

Antitumor and antibacterial activity of novel menthyl- and bornyl-substituted 2-hydroxypropylphosphonium and arsonium salts

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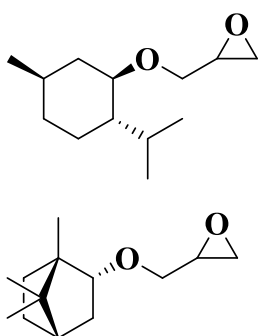
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Experimental section

Chemistry

The NMR spectra were recorded at 25°C using a Bruker Avance-400 NMR spectrometer (400.0 MHz, ^1H ; 100.6 MHz, ^{13}C ; 162 MHz, ^{31}P), a Bruker Avance-500 NMR spectrometer (500.0 MHz, ^1H ; 125.75 MHz, ^{13}C ; 201.7 MHz, ^{31}P) and a Bruker Avance-600 NMR spectrometer (600.0 MHz, ^1H ; 150.9 MHz, ^{13}C ; 242 MHz, ^{31}P) in CDCl_3 . Chemical shifts were referenced to the residual solvent peak and reported in ppm (δ scale), and all coupling constant (J) values were given in Hz. IR spectra were recorded using a Bruker Vector 22 spectrometer and Bruker Tensor 27 spectrometer for samples in KBr pellets or in films. MALDI mass spectra were acquired on a Bruker MALDI-MS Ultraflex III spectrometer. 2,5-Dihydroxybenzoic acid (5 mg/mL in methanol) and 4-nitroanilin (5 mg/mL in methanol) were used as matrices. Electrospray ionization mass spectra (ESI-MS) were obtained on an AmazonX mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). Measurements were performed in positive ion mode in the m/z range from 200 to 1000 Da. The capillary voltage was 4500 V. Data were processed using DataAnalysis 4.0 software (Bruker Daltonik GmbH, Bremen, Germany). Melting points were determined on a Melting Point Apparatus Stuart SMP10. Elemental analysis was accomplished with an automated Euro-Vector EA3000 CHNS-O elemental analyzer (Euro-Vector, Italy). The progress of reactions and the purity of products were monitored by TLC on Sorbfil plates (IMID Ltd., Russian Federation). TLC plates were visualized under UV light. The targeted substances were isolated using dry column vacuum chromatography (DCVC) on silica gel KSKG ($< 63 \mu\text{m}$, Khrom Lab Co. Ltd, Russian Federation) with $35\text{mm} \times 55\text{mm}$ column. Solvents were purified and dried by standard protocols.

2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy)methyl)oxirane (1a) and 2-(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxy)methyl)oxirane (1b)



To the corresponding terpenoid alcohol (20 mmol) were added ($\pm$)-epichlorohydrin (1.68 g, 18 mmol) and 0.5 mol% of aluminum triflate (43 mg, 91 μmol). The reaction mixture was stirred at 60°C for 4.5 hours. It was cooled to 0°C, and aqueous potassium hydroxide (50%, 5.1 g, 91 mmol) and 10 mol% $\text{Bu}_4\text{N}^+\text{BF}_4^-$ (600 mg, 1.8 mmol) were added portionwise. The resulting mixture was stirred for 3 hours at room temperature, then poured onto iced water (100 ml), and the layers were separated. The aqueous layer was extracted with ether ($3 \times 10 \text{ ml}$), the combined ether solutions were dried over Na_2SO_4 , the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica using a linear gradient elution system from 100 % to 40 % (by volume) petroleum ether/diethyl ether. The spectral characteristics of the obtained product coincide with the literature data.^{S1,S2}

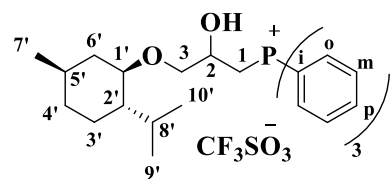
^{S1} H. Obase, H. Tatsuno, K. Goto, K. Shigenobu, Y. Kasuya, Y. Yamada, K. Fujii, and S. Yada, *Chem. Pharm. Bull.*, 1978, **26**, 1443; <https://doi.org/10.1248/cpb.26.1443>.

^{S2} A. Akira, A. Teruyoshi, M. Takashi, H. Toshimitsu, *Patent EP1201635 A1*, 2002; <https://patentimages.storage.googleapis.com/1f/7e/35/d868f236a80c47/EP1201635B1.pdf>.

General procedure for the synthesis of compounds 2,3

Triphenylphosphine (90 mg, 343 μ M) or triphenylarsine (105 mg, 343 μ M) were dissolved in CH_2Cl_2 (10 ml) under argon. The mixture was cooled in an ice bath, and triflic acid (31 μ l, 343 μ M) was added dropwise. After stirring for 10 minutes, a solution of the corresponding epoxide **1** (412 μ M) in CH_2Cl_2 (15 ml) was added dropwise under continuous argon flow. The mixture was stirred for additional 1 hour at 0 $^\circ\text{C}$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica using a linear gradient eluent system from 100 to 10% (by volume) benzene–acetonitrile.

(2-Hydroxy-3-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)propyl)triphenylphosphonium trifluoromethanesulfonate (2a)



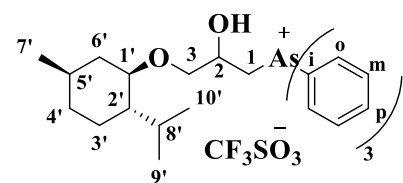
Colorless solid, TLC R_f = 0.63 (benzene / acetonitrile = 2/3), T_m = 138-

140 $^\circ\text{C}$, yield: 156 mg (73%); IR (KBr): 3399, 3064, 2955, 2924, 2870, 1980, 1911, 1826, 1711, 1615, 1589, 1486, 1456, 1440, 1385, 1368, 1344, 1279, 1259, 1225, 1158, 1113, 1055, 1031, 998, 975, 921, 889, 847, 826, 784, 749,

723, 691, 639, 573, 543, 517, 499, 464, 429 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.75 (m, $^3J_{HH}$ = 7.2 Hz, $^5J_{PH}$ = 2.0 Hz, $^4J_{HH}$ 1.5 Hz, 3 H, $\text{H}^{\text{Ar}}_{\text{para}}$), 7.68 (m, $^3J_{PH}$ = 12.5 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5 Hz, 6 H, $\text{H}^{\text{Ar}}_{\text{ortho}}$), 7.64 (m, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 3.6 Hz, 6 H, $\text{H}^{\text{Ar}}_{\text{meta}}$), 4.09 (br. s, 1 H, H^2), 3.87 – 3.76 (m, 1 H, H^1_{A}), 3.71 – 3.58 (m, 1 H, H^3_{A}), 3.58 – 3.41 (m, 2 H, H^1_{B} overlapped with H^3_{B}), 3.12 (ddd, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 3.9 Hz, 1 H, $\text{H}^{1'}(d_1)$), 3.14 (ddd, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 3.9 Hz, 1 H, $\text{H}^{1'}(d_2)$), 2.16 – 1.98 (m, 2 H, $\text{H}^{8'}$ overlapped with $\text{H}^{6'_{\text{A}}}$), 1.69 – 1.52 (m, 2 H, $\text{H}^{3'_{\text{A}}}$ overlapped with $\text{H}^{4'_{\text{A}}}$), 1.34 (br. s, 1 H, $\text{H}^{5'}$), 1.24 – 1.12 (m, 1 H, $\text{H}^{2'}$), 1.07–0.93 (m, 1 H, $\text{H}^{4'_{\text{B}}}$), 0.93 – 0.84 (m, 6 H, $\text{H}^{9'}$ overlapped with $\text{H}^{7'}$), 0.79 (m, $^2J_{HH}$ = 12.1 Hz, 2 H, $\text{H}^{3'}$ overlapped with $\text{H}^{6'_{\text{B}}}$), 0.73 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, $\text{H}^{10'}(d_1)$), 0.70 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, $\text{H}^{10'}(d_2)$); ^{13}C – $\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3): δ = 134.98 (d, $\text{C}^{\text{Ar}}_{\text{para}}$, $^4J_{PC}$ = 2.9 Hz), 133.83 (d, $^2J_{PC}$ = 10.0, $\text{C}^{\text{Ar}}_{\text{ortho}}(d_1)$), 133.81 (d, $^2J_{PC}$ = 10.1 Hz, $\text{C}^{\text{Ar}}_{\text{ortho}}(d_2)$), 130.29 (d, $^3J_{PC}$ = 12.8 Hz, $\text{C}^{\text{Ar}}_{\text{meta}}$), 120.67 (q, $^1J_{CF}$ = 320.6 Hz, CF_3), 118.73 (d, $^1J_{PC}$ = 87.1 Hz, $\text{C}^{\text{Ar}}_{\text{ipso}}(d_1)$), 118.70 (d, $^1J_{PC}$ = 87.1 Hz, $\text{C}^{\text{Ar}}_{\text{ipso}}(d_2)$), 80.08 (s, $\text{C}^{1'}(d_1)$), 79.92 (s, $\text{C}^{1'}(d_2)$), 71.71 (d, $^3J_{PC}$ = 15.0 Hz, $\text{C}^3(d_1)$), 71.62 (d, $^3J_{PC}$ = 14.4 Hz, $\text{C}^3(d_2)$), 65.82 (d, $^2J_{PC}$ = 5.8 Hz, $\text{C}^2(d_1)$), 65.72 (d, $^2J_{PC}$ = 5.6 Hz, $\text{C}^2(d_2)$), 48.22 (s, $\text{C}^{2'}$), 40.37 (s, $\text{C}^{6'}(d_1)$), 40.29 (s, $\text{C}^{6'}(d_2)$), 34.45 (s, $\text{C}^{4'}$), 31.35 (s, $\text{C}^{5'}(d_1)$), 31.33 (s, $\text{C}^{5'}(d_2)$), 28.51 (d, $^1J_{PC}$ = 55.0 Hz, $\text{C}^1(d_1)$), 28.47 (d, $^1J_{PC}$ = 54.5 Hz, $\text{C}^1(d_2)$), 26.03 (s, $\text{C}^{8'}(d_1)$), 25.90 (s, $\text{C}^{8'}(d_2)$), 23.26 (s, $\text{C}^{3'}(d_1)$), 23.20 (s, $\text{C}^{3'}(d_2)$), 22.21 (s, $\text{C}^{7'}$), 20.99 (s, $\text{C}^{9'}$), 16.20 (s, $\text{C}^{10'}(d_1)$), 16.17 (s, $\text{C}^{10'}(d_2)$); ^{31}P – $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ = 24.4 (s, d_1), 24.31 (s, d_2); ESI-MS, m/z 475.46 $[\text{M} - \text{CF}_3\text{SO}_3]^+$. Anal. calcd. for $\text{C}_{31}\text{H}_{40}\text{O}_2\text{P}^+$: 475.28; Calcd. for $\text{C}_{32}\text{H}_{40}\text{F}_3\text{O}_5\text{PS}$: C, 61.53; H, 6.45; Found: C, 61.32; H, 6.61.

(2-Hydroxy-3-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)propyl)triphenylarsonium

trifluoromethanesulfonate (3a)

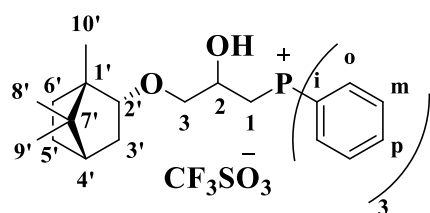


Colorless solid, TLC R_f = 0.63 (benzene / acetonitrile = 2/3), T_m = 133°C, yield: 178 mg (78%); IR (KBr): 3396, 2955, 2930, 2869, 1441, 1286, 1247, 1161, 1115, 1086, 1030, 998, 743, 690, 639, 573, 517, 477 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.75 – 7.68 (m, 3 H, $\text{H}^{\text{Ar}}_{\text{para}}$), 7.69 – 7.60 (m,

12 H, $\text{H}^{\text{Ar}}_{\text{ortho}}$ overlapped with $\text{H}^{\text{Ar}}_{\text{meta}}$), 4.22 (br. s, 1 H, OH), 4.17 (m, $^3J_{\text{HH}} = 5.7 - 5.9$ Hz, 1 H, H^2), 3.78 (dd, $^2J_{\text{HH}} = 10.9$ Hz, $^3J_{\text{HH}} = 5.6$ Hz, 1 H, H^3_{A} (d_1)), 3.75 (dd, $^2J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 5.2$ Hz, 1 H, H^3_{A} (d_2)), 3.70 – 3.56 (m, 2 H, H^3_{B} overlapped with H^1_{A}), 3.52 (dd, $^2J_{\text{HH}} = 6.4$ Hz, $^3J_{\text{HH}} = 3.1$ Hz, 1 H, H^1_{B} (d_1)), 3.49 (dd, $^2J_{\text{HH}} = 6.4$ Hz, $^3J_{\text{HH}} = 3.1$ Hz, 1 H, H^1_{B} (d_2)), 3.10 (ddd, $^3J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 6.2$ Hz, $^3J_{\text{HH}} = 4.2$ Hz, 1 H, $\text{H}^{1'}(d_1)$), 3.08 (ddd, $^3J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 6.2$ Hz, $^3J_{\text{HH}} = 4.3$ Hz, 1 H, $\text{H}^{1'}(d_2)$), 2.12 – 1.99 (m, 2 H, $\text{H}^{8'}$ overlapped with $\text{H}^{6'_{\text{A}}}$), 1.66 – 1.52 (m, 2 H, $\text{H}^{3'_{\text{A}}}$ overlapped with $\text{H}^{4'_{\text{A}}}$), 1.39 – 1.24 (m, 1 H, $\text{H}^{5'}$), 1.23 – 1.10 (m, 1 H, $\text{H}^{2'}$), 1.07–0.93 (m, 1 H, $\text{H}^{4'_{\text{B}}}$), 0.94 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3 H, $\text{H}^{9'}$), 0.91 (d, $^3J_{\text{HH}} = 6.8$, 3 H, $\text{H}^{7'}$), 0.89 – 0.81 (m, 2 H, $\text{H}^{3'}$ overlapped with $\text{H}^{6'_{\text{B}}}$), 0.81 (s, 3 H, $\text{H}^{10'}$ (d_1)), 0.79 (s, 3 H, $\text{H}^{10'}$ (d_2)). $^{13}\text{C} - \{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ = 134.02 (s, $\text{C}^{\text{Ar}}_{\text{para}}$), 132.85 (s, $\text{C}^{\text{Ar}}_{\text{ortho}}$), 130.80 (s, $\text{C}^{\text{Ar}}_{\text{meta}}$), 122.15 (s, $\text{C}^{\text{Ar}}_{\text{ipso}}$), 120.75 (q, CF_3 , $^1J_{\text{CF}} = 320.1$ Hz), 80.09 (s, $\text{C}^{1'}$ (d_1)), 80.05 (s, $\text{C}^{1'}$ (d_2)), 71.37 (s, C^2 (d_1)), 71.27 (s, C^2 (d_2)), 65.87 (s, C^3), 48.27 (s, $\text{C}^{2'}$), 40.36 (s, $\text{C}^{6'}$ (d_1)), 40.30 (s, $\text{C}^{6'}$ (d_2)), 34.53 (s, $\text{C}^{4'}$), 32.29 (s, C^1 (d_1)), 32.24 (s, C^1 (d_2)), 31.42 (s, C^5), 26.04 (s, $\text{C}^{8'}$ (d_1)), 25.95 (s, $\text{C}^{8'}$ (d_2)), 23.32 (s, $\text{C}^{3'}$), 22.27 (s, $\text{C}^{7'}$), 21.04 (s, $\text{C}^{9'}$ (d_1)), 21.03 (s, $\text{C}^{9'}$ (d_2)), 16.25 (s, $\text{C}^{10'}$); ESI-MS, m/z 519.40 $[\text{M} - \text{CF}_3\text{SO}_3]^+$. Calcd. for $\text{C}_{31}\text{H}_{40}\text{AsO}_2^+$: 519.23; Anal. calcd. for $\text{C}_{32}\text{H}_{40}\text{AsF}_3\text{O}_5\text{S}$: C, 57.48; H, 6.03; Found: C, 57.16; H, 6.28.

