Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 2282

www.rsc.org/greenchem

PAPER

Microwave-assisted hydrolysis of phosphonate diesters: an efficient protocol for the preparation of phosphonic acids†

Petr Jansa,* Ondřej Baszczyňski, Eliška Procházková, Martin Dračínský and Zlatko Janeba*

Received 12th April 2012, Accepted 24th May 2012
DOI: 10.1039/c2gc35547g

A new highly efficient method for the hydrolysis of acyclic nucleoside phosphonate diesters (or generally of any organophosphonates) to the corresponding phosphonic acids has been developed. This novel methodology employs inexpensive hydrochloric acid in equimolar amounts to the number of ester groups present in the molecule and thus, avoids using trimethylsilyl halogenides, the standard reagents for these types of transformations. Moreover, simple and easy work-up of the reaction mixture affords very clean products in high yields (usually 77–93%). Another advantage of the described hydrolysis of phosphonate diesters is the fact that the course of the reaction can be instantly monitored through pressure changes in the reaction vessel. This 'green' method has also been successfully used for the preparation of otherwise synthetically difficult to access (phosphonomethoxy)ethyl (PME) derivatives of guanine (PMEG) and hypoxanthine (PMEHx), and furthermore, the method gains access to important novel acyclic nucleoside phosphonates derived from 2-chlorohypoxanthine and from xanthine (*e.g.* PMEX).

Introduction

Acyclic nucleoside phosphonates (ANPs),[1] which represent catabolically stable nucleotide analogues, are an important group of antimetabolites with a wide range of important biological properties.[2] Three ANPs have been approved worldwide for clinical use:[3] HPMPC (cidofovir, Vistide®) for the treatment of CMV retinitis in AIDS patients,[3,4] PMEA (as its oral prodrug adefovir dipivoxil, Hepsera®) for the treatment of chronic HBV infections,[3] and PMPA (as its oral prodrug tenofovir disoproxil fumarate, Viread®) for the treatment of HIV (itself or in combination with other antivirals) and chronic HBV infections.[3] Like various nucleotides,[5] ANPs usually have to be administered in the form of their prodrugs, due to their poor bioavailability.[6] Although a novel and efficient method for the conversion of phosphonate diesters directly into the corresponding diamides (bis-amidates) has been recently developed in our lab,[7] a general and widely used synthetic strategy for the synthesis of the desired phosphonate prodrugs starts with an introduction of protected phosphonate moiety into the corresponding organic precursor, followed by removal of the alkyl ester groups, and finally introduction of the lipophilic promoieties to mask the ionizable phosphonate group.

There are several synthetic ways to prepare diverse phosphonate diesters,[8] and most recently, some new approaches have been reported.[9] The next important synthetic step in the synthesis of the ANPs prodrugs is hydrolysis of the alkyl esters groups to the corresponding free phosphonic acids. The synthesis of free phosphonic acids is still a challenge in organic medicinal chemistry and there is an urgent need to develop an efficient method for the hydrolysis of relevant phosphonate diesters to free phosphonic acids.

One option for the preparation of phosphonic acids is an alkaline hydrolysis of their diesters, but this method has a number of drawbacks. First, the tetrahedral geometry on the phosphorus atom makes hydrolysis by the $B_{AC}2$ mechanism almost impossible. The only feasible pathway is hydrolysis by the $B_{AL}2$ mechanism, to which only primary alkyl esters (especially methyl esters) are susceptible. In this case, the hydrolysis of a diester usually ends at the stage of a stable monoester that is difficult to further hydrolyze due to the resulting negative charge.[10] Sterically hindered isopropyl diesters are hydrolyzed into the corresponding monoesters only under harsh reaction conditions and/or with strong nucleophiles (*e.g.* azides).[11]

Another widely used synthetic approach to the synthesis of free phosphonic acids is acidic hydrolysis of the corresponding alkyl diesters (more than 90 000 citations in the Chemical Abstracts database). Such a hydrolysis can be catalyzed by various Lewis or mineral acids. The method of choice for both laboratory and industrial scales is a reaction of the phosphonate diesters with trimethylsilyl (TMS) bromide, chloride or iodide.[12] Nevertheless, the application of TMS halogenides has a number of fundamental disadvantages including high price, corrosive properties, toxicity, volatility, moisture sensitivity, and formation of impurities.

