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Diastereoface Selectivity in Radical-Mediated C-C Bond Formation of Uridine 5'-Monoselenoacetals

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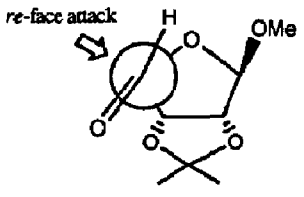
Key Words: radical reaction; Cram's rule; uridine; monoselenoacetal; diastereoselectivity

Abstract: *Intramolecular radical reaction of 2',3'-O-isopropylideneuridine 5'-monoselenoacetal 6 appeared to result in reverse stereoselectivity to that of the corresponding 5'-aldehyde (3). Intermolecular version of this reaction by using allyltributylstannane as a radical acceptor showed preferential anti-Cram diastereoface selection.*

Nucleophilic 1,2-addition of allyl organometallics to 5-aldehyde of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1**) has been reported and its stereoselectivity is summarized on the basis of Cram's rule.[1] That is, the use of allylmagnesium bromide or allyltrimethylsilane/BF_3-OEt_2 permits preferential *re*-face attack to the unchelated aldehyde having a C4-C5 conformation depicted in the structure **1**, which yields the allylated carbinol of (5*R*)-configuration (**2**). Presumably due to its well-defined stereochemistry, the reaction of allylmagnesium bromide with 2',3'-*O*-isopropylideneuridine 5'-aldehyde (**3**) has been employed as a key step in the total synthesis of a nucleoside antibiotic, octosyl acid A.[2]



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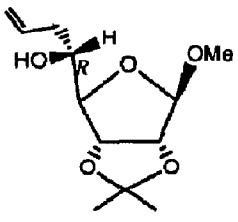

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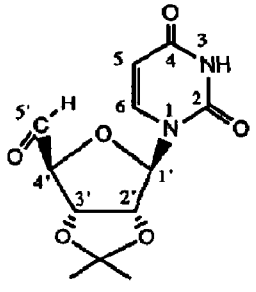
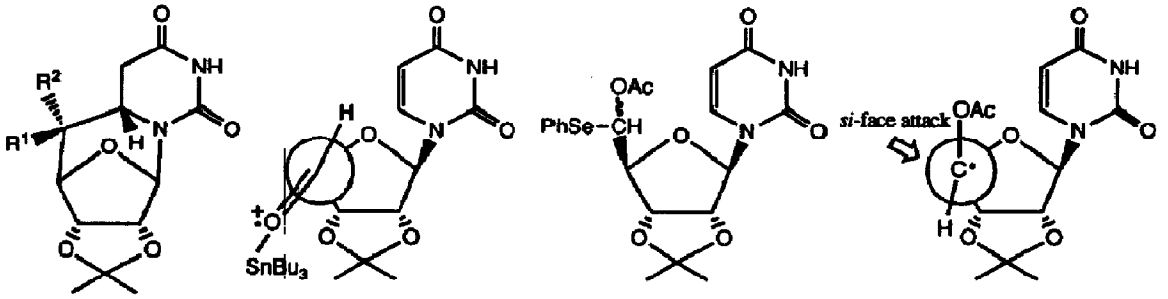


3

It has been demonstrated that stereochemical course of certain radical reactions also follows Cram's rule.[3] Ueda *et al.* reported that, when **3** was reacted with Bu_3SnH in the presence of AIBN, a radical-mediated intramolecular nucleophilic addition to the 5,6-double bond took place to give (5'*S*, 6*S*)-isomer **4** exclusively.[4] This result can be interpreted by assuming that the α-stannyloxy 5'-carbon-radical generated from **3** would have been at work with a C4'-C5' conformation like **5** and the uracil moiety reacted from 5's *si*-face.[5]

A recent report concerning radical cyclization of a uridine derivative having a silylated monoselenoacetal structure at the 5'-position[6] led us to publish here the results of our study. In this communication, we describe that stereochemical outcome of intramolecular radical reaction of uridine 5'-monoselenoacetal **6** is reverse to the above precedent of Ueda *et al.* with respect to the 5'-position. We have also examined the intermolecular version of this reaction by using allyltributylstannane and observed the preferential formation of anti-Cram product. Factors governing the stereoselectivity are briefly discussed.



