Bull Soc Chim Fr (1995) 132, 575-584

The preparation of fused tricycles using allylsilane-based "A + C → ABC" annulation strategies†

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(received 23 January 1995, accepted 30 March 1995)

Summary – Studies directed towards the preparation of the basic carbocyclic skeleton of three synthetically challenging, biologically important natural products (ikarugamycin, phorbol and taxol) featuring allylsilane-based annulation strategies are presented.

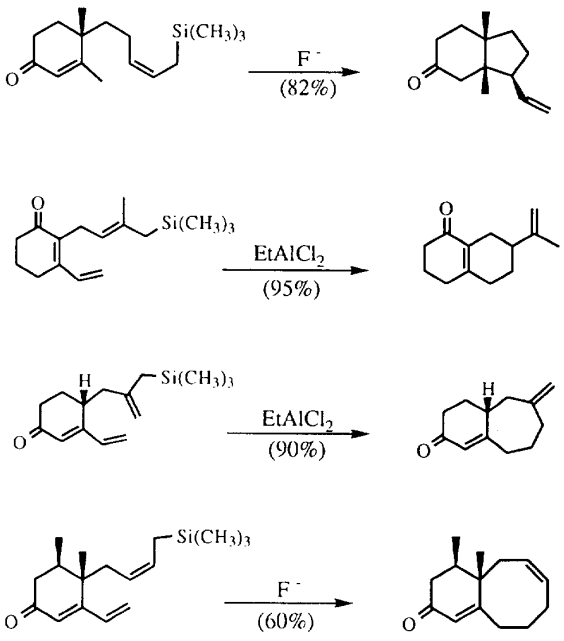
intramolecular allylsilane annulation

Introduction

In light of their remarkable versatility and broad synthetic utility, it is not surprising that reactions of allylsilanes are a popular method for both inter- and intramolecular carbon-carbon bond formation [1]. Our contributions in this active field focus on developing new annulation procedures. After showing that intramolecular allylsilane cyclizations could be used to form monocyclic systems [2], we established the usefulness of this methodology for the construction of bicyclic systems. Representative examples for annulating five-, six-, seven- or eight-membered rings are illustrated in scheme 1 [3,4]. These procedures have also been featured in the syntheses of several bicyclic sesquiterpenes [5].

The next phase in the development of this methodology was to confirm its usefulness for assembling challenging polycyclic systems. An attractive strategy for constructing tricyclic molecules is based on the formation of a central ring by cyclizing two functionalized rings linked by a tether, as generalized in figure 1. Such an "A + C → ABC" strategy was featured on our attempted synthesis of hirsutene [6] and in our successful synthesis of the dolastane diterpene 14-deoxyisoamijiol (scheme 2) [7]. The cyclization of substrates **1** and **2** not only assembled the basic triquinane and dolastane skeleton, respectively, but also established the correct ring fusion stereochemical relationships. In both cases, sufficient functionality exists in the "A" and "C" rings of the cyclized products to permit further synthetic manipulations.

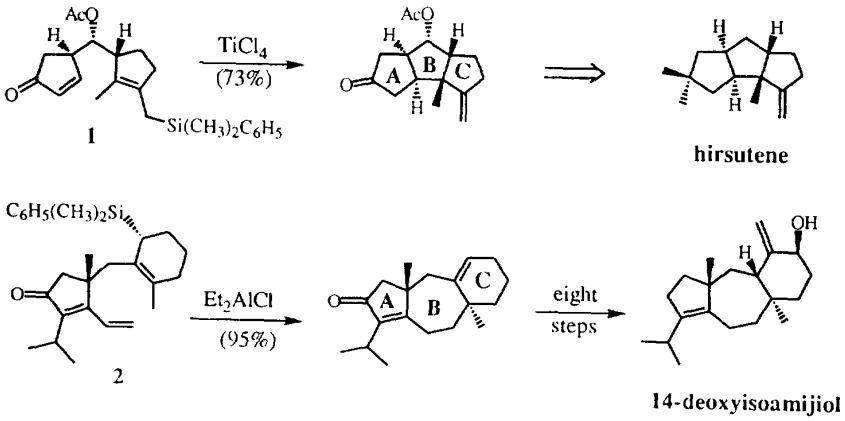
The ability to assemble polycyclic frameworks with complete control of the ring fusion stereochemistry make allylsilane-based annulations a powerful synthetic method. This manuscript describes our model studies using "A + C → ABC" strategies to prepare the carbocyclic frameworks characteristic of ikarugamycin **3**, phorbol **4** and taxol **5**, three physiologically important medium-sized terpenoids (fig 2) [8].



Scheme 1

† Dedicated to Professor Raymond Calas in appreciation of his 45 years of pioneering research in organosilicon chemistry.

