Acyclic to cyclic aminophosphonic and phosphinic acids

David Virieux*, Jean-Noël Volle, and Jean-Luc Pirat*

AM2N, Institut Charles Gerhardt, UMR 5253, ENSCM, 8, rue de l'Ecole Normale, F-34296 Montpellier, France
E-mail: david.virieux@enscm.fr, jean-luc.pirat@enscm.fr

In honor of Prof. Pawel Kafarski on the occasion of his 63rd anniversary

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.420

Abstract
The results presented in this account deal with the synthesis of acyclic α- or β-amino-phosphonates or phosphinates and with the synthesis of heterocyclic compounds, where the phosphorus and/or the nitrogen atoms can be embedded in the heterocyclic core, showing new perspectives in bioactive molecules.

Keywords: Aminophosphonate, aminophosphinate

Introduction

When life arose on earth, the α-amino carboxylic acids became with nucleic acids the central molecular bricks of the living organisms.[1] In parallel, alkylphosphonic acids were discovered in the Murchison meteorite probably providing a supply of organic phosphorus for the earliest stages of chemical evolution.[2] More elaborated phosphorus compounds, such as ciliatine (ie 2-aminoethane phosphonic acid) and the related derivatives were found later in bacteria, protozoa and other higher species.[3] Among them, the α-aminophosphonic or α–phosphinic acids which have the P-C-N scaffold are generally considered as the biological mimes of the corresponding aminocarboxylic acids. They are also found in secondary metabolites and interestingly even the simplest exhibit biological activities as antibiotics. Nonetheless, if the phosphorus acidic group is often regarded as a surrogate of the carboxylic one, organophosphorus chemists evidenced that such structures possess effectively similar properties but also unique features.[4]

What make attractive the phosphorus analogues compared to the carboxylic acids are their tetrahedral geometry which is analogous to the transition state involved in the peptide bond cleavage, as well as, their outstanding ability to act as a hydrogen bond acceptors or metal cation complexing agents. These properties contributed to the elaboration of efficient matrix

metalloproteinase inhibitors[5], herbicides[6], treatments for calcium metabolism disorders and they opened new perspectives to seek for original bioactive molecules.

In this context, we explored sometimes jointly with Prof. Karfarski team this exciting and challenging chemistry. The past few years were focused on two different directions: The first one dealt with the synthesis of acyclic aminophosphonates or aminophosphinates and the second one on the synthesis of heterocyclic compounds where the phosphorus and/or the nitrogen atoms can be embedded in the heterocyclic core.

Acyclic derivatives

Peptaibols are an unusual class of short length peptides which often present antibacterial or antifungal properties.[7] Most peptaibols contains high levels of non-proteogenic amino-acids. From the later, the unusual *C,C*-disubstituted amino-acids are attractive as they are often resistant to proteolytic enzymes. In this context, we developed a generalization of the Kabachnik-Fields reaction in three step procedure for the synthesis of diarylaminomethylphosphonates which can be considered as the analogues of these non-proteogenic amino-acids (Figure 1).

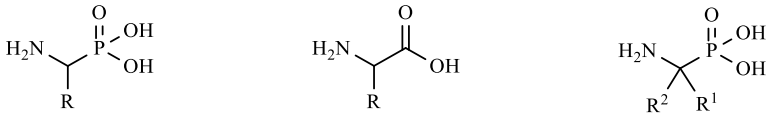
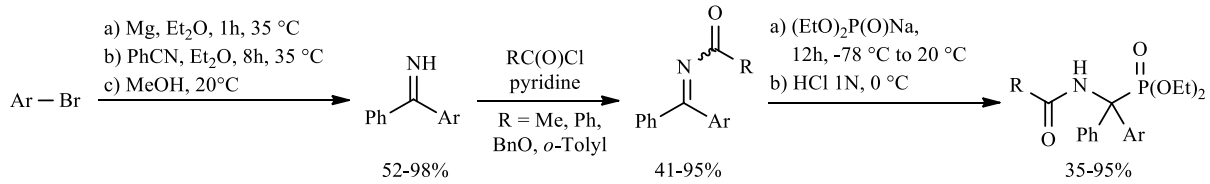


Figure 1

The first step consisted in the formation of C,C-disubstituted imines by reacting arylmagnesium bromide with benzonitrile (Scheme 1). Then the reaction of benzylchloroformate allowed the introduction of a protective group which can be specifically cleaved later in the synthesis. The last step was performed using sodium phosphite and afforded the disubstituted aminophosphonates in 35% to 95% yields.[8]



Scheme 1

Because phosphonic acids are considered as highly polar groups, they show sometimes very low bioavailability. To circumvent this drawback, this functional group can be advantageously replaced by a phosphinic acid. In this context, we investigated the possibility to use

hydroxymethylphosphinic group as a surrogate of phosphonic acids and then to form α,α'-difunctionnalized phosphinic acid derivatives (Figure 2).[9]

