

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

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, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

A New Cyclic Phosphoramidate D4T Prodrug Approach *cycloAmb-D4T-Phosphoramidates*

Martina Lorey^a; Chris Meier^a

^a Institut für Organische Chemie, Universität Hamburg, Hamburg, Germany

To cite this Article Lorey, Martina and Meier, Chris(1999) 'A New Cyclic Phosphoramidate D4T Prodrug Approach *cycloAmb-D4T-Phosphoramidates*', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 947 — 948

To link to this Article: DOI: 10.1080/15257779908041608

URL: <http://dx.doi.org/10.1080/15257779908041608>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

A NEW CYCLIC PHOSPHORAMIDATE d4T PRODRUG APPROACH CYCLOAMB-d4T-PHOSPHORAMIDATES

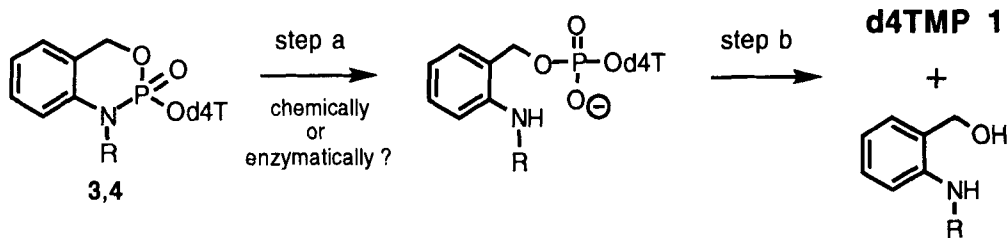
Martina Lorey and Chris Meier*

Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6,
D-20146 Hamburg, Germany

Abstract: A new potential phosphoramidate prodrug approach for d4T **1** is described. In hydrolyses studies the *cyclo*Amb-d4T-phosphoramidates **2** and **3** proved to deliver d4TMP following a tandem reaction.

Here we present the synthesis and some properties of a new potential pro-nucleotide approach as neutral prodrug of d4TMP **1** of the antivirally active nucleoside analogue d4T **2**. As for the previously reported *cyclo*Sal-NMPs¹, the *cyclo*aminobenzyl-d4T-phosphoramidates **3** and **4** (*cyclo*Amb-d4T-phosphoramidate, Scheme 1) were designed to release the nucleotide **1** *selectively* by controlled, chemically induced hydrolysis following a tandem mechanism. The concept involves a successive, coupled cleavage of the amide- and the benzylolester of the phosphoramidate based on the different stabilities of these bonds.

Scheme 1: The proposed hydrolysis pathway of *cyclo*Amb-d4T-phosphoramidates **3,4**



R = H, *cyclo*Amb-d4T-phosphoramidate **3**

R = CH₃, *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4**

*Cyclo*Amb-d4T-phosphoramidate **3** was synthesized using phosphorus(V)-chemistry. In contrast to the P(III)-chemistry use in the case of the *cyclo*Sal-NMPs, here we preferred the P(V)-reagents due to the reactivity of the amino-group in 2-aminobenzyl alcohol. D4T was

Table: PCs, log*P* and chemical hydrolysis half-lives in phosphate buffer

Compounds	PC 1-octanol/PB	log <i>P</i> 1-octanol/PB	t _{1/2} in 25 mM PB at pH 7.3 [h]
d4T 2	0.15	-0.82	--
3 (fast-diastereomer)	1.9	0.28	60.7
3 (slow-diastereomer)	2.3	0.36	41.5
4	2.4	0.38	< 3% in 100 h
<i>cyclo</i> Sal-d4TMP	1.9	0.28	4.6

converted to the phosphorusdichloridate with P(O)Cl₃ in the presence of triethylamine (TEA) in dry THF at -10°C. By further treatment with a solution of 2-aminobenzyl alcohol and TEA in THF, the cyclic phosphoramidate **3** was obtained in 38% yield. *Cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4** could not be prepared by this approach. Here, again P(III)-chemistry lead to the successful isolation of the amidate diester: *N*-Methyl-aminobenzyl alcohol was reacted with phosphorus trichloride in the presence of TEA to yield the cyclic chlorophosphoramidite. In the following "one-pot" reaction, d4T was treated with this cyclic chlorophosphoramidite in the presence of diisopropylethylamine (DIPEA) to obtain the *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidite which was subsequently oxidized with *t*-butylhydroperoxide (TBHP) to give the title compound **4** in 17% yield.

The partition coefficients (PC) in 1-octanol/phosphate buffer (PB), pH 6.8 are a qualitative estimation of the lipophilic properties of *cyclo*Amb-d4T-phosphoramidates **3** and **4**. The PCs of **3** and **4** were by a factor 12-16 higher relative to d4T **2** and in the same order of magnitude as the corresponding *cyclo*Sal-d4TMP (Table).

As a first model for the physiological milieu, *cyclo*Amb-d4T-phosphoramidates **3** and **4** were hydrolyzed in 25 mM phosphate buffer, pH 7.3 at 37°C. The chemical hydrolyses were followed by means of HPLC. Under these conditions, *cyclo*Amb-d4T-phosphoramidate **3** was degraded with a t_{1/2} of about 50 h. In contrast, the *N*-methylated *cyclo*-Amb-d4T-phosphoramidate **4** showed less than 3% degradation within 100 h. In comparison to *cyclo*Sal-d4TMP¹, the half-lives were increased by a factor 9-13 for the *cyclo*Amb-d4T-phosphoramidate **3**, while *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4** showed scarcely degradation. Antiviral cell tests of **3** and **4** are in progress.

Reference

1. Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J.; *J. Med. Chem.* **1998**, *41*, 1417-1427; Meier, C.; *Synlett* **1998**, 233-242.