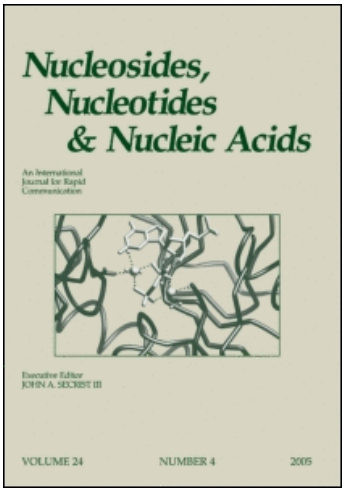

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C. Scalfi-happ[a]; E. Happ[a]; S. Chladek[a]
[a] Dept. of Chemistry, Michigan Cancer Foundation, Detroit, Michigan, USA

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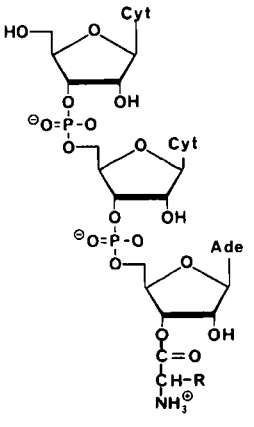
NEW APPROACH TO THE SYNTHESIS OF 2'(3')-O-AMINOACYL-OLIGORIBONUCLEOTIDES RELATED TO THE 3'-TERMINUS OF AMINOACYL TRANSFER RIBONUCLEIC ACID

C. Scalfi-Happ, E. Happ and S. Chládek,* Dept. of Chemistry, Michigan Cancer Foundation, Detroit, Michigan 48201, USA

Abstract: A new methodology for the synthesis of 2'(3')-O-aminoacyl oligonucleotides based on an unique combination of protecting groups is described. The blocking scheme allows a simple two step deblocking procedure, which provides easy access to the target compounds.

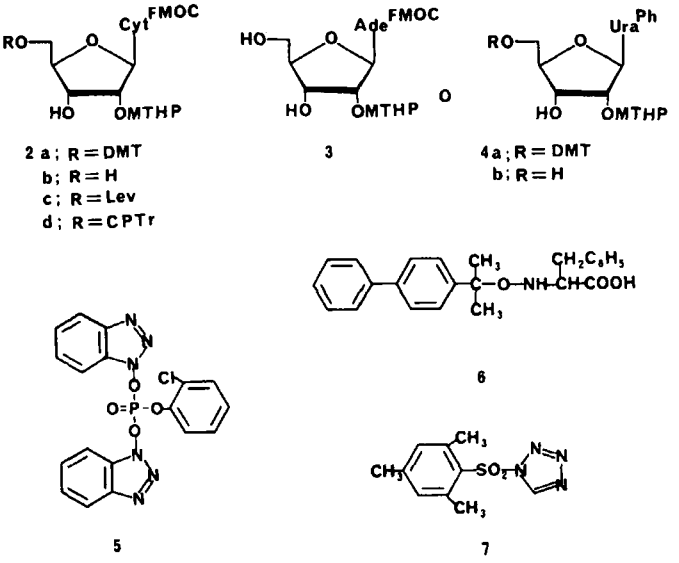
2'(3')-O-Aminoacyloligoribonucleotides (as e.g. derivatives of C-C-A; 1) with a sequence related to the natural 3'-terminus of aa-tRNA can function as simplified analogs in several subreactions of protein biosynthesis. Compounds such as 1 specifically interact with recognition sites on elongation factor Tu or ribosomes which normally accomodate the 3'-terminus of aa-tRNA, and can thus be used for studies of a role of the 3'-terminus of aa-tRNA in protein biosynthesis[1]. The considerable use of these compounds in such biochemical investigations provided the major stimulus for an appropriate chemical synthesis.



