Facile Two-step Synthesis of Methyl Bis(2,2,2-trifluoroethyl)phosphonoacetate by Exploiting Garegg–Samuelsson Reaction Conditions

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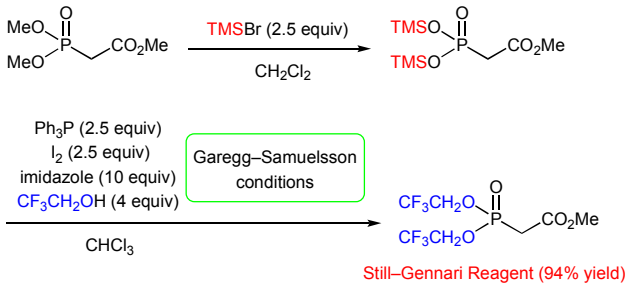

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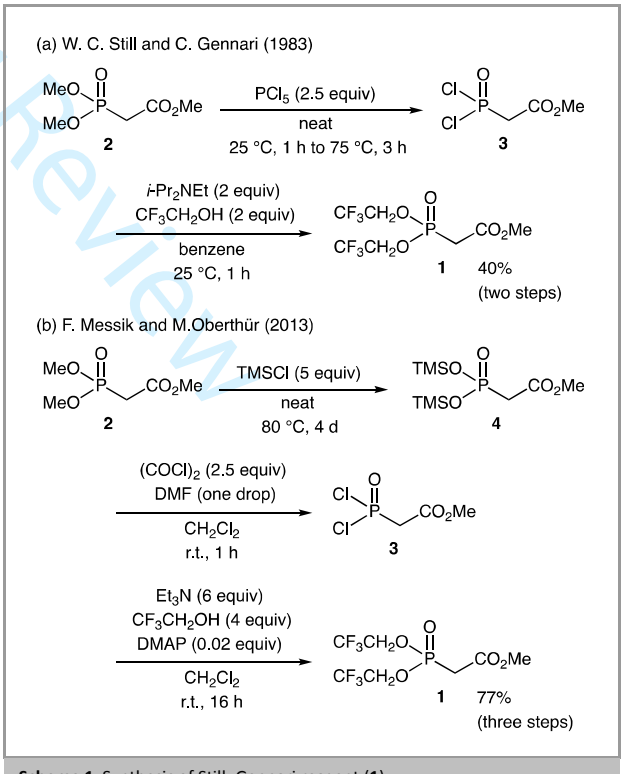
Abstract A facile two-step synthesis of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent) has been developed by exploiting Garegg–Samuelsson reaction conditions. Starting from trimethyl phosphonoacetate, Still–Gennari reagent was prepared in 94% yield via methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate intermediate. This synthetic procedure was also used to prepare some kinds of Horner–Wadsworth–Emmons reagents and related compounds.

Key words Horner–Wadsworth–Emmons reagents, Still–Gennari reagent, phosphorus, Garegg–Samuelsson reaction conditions, 2,2,2-trifluoroethanol

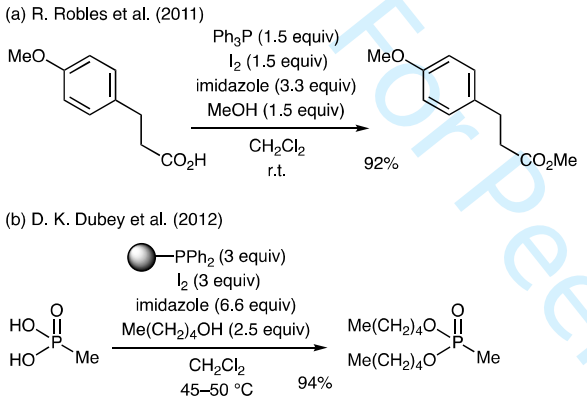
The Horner–Wadsworth–Emmons (HWE) reaction is one of the most useful carbon–carbon double bond forming reactions for the stereoselective synthesis of α,β-unsaturated esters from aldehydes or ketones.[1,2] The stereoselectivity of the HWE reaction depends cardinally on the characteristics of the HWE reagent. In the *Z*-selective synthesis of α,β-unsaturated esters, a well-known HWE reagent is methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent, **1**), which was developed by W. C. Still and C. Gennari in 1983.[3,4] They prepared Still–Gennari reagent (**1**) from trimethyl phosphonoacetate (**2**) and 2,2,2-tifluoroethanol via methyl 2-(dichlorophosphoryl)acetate (**3**) in 40% yield in two steps as shown in Scheme 1 (a).[5] Still–Gennari reagent (**1**) is now commercially available, but it is expensive. In 2013, F. Messik and M. Oberthür published an improved method of synthesizing **1** in 77% yield in three steps as shown in Scheme 1 (b).[6] The procedure takes more than 5 days, but it is an inexpensive and reliable route to producing Still–Gennari reagent (**1**) on even a multi-gram scale. Recently, we reported an efficient method of synthesizing glycerophospholipids and their fluorine-containing analogues starting from Still–Gennari reagent (**1**).[7]



Scheme 1 Synthesis of Still–Gennari reagent (**1**)

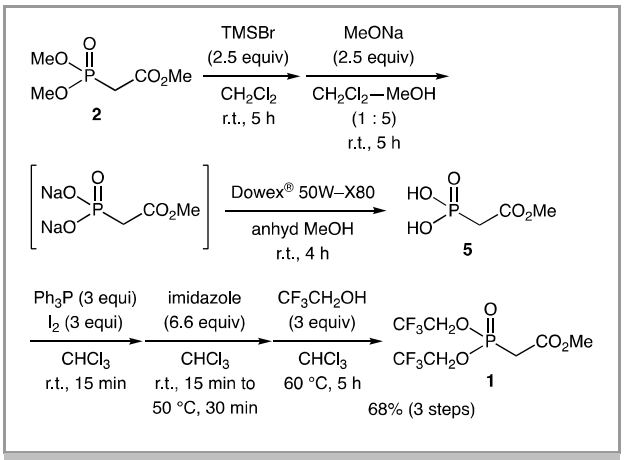
On the other hand, R. Robles and co-workers reported a mild method for the esterification of carboxylic acids with primary alcohols employing the Garegg–Samuelsson reagent system,[8,9] which was developed to convert a hydroxyl group into an iodo group, as shown in Scheme 2 (a).[10] In this reaction, an esterification of carboxylic acids with primary alcohol via a

phosphonium–carboxylate salt intermediate was achieved in the presence of Ph_3P, iodine, and imidazole (Garegg–Samuelsson reagent system). As illustrated in Scheme 2 (b), a mild and efficient esterification of alkylphosphonic acids using the Garegg–Samuelsson reagent system was also developed by D. K. Dubey and co-workers.[11] In view of the reactivity of methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**) with oxalyl chloride in Scheme 1 (b), we supposed that the bis(trimethylsilyl) derivative **4** could furnish a phosphonium–phosphonate salt intermediate under Garegg–Samuelsson reaction conditions. Herein, we describe a facile two-step procedure for the preparation of Still–Gennari reagent (**1**) from trimethyl phosphonoacetate (**2**) via methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**) as an intermediate.



Scheme 2 Esterification of carboxylic acid and phosphonic acid under Garegg–Samuelsson reaction conditions

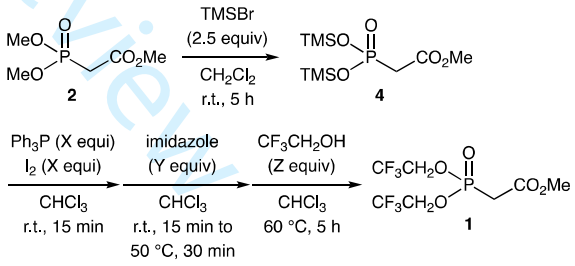
First, we investigated a synthesis of Still–Gennari reagent (**1**) via (2-methoxy-2-oxoethyl)phosphonic acid (**5**) starting from trimethyl phosphonoacetate (**2**). Trimethyl phosphonoacetate (**2**) was treated with trimethylsilyl bromide (2.5 equiv) and sodium methoxide (2.5 equiv) to afford the corresponding phosphonic acid disodium salt, which was then treated with cationic exchange resin Dowex® 50W-X80 (cationic form) in anhydrous MeOH.[12] The resulting (2-methoxy-2-oxoethyl)phosphonic acid (**5**) was transformed into Still–Gennari reagent (**1**) based on Garegg–Samuelsson reaction conditions as shown in Scheme 3.[11] However, the experimental procedure was complicated and yields of **1** were moderate (up to 68% yield) despite the intensive optimization of the reaction conditions.



Scheme 3 Synthesis of Still–Gennari reagent (**1**) via (2-methoxy-2-oxoethyl)phosphonic acid under Garegg–Samuelsson reaction conditions

In order to improve the conversion of trimethyl phosphonoacetate (**2**) to Still–Gennari reagent (**1**), we next investigated the use of methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**) instead of (2-methoxy-2-oxoethyl)phosphonic acid (**5**) as an intermediate. The results are summarized in Table 1. The best results were achieved by employing 2.5 equiv of Ph_3P, 2.5 equiv of iodine, 10 equiv of imidazole, and 4 or 5 equiv of 2,2,2-trifluoroethanol (Entries 7 and 9).[13] This reaction was carried out on a gram scale without a change in the yield of Still–Gennari reagent (**1**) (entry 9).

