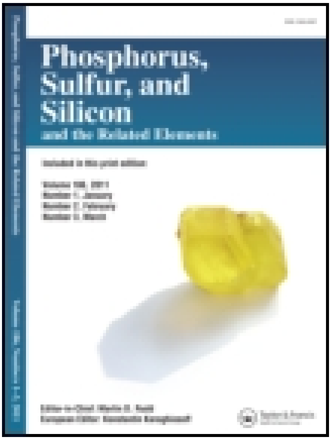


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# Asymmetric Synthesis of Aminophosphonic Acids

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# Asymmetric Synthesis of Aminophosphonic Acids

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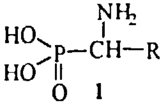
A new synthesis of chiral α- and β-aminophosphonic acids is described which involves a highly diastereoselective addition of phosphite and phosphonate anions to enantiopure sulfinimines.

*Keywords:* aminophosphonic acids; sulfinimines; asymmetric synthesis

Aminophosphonic acids 1 and 2, the phosphonic analogues of naturally occuring aminoacids, are attracting increasing interest, mainly due to their interesting biological properties.[1]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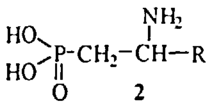
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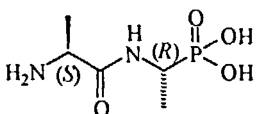
* Fax: (048–42) 684–71–26

Some of these compounds have been reported to show antibacterial, antibiotic and antiviral properties as well as pesticidal, insecticidal and herbicidal activity. Therefore, they have found diverse industrial applications, eg. in pharmaceuticals and agrochemicals.

The bioactivity of aminophosphonic acids strongly depends on their structure, and especially on the chirality at the stereogenic α- and β-carbon atom. Thus, for example the (*S*, *R*) diastereomer of alafosfalin (**3**) shows significant activity against Gram-positive microorganisms, whereas the other diastereomers are less potent. Similarly, the (*S*) enantiomer of 2-amino-4-phosphonobutanoic acid (**4**) is 20-40 times more active than the (*R*)-form in the suppresion of glutamate mediated neurotransmission.



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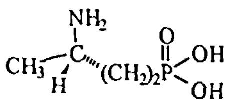
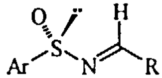


**4**

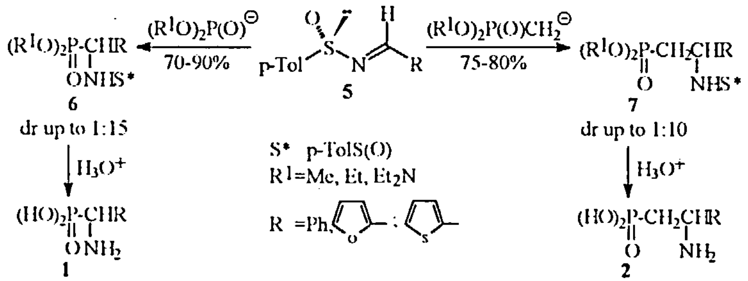
For these reasons, the number of syntheses of chiral, non-racemic aminophosphonic acids have been devised during the past two decades.[2] Among them the asymmetric additions of dialkyl or trialkyl phosphites to chiral imine derivatives were found to be a very useful approach. However, in contrast to the widely investigated α-aminophosphonic acids, the synthetic approaches to chiral, racemic and enantiomeric β-aminophosphonic acids are few in number and of limited applicability.

Searching for a simple, general and efficient method for the synthesis of optically active α- and β-aminophosphonic acids **1** and **2** we turned our attention to enantiomerically pure sulfinimines **5** as chiral auxiliares.




5

In addition to their ready availability[3] they contain an arylsulfinyl moiety as a powerful stereodirecting group inducing high diastereoselectivity and an activated carbon-nitrogen double bond prone to attack by nucleophilic reagents.

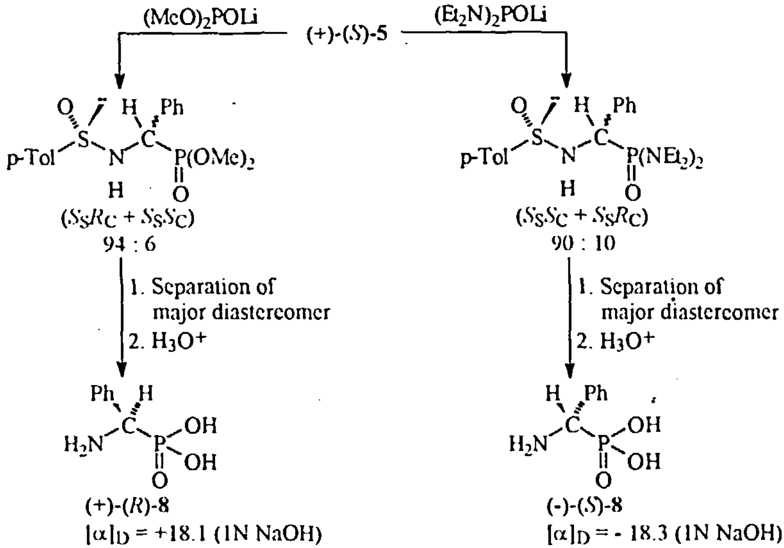



SCHEME 1

It was found that the imine **5** react with dialkyl phosphite anions[4] and dialkyl phosphonate carbanions[5] to give corresponding diastereomeric adducts **6** and **7** in high yields and good diastereoselectivity (Scheme 1).

The major diastereomers of N-sulfinylaminophosphonates **6** and **7** were isolated by flash chromatography and converted to the corresponding free $\alpha$- and $\beta$-aminophosphonic acids **1** and **2** by heating under reflux for 7 h in a mixture of glacial acetic acid and hydrochloric acid (36% aq).

It is interesting to point out that the addition dialkyl phosphite and diamido phosphite anions to (+)-(*S*)-sulfinimine **5** showed the contrasting stereochemical outcome leading to $\alpha$-aminobenzylphosphonic acids **8** with opposite chirality at the $\alpha$-carbon atom (Scheme 2).



SCHEME 2


## *References*

[1] For a comprehensive review on the biological activity of aminophosphonic acids see: P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, **1991**, 63, 193.

[2] For comprehensive reviews, see: D. Dhawan and D. Redmore, *Phosphorus and Sulfur*, **1987**, 32, 119; V.P. Kukhar. V.A. Soloshonok and V.A. Solodenko, *Phosphorus, Sulfur and Silicon*, 1994, 92, 239.

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