

**SYNTHESIS OF β -SILYL KETONES VIA REACTION OF TRIMETHYLSILYL LITHIUM
WITH UNSATURATED HYDRAZONES. APPLICATION TO THE SYNTHESIS OF BREVICOMIN**

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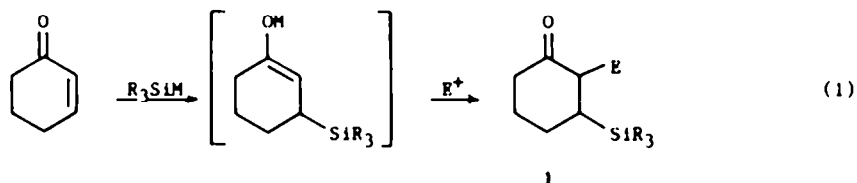
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(Received in UK 22 December 1987)

Summary: Trimethylsilyllithium undergoes conjugate addition to dimethylhydrazones of α,β -unsaturated ketones. The resulting metalloenamine intermediates can be alkylated, and the resulting hydrazone products cleaved to give α -substituted- β -silyl ketones. These reactions, together with a silicon-directed Baeyer-Villiger reaction, have been applied to the synthesis of brevicomin.

Several years ago, we demonstrated that Baeyer-Villiger reactions of β -trimethylsilyl ketones are directed by the silicon to give esters of β -hydroxysilanes.² Since β -hydroxysilanes of defined stereochemistry can be converted to olefins of defined stereochemistry via stereospecific β -elimination reactions,³ these reactions can be used to convert cyclic β -silyl ketones (γ -keto-silanes) to olefinic carbonyl compounds with control of double bond stereochemistry.² Subsequently the Beckmann fragmentation reactions of β -silyl ketones have been found to be directed by silicon to yield olefinic nitriles,⁴ and related fragmentation reactions of γ -hydroxysilanes and -stannanes, leading to olefinic carbonyl compounds, have also been investigated.⁵⁻⁷ [β -Silyl ketones have also been used as precursors to enones, with the silyl group serving as a protecting group for the double bond.⁸]

For these reactions to be most useful in organic synthesis, methods for the synthesis of α -substituted- β -silyl ketones of defined stereochemistry are needed. Of the various methods reported for the preparation of β -silyl ketones,⁸⁻¹¹ the conjugate addition reactions of enones with Me_3SiLi reported by Still,⁹ and of $(\text{PhMe}_2\text{Si})_2\text{CuLi}$ and other silyl cuprate reagents reported by Fleming,^{8b,d,10} promise to be the most versatile. These reactions initially generate enolates which can, in principle, be trapped by a variety of electrophiles to give a variety of α -substituted- β -silyl ketones (1) (see eq 1). However, these types of enolates have only been reacted



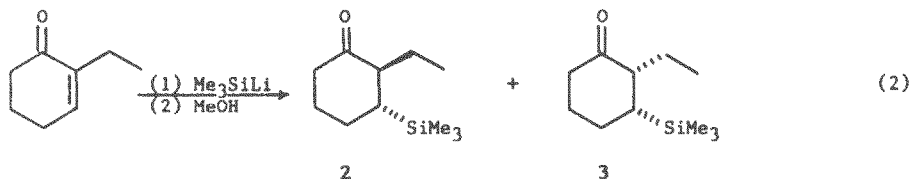
with reactive alkylating agents such as methyl iodide and allyl bromide, giving the alkylated ketones^{8b,d,9,10b,c} (as well as with proton sources, giving the unalkylated ketones, and with Me_3SiCl , giving the silyl enol ethers). The stereochemistry of the product (1, $\text{E} = \text{R} = \text{Me}$) from the reaction with methyl iodide was shown to be *trans*.⁹ Attempted reactions of these types of enolates with less reactive alkylating agents such as primary alkyl iodides were not successful.^{8b,d,9,12}

In the course of our work on the use of Baeyer-Villiger reactions of β -silyl ketones in synthesis, we required a more versatile synthesis of α -substituted- β -silyl ketones. We report here that Me_3SiLi undergoes conjugate addition to α,β -unsaturated dimethylhydrazones; that the

resulting metalloenamine intermediates undergo alkylation with a variety of alkylating agents, including less reactive alkylating agents such as hexyl bromide; and that the resulting hydrazones can be hydrolyzed with oxalic acid, or preferably cleaved with *N*-bromosuccinimide in aqueous acetone, to give α -substituted- β -silyl ketones.

We also report the use of these reactions in the synthesis of both *exo*- and *endo*-brevicomins. The *exo* isomer is the principal aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.¹³ The brevicomins are cyclic acetals of dihydroxy ketones, and therefore could be prepared from *cis* or *trans* olefinic ketones 24 or 25.¹⁴ Our approach (Scheme 2) involves the preparation of 24 and/or 25 from *trans*-2-ethyl-3-trimethylsilylcyclohexanone (2) (or the *cis* isomer 3) using the above-mentioned silicon-directed Baeyer-Villiger reactions which we developed several years ago.²

Results and Discussion. In order to prepare the silyl ketone 2, we initially tried a variation of Still's reaction.⁹ Using a procedure analogous to that which successfully converted cyclohexenone to the α -methyl- β -silyl compound 1 ($E = R = \text{Me}$, eq 1), cyclohexenone was treated with Me_3SiLi (prepared by treatment of $\text{Me}_3\text{SiSiMe}_3$ with MeLi)⁹ followed by ethyl iodide. A mixture of products was obtained, two of which were identified by VPC analysis to be the alkylated silyl ketone, 2-ethyl-3-trimethylsilylcyclohexanone (2) (27%) and the unalkylated silyl ketone, 3-trimethylsilylcyclohexanone (33%). Proton transfer apparently successfully competes with alkylation in this system. As a different approach, we investigated the addition of Me_3SiLi to 2-ethylcyclohexenone followed by protonation with methanol, which might be expected to generate the *cis* isomer 3.¹⁵ However, this reaction produced a mixture of *trans*- and *cis*-2-ethyl-3-trimethylsilylcyclohexanones (2 and 3) in nearly equal amounts (eq 2) (4:5 ratio of 2:3 by VPC analysis).

