Electronic Supplementary Information

An efficient oxa-Michael addition to diethyl vinylphosphonate under mild reaction conditions

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1. Experimental Section

1.1. Methods.

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa, and compounds were dried at 2 kPa over P_2O_5. TLC was performed on TLC aluminium sheets – silica gel 60 F_{254} (Merck), chromatographic systems are described in the main text. Column chromatography was performed on silica gel 230-400 mesh, 60 Å (Merck). ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 600 spectrometer (^{1}H at 600 MHz and ^{13}C at 151 MHz) and/or Avance 500 spectrometer (500 Mhz and 126 MHz) in $CDCl_3$ or CD_3OD and referred to TMS or residual solvent signal. The numbering system for assignment of NMR signals is undermentioned. GC/MS spectra were obtained from Agilent 5975B MSD coupled to 6890N gas chromatograph. Mass range was to 1050 u. and GC was equipped with split/splitless injector and HP-5 capillary column. Mass spectra were measured on Q-Tof micro (Waters) using ESI technique. Optical rotations were measured on an AUTOPOL IV polarimetr (Rudolph research analytical) at 20 °C; $[\alpha]_D$ values are given [10^{-1} deg cm^2 g^{-1}] and concentrations *c* are [g/100 ml].

1.2. Materials and solvents.

Starting compounds were purchased from Sigma-Aldrich (Prague, Czech Republic). Diethyl vinylphosphonate (**7**) was purchased from Epsilon-Chemie (Guipavas, France). *Tert*-Butanol was stored over molecular sieves (4 Å). Racemic 1-fluoro-3-(trityloxy)propan-2-ol (**1**) was prepared according to literature.[1]

1.3. General procedures for the oxa-Michael addition to diethyl vinylphosphonate (DEVP).

Method A (for mono-alkylations): The corresponding alcohol (1 mmol) and cesium carbonate (325 mg, 1 mmol) were placed into a reaction vial (10 mL). Dry *tert*-butanol (1 mL) was added and the vial was sealed with a septum. The mixture was vigorously stirred for 15 min. DEVP (234 μL, 1.5 mmol) was added and the mixture was stirred for another 24 hours. The reaction was quenched with saturated aqueous NH_4Cl solution. Water phase was extracted with EtOAc (3 x 20 mL) or, in case of the nucleoside analogs with $CHCl_3$ (3 x 20 mL. Organic phase was collected and dried over Na_2SO_4. The solution was filtered and evaporated in *vacuo* (40 °C, 2 mbar). Crude compound was purified by flash chromatography (hexane/EtOAc or $CHCl_3$/MeOH).

Method B (for bis-alkylations): Alcohol (1 mmol) and cesium carbonate (650 mg, 2 mmol) was placed into a reaction vial (10 mL). Dry *tert*-butanol (1 mL) was added and the vial was sealed with a septum. The mixture was vigorously stirred for 15 min. DEVP (390 μL, 2.5 mmol) was added and the mixture was stirred for another 24 hours. Reaction was quenched by saturated aqueous NH_4Cl. Water phase was 3 x extracted with EtOAc (20 mL in case of nucleoside analogs $CHCl_3$ was used). Organic phase was collected and dried over Na_2SO_4. The solution was filtered and evaporated in *vacuo* (40 °C, 2 mbar). Crude compounds were purified by flash chromatography (Hexane/EtOAc or $CHCl_3$/MeOH).

Diethyl 2-(1,3-bis(benzyloxy)propan-2-yloxy)ethylphosphonate (19).

Method A: From compound **9** (545 mg, 2 mmol) was obtained compound **19** (751 mg, 86 %). ESI [$M+Na^+$] 459.2 (100). HRMS (ESI) calcd for $C_{23}H_{33}O_6NaP$ [$M+Na^+$]: 459.1907, found: 459.1905. ^1H NMR ($CDCl_3$): 7.34-7.24 (m, 10H, 2‘, 3‘, 4‘); 4.56-

