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INTRAMOLECULAR ADDITIONS OF ALLYLSILANES TO CONJUGATED DIENONES. TWO SYNTHESES OF (±)-EPI-WIDDROL.[1†]

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†Dedicated to Professor Walter Gensler (1917-1987)

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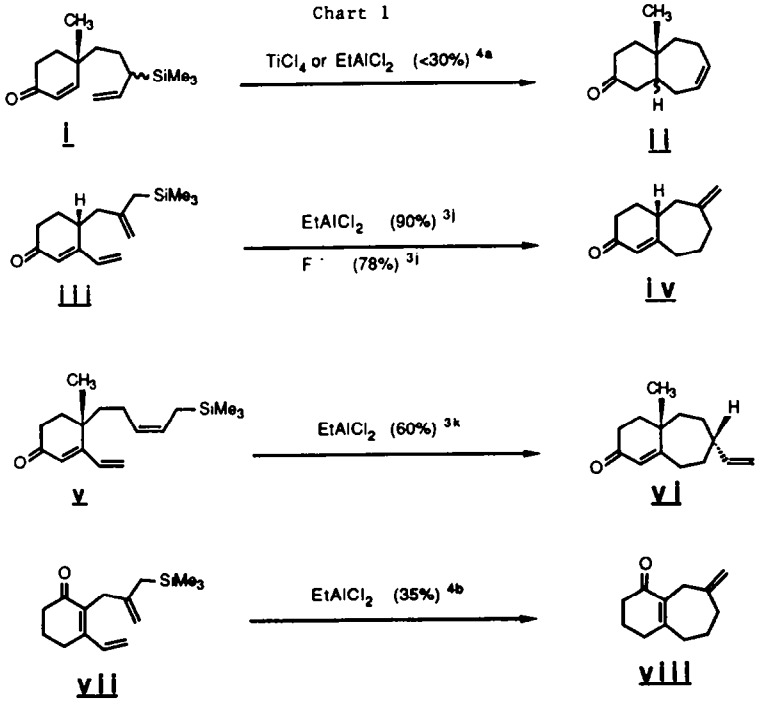
SUMMARY: Two stereospecific total syntheses of epi-widdrol (1) are reported. The first synthesis features the cyclization of dienone 3a to construct bicyclic adduct 4a which is converted to epi-widdrol using conventional procedures. A second synthesis exploits the cyclization of dienone 17 to prepare functionalized bicyclo[5.4.0]undecene 18, which is converted to a known epi-widdrol precursor.

INTRODUCTION: Although many reactions of allylsilanes are known, their use as key intermediates in the synthesis of natural products has been limited.[2] In addition, few general methods exist which efficiently annulate five- through eight-membered rings. The intramolecular addition of allylsilanes to electrophilic olefins represents a unique solution to these challenges.[3] Chart 1 illustrates four cyclizations, developed in our laboratories,[4] which annulate a cycloheptane ring.[5] The cyclization of a 4-iso-butenyl-dienone,[6] such as trienone iii, was recently utilized in a stereospecific synthesis of perforenone, a marine metabolite containing a 6,7-bicyclic skeleton.[3i,j] In this manuscript we report the total synthesis of epi-widdrol (1) via two of the cycloheptane annulation strategies shown below.

Chart 1



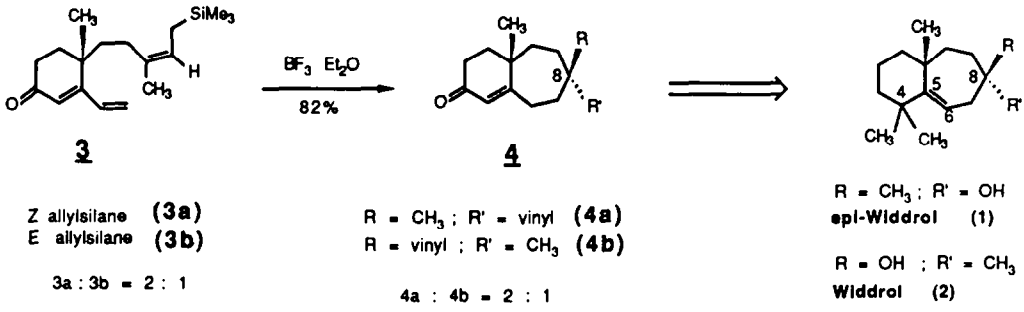
i ii iii iv v vi vii viii

RESULTS AND DISCUSSION:

First Synthesis:

While establishing the scope of intramolecular additions of allylsilanes to dienones, we observed that the cyclization of 3 occurred in 82% yield and produced a 2:1 mixture of epimers, 4a and 4b, unlike the cyclization of v,[3k] which was stereospecific (Eq. 1). Rationalization for the diastereoselectivity of these cyclizations is discussed in another manuscript.[7]

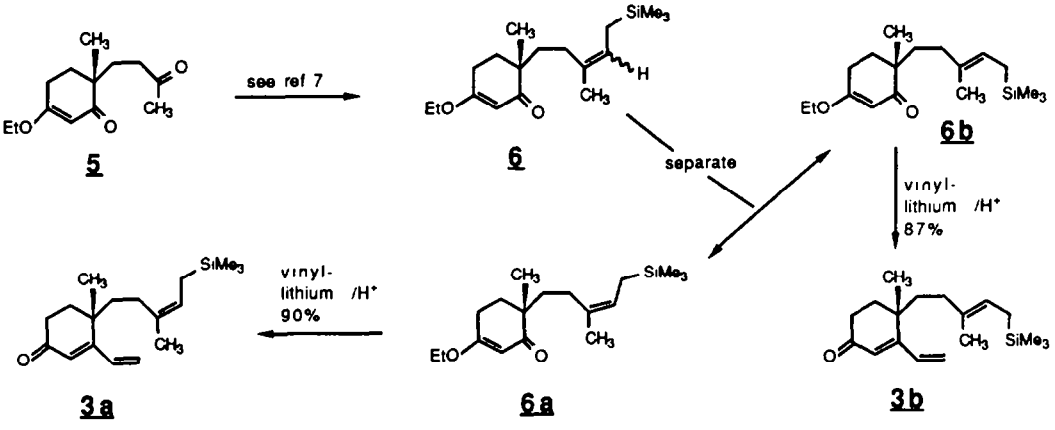
Equation 1



Enones 4a and 4b represent logical precursors to epi-widdrol[8] and widdrol (2),[9-11] respectively. The enone unit present in these substrates permits elaboration of the cyclohexane ring and introduction of the C(5)-C(6) double bond, while the C(8) vinyl group allows generation of the requisite tertiary alcohol with complete stereochemical control. We predicted that the geometry of the allylsilane would dictate the resulting stereochemistry at C(8), since trienone 3 was derived from diketone 5[7] via a Seyferth-Wittig reaction[12] and consisted of a 2:1 mixture of E and Z isomers. If this conjecture proved valid, such stereoselectivity could be used to synthesize the basic carbon framework of widdrol or epi-widdrol by cyclizing the appropriate tri-substituted allylsilane precursor.

In order to test this strategy, we proceeded to separate the E and Z isomers of 6 (Eq. 2). Their olefin geometries were assigned based on DIFNOE experiments.[13] Treatment with vinyllithium, followed by mild acid hydrolysis, yielded trienones 3a and 3b.

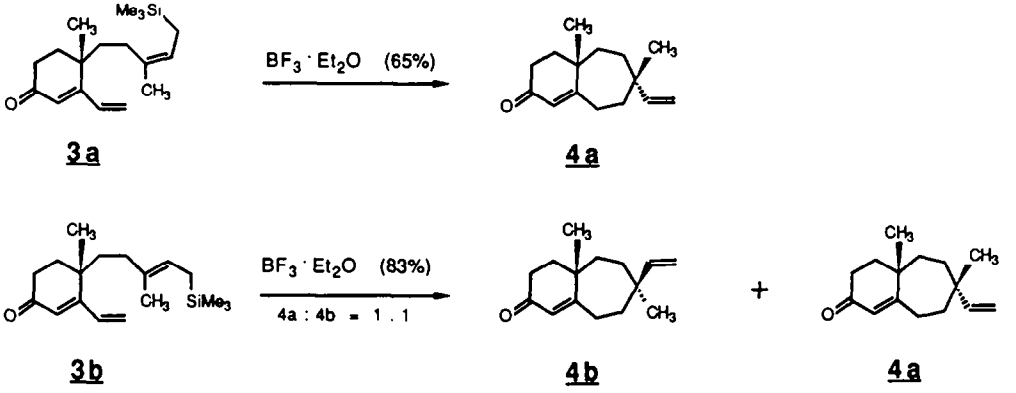
Equation 2



Cyclization of 3a, which possesses a Z allylsilane moiety, produced a single adduct in which the stereochemistry at C(8) which could not be assigned based on spectral properties (Eq. 3). Meanwhile, cyclization of 3b, which has an E allylsilane, generated an inseparable 1:1 mixture of isomers 4a and 4b. In general, an E allylsilane is more reactive than the Z geometric isomer. However, the inverse of this generalization was observed in the cycli-

zations of 3a and 3b; the reason for this difference is presently not understood. Other catalysts were examined to improve the diastereoselectivity of the cyclization of 3b. Although $TiCl_4$ promoted cyclization, prolonged reaction times caused the adduct to suffer decomposition. Milder Lewis acids, such as $EtAlCl_2$, gave only protodesilylation products and unreacted starting material.

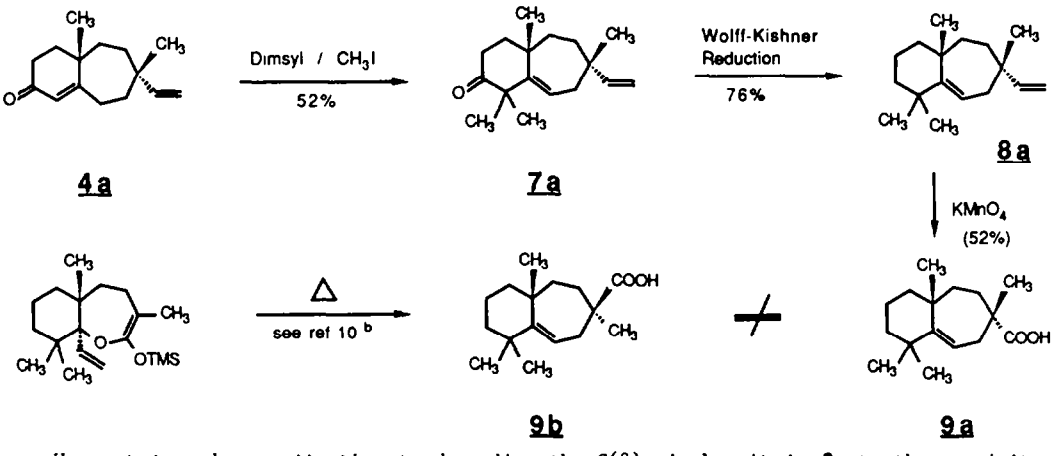
Equation 3



We initially assumed that the selective cyclization product 4a possessed the desired trans relationship between the C(4) and C(8) methyl groups necessary for widdrol. Conversion of this material to an intermediate (9b, Eq. 4) in Danishefsky's widdrol synthesis[10b] would establish the relationship between the two methyl groups. The structures shown in Eqs. 3 through 5 were based on this comparison. They indicate that our initial assumption was incorrect.