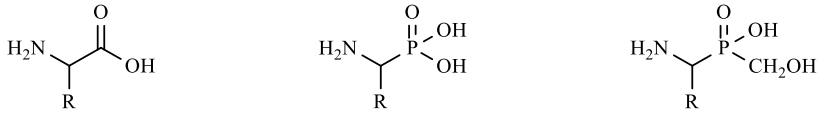
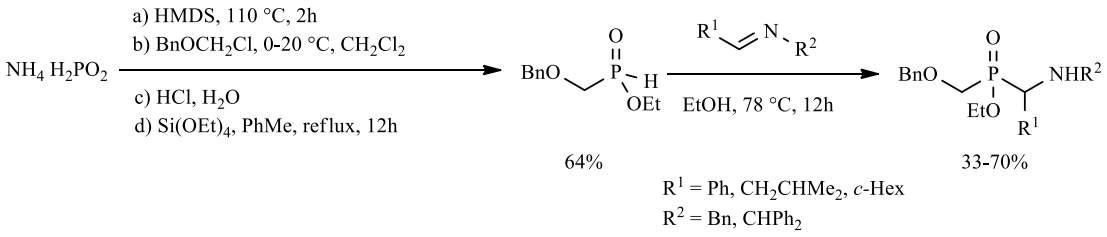


Figure 2

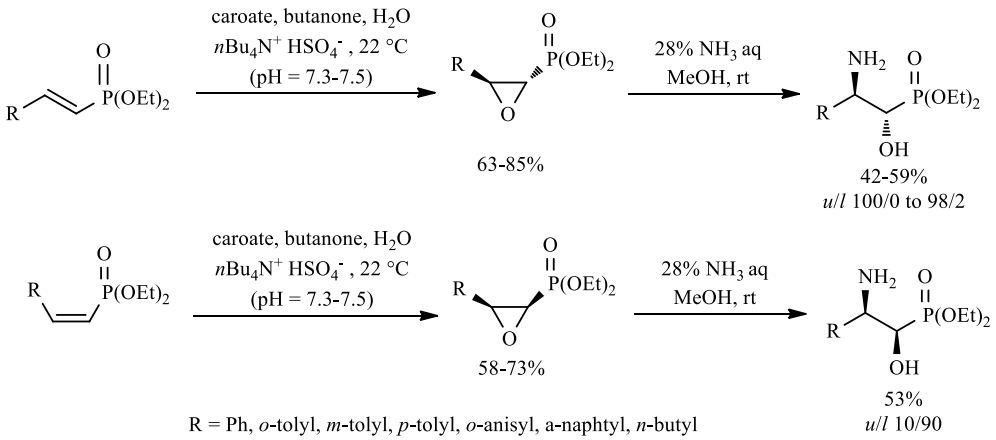
Then, aminoalkyl-hydroxymethylphosphinates can be synthesized straightforwardly from hypophosphorous acid (Scheme 2). The first step of the sequence consisted in the reaction of ammonium hypophosphite with HMDS. The resulting *H*-silylphosphonite[10] was reacted with benzyloxymethyl chloride and esterified[11] into the corresponding phosphinate in 64% yield. Finally, the reactions of various aldimines or 1,3,5-*N*-benzyl-1,3,5-hexahydrotriazine led to the formation of the α-amino derivatives as a mixture of diastereomers generally without any stereoselectivity.



Scheme 2

In the continuation of our work, we considered 1,2-epoxyphosphonates are versatile building blocks for the formation of β-amino-α-hydroxyphosphonates (Scheme 3).[12] Their synthesis was accomplished starting from *E*- or *Z*-alkenylphosphonate precursors which were obtained respectively by the Wittig-Horner reaction of tetraethyl methylenebisphosphonate with aromatic aldehydes or by hydrogenation of the appropriate alkynylphosphonates using the Lindlar palladium catalyst. Then, the epoxidation by dioxirane generated *in situ* from butanone and the potassium peroxymonosulfate (caroate) led to the corresponding *trans*- or *cis*-epoxides. The oxidation reaction appeared quite general; however, alkyl substituted *trans*-epoxyphosphonates revealed to be unstable in the reaction mixture and their purification revealed unsuccessful.

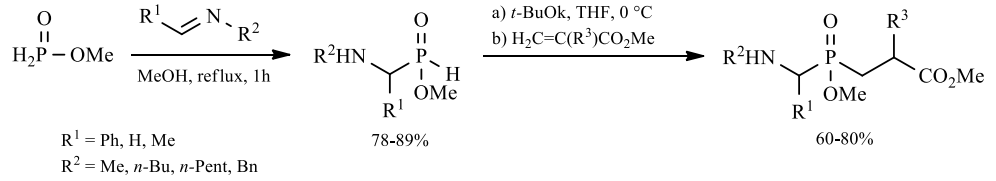
The amination reaction gives high regioselectivity and β-aminophosphonates were formed almost exclusively in yields ranging from 42% to 59%. The respective positions of both hydroxy and amino groups were assertained by comparison of the chemical shifts and the coupling constants in ^{13}C NMR.



