Electronic supplementary materials *Mendeleev Commun.*, 2019, **29**, 435–437

Versatile approach to the synthesis of naphthoquinone phosphonium salts and evaluation of their biological activity

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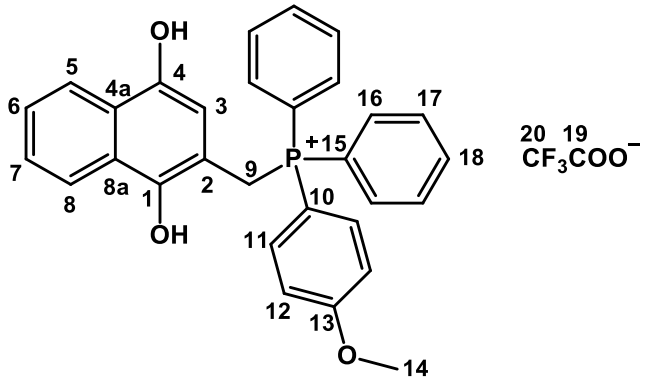
General remarks

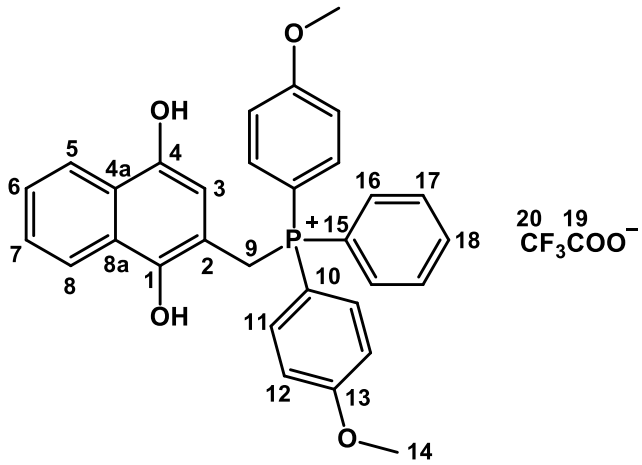
NMR experiments were carried out using a Bruker Avance-400 spectrometer [USA, 400.1 MHz (^{1}H), 162.0 MHz, (^{31}P), 100.6 MHz (^{13}C)] or Avance-600 one [600.1 MHz (^{1}H), 242.9 MHz, (^{31}P), 150.9 MHz (^{13}C)]. Chemical shifts are reported in δ (ppm) relative to the residual ^{1}H and ^{13}C signals of $CHCl_3$, DMSO or H_3PO_4 as the external standard for ^{31}P. IR spectra were measured on a Bruker Vector-22 spectrometer (USA) as suspensions in nujol. Melting points were obtained using a Cole-Parmer Stuart digital SMP10 apparatus (USA) and were uncorrected. ESI mass spectra were recorded on a Bruker Daltonik Amazon X spectrometer (Germany). Elemental analyses for C, H and N were performed using a Euro Vector 2000 CHNS-3 analyzer (Italy). Phosphorus content (%) was determined by pyrolysis in oxygen stream. All the manipulations were performed in argon atmosphere. All the solvents were dehydrated according to standard methods. The starting materials were used immediately after the distillation or recrystallization.

Experimental Procedures

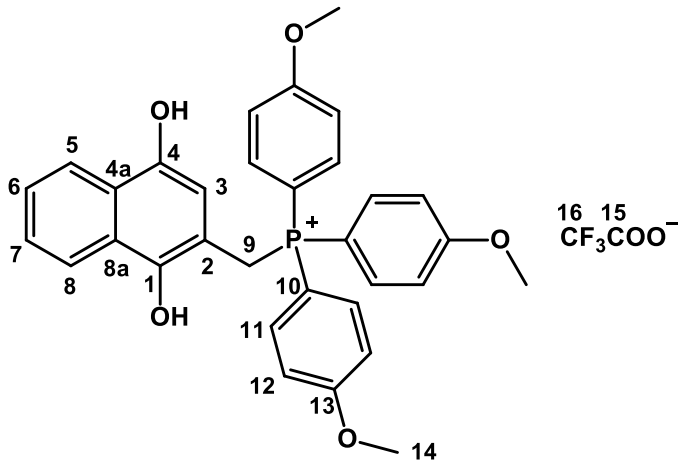
H-phosphonium salts **2a-c**. To a solution of phosphine **3a–c** (1 g) in CH_2Cl_2 (5.5 ml), an equimolar quantity of trifluoroacetic acid was added dropwise with constant stirring and with bubbling of dry argon. The reaction mixture was stirred for 1 h. The resulting triarylphosphonium trifluoroacetate was used in the subsequent reaction without isolation.



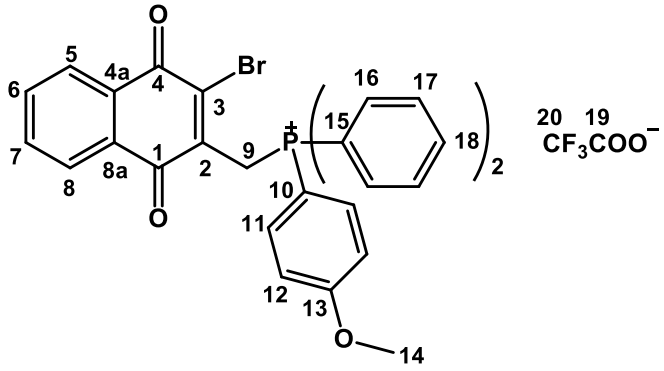
(1,4-Dihydroxynapht-2-ylmethyl)(4-methoxyphenyl)diphenylphosphonium trifluoroacetate **4a.** To a solution of H-phosphonium salt **2a** (0.46 g, 1.14 mmol) in CH_2Cl_2 (8 ml), a solution of 2-methyl-1,4-naphthoquinone (0.19 g, 1.14 mmol) in CH_2Cl_2 (5 ml) was added dropwise with constant stirring, cooling in a water bath and with bubbling of dry argon. The reaction mixture was stirred for 0.5 h. After 24 h of standing the red reaction mixture was evaporated *in vacuo* (14 Torr) to give a pink precipitate of compound **4a**, which was purified by recrystallization from acetone–diethyl ether (1 : 10). Yield 0.61 g (92%), mp 215–217 °C. IR (nujol) (ν_{max}, cm^{-1}): 3069, 2726, 1918, 1796, 1673, 1633, 1593, 1566, 1505, 1305, 1268, 1239, 1199, 1187, 1178, 1154, 1130, 1113, 1074, 1019, 998, 959, 851, 839, 803, 770, 750, 720, 694, 623, 557, 532, 514, 486, 414. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, OMe), 5.02 (d, $^2J_{HP}$ 14.9 Hz, 2H, CH_2), 6.37 (d, $^4J_{HP}$ 1.4 Hz, 1H, H^3), 7.22 (dd, $^3J_{HH}$ 9.1 Hz, $^4J_{PH}$ 2.6 Hz, 2H, H^{12}), 7.44 (m, 2H, H^6, H^7), 7.54 (dd, $^3J_{PH}$ 12.0 Hz, $^3J_{HH}$ 8.9 Hz, 2H, H^{11}), 7.61 (ddd, $^3J_{PH}$ 12.2 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.4 Hz, 4H, H^{16}), 7.66 (ddd, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 7.5 Hz, $^4J_{PH}$ 3.6 Hz, 4H, H^{17}), 7.85 (td, $^3J_{HH}$ 7.0 Hz, $^5J_{PH}$ 1.5 Hz, 2H, H^{18}), 7.85 (dt, $^3J_{HH}$ 6.6-7.3 Hz, $^4J_{HH}$ 1.5, 2H, H^{18}), 7.96 (m, 1H, H^8), 8.02 (m, 1H, H^5), 8.95 (br. s, 1H, OH), 9.60 (br. s, 1H, OH). ^{13}C–{^{1}H} (^{13}C) NMR (100.6 MHz, DMSO-d_6) δ_C: 25.06 [d (tdd), $^1J_{HC}$ 135.3 Hz, $^2J_{PC}$ 48.4 Hz, $^4J_{HC}$ 3.7 Hz, C^9], 56.33 [s (q), $^1J_{HC}$ 145.6 Hz, C^{14}], 108.32 [d (dt), $^1J_{PC}$ 92.1 Hz, $^3J_{HC}$ 8.1 Hz, C^{10}], 109.09 [d (m), $^2J_{PC}$ 9.2 Hz, overlap with C^3 signal, C^2], 110.02 [s (br.ddd), $^1J_{HC}$ 158.5 Hz, $^3J_{PC}$ 3.7 Hz, overlap with C^2 signal, C^3], 116.30 [d (ddd), $^1J_{HC}$ 165.1 Hz, $^3J_{PC}$ 13.6 Hz, $^2J_{HC}$ 4.4 Hz, C^{12}], 117.81 [q (q), $^1J_{FC}$ 300.4 Hz, C^{20}], 119.52 [d (dt), $^1J_{PC}$ 85.1 Hz, $^3J_{HC}$ 8.8 Hz, C^{15}], 122.58 [s, s (dm), $^1J_{HC}$ 162.8 Hz, C^5, C^8], 125.73 [s (dd), $^1J_{HC}$ 160.3 Hz, $^3J_{HC}$ 8.1 Hz, overlap with C^{8a} signal, C^6], 125.76 [s (m), C^{4a}], 126.14 [s (dd), $^1J_{HC}$ 160.7 Hz, $^3J_{HC}$ 8.4 Hz, overlap with C^{8a} signal, C^7], 126.47 [d (m), $^4J_{PC}$ 3.7 Hz, overlap with C^7 signal, C^{8a}], 130.35 [d (ddd), $^1J_{HC}$ 167.2 Hz, $^3J_{PC}$ 12.1 Hz, $^3J_{HC}$ 7.3 Hz, C^{17}], 134.15 [d (ddd), $^1J_{HC}$ 164.1 Hz, $^2J_{PC}$ 9.9 Hz, $^3J_{HC}$ 7.7 Hz, C^{16}], 135.19 [d (dm), $^1J_{HC}$ 165.8 Hz, $^4J_{PC}$ 3.3 Hz, C^{18}], 136.60 [d (ddd), $^1J_{HC}$ 163.6 Hz, $^2J_{PC}$ 11.4 Hz, $^3J_{HC}$ 7.7 Hz, C^{11}], 144.70 [d (m), $^3J_{PC}$ 8.1 Hz, C^1), 146.18 (d (br. d), $^4J_{PC}$ 2.6 Hz, C^4], 158.26 [q (q), $^2J_{FC}$ 31.2 Hz, C^{19}], 164.69 [d (m), $^4J_{PC}$ 2.9 Hz, C^{13}]. ^{31}P–{^{1}H} (^{31}P) NMR (162.0 MHz, DMSO-d_6) δ_P: 20.41 s (br. s). Found (%): C, 66.41; H, 4.52; P, 5.39. Calc. for $C_{32}H_{26}F_3O_5P$ (%): C, 66.44; H, 4.53; P, 5.35.



