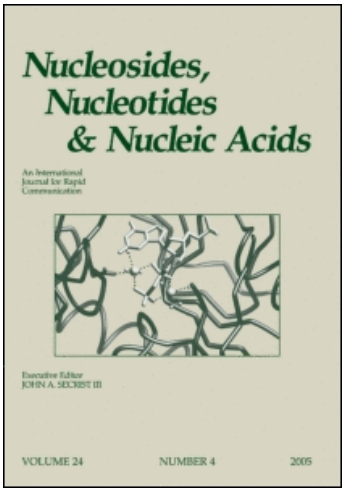


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# Unusual Lability of 5′-*O*-*tert*-Butyldimethylsilyl Group On 4″-Acyl TSAO Derivatives†

**Sonia de Castro,[1] María-Jesús Pérez-Pérez,[1] Esther Lobatón,[1] Erik De Clercq,[2] Jan Balzarini,[2] María-José Camarasa,[1] and Sonsoles Velázquez[1,*]**

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TSAO-m$^3$T (**1**) is the prototype compound of a unique family of HIV-1-specific non-nucleoside reverse transcriptase inhibitors (NNRTIs) that seems to interact at the interface between the p51 and p66 reverse transcriptase (RT) subunits.[1,2] As part of our program on the synthesis of a "second generation" of TSAO derivatives directed against TSAO-resistant HIV-1 strains (GluB138Lys), we focused on the preparation of TSAO derivatives that contain carbonyl groups at the 4″ position of the spiro moiety, that may form H-bonds with the $NH_2$ group of Lys 138 of the mutant HIV-1 RT. We found that compound **2** (Fig. 1) bearing an oxalyl moiety at the 4″ position showed an unusual lability of the 5′-*O*-*tert*-butyldimethylsilyl group (TBDMS) in DMSO solution. This facile desilylation was not observed, previously, with the more than 500 TSAO derivatives prepared so far.[2]

In this communication we investigated the nature of this unexpectedly facile desilylation. Several modifications on the TSAO-oxalyl derivative **2**, following standard synthetic procedures, were carried out. Thus, introduction of different

†This paper is dedicated to the memory of Dr. Manfred Stud.

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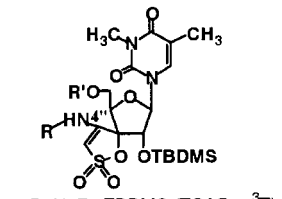



**3** R=$COCF_3$, R'=TBDMS
**4** R=$COCH_3$, R'=TBDMS
**5** R=$CONH_2$, R'=TBDMS
**6** R=$CONHCH_2CH_3$, R'=TBDMS
**7** R= COCOOH, R'=TBDMS
**8** R=$COCONH_2$, R'=TBDMS
**9** R=$COCONHCH_3$, R'=TBDMS
**10** R=COCON◇, R'=TBDMS
**11** R=$COCOOCH_3$, R'=TDS
**12** R=$COCOOCH_3$, R'=Bn
**13** R=$COCOOCH_3$, R'=$COOCH_3$

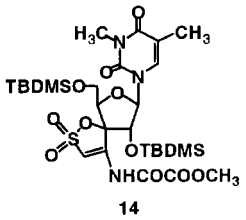



*Figure 1.*

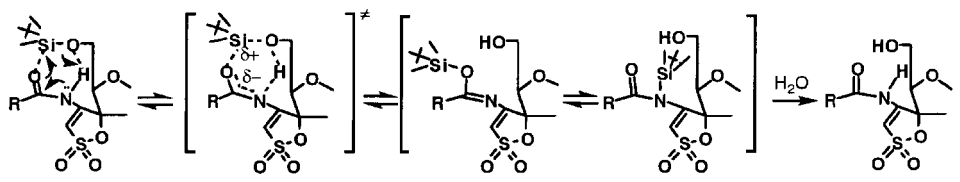
oxalyl-type carbonyl moieties and other carbonyl groups at the 4″ position of the 3′-spiro moiety led to compounds **3**–**10**. Replacement of the labile 5′-TBDMS by other groups gave compounds **11**–**13**. Finally, for comparative purposes, the *xylo* oxalyl TSAO nucleoside derivative **14** was also prepared.

The stability of compound **2**, in different solvents, was studied by $^1$H-NMR experiments. Although compound **2** gets spontaneously desilylated in DMSO-$d_6$ solution on standing in a NMR tube, it was stable in $CDCl_3$, $CD_3OD$ or $(CD_3)_2CO$ solutions. Comparative stability studies of compounds **2**–**14**,in DMSO solution, were also carried out and their conversion into the corresponding 5′-deprotected derivatives in function of time was followed by HPLC. These studies provided the following insights into the hydrolysis (desilylation) reaction:

1. The higher electrophylic character of the 4″-carbonyl the faster the 5′-TBDMS deprotection (**3** > **2** ⋙ **4**–**6**).
2. The desilylation process appears to be also dependent on the nature of the substituent at the oxalyl moiety (**2** ≫ **10** > **9** > **8** > **7**).
3. The rate of desilylation depends on the nature of the silyl group at 5′-position (**2** > **11**).

However, under the same reaction conditions, the 5′-acyl derivative **13** was stable.

A possible mechanism for the desilylation process is outlined in Sch. 1. The proposed mechanism suggests that a direct interaction between the 4″-substituent and the 5′-silyloxy functionalities is critical for the facile desilylation. This was demonstrated when the *xylo* oxalyl ester compound (**14**) was subjected to the same experimental conditions (DMSO) and proved to be stable.




*Scheme 1.*





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Scarce examples of enhanced hydrolytic cleavage of a silyloxy function by neighbouring group participation have been reported.[3] Our results complement these previous findings and suggest a generality for this type of process.

## ACKNOWLEDGMENTS

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