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The Tandem Radical Cyclization Approach to Angular Triquinanes. Model Studies and the Total Synthesis of (±)-Silphiperfolene and (±)-9-Episilphiperfolene

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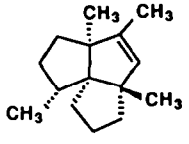
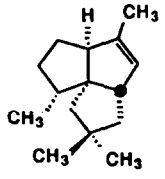
Abstract: *Models studies and the total synthesis of silphiperfol-6-ene (**4**, seven steps) and 9-episilphiperfol-6-ene (**14**, five steps) are reported. The use of a tandem radical cyclization permits rapid construction of the requisite tricyclic nucleus. In the most direct approach, the key tandem cyclization (**18** → **19**) produces the C-9 epimer as the major product. In a modified approach, cyclization of the dioxolane ketal derived from **18** (**27** → **28**) produces a useful excess of the natural isomer. Interesting observations on the rapid prototropic isomerization of a vinyl silane to an allyl silane (**21** → **22** + **23**) are also discussed.*

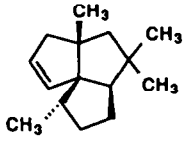
Introduction: Research directed towards the preparation of members of the angular triquinane class of sesquiterpenes has progressed rapidly over the past several years. A series of comprehensive reviews by Paquette, an active contributor in the area, summarizes recent developments.[2] This class of compounds is represented by the hydrocarbons isocomene (**1**), pentalenene (**2**), silphinene (**3**), and silphiperfol-6-ene (**4**). A variety of oxygenated relatives are also known. The tricyclo[6.3.0.0^{1,5}]undecane ring system is also embedded in several more complex natural products including laurenene and retigeranic acid.[3]



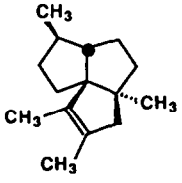
1 Isocomene



2 Pentalenene



3 Silphinene

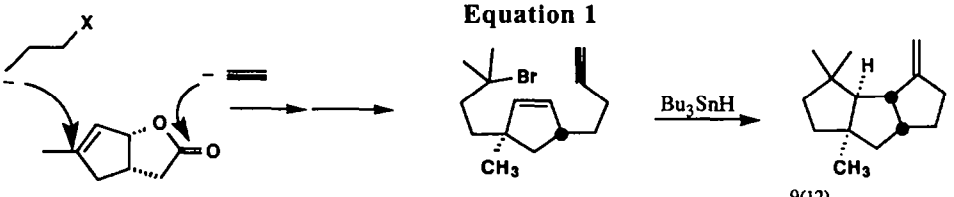


4 Silphiperfolene

Many synthetic studies have approached the interesting problems posed by the multiply-fused five-membered rings and a number of general solutions have emerged. Most strategies have involved the sequential construction of each five-membered ring in the appropriate angular arrangement. A notable exception is the π-arene olefin cycloaddition strategy of Wender.[4] We have undertaken the development of a unified strategy to the angular, linear, and propellane classes of triquinanes. The cornerstone of the strategy is the realization that the ability to sequence hexenyl radical cyclizations permits the efficient construction of two (or more)[5] cyclopentane rings in a single step.[6]

Research in the area of linear triquinanes has resulted in the development of a tandem radical cyclization approach to hirsutene[7a,b] and $\Delta^{9(12)}$-capnellene[7c] and has recently culminated in a synthesis of the highly oxygenated sesquiterpene coriolin.[8] Thus, both simple and complex linear triquinanes of differing substitution patterns are available by tactical variations of the same basic strategy. The approach to $\Delta^{9(12)}$-capnellene is succinctly summarized in Equation 1. The radical cyclization precursor **5** is readily available in six steps from simple lactone **6**. Treatment of **5** with tri-*n*-butyltin hydride induces the tandem cyclization and produces capnellene in good overall yield. The synthesis is remarkably short and efficient, and complete stereocontrol is achieved by the use of the preformed central cyclopentene ring as a cyclization template.

Equation 1

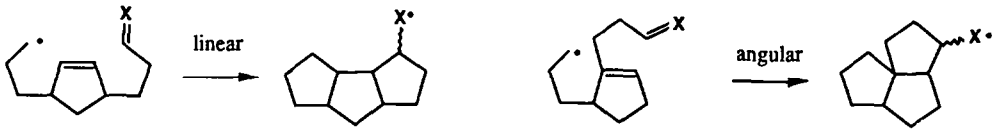


6 **5** $\Delta^{9(12)}$-capnellene

The extension of this tandem radical cyclization strategy to the formation of angular triquinanes involves only the repositioning of a side chain on the cyclization template. This relocates one of the outer rings with respect to the central preformed ring. The analysis is summarized in Equation 2.

[+]Taken in part from the Ph.D. Thesis of S.-C.Kuo, University of Pittsburgh, 1986

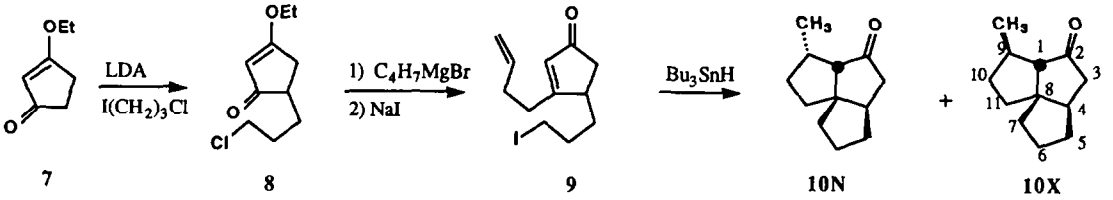
Equation 2



Silphiperfol-6-ene, first isolated by Bolhmann and Jakupovic from the roots of *Silphium perfolatium*, was selected as a representative target for initial investigation. Several related derivatives have also been isolated. [9] (–)-Silphiperfol-6-ene was prepared in fifteen steps from (+)-pulegone by Paquette in 1984.[10] Just prior to the preliminary communication of our studies, the arene-olefin cycloaddition approach to silphiperfolene and two isomers was reported by Wender and Singh.[4] A variation of the tricyclooctanone strategy directed towards silphiperfolene was communicated by Demuth and Hinsken.[12] Very recently, Meyers and Lefker have developed a new synthesis of optically active cyclopentenones and applied this method to the preparation of the tandem cyclization precursor **18**. As a result, they obtain (–)-silphiperfolene and their work is described in the accompanying paper. We now report the details of our total synthesis of (±)-silphiperfolene including relevant model studies and interesting ancillary observations on the desilylation of a vinyl silane.

