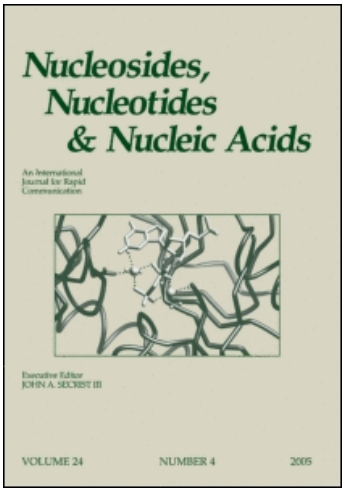

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Gosselin, Gilles , Bergogne, Marie-Christine and Imbach, Jean-Louis(1990) 'Stereospecific Synthesis and Biological Evaluation of 9-α-D-Ribofuranosylguanine (α-Guanosine)', Nucleosides, Nucleotides and Nucleic Acids, 9: 1, 81 — 87
To link to this Article: DOI: 10.1080/07328319008045111
URL: http://dx.doi.org/10.1080/07328319008045111

NUCLEOSIDES & NUCLEOTIDES, 9(1), 81-87 (1990)

STEREOSPECIFIC SYNTHESIS AND BIOLOGICAL EVALUATION OF 9-α-D-RIBOFURANOSYLGUANINE (α-GUANOSINE)

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ABSTRACT - Starting from D-ribose, the title compound **8** was prepared by a multistep approach in 6.6% overall yield. In none of the biological assays in which it was evaluated did α-guanosine demonstrate appreciable activity.

INTRODUCTION

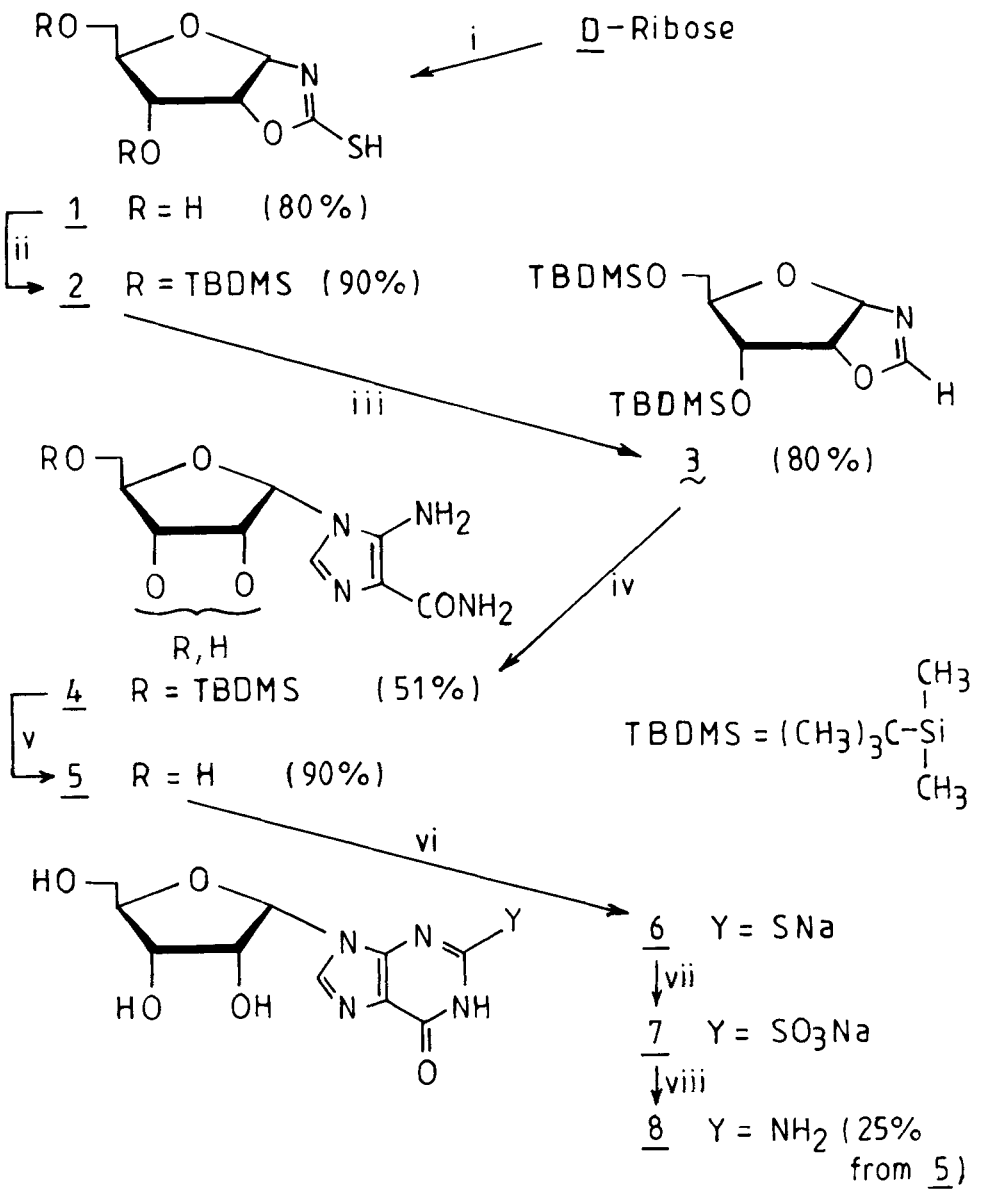
Recent interest in the field of modified oligonucleotides[1] led us to consider the potential relevance of unnatural sugar configurations. First we investigated oligodeoxynucleotides consisting of α-anomeric deoxynucleotide units, and these compounds show attractive biological properties.[2] Now we are in the process of extending these studies on α-oligoribonucleotides, and for this purpose we need as starting synthons the four α-D-ribofuranonucleosides of the naturally occuring bases in nucleic acids. A thorough literature survey revealed that little attention has been given to the synthesis and biological evaluation of this class of compounds. In part, this lack of attention may be attributed to the difficulty in synthesizing glycosides with the *cis*-1',2' configuration, as well as the generally accepted

