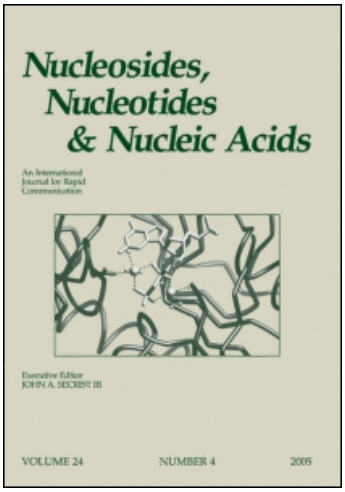


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of [1-[2',5'-*bis*-*O*-(*t*-Butyldimethylsilyl)-β- L-ribofuranosyl] thymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) (L-TSAO-T)

Simon Ingate[a]; Ana San-Félix[a]; Erik De Clercq[b]; Jan Balzarini[b]; Maríia-José Camarasa[a]
[a] Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, Madrid, Spain [b] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

To cite this Article Ingate, Simon , San-Félix, Ana , De Clercq, Erik , Balzarini, Jan and Camarasa, Maríia-José(1995) 'Synthesis of [1-[2',5'-*bis*-*O*-(*t*-Butyldimethylsilyl)-β- L-ribofuranosyl] thymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) (L-TSAO-T)', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 299 — 301
To link to this Article: DOI: 10.1080/15257779508012366
URL: http://dx.doi.org/10.1080/15257779508012366

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 299-301 (1995)

SYNTHESIS OF [1-[2',5'-BIS-*O*-(*t*-BUTYLDIMETHYLSILYL)-β-L-RIBOFURANOSYL]THYMINE]-3'-SPIRO-5"-(4"-AMINO-1",2"-OXATHIOLE-2",2"-DIOXIDE) (L-TSAO-T)

Simon Ingate[1], Ana San-Félix[1], Erik De Clercq[2], Jan Balzarini[2], and María-José Camarasa*[1]

Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, 3. 28006 Madrid, Spain[1]
Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000, Leuven, Belgium[2]

Abstract: Derivatives of TSAO-T based upon pentofuranose sugars with the L-configuration have been prepared and evaluated as inhibitors of HIV-1 induced cytopathicity.

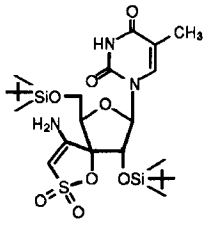
INTRODUCTION

Since the discovery that the TSAO family of compounds, the prototype of which is [1-[2',5'-Bis-*O*-(*t*-butyldimethylsilyl)-β-D-*ribo*-furanosyl]thymine]-3´-spiro-5"-(4"-amino-1", 2"-oxathiole-2",2"-dioxide) designated here as D-TSAO-T **1**,[1] are highly potent, specific HIV-1 reverse transcriptase inhibitors; many modifications of the basic structure have been studied.[2-5]

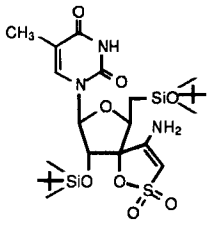
Some 2',3'-dideoxy-L-pyrimidine nucleosides such as β-L-ddC and (-)-2',3'-dideoxy-3'-thiacytidine [(-)-3TC] exhibit strong anti-HIV activity in cell culture and are targeted at the retroviral reverse transcriptase.[6,7] With this in mind and to compare its activity with D-TSAO-T **1**, the synthesis of the L-isomer of TSAO-T, henceforth known as L-TSAO-T **2**, was carried out.

Furthermore, studies on the effects of changing the nature of the protecting groups at the 2'-*O* and 5'-*O* positions on the antiviral activity [5] have shown the relative importance of the 5'-*O*-*t*-BDMS substituent. It was of particular interest to see if the position of this group was vital to the inhibitory function of TSAO-T. Since it was not known if a change in the configuration at the *C*-4 position would affect the accessability of the amino group at *C*-4" of the spiro moiety it was of importance to synthesise both the L-*arabino* **3** and L-

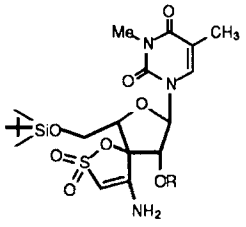
lyxo **4** isomers of TSAO-T. Thus, a synthetic route starting with L-*arabino*-thymine **8** was devised.



