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Notes

Stereoselective Synthesis of Racemic Occidentalol and Related Cis-Fused Hexahydronaphthalenes from *m*-Toluic Acid

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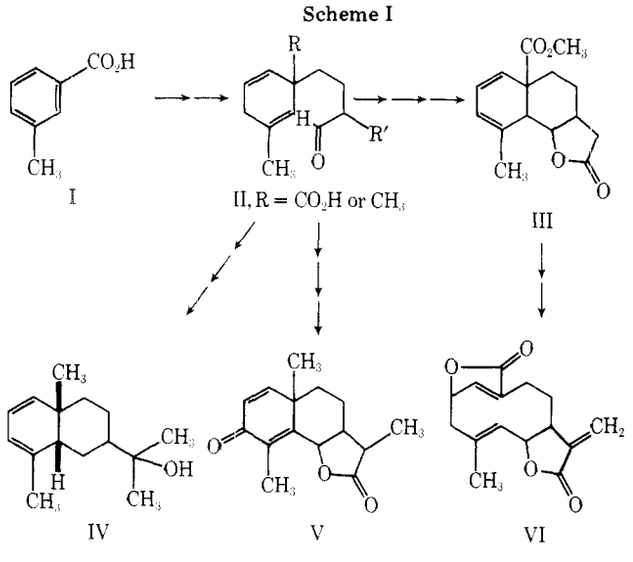
In connection with a program aimed at the development of new synthetic routes to sesquiterpenes of possible medicinal interest we wished to evaluate the potential of Scheme I as a

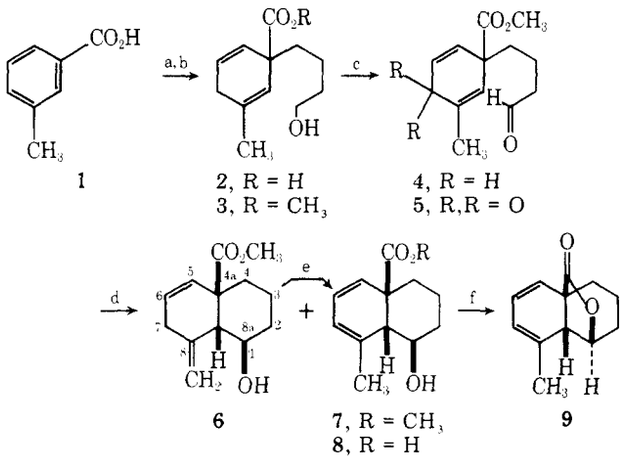
Scheme I



general approach to eudesmanes and germacranes.[1] The crux of this approach depends upon the cyclization of a suitably substituted 3-methyl-2,5-cyclohexadienyl aldehyde II, derivable through reduction–alkylation of a *m*-toluic acid precursor (I), to a eudesmanolide (e.g., V) or eudesmane (e.g., IV). Conceivably such a scheme could also lead to substances with the interesting germacranolide skeleton VI containing two α,β-unsaturated γ-butyrolactones.[2,3] Clearly the attainment of even the simplest of the synthetic objectives depicted above will require experimentally derived knowledge of the stereochemistry and regiochemistry of the cyclohexadienyl aldehyde cyclization process. This note describes our work on the synthesis and cyclization of dienic ester aldehyde II (R = CO_2CH_3; R′ = H), the methyl analogue (II, R = CH_3; R′ = H), and the α-methylene derivative (II, R = CH_3; R′ = CH_2) and the subsequent conversion of the cyclization product of the latter aldehyde to racemic occidentalol (IV), a cis-fused eudesmane sesquiterpene containing a homoannular 1,3-diene moiety.[4]

The hydroxy acid **2** was efficiently prepared by treating *m*-toluic acid (**1**) with lithium in ammonia to generate the carboxylic dianion which was alkylated in situ[5] with commercially available 4-phenoxybutyl bromide.[6] The ammonia solution was then treated with lithium and *tert*-butyl alcohol to reduce the phenoxy ring. Removal of the ammonia and acidic hydrolysis cleaved the resulting dihydrophenyl (enol) ether[7] and afforded the crystalline hydroxy acid **2** in 95% yield. Esterification with methanolic *p*-toluenesulfonic acid yielded the ester **3** quantitatively. Oxidation of this substance with

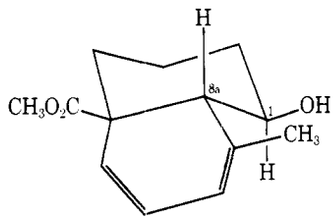
Chart I[a]



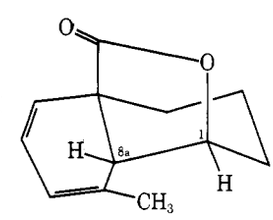
[a] a, Li, NH_3; $Br(CH_2)_4OPh$; Li, NH_3, *t*-BuOH; HCl, H_2O; b, CH_3OH, *p*-TsOH; c, $C_5H_5N{\cdot}CrO_3{\cdot}HCl$; d, ZnI_2, CH_2Cl_2; e, KOH, *t*-BuOH; f, DCC.

pyridinium chlorochromate[8] gave the ester aldehyde **4** in 70–80% yield along with the product of allylic oxidation, dienone aldehyde **5**. The Collins' chromium trioxide–pyridine reagent[9] was somewhat less effective (60–70% yield of **4**) as were several variations of the DCC–Me_2SO Moffatt procedure[10] for primary alcohol oxidation.

