methylene chloride). After concentration of the solvent, **3** was crystallized from diethyl ether/hexane (80 mg, 57%): HPLC, column A (A/B, 25:75), t_R = 5.96 min (coelution with the natural nordidemnin B); HRFABMS, *m/e* (M^+ + H) 1098.61 ($C_{56}H_{88}N_7O_{15}$ requires 1098.63); CD (methanol) $[\theta]_{218}$ +212, $[\theta]_{234}$ +145, $[\theta]_{295}$ −72 (natural nordidemnin B, $[\theta]_{219}$ +221, $[\theta]_{234}$ +153 $[\theta]_{296}$ −67.

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Registry No. **3**, 117710-03-9; **4**, 117710-04-0; **5**, 117710-05-1; (3*S*)-**6**, 117710-06-2; **7a**, 117710-07-3; **8**, 117710-08-4; **9**, 65138-05-8; **10**, 117710-09-5; **10** (free acid), 117710-20-0; **11**, 117710-10-8; (2*S*)-**12**, 117710-11-9; (2*R*)-**12**, 117773-51-0; **13**, 73584-84-6; **14**, 117710-12-0; **15**, 117710-13-1; **15** (BOC-deprotected)·TFA, 117710-23-3; **15** (BOC-deprotected), 117710-22-2; **16**, 33294-56-3; **17**, 117710-14-2; **17** (BOC-deprotected)·TFA, 117710-25-5; **18**, 117710-15-3; **18** (BOC-deprotected)·TFA, 117710-27-7; **18** (BOC-deprotected), 117710-26-6; **19** (2*S*-HIP epimer), 117710-16-4; **19** (2*R*-HIP epimer), 117773-52-1; **19** (free acid, 2*S*-HIP epimer), 117710-34-6; **19** (free acid, 2*R*-HIP epimer), 117773-55-4; **20** (2*S*-HIP epimer), 117710-29-9; **20** (2*R*-HIP epimer), 117773-54-3; **21**, 117710-17-5; **21** (*N*-deprotected), 117733-99-0; **22**, 117710-30-2; **22** (*N*-deprotected), 117710-31-3; **23**, 67971-34-0; **23** (*N*-deprotected)·TFA, 117710-33-5; **24**, 117710-18-6; **25**, 117710-19-7; COMODD, 115491-90-2; BOC-D-Val-OH, 22838-58-0; AcOEt, 141-78-6; BOC-MeTyr(CH_2Ph)-OH, 64263-81-6; BOC-MeTyr-OH, 82038-34-4; BOC-MeTyr(Me)-OMe, 117710-21-1; Cbz-Thr-OH, 19728-63-3; BOC-Leu-OH, 13139-15-6; $CH_3CH_2C(O)SBu$-*t*, 61540-13-4; Cbz-D-MeLeu-OH, 65635-85-0; (*S*)-$CH_3CH(OH)CO$-OH, 79-33-4.

Synthesis of Phosphonates from α-Hydroxy Carbonyl Compounds and Dialkyl Phosphorochloridites

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In the presence of a Lewis acid, dialkyl phosphorochloridites react with α-hydroxy ketones to afford β-keto phosphonates and with α-hydroxy esters to afford phosphonic acid diesters. These reactions provide convenient access to a variety of structures, including β-keto phosphonates that are fully substituted at the α-carbon.

In recent years, interest in phosphonate chemistry has expanded dramatically for a variety of reasons. Phosphonates bearing α-hydrogen can be readily ionized and the resulting anions used in a number of carbon–carbon bond forming reactions. For example, the Wadsworth–Horner–Emmons condensation,[2] in which a stabilized phosphonate anion reacts with an aldehyde or ketone, has become a very popular method for the synthesis of α,β-unsaturated ketones and esters.[3] Phosphonates fully substituted at the α-carbon do not find such frequent use as synthetic intermediates, but because the geometry and spatial demands of pentavalent phosphorus are comparable to those of quaternary carbon, the isosteric replacement of carbon with phosphorus has been studied in biologically active molecules.[4] Phosphonate analogues of a number of biologically active phosphates also have been prepared[5] and studied for their biological activity. Finally, the hypothesis that phosphonates model the transition states of a variety of biologically important carboxylate reactions has culminated in the synthesis of antibodies to specific phosphonates, with the objective of obtaining synthetic enzymes.[6]

In marked contrast to the number of investigations that incorporate phosphonate reagents or focus on the biological activities of phosphonates, relatively little work has appeared describing general new syntheses of this functionality. The most commonly used methods for preparing phosphonates remain the classical Arbuzov reaction[7] and the elaboration of simpler alkyl phosphonate anions.[8]

Our research has focused on developing new, potentially general routes to β-keto phosphonates, and we recently have reported two different approaches. The first route relies on formation of a vinyllithium reagent from an α-bromo ketone enolate and reaction of this intermediate with a phosphorochloridate.[9] More recently we have discovered a 1,3-phosphorus migration, which provides access to β-keto phosphonate derivatives of cyclic ketones via rearrangement of vinyl phosphates.[10] In this paper, we describe a preparation of β-keto phosphonates from α-hydroxy ketones, and a parallel reaction which affords phosphonic acid diesters from α-hydroxy esters.

(1) Fellow of the Alfred P. Sloan Foundation, 1985–1989.

(2) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. Horner, L.; Hoffmann, H.; Wippell, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. Horner, L.; Hoffmann, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber.* **1962**, *95*, 581.

(3) Wadsworth, W. S., Jr. *Org. React. (N.Y.)* **1977**, *25*, 73.

