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SOLID-PHASE SYNTHESIS OF PEPTIDOMIMETIC OLIGOMERS WITH A PHOSPHODIESTER BACKBONE[1]

Peishan Lin and A. Ganesan*

Institute of Molecular and Cell Biology, National University of Singapore, 30 Medical Drive, Singapore 117609.

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Abstract: An unnatural biopolymer is described in which amino acid side-chains are presented along a negatively charged phosphodiester backbone. For this purpose, a series of phosphoramidite monomers was prepared from chiral 1,2-diols. These were efficiently converted into oligomers using standard coupling conditions on an automated DNA synthesizer.

In recent years, the preparation of chemical libraries by solid-phase or solution protocols has emerged as a powerful enabling technology for the discovery of biologically active compounds.[2] Among these efforts, the design and synthesis of peptidomimetic oligomers provides exciting opportunities to probe structure-function relationships. Such "unnatural biopolymers"[3] (e.g. peptoids[4], β-peptides[5], oligopyrrolinones[6], peptidosulfonamides[7], oligocarbamates[8], oligoureas[9], azatides[10], and ethoxyformacetals[11]) may have markedly different physicochemical properties than natural peptides, including a superior pharmacological profile for development into therapeutic agents.

We were interested in a peptidomimetic (**1**, Figure 1) with a larger distance between side-chains and a negatively charged backbone. Conceptually, peptidomimetic **1**, with amino acid side-chains displayed on a phosphodiester backbone, is the converse of a peptide nucleic acid[12] (PNA), where nucleic acid bases are attached to a peptide backbone. Although several groups have prepared unnatural biopolymers based on phosphodiesters[13] and phosphoramidates[14], their systematic use for presentation of amino acid side-chains is unexplored. Here, we report a suitable set of monomer phosphoramidites **2**, which are readily elaborated into oligomers using an automated DNA synthesizer.

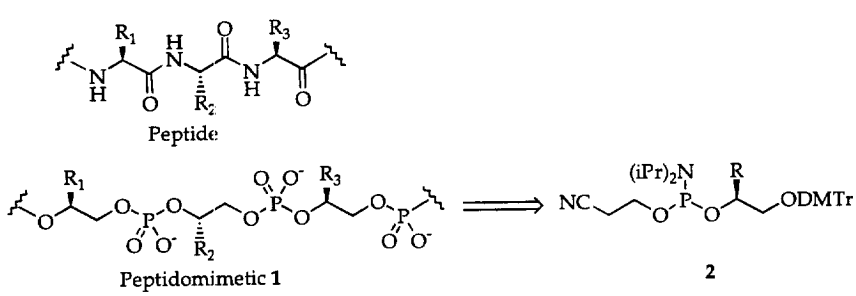

Figure 1

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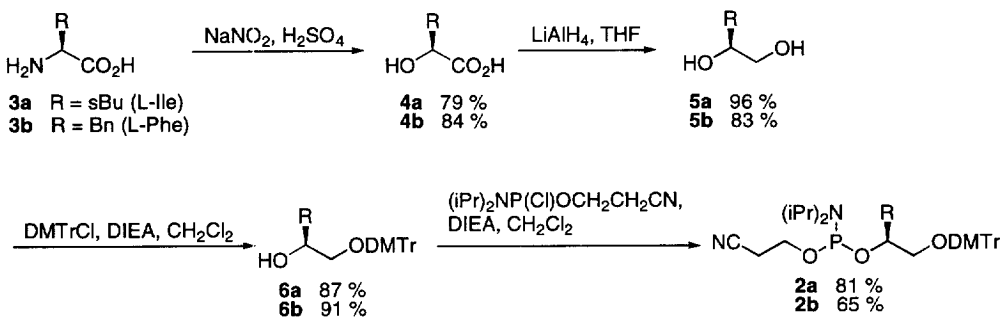
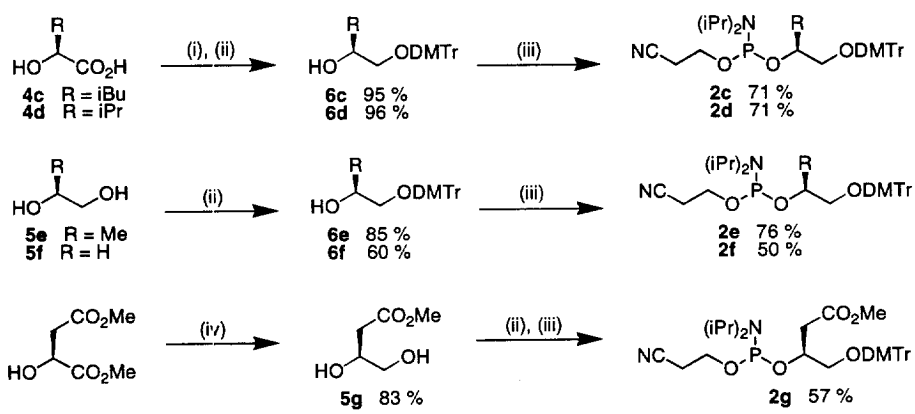
Our strategy for phosphoramidite synthesis began with the stereospecific oxidative deamination[15] of amino acids (**3**) to generate chiral α-hydroxy acids (**4**), as illustrated for isoleucine and phenylalanine[16] (Scheme 1). The α-hydroxy acids were reduced to 1,2-diols (**5**), which yielded alcohols (**6**) upon monoprotection with the dimethoxytrityl (DMTr) group. Phosphitylation furnished the desired phosphoramidites (**2a, 2b**), which function as Ile- and Phe-mimetic monomers respectively.



