

New Phosphorus Analogs of Bevirimat: Synthesis, Evaluation of Anti-HIV Activity and Molecular Docking Study

Elwira Chrobak^{1}, Krzysztof Marciniak¹, Aleksandra Dąbrowska², Paweł Pęczak¹, Ewa Bębenek¹, Monika Kadela-Tomanek¹, Andrzej Bak³, Maria Jastrzębska³, Stanisław Boryczka¹*

¹ Medical University of Silesia in Katowice, School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec, Department of Organic Chemistry, 4 Jagiellońska Str., 41-200 Sosnowiec, Poland; kmarciniak@sum.edu.pl (K.M.); pawel.marek.pecak@gmail.com (P.P.); ebebenek@sum.edu.pl (E.B.); mkadela@sum.edu.pl (M.K.-T.); boryczka@sum.edu.pl (S.B.)

² National Medicines Institute, 30/34 Chełmska Str., 00-725 Warszawa, Poland; aleksandra_dabrowska@o2.pl (A.D.)

³ Institute of Chemistry, University of Silesia, 9 Szkolna Str., 40-007 Katowice, Poland; andrzej.bak@us.edu.pl (A.B.);

⁴ Silesian Center for Education and Interdisciplinary Research, University of Silesia, Institute of Physics, Department of Solid State Physics, 75 Pułku Piechoty 1a, 41-500 Chorzów, Poland; maria.jastrzebska@us.edu.pl (M.J.)

*Corresponding author

E-mail address: echrobak@sum.edu.pl

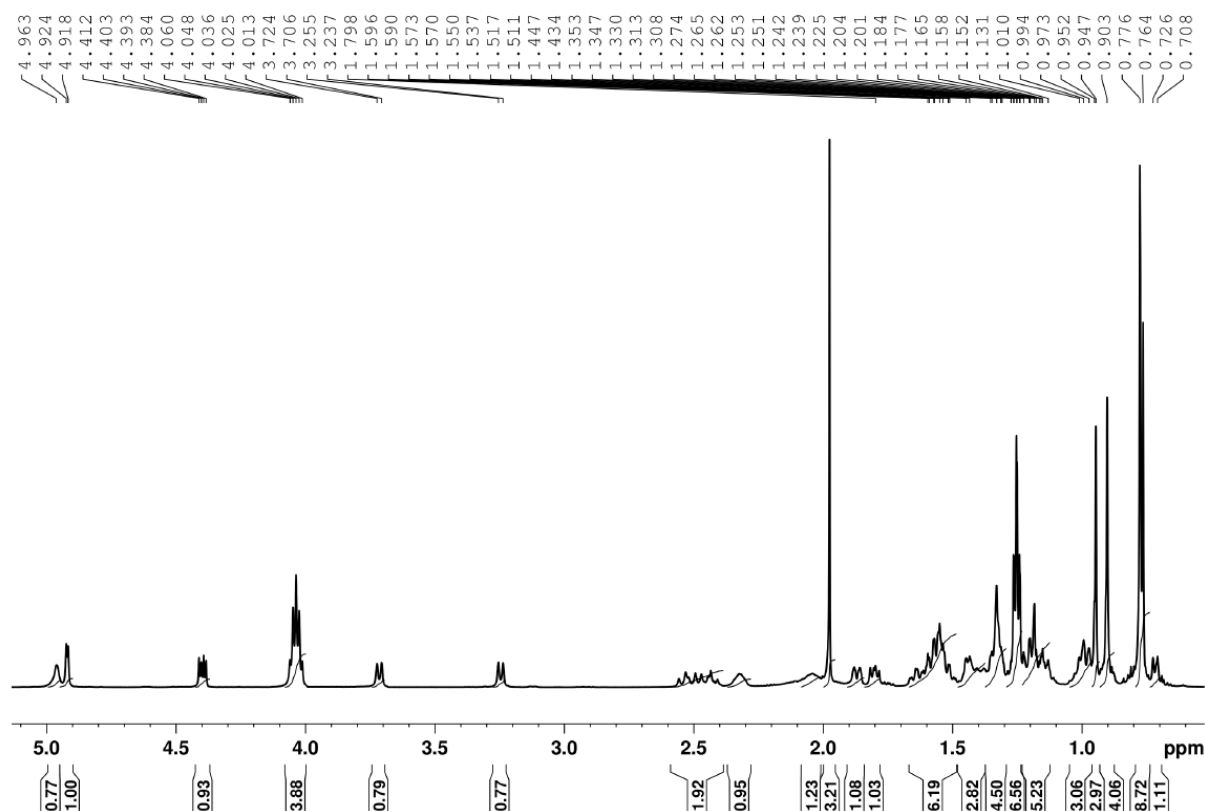
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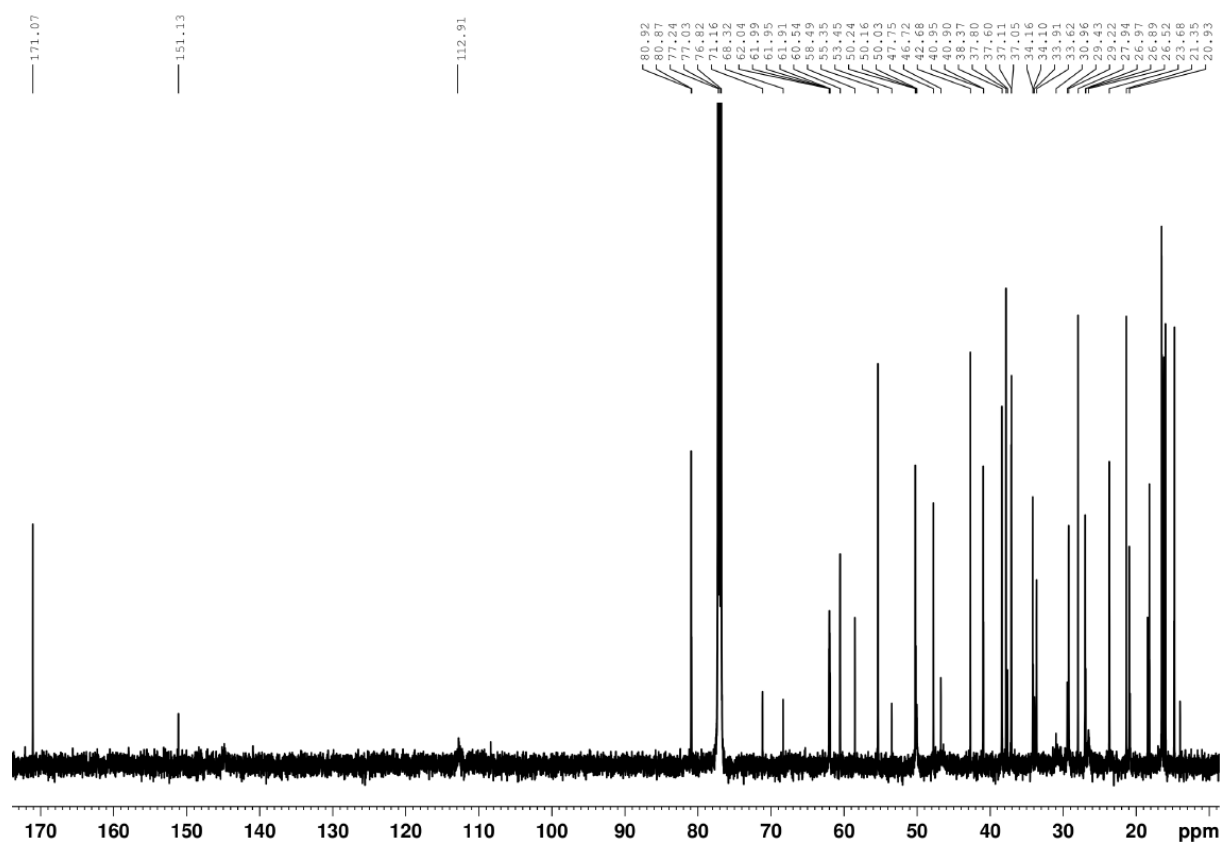
3-Acetyl-30-diethoxyphosphorylbetulin 5

Yield 61%; mp 118-122 °C; R_f = 0.37 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3439, 2941, 1732, 1246, 1028, 648; ^1H NMR (CDCl_3) δ (ppm): 4.96 (m, 1H, H29), 4.92 (m, 1H, H29), 4.40 (m, 1H, H3), 4.05 (m, 4H, 2 x OCH_2CH_3), 3.72 (m, 1H, H28), 3.25 (m, 1H, H28), 2.50 (m, 2H, H30), 2.40 (m, 1H, H19), 1.98 (s, 3H, $\text{C}(\text{O})\text{CH}_3$), 1.25 (m, 6H, 2 x OCH_2CH_3), 1.20 – 2.05 (m, 23H, CH, CH_2), 0.95 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.78 (s, 6H, 2 x CH_3), 0.76 (s, 3H, CH_3), 0.72 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 171.1, 151.1, 112.9, 80.9, 71.2, 68.3, 61.9, 60.5, 58.5, 55.3, 50.2, 50.1, 47.7, 42.7, 41.0, 40.9, 38.4, 37.8, 37.1, 37.0, 34.1, 33.9, 33.6, 29.2, 27.9, 27.0, 26.9, 23.7, 21.3, 20.9, 18.4, 18.1, 16.4, 16.2, 16.0, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 27.8; HR-MS (APCI) m/z : $\text{C}_{36}\text{H}_{60}\text{O}_6\text{P}$ [(M-H) $^-$], Calc. 619.4128; Found 619.4136.

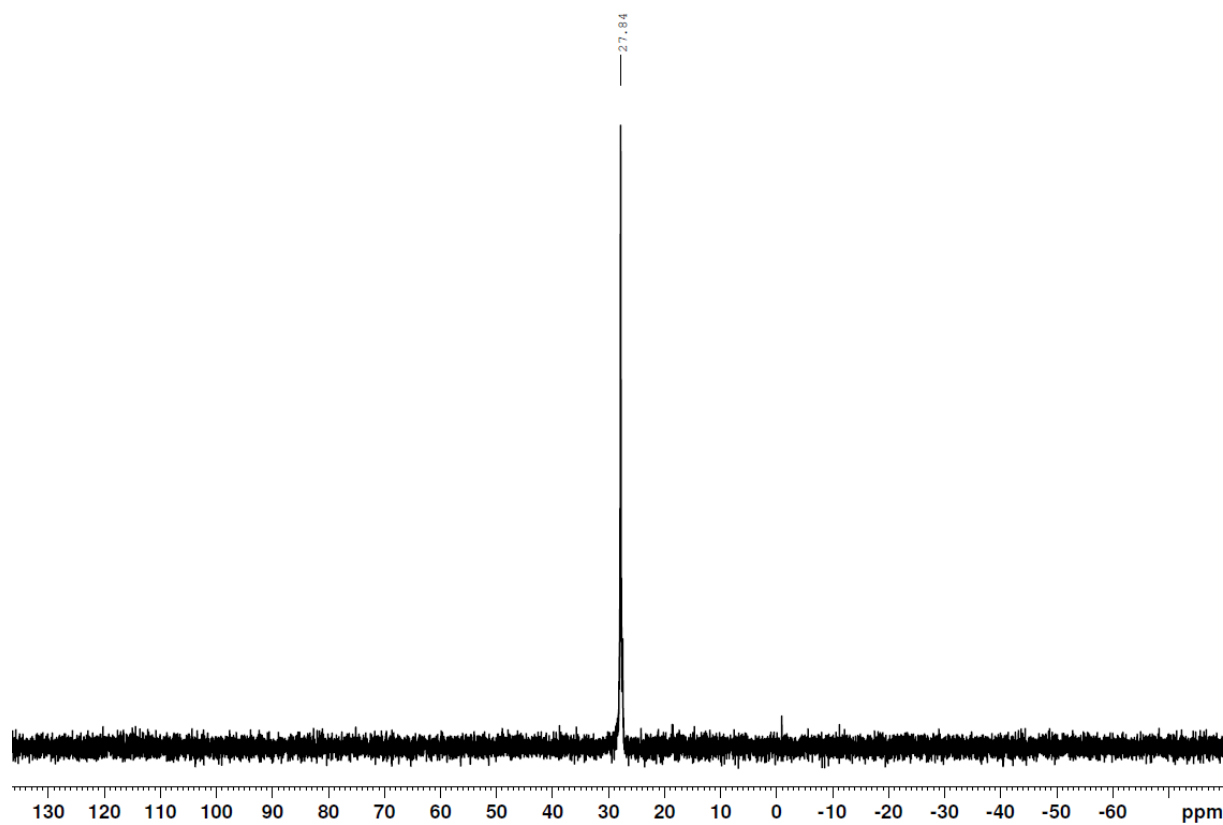
^1H NMR



^{13}C NMR



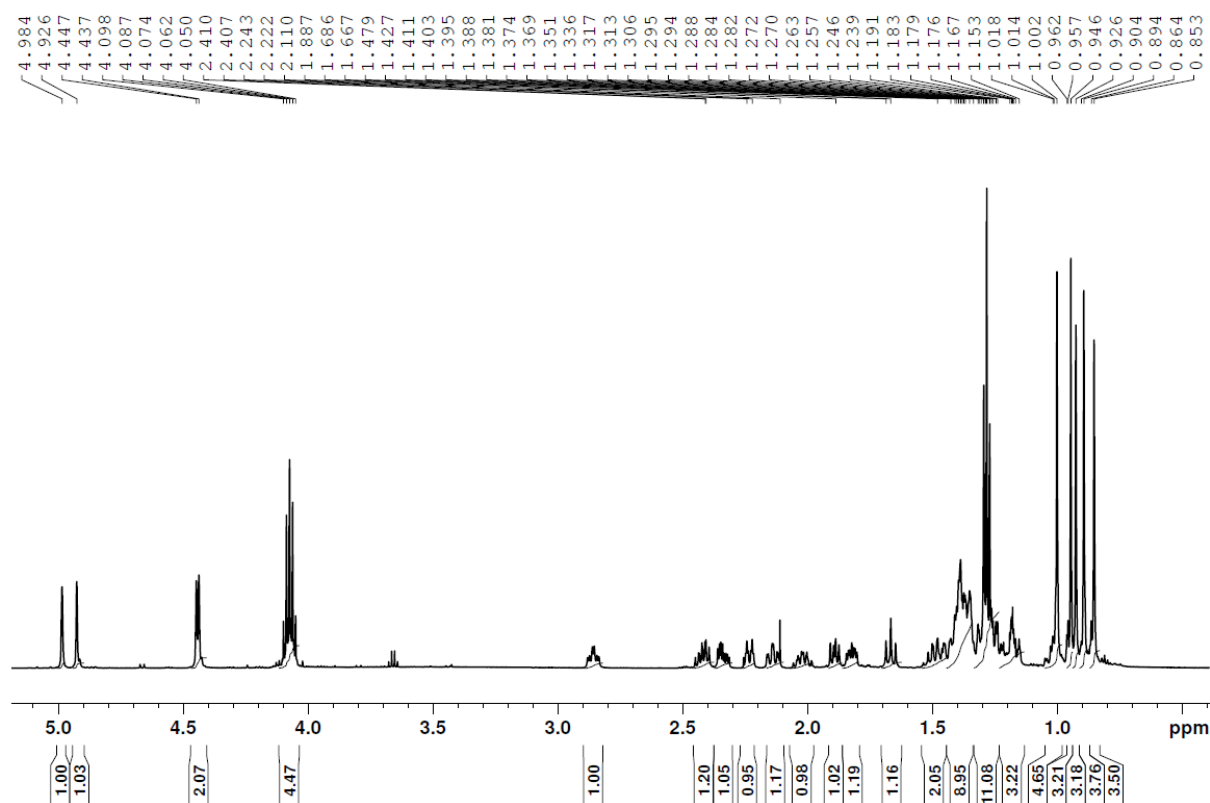
^{31}P NMR



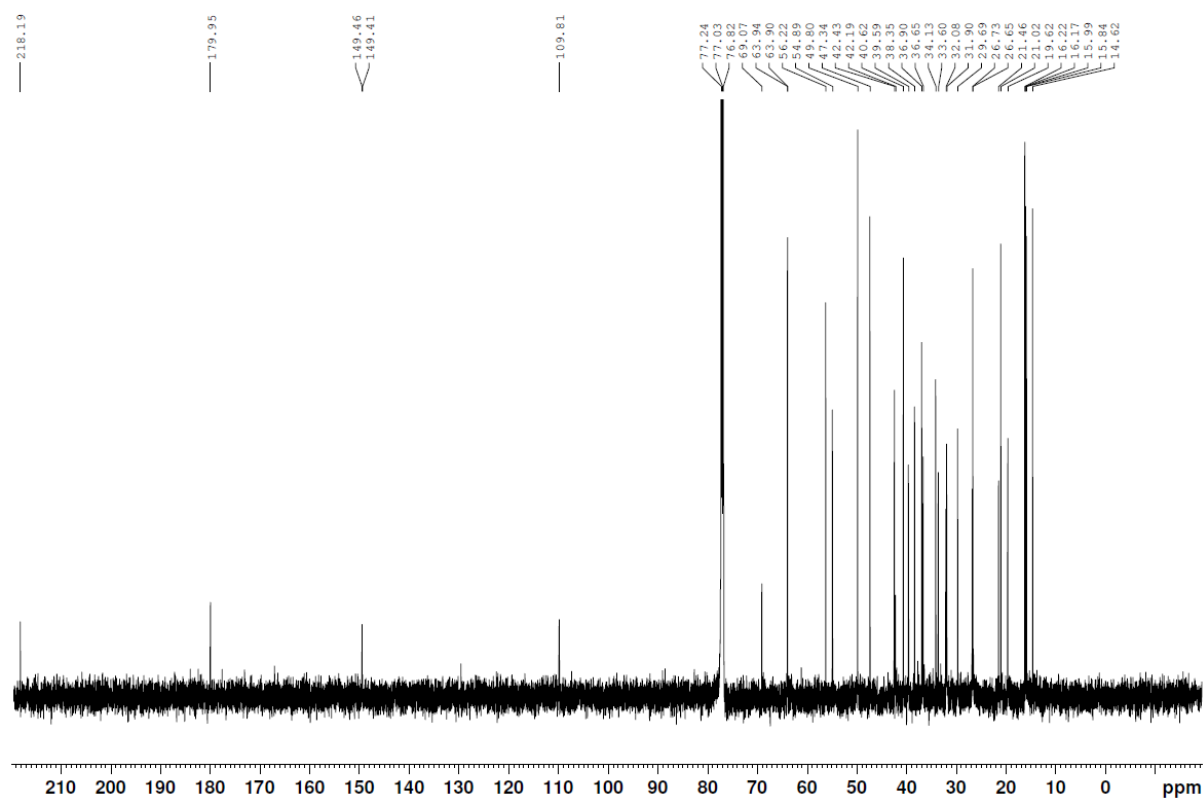
30-Diethoxyphosphoryloxybetulonic acid 6

Yield 62%; mp 220-223 °C; $R_f = 0.33$ (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 2967, 1701, 1257, 1039; ^1H NMR (CDCl_3) δ (ppm): 4.98 (m, 1H, H₂₉), 4.93 (m, 1H, H₂₉), 4.44 (d, $J=6$ Hz, 2H, H₃₀), 4.07 (m, 4H, OCH_2CH_3), 2.85 (m, 1H, H₁₉), 0.90 – 2.55 (m, 24 H, CH, CH_2), 1.27 (m, 6H, OCH_2CH_3), 1.02 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.85 (s, 3H, CH_3); ^{13}C NMR (CDCl_3) δ (ppm): 218.2, 179.9, 149.4, 109.8, 69.1, 63.9, 63.9, 56.2, 54.9, 49.8, 47.3, 42.4, 42.2, 40.6, 39.6, 38.4, 36.9, 36.7; 34.1, 33.6, 32.0, 31.9, 29.7, 26.7, 26.6, 21.5, 21.0, 19.6, 16.2, 16.2, 16.0, 15.8, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): -0.97; HR-MS (APCI) m/z : $\text{C}_{34}\text{H}_{54}\text{O}_7\text{P}$ [(M-H)⁻], Calc. 605.3607; Found 605.3617.

