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Asymmetric synthesis of (α-amino)phosphonic acid amphiphiles using chiral P–H spirophosphoranes†

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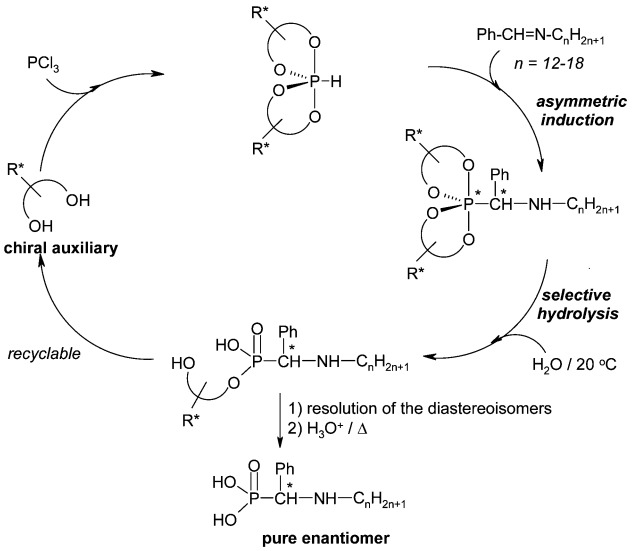
Chiral P–H spirophosphoranes reacted with long-chain prochiral aldimines and, after selective hydrolysis, afforded (α-amino)phosphonic acid amphiphiles in both enantiopure forms.

As phosphorus isosteres of natural amino acids, (α-amino)phosphonic acids have received wide attention in the past few decades due to their potential biological activity and their structural characteristics (stability, complexation power, acidity).[1] As these properties depend on the chirality of (α-amino)phosphonic acids, numerous asymmetric synthesis have been developed, furnishing pure enantiomers or racemic mixtures.[1–4] Adding an aliphatic long chain can lead to phosphorus amphiphiles, synthetic analogs of natural phospholipids, with some additional properties: surfactant characteristics, formation of supramolecular aggregates and colloids by self-organization.[5,6] Recently, we described the synthesis of (α-amino)phosphonocarboxylic- and (α-amino)phosphonic acid amphiphiles based on the Pudovik reaction between P–H spirophosphoranes (from non-chiral α-hydroxyacids) and long-chain prochiral aldimines.[7] Using such P–H spirophosphorane as a racemic mixture afforded, after selective hydrolysis, the phosphonic amphiphiles as racemics.

Here we present the results using two kinds of chiral spirophosphoranes, from enantiopure α-hydroxyacid or tartrates. Scheme 1 shows the principle of this asymmetric synthesis.

P–H spirophosphorane were nearly quantitatively synthesized by reaction between trichlorophosphine and α-bifunctionnal chiral auxiliaries. Spirophosphorane **1** was prepared in 95% yield from (*S*)-α-hydroxyisovaleric acid[8] (obtained by nitrosation of the natural valine[9]) and spirophosphoranes **2–3** were synthesized from enantiopure tartrates (as α-diols), in the presence of sodium acetate, to catch the formed HCl and favour the spirophosphorane formation.[10] We obtained (*R*)-**2** and (*S*)-**2** from (*R,R*)- and (*S,S*)-diethyltartrate, and (*R*)-**3** from (*R,R*)-dibutyltartrate (Scheme 2), in high yields (> 90%).

The main difference between these two kinds of compounds is the presence or not of an intracyclic carbonyl moiety. In the case of **1**, this function can stabilize the pentacoordinated structure and increases significantly the energy of stereomutation. So the spirophosphorane **1** was obtained as a mixture of two diastereoisomers in a 35 : 65 ratio, as determined by ^{31}P NMR. No equilibrium was observed between these two isomers even with heating; this compound can be considered as stereochemically stable. On the other hand, spirophosphoranes **2–3**, possessing no intracyclic carbonyl moieties, can undergo the phosphite–phosphorane tautomeric equilibrium.[11] This structural lability was observed by ^{31}P NMR: the spirophosphorane gave a high-field signal (δ = −22) whereas the tautomeric phosphite appeared as a very weak signal (< 5%) at δ = +145. In each case, only one signal was observed in NMR

