Pentacyclic Triterpene Synthesis. 6. Synthesis of a Bicyclic Intermediate Corresponding to Rings D and E of β-Amyrin[1]

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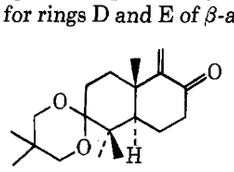
Bicyclic allylic bromide **2**, a viable synthon for rings D and E of the pentacyclic triterpenes of the germanicane class, has been synthesized.

In the preceding paper, we reported the synthesis of optically pure enone **1**, a potentially useful synthon for rings A and B in a general convergent synthesis of pentacyclic triterpenes.[2] In this paper, we report the synthesis of allylic bromide **2**, a synthon for rings D and E of β-amyrin.



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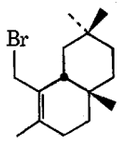


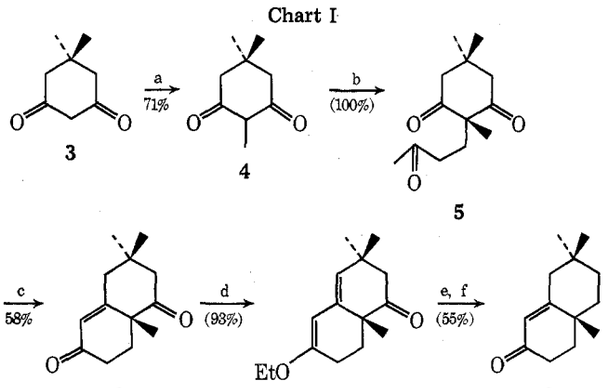
2

Initially, we chose octalone **8**, previously prepared by Halsall,[3] as a convenient starting material for the preparation of **2**. As the Halsall method for the preparation of **8** proved inconvenient on a large scale, we explored alternative methods for its synthesis. Our first synthesis of this material is outlined in Chart I. By this route, octalone **8** is available from dimedone (**3**) in 21% overall yield. Subsequently, we developed the more convenient method summarized in Chart II. Compound **8** is obtained from **3** in substantially higher overall yield by this route (28%), which also proved to be much more adaptable to large-scale synthesis.

Halsall had previously reported that hydrogenation of **8** leads exclusively to the *cis*-decalone **12**.[3] However, as this assignment appears to have been made purely on analogy to similar hydrogenations of steroid enones, we carried out a more rigorous stereochemical proof (Chart III). Enone **8** was reduced catalytically (Pd/C in ethyl acetate or ethanol) and by lithium in ammonia. The products, saturated ketones **12** and **13**, were reduced by the Wolff–Kishner method to give trimethyldecalins **14** and **15**, which are readily separable by capillary GLC. Wolff–Kishner reduction of dione **16**, of known cis stereochemistry,[6] also affords isomer **14**, thus establishing the cis stereochemistry of decalone **12**.

Since decalone **12** undergoes preferential enolization toward C-3,[3] it is necessary to block this position in order to functionalize C-1. Bromination of **12** yields bromo ketone **17** in quantitative yield. Dehydrobromination of **17**, with calcium carbonate in refluxing dimethylacetamide, yielded enone **18**,

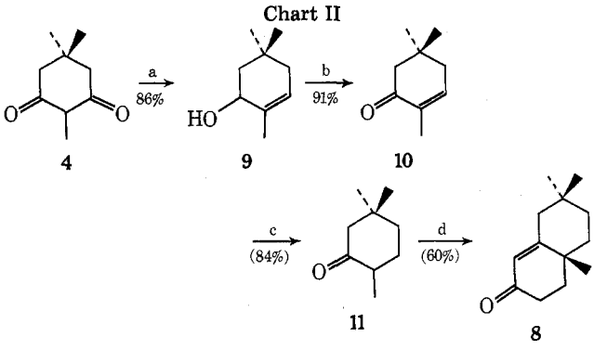
Chart I



3 **4** **5** **6** **7** **8**

a, NaOH, CH_3I, H_2O;[4] b, $CH_3COCH{=}CH_2$, C_2H_5OH, KOH; c, *p*-TsOH, C_6H_6 $-H_2O$; d, $CH(OEt)_3$, C_6H_6, HCl; e, N_2H_4, $(HOCH_2CH_2)_2O$, KOH; f, dioxane, H_2O, H_2SO_4.

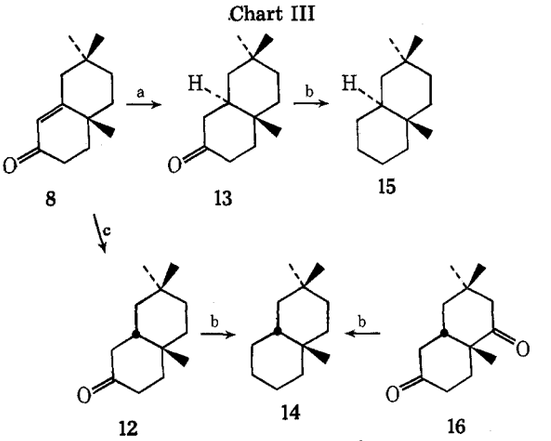
Chart II



4 **9** **10** **11** **8**

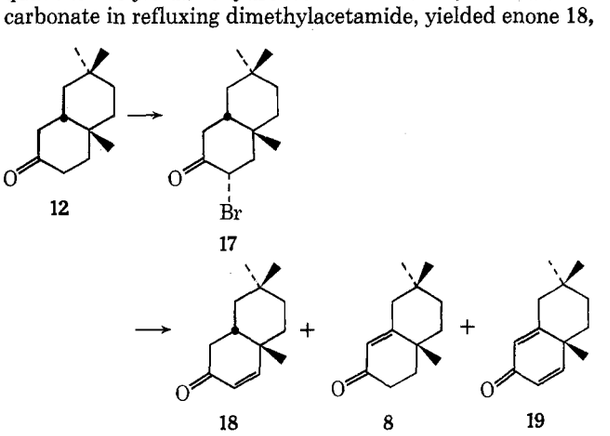
a, $LiAlH_4$, ether; b, H_2CrO_4, C_6H_6, H_2O; c, H_2, Pd/C; d, $CH_3COCH{=}CH_2$, C_6H_6, H_2SO_4.[5]

Chart III



8 **13** **15** **12** **14** **16**

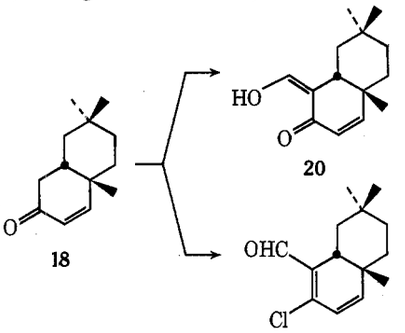
a, Li, NH_3; b, N_2H_4, $(HOCH_2CH_2)_2O$, KOH; c, H_2/Pd.



12 **17** **18** **8** **19**

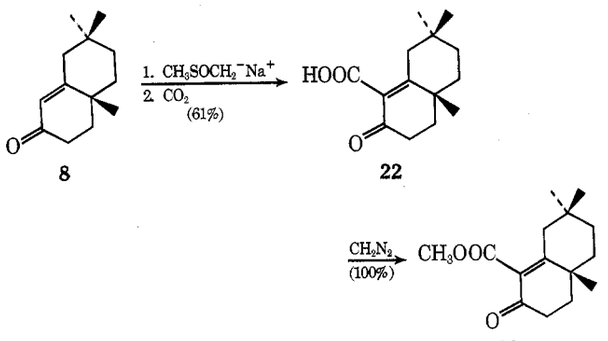
contaminated with 10–20% of enone **8** and a trace of dienone **19** (probably arising from a trace of a dibromo ketone).

