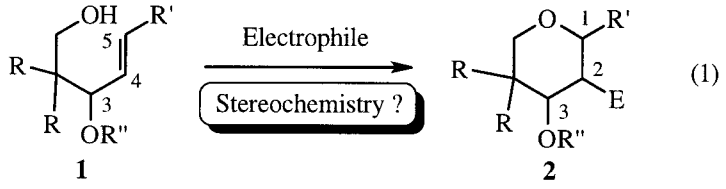
SUBSTITUENT EFFECTS ON THE STEREOCHEMICAL COURSE OF ELECTROPHILE-INITIATED TETRAHYDROPYRAN-FORMING REACTIONS: A POSSIBLE STEREOELECTRONIC EFFECT

David J. Hart* and Suzanne Patterson, and Alain Zakarian

Department of Chemistry, The Ohio State University, 100 W. 18th Ave., Columbus, Ohio 43210, USA

Abstract — A series of 4-penten-1,3-diol derivatives were prepared and treated with phenylselenenyl chloride to provide tetrahydropyrans. The stereochemical course of the reactions is consistent with a chair-like transition state in which the oxygen substituent at the 3-position largely occupies an axial site. A structurally related 3-methyl-4-penten-1-ol derivative gave a major product consistent with a chair transition state in which the methyl group occupies an equatorial site.

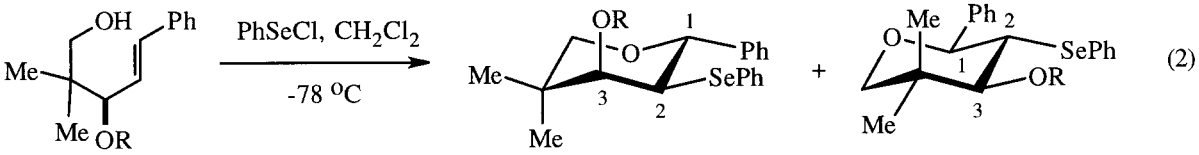
During the course of studies directed toward natural products with tetrahydropyran substructures, we have studied the stereochemical course of electrophile-initiated cyclizations of 5-aryl-4-penten-1-ols.[1-4] This work has recently been extended to cyclizations of the type shown in equation 1 (**1** → **2**).[5] This communication describes results that reveal an unexpected stereochemical preference dictated by the 3-oxygen substituent.



1 **2** (1)

Studies began by examining the reactions shown in equation 2. Thus, treatment of alcohol (**3**) with phenylselenenyl chloride in dichloromethane at -78 °C gave a 96% yield of a 3:1 mixture of diastereomeric tetrahydropyrans (**4**) and (**5**), respectively.[6,7] The stereochemical assignment for **4** was based on an 11 Hz coupling between H_1 and H_2, indicative of a *trans* relationship, and the appearance of H_3 as a broad singlet, indicative of a *cis* relationship with H_2. On the other hand, in **5** both H_1 and H_3 were coupled to H_2 by 11 Hz.[8] Similar treatment of **6** with phenylselenenyl chloride gave a 4:1 mixture of tetrahydropyrans (**7**) and (**8**) in 90% yield.[6]

It is notable that if the cyclizations described in equation 2 occur *via* a chair-like transition state, the chair in which the allylic oxygen is axially disposed is preferred. This can be explained by a combination of steric effects (avoidance of a gauche interaction between the C_3 substituent and the adjacent geminal methyl groups) and electronic effects (the C_3 oxygen can behave as an electron-withdrawing group, and thus deactivating group, when equatorially disposed through CO_{σ^*}—$C{=}C_{\pi}$ overlap, but not when axially disposed).[9,10] To examine the role of steric effects in the process it was decided to study a substrate lacking the *gem*-dimethyl group. Therefore 4-penten-1,3-diol derivative (**9**) was prepared using the 3-step reaction sequence described without comment in Table 1.



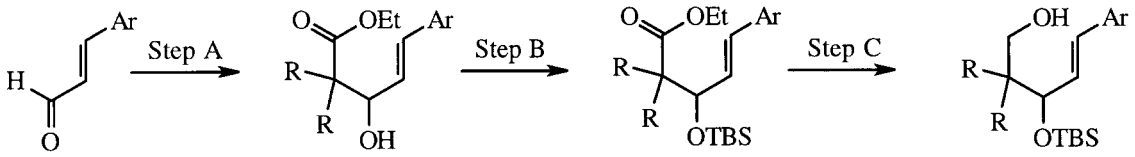
(2)

3 R = CH_2OCH_3
6 R = $SiMe_2t$-Bu (TBS)

4 R = CH_2OCH_3 96% (3:1) **5** R = CH_2OCH_3
7 R = $SiMe_2t$-Bu 90% (4:1) **8** R = $SiMe_2t$-Bu

Treatment of **9** with phenylselenenyl chloride gave a 4:1 mixture of tetrahydropyrans (**10**) and (**11**) in 90% yield (equation 3). Once again the stereochemistry of the tetrahydropyrans was based on the appearance of H_2 as either a doublet of doublets (J = 11, 3 Hz) in **10** and as a triplet (J = 11 Hz) in **11**. This result indicates that the *gem*-dimethyl group does not play a role in the stereochemical course of the reactions shown in equation 2.

