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

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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.[1]

We have already carried out ring-opening of 4′,5′-epoxynucleosides with organosilicon[2] or an organoaluminum[3] 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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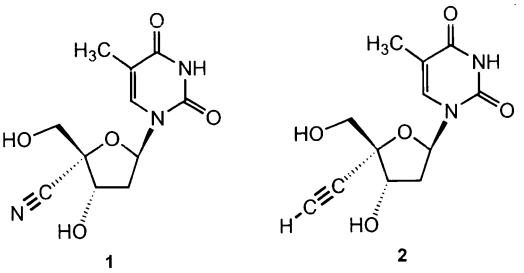
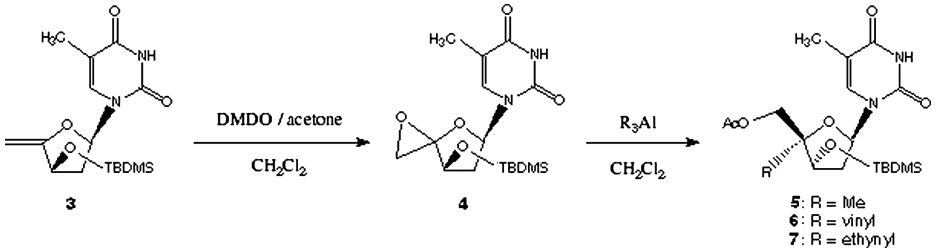



**FIGURE 1** 4′-C-Cyano-(**1**) and 4′-C-ethynylthymidine (**2**).




**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).[4] 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 $Pb(OCOR)_4$ allows introduction of an acyloxy leaving group to the 4′-position, and that nucleophilic ethynylation of the resulting 4′-acyloxy

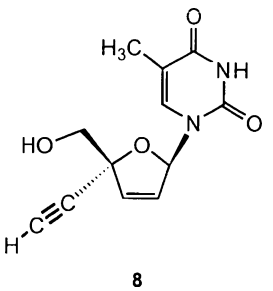
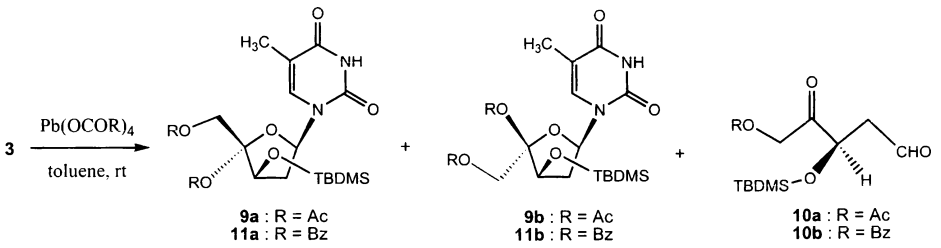



**FIGURE 2** 2′,3′-didehydro-3′-deoxy-4′-C-ethynylthymidine (4′-Ed4T).




**SCHEME 2** Diacyoxylation of **3** with Pb $(OCOR)_4$.

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

## RESUTS AND DISCUSSION

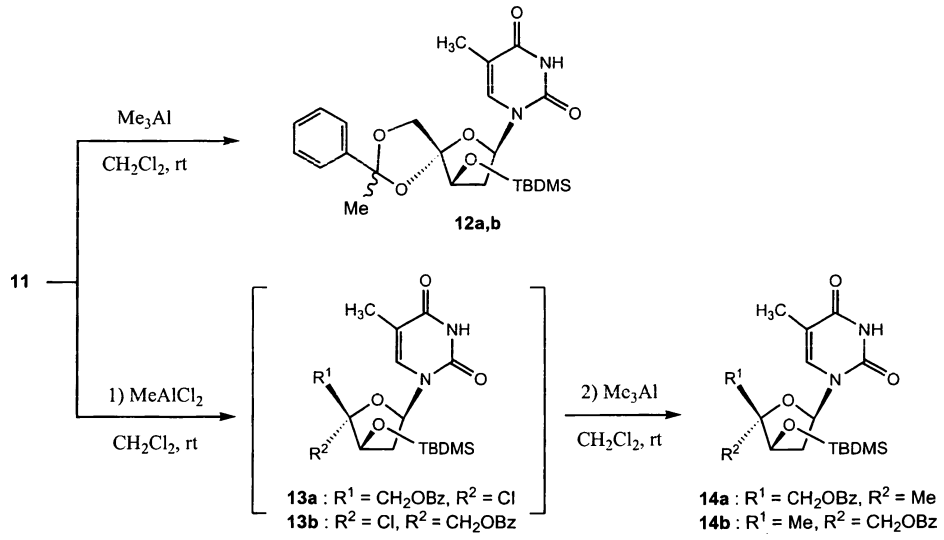
### Diacyloxylation of 4′,5′-Unsaturated Thymine Nucleoside

