Preparation of Methyl 2-[Bis(trimethylsiloxy)phosphoryl]-3,3,3-trifluoro-2-(trimethylsiloxy)propionate and Some Derivatives – Molecular Structure of Methyl 2-[Bis(trimethylsiloxy)phosphoryl]-3,3,3-trifluoro-2-hydroxypropionate☆

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Methyl trifluoropyruvate (**1**) and tris(trimethylsilyl) phosphite (**3**) reacted to give methyl 2-[bis(trimethylsiloxy)phosphoryl]-3,3,3-trifluoro-2-(trimethylsiloxy)propionate (**4**). Partial hydrolysis furnished propionate **6**, the molecular structure of which was obtained in the solid state. Attempted trimethylsilylation of the methylcarboxylato group in **4** using iodotrimethylsilane caused the formation of bis(trimethylsilyl) [(2,2-difluoro-1-trimethylsiloxy)ethenyl]phosphonate (**8**). For comparison, methyl pyruvate (**2**) and **3** gave methyl 2-[bis(trimethylsiloxy)phosphoryl]-2-(trimethylsiloxy)propionate (**5**).

Methyl trifluoropyruvate[1] (methyl trifluoro-2-oxopropionate) is a versatile building block in fluoroorganic chemistry for synthesizing compounds with potential bioactivity[2,3]. From ethyl trifluoropyruvate the two possible enantiomers of 3,3,3-trifluoro-2-hydroxypropionic acid (3,3,3-trifluorolactic acid) can be obtained[4]. The reactivity towards phosphorus-centered nucleophiles has been investigated to a certain extent[5,6], e.g. with tris(trimethylsilyl) iminoaminophosphine a $\lambda^5\sigma^4$-oxaphosphirane and 1,3,2$\lambda^5\sigma^4$-dioxaphospholene were formed. Since we succeeded in obtaining derivatives of the fluoro analogue of a clinically used antiresorption and anticalcification substance, namely trifluoroetidronic acid [(2,2,2-trifluoro-1-hydroxyethylidene)bisphosphonic acid] from bis(trimethylsilyl) trifluoroacetylphosphonate, and had studied its in vitro activity[6] we became interested in a compound in which *one* phosphoryl moiety was exchanged for a carboxyl or alkoxycarbonyl group to yield 2-phosphoryl-3,3,3-trifluorolactates. Here we describe the reaction of methyl trifluoropyruvate and methyl pyruvate with tris(trimethylsilyl) phosphite[7].

Results and Discussion

Methyl trifluoropyruvate (**1**) and methyl pyruvate (**2**) reacted with tris(trimethylsilyl)phosphite (**3**) to give the respective methyl 2-[bis(trimethylsiloxy)phosphoryl]lactates **4** and **5**, which are moisture-sensitive liquids (see Scheme 1). The phosphorus atom probably attacked the keto carbon C2 and, after a 1,4 trimethylsilyl shift and O=P bond formation, the products were obtained according to a previously proposed mechanism[6,8]. Under the conditions applied there was no obvious difference in reactivity between pyruvate **1** and **2** towards phosphite **3**. Stepwise hydrolysis of compound **4** afforded methyl 2-[bis(trimethylsiloxy)phosphoryl-3,3,3-trifluoro]lactate (**6**), a colorless solid (m.p. 57°C) and finally the viscous methyl (3,3,3-trifluoro-2-phosphoryl)lactate (**7**). An attempt to convert the C(O)-OMe group in compound **4** into a $C(O)OSiMe_3$ moiety using iodotrimethylsilane resulted in the formation of methyl iodide, fluoro trimethylsilane and the unexpected bis(trimethylsilyl) [(2,2-difluoro-1-trimethylsiloxy)ethenyl]-phosphonate (**8**) (Scheme 1); no reaction was observed when the same reaction was tried with bromotrimethylsilane. The expected trimethylsilyloxycarbonyl derivative was probably formed and decarboxylated accompanied by the loss of fluorotrimethylsilane.

Because we had no success growing appropriate single crystals of the phosphoryl lactate **7** for X-ray diffraction measurements, we carried out a solid-state structure determination of compound **6**. Its molecules were found to be arranged pairwise in the unit cell, connected through *one* P=O···HOC hydrogen-bonded bridge [O(4)···O(1a) 262.3 pm[9]]. There is no comparable interaction of the MeO(O)C group. The molecular structure of **6** (see Table 1 and Figure

