**Methyleneoxocane 67**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 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).

**Acknowledgment.** Support of this research by NSF Grant CHE-86-18451 is gratefully acknowledged. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

**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 $\Delta^4$-Oxocenes from Lewis Acid Promoted Cyclizations of 5-Hexenyl Acetals. Evidence for a Concerted Ene Cyclization Mechanism

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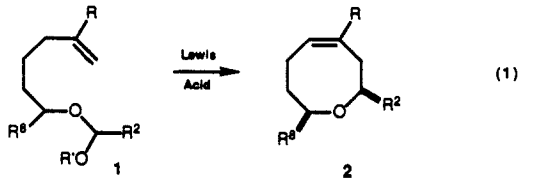
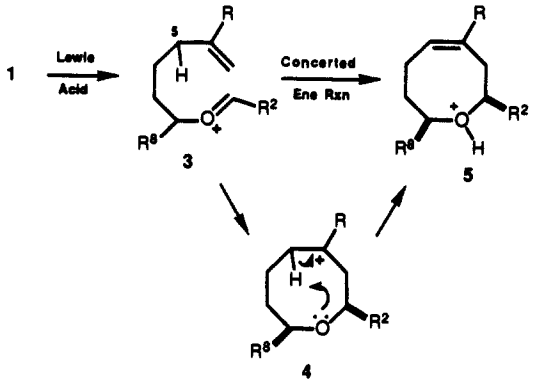
**Abstract:** Both the intermolecular (kinetic) and intramolecular (product) hydrogen-deuterium isotope effects were determined to be 1.65 for the formation of 2-methyl-4-(trimethylsilyl)-$\Delta^4$-oxocene (**20**) from the $SnCl_4$-promoted cyclization of acetals **19**, **30**, and **31** (eq 6). In other experiments silyl acetal **32** was found to cyclize in the presence of $SnCl_4$ to form the silyl-$\Delta^4$-oxocene **34** and the alkylideneoxepane **35** in 2:1 ratio (eq 7). Both results provide strong evidence that the formation of 4-(trimethylsilyl)-$\Delta^4$-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 $\Delta^4$-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 $\Delta^4$-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 $\Delta^4$ isomer regioselectively as a result of transannular deprotonation of the 4-oxocanyl cation **4**.[5-8]

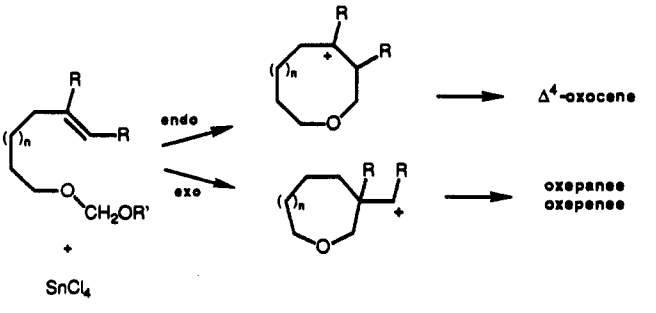


(1)

**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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(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 $\beta$-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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Table I. $SnCl_4$-Promoted Exchange of Formaldehyde Acetals **6** and **7**[a]

| time, min | acetal rec,[b] % | acetal composition,[b,c] % | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| 0 | (100) | 50 | 50 | | | | | |
| 5 | 49 | 17 | 70 | 10 | 1 | | 2 | |
| 30 | 44 | 15 | 57 | 8 | 3 | 2 | 5 | 10 |
| 120 | 34 | 11 | 32 | 7 | 8 | 7 | 12 | 23 |

[a] In $CH_2Cl_2$ at 0 °C; 1 equiv of $SnCl_4$, 0.05 M starting concentration of each acetal. [b] By capillary GC analysis using decane as an internal standard. Mean values from two experiments. [c] Products were identified by independent synthesis.

moted transformation of 5-hexenyl acetals to $\Delta^4$-oxocenes. Two experimental probes were employed: (1) Kinetic and product hydrogen–deuterium isotope effects were compared. Since first introduced by Stephenson,[10] this comparison has proven to be a powerful tool for establishing concert (or lack thereof) in ene reactions,[11] including those of aldehyde and ketone enophiles.[12-14] Nonequivalence of these isotope effects provides strong evidence for a stepwise process.[10-14] (2) The partitioning of 5-alkenyl acetals between exocyclization to form seven-membered-ring products and endocyclization to form eight-membered-ring products was explored (Scheme II). Since both modes of cyclization are devoid of stereoelectronic constraints,[15] the ring size of the products produced should reflect the electronic bias of the alkene if cyclization occurs in a stepwise fashion by way of cyclic carbenium ion intermediates.