Having assembled a 6,7-bicyclic ring system, we next set out to appropriately functionalize the cyclohexane ring; this required the generation of the C(4) geminal-methyl groups and removal of the C(3) carbonyl. These transformations were achieved as follows (Eq. 4). Alkylation of the enolate of enone 4a with methyl iodide under conditions of thermodynamic control produced the desired C(4) geminal pairing and moved the C(4)-C(5) olefin into the cycloheptane ring. Wolff-Kishner reduction resulted in the removal of the C(3) carbonyl in 76% yield.[14,15]

Equation 4

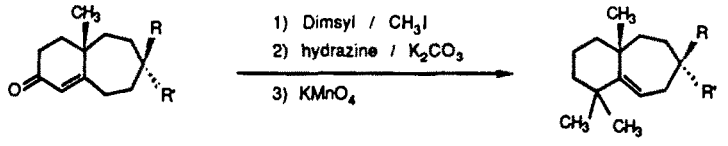


We next turned our attention to degrading the C(8) vinyl unit in 8a to the requisite tertiary alcohol. Diene 8a was oxidized to acid 9a via ApSimon's modification[16] of the Lemieux-von Rudloff oxidative procedure.[17] Unfortunately, as mentioned earlier, TLC and and NMR analysis indicated that 9a was isomeric with an authentic sample. Acid 9a was stereospecifically converted to epi-widdrol via a known three-step carboxy inversion process.[18,10b]

Analogously, we carried the inseparable mixture of adducts obtained via the cyclization of **3b** through the same sequence of steps (Eq. 5). Acids **9a** and **9b** were separable. Isomer **9b**, which constituted half of the material, was identical to Danishefsky's known widdrol precursor, thus constituting a formal synthesis.

We were curious whether changing the nature of the silicon ligands would modify the stereoselectivity of the cyclization. Despite the multitude of methods known for preparing allylsilanes, few permit the stereoselective preparation of tri-substituted allylsilanes. The method developed by Fleming and co-workers is an exception. They reported that treatment of an allylic acetate with the silyl cuprate derived from phenyldimethylchlorosilane forms the least substituted allylsilane in high yield.[19] Applying this method to lactone **10**,[20]

Equation 5



R = CH_3 ; R' = vinyl **(4a)**
R = vinyl ; R' = CH_3 **(4b)**

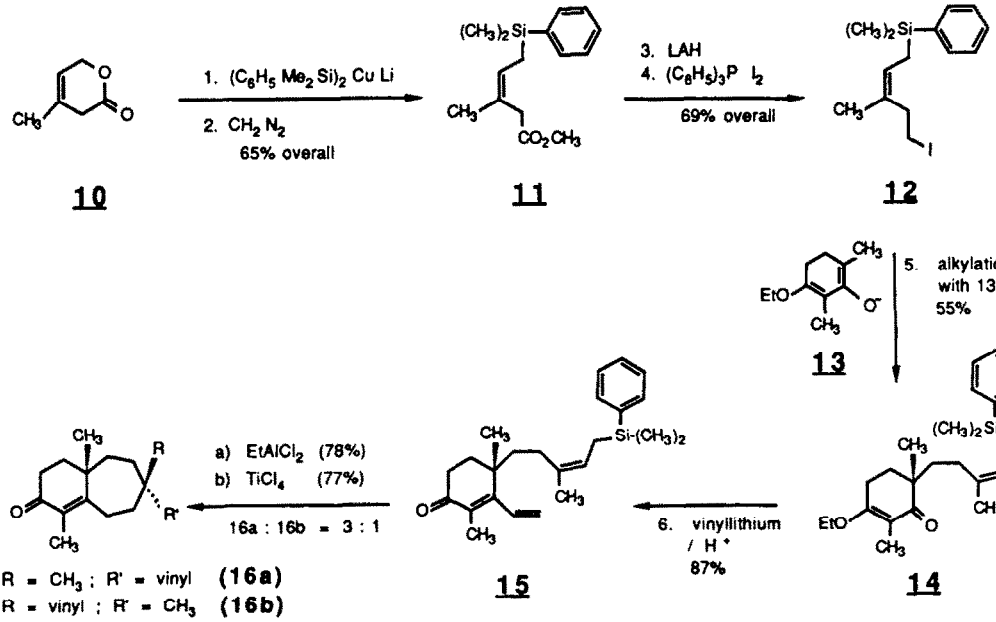
4a : 4b = 1 : 1

R = CH_3 ; R' = COOH **(9a)**
R = COOH ; R' = CH_3 **(9b)**

9a : 9b = 1 : 1

a cyclic allylic acetate, we generated an allylsilane acid which was immediately esterified to provide **11** in 65% yield (Eq. 6).[21] Lithium aluminum hydride reduction of **11** provided an alcohol which was converted into homoallylic iodide **12** using diiodotriphenylphosphorane.[22] The kinetic enolate generated from 2,6-dimethyl-3-ethoxy-2-cyclohexen-1-one (**13**) was alkylated with **12** to give ketone **14** in 55% yield.[23] Note that this alkylation proceeds in good yield despite the use of an electrophile prone to elimination.[24] Ketone **14** was then converted to trienone **15** as shown.

Equation 6



10 **11** **12** **13** **14** **15**

R = CH_3 ; R' = vinyl **(16a)**
R = vinyl ; R' = CH_3 **(16b)**

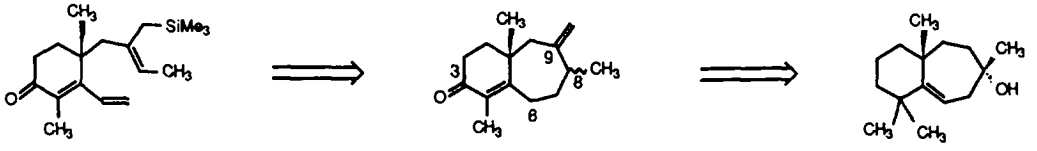
The cyclization of **15** was troublesome. On occasion large excesses (6 equivalents) of boron trifluoride etherate were required to complete reaction. Not only was **15** less reactive

than its trimethylsilyl analogue, but this compound generated a 3:1 mixture of C(8) epimers; NMR analysis indicated that the predominant isomer was the epi-widdrol precursor **4a**.[25] Use of $TiCl_4$ also furnished an identical epimeric mixture of enone **16** in 77% yield; however, the presence of phenyldimethylsilyl-containing byproducts complicated its purification. Enone **16** was carried through the remaining steps of the synthesis to afford epi-widdrol and widdrol in a 3:1 ratio.

Second Synthesis:

An alternative synthesis of epi-widdrol features the Lewis acid-catalyzed cyclization of a 4-iso-butenyl dienone to assemble the basic carbon framework (cf. **17**→**18**, Eq. 7).

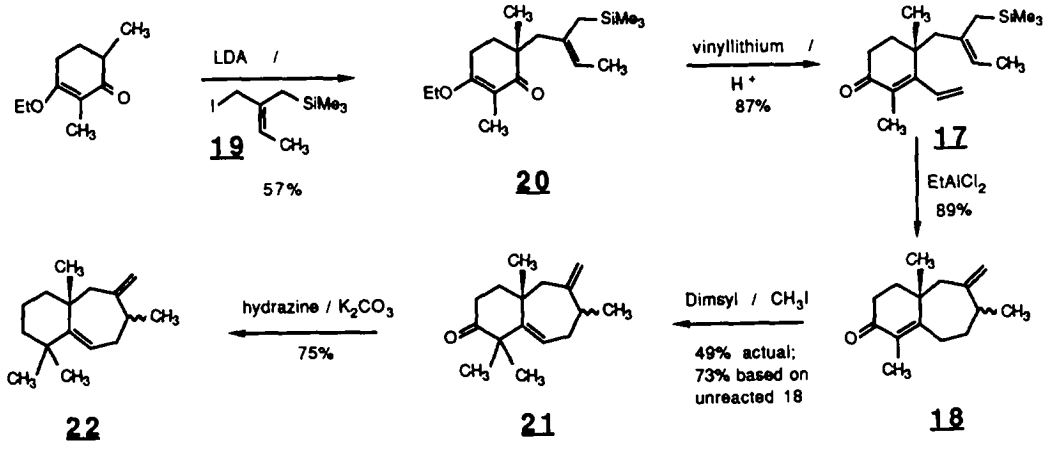
Equation 7



17 **18** **1**

This synthesis begins with the alkylation of the kinetically derived enolate of 2,6-dimethyl-3-ethoxy-2-cyclohexen-1-one with iodide **19**.[31] Generation of the complete skeletal system was accomplished in a fashion analogous to the first synthesis: 1) addition of vinyllithium, 2) mild acid hydrolysis, 3) intramolecular addition of the allylsilane, 4) introduction of the gem-dimethyl unit, and 5) Wolff-Kishner reduction. These five transformations were achieved in 42% overall yield (Eq. 8).

