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Synthesis of Novel Fluorinated Bisphosphonates and Bisphosphonic Acids[1]

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The synthesis of novel fluorinated bisphosphonates with two, three, four, and six difluoromethylene groups (**1a, 1b, 8, 12,** and **15**) (44–78%) by different approaches is described. The bisphosphonates were converted to the corresponding trimethylsilyl esters which on treatment with deionized water afforded the respective bisphosphonic acids (**6, 10,** and **14**) in good yields.

Introduction

Phosphorus compounds play a vital role in all living organisms. A number of bisphosphonates and bisphosphonic acids have been investigated for their diverse biological activity.[2] Methylenebisphosphonates and their α-halogenated derivatives have attracted considerable interest since these compounds show antiviral activity,[3] inhibit bone resorption,[4] and find application as ligands in radiopharmaceuticals.[5] For example, (chloromethylene)bisphosphonate inhibits the RNA transcriptase activity of the influenza virus more effectively than methylene bisphosphonate;[6] dichloromethylene bisphosphonic acid has been found to be active in bone and calcium phosphate metabolism.[4b,6] Recently, mono- and difluoromethylene bisphosphonates have been also shown to exhibit interesting biological properties; they are potential candidates for phosphate analogues[7] and inhibit bone lysis.[8] Unlike other substituents, fluorine does not introduce large steric perturbations and imparts increased hydrolytic stability as well as oxygen solubility. These properties make them useful compounds in other applications, e.g., as substitutes for or additives to H_3PO_4 in fuel cell electrolytes.[9] With this possibility in mind, we recently carried out the preparation of a number of (perfluoroalkylidene)-α,ω-bisphosphonates and their conversion to the corresponding bisphosphonic acids.

In contrast to the plethora of examples of phosphonates and bisphosphonates, there are only a handful of reports that focus on fluorinated analogues. This marked paucity of reports on fluorinated phosphonates can be attributed to the lack of useful methods of preparation of these compounds, since the conventional methods of synthesizing phosphonates and bisphosphonates cannot usually be applied in the highly fluorinated cases. The first preparation of $(EtO)_2P(O)CF_2P(O)(OEt)_2$ was achieved[10a] by treating diethyl phosphite anion with diethyl (bromodifluoromethyl)phosphonate in toluene. This reaction involves the abstraction of positive bromine from $(EtO)_2P(O)CF_2Br$ to afford the phosphonate anion, $(EtO)_2P(O)CF_2^-Na^+$, followed by *in situ* acylation.[10b] Related fluorinated anions, to be formed *via* reaction of phosphite anions with ω-bromoperfluorinated phosphonates, have not been reported to undergo a similar *in situ* acylation.

$$(EtO)_2P(O)CF_2Br + (EtO)_2PONa \xrightarrow{\text{toluene}} \underset{47\%}{(EtO)_2P(O)CF_2P(O)(OEt)_2} \quad (1)$$

Later, the electrophilic fluorination of the carbanion generated from $(EtO)_2P(O)CH_2P(O)(OEt)_2$ with perchloryl fluoride was reported to give a mixture of mono and difluoromethylene bisphosphonates.[7a,11] The use of ClO_3F

$$(EtO)_2P(O)CH_2P(O)(OEt)_2 \xrightarrow[ClO_3F]{NaH} (EtO)_2P(O)CFHP(O)(OEt)_2 + (EtO)_2P(O)CF_2P(O)(OEt)_2 \quad (2)$$

can be hazardous, and hence, this method has not been widely employed. Recently, preparation of $(EtO)_2P(O)CF_2P(O)(OEt)_2$ from CF_2Br_2 and $NaOP(OEt)_2$ has also been reported[12] *via* a modification of the initial procedure.[10b] The preparation of tetraethyl (1,2-difluoroethenediyl)bisphosphonate[13] and tetraethyl (3,3,4,4,5,5-hexafluoro-1-cyclopentene-1,2-diyl)bisphosphonate[14] have also been reported; however, to our knowledge the synthesis of bisphosphonates of the type $(EtO)_2P(O)(CF_2)_nP(O)$-

$$CF_2Br_2 + (EtO)_2PONa \rightarrow \underset{40\%}{(EtO)_2P(O)CF_2P(O)(OEt)_2} \quad (3)$$

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$(OEt)_2$ with $n > 1$ are currently unknown. Herein, we report the facile synthesis of a number of new (perfluoroalkylidene)-α,ω-bisphosphonates *via* different approaches from commercially available starting materials and their conversion to the corresponding bisphosphonic acids.

