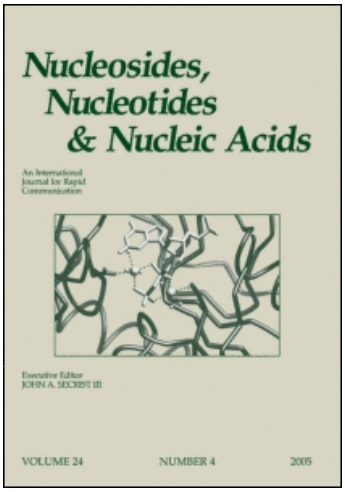

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SYNTHESIS AND ANTI-HIV-1 ACTIVITY OF 4- AND 5-SUBSTITUTED 1,2,3-TRIAZOLE-TSAO DERIVATIVES

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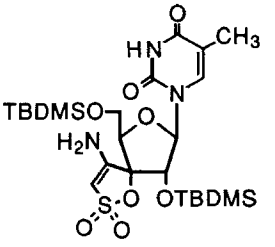
Abstract: *Several 4- or 5-monosubstituted and 4,5-disubstituted 1,2,3-triazole analogues of the anti- HIV-1 lead compound [1-[2',5'-bis-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide) (TSAO-T) have been prepared and evaluated for their inhibitory effect against HIV-1-induced cytopathicity.*

INTRODUCTION

TSAO nucleoside analogues represent an entirely new class of HIV-1-specific agents[1,2] whose prototype compound is [1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide) (designated as TSAO-T, **1**). They are targeted at the HIV-1-encoded reverse transcriptase (RT) with which they interact at a non-substrate binding site[3,4] and they are not antivirally effective against HIV-2 and other (retro)viruses[1-4]. TSAO derivatives are the first HIV-1-specific RT inhibitors for which a well-defined part of the molecule (i.e. the 4"-amino group at 3'-spiro of the ribose moiety) has been identified as an essential pharmacophore interacting with a well-defined moiety (the -COOH group of Glu-138) of HIV-1 RT[5]. Moreover, TSAO molecules represent a unique structural class of compounds for which the p51 subunit of the RT heterodimer plays a crucial role in the recognition of, and resistance to, the TSAO derivatives.[6]



TSAO-T (**1**)

In order to determine the interaction points of TSAO compounds with the HIV-1 RT and to reveal the role that the nucleobase may play in this interaction, we report here the synthesis and anti-HIV-1 activity of a series of TSAO analogues in which the thymine moiety of the lead compound (**1**) has been replaced by a series of 1,2,3-triazoles substituted with groups that may be involved in the interaction of the TSAO derivatives with the RT enzyme.

CHEMISTRY AND BIOLOGICAL RESULTS

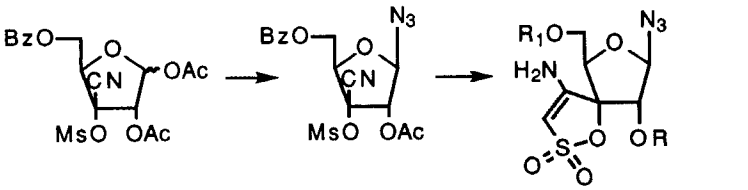
The 1,2,3-triazole 3'-spironucleosides were stereoselectively prepared by 1,3-dipolar cycloaddition of the suitably functionalized and protected ribofuranosyl azide intermediate **5** to differently substituted acetylenes to give, exclusively, β-D-ribo spiro nucleosides. The *ribo* configuration of the nucleosides was determined by the configuration of the starting cyanohydrin used in the preparation of the cyanomesylate of ribose (**2**)[2].

Reaction of **2** (Scheme 1) with trimethylsilyl azide and stannic chloride gave the β-D-ribofuranosyl azide **3** (80%).

Treatment of cyanomesylate **3** with DBU, followed by deprotection with methylamine provided the fully deprotected compound **4**, which, by reaction with an excess of *tert*-butyldimethylsilyl chloride gave the 2',5'-bis-*O*-silylated azide derivative **5**.