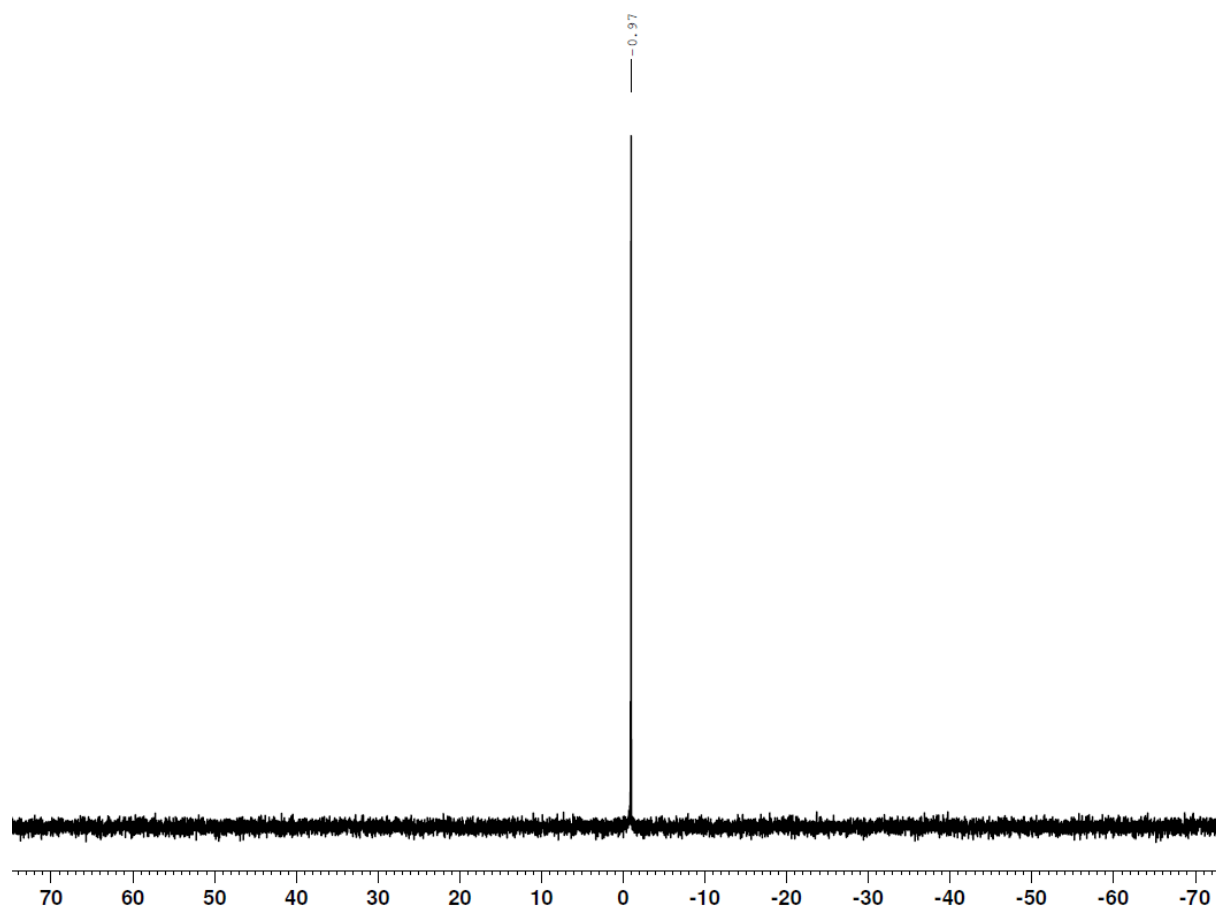
^1H NMR



^{13}C NMR



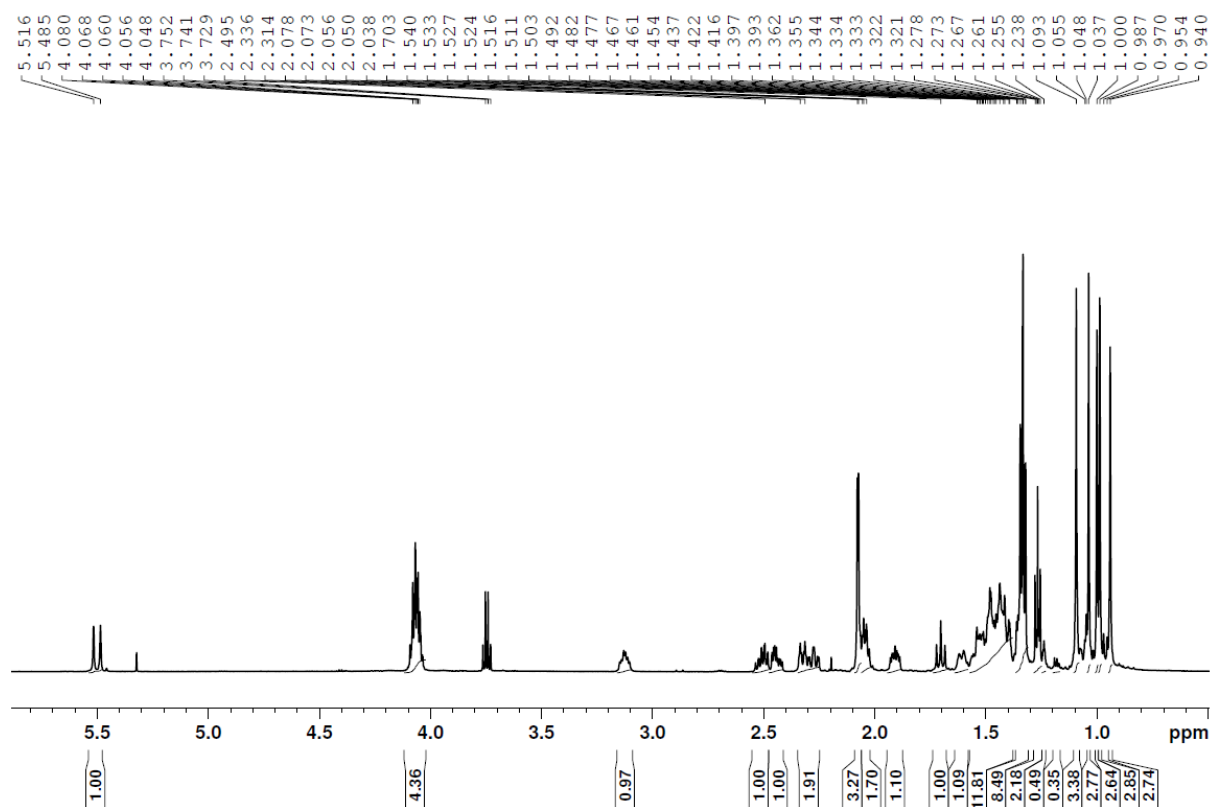
^{31}P NMR



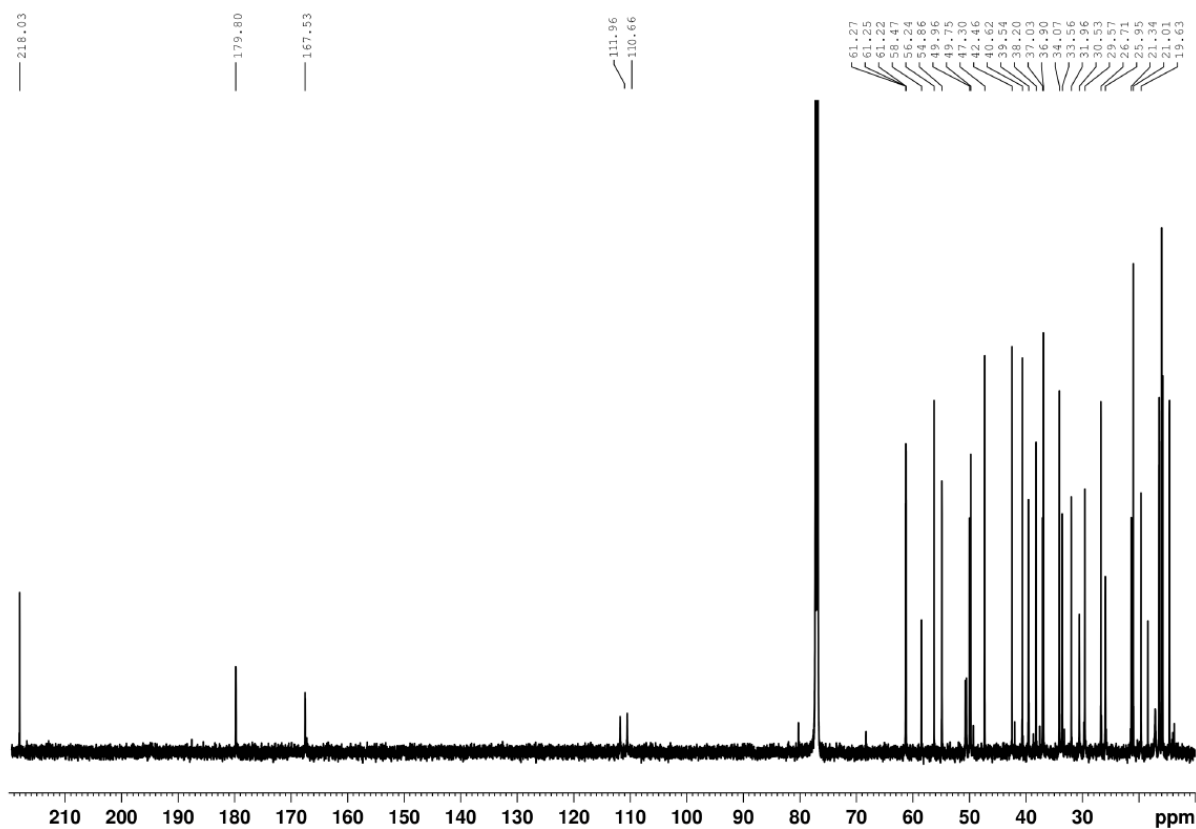
29-Diethoxyphosphorylbetulonic acid 7

Yield 31%; mp 244-245 °C, R_f = 0.56 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 2956, 1717, 1236, 972, 799; ^1H NMR (CDCl_3) δ (ppm): 5.52 (d, 1H, $^2J_{\text{PH}}=18.6$ Hz, H29), 4.06 (m, 4H, 2x OCH_2CH_3), 3.13 (m, 1H, H19), 2.50 (m, 1H, H2), 2.45 (m, 1H, H2), 2.08 (d, $J=3$ Hz, 3H, H30), 0.93–2.36 (m, 22H, CH, CH_2), 1.33 (m, 6H, 2 x OCH_2CH_3), 1.10 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (CDCl_3) δ (ppm): 218.0, 179.8, 167.5, 111.2, 61.3, 61.2, 58.5, 56.2, 54.9, 50.7, 50.5, 50.0, 49.7, 47.3, 42.5, 40.6, 39.5, 38.2, 37.0, 36.9, 34.1, 33.6, 32.0, 30.5, 29.6, 26.7, 25.9, 21.3, 21.0, 19.6, 16.4, 16.0, 15.8, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): 18.75; HR-MS (APCI) m/z : $\text{C}_{34}\text{H}_{54}\text{O}_6\text{P}$ [(M-H) $^-$], Calc. 589.3658; Found 589.3664.

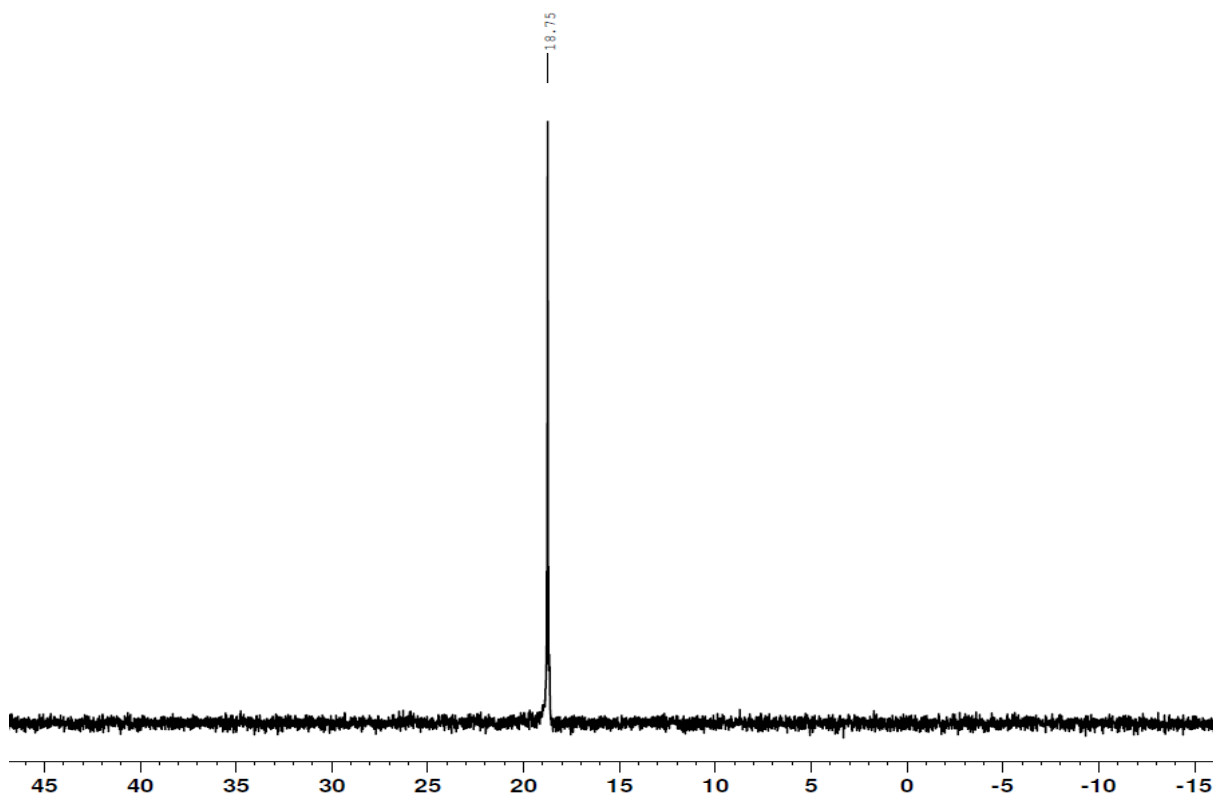
^1H NMR



^{13}C NMR



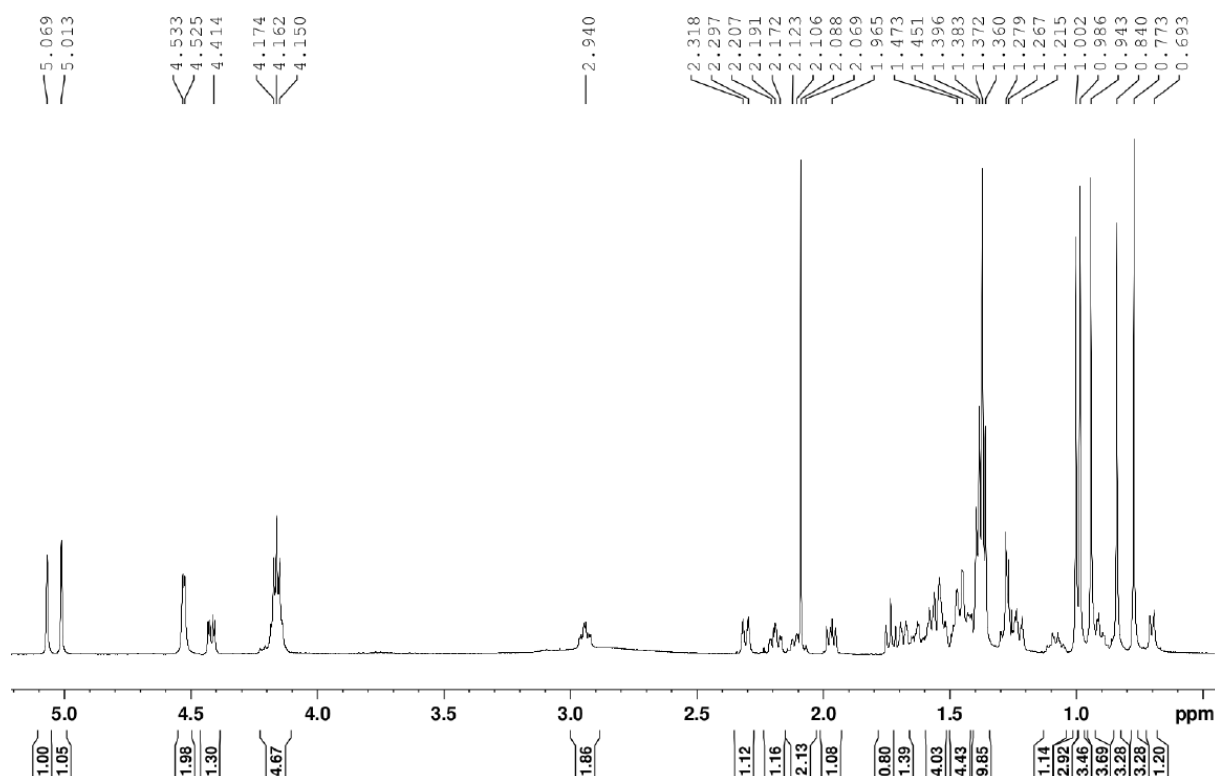
^{31}P NMR



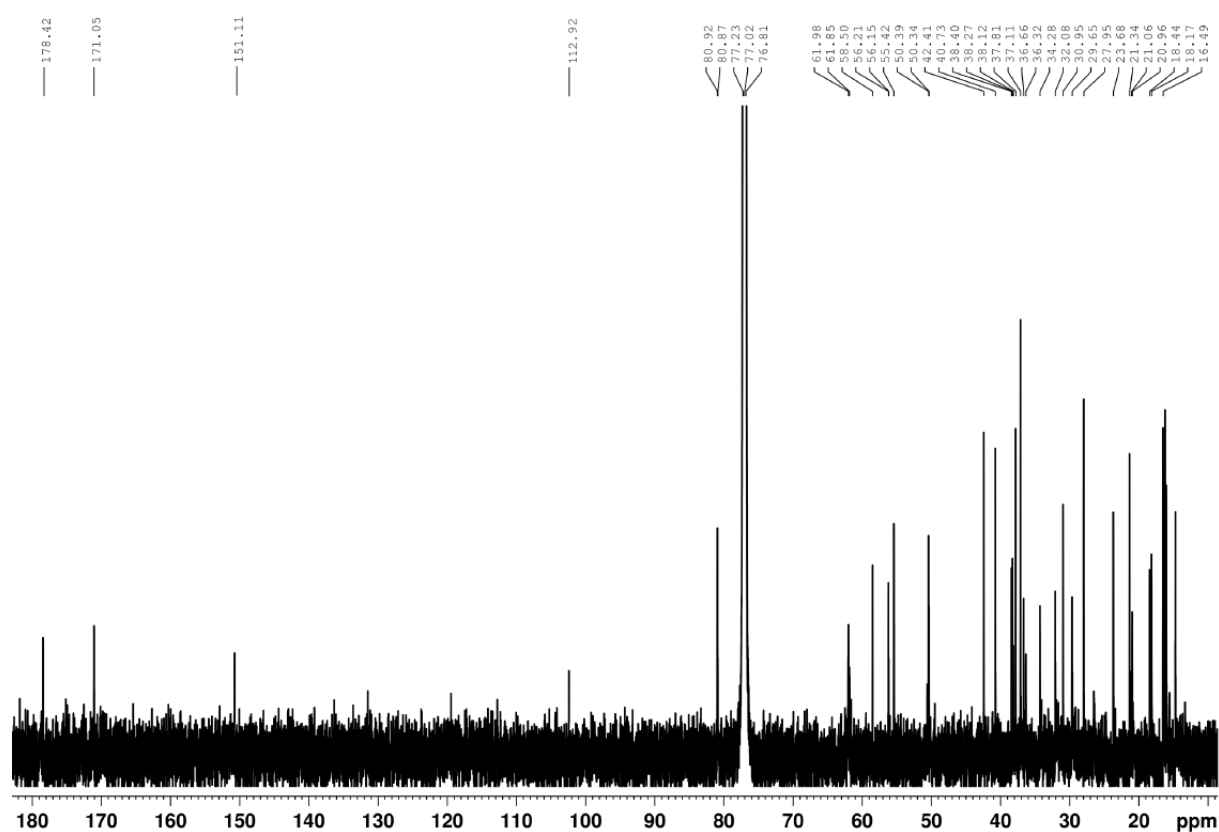
3-O-Acetyl-30-diethoxyphosphorylbetulinic acid **8**

Yield 63%; mp 231-233 °C; R_f = 0.35 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3434, 2943, 1738, 1246, 1024, 753; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.01 (m, 1H, H29), 4.53 (m, 2H, H30), 4.41 (m, 1H, H3), 4.16 (m, 4H, 2 x OCH_2CH_3), 2.94 (m, 1H, H19), 2.09 (s, 3H, $\text{C}(\text{O})\text{CH}_3$), 1.20 – 2.35 (m, 23 H, CH, CH_2), 1.37 (m, 6H, 2 x OCH_2CH_3), 1.00 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.70 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 178.5, 171.0, 151.1, 112.9, 80.9, 61.9, 58.5, 56.2, 56.1, 55.4, 50.4, 50.3, 42.4, 40.7, 38.4, 38.3, 38.1, 37.8, 37.1, 36.7, 36.3, 34.3, 32.1, 30.9, 29.6, 27.9, 23.7, 21.3, 21.0, 18.4, 18.2, 16.4, 16.2, 16.0, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 28.0; HR-MS (APCI) m/z : $\text{C}_{36}\text{H}_{58}\text{O}_7\text{P}$ $[(\text{M}-\text{H})^-]$, Calc. 633.3920; Found 633.3913.

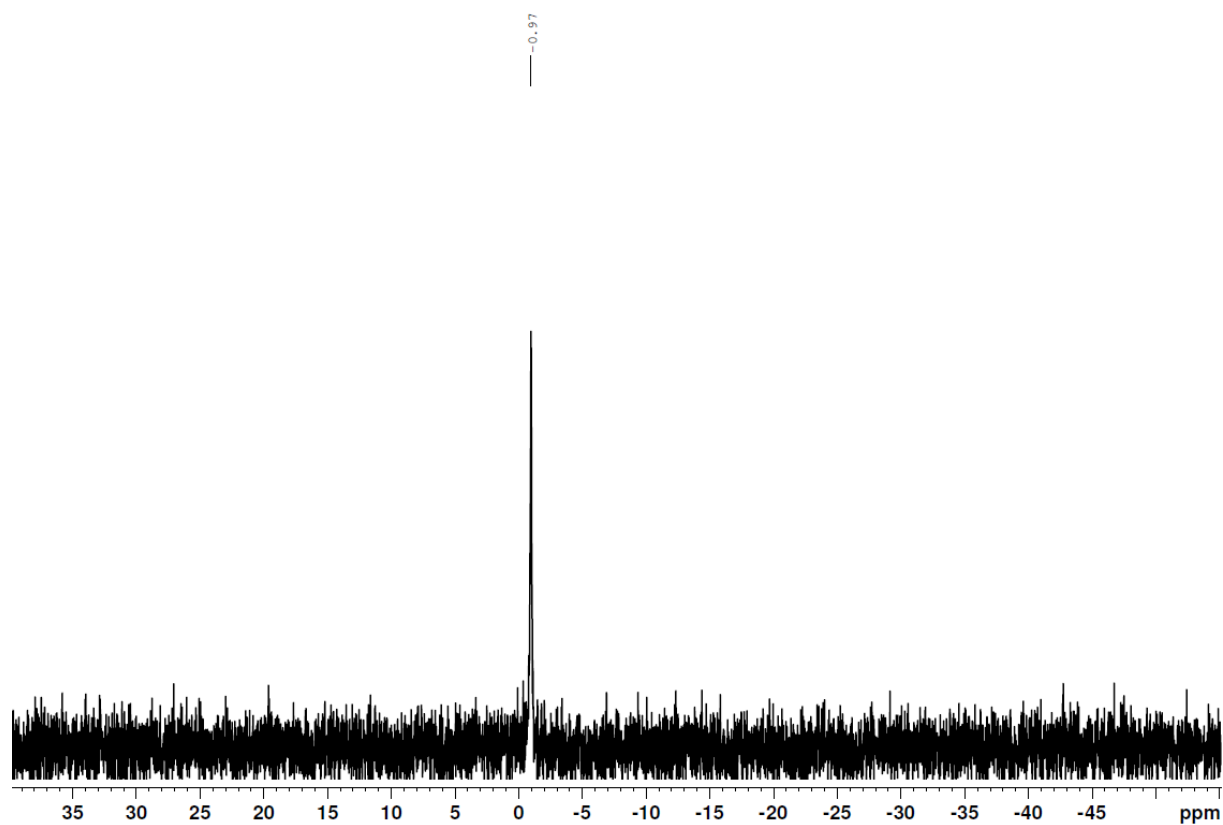
^1H NMR



^{13}C NMR



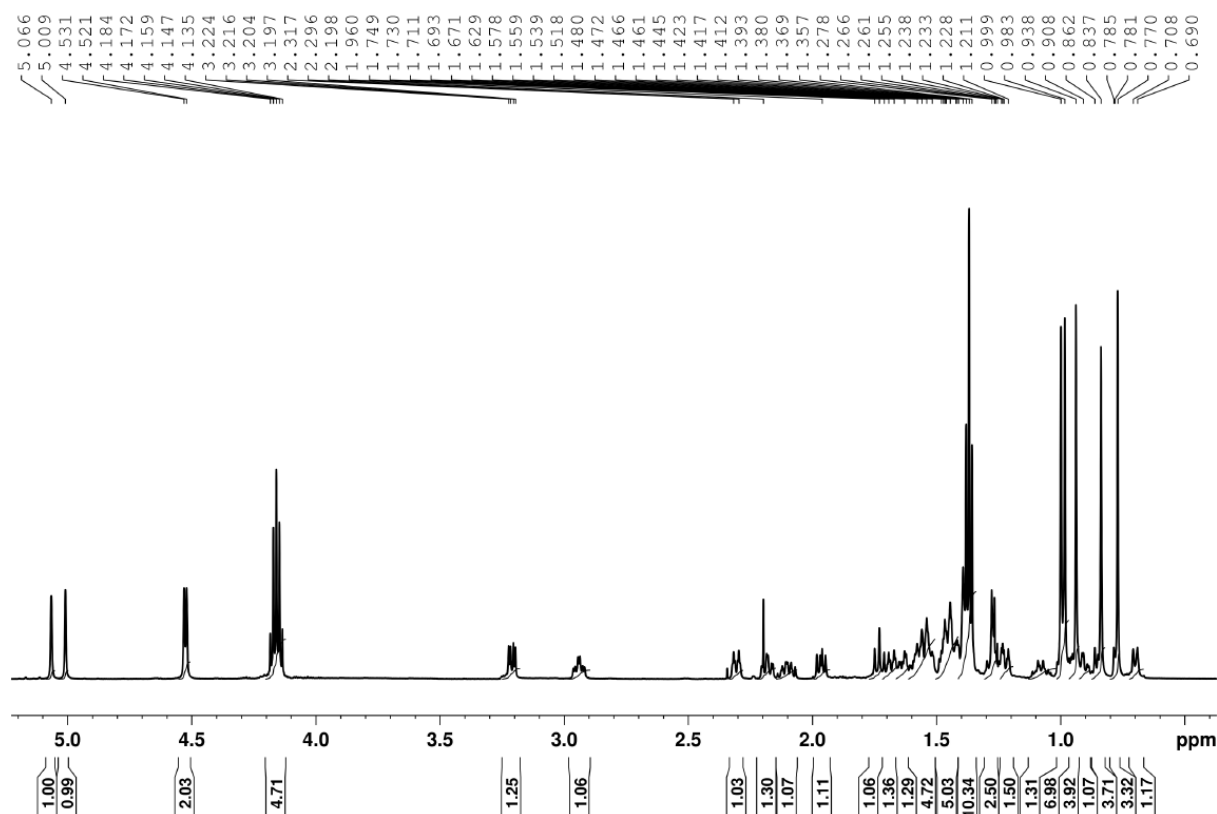
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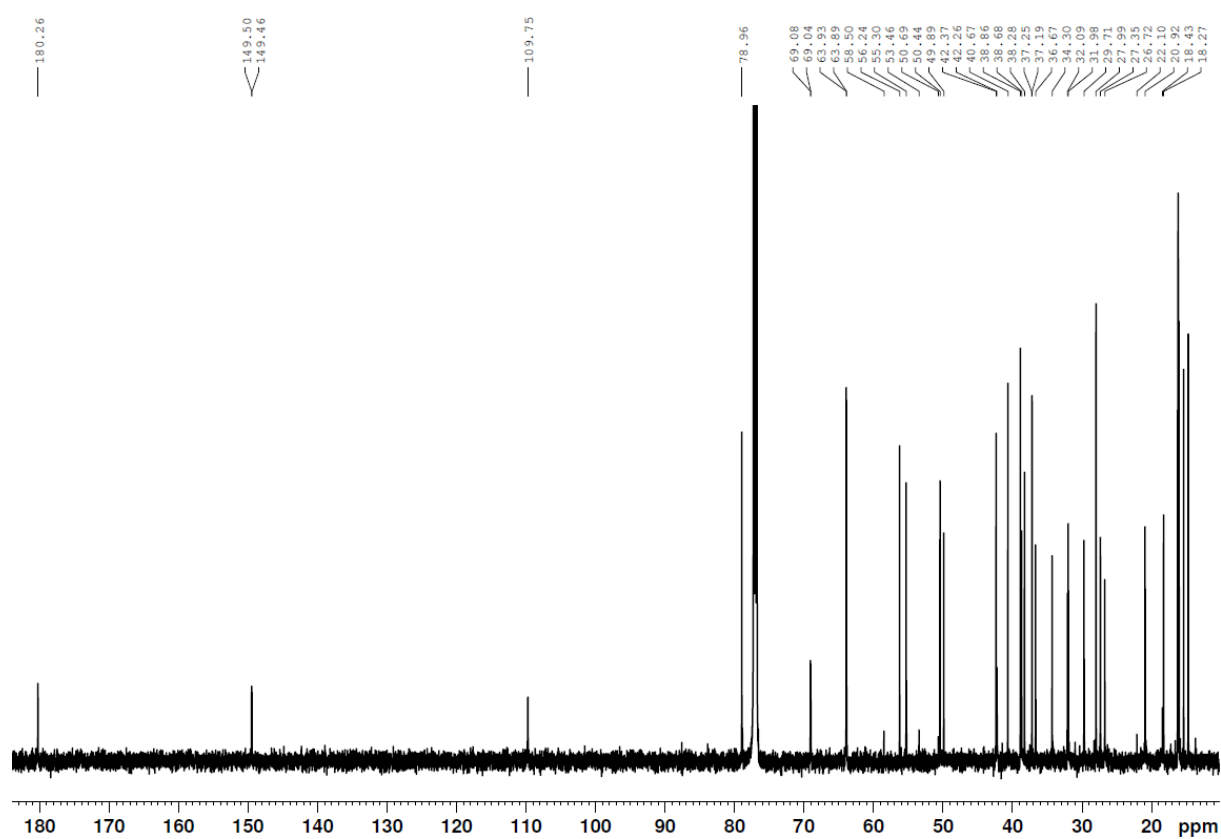
30-Diethoxyphosphorylbetulinic acid **9**

