A MODULAR, REARRANGEMENT APPROACH TOWARD MEDICINALLY RELEVANT PHOSPHINIC STRUCTURES

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SUPPORTING INFORMATION

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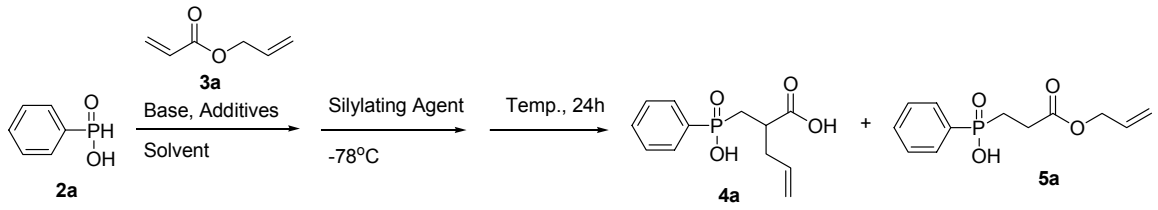
Experimental Section

1. General. Dry methylene chloride (CH_2Cl_2) was obtained by distillation of commercially available predried solvent from NaH. Reagents were purchased at the highest commercial quality from Aldrich, Acros and Fluka, and were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (E. Merck silica gel $60F_{254}$) and components were visualized by the following methods: UV light absorbance, and/or charring after spraying with a solution of NH_4HSO_4 ,and/or an aqueous solution of cerium molybdate/H_2SO_4 ("Blue Stain"), and heating. Purification of compounds by column chromatography was carried out on silica gel (Merck, 70-230 mesh) and the indicated solvents. RP-HPLC analyses were performed on a Hewlett Packard 1100 model (C_{18}-Cromasil-RP, 5 μm, UV/Vis detector, flow: 0.5 mL/min, 254 and/or 280 nm detection) by using the following gradients of buffers A and B (A buffer : 90% H_2O with 0.1% TFA, 10% CH_3CN; B buffer: 10% H_2O with 0.09% TFA, 90% CH_3CN): 0 min: 30% B, 20 min: 60% B, 50 min: 100% B, 60 min: 40% B. Reported retention times (where more than one) correspond to different diastereoisomers. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian 200 MHz Mercury spectrometer. ^1H and ^{13}C spectra are referenced according to the residual peak of the solvent based on literature data.[1] ^{31}P NMR chemical shifts are reported in ppm downfield from 85% H_3PO_4 (external standard). ^{13}C and ^{31}P NMR spectra are fully proton decoupled. ESI mass spectral analyses were performed on a mass spectrometer MSQ Surveyor, Finnigan using direct sample injection. Negative or positive ion ESI spectra were acquired by adjusting the needle and cone voltages accordingly.

[1] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512 – 7515

HRMS spectra were registered using a 4800 MALDI-TOF mass spectrometer (Applied Biosystems, Foster City, USA) in positive reflectron mode in the m/z range of 100-700.

2. Screening of reaction conditions.



Entry	Silylating agent	Base	Temp	Solvent	Additives	4a:5a	Yield[a]
1	HMDS (6eq)[b]	-	rt	CH_2Cl_2	-	51:49	46
2	BSA (5eq)[c]	-	rt	CH_2Cl_2	-	75:25	>99
3	BSA (solvent)[d]	-	rt	-	-	55:45	>99
4	TMSCl (7eq)	DBU (7eq)	rt	CH_2Cl_2	-	29:71	>99
5	TMSCl (7eq)	DMAP (7eq)	rt	CH_2Cl_2	-	33:67	>99
6	TMSCl (7eq)	DBN (7eq)	rt	CH_2Cl_2	-	3:97	85
7	TMSCl (7eq)	Et_3N (7eq)	rt	CH_2Cl_2	-	77:23	>99
8	TMSCl (7eq)	DMAP (7eq)	rt	CH_2Cl_2	-	33:67	>99
9	TMSCl (7eq)	imidazole (7eq)	rt	CH_2Cl_2	-	0:100	>99
10	TMSCl (7eq)	NMM (7eq)	rt	CH_2Cl_2	-	21:79	>99
11	TMSCl (7eq)	DABCO (7eq)	rt	CH_2Cl_2	-	49:51	>99
12	TMSCl (7eq)	DIPEA (7eq)	rt	CH_2Cl_2	-	91:9	>99
13	TMSCl (7eq)	DIPEA (7eq)	rt	DMF	-	81:19	>99
14	TMSCl (7eq)	DIPEA (7eq)	rt	THF	-	84:16	>99
15	TMSCl (7eq)	DIPEA (7eq)	rt	MeCN	-	84:16	>99
16	TMSCl (7eq)	DIPEA (7eq)	60°C	MeCN	-	71:29	>99
17	TMSCl (3eq)	DIPEA (3eq)	rt	CH_2Cl_2	-	62:38	>99
18	TMSCl (4eq)	DIPEA (4eq)	rt	CH_2Cl_2	-	83:17	>99
19	TMSCl (6eq)	DIPEA (6eq)	rt	CH_2Cl_2	-	85:15	>99
20	TMSCl (8eq)	DIPEA (8eq)	rt	CH_2Cl_2	-	88:12	>99

21	TMSCl (10eq)	DIPEA (10eq)	rt	CH_2Cl_2	-	89:11	>99
22	TMSCl (12eq)	DIPEA (12eq)	rt	CH_2Cl_2	-	89:11	>99
23	TMSCl (3.5eq)	DIPEA (8eq)	rt	CH_2Cl_2	-	66:34	>99
24	TMSCl (9eq)	DIPEA (4eq)	rt	CH_2Cl_2	-	80:20	>99
25	TMSCl (7eq)	DIPEA (7eq)	rt	CH_2Cl_2	LiCl (1.1eq)	11:89	>99
26	TMSOTf (7eq)	DIPEA (7eq)	rt	CH_2Cl_2	-	57:43	>99
27	TMSCl (7eq)	DIPEA (7eq)	40°C	CH_2Cl_2	-	84:16	>99
28	TMSCl (7eq)	DIPEA (7eq)	0°C	CH_2Cl_2	-	44:56	>99

[a]Overall yield of **4a** and **5a**, as determined by NMR. [b]**2a**, HMDS (6 equiv), 110°C, 3h, then cool to rt and addition of CH_2Cl_2, **3a** (1.1 equiv), 36h. [c] **2a**, BSA (5 equiv), CH_2Cl_2, **3a** (1.1 equiv), rt, 24h. [d] **2a**, BSA (7 equiv), **3a** (1.1 equiv), rt, 24h.

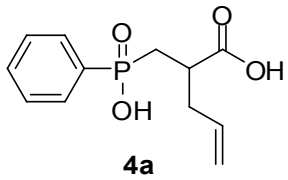
3. General Procedure for the Reaction between Phosphinic Acids 2 and Acrylates 3.

A solution of the corresponding acrylate **3** (1.1 eq), phosphinic acid **2** (1.0 eq) and Hunig's base (7.0 eq) in CH_2Cl_2 (2 ml for 1 mmol scale) in a Schlenk flask was degassed by applying three freeze-pump-thaw cycles. The mixture was cooled to -78 °C and purged with Ar for 15 min. Then, precooled at -78 °C freshly distilled TMSCl (7.0 eq) was added to the reaction vessel at once. The temperature was slowly raised to 25 °C and the clear solution was stirred overnight at room temperature. After the end of the reaction, the mixture was cooled to 0°C, abs. EtOH (1 ml for 1 mmol scale) was added dropwise and stirring at room temperature for 30 min followed. Removal of volatiles under vacuum afforded a viscous oil that was dissolved in AcOEt. The resulting solution was washed with HCl 1M (× 3) and brine, dried over Na_2SO_4 and concentrated in vacuo. Phosphinates **4a-k** were obtained after silica gel column chromatography, using $CHCl_3$/MeOH/AcOH 7:0.1:0:1 → 7:0.3:0:3 as eluent solvent system**.** Solvent system

$CHCl_3$/MeOH/AcOH 7:0.1:0.1 was maintained as eluent until less polar impurities and the bulk of by-product of type **5** were removed. Then, the solvent system was gradually changed to $CHCl_3$/MeOH/AcOH 7:0.3:0.3 until the target compounds of type **4** were fully recovered.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}pent-4-enoic acid (4a)

Acrylate **3a** (86 mg, 0.77 mmol), phosphinic acid **2a** (100 mg, 0.70 mmol), Hunig's base (0.86 ml, 4.90 mmol), TMSCl (0.62 ml, 4.90 mmol), CH_2Cl_2 (1.4 ml). Yield 151 mg, 85%.

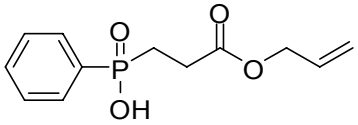


4a

4a. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.78 – 7.42 (m, 5H, Ar), 5.63 (ddt, J = 15.5, 11.6, 6.8 Hz, 1H, C*H*=CHH), 5.00 (s, 1H, CH=C*H*H), 4.94 (dt, J = 6.5, 2.0 Hz, 1H, CH=CH*H*), 2.65-2.43 (m, 1H, C*H*CO), 2.35-2.15 (m, 2H, CH_2CH=CH_2), 2.12 (dt, J = 14.7, 7.2 Hz, 1H, PC*H*H), 1.85 (dt, J = 14.7, 6.0 Hz, 1H, PCH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7, 133.8, 132.3, 131.2 (d, $^1J_{PC}$ = 130.6 Hz), 131.1, 130.1, 128.6, 128.3, 118.2, 38.9, 37.4 (d, $^3J_{PC}$ = 10.1 Hz), 31.4 (d, $^1J_{PC}$ = 99.7 Hz); ^{31}P NMR (81 MHz, d_6-DMSO): δ 35.9; HPLC t_R = 14.6 min; ES-MS m/z: calcd for $[C_{12}H_{15}O_4P + H]^+$ 255.1; found: 255.0; HRMS (m/z): [MH]+ calcd. for $C_{12}H_{15}O_4P$, 255.0786 found, 255.0790.

Allyl 3-[hydroxy(phenyl)phosphinoyl]propionate (5a)

Isolated during the above described preparation of **4a**. Yield of isolated product: 12 mg, 7%.

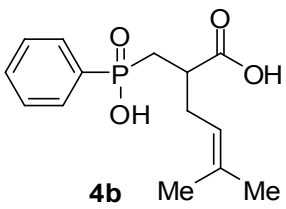


5a

5a. Viscous oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 – 7.60 and 7.55 – 7.30 (m, 5H, Ar), 5.83 (ddt, J = 17.2, 10.3, 5.7 Hz, 1H, C*H*=CHH), 5.27 (dq, J = 17.2, 1.3 Hz, 1H, CH=C*H*H), 5.21 (dq, J = 10.3, 1.3 Hz, 1H, CH=CH*H*), 4.47 (dt, J = 5.7, 1.3 Hz, 2H, OCH_2), 2.56 – 2.37 (m, 2H, CH_2CO), 2.21 – 2.02 (m, 2H, PCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7 (d, $^{3}J_{PC}$ = 17.5 Hz), 132.2, 131.8, 131.2, 131.1 (d, $^{1}J_{PC}$ = 131.5 Hz), 130.0, 128.5, 128.3, 118.3, 65.4, 26.8, 24.6; ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.1; HPLC t_R = 16.6 min; ES-MS m/z: calcd for $[C_{12}H_{15}O_4P + H]^+$ 255.1; found: 255.0; HRMS (m/z): [MH]+ calcd. for $C_{12}H_{15}O_4P$, 255.0786 found, 255.0790

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-5-methylhex-4-enoic acid (4b)

Acrylate **3b** (108 mg, 0.77 mmol), phosphinic acid **2a** (100 mg, 0.70 mmol), Hunig's base (0.86 ml, 4.90 mmol), TMSCl (0.62 ml, 4.90 mmol), CH_2Cl_2 (1.4 ml). Yield 156 mg, 79%.

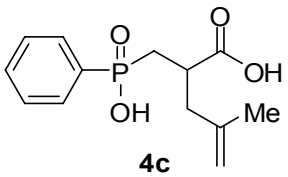


4b

4b. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.80 – 7.42 (m, 5H, Ar), 4.94 (t, J = 6.9 Hz, 1H, C*H*=CMe_2), 2.57 – 2.35 (m, 1H, C*H*CO), 2.32 – 1.63 (m, 3H, PC*H*H, CH_2CH=CMe_2), 1.83 (dt, J = 14.7, 6.0 Hz, 1H, PCH*H*), 1.61 (s, 3H, C(CH_3)(CH_3)), 1.51 (s, 3H, C(CH_3)(CH_3)); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3 (d, $^{3}J_{PC}$ = 5.5 Hz), 135.1, 132.1, 131.4 (d, $^{1}J_{PC}$ = 132.4 Hz), 131.1, 130.9, 128.5, 128.2, 119.6, 39.4, 31.9 (d, $^{3}J_{PC}$ = 10.7 Hz), 31.4 (d, $^{1}J_{PC}$ = 99.6 Hz), 25.7, 17.7; ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.6; HPLC t_R = 17.7 min; ES-MS m/z : calcd for $[C_{12}H_{19}O_4P - H]^-$ 281.1; found: 281.3; HRMS (m/z): [MH]+ calcd. for $C_{14}H_{19}O_4P$, 283.1099 found, 283.1110.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-4-methylpent-4-enoic acid (4c)

Acrylate **3c** (146 mg, 1.16 mmol), phosphinic acid **2a** (150 mg, 1.05 mmol), Hunig's base (1.29 ml, 7.39 mmol), TMSCl (0.94 ml, 7.39 mmol), CH_2Cl_2 (2 ml). Yield 194 mg, 69%.

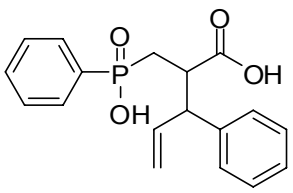


4c

4c. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.81 – 7.32 (m, 5H, Ar), 4.69 (s, 1H, C=C*H*H), 4.60 (s, 1H, C=CH*H*), 2.73 – 2.53 (m, 1H, C*H*CO), 2.19 (t, J = 7.0 Hz, 2H, CHCH_2C(Me)), 2.04 (dt, J = 14.8, 7.7 Hz, 1H, PC*H*H), 1.76 (dt, J = 14.6, 4.7 Hz, 1H, PCH*H*), 1.49 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.1, 141.3, 132.3, 131.1, 130.9, 131.0 (d, $^1J_{PC}$ = 131.5 Hz), 128.5, 128.2, 113.8, 41.7 (d, $^3J_{PC}$ = 13.0 Hz), 37.5, 31.3 (d, $^1J_{PC}$ = 99.5 Hz), 21.5; ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.4; HPLC t_R = 16.1 min; ES-MS m/z: calcd for $[C_{13}H_{17}O_4P - H]^-$ 267.1; found: 267.3; HRMS (m/z): [MH]+ calcd. for $C_{13}H_{17}O_4P$, 269.0943 found, 269.0939.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-4-phenylpent-4-enoic acid (4d)

Acrylate **3d** (292 mg, 1.55 mmol), phosphinic **2a** (200 mg, 1.41 mmol), Hunig's base (1.72 ml, 9.87 mmol), TMSCl (1.25 ml, 9.87 mmol), CH_2Cl_2 (3 ml). Yield 419 mg, 90%.



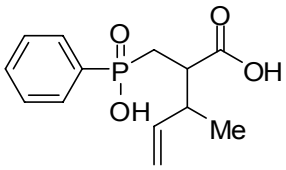
4d

4d. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.73 – 7.00 (m, 10H, Ar), 6.06 – 5.75 (m, 1H, C*H*=CH_2), 5.14 - 4.89 (m, 2H, CH=CH_2), 3.48 – 3.29 (m, 1H, C*H*Ph), 2.79 (dq, J = 10.0, 9.8 Hz, 1H, C*H*CO), 2.02 (m, 1.3H, PCH_2 of minor isomer + PCH*H* of major isomer), 1.50 (t, J = 14.7 Hz, 0.7H, PC*H*H of major isomer); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.1, 177.7, 140.4, 140.1, 138.2, 137.6, 132.1, 131.1, 131.1 (d, $^1J_{PC}$ = 132.3 Hz), 130.9, 129.4, 128.8, 128.5, 128.2, 128.1, 127.8, 127.7, 126.9, 126.8, 117.8,

116.6, 54.0, 53.7, 53.4, 45.0, 44.6, 31.2 (d, $^{1}J_{PC}$ = 99.7 Hz); ^{31}P NMR (81 MHz, $CDCl_3$) δ 43.5; HPLC t_R = 19.4 min; ES-MS m/z : calcd for $[C_{18}H_{19}O_4P + H]^+$ 331.1; found: 331.1; HRMS (m/z): [MH]+ calcd. for $C_{18}H_{19}O_4P$, 331.1099 found, 331.1089.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-3-methylpent-4-enoic acid (4e)

Acrylate **3e** (146 mg, 1.16 mmol), phosphinic acid **2a** (150 mg, 1.05 mmol), Hunig's base (1.29 ml, 7.39 mmol), TMSCl (0.94 ml, 7.39 mmol), CH_2Cl_2 (2 ml). Yield 220 mg, 78%.

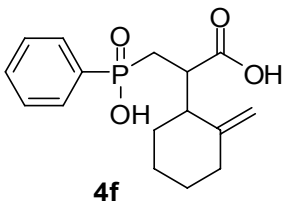


4e

4e. White solid: M.p. 98 – 100^{o}C; ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.76 – 7.40 (m, 5H, Ar), 5.73 – 5.44 (m, 1H, C*H*=CH_2), 5.03 – 4.86 (m, 2H, CH=C*H*$_2$), 2.62 – 2.24 (m, 2H, MeC*H*C*H*CO), 2.22 – 1.97 (m, 1H, PCH*H*), 1.83, (dt, *J* = 14.7, 1.7 Hz, 0.34H, PC*H*H of minor isomer), 1.74 (dt, *J* = 14.9, 2.9 Hz, 0.66H, PC*H*H of major isomer), 0.89 (d, *J* = 6.6, 3H, C*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.3, 177.9, 140.0, 139.7, 132.2, 131.3 (d, $^{1}J_{PC}$ = 131.6 Hz), 131.1, 130.9, 128.5, 128.2, 116.3, 115.6, 44.5, 43.8, 41.6 (d, $^{3}J_{PC}$ = 13.8 Hz), 40.3 (d, $^{3}J_{PC}$ = 13.4 Hz), 30.8 (d, $^{1}J_{PC}$ = 99.8 Hz), 29.2 (d, $^{1}J_{PC}$ = 99.5 Hz), 17.9, 15.7; ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.9, 44.4; HPLC t_R = 17.0 min; ES-MS m/z: calcd for $[C_{13}H_{17}O_4P + H]^+$ 269.1; found: 269.1; HRMS (m/z): [MH]+ calcd. for $C_{13}H_{17}O_4P$, 269.0943 found, 269.0933.

3-[Hydroxy(phenyl)phosphinoyl]-2-(2-methylenecyclohexyl)propanoic acid (4f)

Acrylate **3f** (193 mg, 1.16 mmol), phosphinic acid **2a** (150 mg, 1.05 mmol), Hunig's base (1.29 ml, 7.39 mmol), TMSCl (0.94 ml, 7.39 mmol), CH_2Cl_2 (2 ml). Yield 223 mg, 69%.