Unfortunately, enone **18** proved intractable in all attempts to functionalize C-1. Attempted reaction of **18** with sodium hydride and dimethyl carbonate under a variety of conditions led only to recovered enone. Reaction of **18** with ethyl formate and sodium ethoxide gave a complex mixture. In addition to unreacted starting enone, we were able to isolate β-keto aldehyde **20** as an impure material in rather low yield. Vilsmeier addition (phosphoryl chloride, dimethylformamide, trichloroethylene) on **18** gave chloro aldehyde **21** in about 20% yield,

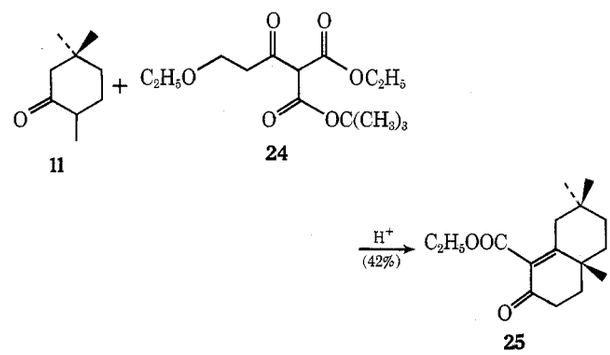


but this yield could not be improved by numerous modifications.

With these difficulties, we turned to direct functionalization of C-1 in enone **8**. Carbonation of the anion produced in the reaction of enone **8** with methylsulfinylmethylide in dimethyl sulfoxide gives keto acid **22** in 61% yield. Diazomethane esterification of **22** affords methyl ester **23** in quantitative yield.

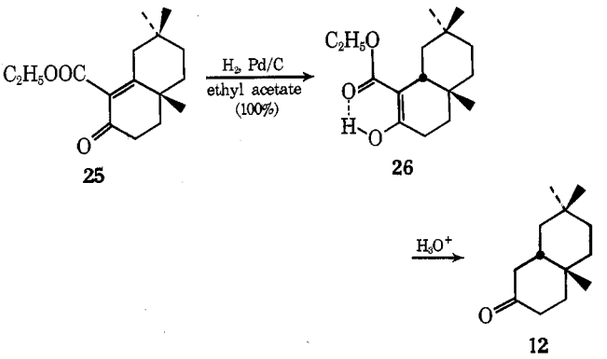


An alternative preparation of keto ester **25** involves an adaptation of the Nazarov annelation.[1b] Reaction of 2,5,5-trimethylcyclohexanone (**11**) with keto diester **24** in refluxing benzene with a catalytic quantity of H_2SO_4 yields β-keto ester **25** in 42% yield. The overall yields of β-keto esters **23** or **25** by the foregoing routes are comparable (37% and 42% from 2,5,5-trimethylcyclohexanone). Although the latter method



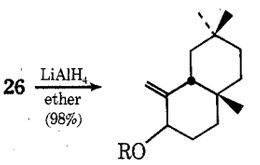
gives a higher yield of keto ester **25**, the annelation reaction requires an extended reaction time.[7] On the other hand, the preparation of keto ester **23** requires the use of diazomethane for esterification.[8]

Catalytic hydrogenation of **25** (Pd/C in ethyl acetate) yields the crystalline β-keto ester **26**, shown to be a single stereoisomer by hydrolysis and decarboxylation to *cis*-decalone **12**.

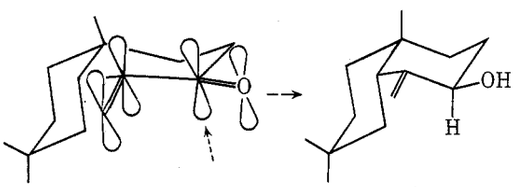


Compound **26** apparently exists totally in the chelated enolic form as shown, since it shows carbonyl absorption at 1650 cm^{-1} and enol ether double bond absorption at 1620 cm^{-1}. The diastereotopic methylene protons of the ethyl group appear as quartets at δ 4.14 and 4.16 ppm.

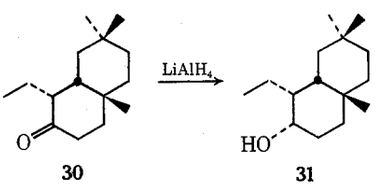
Lithium aluminum hydride reduction of **26**[9] affords allylic alcohol **27** in high yield. The ^1H NMR spectrum of alcohol **27**



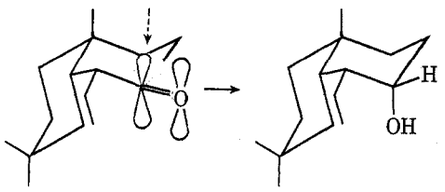
indicates that the hydroxy group occupies the equatorial position. The carbinol proton appears as a broad absorption ($W_{1/2}$ = 15 Hz, δ 4.15 ppm) characteristic of an axial proton.[10] The corresponding proton in acetate **28** appears at δ 5.32 ppm and has $W_{1/2}$ = 15 Hz. Since the *gem*-dimethyl group should fix the decalin in a single chair–chair conformation, it appears that attack of hydride on the presumed intermediate enone **29** occurs exclusively from the axial direction. Such axial at-



tack in a cyclohexanone having an axial substituent at C-3 is unusual. For example, decalone **30** undergoes reduction exclusively to axial alcohol **31**, in which the carbinol proton ap-

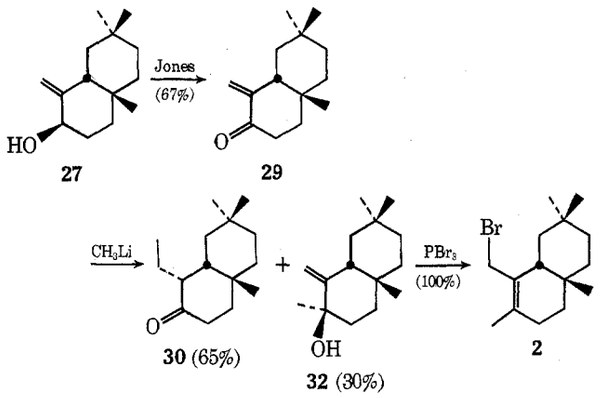


pears as a double doublet (J = 3 and 5 Hz) centered at δ 3.82 ppm. In this case, attack of hydride occurs from the equatorial direction.



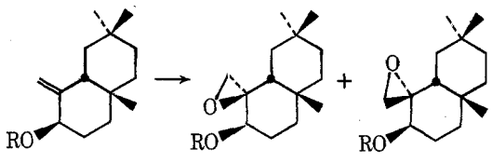
30 31

Oxidation of allylic alcohol **27** (Jones reagent[11]) affords enone **29** in 67% yield. Enone **29** reacts with methyllithium in ether to give the 1,4-addition product **30** in 65% yield, along with 30% of the 1,2-addition product **32**. Ketone **30** and alcohol **32** are conveniently separable by column chromatography. Treatment of tertiary allylic alcohol **32** with phosphorus tribromide in ether gives primary allylic bromide **2** in quantitative yield.