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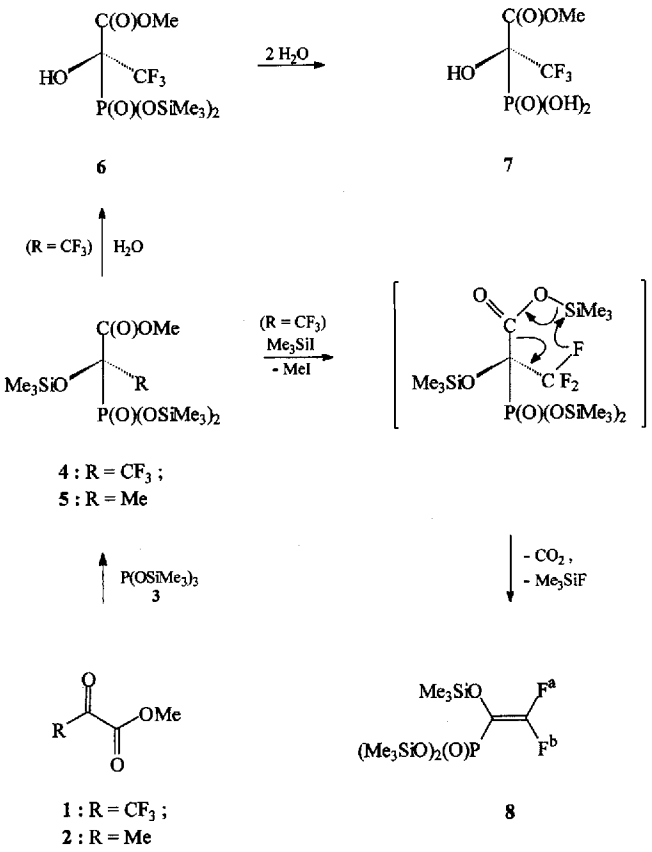
Scheme 1



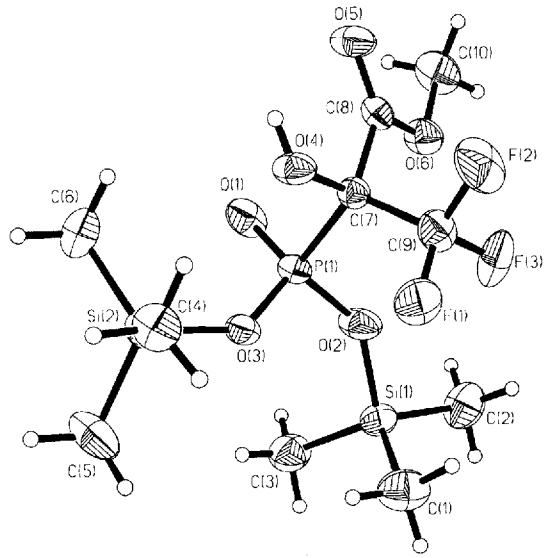
1) showed a not unexpected slightly distorted geometry at P(1). The P(1)–C(7)–C(8) angle was observed to be 108.02°, correlating to the relatively long P(1)–C(7) (185.1 pm) and C(7)–C(8) (154.5 pm) bonds. Similar P–C, P–O [P=O and P–O(H, $SiMe_3$)] bond lengths were found in $CF_3C(OH)[P(O)(OSiMe_3)_2][P(O)(OSiMe_3)OH]$[6].

Table 1. Selected bond distances (pm) and bond angles (°) of compound **6**

P(1)–O(1)	145.8(2)	P(1)–O(2)	153.5(2)
P(1)–O(3)	154.9(2)	P(1)–C(7)	185.1(2)
C(7)–O(4)	139.4(3)	C(7)–C(9)	152.5(3)
C(7)–C(8)	154.5(3)	C(8)–O(5)	118.8(3)
O(1)–P(1)–O(2)	115.3(1)		
O(1)–P(1)–O(3)	115.96(9)		
O(2)–P(1)–O(3)	106.09(9)		
O(1)–P(1)–C(7)	107.3(1)		
O(2)–P(1)–C(7)	106.8(1)		
P(1)–O(2)–Si(1)	143.2(1)		
P(1)–O(3)–Si(2)	137.5(1)		
P(1)–C(7)–C(8)	108.0(1)		
P(1)–C(7)–C(9)	115.9(2)		

The ^{1}H-, ^{19}F-, ^{31}P- and (for **8** only) ^{13}C-NMR data of the new compounds are consistent with the proposed constitutions. The chiral center at C2 in the pyruvate derivatives did not cause a measurable magnetic nonequivalence of the Me_3SiO groups at phosphorus. The ^{19}F spectrum for **8** clearly showed resonances due to fluorine nuclei *trans* (F^a, $\delta = -91.8$, $^3J_{PF} = 27.8$ Hz) and *cis* (F^b, $\delta = -105.3$, $^3J_{PF} = 19.4$ Hz) to phosphorus with $|^3J_{PF(trans)}| > |^3J_{PF(cis)}|$[10]. The ^{13}C-NMR shift values $\delta = 158.4$ and 109.1 were assigned to sp^2 carbon atoms $F_2C=$ and $=CP$; the direct coupling constants $^1J_{F^aC} = 292.0$, $^1J_{F^bC} = 296.0$ (the assignment for F^a and F^b is tentative) and $^1J_{PC} = 250.0$ Hz are typical for this class of compounds[11].

