Synthesis of 1′-*C*-Fluoromethyl-ddC by Selectfluor-Induced Glycosylation of *exo*-Glycals

Pineda Molas, Yolanda Díaz, M. Isabel Matheu,* Sergio Castillón*

Departament de Química Analítica i Química Orgànica, Facultat de Química, Universitat Rovira i Virgili, Pl. Imperial Tarraco 1, 43005 Tarragona, Spain
Fax +34(9775)59563; E-mail: matheu@quimica.urv.es; E-mail: castillon@quimica.urv.es
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Abstract: 1′-*C*-fluoromethyl-ddC has been synthesized from 4-pentene-1,2-diol which is easily obtained from glycidol. The key steps are the synthesis of an *exo*-glycal by a 5-*exo* iodo-cyclization of a 4-pentene-1,2-diol and elimination, and a fluoro-glycosylation using an *exo*-glycal as glycosyl donor.

Key words: nucleosides, fluorine, glycosylation, electrophilic addition, cyclization

2′,3′-Dideoxynucleosides are among the most powerful agents against HIV.[1] AZT, d4T and ddC are pyrimidinyl nucleosides currently used in HIV treatment. Some 1′-C-branched nucleosides such as angustmycin[2] and hydantocidin[3] are of natural origin. In this sense, the synthesis of hydanticidin homologues has been described,[4] and side chain introduction has been investigated in order to modify properties of natural nucleosides.[5] However, only a few examples of 1′-*C*-branched-2′,3′-dideoxy derivatives are known. Thus, a derivative of 1′-*C*-methyl-AZT[6] (**1**, X = CH_3), 1′-*C*-cyano-d4T[7] (**2**, X = CN) and one example of 1′-*C*-cyano-2′-deoxycytidine have been reported. No examples of 1′-*C*-branched-2′,3′-dideoxycytidine (**3**) have been described (Figure 1).[8]

1′-Branched nucleosides are usually synthesized by introducing a chain at position 1′ into natural nucleosides

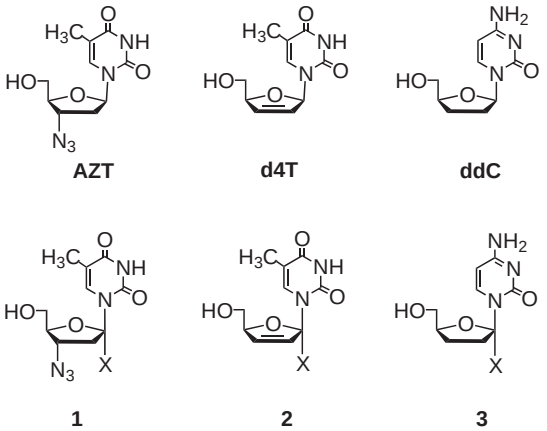
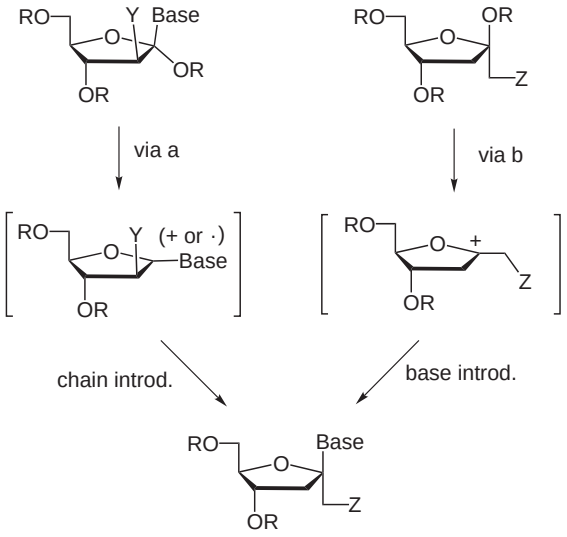


Figure 1

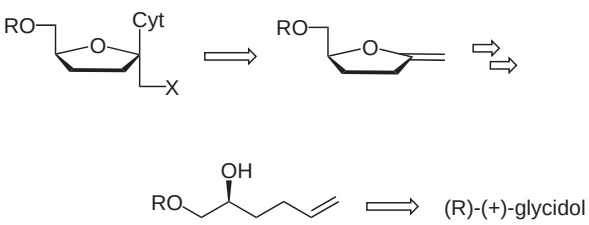
through a substitution[9] or a radical[5,10] reaction (Scheme 1, via a), or by glycosylation of a ketose (Scheme 1, via b).[11] In this case, fructose in its furanose form has been the most widely used starting material.