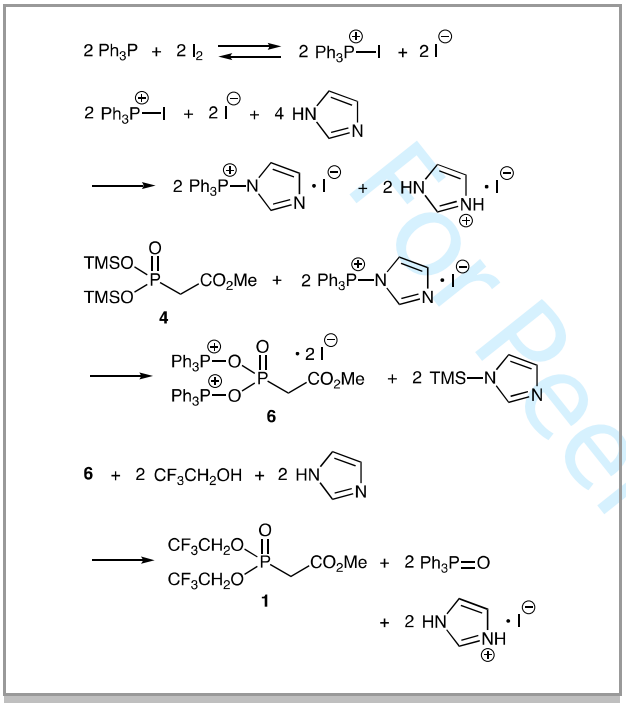
Table 1 Synthesis of Still–Gennari Reagent (**1**) via Methyl Bis(trimethylsiliy)phosphonoacetate under Garegg–Samuelsson Reaction Conditions



Entry	X (equiv)	Y (equiv)	Z (equiv)	Yield of **1** (%)[a]
1	3	6.6	3	61
2	3	6.6	4	63
3	3	6.6	5	69
4	3	8.8	5	90
5	3	10	5	91
6	2.5	8.8	5	88
7	2.5	10	5	94
8	2.2	10	5	87
9	2.5	10	4	94 (91)[b]
10	2.5	10	3	32

[a] Isolated yield.
[b] A gram scale reaction.

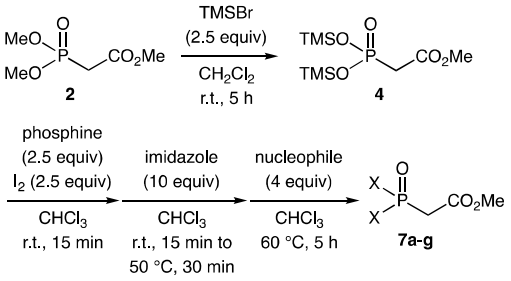
Plausible reaction mechanism for the esterification of methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**) using the Garegg–Samuelsson reagent system was considered as shown in Scheme 4. D. K. Dubey and co-workers proposed a dicationic salt as an active species, which was formed from alkylphosphonic acid and Ph_3P.[10,11] Thus, it is reasonable to assume that the similar dicationic salt **6** results from the reaction of the bis(trimethylsilyl) derivative **4** with the Ph_3P-imidazole species in our case. Finally, Still–Gennnari reagent (**1**) is obtained by the nucleophilic substitution at the phosphorous atom of **6** by 2,2,2-trifluoroethanol.



Scheme 4 Plausible reaction mechanism for the esterification of methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**) under Garegg–Samuelsson reaction conditions

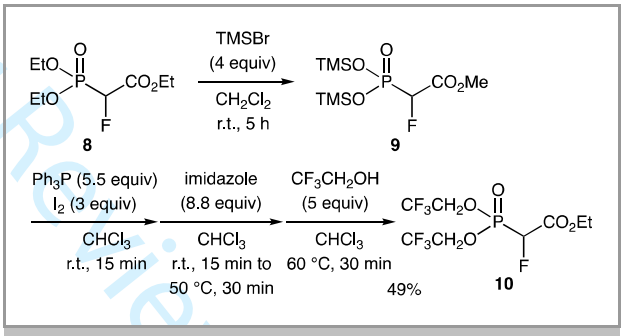
To explore the application of this procedure for the synthesis of HWE reagents and related compounds, some examples of nucleophiles were preliminarily employed in place of 2,2,2-trifluoroethanol. Our procedure worked well and afforded the corresponding derivatives **7a-g** as shown in Table 2.[14] In entries 1–3, tris(*o*-tolyl)phosphine was used instead of Ph_3P, because the resulting triphenylphosphine oxide waste was difficult to separate from the reaction products **7a-c**. Ethyl diphenylphosphonoacetate (Ando reagent)[15] is useful *Z*-selective HWE reagent similar to Still–Gennari reagent (**1**), and Ando-type reagent **7d** was obtained in 94% yield as shown in entry 4. Methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-2-bromoacetate, which is an α-brominated Still–Gennari-type reagent, is known as a useful reagent in the stereoselective synthesis of (*E*)-α-bromoacrylates.[16,17] Thus, we performed the reaction of triethyl 2-fluoro-2-phosphonoacetate (**8**)[18,19] and 2,2,2-trifluoroethanol under similar conditions (Scheme 5). As a result, ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-2-fluoroacetate (**10**), which is an α-fluorinated Still–Gennari-type reagent, was synthesized as a novel compound in 49% yield.[20]

Table 2 Synthesis of Some Kinds of HWE Reagents and Related Compounds **7a-g** via Methyl Bis(trimethylsilyl)phosphonoacetate under Garegg–Samuelsson Reaction Conditions



Entry	Phosphine	Nucleophile	Yield of **7** (%)[a]
1	(*o*-tolyl)$_3$P	EtOH	95 (**7a**: X = EtO)
2	(*o*-tolyl)$_3$P	*i*-PrOH	79 (**7b**: R[1] = *i*-PrO)
3	(*o*-tolyl)$_3$P	*sec*-BuOH	82 (**7c**: X = *sec*-BuO)[b]
4	Ph_3P	PhOH	94 (**7d**: X = PhO)
5	Ph_3P	2,4-$F_2C_6H_3OH$	82 (**7e**: X = 2,4-$F_2C_6H_3O$)
6	Ph_3P	PhSH	85 (**7f**: X = PhS)
7	Ph_3P	$PhNH_2$	86 (**7g**: X = PhNH)

[a] Isolated yield.
[b] Diastereomeric mixture.



Scheme 5 Synthesis of α-fluorinated Still–Gennari-type reagent **10** via methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}-2-fluoroacetate (**9**) under Garegg–Samuelsson reaction conditions

In conclusion, we have developed a novel and efficient two-step procedure for the synthesis of Still–Gennari reagent (**1**) and related HWE reagents based on Garegg–Samuelsson reaction conditions. The method is simple, reliable, and inexpensive. Further studies of the reaction mechanism underlying the synthetic procedure and the HWE reaction of the resultant compounds such as **7e-g** and **10** are underway in our laboratory.

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(13) **Preparation of Methyl Bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent, 1)**[5,6]
TMSBr (90 µL, 0.691 mmol) was added at r.t. to a solution of trimethyl phosphonoacetate (**2**; 50.3 mg, 0.276 mmol) in anhydrous CH_2Cl_2 (0.55 mL). After stirring at r.t. for 5 h under argon, evaporation of the reaction mixture in vacuo gave methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**), which was used without further purification. Ph_3P (181 mg, 0.691 mmol) and I_2 (175 mg, 0.691 mmol) were added to a solution of **4** in anhydrous $CHCl_3$ (1.8 mL) at r.t. under argon. After stirring at r.t. for 15 min under argon, imidazole (188 mg, 2.76 mmol) was added. The reaction mixture was stirred for 15 min at r.t. and then for 30 min at 50 °C. Afterwards, 2,2,2-trifluoroethanol (79 µL, 1.10 mmol) was added and the reaction mixture was stirred at 60 °C for 5 h. After filtration of the reaction mixture, the filtrate was evaporated in vacuo to give a crude product **1**, which was purified by silica gel [Silica Gel PSQ 60B (Fuji Silysia Chemical)] column chromatography [*n*-hexane–EtOAc (2:1)] to afford **1** (82.3 mg, 94%) as a colorless oil.
IR (neat): 1747, 1265, 1174, 1072, 963 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.51-4.42 (m, 4H), 3.78 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 21.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (d, $^2J_{C,P}$ = 4.5 Hz), 122.5 (qd, $^1J_{C,F}$ = 277.1 Hz, $^3J_{C,P}$ = 8.2 Hz), 62.7 (qd, $^2J_{C,F}$ = 38.2 Hz, $^2J_{C,P}$ = 5.5 Hz), 53.1, 33.8 (d, $^1J_{C,P}$ = 145.1 Hz). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_7H_9F_6O_5PNa$: 340.9990; found: 340.9982. Anal. Calcd for $C_7H_9F_6O_5P$: C, 26.43; H, 2.85. Found: C, 26.28; H, 2.89.

(14) **Methyl 2-[Bis(phenylthio)phosphoryl]acetate (7f)**
Colorless oil; yield: 79.5 mg (85%). IR (neat): 3059, 2952, 1737, 1473, 1439, 1268, 1220, 1107, 1023, 1002 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.63-7.59 (m, 4H), 7.45-7.36 (m, 6H), 3,77 (s, 3H), 3.30 (d, $^2J_{H,P}$ = 16.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1 (d, $^2J_{C,P}$ = 4.6 Hz), 136.0 (d, $^3J_{C,P}$ = 4.4 Hz), 129.8 (d, $^5J_{C,P}$ = 2.8 Hz), 129.5 (d, $^4J_{C,P}$ = 2.1 Hz), 125.3 (d, $^2J_{C,P}$ = 6.5 Hz), 52.8, 42.6 (d, $^1J_{C,P}$ = 61.4 Hz). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{15}O_3PS_2Na$: 361.0098; found: 361.0069. Anal. Calcd for $C_{15}H_{15}O_3PS_2$: C, 53.24; H, 4.47. Found: C, 52.96; H, 4.67.
Methyl 2-[Bis(phenylamino)phosphoryl]acetate (7g)
Pale yellow columns ($CHCl_3$/*n*-hexane); mp 115.0-116.0 °C; yield: 71.9 mg (86%). IR (KBr): 3330, 3185, 1731, 1602, 1502, 1434, 1397, 1282, 1268, 1242, 1207, 1181, 1106 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23-7.17 (m, 4H), 7.16-7.12 (m, 4H), 6.99-6.93 (m, 2H), 6.25 (br s, 2H), 3.65 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 19.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (d, $^2J_{C,P}$ = 4.5 Hz), 139.5, 129.3, 122.4, 118.9 (d, $^2J_{C,P}$ = 6.4 Hz), 52.8, 35.9 (d, $^1J_{C,P}$ = 103.8 Hz). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{17}N_2O_3PNa$: 327.0874; found: 327.0858. Anal. Calcd for $C_{15}H_{17}N_2O_3P$: C, 59.21; H, 5.63; N, 9.21. Found: C, 59.18; H, 5.66; N, 8.98.

