Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2010, **20**, 226–228
Mendeleev Communications

Stereospecific cascade cyclization reaction with the formation of tetracyclic hexacoordinated phosphorus derivatives

Mikhail A. Pudovik,* Lyudmila K. Kibardina, Svetlana A. Terent'eva, Alexander R. Burilov, Olga N. Kataeva, Galina A. Chmutova, Shamil K. Latypov, Oleg G. Sinyashin and Vladimir A. Alfonsov

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 755 322; e-mail: pudovik@iopc.knc.ru

DOI: 10.1016/j.mencom.2010.06.015

A new type of stereospecific cascade cyclization was observed in the phosphorylation reaction of *N*,*N*′-bis(salicylidene)ethylenediimine with alkylenechlorophosphites, which resulted in the formation of tetracyclic hexacoordinated phosphorus derivatives containing the P–C–N fragment with a chiral carbon atom in the α-position to phosphorus.

The development of new approaches to the synthesis of cyclic structures involving intramolecular transformations of polyfunctional three- and four-coordinated phosphorus derivatives has been a subject of our latest interest. In particular, the addition of proton nucleophiles to chloromethyliso(thio)cyanatophosphonates-(phosphinates) resulted in a series of phosphorylated ureas, thioureas, uretanes and amides, which undergo intramolecular cyclization to give saturated and unsaturated phosphorus and organoelement heterocycles.[1–3]

Note that cyclization reactions resulting in the formation of an asymmetric centre in the molecules of organophosphorus compounds, as a rule, proceed with high stereoselectivity and can be used in the synthesis of enanthiopure substances.[4] The stereoselective synthesis of organophosphorus compounds is of considerable current interest because they exhibit biological activity.

We have tested a new approach to obtain polycyclic phosphorus compounds *via* the reaction of alkylenechlorophosphites with diimine **1**, which was obtained from salicylic aldehyde and ethylene diamine in a 2:1 ratio.[5] Phosphorylation of compound **1** with an equimolar amount of ethylenechlorophosphite **2a** without a base resulted in the formation of product **6a**† with the phosphorus chemical shift ^{31}P {^{1}H} –118.41 ppm characteristic of a hexacoordinated phosphorus atom.

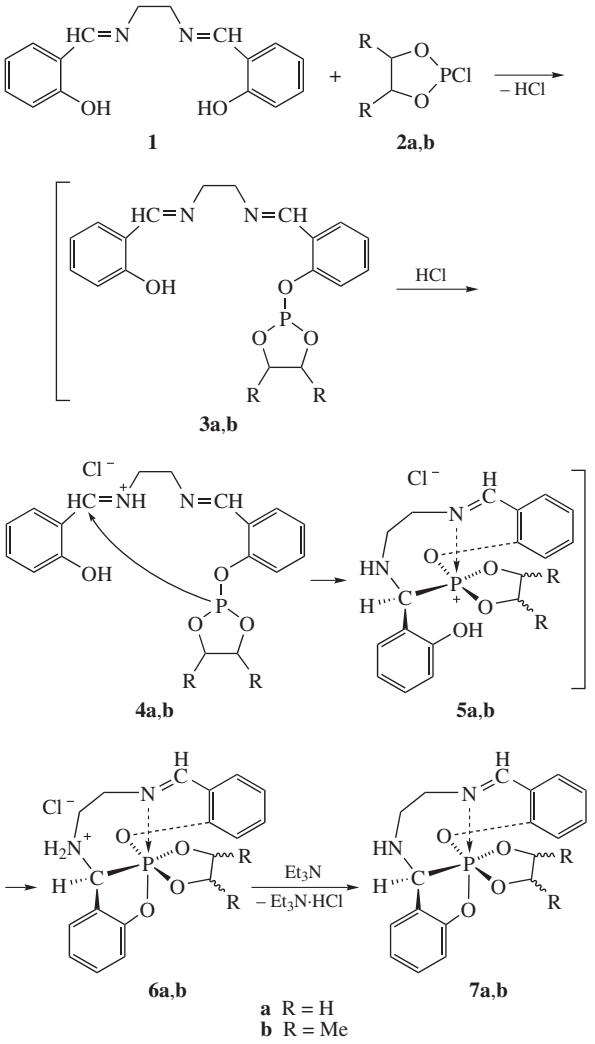
According to the elemental analysis, the product contained chlorine while IR spectra proved the presence of an ammonium fragment (NH^+). Compound **6a** being treated by triethylamine gave product **7a**‡ with a singlet δ_P –105.22 ppm in the ^{31}P {^{1}H} NMR spectrum. Compound **7a** was characterized by 1D/2D ^{1}H, ^{13}C and ^{31}P NMR experiments (^{1}H–^{1}H COSY, ^{1}H–^{31}P/^{1}H–^{13}C HSQC/HMBC). This structure has two chiral centres, phosphorus and carbon atoms, that assume the formation of a diastereomeric mixture. However, the NMR spectra of products **6a**, **7a** indicate the formation of only one diastereomer, *i.e.*, the cascade cyclizations proceed stereospecifically. The correlation between experimental and calculated [GIAO B3LYP/6-31G(d)//HF/6-31G] proton chemical shifts showed that the only diastereomer possessing the opposite configurations of the chiral centres at carbon and phosphorus atomes is formed.

