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Nucleophilic transformations of cyclic phosphate triesters

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Abstract—Reactions of cyclic phosphate triesters, such as 2-ethoxy-1,3,2-dioxaphospholane 2-oxide, with Grignard reagents such as phenyl-, alkyl-, ethynyl-, and allyl-magnesium halides result in ring opening leading to the corresponding phosphonates, via nucleophilic attack of carbon on the phosphorus atom. Treatment of 2-ethoxy-1,3,2-dioxaphospholane 2-oxide with sodium borohydride yields ethyl 2-hydroxyethyl phosphite. This reaction is exclusive for the five-membered cyclic system: under these conditions acyclic phosphate triesters, such as triethyl phosphate, are unreactive and the analogous six-membered ring system, 2-ethoxy-1,3,2-dioxaphosphorinane 2-oxide reacts only partially to give unidentified phosphate esters and traces of phosphonate products. Both compounds were inert to $NaBH_4$.

Phosphonic acids and their ester derivatives are commonly employed in synthesis for C–C bond formation.[1] Their potential contribution to biological activities,[2] as well as their use as transition state analogs in the production of catalytic antibodies for a wide variety of reactions[3] has been studied extensively.

Phosphorus–carbon bond formation leading to tetracoordinate phosphorous compounds has been a subject of extensive research for over a century.[4] Most of the known methods involve addition to trivalent phosphorus-containing compounds.[5] Other methods, involving catalytic hydrophosphorylation of olefins[6] and alkynes,[7] have also been reported recently.

Attack by carbanions on phosphates are rare.[8] A few examples are known, in which phosphate triesters (i.e., triethyl and tributyl phosphate) react with 2 equiv of alkyllithium reagents to form α-substituted alkyl phosphonates.[9]

The use of Grignard rather than lithium reagents is far less promising.[8] Alkylation on phosphorus of phosphate triesters usually requires harsh conditions (e.g., elevated temperatures) and results in poor to moderate yields. The reaction usually forms the corresponding phosphinate and, mainly, the phosphine oxide as the major product.[10] When phosphate or thiophosphate triesters were treated with allylic Grignard reagents, a C–C cross-coupling reaction, rather than nucleophilic attack on phosphorus, took place, forming phosphoric acid diesters as by-products.[11] Similar cross-coupling reactions were also observed when trialkyl phosphates were reacted with bulky Grignard reagents (i.e., triphenylmethylmagnesium chloride and mesitylmagnesium bromide).[12]

It is well documented that five-membered cyclic phosphorus compounds are more reactive toward nucleophilic attack than their acyclic or six-membered analogs.[13] In some cases, like catalytic hydrophosphorylation reactions, five-membered rings were found to be reactive while the open-chain and six-membered analogs were inert, even though the ring remained intact.[6] Even more striking is the fact that the reaction of 2-alkyl-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide with *n*-BuLi results in opening of the five-membered ring and P–C bond formation,[14] rather than the normal generation of an α-carbanion via deprotonation.[15] A thorough investigation of the base-catalyzed hydrolysis of 2-methoxy- and 2-ethoxy-1,3,2-dioxaphospholane 2-oxide **1** indicated that this unique reactivity toward hydroxide ions is the result of a combination of the relief of the strain of the ring and stereoelectronic effects in the transition state.[16] Edmundson et al. reported the reaction of 2-chloro-1,3,2-dioxaphospholane 2-oxide with phenyl

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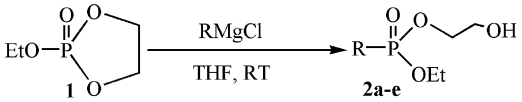
Grignard reagents.[17] They were able to isolate 2-hydroxyethyl diphenylphosphinate, which results from double arylation of the phosphorus center (presumably by displacement of the chlorine followed by ring opening), while no traces of the mono-arylation product, 2-phenyl-1,3,2-dioxaphospholane 2-oxide, were found.

