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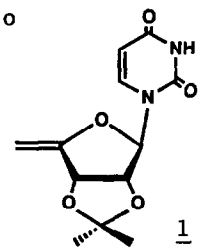
ADDITION OF CARBON RADICALS TO 4',5'-UNSATURATED URACILNUCLEOSIDES BY THE USE OF ORGANOSELENIUM REAGENTS: A NEW STEREOSELECTIVE ENTRY TO C-C BOND FORMATION AT THE 5'-POSITION

KAZUHIRO HARAGUCHI, HIROMICHI TANAKA, AND TADASHI MIYASAKA*
School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Summary Addition of carbon radicals generated from organoselenium reagents (PhSeR: R= COPh, CO_2Et, CH_2CO_2Et, CH_2COMe, and CH_2CN) to 4',5'-unsaturated uracilnucleosides was found to provide a highly efficient entry to C-C bond formation at the 5'-position, the stereochemical outcome of which is dependent upon the hydroxyl protecting group.

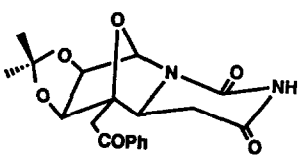
Several methods have been described for effecting C-C bond formation in the base moiety of nucleosides,[1] however the reactions so far known to be applicable to the sugar portion have been limited in number. Most reports have dealt with either Wittig reactions or nucleophilic addition reactions of keto and aldehyde derivatives of nucleosides.[2,3]

In our continuing studies on the use of organometallics in nucleoside chemistry,[1,3c,4] we were interested in constructing a C-C bond in the sugar portion by the use of 4',5'-unsaturated nucleosides such as 1. However, the exocyclic enol ether moiety of 1 is very sensitive to acid or base to result in some elimination products. In order to overcome this difficulty, we designed the addition of carbon radicals carried out under neutral conditions.[5] A recent communication on intermolecular addition of acyl radicals, generated from phenyl selenoesters, to an electron deficient alkene[6] prompted us to report our own results obtained from such reactions in 4',5'-unsaturated uracilnucleosides system.



1

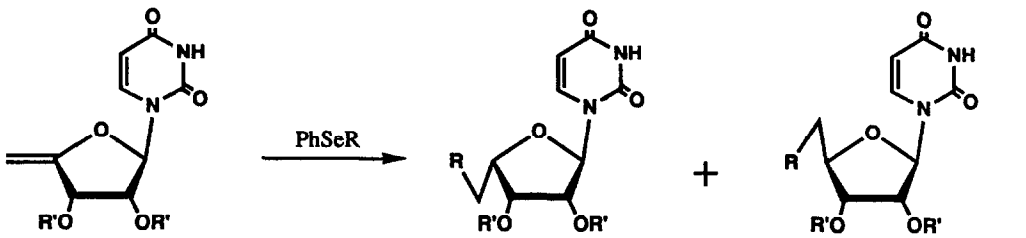
When a mixture of 1 and PhSeCOPh (4.2 equiv) in benzene was treated with Bu_3SnH (TBTH, 4.2 equiv) and AIBN at refluxing temperature for 4 h, the sole product was isolated in 26% yield. It was appeared to be a 5,6-dihydro-6,4'-cyclonucleoside 2,[7] which apparently resulted from intramolecular addition of the initially formed C-4' radical to the enone.



2

Since protection with the 2',3'-O-isopropylidene group is known to allow the sugar portion to approach the base moiety (C3'-endo conformation),[8] we turned to the use of 2',3'-bis-O-(tert-butyldimethylsilyl) (TBDMS) derivative 3,[9] which is considered to have a C2'-endo conformation.

Upon reacting 3 with benzoyl radical under similar conditions, again only one product (4: 38%) was formed. The ^{1}H-NMR spectrum of this product clearly showed the presence of a 5,6-double bond and therefore indicated that the C-4' radical reacted exclusively with TBTH. The stereochemistry of 4, an α-L-lyxo-furanosyl structure, was assigned based on its NOESY spectrum——NOE correlation was observed between H-4' and H-6. When 8.0 equiv of the selenium reagent was



3 R'= TBDMS
9 R'= Ac
18 R'= H

α-L-Lyxofuranosyl deriv. denoted by "lyxo" in Table 1

β-D-Ribofuranosyl deriv. denoted by "ribo" in Table 1

Table 1 Radical addition reaction to 3, 9, and 18*

Entry	Compd.	Radical Source	Product	R	R'	Isolated yield(%)
1	3	PhSeCOPh	4(lyxo)	COPh	TBDMS	73
2	3	PhSeCOEt	——	——	——	0
3	3	$PhSeCO_2Et$	5(lyxo)	CO_2Et	TBDMS	55
4	3	$PhSeCH_2CO_2Et$	6(lyxo)	CH_2CO_2Et	TBDMS	89
5	3	$PhSeCH_2COMe$	7(lyxo)	CH_2COMe	TBDMS	88
6	3	$PhSeCH_2CN$	8(lyxo)	CH_2CN	TBDMS	61
7	9	$PhSeCO_2Et$	10(lyxo)	CO_2Et	Ac	37
			11(ribo)	CO_2Et	Ac	28
8	9	$PhSeCH_2CO_2Et$	12(lyxo)	CH_2CO_2Et	Ac	46
			13(ribo)	CH_2CO_2Et	Ac	38
9	9	$PhSeCH_2COMe$	14(lyxo)	CH_2COMe	Ac	41
			15(ribo)	CH_2COMe	Ac	32
10	9	$PhSeCH_2CN$	16(lyxo)	CH_2CN	Ac	29
			17(ribo)	CH_2CN	Ac	20
11	18	$PhSeCO_2Et$	19(ribo)	CO_2Et	H	30
			20(lyxo)	CO_2Et	H	5
12	18	$PhSeCH_2CO_2Et$	21(ribo)	CH_2CO_2Et	H	45
			22(lyxo)	CH_2CO_2Et	H	7
13	18	$PhSeCH_2COMe$	23(ribo)	CH_2COMe	H	49
14	18	$PhSeCH_2CN$	24(ribo)	CH_2CN	H	32
			25(lyxo)	CH_2CN	H	3