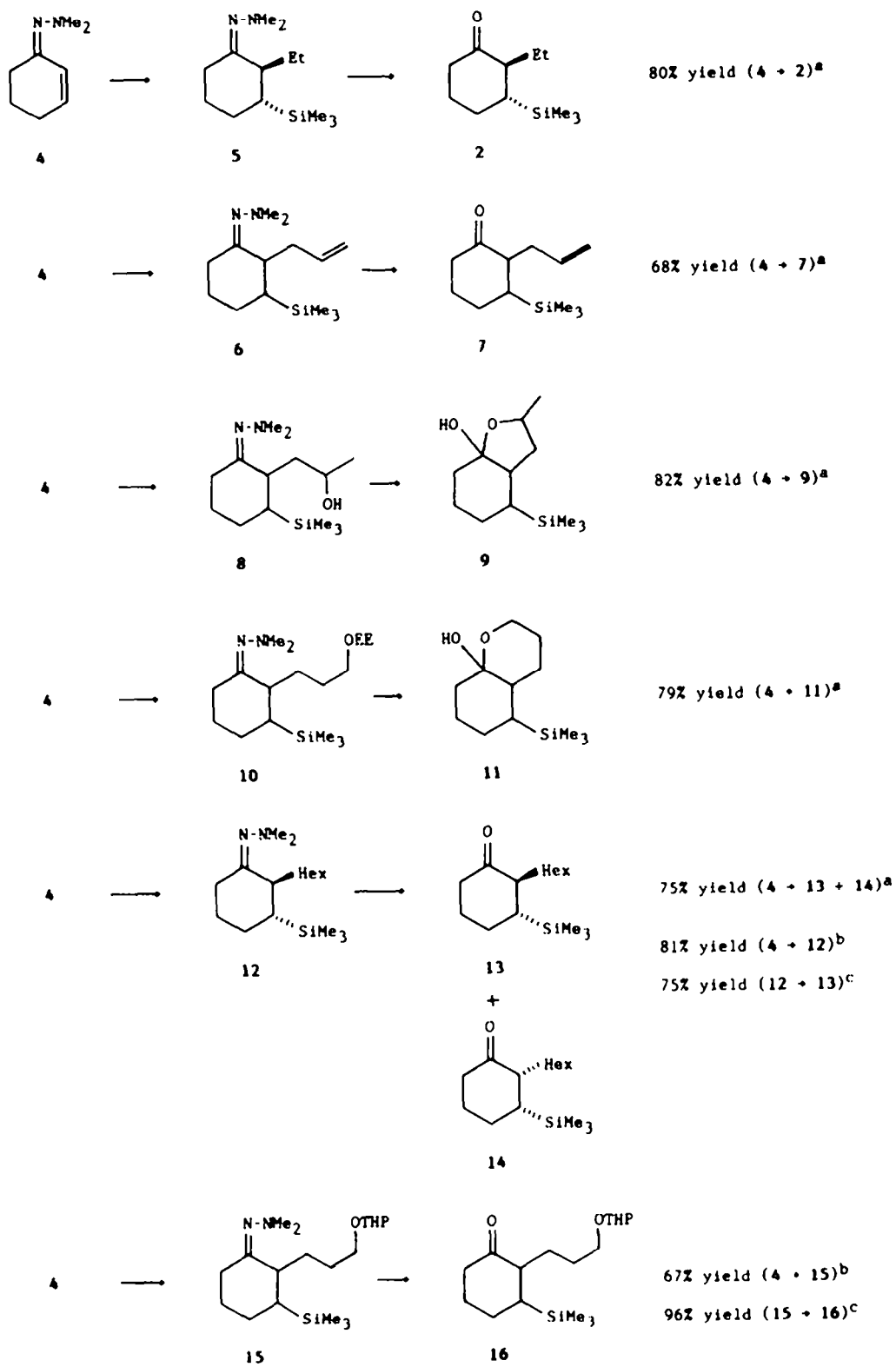


We therefore investigated other routes to β -silyl ketones, and have found that Me_3SiLi undergoes conjugate addition to α,β -unsaturated hydrazones,¹⁶ and that the resulting metalloenamine intermediates, which are considerably more nucleophilic than enolates,¹⁷ can be alkylated with ethyl iodide and with other alkylating agents. Cyclohexenone *N,N*-dimethylhydrazone (4)¹⁸ was prepared in 89% yield by reaction of cyclohexenone with dimethylhydrazine in benzene using a Dean-Stark trap. Treatment of the hydrazone (4) with Me_3SiLi in THF/HMPA followed by EtI using conditions similar to those used to prepare 1 ($E = R = \text{Me}$) from cyclohexenone and Me_3SiLi ⁹ (eq 1), gave a product which appeared to be the alkylated silyl hydrazone (5) by spectral and VPC analysis. Hydrolysis of the crude product with 0.5 *M* oxalic acid (room temperature, 24 h) gave *trans*-2-ethyl-3-trimethylsilylcyclohexanone (2) in 80% yield from 4. Comparison of the product with the *cis*-*trans* mixture obtained from the above reaction of 2-ethylcyclohexenone with Me_3SiLi suggested that the product was 98% *trans*. To confirm the stereochemical assignments, this product was treated with NaOMe in MeOH for 24 h, giving a *cis*-*trans* mixture (60:40 mixture of 2:3 by VPC analysis). The *cis*-*trans* mixture obtained from 2-ethylcyclohexenone (4:5 ratio of 2:3) was similarly treated with NaOMe in MeOH to give a 60:40 mixture of 2 and 3.

In early attempts to prepare silyl ketone 2 from hydrazone 4, VPC analysis of the crude alkylated hydrazone (5) frequently showed a byproduct of higher retention time in varying amounts. By analogy to previous work in our laboratories on the reaction of Me_3SiLi with cyclohexenone,^{2,4c} this was assumed to be a disilyl compound; it could be minimized by careful attention to time and temperature control.

Treatment of the hydrazone 4 with Me_3SiLi as above followed by a variety of other electrophiles (allyl bromide, propylene oxide, the ethoxyethyl ether of 3-bromopropanol, and hexyl bromide), and hydrolysis of the crude products with oxalic acid (Procedure A) gave a variety of α -substituted- β -silyl ketones or their derivatives (7, 9, 11, and 13 + 14; see Scheme 1).