Yield 66%; mp 264-266 °C; R_f = 0.31 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3431, 2941, 1716, 1244, 1030; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.01 (m, 1H, H29), 4.52 (d, 2H, H30), 4.16 (m, 4H, OCH_2CH_3), 3.21 (m, 1H, H3), 2.95 (m, 1H, H19), 1.38 (m, 6H, OCH_2CH_3), 0.75 – 2.35 (m, 23 H, CH, CH_2), 1.00 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.70 (m, 1H, H-5); ^{13}C NMR (CDCl_3) δ (ppm): 180.3, 149.5, 109.7, 79.0, 69.1, 63.9, 63.9, 56.2, 55.3, 50.4, 49.9, 42.4, 42.3, 40.7, 38.9, 38.7; 38.3, 37.2, 36.7, 34.3, 32.1, 32.0, 29.7, 28.0, 27.3, 26.7, 20.9, 18.3, 16.2, 16.2, 16.1, 16.0, 15.4, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): -0.98; HR-MS (APCI) m/z : $\text{C}_{34}\text{H}_{56}\text{O}_7\text{P}$ [(M-H)], Calc. 607.3764; Found 607.3757.

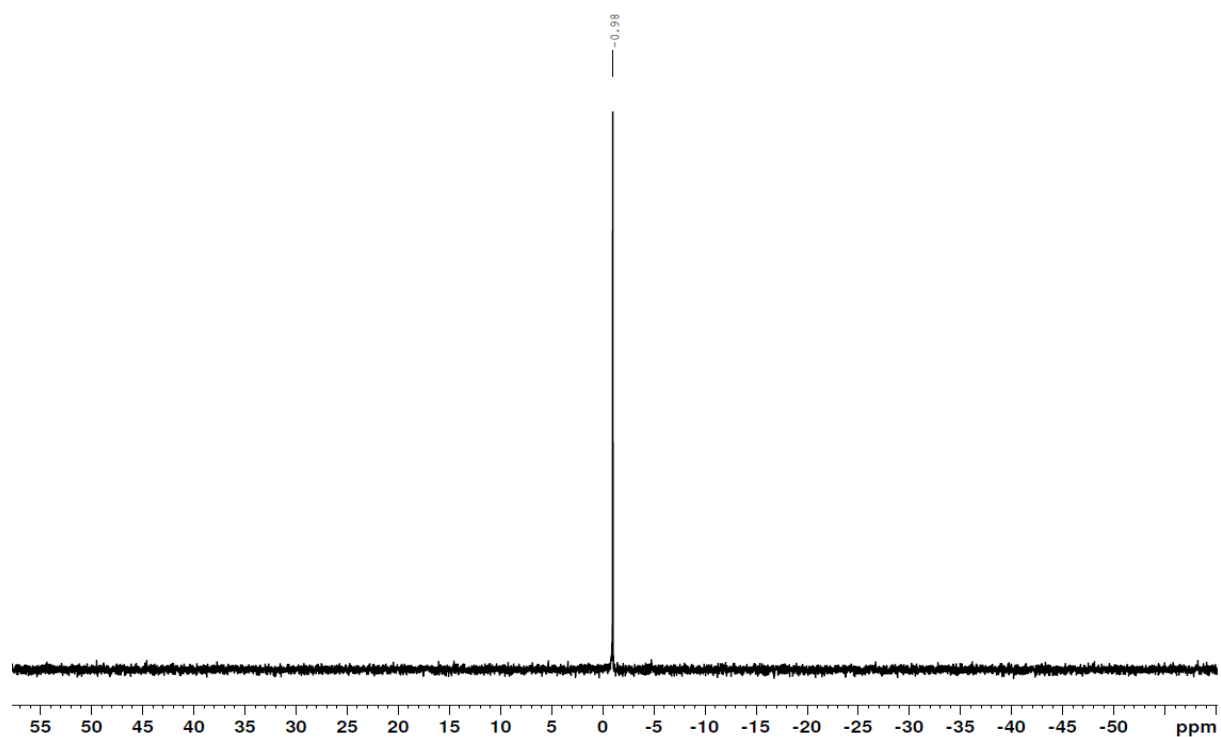
^1H NMR



^{13}C NMR



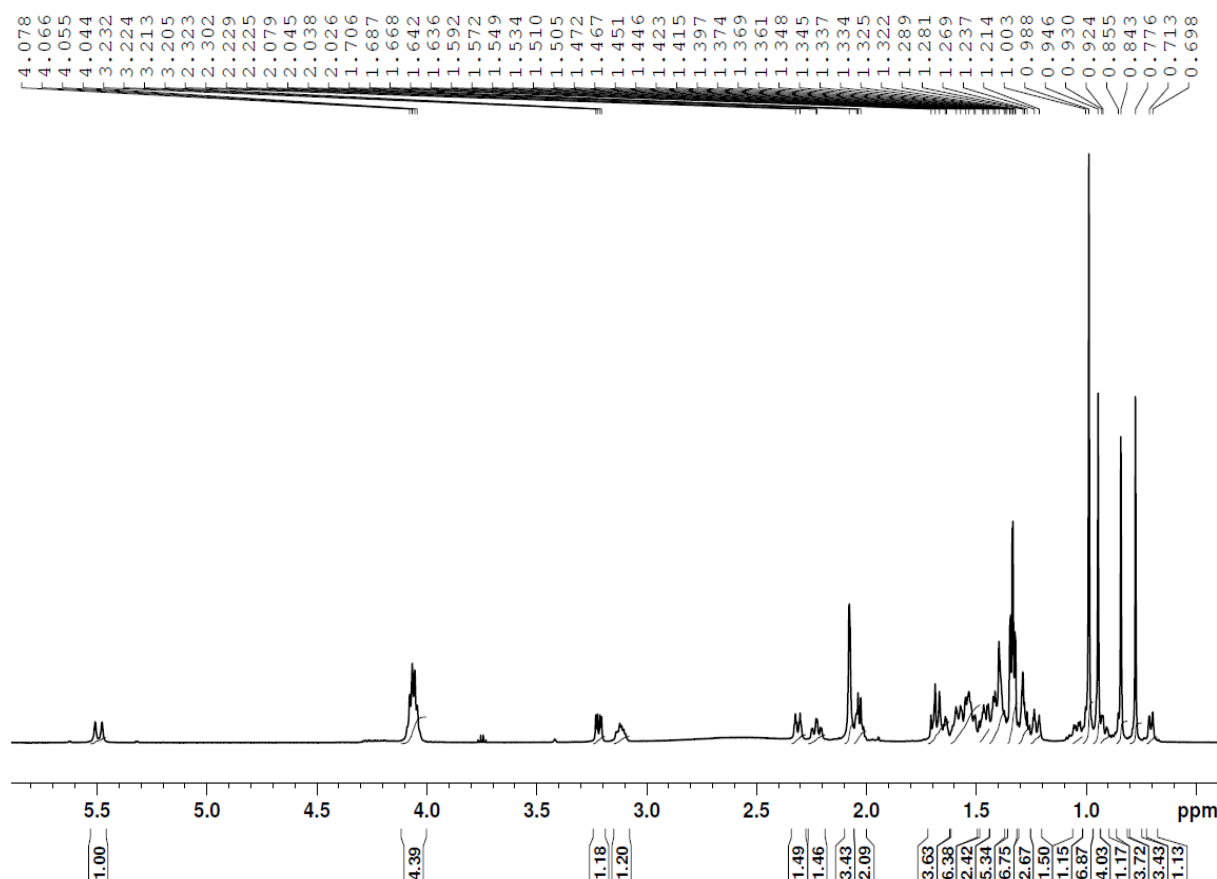
^{31}P NMR



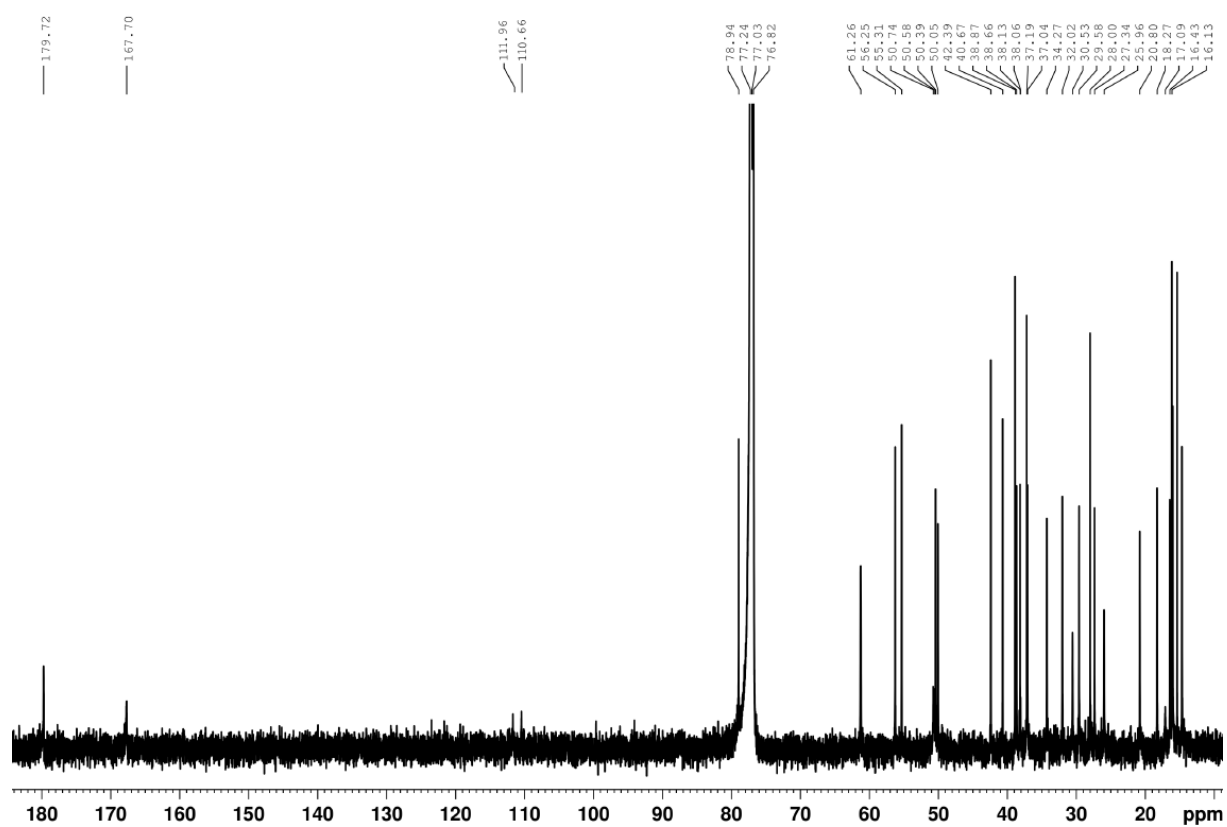
29-Diethoxyphosphorylbetulinic acid 10

Yield 50%; mp 271-273 °C; R_f = 0.31 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3417, 1707, 1227, 1027, 751; ^1H NMR (CDCl_3) δ (ppm): 5.49 (d, 1H, $^2J_{\text{PH}}=18.6$, Hz, H29), 4.06 (m, 4H, 2x OCH_2CH_3), 3.22 (m, 1H, H3), 3.12 (m, 1H, H19), 2.08 (d, $J=3\text{Hz}$, 3H, H30), 0.90–2.10 (m, 23 H, CH, CH_2), 1.34 (m, 6H, 2 x OCH_2CH_3), 0.99 (s, 6H, 2 x CH_3), 0.95 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.71 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 179.7, 167.7, 111.2, 78.9, 61.2, 56.2, 55.3, 50.7, 50.4, 50.0, 42.4, 40.7, 38.9, 38.7, 38.1, 38.1, 37.2, 37.0, 34.3, 32.0, 30.5, 29.6, 28.0, 27.3, 26.0, 20.8, 18.3, 17.1, 16.4, 16.1, 16.0, 15.4, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 18.80; HR-MS (APCI) m/z : $\text{C}_{34}\text{H}_{56}\text{O}_6\text{P}$ [(M-H) $^-$], Calc. 591.3815; Found 591.3823.

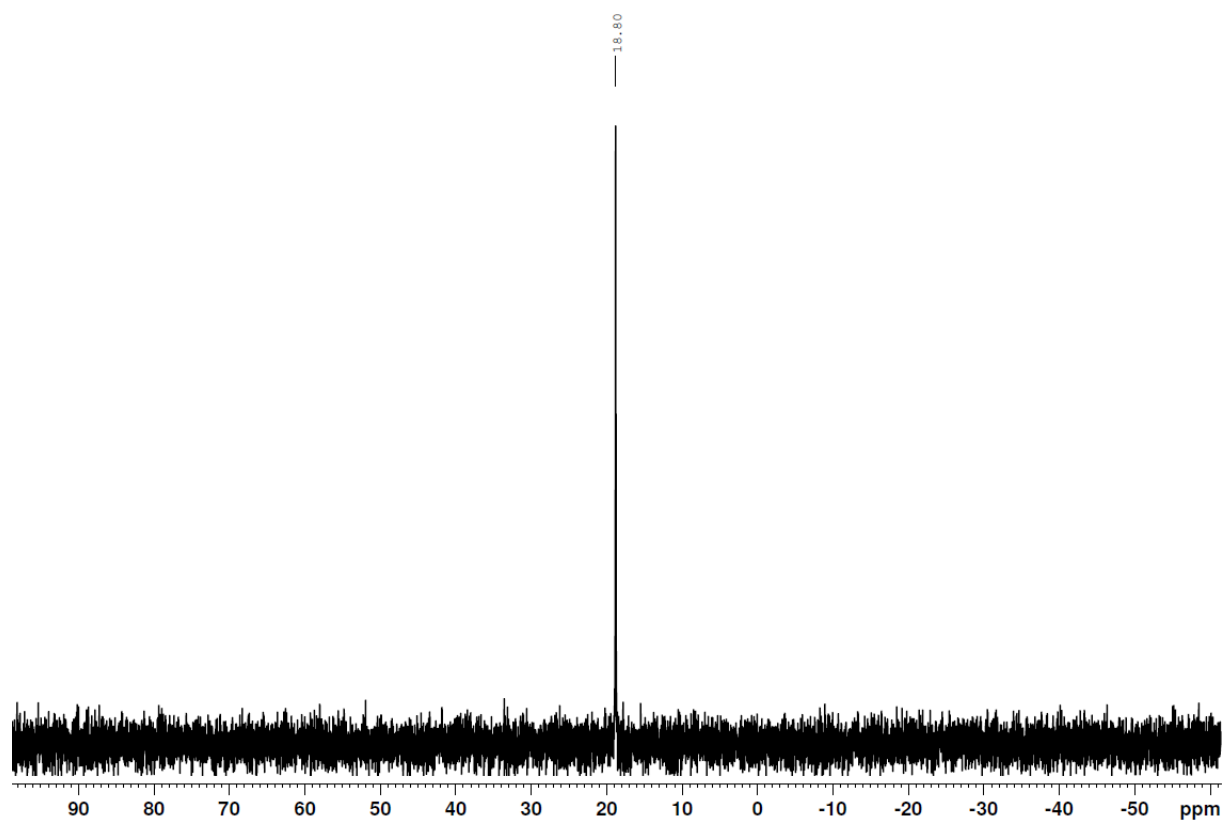
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^{13}C NMR



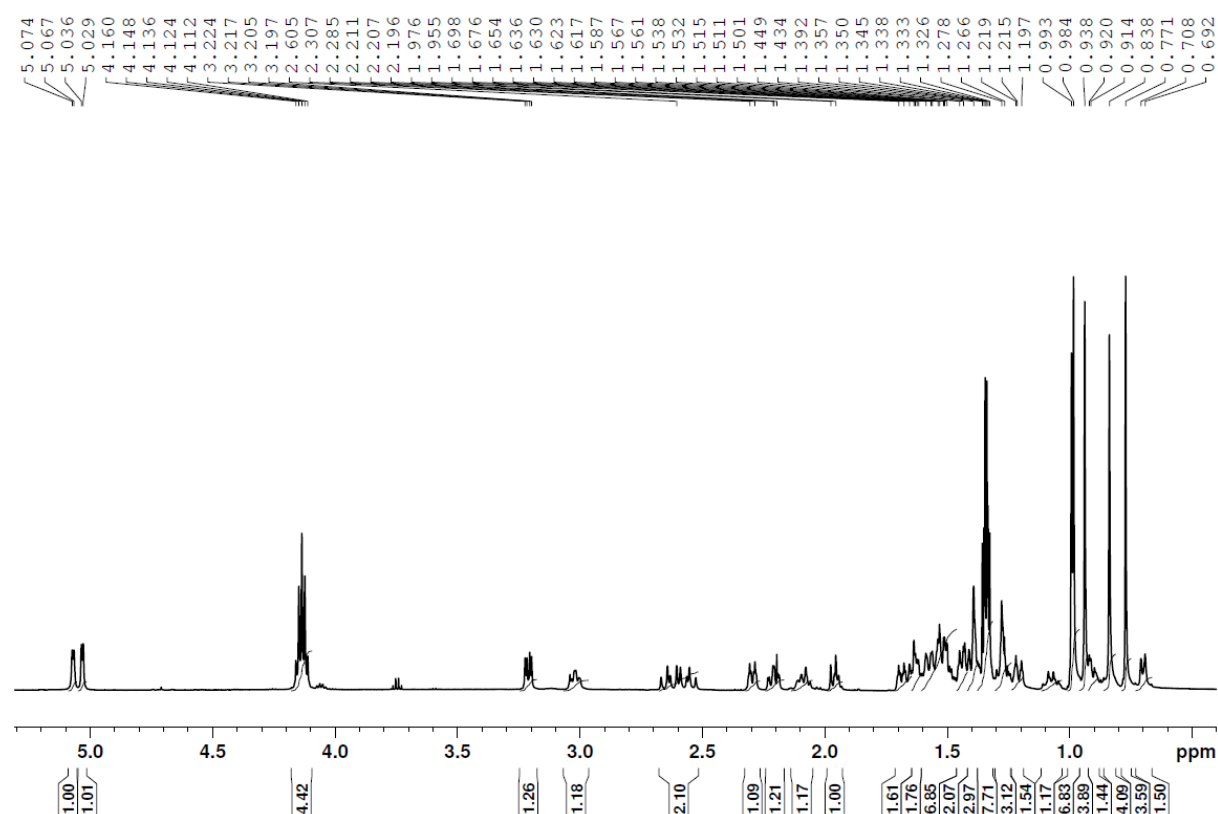
^{31}P NMR



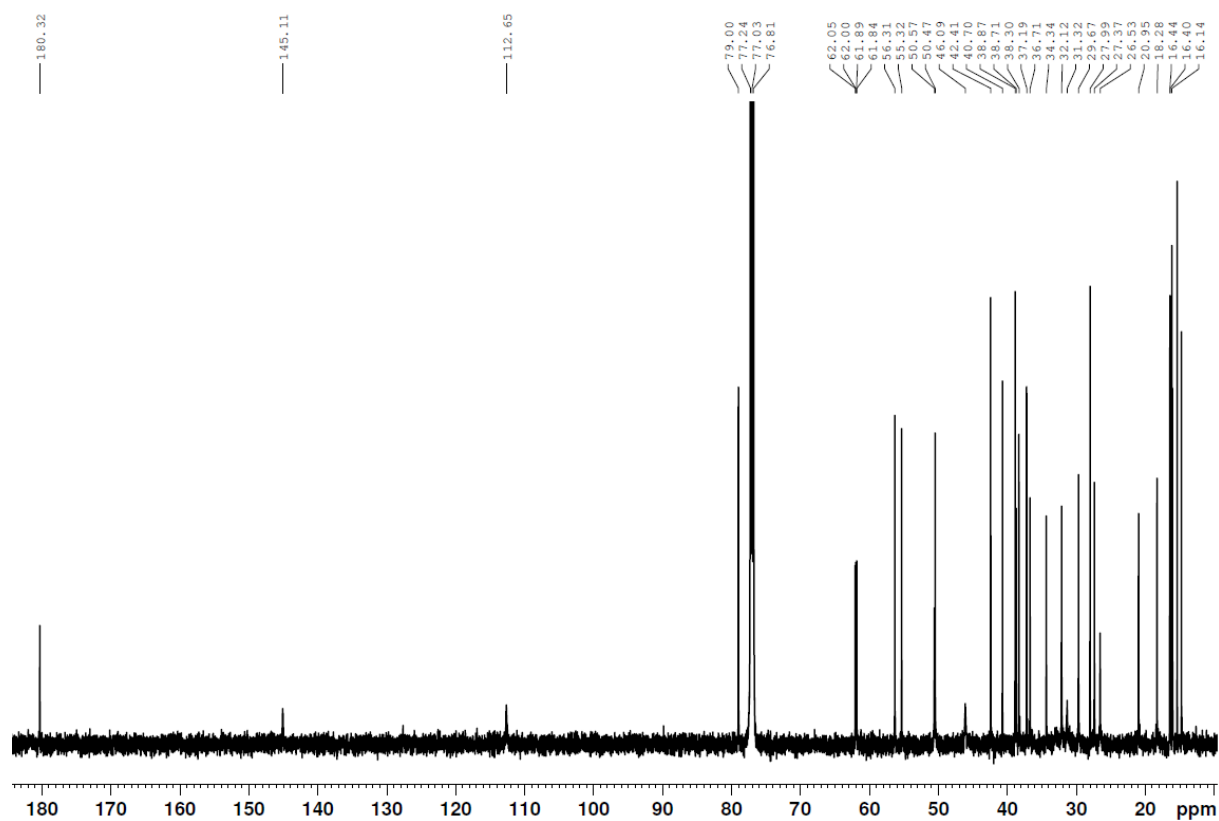
30-Diethoxyphosphorylbetulinic acid 11

Yield 66%; mp 266-268 °C; R_f = 0.31 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3431, 1681, 1236, 1024, 751; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.03 (m, 1H, H29), 4.13 (m, 4H, 2 x OCH_2CH_3), 3.21 (m, 1H, H3), 3.02 (m, 1H, H19), 2.60 (m, 2H, H30), 1.20 – 2.30 (m, 23 H, CH, CH_2), 1.35 (m, 6H, 2 x OCH_2CH_3), 0.99 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.70 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 180.3, 145.11, 112.9, 79.0, 62.0, 62.0, 61.9, 61.8, 56.3, 55.3, 50.6, 50.5, 46.1, 42.4, 40.7, 38.9, 38.7, 38.3, 37.2, 36.7, 34.3, 32.1, 31.3, 29.7, 28.0, 27.4, 26.5, 21.0, 18.3, 16.4, 16.1, 15.4, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 27.9; HR-MS (APCI) m/z : $\text{C}_{34}\text{H}_{56}\text{O}_6\text{P}$ [(M-H)], Calc. 591.3815; Found 591.3827.

