α-Carbonyl Radical Cyclization Approach toward Angular Triquinanes: Total Synthesis of Enantiomerically Pure (−)-5-Oxosilphiperfol-6-ene

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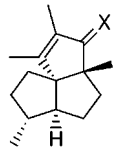
An α-carbonyl radical cyclization approach toward synthesis of angular triquinanes is described. As a model study, conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride to enone **7** followed by trapping of the enolate with chlorotrimethylsilane gave trimethysilyl enol ether **8**. Iodination of **8** with a mixture of NaI and *m*-CPBA afforded iodo ketone **6**. Radical cyclization of **6** effected by Bu_3SnH and AIBN gave **5**. Epoxidation of **5** with *m*-CPBA yielded epoxy ketone **9**. Desilylation and rearrangement of **9** by formic acid gave aldehyde **4**. Aldol condensation and dehydration furnished angular triquinane skeleton **3**. Total synthesis of (−)-5-oxosilphiperfol-6-ene (**1**) was accomplished in 12 steps starting from keto ester **14** based on this route. Conjugate addition of 3-hexynylmagnesium bromide to chiral ester **13** followed by treatment with chlorotrimethylsilane gave intermediate **15**. Iodination of **15** with a mixture of NaI and *m*-CPBA gave α-iodo ester **12**. Intramolecular radical cyclization of **12** gave ester **11**. Reduction of **11** by $LiAlH_4$ yielded alcohol **16**. On treatment with *m*-CPBA, alcohol **16** was converted to the corresponding epoxide **17**, which was subjected to the epoxy−ketone rearrangement using BF_3 etherate as a catalyst to give ethyl ketone **18**. Subsequent oxidation of **18** with PCC afforded aldehyde **10**. Intramolecular aldol condensation of **10** yielded tricyclic compound **19**. Methylation of **19** gave **20**. Conjugate addition of lithium dimethylcuprate to **20** followed by trapping of the resulting enolate with chlorotrimethylsilane gave **21**. Oxidation of **21** by DDQ afforded enantiomerically pure (−)-5-oxosilphiperfol-6-ene (**1**). Racemic (±)-**1** was also synthesized in the same manner in order to determine the optical purity of chiral product (−)-**1**. The gas chromatographic analysis with a chiral column proved that **1** has high enantiomeric purity. A single-crystal X-ray analysis of 2,4-dinitrophenylhydrazone **22** was performed to unambiguously confirm the stereochemistry of **19**.

Introduction

5-Oxosilphiperfol-6-ene (**1**) and silphiperfol-6-ene (**2**), isolated from the stem of *Espeletiopsis guacharaca*[1a] and the root of *Silphium perfoliatum*,[1b] are structurally related angular triquinanes. This class of natural products with the multiply fused five-membered ring skeleton has been a challenging target for total synthesis. Various approaches toward the total syntheses of triquinanes have been reported.[2] Particularly, free radical cyclizations are among the most effective methodologies for the synthesis of angular and linear triquinanes.[3] A few elegant total and formal syntheses of 5-oxosilphiperfol-6-ene (**1**) and silphiperfol-6-ene (**2**) have also appeared.[4]



1 X = O
2 X = H_2

We have recently reported α-carbonyl radical cyclization reactions and their applications toward total syntheses of natural products such as (±)-modhephene and (−)-dendrobine.[5] As a continuation of our study in this area, we here report the application of α-carbonyl radical

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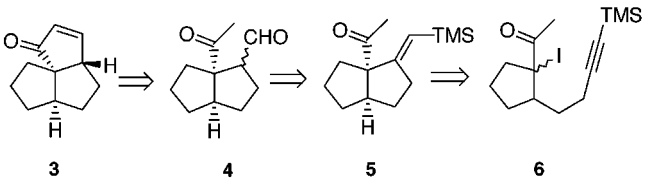
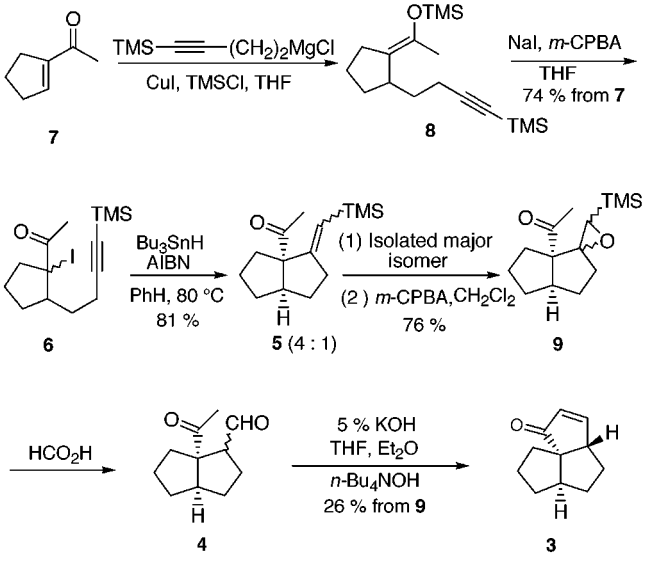
Scheme 1



Scheme 2



cyclization toward a general synthesis of angular triquinanes as well as a total synthesis of enantiomerically pure (−)-5-oxosilphiperfol-6-ene (**1**).

