

This article was downloaded by: [130.132.123.28]

On: 03 January 2015, At: 03:52

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/Incn19>

Synthesis of Trimeric Cordycepin-Vitamin Conjugates as Improved Antiviral Agents

Marita Wasner^a & Wolfgang Pfeleiderer^a

^a Department of Chemistry, University of Konstanz, P. O. Box 5560
D-78434, Konstanz, Germany

Published online: 16 Feb 2007.

To cite this article: Marita Wasner & Wolfgang Pfeleiderer (1995) Synthesis of Trimeric Cordycepin-Vitamin Conjugates as Improved Antiviral Agents, *Nucleosides and Nucleotides*, 14:3-5, 1101-1104

To link to this article: <http://dx.doi.org/10.1080/15257779508012544>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

SYNTHESIS OF TRIMERIC CORDYCEPIN-VITAMIN CONJUGATES AS IMPROVED ANTIVIRAL AGENTS

Marita Wasner, Wolfgang Pfeleiderer[†]

Department of Chemistry, University of Konstanz, P.O.Box 5560
D-78434 Konstanz / Germany

Abstract: The chemical syntheses of various cordycepin trimers carrying vitamin E, D₂ and A via a succinate linker at the 2'-O- and 5'-O-position are described. The conjugates were characterized by physical means and used for biological investigations.

It has been established that the (2-5)OligoA/RNase L pathway is part of the antiviral activity of interferon¹. Consequently, 2',5'-oligoadenylates were modified in order to get a novel chemotherapeutic possibility for the control of virus and cell growth. One of the analogues is the cordycepin trimer core 3'd(A2'p5'A2'p5'A)² which shows biological activity, metabolic stability and no toxicity to cells³. It has recently been found that the 2'-O- and 5'-O-cholesterol conjugates of Co₃ exhibit a highly increased anti-HIV-1 activity which can be up to 1 000-fold in comparison with Co₃⁴. This fact is most likely attributed to an improved cellular uptake of these conjugates bearing a hydrophobic handle. These promising results led to the synthesis of other trimeric cordycepin conjugates carrying vitamin E, D₂ and A via a succinate linker at the 2'-O- and 5'-O-position of the terminal ends.

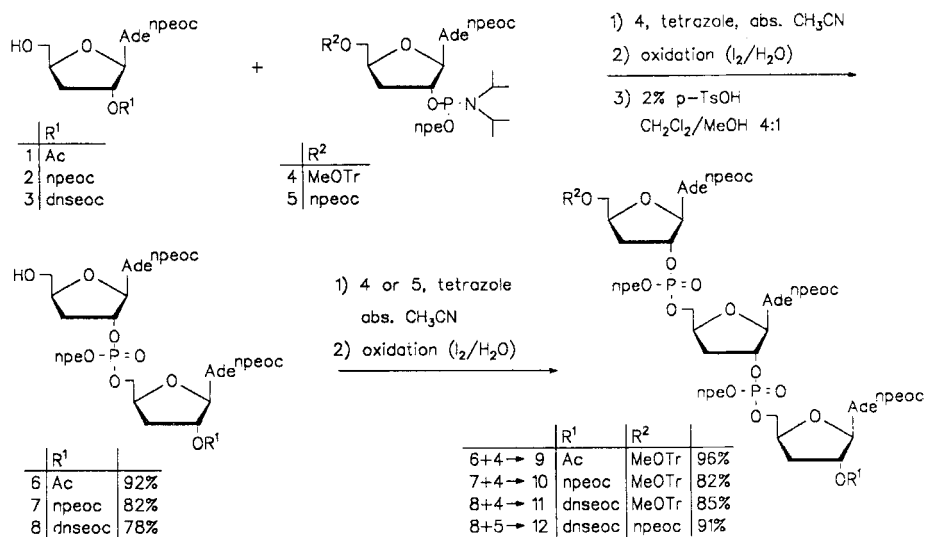
The attachment of the vitamins through ester bonds needed a special blocking group strategy using the 2-(4-nitrophenyl)ethyl (npe), the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) and the dansylethoxycarbonyl (dnseoc) group for a unified protection cleavable by a β-elimination process without harming the ester functions.

