2×10^{-4} and 4×10^{-5} s^{-1}, respectively, where k_{-1} is derived from K_{eq} and k_1. In a separate experiment, the rate of iminium insertion is determined by treating the equilibrium mixture of $[7]^{2+}$ and $[8]^{2+}$ with 10 equiv of CD_3CN in CD_3OD and measuring the rate of formation of $[Os(NH_3)_4((+)ValOMe)(CD_3CN)](OTf)_2$. By this procedure, a specific rate is measured as $k_2 = 3 \times 10^{-5}$ s^{-1}, a value in good agreement with that for k_{-1} calculated directly from K_{eq}.[23]

A detailed investigation of the stereochemical, kinetic, and thermodynamic aspects of the ValOMe system is currently in progress as are efforts to establish the generality of this reaction as a synthetic route to η^2-iminium complexes.

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(23) A rate of insertion, $k_{-1} = 7.5 \times 10^{-5}$ s^{-1}, was determined by cyclic voltammetry in CH_3CN. The concentration of $[Os(NH_3)_4(ValOMe)(CH_3CN)](OTf)_2$ was monitored through comparison with an internal standard ($CoCp_2^+$).

Stereochemical Course of Direct Ring Closures of Complex Homoallylic Alcohols to Substituted Tetrahydrofurans†

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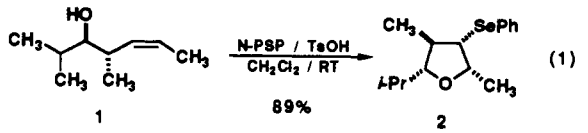
The stereoselective synthesis of highly substituted tetrahydrofurans from homoallylic alcohol precursors has only recently been reported. We have employed a three-step procedure that utilized epoxy alcohol intermediates.[1] Kang and co-workers found that simple homoallylic alcohols containing a trans double bond could be cyclized to either 2,5-syn- or 2,5-anti-substituted tetrahydrofurans with good to excellent stereochemical control.[2] These conversions have been mediated by organoselenium reagents in reactions whose stereochemical outcome has been quite solvent dependent. We sought to expand the synthetic potential of these conversions by investigating, in a systematic manner, the direct closure of homoallylic alcohols to tetrasubstituted tetrahydrofurans. This report accurately characterizes, for the first time, the stereochemical outcome of these very efficient and synthetically useful reactions.

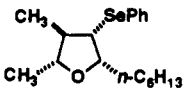
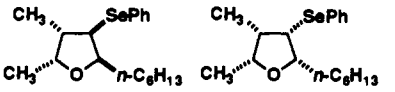
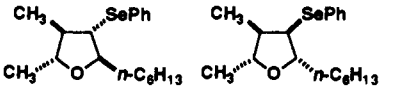
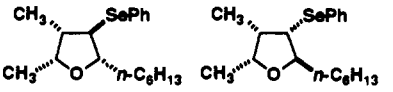
Use of the *N*-(phenylseleno)phthalimide (N-PSP) reagent introduced by Nicolaou[3] with substrate **1** resulted in the rapid and stereoselective production of tetrahydrofuran **2** (eq 1). While

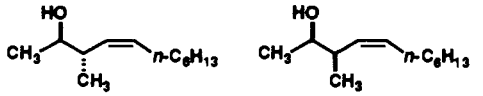


1 2 (1)

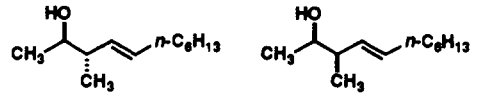
this is the same product previously made by the three-step sequence,[1] the improved yield and the simplicity of this direct conversion prompted us to survey the generality of this chemistry with substrates **3–6**. The results are shown in Table I.[4,5] In all cases high yields of ring-closed products were obtained within 3 h under the N-PSP conditions. Both anti and syn *Z*-olefins (**3** and **4**) gave essentially single products whose stereochemical assignments were consistent with earlier observations.[1] Anti, *E*-olefin **5** was less selective, providing a 4:1 ratio of **10**:**11**. Syn, *E*-olefin **6** gave a very slight excess of isomer **12** over its reaction partner **13**. All products (**7–13**) were reduced with tributyltin hydride (AIBN, PhH, reflux) to give trialkylated tetrahydrofurans **14–17**.