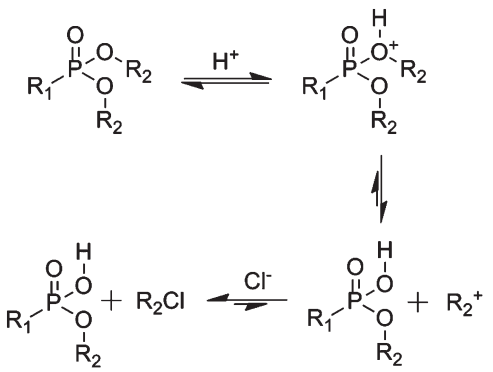
Another method for hydrolysis uses mineral acids, especially the most commonly used hydrohalogenic acids (more than

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, CZ-16610 Prague 6, Czech Republic. E-mail: jansa@uochb.cas.cz, janeba@uochb.cas.cz; Fax: +420 220183560; Tel: +420 220183143

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2gc35547g

40 000 citations in the Chemical Abstracts database). Hydrobromic acid is more effective than hydrochloric acid,[13] but it is much more costly. Moreover, the corresponding alkyl bromide is formed during the hydrolysis with HBr (analogous to the use of TMS bromide), which is a highly reactive alkylating agent. Hydrochloric acid is in general a less expensive option and the resulting alkyl chloride is less prone to alkylations, but the reactivity of HCl is low and higher reaction temperatures and longer reaction times (tens to hundreds of hours) are usually required.[14] The study[15] of the mechanism of the acid-catalyzed hydrolysis of phosphonate diesters and phosphate triesters with HCl suggested that relatively stable carbocations are formed during the hydrolysis of isopropyl or *tert*-butyl esters. The reaction can thus be labeled as hydrolysis of the $A_{AL}1$ type, where the oxygen atom of the ester function is protonated in the first step (Scheme 1). In the rate determining step, the protonated ester releases the relevant carbocation, which further recombines with the present chloride anion to give alkyl chloride.

Following the assumption that stabilization of the carbocation can speed up the reaction, such a hydrolysis may be accelerated by increasing the polarity of the environment. A super-polar environment in microwave-heated organic reactions may be one of the factors responsible for the acceleration of the studied reactions.[16]



Scheme 1 The mechanism of acid-catalyzed hydrolysis of phosphonate diesters (for alkyls forming relatively stable carbocations).

For this reason, it seemed logical to run acid-catalyzed hydrolysis using microwave irradiation. Herein we report on the optimized microwave (MW)-assisted hydrolysis of acyclic nucleoside phosphonate diesters to the corresponding phosphonic acids.[17]

Results and discussion

Our original theory was that application of an equimolar amount of HCl for each ester functionality should be sufficient to complete the hydrolysis of phosphonate diesters and all HCl used would be consumed. In this case, a neutral reaction mixture containing only pure product and volatile alkyl chlorides would be obtained, eliminating laborious isolation and purification techniques (chromatography, desalination, *etc*.) and giving such a method great advantage over the methods currently used.

Standard 0.5 M and 1.0 M HCl solutions were prepared for precise dosing of the required amounts of the acid during our initial hydrolytic experiments. During the first set of experiments, another great advantage of this hydrolytic method was discovered: since the reaction is conducted in a closed reaction vessel, the course of the reaction can be observed by monitoring the pressure in the reaction vessel. Fig. 1 shows monitoring of the reaction temperature and pressure during the hydrolysis of isopropyl diester **1** (1 mmol) in 4 ml of 0.5 M HCl (2 mmol of HCl) using a CEM Discover reactor, leading to the formation of the free phosphonic acid **9** (Scheme 2, entry 1, Table 1). After approximately 2.5 min the set reaction temperature (dashed line) of 130 °C was reached, while the reaction pressure (solid line) inside the apparatus continued to rise gradually as isopropyl chloride was being formed. The pressure stopped rising after approximately 7 min when the reaction had reached full conversion. This was confirmed by running the set of experiments with identical reaction mixtures heated for 4, 5, 6 and 7 min, respectively. While the reaction mixture heated for 6 min contained traces of the starting compound **1**, it was no longer observed in the sample heated for 7 min.

Subsequently, without lengthy optimizations we carried out the hydrolysis of isopropyl diesters **2–8** under similar reaction

