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3-Deoxy-3,3-difluoro-D-arabinofuranose: First Stereoselective Synthesis and Application in Preparation of *gem*-Difluorinated Sugar Nucleosides

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The design and synthesis of *gem*-difluorinated sugar nucleosides were described. The key intermediate, 3-deoxy-3,3-difluoro-D-arabinofuranose **9**, was first stereoselectively prepared from the chiral *gem*-difluorohomoallyl alcohol **12**. The kinetic formation of single *anti*-**14** in the benzylation of **12** could be accomplished by controlling the amount of sodium hydride used. The dihydroxylation of **14** (a mixture of anti and syn isomers) followed by deprotection and oxidation stereoselectively afforded furanose **9** with the arabino configuration at the C2 position. N^1-(3-Deoxy-3,3-difluoro-β-D-arabinofuranosyl)cytosine **6** was prepared from **9** by the glycosylation reaction. 4′-Thiofuranose **25** was easily synthesized from **9**. The oxidation of **25** followed by the condensation with silylated N^4-benzoylcytosine (Pummerer reaction) failed to give our desired protected nucleoside L-3′-deoxy-3′,3′-difluoro- 4′-thiocytidine **27′**, but the regioisomer **27** was obtained. The regiochemistry of the Pummerer reaction was determined by the kinetic acidity of the α-proton of 4′-thiofuranose **25**.

Introduction

The demand for new antiviral and anticancer agents has led to the discovery of a class of modified nucleosides. Fluorinated nucleosides are attractive compounds, with the fluorine incorporated either into the nucleobase or sugar moiety. The introduction of fluorine into the sugar moiety of some nucleosides resulted in compounds with a broad spectrum of antiviral and anticancer activities.[1] Fluorine atom is a good mimic of a proton (small size) or hydroxyl group (similar polarity). Many nucleoside analogues in which fluorine is substituted for hydrogen or hydroxyl on a carbohydrate carbon are known and of considerable interest because of their biological activities. For example, replacement of the 2′-β-hydrogen atom (arabino configuration) or the 3′-hydroxyl group of natural thymidine by fluorine afforded new nucleosides with potent antiviral properties, FMAU[2] (**1**, Figure 1) and FLT[3] (**2**, Figure 1), respectively. The *gem*-difluoromethylene (CF_2) has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen.[4] Analogues of di- and triphosphates in which the CF_2 group has replaced the pyrophosphate oxygen have been used as substrates in enzymatic reactions.[4c,d,5] Since then, the CF_2 group was used extensively to modify not only nucleotide but also nucleoside analogues. For example, 2′-deoxy-2′,2′-difluorocytidine (gemcitabine, **3**, Figure 1) has been approved as a drug for solid tumor treatment.[6] However, the 3′-deoxy-3′,3′-difluoro nucleosides have been much less studied,[7] which is probably due to the shortcomings of existing synthetic methods. Recently, a number of the L-configuration nucleoside analogues, the enantiomers of the natural D-nucleosides, have emerged as potent anti-

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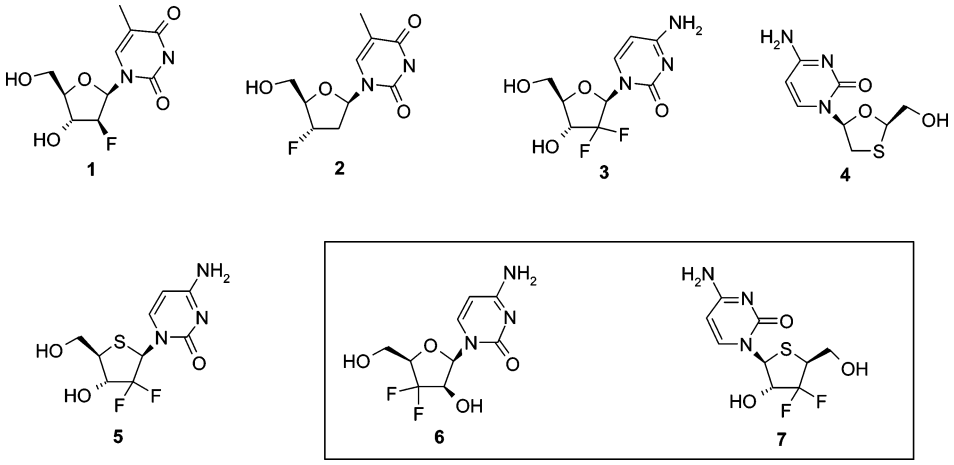
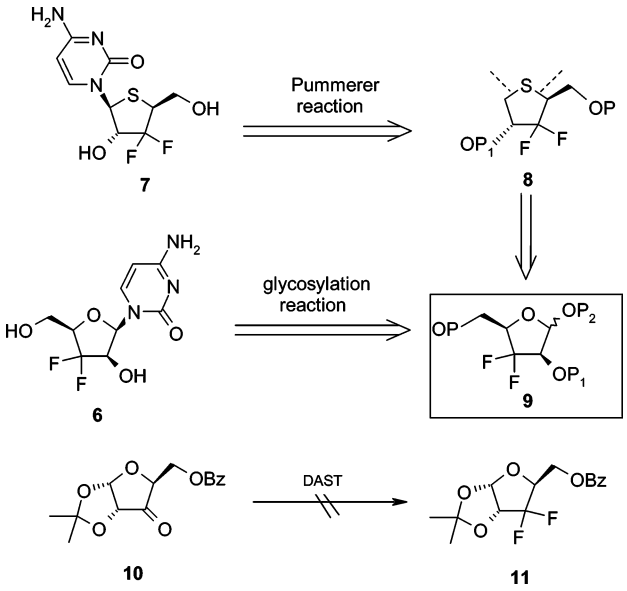