* Correspondence and reprints



Scheme 2

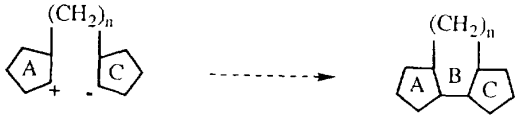


Fig 1

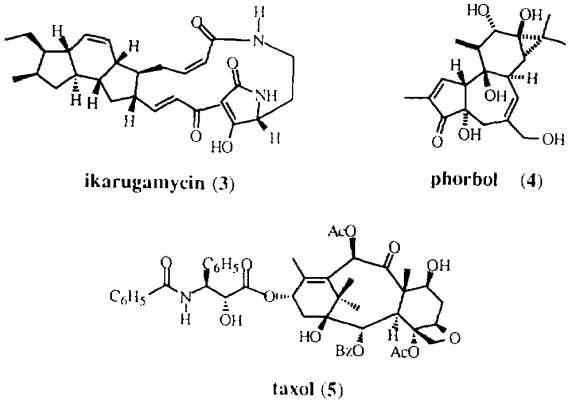


Fig 2

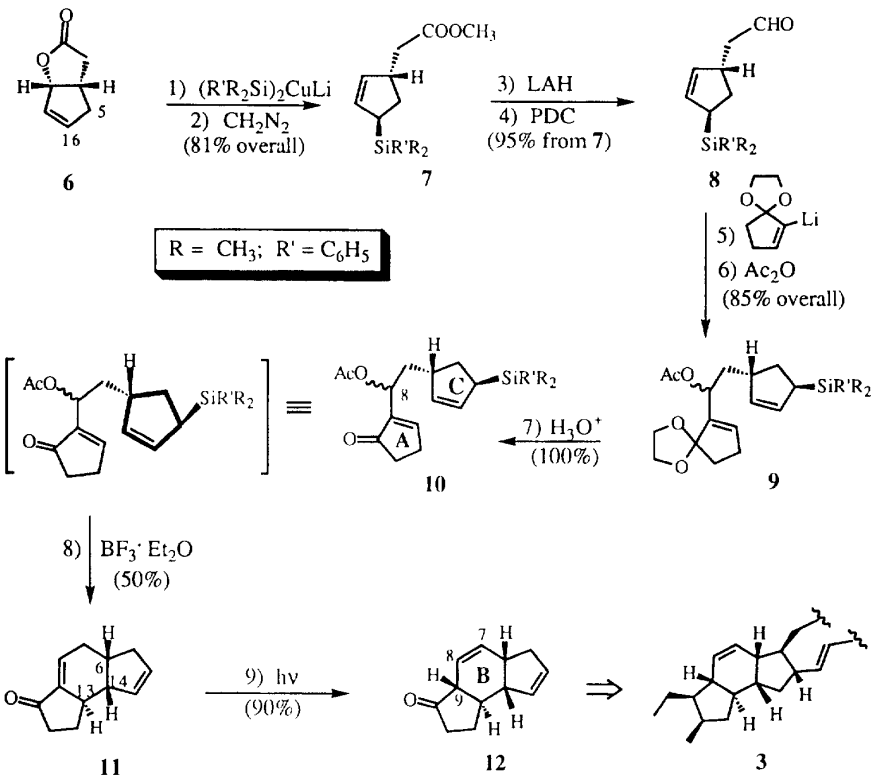
Synthesis of the carbocyclic nucleus of ikarugamycin

Ikarugamycin **3**, a pentacyclic antibiotic possessing specific antiprotozoal activity, was first isolated by Jomon *et al* [9]. Its biological properties include strong specific antiprotozoal activity, *in vitro* antiamoebic activity, and activity against some Gram-positive bacteria. Not surprisingly, its novel structure and wide ranging biological activity have stimulated considerable interest [10].

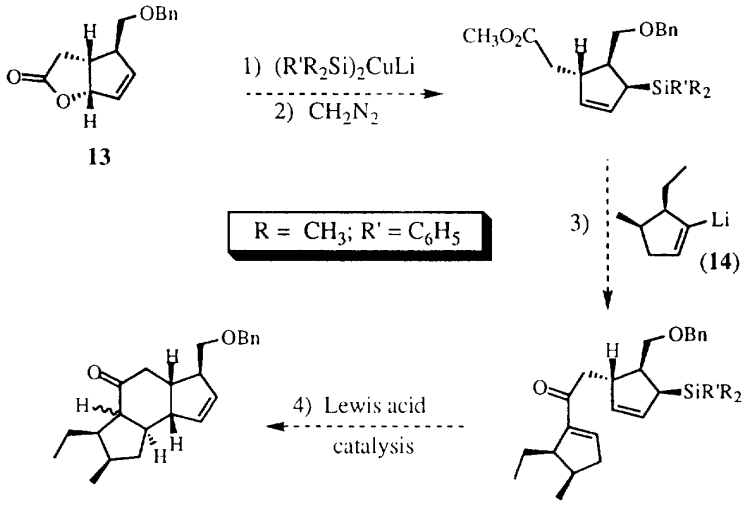
We constructed the carbocyclic nucleus of ikarugamycin via an "A + C → ABC" approach as summarized in scheme 3. The first transformation exploits Fleming's discovery that the treatment of allylic acetates with silylcuprates produces allylsilanes [11]. In particular, treatment of lactone **6** with the silylcuprate derived from phenyldimethylchlorosilane affords an acid intermediate, which is esterified prior to isolation and characterization. The stereochemistry shown in allylsilane **7** is consistent with Curran's investigation of the organocopper-promoted S_N2' openings of vinyl lactones [12]. Reduction and oxidation of ester **7** provides aldehyde **8**. The conversion of aldehyde **8** to cyclization precursor [10] required only the coupling of **8** with the vinyllithium reagent derived from the transmetallation of 2-bromo-2-cyclopentenone ethylene ketal [13], followed by acetylation and acid-catalyzed deketalization. This seven-step sequence produces enone **10** in greater than 50% overall yield from lactone **6**.

Trajectory requirements for successful Michael addition demand that in the transition state the two planar units achieve a parallel orientation [14]. When this relationship is obtained for substrate **10**, the two five-membered rings are offset, which leads to the observed stereochemistry indicated for C(6), C(14) and C(13) in **11**. Treatment of enone **10** with excess boron trifluoride etherate gave a 50% yield of enone **11**, along with a 20% yield of an uncyclized protodesilylated by-product. Note that under the reaction conditions β-elimination of the C(8) acetate occurs generating enone **11**. Enone **11** has several attractive features as a potential precursor for the tricylic nucleus of ikarugamycin. Of particular importance is the requisite the *anti*, *cis*-relationship of the "B" and "C" ring fusions. The "A" ring enone moiety allows the introduction of the C(0) asymmetric center as well as migration of the C(9), C(8)-double bond to C(8) and C(7) using photoisomerization (cf, enone **12**). Based on extensive high field NMR studies, we believe that ketone **12** has the desired *trans* A/B ring junction [32].

Scheme 4 presents our ongoing synthesis of the *as*-hydrindacene nucleus of ikarugamycin. The key starting materials for this work are the optically active bicyclic lactone **13**, an intermediate derived in seven steps from norbornadiene [16], and cyclopentenyllithium reagent **14** [17]. This sequence is quite similar to our model study and is expected to be straightforward.



