NMR: δ 138.78, 138.74, 134.79, 128.23, 127.73, 127.44, 127.38, 127.34, 116.97, 76.57, 75.30, 72.82, 70.64, 38.31, 38.15, 30.13, 18.09. IR (thin film): 3029.6, 2928.1, 2857.0, 1496.0, 1453.8, 1361.4, 1205.5, 1095.9, 1028.0, 995.2, 913.1, 734.9, 696.9 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.43; H, 8.70. Found: C, 81.54; H, 8.74.

(4*R,6*S**)-4,7-Bis(benzyloxy)-6-(1-methylethyl)-1-heptene (13b).** Isolated by flash chromatography in 86% yield as an 18.4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30 (m, 10 H), 5.80 (m, 1 H), 5.10 (d, J = 11 Hz, 1 H), 5.04 (d, J = 6 Hz, 1 H), 4.56 (d, J = 11.5 Hz, 1 H), 4.39 (d, J = 11.5 Hz, 1 H), 4.45 (d, J = 13 Hz, 1 H), 4.37 (d, J = 13 Hz, 1 H), 3.50 (m, 1 H), 3.33 (d, J = 5.5 Hz, 2 H), 2.35 (m, 2 H), 1.80 (m, 2 H), 1.60-1.30 (m, 2 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.90, 138.79, 134.93, 128.21, 127.69, 127.46, 127.34, 127.32, 116.92, 76.90, 72.87, 71.38, 70.78, 40.14, 38.73, 33.15, 28.85, 19.85, 18.94. IR (thin film): 2956.1, 2886.4, 2869.8, 1453.9, 1365.2, 1094.6, 1028.0, 994.0, 912.5, 734.2, 696.6 cm^{-1}. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.76; H, 9.15. Found: C, 81.77; H, 9.13.

(2R*,4S*)-2,5-Bis(benzyloxy)-4-methylpentanenitrile (13c). Isolated by flash chromatography in 90% yield as a 6:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (m, 10 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.44 (d, J = 11.4 Hz, 1 H), 4.42 (s, 2 H), 4.27 (dd, J = 5.8, 8.4 Hz, 1 H), 3.27 (dd, J = 2.6, 8.7 Hz, 1 H), 3.24 (dd, J = 2.6, 8.7 Hz, 1 H), 2.20-1.65 (m, 3 H), 0.95 (d, J = 6.7 Hz, 3 H). ^{13}C NMR: δ 138.23, 135.98, 128.49, 128.29, 128.26, 128.14, 127.51, 127.48, 118.48, 74.53, 72.85, 72.12, 66.32, 37.70, 29.74, 17.28. IR (thin film): 3031.2, 2959.1, 2930.0, 2869.4, 1496.3, 1454.4, 1396.2, 1363.7, 1331.8, 1254.2, 1207.8, 1094.0, 1027.8, 912.2, 738.3, 698.7, 610.9 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.73; H, 7.72.

(2R*,4R*)-2,5-Bis(benzyloxy)-4-phenylpentanenitrile (13d). Isolated by flash chromatography in 87% yield as a 4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25 (m, 15 H), 4.72 (d, J = 12 Hz, 1 H), 4.43 (m, 2 H), 4.37 (d, J = 12 Hz, 1 H), 4.03 (t, J = 8.1 Hz, 1 H), 3.55 (d, J = 8.1 Hz, 2 H), 2.42 (m, 1 H), 2.21 (m, 1 H), 2.18 (m, 1 H). ^{13}C NMR: δ 140.58, 137.92, 135.86, 128.63, 128.40, 128.26, 128.17, 127.98, 127.59, 127.52, 127.45, 127.07, 118.06, 73.83, 72.83, 72.08, 66.72, 41.68, 36.41. IR (thin film): 3059.8, 3027.0, 2863.1, 1494.9, 1451.1, 1396.3, 1363.5, 1333.3, 1204.6, 1092.4, 1026.6, 911.6, 741.8, 698.0 cm^{-1}. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.82; H, 6.78. Found: C, 80.60; H, 6.75.

(2R*,4R*)-2,5-Bis(benzyloxy)-4-(1-methylethyl)pentanenitrile (13e). Isolated by flash chromatography in 89% yield as a 9.5:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30 (m, 10 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.36 (d, J = 5.3 Hz, 2 H), 4.28 (dd, J = 2.5, 4.2 Hz, 1 H), 3.33 (d, J = 4.8 Hz, 2 H), 2.05-1.65 (m, 4 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H). ^{13}C NMR: δ 138.24, 136.11, 128.48, 128.32, 128.23, 128.16, 127.56, 127.54, 118.91, 72.97, 72.12, 71.12, 66.47, 39.81, 33.76, 29.14, 19.61, 19.17. IR (thin film): 3064.1, 3031.1, 2960.0, 1496.1, 1454.6, 1388.8, 1380.2, 1369.2, 1251.7, 1207.5, 1090.0, 1036.1, 1027.8, 738.2, 696.6 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07. Found: C, 78.25; H, 8.11.

(4R*,5R*)-4,7-Bis(benzyloxy)-5-methyl-1-heptene (20a). Isolated by flash chromatography in 81% yield as a 1:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31 (m, 10 H), 5.90 (m, 1 H), 5.07 (d, J = 16 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 4.50 (m, 4 H), 3.50 (m, 2 H), 3.29 (m, 1 H), 2.30 (m, 2 H), 1.90 (m, 2 H), 1.50 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.93, 138.57, 135.66, 128.26, 128.16, 127.60, 127.54, 127.39, 127.29, 116.50, 82.19, 72.68, 71.55, 68.47, 35.34, 32.57, 32.45, 14.41. IR (thin film): 3060.3, 3025.0, 2931.0, 2860.5, 1495.9, 1448.9, 1360.8, 1096.4, 908.3, 732.1, 696.8 cm^{-1}. HRMS Calcd for $C_{22}H_{29}O_2$ (M + 1): 325.2160. Found: 325.2171.

(4R*,5S*)-4,7-Bis(benzyloxy)-5-(1-methylethyl)-1-heptene (20b). Isolated by flash chromatography in 70% yield as an 4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29 (m, 10 H), 5.84 (m, 1 H), 5.06 (d, J = 13.8 Hz, 1 H), 5.02 (d, J = 8.3 Hz, 1 H), 4.46 (m, 4 H), 3.45 (m, 3 H), 2.31 (m, 2 H), 1.95-1.38 (m, 4 H), 0.88 (t, J = 6.5 Hz, 6 H). ^{13}C NMR: δ 138.97, 138.67, 136.02, 128.31, 128.21, 127.59, 127.43, 127.31, 116.43, 80.50, 72.72, 71.38, 70.15, 42.85, 35.35, 27.93, 26.72, 21.55, 19.43. IR (thin film): 2942.8, 2860.5, 1490.1, 1448.9, 1360.8, 1084.6, 908.3, 732.1, 696.8 cm^{-1}. HRMS Calcd for $C_{24}H_{33}O_2$ (M + 1): 353.2480. Found: 353.2473.

(2R*,3S*)-2,5-Bis(benzyloxy)-3-methylpentanenitrile (20c). Isolated by flash chromatography in 74% yield as a 3:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33 (m, 10 H), 4.82 (d, J = 11.7 Hz, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 4.43 (m, 2 H), 4.07 (d, J = 4.5 Hz, 1 H), 3.45 (t, J = 6.5 Hz, 2 H), 2.17 (m, 1 H), 1.89 (m, 1 H), 1.56 (m, 1 H), 1.06 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.27, 136.13, 128.67, 128.49, 128.43, 128.30, 128.23, 127.76, 117.87, 72.92, 72.31, 71.97, 67.39, 33.98, 31.81, 15.09. IR (thin film): 3022.2, 2922.2, 2855.6, 1455.6, 1361.1, 1205.6, 1094.4, 738.9, 694.4 cm^{-1}. HRMS Calcd for $C_{20}H_{23}NO_2$: C, 309.1729. Found: 309.1716.

(2R*,3R*)-2,5-Bis(benzyloxy)-3-(1-methylethyl)pentanenitrile (20d). Isolated by flash chromatography in 72% yield as a 12:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (m, 10 H), 4.80 (d, J = 11.6 Hz, 1 H), 4.42 (d, J = 11.6 Hz, 1 H), 4.44 (m, 2 H), 4.21 (d, J = 4.3 Hz, 1 H), 3.50 (m, 2 H), 2.10-1.70 (m, 4 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H). ^{13}C NMR: δ 138.35, 136.06, 128.54, 128.34, 128.27, 128.09, 127.59, 127.54, 118.16, 72.75, 72.14, 70.34, 68.60, 44.05, 28.66, 26.97, 20.49, 19.03. IR (thin film): 3048.5, 2954.5, 2860.5, 1496.0, 1454.8, 1366.7, 1208.0, 1084.6, 737.9, 696.8 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07. Found: C, 78.03; H, 8.31.

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Enantioselective Total Synthesis of (-)-Subergorgic Acid

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Abstract: A completely stereocontrolled total synthesis of (-)-subergorgic acid (**1**) has been accomplished. The starting β-hydroxy ketone was prepared in optically pure condition by lipase-promoted hydrolysis of the racemic chloroacetate. Following arrival at **5**, ring A was introduced by a reaction sequence that included a Mukaiyama-type aldol condensation and subsequent photochemical oxidation with (diacetoxyiodo)benzene and iodine. To permit proper functionalization within ring C, the carbonyl group in **16** was transformed into an internal double bond by Pd(II)-promoted reduction of the derived enol triflate with formate ion. Elaboration to **1** from **18** proceeded via a series of regio- and stereoselective reactions, several of which had to cope with the high steric compression levels associated with neopentyl sites. Notwithstanding, the progressive advance to more highly functionalized intermediates was accomplished with very reasonable efficiency.

In 1982, during the course of an investigation of the chemical constituents of gorgonians from the South China Sea, Wu, Yiao, and Long discovered subergorgic acid (**1**),[2] a substance that they came to regard as the near-perfect agent for chemical self-protection available to Pacific corals.[3] In actual fact, **1** is an unusually powerful cardiotoxic agent having the capacity for inhibiting neuromuscular transmission at levels below 0.20 μg/mL.[4] The

(1) National Science Foundation Postdoctoral Fellow, 1990-1992.

(2) Wu, Z.; Yiao, Z.; Long, K. *Zhongshan Daxue Xuebao, Ziran Kexueban* **1982**, 69; *Chem. Abstr.* **1983**, *98*, 68827d.