After examining numerous Lewis acids we found zinc iodide in methylene chloride to most effectively catalyze the cyclization of diene aldehyde **4**.[11] The product obtained in quantitative yield consisted of a 1:3 mixture of dienic alcohols **6** and **7** which could be separated by high-pressure liquid chromatography. Interestingly, we found that the nonconjugated isomer **6** could be smoothly converted to the conjugated dienic acid **8** upon saponification of the crude cyclization mixture and esterification of the crystalline acid **8**. The stereochemistry of this hydroxy ester was assigned on the basis of the NMR spectrum which showed axial–axial coupling for the ring fusion hydrogen (H-8a) and conversion of the acid **8** to lactone **9** whose NMR spectrum showed no H-8a axial–axial coupling (see below). These findings are uniquely satisfied by the *cis,anti* isomer **7**.



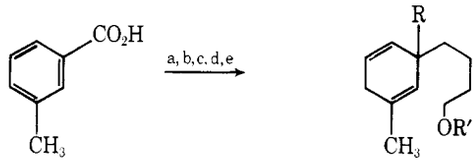
7 ($J_{8a,1}$ = 10 Hz)



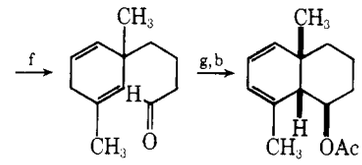
9 ($J_{8a,1}$ = 4 Hz)

We next turned our attention to the preparation and cyclization of dienic aldehyde **15**. These studies, outlined in Chart II, followed the basic scheme devised for ester aldehyde

Chart II[a]



10, R = CO_2H; R′ = CH_2Ph
11, R = CH_2OH; R′ = CH_2Ph
12, R = CH_2OTs; R′ = CH_2Ph
13, R = CH_3; R′ = CH_2Ph
14, R = CH_3; R′ = H



15 16

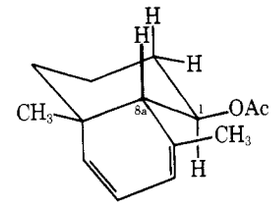
[a] a, Li, NH_3; $Br(CH_2)_4OCH_2Ph$; HCl; b, $LiAlH_4$; H_2O; c, *p*-TsCl, C_5H_5N, d, $LiB(Et)_3H$, HMPA; e, Li, NH_3, *t*-BuOH; f, NCS, Me_2S, CH_3Ph; g, Ac_2O, EtOAc, $HClO_4$.

4 except for several minor, but necessary, modifications. Reduction of *m*-toluic acid (**1**) with lithium in ammonia followed by alkylation of the carboxylic dianion with 4-benzyloxybutyl bromide and then careful acidification afforded the acid **10** in 97% yield. The use of 4-phenoxybutyl as the side chain proved unsatisfactory because of difficulties encountered at a later stage in the sequence during hydrolysis of the dihydrophenyl (enol) ether.[7] The resulting dienol **14** contained significant impurities arising from double bond isomerizations indicating a surprising acid lability of this 1-methyl-1,4-cyclohexadienyl system as compared to the carbomethoxy analogue **3**.

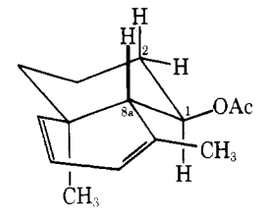
Net hydrogenolysis of the carboxyl group of acid **10** was effected by reduction with lithium aluminum hydride, conversion of the resulting alcohol **11** to tosylate **12** using *p*-toluenesulfonyl chloride in pyridine, and reduction of this derivative with lithium triethylborohydride in hexamethylphosphoramide to give diene **13** in 86% overall yield.[12] Initial attempts to reduce the reactive bis-homoallylic tosylate **12** with less nucleophilic hydrides or dissolving metals led to diverse rearrangement and solvolysis products.

The benzylic ether **13** underwent hydrogenolysis in 90% yield upon treatment with sodium in ammonia–*tert*-butyl alcohol. Oxidation of the resulting alcohol **14** with chromium trioxide–pyridine or pyridinium chlorochromate caused extensive allylic oxidation. Corey's *N*-chlorosuccinimide–dimethyl sulfide method[13] proved effective, however, and aldehyde **15** could be thus prepared in 95% yield.

Attempted cyclization of diene aldehyde **15** with various Lewis acid catalysts such as zinc halides, including zinc iodide, stannic chloride, and boron trifluoride led to complex mixtures of products. Much more promising results were obtained using acetic anhydride–perchloric acid in ethyl acetate to promote the cyclization whereupon the acetate **16** was secured in 63% yield as the only dienic substance.[14] The remaining material consisted of olefins and the acylal derivative of aldehyde **15**. The stereochemistry of the cyclization product **16** is based on the observed H-1 splitting pattern in its NMR spectrum[15] and by analogy to the results described above for aldehyde **4**. As shown below, the NMR analysis fails to distinguish the cis,anti from the trans,anti isomer. The assignment must therefore be regarded as tentative.