Scheme 3

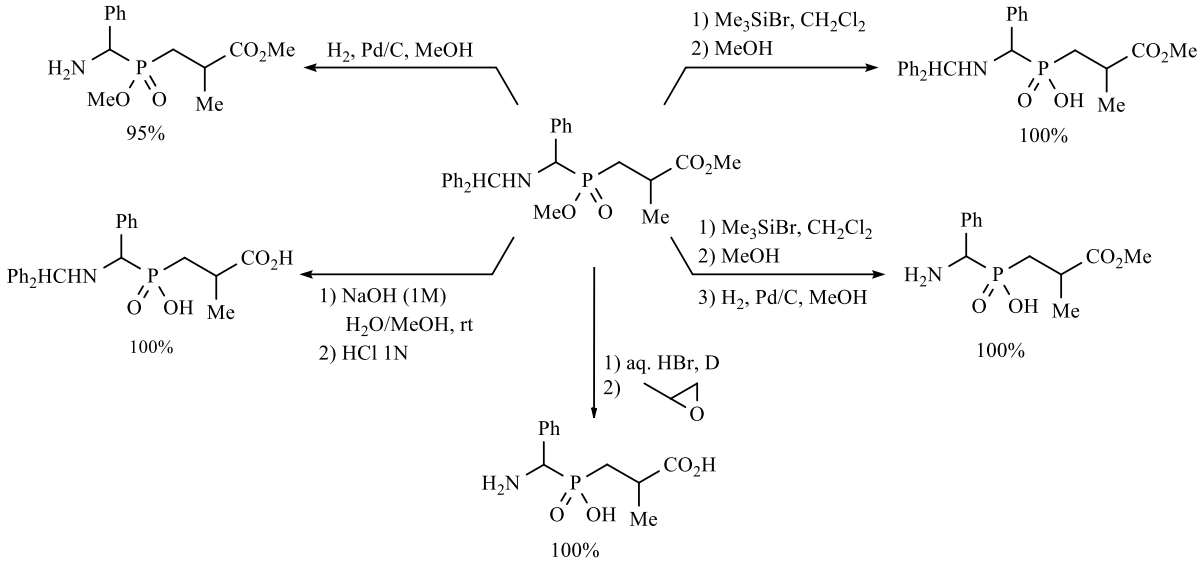
Phosphinopeptides are revealed to be active on many medicinally relevant enzymes. These peptidomimetic phosphinate inhibitors possess high complexing abilities and conceptually are considered as transition state analogues of the presumed tetrahedral intermediate observed during the peptidic bond cleavage. They can act as inhibitors of matrix metalloproteinases (MMP) which are thought to be essential for the diverse invasive processes.[13] Since, MMPs contain a zinc atom in their catalytic domain, various chelating scaffold were developed to inhibit MMP activity. This approach successfully led to Fosinopril a marketed prodrug, active on the angiotensin-converting enzyme (ACE).[14]

In this context, we developed a general one pot synthesis of phosphinopeptides. Using methyl hypophosphite as precursor, the Kabachnik-Field hydrophosphination of imines followed by a direct Michael addition of the resulting *H*-phosphinate to electron-deficient olefins, allowed the formation of the pseudo-dipeptides (Scheme 4).[15]



Scheme 4

In order to extend the value of phosphinopeptides as building blocks for the elongation of the peptidic backbone, selective deprotections of the carboxylic acid or the amino group were led. In general, quantitative yields were observed for each deprotective process (Scheme 5).



Scheme 5

Even if this approach was successful, the lack of control of the stereogenic centers prompted us to consider the synthesis of more constrained species in order to address the chirality.

Phosphorus heterocycles

Our latest contributions on the synthesis of α-aminophosphonic or phosphinic acids derivatives were focused on heterocyclic derivatives. First of all, phosphorus heterocycles have proven that they are considerably more resistant to the ring opening/closure that occurs between the open-chain and the cyclic forms of carboxylic lactone allowing the synthesis of more stable structures.[16] Moreover, the introduction of conformational constraints in amino acids or peptides also provides useful informations on structural requirements for bioactivities or even new active structures.[17] Then constrained or rigidified α-aminophosphinic acids possess original features: owing to the tetrahedral character of phosphorus compared to the *sp*^{2} hybridized carboxylic acid, it is then possible to have an access to compounds where the phosphorus or the nitrogen atoms are inside or outside the heterocyclic core (Figure 3).

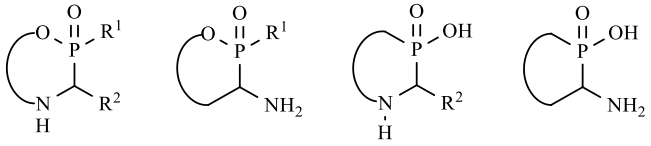
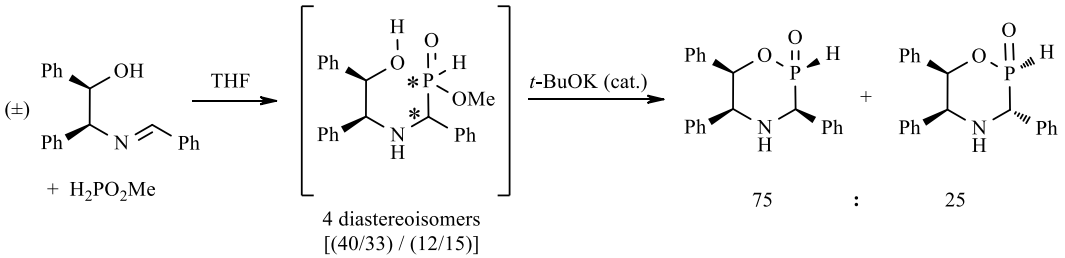


Figure 3

As a part of our search for new biologically active compounds in the field of human health or plant protection, we were interested in including such P-C-heteroatom motif into heterocyclic structures.