3-((1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yloxy)-2-hydroxypropyl)-triphenylphosphonium

trifluoromethanesulfonate (2b)

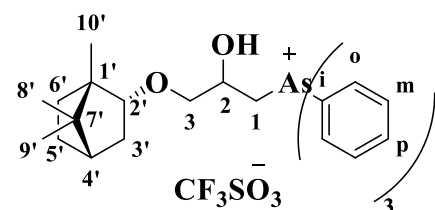


Colorless solid, TLC R_f = 0.63 (benzene / acetonitrile = 2/3), T_m = 133–135°C, yield 150 mg (69%); IR (KBr): 3374, 3066, 2952, 2876, 1487, 1439, 1388, 1288, 1251, 1154, 1113, 1030, 998, 886, 836, 795, 752, 721, 691, 638, 573, 540, 502 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.75 (m,

$^3J_{\text{HH}} = 7.2$ Hz, $^5J_{\text{PH}} = 2.0$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 3 H, $\text{H}^{\text{Ar}}_{\text{para}}$), 7.68 (m, $^3J_{\text{PH}} = 12.5$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 6 H, $\text{H}^{\text{Ar}}_{\text{ortho}}$), 7.64 (m, $^3J_{\text{HH}} = 7.2$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, $^4J_{\text{PH}} = 3.6$ Hz, 6 H, $\text{H}^{\text{Ar}}_{\text{meta}}$), 4.19 – 4.05 (br s, 1 H, H^2), 3.74 – 3.46 (m, 5 H, H^1 overlapped with H^3 and $\text{H}^{2'}$), 2.81 (br s, 1 H, OH), 2.20 – 2.06 (m, 1 H, $\text{H}^{3'_{\text{A}}}$), 1.91 – 1.78 (m, 1 H, $\text{H}^{6'_{\text{A}}}$), 1.75 – 1.65 (m, 1 H, $\text{H}^{5'_{\text{A}}}$), 1.63 (m, $^3J_{\text{HH}} = 4.4$ Hz, 1 H, $\text{H}^{4'}$), 1.28 – 1.10 (m, 2 H, $\text{H}^{5'_{\text{B}}}$ overlapped with $\text{H}^{6'_{\text{B}}}$), 0.99 (ddd, $^2J_{\text{HH}} = 12.8$ Hz, $^3J_{\text{HH}} = 8.8$ Hz, $^3J_{\text{HH}} = 3.2$ Hz, 1 H, $\text{H}^{3'_{\text{B}}}$), 0.88 – 0.78 (m, 9 H, $\text{H}^{8'}$ - $\text{H}^{10'}$); $^{13}\text{C} - \{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ = 135.03 (d, $^4J_{\text{PC}} = 2.6$ Hz, $\text{C}^{\text{Ar}}_{\text{para}}$), 133.93 (d, $^2J_{\text{PC}} = 10.3$ Hz, $\text{C}^{\text{Ar}}_{\text{ortho}}$), 130.36 (d, $^3J_{\text{PC}} = 12.8$ Hz, $\text{C}^{\text{Ar}}_{\text{meta}}$), 118.90 (d, $^1J_{\text{PC}} = 87.1$ Hz, $\text{C}^{\text{Ar}}_{\text{ipso}}$), 85.80 (s, $\text{C}^{2'}$ (d_1)), 85.69 (s, $\text{C}^{2'}$ (d_1)), 73.14 (d, $^3J_{\text{PC}} = 15.4$ Hz, C^3 (d_1)), 73.03 (d, $^3J_{\text{PC}} = 15.1$ Hz, C^3 (d_2)), 65.75 (d, $^2J_{\text{PC}} = 5.8$ Hz, C^2 (d_1)), 65.64 (d, $^2J_{\text{PC}} = 5.6$ Hz, C^2 (d_1)), 49.39 (s, $\text{C}^{1'}$), 48.01 (s, $\text{C}^{7'}$ (d_1)), 48.00 (s, $\text{C}^{7'}$ (d_1)), 45.01 (s, $\text{C}^{4'}$), 36.21 (s, $\text{C}^{3'}$ (d_1)), 36.12 (s, $\text{C}^{3'}$ (d_1)), 28.38 (s, $\text{C}^{6'}$), 28.25 (d, $^1J_{\text{PC}} = 53.9$ Hz, C^1 (d_1)), 28.22 (d, $^1J_{\text{PC}} =$

54.2 Hz, C¹ (*d*₁)), 26.91 (s, C^{5'} (*d*₁)), 26.89 (s, C^{5'} (*d*₂)), 19.85 (s, C^{8'}), 18.92 (s, C^{9'}), 14.26 (s, C^{10'} (*d*₁)), 14.21 (s, C^{10'} (*d*₂)); ³¹P – {¹H} NMR (162 MΓII, CDCl₃): δ = 24.9 (s, *d*₁), 24.87 (s, *d*₂); MALDI-MS, *m/z* 473.3 [M – CF₃SO₃]⁺. Calcd. for C₃₁H₃₈O₂P⁺: 473.3; Anal. calcd. for C₃₂H₃₈F₃O₅PS: C, 61.73; H, 6.15; Found: C, 61.70; H, 6.17

3-((1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yloxy)-2-hydroxypropyl)triphenylarsonium



trifluoromethanesulfonate (3b)

Colorless solid, TLC *R_f* = 0.63 (benzene / acetonitrile = 2/3), *T_m* = 128–130°C, yield: 147 mg (63%); IR (KBr): 3347, 3063, 2982, 2951, 2876, 1486, 1441, 1387, 1288, 1248, 1225, 1156, 1115, 1087, 1030, 999, 866, 745, 690, 638, 573, 518, 460 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.80 – 7.59 (m, 15 H, Ph), 4.30 – 4.18 (m, 1 H, H²), 3.79 – 3.51 (m, 5 H, H¹ overlapped with H³ and H^{2'}), 2.39 – 2.04 (m, 2 H, H^{3'}_A overlapped with OH), 1.91 – 1.78 (m, 1 H, H^{6'}_A), 1.76 – 1.58 (m, 2 H, H^{5'}_A overlapped with H^{4'}), 1.27 – 1.11 (m, 2 H, H^{5'}_B overlapped with H^{6'}_B), 0.96 (m, ²*J_{HH}* = 12.8 Hz, 1 H, H^{3'}_B), 0.84 (s, 3 H, H^{10'}), 0.82 (s, 6 H, H^{8'} overlapped with H^{9'}); ¹³C – {¹H} NMR (100.6 MHz, CDCl₃): δ = 134.04 (s, C^{Ar}_{para}), 133.00 (s, C^{Ar}_{ortho}), 130.85 (s, C^{Ar}_{meta}), 122.28 (s, C^{Ar}_{ipso}), 85.81 (s, C^{2'} (*d*₁)), 85.78 (s, C^{2'} (*d*₂)), 72.86 (s, C³ (*d*₁)), 72.80 (s, C³ (*d*₂)), 65.88 (s, C² (*d*₁)), 65.80 (s, C² (*d*₂)), 49.40 (s, C^{7'}), 48.03 (s, C^{1'}), 45.00 (s, C^{4'}), 36.21 (s, C^{3'}), 32.43 (s, C¹), 28.38 (s, C^{6'}), 26.85 (s, C^{5'}), 19.86 (s, C^{8'}), 18.93 (s, C^{9'}), 14.24 (s, C^{10'}); MALDI-MS, *m/z* 517.4 [M–CF₃SO₃]⁺. Calcd. for C₃₁H₄₀AsO₂⁺: 517.2; Anal. calcd. for C₃₂H₃₈AsF₃O₅S: S, 57.66; H, 5.75; Found: C, 57.61; H, 5.76

Biology.

Cell Toxicity Assay (MTT- assay).

Cell viability was assessed using the standard colorimetric MTT assay. Briefly, cells were seeded in 96-well plates at a density of 5 × 10³ cells per well. After 48 hours of incubation, the culture medium was replaced with fresh medium containing the test compounds at concentrations ranging from 0.1 to 100 μM. The compounds were solubilized in medium supplemented with 1% DMSO. Absorbance was recorded at 540 nm using an Invitrologic microplate reader (Russia). The M-HeLa clone 11 human, epithelioid cervical carcinoma, strain of HeLa, clone of M-HeLa; human alveolar adenocarcinoma cells (A549); human duodenal cancer cell line (HuTu 80); human breast adenocarcinoma cells (MCF-7); glioblastoma cell line (T98G); Wi-38 VA-13 cell culture, subline 2RA (human embryonic lung) from the shared research facility "Vertebrate cell culture collection" of the Institute of Cytology of the Russian Academy of Sciences, PC-3 human Caucasian prostate adenocarcinoma from Type Culture Collection (ATCC, Manassas, VA, USA) were used in the experiments. The cells were cultured on a standard nutrient medium "Igla" produced by the Moscow Institute of Poliomyelitis and Viral Encephalitis. M.P.Chumakov by Pan-Eco with the addition of 10% fetal calf serum and 1% nonessential amino acids (NEAA).

Statistical analysis

The IC₅₀ values were calculated using the online calculator MLA – Quest Graph™ IC50 Calculator AAT Bioquest, Inc, June 23, 2025. Tabular and graphical data contains averages and standard error. Experiments for all compounds were repeated three times.

Antimicrobial activity

The antimicrobial activity of the tested compounds was evaluated using the broth microdilution method in 96-well plates with Mueller-Hinton broth. The assay was performed against a panel of reference strains, including the Gram-positive bacteria *Staphylococcus aureus* ATCC 6538, *Bacillus cereus* ATCC 10702, and *Enterococcus faecalis* ATCC 29212, as well as the Gram-negative bacteria *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 9027, obtained from the SCPM-Obolensk collection. Additionally, two clinical methicillin-resistant *S. aureus* (MRSA-1 and MRSA-2) isolates from patients with chronic tonsillitis and sinusitis were included. All experiments were conducted in triplicate.

Hemolytic Assay

The hemolytic activity of phosphonium **2a,b** and arsonium **3a,b** salts was assessed by comparing the optical density of a solution containing the test compound with the optical density of blood at 100% hemolysis. Rat erythrocytes were used as the object of study. Erythrocytes with EDTA (1.8 mg/ml) were washed three times with physiological solution (0.9% NaCl), centrifuged for 10 min at 800 rpm and resuspended in physiological solution (0.9% NaCl) to a concentration of 10%. The studied concentrations (0.1–500 µM) were prepared in physiological solution (0.9% NaCl) (with the addition of 5% DMSO). The compounds in the appropriate dilution (450 µl) were added to 50 µl of 10% erythrocyte suspension. Samples were incubated for 1 hour at 37°C and centrifuged for 10 minutes at 2000 rpm. Hemoglobin release was monitored by measuring the optical density of the supernatant using an InvitroLogic microplate reader (Russia) at $\lambda = 540$ nm. A control sample corresponding to zero hemolysis (blank experiment) was prepared by adding 50 µl of 10% red blood cell suspension to 450 µl of saline (0.9% NaCl). A control sample corresponding to 100% hemolysis was prepared by adding 50 µl of 10% red blood cell suspension to 450 µl of distilled water.

Blood sampling for hemolysis and agglutination analysis was performed from the tail tip of outbred Wistar rats (males, 3-4 months old, body weight 300-350g) in accordance with the protocol of the Ethics Committee of the Federal Research Center of the Kazan Scientific Center of the Russian Academy of Sciences No. 24/1 dated October 4, 2024.

Table S1. Hemolytic activity of phosphonium (**2a,b**) and arsonium (**3a,b**) salts