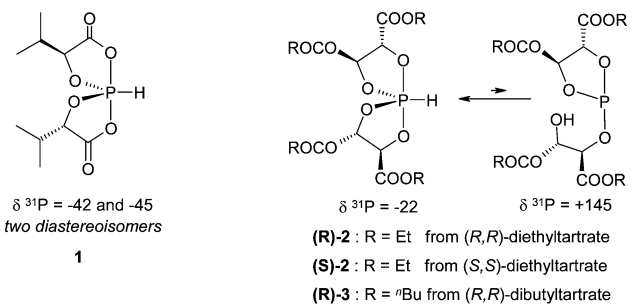


Scheme 1 General method for the asymmetric synthesis of (α-amino)phosphonic acid amphiphiles.

for the two diastereoisomers of the P–H spirophosphorane. This might mean that only one isomer was formed or, more likely, that the two diastereoisomers are in fast equilibrium, due to their structural lability.[12]

When P–H spirophosphorane **1** was mixed with the long-chain aldimine **4** (*n* = 18), an addition reaction occurred instantaneously (Scheme 3), as monitored by ^{31}P NMR: the signals from **1** (δ ^{31}P ~ −44, $^{1}J_{PH}$ ~ 910 Hz) disappeared completely and were replaced by four more deshielding signals (δ ^{31}P ~ −27) of the corresponding P–C spirophosphorane **7** (4 diastereoisomers). The replacement of the P–H bond by a P–C one was confirmed by the disappearance of the $^{1}J_{PH}$ coupling constant, replaced by a $^{1}J_{CP}$ ~ 180 Hz and a $^{2}J_{PH}$ ~ 20 Hz. Smooth hydrolysis of this mixture furnished nearly quantitatively the (α-amino)phosphono carboxylic acid **8** as two diastereoisomers **8A** and **8B** (**8A** is the diastereoisomer with the most deshielding (^{31}P NMR signal). Both bear the same (*S*)-isovaleryl group and they only differ by the carbon configuration of the P–C* bond.

One important point to note is that the ratio of the four diastereoisomers of **7** varied over one hour, as monitored by ^{31}P



Scheme 2 Synthesized chiral P–H spirophosphoranes **1–3**.

† Electronic supplementary information (ESI) available: Complete experimental procedures and physico-chemical properties. See http://www.rsc.org/suppdata/cc/b3/b304420c/

‡ This paper is dedicated to Dr Guita Etemad-Moghadam who directed this work and regrettably passed away in March 2002.

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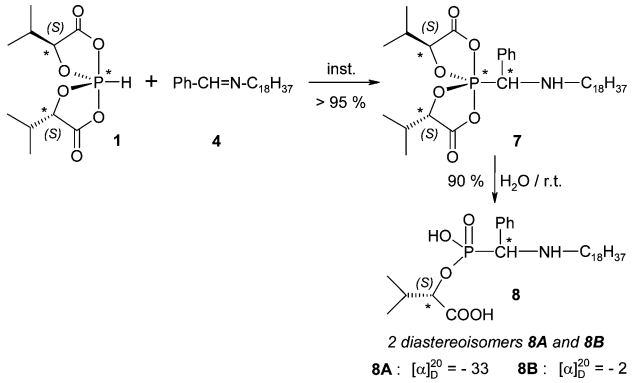


Scheme 3 Synthesis of chiral monoester **8** by stereoselective Pudovik addition between chiral P–H spirophosphorane **1** and aldimine **4**.

NMR; no further changes were observed after this time. Therefore, hydrolysis of these different mixtures afforded **8A** and **8B** in totally different ratios, as a function of the timing of water addition to the crude reaction mixture (Table 1).

This observation shows that the equilibrium between the diastereoisomers **7** is not only due to simple pseudorotations but also requires the lability of the P–C bond. This phenomenon involves also an equilibrium between the two diastereoisomers of the P–H spirophosphorane **1**. This equilibrium was not observed previously and seems to be catalysed by the imine. This property is very interesting because the ratio of **8A** and **8B** and the sense of diastereoselectivity can be easily controlled by simply changing the time of hydrolysis. The diastereoisomers of **8** were separated and purified by selective crystallization, yielding enantiopure forms, with moderate yields: **8A** in 13% and **8B** in 44% (starting with **8A** : **8B** = 15 : 85).

