Microwave-Assisted Hydrolysis of Phosphonates Diesters: An Efficient Protocol for the Preparation of Phosphonic Acids

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Supporting information

General information. Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 13 Pa. Melting points were determined on a Büchi B-540 and are uncorrected. Analytical TLC was performed on silica gel 60 F_{254} plates (Merck). Column chromatography was performed on silica gel 60 μm (Merck). Mass spectra were measured on a a LTQ Orbitrap XL (Thermo Fisher Scientific) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 500 (^{1}H at 500 MHz and ^{13}C 125.7 MHz) in D_2O (referenced to dioxane as an internal standard δ = 3.75 ppm and δ = 67.19 ppm, respectively). Complete assignment is based on heteronuclear correlation experiments HSQC and H,C-HMBC. Chemical shifts (δ) are in ppm and coupling constants (*J*) in Hz. Optical rotations were measured on Autopol IV polarimeter (Rudolph Research Analytical, U.S.A.) at 20 °C, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentrations are given in g/100 mL. The purity of compounds was determined by elemental analysis (C, H, N) measured on Perkin–Elmer CHN Analyzer 2400, Series II (Perkin–Elmer). The microwave-assisted (MW-assisted) reactions were carried out in the following MW syntheses instruments: Type I – CEM Discover®, single-mode cavity with focused MW heating (MW power supply 0-300 W, 1 W increments, IR temperature sensor, open or closed vessel mode, pressure range 0-20 bar, 10 ml or 80 ml vials); Type II – Milestone BatchSYNTH®, single-mode cavity, scale-up (MW power supply 0-1000 W, 10 W increments, internal temperature sensor, batch mode, pressure range 0-30 bar, 250 ml vessel); Type III – Milestone FlowSYNTH®, (MW power supply 0-1000 W, 10 W increments, internal temperature sensor, flow mode, pressure range 0-30 bar, 200 mL reaction cell volume, flow rate 10-100 mL/min). Starting phosphonate diesters were synthesized at the Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic.[1,3-9]

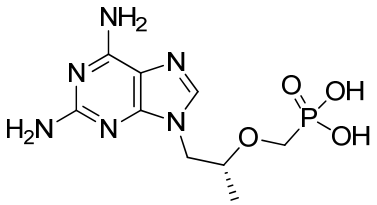
General procedure for the microwave-assisted hydrolysis of phosphonate diesters.

A mixture of the starting phosphonate diester (1.0 mmol) in the aqueous HCl solution (1.0 or 2.0 mmol of 0.5 M or 1.0 M HCl solution) was placed, with a magnetic stirring bar, into 10 mL

reaction tube and sealed. The reaction mixture was heated in the microwave reactor (Type I) at 130-140 °C until constant pressure (20-30 min). The reaction mixture was cooled down to 0 °C and precipitated product was filtered off, washed (water, EtOH, and acetone), and dried *in vacuo*. The products can be crystallized from water for better purity.

(*R*)-(((1-(2,6-Diamino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)phosphonic acid (9).[1]

Reaction conditions: a) Microwave reactor Type I, starting compound **1** (1.0 mmol), 130 °C for 10 min, yield 77% of **9**; b) Microwave reactor Type II, starting compound **1** (100.0 mmol), 130°C for 10 min, yield 79% of **9**.



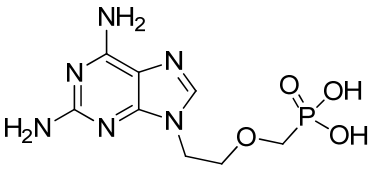
9

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[1] For $C_9H_{15}N_6O_4P$ (302.1) calculated (%): C 35.77; H 5.00; N 27.81; found (%): C 35.54; H 5.23; N 27.59. MS ESI(-), *m*/*z* (%): 301 [M^-] (100). Optical purity (99.2 %) was determined by capilary electrophoresis.[2] Chemical purity was determined by X-ray fluorescence analyzer SPECTRO iQ II and confirmed that compound **9** did not contain silicon or any other elements higher than sodium.

Scale-up for compound 9 under continuous flow conditions: A mixture of compound **1** (50 mmol, 19.3 g) in the aqueous HCl solution (0.25 M, 400 mL) was heated in the microwave reactor (Type III) at 140 °C at flow rate of 12 mL/min till full conversion. The reaction was monitored by TLC. The reaction mixture was cooled down to 0 °C and precipitated product was filtered off and washed (water). The crude product was crystallized (water), crystals were washed (water, EtOH, and acetone) and dried *in vacuo* to give 10.9 g (72%) of compound **9**.

