SUPPORTING INFORMATION

Preparation of Benzylphosphonates via a Palladium(0)-Catalyzed Cross-coupling of H-Phosphonate Diesters with Benzyl Halides. Synthetic and Mechanistic Studies

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Purification of benzylphosphonates 1-13: Silica gel chromatography, using **A.** pentane : EtOAc 1:1→0:1 or **B.** CH_2Cl_2:MeOH 10:0→9:1; or extraction **C.** Residue was partitioned between EtOAc (50 mL) and aq. 1 M NaOH (50 mL) and the organic phase extracted twice with aq. 1 M NaOH (2×50 mL). Combined aqueous layers were acidified with 6 M HCl, and extracted 3 times with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water, dried with Na_2SO_4, and evaporated. Purity of the isolated compounds >98% (^{1}H NMR spectroscopy)

Diethyl benzylphosphonate (1). Purified with **A**; yellow oil, 203 mg yield (89 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.34-7.25 (m, 5H), 4.03 (m, 4H), 3.17 (d, J = 21.5 Hz, 2H), 1.26 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8 (d, $^2J_{P\text{-}C}$ = 8.8 Hz), 129.9 (d, $^3J_{P\text{-}C}$ = 6.7 Hz), 128.7 (d, $^4J_{P\text{-}C}$ = 2.9 Hz), 127.0 (d, $^5J_{P\text{-}C}$ = 3.7 Hz), 62.3 (d, $^2J_{P\text{-}C}$ = 6.6 Hz), 33.9 (d, $^1J_{P\text{-}C}$ = 137.9 Hz), 16.5 (d, $^3J_{P\text{-}C}$ = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.4; HRMS: *m/z* 251.0818 ($[M+Na]^+$, $C_{11}H_{17}NaO_3P^+$ calcd. 251.0808).

Diethyl (4-methylbenzyl)phosphonate (2). Purified with **A**; yellow oil, 233 mg yield (88 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.20-7.09 (m, 4H), 4.01 (m, 4H), 3.11 (d, J = 21.4 Hz, 2H), 2.32 (d, J = 2.3 Hz, 3H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (d, $J_{P\text{-}C}$ = 3.7 Hz), 129.7 (d, $J_{P\text{-}C}$ = 6.6 Hz), 129.3 (d, $J_{P\text{-}C}$ = 3.1 Hz),

128.5 (d, J_{P-C} = 9.0 Hz), 62.1 (d, J_{P-C} = 6.7 Hz), 33.4 (d, J_{P-C} = 138.5 Hz), 21.2, 16.5 (d, J_{P-C} = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.7; HRMS: *m/z* 265.0975 ($[M+Na]^+$, $C_{11}H_{17}NaO_3P^+$ calcd. 265.0964).

Diethyl (4-methoxybenzyl)phosphonate (3). Purified with **A**; yellow oil, 225 mg yield (87 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.21 (m, 2H), 6.84 (m, 2H), 4.03 (m, 4H), 3.79 (s, 3H), 3.08 (d, J = 21.6 Hz, 2H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (d, J_{P-C} = 3.6 Hz), 130.8 (d, J_{P-C} = 6.5 Hz), 123.5 (d, J_{P-C} = 9.2 Hz), 114.1 (d, J_{P-C} = 3.0 Hz), 62.2 (d, J_{P-C} = 6.6 Hz), 55.3, 32.9 (d, J_{P-C} = 139.5 Hz), 16.5 (d, J_{P-C} = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.8; HRMS: *m/z* 281.0925 ($[M+Na]^+$, $C_{12}H_{19}NaO_4P^+$ calcd. 281.0913).

Diethyl (4-fluorobenzyl)phosphonate (4). Purified with **A**; yellow oil, 236 mg yield (96 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.28 (m, 2H), 7.02 (m, 2H), 4.03 (m, 4H), 3.12 (d, J = 21.4 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (dd, $^5J_{P-C}$ = 4.8 Hz, $^1J_{F-C}$ = 245.4 Hz), 131.2 (dd, $^3J_{P-C}$ = 6.6 Hz, $^3J_{F-C}$ = 8.1 Hz), 127.4 (dd, $^2J_{P-C}$ = 9.0 Hz, $^4J_{F-C}$ = 3.4 Hz), 115.4 (dd, $^4J_{P-C}$ = 3.0 Hz, $^2J_{F-C}$ = 21.5 Hz), 62.1 (d, $^2J_{P-C}$ = 6.6 Hz), 32.9 (d, $^1J_{P-C}$ = 139.4 Hz), 16.4 (d, $^3J_{P-C}$ = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.1 (d, $^6J_{P-F}$= 5.9 Hz); HRMS: *m/z* 269.0727 ($[M+Na]^+$, $C_{11}H_{16}FNaO_3P^+$ calcd. 269.0713);

Diethyl (4-chlorobenzyl)phosphonate (5). Purified with **A**; yellow oil, 234 mg yield (90 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.31-7.21 (m, 4H), 4.07-3.97 (m, 4H), 3.11 (d, J = 21.7 Hz), 1.25 (t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1 (d, $^5J_{P-C}$ = 4.1 Hz), 131.3 (d, $^3J_{P-C}$ = 6.7 Hz), 130.5 (d, $^2J_{P-C}$ = 9.1 Hz), 128.9 (d, $^4J_{P-C}$ = 3.1 Hz), 62.4 (d, $^2J_{P-C}$ = 6.8 Hz), 33.4 (d, $^1J_{P-C}$ = 138.7 Hz), 16.6 (d, $^3J_{P-C}$ = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.7; HRMS: *m/z* 285.0418 ($[M+Na]^+$, $C_{11}H_{16}FNaO_3P^+$ calcd. 285.0418);

Diethyl (4-bromobenzyl)phosphonate (6). Purified with **A**; yellow oil, 249 mg yield (86 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.45-7.40 (m, 2H), 7.19-7.14 (m, 2H), 4.06-

3.97 (m, 4H), 3.08 (d, J = 21.7 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8 (d, $^4J_{P\text{-}C}$ = 3.1 Hz), 131.6 (d, $^3J_{P\text{-}C}$ = 6.6 Hz), 131.0 (d, $^2J_{P\text{-}C}$ = 9.1 Hz), 121.1 (d, $^5J_{P\text{-}C}$ = 4.7 Hz), 62.3 (d, $^2J_{P\text{-}C}$ = 6.8 Hz), 33.4 (d, $^1J_{P\text{-}C}$ = 138.6 Hz), 16.5 (d, $^3J_{P\text{-}C}$ = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.4; HRMS: *m/z* 328.9915 ($[M+Na]^+$, $C_{11}H_{16}FNaO_3P^+$ calcd. 328.9913);

Diethyl (4-vinylbenzyl)phosphonate (7). Purified with **A**; colorless oil, 207 mg yield (92 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.37-7.33 (m, 2H), 7.27-7.24 (m, 2H), 6.69 (dd, J = 17.6 Hz, 10.8 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 4.06-3.96 (m, 4H), 3.14 (d, J = 21.8 Hz, 2H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (d, $^6J_{P\text{-}C}$ = 2.0 Hz), 136.3 (d, $^5J_{P\text{-}C}$ =3.9 Hz), 131.3 (d, $^2J_{P\text{-}C}$ = 9.5 Hz), 130.0 (d, $^3J_{P\text{-}C}$ = 6.6 Hz), 126.5 (d, $^4J_{P\text{-}C}$ =3.2 Hz), 113.8 (d, $^7J_{P\text{-}C}$ = 1.5 Hz), 62.2 (d, $^2J_{P\text{-}C}$ = 6.7 Hz), 33.7 (d, $^1J_{P\text{-}C}$ = 138.3 Hz), 16.7 (d, $^3J_{P\text{-}C}$ = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.2; HRMS: *m/z* 277.0944 ($[M+Na]^+$, $C_{12}H_{19}NaO_6P^+$ calcd. 277.0964);

Diethyl (3-pyridylmethyl)phosphonate (8). Purified with **A**; yellow oil, 217 mg yield (92 %). ^{1}H NMR (400 MHz, CDCl3): δ 8.51-8.47 (m, 2H), 7.66 (m, 1H), 7.24 (m, 1H), 4.07-4.03 (m, 4H), 3.11 (d, J = 21.7 Hz, 2H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $^3J_{P\text{-}C}$ = 7.5 Hz), 148.4 (d, $^5J_{P\text{-}C}$ = 3.7 Hz), 137.2 (d, $^3J_{P\text{-}C}$ = 5.8 Hz), 128.0 (d, $^2J_{P\text{-}C}$ = 9.1 Hz), 123.5 (d, $^4J_{P\text{-}C}$ = 2.9 Hz), 62.4 (d, $^2J_{P\text{-}C}$ = 6.9 Hz), 31.1 (d, $^1J_{P\text{-}C}$ = 139.6 Hz), 16.5 (d, $^3J_{P\text{-}C}$ =5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.1; HRMS: *m/z* 252.0751 ($[M+Na]^+$, $C_{10}H_{16}NNaO_3P^+$ calcd. 252.0760);

Diethyl (4-carboxybenzyl)phosphonate (9). Purified with **C**; white solid, 271 mg yield (99 %). ^{1}H NMR (400 MHz, CDCl3): δ 8.03 (d, H_{Ar}, J = 8.0 Hz, 2H), 7.40 (dd, H_{Ar}, J = 8.3, 2.4 Hz, 2H), 4.12-4.02 (m, 4H), 3.26 (d, $J_{P\text{-}C}$ = 22.3 Hz, 2H), 1.27 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 137.6 ($^2J_{P\text{-}C}$ = 9.3 Hz), 130.5 ($^4J_{P\text{-}$

$_C$ = 3.0 Hz), 130.0 ($^3J_{P-C}$ = 6.5 Hz), 128.7 ($^5J_{P-C}$ = 3.6 Hz), 62.7 ($^2J_{P-C}$ = 6.9 Hz), 34.1 ($^1J_{P-C}$ = 137.8 Hz), 16.5 ($^3J_{P-C}$ = 6.0 Hz);

^{31}P NMR (162 MHz, $CDCl_3$): δ 25.6; HRMS: *m/z* 295.0689 ($[M+Na]^+$, $C_{11}H_{16}FNaO_3P^+$ calcd. 295.0706);

Ethyl 5-diethylphosphonomethylfuran-2-carboxylate (10). Purified with **A**; yellow oil, 262 mg yield (99 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.10 (d, J = 3.4 Hz, 1H), 6.39 (dd, J = 3.8, 3.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.15-4.06 (m, 4H), 3.29 (d, J = 21.4 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 150.7 (d, $^2J_{P-C}$ = 8.0 Hz), 144.3 (d, $^4J_{P-C}$ = 3.3 Hz), 119.2 (d, $^4J_{P-C}$ = 3.2 Hz), 110.7 (d, $^3J_{P-C}$ = 6.4 Hz), 62.7 (d, $^2J_{P-C}$ = 6.6 Hz), 61.0, 27.2 (d, $^1J_{P-C}$ = 143.1 Hz), 16.4 (d, $^3J_{P-C}$ = 6.0 Hz), 14.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.6; HRMS: *m/z* 313.0809 ($[M+Na]^+$, $C_{12}H_{19}NaO_6P^+$ calcd. 313.0811);

Ethyl *n*-pentyl benzylphosphonate – mixture of diastereoisomers (11). Purified with **A**; yellow oil, 238 mg yield (88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.34-7.25 (m, 5H), 4.05-3.87 (m, 4H), 3.17 (d, J = 21.5 Hz, 2H), 1.61-1.54 (m, 2H), 1.31-1.24 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8 (d, $^2J_{P-C}$ = 9.2 Hz), 129.9 (d, $^3J_{P-C}$ = 6.7 Hz), 128.7 (d, $^4J_{P-C}$ = 2.9 Hz), 127.0 (d, $^5J_{P-C}$ = 3.7 Hz), 66.2 (d, $^2J_{P-C}$ = 7.0 Hz) 62.3 (d, $^2J_{P-C}$ = 6.6 Hz), 33.9 (d, $^1J_{P-C}$ = 137.9 Hz), 30.3 (d, $^3J_{P-C}$ = 6.1 Hz), 27.7, 22.3, 16.5 (d, $^3J_{P-C}$ = 6.2 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.4; HRMS: *m/z* 293.1269 ($[M+Na]^+$, $C_{11}H_{17}NaO_3P^+$ calcd. 293.1277);

(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl ethyl benzylphosphonate – mixture of diastereoisomers (12). Purified with **A**; yellow oil, 233 mg yield (74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 4.18 (m, 1H), 3.70 and 3.68 (2×t, J = 5.6 Hz, 1H), 3.185 and 3.179 (2×d, J = 21.8 Hz, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 1.24 (t, J =

7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.42 and 131.38 (2×d, $J_{P\text{-}C}$ = 9.1 Hz), 129.94 and 129.92 (2×d, $J_{P\text{-}C}$ = 6.7 Hz), 128.7 (d, $J_{P\text{-}C}$ = 3.0 Hz), 127.1 (d, $J_{P\text{-}C}$ = 3.5 Hz), 109.9, 74.48 and 74.45 (d, $J_{P\text{-}C}$ = 6.8 Hz), 66.2 (d, $J_{P\text{-}C}$ = 4.8 Hz), 66.04 and 66.01 (2×d, $J_{P\text{-}C}$ = 6.8 Hz), 62.55 and 62.50 (2×d, $J_{P\text{-}C}$ = 6.6 Hz), 33.77 and 33.75 (2×d, $J_{P\text{-}C}$ = 138.3 Hz), 26.9, 25.41, 25.40, 16.5 (d, $J_{P\text{-}C}$ = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 27.03 and 27.01; HRMS: *m/z* 337.1167 ($[M+Na]^+$, $C_{11}H_{17}NaO_3P^+$ calcd. 337.1175);

Cholesteryl ethyl benzylphosphonate – mixture of diastereoisomers (13). Purified with **A**; white amorphous solid, 500 mg yield (88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 5.34 and 5.26 (2×m, 1H), 4.16 (m, 1H), 4.03-3.94 (m, 2H), 3.14 (d, J = 21.7 Hz, 2H), 2.40-0.80 (m, 43H), 0.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (d, $J_{P\text{-}C}$ = 3.7 Hz), 132.0 (d, $J_{P\text{-}C}$ = 9.1 Hz), 129.98 and 129.96 (2×d, $J_{P\text{-}C}$ = 6.7 Hz), 128.60 and 128.58 (2×d, $J_{P\text{-}C}$ = 2.4 Hz), 126.94 and 126.91 (2×d, $J_{P\text{-}C}$ = 3.6 Hz), 122.93 (d, $J_{P\text{-}C}$ = 4.0 Hz), 76.85 and 76.79 (2×d, $J_{P\text{-}C}$ = 6.8 Hz), 62.05 and 61.98 (2×d, $J_{P\text{-}C}$ = 7.2 Hz), 56.8, 56.3, 50.1, 42.43, 40.6 (d, $J_{P\text{-}C}$ = 3.3 Hz), 40.1 (d, $J_{P\text{-}C}$ = 4.8 Hz), 39.8, 39.6, 37.08, 37.04, 36.51, 36.49, 36.3, 35.9, 35.1, 33.8, 32.00, 31.96, 31.06, 30.26, 30.23, 29.89, 29.84, 28.35, 28.14, 24.4, 24.0, 23.0, 22.7, 21.2, 19.4, 18.8, 16.53, 16.47, 12.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.52 and 25.48; HRMS: *m/z* 591.3948 ($[M+Na]^+$, $C_{36}H_{57}NaO_3P^+$ calcd. 591.3938);

5'-*O*-(*tert*-Butyldiphenylsilyl)thymidin-3'-yl 3'-*O*-(dimethoxytrityl)thymidin-5'-yl benzylphosphonate – mixture of diastereoisomers (14). Off-white amorphous solid, 511 mg (88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54, 9.39, 9.35 (3×s, $H3_a$, $H3_b$, 2H), 7.72-6.80 (m, H_{Ar} + $H6_a$, $H6_b$, 30H), 6.48-6.26 (m, $H1'_a$, $H1'_b$, 2H), 5.02, 4.92 (2×t, $H3'_a$, J = 6.4 Hz, 1H), 4.24-3.44 (m, $H3'_b$, $H4'_a$, $H4'_b$, $H5'_a$, $H5''_a$, $H5'_b$, $H5''_b$, 2×OCH_3, 13H), 3.28-3.00 (m, PCH_2, 2H), 2.47-1.99 (m, $H2'_a$, $H2''_a$, $H2'_b$, 3H), 1.92,

1.90 (2×s, $H5_b$, 3H), 1.56, 1.54 (2×s, $H5_a$, 3H), 1.54 (m, H2"$_b$, 1H), 1.08, 1.06 (2×s, tB-Si, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 163.9, 158.9, 150.6, 150.5, 145.0, 144.9, 136.18, 136.11, 136.05, 136.03, 135.9, 135.6, 135.4, 135.3, 134.9,133.0, 132.9, 132.8, 132.5, 132.13, 132.08, 130.33, 130.26, 130.16, 129.8, 129.75, 129.72, 129.12, 128.89, 128.87, 128.41, 128.33, 128.18, 128.10, 128.06, 127.53, 127.32, 125.4, 113.5, 113.4, 111.70, 111.64, 111.4, 111.3, 111.2, 87.6, 87.5, 87.2, 86.1, 85.9, 85.53, 85.47, 85.3, 84.8, 84.4, 84.3, 84.2, 77.6 ($J_{P\text{-}C}$ = 6.4 Hz), 77.5 ($J_{P\text{-}C}$ = 6.3 Hz), 74.1, 73.8, 72.3, 65.6, 64.3, 63.8, 60.5, 55.37, 55.34, 41.1, 39.6, 39.2, 39.1, 33.9 ($J_{P\text{-}C}$ = 138 Hz), 27.1, 21.5, 21.1, 19.4, 14.3, 12.7, 12.2, 12.05, 11.98; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.2 and 27.1; HRMS: *m/z* 1183.4261 ($[M+Na]^+$, $C_{64}H_{69}N_4NaO_{13}PSi^+$ calcd. 1183.4260);