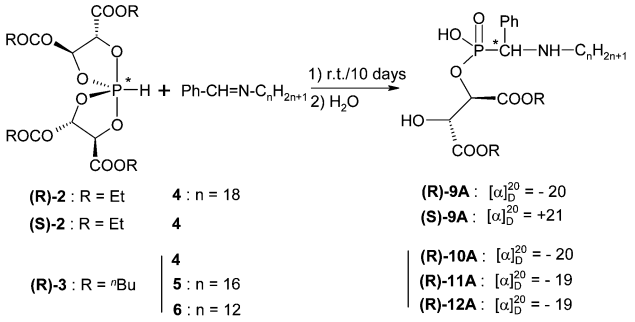
The Pudovik addition reactions between P–H spirophosphoranes **2–3** and long-chain aldimines **4** (n = 18), **5** (n = 16) or **6** (n = 12) were very slow, since they needed at least 10 days. During the reaction, the spiranic P–C adducts (δ ^{31}P ~ −11) decomposed slowly, leading first to P–C monocyclic phosphonates (δ ^{31}P ~ +45) then the desired monoesters **9–12** (δ ^{31}P ~ +8) started to accumulate. When the NMR signal of the P–H spirophosphoranes decreased below 5%, the crude mixture was then mixed with water to complete the hydrolysis reaction (Scheme 4). Monoesters **9–12** were obtained in a high yield (> 75%) as monitored by ^{31}P NMR of the crude mixture.

However, no significant stereoselectivity was observed: the monoesters **9–12** were formed as two diastereoisomers **9A–12A** and **9B–12B** (**A** having a more deshielding NMR signal than **B**), in a **A** : **B** = 55 : 45 ratio in all cases. This lack of diastereoselectivity, comparedto the reaction with compound **1**, might be due to the structural lability of spirophosphoranes **2–3**. The absence of the carbonyl intracyclic group may also reduce the acidity and the reactivity of the P–H bond. The stereochemistry of monoesters **9–12** had a very strong influence on their physico-chemical properties. Diastereoisomers **A** precipitated in a pure form (isolated yields about 40% from **A** : **B** = 55 : 45) in the presence of Et_2O or acetone, whereas isomers **B** remained soluble in most organic solvents or precipitated with all the impurities in polar solvents; they were not purified. Although only one diastereoisomer of the monoester was readily obtained with tartrates, they are commercially available

Table 1 Influence of time on the ratio between the diastereoisomers of **7** and on the ratio of **8A** to **8B** obtained by hydrolysis of **7**

	Diastereoisomers of **7**				**8A** and **8B**	
δ ^{31}P[a]	−26.3	−27.3	−27.7	−28.3	10.8	9.3
% after 5 min	55	10	26	8	***65***	35
% after 1 h	4	83	1	12	15	***85***

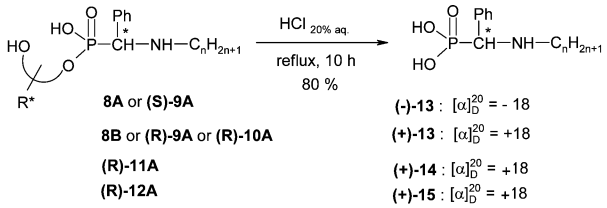
[a] In $CDCl_3$ for **7**, in $CHCl_3$–AcOH for **8**



Scheme 4 Synthesis of monoesters **9–12** from P–H spirophosphoranes **2–3** and aldimines **4–6**

in both enantiopure forms and both enantiomers of monoesters **9–12** can be prepared.

The enantiopure monoesters **8–12** were then converted in 80% yield into the corresponding enantiopure free (α-amino)alkylphosphonic acids **13–15** by drastic hydrolysis with concentrated hydrochloric acid under reflux[7] (Scheme 5). The P–C bond was very stable under these conditions and racemization did not occur.



Scheme 5 Synthesis of enantiomerically pure α-aminophosphonic acids **13–15** by acidic treatement of monoesters **8–12**

In conclusion, we described the asymmetric synthesis of α-aminophosphonic acid amphiphiles, *via* Pudovik addition reaction between chiral P–H spirophosphoranes and long-chain aldimine. Since the chirality could play a crucial role on the supramolecular properties, self-organization of these chiral amphiphiles is now actively studied.

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