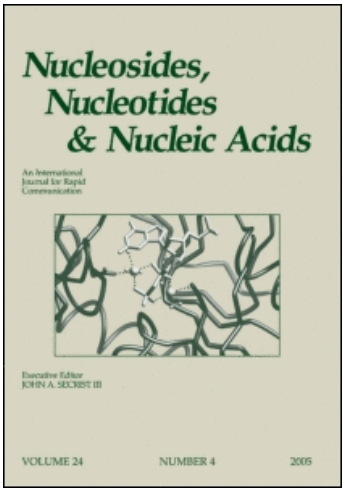

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Alternate Approaches to the Synthesis of 2'-*O*-Me Nucleosides

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ALTERNATE APPROACHES TO THE SYNTHESIS OF 2'-*O*-Me NUCLEOSIDES

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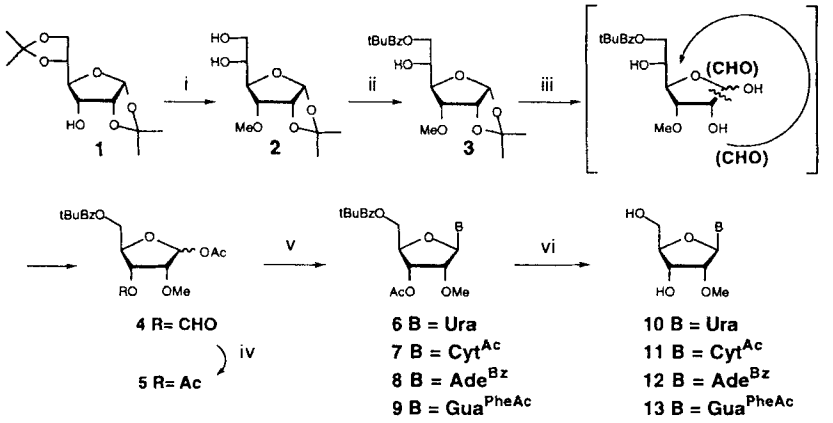
Abstract Three different approaches to the synthesis of 2'-*O*-methyl nucleosides starting from the corresponding nucleoside or commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **1** are described.

Synthetic hammerhead ribozymes having multiple 2'-*O*-Me modifications have increased nuclease resistance while retaining almost wild-type catalytic activity.[1] Since the synthesis of such ribozymes requires large quantities of 2'-*O*-Me ribonucleoside 3'-*O*-phosphoramidites we investigated alternate synthetic approaches to 2'-*O*-Me nucleosides.

In the synthesis of 2'-*O*-Me nucleosides, considerable effort was directed toward developing methods for the efficient and regioselective alkylation of protected ribonucleosides.[2-4] An attractive alternative is the Vorbrüggen condensation of 2'-*O*-alkyl ribofuranose with silylated bases.[5-7] Along these lines we developed three alternate synthetic routes to 2'-*O*-Me nucleosides.

A: Retrosynthetic analysis showed that 3-*O*-alkylated derivatives of 1,2:5,6-di-*O*-isopropylidene(IP)-α-D-allofuranose (**1**) could be transformed to the related 2'-*O*-alkyl ribofuranosides by selective degradation of the C1-C2 bond with subsequent cyclization[8] of the generated C2-formyl group to the C5-OH. Commercially available 1,2:5,6-di-*O*-(IP)-α-D-allofuranose (**1**) was methylated using MeI/NaH and, without isolation, selectively deprotected with 80% AcOH (22 h, RT). The resulting diol was regioselectively acylated by treatment with *t*-BuBzCl/Pyr/CH_2Cl_2 (-30 °C) providing 6-*O*-*t*-BuBz derivative **3** in 80% yield. The last reaction could be performed utilizing Bu_2SnO activation[2] with comparable yields but more difficult isolation. Removal of the 1,2-isopropylidene group by treatment with 90% CF_3COOH followed by $NaIO_4$ oxidation and acetylation led to a mixture of acetates **4** and **5**. Careful treatment of the 3-*O*-formyl intermediate with a catalytic amount of NaOMe/MeOH and subsequent acetylation provided