5'-*O*-(*tert*-Butyldiphenylsilyl)thymidin-3'-yl N^4-benzoyl-3'-*O*-(dimethoxytrityl)deoxycytidine-5'-yl benzylphosphonate – mixture of diastereoisomers (15). Off-white amorphous solid, 531 mg (85 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97, 8.91 (2×bs, $H3_a$ and C4NH_b, 2H), 8.08-6.79 (m, H_{Ar}, $H6_a$, $H5_b$, $H6_b$, 36H), 6.47-6.26 (m, H1'$_a$, H1'$_b$, 2H), 4.97 and 4.90 (2×t, H3'$_a$, J = 6.0 and 6.2 Hz, 1H), 4.17 (m, H2'$_b$, 1H), 4.07-3.62 (m, 10H), 3.51-3.41 (m, H5'$_a$, 2H), 3.14-2.95 (m, PCH_2, 2H), 2.47 (m, H4'$_b$, 1H), 2.37-2.05 (2×m, H2'$_a$, 2H), 1.54, 1.49 (2×s, H5, 3H), 1.49 (m, H2"$_b$, 1H), 1.09, 1.04 (2×s, tB-Si, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 162.4, 158.9, 150.3, 144.94, 144.91, 136.14, 136.12, 136.06, 135.6, 135.4, 135.34, 135.28, 135.08, 135.00, 133.2, 132.9, 132.8, 132.1, 130.36, 130.33, 130.29, 130.24, 129.83, 129.76, 129.0, 128.96, 128.92, 128.43, 128.39, 128.2, 128.1, 127.8, 127.59, 127.56, 127.36, 113.6, 113.4, 111.6, 111.4, 111.24, 88.0, 87.66, 86.28, 86.26, 85.53, 84.47, 85.19, 85.13, 85.03, 84.96, 84.82, 84.6, 84.2, 77.8 (d, $J_{P\text{-}C}$ = 6.0 Hz), 77.5 (d, $J_{P\text{-}C}$ = 6.3 Hz), 74.2, 74.1, 72.4, 65.31 (d, $J_{P\text{-}C}$ = 6.3 Hz), 65.19 (d, $J_{P\text{-}C}$ = 6.4 Hz), 64.3, 63.83, 63.81, 62.5, 55.40, 55.37, 41.9, 40.9, 39.7, 39.23, 39.17, 34.06 (d,

$J_{P\text{-}C}$ = 136.4 Hz), 33.99 (d, $J_{P\text{-}C}$ = 138.2 Hz), 27.1, 19.47, 19.44, 12.2, 12.1, 12.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.0 and 27.5; HRMS: *m/z* 1272.4514 ($[M+Na]^+$, $C_{70}H_{72}N_5NaO_{13}PSi^+$ calcd. 1272.4526);

5'-*O*-(*tert*-Butyldiphenylsilyl)thymidin-3'-yl N^2-*iso*-butyryl-3'-*O*-(dimethoxytrityl)deoxyguanosine-5'-yl benzylphosphonate – mixture of diastereoisomers (16). Off-white amorphous solid, 502 mg (80 %). ^{1}H NMR (400 MHz, CDCl3): δ 12.10, 12.05 (1H, 2×s, C2N*H*$_b$), 10.52, 10.49 (2×s, H3$_b$, 1H), 9.08, 8.98 (2×s, H3$_a$, 1H) 7.72-6.75 (m, H_{Ar} + H6$_a$, H8$_b$, 30H), 6.43-6.07 (2×dd + m, H1'$_a$, H1'$_b$, 2H), 5.03, 4.78 (2×m, H3'$_a$, 1H), 4.28-3.44 (m, H3'$_b$, H4'$_a$, H4'$_b$, H5'$_a$, H5"$_a$, H5'$_b$, H5"$_b$, 2×OC*H*$_3$, 13H), 3.19-2.95 (m, PC*H*$_2$, 2H), 2.70-1.65 (m, H2'$_a$, H2"$_a$, H2'$_b$, H2"$_b$, $(CH_3)_2CH$, 5H), 1.59, 1.50 (s, C*H*$_{3a}$, 3H), 1.22, 1.18, 1.09, 1.07 (4×d, $(CH_3)_2CH$, *J* = 6.4-7.0 Hz, 6H), 1.06, 1.00 (2×s, tB-Si, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 179.5, 178.6, 171.1, 163.5, 163.4, 158.8, 155.6, 155.4, 155.0, 150.3, 150.2, 147.7, 147.6, 147.5, 147.3, 146.8, 145.0, 144.8, 144.5, 139.7, 139.6, 136.2, 136.1, 136.0, 135.8, 135.7, 135.43, 135.40, 135.1, 135.0, 134.7, 132.4, 132.0, 130.3, 130.2, 130.1, 130.0, 129.5, 129.4, 128.79, 128.72, 128.2, 128.0, 127.9, 127.52, 127.47, 127.4, 127.3, 127.24, 127.17, 127.1, 123.3, 122.9, 113.4 (arom. + C2$_a$, C2$_b$, C4$_a$, C4$_b$, C5$_b$, C6$_a$, C6$_b$, C8$_b$, C=O), 111.6, 111.5 (C5$_a$), 87.7, 87.6, 87.5, 87.3, 87.1, 87.0, 85.8, 85.5, 84.5, 84.4, 84.3 (C1'$_a$, C1'$_b$, C4'$_a$, C4'$_b$, Ar$_3$*C*), 78.2, 77.0 (d, C3'$_a$, *J* = 7.0 Hz), 74.4, 74.3 (C3'$_b$), 66.1, 66.0, 63.8, 63.6 (C5'$_a$, C5'$_b$), 55.3, 55.2 (*C*H$_3$O), 39.3, 39.1, 37.8, 37.4, 36.3, 35.7, 35.6 (C2'$_a$, C2'$_b$, $(CH_3)_2CH$), 33.4, 33.0 (2×d, P*C*H$_2$, *J* = 139 Hz), 26.9 ((*C*H$_3$)$_3$CSi), 19.4, 19.3, 19.2, 19.0, 18.9, 18.7, 18.3 ((*C*H$_3$)$_2$CH, (CH$_3$)$_3$*C*Si), 12.0, 11.8 (*C*H$_{3a}$); ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.5 and 26.7; HRMS: *m/z* 1278.4752 ($[M+Na]^+$, $C_{68}H_{74}N_7NaO_{13}PSi^+$ calcd. 1278.4744);

5'-*O*-(*tert*-Butyldiphenylsilyl)thymidin-3'-yl N^6-benzoyl-3'-*O*-(dimethoxytrityl)deoxyadenosin-5'-yl benzylphosphonate – mixture of diastereoisomers (17). Off-white amorphous solid, 516 mg (81 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93, 9.76, 9.62, 9.38 (4×s, $H2_b$, C6NH_b, 2H), 8.80, 8.77 (2×s, $H3_a$, 1H): 8.25-6.81 (m, H_{Ar}, $H6_a$, $H8_b$, 35H), 6.52-6.17 (m, H1'$_a$, H1'$_b$, 2H), 4.93-4.82 (m, H3'$_a$, 1H), 4.45-4.35 (m, H3'$_b$, 1H), 4.13 (m, H4'$_b$, 1H), 3.96 (m, H5'$_b$, 1H), 3.83-3.72 (m, H5"$_b$, 2×OCH_3, 7H), 3.69 (dd, H5'$_a$, J = 11.5, 2.5 Hz, 1H), 3.63 (m, H4'$_a$, 1H), 3.37 (m, H5"$_a$, J = 11.5, 2.5 Hz, 1H,), 3.14-2.91 (m, PCH_2, 2H), 2.32-1.86 (m, H2'$_a$, H2"$_a$, H2'$_b$, H2"$_b$, 4H), 1.42 (m, CH_{3a}, 3H), 1.01, 1.00 (2×s, (CH_3)$_3$Si, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 165.2, 164.0, 164.8, 163.8, 163.6, 158.8, 158.7, 152.6, 152.3, 151.8, 151.6, 150.7, 150.3, 149.9, 149.7, 145.0, 144.8, 144.7, 142.7, 141.7, 141.1, 136.3, 136.2, 135.9, 135.85, 135.81, 135.5, 135.4, 135.1, 134.8, 133.9, 133.5, 133.4, 132.8, 132.7, 132.5, 132.0, 131.9, 130.3, 130.2, 130.1, 130.0, 129.7, 129.6, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.97, 127.90, 127.3, 127.2, 123.6, 123.4, 113.4 (arom. + $C2_a$, $C4_a$), 111.4, 111.3 ($C5_a$), 87.4 (Ar_3C), 85.9 (d, J = 3.5 Hz), 85.3 (d, J = 6.0 Hz), 84.7 (d, J = 7.4 Hz), 84.5 (d, J = 7.4 Hz) (C4'$_b$, C4'$_b$), 84.8, 84.3, 84.1, 83.9 (C1'$_a$, C1'$_b$), ~77.5 (C3'$_a$), 74.1, 73.8 (C3'$_b$), 65.6 (d, J = 7.6 Hz), 65.0 (d, J = 7.2 Hz) (C5'$_b$), 63.6, 63.5 (C5'$_a$), 55.2 (CH$_3$O), 39.6, 39.4, 39.0 (d, J = 5.6 Hz), 38.8 (C2'$_a$, C2'$_b$), 33.7, 33.5 (2×d, PCH$_2$, J = 137 Hz), 26.9 ((CH$_3$)$_3$CSi), 19.25, 19.23 ((CH$_3$)$_3$$C$Si), 11.7 ($CH_{3a}$); ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.1 and 27.3; HRMS: *m/z* 1296.4626 ([M+Na]$^+$, $C_{71}H_{72}N_7NaO_{12}PSi^+$ calcd. 1296.4638);

Diethyl benzylphosphonothioate (18). Colorless oil, 193 mg yield (79 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 4.10-3.96 (m, 4H), 3.36 (d, J = 19.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7 (d, J_{P-C} = 8.7 Hz), 130. 3 (d, J_{P-C} = 6.5 Hz), 128.4 (d, J_{P-C} = 3.6 Hz), 127.2 (d, J_{P-C} = 4.4 Hz), 63.0 (d, J_{P-}

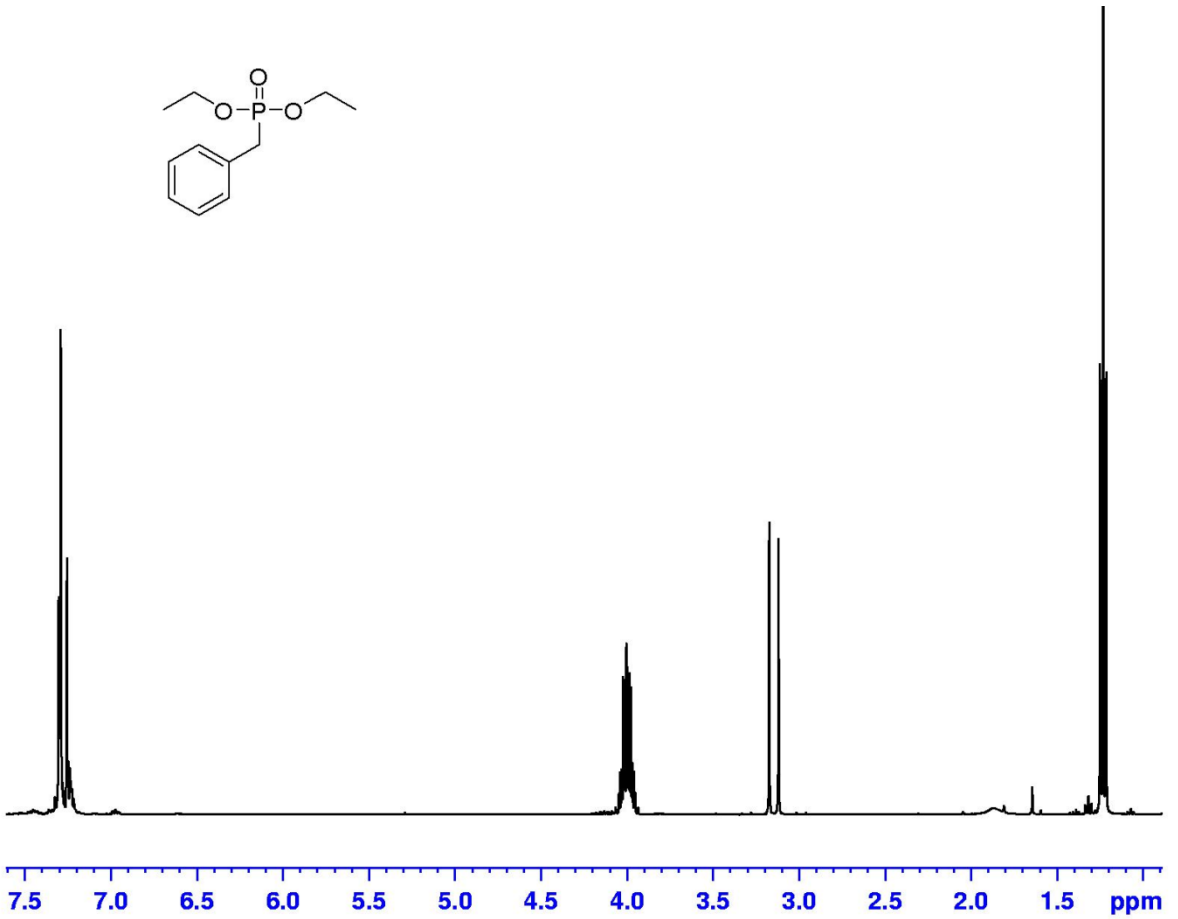
$_C$ = 7.1 Hz), 42.7 (d, J_{P-C} = 108.3 Hz), 16.2 (d, J_{P-C} = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 93.5; HRMS: *m/z* 267.0586 ($[M+Na]^+$, $C_{11}H_{17}NaO_2PS^+$ calcd. 267.0579);

5'-*O*-(*tert*-Butyldiphenylsilyl)thymidin-3'-yl ethyl benzylphosphonothioate – mixture of diastereoisomers (19). White amorphous solid, 282 mg yield (83 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (bs, H3, 1H), 7.67-7.60 (m, H_{Ar}, 4H), 7.49-7.16 (m, H_{Ar} and H6, 12H), 6.40 (m, H1', 1H), 5.33 and 5.15 (2×m, H3', 1H), 4.13 (m, H4', 0.5H), 4.12-3.96 (m, POCH_2, 2H), 3.91-3.86 (m, H5', 1H), 3.79 (dd, H5', *J* = 11.5, 1.8 Hz, 0.5H), 3.72 (m, H4', 0.5H), 3.67 (dd, H5', *J* = 11.5, 2.1 Hz, 0.5H), 3.41 and 3.38 (2×d, PCH_2, *J* = 19.2 Hz, 2H), 2.45 (dd, H2', *J* = 13.8, 5.1 Hz, 0.5H), 2.24-2.15 (m, H2', 1H), 2.05 (m, H2', 0.5H), 1.59 and 1.57 (2×s, H5, 3H), 1.28 and 1.18 (2×t, $POCH_2CH_3$, *J* = 7.1 Hz, 3H), 1.06 and 1.05 (2×s, tB-Si, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.70, 163.67, 150.47, 135.77, 135.77, 135.3, 135.07, 135.04, 133.0, 132.9, 132.0, 131.9, 130.90 and 130.87 (2×d, J_{P-C} = 8.3 Hz), 130.40 and 130.37 (2×d, J_{P-C} = 6.4 Hz), 130.32, 130.2, 128.63, and 128.5 (2×d, J_{P-C} = 3.8 Hz), 128.2, 128.1, 127.6 and 127.5 (2×d, J_{P-C} = 4.4 Hz), 111.67, 111.63, 86.30, 86.28, 86.01, 85.96, 84.54, 84.48, 77.9 and 77.2 (2×d, J_{P-C} = 6.7 Hz), 63.90, 63.84, 63.3 and 63.0 (2×d, J_{P-C} = 7.4 Hz), 42.9 (d, J_{P-C} = 107.5 Hz), 42.6 (d, J_{P-C} = 108.3 Hz), 39.80, 39.76, 39.28, 39.21, 31.4, 27.1, 19.49, 19.46, 16.31 and 16.16 (2×d, J_{P-C} = 7.2 Hz), 12.15, 12.09; ^{31}P NMR (162 MHz, $CDCl_3$): δ 95.1 and 94.5 ; HRMS: *m/z* 701.2260 ($[M+Na]^+$, $C_{35}H_{43}N_2NaO_6PSSi^+$ calcd. 701.2241);

Benzyl-(5-(diphenylphosphino)-9,9-dimethyl-9*H*-xanthen-4-yl)diphenylphosphonium bromide.

Xantphos (0.2 mmol, 116 mg) and benzyl bromide (0.6 mmol, 72 μL) was refluxed in THF (3 mL) overnight. After cooling (0 °C) the reaction mixture, the precipitated crystals were filtered off and washed with cold diethyl ether to obtain the pure compound in 72 % (108 mg) yield after evaporation.

