ditions for the sake of comparison and the corresponding $S_{RN}1$ products **2o,p**, **3m**, **4m**, and **6m** have spectroscopic data consistent with their structure.

The reaction of **1o** with Nu_2 was not precedented and gave **3o** + **6o**, unknown in the literature.

2-[(2-Chlorophenyl)thio]pyridine (3o): mp 40 °C; ^{1}H NMR δ 6.2–7.0 (m, 2 H), 7.0–7.5 (m, 5 H), 8.20 (dd, 1 H); MS 223, 221 (M^+), 222, 220, 186, 185. Anal. Calcd for $C_{11}H_8ClNS$: C, 59.63; H, 3.61; N, 6.32. Found: C, 59.50; H, 3.82; N, 6.15.

1,2-Bis(pyridin-2-ylthio)benzene (6o): mp 67–68 °C; ^{1}H NMR δ 7.10 (m, 4 H), 7.3–7.8 (m, 6 H), 8.40 (dd, 2 H); MS 296 (M^+), 218, 186. Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.86; H, 4.05; N, 9.44. Found: C, 64.8; H, 3.91; N, 9.52.

The reaction between **1p** and Nu_2 or Nu_3, not precedented either, gave (**3p** + **6p**) or **4p**.

2-[(4-Chlorophenyl)thio]pyridine (3p): oil; ^{1}H NMR δ 7.0 (m, 2 H), 7.45 (m, 5 H), 8.50 (dd, 1 H); MS 223–221 (M^+), 222–220, 185 (lit.[24] no spectroscopic data).

1,4-Bis(pyridin-2-ylthio)benzene (6p): mp 103–105 °C; ^{1}H NMR δ 7.1 (m, 4 H), 7.6 (m, 6 H), 8.50 (dd, 2 H); MS 296 (M^+), 295, 186. Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.86; H, 4.05; N, 9.44. Found: C, 64.57; H, 4.08; N, 9.59.

2-[(4-Chlorophenyl)thio]pyrimidine (4p): mp 73–74 °C; ^{1}H NMR δ 6.90 (t, 1 H), 7.3–7.55 (m, 4 H), 8.40 (d, 2 H); MS 224–222 (M^+) (lit.[25] mp 73–74 °C; no spectroscopic data).

[(3-Chlorophenyl)thio]benzene (2m): oil; ^{1}H NMR δ 6.90 (s, 1 H), 6.9–7.4 (m, 8 H). MS 222–220 (M^+), 184 (lit.[26] no spectroscopic data).

Registry No. **1m**, 625-99-0; **1o**, 615-41-8; **1p**, 637-87-6; **3m**, 106920-23-4; **3o**, 122899-23-4; **3p**, 28856-69-1; **4m**, 73226-33-2; **4p**, 26547-31-9; **5m**, 122899-24-5; **5o**, 122899-25-6; **5p**, 122899-26-7; **6m**, 119993-76-9; **6o**, 60372-34-1; **6p**, 39544-83-7; Nu_1·K, 3111-52-2; Nu_2·K, 79236-86-5; Nu_3·K, 57590-85-9; Nu_4·K, 96592-02-8; Nu_5·K, 57590-84-8; Nu_6·K, 7778-70-3; Nu_7·K, 80882-73-1; 4-quinolyl radical, 115826-07-8.

(24) King, K. F.; Bauer, L. *J. Org. Chem.* **1971**, *36*, 1641.

(25) Brown, D. J.; Ford, P. W. *J. Chem. Soc. C* **1969**, 2720.

(26) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830.

Preparation of Seven-Membered-Ring Cyclic Ethers and 3-Alkylidenetetrahydropyrans from the Cyclization of Oxonium Cations Derived from Unsubstituted and Silicon-Containing 4-Alken-1-ols[1]

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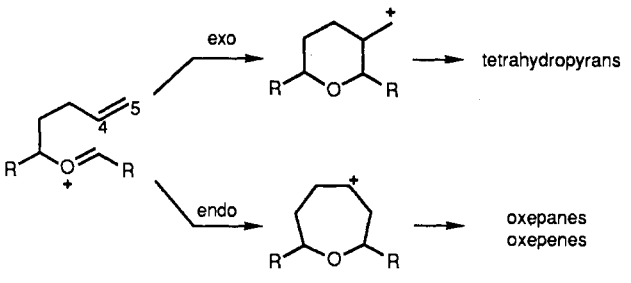
Received July 11, 1989

Lewis acid promoted cyclization of mixed acetals derived from 4-alken-1-ols provides direct access to seven- or six-membered cyclic ethers. Ring size is determined primarily by the electronic bias of the alkene participant. Of particular significance are (a) the formation of 2,3,6,7-tetrahydrooxepins from the cyclization of acetals **10**, **12**, and **13** derived from 4-(trimethylsilyl)-4-penten-1-ol, (b) the completely stereoselective formation of the *cis*-2,7-disubstituted-2,3,6,7-tetrahydrooxepin **14** from **13**, and (c) the stereospecific cyclization of acetals derived from (*E*)- and (*Z*)-4-nonen-1-ol to afford the (*E*)- and (*Z*)-pentylidenetetrahydropyrans **21** and **23**, respectively. The divergent behavior of acetals **24** and **26** highlights the close balance that exists between simple cyclization and more complex rearrangement pathways.

The formation of cyclic ethers by C–C bond-forming cationic cyclization reactions has been known for nearly 40 years,[3] although this approach to oxacyclics is less common than strategies involving C–O bond formation. Prins–Kriewitz cyclization[4] of oxonium cation intermediates (α-alkoxycarbenium ions) derived from the condensation of homoallylic alcohols and carbonyl compounds is a standard method for forming hydropyran derivatives and has received renewed attention of late.[1,5] A notable example, due to Ohloff and co-workers,[6] is a key step in a commercial synthesis of muscone (eq 1). In marked contrast, there exist only a few reports[5i,7] of forming seven-membered ring ethers (oxacycloheptanes or oxepanes)[8] from the cyclization of oxonium cations derived from 4-alken-1-ols.

Scheme I



In this paper we report details of our studies of Lewis acid promoted cyclization reactions of mixed acetals de-

(1) A small part of this study was reported in preliminary form; see: Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.

(2) COSNET-SEP Mexico Graduate Fellow, 1982–1986.

(3) Williams, P. H.; Ecke, G. G.; Ballard, S. A. *J. Am. Chem. Soc.* **1950**, *72*, 5738.

(4) For brief reviews of Prins cyclization reactions that form carbocycles, see: (a) Thieme, J. In *Methoden der Organischen Chemie*, Houben-Weyl, Ed.; Thieme: Stuttgart, 1980; Vol. VI/1a, Part 2, pp 793–799. (b) Snider, B. S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: New York; Vol. 5, in press.

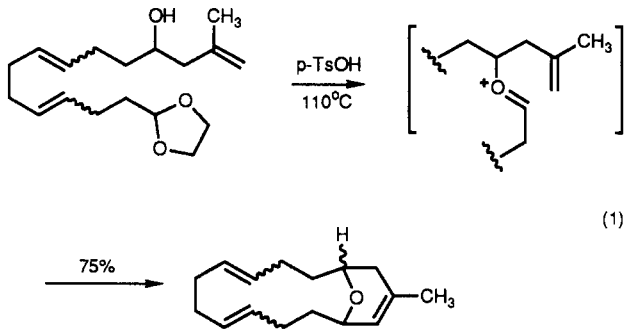
(5) Recent examples include: (a) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (b) Nishiyama, H.; Narimatsu, S.; Sakuta, K.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1982**, 459. (c) Kay, I. T.; Williams. E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (d) Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653. (e) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925. (f) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275. (g) Nussbaumer, C.; Fråter, G. *Helv. Chim. Acta* **1987**, *70*, 396. (h) Nussbaumer, C.; Fråter, G. *J. Org. Chem.* **1987**, *52*, 2096. (i) Lolkema, L. D. M.; Hiemstra, H.; Moolweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365. See also ref 1.

(6) Schulte-Elte, K. H.; Hauser, A.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 2673.

(7) (a) Kocienski, P.; Cockerill, G. C. *J. Chem. Soc., Chem. Commun.* **1983**, 705. (b) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911.

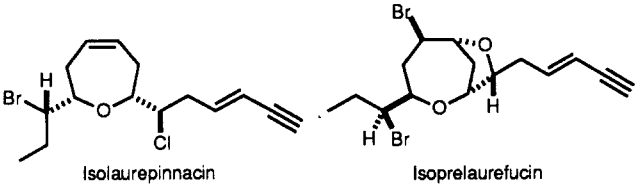
(8) For a brief review of the synthesis and chemistry of seven-membered ring ethers, see: Boyd, D. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Lwowski, W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, Chapter 5.17.

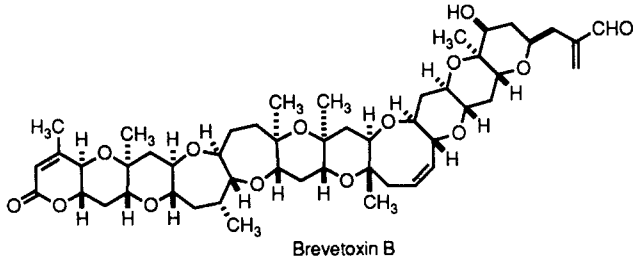
0022-3263/89/1954-5695$01.50/0 © 1989 American Chemical Society



(1)

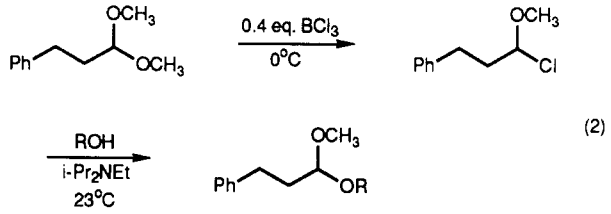
rived from 4-alken-1-ols.[1,9] One objective of our investigations in this area was to ascertain whether silicon substituents on carbons 4 or 5 of the alkene could effectively control the mode of ring closure to favor endocyclic cyclization[10] and thus provide seven-membered ring ether products predominantly (see Scheme I). Silicon has often been employed as a "control element" in cationic cyclization reactions,[11] and reports from our laboratories have demonstrated the utility of vinylsilane-terminated cyclization reactions for the preparation of a wide variety of unsaturated heterocyclic systems,[12] including alkaloids,[13] antibiotics,[14] and marine natural products.[15] A second objective of this study was to explore the stereochemistry of cyclizations that form 2,7-disubstituted oxepanes, since substituted seven-membered oxacycles are found in several bioactive marine natural products including the polyoxacyclic brevetoxins, isolaurepinnacin, and isoprelaurefucin.[16]





Results

The starting 4-alken-1-ols were prepared by straightforward sequences that are detailed in the supplementary material (see the paragraph at the end of the paper). Literature methods were employed also to prepare (2-methoxyethoxy)methyl (MEM) ethers[17] and 1-ethoxyethyl ethers,[18] while other mixed acetals were most often prepared[15] from the reaction of an α-chloro ether (prepared in situ from an acetal)[15,19] with the 4-alken-1-ol as is illustrated in eq 2. All Lewis acid promoted cyclization reactions were conducted in dichloromethane at substrate concentrations of ca. 0.03 M.



(2)

Terminal Alkenes. Results of the cyclization of mixed acetals 1 and **5** containing a terminal vinyl group are summarized in Scheme II. The two stereoisomeric 4-chlorooxepanes **2** were formed in a ca. 3:2 ratio (50–55% yield) and could be separated by careful chromatography on silica gel. The major isomer (**2a**) thus obtained was contaminated with ~15% of an unknown impurity, while the minor 4-chlorooxepane isomer (**2b**) was contaminated with ~13% of one of the two stereoisomers of the 5-chlorooxepane **4**. Both stereoisomers of **2** were converted in good yield to 2-(2-phenylethyl)oxepane (**3**) upon dehalogenation with Bu_3SnH.[20] The structure of **3** followed de novo from ^1H NMR, ^{13}C NMR, and mass spectral data (see Experimental Section).

Homonuclear ^1H NMR decoupling experiments allowed the position of the chlorine in **2a** and **4** to be rigorously established. Decoupling the hydrogens of the phenylethyl side chain unambiguously defined the methine hydrogen α to oxygen. In the case of **2a**, this hydrogen (δ 3.38) and the methine hydrogen α to chlorine (δ 4.03) were both vicinally coupled to the same methylene group (C-3). In the case of **4**, it was the methylene hydrogens α to oxygen (δ 3.91 and 3.44) that were vicinally coupled to the same methylene group (C-6) as the methine hydrogen (δ 4.30) α to chlorine.

It was also readily established that the 4-chlorooxepanes **2a** and **2b** interconvert under the conditions employed to cyclize **1**. Thus treatment of **2a** (ca. 85% pure) with 3 equiv of $EtAlCl_2$ at −78 (1 h) → 0 °C (4 h) provided a 54:32:14 mixture (by capillary GC analysis) of **2a**, **2b**, and **4**, respectively. Similarly, a sample of **2b** (contaminated with ca. 13% of **4**) was converted under identical conditions to a 30:47:23 mixture of **2a**, **2b**, and **4**, respectively. Attempts to carry out these equilibrations for extended periods at 0 °C or room temperature led to extensive decomposition.

Cyclization of acetal **5** in the presence of 3 equiv of $EtAlCl_2$ at −78 → 23 °C gave four major products (in a ratio of 10:10:4:1) in a combined yield of 67% after purification on silica gel. Qualitatively similar results were obtained when the Lewis acid was $SnCl_4$. The ratio of isomers formed from cyclization of **5** with $EtAlCl_2$ or $SnCl_4$ remained constant with time as determined by capillary GC analysis. Upon dechlorination,[20] this four-component mixture was converted to a ca. 5:1 mixture of two major products: the 2,7-disubstituted oxepane **8** and the 2,5-

(9) The pioneering contributions of the Johnson group in the development of acetal–alkene cyclizations for the synthesis of carbocycles has been reviewed.[4a]

(10) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(11) For an authorative review see: Fleming, I.; Dunogues, J. *Org. React.*, in press.

(12) For reviews see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59.

(13) (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669. (c) Burk, R. M.; Overman, L. E. *Tetrahedron Lett.* **1984**, *25*, 5739. (d) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(14) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115.

(15) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

(16) For reviews, see: Faulkner, D. J. *Nat. Prod. Rept.* **1987**, *4*, 539; **1986**, *3*, 1; **1984**, *1*, 251, 551. Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1.