Reagents and Conditions: *i)* MeI/NaH, 80% AcOH; *ii)* *t*-BuBzCl, Pyr/CH_2Cl_2 (-30 °C); *iii)* 90% CF_3COOH, 1M $NaIO_4$, Ac_2O/Pyr; *iv)* Pyr/H_2O, reflux, Ac_2O/Pyr; *v)* B^{TMS}, $CF_3SO_3SiMe_3$; *vi)* 1M NaOH/dioxane, 0 °C.

FIGURE 1

Synthesis of 2'-*O*-Me-Nucleosides from D-Allose

only diacetate **5**. A more reproducible method involved deformylation with 80% Pyr-H_2O (refluxing, 1.5 h) and subsequent acetylation which led to diacetates **5** (α,β-mixture) in 75% yield starting from **3.** Vorbrüggen condensation with silylated nucleobases in the presence of $CF_3SO_3SiMe_3$ (CH_3CN, sugar/base/ catalyst : 1/1.2/1.5; pyrimidines - RT, 16 h; purines - boiling 3-5 h) resulted in protected 2'-*O*-Me nucleosides (**6-9**) in 55-70% yield. Subsequent selective deprotection (1M NaOH/dioxane, 0 °C) led to the base protected synthons **10-13** suitable for phosphoramidite preparation.

B: The 3'-*O*-TBDMS-derivatives of protected ribonucleosides are byproducts obtained during the preparation of 2'-*O*-TBDMS derivatives - key building blocks in oligoribonucleotide synthesis.[9] At the same time, 3'-*O*-TBDMS-isomers could be useful starting compounds in the preparation of 2'-*O*-methyl-3'-*O*-phosphoramidites. We explored this possibility on cytidine derivative **14**. Reaction of 3'-*O*-TBDMS-5'-*O*-DMT-N^4-*i*-Bu-cytidine (**14**) with Ag_2O-CH_3I using a modified method of Ohtsuka *et al.*[4] yielded 3'-*O*-TBDMS-5'-*O*-DMT-N^4-*i*-Bu-2'-*O*-methyl cytidine (**15**) in 26% yield. The 2'-*O*-TBDMS isomer **16** was also obtained (22% yield) along with the starting 3'-*O*-isomer (18%). When 2'-*O*-TBDMS-5'-*O*-DMT-N^4-*i*-Bu-cytidine (**16**) was subjected to the same reaction conditions, the same mixture of products was obtained. These results show that

