Table I. Arrhenius Parameters for Reactions 1-4[a]

i	*j*	*T*, K	ICVT	ICVT/LAG	CEQB/G	experiment[b]
1		1400-1900	36, 14.0	35, 13.6	48, 14.4	37, 14[c]
		318-471	6.0, 10.7	0.6, 7.9	0.7, 7.95	0.4 ± 0.1, 7.8 ± 0.1[d]
1	2	422-472	1.4, 0.8	0.7, 1.8	0.4, 2.3	0.3 ± 0.2, 2.4 ± 0.5
1	3 + 4	422-472	1.3, 0.2	1.3, 0.2	0.9, 0.5	2.3 ± 1.1, -0.3 ± 0.4
3	4	373-500	1.1, 0.5	0.4, 1.9	0.3, 2.1	0.5 ± 0.1, 1.5 ± 0.2

[a] Left entry, A_i in 10^{-11} cm^3 molecule^{-1} s^{-1} or unitless A_{ij}; right entry, E_i or E_{ij} in kcal/mol. [b] Uncertainties are one standard deviation. [c] The results of ref 4 over the *T* range indicated and of a fit over the same *T* range to the rate constants of ref 9 agree to the two significant figures shown. [d] Reference 6.

Combining the new measurements with previous data[5,6] on reactions 1 and 2 yields rate constants and their ratios for all four reactions. Further details will be published elsewhere.[11]

Three theoretical approaches are employed: improved canonical variational theory with classical reaction coordinate motion (ICVT),[2g] ICVT with a least-action ground-state transmission coefficient to account for tunneling (ICVT/LAG),[2o] and reduced-dimensionality quantum calculations with an adiabatic incorporation of bending motion (denoted more specifically as collinear exact quantum with ground-state bend or CEQB/G).[7] Details of the calculations for k_3 and k_4 are identical with those for k_1 and k_2 reported elsewhere.[7,8] The ICVT/LAG and CEQB/G calculations are our best theoretical estimates of the three-dimensional rate constants, whereas the ICVT calculations provide our best estimate of the classical reaction coordinate overbarrier contribution. Rate constants correspond to a sum of contributions from the ^{3}A′ and ^{3}A″ potential energy surfaces and are based on analytic fits[7,8] of ab initio calculations[7,12] of these surfaces with no semiempirical parameters. The classical barrier height for both surfaces is 12.58 kcal/mol.

For the present report previous results for reactions 1 and 2 and new results for 3 and 4 are fit to Arrhenius forms $k_i = A_i \exp(-E_i/RT)$ and $k_i/k_j = A_{ij} \exp(E_{ij}/RT)$. Since the parameters depend on the temperature range used for the fit, this is indicated in every case.

Tabel I first compares the experimental and theoretical Arrhenius parameters for k_1 at high and low temperatures. At 1400-1900 K, theory and experiment[4,9] agree well, whether or not tunneling is included. At 318-471 K the preexponential factor and the activation energy are lower and the inclusion of tunneling lowers them further. The lower values are in much better agreement with experiment than are the ICVT values calculated without tunneling. We turn to the KIE's for a further confirmation of theory. In two of the three examples (k_1/k_2 and k_3/k_4) the difference in activation energies and the ratio of preexponential factors seen in the experimental data can be explained only if tunneling is included. In the third case the predicted correction due to tunneling is too small to be discerned experimentally.

In general there is good agreement between the ICVT/LAG and CEQB/G calculations and the experimental results. This provides confidence in the LAG method which can be used to estimate for each reaction the percentage of ground-state reactive events that occur by tunneling. At 400 K the estimated percentages are 76%, 57%, 80%, and 58% for reactions 1-4, respectively. The trends in Table I also indicate that the ICVT/LAG method actually somewhat underestimates the tunneling effect so these are approximate lower bounds. We conclude that tunneling dominates these hydrogen-atom transfers at 400 K, and it must be included in interpreting the KIE's or in understanding or modeling the detailed dynamics. The LAG method predicts further that the percentage of reaction occurring by tunneling increases as the temperature is lowered, e.g., for reaction 1, to 86% at 350 K and 94% at 300 K.

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Registry No. HD, 13983-20-5; O, 17778-80-2.

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Efficient Preparations of 8- and 9-Membered Cyclic Ethers

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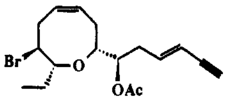
The preparation of medium rings remains one of the more difficult problems in organic synthesis since cyclization reactions are compromised both by entropic effects and developing transannular interactions.[2] The isolation[3] of a variety of medium-ring cyclic ethers from marine sources, e.g., laurencin (**1**), has heightened interest in developing efficient methods for preparing these heterocycles. Progress in this area has recently been recorded[4] by, among others, the groups of Trost,[4a] Kocienski,[4b] Schreiber,[4c] and Nicolaou.[4d] In this paper we demonstrate for the first time that eight- and nine-membered cyclic ethers containing Δ^4 unsaturation can be prepared in good yields by direct cyclization of simple unsaturated acetals. We report also that the alkyl side chains characteristic of many eight-membered ring oxacyclic marine natural products[2] can be stereoselectivity introduced in the cyclization step.