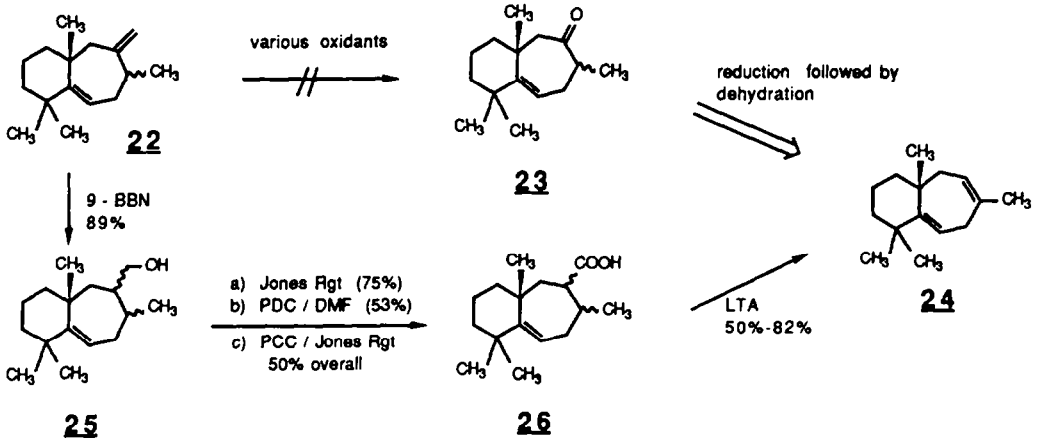
Equation 8



Models of diene **22** suggested that the C(5)-C(6) tri-substituted olefin was far more hindered than the C(9) exocyclic olefin. We hoped that this would permit their differentiation.

Two routes were examined to prepare diene **24** from **22**. The first approach required the preparation of ketone **23** and its subsequent reduction and dehydration (Eq. 9). Unfortunately, typical oxidative cleavage reagents such as ozone or potassium permanganate[17] were non-selective; oxidation of the tri-substituted double bond often predominated. In contrast, the sterically bulky oxidant osmium tetroxide failed to react with either double bond. Unable to realize ketone **23**, we turned to an alternative pathway. Treatment of diene **22** with 9-BBN,

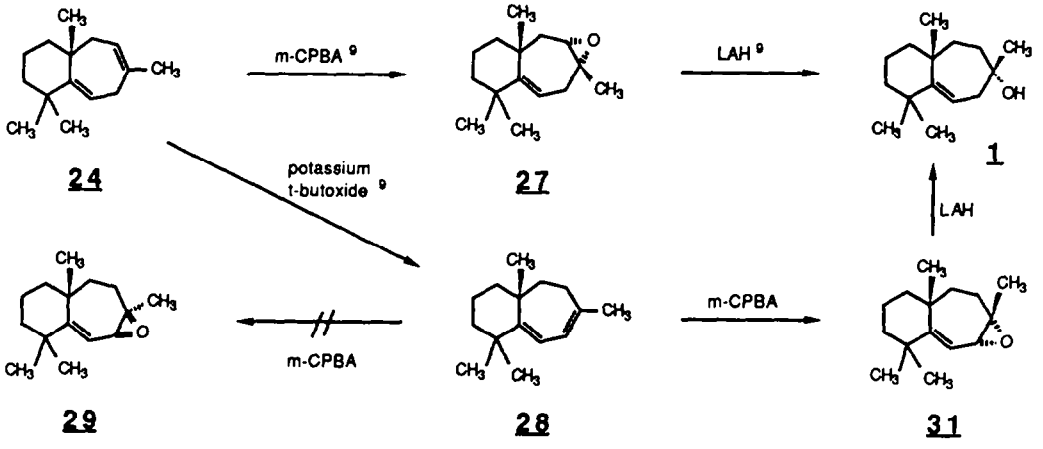
Equation 9



followed by oxidative work-up, gave exclusively alcohol 25 in 77% yield. Oxidation of this compound to acid 26 could be achieved in a number of ways. Oxidative decarboxylation of 26 using lead tetraacetate[26] gave diene 24 directly, although yields were inconsistent.

Equation 10 illustrates two routes used to prepare epi-widdrol from diene 24. The preparation of epoxide 27 from 24 and its reduction to 1 has been reported by Dauben and co-workers.[9] We speculated that isomerization of diene 24 to conjugated diene 28 might lead to a conformation favorable for epoxidation from the β-face of the molecule (cf. 29).[27] However, epoxidation of 28 furnished a single epoxide which yielded epi-widdrol upon reduction with LAH. In contrast to the reduction of epoxide 27, which required 18 hours at 85°C for completion, opening of epoxide 30 at the allylic position occurred within several hours at room temperature.

Equation 10



Conclusion: Our pioneering studies have demonstrated that the intramolecular addition of allylsilanes to electrophilic olefins represents a fundamentally new approach to carbocyclic bond construction. The syntheses of epi-widdrol described above exemplify the directness of this annulation strategy in assembling carbon skeletons. Moreover, the ability of this methodology to diastereoselectively generate polyfunctionalized systems predictably will facilitate the design of synthetic routes to more complex natural products.

EXPERIMENTAL SECTION

General: Routine ^1H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane at 0.00 ppm. The data reported as integer numbers are accurate to within ± 10%. ^1H NMR data are presented as follows: chemical shift (multiplicity, number of protons, coupling constants in Hertz). Fourier transform NMR spectra were determined in $CDCl_3$ on a JEOL FX 90Q 90MHz (^1H)/22.5 MHz (^{13}C) instrument or a JEOL FX 270 MHz instrument with an ^2H internal lock. Infrared (IR) spectra were recorded as thin films between polished sodium chloride plates on a Perkin-Elmer 197 Grating Infrared Spectrometer. All absorption bands are reported in wave numbers (cm^{-1}), which were calibrated against the 1601 cm^{-1} absorption band of polystyrene. Low resolution mass spectra were recorded on a Finnigan 4023 Chromatograph-Mass Spectrometer by a direct probe and are expressed in m/z units. Microanalysis was performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Anhydrous tetrahydrofuran (THF) and diethyl ether were prepared by refluxing with, and distillation from, sodium/benzophenone under a nitrogen atmosphere in a recycling still. Anhydrous hexamethylphosphoramide (HMPA) was prepared by refluxing over and distillation from calcium hydride under a dry nitrogen atmosphere and stored over 4A molecular sieves. Anhydrous toluene and diisopropylamine were prepared by refluxing over and distillation from calcium hydride and stored over sodium metal and potassium hydroxide pellets, respectively.

All reactions were run under an inert atmosphere of nitrogen, and monitored by TLC analysis until the starting material was completely consumed. Unless otherwise indicated, all ethereal workups consisted of the following procedure: The reaction mixture was quenched at room temperature with saturated aqueous ammonium chloride. The organic solvent was removed under reduced pressure on a rotary evaporator and the residue was taken up in ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to constant weight, afforded a crude residue which was purified by flash chromatography using MN silica gel 60 (230-400 mesh ASTM) and distilled reagent grade solvents.

I. Epi-WIDDROL VIA A 4-N-PENTENYL-DIENONE CYCLIZATION.[6]

Preparation of 6a and 6b: Enones **6a** and **6b** were prepared via a Seyferth-Wittig reaction[13] on 3-ethoxy-6-methyl-6-(3-oxobutyl)-2-cyclohexen-1-one.[7] A mixture of 854 mg of the E and Z isomers was separated using a Harrison Chromatotron (2 mm plate, elution with hexanes/ether, 15:1) to afford 300 mg of pure **6a** and 553 mg of pure **6b** (R_f **6a** = 0.74, R_f **6b** = 0.65, hexanes/ether, 1:1).

3-ethoxy-6-methyl-6-[(Z)-3-methyl-5-(trimethylsilyl)-3-pentenyl]-2-cyclohexen-1-one (**6a**): ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H), 1.10 (s, 3H), 1.30-1.40 (m, 5H), 1.34 (t, 3H, J = 6Hz), 1.40-2.00 (m, 9H), 1.67 (s, 3H), 2.30-2.50 (m, 2H), 3.88 (q, 2H, J = 6Hz), 5.10 (t, 1H, J = 9Hz), 5.24 (s, 1H); ^{13}C NMR ($CDCl_3$) 203.6 (s), 175.3 (s), 132.4 (s), 120.2 (d), 101.1 (d), 63.9 (t), 43.1 (s), 34.8 (t), 31.9 (t), 25.8 (t), 25.8 (t), 23.3 (q), 21.9 (q), 18.0 (t), 13.9 (q), -1.8 (q) ppm; IR (film) 3000-2850, 1660, 1620, 1385, 1320, 1300, 1255, 1200, 1160, 1115, 1025, 800 cm^{-1}; mass spectrum, m/z 308 (M+).

3-ethoxy-6-methyl-6-[(E)-3-methyl-5-(trimethylsilyl)-3-pentenyl]-2-cyclohexen-1-one (**6b**): ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.08 (s, 3H), 1.34 (t, 3H, J = 6Hz), 1.36 (d, 2H, J = 6Hz), 1.40-2.00 (m, 9H), 1.52 (s, 3H), 2.33-2.46 (m, 2H), 3.88 (q, 2H, J = 6Hz), 5.15 (t, 1H, J = 9 Hz), 5.23 (s, 1H); ^{13}C NMR ($CDCl_3$) 203.7 (s), 175.3 (s), 132.2 (s), 119.8 (d), 101.0 (d), 63.8 (t), 42.9 (s), 35.6 (t), 34.1 (t), 31.7 (t), 25.8 (t), 21.9 (q), 18.3 (t), 15.6 (q), 13.9 (q), -1.9 (q) ppm; IR (film) 3000-2850, 1660, 1620, 1390, 1365, 1255, 1200, 1120, 1050, 850 cm^{-1}; mass spectrum, m/z 308 (M+).

4-Methyl-4-[(Z)-3-methyl-5-(trimethylsilyl)-3-pentenyl]-3-vinyl-2-cyclohexen-1-one (3a): A solution of 560 mg (1.8 mmol) of **6a** in 20 mL of THF at 0°C was treated dropwise with 1.2 mL of vinyllithium (2.3 M, 2.72 mmol) over a 30-min period. The reaction was then stirred for 45 min at room temperature. Standard ethereal workup provided 1.1 gram of crude residue which was used directly in the next reaction.