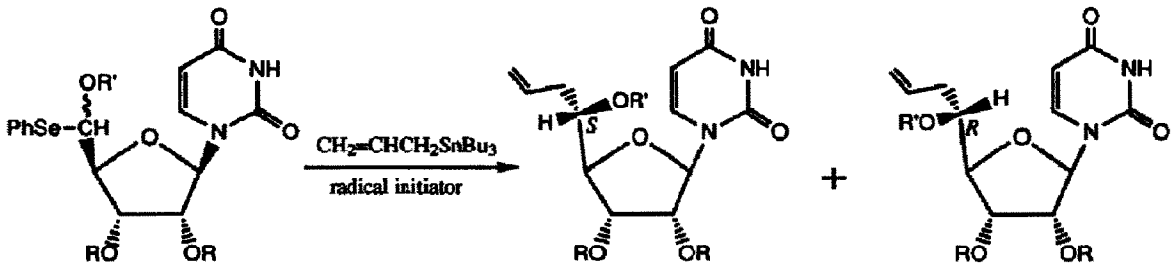
4 (5'*S*) R^1= OH, R^2= H
7 (5'*R*) R^1= H, R^2= OAc

5 **6** **8**

Compound **6** (a mixture of two diastereomers, *ca.* 2:1) was prepared through Pummerer type rearrangement of 5'-deoxy-2',3'-*O*-isopropylidene-5'-phenylselenouridine as reported previously.[7] When homolytic cleavage of the C5'-Se bond in **6** was carried out by adding a benzene solution of Bu_3SnH (2 equiv)/AIBN (0.5 equiv) at refluxing temperature (*via* syringe pump, over 4 h), two isomeric products [FAB-MS *m/z* 327 (M^++H)] were obtained. The major product (mp 182-184 °C, acetone/hexane) isolated in 57% yield appeared to be the (5'*R*, 6*S*)-isomer **7** by virtue of its X-ray crystallographic analysis,[8] while the minor product (16%) was determined to have (5'*S*, 6*S*)-stereochemistry based on ^1H NMR spectroscopy by examining its $J_{4',5'}$ and $J_{5',6}$ values.[9] When the above radical reaction of **6** was performed at room temperature under photochemically initiated conditions, $Bu_3SnH/(Bu_3Sn)_2$/hv/benzene, a higher (5'*R*)-stereoselectivity (7.5:1) was observed, however the combined yield of cyclized products (49%) was rather low due to the formation of a reduction product, 5'-*O*-acetyl-2',3'-*O*-isopropylideneuridine (35%).[10]

The observed dominant formation of **7** suggests that the α-acetoxy 5'-carbon-radical involved in this reaction would have an O4'-O5' *gauche*-conformation[11] as depicted in **8**. The putative conformational difference between **8** and **5** would be explicable in terms of larger group electronegativity of acetyl group (χ 2.864) in the former, which renders the radical species fairly localized, than that of trialkylstannyl group ($SnEt_3$ for example, χ 1.795) in the latter.[12] Based on this assumption, one would anticipate that an external radical acceptor could react preferentially from the *si*-face of **8**, in case where uracil moiety cannot intervene in the reaction. To investigate along this line, **9-11** were prepared from the corresponding 5'-deoxy-5'-phenylseleno derivative and reacted with allyltributylstannane (Scheme 1). These results are summarized in Table 1.

Although the use of acetyl group for 2',3'-*O*-protection completely prevented the intramolecular process, the result obtained by using **9** (entry 1) was discouraging both in terms of yield of the products (**12** and **13**) and stereoselectivity. The (5'*S*)-stereochemistry of **12** (mp 172-174 °C, acetone/hexane) was confirmed by X-ray



9 R= R'= Ac
10 R= TBDMS, R'= Ac
11 R= TBDMS, R'= COPh

12 R= R'= Ac
14 R= TBDMS, R'= Ac
16 R= TBDMS, R'= COPh

13 R= R'= Ac
15 R= TBDMS, R'= Ac
17 R= TBDMS, R'= COPh

Scheme 1

Table 1. Reactions of Uridine 5'-Monoselenoacetals (9-11) with Allyltributylstannane (5 equiv).

Entry	Compd.	Conditions	Yield (%)	Products (ratio)
1	9	AIBN/benzene/reflux, overnight	36	12 and 13 (10:9.5)
2	10	AIBN/benzene/reflux, overnight	84	14 and 15 (3:1)
3	10	AIBN/benzene/reflux, overnight[a]	96	14 and 15 (3.6:1)
4	10	$(Bu_3Sn)_2$/hv/benzene/r.t., 5 h	56	14 and 15 (6:1)
5	10	Et_3B/O_2/THF/r.t., 3 days	0[b]	—
6	11	AIBN/benzene/reflux, overnight	70	16 and 17 (6.6:1)[c]
7	11	$(Bu_3Sn)_2$/hv/benzene/r.t., 4 h	67	16 and 17 (10.2:1)
8	11	$(Bu_3Sn)_2$/hv/benzene/r.t., 4 h[a]	70	16 and 17 (9.9:1)
9	11	$(Bu_3Sn)_2$/hv/toluene/0 °C, 4 h	66	16 and 17 (12.7:1)
10	11	$(Bu_3Sn)_2$/hv/benzene/r.t., 4 h[d]	69	16 and 17 (4.8:1)

a) Allyltriphenylstannane (5 equiv) was used.
b) The starting material (10) was recovered.
c) As a by-product, 5'-*O*-benzoyl-2',3'-bis-*O*-TBDMS-uridine (14%) was also isolated.
d) Allyl chloride (5 equiv) was used.

