Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1249-1252, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02408-5

Stereoselective Methoxyselenenylation of Acyclic Allylic Alcohol Derivatives: A Method for the Synthesis of 1,3-*anti*-Diols

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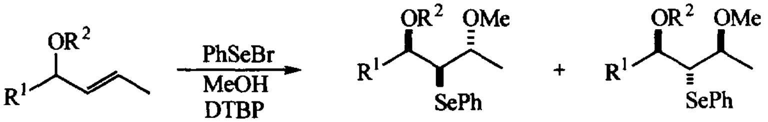
Abstract: Reaction of secondary acyclic *trans*-allylic alcohol derivatives with PhSeBr in the presence of 2,6-di-*t*-butylpyridine in MeOH proceeded in a highly regio- and stereoselective manner and the subsequent reduction and deprotection of the resultant methoxyselenides afforded mostly 1,3-*anti*-diols. The methoxyselenenylation of the acetate derivative of the same allylic alcohol, on the other hand, gave several other isomers along with the 1,3-*anti*-diol derivative.

Oxyselenenylation of allylic alcohols and the subsequent transformation of the resultant oxyselenides would provide valuable 1,2- or 1,3-diols. Although electrophilic selenenylation is one of the most widely used methods for the transformation of olefins,[1] the methodology employing the oxyselenenylation of allylic alcohols has not been recognized as convenient as other methods for the synthesis of 1,2- or 1,3-diols,[2] partly because the regio- and stereochemistry of this reaction has not yet been firmly established. The stereochemistry of the electrophilic selenenylation of cyclic allylic alcohols and the regiochemistry of both cyclic and acyclic allylic alcohols has been documented although the results are sometimes contradictory and the origin of the selectivity is yet unclear.[3-5] The stereochemistry of the selenenylation of acyclic secondary allylic alcohols, on the other hand, has not been reported. Recent reports on the existence of an unusual attractive interaction between selenium and oxygen in selenoiminoquinones[6] and in selenazole nucleosides[7] gave us further impetus to the present work. We envisioned that the attractive interaction between the selenium of the incoming electrophile and the oxygen of the allylic system in a certain conformation might greatly enhance the regio- and stereoselectivity of the oxyselenenylation of acyclic allylic alcohols.

We have indeed found that methoxyselenenylations of acyclic *trans*-allylic alcohol derivatives, **1a**, **b**, **c** and **2a**, **b**, **c**, having a free hydroxy group or a nonparticipating protective group are highly diastereoselective and completely regioselective to afford mainly 1,3-*anti*-diol derivatives (Table 1). For example, to a solution of allylic benzyl ether **2b** (0.95 g, 5.0 mmol) and 2,6-di-*t*-butylpyridine (DTBP, 1.0 equiv.) in methanol (25 ml) was slowly added a methylene chloride solution (2.5 ml) of phenylselenenyl bromide (1.0 equiv.) at room temperature.[8] After the brownish red solution turned into yellow within 30 min, the solvent was evaporated and the residue was 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*-methoxybenzyl ethers, **5b**[9] and **6b**, in 92:8 ratio in 83 % yield. The nonparticipating protective groups did not affect substantially the yield and the outcome of the sterecheomistry, although a slightly better diastereoselectivity was observed with MEM derivatives, **1c** and **2c**. It should also be noted that **2a**, **b**, **c** (R^1 = Et) showed a little higher diastereoselectivity than **1a**, **b**, **c** (R^1 = Me). However, the methoxyselenenylation of acetylated allylic alcohols, **1d** and **2d**, gave not only 1,3- but also 1,2-diol derivatives and other isomers. We have carefully analyzed the products of the methoxyselenenylation of acetate **2d** and have identified three 1,3-methoxyacetates **5d**, **6d**, and **7**, two 1,3-hydroxyacetates **8** and **9**, and two 1,2-hydroxyacetates **10** and **11**. The methoxyselenenylation of benzoate **2e**, on the other hand, gave only three 1,3-methoxybenzoates, **5e**, **6e**, and **12**. Unlike an earlier important report by

