Pergamon

Tetrahedron Letters 40 (1999) 1937–1940

TETRAHEDRON LETTERS

An Alternative Synthesis of Antineoplastic 4'-Thiocytidine Analogue 4'-ThioFAC

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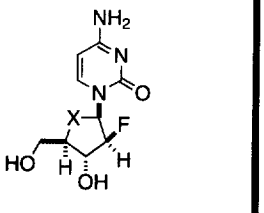
Received 16 November 1998; accepted 28 December 1998

Abstract: We have developed an alternative method for the synthesis of 2'-modified 4'-thionucleosides. The fusion of 3,5-di-*O*-benzoyl-1-bromo-2-deoxy-2-fluoro-4-thio-α-D-arabinofuranose, prepared from 1,2:5,6-diisopropylidene-α-D-allofuranose, with persilylated N^4-acetylcytosine predominantly gave a β-anomer of protected 4'-thionucleoside, which was then deprotected to give 4'-thioFAC.

Previously, we have reported a novel method for the synthesis of 2'-modified 4'-thionucleosides,[1-3] and found that some 2'-substituted-4'-thiocytidine derivatives had potent antineoplastic activities *in vivo* as well as *in vitro*.[1,2,4,5] Among them, 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine (4'-thioFAC, **1**) has shown prominent antitumor activities against various human solid tumor cell lines.[2,5] The most important feature of 4'-thioFAC is that it is an orally active antitumor agent; oral treatment with 4'-thioFAC effectively inhibited the growth of colon and stomach cancer xenografts which had been transplanted into nude mice.[5]



1: X = S (4'-thioFAC)
2: X = O (FAC)

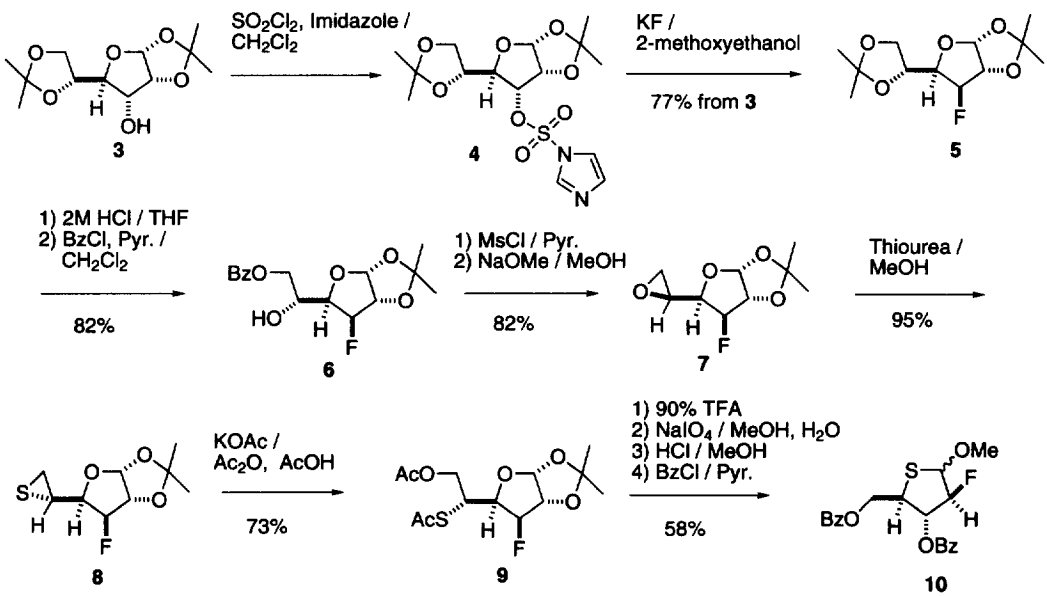
The original synthesis of 4'-thioFAC presented several problems which made its large-scale preparation difficult.[2] For example, an expensive silyl protecting group (*tert*-butyldiphenylsilyl group) and difficult-to-handle reagents, such as DAST, BBr_3, and MCPBA, have been used.[2] Moreover, there was a serious problem at the glycosylation step: the undesired α-isomer was predominantly formed (α : β = 2.5 : 1) and had to be separated from the desired β-isomer by a complicated purification method.[2] To overcome these drawbacks, the development of an alternative synthetic method which can selectively produce β-4'-thioFAC is needed.