Scheme 3

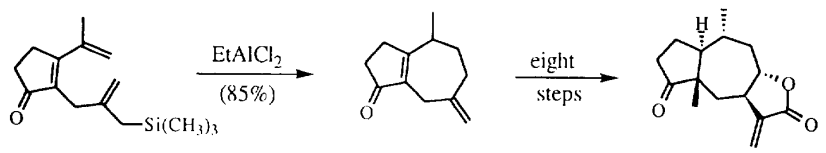


Scheme 4

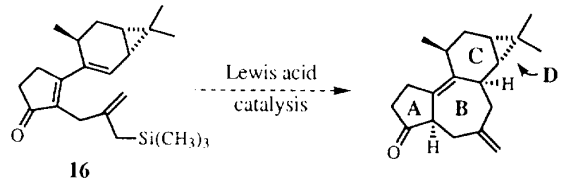
A model study for preparing the ABC ring system of phorbol

Phorbol (**4**), a highly functionalized tetracyclic antibiotic first isolated from the oil of *Croton tiglium* seed [18], contains eight contiguous asymmetric centers and an unusual cyclopropanol/cyclopropylcarbinol system. The cellular target of the phorbol esters has recently been identified as protein kinase, an enzyme involved in the regulation of cellular proliferation [19]. In 1989 Wender *et al* achieved the only synthesis to date of this complex molecule, albeit in 50 steps [20].

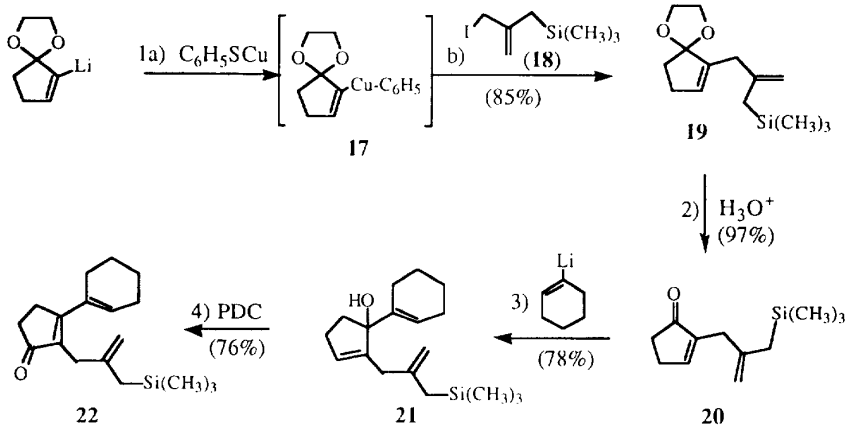
The cyclization shown in scheme 5 was used previously in our laboratory to construct a functionalized perhydroazulene, which permitted the stereoselective synthesis of the pseudoguaianolide graveolide **15**. We were confident that this same methodology could also be used to assemble the carbocyclic nucleus char-



Scheme 5



Scheme 6

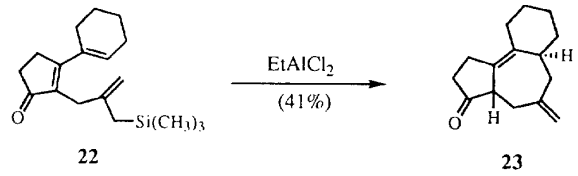


Scheme 7

acteristic of phorbol (scheme 6). Before preparing tricycle **16**, we decided to investigate a simpler cyclization precursor, one lacking the cyclopropyl D ring and the secondary methyl group on the C ring.

The route used to prepare our model system is shown in scheme 7. The Gilman reagent, derived from 2-bromo-2-cyclopenten-1-one ethylene ketal [13], was coupled with iodosilane **18** [22] in 85% yield. Hydrolysis of ketal **19** afforded α-alkylated enone **20** [23]. 1,2-Addition of cyclohexenyllithium to enone **20** generated the bis-allylic tertiary alcohol **21**, which was then subjected to an oxidative rearrangement [24] using excess pyridinium dichromate (PDC) to afford triene **22**. Using this four-step procedure, **22** was prepared in 52% overall yield from 2-bromo-2-cyclopenten-1-one ethylene ketal.

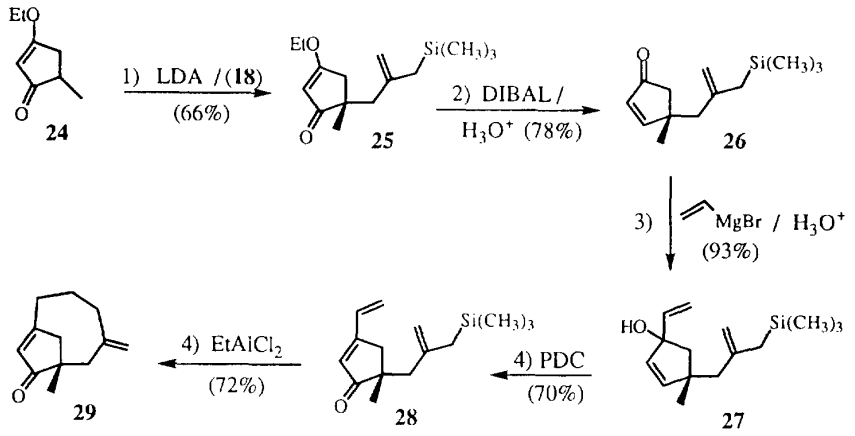
To our satisfaction, treatment of **22** with two or more equivalents of ethylaluminium dichloride gave a 41% yield of enone **23** as a single isomer [32], though cyclization was not observed with less than two equivalents of Lewis acid (scheme 8). This cyclisation produces an unconjugated enone, which resisted isomerization into conjugation upon chromatography or exposure to mild acid [25]. Efforts are underway to prepare a more functionalized analogue of **16** (cf, scheme 6) to further test the viability of this approach.



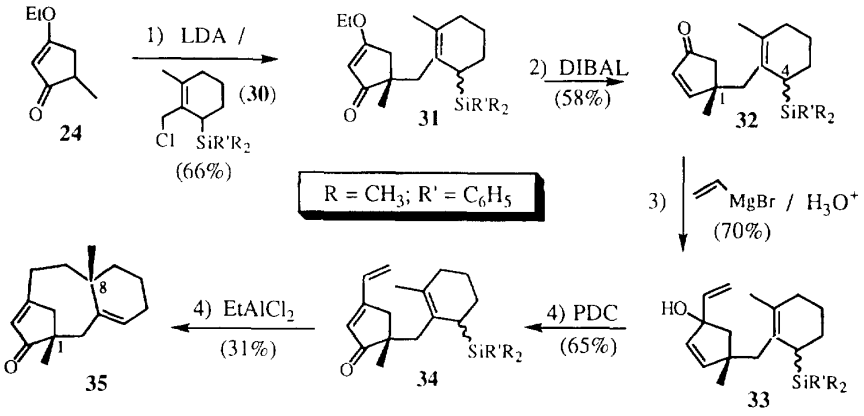
Scheme 8

An allylsilane-based taxane model study

The taxane diterpenes are a series of highly functionalized tricyclic structures containing a sterically congested eight-membered ring. Taxol **5** has shown powerful antitumor activity against human lung and colon, and mice mammary tumors as well as activity in leukemia and ovarian cancer assays [26]. The unusual



Scheme 9



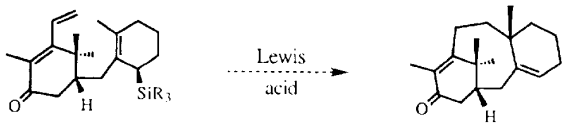
Scheme 10

chemical structure and important biological properties of the taxanes have stimulated considerable interest and a wide diversity of synthetic approaches to the taxane skeleton have emerged [27]. In many cases, the annulation of the central eight-membered ring has been proven to be problematic. Nevertheless, within the past year the teams of researchers under the direction of Holton and Nicolaou have completed syntheses of taxol [28].