(4) For a preparation of phosphorus-containing morphine analogues, cf.: Collins, D. J.; Rowley, L. E.; Swan, J. M. *Aust. J. Chem.* **1974**, *27*, 841 and references cited therein.

(5) Norbeck, D. W.; Kramer, J. B.; Lartey, P. A. *J. Org. Chem.* **1987**, *52*, 2174. Julina, R.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 819. Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron Lett.* **1984**, 5937. Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(6) Pollack, S.; Jacobs, J.; Schultz, P. *Science* **1986**, *234*, 1570. Jacobs, J.; Schultz, P. *J. Am. Chem. Soc.* **1987**, *109*, 2174. Tramontano, A.; Ammann, A. A.; Lerner, R. A. *J. Am. Chem. Soc.* **1988**, *110*, 2282.

(7) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

(8) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5652. Coutrot, P.; Savignac, P.; Mathey, F. *Synthesis* **1978**, 36. Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1987**, 405.

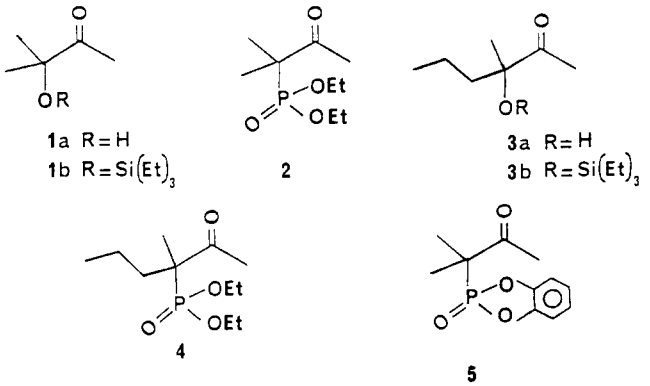
(9) Sampson, P.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 4342.

(10) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, 4265. Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185.

0022-3263/89/1954-0627$01.50/0

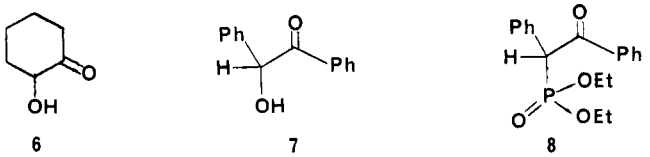
Results and Discussion

As part of a study on C–P bond formation via electrophilic phosphorus reagents, the reaction of diethyl phosphorochloridite with the α-hydroxy ketone **1a** was examined. In the presence of ferric chloride, a single product is formed in nearly quantitative yield, but the ^{31}P NMR spectrum (+27.23 ppm) of this product indicates the phosphonate **2** rather than the expected mixed phosphite.[11] Under analogous conditions, 3-hydroxy-3-methyl-2-hexanone (**3a**) gives the β-keto phosphonate **4** as the sole product. Phosphonate **5** is obtained from reaction of 1,2-phenylene phosphorochloridite with the hydroxy ketone **1a**.

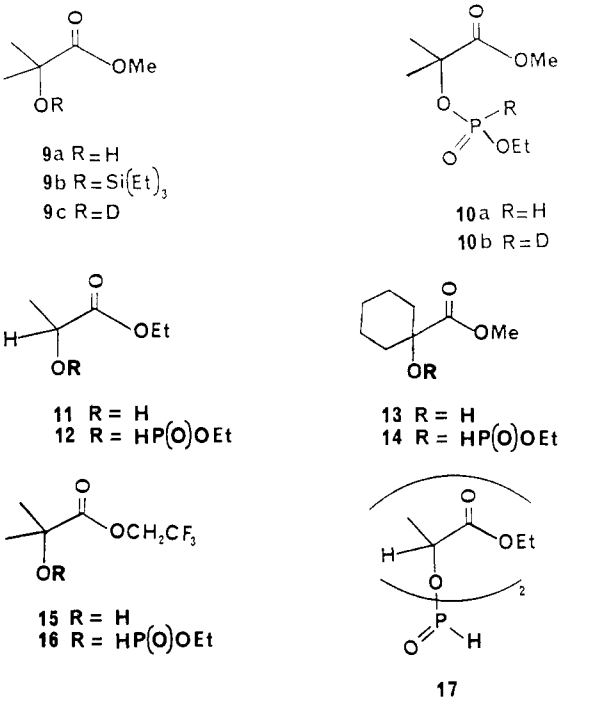


This phosphonate-forming reaction also can be conducted with silyl-protected α-hydroxy ketones. By analogy with the reactivity of carboxylic acid chlorides,[12-14] a P(III) chloride might be expected to replace a silyl group with formation of a mixed phosphite, but the triethylsilyl ethers **1b** and **3b** react with diethyl phosphorochloridite to give the phosphonates **2** and **4**. This observation suggests that use of the methodology may be viable in more complex molecules, where working with a protected alcohol would be advantageous.

The attempted reaction of diethyl phosphorochloridite with 2-hydroxycyclohexanone (**6**) was not successful under these reaction conditions. While this may be a consequence of using a secondary rather than a tertiary alcohol, it is a more likely consequence of an equilibrium with the adipoin dimer which makes derivatization of the hydroxyl group difficult.[15] With benzoin (**7**), where derivatization of the hydroxyl group is more facile, treatment with diethyl phosphorochloridite and a Lewis acid gives the desired phosphonate **8**. Thus, formation of phosphonates from α-hydroxy ketones is not restricted to tertiary alcohols, although such compounds serve well as substrates.



