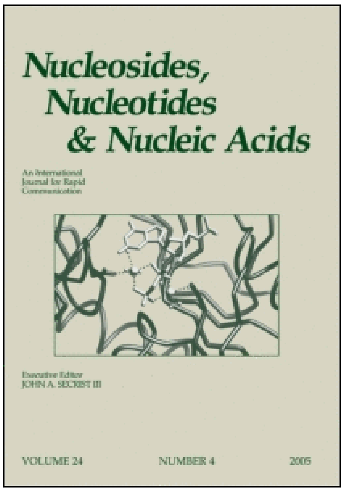

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An Industrial Process for Synthesizing Lodenosine (FddA)

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ABSTRACT

Two industrial synthetic approaches to Lodenosine (**1**, FddA, 9-(2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl) adenine) via a purine riboside or a purine 3′-deoxyriboside are described. Several novel applications of deoxygenation and fluorination methods are compared considering reaction yields, economy, safety and environmental concerns.

Key Words: Anti-HIV; Nucleosides; Lodenosine; Fluorination; Radical reduction.

INTRODUCTION

Lodenosine [9-(2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl) adenine, FddA, **1**] is an acid-stable purine nucleoside analog with activity against human immunodeficiency virus (HIV).[1] It acts as an inhibitor of HIV reverse transcriptase (RT), like other nucleosides derivatives such as zidovudine (AZT), 2′,3′-dideoxyadenosine (**2**, ddA), and didanosine (**3**, ddI) (Fig. 1). FddA was evaluated as one of the most

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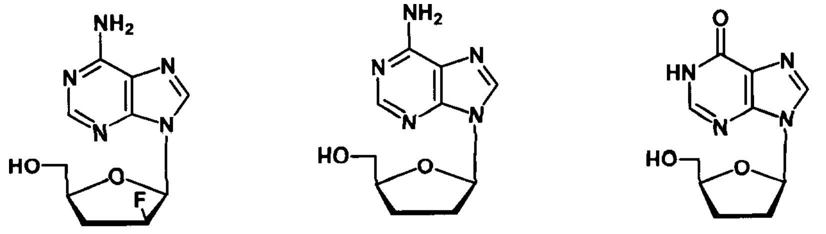
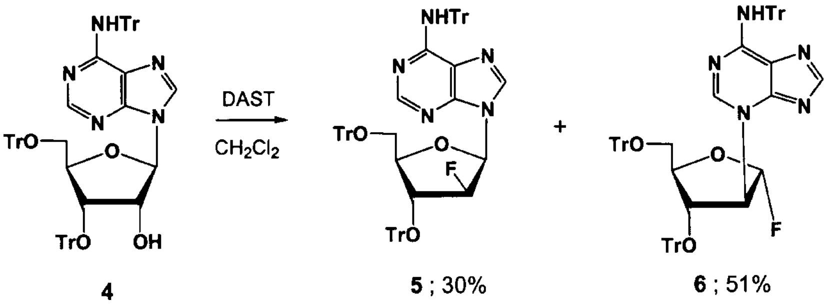


1: FddA (Lodenosine) **2**: ddA **3**: ddI (Didanosine)

Figure 1. 2′,3′-Dideoxy purinenucleosides.

selective inhibitors in a series of 2′,3′-dideoxyadenosines with either an azido, fluorine, or hydroxy group substituted in the "up" or "down" positions of C-2′ and C-3′ of the ribose moiety, although it was less active than the parent compound, ddA, **2**.[2] In addition, it showed the best selectivity index (activity versus cellular toxicity) in the series.[2] An advantage of FddA is its stability under acidic conditions which decompose ddA and ddI.[1a,1b] Other promising aspects are that FddA does not exhibit cross-resistance to AZT, zalcitabine (ddC) and ddI,[3] and even has synergistic activity with AZT.[4] FddA also acts in synergy with other anti-HIV agents including HIV protease inhibitors like Ritonavir, and thus provides new possible combination therapy protocols for HIV.[5] Hence, FddA was developed as a novel anti-HIV agent exhibiting significant advantages in terms of higher stability, high oral bioavailability[6] and effectiveness against strains resistant to existing dideoxynucleosides.[7]

