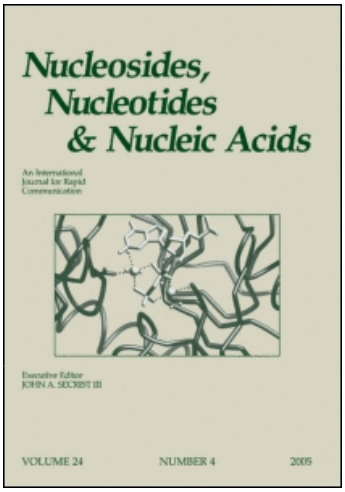


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[*c*]furan Analogue of d4T and Its SATE Pronucleotide

Christophe Len[ab]; Abdelmajid Selouane[a]; Denis Postel[a]; Pierre Villa[a]; Anne-Marie Aubertin[c]; David Egron[d]; Gilles Gosselin[d]; Christian Périgaud[d]
[a] Laboratoire des Glucides, Université de Picardie-Jules Verne, Amiens, France [b] Laboratoire des Glucides, Université de Picardie, Amiens, France [c] Institut de Virologie de la Faculté de Médecine de Strasbourg, Strasbourg, France [d] UMR 5625 CNRS-UMII, Université Montpellier II, Montpellier, France

Online publication date: 09 August 2003

To cite this Article Len, Christophe , Selouane, Abdelmajid , Postel, Denis , Villa, Pierre , Aubertin, Anne-Marie , Egron, David , Gosselin, Gilles and Périgaud, Christian(2003) 'Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[*c*]furan Analogue of d4T and Its SATE Pronucleotide', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 943 — 945
To link to this Article: DOI: 10.1081/NCN-120022691
URL: http://dx.doi.org/10.1081/NCN-120022691

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 943–945, 2003

Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[*c*]furan Analogue of d4T and Its SATE Pronucleotide

Christophe Len,[1,*] Abdelmajid Selouane,[1] Denis Postel,[1] Pierre Villa,[1] Anne-Marie Aubertin,[2] David Egron,[3] Gilles Gosselin,[3] and Christian Périgaud[3]

[1]Laboratoire des Glucides, Université de Picardie-Jules Verne, Amiens, France
[2]Institut de Virologie de la Faculté de Médecine de Strasbourg, Strasbourg, France
[3]UMR 5625 CNRS-UMII, Université Montpellier II, Montpellier, France

ABSTRACT

The anti-HIV activity and stability studies of 1,3-dihydrobenzo[c]furan analogue of d4T are reported. The corresponding mononucleoside phosphotriester derivative bearing a *S*-pivaloyl-2-thioethyl (*t*BuSATE) group, as biolabile phosphate protection, is also studied.

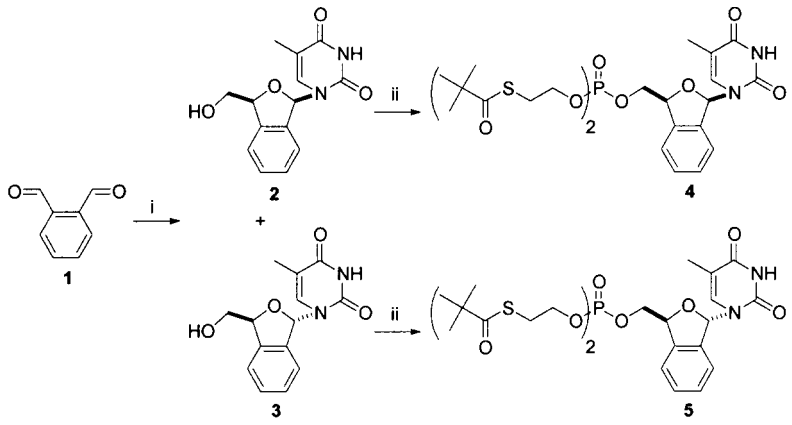
Key Words: 1,3-Dihydrobenzo[*c*]furane; d4T; SATE pronucleotide.

In order to improve the physico-chemical parameters of 2′,3′-didehydro-3′-deoxythymidine (d4T), we have recently reported the synthesis of its 1,3-dihydro-

*Correspondence: Christophe Len, Laboratoire des Glucides, Université de Picardie, 33, rue Saint Leu, Amiens F-80039, France; Fax: +33 3 2282 7568; E-mail: christophe.len@sc.u-picardie.fr.

DOI: 10.1081/NCN-120022691
1525-7770 (Print); 1532-2335 (Online)
www.dekker.com

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1. *Reagents and conditions:* (i) Ref. 1; (ii) bis(*S*-pivaloyl-2-thioethyl) *N*,*N*-diisopropyl phosphoramidite, 1*H*-tetrazole, CH_3CN then *t*BuOOH, toluene.

Table 1. Chemical stability and lipophilicity of nucleoside **2** compared to d4T.

Compounds		**2**	d4T
$t_{1/2}$	pH 7.3	34 days	6 days
	pH 2.0	31 days	5 days
	pH 1.2	18 days	3 days
Log P[a]		0.55	−0.77

[a]Log P determinations were performed using log P dB 4.5 calculations (ACD, Canada).

benzo[*c*]furan derivative (BcFT).[1,2] Briefly, starting from the readily available phthalaldehyde **1**, the enantiomerically pure nucleosides **2** and **3** were obtained in 8% overall yield (Sch. 1).

The chemical hydrolysis of nucleoside **2** and d4T gives rise to the formation of thymine but BcFT was more stable than d4T in all the studied buffers (Table 1). As expected, the introduction of a benzene ring on the sugar residue increases the liphophilicity of the resulting structure.

The possibility to improve the anti-HIV efficiency of nucleoside analogues **2** and **3** using a pronucleotide approach was evaluated. Thus, the mononucleoside phosphotriesters **4** and **5** (Scheme) incorporating the *S*-pivaloyl-2-thioethyl (*t*BuSATE) group as biolabile phosphate protection were synthesised according to a previously published method.[3]

Compounds **2**–**5** were evaluated for their inhibitory effects on the replication of HIV-1 in human T4-lymphoblastoid cells, CEM-SS and MT-4. All compounds were found to be inactive at concentration up to 100 μM.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

REFERENCES

1. Ewing, D.F.; Fahmi, N.-E.; Len, C.; Mackenzie, G.; Pranzo, A. Stereoisomeric pyrimidine nucleoside analogues based on the 1,3-dihydrobenzo[*c*]furan core. J. Chem. Soc. Perkin Trans. **2000**, *1*, 3561–3565.
2. Sélouane, A.; Vaccher, C.; Villa, P.; Postel, D.; Len, C. Enantiomeric d4T analogues and their structural determination. Tetrahedron Asymmetry **2002**, *13*, 407–413.
3. Lefebvre, I.; Périgaud, C.; Pompon, A.; Aubertin, A.M.; Girardet, J.-L.; Kirn, A.; Gosselin, G.; Imbach, J.-L. Mononucleoside phosphotriester derivatives with S-acetyl-2-thioethyl bioreversible phosphate-protecting groups: intracellular delivery of 3′-azido-2′,3′-dideoxythymidine 5′-monohosphate. J. Med. Chem. **1995**, *38*, 3941–3950.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016