**Synthesis of Acyclic Nucleoside Biphosphonates**

Mgr. Silvie Vrbková

Referee´s report

---

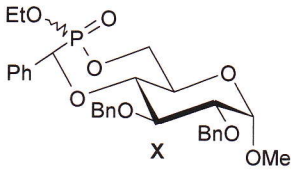
The present dissertation deals with synthesis of several series of biphosphonates extending synthetic methodology elaborated in the group of prof. Holý. Continuing the search for new potential therapeutic agents, tens of new target compounds were prepared and, moreover, most of them were tested for their biological activity. Generally saying, the studied compounds represent not only an important category of nucleoside analogues but it is also expected that they might be an attractive tool in the search for new medicinal agents. It is therefore without any doubt that the theme of the thesis is very actual and represents a challenging problem. It is highly appreciable that the substantial parts of the thesis have been already included into four original papers. This study makes undoubtedly a valuable contribution to the knowledge on the organic chemistry and biology.

The overview of the present state in nucleic acid analogues research is a brief survey in particular of their biological activities and use in medicine as very efficient drugs. Nevertheless, there are some points which are necessary to be mention. Overall set up of the dissertation is rather unusual as it consists of four chapters and each of them describes one set of compounds studied including introduction, results and discussion, conclusions, and experimental part. Unfortunately, this conception makes a reading of thesis difficult. According to my opinion, Ph.D. thesis should be consistent scientific work even in format. The numbering of compounds also does not help; several compounds have the same number and the use of numbers is very rare in the text. Thus, several sentences are not clear (p. 70): *...the lipophilic 1,3-bis(phosphorylethoxy)propan-2-yl derivative was applied the stepwise building of propan-1,3-diol-2-yl derivative on the adenine moiety followed by etherification with*....Finally, several figures are not placed at the right position in the text; therefore the reader must leaf through pages all the time. Minor comments: Term *m/z* must be written in italics as well as *N* and *O* in chemical names. The proper size of letter must be used for configuration prefixes D and L.

Getting some more detailed explanations/information on the comment specified below would be appreciated.

The yield of the alkylation of nucleobases with tosylate **13** was very low. Did you try another activation of secondary hydroxyl group?

When we cleaved ester groups in cyclic phosphonate **X** (*Tetrahedron Lett.*, **44**, 8797-8800 (2003)) with TMSBr or TMSI we found a remarkable selectivity. Employing TMSBr, the ethyl group was cleaved, while TMSI attacked both ester groups. You used TMSI for dealkylation of esters **11** – **15** although TMSBr was efficient in preparation of glycerol based ANBPS. What was the reason for? Did you observe some selectivity? Is the formation of iodo derivatives **21** – **25** unexpected? How can you compare the stability of phosphate group with alkanphosphonate? What is the mechanism of TMSBr or TMSI action?




**Conclusion:**

In spite of the critical remarks I have brought about, the Ph.D. thesis of Mgr. Vrbková evidenced her ability to analyse literature, design and execute experiments, and interpret adequately her own data in comparison with those published by the others. Therefore I recommend, after a successful defence of the thesis, to confer the degree "Philosophiae Doctor" upon the author in accordance with § 47, Article 4 of the Higher Education Act No. 111/1998.

Prague, 08.01.2008

Moravcová

Prof. Ing. Jitka Moravcová, CSc.
Department of Chemistry of Natural Compounds
Institute of Chemical Technology, Prague