Knowing that constructing the central eight-membered ring has plagued several taxane studies, we first sought to verify the usefulness of our allylsilane-based strategy for cyclooctane formation [29]. First, a bicyclic pilot study was investigated, as summarized in scheme 9. Here, alkylation of 3-ethoxy-5-methylcyclopentenone **24** using conditions developed by Stork and Danheiser [30] with iodide **18** provided adduct **25** [31]. DIBAL-H reduction of enone **25** followed by treatment of enone **26** with vinylmagnesium bromide gave tertiary alcohol **27** in high yield. Conjugated **28** was prepared using our oxidative rearrangement procedure. We were delighted to discover that cyclization of trienone **28** produced 5,8-fused enone **29** in 72% yield. The efficiency of this annulation is quite gratifying given that a cyclooctane ring is being formed.

The incorporation of the allylsilane moiety as a part of a cyclic system in an "A + C → ABC" strategy was the next phase of our taxane study. The construction of the requisite precursor closely parallels the sequence used for the preparation of substrate **28**. Alkylation of enone **24** with chloride **30**, a key intermediate in our 14-deoxyisoamjiol synthesis [7] provided adduct **31** [31]. Enone **31** was then converted to cyclization precursor **34**. Compound **34** consists of an equal mixture of diastereomers, because of the relative stereochemistries of the C(1) and C(4) stereocenters (cf, substrate **32**). Treatment of trienone **34** with excess Lewis acid gave tricyclic enone **35** in 31% yield with the stereochemistry of C(1) and C(8) shown based on NOE experiments. Although the yield of this transformation is modest, the balance of the material from this reaction was unreacted **34**. More importantly, NMR data suggest that only one of the diastereomers cyclized [32]. Instead of optimizing this model study, we are currently focusing on the transformation depicted in scheme 11.

The insight gained from the model studies described above will facilitate the design of synthetic routes to prepare these structurally complex, medicinally important target molecules. More importantly, these studies further demonstrate the directness of allylsilane-based annulations to assemble tricyclic systems.



Scheme 11

Experimental section

General

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 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 $MgSO_4$. 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 NM silica gel 60 (230-400 mesh ASTM) and distilled reagent grade solvents. Microanalysis was performed by Atlantic Microlab, Inc, Atlanta, GA. Proton NMR chemical shifts were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference.

Preparation of methyl 4-[(dimethyl phenyl) silyl]-2-cyclopentene-1-acetate **7**

Phenyldimethylchlorosilane (1.70 g, 10.00 mmol) was added to 350 mg of finely cut lithium metal suspended in 15 mL of dry THF. After being stirred for a 90 min period, the solution turned dark red. Continued vigorous stirring for 3 h produced a brownish solution which transferred (via canula) to suspension of 538 mg (6.00 mmol) of copper (I) cyanide in 10 mL of dry THF at 0°C. After 90 min, the reaction mixture was cooled to −60°C and 690 mg (5.00 mmol) of lactone **6** in 5 mL of dry THF was added. The resulting mixture was stirred at −60°C for 12 h. The reaction mixture was quenched by pouring onto 50 mL of 1:1 mixture of saturated aqueous ammonium chloride and saturated aqueous sodium carbonate and extracted with ether (4 × 20 mL portions). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford 2.31 g of crude acid and silicon-containing byproducts.

A solution of the above crude residue in 100 mL of ether was treated with an ethereal (200 mL) solution of diazomethane, prepared from 700 mg of nitrosomethylurea (6.10 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 hexane/ ether, 10:1) provided 1.12 g of ester **7** (81% from **6**) which was homogeneous by TLC analysis [hexane/ether, 3:1, R_f (**6**) = R_f (**7**) = 0.69]).

^{1}H NMR (300 MHz, CCl_4) δ 0.45 (s, 6H), 1.60-2.50 (m, 6H), 3.70 (s, 3H), 5.50-5.60 (m, 1H), 5.70-5.80 (m, 1H), 7.20-7.55 (m, 5H).

Preparation of 4-[(dimethyl phenyl)silyl]-2-cyclopentene-1-carboxaldehyde **8**

To a suspension of 160 mg (4.32 mmol) of LAH in 15 mL of ether at 0°C was added dropwise a solution of 1.12 g (4.32 mmol) of ester **7** 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 purified by chromatography on silica gel (elution with hexane/ether, 2:1) to give 956 mg (90%) of the corresponding alcohol which was homogeneous by TLC analysis (hexane/ether, 2:1, R_f (**7**) = 0.81, R_f (alcohol) = 0.25).

^{1}H NMR (300 MHz, CCl_4) δ 0.31 (s, 6H), 1.30-2.70 (m, 7H), 3.48-3.72 (m, 2H), 5.50-5.75 (m, 2H), 7.20-7.60 (m, 5H).

A solution of 956 mg (0.38 mmol) of the above alcohol in 5 mL of methylene chloride was added to 1.46 g (0.38 mmol) of pyridium dichlorochromate (PDC) in 20 mL of methylene chloride. The reaction mixture was stirred at room temperature for 12 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 (elution with hexane/ether, 3:1) to provide 900 mg of aldehyde **8** (05% from **7**, which was homogeneous by TLC analysis (hexane/ether, 2:1; R_f (alcohol) = 0.43, R_f (**8**) = 0.81).

^{1}H NMR (300 MHz, CCl_4) δ 0.35 (s, 3H), 0.37 (s, 3H), 1.20-3.05 (m, 6H), 5.45-5.80 (m, 2H), 7.20-7.60 (m, 5H), 9.75 (s, 1H).

