C.; Akkerman, O. S.; Bickelhaupt F. *Tetrahedron Lett.* **1982**, *23*, 1497. (b) Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 990.

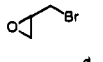
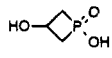
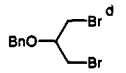
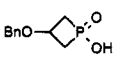
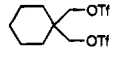
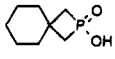
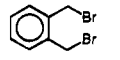
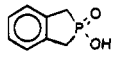
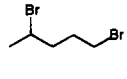
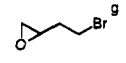
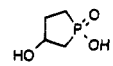
(13) Voronkov, M. G.; Marmur, L. Z. *Zh. Obshch. Khim.* **1970**, *40*, 2135.

(14) (a) Majewski, P. *Phosphorus, Sulfur, Silicon* **1989**, *45*, 151. (b) Ragulin, V. V.; Tsvetkov, E. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1988**, 2652.

(15) Voronkov, M. G.; Marmur, L. Z.; Dolgov, O. N.; Pestunovich, V. A.; Pokrovskii, E. I.; Popel, Y. I. *Zh. Obshch. Khim.* **1971**, *41*, 1987.

(16) Issleib, K.; Mögelin, W.; Balszuweit, A. *Z. Anorg. Allg. Chem.* **1985**, *530*, 16.

Table 2. Cyclic Phosphinic Acids Synthesized by Reaction of BTSP with Dielectrophiles

Entry	Starting Material	Product	Reaction Conditions[a]	Method[b]	Yield (lit. yield) %
1			163°C	A	36 (6)[c]
2			163°C	B	27
3			163°C	A	30
4			110°C	A	75
5			163°C	A	52 (29)[e]
6			163°C	A	59 (28)[f]
7			163°C	A	39
8			163°C	B	42
9			163°C	A	27 (39)[h]
10			163°C	A	75 (32)[c]
11			163°C	A	58
12			163°C	A	43

[a] Refluxing mesitylene: 163 °C. Refluxing toluene: 110 °C. [b] See Experimental Section. [c] Reference 11a. [d] Reference 27. [e] Reference 28. [f] Reference 29. [g] Reference 30. [h] Reference 31.

contamination by other compounds. Hydrolysis of the crude trimethylsilylated cyclic phosphinate at room temperature with saturated aqueous NaCl followed by continuous extraction (method A) directly afforded the corresponding phosphinic acid in excellent purity (Table 2, entries 1, 3, 5, 6, 10, 11, 12). Products which were highly water-soluble were obtained by water hydrolysis at room temperature followed by anion exchange chromatography (method B) to afford a reasonable yield of pure products (Table 2, entries 2, 8).

Choice of the leaving group in the dielectrophile was an important consideration. 1,3-Dichloropropane did not react with BTSP to form phosphetanic acid while BTSP reaction with 1,3-diiodopropane produced the cyclized phosphonium salt (Scheme 2, **9**) as part of a more complex reaction mixture.[17] Only 1,3-dibromopropane reaction with BTSP afforded acceptable yields of phosphetanic acid. On the basis of this observation, dibromides were chosen as the dielectrophiles for most of the examined reactions (Table 2). In contrast to 1,3-dichloropropane which was unreactive toward BTSP, an allylic dichloride was sufficiently reactive to form a phosphol-3-ene product (Table 2, entry 9). No double bond migration was detected.