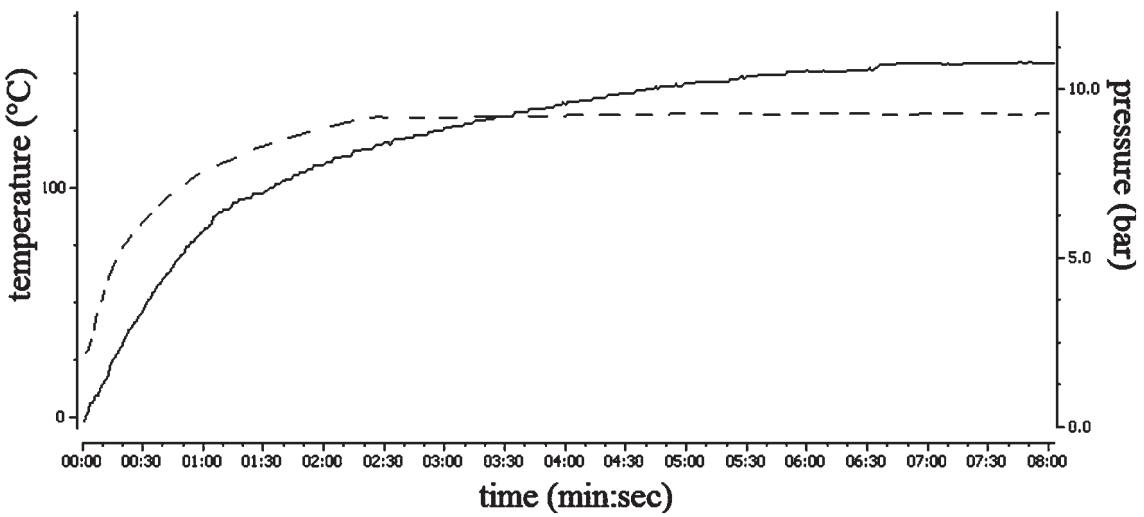
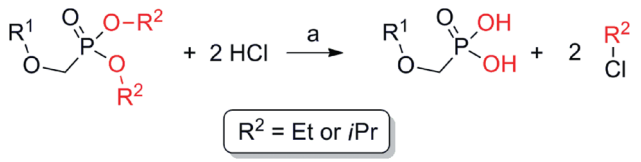


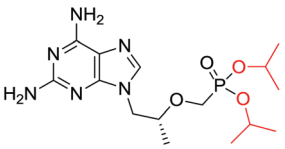
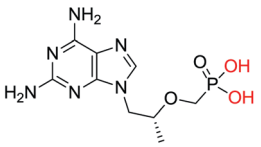
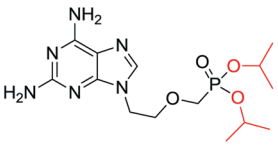
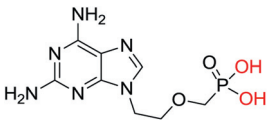
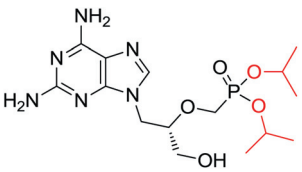
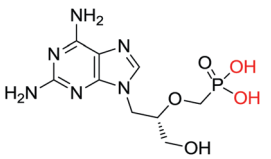
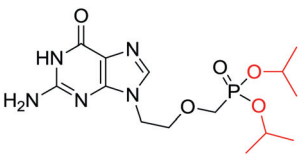
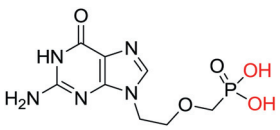
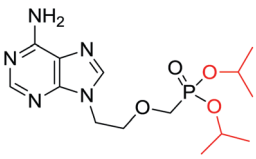
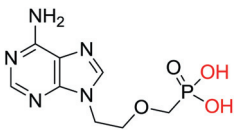
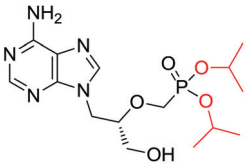
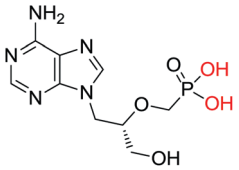
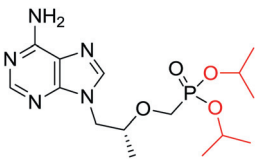
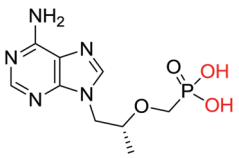
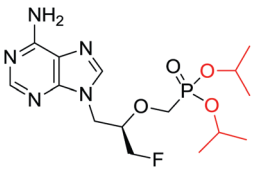
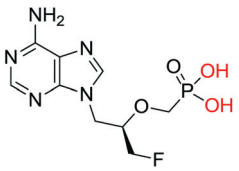
Fig. 1 Monitoring of the reaction pressure (solid line) and the reaction temperature (dashed line) during the MW-assisted hydrolysis of compound **1** to phosphonic acid **9** (Scheme 2). The reaction reached full conversion at ~7 min.



Scheme 2 General scheme for the MW-assisted hydrolysis of phosphonates diesters with HCl. Reagents and conditions: (a) HCl, H_2O, MW, 130–140 °C, 10–20 min.

