was then acidified with excess hydrochloric acid and extracted three times with ether. The combined ethereal solution was washed with water and saturated salt solution and dried over anhydrous sodium sulfate, and then the ether was removed at reduced pressure on the steam bath.

The resulting crude triacid **24** (425 mg, 70%) was heated for 0.5 hr with 3 ml of thionyl chloride. The excess thionyl chloride was removed at reduced pressure, and two 3-ml portions of benzene were successively removed from the residue by distillation, finally at reduced pressure. The resulting material was dissolved in 3 ml of absolute methanol containing 0.098 ml (95 mg, 1.2 mmoles) of dry pyridine, and the solution was stirred for 1 hr while cooled in an ice bath. The reaction mixture was diluted with water and extracted with ether, and the ethereal extracts were washed successively with 2% aqueous sulfuric acid, water, 10% aqueous potassium bicarbonate, and saturated salt solution. After the ethereal solution was dried over anhydrous sodium sulfate, the ether was removed at reduced pressure on the steam bath, and the crude ester anhydride **22** was evaporatively distilled at 150° (0.03 mm). The distillate amounted to 260 mg (62%), and a portion was redistilled at 145° (0.03 mmole) for analysis.

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.21; H, 8.58.

Infrared showed λ_{max}^{film} 5.4, 5.6 (s) (anhydride >C=O), 5.79 μ (s) (ester >C=O).

8β-Carbomethoxy-13-one (23).—A solution of 260 mg (0.74 mmole) of freshly distilled ester anhydride **22** in 5 ml of benzene was added to a stirred suspension of 1.1 g (20 mmoles) of sodium methoxide in 20 ml of benzene under a nitrogen atmosphere. The reaction mixture was stirred and heated under reflux for 4 hr, cooled, andt reated with 15 ml of water. The benzene layer was separated and washed with 5% aqueous sodium hydroxide; the combined aqueous washes were made strongly acidic with concentrated hydrochloric acid. The precipitated organic material was extracted with ether, and the ethereal solution was washed with water and then saturated salt solution. After the ethereal solution was dried over anhydrous sodium sulfate, the solvent was removed at reduced pressure on the steam bath, and the residue was dissolved in 10 ml of acetic acid.

The above acetic acid solution was treated with 5 ml of concentrated hydrochloric acid and 1 ml of water, and the mixture was heated under reflux in a nitrogen atmosphere for 1 hr. The mixture was concentrated at reduced pressure on the steam bath, diluted with 10 ml of water, and the aqueous liquors were extracted with ether. The resulting ethereal solution was washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath.

The above residue was treated with excess ethereal diazomethane, and the material resulting after removal of the ether was chromatographed on 20 g of Florisil. Elution of the column with 500 ml of benzene afforded 70 mg of a yellow oil which crystallized on trituration in petroleum ether (30–60°) at −70°. Crystallization of this solid from ether–petroleum ether (30–60°) afforded 60 mg (30%) of the keto ester **23**, mp 128–133°. The analytical sample, obtained after one further crystallization from the same solvent pair, was in the form of colorless prisms and melted at 135–137°.

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.45; H, 9.85. Found: C, 74.52; H, 9.91.

Infrared showed $\nu_{max}^{HCCl_3}$ 1724 (s, broad) (ester and ketone >C=O), 1200 cm^{-1} (s) (C–O–C).

The infrared spectrum of this synthetic sample was indistinguishable from that of a naturally derived sample.

Acknowledgment.—The authors gratefully acknowledge the receipt of a sample of the keto ester **23** in its optically active form from Professor L. H. Briggs. Partial support from the Research Corporation and the National Science Foundation (G 1984) for this work is gratefully acknowledged. The authors are grateful to the Parke, Davis & Company spectrographic laboratory for measuring several infrared spectra.

Experiments Directed toward the Total Synthesis of Terpenes. VIII. The Total Synthesis of (±)-Kaurene and (±)-Atisirene[1]

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The synthesis of (±)-kaurene **18** from the olefinic aldehyde **19** *via* hydroboration of the double bond and aldol-type cyclization of the C_{14} keto acetal **3** to form the bridged system is recorded. The route makes available as well the substituted bicyclo[2.2.2]octane derivatives through similar cyclization of the isomeric C_{13} keto acetal **2** from the hydroboration and leads to (±)-atisirene **17**.

In the preceding paper[3] in this series we described a scheme whereby the tricyclic keto ester **20** could be prepared and pointed out the utility of such an intermediate for the formation of the bridged system present in the phyllocladene **21**.[4] The key intermediate in the synthesis of the keto ester **20** was the aldehyde **19** which was readily obtained *via* the Claisen rearrangement of the corresponding vinyl ether. The synthesis of the keto ester **20** requires oxidative cleavage of ring C of the aldehyde **19** and recyclization in order to obtain the desired *trans* fusion between rings B and C. The availability of this aldehyde **19** and the necessary *cis* fusion between the B and C rings that results from the vinyl ether rearrangement, make this material particularly attractive for the synthesis of the epimeric keto ester **22**. One might then envisage the conversion of this keto ester **22** to kaurene **18**[5] *via* a similar sequence of reactions to those used by Turner and co-workers[6] for the keto ester **20** → phyllocladene **21** conversion. If such a conversion could be realized, the utility of the olefinic aldehyde and the sequence of reactions by which it was derived would be greatly enhanced. Thus, the same aldehyde would provide entry into both stereochemical series represented by phyllocladene **21** and kaurene **18**. (See Chart I.)

The first part of the proposed transformation of the aldehyde **19** to the keto ester **22** to be solved was the

(1) A preliminary report of part of this work appeared in *J. Org. Chem.*, **27**, 3741 (1962).

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(3) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966).

(4) P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960); L. H. Briggs, B. F. Cain, B. R. Davies, and J. K. Wilmhurst, *Tetrahedron Letters*, **No. 8**, 8 (1959).

(5) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. Wilmhurst, *J. Chem. Soc.*, 1345 (1963).

(6) R. B. Turner and K. H. Gänshirt, *Tetrahedron Letters*, 231 (1961).