FIGURE 1. Rationale for the design of the target molecules **6** and **7**.

viral agents against HIV and HBV.[8] L-Nucleosides are generally endowed with a lower host toxicity while maintaining good antiviral activity in comparison with their corresponding D-nucleosides. One of the first L-nucleoside derivatives, L-2′,3′-dideoxy-3′-thiacytidine (lamivudine, **4**; Figure 1), has been approved by FDA for use in combination therapy against HIV and HBV.[9] 4′-Thionucleosides, in which the furanose ring oxygen is replaced by a sulfur atom, have been studied extensively over the past 10 years because of their potent biological activity.[10] Notably, the resistance of the glycosidic bond of 4′-thionucleosides to enzymatic hydrolysis catalyzed by nucleoside phosphorylase is one of the advantages as nucleoside antiviral agents.[11] This has been applied to the 2′-deoxy-2′,2′-difluorinated nucleosides; e.g., 2′-deoxy-2′,2′-difluoro-4′-thiocytidine (**5,** Figure 1**)** has potent activity against human T-cell leukemia CCRF-HSB-2 cells.[10e,12]

SCHEME 1



Based on the above consideration and our ongoing efforts to develop new antiviral and anticancer agents, we designed our target molecules N^1-(3-deoxy-3,3-difluoro-D-arabinofuranosyl)cytosine (**6**, Figure 1) and L-3′-deoxy-3′,3′-difluoro- 4′-thiocytidine (**7**, Figure 1). The *gem*-difluoromethylene (CF_2) group was at the C3′ position of compounds **6** and **7**. Moreover, compounds **6** and **7** would combine the characteristics of compounds **1**−**5** based on the bioisosteric rationale (Figure 1). Our retrosynthetic analysis (Scheme 1) was based on the thought that the target molecule **7** could be derived from the precursor of type **8**, which could be used to introduce a base moiety at the C1 position via Pummerer rearrangement.[10e,13] We envisioned that the *gem*-difluorinated furanose **9** would be a suitable precursor for **8**. At the same time, the target compound **6** could be prepared from **9** by the glycosylation

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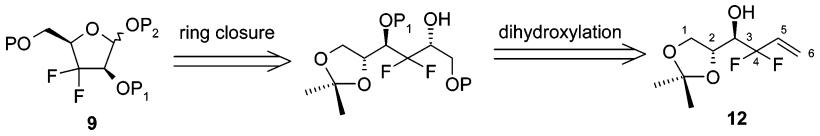
SCHEME 2

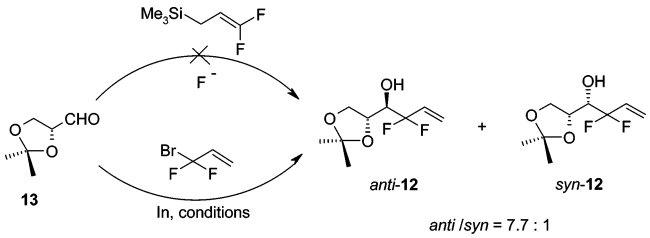


reactions. The preparation of **9**, however, appeared to be a great challenge. The *gem*-difluoromethylene group is frequently prepared through the difluorination of a carbonyl group. The reagents commonly utilized for this transformation are SF_4,[14] SeF_4,[15] MoF_6,[16] $PhSF_3$,[17] and (diethylamino)sulfur trifluoride (DAST).[18] Only DAST is commercially available. However, very few sterically hindered five-membered cyclic ketones have been difluorinated by DAST. *gem*-Difluorinated furanose **9** has not been synthesized via this method. Very recently, Chu et al. reported difluororibose derivative **11** could not be obtained from ketone **10** in the classic fluorinating conditions (Scheme 1).[7c] Even when the reaction was run in neat DAST, no products could be detected, and attempts to increase the reactivity by raising the temperature only caused decomposition of **10**. Furthermore, in the only example of difluorination of an α,α′-trans-disubstituted five-membered cyclic ketone found in the literature, the carbonyl group is relatively unhindered, and the yield is low (25%).[19] Moreover, the synthetic method reported for this type is rare. As *gem*-difluorinated furanose **9** is a key intermediate in the synthesis of our designed target molecules **6** and **7** (Scheme 1), it is necessary to develop a new methodology for its preparation. Herein, we describe the first efficient and stereoselective route to 3-deoxy-3,3-difluoro-D-arabinofuranose **9** and its application in the synthesis of *gem*-difluorinated sugar nucleosides.

Results and Discussion

Synthesis of 3-Deoxy-3,3-difluoro-D-arabinofuranose 9. Scheme 2 illustrated that key intermediate **9** was formally derived from the chiral *gem*-difluorohomoallyl alcohol **12** through dihydroxylation and followed by ring closure. To control the absolute configuration of the target compound, one could perform the synthesis in an enantioselective fashion. To obtain the *gem*-difluorohomoallyl alcohol **12**, the coupling of the *gem*-difluoroallylic metal species with carbonyl compounds was investigated.[20] 1-(*R*)-Glyceraldehyde acetonide **13** was used as the starting material. Initial attempts to synthesize the

SCHEME 3



conditions	yield(%)
In, H_2O, rt.	11
In, H_2O / DMF (1:1), rt.	34
In, DMF, rt.	90

difluorohomoallyl alcohol **12** by the reaction of aldehyde **13** with (α,α-difluoroallyl)silane[21] in the presence of fluoride anion failed to produce the desired compound **12** (Scheme 3). Fortunately, using the *gem*-difluoroalllylindium generated from 3-bromo-3,3-difluoropropene and indium in DMF instead of (α,α-difluoroallyl)silane afforded compound **12** in high yield.[22] The ratio of anti/syn of compound **12** is 7.7/1 determined by ^{19}F NMR. The signal of the difluoromethylene group in *anti*-**12** appeared at higher field than that in *syn*-**12** in the ^{19}F NMR spectrum.[23] Notably, the *anti*-**12** isomer is our desired compound.