Scheme 1



^AProcedure A

^BProcedure B

^CProcedure C

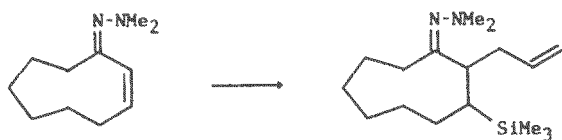
[It should be noted that the α -allyl- β -silyl ketone 7 can be made more efficiently from the reaction of Me_3SiLi with cyclohexenone followed by allyl bromide,¹⁹ since allyl bromide is a reactive alkylating agent.²⁰] The ethoxyethyl protecting group apparently doesn't survive the hydrolysis conditions. [The crude alkylated hydrazone (10, EE = ethoxyethyl) from the alkylation with the ethoxyethyl ether of 3-bromopropanol appeared to have the protecting group intact by spectral and VPC analysis.] Attempted hydrolysis of the crude alkylated hydrazone (12) from the hexyl bromide alkylation under the usual conditions (0.5 M oxalic acid, room temperature, 24 h) resulted in incomplete reaction. Use of a longer reaction time (4 days) led to good conversion to product, but with the product as a *trans-cis* mixture (2:1 ratio of 13:14 by VPC).

We have therefore sought better methods to hydrolyze *N,N*-dimethylhydrazones. We tried some of the other methods developed for regenerating carbonyl compounds from dimethylhydrazones and other derivatives,²¹ and found that *N*-bromosuccinimide (NBS) in aqueous acetone, which has been used to cleave tosylhydrazones,²² is also useful for the cleavage of *N,N*-dimethylhydrazones. We also found that a modified procedure that we had developed for the reaction of cyclohexenone with Me_3SiLi ,^{4c} and which was easier to run and to scale up, can also be used for the reaction of the dimethylhydrazone 4 with Me_3SiLi .

Use of the modified procedure for the silyllithium addition (Procedure B) and the NBS cleavage of the hydrazone (Procedure C) allowed the *trans* α -hexyl- β -silyl ketone 13 to be isolated in high isomeric purity, and allowed a tetrahydropyranyl (THP) ether to be isolated (ketone 16). Additionally, the ketone products from the combination of Procedures B and C show a very clean carbonyl band in the infrared spectrum, while those from Procedure A show a small shoulder on the carbonyl band.

Thus, treatment of the cyclohexenone dimethylhydrazone (4) with Me_3SiLi followed by hexyl bromide gave hydrazone 12, which was purified by distillation, and isolated in 81% yield. Treatment of 12 with NBS in aqueous acetone (ice temperature, 2 min) gave *trans* ketone 13 (97% *trans*) in 75% yield. [When 12 was treated with oxalic acid (room temperature, 4 days), VPC analysis of the crude product showed *trans* ketone 13 and *cis* ketone 14 in a 5:2 ratio. Similarly, treatment of hydrazone 4 with Me_3SiLi followed by the THP ether of 3-bromopropanol gave the alkylated hydrazone 15 in 67% yield after flash chromatography,²³ and treatment of 15 with NBS gave ketone 16 in 96% crude yield. The NMR spectrum indicated that the product was reasonably pure, and that the THP group had survived the cleavage step; however, attempts to purify ketone 16 by flash chromatography or by distillation led to decomposition.

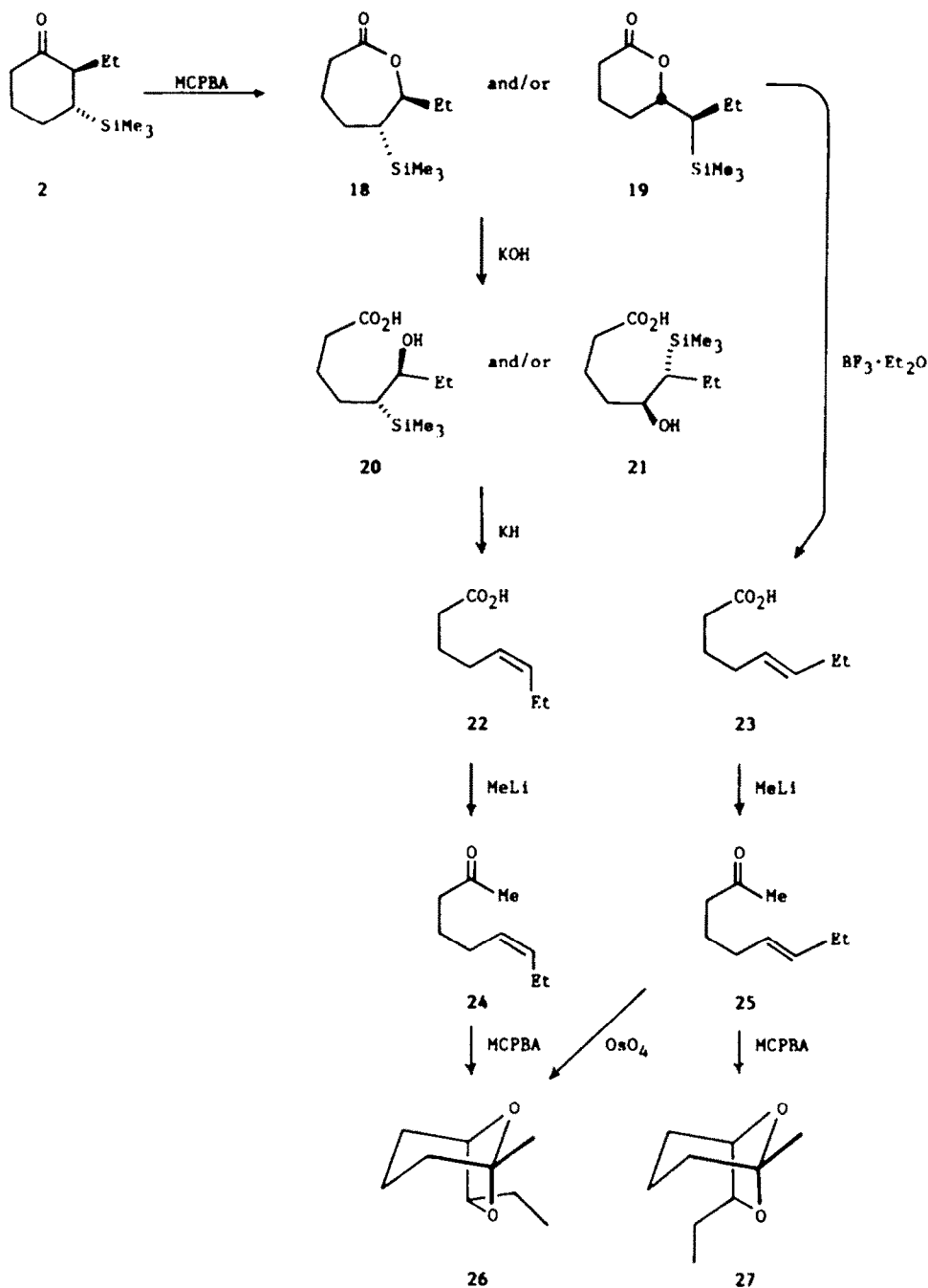
Perhaps not surprisingly, a limitation on the NBS method for regenerating ketones from dimethylhydrazones appears to be the presence of a double bond in the molecule. In preliminary experiments, treatment of the allylated hydrazone 17 (from cyclononenone *N,N*-dimethylhydrazone²⁴ and Me_3SiLi followed by allyl bromide) with NBS under the above conditions led to a tar. [Although 2-allyl-3-trimethylsilylcyclohexanone (7) can be prepared from cyclohexenone with Me_3SiLi followed by allyl bromide,¹⁹ treatment of cyclononenone²⁵ with Me_3SiLi followed by allyl bromide or allyl iodide resulted in complex mixtures. Presumably the enolate derived from cyclononenone and Me_3SiLi is more hindered and less reactive than that derived from cyclohexenone.]



