



Cite this: *RSC Adv.*, 2017, 7, 18211

Efficient strategy toward saturated N,P-heterocycles. Synthesis of 1,2-azaphospholidines and extension to the preparation of azaphosphacane and azaphosphanane higher homologues†

H. Boufroua,^a A. Abdelli,^{ab} F. Bourdreux,^a A. Gaucher,^a G. Clavier,^c M. L. Efrif,^b H. M'rabet^{*b} and D. Prim^{†*a}

Access to a new family of saturated N,P-heterocycles is described. Allylphosphonochloridates react with primary amines through a single synthetic operation involving the formation of N–P and N–C bonds to afford 1,2-azaphospholidines. The N–P bond formation/aza-Michael cyclization sequence is extended to eight- and nine-membered N,N,P-heterocycles. The first lines of a conformational study of diazaphosphacanes are described. DFT calculations allowed the identification of two diastereomers that display preferred boat-chair and twisted-boat-chair conformations.

Received 19th December 2016

Accepted 21st March 2017

DOI: 10.1039/c6ra28420e

rsc.li/rsc-advances

Building and functionalizing heterocycles has stimulated the research of methodological synthetic tools for many years. This thriving field is constantly evolving as the properties of these molecules are highly dependent on the presence of heteroatoms and the way they are connected with each other, the ring size as well as its aromatic or saturated nature. The state of saturation of heterocyclic compounds has been even considered recently as an additional descriptor of the molecular complexity in drug design.¹ The development of reliable synthetic methods, easy to implement, which allow selective access to saturated heterocycles of various sizes and comprising two or more heteroatoms becomes thus an issue of major importance.²

In this context, azaphosphacyclanes represent attractive targets that have focused much attention over the last decades mostly due to their biological and therapeutic properties.³ Indeed, members of this class of P-heterocycles display a wide panel of pharmaceutical and biological activities such as anticancer,⁴ cytotoxicity⁵ or antitumor effects.⁶ N,P-Heterocycles were also used as ligands for complexation of metals.⁷ The modification of their properties can be envisioned through the association of additional substituents at the heterocyclic core or

the modulation of the ring size. Both strategies represent synthetic challenges that directed the interest of the scientific community until recently.³ In this context, 1,2-azaphospholidines, are accessible from main synthetic routes based on the formation of N–P or C–P bonds during the final cyclisation step requiring the preparation of advanced precursors such as γ -amino phosphonochloridates, ammonium-phosphate salts, or Arbuzov-based starting material.⁸ Although more scarcely reported, combination phosphorochloridite derivatives and γ -chloropropylamines, ring expansion of polymethylated 1-azidophosphetanes account for the formation of 1,2-azaphospholidines.⁹ In addition, the ring closure metathesis (RCM) recently emerged as a convenient tool to prepare dihydro-phosphinine oxides that can be considered, using a further functionalization or reduction step, as advanced precursors in sequences leading to 1,2-azaphospholidine targets.¹⁰

In this communication, we disclose a versatile single step methodology towards the preparation of new 1,2-azaphospholidines. We envisioned the preparation of such saturated targets by taking advantage of the propensity of activated allylphosphono derivatives to undergo selective Michael-type additions γ to the P-atom¹¹ and

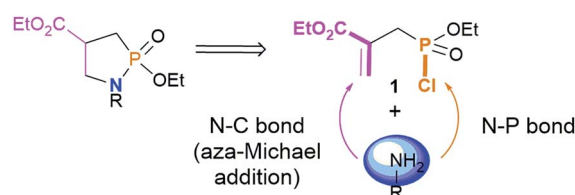


Fig. 1 One pot N–P bond formation – aza-Michael addition sequence.

^aUniversité de Versailles Saint Quentin-en-Yvelines, Institut Lavoisier de Versailles-UMR CNRS 8180, 45 avenue des Etats-Unis, 78035 Versailles, France. E-mail: damien.prim@uvsq.fr

^bUniversité de Tunis El Manar, Faculté des Sciences de Tunis, Laboratoire de Synthèse Organique et Hétérocyclique, 2092 Tunis, Tunisia. E-mail: mrabet.fst@gmail.com

^cENS-Cachan, PPSM-UMR CNRS 853, Bâtiment d'Alembert, 61, avenue du Président Wilson 94235 CACHAN, Cedex, France

† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra and computational details. See DOI: 10.1039/c6ra28420e



the dual reactivity of easily accessible phosphonochloridate **1**¹² (Fig. 1).