Results and Discussion

(Tetrafluoroethane-1,2-diyl)bisphosphonic Acid. Tetraalkyl (tetrafluoroethylene-1,2-diyl)bisphosphonates $(RO)_2P(O)CF_2CF_2P(O)(OR)_2$ (R = Et, **1a**; R = i-Pr, **1b**) were synthesized by the homocoupling of the corresponding dialkyl (iododifluoromethyl)phosphonates. The requisite dialkyl (iododifluoromethyl)phosphonates **3a** and **3b** were prepared in high yields *via* iodination of the respective zinc reagent, $(RO)_2P(O)CF_2ZnBr$, which was generated *in situ* by treatment of the corresponding bromophosphonates, **2a** and **2b**, with activated Zn powder in monoglyme, as reported elsewhere.[15] **2a** and **2b** are easily obtained, in excellent yields, from $(RO)_3P$ (R = Et or i-Pr) and CF_2Br_2.[16]

$$\underset{\substack{\textbf{2a}\ (R = Et)\\ \textbf{2b}\ (R = i\text{-}Pr)}}{(RO)_2P(O)CF_2Br} \xrightarrow[I_2]{\text{Zn/monoglyme,}} \underset{\substack{\textbf{3a},\ 70\%\ (R = Et)\\ \textbf{3b},\ 66\%\ (R = i\text{-}Pr)}}{(RO)_2P(O)CF_2I} \qquad (4)$$

The reductive dimerization of **3a** or **3b** using Zn and Cd was studied. Reaction with a stoichiometric amount of Zn in the optimal solvent system, CH_2Cl_2/DMAC (2:1), gave a mixture of starting material, desired dimer **1a**, organozinc compound, and reduced product **4**, in variable ratios, as monitored by ^{19}F NMR analysis.

$$\textbf{3a} \xrightarrow[CH_2Cl_2/DMAC]{Zn} \textbf{3a} + \textbf{1a} + (EtO)_2P(O)CF_2ZnI + \underset{\textbf{4}}{(EtO)_2P(O)CF_2H} \qquad (5)$$

The best isolated yield of **1a** from this reaction mixture was 49%. The order of addition made little difference, and the zinc reagent, once formed, could not be converted to **1a**. In other solvent systems, larger amounts of $(EtO)_2P(O)CF_2ZnI$ were formed.[15c] Alternative procedures were therefore investigated, and it was found that Cd powder in refluxing CH_2Cl_2 gave far better results, with **1a** or **1b** isolated in 62–69% yield, along with reduced product, $(RO)_2P(O)CF_2H$. The homocoupling of **3a** and **3b** can also be effected in CH_3CN; however, the yields were ~15–20% lower. Under similar conditions, no homocoupling

$$\textbf{3a}\text{ or }\textbf{3b} \xrightarrow[CH_2Cl_2,\ reflux]{Cd} \underset{\substack{\textbf{1a},\ 69\%\ (R = Et)\\ \textbf{1b},\ 62\%\ (R = i\text{-}Pr)}}{(RO)_2P(O)CF_2CF_2P(O)(OR)_2} \qquad (6)$$

was observed either with Cu or Ni powder. Also, the bromophosphonates (**2a** and **2b**) failed to undergo the reductive dimerization with Cd powder in dichloromethane. However, the dimerization of bromophosphonates can be effected *via in situ* generated Ni(0),[17] thus avoiding the conversion of **2a** and **2b** to **3a** and **3b**. Recently, formation of **1a** as a byproduct in the addition of **2a** to various alkenes has been reported.[18]

$$(RO)_2P(O)CF_2Br \xrightarrow[\substack{Et_4NI,\ CH_3CN\\ 45\ ^\circ C,\ 1\ h}]{Zn,\ NiCl_2(PPh_3)_2} \underset{\substack{\textbf{1a},\ 52\%\\ \textbf{1b},\ 47\%}}{(RO)_2P(O)CF_2CF_2P(O)(OR)_2} \qquad (7)$$

In the above reactions, when the product was isolated either by distillation or chromatography, exposure to halide ion in reaction mixtures, over periods of even a day or two, resulted in dramatic reductions in yield, presumably due to the dealkylation of the phosphonate esters by halide ions. Thus, it is essential, for good yields of the product, to remove all Zn or Cd halides prior to distillation or chromatography.

With the bisphosphonates **1a** and **1b** in hand, hydrolysis to the corresponding acid was relatively simple. Since one of our objectives was to test this analogue and related compounds as fuel-cell electrolytes, we needed to develop a procedure that would give us the acid in electrolytically pure form. The ethyl ester **1a** was therefore converted to the corresponding trimethylsilyl ester **5**, which could be isolated by vacuum distillation. The silyl ester was then treated with deionized water to cleanly give the desired acid **6**. The silylation could be conveniently carried out with bromotrimethylsilane,[19] but for large-scale work, a mixture of chlorotrimethylsilane and NaBr in acetonitrile gave comparable yields.[13a]

$$\begin{tikzcd}[column sep=large]
\textbf{1a} \arrow[r, "TMSCl/NaBr", "CH_3CN\text{, reflux}"'] & \underset{\textbf{5},\ 94\%}{(Me_3SiO)_2P(O)CF_2CF_2P(O)(OSiMe_3)_2} \arrow[d, "H_2O"] \\
 & \underset{\textbf{6},\ 83\%}{(HO)_2P(O)CF_2CF_2P(O)(OH)_2{\cdot}H_2O}
\end{tikzcd}$$

The acid, **6**, was subjected to further purification to remove electrolytic impurities by first heating the compound with 50% H_2O_2 and then, after concentration, stirring it with platinum black in an atmosphere of H_2. This cycle was repeated three to four times. Deionized water and dedicated glassware were used throughout, so as to avoid the introduction of ionic impurities. After drying in a vacuum desiccator, the product was obtained as a white, waxy, hygroscopic solid, completely soluble in water. The acid **6** is a monohydrate, as determined by titration with NaOH.