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We have synthesized both *exo*- and *endo*-brevicomins (26 and 27) (in racemic form) from *trans*-2-ethyl-3-trimethylsilylcyclohexanone (2). Treatment of 2 with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride gave a silyl lactone which was presumed to have structure 18 and/or 19 (see Scheme 2) by analogy to our previous work.² Saponification of the crude product gave a silyl hydroxy acid, presumed to have structure 20 and/or 21. Treatment of the crude silyl hydroxy acid

Scheme 2



with KH in THF gave the *cis* olefinic acid 22, and treatment of 22 with methyl lithium gave the *cis* olefinic ketone 24. When 24 was treated with MCPBA followed by 0.1 N HClO_4 , a mixture of *exo*- and *endo*-brevicomins (26 and 27) was obtained in a ratio of 87.5:12.5, respectively. We believe the loss of stereochemical purity may have been due to a small amount of *anti*-elimination (to give the *trans* olefinic acid 23) during the saponification step. Therefore we decided to try to prepare the *trans* olefinic acid (23) directly from the silyl lactone.

Treatment of the silyl lactone (18 and/or 19) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in methylene chloride gave the *trans* olefinic acid 23 in 60% overall yield from 2. Treatment of 23 with methyl lithium gave *trans* olefinic ketone 25 in 70% yield. Although we were unable to determine the isomeric purity of 23 and 25 by VPC comparison with the *cis* isomers (22 and 24) prepared above, their purity could be

inferred from the isomeric purity of the brevicomins. Treatment of trans olefinic ketone 25 with MCPBA in methylene chloride gave endo-brevicomins (27) in 80% yield and 95% isomeric purity (95% 27, 5% 26). Alternatively, treatment of 25 with osmium tetroxide and triethylamine N-oxide in *t*-butyl alcohol²⁶ gave exo-brevicomins (26) in 79% yield and 96% isomeric purity (96% 26, 4% 27).

In conclusion, a variety of α -substituted- β -silyl ketones (including compounds which cannot be easily prepared by other methods) can be prepared from α,β -unsaturated ketone N,N-dimethylhydrazones, by reaction with Me_3SiLi , followed by alkylation with primary alkyl halides or epoxides, and cleavage of the hydrazones with NBS (or hydrolysis with aqueous acid).

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen or argon atmosphere except those involving hydrolysis. Infrared (IR) spectra were obtained using a Beckman IR-33, a Perkin-Elmer 1320, or a Perkin-Elmer 983G infrared spectrometer. Nuclear magnetic resonance (¹H NMR) spectra were obtained using a Varian EM-360, a Hitachi Perkin-Elmer R-600, or a Nicolet NT-200 NMR spectrometer. Chemical shifts are given in parts per million (δ) using CHCl_3 as an internal reference for compounds which contain silicon, and tetramethylsilane for compounds which do not contain silicon. Mass spectra were obtained using a Finnigan 3200E or a Finnigan MAT 4500B gas chromatograph/mass spectrometer system. Exact mass determinations were carried out at the Midwest Center for Mass Spectrometry, University of Nebraska. Vapor phase chromatographic (VPC) analyses were obtained on a Varian Aerograph Model 90-P instrument using helium as the carrier gas. The retention time of a hydrocarbon standard under the given conditions is included. The following columns were used: SE-30 (10% SE-30 on Chromosorb W, 10 ft x 0.25 in.); QF-1 (20% QF-1 on Chromosorb W, 10 ft x 0.25 in.).

The term "evaporative distillation" refers to a bulb-to-bulb distillation in a Kugelrohr apparatus; the temperature following is the oven temperature. The verb "concentrated" refers to removal of solvent on the rotary evaporator.

Tetrahydrofuran (THF) and anhydrous ether were distilled from sodium and benzophenone. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride. Methylene chloride was distilled from P_2O_5 . Cyclohexenone N,N-dimethylhydrazone was prepared by the method of Corey and Enders.¹⁸ 2-Ethylcyclohexenone²⁷ was prepared from 2-propylpyridine²⁸ by the method of Danishefsky and Cain.²⁹

trans- and cis-2-Ethyl-3-trimethylsilylcyclohexanone (2 and 3) from 2-ethylcyclohexanone. To an ice-cooled solution of 0.5 mL (2.5 mmol) of hexamethyldisilane in 2 mL of HMPA was added dropwise 1.6 mL (2.0 mmol) of methylolithium (1.28 M in ether), and the resulting mixture was stirred for 15 min at 0°C. THF (10 mL) was added, the reaction mixture was immediately cooled to -78°C, and the resulting mixture was stirred for 5 min. A solution of 0.186 g (1.5 mmol) of 2-ethylcyclohexenone in 1 mL of THF was added dropwise, and the resulting mixture was stirred for 10 min. Anhydrous methanol (0.50 mL) was added, and the mixture was allowed to slowly warm to 0°C. The mixture was poured into 50 mL of pentane and washed with water (3x), dried (MgSO_4), concentrated, and distilled (80-120°C, oil pump vacuum) giving 0.120 g (40%) of a mixture of 2 and 3 as a colorless liquid: IR (film) 2980, 1720, 1255, 838 cm^{-1} ; NMR (CDCl_3) δ 2.71-0.51 (13 H, broad peaks), 0.01 (9 H, s); mass spectrum m/z (rel. intensity) 198 (M^+ , 3), 183 (8) 169 (34), 75 (50), 73 (100). [The mass spectra of 2 and 3 were identical.] VPC analysis (SE-30, 150°C, $\text{C}_{14}\text{H}_{30}$ = 4.3 min) showed two major peaks at 3.7 min (38%, 2) and 3.9 min (47%, 3). [Other peaks were at 1.5 min (6.9%, 2-ethylcyclohexenone), 9.0 min (3.5%), and 9.7 min (5.2%) (latter two possibly disilyl compounds).]