notion that α-nucleosides are biologically inactive. The latter concept, however, may require reconsideration since several α-nucleosides are now known to exhibit significant antimetabolic properties.[3,4]

This fact has prompted us to unambiguously synthesize and evaluate the α-D-ribofuranosylnucleosides of the natural bases. The synthesis of 9-α-D-ribofuranosyladenine[5] and 1-α-D-ribofuranosyl- cytosine[6] and uracil[7] could be accomplished without insuperable problems following literature procedures. On the other hand the synthesis of 9-α-D-ribofuranosylguanine (**8**) was taken up by an original approach because the procedures reported to date seemed not very convenient. Although three reports concerning **8** have been published, two of them mention α-guanosine only as a side-product obtained after fusion condensation of acetylguanine with a fully acylated D-ribofuranose.[8,9] A more attractive procedure for the synthesis of **8** which involved coupling of the boron trichloride complex of methyl D-ribofuranoside with N^2-palmitoylguanine, has been proposed by Furukawa et al.;[10] however the lack of experimental details has lead to difficulties in reproducing this synthesis.[11] Furthermore, in all of these reports, neither biological evaluation nor full characterization were given for α-guanosine.

SYNTHESIS

A priori, three methods can be envisioned for the preparation of α-guanosine (**8**): (a) glycosylation with a suitably protected D-ribofuranose having in its 2-*O*-position a non-participating group; (b) epimerization of the 2'- or 3'-position, respectively, of α-D-arabino- or α-D-xylofuranosylguanine; (c) construction of the heterocyclic moiety from a D-ribose derivative possessing a 2-oxazoline ring fused in the *cis*-1',2' configuration. We eliminated the first possibility owing to its lack of regioselectivity and stereospecificity. Epimerization was also excluded owing to expected difficulties in preparing α-D-xylo- or α-D-arabinofuranosylguanine and in realizing the appropriate inversion of configuration. Thus, we turned to the third possibility,



- **SCHEME** - *Reagents and conditions*: **i, KSCN; ii, TBDMSCl; iii, Raney Ni; iv, $NH_2CH(CN)CONH_2$; v, TBAF; vi, $NaSC(S)OCH_3$; vii, H_2O_2; viii, NH_3.**

namely building up the heterocyclic moiety, especially since the starting material, α-D-ribofuranothioxooxazolidine **1**, can be easily obtained in good yield.[12] This compound was first transformed to 1-α-D-ribofuranosyl-4-carbamoyl-5-aminoimidazole (**5**) (α-AICA riboside) by minor modification of our procedure already published[13] and then cyclized to α-guanosine (**8**) (Scheme).

Among the different cyclization routes usually implemented during guanine nucleoside synthesis from an AICA derivative,[14,15] we chose the more direct method in which ring closure and purine moiety modifications are carried out successively without isolating the intermediates. Thus, treatment of **5** at 180 °C with sodium methylxanthate (prepared *in situ* from carbon disulfide and methanolic sodium hydroxide) gave **6**, which was oxidized with hydrogen peroxide to **7**. Amination of **7** with ammonia then afforded cristalline **8**, in overall 25% from **5**. Structural assignment for α-guanosine (**8**) was corroborated by elemental analysis and its physical properties.