Compounds	HC ₅₀ µM
2a	>500
2b	478.9
3a	392.8
3b	397.9

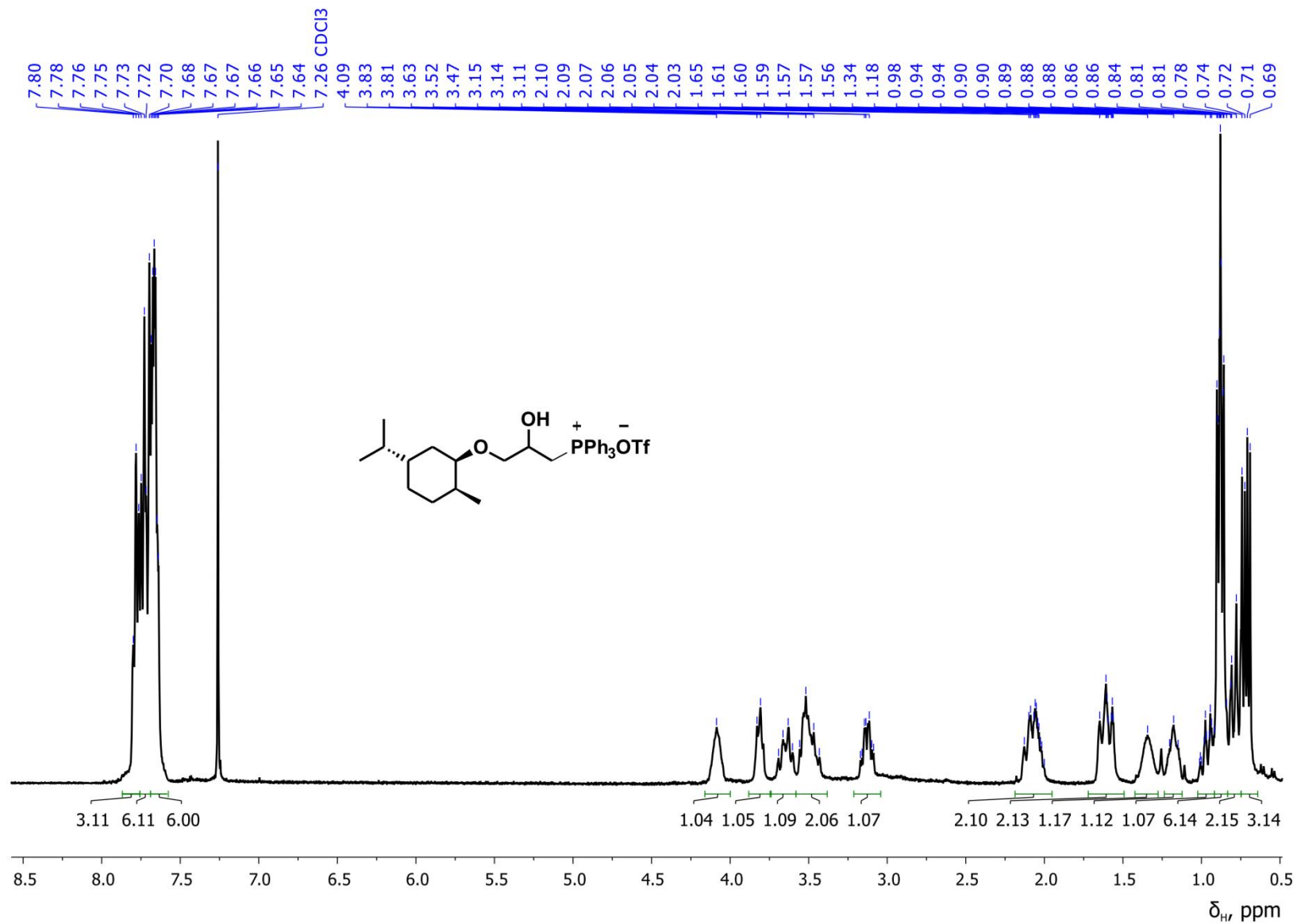


Figure S1. ¹H NMR (400 MHz, CDCl₃) spectrum of compound **2a**

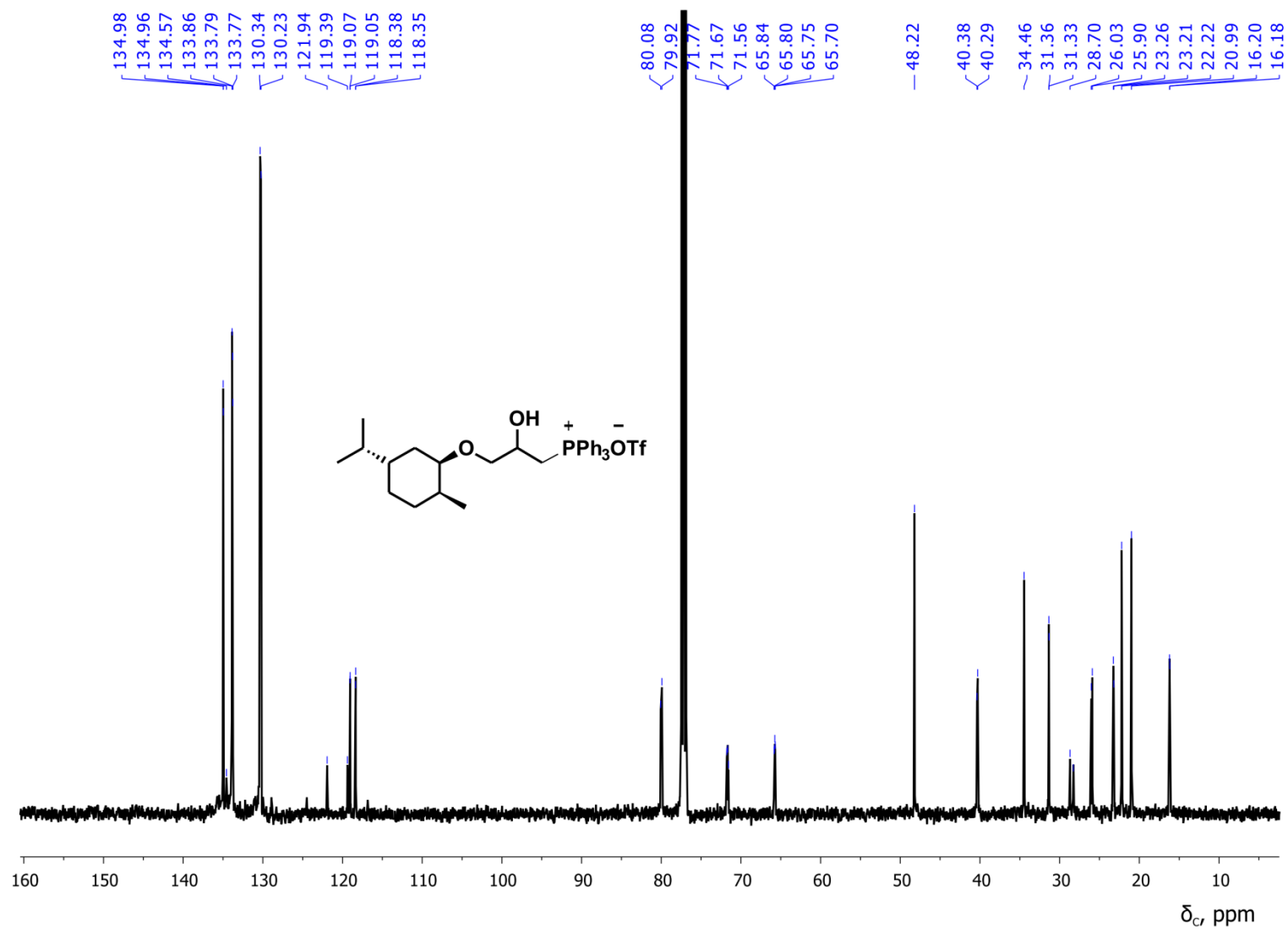


Figure S2. ^{13}C – $\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3) spectrum of compound **2a**

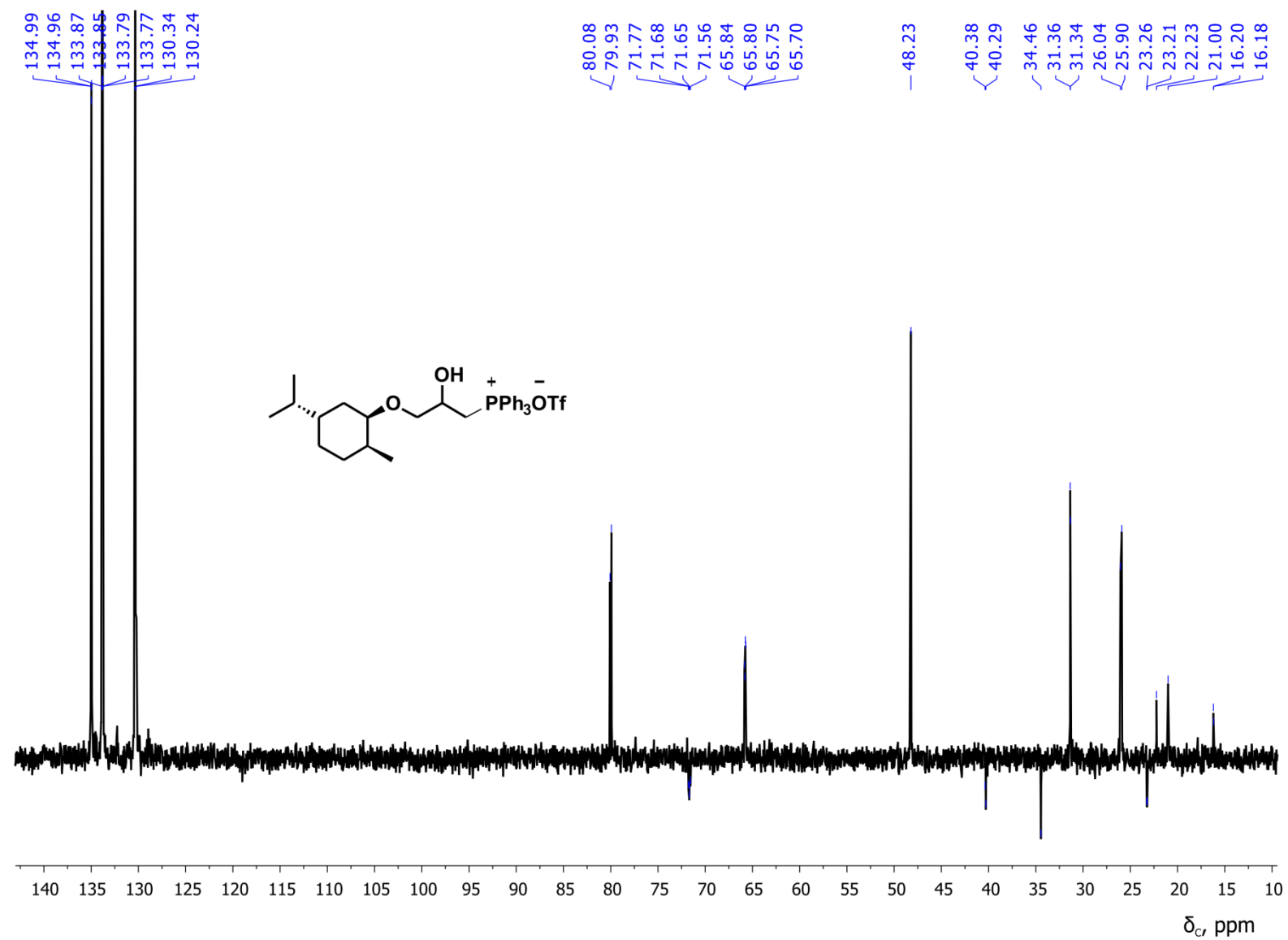


Figure S3. $^{13}\text{C} - \{^1\text{H}\}$ NMR DEPT (125.8 MHz, CDCl_3) spectrum of compound **2a**

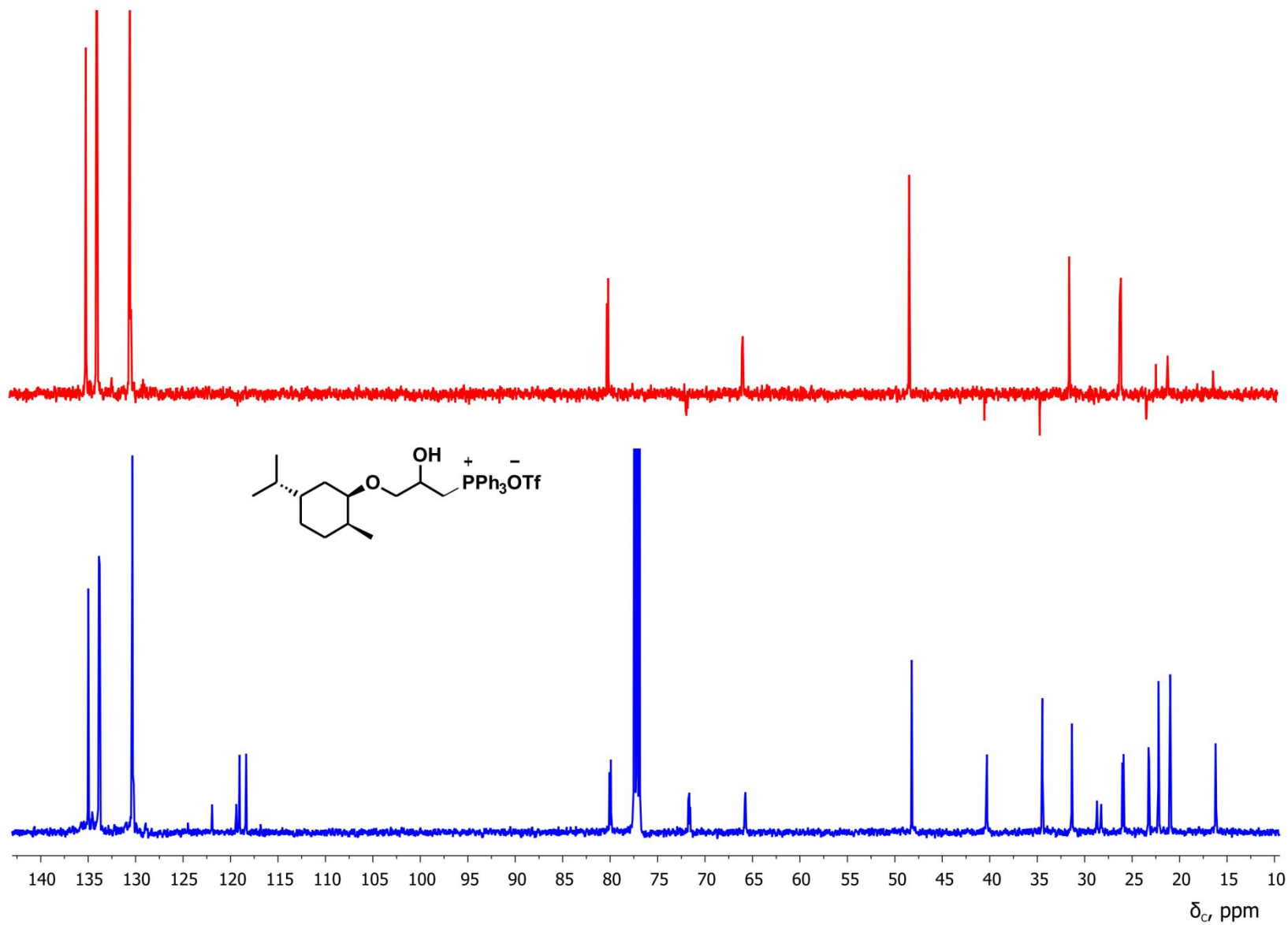


Figure S4. $^{13}\text{C} - \{^1\text{H}\}$ DEPT and $^{13}\text{C} - \{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3) spectra of compound **2a**

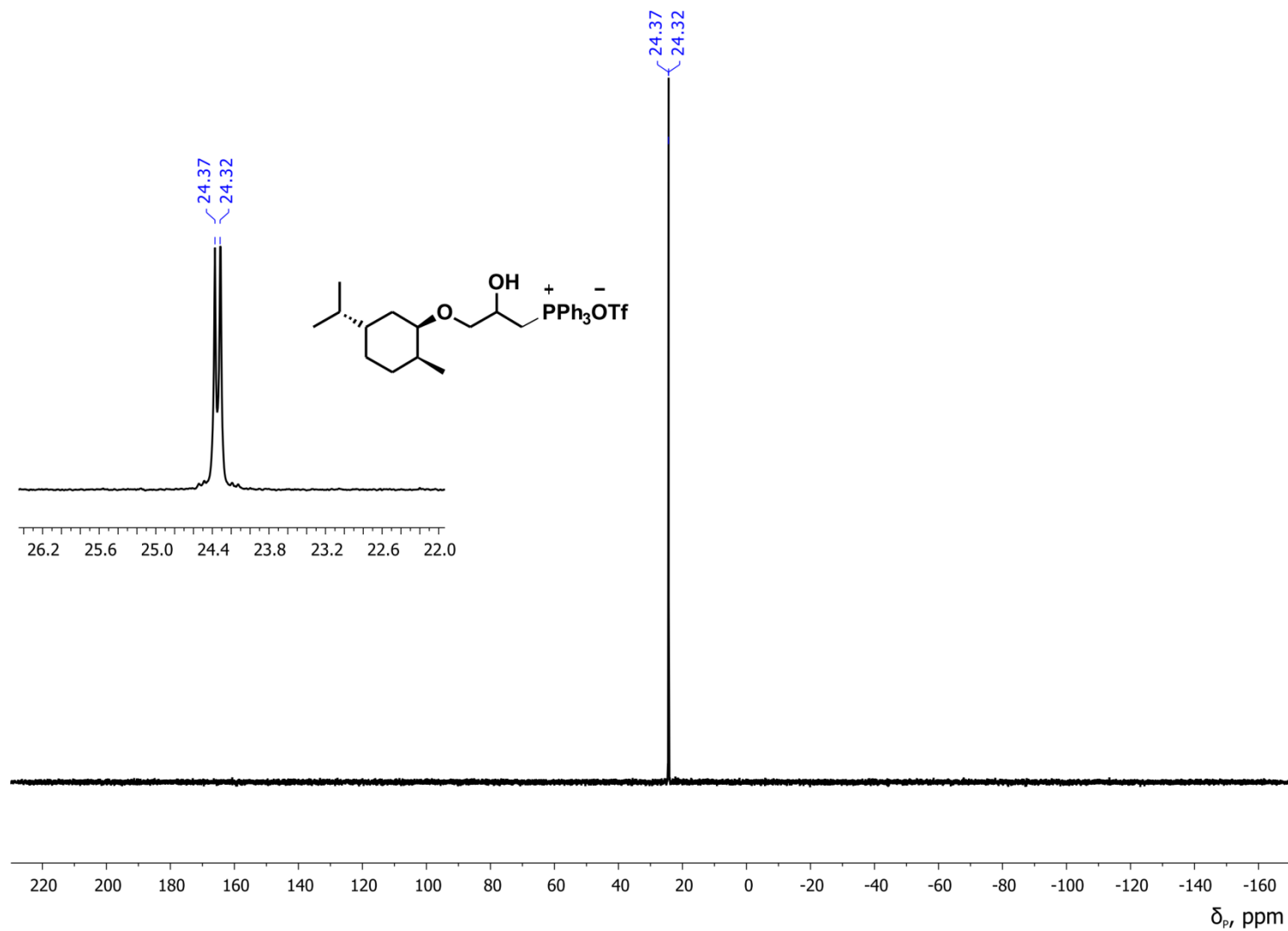


Figure S5. ^{31}P – $\{^1\text{H}\}$ NMR (243 MHz, CDCl_3) spectrum of compound **2a**

