the extraction, and to Prof. M. Hirama of Tohoku University for discussion. This work was supported by a grant-in-aid for oversea research from the Ministry of Education, Science and Culture, Japan, by the French Ministry of Research and Superior Education, by the Pasteur Institute of Paris, and by the French Polynesian Government.

Supplementary Material Available: ^{1}H NMR assignments of **2** at -25 °C in CD_3CN and in pyridine-d_5, NOE difference spectra of **2**, and 2D maps of relayed COSY and 2D-HOHAHA (8 pages). Ordering information is given on any current masthead page. The other 2D and NOE data are also available as supplementary material for the previous communication.[1]

Preparation of Eight-Membered Cyclic Ethers by Lewis Acid Promoted Acetal-Alkene Cyclizations

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Abstract: The Lewis acid promoted cyclization of 20 5-alkenyl acetals is reported. Oxocenes with Δ^4 unsaturation (3,6,7,8-tetrahydro-2*H*-oxocins) can be accessed in this convenient fashion with moderate to excellent efficiency and with perfect regiochemical fidelity. The yield of Δ^4-oxocene increases as the 5-substituent of a 5-hexenyl acetal is varied from H to $SiMe_3$ to SPh. High yields (up to 80%) are obtained in vinyl sulfide-acetal cyclizations only. Cyclizations of vinylsilane or vinyl sulfide acetals derived from secondary alcohols proceed with excellent (>25:1) stereoselectivity to construct, *in a single step*, *cis*-2,8-disubstituted-Δ^4-oxocenes. The competing pathway that is most significant in undermining the yield of Δ^4-oxocene in cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals is not bimolecular oligomerization reactions, but rather cyclization to form 2-oxocanyl cations. The importance of this latter pathway was established by the isolation of oxocanyl acetals (**47**, **48**, and **50**), alkylated oxocanes (**15** and **16**), and 11-oxabicyclo[5.3.1]undecanes (**20** and **54**). These studies establish that carbon-carbon bond-forming cyclizations that form eight-membered-ring ethers can be high yielding even with simple substrates that lack conformational bias.

Although medium rings are not common in materials of natural origin, eight-membered cyclic ethers are important structural features of several marine natural products,[2] e.g., brevetoxin A,[3] laurencin,[4] and laurenyne.[5] Significant biological activity of members of this group,[2-4] in addition to the well-known difficulties in forming medium rings, makes the development of new methods for assembling eight-membered-ring ethers a significant objective.

The construction of medium rings remains one of the more formidable problems in organic synthesis, since cyclization reactions are impeded by developing transannular interactions as well as entropic loss and torsional and angle deformations.[6] Prior to the 1980s few useful procedures existed for preparing eight-membered cyclic ethers.[7] However, during the past decade a number of important new methods have been devised. These approaches fall into three strategy groups: C-O bond-forming cyclizations,[8-13] C-C bond-forming cyclizations,[14-16] and transformations of eight-membered lactones.[17,18]

The objective of our efforts in this area was the development of a cyclization reaction that would (a) assemble eight-membered-ring ethers from simple acyclic precursors and (b) directly install in the cyclic ether product the $\Delta^{4,5}$ unsaturation that is found in a number of marine natural products (see Figure 1). Our approach was stimulated by much earlier studies[19,20] of the thermal

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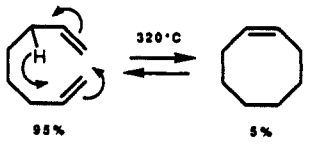
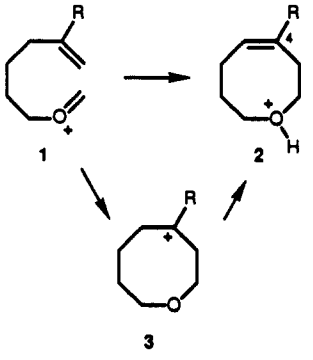
interconversion of 1,7-octadiene and *cis*-cyclooctene (eq 1).



(1)

Although this reaction is of little preparative significance for forming eight-membered carbocycles, it suggested a related intramolecular conversion for assembling Δ^4-oxocenes (eq 2). In



(2)

such an approach, Alder ene cyclization[21] of an oxocarbenium ion (oxonium ion) would derive both kinetic[22,23] and thermodynamic[24] impetus from the positively charged oxygen atom. Alternatively, if the transformation of **1** → **2** took place in a stepwise fashion,[25] initial endocyclization to form **3** (an intramolecular Prins reaction) would be facilitated by electron-releasing substituents R that favor addition of electrophiles to the distal end of the 5-alkenyl double bond. The earlier demonstration by Kocienski and co-workers[15] that 4-oxocanones could be formed by Lewis acid promoted cyclizations of 5-[(trimethylsilyl)oxy]-5-hexenyl acetals provided substantial encouragement for our initial studies in this area.

In this paper we present full details of our exploratory investigations of the formation of eight-membered-ring cyclic ethers by Lewis acid promoted cyclizations of mixed acetals derived from 5-alken-1-ols.[16,26,27] The utility of this strategy for the syntheses of Δ^4-oxocene marine natural products was recently verified in an enantioselective total synthesis of (−)-laurenyne.[28]

Results and Discussion

Lewis acid promoted cyclizations of 20 mixed acetals formed from a variety of 5-alken-1-ols have been examined. Since the double bond of most Δ^4-oxocene natural products is unsubstituted, a particular focus of our investigations was the cyclization of substrates that left hydrogen or "hydrogen equivalents" at the alkenic carbons of the medium-ring ether products.

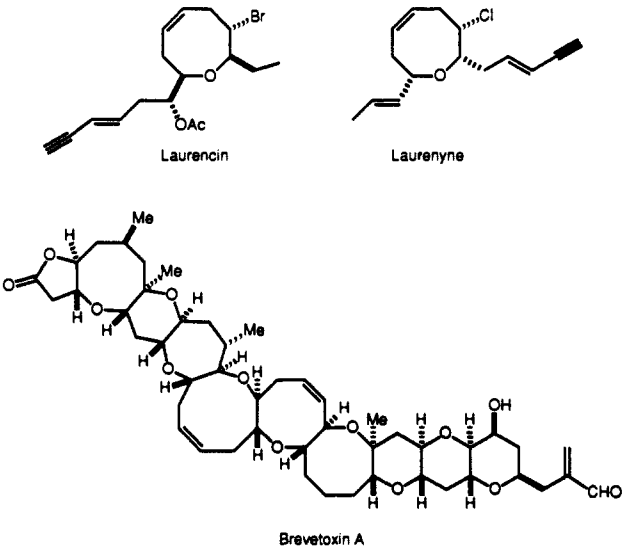


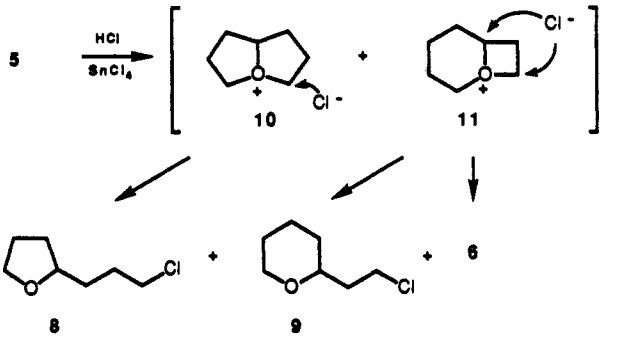
Figure 1. Representative oxocane and oxocene natural products.

Table I. $SnCl_4$-Promoted Cyclization of the Methoxymethyl Ether of 5-Hexen-1-ol (7)

conditions[a]		GLC yield,[b] %		
additive, equiv	time, min	7	5	6
none	5	45	7	3
	25		20	10
	120		14	10
	300		10	10
BSA,[c] 1.05	5	13	19	9
	20		23	12
	270		21	12
2,6-di-*tert*-	5	92	1	
butylpyridine, 1.05	20	62	6	3
	300		25	13

[a] [7] = 0.02 M in CH_2Cl_2, 2.0 equiv of $SnCl_4$, 4 °C. [b] By capillary GLC analysis using decane as an internal standard. [c] *N,O*-Bis(trimethylsilyl)acetamide.

Scheme I



Established methods were employed to prepare (2-methoxyethoxy)methyl (MEM) ethers[29] and 1-ethoxyethyl ethers,[30] while other mixed acetals were prepared from the reaction of an α-chloro ether (prepared in situ from an acetal)[28,31,32] with the appropriate 5-alken-1-ol. Lewis acid promoted cyclizations were typically carried out in CH_2Cl_2 at substrate concentrations of 0.02–0.06 M.

Terminal Alkenes. The MEM ether **4** of 5-hexen-1-ol underwent cyclization at −20 to −5 °C in the presence of 2 equiv of $SnCl_4$

(21) Categorized as a type III intramolecular ene reaction: Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.
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(23) For general discussions, see: Widmer, U.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 75. Blechert, S. *Synthesis* **1989**, *71*.
(24) This conversion transforms a high-energy oxocarbenium ion to a less energetic protonated ether.
(25) Mechanistic details of the conversion of **1** → **2** is the subject of the following paper in this issue.
(26) For early reports of acetal-initiated cyclizations that occur in an endocyclic mode with respect to the acetal initiator to yield oxacyclic products, see: (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.
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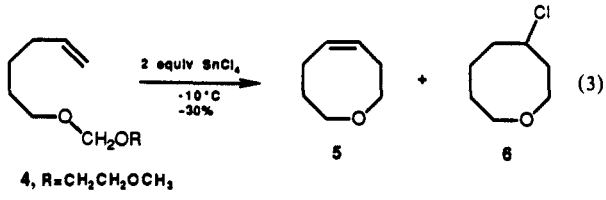
Table II. Cyclization of Acetal 13 with $EtAlCl_2$

conditions[a]			GLC yield,[b] %		
entry	temp, °C	time, min	14	15	16
1	−70	60	8	5	5
2	−60	5	11	9	9
3	−20	720	<1	9	25
4	−5	5	12	10	30
5	−5	720	<1	7	21

[a] [13] = 0.04 M in CH_2Cl_2, 2 equiv of $EtAlCl_2$. [b] By capillary GLC analysis using decane as an internal standard.

to give Δ^4-oxocene (3,6,7,8-tetrahydro-2*H*-oxocin, **5**) and 4-chlorooxocane (**6**) (eq 3).[33] Because of the volatility of **5**, accurate



(3)

4, R=$CH_2CH_2OCH_3$

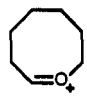
7, R=Me

yields were obtained by ^1H NMR and/or capillary GC internal standard analyses; comparable results were obtained by both methods. Pure samples of the known[34] oxocene **5** and chloride **6** were obtained by preparative GLC. The Δ^4-oxocene regioisomer was formed with high regiochemical fidelity; diagnostic signals of the Δ^2 or Δ^3 regioisomers[35] were not discernable in the 250-MHz ^1H NMR spectrum of the crude cyclization product. However, a triplet signal for an aldehyde byproduct was apparent.

The methoxymethyl (MOM) ether derivative **7** underwent $SnCl_4$-promoted cyclization under comparable conditions to give also a mixture of **5** and **6** (Table I). The decrease in yield of oxocene **5** at longer reaction times most likely results from destruction of **5** by adventitious HCl, since this decrease was arrested when *N*,*O*-bis(trimethylsilyl)acetamide (BSA) or 2,6-di-*tert*-butylpyridine was added. The cyclization of **7** was slower in the presence of the amine additive, while the maximum yields of **5** (20–25%) and **6** (10–13%) were only slightly improved in the presence of either acid scavenger.

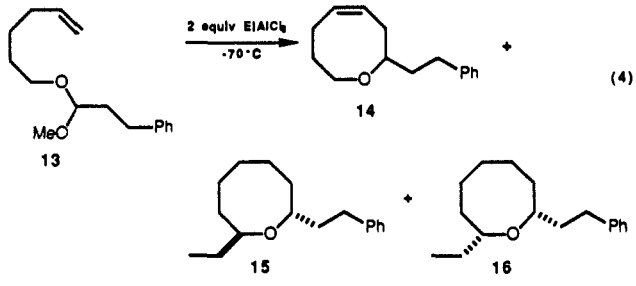
When a sample of oxocene **5** was treated with 2 equiv of $SnCl_4$ at 4 °C for 4 days, it was partially converted to a 2:1:0.1 mixture of chlorides **6**, **8**, and **9** (Scheme I). The latter two known[36,37] ring-contracted products could be isolated by a combination of silica gel chromatography and preparative GLC. A reasonable sequence to account for the formation of these chlorides is provided in Scheme I. That the bicyclo[3.3.0]octyl and bicyclo[4.2.0]octyl oxonium cations **10** and **11** would be formed from the two oxocanyl carbenium ions resulting from HCl addition to **5** is directly precedented in Paquette's earlier studies of oxygen participation in oxocanyl derivatives under solvolytic conditions.[35a,37,38] The results summarized in Table I and Scheme I demonstrate that optimum yields of Δ^4-oxocene products will be obtained only in cyclization reactions that are monitored carefully and carried out at low temperature with high-purity $SnCl_4$ and with the exclusion of moisture. These precautions were exercised in the cyclization reactions of all the subsequent substrates studied.

That Lewis acid promoted cyclizations of simple 5-hexenyl acetals lead to the formation of the 2-oxocanyl carbenium ion **12**, in addition to the expected 4-oxocanyl isomer **3** (the logical precursor of chloride **6**), was hinted at in the formation of the



12

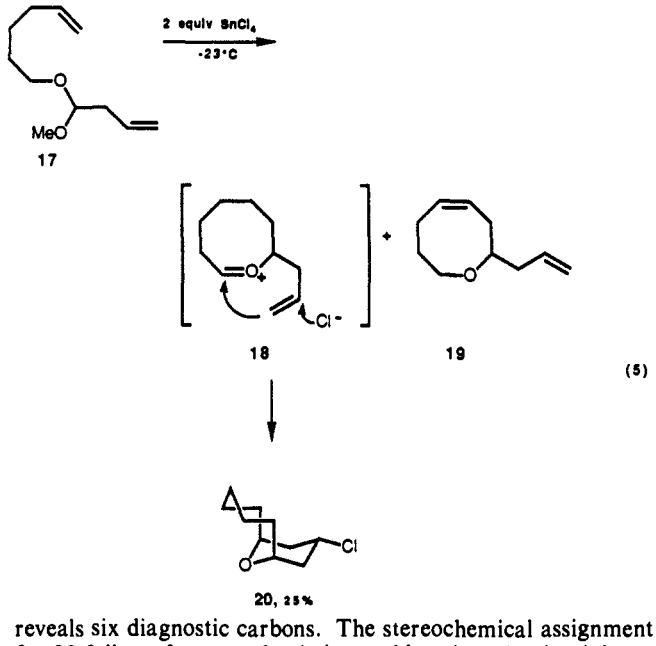
aforementioned aldehyde impurity in the cyclization of **4**. Conclusive evidence for this pathway was uncovered in studies of the cyclization of mixed-acetal **13** with $EtAlCl_2$. This reaction produced, in addition to the Δ^4-oxocene **14**, the stereoisomeric 8-ethyloxocanes **15** and **16** (eq 4). As summarized in Table II,



(4)

$EtAlCl_2$-promoted cyclization of **13** was slow at −70 °C, but proceeded readily at −60 °C or above. Apparent in entries 3 and 5 of this table is the destruction of the oxocene product at longer reaction times. Notable is the fact that the combined GLC yields of eight-membered cyclic ether products was 50% (entry 4) in a cyclization reaction conducted under *non*-high-dilution conditions (at 0.04 M). The stereochemical assignments for **15** and **16** were made on the basis of ^1H and ^{13}C NMR shifts of the methine fragments flanking the ring oxygen. In a thorough study, Holmes and Clark demonstrated that for 2,8-disubstituted oxocanes C-2 and C-8 of the trans isomer are downfield (larger δ) in the ^{13}C NMR of those of the cis isomer, while the opposite order is observed for the ^1H NMR shifts of the attached methine hydrogens.[39]

The 2-oxocanyl carbenium ion intermediate can also be trapped intramolecularly. For example, the crystalline 11-oxabicyclo-[5.3.1]undecane **20** was isolated in 25% yield from $SnCl_4$-promoted cyclization of acetal **17** (eq 5). The ^{13}C NMR spectrum of **20**



(5)

reveals six diagnostic carbons. The stereochemical assignment for **20** follows from mechanistic considerations (antiperiplanar addition to the double bond of **18**).[40] In addition to **20** the 2-allyl-Δ^4-oxocene (**19**) was also formed to a small extent from cyclization of **17**.