Procedure A: 2-Alkylated-3-trimethylsilylcyclohexanone derivatives. To an ice-cooled solution of 0.5 mL (2.5 mmol) of hexamethyldisilane in 2 mL of HMPA was added dropwise 2.0 mmol of methylolithium (as complex with LiBr, in ether), and the resulting pink solution was stirred for 25 min at 0°C. THF (10 mL) was added, the reaction mixture was immediately cooled to -78°C, and the resulting mixture was stirred for 5 min. A solution of 0.138 g (1.00 mmol) of cyclohexenone dimethylhydrazone (4) in 1 mL of THF was added dropwise, and the resulting mixture was stirred

at -78°C for 1 h. Excess alkylating agent was added, and the reaction mixture was stirred for 24 h while warming to room temperature. The resulting mixture was poured into water overlaid with petroleum ether. The organic layer was washed with two portions of water, dried (MgSO_4), and concentrated, giving the alkylated silyl hydrazone.

The crude product was dissolved in 5 mL of ether and 5 mL of petroleum ether, 5 mL of 0.5 M oxalic acid was added, and the resulting mixture was stirred at room temperature for 24 h. The mixture was then poured into saturated NaHCO_3 and extracted with three portions of ether. The combined ether extracts were washed with water, dried (MgSO_4), concentrated, and purified, giving the alkylated silyl ketone.

trans-2-Ethyl-3-trimethylsilylcyclohexanone (2). Using Procedure A, 1.38 g (10.0 mmol) of cyclohexenone dimethylhydrazone (4) was treated with Me_3SiLi (from 5.0 mL (25 mmol) of hexamethyldisilane) followed by ethyl iodide (7.0 mL, 13.65 g, 87.5 mmol), and the crude product was hydrolyzed with oxalic acid. Purification by evaporative distillation (110 - 120°C , oil pump vacuum) gave 1.59 g (80%) of ketone 2 as a clear slightly yellow liquid: IR (film) 2970, 1715, 1250, 835 cm^{-1} ; NMR (CDCl_3) δ 2.45-0.63 (m) overlapping with 0.82 (crude t) (total 13.2 H), 0.00 (8.8 H, s); the mass spectrum was identical to that reported above; exact mass: 198.1444 (calcd for $\text{C}_{11}\text{H}_{22}\text{OSi}$: 198.1440). VPC analysis (SE-30, 180°C , $\text{C}_{14}\text{H}_{30}$ = 3.7 min) showed the major peak at 3.5 min (92% of peak area); less than 2% of the cis isomer (3) was present.

2-Allyl-3-trimethylsilylcyclohexanone (7). Using Procedure A, 0.138 g (1.00 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 0.5 mL (2.5 mmol) of hexamethyldisilane) followed by 0.30 mL (0.419 g, 3.47 mmol) of allyl bromide, and the crude product was hydrolyzed with oxalic acid. Purification by evaporative distillation (80 - 120°C , oil pump vacuum) gave 0.143 g (68%) of ketone 7 as a colorless liquid: IR (film) 3075, 2955, 2860, 1705, 1250, 910, 835 cm^{-1} ; NMR (CDCl_3) δ 5.9-5.3 (1.2 H, m), 5.15-4.80 (2.3 H, m), 2.40-1.00 (10.3 H, m), 0.02 (8.2 H, s); mass spectrum m/z (rel. intensity) 210 (M^+ , 1.2), 195 (1.8), 169 (19), 120 (6), 75 (20), 73 (100); exact mass: 210.1441 (calc for $\text{C}_{12}\text{H}_{22}\text{OSi}$: 210.1440). VPC analysis (SE-30, 170°C , $\text{C}_{15}\text{H}_{32}$ = 4.7 min) showed the major peak at 5.1 min (96%).

Hemiketal 9. Using Procedure A, 0.138 g (1.00 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 0.5 mL (2.5 mmol) of hexamethyldisilane) followed by 0.7 mL (0.58 g, 10 mmol) of propylene oxide, and the crude product was hydrolyzed with oxalic acid. Purification by evaporative distillation (85 - 110°C , oil pump vacuum) gave 0.186 g (82%) of hemiketal 9 as a thick colorless liquid: IR (film) 3420, 2930, 1250, 855, 833 cm^{-1} ; NMR (CDCl_3) δ 4.30 (1.1 H, m), 3.45 (1.1 H, m), 2.47-0.53 (13 H, m (broad)), 0.00 (9 H, s); mass spectrum m/z (rel. intensity) 210 ($(\text{M}-18)^+$, 7), 195 (5), 137 (100), 73 (50); exact mass: 228.1544 (calc for $\text{C}_{12}\text{H}_{24}\text{O}_2\text{Si}$: 228.1546). VPC analysis (SE-30, 170°C , $\text{C}_{14}\text{H}_{30}$ = 3.7 min) showed the major peak at 3.6 min (96%). On the basis of the retention time, the product is believed to undergo dehydration on the VPC column to the enol ether.

Hemiketal 11. Using Procedure A, 0.138 g (1.00 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 0.5 mL (2.5 mmol) of hexamethyldisilane) followed by 0.253 g (1.2 mmol) of ethyl 3-bromopropyl acetaldehyde acetal.³⁰ After aqueous workup, the crude product was placed under oil pump vacuum (50°C) to remove starting material, giving 0.310 g of thick yellow liquid. [The IR spectrum of the crude product showed the expected C=N band at 1620 cm^{-1} ; the NMR spectrum indicated the ethoxyethyl group was intact.] The crude product was hydrolyzed with oxalic acid as above, giving 0.274 g of a semi-solid product. The liquid part was carefully removed with a pipet using cold petroleum ether. The solid part was washed with cold petroleum ether and dried under a stream of nitrogen to give 0.18 g (79%) of hemiketal 11 as a low melting solid: IR (CHCl_3) 3560, 2920, 1235, 1080, 825 cm^{-1} ; NMR (CDCl_3) δ 4.5-0.5 with a major peak at 1.56 (total 16 H), -0.02 (8 H, s); mass spectrum m/z (rel. intensity) 210 ($(\text{M}-18)^+$, 9), 182 (13), 167 (11), 137 (100), 73 (48).

