Stereocontrolled Total Synthesis of α- and β-Santonin

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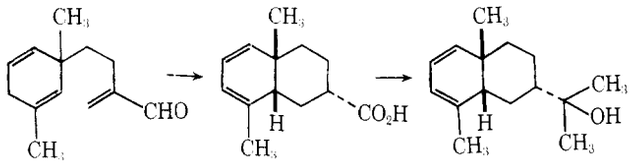
A total synthesis of racemic α- and β-santonin is described. The synthetic sequence involves reduction–alkylation of *m*-toluic acid with lithium in ammonia followed by methyl iodide. Homologation of the resulting 1-methyl-1,4-dihydro-*m*-toluic acid was effected by reduction using lithium aluminum hydride, oxidation with *N*-chlorosuccinimide–dimethyl sulfide reagent, and condensation of the resulting aldehyde with triethyl phosphonoacetate to give the acrylic ester derivative. Reduction with lithium in ammonia–ethanol yielded the propanol-substituted 1,4-dihydro-*m*-xylene, which was transformed to the bromide and alkylated with the lithium salt of the monosulfoxide of formaldehyde diethyl thioacetal. Treatment with acid effected cyclization via the butanal, affording 4a,8-dimethyl-1,2,3,4,4a,8a-hexahydronaphthalen-1-ol (**9**). Oxidation to the ketone and alkylation using ethyl iodoacetate gave the expected keto ester **11**, which was reduced to a mixture of diols. These were separated and the trans isomer was oxidized to the trans lactone **14** using silver carbonate on Celite. Alkylation with methyl iodide yielded the β-methyl isomer **15**, which could be epimerized to the more stable α isomer **16**. Photooxygenation of each of these isomers afforded β-santonin (**17**) and α-santonin (**18**), along with the corresponding endoperoxides **19** and **20**.

We recently described an efficient synthetic sequence leading to cis-fused hexahydronaphthalene derivatives such as IV (Scheme I).[1] The approach involved reduction–alkylation of *m*-toluic acid to the 1,4-dihydrotoluic acid derivative I, reduction to the 1,4-dihydroxylene II, oxidation to the butyraldehyde III, and acid-catalyzed cyclization to the bicyclic product IV.

A variant of the ring-closure step employing the α-methylene butyraldehyde V resulted in a total synthesis of racemic occidentalol VII via the acid VI.[1]

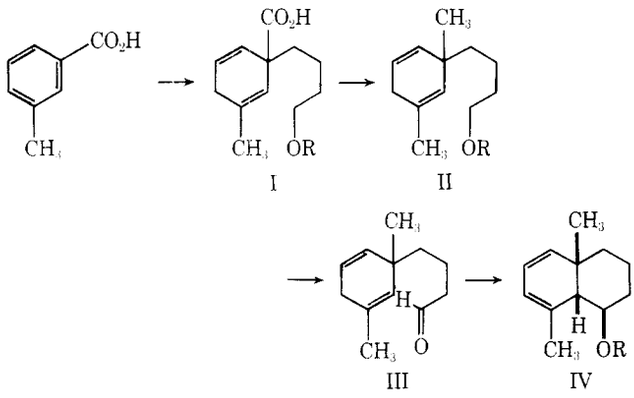


V VI VII

We now describe extensions and variations of this basic synthetic approach as applied to a new stereocontrolled total synthesis of the historically important eudesmanolide α-santonin (**18**) and its less stable epimer β-santonin (**17**).[2]