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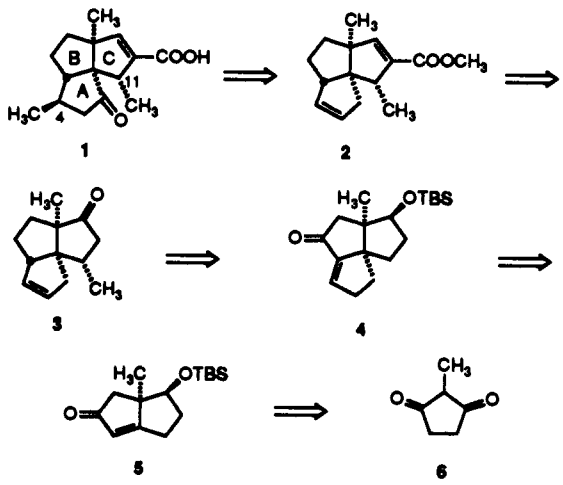
0002-7863/93/1515-49$04.00/0

Scheme I



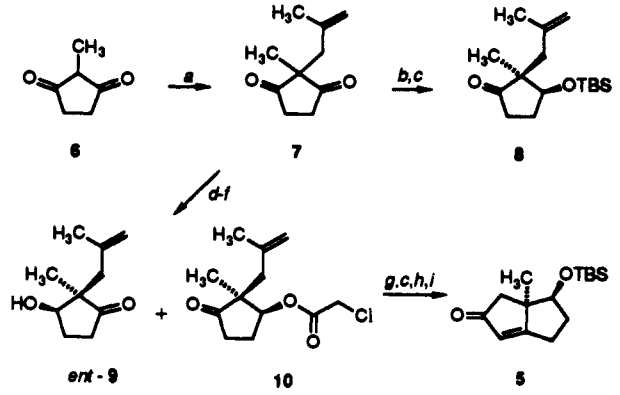
distinctive triquinane framework of **1**, initially based on spectroscopic data,[2] was subsequently confirmed by X-ray crystallographic analysis.[3,5] Anomalous scattering techniques ultimately allowed for the absolute configuration of subergorgic acid to be proposed.[3] In light of the peculiar circumstances surrounding these measurements, however,[6] confirmation of this assignment by enantiomerically defined total synthesis was considered desirable.

Two racemic syntheses of **1** have been reported to date. The first of these, due to Iwata and co-workers,[7] was based on intramolecular alkylation within a functionalized spiro[4,5]dec-6-en-8-one and subsequent construction of ring C via aldol condensation of a dialdehyde produced by ozonolysis of a cyclohexene double bond. The more expeditious Wender approach featured an arene–olefin cycloaddition in tandem with a free radical addition step involving a vinylcyclopropane.[8]

Our interest in subergorgic acid stemmed not only from the considerations given above but also from the close structural similarity of **1** to a number of silphiperfolene sesquiterpenes found in the roots of several *Silphium* species and identified by Bohlmann and Jakupovic as early as 1980.[9] Our group has previously been involved in developing a de novo synthesis of these unsual natural products.[10]

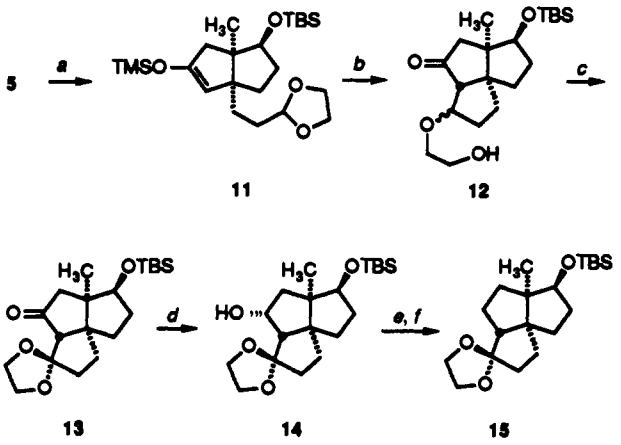
The retrosynthetic strategy contemplated for the present enantiospecific approach to **1** is shown in Scheme I. Brooks et al. had previously demonstrated that enone **5** could be obtained almost optically pure (>98% ee) from 2-methyl-1,3-cyclopentanedione.[11] Michael addition to **5** followed by a simple aldol condensation was expected to establish the tricyclo[6.3.0.0^{1,5}]undecenone **4**. Reductive removal of the ketone functionality in ring B followed by alcohol deprotection, oxidation, and introduction of the secondary methyl group would make **3** available. Modest functional group manipulation within the C ring would lead to **2**. This intermediate was considered to be a suitable precursor to **1** since its concave–convex topography should lend itself particularly well to oxidation of, and highly stereoselective methyl incorporation into, ring A.

Scheme II



[a] CH_2=$C(CH_3)CH_2Br$, 1 N NaOH. [b] Bakers' yeast. [c] TBSCl, imid, DMAP, DMF, 60 °C. [d] $NaBH_4$, EtOH. [e] $ClCH_2COCl$, py, DMAP. [f] Lipase P-30. [g] K_2CO_3, MeOH, THF. [h] O_3, CH_2Cl_2, py; Zn, HOAc. [i] KOt-Bu, t-BuOH, room temperature.

Scheme III



[a]  $-CH_2CH_2MgBr$, $CuBr{\cdot}SMe_2$, TMSCl, DMAP. [b] $TiCl_4$, CH_2Cl_2. [c] $PhI(OAc)_2$, I_2, hv, C_6H_6, Δ. [d] $LiAlH_4$. [e] CH_3SO_2Cl, DMAP, py. [f] $LiEt_3BH$, THF, Δ.

Results and Discussion

Formation of the Tricyclo[6.3.0.0^{1,5}]undecane Core. The prohibitive cost of commercial **6** caused us to examine the various published methods for its preparation.[12] Of these, the remarkable one-step procedure reported by Schick, Lehmann, and Hilgetag[12c] was notably short and provided for the ready acquisition of large amounts of diketone from inexpensive starting materials.[13]

In the Brooks protocol,[11] the C-methallylated derivative **7** was subjected to reduction with baker's yeast and O-silylated to produce **8**. Although asymmetric reduction of **7** in this manner does furnish **8** in high optical purity (98% ee), the processing of yeast cells on a large scale proved to be cumbersome, labor intensive, and inefficient. The isolated yields of β-keto alcohol never exceeded 20–30%. For these reasons, a more workable alternative means for realizing access to **8** was sought (Scheme II).

This goal was attained by reducing **7** with 1 equiv of sodium borohydride in methanol. Prevailing steric factors guide the entry of the nucleophile syn to methyl such that the major product (89% isolated) features the desired cis relationship between the iso-

(4) See footnote 10 of ref 5 where a guinea pig heart assay was employed. The LD_{50} of **1** in mice is 23 mg/kg.[3]

(5) Groweiss, A.; Fenical, W.; He, C.-L.; Clardy, J.; Wu, Z.; Yiao, Z.; Long, K. *Tetrahedron Lett.* **1985**, *26*, 2379.

(6) Wu and his collaborators in Canton satisfactorily accomplished the correct determination of relative and absolute stereochemistry for **1**, but misrepresented the configuration of C-11 in their two-dimensional drawing of the molecule.[3] Incorrect stereochemical features reported in ref 2 were noted by Groweiss et al.,[5] who correctly determined the relative stereochemistry of **1**.

(7) Iwata, C.; Takemoto, Y.; Doi, M.; Imanishi, T. *J. Org. Chem.* **1988**, *53*, 1623.

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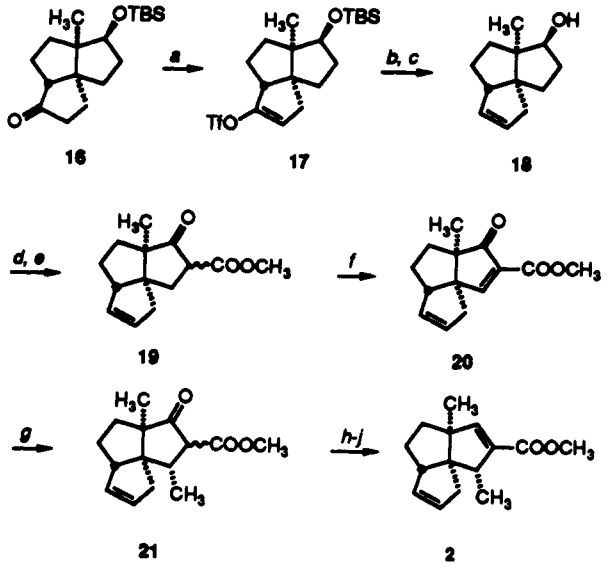
Scheme IV



[a] $KN(SiMe_3)_2$, TMEDA, THF; Tf_2NPh. [b] HCOOH, $(n\text{-}Bu)_3N$, $Pd(OAc)_2(PPh_3)_2$, DMF. [c] HF, CH_3CN, H_2O. [d] PCC, Al_2O_3, CH_2Cl_2. [e] LDA, HMPA, ether; $CH_3OC(O)CN$. [f] DDQ, SiO_2, C_6H_6, room temperature. [g] $(CH_3)_2CuLi$, DMAP, Me_3SiCl, THF. [h] $NaBH_4$, MeOH, 0 °C. [i] CH_3SO_2Cl, DMAP, py. [j] Al_2O_3 (basic), ether.

butenyl and hydroxyl groups. Conversion to the racemic chloroacetate was followed by controlled enzymatic hydrolysis with lipase P-30.[14] When this process was allowed to proceed in modest excess of 50% completion, optically pure *ent*-**9**, $[\alpha]^{23}_D$ −104°, was made available efficiently (50%). Furthermore, saponification of the recovered dextrorotatory acetate **10** (45%) afforded **9**, $[\alpha]^{23}_D$ +103°, the enantiomeric purity of which was also 100%. Thus, this simply executed alternative gives evidence of representing the avenue of choice for procuring *both* enantiomers of **9** readily.

