Stereoselective Synthesis of α-Amino-H-phosphinic Acids and Derivatives

Mario Ordóñez,*a José Luis Viveros-Ceballos,b Francisco J. Sayago,c Carlos Cativiela,*c

a Departamento de Química Orgánica, ISQCH, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico
b Secretaría Académica, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico
c Departamento de Química Orgánica, ISQCH, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico

doi: 10.1002/slc.201600533; Art ID: ss-2016-m0533-sr

Abstract α-Amino-H-phosphinic acids and derivatives are an important group of compounds of synthetic and pharmacological interest, and particular attention has been dedicated toward their stereoselective synthesis in recent years. While some of these compounds show activity by themselves, they are also valuable starting materials in the synthesis of phosphinic bioisosteres of natural peptides, where the hydrolyzable bond is substituted by a phosphinic functionality that mimics the transition state of peptide hydrolysis, thus acting as efficient enzyme inhibitors in which the molecular stereochemistry is demonstrated to be critical. This review summarizes the latest developments on the asymmetric synthesis of acyclic and phosphacyclic α-amino-H-phosphinic acids and derivatives following an order according to the strategy used; in addition, some implications in medicinal chemistry are disclosed.

1 Introduction

Optically active α-aminoalkylphosphonic acids 1 are probably the most important P-analogues of the α-amino acids 2, obtained by isosteric substitution of the planar and less bulky carboxylic acid (CO₂H) by a tetrahedral phosphonic acid functionality (PO₃H₂). These compounds have shown important biological properties, as evidenced by their applications in the biomedical area and agrochemical industry.¹ The significant potential of these amino acid substitutes explains the large number of reports that have arisen over the years on their racemic or asymmetric synthesis.² On the other hand, the optically active α-amino-H-phosphinic acids 3 are also considered as analogues of α-amino acids 2, where now the carboxyl group (CO₂H) is replaced by a tetrahedral and sterically more demanding H-phosphonic acid functionality [P(O)(OH)H] (Figure 1). Strictly from a structural point of view, the α-amino-H-phosphinic acids are much closer to natural α-amino acids and are expected to show better biological activity than the corresponding phosphonic acids.

1.1 Introduction

2 Stereoselective Synthesis of Acyclic α-Amino-H-phosphinic Acids and Derivatives
2.1 Stereoselective C–P Bond Formation (Addition of Phosphorus Compounds to Imines)
2.1.1 Chiral Imine Compounds
2.1.2 Stereoselective C–P Bond Formation (One-Pot, Three-Component Reaction)
2.2 Chiral Amino Compounds
2.3 Stereoselective C–C Bond Formation
2.4 Diastereoselective Alkylations
2.5 Resolution Methodologies
3 Synthesis of Phosphacyclic α-Amino-H-phosphinates
3.1 1,4,2-Oxazaphosphacycles
3.2 Concluding Remarks

Key words α-amino-H-phosphinic acids, α-amino-H-phosphinates, α-amino acids, stereoselective synthesis, biological activity

Figure 1

The α-amino-H-phosphinic acids are currently attracting interest in medicinal chemistry due to their relevance as key intermediates in the synthesis of pseudopeptides,
which have acquired pharmacological importance in influencing physiological and pathological processes, primarily acting as inhibitors for proteolytic enzymes. A number of excellent reviews on various aspects of their activity in natural systems have been published. Additionally, it is well established that the biological activity of α-amino phosphonic and α-aminophosphonic acids depends on the absolute configuration, hence the importance of achieving the synthesis of these compounds in high enantiomeric purity.

In view of the broad biological applications of optically active α-aminophosphonic acids and their peptidic derivatives, in recent years, the development of suitable synthetic methodologies for their preparation in optically pure form has been a topic of significant interest in several research groups. In this context, we report herein a summary of the methods for the stereoselective synthesis of α-amino-H-phosphinic acids and their derivatives covering the last 20 years. In this review article, the compounds have been classified as acyclic and phosphacyclic α-amino-H-phosphonic derivatives. In the first case an order is established according to the strategy used; in this way the procedures can be classified into C–P bond formation using a Pudovik- or Kabachnik–Fields-like reaction, C–C bond formation through diastereoselective alkylation of iminomethylene-phosphinates, resolution methodologies, and the preparation from chiral α-aminophosphonates (Scheme 1).