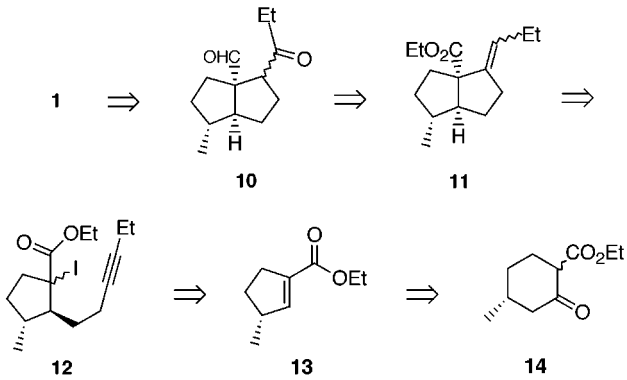
Results and Discussion

The retro-synthetic analysis of angular triquinane skeleton **3** based on α-carbonyl radical cyclization is outlined in Scheme 1. Radical cyclization of α-iodo ketone **6** would afford cis-fused bicyclic intermediate **5**. Compound **5** could be coverted to aldehyde **4** by epoxidation and acid-catalyzed rearrangement. The third ring would be annulated by aldol condensation of **4** to give angular triquinane skeleton **3**.

Copper(I) iodide-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride to enone **7**[6] followed by trapping of the resulting enolate with chlorotrimethylsilane gave trimethylsilyl enol ether **8** (Scheme 2). Treatment of **8** with NaI and *m*-CPBA afforded iodo ketone **6**.[7] Radical cyclization of **6** was effected by tributyltin hydride and AIBN by syringe pump addition to yield **5** as a mixture of geometrical isomers (4:1) with a cis ring juncture. The major isomer of **5** was isolated by silica gel chromatography and was epoxidized with *m*-CPBA to give epoxide **9**. Exposure of **9** with formic acid resulted in desilylation and rearrangement to afford aldehyde **4**. The final ring closure was carried out by the aldol condensation of **4** with 5% KOH[8] followed by dehydration, which gave enone **3** in low yield (26% from **9**). However, attempts to improve the yield of enone **3** were futile.

Therefore we devised another synthetic route for the total synthesis of enantiomerically pure (−)-**1**. The retro-

Scheme 3



synthetic analysis is shown in Scheme 3. The key step would be the radical cyclization of **12**, which would give cis-fused bicyclic intermediate **11**. Compound **11** could be readily transformed into **10** in a few steps. Aldol condensation of **10** would afford an angular triquinane skeleton, which could be converted to (−)-**1** by further transformations. The starting material ethyl (4*R*)-4-methyl-2-oxocyclohexane-1-carboxylate was prepared from (*R*)-pulegone by the method of Djerassi.[9] Compound **14** was treated with *tert*-butyl hypochlorite in methanol followed by heating with Na_2CO_3 and glass powder in xylene to give chiral ester **13** according to the method of Takeda.[10] Copper(I) iodide-mediated conjugate addition of 3-hexynylmagnesium bromide to **13** followed by trapping of the resulting enolate with chlorotrimethylsilane gave ketene acetal **15** (Scheme 4). Without isolation, the crude product **15** was immediately treated with a mixture of NaI and *m*-CPBA in THF to afford α-iodo ester **12** (60% from **13**). Radical cyclization of **12** effected by syringe pump addition of a solution of tributyltin hydride and AIBN in benzene at reflux yielded ester **11** (73%, geometrical isomers 3:1). Reduction of **11** with $LiAlH_4$ afforded alcohol **16** (80%). Compound **16** was epoxidized with *m*-CPBA to give epoxide **17**. The crude product **17** was subjected to an epoxy−ketone rearrangement using 1 equiv of boron triflouride etherate to give **18** (57% from **16**). Oxidation of keto alcohol **18** with pyridinium chlorochromate furnished aldehyde **10**. Aldol condensation of **10** with 5% KOH[8] produced enone **19** (70% from **18**). Enone **19** was subjected to alkylation with lithium diisopropylamide and iodomethane to give enone **20** (82%). Conjugate addition of lithium dimethylcuprate to **20** followed by trapping of the resulting enolate with chlorotrimethylsilane gave the trimethylsilyl enol ether **21**. We assumed that the oxidation of **21** to **1** using $Pd(OAc)_2$ would be a straightforward reaction. To our surprise this reaction did not furnish the desired product. Finally, we carried out the oxidation of **21** with freshly recrystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of *N*,*O*-bis(trimethylsilyl)-2,2,2-trifluoroacetamide (BSTFA)[4a] to afford (−)-5-oxosilphiperfol-6-ene (**1**) (38% from **20**). All spectral data of synthetic (−)-**1** were found to be in good agreement[11] with those reported in the literature.[1a,4a] However, our synthetic (−)-**1** exhibited higher specific rotation {$[\alpha]_D$ =