The first synthesis of FddA, **1**, was reported in 1987 by Herdewijn et al.[2] 3′-Deoxyadenosine (cordycepin) was used as a starting material, and is easily prepared from adenosine using the method reported by Hansske and Robins.[8] 5′-*O*-Tritylcordycepin was treated with diethylaminosulfur trifluoride (DAST) followed by detritylation to give FddA, **1**, in a 10% overall yield after purification. Several years later, we examined a similar reaction with the 5′-*O*-acetyl compound, but the yield was also very poor.[9] At almost the same time as the first synthesis, Marquez and co-workers extensively studied the synthesis of FddA and reported several methods.[10] Some of their approaches involved the coupling of a fluorinated sugar to a purine derivative. Although these reaction sequences provided a better yield of FddA on a laboratory scale, they might not be appropriate for an industrial process, since the reaction sequences required for the synthesis of the fluorinated sugar were rather long and the coupling reaction was of low selectivity. Marquez also reported the synthesis of FddA from ara-A with a shorter reaction sequence.[11] However, since ara-A is a rather expensive starting material, the process is unlikely to be economic. Very recently, an efficient synthesis of FddA was reported by Jin et al.[12] They prepared a fluorinated sugar intermediate very efficiently and also improved the yield for the coupling reaction. They reported an overall yield of 14.9% with a 9-step reaction sequence. Although the process requires chromatography, this route might be one of the most economical processes developed so far.



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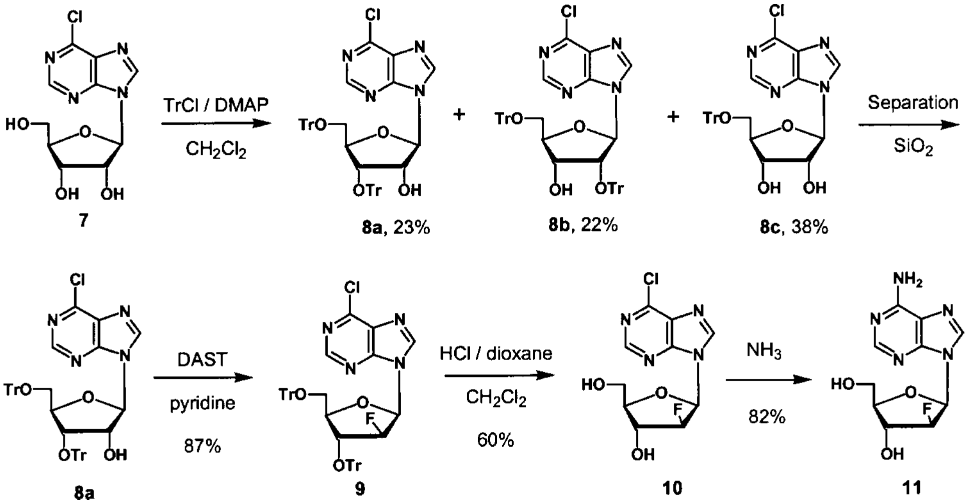
Scheme 1.