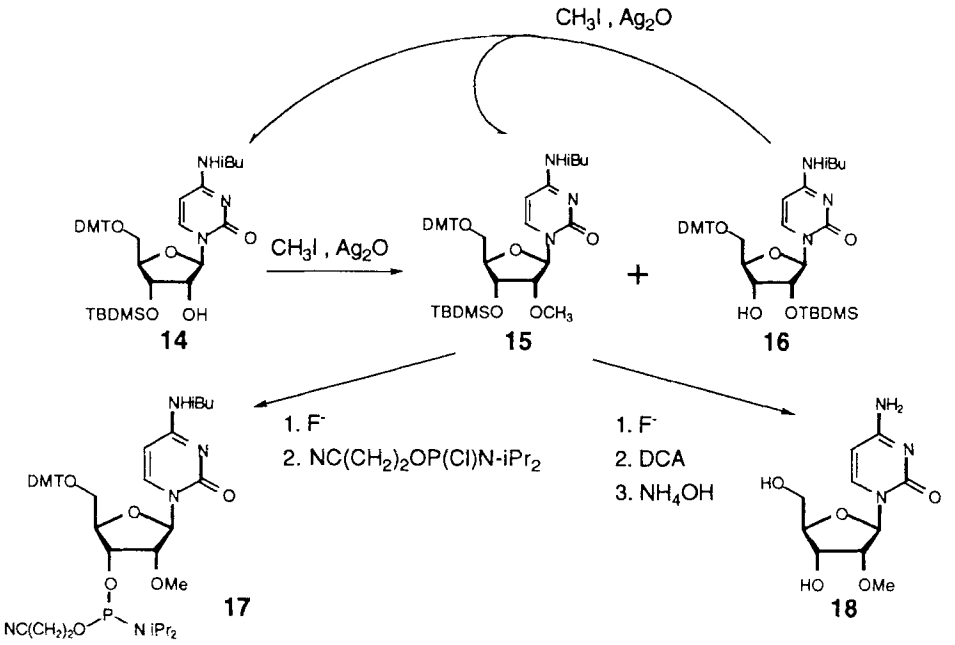
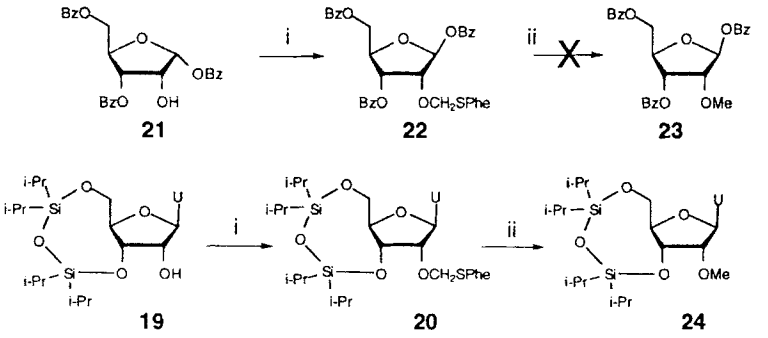


FIGURE 2

Synthesis of 2'-*O*-Me-Cytidine and its 3'-*O*-Phosphoramidite



Reagents and Conditions: *i*) PhSMe, Bz_2O_2, DMAP, Ar/MeCN, 0 °C, 3-4 h; *ii*) Bu_3SnH, Bz_2O_2 or AIBN/toluene.

FIGURE 3

Synthesis of 2'-*O*-Me-Uridine by Radical Reduction

under the above reaction conditions migration of the TBDMS group accompanies the methylation reaction and methylation takes place selectively at the 2'-OH position. Only traces of other products (probably 3'-*O*-methyl and *N*-methylated derivatives) were detected by TLC. Selective 2'-*O*-methylation of nucleosides protected with a bulky group at the 5'-position has been described.[10] If the reaction temperature &/or the reaction time were increased, per-methylation took place decreasing the yield of the desired 2'-*O*-methyl derivative **15**. The 2'-*O*-methyl derivative **15** could be conveniently converted in two steps into the known[11] 3'-*O*-phosphoramidite **17**. The structure of nucleoside **15** was confirmed by a stepwise deprotection to 2'-*O*-methyl cytidine (**18**), which was identical by UV and ^{1}H NMR spectra to an authentic sample.

C: Among different methods of indirect introduction of a methyl group, the use of of 1-alkylthioalkyl intermediates seems to be the most promising.[12] Although methods of synthesis of methylthiomethyl ethers of nucleosides[12] and carbohydrates[13,14] are well developed, their transformation into a methyl group sometimes requires additional steps.[12] We were interested in the testing of more reactive methylthiophenyl ethers as precursors for methyl ethers. We found that methylthiophenyl ethers could be smoothly introduced by treating appropriately protected nucleosides or carbohydrates with PhSMe/Bz_2O_2 in the presence of DMAP. Nucleoside **19** afforded methythiophenyl ether **20** in 65-70% yield, and α-ribofuranose **21** was transformed into β-furanose **22** in 60% yield. Different attempts to radically (Bu_3SnH, Bz_2O_2) reduce the thiophenyl group of furanose **22** were not successful, providing only starting material. However, under the same conditions, nucleoside **20** afforded 2'-*O*-Me derivative **24** in 70% yield.

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