Total Synthesis of 18-Oxo-3-virgene, a Constituent of the Waxy Surface Resins of Tobacco

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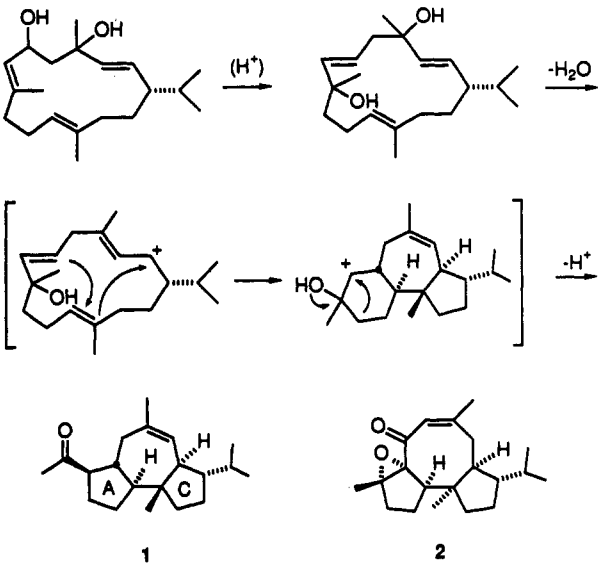
Complete details surrounding the first total synthesis of a virgane diterpene are herein described. Conversion of the known trans-fused hydrindanone **7** to conjugated ketone **8** and properly stereocontrolled 1,4-addition of a side chain set the stage for ring closure and the formation of **6**. Vinylcuprate addition, regioselective silyl enol ether formation, and treatment with (chloromethyl)-carbene led cleanly to **13**. Reductive deoxygenation and regioselective Wacker oxidation subsequently afforded **15**. The oxidation of **15** to **17** and ensuing exposure to lithium in liquid ammonia completed installation of the last two stereogenic centers. Finally, the target carbotricyclic ketone **1** was obtained following exposure of the penultimate alcohol to PCC on alumina.

18-Oxo-3-virgene (**1**) is a ketonic tricyclic diterpene of unique structure that has recently been isolated and characterized by Uegaki et al.[1] The discovery of **1** in the cuticular wax secreted by Virginia 115 cultivars points up the latent capability of tobacco plants to accomplish the chemical modification of 14-membered cembranoids in unusual ways. The proposed biosynthetic route to **1** (Scheme 1)[1] is based upon a putative series of transformations including an allylic alcohol transposition, cationic transannular cyclization, and pinacol-like ring contraction. This pathway is hardly exclusive. More than a decade ago, the team headed up by Wahlberg had already reported[2] the isolation of epoxybasmenone (**2**) from plants of Greek origin.[3] Additional structural variants will surely be found.

The novel architectural features present in **1** commanded our attention.[4] Although its fundamental 5-7-5 tricyclic framework is totally unprecedented, the most provocative feature of **1** is the trans,anti,trans attachment of the peripheral five-membered rings to the cycloheptenyl core. Further, the four associated stereogenic centers form part of a contiguous array of six chiral carbon atoms.

Scheme 1

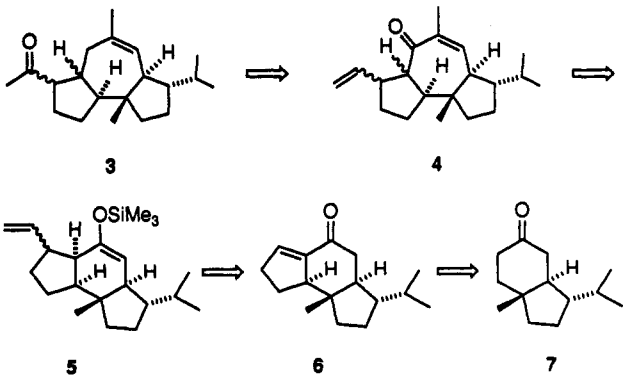


1 **2**

Synthetic Plan

One might consider the elaboration of **1** by some method involving 2-fold cyclopentannulation of the suitably functionalized cycloheptane derivative. However, this strategy suffers from a likely inability to control the conformational features of the seven-membered ring adequately to achieve proper stereochemical regulation. An alternative and potentially simpler plan of action presented itself. The lesser thermodynamic stability of trans-fused hydrindanes relative to their cis counterparts has long been recognized. Nonetheless, reliable methods for gaining fully stereocontrolled access to the more strained derivatives are presently available. This is particularly so for ketone **7**.[5] We favored **7** as the starting material because the entire C ring of **1** was already incorporated therein (Scheme 2).

Scheme 2



3 **4** **5** **6** **7**

The differing levels of substitution predisposed about the α and α' positions flanking the carbonyl group in **7**

• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

(1) Uegaki, R.; Fujimori, T.; Ueda, N.; Ohnishi, A. *Phytochemistry* **1987**, *26*, 3029.

(2) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R.; Berg, J.-E. *Tetrahedron Lett.* **1983**, *24*, 843.

(3) For synthetic efforts in this area, see: (a) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252. (b) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610.

(4) Preliminary communication: Wang, X.; Paquette, L. A. *Tetrahedron Lett.* **1993**, *34*, 4579.

(5) (a) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149. (b) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

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could presumably be used to advantage in achieving the cyclocondensation depicted in **6**. The presumption was that this could be achieved by tandem cuprate addition and aldol cyclization. Since introduction of the first new C–C bond had to be properly stereocontrolled, this protocol was expected to provide adequate flexibility as required. With a conjugated enone established as in **6**, it seemed that 1,4-addition of a vinyl group would lend itself to orderly introduction of the acetyl substituent at a later stage. The anticipated A/B cis stereochemistry projected for **5** would ultimately need to be redressed. This permutation was expected to be feasible following expansion of the central ring.