This new strategy would thus involve the formation of two N–P and N–C bonds in a single operation using a primary amine and allow the installation of unprecedented substituents at both the nitrogen and carbon centers in minimizing the production of waste (–HCl). Our strategy will also be extended to the synthesis of new eight- and nine-membered saturated N,P-heterocycles. First lines of the conformational study of diazaphosphacanes are described.

We started studying the reactivity of phosphonochloridate **1**¹² with a first set of primary amines. Indeed, the reactions of benzyl amine, aniline, 4-aminoindan, 1-adamantylamine and 1-

adamantylmethylamine with the phosphonochloridate **1** were successively examined (Table 1).

In refluxing toluene, the use of 2 eq. of benzylamine was shown optimal and led to the selective formation of 4-ethoxycarbonyl-1,2-azaphospholidines **4a** in 70% yield (entry 1). Attempts to increase yields using an additional base such as Et₃N, DBU to trap HCl or a larger excess of the reacting amine failed. Interestingly, neither the possible aza-Michael adduct nor the phosphoramidate **3** could be detected in the crude material. In contrast, moving from benzylamine to the less nucleophilic aniline (entry 2), gave the corresponding phosphoramidate **3a** in 60% yield. Although anilines may afford the corresponding aza-Michael adduct,¹³ the latter could not be

Table 1 Reaction of phosphonochloridate with various primary amines (isolated yields)

Entry	Amine 2	Time	3 (%)	4 (%)
1		16 h		 4a (70)
2		28 h	 3a (60)	
3		48 h	 3b (58)	
4		72 h	 3c (48)	
5		22 h		 4b (39)

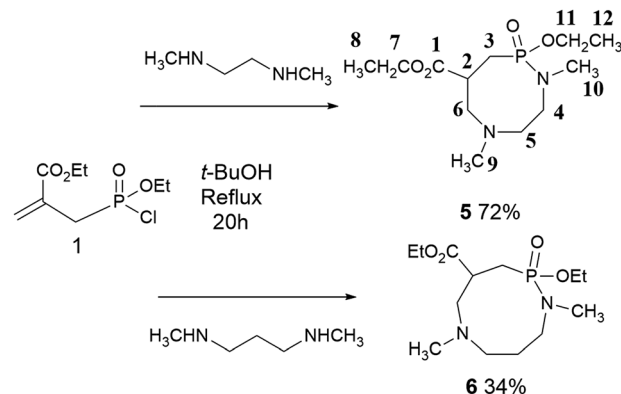


identified under such reaction conditions. Similarly, the reaction of 4-aminoindan under identical reaction conditions led to the formation of phosphoramidate **3b** as a unique product in 58% yield (entry 3). Comparison of adamantyl- and adamantylmethyl-amine gave a similar trend (compare entries 4 and 5). Indeed, phosphonochloridate **1** undergoes selective nucleophilic substitution at the P atom leading to the phosphoramidate **3c** in the presence of the bulky adamantylamine. In sharp contrast, the less sterically constrained adamantylmethyl-amine selectively afforded the expected 4-ethoxycarbonyl-1,2-azaphospholidine **4b** in 39% yield. Although several scenarios could rule the first step of the sequence, the coexistence of two competitive reactions involving the formation of the P–N bond vs. the formation of the C–N bond remains plausible. The most nucleophilic amines might preferentially afford the aza-Michael adduct prior the formation of the N–P bond. In the presence of lesser nucleophilic or bulky and sterically demanding amines such as aniline derivatives, reaction at the more electrophilic phosphorus atom might occur leading to the formation of the P–N phosphoramidate bond. Once the P–N bond formed, the decrease of nucleophilicity of the nitrogen atom lone pair plausibly precludes further aza-Michael cyclisation.

