

shows the important role of this acidic region in the folding of proinsulin.

In our future studies, other regions of C-peptide sequence will be investigated for their involvement in the proinsulin folding. The combined results will provide a clear understanding on the folding behavior of this biologically important prohormone.

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## Regio- and Stereochemistry of Methoxyselenenylation of Acyclic Allylic Alcohol Derivatives and Allylic Phenylselenides

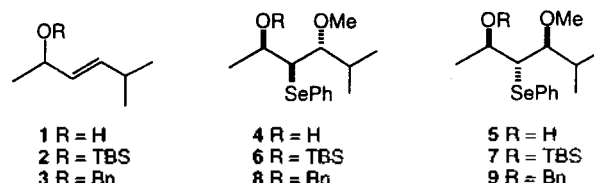
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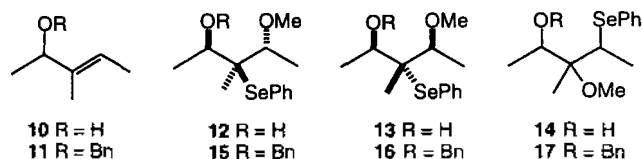
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Oxyselenenylation of olefin and the subsequent transformation have been appreciated as a useful tool in the synthesis of various important natural products.<sup>1</sup> Regio- and stereochemistry of the electrophilic selenenylation of olefin can be understood with the same rules as those of the usual electrophilic addition to olefin. Outcome of the regio- and stereochemistry in the oxyselenenylation of allylic alcohol derivatives, on the other hand, appears to be influenced by the directing effect of the allylic oxygen.<sup>2,3</sup> We have also reported recently the regio- and stereoselective methoxyselenenylation of acyclic allylic alcohol derivatives.<sup>4</sup> Nevertheless, the results on the regio- and stereochemistry of oxyselenenylation of allylic alcohol derivatives are sometimes contradictory and the origin of the selectivity is yet unclear.<sup>2-5</sup> Herein we report further results on the regio- and stereochemistry in methoxyselenenylation of acyclic allylic alcohol derivatives and allylic phenylselenides as well.

It was difficult to determine whether the outcome of regiochemistry was electronic or steric origin with the allylic alcohol derivatives used in earlier works including our own previous work.<sup>2-5</sup> Therefore, we first prepared (E)-5-methyl-3-hexen-2-ol (**1**) which has a bulky isopropyl group in the opposite side of the allylic hydroxyl group with a double bond between. Methoxyselenenylation of **1** and its derivatives **2** and **3** was completely regioselective and highly diastereoselective to afford mainly 1,3-*anti*-diol derivatives (Table 1, entries 1, 2, and 3). For example, to a solution of



allylic alcohol **1** (1.14 g, 10 mmol) and 2,6-di-*t*-butylpyridine (DTBP, 1.0 equiv.) in methanol (45 mL) was slowly added methanol solution (20 mL) of phenylselenenyl bromide (1.3 equiv.). The reaction was conducted under nitrogen atmosphere, at room temperature, and in the flask covered with aluminum foil. After completion of reaction, the reaction mixture was concentrated and partitioned between ether and water. The organic phase was washed with aq. NaHCO<sub>3</sub>, followed by chromatography afforded 1,3-*anti*- and 1,3-*syn*-hydroxymethoxide, **4** and **5**, in 98:2 ratio in 65% yield.<sup>6</sup> We also prepared (E)-3-methyl-3-penten-2-ol (**10**) and its benzyl ether **11**. Methoxyselenenylation of **10** and **11**, on the other hand, afforded not only 1,3-isomers but also 1,2-isomers **14** and **17**, respectively (Table 1, entries 4 and 5). The relative stereochemistry of the products **4-9** and **12-17** was determined by the same procedure as described in our previous work.<sup>4</sup> The result from the reaction of compounds **1**, **2**, and **3** indicates that the steric hindrance around episelenonium ion is not the determining factor for the regioselectivity in the methoxyselenenylation of

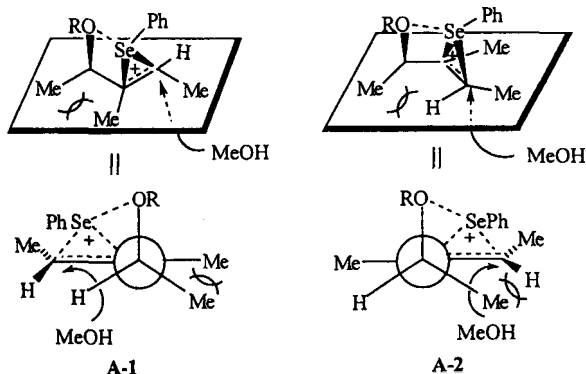
**Table 1.** Methoxyselenenylation of Allylic Alcohol Derivatives, 1, 2, 3, 10, and 11