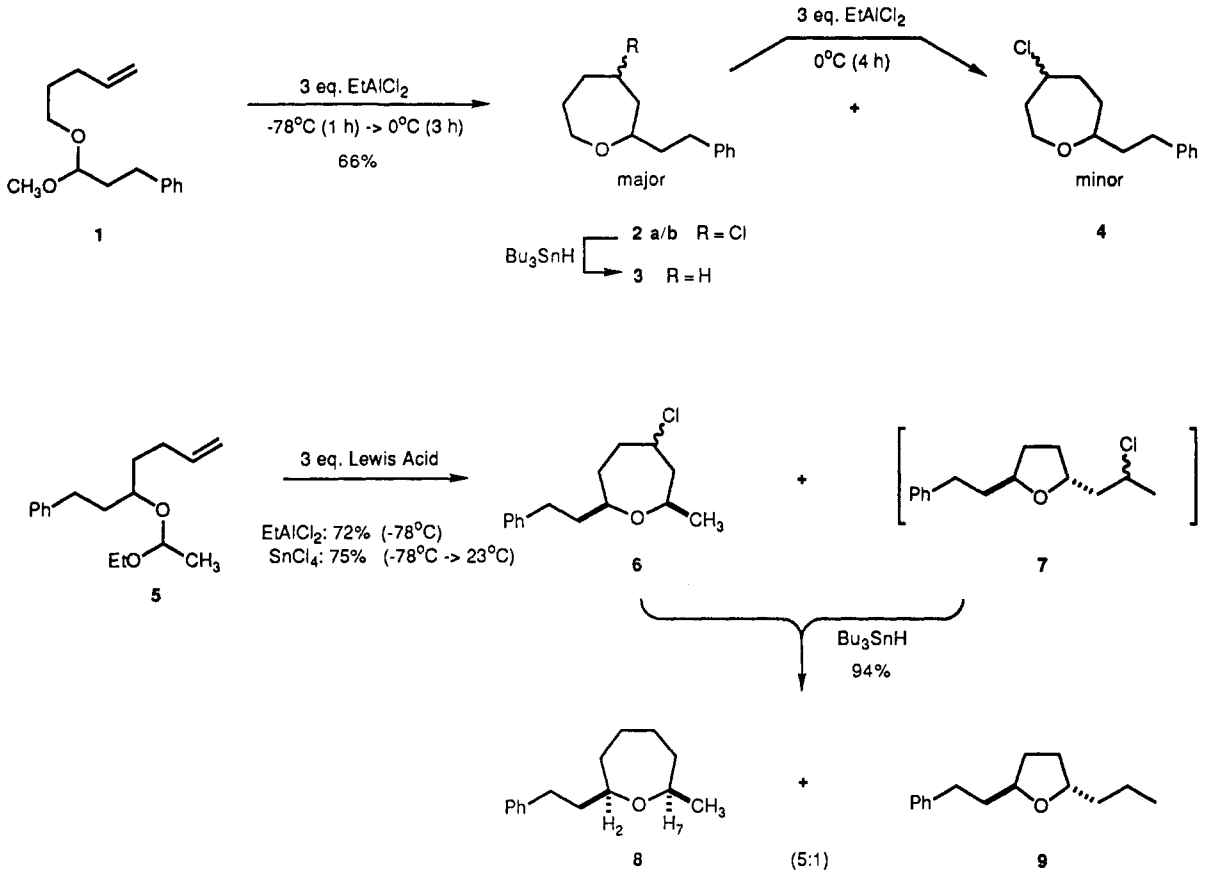
(17) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(18) Chládek, S.; Smrt, J. *Chem. Ind. (London)* **1964**, 1719.

(19) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711.

(20) Menapace, L. W.; Kuivila, H. G. *J. Org. Chem.* **1963**, *28*, 2165. Jacobs, J.; Leibner, J. E. *Ibid.* **1979**, *44*, 449.

Scheme II



disubstituted tetrahydrofuran **9**. The major product was readily isolated in pure form by preparative GLC. The 500-MHz ^1H NMR spectrum (C_6D_6) of **8** showed a diagnostic doublet at δ 1.18 (J = 6.2 Hz) for the methyl hydrogens, which by decoupling could be established to have a vicinal relationship with methine hydrogen H_7 (δ 3.40, ddq, J = 8.1, 4.2, 6.2 Hz). Decoupling experiments also confirmed that methine hydrogen H_2 (δ 3.23, m) was directly attached to the carbon origin of the 2-phenylethyl side chain. The structure of tetrahydrofuran **9**, which could be isolated in only very small amounts by preparative GLC, was established by direct comparison with an authentic sample obtained by catalytic hydrogenation of progenitor **28** (vide infra).

A plausible stereochemical assignment for oxepane **8** can be made on the basis of the ^1H NOE enhancements observed between methine hydrogens H_2 and H_7 (5% $H_2 \rightarrow H_7$, 8% $H_7 \rightarrow H_2$). Electron diffraction[21] and vibrational spectra[22] as well as molecular mechanics calculations[21] suggest that oxepane exists as a mixture of twist-chair conformations. The most stable of these should have the oxygen at C-2 or C-4 of a twist-chair (C_2 symmetry) cycloheptane. Figure 1 shows the four lowest energy conformations (all are twist-chair) that we have found by molecular mechanics calculations for *cis*- and *trans*-2,7-dimethyloxepane using the Gajewski–Gilbert MMX version of the Allinger MM2(77) molecular mechanics force field.[23,24] The measured distance between the methine

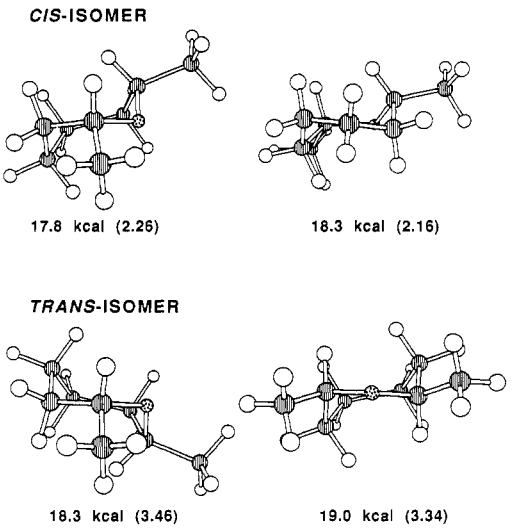


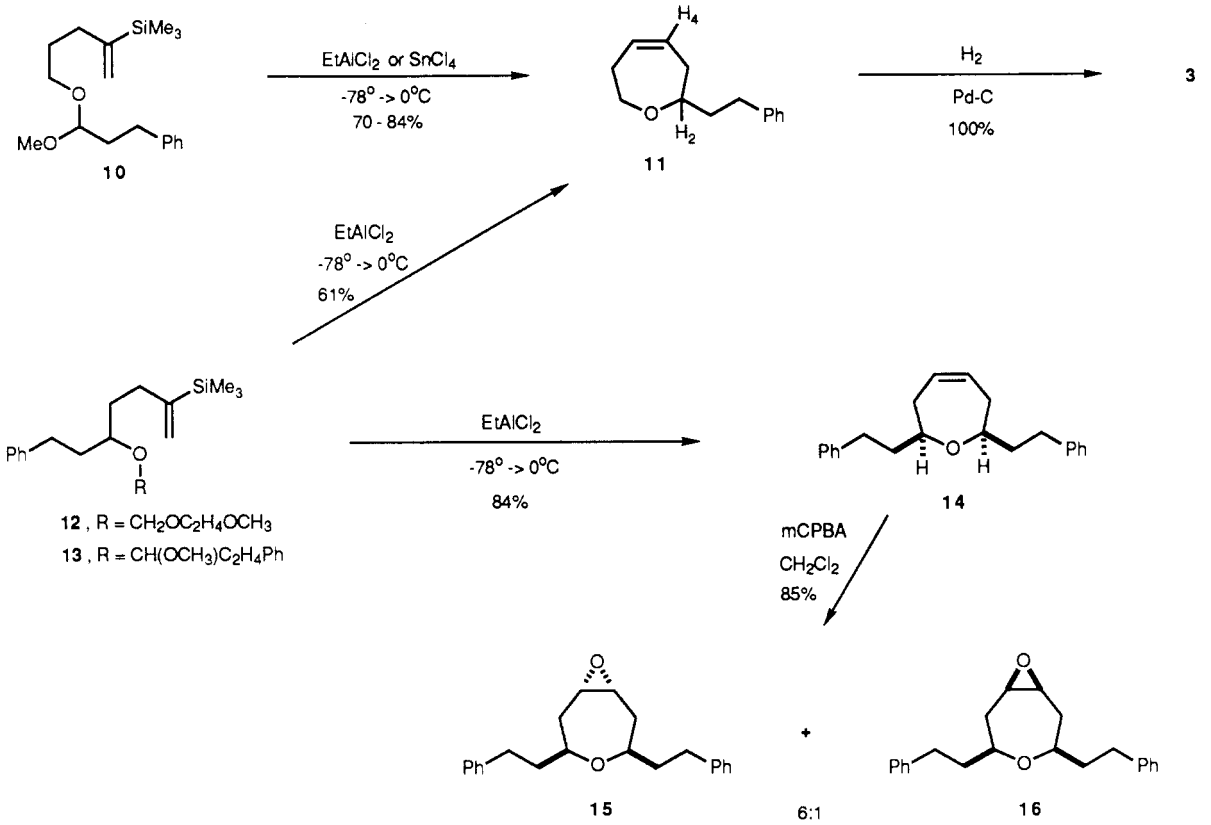
Figure 1. Calculated steric energy and (in parentheses) the distance in angstroms between the C-2 and C-7 methine hydrogens.

hydrogens in these computational models (ca. 2.1 Å in the cis isomers and 3.4 Å in the trans isomers) confirms expectations that the cis isomer should show the larger H_2–H_7 NOE. Unfortunately, the absence of the stereoisomer of **8** prevents rigorous application of this structural criteria.

Alkenes with Silicon Substitution at C-4. There is considerable experimental evidence that indicates that primary β-silyl cations are less stable than α-silyl tertiary

(21) Dillen, J.; Geise, H. J. *J. Mol. Struct.* **1980**, *64*, 239.
(22) Bocian, D. F.; Strauss, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 2866.
(23) PCMODEL Molecular Modeling Software for the Macintosh II, obtained from Serena Software, Bloomington, IN, was used for these calculations. For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; JAI Press: Vol. 2, in press.
(24) (a) The subroutine RANDOMIZ, which is based on Saunder's stochastic approach for exploring molecular mechanics energy surfaces,[24b] was employed in our search for global minimum. (b) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

Scheme III

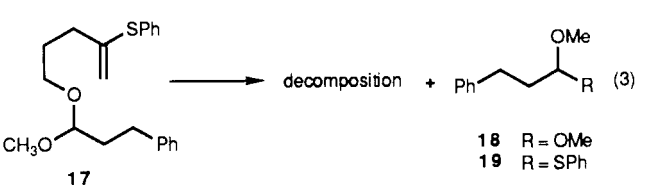


cations.[11,12,25] Thus, we expected that acetals derived from 4-(trimethylsilyl)-4-penten-1-ols would cyclize preferentially in the endocyclic mode to give Δ^4-oxepene (2,3,6,7-tetrahydrooxepin) products. As summarized in Scheme III this expectation proved correct; however, to our surprise[26] the oxepene products produced did not contain silicon. In good yield 2-(2-phenylethyl)-2,3,6,7-tetrahydrooxepin (**11**) was formed from either the mixed aldehyde acetal **10** (84% yield, 6 equiv of $EtAlCl_2$; 70% yield, 1.5 equiv of $SnCl_4$) or the mixed formaldehyde acetal **12** (61% yield, 3 equiv of $EtAlCl_2$). The cyclization of **10** in the presence of 6 equiv of $EtAlCl_2$ was complete within 6 h at −78 °C; thus the yield of **11** was nearly unchanged when the reaction was quenched after 6 h at −78 °C with excess Et_3N.

The structure of oxepene **11** followed directly from decoupled 500-MHz ^1H NMR spectra, which showed that H_2 (δ 3.30, m) and H_4 (δ 5.82, m) were both coupled in a vicinal manner to the methylene hydrogens at C-3 (multiplets at δ 2.32 and 2.18). Catalytic hydrogenation of **11** gave 2-(2-phenylethyl)oxepane (**3**) in quantitative yield. Careful monitoring of the cyclization of **10** by capillary GC provided no evidence for initial formation of a vinylsilane product that was subsequently converted to **11** by protodesilylation.

The stereochemistry of the Δ^4-oxepene-forming cyclization was studied with the mixed aldehyde acetal **13**. Cyclization of **13** in the presence of 6 equiv of $EtAlCl_2$ gave, to the limits of detection by 500-MHz ^1H NMR, the single Δ^4-oxepene product **14**, which was isolated in 84% yield after chromatographic purification. The gross structure of **14** was signaled by its ^{13}C and ^1H NMR spectra, which showed that **14** possessed either reflection or rotation (C_2) symmetry. The stereochemistry of **14** was unambiguously secured by oxidation of **14** with *m*-chloroperoxybenzoic acid to provide a 6:1 mixture of two epoxides. As a result of C_2 symmetry the trans isomer of **14** could form only a single epoxide. Again careful monitoring of the conversion of **13** to **14** by capillary GC provided no evidence for the intervention of a vinylsilane precursor of **14**. Moreover, when a 1:7 mixture of **13** and 4-(trimethylsilyl)-4-oxocene[15] was treated under identical conditions with 6 equiv of $EtAlCl_2$, **14** and the recovered silyloxocene were observed in a ratio of 1:8, respectively; 4-oxocene (3,6,7,8-tetrahydro-2*H*-oxocin) was formed to a negligible extent under these conditions.[28] The successful formation of **11** and **14** when $EtAlCl_2$ was used as the Lewis acid also argues against the intermediacy of a silyloxepene since this Lewis acid is itself a scavenger of HCl.[29]

We also briefly examined the Lewis acid promoted cyclization of vinyl sulfide acetal **17**, since a phenylthio substituent should also stabilize the cation resulting from endocyclic Prins cyclization. Under a variety of cyclization conditions using several Lewis acids ($SnCl_4$, $EtAlCl_2$, BF_3–OEt_2) complex reaction mixtures resulted, from which only the acetals **18** and **19** were isolated (eq 3).



(3)

(25) For a summary of key experimental data as well as a high-level computational study, see: Wierschke, S. F.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.

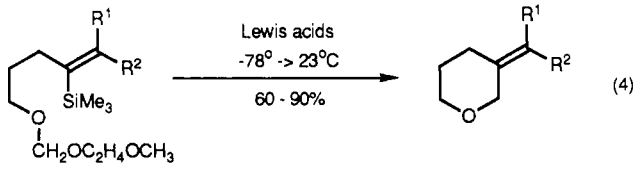
(26) Related cyclizations of acetals prepared from 5-(trimethylsilyl)-5-hexenols afford 4-(trimethylsilyl)-4-oxocenes.[15,27]

(27) Overman, L. E.; Blumenkopf, T. A.; Castañeda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516.

(28) This control experiment is less rigorous than it may appear, since the β-silyl cation formed by protonation of 4-(trimethylsilyl)-4-oxocene would experience more transannular destabilization than the related intermediate formed from a 4-(trimethylsilyl)-4-oxepene.