CHART I

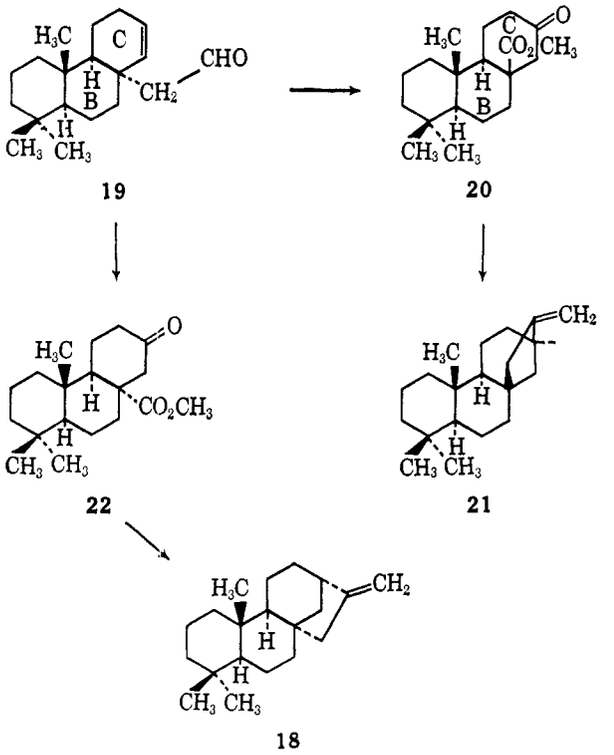
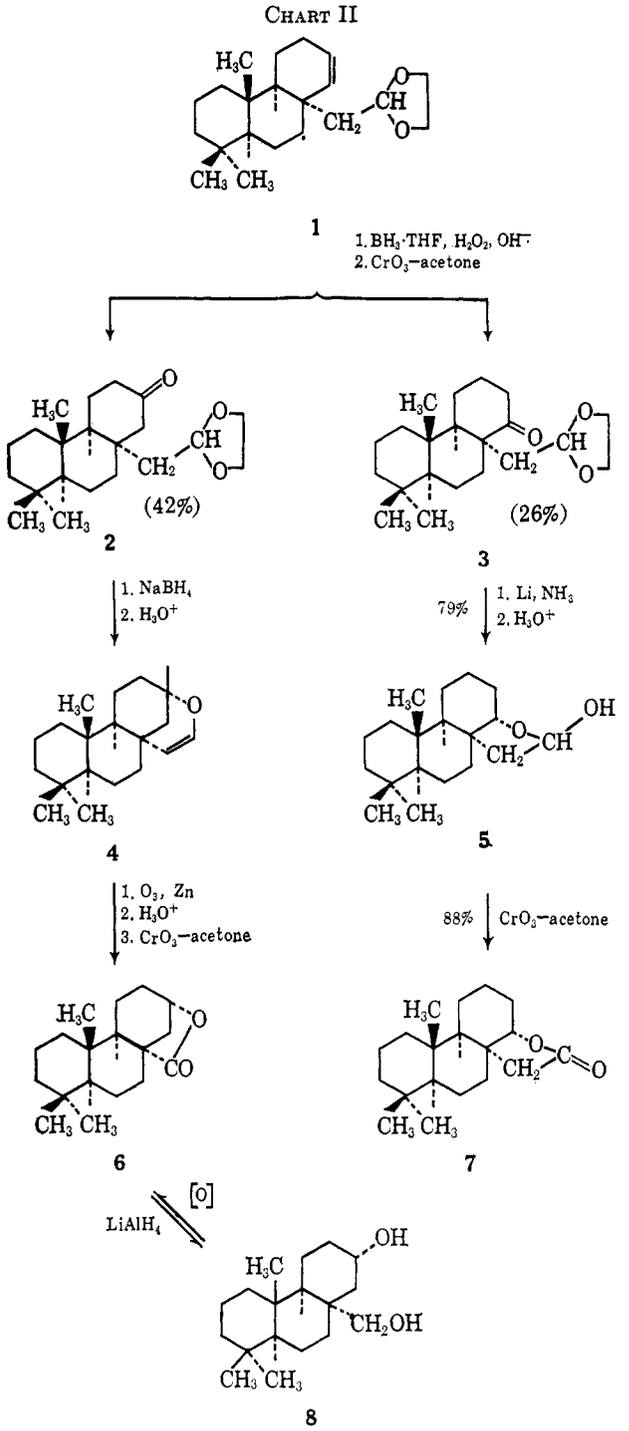


CHART II



introduction of a suitable oxygen function in ring C. Initially it was felt that a ketone function located at C_{13} would be most advantageous, and to this end the aldehyde **19** was first protected as the ethylene acetal **1** and then treated with disiamylborane[7] in order to effect oxygenation of the less hindered 13 position. Unfortunately the double bond of the acetal **1** is apparently severely hindered at both C_{13} and C_{14}, for no oxygenation product at either position could be realized by this method. We next investigated direct hydroboration by diborane,[7] and, while this procedure lacks the selectivity reported for disiamylborane, we were successful in the isolation of ring C oxygenated material as outlined in Chart II.