(33) (a) The higher yield reported for this conversion in our preliminary report[16] was erroneous. (b) Also in error in this preliminary communication were the yields reported for forming nine-membered-ring ethers. In subsequent investigations we have found that oxonenes are formed in low yields only from $SnCl_4$-promoted cyclizations of 6-heptenyl acetals.

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

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(36) Gilman, H.; Hewlett, A. P. *Recl. Trav. Chim.* **1932**, *51*, 93.

(37) Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6760.

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(39) (a) Clark, J. S.; Holmes, A. B. *Tetrahedron Lett.* **1988**, *29*, 4333. (b) We particularly wish to thank Dr. A. Holmes and S. Clark for communicating these data to us prior to publication.

(40) See, inter alia: Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275.

Table III. Formation of 4-(Trimethylsilyl)-Δ^4-oxocene (**25**)

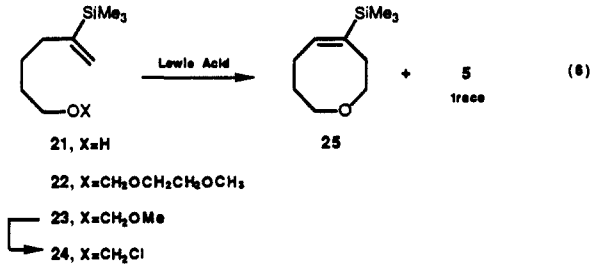
entry	cyclization cond[a] substr, M	Lewis acid, equiv	temp, °C	time, h	yield, % GLC[b]	yield, % isolated
1	**22**, 0.04	$SnCl_4$, 2	−10	14	31	28
2	**22**, 0.01	$SnCl_4$, 2	−10	14	29	31
3	**22**, 0.01	$SnCl_4$, 4	−10	14	38	
4	**22**, 0.01	$SnCl_4$, 8	−10	14	28	
5	**23**, 0.02	$SnCl_4$, 1	−20	1	33	
6	**24**, 0.04	$SnCl_4$, 1	−78	1	40	
7	**24**, 0.10	$SnCl_4$, 1	−78	1	40	39
8	**24**, 0.10	$AgBF_4$, 1[c]	0	1		22

[a] In CH_2Cl_2 unless otherwise noted. [b] By capillary GC analysis using decane as an internal standard. [c] Solvent, CH_3CN.

In summary, eight-membered-ring ethers are formed in low yields (20–40%) from Lewis acid promoted cyclizations of mixed acetals of 5-hexen-1-ol. In spite of this inefficiency, the commercial availability of this alcohol and the fact that the reported cyclizations were conducted at preparatively practical concentrations (0.02–0.04 M) suggest that this simple approach to eight-membered ethers could be of use in some applications.

5-(Trimethylsilyl)-5-hexenyl Acetals. In the hope that Lewis acid promoted cyclizations of related acetals that contain a more nucleophilic alkene group might take place more efficiently, we examined 5-hexenyl acetals that had an electron-releasing substituent at the internal alkene carbon. As noted previously, C-5 substituents that could be replaced by hydrogen after cyclization were of particular interest. Electrophilic attack on 2-(trimethylsilyl)-1-alkenes is known to occur preferentially at the terminal methylene carbon to form a tertiary α-silyl, rather than a primary β-silyl, cation.[41] Since vinyl silicon substituents are also easily removed with nucleophilic acids, we examined cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals.

We initially examined cyclizations of the mixed acetals **22** and **23** and the α-chloro ether **24** (eq 6). All three precursors afforded



4-(trimethylsilyl)-Δ^4-oxocene (**25**) as the predominate cyclic product when treated with Lewis acids (Table III). Capillary GC–MS analysis of the crude product mixture produced from cyclization of the MEM ether **22** with 2 equiv of $SnCl_4$ failed to reveal any isomers of oxocene **25**. The position of the silicon substituent in **25** was signaled by the observation that the C-2 and C-3 methylene hydrogens were an isolated spin system in the ^1H NMR spectrum of this cyclic ether. At long reaction times in cyclizations conducted with $SnCl_4$, **25** underwent slow protodesilylation (presumably by adventitious HCl) to yield Δ^4-oxocene **5**.

The data summarized in Table III show that the MOM ether undergoes $SnCl_4$-promoted cyclization more rapidly than the MEM ether, although the yield of **25** was comparable with either substrates. Significant is the fact that the yield of **25** was nearly identical (ca. 30%)[33a] in cyclizations carried out at 0.01 and 0.04 M. The α-chloro ether **24** underwent $SnCl_4$-promoted cyclization rapidly at −78 °C and afforded a slightly higher isolated yield (39% overall from **23**) of the silyloxocene **25**.

The formation of alkyl-substituted 4-(trimethylsilyl)-Δ^4-oxocenes from Lewis acid promoted cyclizations of a variety of mixed vinylsilane acetals is summarized in Table IV. Under optimum conditions isolated yields were in the range of 30–40%. As in the unsubstituted case, only the Δ^4-oxocene regioisomer was detected; however, these reactions were attended by the formation of a variety of other byproducts, many derived from 2-oxocanyl cation intermediates (vide infra). The experiments conducted with acetal **28** show that yields of silyloxocene are higher in cyclizations

(41) See, e.g.: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857, and references cited therein.

Chart I

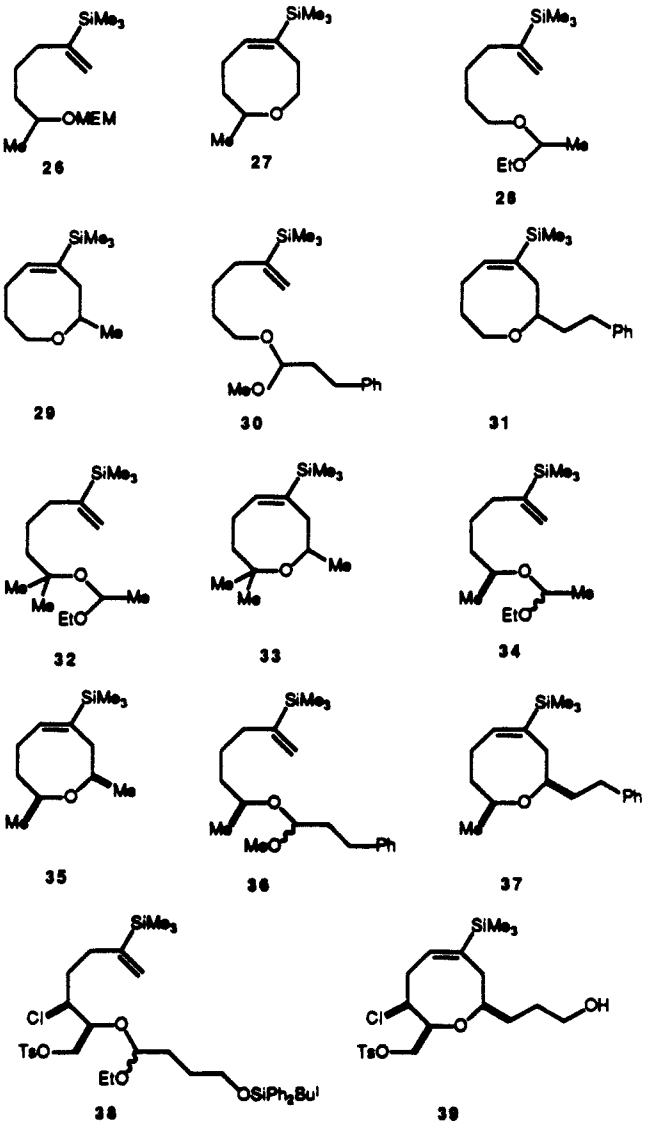
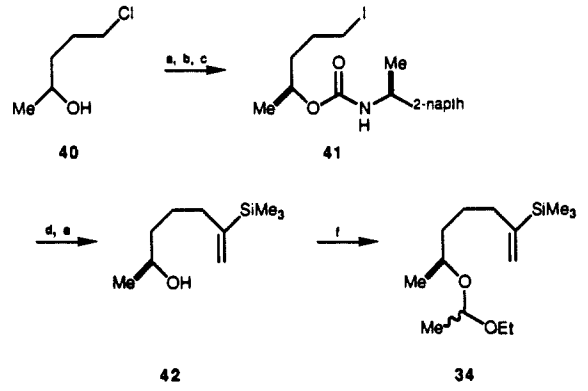


Table IV. Preparation of 4-(Trimethylsilyl)-Δ^4-oxocenes by $SnCl_4$-Promoted Cyclization of Mixed Acetals

acetal, M	cyclization conditions[a] Lewis acid, equiv	temp, °C	time, h	yield,[b] %	oxocene product
26, 0.04	$SnCl_4$, 2	−15	18	39	**27**
28, 0.01	$TiCl_4$, 2	−70	1	16	**29**
0.01	BCl_3, 2	−70	1	11	**29**
0.01	$SnCl_4$, 2	−70	1	37	**29**
0.06	$SnCl_4$, 2	−40	2	30	**29**
30, 0.06	$SnCl_4$, 1	−20	2	13 (20)[c]	**31**
32, 0.04	$SnCl_4$, 2	−70	0.5	34	**33**
34, 0.05	$SnCl_4$, 1.6	−20	1	34[d]	**35**
36, 0.05	$SnCl_4$, 2	−20	2	31	**37**
38, 0.06	$SnCl_4$, 1.9	0	1.5	37[e]	**39**

[a] In CH_2Cl_2. [b] Isolated yield of product whose purity by capillary GC analysis was ≥93%. [c] Chomatographic purification was difficult, which significantly reduced the isolated yield of **31**. [d] A 28:1 mixture of isomers by capillary GC analysis. [e] This reaction was conducted on a 1-g scale; the silyl ether was removed with n-Bu_4NF prior to purification.[28]

Scheme II[a]



[a] Reagents and conditions: (a) ClCOCl; (*S*)-(−)-1-(1-naphthyl)-ethylamine, Et_3N (66%); (b) NaI, $NaHCO_3$, acetone, 50 °C, 24 h (100%); (c) separate diastereomers by HPLC; (d) $(CH_2{=}C(SiMe_3))_2CuCN(Li)_2$. THF, −20 °C (81%); (e) $LiAlH_4$, Et_2O, THF, reflux (90%); (f) ethyl vinyl ether, PPTS, CH_2Cl_2, (78%).

mediated by $SnCl_4$ than with $TiCl_4$ or BCl_3.[42] Mixed "aldehyde" acetals undergo $SnCl_4$-promoted cyclization more rapidly than mixed "formaldehyde" acetals; cyclizations of the former substrates could be carried out at temperatures as low as −70 °C. Significantly, cyclizations to give 2,8-disubstituted-Δ^4-oxocenes proceeded with high stereochemical fidelity to afford the cis-2,8-disubstituted stereoisomers. The structural assignments for the $^4\Delta$-oxocene products summarized in Table IV followed directly from spectroscopic and analytical data. In all cases the position of the double bond and the silyl substituent was established by ^1H NMR decoupling experiments.

The conversion of **38** → **39**[28] affirms that functionality can be introduced in both the nucleophilic and electrophilic portions of the mixed-acetal cyclization substrate. We have discussed elsewhere,[28] however, that heteroatom or alkene functionality cannot be incorporated at the two carbons adjacent to the acetal center. The high-yielding protodesilylation of **39**, which punctuated the conversion of this intermediate to (−)-laurenyne,[28] confirms the "hydrogen equivalency" of the 4-trimethylsilyl oxocenyl substituent.

That the major oxocene product produced from the cyclization of **34** was the cis-2,8-dimethyl stereoisomer was established in a classical fashion. Thus, an enantiomerically enriched sample of acetal **34** was prepared from 5-chloro-2-pentanol[43] as outlined in Scheme II. Separation of intermediate **41** by the general method of Pirkle[44] provided a sample of the *S* isomer of **42** ($[\alpha]_D$ = −4.0, 66% ee),[45] which was subsequently converted to acetal **34**. Cyclization of **34** with 1.6 equiv of $SnCl_4$ at −20 °C provided a 34% yield of the Δ^4-oxocene **35** and an acyclic keto alcohol that showed spectroscopic and analytical data in accord with structure **43** (Scheme III). Homonuclear ^1H NMR decoupling experiments defined that the Me_3Si group of the keto alcohol byproduct resides at C-5 or C-6. The hydroxy ketone **43** could reasonably arise from the 2-oxocanyl cation **44** upon quenching with aqueous base. The ratio of **35** to **43** was nearly identical (1:1.4 by GLC analysis) in $SnCl_4$-promoted cyclizations of **34** conducted at −50 or 0 °C. If octanone **43** is indeed derived from a 2-oxocanyl carbenium ion intermediate, the yield of eight-membered-ring ethers formed initially upon cyclization of **34** is remarkably >80%.

An isomerically pure sample of the major silyl oxocene product **35**, $[\alpha]_D$ = −35.7°, was obtained by preparative GC. Desilylation

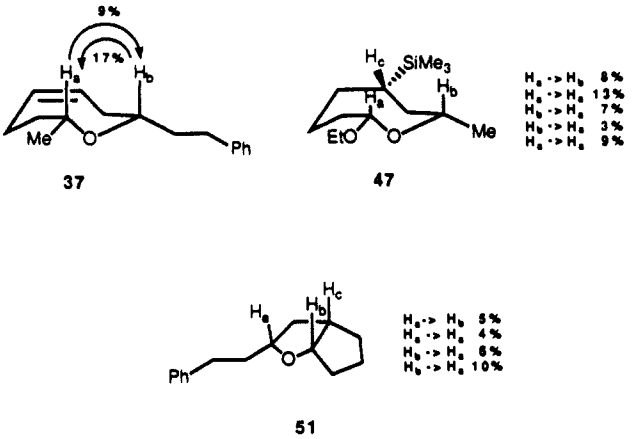
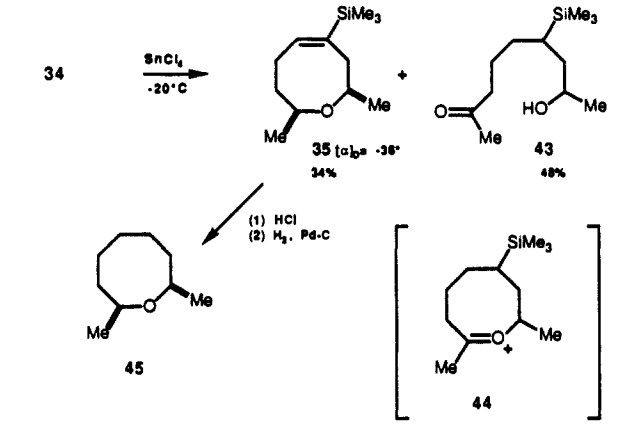


Figure 2.

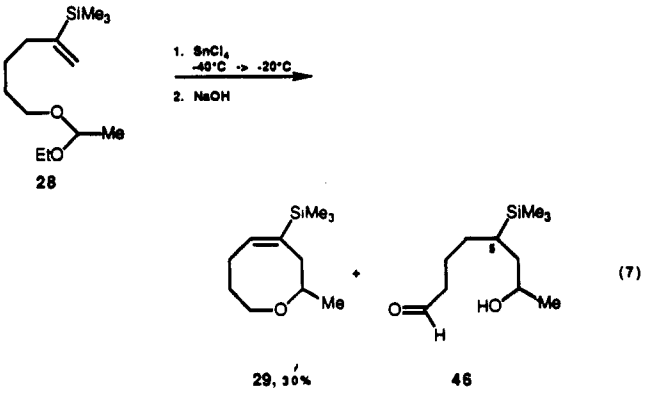
Scheme III



of this material with HCl at room temperature followed by catalytic hydrogenation gave the meso oxocane **45**. Archiral **45** showed no optical rotation at the sodium D line as well as at 578, 546, 435, and 365 nm. Had the 2,8 stereochemistry been trans, this sequence would have produced a chiral C-2 symmetric oxocane.

The cis 2,8-stereochemistry of **39** was also rigorously established, in this case by conversion of **39** to (−)-laurenyne.[28] The similar stereochemistry of **37** is secure in light of these precedents and the large NOE enhancements observed between the C-2 and C-8 methine hydrogens of **37** (see Figure 2).

Detailed investigation of vinylsilane acetals **28** and **30** provided conclusive evidence that the efficiency of forming Δ^4-oxocenes was eroded primarily by competitive formation of 2-oxocanyl carbenium ions upon exposure to Lewis acids. For example, when **28** was treated at −40 °C with 2 equiv of $SnCl_4$ and the reaction subsequently quenched at −20 °C with excess aqueous NaOH (eq 7), the unstable hydroxy aldehyde **46** was isolated in addition to



(7)

oxocene **29** (30%). Hydroxy aldehyde **46** was a single stereoisomer (to the limits of detection by 500-MHz ^1H NMR analysis) and

(42) This contrasts with the silyl enol ether–acetal cyclizations studied by Kocienski and co-workers,[15] where $TiCl_4$ was found to be the preferred Lewis acid.

