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.

Acknowledgment. This work was supported by Hanil Synthetic Fiber, Co.

References

1. Halban, P. A. *J. Biol. Chem.* **1982**, *257*, 13177.
2. (a) Steiner, D. F. *Diabetes* **1978**, *27*, Suppl. 1, 145. (b) Steiner, D. F. *Harvey Lect.* **1984**, *78*, 191.
3. Gross, D. J.; Villa-Komaroff, L.; Kahn, C. R.; Weir, G. C.; Halban, P. A. *J. Biol. Chem.* **1989**, *264*, 21486.
4. Studier, W. F.; Rosenberg, A. H.; Dunn, J. J.; Dubendorff, J. W. *Methods Enzymol.* **1990**, *185*, 60
5. Kim, D.-Y.; Shin, N.-K.; Chang, S.-G.; Shin, H.-C. *Biotechnol. Tech.* **1996**, *10*, 669.
6. Grau, U. *Diabetes* **1985**, *34*, 1174.
7. Wollmer, A.; Brandenburg, D.; Vogt, H.-P.; Schermutski, W. *Hoppe-Seyler's Z. Physiol. Chem.* **1974**, *355*, 1471.
8. (a) Katsoyannis, P. G. *Biochemistry* **1967**, *6*, 2642. (b) Chance, R. E. In *Peptides, Synthesis, Structure and Function*; Rich, D. H.; Gross, E., Eds.; Proc. 7th American Peptide Symposium, Pierce Chemical Co.: 1981; pp 712-728.
9. Wang, C.-C.; Tsou, C.-L. *TIBS* **1991**, *16*, 279.
10. (a) Taylor, N. A.; Doherty, K. *Biochem. J.* **1992**, *286*, 619. (b) Rhodes, C. J.; Lincoln, B.; Shoelson, S. E. *J. Biol. Chem.* **1992**, *267*, 22719.
11. Kaufmann, J. E.; Irminger, J.-C.; Halban, P. A. *Biochem. J.* **1995**, *310*, 869.
12. Powell, S. K.; Orci, L.; Criak, C. S.; Moore, H. P. H. *J. Cell. Biol.* **1988**, *105*, 1843.

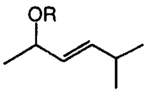
Regio- and Stereochemistry of Methoxyselenenylation of Acyclic Allylic Alcohol Derivatives and Allylic Phenylselenides

Kwan Soo Kim*, Kwang Ook Ahn, and Jong Il Park

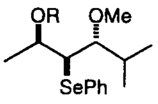
Department of Chemistry, Yonsei University, Seoul 120-749, Korea

Received May 26, 1997

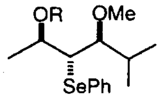
Oxyselenenylation of olefin and the subsequent transformation have been appreciated as a useful tool in the synthesis of various important natural products.[1] Regio- and stereochemistry of the electrophilic selenenylation of olefin can be understood with the same rules as those of the usual electrophilic 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.[2,3] We have also reported recently the regio- and stereoselective methoxyselenenylation of acyclic allylic alcohol derivatives.[4] 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.[2-5] Herein we report further results on the regio- and stereochemistry in methoxyselenenylation of acyclic allylic alcohol derivatives and allylic phenylselenides as well.



1 R = H
2 R = TBS
3 R = Bn

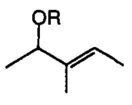


4 R = H
6 R = TBS
8 R = Bn

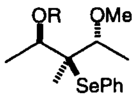


5 R = H
7 R = TBS
9 R = Bn

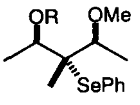
It was difficult to determine whether the outcome of regiochemistry was electronic or steric origin with the allylic alcohol derivatives used in earlier works including our own previous work.[2-5] Therefore, we first prepared (E)-5-methyl-3-hexen-2-ol (**1**) which has a bulky isopropyl group in the 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. $NaHCO_3$ followed by chromatography afforded 1,3-*anti*- and 1,3-*syn*-hydroxymethoxide, **4** and **5**, in 98 : 2 ratio in 65% yield.[6] 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.[4] 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



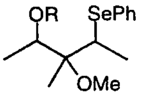
10 R = H
11 R = Bn



12 R = H
15 R = Bn



13 R = H
16 R = Bn



14 R = H
17 R = Bn

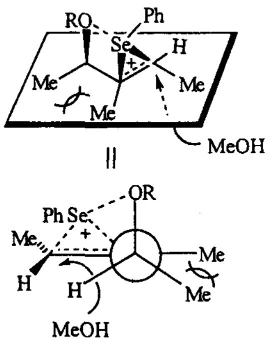
Table 1. Methoxyselenenylation of Allylic Alcohol Derivatives, **1**, **2**, **3**, **10**, and **11**

Entry	Substrate	Products	Ratio 1,3-*anti*/1,3-*syn*/1,2-isomer	Yield[a] %
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)[b]	57
5	**11**	**15/16/17**	53:9:38 (85:15)[b]	55

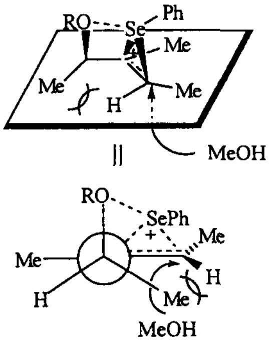
[a] Yield after isolation by flash chromatography. [b] The ratio in parentheses is that of 1,3-*anti* versus 1,3-*syn*.

