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Anomeric Manipulation of Nucleosides: Stereosepecific Entry to 1'-*C*-Branched Uracil Nucleosides

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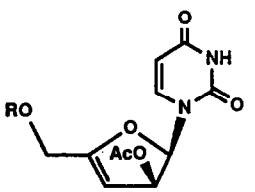
Keywords: 1',2'-unsaturated nucleoside; 1'-C-branched uracil nucleoside; electrophilic addition; organosilicon reagent; C-C bond formation.

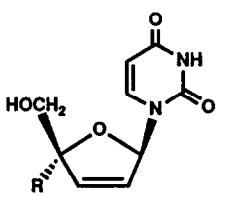
Abstract: Uracil nucleosides variously branched at the anomeric position have been synthesized through stereoselective bromo-pivaloyloxylation of a 1',2'-unsaturated derivative and successive $SnCl_4$-promoted nucleophilic substitution with organosilicon reagents. This constitutes the first example of C-C bond formation at the anomeric position of nucleoside.

Despite the fact that there have been ample precedents for the preparation of unsaturated-sugar nucleosides, their synthetic utility had mostly been limited to simple electrophilic addition reactions with which only non-carbon substituents can be introduced.[1] We have demonstrated through several publications[2] that certain compounds involved in this class serve as versatile starting materials for C-C bond formation in the sugar portion of nucleosides.[3]

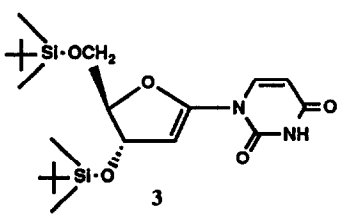
Quite recently, a $SnCl_4$-promoted allylic rearrangement of the 3',4'-unsaturated uracil nucleoside **1** with organosilicon reagents has been reported, which provides a new synthetic route to a series of 4'-*C*-branched derivatives (**2**).[4] One would anticipate that a simple application of this reaction to the 1',2'-unsaturated derivative **3** [5] could lead to the formation of 1'-*C*-branched products. However, in accord with the reported instability of 1',2'-unsaturated nucleosides,[5a] when **3** was treated with allyltrimethylsilane in the presence of $SnCl_4$ (in CH_2Cl_2, below −70 °C, for 1 h), the sole product appeared to be an elimination product **4** (42%). This observation led us to devise an alternative approach to a C-C bond forming reaction at the anomeric position.



1 R= TBDMS or TBDPS



2 R= a carbon substituent



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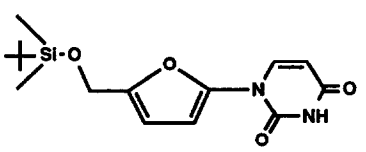

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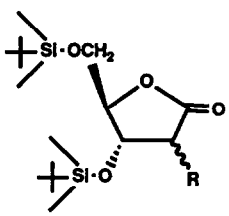
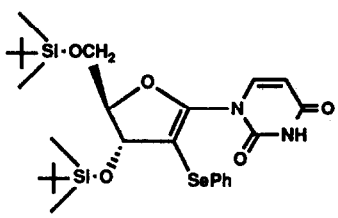
We assumed that Lewis acid-mediated nucleophilic substitution using organosilicon reagents might be one promising synthetic operation to introduce carbon functionalities to the anomeric position.[6] To accomplish this reaction stereoselectively, the presence of a C1'-leaving group as well as a C2'-β-substituent that exerts an anchimeric assistance would be indispensable.

We started with acetoxy-selenation of **3** in order to accommodate these requirements. Compound **3** was treated with PhSeCl and AgOAc in toluene at room temperature.[7] Although the reaction went to completion within a few minutes, attempted chromatographic isolation gave none of the desired adducts, but instead two decomposition products **5** (5%) and **6** (3%) were obtained. Formation of **6** can be explicable, at least in part, in terms of the α-anion stabilizing effect of selenium atom[8] that facilitates elimination of AcOH. Acetoxy-bromination of **3** by using NBS and AcOH in CH_2Cl_2 also failed due to the instability of the adducts which decomposed to uracil and **7** (33%) during silica gel column chromatography. We found the use of pivalic acid in place of AcOH enabled isolation of the adducts. Thus, when **3** was reacted with NBS (2 equiv.) and pivalic acid (5 equiv.) in CH_2Cl_2, a mixture of four possible diastereoisomers (**8**-**11**, 66%) was obtained after silica gel column chromatography (entry 1 in Table 1). These were separated by HPLC. Compound **8** was crystallized from EtOAc-hexane (mp 157-159 °C) and its stereochemistry was determined based on X-ray crystallographic



5 R= SePh
7 R= Br



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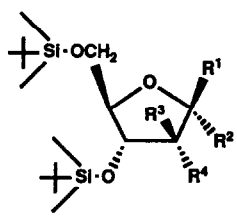