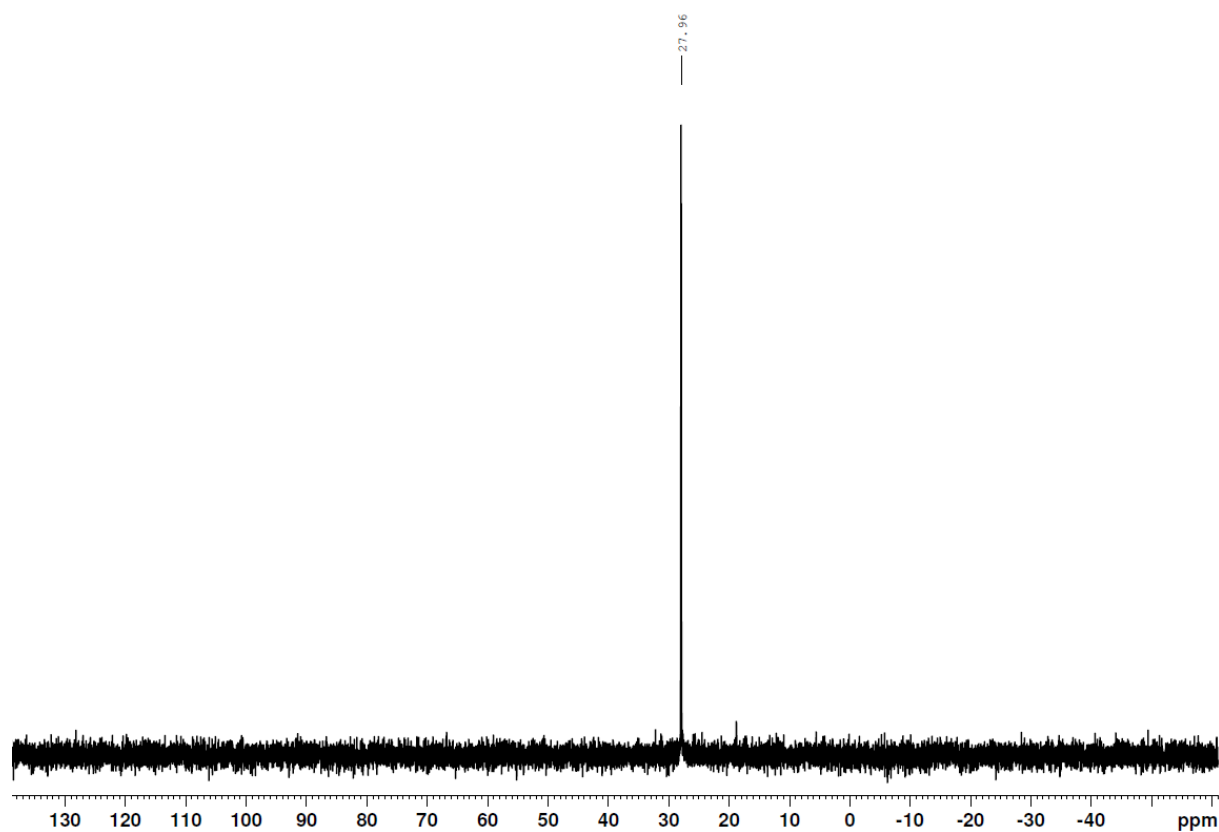
^1H NMR



^{13}C NMR



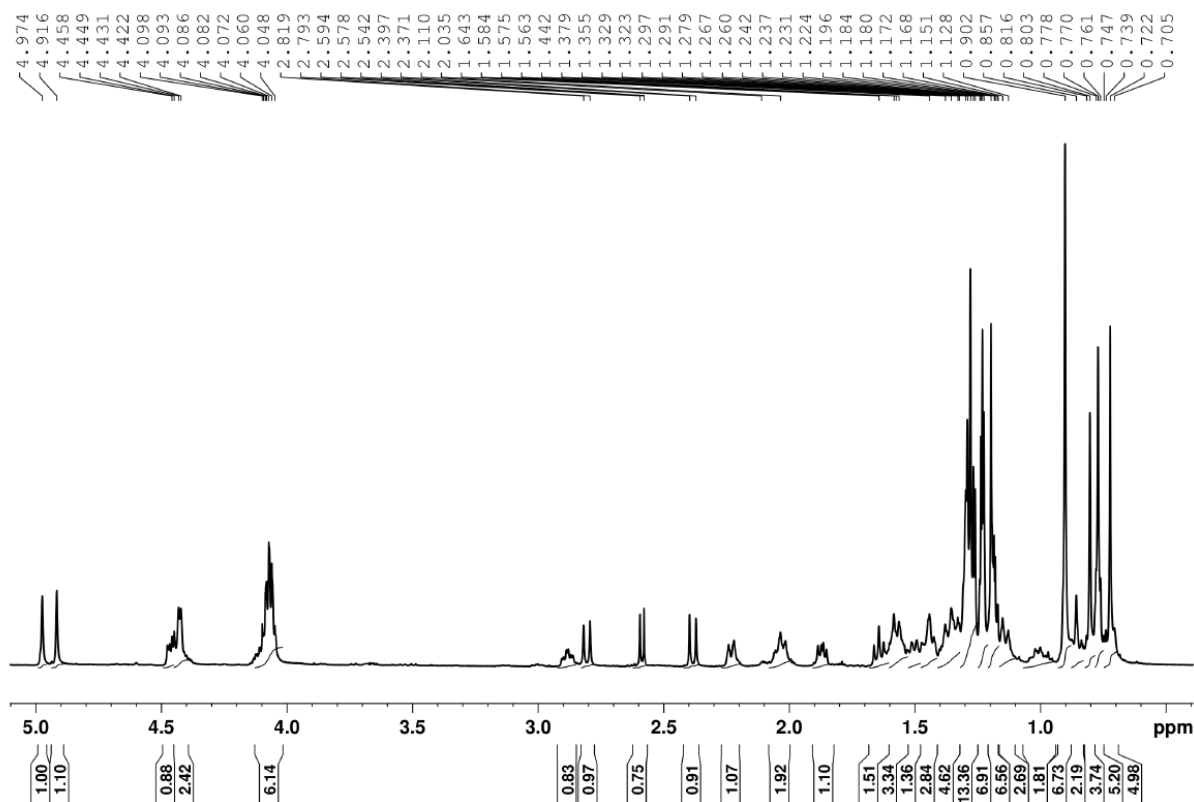
^{31}P NMR



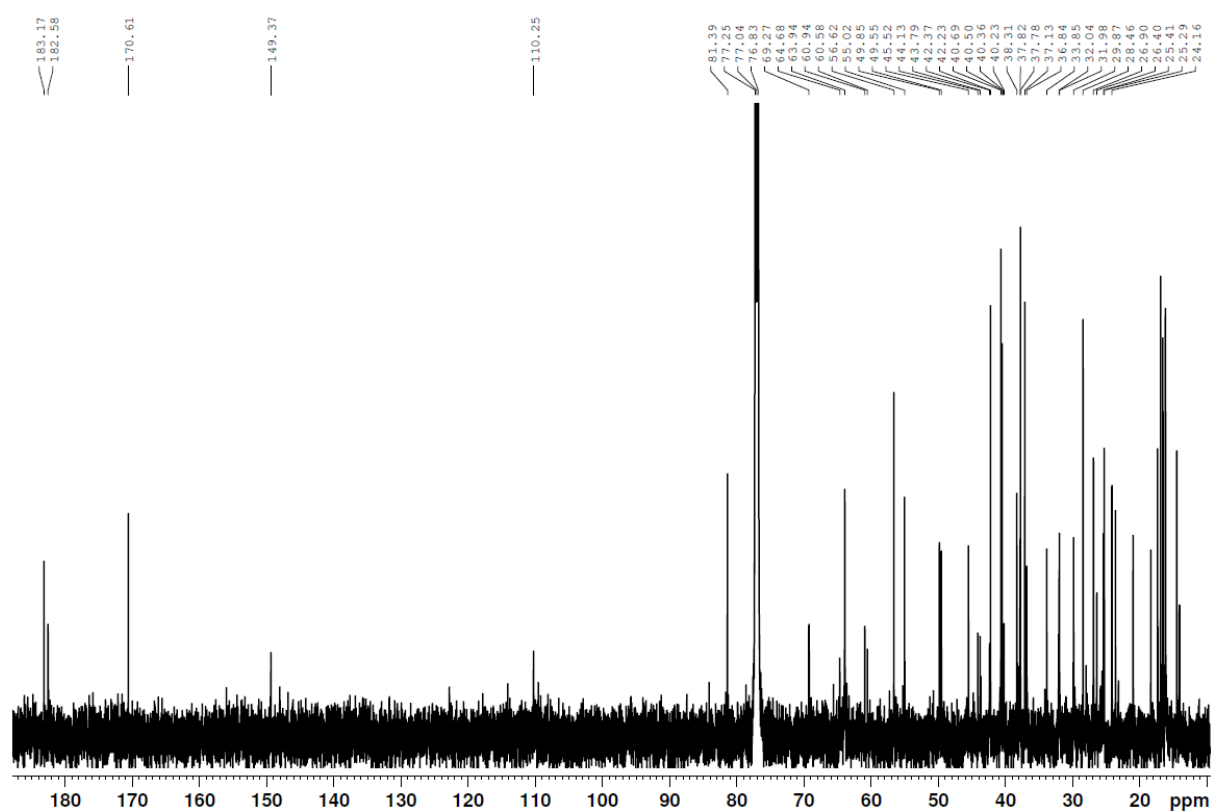
30-Diethoxyphosphoryloxy-3-O-(3',3'-dimethylsuccinyl)betulinic acid 12a

Yield 28%; mp 110-112 °C; R_f = 0.26 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 2947, 1732, 1705, 1240, 1031; ^1H NMR (CDCl_3) δ (ppm): 4.97 (m, 1H, H29), 4.92 (m, 1H, H29), 4.45 (m, 1H, H3), 4.43 (m, 2H, H30), 4.09 (m, 4H, 2 x OCH_2CH_3), 2.89 (m, 1H, H19), 2.82 (d, 1H, J = 15.6 Hz, CH), 2.38 (d, 1H, J = 15.6 Hz, CH), 0.90 – 2.60 (m, 26 H, CH, CH_2), 1.24 (m, 6H, 2 x OCH_2CH_3), 1.20 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 0.90 (s, 6H, 2 x CH_3), 0.78 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.72 (s, 3H, CH_3), 0.71 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 183.1, 182.5, 170.6, 149.4, 110.3, 81.4, 69.3, 63.9, 63.9, 56.6, 55.0, 49.9, 49.5, 45.5, 44.1, 42.2, 40.7, 40.5, 38.3, 37.8, 37.1, 36.8, 33.8, 32.0, 32.0, 29.9, 28.5, 27.0, 26.4, 25.3, 24.2, 23.6, 21.0, 18.4, 17.4, 16.9, 16.6, 16.2, 16.2, 14.5; ^{31}P NMR (CDCl_3) δ (ppm): -1.02; HR-MS (APCI) m/z : $\text{C}_{40}\text{H}_{64}\text{O}_{10}\text{P}$ [(M-H) $^-$], Calc. 735.4237; Found 735.4229.

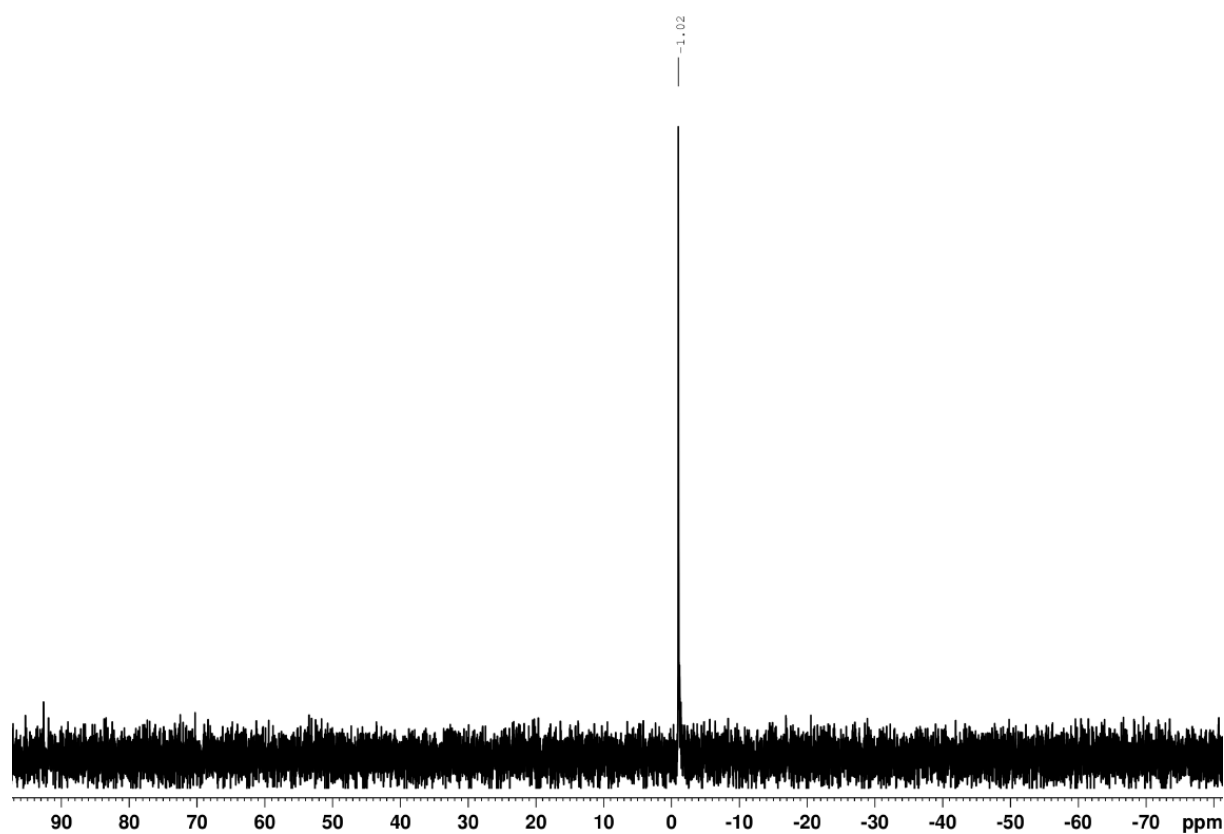
^1H NMR



^{13}C NMR



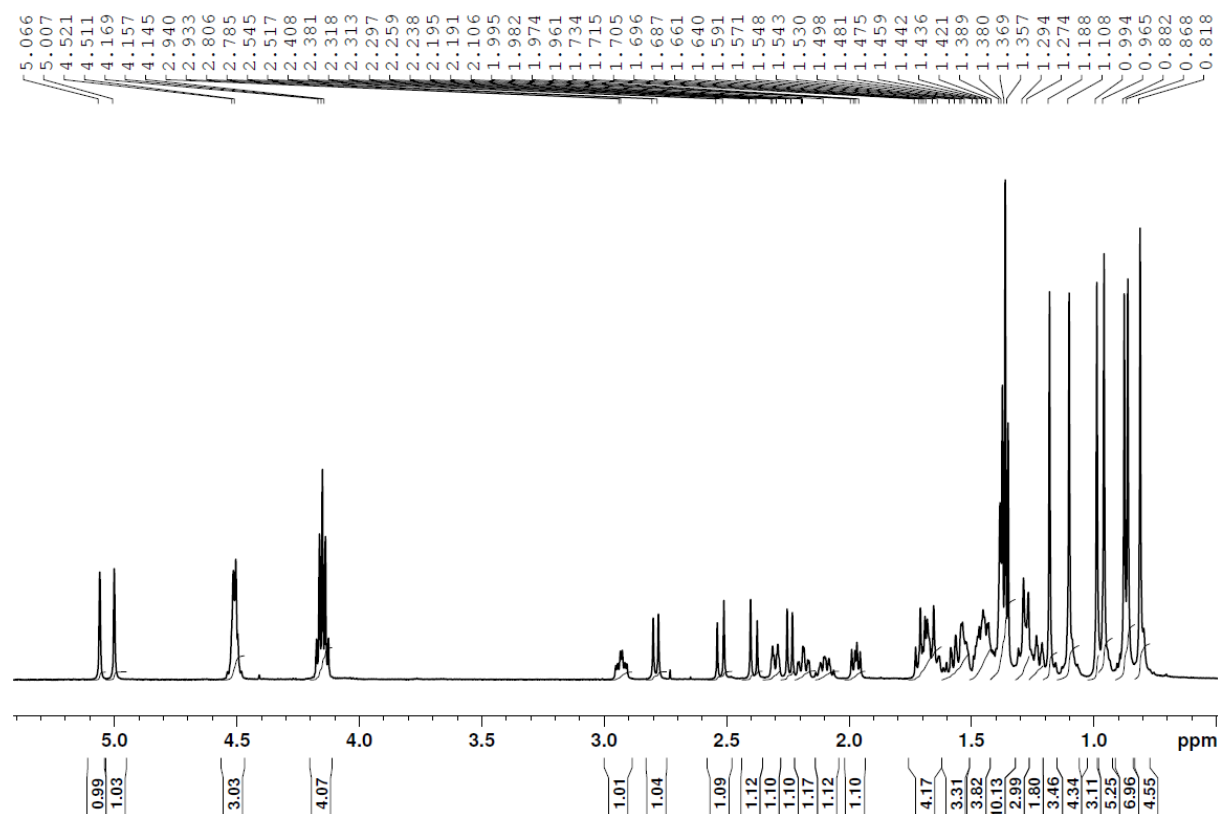
^{31}P NMR



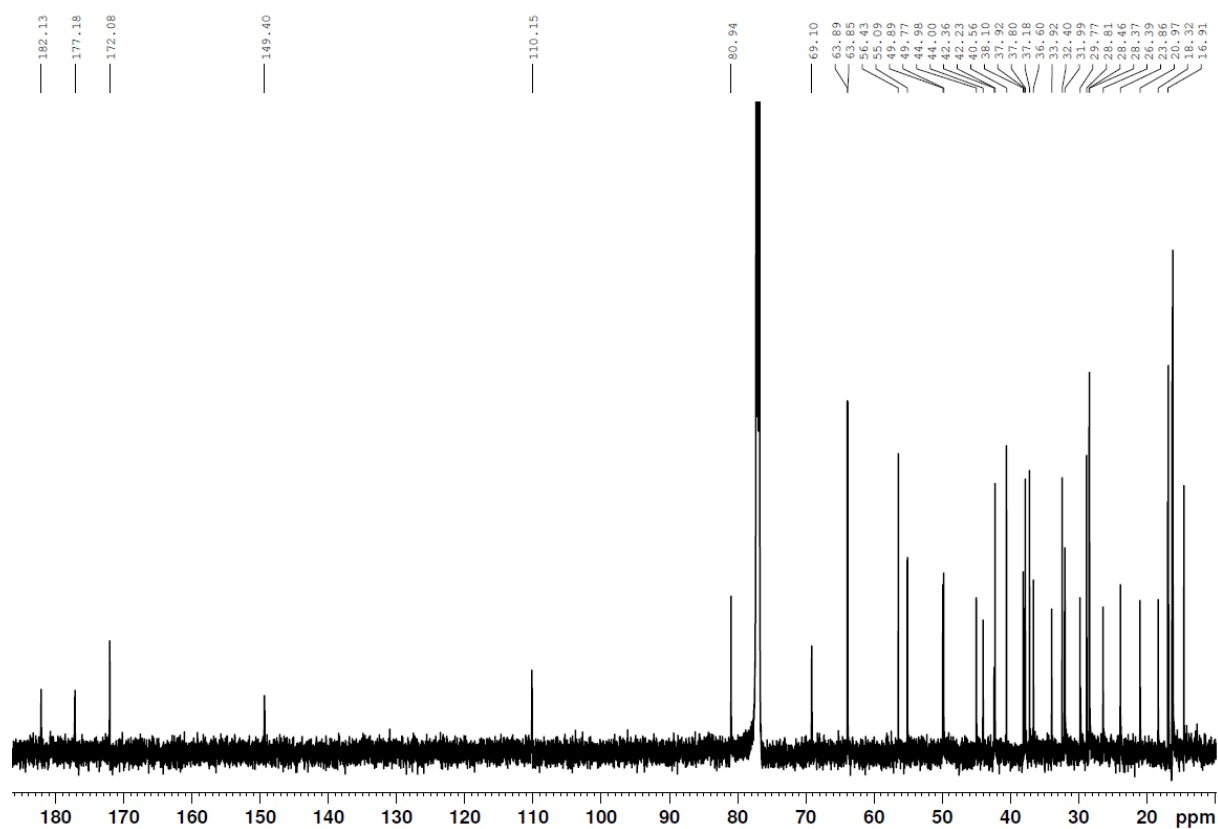
30-Diethoxyphosphoryloxy-3-O-(3,3'-dimethylglutaryl)betulonic acid 12b

Yield 34%; mp 148-150 °C; R_f = 0.28 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 2945, 1726, 1240, 1031; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.01 (m, 1H, H29), 4.51-4.52 (m, 1H, H3 and 2H, H30), 4.16 (m, 4H, 2 x OCH_2CH_3), 2.94 (m, 1H, H19), 2.79 (d, 1H, $J=15.6$ Hz, H4'), 2.53 (d, 1H, $J=15.6$ Hz, H4'), 2.39 (d, 1H, $J=16.2$ Hz, H2'), 2.28 (d, 1H, $J=16.2$ Hz, H2'), 1.37 (m, 6H, 2 x OCH_2CH_3), 0.75 – 2.35 (m, 25 H, CH, CH_2), 1.19 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.82 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 182.1, 177.2, 172.1, 149.4, 110.1, 81.0, 69.1, 63.9, 63.9, 56.4, 55.1, 49.9, 49.8, 45.0, 44.0, 42.4, 42.2, 40.6, 38.1, 37.9, 37.8, 37.2, 36.6, 33.9, 32.4, 32.0, 29.8, 28.8, 28.5, 28.4, 26.4, 23.9, 21.0, 18.3, 16.9, 16.8, 16.3, 16.2, 16.2, 14.5; ^{31}P NMR (CDCl_3) δ (ppm): -0.94; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_{10}\text{P}$ [(M-H) $^-$], Calc. 749.4394; Found 749.4385.

