formed dihydrophenanthrene.[15] No evidence of dimerization or a [2 + 2]-reaction was obtained by GC, GCMS, or HPLC analyses.

Photolysis of 1,2-Diphenylcyclobutene in DMHD. A degassed solution of 4 (400 mg, 1.94 mmol) in 2,5-dimethyl-2,4-hexadiene (DMHD, 20 mL) was irradiated for 15 h at 300 nm. The DMHD was removed in vacuo to give a mixture of *exo*-2,2-dimethyl-1,4-diphenyl-3-(2-methyl-1-propenyl)bicyclo[2.2.0]hexane (**9a**) and *endo*-2,2-dimethyl-1,4-diphenyl-3-(2-methyl-1-propenyl)bicyclo[2.2.0]hexane (**9b**) (1.13:1, GC) as a yellow sticky oil. The crude oil was repeatedly chromatographed on silica gel with pentane to give 86 mg of **9b** and 113 mg of **9a**.

9a: colorless flake (Me_2CO–MeOH), mp 70–71 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.01–7.24 (10 H, m, Ar), 4.62 (1 H, d, J = 9.8 Hz, C=C*H*), 3.40 (1 H, d, J = 9.8 Hz, C=CHC*H*), 3.05 (1 H, ddd, J = 8.0, 8.0, 12.0 Hz, C*H*HCHH), 2.62 (1 H, ddd, J = 8.0, 12.0, 12.0 Hz, one of C*H*HCHH), 2.46 (1 H, ddd, J = 4.0, 12.0, 12.0 Hz, C*H*HCHH), 2.03 (1 H, ddd, J = 4.0, 12.0, 12.0 Hz, C*H*HCHH), 1.65 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.05 (3 H, s, CH_3); IR (KBr) 3090, 3050, 3030, 2980, 2960, 2920, 2850, 1665, 1600, 1575, 1480, 1440, 1385, 1365, 1220, 1130, 1080, 1070, 1040, 860, 760, 710, and 640 cm^{-1}; GCMS, m/e (relative intensity) 316 (M^+, 12.0), 199 (1.3), 183 (0.3), 171 (100), 156 (8.5), 143 (29.5), 129 (23.6), 115 (12.5), 91 (43.1), 77 (9.4), 65 (4.3), and 55 (3.5).

Anal. Calcd for $C_{24}H_{38}$: C, 91.08; H, 8.92. Found: C, 90.93; H, 9.14.

9b: Colorless oil at room temperature, >99% pure by ^1H NMR; ^1H NMR (270 MHz, $CDCl_3$) δ 7.02–7.25 (8 H, m, Ar), 6.69 (2 H, m, Ar), 5.64 (1 H, d, J = 9.8 Hz, C=C*H*), 3.56 (1 H, d, J = 9.8 Hz, C=CHC*H*), 2.93 (1 H, ddd, J = 8.0, 8.0, 12.0 Hz, C*H*HCHH), 2.75 (1 H, ddd, J = 4.0, 8.0, 12.0 Hz, C*H*HCHH), 2.60 (1 H, ddd, J = 8.0, 12.0, 12.0 Hz, C*H*HCHH), 2.14 (1 H, ddd, J = 4.0, 12.0, 12.0 Hz, C*H*HCHH), 1.84 (3 H, s, CH_3), 1.79 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 0.71 (3 H, s, CH_3); IR (film) 3100, 3080, 3050, 2960, 2910, 1670, 1620, 1580, 1510, 1465, 1455, 1390, 1370, 1050, 870, 775, and 725 cm^{-1}; GCMS, m/e (relative intensity) 316 (M^+, 11.4), 199 (1.2), 183 (0.3), 171 (100), 156 (8.5), 143 (30.1), 129 (24.0), 115 (13.0), 105 (6.0), 91 (43.1), 77 (9.7), 65 (4.4), 55 (3.4).

Photolysis of 1,2-Diphenylcyclopentene in 2,5-Dimethyl-2,4-hexadiene. A degassed solution of **5** (0.066 g, 0.30 mmol) in DMHD (3 mL, 0.10 M) was irradiated for 20 h at 300 nm. The only product in the resulting solution was identified as 9,10-cyclopentanophenanthrene by GC and GCMS analysis.

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Registry No. **4**, 3306-02-3; **5**, 1485-98-9; **6**, 41317-87-7; **7**, 4759-04-0; **9a**, 113036-77-4; **9b**, 113085-40-8; DMHD, 764-13-6; TME, 563-79-1; 9,10-cyclopentanophenanthrene, 723-98-8; 9,10-cyclohexanophenanthrene, 5981-10-2.

