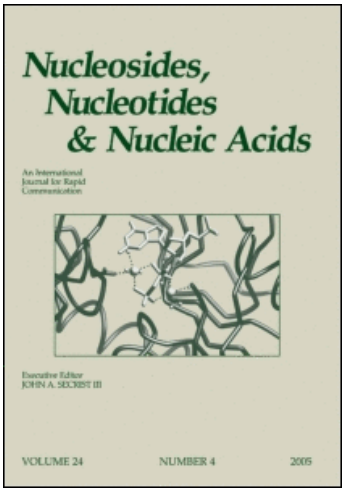

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SYNTHESIS OF 1′-*C*-FLUOROMETHYLADENOSINE

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□ *In search for new antiviral agents, we have been interested in 1′-C-fluoromethyl branched ribonucleosides. In this paper, we describe the synthesis of 1′-C-fluoromethyladenosine via electrophilic fluorination of exo-glycal.*

Keywords 1′-*C*-fluoromethyl branched ribonucleosides; exo-glycal; fluorination

INTRODUCTION

In recent years, there has been an increasing interest in the synthesis of *C*-branched ribonucleosides. Various branchings on the 2′, 3′, or 4′ position of the sugar moiety have been extensively studied for antiviral and antitumor activities. Recently, 2′-*C*-methyl ribonucleosides have been discovered as RNA viruses inhibitors, and NM283 (3′-O-(L-valinyl)-2′-C-methyl-β-D-cytidine, valopicitabine) has been elected as a clinical candidate for HCV treatment.[1–3]

Anomeric branched nucleosides are another class of compounds which has attracted little attention due to synthetic challenges. In search for new antiviral agents, we have been interested in the synthesis of 1′-*C*-fluoromethyl branched ribonucleosides bearing adenine as the base. In this regard, a methodology via electrophilic fluorination of exo-glycals has been reported by others in the literature to synthesize anomeric mixture of 1′-CH_2F-ddC in order to investigate the influence of anomeric branching on an anti-HIV agent.[4]

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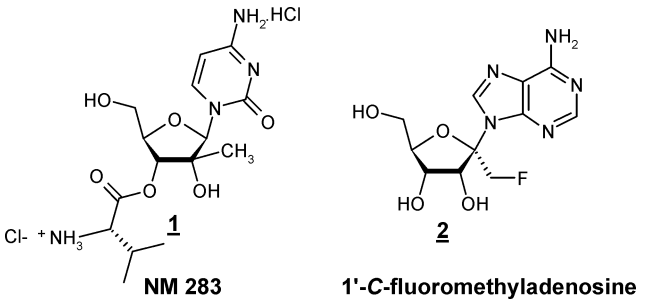


FIGURE 1 valopicitabine (**1**) and 1′-*C*-fluoromethyladenosine (**2**.)

We report here the use of this approach in the ribose series for the synthesis of 1′-*C*-fluoromethyladenosine.

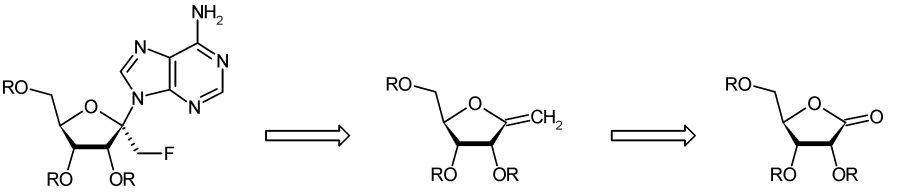
CHEMISTRY

The retrosynthetic approach for the synthesis of 1′-*C*-fluoromethyladenosine is schown below and requires first the preparation of an 1-exomethylene ribofuranose.

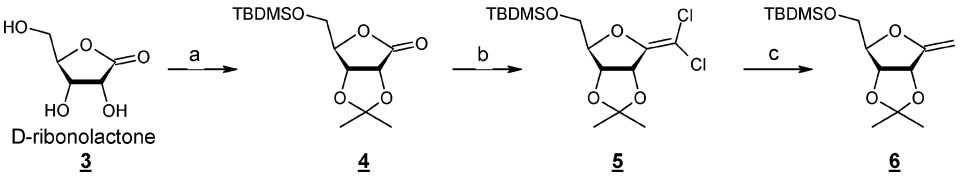
For this purpose, D-ribono-γ-lactone **3** was quantitatively converted to its 2,3-*O*-isopropylidene derivative by treatment with sulfuric acid in acetone. The crude compound was then treated with *tert*-butylchlorodimethylsilane and imidazole in DMF to afford compound **4** in 70% yield. Treatment of **4** with tetrachloromethane in the presence of triphenylphosphine in THF gave the dichloromethylene derivative **5** in a 50% yield.[5] Radical reduction using tri-*n*-butyltin hydride in toluene afforded the expected exo-glycal **6** in good yield (60%).[6]

To complete the synthesis of the desired 1′-*C*-branched ribonucleoside, compound **6** was first treated with silylated 6-chloropurine as nucleophile and Select-Fluor as electrophilic agent.

