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## Nucleosides, Nucleotides and Nucleic Acids

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## AN ALTERNATIVE SYNTHETIC METHOD FOR 4'-C-ETHYNYLSTAVUDINE BY MEANS OF NUCLEOPHILIC SUBSTITUTION OF 4'-BENZOYLOXYTHYMINE NUCLEOSIDE

Kazuhiro Haraguchi, Masanori Sumino, and Hiromichi Tanaka □ School of  
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□ For the synthesis of 2,3'-didehydro-3'-deoxy-4'-C-ethynylthymidine (**8**: 4'-Ed4T), a recently reported promising anti-HIV agent, a new approach was developed. Since treatment of 1-(2,5-dideoxy-β-L-glycero-pent-4-enofuranosyl)thymine with  $Pb(OBz)_4$  allowed the introduction of a 4'-benzoyloxy leaving group, nucleophilic substitution at the 4'-position became feasible for the first time. Thus, reaction between the 4'-benzoyloxy derivative (**11**) and  $Me_3SiC\equiv CAl(Et)Cl$  as a nucleophile led to the isolation of the desired 4'-"down"-ethynyl derivative (**15**) stereoselectively in 62% yield.

**Keywords** Anti-HIV; diacyloxylation; 4',5'-unsaturated nucleoside; nucleophilic substitution; ethynylation; 4'-substituted nucleosides; didehydro-3'-deoxythymidine; organoaluminum reagents; organosilicon reagents

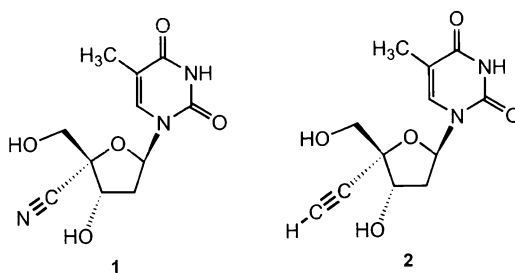
### INTRODUCTION

Recently, 4'-substituted nucleosides have attracted much attention because of the discovery of the potent anti-HIV agents 4'-C-cyano (**1**) and 4'-C-ethynyl (**2**) analogs of thymidine (Figure 1). Synthesis of these 4'-carbon-substituted nucleosides has mostly relied on manipulation of the 4'-hydroxymethyl derivatives of nucleosides or sugars that can be prepared by the well known aldol-Cannizzaro reaction of the corresponding aldehyde.<sup>[1]</sup>

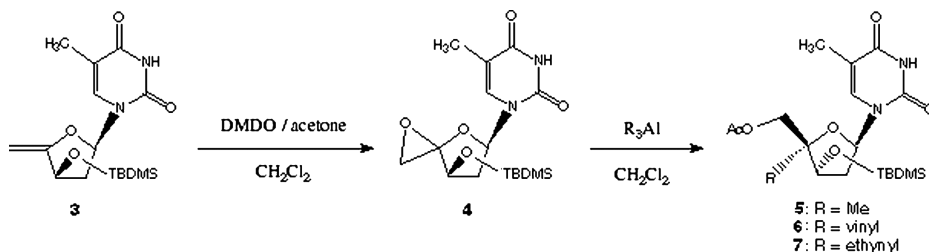
We have already carried out ring-opening of 4',5'-epoxynucleosides with organosilicon<sup>[2]</sup> or an organoaluminum<sup>[3]</sup> reagent. Thus, oxidation of the 4',5'-unsaturated derivative **3** with an acetone solution of dimethyldioxirane (DMDO) gave **4**, which was then reacted with organoaluminum reagents ( $R_3Al$ ) to furnish the 4'-carbon-substituted products (**5–7**) (Scheme 1).

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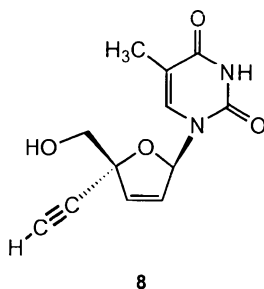


**FIGURE 1** 4'-C-Cyano-(1) and 4'-C-ethynylthymidine (2).

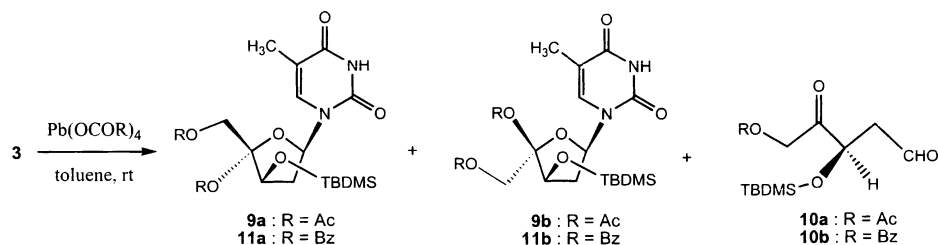


**SCHEME 1** Epoxidation of **3** with DMDO and subsequent ring opening of 4'-5'-epoxythymidine derivative **4** with organoaluminum reagents.