The methodology was next extended to the preparation of several new 4-ethoxycarbonyl-1,2-azaphospholidines **4c–f** as shown in Fig. 2. Under the aforementioned reaction conditions, we were able to cleanly isolate phospholidine targets from methylbenzylamine, 2-pyridinemethylamine, 2-thiophenemethylamine and 2-furanmethylamine in high yields ranging from 58 to 91% regardless of the electronic contribution of the heterocycle.¹⁴ Indeed electron rich thiophene and furane derivatives were isolated in similar yields by comparison with the electron deficient pyridine analogue. Phosphoramidate **3** and 1,2-azaphospholidines **4** display characteristic ³¹P NMR chemical shifts. Indeed, P atoms resonated at 25.1 to 27.5 ppm and 43.3 to 44.2 ppm for compounds **3** and **4** respectively.¹⁵

Our next goal was to react phosphonochloridate **1** with diamines in order to prepare N,P-heterocycles of larger size (Scheme 1). In this context, ethylene- and propylene-diamines would generate unprecedented eight- and nine-membered heterocycles “respectively”.

We focused on *N,N'*-dimethyl secondary amines in order to force each nitrogen atom to either generate the P–N or the C–N bond of the nucleophilic substitution – aza-Michael sequence and avoid the formation of phospholidines. Disappointingly, the use of the aforementioned conditions (in toluene at reflux) led to intractable mixtures of starting material and several P-based products. However, moving from toluene to *t*-BuOH



Scheme 1 First synthesis of diazaphosphocane **5** and diazaphosphonane **6**.

was beneficial to the formation of cyclic products. Indeed, refluxing **1** and 2 eq. *N,N'*-dimethylethylenediamine for 20 h afforded the unprecedented diazaphosphocane **5** in 72% yield. Although several side reactions might take place under these conditions and the formation of ethylene bisphosphoramides could not be ruled out, only compound **5** was cleanly isolated and identified after purification. Our strategy was further extended to the use of *N,N'*-dimethyl-1,3-propylenediamine in order to prepare the corresponding diazaphosphonane **6**. If the reaction tediously led to a mixture of products, the nine-membered N–P architecture was gratifyingly isolated in a fair 34% yield and fully characterized. In contrast to **6**, which showed limited stability over a few days even when stored under careful conditions, diazaphosphocane **5** revealed stable. Both N,N,P-heterocycles exhibit characteristic ³¹P NMR chemical shifts. Indeed, P atoms in **5** and **6** resonate at 35 and 34 ppm in good accordance with a decrease of the ring strain observed when moving from nearly 44 ppm for the five-membered N,P analogues. Both ¹³C and ³¹P NMR data suggest the presence of diastereomers compatible with the presence of two chiral centers that are the P and C2 atoms. Compounds **5** and **6** were obtained as mixtures of two diastereomers that explain enlarged signals displayed in ¹H NMR spectra. In fact, the complexity of ¹H NMR spectra most probably results from the contribution of several fingerprints intrinsic to the molecular structure of **5** and **6**. Gratifyingly, in the case of the stable compound **5**, both diastereomers **5dia1** and **5dia2** could be painfully separated on silica gel chromatography. ¹H NMR spectra of both diastereomer and comparison between them (ESI⁺) showed complementary signals but still display enlarged signals corresponding to the protons supported by the heterocyclic core. Classical variable-temperature NMR experiments were not conclusive and did not allow gaining further structural informations, but questioned about the impact of the joint presence of three heteroatoms within a medium-sized heterocycle.

Indeed, the presence of (i) one phosphorus atoms inducing P–H couplings, (ii) two chiral centers generating diastereomers, (iii) possible inversion of nitrogen atoms lone pairs and (iv) several potential conformations of the saturated flexible medium-sized ring, might all lead to an overlapped contribution of all these

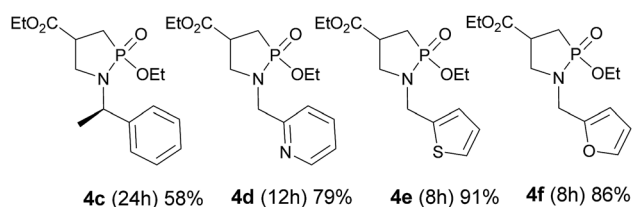


Fig. 2 Access to variously 1,2-azaphospholidines **4**.