2-Hexyl-3-trimethylsilylcyclohexanone (13 and 14). Using Procedure A, 0.138 g (1.00 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 0.5 mL (2.5 mmol) of hexamethyldisilane) followed by 0.21 mL (0.248 g, 1.5 mmol) of hexyl bromide. A solution of

the crude product in 5 mL of ether, 5 mL of petroleum ether, and 5 mL of 0.5 M oxalic acid was stirred at room temperature for 4 days. (After 24 h, the reaction was incomplete). After aqueous workup, the crude product was evaporatively distilled (130°C, oil pump vacuum) giving 0.19 g (75%) of ketones 13 and 14 as a colorless liquid: IR (film) 2930, 2860, 1705, 1250, 835 cm^{-1} ; NMR (CDCl_3) δ 2.58-0.69 (21.7 H, m (broad)), 0.02 (8.2 H, s); mass spectrum m/z (rel. intensity) 254 (M^+ , 0.13), 239 (0.5), 183 (9), 170 (16), 169 (25), 75 (21), 73 (100). VPC analysis (SE-30, 170°C, $\text{C}_{18}\text{H}_{38}$ = 13.6 min) showed two major peaks at 13.0 min (13) and 13.5 min (14) in a 2:1 ratio. A sample for exact mass was purified by preparative VPC (containing both 13 and 14); exact mass: 254.2063 (calcd for $\text{C}_{15}\text{H}_{30}\text{OSi}$: 254.2066).

Procedure B: 2-Alkylated-3-trimethylsilylcycloalkanone dimethylhydrazones. A solution of 10 mL of HMPA and 5.0 mL (25 mmol) of hexamethyldisilane (containing a magnetic stirrer) was cooled in a dry ice-acetone bath (mixture becomes frozen). Then 20 mmol of methylolithium (low halide, in ether) was added on to the frozen mixture followed by 50 mL of THF (in 10 mL portions). The dry ice-acetone bath was replaced with an ice water bath. Within a minute or two, the frozen mixture melted sufficiently so that stirring was possible. The mixture was stirred for 15 min (became bright red, presumed to be due to Me_3SiLi), then immediately cooled in a dry ice-acetone bath. A solution of 2.14 g (15.5 mmol) of cyclohexenone dimethylhydrazone (4) in 10 mL of THF was added, and the resulting mixture was stirred at -78°C for 30 min. Excess alkylating agent was added, and the reaction mixture was stirred for 12 h while warming to room temperature. Pentane (200 mL) was added, and the resulting mixture was poured into 400 mL of water and shaken vigorously. The pentane layer was washed with water (4 x 100 mL), dried (MgSO_4), concentrated, and purified, giving the alkylated silyl hydrazone.

Procedure C: 2-Alkylated-3-trimethylsilylcycloalkanone derivatives. To an ice-cooled (at 5°C) solution of 3.4 mmol of the hydrazone (from Procedure B) in 35 mL of acetone and 12 mL of water was added 13.5 mmol of NaHCO_3 . A solution of 13.5 mmol of N-bromosuccinimide in 35 mL of acetone was added, and the resulting mixture was stirred for 2 min at ice temperature. A saturated NaHSO_3 solution (12 mL) was added, and the resulting mixture was stirred for 1 min, then poured into 250 mL of water and extracted with 60 mL of ether. The water layer was saturated with NaCl and extracted with two portions of ether. The combined organic extracts were washed with two portions of saturated NaHCO_3 , water, dried (MgSO_4), concentrated, and purified, giving the alkylated silyl ketone.

trans-2-Hexyl-3-trimethylsilylcyclohexanone (13). Using Procedure B, 2.14 g (15.5 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 5.0 mL (25 mmol) of hexamethyldisilane) followed by 7.0 mL (50 mmol) of hexyl bromide. The crude product was distilled (bp 109°C, 0.6 mm) giving 3.72 g (81%) of hydrazone 12 as a light green liquid: IR (film) 2930, 2830, 1630, 1470, 1250, 840 cm^{-1} ; mass spectrum m/z (rel. intensity) 296 (M^+ , 18), 281 (7), 212 (12), 168 (12), 139 (100), 116 (20), 73 (Me_3Si^+ , 80). VPC analysis (QF-1, 170°C, $\text{C}_{20}\text{H}_{42}$ = 3.2 min) showed the major peak at 2.5 min (95%).

Using Procedure C, hydrazone 12 (1.0 g, 3.4 mmol) was treated with 13.5 mmol of N-bromosuccinimide. After aqueous workup, the crude product was subjected to flash chromatography (4% EtOAc/96% pentane) giving 0.64 g (75%) of ketone 13: IR (film) 2930, 2859, 1712, 1251, 834 cm^{-1} ; NMR (CDCl_3) δ 2.30 (3 H, m), 1.96-1.0 (15 H, overlapping peaks containing a prominent peak at δ 1.22), 0.83 (3 H, broad t), 0.00 (9 H, s); mass spectrum m/z (rel. intensity) 254 (M^+ , 5), 239 (2), 183 (10), 169 (40), 75 (20), 73 (Me_3Si^+ , 100). VPC analysis (QF-1, 170°C, $\text{C}_{18}\text{H}_{38}$ = 4.9 min) showed peaks at 12.5 min (97%, 13) and 14.5 min (3%, 14).