Results and Discussion: To investigate the prospects for formation of angular triquinanes by a tandem radical cyclization, a simple model study was initiated which addressed several relevant concerns in the preparation of silphiperfolene (Scheme 1). In particular, we were concerned about the effects of a keto-stabilized radical (c.f. **12**) on the stereo- and regiochemistry of the second cyclization. Standard kinetic deprotonation

Scheme 1



of 3-ethoxy-2-cyclopentenone (**7**) with LDA, followed by alkylation of the resulting lithium enolate with iodochloropropane, resulted in the formation of **8**.[13] 1,2-Addition of butenyl magnesium bromide, followed by the usual hydrolytic rearrangement and Finkelstein exchange, produced model cyclization precursor **9** in good overall yield.

Treatment of **9** with 1.1 equivalents of tri-*n*-butyltin hydride (benzene, AIBN, 80°C, 0.05M, 50 min)[14] afforded an 83% yield of a mixture of products after removal of the tin compounds. Separation of this mixture gave a trace of reduced starting material (**9**, I=H) along with two separable tricyclic products (63%) which formed in a ratio of about 4/1. Spectroscopic analysis showed that the angular triquinane skeleton was common to both products[15] and that they differed only in the stereochemistry of the methyl group; the major product possessed an endo methyl group (**10N**) while the methyl group in the minor product was exo (**10X**).[16]

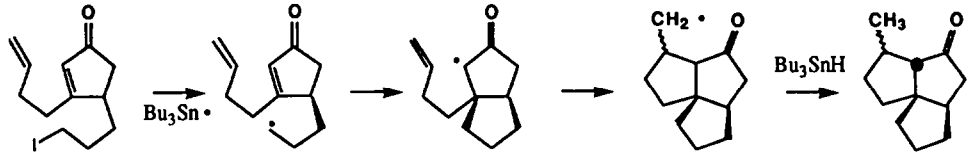
This stereochemistry was assigned from the results of a proton NMR shift reagent study. Upon addition of successive increments of $Eu(fod)_3$, the methyl doublet of the major isomer was shifted downfield at a much more rapid rate than the corresponding resonance of the minor isomer. The results of one experiment are summarized in Table 1. In the major isomer, four other one proton multiplets also showed rapid downfield shifts in this experiment. These resonances were assigned to H_1, $H_{3\alpha}$, $H_{3\beta}$, and H_4. In the minor isomer, a fifth one proton multiplet, assigned to H_9, was also observed to shift rapidly downfield upon addition of $Eu(fod)_3$. Taken together, these data suggest that the methyl group is on the same side of the ring as the carbonyl in the major isomer (**10N**) while H_9 occupies this position in the minor isomer (**10X**).

Table 1
$Eu(fod)_3$-Induced Shift Studies of 10N and 10X in $CDCl_3$

Mole% $Eu(fod)_3$	δ-CH_3 **10N**	δ-CH_3 **10X**
0	0.98	1.12
5	1.38	1.35
20	2.87	2.10
40	3.27	2.82
60	5.35	3.32

The proposed sequence of steps involved in the conversion of **9** to **10** is outlined in Scheme 2. Iodine atom abstraction from **9** produces intermediate radical **11** which suffers the first 5-exo cyclization to produce stabilized radical **12**. It can be anticipated that the location of the butenyl side chain in **11** will significantly retard the initial 5-exo cyclization; however, this retardation is offset in the design by the presence of the strongly activating carbonyl group.[17] Although stabilization of intermediate radicals may retard subsequent cyclizations, **12** closes at a sufficient rate to provide the final radicals **13X/N**,[15,18] which transfer the chain by hydrogen atom abstraction from tin hydride.

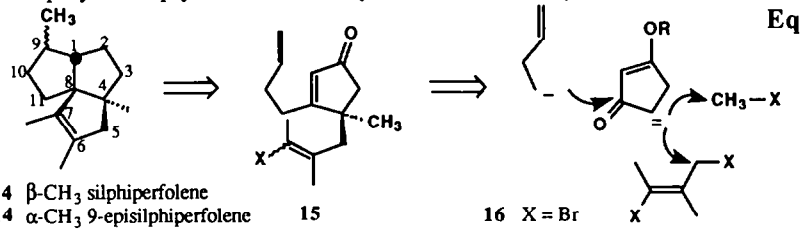
Scheme 2



The ring fusion stereochemistry is strictly controlled since each ring is constrained to close in a cis fashion. The stereochemistry of the methyl group is determined in the second cyclization (**12** → **13**). Folding of the alkene endo to the forming bicyclooctane produces the major product **10N** while the corresponding exo-fold produces the minor product **10X**. The predominance of the endo-methyl isomer is not attractive for the planned silphiperfolene synthesis. However, the formation of this thermodynamically less stable isomer is by no means a surprising result.[19]

Well aware that the stereochemistry of the 9-methyl group would need to be addressed, we began the synthesis of silphiperfolene (**4**). The strategic analysis is outlined in Equation 3. The carbonyl group again serves to permit facile construction of the requisite precursor **15** and ensure the success of the first cyclization. The plan requires the cyclization of a vinyl radical generated from a vinyl halide. The synthetic utility of vinyl radical cyclizations has been elegantly demonstrated by Stork.[20,21] It is well known that vinyl radicals have a very low barrier to inversion and indeed Stork has demonstrated that the stereochemistry of the vinyl halide precursor is irrelevant for a vinyl radical cyclization.[20a,d] The required side chain alkylating agent **16** is readily available in large quantities from ß-bromoangelic acid[22] as described in the Experimental section. The *E*-stereochemistry is employed simply for reasons of synthetic accessibility.

