Pergamon

Tetrahedron Letters, Vol. 36, No. 43, pp. 7807-7810, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01653-8

Diastereocontrol in Glycosylation Reactions: Synthesis of β-D and β-L Dideoxycytidine Analogues

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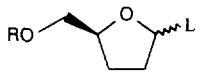
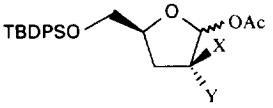
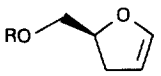
Abstract. Expeditious and diastereoselective total syntheses of the antiviral agents, β-L-ddC, β-L-5FddC and β-D-5FddC have been achieved in four steps from commercially available R-(-)-5-oxo-2-tetrahydrofurancarboxylic and its 2S isomer respectively.

The control of regio-and stereochemistry in the glycosylation of nucleic bases with 2,3-dideoxy sugars is a key transformation in the preparation of biologically important 2',3'-dideoxynucleosides with β-configuration.[1] Extensive synthetic efforts using either Lewis acid catalyzed approaches[2] or SN2-like reactions of 1-halosugars[3,4] have been directed towards the anti-AIDS nucleosides AZT, ddC, ddI and d_4T with marginal success. For example, the highest ratio of β:α anomers reported to date of 3:2 in the Lewis acid mediated reaction of 5-*O*-t-butyldimethylsilyl-2,3-dideoxy-D-glycero-pentofuranose (**1**) with silylated cytosine[2] has been achieved with ethylaluminium dichloride whereas the reaction of 1-chloro sugar derivative (**2**) with silylated cytosine afforded a slightly higher ratio of 7:3.[4] Although a substantial improvement in the desired β-stereoselection has been recently reported in the glycosylation of silylated pyrimidine bases with dideoxyribose derivatives carrying α-phenylselenenyl (**3**),[5] α-phenylsulfenyl (**4**),[6] and gem-diphenylsulfenyl (**5**)[7] moieties and in the electrophilic addition reactions of N-iodosuccinimide in acetic acid[8] or phenylsulfenyl chloride[9,10] to furanoid glycals[11] **6** and **7** and silylated bases, their generality is somewhat limited due to the difficulties encountered in the subsequent reductive step often requiring multistep manipulations (3 steps).

In this letter, we present a concise method for the preparation of the three dideoxy nucleosides β-L-ddC,[2,12] the enantiomer of the clinically approved anti-HIV agent ddC (zalcitabine, HIVID), β-L-5FddC[12] and β-D-5FddC,[13] all of which have been shown recently to possess potent anti-HIV and anti-hepatitis B activities,[14] based on the coupling of furanoids carrying a C-4 carboethoxy moiety with silylated cytosine derivatives mediated by iodotrimethylsilane.[15-17]



