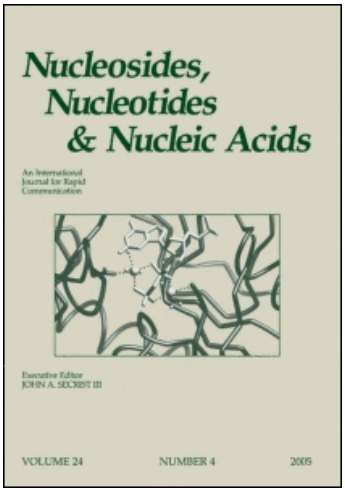

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STEREOSELECTIVE SYNTHESIS OF 1'-*C*-BRANCHED URACIL NUCLEOSIDES FROM URIDINE

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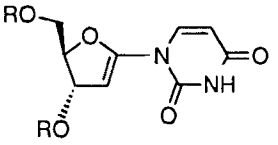
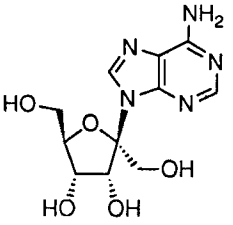
Abstract Face-selective electrophilic addition (bromo-pivaloyloxylation) to 1-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enofuranosyl]uracil (**1**), when combined with nucleophilic substitution using organosilicon or organoaluminum reagents, provides a new and highly divergent C-C bond forming method at the anomeric position.

Through several publications,[1] we have demonstrated that unsaturated-sugar nucleosides serve as versatile synthons for C-C bond formation. As a part of these studies, we planned to develop a new synthetic method for 1'-*C*-branched nucleosides by the use of 1-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enofuranosyl]uracil (**1**),[2] which is readily accessible from uridine. This was, of course, motivated by the occurrence of antitumor antibiotic angustmycin C (**2**) and also by the fact that available synthetic methods for this class of nucleosides always start with sugar precursors[3] and therefore have a considerable limitation in diversity of the anomeric substituents.



1 R= TBDMS



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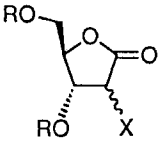
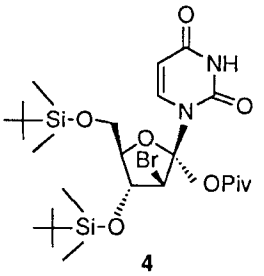


3 X= SePh or Br
R= TBDMS

We assumed that nucleophilic substitution at the anomeric position would be one promising approach to the present purpose.[4] To carry out the reaction stereoselectively, electrophilic addition to **1** was necessary, which allows

introduction of a C-1' leaving group as well as a C-2'-β substituent that exerts an anchimeric assistance. Attempted acetoxy-selenation (PhSeOAc in toluene) and acetoxy-bromination (NBS-AcOH in CH_2Cl_2) of **1** failed, forming unstable adducts which decomposed to the lactone **3**. The formation of **3** indicated that the carbonyl carbon of the introduced acetoxyl group was highly susceptible to nucleophilic attack.

We found that the use of pivalic acid (PivOH) in place of AcOH, provides enough stability to the adducts. Several attempts to optimize the reaction conditions in favor of the formation of the desired β-*anti*-adduct **4** are summarized in Table 1. Although β-face selectivity can be seen throughout entries 1-7, the ratio of *anti*- and *syn*-adducts varies from solvent to solvent. When the reaction was carried out in Et_2O in the presence of Et_3N (entry 7), almost exclusive *anti*-addition occurred, presumably due to increased nucleo-



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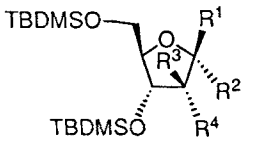
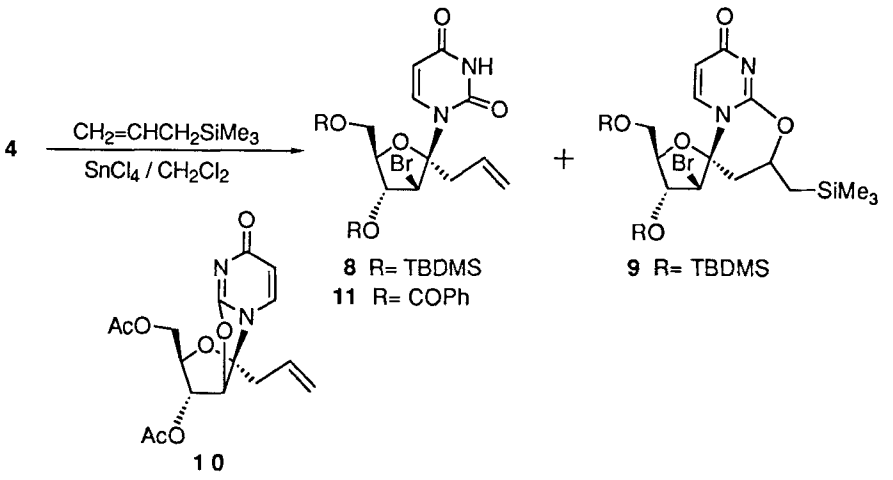