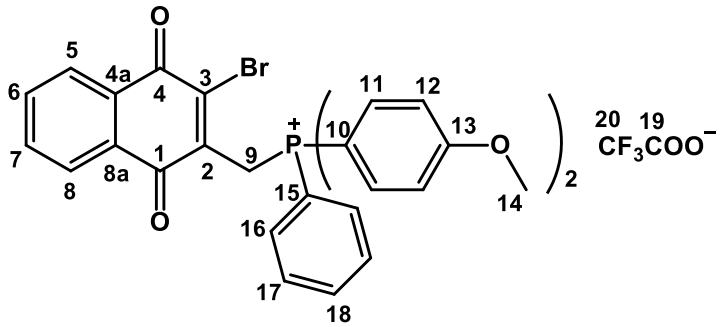
(1,4-Dihydroxynapht-2-ylmethyl)bis(4-methoxyphenyl)phenylphosphonium trifluoroacetate **4b**. To a solution of H-phosphonium salt **2b** (0.42 g, 1.03 mmol) in CH_2Cl_2 (10 ml), a solution of 2-methyl-1,4-naphthoquinone (0.18 g, 1.03 mmol) in of CH_2Cl_2 (5 ml) was added dropwise with constant stirring, cooling in a water bath and with bubbling of dry argon. The reaction mixture was stirred for 0.5 h. After 24 h of standing the red reaction mixture was evaporated *in vacuo* (14 Torr) to give a pink precipitate of **4b**, which was purified by recrystallization from acetone–diethyl ether (1 : 10). Yield 0.60 g (95 %), mp 200–203°C. IR (nujol) (ν_{max}, cm^{-1}): 2726, 1917, 1674, 1625, 1594, 1565, 1505, 1304, 1270, 1198, 1131, 1113, 1077, 1022, 970, 855, 836, 804, 777, 748, 718, 695, 662, 645, 628, 558, 533, 521, 481, 451, 425. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 6H, OMe), 4.96 (d, $^2J_{HP}$ 14.9 Hz, 2H, CH_2), 6.37 (d, $^4J_{PH}$ 1.5 Hz, 1H, H^3), 7.21 (ddd, $^3J_{HH}$ 9.0 Hz, $^4J_{PH}$ 2.6 Hz, 4H, H^{12}), 7.44 (m, 2H, H^6, H^7), 7.51 (dd, $^3J_{PH}$ 11.9 Hz, $^3J_{HH}$ 7.5 Hz, 4H, H^{11}), 7.58 (ddd, $^3J_{PH}$ 12.4 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.4 Hz, 2H, H^{16}), 7.65 (ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{PH}$ 3.5 Hz, 2H, H^{17}), 7.83 (td, $^3J_{HH}$ 7.6 Hz, $^5J_{PH}$ 1.5 Hz, 1H, H^{18}), 8.00 (m, $^3J_{HH}$ 8.7 Hz, $^3J_{HH}$ 6.9 Hz, $^2J_{HH}$ 5.5 Hz, $^2J_{HH}$ 5.4 Hz, 2H, H^5, H^8), 8.98 (br. s, 1H, OH), 9.63 (br. s, 1H, OH). ^{13}C–{^{1}H} (^{13}C) NMR (100.6 MHz, DMSO-d_6) δC: 25.33 [d (tdd), $^1J_{HC}$ 134.6 Hz, $^2J_{PC}$ 50.2 Hz, $^4J_{HC}$ 3.6 Hz, C^9], 56.30 [s (q), $^1J_{HC}$ 145.6 Hz, C^{14}], 109.04 [d (dt), $^1J_{PC}$ 92.4 Hz, $^3J_{HC}$ 8.1 Hz, C^{10}], 109.33 [d (m), $^2J_{PC}$ 9.2 Hz, overlap with C^3 and C^{10} signal, C^2], 110.04 [d (dt), $^1J_{HC}$ 143.0 Hz, $^3J_{PC}$ 3.7 Hz, overlap with C^2 and C^{10} signal, C^3], 116.21 [d (ddd), $^1J_{HC}$ 164.7 Hz, $^3J_{PC}$ 13.6 Hz, $^2J_{HC}$ 4.4 Hz, C^{12}], 118.05 [q (q), $^1J_{FC}$ 300.1 Hz, C^{20}], 120.21 [d (dt), $^1J_{PC}$ 85.8 Hz, $^3J_{HC}$ 7.0, C^{15}], 122.61 [s (dm), $^1J_{HC}$ 162.8 Hz, overlap with C^8 signal, C^5], 125.72 [s (dd), $^1J_{HC}$ 160.3 Hz, $^3J_{HC}$ 8.7 Hz, C^6], 125.75 [s (m), C^{4a}], 126.10 [s (ddd), $^1J_{HC}$ 160.3 Hz, $^3J_{HC}$ 8.4 Hz, overlap with C^{8a} signal, C^7], 126.53 [d (m), $^4J_{PC}$ 3.3 Hz, overlap with C^7 signal, C^{8a}], 130.28 [d (dddd), $^1J_{HC}$ 167.3 Hz, $^3J_{PC}$ 12.5 Hz, $^3J_{HC}$ 7.3 Hz, $^3J_{HC}$ 7.3 Hz, C^{17}], 134.01 [d (dddd), $^1J_{HC}$ 164.3 Hz, $^2J_{PC}$ 9.9 Hz, $^3J_{HC}$ 7.7 Hz, $^3J_{HC}$ 7.3 Hz, C^{16}], 135.03 [d (dm), $^1J_{HC}$ 165.1 Hz, $^4J_{PC}$ 2.9 Hz, C^{18}], 136.31 [d (ddd), $^1J_{HC}$ 163.6 Hz, $^2J_{PC}$ 11.4 Hz, $^3J_{HC}$ 7.7 Hz, C^{11}], 144.67 [d (m), $^3J_{PC}$ 8.1 Hz, $^3J_{HC}$ 3.7 Hz, C^1], 146.66 [d (br. d), $^4J_{PC}$ 2.4 Hz, C^4], 158.31 [q (q), $^2J_{FC}$ 40.8 Hz, C^{19}], 164.57 [d (m), $^4J_{PC}$ 2.9 Hz, C^{13}]. ^{31}P–{^{1}H} (^{31}P) NMR (162.0 MHz, DMSO-d_6) δP: 19.7 s (br. s). Found (%): C, 65.11; H, 4.62; P, 5.09. Calc. for $C_{33}H_{28}F_3O_6P$ (%): C, 65.13; H, 4.64; P, 5.09.



(1,4-Dihydroxynapht-2-ylmethyl)tris(4-methoxyphenyl)phosphonium trifluoroacetate **4c.** To a solution of H-phosphonium salt **2c** (0.44 g, 0.95 mmol) in CH_2Cl_2 (10 ml), a solution of 2-methyl-1,4-naphthoquinone (0.17 g, 0.95 mmol) in CH_2Cl_2 (5 ml) was added dropwise with constant stirring, cooling in a water bath and with bubbling of dry argon. The reaction mixture was stirred for 0.5 h. After 24 h of standing the red reaction mixture was evaporated *in vacuo* (14 Torr) to give a pink precipitate of **4c**, which was purified by recrystallization from acetone–diethyl ether (1 : 10). Yield 0.58 g (95 %), mp 202–205°C. IR (nujol) (ν_{max}, cm^{-1}): 3481, 3069, 1912, 1797, 1671, 1626, 1595, 1566, 1504, 1299, 1267, 1184, 1137, 1113, 1077, 1023, 947, 859, 837, 804, 767, 721, 691, 665, 625, 556, 530, 507, 463, 433, 419. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 9H, OMe), 4.91 (d, $^2J_{HP}$ 14.8 Hz, 2H, CH_2), 6.38 (br. s, 1H, H^3), 7.20 (ddd $^3J_{HH}$ 8.8 Hz, $^4J_{PH}$ 3.2 Hz, 6H, H^{12}), 7.44 (m, 2H, H^6, H^7), 7.50 (dd, $^3J_{PH}$ 12.1 Hz, $^3J_{HH}$ 8.8 Hz, 6H, H^{11}), 8.03 (m, $^3J_{HH}$ 7.1 Hz, $^3J_{HH}$ 7.1 Hz, $^4J_{HH}$ 2.2 Hz, $^4J_{HH}$ 2.2 Hz, 2H, H^5, H^8), 9.04 (br. s, 1H, OH), 9.69 (br. s, 1H, OH). ^{13}C–{^{1}H} (^{13}C) NMR (100.6 MHz, DMSO-d_6) δ_C: 25.67 [d (tdd), $^1J_{HC}$ 134.9 Hz, $^2J_{PC}$ 50.6 Hz, $^4J_{HC}$ 3.9 Hz, C^9], 56.29 [s (q), $^1J_{HC}$ 145.4 Hz, C^{14}], 109.52 [d (dt), $^1J_{PC}$ 92.9 Hz, $^3J_{HC}$ 8.0 Hz, C^{10}], 109.63 [d (m), $^2J_{PC}$ 9.1 Hz, overlap with C^{10} signal, C^2], 110.14 [s (ddd), $^1J_{HC}$ 151.5 Hz, $^3J_{HC}$ 8.3 Hz, $^4J_{HC}$ 4.4 Hz, overlap with C^2 signal, C^3], 116.15 [d (ddd), $^1J_{HC}$ 165.0 Hz, $^3J_{PC}$ 13.0 Hz, $^2J_{HC}$ 4.4 Hz, C^{12}], 117.86 [q (q), $^1J_{FC}$ 300.7 Hz, C^{16}], 122.64 [s (dm), $^1J_{HC}$ 164.0 Hz, overlap with C^{8a} signal, C^8], 122.71 [s (dm), $^1J_{HC}$ 164.0 Hz, overlap with C^8 signal, C^5], 125.70 [s (dd), $^1J_{HC}$ 160.6 Hz, $^3J_{HC}$ 8.0 Hz, C^6], 125.77 [s (m), C^{4a}], 126.08 [s (dm), $^1J_{HC}$ 160.6 Hz, $^3J_{HC}$ 8.3 Hz, overlap with C^{8a} signal, C^7], 126.66 [s (m), overlap with C^7 signal, C^{8a}], 136.19 [d (ddd), $^1J_{HC}$ 163.5 Hz, $^2J_{PC}$ 11.3 Hz, $^3J_{HC}$ 7.5 Hz, C^{11}], 144.69 [d (m), $^3J_{PC}$ 8.0 Hz, $^3J_{HC}$ 3.9 Hz, C^1), 146.72 (s (br. d), $^2J_{HC}$ 2.8 Hz, C^4], 158.46 [q (q), $^2J_{FC}$ 30.7 Hz, C^{15}], 164.52 [d (m), $^2J_{HC}$ 2.5 Hz, C^{13}]. ^{31}P–{^{1}H} (^{31}P) NMR (162.0 MHz, DMSO-d_6) δ_P: 19.2 s (br. s). Found (%): C, 63.91; H, 4.72; P, 4.89. Calc. for $C_{34}H_{30}F_3O_7P$ (%): C, 63.95; H, 4.74; P, 4.85.