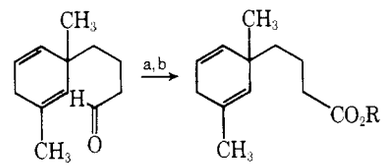
cis,anti (**16**)



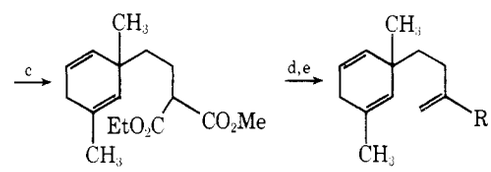
trans,anti

The next phase of our cyclization studies (Chart III) involved unsaturated carbonyl compounds **21**, **22**, and **23**, and

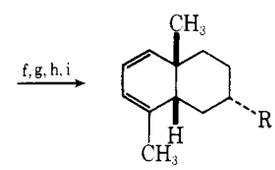
Chart III[a]



15 17, R = H
18, R = Me



19 20, R = CH_2OH
21, R = CHO
22, R = CO_2H
23, R = CO_2CH_3



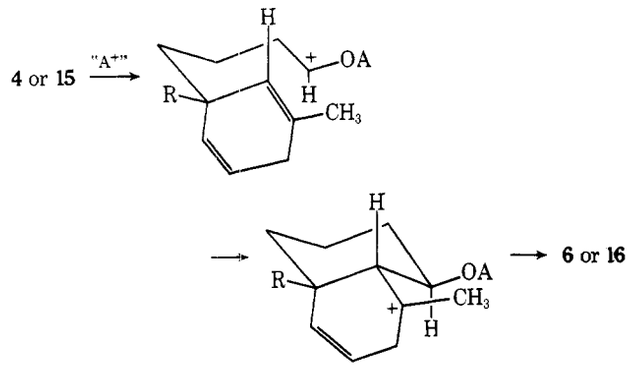
24, R = $CH(OAc)_2$
25, R = CO_2H
26, R = CO_2CH_3
27, R = $C(CH_3)_2OH$

[a] a, Ag_2O; b, CH_3OH, H_2SO_4; c, $LiNR_2$; $ClCO_2Et$; d, NaH; $LiAlH_4$; e, MnO_2; f, Ac_2O, $HClO_4$; g, NaOH, Ag_2O; HCl; h, CH_2N_2; i, CH_3Li.

a successful synthesis of occidentalol (**27**). To that end, aldehyde **15** was oxidized with silver oxide to the acid **17**. The α-methylene derivative **22**, obtained via carboxylic dianion condensation with formaldehyde and elimination of the derived mesylate with diazabicyclo[5.4.0]undec-5-ene,[16] failed to cyclize even after prolonged treatment with various acidic catalysts. Since the ester derivative **23** likewise showed no tendency to form bicyclic products upon acid treatment, we turned to the more promising derivative, aldehyde **21**.[17] Direct methylenation of aldehyde **15** along the lines delineated for acid **17** appeared unpromising owing to the observed lability of this aldehyde toward base. We therefore explored the somewhat lengthier sequence based on our previous work involving malonic enolate reduction–eliminations.[18] Ester **18**

proved surprisingly difficult to carboethoxylate. Treatment with sodium or potassium hydride in diethyl carbonate as solvent resulted in only partial conversion to the malonate despite extended reaction times. Eventually we found that the use of the lithium salt of 2,2,6,6-tetramethylpiperidine as the base[19] and ethyl chloroformate as the acylating agent gave the malonate **19** in 83% yield. Reduction of the sodio enolate with lithium aluminum hydride yielded an impure, unstable allylic alcohol (**20**) which was directly oxidized to aldehyde **21** using manganese dioxide.[18]

Cyclization of unsaturated aldehyde **21** proceeded smoothly and rapidly at 0 °C upon dissolution in acetic anhydride–ethyl acetate containing 70% perchloric acid.[17] The resulting acylal **24** could be directly converted to the acid **25** with sodium hydroxide–silver oxide in aqueous methanol. Treatment of the derived ester **26** with methyllithium afforded racemic occidentalol (**27**), identified by spectral comparison.[20] Thus, the cyclization reaction has again followed a highly regio- and stereoselective course to give a cis-fused conjugated homoannular diene. In this case the apparent high propensity for a trans carboxylic grouping in acid **25** can be accorded no real significance as this center would expectedly epimerize (as the aldehyde) under the conditions employed for saponification of the acylal **24**, in which case thermodynamic considerations control the observed outcome.[4] However, such would not be the case for the cyclizations leading to alcohols **6** and **7** and acetate **16** unless these prove to be reversible reactions. A satisfactory rationale for the observed formation of cis-fused products can be formulated assuming a kinetically controlled approach of the side chain aldehyde–acid complex to the cis face of the more substituted double bond of the cyclohexadiene sytem as depicted below.



Experimental Section[21]

1-(4-Hydroxybutyl)-3-methylcyclohexa-2,5-diene-1-carboxylic Acid (2). To a solution of 15 g of *m*-toluic acid in 100 mL of tetrahydrofuran (THF) and 1.5 L of ammonia was added lithium wire until the blue color persisted. A solution of 38.0 g of 4-phenoxybutyl bromide[6] in 100 mL of THF was added and after stirring for 1 h the solution was treated with 150 ml of *tert*-butyl alcohol. Lithium wire was again added to maintain the blue coloration and after 20 min, 25 g of ammonium chloride was added and the ammonia was allowed to evaporate. The residue was treated with cold concentrated hydrochloric acid and stirred for 45 min to hydrolyze the enol ether. The mixture was made basic with 10% aqueous sodium hydroxide, the neutral material was removed by ether extraction, and the aqueous phase was acidified with cold hydrochloric acid and extracted with ether. The crude solid (22.8 g) thus obtained was recrystallized from methanol–water to give 17.5 g (75%) of acid **2**: mp 103–104 °C; δ_{Me_4Si} ($CDCl_3$) 1.73 (C-3 CH_3), 2.50 (H-4), 3.50 (–CH_2O– triplet, J = 6 Hz), 5.37, 5.70 ppm (H-2, H-5, H-6).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.3; H, 8.6.