The crude alcohol was dissolved in 10 mL of THF and 10 drops of 10% HCl were added. After stirring at room temperature for 45 min, the reaction was quenched by the addition of solid potassium carbonate and then filtered. Following removal of the solvent, the crude trienone was chromatographed on silica gel (elution with hexanes/ether, 10:1) to provide 474 mg (90%) of dienone **3a** which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **6a** = 0.54, R_f **3a** = 0.74); ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.12 (s, 3H), 1.25-2.20 (m, 11H), 1.33 (d, 2H, J = 6Hz), 1.67 (s, 3H), 2.40-2.51 (m, 2H), 5.13 (t, 1H, J = 9Hz), 5.37 (dd, 1H, J = 11 Hz, 2Hz), 5.72 (dd, 1H, J = 17Hz, 2 Hz), 5.97 (dd, 1H, J = 17Hz, 11Hz), 6.13 (s, 1H); ^{13}C NMR ($CDCl_3$) 199.4 (s), 165.6 (s), 134.8 (d), 131.8 (s), 123.4 (d), 120.6 (d), 119.9 (t), 37.4 (s), 37.1 (t), 33.9 (t), 33.1 (t), 26.8 (t), 24.5 (q), 23.2 (q), 18.2 (t), -1.8 (q) ppm; IR (film) 3000-2800, 1675, 1600, 1420, 1385, 1335, 1280, 1250, 1160, 990, 935, 860 cm^{-1}; mass spectrum, m/z 290 (M+).

trans-3,4,4a,5,6,7,8,9-Octahydro-4a,7-dimethyl-7-vinyl-2H-benzocyclohepten-2-one (4a): To 410 mg (1.4 mmol) of trienone **3a** in 20 mL of dry toluene at 0°C was added dropwise 870 µL (7.0 mmol) of freshly distilled boron trifluoride etherate. The reaction mixture was stirred at 0°C for 90 min and then diluted with 100 mL of wet ether, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed on silica gel (elution with hexanes/ether, 5:1) to provide 200 mg (65%) of enone **4a** which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **3a** = 0.69, R_f **4a** = 0.46); ^1H NMR

($CDCl_3$) δ 1.02 (s, 3H), 1.13 (s, 3H), 1.31 (br s, 2H), 1.53-1.85 (m, 4H), 2.07-2.58 (m, 6H), 4.80 (d, 1H, J = 11Hz), 4.85 (d, 1H, J = 17Hz), 5.68 (dd, 1H, J = 17Hz, 11Hz), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$) 199.4 (s), 174.7 (s), 149.9 (d), 127.0 (d), 109.4 (t), 41.3 (t), 38.9 (s), 38.1 (s), 35.4 (t), 34.6 (t), 34.0 (t), 33.7 (t), 29.8 (t), 25.3 (q), 22.8 (q) ppm; IR (film) 3075, 3000-2970, 1660, 1640, 1610, 1450, 1405, 1380, 1360, 1345, 1260, 1235, 1220, 1020, 980, 910 cm^{-1}; mass spectrum, m/z 218 (M+). Anal. Calc'd for $C_{15}H_{22}O$: C, 82.51; H, 10.15. Found: C, 82.36; H, 10.21.

2,3,4,4a,5,6,7,8-Octahydro-1,1,4a,7-tetramethyl-7-vinyl-1H-benzocyclohepten-2-one (7a): To 107 mg of 80% NaH (3.56 mmol) was added 2 mL of freshly distilled DMSO. The resulting mixture was warmed at 75°C until hydrogen evolution ceased [≈ 30 min] and then cooled to room temperature. A solution of 370 mg (1.7 mmol) of **4a** dissolved in 2 mL of DMSO was then added to the reaction mixture. After stirring 1 h at room temperature the solvent was removed in vacuo. The resulting brown residue was dissolved in 15 mL of dry THF and 506 mg (3.56 mmol) of freshly distilled iodomethane were added. The reaction was stirred for 12 h at room temperature. Standard ethereal workup gave 0.5 g of a crude oil. Chromatography of the crude product (elution with hexanes/ether, 8:1) afforded 219 mg (52%) of **7a**, which was homogeneous by TLC analysis (hexanes/ether, 3:1 R_f **4a** = 0.45, R_f **7a** = 0.83): ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.07 (s, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 1.40-1.75 (m, 4H), 1.78-2.18 (m, 2H), 2.28 (dd, 2H, J = 9Hz, 6 Hz), 2.45 (dd, 2H, J = 6Hz, 3Hz), 4.88 (dd, 1H, J = 12Hz, 2Hz), 5.55 (dd, 1H, J = 5Hz, 4Hz), 5.81 (dd, 1H, J = 12Hz, 9Hz); ^{13}C NMR ($CDCl_3$) 215.2 (s), 150.6 (s), 146.4 (d), 121.5 (d), 111.0 (t), 50.5 (s), 39.0 (s), 37.1, 37.1, 35.8, 34.5, 34.4, 29.0 (q), 26.6 (q), 24.0 (q) ppm; IR (film) 3090, 3000-2870, 1710, 1680, 1640, 1460, 1420, 1380, 1260, 1120, 1010, 920 cm^{-1}; mass spectrum, m/z 246 (M+).

trans-3,4,4a,5,6,7,8,9-Octahydro-4a,7-dimethyl-7-vinyl-2H-benzocyclohepten-2-one (8a): A mixture of **7a** (170 mg, 0.7 mmol), hydrazine hydrate (0.2 mL, 6.2 mmol), anhydrous potassium carbonate (1.14 g, 8.3 mmol), and diethylene glycol (8 mL) was placed into a round bottom flask equipped with a short-path distillation apparatus and heated at 160°C for 2 h followed by heating at 230°C for 3 h. The cooled reaction mixture was combined with any distillate, diluted with water, and extracted with ether. The combined organic extracts were washed with cold 10% HCl, dried over anhydrous magnesium sulfate and filtered. Concentration in vacuo, followed by chromatography on silica gel (elution with hexanes), gave 121 mg (76%) of diene **8a** (hexanes, R_f **7a** = 0.05, R_f **8a** = 0.87): ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.09 (br s, 6H), 1.18 (s, 3H), 1.38-1.80 (m, 10H), 2.27 (overlapping dd, 2H, J = 14Hz, 6Hz), 4.80 (br s, 1H), 4.85 (d, 1H, J = 16Hz), 5.50 (dd, 1H, J = 14Hz, 6Hz), 5.84 (dd, 1H, J = 16Hz, 14Hz); ^{13}C NMR ($CDCl_3$) 152.5 (s), 148.0 (d), 118.6 (d), 110.0 (t), 41.7, 41.7, 40.3, 39.2, 36.6, 32.9, 32.0, 31.0-25.0 (br peak), 18.7 ppm; IR (film) 3080, 3050, 2950-2840, 1630, 1460, 1420, 1370, 1000, 910, 850 cm^{-1}. Anal. Calc'd for $C_{17}H_{28}$: C, 87.85; H, 12.14. Found: C, 88.06; H, 12.32.

trans-2,3,4,4a,5,6,7,8-Octahydro-1,1,4a,7-tetramethyl-1H-benzocycloheptene-7-carboxylic acid (9a): The ApSimon modification[16] of the Lemieux-von Rudloff oxidative cleavage[17] was employed. Diene **8a** (120 mg, 0.52 mmol) was dissolved in 25 mL of tert-butanol and treated, with stirring, with a solution of 664 mg (3.1 mmol) of sodium metaperiodate and 3 mg of potassium permanganate in 50 mL of water. The reaction mixture was kept at pH 8 by the addition of 5% aqueous K_2CO_3 [≈1 mL], and stirred until the color of the permanganate was dissipated (3 h). The reaction mixture was then acidified with 20% aqueous hydrochloric acid. Standard ethereal workup provided 67 mg (52%) which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f **8a** = 0.94, R_f **9a** = 0.66): ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.30-1.80 (m, 8H), 1.90-2.10 (m, 2H), 2.18 (dd, 2H, J = 14Hz, 6Hz), 5.58 (t, 1H, J = 7 Hz), no carboxylic acid proton observed; ^{13}C NMR ($CDCl_3$) 184.8 (s), 153.1 (s), 118.0 (d), 44.5, 41.5, 41.0-37.0 (br peak), 36.6, 31.0-34.0 (br peak), 23.0-29.0 (br peak), 17.7 (q) ppm; IR (film) 3100-2500, 1700, 1460, 1400, 1370, 1290, 1230, 1100, 930 cm^{-1}; mass spectrum, m/z 250 (M+).

epi-Widdrol (1): The three-step carboxy-inversion procedure developed by Denney and Sherman[17] was utilized[10b]. A solution of **9a** (70 mg, 0.28 mmol) in 1 mL of dry benzene was treated with 0.1 mL of freshly distilled thionyl chloride. The resulting mixture was stirred at 75°C for 1 h followed by removal of volatiles in vacuo. The crude acid chloride [hexanes/ether, 2:1, R_f **9a** = 0.46, R_f acid chloride = 0.54] was used immediately in the next reaction without purification or characterization.

This acid chloride (≈ 0.28 mmol) was then dissolved in 1 mL of dry pentane, cooled to -25°C, and treated with 58 mg (0.28 mmol) of 85% m-chloroperbenzoic acid and 23 μL (0.28 mmol) of pyridine. The stirred mixture was allowed to warm to room temperature over a 12-h period, filtered, and concentrated. The crude mixed carbonate [R_f acid chloride = 0.51, R_f carbonate = 0.97, hexanes/ether, 2:1] was used immediately in the next reaction without purification or characterization.

To the above crude carbonate (≈ 0.28 mmol), dissolved in 1 mL of anhydrous ether and cooled to 0°C, was added 50 mg of lithium aluminum hydride. The resulting mixture was stirred at 0°C for 30 min and diluted with reagent grade ether. Evaporation of the solvent, after filtration to remove suspended material, gave crude epi-widdrol. Purification on silica gel (elution with hexanes/ether, 2:1) gave 25 mg (40% from **9a**) of pure epi-widdrol which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **1** = 0.50): ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.10 (s, 3H), 1.11 (s, 3H), 1.19 (s, 3H), 1.01-1.94 (m, 23H), 2.00-2.13 (br s, 1H), 2.39 (dd, 1H, J = 14 Hz, 5 Hz), 5.49 (dd, 1H, J = 7Hz, 5Hz); ^{13}C NMR ($CDCl_3$) 118.1 (d), 96.0 (s), 42.5 (s), 41.6 (t), 41.0 (s), 39.3 (q), 39.3 (t), 39.3 (t), 39.2 (t), 38.4 (q), 38.4 (t), 37.0 (s), 32.7 (q), 30.1 (q), 18.1 (t) ppm; IR (film) 3650-3100, 3050-2800, 1460, 1380, 1230, 1120, 760 cm^{-1}; mass spectrum, m/z 204 (M-18). Anal. Calc'd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 81.29; H, 11.40.

4-Methyl-4-[(E)-3-methyl-5-(trimethylsilyl)-3-pentenyl]-3-vinyl-2-cyclohexen-1-one (3b): A solution of 625 mg (2.0 mmol) of **6b** in 25 mL of THF at 0°C was treated dropwise with 1.8 mL of vinyllithium (2.3 M, 4.06 mmol) over a 30-min period and stirred for 45 min at room temperature. Standard ethereal workup provided 0.9 g of crude residue which was used directly in the next reaction.