Preparation of Difluorophosphonoacetic Acid and Its Derivatives

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The preparation of ethyl difluoro(diethoxyphosphinyl)acetate (**1**) has been effected by the acylation of [(diethoxyphosphinyl)difluoromethyl]zinc bromide with ethyl chloroformate in the presence of a catalytic amount of cuprous bromide. Similarly prepared were ethyl difluoro(diethoxyphosphinyl)pyruvate (**2**) and *N,N*-diethyldifluoro(diethoxyphosphinyl)acetamide (**3**). Bromotrimethylsilane selectively reacted with **1** to yield ethyl difluoro[bis(trimethylsiloxy)phosphinyl]acetate (**9**). The remaining ethyl carboxylic ester of **9** reacted with iodotrimethylsilane to produce trimethylsilyl difluoro[bis(trimethylsiloxy)phosphinyl]acetate (**10**), which was subsequently hydrolyzed to yield difluorophosphonoacetic acid (**8**). The phosphonate **9** was gently chlorinated to yield ethyl difluoro(dichlorophosphinyl)acetate (**11**).

Phosphonic acids often exhibit important biological properties by virtue of their similarity to phosphates,[2] while substitution of a fluorine atom in a biologically active molecule often leads to pronounced activity enhancement.[3] Some α-fluorinated alkanephosphonic acids such as difluoromethanediphosphonic acid[4-8] have already been the subject of interest as analogues of biological phosphoryl species. However there is generally a conspicuous lack of methods for the preparation of other difluoromethanephosphonates. Such compounds have been postulated to possess biologically superior properties to those of analogous nonhalogenated phosphonates.[9] However, there are generally few synthetic methods available which lead to other difluoromethanephosphonates.

The phosphonic acids of some common carboxylic acids often have a biological origin and exhibit metabolic activity. Phosphonopyruvic acid occurs naturally[10] and was synthesized several years ago.[11] A structurally similar compound, phosphonoacetic acid, has been shown to inhibit effectively the replication of Herpes viruses[12] as well as suppress the replication of DNA tumor viruses[13] and

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Scheme I

$(EtO)_2P(O)CF_2ZnBr + ClC(O)R \xrightarrow{CuBr} (EtO)_2P(O)CF_2C(O)R$

1, R = OEt 50%
2, R = C(O)OEt 62%
3, R = NEt_2 38%

Table I. Cuprous Bromide Catalyzed Reaction of $(RO)_2P(O)CF_2ZnBr$ 4 with Selected Acyl Chlorides

acyl halide	R	product	yield, %
ClC(O)OEt	Et	$(EtO)_2P(O)CF_2CO_2Et$	50 (67)[a,b]
ClC(O)OEt	*i*-Pr	$(i\text{-}PrO)_2P(O)CF_2CO_2Et$	26
ClC(O)OEt	*n*-Bu	$(n\text{-}BuO)_2P(O)CF_2CO_2Et$	25
$ClC(O)NEt_2$	Et	$(EtO)_2P(O)CF_2C(O)NEt_2$	38
$ClC(O)CO_2Et$	Et	$(EtO)_2P(O)CF_2C(O)CO_2Et$	62
ClC(O)SEt	Et	$(EtO)_2P(O)CF_2C(O)SEt$	0 (54)[a]
ClC(O)Cl	Et	$(EtO)_2P(O)CF_2C(O)Cl$	0 (18)[c]
MeOC(O)OMe	Et	$(EtO)_2P(O)CF_2C(O)OMe$	(0)[a]

[a] ^{19}F NMR spectroscopic yield vs benzotrifluoride. [b] Reaction conducted without CH_3CN. [c] Without cuprous bromide.

influenza A virus.[14] The triethyl ester of difluorophosphonoacetic acid, **1**, was initially reported to have been isolated as a byproduct[15] from the reaction of tetrafluoroethylene oxide and triethyl phosphite.[17]

In a preliminary communication we briefly described an improved synthetic route to triethyl ester **1** and its corresponding acid.[18] Subsequent to our report Blackburn, Brown, and Martin have published additional routes to these compounds.[19] We now report our complete results on the synthesis of the ethyl esters of difluoro(diethoxyphosphinyl)acetate (**1**), difluoro(diethoxyphosphinyl)pyruvate (**2**), *N,N*-diethyldifluoro(diethoxyphosphinyl)acetamide (**3**), and the saponification product difluorophosphonoacetic acid (**8**).

Results and Discussion

A variety of 1,1-difluoro-2-oxo phosphonates may be readily prepared by the previously reported reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide (**4**) with an appropriate acyl halide.[20] The product ketones were isolated in good to excellent yields; however the direct synthesis of a carboxylic ester from the organozinc reagent **4** was not achieved. It was subsequently demonstrated that the reactivity of **4** with organic electrophiles such as allylic halides can be augmented by cuprous salt catalysis[21] and that such catalysis may provide an efficacious reaction with previously unreactive acyl halides.[18]

The organozinc reagent **4** does not react to any appreciable extent with ethyl chloroformate. However, this situation can be easily ameliorated upon addition of a catalytic amount of cuprous bromide to the reaction mixture (Scheme I). The reaction is complete within a period of hours to yield ethyl (diethoxyphosphinyl)difluoroacetate (**1**). Similarly, the ethyl esters of difluorophosphonopyruvate (**2**) and *N,N*-diethyldifluoro(diethoxyphosphinyl)acetamide (**3**) have been prepared when ethyl oxalyl chloride and diethylcarbamoyl chloride were used as substrates, respectively. These results and others are summarized in Table I.