Entry	Substrate	Products	Ratio	Yield <sup>a</sup> %
			1,3- <i>anti</i> /1,3- <i>syn</i> /1,2-isomer	
1	1	4/5	98:2	65
2	2	6/7	93:7	64
3	3	8/9	98:2	66
4	10	12/13/14	68:8:24 (89:11) <sup>b</sup>	57
5	11	15/16/17	53:9:38 (85:15) <sup>b</sup>	55

<sup>a</sup> Yield after isolation by flash chromatography. <sup>b</sup> The ratio in parentheses is that of 1,3-*anti* versus 1,3-*syn*.

allylic alcohol derivatives because C-4 position of the possible intermediate, episelenonium ion is not sterically more hindered than its C-3 position. On the other hand, the result with allylic alcohol derivatives 10 and 11, which have an additional methyl group attached to one of the double bond carbons, shows that the cation character of carbon atoms of the episelenonium ion is also a factor for outcome of the regiochemistry. However, it should be noted that methanol still attacks preferentially the secondary position, C-4 rather than the tertiary position, C-3.

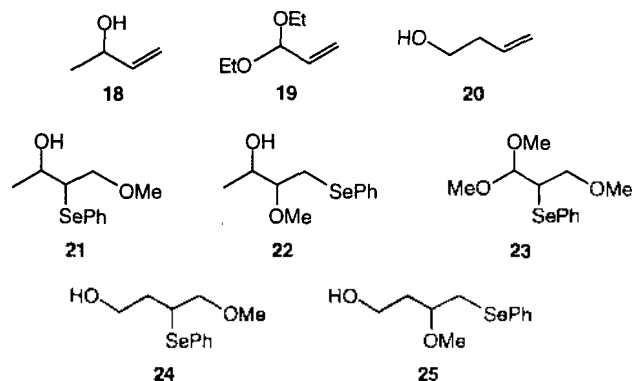
Stereoselectivity in the reaction of 1-3 can be explained by the exactly same way as that in our previous work.<sup>4</sup> On the other hand, the diastereoselectivity in the reaction of 10 and 11 is lower than those in the reaction of 1-3 and thus a substantial amount of 1,3-*syn* isomers, 13 and 16, were formed (Table 1, entries 4 and 5). The lower stereoselectivity in the reaction of 10 and 11 can be rationalized by models A-1 and A-2. Both conformations have the stabilizing interaction between the positive selenium and the al-



lylic oxygen, yet the transition state from A-1 would be more stable than that from A-2 because the unfavorable non-bonding interaction between the methyl group at C-1 and the hydrogen at C-4 in A-2 is more pronounced than the interaction between the methyl group at C-1 and the branched methyl group at C-3 in A-1. The methyl-methyl interaction in model A-1 would be the cause of the lower stereoselec-

tivity in this work since the corresponding model for the reaction of compounds 1-3 does not have the methyl-methyl interaction.

In order to compare the primary carbon and the secondary carbon as the position which methanol attacks, we carried out the methoxyselenenylation of terminal olefins, 18, 19, and 20 with phenylselenenyl bromide at room tem-



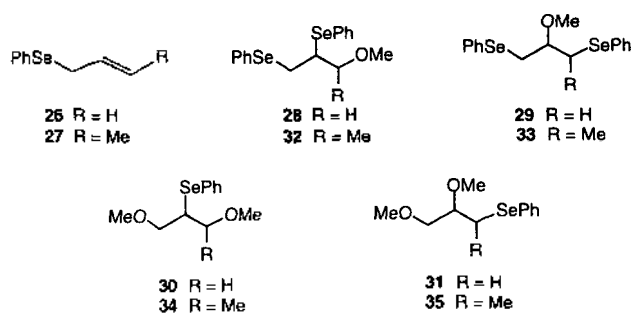
perature. The result in Table 2 shows that methanol attacks preferentially the primary position over the secondary carbon in allylic alcohol 18 and ketene acetal 19 to afford 1,3-isomers, 21 and 23<sup>7</sup> as a major product, respectively, although homoallylic alcohol 20 gave a terminal selenide, 25 as a major product which probably arose by attack of methanol at the secondary carbon of episelenonium ion. Despite the fact that compound 24 was found to be the minor product in the methoxyselenenylation of 20, we think that the hydroxyl oxygen in homoallylic alcohol 20 also exerts the directing effect on the incoming methanol, though smaller effect than with allylic counterparts, based on the fact that ethoxyselenenylation of 1-octene produced exclusively 2-ethoxy-1-phenylselenenyloctane.<sup>8</sup> It should be also mentioned that methoxyselenenylation of compound 19 having two oxygens in allylic position is more regioselective than that of compound 18 having one oxygen at allylic position.