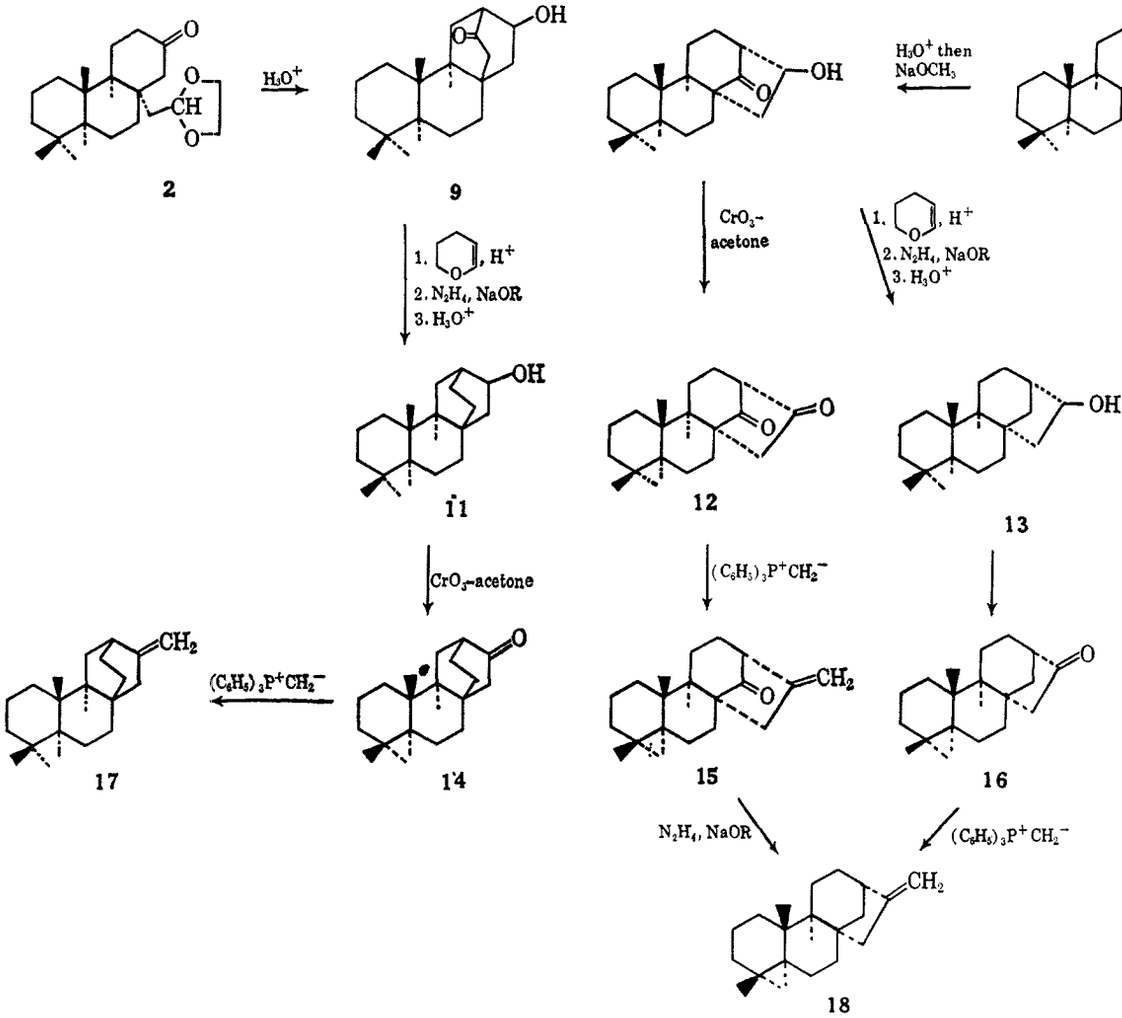
The result of this hydroboration–oxidation sequence was the formation of the two keto acetals **2** and **3**, which were separated by column chromatography. The isomer **3**, formed in lesser amount and less strongly adsorbed, was considered to be the C_{14} keto acetal. This assignment was shown to be correct by reduction of the ketone to an equatorial, α-oriented alcohol with lithium in liquid ammonia. Acid cleavage of the acetal and oxidation of the resulting hemiacetal led to the γ-lactone **5**. The presence of the γ-lactone carbonyl was readily identified in the infrared spectrum of the end product. Of the two possible keto acetals, only the C_{14} keto acetal **3** could lead to such a γ-lactone by this set of reactions.

The keto acetal **2**, formed in preponderate amount and more strongly adsorbed, was then the desired C_{13} keto acetal. By way of providing conclusive proof for this assignment this keto acetal **2**, the ketone, was again reduced, but here so as to generate a significant amount of axial, α-oriented alcohol. In the α orientation the new hydroxyl group can interact with the α-oriented acetaldehyde side chain after it is freed from the protecting acetal. However, aqueous acid cleavage of the acetal of the reduction product unexpectedly did not lead to a hemiacetal, as had been observed in the C_{14} keto acetal **3** series. The product isolated was the enol ether **4**, which was not susceptible to hydration and oxidation to a δ-lactone.

The fact that the enol ether **4** had formed, coupled with the establishment of the keto acetal **3** as the C_{14} keto isomer, is sufficient evidence to establish the keto acetal **2** as the C_{13} keto isomer. The formation of the enol ether **4** provided as well an ideal opportunity to remove one carbon of the acetaldehyde side chain—an operation that was necessary at some stage in order to convert the olefinic aldehyde **19** to the kaurene keto ester **22**. The removal of this carbon was accomplished by a two-stage oxidation of the enol ether

(7) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

CHART III



4. This oxidation sequence afforded the γ-lactone **6** as the end product. While this lactone **6** seems suitable for conversion to the keto ester **22**, we were unsuccessful in various attempts to hydrolyze and oxidize the lactone **6** further. Lithium aluminum hydride reduction of the lactone **6** generated the expected diol **8**, but again this material could not be oxidized without reformation of the lactone **6**. Thus, as ideal as this sequence would seem from a structural viewpoint, the pathway led to an abrupt dead end at the lactone **6**.

Inasmuch as the keto acetals **2** and **3** have already present all the carbon atoms necessary to construct the desired bridged system, we turned our attention to a consideration of methods for the direct cyclization of these keto acetals. The first step of this investigation appeared to be the freeing of the aldehyde function from the protecting acetal grouping and to our surprise and pleasure, this process also solved the problem of the formation of the bridged system as shown in Chart III. The product of acetal cleavage with aqueous acid–acetone solution of both keto acetals **2** and **3** was not the expected keto aldehyde, but the corresponding ketols **9** and **10** formed by aldol-type cyclization. Indeed, later work showed that even under very mild acid conditions at low temperatures, it was not possible to generate the keto aldehydes from their respective keto acetals **2** and **3** without aldol-type cyclization intervening. In each case while a crystalline bridged ketol was formed, it was possible to show that each was a mixture of epimers about the hydroxyl-bearing carbon. Thus, on oxidation of the ketol **10** a single diketone **12** was obtained after the asymmetry of the hydroxyl-bearing carbon was destroyed. The infrared spectrum of this diketone **12** confirmed the conclusion that a bridged system had been formed, as there was absorption presented for both a five-membered ring carbonyl (1765 cm^{-1}) and a six-membered ring carbonyl (1730 cm^{-1}).