4.48 (m, 4H, CH_2-1'); 4.10-4.00 (m, 4H, CH_2-O-P); 3.86 (m, 2H, **CH_2**-CH_2-P); 3.69 (m, 1H, 2); 3.61-3.50 (m, 4H, 1, 3); 2.13 (dm, $J_{C\text{-}H\text{-}P}$ = 18.6, CH_2-P); 1.28 (t, 6H, $J_{CH3\text{-}CH2}$ = 7.1, CH_3); ^{13}C NMR ($CDCl_3$): 138.05 (1'); 128.21 (3'); 127.48 (2'); 127.46 (4'); 78.10 (2); 73.27 (**CH_2**-1'); 69.97 (1, 3); 64.20 (**CH_2**-CH_2-P); 61.45 (d, $J_{C\text{-}O\text{-}P}$ = 6.3, CH_2-O-P); 27.27 (d, $J_{C\text{-}P}$ = 138.5, CH_2-P); 16.26 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.1, CH_3); For $C_{23}H_{33}O_6P$ (436.48) calcd: C, 63.29; H, 7.62; P, 7.10. Found: C, 63.09; H, 7.77; P, 6.94.

Diethyl 2-(1-(benzyloxy)-3-(trityloxy)propan-2-yloxy)ethylphosphonate (20).

Method A: From compound **10** (212 mg, 0.5 mmol) was obtained compound **20** (162 mg, 55 %). ESI [M+Na^+]: 611.0 (100). HRMS (ESI) calcd for $C_{35}H_{41}O_6NaP$ [M+Na^+]: 611.2533, found: 611.2530. This compound was fully characterised after the deprotection of the trityl group (80 % acetic acid, reflux, 2 h) as **diethyl 2-(1-(benzyloxy)-1-hydroxypropan-2-yloxy)ethylphosphonate:** 97 mg (53 % from compound **10**). ESI [M+Na^+]: 369 (100). HRMS (ESI) calcd for $C_{16}H_{28}O_6P$ [M+H^+]: 347.1618, found: 347.1617. ^{1}H NMR ($CDCl_3$): 7.27-7.35 (m, 5H, 2', 3', 4'); 4.53 (s, 2H, CH_2-1'); 4.16-4.05 (m, 4H, **CH_2**-CH_3); 3.98 (m, 1H, **CH_2**-CH_2-P); 3.81 (m, 1H, **CH_2**-CH_2-P); 3.72 (dd, 1H, J_{gem} = 11.7, $J_{3a\text{-}2}$ = 2.8, 3a); 3.62 (m, 1H, 2); 3.59-3.49 (m, 3H, 3b, 1); 2.16-2.02 (m, 2H, CH_2-P); 1.32 (t, 3H, $J_{CH3\text{-}CH2}$ = 7.1, CH_3); 1.31 (t, 3H, $J_{CH3\text{-}CH2}$ = 7.1, CH_3). ^{13}C NMR ($CDCl_3$): 137.98 (1'); 128.34 (3'); 127.62 (4'); 127.54 (2'); 80.02 (2); 73.40 (CH_2-1'); 70.19 (1); 63.93 (d, $J_{C\text{-}C\text{-}P}$ = 5.9, **CH_2**-CH_2-P); 62.17 (3); 61.87 (d, $J_{C\text{-}O\text{-}P}$ = 6.4, **CH_2**-CH_3); 61.57 (d, $J_{C\text{-}O\text{-}P}$ = 6.5, **CH_2**-CH_3); 27.08 (d, $J_{C\text{-}P}$ = 141.5, CH_2-P); 16.32 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.2, CH_3). For $C_{16}H_{29}O_7P$ (monohydrate) (364.37) calcd: C, 52.74; H, 8.02; P, 8.50. Found: C, 52.95; H, 7.98; P, 8.40.

Diethyl 2-(1-phenylpropan-2-yloxy)ethylphosphonate (21).