(Octafluorobutane-1,4-diyl)bisphosphonic Acid. We initially chose to approach the synthesis of this compound *via* the commercially available precursor 1,4-diiodoperfluorobutane (**7**), using the Kato–Yamabe procedure.[20] It was anticipated that the conversion of both iodo functionalities in the molecule into phosphonates would present some difficulties. For example, Shreeve and co-workers

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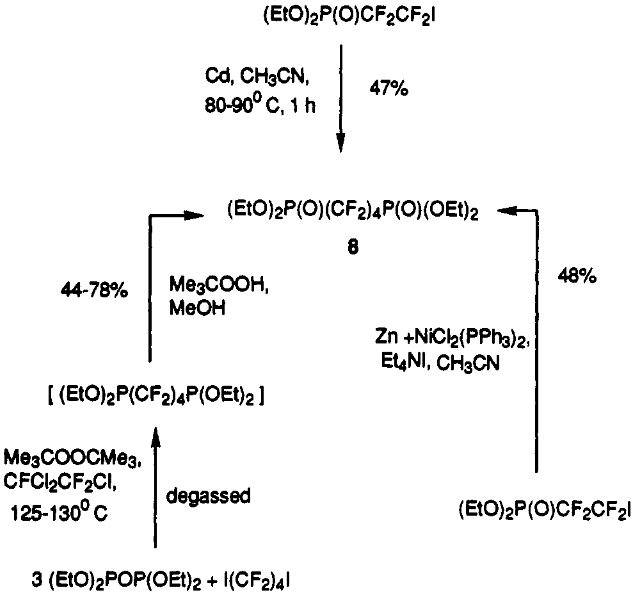
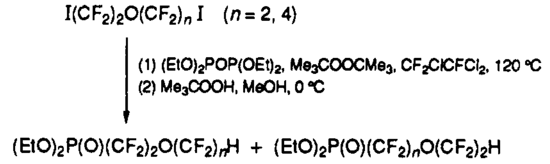
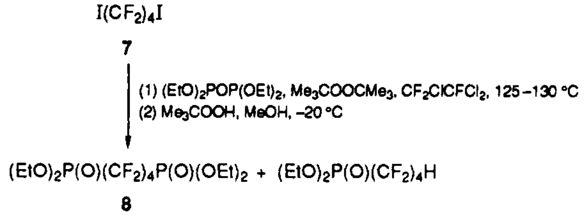
Scheme 1



have reported that reaction of tetraethyl pyrophosphite with the α,ω-diiodides $I(CF_2)_2O(CF_2)_nI$ ($n = 2, 4$)[21] resulted in only mixtures of compounds reduced at one end of the molecule.



When 7 was subjected to these conditions, a mixture of the desired bisphosphonate 8 and the reduced product $(EtO)_2P(O)(CF_2)_4H$ was obtained in variable ratios. If any 1,4-dihydroperfluorobutane was formed, it was lost in the workup and not detected.

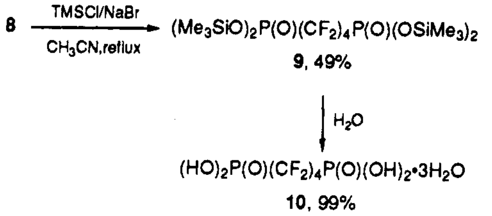


8

By careful temperature control, degassing of the initial mixture, and use of fresh reagents, $I(CF_2)_4I$:$(EtO)_2POP(OEt)_2$:$Me_3COOCMe_3$ in the ratio 1:3:1.5, the formation of $(EtO)_2P(O)(CF_2)_4H$ could be minimized and 8 consistently obtained as the major product (yield ranged from 44 to 78%) (8:$(EtO)_2P(O)(CF_2)_4H$ = 3–4:1) (Scheme 1); the best isolated yield of 8 was 78%.

Cadmium-mediated reductive dimerization of $(EtO)_2P(O)CF_2CF_2I$[23] in CH_3CN at 80–90 °C afforded 8 (47%). Alternatively, coupling of the iodo phosphonate with *in situ* generated Ni(0) from $NiCl_2(PPh_3)_2$ and Zn in the presence of Et_4NI in CH_3CN, at room temperature, also resulted in 8 (48%) (Scheme 1). The corresponding bromophosphonate also undergoes the Ni(0)-assisted coupling at slightly elevated (~45–50 °C) temperature. Also identified by ^{19}F NMR analysis of the reaction mixture was the reduced product, $(EtO)_2P(O)CF_2CF_2H$ (10–20%). Among the solvents (THF, DMSO, Me_2CO, and CH_3CN) used for the Ni(0) coupling, acetonitrile gave the best yield of the desired bisphosphonate.