structural features. We thus turned our attention to theoretical calculations with the aim to understand the complexity of the NMR data and give the first lines of the conformation space study of novel medium-sized heterocycles comprising one P and two N atoms. To this end, we focused in this paper on the diazaphosphocane **5** as the first representative example of this series of heterocycles. Examination of literature data showed that conformational analysis of medium rings has been the subject of sustained attention over the last decades. Within this area the conformation of cyclooctane,¹⁶ cyclononane,¹⁷ fused azocines and azonines¹⁸ but also eight-membered benzoannulated lactams¹⁹ or silicon- and boron-based heterocycles²⁰ have been examined using NMR and DFT techniques. In the latter studies, the shape of the saturated rings are driven by the presence of one or several fragments such as fused aromatic systems, amides or ketones, able to impose a partial rigidity to the backbone. In deep contrast with such relevant eight-membered ring systems described in the literature, unreported diazaphosphocane **5** do not display shape constraints. Apart, from the phosphoramidate P(O)N fragment, for which a possible contribution of a planar PN double bond cannot be excluded, the entire structure remains flexible. Our objectives were to try identifying both diastereomers and further gaining a first set of information towards a more complete study of the entire conformation space of such heterocycles.

We thus started by generating a distribution of conformations using molecular mechanics (MM) for both diastereomers **5a1** and **5a2** (see ESI[†]). We selected the most occurring conformations of lowest energy, for each diastereomers **5a1** and **5a2**. Those conformations were then used for quantum mechanics (QM) structure refinement at B3LYP/6-311++(d,p) level of theory. This basis set has been shown to be an excellent compromise between accuracy and computational time for this particular kind of calculations.²¹ As shown in Fig. 3, both families of computed enantiomers (**5a1/5a1'** and **5a2/5a2'**) display a close but not identical 3D geometry. Indeed, a preferred boat-chair (BC) conformation is calculated for **5a1** instead of a preferred twisted-boat-chair (TBC) conformation for **5a2**. Both preferred conformations are in good agreement with recent conformational studies dealing with medium-sized heterocycles.^{16–20}

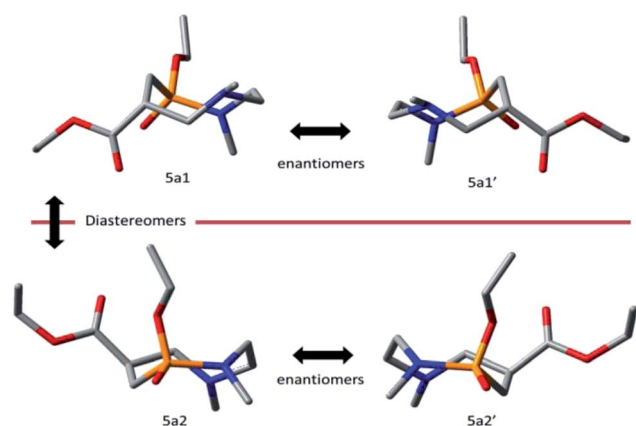


Fig. 3 Computed preferred conformations for diastereomers **5a1**, **5a1'**, **5a2** and **5a2'** (protons are omitted for clarity).

We next tried to assign each of them to their respective experimental data. To this end predictive chemical shifts were computed within the GIAO approximation using DFT at the PBE0/6-311+G(2d,p) level of theory on the preferred conformations **5a1** and **5a2**.^{22,23} Computed details for each diastereomer can be found in the ESI.[†] A careful comparison of scaled experimental and calculated chemical shifts has been carried out for H and C nuclei (see Table ESI[†]).²⁴ Data collected in Table 1 reflect the complexity of both ¹H and ¹³C NMR experimental spectra. Indeed, both separated diastereomer **5dia1** and **5dia2** display a close set of chemical shifts (compare columns 1/2 and 5/6). Computed data (columns 3/4 and 7/8) revealed a similar trend for nuclei 1–3, 7, 8, 11 and 12. In contrast, calculated chemical shifts for nuclei 4–6 and 9–10, exhibit marked deviations between **5a1** and **5a2**. Fig. 4 allowed visualizing $\Delta\delta$ between experimental data for **5dia1** and **5dia2** and between computed data for **5a1** and **5a2**. In both nuclei series, $\Delta\delta$ between experimental and computed data are strongly depending on their location at the diazaphosphocane core. Indeed, protons and carbons 4, 5 and 6 are representatives of a clear overestimation of the computed chemical shifts.²⁵