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.[4] 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 allylic oxygen, yet the transition state from **A-1** would be more stable than that from **A-2** because the unfavorable nonbonding 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 stereoselectivity in this work since the corresponding model for the reaction of compounds **1**-**3** does not have the methyl-methyl interaction.

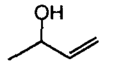


A-1

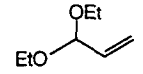


A-2

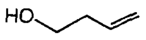
In order to compare the primary carbon and the secondary carbon as the position which methanol attacks, we carried out the methoxyselenenylation of terminal olefins, **18**, **19**, and **20** with phenylselenenyl bromide at room temperature. The result in Table 2 shows that methanol attacks preferentially the primary position over the secondary carbon in allylic alcohol **18** and ketene acetal **19** to afford 1,3-isomers, **21** and **23**[7] 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.[8] 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.



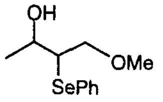
18



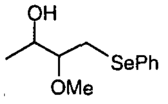
19



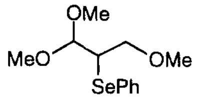
20



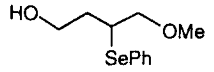
21



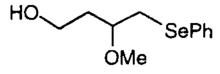
22



23



24



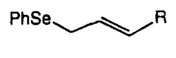
25

In order to know whether atoms other than oxygen in allylic position, such as nitrogen, sulfur, or selenium, also influence the regioselectivity of oxyselenenylation 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 dimethoxyselenides **34** and **35** in 67% yield. At -78 °C, however, methoxyselenenylation of **27** afforded only methoxydiselenides **32** and **33** in 10% yield.[9] Methoxyselenenylation of **26** provided a similar result as shown in Table 3. The ratio of **28** and **29**, 8/42,

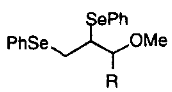
Table 2. Methoxyselenenylation of Terminal Olefins, **18**, **19**, and **20**

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

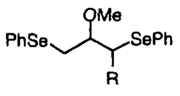
[a] Yield after isolation by flash chromatography.



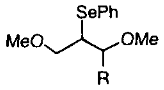
26 R = H
27 R = Me



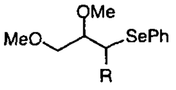
28 R = H
32 R = Me



29 R = H
33 R = Me



30 R = H
34 R = Me



31 R = H
35 R = Me

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

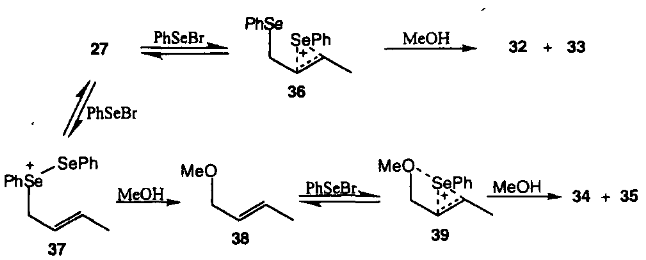
Entry	Substrate	Temp. °C	Products	Ratio	Yield[a] %
1	**26**	25	**28/29/30/31**	8:42:33:17	77
2	**26**	−78	**28+29**		20[b]
3	**27**	25	**32/33/34/35**	26:8:9:57	66
4	**27**	−78	**32+33**		10[b]

[a] Yield after isolation by flash chromatography. [b] 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 phenylselenides 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.[10,11]

Formation of unexpected dimethoxyselenides **34** and **35** can be explained by assuming an intermediate **37** in Scheme 1. Addition of phenylselenenyl bromide to phenyselenide **27** would give either selenium ion **37**, in which phenyselenide 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 alkoxides gives mostly or exclusively 1,3-dialkoxides as shown in our present and previous works.[4] 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 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.[12] We are currently pursuing the preparation of the stable episelenonium ions of allylic alcohol derivatives and investigating their structures by NMR spectroscopy.



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

Acknowledgment. This research was supported by a grant from Basic Research Institute Program, Ministry of Education (BSRI-96-3422). Support from OCRC is also acknowledged.

References

1. Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, 1984.
2. Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258-1267.
3. Cooper, M. A.; Ward, A. D. *Tetrahedron Lett.* **1995**, *36*, 2327-2330.
4. Kim, K. S.; Park, H. B.; Kim, J. Y.; Ahn, Y. H.; Jeong, I. H. *Tetrahedron Lett.* **1996**, *37*, 1249-1252.
5. Haughan, A. F.; Knight, J. R.; Sweeney, J. B. *Tetrahedron Lett.* **1994**, *35*, 1781-1784.
6. Although the yield was not high, the regioisomers were not detected at all in the reaction mixture.
7. Acid catalyzed transacetalization occurred probably by acidic 2,6-di-*t*-butylpyridinium bromide which was generated during the reaction.
8. Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1978**, 799-802.
9. The yield of products **32** and **33** was low because the rate of the methoxyselenenylation became slower than that of the decomposition of phenylselenenyl bromide to diphenyldiselenide at low temperature, but other isomers or products were not produced.
10. Barton, D. H. R.; Hall, M. B.; Lin, Z.; Parekh, S. I.; Reibenspies, J. *J. Am. Chem. Soc.* **1993**, *115*, 5056-5059.
11. Burling, F. T.; Goldstein, B. M. *J. Am. Chem. Soc.* **1992**, *114*, 2313-2320.
12. Symmetrical episelenonium ions of simple olefins have been observed by ^{1}H and ^{13}C NMR spectroscopy. See: Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, 3991-3994.