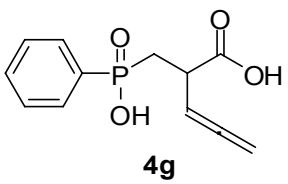


4f

4f. White solid: M.p. 147 – 149°C; ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.78 – 7.41 (m, 5H, Ar), 4.73 (s, 0.1H, C=CH*H* of minor isomer), 4.60 (s, 1H, C=CH*H* of major isomer + C=C*H*H of minor isomer), 4.50 (s, 0.9H, C=CH*H* of major isomer), 2.92 – 2.70 (m, 1H, C*H*CO), 2.32 – 1.74 (m, 5H, (CH_2)(C*H*)C=CH_2, PCH_2), 1.59 – 1.16 (m, 6H, (CH_2)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) (signals corresponding to the major isomer) δ 178.9, 148.6, 132.1, 131.5 (d, $^{1}J_{PC}$ = 133.1 Hz), 131.2, 131.0, 128.5, 128.3, 108.3, 45.7, (d, $^{3}J_{PC}$ = 14.1 Hz), 40.4, 34.0, 29.7 (d, $^{1}J_{PC}$ = 99.5 Hz), 28.3, 27.8, 23.0; ^{31}P NMR (81 MHz, d_6-DMSO) δ 36.5, 35.9; HPLC t_R = 18.9 min; ES-MS m/z: calcd for $[C_{16}H_{21}O_4P - H]^-$ 307.1; found: 307.4; HRMS (m/z): [MH]+ calcd. for $C_{16}H_{21}O_4P$, 309.1255 found, 309.1252.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-pent-3,4-dienoic acid (4g)

Acrylate **3g** (128 mg, 1.16 mmol), phosphinic acid **2a** (150 mg, 1.05 mmol), Hunig's base (1.29 ml, 7.39 mmol), TMSCl (0.94 ml, 7.39 mmol), CH_2Cl_2 (2 ml). Yield 175 mg, 66%.

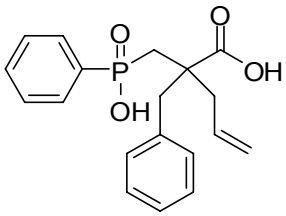


4g

4g. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.77-7.30 (m, 5H, Ar), 5.23 (q, J = 6.9 Hz, 1H, C*H*=·=CH_2), 4.81 (dd, J = 2.5, 6.9 Hz, 2H, CH=·=CH_2), 3.20-3.00 (m, 1H, C*H*CO), 2.28 (dt, J = 7.4, 15.0 Hz, 1H, PC*H*H), 1.97 (ddd, J = 6.1, 13.7, 15.0 Hz, 1H, PCH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.0, 176.9 (d, $^{3}J_{PC}$ = 6.9 Hz), 132.4, 131.3 (d, $^{1}J_{PC}$ = 133.6 Hz), 131.2, 131.0, 128.6, 128.3, 89.4 (d, $^{3}J_{PC}$ = 13.4 Hz), 78.4, 38.7, 31.8 (d, $^{3}J_{PC}$ = 98.7 Hz); ^{31}P NMR (81 MHz, $CDCl_3$) δ 43.8; HPLC t_R = 14.3 min; ES-MS m/z: calcd for $[C_{12}H_{13}O_4P + H]^+$ 252.1; found: 253.3; HRMS (m/z): [MH]+ calcd. for $C_{12}H_{13}O_4P$, 253.0630 found, 253.0628.

2-Benzyl-2-{[hydroxy(phenyl)phosphinoyl]methyl}pent-4-enoic acid (4h)

Acrylate **3h** (156 mg, 0.77 mmol), phosphinic acid **2a** (100 mg, 0.70 mmol), Hunig's base (0.86 ml, 4.90 mmol), TMSCl (0.62 ml, 4.90 mmol), CH_2Cl_2 (1.4 ml). Reaction time 48h. Yield 219 mg, 91%.

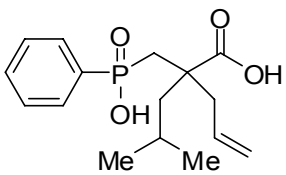


4h

4h. White solid: M.p. 140 – 142°C; ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.81 – 7.13 (m, 10H, Ar), 5.82 – 5.59 (m, 1H, C*H*=CH_2), 5.02 (s, 1H, CH=CH*H*), 4.95 (dd, J = 5.2, 2.4 Hz, 1H, CH=C*H*H), 3.27 (d, J = 13.2 Hz, 1H, PhC*H*H), 2.95 (d, J = 13.2 Hz, 1H, PhCH*H*), 2.64 – 2.41 (m, 2H, CH_2CH=CH_2), 2.10 (dd, J = 15.5, 13.2 Hz, 1H, PC*H*H), 1.88 (dd, J = 15.5, 13.2 Hz, 1H, PCH*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 180.2 (d, $^3J_{PC}$ = 9.5 Hz), 136.5, 134.7, 133.1, 132.0, 130.8, 130.6, 130.4, 128.5, 128.2, 128.1, 126.7, 119.5, 49.9 (d, $^3J_{PC}$ = 3.8 Hz), 42.1, 39.5, 34.3 (d, $^1J_{PC}$ = 99.4 Hz); ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.9; HPLC t_R = 21.4 min; ES-MS m/z: calcd for $[C_{19}H_{21}O_4P + H]^+$ 345.1; found: 345.0; HRMS (m/z): [MH]+ calcd. for $C_{19}H_{21}O_4P$, 345.1255 found, 345.1249.

2-{[Hydroxy(phenyl)phosphinoyl]methyl}-2-isobutylpent-4-enoic acid (4i)

Acrylate **3i** (130 mg, 0.77 mmol), phosphinic acid **2a** (100 mg, 0.70 mmol), Hunig's base (0.86 ml, 4.90 mmol), TMSCl (0.62 ml, 4.90 mmol), CH_2Cl_2 (1.4 ml). Reaction time 48h. Yield 182 mg, 84%.



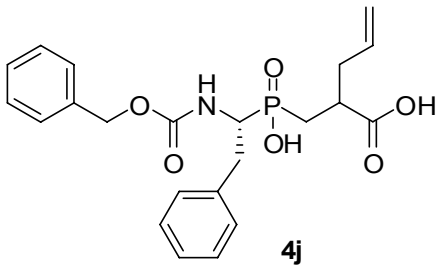
4i

4i. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.80 – 7.40 (m, 5H, Ar), 5.77 – 5.49 (m, 1H, C*H*=CH_2), 5.02 (s, 1H, CH=CH*H*),

4.95 (s, 1H, CH=C*H*H), 2.67 (dd, *J* = 13.3, 7.3 Hz, 1H, C*H*HCH=CH_2), 2.40 (dd, *J* = 13.0, 6.6 Hz, 1H, CH*H*CH=CH_2), 2.15 (dd, *J* = 15.6, 13.3 Hz, 1H, PC*H*H), 2.05 (dd, *J* = 15.5, 13.2 Hz, 1H, PCH*H*), 1.80 –1.37 (m, 3H, $CH_2CH(CH_3)_2$), 0.74 (br s, 6H, $CH_2CH(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.7 (d, $^3J_{PC}$ = 9.4 Hz), 133.6 (d, $^1J_{PC}$ = 131.6 Hz), 133.0, 131.9, 130.8, 130.6, 128.5, 128.2, 119.3, 47.6 (d, $^3J_{PC}$ = 3.5 Hz), 46.2 (d, $^3J_{PC}$ = 9.7 Hz), 38.9, 35.4 (d, $^1J_{PC}$ = 99.2 Hz), 24.3, 23.5, 23.4; ^{31}P NMR (81 MHz, $CDCl_3$) δ 44.5; HPLC t_R = 20.9 min; ES-MS m/z: calcd for $[C_{16}H_{23}O_4P + H]^+$ 311.1; found: 311.1; HRMS (m/z): [MH]+ calcd. for $C_{16}H_{23}O_4P$, 311.1412 found, 311.1383.

2-{[(1*R*)-1-{[(Benzyloxy)carbonyl]amino}-2-phenylethyl(hydroxyl)phosphinoyl] methyl}pent-4-enoic acid (4j)

Acrylate **3a** (79 mg, 0.70 mmol), phosphinic acid **2b** (200 mg, 0.63 mmol), Hunig's base (0.77 ml, 4.41 mmol), TMSCl (0.56 ml, 4.41 mmol), CH_2Cl_2 (1.3 ml). Yield 141 mg, 52%.



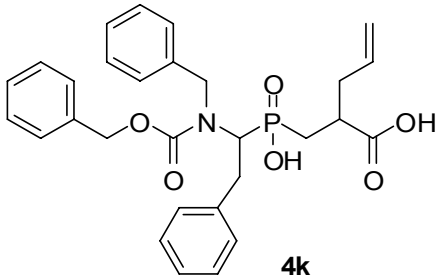
4j

4j. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ 7.79 – 7.53 (m, 1H, NH), 7.38 – 6.91 (m, 10H, Ar), 5.89 – 5.45 (m, 1H, C*H*=CH_2), 5.21 – 4.64 (m, 4H, OCH_2Ph, CH=CH_2), 4.08–3.74 (m, 1H, PC*H*CH_2Ph), 3.19 – 2.94 (m, 1H, CH*H*Ph), 2.91 – 2.58 (m, 2H, C*H*HPh, PCH_2CH), 2.39 – 2.17 (m, 2H, CH_2CH=CH_2), 2.20 – 1.89 (m, 1H, PCH*H*), 1.87 – 1.54 (m, 1H, PC*H*H); ^{13}C NMR (50 MHz, d_6-DMSO) δ 175.8 (d, $^3J_{PC}$ = 9.0 Hz), 156.6 (d, $^3J_{PC}$ = 4.1 Hz), 139.1, 138.8, 137.8, 135.6, 129.6, 128.8, 128.7, 128.1, 127.6, 127.5, 126.7, 117.9, 65.7, 53.2 (d, $^1J_{PC}$ = 106.1 Hz), 37.9, 37.4 (d, $^3J_{PC}$ = 9.1 Hz), 33.3, 27.8 (d, $^1J_{PC}$ = 90.8 Hz); ^{31}P NMR (81

MHz, d_6-DMSO) δ 51.4, 51.2, HPLC t_R = 23.7 min. ES-MS m/z: calcd for $[C_{22}H_{26}NO_6P - H]^-$ 430.1; found: 430.4; HRMS (m/z): [MH]+ calcd. for $C_{22}H_{26}NO_6P$, 432.1576 found, 432.1570.

2-{[1-{[(Benzyloxy)carbonyl]benzylamino}-2-phenylethyl(hydroxyl)phosphinoyl] methyl}pent-4-enoic acid (4k)

Acrylate **3a** (39 mg, 0.35 mmol), phosphinic acid **2b** (130 mg, 0.32 mmol), Hunig's base (0.39 ml, 2.24 mmol), TMSCl (0.28 ml, 2.24 mmol), CH_2Cl_2 (0.8 ml). Yield 140 mg, 84%.



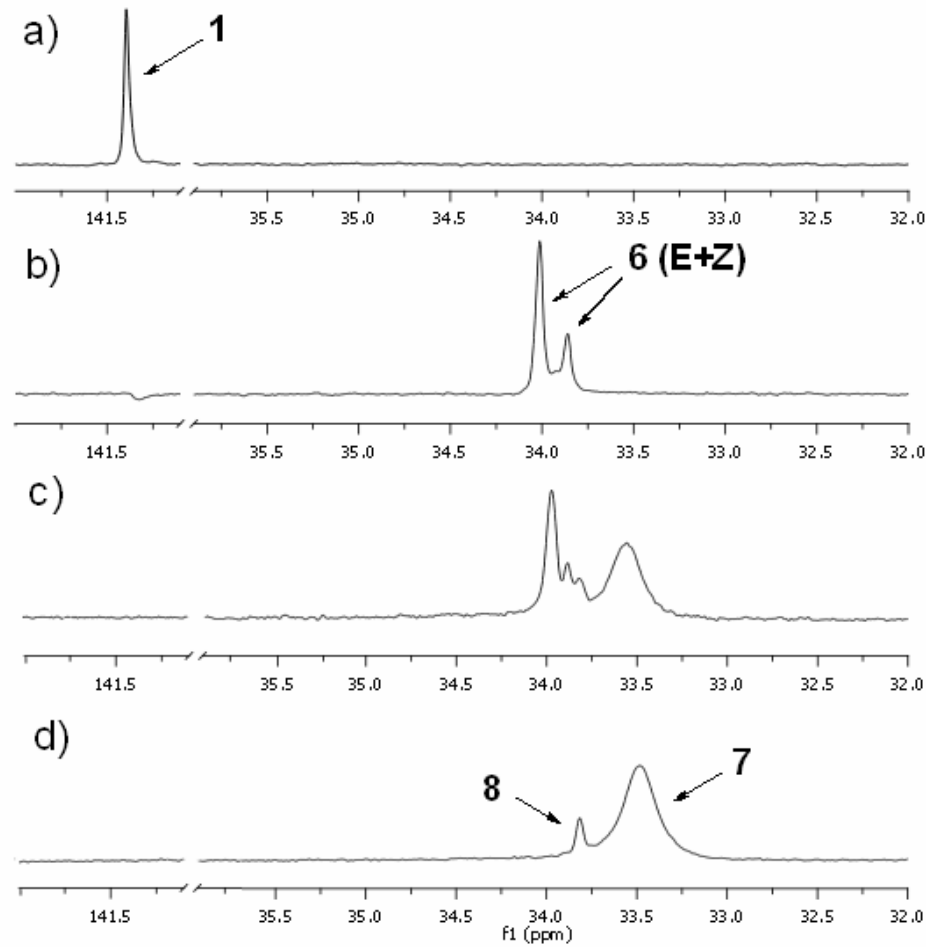
4k

4k. Viscous oil: ^{1}H NMR (200 MHz, d_6-DMSO) δ (rotamers) 7.48 – 6.57 (m, 15H, Ar), 5.80 – 5.43 (m, 1H, C*H*=CH$_2$), 5.15 – 4.20 (m, 7H, OC*H*$_2$Ph, CH=C*H*$_2$, NC*H*$_2$Ph, PC*H*CH$_2$Ph), 3.28 – 2.56 (m, 3H, C*H*$_2$Ph, PCH$_2$C*H*), 2.39 – 2.19 (m, 2H, C*H*$_2$CH=CH$_2$), 2.14 – 1.85 (m, 1H, PCH*H*), 1.83 – 1.45 (m, 1H, PC*H*H); ^{13}C NMR (50 MHz, d_6-DMSO) δ (rotamers) 175.2 (d, $^3J_{PC}$ = 8.9 Hz), 156.2 (d, $^3J_{PC}$ = 7.8 Hz), 138.8, 138.3, 137.8, 137.5, 136.4, 135.0, 130.2, 128.7, 128.4, 128.2, 127.9, 127.4, 127.2, 126.6, 126.3, 117.5, 66.8, 66.6, 57.0 (d, $^1J_{PC}$ = 105.0 Hz), 56.7 (d, $^1J_{PC}$ = 104.8 Hz), 47.6, 38.1, 37.4, 37.2, 37.0, 36.8, 31.6, 28.9 (d, $^1J_{PC}$ = 89.5 Hz), 28.4 (d, $^1J_{PC}$ = 89.5 Hz); ^{31}P NMR (81 MHz, d_6-DMSO) δ 45.4, 45.1, 44.7, 44.4 (rotamers); HPLC t_R = 31.8 min (br). ES-MS m/z: calcd for $[C_{29}H_{32}NO_6P - H]^-$ 520.2; found: 520.4; HRMS (m/z): [MH]+ calcd. for $C_{29}H_{32}NO_6P$, 522.2046 found, 522.2046.

4. General Procedure for the Three-Component Reaction between Phosphinic Acids, Acryloyl Chlorides and Allylic (or Propargylic) Alcohols.

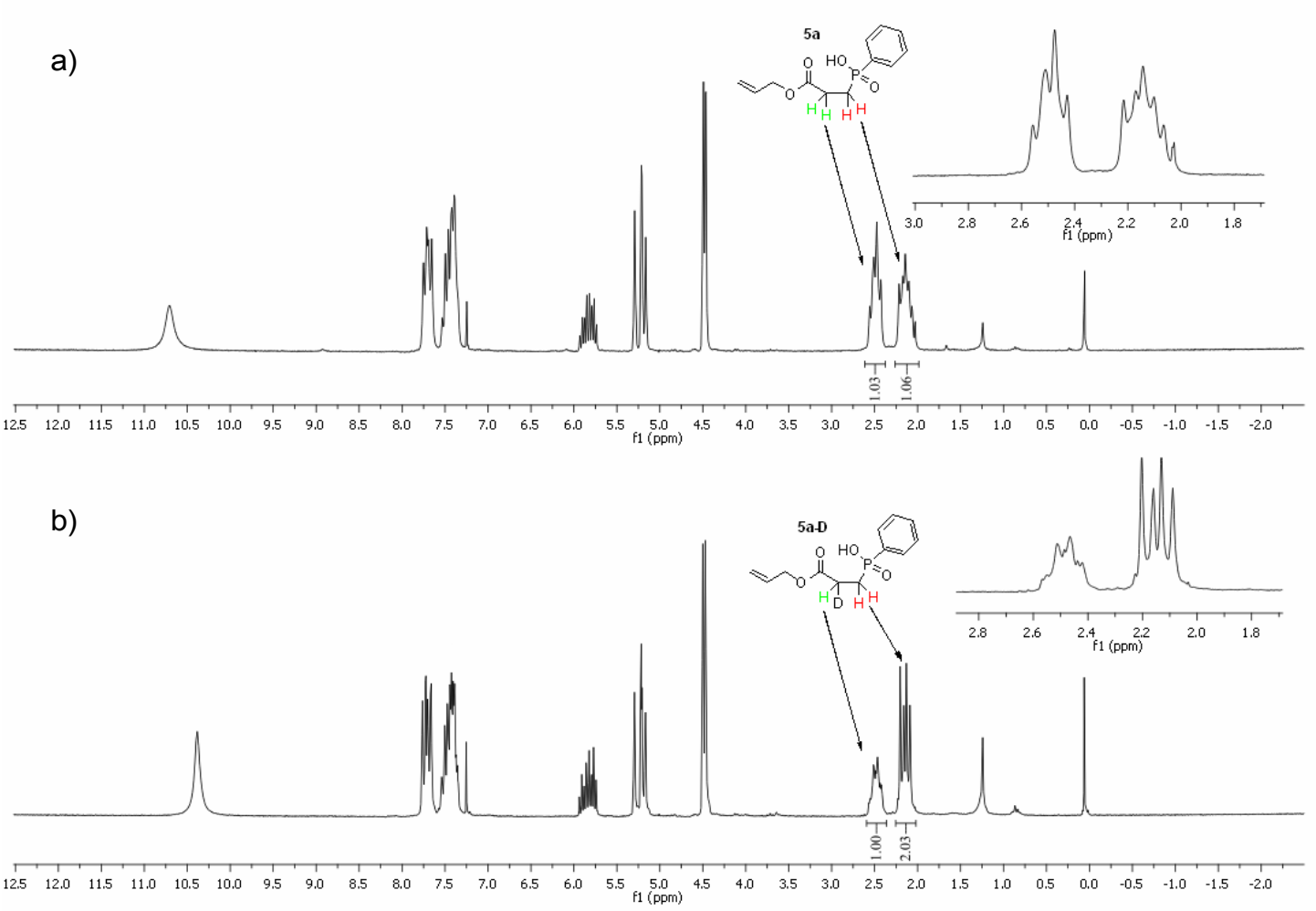
In a solution of the allylic (or propargylic) alcohol (1.4 eq) in dry CH_2Cl_2 (2 ml for 1 mmol scale) in a Schlenk flask, Hunig's base (10 eq) is added and the mixture is cooled at 0 ^oC under inert atmosphere. At this temperature, the corresponding acryloyl chloride (1.1 eq) is added dropwise and the mixture is stirred for 1 h at rt. Then, a solution of phosphinic acid (1.0 eq) and Hunig's base (2.0 eq) in dry CH_2Cl_2 (1 ml for 1 mmol scale) was added and the final mixture was degassed by applying three freeze-pump-thaw cycles. The degassed mixture was cooled to -78 ^oC and purged with Ar for 15 min. Then, precooled at -78 ^oC freshly distilled TMSCl (11.0 eq) was added to the reaction vessel at once. The temperature was slowly raised to 25 ^oC and the clear solution was stirred overnight at room temperature. After the end of the reaction, the mixture was cooled to 0^oC, abs. EtOH (2 ml for 1 mmol scale) was added dropwise and stirring at room temperature for 30 min followed. Isolation of the final products was performed according to the two-component procedure described above (paragraph 3). The isolated products were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy and the spectra were in all cases identical to those obtained from the corresponding products prepared by the two-component protocol.

