Tetrahedron Letters, Vol. 33, No. 20, pp. 2841-2844, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereoselective Synthesis of 4'-*C*-Branched 2',3'-Didehydro-2',3'-dideoxy Nucleosides Based on $SnCl_4$-Promoted Allylic Rearrangement

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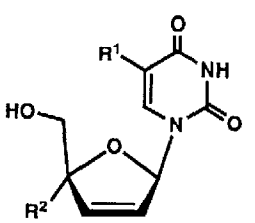
Keywords: 3',4'-unsaturated uracil nucleoside; allylic rearrangement; organosilicon reagent; 2',3'-didehydro-2',3'-dideoxyuridine; 4'-C-branched nucleoside.

Abstract: *Based on $SnCl_4$-promoted allylic rearrangement between a 3',4'-unsaturated uracil nucleoside and organosilicon reagents, stereoselective introduction of carbon functionalities to the 4'-position has been accomplished, disclosing a new entry for a series of 4'-C-branched nucleosides of biological interests.*

Although unsaturated-sugar nucleosides can be considered to constitute a versatile class of compounds for synthesizing branched-sugar nucleosides, such synthetic manipulation had long been unexploited presumably due to their instability. In fact, majority of their reactions so far reported are simple electrophilic addition with which only non-carbon substituents can be introduced.[1] We already demonstrated that some compounds involved in this class such as 4',5'-unsaturated derivatives,[2] nucleosidic enol esters,[3] and 2',3'-vinyl bromides[4] actually serve as synthons for constructing C-C bonds in the sugar portion.[5] The fact that there have been basically only two approaches available to introduce carbon functionalities to the 4'-position of nucleosides[6,7] combined with promising anti-HIV (Human Immunodeficiency Virus) activity of 3'-deoxy-2',3'-didehydrothymidine (D4T: **1**)[8,9] prompted us to develop a new synthetic method for a series of 4'-*C*-branched 2',3'-didehydro-2',3'-dideoxyuridines (**2**). In this communication, we describe on the reaction between a 3',4'-unsaturated uracil nucleoside and organosilicon reagents by way of an allylic rearrangement.

A recent report from our laboratory shows that nucleophilic cleavage of various types of anhydro structures in uracil nucleosides with phenylselenide anion provides an efficient method for the preparation of selenium-containing derivatives.[10] Since these products, upon oxidation to the corresponding selenoxide, undergo *syn*-elimination under mild conditions, this approach permits a highly general synthesis of unsaturated-sugar nucleosides.[10]



1 R^1= Me, R^2= H
2 R^1= H, R^2= a carbon substituent

During this study, it was found that, although **3** has two β-*syn*-hydrogens to the phenylseleno group and both of its β- and β'-carbons bear an electronegative substituent (2'-hydroxyl group and $O^{4'}$-atom), regiochemistry of its selenoxide elimination can be altered by a simple acetylation. That is, while the two posssible elimination pathways occur comparably in the case of **3**, the corresponding 2'-*O*-acetyl derivative (**4a**) gave the 3',4'-unsaturated product (**5a**) exclusively in 88% yield (Chart 1).[11] Considering the structural feature of **5a**, it occurred to us that, under suitable conditions, its reaction with carbon nucleophiles might have a possibility to effect the synthesis of **2** through an allylic rearrange-

ment. A major concern in performing this conversion was, of course, an anticipated propensity of **5a** to undergo elimination that yields a furane derivative.

γ-Substitution of allyl acetates has been realized by the use of $BuCu{\cdot}BF_3$.[12] However, in our case, the reaction resulted in quantitative recovery of the starting material (**5a**). The use of other organometallic reagents

