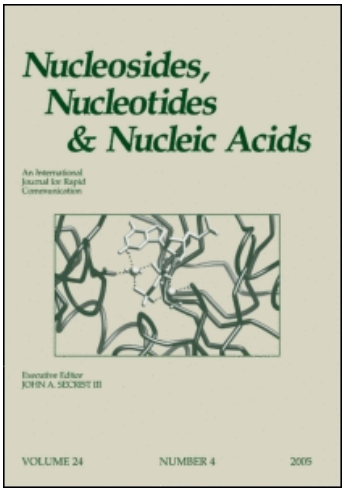


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 3'-Deoxyadenylate Trimer

F. Himmelsbach[a]; E. Uhlmann[a]; R. Charubala[a]; W. Pfleiderer[a]
[a] Fakultät für Chemie, Universität Konstanz, Konstanz

To cite this Article Himmelsbach, F. , Uhlmann, E. , Charubala, R. and Pfleiderer, W.(1985) 'Synthesis of 3'-Deoxyadenylate Trimer', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 195 — 198
To link to this Article: DOI: 10.1080/07328318508077852
URL: http://dx.doi.org/10.1080/07328318508077852

NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 195-198 (1985)

SYNTHESIS OF 3'-DEOXYADENYLATE TRIMER

F. Himmelsbach, E. Uhlmann, R. Charubala and W. Pfleiderer
Fakultät für Chemie,Universität Konstanz,Postfach 5560,D-7750 Konstanz

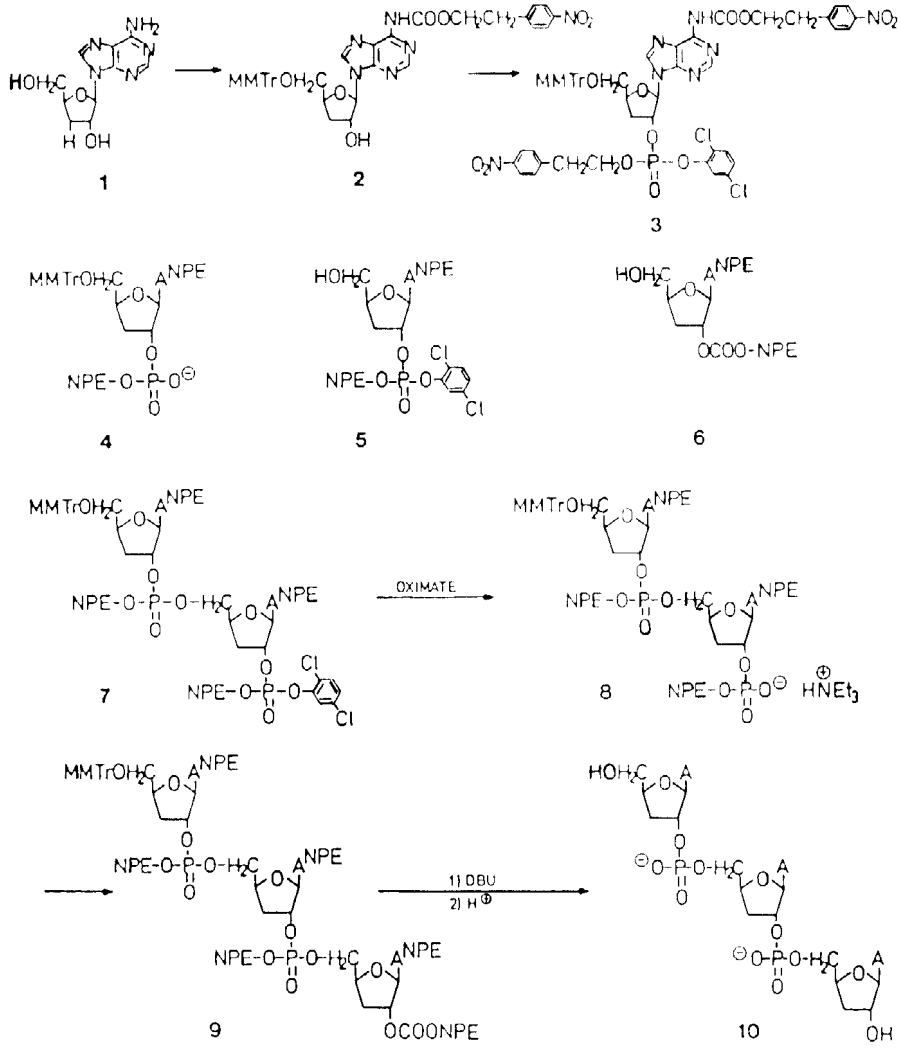
Summary: The trimeric 3'-deoxyadenylyl-(2',5')-3'-deoxyadenylyl-(2',5')-3'deoxyadenosine (10), which exhibits antiviral and antitumor activity in man, mammals, and plants respectively, was synthesized in preparative scale using three different blocking group combinations.

The interesting biological properties of the oligonucleotide 5'-O-triphosphoryl adenylyl-(2',5')-adenylyl-(2',5')-adenosine (pppA2'p5'-A2'p5'A)[1] as a strong inhibitor of cellfree protein synthesis forced various groups to synthesize this low molecular weight unusual oligonucleotide as well as its core by chemical means using mainly the phosphotriester approach by varying the blocking group combinations[2].