Table I. Ring Closure of Homoallylic Alcohols by Organoselenium Reagents

Olefin	Reagent	Yield (%)	Products
3	N-PSP	92	 **7**
4	N-PSP	84	 **8** 97 : 3 **9**
5	N-PSP	90	 **10** 81 : 19 **11**
5	PhSeCl CH_3CN	90	**10** 93 : 7 **11**
6	N-PSP	85	 **12** 54 : 46 **13**
6	PhSeCl CH_3CN	88	**12** 83 : 17 **13**



3 **4**



5 **6**

Stereochemistry can be accurately assessed in these systems by the chemical shift method described by Williams et al.[6,9] The diastereotopic hydrogens of the ring methylene for stereoisomers **14** and **15** are separated by less than 0.3 ppm due to their similar magnetic environment. For the same methylene group in the 3,5-syn isomers **16** and **17** the two protons show a 1 ppm shift

† Dedicated to Professor A. I. Meyers on the occasion of his 60th birthday.

(1) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995-8997.

(2) (a) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917-5920. (b) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Ibid.* **1991**, *32*, 4015-4018.

(3) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704-3706.

(4) All yields refer to isolated, chromatographed, and spectroscopically pure materials.

(5) Elemental analyses were obtained on these compounds.

(6) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641-2644.

(7) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483-4485.

(8) Williams, D. R.; Phillips, J. G. *Tetrahedron* **1986**, *42*, 3013-3019.

(9) The stereochemical assignments of these authors were supported by crystal structure determinations.

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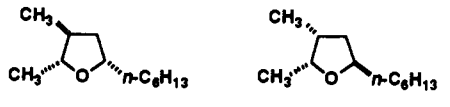
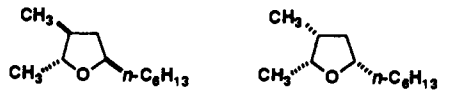


14

15

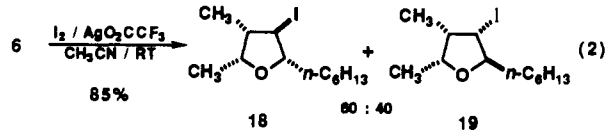


16

17

difference due to the diamagnetic shielding experienced by the proton syn to the two alkyl groups. Identical shift patterns have been observed by Semmelhack and Zhang for a series of 2,3,5-trialkyltetrahydrofurans.[7,9] A similar analysis of the cyclization products themselves is possible. The chemical shift of the proton on the carbon bearing selenium is influenced by the number of syn alkyl neighbors present in the structure. This resonance is centered at 2.8 ppm when both neighbors are syn (**10** and **12**), 3.5 ppm when there is a single syn alkyl group (**2**, **7**, **8**, **11**, and **13**), and 3.9 ppm when both syn neighbors are hydrogen (**9**). The numerous examples of phenylthio-substituted tetrahydrofurans, also by Williams,[8,9] show identical trends. Finally, we have prepared an authentic sample of **10** by independent synthesis using our previously described methodology.[1]

At this point, a paper by Lipshutz and Barton appeared[10] which reported the use of benzeneselenenyl chloride in acetonitrile to effect ring closures of substrates stereochemically analogous to those in our study. In particular, they claimed exclusive formation of single isomers from the *E*-olefin substrates. As shown in Table I, these conditions, when applied to **5** and **6**, did improve the stereoselectivity for the indicated major product. However, the stereochemical assignments reported by Lipshutz and Barton are incorrect.[11] Since their study also reported an unprecedented syn mode of addition in iodine-induced cyclizations, we have used their conditions (I_2, AgO_2CCF_3, CH_3CN) with olefinic alcohol **6** (eq 2). The resulting 60:40 mixture of **18**:**19**[4] is consistent with



(2)

the normal and expected anti addition pathway. Reduction of **18** (Bu_3SnH, AIBN, PhH) gave **17** while similar treatment of **19** provided **15**. Thus, for the examples that we have studied, we find significant errors in the stereochemical assignments made by Lipshutz and Barton.[12]

In conclusion, we can say that it is now possible to ring close the four isomeric homoallylic alcohols, **3**–**6**, with good to complete stereocontrol by the judicious choice of phenylselenation conditions.[13] In all cases the favored product has an anti relationship of the phenylseleno group to the adjacent methyl. Reduction then provides selective access to 2,3,5-trisubstituted tetrahydrofurans (e.g., **14**–**17**). These results now allow the rational planning of syntheses of natural and unnatural products wherein these stereochemical patterns are commonly sought.

Supplementary Material Available: Cyclization procedures, NMR spectra, and a complete discussion of the assignments for tetrahydrofurans **2** and **7**–**19** (17 pages). Ordering information is given on any current masthead page.

(10) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084–1086.

(11) These authors based their stereochemical assignments exclusively on NOE measurements.

(12) Only in the formation of **8** from 4 do the results we have obtained with substrates **3**–**6** match the selenoetherification results of these authors.[10] Attempted iodoetherifications of **3**–**6** give no indication of a novel syn addition mode.

(13) Reaction of **6** with benzeneselenenyl chloride in acetonitrile at low temperature (<−30 °C) improved the **12**:**13** ratio to 92:8.