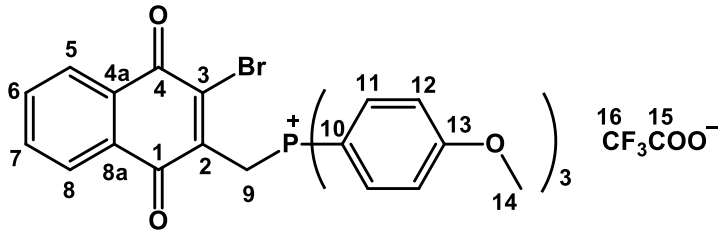


(3-Bromo-1,4-dioxonaphth-2-ylmethyl)(4-methoxyphenyl)diphenylphosphonium trifluoroacetate **5a.** To a solution of phosphonium salt **4a** (0.40 g, 0.69 mmol) in CH_2Cl_2 (10 ml), a double excess of bromine (0.07 ml, 1.38 mmol) was added with constant stirring. After the evolution of hydrogen bromide ceased (control by litmus, 2 h later), the orange reaction mixture was evaporated *in vacuo* (14 Torr), the orange residue was purified by recrystallization from diethyl ether (10 ml). Yield of yellow-orange precipitate 0.43 g (95 %), mp 199–201°C. IR (nujol) (ν_{max}, cm^{-1}): 2729, 1780, 1672, 1658, 1591, 1566, 1504, 1307, 1276, 1253, 1185, 1112, 1022, 997, 959, 885, 830, 813, 759, 746, 715, 697, 665, 543, 512, 410. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.88 (s, 9H, H^{14}), 5.25 (d, $^2J_{PCH}$ 15.2 Hz, 2H, H^9), 7.16 (d, $^3J_{HH}$ 5.8 Hz, 2H, H^{12}), 7.63 (m, 4H, H^{16}), 7.76 (m, 11H, H^5, H^7, H^8, H^{11}, H^{17}, H^{18}), 8.04 (d, $^3J_{HH}$ 7.3 Hz, 1H, H^6). ^{13}C–{^{1}H} (^{13}C) NMR (150.9 MHz, $CDCl_3$) δ_C : 30.78 [d (td), $^1J_{HC}$ 134.8 Hz, $^1J_{PC}$ 51.4 Hz, C^9], 56.29 [s (q), $^1J_{HC}$ 145.6 Hz, C^{14}], 106.58 [d (dt), $^1J_{PC}$ 94.2 Hz, $^3J_{HC}$ 7.7–8.0 Hz, C^{10}], 114.96 [q (q), $^1J_{FC}$ 286.9 Hz, C^{20}], 116.45 [d (ddd), $^1J_{HC}$ 164.9 Hz,$^3J_{PC}$ 14.1 Hz, $^3J_{HC}$ 3.6 Hz, C^{12}], 118.34 [d (dt), $^1J_{PC}$ 87.1 Hz, $^3J_{HC}$ 8.0-8.2 Hz, C^{15}], 127.95 [s (dd), $^1J_{HC}$ 166.7 Hz, $^3J_{HC}$ 7.2 Hz, C^8], 127.95 [s (dd), $^1J_{HC}$ 167.5 Hz, $^3J_{HC}$ 6.6 Hz, C^5], 130.43 [s (dd), $^3J_{HC}$ 6.6 Hz, C^{8a}], 130.43 [s (dd), $^3J_{HC}$ 6.1-6.9 Hz, C^{4a}], 130.43 [d (ddd), $^1J_{HC}$ 165.8 Hz, $^3J_{PC}$ 13.0 Hz, $^3J_{HC}$ 5.2 Hz, C^{17}], 134.10 [d (dm), $^1J_{HC}$ 162.3 Hz, $^2J_{PC}$ 9.9 Hz, C^{16}], 134.96 [s, s (two d), $^1J_{HC}$ 164.7 Hz, $^1J_{HC}$ 164.5 Hz, C^6, C^7], 135.43 [s (dm), $^1J_{HC}$ 197.6 Hz, C^{18}], 136.51 [d (ddd), $^1J_{HC}$ 164.75 Hz, $^2J_{PC}$ 11.6 Hz, $^3J_{HC}$ 4.7 Hz, C^{11}], 142.17 [d (m), $^3J_{PC}$ 10.2 Hz, C^2], 143.99 [d (m), $^2J_{PC}$ 11.1 Hz, C^3], 158.09 [q (q), $^2J_{FC}$ 40.3 Hz, C^{19}], 165.27 [s (s), C^{13}], 176.14 [s (s), C^4], 180.65 [s (s), C^1]. ^{31}P–{^{1}H} (^{31}P) NMR (242.9 MHz, $CDCl_3$) δ_P: 22.7 br. s (s). Mass-spectrum (ESI), *m*/*z*: 541.2 $[M]^+$ ($C_{30}H_{23}BrO_3P$). Found, (%): C 58.60, H 3.49, P 4.76. $C_{32}H_{23}BrF_3O_5P$. Calc. (%): C 58.64, H 3.54, P 4.73.



(3-Bromo-1,4-dioxonaphth-2-ylmethyl)bis(4-methoxyphenyl)phenylphosphonium trifluoroacetate **5b.** To a solution of phosphonium salt **4b** (0.26 g, 0.37 mmol) in CH_2Cl_2 (10 ml), a double excess of bromine (0.04 ml, 0.74 mmol) was added with constant stirring. After the evolution of hydrogen bromide ceased (control by litmus, 2 h later), the orange reaction mixture was evaporated *in vacuo* (14 Torr) till the formation of yellow-orange residue, which was purified by recrystallization from diethyl ether (10 ml). Yield 0.45 g (90 %), mp 80–82°C. IR (nujol) (ν_{max},

cm^{-1}): 2726, 1777, 1675, 1591, 1565, 1502, 1301, 1268, 1184, 1111, 1017, 961, 887, 835, 813, 744, 721, 701, 676, 541, 511, 426. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 9H, H^{14}), 5.03 (d, $^2J_{PH}$ 15.2 Hz, 2H, H^9), 7.16 (d, $^3J_{HH}$ 5.8 Hz, 4H, H^{12}), 7.69 (m, 11H, H^5, H^8, H^{11}, H^{16}, H^{17}, H^{18}), 7.84 (d, $^3J_{HH}$ 6.6 Hz, 1H, H^7), 8.07 (d, $^3J_{HH}$ 6.9 Hz, 1H, H^6). ^{13}C–{^{1}H} (^{13}C) NMR (100.6 MHz, $CDCl_3$) δ_C: 30.95 [d (td), $^1J_{HC}$ 136.4 Hz, $^1J_{PC}$ 52.1 Hz, C^9], 56.31 [s (q), $^1J_{HC}$ 145.6 Hz, C^{14}], 107.10 [d (dt), $^1J_{PC}$ 95.1 Hz, $^3J_{HC}$ 7.0-7.9 Hz, C^{10}], 114.91 [q (q), $^1J_{FC}$ 286.8 Hz, C^{20}], 116.43 [d (dd), $^1J_{HC}$ 165.1 Hz, $^3J_{PC}$ 14.3 Hz, $^3J_{HC}$ 3.5 Hz, C^{12}], 118.80 [d (dm), $^1J_{PC}$ 87.7 Hz, $^3J_{HC}$ 8.2–8.5 Hz, C^{15}], 127.36 [s (dd), $^1J_{HC}$ 167.0 Hz, $^3J_{HC}$ 7.2 Hz, C^8], 127.98 [s (dd), $^1J_{HC}$ 167.2 Hz, $^3J_{HC}$ 6.0 Hz, C^5], 130.38 [s (dd), $^3J_{HC}$ 6.6 Hz, $^3J_{HC}$ 5.9 Hz, C^{8a}], 130.39 [d (ddd), $^1J_{HC}$ 165.8 Hz, $^3J_{PC}$ 12.8 Hz, $^3J_{HC}$ 6.9-7.3 Hz, C^{17}], 130.58 [s (dd), $^1J_{HC}$ 166.1 Hz, $^3J_{HC}$ 7.0 Hz, C^{4a}], 133.98 [d (br. dm), $^1J_{HC}$ 137.6 Hz, $^2J_{PC}$ 10.3 Hz, C^{16}], 134.91 [s (d), $^1J_{HC}$ 139.4 Hz, $^3J_{HC}$ 7.7 Hz, C^7], 134.92 [s (d), $^1J_{HC}$ 139.4 Hz, $^3J_{HC}$ 7.7 Hz, C^6], 135.32 [d (br. d), $^1J_{HC}$ 136.0 Hz, $^4J_{PC}$ 2.9 Hz, C^{18}], 136.34 [d (ddd), $^1J_{HC}$ 148.8 Hz, $^2J_{PC}$ 11.7 Hz, $^3J_{HC}$ 6.9-7.0 Hz, C^{11}], 142.06 [d (dd), $^2J_{PC}$ 9.9 Hz, C^2], 143.98 [d (d), $^3J_{PC}$ 10.5 Hz, C^3], 157.42 [q (q), $^3J_{FC}$ 40.8 Hz, C^{19}], 165.19 [s (s), $^4J_{PC}$ 2.9 Hz, C^{13}), 176.16 (d (dd), $^3J_{HC}$ 3.2-3.6 Hz, $^3J_{PC}$ 2.6 Hz, C^1], 180.60 [s (s), $^4J_{PC}$ 2.2 Hz, C^4]. ^{31}P–{^{1}H} (^{31}P) NMR (162.0 MHz, $CDCl_3$) δ_P: 20.5 s (m). Mass-spectrum (ESI), *m*/*z*: 573.2 $[M]^+$ ($C_{31}H_{25}BrO_4P$). Found (%): C 57.80, H 3.65, P 4.56. $C_{33}H_{25}BrF_3O_6P$. Calc. (%): C 57.83, H 3.68, P 4.52.