Benzylation of **12** was easily accomplished with sodium hydride (1.6 equiv) and catalytic tetrabutylammonium iodide, followed by benzyl bromide in 93% yield, but the ratio of anti/syn of **14** was changed to 5.7/1 (Scheme 4). This was due to the electron-withdrawing effect of the difluoromethylene group, which could make the hydrogen of the C3 position possess some acidity. The configuration of the C3 position was slightly racemized under basic conditions (see the following section for detailed discussion). The Os-catalyzed dihydroxylation of compounds **14** gave the mixture of compound **15** and **16** in 95% yield (**15**/**16** ≈ 1/1). Compounds **15** and **16** could be separated by column chromatography. Fortunately, when compound **14** was subjected to the reaction conditions of catalytic asymmetric dihydroxylation (AD) of 3,3,3-trifluoropropene reported by Sharpless et al. using $(DHQ)_2PYR$ as a

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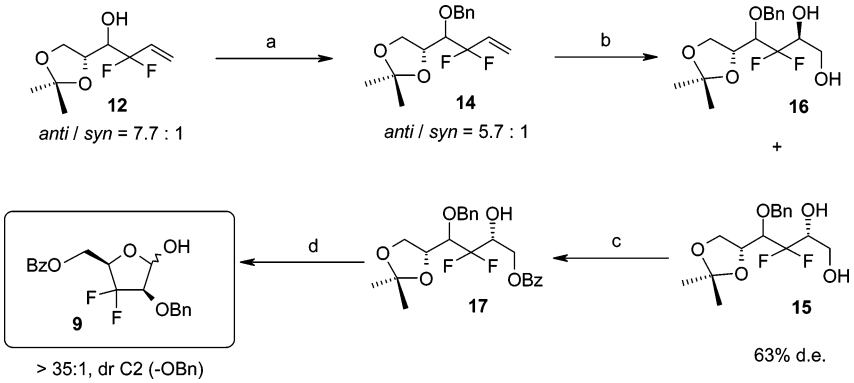
SCHEME 4 . Synthesis of 3-Deoxy-3,3-difluoro-D-arabinofuranose 9[a]



[a] Key: (a) NaH (1.6 equiv), BnBr, TBAI, THF, 0 °C, 12 h; (b) $(DHQ)_2PYR$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 63% de, or OsO_4, NMNO, acetone/H_2O, rt, 2 d; (c) BzCl, Py, CH_2Cl_2, −78 °C, 2 h; (d) (i) 75% AcOH, 50 °C, 1.5 h, (ii) $NaIO_4$, acetone/H_2O, rt., 1.5 h.

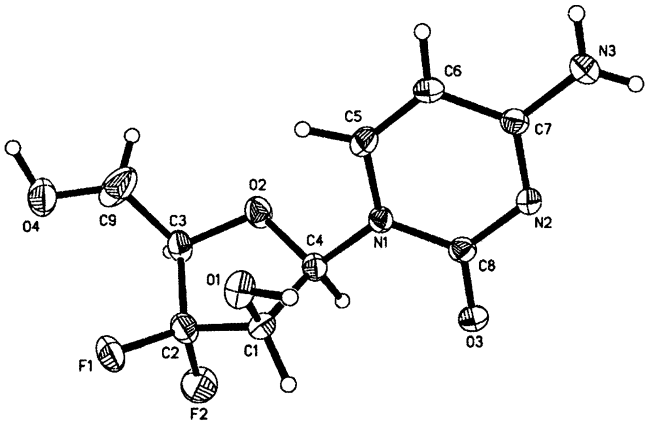


FIGURE 2. ORTEP drawing of the X-ray crystallographic structure of **6**.

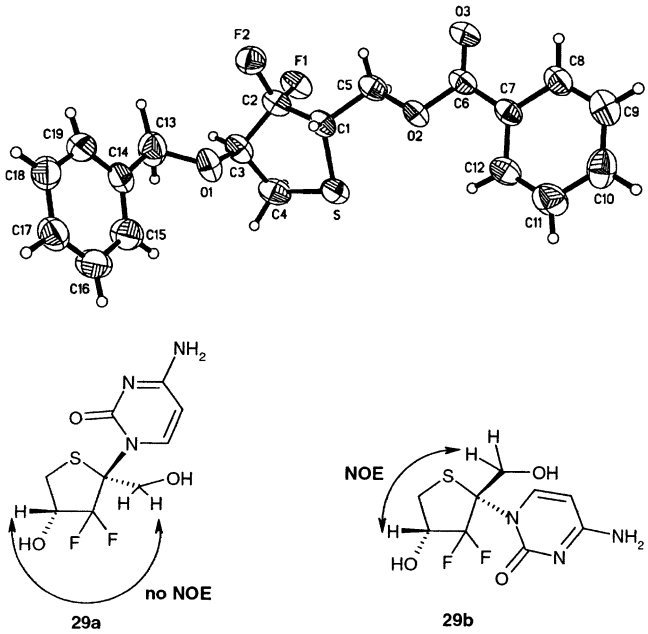


FIGURE 3. ORTEP drawing of the X-ray crystallographic structure of **8** and NOE correlations from NOESY spectra of **29a** and **29b**.