Aside from the results with 2-hydroxycyclohexanone, there is additional evidence to support the importance of the carbonyl group to the viability of this reaction. No phosphonates were detectable by ^{31}P NMR when monofunctional alcohols were treated under these conditions. When the methyl ester **9a** or its TES derivative **9b** was treated with diethyl phosphorochloridite and a Lewis acid under the same protocol, the spectroscopic data of the product required different phosphorus functionality. The ^{1}H and ^{31}P NMR spectra clearly indicate that this product contains a P–H bond and ultimately, the structure of the H-phosphonate diester **10a** was assigned. Following this discovery, the reaction was explored with the α-hydroxy esters **11**, **13**, and **15**. In each case, reaction with diethyl



phosphorochloridite and a Lewis acid gave the H-phosphonate diester (**12**, **14**, and **16**, respectively). However, when the hydroxy ester **11** was treated with 1,2-phenylene phosphorochloridite, the symmetrical H-phosphonate diester **17** was obtained instead of a mixed diester.

Several different Lewis acids were employed in these reactions, without any detectable effect on the product distribution. However, when $TiCl_4$ was employed, complete reaction was observed within a few hours at room temperature, while with $FeCl_3$ the reaction requires about 8 h under analogous conditions, and with $AlCl_3$ the same reaction showed only 50% conversion after 2 days.

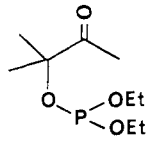
Experiments with isotopically labeled substrates have been used to define the source of the P–H hydrogen in the H-phosphonate products. For example, when the hydroxy ester **9a** was treated with $(EtO)_2PCl/FeCl_3$ in $CDCl_3$ and quenched by addition of DCl in D_2O, there was no detectable deuterium incorporation in the product. On the other hand, when the original ester was prepared with 50% deuterium incorporation in the OH group (**9c**), the expected H-phosphonate diester (**10b**) was obtained with 50% deuterium incorporation in the P–H bond (i.e., 100% D retention).

Because one ethyl group of the starting phosphorochloridite is eliminated in the reaction process leading to the H-phosphonate diesters, an experiment was conducted to establish its fate. For this experiment a glass tube with two U-shaped traps was added to the reaction vessel, with the first trap kept at −40 °C and the second kept below −100 °C, and the reaction flask was swept with a stream

(11) For applications of chlorophosphites in the preparation of mixed phosphite esters, cf.: Meek, J. L.; Davidson, F.; Hobbs, F. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2317 and references cited therein.
(12) Roussis, V.; Gloer, K.; Wiemer, D. F. *J. Org. Chem.* **1988**, *53*, 2011.
(13) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525.
(14) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.
(15) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4226.

of N_2. GCMS analysis of the condensed volatiles showed the presence of a substantial amount of chloroethane, presumably resulting from chloride ion attack at the methylene carbon of a phosphorus ester intermediate.

A detailed mechanism to account for this series of reactions is not yet available. One rationalization of these transformations can be based on phosphenium ion chemistry,[16] i.e., a formal phosphenium ion insertion into the C–OH bond of the α-hydroxy ketones and the CO–H bond of the hydroxy esters. An alternative sequence involves initial formation of a mixed phosphite in each case, followed by a Lewis acid catalyzed rearrangement to the observed products.[17] To test the later sequence, the phosphites **18** and **19** were prepared by treatment of compounds **1a** and **9a** with $(EtO)_2PCl$ in pyridine,[11] and their identity was confirmed by oxidation[18] to the phosphates **20** and **21**. When treated with $FeCl_3$, followed by an



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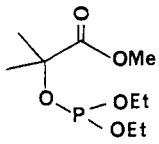

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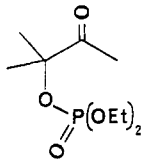

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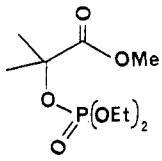

21

aqueous workup, the phosphite **18** rearranges to the phosphonate **2** while the phosphite **19** affords the H-phosphonate diester **10a**. In each case, the phosphonate was accompanied by a small amount of the corresponding phosphate (**20** or **21**). While these experiments do not prove unequivocally that mixed phosphites are intermediates in this conversion of α-hydroxy ketones to β-keto phosphonates, they are consistent with such a reaction sequence.

In conclusion, the Lewis acid catalyzed reaction of an α-hydroxy ketone with a dialkyl phosphorochloridite constitutes a synthesis of β-keto phosphonates that is complementary to traditional approaches. It should be of special value in preparation of β-keto phosphonates where the α-carbon is fully substituted, for the Arbuzov reaction cannot be used to prepare such compounds.[7,19,20]

Experimental Section

Flash column chromatography was done on Merck grade 60 silica gel (230–400 mesh), while radial chromatography was done with a Chromatotron apparatus using Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H, ^2H, ^{13}C, ^{19}F, and ^{31}P) were recorded on either a JEOL FX-90Q or a Brucker WM-360 spectrometer, using deuteriochloroform as the solvent unless otherwise noted. The ^1H and ^{13}C chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$, while the ^{31}P chemical shifts are reported in parts per million relative to H_3PO_4 (external standard). Low-resolution electron-impact (EI) mass spectra were recorded with a Hewlett-Packard 5985B instrument operating at 70 eV; only selected ions are reported here. High-resolution mass spectra were recorded on an AEI MS-30 instrument at the University of Minnesota Mass Spectrometry Service Laboratory, or on a VG Instruments ZAB-HF spectrometer at the University of Iowa Mass Spectrometry Facility. Microanalyses were conducted by Desert Analytics, Tucson, AZ.