Various examples where steric constraints might interfere with dielectrophile reaction with BTSP were also examined to better define the scope of the reaction. Reaction of 1,4-dibromopentane was studied (Table 2, entry 7) to determine if a secondary electrophilic carbon center could be tolerated in the cyclization. The corresponding C-2-substituted cyclic phosphinic acid was obtained without difficulty. BTSP reactions with dielectrophiles possessing neopentyl reaction centers were then examined. 1,1-Bis(bromomethyl)cyclohexane[18] or the corresponding diiodide or ditosylate[18] did not afford the desired heterocycle and were recovered unchanged. To remedy this apparent lack of reactivity, the ditriflate (Table 2, entry 4) was prepared and submitted to the reaction conditions. While refluxing in mesitylene resulted in extensive decomposition of the triflate, unreacted triflate dielectrophile was recovered from a benzene solution that had been heated at reflux for 2 h. Adjusting the reaction temperature to that of refluxing toluene ultimately led to formation of the desired heterocycle (Table 2, entry 4). The formation of the spirobicyclo phosphinic acid provides a useful example of the extent of reaction tuning that is required in sterically hindered cases even when a dielectrophile having a very good leaving group is employed.

Examination of the proposed mechanism (Scheme 2) indicated that 1 mol of trimethylsilyl halide should be produced for each mole of product formed. Trimethylsilyl halides are known to regioselectively open epoxides (catalytically or thermally) to afford the corresponding halohydrin where the halogen is attached to the least substituted carbon.[19] The TMSBr formed after the initial nucleophilic displacement of bromide by BTSP might therefore react with the oxirane to yield a bromohydrin, thereby generating the second electrophilic site needed for cyclization. In agreement with this projected reactivity, reaction of BTSP with two ω-bromo 1,2-epoxides in refluxing mesitylene produced cyclic phosphinic acids with a C-3 hydroxyl substituent (Table 2, entries 2, 8). Other mechanistic formulations that can account for the observed products are possible. The reaction, for example, may not proceed through a discrete bromohydrin intermediate. TMSBr might instead assist ring opening by forming a complex with the oxirane oxygen.[19] Whatever the mechanism might be, the reaction of a bromo epoxide with BTSP provides a particularly simple entry into C-3-substituted cyclic phosphinic acids.

Conclusion. The range of cyclic phosphinic acids that can be synthesized from BTSP will ultimately reflect the range of functional groups that are reactive with BTSP. Carbonyls[20] and imines[21] are precedented to react with BTSP while alkenes[22] are reactive under radical conditions. Garnering these reactivities into syntheses of new

(17) Iodotrimethylsilane is known to form phosphonium ions by *O*-alkylation of phosphates, phosphonates, and phosphinates: Schmidbaur, H.; Seeber, R. *Chem. Ber.* **1974**, *107*, 1731. Hydrolysis of the phosphonium salt also provides phosphetanic acid.

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cyclic phosphinic acids is just beginning.[23] Continual expansion in the structural diversity of available cyclic phosphinic acids is important given applications in research areas well removed from isosteric and nonisosteric analogues of phosphodiesters and phosphate monoester-mediated proton transfer. For instance, acyclic phosphinic acids have been successfully used as mimics of the tetrahedral adduct formed during peptide hydrolysis.[24] Conformational restrictions imposed by incorporation of cyclic phosphinic acids as the tetrahedral adduct mimic may lead to even more potent protease inhibitors. Cyclic phosphinic acids and other phosphorus heterocycles that can be derived from these molecules[4] are also increasingly being used as chiral ligands and auxiliaries.[25]

With in situ generation of BTSP from the reaction of ammonium hypophosphite and hexamethyldisilazane, BTSP reaction with dielectrophiles is a straightforward procedure. This reaction has afforded the highest yield achieved to date of phosphetanic acid. Reasonably good yields (27–75%) of four-, five-, six-, seven-, and eight-membered cyclic phosphinic acids are also obtained. Dielectrophiles with a variety of different substituents at C-2 and C-3 react with BTSP as do dielectrophiles possessing substantial levels of steric congestion. Parameters having a significant impact on product yield appear to be the dielectrophile's leaving group and reaction temperature. Generally, alkyl bromides are the electrophilic centers best suited for reaction with BTSP while refluxing mesitylene provides the most generally useful reaction temperature and solvent environment. Overall, the double Arbusov reaction between BTSP and dielectrophiles appears to be the most versatile and convenient methodology thus far identified for the synthesis of cyclic phosphinic acids.