((2-(2,6-Diamino-9*H*-purin-9-yl)ethoxy)methyl)phosphonic acid (10).[3]

Reaction conditions: Microwave reactor Type I, starting compound **2** (1.0 mmol), 130 °C for 20 min, yield 78% of **10**.

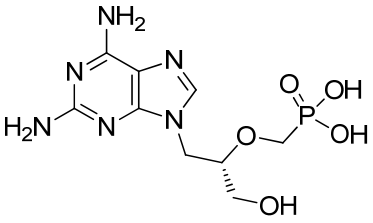


10

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[3] For $C_8H_{13}N_6O_4P$ (288.1) calculated (%): C 33.34; H 4.55; N 29.16; found (%): C 33.54; H 4.84; N 29.03. MS ESI(-), *m*/*z* (%): 287 [M^-] (100).

(*S*)-(((1-(2,6-Diamino-9*H*-purin-9-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid (11).[4]

Reaction conditions: Microwave reactor Type I, starting compound **3** (1.0 mmol), 130 °C for 20 min, yield 77% of **11**.

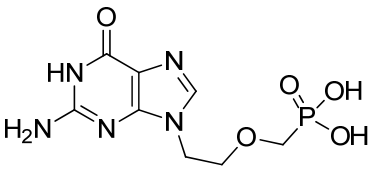


11

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[4] $[\alpha]_D$ –24.8° (*c* 0.38, H_2O/NH_3). For $C_9H_{14}N_5O_6P$ (318.1) calculated (%): C 33.86; H 4.42; N 21.94; found (%): C 33.65; H 4.67; N 21.72. MS ESI(-), *m*/*z* (%): 317 [M^-] (100).

((2-(2-Amino-6-oxo-1*H*-purin-9(6*H*)-yl)ethoxy)methyl)phosphonic acid (12).[3]

Reaction conditions: a) Microwave reactor Type I, starting compound **4** (1.0 mmol), 140 °C for 10 min, yield 93 % of **12**; b) Microwave reactor Type II, starting compound **4** (50.0 mmol), 140°C for 10 min, yield 91% of **12**.

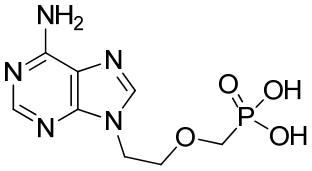


12

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[3] For $C_8H_{12}N_5O_5P$ (289.1) calculated (%): C 33.23; H 4.18; N 24.22; found (%): C 33.43; H 4.37; N 24.16. MS ESI(-), *m*/*z* (%): 288 [M^-] (100), 310 [M^-Na] (21); HRMS ESI(-) calculated (*m*/*z*): 288.0502; found: 288.0492.

((2-(6-Amino-9*H*-purin-9-yl)ethoxy)methyl)phosphonic acid (13).[5]

Reaction conditions: a) Microwave reactor Type I, starting compound **5** (1.0 mmol), 140 °C for 10 min, yield 92 % of **13**; b) Microwave reactor Type II, starting compound **5** (100.0 mmol), 140°C for 10 min, yield 95% of **13**.

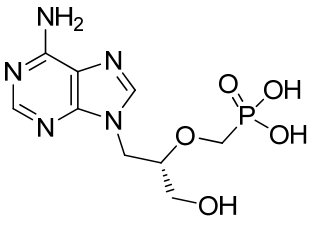


13

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[5] For $C_8H_{12}N_5O_4P$ (273.1) calculated (%): C 35.17; H 4.43; N 25.64; found (%): C 35.28; H 4.59; N 25.43. MS ESI(-), *m*/*z* (%): 272 [M^-] (100), 294 [M^-Na] (17).

(*S*)-(((1-(6-Amino-9*H*-purin-9-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid (14).[6]

Reaction conditions: a) Microwave reactor Type I, starting compound **6** (1.0 mmol), 140 °C for 10 min, yield 88 % of **14**; b) Microwave reactor Type II, starting compound **6** (50.0 mmol), 140°C for 10 min, yield 92% of **14**.