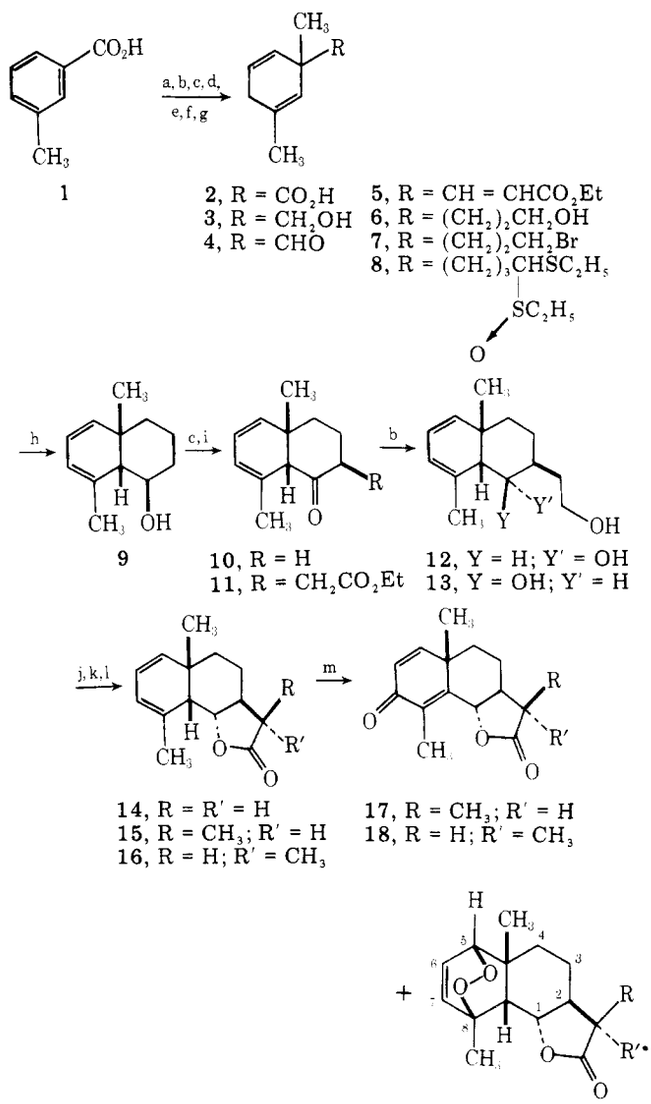
Our first departure from the previous synthesis of the key intermediate, alcohol **9**, involved reduction–*methylation* of *m*-toluic acid to the 1,4-dihydrotoluic acid **2** followed by side-chain introduction via the carboxylic acid substituent. The most satisfactory sequence examined thus far involves reduction with lithium aluminum hydride to the alcohol **3** followed by oxidation with dimethyl sulfide–*N*-chlorosuccinimide to aldehyde **4**.[3] Condensation with triethyl phosphonoacetate gave the acrylate **5** which was reduced to the alcohol

Scheme I



I II III IV

Chart I[a]



1

2, R = CO_2H
3, R = CH_2OH
4, R = CHO
5, R = $CH=CHCO_2Et$
6, R = $(CH_2)_2CH_2OH$
7, R = $(CH_2)_2CH_2Br$
8, R = $(CH_2)_3CHSC_2H_5$ (SC_2H_5, O)

9

10, R = H
11, R = CH_2CO_2Et

12, Y = H; Y′ = OH
13, Y = OH; Y′ = H

14, R = R′ = H
15, R = CH_3; R′ = H
16, R = H; R′ = CH_3

17, R = CH_3; R′ = H
18, R = H; R′ = CH_3

19, R = CH_3; R′ = H
20, R = H; R′ = CH_3

[a] (a) Li, NH_3, CH_3I; (b) $LiAlH_4$; (c) Me_2S,NCS, Et_3N; (d) NaH, $(EtO)_2POCH_2CO_2Et$; (e) Li, NH_3, EtOH; (f) Ph_3P, NBS; (g) $EtSCH_2S(\rightarrow O)Et$, BuLi; (h) $HClO_4$, H_2O; (i) $(i\text{-Pr})_2$-NLi, ICH_2CO_2Et; (j) Ag_2CO_3–Celite, (k) $(i\text{-Pr})_2NLi$, CH_3I; (l) $(i\text{-Pr})_2NLi$; (m) O_2, hematoporphyrin, *hν*.