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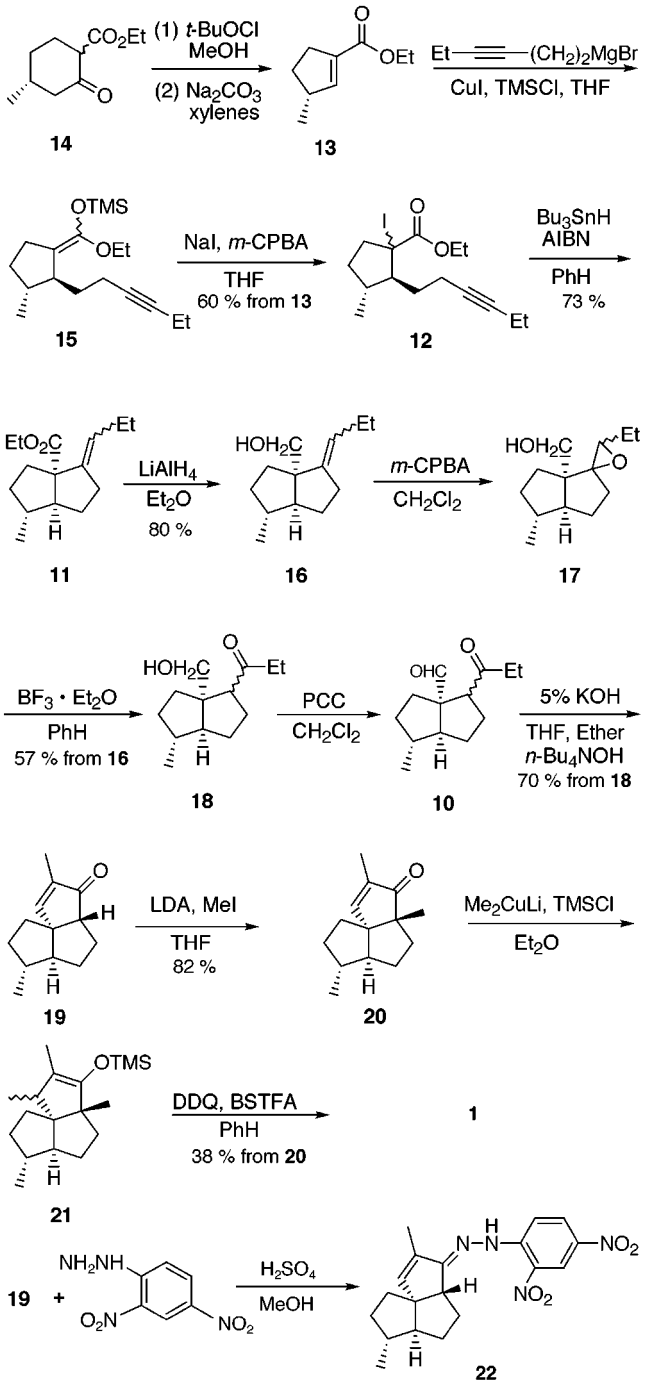
(11) ^{1}H and ^{13}C NMR, IR, and MS of **1** are in good agreement with those spectra received from Professor M. Demuth.

Scheme 4



−82.2 (c = 1.3)} in comparison to the literature values {$[\alpha]_D$ = −40 (c = 1.3),[1a] $[\alpha]_D$ = −39.5 (c = 0.34)[4a]}.

To check the enantiomeric purity of our product, we also synthesized racemic (±)-**1** starting from racemic (±)-**14** by the same route. The gas chromatographic analysis of the enantiomerically pure (−)-**1**, racemic (±)-**1,** and the 1:1 mixture of (−)-**1** and (±)-**1** with a chiral column is shown in Figure 1. The result confirmed that our product is of high enantiomeric purity (>99%). Furthermore, to unambiguously establish the absolute stereochemistry of our product, we tried to synthesize a crystalline derivative of (−)-**1** for X-ray analysis. However, we were not successful in making the crystalline derivative of (−)-**1,** but we did finally synthesize 2,4-dinitrophenylhydrazone **22** from **19,** whose single-crystal X-ray analysis is shown in Figure 2. The crystal structure drawing of **22** clearly

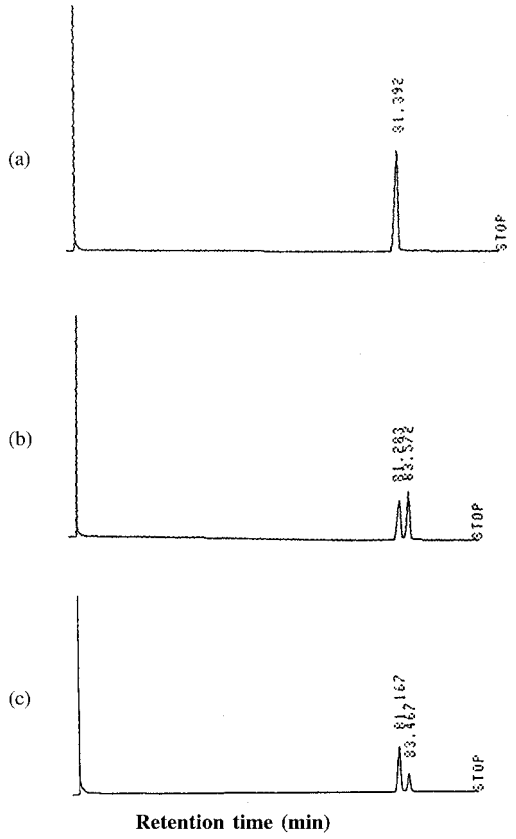


Figure 1. Analysis of the optical purity of (−)-**1** by gas chromatography with a chiral column (SGE 25QC2/CYDEX-B 0.25; temperature, 125 °C isothermal). Gas chromatogram of (a) enantiomerically pure (−)-**1**, (b) racemic (±)-**1**, (c) 1:1 mixture of (−)-**1** and (±)-**1**.