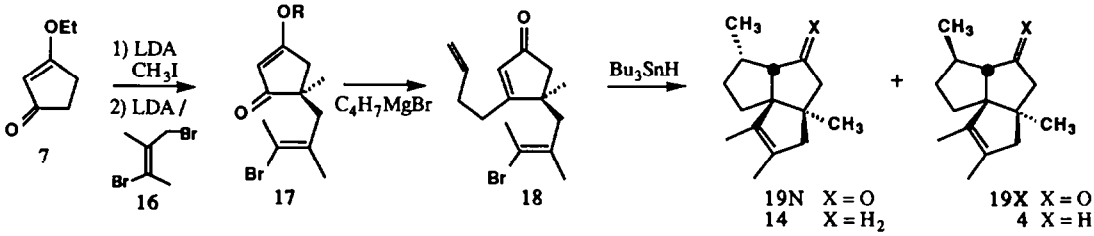
Equation 3



Sequential alkylation of **7** with methyl iodide and allyl vinyl dibromide **16** (Scheme 3) provided **17** in 45% overall yield after chromatographic purification. Subsequently, it was found that the use of the corresponding 2°-butyl enol ether in place of **7**, and the substitution of DMPU[23] for HMPA in both steps, afforded **17** via the same sequence in an improved overall yield of 56%. Addition of butenyl magnesium bromide and hydrolytic work-up provided cyclization precursor **18** in 79% purified yield.

Standard tin hydride-mediated tandem cyclization of **18** afforded a crude product which was directly purified by medium pressure liquid chromatography to provide a 66% isolated yield of an inseparable mixture of tricyclic stereoisomers **19N** and **19X** in a ratio of 3/1.[15] The anticipated stereochemical outcome was confirmed by modified Wolff-Kishner reduction[10] of **19N/X** to provide a mixture of silphiperfolene (**4**) and 9-episilphiperfolene (**14**) in which the unnatural epimer **14** was the major component. The epimers were separable only by gas chromatography and the identity of the minor isomer with authentic silphiperfolene was confirmed by comparison with an authentic sample kindly provided by Professor Paquette.

Scheme 3

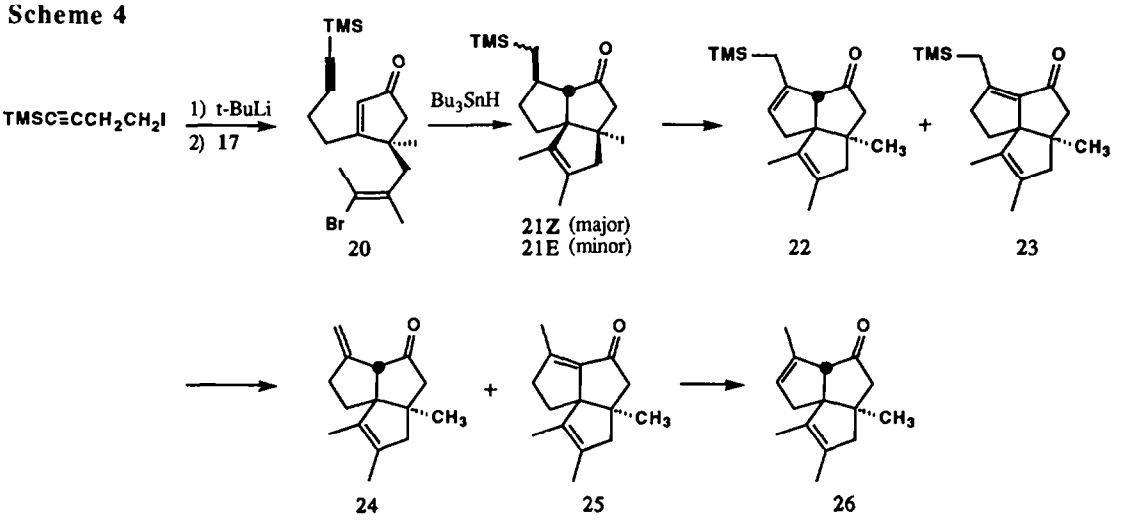


This short synthesis of silphiperfolene and its epimer clearly demonstrates the utility of the tandem radical cyclization approach for the preparation of angular triquinanes. However, since moderate stereoselection for the undesired epimer was exhibited in the second radical cyclization, we were prompted to search for a direct method to reverse the stereochemical outcome. Several solutions were simultaneously investigated. In a first approach, an acetylene terminator was employed in the radical cyclization. This would produce an alkene at C9-C15 (c.f. **24**) and defer the stereochemical question to a subsequent step.[24] This route, summarized in Scheme 4, was soon abandoned in favored of a modified radical cyclization pathway. However, some interesting chemistry was encountered.

Halogen-metal exchange between 4-iodo-1-trimethylsilyl-1-butyne and *t*-butyllithium, followed by addition of **17**, produced a 50% yield of **20** alongside 50% of recovered **17**. After chromatographic separation, pure **20** was subjected to tin hydride cyclization to produce a 2.4/1 mixture of **21Z** and **21E** in 78% yield.[25a] The stereochemistry of the vinyl silanes was readily assigned with the aid of proton NMR (see Experimental). Desilylation of **21Z** or **21E** with $BF_3 \cdot Et_2O$ in methylene chloride (0 °C, 6 h) smoothly produced the exocyclic alkene 2-oxosilphiperfol-6(7),9(15)-diene (**24**). Prolonged exposure of **24** to $BF_3 \cdot Et_2O$ (CH_2Cl_2, 25 °C, 40 h) resulted in isomerization to the 6(7),9(10)-diene **26**. No intermediates were detected. However, we felt that the conjugated diene **25**, although less stable than **26**,[26] was a reasonable candidate.

In an effort to secure **25** for a possible dissolving metal reduction, a **21Z/21E** mixture in benzene was exposed to a small amount of 60% HI for 4 h at 25 °C (Scheme 4). Indeed **25** was formed in approximately equal proportions with **26**. Enone **25** was separated and characterized by NMR. Prolonged exposure of the mixture to HI again resulted in conversion to **26**.