Preparation of 2-(1-acetoxy-2-{4-[(dimethyl phenyl) silyl]-2-cyclopentenyl}ethyl)-2-cyclopenten-1-one **10**

To a solution of 857 mg of 2-bromo-2-cyclopenten-1-one ethylene ketal (4.18 mmol) in 10 mL of ether in a separate flask at −78°C was added dropwise 1.81 mL of 2.5 M *n*-butyllithium (4.52 mmol) in hexanes over a 15 min period. The resulting solution of 2-lithio-2-cyclopenten-1-one ethylene ketal was stirred at −78°C for a 25 min period.

To the above solution at −78°C was added a solution of 850 mg of aldehyde **8** (3.48 mmol) in 5 mL of dry ether. The reaction mixture stirred at −78°C for a 2 h period and then quenched with 2 mL of saturated aqueous ammonium chloride. Standard ethereal workup furnished a crude adduct which was used directly in the next reaction.

To a solution of the above crude alcohol (1.10 g, 2.97 mmol) in 2 mL of pyridine was added 2 mL of acetic anhydride and 5.0 mg of *N*, *N*-dimethylaminopyridine. The resulting mixture was stirred at room temperature for 90 min. Standard ethereal workup yielded a crude yellow oil which was purified via column chromatography (elution with ether) to yield 1.04 g of acetate **9** (85% from **8**) which was homogeneous by TLC analysis (hexane/ether, 2:1, R_f (alcohol) = 0.25, R_f (**9**) = 0.45).

^{1}H NMR (300 MHz) δ 0.26 (s, 6H), 1.50-2.50 (m, 10H), 3.85-4.05 (m, 4H), 5.35-5.70 (m, 2H), 6.00-6.10 (m, 1H), 7.27-7.56 (m, 5H).

A solution of 1.10 g of ketal **9** (2.97 mmol) in 50 mL of THF and 2 mL of 1 N aqueous sulfuric acid was stirred until TLC analysis revealed complete consumption of the starting material (approx 5 min). The reaction was quenched by the addition of an equal volume of saturated aqueous $NaHCO_3$. Standard ethereal workup, followed by chromatography (hexanes/ether, 10:1), gave 993 mg (100% yield) of enone **10** which was homogeneous by TLC analysis (hexanes/ether, 5:1, R_f (**9**) = 0.50, R_f (**10**) = 0.21).

^{1}H NMR (300 MHz) δ 0.30-0.40 (m, 6H), 1.50-2.60 (m, 10H), 5.35-5.60 (m, 2H), 5.60-5.70 (m, 1H), 7.15-7.50 (m, 5H).

Cyclization of **10**

To 92 mg (0.25 mmol) of enone **10** in 1.5 mL of dry toluene at 0°C was added dropwise 60 μL (0.50 mmol) of freshly

distilled boron trifluoride etherate. The reaction mixture was stirred at 0°C for 4 h and then diluted with 10 mL of wet ether, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed (elution with hexanes/ether, 1:1) to provide 19 mg of cyclized enone **11** which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f (**10**) = 0.38, R_f (**11**) = 0.76).

^{1}H NMR (300 MHz) δ 1.20-2.65 (m, 11H), 5.73-5.82 (m, 1H), 5.85-5.90 (m, 1H), 6.85-6.95 (m, 1H).

^{13}C NMR (62.5 MHz) 216.1, 145.3, 137.1, 137.0, 133.4, 47.4, 36.3, 33.9, 33.2, 30.7, 24.2, 22.0 ppm.

Preparation of 3,3a,3b,6,6a,9-hexahydrocyclo- penta-[e]inden-1-(2H)-one **12** *using hν*

A solution of enone **11** (19 mg, 0.11 mmol) in 5 mL of freshly distilled cyclohexane was irradiated at 364 nm for 48 h at room temperature. The reaction mixture was concentrated *in vacuo* to give a crude yellow oil, which was purified *via* column chromatography (elution with hexanes/ether, 1:1) to furnish 17.1 mg (90%) of enone **12**. Enone **12** was homogeneous by TLC analysis (hexanes/ether, 6:1, R_f (**11**) = 0.76, R_f (**12**) = 0.61).

Preparation of 3-(1-cyclohexenyl)-2-{2-[(trimethylsilyl)-methyl]allyl}-2-cyclopenten-1-one **22**

A solution of phenylthiocopper(I) was prepared in the following manner. To a solution of 3.49 mL of thiophenol (30.00 mmol) in 200 mL of anhydrous ether at 0°C was added 15.6 mL of 2.5 M *n*-BuLi (39.00 mmol) in hexane dropwise over a 10 min period. After an additional 30 min at 0°C, 6.30 g of copper(I) iodide (33.00 mmol) dissolved in 80 mL of ether was added to the ethereal solution of phenylthiolithium. The resulting heterogeneous mixture of phenylthiocopper(I) was stirred at 0°C for 1 h and then cooled to −78°C.

A solution of 2-lithio-2-cyclopentenone ethylene ketal (36.00 mmol) was prepared as described in the preparation of acetate **8**.

The mixture of phenylthiocopper(I) was added rapidly (via cannula) to the solution of 2-lithio-2-cyclopenten-1-one ethylene ketal and the reaction mixture was stirred for a 30 min period at −70°C. 3-Iodo-2-(trimethylsilylmethyl)propene (**18**) (9.14 g, 36 mmol) was added in a single portion and the reaction mixture was stirred at −78°C for 30 min and then warmed to −30°C over a 30 min period. The reaction mixture was diluted at −30°C with 200 mL of ether and 20 mL of 10% sodium carbonate solution and then stirred for 1.5 h at room temperature. The yellowish copper complex was removed via vacuum filtration. The organic phase was then separated from the filtrate. Standard ethereal workup, followed by chromatography (H/E, 10:1), provided 6.72 g (85% yield) of 6-{2-[(trimethylsilyl)methyl]allyl}-1,4-dioxaspiro[4.4]non-6-ene (**19**) which was homogeneous by TLC analysis (hexanes/ether, 5:1, R_f (**18**) = 0.48, R_f (**19**) = 0.54).