Diethyl (1,1-Dimethyl-2-oxopropyl)phosphonate (2). General Procedure. Diethyl phosphorochloridite (305 mg, 1.96 mmol) was added dropwise to a cold (0 °C) mixture of the alcohol **1a** (200 mg, 0.96 mmol) and $FeCl_3$ (315 mg, 1.96 mmol) in anhydrous hexane (10 mL), and the reaction mixture was allowed to reach room temperature overnight. The resulting solution was washed with H_2O (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried ($MgSO_4$). Concentration in vacuo, followed by purification of the residue by column chromatography (90% $CHCl_3$, 10% EtOAc), gave 430 mg (92%) of pure β-keto phosphonate **2**: ^1H NMR δ 4.17 (m, 4 H), 2.34 (s, 3 H), 1.42 (d, J_{HP} = 16.7 Hz, 6 H), 1.32 (t, J = 7.1 Hz, 6 H); ^{13}C NMR 206.6, 62.7 (d, J_{CP} = 8.0 Hz), 50.6 (d, J_{CP} = 130.5 Hz), 27.4, 20.3 (d, J_{CP} = 5.0 Hz), 16.4 (d, J_{CP} = 5.6 Hz); ^{31}P NMR +27.2; EIMS, m/z (relative intensity 222 (M^+, 0.1), 180 (55), 165 (7), 153 (18), 138 (89), 123 (100), 105 (35), 93 (21), 81 (55), 65 (46), 43 (42). Anal. Calcd for $C_9H_{19}O_4P$: C, 49.05; H, 8.62. Found: C, 48.66; H, 8.43.

Preparation of Phosphonate 2 from Silyl Ether 1b. The triethylsilyl ether **1b** (100 mg, 0.46 mmol), diethyl phosphorochloridite (150 mg, 0.96 mmol), and $FeCl_3$ (154 mg, 0.96 mmol) were allowed to react in anhydrous hexane (15 mL), according to the procedure given above. Standard workup and purification by column chromatography (90% $CHCl_3$, 10% EtOAc) afforded 70 mg (67%) of compound **2**.

Diethyl (1-Methyl-1-propyl-2-oxopropyl)phosphonate (4). 3-Hydroxy-3-methyl-2-hexanone (500 mg, 3.85 mmol), diethyl phosphorochloridite (720 mg, 4.61 mmol) and $FeCl_3$ (742 mg, 4.61 mmol) were allowed to react in anhydrous hexane (20 mL), according to the procedure given above. Standard workup and purification by column chromatography (40% EtOAc, 60% hexane) afforded 980 mg (96%) of pure compound **4**: ^1H NMR δ 4.17–4.11 (m, 4 H), 2.32 (s, 3 H), 2.14–2.11 (m, 2 H), 1.78–1.58 (m, 2 H), 1.37 (d, J_{HP} = 16.9 Hz, 3 H), 1.33 (t, J = 7.1 Hz, 6 H), 0.93 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 205.6, 62.2 (d, J_{CP} = 7.4 Hz), 52.4 (d, J_{CP} = 128.6 Hz), 40.5, 34.9 (d, J_{CP} = 4.4 Hz), 27.4, 17.0 (d, J_{CP} = 13.0 Hz), 16.0 (d, J_{CP} = 5.6 Hz), 14.0; ^{31}P NMR +27.0; EIMS, m/z (relative intensity) 250 (M^+, 0.4), 221 (0.1), 208 (31), 179 (100), 151 (28), 138 (12), 123 (34), 109 (5), 81 (8), 69 (6), 43 (6). Anal. Calcd for $C_{11}H_{23}O_4P$: C, 52.79; H, 9.26. Found: C, 52.40; H, 9.52.

Preparation of Phosphonate 4 from the Silyl Ether 3b. The triethylsilyl ether **3b** (500 mg, 2.05 mmol), diethyl phosphorochloridite (625 mg, 4.0 mmol), and $FeCl_3$ (644 mg, 4.0 mmol) were allowed to react in anhydrous hexane (10 mL), according to the general procedure. Standard workup gave 246 mg (48%) of pure compound **4**.

3-(1,3,2-Benzodioxaphosphol-2-yl)-3-methyl-2-butanone *P*-Oxide (5). 3-Hydroxy-3-methyl-2-butanone (600 mg, 5.88 mmol), 1,2-phenylene phosphorochloridite (1.023 g, 5.88 mmol), and $FeCl_3$ (946 mg, 5.88 mmol) were allowed to react in anhydrous CH_2Cl_2 (20 mL), according to the general procedure. Standard workup and purification by column chromatography (48% EtOAc, 48% hexane, 4% EtOH) gave 750 mg (52%) of compound **5**: ^1H NMR δ 7.03–6.92 (m, 4 H), 2.24 (s, 3 H), 1.43 (d, J = 16.8 Hz, 6 H); ^{13}C NMR 210.7, 147.5, 143.7, 126.1, 121.7, 120.5, 118.0, 50.0 (d, J_{CP} = 134 Hz), 30.9, 20.6; ^{31}P NMR +25.1; EIMS, m/z (relative intensity) 240 (M^+, 12), 198 (78), 156 (100), 139 (30), 109 (14), 86 (13), 65 (7), 43 (10); HRMS calcd for $C_{11}H_{13}O_4P$ 240.0548, found 240.0549.