To this end, we sought to apply the improved synthesis of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (FAC, **2**), 4'-oxy counterpart of 4'-thioFAC reported by Watanabe,[6] to the synthesis of 4'-thioFAC. In this communication, we report both the alternative synthesis of a 2-fluoro-4-thiosugar derivative, and its stereoselective coupling with persilylated N^4-acetylcytosine, which led to 4'-thioFAC.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00048-9

Following Watanabe's report,[6] commercially available 1,2:5,6-diisopropylidene-α-D-allofuranose **3** should be fluorinated at the C-3 position. Instead of the original method, we used the method developed by Bristol-Myers group[7] with a slight modification. Treatment of **3** with sulfuryl chloride and imidazole in dichloromethane gave an imidazoyl sulfate **4**, which was treated with potassium fluoride in refluxing 2-methoxyethanol to give a 3-fluorinated compound **5** in 77% yield from **3**. Compound **5** was selectively deblocked at the 5,6-isopropylidene group, and the resulting diol was selectively benzoylated at the primary hydroxyl group to give 6-benzoate **6**. Mesylation at the C-5 position of **6** and subsequent treatment with sodium methoxide gave 5,6-epoxide **7** in 82% yield with inversion of the C-5 stereochemistry. The 5,6-epoxide **7** was treated with thiourea in refluxing methanol to give a 5,6-thiirane derivative **8**, the C-5 configuration of which was controlled since it was to be a D-sugar. Cleavage of the 5,6-thiirane ring of **8** was achieved by the treatment with potassium acetate in refluxing acetic anhydride and acetic acid (5 : 1)[8] for 2 days to give a diacetate derivative **9** in 73% yield. The desired 2-fluoro-4-thio sugar **10** was obtained from **9** by 1) acidic hydrolysis of isopropylidene group, 2) oxidation with $NaIO_4$, 3) treatment with acidic methanol, and 4) benzoylation. (Scheme 1)

Scheme 1



As mentioned above, an important goal in this alternative synthesis was to improve the β-stereoselectivity at the glycosylation step. In previous studies by us[1-3] and other groups,[9-13] Lewis acid-catalyzed glycosylation between 4-thiosugar derivatives and nucleobases tended to give α-anomers as major products. Therefore, a glycosylation reaction which would not require a Lewis acid catalyst may improve the β-

stereoselectivity. On the other hand, the previous synthesis of FAC and its related compounds showed that bromination at the anomeric position of the 2-fluoroarabinose derivative selectively gave the corresponding 1-α-bromide, nucleophilic substitution of which with persilylated pyrimidine bases gave β-2-fluoro-arabino pyrimidine nucleosides exclusively.[6,7,14] This encouraged us to investigate the condensation, without Lewis acids, of silylated cytosine and 1-bromo-4-thiosugar, which could be obtained from **10**.

Acetolysis of the 1-methoxy group of **10** gave 1-acetate **11**[15] in good yield. Treatment of **11** with HBr / acetic acid in dichloromethane gave the corresponding 1-bromide **12**. Due to the instability of **12**, it was difficult to confirm its structure and the ratio of α- and β-anomers. It was assumed that the stereoelectronic effect of the 2-fluoro substituent might make a formation of the α-bromide **12** favored, as in the case of the 4-oxy derivative.

Scheme 2

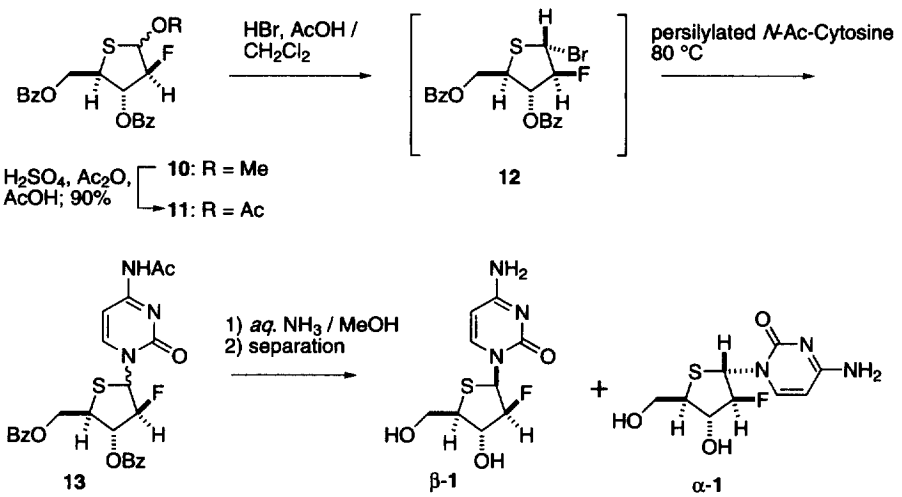


Table 1: Summary of the glycosylation reaction

		yield (from 1-*O*-acetate **11**)		
entry	Conditions	glycosylation	β-**1**	α-**1**
1	$ClCH_2CH_2Cl$, 80 °C, 2 days	trace	-	-
2	neat, 80 °C, 5 h	59% (α : β = 1 : 4)	33%	8%