5. Monitoring of the reaction between 2a and 3a by ^{31}P NMR spectroscopy.

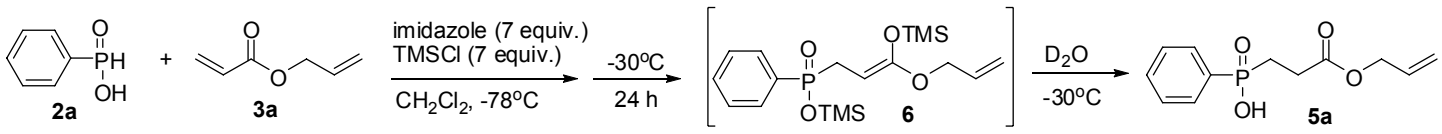


Reaction conditions: **3a** (1.1 equiv), *i*Pr_2EtN (7 equiv), **2a**, $CDCl_3$, then TMSCl (7 equiv) at -78°C, warm to -30°C. (a) initialization of the reaction at -30°C; (b) after 48h at -30°C; (c) 30 min after warming the reaction at 25°C; (d) after 5h at 25°C.

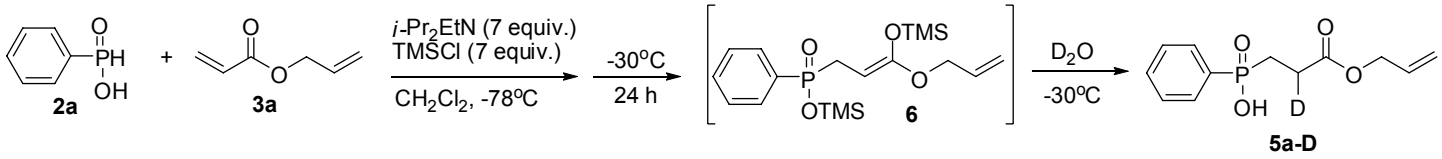
6. Comparison of ^{1}H NMR spectra of products 5a and 5a-D obtained from labelling experiments.



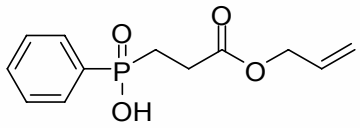
a) ^{1}H NMR spectrum of the product obtained from the following procedure (base: imidazole)



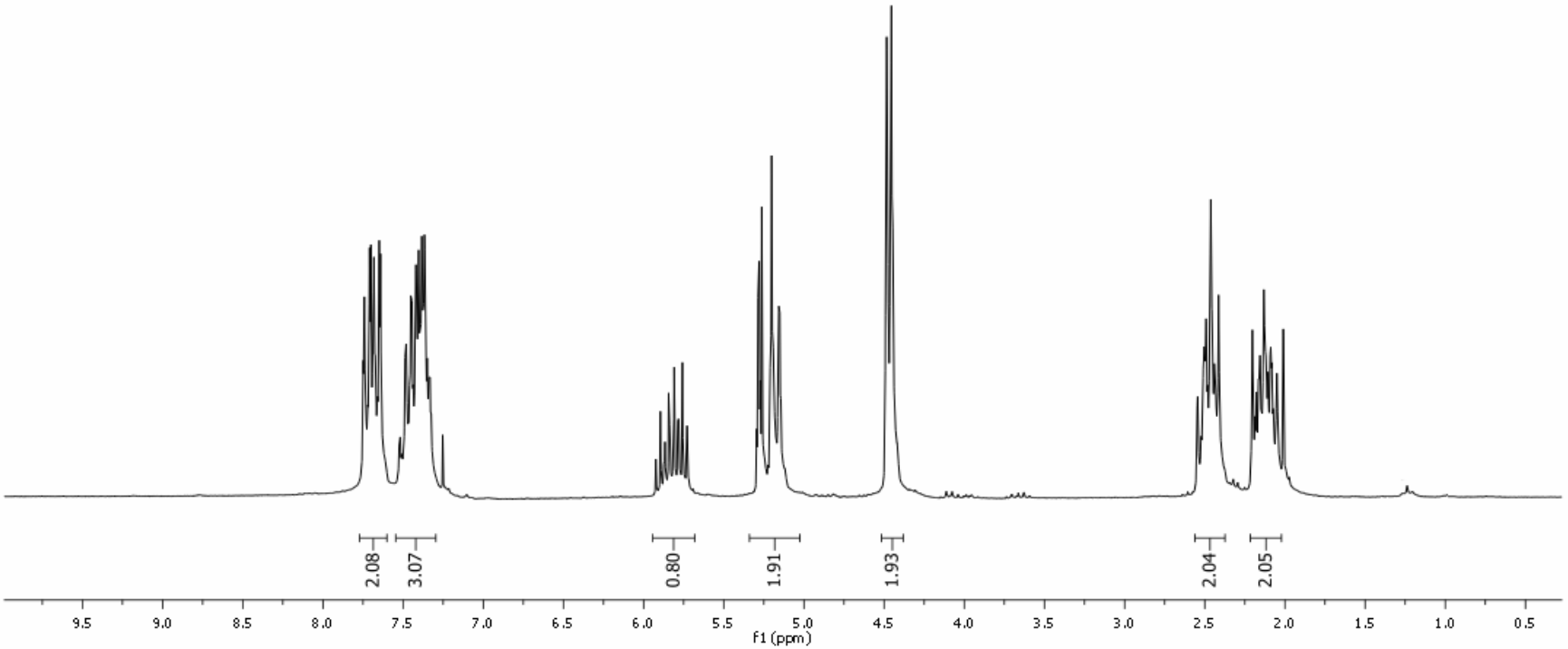
b) ^{1}H NMR spectrum of the product obtained from the following procedure (base: Hunig's base)



Copies of NMR spectra of compounds **4a**-**k** and **5a**


O
O
P
OH
O

5a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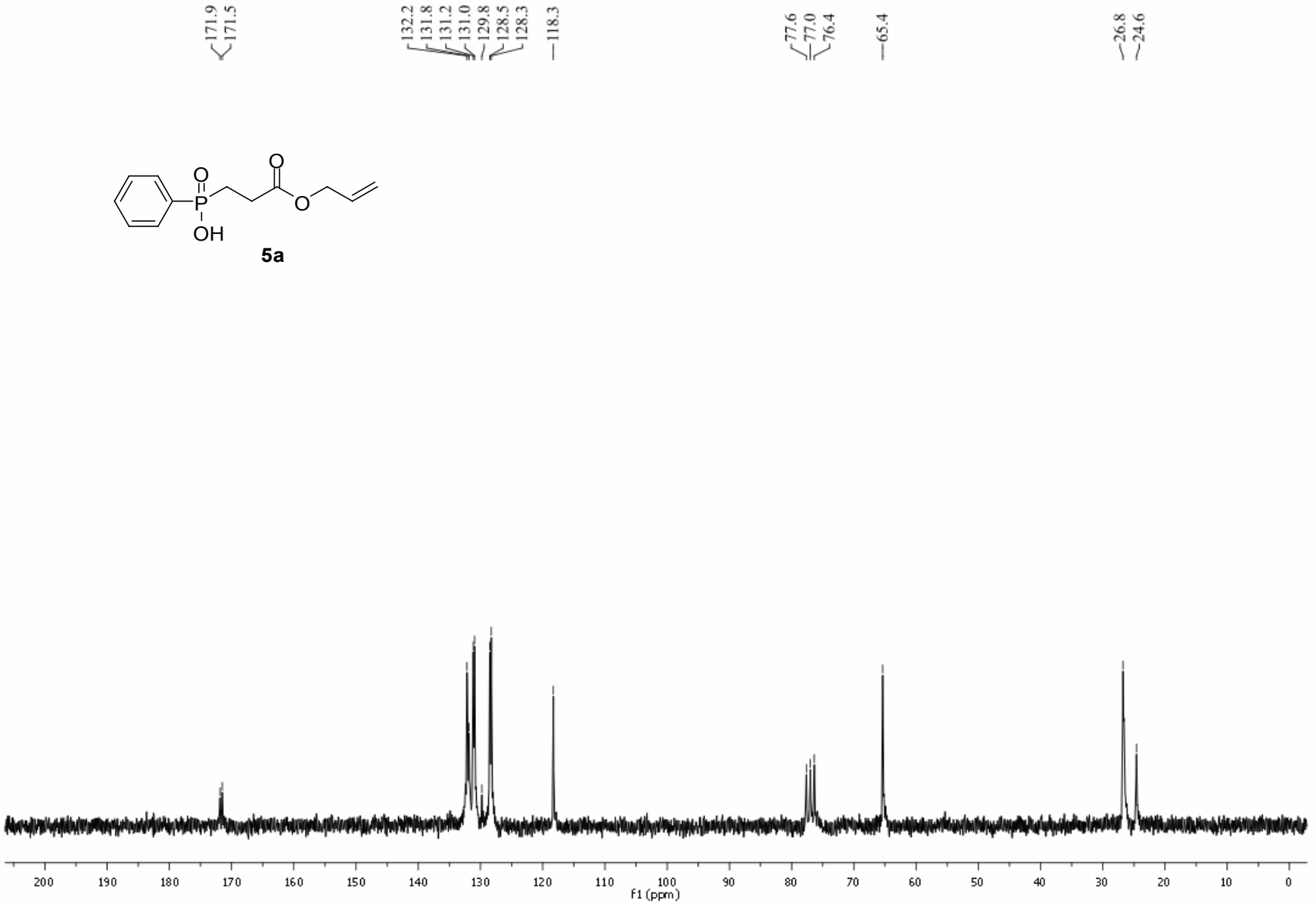
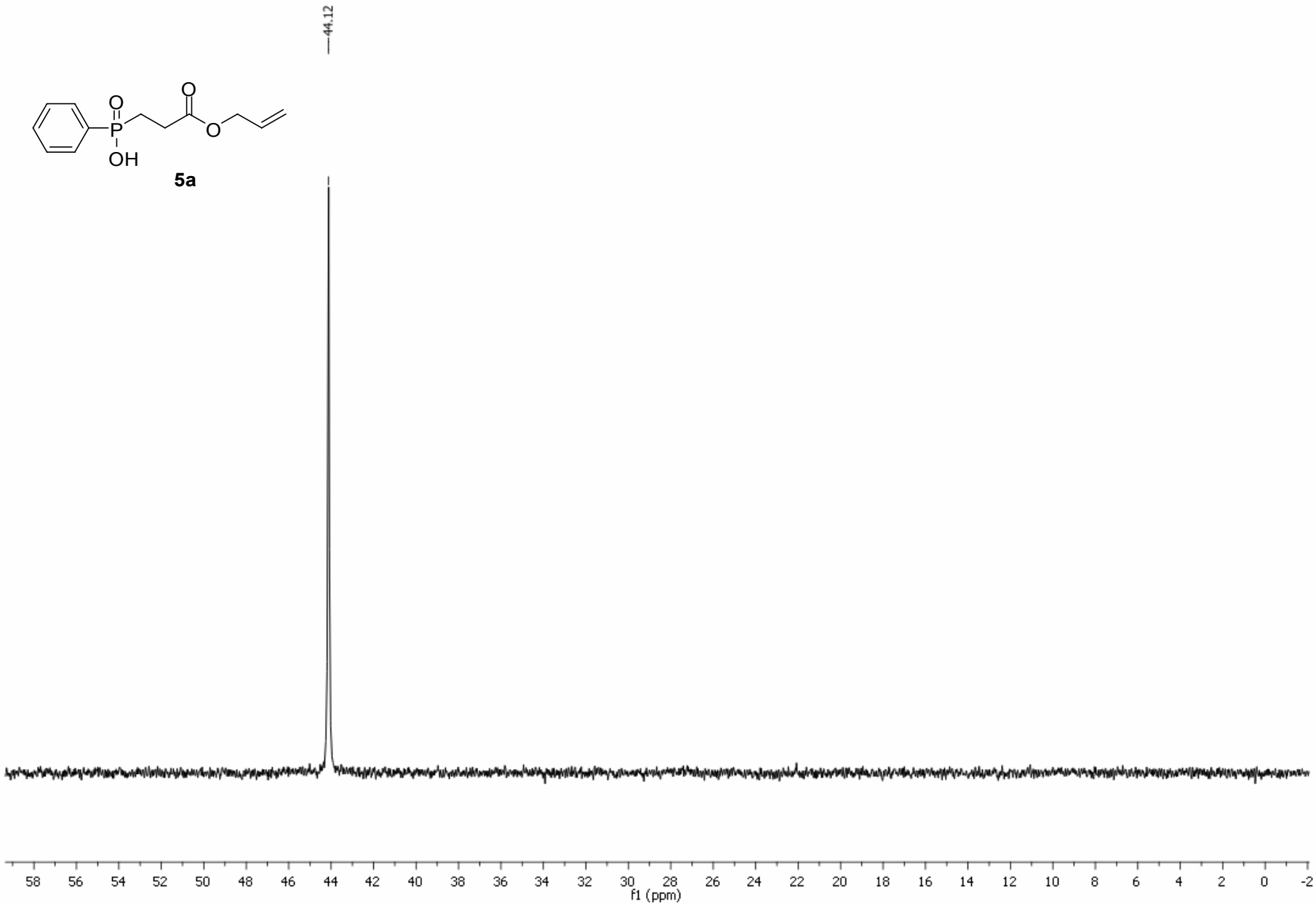
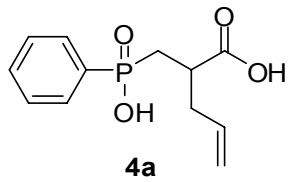
3.07
0.80
1.91
1.93
2.04
2.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


171.9
171.5
132.2
131.8
131.2
131.0
129.8
128.5
128.3
118.3
77.6
77.0
76.4
65.4
26.8
24.6
O
O
P
OH
O
f1 (ppm)