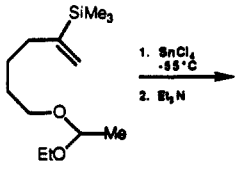
(43) Cannon, G. W.; Ellis, R. C.; Leal, J. R. In *Organic Syntheses*; Wiley, New York, 1963; Collect. Vol. No. IV, p 597. Gerlach, H.; Kunzler, P.; Dertle, K. *Helv. Chim. Acta* **1978**, *61*, 1226.

(44) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839.

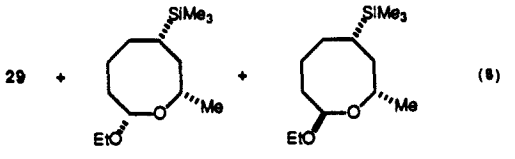
(45) Based on the Pirkle elution order model[44] with 3-iodopropyl being more "repulsive" to silica gel.

homonuclear ^{1}H NMR decoupling experiments confirmed that the Me_3Si and OH groups were 1,3-related.

A key finding occurred when the cyclization of **28** was carried out at −55 °C and the reaction was quenched at this temperature with excess Et_3N prior to aqueous work up. This experimental protocol provided the two stereoisomeric oxocane acetals **47** and **48**, in addition to oxocene **29** (eq 8). Although we were not able



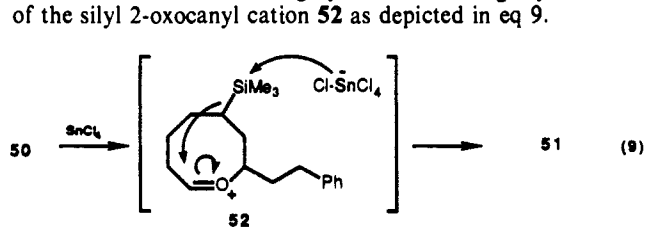
28



47 **48** (8)

to isolate sufficient quantities of **47** and **48** to obtain accurate GC response factors, these acetals were likely formed to at least the extent of oxocene **29** (capillary GC peak area ratios for **29**:**47**:**48** were 1.4:1:1). Analytical samples of the labile acetals **47** and **48** could be obtained by preparative GC. The large ^{1}H NMR NOE observed between the C-2 and C-8 methine hydrogens of **47**, and the lack of corresponding enhancements for **48**, allowed the stereochemistry of the C-2 and C-8 substituents to be unambiguously specified. In the case of the cis isomer **47**, a large NOE was also observed between the C-2 and C-8 methine hydrogens and the upfield C-6 methine hydrogen α to silicon. These NOE data provide evidence for the cis orientation of the Me_3Si group of **47** (see Figure 2). As expected, treatment of acetal **47** with a trace of aqueous acid afforded the ring-opened hydroxy aldehyde **46**.

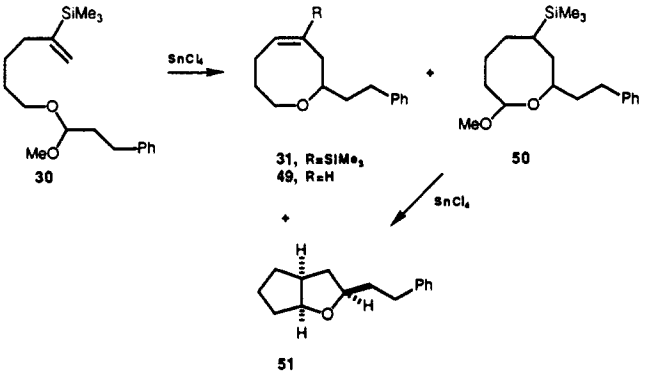
An even more complex reaction manifold emerged with vinylsilane acetal **30** (Scheme IV). Treatment of **30** with 2 equiv of $SnCl_4$ at −20 °C yielded a complex product mixture, which could be resolved (inefficiently) only by repetitive flash chromatography. Isolated this way, in addition to oxocene **31** (13%), was the 1-oxabicyclo[3.3.0]octane **51** (18%). The structure of **51** followed de novo from NMR and mass spectral data, while ^{1}H NMR NOE experiments (summarized in Figure 2) provided clear definition of stereochemistry. The origin of **51** became clear when we isolated the silyl oxocane acetal **50** from exposure of acetal **30** to $SnCl_4$ at −70 °C. Careful capillary GC monitoring of this latter experiment showed that **50** built up to a maximum within 30 min and decreased (as **51** grew in) over the next 90 min. A pure sample of a single stereoisomer of **50** could be isolated by preparative GLC. The similarity of its high-field ^{1}H NMR spectrum (δ 4.54, C-2 H) with that of **48** (δ 4.61, C-2 H) suggests that **50** is the trans 2,8-stereoisomer. The formation of **51** can then be formulated as arising by transannular S_E2 cyclization[46] of the silyl 2-oxocanyl cation **52** as depicted in eq 9.



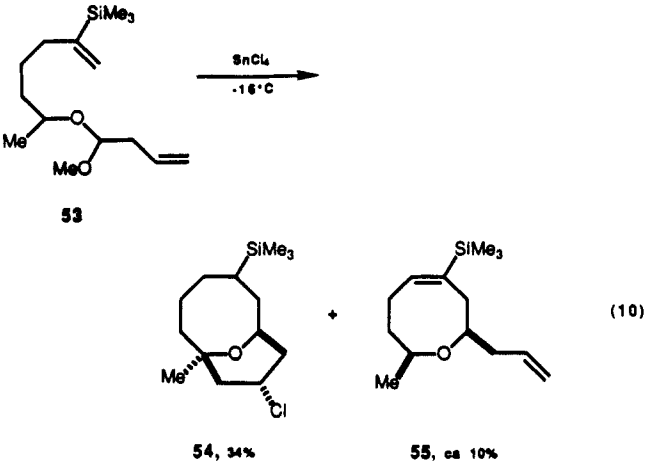
52

Sequential biscyclizations, identical with the one described for preparing **20**, can be employed to prepare silicon-containing 11-oxabicyclo[5.3.1]undecanes. As summarized in eq 10, cyclization of the dienyl acetal **53** provided the crystalline oxabicyclic chloride

Scheme IV



54 in 34% yield in addition to a low yield (ca. 10%) of the silyl oxocene **55**.



5-(Phenylthio)-5-hexenyl Acetals. Since an α-sulfenyl group is a more powerful carbenium ion stabilizing substituent than an α-silyl group,[47] we examined Lewis acid promoted acetal–vinyl sulfide cyclizations. Of all the cyclization terminators studied in our laboratories, the vinyl sulfide provides by far the highest yields of Δ^4-oxocene products.

The preparation of the requisite vinyl sulfide acetals is summarized in Scheme V. The most direct sequence employs the palladium-catalyzed cross-coupling method recently reported by Suzuki.[48] This approach assembles the 5-(phenylthio)-5-hexenol from a homoallylic alcohol and 1-bromo-1-(phenylthio)ethylene (**57**). Alternatively, the lithium derivative of **57**[49] can be alkylated with a silyl-protected 4-iodobutanol. The *purity of the mixed acetal* (**60** or **61**) *was subsequently demonstrated to be critically important in obtaining high cyclization yields.* In particular any dimethyl acetal (the precursor of the α-chloro ether)[28,31] must be removed by careful silica gel chromatography.

A number of Lewis acids and reaction conditions were examined for the cyclization of mixed-acetal **60** (Scheme VI).[50] Attempted cyclization in CH_2Cl_2 with $SnCl_4$ (−70 °C), Et_2AlCl (−30 °C), or $MeAlCl_2$ (−30 °C) led only to decomposition, while *tert*-butyldimethylsilyl triflate (−30 °C) afforded the sulfenyloxocene **62** in low yield only. Boron trifluoride etherate was found to be the optimum Lewis acid; however, the choice of solvent was also found to be critical. Cyclizations conducted with 2 equiv of BF_3-OEt_2 in CH_2Cl_2, Et_2O, or CH_3CN afforded the Δ^4-oxocene

(46) Weber, W. P. *Silicon Reagents for Organic Synthesis*, Springer-Verlag: Berlin, 1983.

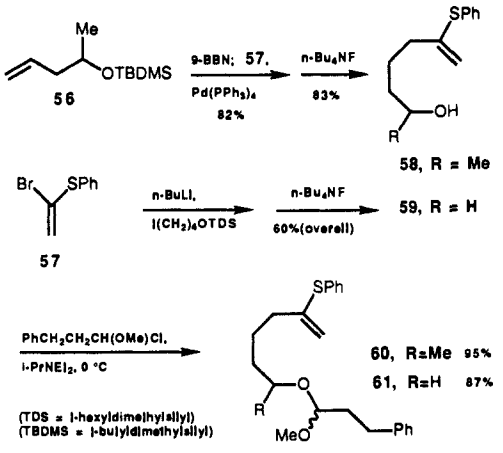
(47) Pau, J. K.; Ruggera, M. B.; Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 4242, and references cited therein.

(48) Hoshino, Y.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 3983.

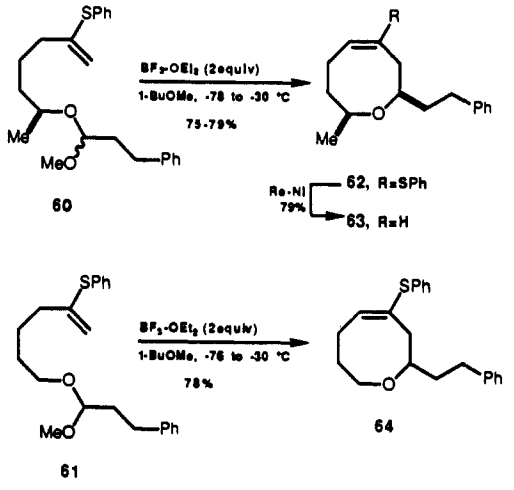
(49) Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200. Cookson, R. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 990. Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.

(50) Small amounts of the *O,S*-acetal, 1-methoxy-1-(phenylthio)-3-phenylpropane,[32] were isolated from some cyclization reactions of vinyl sulfide acetals **60** and **61**.

Scheme V



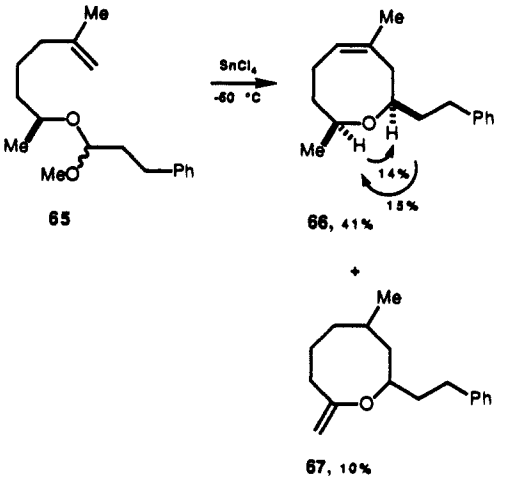
Scheme VI



62 in yields of 25–50%, while the use of CH_3NO_2 led to decomposition of acetal **60**.[50] The optimum diluent is *tert*-butyl methyl ether and in this solvent the cyclization of **60** is *remarkably clean and affords the sulfenyloxocene* **62** *in yields of 75–79%* in reactions carried out on scales of 50–250 mg. Under identical conditions acetal **61** is converted to the Δ^4-oxocene **64** in 78% yield. Since the two stereoisomers of acetal **60** could be separated by chromatography, we had the opportunity to examine cyclizations of each. The yield of **62** was found to be essentially the same in $BF_3{\cdot}OEt_2$-promoted cyclizations of either stereoisomer. As with the cyclizations of the related vinylsilane acetals, no trace of other oxocene regioisomers was apparent in the 300-MHz ^1H NMR spectrum of the crude products formed from **60** or **61**. Also noteworthy is the fact that *no* products derivable from a 2-oxocanyl cation were detected in the vinyl sulfide–acetal cyclizations.

The cis stereochemistry for the 4-(thiophenyl)-Δ^4-oxocene **62** was signaled by the large NOE seen between the C-2 and C-8 methine hydrogens in the 2D NOESY spectrum of **62**. Chemical confirmation of this stereochemical assignment was obtained by desulfurization of **62** with Raney nickel to yield oxocene **64**, which was identical with a sample prepared from silyl oxocene **37** by protodesilylation.

5-Methyl-5-hexenyl Acetals. We briefly examined one 5-hexenyl acetal that contained an electron-releasing substituent at C-5 which could not be readily converted to hydrogen. The cyclization of acetal **65** with $SnCl_4$ at −60 °C provided eight-membered-ring products in 50% yield (eq 11). Isolated after chromatographic separation was the 2,4,8-trialkyl-Δ^4-oxocene **66** (41%) and the labile enol ether **67** (10%). The cis stereochemistry of **66** was signaled by the large NOEs observed between the C-2 and C-8 methine hydrogens, while the structure of **67** followed from the diagnostic high-field signals (δ 4.34 and 4.15) observed for the exocyclic methylene hydrogens in the ^1H NMR spectrum. Labile enol ethers of this type have been prepared by Holmes and co-workers in good yields from the reaction of heptanolactones with the Tebbe reagent.[17]



(11)

Discussion

The results summarized here, together with the studies of Kocienski[15] and Miginiac,[13] demonstrate that a variety of eight-membered-ring ethers can be prepared in moderate to excellent yields by Lewis acid promoted cyclizations of 5-alkenyl acetals. In particular, we report that eight-membered-ring ethers containing Δ^4 unsaturation can be obtained in this way with perfect regioselectivity. The yield of Δ^4-oxocene increases as the 5-substituent of a 5-hexenyl acetal is varied from H to $SiMe_3$ to SPh. Vinyl sulfide–acetal cyclizations provide the Δ^4-oxocenes in *yields of 75–80% in cyclization reactions conducted under non-high-dilution conditions* (at 0.05 M). Moreover, cyclizations of vinylsilane or vinyl sulfide acetals derived from secondary alcohols proceed with excellent (>25:1) stereoselectivity, assembling in a single step the *cis*-2,8-disubstituted-Δ^4-oxocene ring, which is a characteristc structural feature of many eight-membered-ring ether marine natural products.[2]

As the results presented here attest, the reactions of 5-alkenyl acetals with Lewis acids can be complex and can afford a variety of cyclic and acyclic products. The reaction pathways that have been conclusively established by our investigations are indicated with solid arrows in Scheme VII. In cyclizations of silyl acetals, the competing reaction pathway that is most important in undermining the yield of the 4-silyl-Δ^4-oxocene products **2** (R = $SiMe_3$) is not bimolecular oligomerization,[51] but rather cyclization to form the 2-oxocanyl cations **12**. The isolation of oxacanyl acetals **47**, **48**, and **50**, the alkylated oxocanes **15** and **16**, and 11-oxabicyclo[5.3.1]undecanes **20** and **54** conclusively establishes the importance of this latter pathway. The acyclic 7-hydroxy aldehydes and ketones that are often detected (after hydrolytic workup) in significant amounts in Lewis acid promoted cyclizations of 5-alkenyl acetals (see Scheme III and eq 7) undoubtedly derive in part (if not exclusively) from 2-oxocanyl cation intermediates.

A hallmark of Lewis acid promoted cyclization reactions of 5-alkenyl acetals is the complete selectivity seen in forming the Δ^4-oxocene regioisomer. This regiochemical fidelity is consistent with the conversion of **1** → **2** occurring by an intramolecular Alder ene pathway and the results reported in the accompanying paper provide strong support for this proposal for the case of cation **1** containing silicon substitution at C-7. However, it merits note that the C–C bond-forming and C–H bond-cleavage steps probably need not occur in concert for the formation of the Δ^4 isomer to be highly favored, since participation of the ether oxygen in **3** to remove the C-5 hydrogen should be a favorable transannular process.[52]

(51) The observation that reducing the acetal concentration below ca. 0.05 M does not improve the yield of oxocene products strongly supports this assertion.

(52) Prelog, V.; Traynham, J. G. In *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience: New York, 1963; Part I, p 593 ff. Cope, A. C.; Martin, M. M.; McKervey, M. A. *Q. Rev., Chem. Soc.* **1966**, *20*, 119.