With a secure supply of (+)-**9** in hand, its conversion to **5** was accomplished as before, except for the ozonolytic cleavage.[11] This enone proved highly receptive to conjugate addition reactions involving cuprate reagents.[15] Of these, the Grignard of 2-(2-bromoethyl)-1,3-dioxolane[16] and a copper bromide–dimethyl sulfide complex proved ideally suited to ultimate A-ring construction. When brought together in the presence of Me_3SiCl and DMAP, smooth conversion to silyl enol ether **11** (90%) was realized (Scheme III). Direct exposure of this intermediate to titanium tetrachloride in CH_2Cl_2 solution[17] promoted cyclization to **12** as a 1:1 mixture of diastereomers (70%). In order to obviate the need for chromatographic separation and, of more long-range importance, to return C-4 to the protected carbonyl level, γ-hydroxy ether **12** was irradiated with (diacetoxyiodo)benzene and iodine in benzene solution.[18] Intramolecular hydrogen abstraction by alkoxy radicals generated in situ by this means gave keto ketal **13** in 75% yield along with variable small amounts of the corresponding dione. The latter minor product is an artifact of this reaction, resulting instead from partial hydrolysis during workup because of the heightened susceptibility of **13** to attack by moisture.

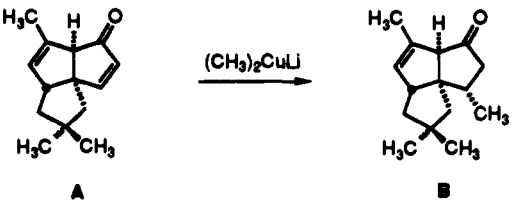
Subsequent hydride reduction and mesylation of **14** followed by exposure to lithium triethylborohydride conveniently provided **15** as long as the latter reaction was performed in the temperature range of 45–55 °C. Higher temperatures promoted rapid elimination of the mesylate functionality, while reduction proceeded too slowly (often not at all) below 45 °C.

Setting the C-Ring Substitution Pattern. Next, we focused our attention on the conversion of **15** to the α,β-unsaturated keto ester **20** (Scheme IV). The conversion of ketones to enol triflates is well-known,[19] and **15** was therefore sequentially hydrolyzed to give **16** and treated with potassium hexamethyldisilazide in combination with *N*-phenyltriflimide and TMEDA as solutes in THF. The deprotonation was expectedly regiospecific to afford **17** as the only regioisomer. Reduction of **17** to the corresponding alkene was readily accomplished upon its exposure to formic acid and tri-*n*-butylamine in the presence of a catalytic quantity of $Pd(OAc)_2(PPh_3)_2$.[20] Immediate deprotection of the hydroxyl group provided tricyclic alcohol **18** in 84% overall yield from **16**.

The hydroxyl group in **18** suffers from steric congestion, a state of affairs reflected in the difficulties experienced during oxidation studies. The Swern reagent[21] proved insufficiently reactive, and only slow decomposition was seen under typical Jones conditions.[22] With pyridinium chlorochromate on supports such as Celite or molecular sieves,[23] the desired ketone was obtained in yields well below 50%. With the substitution of PCC embedded on alumina,[24] a reproducible efficiency of 90% was consistently observed.

α-Carbomethoxylation of this intermediate with methyl cyanoformate according to Mander[25] produced **19** and set the stage for DDQ oxidation to **20**. Conventional wisdom dictates that such reactions be carried out in refluxing benzene.[26] However, **19** was very slowly oxidized under these conditions, produced a considerable number of byproducts after 2 days, and afforded **20** in an unacceptably low yield. By making the critical modification of adding silica gel to the reaction mixture, the oxidation could be performed at room temperature and was met with a substantial increase in yield (67%).

Our projected continuation of the synthesis required conjugate addition of a methyl group in the manner indicated by the progression **20** → **21**. The steric shielding flanking both faces of this double bond is rather closely balanced, thereby lowering one's confidence in predicting the possibly preferred π-facial selection during nucleophilic attack. The closest available analogy is the conversion to **A** to **B** reported by Paquette and Annis in their successful quest of pentalenene.[27] In this instance, the addition



(14) See, for example: (a) Schwartz, A.; Maden, P.; Whitesell, J. K.; Lawrence, J. P. *Org. Synth.* **1990**, *69*, 1. (b) Maleczka, R. E., Jr.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 6538.

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of lithium dimethylcuprate to **A** gave **B** by exclusive attack on the α-face.

To reduce the desired construct to practice, **20** was treated with lithium dimethylcuprate in the presence of both Me_3SiCl and DMAP.[28] The latter two reagents were required for the methyl addition to proceed in optimal yield. Satisfyingly, **21** was obtained as the only identifiable product (74%). Like **19**, **21** exists as a mixture of keto and enol tautomers. It therefore proved difficult to establish the configuration of the newly introduced stereogenic center at this stage. Conclusive proof that the methyl group had entered exclusively from the desired α-face was subsequently derived from NOE experiments performed on **22**.

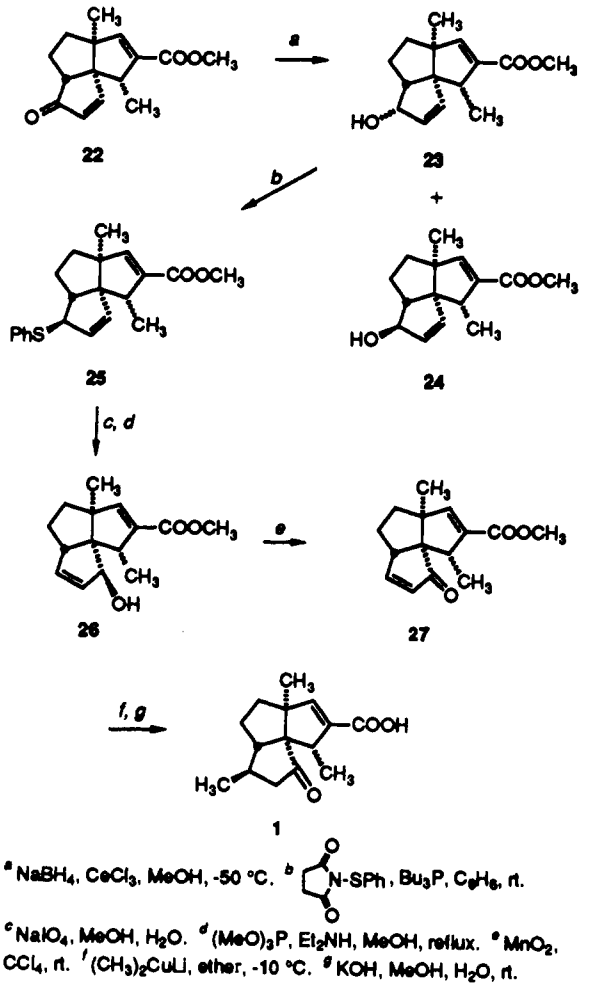
The ketone carbonyl group in **21** was chemoselectively reduced with sodium borohydride. Generated by this means was a 12:1 mixture of β-hydroxy esters, with the major isomer resulting from convex attack. The production of a pair of isomers was of no concern since the hydroxy-bearing carbon was destined to become sp^2-hybridized. In an effort to gain a better appreciation of the pending elimination, these epimers were separated and individually converted into their mesylates. These activated systems were sufficiently stable to be purified by means of silica gel chromatography. They also proved unresponsive to bases such as DBU and LDA. We attribute this inertness to the inability of such relatively bulky bases to abstract an α-carbomethoxy proton that finds itself in a highly congested environment. This problem was nicely circumvented, however, by making recourse to activated alumina[29] and taking advantage of the kinetic acceleration customarily associated with substrate absorption. By this means, **2** could be routinely obtained in 87% yield.

Completion of the Synthesis. With the acquisition of **2**, the B and C rings of subergorgic acid were fully elaborated. In considering how to finalize matters in ring A, we favored a sequence that would culminate in 1,4-addition of the methyl group to **27**. Introduction of the final carbon at this penultimate stage would benefit from superb stereochemical control in the proper direction.[30]

In light of the structural features of **2**, it appeared certain that allylic oxidizing agents would be forced to engage its unconjugated double bond in an ene-like process in order to skirt severe steric compression. We did not anticipate, however, that reagent systems such as the CrO_3–3,5-dimethylpyrazole complex,[10,31] sodium chromate,[32] and selenium dioxide[33] would primarily promote its decomposition. An exception to this trend was uncovered with PDC and *tert*-butyl hydroperoxide,[34] which operated on **2** to give **22** in quite useful amounts (69% based on unreacted **2**). Clearly, ring A does not succumb readily to attack by the more conventional oxidizing agents.

Luche reduction[35] of **22** made available an 85:15 mixture of alcohols **23** and **24** (Scheme V). Predominant exo attack of hydride, as expected on steric grounds, is compatible with the vicinal coupling constants observed for the individual carbinol protons (J = 8 Hz for **23** and J = 3 Hz for **24**). Further confirmation of these stereochemical assignments was achieved by appropriate NOE experiments. The major stereoisomer **23** (79% isolated) was converted into the transposed enone **27** in a four-step sequence commencing with an S_N2 displacement induced by

Scheme V



N-(phenylthio)succinimide and tri-*n*-butylphosphine.[36] Although the resulting sulfide **25** (79%) underwent essentially quantitative oxidation to a 1:1 mixture of sulfoxide stereoisomers, both underwent totaly stereoselective Evans–Mislow rearrangement[37] to **26** (91%) when heated with trimethyl phosphite and diethylamine in methanol. No departure from syn-facial operation of the intramolecular [2,3] sigmatropic shift could be found. Oxidation of **26** with manganese dioxide in CCl_4[38] delivered **27** in 96% yield.

Assignment of stereochemistry to the intermediates follows from chemical evidence, the small vicinal coupling constants observed for C*H*X (X = SPh, SOPh) in **25** and its sulfoxides, and the diagnostic NOE enhancements observed for **26**.