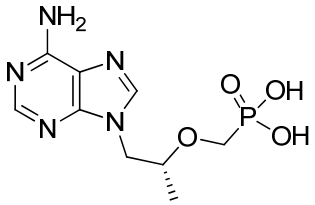


14

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[6] $[\alpha]_D$ −13.4° (*c* 0.35, H_2O/NH_3). For $C_9H_{14}N_5O_5P$ (303.1) calculated (%): C 35.65; H 4.65; N 23.10; found (%): C 35.47; H 4.83; N 23.02. MS ESI(-), *m*/*z* (%): 303 [M^-] (100).

(*R*)-(((1-(6-Amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)phosphonic acid (15).[7]

Reaction conditions: a) Microwave reactor Type I, starting compound **7** (1.0 mmol), 140 °C for 10 min, yield 91 % of **15**; b) Microwave reactor Type II, starting compound **7** (50.0 mmol), 140°C for 10 min, yield 90 % of **15**.

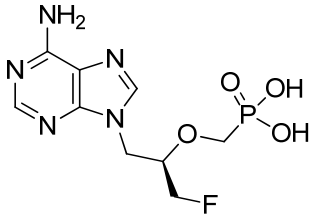


15

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[7] $[\alpha]_D$ −19.2° (*c* 0.5, H_2O/NH_3). For $C_9H_{14}N_5O_4P$ (287.1) calculated (%): C 37.64; H 4.91; N 24.38; found (%): C 37.49; H 5.17; N 24.27. MS ESI(-), *m*/*z* (%): 301 [M^-] (100).

(*R*)-(((1-(6-Amino-9*H*-purin-9-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (16).[8,9]

Reaction conditions: Microwave reactor Type I, starting compound **8** (1.0 mmol), 140 °C for 10 min, yield 93 % of **16**.

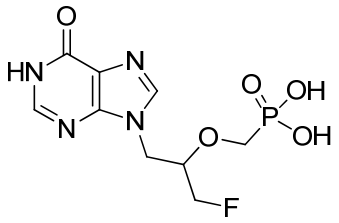


16

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[8,9] $[\alpha]_D$ +8.4° (*c* 0.24, H_2O/NH_3). For $C_9H_{13}FN_5O_4P$ (305.1) calculated (%): C 35.42; H 4.29; N 22.95; found (%): C 35.63; H 4.48; N 22.81. MS ESI(-), *m*/*z* (%): 304 [M^-] (100).

(*R*,*S*)-(((1-Fluoro-3-(6-oxo-1*H*-purin-9(6*H*)-yl)propan-2-yl)oxy)methyl)phosphonic acid (23).[8,9]

Reaction conditions: Microwave reactor Type I, starting compound **17** (1.0 mmol), 140 °C for 10 min, yield 82 % of **23**.

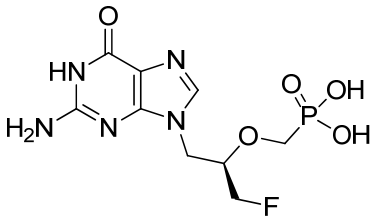


23

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[8,9] For $C_9H_{12}FN_4O_5P$ (306.1) calculated (%): C 35.30; H 3.95; N 18.30; found (%): C 35.43; H 4.20; N 18.17. MS ESI(-), *m*/*z* (%): 305 [M^-] (100). HRMS ESI(-) calculated (*m*/*z*): 305.0451; found: 305.0450.

(*R*)-(((1-(2-Amino-6-oxo-1*H*-purin-9(6*H*)-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (24).[8,9]

Reaction conditions: Microwave reactor Type I, starting compound **18** (1.0 mmol), 140 °C for 10 min, yield 83 % of **24**.

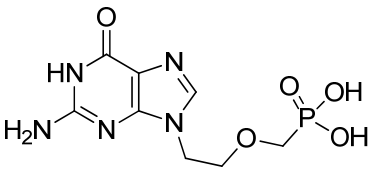


24

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[8,9] $[\alpha]_D$ +25.3° (*c* 0.3, H_2O). For $C_9H_{13}FN_5O_5P$ (321.1) calculated (%): C 33.65; H 4.08; N 21.80; found (%): C 33.68; H 4.25; N 21.59. MS ESI(-), *m*/*z* (%): 320 [M^-] (100).

((2-(2-Amino-6-oxo-1*H*-purin-9(6*H*)-yl)ethoxy)methyl)phosphonic acid (25).[3]

Reaction conditions: Microwave reactor Type I, starting compound **19** (1.0 mmol), 140 °C for 10 min, yield 90 % of **25**.