Table 1: Synthesis of Cyclization Substrates[11]

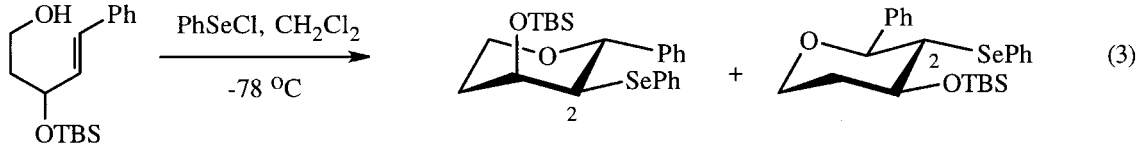


A: $R_2C{=}C(OEt)(OLi)$, THF B: TBSCl, imidazole C: DIBAL-H

Synthesis of	R	Ar	Yields (%) Step A	Step B	Step C
9	H	Ph	91	93	79
12	Me	*E*-CH=CHPh	78	84	87
15	H	*E*-CH=CHPh	50	98	71
18	Me	*E*-CH=CHPMP	51	72	85

It was next decided to extend this process to substrates with C_5-styryl groups. Therefore cyclization substrates (**12**, **15** and **18**) were prepared (Table 1) and subjected to the aforementioned cyclization conditions (equation 4). Each reaction delivered a 4:1 mixture of diastereomeric pyrans in modest to good yield.[12] The C_3 alkoxy group occupied an axial site in the major product in each case.[13] It is also notable

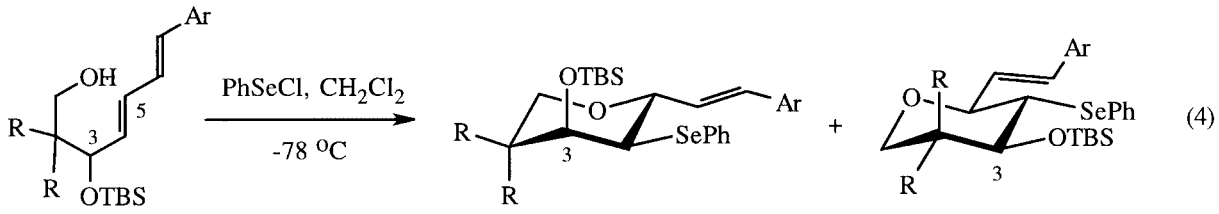
that the styryl group survives the reaction without suffering competitive addition of phenylselenenyl chloride.



(3)

9 **10** 90% (4:1) **11**

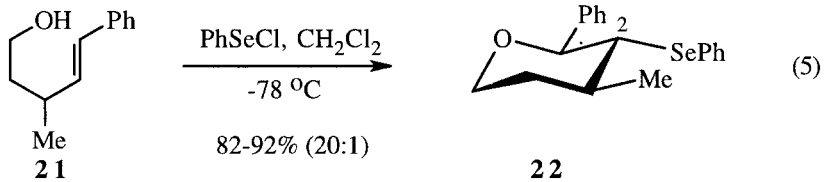
If the diastereoselectivity observed in the aformentioned cyclizations was due to a stereoelectronic effect, it was reasoned that replacing the C_3 alkoxy group with an electron donating substitutent might reverse the sense of stereoselectivity. In other words cyclization might occur from a conformation in which the C_3 substituent occupied an equatorial site. Therefore alcohol (**21**) was prepared and examined.[14] Indeed treatment of **21** with phenylselenenyl chloride provided **22** in 82-92% yield with at least 20:1 diastereoselectivity.[15] The stereochemistry of **22** was once again based largely upon the appearance of H_3 as a triplet (J = 11 Hz).



(4)

12 R = Me Ar = Ph **13** R = Me Ar = Ph 69% (4:1) **14** R = Me Ar = Ph
15 R = H Ar = Ph **16** R = H Ar = Ph 39% (4:1) **17** R = H Ar = Ph
18 R = Me Ar = *p*-methoxyphenyl **19** R = Me Ar = PMP 76% (4:1) **20** R = Me Ar = PMP

In summary, the electrophile-initiated cyclization route to tetrahydropyrans has been extended to accommodate placement of alkoxy groups at C_4 of the tetrahydropyran. This may have some synthetic value given that many tetrahydropyran-containing natural products are oxygenated at C_4.[16] Furthermore, this study has uncovered another example of a cyclization that may occur *via* a chair-like transition state in which a backbone substituent prefers to occupy an axial rather than equatorial site.[17] We suggest that this unusual preference may be due to a stereoelectronic effect.