Purification of 8 proved to be a problem, since it tended to partially decompose on attempted vacuum distillation. 8 was partially purified by removal of most of the byproducts *via* distillation; for multigram preparation, a conventional short-path distillation apparatus was used, but for smaller amounts (<1 g), bulb-to-bulb distillation (via Büchi Kügelrohr apparatus) was convenient. The bisphosphonate 8 was then silylated with TMSCl/NaBr to the corresponding trimethylsilyl ester 9 which could be distilled without significant decomposition. The isolated yield of 9 was 49% based on 8. Hydrolysis of 9 with deionized water gave, as before, the desired bisphosphonic acid 10.



Unlike 6, 10 is not soluble in water in all proportions, as might have been expected from its relatively long hydrophobic chain. It is also surface-active, and its dilute solution readily forms a stable foam, which caused some problems in drying and purifying this compound, since attempts to remove water by heating, or to concentrate under vacuum, resulted in losses due to severe foaming. To concentrate aqueous solutions of 10, we resorted to freeze–drying, to avoid these losses. This technique was successful, although slow, and we were able to take the product through four cycles of the purification procedure described earlier. Final freeze–drying gave the compound as a waxy solid which is a trihydrate, as determined by titration with NaOH.

(Hexafluoropropane-1,3-diyl)bisphosphonic Acid. The Kato–Yamabe procedure was also used in the synthesis of this compound. The starting material, 1,3-diiodoperfluoropropane 11, was prepared by the literature method.[22]

$$ClCO(CF_2)_3COCl \xrightarrow[200\ °C]{KI} I(CF_2)_3I$$

The bisphosphonate 12 could be prepared by the modified Kato–Yamabe procedure with tetraethyl pyrophosphite and 11. The ratio of the reactants and reaction conditions were the same as that used for the preparation of 8. The procedure used to convert 12 to the corresponding bisphosphonic acid 14 (Scheme 2) was identical to that used to convert 8 to 10. The overall yield was a modest 20%. The physical properties of the final product were similar to those of 10. 14 is not soluble in water in all proportions, but its aqueous solution had less tendency to foam; 14 was subjected to the same purification procedure described for the other bisphosphonic acids. Final drying in a vacuum dessiccator gave a white, waxy

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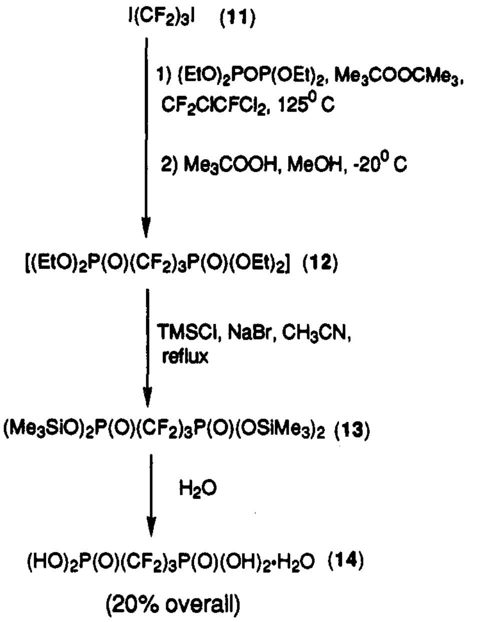
Scheme 2



solid. Molecular weight determination of **14** by titration indicated that the compound is a monohydrate.

Tetraethyl (Decafluorohexane-1,6-diyl)bisphosphonate. Tetraethyl (decafluorohexane-1,6-diyl)phosphonate (**15**) was obtained *via* cadmium-mediated reductive coupling of $(EtO)_2P(O)(CF_2)_3I$[23] in 59% yield.

In summary, we have developed synthetic routes to new fluorinated bisphosphonates from commercially available precursors in good yields. The facile conversion of the prepared bisphosphonates to the corresponding bisphosphonic acids is also demonstrated.

Experimental Section

General. All boiling points are uncorrected. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^{1}H and ^{13}C{^{1}H} against internal TMS, and ^{31}P{^{1}H} against external 85% H_3PO_4, respectively. FT-IR spectra were recorded as CCl_4 solutions. Mass spectra were acquired at 70 eV. Low-resolution (LRMS) and high-resolution mass spectra (HRMS) were obtained in the FAB mode with 3-nitrobenzyl alcohol (3-NBA) as the matrix. Elemental analyses were performed by Schwarzkopf Laboratories, Woodside, NY, or Galbraith Laboratories, Knoxville, TN. All reactions were conducted in oven-dried glassware.