(3-Bromo-1,4-dioxonaphth-2-ylmethyl)tris(4-methoxyphenyl)phosphonium trifluoroacetate **5c.** To a solution of phosphonium salt **4c** (0.39 g, 0.53 mmol) in CH_2Cl_2 (10 ml), a double excess of bromine (0.05 ml, 1.06 mmol) was added with constant stirring. After the evolution of hydrogen bromide ceased (control by litmus, 2 h later), the orange reaction mixture was evaporated *in vacuo* (14 Torr), the residue was purified by recrystallization from diethyl ether (10 ml). The obtained yellow-orange precipitate of **5c** was filtered off and dried *in vacuo* (14 Torr). Yield 0.36 g (95 %), mp. 97–99°C. IR (nujol) (ν_{max}, cm^{-1}): 2725, 1920, 1777, 1676, 1661, 1592, 1567, 1504, 1301, 1270, 1185, 1112, 1019, 962, 888, 835, 815, 766, 719, 701, 676, 543, 508, 427. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 9H, H^{14}), 4.88 (d, $^2J_{PH}$ 15.2 Hz, 2H, H^9), 7.12 (d, $^3J_{HH}$ 6.1 Hz, 6H, H^{12}), 7.65 (dd, $^3J_{PH}$ 11.8 Hz, $^3J_{HH}$ 8.7 Hz, 6H, H^{11}), 7.74 (m, 2H, H^5, H^8), 7.82 (d, $^3J_{HH}$ 7.2 Hz, 1H, H^7), 8.03 (d, $^3J_{HH}$ 7.2 Hz, 1H, H^6). ^{13}C–{^{1}H} (^{13}C) NMR (150.9 MHz, $CDCl_3$) δ_C: 31.04 [d (td), $^1J_{HC}$ 136.3 Hz,$^1J_{PC}$ 52.8 Hz, C^9], 56.20 [s (q), $^1J_{HC}$ 145.7 Hz, C^{14}], 107.86 [d (dt), $^1J_{PC}$ 95.4 Hz, $^3J_{HC}$ 8.3 Hz, $^3J_{HC}$ 8.0 Hz, C^{10}], 114.95 [q (q), $^1J_{FC}$ 286.6 Hz, C^{16}], 116.28 [s (ddd), $^1J_{HC}$ 149.3 Hz, $^3J_{PC}$ 14.1 Hz, $^2J_{HC}$ 4.1 Hz, C^{12}], 127.36 [s (dd), $^1J_{HC}$ 167.2 Hz, $^3J_{HC}$ 6.6 Hz, C^8], 137.97 [s (dd), $^1J_{HC}$ 166.7 Hz, $^3J_{HC}$ 6.6 Hz, C^5], 130.43 [s (t), $^3J_{HC}$ 6.9 Hz, $^3J_{HC}$ 5.8 Hz, C^{8a}], 130.60 [s (t), $^3J_{HC}$ 6.9 Hz, $^3J_{HC}$ 5.8 Hz, C^{4a}], 134.91 [s (dd), $^1J_{HC}$ 164.7 Hz, $^2J_{HC}$ 3.0 Hz, C^7], 134.92 [s (dd), $^1J_{HC}$ 163.9 Hz, $^2J_{HC}$ 3.3 Hz, C^6], 136.14 [d (ddd), $^1J_{HC}$ 163.4 Hz, $^2J_{PC}$ 10.8 Hz, $^3J_{HC}$ 7.5 Hz, C^{11}], 142.19 [d (dd), $^2J_{PC}$ 9.9 Hz, C^2], 143.81 [d (d), $^3J_{PC}$ 10.5 Hz, C^3], 157.40 [q (q), $^2J_{FC}$ 40.4 Hz, C^{15}], 165.08 [s (s), C^{13}], 176.23 [s (s), C^1], 180.59 [s (s), C^4]. ^{31}P–{^{1}H} (^{31}P) NMR (242.9 MHz, $CDCl_3$) δ_P: 19.8 s (m). Mass-spectrum (ESI), *m*/*z*: 603.2 $[M]^+$ ($C_{32}H_{27}BrO_5P$). Found (%): C 57.04, H 3.80, P 4.36. $C_{34}H_{27}BrF_3O_7P$. Calc. (%): C 57.08, H 3.80, P 4.33.

Experimental Biological Procedures

The cytotoxic effect of phosphonium salts **4a–c** was estimated by counting living cells using a Cytell Cell Imaging multifunctional system (GE Helthcare Life Science, Sweden) equipped with a Cell Viability BioApp application that provides an accurate counting of the number of cells and estimation of their viability based on fluorescence intensity.[1] The tumor cell cultures used in the experiments included M-HeLa clone 11 (human cervix carcinoma), MCF7 (human breast carcinoma, pleural fluid), A-549 (human lung adenocarcinoma) and PC-3 (human prostate adenocarcinoma). Normal cell lines included WI-38 (human lung fibroblasts) and Chang liver (human hepatic cells). The cell lines were obtained from collections of the Institute of Cytology of the Russian Academy of Sciences, St. Petersburg, and Scientific-Research Institute of Virology of the Russian Academy of Medical Sciences, Moscow.

Degree of cell growth inhibition under the influence of test compound was calculated by the formula:

$$N\ (\%) = (1 - \text{experiment/control}) \times 100$$

IC_{50} was determined according to the curve of cell culture growth *vs*. compound concentration (concentration causing inhibition of cell growth by 50%). A new compound is considered as cytotoxic if $IC_{50} < 10^{-4}$ mol l^{-1}.[2]

1. A. D. Voloshina, V. E. Semenov, A. S. Strobykina, N. V. Kulik, E. S. Krylova, V. V. Zobov and V. S. Reznik, *Russ. J. Bioorg. Chem.*, 2017, **43**, 170 (*Bioorg. Khim.*, 2017, **43**, 197).
2. *Rukovodstvo po provedeniyu doklinicheskih issledovanii lekarstvennyh sredstv (Manual for preclinical studies of drugs)*, ed. A. N. Mironov, Grif i K, Moscow, 2012, part 1 (in Russian).

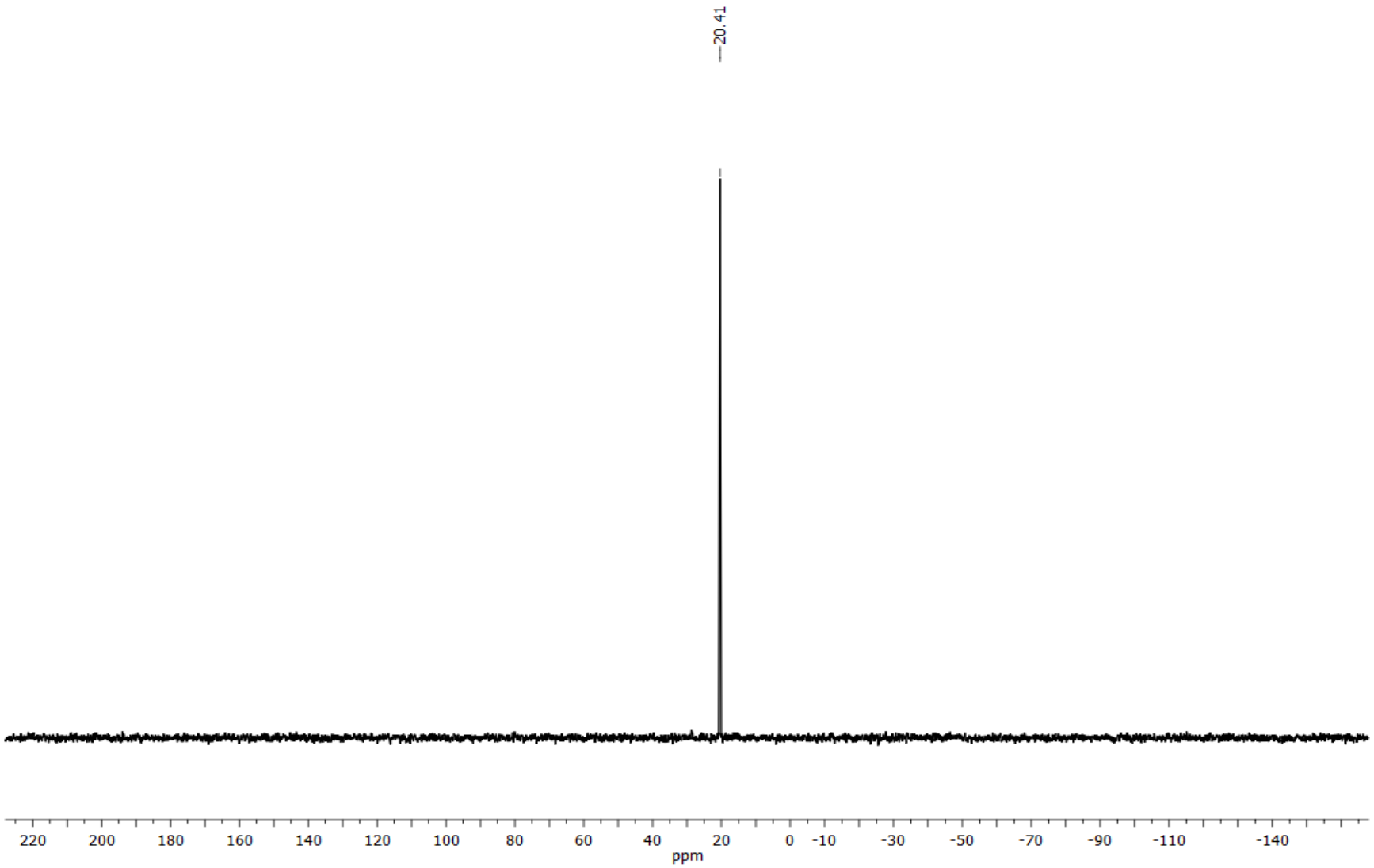


Figure S1 $^{31}P–\{^{1}H\}$ NMR spectrum of phosphonium salt **4a** (162.0 MHz, DMSO-d_6).