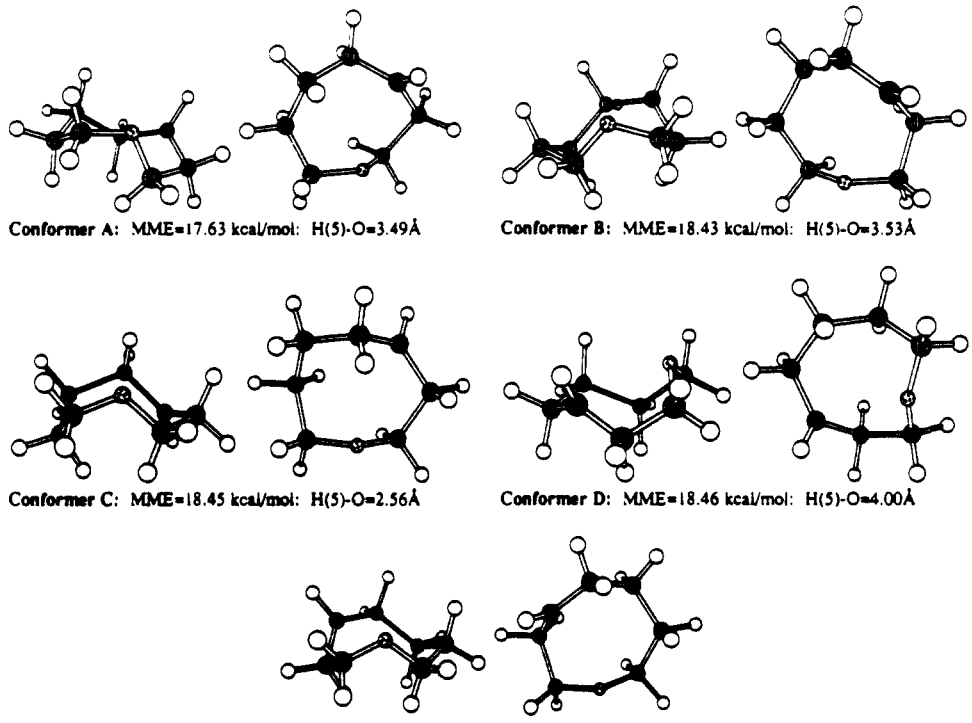
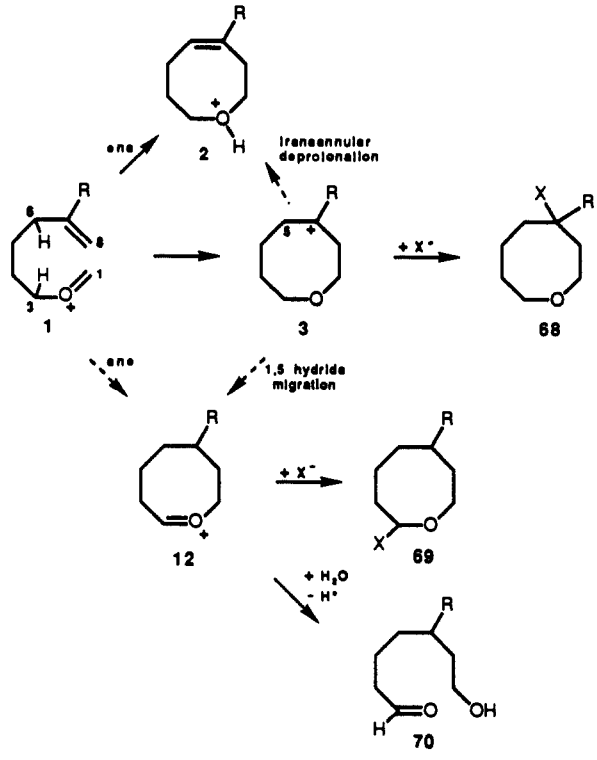


Figure 3. Five lowest energy conformations for the 4-oxocanyl cation as determined by molecular mechanics calculations. An additinal two conformations are within 2 kcal/mol of the minimum.

Scheme VII



The results of a molecular mechanics study of the low-energy conformations of the 4-oxocanyl cation are summarized in Figure 3.[53-55] All low-energy forms found for cation **3** are boat-chair conformations,[56] which is not surprising since all available evidence indicates that both oxocane and cyclooctanone exist in this form.[57,58] Conformation C of carbenium ion **3**, which is only 0.8 kcal/mol less stable than the minimum-energy conformation, is ideally suited for transannular removal of the axial C-5 hydrogen by the ring oxygen (H_5–O distance, 2.6 Å).[59,60]

The 2-oxocanyl cation could also derive from **3** by a 1,5 hydride migration, or directly from **1** by an intramolecular Alder ene reaction involving the C_3–H σ bond. There is, at the time of this writing, no experimental evidence pertinent to this interesting mechanistic issue. The ready occurrence of transannular 1,5 hydride migrations is perhaps the most characteristic feature of cyclooctyl carbenium ions.[52] Barriers for such hydride shifts are extremely small,[61] and under conditions favoring free cations, strong evidence exists that the cyclooctyl carbenium ion exists in the μ-hydrido-bridged form **71** (X = CH_2).[62] The lowest energy conformation found for the 4-oxocanyl cation in our molecular mechanics study (A, Figure 3) could readily evolve to **71** (X = O).

The cis stereoselectivity of cyclizations that form 2,8-disubstituted-Δ^4-oxocenes was expected at the outset of our investigations. The simplest model would anticipate this stereochemical outcome (regardless of the mechanism of ring formation) on the

(53) 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. *Advances in Molecular Modeling*; JAI Press: Greenwich, CT, Vol. 2, in press.

(54) The subroutine RANDOMIZ, which is based on Saunder's stochastic approach for exploring molecular mechanics energy surfaces,[55] was employed in our search for the global minimum.

(55) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

(56) In addition to the five conformations shown in Figure 3, two additional minima (E_{MMX} = 19.20 and 19.45) were found within 3 kcal of the global minimum.

(57) For excellent reviews covering experimental and computational studies of the conformational properties of eight-membered rings, see: (a) Anet, F. A. L. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH: New York, 1988, Chapter 2. (b) Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169. (c) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982; pp 101–104, 219.

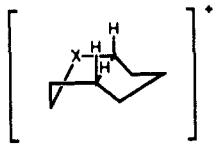
(58) For recent electron diffraction, molecular mechanics, and ab initio studies of cyclooctane, see: Dorofeeva, O. V.; Mastryukov, V. S.; Allinger, N. L.; Almenningen, A. *J. Phys. Chem.* **1985**, *89*, 252. Siam, K.; Dorofeeva, O. V.; Mastryukov, V. S.; Ewbank, J. D.; Allinger, N. L.; Schäfer, L. *THEOCHEM* **1988**, *41*, 93.

(59) The barrier (ΔG) for ring inversion of oxocene is 7.4 kcal/mol.[60] Thus, conformational interconversions should be rapid even at −70 °C.

(60) Anet, F. A. L.; Degen, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 1390.

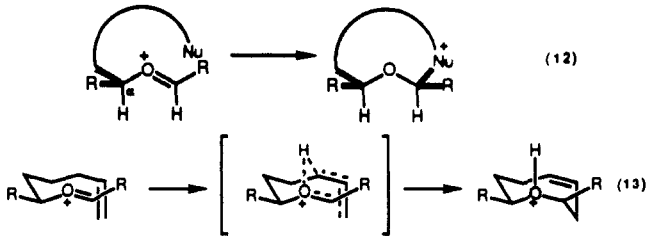
(61) For a recent experimental study and leading references, see: Schneider, H.-J.; Heiske, D. *J. Am. Chem. Soc.* **1981**, *103*, 3501.

(62) Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1979**, *101*, 3240. Kirchen, R. P.; Okazawa, N.; Ranganayakulu, K.; Rauk, A.; Sorensen, T. S. *Ibid.* **1981**, *103*, 597.



71

basis that cyclization of the more stable (*E*)-oxocarbenium ion[63] should occur preferentially in a local conformation having the smallest substituent at the α-carbon (hydrogen) in the plane of the partial C–O π bond[32,64] (eq 12). Alternatively, the cis stereoisomer would be expected to arise from the (*E*)-oxocarbenium ion by an intramolecular ene mechanism proceeding via a boat–chair bicyclo[3.3.1]nonane transition state (eq 13).[65,66]



(12)

(13)

Conclusion

Eight-membered-ring ethers can be conveniently prepared by Lewis acid promoted carbon–carbon bond-forming cyclizations of 5-alkenyl acetals. The cyclization to form the eight-membered ring can take place with remarkable efficiency, even with simple straight-chain acetals that lack substituents which favor coiled conformations. However, partitioning among several product manifolds can take place and high yields of Δ^4-oxocenes are obtained only in cyclizations of 5-(thiophenyl)-5-alkenyl acetals. Oxocenes with Δ^4 unsaturation are accessed in this way with perfect regiochemical fidelity. This cyclization approach to eight-membered-ring ethers can be employed not only to construct the medium ring and regioselectively incorporate unsaturation, but also to install cis-oriented side chains adjacent to the ether oxygen. The utility of this approach for the synthesis of functionalized Δ^4-oxocenes was recently demonstrated in our enantioselective total synthesis of the marine nonisoprenoid natural product (–)-laurenyne.[28]

Experimental Section[67]

The preparation of 4-(trimethylsilyl)-4-penten-1-ol has been described,[28] while the straightforward syntheses of the other 5-alken-1-ols used to prepare mixed-acetal cyclization substrates can be found in the supplementary material. The preparation of mixed-acetal **60** is detailed fully here. Other mixed acetals were synthesized in conventional fashion;[28-32] full characterization data for these intermediates are provided in the supplementary material.

Preparation of 6-(Phenylthio)-6-hepten-2-ol (58). The general procedure of Suzuki was followed.[48] To a solution of the *tert*-butyldimethylsilyl ether of 1-penten-2-ol (1.00 g, 5.00 mmol) and THF (5 mL) at 0 °C was added dropwise a solution of 9-BBN in THF (12.5 mL, 6.25 mmol, 0.5 M; Aldrich). The reaction was maintained at 0 °C for 1 h and then at 23 °C for 3 h. A solution of 1-bromo-1-(phenylthio)ethene (1.14 g, 5.30 mmol) and benzene (25 mL), $Pd(PPh_3)_4$ (80 mg, 0.15 mmol), and 3 N NaOH (5 mL) were then added and the resulting mixture was heated at reflux for 4 h. After cooling to room temperature, H_2O (5 mL) and hexane (50 mL) were added and the phases were separated. The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (1:50 EtOAc–hexane) to give 1.38 g (82%) of the vinyl sulfide silyl ether **58a**, which was immediately desilylated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–7.4 (m, 2 H), 7.4–7.3 (m, 3 H), 5.17 (br s, 1 H), 4.90 (app s, 1 H), 3.9–3.75 (m, 1 H, H-2), 2.35–2.2 (app t, J = 7.2 Hz, 2 H, H-5), 1.7–1.4 (m, 4 H), 1.13 (d, J = 5 Hz, 3 H, H-1), 0.91 (s, 9 H, *t*-Bu), 0.07 (s, 6 H, MeSi).

A solution of the silyl ether **58a** (700 mg, 1.91 mmol), THF (50 mL), and *n*-Bu_4NF (7.6 mL of a 1.1 M solution in THF; Aldrich) was heated for 1 h at 60 °C. After this solution was cooled to 23 °C, saturated aqueous NH_4Cl solution (25 mL) was added, the phases were separated, and the organic phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The remaining residue was purified by chromatography on silica gel (1:20–1:2 EtOAc–hexane) to give 347 mg (83%) of alcohol **58**: 94% pure by GLC analysis; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2 H), 7.38–7.28 (m, 3 H), 5.16 (m, 1 H), 4.89 (s, 1 H), 3.85–3.75 (m, 1 H, H-2), 2.30–2.22 (app t, J = 7.2 Hz, 2 H, H-5), 1.76–1.36 (m, 4 H), 1.30 (app d, J = 4.6 Hz, 1 H), 1.19 (d, J = 6.1 Hz, 3 H); IR (film) 3359, 2964, 2932, 2862, 1608, 1478, 1440, 1374, 1126, 1090, 750 cm^{-1}; MS (CI, 70 eV) *m/e* 223 (MH, 5), 205 (M – H_2O, 11), 114 (20), 113 (100), 95 (8); MS (EI, 70 eV) *m/e* 222.1081 (222.1078 calcd for $C_{13}H_{18}OS$, M, 6), 135 (31), 110 (100), 95 (29), 71 (37).

2-(1-Methoxy-3-phenylpropoxy)-6-(phenylthio)-6-heptene (60). To a stirring solution of **58** (224 mg, 1.0 mmol), dry CH_2Cl_2 (5 mL), and *i*-Pr_2NEt (0.5 mL, 3 mmol), at –5 °C was added freshly prepared[32] 1-chloro-1-methoxy-3-phenylpropane (0.2 mL, 1.2 mmol), and the reaction mixture was maintained at 0 °C for 1 h and at 23 °C for 1 h. The reaction was then concentrated and the residue was purified by flash chromatography (30:1 hexane–EtOAc), which partially separated the acetal diastereomers: combined yield, 352 mg (95%).

High-R_f diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.45 (m, 10 H), 5.16 (m, 1 H), 4.88 (s, 1 H), 4.52 (t, J = 5.6 Hz, 1 H), 3.65–3.75 (m, 1 H, H-2), 3.30 (s, 3 H), 2.62–2.73 (m, 2 H), 2.26 (app t, J = 6.9 Hz, 2 H, H-5), 1.85–1.99 (m, 2 H), 1.38–1.74 (m, 4 H), 1.10 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 141.7, 133.1, 129.0, 128.3, 127.7, 125.8, 112.9, 100.8, 71.8, 51.5, 36.5, 36.4, 35.1, 30.9, 24.4, 19.9; IR (film) 3027, 2940, 2929, 2863, 1606, 1476, 1455, 1440, 1375, 1203, 1177, 1154, 1116, 1000, 750 cm^{-1}; MS (CI) 371.2060 (<1%, 371.2044 calcd for $C_{23}H_{31}O_2S$), 339.1775 (339.1782 calcd for $C_{22}H_{27}OS$, MH – MeOH).

Low-R_f diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.44 (m, 10 H), 5.15 (m, 1 H), 4.89 (s, 1 H), 4.49 (t, J = 5.6 Hz, 1 H), 3.60–3.66 (m, 1 H, H-2), 3.31 (s, 3 H), 2.65–2.75 (m, 2 H), 2.24 (app t, J = 7.3 Hz, 2 H, H-5), 1.90–1.96 (m, 2 H), 1.36–1.68 (m, 4 H), 1.21 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 141.8, 133.2, 133.0, 129.1, 128.4, 127.7, 125.8, 113.0, 102.5, 73.4, 51.5, 36.5, 36.0, 35.2, 30.9, 24.2, 21.0.

Preparation of *cis*-3,6,7,8-Tetrahydro-2*H*-oxocin (5) and 4-Chlorooxocane (6). A solution of MEM ether **4** (445 mg, 2.36 mmol, dried immediately before use by azeotroping with benzene at 23 °C and 20 mm) and dry CH_2Cl_2 (90 mL) was cooled in a –10 °C ice–salt bath. To this stirred solution was added dropwise a 1 M CH_2Cl_2 solution of $SnCl_4$ (5.0 mL, 5 mmol). The resulting solution was maintained at –10 °C for 18 h and at –5 °C for 6 h. The reaction then was quenched by the addition of 5% NaOH (100 mL) followed by extraction with CH_2Cl_2 (2 × 70 mL). The combined organic phases were washed with brine, and the bulk of the CH_2Cl_2 was removed via fractional distillation through a 6-in. Vigreux column. Analysis of this concentrate by 500-MHz ^{1}H NMR showed a diagnostic multiplet at δ 5.70–5.85 (2 H, CH=CH) for **5**, a diagnostic multiplet centered at δ 4.3 (1 H, CHCl) for **6**, residual CH_2Cl_2 (δ 5.28), and a trace of an aldehyde triplet at δ 9.75. The yields of **5** (17%) and **6** (13%) were quantified by adding 1,4-dimethoxybenzene (23.2 mg, 0.168 mmol) and carefully integrating the aromatic singlet of this internal standard (δ 6.83) vs the diagnostic signals of **5** and **6** noted previously.