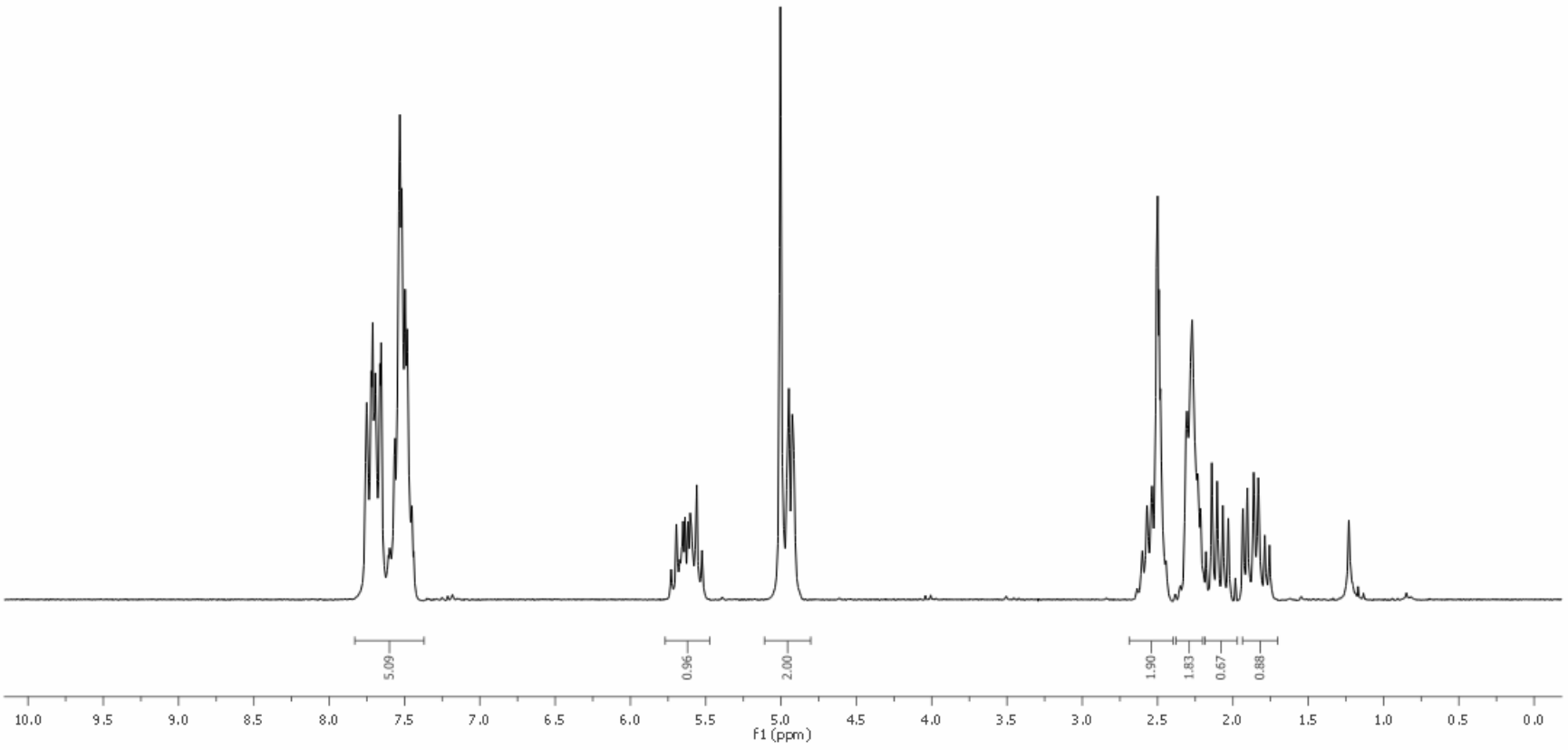
5a


44.12
O
O
P
OH
O
58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2
f1 (ppm)

5a


O
O
P
OH
OH

4a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1.83
0.67
0.88
10.0
9.5
9.0
8.5
8.0
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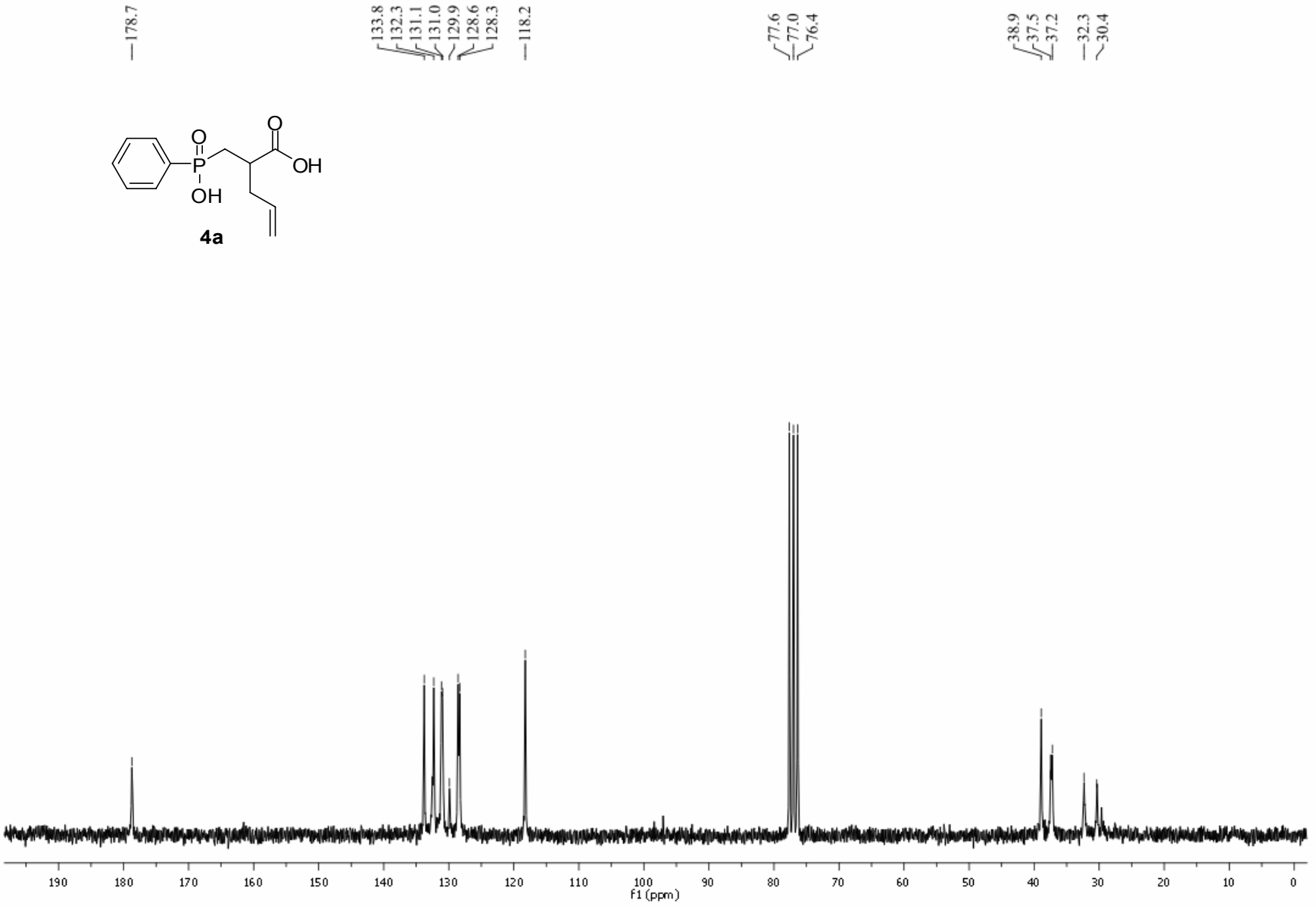
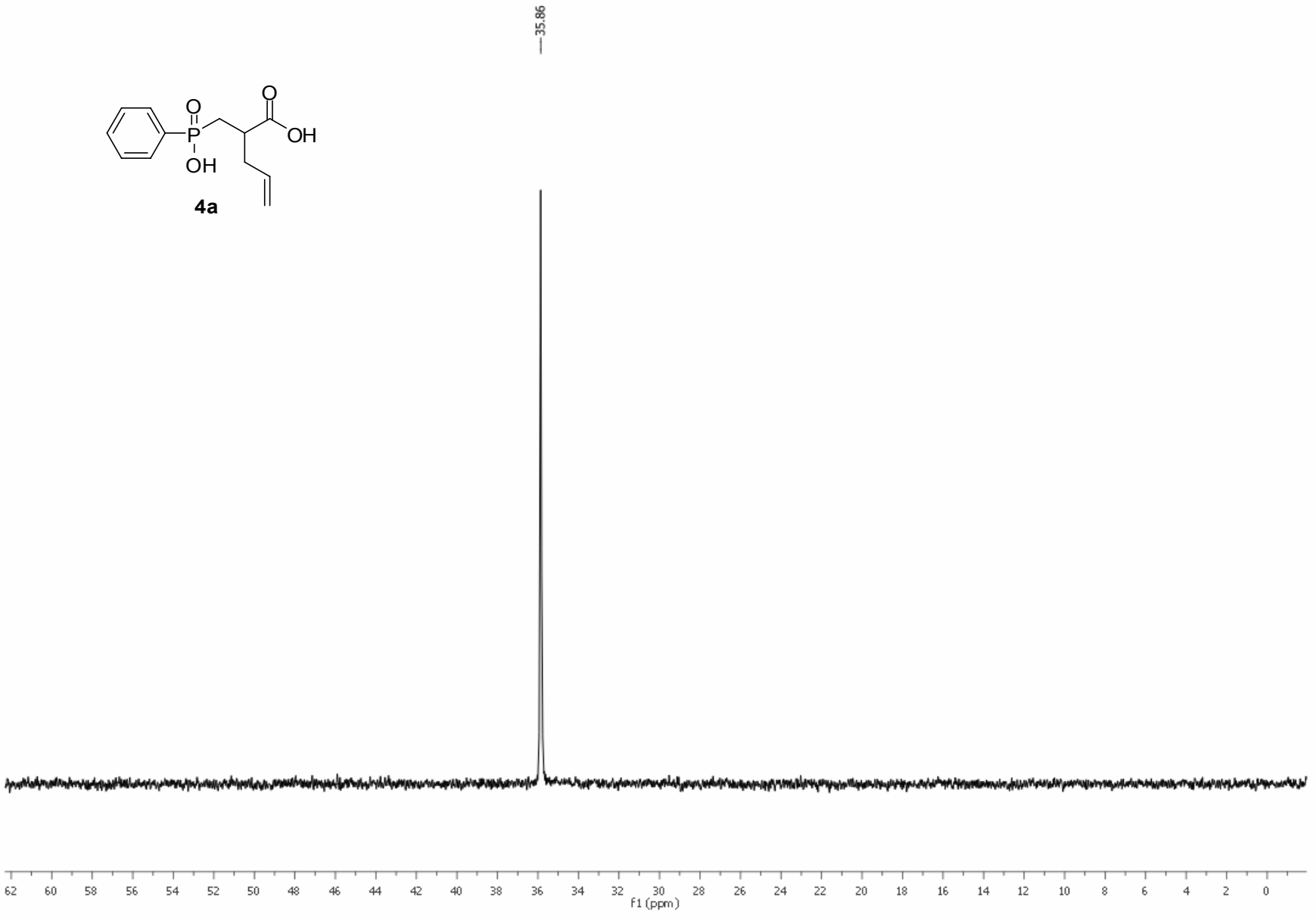
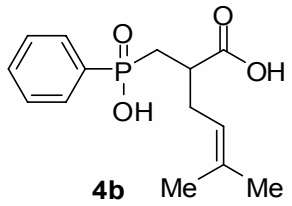
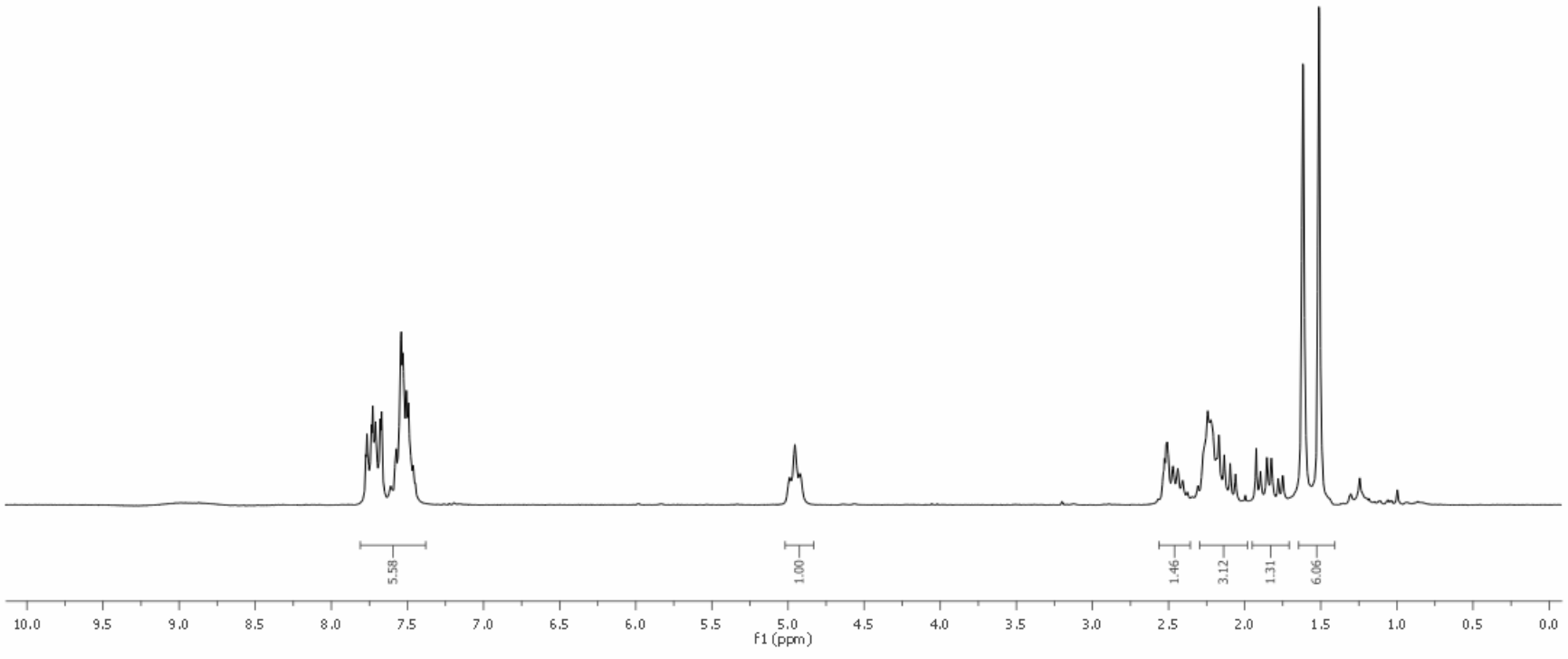
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.7
133.8
132.3
131.1
131.0
129.9
128.6
128.3
118.2
77.6
77.0
76.4
38.9
37.5
37.2
32.3
30.4
O
P
OH
O
OH
4a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


35.86
O
P
OH
OH
O
4a
62 60 58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0
f1 (ppm)


O
O
P
OH
OH
Me
Me

4b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1.00
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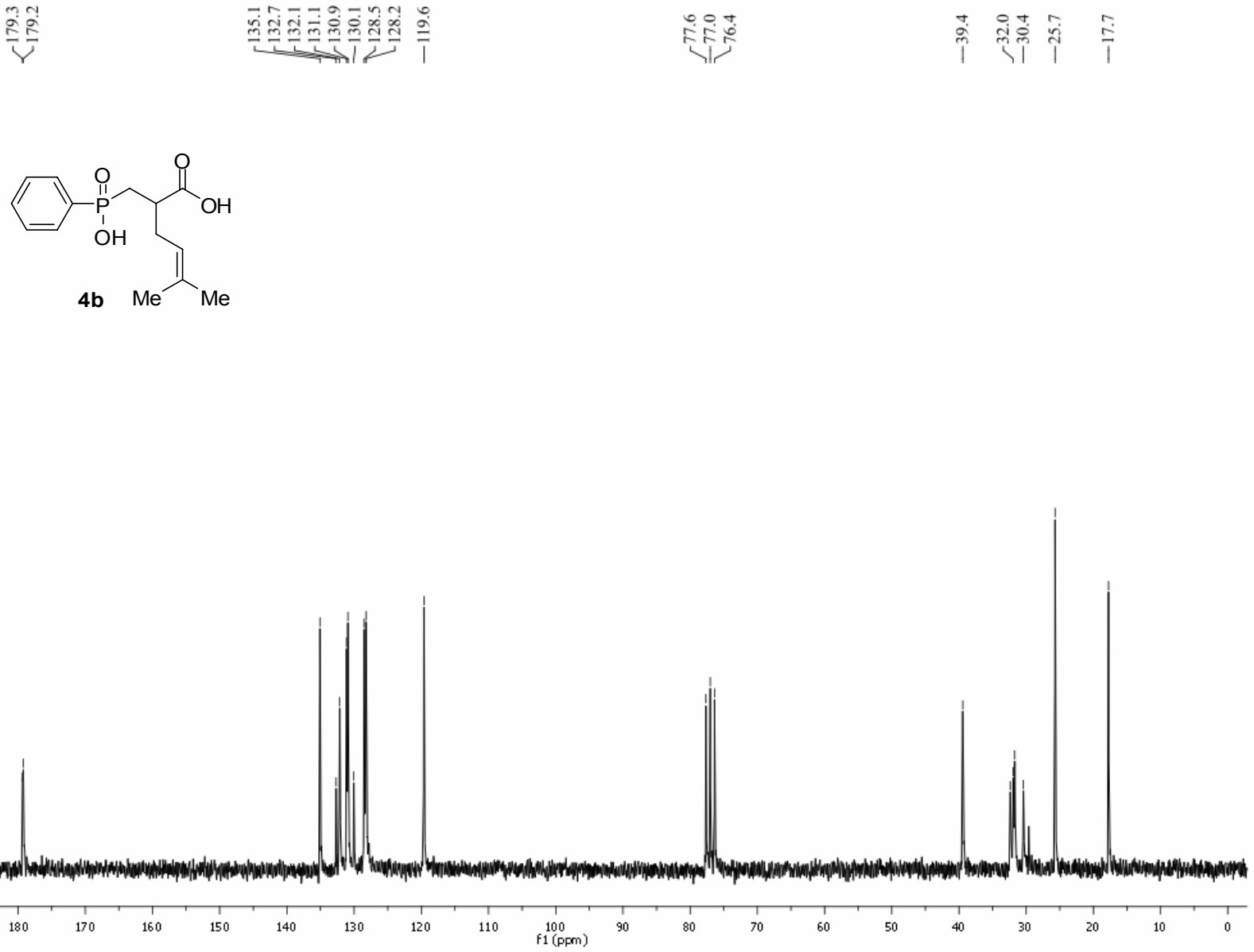
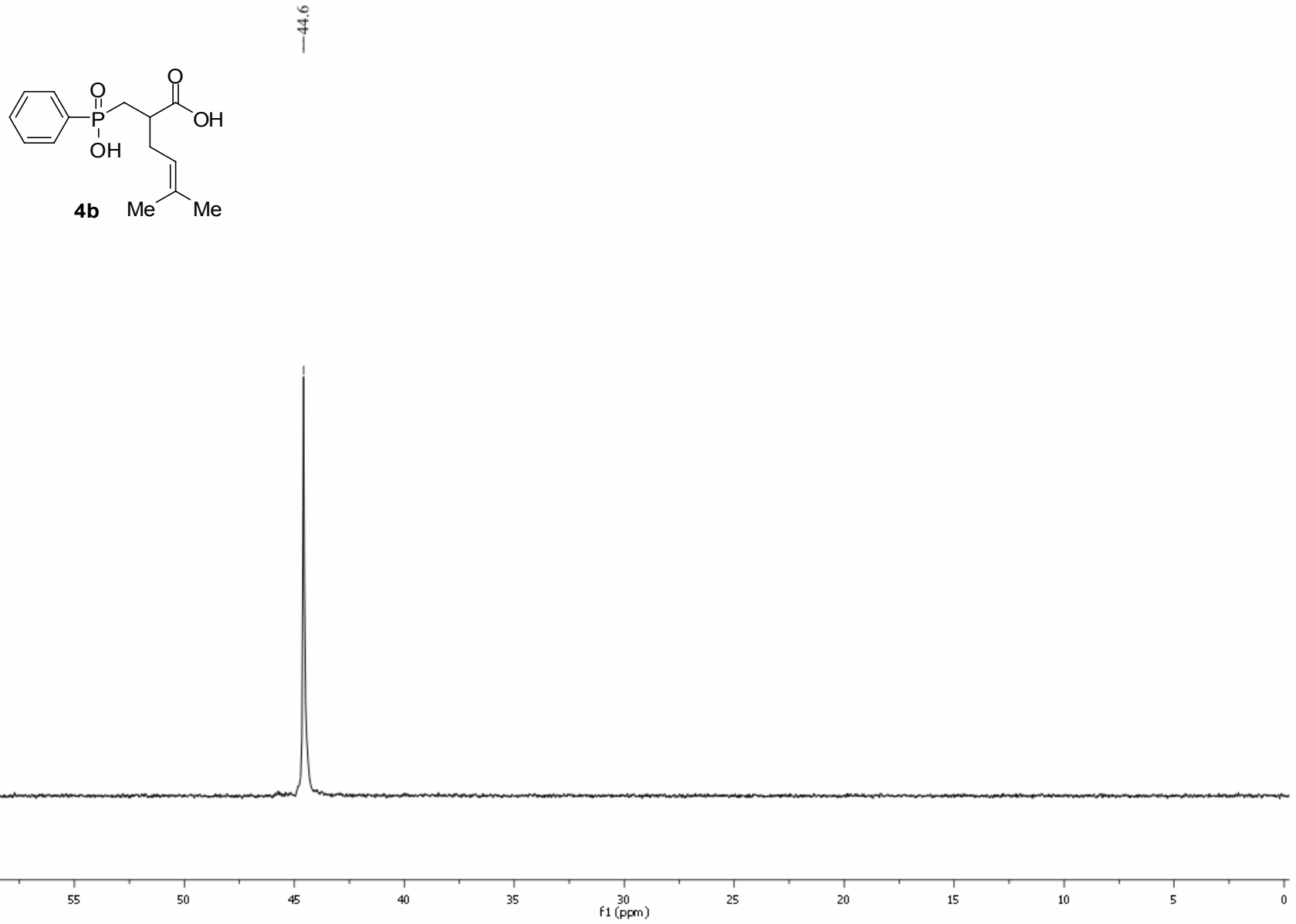
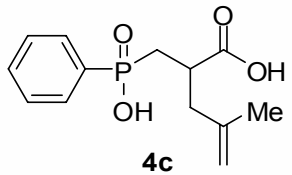
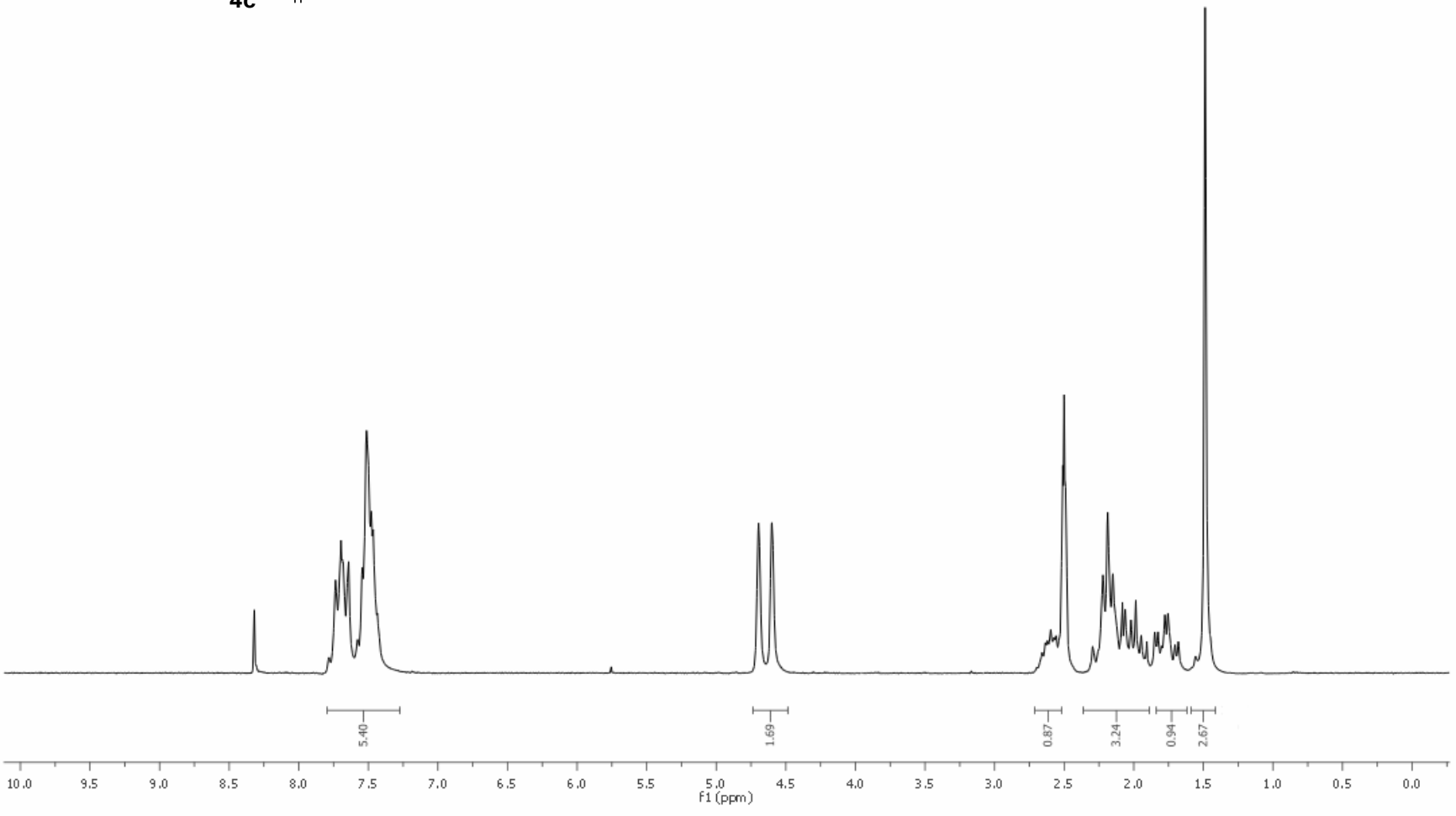
3.12
1.31
6.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


179.3
179.2
135.1
132.7
132.1
131.1
130.9
130.1
128.5
128.2
119.6
77.6
77.0
76.4
39.4
32.0
30.4
25.7
17.7
O
O
P
OH
OH
4b
Me
Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