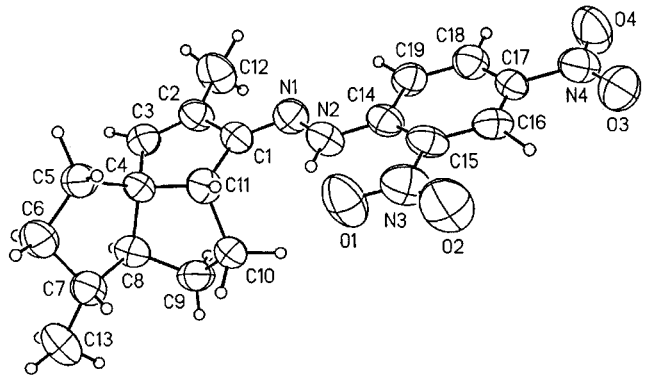


Figure 2. Molecular drawing of 2,4-dinitrophenylhydrazone **22** generated by SHELXTL PLUS.

verifies the relative and absolute configuration of all the stereogenic centers in compound **19**. These results and all the spectral data confirmed the structure and optical purity of (−)-**1**.

Conclusion

We have developed a general method toward the total synthesis of angular triquinanes based on an α-carbonyl radical cyclization reaction, and a total synthesis of enantiomerically pure (−)-5-oxosilphiperfol-6-ene (**1**) has been accomplished. Gas chromatography analysis of racemic (±)-**1** and (−)-**1** with a chiral column clearly demonstrated that our product has high optical purity.

The single-crystal X-ray analysis of **22** provided additional evidence for the absolute stereochemistry of our chiral product (−)-**1**. This method is potentially useful for the total synthesis of more complex angular triquinanes and related natural products.

Experimental Section

General Method. Melting points were determined with an open capillary tube and were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 300 or 400 MHz. ^{13}C NMR were recorded at 100.6 MHz. Mass spectra were recorded by electron impact (70 eV) or FAB ionization. IR spectra were recorded on an FT-IR spectrometer using NaCl film with neat samples. Optical rotations were measured at room temperature (25 °C) on a JASCO DIP-360 polarimeter. Single-crystal X-ray analysis was performed on a Siemens SMART CCD diffractometer. Gas chromatographic analysis was performed with a chiral column (SGE 25QC2/CYDEX-B 0.25).

1-{(2*R)-1-Iodo-2-[4-(trimethylsilyl)-3-butynyl]cyclopentyl}-1-ethanone (6).** To magnesium turnings (336 mg, 13.8 mmol) in THF (2 mL) was added 1,2-dibromoethane (0.01 mL). The mixture was heated to reflux. To this mixture were added 4-chloro-1-trimethylsilyl-1-butyne (1.14 g, 7.12 mmol) and 1,2-dibromoethane (0.1 mL) in THF (10 mL) by a syringe pump (0.1 mL/min). After the addition, the reaction mixture was heated to reflux for an additional hour and cooled to −78 °C. CuI (1.34 g, 7.04 mmol) was added and the reaction mixture was stirred for 30 min. To this mixture was added **7** (313 mg, 2.85 mmol) in THF (8 mL) dropwise, followed by chlorotrimethylsilane (0.43 mL, 3.40 mmol) and triethylamine (0.4 mL, 2.89 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After filtration, the reaction mixture was washed with saturated Na_2CO_3 solution and brine and then dried ($MgSO_4$). Filtration and concentration gave crude product **8** (205 mg). The crude product was not purified and used for the next step.

To a solution of **8** (195 mg) and NaI (110 mg, 0.73 mmol) in anhydrous THF (10 mL) was added *m*-CPBA (134 mg, 0.77 mmol) in THF (4 mL) dropwise at 0 °C. After warming to room temperature, the reaction mixture was stirred for 30 min and then diluted with ether (10 mL). The solution was washed with water, saturated $Na_2S_2O_3$, saturated Na_2CO_3, and brine. The organic solution was dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 20:1) afforded a yellow liquid **6** (125 mg, 74% from **7**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.09 and 0.10 (2s, 9 H), 1.16−1.50 (m, 3 H), 1.65−1.81 (m, 2 H), 1.89−2.03 (m, 2 H), 2.07−2.43 (m, 4 H), 2.47 and 2.55 (2s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 0.05, 0.10, 18.2, 18.7, 20.5, 21.2, 26.5, 26.7, 28.1, 28.3, 29.4, 37.1, 38.1, 42.1, 47.0, 51.0, 65.0, 68.5, 84.6, 85.6, 105.8, 107.0, 202.69, 202.74; IR (neat) 2173, 1700, 1696 cm^{-1}; MS (FAB) *m*/*z* 363 (M^+ + H, 30), 347 (23), 147 (100); HRMS (FAB) calcd for $C_{14}H_{23}IOSi$ (M^+ + H) 363.0643, found 363.0637.

1-{(3a*S,6a*R**)-3-[(*E*)- or -(*Z*)-1-(Trimethylsilyl)methylidene]perhydro-3-pentalenyl}-1-ethanone (5).** A solution of **6** (821 mg, 2.27 mmol) in benzene (113 mL) was heated to reflux. To this refluxing solution was added a solution of tributyltin hydride (0.67 mL, 2.49 mmol) and AIBN (19 mg, 0.12 mmol) in benzene (31 mL) by a syringe pump over a period of 6 h. The reaction mixture was then refluxed for an additional hour and cooled to room temperature. After concentration, the residue was dissolved in Et_2O (20 mL). To the Et_2O solution was added saturated KF solution (10 mL) and the mixture stirred for 2 h. The organic layer was separated and the aqueous layer was extracted again by ether (20 mL × 2). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine. The solution was then dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 10:1) gave **5** (48 mg, ratio of isomers = 4:1, 81%). The major isomer was separated and purified by silica gel chromatography. Data for the major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 9 H), 1.34−1.63 (m, 5 H), 1.69−1.78 (m, 1 H), 1.98−2.07 (m, 1 H), 2.06 (s, 3 H), 2.3 (dt, J = 12.0 Hz, J = 7.6 Hz, 1 H), 2.37−2.54 (m, 2 H), 2.68−2.74 (m, 1 H), 5.29 (t, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −0.5, 25.7, 26.0, 31.7, 33.5, 33.6, 36.4, 47.4, 74.3, 121.0, 165.5, 208.8; IR (neat) 1700, 1615 cm^{-1}; MS (EI) *m*/*z* 236 (M^+, 47), 221 (100), 193 (37), 73 (44); HRMS calcd for $C_{14}H_{24}OSi$ 236.1596, found 236.1589.