Experimental Section

General Chemistry. Although the methodology presented here relies on in situ generation of BTSP and no fires occurred during the course of this investigation, CAUTION should still be exercised since neat BTSP is highly pyrophoric. The decomposition of BTSP appears to be complete after the reaction time employed (12–18 h), and no problems have been observed during workup as described. Melting points were uncorrected and were determined using a Mel-Temp II melting point apparatus. Organic solutions of products were dried over $MgSO_4$. See ref 1 for other general experimental information.

Ammonium Hypophosphite. $H_2PO_2NH_4$ was prepared according to a literature procedure:[26] H_3PO_2 (50 wt % in H_2O, 100 mL, 0.965 mol) was treated at 0 °C with ammonium carbonate (46 g, 0.480 mol) in portions. After addition was complete, the ice bath was removed and the mixture was stirred at rt for 12 h. The colorless solution obtained was concentrated in vacuo to afford a white paste which was recrystallized from acetone. Drying the resulting solid over P_2O_5 under high vacuum afforded white crystals (53 g, 66%) which were stored over P_2O_5 in a desiccator.

1,1-Bis[[(trifluoromethanesulfonyl)oxy]methyl]-cyclohexane. 1,1-Bis(hydroxymethyl)cyclohexane[18] (2.05 g, 14.2 mmol) was dissolved in CH_2Cl_2 (50 mL) and pyridine (2.5 mL, 31.3 mmol). Triflic anhydride (4.8 mL, 28.4 mmol) was added at −20 °C to the reaction mixture. A thick precipitate was rapidly obtained at which point the cold bath was removed. After 2 h at rt, the reaction mixture was partitioned between ice–water and EtOAc, and the resulting organic layer was washed successively with aqueous $CuSO_4$ (1×), brine (1×), aqueous $NaHCO_3$ (1×), and brine (1×). Concentration afforded an orange oil which was redissolved in hexane. Filtration through a silica pad, elution with EtOAc/hexane (1:1, v/v), and concentration afforded a slightly yellow oil which rapidly crystallized at −20 °C into a white solid (5.82 g, 100%): mp = 36–38 °C; ^{1}H NMR ($CDCl_3$) δ 4.43 (s, 4 H), 1.53 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 118.6 (q, J = 318 Hz), 77.3, 38.4, 28.5, 25.2, 20.5. Anal. Calcd for $C_{10}H_{14}F_6O_6S_2$: C, 29.41; H, 3.46. Found: C, 29.57; H, 3.43.

General Procedure for the Synthesis of Cyclic Phosphinic Acid (Table 2). A mixture of dielectrophile (2.5–5.0 mmol), HMDS (5 or 10 equiv), and $H_2PO_2NH_4$ (2 or 5 equiv) was refluxed in mesitylene (~10 mL/mmol dielectrophile) overnight under Ar. After cooling, the reaction mixture was concentrated in vacuo to a heterogeneous mixture consisting of a yellow oil and a white solid. Hydrolysis and product purification were carried out by use of one of the following methods:

Method A. The crude reaction mixture was hydrolyzed with brine at rt, filtered, then extracted with EtOAc for 24 h in a continuous extractor. Concentration afforded the phosphinic acid.

Method B. The crude reaction mixture was dissolved in EtOAc, filtered, concentrated in vacuo, and hydrolyzed with distilled water at rt. The resulting solution was loaded onto a column of AG-1 X8 (20 mL) and was then eluted with a linear gradient (300 mL + 300 mL, 0–100 mM) of triethylammonium bicarbonate (pH 7.2). Fractions containing phosphinic acid were concentrated to dryness. The resulting oil was azeotroped four times with 2-propanol, dissolved in water, and passed down a short column of Dowex 50 (H^+). Concentration under high vacuum afforded the phosphinic acid.

Table 2, Entry 1. 1-Hydroxyphosphetane 1-Oxide.[6,11a] Slightly yellow wax (0.278 g, 36%): ^{1}H NMR (D_2O), ^{13}C NMR (D_2O), ^{31}P NMR (D_2O), and HRMS were consistent with literature[11a] data.