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



1,3-*anti*

1,3-*syn*

1 $R^1 = Me$
2 $R^1 = Et$

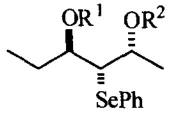
3 $R^1 = Me$
5 $R^1 = Et$

4 $R^1 = Me$
6 $R^1 = Et$

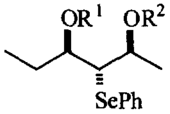
substrate	R^2	products	ratio *anti*/*syn*/others	yield[a] %
1a	H	**3a/4a**	92 : 8	73
1b	Bn	**3b/4b**	90 : 10	93
1c	MEM	**3c/4c**	95 : 5	80
1d	Ac	**3d/4d**[b]	87 : 13[b]	55[b]
2a	H	**5a/6a**	98 : 2	70
2b	Bn	**5b/6b**	92 : 8	83
2c	MEM	**5c/6c**	98 : 2	83
2d	Ac	**5d/6d/7/8+9/10+11**	41:3.5:13.5:38:4	90
2e	Bz	**5e/6e/12**	72:4:24	83

[a] Yield after isolation by flash chromatography. [b] Other isomers formed were not identified.

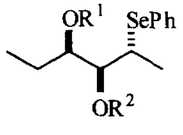
Liotta *et al.* on the chloroselenenylation of acyclic and cyclic allylic acetates,[3] the acetyl group in the present work was not found to be a better directing group than others with regard to the regio- and stereoselectivity. Although acetates **1d** and **2d** and benzoate **2e** generated a substantial amount of other isomers, the ratio of 1,3-*anti* and 1,3-*syn* products fell in the same range as others; 87:13 for **3d/4d**, 92:8 for **5d/6d**, and 95:5 for **5e/6e**. The 1,3- and 1,2-diol derivatives obtained in the methoxyselenenylation were converted to their corresponding diols in high yields by reductive deselenation and subsequent deprotection. For example, reduction of selenide **5b** with $(n\text{-Bu})_3SnH$ in benzene in the presence of AIBN afforded compound **13**[10] in 92 % yield and the deprotection of **13** with $(n\text{-Bu})_4NI$ and $BF_3{\cdot}OEt_2$ in chloroform provided 1,3-*anti*-diol **14** in 64 % yield. The stereochemistry of 1,3-diol derivatives **3** and **4** was readily established since their conversion led to known diols, namely (±)-2,4-pentanediol and *meso*-2,4-pentanediol, respectively. The configuration of 1,3-diol derivatives **5** and **6**, on the other hand, was determined by the comparison of the ^{13}C NMR chemical shifts for each acetal carbon of their acetonides[11] on the basis of an established method.[12] Once the relative



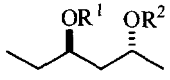
7 $R^1 = Ac, R^2 = Me$
12 $R^1 = Bz, R^2 = Me$



8 $R^1 = Ac, R^2 = H$
9 $R^1 = H, R^2 = Ac$



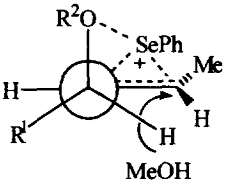
10 $R^1 = Ac, R^2 = H$
11 $R^1 = H, R^2 = Ac$
15 $R^1, R^2 = H$



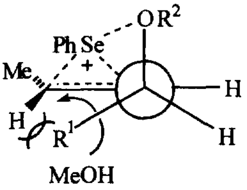
13 $R^1 = Bn, R^2 = Me$
14 $R^1, R^2 = H$

stereochemistry at carbons bearing oxygen was determined, the configuration at the carbon bearing the phenylseleno group could be also assigned on the basis of the ^{1}H NMR coupling constants and NOE data of acetonides containing the phenylseleno group. Similary, the stereochemistry of 1,2-hydroxyacetates **10**[13] and **11** was also determined by the examination of the ^{1}H NMR data of the methylene acetal and deselenated methylene acetal[14] of diol **15** on the basis of a known method[15] and by NOE experiments.