The beginning of this story started with the synthesis of a new class of compounds, the 2*H*-2-oxo-1,4,2-oxazaphosphinanes. The synthesis of the 5,6-diphenyl-1,4,2-oxazaphosphinanes was achieved by the tandem addition/cyclization (Scheme 6), through a base catalyzed process. Two diastereomeric oxazaphosphinanes were obtained in a ratio 75 : 25 in 65% yield. This process involved the imine of the 1,2-diphenyl ethanolamine with benzaldehyde and methyl hypophosphite.[18] The control of chirality was asserted later by X-ray experiment.

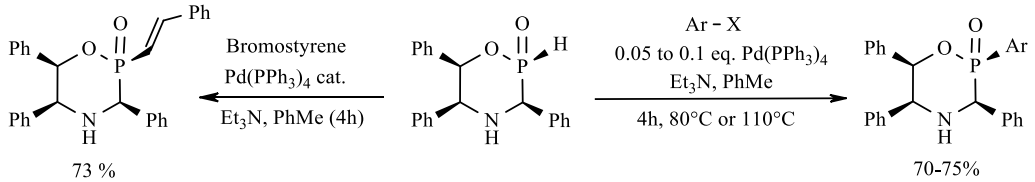


Scheme 6

Interestingly, the major diastereomer was easily isolated by preferential crystallization from the crude reaction mixture. The presence of the reactive P-H function on the same side of the two bulkiest phenyl groups led us to consider the control of chirality on further reactions. Then the reactivity of 2*H*-2-oxo-1,4,2-oxazaphosphinane was investigated using this stereoisomer.

Pallado-catalyzed P-arylation and P-vinylation reactions

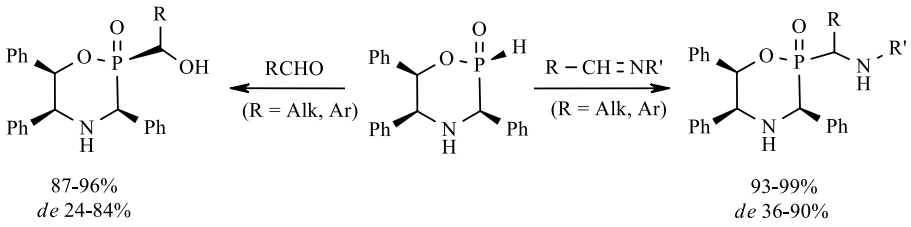
Arylation took place in the conditions usually described in the literature. The major diastereomer was arylated using various aryl halides and catalytic amounts of palladium tetrakis(triphenylphosphine) (10 mol%) in the presence of triethylamine as a base in dry refluxing toluene. Only one diastereoisomer was obtained in good yields (69 to 75%) in accordance with the well established retention of configuration at the phosphorus center during the process. Vinylation of 2*H*-2-oxo-1,4,2-oxaza phosphinanes was also performed with β-bromostyrene the conditions used above and afforded quantitatively the expected styryl oxazaphosphinane.[19]



Scheme 7

Diastereoselective addition to aldehydes and imines

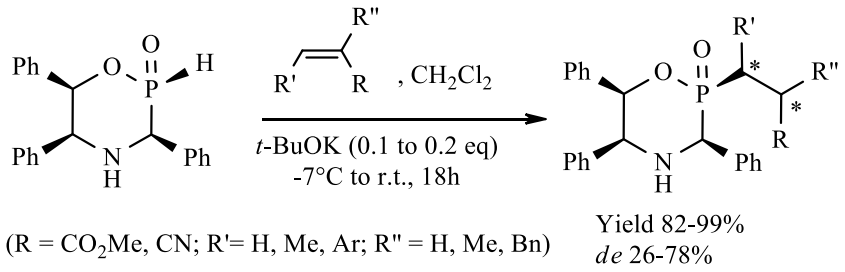
2*H*-2-oxo-1,4,2-oxazaphosphinanes were investigated as chiral reagents for diastereoselective additions. they reacted easily with aldehydes or aldimines, under nucleophilic or electrophilic activations, with good diastereoisomeric excesses affording an effective way for stereoselective syntheses of hydroxyalkyl- or aminoalkyl-P-substituted phosphorus heterocycles (Scheme 8). The diastereoselectivities using electrophilic activation for the reaction of imines presented a strong Lewis acid dependence. Zinc chloride, as a bidentate metal cation, afforded the highest diastereomeric excess in comparison to the other ones such as lithium perchlorate or boron trifluoride etherate corroborating our diastereoselection model.[18a]



Scheme 8

Diastereoselective Michael addition to olefins

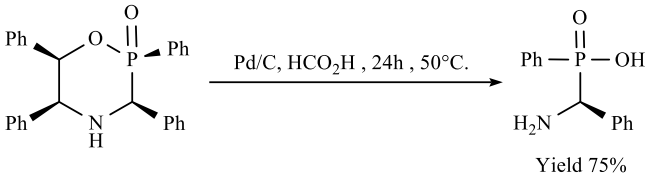
In a second set of experiments, α-substituted, β-substituted or cyclic electron-deficient olefins were used in order to investigate the influence of steric hindrance on the Michael addition (Scheme 9). Moreover, the resulting products could be perceived as constrained analogues of the phosphinopeptides presented above. This diastereoselective Michael addition occurred in very good to excellent yields (82-99%) with complete retention of configuration at the phosphorus atom. Only two diastereomers were obtained but the best diastereomeric excesses were observed when R' was not a hydrogen atom.[20]



Scheme 9

In conclusion to this section, 2*H*-2-oxo-1,4,2-oxazaphosphinanes were effective building blocks in P-arylations or P-vinylations, as well as nucleophilic reagents allowing the stereoselective hydrophosphinylation of aldehydes, imines or electron deficient olefins. Finally,

enantiopure α-amino phosphinic acids were generated by selective cleavage of the benzylic position using formic acid as mild hydrogen donor (Scheme 10).