44.6
O
O
P
OH
OH
4b
Me
Me
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)


O
O
P
OH
OH
Me

4c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0.94
2.67
10.0
9.5
9.0
8.5
8.0
7.5
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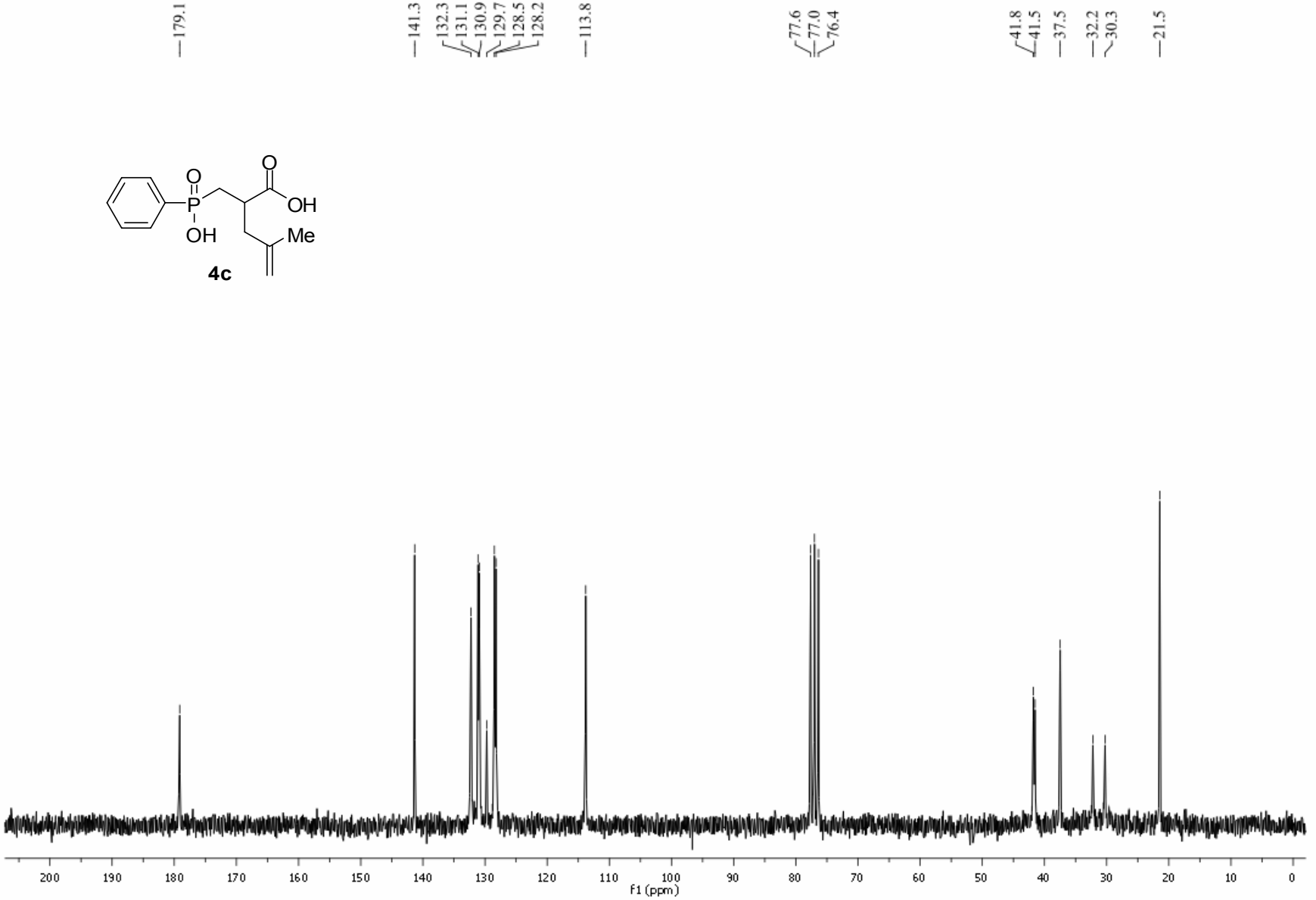
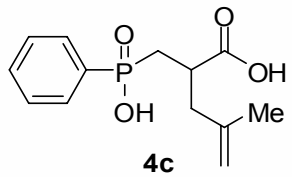
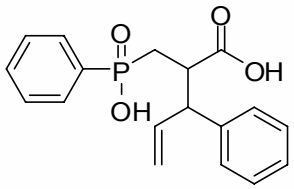
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

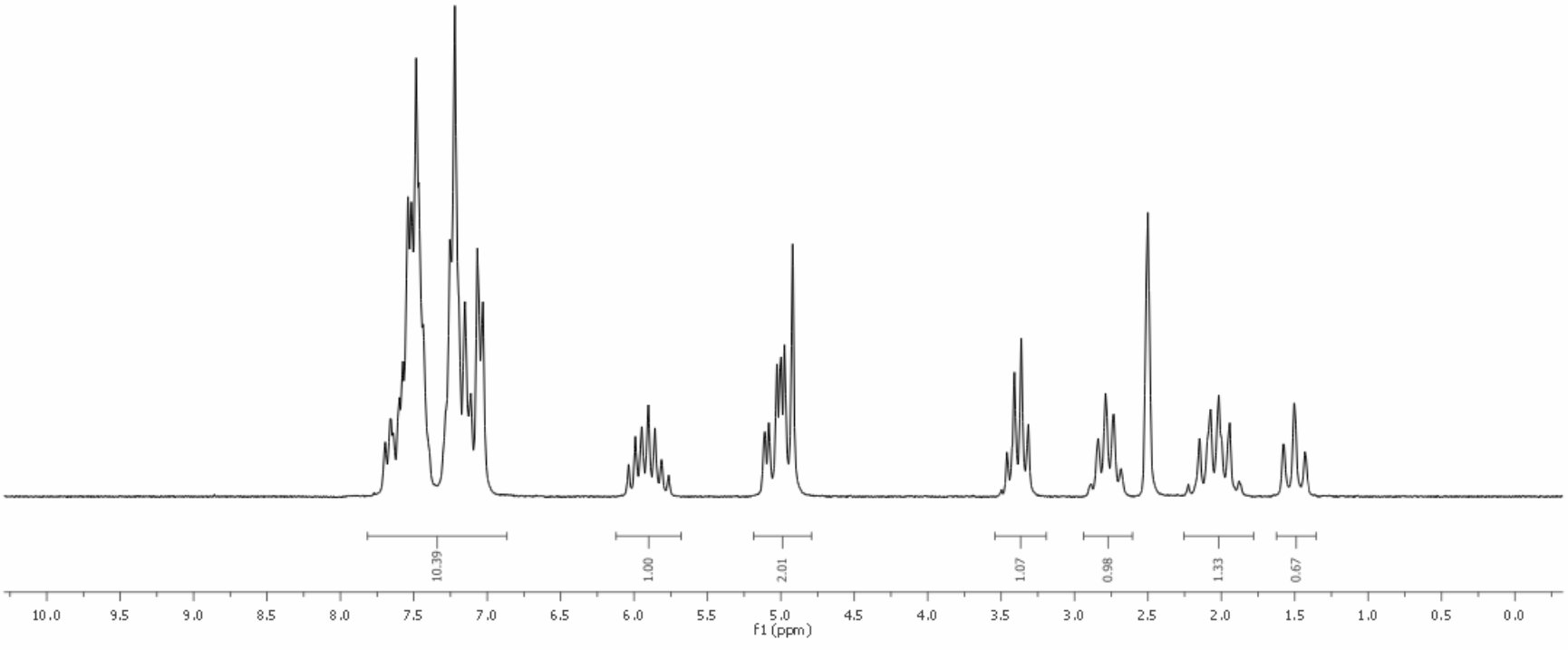

179.1
141.3
132.3
131.1
130.9
129.7
128.5
128.2
113.8
77.6
77.0
76.4
41.8
41.5
37.5
32.2
30.3
21.5
O
P
OH
OH
O
OH
Me
4c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



4c


O
O
P
OH
OH

4d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1.07
0.98
1.33
0.67
10.0
9.5
9.0
8.5
8.0
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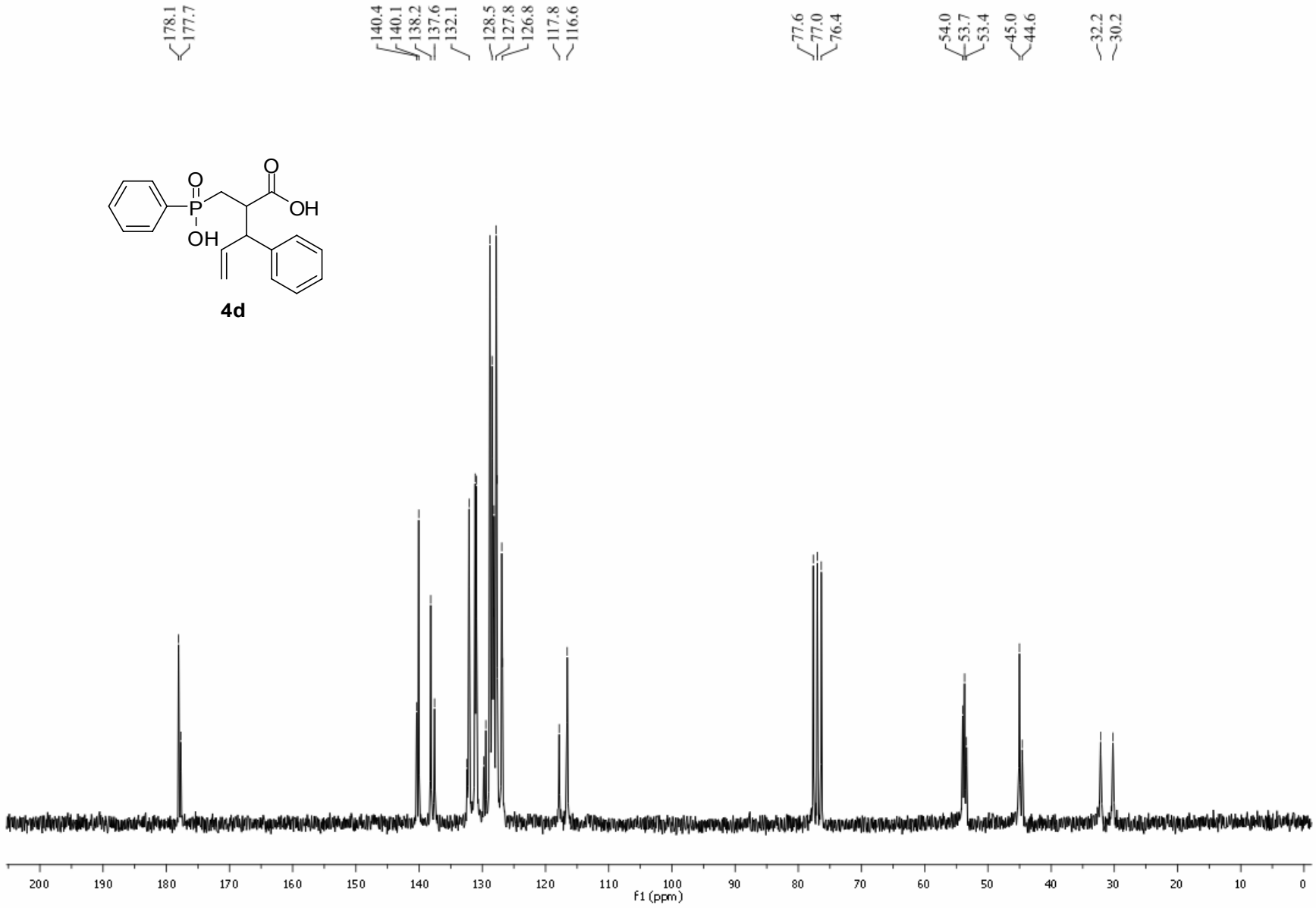
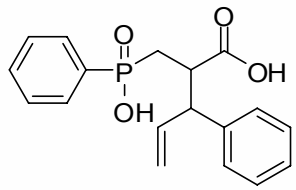
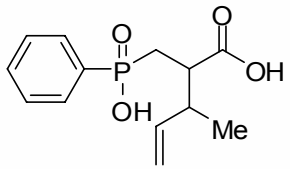
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.1
177.7
140.4
140.1
138.2
137.6
132.1
128.5
127.8
126.8
117.8
116.6
77.6
77.0
76.4
54.0
53.7
53.4
45.0
44.6
32.2
30.2
O
O
P
OH
OH
4d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