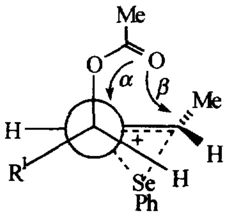
Predominant formation of 1,3-*anti* products, **3** and **5**, over 1,3-*syn* products, **4** and **6**, can be rationalized by simple models **A-1** and **A-2**. Although both conformations have the stabilizing interaction between the positive selenium and the allylic oxygen, **A-1** would lead to a lower energy transition state than **A-2** because of the unfavorable nonbonding interaction between R^1 and the olefinic hydrogen in A-2. When a participating acyl group is present in the allylic system, not only models **A-1** and **A-2** but also participating models are required in order to explain the generation and stereochemistry of the products. In the methoxyselenenylation of acetate **2d**, there would be two possible conformations **B-1** and **B-2** available in which the carbonyl oxygen of the acetyl group can intramolecularly attack the episelenonium ion from its back side. The reaction of **2d** would proceed through the lower energy transition state derived from **B-1** rather than that from **B-2**, because of the unfavorable interaction between R^1 and the vinylic H in **B-2**, to afford 1,2-*syn*- and 1,3-*syn*-oxonium ions, **16** (through α-attack) and **17** (through β-attack) as shown in Scheme 1.[16] Then, if methanol attacks C-2 of **17**, the 1,3-*anti*-diol derivative **7** will be produced while the attack of methanol on the acetal carbon of **17** will give orthoester **18** which on workup would be hydrolyzed to afford 1,3-*syn*-hydroxyacetates **8** and **9**, Similary, 1,2-



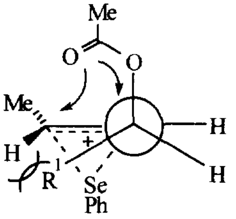
A-1



A-2

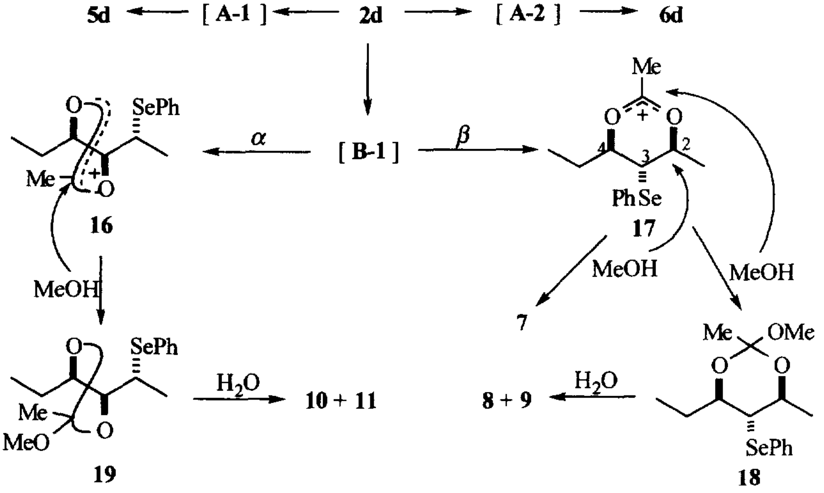


B-1



B-2

Scheme 1. Plausible mechanism for the methoxyselenenylation of acetate **2d**



syn-hydroxyacetates **10** and **11** could be also formed by way of oxonium ion **16** and orthoester **19**.[17] The formation of 1,3-*anti*-methoxybenzoate **12** from benzoate **2e** also can be explained by assuming the reaction between 1,3-*syn*-oxonium ion and methanol in the similar manner to the formation of **7** from **2d** by way of **17** and **18**. We are currently investigating the effect of other protective groups on the diastereoselectivity and seeking the conditions for the selective formation of 1,2-diols.

Acknowledgement: This research was supported by a grant from Basic Science Research Institute Program, Ministry of Education (BSRI-95-3422). Support from OCRC is also acknowledged.