Scheme 10

Furthermore, a critical issue for innovation in drug discovery is the search for new pharmacophores or bioisosteric groups in order to modulate the metabolic and/or the pharmacokinetic properties of drugs. Looking the oxazaphosphinane core, we showed an analogy between the lactol group and phosphinolactone with a close correspondence of these two structures both in term of polarity and presumably biological activity. From a structural point of view, the tetrahedral geometry of the phosphinolactone group can be directly addressed as a mime of the hemiketal function. In contrast, the *sp*^{2} hybridized ester group of the phosphinolactone sugar ring possesses a partial analogy with lactol and therefore it can be considered only as an imperfect bioisostere (Figure 4).

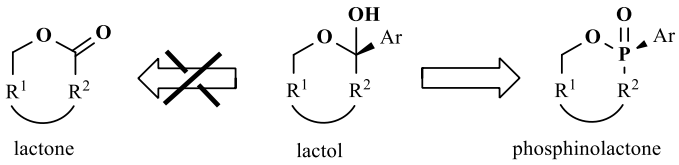


Figure 4

In continuation of our previous work on oxazaphosphinane, we envisioned them as structural analogues of *C*-arylmorpholinols. For illustration, hydroxybupropion is the major active metabolite of the Bupropion (Wellbutrin® marketed in the United States for the treatment of depression), and is twice more specific towards the noradrenergic system than bupropion (Figure 5). Thereafter, a structure-activity relationship study on the 2-arylmorpholinol core allowed the discovery of morpholinol 155U88 which possesses an *in vitro* specific affinity fifteen-fold higher than hydroxybupropion towards the enzymes responsible for the capture of noradrenaline. The strong activity of 2-arylmorpholinols on the noradrenergic systems could thus open a new therapeutic way for the treatment of depression and attention deficit hyperactivity disorder (ADHD).[21]

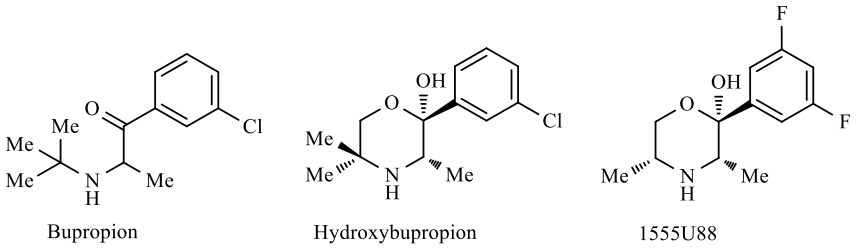
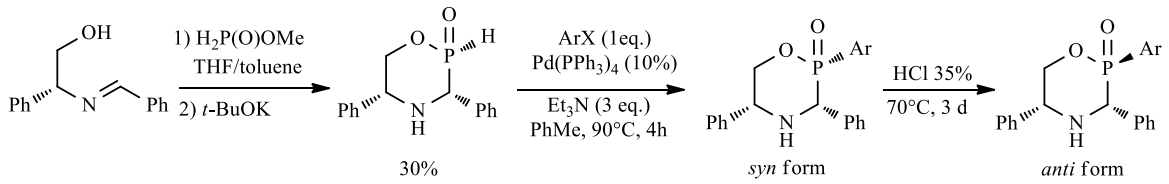


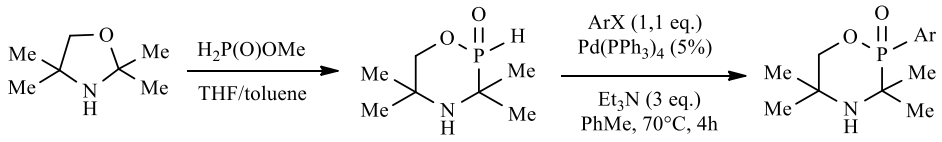
Figure 5

We reported the synthesis of these new oxazaphosphinanes in both enantiomeric *syn* and *anti* forms. The preparation of the *anti*-stereoisomers required the creation of two vicinal stereogenic centers. They were introduced by a three step procedure, a diastereoselective addition-cyclization reaction, which gave an oxazaphosphinane with a reactive P-H bond, followed by a *P*-arylation. Interestingly the last step was a complete and selective epimerization at the phosphorus atom under acidic conditions. The reaction furnished the thermodynamic anti-diastereomer almost quantitatively (Scheme 11).[22]