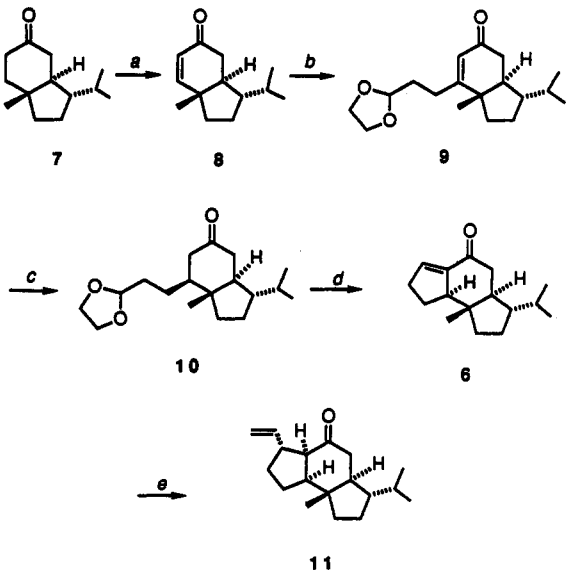
An especially concise means for accomplishing the ring enlargement was discerned to involve a carbenoid ring expansion. The silyl enol ether functionality in **5** was certain to guarantee regioselectivity during capture of the (chloromethyl)carbene reagent. With the final methyl group properly installed as in **4**, removal of the carbonyl oxygen was the next step. To do this with maximum efficiency, any potential allylic rearrangement would need to be controlled. Since the two allylic termini in **4** are sterically shielded to roughly comparable levels, a solution to this significant problem based on nonbonded interactions was not entirely obvious. We anticipated therefore that control of the locus of the double bond would be no simple matter.

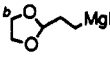
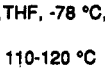
Finally, kinetically controlled Wacker oxidation[6] should easily distinguish between the two sites of unsaturation in this advanced intermediate. The opinion was that once **3** was in hand the proper stereochemistry could be introduced at the pair of stereogenic carbon atoms residing within the A ring.

Results

Although the phenylselenenylation of **7** proved not to be adequately regiocontrolled,[7] direct bromination of this ketone with pyridinium hydrobromide perbromide in acetic acid[8] was. Without purification, the dehydrobromination of this intermediate was effected with lithium carbonate and lithium bromide in hot dimethylformamide[9] to deliver **8** in 85% overall yield (Scheme 3). Having secured **8**, we immediately proceeded to perform a conjugate addition involving the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxolane[10] and the cuprous bromide–dimethyl sulfide complex. It was quickly recognized on the strength of NOE and COSY studies that the resultant product did not possess the requisite β configuration. Not unexpectedly, the organometallic attacked the enone

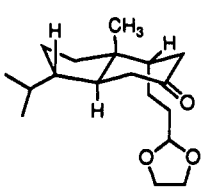
Scheme 3



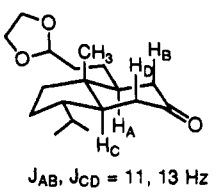
[a] Py·HBr$_3$, HOAc; Li_2CO_3, LiBr, DMF, 110-120 °C. [b]  MgBr, CuBr·Me_2S, DMAP, THF, -78 °C, then Me_3SiCl; NBS,  THF, 0 °C; Li_2CO_3, LiBr, DMF, 110-120 °C [c] H_2 (1 atm), Pd-C, THF, [d] 1 N HCl, THF, Δ. [e] CH_2=$CHSnBu_3$, $Me_2Cu(CN)Li_2$ THF, -78 °C; NH_4Cl, H_2O.

preferentially from the axial direction to furnish **12**.[11] This complication was quickly rectified by capping the cuprate addition with *in situ* silylation, followed directly by bromination of the silyl enol ether with NBS in the presence of propylene oxide,[12] and dehydrobromination as before to generate **9** (65% overall).

Reintroduction of the double bond in this fashion was undertaken in an effort to take advantage of an anticipated comparably strong kinetic bias for reagent delivery to the α surface of **9**. Indeed, hydrogenation of this enone over Pd–C led with exceptional stereoselectivity to **10**. The stereochemical assignment to **10** follows convincingly from inspection of selected key coupling constants as determined in $CDCl_3$ at 300 MHz.



12



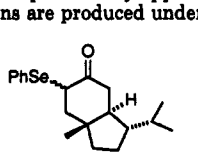
J_{AB}, J_{CD} = 11, 13 Hz

10

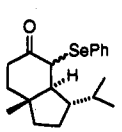
The response of **10** to being heated with 1 N HCl in tetrahydrofuran for several days was highly efficient conversion to the tricyclic enone **6**. Subsequent exposure of **6** to the mixed higher-order species produced by mixing tri-*n*-butylvinylstannane with $Me_2Cu(CN)Li_2$[13] succeeded in producing **11**. That the 1,4-addition and subsequent protonation had both occurred from the less hindered surface of **6** was again evident from high-field COSY and NOE studies as indicated.

(6) Tsuji, J. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Eds.; Pergamon Press, New York, 1991; Vol. 7, Chapter 3.4.

(7) The combined use of LDA and PhSeCl afforded a mixture of **i** and **ii**, the 5:1 ratio presumably approximating the extent to which the two enolate anions are produced under these conditions.



i



ii

(8) Devanathan, V. C.; Bhagan, V. U.; Arumugam, N. *Ind. J. Chem.* **1983**, *22B*, 766.

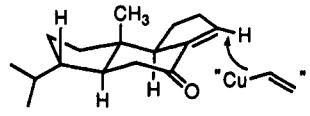
(9) Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792.