ligand,[24] compound **15** was isolated in 60% yield (dr **15**/**16** = 4.4/1) (Scheme 4). Selective benzoylation at the primary hydroxyl group of the resulting diol **15** at −78 °C gave benzoate **17** in 90% yield. The conversion of **17** to the desired intermediate **9** was achieved by the following two steps: (1) the acidic hydrolysis of the isopropylidene group by treatment with 75% acetic acid at 50 °C and (2) the oxidative scission of the resulting diol with sodium periodate and subsequent cyclization. Compound **9** was obtained in 94% yield from **17**. It was noteworthy that the compound **9** (>35/1, C2 (−OBn) dr determined by ^{19}F NMR before column**)** was formed in two isomers. Both ^{1}H NMR and ^{19}F NMR spectra showed the ratio of these two isomers was 1:1. This was a stereospecific conversion resulting in the formation of the furanose **9** withan arabino configuration at C2 position (see the following section for detailed discussion). The C2 absolute configuration of **9** was determined by the X-ray crystal structure of **6** and **8** (Figures 2 and 3). Thus, we first succeeded in stereoselectively synthesizing the 3-deoxy-3,3-difluoro-D-arabinofuranose **9** from aldehyde **13** in an efficient way (34% overall yield, six steps).

Epimerization of Compound 12 in Benzylation. As shown in Scheme 4, when **12** was subjected to benzylation reaction conditions, the ratio of anti/syn was changed from 7.7/1 (**12**) to 5.7/1 (**14**). To study the epimerization of compound **12**, different equivalents of sodium hydride were used in the benzylation (Table 1). Surprisingly, when the *gem*-difluorohomoallyl alcohol **12** reacted with less than 1.0 equiv of sodium hydride, only one isomer *anti*-**14** was obtained (entries 1 and 2). Furthermore, the more sodium hydride was used, the less compound **12** was recovered, and the more *syn*-**12** was enriched in the recovered **12**. Notably, based on the yield and the ratio of anti/syn-recovered **12** and formed **14**, respectively (entries 1−2), no epimerization happened in recovered **12** and product **14**. These results suggested that this was a kinetic resolution and the reactivity of *anti*-**12** seemed to be much more active than that of *syn*-**12**. So we can obtain the single *anti*-**14** by controlling the amount of sodium hydride used in the benzylation of compound **12**. The ratio of *anti*/*syn*-**14** was similar to that of *anti*/*syn*-**12** in the case of 1.0 equiv of sodium hydride

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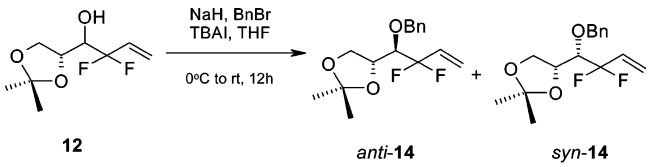
TABLE 1. Benzylation of 12 with Different Equivalents of Sodium Hydride



entry	NaH (equiv)	product **14** anti/syn[a]	recovered **12** anti/syn[a]	yield[b] (%)
1	0.6	21.0/1	2.8/1	(35.6);[c] 75.5
2	0.8	21.8/1	1.8/1	(25.0);[c] 78.5
3	1.0	8.2/1		80.0
4	1.2	6.1/1		87.4[d]
5	1.6	5.7/1		93.1[d]

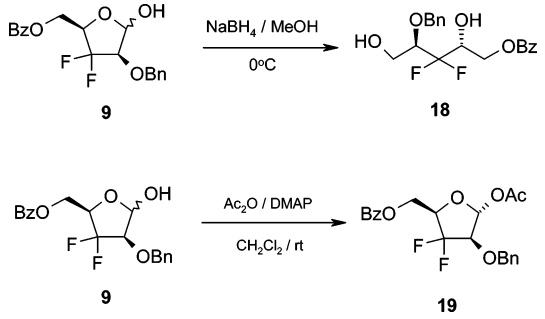
[a] Determined by ^{19}F NMR before column chromatography purification. [b] Isolated yield based on the NaH. [c] Recovery of the substrate **12**. [d] Isolated yield based on the compound **12**.

(entry 3). When 1.2 equiv of sodium hydride was used, the epimerization happened, and the ratio of *anti*/*syn*-**14** was 6.1/1 (entry 4). Interestingly, when 1.6 equiv of sodium hydride was used, further epimerization happened, but product **14** was isolated in the highest yield (entry 5). No doubt, the epimerization of product **14** at the C3 position did not happen until it was formed. The more excess base was used, the more epimeric product *syn*-**14** was obtained. Although the *gem*-difluoromethylene (CF_2) has been suggested as an isopolar and isosteric substituent for oxygen, it is still an electron-withdrawing group and thus could make the hydrogen of C3 position in **14** with some acidity. The excessive base could make the racemization happen.

The Stereospecific Conversion of 17 to the Furanose 9 with Arabino Configuration at the C2 Position. As described in Scheme 4, the C2 (−OBn) configuration of **17** was stereospecifically transformed into a single arabino configuration in compound **9**. To further verify this stereospecific transformation, a series of experiments were examined. It would be expected that an optically pure product could be obtained in the ring opening of furanose **9** if it was a 1/1 mixture of α/β anomers. In addition, in our previous paper,[25] acetylation of lactol with acetic anhydride would give almost a single anomer at room temperature, when the C2 position at the lactol was substituted with a large group in a single configuration. This is due to the assitance of the neighboring group participation. Accordingly, treatment of furanose **9** with sodium borohydride in methanol gave the diol **18** in quantitative yield (Scheme 5). Both ^{19}F NMR and ^{1}H NMR spectra of the crude reaction mixture showed that only one compound was produced. At the same time, as it would be expected, 3-deoxy-3,3-difluoro-D-arabinofuranose **9** was subjected to acetic anhydride at room temperature, the α anomer **19** was obtained nearly as a single product (Scheme 5, α/β = 17.0/1 determined by ^{19}F NMR before column, 94% yield). These results further confirmed that the C2 (−OBn) in compound **9** had the arabino configuration.

