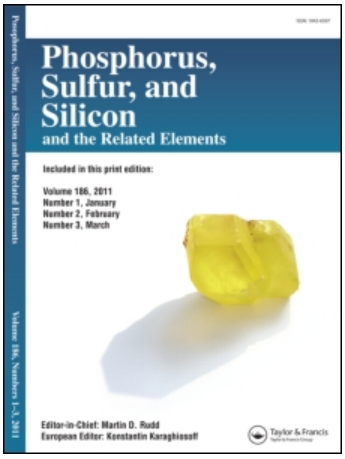


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# Synthesis of Enantiomeric Aminophosphonic Acids and Peptides

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# SYNTHESIS OF ENANTIOMERIC AMINOPHOSPHONIC ACIDS AND PEPTIDES

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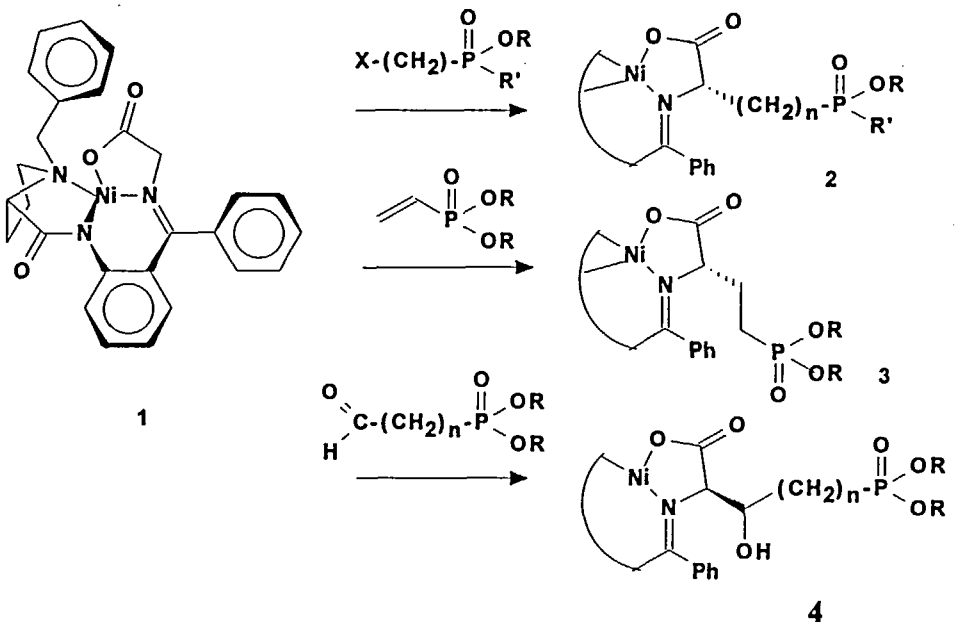
Abstract Synthesis of enantiomeric amino phosphonic acids APA is described by using chiral auxiliary reagent or enzymatic resolution of racemic mixtures of APA phenacyl derivatives. Peptides with APA residue were obtained by application of trimethylsilyl derivatives or condensation in the presence of enzyme-papain

*Key Words : aminophosphonic acids, enantiomers, peptides, enzymes*

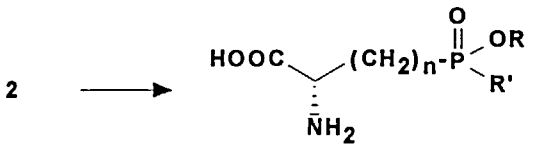


Today the most interest point in preparation of aminophosphonic acids , as in many other cases for bioactive compounds, is synthesis of stereochemically individual substances. To prepare enantiomers of amino acids with phosphonyl and phosphinyl groups in ω-position we have applied chiral auxiliary reagent containing glycine fragment. Started Ni-complex **1** could be easily obtained by reaction (*S*)-N-benzylprolyl-*o*-aminobenzophenone with glycine and $Ni(NO_3)_2$ in methanol solution. In the complex the acidity of C-H bond on glycine residue is enough to generate carbanion under action of organic or inorganic bases such as triethylamine or sodium methylate. We found the complex **1** is easy alkylated with haloalkylphosphonates and -phosphinates in acetonitrile solution of potassium hydroxide in presence of phase-transfer catalyst $Bu_4N^+ Br^-$. As a result of reaction the diastereomeric mixture of new complexes **2** and its diastereomer is formed in ~ 65 % yield and 10:1 ratio. Complexes were isolated from reaction mixture by preparative chromatography on silica.