The crude product from another run was separated by GLC to give analytical samples of **5** and **6**. **Δ^4-Oxocene 5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.70–5.86 (m, 2 H, H-4, H-5), 3.60–3.67 (m, 4 H, H-2, H-8), 2.17–2.28 (m, 4 H, H-3, H-6), 1.60–1.70 (m, 2 H, H-7); ^{13}C NMR (63 MHz, $CDCl_3$), δ 131.3 (CH), 128.9 (CH), 71.8 (CH_2), 69.9 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 23.8 (CH_2); IR (film) 3018, 3003–2860, 1112 cm^{-1}; MS (EI 70 eV) *m/e* (112.0888 calcd for $C_7H_{12}O$, M, 5), 84 (28), 67

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

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

(65) The chair–chair conformation of bicyclo[3.3.1]nonane is slightly more stable than the boat–chair form.[66] However, the Δ^4-oxocene product would be considerably more stable in a boat–chair conformation.[57a]

(66) See: Reference 57c, pp 112–113, and references cited therein.

(67) General experimental details were recently described.[68] $SnCl_4$ was distilled from P_2O_5 and stock solutions were stored under Ar in a glass ampule fitted with a three-way stopcock. Dichloromethane and BF_3·OEt_2 were distilled from CaH_2; *tert*-butyl methyl ether was distilled from KOH. Analytical GC analyses were performed with a Hewlett-Packard 5790 chromatograph equipped with a 25-m, SP-2100 fused-silica capillary column. Preparative GC separations were performed with a Varian 90-P chromatograph, utilizing glass columns packed with 10% SP-2330 on 100/200 Supelcoport. Unless noted otherwise, column chromatography utilized E. Merck silica gel 60 (230–400 mesh). Optical rotations were measured at room temperature with a Perkin-Elmer 241 MC polarimeter.

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

(33). The ^{1}H NMR spectrum of this sample was indistinguishable from an authentic spectrum of Δ^4-oxocene provided by Prof. L. Paquette.

Spectral data for 4-chlorooxocane (6): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.27–4.37 (m, 1 H, H-4), 3.60–3.88 (m, 4 H, H-2, H-8), 2.11–2.37 (m, 4 H, H-3, H-5), 1.53–1.86 (m, 4 H, H-6, H-7). Irradiation of the signal at δ 4.27–4.37 (H-4) caused the partial collapse of the signal at δ 2.11–2.37 (H-3 and H-5). Irradiation of the signal at δ 3.60–3.88 (H-2 and H-8) produced no change in the signal at δ 4.27–4.37 (H-4). ^{13}C NMR (63 MHz, $CDCl_3$) δ 69.2, 66.8, 61.3, 37.2, 36.0, 30.0, 22.3; IR (film) 2928, 2869, 111, 1098, 1088 cm^{-1}; MS (EI, 70 eV) *m/e* 148.0655 (148.0644 calcd for $C_7H_{13}OCl$, M, 10), 113 (2), 112 (60), 95 (28), 84 (100).

Preparation of 4-Chlorooxocane (6), 2-(3-Chloropropyl)tetrahydrofuran (8),[36] and 2-(2-Chloroethyl)tetrahydropyran (9)[37] from Oxocene 5. A solution of **5** (20 mg, 0.18 mmol) and dry CH_2Cl_2 (10 mL) was cooled to −78 °C, and $SnCl_4$ (0.45 μL, 0.38 mmol) was added. The reaction was maintained for 4 days at 4 °C (in a refrigerator) and at the end of that time was worked up as described for the preparation of **5**. Capillary GC analysis showed that this sample was a 8:2:1:0.1 mixture of **5**:**6**:**8**:**9**, respectively. In other similar experiments the extent of conversion to chlorides **6**, **8**, and **9** varied widely, consistent with promotion of the reaction by adventitious HCl. Pure samples of **8** and **9** were obtained by a combination of silica gel chromatography (HF 512, 9:1 pentane–Et_2O) and preparative GLC.

Spectral data for 8:[36] ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.56–3.91 (m, 5 H, $CHOCH_2$, CH_2Cl), 1.43–2.03 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.3, 68.3, 45.8, 33.4, 31.5, 30.2, 26.8; IR (film) 2960, 2945, 1075, 733 cm^{-1}; MS (CI) *m/e* 151, 149 (MH); MS (EI, 70 eV) *m/e* 71.0499 (71.0491 calcd for C_4H_7O, M − $CH_2CH_2CH_2Cl$).

Spectral data for 9:[37] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (app dt, J = 2.5, 11.1 Hz, 1 H, H-6), 3.50–3.79 (m, 2 H, CH_2Cl), 3.40–3.49 (m, 2 H, H-2, H-6), 1.91–1.97 (m, 2 H, CH_2CH_2Cl), 1.76–1.86 (m, 2 H), 1.20–1.64 (m, 4 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 74.6, 68.6, 41.7, 39.6, 32.0, 26.3, 23.6; IR (film) 2940, 2049, 1088, 1048, 867, 862, 733 cm^{-1}; MS (CI) *m/e* 151, 149 (MH); MS (EI, 70 eV) *m/e* 148.0650, 150.0642 (148.0655 calcd for $C_7H_{13}{}^{35}ClO$, 150.0625 for $C_7H_{13}{}^{37}ClO$), 85.0656 (85.0653 calcd for C_5H_9O, M − CH_2CH_2Cl).

Preparation of 2-(2-Phenylethyl)-3,6,7,8-tetrahydro-2*H*-oxocin (14) and *cis*- and *trans*-8-Ethyl-2-(2-phenylethyl)oxocane (16 and 15). To a stirring solution of acetal **13** (500 mg, 2.01 mmol) and CH_2Cl_2 (50 mL) at −70 °C was added $EtAlCl_2$ (2.3 mL of a 1.8 M solution in heptane, 4.1 mmol). The reaction was maintained at −70 °C for 1 h and quenched at −70 °C by the addition of Et_3N (2.5 mL). The reaction mixture was allowed to warm to 23 °C and was then poured into 5% NaOH (20 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 10 mL) and the combined organic phases were rinsed with brine (20 mL), dried (K_2CO_3), and concentrated to afford 478 mg of a crude product, which was a ca. 1:1:1 mixture of **14**:**15**:**16** by GLC analysis. Pure samples were obtained by preparative GLC.

Spectral data for oxocene 14: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, PhH), 5.78–5.69 (m, 2 H, CH=CH), 4.00 (ddd, J = 2.5, 4.9, 12.0 Hz, 1 H, H-8), 3.42 (dt, J = 3.4, 11.8, 1 H, H-8), 3.28–3.32 (m, 1 H, H-2), 2.78–2.84 and 2.64–2.70 (m, 1 H each, $PhCH_2$), 2.40–2.48 (m, 1 H, H-6), 2.23–2.29 (m, 1 H, H-3), 2.05–2.16 (m, 2 H, H-3, H-6), 1.84–1.96 (m, 2 H, H-7, $PhCH_2CH_2$), 1.63–1.70 (m, 1 H, $PhCH_2CH_2$), 1.43–1.49 (m, 1 H, H-6), decoupling experiments showed that the vinylic hydrogens (δ 5.7) and C-2 hydrogen (δ 3.3) were both coupled to the C-3 CH_2 group (δ 2.26); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 131.0, 128.5, 128.2, 127.9, 125.6, 80.2, 68.2, 37.8, 33.9, 32.4, 30.5, 23.5; MS (EI, 70 eV) *m/e* 216.1509 (216.1514 calcd for $C_{15}H_{20}O$, M, 11), 188 (5), 157 (6), 134 (33), 117 (29), 104 (29), 92 (100), 91 (92).

Spectral data for *cis*-oxocane 16: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.30 (m, 5 H, PhH), 3.48–3.52 (m, 1 H, OCH), 3.36–3.40 (m, 1 H, OCH), 2.82–2.88 and 2.60–2.66 (m, 1 H each, $PhCH_2$), 1.56–1.87 (m, 9 H), 1.40–1.48 (m, 5 H), 0.97 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 128.4, 128.3, 125.6, 81.2, 78.9, 38.9, 33.9, 32.9, 32.6, 29.6, 27.0, 23.9, 10.9; IR ($CHCl_3$) 3088, 3062, 3031, 2931, 2856, 1606, 1494, 1456, 1375, 1200, 1131, 1084, 1075, 912 cm^{-1}; MS (EI, 70 eV) *m/e* 246.1974 (M, 246.1984 calcd for $C_{17}H_{26}O$), 228 (8), 123 (17), 117 (31), 104 (48), 91 (100), 55 (38).

Spectral data for *trans*-oxocane 15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.30 (m, 5 H, PhH), 3.66–3.71 (m, 1 H, OCH), 3.56–3.61 (m, 1 H, OCH), 2.72–2.78 and 2.63–2.69 (m, 1 H each, $PhCH_2$), 1.81–1.88 (m, 1 H), 1.38–1.70 (m, 13 H), 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.3, 125.6, 75.3, 74.0, 38.4, 32.5, 32.2, 29.7, 26.6, 26.1, 25.8, 10.6; IR ($CHCl_3$) 3088, 3062, 3031, 2931, 2856, 1494, 1456, 1200, 1131, 1094, 912 cm^{-1}; MS (EI, 70 eV) *m/e* 246.1979 (246.1984 calcd for $C_{17}H_{26}O$, M, 0.6), 228 (4), 217 (1), 117 (24), 104 (42), 91 (100).

Preparation of 9-Chloro-11-oxabicyclo[5.3.1]undecane (20). To a stirring solution of acetal **17** (1.50 g, 8.14 mmol) in CH_2Cl_2 (200 mL) at −23 °C was added $SnCl_4$ (16.3 mL of a 1 M solution in CH_2Cl_2) and the reaction was maintained at −23 °C for 1.5 h. The reaction was quenched by the addition of a 1:1 solution of Et_3N and CH_2Cl_2 (32 mL). The resulting mixture was allowed to warm to 23 °C and a 5% NaOH solution (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic phases were rinsed with brine (50 mL), dried (K_2CO_3), and concentrated. The residue was purified by column chromatography (1:10 Et_2O–pentane) to afford a clear colorless oil (530 mg, 34%) which was ca. 80% bicycloundecane **20** by GLC analysis. This material was sublimed [40 °C (20 mm)] to obtain an analytical sample: mp 62–62.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (app dt, J = 5.2, 10.8 Hz, 1 H, H-9), 3.94 (app dt, J = 6.2, 6.2 Hz, 2 H, H-1, H-7), 2.00–2.09 (m, 4 H, H-8, H-10), 1.78–1.87 (3 H, H-3, H-4, H-5), 1.68–1.74 (m, 2 H, H-2, H-6), 1.55–1.62 (m, 2 H, H-2, H-6), 1.45–1.52 (m, 2 H, H-3, H-5), 1.24–1.25 (m, 1 H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.4 (CH), 51.0 (CH), 40.1 (CH_2), 34.5 (CH_2), 31.7 (CH_2), 24.7 (CH_2); IR (film) 3075, 2925, 2856, 1725, 1644, 1469, 1444, 1075 cm^{-1}; MS (EI, 70 eV) *m/e* 188.0955 (188.0968 calcd for $C_{10}H_{17}O^{35}Cl$, M) 153 (6), 123 (12), 81 (30), 67 (72), 55 (100). Anal. Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.08. Found: C, 63.57; H, 9.13.

Preparation of 4-(Trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (25) from $SnCl_4$-Promoted Cyclization of MEM Ether (22). To a stirring solution of **22** (110 mg, 0.42 mmol) and CH_2Cl_2 (29 mL) at −10 °C was added dropwise over 1 min $SnCl_4$ (1.0 mL of a 1 M solution in CH_2Cl_2). The reaction was maintained at −10 °C for 14 h and then quenched by pouring it into 15% NaOH (30 mL). The organic fraction was separated, washed with brine (10 mL), dried (K_2CO_3), and concentrated. Purification of the residue by column chromatography (1:10 Et_2O–pentane) afforded **25** as a colorless oil (24.3 mg, 31%), which was 100% pure by capillary GC analysis. Also apparent in the crude product is an aldehyde and oxocene **5**, which can be isolated by preparative GC. **Silyloxocene 25**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.05 (t, J = 8.0 Hz, 1 H, C=CH), 3.59 (app t, J = 5 Hz, 2 H, H-2), 3.57 (app t, J = 5 Hz, 2 H, H-8), 2.36 (t, J = 5.4 Hz, 2 H, H-3), 2.30 (dt, J = 1 Hz, 9.0 Hz, 2 H, H-6), 1.63 (app pent, J = 6 Hz, 2 H, H-7), 0.07 (s, 9 H, $SiMe_3$), irradiation of the apparent triplet at δ 2.36 (H-3) resulted in the collapse of the signal at 3.59 (H-2); IR (film) 2915, 1242, 1108, 829 cm^{-1}; MS (EI, 32 eV) *m/e* 185 (MH, 1), 184 (M, 3), 169 (4), 156 (7), 116 (18), 103 (28), (55), 73 (100); MS (EI, 70 eV) *m/e* 184.1276 (184.1278 calcd for $C_{10}H_{20}OSi$).

Preparation of 25 from MOM Ether 23 by $SnCl_4$-Promoted Cyclization of α-Chloro Ether 24. To a stirring solution of BCl_3 (0.7 mL of a 1 M solution in CH_2Cl_2) at −15 °C in CH_2Cl_2 (10 mL) was added a solution of the MOM ether **23** (500 mg, 2.31 mmol) in CH_2Cl_2 (5 mL). The reaction was maintained at −15 °C for 2 h and then concentrated in vacuo to afford **24** as an unstable pale yellow oil (485 mg, 95%). This sample was immediately dissolved in 2 mL of CH_2Cl_2 and added dropwise to a stirring solution of $SnCl_4$ (2.5 mL of a 1 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) at −78 °C. The resulting solution was maintained at −70 °C for 1 h and then poured into a rapidly stirring solution of cold (0 °C) 15% NaOH (30 mL). The organic fraction was washed with brine (2 × 30 mL), dried (K_2CO_3), and concentrated. The residue was purified by column chromatography (1:3 Et_2O–pentane) to afford 166 mg (39% overall from **23**) of silyloxocene **25** as a clear colorless oil, which was 95.8% pure by GC analysis.

Preparation of 8-Methyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (27). To dry CH_2Cl_2 (3 mL) was added a solution of $SnCl_4$ in CH_2Cl_2 (1.6 mL of a 1 M solution in CH_2Cl_2), the reaction vessel was cooled to −15 °C (internal temperture), and a solution of acetal **26** (85 mg, 0.31 mmol) and dry CH_2Cl_2 (3.2 mL) was then added over 40 min by syringe pump. The resulting solution was maintained at −15 °C (internal temperature) for 18 h and then cooled to −50 °C. Triethylamine (0.5 mL, 3.6 mmol) was then added, the resulting solution was stirred at −50 °C for 10 min, and then saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2, washed with brine, dried (K_2CO_3), and concentrated. The residue was purified by flash chromatography (30:1–20:1 hexane–EtOAc) to afford 24 mg (39%) of **27** as a clear colorless oil, which showed no detectable impurities by 250-MHz ^{1}H NMR analysis: (250 MHz, $CDCl_3$) δ 6.03 (ddd, J = 1.4, 6.7, 9.4 Hz, 1 H, H-5), 3.90 (ddd, J = 3.4, 5.6, 12.1 Hz, 1 H, H-2), 3.35 (m, 1 H, H-8), 3.25 (ddd, J = 2.3, 9.6, 12.1 Hz, 1 H, H-2), 2.50 (m, 2 H, H-3, H-6), 2.22 (ddd, J = 2.3, 5.6, 14.4 Hz, 1 H, H-3), 2.02 (m, 1 H, H-6), 1.52 (m, 2 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.05 (s, 9 H); IR (film) 3010, 2950, 2870, 1620, 1255, 1115, 840 cm^{-1}; MS (CI) *m/e* 199 (MH), 181, 143, 105, 75; MS (EI, 20 eV) *m/e* 198.1427 (198.1440 calcd for $C_{11}H_{22}OSi$).