(29) See, e.g.: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

Lewis acid promoted cyclizations of vinylsilane acetals **20** and **22** proceeded, as expected,[12] in the exocyclic sense (via secondary β-silyl cation intermediates) to afford stereospecifically the (*Z*)- and (*E*)-3-pentylidenetetrahydropyrans **21** and **23**, respectively (eq 4). Several Lewis



(4)

20 $R^1 = H, R^2 = Bu^n$ **21** $R^1 = H, R^2 = Bu^n$

22 $R^1 = Bu^n, R^2 = H$ **23** $R^1 = Bu^n, R^2 = H$

acids were examined, and only the more reactive ones were effective; successful cyclizations were obtained with $EtAlCl_2$, $TiCl_3(OPr^i)$, $TiCl_4$, and $SnCl_4$. The stereospecificity of the $SnCl_4$-promoted cyclizations was examined carefully by using capillary GC conditions that cleanly separated **20–23**. These experiments showed no detectable crossover in the conversions of **20** → **21** and **22** → **23**; we determined that 0.5% of crossover product would have been detected. As a control experiment, the $SnCl_4$-promoted cyclization of a 87.1:12.9 mixture of **20**:**22** was examined and afforded **21** and **23** in a ratio of 87.5:12.5. Stereochemical assignments for pentylidenetetrahydropyrans **21** and **23** followed unambiguously from diagnostic ^{13}C NMR shifts of C-2: 67.0 ppm for **21** and 75.0 ppm for **23**.[30]

Alkenes with Silicon Substitution at C-5. Four substrates were examined, and the results of their Lewis acid promoted cyclizations are summarized in Scheme IV. As anticipated,[12] in the presence of an excess of $SnCl_4$, $EtAlCl_2$, or Et_2AlCl the mixed formaldehyde acetal **24** was converted in good yield to the Δ^3-oxepene **25**. The structure of **25** followed unambiguously from spectral, analytical and chemical data. For example, the 500-MHz ^1H NMR spectrum showed diagnostic signals at δ 4.34 and 4.05 for the diastereotopic C-7 methylene hydrogens, while oxepene **25** was converted to oxepane **3** in good yield upon catalytic hydrogenation. In marked contrast, the *E* stereoisomer of **24**, available from **24** via bromine radical catalyzed alkene equilibration,[31] afforded a complex mixture of many products when treated under similar conditions with $SnCl_4$ (−78 → 0 °C).

To our surprise, the closely related mixed aldehyde acetal **26** did not afford preparatively significant amounts of an oxepene product when treated with excess $SnCl_4$, $EtAlCl_2$, or Et_2AlCl at temperatures between −78 °C and room temperature. The reaction of **26** in the presence of 3 equiv of $SnCl_4$ (−78 → 0 °C, NaOH quench) was the cleanest and afforded a 1.5:1 mixture of stereoisomeric tetrahydrofurans **27** and **28**, which were isolated in 50–60% combined yield after chromatographic purification. These stereoisomers could be partially separated by preparative GLC and their structures could be assigned de novo from ^1H NMR and mass spectral data. The 500-MHz ^1H NMR spectrum (in C_6D_6) of **27** showed an apparent doublet of triplets for H_2 at δ 4.23 which was vicinially and allylically coupled to the two vinylic hydrogens of the 1-propenyl side chain. Decoupling experiments also established that the 2-phenylethyl group is attached to the carbon bearing H_5 (m at δ 3.89). That **27** was the 2,5-cis stereoisomer followed from the ^1H NMR HOE enhancements observed between H_2 and H_5 (3% H_2 → H_5, 5% H_5 → H_2). No ^1H NOE enhancements were observed between H_2 and H_5 of the trans stereoisomer **28**. Catalytic hydrogenation of the trans isomer **28** provided tetrahydrofuran **9**, which was indistinguishable from a sample of **9** produced from **5** (see Scheme II).

Cyclization of the 5-bromo-5-(trimethylsilyl)-4-pentenyl acetal **29** occurred preferentially in the exocyclic mode to give tetrahydropyran **30** as the predominant product (capillary GLC analysis) using $SnCl_4$ (10 equiv, −40 °C), $TiCl_4$ (4 equiv, −40 °C), or $EtAlCl_2$ (6 equiv, −50 °C or −78 → 23 °C) as the acetal activator. Tetrahydropyran **30** was isolated as a crystalline mixture of two stereoisomers, which could be separated (in low yield) by preparative GLC. A second product, likely 3-bromo-3-oxepene **31**, was detected by GLC and ^1H NMR analysis (diagnostic vinylic signal at δ 6.21 and a two-hydrogen singlet at δ 4.34 assignable to the C-2 methylene hydrogens of **31**). However, we never isolated a pure sample of this product. Worth noting is the clean ethylation to give *n*-propyl ether **32** that occurred when **29** was treated at 0 → 23 °C with 3 equiv of Et_2AlCl.

The vinylsilane acetal **33** also cyclized in the exocyclic mode to give one major product, the 3-alkenyltetrahydropyran **34**, when exposed to either $SnCl_4$ (1.5 equiv, −78 → 23 °C) or $EtAlCl_2$ (6 equiv, −78 → 0 °C or at −30 °C). These reactions provided a number of products in addition to **34**, and as a result a pure sample of **34** was obtained by preparative GLC separation. When the cyclization of **33** was carried out at −35 °C in the presence of 7 equiv of $EtAlCl_2$, 500-MHz ^1H NMR analysis of the crude product using diethyl fumarate as an internal standard indicated that tetrahydropyran **34** was formed in 70–75% yield. The structure of **34** followed directly from its decoupled 500-MHz ^1H NMR spectrum. Key to this analysis was the demonstration that H_3 (δ 2.50, m) was coupled to an adjacent vinylic hydrogen (δ 5.10, dd, J = 9.7 and 10.5 Hz) and also to both the equatorial (δ 3.57, dd, J = 11 and 3.6 Hz) and axial (δ 3.33, dt, J = 11 and 2.8 Hz) hydrogens at C-2.

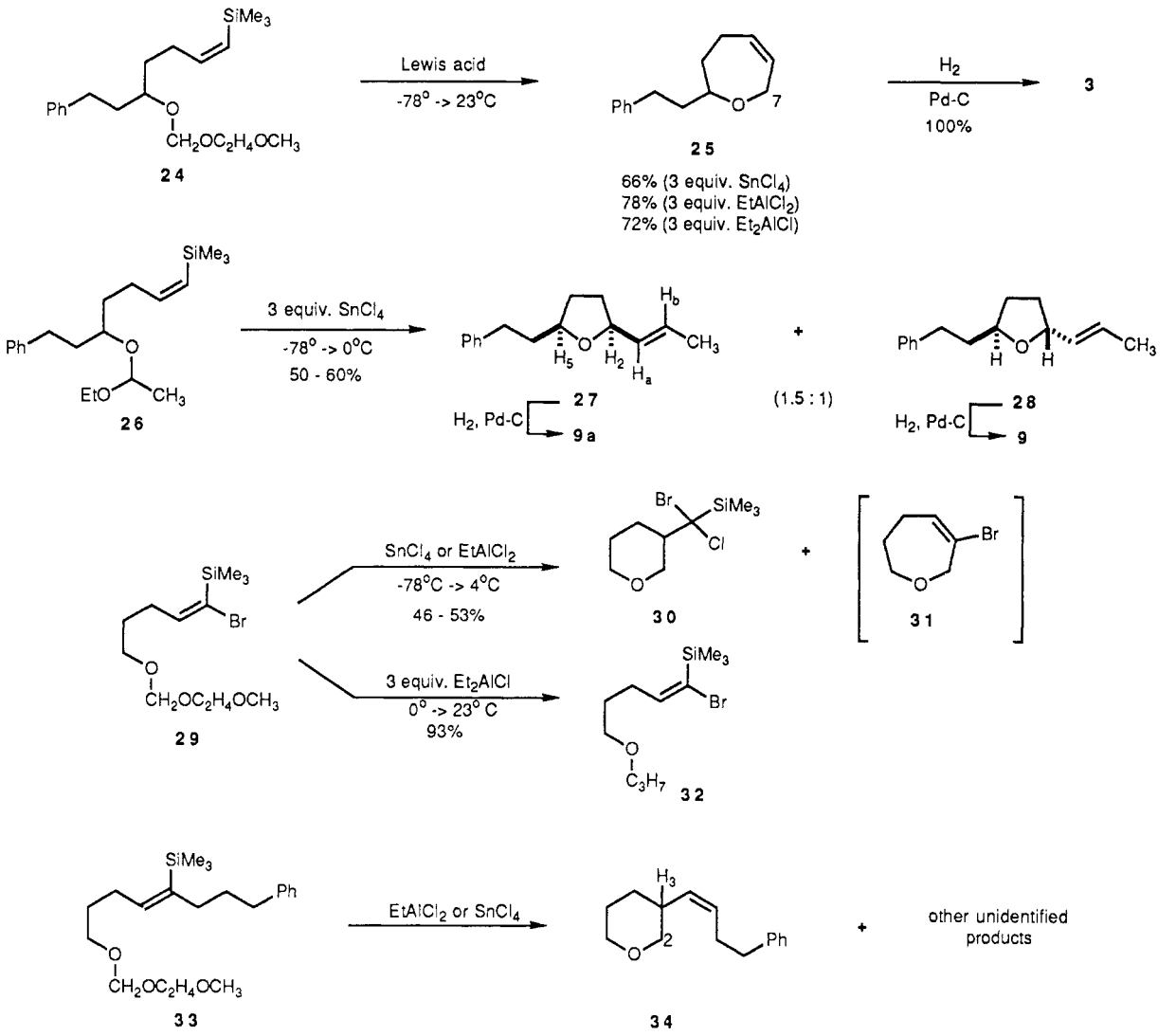
Discussion

Synthesis. Prins–Kriewitz cyclizations of mixed acetals derived from 4-penten-1-ols affords 2-substituted and 2,7-disubstituted oxepanes (see Scheme II) in moderate yield. This sequence complements the recently reported formation of these heterocycles by the direct condensation of 4-alken-1-ols with aldehydes[7b,32] as well as other modern methods that involve C–O bond formation.[33] Of greater significance and utility in synthesis is the clean formation of Δ^4-oxepenes (2,3,6,7-tetrahydrooxepins) from mixed acetals of 4-(trimethylsilyl)-4-penten-1-ols (see Scheme III). The formation of Δ^4-oxepenes containing side chains at C-2 and C-7 in high yields and with excellent cis stereoselectivity suggests that this chemistry may be useful for the preparation of marine natural products such as isolaurepinnacin.

The *stereospecific* formation of 3-alkylidenetetrahydropyrans **21** and **23** in high yields from the cyclization of vinylsilane acetals **20** and **22** is also notable. To our knowledge this is the only method currently available for preparing either tetrahydropyran alkylidene stereoisomer.[34]

(30) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; pp 112–118.
(31) Zweifel, G.; On, H. P. *Synthesis* **1980**, 803.
(32) The evidence (half-height widths of ^1H NMR absorptions for methine hydrogens) reported in this communication[7b] would not appear to unambiguously specify the stereochemistry of the 4-chloro-7-methyl-2-isopropyloxepane formed from 5-hexen-1-ol and isobutyraldehyde.
(33) See, inter alia: Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. Whitby, R.; Yeates, C.; Kocienski, P.; Costello, G. *J. Chem. Soc., Chem. Commun.* **1987**, 429.

Scheme IV

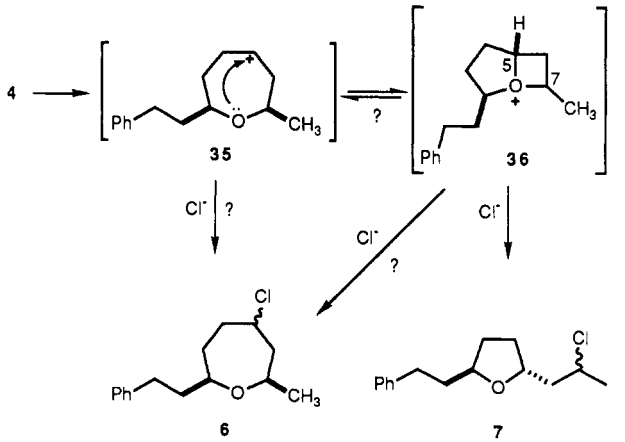


The extent (>99.5%) to which the silicon substituent controls the stereochemistry of the alkylidene double bond is striking. These conversions provide another demonstration[12] of the utility of vinylsilane cyclizations that proceed in the exocyclic mode (with respect to the silylalkene) for forming heterocycles with exocyclic unsaturation.

The competitive formation of tetrahydrofurans from acetals **5** and **26** illustrates the major limitations we have encountered in using oxonium ion initiated cyclizations for forming seven-membered cyclic ethers. In particular, the divergent behavior of acetals **24** and **26** highlights the close balance that exists between simple cyclization and more complex rearrangement pathways.

Mechanism. The mode of cyclization (endocyclic or exocyclic) of the acetal substrates examined in this study appears to be controlled predominantly by the electronic nature of the alkene nucleophile. The results obtained with vinylsilane cyclization terminators (Schemes III and IV) are consistent with currently accepted orders of carbocation stability: secondary β-silyl > tertiary α-silyl > primary β-silyl > secondary.[11,12,25] The notable exception, formation of **34** from vinylsilane acetal **33**, is best rationalized (vide infra) as proceeding preferentially via a tertiary α-silyl, rather than a secondary β-silyl, cation intermediate.

Scheme V



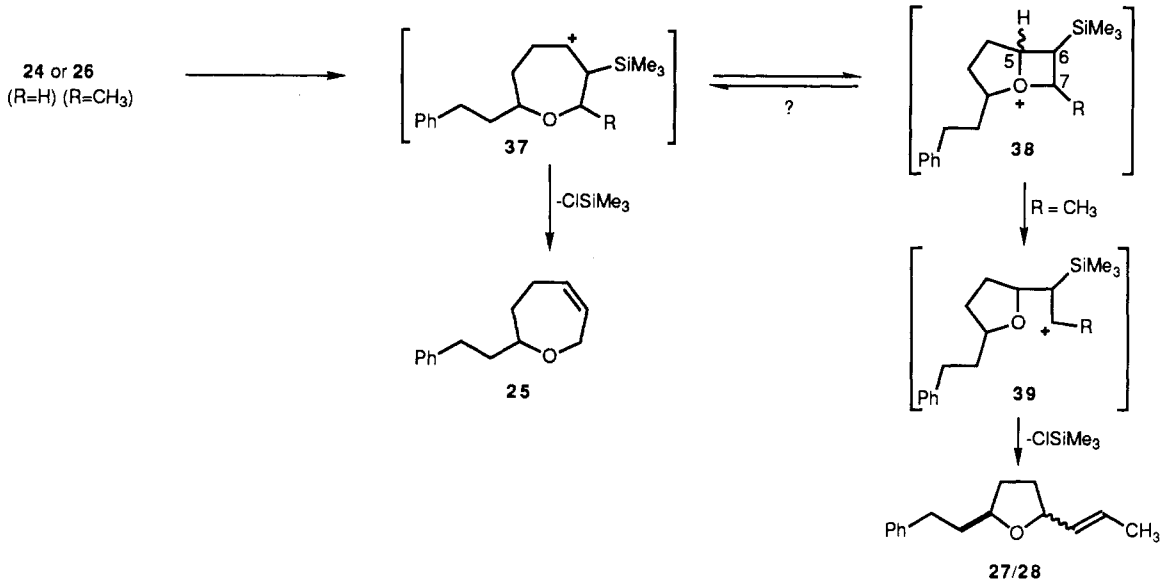
Apparently, in this case, the kinetic preference[35] for six-membered (rather than seven-membered) ring formation overwhelms electronic effects.