^{1}H NMR (400 MHz, CDCl3): δ 8.01 and 7.99 (2×s, 1H), 7.68-7.60 (m, 2H), 7.54-7.44 (m, 9H), 7.36-7.26 (m, 2H), 7.23-7.15 (m, 7H), 7.12-7.15 (m, 7H), 7.12-7.05 (m, 5H), 6.96-6.88 (m, 4H), 6.64 (m, 1H), 5.23 (dd, $^{2}J_{P\text{-}H}$ = 16 Hz and $^{8}J_{P\text{-}H}$ = 4 Hz), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 151.0, 151.4, 135.7, 135.6, 135.5, 135.4, 135.0, 134.7, 134.2, 134.1, 133.5, 133.3, 132.9, 131.0, 130.1, 130.0, 129.6, 128.9, 128.8, 128.7, 128.5, 127.8, 125.6, 125.5, 125.3, 124.4, 124.2, 118.1, 117.3, 104.8, 104.0, 34.7, 32.4, 30.8 (dd, $J_{P\text{-}C}$ = 46.7, 14.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.1 and -21.3 ; HRMS: *m/z* 771.1560 ($[M+Na]^+$, $C_{46}H_{39}BrNaOP_2^+$ calcd. 771,1552);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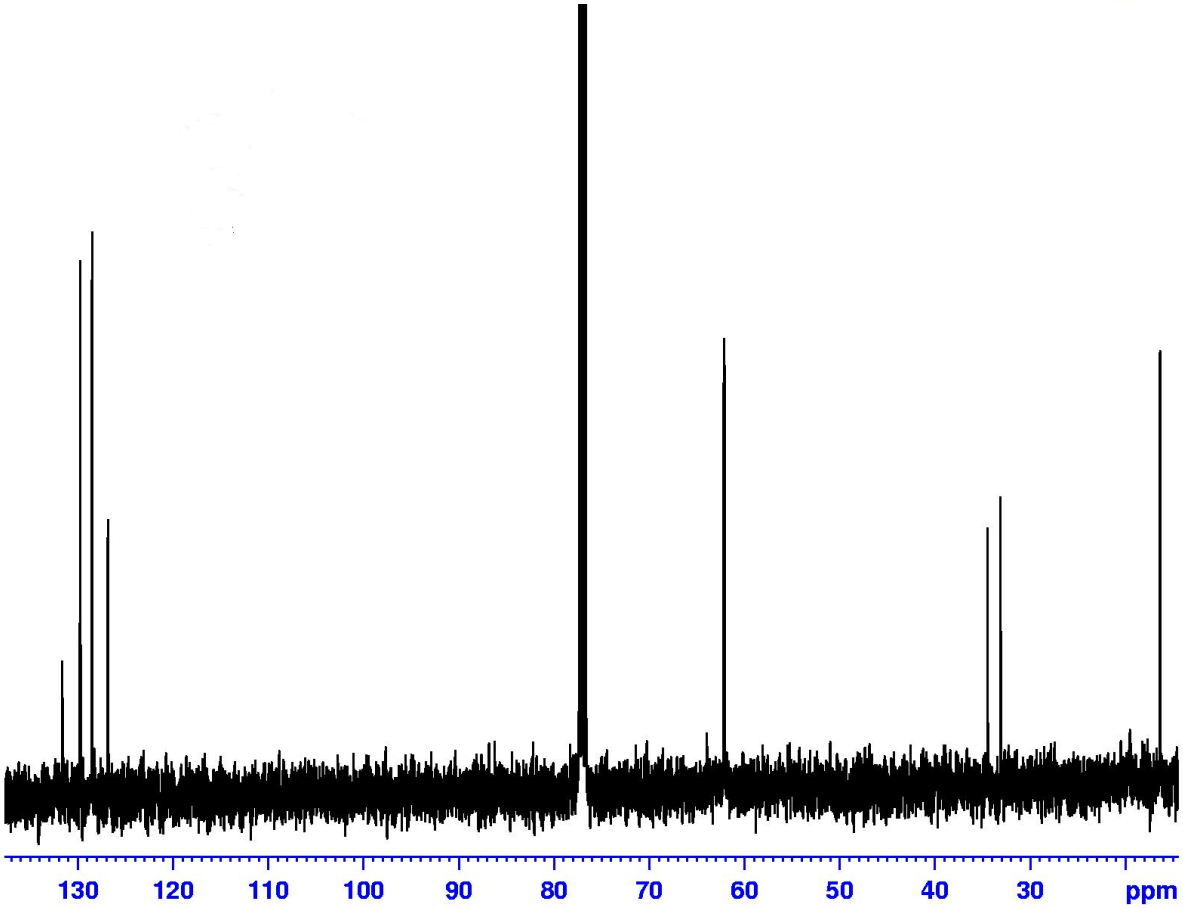
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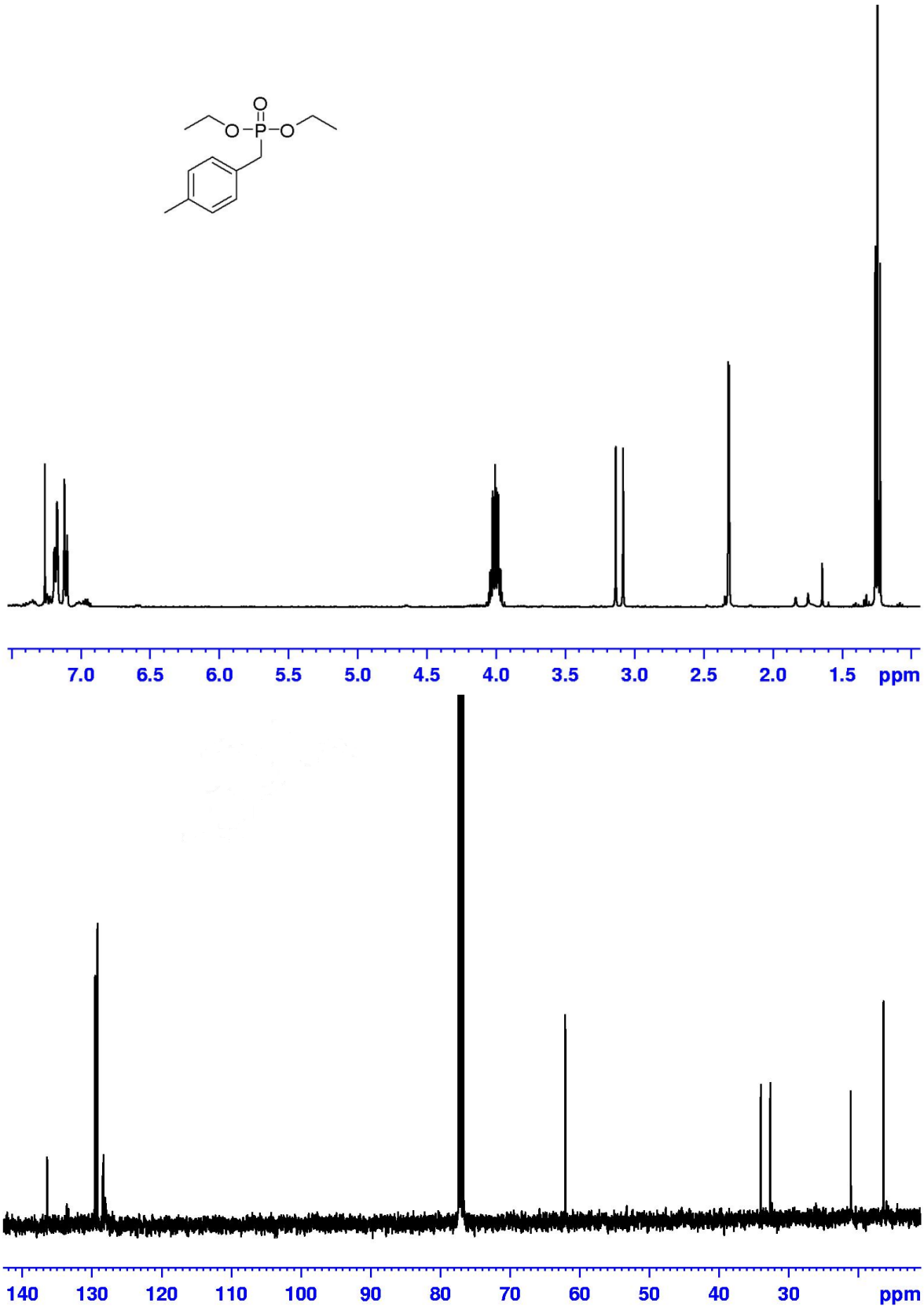