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(20) **Ethyl 2-[Bis(2,2,2-trifluoroethoxy)phosphoryl]-2-fluoroacetate (10)**
Colorless oil; yield: 46.1 mg (49%). IR (neat): 2983, 2947, 1770, 1456, 1420, 1374, 1271, 1174, 1068, 1021, 963 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.34 (dd, $^2J_{H,F}$ = 46.4 Hz, $^2J_{H,P}$ = 12.8 Hz, 1H), 4.60-4.43 (m, 4H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4 (dd, $^2J_{C,F}$ = 21.8 Hz, $^2J_{C,P}$ = 1.9 Hz), 122.1 (qdd, $^1J_{C,F}$ = 277.8 Hz, $^3J_{C,P}$ = 8.0 Hz, $^5J_{C,F}$ = 5.6 Hz), 84.3 (dd, $^1J_{C,F}$ = 199.7 Hz, $^1J_{C,P}$ = 168.0 Hz), 63.5 (qd, $^2J_{C,F}$ = 38.8 Hz, $^2J_{C,P}$ = 5.9 Hz), 63.3, 13.9. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_8H_{10}F_7O_5PNa$: 373.0052; found: 373.0046. Anal. Calcd for $C_8H_{10}F_7O_5P$: C, 27.44; H, 2.88. Found: C, 27.49; H, 3.10.

Supporting Information

for

Facile Two-step Synthesis of Methyl Bis(2,2,2-trifluoroethyl)phosphonoacetate by Exploiting Garegg–Samuelsson Reaction Conditions

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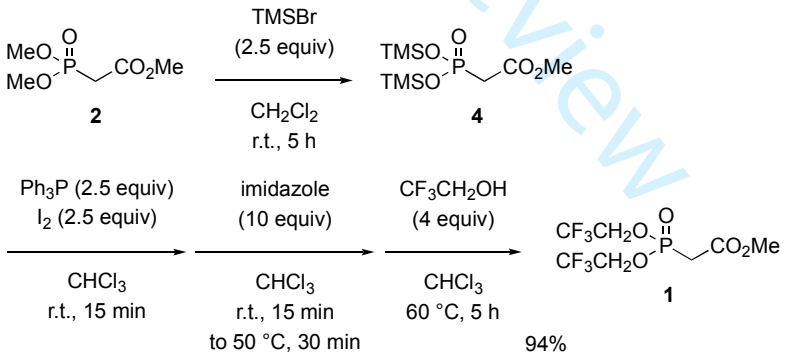
1. General Information

IR spectra were obtained with a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with a Bruker AV500 spectrometer. Chemical shifts are given in δ values (ppm) using TMS as an internal standard. HRMS (ESI) were recorded with a Waters LCT Premier spectrometer. Elemental combustion analyses were performed with a J-SCIENCE LAB JM10. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel PSQ 60B (Fuji Silysia Chemical)]. Anhydrous CH_2Cl_2, MeOH, and $CHCl_3$ were used as purchased from Kanto Chemical. All other reagents were used as purchased.

2. Experimental Procedures and Compound Characterizations

General procedure for the preparation of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent, 1) and HWE reagents 7a-g, 10

Methyl Bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent, **1**)



TMSBr (90 μL, 0.691 mmol) was added at r.t. to a solution of trimethyl phosphonoacetate (**2**; 50.3 mg, 0.276 mmol) in anhydrous CH_2Cl_2 (0.55 mL). After stirring at r.t. for 5 h under argon, evaporation of the reaction mixture in vacuo gave methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**4**), which was used without further purification. Ph_3P (181 mg, 0.691 mmol) and I_2 (175 mg, 0.691 mmol) were added to a solution of **4** in

anhydrous $CHCl_3$ (1.8 mL) at r.t. under argon. After stirring at r.t. for 15 min under argon, imidazole (188 mg, 2.76 mmol) was added. The reaction mixture was stirred for 15 min at r.t. and then for 30 min at 50 °C. Afterwards, 2,2,2-trifluoroethanol (79 µl, 1.10 mmol) was added and the reaction mixture was stirred at 60 °C for 5 h. After filtration of the reaction mixture, the filtrate was evaporated in vacuo to give a crude product **1**, which was purified by column chromatography [Silica Gel PSQ 60B: *n*-hexane–EtOAc (2:1)] to afford **1** (82.3 mg, 94%) as a colorless oil.

IR (neat) 1747, 1265, 1174, 1072, 963 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.51–4.42 (m, 4H), 3.78 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 21.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.2 (d, $^2J_{C,P}$ = 4.5 Hz), 122.5 (qd, $^1J_{C,F}$ = 277.1 Hz, $^3J_{C,P}$ = 8.2 Hz), 62.7 (qd, $^2J_{C,F}$ = 38.2 Hz, $^2J_{C,P}$ = 5.5 Hz), 53.1, 33.8 (d, $^1J_{C,P}$ = 145.1 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_7H_9F_6O_5PNa$: 340.9990; found: 340.9982. Anal. Calcd for $C_7H_9F_6O_5P$: C, 26.43; H, 2.85. Found: C, 26.28; H, 2.89.

Methyl 2-(Diethoxyphosphoryl)acetate (**7a**)

Colorless oil; yield: 55.0 mg (95%). IR (neat) 2986, 1742, 1277, 1121, 1023, 971 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.22–4.14 (m, 4H), 3.75 (s, 3H), 2.98 (d, $^2J_{H,P}$ = 21.6 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.3 (d, $^2J_{C,P}$ = 6.3 Hz), 62.7 (d, $^2J_{C,P}$ = 6.3 Hz), 52.6, 34.2 (d, $^1J_{C,P}$ = 134.5 Hz), 16.3 (d, $^3J_{C,P}$ = 6.3 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_7H_{15}O_5PNa$: 233.0555; found: 233.0539.

Methyl 2-(Diisopropoxyphosphoryl)acetate (**7b**)

Colorless oil; yield: 52.3 mg (79%). IR (neat) 3476, 2982, 1743, 1437, 1387, 1275, 1178, 1104, 989 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.81–4.71 (m, 2H), 3.74 (s, 3H), 2.94 (d, $^2J_{H,P}$ = 21.7 Hz, 2H), 1.34 (d, *J* = 6.2 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.5 (d, $^2J_{C,P}$ = 6.2 Hz), 71.5 (d, $^2J_{C,P}$ = 6.4 Hz), 52.4, 35.3 (d, $^1J_{C,P}$ = 134.8 Hz), 24.1 (d, $^3J_{C,P}$ = 3.6 Hz), 23.8 (d, $^3J_{C,P}$ = 5.4 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{19}O_5PNa$: 261.0868; found: 261.0861.

Methyl 2-(Di-*sec*-butoxyphosphoryl)acetate (**7c**) (mixture of diasereomers)

Colorless oil; yield: 60.8 mg (82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.60–4.49 (m, 2H), 3.73 (s, 3H), 2.95 (d, $^{2}J_{H,P}$ = 21.7 Hz, 2H), 1.73–1.55 (m, 4H), 1.36–1.30 (m, 6H), 0.97–0.91 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.5 (d, $^{2}J_{C,P}$ = 6.4 Hz), 76.16, 76.15, 76.11, 76.09, 76.07, 76.06, 52.3, 36.2, 35.9, 35.7, 35.1, 34.9, 34.6, 30.58, 30.54, 30.41, 30.39, 30.36, 30.34, 21.43, 21.41, 21.40, 21.38, 21.15, 21.11, 21.10, 21.07, 9.41, 9.38, 9.35. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{23}O_5PNa$: 289.1181; found: 289.1159.

Methyl 2-(Diphenoxyphosphoryl)acetate (**7d**)

Colorless oil; yield: 79.4 mg (94%). IR (neat) 2953, 1742, 1590, 1489, 1285, 1187, 1162, 1119, 940 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 4H), 7.25–7.17 (m, 6H), 3.77 (s, 3H), 3.28 (d, $^{2}J_{H,P}$ = 21.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.2 (d, $^{2}J_{C,P}$ = 6.3 Hz), 150.0 (d, $^{2}J_{C,P}$ = 8.3 Hz), 129.8, 125.6, 120.6 (d, $^{3}J_{C,P}$ = 4.5 Hz), 52.8, 33.8 (d, $^{1}J_{C,P}$ = 137.4 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{15}O_5PNa$: 329.0555; found: 329.0526.

Methyl 2-[Bis(2,4-difluorophenoxy)phosphoryl]acetate (**7e**)

Colorless oil; yield: 86.2 mg (82%). IR (neat) 3064, 2958, 1747, 1619, 1507, 1439, 1302, 1249, 1183, 1145, 1121, 1100, 970, 931 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35–7.28 (m, 2H), 6.96–6.90 (m, 2H), 6.87–6.81 (m, 2H), 3.79 (s, 3H), 3.42 (d, $^{2}J_{H,P}$ = 21.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.7 (d, $^{2}J_{C,P}$ = 5.5 Hz), 159.7 (dd, $^{1}J_{C,F}$ = 248.1 Hz, $^{3}J_{C,F}$ = 10.2 Hz), 153.5 (ddd, $^{1}J_{C,F}$ = 251.9 Hz, $^{3}J_{C,F}$ = 12.1 Hz, $^{3}J_{C,P}$ = 4.9 Hz), 133.9–133.7 (m), 123.5 (dd, $^{3}J_{C,F}$ = 9.7 Hz, $^{3}J_{C,F}$ = 2.5 Hz), 111.5 (dd, $^{2}J_{C,F}$ = 22.8 Hz, $^{4}J_{C,F}$ = 3.1 Hz), 105.4 (dd, $^{2}J_{C,F}$ = 27.1 Hz, $^{2}J_{C,F}$ = 22.4 Hz), 53.0, 34.1 (d, $^{1}J_{C,P}$ = 139.8 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{11}F_4O_5PNa$: 401.0178; found: 401.0156. Anal. Calcd for $C_{15}H_{11}F_4O_5P$: C, 47.63; H, 2.93. Found: C, 47.43; H, 3.23.