The crude alcohol was dissolved in 10 mL of THF and 10 drops of 10% HCl were added. After stirring at room temperature for 45 min, the reaction was quenched by the addition of solid potassium carbonate and then filtered. Following removal of the solvent, the crude trienone was chromatographed on silica gel (elution with hexanes/ether, 10:1) to provide 524 mg (89%) of trienone **3b** which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **6b** = 0.67, R_f **3b** = 0.74): ^{1}H NMR ($CDCl_3$) δ -0.10 (s, 9H), 1.17 (s, 3H), 1.37 (d, 2H, J = 6Hz), 1.53 (s, 3H), 1.50-2.20 (m, 9H), 2.40-2.50 (m, 2H), 5.16 (t, 1H, J = 8Hz), 5.36 (dd, 1H, J = 12Hz, 2Hz), 5.70 (dd, 1H, J = 16Hz, 2Hz), 6.10 (s, 1H), 6.44 (dd, 1H, J = 16Hz, 12Hz); ^{13}C NMR ($CDCl_3$) 199.3 (s), 165.7 (s), 134.0 (d), 131.8 (s), 123.4 (d), 120.4 (d), 119.8 (t), 38.1 (t), 37.3 (s), 34.4 (t), 33.9 (t), 33.1 (t), 24.6 (q), 18.5 (t), 15.7 (q), -1.8 (q) ppm; mass spectrum, m/z 290 (M+).

A mixture of 4a and cis-3,4,4a,5,6,7,8,9-Octahydro-4a,7-dimethyl-7-vinyl-2H-benzocyclohepten-2-one (4b): To 335 mg (1.1 mmol) of trienone **3b** in 15 mL of dry toluene at 0°C was added dropwise 710 μL (5.7 mmol) of freshly distilled boron trifluoride etherate. The reaction mixture was stirred at 0°C for 2 h and then diluted with 100 mL of wet ether, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed (elution with hexanes/ether, 4:1) to provide 210 mg (83%) of enones **4a** and **4b** which were homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **3b** = 0.69, R_f **4** = 0.47): ^{1}H ($CDCl_3$) δ 0.92 (s, 1.5 H), 1.08 (s, 1.5 H), 1.12 (s, 1.5 H), 1.18 (s, 1.5 H), 1.21-2.6 (m, 12 H), 4.80-4.95 (m, 1 H), 4.95-5.15 (m, 1 H), 5.71 (dd, 0.5 H, J = 18 Hz, 13 Hz), 5.74 (dd, 0.5 H, J = 18 Hz, 13 Hz), 5.83 (s, 0.5 H), 5.85 (s, 0.5 H); mass spectrum, m/z 218 (M+). This data represents a 1:1 mixture of C(8) isomers based on NMR intergration.

cis-3,4,4a,5,6,7,8,9-Octahydro-4a,7-dimethyl-7-vinyl-2H-benzocyclohepten-2-one (9b): Treatment of 265 mg (1.2 mmol) of a 1:1 mixture of **4a** and **4b** with 48 mg of 85% sodium hydride (1.58 mmol) and 0.18 mL of iodomethane (2.8 mmol) as previously described in the preparation of **7a** gave 177 mg (34%) of **7a** and its C(8) isomer as an inseparable mixture: ^{1}H NMR ($CDCl_3$) δ 0.90-2.05 (m, 20 H), 2.20-2.65 (m, 2H), 4.80-4.95 (m, 2H), 5.51-5.65 (m, 1H), 5.71-5.93 (m, 1H); IR (film) 3100, 3050-2800, 1720, 1680, 1645, 1470, 1380, 1235, 1050, 1000, 915 cm^{-1}. Continued elution provided 117 mg (44%) of unreacted starting material.

Treatment of the above material (100 mg, 0.4 mmol) with 0.12 mL of hydrazine and 673 mg of K_2CO_3 (4.8 mmol) as previously described in the preparation of **8a** furnished 110 mg (78%) of diene **8a** and its C(8) isomer (**8b**) as an inseparable mixture: ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.05 (s, 6H), 1.15 (s, 3H), 0.80-2.40 (m, 24H), 4.57-4.93 (m, 1H), 4.95-5.2 (m, 1H), 5.2-5.6 (m, 1H). This data represents a 1:1 mixture of **8a** and **8b**.

The above mixture of dienes (60 mg, 0.25 mmol) was dissolved in 13 mL of tert-butanol and treated, with stirring, with a solution of 332 mg (1.55 mmol) sodium metaperiodate and 1 mg potassium permanganate in 25 mL of water. The reaction mixture was kept at pH 8 by the addition of 5% aqueous K_2CO_3 [≈1 mL], and stirred until the permanganate color disappeared (4 h). The reaction mixture was then acidified with 20% aqueous hydrochloric acid. Standard ethereal workup provided 56 mg of a mixture of crude acids **9a** and **9b**, which were separable by chromatography on silica gel (elution with hexanes/ether, 3:1) to furnish 15 mg (23%) of **9a** [R_f **9a** = 0.69, hexanes/ether, 1:1] identical to that previously characterized and 16 mg (25%) of acid **9b** which was homogeneous by TLC analysis [R_f **9b** = 0.55, hexanes/ether, 1:1]: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 6H), 1.17 (s, 3H), 1.18 (s, 3H), 1.10-2.10 (m, 24H), 2.74 (dd, 1H, J = 14Hz, 6Hz), 5.51 (dd, 1H, J = 9Hz, 9Hz). This material was identical to an authentic sample kindly provided by Professor Samuel Danishefsky.

(Z)-3-Methyl-5-(dimethylphenylsilyl)-3-pentenyl iodide (12): Dimethylphenylchlorosilane (2.1 g, 12.3 mmol), lithium metal (431 mg, 61.6 mmol) and dry THF (15 mL) were stirred, under nitrogen, for 17 h. The resulting red solution was added to copper(I)iodide (662 mg, 7.4 mmol) in 10 mL of THF at 0°C under nitrogen. The mixture was stirred at 0°C for 90 min and then cooled to -50°C. A solution of 690 mg (6.1 mmol) of lactone **10**[20] dissolved in 15 mL of dry THF was added. The resulting mixture was stirred at -60°C for a 12-h period, warmed to -10°C, and then poured into 300 mL of a saturated solution of ammonium chloride and sodium carbonate (a 1:1 mixture). Standard ethereal workup afforded 1.3 g of an oily residue which was used immediately in the next reaction without further purification or characterization [R_f **10** = 0.65, R_f acid = 0.47, hexanes/ether, 3:1].

A solution of 1.3 g (6.1 mmol) of the above crude acid in 100 mL of ether was treated with an ethereal (200 mL) solution of diazomethane, prepared from 1.37 g of nitrosomethylurea (12.3 mmol), and stirred at room temperature for 1 h. Excess diazomethane was consumed by the careful dropwise addition of glacial acetic acid. The ethereal phase was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Chromatography of the residue on silica gel (elution with hexanes/ether, 10:1) provided 1.05 g (65% from **10**) of (Z)-methyl-3-methyl-5-(dimethylphenylsilyl)-3-pentenoate (**11**) which was homogeneous by TLC analysis (hexanes/ether, 3:1, R_f acid = 0.68, R_f **11** = 0.84): ^{1}H NMR (CCl_4) δ 0.23 (s, 6H), 1.55 (d, 2H, J = 7Hz), 1.67 (br s, 3H), 2.85-2.90 (m, 2H), 3.55 (s, 1.5H), 3.60 (s, 1.5H), 5.23 (t, 1H, J = 6Hz), 7.00-7.35 (m, 5H); IR (film) 3050-2870, 1740, 1440, 1420, 1260, 1160, 1125, 1020 cm^{-1}. This data represents a mixture of conformers due to restricted rotation of the tri-alkylsilyl unit.

To a suspension of 116 mg (3.0 mmol) of LAH in 15 mL of ether at 0°C was added dropwise a solution of 500 mg (1.9 mmol) of ester **11** in 5 mL of ether over a 10-min period. The reaction mixture was stirred at 0°C for 45 min and diluted with reagent grade ether. Evaporation of the solvent, following filtration to remove suspended matter, afforded an oily

residue which was purified by chromatography on silica gel (elution with hexanes/ether, 2:1) to give 400 mg (90%) of pure (Z)-3-methyl-5-(dimethylphenylsilyl)-3-penten-1-ol which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f 11 = 0.81, R_f alcohol = 0.25): ^{1}H NMR (CCl_4) δ 0.21 (s, 6H), 0.85 (br s, 1H), 1.36 (br s, 1H), 1.50 (br s, 1H), 1.57 (s, 3H), 2.03 (t, 2H, J = 6Hz), 3.35 (t, 2H, J = 7Hz), 5.03 (t, 0.5H, J = 6Hz), 5.13 (t, 0.5H, J = 6Hz), 7.00-7.35 (m, 5H); IR (film) 3650-3100, 3050, 2980-2800, 1420, 1240, 1150, 1110, 1090, 1040, 830 cm^{-1}. This data represents a mixture of conformers due to hindered rotation of the tri-alkylsilyl unit.

To a solution of 200 mg (0.85 mmol) of the above alcohol in 4 mL of dry ether at room temperature was added 471 mg (1.8 mmol) of triphenylphosphine and 0.45 mL of HMPA (2.56 mmol). To this mixture was added 434 mg (1.7 mmol) of finely ground iodine. The resulting reddish-brown solution was stirred 12 h at room temperature. The mixture was poured into 70 mL of cold saturated aqueous sodium bicarbonate and extracted four times with 100 mL of ether. The ethereal extracts were combined and washed with cold saturate thiosulfate, brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a residue which also contained triphenylphosphine. Tituration of this residue with pentane afforded an oily residue. Chromatography on silica gel (elution with hexanes) furnished 226 mg (77%) of iodide (12) which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f alcohol = 0.30, R_f 12 = 0.97): ^{1}H NMR (CCl_4) δ 0.31 (s, 6H), 1.50 (d, 2H, J = 6Hz), 1.67 (s, 3H), 2.30-2.60 (m, 2H), 2.70-3.20 (m, 2H), 5.17 (t, 1H, J = 7Hz), 7.10-7.35 (m, 5H). This data represents a mixture of conformers due to hindered rotation of the tri-alkylsilyl unit.