Scheme 4

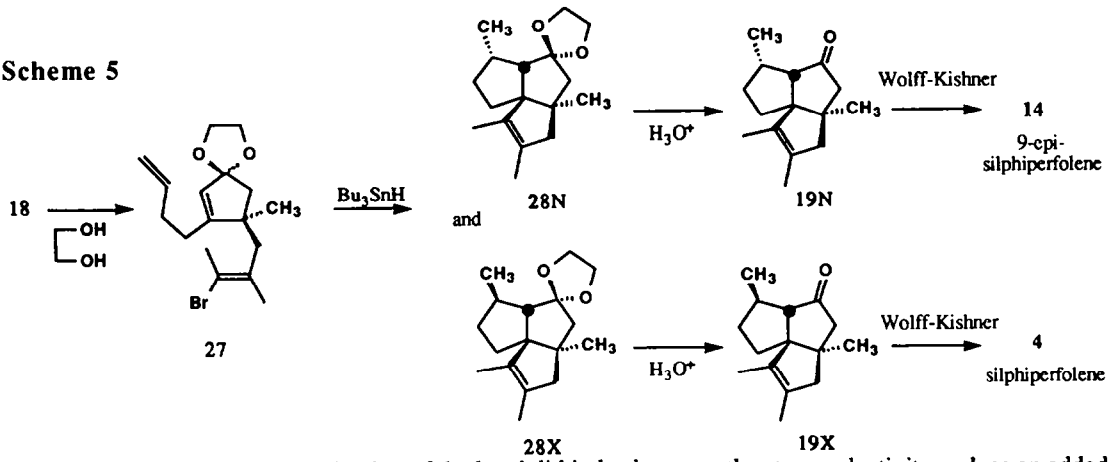


In order to optimize conditions for formation of **25**, a **21Z/21E** mixture was dissolved in benzene-d_6 and a small amount of 60% HI was added. The ratio of products was monitored by ^1H NMR. After only 1 min at 25 °C, resonances for the starting vinyl silanes were completely replaced by two new products in a ratio of 2/3. To our surprise, the primary products were different from all of the desilylated products. The minor isomer exhibited a TMS resonance at δ 0.06 and a vinyl proton at δ 5.10. The major isomer exhibited a TMS resonance at δ 0.05 but no vinyl resonance. Based on this spectroscopic evidence, as well as subsequent reactions, the structures of these products were tentatively assigned as allyl silanes **22** and **23**, respectively.[25b] After 7 min, the resonances for **24** were clearly detectable and **25** and **26** began to appear after 25 min. After 1 h, the resonances assigned to **22** and **23** had completely disappeared. The exact timing of all the steps cannot be determined with the information in hand. However, upon exposure to HI, vinyl silane **21** apparently isomerizes by a prototropic shift to allyl silanes **22** and **23** prior to desilylation. Assuming that protonation occurs on the carbon bearing silicon, to provide a tertiary cation, the formation of **22** and **23** indicates that loss of a ß-proton from this cation is substantially more facile than loss of a ß-trimethylsilyl group. This effect may be related to the acidity of the corresponding proton for **23** and to the stability of the resulting alkene for **22**.

Before reductions of **24-26** were ever undertaken, a simple modification of the radical cyclization approach was uncovered which served to nearly triple the overall yield of silphiperfolene at the expense of two additional steps. It was reasoned that placement of a sizable endo substituent in a 1,3-orientation to the forming stereogenic center at C-9 should disfavor the formation of the endo-methyl isomer. The use of a ketal derived from **18** for this purpose was attractive since it would not involve the introduction of unneeded stereochemistry at C-2. Of course a ketal would put substituents on both the exo- and endo-faces of the forming ring during the second cyclization; however, it seemed reasonable to assume that 1,3-endo interactions should be more severe that 1,3-exo interactions, resulting in a tip towards formation of the exo-product.

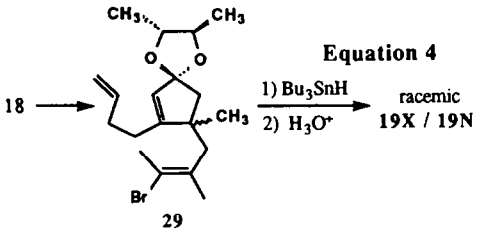
Treatment of **18** with ethylene glycol under standard conditions produced a nearly quantitative yield of sensitive allylic ketal **27** (Scheme 5). While **27** could be purified by flash chromatography, partial hydrolysis occurred resulting in the recovery of significant amounts of **18**. Best overall yields were obtained by the direct tin hydride-mediated cyclization of crude **27**. This produced tricyclic ketals **28X/28N** in a ratio of 2.5/1. We were pleased to find that **28X** and **28N** were separable by medium pressure liquid chromatography. Even more gratifying was the observation that hydrolysis of the major isomer **28X** produced pure ketone **19X**, which had previously been obtained as the minor component of the inseparable mixture **19X/19N**. Upon hydrolysis of the minor tricyclic ketal **28N**, the tricyclic ketone **19N** was isolated. Yields in each hydrolysis

Scheme 5



exceeded 80%. Thus, the introduction of the ketal did indeed reverse the stereoselectivity and, as an added bonus, permitted the separation of the two stereoisomers. Pure silphiperfolene and episilphiperfolene were readily obtained by Wolff-Kishner reduction of the **19X** and **19N**, respectively. It should be noted that the high reactivity toward cyclization of the initial vinyl radical (relative to an alkyl radical) is probably a key to the success of the modified sequence since ketalization removes the activating group in the first cyclization.[20]

In an effort to improve the stereoselectivity, we attempted to prepare other ketals of **18**. However, attempted ketalization with 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, or ethanol under standard conditions resulted in the recovery of starting enone. Interestingly, a diastereomeric mixture of ketals **29** (1/1) was formed upon treatment of **18** with (*R*,*R*)-2,3-butanediol (Equation 4). Separation of the diastereomers, which would have effected resolution, was very difficult. Furthermore, cyclization of **29** produced a mixture of (presumably four) diastereomers which was directly hydrolyzed to give a 2.5/1 ratio of **19X/19N**. While we assumed that both of the diastereomers of **29** produced the same exo/endo ratio, this was not demonstrated. Thus the exo/endo ratio is the same as for the simple dioxolane ketal but the separation advantage has been lost.