The proposed mechanism of this stereospecific transformation was described in Scheme 6. The aldehyde

SCHEME 5. Ring Opening and Acetylation of Furanose 9



intermediates **I** and **II** formed from compound **17** were in tautomeric equilibrium, and anomerization at this carbon could occur easily due to the electron-withdrawing effect of difluoromethylene (Scheme 6). The stereospecific formation of the furanose **9** from intermediate **I** with the arabino configuration at C2 position was thought to be faster than the formation of furanose **9′** from intermediate **II**. At the same time, the intermediate **II** could be easily transformed into intermediate **I** via conformer **III** due to the energy deference between these two intermediates. In addition, the attack of the free hydroxyl group of **I** on the carbonyl group (possible from both the *re* and *si* face of the aldehyde moiety) resulted in a 1:1 mixture of α/β anomers of **9**.

Furthermore, the formation of **9** from intermediate **I** was proved through the transformation of *anti*-**14** (Scheme 7). The *anti*-**14** was obtained through kinetic resolution of **12**. The transformation of *anti*-**14** to **9** was carried out under the same reaction conditions as described in Scheme 4 for **14**. Both ^{1}H NMR and ^{19}F NMR spectra of **9** synthesized from *anti*-**14** were identical to those of compound **9** prepared from **14** (Scheme 4). It should be mentioned that ^{1}H NMR and ^{19}F NMR spectra were determined before column chromatography so that any products could not be lost. These results suggested that the *S*-configuration of the C2 position at intermediate **II** should turn into the *R*-configuration and the furanose **9** was formed from the intermediate **I**.

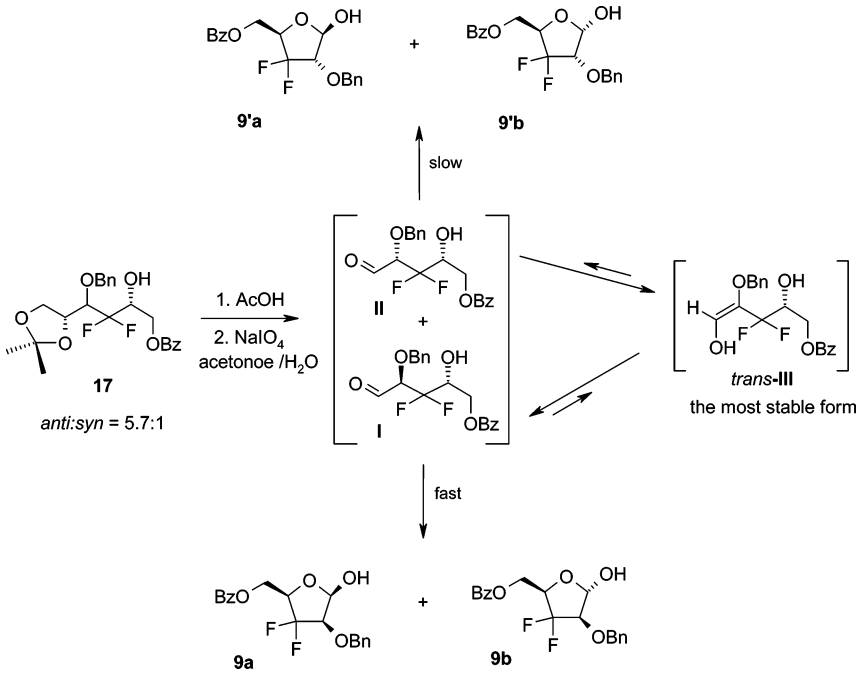
Synthesis of N^1-(3-Deoxy-3,3-difluoro-D-arabinofuranosyl)cytosine 6. The Vorbruggen glycosylation reaction of pyrimidines with peracylated ribose usually proceeds efficiently and stereoselectively at room temperature to yield the β-anomer.[26] However, the glycosylation of silylated N^4-benzoylcytosine with **19** in the presence of either trifluoromethylsilyl trifluoromethanesulfonate or $SnCl_4$ at room temperature failed to give any protected N^1-(3-deoxy-3,3-difluoro-D-arabinofuranosyl)-cytosine **20**. Fortunately, when the reaction temperature rose to 80 °C, the nucleoside **20** was isolated in 70% yield as a mixture of two isomers (**20a**/**20b** = 1/1, Scheme 8) along with the recovery of **19** (9%). Compounds **20a** and **20b** could be resolved by column chromatography. This may be explained in terms of the so-called armed−diarmed principle reported by Mootoo et al.[27] Deprotec-

(25) Zhang, X.; Qing, F.-L.; Yu, Y. *J. Org. Chem.* **2000**, *65*, 7075.

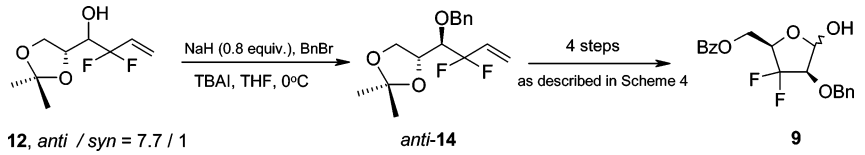
(26) (a) Niedballa, U.; Vorbruggen, H. *J. Org. Chem.* **1974**, *39*, 3654. (b) Niedballa, U.; Vorbruggen, H. *J. Org. Chem.* **1976**, *41*, 2084. (c) Vorbrugen, H. Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234. (d) Vorbruggen, H.; Hofle, G. *Chem. Ber.* **1981**, *114*, 1256.

