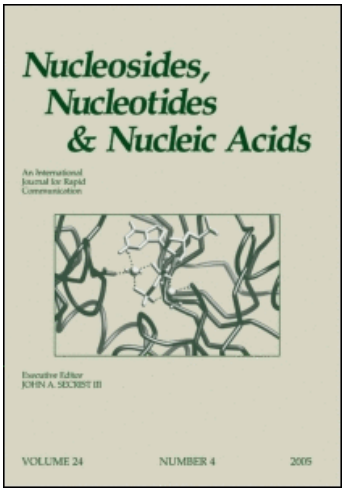

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SYNTHESIS AND ANTIVIRAL EVALUATION OF 3′-C-TRIFLUOROMETHYL NUCLEOSIDE DERIVATIVES BEARING ADENINE AS THE BASE

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ABSTRACT

3′-deoxy-3′-*C*-trifluoromethyl- (**3**), 2′,3′-dideoxy-3′-*C*-trifluoromethyl- (**5**) and 2′,3′-dideoxy-2′,3′-didehydro-3′-*C*-trifluoromethyladenosine (**6**) derivatives have been synthesized and their antiviral properties examined. All these derivatives were stereospecifically prepared by glycosylation of adenine with a trifluoromethyl sugar precursor (**1**), followed by appropriate chemical modifications. The prepared compounds were tested for their activity against HIV, but they did not show an antiviral effect.

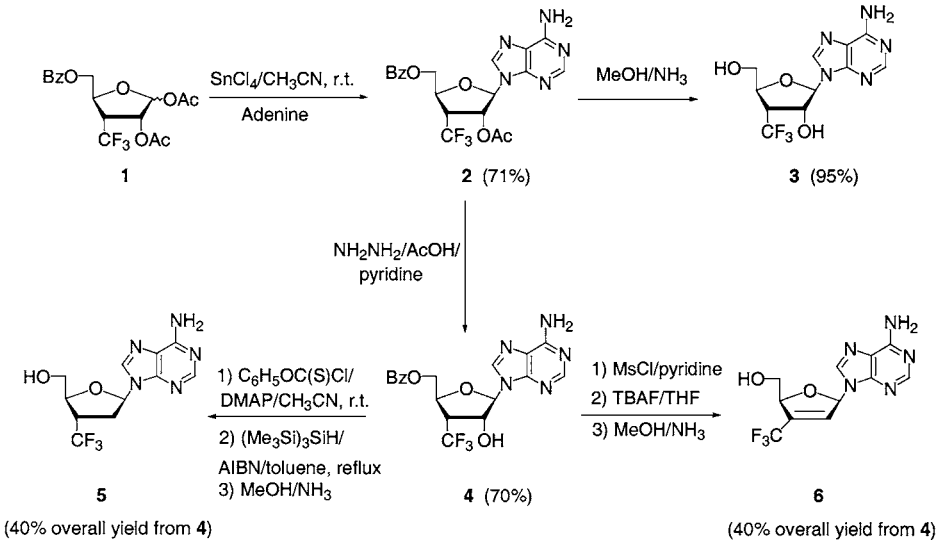
INTRODUCTION

It has been found that many 2′,3′-dideoxynucleosides and their 2′,3′-unsaturated counterparts show potent activity against human immunodeficiency virus (HIV) (1). In order to discover new nucleoside derivatives with antiviral activity, modifications of the base and/or sugar moiety of natural nucleosides can be attempted. As a part of our ongoing research on this topic, we have synthesized, from a common trifluoromethyl sugar precursor, various 3′-*C*-trifluoromethyl nucleoside derivatives bearing adenine as the base. Many advantages can be expected from the presence of a CF_3 group on the sugar moiety of nucleosides, including high lipophilicity and increased chemical and/or enzymatic stability. Herein, we report the synthesis (in a stereospecific manner), chemical stability studies as well as the results of

the biological evaluations of hitherto unknown 3′-deoxy- 3′-*C*-CF_3, 2′,3′-dideoxy-3′-*C*-CF_3 and 2′,3′-unsaturated-3′-*C*-CF_3 nucleoside derivatives of adenine (**3**, **5** and **6**).