## Results and Discussion

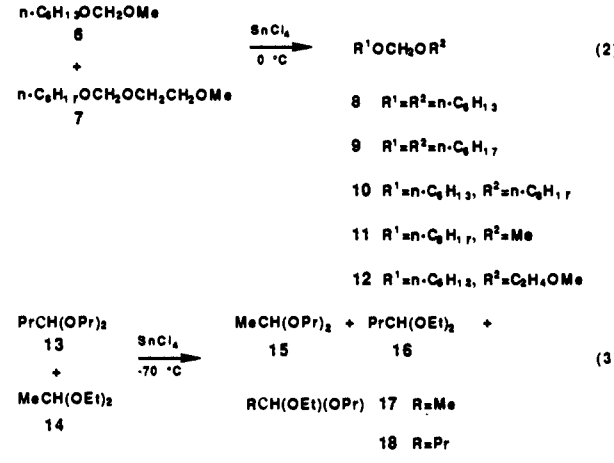
The precise mechanism of activation of an acetal by a Lewis acid could impact the kinetic isotope experiments we planned. Recent NMR studies by Denmark and co-workers have shown that the reaction of acetals with $SnCl_4$ at −78 °C does not form detectable amounts of an oxocarbenium (oxonium) ion, but rather two hexacoordinate complexes, $R'CH(OR)_2SnCl_4$ and $[R'CH(OR)_2]_2SnCl_4$, depending upon stoichiometry.[16,17] There are two limiting mechanisms for the Lewis acid promoted reaction of a nucleophile with an acetal: an $S_N1$ reaction proceeding via an oxocarbenium ion intermediate (e.g., **1** → **3** → **4** in Scheme I) or an $S_N2$ pathway.[17,18] Mixed "aldehyde" acetals **1** ($R^2$ = alkyl) undergo $SnCl_4$-promoted cyclization at temperatures 30–60 °C below that required for the corresponding "formaldehyde" acetals (**1**, $R^2$ = H).[2] This observation argues strongly against an $S_N2$ pathway for the formation of $\Delta^4$-oxocenes from 5-hexenyl acetals upon activation with this Lewis acid. The observed trends in acetal reactivity suggest (at least in the case of mixed "formaldehyde" acetals) that ionization to an oxocarbenium ion might be rate-limiting.[18b] Clearly, any comparison of kinetic and product hydrogen–deuterium isotope effects could shed light on the mechanism of the ene cyclization step only if oxocarbenium ion formation were *not* rate-limiting.

Table II. $SnCl_4$-Promoted Exchange of Acetals **13** and **14**[a]

| time, min | acetal rec,[b] % | acetal composition,[b,c] % | | | | | |
|---|---|---|---|---|---|---|---|
| | | **13** | **14** | **15** | **16** | **17** | **18** |
| 0 | (100) | 52 | 48 | | | | |
| 5 | 81 | 13 | 12 | 15 | 11 | 24 | 23 |
| 60 | 86 | 12 | 12 | 15 | 11 | 26 | 24 |
| 120 | 72 | 8 | 13 | 16 | 11 | 34 | 18 |

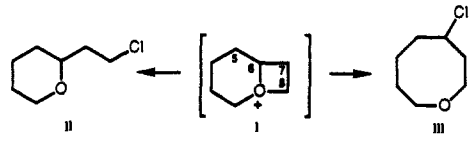
[a] In $CH_2Cl_2$ at −70 °C; 1 equiv of $SnCl_4$, 0.05 M starting concentration of each acetal. [b] By capillary GC analysis using decane as an internal standard. [c] Products **15** and **16** were identified by independent synthesis, while **17** and **18** were characterized by GC–MS analysis.

**Acetal Exchange.** To pursue the facility with which acetals are activated for nucleophilic attack by $SnCl_4$, we have examined the $SnCl_4$-promoted exchange of alkoxy substituents in representative formaldehyde and aldehyde acetals. Although exchange reactions of alcohols and acetals under protic conditions have received considerable study, Lewis acid promoted exchange reactions of acetals, to the best of our knowledge, have been little investigated.[19,20] The reactions we have examined are shown in eqs 2 and 3, and the data obtained are summarized in Tables I




(7) First suggested by Yang: Yang, N. C.; Yang, D. H.; Ross, C. B. *J. Am. Chem. Soc.* **1959**, *81*, 133.

(8) An alternate rationale would invoke a 1-oxabicyclo[4.2.0]octyl cation i (formed directly from **3** or from **4**) as the immediate precursor of the $\Delta^4$-oxocene product. Regioselectivity in this scenario would derive from the much better antarafacial orientation (with respect to the $C_6$–O $\sigma$ bond) of the equatorial cyclohexyl hydrogen at C-5 than either of the cyclobutyl hydrogens at C-7. Evidence against the intermediacy of i was obtained in the $SnCl_4$-promoted cyclization of the MEM ether of 5-hexen-1-ol. This reaction gave, under kinetic conditions, a mixture of 4-chlorooxocane (iii) and $\Delta^4$-oxocene; 2-(2-chloroethyl)tetrahydropyran (ii) was not formed.[2] The absence of ii would not be expected if i were present, since under kinetic acetolysis conditions i experiences opening by acetate anion 3 times faster at C-6.[9]




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

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(11) Dolbier, W. R., Jr. In *Isotopes in Molecular Rearrangements*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1975; Vol. 1, pp 51–57. Beak, P.; Berger, K. *J. Am. Chem. Soc.* **1980**, *102*, 3848. Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226. Cheng, C.-C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910. Starflinger, W.; Kresze, G.; Huss, K. *J. Org. Chem.* **1986**, *51*, 37. Orfanopoulos, M.; Foote, C. S.; Smonou, I. *Tetrahedron Lett.* **1987**, *28*, 15. Orfanopoulos, M.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6583.