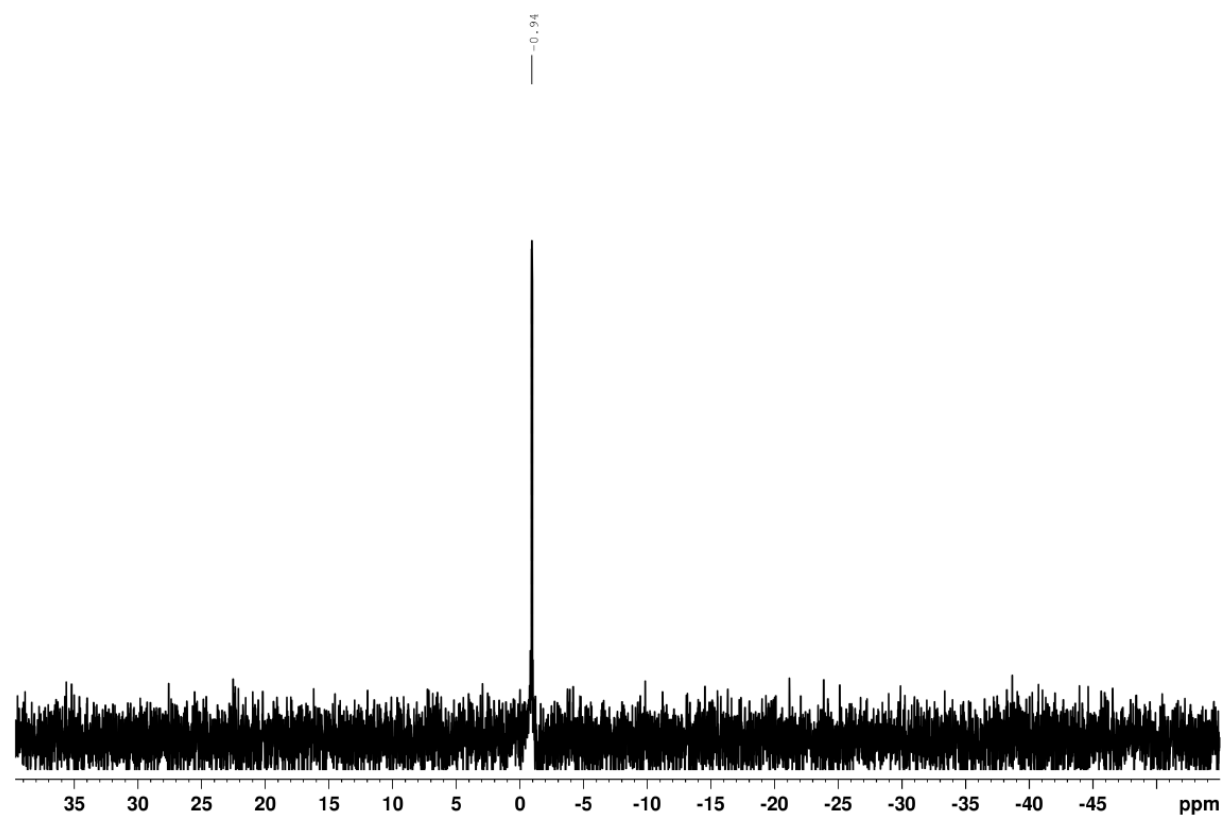
^1H NMR



^{13}C NMR



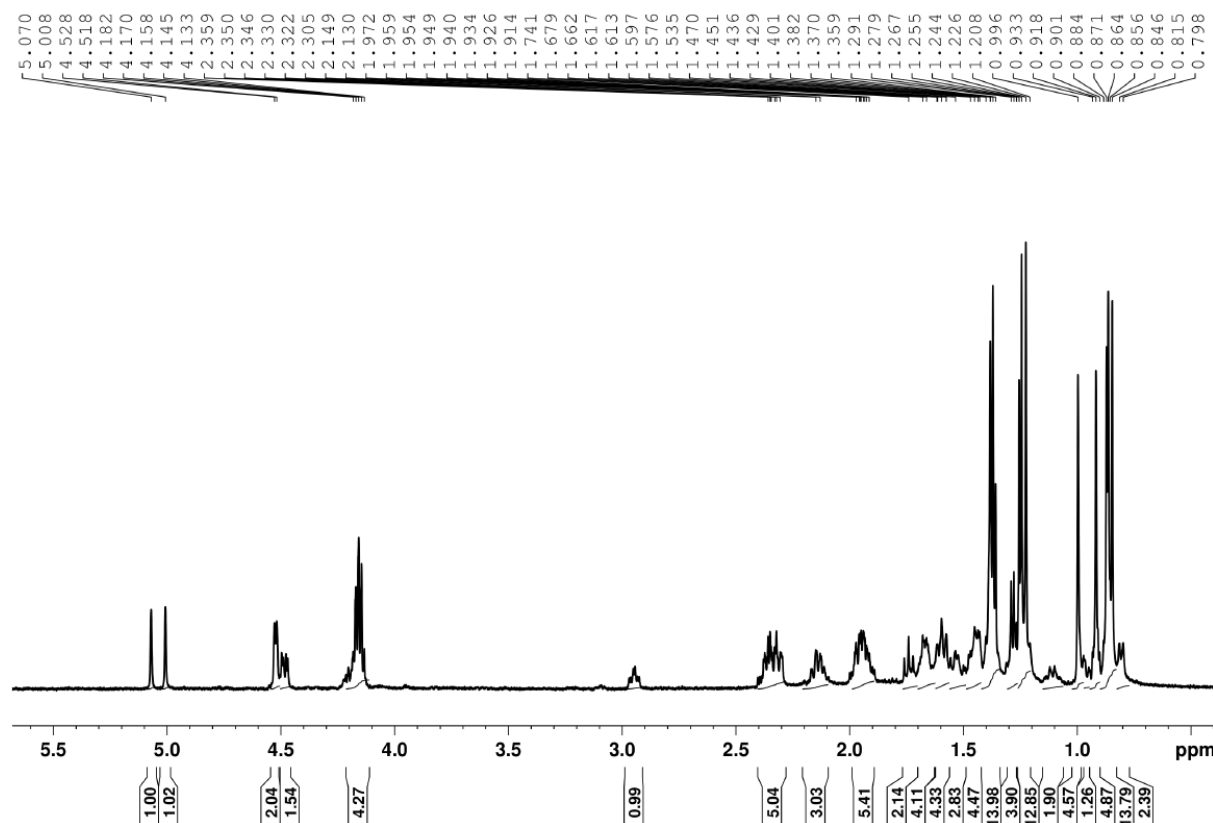
^{31}P NMR



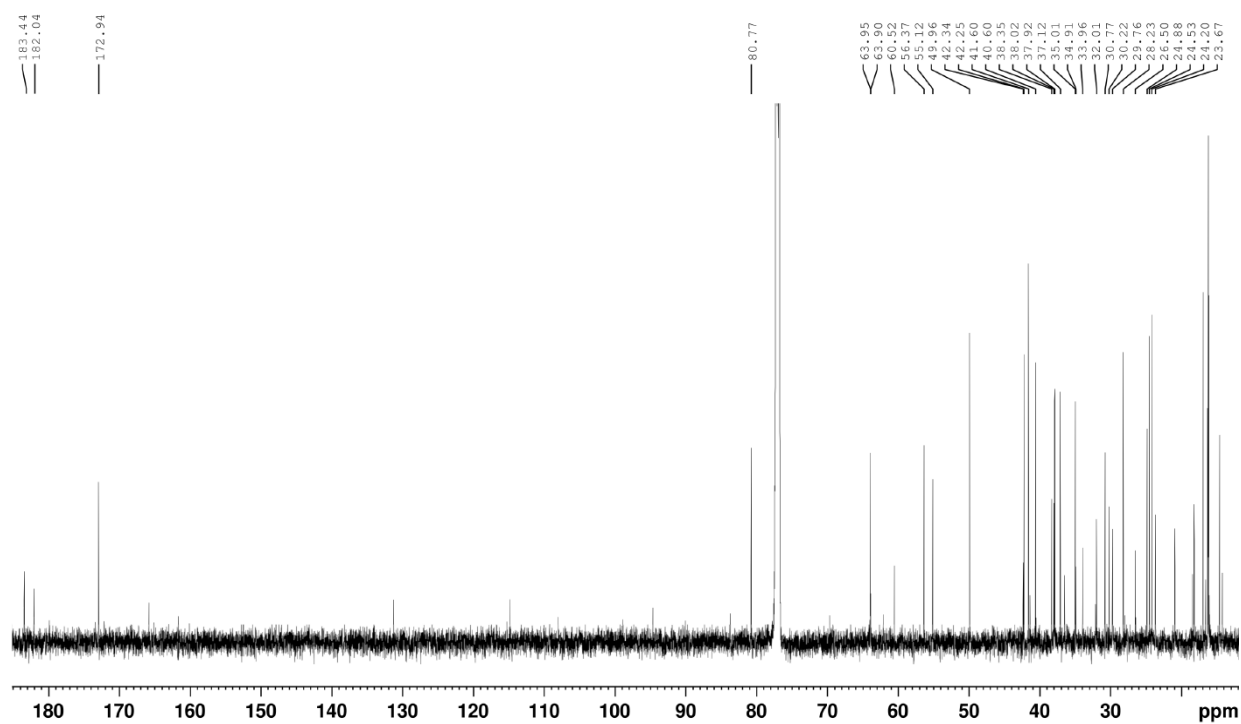
30-Diethoxyphosphoryloxy-3-O-(4',4'-dimethylglutaryl)betulonic acid 12c

Yield 32%; mp 136-138 °C; R_f = 0.27 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3213, 2998, 1732, 1699, 1242, 1031; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.01 (m, 1H, H29), 4.52 (d, 2H, H30), 4.49 (m, 1H, H3), 4.16 (m, 4H, 2 x OCH_2CH_3), 2.95 (m, 1H, H19), 1.37 (m, 6H, 2 x OCH_2CH_3), 0.75 – 2.35 (m, 27 H, CH, CH_2), 1.24 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.81 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 183.4, 182.0, 172.9, 131.3, 114.3, 80.8, 69.1, 63.9, 63.9, 60.5, 56.4, 55.1, 50.0, 42.3, 42.2, 41.6, 40.6, 38.4, 38.0, 37.9, 37.1, 35.0, 34.9, 34.0, 32.0, 30.8, 30.2, 29.8, 28.2, 26.5, 24.9, 24.5, 24.2, 23.7, 20.9, 18.2, 17.0, 16.3, 16.2, 16.2, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): -0.98; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_{10}\text{P}$ [(M-H) $^-$], Calc. 749.4394; Found 749.4386.

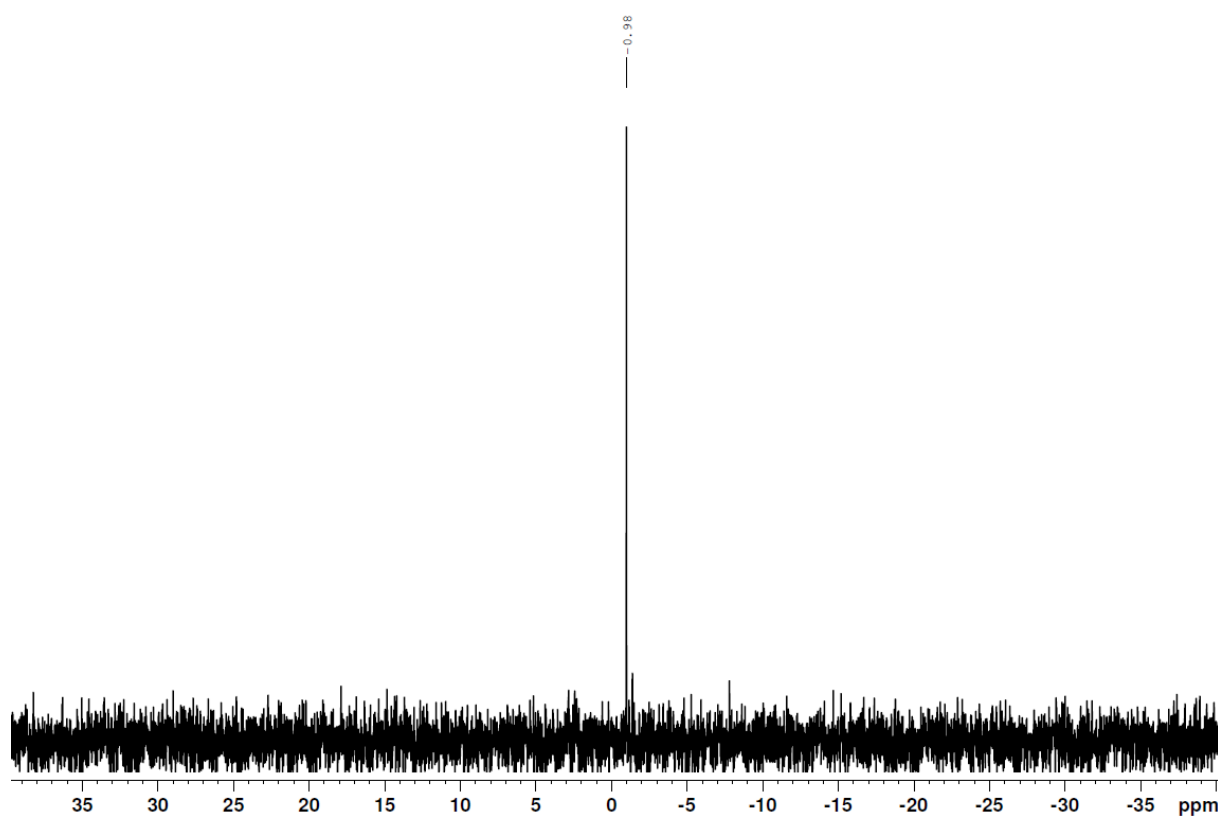
^1H NMR



^{13}C NMR



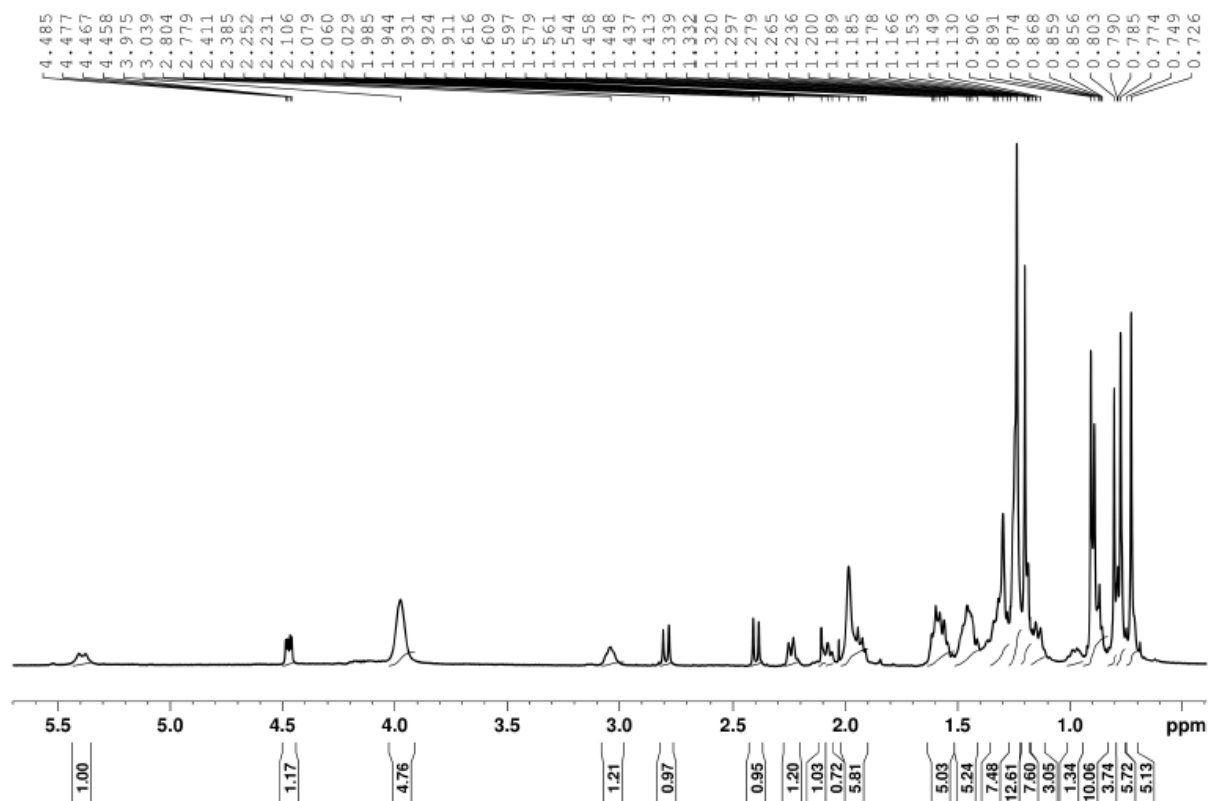
^{31}P NMR



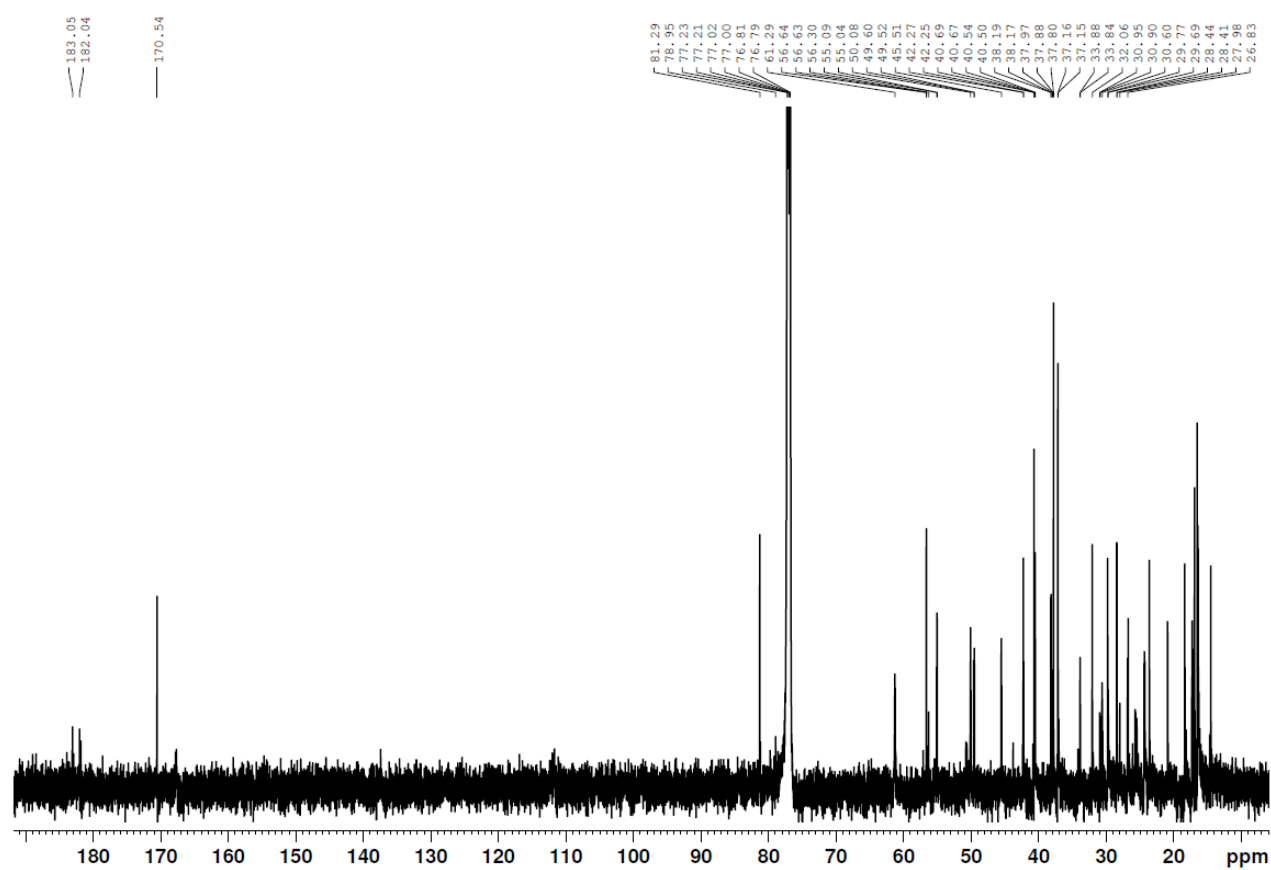
29-Diethoxyphosphoryl-3-O-(3',3'-dimethylsuccinyl)betulonic acid 13a

Yield 22%; mp 150-154 °C; R_f = 0.13 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3550, 2945, 1728, 1219, 1024, 752; ^1H NMR (CDCl_3) δ (ppm): 5.39 (m, 1H, H29), 4.47 (m, 1H, H3), 3.97 (m, 4H, 2 x OCH_2CH_3), 3.04 (m, 1H, H19), 2.80 (d, 1H, J = 15.6 Hz, CH), 2.40 (d, 1H, J = 15.6 Hz, CH), 1.20 – 2.30 (m, 24 H, CH, CH_2), 1.98 (br. s, 3H, CH_3), 1.25 (m, 6H, 2 x OCH_2CH_3), 1.23 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.73 (s, 3H, CH_3); ^{13}C NMR (CDCl_3) δ (ppm): 183.0, 182.0, 170.5, 111.3, 81.3, 61.3, 56.6, 55.1, 50.1, 49.6, 49.5, 45.5, 42.3, 42.2, 40.7, 40.5, 38.2, 37.9, 37.2, 37.1, 33.9, 33.8, 30.9, 30.6, 29.8, 29.7, 28.4, 28.0, 26.8, 26.8, 25.7, 24.3, 23.6, 18.4, 17.3, 16.9, 16.5, 16.4, 16.3, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 18.6; HR-MS (APCI) m/z : $\text{C}_{40}\text{H}_{64}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 719.4288; Found 719.4275.