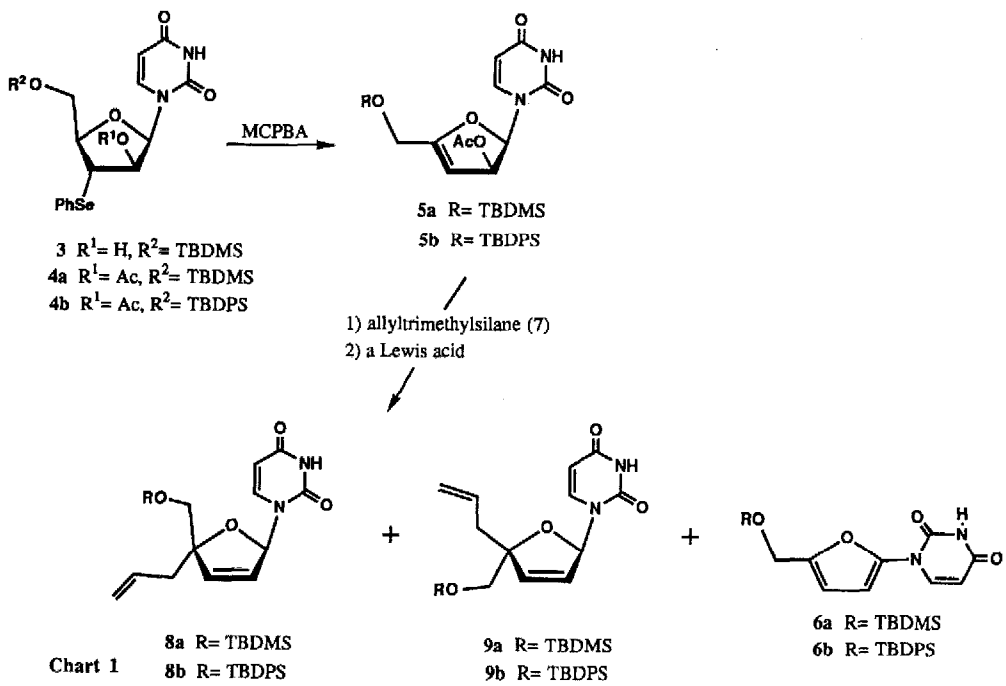
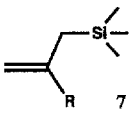


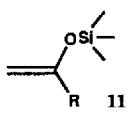
Chart 1

such as Me_3Al and Me_2CuLi also failed, forming the furane derivative **6a** (29%) in the former and deacetylated product (44%) in the latter.[13] In contrast to these results, when $BF_3{\cdot}OEt_2$ (5 equiv) was added to a mixture of **5a** and allyltrimethylsilane (**7**, 5 equiv) in CH_2Cl_2 at −78 °C and the mixture was allowed to react at −40 °C for 7 h, the desired product **8a** (30%) and its stereoisomer **9a** (6%) were formed along with **6a**. This reaction was reexamined by changing the *tert*-butyldimethylsilyl (TBDMS) group in **5a** to a more stable *tert*-butyldiphenylsilyl (TBDPS) group. Compound **5b** was prepared in 90% yield from **4b**. Upon treatment of **5b** with **7** in a similar manner to the case of **5a**, **8b** (33%) and **9b** (14%) were obtained together with **6b** (30%). In the ^1H NMR spectrum of **8b** in $CDCl_3$, the resonance of H-5 was observed at δ 5.13 ppm, being shifted upfield compared with that of **9b** (δ 5.69 ppm). Since the signals for H-5 of **8a** and **9a** appeared at almost the same region (δ 5.65 and 5.68 ppm, respectively), the origin of the observed upfield shift of **8b** is undoubtedly due to the magnetic anisotropy of the TBDPS group. This suggests the stereochemistry of these products to be as depicted in Chart 1.[14] Desilylation of **8b** with tetrabutylammonium fluoride (TBAF) in THF gave 4'-allyl-2',3'-dide-hydro-2',3'-dideoxyuridine (**2**: R^1= H, R^2= allyl) in high yield. When 10 equiv of **7** were used, the yield of **8b** increased to 53% (**9b**: 11%), though a 34% yield of **6b** was also formed. It should be mentioned that, when the reaction temperature was maintained at −40 °C from the begining, **6b** was the sole product. Pre-mixing of the two reagents gave the same result.

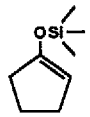
We finally found that the use of $SnCl_4$ as a Lewis acid in the above reaction of **7** gave the following dramatic changes. 1) The reaction goes to completion at −78 °C (for 7 h). 2) A high degree of stereoselectivity was attained with an increased yield of the desired product (**8b**: 74% *vs.* **9b**: 5%). 3) The formation of **6b** was eliminated completely. The reaction of **5b** with several types of other organosilicon reagents (**10-14**) allowed to synthesize a series of 4'-*C*-substituted 2',3'-didehydro-2',3'-dideoxyuridines (**15-24**), the results of which are