(10) (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122. (b) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

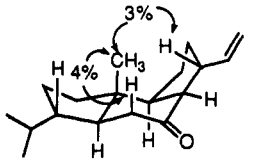
(11) Unlike the sensitivity of a bicyclo[4.2.0]oct-3-en-2-one to specific reaction conditions [Zhao, S.-K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447], the stereoselectivity of conjugate addition to **8** was invariably α irrespective of the cuprate and its mode of delivery.

(12) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

(13) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.



6

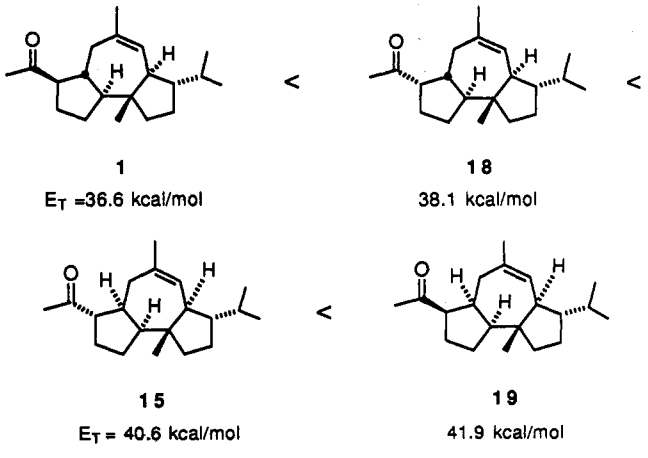


11

The success of the scenario just outlined led next to evaluation of the ring expansion process. Exposure of **11** to lithium diisopropylamide in cold (−78 °C) THF produced the less substituted enolate anion via kinetic deprotonation. Following O-silylation,[14] this intermediate was treated directly with (chloromethyl)carbene as generated from 1,1-dichloroethane and *n*-butyllithium.[15] The resulting (chlorosiloxy)cyclopropane was heated in methanol containing triethylamine. This series of steps provided the pivotal ketone **13** in 59% overall yield.

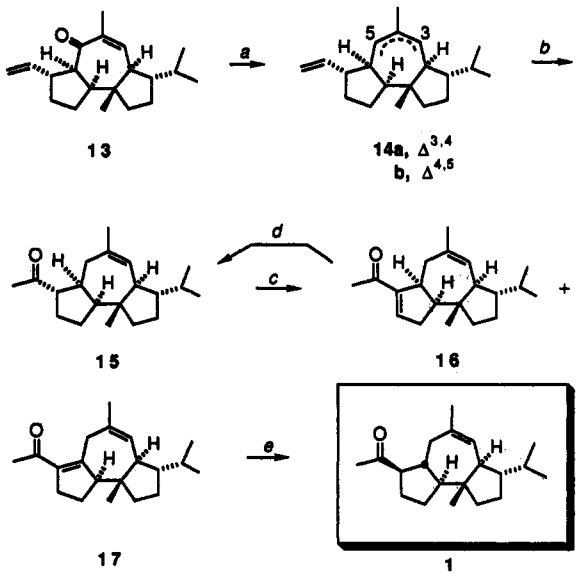
Without belaboring the issue, the most satisfactory means uncovered for reductively excising the carbonyl oxygen in **13** involved application of Ireland's phosphoramidate cleavage technology[16] (Scheme 4). Although the individual stages of the three-step sequence were efficient, the reductive maneuver invariably produced the $\Delta^{3,4}$- and $\Delta^{4,5}$-isomers in a 1.3:1 ratio. Exclusive regioselectivity was never observed; nor did **14a** and **14b** prove chromatographically separable. Nevertheless, it was satisfying to find that the Wacker oxidation[17] was indeed fully regioselective and high-yielding. Further, pure **15** could be conveniently separated from its diastereomer in pure condition.

At this stage, MM2 calculations[18] involving the ketone subset **1**, **15**, **18**, and **19** provided considerable impetus to our strategic planning. A particularly pertinent finding was the obvious thermodynamic preference for trans A/B fusion when the balance of the carbotricyclic framework was required to be oriented anti,trans to theA ring. This



result and the tandem observation that **1** is 1.5–5.3 kcal/mol more stable than the other three diastereomers occasioned no surprise. As is often seen, Nature effectively

Scheme 4



[a] $NaBH_4$, $CeCl_3$, MeOH, -40 °C; *n*-BuLi, $ClP(O)(NMe_2)_2$, THF-TMEDA (4:1);Li, NH_3. [b] $PdCl_2$, $CuCl_2$, O_2, DMF-H_2O (10:1). [c] Me_3SiI, $(Me_3Si)_2NH$, CH_2Cl_2, -20 °C → +20 °C; PhSeCl, THF, 0 °C; H_2O_2, THF, 0 °C. [d] $[(Ph_3P)CuH]_6$, Me_3SiCl, C_6H_6. [e] Li, NH_3, -78 °C; PCC, Al_2O_3.

elaborates complex structures with proper regard for the global energetics of the system. As reflected in Figure 1, cis A/B ring fusion induces adoption of a substantially folded topography that prefers accommodation of the acetyl group as in **15**. When this substituent is oriented β, however, the proximal angular hydrogen strongly prefers to be oriented as in **1** and not as in **19**. Since the acetyl group is subject to epimerization whereas the nearby angular hydrogen is not, the latter stereogenic center first had to be modified.

To this end, **15** was oxidized by preliminary conversion to its *thermodynamic* silyl enol ether with trimethylsilyl iodide and hexamethyldisilazane.[19] Ensuing phenylselenenylation of this intermediate and treatment with hydrogen peroxide in THF at 0 °C was next undertaken. Models indicated the stereoelectronic requirements for selenoxide elimination to be excellent in either direction. In the absence of any particular bias, the expectation was that the thermodynamically more favored **16** would be formed more rapidly than **17**. Indeed, the isolated yields of these enones following chromatographic separation were 70% and 26%, respectively. Since **16** could be efficiently returned to **15** by reduction with the triphenylphosphine–copper hydride tetramer,[20] the undesired isomer could be readily recycled.