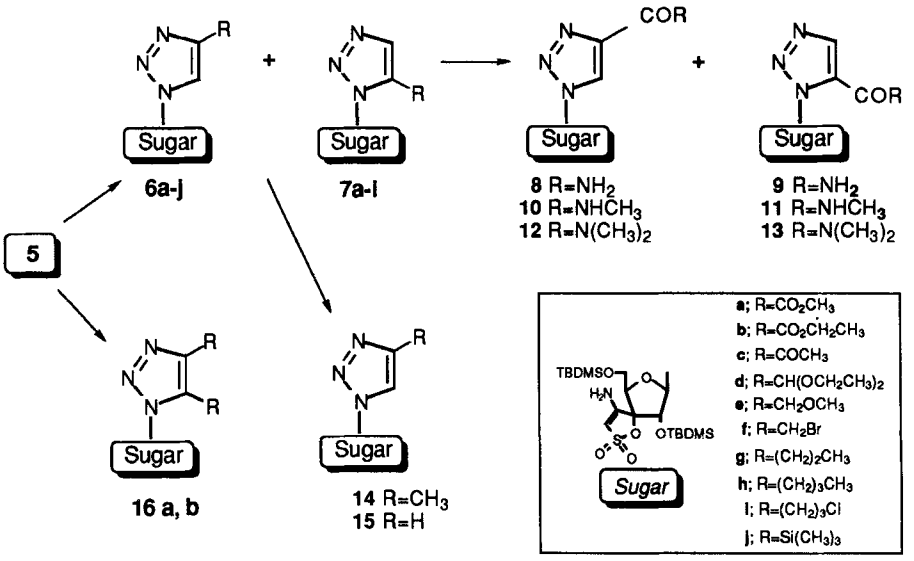
Cycloaddition of azide **5** to unsymmetrical acetylenes (Scheme 2) afforded mixtures of the two possible 4- and 5-substituted nucleosides **6** and **7**, respectively.The proportion of **6** and **7** depends on both steric and electronic factors[7,8].

Treatment of **6a** and **7a** with ammonia, methylamine or dimethylamine afforded the 4- and 5-unsubstituted carbamoyl (**8** and **9**), N-methylcarbamoyl (**10** and **11**) and N,N-



2 **3** **4** R = R1 = H
5 R = R1 = TBDMS

SCHEME 1



SCHEME 2

dimethylcarbamoyl (**12** and **13**) derivatives, respectively. Catalytic hydrogenation of **6f** in methanol containing aqueous ammonia, in the presence of 10% palladium on charcoal, gave the 4-methyl-1,2,3-triazole derivative **14.**

Finally, 1,3-dipolar cycloaddition of azide **5** to symmetric acetylenes gave disubstituted spironucleosides **16a** or **16b.**

The 1,2,3-triazole TSAO derivatives synthetized, were evaluated for their inhibitory activity on HIV-1- and HIV-2-induced cytopathicity in MT-4 cells and syncytium formation in CEM cell cultures. None of the test compounds were active against HIV-2.

In general, most of the 4-and 5-substituted 1,2,3-triazole TSAO derivatives proved more inhibitory to HIV-1 than the unsubstituted compound **15**. The nature of the substituent of the triazole plays an important role for the activity. However, the position of the substituent does not markedly affect the antiviral activity and the cytotoxicity. The disubstituted 1,2,3-triazole-TSAO derivatives **16a** and **16b** showed an antiviral activity that was not superior to that of the respective 4- and 5-monosubstituted compounds.

The ester- and the alkyl- substituted compounds were markedly less toxic than the other 1,2,3-triazole-TSAO derivatives.

It should be noted that introduction at position C-5 of the triazole moiety of a dimethyl-substituted carbamoyl function, gave the most active compound of this series

(**13**).This compound showed an anti-HIV-1 activity (50% effective concentration: 0.056-0.52 μM) comparable to that of the prototype compound TSAO-T.

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