Figure 1. Molecular structure of compound **6**



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Experimental Section

The appropriate precautions for handling moisture- and oxygen-sensitive compounds were observed throughout this work. – Analyses: Mikroanalytisches Laboratorium Beller Göttingen. – MS: Varian-MAT CH 7A spectrometer at 70 eV (EI). – NMR: Bruker AC 80 instrument at 80.13 MHz (^{1}H, standard TMS), 75.39 MHz (^{19}F, standard CCl_3F) and 32.44 MHz (^{31}P, standard 85% H_3PO_4). Highfield shifts from TMS, CCl_3F and 85% H_3PO_4 were given negative signs. – Compound **1** and **3** were prepared according to literature procedures[1,7].

Methyl 2-[Bis(trimethylsiloxy)phosphoryl]-3,3,3-trifluoro-2-(trimethylsiloxy)propionate (**4**): Compound **1** (3.62 g, 20 mmol) and 5.96 g (20 mmol) of phosphite **3** in 5 ml of diethyl ether were warmed up from 0°C to ambient temperature and stirred for 30 min. Distillation at 95°C/0.01 torr gave 6.80 g (75%) of **4**. – MS (50°C); *m/z* (%): 439 (3) $[M - Me]^+$, 382 (32) $[M - Me_2SiCH_2]^+$, 367 (97) $[M - Me - Me_2SiCH_2]^+$, 347 (24) $[M - MeF - Me_3Si]^+$, 323 (33) $[M - Me_2SiCH_2 - C(O)OMe]^+$, 307 (43) $[M - Me_3SiO-SiMe_2]^+$, 229 (74) $[M - (Me_3SiO)_2P(O)]^+$, 225 (95) $[(Me_3SiO)_2P(O)]^+$, 147 (100) $[Me_3SiOSiMe_2^+]$, 73 (98) $[Me_3Si^+]$, 59 (12) $[C(O)OMe^+]$ and other fragments. – ^{1}H NMR ($CDCl_3$): $\delta = 0.10$ (s, 9H, $SiMe_3$), 0.21 (s, 18H, $SiMe_3$), 3.72 [s, 3H, C(O)OMe]. – ^{19}F NMR ($CDCl_3$): $\delta = -75.5$ (d, 3 F, CF_3, $^3J_{PF} = 6.2$ Hz). – ^{31}P NMR ($CDCl_3$): $\delta = -10.8$. – $C_{13}H_{30}F_3O_6PSi_3$ (454.59): calcd. C 34.35, H 6.65, F 12.50, P 6.80; found C 34.84, H 6.47, F 12.50, P 6.80.

Methyl 2-[Bis(trimethylsiloxy)phosphoryl]-2-trimethylsiloxy propionate (**5**): Compound **2** (2.04 g, 20 mmol) and 5.96 g (20 mmol)

of phosphite **3** in 5 ml of diethyl ether were warmed up from 0 °C to ambient temperature and stirred for 30 min. Distillation at 110 °C/0.01 torr gave 6.50 g (81%) of **5**. – MS (58 °C); *m/z* (%): 400 (12) [M^+], 385 (100) [M^+ – Me], 211 (74) [$Me_3SiO(Me_2SiO)P(O)H^+$], 147 (16) [$Me_3SiOSiMe_2^+$], 73 (34) [Me_3Si^+] and other fragments. – ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 9H, $SiMe_3$), 0.21 (s, 18H, $SiMe_3$), 1.59 (d, 3H, $^3J_{PH}$ = 16.8 Hz), 3.72 [s, 3H, C(O)OMe]. – ^{31}P NMR ($CDCl_3$): δ = 0.2. $C_{13}H_{33}O_6PSi_3$ (400.63): calcd. C 38.97, H 8.30, P 7.73; found C 38.87, H 8.30, P 7.72.

Methyl 2-[Bis(trimethylsiloxy)phosphoryl]-3,3,3-trifluoro-2-hydroxypropionate (**6**): A solution of 2.30 g (9 mmol) of **4** in 5 ml of diethyl ether was exposed to moist air. After 6 d crystals of **6** were formed (m.p. 57 °C). – MS (87 °C); *m/z* (%): 382 (24) [M^+], 367 (100) [M^+ – Me], 347 (28) [M^+ – Me – HF], 225 (74) [$(Me_3SiO)_2P(O)^+$], 147 (12) [$Me_3SiOSiMe_2^+$], 73 (34) [Me_3Si^+] and other fragments. – ^{1}H NMR ($CDCl_3$): δ = 0.18 (s, 18H, $SiMe_3$), 3.60 [s, 3H, C(O)COMe], 5.80 (s, 1H, OH). – ^{19}F NMR ($CDCl_3$): δ = −72.8 (s, CF_3). – ^{31}P NMR ($CDCl_3$): δ = −9.6. – $C_{10}H_{22}F_3O_6PSi_2$: calcd. 382.06448; found 382.06376 (MS).