^{1}H NMR (90 MHz) δ 0.00 (s, 9H), 1.54 (br s, 2H), 1.90-2.12 (m, 2H), 2.18-2.42 (m, 2H), 2.67 (br s, 2H), 3.92 (s, 4H), 4.54-4.73 (m, 2H), 5.69-5.81 (m, 1H).

^{13}C NMR (22.5 MHz) 145.2 (s), 141.1 (s), 132.2 (d), 119.9 (s), 109.0 (t), 65.0 (t), 65.0 (t), 35.6 (t), 34.7 (t), 27.7 (t), 26.0 (t), −1.4 (q) ppm.

IR (film) 1 640, 1 425 cm^{-1}.

Mass spectrum, m/z 252 (M^+).

A solution of 6.72 g of ketal **19** (26.60 mmol) in 50 mL of THF and 2 mL of 1 N aqueous sulfuric acid was stirred until TLC analysis revealed complete consumption of the starting material (approx 5 min). The reaction was quenched by the addition of an equal volume of satured aqueous $NaHCO_3$. Standard ethereal workup, followed by chromatography (hexane/ether, 10:1), gave 5.13 g (97% yield) of 2-[2-(trimethylsilylmethyl)allyl]-2-cyclopenten-1-one **20**) which was homogeneous by TLC analysis (hexane/ether, 5:1, R_f (**19**) = 0.54, R_f (**20**) = 0.42).

^{1}H NMR (90 MHz) δ 0.00 (s, 9H), 1.47 (s, 2H), 2.28-2.44 (m, 2H), 2.45-2.63 (m, 2H), 2.78 (br s, 2H), 4.55 (br s, 2H), 7.23-7.37 (m, 1H).

^{13}C NMR (62.5 MHz) 209.2 (s), 158.8 (d), 144.2 (s), 144.2 (s), 109.0 (t), 34.4 (t), 33.4 (t), 26.5 (t),26.3 (t), −1.4 (q) ppm.

IR (film) 1 710, 1 635 cm^{-1}.

Mass spectrum, m/z 208 (M^+).

Anal calc for $C_{12}H_{20}OSi$, C = 69.19%, H = 9.68%; Found : C = 68.82%, H = 9.68%.

t-Butyllithium (4.10 mL, 7.00 mmol, 1.7 M in pentane) was added dropwise over a 10 min period to a solution of 1-bromo-1-cyclohexene (561 mg, 3.48 mmol) in 10 mL of dry ether at −78°C. The reaction mixture was allowed to warm to 0°C over a 2 h period and then cooled to −70°C. A solution of enone **20** (250 mg, 1.20 mmol) dissolved in 3 mL of dry ether was added dropwise to the cold alkenyllithium solution. The resulting mixture was allowed to warm to 10°C over a 3 h period. Standard ethereal workup, followed by column chromatography (elution with hexanes/ether, 1:1), furnished 272 mg of 2-{2-[(trimethylsilyl)methyl]allyl}-2-cyclopenten-1-ol (**21**) (78%) which homogeneous by TLC analysis (hexanes/ether, 1:1, R_f (**20**) = 0.72, R_f **21**) = 0.88).

^{1}H NMR (300 MHz) δ 0.03 (s, 9H), 1.50-1.80 (m, 9H), 1.55 (s, 2H), 2.05-2.25 (m, 4H), 2.90 (br s, 1H), 3.05 (br s, 1H), 4.56 (br s, 1H), 4.59 (br s, 1H), 5.70-5.80 (br t, 1H), 6.05-6.20 (m, 1H).

^{13}C NMR (62.5 MHz) 149.7, 146.2, 144.5, 133.3, 130.2, 127.6, 124.5, 109.0, 38.9, 38.4, 28.8, 26.9, 25.4, 23.0, 22.1, −1.3 ppm.

To a suspension of 340 mg of PDC (0.89 mmol) in 10 mL of anhydrous CH_2Cl_2 was added a solution of 130 mg of alcohol **21** (0.49 mmol) in 5 mL of CH_2Cl_2 at 0°C. The reaction mixture was then stirred for 3 h at 0°C. Diethyl ether (50 mL) was added and the mixture was filtered through a plug of glass wool; the solids were washed with ether. Standard ethereal workup, followed by chromatography (elution with hexanes/ether, 2:1, furnished 105 mg (76% yield) of trienone **22** which was homogeneous by TLC analysis (hexanes/ether, 5:1, R_f (**21**) = 0.60, R_f (**22**) = 0.45).

^{1}H NMR (250 MHz) δ 0.10 (s, 9H), 1.60-1.80 (m, 6H), 1.62 (s, 2H), 2.20-2.35 (m, 4H), 2.40-2.50 (m, 2H), 2.65-2.75 (m, 2H), 3.00 (br s, 2H), 4.28 (s, 1H), 4.53 (s, 1H), 6.10-6.20 (br t, 1H).

^{13}C NMR (250 MHz) 209.7, 171.2, 144.7, 136.1, 134.8, 130.8, 107.2, 32.6, 32.7, 28.3, 28.0, 26.6, 25.7, 22.4, 21.6, −1.2 ppm.

Preparation of tricycle **23**

To a solution of 60 mg of trienone **22** (0.208 mmol) in 4 mL of anhydrous toluene at −10°C was added rapidly 300 μL of ethylaluminium dichloride (1.50 M in toluene, 0.41 mmol). The reaction mixture was warmed to room temperature over a 90 min period and then quenched. Standard ethereal workup, followed by chromatography (hexanes/ether, 1:1), gave 32 mg of unreacted trienone **22** and 11 mg of enone **23** (41% yield based on recovered **22**) which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f (**23**) = 0.50, R_f (**2**) = 0.47).

^{1}H NMR (250 MHz) δ 1.60-2.60 (m, 18H), 4.68 (s, 1H), 4.72 (s, 1H).

Preparation of 5-methyl-5-{2-(trimethylsilyl)methyl] allyl}-3-vinyl-2-cyclopenten-1-one **28**

To a solution of lithium diisopropylamide, prepared from 0.52 mL (3.68 mmol) of diisopropylamine in 1 mL of dry THF and 2.11 mL of *n*-butyllithium (1.6 M in hexanes, 3.38 mmol) at −78°C, was added a solution of 430 mg (3.07 mmol) 5-methyl-3-ethoxy-2-cyclopenten-1-one (**24**) in 2 mL of THF containing 0.82 g (4.60 mmol) of HMPA over a 10 min period (via syringe pump). After an additional 90 min at −78°C, 1.01 g (3.99 mmol) of silyl iodide **18** was added. (We have found that the alkylation of the cross-conjugated enolates of cyclopentenone derivatives alkylate best when the total reaction concentration is ca 1 M.) The reaction was stirred at −78°C for 1 h and then allowed to warm to room temperature over a 10 h period. Standard ethereal workup provided 398 mg of crude which was purified on silica gel (elution with hexanes/ether, 3:1) to afford 346 mg (66%) of **25** which was homogeneous on TLC analysis (hexanes/ether, 3:1, R_f (**24**) = 0.12, R_f (**25**)n = 0.29).