During this study, 2',3'-didehydro-3'-deoxy-4'-C-ethynylthymidine (**8**: 4'-Ed4T) prepared from **7** was found to be more potent against HIV than the parent compound stavudine (d4T) and much less toxic to various cells and also to mitochondrial DNA synthesis (Figure 2).<sup>[4]</sup> To further evaluate **8** in animal studies, we were in need of an alternative synthetic method that is suitable for its large scale preparation, since the route shown in Scheme 1 has a drawback in that a highly concentrated acetone solution of DMDO is inaccessible. In this study, we demonstrate that the reaction between **3** and Pb(OCOR)<sub>4</sub> allows introduction of an acyloxy leaving group to the 4'-position, and that nucleophilic ethynylation of the resulting 4'-acyloxy



**FIGURE 2** 2',3'-didehydro-3'-deoxy-4'-C-ethynylthymidine (4'-Ed4T).



**SCHEME 2** Diacyloxylation of **3** with  $\text{Pb}(\text{OCOR})_4$ .

derivative with an organoaluminum reagent enable us to prepare the title compound (**8**) in a fairly large scale.<sup>[5]</sup>

## RESULTS AND DISCUSSION

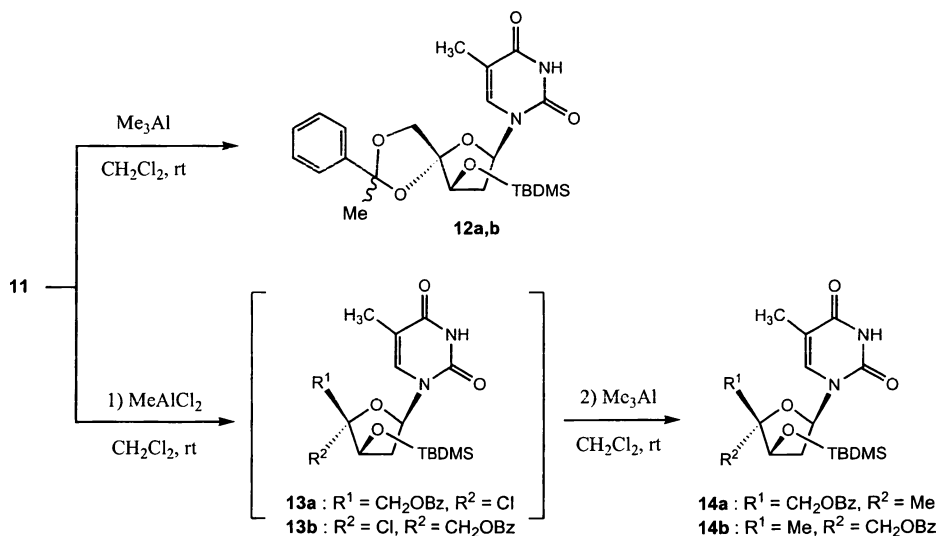
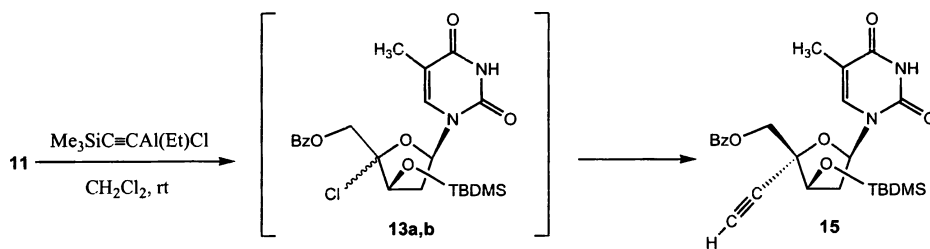
### Diacyloxylation of 4',5'-Unsaturated Thymine Nucleoside

When the reaction of **3** with  $\text{Pb}(\text{OAc})_4$  was carried out in toluene at room temperature, the 4'-acetoxy derivative **9a** was obtained (Scheme 2), but the yield was only 28%. The main product in this reaction was the depicted aldehyde **10a** (60%). After several attempts, the presence of  $i\text{-Pr}_2\text{NEt}$  was found to prevent the formation of **10a**, but the yield of **9** (32%, **9a/9b** = 1/0.4) remained unchanged. This result led us to examine the use of another lead tetracarboxylate. When  $\text{Pb}(\text{OBz})_4$  was reacted with **3** in the presence of  $i\text{-Pr}_2\text{NEt}$  in toluene at room temperature, the 4'-benzoyloxy derivative **11** was obtained in 71% yield (**11a/11b** = 1/0.8) without forming the aldehyde **10b**.