* All reactions were carried out for 4 h either in refluxing benzene (entries 1-10) or in DMF at 60-70°C (entries 11-14) by using PhSeR (8.0 equiv), TBTH (8.0 equiv), and TBTH (0.5 equiv).

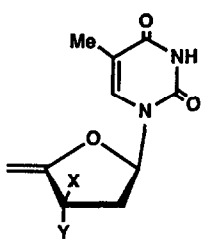
used in this reaction, 4 was isolated in a higher yield of 73% (see Table 1). On the other hand, use of PhSeCOEt (8.0 equiv) resulted in complete recovery of the starting material.[10] These observations prompted us to investigate further using a series of more electrophilic radicals. The results of experiments undertaken along these lines are summarized in Table 1.

It should be noted that all the reactions of 3 (entries 1 and 3-6) gave solely a product (4-8) having an α-L-lyxofuranosyl structure. This stereochemical outcome can be explained in terms of spatial shielding imposed by the bulky TBDMS group in 3 when the C-4' radical reacts with TBTH. Therefore, we next carried out the addition reaction by changing to a small protecting group.

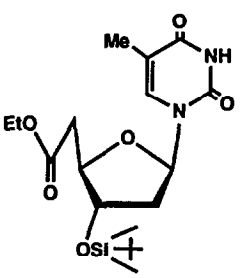
In accord with the above assumption, when 2',3'-di-O-acetyl derivative 9 was reacted with the respective radical, both α-L-lyxofuranosyl and β-D-ribofuranosyl derivatives (10-17) were isolated with a slight excess of the former as given in entries 7-10. Stereochemical assignment was unambiguously given to both types of product at this stage by comparing a pair of NOESY spectra.

In order to encourage stereoselectivity in the formation of the β-D-ribofuranosyl derivative, this method was ultimately extended to the corresponding free nucleoside, 1-(5-deoxy-β-D-erythro-pento-4-enofuranosyl)uracil (18). The choice of solvent appeared to be crucial: no reaction took place in MeCN and an unknown product having a phenylselenenyl group was obtained in MeOH. We found that the addition products were produced when a DMF solution of 18 was treated with the organoselenium reagents in the presence of TBTH and AIBN at 60-70°C. As can be seen in entries 11-14 for the formation of 19-25, stereoselectivity could be controlled to a greater extent with the desired β-D-ribofuranosyl derivatives[11] predominating——entry 13 gave 23 exclusively.

Finally, the application of this radical reaction to 2'-deoxy-4',5'-unsaturated nucleosides, such as 26 and 27, was examined briefly. When 26 was sub-



26 X= H, Y= OTBDMS
27 X= OAc, Y= H



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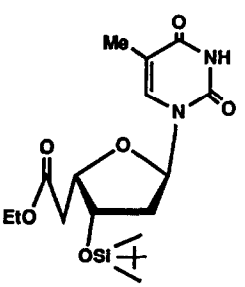

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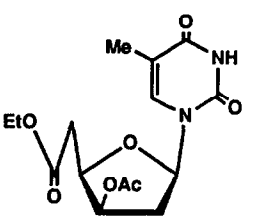

30

jected to the reaction with $PhSeCO_2Et$, almost equal amounts of both diastereomers (28: 27%, 29: 29%) were formed. This suggests that the previously mentioned stereospecific addition to 3 would be a reflection of a buttressing effect exerted by the 2'-substituent on the 3'-O-TBDMS group. In contrast to the case of 26, the same reaction of 27 resulted in the formation of 30 (79%) as the sole product. This indicates that approach of TBTH from the α-face of the

C-4' radical intermediate is facilitated by the additional presence of the base moiety.[12)]

ACKNOWLEDGEMENT The authors thank Dr. S. N. Farrow, National Cancer Centre, for reading the manuscript.

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6) D. L. Boger and R. J. Mathvink, J. Org. Chem., 54, 1777 (1989).

7) Although the ^{1}H-NMR spectrum indicated 2 was diastereomerically pure, the absolute configuration at the C-6 position has not been determined.

8) D. V. Santi and C. F. Brewer, J. Am. Chem. Soc., 90, 6236 (1968) and references cited therein.

9) Compound 3 was prepared from 2',3'-bis-O-TBDMS-O^2,5'-cyclouridine by treating with $(PhSe)_2/NaBH_4$ and successive selenoxide fragmentation.

10) Typical acyl radical has been reported to have nucleophilic character: P. Gottschalk and D. C. Neckers, J. Org. Chem., 50, 3498 (1985).

11) These products were separated after converting to the corresponding di-O-acetyl or bis-O-TBDMS derivatives.

12) All the compounds involved in the present study gave physical data consistent with their structures.

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