Method A: From compound **11** (272 mg, 2 mmol) was obtained compound **21** (529 mg, 88 %). ESI [M+Na^+] 323.1 (100). HRMS (ESI) calcd for $C_{15}H_{25}O_4NaP$ [M+Na^+]: 323.1383, found: 323.1382. ^{1}H NMR ($CDCl_3$): 7.33-7.17 (m, 5H, 2', 3', 4'); 4.13-4.02 (m, 4H, **CH_2**-CH_3); 3.73 (m, 1H, CH_{2a}-O-2); 3.66-3.57 (m, 2H, CH_{2b}-O-2, 2); 2.90 (dd, 1H, J_{gem} = 13.6, $J_{1a\text{-}2}$ = 6.3, 1a); 2.62 (dd, 1H, J_{gem} = 13.6, $J_{1b\text{-}2}$ = 6.7, 1b); 2.09-1.99 (m, 2H, CH_2-P); 1.31 (m, 6H, CH_2-**CH_3**); 1.13 (d, 3H, $J_{3\text{-}2}$ = 6.2, 3); ^{13}C NMR ($CDCl_3$): 138.56 (1'); 129.20 (2'); 127.98 (3'), 125.89 (4'); 76.74 (2); 62.26 (**CH_2**-O-2); 61.33 (m, **CH_2**-CH_3); 42.75 (1);

27.01 (d, $J_{C\text{-}P}$ = 138.7, CH_2-P); 19.24 (3); 16.19 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.2, CH_2-**CH_3**); For $C_{15}H_{25}O_4P$ (300.33) calcd: C, 59.99; H, 8.39; P, 10.31. Found: C, 59.72; H, 8.28; P, 10.44.

Diethyl {[(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-yl)oxy]ethyl}phosphonate (22)

Method A: From compound **12** (520 mg, 2 mmol) was obtained compound **22** (429 mg, 51 %). ESI [M+Na^+] 447 (100). HRMS (ESI) calcd for $C_{18}H_{33}O_9NaP$ [M+Na^+]: 447.1754, found: 447.1753. ^{1}H NMR ($CDCl_3$): 5.85 (d, 1H, $J_{1\text{-}2}$ = 3.7, 1); 4.59 (d, 1H, $J_{2\text{-}1}$ = 3.7, 2); 4.28 (dt, 1H, $J_{5\text{-}6b}$ = 5.8, $J_{5\text{-}6a}$ and $J_{5\text{-}4}$ = 8.2, 5); 4.14-4.04 (m, 6H, **CH_2**-CH_3, 4, 6a); 3.99 (dd, 1H, J_{gem} = 8.6, $J_{6b\text{-}5}$ = 5.5, 6b), 3.91-3.76 (m, 3H, **CH_2**-CH_2-P, 3); 2.14-2.07 (m, 2H, P-CH_2); 1.49 and 1.42 and 1.35 and 1.31 (4 x s, 4 x 3H, CH_3-*i*Pr); 1.33 (m, 6H, CH_2-**CH_3**); ^{13}C NMR ($CDCl_3$): 111.80 (1); 109.00 (5); 105.22 (1); 82.39 (2); 82.26 (3); 80.95 (4); 72.31 (5); 67.26 (6); 64.52 (**CH_2**-CH_2-P); 61.63 (m, **CH_2**-CH_3); 27.05 (d, $J_{C\text{-}P}$ = 139.7, CH_2-P); 26.82 and 26.77 and 26.18 and 25.37 (4x CH_3); 16.40 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.2, CH_2-**CH_3**); For $C_{18}H_{33}O_9P$ (424.42) calcd: C, 50.94; H, 7.84; P, 7.30. Found: C, 50.87; H, 7.69; P, 7.43.

Diethyl 2-(2-phenyl-1,3-dioxan-5-yloxy)ethylphosphonate (23).

Metod A: From compound **13** (1.80 g, 10 mmol) was obtained compound **23** (1.70 g, 49 %). ESI [M+Na^+] 367 (100). HRMS (ESI) calcd for $C_{16}H_{25}O_6NaP$ = 367.1281, found: 367.1281. ^{1}H NMR ($CDCl_3$): 7.51 (m, 2H, 2‘); 7.32-7.38 (m, 3H, 3‘,4‘); 5.56 (s, 1H, 2); 4.33-4.37 (m, 2H, **4,6a**); 4.05-4.18 (m, 6H, **CH_2**-CH_3, 4,6b); 3.82-3.87 (m, 2H, **CH_2**-CH_2-P); 3.34 (p, 1H, $J_{5\text{-}4}$ = $J_{5\text{-}6}$ = 1.7, 5); 2.22 (dm, 2H, $J_{H\text{-}C\text{-}P}$ = 18.5, **CH_2**-P); 1.32 (t, 6H, J = 7.0, CH_3). ^{13}C NMR ($CDCl_3$): 138.02 (1’); 128.83 (4’); 128.13 (3’); 126.05 (2’); 101.19 (2); 71.11 (5); 68.85 (4,6); 62.92 (**CH_2**-CH_2-P); 61.66 (d, $J_{C\text{-}O\text{-}P}$ = 6.3, P-O-**CH_2**); 27.24 (d, $J_{C\text{-}P}$ = 138.9, **CH_2**-P); 16.38 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.1, **CH3**).