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8. In the absence of DTBP, the reaction became less clean and the lower yield was observed. Temperature and solvent did not appreciably affect the stereochemistry and the yield, although the reaction time increased at lower temperature (0°C) or by using methylene chloride/ MeOH solution.
9. Compound **5b**: ^{1}H NMR (CDCl$_3$) δ 0.92 (t, J = 7.5 Hz, 3 H), 1.28 (d, J = 6.17 Hz, 3 H), 1.92 (m, 2 H), 3.18 (dd, J = 8.43, 1.76 Hz, 1 H), 3.23 (s, 3 H), 3.64 (dq, J = 8.43, 6.17 Hz, 1 H), 3.86 (dt, J = 6.84, 1.76 Hz, 1 H), 4.53 and 4.65 (ABq, J = 11.8 Hz, 2 H), 7.22-7.30 (m, 5 H), 7.32-7.35 (m, 3 H), 7.56-7.59 (m, 2 H); MS (EI) *m/z* (rel intensity) 376 (M$^+$, 1.3), 198 (5.8), 197 (5.7), 158 (2.6), 157 (10.2), 155 (5.5), 91 (100), 59 (5.3). All new compounds gave satisfactory spectroscopy and/or microanalytical data.
10. Compound **13**: ^{1}H NMR (CDCl$_3$) δ 0.93 (t, J = 7.45 Hz, 3 H), 1.14 (d, J = 6.14 Hz, 3 H), 1.54-1.72 (m, 2 H), 3.27 (s, 3 H), 3.49-3.62 (m, 2 H), 4.45 and 4.60 (ABq, J = 11.5 Hz, 2 H), 7.25-7.36 (m, 5 H); MS (EI) *m/z* (rel intensity) 190 (7.6), 161 (14.0), 107 (12.8), 91 (100), 84 (26.6), 59 (16.1).
11. Acetonide of diol **14**: ^{1}H NMR (CDCl$_3$) δ 0.91 (t, J = 7.40 Hz, 3 H), 1.19 (d, J = 6.30 Hz, 3 H), 1.36 (s, 6 H), 1.39-1.66 (m, 4 H), 3.65-3.77 (m, 1 H), 3.91-4.04 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 100.4, 68.3, 63.0, 40.0, 29.0, 25.2, 25.0, 21.8, 9.8; MS (EI) *m/z* (rel intensity) 143 (75.1), 83 (87.3), 59 (100), 43 (54.9).
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13. Compound **10**: ^{1}H NMR (CDCl$_3$) δ 0.85 (t, J = 7.42 Hz, 3 H), 1.46 (d, J = 7.15 Hz 3 H), 1.54-1.72 (m, 2 H), 2.06 (s, 3 H), 2.56 (brs, 1 H), 3.35 (dq, J = 7.15, 4.95 Hz, 1 H), 3.61-3.71 (m, 1 H), 4.99-5.07 (m, 1 H), 7.19-7.29 (m, 3 H), 7.47-7.60 (m, 2 H).
14. Methylene acetal of **15**: ^{1}H NMR (CDCl$_3$) δ 0.98 (t, J = 7.42 Hz, 3 H), 1.48 (d, J = 7.02 Hz, 3 H), 1.55-1.75 (m, 2 H), 3.25-3.33 (m, 1 H), 3.75 (dd, J = 5.22, 7.14 Hz, 1 H), 3.79-3.89 (m, 1 H), 5.00 (s, 2 H), 7.25-7.34 (m. 3 H), 7.56-7.61 (m, 2 H). Deselenated methylene acetal of **15**: ^{1}H NMR (CDCl$_3$) δ 1.01 (t, J = 7.42 Hz, 6 H), 1.51-1.66 (m, 4 H), 3.45-3.54 (m, 2 H), 4.97 (s, 2 H).
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16. Exclusive generation of products through **B-1** might also be explained by assuming the oxonium ion-like cyclic transition states. The cyclic transition states from **B-1** forming oxonium ions **16** and **17** would be in the lower energy than those from **B-2** forming the corresponding oxonium ions.
17. We observed the formation of intermediates, probably orthoesters **18** and **19**, on TLC during the reaction but were unable to isolate them owing to their instability.

(*Received in Japan* 27 *October* 1995; *revised* 8 *December* 1995; *accepted* 18 *December* 1995)