Isolation of 2-Methyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (29) and 7-Hydroxy-5-(trimethylsilyl)octanal (46) from $SnCl_4$-Promoted

Cyclization of 28. To a stirring solution of $SnCl_4$ (1.6 mL of 1 M solution in CH_2Cl_2) and CH_2Cl_2 (10 mL) at −40 °C was added dropwise over 1 min a solution of acetal **28** (200 mg, 0.82 mmol) and CH_2Cl_2 (2 mL). The reaction was maintained at −40 °C for 2 h, allowed to warm to −20 °C, and then quenched by the addition of 15% NaOH (5 mL). The organic phase was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL). The organic layers were combined and washed with brine (5 mL), dried (K_2CO_3), and concentrated. The residue was purified by column chromatography (1:10 Et_2O–pentane) to afford 49 mg (30%) of oxocene **29** as a sweet smelling oil and 112 mg of impure aldehyde **46**. Analytical samples of each compound were obtained by preparative GC. **Oxocene 29**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.97–6.00 (m, 1 H, CH=C), 3.89 (ddd, *J* = 1.4, 3.8, 8.9 Hz, 1 H, C*H*HO), 3.33–3.39 (m, 1 H, OC*H*Me), 3.30 (dt, *J* = 3.6, 12.1 Hz, 1 H, CH*H*O), 2.54–2.62 (m, 1 H, H-6), 2.28 (dd, *J* = 11.1, 14.0 Hz, 1 H, H-3), 2.12 (d, *J* = 14.0 Hz, 1 H, H-3), 2.04–2.09 (m, 1 H, H-6), 1.89–1.96 (m, 1 H, H-7), 1.32–1.38 (m, 1 H), 1.23 (d, *J* = 6.3 Hz, 3 H, Me), 0.08 (s, 9 H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 139.1, 77.9, 67.6, 38.1, 29.9, 24.3, 23.2, −1.7; IR (film) 3056, 2956, 1612, 1119, 1038, 981, 869, 838, 756 cm^{-1}; MS (EI, 70 eV) *m/e* 198.1542 (M, 198.1440 calcd for $C_{11}H_{22}OSi$), 183 (1), 170 (2), 156 (3), 139 (7), 111 (11), 73 (100), 59 (14). **Aldehyde 46**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1 H, CHO), 3.83–3.87 (m, 1 H, H-7), 2.38–2.45 (m, 2 H, H-2), 1.67–1.73 (m, 1 H, H-3), 1.58–1.65 (m, 1 H, H-3), 1.44–1.54 (m, 2 H, H-6), 1.23–1.36 (m, 2 H, H-4), 1.19 (d, *J* = 6.1 Hz, 3 H, CH*Me*), 0.63–0.68 (m, 1 H, C*H*$SiMe_3$), 0.01 (s, 9 H, $SiMe_3$). Irradiation of the signal at δ 3.83–3.87 causes the partial collapse of the signals at δ 1.44–1.54 (C-6 CH_2) and 1.19 (CH*Me*). Irradiation of the signal at δ 1.44–1.54 causes the partial collapse of the signals at δ 3.83–3.87 and 0.68–0.63 (C-5 C*H*$SiMe_3$). Irradiation of the signal at δ 0.63–0.68 causes the partial collapse of the signals at δ 1.44–1.54 and 1.23–1.36.

Isolation of *cis*-2-Ethoxy-8-methyl-6-(trimethylsilyl)oxocane (47) and *trans*-2-Ethoxy-8-methyl-6-(trimethylsilyl)oxocane (48) from $SnCl_4$-Promoted Cyclization of 28. To a stirring solution of $SnCl_4$ (0.8 mL of a 1 M solution in CH_2Cl_2) and CH_2Cl_2 (8 mL) at −55 °C was added dropwise over 1 min a solution of **28** (100 mg, 0.41 mmol) in CH_2Cl_2 (2 mL). The reaction was maintained at −65 °C for 5 min and then quenched by the addition of Et_3N (0.4 mL). The reaction was allowed to warm to −20 °C and 15% NaOH (5 mL) was added. The reaction mixture was allowed to warm to room temperature. The organic phase was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL). The organic layers were combined and washed with brine (5 mL), dried (K_2CO_3), and concentrated to afford 76 mg of a crude product, which capillary GLC analysis showed contained oxocene **29** and cyclic acetals **47** and **48** in a 1.4:1:1 ratio, respectively. Analytical samples of **47** and **48** were obtained by preparative GC.

Spectral data for cis isomer 47: ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 3.9, 8.3 Hz, 1 H, OCHO), 3.80 (dq, *J* = 7.2, 9.1 Hz, 1 H, OCH), 3.50–3.56 (m, 1 H, OC*H*Me), 3.36 (dq, *J* = 7.1, 7.1 Hz, 1 H, OCH), 1.92–1.95 (m, 1 H), 1.62–1.79 (m, 2 H), 1.53–1.58 (m, 2 H), 1.33–1.44 (m, 3 H), 1.28 (d, *J* = 6.2 Hz, 3 H, CH*Me*), 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2Me), 0.52 (app dt, *J* = 4.2, 10.1 Hz, 1 H, C*H*$SiMe_3$), −0.04 (s, 9 H, $SiMe_3$); ^{13}C (125 MHz, $CDCl_3$) δ 105.7 (CH), 80.6 (CH), 62.3 (CH_2), 38.2 (CH_2), 35.7 (CH_2), 28.6 (CH_2), 25.3 (CH_2), 25.2 (CH), 22.6 (CH_3), 15.0 (CH_3), −3.7 (CH_3); IR ($CHCl_3$) 2975, 1126, 1104, 1046, 1024 cm^{-1}; MS (CI) *m/e* 245.1929 (245.1937 calcd for $C_{13}H_{29}O_2Si$). NOE experiments: Irradiation of the signal at δ 4.80 produced an 8% enhancement in the signal at δ 3.50–3.56 and a 13% enhancement in the signal at δ 0.52. Irradiation of the signal at δ 3.50–3.56 produced a 7% enhancement in the signal at δ 4.80 and a 3% enhancement in the signal at δ 0.52. Irradiation of the signal at δ 0.52 produced a 9% enhancement in the signal at δ 4.80.

Spectral data for trans isomer 48: ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (dd, *J* = 2.1, 10.4 Hz, 1 H, OCHO), 4.00–4.10 (m, 1 H, OC*H*Me), 3.78–3.90 (m, 1 H, OCH), 3.41–3.52 (m, 1 H, OCH), 2.00–2.15 (m, 1 H), 1.47–1.77 (m, 6 H), 1.29–1.42 (m, 1 H), 1.21 (t, *J* = 6.2 Hz, 3 H, CH_2Me), 1.13 (d, *J* = 5.4 Hz, 3 H, CH*Me*), 0.56–0.50 (m, 1 H, C*H*$SiMe_3$), −0.02 (s, 9 H, $SiMe_3$); ^{13}C (125 MHz, $CDCl_3$) δ 101.7 (CH), 68.6 (CH), 62.2 (CH_2), 38.3 (CH_2), 27.6 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 23.9 (CH), 22.2 (CH_3), 15.1 (CH_3), −3.6 (CH_3); IR ($CHCl_3$) 2970, 2954, 1711, 1249, 1133, 1108, 1087 cm^{-1}; MS (CI) *m/e* 245.1950 (245.1937 calcd for $C_{13}H_{29}O_2Si$). NOE experiments: Irradiation of the signal at δ 4.00–4.10 produced a 4% enhancement in the signal at δ 0.56–0.50. Irradiation of the signal at δ 0.56–0.50 produced a 6% enhancement in the signal at δ 4.10–4.00.

$SnCl_4$-Promoted Cyclization of Acetal 30. Preparation of 2-(2-Phenylethyl)-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (31) and (2*R,3a*S**,6a*S**)-2-(Phenylethyl)-1-oxabicyclo[3.3.0]octane (51).** To a stirring solution of acetal **30** (167 mg, 0.52 mmol) and dry CH_2Cl_2 (10 mL) at −20 °C was added $SnCl_4$ (1.1 mL of a 1 M solution in CH_2Cl_2). The reaction was maintained at −20 °C for 2 h and then quenched with cold (~0 °C) aqueous 1 M NaOH (5 mL). The resulting mixture was extracted with CH_2Cl_2 (20 mL), and the extracts were washed with saturated $NaHCO_3$ (10 mL) and brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by multiple flash chromatography (1:1 hexane–CH_2Cl_2) to give 20 mg (13%) of oxocene **31** (96% pure by capillary GC analysis), 20 mg of the cyclopentatetrahydrofuran **51** (18%) (94% pure by capillary GC analysis), 12 mg of a 1:1 mixture **31** and **51**, and 15 mg of uncharacterized products. **Oxocene 31**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5 H, Ph), 5.98 (ddd, *J* = 1.6, 6.6, 9.5 Hz, 1 H, H-5), 3.97 (ddd, *J* = 1.8, 5.4, 11.8 Hz, 1 H, H-8), 3.26 (dt, *J* = 3.7, 11.8 Hz, 1 H, H-8), 3.11 (dt, *J* = 3.7, 9.4 Hz, 1 H, H-2), 2.90–2.75 (m, 1 H, PhC*H*), 2.72–2.52 (m, 2 H), 2.45 (m, 1 H), 2.10 (app dd, *J* = 0.9, 14.1 Hz, 1 H, H-3), 2.12–1.84 (m, 2 H), 1.80–1.64 (m, 2 H), 1.45–1.30 (m, 1 H), 0.03 (s, 9 H, $SiMe_3$). Irradiation of the signal at δ 3.11 (H-2) causes the partial collapse of the signal at δ 2.60 (H-3) and at δ 1.64–1.80 ($PhCH_2CH_2$). Irradiation of the signal at δ 2.10 (H-3) causes the partial collapse of the signal at δ 2.60 (H-3) and loss of the long-range coupling to the signal at δ 5.98 (H-5). ^{13}C (75 MHz, $CDCl_3$) δ 142.3, 141.3, 139.0, 128.5, 128.3, 125.6, 81.4, 68.1, 38.7, 36.7, 32.6, 30.0, 29.7, 24.4, −1.73; IR (film) 3027, 2949, 2926, 2869, 1457, 1247, 1107, 863, 747, 698 cm^{-1}; MS (CI) *m/e* 289 (MH); MS (EI, 70 eV) *m/e* (288.1909 calcd for $C_{18}H_{28}OSi$).

Bicyclic ether 51: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.30 (m, 2 H), 7.16–7.22 (m, 3 H), 4.35 (t, *J* = 6.2 Hz, 1 H, H-6), 3.62 (m, 1 H, H-2), 2.74 (app ddd, *J* = 6.0, 10.0, 13.9 Hz, 1 H, PhC*H*), 2.66 (m, 1 H, H-3), 2.63 (m, 1 H, PhCH), 2.19 (ddd, *J* = 4.9, 9.3, 12.1 Hz, 1 H, H-2), 1.95 (m, 1 H, $PhCH_2CH$), 1.86 (app dd, *J* = 6.5, 3.4 Hz, 1 H, H-5), 1.80 (m, 1 H, $PhCH_2CH$), 1.65 (m, 1 H, H-5), 1.52–1.58 (m, 2 H, H-4), 1.38–1.52 (m, 2 H, H-6), 1.05 (ddd, *J* = 8.0, 10.6, 12.0 Hz, 1 H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2 (C), 128.3 (CH), 128.2 (CH), 125.7 (CH), 84.6 (CH), 79.2 (CH), 42.8 (CH), 40.5 (CH_2), 36.2 (CH_2), 33.8 (CH_2), 33.2 (CH_2), 32.6 (CH_2), 23.3 (CH_2); IR (film) 2953, 2939, 2863, 1454, 1064, 1050, 1045, 1033, 745, 699 cm^{-1}; MS (CI) *m/e* 217 (MH); MS (EI, 70 eV) *m/e* 216.1510 (216.1514 calcd for $C_{15}H_{20}O$).

$SnCl_4$-Promoted Cyclization of 30 at −78 °C. Isolation of 8-(2-Phenylethyl)-2-methoxy-5-(trimethylsilyl)oxocane (50). To a stirring solution of **30** (101 mg, 0.32 mmol) and dry CH_2Cl_2 (6.3 mL) at −70 °C was added $SnCl_4$ (0.63 mL of 1 M solution in CH_2Cl_2, 0.63 mmol). Aliquots were removed at intervals (5, 10, 15, 30, 60, and 120 min) and quenched at −78 °C with 1:1 Et_3N–CH_2Cl_2 (1:1) followed by saturated aqueous $NaHCO_3$ at 23 °C; the organic layer was analyzed by capillary GC. The first four aliquots (5–30 min) showed the presence of three compounds: oxocene **31**, oxocane **50**, and the oxabicyclo[3.3.0]octane **51**. Between 30 min and 2 h the GC signal for **50** decreased as the GC signal for **51** increased. After 2 h, **50** was no longer present.

Quenching a comparable reaction mixture after 30 min, followed by preparative GC separation, provided a pure sample of oxocane acetal **50**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.35 (m, 5 H), 4.54 (dd, *J* = 2.0, 10.4 Hz, 1 H, OCHO), 3.97 (m, 1 H, H-2), 3.47 (s, 3 H, OMe), 2.69 (app t, *J* = 8.4 Hz, 2 H, $PhCH_2$), 2.00–2.15 (m, 1 H), 1.75–1.90 (m, 2 H), 1.50–1.75 (m, 5 H), 1.25–1.45 (m, 2 H), 0.46–0.56 (m, 1 H, C*H*$SiMe_3$) −0.05 (s, 9 H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.4, 128.3, 125.7, 104.1, 72.8, 55.5, 39.9, 35.6, 27.5, 25.7, 25.6, 22.2, −3.6; IR (film) 3027, 2950, 2901, 2859, 2832, 1454, 1248, 1129, 1074, 1039, 943, 865, 834, 747, 700 cm^{-1}; MS (CI) *m/e* 321 (MH), 305, 289, 271, 217, 199, 117, 99, 91, 73; MS (EI, 70 eV) *m/e* 320.2168 (320.2172 calcd for $C_{19}H_{32}O_2Si$).

Preparation of 2-(2-Phenylethyl)-3,6,7,8-tetrahydro-2*H*-oxocin (49) from Silyloxocene 31: A solution of **31** (15.7 mg, 0.05 mmol) and 2 mL of a HCl–Et_2O solution (~0.8 M) was maintained at 23 °C for 16 h. An additional 2 mL of HCl–Et_2O solution was added and the mixture was heated at reflux for 2 h. The reaction was quenched with 5% NaOH (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give 11 mg (94%) of crude **49** (92% pure by capillary GC analysis): ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.35 (m, 5 H), 5.65–5.80 (m, 2 H), 3.95–4.05 (m, 1 H), 3.36–3.47 (m, 1 H), 3.24–3.35 (m, 1 H), 2.75–2.87 (m, 1 H), 2.61–2.74 (m, 1 H), 2.35–2.50 (m, 1 H), 2.20–2.35 (m, 1 H), 1.80–2.20 (m, 2 H), 1.40–1.75 (m, 4 H); IR (film) 3024, 2927, 2862, 2858, 1455, 1105, 1031, 747, 699 cm^{-1}; MS (CI) *m/e* 217 (MH), 199, 131, 117, 101, 91, 83, 71.

Preparation of (*E*)-2,8,8-Trimethyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (33). To a stirring solution of acetal **32** (53.5 mg, 0.20 mmol) and CH_2Cl_2 (5 mL) at −72 °C was added $SnCl_4$ (0.40 mL of a 1 M solution in CH_2Cl_2, 0.40 mmol). The reaction was maintained at −72 °C for 30 min and then quenched by the addition of a 1:1 solution of Et_3N and CH_2Cl_2 (0.8 mL). The mixture was warmed to room temperature and a 5% NaOH solution (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined organic phases were rinsed with brine (10

mL), dried (K_2CO_3), and concentrated. The residue was purified by column chromatography (1:20 EtOAc–hexanes) to afford 19 mg (42%) of **33** as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (t, J = 6.2 Hz, 1 H, H-5), 3.72–3.78 (m, 1 H, H-2), 2.49 (dd, J = 2.3, 15.2 Hz, 1 H, H-3), 2.38–2.45 (m, 1 H, H-6), 2.18 (dd, J = 5.0, 15.0 Hz, 1 H, H-3), 2.06–2.15 (m, 1 H, H-6), 1.85 (dd, J = 10.9, 14.1 Hz, H-7), 1.63 (dt, J = 2.4, 8.0 Hz, 1 H, H-7), 1.23 (s, 3 H, Me), 1.19 (s, 3 H, Me), d, 1.14 (d, J = 6.5 Hz, 3 H, CH*Me*), 0.36 (s, 9 H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 137.4, 74.5, 69.1, 40.0, 36.4, 30.6, 26.4, 25.7, 24.2, -1.7; IR (film) 2975, 2931, 1250, 831, 750 cm^{-1}; MS (EI, 70 eV) m/e 226.1731 (226.1753 calcd for $C_{13}H_{26}OSi$, 1), 183 (3), 167 (6), 111 (22), 108 (21), 73 (100).