Methyl 1-(4-Hydroxybutyl)-3-methylcyclohexa-2,5-diene-1-carboxylate (3). A solution of 13.2 g of hydroxy acid **2** and 0.2 g of *p*-toluenesulfonic acid in 125 mL of methanol was heated at reflux for 6 h. Most of the methanol was removed under reduced pressure, water was added, and the product was extracted with ether to give 14.1 g of ester **3**: bp 147 °C (0.1 Torr); IR (film) 3050, 1740, 1440, 1390, 1240, 940 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.73 (C-3 CH_3), 2.50 (H-4), 3.47 (–CH_2O– triplet, J = 6 Hz), 3.60 (CH_3O–), 5.37, 5.70 ppm (H-2, H-5, H-6).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.65; H, 8.9.

Methyl 1-(3-Formylpropyl)-3-methylcyclohexa-2,5-diene-1-carboxylate (4). A mixture of 5.0 g of alcohol **3** and 7.0 g of pyridinium chlorochromate[8] in 200 mL of methylene chloride was stirred at room temperature for 1 h. The mixture was filtered through Florisil and distilled to give 4.5 g (90%) of aldehyde **4**: bp 120 °C (0.1 Torr); IR (film) 3050, 2704, 1725, 1215, 1095, 925 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.75 (C-3 CH_3), 2.30 (–CH_2CHO triplet, J = 7 Hz), 3.60 (CH_3O), 5.37, 5.78 (H-2, H-5, H-6), 9.66 ppm (–CHO triplet, J = 1 Hz).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.0; H, 8.2.

Cyclization of Aldehyde Ester 4 with Zinc Iodide. A solution of 25 g of aldehyde **4** and 3.7 g of zinc iodide in 100 mL of methylene chloride was stirred at room temperature overnight. The product (23 g, 91%), isolated with ether, consisted of a 1:3 mixture of alcohols **6** and **7** which could be separated using high-pressure liquid chromatography on Porosil to give the pure isomers whose properties are described below.

Methyl 1β-Hydroxy-8-methylene-1,2,3,4,4a,7,8,8aβ-octahydronaphthalene-4aβ-carboxylate (6): bp 130 °C (0.1 Torr); IR (film) 3051, 2898, 1738, 1240, 1219, 900 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.78 (H-6, half of AB quartet split into a triplet, $J_{6,5}$ = 9, $J_{6,7}$ = 3 Hz), 5.39 (H-5, half of AB quartet, $J_{5,6}$ = 9 Hz), 4.91 (C=CH_2), 3.58 (–OCH_3), 2.75 (H-7 multiplet), 2.49 ppm (H-8a doublet, J = 9 Hz).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.03; H, 8.27.

Methyl 1β-Hydroxy-8-methyl-1,2,3,4,4a,8aβ-hexahydronaphthalene-4aβ-carboxylate (7): bp 130 °C (0.1 Torr); IR (film) 2970, 2898, 1738, 1242, 1215, 1065, 1020 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.88 (H-6, half of AB quartet split into a doublet, $J_{6,5}$ = 9, $J_{6,7}$ = 5 Hz), 5.67 (H-7 doublet, J = 5 Hz), 5.26 (H-5, half of AB quartet, $J_{5,6}$ = 9 Hz), 3.58 (–OCH_3), 2.20 (H-8a doublet, J = 9 Hz), 1.95 ppm (C-8 CH_3), A sample was converted to the *tert*-butyldimethylsilyl ether, mp 97–98 °C, by the procedure of Corey.[22]

Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.6; H, 9.7.

1β-Hydroxy-8-methyl-1,2,3,4,4a,8aβ-hexahydronaphthalene-4aβ-carboxylic Acid (8). A. From Ester 6. A solution of 0.70 g of ester **6** in 6 mL of *tert*-butyl alcohol containing 0.70 g of powdered potassium hydroxide[23] was stirred at reflux for 3 h. The mixture was diluted with water and washed with ether. The aqueous phase was acidified with aqueous hydrochloric acid and extracted with ethyl acetate to give 0.61 g of acid **8**. Recrystallization from ethanol afforded 0.47 g (72%) of acid: mp 234–236 °C; IR (KBr) 3500, 1690, 1590, 1265, 1210, 1155, 1060, 995, 930, 872 cm^{-1}. A sublimed sample melted at 238–239 °C.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 7.75.

A small sample of this acid was esterified with ethereal diazomethane to give ester **7** quantitatively.

B. From the Crude Cyclization Reaction Products. A 3.76-g sample of aldehyde **4** was cyclized with zinc iodide in methylene chloride as described above. The crude mixture of esters **6** and **7** was subjected to saponification with potassium hydroxide in *tert*-butyl alcohol as outlined in part A to give 1.99 g (56%) of acid **8**, mp 234–236 °C.