Having accomplished the first phase of the kaurene synthesis—namely, the formation of the carbon-bridged system—we turned our attention to the modification of this skeleton in the direction of the diterpene itself. The structure of the diketone **12** suggests that the steric environment of the two carbonyl groups is significantly different and that the C_{14} ketone must be much more hindered than the C_{16} ketone. This consideration led us to believe that we would observe selective reactions of this diketone **12** in spite of the presence of the two identical functional groups. This indeed proved to be the case, for even in the presence of an excess of methylenetriphenylphosphorane[8] only a monocondensation product was observed, and the olefinic ketone **15** was generated in high yield. Wolff–Kishner reduction of this ketone **15** under the forcing

(8) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954).

conditions developed by Barton and co-workers[9] then neatly afforded (±)-kaurene **18**. The solution infrared spectrum and proton magnetic resonance spectrum of the synthetic (±)-kaurene **18** were identical with the corresponding spectra of natural (−)-kaurene.

It later proved more efficient to remove the C_{14} ketone prior to applying the Wittig olefin synthesis, as the products were more readily purified. In order to prevent reverse aldol-type cleavage of the ketol **10**, the alcohol was first protected as the tetrahydropyranyl ether and then forcing Wolff–Kishner reduction conditions applied. In this fashion the alcohol **13**—still a mixture of epimers about the hydroxyl-bearing carbon—was available, and on oxidation with Jones reagent[10] led to a single ketone **16**. Condensation of this ketone **16** with methylenetriphenylphosphorane[8] again generated (±)-kaurene **18**, but in a more readily purifiable state.

The availability of the keto acetal **2**—originally felt to be the key intermediate in the kaurene synthesis—presented the opportunity to prepare similar bicyclo[2.2.2] derivatives *via* the ketol **9**. Thus the ketol **9** was converted to the monoketone **14** by way of the alcohol **11** which was obtained by modified Wolff–Kishner reduction of the derived tetrahydropyranyl ether. Again oxidation[10] of the alcohol **11** reduced what was a mixture of epimers about the hydroxyl-bearing carbon to a single compound. Condensation of this ketone **14** with methylenetriphenylphosphorane[8] generated the olefin **17**, which has recently been isolated by Dev and co-workers[11] and named atisirene. The spectral properties of our synthetic material proved to be of value in the structural work undertaken by these workers. Thus, this synthesis has led to the production of both (±)-kaurene (**18**) and (±)-atisirene (**17**). The availability of these synthetic hydrocarbons made possible later investigations directed toward introducing oxygen function into the D ring of the system.

Experimental Section[12]

Acetal 1.—A solution of 3.80 g of the aldehyde **19** in a mixture of 150 ml of benzene and 5 ml of ethylene glycol containing 30 mg of *p*-toluenesulfonic acid was heated under reflux in a Dean–Stark water separator for 4 hr. The cooled reaction mixture was poured into 50 ml of saturated aqueous sodium bicarbonate solution; the organic layer was separated and dried over anhydrous potassium carbonate. Removal of solvent gave 4.41 g of acetal **1** as a clear, colorless oil which was sufficiently pure for further experimentation. A sample crystallized from methanol had mp 51–53°.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.94; H, 10.57.

Infrared showed λ_{max}^{film} 8.85 μ (s) (C–O–C).

Keto Acetals 2 and 3.—A solution of 11 g (0.035 mole) of the olefin acetal **1** in 230 ml of dry tetrahydrofuran was treated with 100 ml of a 0.73 *M* solution of diborane in tetrahydrofuran, and the reaction mixture was stirred in a nitrogen atmosphere for 1.5 hr. After treatment with 55 ml of 10% aqueous sodium hydroxide and then 55 ml of 30% hydrogen peroxide, the mixture was stirred and heated under reflux for 30 min, cooled, and extracted with ether. The ethereal solution was washed with water, saturated salt solution, and then dried over anhydrous sodium sulfate. Removal of the ether at reduced pressure on the steam bath afforded a clear, viscous oil which was not further purified but submitted directly to oxidation.

A solution of the crude alcohols above in 500 ml of acetone was cooled in an ice bath and then 10.0 ml of 8 *N* aqueous chromic acid was added dropwise with stirring. After the addition was complete 250 ml of 5% aqueous potassium carbonate was added and most of the acetone was removed by distillation at reduced pressure. The aqueous liquors were extracted with ether, and the ethereal solution was washed with water, saturated salt solution, and dried over anhydrous sodium sulfate. The oil that remained after evaporation of the ether was chromatographed on 880 g of alumina. Elution of the column with 16 l. of 30% ether–petroleum ether (30–60°) and crystallization of the solid obtained after evaporation of the solvents from petroleum ether (30–60°) afforded 3.00 g (26%) of keto acetal **3**, mp 84.5–85.5°. The analytical sample, obtained after sublimation of a portion of this material at 80° (0.03 mm), melted at the same temperature.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.37; H, 10.15.

Infrared showed $\lambda_{max}^{HCCl_3}$ 5.88 (s) (ketone >C=O), 8.85 μ (s) (C–O–C).

Continued elution of the column with 26 l. of 50% ether–petroleum ether and crystallization of the solid obtained after evaporation of the solvent from petroleum ether (60–75°) afforded 4.88 g (42%) of keto acetal **2**, mp 138.5–140°. The analytical sample, obtained after one further crystallization from the same solvent, melted at the same temperature.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.54; H, 10.26.

Infrared showed $\lambda_{max}^{HCCl_3}$ 5.88 (s) (ketone >C=O), 8.85 μ (s) (C–O–C).