Preparation of 5-Chloro-2-pentyl *N*-[1-Naphthyl)ethyl]carbamate. Following a general literature procedure[44] a solution of phosgene in toluene (12.5%, 100 mL, 127.5 mmol) was cooled to 0 °C and a solution of alcohol **40**[43] (8.0 g, 65.2 mmol), Et_3N (9.0 mL, 65 mmol), and toluene (100 mL) was added dropwise over 40 min. After addition was complete, the resulting mixture was stirred for 1 h and then the excess phosgene was removed in vacuo. The resulting solution was filtered through cotton under an N_2 atmosphere and the separated solid was washed with dry CH_2Cl_2 (50 mL). The solvents were removed in vacuo and the resulting yellow oil was dissolved in dry CH_2Cl_2 (70 mL). To this solution at 20 °C was added a solution of (*S*)-(−)-1-(1-naphthyl)ethylamine (11.0 g, 64 mmol) and Et_3N (9.0 mL, 65 mmol) in CH_2Cl_2 (70 mL). The reaction was stirred at 23 °C for 48 h, diluted with CH_2Cl_2, and washed sequentially with 10% HCl, H_2O, and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (20:1, 15:1, 10:1, 5:1 hexane–ethyl acetate) to afford 13.6 g (66%) of a mixture of diastereomers as a viscous oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20–7.40 (m, 7 H, Ar*H*), 5.68 (br s, 1 H, NC*H*Me), 5.04 (br d, J = 6.5 Hz, 1 H, NH), 4.90 (m, 1 H, OC*H*Me), 3.50 (t, J = 6.6 Hz, 2 H, CHCl), 1.95–1.50 (m, 7 H), 1.21 (d, J = 6.3 Hz, 3 H, OCH*Me*; IR (film) 3416, 3325, 3050, 2973, 1700, 1511, 1244, 1054, 798 cm^{-1}; MS (CI) m/e 322 (MH), 320 (MH), 216, 166, 155, 107, 105, 88; MS (EI, 70 eV) m/e 321.1313 (M, 321.1309 calcd for $C_{18}H_{22}O_2NCl$), 319.1321 (319.1339 calcd for $C_{18}H_{22}O_2NCl$).

Preparation of 5-Iodo-(*S*)-2-pentyl *N*-[1-(1-Naphthyl)ethyl]carbamate (41). A mixture of NaI (44.0 g, 294 mmol, flame dried under vacuum), $NaHCO_3$ (2.25 g, 26.8 mmol), acetone (220 mL), and the chloride from the previous step (14.6 g, 45.6 mmol) was maintained at 50 °C for 30 h, cooled, and quenched with 10% $Na_2S_2O_3$–10% $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with Et_2O, washed with brine, dried (K_2CO_3), and concentrated. The residue was purified by flash chromatography (10:1–5:1 hexane–EtOAc) to afford 19 g (100%) of a pale yellow oil. This diastereomeric mixture could be partially resolved by preparative HPLC using a Waters Prep 500 LC system (100:15:2 hexane–EtOAc–2-propanol, two recycles). The leading and tailing edge of each peak was collected and the middle section was submitted to recycle. In this manner, there was obtained 5.2 g (27%) of material extensively enriched in the more mobile isomer [R_f 0.59 (silica gel, 100:15:2 hexane–EtOAc–2-propanol, three developments)], 1.7 g (9%) of mixed fractions, and 9.5 g (51%) of material enriched in the less mobile isomer (R_f 0.53, silica gel, 100:15:2 hexane–EtOAc–2-propanol, three developments). The more mobile isomer **41** displayed the following spectral characteristics: $[\alpha]_D$ = −62.30° (c = 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.40–8.20 (m, 7 H, ArH), 5.65 (m, 1 H, NCH), 4.75–5.05 (m, 2 H), 3.15 (t, J = 6.8 Hz, 2 H, CH_2I), 1.45–1.95 (m, 7 H), 1.15–1.35 (m, H, OCHMe); IR (film) 3416, 3325, 3051, 2973, 1701, 1511, 1230, 1054, 780 cm^{-1}; MS (CI) m/e 258, 197, 155, 141; MS (EI, 70 eV) m/e 411.0670 (411.0695 calcd for $C_{18}H_{22}O_2IN$).

Preparation of 6-(Trimethylsilyl)-2-hept-6-(*S*)-enyl *N*-[1-(1-Naphthyl)ethyl]carbamate. To a solution of (α-bromovinyl)trimethylsilane (11.2 mL, 72.7 mmol) and dry THF (50 mL) at −78 °C was added *s*-BuLi–cyclohexane (1.35 M, 53 mL, 71.6 mmol) dropwise over 20 min. The reaction was maintained at −78 °C for 1 h and then transferred by cannula to a slurry of CuCN (3.2 g, 35.7 mmol) in THF (50 mL) at −78 °C. The cuprate solution was warmed to −10 °C (internal temperature), the resulting green-blue solution was cooled to −78 °C, and a solution of iodide **41** (4.5 g, 10.9 mmol) and dry THF (20 mL) was added dropwise over 10 min. The reaction was maintained at −78 °C for 1 h, −20 °C for 5 h, and at −10 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with Et_2O, and washed sequentially with concentrated NH_4OH (2×), H_2O, and brine. The colorless organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (30:1, 15:1, 10:1, 5:1 hexane–ethyl acetate) to afford 3.4 g (81%) of the vinylsilane carbamate (83:17 mixture of diastereomers by capillary GC analysis) as a clear colorless oil and 0.76 g (17%) of recovered iodide: $[\alpha]_D$ = −51.40° (c = 1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–8.20 (m, 7 H, ArH), 5.65 (m, 1 H, NCH), 5.52 (d, J = 1.2 Hz, 1 H, C=CH), 5.30 (d, J = 2.7 Hz, 1 H, C=CH), 4.96 (br d, J = 4.1 Hz, 1 H, NH), 4.86 (m, 1 H, OC*H*Me), 2.11 (t, J = 6.5 Hz, 2 H, CH_2C=CH_2), 1.70–1.10 (m, 10 H), 0.06 (s, 9 H, $SiMe_3$); IR (film) 3329, 3050, 2950, 1702, 1596, 1523, 1251, 1058, 839, 799 cm^{-1}; MS (EI, 70 eV) m/e 383.2279 (M, 383.2280 calcd for $C_{23}H_{33}O_2NSi$).

Preparation of (*S*)-2-Hydroxy-6-(trimethylsilyl)hept-6-ene (42). A slurry of $LiAlH_4$ (388 mg, 10.2 mmol) and dry Et_2O (40 mL), was cooled to 0 °C. To this mixture was added a solution of the carbamate from the previous step (1.9 g, 4.96 mmol) and THF (30 mL). The reaction was allowed to warm to 23 °C and was then heated to reflux for 18 h. The reaction was cooled and quenched with H_2O (0.38 mL), 15% NaOH (0.38 mL), and H_2O (1.1 mL). The mixture was stirred an additional 1.5 h, filtered, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (10:1, 5:1, 1:1 hexane–EtOAc) afforded 832 mg (90%) of alcohol **42** as a clear colorless oil: $[\alpha]_D$ = −4.00° (c = 1.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, J = 1.4 Hz, 1 H, C=CH), 5.32 (d, J = 2.9 Hz, 1 H, C=CH), 3.82 (m, 1 H, CHO), 2.15 (t, J = 6.5 Hz, 2 H, CH_2C=C), 1.30–1.65 (m, 5 H), 1.20 (d, J = 6.1 Hz, 3 H, $CHCH_3$), 0.09 (s, 9 H, $SiMe_3$); IR (film) 3353, 3051, 2959, 1251, 836 cm^{-1}; MS (CI) m/e 187 (MH); MS (EI, 22 eV) m/e 171.1184 (171.1205 calcd for $C_{10}H_{22}OSi$, M − CH_3).

Preparation of 2(*S*)-2-(1-Ethoxyethoxy)-6-(trimethylsilyl)hept-6-ene (34). To a solution of alcohol **42** (800 mg, 4.3 mmol) and dry CH_2Cl_2 (30 mL) at 0 °C under argon was added freshly distilled ethyl vinyl ether (0.75 mL, 7.84 mmol) and a catalytic amount of pyridine-*p*-toluenesulfonate (~20 mg). The reaction was maintained at 0 °C for 4 h and at 23 °C for 1.5 h and was then quenched with anhydrous K_2CO_3 (~2 g) followed by concentration in vacuo. The residue was purified by flash chromatography (200:1 hexane–Et_3N to 200:2:1 to 200:4:1 hexane–EtOAc–Et_3N) to afford 866 mg (78%) of acetal **34** as a mixture of diastereomers: $[\alpha]_D$ = −3.10° (c = 1.14, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.54 (br s, 1 H, C=CH), 5.32 (d, J = 2.8 Hz, 1 H, C=CH), 4.74 (dq, J = 5.3, 12.2 Hz, 1 H, OC*H*MeO), 3.42–3.80 (m, 3 H), 2.14 (br t, 2 H, CH_2C=C), 1.35–1.64 (m, 4 H), 1.30 (d, J = 5.3 Hz, 3 H), 1.18 (m, 3 H, CH_2Me), 1.12 (d, J = 6.0 Hz, 3 H), 0.08 (s, 9 H, $SiMe_3$); IR (film) 3060, 2980, 2950, 1255, 1130, 1105, 840 cm^{-1}; MS (CI) m/e 259 (MH); MS (EI, 20 eV) m/e 213.1658 (213.1675 calcd for $C_{14}H_{30}O_2Si$ − C_2H_5O).

Preparation of 2(*R*),8(*S*)-Dimethyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (35). To dry CH_2Cl_2 (45 mL) at −25 °C (bath temperature) was added a 1 M CH_2Cl_2 solution of $SnCl_4$ (4.5 mL, 4.5 mmol) followed by a solution of optically active acetal **34** (750 mg, 2.9 mmol) and CH_2Cl_2 (10 mL). The reaction was maintained at −20 °C (bath temperature) for 50 min and then poured into ice cold 5% NaOH. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (50:1, 10:1, 5:1, 1:1 hexane–EtOAc) gave 210 mg (34%) of oxocene **35** and 318 mg (48%) of keto alcohol **43**. The oxocene fraction contained 3.4% of an impurity of similar retention time (capillary GC analysis) which is assumed to be the trans stereoisomer. An isomerically pure sample of **35** was obtained by preparative GLC.

Spectral data for oxocene 35: R_f 0.60 (silica gel, using 10:1 hexane–EtOAc), $[\alpha]_D$ = −35.7° (c = 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.00 (ddd, J = 1.8, 6.4, 9.7 Hz, 1 H, H-5), 3.46 (m, 1 H, H-8), 3.33 (dq, J = 6.4, 9.1 Hz, 1 H, H-2), 2.65 (m, 1 H, H-6), 2.45 (ddd, J = 1.8, 9.8, 14.0 Hz, 1 H, H-3), 2.13 (d, J = 14.0 Hz, 1 H, H-3), 2.00 (m, 1 H, H-6), 1.38–1.70 (m, 2 H), 1.24 (d, J = 6.4 Hz, 3 H, C-2 Me), 1.09 (d, J = 6.3 Hz, 3 H, C-8 Me), 0.06 (s, 9 H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 139.6, 77.0, 74.0, 38.4, 37.0, 24.8, 23.8, 22.2, −2.0; IR (film) 3020, 2980, 2950, 1620, 1255, 1125, 1000, 840 cm^{-1}; MS (CI) m/e 213 (MH); MS (EI, 20 eV) m/e 212.1596 (M, 212.1597 calcd for $C_{12}H_{24}OSi$). Anal. Calcd for $C_{12}H_{24}OSi$: C, 67.85; H, 11.39. Found: C, 67.95; H, 11.44.

Spectral data for octanone 43: R_f 0.46 (silica gel, 1:1 hexane–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85 (m, 1 H, MeC*H*OH), 2.42 (app t, J = 7.3 Hz, 2 H, $MeCOCH_2$), 2.13 (s, 3 H, CH_3CO), 1.15–1.75 (7 H), 1.17 (d, J = 6.1 Hz, 3 H, CH_3CHOH), 0.64 (m, 1 H, C*H*$SiMe_3$), 0.00 (s, 9 H, $SiMe_3$); irradiation of the apparent triplet at δ 2.42 had no effect on the multiplet at δ 0.64; IR (film) 3440, 2970, 1725, 1260, 840 cm^{-1}. Treatment of a sample of comparable material with Ac_2O and pyridine provided the monoacetate derivative: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.90 (m, C*H*OAc), 2.04 (s, CH_3CO).

Preparation of *cis*-2,8-Dimethyloxocane (45). Et_2O (5 mL) was saturated with dry HCl and a sample of **35** (74 mg, 0.35 mmol, purified by preparative GC) was added. After 11 h at 23 °C, protodesilylation was 98% complete (capillary GC analysis) and the reaction was concentrated in vacuo (carefully) to afford a volatile pale yellow residue. An aliquot (ca. 10 mg) was purified by preparative GC to afford a pure sample of *cis*-2,8-dimethyl-3,6,7,8-tetrahydro-2*H*-oxocin: $[\alpha]_D$ = −34.10° (c = 0.38, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.72 (m, 2 H, H-3,

H-4), 3.44–3.72 (m, 2 H, H-1, H-8), 2.50 (m, 1 H), 1.90–2.36 (m, 3 H), 1.45–1.72 (m, 2 H, H-6), 1.19 (d, J = 6.3 Hz, 3 H), 1.12 (d, J = 6.3 Hz, 3 H).

The remaining crude product was hydrogenated (10% Pd–C, EtOAc, 23 °C), and the resulting crude mixture was filtered through a small plug of alumina and the eluent partially concentrated in vacuo (carefully) to afford a volatile oil. Purification by preparative GC afforded 24.9 mg (50%) of oxocane **45** as a volatile oil: $[\alpha]_D = 0.0°$, $[\alpha]_{578} = 0°$, $[\alpha]_{546} = 0°$, $[\alpha]_{435} = 0.0°$, $[\alpha]_{365} = 0.0°$ (c = 1.25, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (m, 2 H, H-1, H-8), 1.20–1.85 (m, 10 H), 1.14 (d, J = 6.3 Hz, 6 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.9, 35.4, 27.0, 24.5, 22.6; IR (film) 2924, 1447, 1370, 1103, 1089, 1053 cm^{-1}; MS (CI) m/e 143 (MH), 127, 125, 99; MS (EI, 70 eV) m/e 142.1358 (M, 142.1357 calcd for $C_9H_{18}O$).

Prepartion of 8-Methyl-2-(2-phenylethyl)-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (37). To a stirring solution of acetal **36** (40.8 mg, 0.12 mmol) and dry CH_2Cl_2 (2.5 mL) at −50 °C was added dropwise 0.25 mL of a 1 M solution of $SnCl_4$ in CH_2Cl_2. The reaction mixture was maintained at −20 °C for 2 h and then quenched with 0.5 mL of a 1:1 solution of CH_2Cl_2–Et_3N. The resulting mixture was allowed to warm to room temperature and saturated aqueous $NaHCO_3$ (1 mL) and H_2O (2 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with H_2O (3 × 20 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (4:1 hexane–CH_2Cl_2) to afford 11.4 mg (31%) of clear colorless oil, which was 95% pure by capillary GC analysis: ^1H NMR (300 MHz, $CDCl_3$) δ 7.14–7.32 (m, 5 H), 6.00 (ddd, J = 1.7, 6.5, 9.7 Hz, 1 H, H-5), 3.35–3.49 (m, 1 H, H-8), 3.12 (dt, J = 3.2, 9.6 Hz, 1 H, H-2), 2.84–2.96 (m, 1 H, PhCH), 2.55–2.75 (m, 2 H), 2.50 (ddd, J = 1.6, 10.1, 14.0 Hz, 1 H, H-3), 2.10 (d, J = 14.0 Hz, 1 H, H-3), 1.95–2.05 (m, 1 H, H-6), 1.82–1.95 (m, 1 H), 1.60–1.78 (m, 2 H), 1.45–1.60 (m, 1 H, H-7), 1.15 (d, J = 6.3 Hz, 3 H), 0.03 (s, 9 H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 140.9, 139.6, 128.4, 128.3, 125.6, 81.1, 74.6, 39.0, 37.4, 37.2, 32.9, 25.0, 22.0, −1.9; IR (film) 3027, 2953, 2925, 2858, 1456, 1247, 1097, 870, 833, 749, 698 cm^{-1}; MS (Cl) m/e 303 (MH), 221, 213, 207, 186, 169, 143, 131, 117, 109, 97, 95, 91, 73; MS (EI, 70 eV) m/e 302.2066 (M, 302.2066 calcd for $C_{19}H_{30}OSi$). Homonuclear decoupling of **37**: Irradiation of the signal at δ 6.00 (H-5) causes the partial collapse of the signals at δ 2.50 (H-3), 2.65 (H-6), and 2.00 (H-6). Irradiation of the signal at δ 3.42 (H-8) causes the collapse of the signal at δ 1.15 from a doublet to a singlet and the partial collapse of the signal at δ 1.55 (H-7). Irradiation of the signal at δ 3.12 (H-2) causes the collapse of the signal at δ 2.50 (H-3) and at δ 1.90. Irradiation of the signal at δ 2.90 causes the partial collapse of the signals at δ 2.70, 1.90, and 1.70. ^1H NOE experiments for **37**: Irradiation of the signal at δ 3.49–3.35 (H-8) produced a 10% enhancement of the signal at δ 3.12 (H-2), while irradiation of the signal at δ 3.12 (H-2) produced at 18% enhancement of the signal at δ 3.49–3.35 (H-8).