2 Stereoselective Synthesis of Acyclic α-Amino-H-phosphinic Acids and Derivatives

2.1 Stereoselective C–P Bond Formation (Addition of Phosphorus Compounds to Imines)

The nucleophilic addition of phosphorus compounds (hypophosphorous acid, trimethylsilyl phosphonites or alkyl phosphinates) to imines, a Pudovik-like reaction, is an appropriate procedure for the preparation of α-amino-H-phosphinates. This hydrophosphinylation of aldmines and ketimines has the advantage that one or both of the reactants can incorporate a chiral auxiliary, although the reaction can also be carried out from non-chiral phosphorus compounds and non-chiral imines in the presence of a chiral catalyst.

2.1.1 Chiral Imine Compounds

Optically active α-amino-H-phosphinic acids can be easily obtained using chiral imines as substrates. For example, Lewkowski et al. reported the highly diastereoselective addition of hypophosphorous acid to N-(R)-α-methylbenzyl aldmines derived from heteroaromatic, aromatic, α,β-unsaturated and aliphatic aldehydes. Thus, the hydrophosphinylation reaction of the chiral Schiff bases 4a–f with hypophosphorous acid (H₃PO₃) in acetonitrile at reflux for five hours produced the α-amino-H-phosphinic acids (R,S)-5a–f in moderate yields and high diastereoselectivities (Scheme 2). Interestingly, in a separate publication, Lewkowski found that the addition of hypophosphorous acid to the Schiff base (R)-4g proceeded in a different way, obtaining the α-amino-H-phosphonic acid 5g in 65% yield and 50% diastereoisomeric excess. This result was attributed to the interaction of the central iron ion with the hypophosphorous acid during the attack on the azomethine bond.
Additionally, Lewkowski et al.10 carried out the condensation reaction of α-amino-H-phosphinic acid 5g, with cholesterol and O,O′-i-propyldieneadenosine in the presence of dicyclohexylcarbodiimide (DCC) in CH2Cl2, obtaining the α-amino-H-phosphinates 10a–d in moderate yield and 2:1 diastereoisomeric ratio (Scheme 4). The pure (S,S)-9 diastereoisomer, obtained by semi-preparative HPLC separation, was used in the preparation of an α-aminophosphinic pseudopeptide isostere of a potent β-secretase (BACE1) inhibitor, wherein the stereoisomer with R configuration at position 1′ proved to be the most potent inhibitor.11

Taking into account that the addition of hypophosphorous acid to achiral N-alkyl terephthalic imines has been reported to be 100% diastereoselective and leads only to the meso derivatives,12 Lewkowski et al.13 achieved the addition of hypophosphorous acid to the bifunctional N-(R)-α-methylbenzyl Schiff base 10a expecting to obtain the (S,S)-diastereoisomer, considering that the addition of hypophosphorous acid to chiral N-(R)-α-methylbenzyl Schiff bases gives exclusively a single diastereoisomer.8 However, the nucleophilic addition of hypophosphorous acid to the Schiff base 10a in acetonitrile at reflux afforded the three possible diastereoisomers of 11a in 97% yield with a 4:1:1 diastereoisomeric ratio. Low diastereoisomeric ratios (2:1:1) were obtained using L-α-amino acid esters 10b–d (Scheme 5). Apparently, the chiral assistance of these chiral auxiliaries is competing with the natural stereochemical course of the addition to terephthalic imines.13b

In a similar way, the nucleophilic addition of hypophosphorous acid to the N-(S)-α-naphthylethyl aldimine 7 in anhydrous THF at 0 °C gave the α-amino-H-phosphinic acids (S,R)-8 and (S,S)-9 in moderate yield and 2:1 diastereoisomeric ratio (Scheme 4). The pure (S,S)-9 diastereoisomer, obtained by semi-preparative HPLC separation, was used in the preparation of an α-aminophosphinic pseudopeptide isostere of a potent β-secretase (BACE1) inhibitor, wherein the stereoisomer with R configuration at position 1′ proved to be the most potent inhibitor.11