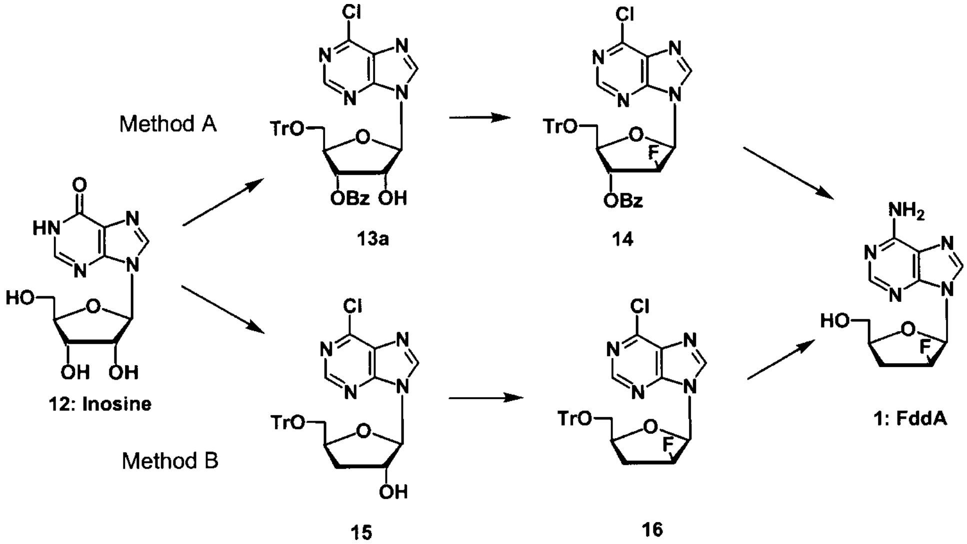
In 1992, Pankiewicz, Watanabe and their co-workers reported a fluorination reaction of $O^{3'}$, $O^{5'}$, N^6-tritrityladenosine **4** with DAST.[13] Remarkably, they found that 30% of the desired product **5** was obtained along with an accompanying formation of the purine base rearrangement product **6** in a 51% yield (Sch. 1). We speculate that this same rearrangement might be the reason for the low yield in the Herdewijn synthesis.

SYNTHETIC STRATEGY

In the course of studies on the synthesis and activities of 6-chloropurine nucleoside analogs, Maruyama et al. found that this type of base rearrangement could be completely suppressed by introducing a chlorine atom at the 6-position of the purine base.[14] Thus, the reaction of the 3′, 5′-ditrityl derivative **8a** of the 6-chloropurine riboside **7** with DAST gave an 87% fluorinated product **9** (Sch. 2). Compound **9** was then successfully converted into F-ara-A **11**.



Scheme 2.



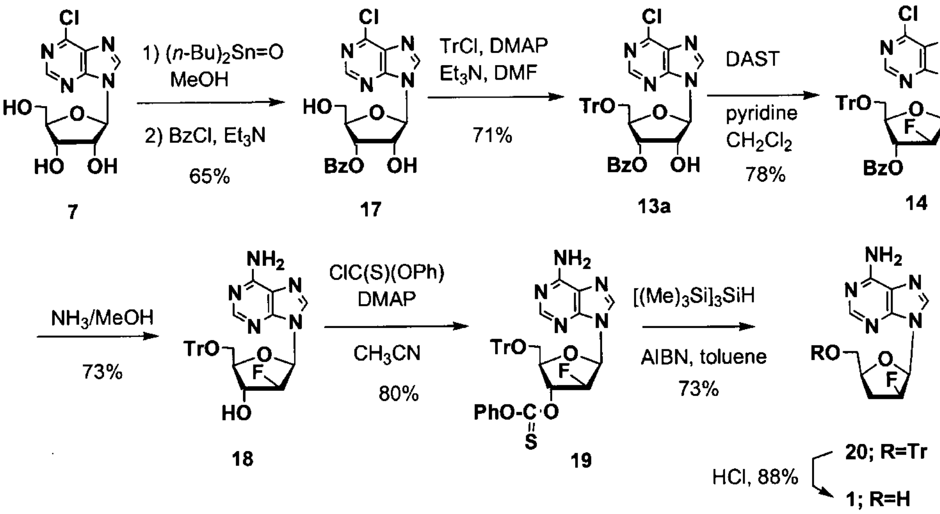
Scheme 3.