In another experiment, hydrazone 12 was hydrolyzed with 0.5 M oxalic acid as in Procedure A (room temp, 4 days). VPC analysis under the above conditions showed peaks at 12.5 min (58%, 13) and 14.5 min (24%, 14).

trans-2-(3-Tetrahydropyranyloxypropyl)-3-trimethylsilylcyclohexanone (16). Using Procedure B, 2.14 g (15.5 mmol) of cyclohexenone dimethylhydrazone (4) was treated with trimethylsilyllithium (from 5.0 mL (25 mmol) of hexamethyldisilane) followed by 5.0 g (22 mmol) of 3-bromopropanol tetrahydropyranyl ether.³¹ The reaction mixture was stirred for 12 h at -78°C. The cold

bath was removed, and 200 mL of pentane was added. After aqueous workup, the last traces of starting material were removed under oil pump vacuum (80-90°C), and the residue was subjected to flash chromatography (30% EtOAc/70% pentane) giving 3.68 g (67%) of the hydrazone 15: IR (film) 2949, 2857, 1626, 1249, 1035, 836 cm^{-1} ; NMR (CDCl_3) δ 4.53 (1 H, crude t), 3.87-3.61 (2 H, m), 3.54-3.30 (2 H, m), 3.16-2.97 (1 H, m), 2.37 (6 H, s), 1.94-1.35 (18 H, overlapping peaks), 0.99 (1 H, m), -0.03 (9 H, s); mass spectrum m/z (rel. intensity) 354 (M^+ , 35), 339 (1), 269 (25), 253 (15), 212 (10), 139 (80), 85 (50), 73 (Me_3Si^+ , 100).

Using Procedure C, hydrazone 15 (1.3 g, 3.67 mmol) was treated with 14.4 mmol of *N*-bromo-succinimide. After aqueous workup, 1.1 g (96% crude yield) of ketone 16 was obtained as a nearly colorless liquid: IR (film) 2946, 2866, 1709, 1250, 1035, 836 cm^{-1} ; NMR (CDCl_3) δ 4.54 (1 H, crude t), 3.91-3.62 (2 H, m), 3.55-3.29 (2 H, m), 2.47-2.21 (3 H), 2.10-1.42 (15.6 H, overlapping peaks), 1.05 (0.5 H, m), 0.02 (7 H, s); mass spectrum m/z (rel. intensity) 210 (M^+ - 102, 10), 195 (1), 182 (15), 137 (100), 73 (Me_3Si^+ , 35).³² Attempts to distill ketone 16 or purify it by flash chromatography led to decomposition.

Baeyer-Villiger reaction of silyl ketone 2. To a solution of 6.76 g (33.3 mmol) of MCPBA (85%) in 175 mL of methylene chloride was added dropwise a solution of 3.30 g (16.6 mmol) of silyl ketone 2 in 10 mL of methylene chloride. The resulting mixture was stirred at room temperature for four days. Saturated NaHSO_3 was added, and the mixture was vigorously stirred for 15 min. The layers were separated, and the aqueous layer was extracted with methylene chloride (2x) and with ether. The combined organic layers were washed with 1 *N* NaOH, saturated NaHCO_3 , were dried (MgSO_4), and concentrated. The last traces of solvent were removed with a stream of nitrogen giving 3.360 g (94% crude yield as lactone 18 and/or 19) of a slightly yellow liquid: IR (film) 2970, 1740, 1255, 1035, 840 cm^{-1} ; NMR (CDCl_3) δ 4.48 (1 H, m), 2.70 - 1.22 (8 H, broad m), 0.96 (4 H, crude t), 0.08 (9 H, s). The product appeared to be unstable to VPC analysis.

trans-5-Octanoic acid (23). To an ice-cooled solution of 3.311 g of the above lactone in 100 mL of methylene chloride, 8.0 mL of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was added dropwise. The reaction mixture was warmed to room temperature, and stirred for 3 hours at room temperature, then poured into saturated NaHCO_3 overlaid with ether. The layers were separated, and the organic layer was extracted twice with saturated NaHCO_3 . Methylene chloride was added to the combined aqueous extract, and the mixture was cooled in an ice bath, and acidified to pH 1 with 1 *M* H_2SO_4 . The layers were separated, and the aqueous layer was extracted with methylene chloride (3x). The methylene chloride extract was dried (MgSO_4), concentrated, and evaporatively distilled (120°C, oil pump vacuum) to give 1.392 g (60% from 2) of trans olefinic acid 23 as a colorless liquid, having an IR spectrum in agreement with that reported;³³ NMR (CDCl_3) δ 5.42 (2 H, s broad), 2.50-1.20 (8 H, m), 0.96 (3 H, t, $J = 7$ Hz); mass spectrum m/z (rel. intensity) 142 (M^+ , 3), 124 (15), 96 (14), 82 (43), 67 (64), 55 (60), 41 (100). VPC analysis (SE-30, 170°C, $\text{C}_{12}\text{H}_{26} = 2.0$ min) showed the only peak at 1.7 min (100% peak area).

trans-6-Nonen-2-one (25). To an ice-cooled solution of 0.770 g (5.41 mmol) of trans olefinic acid 23 in 80 mL of anhydrous ether was added dropwise 6.9 mL (10.8 mmol) of methyl lithium (1.56 *M* in ether). The resulting mixture was stirred at room temperature for 4 h, then poured into 200 mL of crushed ice containing 40 mL of 1 *N* HCl, and the layers were separated. The aqueous layer was extracted with ether (3x), and the combined organic layers were washed with saturated NaHCO_3 , water, dried (MgSO_4), concentrated, and evaporatively distilled (110°C, 25 mm) to give 0.528 g (70% yield) of the trans olefinic ketone 25 as a colorless liquid, having IR and NMR spectra in agreement with those reported;^{14h,i,1} mass spectrum m/z (rel. intensity) 140 (M^+ , 1.3), 125 (1.3), 111 (2), 82 (29), 67 (68), 55 (19), -3 (100). VPC analysis (SE-30, 170°C, $\text{C}_{10}\text{H}_{22} = 1.3$ min) showed the major peak at 1.5 min (98% of peak area).

endo-Brevicomin (27). Trans olefinic ketone 25 (0.100 g, 0.71 mmol) was treated with 0.175 g (0.86 mmol) of 85% MCPBA in 9 mL of methylene chloride (0°C, 1 h).³⁴ Evaporative distillation (60-65°C, 20 mm) of the crude product gave 0.089 g (80%) of endo-brevicomin (27) as a colorless liquid, having IR, NMR, and mass spectra in agreement those reported.^{13b} VPC analysis (SE-30, 130°C, $\text{C}_{11}\text{H}_{24} = 3.7$ min) showed two peaks at 2.8 min (5%, 26) and 3.3 min (95%, 27).