Recently, we described an efficient procedure for synthesizing biologically active isonucleosides based on the iodo-cyclization of pentenetriols.[12] In this paper, we report the synthesis of 1′-*C*-halomethyl derivatives of ddC from *exo*-glycals, which in turn can be obtained from hexenediols through an iodo-cyclization (Scheme 2).



Scheme 1

In contrast to endocyclic glycals which have been extensively used as important glycosyl donors,[13] *exo*-glycals have a shorter history in this field. However, they are becoming important as useful intermediates in the synthesis of *C*-glycosides,[14] and *C*-disaccharides.[14c,d]



Scheme 2

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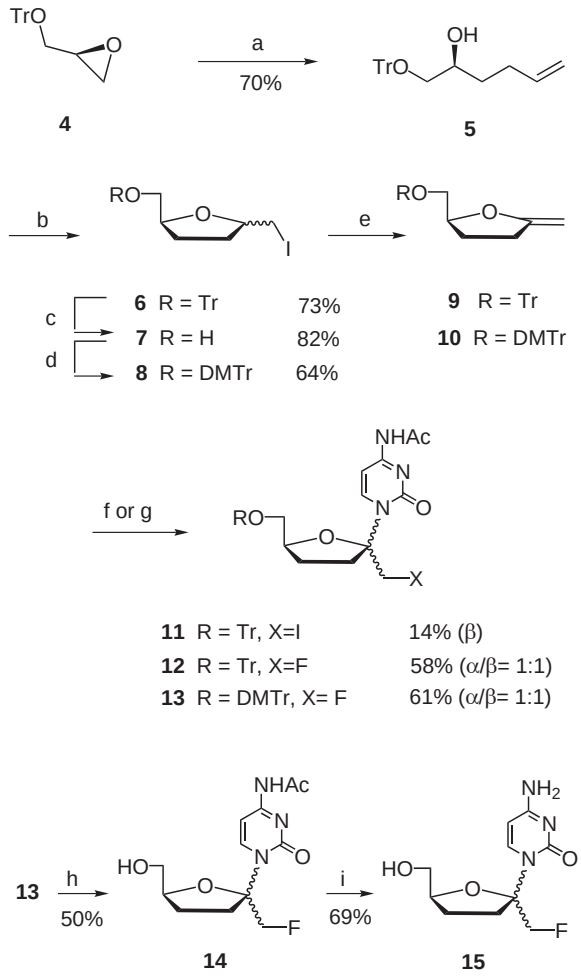
We thought that *exo*-glycals could be appropriate starting materials for preparing 1′-branched nucleosides. Initially, we obtained alcohol **5**[15] from (*R*)-glycidol by protecting the hydroxyl group as trityl ether and subsequent reaction with allylmagnesium bromide (Scheme 3). The iodine-induced cyclization of alcohol **5** was performed under kinetic control.[16] Under these conditions, the reaction is irreversible and the exo cyclization product is preferred. In this way, furanose **6** was obtained as a 1:1 diastereomeric mixture in 73% yield as a result of a 5-*exo* cyclization.[17]

From the tetrahydrofuran derivative **6** a base promoted elimination can provide the desired *exo*-glycal.[18] The elimination was attempted using AgF and DBU, but the results were best when *t*-BuOK was used. In this case the starting material reacted quantitatively to give the exocyclic glycal **9**. Compound **9** proved to be stable enough to be characterized by NMR techniques but it slowly decomposes on standing.



Scheme 3 a) CH_2=CH-CH_2MgBr, Et_2O, –20 °C to 0 °C, 1.5 h; b) I_2, Na_2CO_3, CH_3CN, 45 min, 0 °C; c) TFA, $CHCl_3$, r.t. 3 h; d) DMTrCl, pyridine, DMAP, r.t., 3 h; e) *t*-BuOK, CH_2Cl_2, r.t., 2.5 h; (**9**), 40 min (**10**). f) N^4-AcCyt($SiMe_3$)$_2$, NIS, CH_2Cl_2, r.t., 2 h; g) N^4-AcCyt($SiMe_3$)$_2$, Selectfluor, CH_3NO_2, r.t., 3 h (**12**), 25 min (**13**); h) HOAc 80%, r.t. 15 min; i) NH_3, MeOH, r.t., 1 h.

Particularly, when we attempted purification by flash chromatography it isomerized towards the endocyclic derivative. So, we decided to use it directly in the glycosylation step without further purification.