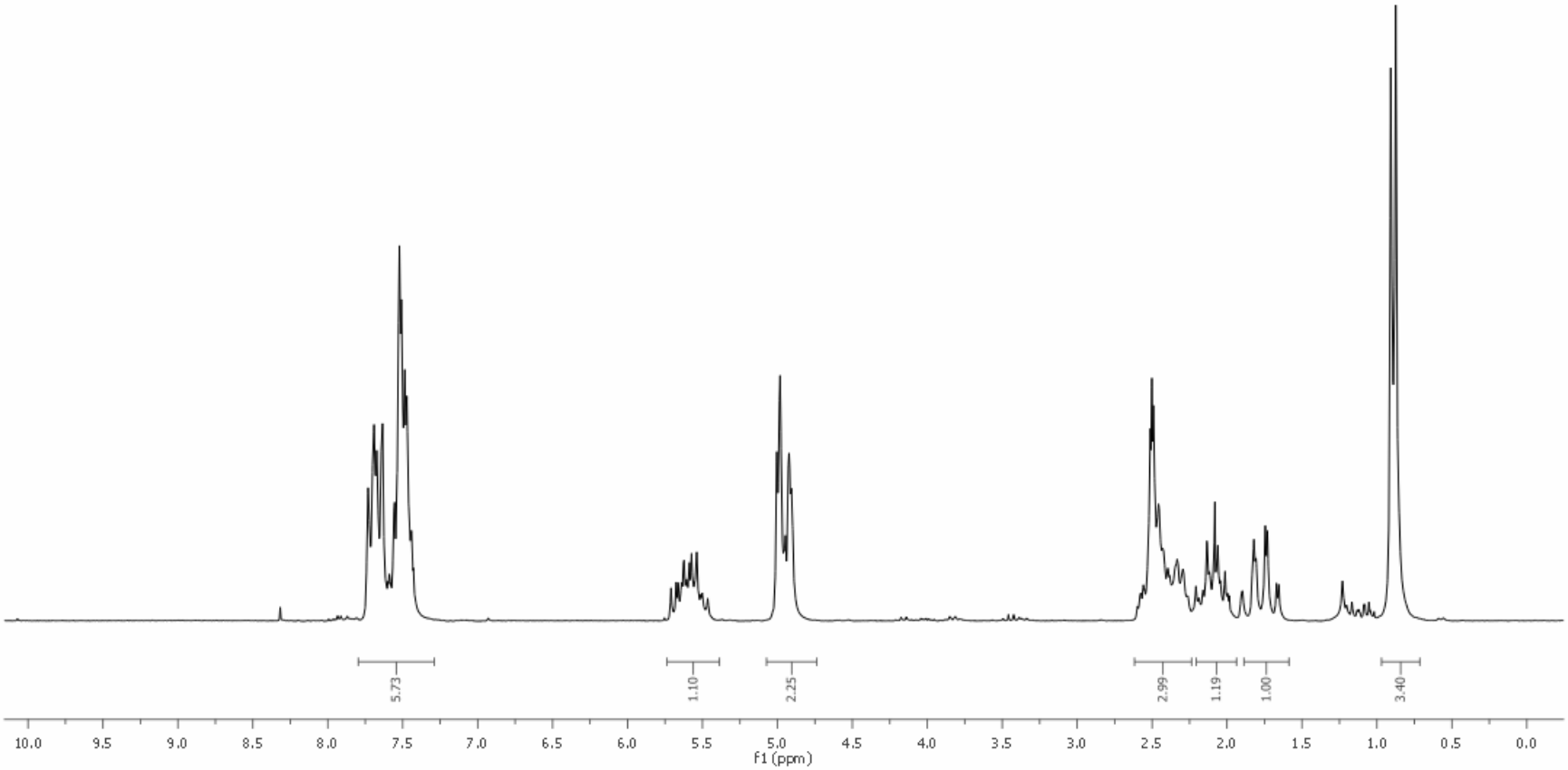

O
O
P
OH
OH

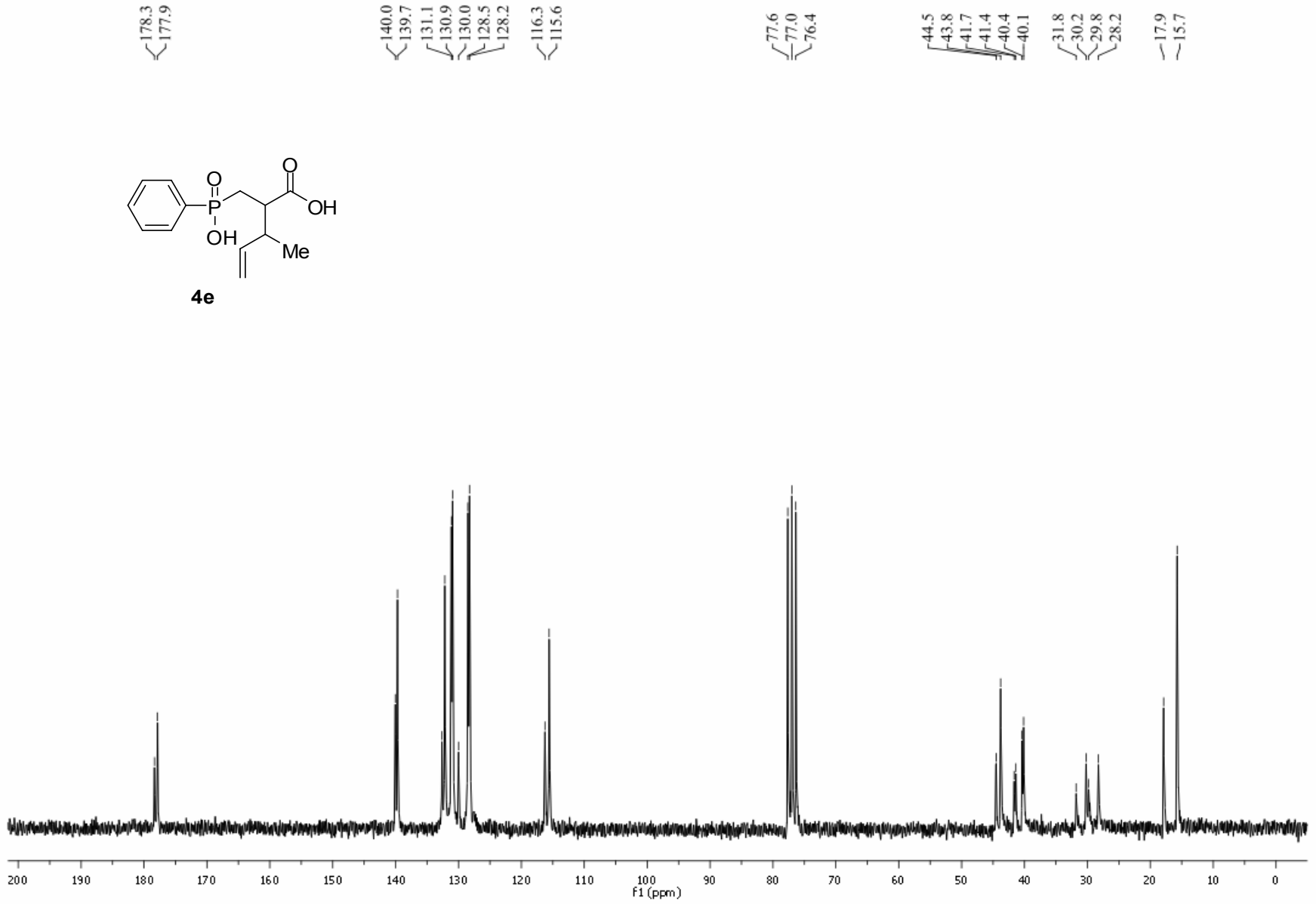
4d

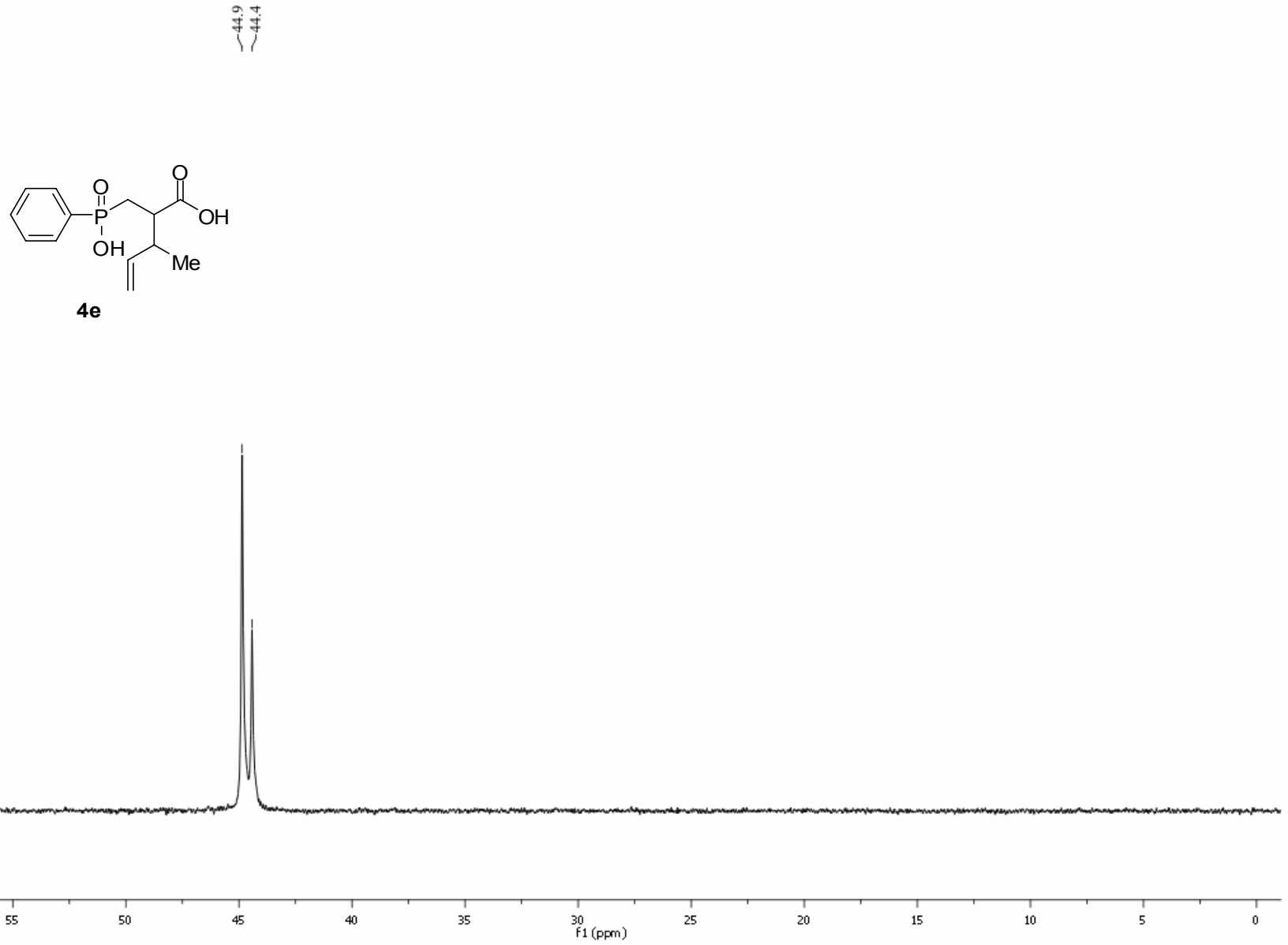
43.5
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
f1 (ppm)


O
O
OH
P
OH
Me

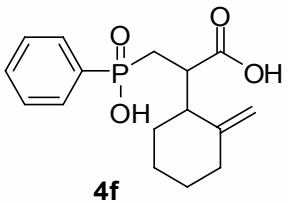
4e


5.73
1.10
2.25
2.99
1.19
1.00
3.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

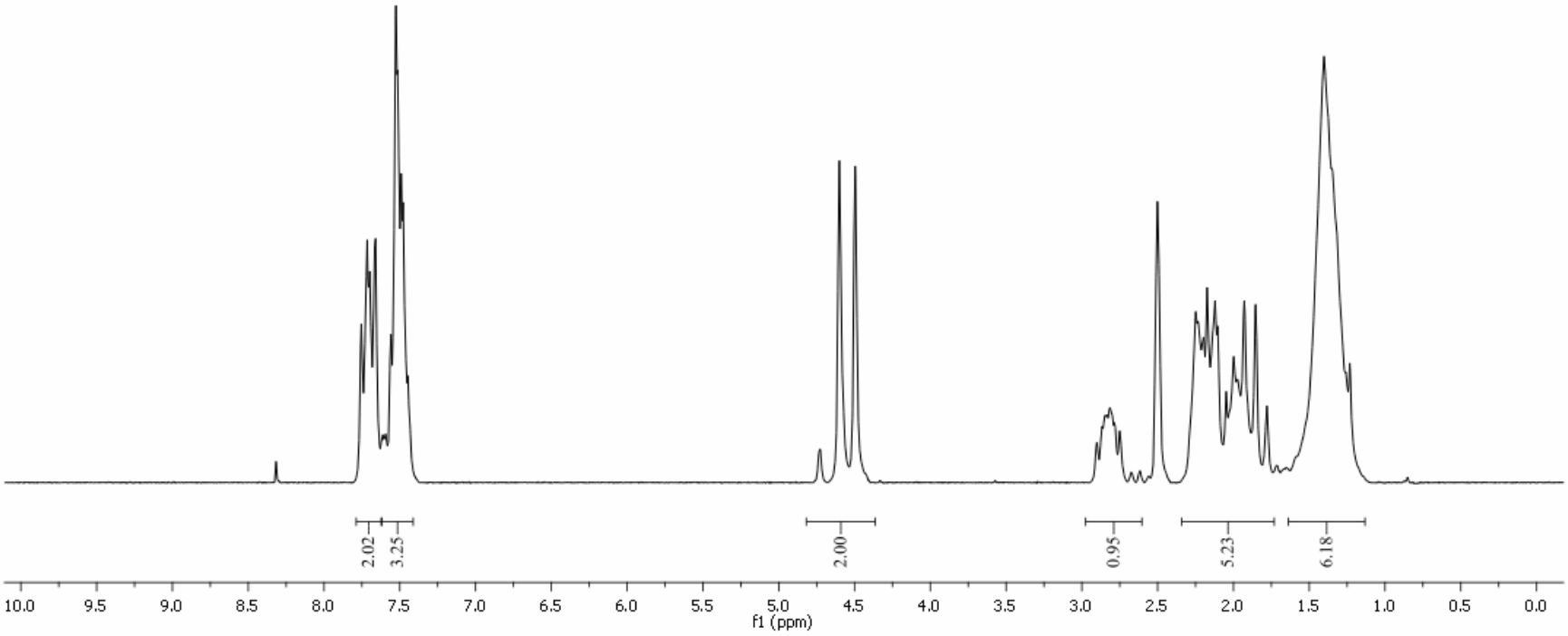

178.3
177.9
140.0
139.7
131.1
130.9
130.0
128.5
128.2
116.3
115.6
77.6
77.0
76.4
44.5
43.8
41.7
41.4
40.4
40.1
31.8
30.2
29.8
28.2
17.9
15.7
O
O
OH
P
OH
Me
4e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

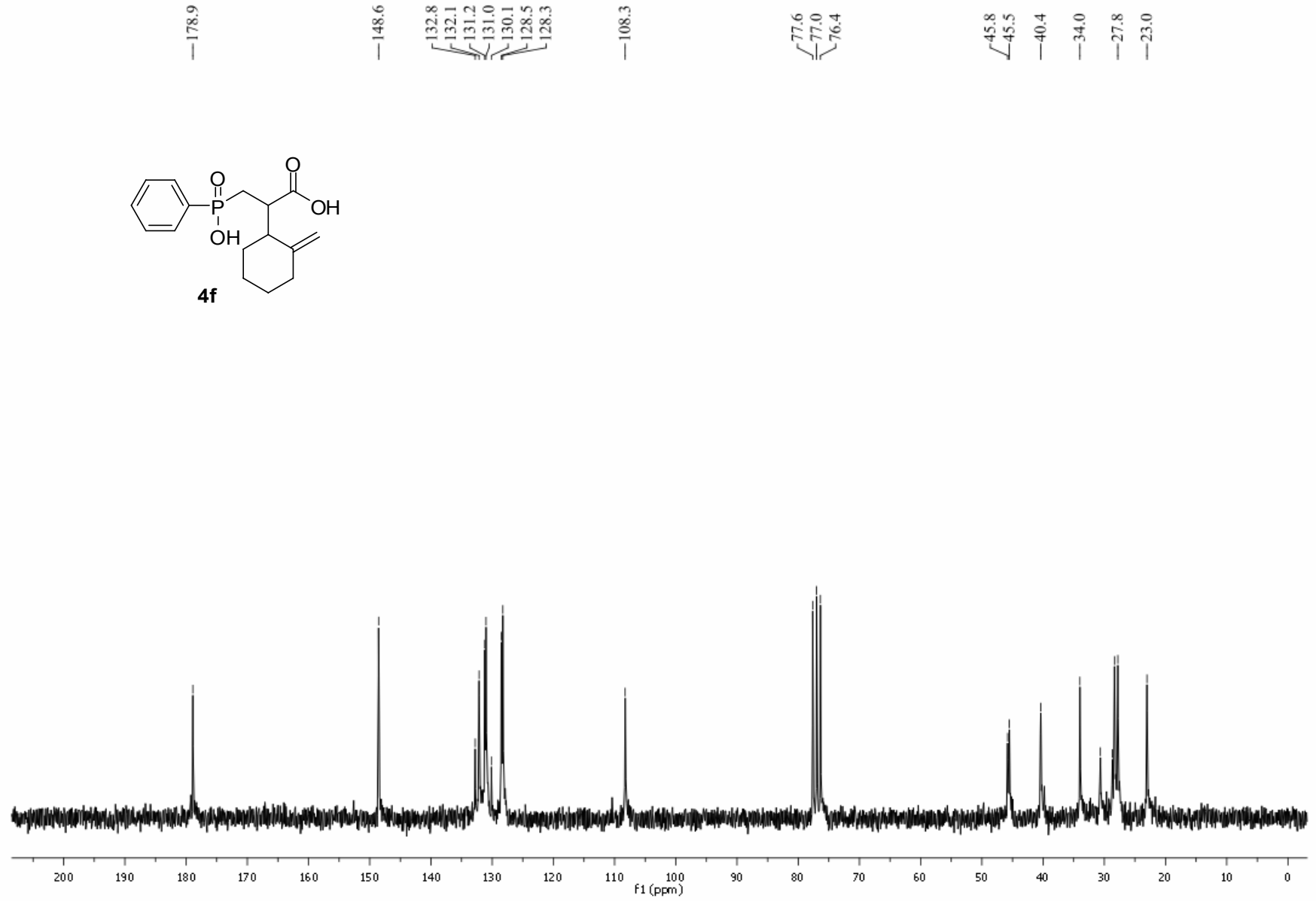


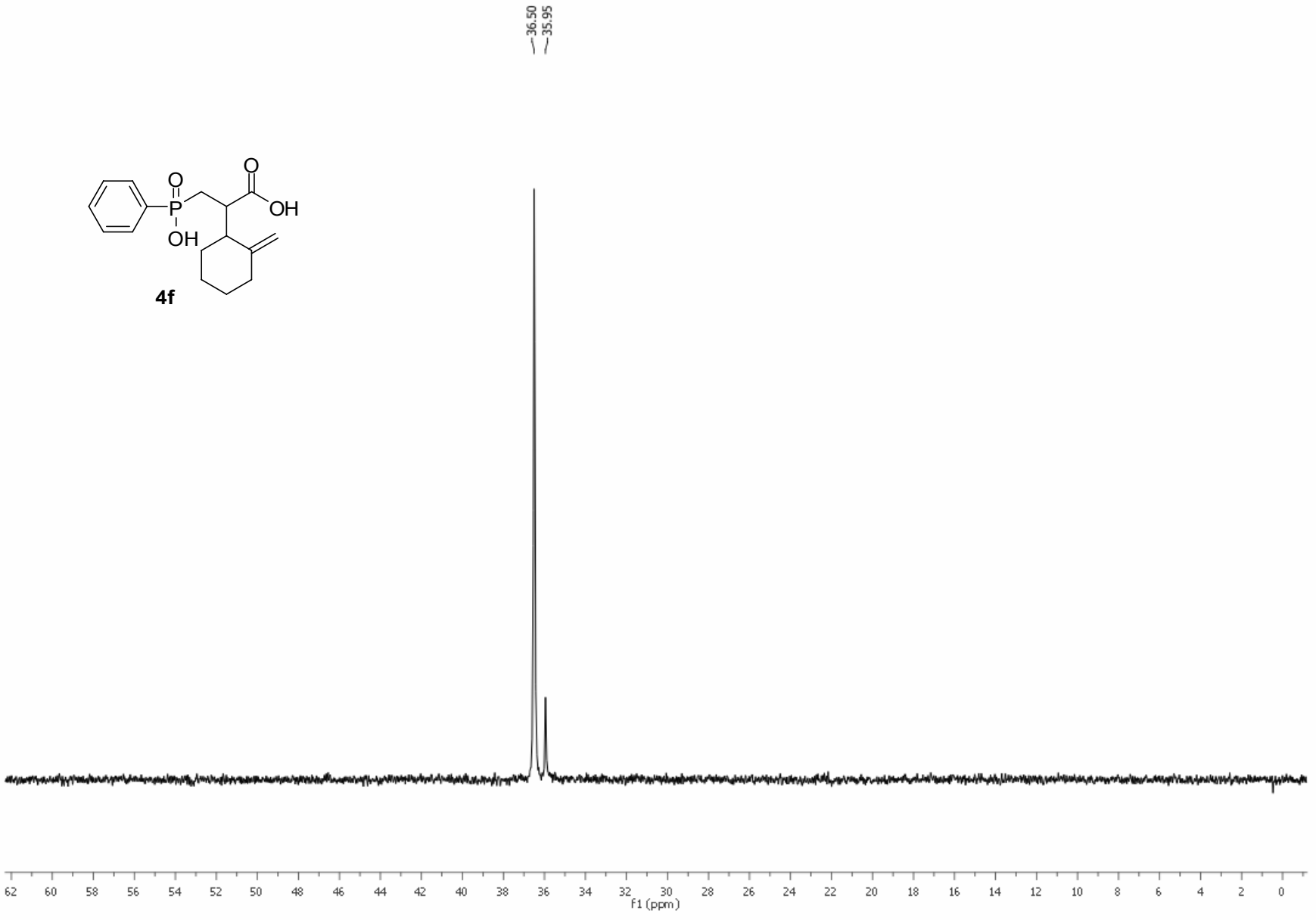
4e

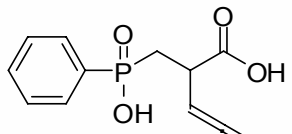

O
O
OH
P
OH

4f

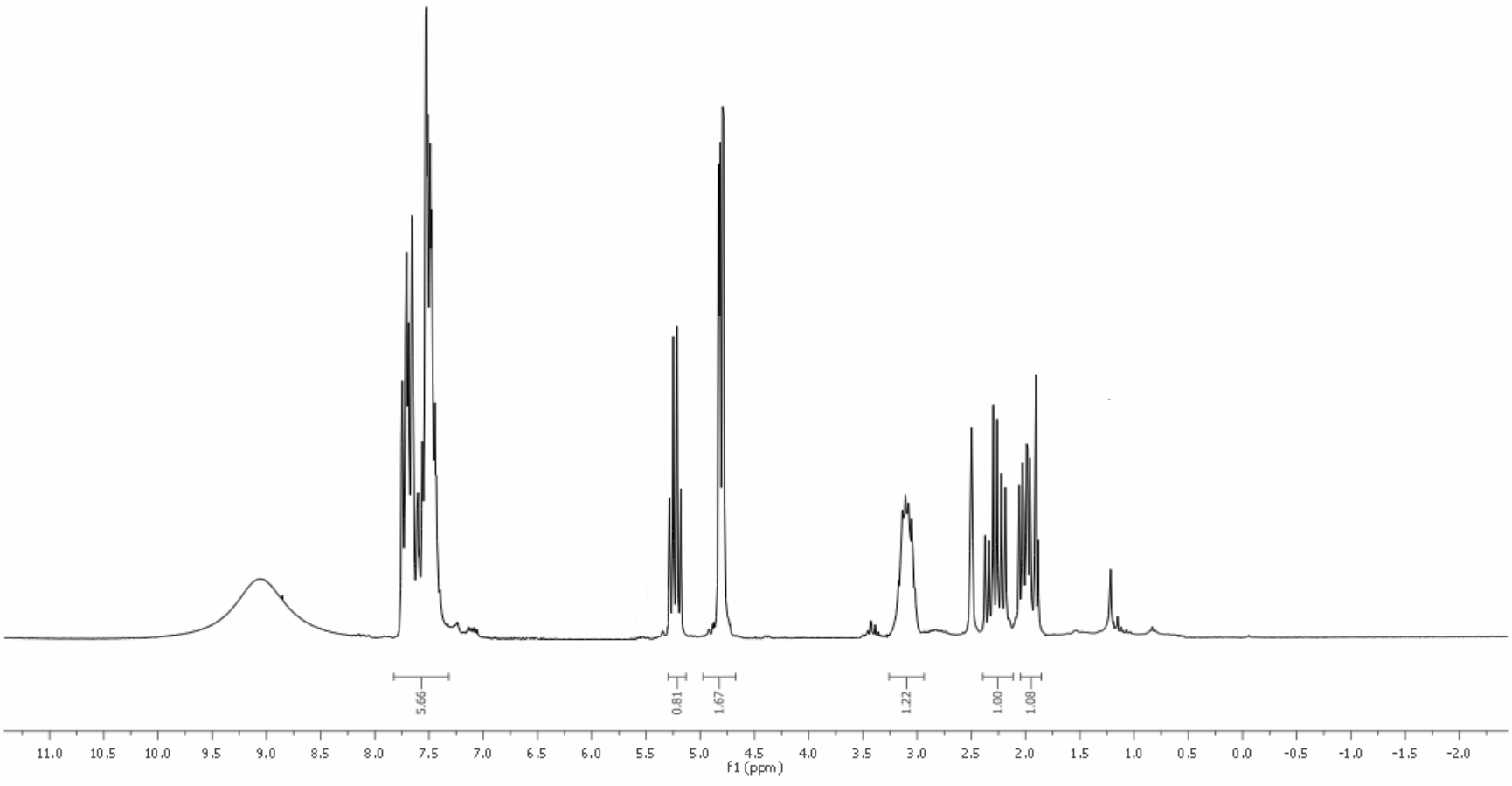

2.02
3.25
2.00
0.95
5.23
6.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

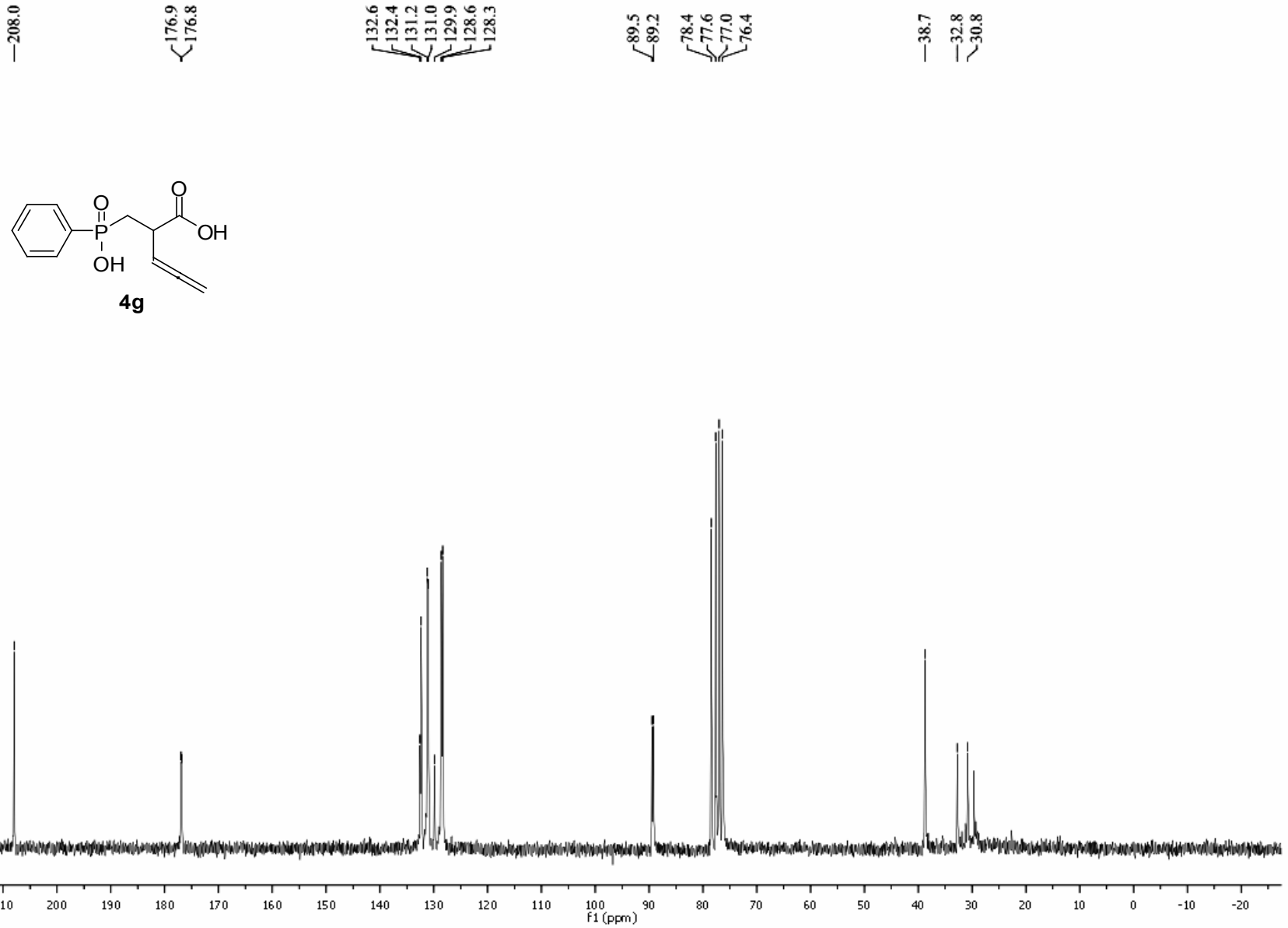

178.9
148.6
132.8
132.1
131.2
131.0
130.1
128.5
128.3
108.3
77.6
77.0
76.4
45.8
45.5
40.4
34.0
27.8
23.0
O
O
OH
P
OH
4f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