Results: The chemical solution syntheses of the cordycepin trimers carrying vitamins at the 2'-O- and 5'-O-terminal ends via succinyl spacer (see **19 -21** and **25 - 27**) were achieved by the phosphoramidite approach:

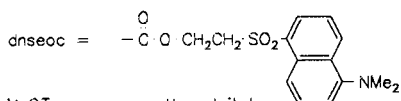
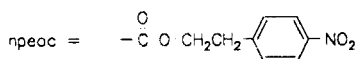
The differently 2'-O-protected compounds **1 - 3** were condensed with phosphoramidite **4** to give on subsequent oxidation and detritylation the dimers **6 - 8**. For further chain elongation, these dimers were treated with phosphoramidite **4** and **5**, respectively, and after oxidation with I_2/H_2O /pyridine the corresponding fully protected trimers **9 - 12** were obtained. In order to get the 2'-OH-trimers, the 2'-O-acetyl- and 2'-O-npeoc protected compounds **9** and **10** were treated with K_2CO_3 in abs. MeOH to give compound **13** in 75 and 69% yield, respectively. Another possibility to get the 2'-OH-building block is the selective β -elimination of the dnseoc-group in compound **11** and **12** with diluted DBU in abs. pyridine.

Starting material for the 5'-O-conjugates is trimer **15** which was prepared by acid treatment of compound **10**.

The following conjugate syntheses proceeded in an almost analogous manner: In a one-pot reaction the fully protected trimeric conjugates **16 -18** were obtained by treating starting compounds **13** and **14** first with succinic anhydride and DMAP followed by esterification via carbodiimide method with the vitamins E, D_2 and A. The vitamin D_2 and A conjugates afforded a unified npeoc-protection due to the acid lability of these compounds. The final deblocking was achieved subsequently by β -elimination with DBU to remove the npe- and npeoc-groups to get **20** and **21**. In the case of **19**, further detritylation by acetic acid was necessary. Formation and deblocking of the trimeric 5'-O-conjugates took place in a similar manner: the 5'-OH-building block **15** was first modified with succinic anhydride and subsequently esterified with the vitamins E, D_2 and A in the presence of EDC as condensing agent to give compounds **22 - 24**. Deblocking was performed with 0.5 molar DBU in abs. pyridine leading to the conjugates **25 - 27**. The free cordycepin conjugates were isolated as colourless (**19**, **20**, **25**, **26**) and pale yellow (**21**, **27**) powders, respectively, by washing the solid with abs. CH_3CN . The free vitamin A conjugates, however, turned out to show some instability in aqueous solution.