Equation 4

In summary, the tandem radical cyclization approach provides a facile entry into the tricyclo-[6.3.0.0^{1,5}]undecane ring system characteristic of angular triquinane natural products. The availability of cyclization precursors combines with the efficiency of the tandem radical cyclization to provide an unusually short synthetic sequence. Ring fusion stereochemistry is strictly controlled while some flexibility in control at an adjacent stereocenter is exhibited by variation of substituents. While the present work provides silphiperfolene in racemic form, A. I. Meyers and B. Lefker have recently developed a new cyclopentenone annulation which permits a facile preparation of optically pure cyclization precursor **18**. This work is described in the accompanying paper.[27]

Experimental

General: All reactions were run under a nitrogen atmosphere unless noted. Temperatures of reactions refer to bath temperatures. Solvents were dried as follows: THF, Et_2O, benzene, (Na/benzophenone); toluene, Et_3N, diisopropylamine, CH_2Cl_2, HMPA, diisopropylethylamine, DMF, DMSO, DMPU (CaH_2). Tri-*n*-butyltin hydride was purchased from Aldrich and purified by vacuum distillation (bp 80 °C/0.4 mm). Flash and medium pressure (MPLC) liquid chromatography were performed with Kieselgel 60 (230-400 mesh). Medium pressure chromatography was also done on pre-packed EM Lobar LiChroprep Si/60 columns. Thin layer chromatography was performed on Merck silica gel 60 pre-coated plates. All reported boiling and melting points are uncorrected. The temperatures recorded during Kugelrohr distillations refer to oven temperatures.

3-Ethoxy-5-(3-chloropropyl)cyclopent-2-en-1-one (8).

To a solution of LDA (19 mmol) in dry THF (10 mL) at –78 °C was added dropwise a solution of **7** (1.75 g, 13.9 mmol) in THF (10 mL). After 45 min at –78 °C, a solution of 3-chloro-1-iodopropane (2.22 mL) and HMPA (4.8 mL) in dry THF (10 mL) was added dropwise. The reaction was stirred for 12 h at –85 °C, then quenched with wet ethyl acetate. The organic phase was washed with water and brine, and dried over $MgSO_4$. After evaporation under reduced pressure, 5.16 g of crude product containing excess 3-chloro-1-iodopropane was obtained. The crude product was purified by flash chromatography

(50% EtOAc in hexane) to give **8** (1.26 g, 45%) and recovered **7** (0.32 g, 18%): ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 1H), 4.05 (q, 2H), 3.55 (dt, 2H), 2.78 (dd, 1H), 2.49 (m, 1H), 2.30 (dd, 1H), 1.99-1.70 (m, 3H), 1.60 (m, 1H), 1.41 (t, 3H).

3-(But-3-enyl)-4-(3-chloropropyl)-cyclopent-2-en-1-one.

To a solution of **8** (1.26 g, 6.24 mmol) in THF (10 mL) at −15 °C was slowly added 3-butenyl magnesium bromide (20 mL, 1 M in THF). After being stirred for 6 h at room temperature, the reaction mixture was quenched with wet ether. The organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 3.64 g of crude product. This was purified by flash chromatography (33% EtOAc in hexane) to give the product (1.26 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1H), 5.82 (m, 1H), 5.10 (m, 2H), 3.58 (t, 2H), 2.87 (bs, 1H), 2.58 (m, 2H), 2.37 (m, 3H), 2.10 (dd, 1H), 2.00 (m, 1H), 1.78 (m, 2H), 1.40 (m, 1H); MS *m/e* 212 (M+), 177, 149, 135, 121, 107.

3-(But-3-enyl)-4-(3-iodopropyl)-cyclopent-2-en-1-one (9).

^{1}H NMR ($CDCl_3$) δ 5.97 (s, 1H), 5.82 (m, 1H), 5.10 (m, 2H), 3.20 (m, 2H), 2.85 (bs, 1H), 2.55 (m, 2H), 2.35 (m, 3H), 2.08 (dd, 1H), 1.85 (m, 3H), 1.37 (m, 1H); MS *m/e* 305, 304 (M+), 276, 262, 250, 222, 177, 149, 135, 122, 107.

2-Oxo-9-(endomethyl)tricyclo-[6.3.0.0^{4,8}]undecane (10N) and 2-Oxo-9-(exomethyl)tricyclo-[6.3.0.0^{4,8}]undecane (10X).

A solution of **9** (269 mg, 0.885 mmol), tri-*n*-butyltin hydride (0.27 mL, 1 mmol) and AIBN (11 mg) in dry benzene (20 mL) was heated at 80 °C for 50 min. The reaction mixture was evaporated under reduced pressure and filtered through a short column (silica gel, 20% ether in petroleum ether) to give 0.347 g of crude product containing tin impurities. The product was further purified by MPLC (20/1 pet-ether/ether) to give a mixture (122 mg) which contained the two stereoisomers and a trace amount of tin impurities. The resulting mixture was resubjected to MPLC (20/1 pet-ether/ether) to afford the endo isomer **10N** (68 mg) and a mixture of **10X/10N** (23 mg, exo/endo=4/1). The endo isomer was further purified by Kugelrohr distillation (20 mm Hg, 150 °C) to give **10N** (48 mg) as a clear oil: **10N** ^{1}H NMR ($CDCl_3$) δ 2.45 (dd, 1H), 2.40-1.10 (m, 14H), 0.98 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 221.7 (s), 63.2 (d), 59.9 (s), 48.7 (t), 46.1 (d), 42.1 (t), 41.0 (t), 39.1 (d), 35.6 (t), 35.2 (t), 25.9 (t), 15.7 (q); IR ($CHCl_3$) 2950, 2860, 1720 cm^{-1}; MS *m/e* 178 (M+), 163, 149, 135, 123; MS *m/e* Calcd. for $C_{12}H_{18}O$: 178.1358, found: 178.1362; Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.49; H, 10.11. **10X**; ^{1}H NMR ($CDCl_3$) δ 2.64 (dd, 1H), 2.35-1.10 (m, 14H), 1.12 (d, 3H); IR ($CHCl_3$) 2950, 2860, 1720 cm^{-1}.

(*E*)-2-Methyl-3-bromobut-2-en-1-ol.

A solution of β-bromoangelic acid[22] (17.50 g, 0.067 mol) in THF (200 mL) was slowly added to a suspension of LAH (3.7 g) in THF (800 ml) at room temperature. The reaction mixture was heated at reflux for 3 h, then cooled to 0 °C. Water (3.8 mL) was added *slowly* dropwise, (*caution exothermic!*) followed by NaOH (3.8 mL, 3N), and water (11.5 mL). The white suspension was filtered and the solid was washed with ether. The combined organic solution was concentrated under reduced pressure and distilled (20 mm Hg, 120 °C) to give the alcohol (11.13 g, 69%): ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 2H), 2.40 (s, 3H), 1.98 (s, 3H).