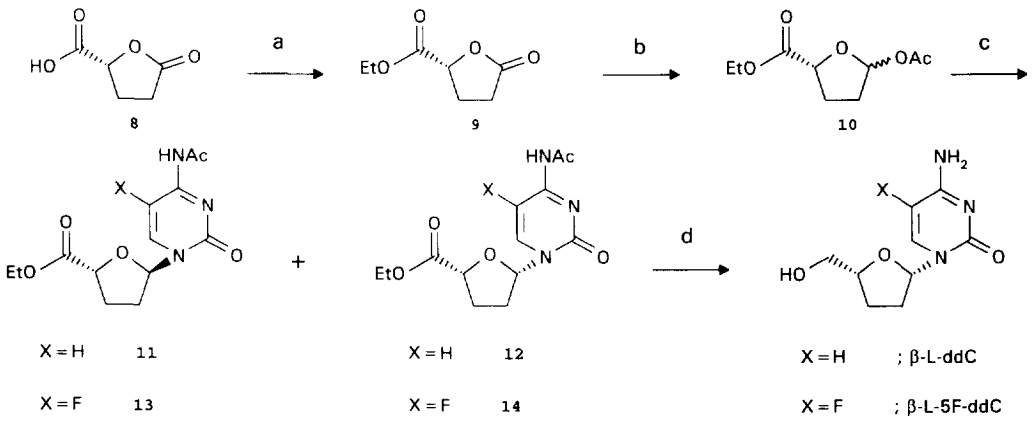




1. R=TBDMS; L=OAc
2. R=$PhCO_2$; L=Cl
3. X=H; Y=SePh
4. X=H; Y=SPh
5. X=Y=SPh
6 R=t-$BuCO_2$
7. R_1=TBDPS

The introduction of absolute stereochemistry at an earlier stage in the synthesis was achieved starting with the butyrolactone derivative 8 available in high enantiomeric purity from D-glutamic acid.[2] Esterification of acid 8 with ethanol afforded the corresponding ester **9** which was chemoselectively reduced with disiamylborane in THF at 0°C. Acetylation of the crude lactol mixture at low temperature furnished a mixture of α and β acetates **10** in a ratio of 5:4. Glycosylation of persilylated N-acetylcytosine with **10** in the presence of one equivalent of iodotrimethylsilane produced a mixture of dideoxycytidine analogues **11** and **12** in a 4:1 ratio favouring the β-anomer as evidenced by the 'H NMR (300 MHz) spectra of the base 6-H protons (Δδ=1.31 ppm). After separation, the major isomer **12** was efficiently converted to β-L-ddC in one pot by deacetylation with TFA in ethanol followed by reduction with sodium borohydride (Scheme 1). When the coupling of **10** was performed with persilylated N-acetyl-5-fluorocytosine the expected mixture of nucleoside analogues **13** and **14** was obtained in a ratio of 5.5:1 favouring the β-anomer **14**. Compound **14** was then isolated from the reaction mixture by fractional recrystallization and converted to β-L-5FddC as shown in Scheme 1.

Scheme 1

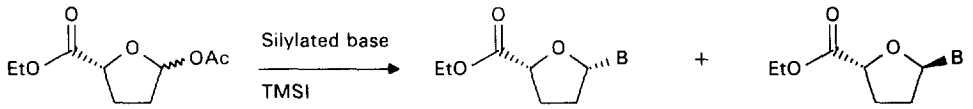


Reagents and conditions: **a.** DCC, DMAP, EtOH, CH_2Cl_2, >95%. **b.** 1. 2,3-dimethyl-2-butene, BH_3-THF, THF. 2. AcCl, pyridine, DMAP, CH_2Cl_2, 60%, 2 steps. **c.** 1. N -acetylcytosine or N -acetyl-5-fluorocytosine TBDMSOT$_f$, 2,6-lutidine CH_2Cl_2. 2. TMSI, room temperature, 2 h. 60%. 3. Fractional recrystallization. **d.** 1. TFA, EtOH, reflux 3 h. 2. $NaBH_4$, EtOH/CH_2Cl_2, room temperature 3 h. 3. NH_3(g), MeOH, 60%, 3 steps.

Since the S-enantiomer of lactone **8** is commercially available from L-glutamic acid we applied the four step synthetic protocol described in Scheme 1 but starting with the antipode of **8** and accomplished the synthesis of the antiviral agent β-D-5FddC.[13]

The high β-stereocontrol was also achieved in good yields in the coupling of **10** with other pyrimidine bases (Table 1), suggesting a practical generality of this reaction.[18] However, from a synthetic standpoint, limitation of the hydride reduction step of the azacytidine analogue (entry 3) was noted in the attempted synthesis of β-L-5-aza ddC resulting in a substantial reduction of the N_5=C_6 moiety of the base.[19]

Table 1



Entry	Silylated Base	Ratio (β:α)	Yield (%)
1	N-Ac-Cytosine	4:1	72
2	N-Ac-5-fluorocytosine	5.5:1	77
3	5-azacytosine	5:1	75
4	Uracil	6:1	77

In conclusion, we have established that high β-stereocontrol can be achieved in the glycosylation of pyrimidine bases with dideoxy sugars to reveal important antiviral agents (β-L-ddC, β-L-5FddC and β-D-5FddC) without the assistance of a substitutent at 2' and 3' sites.[16] We have also shown that these reactions proceeded without any detectable racemization.[17, 20]

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20. Satisfactory spectral and elemental analyses data (C,H,N) were obtained. We thank the bioanlaytical group for HLPC analyses.

(*Received in USA* 29 *June* 1995; *revised* 22 *August* 1995; *accepted* 23 *August* 1995)