7 R= H
10 R= Me

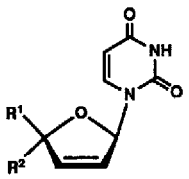


11 R=Me
12 R= Ph



13

14



8b R^1= $CH_2OTBDPS$, R^2= allyl
9b R^1= allyl, R^2= $CH_2OTBDPS$
15 R^1= $CH_2OTBDPS$, R^2= 2-methylallyl
16 R^1= 2-methylallyl, R^2= $CH_2OTBDPS$
17 R^1= $CH_2OTBDPS$, R^2= acetonyl
18 R^1= acetonyl, R^2= $CH_2OTBDPS$
19 R^1= $CH_2OTBDPS$, R^2= phenacyl
20 R^1= phenacyl, R^2= $CH_2OTBDPS$
21 R^1= $CH_2OTBDPS$, R^2= cyclopentanon-2-yl
22 R^1= cyclopentanon-2-yl, R^2= $CH_2OTBDPS$
23 R^1= $CH_2OTBDPS$, R^2= CN
24 R^1= CN, R^2= $CH_2OTBDPS$

Table 1. Reaction of **5b** with Organosilicon Reagents.[a)]

Entry	Reagent	Reaction Time (h)	Isolated Yield of Product
1	**7**	7	**8b** (74%), **9b** (5%)
2	**10**	7	**15** (75%), **16** (5%)
3	**11**	1	**17** and **18** (*ca.* 6:1, 51%)
4	**12**	0.5	**19** and **20** (*ca.* 6:1, 64%)
5	**13**	0.5	**21** (68%), **22** (2%)
6	**14**	1	**23** and **24** (*ca.* 2:1, 64%)

a) All reactions were carried out at -78 °C in THF by the use of $SnCl_4$ (5 equiv) and an appropriate organosilicon reagent (10 equiv).

summarized in Table 1. The result obtained by the use of **7** is also included (entry 1). Both in terms of the yield of products and the reaction time, no significant difference was observed between the reactions of **7** and **10** (entry 2).[15] Silyl enol ethers (**11-13**) uniformly react with **5b** within 1 h (entries 3-5).[16] However, in entries 3 and 4, the stereoselectivity is rather low and the diastereomeric isomers were obtained as inseparable mixtures.[17] It should deserve a further comment that an additional unstable product was obtained in entries 4 (14%) and 5 (17%). The MS spectra of these products showed that they are isomeric to **19** and **21**, respectively. From their ^1H NMR evidence,[18] we assume these to be 3',4'-unsaturated 2'-*C*-substituted products derived from the α-attack of the reagents. Entry 6 indicates that this approach provides an alternative and even much simpler method to prepare 4'-cyano nucleosides.[9a,19] Separation of **23** was carried out by treatment of the inseparable mixture with TBAF followed by acetylation.[20]

In conclusion the present study has shown that $SnCl_4$ is a highly effective Lewis acid in performing the conversion of **5b** to a series of 4'-*C*-substituted 2',3'-didehydro-2',3'-dideoxyuridines. Since the reaction proceeds stereoselectively without forming **6b**, this approach may find widespread use in the synthesis of biologically interesting derivatives. We are currently investigating on the scope and limitations of this $SnCl_4$-promoted allylic rearrangement with the intention to elucidate factors controlling its stereo- and regioselectivity.

Acknowledgement. The authors are grateful to Professor A. Hosomi for helpfull advice on the preparation of allylsilanes. This work has been financially supported by Uehara Memorial Foundation (to K. H.) and in part by the Naito Foundation (to H. T.).

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14. This was further confirmed by X-ray crystallographic analysis of **8a**.
15. Allylsilanes in which the C-C double bond is substituted by alkyl groups are more reactive toward electrophiles than **7**. For an example: Carr, S. A.; Weber, W. P. *J. Org. Chem.* **1985**, *50*, 2782-2785.
16. In entry 5, each of **21** and **22** consists of two diastereomers about α-carbon of the cyclopentan-2-yl moiety.
17. In the cases of entries 3, 4, and 6, diastereomeric ratio was determined by inspecting the integrated ^1H NMR spectra of the mixture of products.
18. ^1H NMR signals due to H-1' and CH_2-5' of these products appear as a doublet and a singlet, respectively. This contrasts to the 2',3'-unsaturated products which show H-1' as a characteristic double-doublet ,due to the presence of an extra allylic coupling, and CH_2-5' as two sets of doublets.
19. 4'-Cyanothymidine has been reported to inhibit HIV in certain cells: see reference 9a.
20. Stereochemistry of the resulting acetate was established again based on X-ray crystallography.

(Received in Japan 29 January 1992)