5 R^1= OPiv, R^2= uracil-1-yl, R^3= Br, R^4= H
6 R^1= OPiv, R^2= uracil-1-yl, R^3= H, R^4= Br
7 R^1= uracil-1-yl, R^2= OPiv, R^3= H, R^4= Br

Table 1. Bromo-Pivaloyloxylation of 1 [a]

Entry	Solvent	PivOH (equiv.)	NBS (equiv.)	Yield (%)	Ratio of **4-7** [b] (**4** : **5** : **6** : **7**)	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	CCl_4	5	2	68	46 : 32 : 12 : 10	1.4 / 1	3.5 / 1
3	benzene	5.4	2	67	45 : 35 : 12 : 8	1.3 / 1	4 / 1
4	CH_2Cl_2	22	1.3	80	54 : 18 : 19 : 9	2.7 / 1	2.6 / 1
5	EtOAc	25	1.2	77	37 : 38 : 7 : 18	1 / 1.3	3 / 1
6	ether	24	1.2	82	33 : 50 : 4 : 13	1 / 1.7	4.9 / 1
7	ether [c]	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] The ratio of **4-7** was determined based on ^{1}H NMR spectroscopy by integrating H-6.
[c] Triethylamine (5 equiv.) was added.

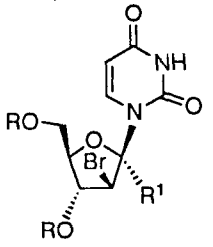


Scheme 1

philicity of PivOH. It may deserve a comment that **4** was isolated in 55% yield simply by short column chromatographic work-up followed by crystallization.

Nucleophilic substitution at the anomeric position of **4**, when carried out by the use of allyltrimethylsilane and $SnCl_4$, gave two products: **8** (65%) and **9** (25%), as depicted in Scheme 1. Treatment of **8** with Bu_4NF followed by Ac_2O gave **10**, the stereochemistry of which was confirmed by X-ray crystallographic analysis. Compound **9**, formed by intramolecular trap of the incipient silicon-stabilized carbocation, can be converted to **11** upon treatment with Bu_4NF in the presence of benzoic anhydride.

Similar reaction carried out by using cinnamyltrimethylsilane gave **12**; the cyclized product corresponding to **9** was not obtained. Other organosilicon reagents, including cyanotrimethylsilane and silyl enol ethers, also worked in this reaction to give **13**-**16** (yields of the isolated products are shown in parentheses).



12 R^1= CH(Ph)CH=CH_2 (52%, a mixture of two isomers)
13 R^1= CN (80%)
14 R^1= CH_2COPh (69%)
15 R^1= CH_2COMe (30%)
16 R^1= cyclopentanon-2-yl (32%, single isomer)

17 R^1= Me (73%)
18 R^1= Et (57%)
19 R^1= CH_2CHMe_2 (10%)
20 R^1= C≡CPh (69%)
21 R^1= $C{\equiv}CC_4H_9$ (86%)
22 R^1= $C{\equiv}CSiMe_3$ (76%)

For the introduction of simple alkyl groups to the anomeric position of **4**, trialkylaluminum reagents were found to be suitable, which is illustrated by the preparation of **17-19**. The low yield observed in the case of **19** is due to nucleophilic attack of hydride generated from the reagent.

It has been reported that the reactivity order of aluminum ligands is alkynyl > alkyl. However, when **4** was reacted with $Et_2AlC{\equiv}CPh$ in CH_2Cl_2, both **20** (15%) and **18** (9%) were formed together with a large amount of recovered **4** (54%). After several attempts, we found $R^1C{\equiv}CAlEtCl$ gave high yields of 1'-*C*-alkynylated products (**20-22**) without forming **18**.

In conclusion, the present study shows that the 1',2'-unsaturated nucleoside **1**, readily accessible from uridine, serves as useful precursor for the synthesis of 1'-*C*-branched derivatives of various types. It is worth noting that the reactions of **4** with organosilicon and organoaluminum reagents proceed stereospecifically to furnish uniformly the β-isomer.

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