In these cases, variations of $\Delta\delta$ ranging from 0.00 to 0.27 ppm for protons and from 0.00 to 6.17 ppm for carbons were observed. In fact these nuclei belong to the more flexible fragment of the diazaphosphocane. Their chemical shifts are thus deeply impacted by tiny conformations modifications and

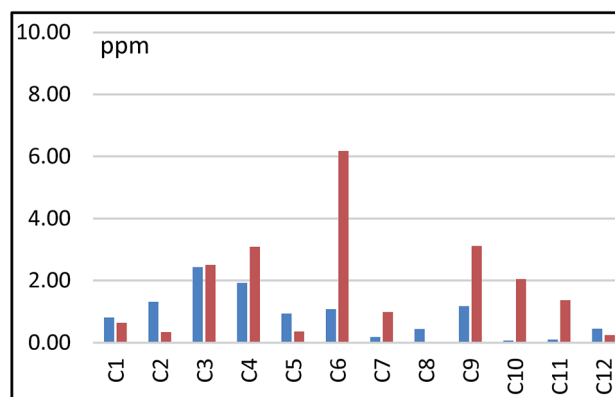
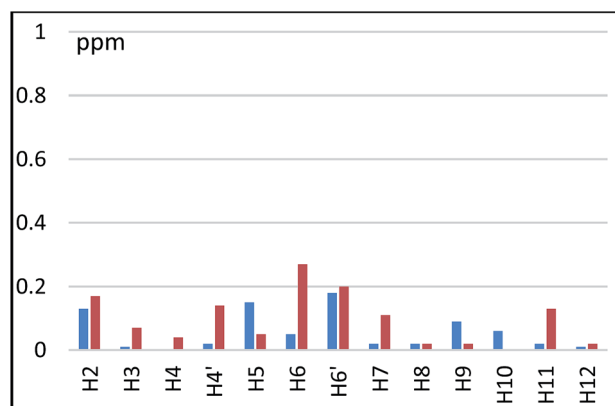


Fig. 4 Comparison of $\Delta\delta$ between experimental data for **5dia1** and **5dia2** in blue and between computed data for **5a1** and **5a2** in red.



may result from a contribution of several conformations. Other nuclei, such as 1, 2, 3 located at more rigid fragments of the heterocycle or at pendant ethyl groups exhibit lower variation of $\Delta\delta$ being thus less affected by conformational changes. Nuclei 9 and 10 are also worthy to be observed. If comparison of experimental and computed protons chemical shifts seemed more accurate, the corresponding carbons display largest variation of $\Delta\delta$. The differences observed for the carbon of the methyl groups positioned on both nitrogen atoms of the heterocycle perfectly illustrate the joint impact of conformational changes of the cycle, the inversion of the nitrogen atom lone pairs and the presence of the phosphorus atom. The presence of the phosphorus atom and the possible formation of a planar phosphoramidate moiety limit the degree of freedom of the nitrogen atoms substituted by C10, which consequently conducted to a smaller $\Delta\delta$ deviation than for C9.

With the aim to identify which experimental data set could match the calculated data, we undertook to compare computed and experimental chemical shifts by pairing NMR data and to calculate corrected mean absolute error (CMAD) as shown in Table 2 (ESI†).²⁶ The CMAD are very close in each case. Indeed, the latter range between 0.13 and 0.16 for ¹H (see Tables 2 and 3 ESI†) and between 1.52 and 2.57 for ¹³C. A first trend shows that the combination **dia2–5a2** seems the most consistent for both nuclei. This first approximation should also lead to lower CMAD for the **dia1–5a1** pair. Unfortunately, CMAD of 1.73 and 0.14 calculated for ¹³C and ¹H respectively do not allow a complete discrimination of both experimental and calculated pairs.

Conclusions

In summary, we have described an efficient approach for the preparation of a novel family of 1,2-azaphospholidines. The synthetic method combines the formation of an N–P and a N–C bond from a phosphonochloridate precursor and an intramolecular aza-Michael cyclization. This methodology was next successfully extended to prepare eight- and nine-membered saturated N,N,P-heterocycles by reacting the corresponding phosphonochloridate with 1,2- and 1,3-diamines respectively. The overlap of several conformational contributions led to complex analytical data. These observations encouraged us to complement the synthesis of these heterocycles with a first approach to the study of their conformational space. This first set of evidence arising from DFT calculations is in complete agreement with the presence of multiple conformations for both diastereomers of **5**. A preferred boat-chair (BC) as well as a preferred twisted-boat-chair (TBC) conformation was evidenced for **5a1** and **5a2** respectively. Our study represents a major challenge because these fully saturated heterocycles do not display any planar pattern but are set by an important degree of flexibility, possible interconversions at both nitrogen atoms, and further include one phosphorus atom which induces additional couplings. In this communication, we describe the basis for further study of the conformational space of medium-sized saturated heterocycles comprising several heteroatoms. The latter will require taking into account the contribution of all populations of conformers through a further