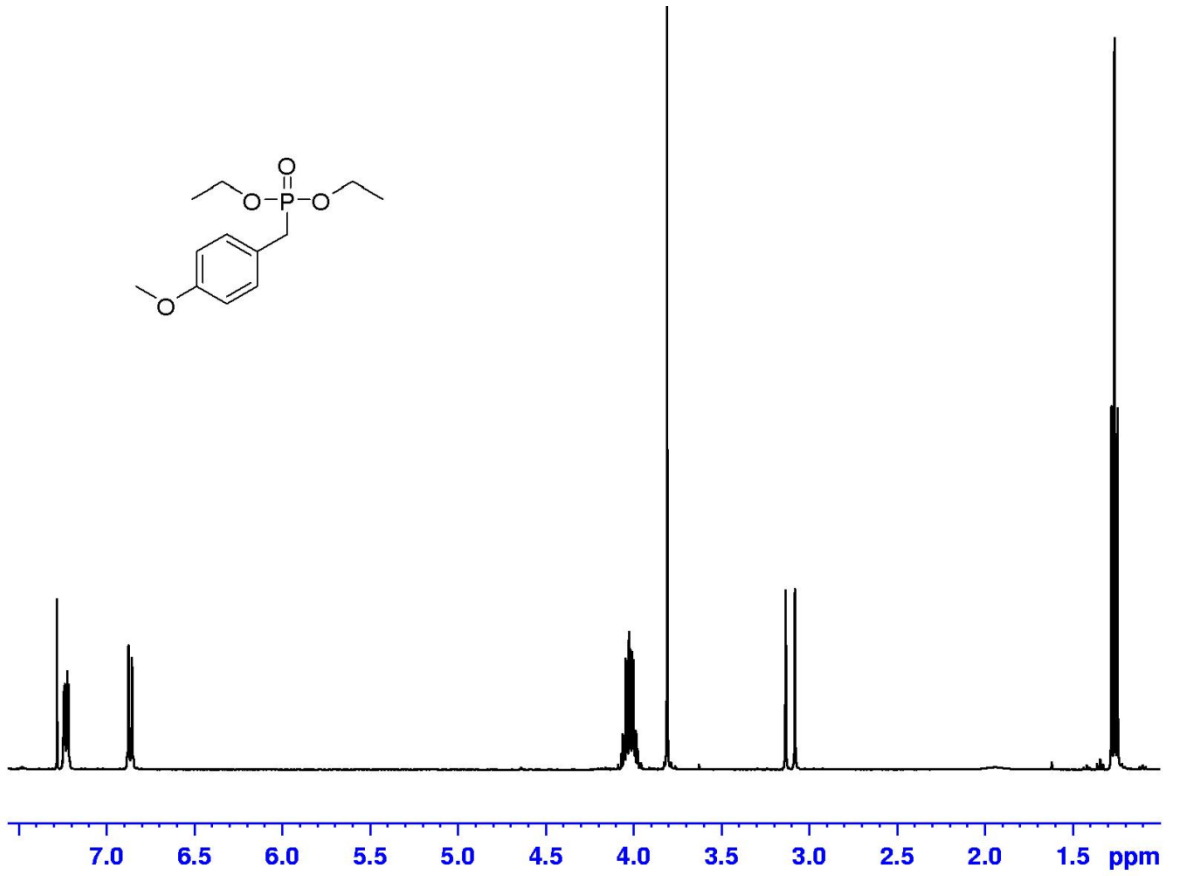

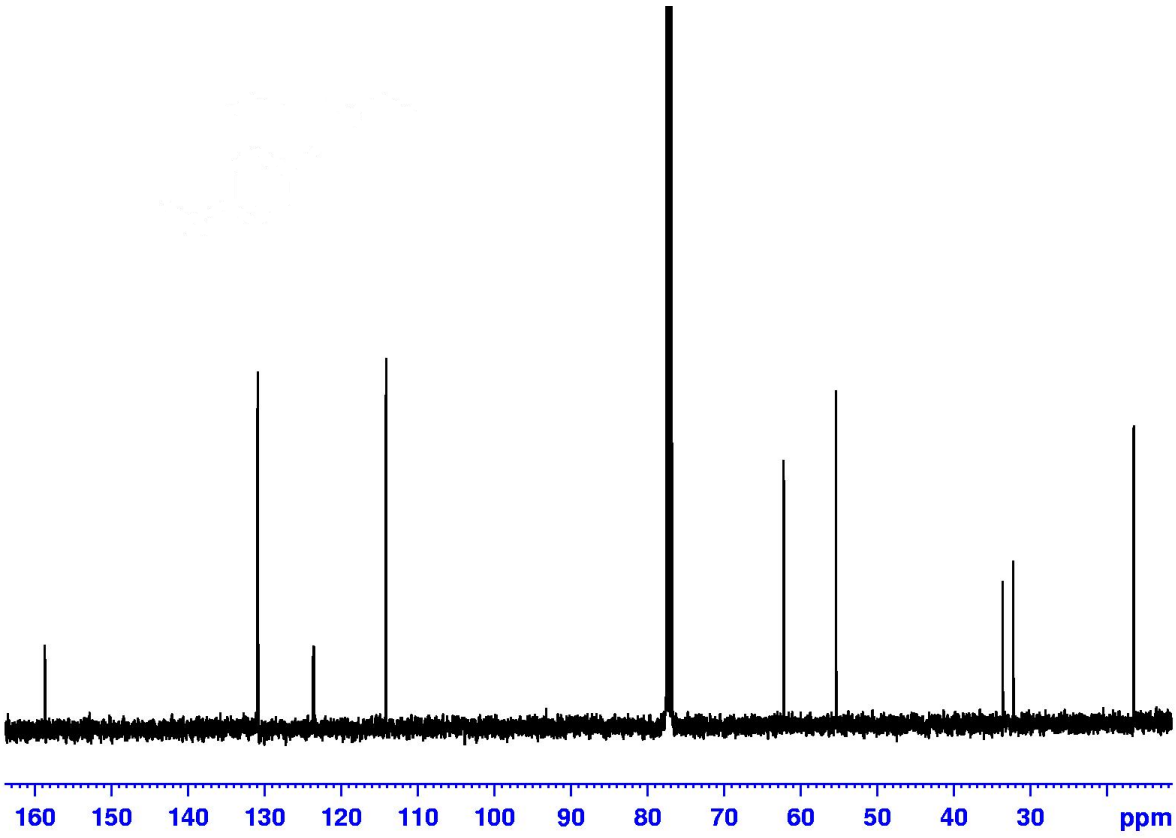

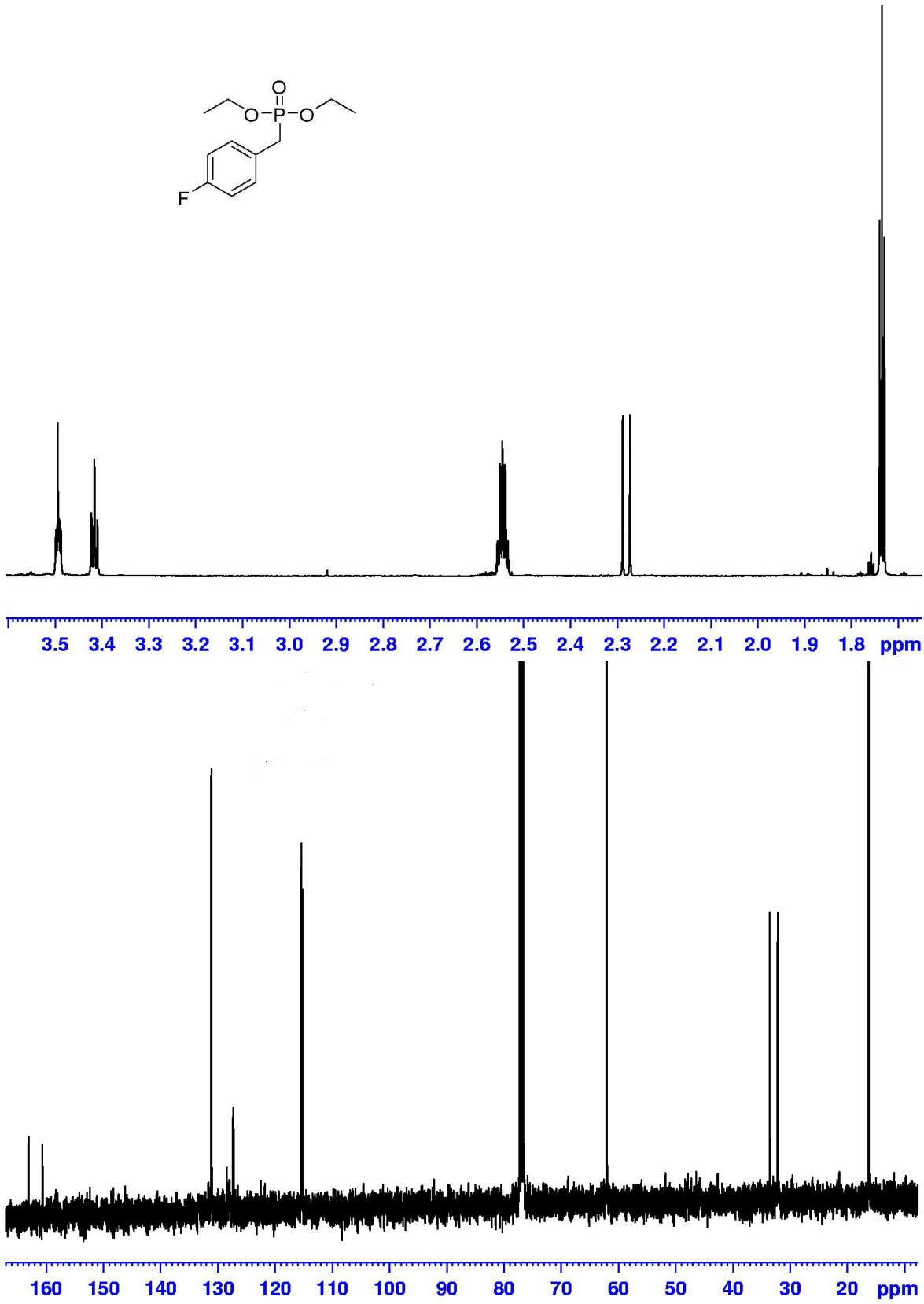

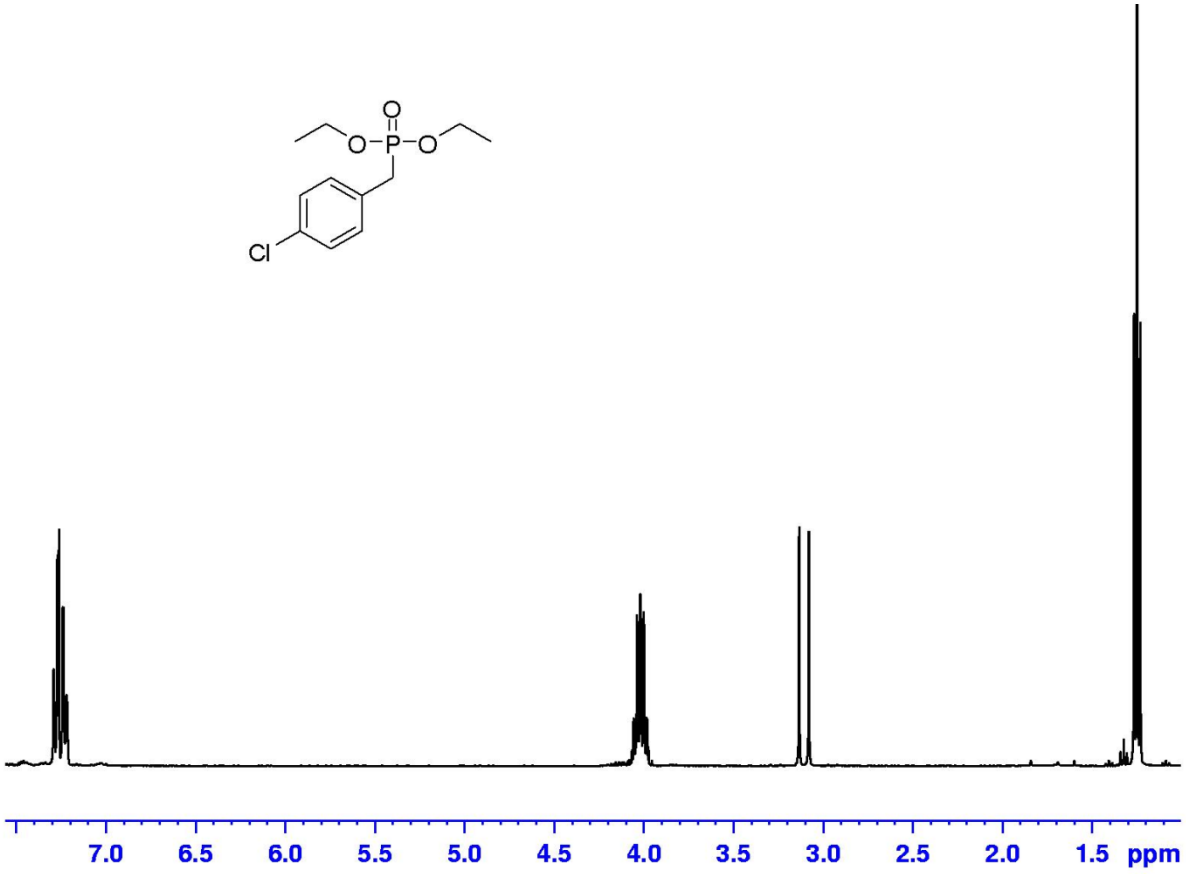

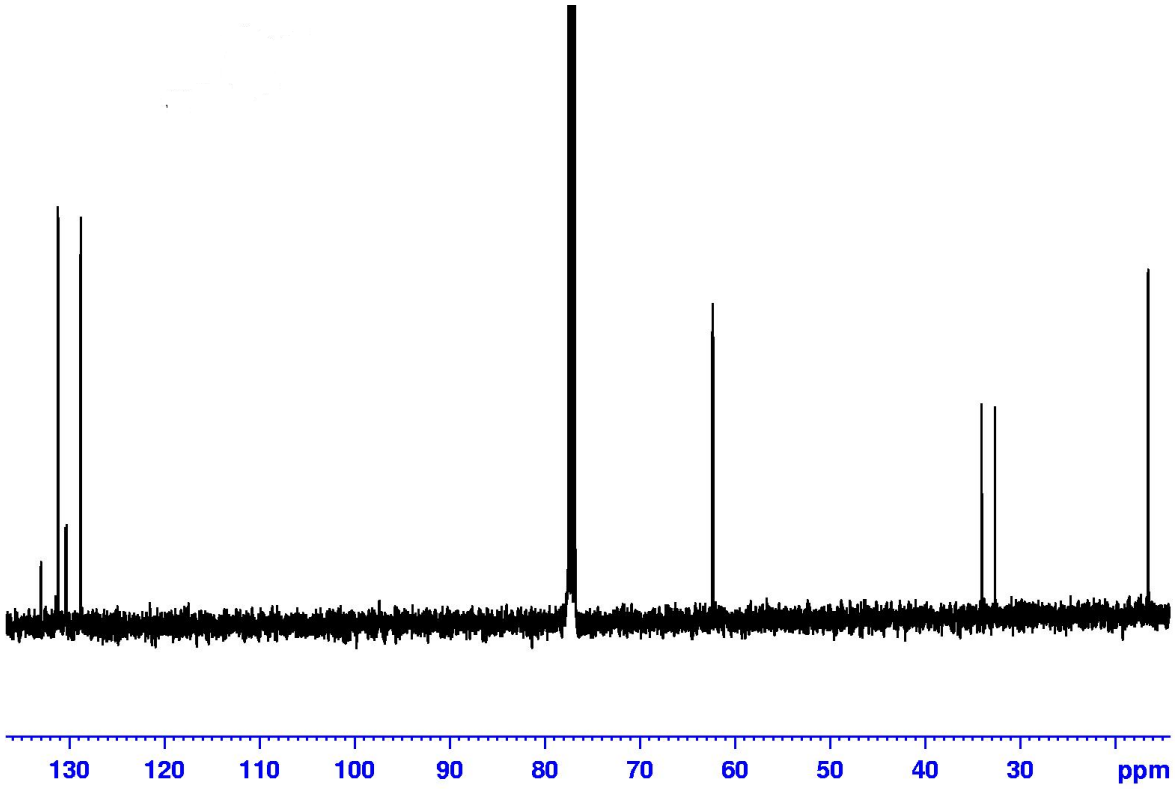

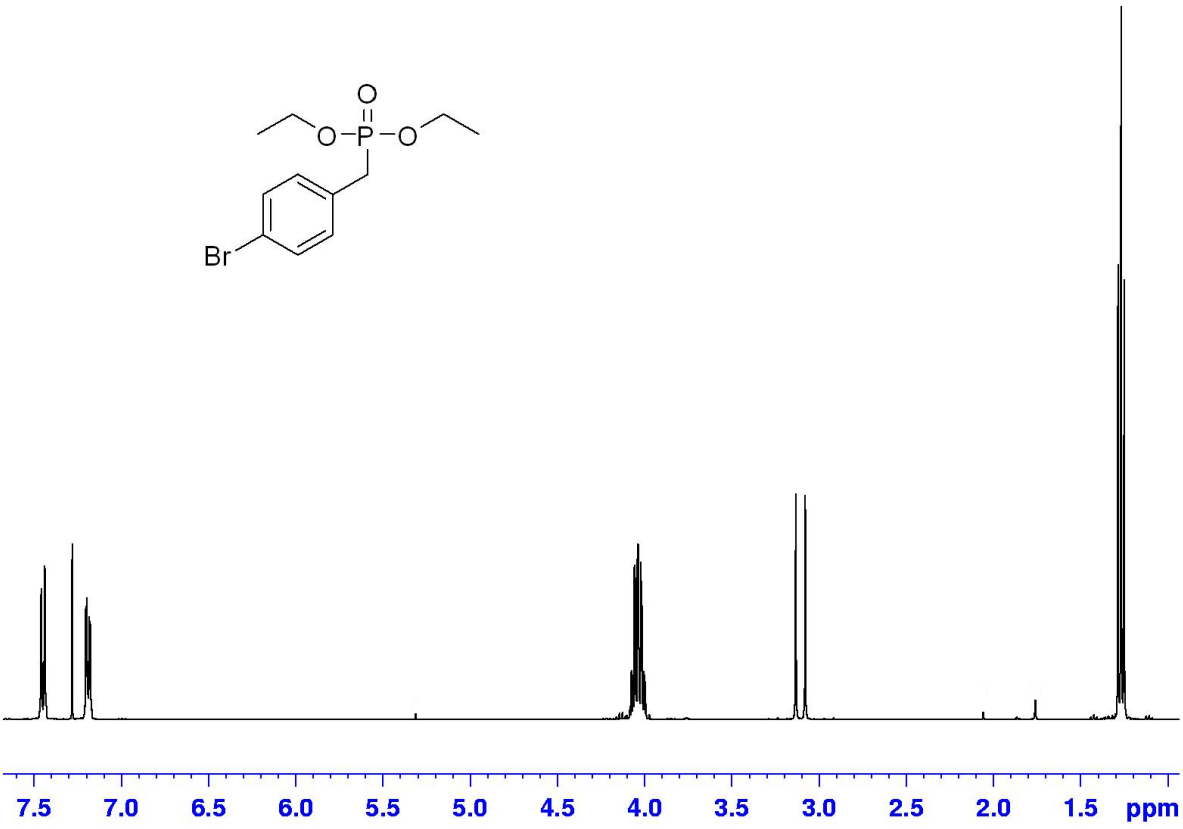
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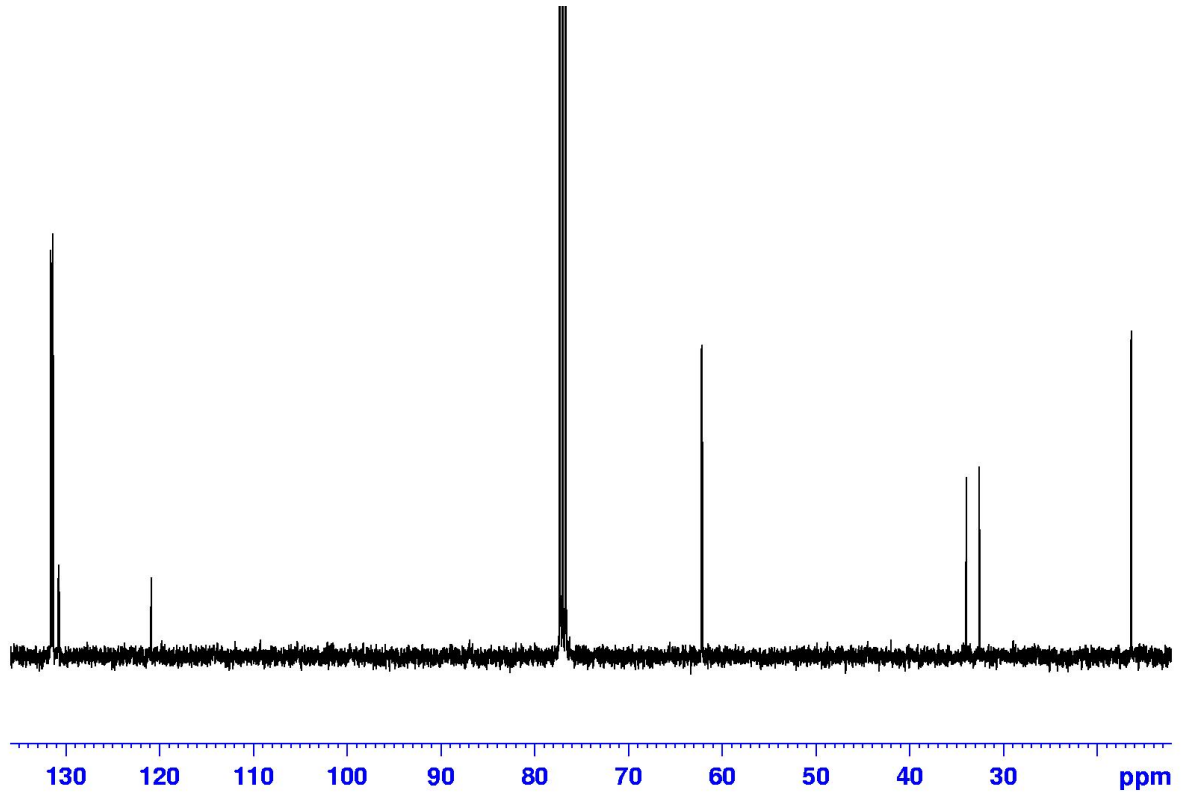
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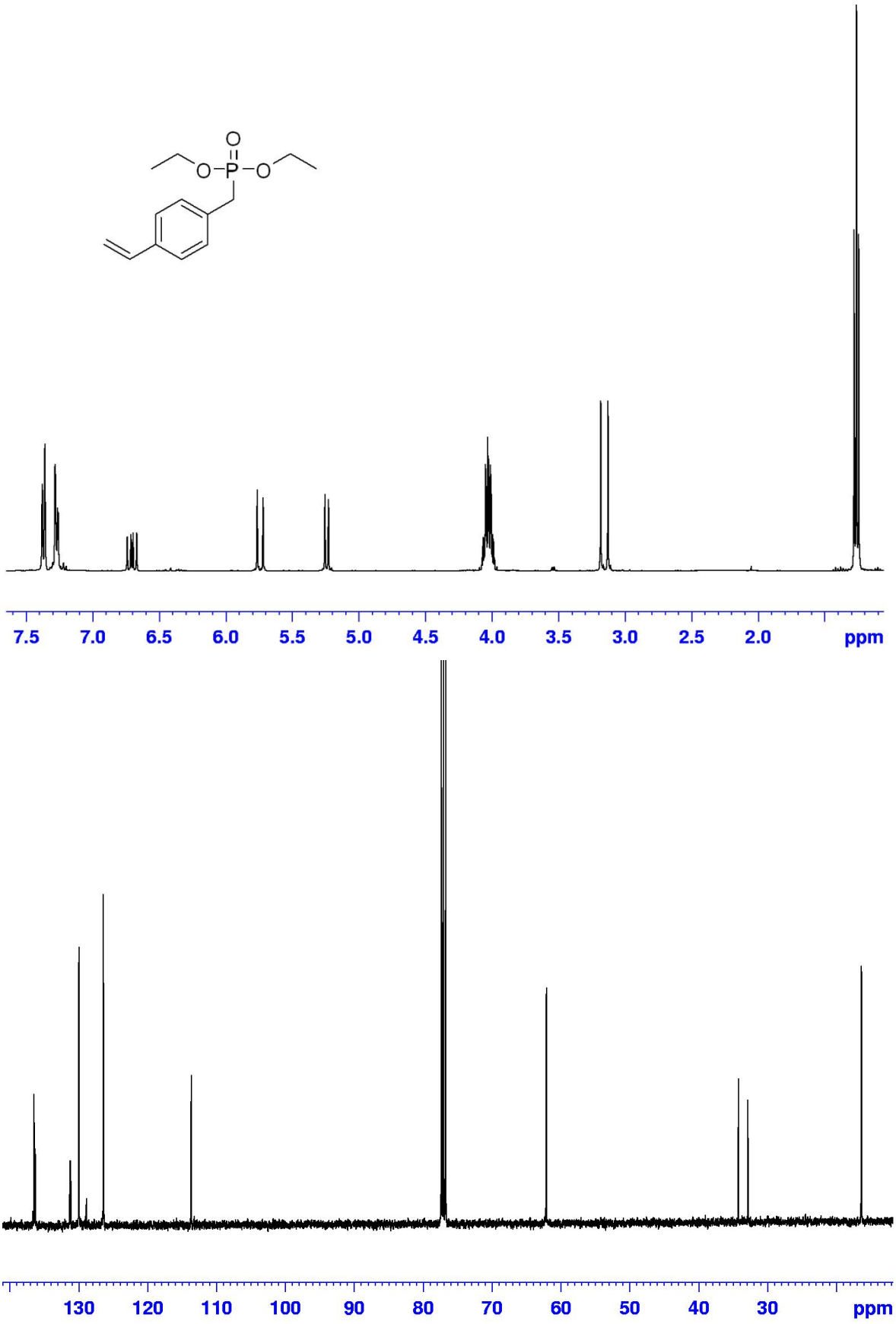