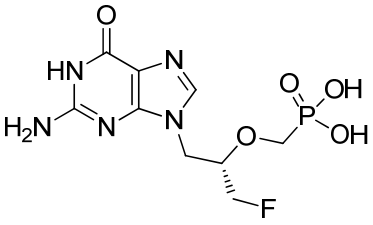


25

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[3] For $C_8H_{12}N_5O_5P$ (289.1) calculated (%): C 33.23; H 4.18; N 24.22; found (%): C 33.17; H 4.43; N 24.07. MS ESI(-), *m*/*z* (%): 288 [M^-] (100), 310 [M^-Na].

(*S*)-(((1-(2-Amino-6-oxo-1*H*-purin-9(6*H*)-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (26).[8,9]

Reaction conditions: Microwave reactor Type I, starting compound **20** (1.0 mmol), 140 °C for 10 min, yield 85 % of **26**.

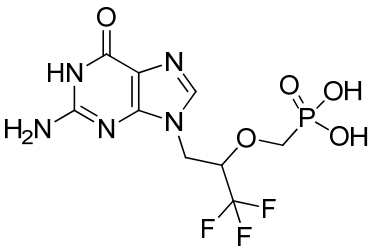


26

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[8,9] $[\alpha]_D$ –26.7° (*c* 0.3, H_2O). For $C_9H_{13}FN_5O_5P$ (321.1) calculated (%): C 33.65; H 4.08; N 21.80; found (%): C 33,57; H 4,23; N 21,64. MS ESI(-), *m*/*z* (%): 320 [M^-] (100), 342 [M^-Na].

(*R*,*S*)-(((3-(2-Amino-6-oxo-1*H*-purin-9(6*H*)-yl)-1,1,1-trifluoropropan-2-yl)oxy)methyl)phosphonic acid (27).

Reaction conditions: a) Microwave reactor Type I, starting compound **21** (1.0 mmol), 140 °C for 10 min, yield 87 % of **27**.

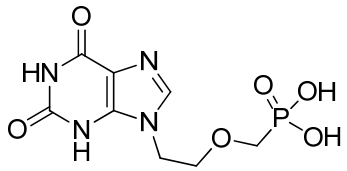


27

^{1}H NMR (D_2O): 8.21 s, 1H (H-8’’); 4.43 m, 1H (H-1’a); 4.31 – 4.43 m, 2H (H-1’b, H-2’); 3.84 dd, 1H, *Jgem* = 12.5, *J*(1,P) = 9.6 a 3.46 dd, 1H, *Jgem* = 12.5, *J*(1,P) = 9.3 (CH_2P). ^{13}C NMR (D_2O): 173.46 (C-6’’); 156.60 (C-2’’); 153.34 (C-4’’); 137.67 (C-8’’); 123.42 q, *J*(3’,F) = 286.3 (C-3’); 116.63 (C-5’’); 77.58 qd, *J*(2’,F) = 29.6, *J*(2’,P) = 12.7 (C-2’); 71.24 d, *J*(1,P) = 153.1 (C-1); 42.46 (C-1’). For $C_9H_{11}O_5N_5F_3P$ + 1.5 H_2O (348.2) calculated (%): C 24.17; H 4.73; N 15.66; F 12.74; found (%): C 24.34; H 4.82; N 15.55; F 12.90%. MS ESI(-), *m*/*z* (%): 356 [M^-] (100); HRMS ESI(-) calculated (*m*/*z*): 356.0372; found: 356.0368.

((2-(2,6-Dioxo-2,3-dihydro-1*H*-purin-9(6*H*)-yl)ethoxy)methyl)phosphonic acid (28).

Reaction conditions: Microwave reactor Type I, starting compound **22** (1.0 mmol), 150 °C for 20 min, yield 80 % of **28**.