Scheme 11

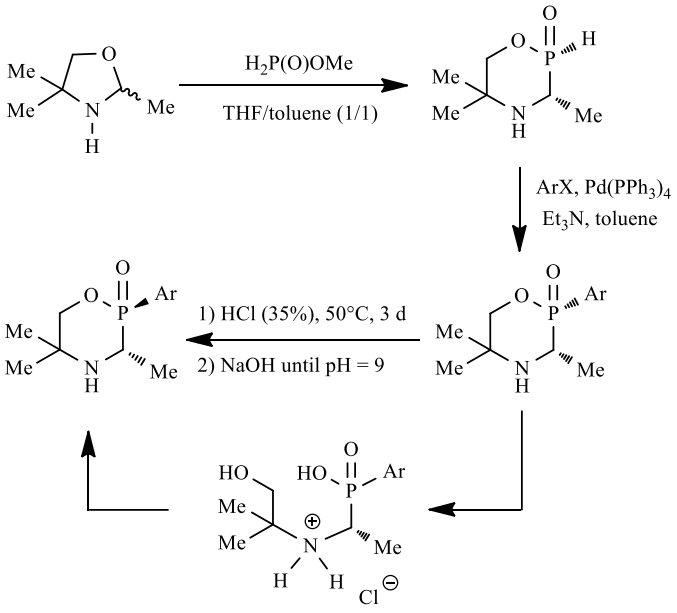
3,3,5,5-Tetramethyl phosphinyl analogues were synthesized using a similar approach. A nucleophilic addition of methyl hypophosphite on an opened oxazolidine, followed by an intramolecular cyclization yielded 71% of the desired oxazaphosphinane (Scheme 12). Various P-aryl derivatives in tetramethyl series were consecutively synthesized as racemic mixtures in 57 to 95% yields.[23]



Scheme 12

Finally, we applied this strategy for the access to trimethyl derivatives, i.e., the corresponding analogues in phosphinate series of hydroxybupropion. The first step consisted in the reaction of methyl hypophosphite with 2,4,4-trimethyl-1,3-oxazolidine to give the expected *H*-

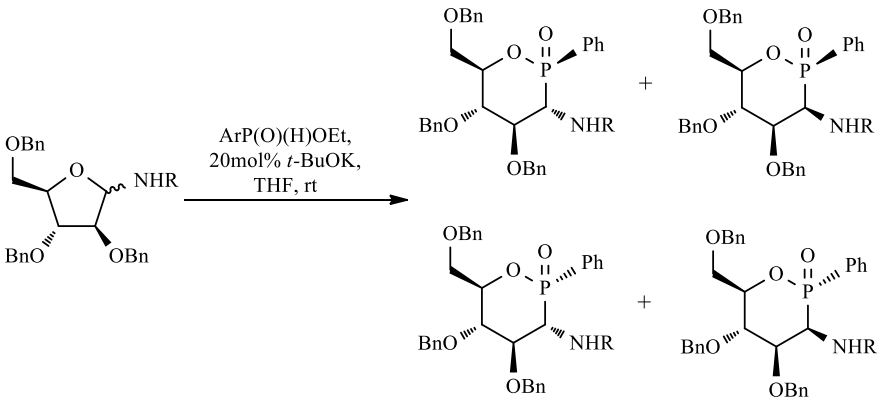
oxazaphosphinane with the *syn* configuration. Then after *P*-arylation reaction, the previously developed selective epimerization in strong acidic media led to the phosphinolactone analogues of hydroxybupropion (Scheme 12).



Scheme 12

Screened for their biological activity in the forced swimming test with mice, the behavioral data demonstrated, firstly the ability of 1,4,2-oxaphosphinanes to diffuse through the blood-brain barrier, and secondly to induce a biological response higher than our reference compound, the hydroxybupropion.[24]

In parallel to the oxazaphosphinane, we developed another phosphinolactone subunit, half-way between *C*-aryl-glycosides and phosphonosugars and having an exocyclic amino group. This new family, was obtained by the reaction of tetra(*O*-benzyl protected) aza-arabinofuranose with various ethyl arylphosphinates in the presence of catalytic amount of potassium *tert*-butoxide (Scheme 13).[25] This tandem sequence involved first, the nucleophilic Pudovik addition of *H*-phosphinate anions to the opened-chain form of azasugar, followed by a transesterification reaction, affording the six-membered ring, α-aminophosphinolactones. Four enantiopure diastereomers were formed during the process with only a moderate diastereoselectivity was observed.

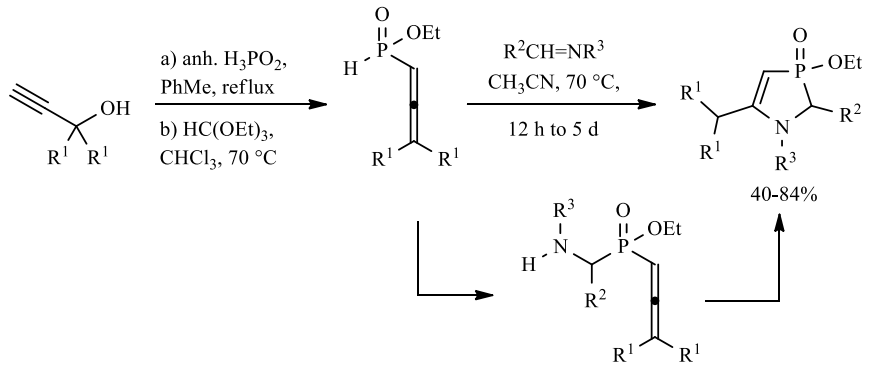


Scheme 13

This new family of oxaphosphinanes showed the ability to induce a cytotoxicity on C6 glial strain at μmolar concentrations.[26] The determination of the biological target and the mode of action of these compounds are currently under investigation and will be published soon.