Facial Amphiphiles

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There is currently a great deal of interest in the design and study of novel amphiphiles. Evidence in the literature indicates that helical peptides with facial amphiphilicity have interesting effects on phospholipid membranes. In some contexts, they bind to the membrane interface and help target adjacent peptide sequences to membrane-bound receptors.[1] In other contexts they cause membrane fusion[2] or permeabilization.[3] The separation of polar and nonpolar domains along the long axis of the peptides to produce structures with a hydrophobic face and a hydrophilic face—what we call *facial amphiphilicity* to distinguish it from the head-to-tail amphiphilicity seen in typical polar lipids—is thought to be critical for the observed effects on membranes. Whether nonpeptidic molecules with a similar distribution of polar and nonpolar domains can mimic some of the effects of amphiphilic peptides is a question that has been raised but not addressed,[1b] in part because there are few natural examples of such molecules. We report herein the synthesis and crystallographic characterization of two nonpeptidic facial amphiphiles as a first step in answering this question.[4,5]

The synthetic amphiphiles are glycosylated derivatives of cholic acid (**4**) and *allo*-cholic acid (**5**). Cholic acid was chosen as a starting structure because it is rigid and has three hydroxyls oriented along one face. It is already moderately amphiphilic.[6] Glycosylation of the axial hydroxyls at C-7 and C-12 produces derivatives with a similar hydrophobic face but a much more hydrophilic polyhydroxylated face.[7] Compounds **4** and **5** were synthesized from the readily available C-3 protected cholic acid (**1**) and *allo*-cholic acid (**2**) methyl esters,[8] respectively, by the procedure outlined in Scheme I.[9] The key step is glycosylation of the hindered C7 and C12 hydroxyls using perbenzylated glycosyl sulfoxide **3**.[10] As far as we know, this is the only glycosylation

(1) (a) Kaiser, E. T.; Kezdy, F. J. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1137. (b) Kaiser, E. T.; Kezdy, F. J. *Science* **1984**, *223*, 249. (c) Kaiser, E. T.; Kezdy, F. J. *Annu. Rev. Biophys. Biophys. Chem.* **1987**, *16*, 561.

(2) (a) Terwilliger, T. C.; Weissman, L.; Eisenberg, D. *Biophys. J.* **1982**, *37*, 353. (b) Lear, J. D.; DeGrado, W. F. *J. Biol. Chem.* **1987**, *262*, 6500. (c) Suenaga, M.; Lee, S.; Park, N. G.; Aoyagi, H.; Kato, T.; Umeda, A.; Amako, K. *Biochim. Biophys. Acta* **1989**, *981*, 143. (d) Takahashi, S. *Biochemistry* **1990**, *29*, 6257.

(3) (a) Hall, J. E.; Vodyanoy, I.; Balasubramanian, T. M.; Marshall, G. R. *Biophys. J.* **1984**, *45*, 233. (b) Lear, J. D.; Wasserman, Z. R.; DeGrado, W. F. *Science* **1988**, *240*, 1177. (c) Tosteson, M. T.; Alvarez, O.; Hubbell, W.; Bieganski, R. M.; Attenbach, C.; Caporales, L. H.; Levy, J. J.; Nutt, R. F.; Rosenblatt, M.; Tosteson, D. C. *Biophys. J.* **1990**, *58*, 1367. (d) Oiki, S.; Madison, V.; Montal, M. *Proteins: Struct. Funct., Genet.* **1990**, *8*, 226.

(4) Another type of facial amphiphile was recently reported: Stein, T. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 3943. This paper also contains a good summary of different types of amphiphiles and leading references.

(5) For other unnatural amphiphiles see, for example: (a) Menger, F. M.; Whitesell, L. G. *J. Org. Chem.* **1987**, *52*, 3793. (b) Menger, F. M.; Littau, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 1451.

(6) (a) Armstrong, M. J.; Carey, M. C. *J. Lipid Res.* **1982**, *23*, 70. (b) Roda, A.; Hofmann, A. F.; Mysels, K. J. *J. Biol. Chem.* **1983**, *258*, 6362. (c) Hofmann, A. F.; Mysels, K. J. *Colloids Surf.* **1988**, *30*, 145.

(7) Others have modified cholic acid to make host molecules. See, for example: (a) Burrows, C. J.; Sauter, R. A. *J. Incl. Phenom.* **1987**, *5*, 117. (b) Bonar-Law, R. P.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 574.

(8) Zhu, X.; Amouzou, E.; McLean, S. *Can. J. Chem.* **1987**, *65*, 2447.

(9) All new compounds were characterized by ^1H and ^{13}C NMR and FAB MS.

(10) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

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