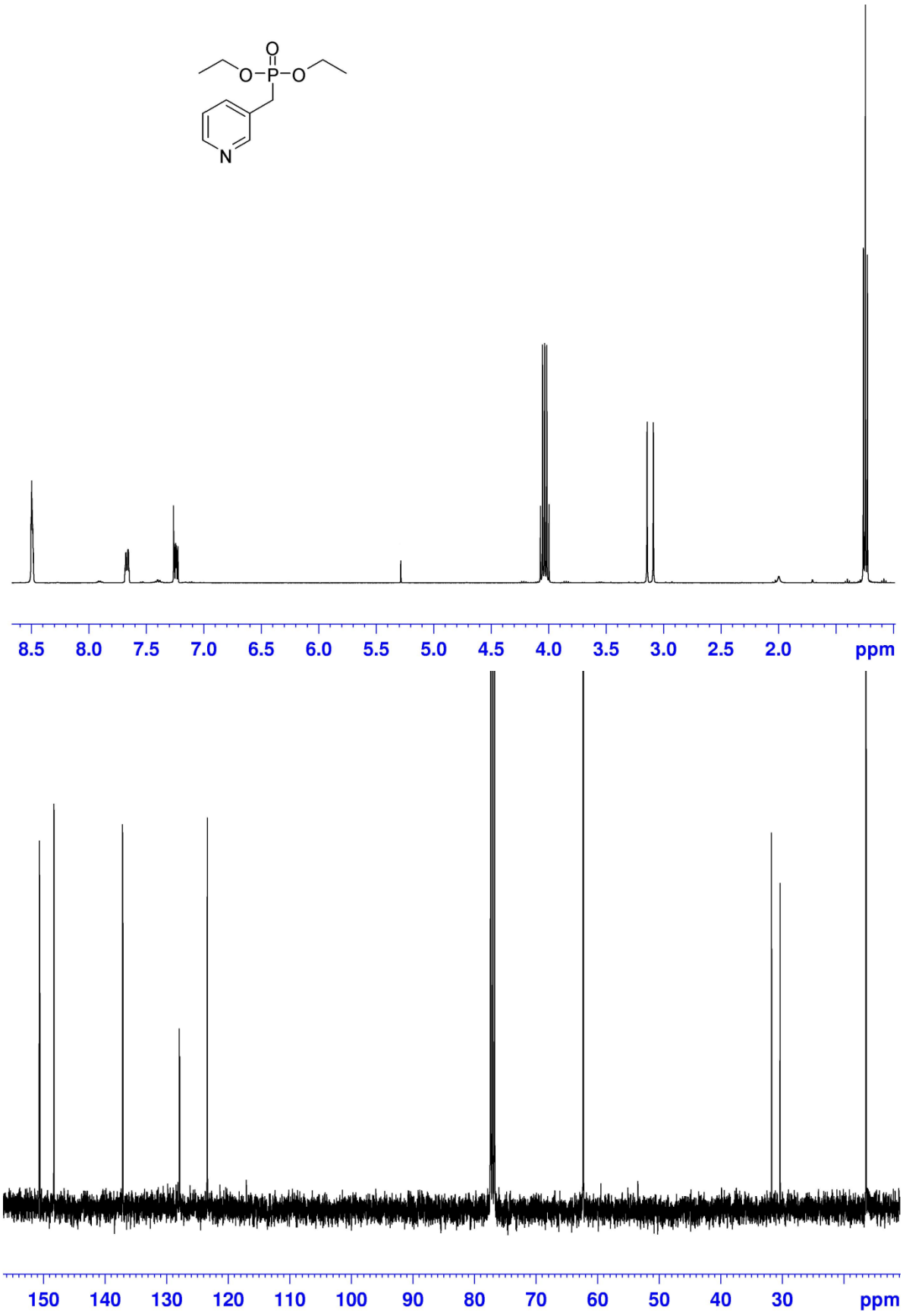

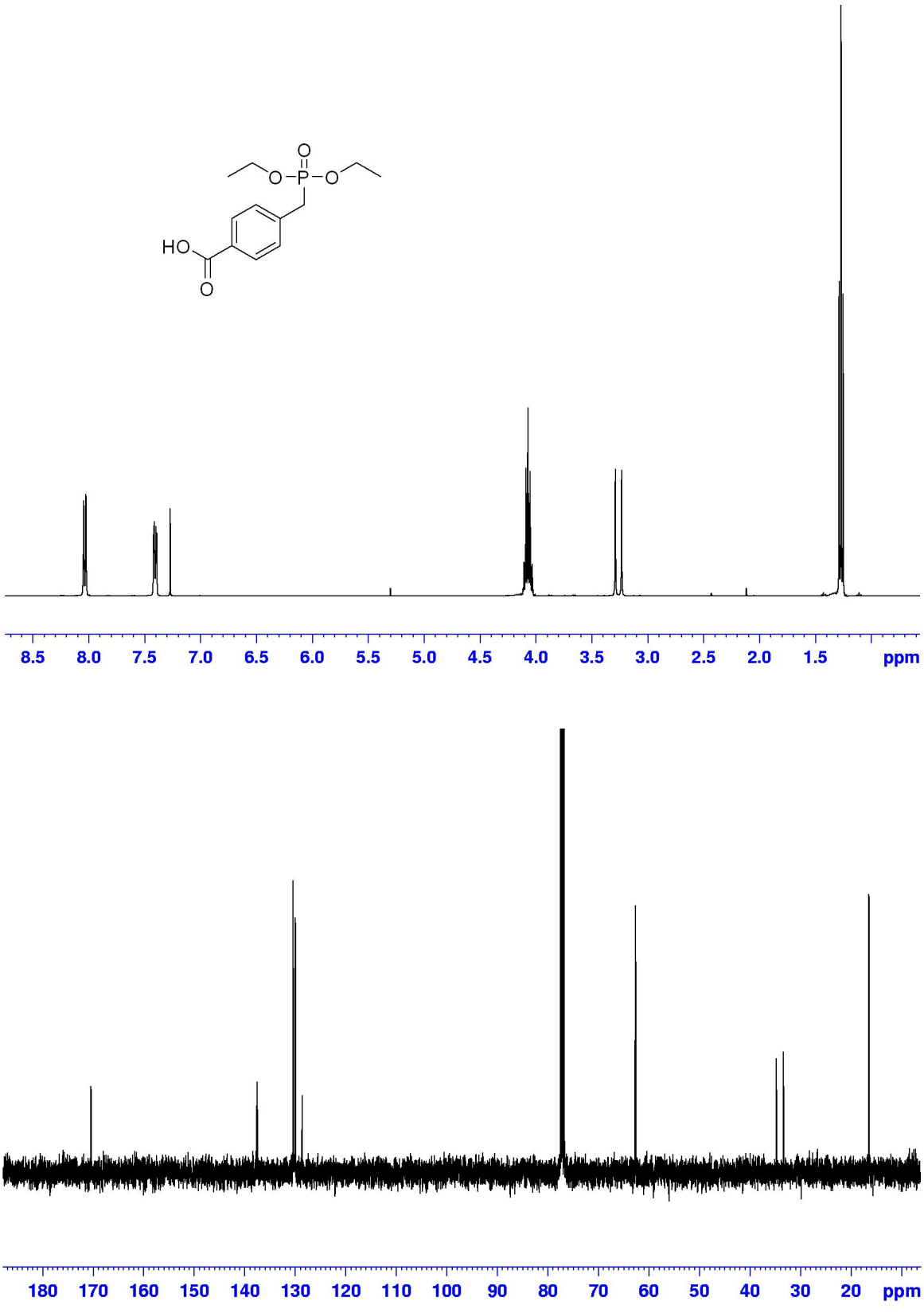

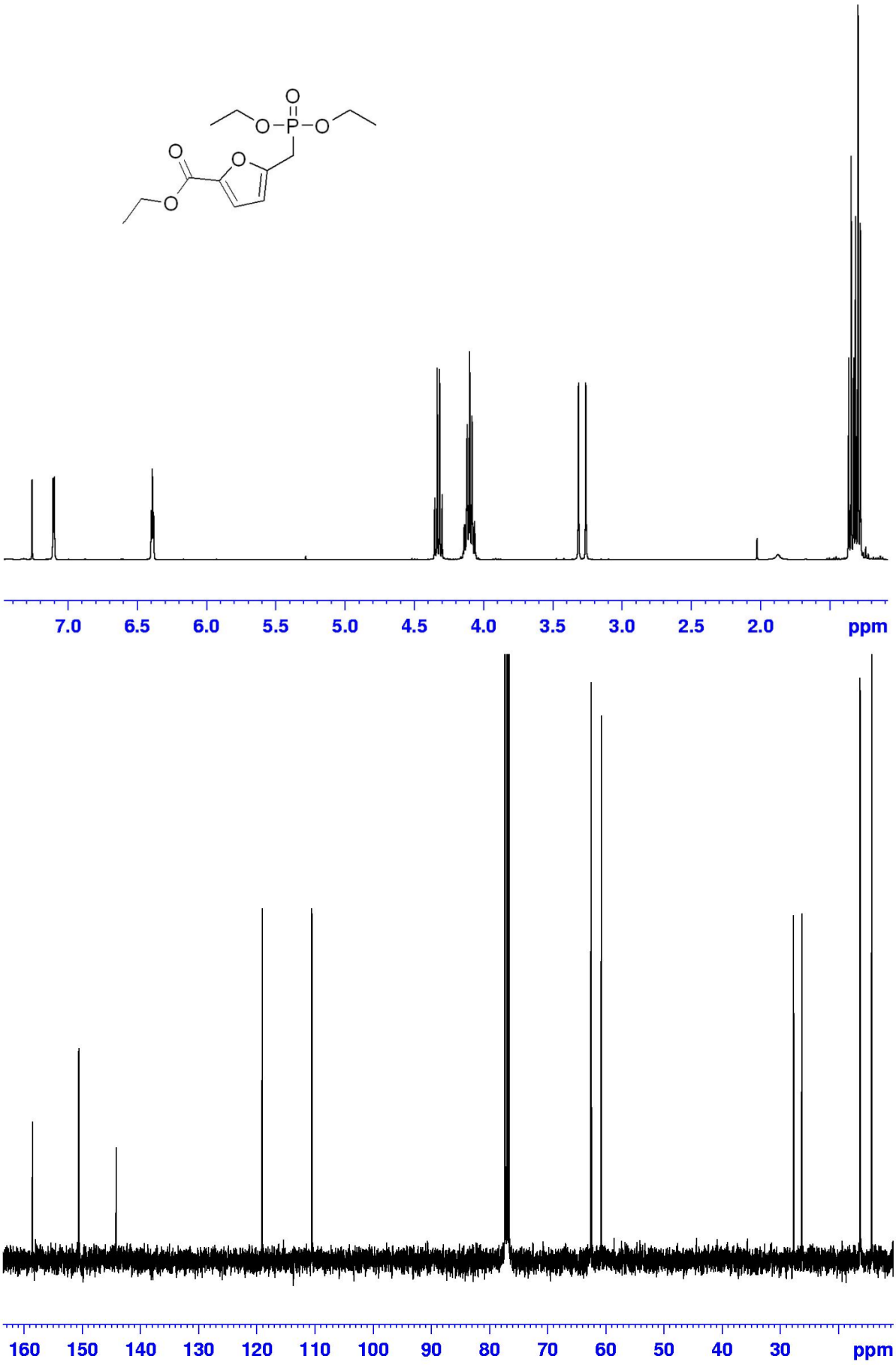

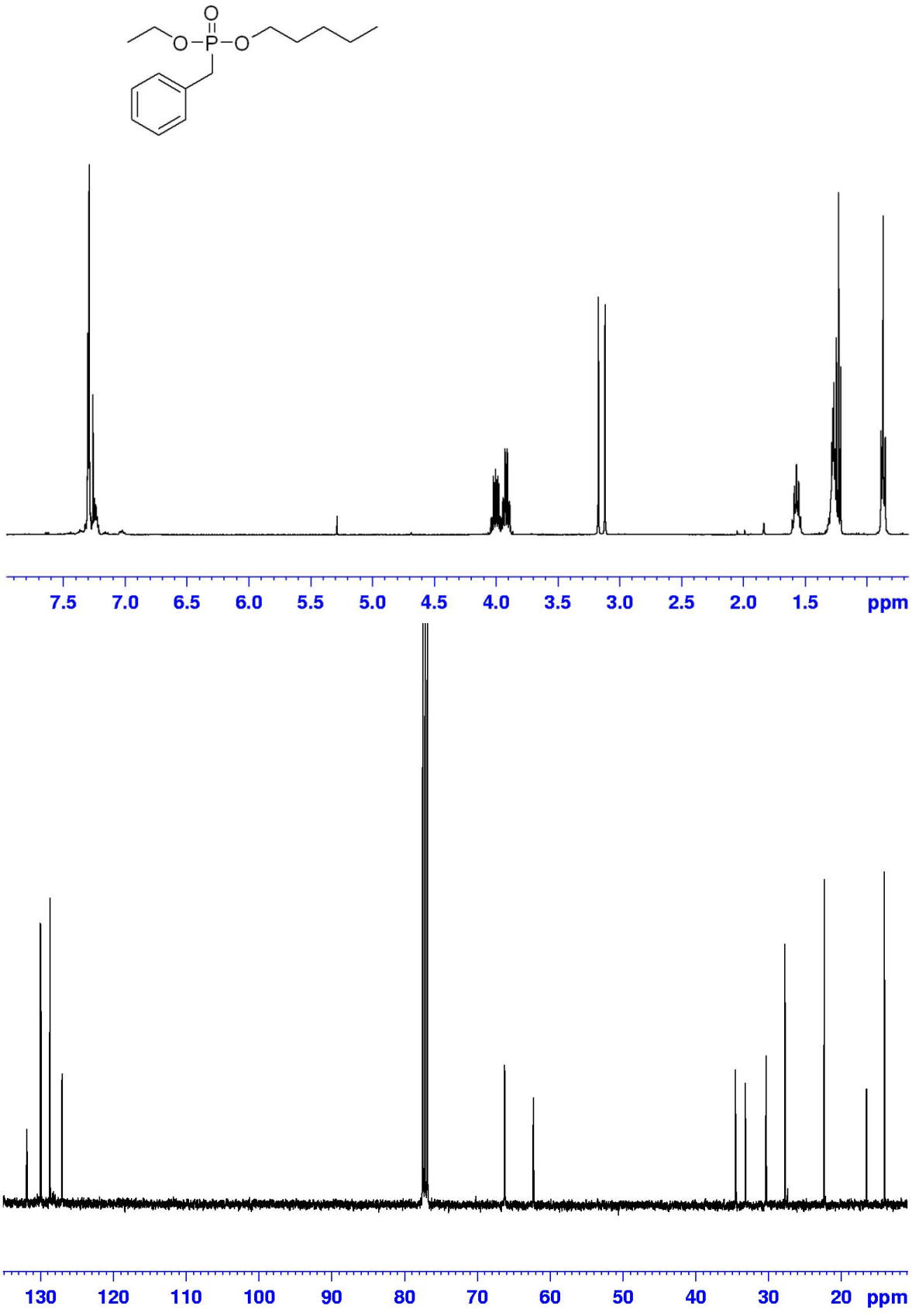

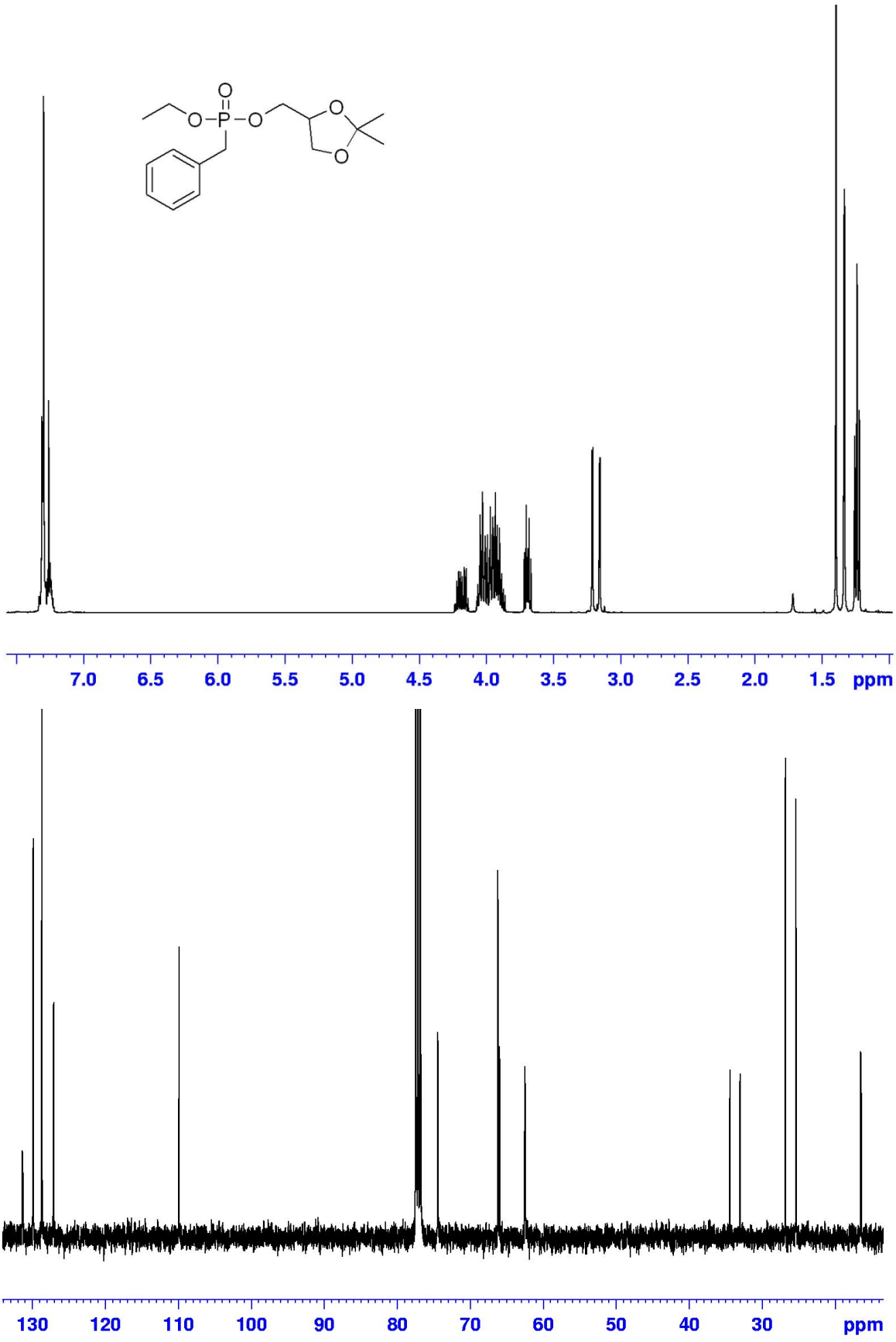

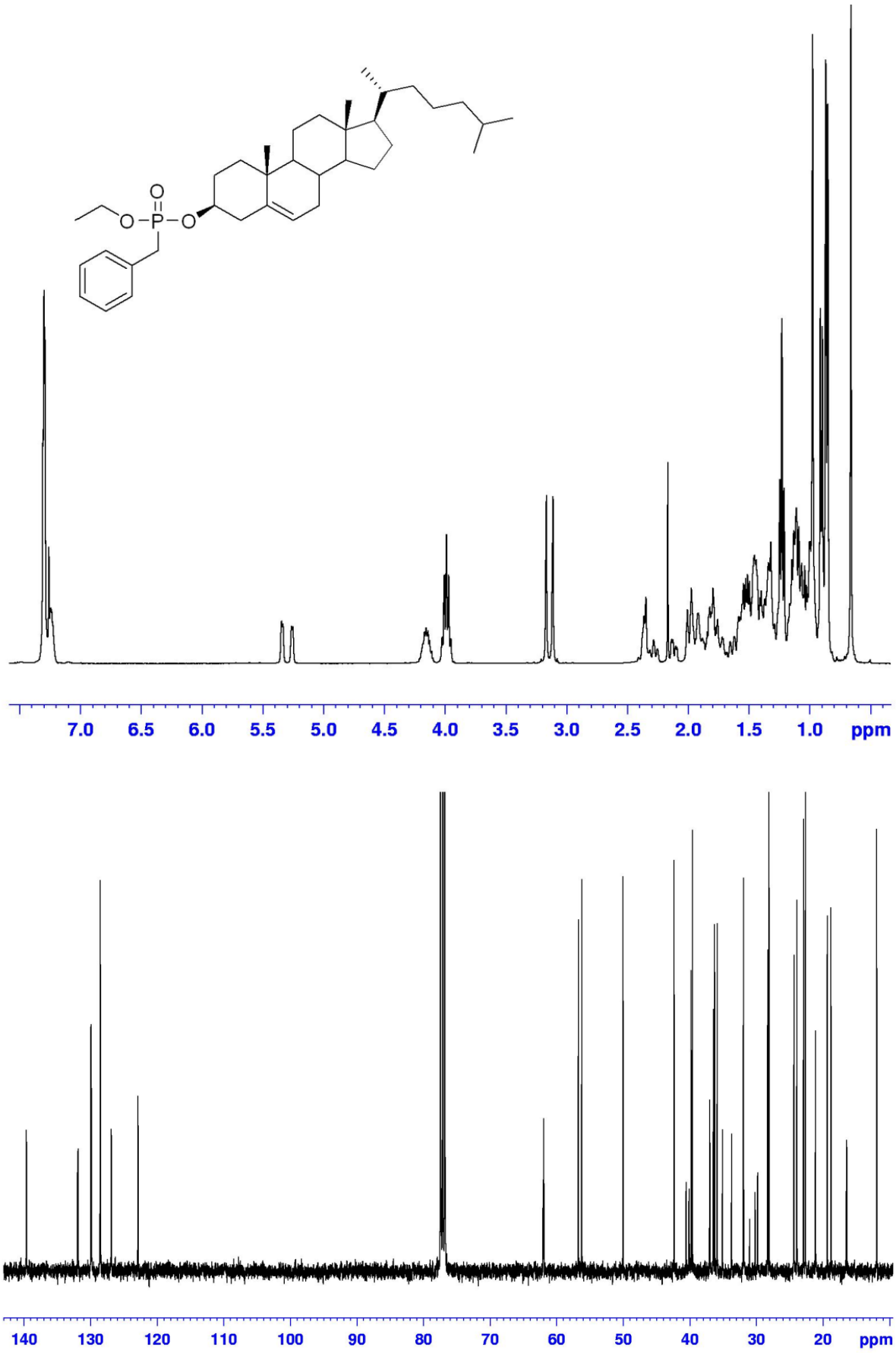