SYNTHESIS

The synthesis began with the preparation of the trifluoromethyl sugar precursor, namely, 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-trifluoromethyl-β-D-ribofuranose (**1**) which was obtained in 37% overall yield from commercially available diacetone-D-glucose following a modified procedure initially developed by Portella et al. (2) (Scheme). A glycosylation reaction with adenine and the suitably 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-trifluoromethyl-β-D-ribofuranose (**1**) using stannic [tin(IV)] chloride as a catalyst afforded the protected derivative **2**. Deprotection of **2** with methanolic ammonia provided the desired nucleoside **3**. In order to prepare the target compounds **5** and **6**, regioselective 2′-*O*-deacylation of **2** was accomplished to give the intermediate **4**. The latter was then converted to the 2′,3′-dideoxy-3′-*C*-CF_3-nucleoside derivative **5** *via* a radical reductive process and subsequent deprotection with methanolic ammonia. On the other hand, introduction of a double bound between the 2′ and 3′ positions was achieved from **4** *via* a base-promoted β-elimination of the corresponding 2′-*O*-mesylate derivative by treatment with TBAF in THF. Finally, treatment with methanolic ammonia gave the 2′,3′-unsaturated-3′-*C*-CF_3-nucleoside derivative **6**.



Scheme.

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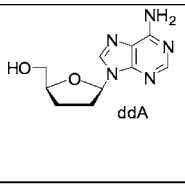
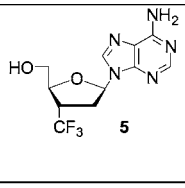
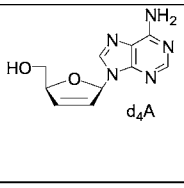
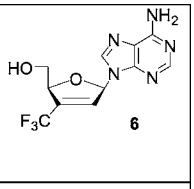
Table.

	 ddA	 5	 d_4A	 6
pH 2 $T_{1/2}$	20 min	89 h	< 1 min	8.9 h
pH 7 $T_{1/2}$	stable	stable	53 h	stable

Structural assignments for all the compounds synthesized in this work were based on elemental analysis and physicochemical properties (melting point, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, UV, mass spectra and optical rotation) (3).

CHEMICAL STABILITY STUDIES

Owing to the high electron withdrawing power of the CF_3 group and its potential stabilizing effect on the lability of a glycosyl-purine bound, we have examined the stability at buffer pH 2 and 7 of the nucleosides **5** and **6** compared to ddA and d_4A (Table). These results show the benefit of the trifluoromethyl group regarding the chemical stability of the 2′,3′-dideoxy-3′-*C*-CF_3- and 2′,3′-unsaturated nucleoside derivatives of adenosine.

BIOLOGICAL EVALUATIONS

The nucleosides **3**, **5** and **6** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems. None of these compounds showed significant antiviral activity nor cytotoxicity at the highest concentration tested (generally 100 μM). The anti-HIV assays on cell culture were performed by following previously established procedures as described in ref. 4.

CONCLUSION

From this work, it appears that 3′-*C*-trifluoromethyl nucleoside derivatives of adenine do not inhibit the replication of HIV. Evaluation of these compounds against a broad range of other viruses, as well as the synthesis of 3′-*C*-CF_3-nucleoside derivatives bearing other purine and pyrimidine bases are currently in progress in our laboratory. It is noteworthy that during the course of our studies, the synthesis

and the anti-HIV evaluation of some 3′-C-CF_3-nucleoside derivatives of cytosine have been reported (5).

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REFERENCES

1. De Clercq, E. *Clin. Microb. Rev.*, **1995**, *8*, 200–239.
2. Lavaire, S.; Plantier-Royon, R.; Portella, C. *Nucleosides Nucleotides*, **1998**, *17*, 2267–2280.
3. Selected NMR data. Compound **5**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.66 (m, 1H), 2.95 (m, 1H), 3.45–3.74 (m, 3H), 4.22 (m, 1H), 5.37 (t, 1H, $J = 5.3$ Hz)), 6.30 (t, 1H, $J = 6.4$ Hz), 7.35 (br s, 2H), 8.13 (s, 1H), 8.36 (s, 1H); Compound **6**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.61–3.69 (m, 2H), 5.12 (m, 1H), 5.36 (t, 1H, $J = 5.0$ Hz), 6.99 (d, 1H, $J = 1.7$ Hz), 7.06 (br s, 1H), 7.31 (br s, 2H), 8.14 (s, 1H), 8.20 (s, 1H).
4. Meier, C.; Aubertin, A.-M.; de Monte, M.; Faraj, A.; Sommadossi, J.-P.; Périgaud, C.; Imbach, J.-L.; Gosselin, G. *Antiviral Chem. Chemother.*, **1998**, *9*, 41–51.
5. Sharma, P. K.; Nair, V. *Nucleosides Nucleotides & Nucleic Acids*, **2000**, *19*, 757–774.

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