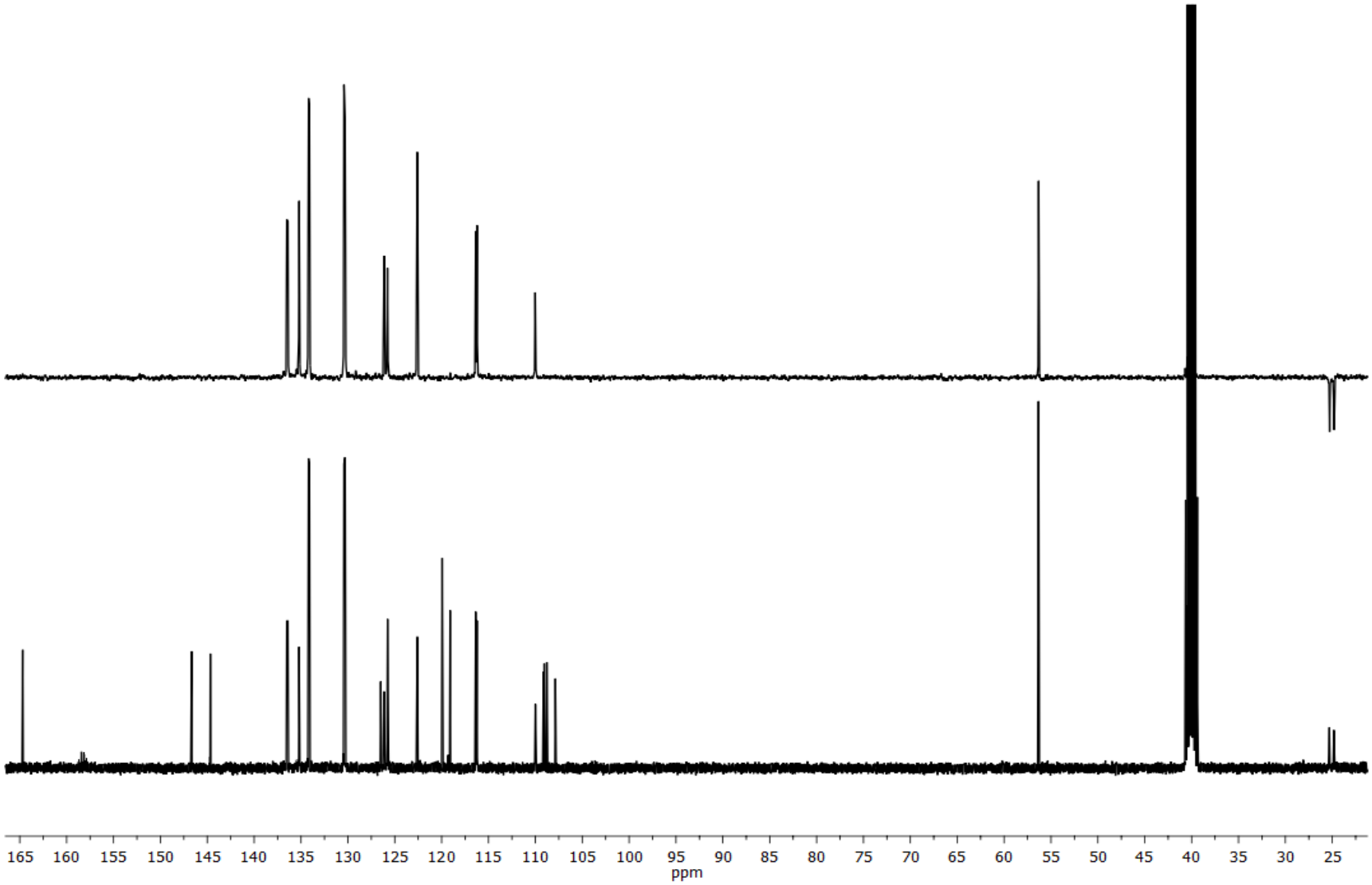


Figure S2 $^{13}C–\{^{1}H\}/^{13}C$-dept NMR spectra of phosphonium salt **4a** (100.6 MHz, DMSO-d_6).

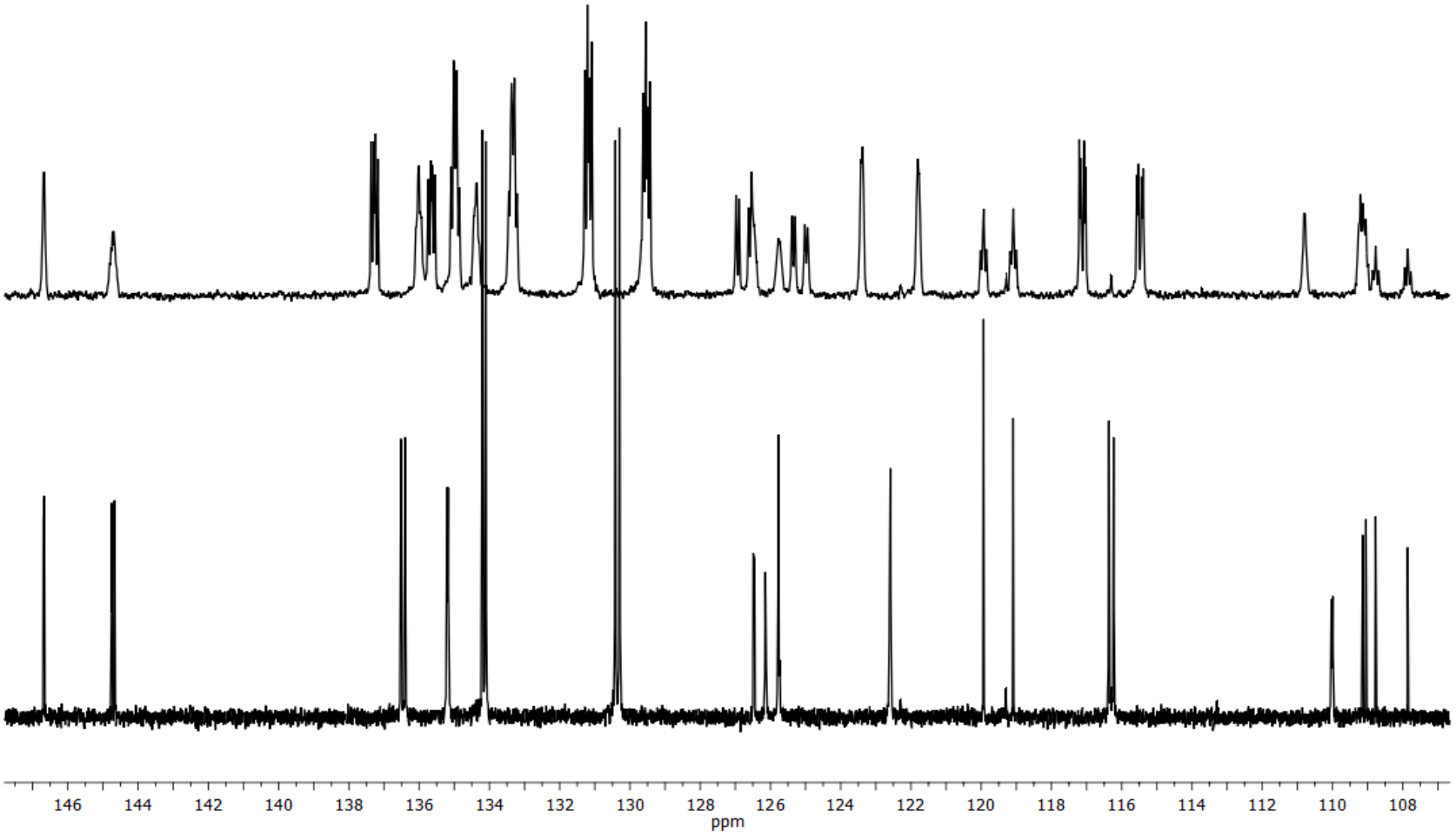


Figure S3 Fragments of $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **4a** (100.6 MHz, DMSO-d_6).