2,6-Dimethyl-3-ethoxy-6-[(Z)-3-methyl-5-(dimethylphenylsilyl)-3-pentenyl]-2-cyclohexen-1-one (14): To a solution of lithium diisopropylamide, prepared from 290 µL (2.0 mmol) of diisopropylamine in 2 mL of dry THF and 1.2 mL of n-butyllithium (1.6 M in hexanes, 1.9 mmol) at -15°C, was added a solution of 288 mg (1.7 mmol) of 2,6-dimethyl-3-ethoxy-2-cyclohexen-1-one (13) in 3 mL of THF containing 0.3 mL (1.7 mmol) of HMPA over a 30-min period (via syringe pump). After an additional 30 min at 0°C, the reaction mixture was cooled to -78°C and 620 mg (1.8 mmol) of iodide 12 were added. The reaction was allowed to gradually warm to room temperature overnight (12 h). Standard ethereal workup provided 1.3 g crude residue which was purified on silica gel (elution with hexanes/ether, 5:1) to afford 326 mg (50%) of 14 which was homogeneous on TLC analysis (hexanes/ether, 1:1; R_f 13 = 0.34, R_f 14 = 0.68): ^{1}H NMR (CCl_4) δ 0.31 (s, 6H), 1.38 (t, 3H, J = 7Hz), 1.20-2.10 (m, 14H), 1.63 (s, 3H), 2.30-2.60 (m, 2H), 3.97 (q, 2H, J = 6Hz), 5.07 (t, 1H, J = 7Hz), 7.11-7.53 (m, 5H); mass spectrum, m/z 384 (M+). This data represents a mixture of conformers due to restricted rotation of the tri-alkylsilyl unit.

2,4-Dimethyl-4[(Z)-3-methyl-5-(dimethylphenylsilyl)-3-pentenyl]-3-vinyl-2-cyclohexen-1-one (15): A solution of 320 mg (0.83 mmol) of 14 in 5 mL of THF at 0°C was treated dropwise with 0.72 mL of vinyllithium (2.3 M, 1.67 mmol) over a 30-min period. The reaction was then stirred for 45 min at room temperature. Standard ethereal workup provided 511 mg of crude residue which was used directly in the next reaction.

The crude alcohol was dissolved in 20 mL of THF and 15 drops of 10% HCl were added. After stirring at room temperature for 25 min, the reaction was quenched by the addition of solid potassium carbonate and then filtered. Following removal of the solvent, the crude trienone was chromatographed on silica gel (elution with hexanes/ether, 10:1) to provide 255 mg (84%) of dienone 15 which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f 14 = 0.68, R_f 15 = 0.79), ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 6H), 1.01 (s, 1.5H), 1.06 (s, 1.5H), 0.80-2.10 (m, 14H), 1.51 (br s, 3H), 1.67 (br s, 3H), 2.15-2.4 (m, 2H), 4.85-5.45 (m, 3H), 6.13 (dd, 1H, J = 16Hz, 12Hz), 7.00-7.40 (m, 5H); mass spectrum, m/z 366 (M+). This data represents a mixture of conformers due to restricted rotation of the tri-alkylsilyl unit.

3,4,4a,5,6,7,8,9-Octahydro-1,4a,7-trimethyl-7-vinyl-2H-benzocyclohepten-2-one (16) using $EtAlCl_2$: To 250 mg (0.68 mmol) of trienone 15 in 8 mL of dry toluene at 0°C was added dropwise 100 µL (0.82 mmol) of freshly distilled boron trifluoride etherate. The reaction mixture was stirred at room temperature for 60 min. Additional $BF_3 \cdot Et_2O$ (0.5 ml, 4.1 mmol) was added and the resulting mixture stirred 30 additional minutes. The reaction mixture was diluted with 100 mL of wet ether, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed (elution with hexanes/ether, 10:1) to provide 90 mg (57%) of enone 16 which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f 15 = 0.69, R_f 16 = 0.46) and 45 mg (18%) of unreacted 15: ^{1}H NMR (CCl_4) δ 0.84 (s, 0.75H), 1.03 (s, 3H), 1.08 (s, 2.25H), 1.00-2.50 (m, 21H), 1.63 (s, 3H), 4.75 (dd, 1.5H, J = 10Hz, 9Hz), 4.95 (dd, 0.5, J = 9Hz, 9Hz), 5.57 (dd, 1H, J = 17Hz, 14Hz); mass spectrum, m/z 232 (M+). Anal. Calc'd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.44; H, 10.60. This data represents a 3:1 mixture of C(8) diastereomers based on NMR integration.

Preparation of 16 using $TiCl_4$: To 90 mg (0.24 mmol) of 15 in 5 mL of dry methylene chloride at -78°C was added 3 drops of titanium tetrachloride. The reaction was stirred for 30 min at -78°C and then 0.5 mL of water added. Standard ethereal workup provided 97 mg of a crude residue which was purified via column chromatography (elution with hexanes/ether, 6:1) to afford 44 mg (77%) of 16 [R_f 15 = 0.78, R_f 16 = 0.56, hexanes/ether, 1:1] consisting of a 3:1 mixture of C(8) isomers based on NMR integration.

II. epi-WIDDROL VIA A 4-ISO-BUTENYL-DIENONE CYCLIZATION.[6]

2,6-Dimethyl-3-ethoxy-6-[2-[(trimethylsilyl)methyl]-2-butenyl]-2-cyclohexen-1-one (20): To a solution of lithium diisopropylamide, prepared from 7.0 mL (50 mmol) of diisopropylamine in 50 mL of dry THF and 18.3 mL of n-butyllithium (2.5 M in hexanes, 45.8 mmol) at 0°C, was

added a solution of 7 g of 2,6-dimethyl-3-ethoxy-2-cyclohexen-1-one in 25 mL of THF containing 7.4 mL (41.6 mmol) of HMPA over a 90-min period (via syringe pump). After an additional 30 min at 0°C, 12.3 g (45.8 mmol) of (Z)-2-[(trimethylsilyl)methyl]-2-buten-1-yl iodide (**19**) was added. The reaction was allowed to gradually warm to room temperature overnight (14 h). Standard ethereal workup provided 8.9 g of crude residue which was purified on silica gel (elution with hexanes/ether, 5:1) to afford 7.35 g (57%) of **20** which was homogeneous on TLC analysis (hexanes/ether, 1:1; R_f enone = 0.50, R_f **20** = 0.87): ^{1}H NMR ($CDCl_3$) δ -0.05 (s, 9H), 1.05 (s, 3H), 1.40 (t, 3H, J = 6 Hz), 1.20-2.70 (m, 17H), 1.80 (br s, 3H), 4.05 (q, 2H, J = 6 Hz), 5.05 (q, 1H, J = 5 Hz); ^{13}C NMR ($CDCl_3$) 203.0 (s), 169.0 (s), 134.0 (s), 120.0 (d), 113.5 (s), 63.0 (t), 46.0 (s), 43.5 (s), 32.5 (s), 23.5, 22.8, 22.7, 16.0, 14.7, 8.5 (q), 0.0 (q) ppm; IR (film) 3000-2800, 1630, 1360, 1250, 1110, 860 cm^{-1}; mass spectrum, m/z 308 (M+).

2,4-Dimethyl-4-[2-[(trimethylsilyl)methyl]-2-butenyl]-3-vinyl-2-cyclohexen-1-one (17): A solution of 4.0 g (12.9 mmol) of **20** in 50 mL of THF at 0°C was treated dropwise with 11.3 mL of vinyllithium (2.3 M, 26 mmol) over a 30-min period. The reaction was then stirred for 45 min at room temperature. Standard ethereal workup provided 4.1 g of crude residue which was used directly in the next reaction.

The crude alcohol was dissolved in 20 mL of THF and 60 drops of 10% HCl were added. After stirring at room temperature for 45 min, the reaction was quenched by the addition of solid potassium carbonate and then filtered. Following removal of the solvent, the crude dienone was chromatographed on silica gel (elution with hexanes/ether, 10:1) to provide 3.3 g (87%) of dienone **17** which was homogeneous by TLC analysis (hexanes/ether, R_f **20** = 0.61, R_f **17** = 0.76): ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.00 (s, 3H), 1.20-2.70 (m, 14H), 1.85 (br s, 3H), 5.00 (t, 1H, J = 9Hz), 5.00 (dd, 1H, J = 18 Hz, 2 Hz), 5.12 (dd, 1H, J = 10 Hz, 2 Hz), and 5.30 (dd, 1H, J = 18 Hz, 10 Hz); ^{13}C NMR ($CDCl_3$) 199.0 (s), 161.5 (s), 134.3 (d), 134.0 (s), 130.3 (s), 121.1 (t), 120.0 (d), 46.5, 39.0, 34.0, 33.5, 27.0, 23.3, 14.7, 13.5, -0.5 (q) ppm; IR (film) 3050-2800, 1675, 1600, 1420, 1380, 1340, 1300, 1260, 1170, 1020, 1000, 940, 880-840 cm^{-1}; mass spectrum, m/z 290 (M+). Anal. Calc'd for $C_{20}H_{30}OSi$: C, 76.35; H, 9.61. Found: C, 76.79; H, 9.45.

3,4,4a,5,6,7,8,9-Octahydro-1,4a,7-trimethyl-6-methylene-2H-benzocyclohepten-2-one (18): To 3.3 g (11.3 mmol) of trienone **17** in 50 mL of dry toluene at 0°C was added dropwise 11.8 mL of a 1.45 M solution of ethylaluminum dichloride in toluene (Alfa). The reaction mixture was stirred at 0°C for 30 min and then diluted with 300 mL of wet ether, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed on silica gel (elution with hexanes/ether, 7:1) to provide 2.2 g (89%) of enone **18** which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f **17** = 0.70, R_f **18** = 0.50): ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 1H, J = 6Hz), 1.10 (d, 2H, J = 6Hz), 1.17 (s, 3H), 1.4-2.0 (m, 7H), 2.00-2.70 (m, 7H), 4.60 (s, 0.65H), 4.71 (s, 0.35H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$) 198.7 (s), 165.6 (s), 149.5 (s), 149.2 (s), 130.6 (s), 113.5 (t), 112.2 (t), 49.8, 43.8, 41.3, 39.1, 38.6, 34.1, 33.9, 33.5, 33.3, 28.8, 25.4, 25.0, 23.1, 20.1, 19.6, 10.6 (q) ppm; IR (film) 3050, 3000-2800, 1620, 1450, 1380, 1360, 1340, 1300, 1230, 1200, 1100, 1020, 910 cm^{-1}; mass spectrum, m/z 218 (M+). Anal. Calc'd for $C_{15}H_{20}O$: C, 82.51; H, 10.15. Found: C, 82.36; H, 10.23. This data represents a 2:1 mixture of C(8) diastereomers based on NMR integration.