8 R^1= uracil-1-yl, R^2= $OC(O)CMe_3$, R^3= Br, R^4= H
9 R^1= $OC(O)CMe_3$, R^2= uracil-1-yl, R^3= Br, R^4= H
10 R^1= $OC(O)CMe_3$, R^2= uracil-1-yl, R^3= H, R^4= Br
11 R^1= uracil-1-yl, R^2= $OC(O)CMe_3$, R^3= H, R^4= Br

Table 1. Bromo-pivaloyloxylation of **3**.[a]

Entry	Solvent	pivalic acid (equiv.)	NBS (equiv.)	Yield (%)	Ratio of diastereomers[b] (**8** : **9** : **10** : **11**)	Ratio of *anti* / *syn*	Face-selectivity (β / α)
1	CH_2Cl_2	5	2	66	62 : 6 : 26 : 6	7.3 / 1	2.1 / 1
2	benzene	5.4	2	67	45 : 35 : 12 : 8	1.3 / 1	4 / 1
3	CH_2Cl_2	22	1.3	80	54 : 18 : 19 : 9	2.7 / 1	2.6 / 1
4	EtOAc	25	1.2	77	37 : 38 : 7 : 18	1 / 1.3	3 / 1
5	dioxane	25	1.2	80	33 : 48 : 7 : 12	1 / 1.5	4.3 / 1
6	ether	24	1.2	82	33 : 50 : 4 : 13	1 / 1.7	4.9 / 1
7[c]	ether	5	1.2	91	82 : 1 : 17 : 0	99 / 1	4.9 / 1

[a] All reactions were carried out at room temperature for 0.5 h.
[b] Calculated based on ^1H NMR spectroscopy by integrating H-6.
[c] Triethylamine (5 equiv.) was added.

analysis. In the case of **11**, its conversion to an O^2,2'-anhydro derivative upon brief treatment with DBU in CH_2Cl_2 gave confirmation for the structure. The assignment of the structures to **9** and **10** was done by analogy to **8** and **11**, respectively, in their ^1H NMR spectra.

As can be seen from entries 1-6 in Table 1, the incipient bromonium ion was formed preferentially at the β-face irrespective of the solvent employed, whereas the ratios of *anti- vs. syn*-addition are variable, presumably reflecting the extent of intervention of an oxonium intermediate. Ether gave the highest face-selectivity (entry 6). Furthermore, as shown in entry 7, almost exclusive *anti*-addition could be attained by adding Et_3N which increases nucleophilicity of pivalic acid. When the reaction of **3** was carried out in a fairly large scale (20-30 mmol) under the conditions given in entry 7, **8** was isolated in 55% yield simply by short column chromatographic workup followed by crystallization.

Compound **8** was reacted with various types of organosilicon reagents in CH_2Cl_2 in the presence of $SnCl_4$ as shown in Chart 1 (isolated yields are shown in parentheses). When allyltrimethylsilane was used, the desired 1'-*C*-allyl derivative **12** was accompanied by a highly polar product.[9] The ^1H NMR and MS spectra of this product were in good agreement with **13**, the structure of which indicated that an intramolecular trap of the silicon-stabilized β-carbocation intermediate with the base moiety had taken place.[10] Both **12** and **13** gave the same O^2,2'-anhydro derivative **14** upon treatment with TBAF in THF.[11] Other organosilicon reagents including silyl enol ethers also work in the reaction with **8** to furnish **15-19**. It should deserve a comment that isomeric products derived from β-face attack of the nucleophiles were hardly detectable throughout these reactions.

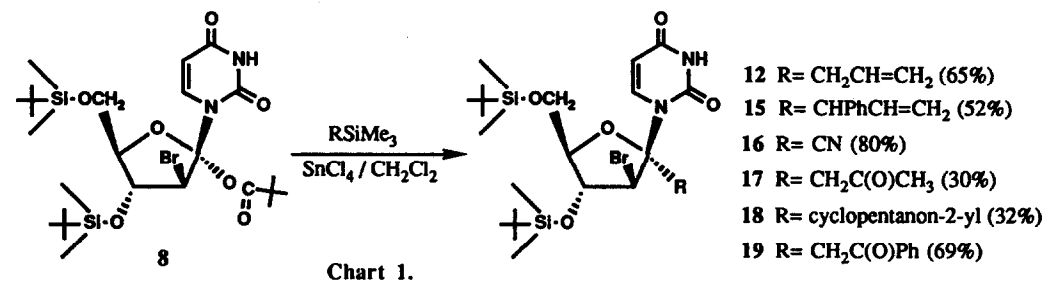
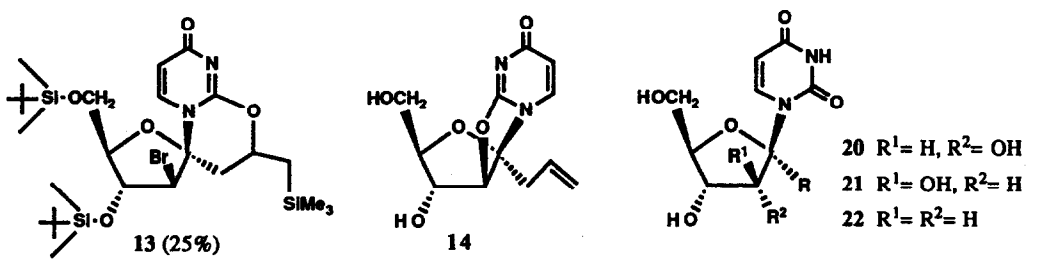