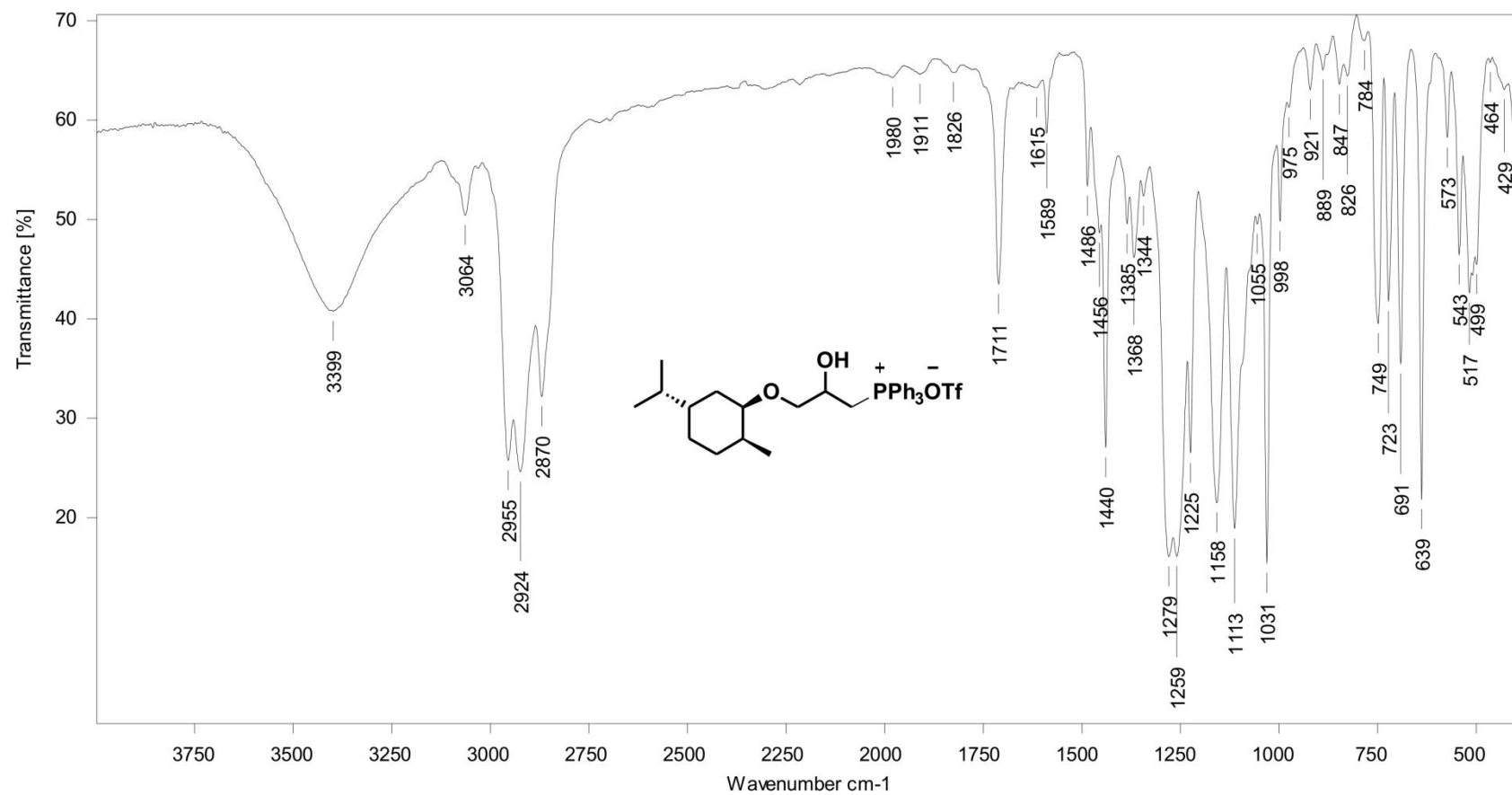


Figure S6. IR spectrum (KBr) of compound **2a**

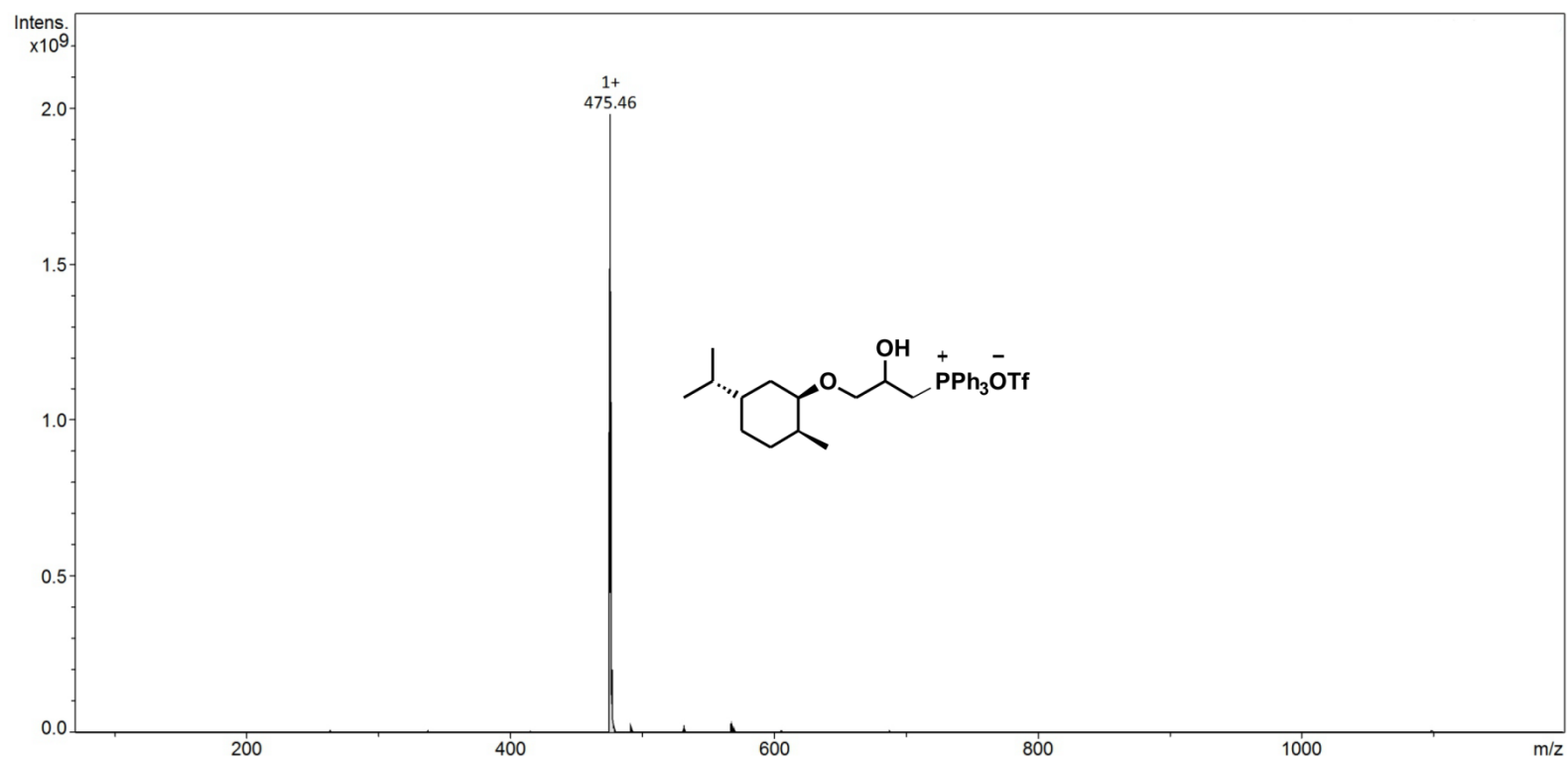


Figure S7. ESI-MS spectrum of compound **2a**

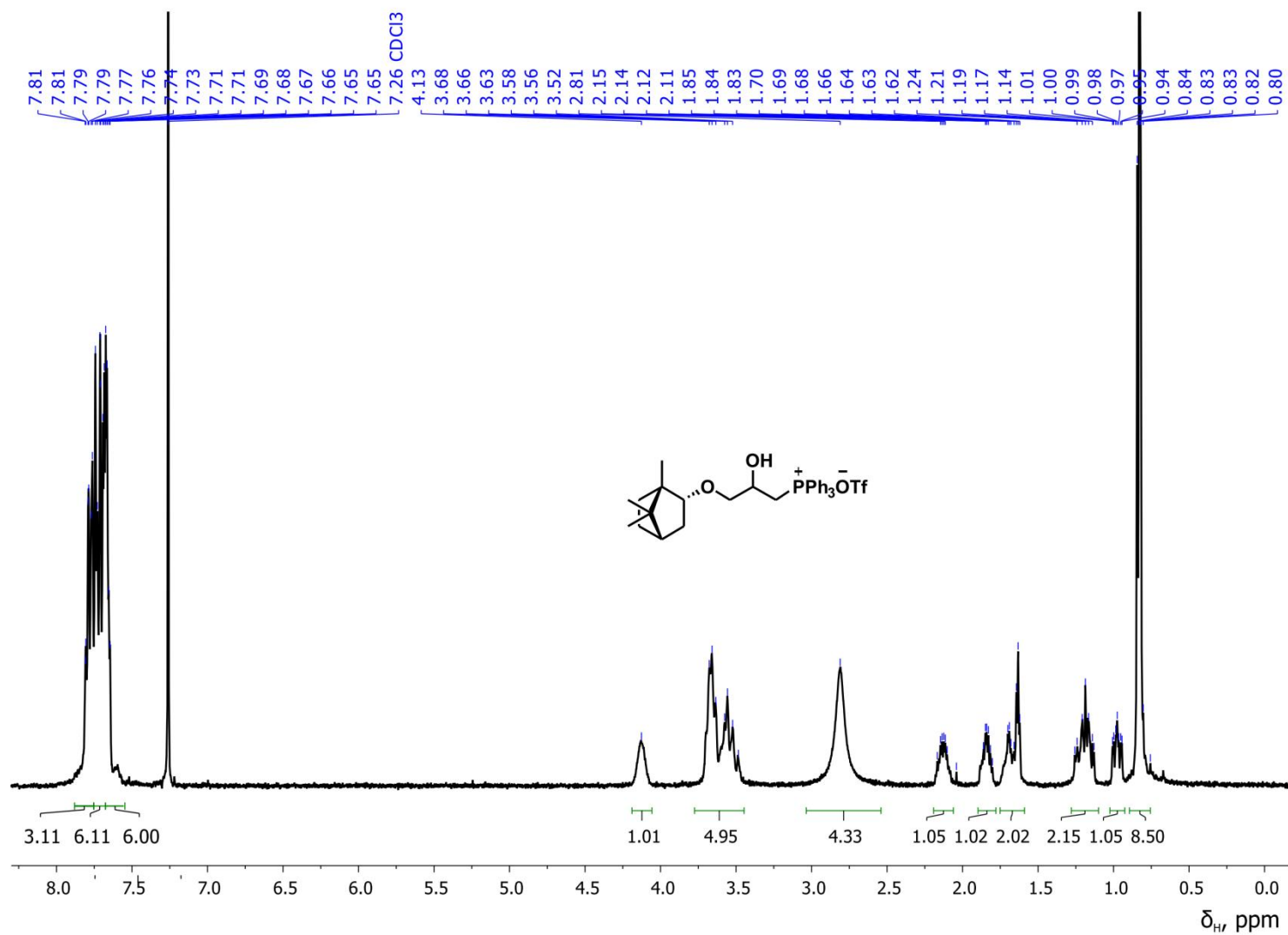


Figure S8. ¹H NMR (400 MHz, CDCl₃) spectrum of compound **2b**

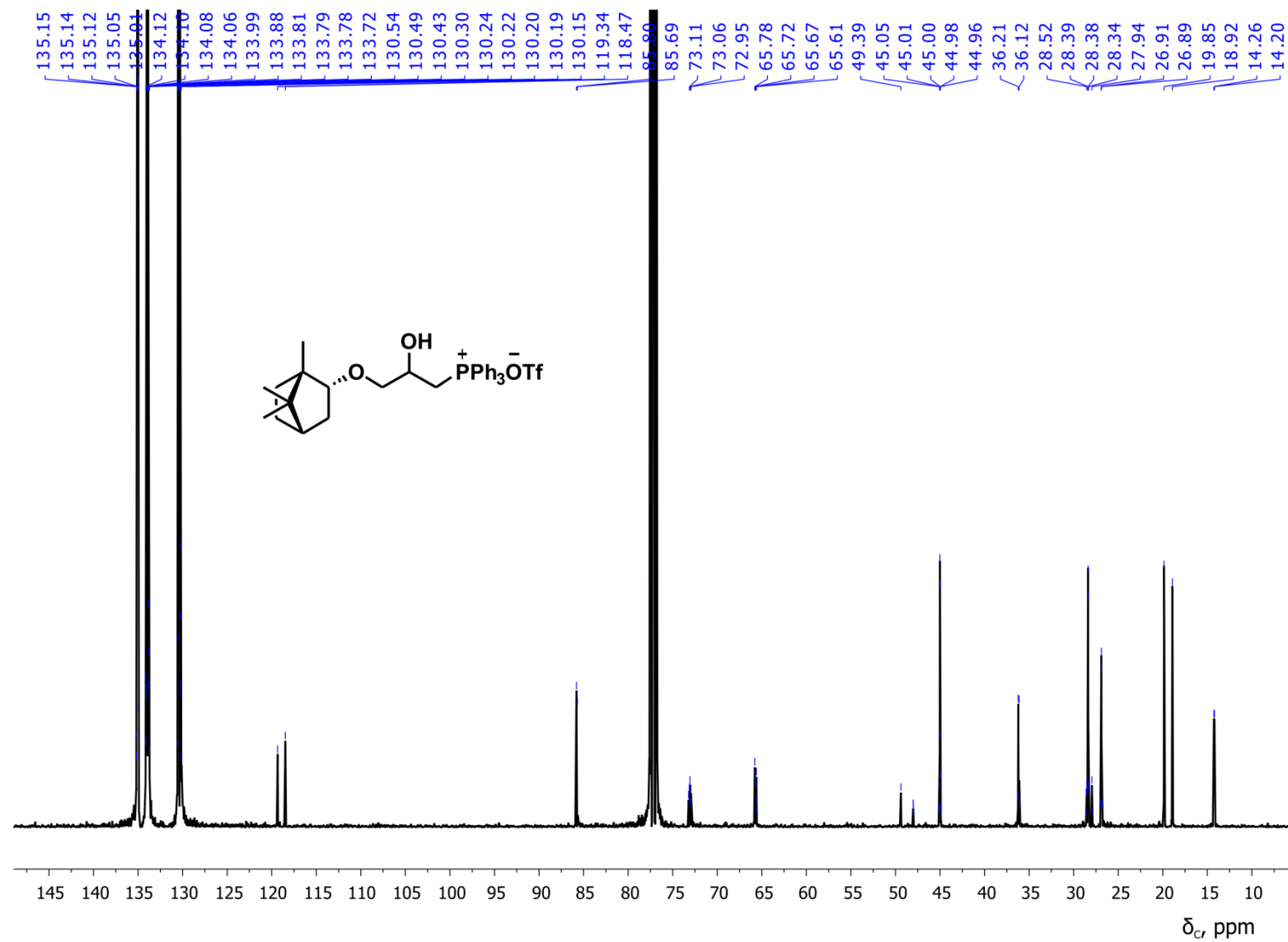


Figure S9. $^{13}\text{C} - \{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) spectrum of compound **2b**