The addition of lithium dimethylcuprate to **27** produced a stereoisomerically pure ester (88%), the saponification of which afforded (–)-subergorgic acid (**1**). The synthetic material exhibits a melting point of 174–175 °C, is characterized by an optical rotation of $[\alpha]^{19}_D$ –143.5° (c 0.64, $CHCl_3$), and is identical by ^1H and ^{13}C NMR comparison to the substance isolated from *Subergorgia suberosa*.[39] The natural material showed $[\alpha]^{20}_D$ –147.2° (c 0.85, $CHCl_3$) and mp 174–175 °C, undepressed upon admixture with an independently prepared sample. For comparison, the original communication[2] defined (–)-**1** as exhibiting mp 200–202 °C and $[\alpha]_D$ –139°. It is possible that a crystalline polymorph had been obtained by these workers. The Scripps group listed the melting point as 179–180 °C and the optical rotation as $[\alpha]_D$ –23°. We have since come to learn that the latter figure

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is erroneous due to a miscalculation made in the course of the measurement.[40]

Summary. (-)-Subergorgic acid (**1**) has been elaborated in high optical purity from (2*R*,3*S*)-3-hydroxy-2-methyl-2-(2-methyl-2-propenyl)cyclopentanone. Since the stereochemistry at C-2 of this building block is not jeopardized during the course of the total synthesis, the absolute configuration of **1** can be considered to be unequivocally confirmed by experiment. Following a most efficient lipase-catalyzed hydrolysis to obtain this β-hydroxy ketone in 100% ee condition, the target triquinane was assembled by sequential five-ring annulation. The synthesis features tandem application of a Mukaiyama aldol cyclization and (diacetoxyiodo)benzene-promoted oxidation to generate a pivotal β-keto ketal intermediate. Also of note is the implementation of a reductive carbonyl olefination scheme mediated by Pd-catalyzed reduction of an enol triflate. Furthermore, the global scheme demonstrates the relative ease with which neopentyl centers may be chemically modified to provide more highly functionalized advanced intermediates.

Experimental Section

Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter; concentrations are given in grams/100 mL. Infrared spectra were recorded with a Perkin-Elmer 1320 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker WP 300 and AC 300 FT spectrometers. Exact mass measurements were made with a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were undertaken at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(2α,3α)-3-Hydroxy-2-methyl-2-(2-methyl-2-propen-1-yl)-1-cyclopentanone. To a solution of 100 g (0.60 mol) of **7**[13] in 1 L of absolute ethanol at 0 °C was added $NaBH_4$ (5.7 g, 0.15 mol). After 20 min of stirring at 0 °C, 10% HCl was added until the solution tested slightly acidic with pH paper. This solution was then neutralized with saturated $NaHCO_3$ solution, and the ethanol was removed by rotary evaporation. The residue was taken up in water (300 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried, the solvent was removed in vacuo, and the crude product was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 90 g (89%) of the keto alcohol as a clear colorless oil: IR (neat, cm^{-1}) 3500, 3070, 2980, 1735; ^{1}H NMR (300 MHz, C_6D_6) δ 4.82 (s, 1 H), 4.78 (s, 1 H), 3.61 (s, 1 H), 2.51 (d, *J* = 14.6 Hz, 1 H), 2.38 (d, *J* = 14.6 Hz, 1 H), 2.30–1.80 (m, 2 H), 1.66 (s, 3 H), 1.60–1.20 (m, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 220.7, 143.0, 114.4, 77.4, 53.5, 38.1, 33.4, 27.9, 24.2, 19.9.

(1α,2α)-2-Methyl-2-(2-methylallyl)-3-oxocyclopentyl Chloroacetate. To a cold (0 °C) solution of 1.9 g (11.3 mmol) of the preceding keto alcohol and 1.4 mL (17 mmol) of pyridine in THF (20 mL) was added 2.0 mL (13.6 mmol) of chloroacetyl chloride. After 30 min the mixture was allowed to warm room temperature over 4 h and poured into a separatory funnel containing ether (300 mL) and water (50 mL). The organic phase was washed with 10% HCl (50 mL), water (50 mL), saturated $NaHCO_3$ solution (50 mL), and brine (25 mL) prior to drying. Purification of the residue by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 2.67 g (97%) of pure ester: IR (neat, cm^{-1}) 3070, 2980, 1785, 1740, 1640, 1455, 1410, 1270, 1175, 1065, 905, 800; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (t, *J* = 3.2 Hz, 1 H), 4.77 (s, 1 H), 4.68 (s, 1 H), 3.30 (s, 2 H), 2.42 (AB q, *J* = 14 Hz, 2 H), 2.10–1.40 (m, 4 H), 1.51 (s, 3 H), 0.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 216.1, 165.8, 141.7, 115.3, 81.0, 51.8, 40.5, 38.1, 32.8, 25.4, 23.9, 19.5; MS *m*/*z* (M$^+$) calcd 244.0867, obsd 244.0859. Anal. Calcd for $C_{12}H_{17}O_3Cl$: C, 58.90; H, 7.00. Found: C, 59.25; H, 7.15.

Lipase Hydrolysis of the Chloroacetate. A rapidly stirred mixture of the racemic chloroacetate (1.68 g, 6.89 mmol), pH 7.0 buffer (100 mL), and lipase P-30 (Amano) (0.3 g) was treated with 0.5 N NaOH (8.26 mmol, 0.6 equiv) at a rate such as to maintain a pH range of 7.2–7.3 over a 20-h period. The reaction mixture was diluted with ether (500 mL), filtered, and concentrated to leave an oil that was purified on silica gel. Isolated were 575 mg (50%) of *ent*-**9**, $[\alpha]^{23}_D$ −104° (*c* 1.22, $CHCl_3$) and 756 mg (45%) of **10**, $[\alpha]^{23}_D$ +130° (*c* 1.62, $CHCl_3$).

Hydrolysis of 10. Optically Pure (2*S*,3*R*)-3-Hydroxy-2-methyl-2-(2-methyl-2-propen-1-yl)-1-cyclopentanone. A mixture of the preceding ester (3.77 g, 15.4 mmol), K_2CO_3 (539 mg, 3.9 mmol), THF (75 mL), and methanol (75 mL) was stirred at 0 °C for 0.5 h and then partitioned between ether (600 mL) and water (100 mL). The separated organic phase was washed with brine (25 mL), dried, filtered, and concentrated. The residue was purified by silica gel chromatography to give 2.4 g (93%) of pure keto alcohol, $[\alpha]^{23}_D$ +103° (c 1.85, $CHCl_3$) [lit.[11] $[\alpha]_D$ +99.0° (*c* 7.6, $CHCl_3$)].

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-2-(2-methyl-2-propen-1-yl)cyclopentanone.[11] To a solution of 90 g (0.54 mol) of the (+)-ketol in 1 L of DMF were added 98.8 g (1.45 mol) of imidazole, 1.07 g (8.8 mmol) of 4-(dimethylamino)pyridine, and 133 g (0.88 mol) of *tert*-butyldimethylsilyl chloride. After being heated at 60 °C for 16 h, the reaction mixture was allowed to cool to room temperature, poured into 1.5 L of CH_2Cl_2, washed with water (3 × 500 mL) and brine (2 × 250 mL), and then dried. The solvent was removed by rotary evaporation, and the resulting oil was purified either by column chromatography (silica gel, 10% ethyl acetate in petroleum ether) or by vacuum distillation (120 °C at 0.1 mmHg) to give 134 g (88%) of oily O-silylated product: IR (neat, cm^{-1}) 3030, 2960, 2860, 1750, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 1 H), 4.70 (s, 1 H), 4.06 (t, *J* = 5.6 Hz, 1 H), 2.50–1.85 (m, 6 H), 1.72 (s, 3 H), 0.97 (s, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H).

(2*S*,3*S*)-2-Acetyl-3-(*tert*-butyldimethylsiloxy)-2-methylcyclopentanone. The above product (218 g, 0.77 mol) was dissolved in 3 L of CH_2Cl_2 and 350 mL of pyridine and then cooled to −78 °C. Ozone was introduced to the solution via a fritted glass tube over on 11-h period (the progress of reaction was monitored by thin-layer chromatography; 10% ethyl acetate in petroleum ether as eluent). Zinc dust (106 g, 1.62 mol) and acetic acid (350 mL) were added to the orange solution, and the resulting slurry was stirred at −78 °C for 1 h, slowly warmed to 0 °C over a 1-h period (*Caution*: *an exotherm occurs at −10 °C*), and stirred at 0 °C for 30 min. The remaining zinc was removed by suction filtration through a Celite pad, and the resulting green solution was washed with water (4 × 1 L) and saturated $NaHCO_3$ solution (3 × 1 L) prior to drying. Solvent removal by rotary evaporation and purification of the residue by distillation (120 °C, 0.2 mmHg) gave 188 g (86%) of the dione as a colorless oil: $[\alpha]^{23}_D$ +65° (*c* 2.0, $CHCl_3$); IR (neat, cm^{-1}) 2960, 2930, 1740, 1715, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (t, *J* = 3.5 Hz, 1 H), 2.70 (AB m, 2 H), 2.60–2.10 (m, 3 H), 2.09 (s, 3 H), 1.90 (m, 1 H), 1.04 (s, 3 H), 0.83 (s, 9 H), 0.07 (s, 3 H), −0.01 (s, 3 H).

(6*S*,6a*R*)-6-(*tert*-Butyldimethylsiloxy)-4,5,6,6a-tetrahydro-6a-methyl-2(1*H*)-pentalenone (5). To a solution of the above dione (188 g, 0.66 mol) in *tert*-butyl alcohol (3 L, distilled over calcium hydride) was added potassium *tert*-butoxide (74.6 g, 0.66 mol). After 35 min, the reaction mixture was quenched by the addition of 10% HCl until slightly acidic to pH paper. Saturated $NaHCO_3$ solution was added to achieve neutralization, and the *tert*-butyl alcohol was removed by rotary evaporation. Water (250 mL) was added to the residue, which was then extracted with petroleum ether (3 × 1 L), dried, and concentrated. Vacuum distillation of the crude product (120 °C, 0.1 mmHg) gave 130 g (74%) of **5** as a pale orange oil: $[\alpha]^{23}_D$ +136° (*c* 2.0, $CHCl_3$); IR (neat, cm^{-1}) 3070, 2960, 2930, 2850, 1705, 1630, 1255, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1 H), 3.92 (d, *J* = 4.2 Hz, 1 H), 2.70 (m, 3 H), 2.45 (m, 1 H), 2.04 (d, *J* = 17 Hz, 1 H), 1.87 (m, 1 H), 1.11 (s, 3 H), 0.83 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); MS *m*/*z* (M$^+$ − C_4H_9) calcd 209.0997, obsd 209.1023.

(3a*R*,5a*R*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)octahydro-3-(2-hydroxyethoxy)-5a-methylcyclopenta[*c*]pentalen-4(5*H*)-one (12). THF (300 mL) and one crystal of iodine were added to 3.62 g (0.15 mol) of flame-dried magnesium turnings. A solution of 27.2 g (0.15 mol) of 2-(2-bromoethyl)-1,3-dioxolane[16] in 15 mL of THF was placed in an addition funnel, and half of the solution was added to the magnesium turnings. The THF solution quickly warmed to the reflux temperature, and the remainder of the alkyl halide was added at a rate such as to maintain the solvent at reflux. After complete addition of the 2-(2-bromoethyl)-1,3-dioxolane (approximately 45 min), the reaction mixture was stirred for 1 h and then cooled to 0 °C.