Diethyl 2-(4-hydroxy-4-methylpentan-2-yloxy)ethylphosphonate (24).

Method B: From compound **14** (236 mg, 2 mmol) was obtained compound **24** (252 mg, 45 %). ESI [M+Na^+] 305.1 (100). HRMS (ESI) calcd for $C_{12}H_{27}O_5NaP$ [M+Na^+]: 305.1488, found: 305.1487. ^{1}H NMR ($CDCl_3$): 4.08 (m, 4H, **CH_2**-CH_3); 3.88-3.77 (m, 2H, 2, **CH_{2a}**-CH_2-P); 3.53 (m, 1H, **CH_{2b}**-CH_2-P); 2.11-.1.97 (m, 2H, CH_2-P); 1.73 (dd, 1H, J_{gem} = 14.7, J_{3a-2} = 10.7, 3a); 1.47 (dd, J_{gem} = 14.7, J_{3b-2} = 2.6, 3b); 1.33 (2 x t, 6H, $J_{CH3-CH2}$ = 7.1, CH_2-**CH_3**); 1.25 and 1.19 (2 x s, 2 x 3H, 5); 1.18 (d, 3H, J_{1-2} = 6.0, 1); ^{13}C NMR ($CDCl_3$): 74.08 (2), 69.87 (4); 61.89 (d, J_{C-C-P} = 1.7, **CH_2**-CH_2-P); 61.69 (m, **CH_2**-CH_3), 48.96 (3); 31.00 and 28.13 (5); 27.27 (d, J_{C-P} = 140.5, CH_2-P); 19.70 (1); 16.36 (m, CH_2-**CH_3**); For $C_{12}H_{27}O_5P$ (282.31) calcd: C, 51.05; H, 9.64; P, 10.97. Found: C, 50.84; H, 9.62; P, 11.05.

3-Benzyloxy-1,2-bis[(diethoxyphosphoryl)ethoxy]propane (25).

Method B: From compound **15** (364 mg, 2 mmol) was obtained compound **25** (569 mg, 56 %). ESI [M+Na^+] 533.2 (100). HRMS (ESI) calcd for $C_{22}H_{40}O_9NaP_2$ [M+Na^+]: 533.2040, found: 533.2038. ^{1}H NMR ($CDCl_3$): 7.36-7.26 (m, 5H, 2‘, 3‘, 4‘); 4.53 (s, 2H, CH_2-1‘); 4.13-4.04 (m, 8H, **CH_2**-CH_3); 3.84 (m, 2H, **CH_2**-O-2); 3.63 (m, 2); 3.58-3.48 (m, 4H, 1, 3); 2.96 (m, 2H, **CH_2**-O-1), 2.16-2.05 (4H, CH_2-P); 1.33-1.29 (m, 12H, CH_2-**CH_3**); ^{13}C NMR ($CDCl_3$): 138.04 (C-1‘); 128.29 (C-3‘); 127.56 (C-4‘); 127.53 (C-2‘); 77.98 (C-2); 73.33 (**CH_2**-1‘); 70.62 (C-1); 69.78 (C-3); 65.28 (**CH_2**-O-1); 64.27 (**CH_2**-O-2); 61.51 (m, **CH_2**-CH_3); 27.30 (d, J_{C-P} = 138.6, **CH_2**-CH_2-O-2); 26.88 (d, J_{C-P} = 139.4, **CH_2**-CH_2-O-1); 16.34 (m, CH_2-**CH_3**); For $C_{22}H_{40}O_9P_2$ (510.50) calcd: C, 51.76; H, 7.90; P, 12.13; Found: C, 50.60; H, 7.78; P, 12.35.