exo-Brevicomín (26). To a solution of 0.300 g (2.14 mmol) of the trans olefinic ketone 25 in 5 mL of *t*-butyl alcohol was added 0.323 g (2.91 mmol) of trimethylamine N-oxide dihydrate, 0.2 mL of pyridine, and 1.3 mL of water. To this was added 0.3 mL of a solution of osmium tetroxide in *t*-butyl alcohol (2.5% w/v), and the resulting reaction mixture was heated at reflux for 20 h.³⁵ The mixture was cooled to room temperature, and 15 mL of saturated NaHSO₃ was added. The mixture was saturated with sodium chloride, acidified with 20 mL of concentrated HCl (to pH 2), and stirred for 2 h at room temperature. The resulting mixture was extracted five times with ether, and the ether extracts were washed with saturated NaHCO₃, saturated NaCl, water, and were dried (MgSO₄) and concentrated. The *t*-butyl alcohol was removed by distillation (room temperature, 100-50 mm), and the residue was evaporatively distilled (100°C, oil pump vacuum) to give 0.265 g (79%) of exo-brevicomín 26 as a colorless liquid, having IR and NMR spectra in agreement with those reported.^{13b} VPC analysis (SE-30, 140°C, C₁₁H₂₄ = 2.5 min) showed peaks at 2.0 min (96%, 26) and 2.4 min (4%, 27).

exo-Brevicomín (26) from silyl ketone 2 via cis-5-octenoic acid (22). Using a procedure similar to that described above for the preparation of the trans acid 23, 1.50 g of silyl ketone 2 was subjected to Baeyer-Villiger conditions giving 1.26 g (78% crude yield) of lactone (18 and/or 19), having similar IR and NMR spectra to those described above.

To a solution of 0.944 g (14.3 mmol) of potassium hydroxide (85%) in 43 mL of water and 36 mL of methanol was added dropwise a solution of 1.06 g (4.94 mmol) of the crude lactone in 5 mL of methanol. The resulting mixture was stirred at room temperature for 26 h, and then poured into water overlaid with ether, and shaken well. The layers were separated, and the ether layer was extracted with saturated NaHCO₃ (and discarded). Ether was added to the combined aqueous extract, and the resulting mixture was cooled in an ice bath and acidified to pH 4 (using a solution of buffer prepared from 13 g of NaH₂PO₄·H₂O and 5 mL of concentrated H₂SO₄ in 100 mL of water). The layers were separated, and the aqueous layer was extracted with ether (3x). The combined organic layers were dried (MgSO₄) and concentrated to give 0.98 g (85% crude yield) of silyl hydroxy acid (20 and/or 21) as a clear yellow liquid: IR (film) 3450 (broad), 2980, 1720, 1255, 1030, 840 cm⁻¹; NMR (CDCl₃) δ 4.46 (2 H, m), 3.70-0.66 (broad peaks) overlapping with 3.47 (s, exchanges with D₂O) and 0.96 (crude t) (total of 14.8 H), 0.06 (7.1 H, s).

To a suspension of potassium hydride (4.52 g of a 22.5% slurry in oil, washed with 3 x 15 mL of petroleum ether, 25.4 mmol) in 40 mL of THF was added a solution of 0.77 g (3.31 mmol) of the silyl hydroxy acid in 5 mL of THF. The resulting mixture was stirred at room temperature for 5 h, then carefully added (with a syringe) to 60 mL of saturated NaHCO₃ overlaid with 60 mL of ether. The layers were separated, and the ether layer was extracted with saturated NaHCO₃ (2x) (and discarded). To the combined aqueous extract was added 60 mL of ether, and the mixture was cooled in an ice bath, and acidified to pH 3 with 3 M H₂SO₄. The layers were separated, and the aqueous layer was extracted with ether (3x). The combined organic layers were washed with water, dried (MgSO₄), concentrated, and evaporatively distilled (120°C, oil pump vacuum) to give 0.40 g (85%) of cis-5-octenoic acid 22 as a slightly yellow liquid, having an IR spectrum in agreement with that reported³³ for 22 except for the presence of a small peak at 965 cm⁻¹, presumably due to the trans isomer (23); NMR (CDCl₃) δ 5.38 (2 H, m), 2.45-1.25 (8 H, m broad), 0.94 (3 H, t, *J* = 7 Hz). The mass spectrum was essentially identical to that of the trans isomer (23). VPC analysis (SE-30, 170°C, C₁₂H₂₆ = 2.0 min) showed the major peak at 1.7 min (98%).

Using a procedure similar to that described above for the preparation of trans-6-nonen-2-one (25) from acid 23, 0.280 g (1.97 mmol) of cis olefinic acid 22 in 30 mL of anhydrous ether was treated with 2.5 mL (3.9 mmol) of methyl lithium (1.56 M in ether). Evaporative distillation of the crude product (50°C, oil pump vacuum) gave 0.110 g (40% yield) of the cis olefinic ketone 24 as a colorless liquid, having IR and NMR spectra in agreement with those reported,¹⁴ⁱ and a mass spectrum very similar to that of the trans isomer 25. The low yield may have been due to loss of sample during removal of solvent and during distillation. VPC analysis (SE-30, 170°C, C₁₀H₂₂ = 1.3 min) showed the major peak at 1.5 min (97% of peak area).

Olefinic ketone 24 (0.065 g) was treated with MCPBA in methylene chloride³⁶ followed by HClO₄

to give 0.057 g (79%) of *exo*-brevicomín (26) as a colorless liquid, having IR, NMR, and mass spectra in agreement with those reported.^{13b} VPC analysis (SE-30, 130°C, C₁₀H₂₂ = 2.5 min) showed the major peaks at 2.8 min (87.5% of peak area, 26) and 3.3 min (12.5% of peak area, 27).

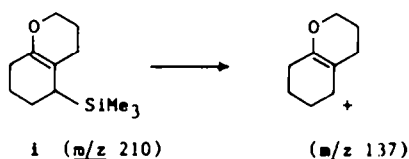
Acknowledgments. We thank the National Science Foundation and the National Institutes of Health (MBRS Program) for support of this work.

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35. The transformation of trans olefinic ketone **25** to exo-brevicommin (**26**) has been carried out under similar conditions.^{14d,l}
36. The transformation of the cis olefinic ketone **24** to exo-brevicommin (**26**) has been carried out under similar^{14a,b,f,i,j} conditions. IR and NMR spectra of the crude product (before treatment with HClO₄) were very similar to those of exo-brevicommin, suggesting that the acid treatment was unnecessary under our conditions.