statistical analysis in order to refine the correlations with experimental data. A more complete study of conformations in the diazaphosphacane and diazaphosphonane series is currently underway and will be reported in due course.

Notes and references

- 1 T. J. Ritchie, S. J. F. MacDonald, R. J. Young and S. D. Pickett, *Drug Discovery Today*, 2011, **16**, 164; T. J. Ritchie and S. J. F. MacDonald, *Drug Discovery Today*, 2009, **14**, 1011; F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
- 2 C.-V. T. Vo, M. U. Luescher and J. W. Bode, *Nat. Chem.*, 2014, **6**, 310.
- 3 For recent overview see: R. Brewster, M.-C. Vandergeten and F. Montel, *Eur. J. Org. Chem.*, 2014, 905; H. Akbas, A. Okumus, Z. Kılıç, T. Hökelek, Y. Süzen, L. Y. Koç, L. Açık and Z. B. Çelik, *Eur. J. Med. Chem.*, 2013, **70**, 294; V. Point, R. K. Malla, F. Carriere, S. Canaan, C. D. Spilling and J.-F. Cavalier, *J. Med. Chem.*, 2013, **56**, 4393.
- 4 A. Paci, T. Martens and J. Royer, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1347; G. Zon, *Prog. Med. Chem.*, 1982, **19**, 205.
- 5 P. Maynard-Faure, C. Gonser, V. Vaime and D. Bouchu, *Tetrahedron Lett.*, 1998, **39**, 2315.
- 6 Q. Sun, R.-T. Li, W. Guo, J.-R. Cui, T.-M. Cheng and Z.-M. Ge, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3727.
- 7 S. S. Krishnamurthy, V. Sreenivasa Reddy, A. Chandrasekaran and M. Nethaji, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **64**, 99.
- 8 I. Natchev, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3699; D. J. Collins, P. F. Drygala and J. M. Swan, *Tetrahedron Lett.*, 1982, **23**, 1117; D. J. Collins, J. W. Hetherington and J. M. Swan, *Aust. J. Chem.*, 1974, **27**, 1759; O. V. Bykhovskaya, I. M. Aladzheva, D. I. Lobanov, P. V. Petrovskii, K. A. Lyssenko, I. V. Fedyanin and T. A. Mastryukova, *Russ. Chem. Bull.*, 2005, **54**, 2642; I. M. Aladzheva, D. I. Lobanov, O. G. V. Bykhovskaya, P. V. Petrovskii, K. A. Lyssenko and T. A. Mastryukova, *Heteroat. Chem.*, 2003, **14**, 596.
- 9 I. M. Aladzheva, O. V. Bykhovskaya, P. V. Petrovskii, K. A. Lyssenko, M. Y. Antipin and T. A. Mastryukova, *Russ. Chem. Bull.*, 2005, **54**, 2635; M. J. P. Harger, *J. Chem. Soc. D*, 1971, 442.
- 10 A. Abdelli, F. Bourdreux, A. Gaucher, M. L. Efrif, H. M'rabet and D. Prim, *Tetrahedron Lett.*, 2016, **57**, 379 and reference cited therein; P. R. Hanson and D. S. Stoianova, *Tetrahedron Lett.*, 1999, **40**, 3297; D. S. Stoianova and P. R. Hanson, *Org. Lett.*, 2000, **2**, 1769.
- 11 A. Abdelli, M. L. Efrif, A. Gaucher, H. M'rabet and D. Prim, *Tetrahedron Lett.*, 2015, **56**, 5397; A. Abdelli, A. Gaucher, M. L. Efrif, H. M'rabet and D. Prim, *Tetrahedron Lett.*, 2015, **56**, 1679; A. Abdelli, H. M'rabet, M. L. Efrif, A. Gaucher and D. Prim, *J. Sulfur Chem.*, 2014, **35**, 674.
- 12 Phosphonochloridate **1**, was readily prepared in 91% yield from allylphosphonate precursor with oxalyl chloride in dichloromethane according to known procedures (see ESI†): M. Lewandowska, P. Ruzskowski, D. Baraniak, A. Czarnecka, N. Kleczewska and L. Celewicz, *Eur. J. Med.*