However, this process had drawbacks: the yield of 3′,5′-ditritylation was very low and the product **8a** had to be purified by column chromatography. To apply this methodology to synthesize FddA, **1**, the selective protection of the 3′- and 5′-positions by a different group is necessary. Another important factor for industrial synthesis is the fluorination reagent. We found that DAST is not a suitable agent because of its availability, safety and cost on a large scale.

Based on this consideration, we attempted to develop two different routes to FddA from inosine (Sch. 3). Method A involves fluorination, followed by deoxygenation of the 3′-OH group in the later stages of the synthesis. For this purpose, it was necessary to achieve selective protection of the 3′ and 5′ positions of the 6-chloropurine riboside. On the other hand, Method B involves the synthesis of 6-chloropurine 3′-deoxyriboside with the fluorination step in the later part of the synthesis.

A Synthesis of FddA via 6-Chloropurine Riboside (Method A-1)[15]

We first used the 2′,3′-*O*-di-*n*-butylstannylene complex of 6-chloropurine riboside to introduce only one benzoyl group at the 2′-OH and/or 3′-OH. Thus, 6-chloropurine riboside **7** was successively treated with di-*n*-butyltin oxide and excess benzoyl chloride (BzCl) in the presence of triethylamine (Et_3N) in MeOH. After the usual work-up and purification by silica gel chromatography, an inseparable mixture of 3′-*O*-benzoate **17** and 2′-isomer was subjected to crystallization from MeOH to afford 96.1% pure 3′-*O*-benzoate **17** in 65% yield in crystalline form. Compound **17** was reacted with trityl chloride (TrCl) in the presence of Et_3N and 4-dimethylaminopyridine (DMAP) in *N*,*N*-dimethylformamide (DMF). Thin-layer chromatography analysis indicated a small amount of migration of the benzoyl



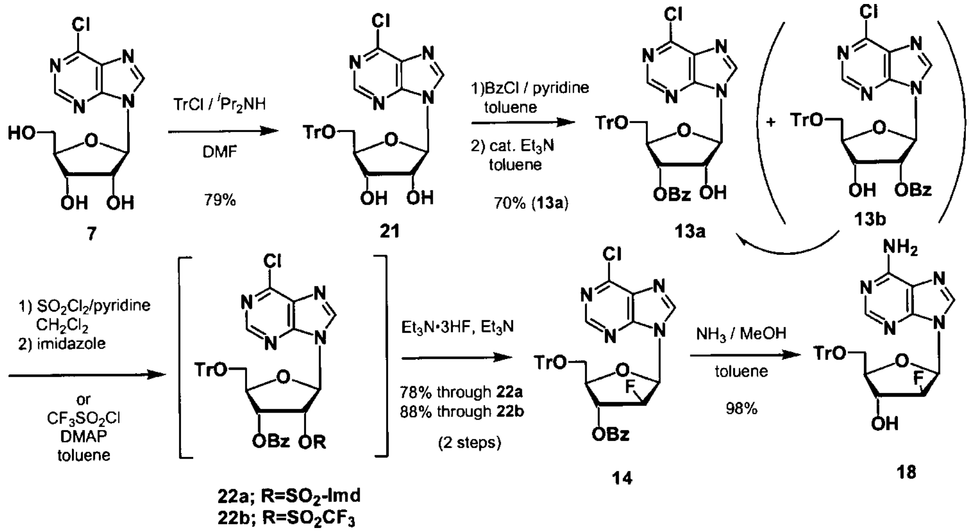
Scheme 4.

group from the 3′-position to the 2′-position under these reaction conditions. Fortunately, however, the desired 3′-*O*-benzoate **13a** was obtained in a 71% yield with 98% purity after crystallization from MeOH (Sch. 4). Since the fluorination reaction with DAST should be carried out in the presence of amine to protect the 5′-*O*-trityl group, the stability of 3′-*O*-benzoate **13a** was checked before the reaction. Thus, the compound was heated under reflux with 6 equiv. of pyridine in CH_2Cl_2 for 5 h. To our delight, only 3.1% of the 2′-*O*-benzoate **13b** was observed in the mixture. We then examined the reaction of **13a** with DAST using the same conditions and obtained the product **14** in a 78% yield.