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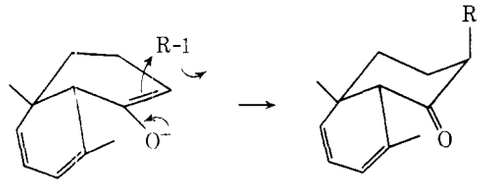
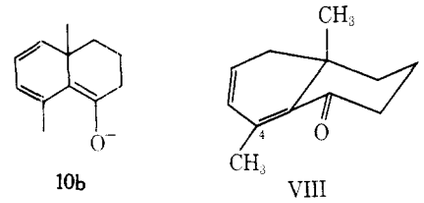
6 with lithium in ammonia–ethanol. The derived bromide 7 afforded the thioacetal monosulfoxide 8 upon treatment with the lithio derivative of ethyl thioethoxymethyl sulfoxide.[4] Treatment of this sulfoxide derivative with perchloric acid led directly to alcohol **9**, presumably via the derived butyraldehyde. The entire sequence to this point can be effected in 40% overall yield.[5]

Oxidation of alcohol **9** using dimethyl sulfide–*N*-chlorosuccinimide gave ketone **10**. This ketone, upon treatment with lithium diisopropylamide and ethyl iodoacetate, yielded the expected kinetic alkylation product, keto ester **11**.

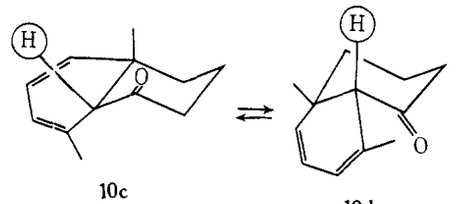
Our expectation of this reaction outcome was based on steric and stereoelectronic considerations. Accordingly, the concave geometry of dienone **10** and any intrinsic preference for axial alkylation should favor attack on the enolate **10a** from the convex (top) face as shown below.[6] We were not particularly concerned about formation of the bridgehead enolate **10b** and/or isomerization of ketone **10** for two reasons. In the first place, the ring fusion α-hydrogen of dienone **10** cannot assume a favorable perpendicular orientation to the β,γ double bond *and* the ketone carbonyl simultaneously (see **10c** ⇆ **10d**). Hence, we would not expect any enhanced kinetic acidity for this hydrogen.[7] Secondly, the *cis*-fused dienone **10** should be more stable than the corresponding trans-fused isomer or the possible conjugated enone isomers. In the trans-fused dienone, compression of the diequatorial dihedral angle by the planar butadiene bridge would introduce considerable strain to the cyclohexanone ring. Conjugation of the double bond(s), on the other hand (e.g., VIII), would force the angular methyl group into an axial orientation and would also bring the C-4 vinyl methyl and ketone oxygen into close proximity.[8]



10a 11 (R = CH_2CO_2Et)



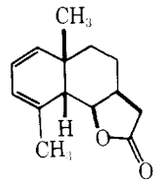
10b VIII



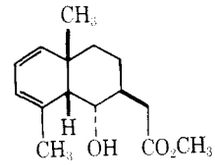
10c 10d

Concordant with the foregoing analysis, we found that treatment of dienone **10** with potassium *tert*-butoxide in *tert*-butyl alcohol gave mainly unchanged dienone and a small amount of conjugated ketone(s).

Attempts at selective reduction of the ketonic carbonyl of keto ester **11** using borohydride reagents met with limited success. Product mixtures consisting of cis lactone **21** and, presumably, hydroxy ester **22** were contaminated by difficultly separable by-products. While these appeared to arise from ester reduction, positive identification could not be made. Reductions with lithium aluminum hydride, on the other hand, gave only the two easily separable diols **12** and **13**. At −96 °C the desired trans isomer **12** predominated, whereas at 0 °C the cis isomer **13** was slightly favored. Oxidation of diol **12** with silver carbonate on Celite yielded the trans lactone **14**.[9]



21



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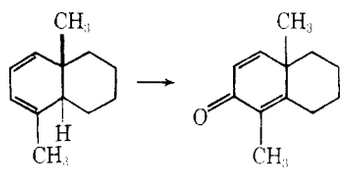
Molecular models indicate that lactone **14** should undergo enolate methylation from the convex face, leading to the thermodynamically less stable epimer **15**. In fact, treatment of lactone **14** with 1 equiv of lithium diisopropylamide followed by methyl iodide gave a single product (**15**) subsequently converted through sensitized photochemical oxygenation to β-santonin (**17**).[10] Epimerization of lactone **15** with lithium diisopropylamide afforded a new lactone (**16**) which was similarly oxidized to α-santonin (**18**). In each case, a significant amount of endoperoxide (**19**, isolated; **20**, presumed) was produced. Changes in solvent and sensitizer did not markedly influence the ratio of the two product types.[10]