Methyl 2-[Bis(phenylthio)phosphoryl]acetate (**7f**)

Colorless oil; yield: 79.5 mg (85%). IR (neat) 3059, 2952, 1737, 1473, 1439, 1268, 1220, 1107, 1023, 1002 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.63–7.59 (m, 4H), 7.45–7.36 (m, 6H), 3.77 (s, 3H), 3.30 (d, $^2J_{H,P}$ = 16.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.1 (d, $^2J_{C,P}$ = 4.6 Hz), 136.0 (d, $^3J_{C,P}$ = 4.4 Hz), 129.8 (d, $^5J_{C,P}$ = 2.8 Hz), 129.5 (d, $^4J_{C,P}$ = 2.1 Hz), 125.3 (d, $^2J_{C,P}$ = 6.5 Hz), 52.8, 42.6 (d, $^1J_{C,P}$ = 61.4 Hz). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{15}O_3PS_2Na$: 361.0098; found: 361.0069. Anal. Calcd for $C_{15}H_{15}O_3PS_2$: C, 53.24; H, 4.47. Found: C, 52.96; H, 4.67.

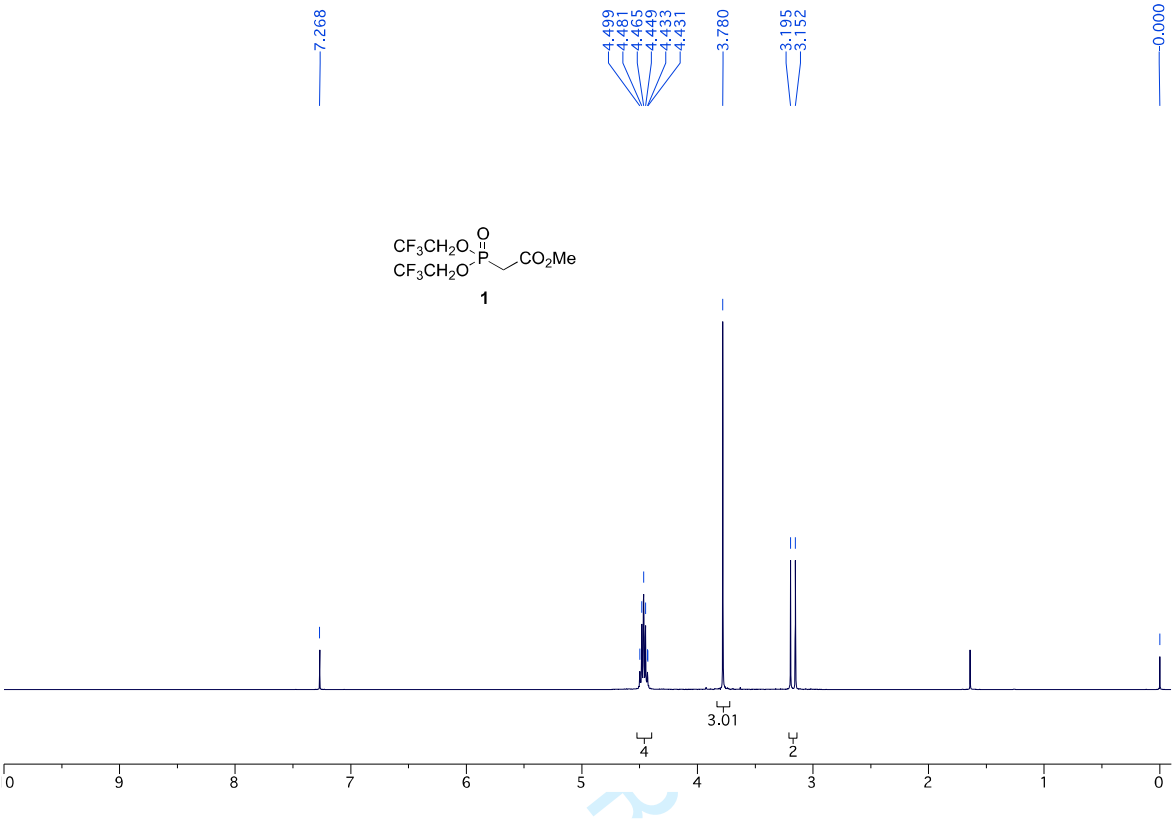
Methyl 2-[Bis(phenylamino)phosphoryl]acetate (**7g**)

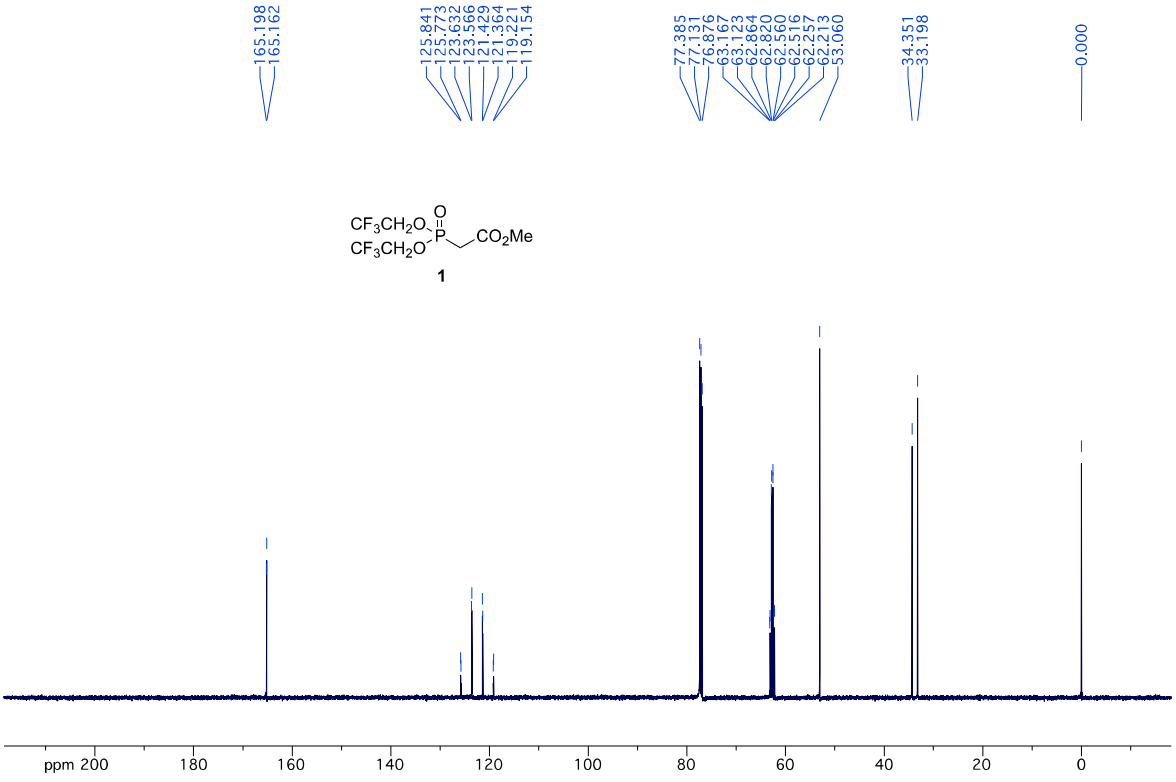
Pale yellow columns ($CHCl_3$/*n*-hexane); mp 115.0–116.0 °C; yield: 71.9 mg (86%). IR (KBr) 3330, 3185, 1731, 1602, 1502, 1434, 1397, 1282, 1268, 1242, 1207, 1181, 1106 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.23–7.17 (m, 4H), 7.16–7.12 (m, 4H), 6.99–6.93 (m, 2H), 6.25 (br s, 2H), 3.65 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 19.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4 (d, $^2J_{C,P}$ = 4.5 Hz), 139.5, 129.3, 122.4, 118.9 (d, $^2J_{C,P}$ = 6.4 Hz), 52.8, 35.9 (d, $^1J_{C,P}$ = 103.8 Hz). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{17}N_2O_3PNa$: 327.0874; found: 327.0858. Anal. Calcd for $C_{15}H_{17}N_2O_3P$: C, 59.21; H, 5.63; N, 9.21. Found: C, 59.18; H, 5.66; N, 8.98.

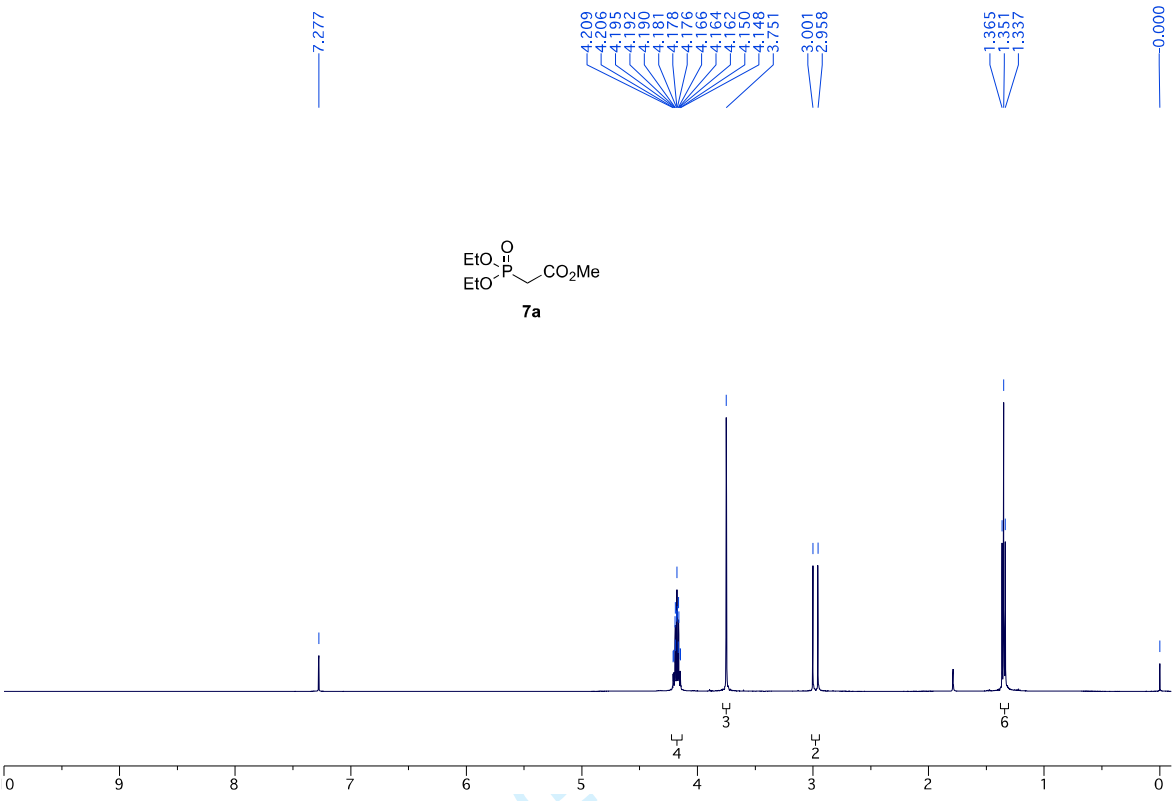
Ethyl 2-[Bis(2,2,2-trifluoroethoxy)phosphoryl]-2-fluoroacetate (**10**)