Taking into account that the addition of hypophosphorous acid to achiral N-alkyl terephthalic imines has been reported to be 100% diastereoselective and leads only to the meso derivatives,12 Lewkowski et al.13 achieved the addition of hypophosphorous acid to the bifunctional N-(R)-α-methylbenzyl Schiff base 10a expecting to obtain the (S,S)-diastereoisomer, considering that the addition of hypophosphorous acid to chiral N-(R)-α-methylbenzyl Schiff bases gives exclusively a single diastereoisomer.8 However, the nucleophilic addition of hypophosphorous acid to the Schiff base 10a in acetonitrile at reflux afforded the three possible diastereoisomers of 11a in 97% yield with a 4:1:1 diastereoisomeric ratio. Low diastereoisomeric ratios (2:1:1) were obtained using L-α-amino acid esters 10b–d (Scheme 5). Apparently, the chiral assistance of these chiral auxiliaries is competing with the natural stereochemical course of the addition to terephthalic imines.13b

A specific and mild hydrophosphinylating agent is bis(trimethylsilyl)phosphonite (BTSP), the first application of which in the synthesis of α-aminophosphinic acids was described by Grobelny.14 Using this reagent, Goldeman and Boduszek15 carried out the hydrophosphinylation reaction of the chiral imines 12a–c in CH2Cl2 at room temperature, obtaining the intermediate silyl esters 13a–c, which on treatment with MeOH were easily converted into α-amino-H-phosphinic acids 14a–c in 60–69% yield and 58:42 to 61:39 diastereoisomeric ratios. The major diastereoisomers (S,R)-14a–c were isolated after crystallization from acetone or acetone-diethyl ether (Scheme 6).
On the other hand, Yuan and Zhang\textsuperscript{16} reported a facile and highly stereoselective synthesis of α-aminophosphinates, which resulted in the first direct experimental evidence supporting their stereogenic nature at the phosphorus atom. Thus, the nucleophilic addition of ethyl diethoxymethylphosphinate to N-(tert-butanesulfinyl)ketimines (S)-15a–r in CH\textsubscript{2}Cl\textsubscript{2} using R\textsubscript{2}CO\textsubscript{3} as a base at room temperature afforded the α-aminophosphinates (R\textsubscript{x},S\textsubscript{y},R\textsubscript{y})-16a–r and (R\textsubscript{x},S\textsubscript{y},S\textsubscript{y})-17a–r as the major diastereomers in good yields (Scheme 7).

Additionally, the compounds (R\textsubscript{x},S\textsubscript{y},R\textsubscript{y})-16a–r and (R\textsubscript{x},S\textsubscript{y},S\textsubscript{y})-17a–r can be readily converted into their corresponding optically active α-amino-H-phosphinic acids. For example, the hydrolysis of 16a–c and 17a–c with 4 M HCl at reflux, followed by treatment with propylene oxide and ethanol gave the enantiomERICALLY pure α-amino-H-phosphinic acids (R)-18a–c in 61–94% yield (Scheme 8).\textsuperscript{16}

Recently, Yuan and Yao\textsuperscript{17} reported the first systematic study on the stereoselective synthesis of α-amino-H-phosphinic acids bearing natural protein amino acid residues. In this context, the nucleophilic addition of ethyl diethoxymethylphosphinate to (S)-sulfonamides 19a–g in the presence of R\textsubscript{2}CO\textsubscript{3} as a base at room temperature gave the α-aminophosphinates (R\textsubscript{x},S\textsubscript{y})-20a–g in good yields, which after cleavage of the N-tert-butanesulfinyl group by treatment with 4 M HCl-MeOH at room temperature produced the α-aminophosphinates (R\textsubscript{x})-21a–g in 65–100% yield and in modest to excellent diastereoisomeric ratios (Scheme 9).
In a similar way, the addition of ethyl diethoxymethylphosphonate to (S)-sulfanimides 19h–p in the presence of Rb₂CO₃ at room temperature produced the α-aminophosphinates (R,C₅ₛ)₂–20h–p in 64–94% yield, which on hydrolysis with 4 M aqueous HCl at reflux followed by treatment with propylene oxide in ethanol gave the optically active α-amino-H-phosphinic acids (R)–22h–p in good yields and moderate to high enantioselectivities (Scheme 10).17

![Scheme 10](image)

2.2 Stereoselective C–P Bond Formation (One-Pot, Three-Component Reaction)

2.2.1 Chiral Amino Compounds

Possibly, the experimentally simplest proposal to prepare optically active α-amino-H-phosphinic acids is the ‘one-pot’, three-component reaction, where the reactants are placed together with or without solvent and catalyst, which is identical to the Kabachnik–Fields reaction widely studied in the synthesis of α-aminophosphonates.18 In this regard, the ‘one-pot’, three-component reaction of (R)–α-methylbenzylamine, anhydrous hypophosphorus acid and the appropriate aldehyde in EtOH or MeCN at reflux2–19 produced the N-protected α-amino-H-phosphinic acids (R,S)–5a–g–m in 20–49% yield as single diastereoisomers. Simultaneous N-deprotection and oxidation of the H-phosphinic acid with Br₂/H₂O at 70 °C followed by treatment with propylene oxide in EtOH at reflux afforded the α-aminophosphonic acids (S)–23a,c,h–m in 73–92% yield and with 89–100% enantiomeric excess (Scheme 11).