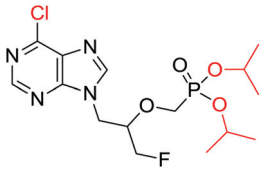
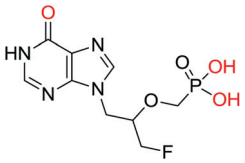
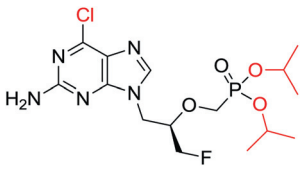
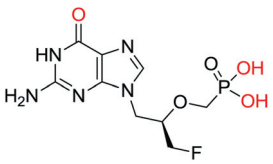
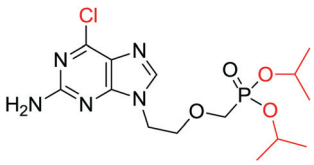
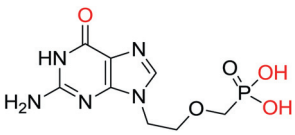
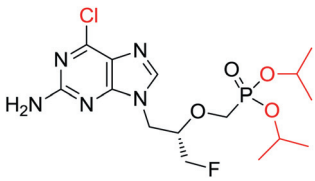
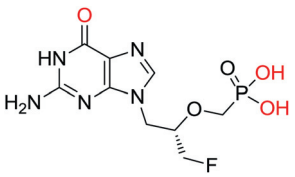
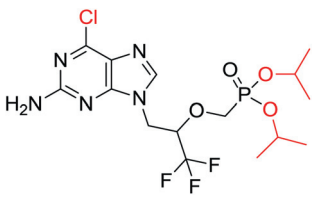
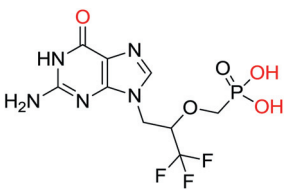
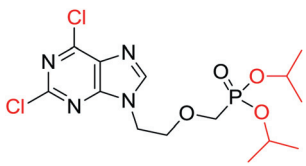
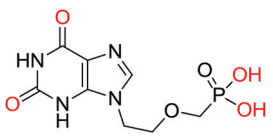
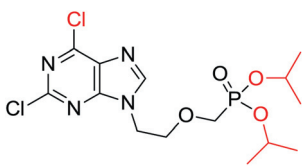
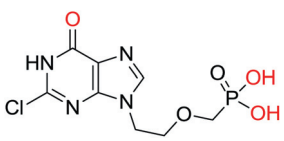
conditions (entries 2–8, Table 1, Scheme 2), obtaining free phosphonic acids **10–16** in high yields (77–93%). Important ANPs like PMEG (**12**, entry 4), adefovir (**13**, PMEA, entry 5), and tenofovir (**15**, PMPA, entry 7) were efficiently prepared by the described method (Table 1). Partial hydrolysis of the amino group at the C-6 position leading to the corresponding guanine derivatives (up to 10% of the by-products) was observed in the case of treatment of diaminopurine (DAP) derivatives **2** and **3** with 1.0 M HCl at 140 °C. The side reactions were considerably

Table 1 MW-assisted hydrolysis of phosphonate diisopropyl esters with HCl (Scheme 2)

Entry	Starting material		Product		Isolated yield[a]
1		**1**		**9**	77%, 79%[b]
2		**2**		**10**	78%
3		**3**		**11**	77%
4		**4**		**12**	93%, 91%[c]
5		**5**		**13**	92%, 95%[b]
6		**6**		**14**	88%, 92%[c]
7		**7**		**15**	91%, 90%[c]
8		**8**		**16**	93%

[a] 1 mmol scale. [b] 100 mmol scale. [c] 50 mmol scale.

Table 2 MW-assisted hydrolysis of isopropyl esters of phosphonates with HCl (Scheme 2) with the simultaneous hydrolysis of the chlorine atom(s) on the purine moiety

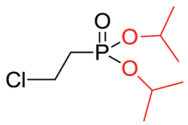
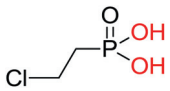
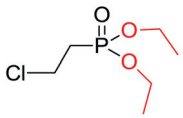
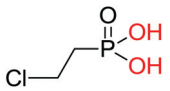
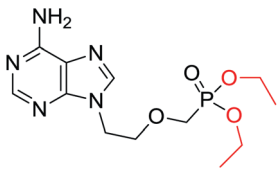
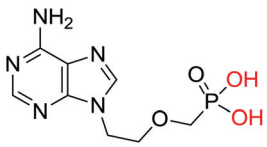
Entry	Starting material		Product		Isolated yield[a]
1		**17**		**23**	82%
2		**18**		**24**	83%
3		**19**		**25**	90%
4		**20**		**26**	85%
5		**21**		**27**	87%
6		**22**		**28**	80%
7		**22**		**29**	40%