Scheme II

$4 + Cl_2CO \longrightarrow (EtO)_2P(O)CF_2C(O)Cl$ (**6**)

EtOH → $(EtO)_2P(O)CF_2CO_2Et$ (**1**)

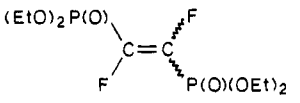
KF → $(EtO)_2P(O)CF_2C(O)F$ (**7**)

Scheme III[a]

1 $\xrightarrow{i}$ $(Me_3SiO)_2P(O)CF_2CO_2Et$ (**9**) $\xrightarrow{ii}$ $(Me_3SiO)_2P(O)CF_2CO_2SiMe_3$ (**10**) $\xrightarrow{iii}$ $(HO)_2P(O)CF_2CO_2H$ (**8**)

[a] (i) 2 $BrSi(CH_3)_3$; (ii) $ISi(CH_3)_3$; (iii) H_2O.

The cuprous bromide catalyzed reactions of **4** with acyl halides are generally conducted in the presence of acetonitrile as a cosolvent. Yet, ethyl difluoro(diethoxyphosphinyl)acetate (**1**) could also be formed in good yield in the absence of a coordinating cosolvent. For example, a 69% ^{19}F NMR yield of **1** was obtained from a 0.20 mol CuBr catalyzed reaction of organozinc **4** and ethyl chloroformate in the absence of acetonitrile. However, an 11% yield of a mixture of isomeric byproducts, which have been tentatively characterized as (*E*)- and (*Z*)-1,2-difluoroethylenediyl)bisphosphonate **5**[22] was also obtained. In the presence of a coordinating cosolvent, **5** was not observed.



5

The substitution of nickel chloride for cuprous bromide did not promote a catalytic transformation. An admixture of **4** and ethyl chloroformate in the presence of $NiCl_2$ remained unchanged after 26 h at room temperature.

The reaction of **4** with ethyl chlorothioformate produced a viscous black oil from which an organic product could not be isolated. However, analysis by ^{19}F NMR spectroscopic integration indicated that *S*-ethyl difluoro(diethoxyphosphinyl)thioacetate had been formed in 54% yield.

In contrast to the above results, CuBr did not prove to be a good catalyst for the reaction of **4** and phosgene. The yield of the desired product, difluoro(diethoxyphosphinyl)acetyl chloride (**6**), was higher and contained fewer extraneous side products upon exclusion of the cuprous bromide catalyst. However, the yield of **6** amounted to only 18% of the observable fluorinated reaction products.

The acyl chloride **6** could not be isolated due to its hydrolytic nature. However, it was partially characterized by its chemical conversion to ethyl ester **1** upon reaction with ethanol and its conversion to acyl fluoride **7** upon reaction with potassium fluoride (Scheme II).

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(22) Full details of these compounds will be reported elsewhere. *E*:*Z* = 73:27, bp 112–155 °C (0.02 mmHg). Anal. Calcd for $C_{10}H_{20}F_2O_6P_2$: C, 35.72; H, 6.00. Found: C, 36.05; H, 5.95.

Scheme IV

$$(Me_3SiO)_2P(O)CF_2CO_2Et + 2\ PCl_5$$

9

$$\downarrow$$

$$Cl_2P(O)CF_2CO_2Et + 2\ ClSiMe_3 + 2\ POCl_3$$

11

The complete hydrolysis of ester **1** would yield the corresponding difluorophosphonoacetic acid (**8**). The simplest transformation of **1** to **8** would involve the hydrolysis of the alkyl ester with concentrated hydrochloric acid followed by careful evaporation after hydrolysis. Such a method has been used to prepare quantitatively phosphonoacetic acid.[23]

Preliminary experiments involving the HCl hydrolysis of tetraethyl difluoromethanediphosphonate showed that it is extremely difficult to remove all of the HCl from the reaction mixture by evaporation.[24] Therefore, a small but significant amount of hydrochloric acid would always be present as a contaminant in the final product.

The possibility of obtaining a contaminated sample of difluorophosphonoacetic acid is eliminated by the prior conversion of the ethyl phosphonic esters to trimethylsilyl phosphonic esters. Trimethylsilyl phosphonates are conveniently obtained by the reaction of an alkanephosphonate ester with bromotrimethylsilane.[25] Thus, **1** is selectively converted to the *bis*(trimethylsilyl)-phosphonate **9** in 89% isolated yield upon stirring with an excess of bromotrimethylsilane at room temperature (Scheme III).