(27) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

SCHEME 6. Proposed Mechanism of the Stereospecific Conversion of Compound 17 to Furanose 9 with Arabino Configuration at the C2 Position



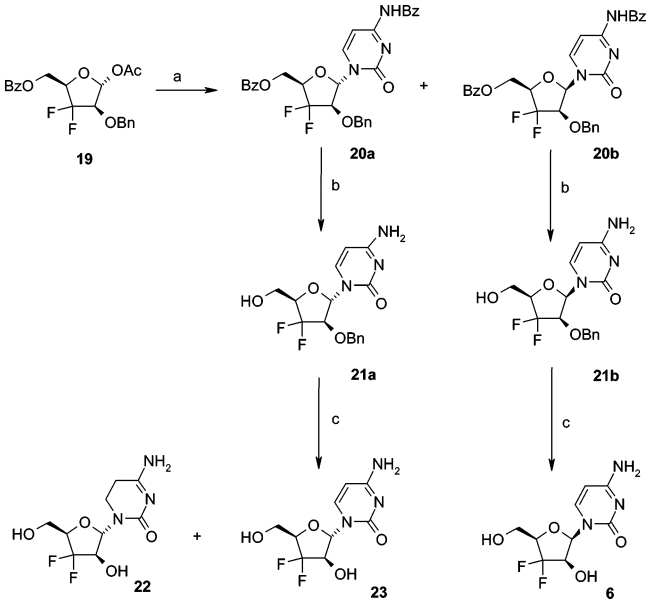
SCHEME 7. Synthesis of 9 from anti-14



tion of the benzoyl of **20a** and **20b** in the presence of a saturated solution of ammonia in methanol gave the C2′ position benzyl-protected α-cytidine **21a** in 92% yield and *β*-cytidine **21b** in 88% yield, respectively. The 2′-benzyl group of **21a** was removed with hydrogen and 20% Pd-$(OH)_2$ on charcoal in methanol and cyclohexane at room temperature for 12 h.[28] It was found that over-hydrogenated compound **22** was formed in 76% yield. When the reaction time was shortened to 2.5 h (the starting material just disappeared), 49% of the N^1-(3-deoxy-3,3-difluoro-α-D-arabinofuranosyl)cytosine **23** was obtained along with 10% of over-hydrogenated product **22**. Attempts to improve the yield of **23** under other hydrogenation conditions failed. For example, treatment of **21a** with hydrogen in the presence of Pd/C in THF at room temperature resulted in the cleavage of the glycosyl bond. To our delight, hydrogenation of **21b** under the catalysis of 20% $Pd(OH)_2$ on charcoal in methanol and cyclohexane afforded our target molecule N^1-(3-deoxy-3,3-difluoro-*β*-D-arabinofuranosyl)cytosine **6** in 83% yield. This indicated that protected cytidine **21a** was more reactive than **21b**.

The configuration of the anomeric center was assigned mainly by ^{1}H NMR, in which the anomer with H4′ at lower field was assigned as the α anomer and the one at higher field was assigned as the *β* anomer on the basis of the deshielding effect of the base moiety.[29] This assignment was further confirmed by the X-ray crystallography of **6** (Figure 2).

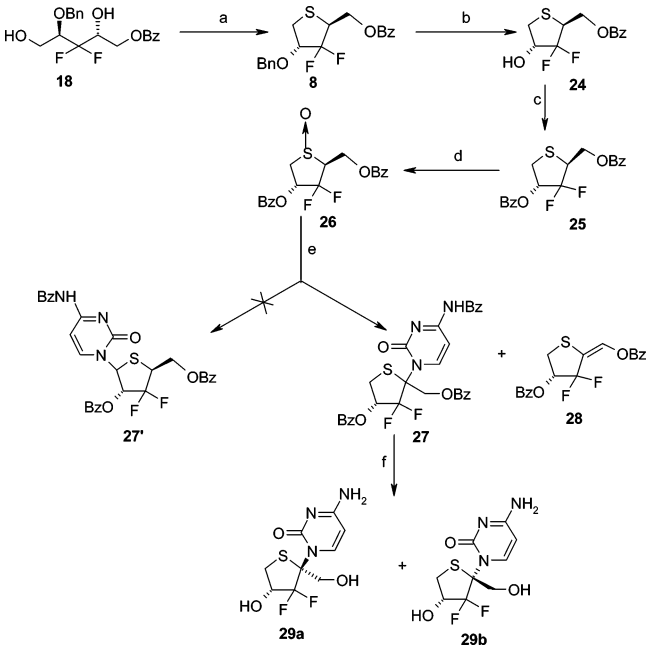
SCHEME 8. Synthesis of N^1-(3-Deoxy-3,3-difluoro-D-arabinofuranosyl)cytosine 6[a]



[a] Key: (a) N^4-benzoylcytosine, *N*,*O*-bis(trimethylsilyl)acetamide, TMSOTf, CH_3CN, from 0 to 80 °C, 36 h; (b) saturated NH_3/MeOH, rt, 12 h; (c) H_2 (1 atm), 20% of $Pd(OH)_2$ on charcoal, MeOH/cyclohexane (3:1), rt, 2.5 h.

(28) Tippie, M. A.; Martin, J. C.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *Nucleosides Nucleotides* **1984**, *3*, 525.