Preparation of Phosphonate 8. Benzoin (500 mg, 2.36 mmol), diethyl phosphorochloridite (736 mg, 4.72 mmol), and $FeCl_3$ (767 mg, 4.72 mmol) were allowed to react according to the general procedure. After 24 h, because a significant amount of starting material remained unreacted, an additional 1 equiv of diethyl phosphorochloridite (368 mg, 2.36 mmol) and $FeCl_3$ (384 mg, 2.36 mmol) was added. After an additional 24 h, standard workup

(16) Cowley, A. H.; Kemp, R. A. *Chem. Rev.* **1985**, *85*, 367. Maryanoff, B. E.; Hutchins, R. O. *J. Org. Chem.* **1972**, *37*, 3475.

(17) For related rearrangements, cf.: Haines, R. J.; Du Preez, A. L.; Marais, I. L. *J. Organomet. Chem.* **1971**, *28*, 405. Huché, M.; Cresson, P. *Tetrahedron Lett.* **1972**, 4933.

(18) Perich, J. W.; Alewood, P. F.; Johns, R. B. *Synthesis* **1986**, 572.

(19) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

(20) Taken in part from the Ph.D. Thesis of V. Roussis, University of Iowa, July 1987.

gave 510 mg (65%) of compound **8**: ^{1}H NMR δ 8.09–7.80 (m, 2 H), 7.55–7.51 (m, 2 H), 7.43–7.33 (m, 5 H) 5.37 (d, J_{HP} = 22.0 Hz, 1 H), 4.17–4.08 (m, 4 H), 1.21 (q, J = 7.0 Hz, 6 H); ^{13}C NMR 193.6, 136.5, 133.3, 131.4 (d, J_{CP} = 9 Hz), 129.7, 129.6, 128.9, 128.7, 128.5, 127.9, 127.8, 63.3, (d, J_{CP} = 7.0 Hz), 62.9 (d, J_{CP} = 7.0 Hz), 54.35 (J_{CP} = 138 Hz), 16.3 (d, J_{CP} = 5.8 Hz); EIMS, m/z (relative intensity) 332 (M^+, 1), 304 (1), 178 (4), 165 (30), 152 (18), 109 (23), 105 (85), 91 (36), 81 (38), 77 (100), 51 (37); HRMS calcd for $C_{18}H_{21}O_4P$ 332.1178, found 332.1182.

Methyl 2-[(Ethoxyphosphinyl)oxy]-2-methylpropanoate (10a). Methyl 2-hydroxyisobutyrate (200 mg, 1.69 mmol), diethyl phosphorochloridite (265 mg, 1.69 mmol), and $FeCl_3$ (272 mg, 1.96 mmol) were allowed to react in anhydrous hexane (10 mL), according to the general procedure. Workup in the usual manner and purification by column chromatography (40% EtOAc, 60% hexane) gave 315 mg (89%) of pure compound **10a**: ^{1}H NMR δ 7.08 (d, J_{HP} = 722.5 Hz, 1 H), 4.18–4.11 (m, 2 H), 3.80 (s, 3 H), 1.74 (s, 3 H), 1.63 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 172.9, 82.0 (d, J_{CP} = 8.5 Hz), 61.3 (d, J_{CP} = 6.3 Hz), 52.9, 27.2, 16.2 (d, J_{CP} = 6.8 Hz); ^{31}P NMR +4.6; EIMS, m/z (relative intensity) 210 (M^+, 0.6), 209 (5), 181 (3), 165 (12), 151 (99), 137 (5), 123 (13), 111 (80), 97 (9), 83 (100), 73 (22), 59 (43); HRMS calcd for $C_7H_{15}O_5P$ 210.0656, found 210.0656.

Preparation of Phosphonate 10a from Triethylsilyl Ether 9b. The triethylsilyl ether **9b** (500 mg, 2.12 mmol), diethyl phosphorochloridite (625 mg, 4.0 mmol), and $FeCl_3$ (644 mg, 4.0 mmol) were allowed to react in anhydrous hexane (10 mL), to obtain compound **10a**, identical with that prepared earlier.

Ethyl 2-[(Ethoxyphosphinyl)oxy]propanoate (12). *S*-(−)-Ethyl lactate (300 mg, 2.54 mmol) was treated with diethyl phosphorochloridite (396 mg, 2.54 mmol) and $FeCl_3$ (409 mg, 2.54 mmol) in anhydrous hexane (10 mL), to obtain, after standard workup and purification by column chromatography (30% EtOAc, 70% hexane), 443 mg (83%) of pure compound **12**: ^{1}H NMR δ 7.05 (d, J_{HP} = 721.8 Hz, 1 H), 4.97 (m, 1 H), 4.27–4.13 (m, 4 H), 1.59 (dd, J = 7.0, J_{HP} = 3.6 Hz, 3 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR 170.8, 71.1 (d, J_{CP} = 6.2 Hz), 61.9, 61.7, 19.0, 16.2 (d, J_{CP} = 6.0 Hz), 14.1; ^{31}P NMR +7.8; EIMS, m/z (relative intensity) 210 (M^+, 1), 209 (13), 193 (8), 181 (9), 165 (100), 153 (7), 137 (60), 121 (26), 111 (19), 93 (89), 65 (27). Anal. Calcd for $C_7H_{15}O_5P$: C, 40.00; H, 7.19. Found: C, 39.88; H, 7.42.

