A Facile Synthesis of 3'-Deoxy-3'-fluorothymidine *via* a Highly Stereoselective Glycosylation with 2,3-Dideoxy-3-fluoro-D-*erythro*-pentofuranosyl Diethyl Phosphite

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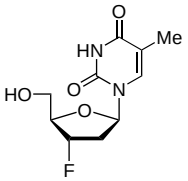
Received 20 May 1999

Abstract: Coupling of 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranosyl diethyl phosphite with 2,4-bis(trimethylsilyl)thymine under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provides a facile and highly stereoselective entry to 3'-deoxy-3'-fluorothymidine (FLT), wherein the use of propionitrile as a solvent as well as the α-configuration of the fluorine atom at C3 has been proven to be responsible for the high β-selectivity of up to 91:9.

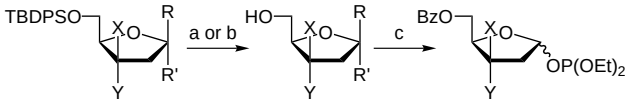
Key words: FLT, glycosylation, pentofuranosyl phosphite, nitrilium ion, electrostatic interaction

Since the discovery of 3'-azido-3'-deoxythymidine (AZT) as an antiretroviral agent, a number of 3'-substituted-2',3'-dideoxynucleoside analogues have been synthesized and evaluated for their antiviral activity against human immunodeficiency virus (HIV).[1] Among them, 3'-deoxy-3'-fluorothymidine (FLT, **1**) has been demonstrated to be a more potent inhibitor of HIV replication than AZT.[2] While its toxicity precludes further investigation, an enormous amount of effort has been devoted to the design and synthesis of its analogues to show a selectivity against HIV.[3] In this regard, one of the major drawbacks in a convergent strategy has been the poor to modest β-selectivity observed with direct coupling between 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranosyl derivative and nucleoside bases, which is a general trend with the synthesis of other 2'-deoxyribonucleosides.[4] As part of a program to extend the recently developed glycosylation method capitalizing on diethyl phosphite as a leaving group,[5] our interest has been centered on the feasibility of the stereocontrol by means of the glycosyl phosphite method.[6] We herein wish to report a highly stereoselective construction of 2'-deoxy-β-*N*-glycosidic linkage in FLT synthesis by employing 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranosyl diethyl phosphite **2** as a glycosyl donor in the presence of TMSOTf.



FLT (**1**)

The furanosyl diethyl phosphite **2**[7] was obtained from the corresponding furanose *via* coupling with diethyl phosphorochloridite, which was prepared by demethylation of methyl 2,3-dideoxy-3-fluoro-5-*O*-benzoyl-β-D-*erythro*-pentofuranoside (**3**)[8a] with $BCl_3 \cdot S(CH_3)_2$.[9] All the reported coupling procedures to give 5'-*O*-protected FLT take advantage of the Vorbrüggen glycosylation method,[10] wherein the β:α ratios ranging from 2.2:1 to 5:1 are observed.[8a,11,12] Particularly noteworthy is that acetonitrile is used as a solvent in all cases, while no explanation for this solvent is presented. Armed with the instructive precedents, we were gratified to find that condensation of **2** (1.0 equiv) with 2,4-bis(trimethylsilyl)thymine (**4**) (1.5 equiv) in the presence of TMSOTf (1.0 equiv) in propionitrile at -50 °C proceeded smoothly to give the 5'-*O*-benzoyl-protected FLT **5** in 89% yield and with the β:α ratio of 91:9 (Table 1, entry 1), which, upon deprotection and subsequent ready separation,[11c] furnished FLT (**1**) in 86% yield.



6 X=R=H, Y=OH R'=OAllyl
7 X=OH, Y=R'=H R=OAllyl
8 X=F, Y=R=H R'=OAllyl
9 X=R'=H, Y=I R=OAllyl
10 X=F, Y=H
11 X=H, Y=I

Table 1 Glycosylation of nucleoside base **4** with furanosyl diethyl phosphite **2**[a,b]

Entry	Solvent	Temp (°C)	Yield[c] (%)	β:α[d]
1	EtCN	-50	89	91:9
2	EtCN	-30	75	84:16
3	CH_2Cl_2	-50	80	79:21
4	toluene	-50	72	63:37
5	Et_2O	-50	75	42:58

[a] The anomeric ratio of the phosphite: 64:36. [b] Donor/acceptor/promoter molar ratio=1.0/1.5/1.0. [c] Isolated total yield based on the donor used. [d] The ratio was determined by 500 MHz ^{1}H NMR.