(12) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200.

(13) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

(14) Song, Z.; Chrisope, D. R.; Beak, P. *J. Org. Chem.* **1987**, *52*, 3938.

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

(16) For recent investigations of the structure of Lewis acid acetal complexes, see: (a) Denmark, S. E. In *Selectivities in Lewis Acid-Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989; Chapter 13. (b) Denmark, S. R.; Willson, T. M.; Almstead, N. G., submitted for publication.

(17) For an insightful study of the $S_N1/S_N2$ question in Lewis acid promoted allylsilane–acetal cyclizations, see: Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

(18) (a) Mechanisms on the $S_N2$ extreme have been proposed to rationalize the stereochemical outcome of the addition of nucleophiles to chiral acetals; see, inter alia: Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755. Reference 16b. (b) An $S_N1$ mechanism has been suggested for the trimethylsilyl triflate catalyzed reaction of enol silyl ethers and acetals: Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259.

(19) Denmark has reported that equilibration of the 1:1 $SnCl_4$ complex of *trans*-4,5-dimethyl-1,3-dioxolanes with an oxocarbenium ion is rapid on the NMR time scale at −78 °C: Denmark, S. R. Lecture presented at the NATO Conference on Selectivity in Lewis Acid-Promoted Reactions, Glyfada-Athens, Greece, October 2–7, 1988.

(20) (a) For an earlier study of acetal exchange, see: Gazizova, L. B.; Imashev, U. B.; Musavirov, R. S.; Kantor, E. A.; Zlotskii, S. S.; Kuzmichev, A. A.; Rakhmankulov, D. L. *Zh. Org. Khim.* **1981**, *17*, 275. (b) For a recent study of the relative reactivity of acetals in Lewis acid catalyzed reactions, see: von der Brüggen, U.; Lammers, R.; Mayr, H. *J. Org. Chem.* **1988**, *53*, 2920.

**Table III.** Measured Kinetic (Intermolecular) and Product (Intramolecular) Isotope Effects for the Formation of Oxocene **20**[a]

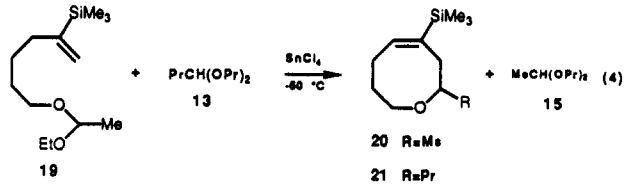
| temp °C | time, min | $SnCl_4$, equiv | acetal concn, M | conv,[b] % | $k_H/k_D$[c] inter | intra |
|---|---|---|---|---|---|---|
| −20 | 60 | 0.4 | 0.01 | 48 | | 1.64 ± 0.05 |
| −65 | 5 | 2.0 | 0.04 | 67 | | 1.64 ± 0.05 |
| −20 | 60 | 0.4 | 0.01 | 48 | 1.69 ± 0.10 | |
| −50 | 10 | 0.2 | 0.02 | 33 | 1.61 ± 0.06 | |

[a] In $CH_2Cl_2$. [b] Determined from the yield of isolated **20**, using 33% as the yield for complete conversion; see ref 2. [c] The mean ±1$\sigma$ from two to three experiments.

and II. Five of the eight possible products of eq 2 were quantified, while all four possible acetal exchange products of eq 3 were detected and quantified. The three missing formaldehyde acetals ($MeOCH_2OMe$, $MeOCH_2OCH_2CH_2OMe$, and $MeOCH_2CH_2OCH_2OCH_2CH_2OMe$) are $H_2O$ soluble and would have been "lost" in the aqueous layer prior to GLC analysis.

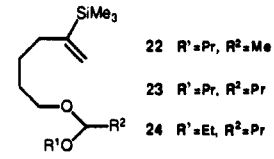
Acetals **6** and **7** underwent exchange only when the temperature was raised to −10 to 0 °C, while exchange of acetals **13** and **14** was rapid at −70 °C. For the aldehyde-derived acetals, the equilibrium mixture of the six possible acetal products was formed within 5 min at −70 °C (Table II). In this case mass recovery was high (80–85%) and the symmetrical (**13–16**) and unsymmetrical (**17** and **18**) acetals were present in approximately their expected statistical ratios (1:2). Although the formaldehyde acetal exchange results are less significant, because of the lower mass balances obtained, the data in Table I demonstrate that a methoxymethyl (MOM) ether undergoes $SnCl_4$-promoted exchange somewhat more rapidly than a methoxyethoxymethyl (MEM) ether. The close similarity between the conditions of the $SnCl_4$-promoted alkoxy-exchange reaction of formaldehyde acetals **6** and **7** and those of the cyclization of MOM or MEM ethers of 5-hexen-1-ols[21] suggests that oxocarbenium ion formation is rate-limiting in the cyclizations of formaldehyde acetals to yield $\Delta^4$-oxocenes.[22]