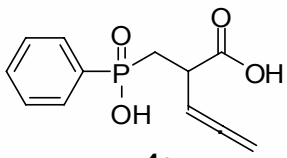

36.50
35.95
O
OH
O
P
OH
4f
62 60 58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0
f1 (ppm)


O
O
P
OH
OH

4g

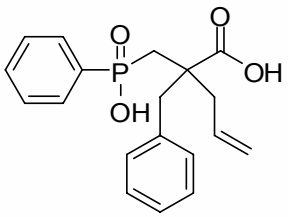

5.66
0.81
1.67
1.22
1.00
1.08
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)


208.0
176.9
176.8
132.6
132.4
131.2
131.0
129.9
128.6
128.3
89.5
89.2
78.4
77.6
77.0
76.4
38.7
32.8
30.8
O
O
P
OH
OH
4g
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

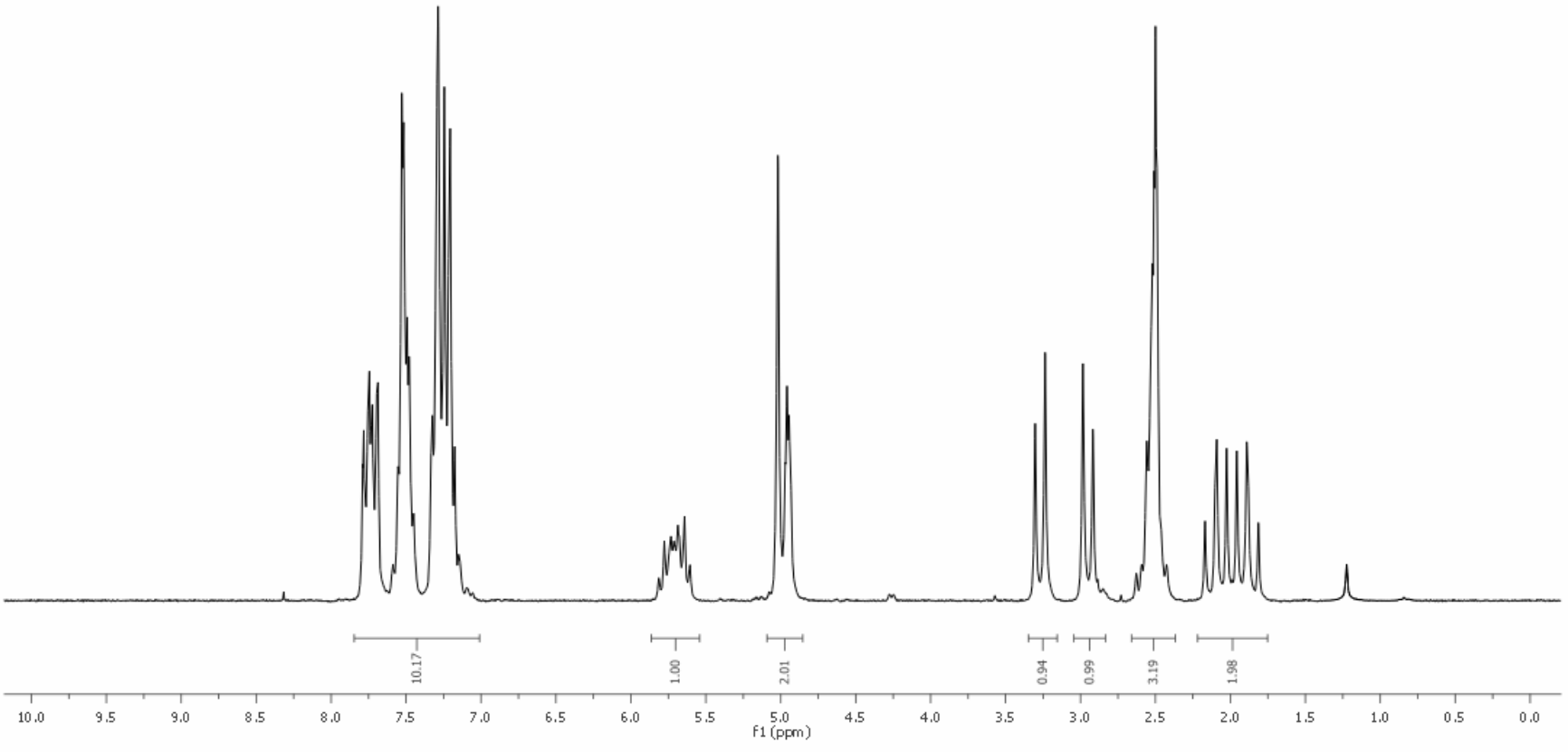

O
P
OH
O
OH

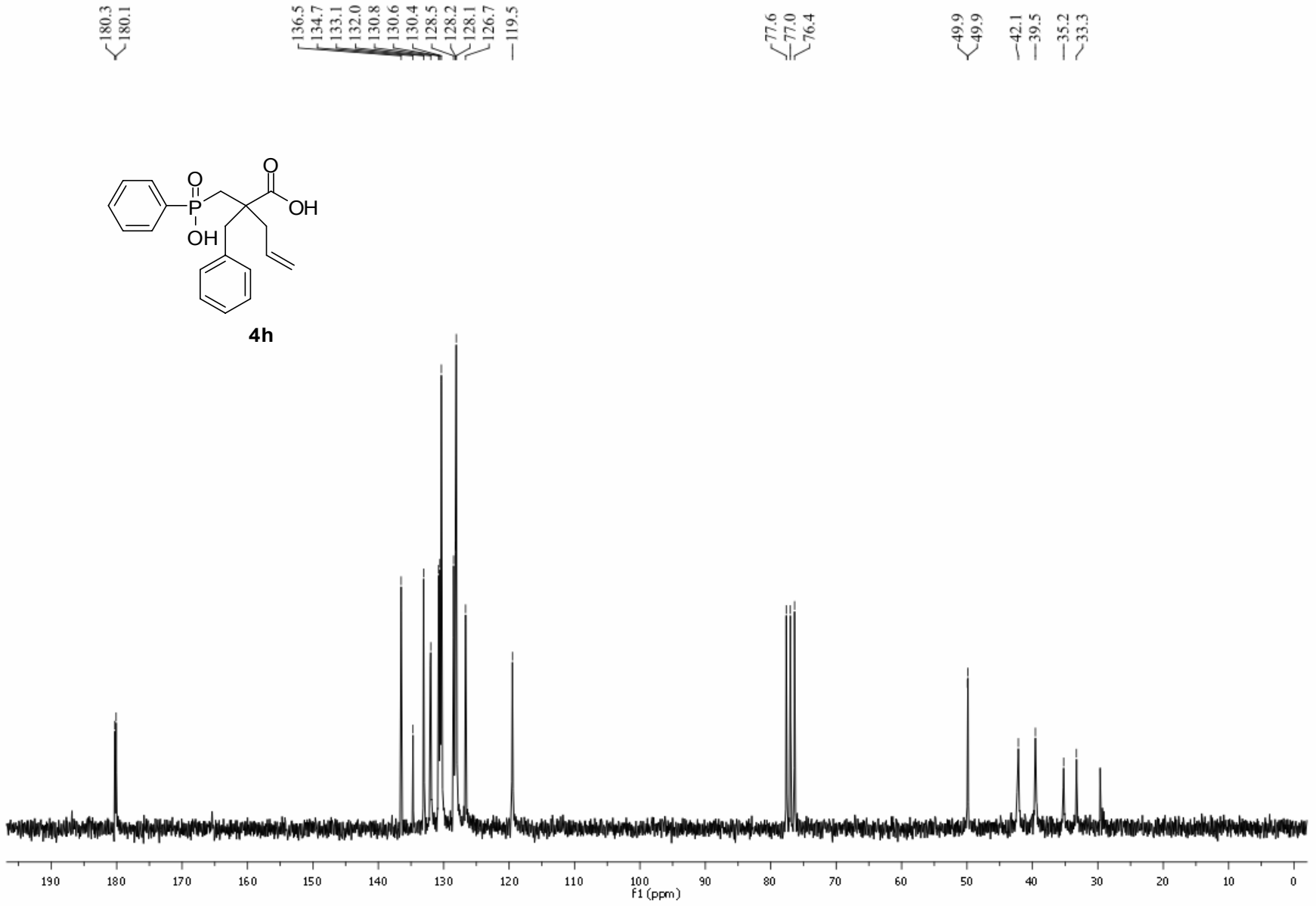
4g

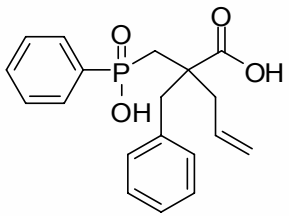
43.8
62 60 58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2
f1 (ppm)


O
O
P
OH
OH

4h

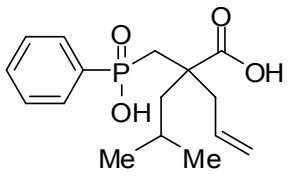

10.17
1.00
2.01
0.94
0.99
3.19
1.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


180.3
180.1
136.5
134.7
133.1
132.0
130.8
130.6
130.4
128.5
128.2
128.1
126.7
119.5
77.6
77.0
76.4
49.9
49.9
42.1
39.5
35.2
33.3
O
P
OH
O
OH
4h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
P
OH
OH

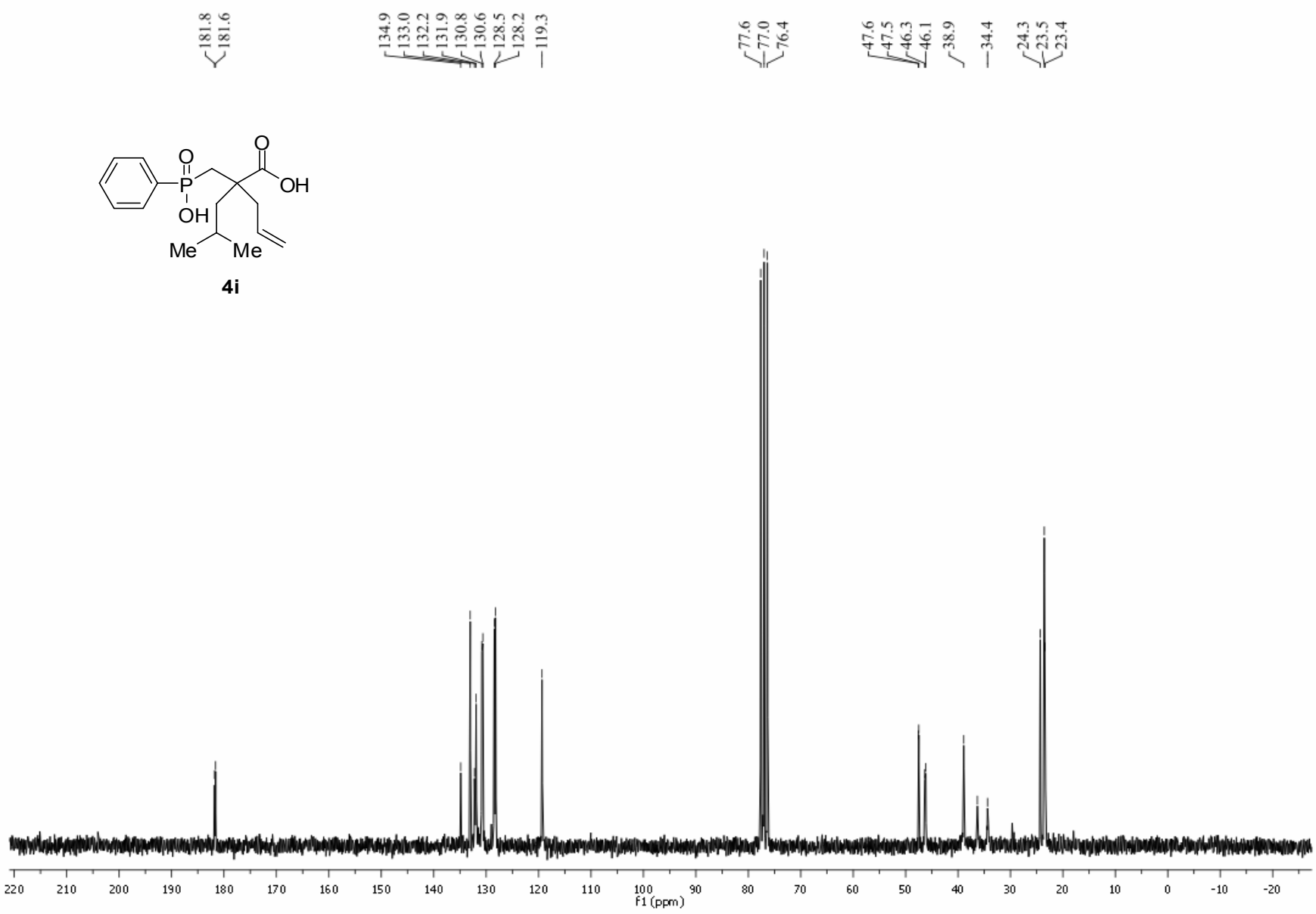
4h

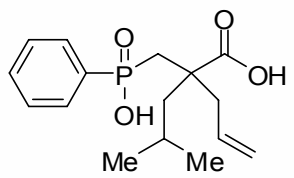
44.9
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
f1 (ppm)


O
O
P
OH
OH
Me
Me

4i

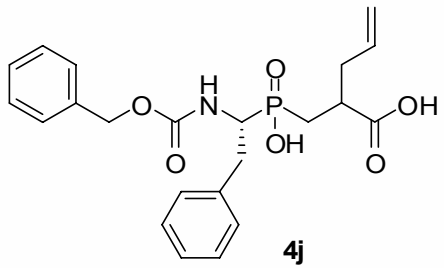
4.98
0.92
1.79
0.87
0.91
1.86
2.74
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


181.8
181.6
134.9
133.0
132.2
131.9
130.8
130.6
128.5
128.2
119.3
77.6
77.0
76.4
47.6
47.5
46.3
46.1
38.9
34.4
24.3
23.5
23.4
O
O
P
OH
OH
Me
Me
4i
f1 (ppm)