1β-Hydroxy-8-methyl-1,2,3,4,4a,8aβ-hexahydronaphthalene-4aβ-carboxylic Acid Lactone (9). A solution of 0.45 g of hydroxy acid **8** and 0.67 g of dicyclohexylcarbodiimide in 15 mL of chloroform was stirred at room temperature overnight. Water and acetic acid were added and the product was isolated by extraction with ether. Material thus obtained was chromatographed on silica gel to give 0.31 g (75%) of lactone **9**: bp 135 °C (0.1 Torr); δ_{Me_4Si} ($CDCl_3$) 5.80 (m, vinyl H), 4.80 (H-1 triplet, J = 5 Hz), 3.06 (H-4a doublet, J = 5 Hz), 1.97 ppm (C-8 CH_3 triplet, J = 1 Hz): IR (film) 1782, 1450, 1350, 1300, 1235, 1182, 1070, 1000, 970, 930, 895, 880 cm^{-1}.

The lactone crystallized upon standing. Recrystallization from hexane afforded the analytical sample, mp 78–79 °C.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.9; H, 7.5.

1-(4-Benzyloxybutyl)-3-methylcyclohexa-2,5-diene-1-carboxylic Acid (10). To a solution of 30.0 g (0.22 mol) of *m*-toluic acid in 1.5 L of ammonia and 300 mL of anhydrous tetrahydrofuran was added in small pieces enough lithium wire to maintain the blue color. A solution of 70.0 g (0.31 mol) of 4-benzyloxybutyl bromide in 100 mL of THF was then rapidly added. At this point the reaction mixture went from blue to orange to water-white in color. After stirring for 1

h the reaction was quenched with solid ammonium chloride and the ammonia was allowed to evaporate The residue was taken up in water, washed once with ether to remove nonacidic components, and carefully acidified with concentrated hydrochloric acid. The acid was then isolated by ether extraction to afford 64.3 g (97.5%) of acid **10**: IR (film) 1700, 1455, 1380, 1365, 1110, 1015, 930, 910, 840, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.04 (Ph), 5.65, 5.42 (H-2, H-6), 4.50 ($-OCH_2-$), 1.70 ppm (C-3 CH_3).

This material, a viscous, nondistillable oil, was used without further purification.

1-(4-Benzyloxybutyl)-1-hydroxymethyl-3-methylcyclohexa-2,5-diene (11). To a suspension of 12.2 g (0.32 mol) of lithium aluminum hydride in 400 mL of ether at 0 °C was slowly added a solution of 64.3 g (0.214 mol) of acid **10** in 200 mL of ether. After the addition was complete the reaction mixture was allowed to stir for 2 h while warming to room temperature. To prevent the vigorous evolution of hydrogen that normally results upon quenching with water, the excess lithium aluminum hydride was destroyed by first adding 30 mL of acetone; then 12 mL of water, 24 mL of 10% sodium hydroxide, and 24 mL of water were successively added. The resulting white, granular precipitate was filtered and the solvent was removed in vacuo to afford 56.5 g (94%) of **11** as a clear, viscous oil: IR (film) 3450, 1495, 1450, 1380, 1360, 1200, 1100, 1020, 935, 730, 690 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.23 (Ph), 5.82 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 3$ Hz), 5.30 (H-6, half of AB quartet split into multiplets, $J_{5,6} = 10, J_{4,6} = 2$ Hz), 5.05 (H-2), 4.4 ($-CH_2Ph$), 3.2 ($HOCH_2-$), 3.35 ($-OCH_2-$ triplet, $J = 4$ Hz), 2.5 (H-4), 1.72 ppm (C-3 CH_3).

The analytical sample, bp 145 °C (0.15 Torr), was secured by short-path distillation.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.14. Found: C, 79.5; H, 9.2.

1-(4-Benzyloxy)-1-tosyloxymethyl-3-methylcyclohexa-2,5-diene (12). A solution of 56.5 g (0.199 mol) of alcohol **3**, 44.0 g of *p*-toluenesulfonyl chloride, and 250 mL of pyridine was stirred at 0 °C overnight, poured onto ice-water, and extracted with ether. The combined ether extracts were washed three times with 2% sulfuric acid, once with water, and then with saturated brine. The ether layer was dried over magnesium sulfate and solvent was removed affording 86.2 g (100%) of the tosylate **12** as a slightly yellow, viscous oil: IR (film) 1601, 1595, 1500, 1370, 1195, 960, 820, 720, 710 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.45 (aromatic H's, doublet of doublets, $J = 9$ Hz, $\Delta\nu = 27$ Hz), 7.21 (aromatic H's, Ph), 5.74 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 4$ Hz), 5.27 (H-6, half of quartet split into multiplets, $J_{5,6} = 10$ Hz), 4.97 (H-2), 4.38 ($-CH_2Ph$), 3.60 (C-1 $-CH_2O-$), 3.30 (side chain $-CH_2O-$, triplet, $J = 6$ Hz), 2.38 (H-4 and aryl CH_3), 1.63 ppm (C-3 CH_3).

This material, a viscous oil, decomposed upon attempted purification and was therefore used directly.