![Scheme 11](image)

2.3 Stereoselective C–C Bond Formation

2.3.1 Diastereoselective Alkylation

An alternative method for the synthesis of α-aminooalkyl-H-phosphinic acids involves the alkylation of iminomethylenephosphinates. In this regard, Yokomatsu et al.20 carried out the reaction of 1,1-diethoxyethyl(aminomethylephosphinate derivatives. In this context, the reaction of (S)–picolineborane (R,S)–29 in toluene at reflux to produce the α-aminophosphinic acids is the following:

α-aminoaldehydes with 89–100% enantiomeric excess (Scheme 11).

![Scheme 11](image)
subsequent reaction with p-toluenesulfonyl chloride (TsCl) and Et$_3$N provided the tosylamides (S,S$_p$)-31a,b in 47% and 58% yield, respectively, which on deprotection of the ketal moiety by treatment with TMSCl/EtOH at room temperature furnished the α-aminoalkyl-H-phosphinates (S,R$_p$)-32a,b in 74% and 93% yield, respectively. In a similar way, (R$_p$)-29 was transformed into α-aminoalkyl-H-phosphinate (R,S$_p$)-32a (Scheme 13).20

On the other hand, the diastereoselective synthesis of Pro-Phe phosphinyl dipeptide isosteres was accomplished from optically active 1,1-diethoxymethyl(aminomethyl)phosphinate (R$_p$)-29,21 which was obtained in five steps from 1,1-diethoxymethyl(hydroxymethyl)phosphinate 33 via a lipase-catalyzed acylation.22 Thus, the reaction of (R$_p$)-29 with LiHMDS/LiCl in THF at 0 °C followed by addition of 3-iodopropan-1-ol silyl ether and subsequent cleavage of the O–TBDDS bond with TBAF, produced the iminoalkylphosphinate (R,R$_p$)-34 in 42% yield and a 7:1:1 diastereoisomeric ratio. The hydrogenolysis of (R,R$_p$)-34 using Pd(OH)$_2$/C in methanol at room temperature followed by addition of TsCl/Py, afforded the N-tosyl amide (R,R$_p$)-35 in 62% yield, which on reaction with MsCl followed by treatment with K$_2$CO$_3$ in DMF at room temperature furnished the prolinephosphinate derivative (R,R$_p$)-36 in 79% yield. Finally, removal of the 1,1-diethoxymethyl moiety of (R,R$_p$)-36 by reaction with TMSCl/EtOH gave the H-phosphinate (R,S$_p$)-37 in 84% yield, which is a key intermediate in the synthesis of Pro-Phe phosphinyl dipeptide derivatives (Scheme 14).

Scheme 13

Scheme 14

2.4 Resolution Methodologies

Strategies involving the resolution of racemic compounds have also been shown to be effective for the preparation of optically enriched α-amino-H-phosphinic acids. For example, one of the most widely employed methodolo-
gies is that described by Dingwall et al.\textsuperscript{23} in which a series of phosphinic analogues of proteinogenic amino acids was resolved by recrystallization of the (R)- and (S)-α-MBA salts of their N-Cbz derivatives. Thus, the N-Cbz-protected phosphinic analogue of phenylalanine (±)-38a was treated with (R)-α-MBA in ethanol at reflux, followed by crystallization and subsequent stirring with a slight excess of 45% HBr/AcOH and propylene oxide to produce the enantiomerically pure α-amino-\textit{H}-phosphinic acid (±)-38a, which represents a valuable starting material in the synthesis of phosphinic pseudopeptides of pharmacological interest (Scheme 15).