crystallography.[8,13] As can be seen in entries 2-4, **10** having 2',3'-bis-*O*-TBDMS protection gave a higher yield of the allylated products (**14** and **15**) with an improved (5'*S*)-selectivity. Inspection of a molecular model showed a severe steric hindrance between the 3'-*O*-TBDMS and the 5'-*O*-acetyl groups when the radical intermediate takes a O4'-O5' *anti*-conformation (a buttressing effect exerted by the 2'-*O*-TBDMS group may also be working as an additional factor to increase the diastereoselectivity). In contrast to the reactions of **3** and **6**, it is conceivable that the above-mentioned steric hindrance is more important than the electronic effect in these cases, since the radical-mediated allylation of the corresponding 5'-aldehyde also resulted in the preferential formation of the (5'*S*)-isomer (AIBN/benzene/reflux, overnight, 5'*S* : 5'*R* = 3.6:1).[14]

It would be reasonable to expect that a bulkier 5'-*O*-protecting group further encourages the (5'*S*)-stereoselection. This turned out to be the case as listed in entries 6-10 where **11** was reacted to form **16** and **17**. Even the reaction of **11** in refluxing benzene (entry 6) gave a slightly higher selectivity than that of **10** carried out at room temperature (entry 4). The highest (5'*S*)-selectivity was attained upon reacting **11** at 0 °C in toluene (entry 9). Entry 10 shows an inexpensive reagent allyl chloride[15] can be used in place of allyltributylstannane only at the expense of the stereoselectivity.

In conclusion, although 1,2-asymmetric induction of simple α-oxycarbon radicals has been reported to follow Cram's rule,[3] the present study indicates that both electronic and steric effects of the substituent of the oxygen can alter diastereoface selectivity of the reaction, forming mainly anti-Cram product in certain cases.

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5) An intramolecular aldol reaction of 5-hydroxy-2',3'-*O*-isopropylideneuridine 5'-aldehyde has been reported and the sole formation of 2',3'-*O*-isopropylidene-6,5'(*S*)-cyclo-5-hydroxyuridine was explained in a similar manner based on Cram's rule: Rabi, J. A.; Fox, J. J. *J. Org. Chem.* **1972**, *37*, 3898-3901.

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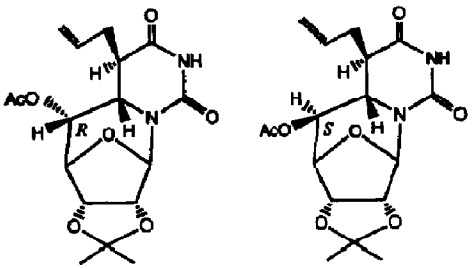
8) The atomic coordinates for **7** and **12** are availabe on request from the Cambridge Crystallographic Data Centre, University of Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

9) The *J* values (400 MHz) used to determine the stereochemistry of the minor product are shown below together with those of **7**. The minor product: $J_{4',5'}$= 4.6 Hz, $J_{5',6}$= 9.5 Hz. Compound **7**: $J_{4',5'}$= 2.2 Hz, $J_{5',6}$= 3.5 Hz.

10) When allyltributylstannane (2 equiv) was used in stead of Bu_3SnH in this reaction, the combined yield of cyclized products increased significantly (84.7%: A 78% and B 6.7% yields).



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13) Through the experiments listed in Table 1, it became apparent that the H-6 resonance of the (5'*S*)-isomers (**12**, **14**, and **16**) uniformly observed at a lower field (around δ 7.9 ppm) than that of the (5'*R*)-counterpart (**13**, **15**, and **17**, around δ 7.2 ppm).

14) The 5'-aldehyde was prepared by oxidation of 2',3'-bis-*O*-TBDMS-uridine and, after purification by short-column chromatography, was directly used for the radical reaction (overall combined yield of the products: 38%). The oxidation was carried out according to the published procedure: Camarasa, M.-J.; De las Heras, F. G.; Pérez-Pérez, M. J. *Nucleosides Nucleotides* **1990**, *9*, 533-546.

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