(*E*)-1,3-Dibromo-2-methylbut-2-ene (16).

Gaseous HBr was bubbled through a solution of the above alcohol (11.13 g, 67.5 mmol) in CH_2Cl_2 (90 mL) at room temperature for 20 min. The reaction mixture was stirred for an additional 1 h, then washed with water, $NaHCO_3$, and brine, and dried over $MgSO_4$. Concentration and purification by Kugelrohr distillation (bp 130 °C, 20 mm Hg) gave **16** (11.3 g, 80%): ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 2H), 2.38 (s, 3H), 1.98 (s, 3H).

3-Ethoxy-5-methyl-5-[(*E*)-2-methyl-3-bromobut-2-enyl]cyclopent-2-en-1-one (17).

Prepared according to the experimental for **8**. A colorless oil **17** (1.12 g, 55%) was obtained after flash chromatography (8% EtOAc in hexane): ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 1H), 4.05 (q, 2H), 2.65 (d, 1H), 2.54 (d, 1H), 2.33 (d, 1H), 2.30 (s, 3H), 2.28 (d, 1H), 1.80 (s, 3H), 1.41 (t, 3H), 1.15 (s, 3H); IR ($CHCl_3$) 3000, 1680, 1590, 1380, 1345 cm^{-1}; MS *m/e* 207 (M+), 179, 140, 111; Anal. Calcd. for $C_{13}H_{19}O_2Br$: C, 54.37; H, 6.65. Found: C, 54.01; H, 6.71.

3-(But-3-enyl)-4-methyl-4-[(*E*)-2-methyl-3-bromobut-2-enyl]cyclopent-2-en-1-one (18).

Prepared according to the experimental for **9**. The compound was purified by flash chromatography (10% EtOAc in hexane) to provide **18** (310 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 5.92 (s, 1H), 5.85 (m, 1H), 5.11 (d, 1H), 5.06 (d, 1H), 2.59 (d, 1H), 2.47 (d, 1H), 2.38 (m, 4H), 2.31 (bs, 3H), 2.21 (d, 1H), 2.14 (d, 1H), 1.80 (bs, 3H), 1.24 (s, 3H); IR ($CHCl_3$) 2950, 2920, 1680, 1605 cm^{-1}; MS *m/e* 298 (M+), 296, 217, 150; MS m/e Calcd. for $C_{15}H_{21}O$ (M–Br): 217.1623. Found: 217.1627; Anal. Calcd. for $C_{15}H_{21}OBr$: C, 60.61; H, 7.12. Found: C, 60.27; H, 7.05.

3-(4-[Trimethylsilyl]but-3-ynyl)-4-methyl-4-(2-methyl-3-bromobut-2-enyl)cyclopent-2-en-1-one (20).

^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1H), 2.70-2.50 (m, 4H), 2.37 (s, 2H), 2.20 (dd, 2H), 1.85 (s, 3H), 1.60 (s, 3H), 1.30 (s, 3H), 0.18 (s, 9H).

(*E*)- and (*Z*)-15-(Trimethylsilyl)silphiperfol-6(7),9(15)-diene (21E/21Z).

Prepared according to the procedure for **10**. Evaporation of the solvent gave a residue which afforded two isomers **21E** (44 mg, 55%, less polar) and **21Z** (18.5 mg, 23%) upon purification by flash chromatography (0.1% EtOAc in hexane): **21E** (major) ^{1}H NMR ($CDCl_3$) δ 5.52 (bs, 1H), 3.07 (bs, 1H), 2.57 (d, 1H), 2.45-2.10 (m, 5H), 1.78 (m, 1H), 1.65 (m, 1H), 1.62 (s, 3H), 1.54 (s, 3H), 1.10 (s, 3H), 0.12 (s, 9H); ^{1}H NMR (benzene-d_6) δ 5.63 (bs, 1H), 3.18 (bs, 1H), 2.40-1.00 (m, 8H), 1.39 (s, 3H), 1.36 (s, 3H), 0.80 (s, 3H), 0.08 (s, 9H); IR ($CHCl_3$) 2950, 1720 cm^{-1}; MS *m/e* 287 (M–1), 231, 205. **21Z** (minor) ^{1}H NMR ($CDCl_3$) δ 5.67 (m, 1H), 2.98 (bs, 1H), 2.50-2.20 (m, 5H), 2.15 (d, 1H), 1.90-1.75 (m, 2H), 1.60 (s, 3H), 1.54 (s, 3H), 1.12 (s, 3H), 0.08 (s, 9H). ^{1}H NMR (benzene-d_6) δ 6.50 (m, 1H), 3.00 (bs, 1H), 2.35 (m, 2H), 2.15 (d, 2H), 2.01 (d, 1H), 1.85 (d, 1H), 1.60 (m, 2H), 1.40 (s, 3H), 1.27 (s, 3H), 0.90 (s, 3H), 0.13 (s, 9H); IR ($CHCl_3$) 2950, 1725 cm^{-1}; MS *m/e* 288 (M+), 273, 172.

2-Oxosilphiperfol-6(7),9(15)-diene (24).

To a solution of **21E** (7.3 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was added BF_3•OEt_2 (0.005 mL) at –78 °C. After stirring for 1 h at –78 °C and 6 h at 0 °C, the reaction mixture was diluted with ether (30 mL), washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 9 mg of crude product. This was purified by flash chromatography (silica gel, 4% EtOAc in hexane) to give **24** (5.2 mg, 95%). Compound **21Z** was converted to the same product under the same conditions: ^{1}H NMR ($CDCl_3$) δ 5.10 (d, 1H), 4.99 (d, 1H), 2.97 (bs, 1H), 2.50-2.12 (m, 6H), 1.90-1.68 (m, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.12 (s, 3H); ^{1}H NMR (benzene-d_6) δ 5.47 (d, 1H), 5.00 (d, 1H), 2.91 (bs, 1H), 2.22 (m, 2H), 2.12 (q, 2H), 1.95 (d, 1H), 1.50 (m, 2H), 1.38 (s, 3H), 1.25 (s, 3H), 0.82 (s, 3H); IR ($CHCl_3$) 3000, 2950, 1720 cm^{-1}; MS *m/e* 217, 216 (M+), 215, 205, 174, 159, 149, 134, 119.

2-Oxosilphiperfol-6(7),9(10)-diene (26).