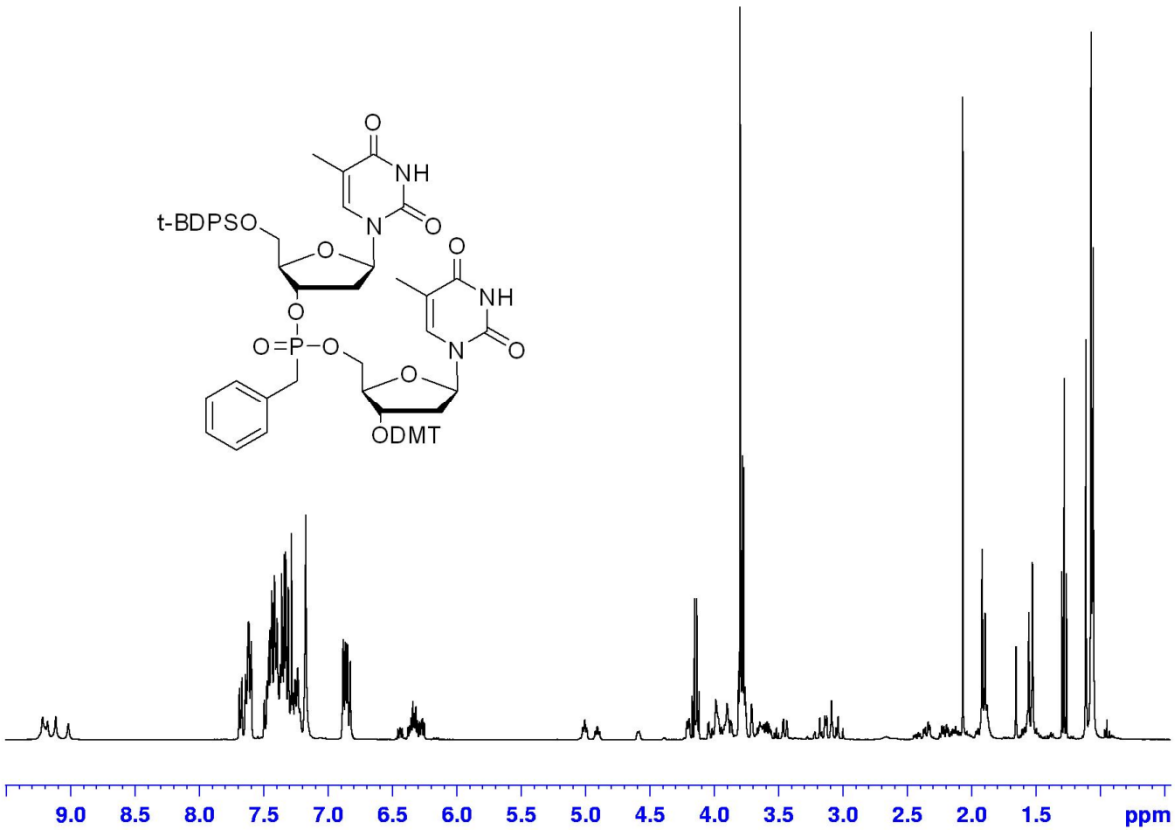

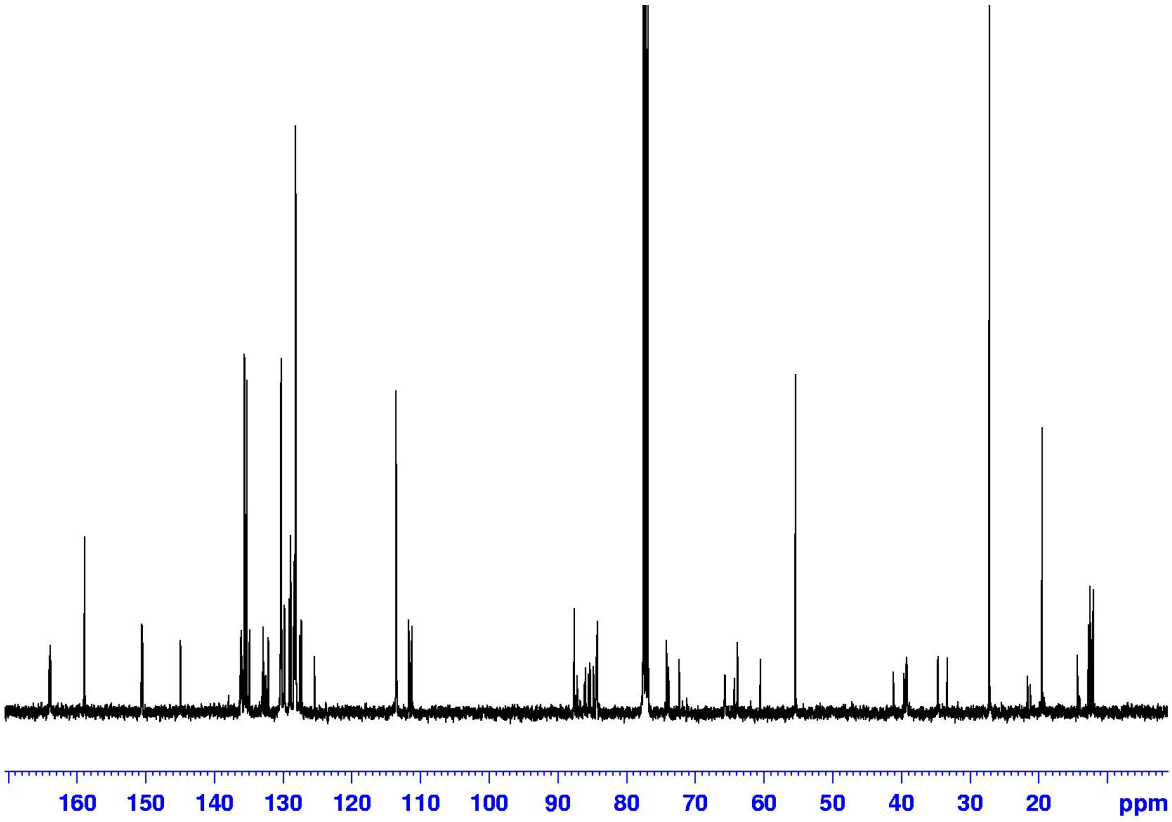

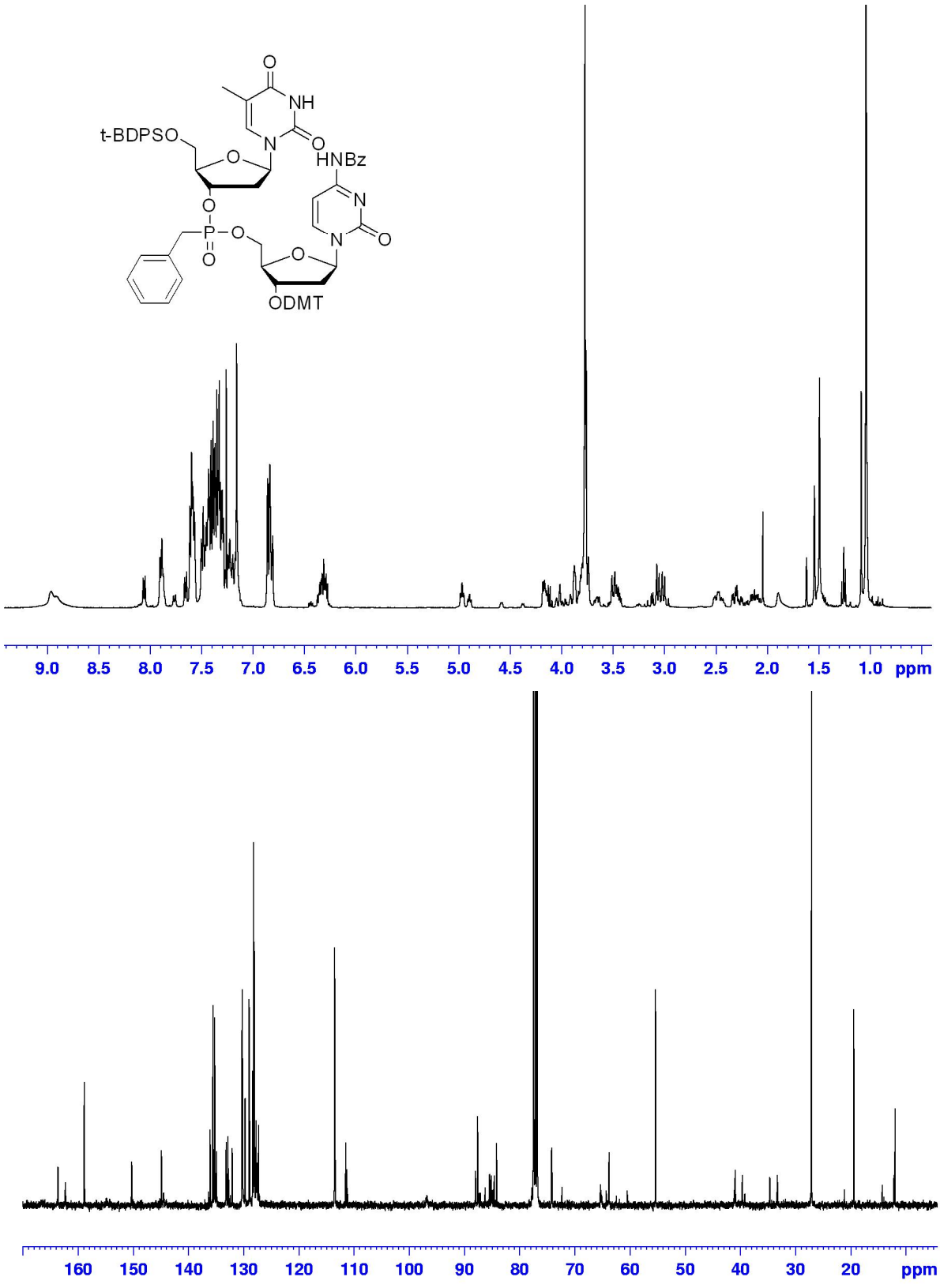

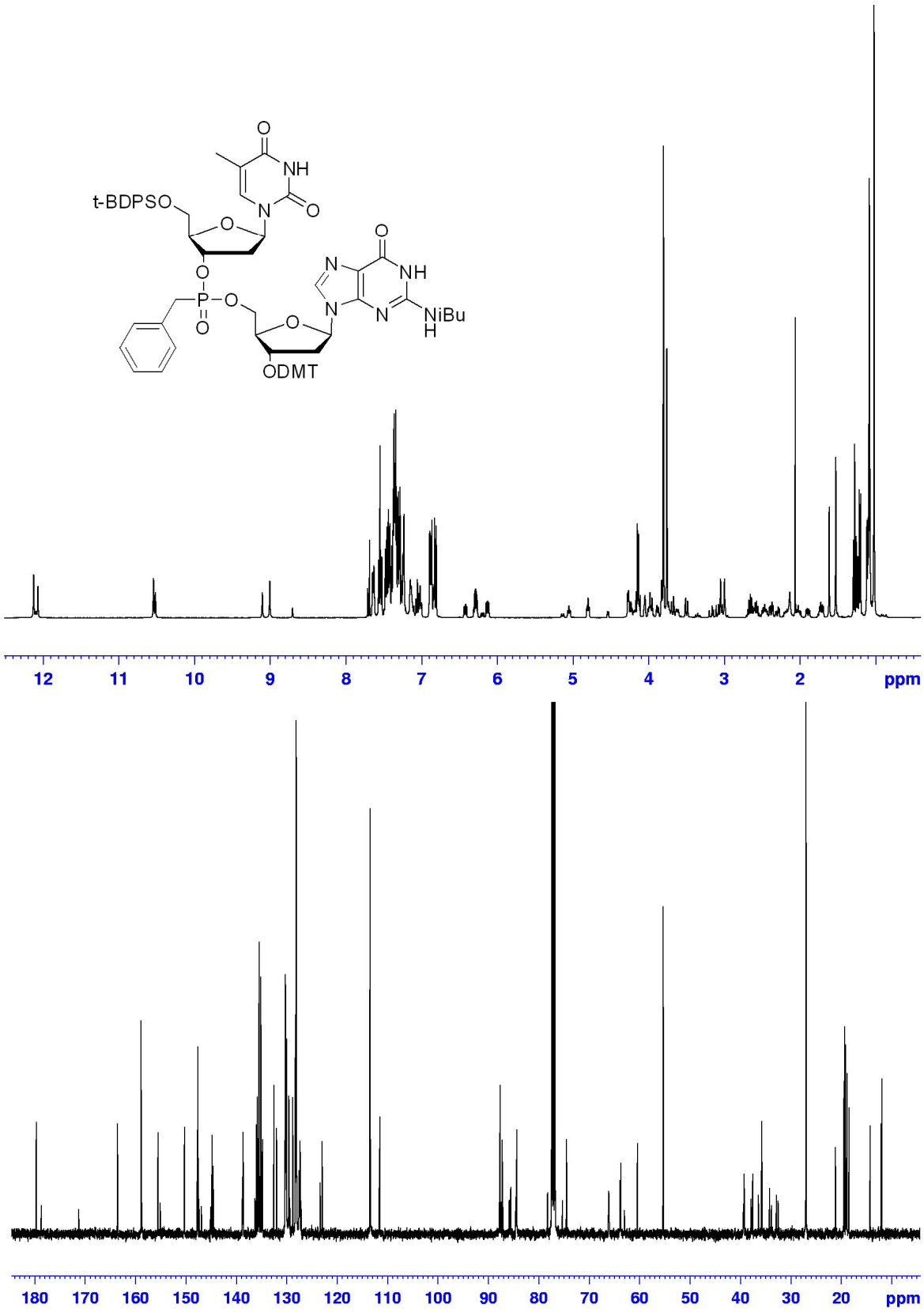
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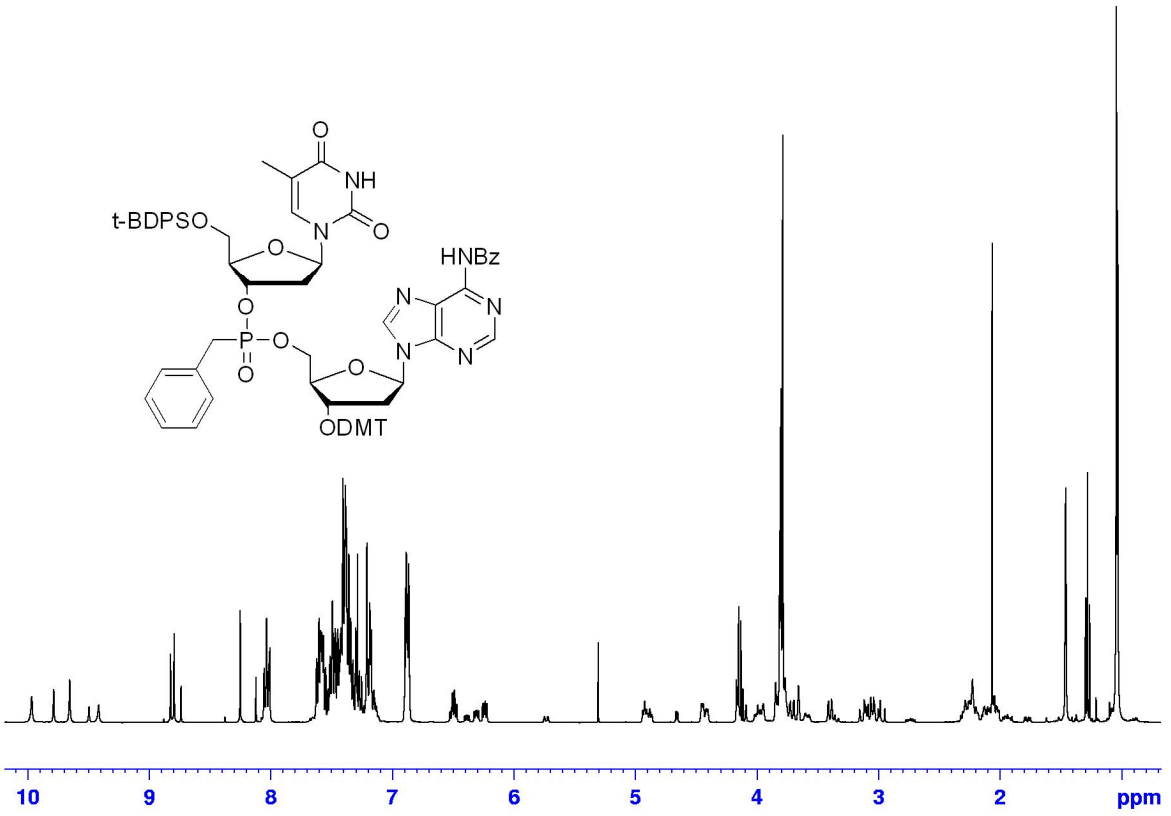