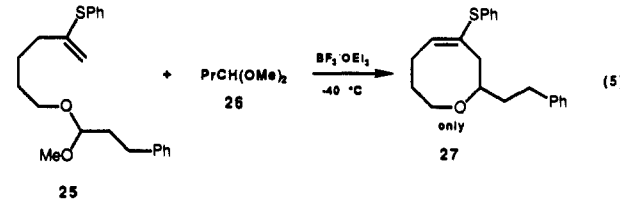
Comparison of the data summarized in Table II with the cyclization reactions of related aldehyde-derived acetals reported in ref 2 suggests that acetal activation might be more rapid than the cyclization of mixed silyl acetals such as **19**. Direct evidence to this end was obtained by carrying out the $SnCl_4$-promoted cyclization of **19** (0.02 M in $CH_2Cl_2$) in the presence of 1 equiv of acetal **13** (eq 4). This reaction afforded, as major products,




the $\Delta^4$-oxocenes **20** and **21** and 1,1-dipropoxyethane (**15**). Also detected in smaller amounts were acetals **17** and **18** and, at short reaction times (5 min), the 5-(trimethylsilyl)-5-hexenyl acetals **22–24**. The structures of **21** and **24** were confirmed by independent synthesis, while acetals **22** and **23** were characterized by combined GLC–MS analysis. When the reaction of eq 4 was quenched after 5 min at −70 °C, oxocenes **20** and **21** were present in a ratio of 3.5:1; after 10 min this ratio was 1.7:1, and after 30 min it was 1.6:1. These results demonstrate that acetal exchange and cyclization of a 5-(trimethylsilyl)-5-hexenyl acetal take place at roughly comparable rates.

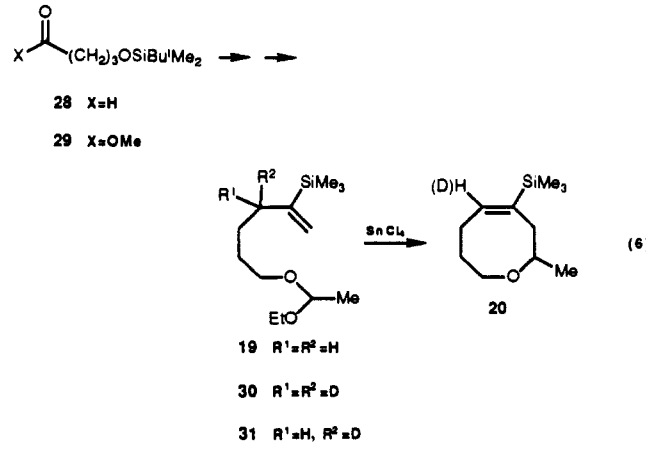
A related experiment with cyclization substrates that contain the more nucleophilic vinyl sulfide moiety[2] demonstrated that $BF_3{\cdot}OEt_2$-promoted cyclization of **25** to form the 4-(thiophenyl)-$\Delta^4$-oxocene **27** occurs faster than acetal exchange (eq 5). Thus, when a 1:1 mixture of acetals **25** and **26** was treated with $BF_3{\cdot}OEt_2$ at −40 °C and the reaction mixture analyzed by GLC–MS, only oxocene **27** was detected.




**Kinetic and Product Hydrogen–Deuterium Isotope Effect Experiments.** The results of the acetal-exchange experiments had several implications for our planned kinetic isotope effect (KIE) experiments: (1) To ensure that the cyclization step was at least partially rate-limiting, we would have to employ an aldehyde acetal initiator and the 5-(trimethylsilyl)-5-hexenyl cyclization terminator. (2) Since the hydrogens at C-5 of the 4-oxocanyl cation intermediate **4** would be distereotopic if $R^2$ and $R^8 \neq H$, the two C-5 hydrogens would not strictly compete in an intramolecular competition experiment. If diastereoselectivity were high in loss of the C-5 hydrogen (or deuterium), the measured KIE from intramolecular competition could be equal to unity even in a stepwise process. (3) The magnitude of the observed KIE would be attenuated by the extent to which oxocarbenium ion formation were rate-limiting.[23]

The precursors of the deuterium-labeled acetals **30** and **31** were prepared from aldehyde **28** or ester **29** by reduction with $LiAlD_4$. The isotopic purity of **30** (98% $d_2$) and **31** (98% $d_1$) was determined by $^1H$ NMR integration; the former measurement used the $^{13}C$ satellite of the OMe groups, of addeed *p*-methoxyanisole as an internal reference.