The formation of tetrahydrofurans from the cyclization of oxonium cations derived from 4-alken-1-ols can be rationalized by transannular participation of the ether oxy-

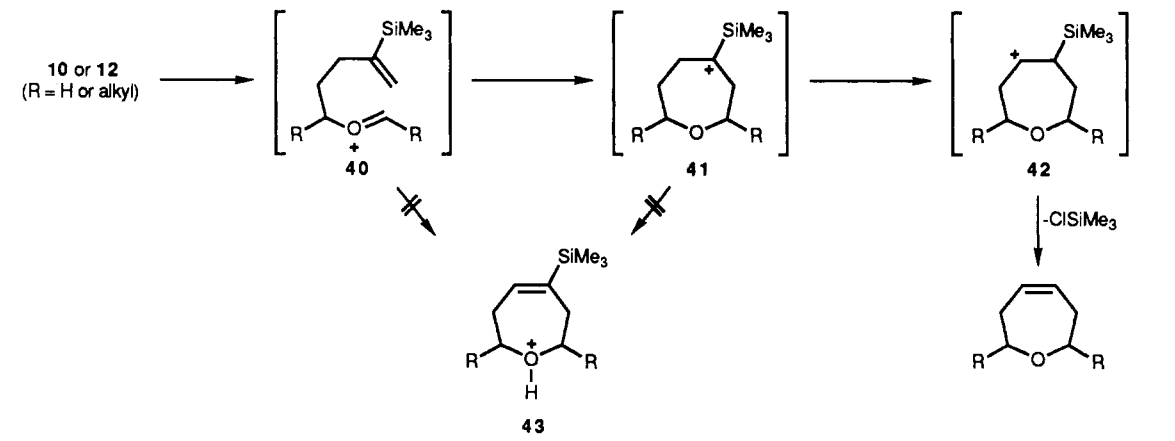
(34) The preparation of (*E*)-3-alkylidenetetrahydropyrans from cyclopropane intermediates has been reported: Danheiser, R. L.; Morin, J. M., Jr.; Yu, M.; Basak, A. *Tetrahedron Lett.* **1981**, *22*, 4205.

(35) Six-membered rings are typically formed by cyclization reactions orders of magnitude faster than seven-membered rings. For a recent summary and leading references, see: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

Scheme VI



Scheme VII



gen in an initially formed 4-oxepanyl cation **35** as illustrated in Scheme V. Reaction of the resulting 1-oxabicyclo[3.2.0]heptanyl oxonium ion **36** with chloride at C-7 would lead to the rearranged tetrahydrofuran products. The observed trans stereochemistry of **7** would directly evolve from an energetic preference for forming **36** with the phenethyl side chain on the convex face of the bicycloheptane ring system. Oxonium ion **36** could serve also as the direct precursor of the 4-chlorooxepanes **6**. Transannular participation of an ether oxygen has considerable precedent in the homologous eight-membered ring series.[36] We also note that **36** could, in principle, be formed directly from **4** by an intramolecular [2+2] cycloaddition pathway, although, to the best of our knowledge, hetero [2+2] cycloadditions of oxonium cations have not been documented.

The divergent behavior of vinylsilane acetals **24** and **26** can also be understood on the basis of the intervention of 1-oxabicyclo[3.2.0]heptanyl oxonium ion intermediates (Scheme VI). For example, cation **38** would be more prone to cleavage of the 1–7 bond in an S_N1 sense if R were a cation-stabilizing group such as CH_3 than if R were H. Thus, the formation of significant amounts of rearranged tetrahydrofuran products from **26** and not from **24** is reasonable. It is of course conceivable that **25** and **27/28** arise directly from cation **38** by direct fragmentation. The stereoelectronics of this process (i.e., the overlap of the C_6–Si σ bond with the C_5–O σ bond) are far from ideal, and, thus, we have not formally depicted this pathway in Scheme VI.[37]

We cannot unambiguously rule out the possibility that the 4-chlorooxepanes **2a** and **2b** are also produced (and interconvert) via a 1-oxabicyclo[3.2.0]heptanyl oxonium ion intermediate. However, this proposal is not supported by the fact that at 0 °C these stereoisomers interconvert without detectable formation of rearranged tetrahydrofurans. Presumably, the 5-chlorooxepane **4** (see Scheme II) is produced from **2** by 1,2-hydride rearrangement of the 4-oxepanyl cation resulting from Lewis acid promoted ionization of the C–Cl σ bond of **2**. Other 1,2 hydride migrations (e.g., to form a 3-oxepanyl cation) would be disfavored by the inductive effect of the ring oxygen.

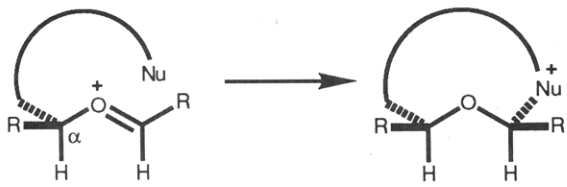
One of the more unexpected results of this study was that the cyclization of vinylsilane acetals **10**, **12**, and **13** yielded Δ^4-oxepene products that do not contain the trimethylsilyl group. These products presumably arise from the pathway summarized in Scheme VII in which the initially formed 4-oxepanyl cation **41** rapidly undergoes 1,2 hydride migration to give the β-silyl cation isomer **42**. This

(36) See, e.g.: Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6760.

(37) Other mechanistic variants on this scheme would involve the reaction of **35** with chloride to give β-chlorosilanes related to **34** and **39**, which then undergo loss of Me_3SiCl.

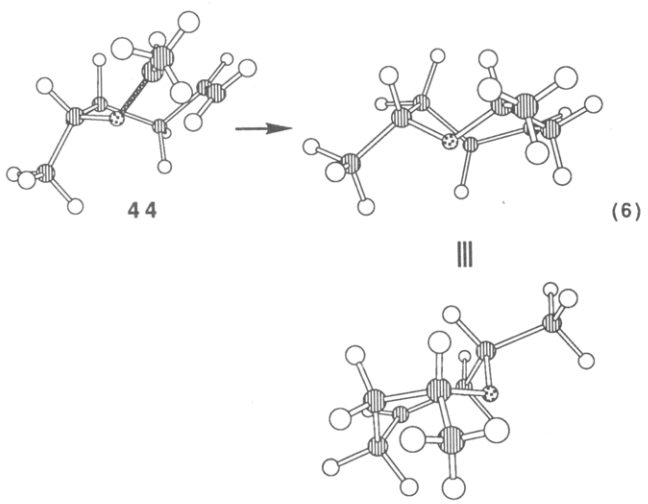
latter intermediate then suffers loss of the β-silicon to afford the observed $^4\Delta$-oxepene products. Not shown in this scheme is the possible (vide supra) interconversion of both **41** and **42** with the related bicyclic oxonium cations resulting from transannular ether participation. Most notable is the fact that **40** (by direct intramolecular ene cyclization) or **41** (by intramolecular general base-assited deprotonation) do *not* form the 4-(trimethylsilyl)-4-oxepanyl product **43**. Silyl Δ^4-oxocenes of this general type are the predominant products observed in cyclizations of one-carbon homologues that form eight-membered cyclic ethers.

The stereoselective formation of seven-membered ring ethers with cis-oriented side chains at C-2 and C-7 from the cyclization of mixed acetals **5** and **13** is readily rationalized by preferential cyclization of the more stable (*E*)-oxonium ion stereoisomer[38] via a local conformation having the smallest substituent at C-α (hydrogen) in the plane of the partial C–O π bond.[39] This argument is presented schematically in eq 5 to highlight the fact that



(5)

cis stereoselectivity would be expected from this model whenever the length of the tether delivering the intramolecular nucleophile is short enough to favor addition of the nucleophile from the α face. In the case at hand, cyclization of oxonium ion **44** in a synclinal sense[40] would lead directly to a low-energy conformation of a 2,7-disubstituted-4-oxepanyl cation as depicted in eq 6.



(6)

Conclusion

Lewis acid promoted cyclizations of mixed acetals derived from 4-alken-1-ols afford five-, six-, or seven-membered ring cyclic ether products depending upon the nature of the alkene nucleophile and the oxonium ion electrophile. Acetals containing terminal alkene, 5-(trimethylsilyl)-4-alkene, or 4-(trimethylsilyl)-4-alkene nucleophilic components all cyclize in the endocyclic sense (in accord with the electronic bias of the alkene) to give seven-membered oxacyclic products. Cyclizations of acetals containing the 4-(trimethylsilyl)-4-alkene unit proceed with excellent efficiency to achieve the first useful direct construction of the 2,3,6,7-tetrahydrooxepin ring system. Cyclizations of disubstituted substrates of this latter type, moreover, proceed with complete stereoselectively to yield *cis*-2,7-disubstituted-2,3,6,7-tetrahydrooxepins and, thus, assemble in one step the key structural elements of marine natural products such as isolaurepinnacin.

Experimental Section[41]

5-((1-Methoxy-3-phenyl)propoxy)-1-pentene (1). Following the general procedure of Overman and Thompson,[15] crude 1-chloro-1-methoxy-3-phenylpropane[19] (13 mmol) was added dropwise to a solution of 4-penten-1-ol (0.565 g, 6.56 mmol), *i*-Pr_2NEt (2.3 mL, 13 mmol), and dry CH_2Cl_2 (33 mL) at room temperature. The resulting solution was maintained at room temperature for 12 h, then washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), saturated aqueous NaCl (50 mL), and dried over K_2CO_3. Concentration and purification of the residue on silica gel (solvent gradient: 40:1 hexane–EtOAc → 20:1 hexane–EtOAc) gave acetal **1** in addition to an unknown, more volatile impurity. The volatile impurity was removed in vacuo (90 °C, 0.4 mmHg) leaving behind 0.98 g (64%) of acetal **1** (98% pure by GLC analysis[43]) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.35 (m, 5 H, Ph), 5.86 (ddt, *J* = 16.9, 10.3, 6.6 Hz, H_2C=C*H*), 4.98–5.10 (m, H_2C=CH), 4.45 (t, *J* = 5.7 Hz, OCHO), 3.63 (dt, *J* = 9.4, 6.5 Hz, 1 H, CH_2O), 3.46 (dt, *J* = 9.4, 6.6 Hz, 1 H, CH_2O), 3.36 (s, OCH_3), 2.68–2.74 (m, PhCH_2), 2.15–2.22 (m, 2 H), 1.93–2.00 (m, 2 H), 1.67–1.77 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 138.6, 128.8, 126.2, 115.2, 103.5, 65.5, 53.0, 35.0, 31.3, 30.8, 29.5; IR (film) 3056, 2937, 1644, 1606, 1494, 1456, 1125, 1069, 912, 750, 700 cm^{-1}; MS (EI), *m/z* 234.1613 (M, 234.1620 calcd for $C_{15}H_{22}O_2$) 202 (5%), 148 (32%), 129 (53%), 117 (39%), 105 (16%), 91 (100%), 84 (12%), 70 (12%).

4-Chloro-2-(2-phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (2a,b). $EtAlCl_2$ (0.33 mL of a 25.9% solution in heptane, 0.53 mmol) was added dropwise to a solution of acetal **1** (41.1 mg, 0.175 mmol) and dry CH_2Cl_2 (5.8 mL) at −78 °C. The resulting solution was maintained at −78 °C for 1 h and at 0 °C for 3 h, then the reaction was quenched with cold (0 °C) 15% NaOH (3 mL), and the resulting mixture was allowed to warm to room temperature. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic fractions were washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), saturated aqueous NaCl (10 mL) and were dried over $MgSO_4$. Concentration and separation of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 100:1 hexane–EtOAc) gave **2a** (15.2 mg) and **2b** (12.2 mg) in 66% combined yield.

2a: ^{1}H NMR shows ~15% of an unknown impurity that is not **2b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, Ph), 4.03 (app tt, *J* = 3.7, 11.0 Hz, ClCH), 3.84 (ddd, *J* = 5.4, 9.5, 12.1 Hz, 1 H, H_2CO), 3.65 (ddd, *J* = 4.4, 5.8, 12.0 Hz, 1 H, H_2CO), 3.35–3.40 (m, OC*H*CH_2), 2.78 (ddd, *J* = 5.1, 9.3, 13.7 Hz, 1 H, PhCH_2), 2.64 (ddd, *J* = 7.5, 8.8, 13.8 Hz, 1 H, PhCH_2), 2.20–2.29 (m, ClCCH_2CHO), 1.91–2.11 (m, Cl(H)C$CH_2CH_2CH_2$O), 1.76–1.90 (m, OCHCH_2CH_2Ph), 1.63–1.74 (m, Cl(H)CC$H_2CH_2CH_2$O); IR (film) 3026, 2948, 2935, 1496, 1454, 1118, 752, 700 cm^{-1}; MS (CI), *m/z* 241 (MH), 239, (MH), 203, 185, 131, 117, 85, 81, 71; MS (EI), *m/z* 240 (M, 2%), 238 (M, 5%), 202 (21%), 152 (19%), 143 (12%), 133 (21%), 129 (16%), 117 (55%), 104 (44%), 97 (27%), 91

(38) Inversion and rotation barriers for oxonium ions are sufficiently low that reaction via only the more stable *E* stereoisomer is expected: Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.

(39) Wiberg, K. B.; Schreiber, S. L. *J. Org. Chem.* **1988**, *53*, 783, and references therein.

(40) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(41) General experimental details were recently reported.[42] Benzene, CH_2Cl_2, *i*-Pr_2NEt, NEt_3, and hexane were distilled from CaH_2 immediately before use. (2-Methoxyethoxy)methyl chloride (MEM-Cl, Aldrich) was flushed through a plug of activity IV basic alumina before use. Diisobutylaluminum hydride (DIBAL, neat), Et_2AlCl (neat), and $EtAlCl_2$ (heptane solution) were obtained from Texas Alkyls, Inc. $SnCl_4$ and $TiCl_4$ were distilled from P_2O_5 and used as solutions in CH_2Cl_2.

(42) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

(43) Capillary GLC analysis was conducted with a Hewlett-Packard 5880A gas chromatograph equipped with a 30 m × 0.32 mm J & W DB-5 column. Temperature programming was from 70 to 280 °C at 10 °C/min.

(100%), 71 (16%). Characteristic resonances of the unknown impurity: δ 4.25–4.30 (m), 3.79–3.82 (ddd), 3.56–3.62 (m).

Key ^{1}H decoupling experiments on **2a** (500 MHz, $CDCl_3$): Irradiation at δ 2.64 (ddd, 1 H, $PhCH_2$) partially collapsed the ddd at 2.78 (1 H, $PhCH_2$) and the m at 1.76–1.90 (2 H, $PhCH_2CH_2$). Irradiation at δ 3.35–3.40 (m, $PhCH_2CH_2CHO$) partially collapsed the m at δ 1.76–1.90 (2 H, $PhCH_2CH_2$) and the m at δ 2.20–2.29 (2 H, $ClCCH_2CHO$). Irradiation at δ 2.20–2.29 (m, 2 H, $ClCCH_2CHO$) collapsed the m at 3.35–3.40 ($PhCH_2CH_2CHO$) to a dt, the app tt at δ 4.03 (ClCH) to an app t and partially collapsed the m at δ 1.91–2.11 (2 H, $ClC(H)CH_2CH_2CH_2O$). Irradiation at δ 4.03 (app tt, ClCH) partially collapsed the m at δ 2.20–2.29 (2 H, $ClCCH_2CHO$) and the m at δ 1.91–2.11 (2 H, $ClC(H)CH_2CH_2CH_2O$). Irradiation at δ 3.84 (ddd, 1 H, $H_2COCHCH_2CH_2Ph$) partially collapsed the ddd at δ 3.65 (1 H, $H_2COCHCH_2CH_2Ph$) and had no effect at δ 3.35–3.40 (m, $PhCH_2CH_2CHO$). Irradiation at δ 3.65 (ddd, 1 H, $H_2COCHCH_2CH_2Ph$) partially collapsed the ddd at δ 3.84 (1 H, $H_2COCHCH_2CH_2Ph$) and had no effect at δ 3.35–3.40 (m, $PhCH_2CH_2CHO$).