Interestingly, oxygenation of the trans-fused diene **23** affords the cyclohexadienone product **24** in high yield.[11] Evidently, the ring fusion hydrogen possesses the ideal geometric orientation for abstraction in this case. We had hoped that the trans-fused lactone would constrain the cis-fused dienes **15** and **16** into a similar conformational arrangement. However, the alignment would appear less favorable here, judging from the lowered efficiency of the ene vs. 4 + 2 addition process. As expected, the cis-fused diene lactone **21** gave only the endoperoxide product upon sensitized oxygenation. Here the ring fusion hydrogen is nearly coplanar with the diene system and ene participation is thereby rendered unfavorable. Thus, the *trans*-fused lactone of dienes **15** and **16** exerts some conformational control in the desired sense, but the degree falls short of expectation.



23 24

Experimental Section[12]

1-Carboxy-1,3-dimethylcyclohexa-2,5-diene (2). A solution of 50.0 g (0.368 mol) of *m*-toluic acid in 1.5 L of ammonia and 100 mL of tetrahydrofuran was treated with lithium wire until the blue color persisted. When lithium addition was complete the reaction was stirred for 15 min and then 33.0 mL (0.525 mol) of methyl iodide was added. At this point, the mixture underwent a color change from red to white. Stirring was continued for 15 min and then ammonium chloride was added to quench the reaction. Evaporation of ammonia, acidification with concentrated hydrochloric acid, and isolation with ether afforded 57.0 g (101%) of the dienic acid **2** as a viscous oil: IR (film) 1705, 1260, 1115, 930, 735 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.72 (br s, vinyl H, 2 H), 5.46 (m, vinyl H, 1 H), 2.51 (br s, allylic CH_2–), 1.72 (s, vinyl CH_3), 1.29 (s, quaternary CH_3) ppm.

1-Hydroxymethyl-1,3-dimethylcyclohexa-2,5-diene (3). To a slurry of 28.0 g (0.736 mol) of lithium tetrahydridoaluminate in 1.0 L of ether at 0 °C was slowly added a solution of 48.0 g (0.318 mol) of the dienic acid **2** in 400 mL of ether. The reaction was allowed to stir for an additional hour after the addition was complete. After the successive addition of 28.0 mL of water, 56.0 mL of 10% sodium hydroxide, and 56.0 mL of water, the precipitated salts were filtered and the solvent was removed to afford, after distillation, 36.5 g (83%) of the alcohol **3**: bp 48.5 °C (0.5 Torr); IR (film) 3400, 1690, 1645, 1040,

930, 910, 835, 720 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.83 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3.5 Hz, vinyl H), 5.41 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz, 1 H), 5.12 (m, vinyl H, 1 H), 3.27 (s, $-CH_2O-$), 2.56 (br s, allylic $-CH_2-$), 1.72 (d, J = 1.2 Hz, vinyl CH_3), 0.96 (s, quaternary CH_3) ppm.

1-Formyl-1,3-dimethylcyclohexa-2,5-diene (4). To a flask fitted with a low-temperature thermometer was added 600 mL of methylene chloride and 144 g (0.109 mol) of *N*-chlorosuccinimide. The slightly turbid solution was cooled to 0 °C and treated with 10.6 mL (0.145 mol) of dimethyl sulfide which resulted in the formation of a flocculent white precipitate.[3] The mixture was cooled to −25 °C and a solution of 10.0 g (0.072 mol) of the alcohol **3** in 50.0 mL of methylene chloride was slowly added to maintain the temperature below −22 °C. The mixture was stirred at −25 °C for an additional 2 h, and then 18.0 mL of triethylamine was added. The mixture was poured into water and isolated with methylene chloride to afford 9.0 g (92%) of the aldehyde **4** after distillation: bp 72 °C (17.0 Torr); IR (film) 2700, 1725, 1380, 1020, 930, 910, 825, 715 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.95 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.41 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz), 5.12 (m, 1 H), 2.62 (br s, allylic CH_2-), 1.76 (s, vinyl CH_3), 1.18 (s, quaternary CH_3) ppm. The 2,4-dinitrophenylhydrazone, mp 145–146 °C, was prepared.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.8; H, 5.10; N, 17.92.