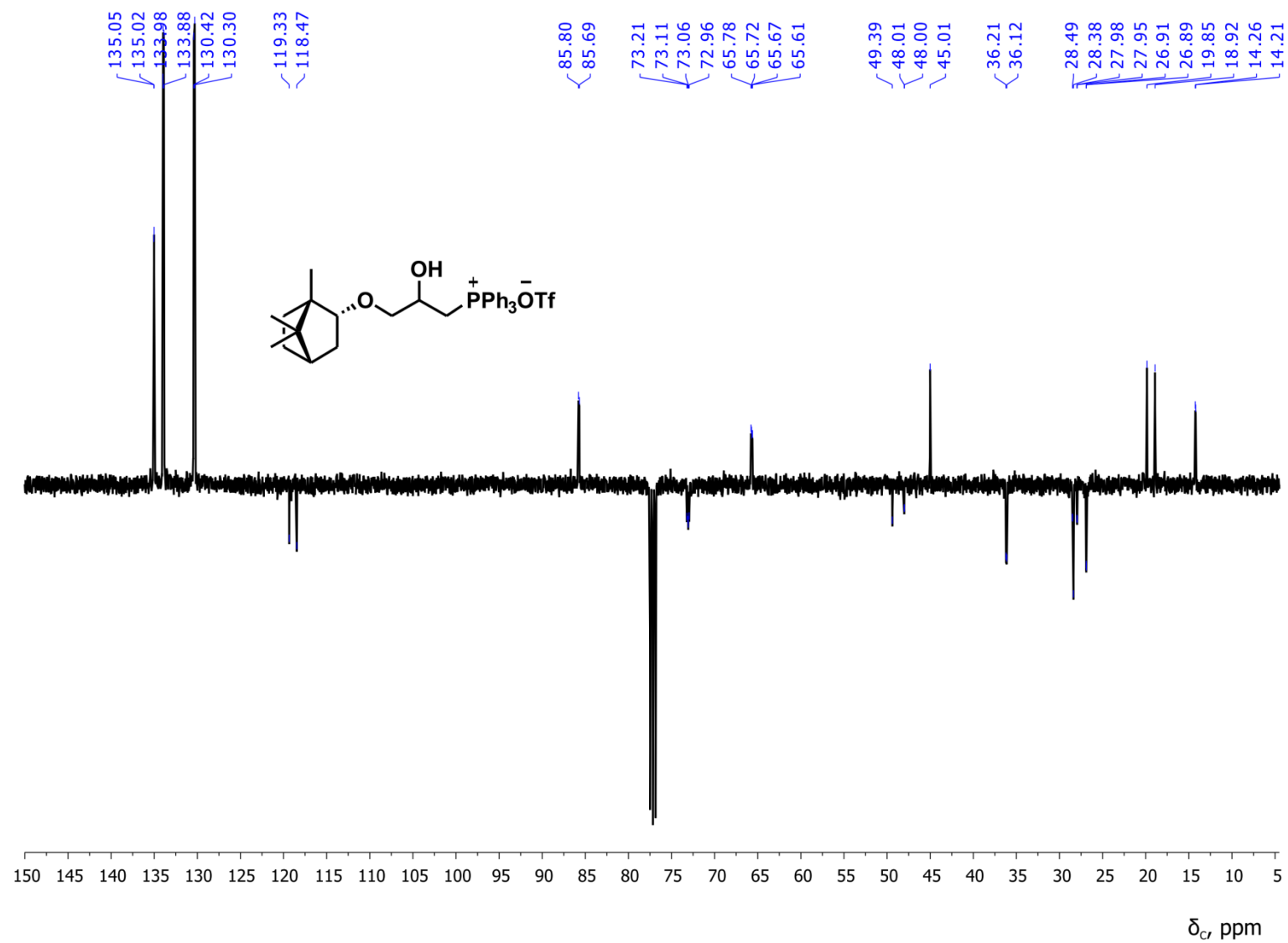


Figure S10. ^{13}C – $\{^1\text{H}\}$ NMR APT (100.6 MHz, CDCl_3) spectrum of compound **2b**

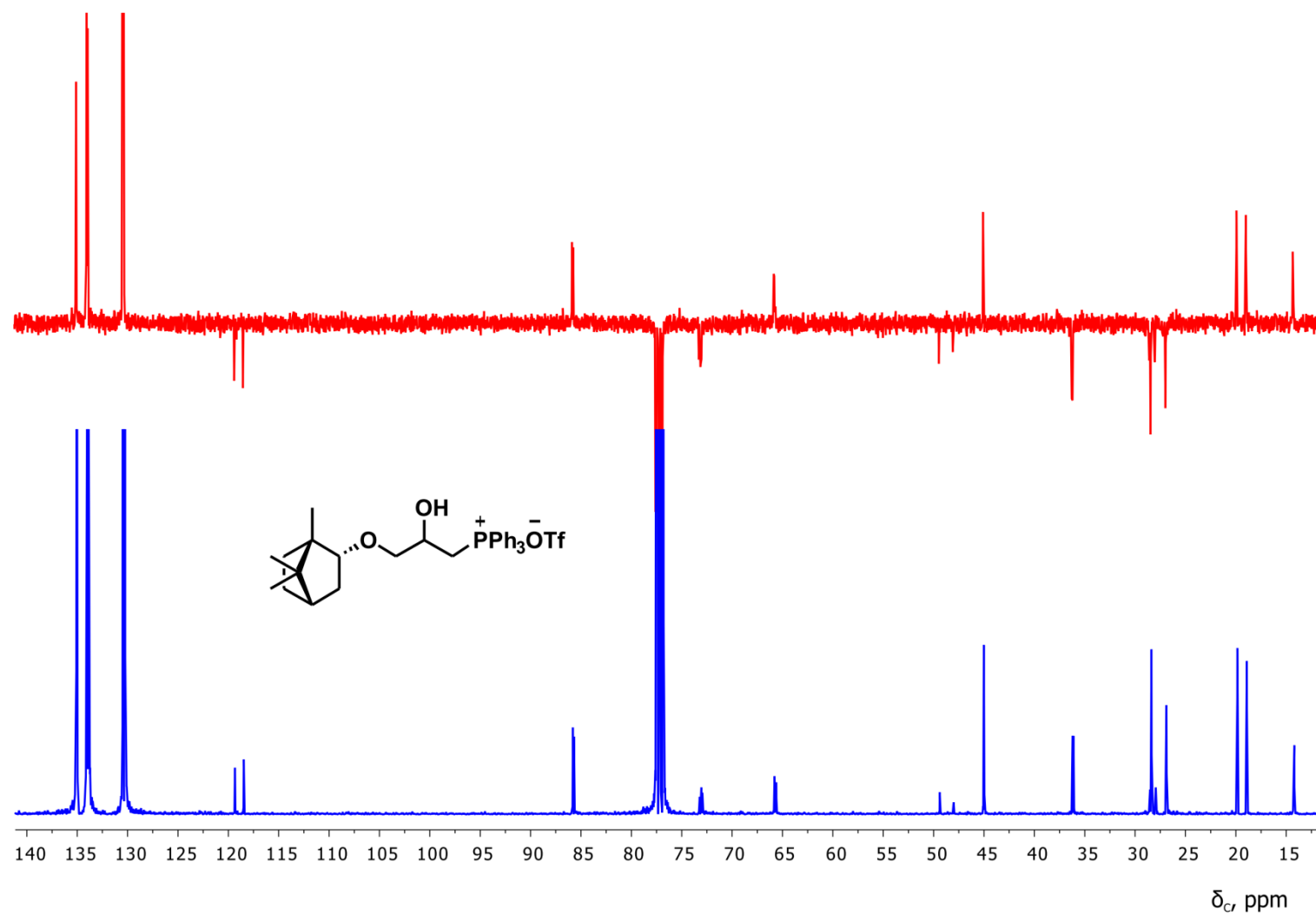


Figure S11. $^{13}\text{C} - \{^1\text{H}\}$ APT and $^{13}\text{C} - \{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) spectra of compound **2b**

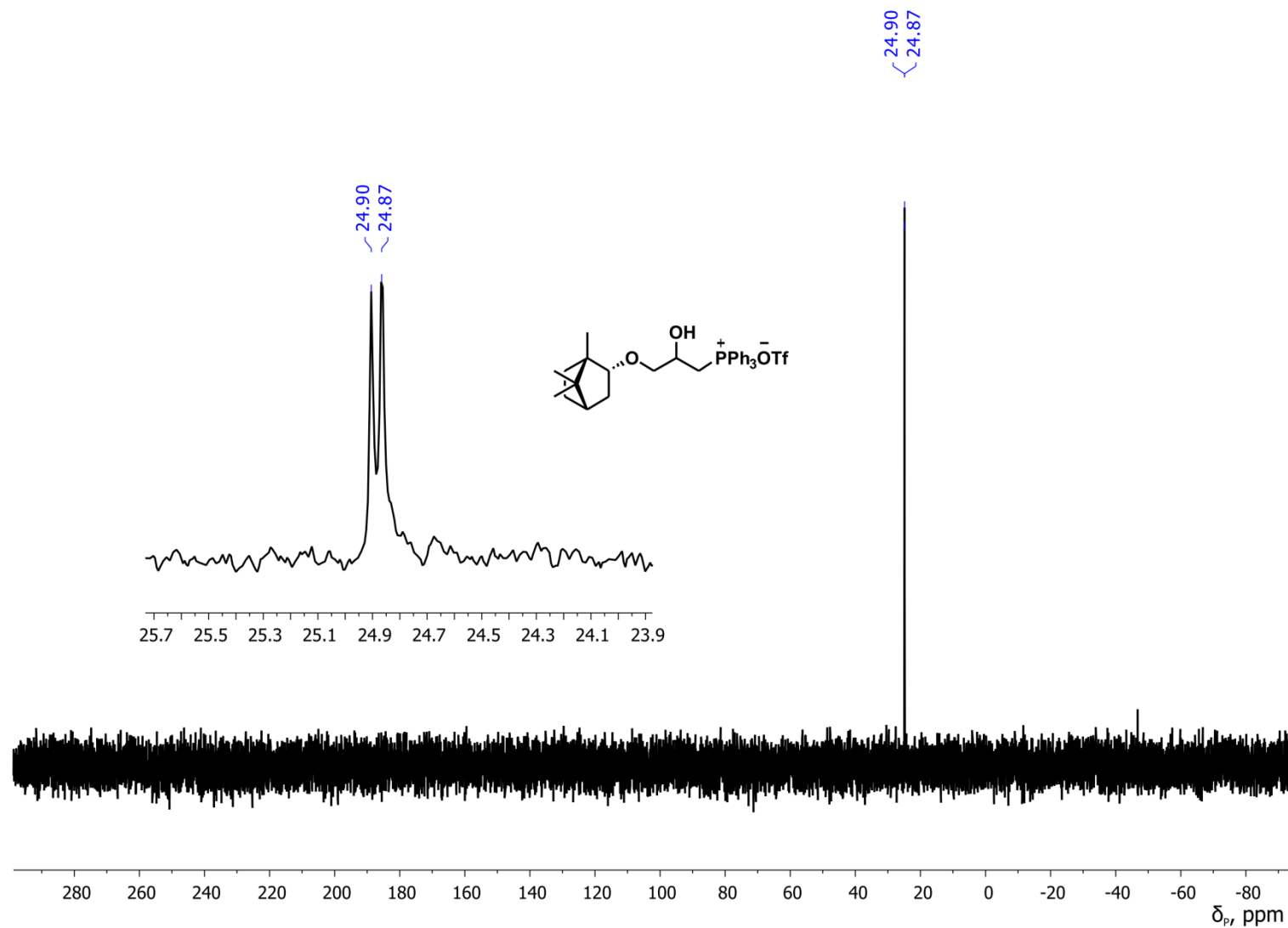


Figure S12. ^{31}P – $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) spectrum of compound **2b**