9-{3-[(Diethoxyphosphoryl)ethoxy]-2-hydroxypropyl}adenine (26).

Method A: From compound **16** (105 mg, 0.5 mmol) was obtained compound **26** (22 mg, 12 %). ESI [M+Na^+] 396 (100). HRMS (ESI) calcd for $C_{14}H_{25}O_5N_5P$ [M+H^+]: 374.1588, found: 374.1587. ^{1}H NMR (CD_3OD): 8.20 (s,

1H, 2); 8.12 (s, 1H, 8); 4.40 (dd, 1H, J_{gem} = 14.2, $J_{1'a\text{-}2'}$ = 3.9, 1'a); 4.23 (dd, 1H, J_{gem} = 14.2, $J_{1'b\text{-}2'}$ = 7.8, 1'b); 4.15-4.07 (m, 5H, **CH_2**-CH_3, 2'); 3.75-3.68 (m, 2H, 4'); 3.46-3.52 (m, 2H, 3'); 2.16 (dt, 2H, $J_{5'\text{-}4'}$ = 7.0, $J_{5'\text{-}P}$ = 18.2, 5'); 1.33 (t, 6H, $J_{CH3\text{-}CH2}$ = 7.0, CH_2-**CH_3**). ^{13}C NMR ($CDCl_3$): 157.22 (6); 153.59 (2); 150.91 (4); 143.69 (8); 119.84 (5); 73.58 (3'); 69.53 (2'); 66.21 (d, $J_{4'\text{-}P}$ = 2.9, 4'); 63.35 (d, $J_{CH2\text{-}P}$ = 6.5, **CH_2**-CH_3); 47.89 (1'); 27.10 (d, $J_{5'\text{-}P}$ = 140.3, 5'); 16.71 (d, $J_{CH3\text{-}P}$ = 6.1, CH_2-**CH_3**). For $C_{14}H_{24}N_5O_5P$ (373.34) calcd: C, 45.04; H, 6.48; N, 18.76; P, 8.30. Found: C, 45.07; H, 6.64; N, 18.48; P, 8.13.

9-{3-[(Diethoxyphosphoryl)ethoxy]-2-hydroxy-2-methylpropyl}adenine (27).

Method A: From compound **17** (112 mg, 0.5mmol) was obtained compound **27 (**25 mg, 13 %). ESI [M+H^+] 388 (100). HRMS (ESI) calcd for $C_{15}H_{27}O_5N_5$ [M+H^+]: 388.1744, found 388.1745. ^{1}H NMR ($CDCl_3$): 8.32 (s, 1H, 2); 8.10 (s, 1H, 8); 6.62 (bs, 2H, NH_2); 4.34 (d, 1H, J_{gem} = 14.3, 1'a); 4.26 (d, 1H, J_{gem} = 14.3, 1'b); 4.18-4.06 (m, 4H, **CH_2**-CH_3); 3.67-3.78 (m, 2H, **CH_2**-CH_2-P); 3.38-3.32 (m, 2H, 3'); 2.09-2.03 (m, 2H, 5'); 1.35-1.31 (m, 6H, CH_2-**CH_3**); 1.15 (s, 3H, CH_3-2'). ^{13}C NMR ($CDCl_3$): 154.54 (6); 150.85 (2); 150.32 (4); 142.90 (8); 118.77 (5); 75.94 (3'); 71.94 (2'); 65.53 (d, $J_{C\text{-}C\text{-}P}$ = 4.6, **CH_2**-CH_2-P); 61.87-61.81 (m, **CH_2**-CH_3); 50.95 (1'); 26.60 (d, $J_{C\text{-}P}$ = 141.5, CH_2-P); 22.40 (**CH_3**-2'); 16.41 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.1, CH_2-**CH_3**). For $C_{15}H_{26}N_5O_5P$ (387.37) calcd: C, 46.51; H, 6.77; N, 18.08; P, 8.00. Found: C, 46.71; H, 6.96; N, 17.81; P, 7.82.

9-{3-[(Diethoxyphosphoryl)ethoxy]-2-[(diisopropoxyphosphoryl)methoxy]propyl}-adenine (28).

