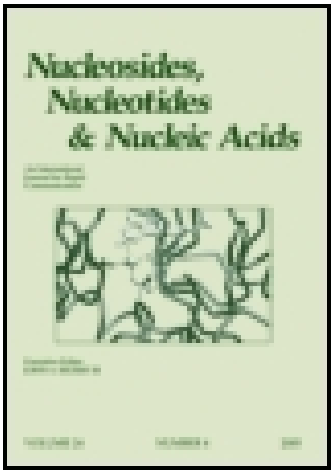

Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

Synthesis of Trimeric Cordycepin-Vitamin Conjugates as Improved Antiviral Agents

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Published online: 16 Feb 2007.

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 1101-1104 (1995)

SYNTHESIS OF TRIMERIC CORDYCEPIN-VITAMIN CONJUGATES AS IMPROVED ANTIVIRAL AGENTS

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Abstract: The chemical syntheses of various cordycepin trimers carrying vitamin E,D_2 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 interferon[1]. 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 cells[3]. It has recently been found that the 2'-O- and 5'-O-cholesterol conjugates of Co_3 exhibit a highly increased anti-HIV-1 activity which can be up to 1 000-fold in comparision with Co_3[4]. 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, D_2 and A via a succinate linker at the 2'-O- and 5'-O-position of the terminal ends.

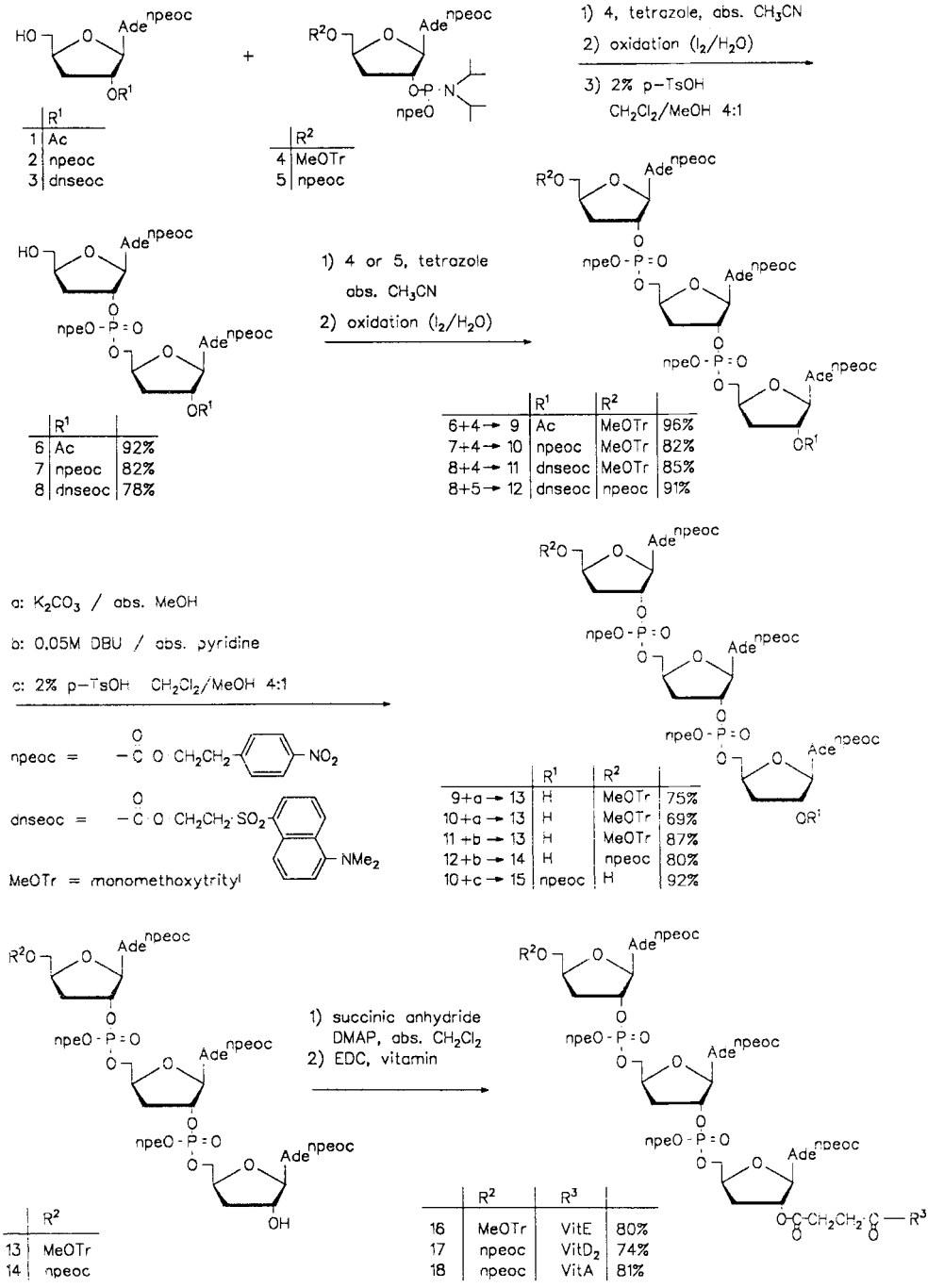
The attachment of the vitamins through ester bonds needed a special blocking group strategy using the 2-(4-nitrophenyl)ethyl (npe), the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) and the dansylethoxycarbonyl (dnseoc) group for a unified protection cleavable by a ß-elimination process without harming the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