The 3′-*O*-benzoyl-5′-*O*-trityl protecting system has two advantages: it is easy to introduce the protecting group compared with the di-*O*-trityl group and the selective removal of either the 3′- or 5′-*O*-protecting group proceeds smoothly. Thus, deprotection of the 3′-*O*-benzoyl group and displacement of the 6-chloro group of **14** could be accomplished by treatment with ammonia in MeOH to afford **18** in a 73% yield. Deoxygenation of the 3′-hydroxy group was achieved by the conventional method. Compound **18** was treated with phenyl chlorothionoformate to give **19** in an 80% yield. The product was then treated with tris(trimethylsilyl)silane in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) in toluene under N_2 atmosphere to give **20** as white crystals in a 73% yield. Acid treatment of **20** gave the desired 9-(2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl)adenine (FddA, **1**) as prisms in an 88% yield. Analytical data for this sample were identical in all respects to the published data.

An Improved Synthesis of FddA via 6-Chloropurine Riboside (Method A-2)[16]

The more efficient protection methodology we developed is shown in Sch. 5. The selective 5′-*O*-tritylation of 6-chloropurine riboside (79%) was performed with 2



Scheme 5.

equiv. of trityl chloride in the presence of diisopropylamine ($i\mathrm{Pr}_2\mathrm{NH}$) in DMF at 40°C (Sch. 6). Selective benzoylation of the 3′-position was carried out using excess benzoyl chloride in the presence of pyridine in toluene followed by treatment with a catalytic amount of triethylamine in the same solvent to give **13a** in a 70% yield. Before fluorination, the 2′-hydroxy group of **13a** was converted to imidazolesulfonate **22a** or trifluoromethanesulfonate **22b**. Compound **22a** was treated with $\mathrm{Et_3N{\cdot}3HF}$ in toluene at 70°C to give **14** in a 78% yield, including imidazolesulfonation. The trifluoromethanesulfonate **22b**, which was quantitatively obtained from **13a**, was reacted with 6 equiv. of $\mathrm{Et_3N{\cdot}3HF}$ and 3 equiv. of $\mathrm{Et_3N}$ in ethyl acetate (EtOAc) at reflux temperature. Fluorination proceeded very smoothly to give **14** in an 88% yield. To the best of our knowledge, this is the highest reported yield in fluorination at the 2′-position of a purine riboside. Next, we treated compound **14** with ammonia to give **18** by simultaneous 6-amination and 3′-benzoyl deprotection in almost quantitative yield.

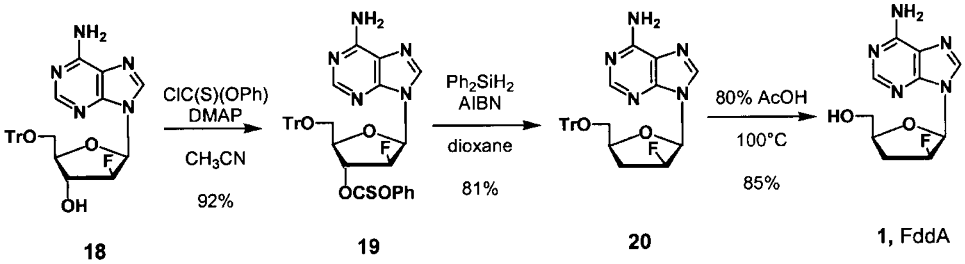
To complete the synthesis of F-ddA, deoxygenation of the 3′-hydroxy group in **18** was carried out by the Barton-McCombie method[17] with silane, thus avoiding the use of toxic tin hydride. Compound **18** was converted with phenyl chlorothionoformate to the 3′-*O*-thiocarbonyl derivative **19** in a 92% yield. The product was then subjected to deoxygenation with various silanes in the presence of AIBN. The results are summarized in Table 1.

