CHEMICAL SYNTHESIS OF AN UNDECARIBONUCLEOSIDE DECAPHOSPHATE CONSTITUTING THE 3'-TERMINAL ACCEPTOR STEM SEQUENCE OF YEAST $tRNA^{Phe}$.

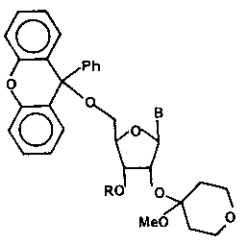
M. Kwiatkowski[1], J. Heikkilä[1], S. Björkman[1], H. Seliger[2] and Jyoti Chattopadhyaya[1]

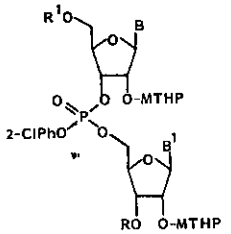
[1] Department of Microbiology, The Biomedical Center, Box 581, University of Uppsala, S-751 23 Uppsala, Sweden.

[2] Sektion Polymere, Universität Ulm, Oberer Eselsberg, D-7900 Ulm, West Germany.

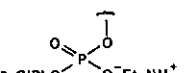
The preparation of $5'r(HO\text{-}ApApUpUpCpGpCpApCpCpA\text{-}OH)3'$, by the phosphotriester approach, is described using fully protected tri-and tetra-ribonucleotide blocks. The salient features include the employment of 9-phenylxanthen-9-yl (Pixyl)[1] as a 5'-protecting group, 4-methoxytetrahydropyranyl- (MTHP)[2] as a 2'-protecting group and fluoren-9- methyl-(FM)[3] as a 3'-terminal phosphate protecting group. Thus, successful employment of fluoren-9-methyl as a phosphate protecting group has enabled us to carry out a block synthesis strategy leading to oligoribonucleotides in high overall yields.

The key ribonucleoside building blocks, (general formula: (1)), were prepared starting from 3',5'-di-O-1,1,3,3-tetraisopropyldisiloxane- 1,3-d-yl-[4] derivatives of the corresponding-N-protected ribonucleosides and uridine. They were then converted[5] to the 2-chlorophenylphospho-diester salts, (general formula: (2)). These phosphodiester salts were then regioselectively[6] condensed with a 3', 5'-dihydroxy ribonucleoside block to obtain partially protected (3' 5')-diribonucleotide blocks, (general formula: (3)), or a fully protected mononucleotide block (4). (3) could be easily converted to (5) with the help of 2-chlorophenylphosphorobis-(1,2,4-triazolide) in an usual way[5]. The phosphodiester salts, (general formula: (5)) could be used as a 5'-protected component for a further condensation with a 5'-hydroxy block. The 5'-hydroxy blocks were prepared by selective removal of the pixyl group by $ZnBr_2$ in CH_2Cl_2 at 0°C when the MTHP group was completely stable. (5) could also be employed in the preparation of the 5'-hydroxy blocks, (general formula: (7)), after the protection of the 3'-phosphodiester at the level of a triester with the help of fluoren-9-methyl-(FM) group. The fully protected phospho-triesters, (4) and (6), were completely stable under the conditions of normal manipulations during the synthesis; yet the FM group could be conveniently deprotected selectively to generate the phosphodiester salts within an hour at 20°C with the help of Et_3N (10 equiv.) in dry pyridine solution. The 5'-protected phosphodiester salts were then coupled to the appropriate 5'-hydroxy blocks to give the fully protected tri- and tetra- oligoribonucleotide blocks. They were then subsequently assembled to obtain the undecaribonucleotide, which was eventually de-protected to obtain the target sequence.

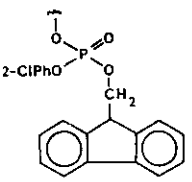




PHOSPHODIESTER =



PHOSPHOTRIESTER =



(1) R = H,

(2) R = PHOSPHODIESTER;

(4) R = PHOSPHOTRIESTER,

(3) R = H; R^1 = PIXYL;

(5) R = PHOSPHODIESTER
R^1 = PIXYL;

(6) R = PHOSPHOTRIESTER
R^1 = PIXYL;

(7) R = PHOSPHOTRIESTER
R^1 = H,

References:

1. J.B. Chattopadhyaya and C.B. Reese, J.C.S. Chem. Comm. 639 (1978)
2. C.B. Reese, R. Saffhill and J.E. Sulston, J.Am. Chem. Soc. 89, 3366 (1967).
3. C. Gioeli and J.B. Chattopadhyaya, Chemica Scripta 19, 235 (1982).
   N. Balgobin and J.B. Chattopadhyaya, Chemica Scripta 20, 133 (1982).
   These two papers show the application of the FM group in DNA synthesis
4. W.T. Markiewicz, J. Chem. Res.(S) 24 (1979)
5. J.B. Chattopadhyaya and C.B. Reese, Tetrahedron Letts. 5059 (1979).