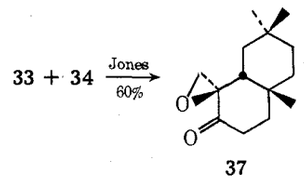
27 29 30 (65%) 32 (30%) 2

Although the synthesis of our target compound **2** was achieved in this manner, the large amount of 1,4 addition to enone **29** precludes the use of this route for viable synthesis. Consequently, we examined other methods for elaboration of alcohol **27**. Oxidation with *m*-chloroperoxybenzoic acid (MCPA) affords epoxy alcohols **33** and **34** in a ratio of 3:1. The predominant top-face oxidation of the double bond appears to be only in part due to direction by the hydroxy group, as acetate **28** gives epoxy acetates **35** and **36** in a ratio of 3:2.



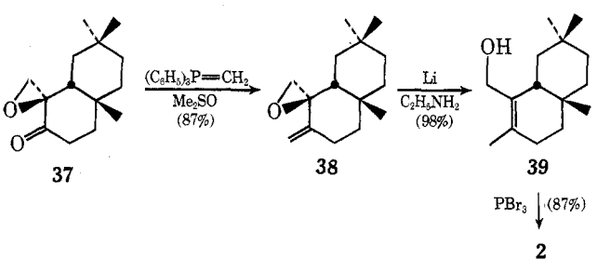
27, R = H; **28**, R = CH_3CO **33**, R = H; **35**, R = CH_3CO **34**, R = H; **36**, R = CH_3CO

Jones oxidation[11] of the mixture of **33** and **34** gives keto epoxide **37** in 60% yield after purification. The oxidation



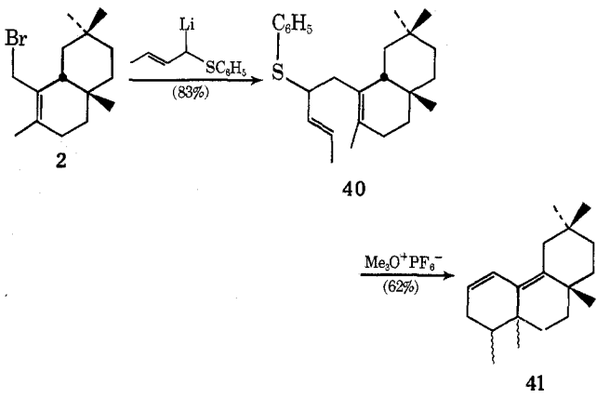
37

product from the minor isomer **34** is presumably lost in purification. Wittig methylenation of **37**, under forcing conditions (see Experimental Section), affords epoxy alkene **38** in yields as high as 87%. Reduction of unsaturated epoxide **38** with lithium in anhydrous ethylamine affords allylic alcohol **39**, which reacts with phosphorus tribromide in ether to give allylic bromide **2** as the sole product. After completion of this work,[1a] van Tamelen, Seiler, and Wierenga reported an alternative synthesis of compound **2**,[12] which they utilized in a biomimetic synthesis of δ-amyrin, β-amyrin, and germanicol. Horan, McCormick, and Arigoni have utilized a sample of **2**, prepared in our laboratory, in an in vivo synthesis of β-amyrin.[13]



37 38 39 2

Preliminary experiments directed toward the further elaboration of allylic bromide **2** have been encouraging. Bromide **2** reacts with phenyl crotyl sulfide anion to give sulfide **40**. When this material is treated with trimethyloxonium hexafluorophosphate in methylene chloride, diene **41** may be



2 40 41

isolated in approximately 60% yield. The structure of **41** is assigned on the basis of its composition and ^1H NMR and uv spectra (one vinyl H, λ_{max} 244 nm, ϵ 4710 M^{-1}). The stereochemistry of this material has not been ascertained. Further experiments will be directed toward coupling bromide **2** with a synthon for rings A and B[2] and completing a synthesis of a pentacyclic triterpene by this route.

Experimental Section

Melting points (Pyrex capillary) are uncorrected. The following instrumentation was used to record spectra: infrared (ir), Perkin-Elmer 137 and 237; ultraviolet (uv), Perkin-Elmer 202; mass spectra, Varian MS-12, Varian M-66, and Consolidated 21-110B; proton magnetic resonance (^1H NMR), Varian A-60 and T-60. The line positions for ^1H NMR spectra are given in the δ scale as parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the order (number of protons, multiplicity, proton assignments). Gas–liquid partition chromatography (GLC) analyses were performed on a Varian Aerograph 90-P instrument. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, Calif.

2,5,5-Trimethyl-2-(3-oxobutyl)cyclohexane-1,3-dione (5). A solution containing 105.2 g (0.684 mol) of dione **4**,[4] 1000 ml of methanol, 100 g (1.43 mol) of methyl vinyl ketone, and 1.5 g of potassium hydroxide was refluxed for 27 h. The solvent was evaporated and the residue was diluted with ether, washed with 10% aqueous sodium carbonate and water, and then dried over magnesium sulfate. Evaporation of the solvent yielded 152.5 g (100%) of a yellow oil. Examination of this oil by ^1H NMR showed it to be almost entirely trione **5** with a small amount of dione **6** present: ^1H NMR (CCl_4) δ 0.88 (3 H, s, Me), 1.07 (3 H, s, Me), 1.14 (3 H, s, Me), 2.03 (3 H, s, acetyl Me); ir (neat) 1735, 1700 cm^{-1}.

4a,7,7-Trimethyl-4,4a,7,8-tetrahydronaphthalene-2(3*H*),-5(6*H*)-dione (6). A mixture containing 149.3 g (0.667 mol) of trione **5** and 55 g of *p*-toluenesulfonic acid in 3000 ml of benzene was refluxed with separation of water. After 48 h, the solution was cooled, washed

with 10% aqueous sodium carbonate and water, and then dried over magnesium sulfate. Evaporation of solvent gave 131.1 g of a red-brown solid. Distillation yielded 84.4 g of a yellow solid (bp 125–140 °C at 0.2 Torr) which was washed with hexane to yield 79.3 g (58%) of white dione **6**: mp 92–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.78 (3 H, s, Me), 1.16 (3 H, s, Me), 1.43 (3 H, s, Me), 5.79 (1 H, d, vinyl H); ir (CCl_4) 1715, 1675, 1620 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.61.

2-Ethoxy-4a,7,7-trimethyl-3,4,6,7-tetrahydronaphthalen-5(4a*H*)-one (7). A solution containing 13.5 g (65.5 mmol) of dione **6**, 10.4 g (70.5 mmol) of triethyl orthoformate, 50 ml of benzene, and 1 ml of 95% ethanol containing 2 drops of concentrated hydrochloric acid was refluxed for 3.5 h, then cooled and poured into 5% aqueous sodium hydroxide. After base extraction, the organic phase was washed with water and dried over $MgSO_4$. Evaporation of the solvent yielded 15.1 g of yellow oil which was distilled to give 14.2 g (93%) of light yellow oil (bp 113–114 °C at 0.4 Torr). The ^{1}H NMR spectrum showed that the keto enol ether **7** was the sole product: ^{1}H NMR (CCl_4) δ 0.98 (3 H, s, Me), 1.13 (3 H, s, Me), 1.20 (3 H, s, Me), 1.27 (3 H, t, Me, J = 7 Hz), 3.74 (2 H, q, OCH_2, J = 7 Hz), 5.10 (2 H, broad s, vinyl H).