The X-ray structural study[12] of compound **6** (single crystal 0.85 × 0.4 × 0.2 mm, monoclinic $P2_1/n$ with a = 1222.70(10), b = 948.70(10), c = 1600.6(2) pm, α = 90°, β = 95.490(10)°, γ = 90°, Z = 4, D = 1.374 Mg/m^3, absorption coefficient 0.326 mm^{-1}, difference electron density 381 and −473 e · nm^{-3}) was performed at 173(2) K on a Siemens P4 diffractometer using graphite-monochromated Mo-K_α radiation (λ = 71.073 pm), Θ-range 2.56–27.50°, reflections measured 5485, unique reflections 4236 (R_{int} = 0.1024). The structure was solved by direct methods and refined by full-matrix least squares at F^2 using SHELXTL PLUS (VMS); goodness of fit at F^2 0.892; final R values [$I > 2\sigma(I)$], $R1$ = 0.0441, $wR2$ = 0.0984; R value (all reflections) $R1$ = 0.0693, $wR2$ = 0.1047.

Methyl 3,3,3-Trifluoro-2-hydroxy-2-phosphorylpropionate (**7**): Compound **4** (2.30 g, 5 mmol) and 5 ml MeOH/H_2O (1:1) were heated to 60 °C for 1 h. After pumping off all volatiles in vacuo, 1.68 g (100%) of **7** remained as a colorless viscous liquid. MS; *m/z* (%): FAB positive (NBA) 239 (54) [M^+ + H]; FAB negative (NBA) 237 (100) [M^+ – H]. – ^{1}H NMR (CD_3CN): δ = 4.10 [s, 3H, C(O)COMe], 5.80 (s, 1H, COH), 11.8 (s, 2H, POH). – ^{19}F NMR (CD_3CN): δ = −71.6 (s, CF_3). – ^{31}P NMR: δ = −13.0. $C_4H_6F_3O_6P$ (238.06).

Bis(trimethylsilyl)[(2,2-Difluoro-1-trimethylsiloxy)ethenyl]-phosphonate (**8**). Compound **4** (3.00 g, 7.5 mmol) and 5.00 g (25 mmol) of iodotrimethylsilane were reacted at 60 °C for 2 d. After pumping off all volatiles in vacuo, 1.00 g of freshly activated copper powder was added and the mixture held for 1 h at 60 °C. Distillation at 80 °C/0.01 torr gave 2.00 g (73%) of **7**. – MS; *m/z* (%): 360 (6) [M^+], 287 (8) [M^+ – $SiMe_3$], 271 (68) [M^+ – $OSiMe_3$], 211 (100) [$Me_3SiO(Me_2SiO)P(O)H^+$], 147 (32) [$Me_3SiOSiMe_2^+$], 73 (88) [Me_3Si^+] and other fragments. – ^{1}H NMR ($CDCl_3$): δ = 0.21 [s, 18H, $POSiMe_3$], 0.28 [s, 9H, $COSiMe_3$]. – ^{19}F NMR ($CDCl_3$): δ = −91.8 (dd, 1 F, F^a, $^2J_{FF}$ = 46.5, $^3J_{PF}$ = 27.8 Hz), −105.3 (dd, 1 F, F^b, $^2J_{FF}$ = 46.5, $^3J_{PF}$ = 19.4 Hz). – ^{31}P NMR ($CDCl_3$): δ = −11.3. ^{13}C NMR: δ = 158.4 (ddd, F_2C=, $^1J_{F^aC}$ = 292.0, $^1J_{F^bC}$ = 298.0, $^2J_{PC}$ = 48.6 Hz), 109.1 (ddd,P, $^1J_{PC}$ = 250.0, $^2J_{FC}$ = 38.0, $^2J_{FC}$ = 11.0 Hz), 2.0 (s, $COSiMe_3$), 0.5 (s, $POSiMe_3$). – $C_{11}H_{27}F_2O_3PSi_3$ (360.56): calcd. C 35.64, H 7.55, F 10.54, P 8.59; found C 35.84, H 7.47, F 11.00, P 8.80.

☆ Dedicated to Prof. Dr. mult. Dr. h. c. *Alois Haas* on the occasion of his 65th birthday.

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