The preparation of H-phosphonates (also known as dialkyl phosphites) has also been a subject of intensive research both from synthetic and biological aspects.[18] A few methods are known for the preparation of this type of compound. Probably the most cited method is the hydrolysis of phosphorochloridites, which are easily prepared by alcoholysis of PCl_3.[19] In a rare example, a phosphate triester was converted to a H-phosphonate by a two-step process: mono-chlorination to the phosphorochloridate, followed by reduction with sodium borohydride in refluxing dioxane.[20] To the best of our knowledge, there is no precedent for the direct reduction of phosphate triesters with mild reducing agents, such as sodium borohydride, giving access to this class of compounds.

We report here a novel reaction in which nucleophilic attack of various Grignard reagents on the phosphorus atom of **1** is followed by ring opening, resulting in the formation of the corresponding phosphonates **2a–e** (Scheme 1). Reduction of **1** with $NaBH_4$ to the corresponding H-phosphonate is outlined in Scheme 2.

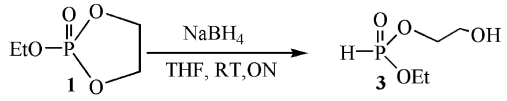
2-Ethoxy-1,3,2-dioxaphospholane 2-oxide **1**, easily prepared according to a literature procedure,[16] reacted with phenyl-, methyl-, ethyl-, ethynyl-, and allyl-magnesium chlorides, under mild conditions (room temperature, inert atmosphere) to give the corresponding phosphonates (**2a–e**) in good yields.[21] In some cases, traces (<5%, by NMR integration) of the corresponding phosphinate was found in the ^{31}P spectrum of the crude reaction mixtures. Triethyl phosphate and the six-membered ring system, 2-ethoxy-1,3,2-dioxaphosphorinane 2-oxide, did not react with these Grignard reagents, under the same conditions. A summary of the reaction conditions and yields of the phosphonates obtained are presented in Table 1.

Reaction of **1** with 1 equiv of phenylmagnesium chloride, for 16 h, resulted in 75% conversion to ethyl 2-hydroxyethyl phenylphosphonate **2a**.[22] No other



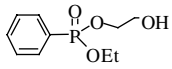
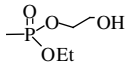
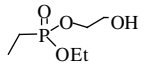
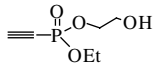
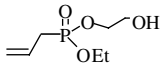
R= **a.** Ph, **b**. CH_3, **c.** CH_3CH_2, **d**. HC≡C, **e**. CH_2=$CHCH_2$

Scheme 1. Reaction of **1** with Grignard reagents.



Scheme 2. Reaction of **1** with sodium borohydride.

Table 1. Summary of the reactions of **1** with RMgCl reagents

Compound no	Reaction time/no of equivalents of RMgCl	Product	Yield (%)
2a	16 h/2 equiv		80
2b	2 h/2 equiv		75
2c	16 h/2 equiv		74
2d	16 h/3 equiv		70
2e	16 h/2 equiv		30

products, besides the starting material, could be observed in the ^{31}P NMR spectrum. When 2 equiv of phenylmagnesium chloride were used, almost full conversion to **2a** was observed.[23] An additional by-product (<5%, by integration), ethyl diphenylphosphinate was detected in the ^{31}P spectrum at 32.0 ppm. GC–MS of the crude reaction mixture exhibited, in addition to **2a**, two more minor products corresponding to ethyl diphenylphosphinate and 2-hydroxyethyl diphenylphosphinate (m/z = 246 [M^+] and m/z = 262 [M^+], respectively). The desired product was isolated in 80% yield.