The results of conventional competition isotope effect measurements are summarized in Table III. The product (intramolecular) and kinetic (intermolecular) isotope effects were found to be identical within our experimental precision. The value of 1.65 we observe is larger than what would be expected from secondary effects,[11] yet smaller than isotope effects measured for the thermal ene reaction of oxomalonate with allylbenzene [$(k_H/k_D)_{inter} = (k_H/k_D)_{intra} = 3.31$][12] or observed by intramolecular competition in the $Me_2AlCl$-promoted reaction of various deuterated 2,3-dimethyl-2-butenes with formaldehyde.[13] On the other

(21) Typically conducted at −10 °C for several hours, MOM ethers cyclize somewhat faster than comparable MEM ethers.[2]

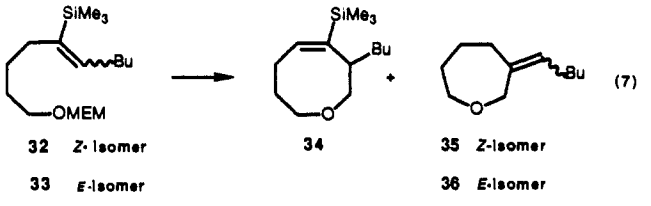
(22) Consistent with this conclusion is the fact that $SnCl_4$-promoted cyclizations (−10 °C) of mixtures of $CH_2{=}C(SiMe_3)CH_2(CH_2)_3OCH_2OCH_2CH_2OMe$ and $CH_2{=}C(SiMe_3)CD_2(CH_2)_3OCH_2OCH_2CH_2OMe$ showed no detectable hydrogen–deuterium isotope effect.

(23) For example, if $k_H/k_D = 2.5$ and the initially formed oxocarbenium ion is present in low steady- state concentration and is partitioned equally between conversion of $\Delta^4$-oxocene and reversal to the starting acetal, the observed $k_H/k_D$ would be 1.75.

hand, the KIEs we observe are significantly larger than the very small kinetic and product isotope effects, ($k_H/k_D \cong 1.1$, measured for the $SnCl_4$-promoted reaction of oxomalonate with allylbenzene.[12]

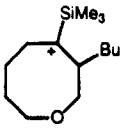
The kinetic (intermolecular) isotope effect of 1.65 that we observe rules out a mechanism in which a 4-oxocanyl cation intermediate is formed irreversibly in the rate-limiting step. The equivalence of the observed product and kinetic hydrogen–deuterium isotope effects provides clear evidence that the formation of the $\Delta^4$-oxocene occurs by a (concerted) process in which C–H bond cleavage accompanies C–C bond formation. The small magnitude of the observed $k_H/k_D$ could result from oxocarbenium ion formation being partially rate-limiting.[23] Alternatively, the low hydrogen–deuterium isotope effect could arise from the nature of the intramolecular ene transition state.[24] The concerted conversion of **3** → **5** would take place via a bicyclo[3.3.1]nonyl transition state (see **39**) that would have a more acute C–H–O bond angle than that of related bimolecular ene reactions.[25] Low primary isotope effects have been reported for acute angle proton-transfer reactions.[26,27] We would also note that reversible formation of a complex[28] between the oxocarbenium ion and the vinylsilane prior to a concerted cycloaddition could also reduce the magnitude of the observed ($k_H/k_D$) ratio, as has recently been stressed by Beak.[14]

**Competition between Forming Seven- and Eight-Membered Cyclic Ethers.** The stereoisomeric 5-(trimethylsilyl)-5-decenyl acetals **32** and **33** underwent cyclization at −15 °C when treated with 2 equiv of $SnCl_4$ to give mixtures of the $\Delta^4$-oxocene **34** and the stereoisomeric 3-pentylideneoxepanes **35** and **36** (eq 7). The (*E*)-vinylsilane acetal **32** afforded oxocene **34** as the major product (**34**:**35** = 2:1 by GLC analysis), while the *Z* stereoisomer afforded the (*E*)-pentylideneoxepane **36** with high selectivity (**36**:**34** = 17:1 by GLC analysis).

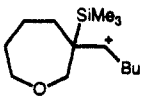



**32** *Z*-Isomer **33** *E*-Isomer **34** **35** *Z*-Isomer **36** *E*-Isomer (7)

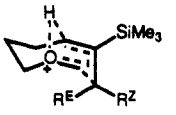
A variety of electrophilic reactions of trisubstituted vinylsilanes proceed exclusively by bonding of the electrophile to the vinylic carbon bearing the silicon substituent,[29,30] a result that reflects the greater stability of a $\beta$-silyl secondary than an $\alpha$-silyl tertiary carbenium ion. Thus, preponderant formation of oxocene **34** from cyclization of **32** is a striking result. Since eight-membered rings are typically formed orders of magnitude more slowly than comparable seven-membered rings[31] and neither mode of cyclization of **32** has any apparent stereoelectronic constraints, the predominant formation of oxocene **34** is inconsistent with the competitive formation of carbenium ions **37** and **38** from **32**. However, this result could be accommodated in a mechanistic scheme wherein **34** is formed by a concerted ene reaction, which has a slightly lower energy barrier than competitive Prins cyclization of **32** to form the $\beta$-silyl oxepanyl cation **38**. That the *E* stereoisomer **33** cyclizes to afford primarily oxepane **36** is readily explicable in this