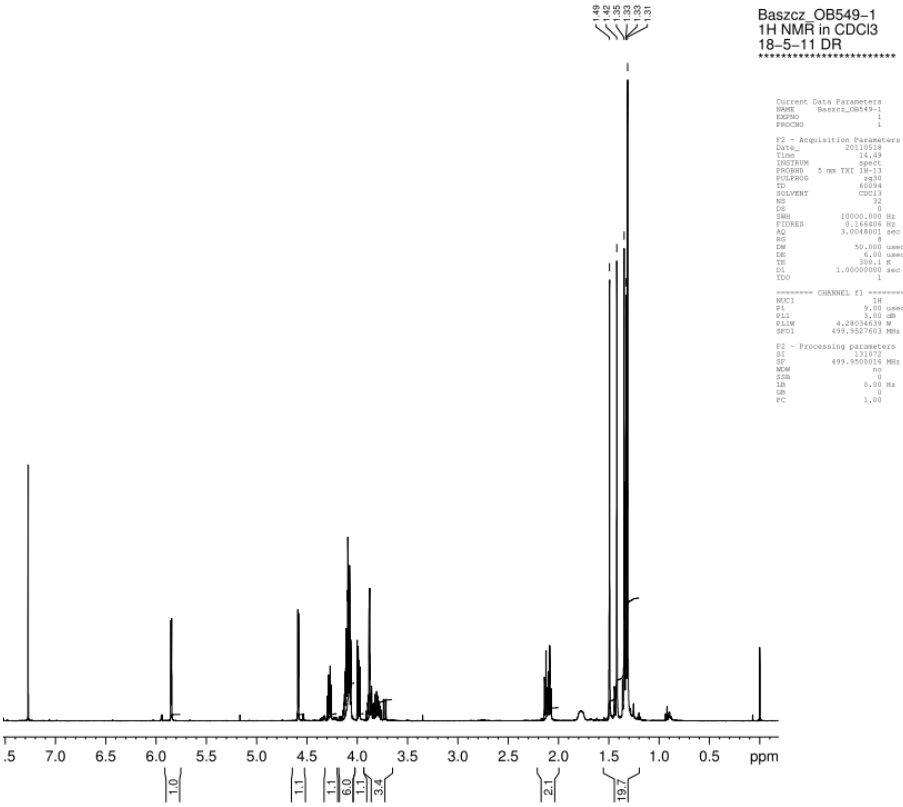
Method A: From compound **18** (100 mg, 0.26 mmol) was obtained compound **28** (20 mg, 14 %). ESI [M+H^+] 552 (100). ^{1}H NMR ($CDCl_3$): 8.32 (s, 1H, 2); 8.14 (s, 1H, 8); 6.83 (bs, 2H, NH_2); 4.73-4.64 (m, 2H, CH-*i*Pr); 4.51 (dd, 1H, J_{gem} = 14.5, $J_{1'a\text{-}2'}$ = 3.8, 1'a); 4.32 (dd, 1H, J_{gem} = 14.5, $J_{1'b\text{-}2'}$ = 6.8, 1'b); 4.15-4.07 (m, 4H, **CH_2**-CH_3); 3.98 (m, 1H, 2'); 3.88 (dd, 1H, J_{gem} = 13.8, $J_{H\text{-}C\text{-}P}$ = 8.5, **CH_{2a}**-O-2'); 3.74 (dd, 1H, J_{gem} = 13.8, $J_{H\text{-}C\text{-}P}$ = 9.0, **CH_{2b}**-O-2'); 3.74-3.67 (m, 2H, CH_2-O-3'); 3.55-3.50 (m, 2H, 3'); 2.10 (dt, 2H, $J_{H\text{-}C\text{-}P}$ = 18.7, $J_{CH2\text{-}CH2}$ = 7.3, CH_2-**CH_2**-