The formation of polycyclic product **6a** can be described as follows. First, as it was proved by NMR spectroscopy, the replacement of chlorine by the *o*-OH group of a salicylic fragment affords phosphite **3a** (δ_P 129.1 ppm) and hydrogen chloride. The latter protonates an imine nitrogen atom thus increasing the electrophilicity of the C=N bond. Second, the P^{III} atom attacks the activated imino group with the formation of the P–C bond to give an asymmetric carbon atom. The next step is the stereospecific cyclization of oxaphosphorine *via* an attack of the second phenolic group at the phosphorus atom, which leads to a new chiral centre at the phosphorus atom; it is determined by the configuration of the chiral carbon atom. The stereochemistry of these interactions most likely depends on the coordination of nitrogen to phosphorus already at the early steps, and it is clearly pronounced in products **6** and **7**. The P–N coordination bond lengths in compounds **6a** and **7a** are 1.951(2) and 1.996(2) Å, respectively. Similar intramolecular coordination was observed earlier in pentacoordinated phosphorus derivatives.[6–8]

In order to analyze the diastereoselectivity of these reactions, we introduced asymmetry into the initial cyclic chlorophosphite and studied the interaction of racemic *d*,*l*-2,3-dimethylethylenechlorophosphite **2b** with imine **1**. The reaction proceeds in a similar way to give products **6b** and **7b** in high yields with the

† *1,1-Ethylenedioxy-3,4,11,12-dibenzo-6-aza-9-ammonia-2,13-dioxa-1-phosphabicyclo[8.3.0^{1,10}]tridecatri-3,5,11-ene chloride* **6a**. The mixture of **1** (1.34 g, 5.0 mmol) and **2a** (0.64 g, 5.0 mmol) in methylene chloride (15 ml) was kept for 24 h, the residue was removed by filtration, washed with diethyl ether and dried in a vacuum. Yield, 82%; mp 211 °C. IR (ν/cm^{-1}): 1628 (C=N), 2928, 3437 (NH_2^+). ^{31}P NMR (162.96 MHz, $CDCl_3$) δ: –118.41. MS, *m*/*z*: 394.8 $[M]^+$. Found (%): C, 54.99; H, 4.97; N, 6.72; P, 7.56. Calc. for $C_{18}H_{20}ClN_2O_4P$ (%): C, 54.75; H, 5.10; N, 7.09; P, 7.84.