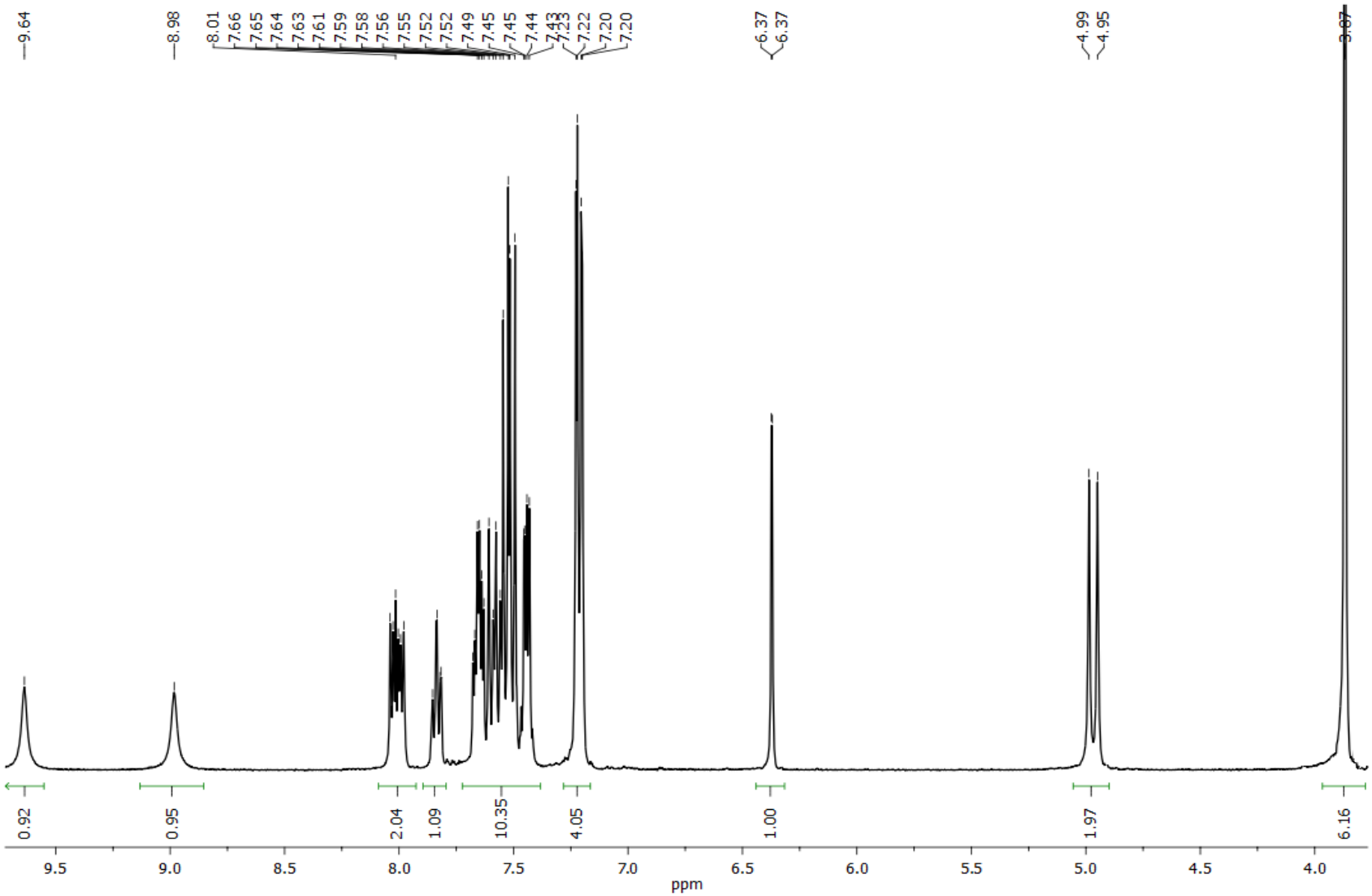


Figure S4 ^{1}H NMR spectrum of phosphonium salt **4b** (400 MHz, DMSO-d_6).

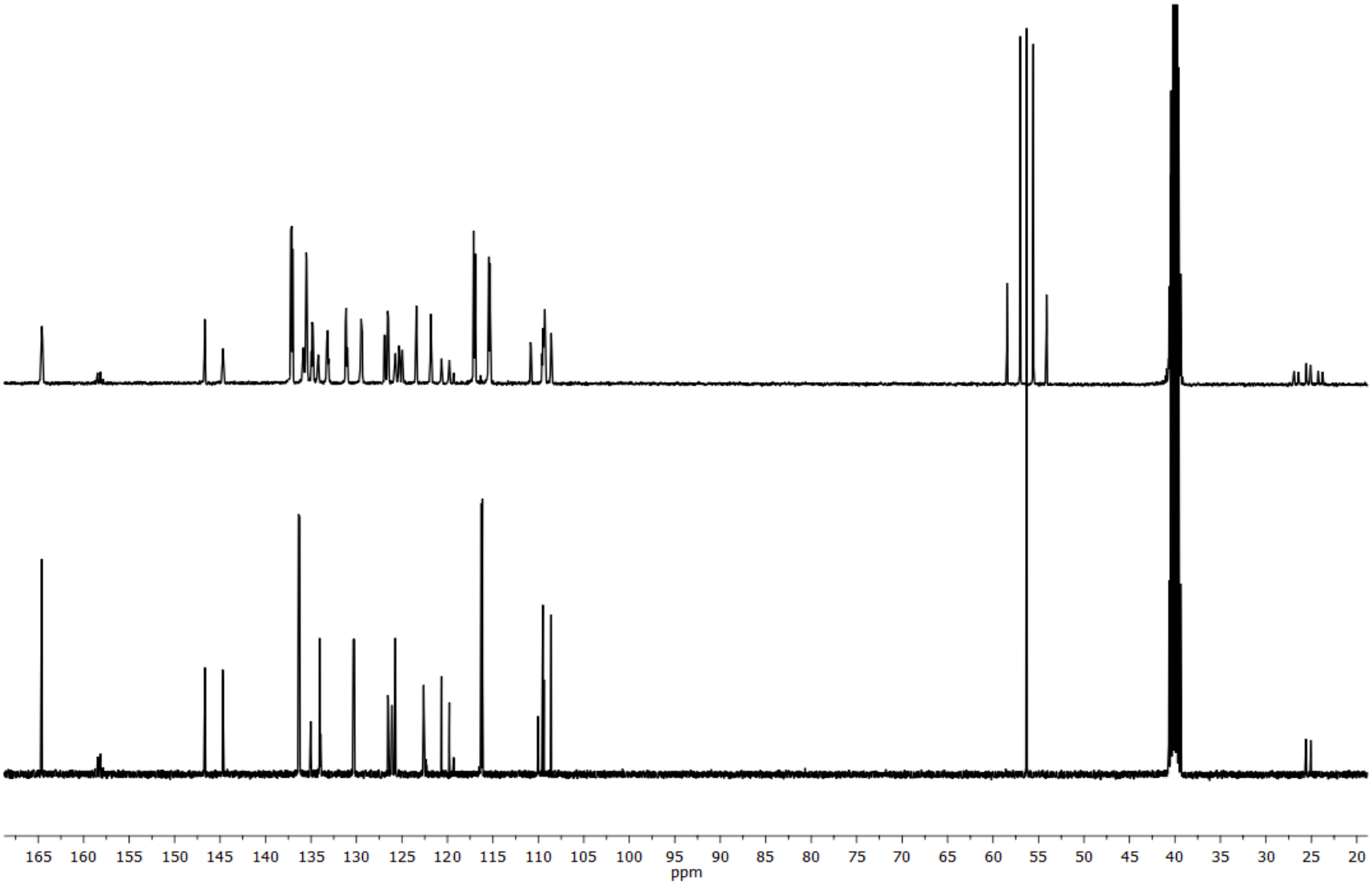


Figure S5 $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **4b** (100.6 MHz, DMSO-d_6).

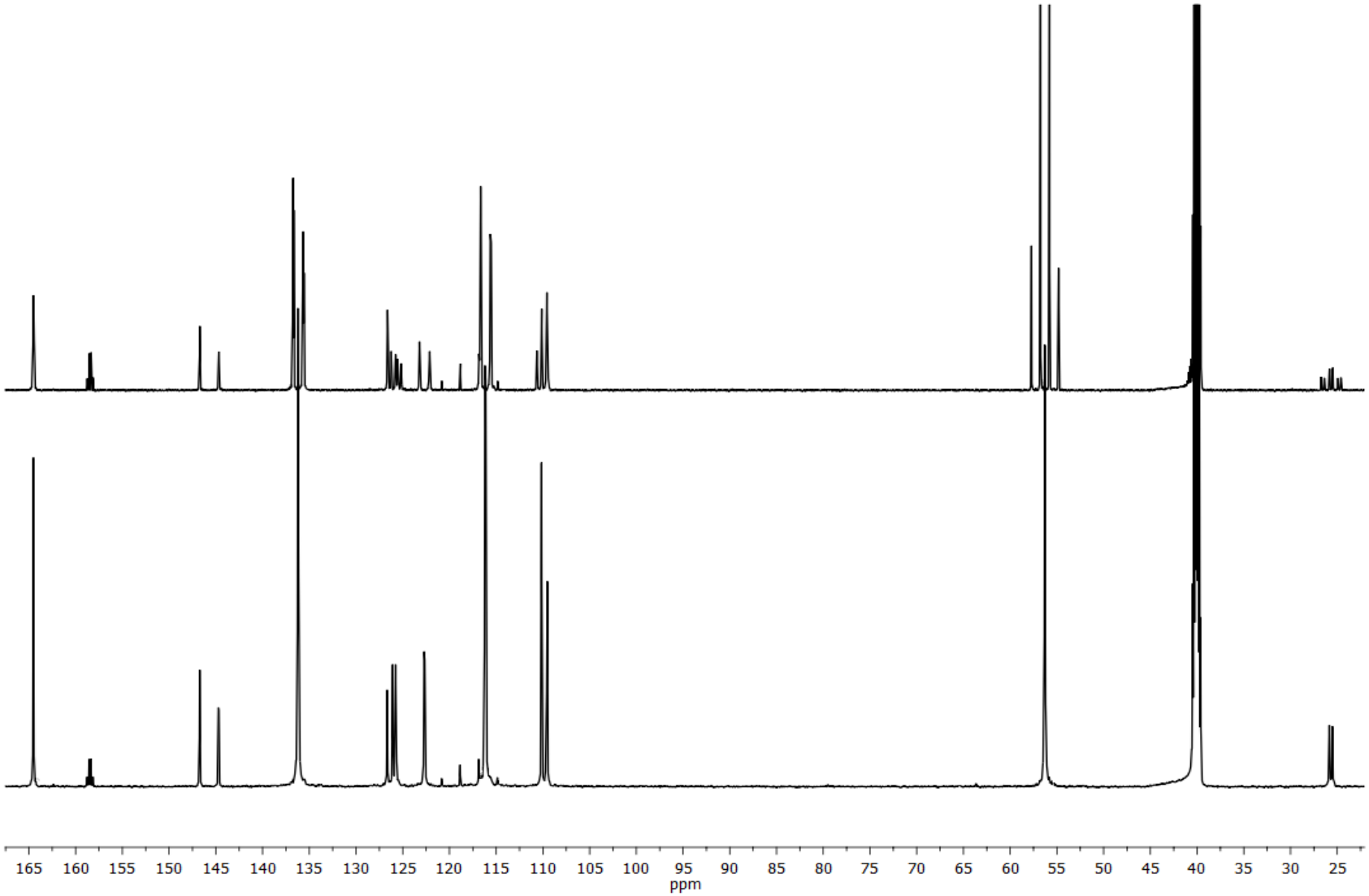


Figure S6 $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **4c** (150.9 MHz, DMSO-d_6).