- Chem.*, 2013, **67**, 188; N. Coşkun and M. Çetin, *Tetrahedron*, 2000, **56**, 2053; K. T. Sprott and P. R. Hanson, *J. Org. Chem.*, 2000, **65**, 4721.
- 13 For a recent example see: Z. Amara, E. Drege, C. Trouffard, P. Retailleau, M.-E. Tran Huu-Dau and D. Joseph, *Chem.-Eur. J.*, 2014, **20**, 15840.
- 14 Phospholidine derivatives are sensitive to air moisture generating the corresponding phosphoric acids by hydrolysis of the P-N bond and have thus to be carefully stored under Ar atmosphere and at low temperature as already observed and described in the literature. See: P. Fourgeaud, C. Midrier, J.-P. Vors, J.-N. Volle, J.-L. Pirat and D. Virieux, *Tetrahedron*, 2010, **66**, 758; Y. Machida and I. Saito, *J. Org. Chem.*, 1979, **44**, 865.
- 15 The presence of a set of two ^{31}P chemical shifts between 41 and 46 ppm was in complete accordance with the formation of mixtures of diastereomers. In some cases, diastereomers could be separated. See ESI.†
- 16 J. P. Fitzgerald, *J. Chem. Educ.*, 1993, **70**, 988; W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981.
- 17 F. A. L. Anet and J. J. Wagner, *J. Am. Chem. Soc.*, 1971, **93**, 5266.
- 18 M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. P. J. White, K. K. Hii, P. N. Horton and M. B. Hursthouse, *J. Org. Chem.*, 2005, **70**, 1552.
- 19 A. Witosinska, B. Musielak, P. Serda, M. Owinska and B. Rys, *J. Org. Chem.*, 2012, **77**, 9784.
- 20 L. P. Burke, A. D. DeBellis, H. Fuhrer, H. Meier, S. D. Pastor, G. Rihs, G. Rist, R. K. Rodebaugh and S. P. Shum, *J. Am. Chem. Soc.*, 1997, **119**, 8313; H. Braunschweig, I. Krummenacher, L. Mailänder and F. Rauch, *Chem. Commun.*, 2015, **51**, 14513.
- 21 For recent uses of this basis set see: P. R. Rablen, S. A. Pearlman and J. Finkbiner, *J. Phys. Chem. A*, 1999, **103**, 7357; M. A. Muñoz and P. Joseph-Nathan, *Magn. Reson. Chem.*, 2009, **47**, 578; B. Musielak, T. A. Holak and B. Rys, *J. Org. Chem.*, 2015, **80**, 9231.
- 22 PBE0 method revealed recently useful in the elucidation of complex natural heterocyclic molecules. See: K. M. Snyder, J. Sikorska, T. Ye, L. Fang, W. Su, R. G. Carter, K. L. McPhail and P. H.-Y. Cheong, *Org. Biomol. Chem.*, 2016, **14**, 5826.
- 23 Comparison of calculated and experimental chemical shifts have been realized see Table ESI.†
- 24 For ^1H and ^{13}C empirical scaling see: G. K. Pierens, *J. Comput. Chem.*, 2014, **35**, 1388. For ^{31}P empirical scaling see: S. K. Latypov, F. M. Polyancev, D. G. Yakhvarov and O. G. Sinyashin, *Phys. Chem. Chem. Phys.*, 2015, **17**, 6976.
- 25 Additional study at B3LYP/6-311++G(d,p) level of theory as well as full details of comparison of $\Delta\delta$ between experimental data for **5dia1** and **5dia2** in bleu and between computed data for **5a1** and **5a2** in red are presented in ESI.†
- 26 For recent application of CMAD see: M. W. Lodewyk, C. Soldi, P. J. Jones, M. M. Olmstead, J. Rita, J. T. Shaw and D. J. Tantillo, *J. Am. Chem. Soc.*, 2012, **134**, 18550.