1-Carbomethoxycyclohexyl Ethyl Phosphonate (14). Methyl 1-hydroxycyclohexane-1-carboxylate (250 mg, 1.57 mmol), diethyl phosphorochloridite (254 mg, 1.57 mmol), and $FeCl_3$ (253 mg, 1.57 mmol) were allowed to react in anhydrous hexane (15 mL), according to the general procedure. Workup in the usual manner and purification by column chromatography (40% EtOAc, 60% hexane) afforded 392 mg (86%) of pure compound **14**: ^{1}H NMR δ 7.13 (d, J_{HP} = 723.95 Hz, 1 H), 4.22–4.17 (m, 2 H), 3.80 (s, 3 H), 2.31–2.70 (m, 1 H), 2.02 (m, 1 H), 1.88 (m, 2 H), 1.80–1.61 (m, 6 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 173.2, 84.3 (d, J_{CP} = 8.7 Hz), 61.2 (d, J_{CP} = 5.9 Hz), 52.7, 34.5, 34.2, 24.7, 21.0, 20.9, 16.2 (d, J_{CP} = 6.9 Hz); ^{31}P NMR 4.7; EIMS, m/z (relative intensity) 250 (M^+, 0.1), 249 (1), 205 (3), 191 (100), 163 (22), 140 (15), 111 (24), 99 (7), 81 (79), 65 (8), 59 (8). Anal. Calcd for $C_{10}H_{14}O_5P$: C, 48.00; H, 7.65. Found: C, 47.53; H, 7.89.

2,2,2-Trifluoroethyl 2-[(Ethoxyphosphinyl)oxy]-2-methylpropanoate (16). Trifluoroethyl 2-hydroxyisobutyrate (**15**, 300 mg, 1.61 mmol),[20] diethyl phosphorochloridite (301 mg, 1.93 mmol), and $FeCl_3$ (310 mg, 1.93 mmol) were allowed to react in anhydrous hexane (10 mL) to obtain, after purification by column chromatography (40% EtOAc, 60% hexane), 320 mg (72%) of pure compound **16**: ^{1}H NMR δ 7.03 (d, J_{HP} = 722.41 Hz, 1 H), 4.64–4.51 (m, 2 H), 4.22–4.13 (m, 2 H), 1.77 (s, 3 H), 1.69 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 171.2 (d, J_{CP} = 2.3 Hz), 122.7 (q, J_{CF} = 276.9 Hz), 81.3 (d, J_{CP} = 7.4 Hz), 61.7 (q, J_{CCF} = 31.9 Hz), 61.5 (d, J_{CP} = 5.7 Hz), 26.94, 26.88, 16.1 (d, J_{CP} = 6.1 Hz); ^{19}F NMR −74.39; ^{31}P NMR +4.8; EIMS, m/z (relative intensity) 278 (M^+, 0.5), 277 (7), 233 (19), 217 (3), 165 (8), 151 (100), 141 (6), 123 (8), 111 (49), 83 (37); HRMS calcd for $C_8H_{14}F_3O_5P$ 277.0452 (M^+ − 1), found 277.0444.

Diethyl 2,2′-[Phosphinylidenebis(oxy)]bis(propanoate) (17). The reaction of *S*-(−)-ethyl lactate (600 mg, 3.38 mmol), 1,2-phenylene phosphorochloridite (882 mg, 3.38 mmol), and $FeCl_3$ (554 mg, 3.38 mmol) in anhydrous CH_2Cl_2 (20 mL), according to the general procedure, gave 1.16 g (81%) of pure compound **17**: ^{1}H NMR δ 7.17 (d, J_{HP} = 741.74 Hz, 1 H), 5.09–4.95 (m, 2 H), 4.27–4.20 (m, 4 H), 1.59 (dd, J = 7.0, J_{HP} = 4.0 Hz, 6 H), 1.30 (t, J = 7.2 Hz, 6 H); ^{13}C NMR 170.5 (d, J_{CP} = 4.0 Hz), 170.2 (d, J_{CP} = 4.0 Hz), 71.2 (d, J_{CP} = 6.0 Hz), 70.7 (d, J_{CP} = 6.0 Hz), 61.8, 61.6, 19.2 (d, J_{CP} = 5.6 Hz), 18.8 (d, J_{CP} = 6.3 Hz), 14.0, 14.0; ^{31}P NMR +6.6; EIMS, m/e (relative intensity) 281 (M^+ − 1, 0.2), 237 (3), 209 (4), 165 (100), 153 (4), 137 (76), 118 (6), 109 (44), 102 (7), 92 (6), 83 (6); HRMS calcd for $C_8H_{14}O_6P$ 237.0528 (M^+ − OEt), found 237.0525.

Methyl 2-[(Ethoxyphosphinyl)oxy]-2-methylpropanoate, 50% D (10b). Deuteriated methyl 2-hydroxyisobutyrate **9c** (300 mg, 2.52 mmol, 50% deuterium incorporation as determined by MS),[20] diethyl phosphorochloridite (472 mg, 3.02 mmol), and $FeCl_3$ (486 mg, 3.02 mmol) were allowed to react in anhydrous CH_2Cl_2 (15 mL) according to the general procedure to obtain compound **10b**: yield, 460 mg (87%); ^{1}H NMR identical with that reported for **10a**, apart from the intensity of the P–H resonance; ^{2}H NMR 7.02 (d, J = 110.6 Hz); ^{31}P NMR +4.6; EIMS, m/z (relative intensity) 209 (M^+ − 2, 12), 181 (4), 152 (100), 151 (99), 138 (6), 137 (4), 112 (57), 111 (62), 84 (46), 83 (46).