1-(4-Benzyloxybutyl-1,3-dimethylcyclohexa-2,5-diene (13). To a 2-L flask fitted with a thermometer, condensor, and argon inlet were added 86.2 g (0.199 mol) of tosylate **12**, 650 mL of hexamethylphosphoric triamide, and 650 mL of 1 M lithium triethylborohydride in THF.[12] The resulting mixture was heated to 50 °C overnight, cooled, and quenched slowly with water. Extraction with hexane afforded 49.5 g (92%) of diene **13** as a clear oil: IR (film) 1495, 1455, 1365, 1200, 1100, 1020, 935, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.20 (aromatic H's), 5.61 (H-5, half of AB quartet split into triplet, $J_{5,6} = 10, J_{4,5} = 4$ Hz), 5.30 (H-6, half of quartet split into multiplet, $J_{5,6} = 10$ Hz), 4.40 ($-CH_2Ph$), 3.32 ($-CH_2O-$ triplet, $J = 7$ Hz), 2.42 (H-4), 1.64 (C-3 CH_3), 0.95 ppm (C-1 CH_3).

The analytical sample, bp 120 °C (0.03 Torr), was secured by short-path distillation.

Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.62. Found: C, 84.35; H, 9.6.

1-(4-Hydroxybutyl)-1,3-dimethylcyclohexa-2,5-diene (14). A solution of 49.5 g (0.183 mol) of ether **13** in 1.5 L of ammonia, 150 mL of *tert*-butyl alcohol, and 200 mL of THF was treated with small pieces of sodium until the blue color persisted for roughly 10 min. Solid ammonium chloride was added to discharge the color, the ammonia was allowed to evaporate, and the product was taken up in water and isolated with ether to afford 29.3 g (90%) of alcohol **14**: bp 120 °C (0.1 Torr); IR (film) 3350, 1450, 1375, 1360, 1060, 1050, 935, 885, 720 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.63 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 3$ Hz), 5.30 (H-6), half of AB quartet split into quartets, $J_{5,6} = 10, J_{4,6} = 2$ Hz), 3.45 ($-OCH_2-$ triplet, $J = 7$ Hz), 2.45 (H-4), 1.65 (C-3 CH_3), 0.95 ppm (C-1 CH_3).

The analytical sample, bp 70–72 °C (0.05 Torr), was secured by distillation.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.8; H, 11.4.

1-(3-Formylpropyl)-1,3-dimethylcyclohexa-2,5-diene (15). To a flask fitted with a low-temperature thermometer were added 450 mL of toluene and 13.1 g (97.5 mmol) of *N*-chlorosuccinimide. The solution was cooled to 0 °C and treated with 9.5 mL (0.129 mol) of dimethyl sulfide which resulted in the formation of a flocculent white precipitate.[13] The mixture was cooled to −20 °C and a solution of 11.2 g (62.0 mmol) of the alcohol **6** in 50 mL of toluene was slowly added to maintain the temperature below −15 °C. The mixture was stirred at −20 °C for an additional 2.5 h, then 13.5 mL of triethylamine in 50 mL of toluene was added. The mixture was diluted with 200 mL of ether, poured into water, and extracted with ether to afford 10.4 g (95%) of the aldehyde **15** as a clear oil: bp 60 °C (0.02 Torr); IR (film) 2725, 1630, 1495, 1460, 1380, 935, 730, 690 cm^{-1}; δ_{Me_4Si} (CCl_4) 9.60 (CHO triplet, $J = 1.5$ Hz), 5.66 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 3$ Hz), 5.28 (H-6, half of AB quartet split into quartets, $J_{5,6} = 10, J_{4,6} = 2$ Hz), 5.04 (H-2), 2.44 (H-4), 1.68 (C-3 CH_3), 0.95 ppm (C-1 CH_3).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.7; H, 10.4.

4aβ,8-Dimethyl-1,2,3,4,4a,8aβ-hexahydronaphth-1β-yl Acetate (16). A solution of 10.9 g (61.5 mmol) of aldehyde **15** in 40 mL of ethyl acetate was added with stirring to a solution of 45 mL of acetic anhydride and 10 mL of 70% perchloric acid in 200 mL of ethyl acetate maintained at 0 °C.[14] After 15 min, solid sodium bicarbonate was added, and the mixture was poured into water and extracted with ether. Material thus obtained was chromatographed on silica gel to give an early fraction of olefins, middle fractions containing 8.5 g (63%) of acetate **16** and later fractions containing the acylal derivative of aldehyde **15**. Acetate **16** had the following characteristics: IR (film) 1740, 1630, 1590, 1256, 1175, 1140, 1100, 1060, 1050, 1030, 975, 940, 880, 850, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.73 (H-3, half of AB quartet split into doublets, $J_{3,4} = 8, J_{2,3} = 6$ Hz), 5.50 (H-2 doublet, $J = 6$ Hz), 5.17 (H-4, half of AB quartet, $J_{3,4} = 8$ Hz), 4.53 (H-1, doublet of triplets, $J_{1,8a} = 10, J_{1,2} = 4$ Hz), 1.87 (CH_3CO), 1.83 (C-8 CH_3), 0.88 ppm (C-4a CH_3).

This material solidified upon standing. A sample crystallized from hexane at −25 °C had mp 38–40 °C.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.6; H, 9.2.