	R¹
1	Ac
2	npeoc
3	dnseoc

	R²
4	MeOTr
5	npeoc

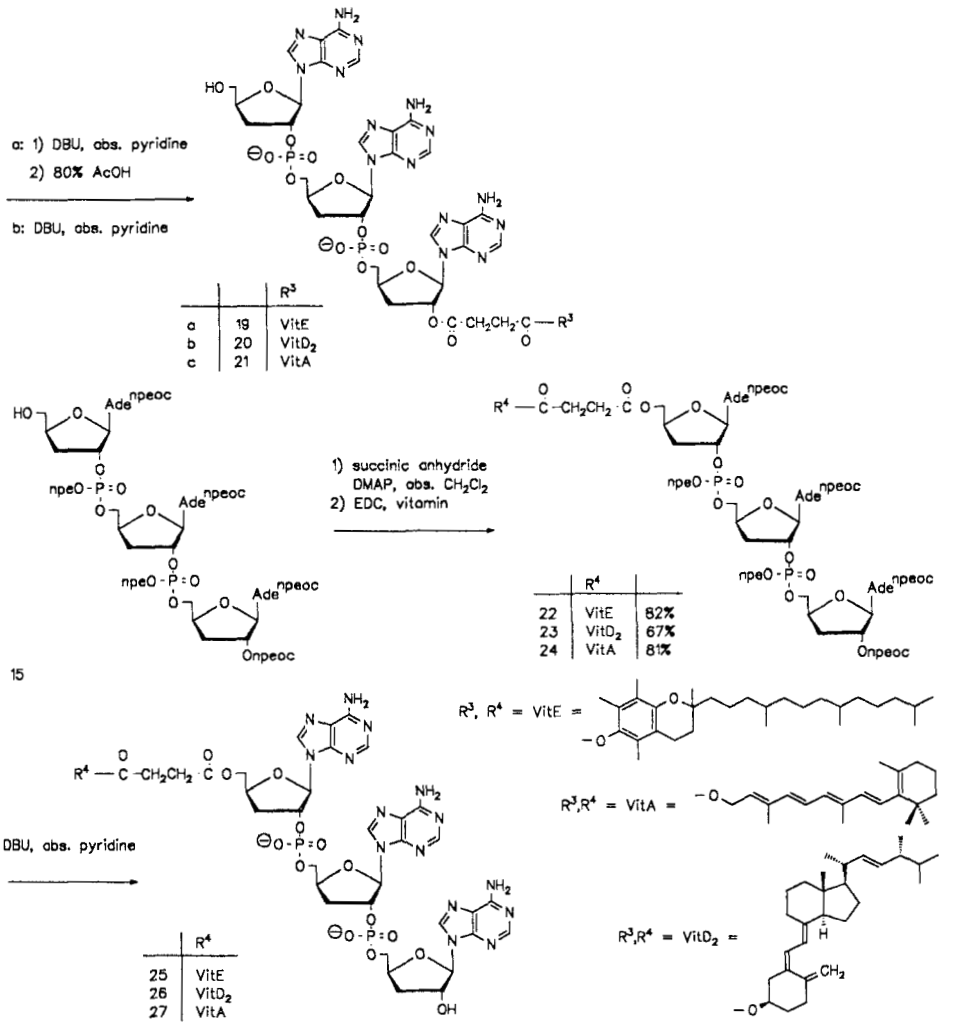
	R¹	
6	Ac	92%
7	npeoc	82%
8	dnseoc	78%

	R¹	R²	
6+4→ 9	Ac	MeOTr	96%
7+4→ 10	npeoc	MeOTr	82%
8+4→ 11	dnseoc	MeOTr	85%
8+5→ 12	dnseoc	npeoc	91%

	R¹	R²	
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%

	R²
13	MeOTr
14	npeoc

	R²	R³	
16	MeOTr	VitE	80%
17	npeoc	$VitD_2$	74%
18	npeoc	VitA	81%



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