2,3,4,4a,5,6,7,8-Octahydro-6-methylene-1,1,4a,7-tetramethyl-1H-benzocyclohepten-2-one (21): To 212 mg of 80% NaH (7.0 mmol) was added 3 mL of freshly distilled DMSO. The resulting mixture was warmed at 75°C until hydrogen evolution ceased [≈ 1 h] and then cooled to room temperature. A solution of 1.10 g (5.04 mmol) of enone **18** dissolved in 4 mL of DMSO was then added to the reaction mixture. After stirring 1 h at room temperature the solvent was removed in vacuo. The resulting residue was dissolved in 10 mL of dry THF and 0.44 mL (7.06 mmol) of freshly distilled iodomethane was then added. The reaction was stirred for 30 min at room temperature. Standard ethereal workup gave 1.32 g of a crude oil. Chromatography of the crude product on silica gel (elution with hexanes/ether, 7:1) afforded 354 mg (32%) of recovered **18** and 580 mg of **21** (49% yield or 73% conversion based on unreacted **18**), which was homogeneous by TLC analysis (hexanes/ether, 3:1, R_f **18** = 0.50, R_f **21** = 0.73): ^{1}H NMR (CCl_4) δ 1.03 (s, 3H), 1.05 (d, 3H, J = 6Hz), 1.10 (s, 6H), 1.30-2.60 (m, 9H), 4.60 (s, 1H), 4.75 (s, 1H), 5.56 (t, 1H, J = 8Hz); ^{13}C NMR ($CDCl_3$) 215.4 (s), 151.7 (s), 150.9 (s), 122.5 (d), 111.4 (t), 50.1, 48.4, 47.8, 39.5, 39.2, 38.2, 36.0, 35.0. 34.3, 33.1, 29.3, 27.2, 26.8, 24.7, 23.3, 22.0, 19.5 ppm; IR (film) 3070, 2950, 2930, 2880, 1720, 1650, 1460, 1420, 1380, 1200, 1120, 1040, 0, 800 cm^{-1}; mass spectrum, m/z 232 (M+). This data represents a 2:1 mixture of C(8) diastereomers based on NMR integration.

2,3,4,4a,5,6,7,8-Octahydro-6-methylene-1,1,4a,7-tetramethyl-1H-benzocycloheptene (22): A mixture of **21** (450 mg, 1.9 mmol), hydrazine (0.56 mL, 17.4 mmol), anhydrous potassium carbonate (3.21 g, 23.2 mmol), and diethylene glycol (10 mL) was placed into a round bottom flask equipped with a short-path distillation apparatus and heated at 160°C for 2 h followed by heating at 230°C for 4 h. The cooled reaction mixture was combined with any distillate, diluted with 10 mL water, and extracted with ether. The combined organic extracts were washed with cold 10% HCl, dried over anhydrous magnesium sulfate, and filtered. Concentration in vacuo followed by chromatography on silica gel (elution with hexanes) gave 316 mg (75%) of pure diene **22** (hexanes, R_f **21** = 0.08, R_f **22** = 0.91): ^{1}H NMR ($CDCl_3$) δ 0.90-1.15 (m, 12H), 1.15-2.50 (m, 11H), 4.55 (s, 1H), 4.60 (s, 1H), 5.47 (t, 1H, J = 7Hz); ^{13}C NMR ($CDCl_3$) 152.6 (s), 120.4 (d), 110.3 (t), 109.3 (s), 51.5 (t), 49.5, 42.7, 41.6, 41.1, 40.1, 39.5, 37.7, 36.7, 35.0, 33.3, 32.9, 32.0, 31.7, 26.0, 22.3 (q), 19.6 (q), 18.7 (q) ppm; IR (film) 3080, 3000-2750, 1645, 1380, 1330, 1240, 1180, 1000, 900, 845 cm^{-1}; mass spectrum, m/z 218 (M+). Anal. Calc'd for $C_{16}H_{26}$: C, 87.99; H, 12.00. Found: C, 87.91; H, 11.94. This data represents a 2:1 mixture of C(8) diastereomers based on NMR integration.

2,3,4,4a,5,6,7,8-Octahydro-6-hydroxymethyl-1,1,4a,7-tetramethyl-1H-benzocycloheptene (25): To 82 mg (0.37 mmol) of diene **22** dissolved in 4 mL of dry THF maintained at -5°C was added dropwise 1.5 mL of 9-BBN (0.5 M in THF, Aldrich) over a 30-min period. The reaction mixture was stirred 14 h at 0°C and an additional 3 h at room temperature. The reaction mixture was then treated with 1.5 mL of 3 N sodium hydroxide, 1.5 mL of 30% hydrogen peroxide, and 140 mg of potassium carbonate dissolved in 1.5 mL of water. The resulting solution was then stirred for 45 min at room temperature. Standard ethereal workup provided 88 mg of a crude residue which was chromatographed on silica gel (elution with hexanes/ether, 7:1) to afford 66 mg (89%) of pure alcohol **25** (hexanes/ether, 2:1, R_f **22** = 0.89, R_f **25** = 0.50-0.55): ^1H NMR (CCl_4) δ 0.70-2.10 (m, 25H), 3.1-3.50 (m, 2H), 5.25-5.55 (m, 1H); IR (film) 3650-3100, 3050, 3000-2800, 1640, 1470, 1385, 1080, 1020, 850 cm^{-1}; mass spectrum, m/z 236 (M+). This data represents a mixture of C(7) and C(8) diastereomers.

2,3,4,4a,5,6,7,8-Octahydro-1,1,4a,7-tetramethyl-1H-benzocycloheptene-6-carboxylic acid (26): Preparation of **26** was carried out via the following three procedures:

(a) A solution of 99 mg (0.42 mmol) of alcohol **25** in 3 mL of methylene chloride was added to 237 mg (0.63 mmol) of pyridium dichlorochromate (PDC) in 2 mL of methylene chloride. The reaction mixture was stirred at room temperature for 20 h and diluted with 20 mL of methylene chloride. The resulting mixture was filtered and concentrated in vacuo. The crude residue was chromatographed on silica gel (1 gram, elution with hexanes/ether, 3:1) to give 94 mg (95%) of 2,3,4,4a,5,6,7,8-octahydro-1,1,4,7-tetramethyl-1H-benzocycloheptene-6-formaldehyde which was homogeneous by TLC analysis (R_f **25** = 0.43, R_f **aldehyde** = 0.89, hexanes/ether, 2:1): ^1H NMR (CCl_4) δ 0.8-2.5 (m, 24 H), 5.37 (t, 0.5 H, J = 7 Hz), 5.45 (t, 0.5 H, J = 7 Hz), 0.42 (br s, 1H).

A solution of the above aldehyde (94 mg) in 5 mL of acetone (reagent grade) cooled to 0°C was treated with 0.2 mL of standard Jones Reagent. After 30 min, the reaction was warmed to room temperature and quenched with 2-propanol to consume the excess oxidizing reagent. The reaction was decanted and evaporated leaving an oily residue. Purification on silica gel (elution with hexanes/ether, 2:1) provided 50 mg (50%) of acid **26** (R_f **aldehyde** = 0.89, R_f **26** = 0.50, hexanes/ether, 2:1): ^1H NMR (CCl_4) δ 0.70-2.80 (m, 24H), 5.54 (t, 1H, J = 7Hz), 10.70-11.10 (br s, 1H); IR (film) 3500-2500, 1700, 1470, 1420, 1395, 1320, 1300, 1220, 1180, 1160, 1150, 1000, 875 cm^{-1}; mass spectrum, m/z 250 (M+).

(b) A solution of 60 mg (0.25 mmol) of alcohol **25** in 2 mL of N,N-dimethylformamide was added to 335 mg (0.89 mmol) of pyridium dichlorochromate (PDC) in 2 mL of N,N-dimethylformamide. The reaction mixture was stirred at room temperature for 12 h; TLC analysis indicated that the oxidation was incomplete. Additional PDC (240 mg, 0.64 mmol) was then added. The resulting reaction mixture was stirred at room temperature for an additional 14 h and diluted with 50 mL of water and extracted with 3 x 50 mL portions of a mixture of ether/pentane (1:1). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed on silica gel (elution with hexanes/ether, 3:1) to give 34 mg (53%) of **26** which was identical to that previously characterized.

(c) A solution of alcohol **25** (220 mg, 0.93 mmol) in 20 mL of acetone (reagent grade) cooled to 0°C was treated with standard Jones Reagent until TLC analysis indicated all starting material had been consumed. After 30 min, the reaction was warmed to room temperature and quenched with 2-propanol to consume the excess oxidizing reagent. The reaction was diluted with 100 mL of acetone and the acetone solution was decanted and evaporated leaving an oily residue. Purification on silica gel (elution with hexanes/ether, 2:1) provided 175 mg (75%) of acid **26**.

2,3,4,4a,5,8-Hexahydro-1,1,4a,7-tetramethyl-1H-benzocycloheptene (24): Cupric acetate monohydrate (5 mg, 0.0028 mmol), lead tetraacetate (124 mg, 0.28 mmol), and 65 mg (0.28 mmol) of carboxylic acid **26** were added to 2 mL of dry benzene in a thick-walled three-neck 50 mL round bottom flask. Argon was bubbled into the stirred reaction mixture for a 15-min period to purge the system of oxygen. The reaction vessel was then sealed and heated at 80°C for 4 h. Standard ethereal workup provided 31 mg of a crude oil which was purified by chromatography on silica gel (elution with hexanes/ether, 10:1) to provide 24 mg of diene **24** (52%) which was homogeneous by TLC analysis (hexanes/ether, 3:1, R_f **26** = 0.45, R_f **24** = 0.95); ^1H NMR (CCl_4) δ 1.00 (s, 3H), 1.04 (s, 3H), 1.10 (s, 3H), 0.90-2.00 (m, 18H), 1.68 (br s, 3H), 2.20-2.60 (m, 3H), 3.09 (d, 1H, J = 20Hz), 5.20-5.50 (m, 2H); ^{13}C NMR ($CDCl_3$) 152.7 (s), 137.8 (s), 123.0 (d), 117.9 (d), 44.0 (t), 42.2 (t), 41.1 (t), 37.9 (s), 37.3 (s), 35.2 (t), 33.1 (q), 30.9 (q), 27.0 (q), 24.5 (q), 18.8 (t) ppm; IR (film) 3000-2850, 1460, 1380, 1220, 1000, 840 cm^{-1}; mass spectrum, m/z 204 (M+). Anal. Calc'd for $C_{15}H_{24}$: C, 88.16; H, 11.83. Found: C, 87.90; H, 11.81.

