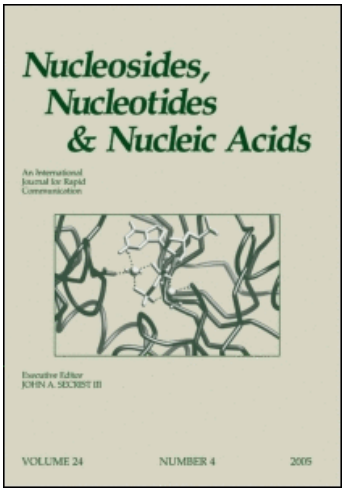

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Studies on the Synthesis of O-Ribosyl-Adenosine - a new Minor Nucleoside Of tRNA

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STUDIES ON THE SYNTHESIS OF O-RIBOSYL-ADENOSINE - - A NEW MINOR NUCLEOSIDE OF tRNA¶

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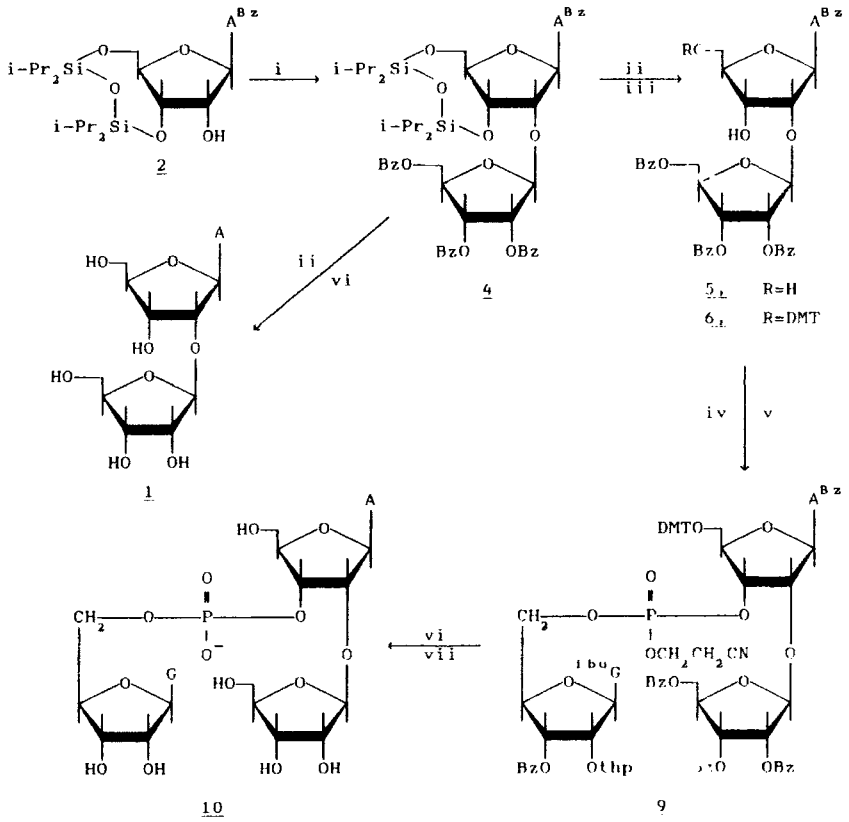
Abstract: A synthesis of new minor nucleoside of yeast tRNA, O-β-D-ribofuranosyl-(1"-->2')-adenosine ([A*], 1) and a dinucleosidemonophosphate [A*]pG (10) is presented.

Recently a new minor nucleoside was found in yeast methionine initiator tRNA for which the structure of the phosphorylated O-β-D-ribofuranosyl-(1"-->2')-adenosine (A*) was proposed.[1] In order to verify the above structural hypothesis we have undertaken studies aiming at the synthesis of dephosphorylated A* ([A*], 1), different selectively monophosphorylated derivatives of 1 and oligonucleotides (initially dimers) containing the above nucleosidic units. The investigation of structural and chemical properties of these compounds should answer questions concerning the biological function of the discussed hypermodification of adenosine.

In this communication the preliminary results of the synthesis of 1 and a dimer [A*]pG (10) are presented. Thus, 3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-6-N-benzoyladenosine[2] (2) was reacted with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (3) preactivated with tin(IV) chloride in 1,2-dichloroethane. The β configuration of 2'-O-ribosyl residue was expected as in the syntheses of ribonucleosides under the same conditions.[3] The structure of product 4 (62% yield) was corroborated by the FAB-MS, ^{1}H and ^{13}C NMR spectra.[4,5] 4 was deprotected to 1 which was then characterized by the UV, ^{1}H and ^{13}C NMR spectra and

¶This paper is dedicated to Professor Colin B. Reese on the occasion of his 60th Birthday in July 1990.



i, 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (3) / $SnCl_4$/ $(CH_2Cl)_2$; ii, TBAF/THF; iii, DMTCl/ pyridine; iv, 2'-O-benzoyl-3'-O-tetrahydropyranyl-2-N--isobutyrylguanosine 5'-O-(2-cyanoethyl)-N,N-diisopropylphosphoramidite (7)/ tetrazole/ CH_3CN; v, I_2/ pyridine/ H_2O; vi, NH_3 aq/ pyridine; vii, CH_3COOH aq. Abbreviations: i-Pr, isopropyl; Bz, benzoyl; DMT, dimethoxytrityl; thp, tetrahydropyranyl; ibu, isobutyryl; TBAF, tetra-n-butylammonium fluoride.