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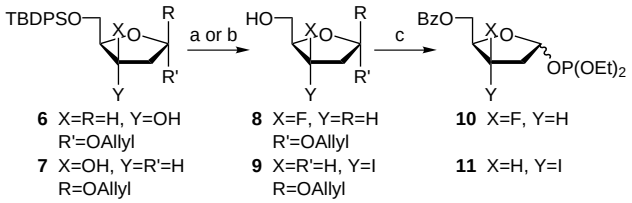
The β-selectivity appeared to increase by lowering the the reaction temperature, however, -50 °C was the limit temperature to allow for the smooth coupling (entries 1 and 2). Switching the solvent from propionitrile to dichloromethane or toluene was found to result in poor β-selectivities (entries 3 and 4), while the use of ether exhibited almost no stereoselectivity (entry 5). Thus, these results, together with the precedents described above, manifested the beneficial effects of nitriles as solvents on β-selectivities, although a remarkably high order of β-selectivity required excellent leaving groups such as a phosphite group at very low temperatures. The dramatic effects of nitriles as solvents on 1,2-*trans*-β-selective glycosidations of D-gluco- and D-galactopyranosyl donors without neighbouring group participation have been well-documented,[13] the role of which is assumed to be due to the predominant formation of α-nitrilium ions (or α-nitrilium-nitrile-conjugate ions).[5a,14] However, there have been reported no similar effects with 2-deoxypentofuranosyl donors.

In order to gain a deep insight into the role of propionitrile as the solvent, we then explored glycosylation with 2,3-dideoxy-3-fluoro-5-*O*-benzoyl-D-*threo*-pentofuranosyl diethyl phosphite (**10**)[7], C3-epimer of **2**, which was prepared from allyl 2-deoxy-5-*O*-(*tert*-butyldiphenylsilyl)-α-D-*erythro*-pentofuranoside (**6**)[8b] as shown in Scheme 1. To our surprise, coupling of **10** with **4** under the foregoing conditions provided the 2'-deoxynucleoside **12** in 74% yield and with the β:α ratio of 37:63 (Table 2, entry 1). From the finding that little



Scheme 1 *Reagents and conditions*: a) (i) Tf_2O (1.2 equiv), pyridine, CH_2Cl_2, 0 °C, 30 min; (ii) Et_3N•3HF (3.0 equiv), EtOAc, 50 °C, 8 h, 56% (2 steps from **6**). b) (i) Ph_3P (3.0 equiv), I_2 (2.0 equiv), imidazole (3.0 equiv), $PhCH_3$-MeCN (2:1), 90 °C, 3 h; (ii) TBAF (1.1 equiv), THF, 68% (2 steps from **7**). c) (i) BzCl, pyridine, CH_2Cl_2; (ii) BCl_3•SMe_2 (1.5 equiv), Et_2O, 30 min; (iii) $ClP(OEt)_2$ (1.2 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, -78 °C, 30 min, 26% (3 steps from **8**), 33% (3 steps from **9**).

variation in stereoselectivities was observed using dichloromethane as the solvent (entry 2), it was suggested that an exceptionally high order of β-selectivity attained by coupling of **2** with **4** at -50 °C might be attributable not only to the use of propionitrile as the solvent but more importantly to the α-configuration of the fluorine atom at C3 in the donor. Furthermore, the significance of the C3-α-fluorine atom with large electronegativity as a stereodirecting element was disclosed by replacing it with the iodine atom, wherein glycosylation with **11**[7], prepared from allyl 2-deoxy-5-*O*-(*tert*-butyldiphenylsilyl)-β-D-*threo*-

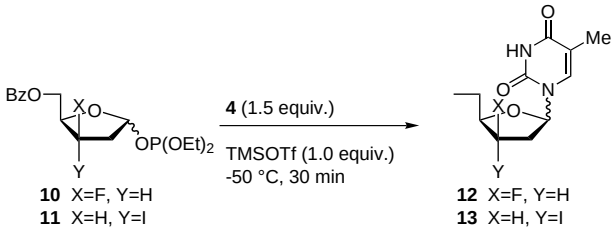


Table 2 Glycosylation of nucleoside base **4** with furanosyl diethyl phosphites **10** and **11**[a,b]

Entry	Donor	Solvent	Yield[c] (%)	β:α[d]	δ^1H[e]
1	**10**	EtCN	74	37:63	6.36 (6.12)
2	**10**	CH_2Cl_2	79	30:70	
3	**11**	EtCN	73	30:70	6.13 (6.10)
4	**11**	CH_2Cl_2	80	23:77	

[a] The anomeric ratio of the phosphites: **10**, 88:12; **11**, 34:66. [b] Donor/acceptor/promoter molar ratio=1.0/1.5/1.0. [c] Isolated total yield based on the donor used. [d] The ratio was determined by 500 MHz ^{1}H NMR. [e] Chemical shifts (δ ppm) in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) for anomeric protons of β anomers. Values in parentheses correspond to those of α anomers.

pentofuranoside (**7**)[8c] as depicted in Scheme 1, displayed modest α-selectivities irrespective of the nature of solvents (entries 3 and 4).