Treatment of **1** with 1 equiv of methylmagnesium chloride for 2 h, gave ethyl 2-hydroxyethyl methylphosphonate **2b** in 32% yield. Using 2 equiv of CH_3MgCl increased the yield to 75%.[24] In both cases small amounts (<2%, by integration) of ethyl dimethylphosphinate and 2-hydroxyethyl dimethylphosphinate (as evident from the ^{31}P NMR spectrum) were also detected. Both compounds were also found by GC–MS (m/z = 138 [M^+] and m/z = 154 [M^+], respectively). Similarly, when **1** was reacted with 2 equiv of ethylmagnesium chloride, for 16 h, ethyl 2-hydroxyethyl ethylphosphonate **2c** was obtained.[25]

The reaction of **1** with ethynylmagnesium chloride, leading to **2d**, is of unique interest. Alkynylphosphonates, which have been frequently used as acyl anion equivalents, have been utilized as intermediates in the synthesis of the antibiotic phosphonomycin.[26] Such derivatives were synthesized by the reaction of dialkyl- or diphenyl phosphorochloridates with alkynylmagnesium bromide.[27] Stirring **1**, for 16 h, at room temperature with 3 equiv of ethynylmagnesium chloride led to a single product **2d**[28] as evident from the ^{31}P NMR spectrum (−10.48 ppm). The proton coupled ^{31}P spectrum revealed a double quintet pattern with a large splitting (J_{H-P} = 13.5 Hz). This large coupling constant was attributed to the ethynylic proton. The ^1H spectrum revealed a doublet at 3.04 ppm with the same coupling constant. The ^{13}C NMR spectrum revealed two doublets at 89.01 (J_{P-C} = 51.6 Hz) and 73.40 (J_{P-C} = 294 Hz) ppm. These chemical shifts and coupling constants are

characteristic of ethynylphosphonates and are similar to those observed for diethyl ethynylphosphonate.[29] The product was isolated in a yield similar to those reported when phosphorochloridates were used as precursors.[27]

Following previous reports indicating the formation of C–C bonds upon reaction with allyl Grignard reagents,[11] we investigated further the reaction of **1** with allylmagnesium halides. Reaction of **1** with 2 equiv of allylmagnesium chloride, for 16 h, gave ethyl 2-hydroxyethyl allylphosphonate **2e** in 30% yield.[30] Using 2 or 3 equiv of allylmagnesium bromide gave similar results. The product **2e** exhibited NMR signals characteristic of allylphosphonates similar to those observed for diethyl allylphosphonate:[31] the ^{31}P NMR signal appeared at 25.55 ppm. The olefinic protons in the ^{1}H spectrum, appeared as three multiplets centered at 5.73, 5.19, and 4.94 ppm and the allylic protons as a doublet of doublets at 3.55 ppm ($J = 9.6$ Hz, 3.0 Hz). The ^{13}C spectrum revealed the olefinic carbons, each appearing as a doublet at 126.55 ($J_{P-C} = 11.8$ Hz) and 119.76 ($J_{P-C} = 14.7$ Hz) and the allylic carbon as a doublet at 30.87 ppm ($J_{P-C} = 140.2$ Hz). A few minor by-products were also observed in the crude reaction mixture. Two of these products were characterized by GC–MS: ethyl diallylphosphinate and 2-hydroxyethyl diallylphosphinate ($m/z = 174$ [M^+] and $m/z = 190$ [M^+], respectively).

Attempts to prepare the corresponding benzyl and vinyl phosphonates under similar conditions were not successful. NMR spectra, recorded for the crude reaction mixtures, indicated that no phosphonates had been formed. Moreover, no olefinic protons were detected in the ^{1}H NMR spectrum of the reaction products between CH_2=CHMgCl and **1**. The ^{31}P spectrum revealed a few signals in the aliphatic phosphate region.

Combining our results and those reported in the literature, regarding the preparation of phosphonates, it seems that the reactivity of organophosphorus compounds toward Grignard reagents follows the order: phospho 1,3,2-dioxaphospholane 2-oxide > phosphoro 1,3,2-dioxaphospholane 2-oxide **1** >> acyclic phosphonates > acyclic phosphates. It is obvious that phosphorochloridates are the most reactive precursors, but as 2-chloro-1,3,2-dioxaphospholane 2-oxide initially yields the reactive cyclic phosphonate, the latter readily undergoes a second attack to form an acyclic phosphinate. Therefore, its utility in the preparation of phosphonates is limited. In contrast, when the less reactive phosphate **1** is used, it reacts with 1 equiv of the Grignard reagent to form a far less reactive species **2**. Acyclic systems react with Grignard reagents under harsh conditions,[10] which are obviously not the case in our reaction. Thus, it is clear that **1** is a much better precursor for the preparation of phosphonates compared with its halogen analog, 2-chloro-1,3,2-dioxaphospholane 2-oxide, or acyclic phosphate triesters.