Scheme 1

In a similar manner, Leu-(**2c**) and Val-(**2d**) mimetic phosphoramidites were prepared from the commercial α-hydroxy acids 4**c** and **4d** respectively (Scheme 2). Phosphoramidites **2b** and **2c** have also been previously synthesized[17] by an alternative procedure involving ring-opening of chiral glycidol. Gly-(**2e**) and Ala-(**2f**) mimetic phosphoramidites were obtained in two steps from the corresponding 1,2-diol according to literature procedures.[18] Regioselective reduction[19] of (S)-dimethyl malate afforded diol (**5g**), which was converted to phosphoramidite **2g** with a methyl ester side-chain. Ammonolysis[20] of the ester during oligonucleotide cleavage from the solid support would result in an Asn-mimetic.



Scheme 2. Reagents: (i) $LiAlH_4$, THF; (ii) DMTrCl, DIEA, CH_2Cl_2; (iii) $(iPr)_2NP(Cl)OCH_2CH_2CN$, DIEA, CH_2Cl_2; (iv)BH_3 / $NaBH_4$, THF.

For increased diversity, three other phosphoramidites, which do not bear a natural amino acid side-chain were also prepared (Figure 2): **2h** is a mimetic for phenylglycine, while **2i**[21] (synthesized from dyphylline) and **2j**[22] (synthesized from L-4-hydroxyproline) contain potential groups for hydrogen-bonding interactions.[23]

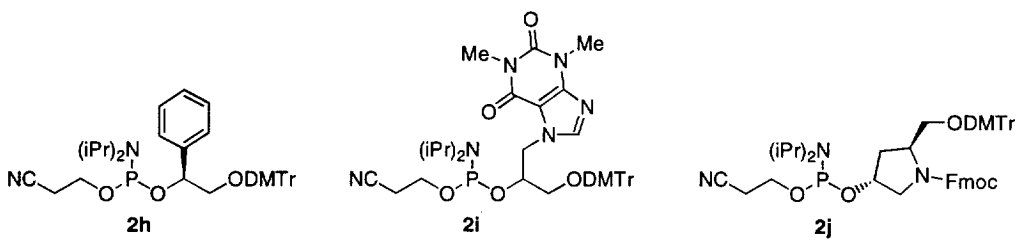


Figure 2

The coupling of phosphoramidites **2a-j** was tested using a Beckmann Oligo 1000M DNA synthesizer. With both 30 nM and 1000 nM columns, coupling yields under standard conditions was highly efficient, as determined by trityl cation release. We have successfully used these phosphoramidites for the synthesis of oligomers ranging in size from dinucleotides to 12-mers. In cases where **2j** was employed, the Fmoc group was deprotected with piperidine[24] prior to resin cleavage.

In conclusion, we have developed a novel peptidomimetic based on the phosphodiester backbone. Preparation of oligomers is greatly simplified by the ability to use existing high-yielding protocols for oligonucleotide synthesis. We have prepared a pooled library of these oligomers suitable for positional scanning, which is presently being screened against biological targets.

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