Relatively high C-H acidity of glycine fragment in chiral auxiliary complex **1** allows to realize Michael addition of vinyl phosphonate ( or phosphinate ) in presence of bases and aldol condensation with corresponding phosphorus-containing aldehydes to yield chiral phosphorus-containing amino acids by other reactions. Unsubstituted phosphorus containing analogs of asparaginic , glutamic, homoglutamic acids, phosphinothricine and β-hydroxy APA are obtained from corresponding complexes .

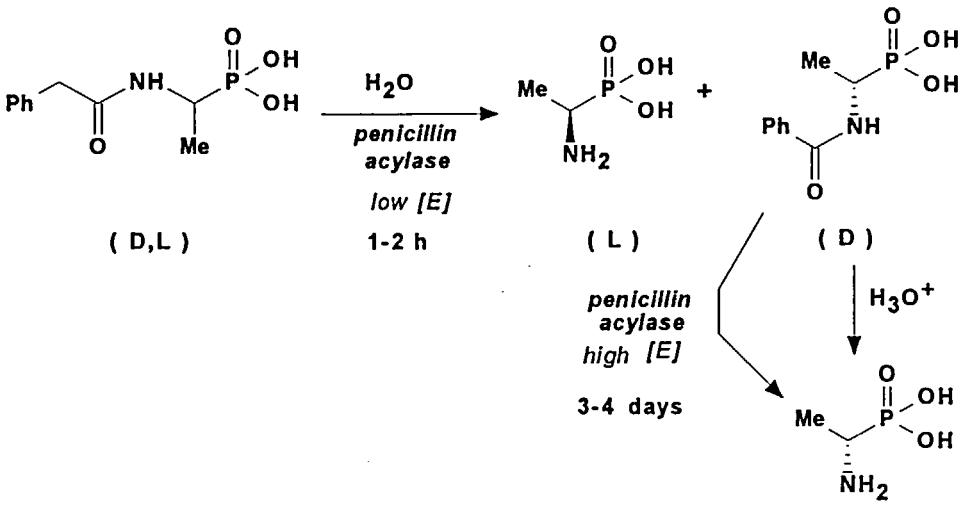


Absolute configuration of α-amino-containing center in obtained complexes has been estimated by ORD spectra. At action of 2N HCl solution in methanol the complexes are transformed into corresponding esters of amino acids and chiral auxiliary reagent - (*S*)-N-benzylprolyl-*o*-aminobenzophenone, for example :



Free amino acids were obtained by hydrolysis with HCl and ammonia. Proposed method of synthesis for ω-phosphonic analogs of dicarboxylic amino acids opens the possibility to obtain desired substances of this type in high yield.

We developed also effective method for the preparation of optically active 1-aminoalkylphosphonic acids with application of enzyme -penicillin acylase. The methods includes a biocatalytic step followed by chromatographic separation of the L-aminophosphonic acid from unreacted D-1-(N-phenylacetylamino)-alkylphosphonic acid and acid hydrolysis of the latter to D-aminophosphonic acid.

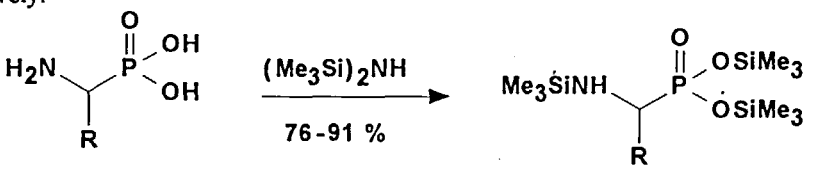



The computer simulation of the process indicates that an increase in enzyme concentration can result in drop of APA optical purity up to 0 as consequence of a significant increase in the rate of D-enantiomer hydrolysis. Indeed, when D-PhAc-Ala$^P$ was incubated with a high enzyme concentration in 50-100 times as large as that used for L-Ala$^P$ preparation over 3-4 days, D-Ala$^P$ was isolated in good yield and excellent optical purity ( ee >99% ). Thus, owing to the high enantioselectivity of the process, the enzymatic hydrolysis of racemic PhAc-Ala$^P$ can be carried out in two separate stages without any special precautions - at low enzyme concentration only the L-enantiomer of the substrate is hydrolyzed, the D-enantiomer can be hydrolyzed with noticeable velocity only by enhanced amounts of the enzyme.