‡ *1,1-Ethylenedioxy-3,4,11,12-dibenzo-6,9-diaza-2,13-dioxa-1-phosphabicyclo[8.3.0^{1,10}]tridecatri-3,5,11-ene* **7a**. The mixture of **6a** (0.9 g, 2.28 mmol) and triethylamine (0.23 g, 2.28 mmol) in methylene chloride (10 ml) was heated for 0.5 h at 40 °C. After 12 h, triethylamine hydrochloride was removed, **7a** was isolated after solvent removal in a vacuum. Yield, 43%; mp 177 °C. IR (ν/cm^{-1}): 1635 (C=N), 3345 (NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, 1H, *J* 4.0 Hz), 7.43 (d, 1H, *J* 7.3 Hz), 7.34 (d, 1H, *J* 7.4 Hz,), 7.31 (dd, 1H, *J* 8.2, 1.9 Hz,), 7.16 (d, 1H, *J* 7.4 Hz), 6.97 (d, 1H, *J* 5.0 Hz), 6.95 (d, 1H, *J* 7.4 Hz), 6.89 (d, 1H, *J* 8.2 Hz), 6.86 (d, 1H, *J* 7.6 Hz), 4.66 (ddd, 1H, *J* 11.6, 11.6, 3.2 Hz), 4.15 (s, 1H), 3.85 (m, 1H), 3.92 (m, 1H), 3.68 (m, 1H), 3.65 (m, 1H), 3.43 (m, 1H), 3.48 (m, 1H), 3.09 (ddd, 1H, *J* 11.6, 11.4, 2.9 Hz), 2.4 (br. m, NH). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 162.0 (d, J_{CP} 13.5 Hz), 162.0 (d, J_{CP} 3.9 Hz), 155.0 (d, J_{CP} 13.8 Hz), 136.1, 131.0, 128.2 (d, J_{CP} 1.9 Hz), 126.8 (d, J_{CP} 22.8 Hz), 126.5 (d, J_{CP} 21.8 Hz), 120.3 (d, J_{CP} 3.9 Hz), 120.1 (d, J_{CP} 0.3 Hz), 119.6 (d, J_{CP} 5.1 Hz), 119.3 (d, J_{CP} 1.3 Hz), 112.3 (d, J_{CP} 10.6 Hz), 69.5 (d, J_{CP} 192.3 Hz), 65.6 (d, J_{CP} 3.2 Hz), 60.2, 58.7 (d, J_{CP} 2.2 Hz), 49.9 (d, J_{CP} 2.6 Hz). ^{31}P NMR (162.96 MHz, $CDCl_3$) δ: –105.48. MS, *m*/*z*: 358.3 $[M]^+$. Found (%): C, 60.11; H, 5.18; N, 7.72; P, 8.37. Calc. for $C_{18}H_{19}N_2O_4P$ (%): C, 60.33; H, 5.34; N, 7.81; P, 8.64.



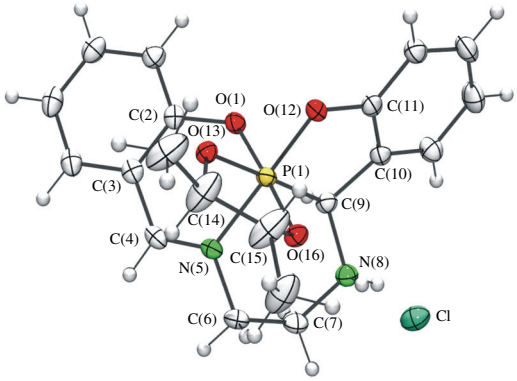


Figure 1 Molecular structure of compound **6b**.

only difference that two diastereomers are formed according to NMR data in a ratio of 2:1 (**6b**)[§] or 4:1 (**7b**)[¶].

Chemical shifts (^{1}H and ^{13}C) for most of the skeleton nuclei of these diastereomers are very similar, the major difference being observed for H(14) and H(15) protons [at the C(14) and C(15) carbon atoms]. Therefore, we can conclude that the polycyclic skeleton in two diastereomers is the same; two sets of signals in the NMR spectra correspond to diastereomers with different orientations of methyl substituents at the dioxaphospholane cycle. Experimentally observed difference in H(14) and H(15) (3.71 and 3.14 ppm, respectively) is in good agreement with calculated values (3.72 and 3.17 ppm, respectively) for the major diastereomer. For the minor diastereomer of **7b** with reverse configurations of Me-substituted C(14) and C(15) carbon atoms, non-equivalence of H(14) and H(15) protons is also reverted (3.23 *vs.* 3.79 ppm) in full agreement with calculations (3.31 *vs.* 3.91 ppm).