Materials. CH_3CN, $CFCl_2CF_2Cl$, and CH_2Cl_2 were distilled from P_2O_5. Monoglyme was distilled from potassium benzophenone–ketyl. Zn and Cd powder were purchased from Aldrich and purified by stirring with dilute HCl (0.4% in water and 3% in acetone, respectively), washing thoroughly with water and acetone, and drying under vacuum overnight. $(EtO)_2POP(OEt)_2$, $Me_3COOCMe_3$, Me_3COOH, $I(CF_2)_4I$, $I(CF_2)_6I$, and $ClCO(CF_2)_3COCl$ were obtained commercially. $I(CF_2)_3I$ was prepared by the reported procedure;[22] $BrCF_2P(O)(OR)_2$ (R= Et or i-Pr) was obtained *via* the method of Flynn and Burton.[16]

Representaive Procedure for the Preparation of Dialkyl (Iododifluoromethyl)phosphonates. Preparation of Diethyl (Iododifluoromethyl)phosphonate (3a). To a stirred suspension of acid-washed Zn powder (34.3 g, 0.52 mol) in monoglyme (300 mL) under N_2 was added $(EtO)_2P(O)CF_2Br$ (133.5 g, 0.5 mol) *via* syringe. (After the addition of ~30 mL $(EtO)_2P(O)CF_2Br$, a few crystals of I_2 were added to the stirred reaction mixture to initiate the reaction; the reaction mixture became warm, and the remaining $(EtO)_2P(O)CF_2Br$ was added over a period of 25 min). The reaction mixture was stirred for 2 h and filtered through a medium-frit Schlenk funnel, under N_2. To the clear filtrate was added I_2 (140 g, 0.55 mol) and the mixture stirred for 24 h under N_2. The resultant reaction mixture was concentrated to about half its volume on a rotary evaporator and poured into a mixture of water (400 mL) and $CHCl_3$ (400 mL). Saturated $NaHSO_3$ was carefully added with swirling until the iodine color disappeared. The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (4 × 150 mL). The combined organic layers were washed with saturated $NaHSO_3$ (100 mL), 2% HCl (100 mL), and brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was distilled at reduced pressure through a 10-cm Vigreux column to give 111.0 g of $(EtO)_2P(O)CF_2I$ (70%): bp 84–86 °C (2 mmHg); ^{19}F NMR ($CDCl_3$) −59.5 (d, $^2J_{P,F}$ = 86 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$) −1.6 (t); ^{1}H NMR ($CDCl_3$) 1.41 (6H, t, $^3J_{H,H}$ = 7 Hz), 4.37 (4H, quint, $^3J_{H,H}$ = $^3J_{P,H}$ = 7 Hz); ^{13}C{^{1}H}NMR ($CDCl_3$) 97.4 (td, $^1J_{P,C}$ = 219 Hz, $^1J_{F,C}$ = 332 Hz), 66.3 (d, $^2J_{POC}$ = 7 Hz), 16.4 (d, $^3J_{POCC}$ = 5 Hz); GC/MS *m/e* (relative intensity) 315 ((M + H)$^+$, 0.1), 314 (M$^+$, 0.1), 299 (0.2), 285 (2), 207 (3), 191 (7), 187 (54), 177 (10), 159 (7), 137 (9), 127 (16), 121 (50), 109 (94), 81 (92), 65 (100).

Diisopropyl (Iododifluoromethyl)phosphonate (3b). Similarly, **3b** was prepared from $(i\text{-}C_3H_7O)_2P(O)CF_2Br$ (69.10 g, 234 mmol), activated Zn (17.63 g, 270 mmol), monoglyme (150 mL), and I_2 (70.0 g, 275 mmol). Fractional distillation at reduced pressure afforded $(i\text{-}C_3H_7O)_2P(O)CF_2I$ (53.10 g, 66% yield): bp 63–65 °C (0.4 mmHg); ^{19}F NMR ($CDCl_3$) −59.9 (d, $^2J_{P,F}$ = 85 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$) −3.41 (t); ^{1}H NMR ($CDCl_3$) 1.37 (d, 6H, $^2J_{H,H}$ = 6 Hz), 1.38 (d, 6H, $^2J_{H,H}$ = 6 Hz), 4.90 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$) 23.5 (d, $^3J_{POC,C}$ = 5 Hz), 24.1 (d, $^3J_{POC,C}$ = 3 Hz), 75.7 (d, $^2J_{POC}$ = 7 Hz), 98.2 (td, $^1J_{C,F}$ = 332 Hz, $^1J_{P,C}$ = 220 Hz); GC/MS *m/e* (relative intensity) 342 (M$^+$, 0.1), 327 (0.5), 285 (56), 259 (17), 215 (24), 191 (3), 177 (9), 175 (5), 173 (100), 153 (8), 133 (33), 131 (43), 123 (21), 107 (26), 101 (7), 91 (43), 89 (33), 81 (11), 69 (25), 65 (64); FT-IR (CCl_4) 2984 (w), 1279 (m), 1127 (m), 1075 (s), 1004 (vs) cm^{-1}.