4a,7,7-Trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (8). A. A solution prepared from 19.0 g (81.3 mmol) of keto enol ether **7**, 500 ml of diethylene glycol, and 130 ml of hydrazine hydrate was warmed to 120 °C over a 2-h period and maintained at this temperature for 30 min. After cooling to 40 °C, 60 g (1.07 mol) of potassium hydroxide was added and the resulting mixture was heated with concurrent distillation until the pot temperature reached 210 °C. After cooling, the reaction mixture and distillate were combined and extracted with petroleum ether. The organic phase was washed with water and dried over magnesium sulfate, and the solvent was evaporated to yield 16.1 g of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.92 (3 H, s, Me), 0.96 (3 H, s, Me), 0.99 (3 H, s, Me), 1.26 (3 H, t, Me, J = 6 Hz), 3.69 (2 H, q, $-OCH_2-$, J = 7 Hz), 4.82 (1 H, s, vinyl H), 4.95 (1 H, d, vinyl H, J = 2 Hz). This material was stirred overnight in 175 ml of p-dioxane containing 50 ml of 10% sulfuric acid. After dilution with water, the product was isolated by ether extraction. The organic phase was washed with water and dried over $MgSO_4$, and the solvent was evaporated to yield 8.6 g (55%) of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.74 (3 H, s, Me), 0.94 (3 H, s, Me), 1.11 (3 H, s, Me), 5.43 (1 H, d, vinyl H); ir (neat) 1670, 1610 cm^{-1}. Recrystallization of the 2,4-dinitrophenylhydrazone from methanol gave red plates, mp 149.5–150.5 °C (lit.[3] mp 148.5–150 °C).

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.03; H, 6.66; N, 14.94.

B. A mixture of 20.0 g (0.14 mol) of ketone **11**, 16.0 g (0.23 mol) of methyl vinyl ketone, 0.1 ml of concentrated sulfuric acid, and 40 ml of benzene was refluxed for 130 h. After 10 h, another 0.5 ml of acid was added. The black mixture was diluted with 50 ml of hexane, washed with 5% sodium hydroxide and water, dried ($MgSO_4$), and evaporated. Short-path distillation with an open flame gave a yellowish liquid which was fractionally distilled to give 16.7 g (60.9%) of clear liquid, bp 86–88 °C (0.2 Torr). The material prepared in this manner was identical spectrally with the material prepared as outlined in part A.[14]

2,5,5-Trimethylcyclohex-2-en-1-ol (9). To a stirring mixture of 89.5 g (2.37 mol) of lithium aluminum hydride in 3 l. of ether was added 121.4 g (0.789 mol) of dione 4[4] over a period of 1 h. Stirring was continued for 88 h and the excess hydride was then decomposed by the addition of aqueous potassium hydroxide. The reaction mixture was filtered and dried over $MgSO_4$, and the solvent was removed in vacuo to yield 94.5 g (85.7%) of colorless liquid: ^{1}H NMR (CCl_4) δ 0.88 (3 H, s, C-5 Me), 0.96 (3 H, s, C-5 Me), 1.69 (3 H, s, C-2 Me), 2.18 (1 H, s, OH), 3.84 (1 H, unresolved double t, C-1 H), 5.22 (1 H, unresolved m, vinyl H); ir (CCl_4) 3350 cm^{-1}.

2,5,5-Trimethylcyclohex-2-en-1-one (10). To a vigorously stirring solution of 93.7 g (0.67 mol) of alcohol **9** in 400 ml of benzene at 5 °C was added a solution prepared from 80.0 g (0.268 mol) of sodium dichromate dihydrate, 335 ml of water, 108 ml of concentrated sulfuric acid, and 35 ml of glacial acetic acid over a 2.5-h period. After an additional 3 h of stirring, the phases were separated and the aqueous portion extracted once with benzene. The combined organic phases were washed with 10% aqueous sodium carbonate and water, then dried over $MgSO_4$. The solvent was distilled at atmospheric pressure to yield 84.0 g (90.8%) of faintly yellow liquid residue. The ^{1}H NMR spectrum of this crude product revealed less than 5% of the β,γ-unsaturated isomer as the only impurity.

2,5,5-Trimethylcyclohexanone (11). A mixture containing 83.4 g (0.61 mol) of enone **10**, 135 ml of ethyl acetate, and 1.0 g of 10% palladium on carbon was hydrogenated (Parr apparatus). After 18 h, the mixture was filtered and the solvent was removed by distillation at atmospheric pressure to obtain 81.1 g (95.7%) of light yellow liquid residue. This was distilled to yield 70.9 g (83.8%) of colorless liquid: bp 75–80 °C (18–22 Torr); ^{1}H NMR (CCl_4) δ 0.80 (3 H, s, C-5 Me), 0.92 (3 H, d, C-2 Me, J = 6 Hz), 1.04 (3 H, s, C-5 Me); ir (CCl_4) 1710 cm^{-1}. The 2,4-dinitrophenylhydrazone was obtained as yellow-orange needles after recrystallization from methanol, mp 121–122 °C (lit.[3] mp 117–119 °C).

Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.49. Found: C, 56.05; H, 6.37; N, 17.35.

4aβ,7,7-Trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (12). To 18.5 g (96.4 mmol) of enone **8** in 200 ml of ethyl acetate was added 1.4 g of platinum oxide. This was hydrogenated until hydrogen uptake ceased (6 min), then the mixture was filtered and the solvent evaporated to yield 18.4 g (99%) of ketone **12**. Crystallization from hexane gave white plates: mp 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (6 H, s, Me), 1.25 (3 H, s, Me); ir (CCl_4) 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.28; H, 11.44.

4aβ,7,7-Trimethyl-10aβ-decahydronaphthalene (14). This hydrocarbon was prepared by Wolff–Kishner reduction of ketone **11** and dione **16**[6] by the following general procedure. A solution containing 0.9 mmol of ketone **11** or dione **16**, 8 ml of freshly distilled diethylene glycol, and 2 ml of 85% hydrazine hydrate was heated at 120 °C for 3 h and then cooled to room temperature. The flask was fitted for distillation, 1 g of KOH was added, and the alkaline mixture was heated to 210 °C over a 5-h period, then maintained at this temperature for an additional 1 h. The combined distillate and reaction mixture was partitioned between ether and water. The phases were separated and the ether phase was washed well with water. After drying over $MgSO_4$, the ether was evaporated to obtain the hydrocarbon product. Analysis by GLC (100 ft × 0.01 in. Apeizon L, 115 °C, He flow 2.5 ml/min) showed that the hydrocarbons obtained from ketone **11** and dione **16** are identical, and different from the hydrocarbon (**15**) obtained from a similar Wolff–Kishner reduction of *trans*-decalone **13**.

3α-Bromo-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (17). To 5.83 g (30.0 mmol) of ketone **12** in 50 ml of glacial acetic acid was added 4.79 g (30.0 mmol) of bromine in 40 ml of glacial acetic acid. The bromine color was discharged immediately upon addition, and the resulting yellow-brown solution was stirred for 19 h, diluted with water, and extracted with benzene. The organic phase was thoroughly washed with water and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 8.36 g (100%) of light yellow bromo ketone **17**: ^{1}H NMR ($CDCl_3$) δ 0.95 (6 H, s, two Me), 1.39 (3 H, s, Me), 4.96 (1 H, dd, C-3 H, J = 14 and 7 Hz); ir (neat) 1735 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}OBr$: C, 57.25; H, 7.69; Br, 29.24. Found: C, 57.09; H, 7.85; Br, 29.22.