As shown by X-ray single crystal diffraction, the crystal taken from the crystallized mixture of diastereomers **6b** was a single racemic diastereomer with opposite configurations of chiral centres at carbon and phosphorus, the one, which is the major component in solution (Figure 1).[††]

The [B3LYP/6-31G(d,p), Gaussian-98] calculations[9] of both diastereomers of **6b** and **7b** performed with full geometry optimization showed that the (*S*,*R*)/(*R*,*S*) diastereomer is much more stable than the (*S*,*S*)/(*R*,*R*) diastereomer (ΔG^{298} = 4.59 and 4.72 kcal mol^{-1} for **6b** and **7b**, respectively). The diastereomers of **7b** with the same configuration of phosphorus and carbon C(9) chiral centres but the inverse configuration of the C(14) and C(15) carbon atoms in the dioxaphospholane ring have small energy difference ΔE(HF/6-31G) = 0.3 kcal mol^{-1} (ΔG^{298} = = 0.26 kcal mol^{-1}).

To summarize, a new type of cascade cyclization has been discovered, which yields new polycyclic six-coordinated phosphorus compounds. This cyclization results in the stereospecific

[§] *1,1-Dimethylethylenedioxy-3,4,11,12-dibenzo-6-aza-9-ammonia-2,13-dioxa-1-phosphabicyclo[8.3.0^{1,10}]tridecatri-3,5,11-ene chloride* **6b** (mixture of diastereomers, 2:1). Yield, 95%; mp 206–209 °C. IR (ν/cm^{-1}): 1629 (C=N), 3433 (NH_2^+). ^{1}H NMR (600 MHz, $CDCl_3$) δ: major isomer: 10.6 (br. s, 1H), 8.40 (d, 1H, *J* 5.6 Hz), 8.17 (d, 1H, *J* 7.7 Hz), 7.45 (dd, 1H, *J* 7.7, 7.7 Hz,), 7.40 (d, 1H, *J* 7.20 Hz,), 7.18 (dd, 1H, *J* 7.7, 7.7 Hz), 7.00 (dd, 1H, *J* 7.7, 7.7 Hz), 6.90 (d, 1H, *J* 7.7 Hz), 6.85 (m, 2H), 5.03 (dd, 1H, *J* 12.2, 12.2 Hz), 4.32 (d, 1H, *J* 8.6 Hz), 4.23 (d, 1H, *J* 12.2 Hz), 4.08 (d, 1H, *J* 12.2 Hz), 3.64 (m, 1H), 3.32 (dd, 1H, *J* 12.2, 12.2 Hz), 3.03 (m, 1H), 2.4 (br. s, NH), 1.02 (d, 3H, *J* 5.6 Hz), 0.98 (d, 3H, *J* 6.3 Hz); minor isomer: 8.42 (d, 1H, *J* 6.8 Hz), 8.15 (d, 1H, *J* 7.7 Hz), 4.75 (dd, 1H, *J* 11.7, 11.7 Hz), 4.30 (d, 1H, *J* 11.3 Hz), 4.20 (m, 1H), 4.10 (m, 1H), 3.76 (m, 1H), 3.34 (m, 1H), 3.06 (m, 1H), 1.12 (d, 3H, *J* 5.6 Hz), 0.86 (d, 3H, *J* 6.3 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: major isomer: 164.3 (d, J_{CP} 2.2 Hz), 160.5 (d, J_{CP} 12.8 Hz), 155.2 (d, J_{CP} 9.9 Hz), 137.2 (s), 131.8 (s), 130.4 (s), 127.9 (d, J_{CP} 20.5 Hz), 121.1 (s), 120.0 (d, J_{CP} 5.6 Hz), 119.6 (s), 119.1 (d, J_{CP} 6.6 Hz), 113.0 (d, J_{CP} 13.6 Hz), 74.5 (s), 73.6 (s), 65.1 (d, J_{CP} 208.0 Hz), 58.0 (s), 47.3 (s), 17.0 (d, J_{CP} 16.9 Hz), 16.9 (d, J_{CP} 9.5 Hz); minor isomer: 165.5 (d, J_{CP} 2.2 Hz), 160.6 (d, J_{CP} 12.1 Hz), 155.0 (d, J_{CP} 9.9 Hz), 137.0 (s), 131.5 (s), 130.4 (s), 127.6 (d, J_{CP} 20.9 Hz), 121.1 (s), 119.9 (d, J_{CP} 5.6 Hz), 119.6 (s), 119.3 (d, J_{CP} 6.6 Hz), 112.8 (d, J_{CP} 13.6 Hz), 73.4 (s), 72.7 (d, J_{CP} 1.5 Hz), 64.6 (d, J_{CP} 206.1 Hz), 56.5 (s), 47.7 (s), 18.2 (d, J_{CP} 9.5 Hz), 17.7 (d, J_{CP} 17.7 Hz). ^{31}P NMR (162.96 MHz, $CDCl_3$) δ: –118.21 (major isomer), –118.50. Found (%): C, 56.44; H, 5.72; N, 6.38; P, 7.26. Calc. for $C_{20}H_{24}ClN_2O_4P$ (%): C, 56.79; H, 5.72; N, 6.62; P, 7.32.