^{1}H NMR (CCl_4) δ 0.00 (s, 9H), 1.13 (s, 3H), 1.37 (t, 3H, J = 7 Hz), 1.45 (s, 2H), 2.15 (ABq, 2H, $\Delta\nu_{AB}$ = 15 Hz, J = 14 Hz), 2.54 (ABq, 2H, $\Delta\nu_{AB}$ = 28 Hz, J = 15 Hz), 3.97 (q, 2H, J = 7 Hz), 5.00 (m, 2H), 5.12 (s, 1H).

IR (film) 3 070, 1 695, 1 625, 1 595 cm^{-1}.

To a solution of enone **25** (509 mg, 1.91 mmol) in 7.0 mL of anhydrous toluene cooled to 0°C was added dropwise 2.10 mL (2.10 mmol) of diisobutylaluminium hydride (1.0 M in toluene) over a 15 min period. The reaction was allowed to stir at 0°C and was monitored by TLC analysis. After a 90 min period, the reaction was quenched by the careful dropwise addition of a saturated aqueous solution of ammonium chloride, diluted with ether and the phases separated. The ethereal layer was dried over anhydrous magnesium sulfate, filtered and concentrated to provide crude alcohol which was used without further purification.

The crude alcohol was diluted with 20 mL of THF and 6 drops of 10% aqueous HCl were added. The resulting solution was stirred at room temperature for a 30 min period. The solution was neutralized with anhydrous potassium carbonate and diluted with ether. Filtration and evaporation of the solvent provided 200 mg of an oily residue. Purification on silica gel (elution with hexanes/ether, 1:2) afforded 242 mg (78%) of **26** which was homogeneous by TLC analysis (hexane/ether, 1:2, R_f (**25**) = 0.79, R_f (**26**) = 0.93).

^{1}H NMR (CCl_4) δ 0.00 (s, 9H), 1.18 (s, 3H), 1.43 (s, 2H), 2.1p (s, 2H), 2.13 (ABq, $\Delta\nu_{AB}$ = 18 Hz, J = 18 Hz), 4.48 (br s, 1H), 4.51 (br s, 1H), 5.78 (d, 1H, J = 6 Hz), 7.23 (d, 1H, J = 6 Hz).

IR (film) 3 070, 2 950, 2 920, 1 060, 850, 800, 700, 640 cm^{-1}.

Mass spectrum, m/e = 222 (M^+).

A solution of 625 mg (2.97 mmol) of **26** in 10 mL of THF at 0°C was treated dropwise with 2.83 mL of vinylmagnesium bromide (2.1 M, 5.95 mmol) over a 30 min period and stirred for 45 min at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL). Standard ethereal workup, followed by column chromatography (elution with hexanes/ether, 1:1), provided 657 mg of alcohol **27** (93%) which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f (**26**) = 0.55, R_f (**27**) = 0.50 and 0.63).

^{1}H NMR (90 MHz, CCl_4) δ 0.00 (s, 9H), 1.00 (s, 1.5H), 1.15 (s, 1.15H), 1.00-2.20 (m, 10H), 4.30-4.50 (m, 2H), 4.65-6.00 (m, 5H). These data represent a 1:1 mixture of diastereomers.

To a suspension of 3.06 g of PDC (8.14 mmol) in 20 mL of anhydrous CH_2Cl_2 was added a solution of 969 mg of alcohol **27** (4.07 mmol) in 10 mL of CH_2Cl_2 at 0°C. The reaction mixture was then stirred for 4 h at 0°C. Diethyl ether (100 mL) was added and the mixture was filtered through a plug of glass wool; the solids were washed with ether. Standard ethereal workup, followed by chromatography (hexanes/ether, 10:1), furnished 678 mg (70% yield) of trienone **28** which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f (**27**) = 0.50 and 0.63, R_f (**28**) = 0.74).

^{1}H NMR (90 MHz, CCl_4) δ 0.05 (s, 9H), 1.00 (s, 3H), 1.20 (s, 2H), 1.20-2.90 (m, 4H), 4.30 (br s, 2H), 5.20-5.35 (m, 1H), 5.50-5.75 (m, 1H), 6.20-6.70 (m, 1H).

Cyclization of **28**

To a solution fo 50 mg of trienone **28** (0.20 mmol) in 1 mL of anhydrous toluene at −10°C was added rapidly 21 μL of ethylaluminium dichloride (1.45 M in toluene, 0.302 mmol). The reaction mixture was warmed to room temperature, stirred for 1 h and then quenched. Standard ethereal workup, followed by chromatography (elution with hexanes/ether, 2:1), gave 36 mg (72% yield) of enone **29** which was homogeneous by TLC analysis (ether, 2:1, R_f (**28**) = 0.50, R_f (**29**) = 0.76).

^{1}H NMR (90 MHz, CCl_4) δ 0.80-2.4 (m, 10H), 4.70 (br s, 2H), 5.95 (s, 1H).

Preparation of 5-methyl-5-({2-methyl-6-[(dimethyl-phenyl) silyl]-1-cyclohexenyl}methyl)-3-vinyl-2-cyclopenten-1-one **34**

To a solution of lithium diisopropylamide, prepared from 121 mg (1.20 mmol) of diisopropylamine in 5 mL of dry THF and 480 μL of *n*-butyllithium (12.5 M in hexanes, 1.20 mmol) at −78°C, was added a solution of 140 mg of **24** (1.00 mmol) in 1 mL of THF containing 2.15 mg (1.10 mmol) of HMPA. After an additional 90 min at −78°C, 1.00 g (3.54 mmol) of 1-(iodomethyl)-6-(trimethylsilyl)-1-cyclohexene (**30**) [7] was added. The reaction was stirred at −78°C for 1 h and then allowed to gradually warm to room temperature over 12 h. Standard ethereal workup provided 1.27 g of crude residue which was purified on silica gel (elution with hexanes/ether, 4:1) to afford 252 mg (66%) of **25** which was homogeneous on TLC analysis (hexanes/ether, 2:1; R_f (**24**) = 0.39, R_f (**31**) = 0.74 and 0.80).