1

a; R=-CH2-C6H5
+ 2'-ISOMER

Access to compounds 1 is complicated by the considerable instability of the aminoacyl ester group[2], which makes a judicious choice of protecting groups a rather difficult task. Previous work reported from our Laboratory[3] has utilized a combination of protecting groups which necessitated a four step deblocking procedure, leading to relatively low yields of desired compounds. In our present work we report



FMOC = 9-FLUORENYLMETHYLOXYCARBONYL
BPOC = BIPHENYLYLISOPROPYLOXYCARBONYL
CPTr = 4,4',4''-TRIS(4,5-DICHLOROPHTALIMIDO)TRITYL
Lev = LEVULINYL

SCHEME 1

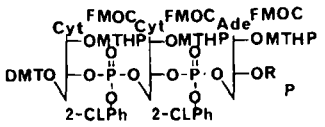
on the new system of blocking groups. This, together with improved phosphorylation procedures[4] provide for an efficient synthesis of longer oligonucleotide chain analogs of the 3'-terminus of aa-tRNA. The key features of our approach are (Scheme 1.):

i) exocyclic amino groups of cytosine and adenine are protected with 3-fluorenylmethyloxycarboyl groups (2 and 3) and 4-hydroxy group of uracil is blocked with a phenyl group (4).

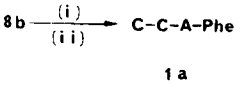
ii) 5'-hydroxyl groups of the 5'-terminal units are protected with 4,4'dimethoxytrityl groups or with levulinyl and 4,4',4"-tris (4,5-dichlorophtalimido)trityl groups (2 and 4). The latter two groups are useful for the synthesis of nucleotide blocks with the free 5'-OH groups since both groups are removable by a mild treatment with hydrazine which does not affect other moieties of the molecule.

iii) 2'-hydroxy groups are protected with 4-methoxy-tetrahydropyran-4-yl groups.

iv) Phosphodiester bond are protected with 2-chlorophenyl groups.



8a; R=H
b; R=BPOC-Phe-



(i) 2-NITROBENZALDOXIMATE; CH_3CN
(ii) HCOOH, 0°

U-C-A-Phe 9
C-U-A-Phe 10
C-C-U-Phe 11
C-C-A-Gly 12
U-C-C-A-Gly 13
C-U-C-C-A-Gly 14

SCHEME 2

v) α-amino moiety of aminoacids is blocked with 2-(4-biphenylyl)isopropyloxycarbonyl group (6).

All these groups are stable during synthesis and can be quantitatively removed in deblocking steps with preservation of the integrity of 3'-5' phospodiester and 2'(3')-O-aminoacyl bonds. Thus, the stepwise condensation of 2a with 2b in the presence of 5, followed by a chain extension with 3 in the presence of 5 led to trinucleotide derivative 8a (Scheme 2). The intermediate 8a was aminoacylated with derivative 6 in the presence of reagent 7 to give compound 8b in nearly quantitative yield. The deblocking of 8b was achieved in only two steps, employing (dry) oximate treatment (to remove FMOC and PhCl groups) and the agency of formic acid to remove DMT, MTHP and BPOC groups) to obtain C-C-A-Phe (1a) in high yield which was purified on reverse phase column. Compounds 9-11 were similarly obtained using uridine components 4a and 4b as well as component 2d. The 2'(3')-O-glycyl derivatives 13 - 14 were prepared via block condensation procedures and employing orthoester methodology, (with use of the levulinyl group for the temporary protection of the 5'-OH moiety) which allows to use a benzoyl group protection of aglycons[3].

The final products 1 and 9-14 were fully characterized by standard chemical (UV, TLC, paper electrophorsis; HPLC) and enzymatic digestion (with ribonuclease A, & snake venom phospodiesterase) methods. In the latter case, the digestion gave rise to expected products in proper ratios.

It is felt that this new method represents a significant improvement in technology to obtain target compounds of even longer chain length. The development (now in progress in our laboratory) of a suitably protected guanosine component should lead to general highly efficient methods for these biologically relevant oligonucleotide derivatives.

ACKNOWLEDGEMENTS

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