Submission of **17** to dissolving metal reduction and oxidation with PCC on alumina afforded a sample of the fully synthetic 18-oxo-3-virgene (**1**) in 80% yield. Since the ^1H and ^{13}C NMR spectra of **1** completely matched those reported by Uegaki et al.,[1] the predictions arrived at on the basis of molecular modeling had been fulfilled.

To sum up, the first synthesis of a virgane diterpene has been achieved. From the positive vantage point, the successful implementation of a fully regiocontrolled carbenoid ring expansion and the need to isolate only nine intermediates are noteworthy. Further, the synthetic

(14) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
(15) Blanco, L.; Amice, P.; Conia, J.-M. *Synthesis* **1981**, 289.
(16) (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1174.
(17) Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 3587.
(18) Initial minimization with MODEL (version KS 2.96), with final optimization in MMX. E_T = total energy. We thank Professors Clark Still and Kosta Steliou for making the requisite software available.
(19) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(20) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

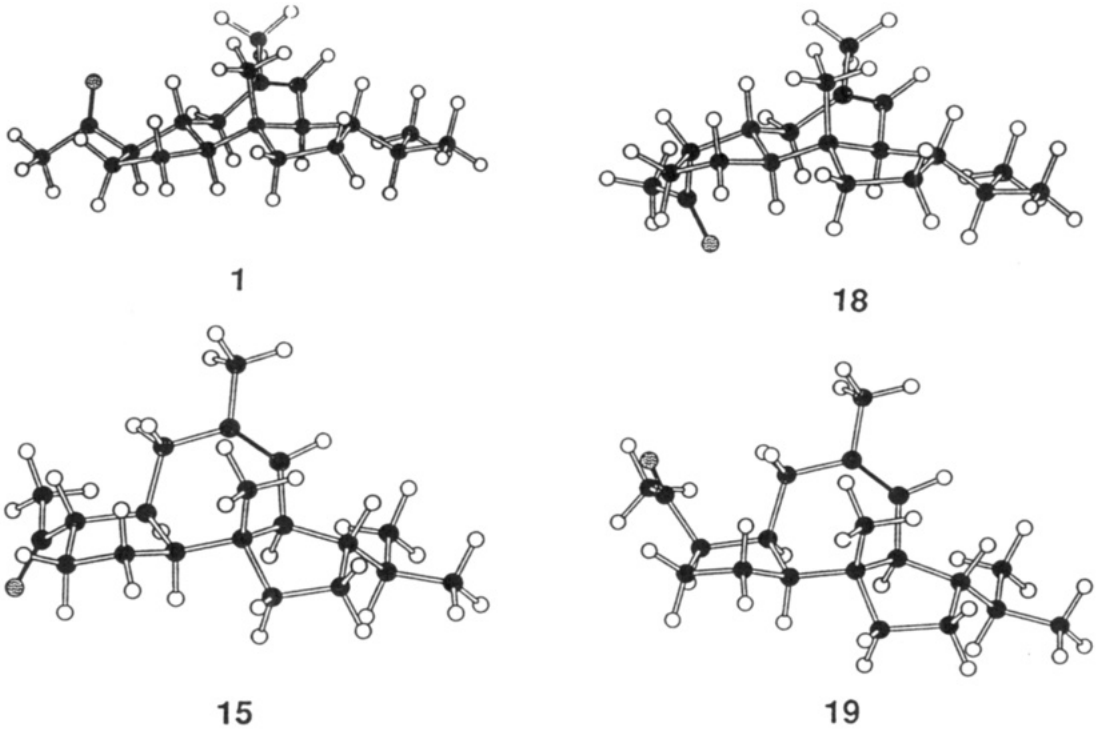


Figure 1. Global minimum energy conformations of **1**, **15**, **18**, and **19** as determined by molecular mechanics calculations (Chem-3D output).

venture features high levels of stereoselectivity. Somewhat disappointing was the fact that protonation of the allylic anion formed by reduction of the allylic phosphoramidate precursor to **14** was not regioselective.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 instrument. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz on a Bruker AC-300 instrument as noted. Mass spectra were recorded on a Kratos MS-30 spectrometer at The Ohio State University Chemical Instrument Center. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods. All reactions involving nonaqueous solutions were performed under an inert atmosphere. Unless otherwise indicated, all separations were carried out under flash chromatography conditions on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvents. The organic extracts were dried over anhydrous magnesium sulfate.

(±)-(3*R,3a*R**,7a*S**)-3a,7a-Dihydro-3-isopropyl-7a-methyl-5(4*H*)-indanone (8).** A solution of **7** (2.7 g, 13.9 mmol) in glacial acetic acid (30 mL) was treated with pyridinium hydrobromide perbromide (4.90 g, 15.3 mmol) in two portions. The resulting red solution was stirred for 20 min during which time a white precipitate was formed. The reaction mixture was poured into ice water (50 mL) and extracted with ether (4 × 100 mL). The combined organic layers were carefully neutralized with saturated $NaHCO_3$ solution, dried, and evaporated. The resulting yellow solid was added to a suspension of dry Li_2CO_3 (2.57 g, 34.8 mmol) and dry LiBr (2.41 g, 27.8 mmol) in dry DMF (30 mL), and the mixture was heated at 110–120 °C for 1.5 h, cooled to rt, poured into saturated NH_4Cl solution (50 mL), and extracted with ether. The combined organic phases were dried and evaporated, and the residue was chromatographed on silica gel (elution with 2% ethyl acetate in petroleum ether) to give 2.28 g (85%) of **8** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 9.8 Hz, 1 H), 5.83 (d, J = 9.8 Hz, 1 H), 2.59 (dd, J = 3.7, 17.3 Hz, 1 H), 2.29 (dd, J = 17.3, 17.5 Hz, 1 H), 1.91–1.43 (series of m, 7 H), 1.00 (s, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.9, 159.2, 128.0, 47.8, 45.9, 43.6, 39.2, 34.8, 29.5, 23.9, 21.5, 19.4, 18.4; MS m/z (M^+) calcd 192.1514, obsd 192.1540.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.18; H, 10.49. Found: C, 80.91; H, 10.48.