To 30 mL of cold (−78 °C) THF were added 14.6 g (71 mmol) of copper bromide–dimethyl sulfide complex and 8.8 g (72 mmol) of DMAP. The slurry was stirred for 10 min, at which point the Grignard solution from above was introduced over a 30-min period via cannula. The reaction mixture was stirred at −78 °C for 1.5 h and treated over 15 min with a cold (−78 °C) solution of 10.0 g (38 mmol) of enone **5** and 10 mL (79 mmol) of trimethylsilyl chloride in 15 mL of THF. The cuprate solution was stirred for 15 min beofre it was quenched with 100 mL of saturated NH_4Cl solution. Petroleum ether (100 mL) was added to the two-phase system, and the solvent was decanted from the solid inorganic salts. The solids were slurried with petroleum ether (2 × 100 mL), which was once again decanted. The combined petroleum ether solutions were washed sequentially with saturated NH_4Cl (2 × 50 mL) and $NaHCO_3$ solutions (3 × 50 mL), dried, and evaporated without heating. Silyl enol ether **11** was partially purified by rapidly forcing it through a column of 30 g of TLC grade silica with 20% ethyl acetate in

(40) Fenical, W. Private communication.

petroleum ether as eluent. The 14 g of unstable product so obtained was routinely used immediately, but could be stored for 1 or 2 days at −10 °C: ^{1}H NMR (300 MHz, C_6D_6) δ 4.86 (t, J = 4.7 Hz, 1 H), 4.56 (s, 1 H), 3.60–3.30 (m, 5 H), 3.17 (d, J = 17 Hz, 1 H), 1.95 (d, J = 17 Hz, 1 H), 1.90–1.30 (m, 8 H), 1.05 (s, 3 H), 0.96 (s, 9 H), 0.17 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

A solution of titanium tetrachloride (70 mL of a 1.0 M solution of CH_2Cl_2, 70 mmol) in 600 mL of CH_2Cl_2 was cooled to −78 °C in a Morton flask. A cold (−78 °C) solution of **11** as obtained above in 200 mL of CH_2Cl_2 was added to the vigorously stirred $TiCl_4$ solution over a 1.5-h period, stirred for 15 min, and treated with 100 mL of saturated $NaHCO_3$ solution. The resulting slurry was poured into a separatory funnel containing 100 mL of CH_2Cl_2, and the aqueous phase was discarded. The organic layer was washed with saturated $NaHCO_3$ solution (3 × 50 mL), dried, and evaporated to leave a residue that was purified by chromatography (silica gel, elution with 1.5% methanol in chloroform). There was obtained 9 g (63% for the two steps) of **12** as an inseparable 1:1 mixture of stereoisomers: IR (neat, cm^{-1}) 3430, 2940, 2920, 2850, 1725, 1250, 1115, 1055, 835, 770; MS m/z ($M^+ - C_4H_9$) calcd 311.1679, obsd 311.1688. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.84. Found: C, 64.75; H, 9.81.

(3a*S*,5a*R*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)hexahydro-5a-methylspiro[cyclopenta[*c*]pentalene-3(3a*H*),2′-[1,3]dioxolan]-4(5*H*)-one (13). To a solution of **12** (0.51 g, 1.4 mmol) in 50 mL of benzene were added (diacetoxyiodo)benzene (0.67 g, 2.1 mmol) and iodine (0.34 g, 1.3 mmol). The violet solution was irradiated for 5 min with a 275-W tungsten lamp, washed with saturated sodium thiosulfate solution (2 × 25 mL) and brine (2 × 25 mL), and then dried and evaporated (*Caution: ketal 13 decomposes if heated*). Purification by chromatography (silica gel, elution with 10% ethyl acetate in petroleum ether) gave 0.38 g (75%) of **13** as a waxy solid: IR (neat, cm^{-1}) 2950, 2920, 2880, 2850, 1735, 1250, 1070, 830, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 1 H), 3.95 (m, 2 H), 3.81 (m, 2 H), 2.60–2.30 (m, 2 H), 2.30–1.40 (m, 9 H), 1.04 (s, 3 H), 0.84 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 213.5, 117.4, 83.0, 71.0, 65.0, 64.9, 58.6, 51.0, 48.4, 38.6, 38.1, 33.7, 33.5, 15.8, 21.1, 18.0, −4.7, −5.0; MS m/z ($M^+ - C_4H_9$) calcd 309.1522, obsd 309.1544.

***tert*-Butyldimethyl[[(3a*R*,5a*R*,6*S*,8a*R*)-octahydro-5a-methylspiro-[cyclopenta[*c*]pentalene-3(3a*H*),2′-[1,3]dioxolan]-6-yl]oxy]silane (15).** To a solution of **13** (12.4 g, 34 mmol) in 750 mL of THF at 0 °C was added 1.5 g (40 mmol) of $LiAlH_4$. The reaction mixture was stirred for 2 h and then quenched by sequential addition of 1.5 mL of 15% NaOH solution and 4.5 mL of water. The mixture was warmed to room temperature and filtered through a pad of Celite. The solids were washed with CH_2Cl_2 (3 × 100 mL), and the filtrates were added to the THF solution. The combined organic phases were dried and concentrated by rotary evaporation to give 11.2 g (90%) of impure alcohol **14**.

To a solution of **14** from above in 250 mL of pyridine were added DMAP (0.19 g, 1.6 mmol) and methanesulfonyl chloride (6.2 mL, 80 mmol). The reaction mixture was stirred for 18 h, poured into 1.0 L of ether, and washed sequentially with water (3 × 300 mL), 10% HCl (2 × 200 mL), saturated $NaHCO_3$ solution (2 × 250 mL), and brine (250 mL). Filtration and removal of solvent gave 14 g (90%) of the derived mesylate.

The mesylate from above was dissolved in 400 mL of THF at 45 °C and treated with $LiEt_3BH$ (100 mL of a 1.0 M THF solution, 0.10 mmol). The reaction mixture was maintained at 45 °C for 72 h, allowed to cool to room temperature, and treated with 250 mL of 10% NaOH. The resulting mixture was stirred for 3 h and the aqueous phase was discarded. The organic layer was washed with brine (3 × 100 mL), dried, and evaporated. Chromatographic purification of the residue (silica gel, elution with 10% ethyl acetate in petroleum ether) gave 4.64 g (43% overall yield for three steps) of **15** as a colorless oil: $[\alpha]^{23}_D$ −14.6° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 2960, 2870, 1470, 1260, 1120, 910, 845, 780; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (m, 4 H), 3.56 (dd, J = 9.7, 6.1 Hz, 1 H), 2.10–1.60 (m, 7 H), 1.60–1.10 (m, 6 H), 0.95 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 118.6, 81.6, 64.7, 63.9, 62.0, 59.5, 54.4, 37.3, 36.8, 35.9, 32.8, 32.3, 27.9, 26.3, 23.2, 18.4, −4.1, −4.7; MS m/z (M^+) calcd 352.2434, obsd 352.2453. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.22; H, 10.28.

(3a*R*,5a*R*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)octahydro-5a-methylcyclopenta[*c*]pentalen-3(3a*H*)-one (16). To a solution of **15** (15.3 g, 43.4 mmol) in acetone (810 mL) and water (90 mL) was added pyridinium *p*-toluenesulfonate (0.87 g, 3.5 mmol). The reaction mixture was heated to reflux for 4 h, cooled to room temperature, and freed of acetone. The residue was taken up in 1.2 L of petroleum ether and washed sequentially with saturated $NaHCO_3$ solution (200 mL), 10% HCl (2 × 150 mL), saturated $NaHCO_3$ solution (2 × 200 mL), and brine (200 mL). The petroleum ether phase was dried and concentrated to give 13.3 g of a residue, the purification of which by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 11.4 g (85%) of **16** as a white solid: mp 39.5–42.0 °C; $[\alpha]^{23}_D$ −62.3° (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 2940, 2920, 2840, 1730, 1460, 1250, 1110, 885, 835, 770; ^{1}H NMR (300 MHz, C_6D_6) δ 3.68 (m, 1 H), 2.25–1.90 (m, 3 H), 1.90–1.70 (m, 2 H), 1.70–1.45 (m, 2 H), 1.45–1.00 (m, 6 H), 0.99 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 219.1, 82.7, 62.7, 58.6, 54.1, 39.4, 36.7, 36.0, 33.7, 30.0, 29.1, 26.1, 23.8, 18.3, −4.2, −4.7; MS m/z (M^+) calcd 308.2171, obsd 308.2180. Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45. Found: C, 69.89; H, 10.41.

(3*S*,3a*R*,5a*S*,8a*R*)-1,2,3,3a,4,5,5a,8-Octahydro-3a-methylcyclopenta[*c*]pentalen-3-ol (18). To a solution of 1.0 g (3.24 mmol) of ketone **16** and 10 mL of TMEDA in 50 mL of THF at −78 °C was added KHMDS (10 mL of a 0.5 M solution in toluene, 5.0 mmol). The mixture was warmed to 0 °C for 15 min, returned to −78 °C, and treated with 1.5 g (4.2 mmol) of $PhN(OTf)_2$ in 5 mL of THF. The reaction mixture was stirred at −78 °C for 2 h, quenched by the addition of 10 mL of saturated NH_4Cl solution, poured into 300 mL of ether, washed with saturated $CuSO_4$ solution (3 × 30 mL) and brine (2 × 50 mL), and then dried. The solution was filtered through a small plug of silica gel (elution with 6% ethyl acetate in petroleum ether) to obtain 1.8 g of vinyl triflate **17** as a faint yellow oil: $[\alpha]^{23}_D$ −4.38° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3010, 2940, 2920, 2840, 1650, 1420, 1205, 1135, 855, 770; ^{1}H NMR (300 MHz, C_6D_6) δ 5.19 (s, 1 H), 3.41 (dd, J = 6.5, 9.2 Hz, 1 H), 2.24–1.10 (m, 11 H), 0.95 (s, 9 H), 0.74 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 149.6, 116.0, 82.3, 59.6, 58.6, 54.1, 36.1, 36.0, 33.5, 28.7, 26.0, 24.5, 24.1, 18.2, −4.3, −4.8 (CF_3 not observed); MS m/z ($M^+ - C_4H_9$) calcd 383.0960, obsd 383.0994.