4aβ,7,7-Trimethyl-4a,5,6,7,8,8aβ-hexahydronaphthalen-2(1*H*)-one (18). A mixture containing 8.36 g (30.0 mmol) of crude bromo ketone **17**, 12.7 g (127 mmol) of calcium carbonate, and 100 ml of dimethylacetamide was warmed to 180 °C over a 1-h period and maintained at this temperature for an additional 20 min. After cooling the calcium carbonate was decomposed by the addition of 10% HCl. The crude product was extracted with benzene, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave 5.68 g of brown liquid which was distilled to yield 5.05 g of yellow liquid, bp 74–92 °C (0.2–0.3 Torr). The ^{1}H NMR spectrum of this material revealed the presence of a small amount (10–20%) of enone **8**, in addition to enone **18**. These were separated by chromatography on neutral alumina by elution with pentane/ether. A trace amount of dienone **19** was also isolated.

Enone 18: ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, s, Me), 0.90 (3 H, s, Me), 1.22 (3 H, s, Me), 2.00 (1 H, d, C-1 equatorial H, J = 17 Hz), 2.83 (1 H, dd, C-1 axial H, J = 17 and 5 Hz), 5.83 (1 H, d, C-3 vinyl H, J = 10 Hz), 6.47 (1 H, dd, C-4 vinyl H, J = 10 and 2 Hz); ir (neat) 1680, 1635 cm^{-1}. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol. The material was obtained as red plates, mp 143.5–144.0 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.22; H, 6.63; N, 15.08.

Dienone 19: ^{1}H NMR (CCl_4) δ 0.72 (3 H, s, Me), 1.02 (3 H, s, Me), 1.18 (3 H, s, Me), 5.82 (1 H, unresolved m, C-1 vinyl H), 5.90 (1 H, dd, C-3 vinyl H, J = 10 and 2 Hz), 6.64 (1 H, d, C-4 vinyl H, J = 10 Hz); ir (neat) 1660, 1630 cm^{-1}. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol as red plates, mp 147–149 °C.

Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C,

61.83; H, 5.75; N, 15.09.

1-Carboxy-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (22). Sodium hydride (0.25 g of a 55.2% mineral oil dispersion, 5.8 mmol) was added to an oven-dried three-neck flask fitted with a reflux condenser, a magnetic stirrer, and a rubber septum. After washing the solid twice with anhydrous hexane, a solution of 22 ml of dimethyl sulfoxide and 1.0 g (5.2 mmol) of enone **8** was added. The mixture was stirred until hydrogen evolution had ceased (2 h) and the dimethyl sulfoxide was removed by distillation in vacuo. The dark residue was dissolved in 20 ml of anhydrous ether and poured into a stirring slurry of 50 ml of ether and crushed dry ice (prepared in a glove bag) cooled in a dry ice/isopropyl alcohol bath. After 6 h, the bath was removed and stirring was continued overnight. The product was extracted with 0.02 N sodium hydroxide. After washing the basic solutions with ether, they were cooled, acidified, and extracted with methylene chloride. The organic solutions were washed with water, dried ($MgSO_4$), and evaporated to afford 770 mg (61.1%) of semisolid material: ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, s, Me), 1.10 (3 H, s, Me), 1.32 (3 H, s, Me), 11.18 (1 H, broad s, COOH).

Anal. Calcd for $C_{14}H_{20}O_3$: mol wt, 215.9847. Found: 215.9839 (high-resolution mass spectrum).

The neutral fractions from the extraction were shown by ^{1}H NMR to be a mixture of enone **8** and its β,γ isomer.

Attempted recrystallization of the acid or its sodium salt was unsuccessful. Some decarboxylation occurred during these attempts at purification. If the final product was isolated by filtration rather than extraction, the monohydrate was isolated as a fine, white solid, mp 100 °C dec.

Anal. Calcd for $C_{14}H_{20}O_3 \cdot H_2O$: C, 66.12; H, 8.72. Found: C, 66.41; H, 8.58.

1-(Methoxycarbonyl)-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (23). Excess diazomethane was added to a solution of 190 mg (0.8 mmol) of **22** and 1 ml of ether, followed by dropwise addition of acetic acid to decompose the excess methylating agent. The resulting solution was evaporated to give 200 mg (100%) of liquid which solidified upon standing. Recrystallization from hexane gave the analytical sample: mp 71.5–72.5 °C; ir (CCl_4) 1742, 1684, 1629, 1462, 1429, 1348, 1326, 1318, 1290, 1236, 1024, 866 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 1.00 (3 H, s, Me), 1.25 (3 H, s, Me), 3.68 (3 H, s, Me).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.61; H, 8.68.

1-(Ethoxycarbonyl)-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (25). This material was prepared by the procedure reported in ref 1b, p 76: ^{1}H NMR (CCl_4) δ 0.80 (3 H, s, Me), 1.0 (3 H, s, Me), 1.23 (3 H, s, Me), 1.24 (3 H, t, ester Me, J = 7 Hz); ir (CCl_4) 1735, 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 8.96.

1-(Ethoxycarbonyl)-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphth-2-ol (26). A mixture of 14.53 g (55 mmol) of β-keto ester **25**, 1.5 g of 10% palladium on carbon, and 150 ml of ethyl acetate was hydrogenated on a Parr apparatus for 16 h. The reaction mixture was filtered and the solvent removed in vacuo to yield 14.56 g (100%) of enolic β-keto ester **26** which solidified on standing. Recrystallization from hexane gave the analytical sample: mp 35.0–38.0 °C; ^{1}H NMR (CCl_4) δ 0.88 (3 H, s, Me), 0.94 (6 H, s, two Me), 1.28 (3 H, t, ester Me, J = 7 Hz), 4.14 (1 H, q, $-OCH_2CH_3$, J = 7 Hz), 4.16 (1 H, q, $-OCH_2CH_3$, J = 7 Hz); ir (CCl_4) 1650, 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.22; H, 9.57.

4aβ,7,7-Trimethyl-1-methylene-8aβ-decahydronaphth-2β-ol (27). To a stirring mixture of 13.87 g (366 mmol) of lithium aluminum hydride in 500 ml of ether was added 24.39 g (91.7 mmol) of β-keto ester **26** in 150 ml of ether over a period of 1 h. Stirring was continued for 22 h and the excess hydride was then decomposed by the successive addition of 14 ml of water, 14 ml of 15% aqueous potassium hydroxide, and 42 ml of water. The mixture was filtered and dried and the solvent was removed in vacuo to give 17.1 g (97.5%) of colorless liquid which crystallized upon standing overnight. The analytical sample (mp 82–83 °C) was prepared by recrystallization from hexane: ^{1}H NMR (CCl_4) δ 0.92 (9 H, s, three Me), 3.14 (1 H, broad s, CHO**H**), 4.15 (1 H, broad unresolved m, C**H**OH), 4.68 (1 H, broad t, vinyl H), 4.92 (1 H, broad t, vinyl H); ir (CCl_4) 3650, 3320, 1655, 905 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.57; H, 11.46.