Biological Evaluation

α-Guanosine (**8**) was evaluated for its *in vitro* inhibitory effects on the replication of a number of DNA viruses (herpes simplex viruses type 1 and 2, vaccinia virus) and RNA viruses (vesicular stomatitis, Coxsackie virus B4, polio virus-1, parainfluenza-3 virus, reovirus-1, Sindbis virus and Semliki forest virus) in three cell systems (primary rabbit kidney, Hela and Vero B cells). From these studies it was apparent that **8** did not cause microscopically detectable alteration of host-cell morphology at a concentration up to 400 μg/mL, and that in none of the antiviral assays in which it was evaluated did α-guanosine demonstrate an appreciable effect. Furthermore, **8** was totally inert in inhibiting the growth of various tumor cells [50% inhibitory dose > 1000 μg/mL for murine leukemia (L1210/0), murine mammary carcinoma (FM3A/0), human B-lymphoblasts (Raji/0 and Namalva) and rat liver (Hepatoma) cells].

EXPERIMENTAL SECTION

General Methods

Evaporation of solvents was done with a rotary evaporator under reduced pressure. Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ultraviolet spectrum (UV) was recorded on an Optica Model 10 spectrophotometer. Proton nuclear magnetic resonances were determined in DMSO-d_6 at ambient temperatures on a Bruker AC300 spectrometer. Chemical shifts are expressed in parts per million, DMSO-d_5 being set at 2.49 ppm as reference; deuterium exchange and decoupling experiments were performed to confirm proton assignments. Fast-atom-bombardment mass spectra were recorded in the positive- and negative-ion modes on a JEOL DX 300 mass spectrometer, with a JMA-DA 5000 mass data system. Elemental analyses were determined by the Service de Microanalyse du CNRS, Division de Vernaison. The chromatographic properties of **8** have been previously described.[16]

9-α-D-Ribofuranosylguanine (8).

To a solution of sodium hydroxide (1.55 g, 38.8 mmol) in anhydrous methanol (14 mL) was added 1-α-D-ribofuranosyl--4-carbamoyl-5-aminoimidazole (**5**)[13] (2.0 g, 7.76 mmol) and then carbon disulfide (2.94 g, 2.34 mL, 38.8 mmol). The reaction mixture was heated in a stainless steel bomb at 180 °C for 3 h. After cooling to 0 °C, the bomb was opened and the reaction mixture was evaporated under vacuum. The residue was dissolved in water (24 mL), and 30% hydrogen peroxide (4.0 mL, 38.8 mmol) was added at 5 °C with stirring. After 1 h, the solution was saturated with ammonia at 0 °C and then heated in a bomb at 120 °C for 2 h. The reaction mixture was evaporated to dryness and three times coevaporated with water. The residue was dissolved in water, and the pH of the solution was adjusted to *ca.* pH 6.0 by addition of Amberlite IR120 [H^+] ion-exchange resin. The resin was filtered and washed well with warm water. The combined washings and filtrate were evaporated to dryness and then dissolved

in a small quantity of water. Crystallization at room temperature afforded 0.55 g (25%) of **8**: mp > 290°C, 219°C start of decomposition (lit.[9] mp 261°C); UV (H_2O) λ_{max} 252 nm (ε, 10,900), 275 nm (sh, ε, 6,900); λ_{min} 223 nm (ε, 1,700); ^1H NMR (DMSO-d_6), δ ppm 10.57 (s, 1H, NH-1), 7.86 (s, 1H, H-8), 6.4 (br s, 2H, NH_2), 6.01 (d, 1H, H-1'; $J_{1',2'}$= 5.3 Hz), 5.46 (d, 1H, OH-2'; $J_{(H,OH)2'}$=5.8 Hz), 5.30 (d, 1H, OH-3'; $J_{(H-OH)3'}$= 5.5 Hz), 4.85 (t, 1H, OH-5'; J = 5.6 Hz), 4.24 (m, 1H, H-2'; $J_{2',3'}$= 5.3 Hz), 4.09 (m, 1H, H-3'; $J_{3',4'}$= 5.3 Hz), 4.00 (m, 1H, H-4'), 3.4 and 3.5 (2m, 2×1H, H-5' and 5"; $J_{5',5"}$= 12.1 Hz; $J_{5',4'}$ and $J_{5",4'}$= 3.2 and 4.2 Hz); $[\alpha]_D^{20}$ + 25.5° (c = 1.02, 0.1N NaOH) {lit.[10a] $[\alpha]_D^{23}$ + 20.5° (c = 1.0, 0.1N NaOH)}; mass spectra (matrix, glycerol), FAB > 0: 284 $(M+H)^+$, 152 $(BH_2)^+$; FAB < 0: 282 $(M-H)^-$.

Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot (0.25\ H_2O)$: C, 41.74; H, 4.73; N, 24.34. Found: C, 41.72; H, 4.49; N, 24.13.

ACKNOWLEDGEMENT

We thank the Centre National de la Recherche Scientifique, France, for the partial support of this research. We would also like to thank Prof. E. De Clercq (Katholieke Universiteit Leuven, Belgium) for kindly performing the biological studies and both referees for helpful comments. The assistance of C. Duguet in typing this manuscript is also greatly appreciated.

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Received June 30, 1989.