1

The method is illustrated by treatment of the (methoxyethoxy)methyl ether[5,6] of 5-hexen-1-ol (**2**) with 2 equiv of $SnCl_4$ at -20 °C for 13 h to give, in 83% yield, a 2:1 mixture of *cis*-3,6,7,8-tetrahydro-2*H*-oxacin (**3**) and 4-chlorooxocane (**4**).[7]

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(1) (a) NIH NRSA Postdoctoral Fellow (GM 09444), 1984, 1986. (d) COSNET-SEP Mexico Graduate Fellow, 1982-1986. (c) NIH NRSA Postdoctoral Fellow (CA 07787), 1985-1986.

(2) See: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 102 and references cited therein.

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(4) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. (b) Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Perkin Trans 1* **1985**, 2093, 2101. (c) Schreiber, S.; Kelly, S. E. *Tetrahedron Lett.* **1984**, 1757. (d) Nicolaou, K. C. Organic Seminar, University of California, Irvine, Jan 30, 1986.

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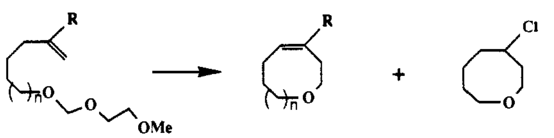
(6) Cyclization reactions were conducted in CH_2Cl_2 at a concentration 0.02-0.05 M and were quenched with aqueous base prior to workup.

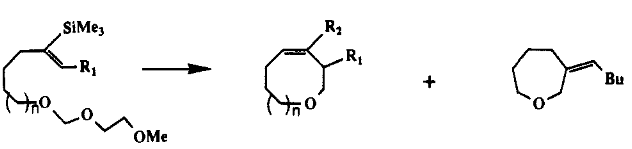
Purification of this mixture on silica gel afforded oxocene **3** in 55% yield. Substituted oxocenes could be prepared in a similar fashion.[6] For example, treatment of vinylsilane acetal **5**[8] with 2 equiv of $SnCl_4$ for 9 h at −15 °C provided the silyl oxocene **6** in 51% yield, together with ca. 10% of **3**.[7,9] In an analogous fashion, **7** was cyclized with 2 equiv of $SnCl_4$ (25° C, 4 days) to give hexahydrooxonins **8** and **9** in 50–60% and 15–20% yields, respectively.[7] Since the nine-membered ring product is formed more slowly, protodesilylation of **8** occurs to a greater extent under the reaction conditions. Comparison of the two-step preparation of **3** from commercially available 5-hexen-1-ol with the original low-yielding synthesis of this oxacyclic[10] underscores the significant advantages of the direct cyclization method.


2 n=1; R=H
5 n=1; R=SiMe$_3$
7 n=2; R=SiMe$_3$

3 n=1; R=H
6 n=1; R=SiMe$_3$
8 n=2; R=SiMe$_3$
9 n=2; R=H

4

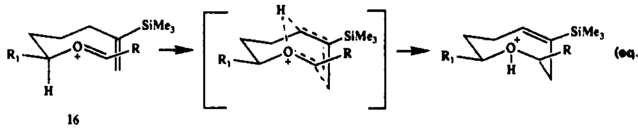
The propensity of acetals derived from 5-alken-1-ols and 6-alken-1-ols to cyclize to form eight- and nine-membered ring products, respectively, is illustrated by the cyclizations[6] of vinylsilane acetals **10** and **13**. Treatment of **10** with 2 equiv of $SnCl_4$ (−15 °C, 19 h) gave, in 70% yield, a 1:1 mixture of oxocene **11** and 3-alkylideneoxepane **12**,[11] while similar (4 °C, 70 h) treatment of **13** afforded the hexahydrooxonins **14** and **15** in 40–50% and 10–20% yields, respectively.[7] It should be emphasized that formation of the seven-membered ring product was observed only with alkene precursors that were trisubstituted, while the mono- and disubstituted alkenes **2**, **5**, and **17** afforded only eight-membered ring products.


10 n=1; R$_1$=n-Bu
13 n=2; R$_1$=Me

11 n=1; R$_1$=n-Bu; R$_2$=SiMe$_3$
14 n=2; R$_1$=Me; R$_2$=SiMe$_3$
15 n=2; R$_1$=Me; R$_2$=H