Alcohol **27** was acetylated for 18 h at room temperature with acetic anhydride in pyridine. Acetate **28** was obtained in about 90% yield: ^{1}H NMR (CCl_4) δ 0.93 (3 H, s, Me), 0.95 (6 H, s, Me's), 2.00 (3 H, s, CH_3CO), 4.75 (2 H, m, vinyl H's), 5.32 (1 H, broad m, $W_{1/2}$ = 22 Hz, >CHOAc); ir (neat) 1740, 1650 cm^{-1}.

4aβ,7,7-Trimethyl-1-methylene-1,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(3*H*)-one (29). To a solution of 1.85 g (8.87 mmol) of alcohol **27** in 60 ml of acetone, cooled in an ice bath, was added 8 ml (32 mmol) of Jones reagent.[11] After 15 min, the excess oxidant was decomposed by the addition of 4 ml of isopropyl alcohol. The reaction mixture was diluted with ether and water and the organic phase was washed with 10% aqueous sodium carbonate and water, then dried. The solvent was removed to yield 1.23 g (67.4%) of slightly yellow liquid: ^{1}H NMR (CCl_4) δ 0.84 (3 H, s, Me), 0.88 (3 H, s, Me), 1.00 (3 H, s, Me), 4.90 (1 H, d, vinyl H, J = 2 Hz), 5.56 (1 H, d, vinyl H, J = 2 Hz); ir (CCl_4) 1685, 1615 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O$: mol wt, 206.1671. Found: 206.1677 (high-resolution mass spectrum).

1α-Ethyl-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (30) and 2α,4aβ,7,7-Tetramethyl-1-methylene-8aβ-decahydronaphth-2β-ol (32). To a stirring solution of 10.95 ml (17.5 mmol) of 1.64 M methyllithium in ether was added 1.203 g (5.84 mmol) of enone **29** in 20 ml of ether over a 10-min period. After an additional 1 h of stirring, the excess methyllithium was decomposed by the addition of 1 ml of 10% HCl. The reaction mixture was diluted with 10% HCl and ether and the layers separated. The organic phase was washed with water and dried. The solvent was removed to yield 1.204 g of light yellow liquid. Spectral analysis of the crude product showed it to be a mixture of starting material, alcohol **32**, and ketone **30**, in a ratio of 1:3:7 (based on ^{1}H NMR). The two products were isolated by chromatography on 50 g of basic alumina (activity 1) eluting with hexane/ether, and purified by crystallization from hexane.

Ketone 30: mp 59–61 °C; ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.90 (3 H, s, Me), 1.28 (3 H, s, Me); ir (CCl_4) 1710 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.75; H, 11.78.

Alcohol 32: mp 82–83.5 °C; ^{1}H NMR (CCl_4) δ 0.94 (9 H, s, three Me), 1.34 (3 H, s, Me), 4.72 (1 H, d, vinyl H, J = 2 Hz), 5.18 (1 H, d, vinyl H, J = 2 Hz); ir (CCl_4) 3650, 3525, 1630, 915 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.19; H, 11.63.

1α-Ethyl-4aβ,7,7-trimethyl-8aβ-decahydronaphth-2α-ol (31). To 26.5 mg (0.7 mmol) of lithium aluminum hydride in 0.8 ml of ether was added 39.0 mg (0.175 mmol) of ketone **30** in 1.4 ml of ether. After stirring for 20 h, the excess hydride was decomposed by the successive addition of 25 ml of water, 25 ml of 15% aqueous KOH, and 75 ml of water. The reaction mixture was diluted with ether and the layers separated. The ether layer was dried ($MgSO_4$) and the solvent removed in vacuo to give 35.0 mg of colorless liquid: ^{1}H NMR (CCl_4) δ 0.82 (3 H, s, Me), 0.92 (3 H, s, Me), 0.96 (3 H, s, Me), 3.81 (1 H, q, C**H**OH, J = 5 Hz); ir (CCl_4) 3650, 3320, 1460, 1040, 1005, 952, 932 cm^{-1}.

Anal. Calcd for $C_{15}H_{28}O$: mol wt, 224.2140. Found: 224.2141 (high-resolution mass spectrum).

1,4aβ,7,7-Tetramethyl-1β,9-oxido-8aβ-decahydronaphth-2β-ol (33) and 4aβ,7,7-Trimethyl-1α,9-oxido-8aβ-decahydronaphth-2β-ol (34). To a stirring solution of 10.0 g (48.1 mmol) of allylic alcohol **27** in 150 ml of chloroform, cooled in an ice bath, was added 10.76 g (53 mmol) of 85% *m*-chloroperoxybenzoic acid in a mixture of 90 ml of chloroform and 10 ml of 95% ethanol. The oxidant was added dropwise over a period of 45 min. The reaction mixture was stirred for 16 h, during which time it warmed to room temperature. Excess peroxy acid was decomposed by the addition of 20% aqueous sodium sulfite. The organic phase was washed with 10% aqueous NaOH and water and then dried. The solvent was removed to give 10.90 g (100%) colorless liquid which crystallized upon standing. The crude product contained **33** and **34** in a ratio, as judged by its ^{1}H NMR spectrum, of 3:1. Two crystallizations from hexane gave epoxy alcohol **33** as a white solid: mp 90.5–92.0 °C; ^{1}H NMR (CCl_4) δ 0.84 (3 H, s, Me), 0.94 (3 H, s, Me), 0.98 (3 H, s, Me), 2.36 (1 H, d, epoxy CH, J = 6 Hz), 2.60 (1 H, d, C**H**OH, J = 3 Hz), 3.08 (1 H, d, epoxy CH, J = 6 Hz), 3.88 (1 H, broad m, C**H**OH); ir (CCl_4) 3630, 3520, 938, 896 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.20; H, 10.51.

1,4aβ,7,7-Tetramethyl-1β,9-oxido-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (37). To a stirring solution of 10.8 g (48.7 mmol) of a 3:1 mixture of epoxy alcohols **33** and **34** in 250 ml of acetone, cooled in an ice bath, was added 40 ml (160 mequiv) of Jones reagent[11] over 1 min. Stirring was continued at 0 °C for 15 min, and the excess Jones reagent was then decomposed by the addition of 20 ml of isopropyl alcohol. The reaction mixture was diluted with ether and water and the organic phase was washed with 10% aqueous Na_2CO_3 and water, then dried. The solvent was removed to give 6.22

g of a slightly yellow solid. Crystallization from hexane gave the analytical sample: mp 93–93.7 °C; ^{1}H NMR (CCl_4) δ 0.86 (3 H, s, Me), 0.95 (3 H, s, Me), 1.28 (3 H, s, Me), 2.79 (2 H, s, epoxy CH_2); ir (CCl_4) 1720, 890 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.46; H, 9.99.