Among these, diphenylsilane was the best of choice to produce a reduction product **20** in an 81% yield, which in turn was treated with 80% acetic acid to give FddA, **1**, of an excellent yield and quality.

Although we successfully synthesized FddA in good yield, several points should be improved. When we examined the cost in further detail, the silane used in the deoxygenation step was found to be relatively expensive. Therefore, we examined other radical reductions and reduction of the xanthate **23** with hypophosphorous acid proved to be the most efficient. Table 2 summarizes the results.[18]

Table 1. Deoxygenation of **19** with silanes.

Run	R	Silane	Solvent	Yield %
1	Ph	$[(Me)_3Si]_3SiH$	Toluene	78
2	Ph	Ph_2SiH_2	Dioxane	81
3	Ph	Ph_2SiH_2	Toluene	74
4	Ph	Ph_2MeSiH	Dioxane	69



Scheme 6.

The best yield, 93%, was obtained when we used 10 equiv. of hypophosphorous acid and 11 equiv. of Et_3N in DME/H_2O (Sch. 7). In summary, we achieved the synthesis of FddA from 6-chloropurine riboside in a 32.8% overall yield and 8 steps.

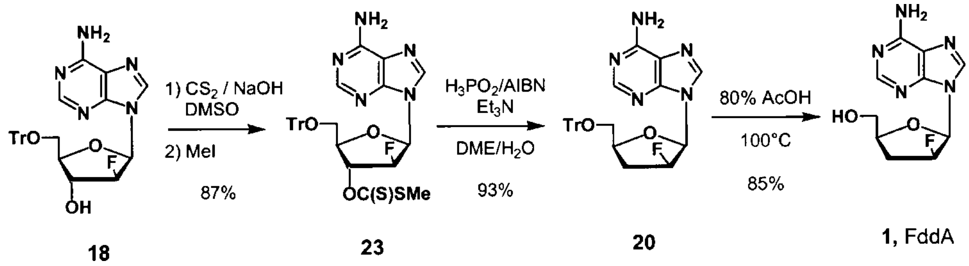
A Synthesis via 6-Chloropurine 3′-Deoxyriboside (Method B)[19]

Although the overall yield for the reaction sequence in Method A-2 was the best thus far, we further investigated other routes in an attempt to lower the production costs. Thus, we attempted the synthesis of 6-chloropurine 3′-deoxyriboside **27** from a readily available inosine, **12**. The synthesis of **27** was achieved as shown in Sch. 8. The acetoxybromination technology used is that which we had already developed

Table 2. Deoxygenation of xanthate **23**.

Run	Solvent	M-H	P-H/eq.	Et_3N/eq.	AIBN/eq.	Temp./°C	Time/hrs	Yield %[a]
1	DME	H_3PO_2	5	10	0.3	Reflux	1	84
2	DME	H_3PO_2	10	20	0.6	Reflux	1.8	86
3	DME	H_3PO_2	10	11	0.6	Reflux	1.8	93
4	DME	H_3PO_2	5	5.5	0.1	Reflux	1.2	90
5	DME	H_3PO_2	2.5	2.8	0.2	Reflux	1.3	90
6	DME	$(MeO)_2P(O)H$	10	–	0.6	Reflux	2	84
7	DME	$(EtO)_2P(O)H$	10	–	0.6	Reflux	2	82

[a] Calculated from the results of HPLC analysis.