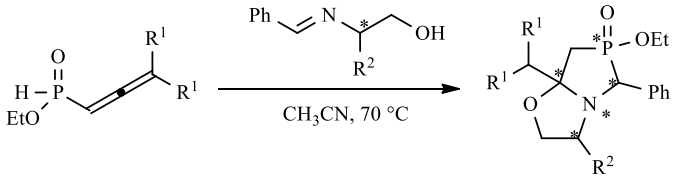
All these results confirmed that the phosphinolactone group might be effectively considered as an efficient bioisostere of lactol group and thus used as an unprecedented scaffold for the elaboration of new drug candidates. These results also opened new directions for the use of aminophosphinates as potential drugs confirming the general interest for heterocyclic structures.

New α-amino-phosphinic heterocycles can be obtained using the outstanding reactivity of *H*-phosphinylallene reagents, a surprisingly quite stable and underrepresented class of both nucleophilic and electrophilic allenes where the electronic properties of the two unsaturated carbon-carbon bonds determine the chemo- or the regioselectivity of reactions. Allenyl *H*-phosphinic esters were obtained in two steps from the combination of anhydrous hypophosphorous acid with respectively, 2-methyl-3-butyn-2-ol and 1-ethynyl-1-cyclohexanol in good yields. Afterward, allenyl *H*-phosphinic acids were quantitatively transformed into their ester forms under neutral conditions by the reaction of triethylorthoformate. These reagents were then allowed to react with imines to afford the azaphospholenes (Scheme 14).[27]



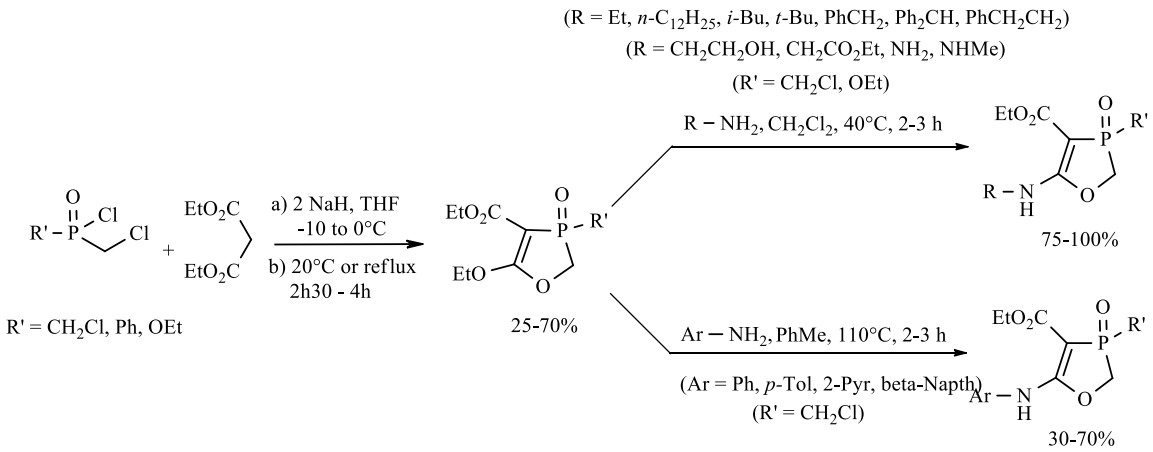
Scheme 14

Subsequently, we examined the behaviour of iminoalcohols in such cyclization process. The reaction of allenes with imines derived from (*R*)- or (*S*)-phenylglycinol, (*S*)-2-amino-butanol or ethanolamine resulted in the formation of the corresponding 1-oxa-3-aza-6-phospha-bicyclo-[3.3.0]octanes in 45 to 80% yields (Scheme 15). The stereochemical outcome of such cyclization was influenced by the R^2 group on the imine and was controlled both kinetically and thermodynamically. A predictive model for diastereoselection was used along with the attribution of all chiral centers of the molecules.



Scheme 15

Finally, to explore the formation of phosphorus heterocycles bearing a β-exocyclic amine, 2,3-dihydro-1,3-oxaphospholes were prepared from the reaction α-chloroalkylphosphinic or phosphonic chlorides with diethyl malonate in the presence of sodium hydride. These phosphorus-heterocycles were then reacted with primary alkyl or aromatic amines affording the β-amino substituted compounds up to quantitatively (Scheme 16).[18a]



Scheme 16

Conclusions

Since the discovery of naturally occurring α-aminophosphonates or phosphinates as powerful antibiotics, Professor Pawel Kafarski has greatly contributed to some break-through and is still

developing the chemistry of such compounds, advancing the scientific and the geographical frontiers, while opening new horizons (bisphosphonates, pseudopeptides, enzymatic resolutions and syntheses, …). This area of chemistry is still growing, showing new promising domains for potential and future biological applications, mainly due to the behavior of the phosphorus atom. Our recent contributions in the synthesis of heterocyclic aminophosphonates or phosphinates showed the emergence of two different families of biologically active derivatives.