1,4aβ,7,7-Tetramethyl-2-methylene-1β,9-oxido-8aβ-decahydronaphthalene (38). A 488-mg sample of 56.8% sodium hydride in mineral oil (11.54 mmol of sodium hydride) was washed several times with hexane under a nitrogen atmosphere. The last traces of hexane were removed under a nitrogen stream and 12.5 ml of dimethyl sulfoxide was added. The mixture was heated at 75 °C under nitrogen until evolution of hydrogen ceased (50 min). The solution was cooled to room temperature and 4.09 g (11.54 mmol) of methyltriphenylphosphonium bromide was added. Solution was effected by mild warming, and the clear yellow liquid was then allowed to stand at room temperature for 30 min. A 1.28-g (5.77 mmol) portion of epoxy ketone **37** was added to the ylide solution and the resulting mixture was heated at 75 °C until no starting material could be observed by TLC analysis (21 h). The reaction mixture was partitioned between hexane and water. After separation, the organic phase was washed with water and dried. The solvent was removed to obtain a light yellow liquid containing a small amount of orange solid. The crude product was taken up in hexane and the triphenylphosphine oxide precipitated after refrigeration at −30 °C for 24 h. Filtration and solvent removal gave 1.10 g (87%) of epoxide **38** as a slightly yellow liquid: ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.93 (3 H, s, Me), 1.10 (3 H, s, Me), 2.40 (1 H, d, epoxy CH, J = 7 Hz), 2.58 (1 H, d, epoxy CH, J = 7 Hz), 4.63 (1 H, unresolved m, vinyl H), 4.80 (1 H, unresolved m, vinyl H); ir (CCl_4) 1655, 1470, 965, 925, 913, 900 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O$: mol wt, 220.1827. Found: 220.1833 (high-resolution mass spectrum).

Yields in this reaction average 70%. It is critical that this reaction be performed under strictly anhydrous conditions.

1-Hydroxymethyl-2,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (39). To a solution of 624 mg (2.84 mmol) of allylic epoxide 38 in 100 ml of ethylamine (distilled from sodium) was added 43.0 mg (6.2 mmol) of lithium. The reaction mixture was stirred for 1.5 h at reflux. Excess lithium was decomposed by the addition of sodium nitrite and the solvent removed under a nitrogen stream. The residue was partitioned between saturated ammonium chloride and ether. The layers were separated and the organic phase was washed with water, dried ($MgSO_4$), and evaporated in vacuo to obtain 619 mg (98%) of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.82 (3 H, s, Me), 0.88 (3 H, s, Me), 0.92 (3 H, s, Me), 1.61 (3 H, s, vinyl Me), 2.40 (1 H, s, OH), 3.77 (1 H, d, CHOH, J = 11 Hz), 4.06 (1 H, d, CHOH, J = 11 Hz); ir (CCl_4) 3650, 3450 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: mol wt, 222.1983. Found: 222.1986 (high-resolution mass spectrum).

1-Bromomethyl-2,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (2). A. To 50 mg (0.23 mmol) of tertiary allylic alcohol **32** in 1.5 ml of ether was added 0.034 ml (0.36 mmol) of phosphorus tribromide. After stirring for 16 h, the reaction mixture was diluted with ether, washed with 5% aqueous Na_2CO_3 and water, and dried ($MgSO_4$). Removal of the solvent in vacuo afforded 60 mg (93.5%) of bromide **2** as a light yellow liquid: ^{1}H NMR (CCl_4) δ 0.86 (3 H, s, Me), 0.94 (3 H, s, Me), 0.97 (3 H, s, Me), 1.68 (3 H, s, vinyl Me), 3.66 (1 H, d, CHBr, J = 10 Hz), 4.13 (1 H, d, CHBr, J = 10 Hz); ir (CCl_4) 2940, 1020 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}Br$: mol wt, 284.1141. Found: 284.1131 (high-resolution mass spectrum).

B. To 400 mg (1.80 mmol) of primary allylic alcohol **39** in 25 ml of ether was added 0.35 ml (3.68 mmol) of phosphorus tribromide. The reaction mixture was stirred for 22 h and then washed with 5% aqueous Na_2CO_3 and water. After drying ($MgSO_4$), the solvent was removed to give 447 mg (87%) of bromide **2** as a faintly yellow liquid. Spectra (^{1}H NMR and ir) of this compound were identical with those obtained for the product prepared by method A.

1-(2-Thiophenyl-3-pentenyl)-2,4aβ,7,7-tetramethyl-3,4,4a,-5,6,7,8,8aβ-octahydronaphthalene (40). A magnetically stirred solution of 540 mg (3.29 mmol) of crotyl phenyl sulfide, 5.66 ml of diazabicyclooctane solution (0.56 M in tetrahydrofuran, 3.16 mmol), and 4.5 ml of anhydrous THF under nitrogen was cooled to −20 °C (carbon tetrachloride/dry ice). n-Butyllithium (1.49 ml, 2.17 M in hexane, 3.24 mmol) was added and the resulting yellow-orange solution stirred for 30 min. A mixture of 450 mg (1.58 mmol) of bromide **2** and 2.7 ml of THF was added and stirring was continued for another 30 min. After 15 min, a solid (probably lithium bromide) began to separate. The bath was removed and after another 1 h, the reaction was quenched with ammonium chloride. The product was diluted with ether, washed with water, saturated brine, dried ($MgSO_4$), and evaporated to give 570 mg of yellowish oil. After Kugelrohr distillation (60 °C, 0.5 Torr) to remove the excess crotyl sulfide, the product was chromatographed (10 g of silica gel, hexane) to give 480 mg (82.6%) of clear oil: ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.90 (6 H, s, Me's), 1.55 (3 H, broad s, Me), 3.46 (1 H, m, >$CHSC_6H_5$), 5.20 (2 H, m, vinyl H's), 7.16 (5 H, m, aromatic H's); ir (neat) 1479, 1458, 1437, 1376, 1361, 963, 739, 691 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}S$: mol wt, 368.2540. Found: 368.2583 (high-resolution mass spectrum).

1,6,6,8a,10a-Pentamethyl-1,2,5,6,7,8,8a,9,10,10a-decahydrophenanthrene (41). A solution of 210 mg (0.56 mmol) of **40**, 220 mg (1.08 mmol) of trimethyloxonium hexafluorophosphate, and 10 ml of methylene chloride was stirred under nitrogen for 4 h. After quenching with saturated Na_2CO_3, the deep purple solution slowly changed to red and then to yellow-orange. The solvent was removed in vacuo and the residue was taken up in ether, washed with water and saturated brine, dried ($MgSO_4$), and evaporated to afford 170 mg of yellow-orange oil. Preparative TLC (hexane) gave 89 mg (61.5%) of yellow oil: ^{1}H NMR (CCl_4) δ 0.88 (18 H, broad s), 5.28 (2 H, broad s, vinyl H's); ir (CCl_4) 1458, 1437 (shoulder), 1377, 1361, 1244, 967, 865 cm^{-1}; uv (hexane) 244 nm (ε 4710).

Anal. Calcd for $C_{19}H_{30}$: mol wt, 258.2348. Found: 258.2344 (high-resolution mass spectrum).

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Registry No.—**2,** 59270-12-1; **4,** 1125-11-7; **5,** 59270-13-2; **6,** 24810-40-0; **7,** 59270-14-3; **8,** 17323-26-1; **8** 2,4-DNP, 59270-15-4; **9,** 59270-16-5; **10,** 42747-41-1; **11,** 33543-18-9; **11** 2,4-DNP, 47300-89-0; **12,** 7056-56-6; **17,** 59270-17-6; **18,** 59270-18-7; **18** 2,4-DNP, 59270-19-8; **19,** 59270-20-1; **19** 2,4-DNP, 59270-21-2; **22,** 59270-22-3; **23,** 59270-23-4; **25,** 35482-84-9; **26,** 59270-24-5; **27,** 35482-86-1; **28,** 59270-25-6; **29,** 59270-26-7; **30,** 59270-27-8; **31,** 59270-28-9; **32,** 59270-29-0; **33,** 35482-87-2; **34,** 59331-27-0; **37,** 35482-88-3; **38,** 35482-89-4; **39,** 35482-90-7; **40,** 59270-30-3; **41,** 59270-31-4; methyl vinyl ketone, 78-94-4; bromine, 7726-95-6; diazomethane, 334-88-3; acetic anhydride, 108-24-7; phosphorus tribromide, 7789-60-8; crotyl phenyl sulfide, 702-04-5.