Hemiacetal 5.—A solution of 583 mg (1.74 mmoles) of the keto acetal **3** in 20 ml of ether was added to a solution of 0.5 g (0.07 mole) of lithium in 200 ml of liquid ammonia, and the deep blue solution was stirred for 1 hr. The reaction mixture was decomposed by the addition of 17 ml of ethanol, and then the ammonia was evaporated in an air jet. The residue was partitioned between ether and water, and the ethereal solution was separated, washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated. The crude alcohol so obtained was not further purified but dissolved in 50 ml of acetone. This solution was treated with 10 ml of 3 *N* hydrochloric acid and allowed to stand at room temperature overnight.

Most of the acetone was then evaporated, and the aqueous liquors were diluted with water and extracted with ether. The ethereal extracts were washed with water, 10% aqueous potassium bicarbonate, water, saturated salt solution, and dried over anhydrous sodium sulfate. Evaporation of the ether at reduced pressure on the steam bath afforded 504 mg of crude, crystalline hemiacetal **5**. Recrystallization of this material from petroleum ether (60–75°) produced 400 mg (79%) of pure material that melted at 124–126°. The analytical sample was obtained after two further crystallizations from the same solvent and melted at 125.5–127°.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.92; H, 11.08.

Infrared showed $\lambda_{max}^{HCCl_3}$ 2.70, 2.85 (free and associated OH), 9.95 μ (C–OH).

γ-Lactone 7.—An ice-cooled solution of 154 mg (0.53 mmole) of hemiacetal **5** in a mixture of 25 ml of ether and 25 ml of acetone was oxidized by the addition of 0.4 ml of 8 *N* aqueous chromic acid. The excess reagent was destroyed with ethanol; the mixture was concentrated by evaporation of the solvents in an air jet; and the residue was partitioned between water and ether. The ethereal solution was separated, washed with water, 10% aqueous potassium bicarbonate, water, saturated salt solution, and dried over anhydrous sodium sulfate. Evaporation

(9) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(11) A. H. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Letters*, 2729 (1965).

(12) Unless otherwise specified, the term "petroleum ether" refers to reagent grade material boiling in the range 30–60°. Melting points were determined on a Kofler hot stage and are corrected for stem exposure. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra that are recorded in microns were measured on a Perkin-Elmer Infracord Model 137 and those recorded in reciprocal centimeters were measured on a Perkin-Elmer Model 237 spectrometer. Strong bonds are marked s; all others reported are of moderated intensity unless otherwise designated. Ultraviolet spectra were determined on a Cary Recording spectrophotometer (Model 11 MS). Florisil refers to the product of the Floridin Co., Tallahassee, Fla., 60–100 mesh.

of the ether and crystallization of the residue from petroleum ether (30–60°) afforded 135 mg (88%) of the γ-lactone **7**, mp 77–79°. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 78–79.5°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.54; H, 10.56.

Infrared showed $\nu_{max}^{HCCl_3}$ 1770 cm^{-1} (s) (γ-lactone >C=O).

Enol Ester 4.—A solution of 946 mg (2.83 mmoles) of keto acetal **2** in 100 ml of isopropyl alcohol was treated with 1.0 g of powdered sodium borohydride. After the reaction mixture was heated under reflux for 1.5 hr, the solvent was removed in an air jet, and the residue was partitioned between water and ether. The ethereal layer was separated, washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath.

The crude alcohol so obtained was dissolved in 100 ml of acetone containing 13 ml of 3 *N* hydrochloric acid, and the solution was heated under reflux for 2 hr. Most of the acetone was removed by evaporation in an air jet, and the aqueous liquors were extracted with ether. The ethereal solution was washed with water, 10% aqueous potassium bicarbonate, water, saturated salt solution, and dried over anhydrous sodium sulfate. The residue that remained on evaporation of the ether was chromatographed on 30 g of alumina. Elution with 250 ml of petroleum ether (30–60°) afforded 465 mg of the enol ether **4** which after crystallization from petroleum ether (60–75°) amounted to 426 mg (55%) and melted at 88–90°. The analytical sample, obtained after sublimation of a portion of this material at 100° (0.01 mm), melted at 88.5–90°.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.96; H, 11.04.

Infrared showed $\nu_{max}^{HCCl_3}$ 1640 (C=CO), 1240 cm^{-1} (s) (C–O–C).

Further elution of the column with 400 ml of ether afforded 244 mg of oily material that could not be crystallized and appeared from its infrared spectrum to be an alcohol. This material was not further investigated.

γ-Lactone 6.—A solution of 426 mg (1.55 mmoles) of the enol ether **4** in 30 ml of dry methylene chloride was cooled to −78° and treated with a stream of ozonized oxygen (1.6 mmoles O_3/min) for 3.25 min. The solution was warmed to −25° and then 2.75 g of zinc dust was added portionwise with vigorous stirring over 1.5 hr while the temperature was maintained between −20° and −15°. The mixture was then warmed to room temperature; the zinc was removed by filtration; and the methylene chloride solution was washed with water, saturated sodium bicarbonate solution, water, saturated salt solution, and dried over anhydrous sodium sulfate.

After removal of the solvent at reduced pressure, the residue was dissolved in 50 ml of acetone containing 6 ml of 3 *N* hydrochloric acid, and the solution was heated under reflux for 1.5 hr. Most of the acetone was evaporated in an air jet, and the aqueous liquors were extracted with 1:1 ether–methylene chloride. The ethereal solution was washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath.

The above residue was dissolved in ether–acetone, and the solution was treated with 1 ml of 8 *N* aqueous chromic acid at room temperature. The excess oxidant was destroyed with ethanol, and the reaction mixture was diluted with water. After thorough extraction of this aqueous solution with ether, the ethereal extracts were washed with water, saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath.

The partially crystalline residue that resulted was crystallized from ethyl acetate and afforded 114 mg (26%) of the γ-lactone **6**, mp 171–173°. Chromatography of the mother liquors on 30 g of Florisil afforded an additional 100 mg (22%) of γ-lactone **6**, mp 171–173°, by elution with 250 ml of benzene. The analytical sample was obtained after two further crystallizations of a portion of this material from ethyl acetate and sublimation at 170° (0.01 mm) and melted at 172–173° with preliminary softening at 171.5°.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.43; H, 10.47.