2′-Deoxy- and 2′,3′-dideoxy-nucleosides have been obtained with high levels of stereoselectivity from endocyclic glycals by PhSeCl,[19] NIS[20] and PhSCl[21] induced glycosylation. *exo*-Glycals, however, have not previously been used in this kind of glycosylations. Initially, we treated **9** with silylated N^4-acetylcytosine using NIS as electrophilic agent.[22] Nucleoside **11**[23] was isolated from the reaction mixture in very low yield. NMR spectra confirmed that glycosylation took place at the anomeric position. NOESY experiments established a β stereochemistry of the glycosidic linkage: protons H-6′ were correlated with H-6 which suggests that the trityloxymethylene group and the base are on the same face of the molecule. Compound **11** proved to be quite unstable on standing.

In an attempt to provide greater stability to the 1′-branched nucleoside, we decided to use electropositive fluorine as activator. Selectfluor[24] has been used recently to synthesize 2-deoxy-2-fluoroglycosides,[25] 2-deoxy-2-fluoro-glycosyl-aminoacids,[26] and nucleosides[27] from endoglycals. With this aim *exo*-glycal **9** was treated with Selectfluor in the presence of the same nucleobase. The desired product **12** was obtained as a 1:1 inseparable α/β mixture in 58% yield. As in the case of furanoid glycals isolation of the primary addition product was not possible.[28] The most significant spectroscopic data supporting structure **12** were the presence in the ^{19}F NMR spectrum of two triplet signals (CH_2F) at δ = –94.50 ppm and –95.21 ppm, respectively.

Attempts to hydrolyze the trityl group with TFA gave a mixture of the degradation products, probably because of the hydrolysis of the glycosidic bond under these conditions. Then, we therefore attempted to exchange the trityl group for the more labile dimethoxytrityl. Thus, treatment of iodine derivative **6** with TFA led to the unprotected compound **7**, which was then treated with DMTrCl to give the dimethoxytrityl ether derivative **8**. The subsequent one pot elimination-addition led to nucleoside **13**[29] in 61% yield as an α/β inseparable mixture. In this case, the deprotection of the hydroxyl group was performed with HOAc 80% in 15 minutes to give **14**. Finally, deprotection of the acetyl group at the base moiety in NH_3/MeOH led to 1′-*C*-fluoromethyl-ddC (**15**).[30] Attempts of separation of **15**, as well as **13** and **14**, by column chromatography, medium pressure liquid chromatography and by radial chromatography were unsuccessful.

In conclusion, 1′-*C*-branched-ddC derivatives have been obtained for the first time using two electrophilically induced reactions, an iodo-cyclization of a suitable protected 5-hexen-1,2-diol as an entry to *exo*-glycals, and a fluoro-glycosylation of the obtained *exo*-glycal.

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(23) **Compound 11:** *t*-BuOK (165 mg, 1.35 mmol) was added to a solution of **6** (220 mg, 0.52 mmol) in dry CH_2Cl_2 (10 mL). The mixture was kept at r.t. for 2.5 h, poured into 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated to obtain **9**. To a solution of the previously obtained *exo*-glycal **9** in CH_2Cl_2 (2.5 mL) N^4-Acetyl-bis(trimethylsilyl)cytosine (0.68 mmol) and NIS (155 mg, 0.68 mmol) were added, and the reaction was kept at r.t. for 2 h, diluted with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated. Purification by column chromatography (Merck silica gel 60, 0.040-0.063 mm, eluent: EtOAc–hexane, 5:3) and radial chromatography (Merck silica gel 60 F_{254}) gave **11** (40 mg, 14% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.79 (s, 1 H, NH), 8.13 (d, 1 H, $J_{6,5}$ = 7.5 Hz, H-6), 7.50–7.46, 7.36–7.24 (2 m, 16 H, H-Ar, H-5), 4.50 (d, 1 H, J_{gem} = 10.8 Hz, H-1′a), 4.30–4.25 (m, 1 H, H-5′), 3.71 (d, 1 H, H-1′b), 3.30–3.22 (m, 2 H, H-6′), 2.97–2.89, 2.75–2.65 (2 m, 2 H, H-3′), 2.27 (s, 3 H, CH_3), 2.00–1.88 (m, 2 H, H-4′). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ(ppm) = 179.0 (CO), 163.0 (C-2), 145.0 (C-6), 143.5 (C-Ar_q), 128.5, 127.8, 127.0 (CH-Ar), 98.2 (C-2′), 95.6 (C-5), 86.7 (C-Ph_3), 80.5 (C-5′), 65.3 (C-6′), 35.3 (C-3′), 27.8 (C-4′), 24.9 (CH_3), 12.1 (C-1′).