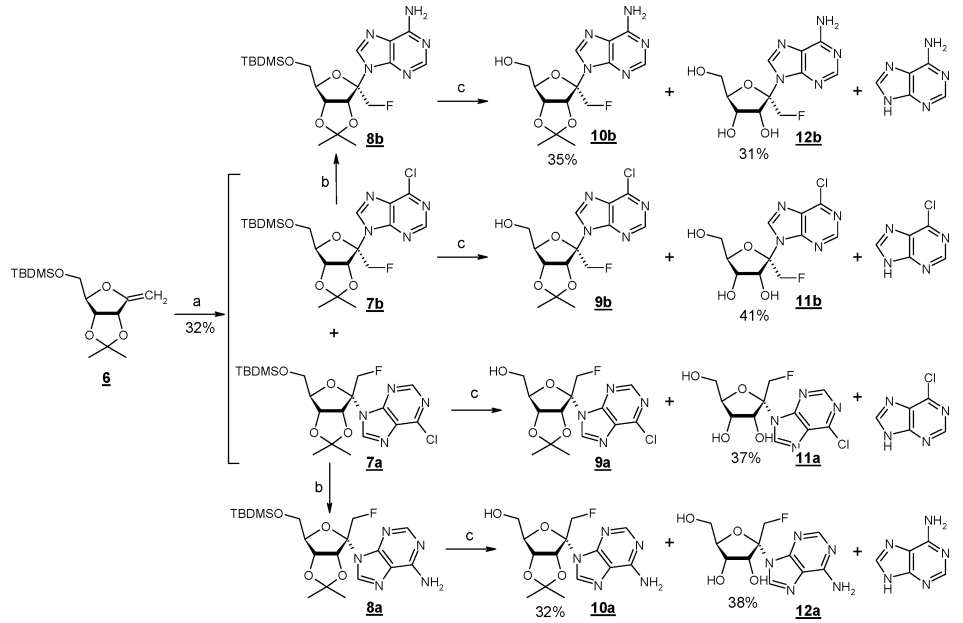
Anomers **7a**/**7b** were isolated in 32% yield in a 1/1 ratio, and easily separated by silica gel column chromatography. Compounds **7a** and **7b** were converted into their adenine derivatives **8a**/**8b** using a saturated solution of ammonia in methanol. In all cases (**7a**/**7b**/**8a**/**8b**), attempts to remove the silyl and isopropylidene protecting groups with TFA/H_2O gave, after optimiza-



SCHEME 1 Retrosynthetic approach for the preparation of 1′-*C*-fluoromethyladenosine derivative.



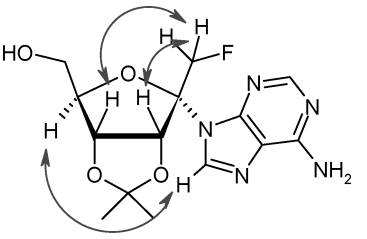
SCHEME 2 Synthesis of the key exo-glycal **6**. Reaqents and conditions: a) (i) Acetone, H_2SO_4, quant. (ii) TBDMSCI, imidazole, DMF, 70% b) CCI_4, PPh_3, THF, 50% c) Bu_3SnH, AIBM, toluene, 60%.



SCHEME 3 Synthesis of anomeric branched ribonucleosides. Reaqents and conditions : a) Silylated 6-chloropurine, SelectFluor, CH_3NO_2, r.t., 5 hours then separation by chromatography b) NH_3/MeOH c) TFA/H_2O, dioxane, 7 hours.

tion, a mixture of the fully deprotected nucleoside, its 2,3-*O*-isopropylidene derivative and the corresponding free base resulting from a glycosidic bond cleavage. Reverse phase column chromatography allowed the separation and isolation of each expected nucleoside **11a**, **11b**,**12a**, and **12b** from the corresponding crude mixture in fair yields (around 35%).

NOe experiments on compound **10a** were carried out in deuteriated DMF to confirm its anomeric configuration. As shown on Scheme 4, correlations between $H_{4'}$ and H_8 was clearly observed. In addition, $H_{2'}$ and $H_{3'}$ both strongly correlate with the fluoromethyl group. All these nOe contacts showed that nucleoside **10a** is an α anomer.



11a

SCHEME 4 nOe correlations of compound **10a.**

CONCLUSION

We have established a synthesis for 1′-*C*-fluoromethyladenosine **12b**. The synthesized compounds **11a**,**11b**,**12a**, and **12b** were evaluated for antiviral activity in cell cultures towards bovine viral diarrhea virus (BVDV, a pestivirus surrogate model of Hepatitis C virus (HCV) for the evaluation of antiviral agents[7]), and as inhibitors of HCV in a subgenomic replicon assay. None of these compounds showed antiviral effect nor cytotoxicity at the highest concentration tested (100 mM).

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