**37**




**38**




**39**

mechanistic scenario, since the butyl group of **33** (which is cis related to the tethered oxocarbenium ion) would experience serious transannular interaction in an intramolecular ene transition state (e.g., **39**).[32,33]

## Conclusion

Two lines of evidence, (a) the equivalence of product and kinetic hydrogen–deuterium isotope effects, and (b) the absence of correlation of cyclization mode (endocyclic or exocyclic) with the stability of potential cyclic carbenium ion intermediates, are fully consistent with the formation of 4-(trimethylsilyl)-$\Delta^4$-oxocenes from 5-(trimethylsilyl)-5-alkenyl acetals occurring by a concerted intramolecular ene reaction.

## Experimental Section[34]

**GLC Analyses.** A Hewlett-Packard 5790 chromatograph equipped with a 25-m, SP-2100 fused-silica capillary column and flame ionization detector was employed. Response factors were determined by triplicate analysis of two different molar ratios of decane and the component. The response factors for **17** and **18** were interpolated from the values for the symmetrical acetals **13** and **14**. Response factors for **9** and **10** were less accurate than others, since samples of these acetals (isolated by preparative GLC) contained 10% of other impurities.

**$SnCl_4$-Promoted Exchange of Acetals 13 and 14.** To a stirring solution of $SnCl_4$ (2.5 mL of a 1 M solution in $CH_2Cl_2$, 2.5 mmol) and $CH_2Cl_2$ (17.5 mL) maintained at −68 °C (internal temperature) was added a solution of **13** (215 mg, 1.24 mmol), **14** (145 mg, 1.23 mmol), decane (177 mg, 1.23 mmol), and $CH_2Cl_2$ (5 mL). Aliquots (1 mL) were removed at 5 min, 1 h, and 2 h in a dry ice cooled syringe. Each aliquot was injected into a dry ice cooled vial containing excess $Et_3N$. This solution was allowed to stir for 15 min and then saturated aqueous $NaHCO_3$ (1 mL) was injected into the vial. The organic layer was then analyzed by capillary GC. Results are presented in Table II. Other exchange experiments were conducted in an identical fashion.

**1-Deuterio-4-[[(1,1-dimethyl)ethyldimethylsilyl]oxy]-1-butanol (40).** To a mixture of $LiAlD_4$ (Aldrich 98 atom % d, 920 mg, 22 mmol) in ether (30 mL) at 0 °C was added to a solution of **28**[35] (2.0 g, 10 mmol freshly prepared by ozonolysis of the *tert*-butyldimethylsilyl ether of 5-penten-1-ol) and ether (20 mL). The reaction was heated at reflux for 3 h and then maintained at 23 °C for an additional 18 h. The reaction was quenched at 0 °C by the sequential dropwise addition of $H_2O$ (1 mL), 15% NaOH (1 mL), and $H_2O$ (3 mL). The resulting mixture was allowed to stir for 1 h, and the precipitated aluminum salts were removed by filtration and rinsed with ether. The combined filtrates were rinsed with brine, dried ($K_2CO_3$), and concentrated to afford alcohol **40** (1.5 g, 76%) as a clear colorless oil, which was used without further purification for the next reaction: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.68 (m, 3 H, $CH_2O$), 2.54 (d, $J$ = 12 Hz, 1 H, OH), 1.65 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 63.6, 62.6 (t), 30.4, 30.1, 26.1, 18.5, 5.2; IR (film) 3360 (br), 2955, 2896, 2887, 1473, 1075, 1006, 814, 661 $cm^{-1}$; MS (CI) *m/e* 206 (MH).

**4-Deuterio-1-[[(1,1-dimethyl)ethyldimethylsilyl]oxy]-4-iodobutane (41).** A 1.5-g (7.3-mmol) sample of **40** was converted to the mesylate derivative in conventional fashion[36] and this intermediate was transformed to the corresponding iodide by heating at 50 °C with NaI (5 g, 30 mmol), $NaHCO_3$ (3 g, 30 mmol), and acetone (60 mL). The resulting colorless mixture was allowed to cool to 23 °C and was diluted with $CH_2Cl_2$ (50 mL). This mixture was washed with $H_2O$, 20% aqueous $Na_2SO_3$, and brine, and the organic extracts were dried ($K_2CO_3$) and concentrated. The residue was purified by column chromatography (silica gel, 3:1 hexane–ethyl acetate) to afford 900 mg (50% from **40**) of pure **41** as a

(24) A type III intramolecular ene reaction using the systemization of Oppolzer.[4a]

(25) A C–H–O angle of 154° is calculated for the concerted ene reaction of formaldehyde with propene: Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

(26) Liotta, D.; Saindane, M.; Waykole, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667.