The results obtained on reacting **1** with carbon nucleophiles tempted us to extend our study to reactions with hydrides. Indeed, reaction of **1** with $NaBH_4$ over night at room temperature led to ethyl 2-hydroxyethyl phosphite **3** following ring cleavage.[32] This result is clearly significant when compared to dialkyl chlorophosphates, which undergo reduction only at elevated temperatures (boiling dioxane).[20] The ^{1}H and ^{13}C NMR spectra of **3** are identical to those previously reported for this compound,[33] and exhibit characteristic signals of dialkyl phosphites (a doublet of quintets pattern with a very large coupling constant of 693 Hz in both proton coupled ^{31}P and ^{1}H spectra). The product **3** was obtained in 66% isolated yield.

Treating **1** with stronger hydrides such as 'super hydride', $LiAlH_4$ and DIBAL-H gave a mixture of products, none of which was characteristic of a dialkyl phosphite system. Triethyl phosphate and the six-membered ring, 2-ethoxy-1,3,2-dioxaphosphorinane 2-oxide, did not react with sodium borohydride under similar conditions.

In conclusion, we have found phospholane **1** to be a superior precursor for a single nucleophilic attack at phosphorus, leading to phosphonates, when compared to its chloro analog 2-chloro-1,3,2-dioxaphospholane-2-oxide or phosphorus triesters. Under reductive conditions this cyclic phosphate triester is easily converted to the H-phosphonate even at room temperature.

References and notes

1. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
2. (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349; (b) Mikolajczyk, M.; Balczewski, P. *Top. Curr. Chem.* **2003**, *223*, 161.
3. Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659.
4. *A Guide to Organophosphorus Chemistry*; Quin, L. D., Ed.; Wiley-Interscience: New York, 2000.
5. For a review see: Engel, R. *Synthesis of Carbon-Phosphorus Bonds*; CRC: Boca Raton, FL, 1988.
6. (a) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407; (b) Reichwein, J. F.; Patel, M. C.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 4303; (c) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315.
7. (a) Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 94; (b) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929.
8. For a recent review see: Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13109.
9. (a) Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1987**, *28*, 405; (b) Savignac, P.; Teulade, M. P.; Patois, C. *Heteroatom Chem.* **1990**, *1*, 211; (c) Savignac, P.; Patois, C. *Org. Synth.* **1995**, *72*, 241.
10. (a) Dawson, N. D.; Burger, A. *J. Org. Chem.* **1953**, *18*, 207; (b) Berlin, K. D.; Peterson, M. E. *J. Org. Chem.* **1967**, *32*, 125; (c) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 4201.
11. Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 5879.
12. Gilman, H.; Gaj, B. J. *J. Am. Chem. Soc.* **1960**, *82*, 6326.
13. (a) Kumomoto, J.; Cox, R., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 4858; (b) Eberhard, A.; Westheimer, F. H. *J. Am. Chem. Soc.* **1965**, *87*, 253; (c) Ahsens, G.; Eriksen, R. *Acta Chem. Scand.* **1965**, *9*, 2463; (d) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.
14. Reichwein, J. F.; Pagenkopf, B. L. *J. Org. Chem.* **2003**, *67*, 1459.