[¶] *1,1-Dimethylethylenedioxy-3,4,11,12-dibenzo-6,9-diaza-2,13-dioxa-1-phosphabicyclo[8.3.0^{1,10}]tridecatri-3,5,11-ene* **7b**: (mixture of diastereomers, 4:1). Yield, 87%; mp 168–172 °C. After heating **7b** with benzene (15 ml) (1 h at 80 °C), the solution was filtered and evaporated in a vacuum. The individual major isomer was isolated. Yield, 37%; mp 172–173 °C. IR (ν/cm^{-1}): 1630 (C=N), 3377 (NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, 1H, *J* 3.4 Hz), 7.42 (dd, 1H, *J* 7.6, 7.6 Hz), 7.33 (d, 1H, *J* 7.6 Hz), 7.23 (dd, 1H, *J* 7.8, 1.5 Hz), 7.16 (dd, 1H, *J* 8.2, 7.6 Hz), 6.96 (d, 1H, *J* 7.6 Hz), 6.93 (dd, 1H, *J* 7.6, 7.6 Hz), 6.89 (d, 1H, *J* 8.2 Hz), 6.86 (dd, 1H, *J* 7.6, 7.6 Hz), 4.91 (ddd, 1H, *J* 11.3, 11.3, 2.9 Hz), 4.13 (s, 1H), 3.71 (m, 1H), 3.69 (d, 1H, *J* 11.3 Hz), 3.48 (dd, 1H, *J* 13.7, 2.9 Hz), 3.14 (m, 1H), 3.08 (dd, 1H, *J* 11.3, 13.7 Hz), 2.3 (br. m, NH), 1.17 (d, 3H, *J* 6.1 Hz), 1.08 (d, 3H, *J* 5.9 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 162.3 (d, J_{CP} 13.1 Hz), 161.6 (d, J_{CP} 3.2 Hz), 155.3 (d, J_{CP} 13.8 Hz), 135.9 (s), 130.9 (s), 128.2 (d, J_{CP} 2.2 Hz), 126.8 (d, J_{CP} 21.8 Hz), 126.7 (d, J_{CP} 21.8 Hz), 120.4 (d, J_{CP} 3.5 Hz), 119.8 (s), 119.7 (d, J_{CP} 4.8 Hz), 119.2 (d, J_{CP} 1.0 Hz), 112.4 (d, J_{CP} 10.9 Hz), 74.1 (s), 72.5 (d, J_{CP} 1.9 Hz), 70.0 (d, J_{CP} 193.3 Hz), 65.8 (d, J_{CP} 2.6 Hz), 49.9 (s), 17.5 (d, J_{CP} 8.3 Hz), 17.3 (d, J_{CP} 17.3 Hz). ^{31}P NMR (162.96 MHz, $CDCl_3$) δ: –107.22. Found (%): C, 62.03; H, 5.77; N, 7.26; P, 7.83. Calc. for $C_{20}H_{23}N_2O_4P$ (%): C, 62.12; H, 5.95; N, 7.24; P, 8.01.

formation of the P–C–N fragment with a chiral carbon atom in the α-position. The reaction can be used to synthesize enantiopure aminophosphonic acid derivatives, which are of importance in bioorganic chemistry.[10]

This work was supported by the Russian Foundation for Basic Research (grant no. 09-03-00029). We are grateful to Dr. R. Fröhlich and Professor P. Metz for using X-ray facilities at the Universities of Münster and Dresden. O.K. acknowledges the support of Deutsche Forschungsgemeinschaft.