General Procedure for Reductive Coupling with Cd Powder (Method A): Preparation of 1b. A mixture of acid-washed Cd powder (2.80 g, 25 mmol), $(i\text{-}C_3H_7O)_2P(O)CF_2I$ (13.68 g, 40.0 mmol), and CH_2Cl_2 (50 mL) was refluxed under N_2 for 45 min; a pale yellow supernatant and a gray residue resulted. The reaction mixture was cooled to room temperature and filtered through a medium fritted funnel and the filtrate concentrated on a rotary evaporator. The residue was extracted with 100 mL of Et_2O, washed with 25 mL of H_2O, 2% HCl (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Removal of all volatile materials from the residue at 100 °C (0.005 mmHg) (standard vacuum line or Kugelrohr apparatus) afforded 5.34 g (62%) of the title compound, which crystallized on cooling (mp = 42 °C): ^{19}F NMR ($CDCl_3$) −120.1 (d, $^2J_{P,F}$ = 93 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$) −0.48 (brt, second order splitting); ^{1}H NMR ($CDCl_3$) 1.38 (d, 12H, $^3J_{H,H}$ = 5 Hz), 1.39 (d, 12H, $^3J_{H,H}$ = 5 Hz), 4.93 (m, 4H); FT-IR (CCl_4) 2985 (w), 1388 (w), 1284 (m), 1112 (s), 1102 (s), 1017 (vs), 1000 (vs) cm^{-1}; LRMS *m/e* (relative intensity) 431 ((M + H)$^+$, 33), 389 (11), 347 (16), 305 (25), 263 (100), 245 (15), 163 (5). Anal. Calcd for $C_{14}H_{28}P_2F_4O_6$: C, 39.05; H, 6.56; F, 17.66; P, 14.40. Found: C, 39.16; H, 6.63; F, 17.71; P, 14.62.

Tetraethyl (Tetrafluoroethane-1,2-diyl)bisphosphonate (1a). Similarly, **1a** was prepared from Cd powder (13.5 g, 0.12 mol), CH_2Cl_2 (150 mL), and $(EtO)_2P(O)CF_2I$ (62.8 g, 0.2 mol): yield 26.0 g (69%); bp 133–147 °C (0.3 mmHg); ^{19}FNMR ($CDCl_3$) −119.7 (d, $^2J_{P,F}$ = 88 Hz); ^{31}P{H} NMR ($CDCl_3$) 1.30 (brt, second order splitting); ^{1}H NMR ($CDCl_3$) 1.40 (12H, t, $^3J_{H,H}$ = 7 Hz), 4.35 (8H, quint, $^3J_{H,H}$ = $^3J_{P,H}$ = 7 Hz); LRMS *m/e* (relative intensity) 375 ((M + H)$^+$, 22), 347 (48), 319 (13), 263 (28), 245 (12), 186 (6).

General Procedure for Coupling *via in Situ* Generated Ni(0). (Method B): Preparation of 1b. A mixture of $NiCl_2(PPh_3)_2$ (2.94g, 4.5 mmol), activated Zn powder (1.95g, 30 mmol), Et_4NI (2.29g, 30 mmol), and CH_3CN (50 mL) was stirred under N_2 for 30 min; the initial green reaction mixture became dark brown. To the solution was added $(i\text{-}C_3H_7O)_2P(O)CF_2Br$ (8.85g, 30 mmol) dropwise and the resulting mixture heated in an oil bath at 45–50 °C with stirring for 1.5 h. The resultant reaction mixture was filtered through a medium fritted funnel, and the filtrate was concentrated on a rotary evaporator. The residue was extracted with CH_2Cl_2 (200 mL) and washed with water (3 × 50 mL) and saturated $NaHSO_3$ solution (~2 mL). The CH_2Cl_2 layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude bisphosphonate as a brown viscous liquid which was chromatographed (silica gel, ethyl acetate/hexane (10/90–50/50)). Removal of all volatiles from the eluant at 100 °C/0.05–0.01 mmHg gave 3.0 g (47%) of the title compound.

Similarly, **1a** was prepared from 30 mmol of $(EtO)_2P(O)CF_2Br$, yield 2.92 g (52%).

General Procedure for the Preparation of Silyl Esters. Preparation of Tetrakis(trimethylsilyl) (Tetrafluoroethane-1,2-diyl)bisphosphonate (5). A mixture of $(EtO)_2P(O)CF_2CF_2P(O)(OEt)_2$ (37.4 g, 0.1 mol), TMSCl (100 mL), NaBr (43 g), and dry acetonitrile (70 mL) was refluxed under N_2 for 6 days. The reaction mixture was then filtered into a 250-mL flask through a Schlenk filter funnel, the residue being washed with a little dry ether. The flask was fitted with a short-path distilling apparatus, and the solvents and the volatile products were removed first under reduced pressure. The silyl ester **5** was collected at 130–154 °C/0.5 mmHg: yield 51.9 g (94%); ^{19}F NMR ($CDCl_3$) −120.4 (d, $^2J_{P,F}$ = 95 Hz); ^{31}P{H} NMR ($CDCl_3$) −17.8(t); ^{1}H NMR ($CDCl_3$) 0.28(s).