15. (a) Takahashi, H.; Fujiwara, K.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1498; (b) Collado, I.; Ezquerra, J.; Mazon, A.; Pedregal, C.; Yruretagoyena, B.; Kingston, A. E.; Tomlinson, R.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2849; (c) Ref. 9.
16. Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Org. Chem.* **1984**, *49*, 4531.
17. Edmundson, R. S.; Wrigley, O. L. *Tetrahedron* **1967**, *23*, 283.
18. For a recent review see: Stawinski, J.; Kraszewski, A. *Acc. Chem. Res.* **2002**, *35*, 952.
19. (a) Nesterov, A. V.; Sabirova, R. A. *J. Gen. Chem. USSR* **1965**, *35*, 1967; (b) Zwierzak, A. *Can. J. Chem.* **1967**, *45*, 2501; (c) Nefant'ev, E. E.; Fursenko, I. V. *J. Gen. Chem. USSR* **1968**, *38*, 1251.
20. Engel, R.; Chakraborty, S. *Synth. Commun.* **1988**, *18*, 665.
21. General procedure for the preparation of **2**: An oven dried flask was charged with **1** (0.5 g, 3.3 mmol) dissolved in anhydrous THF (10 mL). The appropriate amount of Grignard reagent (commercial solutions in THF) was added, and the mixture was stirred over-night at room temperature (2 h in the case of CH_3MgCl). The reaction mixture was quenched with 1 N aq HCl, then Et_2O (10 mL) was added and the layers were separated. The aqueous layer was washed with chloroform (3×50 mL), the organic layers were combined, dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The crude oily product was charged on a silica gel column and the products were eluted with Et_2O–MeOH (20:1).
22. This compound was also obtained, in similar yields, from the corresponding *N*-pyrazolyl phenyl phosphonoamidate and ethylene glycol, see: Felcht, U.; Regitz, M. *Chem. Ber.* **1976**, *109*, 3675.
23. Ethyl 2-hydroxyethyl phenylphosphonate **2a**: ^{1}H NMR ($CDCl_3$, 300 MHz): 7.76–7.72 (m, 1H), 7.42–7.39 (m, 4H), 4.30 (br s, 1H), 4.10–4.00 (m, 4H), 3.77–3.70 (m, 2H), 1.26 (t, 3H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 132.70 (d, J_{P-C} = 3.0 Hz), 131.71 (d, J_{P-C} = 9.9 Hz), 128.52 (d, J_{P-C} = 15.2 Hz), 128.15 (d, J_{P-C} = 169 Hz), 68.13 (d, J_{P-C} = 6.0 Hz), 62.62 (d, J_{P-C} = 5.6 Hz), 61.93 (d, J_{P-C} = 5.7 Hz), 16.15 (d, J_{P-C} = 6.9 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): 16.61. MS-CI (*m*/*z*) 231 (100%) $[M+H]^+$, 230 (10%) $[M]^+$, 213 (8%) $[M-OH]^+$.
24. Ethyl 2-hydroxyethyl methylphosphonate **2b**: ^{1}H NMR ($CDCl_3$, 300 MHz): 4.28 (br s 1H), 4.06 (m, 4H), 3.70 (t, 2H, J_{H-H} = 4.5 Hz), 1.45 (d, 3H, J_{P-H} = 17.7 Hz) 1.26 (t, 3H, J = 4.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 67.70 (d, J_{P-C} = 6.6 Hz), 61.89 (d, J_{P-C} = 6.3 Hz), 61.75 (d, J_{P-C} = 4.8 Hz), 16.21 (d, J_{P-C} = 6.2 Hz), 10.79 (d, J_{P-C} = 145 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): 29.27. MS-EI (*m*/*z*) 168 (60%) $[M]^+$, 141 (95%) $[M-C_2H_3]^+$, 125 (60%) $[M-C_2H_3O]^+$, 99 (100%) $[M-C_4H_5O]^+$.
