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Synthesis and Restricted Conformation of 3',5'-O-(Di-t-butylsilanediyl)ribonucleosides

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The reaction of ribonucleosides with di-t-butylsilyl diester such as dinitrate, diperchlorate and ditriflate in DMF gave selectively 3',5'-O-(di-t-butylsilanediyl)ribonucleosides in high yield. The conformation analysis by ^{1}H NMR spectroscopy and X-ray crystallography showed that the product has a restricted conformation analogous to that observable in 3',5'-cyclic nucleotides.

In an early work on the synthesis of oligoribonucleotides, Khorana et al. used uridine 3',5'-cyclic monophosphate as a key starting material to prepare the 2'-O-tetrahydropyranyl derivative.[1] In this case, the 3',5'-cyclic phosphate can be considered as a bifunctional protecting group.

Recently, a bifunctional disiloxane protecting group, 1,1,3,3-tetraisopropyldisiloxanediyl (TIPDS), has been introduced into the synthetic chemistry of nucleic acids to facilitate the modification of the nucleoside 2'-position.[2] However, there still exists a real need for a new type of bifunctional protecting group.[3]

In this communication, we report the simple methods for the highly selective synthesis of 3',5'-O-di-t-butylsilanediyl-protected ribonucleosides ; the reaction of ribonucleosides with activated di-t-butylsilyl diesters selectively gives high yields of 3',5'-O-(di-t-butylsilanediyl)ribonucleosides (3',5'-O-DTBS-ribonucleosides, 1) which contain the fused ring structure analogous to that of nucleoside 3',5'-cyclic phosphates. We also report the restricted conformation of 3',5'-O-DTBS-ribonucleoside derivatives and its application for the anomeric configuration assignment.

A typical procedure for the preparation of 3',5'-O-(di-t-butylsilanediyl)-uridine (3',5'-O-DTBS-uridine) is as follows : Uridine dissolved in dry N,N-dimethylformamide was evaporated to dryness under reduced pressure and reacted with 1.1 equiv. of di-t-butylsilyl ditriflate in dry N,N-dimethylformamide under nitrogen at 23 °C for 4 min, then liberated triflic acid was immediately neutralized with triethylamine. The cyclic silanediyl derivative was isolated in 94% yield by silica gel chromatography eluting with chloroform containing methanol (100:1, v/v).

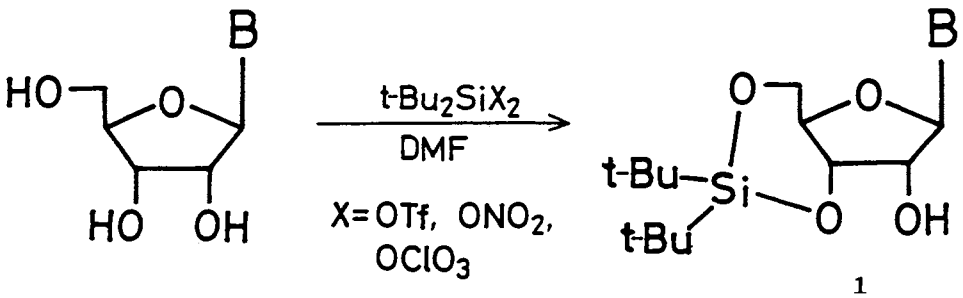
In the preliminary studies with several dialkyldichlorosilanes, we found that di-t-butyldichlorosilane[4] only gave promising products with high selectivity to the primary 5'-hydroxyl group of ribonucleosides, although the reagent was rather unreactive under the usual silylation conditions using imidazole in N,N-dimethyl-

formamide.[5] To improve the reactivity, we examined activated silylating reagents such as di-t-butylsilyl dinitrate, diperchlorate and ditriflate.[6] Di-t-butylsilyl dinitrate and diperchlorate were prepared in situ by reaction of di-t-butyldichlorosilane with 2 equiv. of the corresponding silver salt, respectively. These strong acid components[7] were expected to become good leaving groups and all silyl diesters examined here gave the desired 3',5'-cyclic products via intramolecular cyclization to the 3'-hydroxyl group. The structure was confirmed by their ^{1}H NMR spectra which showed (a) the presence of the free 2'-hydroxyl group, (b) a marked chemical shift discrepancy between the two protons on the 5'-carbon, and (c) H1' as a singlet. These are similarly observable in nucleoside 3',5'-cyclic monophosphates.[8]

In contrast to the wide selection of solvent on using a monofunctional silyl ester reagent such as triisopropylsilyl triflate (e.g. pyridine, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone), only N,N-dimethylformamide was good for the reaction of nucleosides with a bifunctional reagent, di-t-butylsilyl ditriflate.[9]

Consequently, the use of di-t-butylsilyl diester as reagent, N,N-dimethylformamide as solvent and, if necessary, pyridine or 2,6-di-t-butylpyridine[10] as acid scavenger proved to be exceedingly effective and to result in the conversion of a variety of nucleosides and the related compounds to the cyclic silanediyl derivatives in high yield.