2b: ^{1}H NMR shows ~13% of the 5-chloroxepane **4**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, Ph), 4.45–4.49 (m, ClCH), 3.90 (app ddd, J = 5.9, 7.1, 12.2 Hz, 1 H, CH_2O), 3.61–3.68 (m, 2 H, OCH), 2.81 (ddd, J = 5.3, 10.0, 13.7 Hz, 1 H, $PhCH_2$), 2.64 (ddd, J = 6.6, 9.8, 13.7 Hz, 1 H, $PhCH_2$), 2.02–2.18 (m, 5 H), 1.77–1.88 (m, 1 H), 1.66–1.76 (m, 2 H); IR (film) 3026, 2945, 2860, 1497, 1454, 1125, 750, 700 cm^{-1}; MS (CI), m/z 241 (MH), 239 (MH), 203, 185, 159, 133, 117, 85, 71; MS (EI), m/z 240 (M, 2%), 238 (M, 7%), 202 (25%), 152 (21%), 143 (13%), 133 (22%), 129 (16%), 117 (53%), 104 (42%), 97 (29%), 91 (100%), 84 (21%), 71 (22%).

Synthesis of 2-(2-Phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (3) from 2a and 2b. Following the general procedures of Menapace and Leibner,[20] a catalytic amount of AIBN (ca. 1 mg) was added to a solution of **2a** (15.2 mg, 0.0638 mmol), n-Bu_3SnH (19 μL, 0.070 mmol), and dry benzene (1 mL), and the resulting solution was heated at reflux for 14 h. The solution was then concentrated and diluted with hexane (10 mL) and saturated KF (10 mL), and the resulting aqueous layer extracted with hexane (10 mL). The combined organic fractions were washed with saturated aqueous KF (2 × 10 mL) and saturated aqueous NaCl (10 mL) and were dried over $MgSO_4$. Concentration and purification of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 100:1 hexane–EtOAc) gave 12 mg (93%) of oxepane **3** (100% pure by GLC analysis[43]) as a clear oil. The 500-MHz ^{1}H NMR of this product and capillary GC retention time were indistinguishable from that for oxepane **3** produced from hydrogenation of **10**.

Identical reduction of the diastereomer **2b** (12.2 mg, 0.0512 mmol) gave 7.2 mg (69%) of **3**.

Formation of 5-Chloro-2-(2-phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (4) and 2a from 2b. $EtAlCl_2$ (0.17 mL of a 25.9% solution in heptane, 0.27 mmol) was added dropwise to a solution of chloroxepane **2b** (21.5 mg, 0.0900 mmol) and dry CH_2Cl_2 (3.0 mL) at −78 °C. The resulting solution was maintained at −78 °C for 1 h and at 0 °C for 4 h, the reaction was quenched with cold (0 °C) 15% NaOH (3.0 mL), and the resulting mixture was allowed to warm to room temperature. The layers were separated, and the aqueous fraction was extracted with CH_2Cl_2 (10 mL). The combined organic fractions were washed with saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. Concentration gave 20 mg (91%) of a pale yellow oil. GLC analysis[43] showed a mixture of **2a**, **2b**, and **4** present in a 30:47:23 ratio, respectively. Purification by HPLC[44] gave an analytical sample of **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, Ph), 4.28–4.33 (m, 1 H, ClCH), 3.91 (ddd, J = 2.9, 7.0, 13.0 Hz, 1 H, $ClCHCH_2CH_2O$), 3.56–3.61 (m, 1 H, $PhCH_2CH_2CHO$), 3.44 (ddd, J = 2.6, 7.7, 13.1 Hz, 1 H, $ClCHCH_2CH_2O$), 2.77 (ddd, J = 5.3, 9.5, 13.8, 1 H, $PhCH_2$), 2.64 (ddd, J = 7.0, 9.3, 13.8, 1 H, $PhCH_2$), 2.16–2.22 (m, 1 H, $ClCHCH_2CH_2O$), 2.01–2.13 (m, 3 H), 1.83–1.95 (m, 2 H), 1.72 (dddd, J = 2.9, 5.3, 8.3, 15.1 Hz, 1 H, OCH_2CH_2), 1.66 (dddd, J = 4.2, 7.0, 9.6, 13.7 Hz, 1 H, $PhCH_2CH_2CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 128.4, 128.3, 125.7, 77.1, 62.3, 60.8, 41.5, 37.7, 33.8, 32.2, 29.4; MS (CI), m/z 241 (MH), 239 (MH), 203, 185, 131; MS (EI), m/z 240 (M), 238.1106 (M, 238.1124 calcd for $C_{14}H_{19}OCl$), 202 (1%), 160 (2%), 147 (1%), 133 (17%), 117 (35%), 104 (44%), 91 (100%).

Key ^{1}H decoupling experiments on **4** (500 MHz, $CDCl_3$): Irradiation at δ 2.77 (ddd, 1 H, $PhCH_2$) partially collapsed the ddd at δ 2.64 (1 H, $PhCH_2$), the dddd at δ 1.66 (1 H, $PhCH_2CH_2$), and the m at δ 1.83–1.85 (2 H). Irradiation at δ 2.64 (ddd, 1 H, $PhCH_2$) partially collapsed the ddd at δ 2.77 (1 H, $PhCH_2$), the dddd at 1.66 (1 H, $PhCH_2CH_2$), and the m at δ 1.83–1.95 (2 H). Irradiation at δ 1.66 (dddd, 1 H, $PhCH_2CH_2$) partially collapsed the ddd at δ 2.64 (1 H, $PhCH_2$), the ddd at δ 2.77 (1 H, $PhCH_2$), the m at δ 1.83–1.95 (2 H), and the m at δ 3.57–3.61 ($PhCH_2CH_2CHO$). Irradiation at δ 3.57–3.61 (m, $PhCH_2CH_2CHO$) collapsed the dddd at δ 1.66 (1 H, $PhCH_2CH_2$) to a ddd, and the dddd at δ 1.72 (1 H, $PhCH_2CH_2C(H)(O)CH_2$), to a ddd and partially collapsed the m at δ 1.83–1.95 (2 H). Irradiation at δ 3.44 (ddd, 1 H, CH_2O) partially collapsed the m at δ 2.01–2.13 (3 H), the m at δ 2.16–2.22 (1 H, $ClC(H)CH_2CH_2O$), and the ddd at δ 3.91 (1 H, CH_2O) and had no effect at δ 3.56–3.61 (m, $PhCH_2CH_2CHO$). Irradiation at δ 3.91 (ddd, 1 H, CH_2O) partially collapsed the m at δ 2.01–2.13 (3 H), the m at δ 2.16–2.22 (1 H, $ClC(H)CH_2CH_2O$), and the ddd at 3.44 (1 H, CH_2O) and had no effect at δ 3.56–3.61 (m, $PhCH_2CH_2CHO$). Irradiation at δ 2.16–2.22 (m, 1 H, $ClC(H)CH2CH_2O$) partially collapsed the m at δ 2.01–2.13 (3 H), the ddd at δ 3.44 (1 H, CH_2O), the ddd at δ 3.91 (1 H, CH_2O), and the m at δ 4.28–4.33 (ClCH). Irradiation at δ 4.28–4.33 (m, ClCH) collapsed the m at δ 2.16–2.22 (1 H, $ClC(H)CH_2CH_2O$) to a ddd and partially collapsed the m at δ 2.01–2.13 (3 H).

Formation of 5-Chloro-2-(2-phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (4) and 2b from 2a. Following the same procedure as for the isomerization of **2b**, treatment of a solution of **2a** (19.7 mg, 0.0830 mmol) and CH_2Cl_2 (2.8 mL) with $EtAlCl_2$ (0.16 mL of a 25.9% solution in heptane, 0.25 mmol) gave 19 mg of a pale yellow oil (95%). GLC analysis[43] showed a mixture of **2a**, **2b**, and **4** present in a 54:32:14 ratio, respectively.

3-(1-Ethoxyethoxy)-1-phenyl-6-heptene (5). A catalytic amount of PPTS was added to a solution of 1-(2-phenylethyl)-4-penten-1-ol (0.306 g, 1.61 mmol) and ethyl vinyl ether (2.1 mL) at 0 °C.[18] The resulting solution was allowed to warm to room temperature, and after 12 h the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was washed with saturated aqueous NaCl (10 mL) and dried over K_2CO_3. Concentration and purification of the residue on silica gel gave 0.37 g (88%) of **5** (100% pure by GLC analysis[43]) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.32 (m, 5 H, Ph), 5.78–5.91 (m, =CH), 4.95–5.08 (m, $=CH_2$), 4.70–4.76 (m, OCHO), 3.57–3.70 (m, 2 H), 3.45–3.55 (m, 1 H), 2.58–2.82 (m, $PhCH_2$), 2.07–2.22 (m, $=CCH_2$), 1.78–1.90 (m, 2 H), 1.59–1.73 (m, 2 H), 1.34 (dd, J = 0.6, 5.3 Hz, $(O)OCHCH_3$), 1.22 (dt, J = 3.8, 7.0, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 142.2, 138.5, 138.4, 128.3, 128.2, 128.2, 125.7, 125.6, 114.5, 114.4, 98.9, 98.8, 75.3, 60.1, 60.0, 36.5, 35.7, 33.8, 33.3, 31.7, 31.3, 29.6, 29.3, 20.6, 15.3; IR (film) 3078, 3065, 3027, 2978, 2935, 2858, 1641, 1497, 1455, 1393, 1376, 1338, 1126, 1098, 1087, 1058, 1032, 994, 970, 911, 747, 699 cm^{-1}; MS (CI), m/z 263 (MH), 217, 173, 131, 73; MS (EI), m/z 216.1496 (M − C_2H_6O, 3%, 216.1514 calcd for $C_{17}H_{26}O_2$), 172 (6%), 131 (10%), 117 (7%), 104 (10%), 91 (41%), 73 (100%).

Cyclization of Acetal 5 Using $SnCl_4$. $SnCl_4$ (1.9 mL of a 1.0 M solution in CH_2Cl_2, 1.9 mmol) was added dropwise to a solution of acetal **5** (0.169 g, 0.642 mmol) and dry CH_2Cl_2 (22 mL) at −78 °C. The resulting solution was maintained at −78 °C for 1 h and then was allowed to warm to room temperature and maintained there for 4.5 h. The reaction was quenched with 5% NaOH (10 mL), and the resulting aqueous fraction extracted with CH_2Cl_2 (20 mL). The combined organic fractions were washed with H_2O (30 mL) and saturated aqueous NaCl (30 mL) and dried over $MgSO_4$. Concentration and purification of the residue on silica gel (solvent gradient: 200:1 hexane–EtOAc → 20:1 hexane–EtOAc) gave 0.12 g (75%) of oxepanes **6** and tetrahydrofurans **7** as a mixture of diastereomers (56:28:9:7 by GLC analysis[43]): a clear oil; IR (film) 3027, 2932, 2863, 1496, 1454, 1373, 1142, 1111, 1084, 748, 699 cm^{-1}; MS (CI), m/z 255 (MH), 254 (MH), 253 (MH), 217, 199, 175, 173, 131, 117, 104, 91; MS (EI), m/z 252.1295 (M,

(44) Preparatory HPLC was conducted with a Waters 6000A system equipped with a Supelco 25 cm × 10 mm column packed with Supelcosil LC-SI semiprep (5 μm) silica gel using UV detection at 254 nm. Hexane–EtOAc (98:2) was used as the eluent.

6% 252.1281 calcd for $C_{15}H_{21}OCl$), 217 (5%), 216 (7%), 174 (5%), 172 (5%), 143 (15%), 130 (22%), 117 (28%), 105 (19%), 104 (72%), 92 (59%), 91 (100%), 67 (17%), 55 (21%).

Cyclization of 5 Using $EtAlCl_2$. $EtAlCl_2$ (0.22 mL of a 25.9% solution in heptane, 0.34 mmol) was added dropwise to a solution of acetal **5** (30.0 mg, 0.114 mmol) and dry CH_2Cl_2 (3.8 mL) at −78 °C, and the resulting solution maintained at −78 °C for 1.5 h. The reaction was quenched at −78 °C with NEt_3 (0.24 mL, 1.7 mmol), maintained at −78 °C for 0.5 h, further quenched with 5% NaOH (3 mL), and then warmed to room temperature. The resulting aqueous fraction was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic fractions washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration and purification of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 20:1 hexane–EtOAc) gave 21 mg (72%) of oxepanes **6** and tetrahydrofurans **7** as a mixture of diastereomers (42:40:9:9 by GLC analysis[43]).

***cis*-7-Methyl-2-(2-phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (8) and *trans*-5-(2-Phenylethyl)-2-propyl-2,3,4,5-tetrahydrofuran (9).** A 30.3-mg (0.120 mmol) sample of the cyclic ether product mixture produced from the cyclization of **5** with $EtAlCl_2$ was dechlorinated as described for the preparation of **3** to give, after purification on silica gel (solvent gradient: hexane → 400:1 hexane–EtOAc), 25 mg (94%) of a mixture of oxepane **8** and tetrahydrofuran **9** (86:14, 100% pure by GLC analysis). The major product **8** was isolated by preparatory GC[46] (column temperature 105 °C): ^1H NMR (500 MHz, C_6D_6) δ 7.06–7.19 (m, 5 H, Ph), 3.40 (ddq, J = 8.1, 4.2, 6.2 Hz, $OCHCH_3$), 3.19–3.27 (m, $PhCH_2CH_2CHO$), 2.83 (ddd, J = 4.9, 9.1, 14.0 Hz, 1 H, $PhCH_2$), 2.65 (ddd, J = 7.3, 9.1, 13.6 Hz, 1 H, $PhCH_2$), 1.82 (ddt, J = 4.8, 14.2, 9.0 Hz, 1 H, $PhCH_2CH_2$), 1.23–1.61 (m, 9 H), 1.18 (d, J = 6.2 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6) δ 143.0, 128.9, 128.6, 125.9, 78.3, 75.9, 39.5, 38.5, 37.0, 32.8, 25.9, 25.2, 23.2; IR (film) 2968, 2929, 2858, 1455, 1143, 1101, 699, 678 cm^{-1}; MS (CI), m/z 219 (MH), 201, 173, 131, 104, 91; MS (EI), m/z 218.1665 (M, 5%, 218.1671 calcd for $C_{15}H_{22}O$), 200 (4%), 129 (11%), 117 (22%), 104 (100%), 95 (29%), 91 (94%), 65 (16%), 55 (24%).

Spectral evidence for **9**: characteristic resonances of **9** (δ 0.93–0.97 (t), 1.81–1.87 (m), 2.72–2.78 (ddd), 3.93–4.00 (m)) were visible in the 500-MHz ^1H spectrum of a mixture of **8** and **9**. These resonances matched those of a sample of **9** prepared by hydrogenation of **28** and were clearly different from those of the cis stereoisomer prepared from **27**.