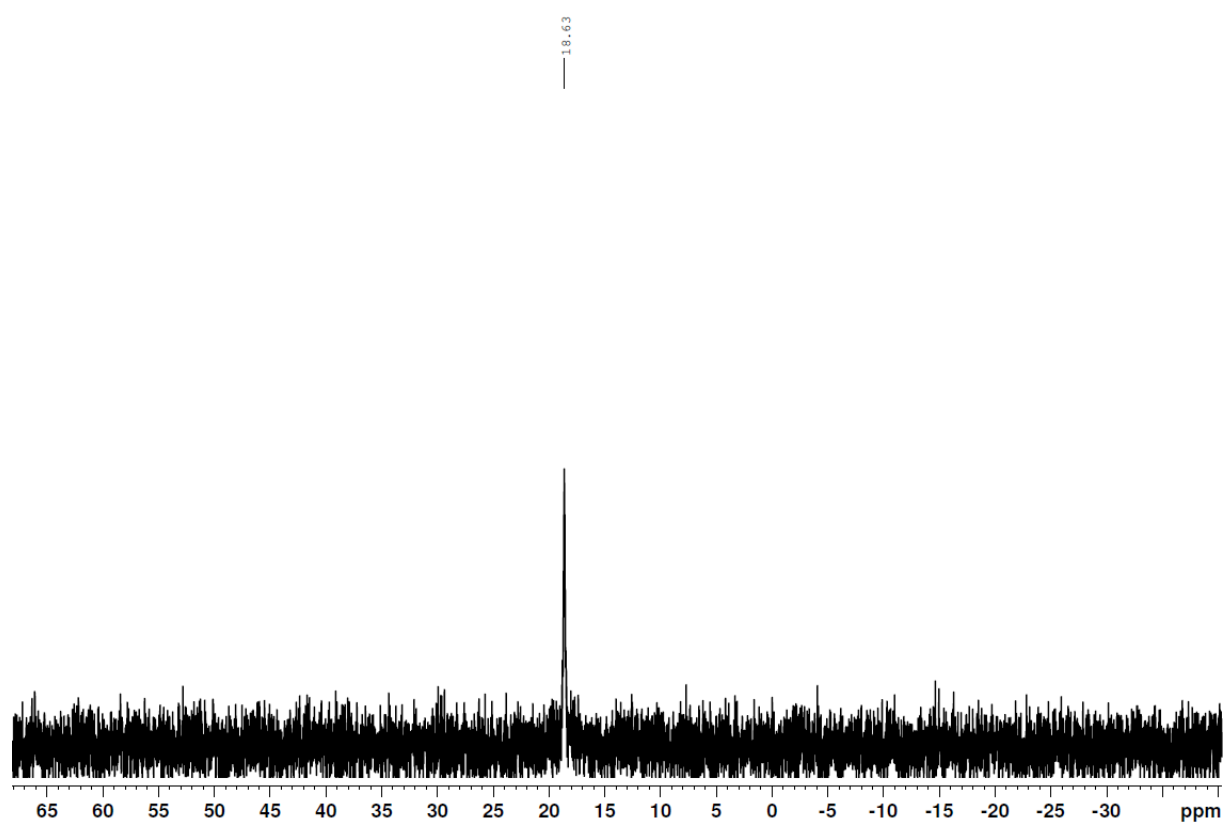
^1H NMR



^{13}C NMR



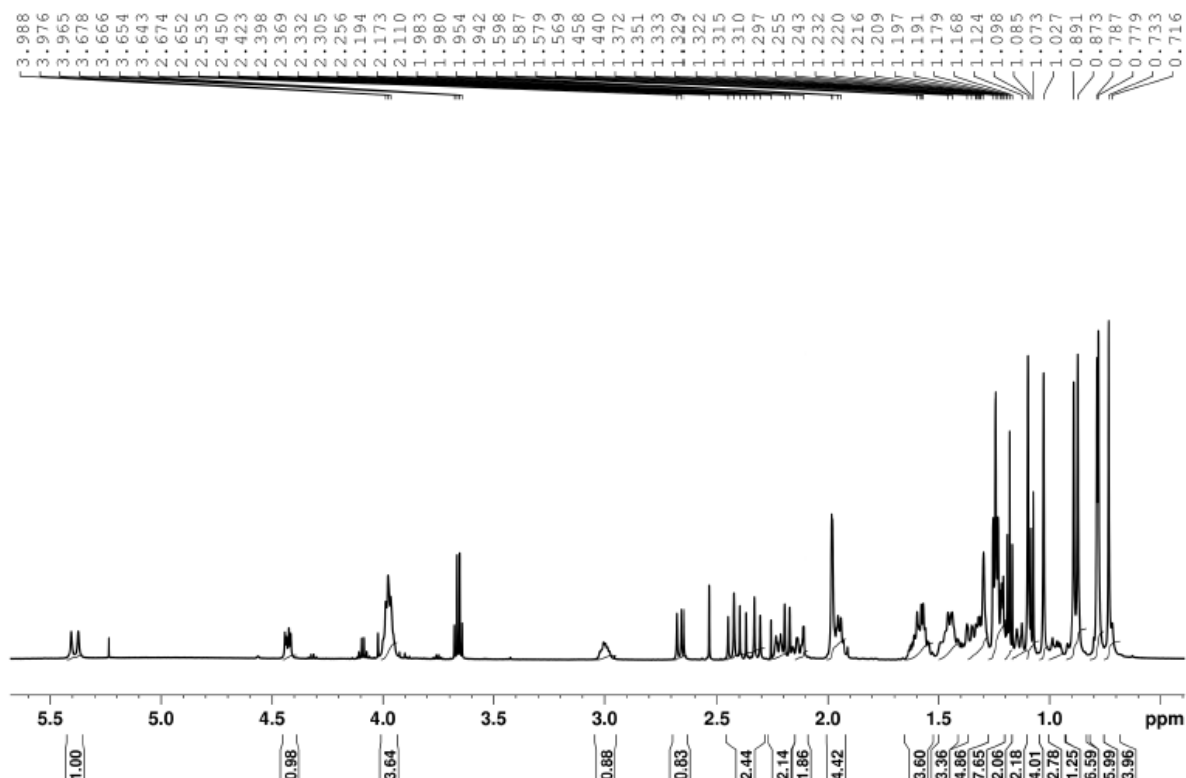
^{31}P NMR



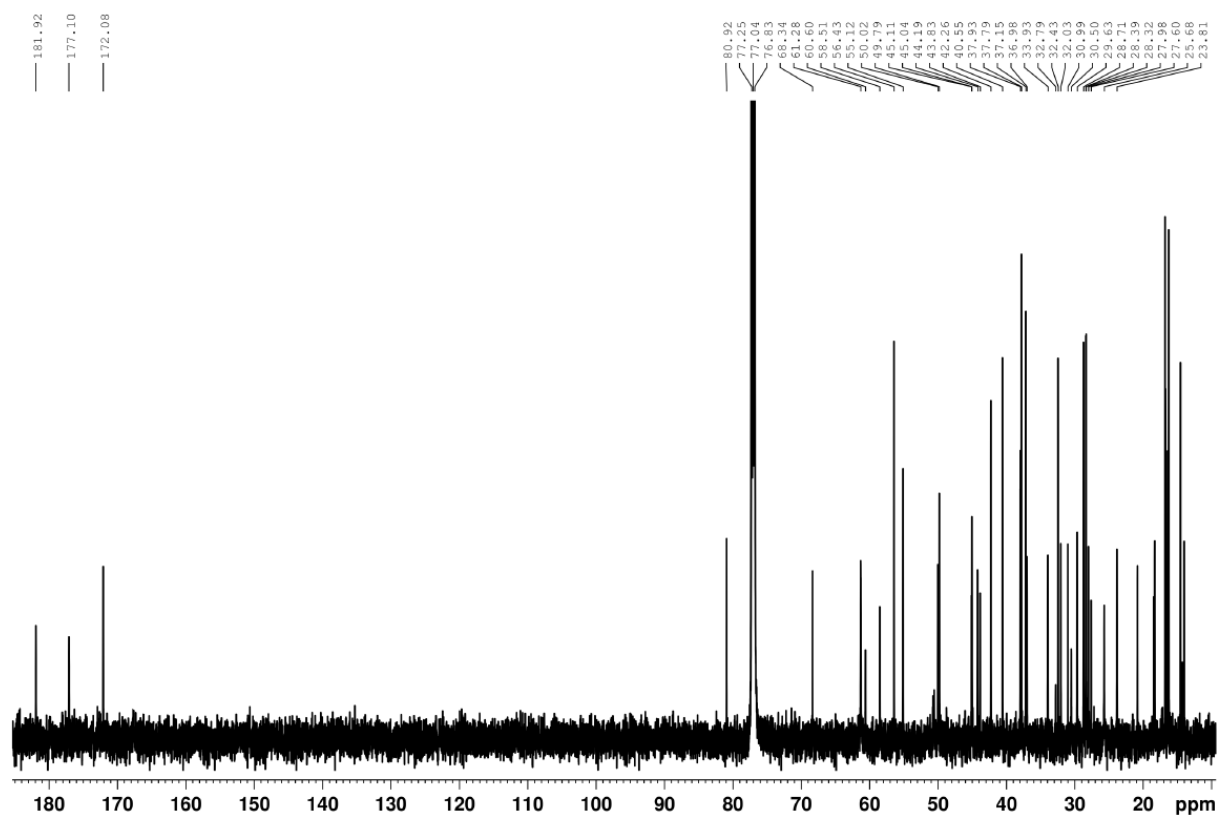
29-Diethoxyphosphoryl-3-O-(3',3'-dimethylglutaryl)betulinic acid 13b

Yield 41%; mp 131-133 °C; R_f = 0.12 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 2945, 1716, 1220, 1028, 754; ^1H NMR (CDCl_3) δ (ppm): 5.39 (d, 1H, $J_{\text{H-P}}$ = 19.2 Hz, H29), 4.43 (m, 1H, H3), 3.98 (m, 4H, 2 x OCH_2CH_3), 3.00 (m, 1H, H19), 2.66 (d, 1H, J = 16.2 Hz, H4'), 2.43 (d, 1H, J = 16.2 Hz, H4'), 2.32 (d, 1H, J = 17.4 Hz, H2'), 2.28 (d, 1H, J = 17.4 Hz, H2'), 0.90 – 2.50 (m, 26 H, CH, CH_2); 1.98 (s, 3H, CH_3), 1.25 (m, 6H, 2 x OCH_2CH_3), 1.10 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.73 (s, 3H, CH_3), 0.72 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 181.9, 177.1, 172.0, 80.9, 68.3, 61.3, 60.6, 58.5, 56.4, 55.1, 50.0, 49.8, 45.1, 45.0, 44.2, 43.8, 42.3, 40.5, 37.9, 37.8, 37.1, 37.0, 33.9, 32.8, 32.4, 32.0, 31.0, 30.5, 29.6, 25.7, 23.8, 20.8, 18.2, 16.4, 16.2, 16.1, 16.0, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): 18.7; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 733.4445; Found 733.4439.

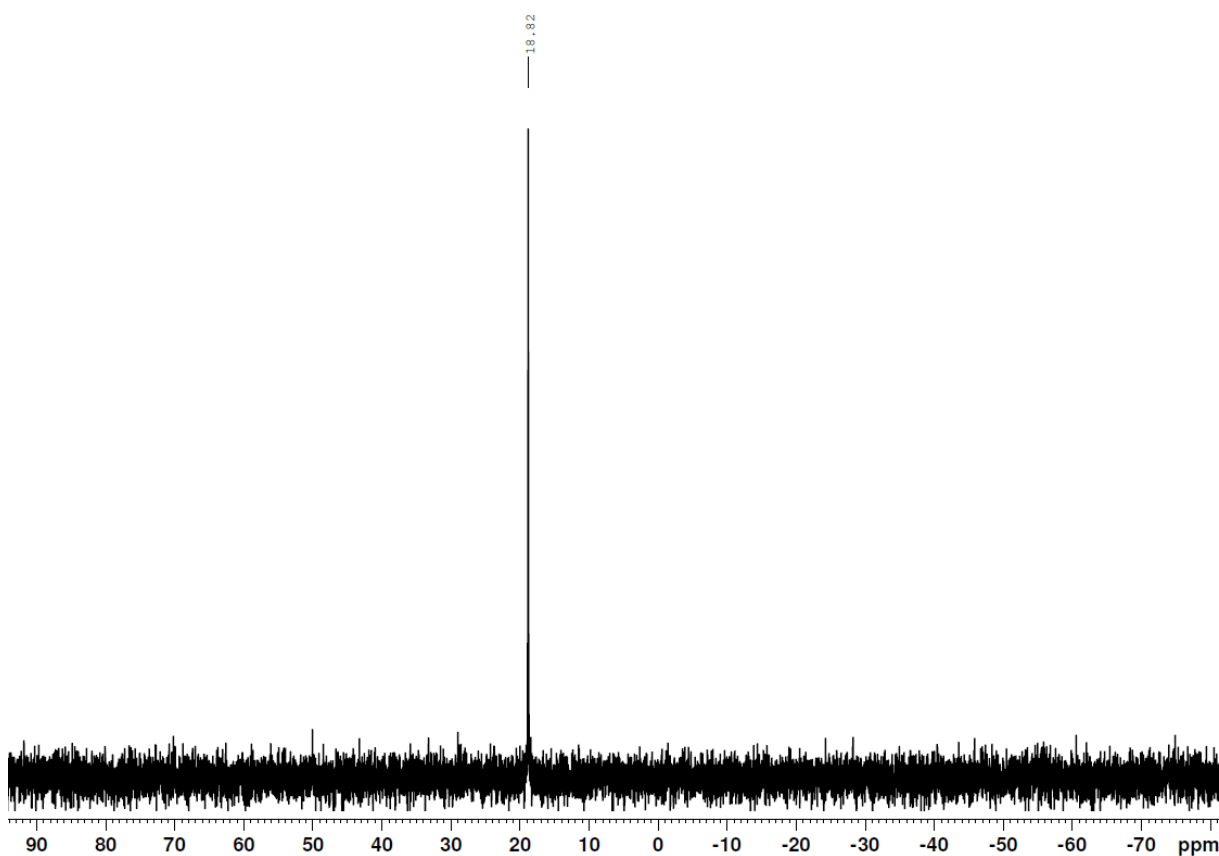
^1H NMR



^{13}C NMR



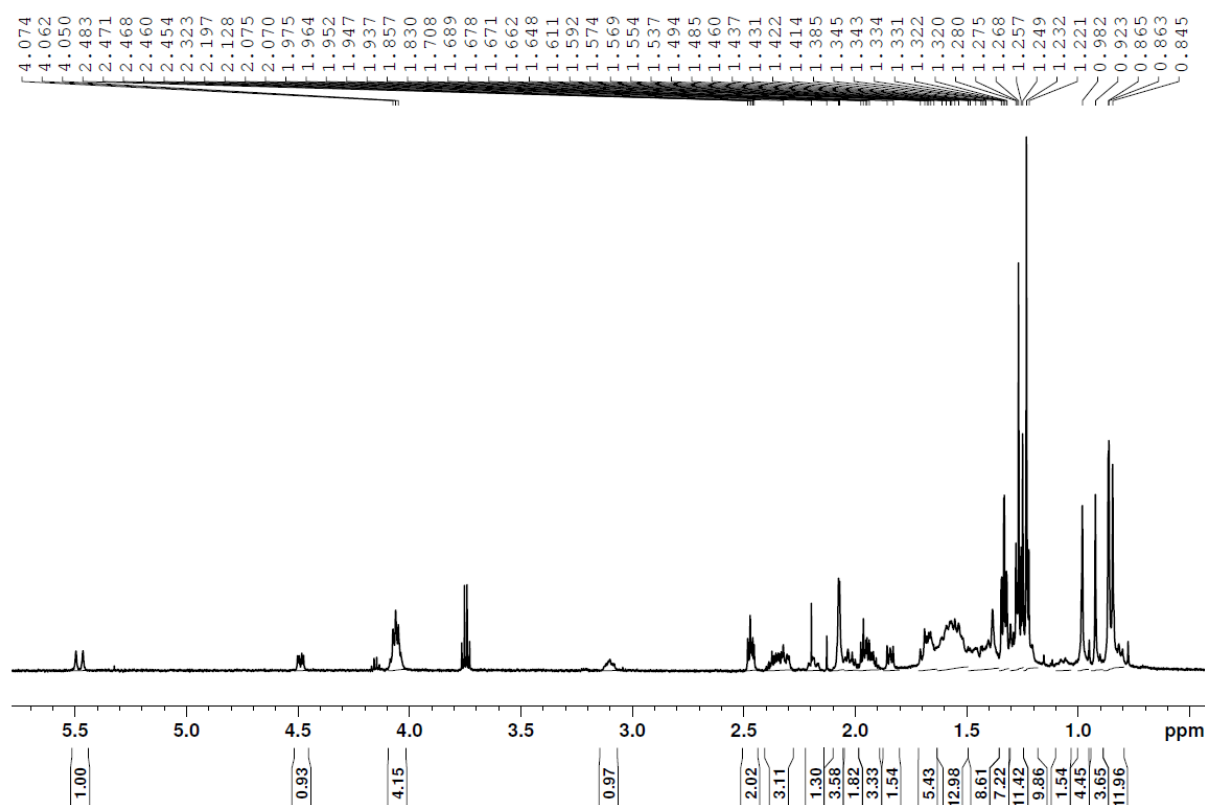
^{31}P NMR



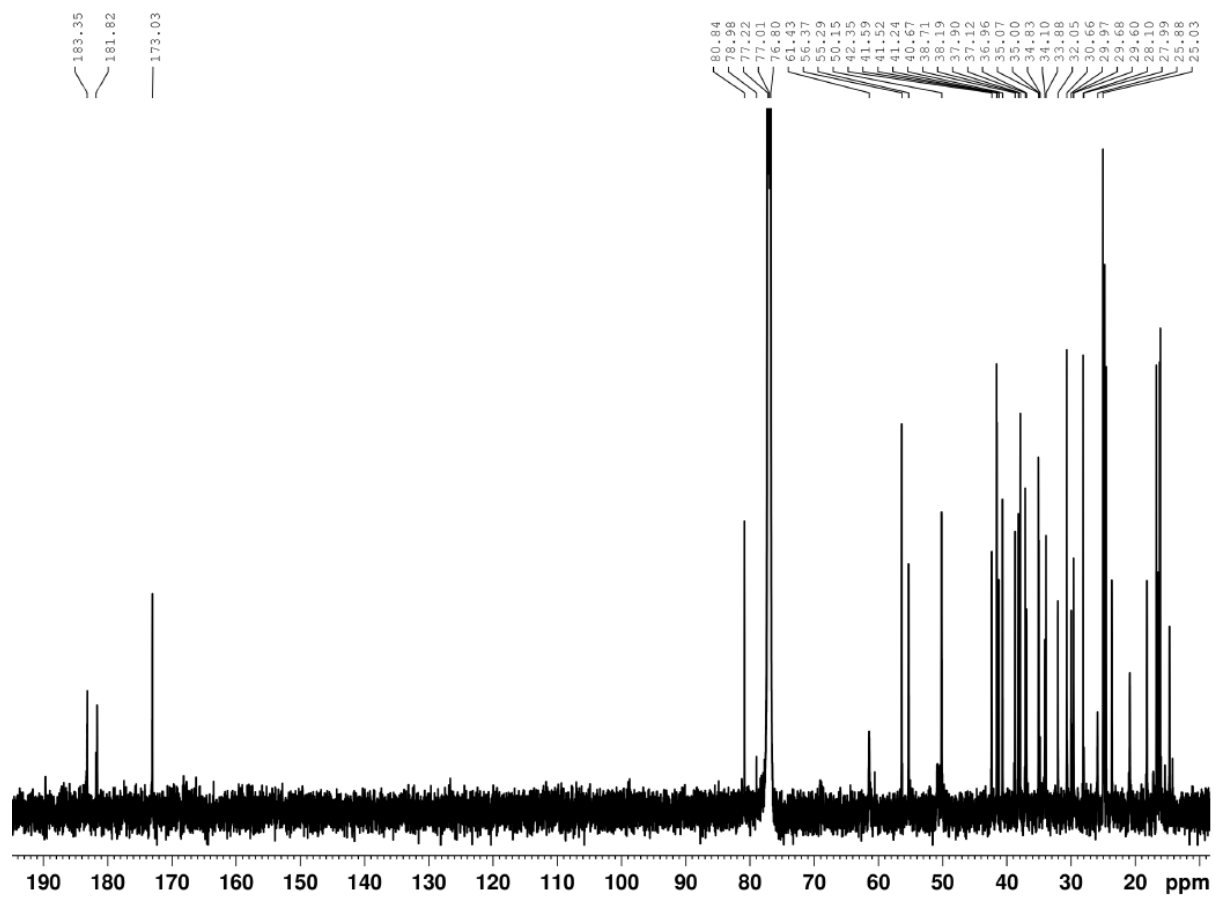
29-Diethoxyphosphoryl-3-O-(4',4'-dimethylglutaryl)betulinic acid 13c

Yield 32%; mp 141-146 °C; R_f = 0.30 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3647, 2945, 1716, 1220, 1028, 754; ^1H NMR (CDCl_3) δ (ppm): 5.48 (d, 1H, $J_{\text{H-P}}$ = 18.6 Hz, H29), 4.49 (m, 1H, H3), 4.06 (m, 4H, 2 x OCH_2CH_3), 3.10 (m, 1H, H19), 2.07 (s, 3H, CH_3), 1.20 – 2.50 (m, 27 H, CH, CH_2), 1.33 (m, 6H, 2 x OCH_2CH_3), 1.27 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.86 (s, 6H, 2x CH_3), 0.84 (s, 3H, CH_3), 0.70 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 183.3, 181.8, 173.0, 80.8, 61.4, 56.4, 55.3, 50.1, 42.3, 41.6, 41.5, 41.2, 40.7, 38.7, 38.2, 37.9, 37.1, 37.0, 35.0, 34.1, 33.9, 32.0, 30.7, 30.0, 29.7, 29.6, 28.1, 25.9, 25.0, 24.8, 24.5, 23.6, 20.8, 18.2, 16.4, 16.2, 16.1, 16.0, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): 18.7; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 733.4445; Found 733.4451.