Infrared showed $\nu_{max}^{HCCl_3}$ 1770 cm^{-1} (s) (lactone >C=O).

Diol 8.—To a slurry of 293 mg (7.8 mmoles) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was added 102 mg (0.37 mmole) of the γ-lactone **6** in 10 ml of the same solvent, and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was decomposed with 0.6 ml of water and 0.48 ml of 10% aqueous sodium hydroxide, and, after the precipitated salts were removed by filtration, the filtrate was evaporated to dryness at reduced pressure on the steam bath. On crystallization of the residue from ethyl acetate, there was obtained 90 mg (87%) of the diol **8**, mp 156–158.5°. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 157–159°.

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.15; H, 11.61.

Infrared showed $\nu_{max}^{HCCl_3}$ 3625, 3380 cm^{-1} (free and associated OH).

Oxidation of this material with 8 *N* chromic acid,[10] potassium permanganate or dichromate led to reconstitution of the γ-lactone **6**.

Bicyclo[2.2.2]octane Series. Ketol 9.—A solution of 250 mg (0.75 mmole) of the keto acetal **2** in 10 ml of acetone containing 2.0 ml of 3 *N* hydrochloric acid was heated under reflux for 15 min. The reaction mixture was cooled, diluted with water and extracted with 1:1 ether–benzene. The organic layer was washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude, crystalline residue was crystallized from acetone and afforded 207 mg (95%) of the ketol **9**, mp 209–211°, in two crops of 152 mg and 55 mg each. The analytical sample, obtained after two further crystallizations from acetone, melted at 210–212°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.40; H, 10.49.

Infrared showed $\nu_{max}^{HCCl_3}$ 3595, 3400 (free and associated OH), 1710 cm^{-1} (s) (ketone >C=O).

(±)-16-Noratisiranol-16 (11).—A suspension of 450 mg (1.55 mmoles) of the ketol **9** in 7.5 ml of dihydropyran was treated with a few crystals of *p*-toluenesulfonic acid and stirred until solution was complete. The reaction mixture was then neutralized with 1.0 g of anhydrous, powdered potassium carbonate. The mixture was diluted with ether and filtered; the solvents were removed from the filtrate at reduced pressure on a 35° water bath.

The above, crude tetrahydropyranyl ether in 2 ml of benzene was added to a solution of 550 mg (23 mg-atoms) of sodium in 25 ml of diethyleneglycol and then 3.5 ml of 95% hydrazine was added. The temperature of the reaction mixture was raised to 160–165° during which time benzene and excess hydrazine were removed by distillation. The temperature was maintained at this level for 4 hr and then raised to 205° where it was maintained for 10 hr. The mixture was then cooled, diluted with water and extracted with 1:1 ether–benzene. The organic layer was washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude, solid desoxytetrahydropyranyl ether so obtained was dissolved in 6.0 ml of ethyl alcohol containing 5.0 ml of a 2% aqueous oxalic acid solution, and the whole was heated under reflux for 45 min. The mixture was then cooled, diluted with water, and extracted with 1:1 ether–benzene. The organic layer was washed with water, 10% aqueous potassium bicarbonate, water, saturated salt solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure on the steam bath. The crystalline residue that remained was crystallized from acetone and afforded 390 mg (91%) of alcohol **11**, mp 148–150° in two crops of 376 mg and 14 mg each. The analytical sample was obtained after two further crystallizations from acetone and melted at the same temperature.

Anal. Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.38; H, 11.66.

Infrared showed $\nu_{max}^{HCCl_3}$ 3595, 3400 cm^{-1} (free and associated OH).

(±)-16-Noratisiranone-16 (14).—An ice-cooled solution of 215 mg (0.78 mmole) of the alcohol **11** in 10 ml of acetone was oxidized with 0.3 ml of 8 *N* aqueous chromic acid solution. After the mixture had been stirred in the cold for 10 min, ethanol was added to destroy the excess oxidant, and then the mixture was diluted with water and extracted with 1:1 ether–benzene. The organic layer was washed with water, saturated salt solution, and dried over anhydrous sodium sulfate, and the solvents were removed at reduced pressure on the steam bath. The crystalline residue was crystallized from acetone and afforded 188 mg (86%) of the ketone **14**, mp 126–129°, in two crops of 143 mg and 45

mg each. The analytical sample, obtained after two further crystallizations from methanol, melted at 128.5–129.5°.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.00; H, 11.13.

Infrared showed $\tilde{\nu}_{max}^{HCCl_3}$ 1710 cm^{-1} (s) (ketone >C=O).

(±)-Atisirene (17).—To a suspension of 785 mg (2.2 mmoles) of methyltriphenylphosphonium bromide in 20 ml of ether under a nitrogen atmosphere was added 2.65 ml of an 0.8 *M* *t*-butanolic potassium *t*-butoxide solution, and the mixture was stirred for 0.5 hr at room temperature. To this red solution was added a solution of 150 mg (0.55 mmole) of the ketone **14** in 20 ml of ether, and the reaction mixture was stirred at room temperature overnight. The resulting suspension was treated with water, diluted with *n*-pentane. The organic layer was separated and washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure in a 35° water bath. When the residue was chromatographed on 6 g of alumina, elution with 170 ml of petroleum ether (30–60°) afforded 147 mg of crystalline hydrocarbon. Crystallization of this material from ethanol resulted in 135 mg (90%) of the olefin **17**, mp 52.5–54°, in two crops of 115 mg and 20 mg each. Two further crystallizations of a small sample from ethanol provided an analytically pure specimen which melted at 54–55.5°.

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.20; H, 11.90.

Infrared showed $\tilde{\nu}_{max}^{HCCl_3}$ 3070 (vinyl H), 1645, 875 cm^{-1} (terminal C=C).