Methyl 4-(1,3-Dimethyl-2,5-cyclohexadienyl)butanoate (18). To a solution of 4.24 g (23.8 mmol) of the aldehyde **15** and 8.12 g (47.6 mmol) of silver nitrate in 100 mL of methanol was added a solution of 3.82 g of sodium hydroxide in 20 mL of water. The reaction mixture was allowed to stir for 1 h and then poured into water. After a single extraction with ether to remove nonacidic impurities, the aqueous solution was acidified with 10% hydrochloric acid and extracted with ether to afford 3.77 g (81.5%) of acid **17**. A solution of 2.46 g (12.7 mmol) of the acid **17** and a catalytic amount of *p*-toluenesulfonic acid in 30 mL of anhydrous methanol was heated to reflux overnight. The solution was cooled, poured into saturated sodium bicarbonate and extracted with ether to give 2.52 g (96%) of the ester **18**: bp 110 °C (0.1 Torr); IR (film) 1740, 1450, 1440, 1360, 1200, 1165, 1010, 935, 715 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.60 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 3$ Hz), 5.27 (H-6, half of AB quartet split into quartets, $J_{5,6} = 10, J_{4,6} = 2$ Hz), 5.01 (H-2), 3.50 (CH_3O-), 2.61 (H-4), 1.67 (C-3 CH_3), 0.98 ppm (C-1 CH_3).[4]

Attempted purification by chromatography and distillation failed to produce a satisfactory analytical sample.

Ethyl 2-Carbomethoxy-4-(1,3-dimethyl-2,5-cyclohexadienyl)butanoate (19). To a solution of 1.59 ml (9.42 mmol) of 2,2,6,6-tetramethylpiperidine, 1.4 mL of hexamethylphosphoric triamide, and 20 mL of anhydrous tetrahydrofuran at −78 °C was added 4.70 mL (9.42 mmol) of 2.0 M *n*-butyllithium. After the solution had stirred for 10 min, a solution of 1.0 g (4.71 mmol) of the ester **18** in 10 mL of tetrahydrofuran was slowly added. Stirring was maintained for 15 min, after which 0.91 mL (9.42 mmol) of ethyl chloroformate was added. Stirring was continued for 30 min at −78 °C and the mixture was poured into water and extracted with ether to afford 1.15 g (83%) of malonate **19**: bp 140 °C (0.1 Torr); IR (film) 1750, 1740, 1455, 1440, 1370, 1100, 935, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.63 (H-5, half of AB quartet split into triplets, $J_{5,6} = 10, J_{4,5} = 3$ Hz), 5.27 (H-6, half of AB quartet split into quartets, $J_{5,6} = 10, J_{4,6} = 1.5$ Hz), 5.00 (H-2), 4.07 ($-OCH_2CH_3$ quartet, $J = 8$ Hz), 3.60 ($-OCH_3$), 3.10 (methine triplet, $J = 8$ Hz), 2.45 (H-4), 1.67 (C-3 CH_3), 1.20 ($-OCH_2CH_3$ triplet, $J = 8$ Hz), 0.97 ppm (C-1 CH_3). Gas chromatography on a 6 ft × 0.125 in., 5% Carbowax 20M column showed less than 10% of impurities.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.7; H, 8.9.

2-Methylene-4-(1,3-dimethyl-2,5-cyclohexadienyl)butanal (21). A solution of 2.95 g (10.0 mmol) of malonate **19** in 10 mL of

1,2-dimethoxyethane was added to a slurry of 454 mg (10.7 mmol) of sodium hydride. The mixture was heated to reflux for 1 h, cooled to 0 °C, and treated with 1.14 g (30.0 mmol) of lithium aluminum hydride. The reaction mixture was again heated to reflux for 2 h, cooled to room temperature, and carefully treated with 30 mL of ethyl formate. Addition to the resulting suspension of 1.1 mL of water, 2.2 mL of 10% sodium hydroxide, and 2.2 mL of water afforded a white suspension which was filtered. The residue, after removal of solvent, was taken up in 20 mL of anhydrous ether and slowly added to a slurry of 0.50 g of lithium aluminum hydride in 50 mL of anhydrous ether and allowed to stir for 1 h. Excess lithium aluminum hydride was destroyed by adding successively 0.5 mL of water, 1.0 mL of 10% sodium hydroxide, and 1.0 mL of water. After filtration of the resulting granular white precipitate, the solvent was removed to afford 2.08 g of allylic alcohol 20: IR (film) 3350, 1450, 1380, 1040, 935, 895, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.51 (H-2, H-5, H-6 multiplet), 4.85 (CH_2=C doublet, J = 7 Hz), 3.91 (-CH_2O-), 2.47 (H-4), 1.70 (C-3 CH_3), 1.00 ppm (C-1 CH_3).

A mixture of 1.80 g (9.43 mmol) of allylic alcohol **20,** 18.8 g of manganese dioxide, and 125 mL of anhydrous benzene was mechanically stirred overnight at room temperature. The mixture was filtered through a pad of Celite to afford 1.50 g of oil containing the aldehyde **21** as the major component. This oil was chromatographed on 120 ml of activity III silica gel with 6% ethyl acetate–hexane to afford 0.51 g (29%) of aldehyde **21:** IR (film) 2725, 1700, 1635, 1460, 1240, 1130, 840, 730 cm^{-1}; δ_{Me_4Si} (CCl_4) 9.45 (-CHO), 6.08 (CH_2=C doublet, J = 1 Hz), 5.82 (CH_2=C), 5.70 (H-5, half of AB quartet split into triplets, $J_{5,6}$ = 10, $J_{4,5}$ = 3 Hz), 5.32 (H-6, half of AB quartet split into quartets, $J_{5,6}$ = 10, $J_{4,6}$ = 2 Hz), 5.09 (H-2), 2.48 (H-4), 1.70 (C-3 CH_3), 1.01 ppm (C-1 CH_3).