Complete hydrolysis to produce **8** is effected through the tris(trimethylsilyl) phosphonate ester **10**. The exhaustive silylation is achieved by conversion of the ethyl carboxylic ester **9** to a trimethylsilyl carboxylic ester by the further reaction of **9** with an additional equivalent of the more reactive iodotrimethylsilane[26] to afford a 67% isolated yield of **10**. Dissolution of **10** in water immediately gave **8**. Concentration by rotary evaporation of the aqueous solution of acid **8** gave a hygroscopic and viscous syrup. From the syrup was obtained the stable monohydrate of the corresponding disodium salt as well as the white crystalline dicyclohexylammonium salt.

A plethora of methods are available for the transformation of alkanephosphonates into alkanephosphonyl dichlorides. One convenient method of special appeal involves the intermediacy of trimethylsilyl phosphonate esters.[27] The reaction of the bis(trimethylsilyl) phosphonate **9** with PCl_5 provided a mild, convenient, and high yield method to prepare ethyl difluoro(dichlorophosphinyl)acetate (**11**). Thus, **11** was obtained in 74% isolated yield upon stirring a solution of **9** and PCl_5 in CH_2Cl_2 overnight, removal of the solvent and the resultant chlorotrimethylsilane and phosphorus oxychloride by simple distillation, and distillation of the crude product under reduced pressure (Scheme IV).

In conclusion, we present a convenient synthesis of a variety of esters, acids, and an amide of difluoromethylene carboxylic phosphonates. The preparation of these compounds is readily accomplished on mole scales, involves the use of nonhazardous starting materials that are easily prepared from commercially available sources, and avoids the formation of the toxic diethyl fluorophosphate, $(EtO)_2P(O)F$.

Experimental Section

General. The reaction flasks and other glass equipment were stored in an oven at 130 °C overnight and assembled under a stream of dry nitrogen. All boiling points were determined during fractional distillation by means of a partial immersion thermometer and are uncorrected. NMR spectra were recorded on a JEOL FX90-Q multinuclear spectrometer, or where noted on a Bruker WM360X spectrometer. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^1H NMR spectra against internal tetramethylsilane, and ^{31}P NMR spectra against an external 85% H_3PO_4 capillary. ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. IR spectra were recorded as thin films on a Beckman Acculab 8 grating IR spectrometer.

Materials. Diethyl bromodifluoromethanephosphonate was prepared by the method of Burton and Flynn.[28] Monoglyme was obtained from the Ansul Chemical Co., Marinette, WI, and was purified and dried by distillation from a sodium benzophenone ketyl. Cuprous bromide was obtained from Aldrich Chemical Co. and was purified by a method similar to that of Osterlof.[29] Zinc powder was activated by being washed with dilute HCl and then distilled water and dried in vacuo overnight at 120 °C. [(Diethoxyphosphinyl)difluoromethyl]zinc bromide was prepared by the procedure that follows. The diisopropylphosphinyl and di-*n*-butylphosphinyl analogues were prepared in a similar manner.

[(Diethoxyphosphinyl)difluoromethyl]zinc Bromide (4). A 2-L round-bottomed flask equipped with a reflux condenser, a nitrogen bubbler, and a Teflon-coated spin bar was cooled in an ice bath. The flask was charged with acid-washed zinc powder (65.4 g, 1.0 g atom) and 500 mL of dry monoglyme. Then 267.0 g (1.0 mol) of diethyl bromodifluoromethanephosphonate was added slowly via a constant addition funnel in order to avoid a vigorous exothermic reaction. After being stirred for 4 days at room temperature, the solution was filtered in a Schlenk funnel (medium frit) to remove any excess zinc powder, leaving [(diethoxyphosphinyl)difluoromethyl]zinc bromide: ^{19}F NMR (MG) −126.1 ppm (d) $^2J_{F,P}$ = 89 Hz; ^{31}P NMR (MG) 14.1 ppm (t); ^{13}C NMR (MG, undecoupled) 16.04 ppm (d, CH_3) $^1J_{C,H}$ = 127 Hz, ~58–59 (−CH_2O−, masked by monoglyme solvent), 140.51 (td, −CF_2−) $^1J_{C,F}$ = 290 Hz, $^1J_{C,P}$ = 119 Hz.