General Procedure for Conversion of Silyl Esters to Bisphosphonic Acids. Preparation of (Tetrafluoroethane-1,2-diyl)bisphosphonic Acid (6). To **5** (51.9 g, 94 mmol) was added deionized water (105 mL), and the mixture was stirred in an ice–water bath for 1 h. The aqueous layer was separated and concentrated under vacuum. The title compound was obtained on drying in a vacuum desiccator over P_2O_5: yield 22.0 g (83%); ^{19}F NMR (D_2O) −120.1 (d, $^2J_{P,F}$ = 88 Hz); ^{31}P{H} NMR (D_2O) −0.20 (t); ^{1}H NMR (D_2O) 10.5 (brs); ^{13}C{H} NMR (D_2O) 117.5 (tdt, $^1J_{F,C}$ = 268 Hz, $^1J_{P,C}$ = 189 Hz, $^2J_{F,C}$ = 37 Hz). Titration with NaOH indicated that **6** is a monohydrate.

Preparation of Tetraethyl (Hexafluoropropane-1,3-diyl)bisphosphonate (12). (Method C). This compound was prepared *via* a slightly modified procedure of Kato and Yamabe.[20] Into a heavy-walled, ~300-mL glass tube, equipped with a Rotaflo stopcock, were introduced $CF_2ClCFCl_2$ (75 mL), $I(CF_2)_3I$ (12.1 g, 30 mmol), $(EtO)_2POP(OEt)_2$ (26 g), and $Me_3COOCMe_3$ (6.6 g). The mixture was degassed, sealed, and heated at 125 °C in an oil bath for 4 h. (**Caution!** *This reaction should be carried out in a well ventilated fume hood, behind a safety shield*). The resultant reaction mixture was allowed to cool to room temperature, transferred to a 250-mL flask, and cooled to 0 °C in an ice bath. A solution of Me_3COOH (22 g) in methanol (50 mL) was added slowly and dropwise over 1 h. The resultant reaction mixture was stirred for 1 h and concentrated on a rotary evaporator. The residue was dissolved in ether (300 mL), washed with saturated Na_2SO_3 (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

The combined products from six duplicate runs such as the above were distilled at 0.1 mmHg, using a short-path apparatus and an oil bath temperature to 120 °C, to remove volatile byproducts. The residue was used in the next step without further purification: ^{19}F NMR ($CDCl_3$) −119.6 (s, 2F), −121.9 (d, 4F, $^2J_{P,F}$ = 93 Hz); ^{31}P{H} NMR ($CDCl_3$) 1.30(t); ^{1}H NMR ($CDCl_3$) 1.40 (t, 12H), 4.35 (m, 8H), $^3J_{H,H}$ = 7 Hz ppm (s); FT-IR (CCl_4) 2986 (w), 1294 (s), 1165 (m), 1143 (s), 1025 (vs) cm^{-1}. LRMS *m/e* (relative intensity) 425 ((M + H)$^+$, 24), 397 (100), 379 (7), 369 (29), 313 (76); HRMS calcd for (M + H)$^+$ $C_{11}H_{21}O_6P_2F_6$ 425.0718, found 425.0703.

Tetrakis(trimethylsilyl) (Hexafluoropropane-1,3-diyl)bisphosphonate (13). **13** was prepared from $(EtO)_2P(O)(CF_2)_3P(O)(OEt)_2$ (26.1 g, crude), TMSCl (55 mL), NaBr (31 g), and dry acetonitrile (55 mL) in the same manner as described for **5**: yield 24.2 g (22% overall from $I(CF_2)_3I$); bp 120–155 °C/0.1 mmHg; ^{19}F NMR ($CDCl_3$) −119.2 (s, 2F), −122.9 (d, 4F, $^2J_{P,F}$ = 95 Hz); ^{31}P{H} NMR ($CDCl_3$) −18.2 (t); ^{1}H NMR ($CDCl_3$) 0.28 ppm (s).

(Hexafluoropropane-1,3-diyl)bisphosphonic Acid (14). Hydrolysis of **13** (24.0 g, 40 mmol) was performed in the same way as described for **6**: yield 90%; ^{19}F NMR (D_2O) −119.1 (s, 2F), −122.5 (4F, d, $^2J_{P,F}$ = 86 Hz); ^{31}P{H} NMR (D_2O) −1.1 ppm (t). Titration with NaOH indicated that **14** is a monohydrate.