(27) For a theoretical treatment of nonlinear proton transfers and isotope effects, see: More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 785.

(28) For a discussion of some of the possible intermediates, see: Reference 13.

(29) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

(30) Fleming, I.; Dunogues, J. *Org. React.* **1989**, *37*, 57.

(31) Sicher, J. *Prog. Stereochem.* **1982**, *3*, 202. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(32) We have discussed in more detail elsewhere the general observation that terminal substituents that are cis to the tether of a nascent ring disfavor endocyclic cyclizations.[33]

(33) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59.

(34) General experimental details are detailed in the preceding paper in this issue.

(35) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 731.

(36) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

clear colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 3.65 (t, $J$ = 6.5 Hz, 2 H, $CH_2O$(TBS)), 3.24 (t, $J$ = 6.2 Hz, 1 H, CHDI), 1.92 (m, 2 H), 3.70 (m, 2 H), 1.64 (m, 2 H), 0.90 (s, 9 H), 0.08 (s, 6 H); IR (film) 2955, 2930, 2894, 2886, 1472, 1256, 1072, 837 cm$^{-1}$; MS (CI) $m/e$ 316 (MH).

**4-(Deuterio-1-(1-ethoxyethoxy)-5-(trimethylsilyl)-5-hexene (31)** was prepared from **41** following the procedure employed[2] to prepare the unlabeled analogue: MS (CI) $m/e$ 246 (MH); MS (EI, 26 eV) $m/e$ 200.1546 (200.1581 calcd for $C_{11}H_{22}DOSi$). The extent of deuteration (98%) was determined by integration of the signal for the allylic hydrogens at $\delta$ 2.1 relative to the signal for the acetal methine hydrogen at $\delta$ 4.7.

**4,4-Dideuterio-1-(1-ethoxyethoxy)-5-(trimethylsilyl)-5-hexene (30).** 1,1-Dideuterio-4-(1-ethoxyethoxy)butan-1-ol was prepared by $LiAlD_4$ reduction of methyl 4-(methoxymethoxy)butanoate, using the same general procedure employed to prepare **40**.[37] This intermediate was converted to **30** along the general lines employed to prepare the unlabeled analogue.[2,37] Acetal **30** was homogeneous by capillary GC analysis and showed the following spectral properties: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.56 (d, $J$ = 3.0 Hz, 1 H) and 5.32 (d, $J$ = 2.9 Hz, 1 H, C(TMS)=$CH_2$), 4.62 (s, 2 H, $OCH_2O$), 3.53 (t, $J$ = 6.4 Hz, 2 H, $CH_2O$), 3.36 (s, 3 H, $OCH_3$), 1.63–1.56 (m, 2 H), 1.50–1.45 (m, 2 H), 0.08 (s, 9 H, $SiMe_3$); $^{13}$C (125 MHz, $CDCl_3$) $\delta$ 152.0, 124.0, 96.4, 67.6, 55.1, 35.4 (m), 29.5, 25.5, −1.4; IR (film) 3050, 2956, 2900, 2850, 1744, 1438, 1250, 848 cm$^{-1}$; MS (CI) $m/e$ 219 (MH); MS (EI, 26 eV) $m/e$ 201.1645 (201.1644 calcd for $C_{11}H_{21}D_2OSi$). The deuterium content of **30** (1.8% residual $^1$H) was determined by integrating the residual signals for the allylic methylene hydrogens ($\delta$ 2.14) of **30** against a $^{13}$C satellite peak of the methoxy group of added 1,4-dimethoxybenzene.

**Determination of Kinetic Isotope Effects.** Acetal **31** (or a 1:1 mixture of acetals **19** and **30**) was treated with $SnCl_4$ under the conditions described in Table III. The oxocene product **20** was isolated and the deuterium content at C-5 determined by triplicate integration of the C-5 vinylic hydrogen ($\delta$ 6.0) vs the most downfield C-8 hydrogen ($\delta$ 3.9). Isotope effects were then calculated: $(k_H/k_D)_{intra}$ = [(integral C-8 H) − (integral C-5H)]/(integral C-5 H); $(k_H/k_D)_{inter}$ = (integral C-5H)/[integral C-8H − (integral C-5H)]. A typical procedure is summarized below.

**Cyclization of 31 at −20 °C with 0.4 Equivalent of $SnCl_4$.** To a stirring solution of $SnCl_4$ (0.08 mL of a 1 M solution in $CH_2Cl_2$, 0.08 mmol) and $CH_2Cl_2$ (18 mL) maintained at −20 °C (internal temperature) was added to a solution of **31** (35 mg, 0.14 mmol) and $CH_2Cl_2$ (2 mL). The reaction was maintained at −20 °C for 1 h and then quenched at −20 °C by the addition of $Et_3N$ (0.1 mL) and then a solution of 5% NaOH (5 mL). The organic layer was washed with brine (20 mL), dried ($K_2CO_3$), and concentrated. The resulting oil was purified by preparative GC[38] (column temperature 80 °C) to provide oxocene **20**.