Colorless oil; yield: 46.1 mg (49%). IR (neat) 2983, 2947, 1770, 1456, 1420, 1374, 1271, 1174, 1068, 1021, 963 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.34 (dd, $^2J_{H,F}$ = 46.4 Hz, $^2J_{H,P}$ = 12.8 Hz, 1H), 4.60–4.43 (m, 4H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.4 (dd, $^2J_{C,F}$ = 21.8 Hz, $^2J_{C,P}$ = 1.9 Hz), 122.1 (qdd, $^1J_{C,F}$ = 277.8 Hz, $^3J_{C,P}$ = 8.0 Hz, $^5J_{C,F}$ = 5.6 Hz), 84.3 (dd, $^1J_{C,F}$ = 199.7 Hz, $^1J_{C,P}$ = 168.0 Hz), 63.5 (qd, $^2J_{C,F}$ = 38.8 Hz, $^2J_{C,P}$ = 5.9 Hz), 63.3, 13.9. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_8H_{10}F_7O_5PNa$: 373.0052; found: 373.0046. Anal. Calcd for $C_8H_{10}F_7O_5P$: C, 27.44; H, 2.88. Found: C, 27.49; H, 3.10.

3. NMR spectra



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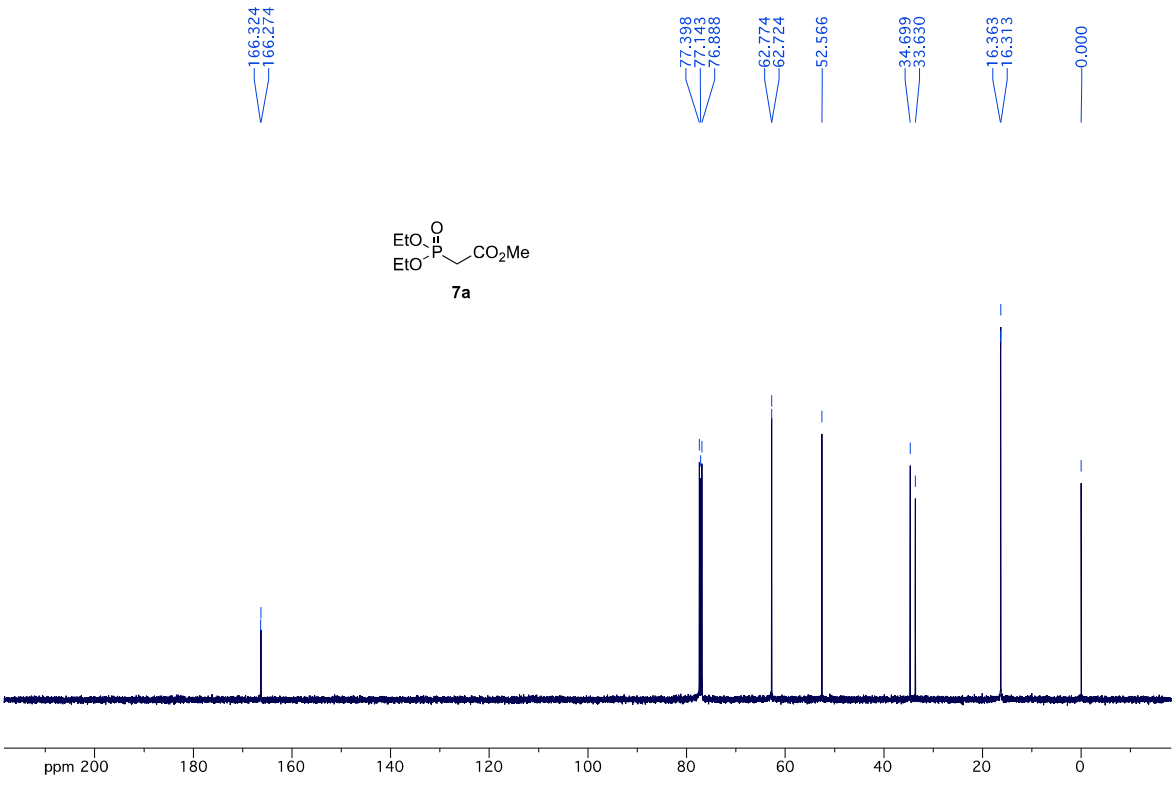
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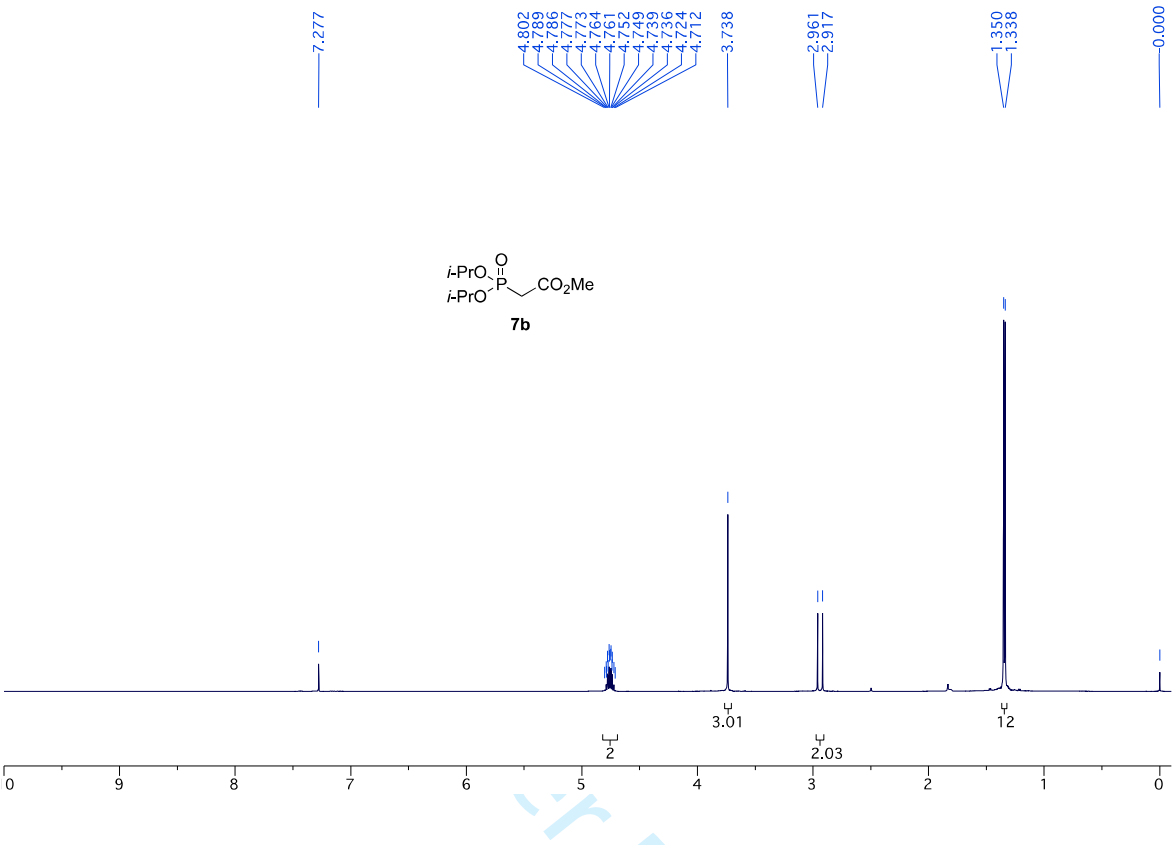
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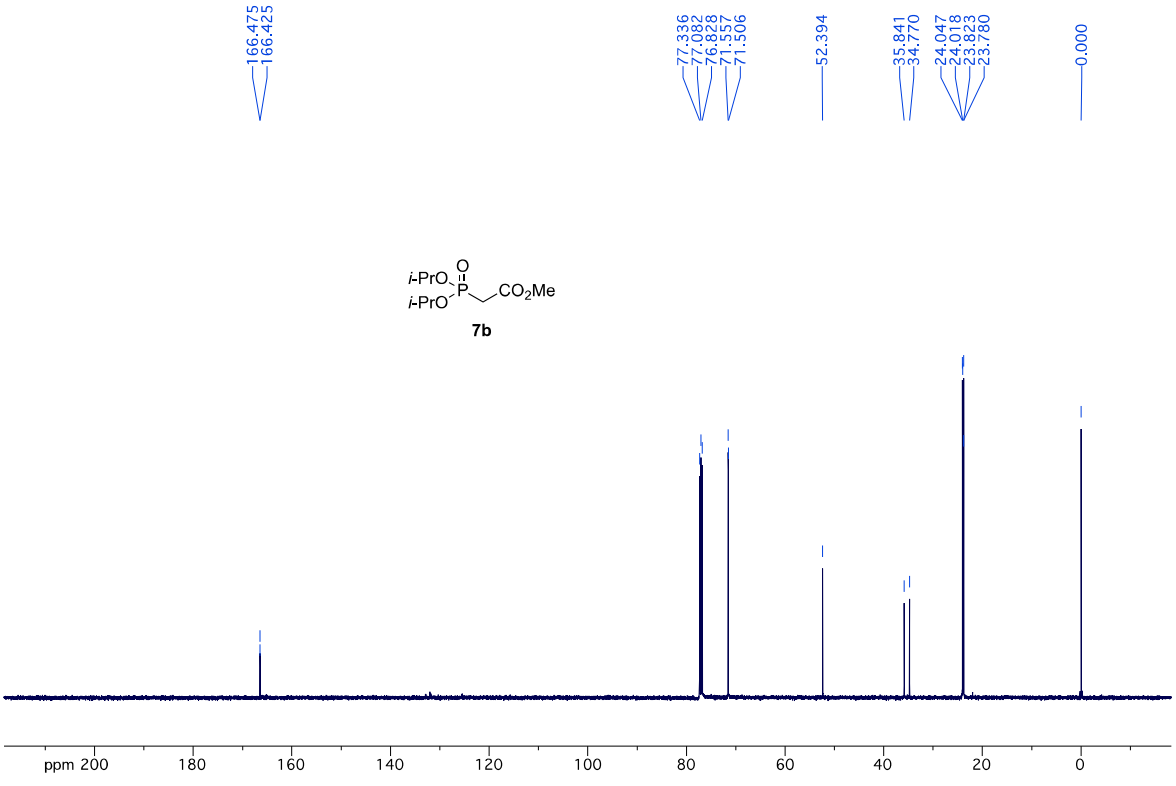