Ethyl Difluoro(diethoxyphosphinyl)acetate (1). A round-bottomed flask was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. To the flask was added a Schlenk filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide that had been prepared in the above procedure. To this mixture was added 250 mL of dry CH_3CN and CuBr (72 g, 0.50 mol), followed by ethyl chloroformate (115 mL, 1.2 mol). The reaction mixture was stirred overnight at room temperature, the volume reduced by rotary evaporation, and the remaining solution poured into 500 mL of water. The insoluble inorganic salts were separated by filtration through a Buchner funnel under aspirator pressure, washed with 100 mL of water, and washed with 100 mL of CH_2Cl_2. The filtrate and washings were combined and separated, and the aqueous portion was twice extracted with 200 mL of CH_2Cl_2. All of the organic portions were combined, dried over anhydrous $MgSO_4$, gravity filtered, concentrated by rotary evaporation, and distilled through a 10-cm Vigreaux column to give 131 g (0.50 mol, 50%, 98% GLPC purity) of the title compound: bp 74–77 °C (0.2 mmHg); n^{21} 1.4027; ^{19}F NMR −117.0 ppm (d) $^2J_{P,F}$ = 98 Hz; ^{31}P NMR 2.52 ppm (t); ^{13}C NMR 13.9 (s, $CH_3CH_2O_2C$) 16.4 ppm (d, CH_3CH_2OP) $^3J_{C,P}$ = 6 Hz, 63.8 (s, $CH_3CH_2O_2C$), 65.4 (d, CH_3CH_2OP) $^2J_{C,P}$ = 6 Hz, 111.2 (td, CF_2) $^1J_{C,F}$ = 204 Hz, 161.9 (td, C=O) $^2J_{C,F}$ = 28 Hz, $^2J_{C,P}$ = 19 Hz; ^1H NMR 1.38 (t, CH_3) $^3J_{H,H}$ = 7.1 Hz, 1.40 (t, CH_3) $^3J_{H,H}$ = 7.0 Hz, 4.34 (dq, 5 lines, −CH_2O−) $^3J_{H,H} \sim {}^3J_{P,H}$ = 7.3 Hz, 4.40 (q); IR (neat) 2985 (w), 1770 (s, C=O), 1480 (w), 1445 (w), 1395 (w), 1370 (w), 1290 (s, P=O), 1050 (m), 1010 cm^{-1} (m).

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Anal. Calcd for $C_8H_{15}F_2O_3P$: C, 36.93; H, 5.81. Found: C, 36.94; H, 5.69.

Ethyl Difluoro(diisopropoxyphosphinyl)acetate. A similar reaction conducted on a scale of 0.10 mol resulted in 7.6 g (0.027 mol, 27%, 100% GLPC purity) of the title compound: bp 60–63 °C/0.07 mmHg; n^{26} 1.4040; ^{19}F NMR −117.6 ppm (d) $^2J_{F,P}$ = 97 Hz); ^{31}P NMR 0.69 ppm (t); ^{1}H NMR 1.37 ppm (t, CH_3CH_2) $^3J_{H,H}$ = 7.1 Hz, 1.41 (d, $(CH_3)_2CH$) $^3J_{H,H}$ = 5.9 Hz, 4.39 (q, $-CH_2O-$), 4.90 (m, $-CH-$) $^3J_{H,H} \sim {}^3J_{P,H}$ = 6.2 Hz; IR (neat) 2990 (m, C—H), 1765 (s, C=O), 1460 (w), 1385 (m), 1290 (s, P=O), 1160 (s), 1110 (s), 1010 cm^{-1} (vs, P—O—R).

Anal. Calcd for $C_{10}H_{19}F_2O_5P$: C, 41.67; H, 6.64. Found: C, 41.58; H, 6.03.

Ethyl Difluoro(di-*n*-butoxyphosphinyl)acetate. Similarly, a 0.05-mol reaction yielded 5.8 g (0.017 mol, 36%, 100% GLPC purity) of the title compound: bp 100–106 °C/0.2 mmHg; ^{19}F NMR −116.3 ppm (d) $^2J_{F,P}$ = 95.9 Hz; ^{31}P NMR 2.91 ppm (t); ^{1}H NMR 0.95 ppm (t, $CH_3CH_2CH_2CH_2OP$) $^3J_{H,H}$ = 7.1 Hz, 1.37 (t, $CH_3CH_2OC(O)$) $^3J_{H,H}$ = 6.7 Hz, 1.24 to 1.80 (m), 4.25 (dq, 5 lines, $CH_2OP(O)$) $^3J_{H,H} \sim {}^3J_{P,H}$ = 6.8 Hz, 4.39 (q, $CH_2OC(O)$) $^3J_{H,H}$ = 7.1 Hz; IR (neat) 2980 (m), 1770 (s, C=O), 1470 (w), 1375 (w), 1290 (s, P=O), 1170 (s), 1030 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{23}F_2O_5P$: C, 45.57; H, 7.33. Found: C, 45.74; H, 7.08.