References

1 N. A. Khailova, N. E. Krepysheva, G. M. Saakyan, R. Kh. Bagautdinova, A. A. Shaimardanova, N. M. Azancheev, I. A. Litvinov, A. T. Gubaidullin, V. V. Zverev, M. A. Pudovik and A. N. Pudovik, *Zh. Obshch. Khim.*, 2002, **72**, 1145 (*Russ. J. Gen. Chem.*, 2002, **72**, 1071).

†† *X-ray crystal structure analysis for* **6b**: $C_{20}H_{28}ClN_2O_6P$, $M = 458.86$, colourless crystal, 0.40×0.25×0.05 mm, monoclinic, space group $P2_1/c$ (no. 14), at 198 K: $a = 8.4519(1)$, $b = 25.2317(3)$ and $c = 10.2769(2)$ Å, $\beta = 102.543(1)°$, $V = 2139.30(5)$ Å^3, $d_{calc} = 1.425$ g cm^{-3}, $\mu = 0.293$ mm^{-1}, empirical absorption correction ($0.892 \leq T \leq 0.986$), $Z = 4$, $\lambda = 0.71073$ Å, ω and φ scans, 31079 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.67$ Å^{-1}, 5497 independent ($R_{int} = 0.086$) and 4033 observed reflections [$I \geq 2\sigma(I)$], 293 refined parameters, $R = 0.050$, $wR_2 = 0.126$, maximum residual electron density 0.94 (–0.76) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. The structures were solved by a direct method using the SHELXS program and refined by the full-matrix least-squares using the SHELXL-97 program on all F^2 data.[11] All non-hydrogen atoms were refined anisotropically. The final residuals were $R = 0.0433$, $R_w = 0.0801$. Data collection: images were indexed, integrated, and scaled using the APEX2 data reduction package.[12] The figure was made using the PLATON program.[13]

CCDC 756413 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

2 G. A. Chmutova, V. V. Zverev, M. A. Pudovik, N. A. Khailova and A. N. Pudovik, *Zh. Obshch. Khim.*, 2003, **73**, 1793 (*Russ. J. Gen. Chem.*, 2002, **73**, 1696).
3 M. A. Pudovik, S. A. Terenteva, R. Z. Musin, N. A. Khailova, O. N. Kataeva, I. A. Litvinov and A. N. Pudovik, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1657 (*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1722).
4 C. Laurenco, D. Bernard and R. Burgada, *Compt. Rend.*, 1974, **278C**, 1301.
5 C. M. Ray and C. P. Prabhakaran, *Indian J. Chem.*, 1995, **34**, 652.
6 K. P. John and R. Schmutzler, *J. Chem. Soc., Dalton Trans.*, 1974, 2466.
7 K. P. John, R. Schmutzler and W. S. Sheldrick, *J. Chem. Soc., Dalton Trans.*, 1974, 1841.
8 Ch. Y. Wong, R. McDonald and R. G. Cavell, *Inorg. Chem.*, 1996, **35**, 325.
9 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98, Revision A.7*, Gaussian, Inc., 1998.
10 *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, eds. V. P. Kukhar and H. R. Hudson, John Wiley & Sons, Chichester, 2000.
11 G. M. Sheldrick, *SHELXS-97 Program for Solution of Crystal Structure*, University of Göttingen, Germany, 1997.
12 *APEX2 (Version 2.1), SAINTPlus. Data Reduction and Correction Program. Version 7.31A*, Bruker Advansed X-ray Solutions, Bruker AXS Inc., Madison, Wisconsin, USA, 2006.
13 A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, 34.

Received: 8th February 2010; Com. 10/3462