Ethyl (*E*)-3-(1,3-Dimethylcyclohexa-2,5-dienyl)propenoate (5). To a slurry of 2.6 g (61.5 mmol, 51% oil dispersion) of sodium hydride in 250 mL of dimethoxyethane was slowly added 12.0 mL (61.0 mmol) of triethyl phosphonoacetate.[13] When the addition was complete, the mixture was stirred for an additional 15 min. A solution of 8.0 g (58.5 mmol) of aldehyde **4** in 50.0 mL of dimethoxyethane was then slowly added. The reaction was then brought to reflux for 1 h. Isolation with ether after addition of water afforded 11.9 g (93%) of the propenoate **5**: bp 130 °C (0.6 Torr); IR (film) 1720, 1645, 1310, 1250, 1160, 1175, 1040, 990, 935, 860, 835, 720, 705 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.83 (half of AB q, $J_{1,2}$ = 16 Hz, 1 H), 5.66 (half of AB q, $J_{1,2}$ = 16 Hz, 1 H), 5.76 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz, 1 H), 5.44 (half of AB q, split into m, $J_{5,6}$ = 10 Hz), 4.15 (t, J = 7.5 Hz, $-OCH_2-$), 2.50 (br s, allylic CH_2-), 1.69 (s, vinyl CH_3), 1.26 (t, J = 7.5 Hz, ethyl CH_3), 1.16 (s, quaternary CH_3) ppm.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.96; H, 8.84.

1-(3-Hydroxypropyl)-1,3-dimethylcyclohexa-2,5-diene (6). A solution of 10.9 g (50.0 mmol) of propenoate **5** in 1.0 L of ammonia, 100 mL of ether, and 150 mL of ethanol was treated with lithium wire until the blue color persisted. Ammonium chloride was then added and the ammonia was allowed to evaporate. Isolation with ether and distillation (bp 70–71 °C, 0.1 Torr) afforded 7.5 g (90.7%) of alcohol **6**: IR (film) 3350, 1690, 1645, 1060, 930, 890, 835, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.65 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.32 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, $J_{4,6}$ = 2 Hz), 5.05 (m, vinyl H), 3.45 (m, $-CH_2O-$), 2.48 (m, allylic $-CH_2-$), 1.18 (s, vinyl $-CH_3$), 0.98 (s, quaternary $-CH_3$) ppm.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.42; H, 10.91. Found: C, 79.69; H, 10.82.

1-(3-Bromopropyl)-1,2-dimethylcyclohexa-2,5-diene (7). To a mechanically stirred solution of 2.0 g (12.0 mmol) of alcohol **6**, 3.4 g (13.0 mmol) of triphenylphosphine, and 20.0 mL of benzene was slowly added 2.22 g (12.5 mmol) of *N*-bromosuccinimide (exothermic).[14] When the addition was complete, stirring was continued for 15 min, 100 mL of hexane was added to precipitate succinimide and triphenylphosphine oxide, and the mixture was filtered. Removal of solvent and distillation (bp 105 °C, 0.15 Torr) afforded 2.52 g (91.5%) of the bromide **7**: IR (film) 1275, 1240, 1210, 1090, 1015, 925, 740, 720, 690 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.65 (half of AB q, split into t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.20 (half of AB q, split into q, $J_{5,6}$ = 10 Hz, J_q = 2 Hz), 5.05 (m, vinyl H), 3.25 (t, J = 7 Hz, $-CH_2Br$), 2.48 (m, allylic $-CH_2-$), 1.69 (s, vinyl $-CH_3$), 0.98 (s, quaternary CH_3) ppm.