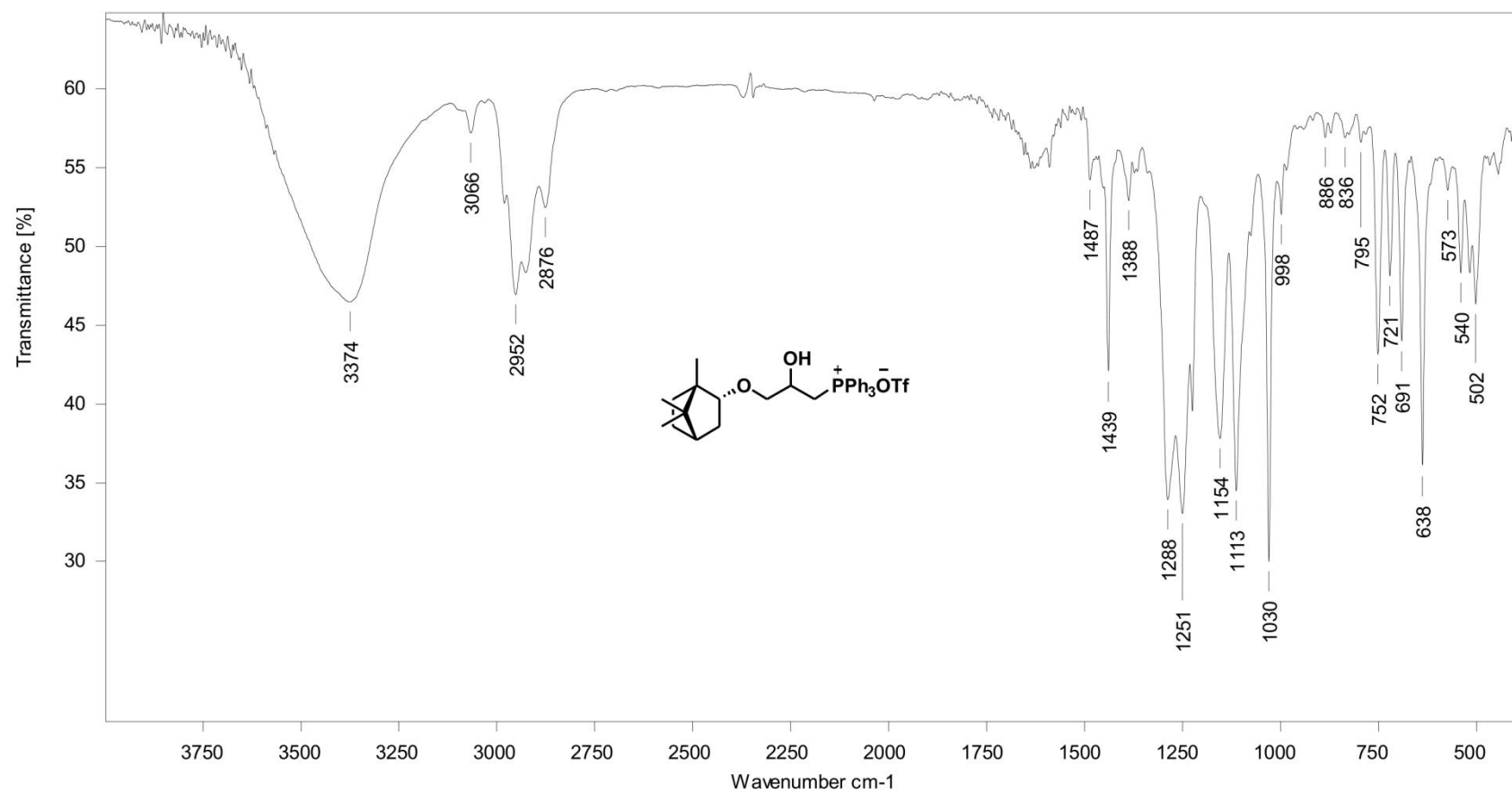


Figure S13. IR spectrum (KBr) of compound **2b**

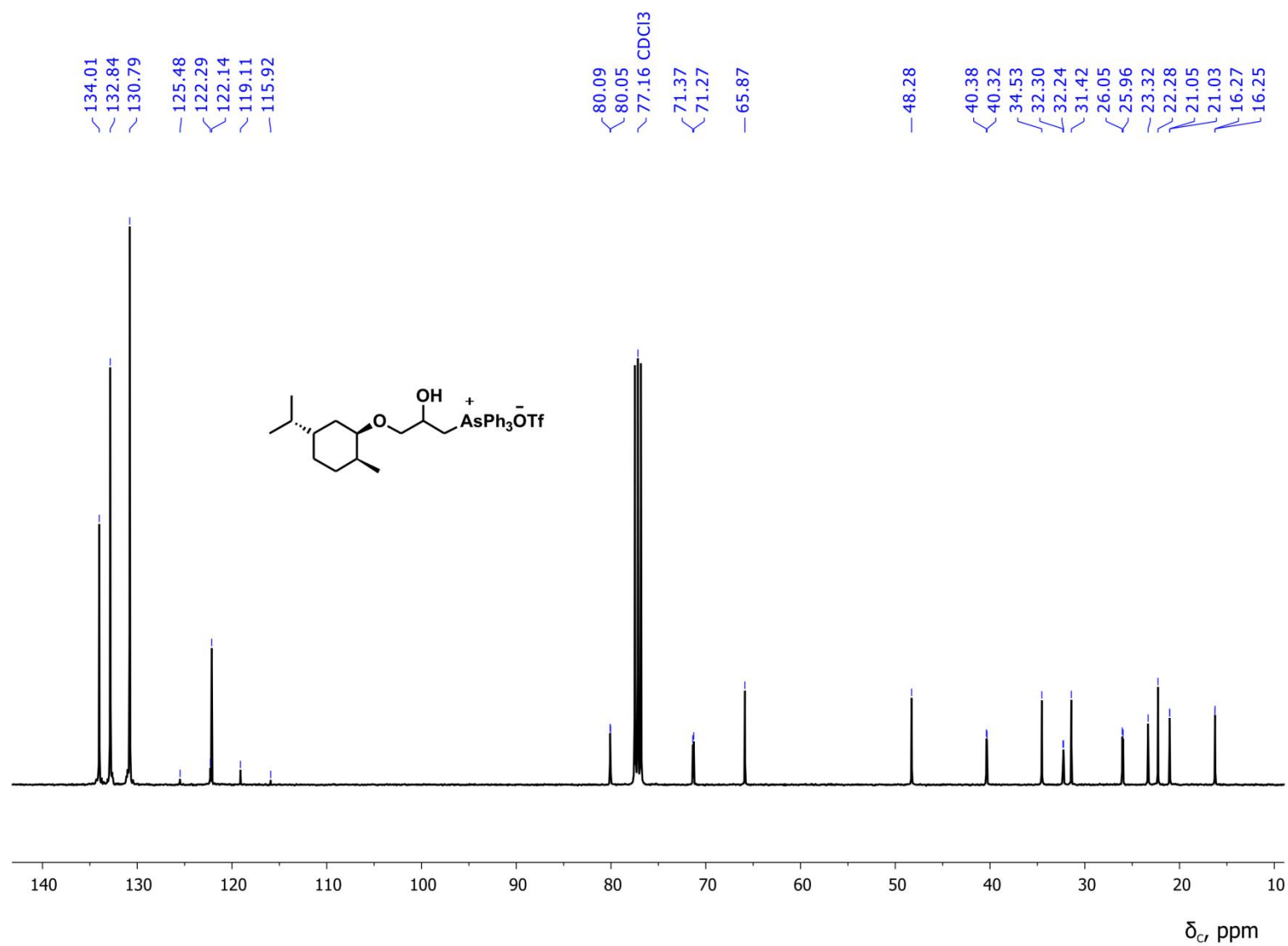


Figure S16. ^{13}C – $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl₃) spectrum of compound **3a**

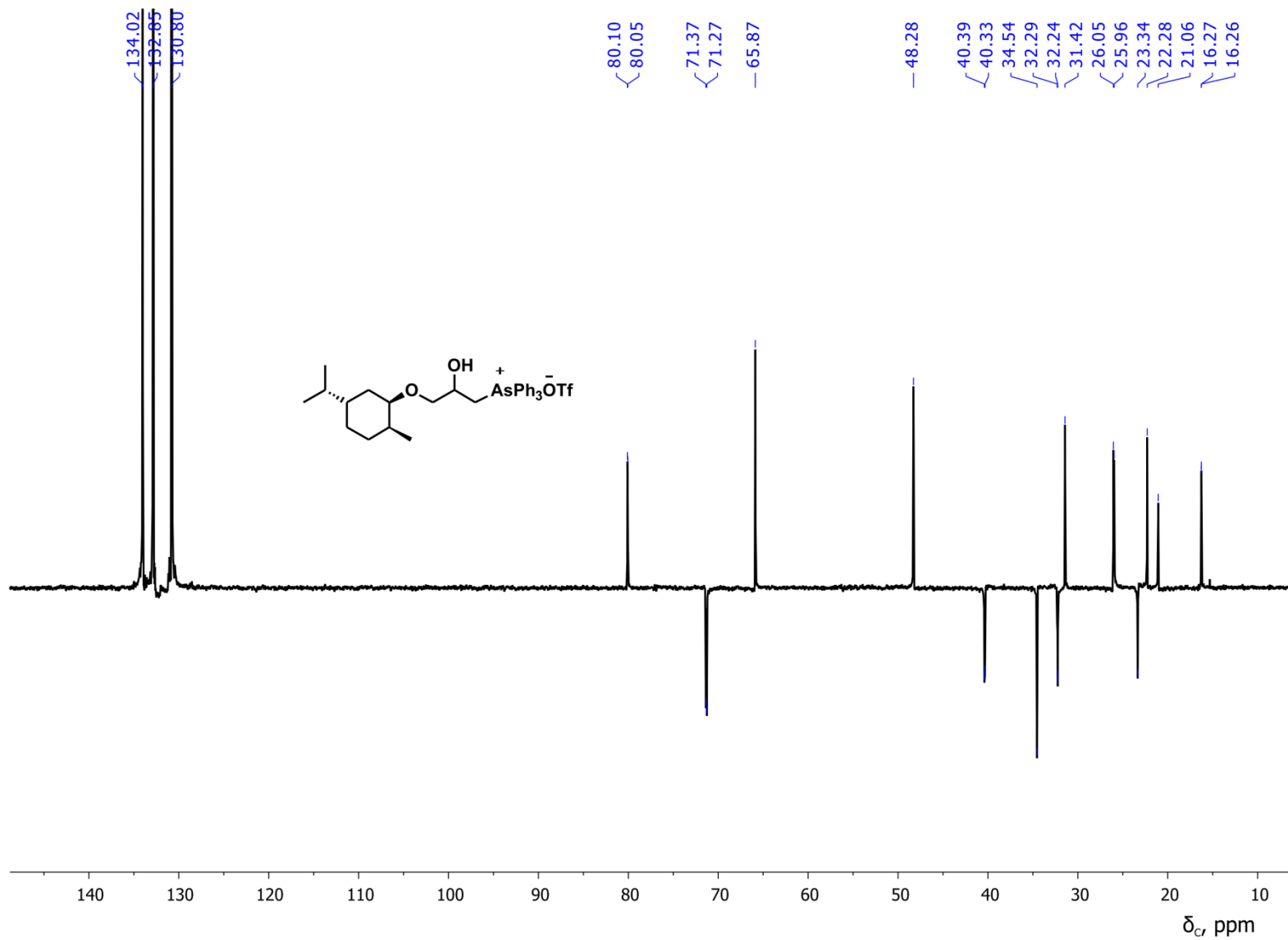


Figure S17. ^{13}C – $\{^1\text{H}\}$ NMR DEPT (100.6 MHz, CDCl_3) spectrum of compound **3a**

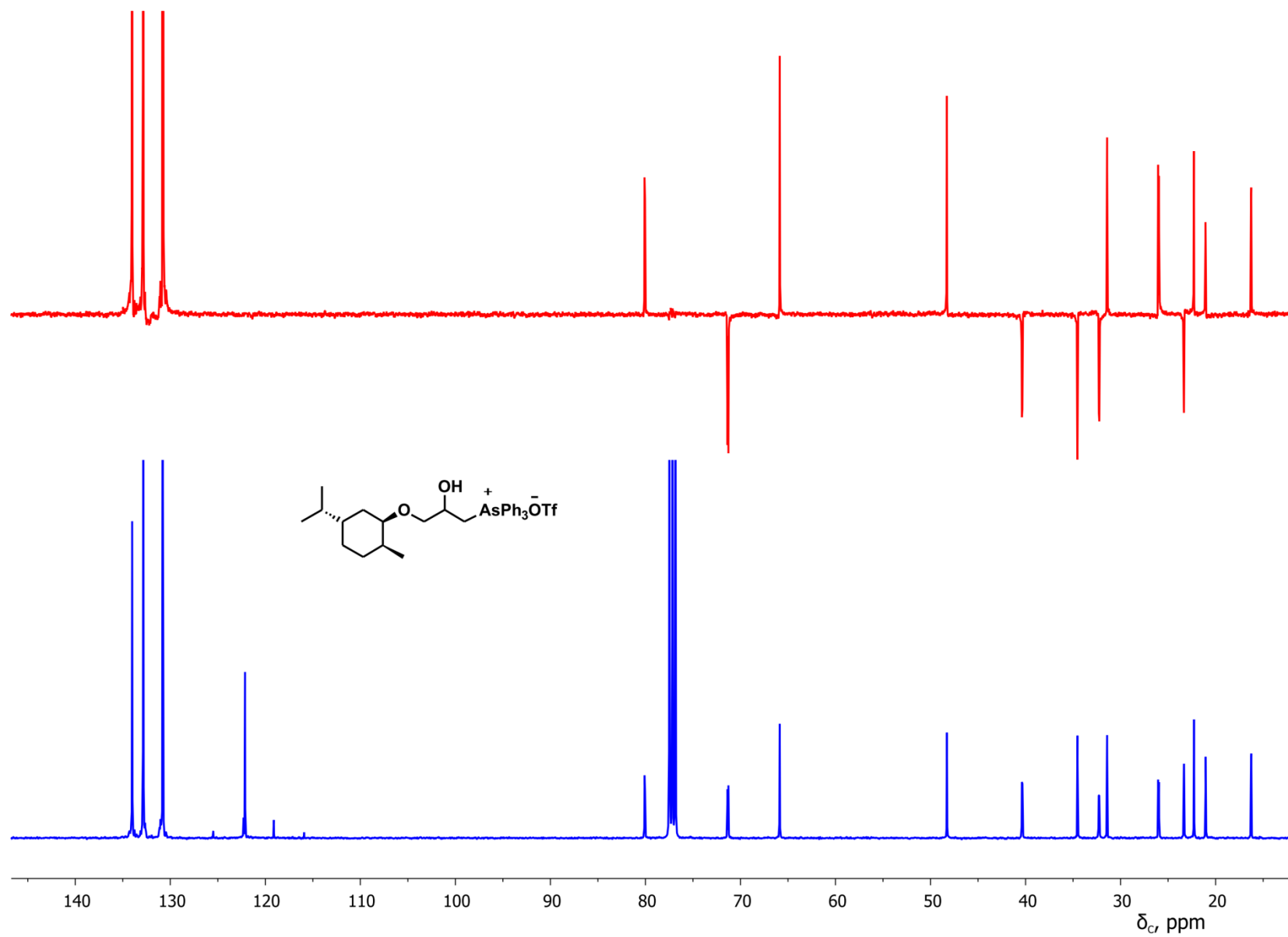


Figure S18. ^{13}C – $\{^1\text{H}\}$ DEPT and ^{13}C – $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) spectra of compound **3a**