Thus, 1-bromide **12** was used, without purification, for the next glycosylation step soon after being prepared from **11**. However, our first attempt to obtain the glycosylated product by the condensation of **12** with the persilylated N^4-acetylcytosine was unsuccessful. As shown in entry 1 of Table 1, the reaction in refluxing 1,2-

dichloroethane gave only trace amounts of the glycosylated product. Interestingly, when this reaction was performed by the fusion of **12** with the persilylated N^4-acetylcytosine at 80°C under reduced pressure, the glycosylated product **13** was formed in a yield of 59%.[16] After deprotection of **13** by treatment with *conc.* NH_3 / MeOH, HPLC analysis of the crude products showed that the desired β-anomer of 4'-thioFAC **1** was predominantly formed (α : β =1 : 4), as we expected. The structures of β-**1** and α-**1** were firmly confirmed by comparison of the instrumental analysis data after isolation.

Acknowledgment: The authors are grateful to Prof. A. Matsuda of Hokkaido University for his useful suggestions during this work. The authors also acknowledge Dr. K. Kodama of Yamasa Corporation for his encouragement.

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[15] ^{1}H-NMR($CDCl_3$) δ ppm 8.06-7.94 (m, 4H, Bz), 7.62-7.30 (m, 6H, Bz), 6.24 (dd, 0.42H, H_{1a}, $J_{1,2}$ = 2.0, $J_{1,F}$ = 14.2 Hz), 6.18 (d, 0.58H, H_{1b}, $J_{1,2}$ = 4.4 Hz), 6.08 (ddd, 0.58H, H_{3b}, $J_{3,4}$ = 7.3, $J_{2,3}$ = 9.3, $J_{3,F}$ = 11.7 Hz), 5.85 (dt, 0.42H, H_{3a}, $J_{2,3}$ = $J_{3,4}$= 3.9, $J_{3,F}$ = 12.2 Hz), 5.39 (ddd, 0.42H, H_{2a}, $J_{1,2}$ = 2.0, $J_{2,3}$ = 3.9, $J_{2,F}$ = 47.9 Hz), 5.31 (ddd, 0.58H, H_{2b}, $J_{1,2}$ = 4.4, $J_{2,3}$ = 9.3, $J_{2,F}$ = 50.8 Hz), 4.69 (dd, 0.58H, H_{5ba}, $J_{4,5a}$ = 6.4, $J_{5a,b}$ = 11.2 Hz), 4.55 (dd, 0.42H, H_{5aa}, $J_{4,5a}$ = 7.8, $J_{5a,b}$ = 11.7 Hz), 4.49 (dd, 0.58H, H_{5bb}, $J_{4,5b}$ = 6.4, $J_{5a,b}$ = 11.2 Hz), 4.47 (dd, 0.42H, H_{5ab}, $J_{4,5b}$ = 1.5, $J_{5a,b}$ = 11.7 Hz), 4.11 (ddd, 0.42H, H_{4a}, $J_{3,4}$ = 4.4, $J_{4,5a}$ = 7.8, $J_{4,5b}$ = 1.5 Hz), 3.74 (q, 0.58H, H_{4b}, $J_{3,4}$ = $J_{4,5a}$ = $J_{4,5b}$ = 6.4 Hz), 2.12, 2.11 (s, total 3H, Ac); Anal. Calcd for $C_{21}H_{19}FO_6S$: C, 60.18; H, 4.58. Found: C, 60.06; H, 4.56.
[16] Typical procedure: To a solution of 3.0 g of **11** (7.2 mmol) in 20 mL of CH_2Cl_2 was added 6.0 mL of 30% HBr / acetic acid solution at room temperature in an argon atmosphere. The mixture was stirred at room temperature for 20 min. The reaction was quenched by the addition of ice water. The whole was extracted with CH_2Cl_2 twice, and the combined organic phase was washed with saturated $NaHCO_3$ and ice water, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual **12** was dissolved in CH_2Cl_2. To a solution of silylated N^4-acetylcytosine (prepared from 1.65 g of N^4-acetylcytosine (10.8 mmol) by refluxing with 5.3 mL of bis(trimethylsilyl)acetamide (21.5 mmol) in 20 mL of 1,2-dichloroethane for 3 h.) was added the CH_2Cl_2 solution of **12**. After the solvents were evaporated, the neat mixture was kept at 80 °C for 5 h under reduced pressure (less than 4 mmHg). After cooling to room temperature, $CHCl_3$ was added, and the undissolved materials were removed by filtration. The filtrate was concentrated and the residue was purified over a silica gel column, giving 2.17 g of **13** (59%) as an amorphous foam.