^{1}H NMR (250 MHz, CCl_4) δ 0.22 (s, 3H), 0.30 (s, 3H), 0.95 (s, 2H), 1.10 (s, 1H), 1.30-1.40 (t, 3H, J = 6 Hz), 1.55 (s, 3H), 1.20-2.80 (m, 17H), 3.80-4.05 (m, 2H), 5.00 (s, 0.67H), 5.13 (0.33H), 7.20-7.50 (m, 5H).

These data represent a 2:1 mixture of diastereomers.

To a solution of enones **31** (756 mg, 1.98 mmol) in 10 mL of anhydrous toluene cooled to 0°C was added dropwise 1.45 mL (2.17 mmol) of diisobutylaluminum hydride (1.5 M in toluene) over a 15 min period. The reaction was allowed to stir at 0°C and was monitored by TLC. Upon completion (30 → 90 min), the reaction was quenched by the careful dropwise addition of a satured aqueous solution of ammonium chloride, diluted with ether and the phases were separated. The ethereal layer was dried over anhydrous magnesium sulfate, filtered and concentrated to provide the crude alcohol which was used without further purification. The crude alcohol was diluted with 20 mL of THF and 10 drops of 10% aqueous HCl were added. The resulting solution was stirred at room temperature for a 30 min period. The solution was neutralized with anhydrous potassium carbonate and diluted with ether. Filtration and evaporation of the solvent provided 511 mg of an oily residue. Purification on silica gel (elution with hexanes/ether, 7:1) afforded 390 mg (58%)

of enones **32** which were homogeneous by TLC analysis (hexanes/ether, 7:1, R_f (**31**) = 0.40 and 0.50, R_f (**32**) = 0.83).

^{1}H NMR (300 MHz, CCl_4) δ 0.20-0.40 (m, 6H), 0.91 (s, 1H), 1.03 (s, 2H), 1.35-2.60 (m, 14H), 5.80-5.90 (m, 1H), 7.00-7.05 (m, 0.5H), 7.15-7.50 (m, 5.5H).

These data represent a 1:1 mixture of diastereomers.

A solution of 390 mg (1.15 mmol) of enone **32** in 30 mL of THF at 0°C was treated dropwise with 2.30 mL of vinylmagnesium bromide (1 M in THF, 2.30 mmol) over a 30 min period and stirred for 10 h at room temperature. The reaction mixture was quenched with aqueous ammonium chloride (3 mL). Standard ethereal workup provided 427 mg of crude residue. Purification via column chromatography (elution with hexanes/ether, 20:1) afforded 146 mg (35%) of two diastereomers of alcohol **33** which were homogeneous by TLC analysis (hexanes/ether, 5:1, R_f (**32**) = 0.35, R_f (**33**) = 52).

^{1}H NMR (250 MHz, CCl_4) δ 0.30-0.45 (m, 6H), 0.87 (s, 1.7H), 0.93 (s, 1.3H), 1.50-2.10 (m, 14H), 2.40-2.55 (m, 1H), 4.95-5.05 (m, 1H), 5.10-5.22 (m, 1H), 5.33-5.48 (m, 1H), 5.65-5.70 (m, 1H), 5.83-6.00 (m, 1H), 7.25-7.60 (m, 5H).

These data represent a 1.7:1.3 mixture of diastereomers.

Continued elution provided 143 mg (34%) of a mixture of other diastereomers of alcohol **33** which was homogeneous by TLC analysis (hexanes/ether, 5:1, R_f (**33**) = 0.31.

^{1}H NMR (300 MHz, CCl_4) δ 0.25-0.35 (m, 6H), 1.00-1.10 (m, 3H), 1.45-2.50 (m, 15H), 4.90-6.05 (m, 5H), 7.20-7.50 (m, 5H).

To a suspension of 301 mg of PDC (0.80 mmol) in 15 mL of anhydrous CH_2Cl_2 was added a solution of 146 mg of alcohol **33** (0.40 mmol) in 25 mL of CH_2Cl_2 at 0°C. The reaction mixture was then stirred for 3 h at 0°C. Diethyl ether (50 mL) was added and the mixture was filtered through a plug of glass wool; the solids were washed with ether. Standard ethereal workup, followed by chromatography (hexanes/ether, 10:1), furnished 95 mg (65% yield) of trienone **34** which was homogeneous by TLC analysis (hexanes/ether, 10:1, R_f (**33**) = 0.30 and 0.40, R_f (**34**) = 0.45).

^{1}H NMR (250 MHz) δ 0.20-0.40 (m, 6H), 0.95-1.20 (m, 3H), 1.30-2.90 (m, 14H), 5.40-6.00 (m, 3H), 6.60-6.80 (m, 1H), 7.20-7.50 (5H).

These data represent a mixture of diastereomers.

Cyclization of **34**

To a solution of 28 mg of trienone **34** (0.077 mmol) in 2.5 mL of anhydrous toluene at 0°C was added rapidly 120 μL of ethylaluminum dichloride (1.80 M in toluene, 0.116 mmol). The reaction mixture was warmed to room temperature, stirred for 3 h and then quenched with five drops of saturated aqueous ammonium chloride. Standard ethereal workup, followed by chromatography (hexanes/ether, 5:1), gave 9 mg (31% yield) of enone 1,8-dimethyltricyclo[9.2.1.$0^{3,8}$]tetradeca-3,11-dien-13-one **35** which was homogeneous by TLC analysis (hexane/ether, 5:1, R_f (**34**) = 0.50, R_f (**35**) = 0.41.

^{1}H NMR (250 MHz) δ 1.15 (s, 3H), 1.20 (s, 3H), 1.00-2.90 (m, 18H), 5.50-5.60 (m, 1H), 6.05 (s, 1H).

The other diastereomer of enone **34** failed to react upon exposure to ethylaluminum dichloride.

Acknowledgment

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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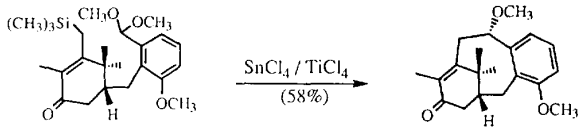

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