5-(1-Methoxy-3-phenylpropoxy)-2-(trimethylsilyl)-1-pentene (10). A solution of 4-(trimethylsilyl)-4-pentenol (0.695 g, 4.39 mmol) and dry CH_2Cl_2 (5.8 mL) was added to a cis/trans mixture of 1-methoxy-3-phenyl-1-propene[45] (0.781 g, 5.27 mmol), and the resulting solution was cooled to 0 °C. PPTS (55 mg, 0.22 mmol) was added, and the resulting solution was maintained at 0 °C for 0.5 h and then warmed to room temperature. Additional PPTS (100 mg, 0.40 mmol) was added in two equal portions at 6 h and at 12 h. After 24 h, the reaction was quenched with K_2CO_3 (0.5 g); concentration and purification of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 100:1 hexane–EtOAc) gave 0.43 g (26%) of acetal **10** (100% pure by GLC analysis[43]) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 5 H, Ph), 5.59 (br s, =CH), 5.35 (br s, =CH), 4.44 (t, J = 5.6 Hz, OCHO), 3.57–3.65 (m, OCH, 1 H), 3.40–3.48 (m, OCH, 1 H), 3.34 (s, OCH_3), 2.70 (t, J = 8.4 Hz, $PhCH_2$), 2.24 (t, J = 7.6 Hz, $=CCH_2$), 1.92–1.99 (m, 2 H), 1.69–1.79 (m, 2 H), 0.11 (s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 141.6, 128.3, 125.8, 125.8, 124.0, 103.0, 65.4, 52.5, 34.5, 32.4, 30.9, 29.0, −1.4; IR (film) 3028, 2954, 2698, 1455, 1126, 1071, 1050, 850, 837, 756, 699 cm^{-1}; MS (EI), m/z 306.1998 (M, 306.2015 calcd for $C_{18}H_{30}O_2Si$), 149 (9%), 117 (26%), 91 (55%), 73 (100%).

2-(2-Phenylethyl)-2,3,6,7-tetrahydrooxepin (11). $EtAlCl_2$ (0.42 mL of a 25.9% solution in heptane, 0.66 mmol) was added dropwise to a solution of acetal **10** (33.7 mg, 0.110 mmol) and dry CH_2Cl_2 (3.7 mL) at −78 °C. The resulting solution was maintained at −78 °C for 0.5 h, then warmed to 0 °C, and maintained there for 5.5 h. The reaction was quenched with cold (0 °C) 2 M NaOH (5 mL), the resulting layers were separated, and the aqueous fraction was extracted with CH_2Cl_2 (10 mL). The combined organic fractions were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration and purification of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 100:1 hexane–EtOAc) gave 19 mg (84%) of oxepene **11** (94% pure by GLC analysis[43]) as a clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, Ph), 5.79–5.84 (m, H_4, =CH), 5.74 (app ddt, J = 8.0, 10.9, 3.0 Hz, =CH), 4.10 (app dt, J = 12.0, 3.8 Hz, 1 H, CH_2O), 3.37–3.42 (m, 1 H, CH_2O), 3.27–3.32 (m, H_2, CHO), 2.80 (ddd, J = 4.9, 9.3, 14.1 Hz, 1 H, $PhCH_2$), 2.68 (ddd, J = 7.3, 9.3, 13.7 Hz, 1 H, $PhCH_2$), 2.44–2.52 (m, 1 H, $=CCH_2CH_2O$), 2.29–2.36 (m, 1 H, $=CCH_2CH_2O$), 2.18 (app ddd, J = 1.5, 7.8, 16.5 Hz, 1 H, $C=CCH_2CHO$), 1.83–1.90 (m, 1 H, $PhCH_2CH_2$), 1.67–1.74 (m, $PhCH_2CH_2$ 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 129.5, 128.5, 128.3, 128.3, 125.6, 79.3, 69.9, 38.6, 37.8, 32.5, 32.2; IR (film) 3024, 2927, 2858, 1344, 1291, 1120, 700, 672 cm^{-1}; MS (CI), m/z 203 (MH), 185, 157, 143, 131, 117, 97, 73; MS (EI), m/z 202.1345 (M, 5%, 202.1358 calcd for $C_{14}H_{18}O$), 184 (2%), 134 (15%), 117 (11%), 105 (6%), 92 (30%), 68 (100%).

Preparation of 11 from the Cyclization of 10 Using $SnCl_4$. $SnCl_4$ (0.16 mL of a 1.0 M solution in CH_2Cl_2, 0.16 mmol) was added dropwise to a solution of acetal **10** (33.0 mg, 0.108 mmol) and dry CH_2Cl_2 (3.6 mL) at −78 °C. The resulting solution was maintained at −78 °C for 2.5 h, then warmed to 0 °C, and stirred for 5.5 h. The reaction was quenched with cold (0 °C) 2 M NaOH (5 mL) and warmed to room temperature, and the aqueous fraction extracted with CH_2Cl_2 (10 mL). The combined organic fractions were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration and purification of the residue on silica gel (solvent gradient: 400:1 hexane–EtOAc → 100:1 hexane–EtOAc) gave 15 mg (70%) of oxepene **11** as a clear oil.

2-(2-Phenylethyl)-2,3,6,7-tetrahydrooxepin (11) from 12. $EtAlCl_2$ (0.28 mL of a 25.9% solution in heptane, 0.44 mmol) was added dropwise to a solution of acetal **12** (51.1 mg, 0.146 mmol) and dry CH_2Cl_2 (4.9 mL) at −78 °C. The resulting solution was maintained at −78 °C for 2 h and then allowed to warm to 0 °C and maintained there for 1 h. The reaction was quenched with cold (0 °C) 15% NaOH (3 mL) and warmed to room temperature. The aqueous fraction was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic fractions were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration and purification of the residue by preparatory silica gel TLC (10:1 hexane-EtOAc, 2 developments) gave 18 mg (61%) of oxepene **11** as a clear oil.

2-(2-Phenylethyl)-2,3,4,5,6,7-hexahydrooxepin (3) from 11. A catalytic amount (ca. 1 mg) of 10% Pd on carbon was added to a solution of oxepene **11** (4.8 mg, 0.024 mmol) and EtOAc (1 mL). The head space was evacuated and purged with H_2 (repeated three times), and resulting mixture stirred under H_2 atmosphere for 1 h. Filtration of the mixture through silica gel and concentration gave 4.8 mg (100%) of oxepane **3** as a clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.16–7.29 (m, 5 H, Ph), 3.88–3.92 (m, OCH), 3.53 (ddd, J = 4.2, 7.8, 12.1 Hz, OCH), 3.40–3.45 (m, OCH), 2.79 (ddd, J = 5.2, 9.7, 14.3 Hz, 1 H, $PhCH_2$), 2.63 (ddd, J = 7.0, 9.5, 13.7 Hz, 1 H, $PhCH_2$), 1.47–1.85 (m, 10 H); ^1H NMR (500 MHz, C_6D_6) δ 7.05–7.16 (m, Ph), 3.73–3.77 (m, 1 H, CH_2O), 3.28 (ddd, J = 3.9, 7.9, 12.0 Hz, 1 H, CH_2O), 3.19–3.24 (m, $PhCH_2CH_2CHO$), 2.78 (ddd, J = 5.1, 9.5, 14.0 Hz, 1 H, $PhCH_2$), 2.61 (ddd, J = 7.1, 9.3, 13.6, 1 H, $PhCH_2$), 1.74–1.81 (m, 1 H, $PhCH_2CH_2$), 1.22–1.57 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 128.5, 128.3, 125.6, 78.8, 68.7, 38.6, 36.2, 32.4, 31.1, 26.6, 25.9; IR (film) 3027, 2928, 2856, 1604, 1497, 1455, 1127, 1117, 749, 699 cm^{-1}; MS (CI), m/z 205 (MH), 187, 173, 159, 131, 117, 104, 99, 91; MS (EI), m/z 204.1515 (M, 12%, 204.1514 calcd for $C_{14}H_{20}O$) 186 (6%), 158 (2%), 130 (10%), 117 (24%), 104 (100%), 99 (31%), 91 (71%), 81 (36%), 78 (14%), 65 (14%), 55 (34%).

Key ^1H decoupling experiments on **3** (500 MHz, C_6D_6): Irradiation at δ 2.78 (ddd, 1 H, $PhCH_2$) partially collapsed the ddd at δ 2.61 (1 H, $PhCH_2$), and the m at δ 1.74–1.81 (1 H, $PhCH_2CH_2$). Irradiation at δ 2.61 (ddd, 1 H, $PhCH_2$) partially collapsed the ddd at δ 2.78 (1 H, $PhCH_2$) and the m at δ 1.74–1.81 (1 H,

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(46) Preparatory GLC was conducted with a Varian 90-P gas chromatograph equipped with a 4 ft × $^1/_8$ in. glass column packed with 10% SP-2330 on 100/120 Supelcoport.
(47) Kuivila, H. G.; Beumel, O. F., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1246.

$PhCH_2CH_2$). Irradiation at δ 1.74–1.81 (m, 1 H, $PhCH_2CH_2$) partially collapsed the ddd at δ 2.61 (1 H, $PhCH_2$), the ddd at δ 2.78 (1 H, $PhCH_2$), and the m at δ 3.19–3.24 ($PhCH_2CH_2CHO$). Irradiation at δ 3.19–3.24 (m, $PhCH_2CH_2CHO$) partially collapsed the m at δ 1.74–1.81 (1 H, $PhCH_2CH_2$) and the m at δ 1.22–1.57 (9 H). Irradiation at 3.73–3.77 (m, 1 H, CH_2O) partially collapsed the ddd at δ 3.28 (1 H, CH_2O) and the m at δ 1.22–1.57 (9 H), and had no effect on the m at δ 3.19–3.24 ($PhCH_2CH_2CHO$). Irradiation at 3.28 (ddd, 1 H, CH_2O) partially collapsed the m at δ 3.73–3.77 (1 H, CH_2O) and the m at δ 1.22–1.57 (9 H) and had no effect on the m at δ 3.19–3.24 ($PhCH_2CH_2CHO$).

5-((2-Methoxyethoxy)methoxy)-7-phenyl-2-(trimethylsilyl)-1-heptene (12). Following the general procedure of Corey,[17] MEM-Cl (0.14 mL, 1.2 mmol) was added dropwise to a solution of 1-phenyl-6-(trimethylsilyl)-6-hepten-3-ol (0.212 g, 0.809 mmol), *i*-Pr_2NEt (0.21 mL, 1.2 mmol), and dry CH_2Cl_2 (0.8 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and maintained there for 5 h. Additional *i*-Pr_2NEt (0.28 mL, 1.6 mmol) and MEM-Cl (0.18 mL, 1.6 mmol) were sequentially added, and the resulting solution was maintained at room temperature for an additional 14 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), the layers were separated, and the aqueous fraction was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over K_2CO_3. Concentration and purification of the residue on silica gel (solvent gradient: 100:1 hexane–EtOAc → 10:1 hexane–EtOAc) gave 0.22 g (79%) of acetal **12** (100% pure by GC[43] analysis) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–7.31 (m, 5 H, Ph), 5.55 (dt, *J* = 1.4, 2.9 Hz, =CH), 5.31–5.32 (m, =CH), 4.75 (s, OCH_2O), 3.70–3.73 (m, 2 H, OCH), 3.63 (t, *J* = 5.8 Hz, 1 H, OCH), 3.52–3.55 (m, 2 H, OCH), 3.38 (s, OCH_3), 2.63 (t, *J* = 7.5 Hz, $PhCH_2$), 2.04–2.25 (m, $=CCH_2$), 1.53–1.74 (m, 4 H), 0.08 (s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 142.8, 128.8, 128.7, 126.1, 124.1, 94.8, 72.1, 67.4, 59.4, 36.4, 34.2, 33.9, 31.7, 27.4, -1.0; IR (film) 3027, 2943, 2888, 1453, 1249, 1108, 1039, 839, 755, 700 cm^{-1}; MS (EI), *m/z* 350.2286 (M, 350.2277 calcd for $C_{20}H_{34}O_3Si$), 131 (2%), 104 (13%), 89 (49%), 73 (62%), 59 (100%).

5-(1-Methoxy-3-phenylpropoxy)-7-phenyl-2-(trimethylsilyl)-1-heptene (13). PPTS (10 mg, 0.040 mmol) was added to a solution of 1-phenyl-6-(trimethylsilyl)-6-hepten-3-ol (0.201 g, 0.767 mmol) 1-methoxy-3-phenyl-1-propene (0.227 g, 1.53 mmol), and dry CH_2Cl_2 (3.0 mL) at 0 °C. The resulting solution was maintained at 0 °C for 15 min and then at room temperature for 2.5 h. Additional enol ether (0.227 g, 1.53 mmol) and PPTS (10 mg, 0.040 mmol) were added, and the resulting solution was maintained at room temperature for 18 h. The reaction was quenched with 0.2 g of solid K_2CO_3, and the organic portion washed with 15% aqueous NaOH (2 × 10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL) and dried over K_2CO_3. Concentration and purification of the residue on silica gel (solvent gradient: 100:1 hexane–EtOAc → 20:1 hexane–EtOAc) gave 0.139 g (44%) of acetal **13** (100% pure by GC[43] analysis) as a mixture of diastereomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.32 (m, 5 H, Ph), 5.53–5.59 (m, =CH), 5.33–5.34 (m, =CH), 4.51–4.56 (m, OCHO), 3.57–3.69 (m, $PhCH_2CH_2CHO$), 3.35 (s, CH_3), 3.33 (s, CH_3), 2.60–2.82 (m, 4 H, $PhCH_2$), 2.13–2.28 (m, $=CCH_2$), 1.62–2.01 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 152.4, 142.8, 142.6, 142.1, 128.8, 128.7, 126.3, 126.1, 124.3, 124.2, 102.4, 77.9, 76.7, 52.2, 52.1, 36.8, 36.0, 35.5, 34.3, 33.6, 32.3, 32.0, 31.8, 31.4, -1.0; IR (film) 3028, 2953, 1604, 1455, 1248, 1117, 1037, 852, 837, 752, 699 cm^{-1}; MS (CI), *m/z* 379.2441 (MH, 379.2457 calcd for $C_{25}H_{35}OSi$), 307, 289, 263, 245, 149, 73; MS (EI), *m/z* 170 (1%), 149 (2%), 117 (8%), 105 (3%), 91 (32%), 73 (100%).

***cis*-2,7-Bis(2-phenylethyl)-2,3,6,7-tetrahydrooxepin (14).** $EtAlCl_2$ (0.34 mL of a 25.9% solution in heptane, 0.55 mmol) was added dropwise to a solution of acetal **13** (37.4 mg, 0.0911 mmol) and dry CH_2Cl_2 (3.3 mL) at -78 °C. The resulting solution was maintained at -78 °C for 20 min and then at 0 °C for 1.5 h. The reaction was quenched with cold (0 °C) 15% aqueous NaOH (5 mL), and the resulting mixture warmed to room temperature. The aqueous layer was extracted with 10 mL of CH_2Cl_2, and the combined organic fractions were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. ^1H NMR (300 MHz) and capillary GC analysis[43] of the crude reaction product showed the presence of only one diastereomer. Purification of the residue on silica gel (20:1 hexane/EtOAc) gave 23.4 mg (84%) of oxepene **14** as a pale yellow oil (100% pure by GC analysis[43]): ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.31 (m, 10 H, Ph), 5.72–5.78 (m, 2 H, =CH), 3.35–3.40 (m, 2 H, CHO), 2.94 (ddd, *J* = 5.0, 9.6, 14.4 Hz, 2 H, $PhCH_2$), 2.73 (ddd, *J* = 6.7, 9.7, 13.8 Hz, 2 H, $PhCH_2$), 2.34 (app dd, *J* = 9.8, 15.3 Hz, 2 H, $=CHCH_2$), 2.17–2.22 (m, 2 H, $=CHCH_2$), 1.97 (ddt, *J* = 5.0, 14.2, 9.4 Hz, 2 H, $PhCH_2CH_2$), 1.75 (dddd, *J* = 3.7, 6.5, 10.2, 13.7 Hz, 2 H, $PhCH_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 129.5, 128.4, 128.3, 125.7, 79.2, 39.0, 38.0, 32.7; IR (film) 3025, 2925, 1603, 1109, 749, 699 cm^{-1}; MS (CI), *m/z* 307 (MH), 289, 172, 131, 117; MS (EI), *m/z* 306.1989 (M, 306.1984 calcd for $C_{22}H_{26}O$), 172 (9%), 130 (40%), 117 (35%), 104 (22%), 91 (100%).