In order to know whether atoms other than oxygen in allylic position, such as nitrogen, sulfur, or selenium, also influence the regioselectivity of oxy-selenenylation of double bonds or not, we prepared allylic phenylselenides 26 and 27. Methoxyselenenylation of 27 with phenylselenenyl bromide at room temperature gave not only methoxydiselenides 32 and 33 but also unexpected dimethoxydiselenides 34 and 35 in 67% yield. At -78 °C, however, methoxyselenenylation of 27 afforded only methoxydiselenides 32 and 33 in 10% yield.<sup>9</sup> Methoxyselenenylation of 26 provided a similar result as shown in Table 3. The ratio of 28 and 29, 8/42,

**Table 2.** Methoxyselenenylation of Terminal Olefins, 18, 19, and 20

Entry	Substrate	Products	Ratio	Yield <sup>a</sup> %
			1,3-/1,2-isomer	
1	18	21/22	93:7	79
2	19	23	100:0	67
3	20	24/25	20:80	63

<sup>a</sup> Yield after isolation by flash chromatography.

**Table 3.** Methoxyselenenylation of Phenylselenenyls **26** and **27**

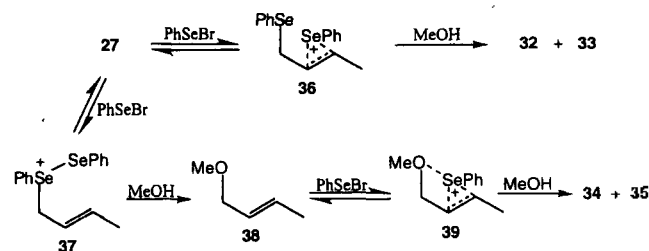
Entry	Substrate	Temp. °C	Products	Ratio	Yield <sup>d</sup> %
1	<b>26</b>	25	<b>28/29/30/31</b>	8:42:33:17	77
2	<b>26</b>	-78	<b>28+29</b>		20 <sup>b</sup>
3	<b>27</b>	25	<b>32/33/34/35</b>	26:8:9:57	66
4	<b>27</b>	-78	<b>32+33</b>		10 <sup>b</sup>

<sup>a</sup> Yield after isolation by flash chromatography. <sup>b</sup> Yield before completion of reaction.

and that of **32** and **33**, 26/8, in the reaction at 25 °C indicate that the selenium of allylic phenylselenenyls is not as influential as the oxygen of allylic alcohols over the outcome of regiochemistry in their methoxyselenenylation although the further investigation is required in order to obtain the exact ratio of isomers. It is noteworthy that there have been reports on existence of an unusual attractive interaction between selenium and oxygen in selenoiminoquinones and in selenazolenucleosides.<sup>10,11</sup>

Formation of unexpected dimethoxyselenenyls **34** and **35** can be explained by assuming an intermediate **37** in Scheme 1. Addition of phenylselenenyl bromide to phenylselenenyl bromide **27** would give either selenium ion **37**, in which phenylselenenyl bromide becomes a good leaving group, or episelenonium ion **36**, which would afford usual products **32** and **33**. Nucleophilic substitution at C-1 of intermediate **37** by methanol would give allylic methoxide **38** of which usual methoxyselenenylation would provide compounds **34** and **35** by way of episelenonium ion **39**. However, the ratio of **34** and **35**, 9/57, can not be readily understood when **38** is assumed as an intermediate since oxyselenenylation of allylic alcohols gives mostly or exclusively 1,3-dialkoxides as shown in our present and previous works.<sup>4</sup> Conversion of **32** and **33** to **34** and **35** was also not observed under the present methoxyselenenylation condition. Therefore, we speculate that another intermediate or pathway might involve for the formation of **34** and **35**.

Although the stereoselectivity of methoxyselenenylation of allylic alcohol derivatives can be reasonably well explained by nonbonding interactions of substituents and the attractive interaction between the allylic oxygen and the selenium in the episelenonium ion, the origin of the regiochemistry is still unclear. We speculate that the origin of

**Scheme 1.** Plausible mechanism for the methoxyselenenylation of **27**.

the regiochemistry is attributable to the nonsymmetrical episelenonium ion due to the attractive interaction between the allylic oxygen and the selenium of the episelenonium ion.<sup>12</sup> We are currently pursuing the preparation of the stable episelenonium ions of allylic alcohol derivatives and investigating their structures by NMR spectroscopy.

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