References and Notes

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(8) Several attempts to accomplish acid-catalyzed esterification of keto acid **22** were not promising.
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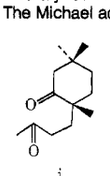
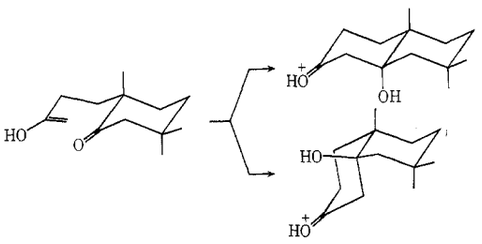
(10) (a) A. Hassner and C. H. Heathcock, *J. Org. Chem.*, **29,** 1350 (1964); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 77.
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(12) E. E. van Tamelen, M. P. Seiler, and W. Wierenga, *J. Am. Chem. Soc.*, **94,** 8229 (1972).
(13) H. Horan, J. P. McCormick, and D. Arigoni, *Chem. Commun.*, 73 (1973).
(14) The two stages in this acid-catalyzed Robinson annelation[5] occur with dramatically different rates. The Michael addition, leading to dione i, occurs



i

fairly rapidly; a benzene solution 3.2 M in ketone **11,** 4 M in methyl vinyl ketone, and containing 2.5 ml of concentrated H_2SO_4 per liter of benzene is completely converted into dione i after 16 h reflux. The subsequent aldol condensation of i, leading to enone **8,** requires refluxing a benzene solution



0.55 M in dione I and containing 8 ml of concentrated H_2SO_4 per liter of benzene for 70 h.

The extreme slowness of this aldol condensation is probably due to the fact that a 1,3-diaxial relationship is created in either of the two modes of cyclization shown.

We,[15] and others,[16] have recently found that the acid-catalyzed method of accomplishing Robinson annelations is facilitated in such cases by refluxing the initially formed dione with ethanolic KOH to accomplish the aldol stage of the annelation.

(15) R. D. Clark, E. G. DelMar, and C. H. Heathcock, unpublished observations.

(16) P. M. Worster, Ph.D. Thesis, University of British Columbia, 1975.

Charge Localization in the Carbonium Ions of Methylbenzanthracenes

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Covalent binding of aromatic hydrocarbons to cellular macromolecules, the first probable step in the tumor-initiating process, requires metabolic activation by monooxygenase enzyme systems. Acid-catalyzed proton–deuterium exchange was used as a model to simulate the electrophilic oxygen atom activated by such enzymes. Kinetics of exchange with deuterium ion for a series of carcinogenic and noncarcinogenic methylbenzanthracenes were studied by NMR in two sets of conditions, i.e., CCl_4–CF_3COOD (85:15 v/v and 50:50 v/v). Deuteration of the potent carcinogen 7,12-dimethylbenz[*a*]anthracene at the most basic position C-12 generated a carbonium ion with charge localized at the complementary 7 position, resulting in the specific deuteration of the attached methyl group. Similarly, selective attack of deuterium ion on C-6 in 3-methylcholanthrene produced a carbonium ion with a high degree of charge localization at C-12b and, consequently, specific deuteration at the adjacent methylene group. This study has revealed that charge localization in the carbonium ion renders this intermediate chemically reactive; such a distinctive property might play a role in the bioactivation of these compounds.

The common feature unifying the wide variety of structures of chemical carcinogens is the electrophilic character[1,2] of the reactive species responsible for binding to cellular macromolecules. Reaction of these electrophiles with biological nucleophilic targets constitutes the first essential step that is critical in the succession of events leading to neoplasia. In the case of the inert polycyclic aromatic hydrocarbons, binding activation is supplied by monooxygenase enzymes.[3,4]

From a chemical standpoint the hydroxylation reaction catalyzed by these nonspecific enzyme systems points to an oxygen atom transfer reaction, the reactive species being an oxygen atom with six electrons in its outer shell.[5,6]

Although an enzymic mechanism may be different from any known chemical mechanism, it still must fall within the framework of basic chemical laws, and the use of a chemical model might provide fruitful information on the complex mechanism of metabolic activation of these compounds. Following this line of reasoning, without pretense of simulating the "oxenoid" character of the enzymically activated oxygen but solely its electron-deficient properties, the kinetics of acid-catalyzed proton–deuterium exchange by NMR were studied for a series of carcinogenic and noncarcinogenic methylbenzanthracenes. These experiments compared the relative reactivities of the most basic positions and the relative basicities of different sites in the same molecule.

The purpose of this approach was to evaluate whether it was possible to generalize the proposed mechanism of hydrocarbon activation[7] to an extensive series of carcinogenic hydrocarbons. In such a mechanism, attack of the enzymically catalyzed oxygen atom at the most reactive substituting positions would form electrophilic centers at sites complementary to the points of activation, and such centers may react with cellular targets.

Results and Discussion

Charge Localization in the Carbonium Ion of 7,12-Dimethylbenz[*a*]anthracene and 3-Methylcholanthrene by NMR. The protonation of 7,12-dimethylbenz[*a*]anthracene (7,12-DMBA) on C-12 in acid medium was previously proposed[8] and charge localization on C-7 in the corresponding arenonium ion was suggested by MO calculations. We have determined the structure of the arenonium ion by comparing the NMR spectra of 7,12-DMBA in neutral and protonated or deuterated acidic solvents (see paragraph at end of paper regarding supplementary material). The ratio of the integrated intensities of the proton peaks in the spectrum of 7,12-DMBA in CCl_4 is, from high to low field, 3:3:5:1:1:2:1. Assignment of the 7-CH_3 (δ 3.00) and 12-CH_3 (δ 3.29) resonances was made by comparison with the spectra of 7-methylbenz[*a*]anthracene (7-MBA) (7-CH_3, δ 3.00) and 12-methylbenz[*a*]anthracene (12-MBA) (12-CH_3, δ 3.32) under the same conditions. A good general correlation exists between the methyl chemical shifts of the 12 monosubstituted methylbenzanthracenes[9] and the corresponding aryl protons of benzanthracene.[10]

The spectrum of 7,12-DMBA in CCl_4–CF_3COOH–H_2SO_4 (volume ratios 50:46.67:3.33) appears generally shifted to lower field with respect to the spectrum in CCl_4. This is attributable to the presence of the positive charge, as well as to the increased polarity of the solvent system. However, the 12-CH_3 group (details of assignment given below) is shifted toward the aliphatic region (δ 1.72) and occurs as a doublet (J = 7.6 Hz). A new quartet at δ 5.61 corresponding to the proton added at the basic 12 position (see below) shows the same coupling constant (J = 7.6 Hz) as the 12-CH_3 doublet. The original compound could be recovered unchanged by dilution with cold water and extraction into CCl_4.