Acknowledgements

The authors are grateful to : Lambert, J.-M., Hervé, A., Drag, M., Coulombeau, A., Monbrun, J., Ciptadi, C., Bekro, Y. A., Tillard, M., Dayde, B., Starck, M., Clarion, L., Kaloyanov, N., Saada, M. C., Filippini, D., Krawczyk, B., Van der Lee, A., Maurice, T., Bakalara, N., Mersel, M., Fourgeaud, P., Daydé, B. for their contribution to these works.
Aventis, Bayer CropScience, ANR, MRT, CNRS and INSERM are also gratefully acknowledged for supporting a part of this work.

References

1. *Aminophosphonic and aminophosphinic acids*, Kukhar, V. P. Hudson, H. R., Eds. Wiley: New York, 2000.
2. de Graaf, R. M.; Visscher, J.; Schwartz, A. W. *Nature* **1995**, *378*, 474.
3. Fields, S. C. *Tetrahedron* **1999**, *55*, 12237.
4. Mucha, A.; Kafarski, P; Berlicki, L. *J. Med. Chem.* **2011**, *54*, 5955.
5. Veerendhar, A.; Reich, R.; Breuer, E. *C. R. Chim.* **2010**, *13*, 1191.
6. Hall, R. G. *Phosphorus, Sulfur Silicon* **2008**, *183*, 258.
7. Duclohier, H. *Curr. Pharm. Des.***2010**, *16*, 3212.
8. Cristau, H.-J.; Lambert, J.-M.; Pirat, J.-L. *Synthesis* **1998**, 1167.
9. Cristau, H.-J.; Hervé, A.; Virieux, D. *Tetrahedron* **2004**, *60*, 877.
10. (a) Boyd, A. C.; Regan A. C. *Tetrahedron Lett.* **1992**, *33*, 813. (b) Boyd, E. A., Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *34*, 4223.
11. (a) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (b) Dumond Y. R.; Baker R. L. Montchamp, J.-L. *Org. Lett*. **2000**, *2*, 3341.
12. (a) Cristau, H.-J.; Pirat, J.-L.; Drag, M.; Kafarski, P. *Tetrahedron Lett.* **2000**, *41*, 9781-9785. (b) Drag, M.; Kafarski, P.; Pirat J.-L.; Cristau, H.-J. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 1153-1156. (c) Drag, M.; Latajka, R.; Gancarz, R.; Kafarski, P.; Pirat J.-L.; Cristau, H.-J. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 2191-2192.
13. Wang, X.; Li, K. F.; Adams, E.; Van Schepdael, A. *Curr. Drug Metabol.* **2011**, *12*, 395.
14. Lejczak, B.; Kafarski, P. *Top. Heterocycl. Chem.* **2009**, *20*, 31.

15. (a) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *Tetrahedron Lett.* **2001**, *42*, 4491. (b) Pirat, J.-L.; Coulombeau, A.; Genevois-Borella, A.; Cristau, H.-J. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 1793. (c) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643-644*, 381.
16. Wadsworth, W. S., Emons, W. D. *J. Am. Chem. Soc.* **1962**, *84*, 610.
17. (a) Strieker, M.; Marahiel, M. A. *ChemBioChem* **2009**, *10*, 607. (b) Undheim, K.; Efskind, J.; Hoven, G. B. *Pure App. Chem.* **2003**, *75*, 279.
18. (a) Cristau, H. J.; Pirat, J. L.; Virieux, D.; Monbrun, J.; Ciptadi, C.; Bekro, Y. A. *J. Organomet. Chem.* **2005**, *690*, 2472. (b) Cristau, H. J.; Monbrun, J.; Tillard, M.; Pirat, J. L. *Tetrahedron Lett.* **2003,** *44*, 3183.
19. Pirat, J. L.; Monbrun, J.; Virieux, D.; Cristau, H. J. *Tetrahedron* **2005**, *61*, 7029.
20. Monbrun, J.; Dayde, B.; Cristau, H.-J., Volle, J.-N.; Virieux, D.; Pirat, J.-L. *Tetrahedron* **2011**, *67*, 540.
21. Morgan, P. F.; Musso, D. L.; Partridge, J. J. *PCT Int. Appl.* **1999**, *WO* 9937305; *Chem. Abstr.* 1999, 131, 111445.
22. Volle, J.-N.; Virieux, D.; Starck, M.; Monbrun, J.; Clarion, L.; Pirat, J.-L. *Tetrahedron Asymm.* **2006**, *17*, 1402.
23. Volle, J.-N.; Kaloyanov, N.; Saada, M. C.; Virieux, D.; Pirat, J. L. *Tetrahedron Lett.* **2007**, *48*, 4695.
24. Volle, J.-N.; Filippini, D.; Krawczyk, B.; Kaloyanov, N.; Van der Lee, A.; Maurice, T.; Pirat, J.-L.; Virieux, D. *Org. Biomol. Chem.* **2010**, *8*, 1438.
25. Volle, J.-N.; Filippini, D.; Virieux, D.; Pirat, J.-L. *Synthesis* **2011**, 2490.
26. Pirat, J.-L.; Virieux, D.; Ludovic, C.; Volle, J.-N.; Bakalara, N.; Mersel, M.; Monbrun, J.; Cristau, H.-J., PCT Int. Appl. **2009**, WO 2009004096.
27. Fourgeaud, P.; Daydé, B.; Vors, J.-P.; Pirat, J.-L.; Virieux, D. *Org. Lett.* **2011**, *13*, 5076.