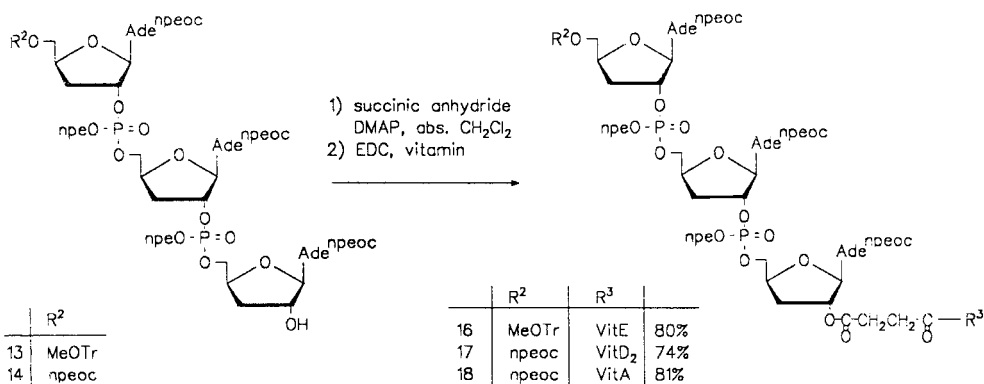
a: K₂CO₃ / abs. MeOH

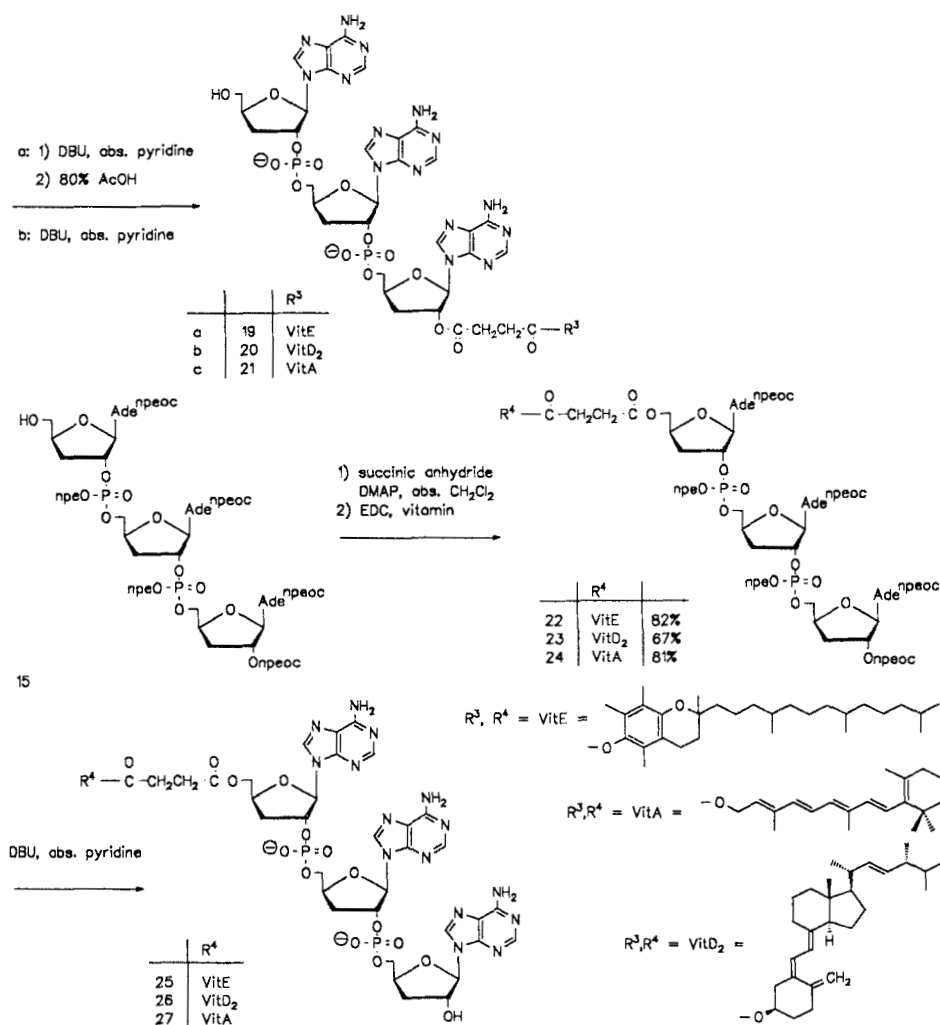
b: 0.05M DBU / abs. pyridine

c: 2% p-TsOH, CH₂Cl₂/MeOH 4:1

MeOTr = monomethoxytrityl

	R ¹	R ²	Yield (%)
9+a → 13	H	MeOTr	75%
10+a → 13	H	MeOTr	69%
11+b → 13	H	MeOTr	87%
12+b → 14	H	npeoc	80%
10+c → 15	npeoc	H	92%





REFERENCES

1. Torrence, P.F. In *Biological Response Modifiers. New Approaches to Disease Intervention*; Torrence P.F., Ed.; Academic Press, Orlando, **1985**, p.77
2. Charubala, R.; Pfeleiderer, W. *Tetrahedron Lett.* **1980**, 21, 4077
3. Doetsch, P.W.; Suhadolnik, R.J.; Sawada, Y.; Mosca, J.D.; Flick, M.B.; Reichenbach, N.L.; Dang, A.Q.; Wu, J.M.; Charubala, R.; Pfeleiderer, W.; Henderson, E.E. *Proc. Natl. Acad. Sci. USA* **1981**, 78, 6699
4. Wasner, M.; Henderson, E.E.; Suhadolnik, R.J.; Pfeleiderer, W. *Helv. Chim. Acta* **1994**, in press