1-{(3a*S,6a*R**)-3-[1-(Trimethylsilyl)-1,2-epoxymethylidene]perhydro-3-pentalenyl}-1-ethanone (9).** To a solution of the major isomer of **5** (132 mg, 0.56 mmol) in dichloromethane (8 mL) was added a solution of *m*-CPBA (106 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. After washing with saturated $NaHCO_3$ solution, the organic layer was dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 10:1) gave a mixture of two diastereomers, **9**, as a colorless liquid (106 mg, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s), 0.12 (s, 4.5 H), 1.18−1.29 (m, 1 H), 1.34−1.43 (m, 1 H), 1.48−1.72 (m, 5.5 H), 1.87−2.26 (m, 3 H), 2.10 (s, 1.5 H), 2.15 (s, 1.5 H), 2.40−2.47 (m, 0.5 H), 2.61−2.68 (m, 0.5 H), 2.84 (q, J = 6.8 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −2.4, −2.2, 26.3, 26.6, 26.7, 27.7, 29.0, 30.6, 30.7, 31.2, 33.5, 33.6, 34.4, 34.7, 46.9, 48.5, 52.3, 52.9, 69.2, 69.9, 70.0, 73.6, 207.3, 210.1; IR (neat) 1730, 1701, 1250 cm^{-1}; MS (El), *m*/*z* 252 (M^+, 2), 209 (100), 193 (11), 119 (27), 91 (25), 73 (59); HRMS calcd for $C_{14}H_{24}O_2Si$ 252.1545, found 252.1556.

(3a*S,5a*R**,8a*S**)-1,3a,4,5,5a,6,7,8-Octahydrocyclopenta[*c*]pentalen-1-one (3).** To compound **9** (91 mg, 0.37 mmol) was added formic acid (98%, 2.2 mL). The reaction mixture was stirred for 50 min and then diluted with Et_2O (20 mL). The organic layer was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). Concentration gave crude product **4** (63 mg).

To a mixture of 5% KOH (5 mL), Bu_4NOH (0.2 mL), and THF (10 mL) were added a solution of **4** (63 mg) in Et_2O (5 mL). The reaction mixture was heated to reflux for 16 h. After cooling to room temperature, the reaction mixture was poured into water (5 mL). The resulting mixture was extracted with Et_2O (10 mL × 2). The organic layer was dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 7:1) afforded **3** as a colorless liquid (15 mg, 26% from **9**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31−1.34 (m, 1 H), 1.49−1.58 (m, 2 H), 1.59−1.63 (m, 2 H), 1.68−1.77 (m, 2 H), 1.88−1.94 (m, 2 H), 2.01−2.08 (m, 1 H), 2.33−2.36 (m, 1 H), 2.88−2.91 (m, 1 H), 6.09 (dd, J = 5.6 Hz, J = 1.3 Hz, 1 H), 7.41 (dd, J = 5.6 Hz, J = 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.9, 28.1, 30.2, 33.2, 35.7, 50.1, 56.1, 65.9, 133.4, 165.8, 214.7; MS (EI) *m*/*z* 162 (M^+, 50), 12 (100); HRMS calcd for $C_{11}H_{14}O$ 162.1045, found 162.1052.

Ethyl (3*R*)-3-Methyl-1-cyclopentene-1-carboxylate (13). To a solution of **14** (6.59 g, 35.8 mmol) in methanol (53 mL) was added *t*-BuOCl (4.6 mL, 40.7 mmol) dropwise in a salt−ice bath. The mixture was stirred for 1 h and kept in the refrigerator at 0 °C for 40 h. After warming to room temperature, the mixture was stirred for additional 4 h. Concentration and distillation under reduced pressure (0.06 mmHg, 60 °C) yielded a colorless liquid (7.7 g). This liquid (7.7 g, 35.2 mmol) was dissolved in xylene (53 mL). To this solution were added anhydrous Na_2CO_3 (8.3 g) and glass powder (32 g). The reaction mixture was heated to reflux for 40 h. Filtration, concentration and silica gel chromatography (hexanes−ethyl acetate, 20:1) gave **13** as a colorless liquid (4.38 g, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (d, J = 6.4 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.40−1.49 (m, 1 H), 2.10−2.20 (m, 1 H), 2.44−2.53 (m, 1 H), 2.55−2.64 (m, 1 H), 2.82−2.92 (m, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 6.62 (q, J = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2, 19.8, 30.9, 31.9, 40.6, 60.0, 135.4, 148.6, 165.6; MS (EI) *m*/*z* 154 (M^+, 8), 139 (2), 125 (4), 109 (19), 81 (100); $[\alpha]_D$ = 101.2 (*c* = 1.1, $CHCl_3$).