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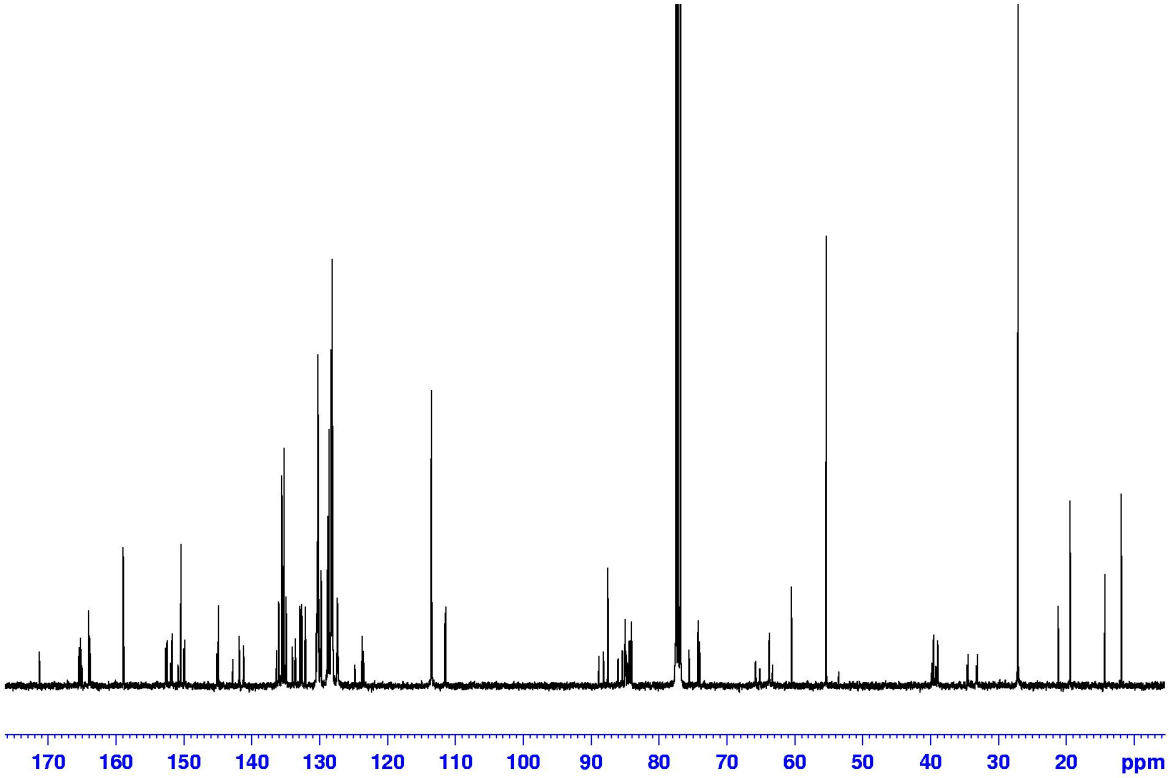
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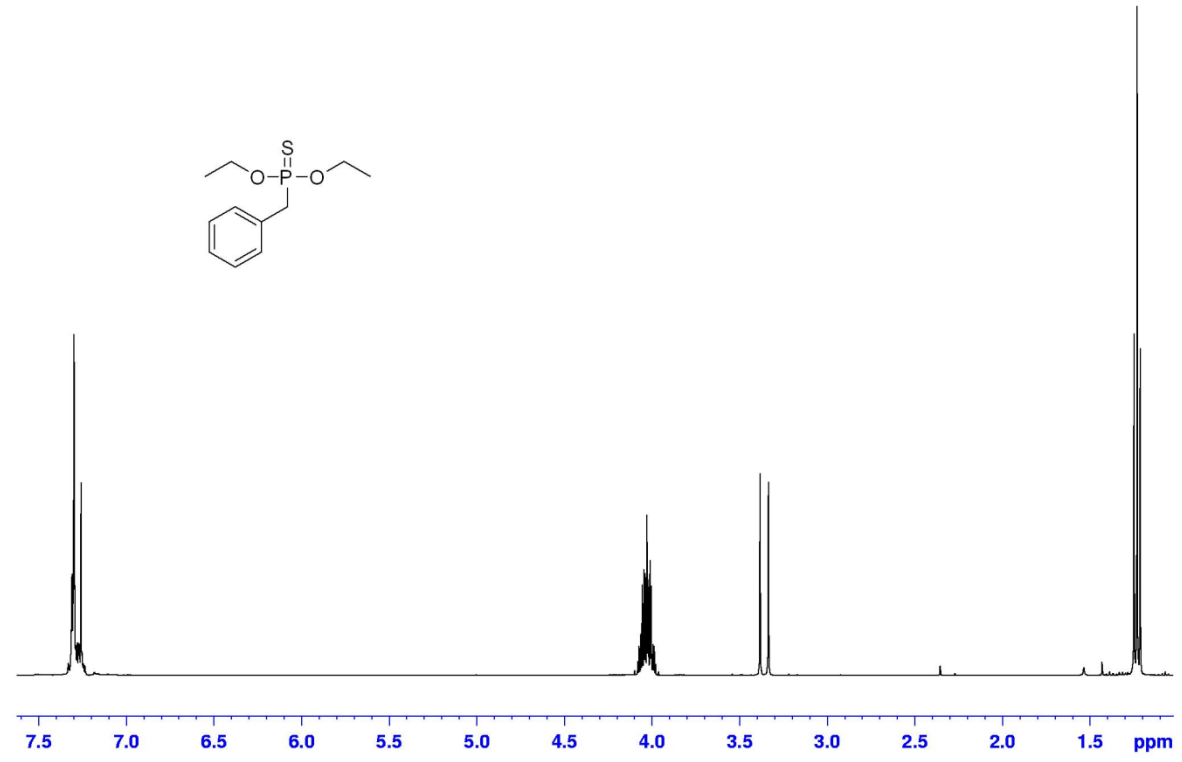
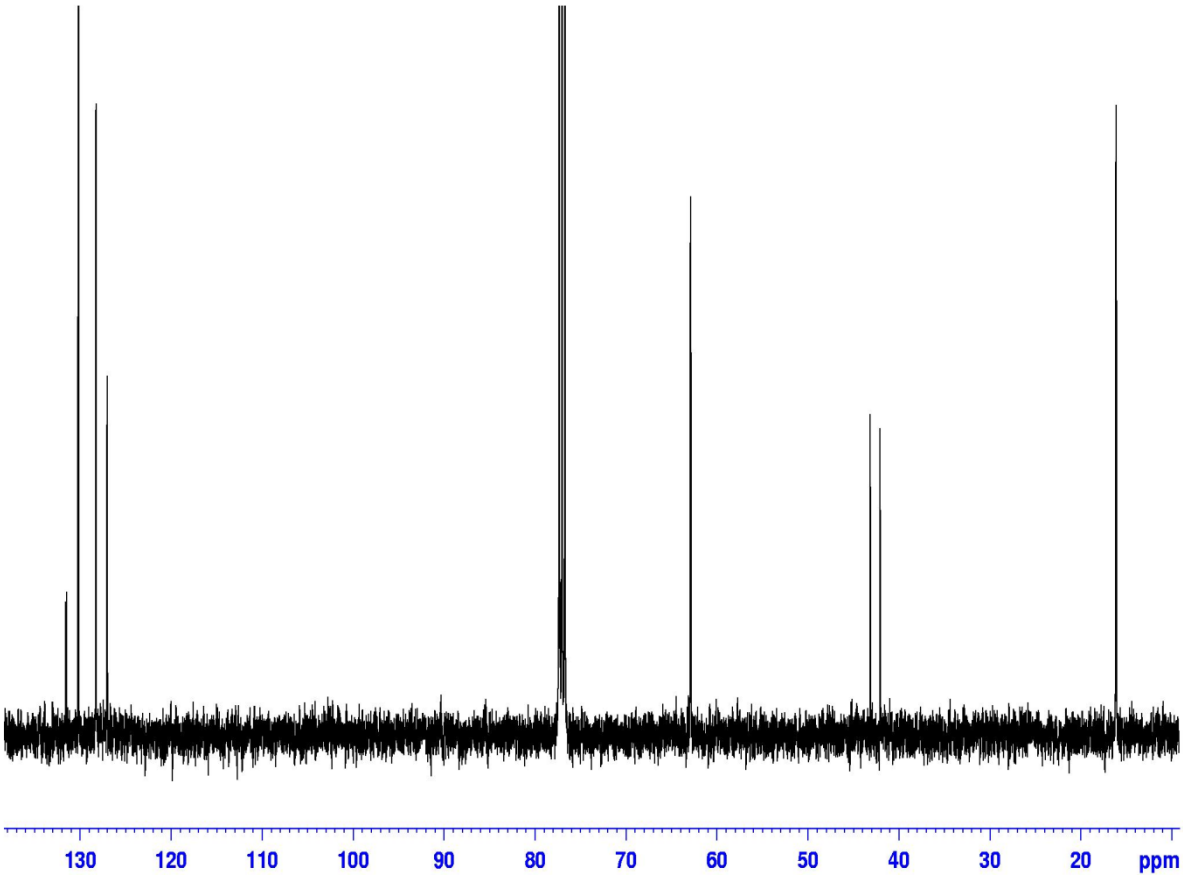
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