The analytical sample was distilled, bp 110 °C (0.02 Torr).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.9; H, 9.7.

Methyl 4aβ,8-Dimethyl-1,2,3,4,4a,8aβ-hexahydronaphthalene-2α-carboxylate (26). A solution of 560 mg (2.70 mmol) of aldehyde **21** in 6 mL of ethyl acetate was added to a solution of 5.0 mL of acetic anhydride and 0.05 mL of perchloric acid in 40 mL of ethyl acetate at 0 °C.[14] The reaction mixture was stirred at 0 °C for 5 min, then poured into saturated sodium bicarbonate solution and extracted with ether to give 0.81 g of acylal **24:** IR (film) 1755, 1445, 1375, 1230, 1100, 1085, 1000, 725 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.85 (OCHO), 5.82 (H-6, doublet of doublets, $J_{5,6}$ = 9, $J_{6,7}$ = 5 Hz), 5.52 (H-7 doublet, $J_{6,7}$ = 5 Hz), 5.32 (H-5 doublet, $J_{5,6}$ = 9 Hz), 2.05 (CH_3CO), 1.79 (C-8 CH_3), 0.86 ppm (C-4a CH_3).

Silver oxide was prepared from a solution of 250 mg (1.70 mmol) of silver nitrate in 8 mL of methanol to which was added dropwise a solution of 300 mg (7.5 mmol) of sodium hydroxide in 5 mL of water. A solution of 120 mg (0.44 mmol) of acylal **24** in 2 mL of methanol was added, the reaction mixture was stirred at room temperature for 3 h and filtered, and the filtrate was extracted with ether following acidification with 10% hydrochloric acid to afford 98 mg of acid **25,** an oil: IR (film) 1700, 1450, 1220, 1080, 1045, 875, 720 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.77 (H-6, doublet of doublets, $J_{5,6}$ = 9, $J_{6,7}$ = 5 Hz), 5.52 (H-7 doublet, J = 5 Hz), 5.23 (H-5 doublet, J = 9 Hz), 1.77 (C-8 CH_3), 0.86 ppm (C-4a CH_3).

To a solution of 560 mg (2.70 mmol) of acid **25** in 10 mL of ether was added an ethereal solution of diazomethane generated by the addition of 955 mg (6.50 mmol) of N-nitroso-N-methylurea to a mixture of 3 mL of 40% potassium hydroxide and 10 mL of ether at 0 °C. After stirring for 10 min the reaction mixture was poured into 10% hydrochloric acid and extracted with ether to afford 558 mg (94%) of ester **26:** bp 110 °C (0.1 Torr); IR (film) 1740, 1440, 1455, 1250, 1200, 1165, 1050, 720 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.78 (H-6, doublet of doublets, $J_{5,6}$ = 9, $J_{6,7}$ = 5 Hz), 5.51 (H-7 doublet, J = 5 Hz), 5.25 (H-5 doublet, J = 9 Hz), 3.57 (OCH_3), 1.78 (C-8 CH_3), 0.85 ppm (C-4a CH_3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.3; H, 9.3.

The spectral properties of this ester were identical with those of an optically active sample prepared by Hortmann.[4]

(±)-Occidentalol (27). A solution of 69 mg (0.315 mmol) of the ester **26** in 2.0 mL of ether at 0 °C was treated with 0.46 mL (1.0 mmol) of 2.2 M methyllithium. After the mixture had stirred for 10 min, it was poured into water and extracted with ether to afford 58 mg (84%) of occidentalol **27:** IR (film) 3400, 1645, 1590, 1380, 1360, 1245, 1015, 945, 920, 900, 880, 850, 780, 760, 720 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.74 (H-2 doublet of doublets, $J_{1,2}$ = 9, $J_{2,3}$ = 5 Hz), 5.45 (H-3 doublet, J = 5 Hz), 5.17 (H-1 doublet, J = 9 Hz), 1.79 (C-4 CH_3), 1.09 (isopropyl CH_3's), 0.84 ppm (C-10 CH_3).[4] A sample secured by preparative liquid chromatography showed spectral properties identical with those reported by Hortmann and Ando.[4]

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Registry No.—**1,** 99-04-7; **2,** 61634-42-2; **3,** 61634-43-3; **4,** 61634-44-4; **6,** 61634-45-5; **7,** 61634-46-6; **7** t-$BuMe_2Si$ ether, 61634-47-7; **8,** 61634-48-8; **9,** 61634-49-9; **10,** 61634-50-2; **11,** 61634-51-3; **12,** 61634-52-4; **13,** 61634-53-5; **14,** 61634-54-6; **15,** 61634-55-7; **16,** 61634-56-8; **17,** 61634-57-9; **18,** 61634-58-0; **19,** 61634-59-1; **20,** 61634-60-4; **21,** 61634-61-5; **24,** 61634-62-6; **25,** 61634-63-7; **26,** 61687-76-1; **27,** 39724-73-7; 4-phenoxybutyl bromide, 1200-03-9; 4-benzyloxybutyl bromide, 60789-54-0; p-toluenesulfonyl chloride, 98-59-9.

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