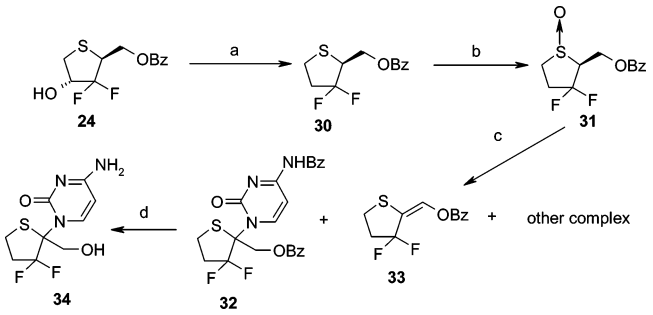
SCHEME 9. Synthesis of Difluorothionucleosides 29 via the Pummerer Reaction[a]



[a] Key: (a) (i) MsCl, Py/CH_2Cl_2, from 0 °C to rt, 12 h; (ii) $Na_2S{\cdot}9H_2O$, DMF, 100 °C, 1 h; (b) BCl_3 (1 M in CH_2Cl_2), MeOH, satd aq $NaHCO_3$, −70 °C, 3 h; (c) Bz_2O, Et_3N, DMAP, CH_3CN, rt, 2 h; (d) *m*-CPBA, CH_2Cl_2, −40 °C, 40 min; (e) silylated N^4-benzoylcytosine, TMSOTf, DCE, 0 °C, 50 min; (f) satd NH_3/MeOH, rt., 12 h.

Attempt To Prepare L-3′-Deoxy-3′,3′-difluoro- 4′-thiocytidine 7. As shown in Scheme 1, 4′-thiofuranose **8** was a key precursor for the synthesis of **7**. To synthesize the 4′-thiofuranose derivatives, the methods reported by Dyson et al. [30] and Leydier et al.[31] seemed to be the most promising. The synthetic tactics involved two consecutive S_N2 reactions of D-ribose. Accordingly, compound **8** was prepared as shown in Scheme 9. Mesylation at the C1 and C4 positions of **18**, followed by treatment with sodium sulfide in DMF, resulted in a ring closure to thiofuranose **8** with a single configuration isomer in 69% yield for the two steps with inversion of the stereochemistry at C4 position. The absolute configuration of compound **8** was determined by X-ray crystal structure (Figure 3). Treatment of **8** with boron trichloride in methylene chloride followed by quenching with methanol and saturated aqueous sodium bicarbonate afforded compound **24** in quantitative yield. The alcohol **24** was reacted with benzoic anhydride, triethylamine, and catalytic DMAP in CH_3CN to give benzoate **25** in quantitative yield. Surprisingly, the oxidation of **25** with *m*-CPBA followed by condensation with silylated N^4-benzoylcytosine failed to give our desired protected nucleosides **27′**, but the regioisomer **27** was obtained in 47% yield (two steps) along with β-elimination product **28** in 22% yield (two steps). The ^{19}F NMR spectrum of compound **27** showed it was an epimeric mixture and the epimeric ratio was 1:1. These two epimeric isomers could not be separated by column chromatography. The removal of benzoyl groups of **27** with a saturated solution of ammonia in methanol provided the separated nucleosides **29a** (41% yield) and **29b** (42% yield). The steric assignments of the final compounds were confirmed by the NOESY experiments of **29a** and **29b** (Figure 3).

SCHEME 10. Synthesis of Difluorothionucleosides 34 via the Pummerer Reaction[a]



[a] Key: (a) (i) PhOC(S)Cl, DMAP, CH_3CN, from 0 °C to rt, 12 h, (ii) Bu_3SnH, AIBN, toluene, 80 °C, 40 min; (b) *m*-CPBA, CH_2Cl_2, −40 °C, 40 min; (c) silylated N^4-benzoylcytosine, TMSOTf, DCE, 0 °C, 30 min; (d) saturated NH_3/MeOH, rt, 12 h.

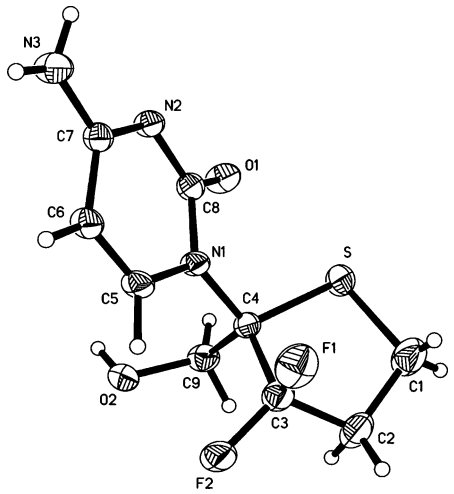


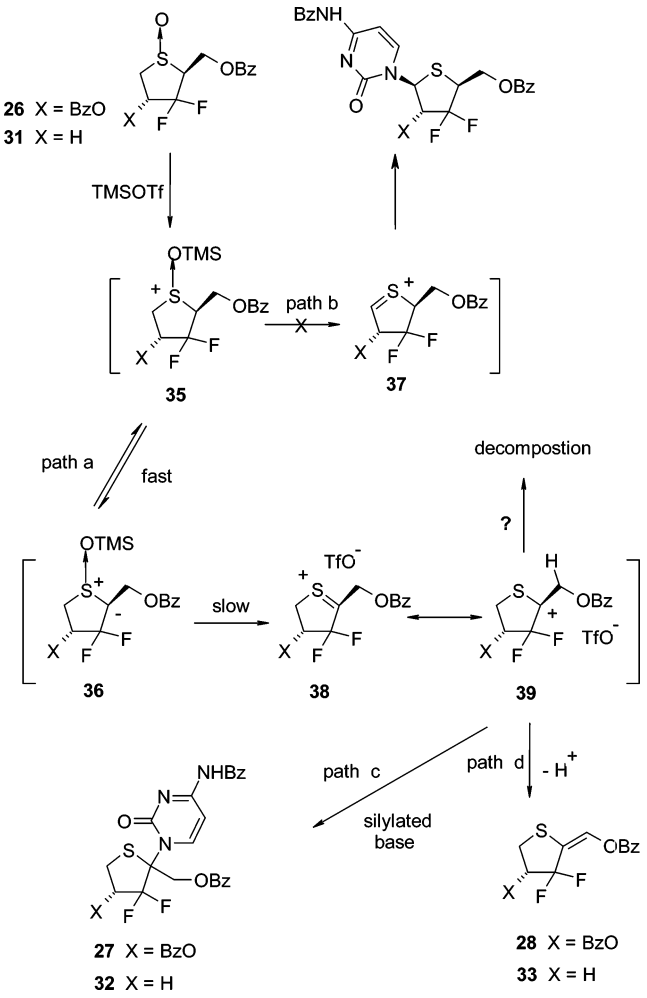
FIGURE 4. ORTEP drawing of the X-ray crystallographic structure of **34**.