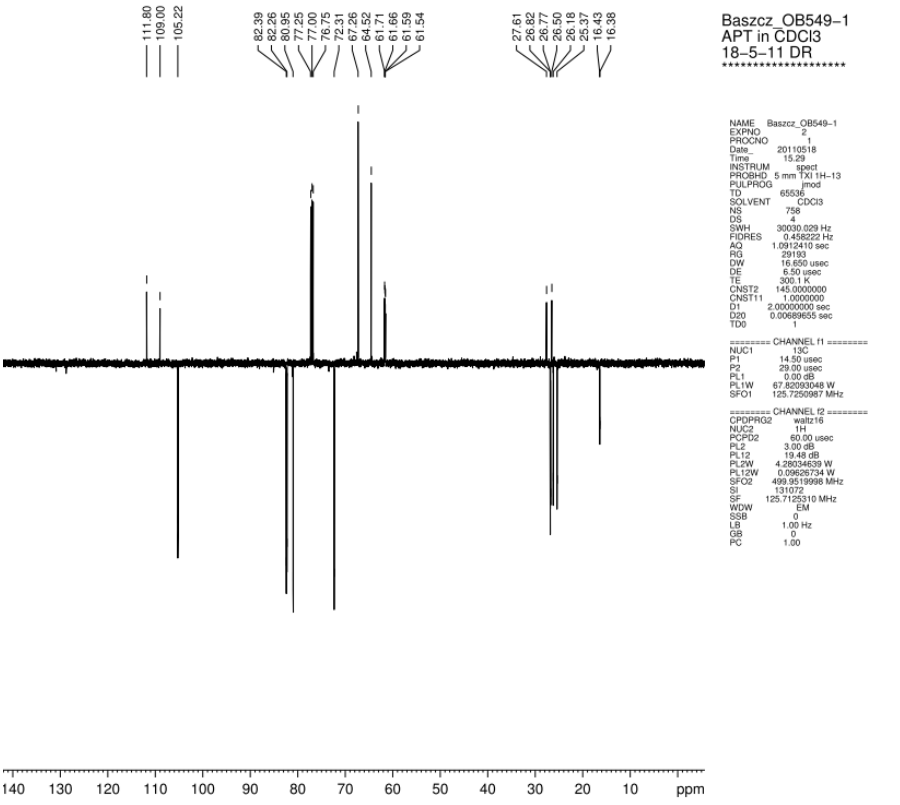
P); 1.34-1.24 (m, 18H, CH_3); ^{13}C NMR ($CDCl_3$): 153.97 (6); 149.92 (2); 149.85 (4); 142.87 (8); 118.82 (5); 78.56 (d, $J_{2'\text{-}P}$ = 10.3); 71.20 (m, CH-*i*Pr); 69.47 (3'); 65.60 (**CH_2**-O-3'); 64.99 (d, $J_{C\text{-}P}$ = 168.7, **CH_2**-O-2'); 61.72 (d, $J_{C\text{-}O\text{-}P}$ = 6.5, **CH_2**-O-P); 44.42 (1'); 26.86 (d, $J_{C\text{-}P}$ = 140.3, CH_2-**CH_2**-P); 24.02-23.90 (m, CH_3-*i*Pr); 16.42 (d, $J_{C\text{-}C\text{-}O\text{-}P}$ = 6.0, CH_2-**CH_3**); For $C_{21}H_{39}O_8P_2$ (551.51) calcd: C, 45.73; H, 7.13; P, 11.23. Found: C, 45.53; H, 7.28; P, 11.19.