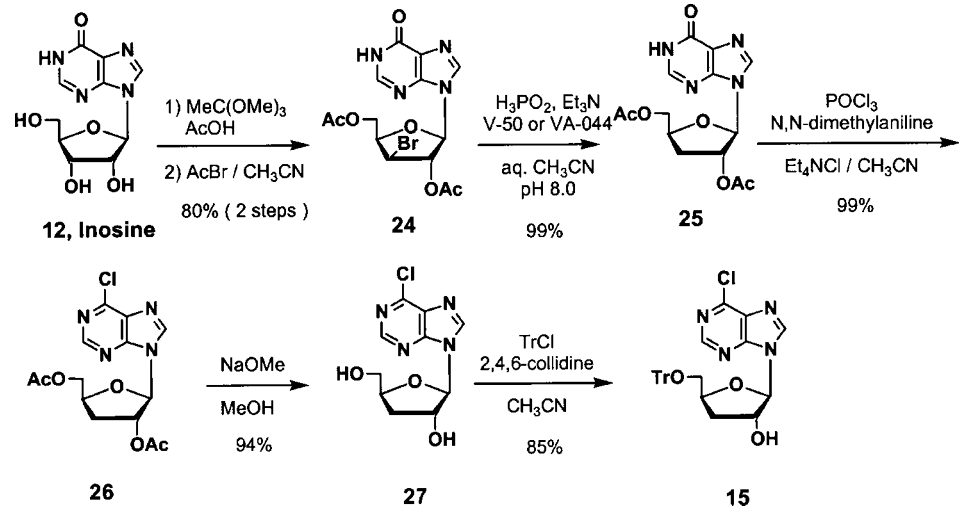


Scheme 7.

for the large scale synthesis of ddA.[20] The reaction proceeded well to afford **24** in an 80% overall yield from **12**. We then carried out the radical debromination of **24** using hypophosphorous acid as a reducing agent in the presence of a water-soluble radical initiator such as V-50 or VA-044 (Fig. 2 to give **25** in almost quantitative yield.[18] When we used AIBN as a radical initiator, we observed a lower isolated yield due to a loss of product during the purification to remove residual AIBN.

6-Chlorination and subsequent deacetylation were carried out in a conventional manner, and the product **27** was tritylated to give **15** for the next fluorination step in 85% yield.

Another high-cost step is fluorination. Accordingly, we examined the use of a perfluoroalkanesulfonyl fluoride such as perfluoro-1-butanesulfonyl fluoride (nonafluoro-1-butanesulfonyl fluoride, $C_4F_9SO_2F$, NfF) or perfluoro-1-octanesulfonyl fluoride ($C_8F_{17}SO_2F$, OctF) for fluorination, and compared the yields with those using other fluorination agents. Vorbrüggen and co-workers reported that the combination of NfF with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in non-polar solvents efficiently converts primary and secondary alcohols into their corresponding



Scheme 8.

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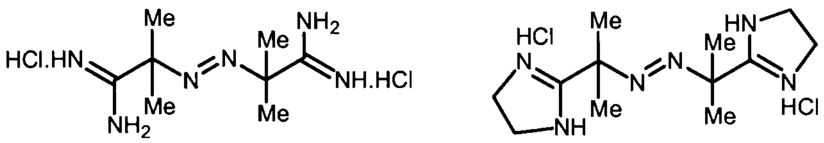


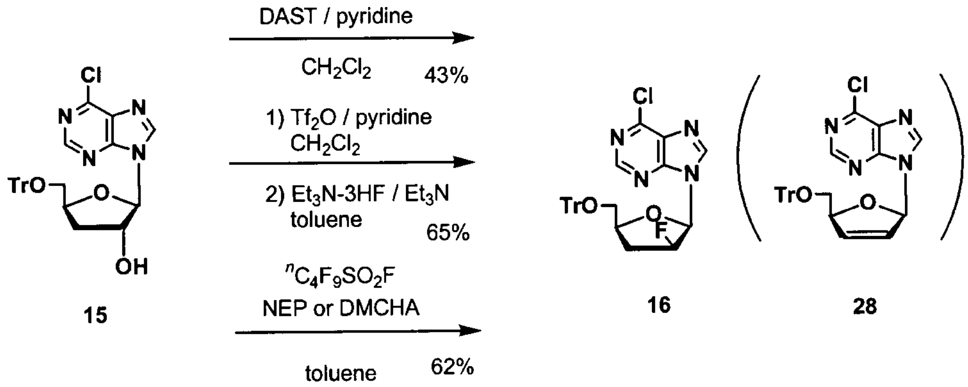
V-50 VA-044

Figure 2.