3-[(Diethoxyphosphino)oxy]-3-methyl-2-butanone (18). Diethyl phosphorochloridite (1.150 g, 7.37 mmol) was added to a solution of 3-hydroxy-3-methyl-2-butanone (500 mg, 4.7 mmol) and pyridine (2 mL) in anhydrous THF (20 mL) kept at approximately −20 °C. The reaction mixture was allowed to warm to room temperature, and after 1 h, when it was judged complete by GC analysis, the white precipitate was removed by filtration under inert atmosphere and the solvent was removed in vacuo. GCMS analysis of the residue (1.065 g, 93% GC yield) indicated 95% pure compound **18**: ^{1}H NMR δ 4.23–3.98 (m, 4 H), 2.26 (s, 3 H), 1.49 (s, 6 H), 1.26 (t, J = 7.0 Hz, 6 H); ^{31}P NMR +142.2; EIMS, m/z (relative intensity) 223 (M^+ + 1, 0.4), 179 (6), 177 (7), 155 (46), 127 (34), 121 (52), 111 (27), 99 (61), 93 (72), 82 (45), 65 (100), 43 (87).

3-[(Diethoxyphosphinyl)oxy]-3-methyl-2-butanone (20). According to the procedure of Perich and co-workers,[18] a solution of I_2 (1.6 g) in THF (5 mL) and water (0.5 mL) was added slowly to a solution of the phosphite **18** (500 mg, 2.25 mmol) in anhydrous THF (15 mL), at 0 °C. The reaction mixture was allowed to warm to room temperature, and the brown precipitate was removed by filtration. After washing of the filtrate with 10% sodium bisulfite (2 × 20 mL) and saturated $NaHCO_3$ (2 × 15 mL), the combined aqueous washings were acidified to pH 3 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (50% hexane, 50% EtOAc), to afford 341 mg (73%) of pure compound **20**: ^{1}H NMR δ 4.15 (q, J = 7.2 Hz, 4 H), 2.30 (s, 3 H), 1.59 (s, 6 H), 1.36 (t, J = 7.2 Hz, 6 H); ^{31}P NMR +6.6; EIMS, m/z (relative intensity) 239 (M^+ + 1, 2.8), 238 (M^+, 0.9), 223 (1), 195 (78), 167 (23), 155 (71), 127 (93), 99 (100), 81 (29), 43 (38).

Preparation of Phosphonate 2 from Phosphite 18. $FeCl_3$ (365 mg, 2.25 mmol) was added to a solution of the phosphite **18** (500 mg, 2.25 mmol) in anhydrous CH_2Cl_2 (15 mL) at −20 °C, and the reaction mixture was allowed to warm to room temperature overnight. The resulting solution was washed with brine (2 × 5 mL) and dried ($MgSO_4$). GCMS analysis indicated two products (ratio 85:15), which were identified by comparison of their retention times and mass spectra with those of authentic samples of the phosphonate **2** (major) and the phosphate **20** (minor).

Methyl 2-[(Diethoxyphosphino)oxy]-2-methylpropanoate (19). Diethyl phosphorochloridite (727 mg, 4.66 mmol) was added to a solution of methyl hydroxyisobutyrate (500 mg, 4.23 mmol) and pyridine (2 mL) in anhydrous THF (20 mL) kept at approximately −20 °C. The reaction mixture was allowed to warm to room temperature, and after 1 h, when judged complete by GC analysis, the white precipitate was removed by filtration under inert atmosphere, and the solvent was evaporated in vacuo. GCMS analysis of the residue (907 mg, 90% GC yield) indicated it to be essentially pure compound **19**: ^{1}H NMR δ 3.90–3.68 (m, 4 H), 3.72 (s, 3 H), 1.58 (s, 3 H), 1.25 (t, J = 6.9 Hz, 6 H); ^{31}P NMR +140.6; EIMS, m/z (relative intensity) 239 (M^+ + 1, 0.6) 238 (M^+, 0.5), 223 (15), 193 (7), 179 (7), 165 (6), 136 (13), 121 (61), 111 (80), 97 (56), 82 (94), 69 (86), 65 (100), 43 (25).

Preparation of Phosphonate 10a from Phosphite 19. $FeCl_3$ (341 mg, 2.1 mmol) was added to a solution of the phosphite **19** (500 mg, 2.1 mmol) in anhydrous CH_2Cl_2 (15 mL) at -20 °C. The reaction mixture was allowed to warm to room temperature overnight, washed with brine (2 × 5 mL), and then dried ($MgSO_4$). GCMS analysis indicated two products (ratio (70:30) identified on the basis of their spectral data as the H-phosphonate diester **10a** (major) and the phosphate **21**: (^{31}P NMR -5.6; EIMS, m/z (relative intensity) 255 ($M^+ + 1$, 0.2), 239 (1), 209 (6), 195 (100), 191 (9), 167 (15), 155 (54), 127 (75), 99 (85), 81 (23), 59 (18)).

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Rapid and Efficient Synthesis of Nucleoside 5′-*O*-(1-Thiotriphosphates), 5′-Triphosphates and 2′,3′-Cyclophosphorothioates Using 2-Chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one