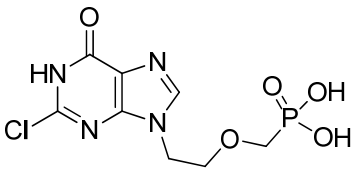


28

^{1}H NMR (D_2O): 7.84 s, 1H (H-8’’); 4.39 t, 2H, *J*(2’,1’) = 5.0 (H-2’); 3.95 t, 2H, *J*(1’,2’) = 5.1 (H-1’); 3.80 d, 2H, *J*(1,P) = 8.5 (CH_2P). ^{13}C NMR (D_2O): 158.78 (C-6’’); 151.53 (C-2’’); 141.18 (C-4’’); 138.37 (C-8’’); 115.97 (C-5’’); 71.04 d, *J*(1’,P) = 10.4 (C-1’); 66.97 d, *J*(1,P) = 159.8 (CH_2P); 44.58 (C-2’). Pro $C_8H_{11}N_4O_6P$ (290.0) vypočteno (%): C 33.11; H 3.82; N 19.31; nalezeno (%): C 33.26; H 4.07; N 19.18. MS ESI(-) *m*/*z* (%): 289 [M^-] (100), 311 [M^-Na].

((2-(2-Chloro-6-oxo-1*H*-purin-9(6*H*)-yl)ethoxy)methyl)phosphonic acid (29).

Reaction conditions: Microwave reactor Type I, starting compound **22** (1.0 mmol), 150 °C for 10 min, yield 40 % of **29**.

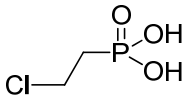


29

^{1}H NMR (D_2O): 8.05 s, 1H (H-8''); 4.32 m, 2H, *J*(2'-1') = 5.3 (H-2'); 3.92 m, 2H, *J*(1'-2') = 5.3 (H-1'); 3.48 d, 2H, *J*(1,P) = 8.4 (CH_2P). ^{13}C NMR (D_2O): 168.21 (C-6''); 154.39 (C-2''); 151.28 (C-4''); 141.97 (C-8''); 122.61 (C-5''); 70.73 d, *J*(1'-P) = 9.9 (C-1'); 69.53 d, *J*(1,P) = 150.0 (CH_2P); 40.01 (C-2'). Pro $C_8H_{10}ClN_4O_5P$ (308.0077) calculated (%): C 31.13; H 3.27; N 18.15; found (%): C 30.94; H 3.25; N 17.86. MS ESI(-), *m*/*z* (%): 307. 309 [M^-] (100). HRMS ESI(-) calculated (*m*/*z*): 306.9999; found: 307.0006.

(2-Chloroethyl)phosphonic acid (33).[10]

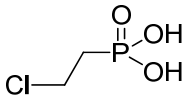
Method A: Reaction conditions: a) Microwave reactor Type I, starting compound **30** (10.0 mmol) and HCl (30 mmol), 100 °C for 10 min, yield 84 % of **33**. b) Microwave reactor Type I, starting compound **30** (10.0 mmol) and HCl (30 mmol), 120 °C for 4 min, yield 87 % of **33**. c) Microwave reactor Type I, starting compound **30** (10.0 mmol) and HCl (30 mmol), 150 °C for 2 min, yield 85 % of **33**.



33

^{1}H NMR and NMR according to the literature.[10] For $C_2H_6ClO_3P$ (144.0) calculated (%): C 16.62; H 4.19; Cl 24.54; found (%): C 16.53; H 4.32; Cl 24.67. MS ESI(+), *m*/*z* (%): 145 a 147 [M^+] (100).

Method B: Reaction conditions: Microwave reactor Type I, starting compound **31** (10.0 mmol) and HCl (30 mmol), 100 °C for 25 min, yield 79 % of **33**.

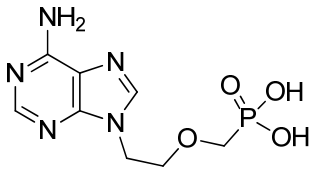


33

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[10] For $C_2H_6ClO_3P$ (144.0) calculated (%): C 16.62; H 4.19; Cl 24.54; found (%): C 16.78; H 4.26; Cl 24.71. MS ESI(+), *m*/*z* (%): 145 a 147 [M^+] (100).

((2-(6-Amino-9*H*-purin-9-yl)ethoxy)methyl)phosphonic acid (13).[5]

Reaction conditions: Microwave reactor Type I, starting compound **32** (1.0 mmol) and HCl (2 mmol), 140 °C for 20 min, yield 78 % of **13**.



13

^{1}H NMR and ^{13}C NMR spectra correspond to literature.[5] For $C_8H_{12}N_5O_4P$ (273.1) calculated (%): C 35.17; H 4.43; N 25.64; found (%): C 35.35; H 4.60; N 25.38. MS ESI(-), *m*/*z* (%): 272 [M^-] (100), 294 [M^-Na] (14).

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