To a solution of 14.6 mg (0.065 mmol) of $Pd(OAc)_2$ in 50 mL of THF was added 34.2 mg (0.13 mmol) of PPh_3. After 10 min, 1.8 g of the vinyl triflate from above was added followed by *n*-Bu_3N (2.3 mL, 9.7 mmol) and formic acid (0.25 mL, 6.6 mmol). The reaction mixture was stirred for 16 h at room temperature, poured into 50 mL of water, and extracted with petroleum ether (4 × 100 mL). The combined organic extracts were washed with 10% HCl (3 × 100 mL), water (3 × 50 mL), and brine (2 × 75 mL) and then dried and concentrated. This product was used directly in the next step.

The TBDMS ether from above was dissolved in 300 mL of aqueous HF/acetonitrile (15 mL of 48% HF and 285 mL of CH_3CN). Ether (400 mL) was added to the stirring reaction mixture after 1 h, and the resulting solution was washed with brine (3 × 100 mL), saturated $NaHCO_3$ solution (3 × 100 mL), and brine (100 mL). The ethereal layer was dried and concentrated in vacuo. Purification by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 0.48 g (84% for three steps) of **18** as a white solid: mp 47.5–51.5 °C; $[\alpha]^{23}_D$ +12.5° (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 3300, 3040, 2930, 2850, 1450, 1100, 1060, 730, 670; ^{1}H NMR (300 MHz, C_6D_6) δ 5.52 (m, 1 H), 5.48 (m, 1 H), 3.54 (dd, J = 6.3, 9.8 Hz, 1 H), 3.20 (br s, 1 H), 2.62 (br s, 1 H), 2.50 (dd, J = 2.0, 17.2 Hz, 1 H), 2.20–1.00 (m, 9 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 134.2, 129.3, 82.4, 62.0, 61.3, 53.1, 42.1, 36.6, 36.1, 33.0, 32.0, 25.2; MS m/z (M^+) calcd 178.1357, obsd 178.1329. Anal. Calcd for $C_{14}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.86; H, 10.22.

(3a*S*,5a*S*,8a*R*)-1,2,4,5,5a,8-Hexahydro-3a-methylcyclopenta[*c*]pentalen-3(3a*H*)-one. To a solution of **18** (1.33 g, 7.5 mmol) in 400 mL of CH_2Cl_2 was added 13.3 g of PCC absorbed on alumina (15% PCC by weight). The slurry was mechanically stirred for 16 h and then filtered through 20 g of Florisil. The solids were extracted with 500 mL of ether, which was combined with the CH_2Cl_2 solution, dried, and evaporated. The residue was purified by chromatography (silica gel, 10% ethyl acetate in petroleum ether) to give 1.18 g (90%) of ketone as a colorless oil: $[\alpha]^{23}_D$ −181.2° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 2950, 2920, 2840, 1730, 1460, 1375; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1 H), 5.45 (m, 1 H), 2.97 (m, 1 H), 2.77 (m, 1 H), 2.50–1.10 (m, 9 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 226.1, 133.6, 129.2, 59.7, 58.6, 58.5, 41.3, 37.6, 37.1, 32.7, 30.0, 17.9; MS m/z (M^+) calcd 176.1201, obsd 176.1181. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.22.

Methyl (3a*R*,5a*S*,8a*S*)-1,2,3,3a,4,5,5a,8-Octahydro-3a-methyl-3-oxocyclopenta[*c*]pentalene-2-carboxylate (19). To a solution of 0.53 mL (3.8 mmol) of *i*-Pr_2NH in 20 mL of ether at −78 °C was added *n*-butyllithium (2.5 mL of a 1.5 M solution in hexane, 3.8 mmol). The mixture was stirred for 5 min before a solution of the above ketone (0.22 g, 1.24 mmol) in 7.5 mL of ether was added. The reaction mixture was warmed to 0 °C for 15 min, cooled back to −78 °C, and treated with 0.20 mL (2.5 mmol) of methyl cyanoformate. The reaction mixture, which rapidly changed from clear and faint yellow to opaque yellow, was stirred for 4 h at −78 °C and 1 h at 0 °C and then cooled back to −78 °C and quenched with 3 mL of saturated NH_4Cl solution. After dilution with

50 mL of ether, the organic phase was washed with brine (3 × 10 mL), dried, and evaporated. The residue was chromatographed on silica gel (elution with 6% ethyl acetate in petroleum ether) to give 0.21 g (71%) of **19** as a colorless oil. This keto ester equilibrates between α and β isomers as well as the enol form: $[\alpha]^{23}_D$ −89.3° (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 3050, 2950, 2870, 1750, 1730, 1660, 1620, 1440, 1255; MS *m/z* (M^+) calcd 234.1256, obsd 234.1243. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.10; H, 7.94.

Methyl (3a*R*,5a*S*,8a*R*)-3,3a,4,5,5a,8-Hexahydro-3a-methyl-3-oxocyclopenta[*c*]-pentalene-2-carboxylate (20). To a solution of 50 mg (0.22 mmol) of **19** in 4 mL of benzene were added 74 mg (0.33 mmol) of DDQ and 16.5 mg of silica gel (TLC grade). The mixture was stirred for 48 h at room temperature, filtered through a sintered glass funnel, and washed with 20 mL of ether. The combined ether and benzene filtrates were washed with saturated $NaHCO_3$ solution (3 × 5 mL) and brine (2 × 5 mL) and then dried and evaporated. Purification of the residue by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 33 mg (67%) of **20** as a waxy solid: $[\alpha]^{23}_D$ +56.2° (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 3040, 3000, 2950, 2870, 2850, 1750, 1715, 1460, 1440, 1000, 800, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.77 (s, 1 H), 5.30 (m, 1 H), 5.10 (m, 1 H), 3.45 (s, 3 H), 2.64 (m, 1 H), 2.25–2.00 (m, 3 H), 1.35–1.00 (m, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 206.5, 175.9, 162.5, 135.0, 133.5, 129.9, 62.5, 59.9, 56.7, 51.2, 38.3, 37.0, 27.2, 21.1; MS *m/z* (M^+) calcd 232.1100, obsd 232.1093. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.13; H, 6.95.

Methyl (1*S*,3a*R*,5a*S*,8a*S*)-1,2,3,3a,4,5,5a,8-Octahydro-1,3a-dimethyl-3-oxocyclopenta[*c*]pentalene-2-carboxylate (21). To a solution of DMAP (0.34 g, 2.8 mmol) and copper(I) bromide–dimethyl sulfide complex (0.44 g, 2.1 mmol) in 40 mL of THF at −78 °C was added methyllithium (2.8 mL of a 1.5 M solution in ether, 4.2 mmol). The reaction mixture was stirred for 20 min, at which point a cold (−78 °C) solution of **20** (0.33 g, 1.4 mmol) and chlorotrimethylsilane (0.35 mL, 2.8 mmol) in 10 mL of ether was introduced via cannula. The solution immediately became bright yellow. The reaction mixture was stirred for 3.5 h at −78 °C and 1 h at 0 °C and then cooled back to −78 °C and quenched with 7 mL of saturated NH_4Cl solution. The resulting mixture was diluted with petroleum ether (300 mL), washed with saturated NH_4Cl solution (3 × 50 mL) and brine (75 mL), and then dried and concentrated. Purification by chromatography (silica gel, elution with 7.5% ethyl acetate in petroleum ether) gave 0.26 g (74%) of **21** as a colorless oil. The product exists as an equilibrium mixture of α and β carbomethoxy isomers as well as the enol form: $[\alpha]^{23}_D$ −40.3° (*c* 1.1, $CHCl_3$); IR (film, cm^{-1}) 3010, 2940, 2860, 1740, 1720, 1650, 1615, 1430, 1340, 1235, 800, 700; MS *m/z* (M^+) calcd 248.1413, obsd 248.1358. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.55; H, 8.11. Found: C, 72.72; H, 8.19.

Sodium Borohydride Reduction of 21. To a solution of 0.26 g (1.05 mmol) of **21** in 20 mL of methanol at 0 °C was added 200 mg (5.2 mmol) of sodium borohydride over a 30-min period. The mixture was stirred for 15 min and then treated with 10% HCl until slightly acidic and saturated $NaHCO_3$ solution until neutral. The methanol was removed by rotary evaporation, and the residue was dissolved in 100 mL of brine. The aqueous solution was extracted with ether (4 × 50 mL). The combined ether solutions were washed with brine (50 mL), dried, and freed of solvent in vacuo. Chromatographic purification of the residue (silica gel, elution with 14% ethyl acetate in petroleum ether) gave 0.19 g (73%) of the β-hydroxy ester and 16.5 mg (6%) of its α-epimer, both as colorless oils.

For the β-hydroxy epimer: $[\alpha]^{23}_D$ +20.7° (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) 3500, 3040, 2950, 2870, 1725, 1435, 1370, 1200, 1170; ^1H NMR (300 MHz, C_6D_6) δ 5.45 (m, 1 H), 5.37 (m, 1 H), 3.71 (t, *J* = 3.9 Hz, 1 H), 3.31 (s, 3 H), 2.94 (d, *J* = 3.4 Hz, 1 H), 2.77 (m, 1 H), 2.55 (dq, *J* = 13, 6.8 Hz, 1 H), 2.40–2.15 (m, 3 H), 2.05 (m, 1 H), 1.87 (d, *J* = 6.7 Hz, 1 H), 1.59 (m, 1 H), 1.21 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.80 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 174.6, 134.9, 129.4, 81.2, 64.5, 57.3, 56.7, 55.0, 42.3, 35.0, 33.2, 30.4, 25.8, 15.1; MS *m/z* (M^+) calcd 250.1569, obsd 250.1531. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 8.84.

For the minor α-hydroxy isomer: $[\alpha]^{23}_D$ +49.0° (*c* 0.9, $CHCl_3$); IR (film, cm^{-1}) 3495, 3015, 2930, 2870, 1705, 1430, 1350, 1205, 1010; ^1H NMR (300 MHz, C_6D_6) δ 5.52 (m, 1 H), 5.32 (m, 1 H), 3.98 (d, *J* = 2 Hz, 1 H), 3.88 (dd, *J* = 5, 2 Hz, 1 H), 3.28 (s, 3 H), 1.71 (dd, *J* = 6.0, 6.7 Hz, 1 H), 2.52 (m, 1 H), 2.38 (AB m, 2 H), 2.16 (dq, *J* = 7.2, 7.2 Hz, 1 H), 1.55–1.45 (m, 2 H), 1.40–1.30 (m, 2 H), 1.25 (s, 3 H), 1.10 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 174.9, 133.4, 130.1, 81.7, 65.1, 62.0, 55.6, 52.2, 50.9, 46.5, 43.1, 36.2, 30.5, 21.4, 15.3; MS *m/z* (M^+) calcd 250.1569, obsd 250.1570.