Chart 1.



In conclusion, we have disclosed here a C-C bond forming reaction at the anomeric position of nucleoside for the first time. By taking advantage of the presence of "2'-up" bromine atom in the resulting 1'-*C*-branched products, further transformations to the derivatives having ribo- (**20**), arabino- (**21**), and 2'-deoxyribo- (**22**) configurations would be possible. Although occurrence of angustmycins A and C as antibiotics stimulated the synthesis of this type of nucleosides,[12] the methods so far available involve initial preparation of an appropriate sugar precursor which is then condensed with a nucleobase to yield both α- and β-anomers in most cases.[13]

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References and Notes

1. For a review: Moffatt, J. G. *Nucleoside Analogues*; Walker, R. T.; De Clercq, E.; Eckstein, F. Eds; Plenum Publishing Corp.: 1979; pp. 71-164.
2. a) Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Tetrahedron Lett.* **1990**, *31*, 227-230. b) Haraguchi, K.; Tanaka, H.; Itoh, Y.; Miyasaka, T. *Ibid.* **1991**, *32*, 777-780. c) Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Ibid.* **1991**, *32*, 3391-3394. d) Haraguchi, K.; Itoh, Y.; Tanaka, H.; Akita, M.; Miyasaka, T. *Tetrahedron* **1993**, *49*, 1371-1390.
3. Nucleosidic α,β-unsaturated selenones have been used for the introduction of carbon substituents to the sugar portion. a) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507-4522. b) Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J. *Ibid.* **1991**, *47*, 3431-3450.
4. Haraguchi, K.; Tanaka, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *Tetrahedron Lett.* **1992**, *33*, 2841-2844.
5. a) Robins, M. J.; Trip, E. M. *Tetrahedron Lett* **1974**, 3369-3372. b) Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 5401-5408.
6. For an example: Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1984**, *25*, 2085-2088.
7. Very recently, an electrophilic addition of PhSeCl to furanoid glycals has been used for the synthesis of 2'-deoxynucleosides: El-Laghdach, A.; Díaz, Y.; Castillón, S. *Tetrahedron Lett.* **1993**, *34*, 2821-2822.
8. Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press: Oxford, 1986.
9. A typical procedure is given below for the synthesis of **12**. To a mixture of **8** (500 mg, 0.79 mmol) and allyltrimethylsilane (628 μL, 3.95 mmol) in CH_2Cl_2 (30 mL), $SnCl_4$ (1.03 mmol, CH_2Cl_2 solution) was added at –40 °C. The reaction mixture was allowed to warm to –20 °C over 2 h, quenched with aqueous $NaHCO_3$ and chromatographed on a silica gel column (10-50% EtOAc in hexane). This gave **12** (295 mg, 65%) and **13** (126 mg, 25%).
10. A similar cyclization has been observed in the reaction between perfluoroacetone and allyltrimethylsilane: Abel, E. W.; Rowley, R. J. *J. Organomet. Chem.* **1975**, *84*, 199-229.
11. Compound **14** was isolated as its 3',5'-di-*O*-acetyl derivative, the stereochemistry of which was confirmed by X-ray crystallography. The atomic coordinates for the acetate are available on request from the Cambridge Crystallographic Data Centre, University of Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
12. Buchanan, J. G.; Wightman, R. H. The Chemistry of Nucleoside Antibiotics. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; John Wiley and Sons, Inc.: New York, 1982; Vol. 6, pp. 253-255.
13. For several recent examples: a) Yoshimura, Y.; Ueda, T.; Matsuda, A. *Tetrahedron Lett.* **1991**, *35*, 4549-4552. b) Mahmood, K.; Vasella, A.; Bernet, B. *Helv. Chim. Acta* **1991**, *74*, 1555-1584. c) Elliott, R. D.; Niwas, S.; Riordan, J. M.; Montgomery, J. A.; Secrist III, J. A. *Nucleosides Nucleotides* **1992**, *11*, 97-119. d) Faivre-Buet, V.; Grouiller, A.; Descotes, G. *Ibid.* **1992**, *11*, 1651-1660.

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