Preparation of Tetraethyl (Octafluorobutane-1,4-diyl)bisphosphonate (8). Compound **8** was prepared from $I(CF_2)_4I$ (13.6 g, 30 mmol), $CF_2ClCFCl_2$ (75 mL), $(EtO)_2POP(OEt)_2$ (26 g), and $Me_3COOCMe_3$ (6.6 g) as described for **12** (Method C). Volatile products from the residue were removed by heating at 120 °C/0.1 mmHg. The crude bisphosphonate was dissolved in CH_2Cl_2, treated with activated charcoal, filtered, and concentrated to give 22.3 g (78%) of the product: ^{19}F NMR ($CDCl_3$) −120.8 (s, 4F), −123.1 (d, 4F, $^2J_{P,F}$ = 90 Hz); ^{31}P{H} NMR ($CDCl_3$) 0.2 (t); ^{1}H NMR ($CDCl_3$) 1.34 (6H, t, $J_{H,H}$ = 7 Hz), 4.12 (4H, quint, $^3J_{H,H}$ = $^3J_{P,H}$ = 7 Hz); FT-IR 2986 (w), 1291 (m), 1185 (s), 1121 (s), 1048 (s), 1026 (vs) cm^{-1}; LRMS *m/e* (relative intensity) 475 ((M + H)$^+$, (6), 447 (8), 379 (7), 419 (3), 391 (2), 363 (5), 186 (6). Anal. Calcd for $C_{12}H_{20}O_6P_2F_8$: C, 30.40; H, 4.25; P, 13.06; F, 32.05. Found: C, 30.30; H, 4.04; P, 12.28; F, 32.06.

Preparation of 8 via Reductive Coupling. A mixture of $(EtO)_2P(O)CF_2CF_2I$ (1.82 g, 5 mmol) and Cd powder (0.336 g, 3 mmol) in CH_3CN (5 mL) was refluxed (80–90 °C) under nitrogen for 1 h and worked up as described for

1b (Method A). Removal of all volatiles from the residue at 85–90 °C/0.02 mmHg afforded 0.55 g (47%) of **8**.

Preparation of 8 via Ni(0) Coupling. A mixture of $NiCl_2(PPh_3)_2$ (0.480 g, 0.75 mmol), acid-washed Zn powder (0.325 g, 5 mmol), Et_4NI (5 mmol), and CH_3CN (5 mL) was stirred at room temperature for 30 min. $(EtO)_2P(O)CF_2CF_2I$[23] (1.82 g, 5 mmol) was added to the reaction mixture, stirred at room temperature for 1 h, and the product was isolated as described for **1b** (Method B). Purification by column chromatography (silica gel, ethyl acetate/hexanes 10/90–50/50) afforded 0.57 g of **8** (48%).

Tetrakis(trimethylsilyl) (Octafluorobutane-1,4-diyl)bisphosphonate (9). $(EtO)_2P(O)(CF_2)_4P(O)(OEt)_2$ (33.0 g, 70 mmol) was converted to the corresponding silyl ester in 49% (22.15 g) yield, as described for **5**: bp 125–157 °C/0.15 mmHg; ^{19}F NMR ($CDCl_3$) −120.5(s, 4F), −123.2 (4F, d, $^2J_{P,F}$ = 95 Hz); ^{31}P{H} NMR ($CDCl_3$) −18.6 (t); ^{1}H NMR ($CDCl_3$) 0.29 ppm (s).

(Octafluorobutane-1,4-diyl)bisphosphonic Acid (10). $(TMSO)_2P(O)(CF_2)_4P(O)(OTMS)_2$ (22.1 g, 34 mmol) was converted to the corresponding bisphosphonic acid as described for **5**. The residue was concentrated by freeze-drying, to prevent foaming, and dried in a vacuum desiccator to afford the title compound in 99% yield: ^{19}F-NMR (D_2O) −120.3 (s, 4F), −122.9 (d, 4F, $^2J_{P,F}$ = 85 Hz); ^{31}P{H} NMR (D_2O) −1.0 ppm (t). Titration with NaOH indicated that **10** is a trihydrate.

Preparation of Tetraethyl (Decafluorohexane-1,6-diyl)bisphophonate (15). A mixture of $(EtO)_2P(O)(CF_2)_3I$ (1.0 g, 2.4 mmol), Cd (0.224 g, 2.0 mmol), and CH_3CN (5 mL) was refluxed under N_2 for 1 h. The product was isolated from the reaction mixture, as described for **8** (Method A). Removal of all volatiles at 100–120 °C/0.05 mmHg gave 0.41 g $(EtO)_2P(O)(CF_2)_6P(O)(OEt)_2$ (**15**) (59% yield): ^{19}F NMR ($CDCl_3$) −120.9 (s, 4F), −122.1 (s, 4F), −122.3 (d, 4F, overlaps, $^2J_{P,F}$ = 90 Hz); ^{31}P{H} NMR ($CDCl_3$) 0.49 (t); ^{1}H NMR ($CDCl_3$) 1.41 (t, 12H, $^3J_{H,H}$ = 7 Hz), 4.37 (m, 8H); FT-IR 2986 (w), 1207 (vs), 1166 (m), 1148 (s), 1050 (s), 1025 (vs) cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_6P_2F_{12}$: C, 29.28; H, 3.51; F, 39.64. Found: C, 29.76; H, 3.26; F, 39.70.

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