Bicyclo[3.2.1]octane Series. Ketol 10.—A solution of 300 mg (0.9 mmole) of the keto acetal **3** in 18 ml of acetone containing 3 ml of 3 *N* hydrochloric acid was heated at reflux for 15 min. Most of the acetone was evaporated in a jet of nitrogen, and the residue was partitioned between water and ether. The ethereal layer was separated, washed with water, saturated aqueous sodium bicarbonate solution, water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude product, which still contained some keto aldehyde, was dissolved in 10 ml of methanol, and the solution was treated with 2 ml of 5% methanolic potassium hydroxide and stirred under a nitrogen atmosphere at room temperature for 2 hr. The solution was neutralized with 10% aqueous sulfuric acid, the methanol was removed by distillation at reduced pressure on the steam bath, and the residue was extracted with 1:1 ether–benzene. The ethereal solution was washed with water, saturated aqueous sodium bicarbonate, water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude, crystalline product, obtained in quantitative yield, was crystallized from hexane and afforded 250 mg (96%) of the ketol **10**, mp 134–136°, in two crops of 236 mg and 14 mg each. This material is a mixture of epimers above the hydroxyl-bearing carbon, and, while the analytical sample, obtained on one further crystallization from hexane, gave satisfactory combustion results, the melting point of the mixture did not improve. For the purposes of the following work it was not necessary to separate these epimers, and no attempt was made to do so.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.68; H, 10.48.

Infrared showed $\tilde{\nu}_{max}^{HCCl_3}$ 3600, 3410 (free and associated OH), 1737 cm^{-1} (s) (ketone >C=O).

Diketone 12.—An ice-cooled solution of 197 mg (0.67 mmole) of the ketol **10** in 10 ml of acetone was oxidized with 0.25 ml of 8 *N* aqueous chromic acid solution, and after stirring for 10 min, the excess oxidant was destroyed with ethanol. Most of the acetone was removed in a jet of nitrogen, and the residue was partitioned between water and 1:1 ether–benzene. The organic layer was separated, washed with water, 10% aqueous potassium bicarbonate, water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The solid residue was crystallized from hexane and afforded 173 mg (90%) of the diketone **12**, mp 195–197°, in two crops of 72 mg and 101 mg each. The analytical sample, obtained after two further crystallizations from methanol, melted at 196–197°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.17; H, 9.83.

Infrared showed $\tilde{\nu}_{max}^{HCCl_3}$ 1765 (s) (five-ring ketone >C=O), 1730 cm^{-1} (s) (six-ring ketone >C=O).

(±)-14-Ketokaurene (15).—A solution of methylenetriphenylphosphorane in 30 ml of ether was prepared under a nitrogen atmosphere by heating a suspension of 2.14 g (6.0 mmoles) of methyltriphenylphosphonium bromide with 7.1 ml of 0.8 *N* *t*-butanolic potassium *t*-butoxide solution. To this red-orange solution was added a solution of 383 mg (1.3 mmoles) of the diketone **12** in 3 ml of benzene and 30 ml of ether, and the mixture was stirred at room temperature for 2 hr. Then 10 ml of water was added, and the solution was diluted with an equal volume of pentane. The organic layer was separated, washed with water, saturated salt solution, and dried over anhydrous sodium sulfate, and the solvents were removed by distillation at reduced pressure on the steam bath. The solid residue was triturated with 100 ml of pentane. After removal of the phosphine oxide by filtration, the filtrate was chromatographed on 25 g of alumina. Elution with 450 ml of 2% ether–petroleum ether (30–60°) afforded 320 mg of crystalline material which on crystallization from methanol resulted in 302 mg (81%) of (±)-14-ketokaurene (**15**), mp 107–109°, in three crops of 155 mg, 115 mg, and 32 mg each. The analytical sample, obtained after one further crystallization from methanol, melted at 108.5–109°.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 84.10; H, 10.60.

Infrared showed $\tilde{\nu}_{max}^{HCCl_3}$ 3075 (vinyl H), 1745 (s) (>C=O), 890 cm^{-1} (term methylene).

(±)-Kaurene B-10. A. From (±)-14-Ketokaurene (15).—A solution of 140 mg (6.1 mg-atoms) of clean sodium in 15 ml of freshly distilled diethylene glycol was prepared under a nitrogen atmosphere by gentle warming, and then hydrazine (previously heated at reflux over sodium hydroxide) was distilled directly into the glycol solution until the reflux temperature was 180°. To this mixture was added 155 mg (0.54 mmole) of (±)-14-keto kaurene **15**, and the whole was heated at reflux overnight under a nitrogen atmosphere. Hydrazine was then removed by distillation until the reflux temperature rose to 210°, and the mixture was maintained at this temperature for an additional 24 hr. The mixture was then cooled, diluted with water, and extracted with 1:1 ether–benzene. The organic layer was washed with water, saturated salt solution, and dried over anhydrous sodium sulfate; the solvents were removed at reduced pressure on the steam bath. The crude product (160 mg of a light yellow oil) was adsorbed on 6 g of alumina; elution with 20 ml of petroleum ether (30–60°) afforded 110 mg of clear, colorless oil, which on evaporative distillation at 120° (0.02 mm) gave 100 mg (68%) of pure (±)-kaurene **18**. The infrared spectrum of this material was identical with that of natural (−)-kaurene. On cooling this material crystallized and melted at 42–46°. The analytical sample, obtained after two crystallizations from ethanol and a further evaporative distillation at 120° (0.02 mm), melted at 44–47°.

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.90; H, 11.97.

Infrared showed $\tilde{\nu}_{max}^{film}$ 3070 (vinyl H), 1655 (>C=C<), 870 cm^{-1} (s) (>C=CH_2).