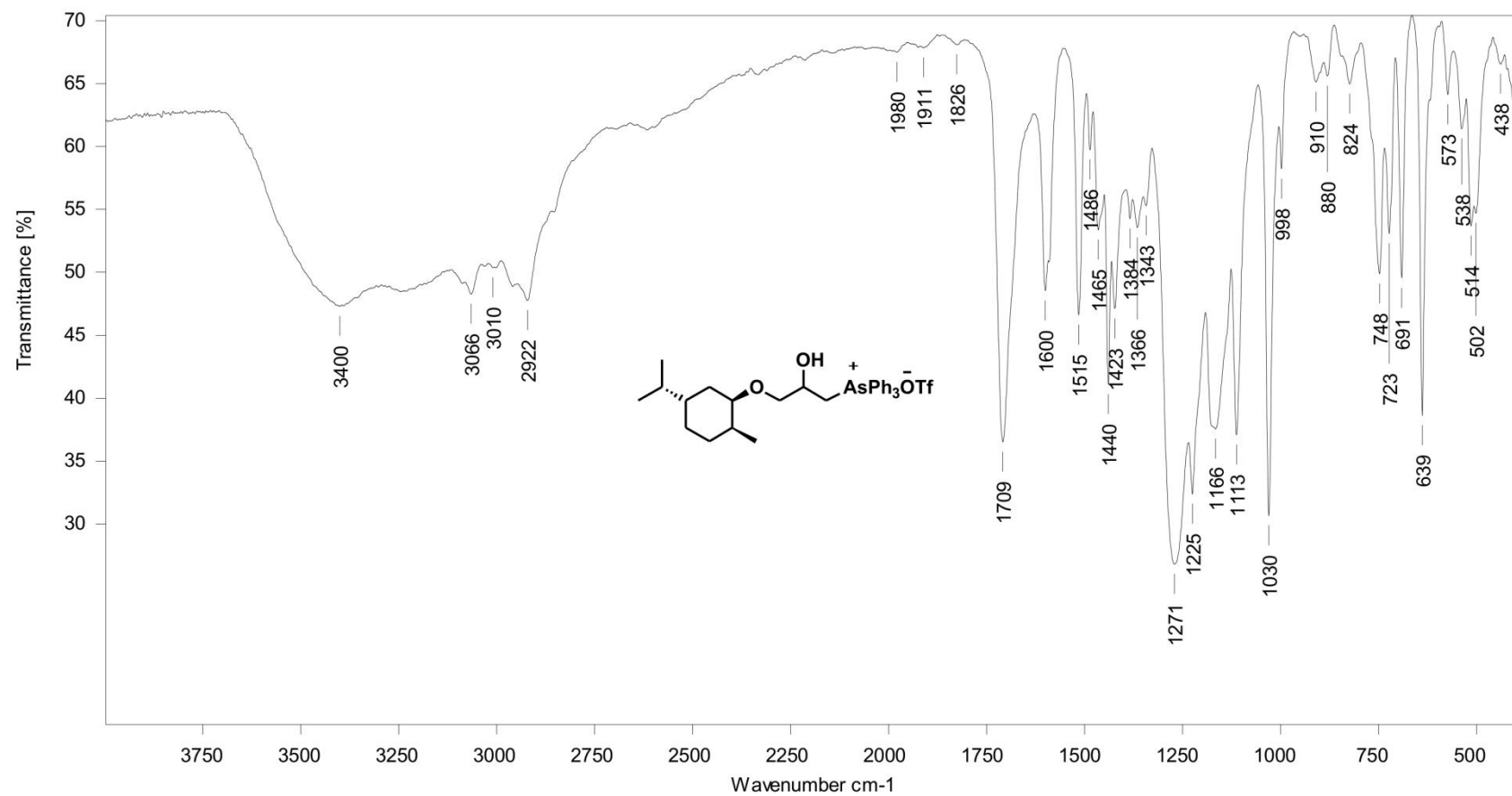


Figure S19. IR spectrum (KBr) of compound **3a**

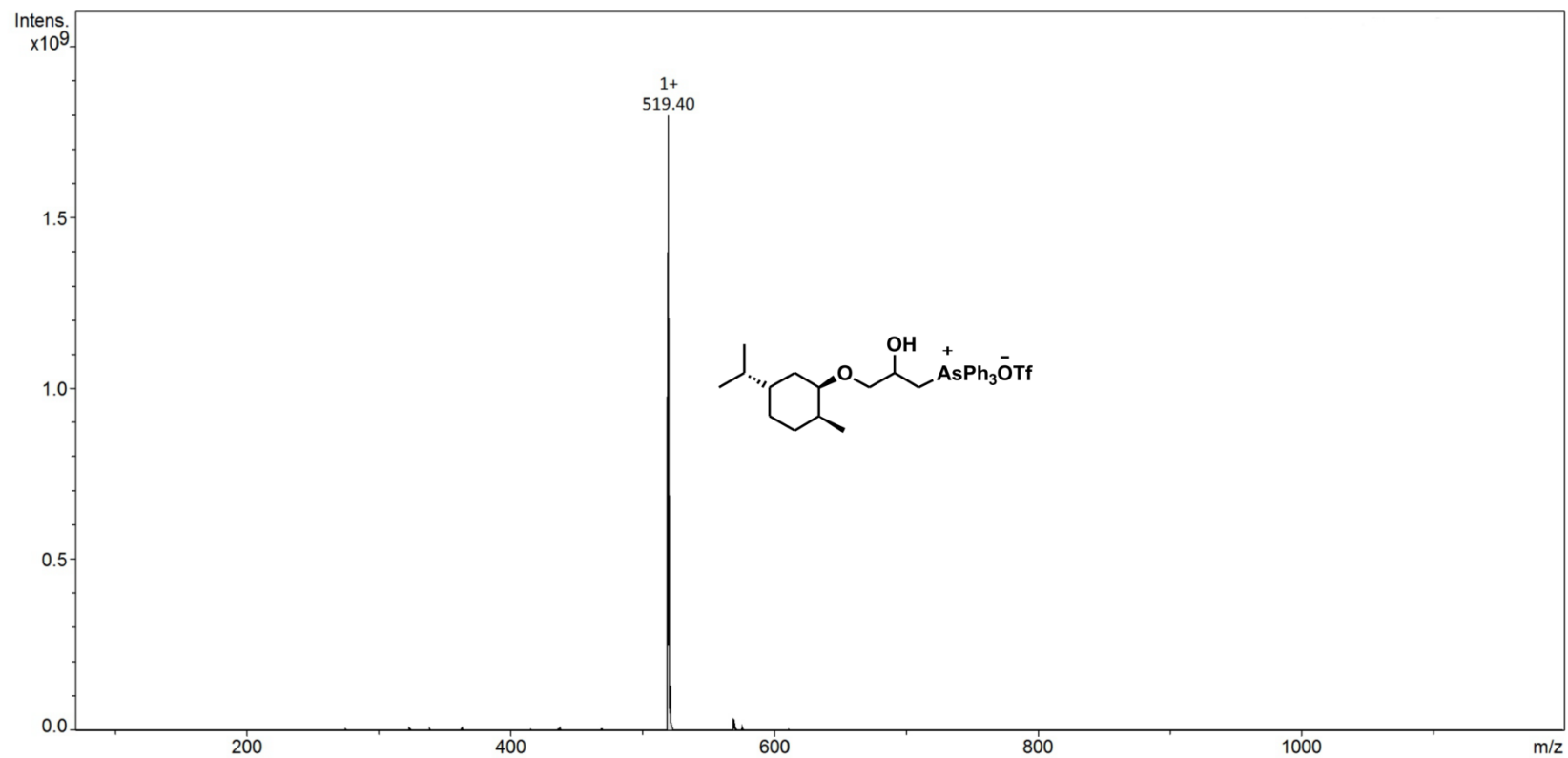


Figure S20. ESI-MS spectrum of compound **3a**

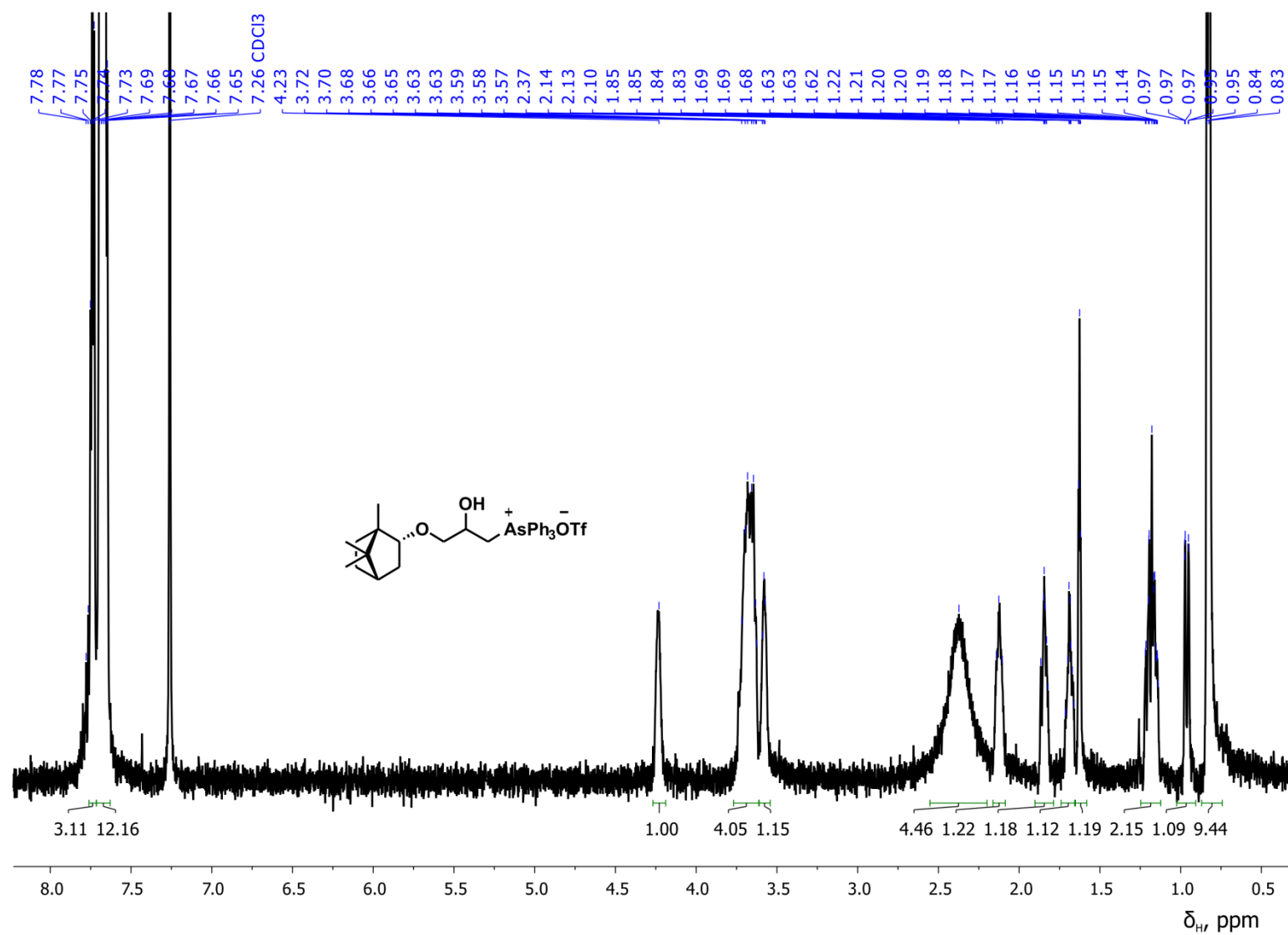


Figure S21. ^1H NMR (400 MHz, CDCl_3) spectrum of compound **3b**

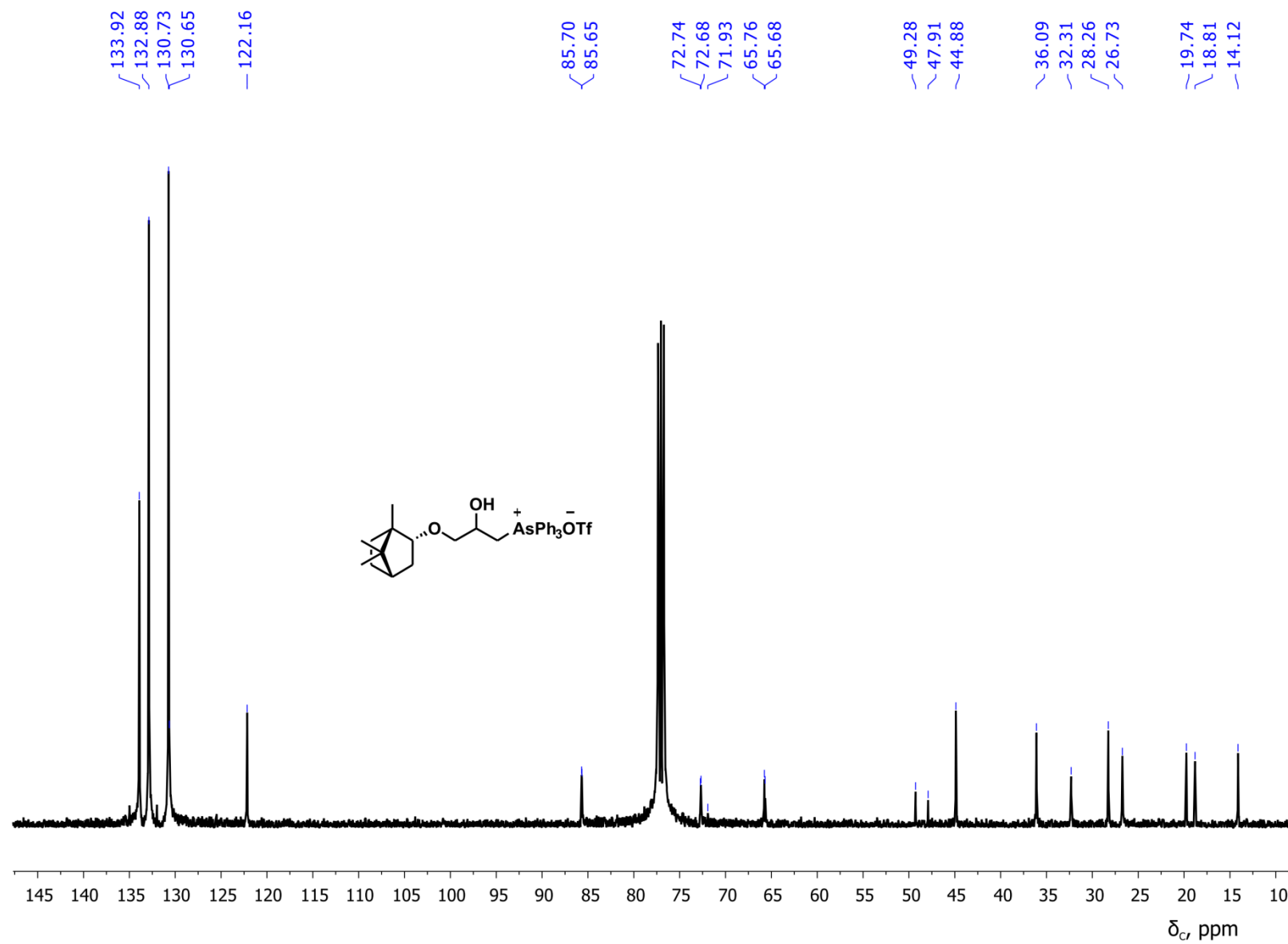


Figure S22. ¹³C – {¹H} NMR (100.6 MHz, CDCl₃) spectrum of compound **3b**

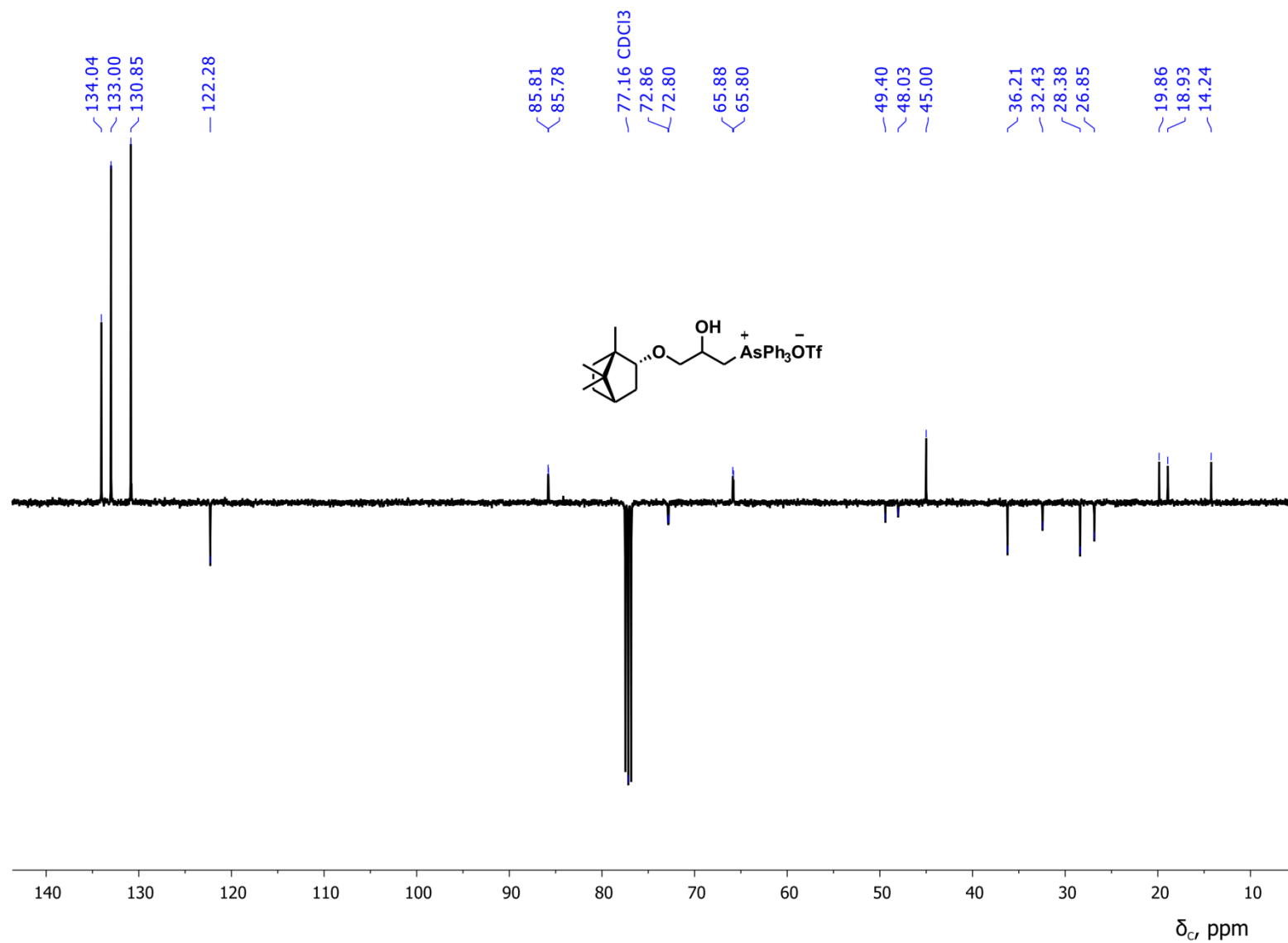