its chromatographic properties were the same as reported for natural 1.[5,6] The EI-MS spectrum of per-trimethylsilylated [A*] was described[1] and the relative intensities of some fragment ions were found to be characteristic and different than for the TMS-derivative of isomeric O-α-D-ribofuranosyl-(1"-->2')-adenosine. The EI-MS spectrum of the TMS derivative of synthetic 1 was identical with that of [A*].[7]

In order to synthesize the dimer [A*]pG (10), the TIPDSi group of 4 was removed with TBAF/THF[2,8] and the resultant 5 (85% yield) was reacted with dimethoxytrityl chloride to give 6 (58% yield) which was

subsequently condensed with 2'-O'benzoyl-3'-O-tetrahydropyranyl-2-N-isobutyrylguanosine 5'-O-(2-cyanoethyl)-N,N-disopropylphoshoramidite[9] (7) activated with tetrazole. The resultant P(III) dimer 8 was oxidized to give a fully protected dimer 9 (67% yield). 9 was deprotected, purified chromatographically and characterized by UV[12] and enzymatic digestion. Initial studies indicate that 10 is a substrate for the polynucleotide kinase.

Further studies on the synthesis and various properties of compounds of the above series will be described elsewhere.

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4. 4: FAB-MS: $M+H^+$ 1058.4 m/z, calc.: $C_{55}H_{64}N_5O_{13}Si_2$ 1058.47 m/z; ^1H NMR($CDCl_3$/TMS): δ (ppm) 8.72 (s, 1, H-2 or 8), 8.13 (s, 1, H-8 or 8), 7.25-8.5 (m, 20, 4xBz), 6.08 (s, 1, H-1'), 5.85 (m, 3, H-1",2",3") 4.82 (m, 5, H-2',3',4",5") 4.10 (m, 3, H-4',5'), 1.05 (m, 28, TIPDSi); ^{13}C NMR($CDCl_3$/TMS): δ (ppm) 166.0, 165.36, 164.98, 164.54 (4xPhC=O),152.60 (C-2), 150.83 C-6), 149.54 (C-4), 141.90 (C-8), 133.93-127.87 (Ph), 123.64 (C-5), 105.87 (C-1"), 88.96 (C-1'), 81.54 (C-4'), 79.81 (C-4"), 78.72 (C-2'), 75.69 (C-2"), 72.76 (C-3"), 70.22 (C-3'), 65.40 (C-5"), 60.30 (C-5'), 17.45, 17.28, 16.85 (C-β-i-Pr), 13.38, 13.00, 12.89, 12.73 (C-α-i-Pr.
5. Synthetized compounds were characterized by TLC in the following solvent systems (by vol.) on E. Merck HF254 silicagel plates: S1 - n-hexane/ $CHCl_3$/ MeOH, 20/75/5; S2 - $CHCl_3$/ MeOH, 95/5; S3 - $CHCl_3$/ MeOH, 9/1; S4 - i-PrOH/ NH_3 aq/ H_2O, 7/1/2; S5 - acetone/ n-hexane/ Et_3N, 45/45/10; on cellulose plates: A - isobutyric acid/ 25% NH_4OH/ H_2O, 50/1.1/28.9.

R_F values: 1: S4 0.60, A 0.77 (liter. [1] 0.77); 4: S1 0.60, S2 0.73, S3 0.81; 5: S3 0.49; 6: S3 0.60; 7: S3 0.45, S5 0.67; 8: S3 0.52; 9: S3 0.48; 10: S4 0.58.

6. 1: UV(MeOH): λ_{max} 260 nm, λ_{min} 232 nm, $A_{250/260}$ 0.79, $A_{280/260}$ 0.27; ^1H NMR(D_2O/TMS): δ (ppm) 8.28 (s, 1, H-2 or 8), 8.16 (s, 1, H-8 or 2), 6.08 (d, 1, $J_{1',2'}$, 6.3 Hz, H-1'); ^{13}C NMR(D_2O/TMS): δ (ppm) 153.60 (C-2), 141.57 (C-8), 106.95 (C-1"), 87.77, 87.23, 83.60 (C-1',4',4"), 79.05, 75.20 C-2',2"), 71.79, 69.89 (C-3',3"), 63.55, 62.31 (C-5',5").
7. Some relative intensities of fragment ions in the EI-GC/MS of the TMS derivative of 1 (m/z and r.i.) 334, 0.84; 512, 9.53; 523, 0.05; 598, 0.30.
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9. 7 was obtained from 5'-O-dimethoxytrityl-2'-O-tetrahydropyranyl-2-N--isobutyrylguanosine[10] by benzoylation with BzCl in pyridine, detritylation[10] with trifluroacetic acid. The resultant 5'-OH guanosine derivative was reacted with bis-N,N-diisopropylamino-2-cyanoethoxyphosphine[11]/tetrazole to give 7: ^{31}P NMR(MeCN/ ext. 85% H_3PO_4): δ 148.67 ppm.
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12. 10: UV(MeOH): λ_{max} 256.5, λ_{min} 226, $A_{250/260}$ 0.96, $A_{280/260}$ 0.44.