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). ^1H and ^13C NMR spectra were measured on a Bruker Avance 600 spectrometer (^1H at 600 MHz and ^13C 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 polarimeter (Rudolph research analytical) at 20 °C; [α]_D values are given [10^{-1} \deg \text{ cm}^2 \text{ g}^{-1}] and concentrations c are [g/100 \text{ 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 NH₄Cl solution. Water phase was extracted with EtOAc (3 x 20 mL) or, in case of the nucleoside analogs with CHCl₃ (3 x 20 mL). Organic phase was collected and dried over Na₂SO₄. The solution was filtered and evaporated in vacuo (40 °C, 2 mbar). Crude compound was purified by flash chromatography (hexane/EtOAc or CHCl₃/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 NH₄Cl. Water phase was 3 x extracted with EtOAc (20 mL in case of nucleoside analogs CHCl₃ was used). Organic phase was collected and dried over Na₂SO₄. The solution was filtered and evaporated in vacuo (40 °C, 2 mbar). Crude compounds were purified by flash chromatography (Hexane/EtOAc or CHCl₃/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 C₂₃H₃₃O₆NaP [M+Na⁺]: 459.1907, found: 459.1905. ¹H NMR (CDCl₃): 7.34-7.24 (m, 10H, 2', 3', 4'); 4.56-
4.48 (m, 4H, CH₂-1’); 4.10-4.00 (m, 4H, CH₂-O-P); 3.86 (m, 2H, CH₂-CH₂-P); 3.69 (m, 1H, 2); 3.61-3.50 (m, 4H, 1, 3); 2.13 (dm, J₇₁₆= 18.6, CH₂-P); 1.28 (t, 6H, J₇₈₇₂= 7.1, CH₃);

¹³C NMR (CDCl₃): 138.05 (1’); 128.21 (3’): 127.48 (2’); 127.46 (4’); 78.10 (2); 73.27 (CH₂-1’); 127.98 (3); 64.20 (CH₂-CH₂-P); 125.89 (4); 27.27 (d, J₇₁₆= 138.5, CH₂-P); 16.26 (d, J₇₁₆= 6.1, CH₃); For C₂₃H₃₃O₆P (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-(benzyl)oxy)-3-(trityloxy)propan-2-ylxyloxy)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 C₃₅H₄₁O₆NaP [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-(benzyl)oxy)-1-hydroxypropan-2-ylxyloxy)ethylphosphonate**: 97 mg (53 % from compound 10). ESI [M+Na⁺]: 369 (100).

HRMS (ESI) calcd for C₁₆H₂₅O₆P [M+H⁺]: 347.1618, found: 347.1617. ¹H NMR (CDCl₃): 7.27-7.35 (m, 5H, 2’, 3’, 4’); 4.53 (s, 2H, CH₂-1’); 4.16-4.05 (m, 4H, CH₂-CH₃); 3.98 (m, 1H, CH₂-CH₂-P); 3.81 (m, 1H, CH₂-CH₂-P); 3.72 (dd, 1H, J₁₆₇ = 11.7, J₃₂ = 2.8, 3a); 3.62 (m, 1H, 2); 3.59-3.49 (m, 3H, 3b, 1); 2.16-2.02 (m, 2H, CH₂-P); 1.32 (t, 3H, J₇₈₇₂ = 7.1, CH₃); 3.11 (t, 3H, J₇₈₇₂ = 7.1, CH₃). ¹³C NMR (CDCl₃): 137.98 (1’); 128.34 (3’); 127.62 (4’); 127.54 (2’); 80.02 (2); 73.40 (CH₂-1’); 70.19 (1); 63.93 (d, J₇₁₆ = 5.9, CH₂-CH₂-P); 62.17 (3); 61.87 (d, J₇₁₆ = 6.4, CH₂-CH₃); 61.57 (d, J₇₁₆ = 6.5, CH₂-CH₃); 27.08 (d, J₇₁₆ = 141.5, CH₂-P); 16.32 (d, J₇₁₆ = 6.2, CH₃). For C₁₆H₂₉O₇P (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-ylxy)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 C₁₅H₂₅O₆NaP [M+Na⁺]: 323.1383, found: 323.1382. ¹H NMR (CDCl₃): 7.33-7.17 (m, 5H, 2’, 3’, 4’); 4.13-4.02 (m, 4H, CH₂-CH₃); 3.73 (m, 1H, CH₂-CH₂); 3.66-3.57 (m, 2H, CH₂-CH₂); 2.90 (dd, 1H, J₉₁ = 13.6, J₁₉₂ = 6.3, 1a); 2.62 (dd, 1H, J₉₁ = 13.6, J₁₉₂ = 6.7, 1b); 2.09-1.99 (m, 2H, CH₂-P); 1.31 (m, 6H, CH₂-CH₃); 1.13 (m, 3H, J₃₂ = 6.2, 3); ¹³C NMR (CDCl₃): 138.56 (1’); 129.20 (2’); 127.98 (3’), 125.89 (4’); 76.74 (2); 62.26 (CH₂-CH₂); 61.33 (m, CH₂-CH₃); 42.75 (1);
27.01 (d, $J_{C-P} = 138.7$, CH$_2$-P); 19.24 (3); 16.19 (d, $J_{C-C-O-P} = 6.2$, CH$_2$-CH$_3$); For C$_{13}$H$_{25}$O$_4$P (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$_9$NaP [M+Na$^+$]: 447.1754, found: 447.1753.