Methyl (1*S*,2*S*,3*S*,3a*R*,5a*R*,8a*R*)-Decahydro-3-hydroxy-1,3a-dimethylcyclopenta[*c*]pentalene-2-carboxylate 3-*O*-Methanesulfonate. To a solution of 0.16 g (0.63 mmol) of the preceding β-hydroxy ester in 20 mL of pyridine was added DMAP (5.6 mg, 0.046 mmol) and methanesulfonyl chloride (0.10 mL, 1.3 mmol). The mixture was stirred for 19 h at ambient temperature, diluted with 450 mL of ether, washed with 10% HCl (3 × 50 mL), saturated $NaHCO_3$ solution (2 × 50 mL), and brine (50 mL), and then dried and evaporated. Purification of the residue by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 0.21 g (100%) of the β-mesylate as a colorless oil: $[\alpha]^{23}_D$ −12.9° (*c* 0.6 $CHCl_3$); IR (film, cm^{-1}) 3030, 2950, 2860, 1735, 1430, 1345, 1175, 880, 790, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (m, 1 H), 5.47 (m, 1 H), 4.84 (d, *J* = 4.9 Hz, 1 H), 3.71 (s, 3 H), 2.96 (s, 3 H), 2.93 (m, 1 H), 2.61 (dd, *J* = 4.9, 13.3 Hz, 1 H), 2.50 (m, 1 H), 2.36 (br d, *J* = 16.9 Hz, 1 H), 2.10 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 1 H), 1.33 (m, 1 H), 1.08 (s, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.7, 134.3, 129.3, 90.4, 64.1, 56.7, 56.5, 54.8, 51.7, 40.8, 38.4, 37.0, 32.8, 29.8, 24.8, 14.4; MS *m/z* (M^+) calcd 328.1344, obsd 328.1338. Anal. Calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.24; H, 7.41.

Identical processing of the α-hydroxy ester (16.5 mg, 0.066 mmol) gave 15.6 mg (72%) of the mesylate as a colorless oil: $[\alpha]^{23}_D$ +11.8° (*c* 0.8, $CHCl_3$); IR (film, cm^{-1}) 3010, 2940, 1735, 1340, 1170, 870, 750; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (m, 1 H), 5.20 (m, 1 H), 4.80 (d, *J* = 6.6 Hz, 1 H), 3.31 (s, 3 H), 2.87 (t, *J* = 6.4 Hz, 1 H), 2.45 (s, 3 H), 2.50–2.30 (m, 3 H), 1.82 (m, 1 H), 1.68 (m, 1 H), 1.45–1.20 (m, 3 H), 1.24 (s, 3 H), 0.99 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.5, 132.9, 130.6, 89.1, 64.4, 60.6, 55.5, 52.9, 50.8, 42.9, 42.0, 38.2, 36.0, 29.0, 22.0, 13.6; MS *m/z* (M^+) calcd 328.1242, obsd 328.1293.

Methyl (1*R*,3a*S*,5a*S*,8a*R*)-1,3a,4,5,5a,8-Hexahydro-1,3a-dimethylcyclopenta[*c*]pentalene-2-carboxylate (2). A. By Elimination of the β-Mesylate. To a solution of the β-mesylate (0.239 g, 0.73 mmol) in 150 mL of ether was added 3.0 g of Woelm alumina (activity I basic, oven-dried). The slurry was stirred for 1 day, and an additional 3.0 g of Woelm alumina was added. After a second day at room temperature, the reaction mixture was filtered and the alumina was rinsed with 300 mL of ether. The combined filtrates were dried and concentrated. Purification of the residue by chromatography (silica gel, elution with 6% ethyl acetate in petroleum ether) gave 0.15 g (87%) of **2** as a colorless oil: $[\alpha]^{23}_D$ −47.2° (*c* 0.8, $CHCl_3$); IR (film, cm^{-1}) 3040, 2940, 2850, 1720, 1630, 1460, 1430, 1270, 1245, 1040, 770; ^1H NMR (300 MHz, C_6D_6) δ 6.42 (s, 1 H), 5.56 (m, 1 H), 5.28 (m, 1 H), 3.49 (s, 3 H), 3.09 (q, *J* = 7.1 Hz, 1 H), 2.81 (m, 1 H), 2.44 (dq, *J* = 17.7, 2.2 Hz, 1 H), 2.26 (dq, *J* = 17.7, 2.2 Hz, 1 H), 1.75–1.25 (m, 4 H), 1.19 (d, *J* = 7.1 Hz, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 164.9, 150.7, 139.7, 133.3, 129.5, 62.6, 61.9, 59.6, 50.8, 50.1, 37.3, 35.9, 29.8, 23.2, 19.0; MS *m/z* (M^+) calcd 232.1463, obsd 232.1459. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.62.

B. By Elimination of the α-Mesylate. To a solution of 15.6 g (0.048 mmol) of the α-mesylate in 7.5 mL of ether was added 0.22 g of Woelm alumina (activity I basic, oven-dried). After 1 day, the slurry was filtered through a sintered glass frit and the alumina was extracted with 100 mL of ether. The ether solutions were combined, dried, and evaporated. Chromatography of the residue (silica gel, 6% ethyl acetate in petroleum ether) gave 8.7 mg (78%) of colorless oily **2**, identical in all respects to the material produced in part A.

Methyl (1*R*,3a*S*,5a*R*,8a*S*)-1,3a,4,5,5a,6-Hexahydro-1,3a-dimethyl-6-oxocyclopenta[*c*]pentalene-2-carboxylate (22). To a solution of 144 mg (0.62 mmol) of **2** in 10 mL of benzene were added PDC (936 mg, 2.56 mmol), Celite (950 mg) and *tert*-butyl hydroperoxide (256 mg of 90% purity, 2.56 mmol). After 2 days, the mixture was diluted with ether (50 mL), filtered through a small pad of Celite, dried, and evaporated. Purification of the residue by chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 53.5 mg (35%, 69% based on recovered **2**) of **22**: $[\alpha]^{19}_D$ −70.4° (*c* 1.18, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 6.95 (d, *J* = 5.8 Hz, 1 H), 6.21 (s, 1 H), 5.94 (d, *J* = 5.8 Hz, 1 H), 3.41 (s, 3 H), 2.82 (q, *J* = 7.1 Hz, 1 H), 2.03 (d, *J* = 9.5 Hz, 1 H), 1.91 (dd, *J* = 12.5, 6.5 Hz, 1 H), 1.33 (dddd, *J* = 13.5, 12.5, 9.5, 6 Hz, 1 H), 1.21 (dd, *J* = 13, 6 Hz, 1 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 0.97 (ddd, *J* = 13.5, 13, 6.5 Hz, 1 H), 0.72 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 209.8, 164.3, 163.2, 149.1, 139.5, 135.5, 65.3, 61.5, 58.8, 50.9, 49.9, 36.0, 27.2, 22.8, 18.5; MS *m/z* (M^+) calcd 246.1254, obsd 246.1255.

Sodium Borohydride Reduction of 22. To a solution of **22** (46.5 mg, 0.189 mmol) in methanol (4 mL) was added cerium trichloride heptahydrate (80 mg, 0.215 mmol) at room temperature, followed after dissolution of the salt by portionwise addition at −50 °C of sodium borohydride (8.0 mg, 0.211 mmol). The reaction mixture was allowed to warm to −10 °C over 30 min, quenched with saturated NH_4Cl solution, and diluted with ether. The organic phase was washed with 5% HCl, water, and brine and then dried and evaporated. ^1H NMR analysis of this product showed **23** and **24** to be present in a ratio of 85:15. Flash chromatography on silica gel (elution with petroleum ether/ether 1:2)

afforded 37.2 mg (79%) of **23** and 6.4 mg (14%) of **24**, both as colorless gums.

For **23**: IR (CCl_4, cm^{-1}) 3620, 3600–3300, 3050, 1720, 1630; ^1H NMR (300 MHz, C_6D_6) δ 6.42 (br d, J = 1 Hz, 1 H), 5.64–5.59 (AB m, 2 H), 4.46 (d, J = 8 Hz, 1 H), 3.43 (s, 3 H), 2.95 (br q, J = 7 Hz, 1 H), 2.14 (m, 1 H), 1.86–1.72 (m, 1 H), 1.55–1.25 (m, 3 H), 1.18 (d, J = 7 Hz, 3 H), 0.92 (s, 3 H), 0.63 (br s, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6, ppm) 164.9, 150.5, 139.1, 134.9, 77.0, 71.0, 59.5, 57.0, 51.6, 50.8, 39.2, 24.7, 22.4, 19.2; MS m/z (M^+) calcd 248.1412, obsd 248.1417.

For **24**: IR (CCl_4, cm^{-1}) 3620, 3600–3300, 3050, 1720, 1630; ^1H NMR (300 MHz, C_6D_6) δ 6.37 (d, J = 1 Hz, 1 H), 5.64 (dd, J = 5.5, 2 Hz, 1 H), 5.57 (dd, J = 5.5, 1 Hz, 1 H), 4.07 (br ddd, J = 3, 2, 1 Hz, 1 H), 3.42 (s, 3 H), 3.02 (br q, J = 7 Hz, 1 H), 1.98 (dddd, J = 8, 3, 1.5, 1 Hz, 1 H), 1.51 (dddd, J = 14, 13, 8, 6 Hz, 1 H), 1.41–1.32 (m, 2 H), 1.21 (d, J = 7 Hz, 3 H), 1.04 (ddd, J = 13, 13, 6.5 Hz, 1 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 164.8, 149.9, 139.3, 135.4, 134.8, 85.2, 69.8, 65.0, 58.7, 51.8, 50.8, 37.2, 30.0, 23.6, 18.5; MS m/z (M^+) calcd 248.1412, obsd 248.1413.