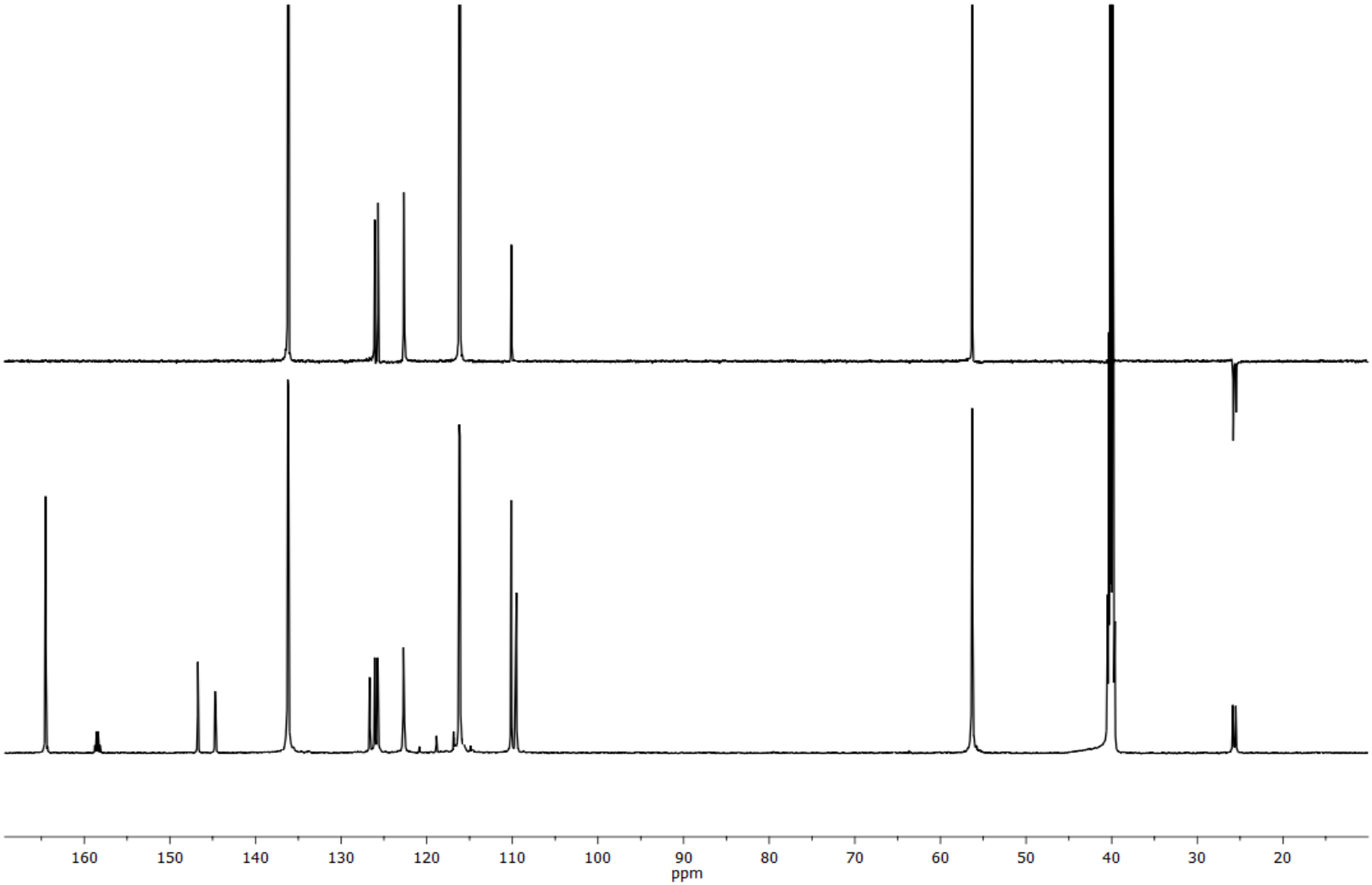


Figure S7 $^{13}C–\{^{1}H\}/^{13}C$-dept NMR spectra of phosphonium salt **4c** (150.9 MHz, DMSO-d_6).

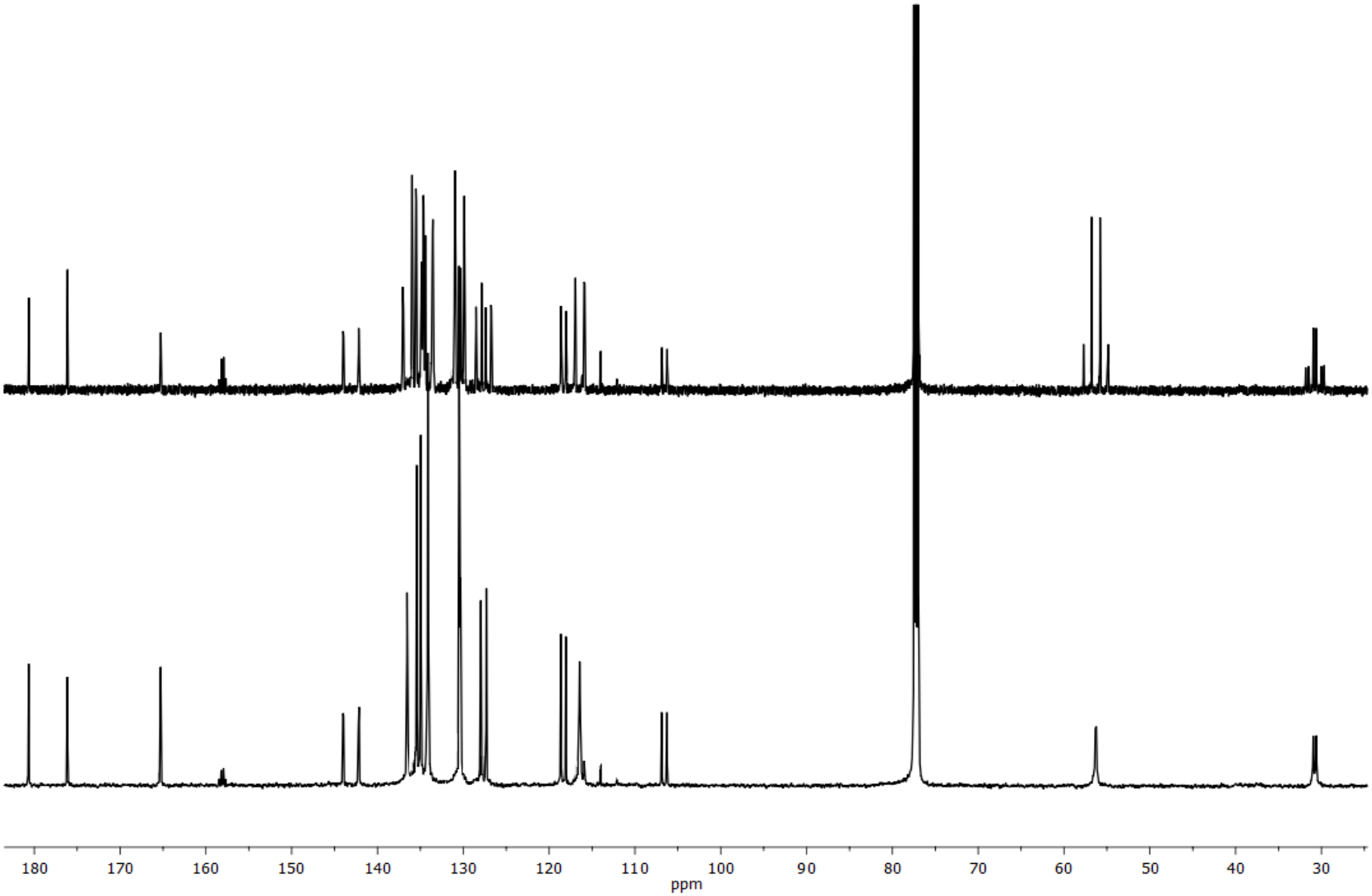


Figure S8 $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **5a** (150.9 MHz, $CDCl_3$).