[a] 1 mmol scale.

suppressed (less than 5% of the guanine derivative) by reducing reaction temperature to 130 °C (prolonged heating was necessary) and using 0.5 M HCl instead. Similarly, hypoxanthine derivatives were observed as by-products during hydrolysis of the adenine analogues **5–8** (in 1 M HCl at 140 °C), but in amounts less than 2%. Moreover, the above mentioned impurities are easy to remove. Guanine and hypoxanthine by-products are much more soluble in water and they remain in the solution during precipitation of the desired product.

Further it was discovered that the reaction conditions for the MW-assisted hydrolysis of phosphonate diesters can lead to simultaneous modifications of the purine moiety, namely to hydrolysis of chloropurines to corresponding oxopurines. We reasoned that only 1 equivalent of HCl should suffice to complete the hydrolysis of both isopropyl esters in the transformation of the 6-chloropurine derivative **17** into the corresponding hypoxanthine derivative **23**, since another equivalent of HCl is generated during the hydrolysis of the chlorine atom at the C-6 position of the purine ring. Indeed, the MW-assisted hydrolysis of compound **17** with 1 equivalent of HCl at 140 °C for 10 min afforded the expected hypoxanthine analogue **23** in an 82% yield (Scheme 2, entry 1, Table 2).

Table 3 Other examples of MW-assisted hydrolysis of phosphonate dialkyl esters with HCl (Scheme 2)

Entry	Starting material		Product		Isolated yield[a]
1		**30**		**33**	84%[a]
2		**31**		**33**	79%[a]
3		**32**		**13**	78%[b]

[a] 10 mmol scale. [b] 1 mmol scale.

Analogously, isopropyl diesters **18–21**, derived from 2-amino-6-chloropurine, were then hydrolyzed to the corresponding guanine derivatives **24–27** in high yields (83–90%). This is a highly successful method for the synthesis of guanine ANPs which are otherwise difficult to access synthetically due to the problematic and non-regioselective alkylation of the guanine bases.[18]

ANPs derived from the xanthine base are even more synthetically challenging compounds. The only examples known so far were prepared from the corresponding guanine analogues by diazotative oxodeamination.[19] Using our method, the 2,6-dichloropurine derivative **22** was transformed into the desired xanthine product **28** in 80% yield (entry 6, Table 2). Moreover, by meticulous control of the reaction conditions partially selective hydrolyses of a single chlorine atom can be achieved to yield the corresponding 2-chlorohypoxanthine compound **29** (entry 7, Table 2), although in a 40% yield only. The rest of the material was identified as compound **28**.

Theoretically, during the hydrolysis of the 2,6-dichloropurine derivatives (*e.g.* compound **22**, Table 2) only a catalytic amount of HCl is necessary. Nevertheless, the experiments showed that a catalytic amount of HCl is not sufficient to complete the reaction due to the fact that the acid-catalyzed hydrolysis of the chlorine atom in the C-2 position of the purine ring occurs at a higher temperature than is necessary for hydrolysis of the isopropyl ester groups. Thus, from our experience, 1 equivalent of HCl is necessary for the full and fast conversion of compound **22** to the free phosphonic acid **28** (entry 6, Table 2).

It was also shown that this method can be in general used for the preparation of other types of phosphonic acids. For example, an important agrochemical compound ethephone (**33**)[20] can be prepared in high yield (84%) by MW-assisted treatment of isopropyl diester **30** with HCl (3 eq.) at 100 °C in only 10 min (entry 1, Table 3).

Finally, we applied our MW-assisted methodology to the hydrolysis of commonly used ethyl esters of phosphonates. Diethyl (2-chloroethyl)phosphonate (**31**) was fully hydrolyzed to ethephone (**33**) with HCl (3 eq.) at 100 °C in 25 min (79% entry 2, Table 3). As expected, the reaction conditions for full hydrolysis of isopropyl diesters were not sufficient for the complete removal of the ethyl groups. Due to lower stability of ethylium (ethyl carbocation) compared to prop-2-ylium, it was necessary to increase the reaction time approximately threefold to achieve the complete conversion of ethyl diester **31** to ethephone (**33**). Similarly, adefovir (**13**) was prepared in 78% yield by treatment of ethyl diester **32** with 2 equivalents of HCl at 140 °C in 30 min (entry 3, Table 3), compared to the 92% yield of **13** from the isopropyl analogue **5** at 140 °C in only 10 min (entry 5, Table 1).