S
O
P
O
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
ppm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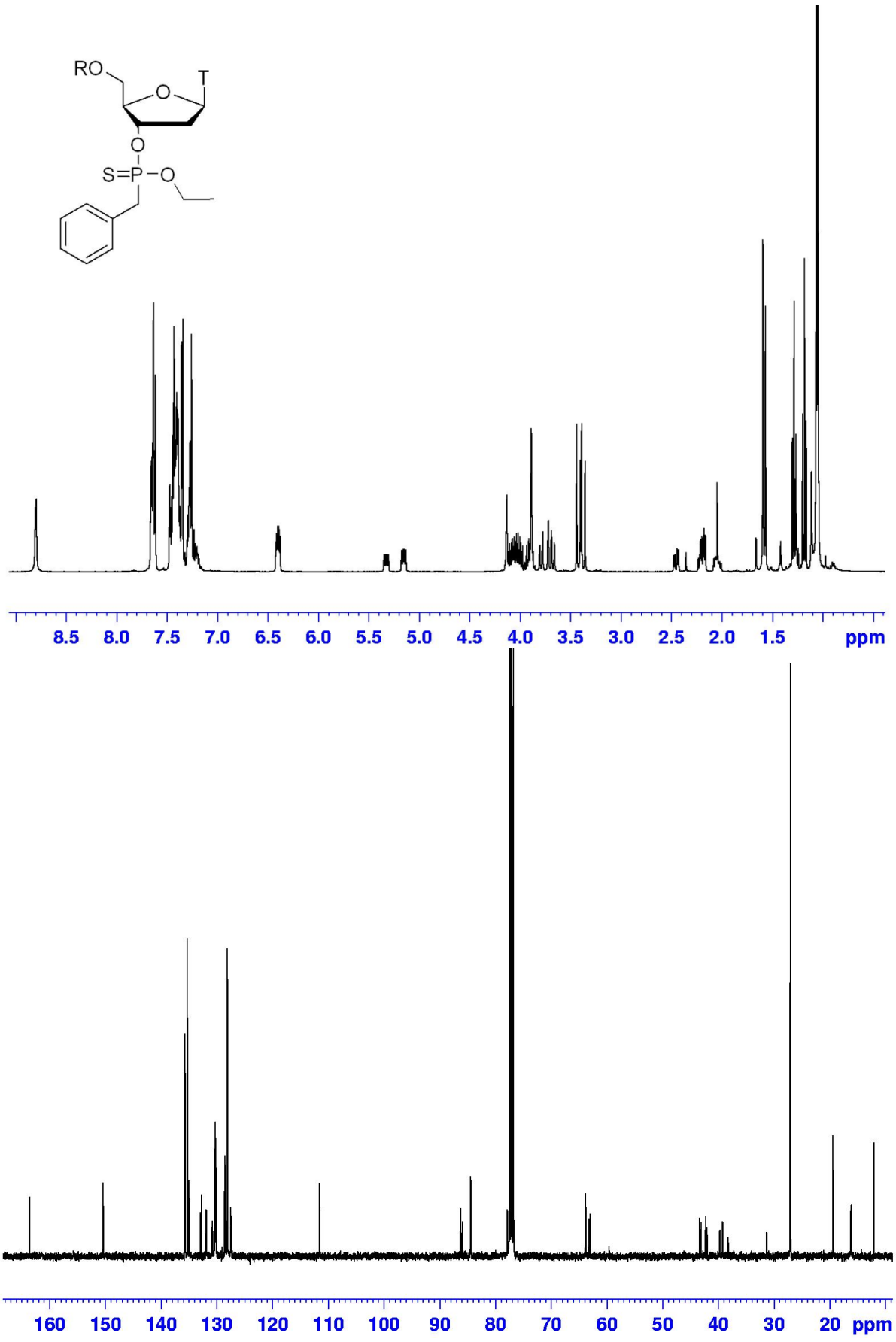
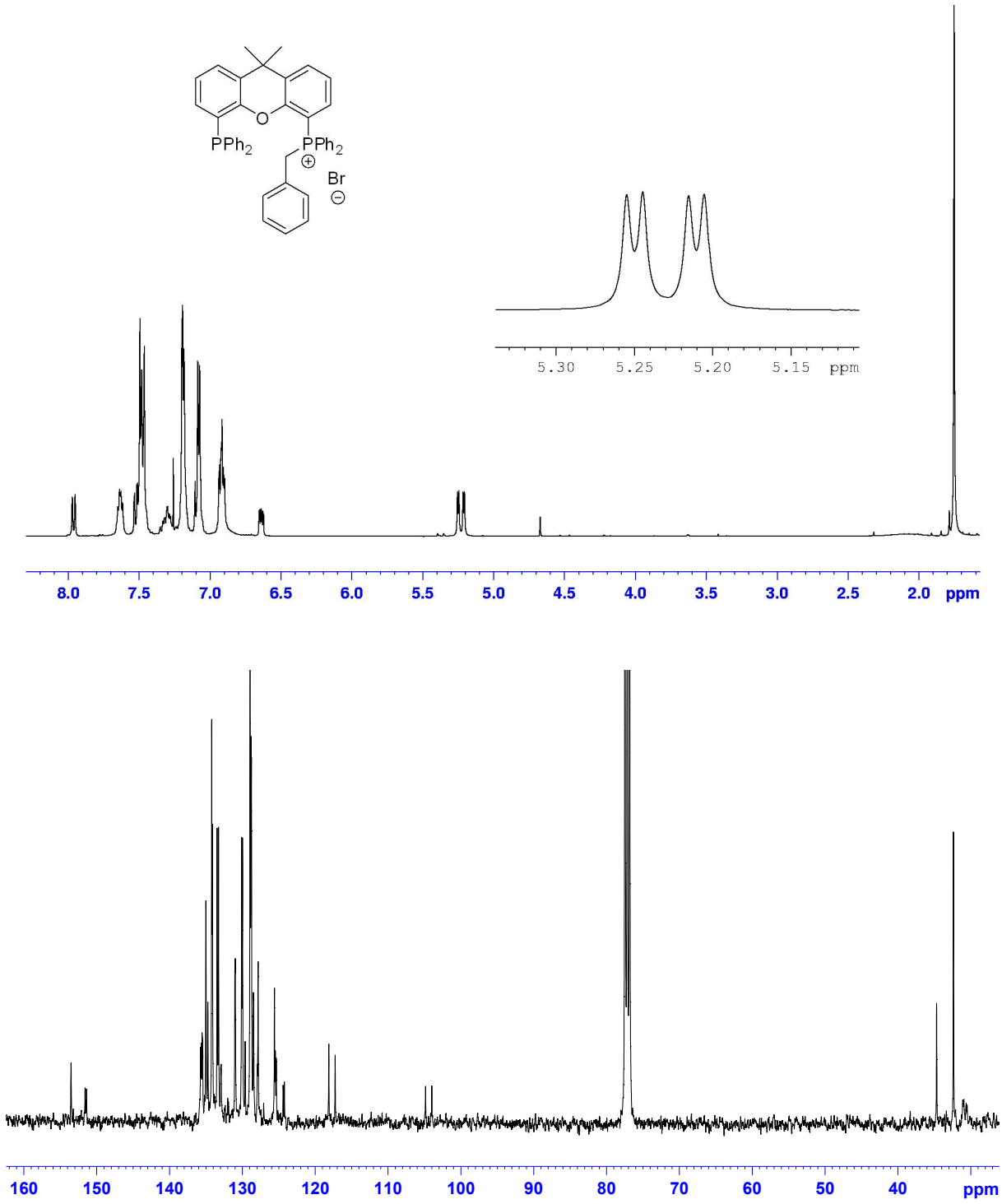
120
110
100
90
80
70
60
50
40
30
20
ppm

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PPh2
Br
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5.20
5.15
ppm
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3.5
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ppm
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140
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110
100
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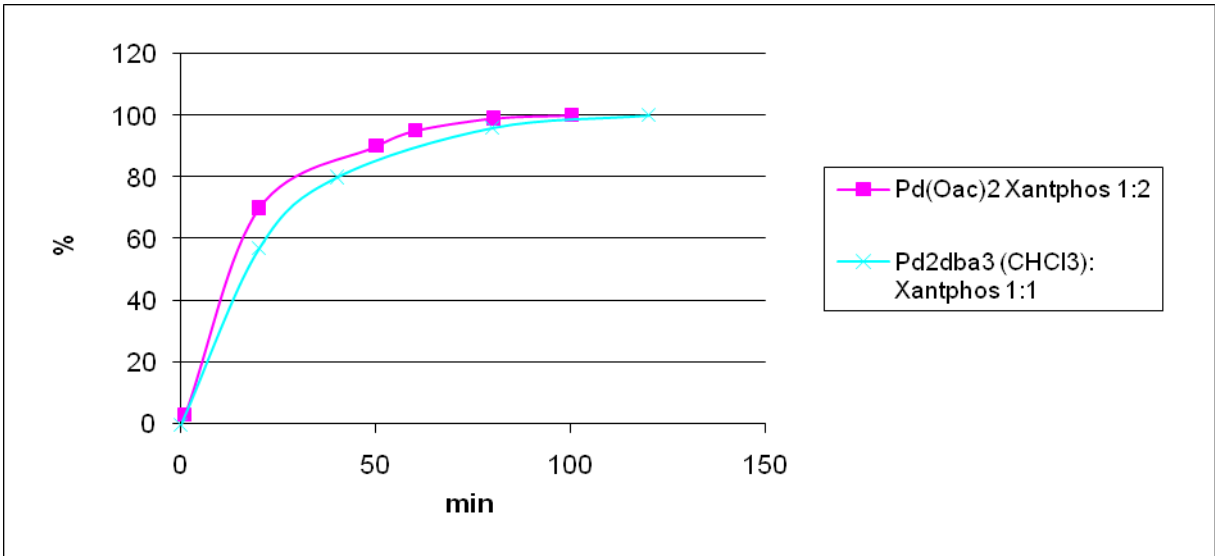


Figure S1. Comparison between 3 mol% $Pd(OAc)_2$ + 6 mol% Xantphos and 1.5 mol% Pd_2dba_3 ($CHCl_3$) + 3 mol% Xantphos in coupling of Bn-Cl with diethyl H-phosphonate under standard reaction conditions.

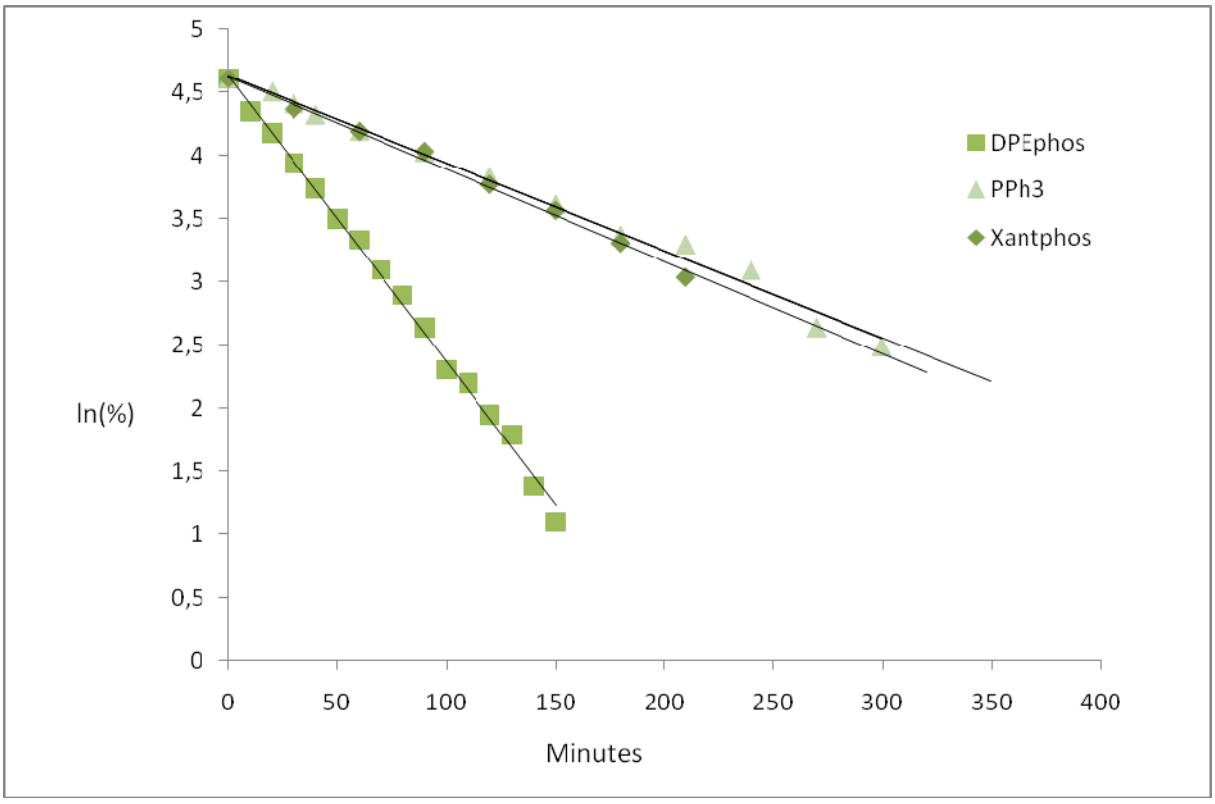
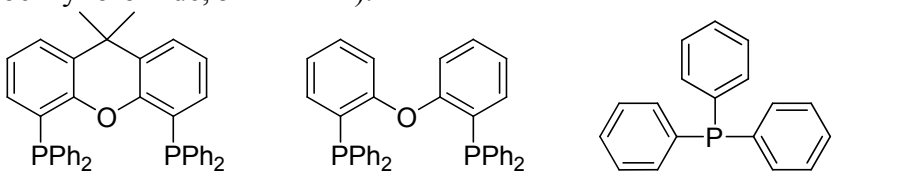


Figure S2. Alkylation of different phosphine ligands with benzyl bromide, in THF at 60 °C (0.10 mmol bidentate ligands or 0.20 mmol triphenylphosphine, 1.0 mmol benzyl bromide, 5 mL THF).



Xantphos DPEphos Triphenylphosphine (TPP)

DPEphos $t_{1/2}$ = 30.5 min
Xantphos $t_{1/2}$ = 91.2 min
Triphenylphosphine $t_{1/2}$ = 100.5 min

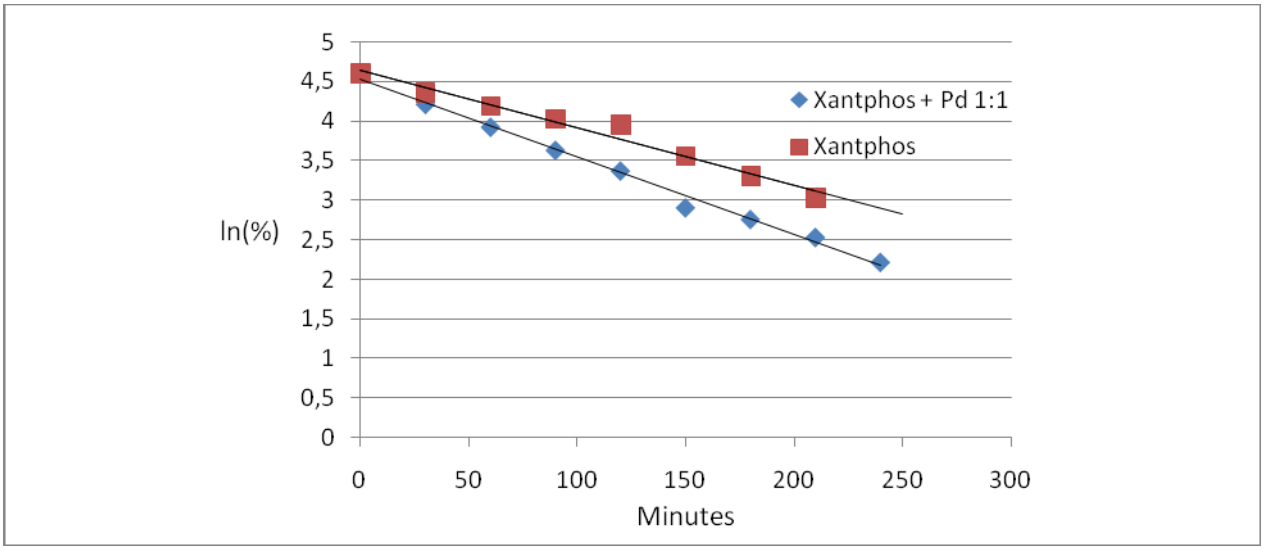


Figure S3. Comparison of xantphos alkylation with benzyl bromide, in presence and absence of $Pd_2dba_3(CHCl_3)$, in THF at 60 °C (0.10 mmol xantphos, 1.0 mmol benzyl bromide, none or 0.05 mmol Pd $Pd_2dba_3(CHCl_3)$, 5 mL THF).

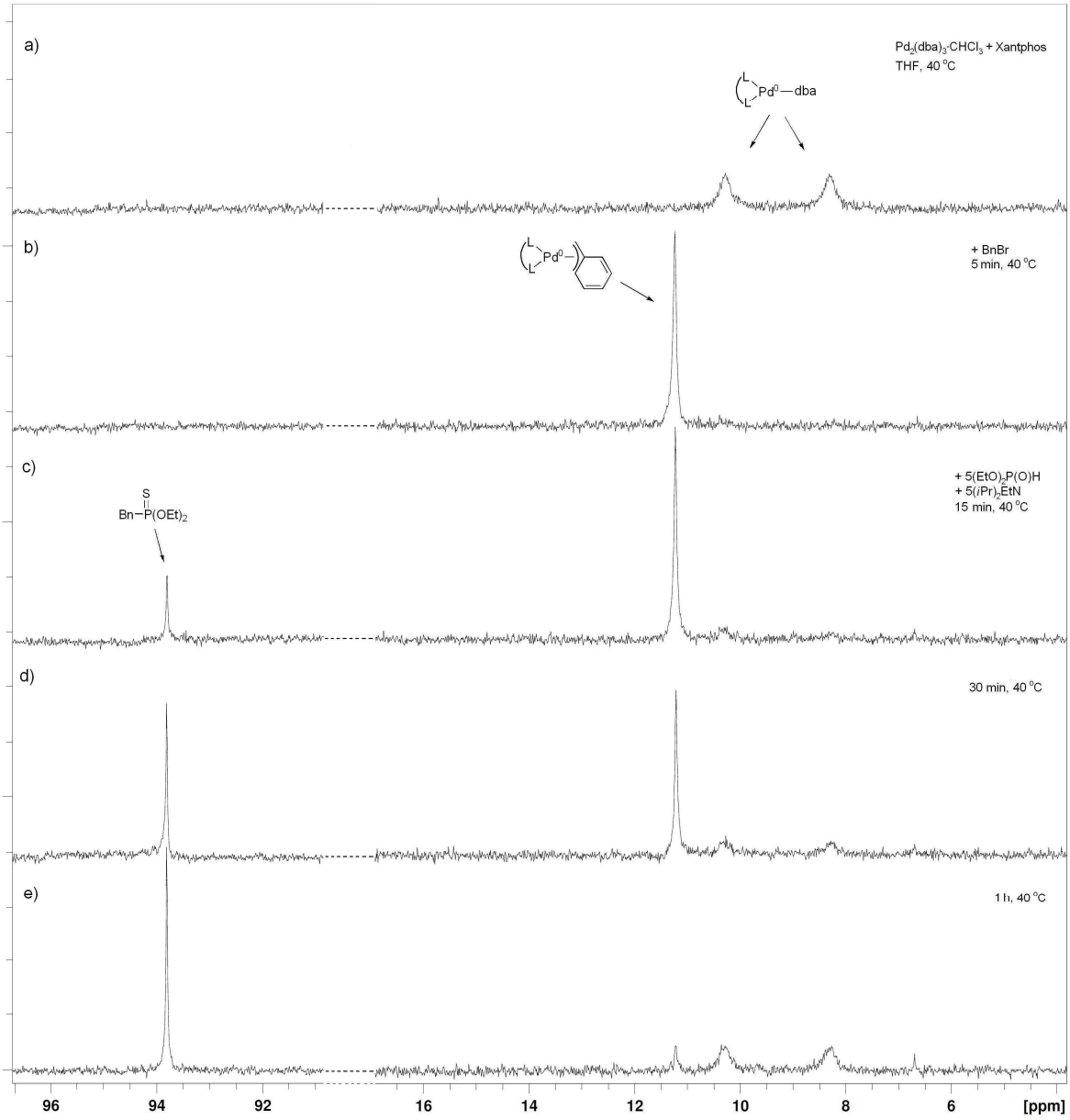


Figure S4. ^{31}P NMR spectra showing the oxidative additon of equimolar amounts of benzyl bromide to $Pd_2(dba)_3(CHCl_3)$]/Xantphos (1:2 mol ratio), followed by the reaction of added diethyl H-phosphonothioate (5 equiv.) and *N,N*-diisopropylethylamine (5 equiv.).