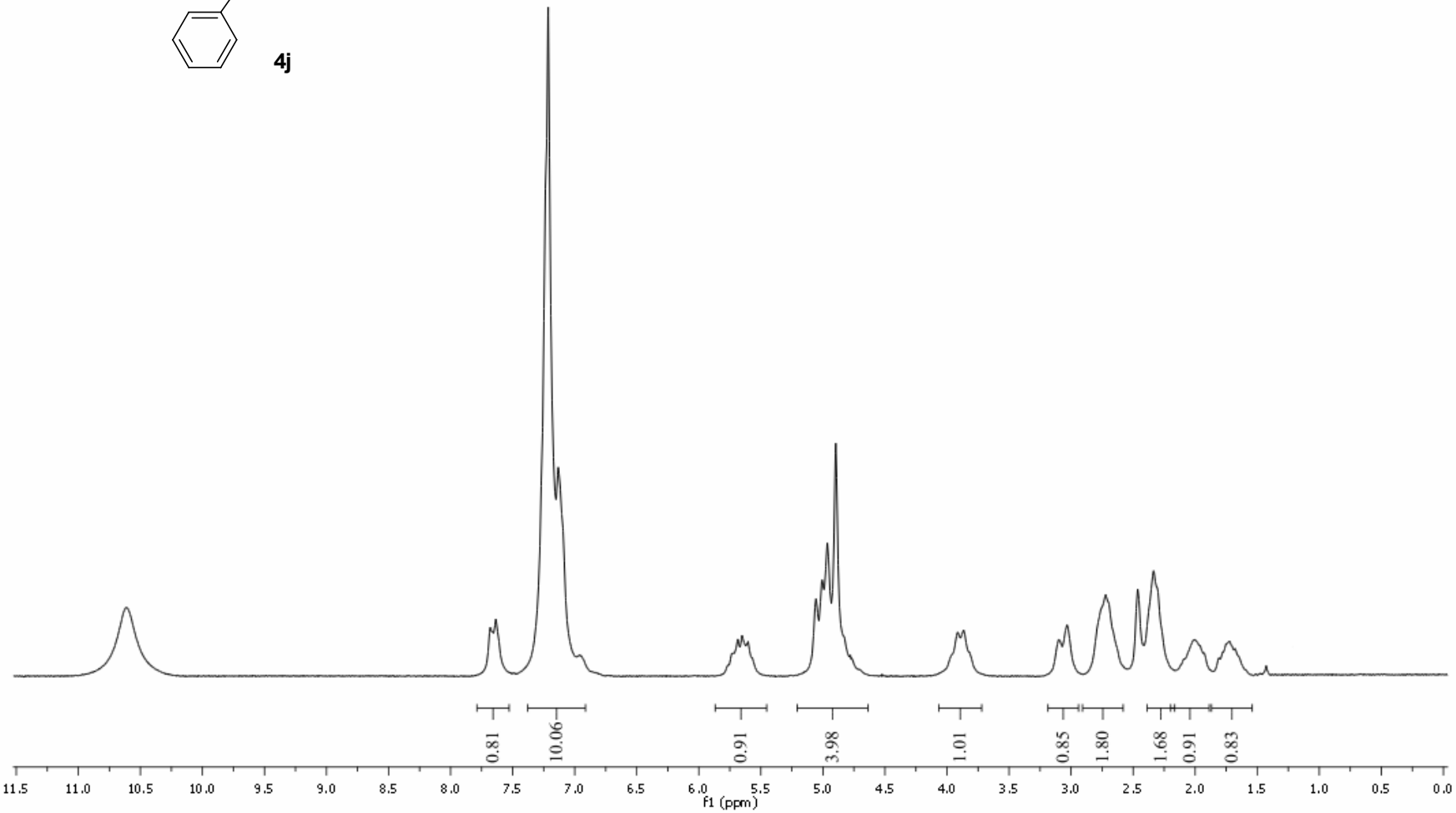

O
O
OH
P
OH
Me
Me

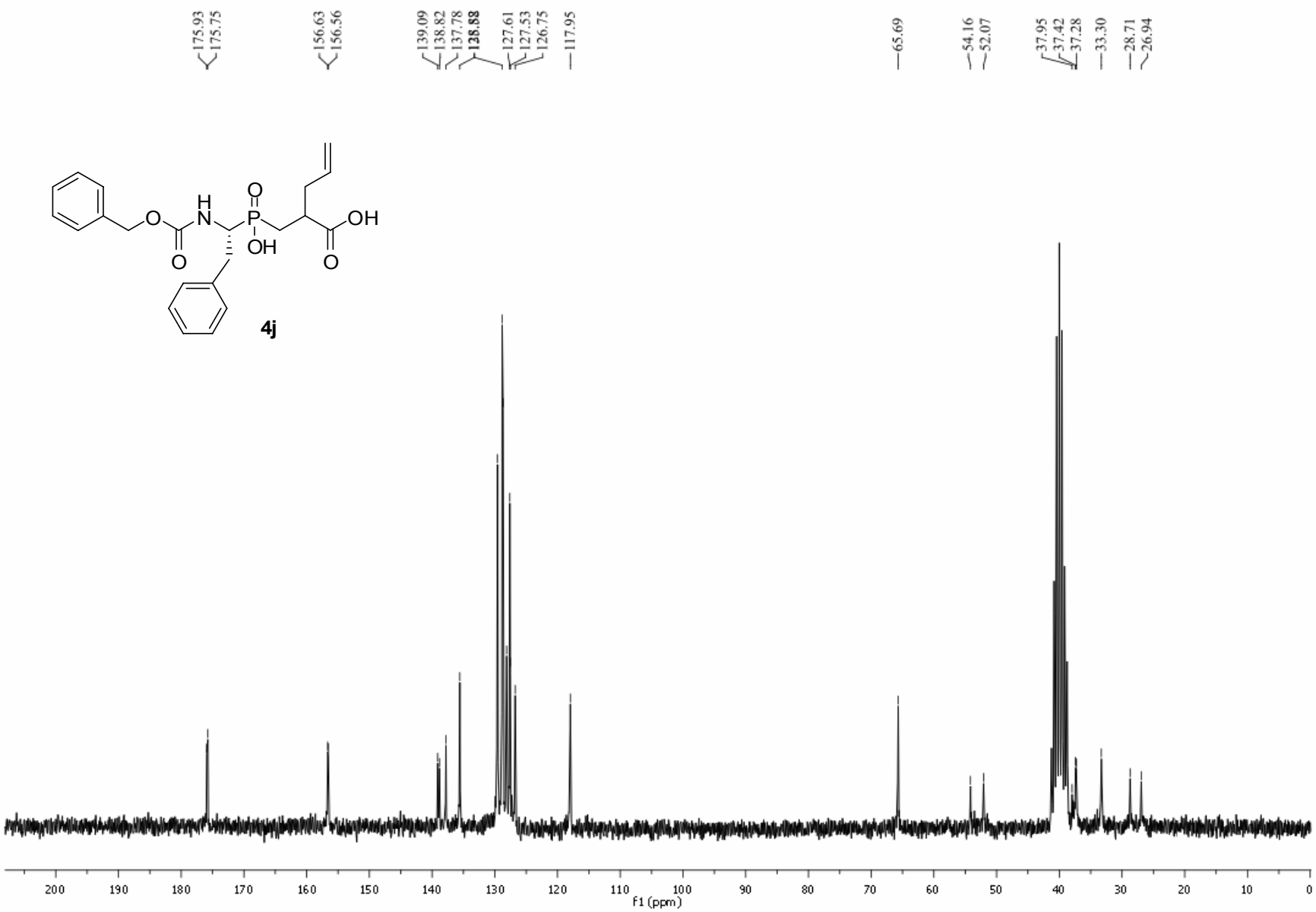
4i

44.5
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
f1 (ppm)

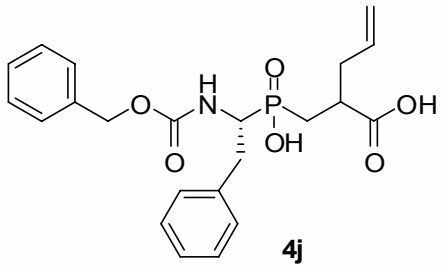

O
H
N
O
P
OH
OH
O
O

4j

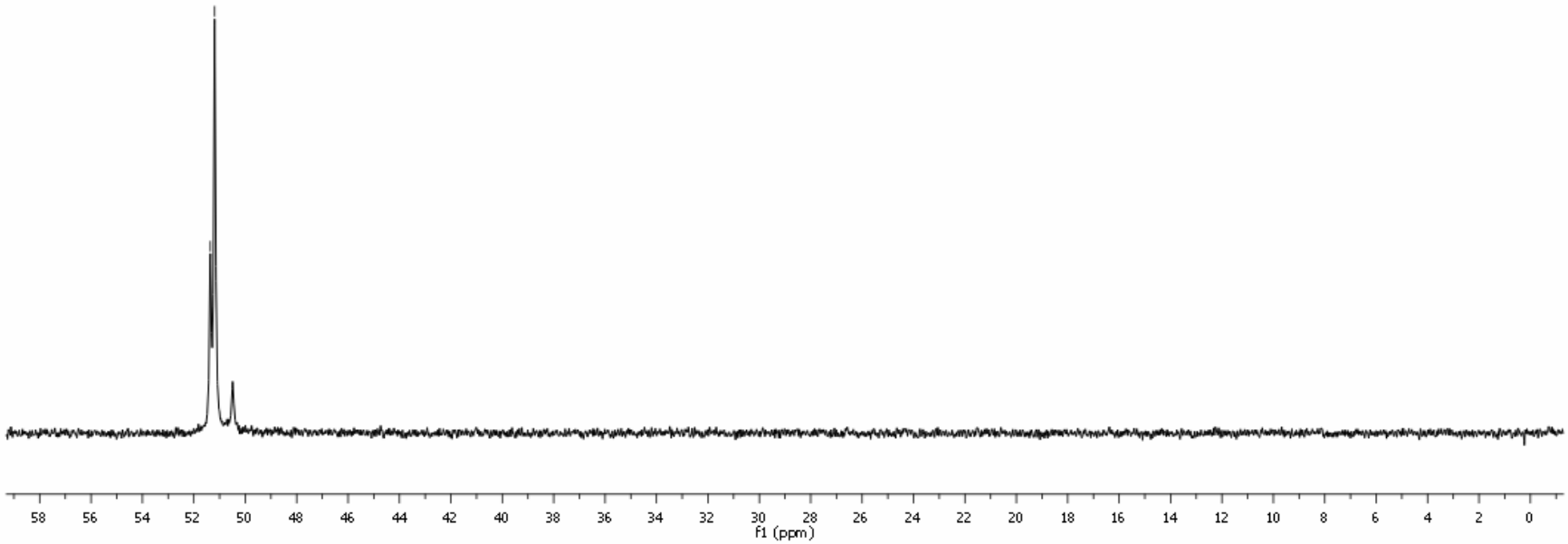

0.81
10.06
0.91
3.98
1.01
0.85
1.80
1.68
0.91
0.83
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

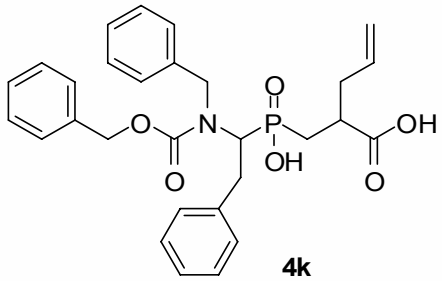

175.93
175.75
156.63
156.56
139.09
138.82
137.78
128.88
127.61
127.53
126.75
117.95
65.69
54.16
52.07
37.95
37.42
37.28
33.30
28.71
26.94
H
N
O
O
P
O
OH
OH
O
4j
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

51.4
51.2

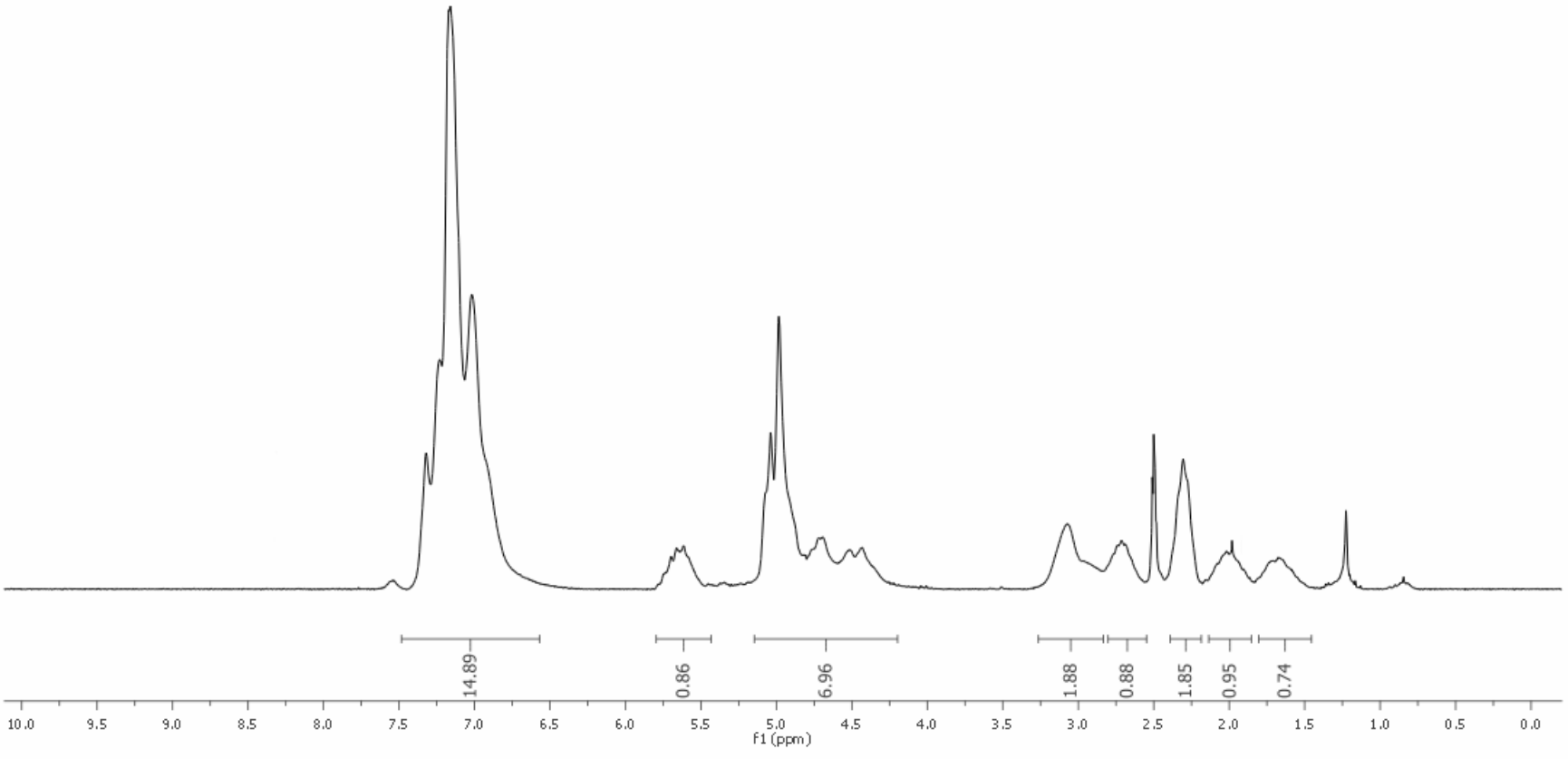

O
H
N
O
P
OH
OH
O
O

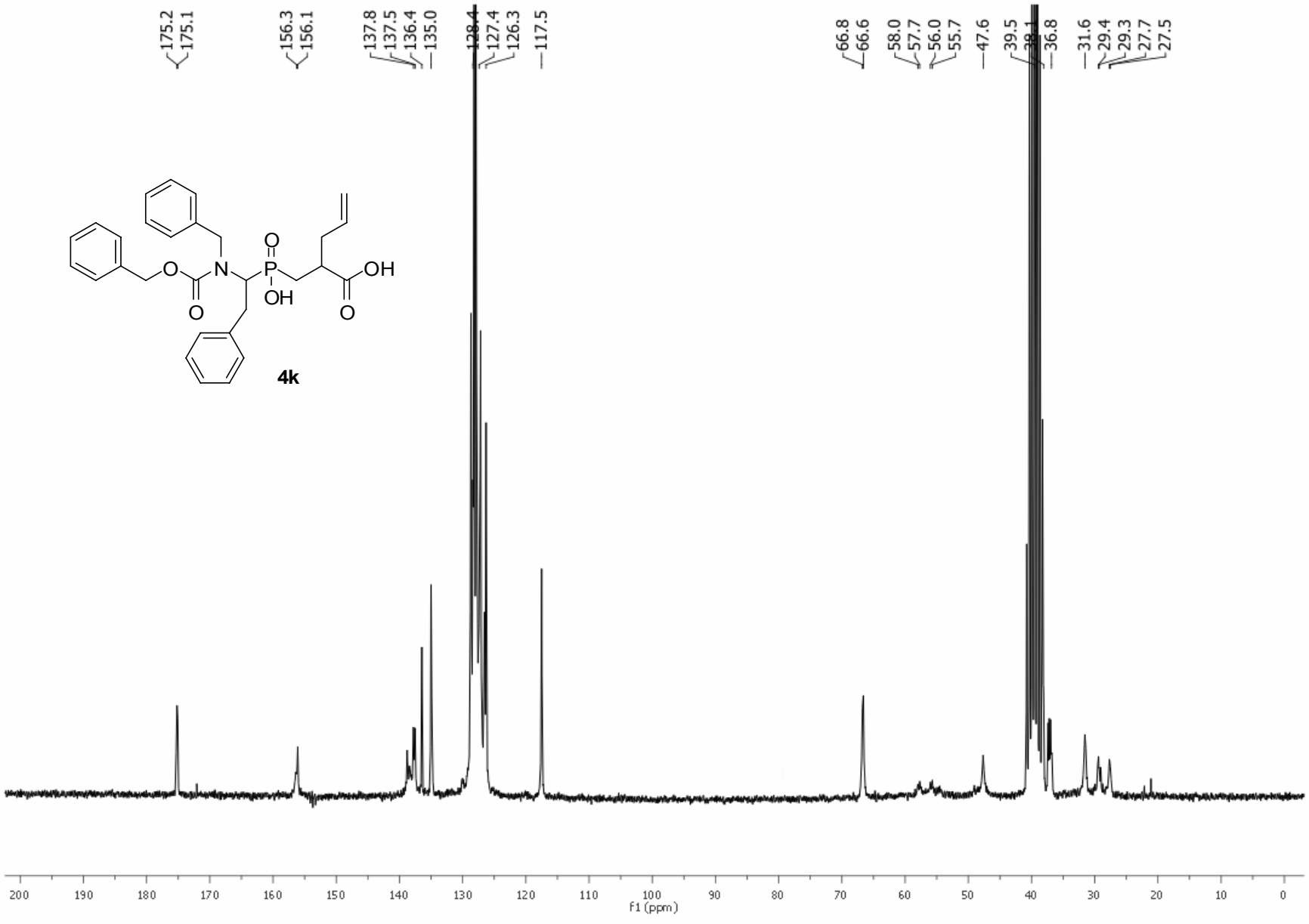
4j

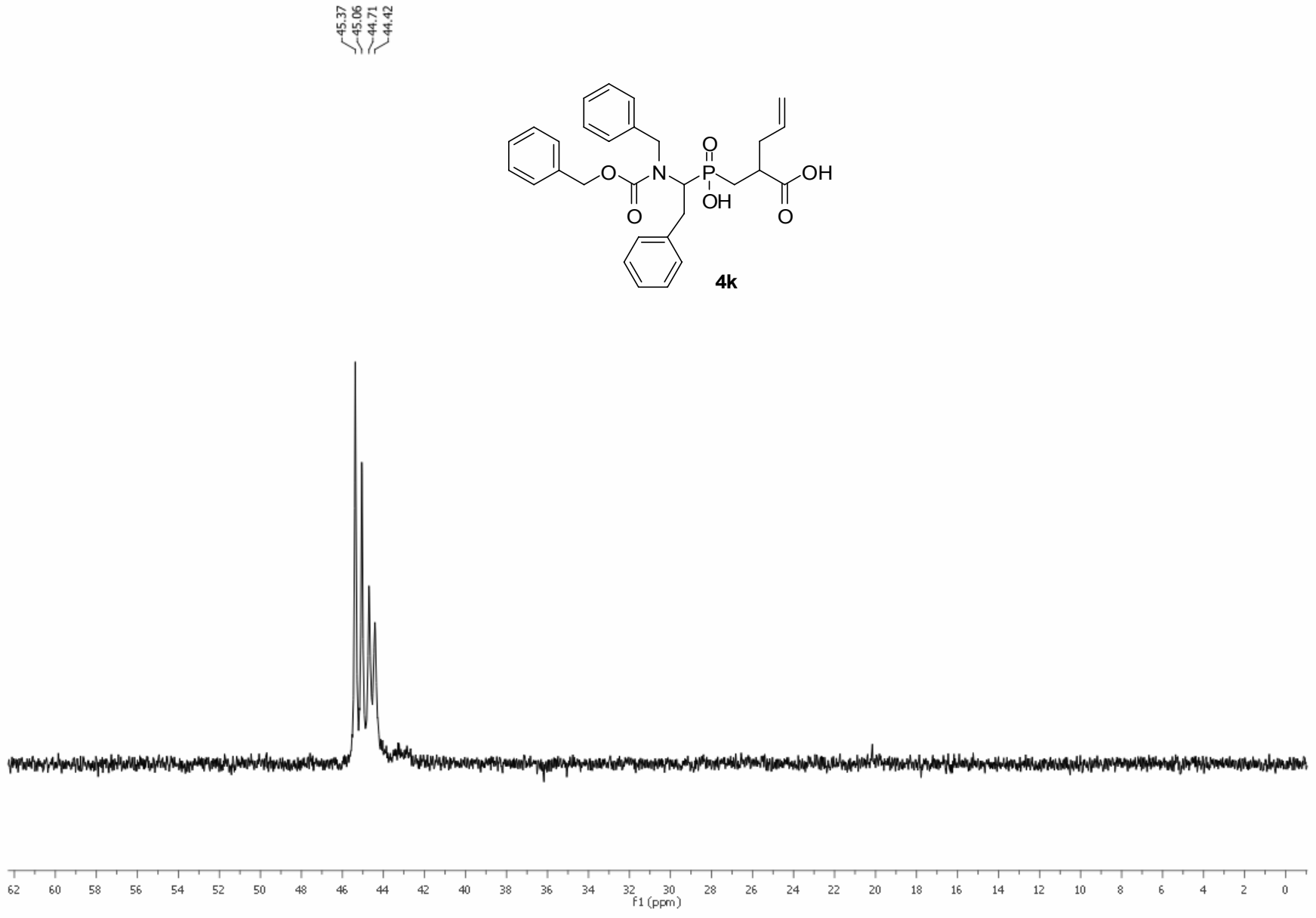

58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0
f1 (ppm)


O
N
P
OH
OH
O
O
O

4k


14.89
0.86
6.96
1.88
0.88
1.85
0.95
0.74
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.2
175.1
156.3
156.1
137.8
137.5
136.4
135.0
128.4
127.4
126.3
117.5
66.8
66.6
58.0
57.7
56.0
55.7
47.6
39.5
38.1
36.8
31.6
29.4
29.3
27.7
27.5
O
N
P
OH
OH
O
O
O
4k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


45.37
45.06
44.71
44.42
O
N
P
OH
OH
O
O
O
4k
62 60 58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0
f1 (ppm)