To a solution of **24** (5 mg, 0.023 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added BF_3•OEt_2 (0.004 mL). After stirring for 2 h at 0 °C, the reaction mixture was warmed up to room temperature and stirred for 40 h. The mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give **26** (4.7 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 5.35 (bs, 1H), 3.00 (bs, 1H), 2.50-1.00 (m, 6H), 1.80 (s, 3H), 1.53 (s, 3H), 1.30 (s, 3H), 1.10 (s, 3H); ^{1}H NMR (benzene-d_6) δ 5.18 (bs, 1H), 2.95 (bs, 1H), 2.40-1.00 (m, 6H), 1.90 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 0.92 (s, 3H).

2-Oxosilphiperfol-6(7),1(9)-diene (25).

To a solution of **21Z** (15 mg, 0.051 mmol) in dry benzene (2 mL) at room temperature was added HI (3 drops, 58%). After stirring for 4 h, the reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1% EtOAc in hexane) to give **25** (5 mg, 44%): ^{1}H NMR ($CDCl_3$) δ 2.95 (m, 1H), 2.55-1.00 (m, 7H), 2.10 (bs, 3H), 1.57 (bs, 6H), 1.02 (s, 3H); ^{1}H NMR (benzene-d_6) δ 2.58 (m, 1H), 2.47 (d, 1H), 2.28 (d, 1H), 2.10-1.20 (m, 5H), 2.02 (bs, 3H), 1.48 (bs, 3H), 1.45 (bs, 3H), 0.83 (s, 3H); MS *m/e* 216 (M+), 189, 175, 161, 148, 135, 119, 105.

3-(But-3-enyl)-4-methyl-4-(*E*-2-methyl-3-bromobut-2-enyl)cyclopent-2-en-1-one, 1,3-dioxolane ketal (27).

A solution of **18** (152 mg, 0.51 mmol), ethylene glycol (0.2 mL) and PPTS (20 mg) in benzene (15 mL) was heated at reflux for 48 h with azeotropic removal of water. The reaction mixture was diluted with EtOAc, washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (10% EtOAc in hexane) gave **27a** (142 mg, 79%). Compound **27a** was partially hydrolyzed to **18** during the purification and was also cleaved on standing in CH_2Cl_2 solution

at 25 °C: ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.38 (s, 1H), 5.05 (dd, 1H), 5.00 (d, 1H), 3.92 (m, 4H), 2.47 (d, 1H), 2.35 (s, 3H), 2.30 (t, 2H), 2.20-2.05 (m, 4H), 1.88 (d, 3H), 1.80 (d, 1H), 1.10 (s, 3H).

9-Epi-2-oxosilphiperfol-6-ene, 1,3-dioxolane ketal (28N) and 2-Oxosilphiperfol-6-ene, 1,3-dioxolane ketal (28X).

A solution of tri-*n*-butyltin hydride (0.16 mL, 0.59 mmol) and AIBN (20 mg) in dry benzene (3 mL) was added through a syringe pump to a solution of crude **27** (167 mg, 0.49 mmol) in dry benzene (12 mL) at 80 °C over 2 h. After the addition, the reaction mixture was heated for an additional 2 h. Evaporation of the solvent and purification by flash chromatography (silica gel, 0.4% ether in petroleum ether) provided **28N** (16 mg, 12.5%), and a mixture of **28N/28X** (67 mg, 52%, **28N/28X**=1/5) Rechromatography of this fraction provided pure **28N:** ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 1H), 3.80 (m, 3H), 2.27 (d, 1H), 2.10 (s, 2H), 1.92 (m, 1H), 1.53 (bs, 3H), 1.50 (bs, 3H), 1.70-1.20 (m, 7H), 1.15 (d, 3H), 1.13 (s, 3H). ^{1}H NMR (benzene-d_6) δ 3.58-3.32 (m, 4H), 2.50 (d, 1H), 2.10 (s, 2H), 2.00-1.60 (m, 7H), 1.50 (s, 3H), 1.42 (s, 3H), 1.35 (d, 3H), 1.29 (s, 3H); IR ($CHCl_3$) 2950, 2870 cm^{-1}; MS *m/e* 262 (M+), 247, 217, 200, 174, 159, 133, 118, 105. **28X** ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 4H), 2.50 (d, 1H), 1.57, (bs, 3H), 1.53 (bs, 3H), 2.02-1.20 (m, 7H), 1.04 (s, 3H), 1.02 (d, 3H); ^{1}H NMR (benzene-d_6) δ 3.45 (s, 4H), 2.70 (d, 1H), 2.20 (m, 1H), 2.08-1.62 (m, 6H), 1.54 (m, 7H), 1.30 (m, 1H), 1.12 (d, 3H), 1.10 (s, 3H); IR ($CHCl_3$) 2950 cm^{-1}; MS *m/e* 262 (M+) 247, 233, 217, 200, 175, 159, 119, 105; MS *m/e* Calcd. for $C_{17}H_{26}O_2$: 262.1933. Found: 262.1932.

2-Oxosilphiperfol-6-ene (19X).

A solution of **28X** (67 mg, 0.256 mmol) and concentrated sulfuric acid (5 drops) in acetone (10 mL) was heated at reflux for 20 min. After evaporation of the solvent, the residue was dissolved in ether, washed with water and brine, and dried over $MgSO_4$. The solvent was carefully removed on a rotary evaporator without heating to give **19X** (56 mg, 100%). This was subjected to Wolff-Kishner reduction without purification. **19N** was prepared as for **19X** in quantitative crude yield. **19X** ^{1}H NMR ($CDCl_3$) δ 2.42-2.22 (AB quartet, 2H), 2.18 (bs, 2H), 2.10-2.00 (m, 2H), 1.85-1.60 (m, 3H), 1.58 (m, 6H), 1.35 (m, 1H), 1.12 (d, 3H), 1.09 (s, 3H); IR ($CHCl_3$) 2950, 1720 cm^{-1}; MS *m/e* 218 (M+), 203, 189, 175, 159, 147, 133, 119, 105; MS *m/e* Calcd. for $C_{15}H_{22}O$: 218.1671. Found: 218.1676.

2-Oxo-9-episilphiperfolene (19N).

