4. Conclusion

A series of novel isosteric 3'-nucleotide analogues (**9a-e** and **10a-e**) was synthesized, α-L- and β-L-prolinol nucleoside *N*-methylphosphonic acids distinguished for the loss of unambiguously defined configuration at the nitrogen atom in 3'-position of prolinol ring. Remarkable conformational differences between α-L- and β-L-prolinol nucleotides determined by NMR study suggest some similarity with the natural 5'-D-nucleotide. The same conformational changes in D-series of prolinol nucleotides fit even better the 3'- and 5'-D-nucleotides.

In addition, a series of four diastereoisomeric synthons **5-8** was prepared from the commercially available *trans*-4-hydroxy-L-proline, giving access to a complete set of prolinol-derived nucleotide analogues bearing α-L-, β-L-, α-D- and β-D-configuration.

In order to constrain the conformational flexibility of the *N*-phosphonomethyl moiety, several protected compounds were subjected to *N*-oxidation or *N*-methylation which gave chiral *N*-oxides or quaternary ammonium salts. However, the synthesis of the respective unprotected phosphonic acids was unsuccessful, probably due to their fast decomposition.

Acylation of the pyrrolidine ring nitrogen atom by several acylphosphonic acid derivatives led to the novel *N*-phosphonoformyl, *N*-phosphonoacetyl and *N*-phosphonothioformyl nucleotide analogues **16-18** with interesting conformational properties and biological activity.

The homo-A chimeric dimer **21** was prepared by direct synthesis in solution; thermal stability of its complex with polyU was found to be identical to that of natural one. Therefore, the synthetic routes to the thymine-containing *N*-phosphonomethyl and *N*-phosphonoformyl monomers **21**, **22**, **25** and **26** were developed for the synthesis of longer oligonucleotides. The monomers were successfully incorporated using phosphotriester method on solid support into short DNAs (9-mers) giving rise to oligomers **27-30**, the hybridization properties of which are being studied.

Most of the target compounds were tested for cytostatic activity; the compounds **10c** and **16** showed very promising results in inhibiton of thymidine phosphorylase. The biological activity of these compounds will be further investigated.