1-(4-Ethylthio-4-ethylsulfinylbutyl)-1,3-dimethylcyclohexa-2,5-diene (8). A solution of 4.70 g (31.3 mmol) of ethylthioethylsulfinylmethane in 40.0 mL of dimethoxyethane at 0 °C was treated with 13.8 mL of 2.29 M *n*-butyllithium in hexane.[4] After the reaction had stirred for 30 min, 7.0 g (31.3 mmol) of the bromide was added. The ice bath was removed and the solution was stirred overnight at room temperature. Isolation with ether afforded 8.67 g (97.7%) of a viscous yellow oil as a mixture of two diastereomers as evidenced by LC and GC. This material was used without further purification since it could not be distilled: IR (film) 1830, 1260, 1050, 1015, 965, 925, 835, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, d of t, $J_{5,6}$ = 10 Hz, $J_{4,5}$ = 3 Hz), 5.35 (H-6, br d, $J_{5,6}$ = 10 Hz), 5.10 (H-2, br s), 1.69 (vinyl CH_3), 0.99 (angular CH_3) ppm.

1β-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphthalene (9). Perchloric acid was added to a solution of 8.67 g (28.8 mmol) of the sulfoxide **8** in 125 mL of ethyl acetate at room temperature. After stirring for 30 min, the mixture was poured into sodium bicarbonate solution and isolated with ether to afford 3.87 g (76.5%) of the alcohol **9** after short-path distillation (bp 100 °C, 0.1 Torr). An analytical sample, mp 66–68 °C, was secured by recrystallization from hexane: IR (film) 3355, 1650, 1590, 1365, 1060, 1050, 1015, 935, 885, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.26 (H-7, d, J = 9.7 Hz), 3.56 (H-1, d of t, J = 10.5, 3.0 Hz), 1.99 (vinyl CH_3, br s), 0.88 (angular CH_3) ppm.

4aβ,8-Dimethyl-3,4,4a,8aβ-tetrahydro-1(2*H*)-naphthalenone (10). To a flask fitted with a low-temperature thermometer and nitrogen inlet was added 200 mL of dichloromethane and 6.30 g (47.3 mmol) of *N*-chlorosuccinimide. The solution was cooled to 0 °C and treated with 4.63 mL (63.0 mmol) of dimethyl sulfide which resulted in the formation of a flocculent white precipitate.[3] The mixture was cooled to −25 °C, and a solution of 5.60 g (31.5 mmol) of the alcohol **9** in 20 mL of dichloromethane was slowly added to maintain the temperature below −20 °C. The mixture was stirred an additional 2.0 h, and then 5.0 mL of triethylamine was added. After stirring an additional 5 min, the mixture was poured into water and extracted with chloroform. This material consisted of a mixture of succinimide and the desired ketone. The succinimide was conveniently removed by filtration through 15 g of silica gel with 5% ethyl acetate–hexane. Removal of the solvent gave 5.22 g (94%) of the ketone **10** which readily crystallized. An analytical sample, mp 61–62 °C, was secured by recrystallization from methanol–water: IR (film) 1705, 1640, 1595, 1340, 1305, 1150, 1070, 1005, 930, 890, 860, 800, 720 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.81 (H-4 and H-5, m), 5.27 (br d, H-6, J = 9.7 Hz), 2.49 (H-8a, s), 1.82 (vinyl CH_3), 1.06 (angular CH_3) ppm.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.94; H, 9.09.

Ethyl 4aβ,8-Dimethyl-3,4,4a,8aβ-tetrahydro-1(2*H*)-naphthalenon-2β-ylacetate (11). To a solution of 0.24 mL (1.20 mmol) of diisopropylamine in 4.0 mL of tetrahydrofuran at −78 °C was added a solution of 0.60 mL (1.20 mmol) of 2.0 M *n*-butyllithium in hexane. The reaction mixture was stirred for 20 min at −78 °C, at which time 200 mg (1.13 mmol) of ketone **10** in 1 mL of tetrahydrofuran and 1.0 mL of hexamethylphosphoroustriamide was added. Stirring at −78 °C was continued for an additional 20 min, and then 0.15 mL (1.36 mmol) of ethyl iodoacetate was added. After 30 min at −78 °C, the reaction mixture was poured into 5% hydrochloric acid, and the product was extracted with ether to afford 218 mg (74%) of keto ester **11** after preparative layer chromatography with 25% ethyl acetate–hexane. An analytical sample, mp 54–55 °C, was secured by recrystallization from hexane: IR (KBr) 1740, 1710, 1650, 1590, 1350, 1300, 1260, 1220, 1160, 1140, 1030, 910, 855, 790, 730 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.35 (H-7, m), 4.05 ($-CH_2O-$, q, J = 7 Hz), 1.75 (vinyl CH_3, br s), 1.21 (CH_3CH_2-, t, J = 7 Hz), 1.01 (angular CH_3) ppm.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.41; H, 8.54.