### Reaction of the 4'-Benzoyloxy Derivative (**11**) with Organoaluminum Reagents

Reaction of the 4'-benzoyloxy derivative (**11**) with 4 equiv of  $\text{Me}_3\text{Al}$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  gave a mixture of two diastereomers of the spiro nucleosides (76%, **12a/12b** = 1/1) as major products (Scheme 3). On the other hand, when **11** was reacted with  $\text{MeAlCl}_2$  under the similar conditions, two isomeric 4'-chlorinated products (**13a**, 53%; **13b**, 14%) were formed. It was found that further treatment of the above reaction mixture containing **13** with  $\text{Me}_3\text{Al}$  (6.0 equiv, at room temperature for 23 h) gave the 4'-C-methyl derivatives (**14a**, 14%; **14b**, 19%) in a one-pot manner. Although the yield of **14** was not high, formation of the spiro derivative **12** was suppressed to a trace amount.

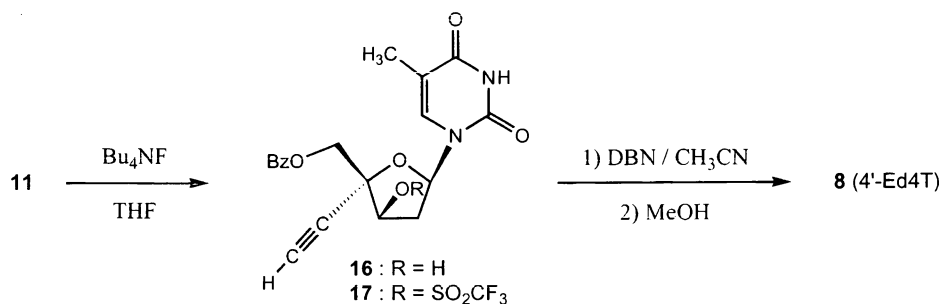
With these experimental results in hand, introduction of an ethynyl group to the 4'-position of **11** was investigated (Scheme 4). One-pot treatment of **11** with  $\text{MeAlCl}_2$  followed by ethyl[trimethylsilyl(ethynyl)]

SCHEME 3 Methylation of **11** with  $\text{Me}_3\text{Al}$ .SCHEME 4 Ethynylation of **11** with  $\text{Me}_3\text{SiC}\equiv\text{CAI(Et)Cl}$ .

aluminum chloride  $\text{Me}_3\text{SiC}\equiv\text{CAI(Et)Cl}$  furnished the 4'-C-ethynyl derivative **15** as a single isomer in 51% yield. During this ethynylation reaction of **11**, we noticed that the ethynylaluminum reagent itself was capable of chlorinating **11** and that the 4'-ethynylation of **13** gradually took place afterward. Thus, when **11** was reacted with 8.0 equiv of  $\text{Me}_3\text{SiC}\equiv\text{CAI(Et)Cl}$  in  $\text{CH}_2\text{Cl}_2$  at room temperature overnight, **15** was formed stereoselectively and isolated in 62% yield by silica gel column chromatography. This ethynylation can be performed in a several-10 g scale.

### Preparation of 4'-Ed4T (**8**)

The above-prepared **15** was converted to **8** by a conventional reaction sequence (Scheme 5). Thus, desilylation of **15** with  $\text{Bu}_4\text{NF}$  in THF gave **16** (97%), which was sulfonylated with  $(\text{CF}_3\text{SO}_2)\text{O}$  in the presence of pyridine in THF. The resulting 3'-triflate **17** was not isolated and subjected to  $\beta$ -elimination with  $\text{DBN}/\text{CH}_3\text{CN}$ . Removal of the 5'-O-benzoyl group was



SCHEME 5 Preparation of 4'-Ed4T (8).

carried out in a one-pot manner by adding MeOH to the elimination mixture. This procedure allowed preparation of the title compound 4'-Ed4T (8) in 69% overall yield from 15.

## CONCLUSION

As an alternative method for the synthesis of 4'-Ed4T (8), a nucleophilic substitution approach was investigated. The first step, introduction of a leaving group to the 4'-position, was accomplished by vicinal diacyloxylation of the 4',5'-unsaturated thymine nucleoside **3** with Pb(OBz)<sub>4</sub> in the presence of *i*-Pr<sub>2</sub>NEt. Nucleophilic ethynylation of the 4'-benzoyloxy group of **11** was successfully carried out by using Me<sub>3</sub>SiC≡CAl(Et)Cl as a nucleophile to give the desired 4'-"down"-C-ethynyl derivative **15** exclusively.

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