$^1$H NMR (CDCl$_3$): 5.85 (d, 1H, $J_{1-2} = 3.7$, 1); 4.59 (d, 1H, $J_{2-1} = 3.7$, 2); 4.28-4.14 (m, 6H, CH$_2$-CH$_3$, 4, 6a); 3.99 (dd, 1H, $J_{gem} = 8.6$, J$_{6b-5, 6a}$ = 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$_3$-iPr); 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, $J_{C-P} = 139.7$, CH$_2$-P); 26.82 and 26.77 and 26.18 and 25.37 (4x CH$_3$); 16.40 (d, $J_{C-C-O-P} = 6.2$, CH$_2$-CH$_3$); For C$_{18}$H$_{33}$O$_9$P (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)**

Method 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$_6$NaP = 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$_{5-4} = J_{5-6} = 1.7$, 5); 2.22 (dm, 2H, J$_{H-C-P} = 18.5$, 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$_{C-O-P} = 6.3$, P-O-CH$_2$); 27.24 (d, J$_{C-P} = 138.9$, CH$_2$-P); 16.38 (d, J$_{C-C-O-P} = 6.1$, CH$_3$).
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_{3}NaP [M+Na⁺]: 305.1488, found: 305.1487. \(^1\)H NMR (CDCl₃): 4.08 (m, 4H, CH₂-CH₃); 3.88-3.77 (m, 2H, 2, CH₂-O-P); 3.53 (m, 1H, CH₂-CH₂-P); 2.11-1.97 (m, 2H, CH₂-P); 1.73 (dd, 1H, \(J_{\text{gem}} = 14.7\), \(J_{3a-2} = 10.7\), 3a); 1.47 (dd, \(J_{\text{gem}} = 14.7\), \(J_{3b-2} = 2.6\), 3b); 1.33 (2 x t, 6H, J_{CH3-CH2} = 7.1, CH₂-CH₃); 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 (CDCl₃): 74.08 (2), 69.87 (4); 61.89 (d, \(J_{C-C-P} = 1.7\), CH₂-CH₂-P); 61.69 (m, CH₂-CH₃), 48.96 (3); 31.00 and 28.13 (5); 27.27 (d, \(J_{C-P} = 140.5\), CH₂-P); 19.70 (1); 16.36 (m, CH₂-CH₃); For C_{12}H_{27}O₃P (282.31) calcd: C, 51.05; H, 9.64; P, 10.97. Found: C, 50.84; H, 9.62; P, 11.05.