(5)

21 **22**

REFERENCES AND NOTES

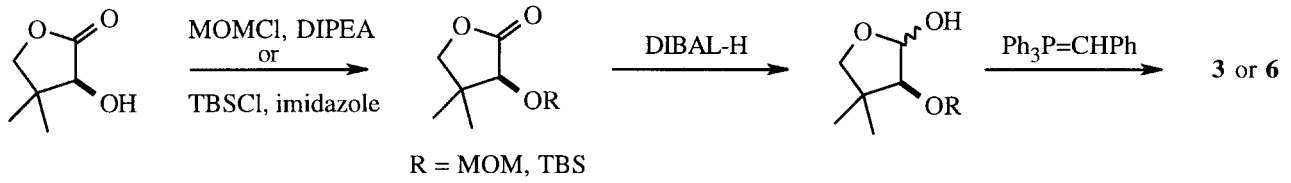
1. This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.
2. D. J. Hart, V. Leroy, G. H. Merriman, and D. G. J. Young, *J. Org. Chem.*, **1992**, *57*, 5670.

3. D. J. Hart, G. H. Merriman, and D. G. J. Young, *Tetrahedron*, **1996**, *52*, 14437.

4. For other examples of tetrahydropyran synthesis *via* electrophile-initiated cycloetherification reactions see: I. Arai, T. D. Lee, R. Hanna, and G. D. Daves, Jr., *Organometallics*, **1982**, *1*, 742 and other articles cited in reference 2.

5. For an account of this work, as well as unsuccessful attempts to cyclize substrates of type **1** where R = C≡CSiMe$_3$ and the corresponding cobalt-alkyne complexes, see: A. Zakarian, MS Thesis, The Ohio State University (1997).

6. Lactones (**3**) and (**6**) were prepared as described in reference 4 as follows:



7. For an early reference on selenoetherification reactions see: K. C. Nicolaou and Z. Lysenko, *Tetrahedron Lett.*, **1977**, 1257.

8. Tetrahydropyrans (**4**) and (**5**) were separable. Compounds (**7**) and (**8**) were analyzed as a mixture.

9. H. B. Henbest and R. A. Wilson, *J. Chem. Soc.*, **1957**, 1958. P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc. (B)*, **1970**, 1374.

10. For a related observation involving a radical cyclization see: T. V. Rajanbabu, *Acc. Chem. Res.*, **1991**, *24*, 139.

11. The aldehydes used in the table were prepared from the sodium salt of glutaconaldehyde: N. P. Lewis, P. W. McKen, and R. J. K. Taylor, *Synlett*, **1991**, *898*.

12. Tetrahydropyrans (**13**) and (**14**) were initally characterized as an inseparable mixture, but were further characterized by deprotection and separation of the resulting alcohols. Tetrahydropyrans (**16**) and (**17**) were separable. Tetrahydropyrans (**19**) and (**20**) were analyzed as a mixture.

13. Stereochemical assignments were based on the same ^{1}H NMR analysis presented for **3**, **6** and **9**.

14. Alcohol (**21**) was prepared by DIBAL-H reduction of the corresponding known ethyl ester: T. Hayashi, A. Yamamoto, and T. Hagihara, *J. Org. Chem.*, **1986**, *51*, 723.

15. Tetrahydropyran was contaminated with two minor products based on the appearance of two small methyl doublets in the upfield region of the ^{1}H NMR spectrum of the mixture. The structures of the minor components are unknown and thus, the ratio quoted here represents a minimum ratio by NMR.

16. For one example see: P. A. Horton, F. E. Koehn, R. E. Longley, and O. J. McConnell, *J. Am. Chem. Soc.*, **1994**, *116*, 6015.

17. Although exceptions exist, equatorial orientation of substituents is usually observed in olefin cyclizations and other reactions whose transition-state geometries are believed to resemble chair cyclohexane, for example polyolefin cyclizations (W. S. Johnson and G. E. Dubois, *J. Am. Chem. Soc.*, **1976**, *98*, 1038), Claisen and Cope rearrangements (C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, **1969**, 2783), and iminium ion initiated olefin cyclizations (A. C. Cope and W. D. Burrows *J. Org. Chem.*, **1965**, *30*, 2163). For two examples wherein substituents appear to occupy axial sites see: D. J. Hart, *J. Am. Chem. Soc.*, **1980**, *102*, 397. K. Nonoshita, K. Maruoka, and H. Yamamoto, *Bull. Chem. Soc. Japan*, **1992**, *65*, 541.

Received, 19th July, 1999