A significant feature of the described MW-assisted hydrolytic method is the simplicity of isolation of the final free phosphonic acids. The reactions can be carried out in relatively concentrated solutions (0.25 M to 1 M), and since all HCl is consumed during the reaction, the desired product often spontaneously and quantitatively precipitates directly from the cooled neutral reaction mixture. Most ANPs were prepared in >98% purity by simple filtration and sequential washing with water, ethanol, and acetone. As already mentioned, the guanine and hypoxanthine impurities formed during acid hydrolysis of 2,6-diaminopurine and adenine analogues, respectively, are compounds with much higher solubility in water, and they remain in the mother liquor, yielding pure ANPs after precipitation from the reaction mixture. On the other hand, if ANPs derived from guanine, hypoxanthine or xanthine are the required products, they can be easily and quantitatively precipitated by simple addition of acetone to the reaction mixture since phosphonic acids (*e.g.* ANPs and ethephone) are practically insoluble in acetone.

As already described above, it is necessary to use at least one equivalent of HCl for the preparation of the desired xanthine analogues from the corresponding 2,6-dichloropurine derivatives. Two more equivalents of HCl are formed during the hydrolysis of the chlorine atoms at the 2,6-dichloropurine moiety, and thus the reaction mixture before work-up contains about one equivalent of HCl. The xanthine derivatives, however,

are not basic enough to form the relevant hydrochlorides,[21] and pure xanthine ANPs (*e.g.* compound **28**, entry 6, Table 2) are isolated easily by addition of acetone. Furthermore, it seems preferable to use acetic acid instead of acetone for the initiation of the crystallization (precipitation) of the xanthine analogues.

It has also been mentioned that when trimethylsilyl bromide is used for hydrolysis of phosphonate diesters, impurities are formed that are quite difficult to remove. Detailed elementary analysis (measured on SPECTRO iQ II X-ray fluorescence analyzer, SPECTRO Analytical Instruments) showed that ANPs prepared using trimethylsilyl bromide[22] had silicon-containing impurities. On the other hand, according to the analogous elementary analysis, compound **9** prepared by our method using MW-assisted hydrolysis (Scheme 2) does not contain silicon nor chlorine atoms, and the purity is >98% according to HPLC analysis. Moreover, compound **9** met the specification in every way for the active pharmaceutical ingredient (>99.5% according to the HPLC) after a single crystallization from water.

Considering the relatively harsh conditions of the MW-assisted hydrolysis, the optical purity of compound **9** was scrutinized using a new method based on capillary electrophoresis of ANPs.[23] The optical purity of compound **9** was determined to be 99.2%. Thus, the studied ANPs do not racemize under the conditions for MW-assisted hydrolysis using HCl.

The scale-up of the described MW-assisted hydrolysis of phosphonate diesters to their corresponding free phosphonic acids was performed on the Milestone Batch and Flow MW reactors (see ESI†). Since continuous flow microwave reactors are highly energetically efficient and thus environmentally friendly,[24] optimized MW-assisted hydrolysis may soon become a method of choice for the large scale syntheses of biologically relevant phosphonic acids. A number of ANPs (**9**, **11**, **12**, **13**, **14**, **21** and **22**) were prepared in multigram scale and compound **9** even to the amount of 250 g (71% after two crystallizations, 99.7% purity according to HPLC). Furthermore, it is important to mention here that despite more than twenty years of intensive research[25] of ANPs yielding such important drugs such as adefovir, cidofovir, and tenofovir, this is the first record of the synthesis of compounds **27**, **28**, and **29**.

Conclusions

In conclusion, effective MW-assisted hydrolysis of acyclic nucleoside phosphonate diesters to their corresponding free phosphonic acids has been developed. The 'green' protocol eliminates the use of harmful chemicals (trimethylsilyl halogenides, excess of hydrogen halogenides) and complicated isolation procedures, gives excellent yields of products in short reaction times, and can be easily scaled-up for industrial use in MW flow reactors.

General experimental 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 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^{-1}). 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 a 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.

Acknowledgements

This work was supported by Ministry of the Interior of the Czech Republic (VG20102015046) and by Gilead Sciences.