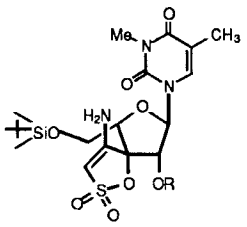
1 D-TSAO-T



2 L-TSAO-T



3 L-ara-TSAO-T



4 L-lyxo-TSAO-T

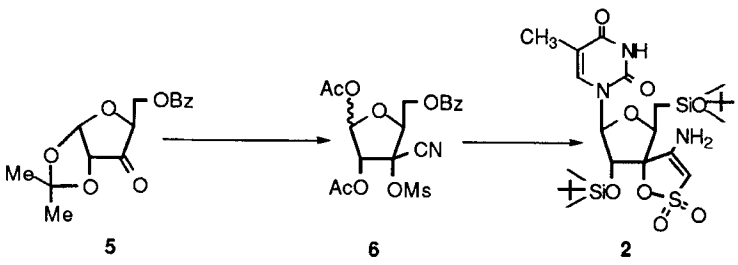
SYNTHESIS

(a) ***The synthesis of L-TSAO-T 2***

Following the procedure for the synthesis of **1**[1] the L-analogue **2** was synthesised from L-xylose via the key intermediates **5** and **6** (Scheme 1).

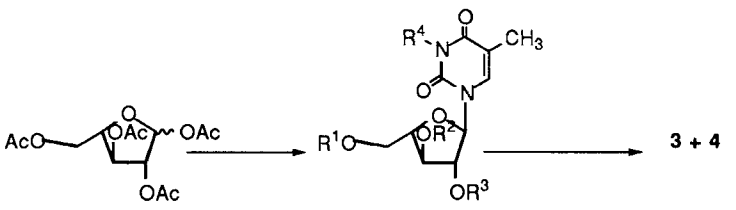
(b) ***The synthesis of L-arabino-TSAO-T 3 and L-lyxo-TSAO-T 4***

Beginning with L-*arabino*-furanose-1,2,3,5-tetraacetate **7**[8] (Scheme 2), glycosylation with persilylated thymine followed by deprotection yielded the nucleoside



5 **6** **2**

Scheme 1



8 $R^1=R^2=R^3=R^4=H$
9 $R^1=R^2=$tBDMS, $R^3=$Bn, $R^4=$Me
10 $R^1=$tBDMS, $R^2=H$, $R^3=$Bn, $R^4=$Me

Scheme 2

8. Silylation with *tert*-BDMSCl in pyridine gave a mixture of products, of which only one disubstituted isomer **9** was isolated (50% yield).

N-Methylation yielded **9** and 2'-*O*-benzylation gave **10**. The 3'-*O*-silyl group was removed selectively with tetrabutylammonium fluoride in dry acetone[9] to give **11**. Oxidation of **11** followed by cyanomesylate formation gave a mixture of the isomers which were ring closed with Cs_2CO_3 in CH_3CN to give the compounds **3** and **4**.

The compounds **1** to **4** have been tested for anti-HIV-1 inhibition in CEM and MT-4 cell lines, but none of the modified compounds (**2** to **4**) have shown significant activity at subtoxic concentrations.

REFERENCES

1 Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E. and Camarasa M.J.; *J.Med.Chem.* **1992**, *35*, 2988-2995.

2 Camarasa, M.J.; Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; and De Clercq, E.; *J.Med.Chem.* **1992**, *35*, 2721-2727.

3 Velázquez, S.; San-Félix, A.; Pérez-Pérez, M.J.; Balzarini, J.; De Clercq, E. and Camarasa, M.J.; *J.Med.Chem.*,**1992**, *36*, 3230-3239.

4 Alvarez, R., San-Félix, A.; Balzarini, J.; De Clercq, E. and Camarasa, M.J.; *Unpublished results.*

5 Ingate, S.T.; San-Félix, A.; Balzarini, J.; De Clercq, E. and Camarasa, M.J.; *in preparation.*

6 Lin, T-S.; Luo M-Z.; Liu, M-C.; Balakrishna Pai, S.; Dutchsman, G.E. and Cheng Y-C.; *Biochem.Pharmacol.*, **1994**, *47*, 171-174.

7 Schinazi, R.F; Chu,W-B; Yeola, S; Liotta, D.C; *Antimicrob.Agents.Chemother.* **1992**, *36*, 672-676.

8 Mizutani, K; Kasai, R; Nakamura, M; Tanaka, M; *Carbohydr.Res.*, **1989**, *185*, 27-38.

9 Adapted from Ogilvie, K.K; Beaucage S.L; Schifman A.L; Theriault , N.Y and Sadana, K.L; *Can.J.Chem.* ,**1978**, *56*, 2768-2780.