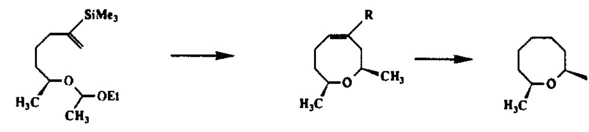
12

Since β-silyl secondary cations are more stable than α-silyl tertiary cations,[8,12] the exclusive formation of nine-membered ring products from **13** and the significant formation of the 8-membered oxacyclic **11** from **10** is striking. One possible mechanistic rationale is that the unsaturated oxocyclic products are formed by an intramolecular ene reaction (eq 1). This type of ene cyclization is known for hydrocarbons, e.g., the interconversion of 1,7-octadiene and *cis*-cyclooctene, however, only at temperatures above 300° C.[13] Such a mechanism would provide an explanation for the formation of cyclic products with only *cis*-Δ^4-unsaturation as well as the propensity for these cyclization reactions to occur in an endocyclic sense to form the larger of the two possible oxacyclic products. Alternatively, the regiochemistry could be rationalized equally well by a cationic cyclization followed by transannular oxygen-assisted deprotonation.[14]


(eq. 1)

16

We anticipated that *cis*-2,8-dialkyl-3,6,7,8-tetrahydro-2*H*-oxocins could be formed from the cyclization of appropriately substituted 5-hexen-1-ol precursors. For example, cyclization of an (*E*)-oxonium ion via conformer **16** which has the R$_1$ substituent oriented in an "equatorial" fashion would lead directly to a *cis*-2,8-dialkyloxocene. In the event, treatment[6] of the ethoxyethyl acetal **17** with 2 equiv of $SnCl_4$ at −20 °C for 1 h gave a 30:1 mixture of *cis*- and *trans*-2,8-dimethyloxocene products.[7,15] To establish that the major product was indeed the cis isomer **18**, this reaction was repeated with a sample of **17** of 66% enantiomeric purity.[16] Purification of the product produced from this nonracemic precursor by preparative GC provided a pure sample of the major isomer **18**, $[\alpha]^{24}_{D}$ −35.7° (*c* 1.95, $CHCl_3$). Protodesilylation of this material (HCl/ether 25° C) provided **19**, $[\alpha]^{24}_{D}$ −34.1° (*c* 0.38, $CDCl_3$), which upon hydrogenation gave the meso product **20**.[18]


17

18 R=SiMe$_3$
19 R=H

20

The unusual efficiency of these medium-ring-forming cyclization reactions together with the mild reaction conditions and their high stereo- and regioselectivities suggest that these reactions may be useful for the synthesis of complex[3] medium-ring cyclic ethers.

Note Added in Proof. Cyclization of the ethoxyethyl ether of 1-methyl-5-hexenol gives **19** directly with similar high diastereoselectivity.

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Supplementary Material Available: NMR and IR spectra for new compounds (18 pages). Ordering information is given on any current masthead page.

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(7) (a) Yields refer to pure (>97%) material isolated by chromatography or distillation. (b) Isomer ratios and product purities were determined by capillary GC analysis. (c) The 8-membered cyclic ethers **3** and **4** do not interconvert under the cyclization conditions.

(8) For leading references to our studies of vinylsilane terminated cyclizations, as well as the preparation of cyclization terminators of this type, see: (a) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59. (b) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.

(9) Careful analysis of the progress of these cyclizations by capillary GC–MS showed that only a *single* oxocene stereo- or regioisomer was produced. These studies also established that **5** gave initially **6** which subsequently underwent slow protodesilylation under the acidic reaction conditions.

(10) Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6751.

(11) Substituents markedly affect the outcome of cyclizations of acetals derived from trisubstituted 5-alken-1-ols of this type. For example, introduction of a *gem*-dimethyl group α to the alcohol oxygen results in predominate formation of alkylideneoxepanes,[8b] as does incorporation of a terminal alkyl group *trans* to the silicon substituent.

(12) Wierschke, S. G.; Chandrasekhar, J.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496 and references cited therein.

(13) Blomquist, A. T.; Taussig, P. R. *J. Am. Chem. Soc.* **1957**, *79*, 3505. Roth, W. R. *Chimia* **1966**, *20*, 229. Crandall, J. K.; Watkins, R. J. *J. Org. Chem.* **1971**, *36*, 91. Lambert, J. B.; Fabricius, D. M.; Napoli, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1793.

(14) Any discussion of the timing of C–C bond formation and C–H bond cleavage must await the results of further experimentation.

(15) This mixture was isolated in 34% yield together with 51% of 8-oxo-4-(trimethylsilyl)nonan-2-ol, which presumably arises from intramolecular 1,5-hydride migration of the initially formed oxocyclooctyl cation intermediate, followed by hydrolysis of the resulting oxonium ion on aqueous workup. We anticipate that this side reaction will be less important in cyclizations directed at **1** and related materials as a result of the electron-withdrawing β-halogen substituent of these targets.

(16) The alcohol was prepared from 5-iodo-2-pentanol that had been chromatographically resolved[17] via the carbamate mixture formed from (*S*)-(−)-[1-(1-naphthyl)ethyl]amine.

(17) See, inter alia: Pirkle, W. H.; Hauke, J. R. *J. Org. Chem.* **1977**, *42*, 1839.

(18) This sample showed no optical rotation at the sodium D line as well as at 578, 546, 435, and 365 nm (*c* 1.25, $CHCl_3$).