The short half lifes of the natural 2',5'-A trimers gave rise to the synthesis of various structurally modified adenylate oligomers including variations of the internucleotide linkage[3], the sugar moiety[4] and even the aglycon[5]. The cordycepin trimer core dA2'p5'A2'p5'A (10) as a closely related structural analog of the naturally occurring inhibitor turned out to possess extended metabolic stability without toxicity to cells and a broad spectrum of biological activities characterized by the inhibition of the transformation of Epstein-Barr virus infected lymphocytes[6], the synthesis of EBV-induced nuclear antigen[7], the Tobacco mosaic virus replication in Tobacco plants[8] and the Chondro sarcoma growth in animals[9].

We concentrated on the chemical synthesis of the cordycepin trimer (10) by applying various blocking groups to the functions of the aglycon, sugar moiety, and the phosphate group. In the first synthesis, cordycepin (1) was benzoylated at the 6-amino group, methoxytritylated

 0732-8311/85/0401-0195$3.50/0



at the 5'-OH group and then phosphorylated by o-chlorophenylphosphorodichloridate at the 2'-OH position followed by cyanoethanol treatment to give the N^6-benzoyl-5'-O-methoxytrityl-3'-deoxyadenosine-2'-(o-chlorophenyl, cyanoethyl)-phosphate. This building block is used to prepare the corresponding phosphodiester by cleavage of the cyanoethyl group and the 5'-deprotected phosphotriester by detritylation. Condensation of these two components gave the fully protected dinucleoside diphosphotriester in 58 % yield. Conversion to the 2'-terminal dimeric phosphodiester and further condensation with N^6,N^6,2'-O-tribenzoyl-3'-de-

oxyadenosine gave the fully blocked cordycepin trimer in 79 % yield. Deprotection of the various blocking groups led to 80 % of the cordycepin trimer ($\underline{\underline{10}}$)[4].

The second approach worked analogously by using N^6-benzoyl-5'-O-methoxytrityl-3'-deoxyadenosine-2-(2,5-dichlorophenyl, p-nitrophenylethyl)-phosphate as the central building block. Deblocking of the 2,5-dichlorophenyl group by the oximate procedure led to a p-nitrophenylethylphosphodiester which was then applied to the condensation steps giving improved yields up to 88 %. Deprotection at the end also worked better and gave 87 % of $\underline{\underline{10}}$.

The most sophisticated recent approach makes use of an unified blocking group strategy using with exception of the 5'-OH group in principle one type of protection for the amino, hydroxy, and phosphate groups. Cordycepin ($\underline{1}$) is first transformed via $\underline{2}$ into 5'-O-methoxytrityl-N^6-p-nitrophenylethoxycarbonyl-3'-deoxyadenosine-2'-(2,5-dichlorophenyl, p-nitrophenylethyl)-phosphate ($\underline{3}$) and N^6,2'-O-di-p-nitrophenylethoxycarbonyl-3'-deoxyadenosine ($\underline{6}$) as the necessary two building blocks. $\underline{3}$ is converted into the phosphodiester $\underline{4}$ and the 5'-deprotected phosphotriester $\underline{5}$ respectively in excellent yields, which are then condensed to give the dimer $\underline{7}$ in 88 % yield. Oximate treatment forms 91 % of $\underline{8}$ which on further condensation with $\underline{6}$ by means of TPSCl and N-methylimidazole gave 91 % yield of the fully blocked trimer $\underline{9}$. Its deprotection can be achieved by only two steps using first DBU in pyridine and then 80 % acetic acid to give 85 % isolated yield of the cordycepin trimer ($\underline{\underline{10}}$).

REFERENCES

1. Torrence, P.F.: Molec. Aspects Med. 5, 129 (1982).
2. Charubala, R.; Uhlmann, E.; Pfleiderer, W.: Liebigs Ann.Chem. 1981, 2392.
3. Charubala, R.; Pfleiderer, W.: Tetrahedron Lett. 1980, 1933.
4. Charubala, R.; Pfleiderer, W.: Tetrahedron Lett. 1980, 4077.
5. Charubala, R.; Pfleiderer, W.: Tetrahedron Lett. 1982, 4789.

6. Doetsch, P.W.; Suhadolnik, R.J.; Sawada, Y.; Mosca, J.D.; Flick, M.B.; Reichenbach, N.L.; Dang, A.D.; Wu, J.M.; Charubala, R.; Pfleiderer, W.; Henderson, E.E.: Proc.Natl.Acad.Sci. USA 78, 6699 (1981)

7. Henderson, E.E.; Doetsch, P.W.; Charubala, R.; Pfleiderer, W.; Suhadolnik, R.J.: Virology 122, 198 (1982).

8. Devash, Y.; Gera, A.; Willis, D.H.; Reichmann, M.; Pfleiderer, W.; Charubala, R.; Sela, I.; Suhadolnik, R.J.: J.Biol.Chem. 259, 3482 (1984).

9. Willis, D.H.; Pfleiderer, W.; Charubala, R.; Suhadolnik, R.J.: J.Fed.Proc. 42, 443 (1983).