Preparation of 9-Chloro-7-methyl-3-(trimethylsilyl)-11-oxabicyclo-[5.3.1]undecane (54) from $SnCl_4$-Promoted Cyclization of Acetal 53. To a stirring solution of acetal **53** (81 mg, 0.30 mmol) and CH_2Cl_2 (7.5 mL) at −16 °C was added $SnCl_4$ (0.6 mL of a 1 M soln in CH_2Cl_2). The reaction was maintained at −16 °C for 1.5 h and then quenched by the addition of a 1:1 solution of Et_3N and CH_2Cl_2 (1.2 mL). The resulting mixture was allowed to warm to 23 °C and a 5% NaOH solution (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL). The combined organic phases were rinsed with brine (2 × 15 mL), dried (K_2CO_3), and concentrated. The residue was purified by preparative GC to afford 28 mg (34%) of a white solid, which contained no detectable impurities by capillary GC analysis: mp 71.5–73 °C; ^1H (500 MHz, $CDCl_3$) δ 4.37 (tt, J = 4.6, 12.0 Hz, 1 H, H-9), 3.86 (dt, J = 6.2, 11.8 Hz, 1 H, H-1), 2.09 (ddd, J = 1.5, 4.0, 12.5 Hz, 1 H, H-10), 1.96–2.06 (m, 2 H), 1.71–1.87 (m, 4 H), 1.49–1.64 (m, 4 H), 1.19 (s, 3 H, CH_3), 0.99 (ddd, J = 2.9, 10.2, 26.4 Hz, 1 H, H-4), 0.77 (ddt, J = 1.5, 6.5, 12.5 Hz, 1 H, H-3), 0.05 (s, 9 H, $SiMe_3$); ^{13}C (125 MHz, C_6D_6) δ 74.1, 73.9, 52.7, 48.4, 40.7, 38.3, 36.1, 33.3, 30.9, 25.6, 24.1, −2.9; ^{13}C (125 MHz, $CDCl_3$) δ 73.9 (C), 73.8 (CH), 51.9 (CH), 47.6 (CH_2), 39.9 (CH_2), 37.9 (CH_2), 35.7 (CH_2), 32.6 (CH_2), 30.4 (CH_3), 25.0 (CH_2), 23.6 (CH), −3.5 (CH_3); IR (film) 2950, 2919, 1250, 1162, 1075, 1056, 912, 881, 856, 837 cm^{-1}; MS (EI, 70 eV) m/e 276 (<1), 274.1510 (M, <1, 1274.1520 calcd for $C_{14}H_{27}OClSi$), 239 (1), 73 (100). Anal. Calcd for $C_{14}H_{27}OCSi$: C, 61.17; H, 9.90. Found: C, 61.26; H, 9.92.

BF_3-OEt_2-Promoted Cyclization of Vinyl Sulfide Acetal 60. Preparation of *cis*-8-Methyl-2-(2-phenylethyl)-4-(phenylthio)-3,6,7,8-tetrahydro-2*H*-oxocin (62). To a stirring solution of acetals **60** (248 mg, 0.669 mmol, a 1:1 mixture of diastereoisomers) and dry *tert*-butyl methyl ether (12 mL) at −78 °C was added dropwise neat BF_3-Et_2O (160 μL, 1.3 mmol). The reaction mixture was maintained at −78 °C (bath temperature) for 1 h and at −30 °C for 3 h. The reaction was quenched by adding 3 N NaOH (5 mL); the phases were separated. The aqueous phase was extracted with EtOAc (2 × 5 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (30:1 hexane–EtOAc) gave 179 mg (79%) of **62** as a clear colorless oil, which contained no impurities (<1% by capillary GC analysis): ^1H NMR (500 MHz, $CDCl_3$) δ 7.14–7.34 (m, 10 H), 5.98 (dd, J = 7.0, 10.3 Hz, 1 H, H-5), 3.50–3.58 (m, 1 H, H-8), 3.42 (dt, J = 3.0, 9.3 Hz, 1 H, H-2), 2.80–2.87 (app ddd, J = 5.2, 10.4, 14.2 Hz, 1 H, PhC*H*), 2.53–2.70 (m, 3 H), 2.10–2.06 (m, 2 H), 1.77–1.87 (m, 1 H), 1.66–1.74 (m, 1 H), 1.53–1.64 (m, 2 H), 1.17 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 134.7, 133.6, 133.3, 130.8, 129.0, 128.4, 128.3, 126.8, 125.6, 80.4, 75.0, 40.7, 38.6, 38.0, 32.8, 25.4, 21.9; IR (film) 3060, 3025, 2962, 2925, 2859, 1583, 1496, 1478, 1454, 1440, 1369, 1134, 1120, 1097, 1025, 741, 698 cm^{-1}; MS (CI) m/e 339 (MH), 229, 211, 205, 131, 117, 105, 99, 91, 85; MS (EI, 70 eV) m/e 338.1703 (338.1704 calcd for $C_{22}H_{26}OS$), 229.1582 (229.1592 calcd for $C_{16}H_{21}O$, M − PhS).

In four other cyclizations conducted identically employing 51–88 mg of acetals **60**, the yield of pure **62** ranged from 76 to 89%.

Preparation of 8-Methyl-2-(2-phenylethyl)-3,6,7,8-tetrahydro-2*H*-oxocin (63) from Sulfenyloxocene 62. To a suspension of 0.5 g of Raney nickel (Aldrich W-2) previously washed with water (5 × 3 mL), ethanol (5 × 3 mL), and acetone (5 × 3 mL) was added a solution of **62** (21 mg, 0.06 mmol) and dry acetone (1 mL). This solution was heated at reflux for 3 h and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, 4:1 hexane–CH_2Cl_2) to afford 13 mg (91%) of **63**, which was indistinguishable by ^1H NMR (500 MHz), ^{13}C NMR (125 MHz), and capillary GC coinjection from a sample prepared from silyloxocene **37**.

Preparation of 2-(2-Phenylethyl)-4-(phenylthio)-3,6,7,8-tetrahydro-2*H*-oxocin (64). To a stirring solution of acetal **61** (49 mg, 0.14 mmol) and dry *tert*-butyl methyl ether (3 mL) at −78 °C under an argon atmosphere was added neat BF_3-Et_2O (33 μL, 0.27 mmol) dropwise. The reaction was maintained at −78 °C for 1 h and at −30 °C for 3 h. Workup and purification as described for the preparation of **62** afforded 35 mg (78%) of **64** as a clear colorless oil, which was >96% pure by capillary GC analysis: ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.34 (m, 10 H), 5.95 (app dd, J = 7.2, 9.9 Hz, 1 H, H-5), 4.02 (ddd, J = 2.0, 5.4, 12.3 Hz, 1 H, H-8), 3.35–3.45 (m, 1 H, H-2), 3.30–3.38 (m, 1 H, H-8), 2.68–2.80 (1, 1 H), 2.46–2.68 (m, 3 H), 2.10 (app dd, J = 1.2, 14.4 Hz, 1 H, H-3), 1.90–2.25 (m, 2 H), 1.76–1.90 (m, 1 H), 1.55–1.66 (m, 1 H), 1.40–1.55 (m, 1 H). Irradiation of the signal at δ 4.02 (H-8) causes the partial collapse of the signal at δ 3.30–3.38 (H-8). Irradiation of the signal at δ 3.35–3.45 (H-2) causes the signal at δ 2.55 (H-3) to collapse to a doublet. ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 134.7, 133.6, 133.2, 130.9, 129.0, 128.5, 128.3, 126.8, 125.7, 80.7, 68.4, 39.8, 38.1, 32.4, 31.0, 25.0; IR (film) 3060, 3025, 2930, 2870, 1583, 1496, 1475, 1438, 1352, 1105, 1025, 742, 698 cm^{-1}; MS (CI) m/e 325 (MH), 215, 191, 117, 91, 71; MS (EI, 70 eV) m/e 324.1534 (M, 324.1548 calcd for $C_{12}H_{24}OS$).

$SnCl_4$-Promoted Cyclization of Acetal 65. Preparation of *cis*-4,8-Dimethyl-2-(2-phenylethyl)-3,6,7,8-tetrahydro-2*H*-oxocin (66) and 4-Methyl-8-methylene-2-(2-phenylethyl)oxocane (67). To a stirring solution of $SnCl_4$ (0.40 mL of a 1 M solution in CH_2Cl_2, 0.40 mmol) in CH_2Cl_2 (20 mL) at −60 °C was added a solution of acetals **65** (56.3 mg, 0.20 mmol) in CH_2Cl_2 (1 mL). The reaction was maintained at −60 °C for 1 h and then was quenched by the addition of Et_3N (0.4 mL). The resulting mixture was allowed to warm to −20 °C and a solution of 5% NaOH (5 mL) was added. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (5 mL), and the combined organic fractions were dried (K_2CO_3) and concentrated. The residue was separated by column chromatography (1:20 Et_2O–pentane) to afford the methyleneoxocane **67** (5.2 mg, 10%) and the Δ^4-oxocene **66** (20.3 mg, 41%) as clear colorless oils.

Oxocene 66: ^1H NMR (500 MHz, $CDCl_3$) δ 7.16–7.29 (m, 5 H, PhH), 5.38–5.42 (m, 1 H, =CH), 3.50–3.54 (m, 1 H, OC*H*Me), 3.26–3.30 (m, 1 H, H-2), 2.86–2.92 and 2.60–2.66 (m, 1 H each, $PhCH_2$), 2.45–2.51 (m, 1 H, H-3), 2.40–2.45 (m, 1 H, H-6), 1.89–1.94 (m, 1 H, H-6), 1.89–1.82 (m, 1 H, H-3), 1.79 (m, 3 H, Me), 1.46–1.71 (m, 4 H), 1.16 (d, J = 6.3 Hz, 3 H, CH*Me*). Irradiation of the C-2 methine hydrogen at δ 3.28 caused collapse of the multiplets at δ 2.48 and 1.85 to a clean AB pattern. ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 135.6, 128.4, 128.3, 125.6, 79.8, 75.0, 40.8, 39.0, 38.1, 32.9, 25.5, 24.3, 22.0, 14.1; IR (film) 3088, 3062, 3025, 2969, 2919, 2856, 1494, 1456, 1375, 1337, 1100, 750, 700 cm^{-1}; MS (EI, 70 eV) m/e 244.1811 (244.1827 calcd for $C_{17}H_{24}O$), 163 (5), 134 (20), 95 (48), 68 (100). ^1H NOE experiments: Irradiation of the signal at δ 3.50–3.54 (H-8) produced a 14% enhancement in the signal at δ 3.26–3.30 (H-2), while irradiation of the signal at δ 3.26–3.30 produced a 15% enhancement in the signal at δ 3.50–3.54.

Methyleneoxocane 67: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.30 (m, 5 H, PhH), 4.34 and 4.15 (s, 1 H each, $=CH_2$), 3.92 (m, 1 H, OCH), 2.83-2.89 and 2.65-2.71 (m, 1 H each, $PhCH_2$), 2.23-2.36 (m, 2 H, $=C(OR)CH_2$), 1.90-1.94 (m, 1 H), 1.60-1.80 (m, 6 H), 1.22-1.50 (m, 2 H), 0.91 (d, J = 6.9 Hz, 3 H, CH_3); MS (EI, 70 eV) m/e 244.1814 (M, 2, 244.187 calcd for $C_{17}H_{24}O$), 226 (3), 186 (8), 153 (6), 139 (12), 117 (21), 104 (53), 91 (100), 71 (34), 55 (17).

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Supplementary Material Available: Experimental procedures and characterization data for the preparation of alcohol and mixed-acetal cyclization precursors (21 pages). Ordering information is given on any current masthead page.

Formation of Δ^4-Oxocenes from Lewis Acid Promoted Cyclizations of 5-Hexenyl Acetals. Evidence for a Concerted Ene Cyclization Mechanism

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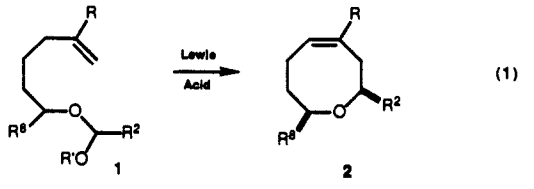
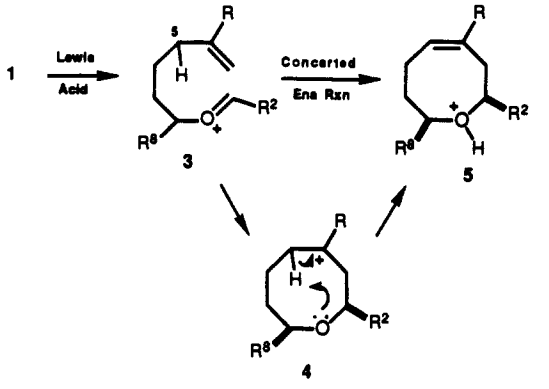
Abstract: Both the intermolecular (kinetic) and intramolecular (product) hydrogen-deuterium isotope effects were determined to be 1.65 for the formation of 2-methyl-4-(trimethylsilyl)-Δ^4-oxocene (**20**) from the $SnCl_4$-promoted cyclization of acetals **19**, **30**, and **31** (eq 6). In other experiments silyl acetal **32** was found to cyclize in the presence of $SnCl_4$ to form the silyl-Δ^4-oxocene **34** and the alkylideneoxepane **35** in 2:1 ratio (eq 7). Both results provide strong evidence that the formation of 4-(trimethylsilyl)-Δ^4-oxocenes from $SnCl_4$-promoted cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals takes place by a concerted intramolecular ene mechanism. Also reported are $SnCl_4$-promoted exchange reactions of formaldehyde- and aldehyde-derived acetals, which occur readily at -10 to 0 °C and -70 °C, respectively (eqs 2 and 3).

In the preceding paper we detailed our exploratory investigations of the preparation of Δ^4-oxocenes from the Lewis acid promoted cyclization of 5-hexenyl acetals (eq 1).[2] High regio- and stereoselectivity are hallmarks of this direct route to unsaturated eight-membered-ring ethers. In all of the cyclization reactions that we have studied, only the Δ^4-oxocene regioisomer is produced. This regiochemical outcome would be expected if the transformation of **1** → **2** occurred by a concerted intramolecular Alder ene reaction (Scheme I).[3,4] Alternatively, as we discussed briefly in the preceding paper, a stepwise process (**3** → **4** → **5**) could also afford the Δ^4 isomer regioselectively as a result of transannular deprotonation of the 4-oxocanyl cation **4**.[5-8]

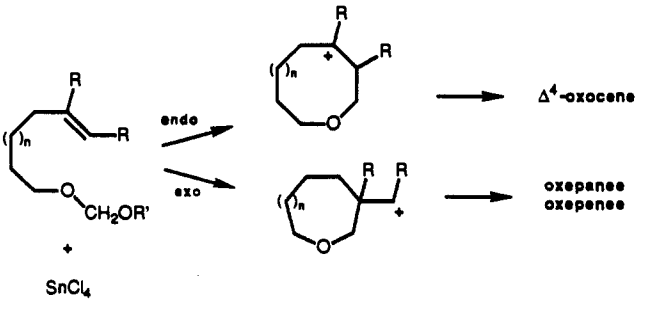


(1)

Scheme I



Scheme II



In this paper we report our investigations of the timing of C-C bond formation and C-H bond cleavage in the Lewis acid pro-

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(2) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) For reviews of the ene reaction, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. Whitesell, J. K. *Ibid.* **1985**, *18*, 280.

(4) For reviews of intramolecular ene reactions, see: (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (b) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*: Springer-Verlag: Berlin, 1984.

(5) Homoallylic alcohols are also formed predominantly in bimolecular Prins reactions.[6] This selectivity has been ascribed to a concerted ene mechanism[3] or rationalized by oxygen participation in removal of the distal β-hydrogen of a carbenium ion intermediate.

(6) For reviews, see: Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *661*. Roberts, C. W. In *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, 1964; Vol. 2, Part 2, p 1175.

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