(±)-(3*R,3a*R**,7a*R**)-7-[2-(1,3-Dioxolan-2-yl)ethyl]-3a,7a-dihydro-3-isopropyl-7a-methyl-5(4*H*)-indanone (9).** A 1.77-g (72.8 mmol) sample of magnesium turnings was flame-dried under N_2, cooled to rt, and covered with dry THF (50 mL). A solution of 2-(2-bromoethyl)-1,3-dioxolane (8.90 g, 52.0 mmol) in dry THF was slowly introduced via cannula. Upon completion of the addition, the mixture was stirred at rt for 20 min prior to transfer via cannula to a cold (−78 °C) mixture of copper(I) bromide–dimethyl sulfide complex (630 mg, 3.10 mmol) and 4-(dimethylamino)pyridine (3.18 g, 26.0 mmol) in dry THF (40 mL). The resulting mixture was stirred for 1 h at −78 °C before the addition of a solution of **8** (2.20 g, 11.5 mmol) and chlorotrimethylsilane (2.70 g, 25 mmol, freshly distilled from CaH_2) in dry THF (10 mL) during 5 min. After being stirred for 30 min at −78 °C, the mixture was quenched with triethylamine (10 mL), dissolved in petroleum ether (50 mL), and subsequently diluted with water (20 mL). The separated aqueous phase was extracted with petroleum ether (2 × 50 mL) and the combined organic layers were dried and evaporated. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) gave 3.91 g (93%) of the silyl enol ether: IR (neat, cm^{-1}) 1720, 1660, 1210, 1200, 1145; ^{1}H NMR (300 MHz, C_6D_6) δ 5.10 (dd, J = 1.6, 5.3 Hz, 1 H), 4.84 (t, J = 4.7 Hz, 1 H), 3.55 (m, 2 H), 3.37 (m, 2 H), 2.25 (dd, J = 5.3, 16.6 Hz, 1 H), 2.07–1.08 (series of m, 13 H), 0.90 (s, 3 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.76 (d, J = 6.4 Hz, 3 H), 0.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.8, 107.8, 105.2, 64.82, 64.77, 47.6, 44.0, 43.3, 42.2, 34.3, 33.5, 33.2, 31.6, 26.8, 26.0, 21.4, 21.0, 19.6, 0.4; MS m/z ($M^+ - SiMe_3$) calcd 293.2116, obsd 293.2049.

To a cold (0 °C) solution of the silyl enol ether (1.34 g, 3.70 mmol) and propylene oxide (1.58 mL, 37.0 mmol) in THF (10 mL) was added *N*-bromosuccinimide (724 mg, 4.07 mmol). This mixture was stirred for 15 min before being quenched with saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The separated aqueous phase was extracted with ether (3 × 50 mL) and the combined organic layers were dried and evaporated to leave the α-bromo ketone, which was added to a mixture of dry Li_2CO_3 (820 mg, 11.10 mmol) and dry LiBr (800 mg, 9.25 mmol)

in dry DMF (20 mL) and heated at 110–120 °C for 30 min. The cooled reaction mixture was poured into saturated NH_4Cl solution (30 mL) and extracted with ether (4 × 50 mL). The combined organic layers were washed with brine, dried, and evaporated. Purification of the residue by MPLC on silica gel (elution with 30% ethyl acetate in petroleum ether) gave **9** (756 mg, 70%) as a colorless oil: IR (neat, cm^{-1}) 1710, 1650, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1 H), 4.92 (t, J = 4.6 Hz, 1 H), 3.95 (m, 2 H), 3.87 (m, 2 H), 2.53 (dd, J = 4.1, 17.5 Hz, 1 H), 2.42–2.35 (m, 2 H), 2.24 (dd, J = 13.5, 17.5 Hz, 1 H), 1.93–1.46 (m, 9 H), 1.03 (s, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.8, 173.9, 123.8, 103.7, 65.0, 48.3, 47.2, 45.9, 38.9, 33.6, 30.9, 29.7, 26.3, 23.7, 21.6, 19.6, 18.4; MS m/z ($M^+ - C_3H_5O_2$) calcd 219.1749, obsd 219.1789.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.99; H, 9.66.

(±)-(3*R,3a*R**,7*R**,7a*S**)-7-[2-(1,3-Dioxolan-2-yl)ethyl]-tetrahydro-3-isopropyl-7a-methyl-5(4*H*)-indanone (10).** A solution of **9** (717 mg, 2.45 mmol) in THF (10 mL) was treated with 2.5 mg of 5% palladium on charcoal and stirred overnight under 1 atm of hydrogen, filtered, and evaporated. The yield of **10** was quantitative: colorless oil; IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, J = 4.4 Hz, 1 H), 3.96 (m, 2 H), 3.83 (m, 2 H), 2.47–2.39 (m, 2 H), 2.14 (dd, J = 14.8, 15.1 Hz, 1 H), 2.04 (dd, J = 16.0, 14.1 Hz, 1 H), 2.00–1.40 (m, 10 H), 1.31–1.12 (m, 2 H), 0.89 (d, J = 5.6 Hz, 3 H), 0.88 (s, 3 H), 0.81 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.7, 104.5, 64.9, 64.8, 51.1, 46.8, 46.4, 44.8, 43.3, 42.2, 37.0, 31.9, 29.3, 26.2, 24.3, 21.8, 17.8, 12.6; MS m/z (M^+) calcd 294.2195, obsd 294.2177.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.29.