Based on the above results, we may now present the stereochemical reaction course shown in Fig.1, while the precise mechanism remains unclear. The present glycosylation with **2** is assumed to proceed through the intermediacy of the α-nitrilium ion stabilized by the electrostatic interaction[15] with the suitably disposed fluorine atom followed by the backside attack of **4** on this intermediate. A similar stabilizing interaction is not expected with **10** because of the steric repulsion between the C4-substituent and the β-nitrilium ion; thus, the reaction may proceed without participation of propionitrile to give nearly the same selectivity as that observed in dichloromethane.

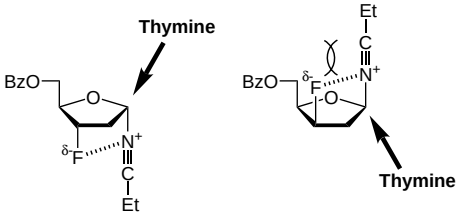


Figure 1 Stereochemical course of glycosylations with **2** and **10**

In conclusion, we have developed a short-step synthesis of FLT by exploiting the glycosyl phosphite method, wherein the key to the success of the present method lies

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in a high-yield coupling in propionitrile at -50 °C. It has also been demonstrated that the α-configuration of the fluorine atom at C3 in the donor is critical to a high order of β-selectivity. We are currently investigating the applicability of our protocol to the synthesis of purine derivatives.

Typical procedure for the preparation of pentofuranosyl diethyl phosphite:

Diethyl phosphorochloridite (0.065 mL, 0.45 mmol) was added to a solution of 5-*O*-benzoyl-2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranose (90 mg, 0.38 mmol) and Et_3N (0.13 mL, 0.94 mmol) in dry CH_2Cl_2 (5 mL) at -78 °C. After stirring at -78 °C for 30 min, the reaction was quenched with ice, followed by stirring at 0 °C for 10 min. The mixture was poured into a two-layer mixture of Et_2O (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole was extracted with EtOAc (30 mL). The organic layer was washed with brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by silica gel column chromatography (8:1:0.5 hexane/EtOAc/Et_3N) furnished the phosphite **2** (95 mg, 70%, α:β=64:36) as a colorless oil. Selected spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (1 H, dd, *J* = 6.6, 5.4 Hz, H-1α), 5.99 (1 H, m, H-1β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.2 (d, *J* = 14.0 Hz, C-1α), 98.4 (dd, *J* = 15.3, 2.3 Hz, C-1β); ^{31}P NMR (109 MHz, $CDCl_3$) δ 138.42 (α), 139.34 (β). HRMS (FAB) calcd for $C_{16}H_{23}FO_6P$ (M^++H) 361.1216, found 361.1191.

Typical procedure for the glycosidation of pentofuranosyl diethyl phosphite:

To a solution of **4** (70 mg, 0.26 mmol) in EtCN (2.5 mL) at -50 °C was added a 1 M solution of TMSOTf in EtCN (0.17 mL, 0.17 mmol), followed by addition of phosphite **2** (62 mg, 0.17 mmol) in EtCN (1 mL). After stirring at -50 °C for 30 min, the reaction was quenched with Et_3N (0.5 mL), and the mixture was poured into a two-layer mixture of Et_2O (10 mL) and sat. aq $NaHCO_3$ (10 mL). The whole was extracted with EtOAc (30 mL), and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by short-path column chromatography on silica gel (1:2 hexane/EtOAc) afforded 5'-*O*-benzoyl-protected FLT **5**[11c] (53 mg, 89%, β:α = 91:9) as a white solid. The ratio was determined by integration of methyl protons at C-5 in 500 MHz ^{1}H NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (3 H, s, 5-Me) (for β-anomer), 1.95 (3 H, s, 5-Me) (for α-anomer).

Acknowledgement

This research was supported in part by a Grant-in-Aid (No.08557119) from the Ministry of Education, Science, Sports and Culture of Japan.

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1437-2096,E;1999,0,08,1274,1276,ftx,en;Y11099ST.pdf

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