Ethyl (2*S*,3*R*)-2-(3-Hexynyl)-1-iodo-3-methylcyclopentane-1-carboxylate (12). To a suspension of magnesium powder (110 mg, 4.52 mmol) in THF (6 mL) was added 1,2-dibromoethane (0.01 mL). The mixture was stirred at room temperature for 20 min and then cooled to 0 °C. To this mixture was added 1-bromo-3-hexyne (365 mg, 2.22 mmol) in

THF (1 mL) over a period of 3 h by a syringe pump and the mixture was stirred for an additional 30 min. The mixture was cooled to −78 °C and CuI (108 mg, 0.56 mmol) was added. After stirring for 30 min, compound **13** (100 mg, 0.65 mmol) in THF (1 mL) was added dropwise followed by chlorotrimethylsilane (0.14 mL, 0.67 mmol) and triethylamine (0.18 mL, 1.3 mmol). The mixture was allowed to warm to room temperature and stirred for 12 h. This reaction mixture was added dropwise to a solution of NaI (446 mg, 2.98 mmol) and *m*-CPBA (87%, 589 mg, 2.97 mmol) in THF (14 mL) at 0 °C. After warming to room temperature, the mixture was stirred for 2 h and then diluted with Et_2O (20 mL). The mixture was washed with water, saturated $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, and brine and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 40:1) gave **12** (142 mg, 60%) as a mixture of two diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81−0.93 (m, 1 H), 1.03−1.17 (m, 5 H), 1.21−1.39 (m, 4 H), 1.50−1.58 (m, 1 H), 1.69−2.01 (m, 3 H), 2.06−2.29 (m, 6 H), 2.34−2.39 (m, 1 H), 4.13−4.20 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.3, 13.7, 13.8, 14.2, 14.3, 17.2, 17.7, 20.7, 21.9, 31.50, 31.7, 33.0, 37.8, 38.3, 39.0, 42.6, 42.6, 48.2, 55.0, 58.8, 59.6, 61.7, 61.8, 78.6, 79.0, 81.8, 82.2, 171.5, 172.0; IR (neat) 1724, 1246 cm^{-1}; MS (FAB) *m*/*z* 363 (M^+ + H, 28), 289 (36), 235 (100), 161 (83); HRMS (FAB) calcd for $C_{15}H_{23}IO_2$ 363.0823 (M^+ + H), found 363.0840.

Ethyl (1*R*,3a*S*,6a*S*)-1-Methyl-4-[(*E*)-propylidene]perhydro-3a-pentalene-carboxylate and Ethyl (1*R*,3a*S*,6a*S*)-1-Methyl-4-[(*Z*)-propylidene]perhydro-3a-pentalenecarboxylate (11). A solution of **12** (89 mg, 0.25 mmol) in benzene (13 mL) was heated to reflux. To this solution was added slowly Bu_3SnH (0.08 mL, 0.29 mmol) and AIBN (4.6 mg, 0.03 mmol) in benzene (3.6 mL) by a syringe pump over a period of 6 h. The mixture was refluxed for an additional hour. After cooling to room temperature, benzene was removed under reduced pressure. The residue obtained was dissolved in Et_2O (8 mL) and saturated KF solution was added. The mixture was stirred at room temperature for 2 h. After filtration, the filtrate was extracted with Et_2O (5 mL × 2). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 40:1) gave **11** as a colorless liquid (42 mg, 73%). Compound **11** was found to be a mixture of geometrical isomers (3:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.4 Hz, 2.25 H), 0.90 (t, J = 7.4 Hz, 0.75 H), 0.94 (d, J = 6.6 Hz, 0.75 H), 0.95 (d, J = 6.6 Hz, 2.25 H), 1.16−1.30 (m, 0.75 H), 1.19 (t, J = 6.8 Hz, 0.75 H), 1.20 (t, J = 6.8 Hz, 2.25 H), 1.41−2.07 (m, 8 H), 2.21−2.64 (m, 3 H), 2.76 (ddd, J = 13.0 Hz, J = 7.2 Hz, J = 2.2 Hz, 0.75 H), 4.03−4.16 (m, 2 H), 5.14 (tt, J = 7.2 Hz, J = 1.8 Hz, 0.75 H), 5.24 (tt, J = 7.2 Hz, J = 2.4 Hz, 0.25 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9, 14.0, 14.1, 14.9, 18.7, 19.2, 22.4, 22.9, 28.5, 28.9, 33.6, 34.7, 34.9, 36.0, 36.2, 36.9, 40.46, 40.54, 57.7, 60.2, 60.3, 61.7, 61.8, 64.0, 123.6, 124.0, 147.3, 147.4, 172.6, 177.4; IR (neat) 1724, 1242 cm^{-1}; MS (EI) *m*/*z* 236 (M^+, 15), 208 (4), 163 (100); HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1777.