(±)-(5a*R,6*R**,8a*R**,8b*S**)-2,5,5a,6,7,8,8a,8b-Octahydro-6-isopropyl-8a-methyl-*as*-indacen-4(1*H*)-one (6).** A solution of **10** (2.17 g, 7.38 mmol) and 1 N HCl (4 mL) in THF (50 mL) was heated at reflux for 3 days, cooled, neutralized with saturated $NaHCO_3$ solution, and extracted with ether (3 × 100 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether). **6** was isolated (1.57 g, 88%) as a colorless oil: IR (neat, cm^{-1}) 1673, 1605; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, J = 5.5, 2.7 Hz, 1 H), 2.76 (m, 1 H), 2.54 (dd, J = 3.9, 18.0 Hz, 1 H), 2.48–2.30 (m, 2 H), 2.27–1.99 (m, 2 H), 1.98–1.18 (series of m, 8 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.2, 143.5, 141.0, 56.1, 50.1, 47.1, 44.2, 41.0, 37.2, 31.9, 30.0, 26.4, 25.4, 21.8, 18.4, 14.0; MS m/z (M^+) calcd 232.1827, obsd 232.1828.

(±)-(3*R,3a*R**,5a*S**,6*S**,8a*S**,8b*S**)-Decahydro-6-isopropyl-8a-methyl-3-vinyl-*as*-indacen-4(1*H*)-one (11).** To a cold (0 °C), magnetically stirred suspension of dry, purified copper(I) cyanide in dry THF (10 mL) was added methyllithium (2.18 mL of 1.5 M halide free in hexane, 3.28 mmol) followed by tri-*n*-butylvinyltin (1.04 g, 3.28 mmol).

This mixture was stirred at rt for 1.5 h, cooled to −78 °C, and treated with a solution of **6** (254 mg, 1.09 mmol) in THF (4 mL) via cannula. After 30 min of stirring at -78 °C, a 9:1 mixture of saturated NH_4Cl and NH_4OH solutions was introduced, the mixture was allowed to warm to rt, and the product was extracted into ether. The combined etheral extracts were dried and evaporated to leave a residue that was purified by silica gel chromatography. **11** was obtained (265 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, C_6D_6) δ 6.01 (ddd, J = 6.4, 10.3, 17.0 Hz, 1 H), 5.24 (dt, J = 1.7, 17.3 Hz, 1 H), 5.07 (dt, J = 1.6, 10.4 Hz, 1 H), 3.02 (m, 1 H), 2.20 (dd, J = 5.4, 18.1 Hz, 1 H), 2.12–0.84 (series of m, 14 H), 0.79 (d, J = 3.5 Hz, 3 H), 0.76 (d, J = 3.5 Hz, 3 H), 0.39 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.4, 142.5, 113.3, 55.5, 52.8, 49.1, 49.0, 44.4, 44.3, 42.6, 39.5, 32.4, 32.0, 27.6, 27.3, 21.6, 20.1, 15.8; MS m/z (M^+) calcd 260.2140, obsd 260.2142.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.01; H, 10.85. Found: C, 82.67; H, 11.07.

(±)-(3*R,3a*R**,6a*R**,7*S**,9a*R**,9b*S**)-1,2,3,3a,6a,7,8,9,9a,9b-Decahydro-7-isopropyl-5,9a-dimethyl-3-vinyl-4*H*-cyclopent[*e*]azulen-4-one (13).** A cold (−78 °C) solution of lithium diisopropylamide (3.27 mmol) in dry THF (5 mL) was introduced via cannula into an equally cold solution of **11** (170 mg, 0.65 mmol) and chlorotrimethylsilane (706 mg, 6.50 mmol) in dry THF (5 mL) under N_2. The reaction mixture was stirred for 30 min at −78 °C, quenched with dry triethylamine (3 mL) in petroleum ether (10 mL), and allowed to warm to rt. Following solvent evaporation, the residue was taken up in petroleum ether (100 mL), filtered to remove insolubles, and evaporated to leave the silyl enol ether in quantitative yield: ^1H NMR (300 MHz, C_6D_6) δ 6.00 (ddd, J = 17.5, 10.0, 7.2 Hz, 1 H), 5.08–4.95 (m, 3 H), 2.61 (ddd, J = 17.3, 10.2, 7.2 Hz, 1 H), 2.35 (tt, J =10.4, 2.3 Hz, 1 H), 1.9–1.0 (series of m, 12 H), 0.97 (d, J = 6.3 Hz, 3 H), 0.90 (d, J = 6.2 Hz, 3 H), 0.73 (s, 3 H), 0.23 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 154.8, 145.2, 111.9, 104.7, 52.4, 50.7, 50.4, 48.8, 46.9, 45.0, 37.5, 34.0, 33.8, 27.8, 25.9, 21.8, 20.7, 16.2, 0.4.

