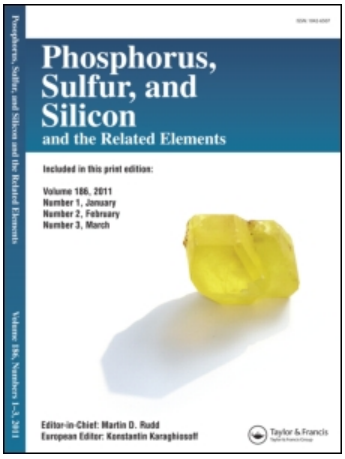


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# New Phosphorus Chemistry Leads to Unnatural Aminoacid Trimers

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# NEW PHOSPHORUS CHEMISTRY LEADS TO UNNATURAL AMINOACID TRIMERS

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*Unnatural or modified amino acids have become important biochemical vectors because of their potential utility in diagnostic or therapeutic medicine. Our ongoing research in hydroxymethyl phosphine chemistry has provided unique reaction pathways to produce unnatural aminoacid. The reaction of tris(hydroxymethyl)phosphine (THP) with chiral aminoacid L-alanine produced trimeric alanine in excellent yields. The X-ray crystal structure of* ***1*** *shows an unusual layered structure with water molecules sandwiched between the layers. Implications of this new chemistry in such emerging areas as chiral technology and drug discovery will be presented.*

*Keywords:* Aminoacids; dimer; hydroxymethyl phosphine; trimer



## INTRODUCTION

Design and development of unnatural or modified aminoacids is a growing area of scientific and biotechnological interest. Unnatural aminoacids are being used in new drug development *via* mechanisms that lead to favorable changes in receptor-ligand interactions. Modification of chemical backbones of aminoacids with fluorescent active moieties and incorporation of such fluorescent aminoacids at specific sites on proteins can be used to study structure and function of receptors. Unnatural aminoacids with fluorescent and radioactive probes can be used in the early diagnosis of deadly diseases in humans. Artificial (or synthetic) aminoacids have also gained considerable prominence because of their utility as nutraceuticals in human food supplements and in animal

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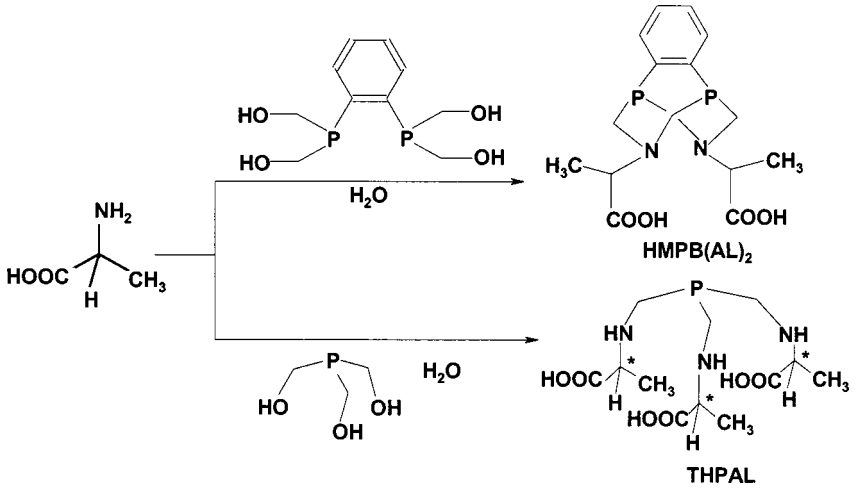
feeds. Despite important applications of unnatural aminoacids in chemical, biomedical, and nutraceutical fields, generalized synthetic strategies for systematic development of artificial (or unnatural) aminoacids are still lacking. As part of our ongoing research effort on the application of phosphorus chemistry in biomedicine,[1–5] we, herein, report a novel synthetic strategy that leads to the development of unnatural aminoacids. Specifically, we discuss the development of dimeric/trimeric aminoacid frameworks via the application of Mannich reactions of hydroxymethyl phosphines (HMP) with aminoacids.

## RESULTS AND DISCUSSION

The addition of trishydroxymethyl phosphine (THP) to five- or six-fold excess of L-Alanine in water produced phosphine functionalized trimeric alanine (THPAL) in >90% yield (Scheme 1). THPAL is a white, air-stable, crystalline compound that is readily soluble in water. The high-resolution fast atom bombardment mass spectrum of THPAL showed a molecular ion $[M+H^+]$ with m/z = 338.0. The $^{31}P$ NMR spectrum of the aqueous solution of THPAL showed a single resonance upfield from THP at −39.9 ppm ($\Delta\delta = \delta$ thpal $- \delta$ thp = −15.6 ppm). Both the $^1H$ and $^{13}C$ NMR spectra are consistent with the proposed trimeric structure (Scheme 1).

Single-crystal X-ray diffraction analysis has provided conclusive evidence for the trimeric constitution of THPAL. The structure consists of THPAL held by strong inter- and intramolecular hydrogen bonds. It




**SCHEME 1** Synthesis of $HMPB(Al)_2$ and THPAL.

is interesting to note that water molecules were embedded within the layers of THPAL. The layered structure of THPAL is unique because it demonstrates peptide-type arrangement of alanine within the trimeric structure.

The finding that bis hydroxymethyl phosphines, in their reactions with aminoacids, produced novel seven-membered peptide-like heterocycles via transannular linkage is significant (Scheme 1).[6] The generality and the vast scope of Mannich-type addition reactions, as outlined in Scheme 1, provide unprecedented opportunities in the development of trimeric and dimeric aminoacids.

The crystal structure of THPAL further reveals that its nitrogens are in protonated form similar to the parent alanine aminoacid. This finding is significant because it demonstrates that the isoelectric point of the modified alanine, THPAL, is similar to that of parent alanine. This means that modification of alanine, as outlined in Scheme 1, will have no adverse effects on biospecificity of aminoacids. Therefore, our new approach to the synthesis of modified aminoacids provides new opportunities in drug design and in the development of nutraceuticals.



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