**General Procedure for $SnCl_4$-Promoted Cyclizations. Preparation of (*Z*)-3-Butylideneoxepane (35) and (*E*)-3-Butyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (34) from (*Z*)-Vinylsilane Acetal 32.** A mixture of vinylsilane acetal **32** (88 mg, 0.28 mmol) and dry $CH_2Cl_2$ (2.8 mL) was added dropwise at −25 °C (bath temperature) over a 1-h period to a solution of $SnCl_4$ (freshly distilled, 70 mL, 0.6 mmol) and dry $CH_2Cl_2$ (2.8 mL). After 36 h at −15 °C, the reaction was quenched by pouring into excess 1 M NaOH solution. The organic layer was separated, the aqueous layer was extracted with pentane, and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (silica gel, 99:1 hexane–ether) gave 39 mg (66%) of a clear, colorless oil, which was shown by capillary GLC and $^1$H NMR analysis to be a 2:1 mixture of **34** and **35**. A pure sample of each compound was prepared by preparative GLC.[38]

**Oxepane 35**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.22 (t, $J$ = 7.0 Hz, 1 H, C=CH), 4.26 (br s, 2 H, $OCH_2C$=C), 3.60 (m, 2 H, $CH_2O$), 2.23 (m, 2 H, C=$CCH_2$), 1.89 (m, 2 H, C=$CCH_2$), 1.59 (m, 4 H), 1.29 (m, 4 H), 0.87 (t, $J$ = 7.0 Hz, 3 H, Me); IR ($CHCl_3$) 2820, 1450, 1070 cm$^{-1}$; MS (EI, 20 eV) $m/e$ 168 (5), 111 (22), 59 (100), 43 (99); HRMS (20 eV) $m/e$ 168.1513 (168.1514 calcd for $C_{11}H_{20}O$).

**Oxocene 34**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.12 (t, $J$ = 8.0 Hz, 1 H, C=CH), 3.86 (dt, $J$ = 4.0, 12.2 Hz, 1 H, $CH_2O$) 3.45 (m, 2 H, $CH_2O$), 3.34 (m, 1 H, $CH_2O$), 2.69 (app $J$ = 6.8 Hz, 1 H, C=CCH), 2.26 (m, 2 H), 1.58 (m, 4 H), 1.27 (m, 4 H), 0.87 (t, $J$ = 6.7 Hz, 3 H, Me); IR ($CHCl_3$) 2920, 1590, 1457, 1243, 1112, 830 cm$^{-1}$; MS (EI, 20 eV) $m/e$ 241 (MH, 1), 240 (M, 6), 225 (9), 183 (2), 73 (67), 59 (100), 43 (69); HRMS $m/e$ 240.1901 (240.1909 calcd for $C_{14}H_{28}OSi$), 225.1677 (225.1674 calcd for $C_{13}H_{25}OSi$, M − Me).

**Preparation of (*E*)-3-Butylideneoxepane (36) and (*E*)-3-Butyl-4-(trimethylsilyl)-3,6,7,8-tetrahydro-2*H*-oxocin (34) from (*E*)-Vinylsilane Acetal 33.** Vinylsilane **33** (102 mg, 0.322 mmol) was treated with $SnCl_4$ (80 mL, 0.70 mmol) at −15 °C for 72 h as described for the cyclization of **32**. Purification of the crude product by flash chromatography (24:1 hexane–ether) gave 36 mg (63%) of a clear, colorless oil, which capillary GLC and $^1$H NMR analysis showed to be a 17:1:2 mixture of **36**, **34**, and an unidentified material. An analytical sample of **36** was obtained by preparative GLC:[38] $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.26 (t, $J$ = 7.0 Hz, 1 H, C=CH), 4.10 (s, 2 H, $OCH_2C$=C), 3.78 (m, 2 H, $CH_2O$), 3.72 (m, 2 H, $CH_2O$), 2.28 (m, 2 H, C=$CCH_2$), 2.01 (m, 2 H, C=$CCH_2$), 1.61 (m, 2 H), 1.31 (m, 4 H), 0.89 (t, $J$ = 7.0 Hz, 3 H, Me); irradiation of the vinylic hydrogen at $\delta$ 5.26 resulted in a large NOE enhancement for the C-2 methylene hydrogens at $\delta$ 4.10; IR ($CHCl_3$) 2918, 1448, 1103 cm$^{-1}$; MS (EI, 30 eV) $m/e$ 169 (MH, 3), 168 (M, 19), 125 (20), 112 (76), 82 (80), 69 (100), 56 (99), 43 (87); HRMS $m/e$ 168.1499 (168.1514 calcd for $C_{11}H_{20}O$).

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**Supplementary Material Available:** Experimental details and characterization data for preparation of **42–48** (5 pages). Ordering information is given on any current masthead page.

(37) Details are provided in the supplementary material.

(38) Preparative GLC was conducted with a 4 ft × $^1/_8$-in. glass column packed with 10% SP-2330 on 100/200 Supelcoport. The carrier flow rate was ca. 50 mL/min.