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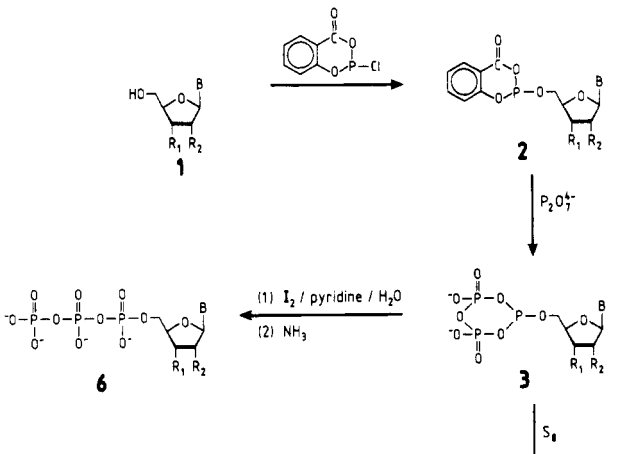
2-Chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one phosphitylates the 5′-hydroxy group of a nucleoside to form an intermediate (**2**), which on subsequent reaction with pyrophosphate produces, in a double displacement process, a P^2,P^3-dioxo-P^1-5′-nucleosidylcyclotriphophite (**3**). Oxidation with sulfur gives a nucleoside 5′-(1-thiocyclotriphosphate) (**4**), which is hydrolyzed to the diastereomeric mixture of a nucleoside 5′-*O*-(1-thiotriphosphate) (**5**). Alternatively, **3** can be oxidized with iodine/water to furnish nucleoside 5′-triphosphates **6**. This reagent can also be applied to the synthesis of nucleoside 2′,3′-cyclic phosphorothioates. Protection of nucleobase functional groups is not required.

Ribonucleoside and 2′-deoxyribonucleoside 5′-*O*-(1-thiotriphosphates) (NTPαS and dNTPαS) are finding widespread application in biochemistry and molecular biology[1] as substrates for DNA and RNA polymerases for sequencing,[2] mutagenesis,[3] and the labeling of hybridization probes.[4] The development of new methods of synthesis for these compounds is therefore warranted.[5] 2-Chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one[6] (salicyl phosphorochloridite) has been employed earlier for the preparation of nucleoside H-phosphonates as synthons in oligonucleotide synthesis.[7] However, this reagent is capable of undergoing three nucleophilic displacement reactions. We have exploited this multifunctionality in developing a facile synthesis of the 5′-*O*-(1-thiotriphosphates) and 5′-triphosphates of the eight common deoxyribonucleosides and ribonucleosides. This compound can also be readily employed for the synthesis of nucleoside

Scheme I



	1 - 4			5 - 6		
	B	R_1	R_2	B	R_1	R_2
a	A^{Bz}	OMeOAc	H	A	OH	H
b	G^{ib}	OMeOAc	H	G	OH	H
c	T	OAc	H	T	OH	H
d	C^{Bz}	OMeOAc	H	C	OH	H
e	A	OAc	OAc	A	OH	OH
f	G	OAc	OAc	G	OH	OH
g	U	O,OC(H,OCH_3)		U	OH	OH
h	C	O,OC(H,OCH_3)		C	OH	OH

Bz, benzoyl; ib, isobutyryl.

(1) For review, see: Eckstein, F. *Annu. Rev. Biochem.* **1985**, *54*, 367-402.

(2) (a) Biggin, M. D.; Gibson, T. J.; Hong, G. F. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 3963-3965. (b) Labeit, S.; Lehrach, H.; Goody, R. S. *DNA* **1986**, *5*, 173-177. (c) Gish, G.; Eckstein, F. *Science* **1988**, *240*, 1520-1522.

(3) (a) Nakamaye, K. L.; Eckstein, F. *Nucleic Acids Res.* **1986**, *14*, 9679-9698. (b) Sayers, J. R.; Schmidt, W.; Eckstein, F. *Nucleic Acids Res.* **1988**, *16*, 791-802. (c) Sayers, J. R.; Schmidt, W.; Wendler, A.; Eckstein, F. *Nucleic Acids Res.* **1988**, *16*, 803-814.

(4) (a) Haase, A. T.; Walker, D.; Stowring, L.; Ventura, P.; Geballe, A.; Blum, H.; Brahic, M.; Goldberg, R.; O'Brien, K. *Science* **1985**, *227*, 189-192. (b) Bahmanyar, S.; Higgins, G. A.; Goldgraeber, D.; Lewis, D. A.; Morrison, J. H.; Wilson, M. C.; Shankar, S. K.; Gajdusek, D. C. *Science* **1987**, *237*, 77-80. (c) Bandtlow, C. E.; Heumann, R.; Schwab, M. E.; Thoenen, H. *EMBO J.* **1987**, *6*, 891-899. (d) Croen, K. D.; Ostrove, M.; Dragovic, L. J.; Smialek, J. E.; Straus, S. E. *New Engl. J. Med.* **1987**, *317*, 1427-1432. (e) Dony, C.; Gruss, P. *EMBO J.* **1987**, *6*, 2965-2975. (f) Soreq, H.; Zamir, R.; Zevin-Sonkin, D.; Zakut, H. *Hum. Genet.* **1987**, *77*, 325-328. (g) Largent, B. L.; Jones, D. T.; Reed, R. R.; Pearson, R. C. A.; Snyder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 2864-2868. (h) Scott, M. O.; Sylvester, J. E.; Heiman-Patterson, T.; Shi, Y.-J.; Fieles, W.; Stedman, H.; Burghes, A.; Ray, P.; Worton, R.; Fischbeck, K. H. *Science* **1988**, *239*, 1418-1420. (i) Sideras, P.; Funa, K.; Zalcberg-Quintana, I.; Xanthopoulos, K. G.; Kisielow, P.; Palacios, R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 218-221.

(5) (a) Methods up to 1983 are reviewed in ref 1. (b) Goody, R. S.; Isakov, M. *Tetrahedron Lett.* **1986**, *27*, 3599-3602.

(6) Cade, J. A.; Gerrard, W. *J. Chem. Soc.* **1960**, 1249-1253.

(7) Marugg, J. E.; Tromp, M., Kuyl-Yeheskiel, E.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1986**, *27*, 2661-2664.

0022-3263/89/1954-0631$01.50/0