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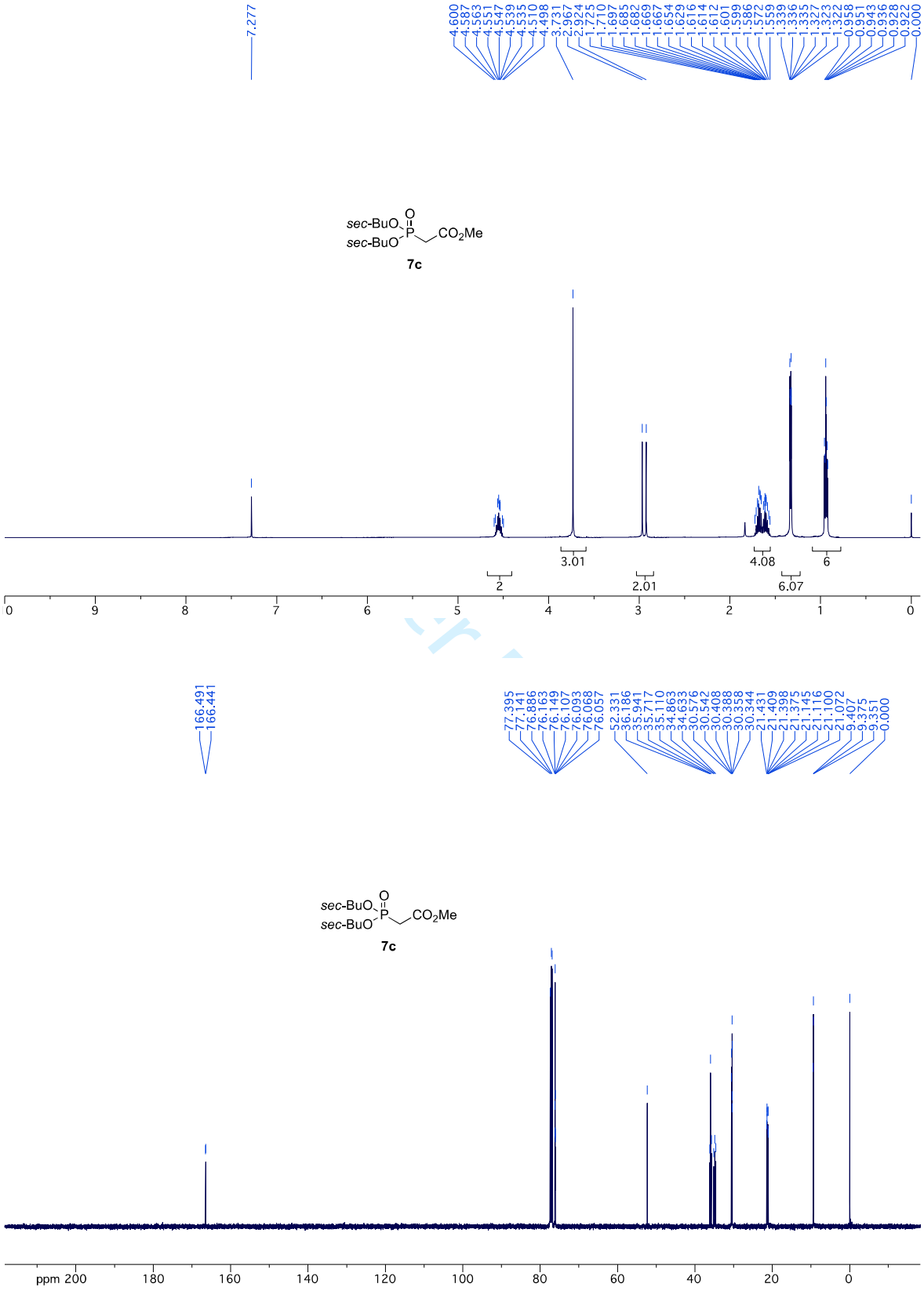
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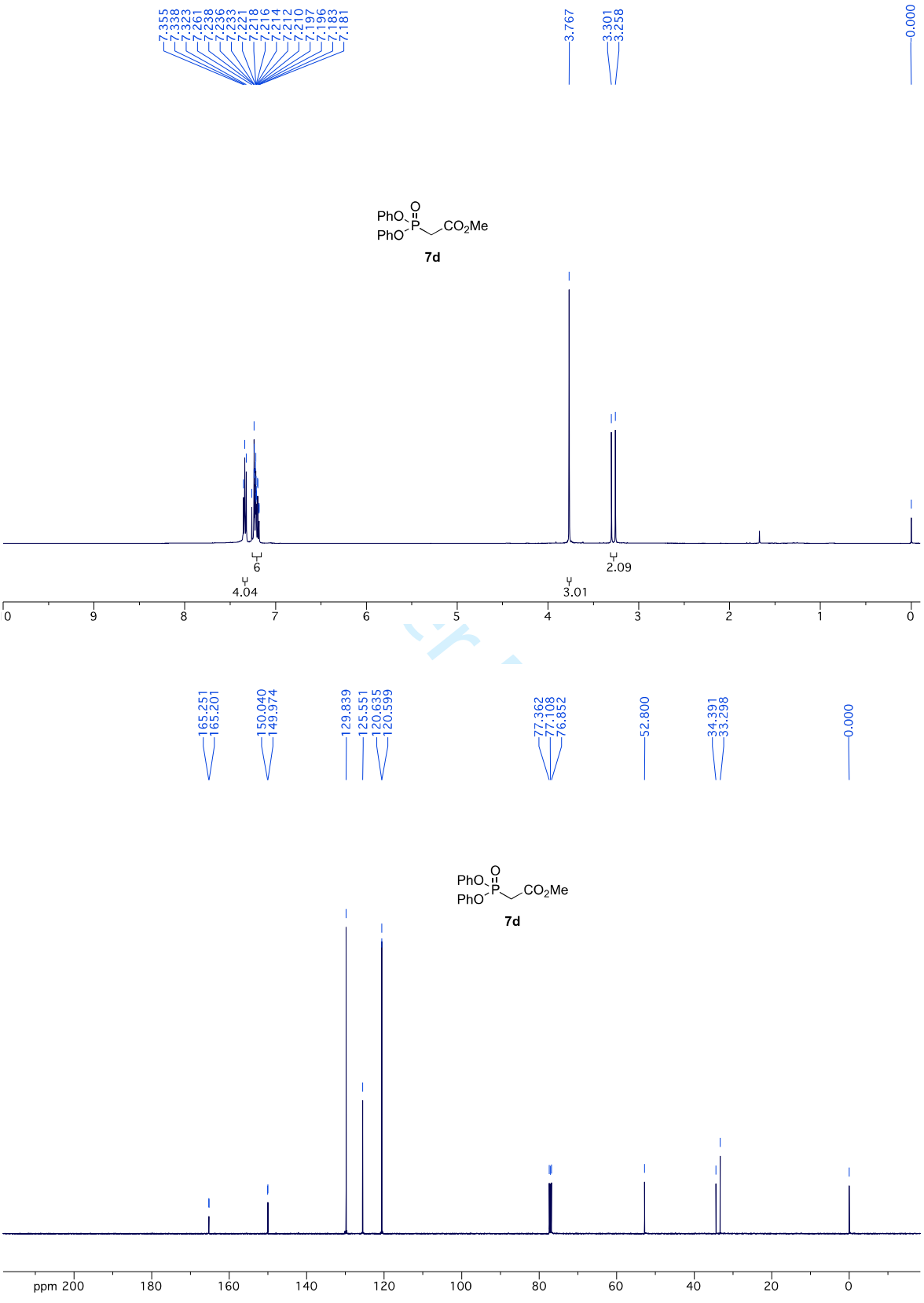
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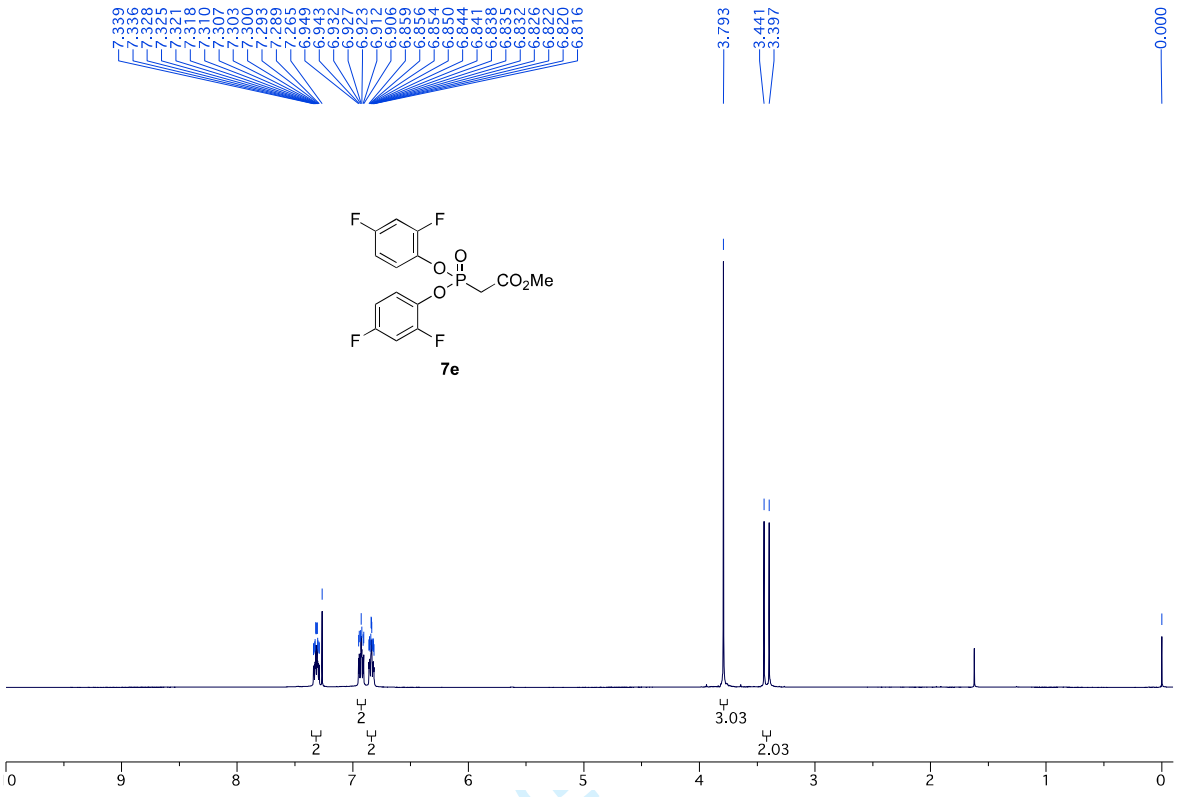
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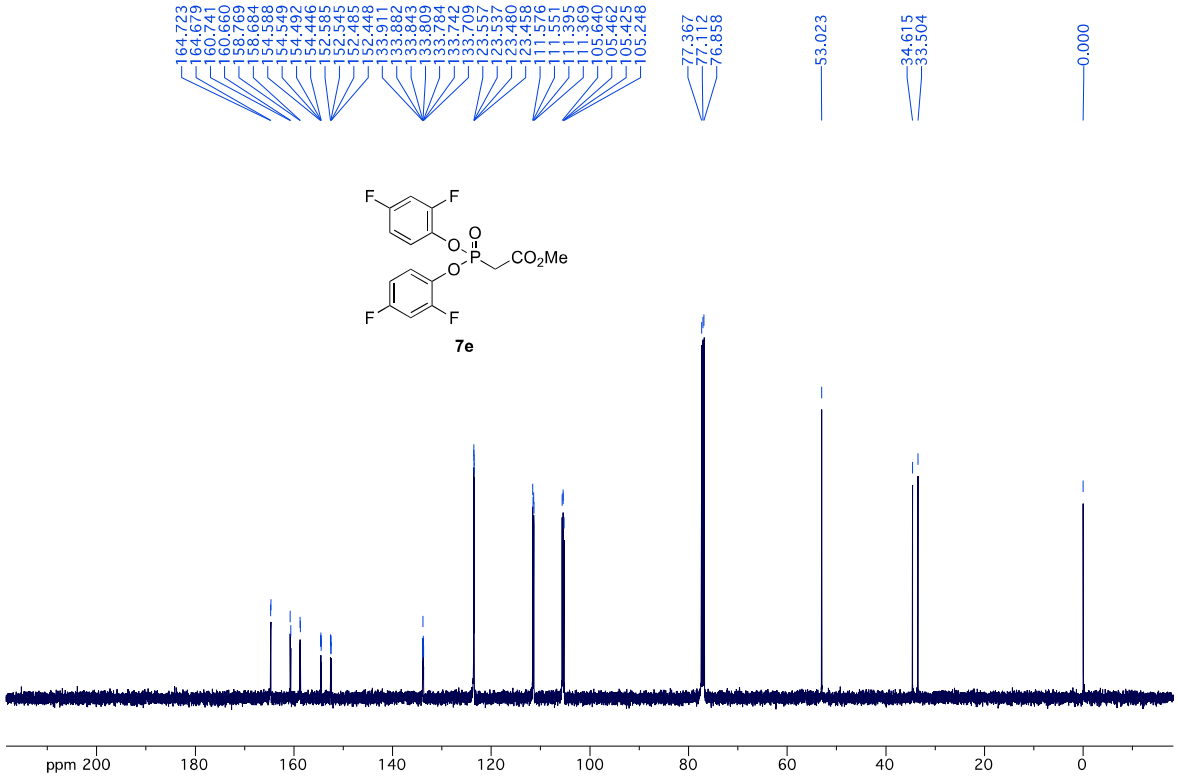
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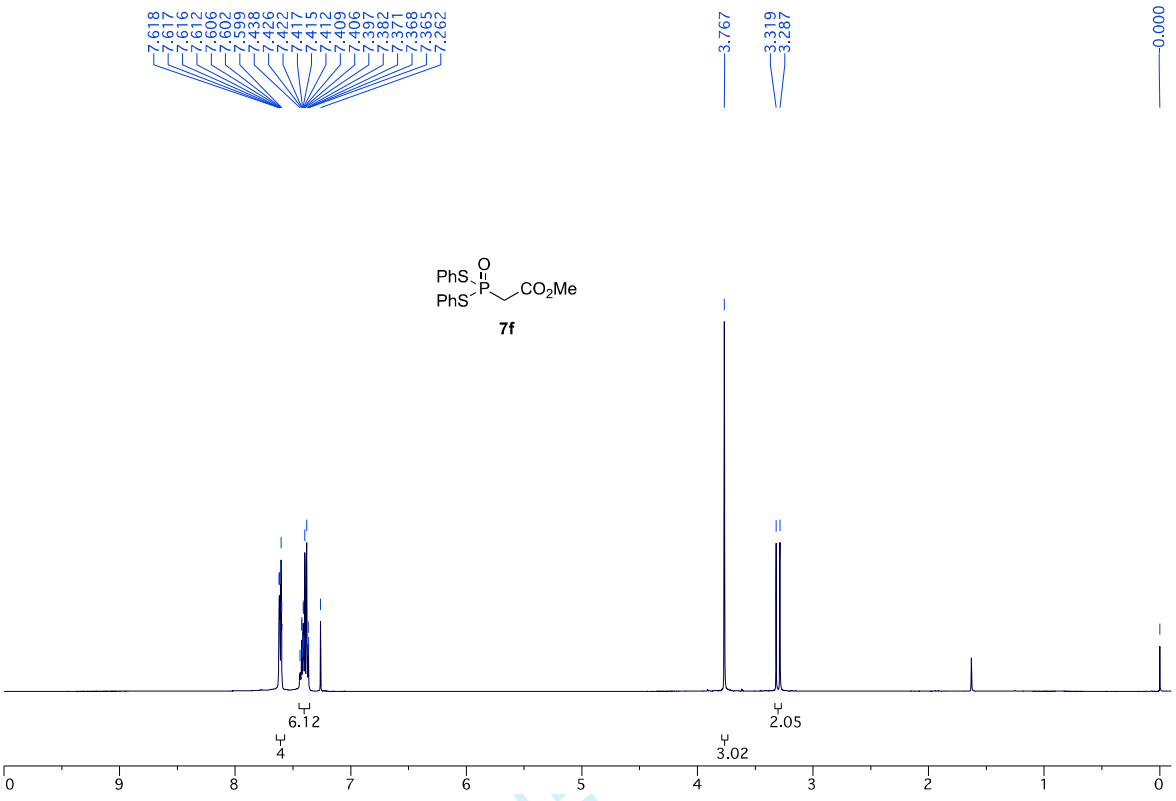
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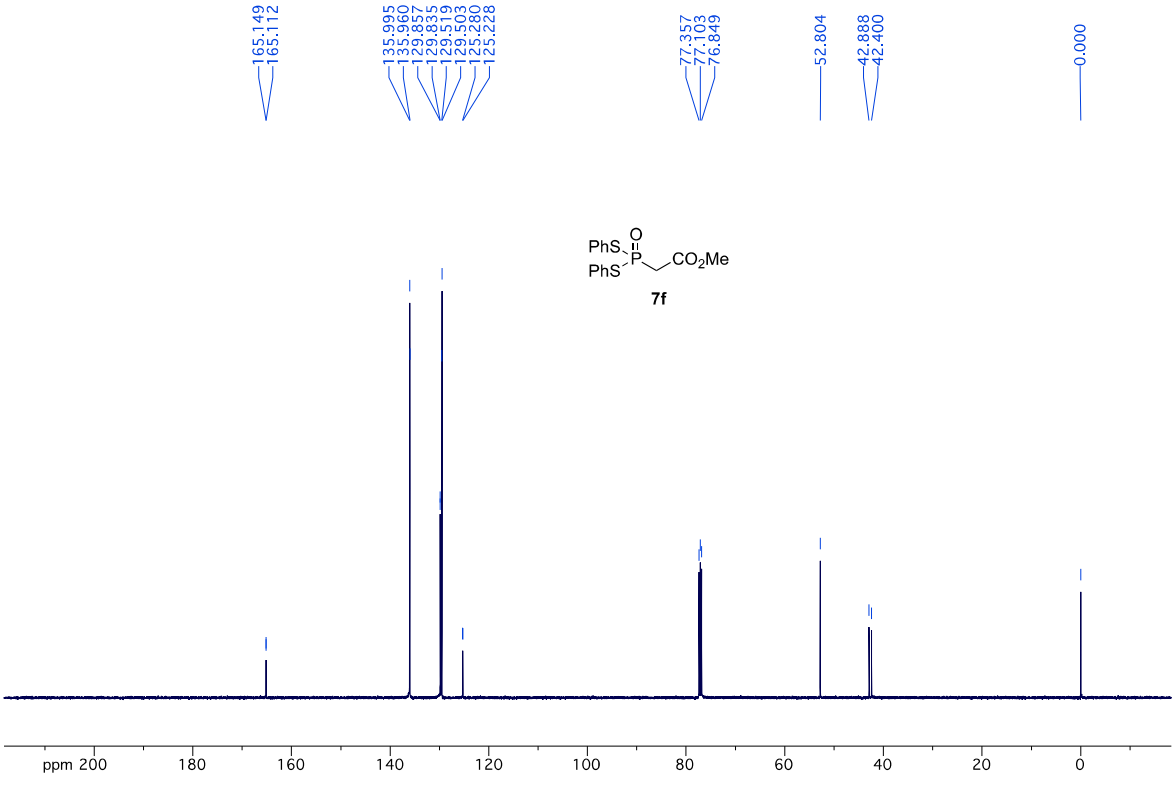