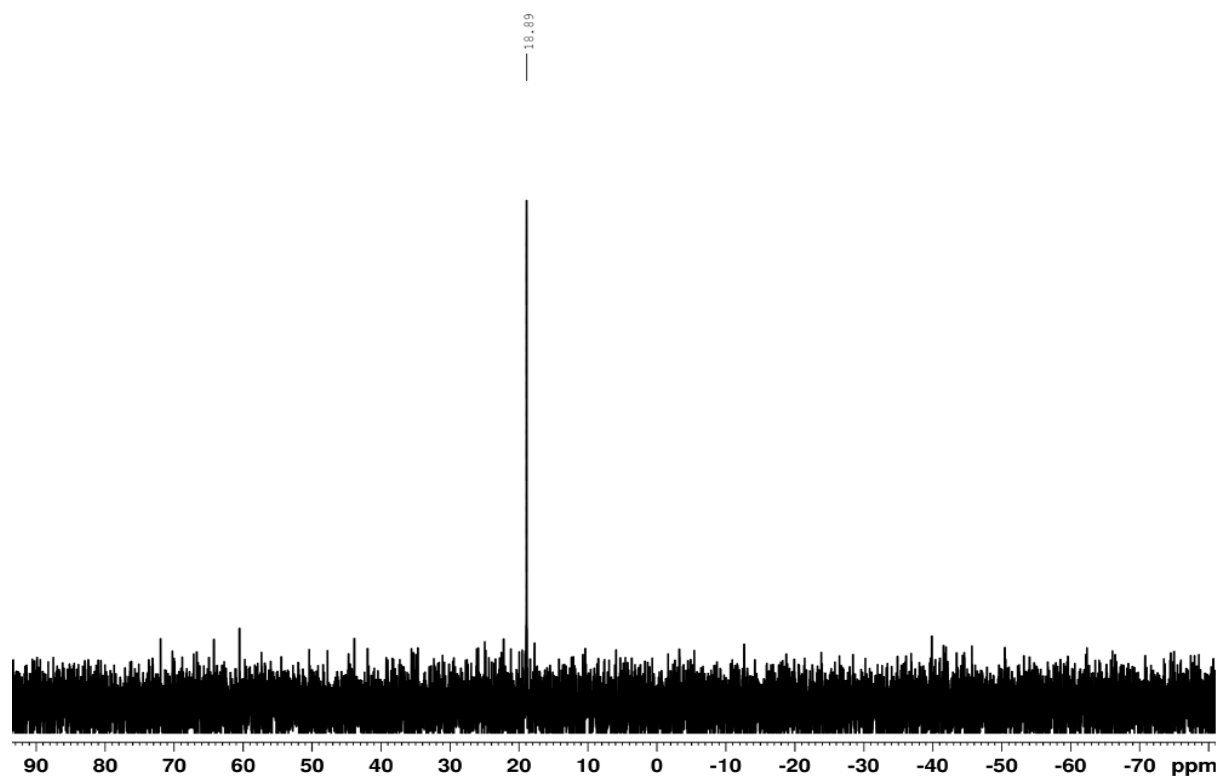
^1H NMR



^{13}C NMR



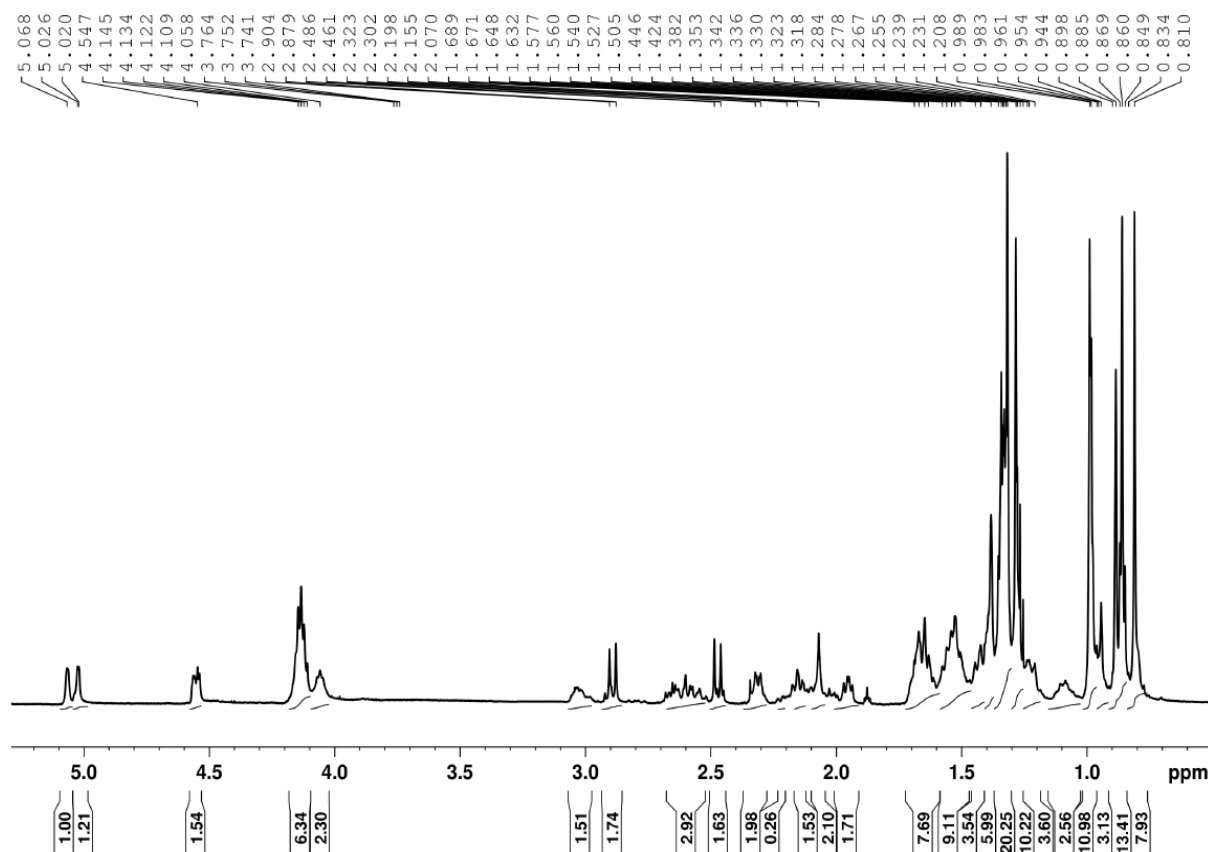
^{31}P NMR



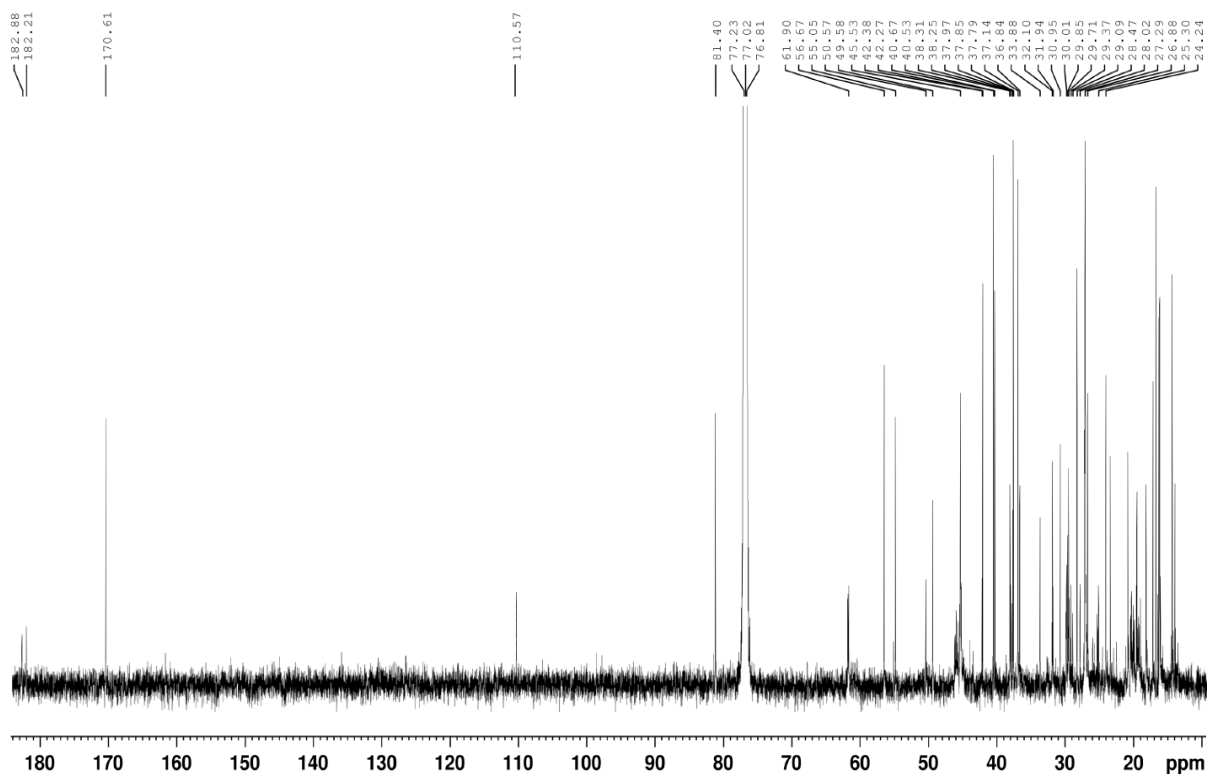
30-Diethoxyphosphoryl-3-O-(3',3'-dimethylsuccinyl)betulinic acid 14a

Yield 20%; mp 122-126 °C; R_f = 0.21 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3500, 2945, 1705, 1219, 1026, 752; ^1H NMR (CDCl_3) δ (ppm): 5.07 (m, 1H, H29), 5.03 (m, 1H, H29), 4.55 (m, 1H, H3), 4.13 (m, 4H, 2 x OCH_2CH_3), 3.13 (m, 1H, H19), 2.89 (d, 1H, J = 15.6 Hz, CH), 2.64 (m, 2H, H30), 2.48 (d, 1H, J = 15.6 Hz, CH), 0.80 – 2.40 (m, 23 H, CH, CH_2), 1.32 (m, 6H, 2 x OCH_2CH_3), 1.30 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.99 (s, 6H, CH_3), 0.90 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.78 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 182.8, 182.2, 170.6, 110.6, 81.4, 61.9, 61.8, 56.7, 50.6, 49.6, 42.4, 40.7, 40.5, 38.3, 37.9, 36.9, 33.9, 32.0, 30.9, 29.8, 28.5, 27.3, 26.9, 24.2, 23.6, 21.0, 19.7, 18.4, 17.4, 16.9, 16.6, 16.4, 14.5, 14.1; ^{31}P NMR (CDCl_3) δ (ppm): 27.9; HR-MS (APCI) m/z : $\text{C}_{40}\text{H}_{64}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 719.4288; Found 719.4276.

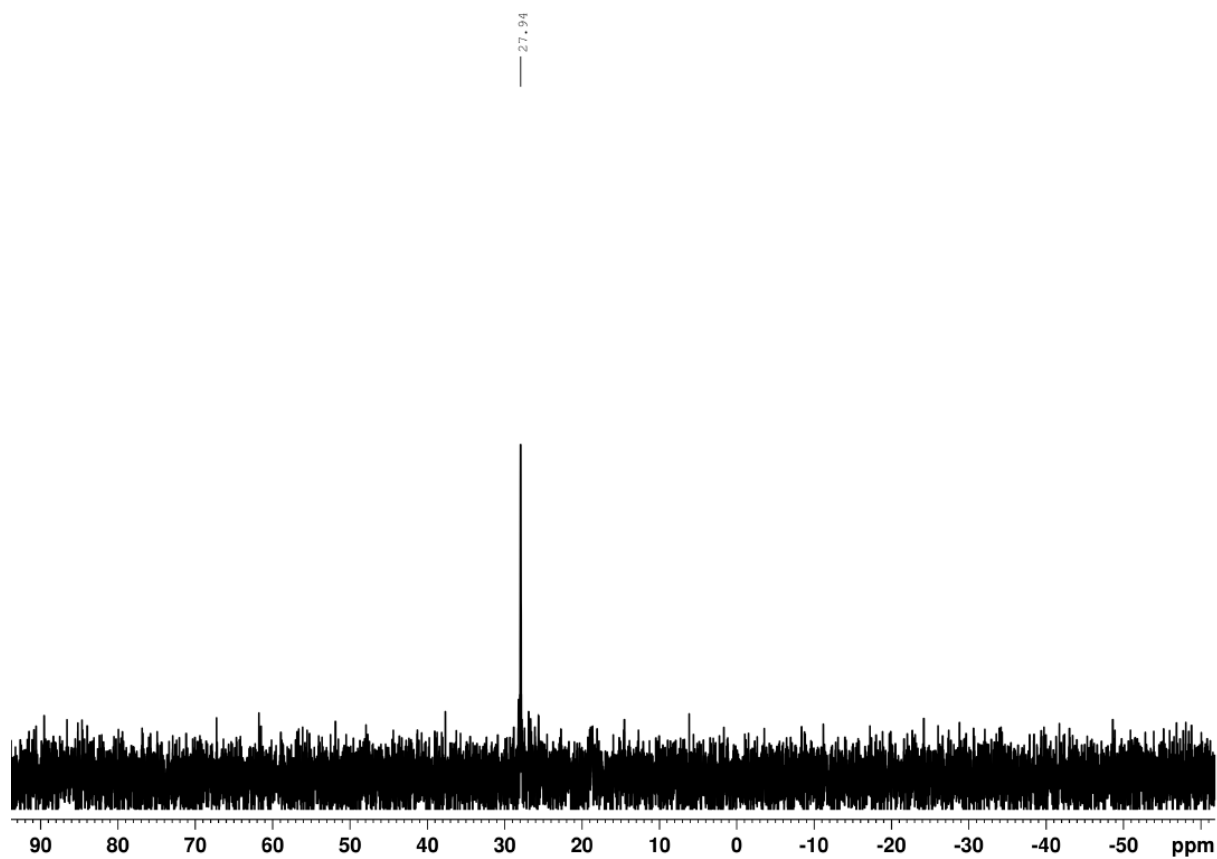
^1H NMR



^{13}C NMR



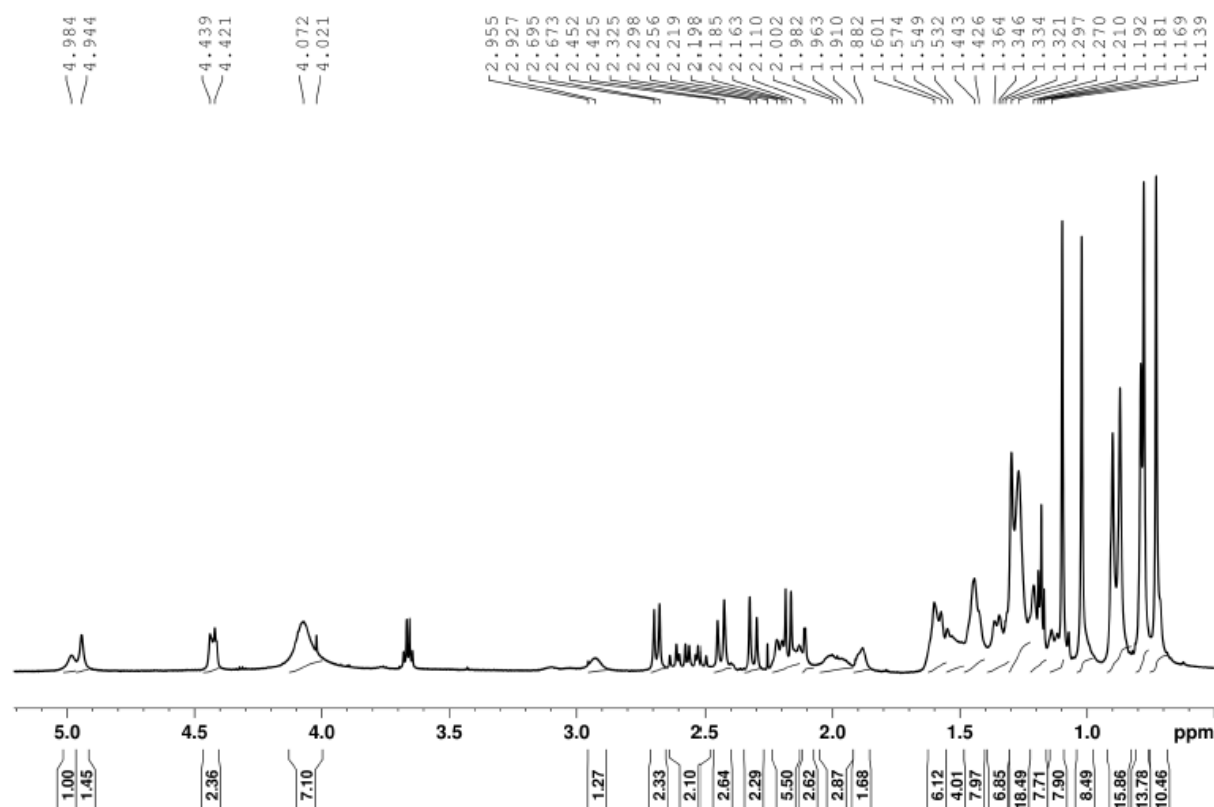
^{31}P NMR



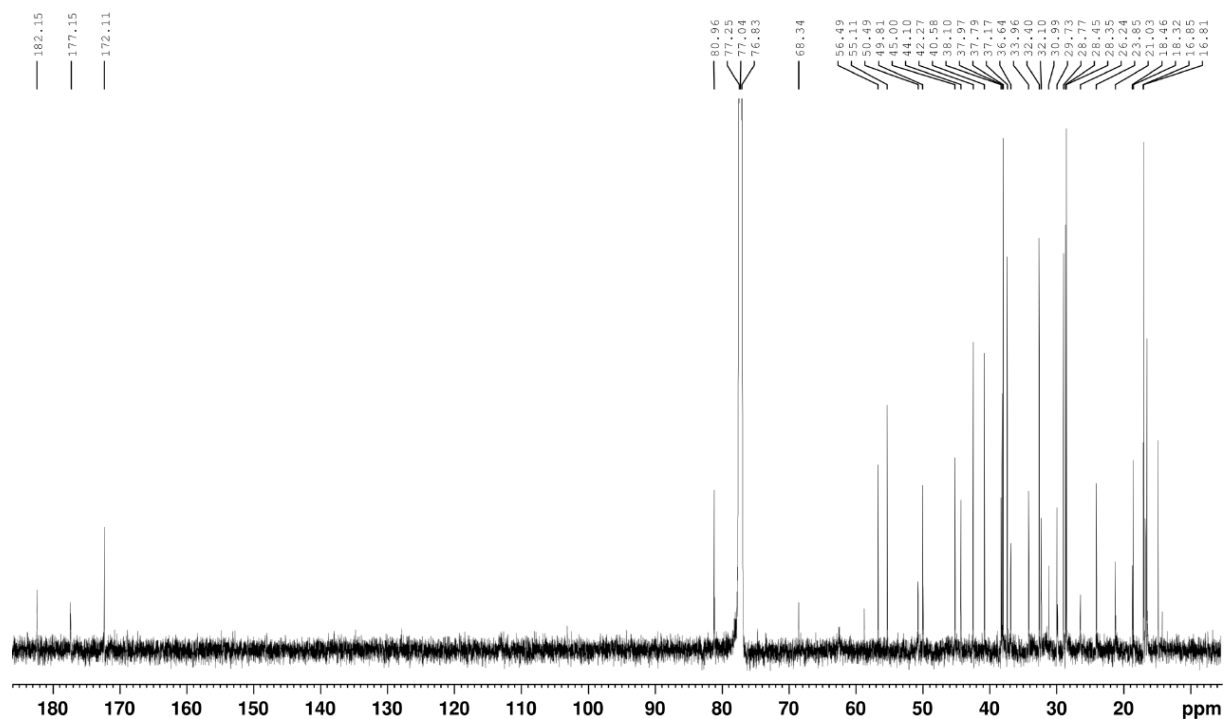
30-Diethoxyphosphoryl-3-O-(3',3'-dimethylglutaryl)betulinic acid 14b

Yield 27%; mp 129-131 °C; R_f = 0.22 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3325, 2947, 1701, 1728, 1221, 1028, 789; ^1H NMR (CDCl_3) δ (ppm): 4.98 (m, 1H, H29), 4.93 (m, 1H, H29), 4.43 (m, 1H, H3), 4.05 (m, 4H, 2 x OCH_2CH_3), 2.95 (m, 1H, H19), 2.68 (d, 1H, $J=13.2$ Hz, H4'), 2.59 (m, 2H, H30), 2.43 (d, 1H, $J=13.2$ Hz, H4'), 2.31 (d, 1H, $J=16.2$ Hz, H2'), 2.17 (d, 1H, $J=16.2$ Hz, H2'), 1.27 (m, 6H, 2 x OCH_2CH_3), 1.10 – 2.30 (m, 29H, CH, CH_2), 1.10 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.73 (s, 3H, CH_3), 0.70 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 182.1, 177.1, 172.1, 81.0, 68.3, 62.3, 58.6, 56.5, 55.1, 50.5, 49.8, 45.0, 44.1, 42.3, 40.6, 38.1, 38.0, 37.8, 37.2, 36.6, 34.0, 32.4, 34.1, 32.1, 31.0, 29.7, 28.8, 28.5, 28.3, 26.2, 23.9, 21.0, 18.3, 16.9, 16.8, 16.6, 16.3, 14.6; ^{31}P NMR (CDCl_3) δ (ppm): 28.0; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 733.4445; Found 733.4435.

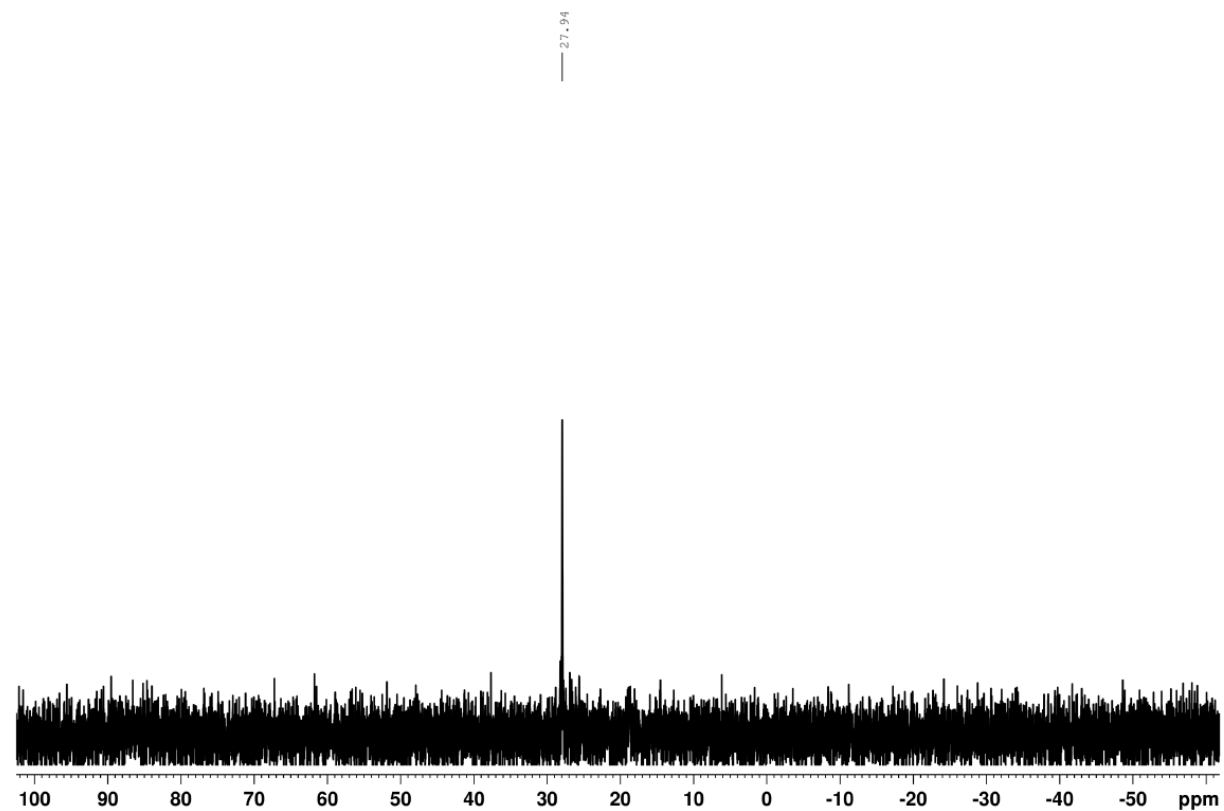
^1H NMR



^{13}C NMR



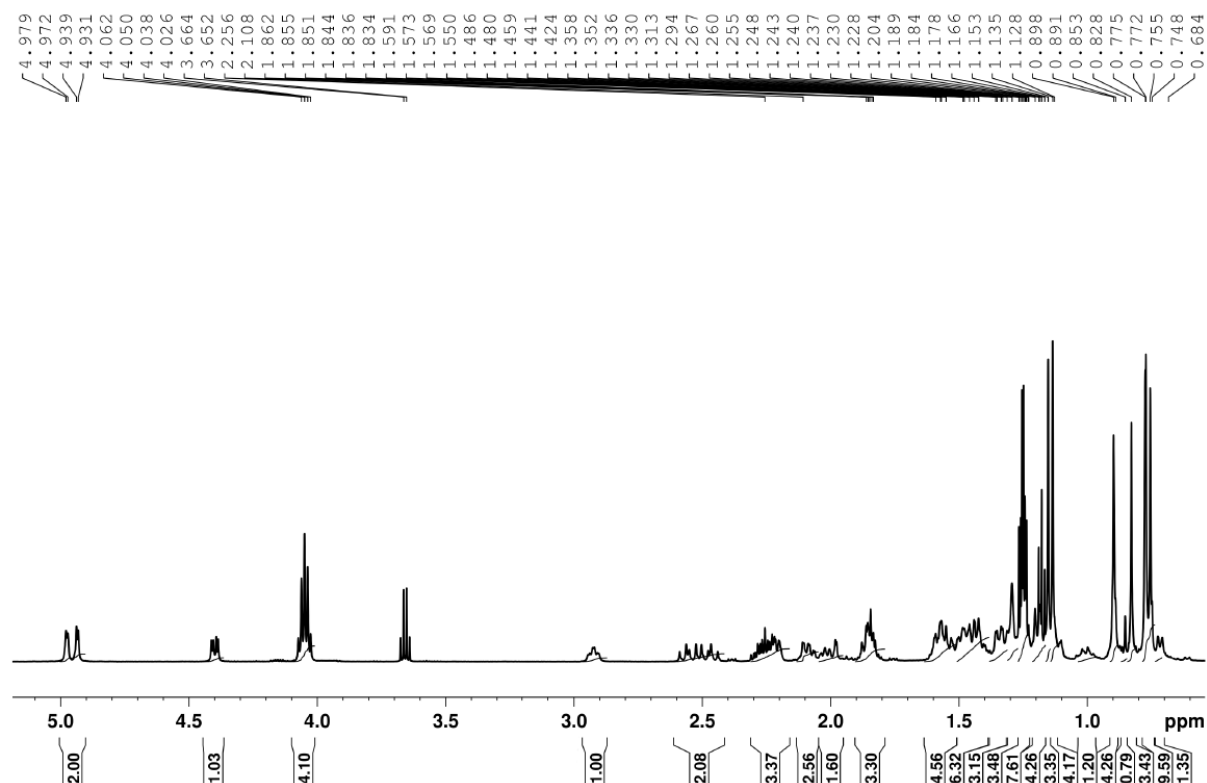
^{31}P NMR



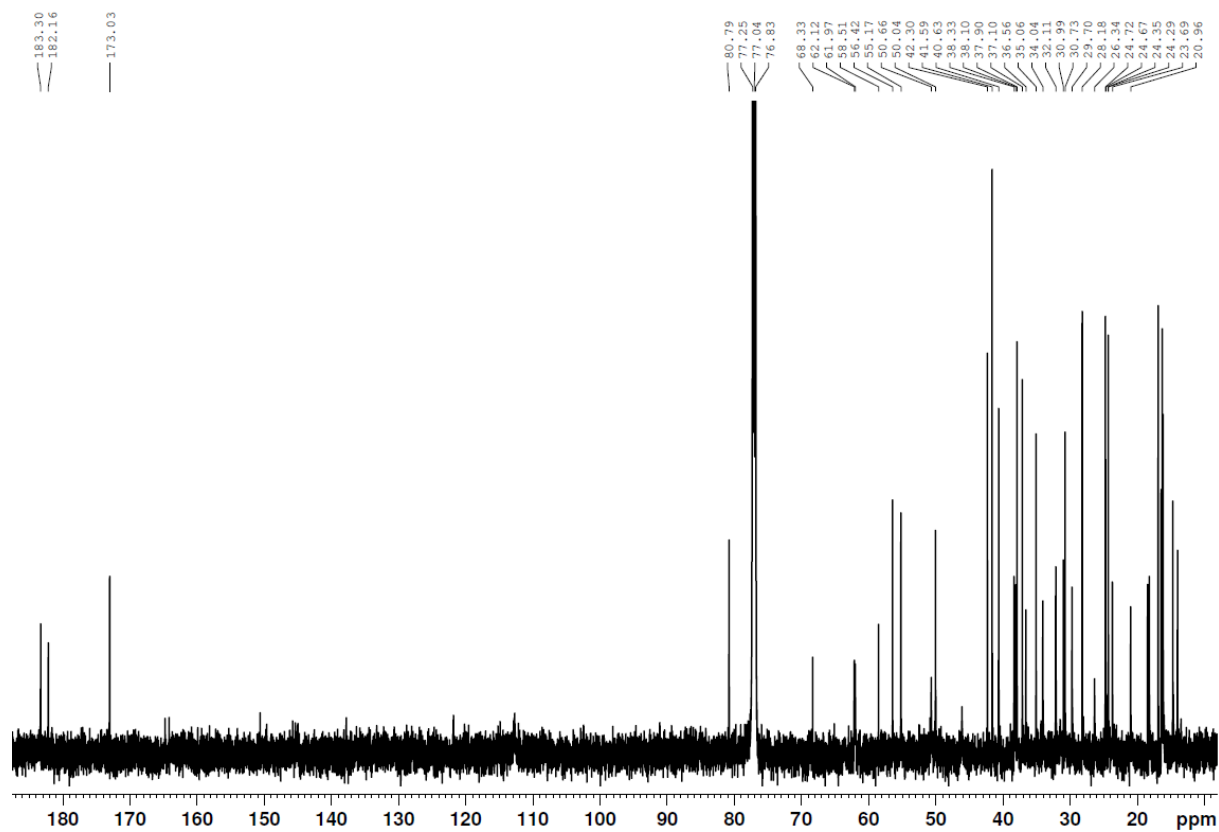
30-Diethoxyphosphoryl-3-O-(4',4'-dimethylglutaryl)betulinic acid 14c