Cyclization of 13 in the Presence of 4-(Trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin. $EtAlCl_2$ (0.12 mL of a 25.9% solution in heptane; 0.20 mmol) was added dropwise to a solution of acetal **13** (13.6 mg, 0.0331 mmol), 4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin[27] (38.6 mg, 0.229 mmol), and dry CH_2Cl_2 (1.1 mL) at -78 °C. The resulting solution was maintained at -78 °C for 10 min and then at 0 °C for 1.5 h. The reaction was quenched with cold (0 °C) 15% aqueous NaOH (1.5 mL), and the resulting mixture was warmed to room temperature. The layers were separated, and the aqueous fraction was extracted with CH_2Cl_2 (10 mL). The combined organic fractions were washed with saturated aqueous NaCl (10 mL) and were dried over K_2CO_3. Integration of a 300-MHz ^1H spectrum of the crude reaction mixture showed that oxepene **14** and the silyl Δ^4- oxocene were present in a 1:8 ratio, respectively. Signals characteristic[27] of 3,6,7,8-tetrahydro-2*H*-oxocin at δ 5.70–5.86 (m, 2 H, =CH) and 1.60–1.70 (m, 2 H, $=CCH_2CH_2$) were not observed in the ^1H NMR spectrum of the product.

2,7-Bis(2-phenylethyl)-4,5-epoxy-2,3,4,5,6,7-hexahydrooxepin (15, 16). *m*-CPBA (~85% peracid content, 5.9 mg, 0.034 mmol) was added to a solution of oxepene **14** (8.2 mg; 0.027 mmol) and dry CH_2Cl_2 (0.9 mL) at 0 °C. The resulting solution was maintained at 0 °C for 15 min and then at room temperature for 6 h. The solution was concentrated, redissolved in Et_2O, and flushed through a plug of activity IV basic alumina. Separation of the concentrated eluent by preparatory silica gel TLC (10:1 hexane/EtOAc, four developments) gave 7.4 mg (85%) of the *trans*-epoxide **15** and 1.2 mg (14%) of the *cis*-epoxide **16**.

15: ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 10 H, Ph), 3.45–3.50 (m, 2 H, H_2), 3.17–3.18 (m, 2 H, H_4), 2.91 (ddd, *J* = 5.2, 10.3, 14.0 Hz, 2 H, $PhCH_2$), 2.67 (ddd, *J* = 6.4, 10.1, 13.8 Hz, 2 H, $PhCH_2$), 2.29–2.34 (m, 2 H, $=CCH_2$), 2.02 (dd, *J* = 10.9, 15.6 Hz, 2 H, $=CCH_2$), 1.88 (ddt, *J* = 5.3, 14.2, 10.0 Hz, 2 H, $PhCH_2CH_2$), 1.73 (dddd, *J* = 3.8, 6.4, 10.2, 14.0 Hz, 2 H, $PhCH_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.4, 128.3, 125.8, 75.6, 55.2, 38.6, 36.5, 32.9; IR (film) 3026, 2924, 1455, 1383, 1342, 1114, 1044, 699 cm^{-1}; MS (CI), *m/z* 323 (MH), 305, 287, 191, 173, 117; MS (EI), *m/z* 322.1917 (M, 322.1933 calcd for $C_{22}H_{26}O_2$), 217 (1%), 171 (1%), 133 (12%), 129 (10%), 117 (18%), 105 (13%), 91 (100%).

16: ^1H NMR (500 MHz, $CDCl_3$) δ 7.19–7.30 (m, 10 H, Ph), 3.55 (dt, *J* = 9.5, 3.8 Hz, 2 H, H_2), 3.03–3.07 (m, 2 H, H_4), 2.86 (ddd, *J* = 5.3, 9.3, 14.2 Hz, 2 H, $PhCH_2$), 2.71 (ddd, *J* = 7.1, 9.2, 16.1 Hz, 2 H, $PhCH_2$), 2.25 (app dd, *J* = 7.1, 14.8 Hz, 2 H, H_3), 1.91 (ddt, *J* = 5.4, 14.5, 9.2 Hz, 2 H, $PhCH_2CH_2$), 1.67–1.75 (m, 2 H, $PhCH_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 128.4, 128.3, 125.8, 76.6, 53.3, 39.0, 38.8, 32.4; MS (CI), *m/z* 323 (MH), 305, 253, 189, 171, 135, 117; MS (EI), *m/z* 322.1916 (M, 322.1933 calcd for $C_{22}H_{26}O_2$), 217 (1%), 171 (2%), 143 (3%), 129 (10%), 105 (12%), 91 (100%).

(*Z*)-3-Pentylidenetetrahydropyran (21). A solution of (*Z*)-1-((2-methoxyethoxy)methoxy)-4-(trimethylsilyl)-4-nonene (**20**, 200 mg, 0.640 mmol) and dry CH_2Cl_2 (30 mL) was cooled to -78 °C. Neat $SnCl_4$ (0.70 mL, 7.5 mmol) was then added dropwise over 20 min at -78 °C, and the reaction mixture was allowed to warm to room temperature. The solution was maintained for 10 h at this temperature and then recooled to -78 °C. A saturated solution of aqueous $NaHCO_3$ (50 mL) was then added at 78 °C over a period of 30 min, and the resulting rapidly stirred mixture was allowed to warm to room temperature. The two layers were separated, and the aqueous layer was extracted with ether (2 × 25 mL). The organic portions were combined, washed with water and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and con-

centrated. Flash chromatography (230–400 mesh silica gel, 20 g, 9:1 hexane:ether) gave 90 mg (89%) of **21** (99% pure by GC analysis[43]) as a colorless sweet-smelling oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.16 (app t, J = 6.2 Hz, =CH), 4.10 (app s, 2 H, H_2), 3.65–3.75 (m, 2 H, H_6), 2.21 (br t, J = 6 Hz, 2 H, H_4), 1.90–2.05 (m, 2 H, =CHCH_2), 1.60–1.75 (m, 2 H, H_5), 1.20–1.35 (m, 4 H, CH_2CH_2CH$_3$), 1.27 (m, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) 134.0, 124.6, 68.5, 67.0, 33.3, 32.3, 28.6, 26.7, 22.3, 13.9; IR (CCl_4) 3020, 2980–2920, 1020, 952, 908 cm^{-1}; MS (CI), m/e 155 (MH), 137, 85; MS (EI), m/e 154.1344 (M, 154.1357 calcd for $C_{10}H_{18}O$).

(*E*)-3-Pentylidenetetrahydropyran (23). In a similar fashion, a solutin of (*E*)-1-(2-methoxyethoxy)methoxy)-4-(trimethylsilyl)-4-nonene (**22**, 220 mg, 0.730 mmol) and dry CH_2Cl_2 (30 mL) was treated with $SnCl_4$ (0.70 mL, 7.5 mmol) to provide, after purification by flash chromatography (230–400 mesh silica gel, 20 g, 9:1 hexane–ether), 100 mg (92%) of **23** (99% pure by GC analysis[43]) as colorless sweet-smelling oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.23 (app t, J = Hz, =CH), 3.95 (app s, 2 H, H_2), 3.68–3.74 (m, 2 H, H_6), 2.28 (m, 2 H, H_4), 2.03–1.95 (m, 2 H, =CHCH_2), 1.59–1.68 (m, 2 H, H_5), 1.24–1.33 (m, 4 H, CH_2CH_2CH$_3$), 0.94–0.89 (m, 3 H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 134.6, 125.7, 75.0, 68.1, 32.2, 28.8, 26.7, 26.1, 22.7, 14.4; IR (CCl_4) 3010–2840, 1090, 950, 905 cm^{-1}; MS (CI), m/e 155 (MH), 137, 97, 85; MS (EI), m/e 154.1346 (M, 154.1357 calcd for $C_{10}H_{18}O$).

2-(2-Phenylethyl)-2,3,4,7-tetrahydrooxepin (25). $EtAlCl_2$ (0.10 mL of a 25.9% solution in heptane, 0.28 mmol) was added to a solution of **24** (32.3 mg, 0.0921 mmol) and dry CH_2Cl_2 (3.0 mL) at −78 °C. The resulting solution was maintained at −78 °C for 3 h, allowed to warm to room temperature, maintained there for 2 h, and then cooled to −78 °C, and quenched with cold (0 °C) 2 M NaOH (5 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Purification of the residue on silica gel (solvent gradient: 99:1 hexane–EtOAc → 49:1 hexane–EtOAc) gave 15 mg (78%) of **25** (95% pure by GLC analysis[43]) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.31 (m, 5 H, Ph), 5.82–5.87 (m, OCH_2CH=C*H*), 5.68–5.72 (m, OCH_2C*H*=CH), 4.34 (app ddd, J = 0.9, 4.9, 16.0 Hz, 1 H, =CH_2O), 4.02–4.07 (m, 1 H, =CH_2O), 3.55–3.60 (m, PhCH_2CH_2C*H*O), 2.79–2.84 (m, 1 H, PhCH_2), 2.65–2.71 (m, 1 H, PhCH_2), 2.35–2.41 (m, 1 H, =CCH_2), 2.13–2.20 (m, 1 H, =CCH_2), 1.87–1.97 (m, 2 H), 1.60–1.75 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 131.9, 130.0, 128.5, 128.3, 125.6, 80.2, 66.9, 37.9, 34.2, 32.2, 25.9; IR (film) 3024, 2928, 2857, 2838, 1496, 1455, 1124, 1046, 749, 699 cm^{-1}; MS (CI), m/z 203 (MH), 185, 131, 117, 91, 81, 80, 70; MS (EI), m/z 202.1364 (M, 202.1357 calcd for $C_{14}H_{18}O$) 130 (8%), 105 (9%), 104 (18%), 92 (33%), 91 (100%), 80 (20%), 79 (20%), 78 (11%), 77 (13%), 70 (32%), 68 (18%), 67 (35%), 65 (18%), 53 (15%).

***cis*- and *trans*-2-(2-Phenylethyl)-5-(1(*E*)-propenyl)-2,3,4,5-tetrahydrofurans (27 and 28).** A solution of $SnCl_4$ (0.28 mL of a 1.0 M solution in CH_2Cl_2, 0.28 mmol) was added dropwise to a solution of mixed acetal **26** (31.7 mg, 0.0948 mmol) and dry CH_2Cl_2 (3.2 mL) at −78 °C. The resulting solution was maintained at −78 °C for 4.5 h, allowed to warm to 0 °C, and maintained there for 1.5 h, and then the reaction was quenched with cold (0 °C) 5% aqueous NaOH (5 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Purification of the residue on silica gel (solvent gradient: 99:1 hexane–EtOAc → 9:1 hexane–EtOAc) gave 12.6 mg (61%) of diastereomers **27** and **28** (1.5:1, 100% pure by GLC analysis[43]) as a clear oil. The major product (**27**) was determined to be cis from DNOE studies at 500 MHz on the crude mixture of **27** and **28**. The stereoisomers could be partially separated by preparatory GC[46] (column temperature 105 °C).

27: (70% pure by GLC analysis;[43] contaminated with 28% of **28**): ^{1}H NMR (500 MHz, C_6D_6) δ 7.11–7.23 (m, 5 H, Ph), 5.54–5.72 (m, 2 H, $H_{a,b}$), 4.23 (dt, J = 13.9, 7.0 Hz, H_2), 3.78 (ddd, J = 4.9, 7.3, 14.6 Hz, H_5), 2.81–2.88 (m, 1 H, PhCH_2), 2.68–2.76 (m, 1 H, PhCH_2), 1.26–1.97 (m, 6 H), 1.61 (app d, $J \approx$ 6.6 Hz, CH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05–7.18 (m, 5 H, Ph), 5.70 (ddq, J = 0.7, 15.2, 6.4 Hz, H_b), 5.50 (ddq, J = 7.5, 15.2, 1.6 Hz, H_a), 4.23 (app dt, J = 14.0, 7.0 Hz, H_2), 3.83–3.89 (m, H_5), 2.77 (ddd, J = 5.7, 10.3, 13.9 Hz, 1 H, PhCH_2), 2.67 (ddd, J = 5.9, 10.2, 14.0 Hz, 1 H, PhCH_2), 1.87–2.09 (m, 3 H), 1.53–1.82 (m, 3 H), 1.69–1.71 (m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 132.4, 128.4, 128.3, 127.6, 127.3, 125.7, 80.1, 79.5, 78.8, 37.8, 37.8, 32.9, 32.5, 32.3, 31.9, 31.6, 31.2, 29.7, 22.7, 17.7, 14.1; IR (film) 3027, 2936, 2859, 1496, 1454, 1048, 965, 747, 690 cm^{-1}; MS (CI), m/z 217 (MH), 199, 175, 157, 143, 129, 117, 95, 71; MS (EI), m/z 216.1515 (M, 20%, 216.1514 calcd for $C_{15}H_{20}O$), 201 (6%), 156 (3%), 130 (36%), 117 (14%), 104 (29%), 91 (100%), 82 (42%), 67 (40%), 55 (54%).

28: (91% pure by GLC analysis;[43] contaminated with 9% of **27**): ^{1}H NMR (500 MHz, C_6D_6) δ 6.88–7.20 (m, 5 H, Ph), 5.50 (ddq, J = 15.1, 0.8, 6.3 Hz, H_b), 5.40 (ddq, J = 15.2, 6.5, 1.5 Hz, H_a), 4.23 (dt, J = 7.2, 6.8 Hz, H_2), 3.79 (ddt, J = 6.1, 4.8, 8.0 Hz, H_5), 2.68 (ddd, J = 5.3, 9.8, 13.7 Hz, 1 H, PhCH_2), 2.54 (ddd, J = 6.8, 9.6, 13.6 Hz, 1 H, PhCH_2), 1.09–1.76 (m, 6 H), 1.45 (app d, $J \approx$ 6.3 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 132.3, 128.3, 128.2, 125.6, 79.5, 78.4, 37.8, 22.9, 32.5, 32.3, 29.7; MS (CI), m/z 217 (MH), 199, 175, 157, 143, 129, 117, 105, 95; MS (EI), m/z 216.1514 (M, 9%, 216.1514 calcd for $C_{15}H_{20}O$), 201 (3%), 175 (5%), 157 (5%), 140 (13%), 130 (27%), 117 (13%), 113 (19%), 104 (30%), 95 (30%), 91 (100%), 67 (25%), 55 (36%).