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(29) **Compound 13:** Following a similar procedure for the synthesis of **9**, *exo*-glycal **10** was prepared starting from **8** (290 mg, 0.52 mmol) in dry CH_2Cl_2 (10 mL) using *t*-BuOK (176 mg, 1.56 mmol). To a solution of *exo*-glycal **10** in CH_3NO_2 (4 mL) N^4-Acetyl-bis(trimethylsilyl)cytosine (1.04 mmol) was added. Selectfluor {1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)} (272 mg, 0.77 mmols) was added and the reaction was kept at r.t. for 25 min. Then, the mixture was diluted with EtOAc, filtered and concentrated to dryness. Purification by radial chromatography (Merck silica gel 60 F_{254}, eluent: CH_2Cl_2–CH_3OH, 50:1) gave 191 mg (61% yield) of **13** as an inseparable diastereomeric mixture.
^1H NMR (400 MHz, $CDCl_3$) diastereomeric mixture: δ (ppm) = 9.90 (br s, 2 H, NH), 8.27 (d, 1 H, *J* = 7.6 Hz, H-6a), 8.19 (d, 1 H, *J* = 8.0 Hz, H-6b), 7.46–7.45 (m, 2 H, H-5a, H-5b), 7.38–7.19, 6.84–6.82 (m, 26 H, H-Ar), 5.03–4.59 (m, 4 H, H1′a, H1′b), 4.48–4.47, 4.31–4.27 (2 m, 2 H, H5′a, H5′b), 3.89 [s, 6 H, CH_3(DMTr)], 3.35–3.17 (m, 4 H, H6′a, H6′b), 2.96–2.36 (m, 4 H, H3′a, H3′b), 2.27 [s, 3 H, CH_3(OAc)], 2.24 [s, 3 H, CH_3(OAc)], 1.93–1.75 (m, 4 H, H-4′a, H-4′b).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 158.5 (C=O), 146.4, 145.0 (C-6), 135.8, 135.6, 135.5, 130.0, 129.9, 128.0, 127.9, 127.7, 126.8 (C-Ar), 113.2, 113.1 (C-2′), 99.2, 96.4 (C-5), 86.3, 86.1 (C-Ph_3), 83.1 ($J_{C,F}$ = 181.3), 83.3 ($J_{C,F}$ = 179.3) (C-1′), 80.9 (C-5′), 65.2, 64.1 (C-6′), 55.1 (OCH_3), 32.8, 32.2 (C-3′), 27.1, 26.4 (C-4′), 24.8 (CH_3).
^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) = –228.03 (t, *J* = 48.9 Hz), –228.73 (t, *J* = 50.0 Hz).

(30) **Compound 15:** A solution of **13** (64 mg, 0.10 mmol) in 0.1 M 80% HOAc was stirred at r.t. for 15 min, then was neutralized with 1 M $NaHCO_3$ and extracted with EtOAc. Purification by radial chromatography (Merck silica gel 60 F_{254}, eluent: CH_2Cl_2–CH_3OH, 25:1) gave **14** (19 mg, 63% yield). Then, a solution of 10% NH_4OH (1 mL) was added to **14** (10 mg, 0.03 mmol) in MeOH. The mixture was kept at r.t. for 1 h. Purification by preparative chromatography (Merck silica gel 60 F_{254}, eluent: CH_2Cl_2–CH_3OH, 10:1) gave **15** as an inseparable α/β mixture (5 mg, 69% yield).
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.09 (d, 1 H, *J* = 7.2 Hz, H-6a), 7.60 (d, 1 H, *J* = 8.0 Hz, H-6b), 5.78 (d, 1 H, H-5a), 5.74 (d, 1 H, H-5b), 4.81–4.60 (m, 4 H, H-1′a, H-1′b), 4.39–4.33, 4.21–4.18 (2 m, 2 H, H-5′a, H-5′b), 3.76–3.55 (m, 4 H, H-6′a, H-6′b), 2.65–2.63, 2.51–2.48 (2 m, 4 H, H-3′a, H-3′b), 2.01–1.98, 1.86–1.83 (2 m, 4 H, H-4′a, H-4′b).
^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) = –225.40 (t, *J* = 50.0 Hz), –226.12 (t, *J* = 50.4 Hz).