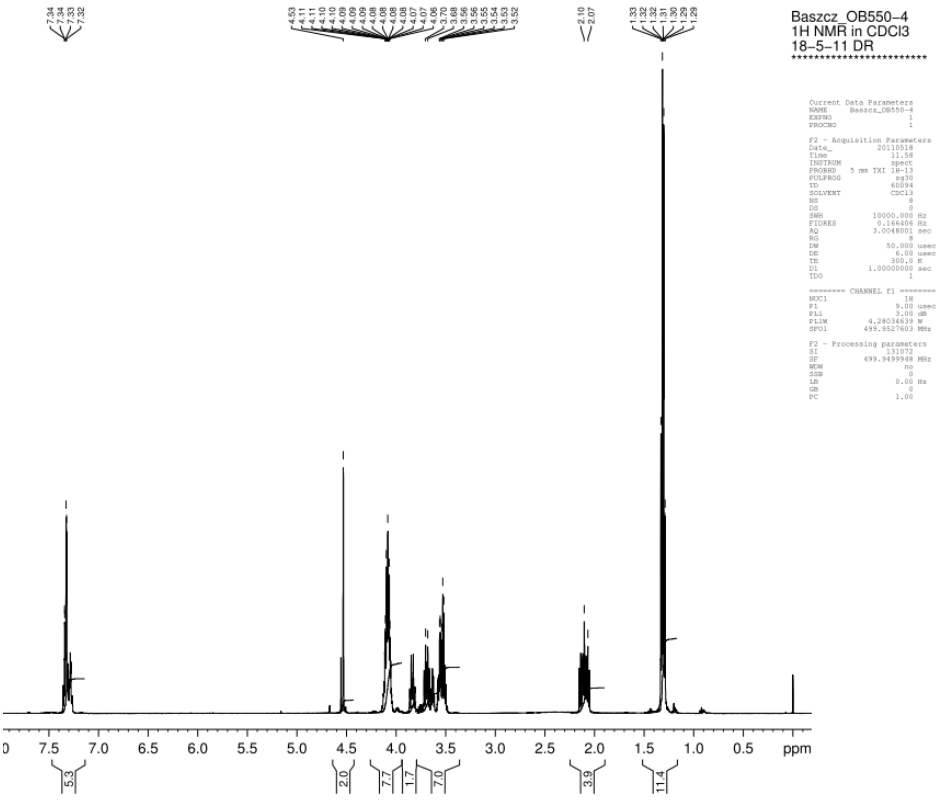
References:

[1)] Baszczynski, O.; Jansa, P.; Dracinsky, M.; Klepetarova, B.; Holy, A.; Votruba, I.; De Clercq, E.; Balzarini, J.; Janeba, Z.: *Bioorg. Med. Chem*. Vol. 19(7), 2114-2124.

1.4. Example of the NMR spectra of the selected products



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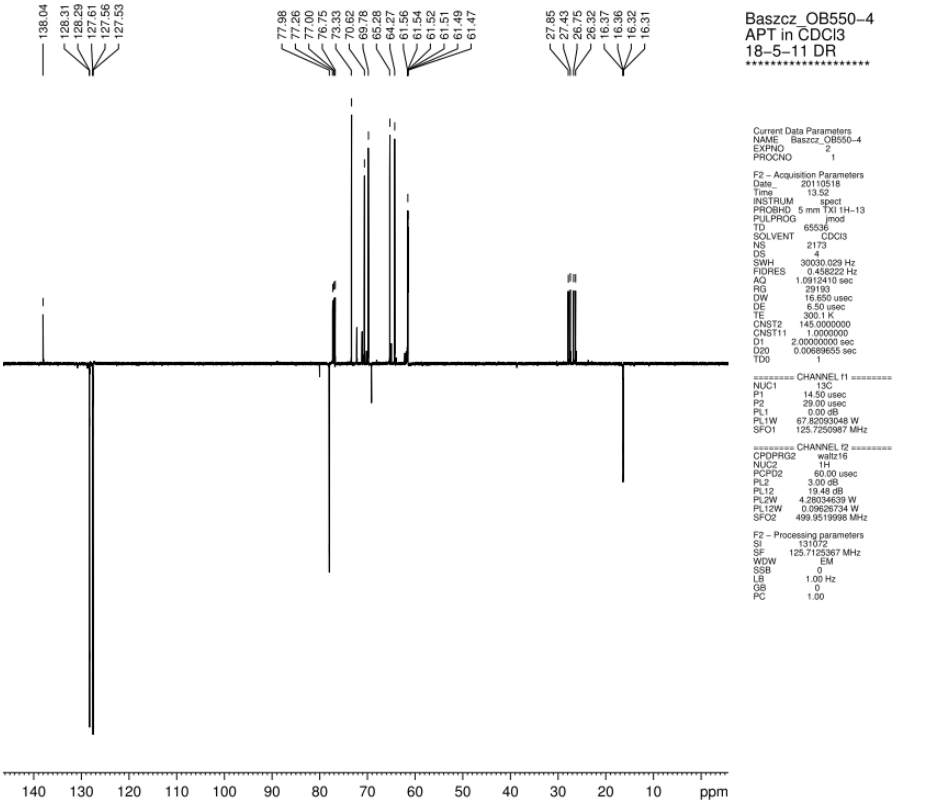
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