On the other hand, Khomutov et al.\textsuperscript{24} reported the reaction of 1-aminoethyl-\textit{H}-phosphinic acid (±)-22h\textsuperscript{25} with Cbz-\textit{l}-Ala-OSu in the presence of NaHCO\textsubscript{3} in dioxane to obtain the corresponding N-Cbz dipeptide as a diastereoisomeric mixture, which after crystallization produced the pure diastereoisomer \((S,R)\)-39 in 39% yield. Cleavage of the N-Cbz group in \((S,R)\)-39 with HBr/AcOH afforded the phosphinopptide \((S,R)\)-40 in 84% yield, which demonstrates fungicidal activity. Additionally, the reaction of \((S,R)\)-40 with bromine water (Br\textsubscript{2}/H\textsubscript{2}O) gave the alafosfalin \((S,R)\)-41 in 90% yield (Scheme 16).

HPLC chiral resolution is another strategy for the preparation of optically pure α-amino-\textit{H}-phosphinic acids. For example, Kessler et al.\textsuperscript{46} performed the enantiomer separation of the N-sulfonylated α-amino-\textit{H}-phosphinic acid 42 using a quinine-based chiral zwitterionic ion-exchange-type stationary phase developed by Hoffmann et al.,\textsuperscript{27} obtaining the enantioenriched α-amino-\textit{H}-phosphinic acids (R)-42 and (S)-42 with 96% and 92% enantiomeric excess, respectively (Scheme 17). The configurational assignments of (R)-42 and (S)-42 were in accordance with the general model of intermolecular interactions and chromatographic elution order that correlates with the α-carbon configuration.\textsuperscript{28} Additionally, the R enantiomer proved to be more potent as an integrin antagonist.

With the aim to assign the configuration of a series of phosphinic pseudopeptide esters, Lämmerhofer et al.\textsuperscript{29} carried out their stereospecific synthesis from the α-amino-\textit{H}-phosphinic acid precursors 38a-d,\textsuperscript{23} which were resolved by chiral HPLC using a set of cinchona-alkaloid-derived chiral anion exchangers 43 and 44 (Scheme 18).

In a similar way, Mucha et al.\textsuperscript{30} obtained all the stereoisomers of a phosphinic dipeptide homophenylalanyl-phenylalanine derivative and tested their inhibitory activity on bizinc cytosolic leucine aminopeptidase (LAP).\textsuperscript{31} The absolute configuration was assigned by using the starting materials (R)-38d and (S)-38d in the synthetic sequence, which
were preparatively resolved by chiral HPLC separation on a quinidine-carbamate-modified silica stationary phase 45 (Scheme 19).

Due to the biological activity of the phosphinic analogues of \( \alpha \)-amino acids, their enzymatic resolution has been addressed, however, only a few chiral active compounds have been obtained to date compared to their phosphonic analogues. Among these examples, Khomutov et al. conducted the enzymatic preparation of the enantiomerically pure \( \alpha \)-amino-\( H \)-phosphinic acid (46) from (±)-22l and benzylthiol using L-methionine-γ-lyase as a biocatalyst, obtaining the desired product in 45% yield. For assignment of the configuration, (R)-46 was treated with Na/NH\(_3\) liq. to afford the thiol derivative (R)-47 in 43% yield, which on reaction with MeI/2 M NaOH gave the known (R)-1-amino-3-methylthiopropylphosphinic acid (22l) in 59% yield (Scheme 20).

### 2.5 Conversion from Chiral \( \alpha \)-Aminophosphonates

Undoubtedly, a useful strategy, but not one that has been explored in detail for the synthesis of optically enriched \( \alpha \)-amino-\( H \)-phosphinic acids, is their conversion from the corresponding enantiomerically pure \( \alpha \)-amino-phosphonic counterparts. Considering this possibility, Pyun et al. carried out the transformation of chiral phosphonate (1S,2S)-48 into \( H \)-phosphinate (1S,2S)-51. Thus, the reaction of the optically pure diethyl (1S,2S)-1-amino-2-vinylcyclopropanephosphonate 48 with benzyl chloroformate and NaHCO\(_3\) followed by treatment with NaI in pyridine at reflux gave the phosphonate monoester (1S,2S)-49 in 88% yield. The reaction of (1S,2S)-49 with oxalyl chloride and DMF in MeCN afforded the phosphonomonochloridate (1S,2S)-50 that, without additional purification, was reduced with LiAlH\(_\text{Ot-Bu}\) in THF at \( -78 \) °C to produce the \( H \)-phosphinate (1S,2S)-51 in 78% yield, which was used in the synthesis of acyclic and cyclic phosphinate analogues of BI-2061 (Scheme 21).
3 Synthesis of Phosphacyclic α-Amino-H-phosphinates

Several strategies for the preparation of P-heterocycles have been described, and several excellent reviews on this topic have been published. In the past 20 years, significant effort has been devoted to synthetic and reactivity studies of this particular class of compounds. Herein, we only report the stereoselective methods recently reported in the literature where the α-amino-H-phosphinate motif is incorporated.