Notes and references

1 E. De Clercq, A. Holý, I. Rosenberg, T. Sakuma, J. Balzarini and P. C. Maudgal, *Nature*, 1986, **323**, 464.
2 (*a*) E. De Clercq, *J. Med. Microbiol.*, 1998, **47**, 1; (*b*) A. Holý, *Curr. Pharm. Des.*, 2003, **9**, 2567; (*c*) E. De Clercq and A. Holý, *Nat. Rev. Drug Discovery*, 2005, **4**, 928; (*d*) A. Holý, *Antiviral Res.*, 2006, **71**, 248; (*e*) E. De Clercq, *Antiviral Res.*, 2007, **75**, 1; (*f*) E. De Clercq, *Biochem. Pharmacol.*, 2007, **73**, 911; (*g*) J. de Jersey, A. Holý, D. Hocková, L. Naesens, D. T. Keough and L. W. Guddat, *Curr. Top. Med. Chem.*, 2011, **11**, 2085.
3 (*a*) E. De Clercq, *Intervirology*, 1997, **40**, 295; (*b*) E. De Clercq, *Clin. Microbiol. Rev.*, 2003, **16**, 569; (*c*) E. De Clercq, *Expert Rev. Anti-Infect.*, 2003, **1**, 21.

4 (*a*) E. De Clercq and A. Holý, *Antimicrob. Agents Chemother.*, 1991, **35**, 701; (*b*) J. Neyts, R. Snoeck, J. Balzarini and E. De Clercq, *Antiviral Res.*, 1991, **16**, 41; (*c*) E. De Clercq, *Rev. Med. Virol.*, 1993, **3**, 85; (*d*) M. J. M. Hitchcock, H. S. Jaffe, J. C. Martin and R. J. Stagg, *Antiviral Chem. Chemother.*, 1996, **7**, 115.

5 C. R. Wagner, V. V. Iyer and E. J. McIntee, *Med. Res. Rev.*, 2000, **20**, 417.

6 (*a*) V. J. Stella, R. T. Borchardt, M. J. Hageman, R. Oliyai, H. Maag and J. W. Tilley, *Prodrugs: Challenges and Rewards*, Springer, New York, 2007; (*b*) R. L. Mackman and T. Cihlar, *Annu. Rep. Med. Chem.*, 2004, **39**, 305; (*c*) M. E. Ariza, *Drug Des. Rev.*, 2005, **2**, 373; (*d*) S. J. Hecker and M. D. Erion, *J. Med. Chem.*, 2008, **51**, 2328.

7 P. Jansa, O. Baszczyňski, M. Dračínský, I. Votruba, Z. Zídek, G. Bahador, G. Stepan, T. Cihlar, R. Mackman, A. Holý and Z. Janeba, *Eur. J. Med. Chem.*, 2011, **46**, 3748.

8 C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981.

9 (*a*) P. Jansa, A. Holý, M. Dračínský, O. Baszczyňski, M. Česnek and Z. Janeba, *Green Chem.*, 2011, **13**, 882; (*b*) O. Baszczyňski, P. Jansa, M. Dračínský, M. M. Kaiser, P. Špaček and Z. Janeba, *RSC Adv.*, 2012, **2**, 1282.

10 I. Kosiova, Z. Tocik, M. Budesinsky, O. Simak, R. Liboska, D. Rejman, O. Paces and I. Rosenberg, *Tetrahedron Lett.*, 2009, **50**, 6745.

11 A. Holý, *Synthesis*, 1998, 381.

12 (*a*) C. E. McKenna and J. Schmidhauser, *J. Chem. Soc., Chem. Commun.*, 1979, 739; (*b*) O. Baszczyňski, P. Jansa, M. Dračínský, B. Klepetářová, A. Holý, I. Votruba, E. de Clercq, J. Balzarini and Z. Janeba, *Bioorg. Med. Chem.*, 2011, **19**, 2114; (*c*) P. Jansa, O. Hradil, O. Baszczyňski, M. Dračínský and Z. Janeba, *Tetrahedron*, 2012, **68**, 865; (*d*) D. Hocková, M. Masojídková and A. Holý, *Collect. Czech. Chem. Commun.*, 2005, **70**, 247; (*e*) M. Krečmerová, M. Masojídková and A. Holý, *Bioorg. Med. Chem.*, 2010, **18**, 387; (*f*) M. Krečmerová, A. Holý, A. Pískala, M. Masojídková, G. Andrei, L. Naesens, J. Neyts, J. Balzarini, E. De Clercq and R. Snoeck, *J. Med. Chem.*, 2007, **50**, 1069; (*g*) P. Doláková, M. Dračínský, M. Masojídková, V. Šolínová, V. Kašička and A. Holý, *Eur. J. Med. Chem.*, 2009, **44**, 2408; (*h*) P. Jansa, V. Kolman, M. Dračínský, A. Kostinová, H. Mertlíková-Kaiserová and Z. Janeba, *Collect. Czech. Chem. Commun.*, 2011, **76**, 1187.