{(1R,3aS,6aS)-1-Methyl-4-[(*E*)-propylidene]perhydro-3-pentalenyl}methanol and {(1R,3aS,6aS)-1-Methyl-4-[(*Z*)-propylidene]perhydro-3-pentalenyl}methanol (16). To a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in Et_2O (5 mL) was added a solution of **11** (130 mg, 0.55 mmol) in Et_2O (2 mL). The mixture was heated to reflux for 3 h. After cooling to room temperature, the reaction mixture was quenched with 5% HCl solution (3 mL). The mixture was extracted with Et_2O (5 mL × 2). The organic layer was washed with brine and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 5:1) gave **16** as a colorless liquid (86 mg, 80%). Compound **16** was found to be a mixture of *E* and *Z* isomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 2.25 H), 0.93 (t, J = 7.4 Hz, 0.75 H), 0.95 (d, J = 6.8 Hz, 0.75 H), 0.96 (d, J = 6.8 Hz, 2.25 H), 1.14−1.26 (m, 1 H), 1.36−1.44 (m, 1 H), 1.49−1.92 (m, 7 H), 1.97−2.08 (m, 2 H), 2.25−2.47 (m, 2 H), 3.44 (AB, J = 10.6 Hz, 1.5 H), 3.63 (AB, J = 10.6 Hz, 0.5 H), 5.14 (tt, J = 7.2 Hz, J = 2.4 Hz, 0.25 H), 5.26 (tt, J = 7.6 Hz, J = 2.0 Hz, 0.75 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.4, 14.8, 18.9, 19.2, 22.2, 22.9, 27.9, 28.0, 28.8, 35.0, 35.2, 35.5, 36.1, 36.4, 40.5, 41.0, 56.0, 58.7, 59.0, 59.7, 69.15, 69.19, 123.1, 124.6, 147.5, 148.5; IR (neat) 3350 cm^{-1}; MS (EI) *m*/*z* 194 (M^+, 3), 176 (8), 163 (75), 147 (15), 57 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1671, found 194.1676.

1-[(3a*S*,4*R*,6a*S*)-6a-(Hydroxymethyl)-4-methylperhydro-1-pentalenyl]-1-propanone (18). To a solution of **16** (42 mg, 0.22 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (87%, 85 mg, 0.43 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After being washed with saturated $NaHCO_3$ solution, the organic layer was dried ($MgSO_4$). Concentration gave crude epoxide **17** (96 mg). To a solution of **17** (96 mg) in benzene (2 mL) was added BF_3·OEt_2 (0.06 mL, 0.49 mmol) at room temperature. The reaction mixture was stirred for 30 min and then washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 3:1) gave **18** as a yellowish liquid (26 mg, 57%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88−1.12 (m, 1 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H), 1.36−1.42 (m, 2 H), 1.44−1.56 (m, 2 H), 1.63−1.66 (m, 1 H), 1.72−1.76 (m, 1 H), 1.86−1.93 (m, 3 H), 2.40−2.62 (m, 3 H), 3.34 (ABd, J = 10.6 Hz, J = 3.2 Hz, 1 H), 3.54 (ABd, J = 10.6 Hz, J = 6.4 Hz, 1 H), 3.72−3.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 7.3, 19.1, 27.9, 29.1, 31.9, 34.4, 35.9, 42.3, 55.7, 57.9, 60.2, 70.1, 215.5; IR (neat) 3417, 1695 cm^{-1}; MS (EI) *m*/*z* 210 (M^+, 2), 192 (12), 163 (20), 135 (100); HRMS calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1631.

(3a*R*,5a*S*,6*R*,8a*S*)-2,6-Dimethyl-3,3a,4,5,5a,6,7,8-octahydrocyclopenta[*c*]pentalen-3-one (19). To a mixture of PCC (630 mg, 2.92 mmol) and a small amount of Celite (0.5 g) in CH_2Cl_2 (20 mL) was added **18** (309 mg, 1.46 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. Filtration through a short column of Florisil and concentration gave **10** as a colorless liquid (279 mg). Without further purification, compound **10** was used for the next step.

To a mixture of 5% aqueous KOH (20 mL), Bu_4NOH (0.02 mL), and THF (40 mL) was added **10** (279 mg) in Et_2O (20 mL) dropwise. The mixture was heated to reflux for 16 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL). The mixture was extracted with Et_2O (30 mL × 3). The combined organic layer was washed with brine and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 10:1) gave **19** as a colorless liquid (198 mg, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J = 6.4 Hz, 3 H), 1.19−1.39 (m, 2 H), 1.46−1.51 (m, 1 H), 1.55−1.72 (m, 3 H), 1.67 (d, J = 1.6 Hz, 3 H), 1.77−1.97 (m, 4 H), 2.22−2.25 (m, 1 H), 7.05 (q, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.9, 20.0, 27.85, 27.88, 35.4, 35.9, 39.4, 56.9, 59.1, 62.0, 138.6, 164.9, 213.1; IR (neat) 1702, 1634 cm^{-1}; MS (EI) *m*/*z* 190 (M^+, 100), 175 (16), 162 (36), 135 (68), 108 (78); HRMS calcd for $C_{13}H_{18}O$ 190.1358, found 190.1367; $[\alpha]_D$ = −72.8 (*c* = 0.52, $CHCl_3$).

Dinitrophenylhydrazone (22). To 2,4-dinitrophenylhydrazine (125 mg) suspended in CH_3OH (5 mL) was added concentrated H_2SO_4 (0.3 mL). To this solution was added a solution of **19** (50 mg, 0.026 mmol) in methanol (2 mL) and the reaction mixture was heated to 60 °C. The orange precipitate formed was filtered and washed with aqueous CH_3OH. The crude product was recrystallized (EtOH) to yield **22** (82 mg, 84%) as orange needles: mp = 127−128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, J = 6.4 Hz, 3 H), 1.15−1.20 (m, 1 H), 1.60−1.90 (m, 8 H), 1.92 (d, J = 2 Hz, 3 H), 2.11−2.40 (m, 2 H), 3.82 (d, J = 9.6 Hz, 1 H), 6.29 (br, 1 H), 7.94 (d, J = 10.4 Hz, 1 H), 8.26 (d, J = 10.4 Hz, 1 H), 9.03 (s, 1 H), 11.13 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.0, 19.7, 27.5, 29.8, 34.7, 36.5, 39.0, 51.8, 57.8, 66.9, 116.2, 123.6, 129.8, 136.0, 137.3, 144.9, 152.0, 169.8; IR (KBr) 3308, 1621, 1591 cm^{-1}; MS (EI) *m*/*z* 370 (M^+, 39), 319 (100), 318 (36), 228 (18), 226 (3); HRMS calcd for $C_{19}H_{22}O_4N_4$ 370.1641, found 370.1658