Ethyl Difluoro(diethoxyphosphinyl)pyruvate (2). A round-bottomed flask was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. To the flask was added a Schlenk-filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide prepared from diethyl bromodifluoromethanephosphonate (26.7 g, 0.10 mol), acid-washed zinc powder (6.6 g, 0.10 mol), and 50 mL of dry monoglyme. To this solution was added CuBr (0.12 g, 0.008 mol). Ethyl oxalyl chloride (9.7 mL, 0.10 mole) was then added dropwise and the mixture stirred overnight. The mixture was filtered through a medium fritted glass Buchner funnel under aspirator pressure and the filtrate was poured into 100 mL of water and extracted thrice with 50 mL of CH_2Cl_2. The organic portions were dried over anhydrous Na_2SO_4, decanted, concentrated by rotary evaporation, and vacuum-distilled through a 10-cm Vigreaux column, collecting the fraction boiling between 86 and 104 °C to give 17.8 g (0.062 mol, 62%, 100% GLPC purity) of the title compound: n^{25} 1.4152; ^{19}F NMR −115.8 ppm (d) $^2J_{P,F}$ = 95 Hz; ^{31}P NMR 2.06 ppm (t); ^{1}H NMR (360 MHz) 1.41 ppm (t) $^3J_{H,H}$ = 7 Hz, 4.36 (dq) $^3J_{H,H}$ = 7.3 Hz, 4.43 (q) $^3J_{H,H}$ = 7.1 Hz; IR (neat) 3200 (s), 3000 (m), 1745 (s, C=O), 1445 (w), 1395 (w), 1370 (w), 1255 (s, P=O), 1160 (s), 1090 (s), 1030 cm^{-1} (s).

Anal. Calcd for $C_9H_{15}F_2O_6P$: C, 37.51; H, 5.25. Found: C, 37.60; H, 5.29.

***N*,*N*-Diethyldifluoro(diethoxyphosphinyl)acetamide (3).** A round-bottomed flask was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. To the flask was added a Schlenk funnel filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide, prepared from diethyl bromodifluoromethanephosphonate (26.7 g, 0.10 mol), acid-washed zinc powder (7.2 g, 0.11 g atom), and 50 mL of dry monoglyme. To this solution was added 25 mL of dry CH_3CN, CuBr (4.2 g, 0.029 mol), and diethylcarbamoyl chloride (13.6 g, 0.10 mol) in one portion. An exothermic reaction developed. After being stirred overnight at room temperature, the reaction mixture was poured into 100 mL of water, and the resulting inorganic solids were separated by suction filtration and washed with 50 mL of CH_2Cl_2. The aqueous phase was thrice extracted with 50 mL of CH_2Cl_2. The organic fractions were combined and dried over anhydrous $MgSO_4$, gravity filtered, concentrated by rotary evaporation, and flash distilled to give 15.3 g of clear distillate. Redistillation and collecting the fraction boiling at bp 94–105 °C (0.2 mmHg) gave 11.0 g (0.038 mol, 38%, 93% GLPC purity) of the title compound: n^{21} 1.4342; ^{19}F NMR −108.8 ppm (d) $^2J_{P,F}$ = 100 Hz; ^{31}P NMR 3.92 ppm (t); ^{1}H NMR 1.18 ppm (t) $^3J_{H,H}$ = 7.0 Hz, 1.38 (t) $^3J_{H,H}$ = 7.0 Hz, 3.42 (q) $^3J_{H,H}$ = 7.0 Hz, 4.34 (dq) $^3J_{H,H} \sim {}^3J_{P,H}$ = 7.3 Hz; IR (neat) 2985 (m), 1755 (w), 1705 (w), 1660 (s, C=O), 1280 (s, P=O), 1130 (m), 1095 (m), 1025 cm^{-1} (s). The physical and spectral data are consistent with the structure, $(EtO)_2P(O)CF_2C(O)NEt_2$. The compound was contaminated with an unknown that could not be separated by spinning band distillation.

***S*-Ethyl Difluoro(diethoxyphosphinyl)thioacetate.** A round-bottomed flask was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. To the flask was added a Schlenk funnel filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide prepared from diethyl bromodifluoromethanephosphonate (66.8 g, 0.25 mol), acid-washed zinc powder (16.3 g, 0.25 g atom), and 100 mL of dry monoglyme. To this solution were added CuBr (1.4 g, 0.01 mol) and ethyl chlorothioformate (26.3 mL, 0.25 mol). An exothermic reaction accompanied by a color change from colorless to black resulted upon addition of the acid halide. The volume of the reaction was reduced by rotary evaporation to produce a viscous oil. The oil was diluted with CH_2Cl_2, which caused the formation of an unknown precipitate. The precipitate was removed by filtration through a medium fritted glass Buchner funnel under aspirator pressure, and the CH_2Cl_2 was removed by rotary evaporation, to again leave a black viscous oil. The attempted flash vacuum distillation did not yield any material as distillate, but the contents of the pot had been converted to tar.

When the reaction was repeated on a 0.010-mol scale the yield was determined by ^{19}F NMR spectroscopy to be 54% $(EtO)_2P(O)CF_2C(O)SEt$ and 11% $(EtO)_2P(O)CF_2H$.

S-Ethyl difluoro(diethoxyphosphinyl)thioacetate: ^{19}F NMR (MG) −113.3 ppm (d) $^2J_{F,P}$ = 98 Hz; ^{31}P NMR 1.6 ppm (t).