Treatment of adenosine and guanosine with di-t-butylsilyl ditriflate and of cytidine[11] with di-t-butylsilyl dinitrate in situ generated gave the corresponding cyclic silanediyl derivatives in 95, 95, and 90% yield, respectively.



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B	Yield/%
uracil-1-yl	94
cytosin-1-yl	90[a]
adenin-9-yl	95
guanin-9-yl	95

a) Ref. 11.
For 2'-deoxyribonucleosides, see text.

The cyclic silanediyl derivatives of 2'-deoxyribonucleosides[12] were also easily prepared according to the procedure described above. Thus, treatment of

thymidine, deoxyuridine, deoxyadenosine, deoxycytidine and deoxyguanosine with di-t-butylsilyl ditriflate gave the cyclic silyl products in 95, 97, 99, 90, and 95% yield, respectively. It should be noted that in comparison with these 3',5'-O-DTBS-2'-deoxyribonucleosides, the ribonucleoside derivatives are sensitive to acidic cleavage of the silyl ring due to the presence of the cis vicinal 2'-hydroxyl function.

The following protecting groups have been successfully introduced into the 2'-hydroxyl function of 3',5'-O-DTBS-ribonucleosides : Acetyl, tetrahydropyranyl, methoxytetrahydropyranyl and t-butyldimethylsilyl. Removal of the DTBS protecting group has been also accomplished by treatment with tributylamine-hydrofluoride reagent under very mild conditions.[13]

Further, the conformation of 3',5'-O-DTBS-ribonucleosides was evaluated by means of ^{1}H NMR spectroscopy and X-ray crystallography.[14] The ^{1}H NMR spectra of 3',5'-O-DTBS-uridine and 3',5'-O-DTBS-adenosine in chloroform were analyzed using NTCFT software on the Nicolet 1180 computer. The coupling constants between the vicinal protons in the furanose moieties of the DTBS derivatives were in good agreement with those for conformationally rigid cyclic UMP and cyclic AMP.[15] This indicates that the introduction of the cyclic silanediyl group into the conformationally flexible furanose ring of ribonucleosides reduced its flexibility. Solid molecular models also suggest the formation of the rigid trans-fused 6 to 5 membered ring system.

X-Ray crystallographic analysis also supported the close similarity of the DTBS derivative to nucleoside 3',5'-cyclic monophosphates with regard to the furanose ring conformation. The pseudorotation angle (P) obtained for 3',5'-O-DTBS-adenosine was 43.4°,[16] indicating the twist conformation $_4T^3$, which is in good agreement with the mean value (45°) reported for nucleoside 3',5'-cyclic monophosphates.[17] These results clearly show that 3',5'-O-DTBS-ribonucleosides are conformationally analogous to nucleoside 3',5'-cyclic monophosphates.

Such conformational rigidity prompted us to correlate ^{1}H NMR signals with the anomeric configuration. Recently, Robins et al. investigated the application of the 3',5'-O-TIPDS derivatives for the anomeric configuration assignment which showed a little ambiguity for the purine nucleoside derivatives attributable to the potential flexibility of the 8 to 5 fused ring system.[18] In the present study, the anomeric proton (H1') signal of the β-anomer of 3',5'-O-DTBS-adenosine in chloroform appeared as a sharp singlet. On the other hand, the spectrum of its α-anomer prepared by treatment of α-adenosine with di-t-butylsilyl ditriflate showed H1' as a doublet ($J_{1',2'}$=3.7 Hz) in Me_2SO. These results are well consistent with the geometry-only method[19] established for β- and α-nucleoside cyclic 3',5'-monophosphates.[20] The preparation of 3',5'-O-DTBS derivatives is simple and convenient compared to that of the corresponding cyclic nucleotides which contains the processes of phosphorylation, cyclization and time-consuming purification.

We expect that the DTBS group will be useful for various modification of nucleosides and other polyhydroxyl compounds and also for the structure elucidation such as anomeric configuration assignment.[21]

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