Yield 26%; mp 119-124 °C; R_f = 0.28 (chloroform/ethanol, 15:1, v/v); IR (KBr) ν (cm^{-1}): 3543, 2945, 1705, 1219, 1026, 751; ^1H NMR (CDCl_3) δ (ppm): 4.98 (m, 1H, H29), 4.93 (m, 1H, H29), 4.90 (m, 1H, H3), 4.04 (m, 4H, 2 x OCH_2CH_3), 2.93 (m, 1H, H19), 2.5 (m, 2H, H30), 1.25 (m, 6H, 2 x OCH_2CH_3), 1.20 – 2.30 (m, 27H, CH, CH_2), 1.15 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.75 (s, 3H, CH_3), 0.72 (s, 3H, CH_3), 0.75 (m, 1H, H5); ^{13}C NMR (CDCl_3) δ (ppm): 183.3, 182.2, 173.0, 80.8, 68.3, 62.0, 61.9, 58.51, 56.4, 55.2, 50.7, 50.0, 42.3, 41.6, 40.6, 38.3, 38.1, 37.9, 37.1, 36.6, 35.1, 34.0, 32.1, 31.0, 30.7, 29.7, 28.2, 26.3, 24.7, 24.3, 23.7, 21.0, 18.2, 16.8, 16.4, 16.1, 16.0, 14.7; ^{31}P NMR (CDCl_3) δ (ppm): 28.0; HR-MS (APCI) m/z : $\text{C}_{41}\text{H}_{66}\text{O}_9\text{P}$ [(M-H) $^-$], Calc. 733.4445; Found 733.4451.

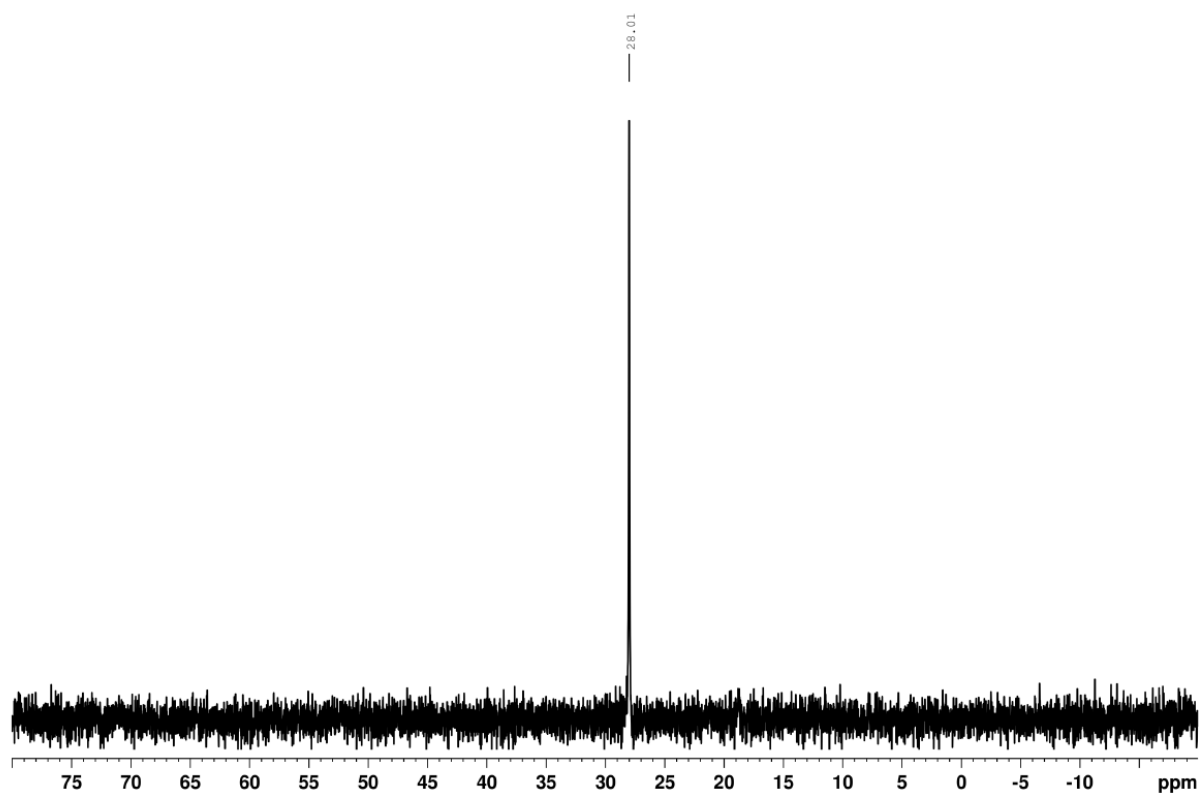
^1H NMR



^{13}C NMR



^{31}P NMR



Charts of changes in cytotoxicity of compounds in the tested concentration range

Figure S1

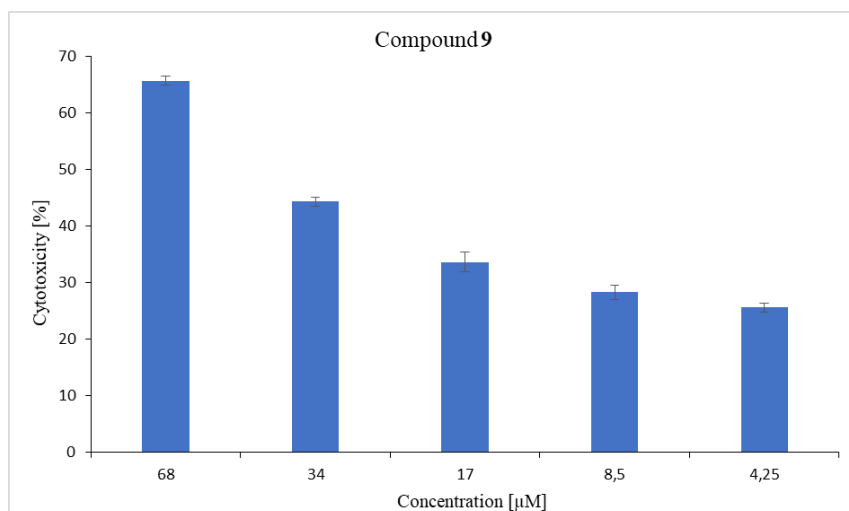


Figure S2

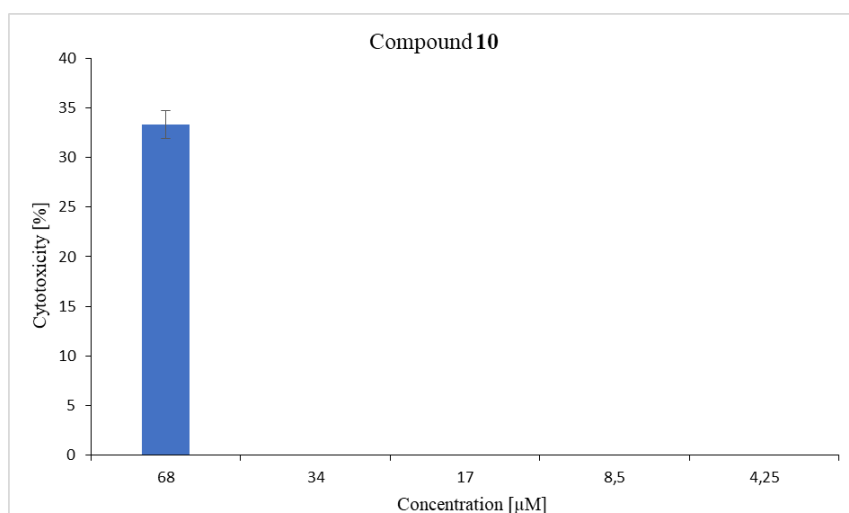


Figure S3

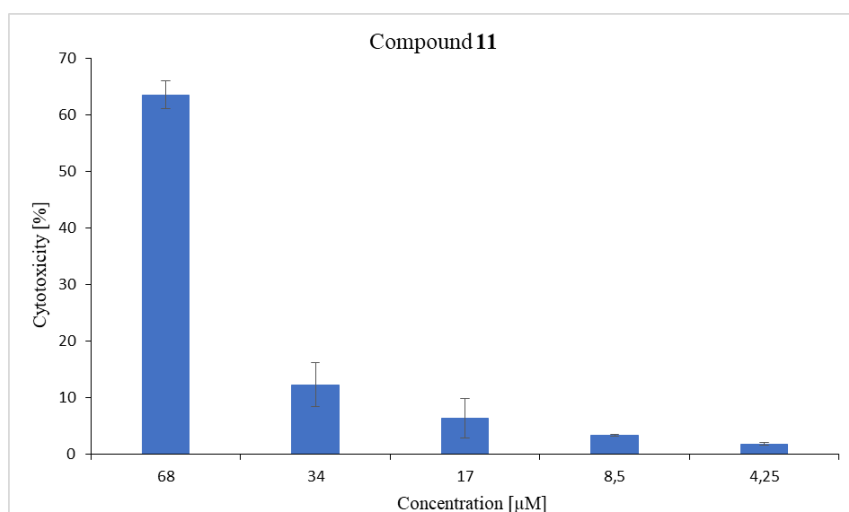


Figure S4

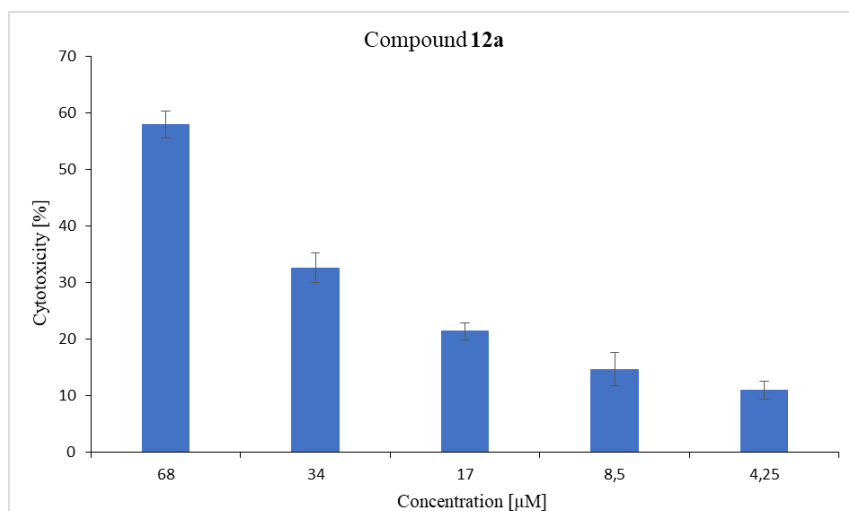


Figure S5

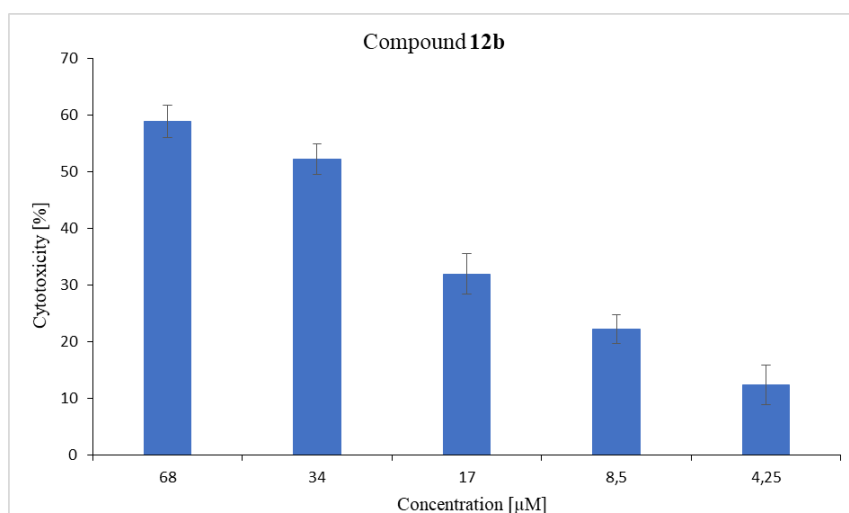


Figure S6

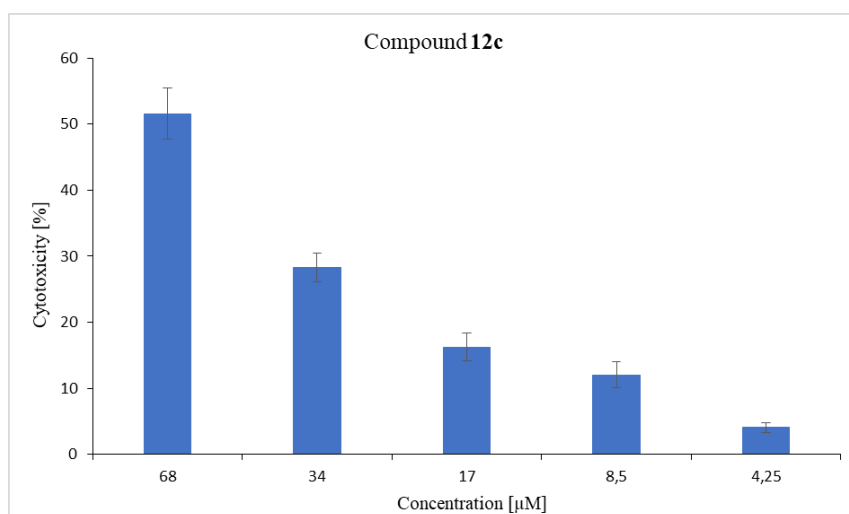


Figure S7

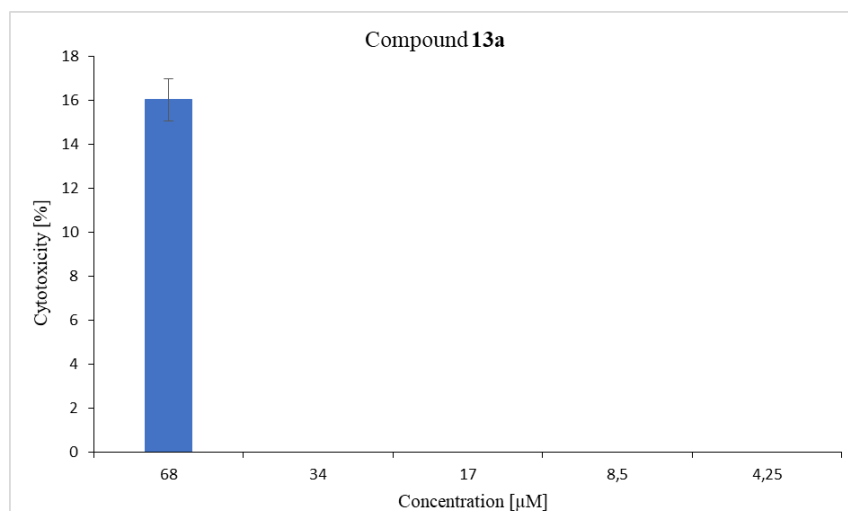


Figure S8

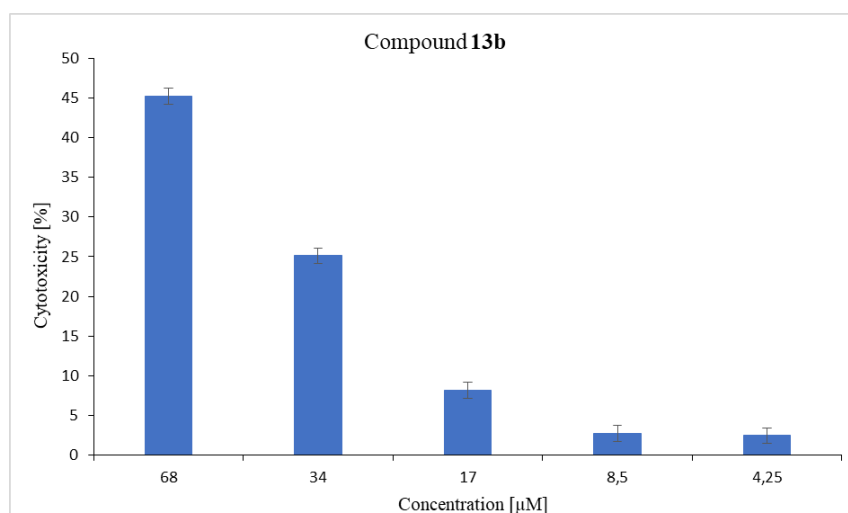


Figure S9

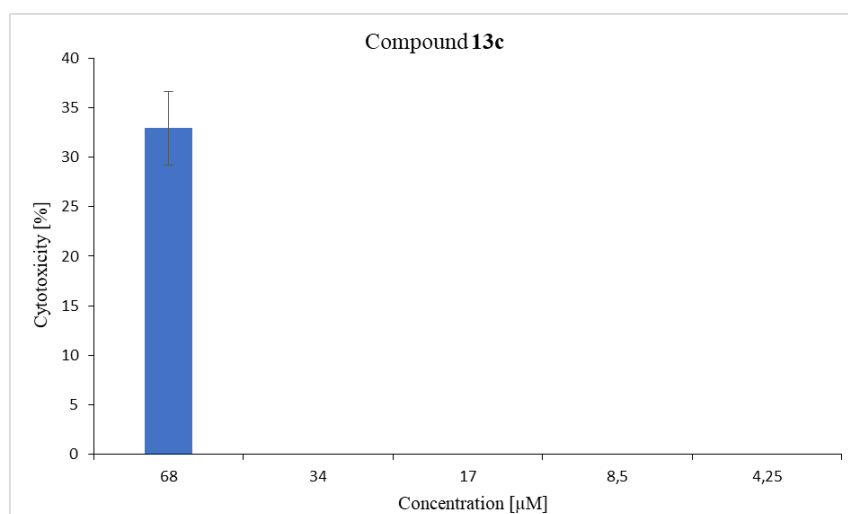


Figure S10

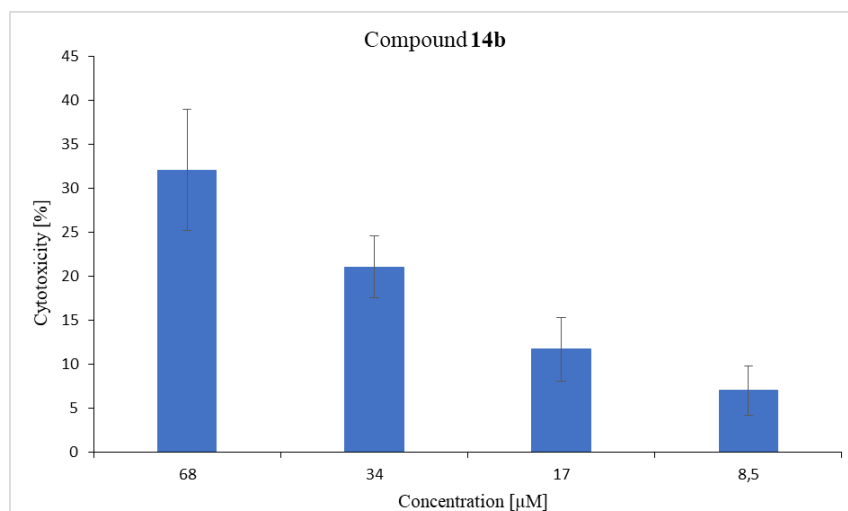


Figure S11

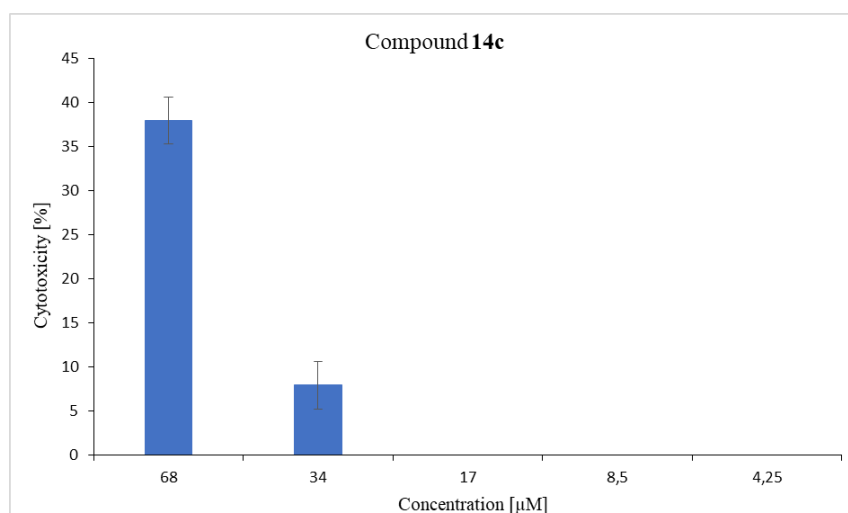


Figure S12

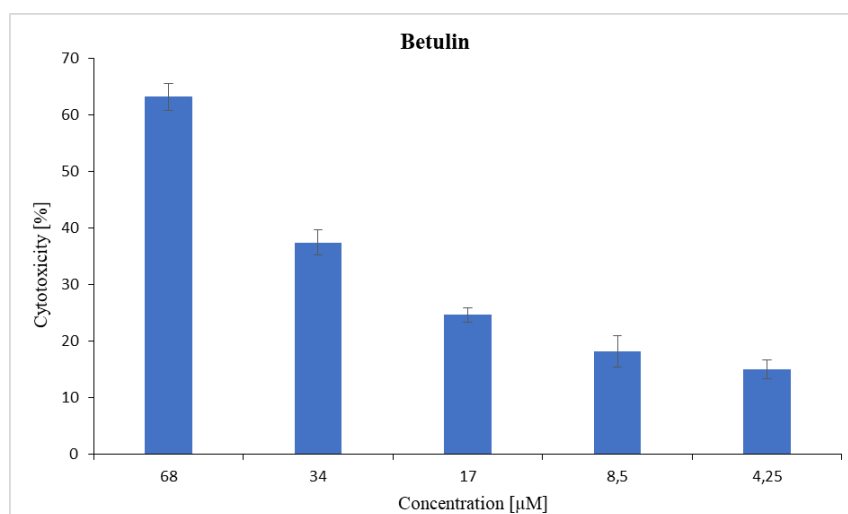


Figure S13