A cold (−40 °C) solution of the above silyl enol ether and 1,1-dichloroethane (2 mL) in dry ether (5 mL) was treated with *n*-butyllithium (1.5 mL of 1.4 M in hexane, 2.1 mmol) during 20 min. The reaction mixture was allowed to warm to 0 °C over 2 h, diluted with ether (10 mL), and evaporated. The residue was taken up in petroleum ether (20 mL) and the insolubles were removed by filtration through a plug of anhydrous $MgSO_4$. The filtrate was evaporated and the remaining oil was dissolved in an 8.5:1.5 mixture of methanol and triethylamine (10 mL) and refluxed for 2 h. After cooling, the solvent was removed and the residue was purified by chromatography on silica gel (elution with 2% ethyl acetate in petroleum ether) to give 110 mg (59%) of **13** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1660; ^1H NMR (300 MHz, C_6D_6) δ 5.96 (s, 1 H), 5.79 (ddd, J = 17.3, 10.0, 7.1 Hz, 1 H), 5.12 (dt, (J = 1.5, 17.1 Hz, 1 H), 4.94 (dt, J = 1.3, 10.2 Hz, 1H), 3.82 (m, 1 H), 2.68 (dd, J = 5.8, 11.2 Hz, 1 H), 2.18–2.14 (m, 1 H), 2.02–1.88 (m, 2 H), 1.95 (s, 3 H), 1.63–1.08 (series of m, 9 H), 0.87 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3 H), 0.53 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.2, 143.2, 139.9, 138.3, 113.1, 61.6, 57.1, 53.9, 49.7, 46.9, 42.8, 32.6, 30.4, 27.9, 24.1, 22.1, 20.5, 17.6, 17.4; MS m/z (M^+) calcd 286.2297, obsd 286.2279.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.85; H, 10.56. Found: C, 83.55; H, 10.65.

(±)-(3*R,3a*R**,6a*S**,7*R**,9a*S**,9b*R**)-2,3,3a,4,6a,7,8,9,9a,9b-Decahydro-7-isopropyl-5,9a-dimethyl-1*H*-cyclopent[*e*]azulen-3-yl Methyl Ketone (15).** A cold (−78 °C), magnetically stirred mixture of **13** (94 mg, 0.324 mmol) and cerium trichloride heptahydrate (121 mg, 0.324 mmol) in methanol (5 mL) was treated with sodium borohydride (12 mg, 0.324 mmol) and allowed to warm to −40 °C. After 2 h, acetone (1 mL) was introduced, the solvents were removed in vacuo, and the residue was purified by silica gel chromatography to provide the alcohol quantitatively: IR ($CHCl_3$, cm^{-1}) 3580, 1475, 1390, 1050, 1005; ^1H NMR (300 MHz, C_6D_6) δ 5.77 (ddd, J = 0.7, 9.8, 17.1 Hz, 1 H), 5.32 (dt, J = 3.7, 1.5 Hz, 1 H), 4.96 (dd, J = 1.4, 17.1 Hz, 1 H), 4.80 (dd, J = 1.9, 10.0 Hz, 2 H), 2.53 (dd, J = 9.8, 18.7 Hz, 1 H), 2.23–1.02 (series of m, 14 H), 1.87 (d, J = 0.8 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.73 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 146.5, 138.7, 128.8, 113.2, 74.1, 56.1, 54.6, 50.9, 50.5, 46.2, 45.1, 42.5, 32.9, 32.5, 28.6, 25.3, 21.8, 21.2, 19.7, 18.1; MS m/z (M^+) calcd 288.2453, obsd 288.2443.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.26; H, 11.19. Found: C, 82.79; H, 11.32.

To a solution of this allylic alcohol (204 mg, 0.71 mmol) in dry THF–TMEDA (4:1, 10 mL) was added *n*-butyllithium (1.17 mL of 1.4 M in hexane, 0.23 mmol). The mixture was stirred for 15 min at rt, cooled to 0 °C, and treated with *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (605 mg, 3.55 mmol). After 1 h of stirring at rt, saturated $NaHCO_3$ solution (4 mL) was introduced and agitation was maintained for an additional 2.5 h. The product was extracted into ether (4 × 20 mL) and the combined organic extracts were dried and evaporated. The residue was submitted directly to reduction.

A solution of the phosphordiamidic chloride from above and dry *tert*-butyl alcohol (210 mg, 2.85 mmol) in dry THF (4 mL) was added at −78 °C to a solution of lithium metal (49 mg, 7.1 mmol) in liquid NH_3 (50 mL, freshly distilled from Li). The reaction mixture was stirred at −45 °C for 2 h before being quenched with water. The ammonia was allowed to evaporate and the products were taken up in ether, washed with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 1% ethyl acetate in hexane) afforded 181 mg

(94%) of an inseparable 1.3:1 mixture of **14a** and **14b** (^{1}H NMR analysis). This material was submitted direclty to Wacker oxidation.

A mixture of the isomeric olefin mixture (52 mg, 0.19 mmol), palladium(II) chloride (13.6 mg, 0.076 mmol), copper(I) chloride (94.4 mg, 0.96 mmol), and DMF–water (10:1, 5 mL) was stirred under an atmosphere of oxygen for 3 days. After the addition of water (2 mL), the aqueous solution was extracted with ether (10 × 10 mL) and ethyl acetate (5 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried, and evaporated. The residue was filtered through a small column of silica and separated into its two components by HPLC (silica gel, elution with 1% ethyl acetate in hexanes) to give 20 mg (37%) of the diastereomer and 25 mg (46%) of **15**.

For the diastereomer: colorless oil; IR ($CHCl_3$, cm^{-1}) 1710, 1470, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, J = 1.4 Hz, 1 H), 3.06–3.01 (m, 1H), 2.69 (ddd, J = 7.4, 10.0, 1.0 Hz, 1 H), 2.25–1.18 (series of m, 14 H), 2.16 (s, 3 H), 1.63 (s, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.86 (s, 3 H), 0.81 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.4, 133.8, 124.9, 61.3, 55.3, 51.8, 48.9, 46.3, 43.9, 42.1, 37.8, 29.6, 29.5, 29.4, 28.7, 27.2, 24.0, 22.1, 17.4, 16.8; MS m/z (M^+) calcd 288.2453, obsd 288.2445.

For **15**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1710, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1 H), 2.62–2.45 (m, 2 H), 2.14 (s, 3 H), 2.26–1.18 (series of m, 14 H), 1.66 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.8, 133.8, 128.3, 58.9, 55.6, 50.2, 50.0, 46.3, 43.4, 42.5, 38.9, 30.6, 29.1, 28.9, 27.7, 26.3, 24.1, 22.0, 18.6, 18.1; MS m/z (M^+) calcd 288.2453, obsd 288.2450.