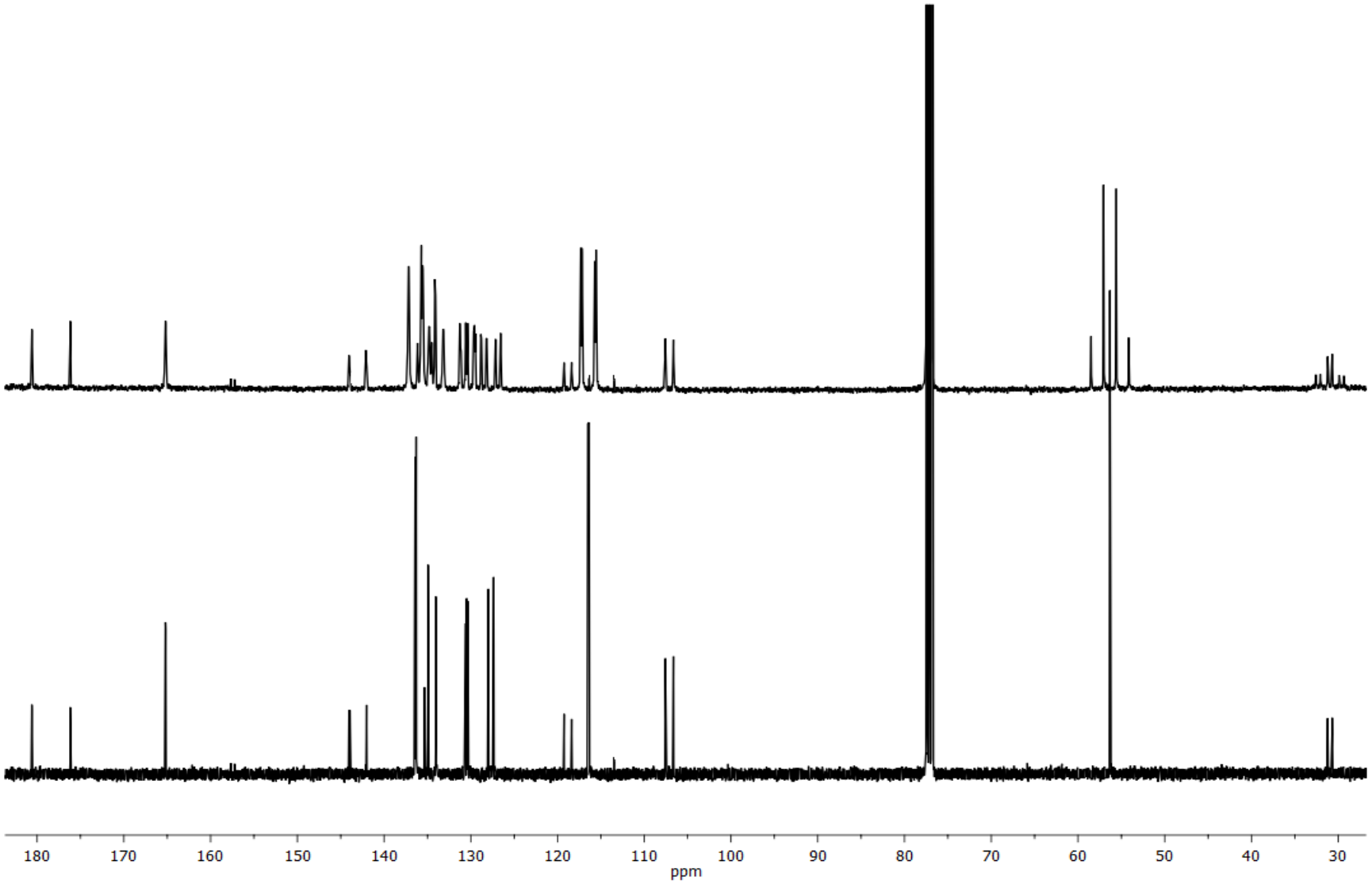


Figure S9 $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **5b** (100.6 MHz, $CDCl_3$).

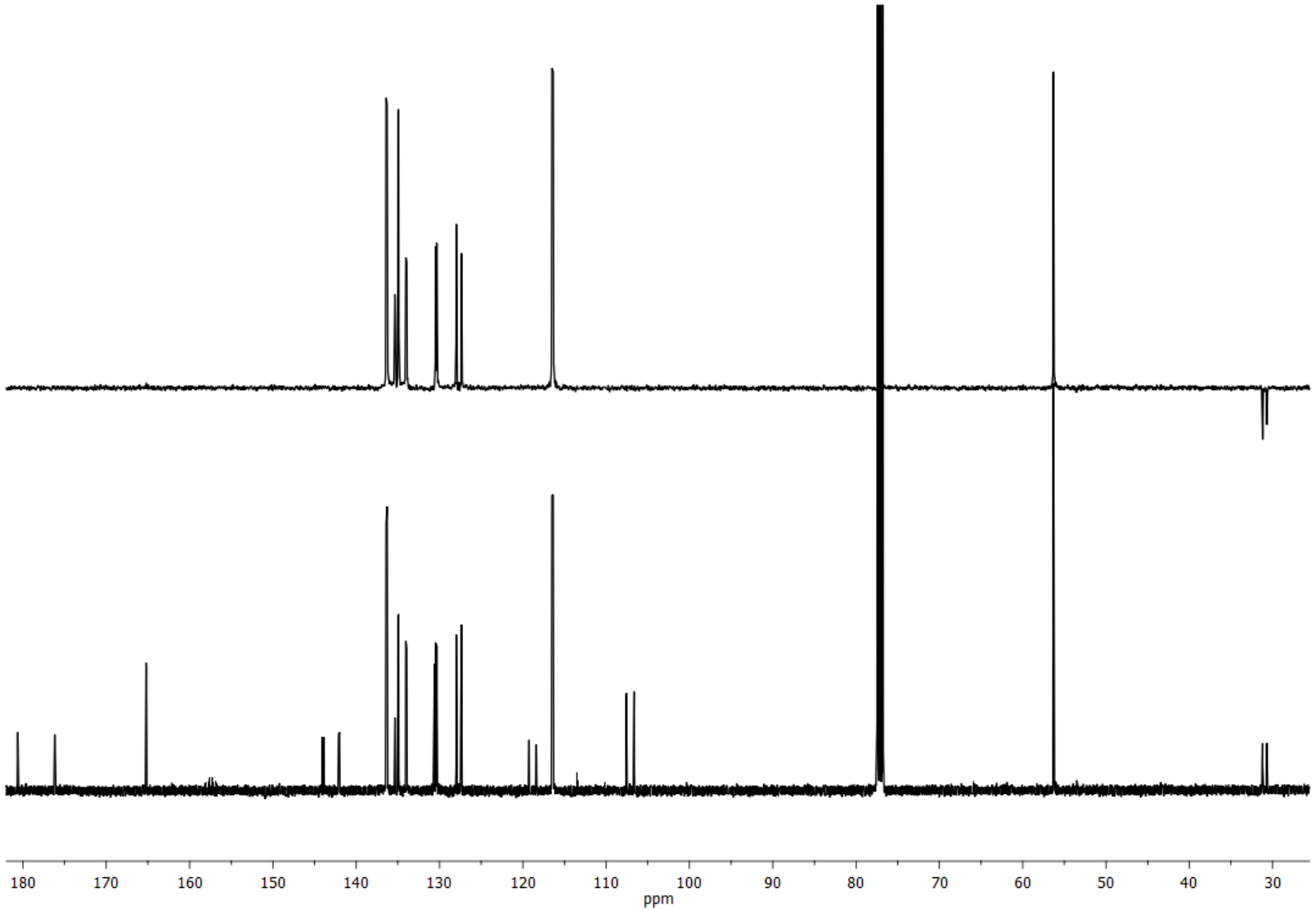


Figure S10 $^{13}C–\{^{1}H\}/^{13}C$-dept NMR spectra of phosphonium salt **5b** (100.6 MHz, $CDCl_3$).

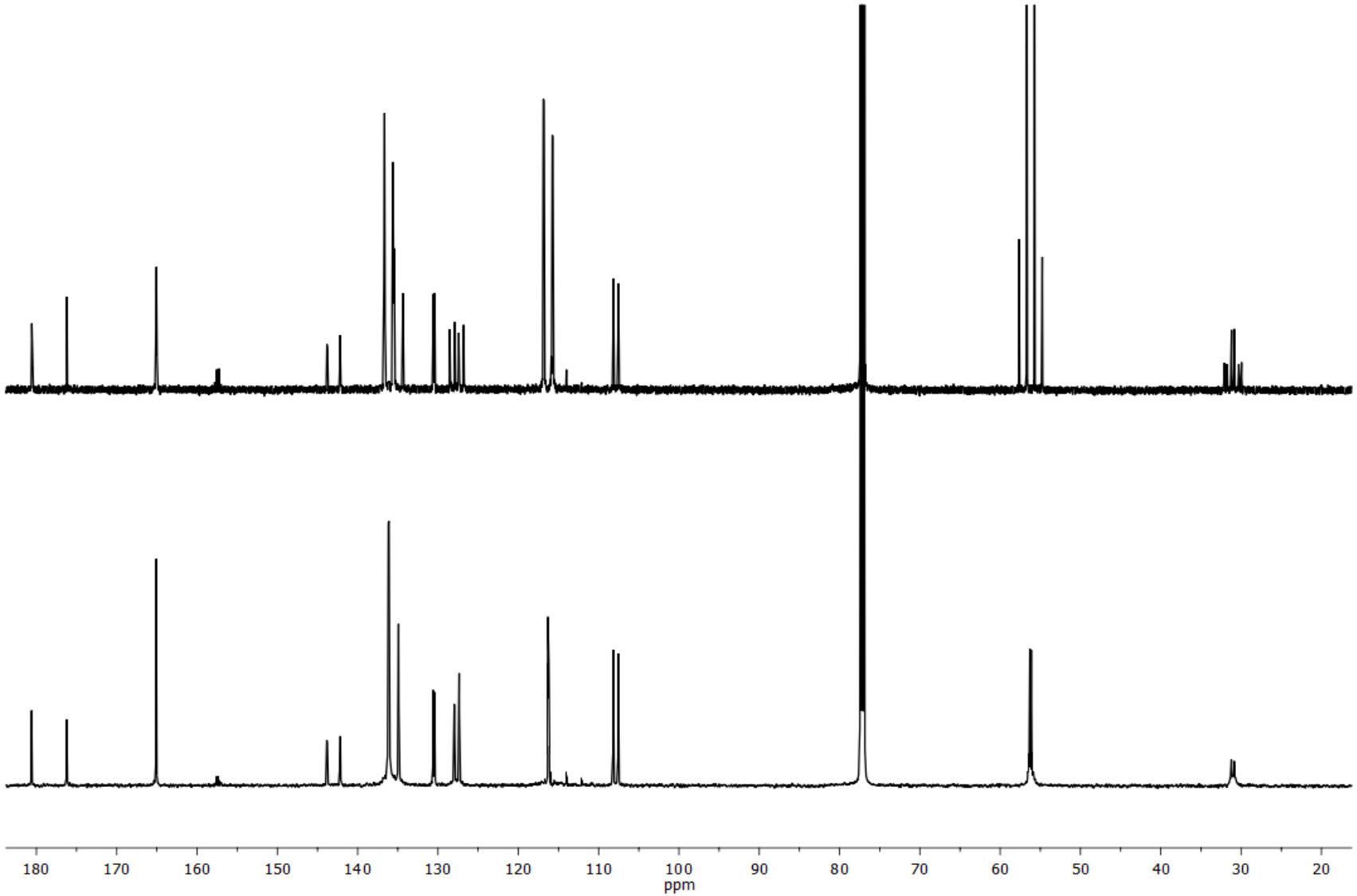


Figure S11 $^{13}C–\{^{1}H\}/^{13}C$ NMR spectra of phosphonium salt **5c** (150.9 MHz, $CDCl_3$).