2,3,4,4a,5,6-Hexahydro-1,1,4a,7-tetramethyl-1H-benzocycloheptene (28): The procedure reported by Dauben and co-workers was used.[9] To a solution of 150 mg (0.73 mmol) of diene **24** in 0.2 mL of dry benzene and 10 mL of dimethylsulfoxide was added 322 mg (2.8 mmol) of potassium tert-butoxide. The reaction mixture was stirred at room temperature for 6 h, and poured into water. Standard ethereal workup afforded 199 mg of a crude oil which was purified via chromatography on silica gel (elution with hexanes) to give 120 mg (80%) of diene **28** which was homogeneous by TLC analysis (hexanes, R_f **24** = 0.97, R_f **28** = 0.96): ^1H NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.01 (s, 3H), 1.11 (s, 3H), 1.78 (s, 3H), 0.90-1.90 (m, 20H), 2.00-2.20 (m, 1H), 2.31-2.48 (m, 1H), 5.50-5.90 (m, 2H).

[4aR*,7S*,8R*]-7,8-Epoxy-2,3,4,4a,5,6,7,8-octahydro-1,1,4a,7-tetramethyl-1H-benzocycloheptene (30): To a solution of 120 mg (0.58 mmol) of diene **28** in 10 mL of dry methylene chloride was added 100 mg of 80% m-CPBA. The reaction was stirred at room temperature for 4 h, and then diluted with 30 mL of pentane. Standard ethereal workup provided 147 mg of crude residue which was chromatographed on silica gel (elution with hexanes/ether, 3:1) to furnish 58 mg

(45%) of epoxide **30** which was homogeneous by TLC analysis (hexanes/ether, 2:1, R_f **28** = 0.95, R_f **30** = 0.75): ^{1}H NMR (CCl_4) δ 1.08 (s, 9H), 1.21 (s, 3H), 0.80-2.10 (m, 22H), 2.75 (d, 1H, J = 6 Hz), 5.50 (d, 1H, J = 7 Hz); mass spectrum, m/z 220 (M+).

Continued elution afforded 23 mg (17%) of a bis-epoxide [R_f = 0.50, hexanes/ether, 2:1]: ^{1}H NMR (CCl_4) δ0.78 (s, 3H), 1.05 (s, 6H), 1.10 (s, 3H), 0.80-1.80 (m, 22H), 2.69 (s, 1H, J = 6Hz), 2.95 (d, 1H, J = 6 Hz).

epi-Widdrol (1): To a suspension of 65 mg of $LiAlH_4$ (1.72 mmol) in 9 mL of dry glyme was added a solution of 80 mg (0.36 mmol) of **30** in 1 mL of glyme. The reaction mixture was stirred at room temperature for 6 h and then diluted with 20 mL of reagent grade ether and quenched with water. Standard ethereal workup afforded 97 mg of an oily residue which was purified on silica gel to afford 63 mg (78%) of epi-widdrol (**1**) which was homogeneous by TLC analysis (R_f **30** = 0.93, R_f **1** = 0.60, hexanes/ether, 2:1) and identical to material previously described.

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FOOTNOTES AND REFERENCES

1. This work was presented in part at the 35th SERM at Raleigh, NC, in October, 1984, and at the 189th National Meeting at the ACS in Miami Beach, April, 1985. A full account of this work was presented at the 38th SERM at Louisville, KY, in November, 1986.

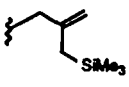
2. For a comprehensive review of allylsilane chemistry prior to 1981, see: Sakurai, H. Pure and Appl. Chem. **1982**, 54, 1. Three independent updated surveys of allylsilane chemistry [by Fleming and Dunogues, Schinzer, and Majetich] are in press.

3. **For cyclopentane annulations using allylsilanes, see:** a) Majetich, G.; Desmond, R.; Casares, A.M. Tetrahedron Lett. **1983**, 24, 1913. b) Majetich, G.; Hull, K.; Defauw, J.; Shawe, T. ibid. **1985**, 26, 2755. c) Majetich, G.; Defauw, J.; Hull, K.; Shawe, T. ibid. **1985**, 26, 4711. d) Majetich, G.; Desmond, R.; Soria, J. J. Org. Chem. **1986**, 51, 1753. e) Schinzer, D. Angew. Chem. Int. Ed. **1984**, 23, 308. **For cyclohexane annulations using allylsilanes, see:** f) Majetich, G.; Hull, K.; Desmond, R. Tetrahedron Lett. **1985**, 26, 2751. g) Majetich, G.; Behnke, M.; Hull, K. J. Org. Chem. **1985**, 50, 3615. **For cycloheptane annulations using allylsilanes, see:** h) Majetich, G.; Defauw, J.; Desmond, R. Tetrahedron Lett. **1985**, 26, 2747. i) Majetich, G.; Ringold, C. Heterocycles **1987**, 25, 271. j) Majetich, G.; Defauw, J.; Ringold, C. J. Org. Chem. **1987**, 52, 0000. k) Schinzer, D.; Steffen, J.; Solyom, S. J. Chem. Soc., Chem. Commun. **1986**, 829. **For cyclooctane annulations using allylsilanes, see:** reference 3f.

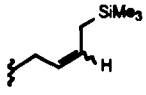
4. a) Unpublished results of Ms. Jean Defauw. b) Unpublished results of Mr. Steven Condon.

5. Long-standing interest in cycloheptane-containing natural products has generated numerous ways to prepare this medium-size ring: **Alkylation Approaches:** a) Grieco, P.A.; Majetich, G.; Ohfune, Y. J. Am. Chem. Soc. **1982**, 104, 4226. b) House, H.O.; Phillips, W.V.; Sayer, T.S.B.; Yau, C.C. J. Org. Chem. **1978**, 43, 700; House, H.O.; Sayer, T.S.B.; Yau, C.C. ibid. **1978**, 43, 2153. **Cationic Rearrangements:** c) Lansbury, P.T.; Serelio, A.E. Tetrahedron Lett. **1978**, 1909. **Divinyl Cyclopropane Rearrangements:** d) Wender, P.A.; Filosa, M.P. J. Org. Chem. **1976**, 41, 3490. e) Marino, J.P.; Kaneko, T. ibid. **1974**, 39, 3175. **3 + 4 Cycloaddition Reactions:** Hoffmann, H.M.R. Angew. Chem., Int. Ed. Engl. **1984**, 23, 1. g) Noyori, R. Acc. Chem. Res. **1979**, 12, 61. h) Hosomi, A.; Otaka, K.; Sakurai, H. Tetrahedron Lett. **1986**, 27, 2881.

6. Three of the cyclizations in Chart 1 are intramolecular additions of an allylsilane moiety to a 3-vinylcycloalkenone. This description is far too general, yet formally derived names are impractical. In order to clarify this situation, we use the following convention: 1) the suffice "dienone" describes the 3-vinylcyclohexenone unit; 2) a locant for the allylsilane appendage is stated; and 3) the nature of the allylsilane side chain is defined either as an iso-alkenyl or n-alkenyl substituent; geometric isomers or substitutions are ignored (see below).



iso - alkenyl



n - alkenyl

Based on these conventions, substrates **iii**, **v**, and **vii** are described as a 4-iso-butenyl-dienone, a 2-iso-butenyl-dienone, and a 4-n-pentenyl-dienone, respectively. The cyclizations of **i**[4a] and **vii**[4b] will be the subject of future reports.

7. Majetich, G.; Defauw, J.; Hull, K.; Shawe, T.; Lowery, R.D. (under review). The preparation of 3-ethoxy-6-methyl-6-(3-oxobutyl)-2-cyclohexen-1-one is described therein.

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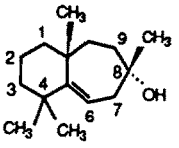
11. Widdrol's numbering system is shown below.[9c]



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13. The DIFNOE experiments were conducted on a JEOL FX270 spectrometer. Irradiation of enone **3a** at 1.67 ppm (the vinylic methyl) showed an enhancement of the vinylic proton resonance at 5.11 ppm (t). Irradiation of enone **3b** at 1.52 ppm (the vinylic methyl) enhanced the allylsilane methylene signal.

14. Failure to use freshly distilled hydrazine hydrate resulted in reduction of the C(3) carbonyl and the C(8) vinyl group, presumably due to in situ formation of diimide.

15. Recently Uyehara and co-workers reported the same strategy to functionalize the cyclohexene ring in their synthesis of widdrol.[10c]

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21. The procedure used to prepare lactone **10** also produces some 4-methyl-3,4-dehydrovalerolactone [≈ 5%]. The reaction of this compound with $(\phi Me_2Si)_2CuLi$ is apparently sluggish as only ester **11** was isolated.

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24. This alkylation failed with the kinetic enolate of 3-ethoxy-6-methyl-2-cyclohexen-1-one.

25. Although the methyl substituent at the α-position of the dienone unit could account for the diminished selectivity of this cyclization, unpublished work from these laboratories suggests that this result is due to the phenyldimethylallylsilane unit.

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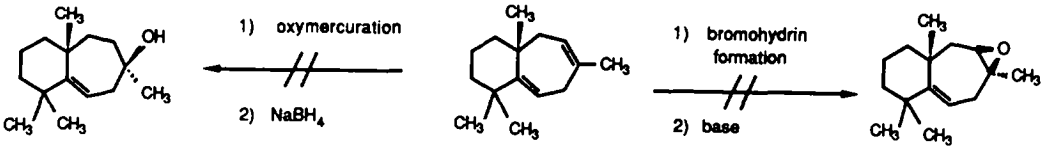
27. Attempts were made to prepare epoxide **31** from diene **24** via bromohydrin formation, followed by base-promoted 1,3-elimination. Although adducts which incorporated the elements of bromine and water were obtained,[28] these adducts failed to furnish **31** upon treatment with various bases. Use of N-bromoacetamide led to complex mixtures of products. Finally, we anticipated that trans-oxymercuration would lead directly to widdrol due to formation of the mercurinium ion on the less hindered α-face of **24**. Although oxymercuration provided a single non-isolatable product,[29] addition of sodium borohydride generated complex mixtures of products, with only trace amounts of widdrol based on TLC analysis. Epi-widdrol was not observed.



2 **24** **31**

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