***trans*-5-(2-Phenylethyl)-2-propyl-2,3,4,5-tetrahydrofuran (9) and Its Cis Stereoisomer 9a.** Tetrahydrofurans **27** and **28** (50.7 mg, 0.234 mmol; 56:44 mixture of diastereomers) were hydrogenated in EtOAc (2 mL) following the procedure described for the preparation of **3** from **11**. Filtration of the crude mixture through Celite and concentration gave 51 mg (100%) of tetrahydrofurans **9** and **9a**. These diastereomers could be partially separated by preparatory GC[46] (column temperature 105 °C).

To correlate the stereochemistry of **27**/**28** to **9**/**9a**, a separate experiment was conducted in which a 2:1 mixture of **27**/**28** was hydrogenated to give **9**/**9a**. The retention times of the product mixture (2:1) were then used to assign **9** as trans and **9a** as cis.

9: (88% pure by GLC analysis;[43] contaminated with 10% of **9a**); ^{1}H NMR (500 MHz, C_6D_6) δ 7.05–7.19 (m, 5 H, Ph), 3.82–3.90 (m, *H*COC*H*), 2.77 (ddd, J = 5.4, 9.8, 13.8 Hz, 1 H, PhCH_2), 2.64 (ddd, J = 6.7, 9.6, 13.7 Hz, 1 H, PhCH_2), 1.84 (dddd, J = 5.4, 8.5, 9.7, 13.3 Hz, 1 H, PhCH$_2$CH_2), 1.18–1.69 (m, 9 H), 0.91 (t, J = 7.3 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ 142.7, 128.8, 128.6, 128.5, 78.3, 77.5, 38.7, 38.4, 33.1, 32.5, 32.4, 19.9, 14.4; IR (film) 2959, 2930, 2871, 1496, 1455, 1093, 716, 699 cm^{-1}; MS (CI), m/z 219 (MH), 201, 175, 140, 131, 105; MS (EI), m/z 218.1669 (M, 7%, 218.1671 calcd for $C_{15}H_{22}O$), 175 (12%), 157 (11%), 140 (24%), 130 (16%), 113 (33%), 104 (17%), 95 (49%), 91 (100%), 69 (24%).

9a: (91% pure by GLC analysis;[43] contaminated with 9% of **9**); ^{1}H NMR (500 MHz, C_6D_6) δ 7.05–7.17 (m, 5 H, Ph), 3.66–3.71 (m, *H*COC*H*), 2.77 (ddd, J = 5.5, 9.8, 13.8 Hz, 1 H, PhCH_2), 2.66 (ddd, J = 6.6, 9.6, 13.7 Hz, 1 H, PhCH_2), 1.87 (dddd, J = 5.6, 7.7, 9.6, 13.2 Hz, 1 H, PhCH$_2$CH_2), 1.68 (dddd, J = 5.0, 6.6, 9.8, 13.4 Hz, 1 H, PhCH$_2$CH_2), 1.50–1.65 (m, 3 H), 1.37–1.47 (m, 1 H), 1.26–1.37 (m, 2 H), 1.15–1.26 (m, 2 H), 0.91 (t, J = 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ 142.7, 128.8, 128.6, 126.0, 79.1, 78.2, 38.8, 38.5, 33.0, 31.3, 19.9, 14.5; IR (film) 3001, 2959, 2931, 2871, 1604, 1496, 1465, 1088, 699, 673 cm^{-1}; MS (CI), m/z 219 (MH), 201, 131, 113, 95, 85, 83, 81, 79, 70; MS (EI), m/z 218.1661 (M, 7%, 218.1671 calcd for $C_{15}H_{22}O$), 175 (13%), 157 (11%), 140 (25%), 130 (15%), 113 (36%), 104 (19%), 95 (48%), 91 (100%), 69 (22%).

3-(Bromochloro(trimethylsilyl)methyl)-3,4,5,6-tetrahydro-2*H*-pyran (30). A solution of $SnCl_4$ (6.6 mL of a 1.0 M solution in CH_2Cl_2, 6.6 mmol) was added dropwise to a solution of **29** (0.216 g, 0.664 mmol) and dry CH_2Cl_2 (35 mL) at −78 °C. The resulting solution was maintained at −78 °C for 0.5 h, then allowed to warm to 4 °C, and maintained at this temperature for 48 h. The reaction was then cooled to −78 °C and quenched by addition via cannula into 2 M NaOH (7.5 mL) at 0 °C. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (3 × 10 mL) and dried over $MgSO_4$. Purification of the residue on silica gel (solvent gradient: hexane → 5:1 hexane–Et_2O) and recrystallization from pentane gave 86 mg (46%) of white crystals: mp 62–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26–4.35 (m, OCH), 3.89–3.94 (m, OCH), 3.40–3.49 (m, 1 H), 3.28–3.36 (m, 1 H), 2.15–2.30 (m, 2 H), 1.59–1.73 (m, 3 H), 0.32 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.7, 70.2, 68.1, 48.7, 26.7, 25.7, −1.5; MS (CI), m/z 289

(MH), 287 (MH), 285 (MH), 205, 115, 97, 79, 73; MS (EI), m/z 283.9990 (M, 283.9999 calcd for $C_9H_{18}OBrClSi$) 139 (9%), 137 (9%), 115 (14%), 103 (13%), 97 (46%), 95 (14%), 93 (35%), 79 (50%), 73 (100%), 69 (18%), 67 (65%), 66 (13%), 65 (25%), 55 (23%). Anal. Calcd for $C_9H_{18}OSiBrCl$: C, 37.82; H, 6.35; Br, 27.99; Cl, 12.41. Found: C, 37.91; H, 6.37; Br, 28.03; Cl, 12.43.

6-Bromo-2,3,4,7-tetrahydrooxepin (31). A solution of $TiCl_4$ (1.6 mL of a 1.0 M solution in CH_2Cl_2, 1.6 mmol) was added to a solution of **29** (0.134 g, 0.411 mmol) and dry CH_2Cl_2 (20 mL) at −45 °C. The resulting solution was maintained at −45 °C for 4 h and was then quenched with cold (0 °C) 2 M NaOH (10 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and dried over $MgSO_4$. GLC analysis[43] showed 5% of bromooxepane **31** and 94% of hydropyran **30** present. Purification by preparatory GC[46] (column temperature 70 °C) gave less than 1 mg (~90% pure) of **31**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (tt, J = 1.3, 5.8 Hz, =CH), 4.33–4.34 (m, $=CCH_2O$), 3.83 (t, J = 6.1 Hz, OCH_2CH_2), 2.24–2.28 (m, 2 H), 1.90–1.95 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.8, 122.2, 75.1, 71.3, 29.0, 26.7.

(*E*)-1-Bromo-5-propoxy-1-(trimethylsilyl)-1-pentene (32). Neat Et_2AlCl (83 μL, 0.66 mmol) was added to a solution of **29** (71.8 mg, 0.221 mmol) and dry CH_2Cl_2 (7.3 mL) at −78 °C. The resulting solution was maintained at −78 °C for 0.5 h, allowed to warm to room temperature, and maintained there for 3.8 h, and then the reaction was quenched with 2 M NaOH (3 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 ×10 mL). The combined organic fractions were washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Concentration and bulb-to-bulb distillation gave **32** (93% pure by GLC analysis[43]) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (t, J = 8.1 Hz, =CH), 3.34–3.43 (m, 4 H, CH_2OCH_2), 2.16–2.26 (m, $=CCH_2$), 1.53–1.75 (m, 4 H), 0.92 (t, J = 7.4 Hz, CH_3), 0.27 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 127.7, 72.6, 69.5, 29.4, 29.0, 22.9, 10.6, 0.12; IR (film) 2960, 2937, 2901, 2862, 2859, 1464, 1456, 1377, 1251, 1117, 840, 759, 696, 630 cm^{-1}; MS (CI), m/z 281 (MH), 279 (MH), 239, 237, 220, 218, 199, 157, 147, 117, 99, 85, 73; MS (EI), m/z 218.0128 (M − C_3H_7O, 41%, 218.0048 calcd for $C_8H_{14}SiBr$), 218 (40%), 203 (19%), 151 (16%), 149 (11%), 148 (34%), 146 (38%), 141 (28%), 139 (100%), 137 (95%).

(*Z*)-8-((2-Methoxyethoxy)methoxy)-1-phenyl-4-(trimethylsilyl)-4-octene (33). Following the procedure of Miller,[48] *s*-BuLi (2.9 mL of a 1.30 M solution in cyclohexane, 3.8 mmol) was added dropwise to a solution of **29** (1.01 g, 3.13 mmol) and dry THF (16 mL) at −78 °C, and the resulting solution maintained at −78 °C for 1.3 h. A solution of 1-bromo-3-phenylpropane (0.67 mL, 4.4 mmol) in dry THF (8.8 mL) at −78 °C was added via cannula to vinyllithium. The resulting solution was maintained at −78 °C for 4 h, −50 °C for 16 h, and 0 °C for 1.5 h, then warmed to room temperature, and quenched with saturated NH_4Cl (5 mL). The resulting layers were separated, and the aqueous fraction was extracted with hexane (30 mL). The combined organic fractions were washed with saturated aqueous NaCl (2 × 30 mL) and dried over K_2CO_3. The reduction product was removed by bulb-to-bulb distillation (70–80 °C, 0.1 mmHg), and the residue left behind purified on silica gel (solvent gradient: 100:1 hexane–EtOAc → 10:1 hexane–EtOAc) to give acetal **33** as a clear oil (98% pure by GLC analysis;[43] 97:3 Z/E): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.32 (m, 5 H, Ph), 5.97 (t, J = 7.3 Hz, =CH), 4.74 (s, OCH_2O), 3.70–3.73 (m, $CH_2OCH_2OCH_2CH_2OCH_3$), 3.55–3.61 (m, $CH_2OCH_2OCH_2CH_2OCH_3$), 3.41 (s, OCH_3), 2.60 (t, J = 7.8 Hz, $PhCH_2$), 2.22 (dd, J = 7.4, 14.9 Hz, $=C(H)CH_2$), 2.13 (t, J = 7.6 Hz, $=C(TMS)CH_2$), 1.61–1.73 (m, 4 H), 0.16 (s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 142.1, 139.4, 128.3, 128.1, 125.5, 95.3, 71.7, 67.1, 66.5, 58.9, 38.0, 35.6, 32.6, 30.0, 28.6, 0.1; IR (film) 3027, 2932, 1612, 1496, 1454, 1249, 1116, 1044, 837, 699, 646 cm^{-1}; MS (CI), m/z 365.2521 (MH, 365.2512 calcd for $C_{21}H_{37}O_3Si$), 289, 242, 217, 199, 187, 157, 149, 131, 117, 89, 77; MS (EI), m/z 216 (1%), 198 (1%), 169 (4%), 156 (3%), 143 (6%), 131 (7%), 117 (8%), 104 (37%), 89 (57%), 73 (100%), 59 (99%).

(*Z*)-3-(4-Phenyl-1-butenyl)-3,4,5,6-tetrahydro-2*H*-pyran (34). $EtAlCl_2$ (0.63 mL of a 25.9% solution in heptane, 0.10 mmol) was added dropwise to a solution of acetal **33** (60.6 mg, 0.166 mmol) and dry CH_2Cl_2 (5.5 mL) at −35 °C. The resulting solution was maintained at −35 °C for 7 h, the reaction was quenched with NEt_3 (0.66 mL, 4.7 mmol), and the resulting solution allowed to warm to room temperature, whereupon 3 mL of 15% NaOH was added. The layers were separated, and the aqueous fraction was extracted with CH_2Cl_2. The combined organic fractions washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. The crude yield of **34** (75%) was determined by 300-MHz ^{1}H NMR integration using diethyl fumarate as an internal standard. A sample of **34** (90% pure by GLC analysis[43]) was obtained by preparatory GC[46] (column temperature 135 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, Ph), 5.44 (dt, J = 7.5, 10.7 Hz, $PhCH_2CH_2C(H)$=), 5.10 (dd, J = 9.7, 10.5 Hz, $PhCH_2CH_2C(H)$=CH), 3.85–3.87 (m, 1 H, $=CCHCH_2OCH_2$), 3.57 (dd, J = 3.6, 11.0 Hz, 1 H, $=CCHCH_2O$), 3.33 (dt, J = 2.8, 11.1 Hz, 1 H, $=CCHCH_2OCH_2$), 3.03 (t, J = 10.7 Hz, 1 H, $=CCHCH_2O$), 2.67 (t, J = 7.6 Hz, $PhCH_2$), 2.47–2.54 (m, $=CCHCH_2O$), 2.39 (app q, $J \approx 7.4$ Hz, 2 H, $=CCH_2$), 1.53–1.66 (m, 3H), 1.19–1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 130.2, 128.5, 128.2, 125.8, 72.1, 68.0, 36.1, 35.3, 30.1, 29.5, 25.4; IR (film) 3027, 2934, 2849, 1606, 1496, 1439, 1088, 1030, 911, 737, 699 cm^{-1}; MS (CI), m/z 217 (MH), 199, 157, 131, 117, 91, 71; MS (EI), m/z 216.1529 (M, 216.1514 calcd for $C_{15}H_{20}O$), 173 (6%), 157 (4%), 143 (5%), 125 (8%), 104 (23%), 91 (100%), 79 (17%), 71 (23%), 67 (26%), 55 (20%).

Acknowledgment. This investigation was supported by Grant GM-30859 from the U.S. Public Health Service. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

Registry No. 1, 123185-96-6; *cis*-**2**, 123185-97-7; *trans*-**2**, 123185-98-8; **3**, 123186-01-6; **4**, 123185-99-9; **5**, 123186-00-5; **6** (isomer 1), 123186-22-1; **6** (isomer 2), 123284-07-1; **7** (isomer 1), 123186-23-2; **7** (isomer 2), 123284-08-2; **8**, 123186-03-8; **9**, 123186-04-9; **9a**, 123186-02-7; **10**, 123186-05-0; **11**, 123186-06-1; **12**, 123186-07-2; **13**, 123186-08-3; **14**, 123186-09-4; **15**, 123186-10-7; **16**, 123284-05-9; **17**, 123186-11-8; **18**, 30076-98-3; **19**, 67975-86-4; **20**, 100350-24-1; **21**, 100350-26-3; **22**, 100350-25-2; **23**, 100350-27-4; **24**, 123186-12-9; **2**, 123186-13-0; **26**, 123186-14-1; **27**, 123186-15-2; **28**, 123284-06-0; **29**, 123186-16-3; **30** (isomer 1), 123186-17-4; **30** (isomer 2), 123186-28-7; **31**, 123186-18-5; **32**, 123186-19-6; **33**, 123186-20-9; **34**, 123186-21-0; 1-chloro-1-methoxy-3-phenylpropane, 123186-24-3; 4-penten-1-ol, 821-09-0; 1-(2-phenylethyl)-4-penten-1-ol, 123186-25-4; ethyl vinyl ether, 109-92-2; 4-(trimethylsilyl)-4-penten-1-ol, 112793-67-6; *cis*-1-methoxy-3-phenyl-1-propene, 60053-39-6; *trans*-1-methoxy-3-phenyl-1-propene, 60053-38-5; 1-phenyl-6-(trimethylsilyl)-6-hepten-3-ol, 123186-26-5; 1-bromo-3-phenylpropane, 637-59-2; 4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin, 123186-27-6.

Supplementary Material Available: Experimental procedures and characterization data for the preparation of acetals **20**, **22**, **24**, **26**, **29**, and **33** and the alcohol precursors of acetals **5**, **10**, **12**, and **13** (12 pages). Ordering information is given on any current masthead page.

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