25. Ethyl 2-hydroxyethyl ethylphosphonate **2c**: ^{1}H NMR ($CDCl_3$, 300 MHz): 4.25 (br s, 1H), 4.11–4.05 (m, 4H), 3.73 (t, 2H, J_{H-H} = 4.7 Hz), 1.73 (dq, 2H, J_{P-H} = 18.4 Hz, J_{H-H} = 7.8 Hz) 1.32 (dt, 3H, J_{P-H} = 0.9 Hz, J_{H-H} = 7.2 Hz), 1.12 (dt, 3H, J_{P-H} = 20.0 Hz, J_{H-H} = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 68.02 (d, J_{P-C} = 6.9 Hz), 62.07 (d, J_{P-C} = 6.3 Hz), 61.90 (d, J_{P-C} = 6.5 Hz), 18.45 (d, J_{P-C} = 143.2 Hz), 16.33 (d, J_{P-C} = 5.9 Hz), 6.37 (d, J_{P-C} = 6.9 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): 32.38. MS-CI (*m*/*z*) 183 (100%) $[M+H]^+$, 182 (15%) $[M]^+$, 165 (5%) $[M-OH]^+$, 137 (25%) $[M-C_2H_5OH]^+$.
26. Christensen, B. G.; Leanza, W. J.; Beattie, T. R.; Patchett, A. A.; Arison, B. H.; Ormond, R. E.; Kuehl, F. A., Jr.; Albers-Schonberg, G.; Jardetzky, O. *Science* **1969**, *166*, 123.
27. (a) Saunders, B. C.; Simpson, P. *Chem. Ind.* **1960**, 47; (b) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2719.
28. Ethyl 2-hydroxyethyl ethynylphosphonate **2d**: ^{1}H NMR ($CDCl_3$, 300 MHz): 4.50 (br s, 1H), 4.10 (m, 4H), 3.74 (t, 2H, J_{H-H} = 4.6 Hz), 3.04 (d, 1H, J_{P-H} = 13.5 Hz), 1.30 (t, 3H, J_{H-H} = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 89.01 (d, J_{P-C} = 51.6 Hz), 73.40 (d, J_{P-C} = 294 Hz), 68.98 (d, J_{P-C} = 6.0 Hz), 63.90 (d, J_{P-C} = 5.7 Hz), 61.23 (d, J_{P-C} = 6.5 Hz), 15.88 (d, J_{P-C} = 7.1 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): −10.48. MS-CI (*m*/*z*) 179 (100%) $[M+H]^+$, 178 (15%) $[M]^+$, 161 (5%) $[M-OH]^+$.
29. Lequan, R.-M.; Pouet, M.-J.; Simonnin, M.-P. *Org. Magn. Reson.* **1975**, *7*, 392.
30. Ethyl 2-hydroxyethyl allylphosphonate **2e**: ^{1}H NMR ($CDCl_3$, 300 MHz): 5.73 (m, 1H), 5.19 (m, 1H), 4.94 (m, 1H), 4.38 (br s, 1H), 4.08 (m, 4H), 3.72 (m, 2H), 3.55 (dd, 2H, J = 9.6, 3.0 Hz), 1.16 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 126.55 (d, J_{P-C} = 11.8 Hz), 119.76 (d, J_{P-C} = 14.7 Hz), 67.80 (d, J_{P-C} = 7.0 Hz), 61.99 (d, J_{P-C} = 6.8 Hz), 61.46 (d, J_{P-C} = 5.7 Hz), 30.87 (d, J_{P-C} = 140.2 Hz), 15.82 (d, J_{P-C} = 6.9 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): 25.55. MS-CI (*m*/*z*) 195 (100%) $[M+H]^+$, 194 (10%) $[M]^+$, 177 (5%) $[M-OH]^+$.
31. Ernst, L. *Org. Magn. Reson.* **1977**, *9*, 35.
32. Preparation of ethyl 2-hydroxyethyl phosphite **3**: An oven dried flask was charged with $NaBH_4$ (0.125 g, 3.3 mmol) suspended in anhydrous THF (10 mL). A solution of **1** (0.5 g, 3.3 mmol) in anhydrous THF (10 mL) was added, and the mixture was stirred over night at room temperature. The reaction mixture was quenched with 1 N HCl to bring the pH < 2, then Et_2O (10 mL) was added and the layers were separated. The aqueous layer was washed with chloroform (3×50 mL), the organic layers were combined, dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The crude oily product was charged on a silica gel column and was eluted with hexane:ethyl acetate (3:1) to afford **3** as a colorless oil (0.334 g, 2.2 mmol, 66% yield).
33. Tzokov, S. B.; Momtcheva, R. T.; Vassilev, N. G.; Kaneti, J.; Petkov, D. D. *J. Am. Chem. Soc.* **1999**, *121*, 5103.