To further confirm the structure of nucleosides **29a**,**b** and the regiochemistry of Pummerer reaction of the *gem*-difluorinated thiofuranose, the Pummerer reaction of *gem*-difluorinated thiofuranose **30** was investigated. Conversion of **24** to the phenoxythiocarbonyl derivative followed by the radical deoxygenation of the latter gave compound **30** in 80% yield (Scheme 10). Interestingly, oxidation of **30** with *m*-CPBA followed by the condensation with silylated N^4-benzoylcytosine also gave the racemic nucleoside **32** (38% yield, two steps) and β-elimination product **33**. Deprotection of compound **32** was accomplished by ammonolysis to give nucleoside **34** in 85% yield. The structure of **34** was determined by ^1H NMR spectroscopy and further confirmed by X-ray crystallography (Figure 4).

To date, numerous investigations have been carried out to clarify the mechanism of the Pummerer reaction.[32] Depending on the structures of the starting sulfoxides,

(29) Chun, B. K.; Olegen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685.
(30) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carbohydr. Res.* **1991**, *216*, 237.
(31) Leydier, C.; Bellon, L.; Barascut, J.-L.; Deydier, J.; Maury, G.; Pelicano, H.; Alaoui, M. A. E.; Imbach, J.-L. *Nucleosides Nucleotides* **1994**, *13*, 2035.

SCHEME 11. Proposed Mechanism of the Pummerer Reaction of *gem*-Difluorinated Sulfoxides 26 and 31



both E1cb and E2 pathways are known to give the α-thiocarbocation intermediates. In our reaction, the E1cb mechanism could be used to explain the formation of the unexpected nucleosides. As illustrated in Scheme 11, trimethylsilylation of the sulfoxide by TMSOTf to give **35** was the initial step of the Pummerer reaction.[31d] In the following step, two properly positioned protons could be removed, so there were two pathways in this step. It is well-known that Elcb Pummerer reactions are observed when the substituted group at the *β*-position of sulfonium salt is an electron-withdrawing group and the more acidic proton is preferable to be removed. Thus, the presence of difluoromethylene in our reaction facilitated proton removal of **35** to produce trimethylsilylsulfonium ylide **36** via path a instead of path b, while at the same time retarding departure of the leaving group due to strong inductive effects of difluoromethylene. Although the steric effect is a major factor in the regiochemistry of the Pummerer reaction, it is less important than the acidity of the α-proton in our reaction. This ylide subsequently underwent concurrent electron reorganization and S−O bond cleavage to give the ion pair **38**. This step was rate determining in the reaction in which proton removal was fast and reversible and S−O bond cleavage was slow. In the final step, condensation of silylated N^4-benzoylcytosine with **39** gave the regioisomer nucleoside **27** or **32**. But in this step, two pathways, nucleophilic attack (path c) and *β*- elimination (path d), would occur. These two paths competed with each other, and path c might be more preferable than path d.

In summary, we have developed a stereoselctive and efficient method to synthesize 3-deoxy-3,3-difluoro-D-arabinofuranose **9**, which was proved to be a useful intermediate for the synthesis of difluoronucleoside analogues. At the same time, we studied the epimerization of compound **14** and found that the benzylation of alcohol **12** with less than 1.0 equiv of sodium hydride could kinetically resolve compound *anti*-**14**. In addition, the stereospecific conversion of the C2 (−OBn) configuration of **17** to a single arabino configuration in compound **9** was studied. The furanose **9** with the arabino configuration at the C2 position was thought to be formed from aldehyde **I,** since the intermediate **II** could be easily transformed into **I** via enolate **III**.

With the difluorinated furanose **9** as the key intermediate, the first synthesis of N^1-(3-deoxy-3,3-difluoro-*β*-D-arabinofuranosyl)cytosine **6** was accomplished in 10 steps. 4′-Thiofuranose **25** was easily synthesized from **9**. The oxidation of **25** followed by the condensation with silylated N^4-benzoylcytosine (Pummerer reaction) failed to give our desired protected nucleoside L-3′-deoxy-3′,3′-difluoro-4′-thiocytidine **27′**, but the regioisomer **27** was obtained. The regiochemistry of the Pummerer reaction was determined by the kinetic acidity of the α-proton of 4′-thiofuranose **25**.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds and crystallographic data for compounds **6**, **8**, and **34** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO034512I

(32) (a) Johnson, C. R.; Sharp, J. C.; Phillips, W. G. *Tetrahedron Lett.* **1967**, 5299. (b) Davenport, D. A.; Moss, D. B.; Rhodes J. E.; Walsh, J. A. *J. Org. Chem.* **1969**, *34*, 3353. (c) Jones, D. N.; Helmy, E.; Whitehouse, R. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1329. (d) Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 909−947 and references therein.