When the reaction of **3** with $Pb(OAc)_4$ 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*-$Pr_2NEt$ 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 $Pb(OBz)_4$ was reacted with **3** in the presence of *i*-$Pr_2NEt$ 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**.

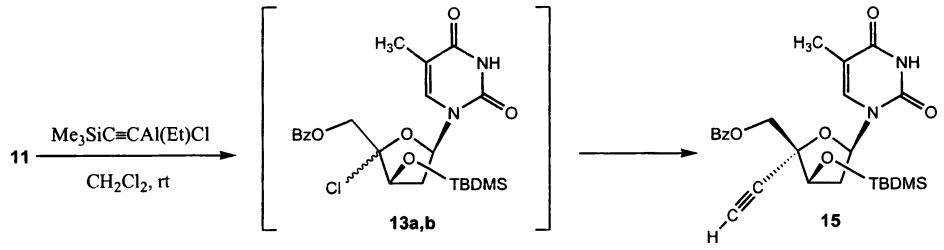
### Reaction of the 4′-Benzoyloxy Derivative (11) with Organoaluminum Reagents

Reaction of the 4′-benzoyloxy derivative (**11**) with 4 equiv of $Me_3Al$ in $CH_2Cl_2$ at 0°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 $MeAlCl_2$ 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 $Me_3Al$ (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 $MeAlCl_2$ followed by ethyl[trimethylsilyl(ethynyl)]




**SCHEME 3** Methylation of **11** with $Me_3Al$.

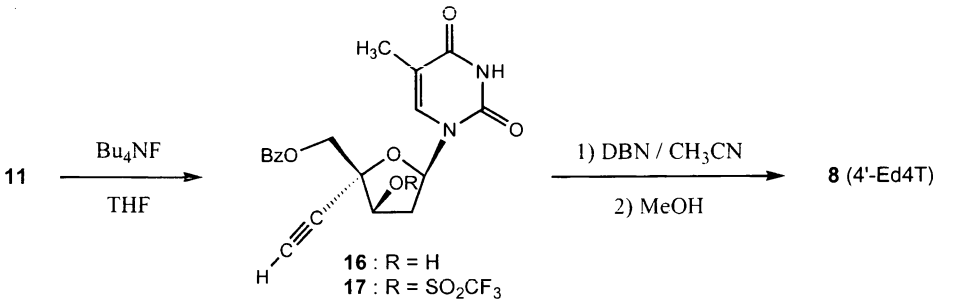



**SCHEME 4** Ethynylation of **11** with $Me_3SiC{\equiv}CAl(Et)Cl$.

aluminum chloride $Me_3SiC{\equiv}CAl(Et)Cl$ 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 $Me_3SiC{\equiv}CAl(Et)Cl$ in $CH_2Cl_2$ 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 coverted to **8** by a conventional reaction sequence (Scheme 5). Thus, desilylation of **15** with $Bu_4NF$ in THF gave 16(97%), which was sulfonylated with $(CF_3SO_2)O$ in the presence of pyridine in THF. The resulting 3′-triflate **17** was not isolated and subjected to $\beta$-elimination with DBN/$CH_3CN$. 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 $Pb(OBz)_4$ in the presence of *i*-$Pr_2NEt$. Nucleophilic ethynylation of the 4′-benzoyloxy group of **11** was successfully carried out by using $Me_3SiC{\equiv}CAl(Et)Cl$ as a nucleophile to give the desired 4′-"down"-C-ethynyl derivative **15** exclusively.

## REFERENCES AND NOTES

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