Difluoro(diethoxyphosphinyl)acetyl Chloride (6) and Difluoro(diethoxyphosphinyl)acetyl Fluoride (7). A round-bottomed flask was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. To the flask was added a Schlenk funnel filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide prepared from diethyl bromodifluoromethanephosphonate (5.3 g, 0.02 mol), acid-washed zinc powder (1.3 g, 0.02 g atom), and 10 mL of dry monoglyme. To this solution was added phosgene (20 mL of a 12.5% solution in toluene, 0.025 mol, MCB), and the reaction mixture was allowed to stir at room temperature without evidence of any exothermic reaction. After 17 h at room temperature the reaction had turned light brown in color and had developed a precipitate. Analysis by normalized ^{19}F NMR spectroscopic integration revealed the mixture to contain 60% $(EtO)_2P(O)CF_2Br$, 4% $(EtO)_2P(O)CF_2Cl$, 18% $(EtO)_2P(O)CF_2C(O)Cl$, 11% $(EtO)_2P(O)CF_2H$, and 7% of an unknown [−114.9 ppm (d) $^2J_{F,P}$ = 93 Hz].

Ethanol (95%) was added to a small portion of the reaction mixture to produce an exothermic reaction and the conversion of difluoro(diethoxyphosphinyl)acetyl chloride to ethyl difluoro(diethoxyphosphinyl)acetate. Ethyl difluoro(diethoxyphosphinyl)acetate was characterized by spiking with an authentic sample.

To the remainder of the reaction mixture was added potassium fluoride (1.1 g, 0.019 mol). The mixture was stirred at room temperature and analyzed by ^{19}F NMR spectroscopy. The difluoro(diethoxyphosphinyl)acetyl chloride had been converted to difluoro(diethoxyphosphinyl)acetyl fluoride, which was hydrolytically unstable and could not be isolated.

Difluoro(diethoxyphosphinyl)acetyl chloride: ^{19}F NMR (MG) −111.1 ppm (d) $^2J_{F,P}$ = 94 Hz; ^{31}P NMR 0.4 ppm (t).

Difluoro(diethoxyphosphinyl)acetyl fluoride: ^{19}F NMR (MG) +24.1 ppm (t, C(O)F) $^3J_{F,F}$ = 12 Hz, −117.7 (dd) $^2J_{F,P}$ = 91 Hz; ^{31}P NMR −0.1 ppm (t).

Ethyl Difluoro[bis(trimethylsiloxy)phosphinyl]acetate (9). Ethyl difluoro(diethoxyphosphinyl)acetate (4.97 g, 0.019 mol) was added to a round-bottomed flask which was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. Bromotrimethylsilane (7.8 mL, 9.0 g, 0.058 mole) was added to the flask and the contents were allowed to stir at room temperature for 3 days. The volatile components were removed in vacuo, and the resulting oil was distilled to yield 6.38 g (0.018 mol, 95% yield, 93% GLPC purity, 4% $BrSiMe_3$) of the title compound: bp 75–80 °C (0.1 mmHg); ^{19}F NMR −118.2 ppm (d) $^2J_{P,F}$ = 100 Hz; ^{31}P NMR −15.7 ppm (t); ^{1}H NMR 0.35 ppm (s), 1.37 (t) $^3J_{H,H}$ = 7.2 Hz, 4.37 (q) $^3J_{H,H}$ = 7.0 Hz.

Trimethylsilyl Difluoro[bis(trimethylsiloxy)phosphinyl]acetate (10). Ethyl difluoro(diethoxyphosphinyl)acetate (42.8 g, 0.165 mol) was added to a round-bottomed flask, which was connected to a nitrogen bubbler and was equipped with a Teflon-coated spin bar. Bromotrimethylsilane (55 mL, 63.8 g, 0.42

mol) was added to the flask and the contents were allowed to stir at room temperature for 4 days. The volatile components were removed by simple distillation and the residue was distilled in vacuo, collecting 44.6 g of liquid boiling between 75 and 80 °C/0.10 mmHg. Iodotrimethylsilane (19 mL, 26.7 g, 0.13 mol) was added to the resultant oil, and the mixture was heated at 100 °C for 1 day with gradual darkening of the solution. The color change is believed to be due to the formation of I_2. Additional $ISiMe_3$ (10 mL, 14.0 g, 0.07 mol) was added and the reaction mixture was again heated for 34 h. The volatile components were removed in vacuo. The resultant oil was decolorized by stirring over acid-washed zinc powder and vacuum distilled through a simple distillation apparatus to yield 44.4 g of a light brown oil. The oil was redistilled through a simple distillation apparatus to yield 41.5 g (0.106 mol, 64%) of the title compound as an oil, which partially solidified in the cold water condenser: bp 88–92 °C (0.3 mmHg); ^{19}F NMR −118.0 ppm (d) $^2J_{F,P}$ = 102 Hz; ^{31}P NMR −16.3 ppm (t); ^1H NMR 0.35 ppm (s, $P(OSiMe_3)_2$), 0.38 (s, CO_2SiMe_3).