Methyl (1*R*,3a*S*,5a*R*,6*R*,8a*S*)-1,3a,4,5,5a,6-Hexahydro-1,3a-dimethyl-6-(phenylthio)cyclopenta[*c*]pentalene-2-carboxylate (25). A premixed solution of tri-*n*-butylphosphine (150 mg, 0.741 mmol) and *N*-(phenylthio)succinimide (145 mg, 0.75 mmol) in benzene (5 mL) was added at room temperature to a solution of **23** (46.2 mg, 0.186 mmol) in benzene (2 mL). The resulting mixture was stirred at room temperature for 6 h, evaporated, and subjected directly to flash chromatography on silica gel (elution with petroleum ether/ether, 20:1). There was obtained 49.9 mg (79%) of **25** as a colorless gum: IR (CCl_4, cm^{-1}) 1720, 1630; ^1H NMR (300 MHz, C_6D_6) δ 7.39–7.33 (m, 2 H), 7.05–6.93 (m, 3 H), 6.35 (d, J = 1 Hz, 1 H), 5.70 (dd, J = 5.5, 2 Hz, 1 H), 5.47 (dd, J = 5.5, 1.5 Hz, 1 H), 3.58 (ddd, J = 3.5, 2, 1.5 Hz, 1 H), 3.39 (s, 3 H), 2.77 (br q, J = 7 Hz, 1 H), 2.45 (br ddd, J = 8, 3.5, 2 Hz, 1 H), 1.51 (dddd, J = 12.5, 12.5, 8, 6 Hz, 1 H), 1.36 (br dd, J = 12, 6 Hz, 1 H), 1.29 (dddd, J = 12.5, 6, 2, 1 Hz, 1 H), 1.15 (ddd, J = 12.5, 12, 6 Hz, 1 H), 1.10 (d, J = 7 Hz, 3 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 164.7, 149.8, 139.1, 135.7, 133.8, 133.4, 132.9 (2 C), 128.9 (2 C), 127.1, 71.1, 61.7, 60.9, 59.3, 51.4, 50.8, 37.2, 31.6, 23.4, 18.4; MS m/z (M^+) calcd 340.1497, obsd 340.1499.

Methyl (1*R*,3a*S*,5a*S*,8*S*,8a*S*)-1,3a,4,5,5a,8-Hexahydro-8-hydroxy-1,3a-dimethylcyclopenta[*c*]pentalene-2-carboxylate (26). To a solution of **25** (49.9 mg, 0.147 mmol) in methanol (6 mL) was added a solution of $NaIO_4$ (50 mg, 0.234 mmol) in water (0.5 mL) at room temperature. After 30 min, more methanol and a second portion of $NaIO_4$ (100 mg, 0.468 mmol) were added. Following a total reaction time of 2 h, all of the **25** had been consumed (TLC), and the sulfoxides were isolated by solvent evaporation and partitioning of the residue between CH_2Cl_2 and brine. The organic phases were dried and concentrated, and this material was used without purification (50.6 mg, 97%). ^1H NMR analysis indicated a 1:1 mixture of diastereomers to be present: IR (CCl_4, cm^{-1}) 1720, 1625, 1245, 1050; ^1H NMR (300 MHz, C_6D_6) δ (diastereomer A) 6.29 (d, J = 1 Hz, 1 H), 5.61 (dd, J = 6, 2 Hz, 1 H), 5.48 (dd, J = 6, 2 Hz, 1 H), 3.40 (s, 3 H), 3.35 (ddd, J = 3.5, 2, 2 Hz, 1 H), 2.65 (br q, J = 7 Hz, 1 H), 2.47 (br dd, J = 8.5, 3.5 Hz, 1 H), 1.50–0.65 (series of m, 4 H), 1.04 (d, J = 7 Hz, 3 H), 0.78 (s, 3 H), δ (diastereomer B) 6.31 (d, J = 1 Hz, 1 H), 5.66 (dd, J = 6, 2 Hz, 1 H), 5.56 (dd, J = 6, 2 Hz, 1 H), 3.38 (s, 3 H), 3.16 (ddd, J = 4, 2, 2 Hz, 1 H), 3.11 (br q, J = 7 Hz, 1 H), 2.71 (br dd, J = 8.5, 4 Hz, 1 H), 1.50–0.65 (series of m, 4 H), 1.14 (d, J = 7 Hz, 3 H), 0.82 (s, 3 H); FAB MS (M^+ + H) calcd 357.2, obsd 357.2.

The sulfoxides from above (50.6 mg, 0.142 mmol) were dissolved in methanol (8 mL), treated with freshly distilled trimethyl phosphite (0.20 mL, 1.70 mmol) and diethylamine (0.08 mL, 0.77 mmol), and refluxed under N_2 for 40 h. After evaporation of the volatiles, **26** was isolated by flash chromatography on silica gel (elution with petroleum ether/ether, 1:1): 33.2 mg (91% from **25**) of colorless needles; mp 99–100 °C (from ether/petroleum ether); IR (CCl_4, cm^{-1}) 3600, 1720, 1635, 1240; ^1H NMR (300 MHz, C_6D_6) δ 6.15 (s, 1 H), 5.63 (ddd, J = 5.5, 2.5, 2 Hz, 1 H), 5.19 (dd, J = 5.5, 2 Hz, 1 H), 4.44 (br ddd, J = 9, 2.5, 1.5 Hz, 1 H), 3.45 (s, 3 H), 3.25 (q, J = 6.5 Hz, 1 H), 2.69 (br dddd, J = 7, 2, 2, 1.5 Hz, 1 H), 1.67 (d, J = 6.5 Hz, 3 H), 1.49–1.35 (m, 1 H), 1.20–1.04 (m, 3 H), 0.95 (s, 3 H), 0.35 (d, J = 9 Hz, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6, ppm) 164.7, 148.8, 140.8, 139.4, 133.5, 79.1, 65.0, 58.6, 57.5, 50.8, 48.0, 36.0, 28.0, 22.5, 20.8; MS m/z (M^+) calcd 248.1412, obsd 248.1421.

Methyl (1*R*,3a*S*,5a*S*,8a*S*)-1,3a,4,5,5a,8-Hexahydro-1,3a-dimethyl-8-oxocyclopenta[*c*]pentalene-2-carboxylate (27). Alcohol **26** (29.3 mg, 0.118 mmol) in CCl_4 (6 mL) was stirred with activated MnO_2[41] (500 mg) for 2 h, at which point the oxidation was complete. Enone **27** was isolated by elution with ether through a short pad of Celite and obtained as a colorless solid: mp 124–125 °C (from ether/petroleum ether); 26.5 mg (96%); $[\alpha]^{19}_D$ +15.4° (c 0.61, $CHCl_3$); IR (CCl_4, cm^{-1}) 1720, 1705, 1630, 1590; ^1H NMR (300 MHz, C_6D_6) δ 6.53 (dd, J = 6, 2.5 Hz, 1 H), 6.24 (d, J = 1 Hz, 1 H), 5.79 (dd, J = 6, 2 Hz, 1 H), 3.40 (s, 3 H), 3.09 (br q, J = 7 Hz, 1 H), 2.48 (br d, J = 9 Hz, 1 H), 1.57 (d, J = 7 Hz, 3 H), 1.40–1.25 (m, 2 H), 1.17–0.94 (m, 2 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 207.4, 164.4, 163.3, 148.5, 139.9, 135.4, 65.0, 60.2, 59.7, 50.9, 49.4, 36.1, 27.9, 23.0, 18.1; MS m/z (M^+) calcd 246.1256, obsd 246.1251.

(−)-Subergorgic Acid (1). A cold (−10 °C) solution of lithium dimethylcuprate [prepared from CuI (85 mg, 0.45 mmol) and methyllithium (0.50 mL of 1.5 M, 0.75 mmol) in ether (3 mL) at −10 °C for 15 min] was introduced dropwise over 2 min into a solution of **27** (26.5 mg, 0.108 mmol) in ether (5 mL). After 10 min of additional stirring at −10 °C, the reaction mixture was quenched by the addition of 5% HCl and worked up by extraction of the product into ether and washing the organic phase with water and brine prior to drying and evaporation. Purification of the residue by flash chromatography (silica gel, elution with petroleum ether/ether, 2:1) afforded 24.8 mg (88%) of the methyl ester of **1** as a colorless oil: IR (CCl_4, cm^{-1}) 1725, 1635; ^1H NMR (300 MHz, C_6D_6) δ 6.19 (d, J = 1 Hz, 1 H), 3.41 (s, 3 H), 2.99 (br q, J = 7 Hz, 1 H), 2.04 (dd, J = 16, 6.5 Hz, 1 H), 1.68–1.62 (m, 1 H), 1.57 (dd, J = 16, 12.5 Hz, 1 H), 1.46–1.07 (series of m, 5 H), 1.36 (d, J = 7 Hz, 3 H), 1.19 (s, 3 H), 0.72 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 215.4, 154.5, 149.3, 137.7, 68.3, 62.7, 61.5, 52.4, 50.9, 49.6, 38.3, 33.3, 28.3, 23.8, 19.6, 18.2; MS m/z (M^+) calcd 262.1569, obsd 262.1556.

A solution of the above ester (24.8 mg, 0.0945 mmol) in methanol (6 mL) was treated with 10% aqueous KOH (2.5 mL, 4.45 mmol), stirred overnight at room temperature, and freed of methanol. The residue was taken up in water and $CHCl_3$, washed with 5% HCl and brine, dried, and evaporated. Flash chromatography (silica gel, elution with petroleum ether/ether, 1:1) of the product afforded 21.8 mg (93%) of **1** as a colorless solid: mp 174–175 °C (from ether/petroleum ether); $[\alpha]^{19}_D$ −143.5° (c 0.64, $CHCl_3$); IR (CH_2Cl_2, cm^{-1}) 3300–2500, 1725, 1685, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 1 Hz, 1 H), 3.00 (br q, J = 7 Hz, 1 H), 2.36 (dd, J = 16.5, 7 Hz, 1 H), 2.08 (br dd, J = 9, 6.5 Hz, 1 H), 1.99 (dd, J = 16.5, 12 Hz, 1 H), 1.84–1.52 (series of m, 5 H), 1.21 (s, 3 H), 1.13 (d, J = 7 Hz, 3 H), 1.11 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 217.6, 169.6, 152.3, 136.6, 68.5, 62.7, 61.8, 51.6, 49.9, 38.3, 33.3, 28.3, 23.4, 19.9, 17.7; MS m/z (M^+) calcd 248.1412, obsd 248.1414.

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