Table 2, Entry 2. 1,3-Dihydroxyphosphetane 1-Oxide. Colorless oil (0.078 g, 27%): ^{1}H NMR (D_2O) δ 4.50 (dtt, J = 28, 8, 5 Hz, 1 H), 3.02 (dddd, J = 16, 14, 8, 1 Hz, 2 H), 2.63 (dddd, J = 19, 16, 5, 1 Hz, 1 H); ^{13}C NMR (D_2O) δ 57.9 (J_{PCC} = 17 Hz), 48.6 (J_{PC} = 72 Hz); ^{31}P NMR (D_2O) δ 40.0; HRMS (EI) calcd for $C_3H_7O_3P$ (M + H^+) 123.0214, found 123.0217.

Table 2, Entry 3. 3-(Benzyloxy)-1-hydroxyphosphetane 1-Oxide. White crystalline solid (0.170 g, 30%): mp = 72–75 °C; ^{1}H NMR ($CDCl_3$) δ 9.93 (br, 1 H), 7.24–7.36 (m, 5 H), 4.42 (s, 2 H), 4.11 (dtt, J = 19, 8, 6 Hz, 1 H), 2.94 (dddd, J = 16, 14, 8, 3 Hz, 2 H), 2.73 (dddd, J = 19, 14, 6, 3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.1, 128.4, 127.9 127.7, 71.1, 61.7 (J_{PCC} = 14 Hz), 44.5 (J_{PC} = 76 Hz); ^{31}P NMR ($CDCl_3$) δ 39.8; HRMS (EI) calcd for $C_{10}H_{13}O_3P$ (M^+) 212.0597, found 212.0592. Anal. Calcd for $C_{10}H_{13}O_3P$: C, 55.60; H, 6.17. Found: C, 55.82; H, 6.35.

Table 2, Entry 4. 2-Hydroxy-2-phosphaspiro[3.5]-nonane 2-Oxide. This was obtained following the general procedure, except that the reaction was carried out in toluene (10 mL) and the solvent used for continuous extraction was methylene chloride. The phosphinic acid was a slightly yellow oil (0.136 g, 75%): ^{1}H NMR ($CDCl_3$) δ 11.42 (br, 1 H), 2.33 (d, J = 16 Hz, 4 H), 1.51 (s, 5 H), 1.33 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 47.3 (J_{PC} = 73 Hz), 38.9 (J_{PCCC} = 14 Hz) 28.0 (J_{PCC} = 20 Hz), 25.2, 23.1; ^{31}P NMR ($CDCl_3$) δ 46.0; HRMS (EI) calcd for $C_8H_{15}O_2P$ (M^+) 174.0805, found 174.0800.

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Table 2, Entry 5. 1-Hydroxyphospholane 1-Oxide.[28] White crystalline solid (0.290 g, 52%): ^{1}H NMR ($CDCl_3$) δ 11.21 (br, 1 H), 1.59–1.95 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 25.2 (J_{PC} = 92 Hz), 23.0 (J_{PCC} = 13 Hz); ^{31}P NMR ($CDCl_3$) δ 80.9. Anal. Calcd for $C_4H_9O_2P$: C, 40.00; H, 7.55. Found: C, 40.12; H, 7.60.

Table 2, Entry 6. 2-Hydroxy-1*H*-phosphindoline 2-Oxide.[29] Yellow oil (0.402g, 59%): ^{1}H NMR ($CDCl_3$) δ 11.53 (br, 1 H), 7.20 (s, 4 H), 3.05–3.20 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 134.9 (J_{PCC} = 13 Hz), 127.4 (J_{PCCC} = 17 Hz) 127.4, 32.1 (J_{PC} = 93 Hz); ^{31}P NMR ($CDCl_3$) δ 70.2. Anal. Calcd for $C_8H_9O_2P$: C, 57.15; H, 5.40. Found: C, 57.13; H, 5.50.