Figure S23. ¹³C – {¹H} NMR APT (100.6 MHz, CDCl₃) spectrum of compound **3b**

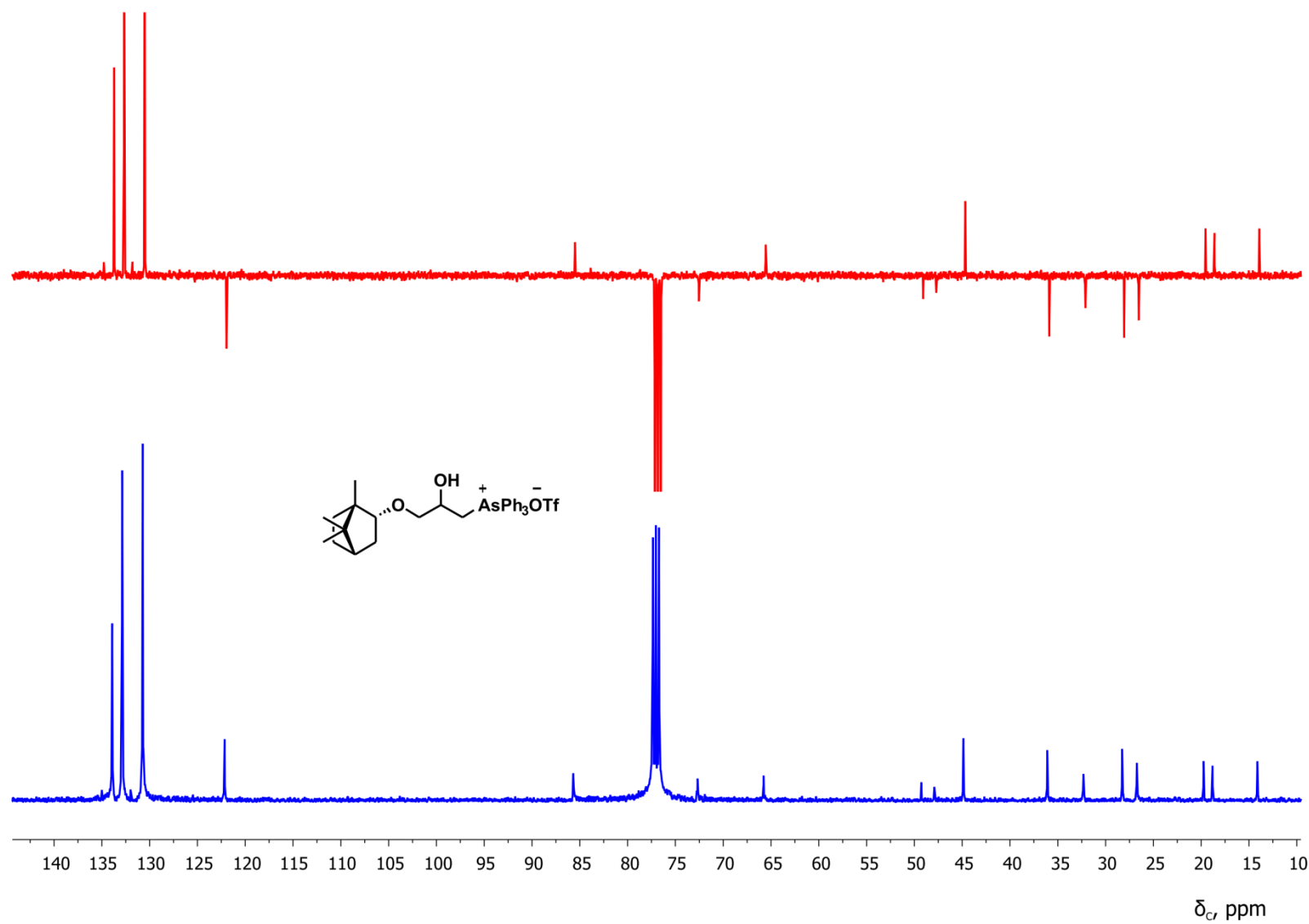


Figure S24. $^{13}\text{C} - \{^1\text{H}\}$ APT and $^{13}\text{C} - \{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) spectra of compound **3b**

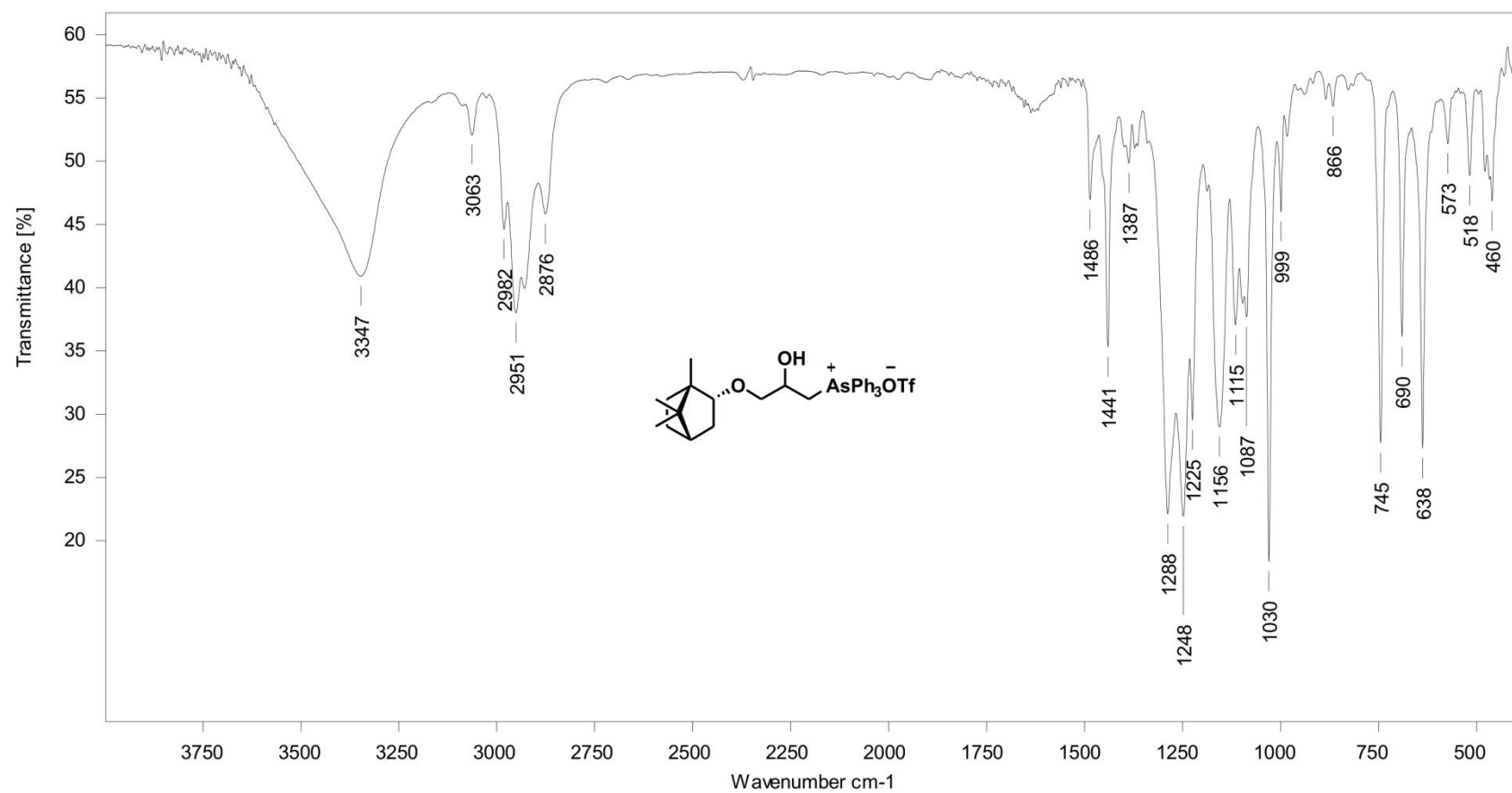


Figure S25. IR spectrum (KBr) of compound **3b**

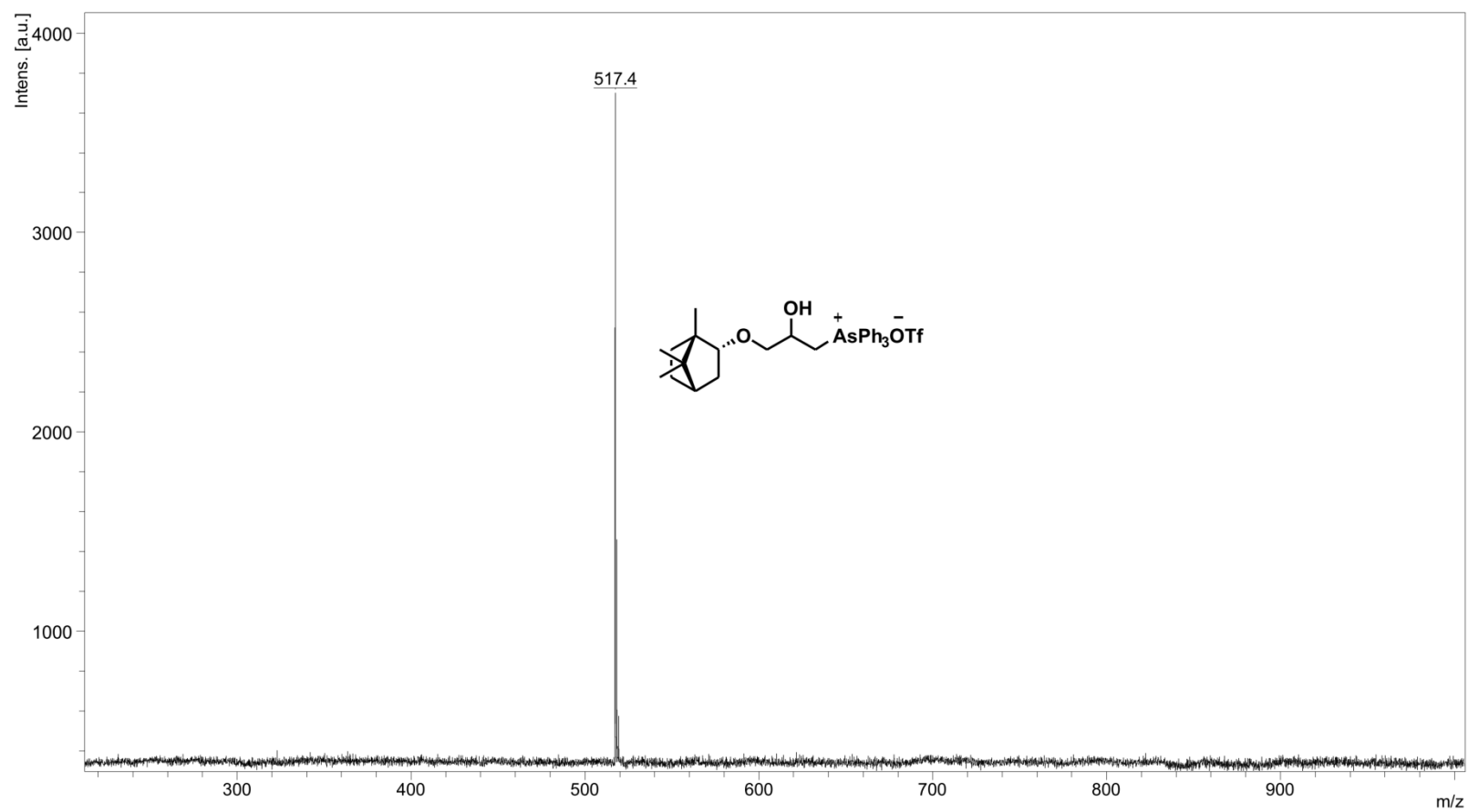


Figure S26. MALDI-MS spectrum of compound **3b**