(±)-Methyl (6a*R,7*S**,9a*S**,9b*R**)-2,4,6a,7,8,9,9a,9b-Octahydro-7-isopropyl-5,9a-dimethyl-1*H*-cyclopent[*e*]azulen-3-yl Ketone (17).** A solution of **15** (15 mg, 0.052 mmol) and hexamethyldisilazane (25 mg, 0.156 mmol) in dry CH_2Cl_2 (2 mL) at −20 °C was treated with freshly distilled trimethylsilyl iodide (21 mg, 0.104 mmol) under N_2. After 1 h, 0.1 mL of hexamethyldisilizane and 5 mL of ether were added and the solvent was evaporated in vacuo. The residue was taken up in petroleum ether, filtered through a plug of anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography on Florisil (elution with petroleum ether) to give 18 mg (97%) of silyl enol ether isomers which were used directly.

To a solution of these silyl enol ethers (31 mg, 0.087 mmol) in anhydrous THF (2 mL) was added phenylselenenyl chloride (25 mg, 0.13 mmol) dissolved in THF (1 mL) through a cannula at 0 °C. After 30 min, the mixture was quenched with triethylamine (0.5 mL), petroleum ether (1.0 mL), and saturated NH_4Cl solution (1.0 mL) in one portion. The aqueous phase was extracted with ether and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with 2% ethyl acetate in petroleum ether) gave 36 mg (93%) of the α-(phenylseleno) ketone as a white solid: ^{1}H NMR (300 MHz, C_6D_6) δ 7.50 (m, 2 H), 6.97 (m, 3 H), 5.27 (s, 1 H), 3.11 (dd, J = 9.0, 15.7 Hz, 1 H), 2.63 (m, 1 H), 2.43–2.25 (m, 3 H), 2.22 (s, 3 H), 1.96–1.40 (series of m, 13 H), 1.53 (t, J = 1.0 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3 H), 0.80 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.6, 136.9, 134.1, 129.3, 129.2, 128.7, 127.8, 71.9, 52.8, 50.8, 50.4, 49.0, 46.8, 44.8, 33.7, 30.94, 30.92, 27.2, 26.5, 24.7, 22.3, 22.2, 19.3, 18.1; MS m/z (M^+) calcd 442.1775, obsd 442.1736.

To a cold (0 °C), magnetically stirred solution of the α-(phenylseleno) ketone (36 mg, 0.081 mmol) in THF (2 mL) was added 9.7 mg (0.122 mmol) of 30% hydrogen peroxide. The reaction mixture was stirred for 2 h, diluted with water, and extracted with ether. The combined organic layers were dried and evaporated, and the residue was subjected to silica gel chromatography (elution with petroleum ether) to give 16 mg (70%) of **16** and 6 mg (26%) of **17**.

For **17**: colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 5.19 (s, 1 H), 4.07 (d, J = 12.5 Hz, 1H), 2.78 (d, J = 12.4 Hz, 1 H), 2.37–1.17 (series of m, 12 H), 2.04 (d, J = 0.7 Hz, 3 H), 1.88 (s, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.60 (s, 3 H); ^{13}C NMR (C_6D_6) ppm 196.8, 151.2, 135.7, 134.5, 129.5, 66.0, 52.1, 50.6, 49.7, 40.2, 34.3, 34.1, 32.1, 30.2, 25.6, 25.2, 25.1, 22.0, 19.3, 15.1; MS m/z (M^+) calcd 286.2297, obsd 286.2302.

For **16**: colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 6.12 (t, J = 2.4 Hz, 1 H), 5.34 (s, 1 H), 3.52 (m, 1 H), 2.45–1.05 (series of m, 12 H), 1.98 (s, 3 H), 1.66 (s, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.8 (s, 3 H), 0.86 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (C_6D_6) ppm 194.4, 149.0, 143.3, 134.7, 127.3, 54.8, 50.6, 49.8, 46.4, 45.9, 44.0, 35.6, 32.6, 30.7, 26.6, 26.3, 24.5, 22.3, 19.6, 18.0; MS m/z (M^+) calcd 286.2297, obsd 286.2294.

Reduction of 16. To a solution of **16** (20 mg, 0.07 mmol) and chlorotrimethylsilane (23 mg, 0.21 mmol) in benzene (2 mL) was added triphenylphosphine–copper hydride hexamer dissolved in benzene (2 mL) via cannula. The reaction mixture was stirred for 1.5 h, diluted with pentane, and filtered through a plug of Celite. The filtrate was concentrated to leave a residue that was chromatographed on Florisil to give 6 mg (25%) of the silyl enol ether and 10 mg (50%) of **15**.

18-Oxo-3-virgene (1). To 50 mL of liquid NH_3 (dried by distillation from Li) was added metallic lithium (10 mg, 1.40 mmol) at −78 °C. After 30 min, a solution of **17** (15 mg, 0.035 mmol) in dry THF (1 mL) was introduced via cannula. The reaction mixture was stirred for 20 min at −78 °C before being treated with water. After the NH_3 had evaporated, the aqueous phase was extracted with ether and the combined organic phases were dried and evaporated. The residual oil was dissolved in CH_2Cl_2 (2 mL) and 56 mg (0.056 mmol) of pyridinium chlorochromate on alumina was added. This mixture was stirred for 4 h, filtered through a plug of Celite, and freed of solvent. Chromatography of the residue on silica gel afforded 12 mg (80%) of **1**, the spectral properties of which were identical to those reported earlier.

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Supplementary Material Available: Final computed atomic coordinates for **1**, **15**, **18**, and **19** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for information.