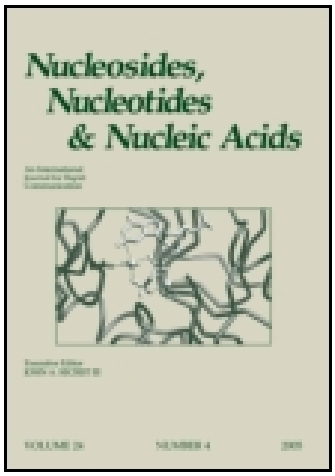

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Synthesis of AZA Analogues of TSAO

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ABSTRACT

TSAO derivatives which were first synthesized in 1992 have shown strong inhibitory effect and selectivity against HIV-1 (Camarasa, M.J.; Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E. J. Med. Chem. **1992**, *35*, 2721–2727). The structure-activity relationship of these derivatives has shown strong binding between the amino acids constituting the reverse transcriptase and the different pharmacophore (tert-butyldimethylsilyl group, amino and sulfonate groups of the TSAO derivatives) (Camarasa, M.J.; San-Félix, A.; Pérez-Pérez, M.J.; Velázquez, S., Alvarez, R.; Chamorro, C.; Jimeno, M.L.; Pérez, C.; Gago, F.; De Clercq, E.; Balzarini, J. J. Carbohydr. Chem. **2000**, *19*, 6403–6406). We described the synthesis of an original TSAO analogue where, basically, the *O*-1″ atom is replaced by a nitrogen atom.

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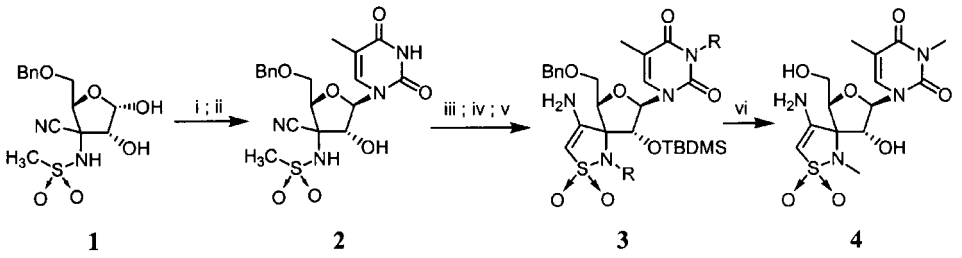

Scheme 1. Reagents and conditions: (i) $SO(Im)_2$, THF; (ii) silylated thymine, 130°C; (iii) TBDMSCl, imidazole, DMF; (iv) MeI, K_2CO_3, MeCN; (v) Cs_2CO_3, MeCN; (vi) C_6H_{10}-$Pd(OH)_2$, EtOH.

Starting from glyco-α-aminonitrile precursors which have been intensively studied in our laboratory and obtained in a stereospecific way,[3,4] successive mesylation and deprotection of a ribo derivative lead to the sulfonamido derivative **1** with an overall yield higher than 95%. Attempts to introduce a nucleic base such as thymine by a Vorbrüggen procedure did not lead to the corresponding nucleoside. This could be obtained, however, by the fusion method. The 1,2-*O*-sulfinyle derivative was prepared with $SO(Im)_2$ in THF with about 85% yield as its exo/endo cyclic form. Finally, condensation of a silylated thymine at 130°C with the 1,2-*O*-sulfinyle resulted in nucleoside **2** with 82% yield. Methylation on the *N*-positions created the precursor for the CSIC reaction. Cyclisation with Cs_2CO_3 afforded 45% yield of the isothiazolic derivative **3**. Deprotection of the benzyl group with C_6H_{10}-$Pd(OH)_2$ followed by silylation with TBDMSCl gave the A-TSAO-m^3T (**4**) in 65% yield.

In a similar way, A-TSAO-T analogue (non alkylated base) was obtained by selective protection of thymine with a BOC group. Then, the cyclisation followed by the one-pot deprotection of both the benzyl and BOC groups with C_6H_{10}-$Pd(OH)_2$ gave the leading compound, after silylation, with 55% yield.

Biological tests have shown selective inhibition on HIV-1 RT.

Investigations to obtain both non alkylated *N*-sulfonamide and substitution on the 5″-*C* are also in progress. In order to investigate SARs different substituents should be introduced on both the nucleic base and the sulfonamide cyclic moiety.

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