(3a*R*,5a*S*,6*R*,8a*S*)-2,3a,6-Trimethyl-3,3a,4,5,5a,6,7,8-octahydrocyclopenta[*c*]pentalen-3-one (20) To a solution of diisopropylamine (0.25 mL, 1.78 mmol) in THF (3 mL) was added *n*-BuLi (2.1 M in hexane, 0.74 mL, 1.55 mmol) at −20 °C. After warming to 0 °C, the mixture was stirred for 30 min and then was cooled to −78 °C. To this solution was added

compound **19** (97.0 mg, 0.51 mmol) in THF (0.5 mL) dropwise. The mixture was allowed to warm to 0 °C and was stirred for 1 h at 0 °C. The mixture was cooled to −78 °C again and CH_3I (0.09 mL, 1.45 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. A saturated solution of NH_4Cl (2 mL) was added to quench the reaction. The mixture was extracted with Et_2O (10 mL × 2). The ether layer was washed with brine and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 10:1) gave **20** as a colorless liquid (76 mg, 82%) along with some unreacted **19** (9 mg, 9%). Data for **20**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.4 Hz, 3 H), 0.98 (s, 3 H), 1.21−1.49 (m, 4 H), 1.57−1.68 (m, 2 H), 1.71 (d, J = 1.4 Hz, 3 H), 1.73−1.84 (m, 2 H), 1.95−2.00 (m, 1 H), 7.02 (q, J = 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.0, 19.4, 20.8, 26.2, 30.6, 35.4, 36.1, 39.2, 57.7, 58.5, 64.1, 136.4, 165.1, 215.7; IR (neat) 1700, 1637 cm^{-1}; MS (EI) m/z 204 (M^+, 100), 189 (37), 176 (24), 135 (26); HRMS calcd for $C_{14}H_{20}O$ 204.1514, found 204.1519; $[\alpha]_D$ = −38.2 (c = 1.3, $CHCl_3$).

(−)-5-Oxosilphiperfol-6-ene (1). To a solution of CuI (380 mg, 2.0 mmol) in Et_2O (16 mL) was added CH_3Li (0.9 M in Et_2O, 4.4 mL, 3.96 mmol) dropwise at 0 °C. After stirring for 5 min, compound **20** (61 mg, 0.3 mmol) in Et_2O (0.6 mL) and chlorotrimethylsilane (0.15 mL, 1.19 mmol) were added dropwise in sequence. The mixture was stirred at 0 °C for 2 h and then quenched with saturated $NaHCO_3$ solution (15 mL). The organic layer was separated and washed with brine and dried ($MgSO_4$). Concentration gave crude product **21**, which was used for the next step without further purification.

To a solution of **21** (89 mg) and freshly recrystallized DDQ (118 mg, 0.52 mmol) in benzene (7.5 mL) was added *N*,*O*-bis(trimethylsilyl)-2,2,2-trifluoroacetamide (BSTFA) (0.2 mL, 0.75 mmol). The mixture was heated to 45 °C and stirred for 48 h. After cooling to room temperature, the mixture was diluted with Et_2O (15 mL), washed with saturated $NaHCO_3$, and dried ($MgSO_4$). Concentration and silica gel chromatography (hexanes−ethyl acetate, 10:1) gave **1** as a colorless solid (25 mg, 38% from **20**): mp = 50−51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.0 Hz, 3 H), 0.96 (s, 3 H), 1.08−1.18 (m, 1 H), 1.20−1.44 (m, 3 H), 1.49−1.63 (m, 2 H), 1.62 (q, J = 1.2 Hz, 3 H), 1.65−1.76 (m, 2 H), 1.81−1.88 (m, 1 H), 1.94 (q, J = 1.2 Hz, 3 H), 1.95−1.99 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.2, 13.1, 19.0, 21.1, 25.9, 28.7, 35.0, 36.6, 39.4, 57.6, 57.9, 67.1, 133.1, 173.7, 214.2; IR (neat) 1698, 1644 cm^{-1}; MS (EI) m/z (rel int) 218 (M^+, 100), 203 (14), 190 (7), 175 (9), 163 (25), 136 (39); HRMS calcd for $C_{15}H_{22}O$ 218.1671, found 218.1675; $[\alpha]_D$ = −82.2 (c = 1.3, $CHCl_3$). Gas chromatography of **1** with a chiral column (SGE 25QC2/CYDEX-B 0.25; temperature, 125 °C isothermal) showed that product **1** is of high enantiomeric purity (>99%, Figure 1).

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Supporting Information Available: X-ray crystallographic data and molecular drawing of compound **22**, ^{1}H NMR spectra of **1**, **3**, **5**, **6**, **9**, **11**−**13**, **16**, **18**−**22**, and ^{13}C NMR spectra of **1**, **3**, **5**, **6**, **9**, **11**−**13**, **16**, **18**−**20** (37 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 ordering information.

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