2-(1-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphthalen-2β-yl)ethanol (12, 13). A solution of 200 mg (0.71 mmol) of the keto ester **11** in 15 mL of anhydrous ether at 0 °C was treated with 68 mg (1.8 mmol) of lithium aluminum hydride and stirred at 0 °C for 1.5 h. The addition of 0.35 mL of water resulted in the precipitation of aluminum salts which were filtered. Removal of solvent afforded 158 mg of the diol mixture. This mixture (1:1) was separated into its two components by preparative liquid chromatrography on a Porasil column with 50% ethyl acetate–hexane.

cis-Diol **13**, mp 113–114 °C, from hexane: IR (film) 3350, 1640, 1590, 1195, 1135, 1080, 1030, 1020, 910, 875, 850, 800, 720 cm^{-1}; NMR δ_{Mi_4Si} (CCl_4) 5.80 (H-5, H-6, m), 5.22 (H-7, d, J = 7 Hz), 3.70 (>CHO–, $-CH_2O-$, m), 1.95 (vinyl CH_3), 0.90 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.81; H, 10.18.

trans-Diol **12**, mp 57–58 °C, from hexane: IR (CCl_4) 3400, 1640, 1590, 1205, 1180, 1130, 1100, 1025, 1000, 985, 935, 880, 840, 815, 700 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.80 (H-5, H-6, m), 5.43 (H-7, d, J = 7 Hz), 3.69 ($-CH_2O$, >CHO–, m), 1.84 (vinyl CH_3, br s), 0.94 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.72; H, 10.19.

2-(1α-Hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (14). To a flask fitted with a Dean–Stark trap, condenser, and mechanical stirrer was added 620 mg (2.78 mmol) of trans diol **12**, 40 g (0.51 g/mmol) of silver carbonate on Celite, and 250 mL of benzene.[9] The mixture was heated to reflux

for 8 h, cooled, and filtered. Removal of solvent and purification by preparative layer chromatography with 10% ethyl acetate–hexane gave 318 mg (52.5%) of the trans lactone **14**. An analytical sample, mp 90–91 °C, was secured by recrystallization from hexane: IR (film) 1785, 1650, 1590, 1385, 1300, 1220, 1200, 1185, 1135, 1050, 1020, 1000, 980, 905, 875, 810, 740 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.67 (H-5, H-6, m), 5.18 (H-7, m), 4.21 (H-1, m), 1.86 (vinyl CH_3), 1.20 (angular CH_3) ppm.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.07; H, 8.37.

2β-Methyl-2-(1α-hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (15). To a solution of 0.069 mL (0.45 mmol) of diisopropylamine in 3 mL of tetrahydrofuran at −78 °C was added a solution of 0.18 mL (0.40 mmol) of 2.29 M *n*-butyllithium in hexane and 0.05 mL of HMPA. The reaction mixture was stirred at −78 °C for 20 min at which time 88 mg (0.40 mmol) of the lactone in 1.0 mL of tetrahydrofuran was introduced. The reaction was stirred at −78 °C for 45 min and a 0.1-mL portion of methyl iodide was added. Stirring was continued for 1 h. The mixture was poured into water and extracted with ether to afford 90 mg (97%) of the methylated lactone **15**, which crystallized upon cooling. An analytical sample, mp 96–97 °C, was secured by recrystallization from hexane: IR ($CHCl_3$) 1780, 1650, 1590, 1195, 1175, 1140, 1110, 1010, 980 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 5.70 (H-5, H-6, m), 5.30 (H-7, m), 4.43 (H-1, d of d, $J_{1,8a}$ = 11.5 Hz, $J_{1,2}$ = 5 Hz), 1.85 (vinyl CH_3), 1.20 (angular CH_3), 1.11 (lactone CH_3, d, J = 7 Hz) ppm.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.64; H, 8.61.