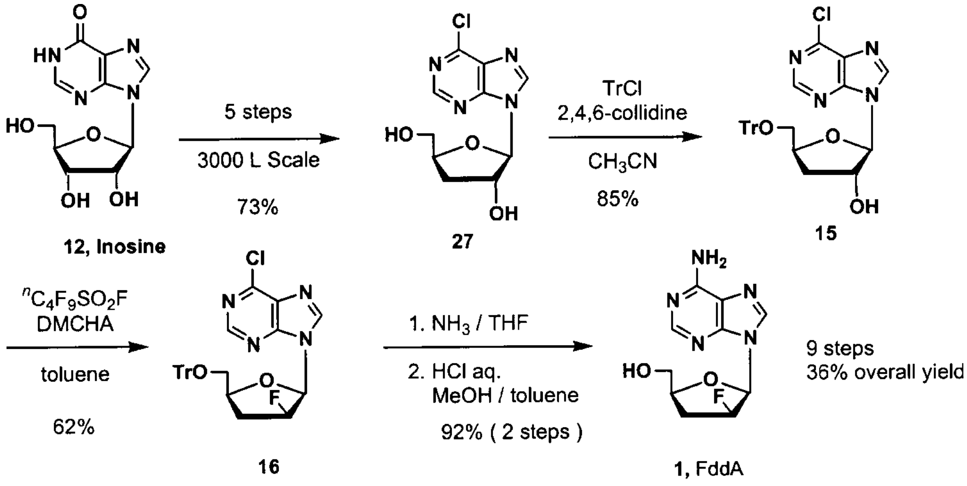
fluorides.[21] In our first experiment, we noticed that NfF reacted slowly with **15** in the presence of Et_3N, even at 50°C. Using pyridine as a base, the reaction did not proceed at all. However, immediately after DBU was added to this mixture, **15** was converted into the fluorinated product **16** and the elimination product **28**. We next sought to improve the ratio of fluorination to elimination. The base must be a good proton acceptor with a moderate basicity to avoid elimination and must also have low nucleophilicity. Among the bases we studied, *N*-ethylpiperidine (NEP) gave better results with regard to both the reaction rate and selectivity. At 50°C, with 4 equiv. of NfF and 2 equiv. of NEP as a base, the reaction went to completion after 44 h with 64 area% in HPLC. *N,N*-Dimethylcyclohexylamine (DMCHA) also seems to be a good substitute for DBU. With 2 equiv. of NfF and 2 equiv. of DMCHA as a base, HPLC analysis indicated a 62.4% yield after aqueous work-up. The yield of **16** from **15** with NfF was much greater than that using DAST and almost the same as the previous 2-step method involving trifluoromethanesulfonylation and fluorination with $Et_3N \cdot 3HF$ (Sch. 9).[22]

We also successfully removed the elimination side-product **28** simply by treating the reaction mixture with 80% acetic acid in toluene at 10°C for 3 h. The desired product was isolated by crystallization without any loss. The second synthesis of F-ddA (Method B) from inosine is outlined in Sch. 10.

6-Chloropurine 3′-deoxyriboside was efficiently synthesized using radical debromination. Fluorination was successfully carried out using perfluoroalkanesulfonyl



Scheme 9.



Scheme 10.

fluoride. Thus, we synthesized FddA in a 36% overall yield and a total of 9 steps. This process is far superior to the previous method.

Unfortunately, the development of FddA was suspended[23] for reasons of toxicity just after the pilot plant production of compound **27** on a 3000-L scale. However, the methodology developed in this study might be very useful for the synthesis of related nucleosides.

ACKNOWLEDGMENTS

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