3.1 1,4,2-Oxazaphosphacycles

The strategies described for the stereoselective synthesis of 1,4,2-oxazaphosphacycles typically involve the diastereoselective nucleophilic addition–cyclization reaction from methyl hypophosphite (H₂PO₂Me) and chiral imino alcohols (Scheme 22).

For example, Pirat et al. addressed the enantioselective synthesis of phosphinic analogues of 2-aryl morpholines, which have shown strong activity on noradrenergic systems. Thus, the diastereoselective addition–cyclization reaction from methyl hypophosphite and the (R)-imino alcohol 52 in PhMe/THF, followed by treatment with potassium tert-butoxide gave the intermediate oxaphosphinane (2R,3R,5R)-54 in 30% yield, through the acyclic derivative 53 (Scheme 23).

In complementary work, Pirat et al. carried out the diastereoselective addition of methyl hypophosphite to the imino alcohol (1R,2S)-55 in PhMe/THF, followed by treatment with potassium tert-butoxide to generate the oxazaphosphinane (2S,3S,5S,6R)-56 in 30% yield (Scheme 24).

4 Concluding Remarks

This review provides an overview of recent efforts toward the stereoselective synthesis of both acyclic and cyclic α-amino-H-phosphinic acids and derivatives and highlights the most relevant synthetic approaches for each contribution. Overall, the nucleophilic addition of diethoxymethyl phosphinates to chiral sulfinamides appears to be the best approach in terms of versatility and the diastereoisomeric ratio of the products, which can be readily converted into the corresponding optically active α-amino-H-phosphinic acids via acid hydrolysis. Even though progress in recent years has been remarkable and a number of optically active α-amino-H-phosphinic derivatives are now available through different strategies, this area is still in its infancy as shown by the demand for stereoselective strategies for the preparation of pure stereoisomers of phosphinic peptides prior to their biological evaluation. Several of these compounds have been obtained by asymmetric synthesis methods, and by using chemical and biocatalytic resolutions, however, chiral HPLC separation still appears underexplored. Although the chiral anion-exchange stationary phases have demonstrated their usefulness for the direct separation of the enantiomers, the resolution of racemic α-amino-H-phosphinic acid precursors has not been explored using stationary phases based on polysaccharide chiral sup-
ports, which would avoid the need for solutions of a particular ionic strength.\textsuperscript{41} It is worth noting the lack of environmentally friendly stereoselective proposals, especially considering that the ‘one-pot’, three-component condensation represents an ideal subject for green chemical reactions.\textsuperscript{2b,d}

Hence, there is still much work to do on the development of solvent-free and microwave-assisted protocols. In addition, the stereoselective synthesis of the $\alpha$-amino-$H$-phosphinic acid analogues of the 20 proteinogenic $\alpha$-amino acids has not yet been completed, leaving a long way to be covered. In this account, we have summarized the progress and have highlighted the shortcomings with the aim to lay the groundwork for further progress in this promising area of research.

**Acknowledgment**

The authors gratefully acknowledge CONACYT (grant 181816, 248868) and PRODEP (project UAM-OR-PTC-379) of Mexico, Ministerio de Economía y Competitividad (grant CTQ2013-40855-R) and Gobierno de Aragón – FSE (research group E40) for their financial support.

**References**


(c) Ordóñez, M.; Sayago, F. J.; Cativiela, C. *Tetrahedron* 2012, 68, 6309.
(d) Keglevich, G.; Bálint, E. *Molecules* 2012, 17, 12821.

(h) Yamagishi, T. *Yakugaku Zasshi* 2014, 134, 915.

(c) Pudovik, A. N.; Komovalova, I. V. *Synthesis* 1979, 81.


(d) Drag, M.; Pawelczak, M.; Kafarski, P. *Chirality* 2003, 15, 5104.


\*M. Ordóñez et al.\*