3-Benzylxoy-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_{46}O₃NaP₂ [M+Na⁺]: 533.2040, found: 533.2038. \(^1\)H NMR (CDCl₃): 7.36-7.26 (m, 5H, 2, 3, 4); 4.53 (s, 2H, CH₂-1'); 4.13-4.04 (m, 8H, CH₂-CH₃); 3.84 (m, 2H, CH₂-O-2); 3.63 (m, 2); 3.58-3.48 (m, 4H, 1, 3); 2.96 (m, 2H, CH₂-O-1), 2.16-2.05 (4H, CH₂-P); 1.33-1.29 (m, 12H, CH₂-CH₃); \(^{13}\)C NMR (CDCl₃): 138.04 (C-1'); 128.29 (C-3'); 127.56 (C-4'); 127.53 (C-2'); 77.98 (C-2); 73.33 (CH₂-1'); 70.62 (C-1); 69.78 (C-3); 65.28 (CH₂-O-1); 64.27 (CH₂-O-2); 61.51 (m, CH₂-CH₃); 27.30 (d, \(J_{C-P} = 138.6\), CH₂-CH₂-O-2); 26.88 (d, \(J_{C-P} = 139.4\), CH₂-CH₂-O-1); 16.34 (m, CH₂-CH₃); For C_{22}H_{46}O₃P₂ (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_{29}O₃N₅P [M+H⁺]: 374.1588, found: 374.1587. \(^1\)H NMR (CD₃OD): 8.20 (s,
1H, 2); 8.12 (s, 1H, 8); 4.40 (dd, 1H, \(J_{\text{gem}} = 14.2\), \(J_{1',-2'} = 3.9\), 1’a); 4.23 (dd, 1H, \(J_{\text{gem}} = 14.2\), \(J_{1'b,-2'} = 7.8\), 1’b); 4.15-4.07 (m, 5H, \(\text{CH}_2\text{CH}_3, 2'\)); 3.75-3.68 (m, 2H, 4’); 3.46-3.52 (m, 2H, 3’); 2.16 (dt, 2H, \(J_{5'-4'} = 7.0, J_{3'-p} = 18.2, 5'\)); 1.33 (t, 6H, \(J_{\text{CH}_3\text{CH}_2} = 7.0, \text{CH}_2\text{CH}_3\)). \(^{13}\)C NMR (CDCl3): 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, \(J_{\text{CH}_2\text{P}} = 6.5, \text{CH}_2\text{CH}_3\)); 47.89 (1’); 27.10 (d, \(J_{5'\text{-p}} = 140.3, 5'\)); 16.71 (d, \(J_{\text{CH}_3\text{P}} = 6.1, \text{CH}_2\text{-CH}_3\)). For \(\text{C}_{14}\text{H}_{24}\text{N}_5\text{O}_3\text{P}\) (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 \(\text{C}_{13}\text{H}_{27}\text{O}_5\text{N}_5\) [M+H\(^+\)]: 388.1744, found 388.1745. \(^1\)H NMR (CDCl3): 8.32 (s, 1H, 2); 8.10 (s, 1H, 8); 6.62 (bs, 2H, NH$_2$); 4.34 (d, 1H, \(J_{\text{gem}} = 14.3, 1'a\)); 4.26 (d, 1H, \(J_{\text{gem}} = 14.3, 1'b\)); 4.18-4.06 (m, 4H, \(\text{CH}_2\text{-CH}_3\)); 3.67-3.78 (m, 2H, \(\text{CH}_2\text{-CH}_2\text{-P}\)); 3.38-3.32 (m, 2H, 3’); 2.09-2.03 (m, 2H, 5’); 1.35-1.31 (m, 6H, \(\text{CH}_2\text{-CH}_3\)); 1.15 (s, 3H, \(\text{CH}_3\text{-2'}\)). \(^{13}\)C NMR (CDCl3): 154.54 (6); 150.85 (2); 150.32 (4); 142.90 (8); 118.77 (5); 75.94 (3’); 71.94 (2’); 65.53 (d, \(J_{\text{C-C-P}} = 4.6, \text{CH}_2\text{-CH}_2\text{-P}\)); 61.87-61.81 (m, \(\text{CH}_2\text{-CH}_3\)); 50.95 (1’); 26.60 (d, \(J_{\text{C-P}} = 141.5, \text{CH}_2\text{-P}\)); 22.40 (\(\text{CH}_3\text{-2'}\)); 16.41 (d, \(J_{\text{C-C-O-P}} = 6.1, \text{CH}_2\text{-CH}_3\)). For \(\text{C}_{13}\text{H}_{26}\text{N}_5\text{O}_3\text{P}\) (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.


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 (CDCl3): 8.32 (s, 1H, 2); 8.14 (s, 1H, 8); 6.83 (bs, 2H, NH$_2$); 4.73-4.64 (m, 2H, CH-$\text{iPr}$); 4.51 (dd, 1H, \(J_{\text{gem}} = 14.5, J_{1'a,-2'} = 3.8, 1'a\)); 4.32 (dd, 1H, \(J_{\text{gem}} = 14.5, J_{1'b,-2'} = 6.8, 1'b\)); 4.15-4.07 (m, 4H, \(\text{CH}_2\text{-CH}_3\)); 3.98 (m, 1H, 2’); 3.88 (dd, 1H, \(J_{\text{gem}} = 13.8, J_{\text{H-C-P}} = 8.5, \text{CH}_2\text{-O-2'}\)); 3.74 (dd, 1H, \(J_{\text{gem}} = 13.8, J_{\text{H-C-P}} = 9.0, \text{CH}_2\text{-O-2'}\)); 3.74-3.67 (m, 2H, \(\text{CH}_2\text{-O-3'}\)); 3.55-3.50 (m, 2H, 3’); 2.10 (dt, 2H, \(J_{\text{H-C-P}} = 18.7, J_{\text{CH}_2\text{-CH}_2} = 7.3, \text{CH}_2\text{-CH}_2\)}.
P); 1.34-1.24 (m, 18H, CH₃); ¹³C NMR (CDCl₃): 153.97 (6); 149.92 (2); 149.85 (4); 142.87 (8); 118.82 (5); 78.56 (d, J₂-P = 10.3); 71.20 (m, CH-iPr); 69.47 (3’); 65.60 (CH₂-O-3’); 64.99 (d, J₃-P = 168.7, CH₂-O-2’); 61.72 (d, J₁-O-P = 6.5, CH₂-O-P); 44.42 (1’); 26.86 (d, J₁-O-P = 140.3, CH₂-CH₂-P); 24.02-23.90 (m, CH₃-iPr); 16.42 (d, J₃-C-O-P = 6.0, CH₂-CH₃); For C₂₁H₃₉O₈P₂ (551.51) calcd: C, 45.73; H, 7.13; P, 11.23. Found: C, 45.53; H, 7.28; P, 11.19.

References:
1.4. Example of the NMR spectra of the selected products