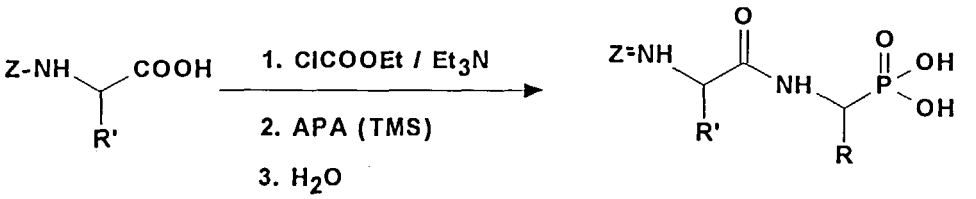
In comparison with N-acylated Ala$^P$, the hydrolysis of 1-(N-phenylacetylamino)ethylphosphonous acid ( PhAc-Ala$^{P\text{-}H}$ ) by penicillin acylase proceeds with moderate enantioselectivity ( $E$ = 1440 in comparison with $E$ = 58 000 for Ala$^P$ ), the rate of D-substrate hydrolysis being relatively high ( $K_D$= 1.37 ·10$^4$ M$^{-1}$s$^{-1}$ ).

1-Aminoalkylphosphonic acids as natural amino acid analogs could be used as components in peptide synthesis. We shown that esters of 1-aminophosphonic acid react easily with mixed anhydrides of N-protected amino acids and pivalic acid obtained in situ from N-acyl amino acids and pivaloyl chloride in the presence of tertiary amine to give phosphonopeptides in good yield. We developed the method allowing to use effectively free aminophosphonic acids for the synthesis of phosphonopeptide with P-terminal aminophosphonic residues. At heating with hexamethyldisilazane APAs easily and in high yield give tris-trimethylsilyl derivatives, which are able to form amide bond

by acylation reaction. In such case the method of mixed anhydrides could be used effectively.

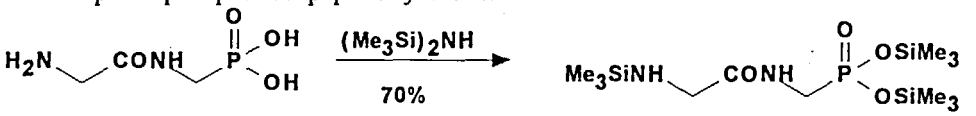



APA (TMS)

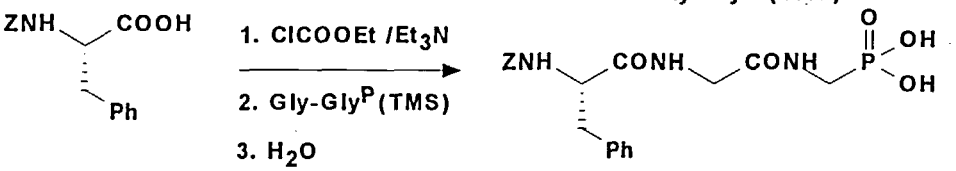



R'/R = H/H, Me/Me, $PhCH_2$/Me, H/$PhCH_2$ , Me/$PhCH_2$, i-Bu/$PhCH_2$

Total removing trimethylsilyl group proceeds under standard process of workup with aqueous solution to give N-protected phosphonopeptides with free phosphonic residue. Silylation could be realized and in the case of phosphonopeptides with following application of trimethylsilyl derivatives in peptide synthesis, as it was shown on example of phosphonotripeptide synthesis.




Gly-Gly$^P$ (TMS)




Z-Phe-Gly-Gly$^P$

Developed method was successfully applied for synthesis of phosphonic analogs of virus replication inhibiting peptide.