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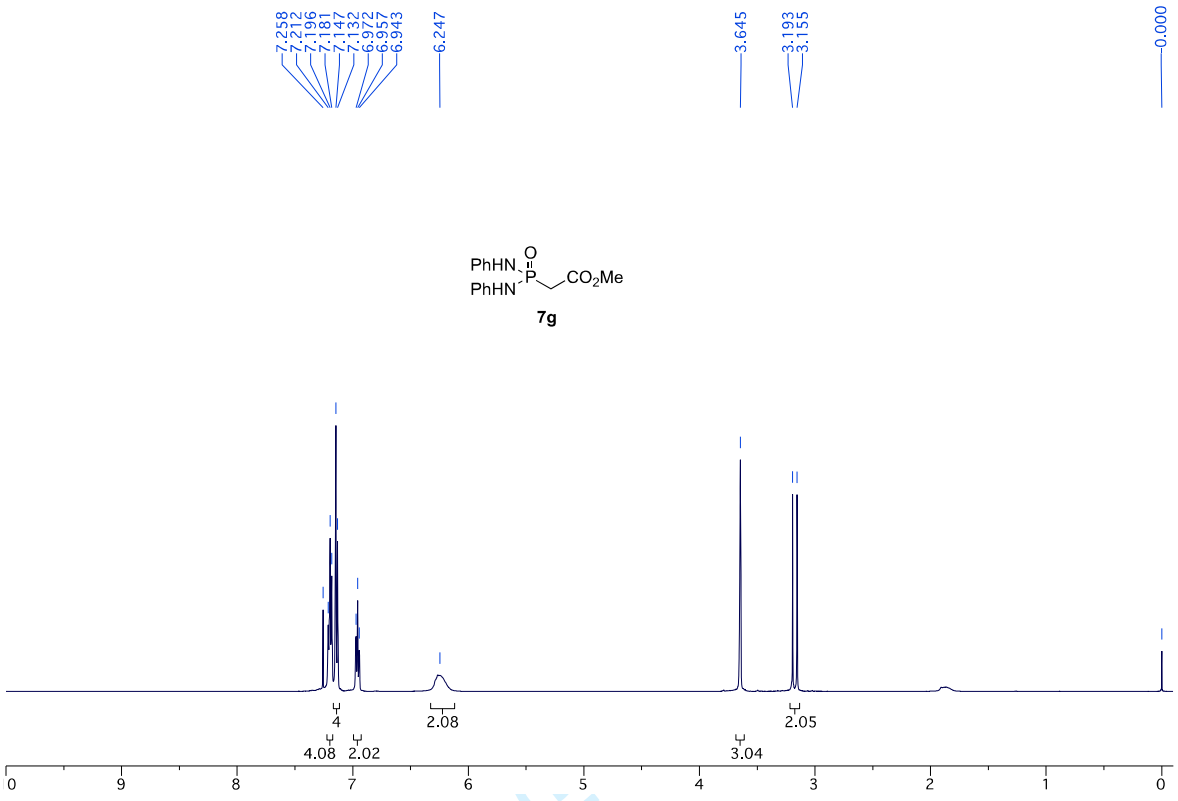
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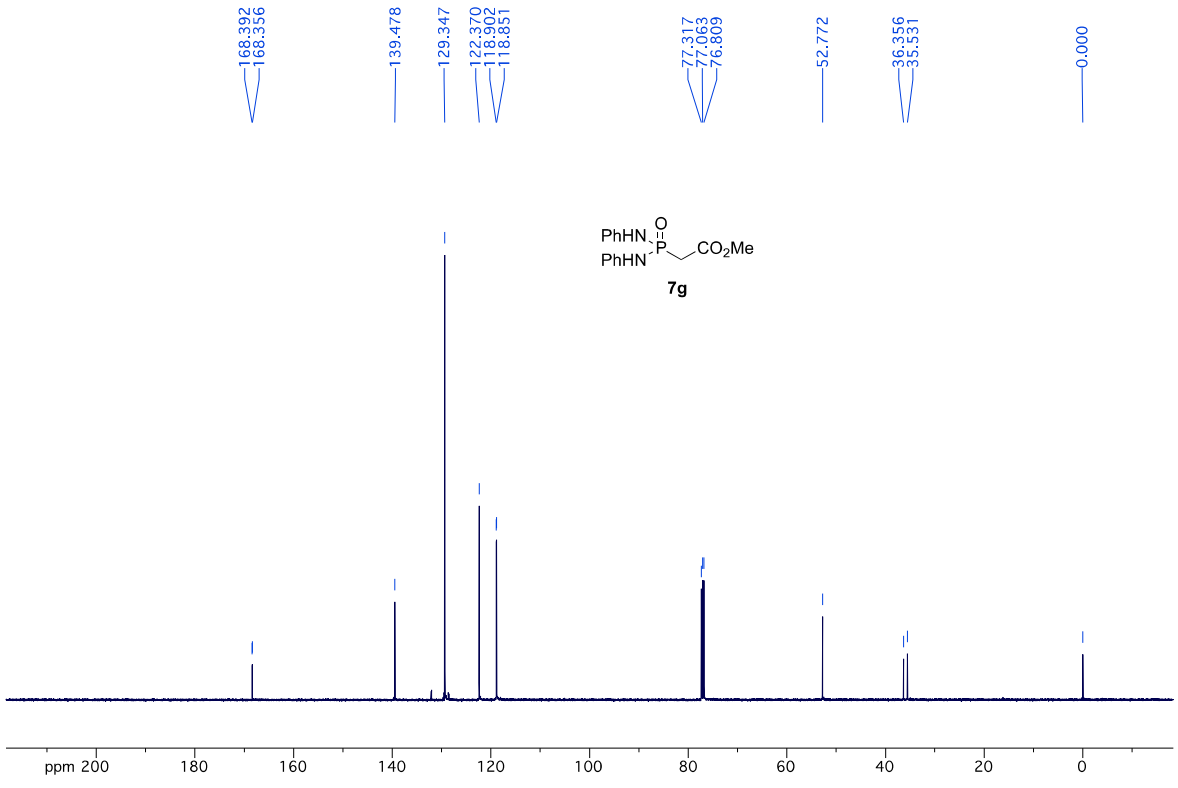
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CO2Me
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140
120
100
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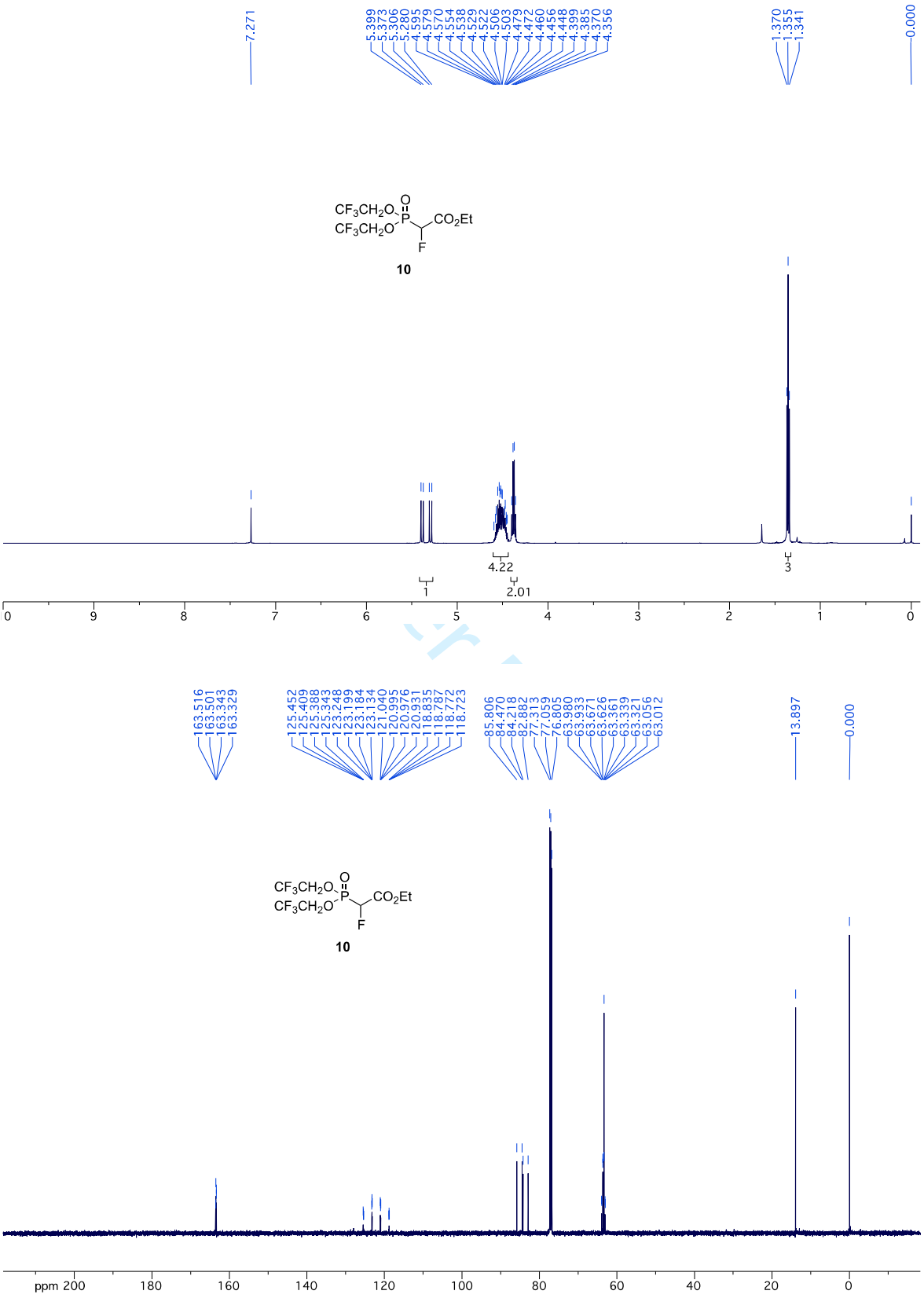
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CF3CH2O
CF3CH2O
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