Hydrolysis of Trimethylsilyl Difluoro[bis(trimethylsiloxy)phosphinyl]acetate. Trimethylsilyl difluoro[bis(trimethylsiloxy)phosphinyl]acetate (41.5 g, 0.106 mol) was dissolved in 300 mL of distilled water in a separatory funnel. The resultant organic phase was separated, and the aqueous phase was extracted with 6 × 50 mL portions of benzene. The bulk of the water was removed by rotary evaporation to yield difluorophosphonoacetic acid as a clear, hygroscopic oil: ^{19}F NMR (H_2O, $CFCl_3$ external standard) −117.6 ppm (d) $J_{P,F}$ = 89 Hz; ^{31}P NMR 0.8 ppm (t).

Dicyclohexylammonium Difluorophosphonoacetate. To an Erlenmeyer flask which contained an aqueous solution of difluorophosphonoacetic acid, which had been formed by dissolution of trimethylsilyl difluoro[bis(trimethylsiloxyphosphinyl)]acetate (1.60 g, 0.004 mol) in 10 mL of distilled water, was added dicyclohexylamine (0.39 mL, 0.35 g, 0.002 mol). Evaporation of the water over a hot plate and recrystallization of the residue from a 1:5 methanol/acetone mixture gave 0.06 g (0.0002 mol, 5%) of the title compound as a single crop of white needles: mp 210–212 °C dec.

Anal. Calcd for $C_{14}H_{26}F_2NO_5P$: C, 47.06; H, 7.33; N, 3.92. Found: C, 47.17; H, 7.07; N, 3.76.

Ethyl Difluoro(dichlorophosphinyl)acetate (11). Ethyl difluoro(diethoxyphosphinyl)acetate (10.0 g, 0.038 mol) was added to a round-bottomed flask which was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. Bromotrimethylsilane (10.3 mL, 11.9 g, 0.078 mol) was added to the flask and the contents were stirred at room temperature. After 2 weeks the volatile components were removed in vacuo. The residue was dissolved in 10 mL of CCl_4 and added dropwise to a solution of PCl_5 (20.0 g, 0.096 mol) dissolved in 75 mL of CCl_4. The homogeneous mixture was stirred overnight at room temperature. The solvent and phosphorus oxychloride were removed by simple distillation, and the resultant oil was distilled to give 7.8 g (0.032 mol, 84%) of the title compound: bp 45–47 °C (0.1 mmHg); ^{19}F NMR −112.0 ppm (d) $^2J_{P,F}$ = 125 Hz; ^{31}P NMR 24.6 ppm (t); ^1H NMR ($SOCl_2$) 1.37 ppm (t) $^3J_{H,H}$ = 7.0 Hz, 4.45 (q); IR (neat) 2995 (w, C—H), 1300 (s, P=O), 1155 (s).

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Registry No. 1, 17843-01-5; 2, 113161-58-3; 3, 113161-59-4; 4 (R = Et), 82845-20-3; 4 (R = *i*-Pr), 82845-21-4; 4 (R = Bu), 82845-22-5; 6, 97480-49-4; 7, 113161-61-8; 8, 91410-83-2; [8] [dicyclohexylamine], 91410-86-5; [8]Na_2, 91410-87-6; 9, 91410-84-3; 10, 91410-85-4; 11, 113161-62-9; $(EtO)_2P(O)CF_2Cl$, 113161-60-7; $(EtO)_2P(O)CF_2Br$, 65094-22-6; $(i\text{-}PrO)_2P(O)CF_2O_2Et$, 113161-63-0; $(n\text{-}BuO)_2P(O)CF_2CO_2Et$, 113161-64-1; $(EtO)_2P(O)CF_2C(O)SEt$, 113161-65-2; $(EtO)_2P(O)CF_2H$, 1478-53-1.

Synthesis of 6,6-Pentamethylene-2-aminosuberic Acid. A Key Intermediate in the Synthesis of Dicarba Analogues of Vasopressin Antagonists

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Two complementary syntheses of the unnatural amino acid, 6,6-cyclopentamethylene-2-aminosuberic acid, Pas (2) are described. The first, starting from methyl cyclohexanecarboxylate (4), yields in ten steps racemic Boc-Pas(OBzl)-OH (3) which is suitably protected for solid phase peptide synthesis. The second method involves the stereospecific synthesis of optically pure Boc-Pas(OBzl)-OH (3L) utilizing the electrochemical coupling, via the Kolbe method of the monobenzyl ester of 1,1-cyclohexanediacetic acid (13) and Boc-L-Glu-OBzl (14). The optical purity of 3L was confirmed by chiral gas chromatographic analysis of its *N*-pentafluoropropionyl diisopropyl ester derivative 15L.

The replacement of the cysteine residue in position one of vasopressin with the deaminocysteine derivative β-mercapto-β,β-cyclopentamethylenepropionic acid, Pmp[1] (1), has been shown to be one of the key factors involved in the development of antagonists of the renal vasopressin (V_2) receptor.[2] In order to enhance the chemical and metabolic stability of these vasopressin antagonists and to begin to evaluate the role the disulfide bond plays in the biologically active conformation, the synthesis of the

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