Table 2, Entry 7. 1-Hydroxy-2-methylphospholane 1-Oxide. Yellow oil (0.186g, 39%): ^{1}H NMR ($CDCl_3$) δ 11.33 (br, 1 H), 1.25–2.18 (m, 7 H), 1.18 (dd, J = 16, 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 31.9 (J_{PCC} = 16 Hz), 31.1 (J_{PC} = 94 Hz), 24.8 (J_{PC} = 89 Hz), 20.4 (J_{PCC} = 10 Hz), 12.2 (J_{PCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 78.5; HRMS (EI) calcd for $C_5H_{11}O_2P$ (M^+) 134.0497, found 134.0498.

Table 2, Entry 8. 1,3-Dihydroxyphospholane 1-Oxide. Colorless oil (0.188 g, 42%): ^{1}H NMR (D_2O) δ 4.44 (d quintet, J = 19, 5 Hz, 1 H), 1.75–2.20 (m, 6 H); ^{13}C NMR (D_2O) δ 71.4 (J_{PCC} = 17 Hz), 36.8 (J_{PC} = 88 Hz), 33.7 (J_{PCC} = 9 Hz), 26.1 (J_{PC} = 86 Hz) ; ^{31}P NMR (D_2O) δ 78.0; HRMS (EI) calcd for $C_4H_9O_3P$ (M^+): 136.0288, found 136.0287.

Table 2, Entry 9. 1-Hydroxyphosphol-3-ene 1-Oxide.[31] Yellow oil (0.101g, 27%): ^{1}H NMR ($CDCl_3$) δ 11.21 (br, 1 H), 5.84 (d, J = 33 Hz, 2 H), 2.41 (d, J = 13 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 126.8 (J_{PCC} = 16 Hz), 30.1 (J_{PC} = 93 Hz); ^{31}P NMR ($CDCl_3$) δ 75.6. Anal. Calcd for $C_8H_9O_2P$: C, 40.69; H, 5.98. Found: C, 40.95; H, 6.22.

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Table 2, Entry 10. 1-Hydroxyphosphorinane 1-Oxide.[11a] White solid (0.225 g, 75%): ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 1.69–1.88 (m, 8 H), 1.39–1.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.6 (J_{PC} = 87 Hz), 26.0 (J_{PCCC} = 8 Hz), 23.4 (J_{PCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 52.6; HRMS (EI) calcd for $C_5H_{11}O_2P$ (M^+) 134.0496, found 134.0495.

Table 2, Entry 11. 1-Hydroxyphosphepane 1-Oxide. White crystalline solid (0.289 g, 58%): mp = 66–70 °C; ^{1}H NMR ($CDCl_3$) δ 11.65 (br, 1 H), 1.21–1.76 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 30.0 (J_{PC} = 88 Hz), 29.2, 20.7; ^{31}P NMR ($CDCl_3$) δ 62.0; HRMS (EI) calcd for $C_6H_{13}O_2P$ (M^+) 148.0648, found 148.0643. Anal. Calcd for $C_6H_{13}O_2P$: C, 48.65; H, 8.84. Found: C, 48.61; H, 8.76.

Table 2, Entry 12. 1-Hydroxyphosphocane 1-Oxide. Yellow oil (0.216 g, 43%): ^{1}H NMR ($CDCl_3$) δ 11.53 (br, 1 H), 1.79–2.02 (m, 8 H), 1.58 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 27.6 (J_{PC} = 89 Hz), 27.2 (J_{PCC} = 1 Hz), 22.8, 20.2 (J_{PCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 61.8; HRMS (EI) calcd for $C_7H_{15}O_2P$ (M^+) 162.0812, found 162.0814.

Acknowledgment. Research was supported by a grant from the National Institutes of Health. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility which is supported, in part, by a grant (DRR-00480) from the Biotechnology Research Technology Program, National Center for Research Resources, National Institutes of Health. The NMR data were obtained on instrumentation that was purchased in part with funds from the NIH (1-S10-RR04750) and NSF (CHE-88-00770 and 92-13241).

JO950546H