13 (*a*) C. Giordano and G. Castaldi, *J. Org. Chem.*, 1989, **54**, 1470; (*b*) P. Kafarski, B. Lejczak and J. Szewczyk, *Can. J. Chem.*, 1983, **61**, 2425; (*c*) D. P. Phillion and S. S. Andrew, *Tetrahedron Lett.*, 1986, **27**, 1477; (*d*) H. Stamm and G. Gerster, *Tetrahedron Lett.*, 1980, **21**, 1623.

14 (*a*) J. W. De Schutter, S. Zaretsky, S. Welbourn, A. Pause and Y. S. Tsantrizos, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5781; (*b*) Z. C. Duan, X. P. Hu, C. Zhang and Z. Zheng, *J. Org. Chem.*, 2010, **75**, 8319; (*c*) S. Hikishima, M. Hashimoto, L. Magnowska, A. Bzowska and T. Yokomatsu, *Bioorg. Med. Chem.*, 2010, **18**, 2275; (*d*) C. E. McKenna, B. A. Kashemirov, K. M. Błazewska, I. Mallard-Favier, C. A. Stewart, J. Rojas, M. W. Lundy, F. H. Ebetino, R. A. Baron, J. E. Dunford, M. L. Kirsten, M. C. Seabra, J. L. Bala, M. S. Marma, M. J. Rogers and F. P. Coxon, *J. Med. Chem.*, 2010, **53**, 3454; (*e*) T. Mendgen, T. Scholz and C. D. Klein, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5757; (*f*) R. Norlin and G. Lindberg, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 599; (*g*) M. J. Pulwer and T. M. Balthazor, *Synth. Commun.*, 1986, **16**, 733; (*h*) C. Selvam, N. Oueslati, I. A. Lemasson, I. Brabet, D. Rigault, T. Courtiol, S. Cesarini, N. Triballeau, H. O. Bertrand, C. Goudet, J. P. Pin and F. C. Acher, *J. Med. Chem.*, 2010, **53**, 2797; (*i*) V. N. Zemlianoy, A. Chernega, A. V. Gutov, A. O. Kolodiazhna and O. I. Kolodiazhnyi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 481.

15 (*a*) V. E. Belskii, *Usp. Khim.*, 1977, **46**, 1578; (*b*) J. R. Cox and M. G. Newton, *J. Org. Chem.*, 1969, **34**, 2600.

16 (*a*) L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199; (*b*) C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250; (*c*) C. O. Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127.

17 P. Jansa, A. Holý, M. Dračínský, O. Baszczyňski, M. Česnek and Z. Janeba, *Collect. Symp. Ser.*, 2011, **12**, 347.

18 (*a*) F. P. Clausen and J. Juhl-Christensen, *Org. Prep. Proced. Int.*, 1993, **25**, 373; (*b*) Z. Janeba and A. Holý, *Nucleosides, Nucleotides Nucleic Acids*, 2001, **20**, 1103.

19 (*a*) M. Česnek, D. Hocková, A. Holý, M. Dračínský, O. Baszczyňski, J. de Jersey, D. T. Keough and L. W. Guddat, *Bioorg. Med. Chem.*, 2012, **20**, 1076; (*b*) D. Hocková, M. Dračínský and A. Holý, *Eur. J. Org. Chem.*, 2010, 2885.

20 (*a*) R. T. Meister, *Farm Chemicals Handbook*, Meister Media Worldwide, 2009, ISSN 0430-0750; (*b*) J. H. Montgomery, *Agrochemicals Desk Reference: Environmental Data*, Lewis Publishers, Chelsea, MI, USA, 2nd edn, 1993, ISBN 0-87371-738-4; (*c*) U.S. Environmental, Protection Agency, *Pesticide Fact Sheet Number 176: Ethephon*, Office of Pesticide Programs, Registration Div., Washington, DC, USA, 1988.

21 A. G. Ogston, *J. Chem. Soc.*, 1935, 1376.

22 A. Holý and M. Masojídková, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1196.

23 V. Šolínová, V. Kašička, P. Sázelová and A. Holý, *Electrophoresis*, 2009, **30**, 2245.

24 J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794.

25 For recent reviews: (*a*) R. Mackman and T. Cihlar, Acyclic and cyclic nucleoside phosphonates, *Methods Princ. Med. Chem.*, 2011, **50**, 91; (*b*) E. De Clercq, *Biochem. Pharmacol.*, 2011, **82**, 99; (*c*) E. De Clercq, *Antiviral Res.*, 2007, **75**, 1.