2α-Methyl-2-(1α-hydroxy-4aβ,8-dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-2β-yl)acetic Acid Lactone (16). A solution of 0.084 mL (0.60 mmol) of diisopropylamine in 4.0 mL of tetrahydrofuran at −78 °C was treated with 0.30 mL of 2.0 M *n*-butyllithium in hexane solution. Stirring at −78 °C was continued for 20 min, at which time 120 mg (0.517 mmol) of the trans lactone **15** was added with the aid of 1.0 mL of tetrahydrofuran. After 30 min at −78 °C, the mixture was poured into water and the product was extracted with ether to give 120 mg (100%) of material which was recrystallized from hexane to give 100 mg of lactone **16**: mp 78–79 °C; IR (CCl_4) 1785, 1590, 1240, 1170, 1140, 1125, 1015, 950 cm^{-1}; NMR δ_{Me_4Si} 5.75 (H-5, H-6, m), 5.30 (H-7, m), 4.25 (H-1, d of d, $J_{1,8a}$ = 10 Hz, $J_{1,2}$ = 5 Hz), 1.85 (vinyl CH_3, br s), 1.20 (angular CH_3), 1.18 (lactone CH_3, d, $J \approx 6$ Hz) ppm.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.34; H, 8.80.

(±)-β-Santonin (17). A solution of 150 mg (0.65 mmol) of the lactone **15** in 200 mL of pyridine and a small amount of hematoporphorin was irradiated with a 150-W flood lamp for 12 h while oxygen was slowly bubbled through the solution.[10] The mixture was kept cool with running water. Removal of solvent and filtration through 15 g of alumina with ether gave 84 mg of the endoperoxide **19** as a crystalline solid, mp 190–191 °C, and 29 mg (19%) of β-santonin (**17**), mp 184–185 °C (lit. mp 186 °C),[15] purified by preparative layer chromatography on silica gel using 50% ethyl acetate–hexane. The NMR spectrum was identical to a published spectrum.[16]

Endoperoxide 19: IR (film) 1770, 1375, 1230, 1215, 1180, 1100, 1005, 980, 945, 925, 850 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.70 (H-6, d of d, $J_{6,7}$ = 10 Hz, $J_{5,6}$ = 4 Hz), 6.34 (H-7, d of d, $J_{6,7}$ = 10 Hz, $J_{1,2}$ = 5 Hz), 4.12 (H-5, d of d, $J_{5,6}$ = 4 Hz, $J_{5,7}$ = 1 Hz), 1.39 (CH_3), 1.42 (CH_3), 1.12 (lactone CH_3, d, J = 5 Hz) ppm.

Anal. Calcd for $C_{15}H_{19}O_4$: C, 68.42; H, 7.65. Found: C, 68.15; H, 7.79.

(±)-α-Santonin (18). A solution of 200 mg (0.86 mmol) of the α-methyl lactone **16** and a small amount of methylene blue in 150 mL of pyridine was irradiated with a 150-W flood lamp while oxygen was slowly bubbled through the solution overnight. Removal of solvent, filtration through 15 g of alumina with ether, and preparative layer chromatography with 50% ethyl acetate–hexane gave 60 mg of α-santonin (**18**) which was spectroscopically identical with an authentic sample, mp 180–181 °C (lit. mp 181 °C).[15]

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Registry No.—**1**, 99-04-7; **2**, 64872-57-7; **3**, 64872-58-8; **4**, 64872-59-9; **4** DNP, 64872-60-2; **5**, 64872-61-3; **6**, 64872-62-4; **7**, 64872-63-5; **8**, 64081-54-5; **9**, 64912-44-3; **10**, 648-72-50-0; **11**, 64872-51-1; **12**, 64872-53-3; **13**, 64872-52-2; **14**, 64872-54-4; **15**, 64912-45-4; **16**, 64912-46-5; **17**, 64912-47-6; **18**, 64912-48-7; **19**, 64872-55-5; methyl iodide, 74-88-4; triethyl phosphonoacetate, 867-13-0; *N*-bromosuccinimide, 128-08-5; ethylthiolthylsulfinylmethane, 37032-97-8; ethyl iodoacetate, 623-48-3.

References and Notes

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