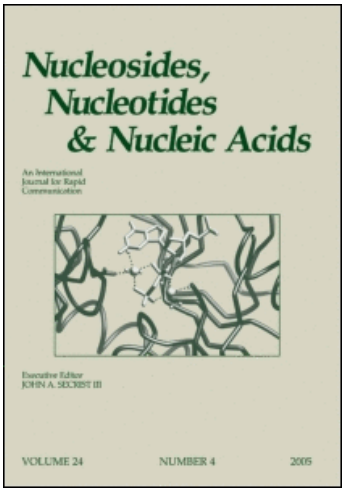

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Synthesis of 2'-5' Adenylate Trimers Containing 3'-Modified β-D-Xylofuranosyl-Adenine Derivatives at the 2'-End

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SYNTHESIS OF 2'-5'ADENYLATE TRIMERS CONTAINING 3'-MODIFIED ß-D-XYLOFURANOSYL-ADENINE DERIVATIVES AT THE 2'-END

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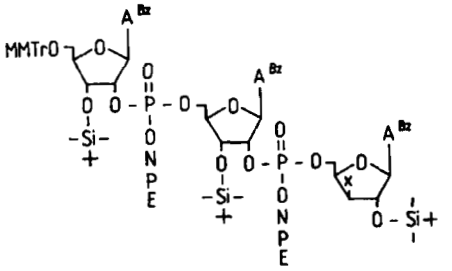
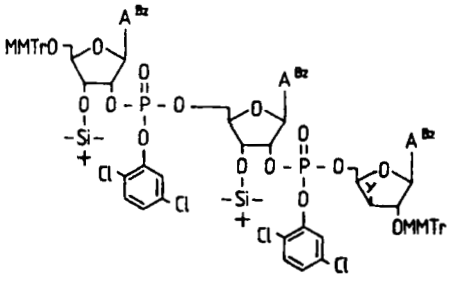
The exciting reports (1,2) on the unusual structure of the oligonucleotide pppA2'p5'A2'p5'A and its biological activity as a strong inhibitor of cell free protein synthesis (3) motivated various research groups to synthesize this low-molecular-weight oligonucleotide and its analogues (4,5). Since the biological activity of the 2'-5'-adenylates is rapidly lost due to cleavage of the 2'-5'-internucleotidic bond by a specific phosphodiesterase working from the 2'-end and affording a 3'-hydroxyl ribo-moiety modifications at this part of the molecule may enhance the stability towards enzymatic degradation and prolong this way the biological activity.

We developed a synthetic program for the preparation of 2'-5'-adenylate trimers in which the 2'-terminal adenosine moiety is replaced by 3'-modified ß-D-xylofuranosyl-adenines such as the 3'-azido-, 3'-fluoro-, 3'-chloro- and 3'-bromo derivative respectively. The syntheses were achieved via the phosphotriester approach using the appropriate building blocks which were condensed by activation of triisopropylbenzenesulfonyl chloride and N-methylimidazole. The selection of the most suitable protecting group for the various functionalities depends mainly upon the stability of the modified xylofuranosyl-adenine moiety in the final deblocking reactions. The p-nitrophenylethyl group (6) could be applied for protection of the internucleotidic linkage in the 3'-azido- and 3'-fluoro case respectively, since all common deblocking steps using DBU in pyridine, aqueous ammonia, 1M tetrabutylammonium fluoride in THF and 80 % acetic acid did not harm the xylo derivatives.

However, the 3'-chloro - and 3'-bromo-ß-D-xylofuranosyl-adenines afforded a different blocking group strategy due to epoxide formation during removal of the 2'-tert.butyldimethylsilyl group with fluoride ion and introduction of a 3'-4' double bond on DBU treatment. Protection of the terminal 2'-hydroxyl group by the monomethoxytrityl residue and the phosphotriester function by the 2,5-dichlorophenyl group turned out to be a suitable combination in the 3'-chloro case which allows deblocking to the free trimeric core without further intramolecular interconversions. Deprotecting of the 3'-bromo derivative is still in progress and will be reported later.



X= N_3, F



Y= Cl, Br

References:

1. I.M. Kerr, R.E. Brown, Proc.Natl.Acad.Sci. USA 75, 256 (1978);
2. B.R.G. Williams, R.R. Golder, I.M. Kerr, FEBS Letters 105, 47 (1979);
3. P.F. Torrence, Molec.Aspects Med. Vol. 5, 171 (1982);
4. R. Charubala, W. Pfleiderer, Tetrahedron Lett. 21, 4077 (1980);
5. G. Gosselin, J.L. Imbach, Tetrahedron Lett. 1981, 4699;
6. F. Himmelsbach, B.S. Schulz, T. Trichtinger, R. Charubala, W. Pfleiderer, Tetrahedron 40, 59 (1984).