^{1}H NMR ($CDCl_3$) δ 2.38 (d, 1H), 2.30-2.05 (m, 5H), 1.85 (m, 2H), 1.70 (m, 1H), 1.58 (s, 3H), 1.50 (s, 3H), 1.25 (m, 1H), 1.13 (s, 3H), 1.00 (d, 3H); IR ($CHCl_3$) 2950, 2925, 2870, 1720 cm^{-1}; MS *m/e* 218 (M+), 175, 159, 133, 119, 105; MS *m/e* Calcd. for $C_{15}H_{22}O$: 218.1671. Found: 218.1676.

Silphiperfolene (4).

A solution of **19X** (56 mg, 0.256 mmol), hydrazine hydrate (1 mL, 98%), and K_2CO_3 (190 mg) in 2-hydroxyethylether (1 mL) was heated at 150 °C for 4 h, then the temperature was raised to 210 °C for 12 h. Part of the reaction mixture was distilled during this time. After cooling, the residue and the distillate were combined and diluted with water. The aqueous phase was extracted with petroleum ether. The petroleum ether extract was washed with water and brine, and dried over $MgSO_4$. The solvent was carefully removed on a rotary evaporator without heating to give **4** (41.5 mg, 79%). The crude product was purified by flash chromatography (petroleum ether) to provide **4** (34.5 mg, 66%): ^{1}H NMR ($CDCl_3$) δ 2.20 (d, 1H), 1.95 (d, 1H), 1.90-1.10 (series of m, 12H), 1.54 (m, 3H), 1.52 (m, 3H), 0.99 (s, 3H), 0.96 (d, 3H); IR ($CHCl_3$) 2940, 2870 cm^{-1}. MS *m/e* 204 (M+), 189, 175, 161, 147, 133, 119, 109, 105.

9-Episilphiperfolene (14).

^{1}H NMR ($CDCl_3$) δ 2.08 (bs, 2H), 2.02-1.00 (series of m, 16H), 0.99 (s, 3H), 0.94 (d, 3H); IR ($CHCl_3$) 2950, 2870 cm^{-1}; MS *m/e* 204 (M+), 203, 189, 175, 161, 147, 133, 119, 105; MS *m/e* Calcd. for $C_{15}H_{24}$: 204.1878. Found: 204.1876.

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References and Notes

(1) Recipient of a Sloan Foundation Fellowship, 1985-87; Dreyfus Teacher-Scholar, 1985-89; Eli Lilly Grantee, 1985-87. Merck Faculty Development Awardee, 1986-87. NIH Research Career Development Awardee, 1987-92.

(2) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1. Professor Paquette informs us that the third review will appear shortly. See also: Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141, and Ramaiah, M. *Synthesis* **1983**, 529.

(3) For a compilation of recent references, see: Paquette, L. A.; Galemmo, R. A., Jr.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem.* **1986**, *51*, 686.

(4) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987 and preceeding articles in the series.

(5) For a triple radical cyclization which illustrates the need for a stereochemical control element, see: Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349.

(6) For a recent review of the application of free radical reactions in organic synthesis with many leading references, see: Giese, B. "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds", Pergamon Press: Oxford, **1986**. See also, Hart, D. J. *Science* **1984**, *223*, 883.

(7) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (c) Curran, D. P.; Chen, M. H. *Tetrahedron Lett.* **1985**, *26*, 4991.

(8) Unpublished results of Dr. Thomas Fevig.

(9) (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. (b) Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Ibid.* **1980**, *19*, 2399. Bohlmann, F.; Wallmeyer, M.; Jakupovic, J.; Ziesche, J. *Ibid*, **1983**, *22*, 1645.

(10) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690.

(11) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106.

(12) Demuth, M.; Hinsken, W. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 973.

(13) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. (b) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968. (c) Koreeda, M.; Liang, Y.; Akagi, H. *J. Chem. Soc., Chem. Commun.* **1979**, 449.

(14) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.

(15) Simple α-keto radicals may give significant amounts of 6-endo products. See: Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477.

(16) The exo/endo nomenclature refers to the relevant diquinane system containing the methyl group of interest.

(17) Much is known about the effect of substituents on the rate of hexenyl radical cyclizations. See: (a) Beckwith, A. L. J.; Ingold, K. U. in "Rearrangements in Ground and Excited States", deMayo, P., ed.; Academic Press, NY, **1980**, pp. 162-283. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (c) Surzur, J.-M. in "Reactive Intermediates", Abramovitch, R. A.; ed. Vol. 2, Chap. 3, Plenum Press, NY, **1981**. (d) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.

(18) Cyclizations may actually become reversible if sufficiently stabilized intermediates are formed. See: Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708.

(19) The predominant formation of endo bicyclooctanes in diverse radical cyclizations has been observed by many groups. For a mechanistic rationale, see reference 7b. For related cyclizations, see: Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311. Wolff, S.; Agosta, W. C. *J. Chem. Res. Synop.* **1981**, 79. For theoretical treatments of the stereochemistry of radical cyclizations, see: Beckwith, A. L. J.; Schiesser, C. *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(20) (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R. Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (c) Stork, G.; Mook, R. Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (d) Baine, N. H. Ph.D. Thesis, Columbia University, 1981.

(21) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

(22) Buckles, R. E.; Mock, G. V. *J. Org. Chem.* **1950**, *15*, 680.

(23) For substitution of dimethyltetrahydropyrimidinone (DMPU) for HMPA, see: Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta.* **1982**, *65*, 385.

(24) Several methods for securing the required stereochemistry were considered. For example, while direct hydrogenation of an alkene would likely produce the undesired endo methyl isomer, reduction of the carbonyl to an endo alcohol, followed by a directed hydrogenation, was one solution considered. Alternatively, dissolving metal reduction of an enone might give the correct stereochemistry.

(25) (a) The selection of the propargyl silane was based on the work of Hart. Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (b) In a related desilylation, an allyl silane has been isolated in 10% yield. See reference 19 in the above paper.

(26) The strain inherent in alkenes such as **25** is well recognized. For example, the parent bicyclooctenone is readily deconjugated at equilibrium. Whitesell, J. K.; Minton, M. A.; Flanagan, W. G. *Tetrahedron* **1981**, *37*, 4451.

(27) Meyers, A. I.; Lefker, B. A. *Tetrahedron*, this issue. See, also: Meyers, A. I.; Lefker, B. A. *Tetrahedron Lett.* **1987**, *28*, 1745.