B. From (±)-16-Norkauranone (16).—A solution of methylenetriphenylphosphorane in 50 ml of ether was prepared under a nitrogen atmosphere from 1.310 g (3.68 mmoles) of methyltriphenylphosphonium bromide and 2.95 ml (3.6 mmoles) of a 1.22 *N* *t*-butanolic potassium *t*-butoxide solution. To this solution was added 250 mg (0.92 mmole) of (±)-16-norkauranone (**16**), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was decomposed with water and diluted with petroleum ether (30–60°), and the organic layer was separated and washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The residue was triturated with *n*-pentane, and the *n*-pentane solutions were passed through 20 g of alumina. Further elution with 200 ml of *n*-pentane gave 214 mg (86%) of (±)-kaurene (**18**) as a clear, colorless oil that crystallized on cooling and melted at 44–47°. This material was identical with that obtained above from (±)-14-ketokaurene **15**, as judged by comparison of the infrared spectra of each sample and the mixture melting point which was undepressed.

(±)-16-Norkauranol (13).—A stirred suspension of 496 mg (1.71 mmoles) of the ketol **10** in 7.5 ml of freshly distilled dihydropyran was treated with a few crystals of *p*-toluenesulfonic acid, and the mixture was stirred until all of the ketol had dissolved. Then 500 mg of potassium carbonate was added; the mixture was stirred for an additional 30 min and then diluted with ether and filtered. Removal of the solvents from the filtrate in a jet of nitrogen left 627 mg of crude tetrahydropyranyl ether as a clear, colorless oil.

To a warm solution of 550 mg (24 mg-atoms) of sodium in 25 ml of diethylene glycol was added the above tetra hydropyranyl ether in 2.0 ml of dry benzene. This solution was treated with 3.5 ml of dry hydrazine (distilled twice from potassium hydroxide), and the temperature of the reaction mixture was raised to 165° and maintained at reflux for 4 hr. Hydrazine was then removed by distillation until the pot temperature rose to 215° where it was maintained for 24 hr. The mixture was then cooled, diluted with water, and extracted with 1:1 ether–benzene. The ethereal solution was washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath.

The crude tetrahydropyranyl ether so obtained was hydrolyzed in 6 ml of ethanol containing 5.0 ml of 2% aqueous oxalic acid. After the reaction mixture had been heated at reflux for 1 hr, the solution was diluted with water and extracted with ether. The ethereal solution was washed with water, 10% aqueous potassium bicarbonate solution, water, and saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude, crystalline alcohol that resulted was crystallized from acetone and afforded 376 mg (80%) of (±)-16-norkauranol **13**, mp 150–151.5°, in two crops of 346 mg and 30 mg each. The analytical sample, obtained after one further crystallization from the same solvent, also melted at 150–151.5°.

Anal. Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.66; H, 11.62.

In spite of the sharp melting point of this alcohol the sample was shown to consist of a mixture of C_{15} epimers by thin layer chromatography. However, since a mixture of alcohol epimers was not a drawback to further work and the mixture could be oxidized to a single ketone (*vide infra*), no attempt was made at this time to resolve the mixture.

(±)-16-Norkauranone (16).—To an ice-cooled solution of 290 mg (1.06 mmoles) of (±)-16-norkauranol (**13**) in 20 ml of acetone was added 0.35 ml of 8 *N* aqueous chromic acid solution, and the mixture was stirred for 10 min. The excess oxidant was destroyed with ethanol, most of the acetone was removed in a jet of nitrogen on the steam bath, and the residue was partitioned between water and 1:1 ether–benzene. The organic layer was separated, washed with water, saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on the steam bath. The crude, crystalline ketone (282 mg, 98%, mp 114–119°) so obtained was crystallized from petroleum ether (30–60°) and afforded 240 mg (83%) of (±)-16-norkauranone **16**, mp 121.5–122.5°. The analytical sample, obtained after one further crystallization from acetone and sublimation at 115° (0.05 mm), melted at 122–123°.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.16; H, 11.00.

Infrared showed $\nu_{max}^{HCCl_3}$ 1734 cm^{-1} (s) (ketone >C=O).

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Experiments Directed toward the Total Synthesis of Terpenes. IX. The Total Synthesis of (±)-Hibaene and the Oxygenation of Some Tetracyclic Diterpenes[1]

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Conversion of the keto acetal **19** to the hydroxy olefin **26**, a model for the C/D ring system of steviol **18**, is delineated. Acid-catalyzed rearrangement of this hydroxy olefin **26** provides entry to the hibaene–stachene system, and the synthesis of racemic hibaene **28** is described. Photosensitized oxygenation of (±)-isokaurene **12** and the analogous olefin **15** provides a pathway for the introduction of hydroxyl functions into these molecules and the synthesis of the C/D ring system of the diterpenoid alkaloids.

In preceding papers in this series[3] we presented a synthetic scheme for the elaboration of the bridged bicyclic derivatives that represent several diterpenes. Thus both stereochemical series represented by phyllocladene **1**[3a] and kaurene **3**[3b] have become available through the same key intermediate aldehyde **2**. With these synthetic diterpenes available, as well as the bicyclo[2.2.2]octane derivative atisirene[3b] **5**, it was of interest to consider procedures whereby an oxygen function could be introduced into the system. Such a transformation was of more than passing interest, for allylic alcohols like **6** and **4** possess the same C/D ring system as do the diterpenoid alkaloids garryine **11**[4] and atisine **9**.[5] Therefore, if a method for the conversion of the corresponding olefins **3** and **5** to these alcohols **6** and **4** can be devised, combination with the earlier synthesis of the bridged systems would provide a pathway from a ring C aromatic derivative, such as **7**, to the key alkaloid intermediates **10** and **8**, and thence to the alkaloids **9** and **11** themselves by known methods. (See Charts I and II.)

The synthetic problem that was to be overcome then, was the oxidation of C_{15} in both olefins **3** and **5** at some convenient stage in their construction. It was, of course, not necessary that this oxidation take place after the construction of the carbon system was complete, but if it were accomplished at an earlier stage, the grouping introduced at C_{15} must be suitably stable to withstand the further transformations necessary. This latter consideration effectively restricts the approach to either a derivative of the olefins **3** and **5** or their precursor ketones. Some preliminary attempts to oxidize these C_{16} ketones in the desired fashion and without extensive degradation of the carbon system proved unrewarding, and we thus turned our attention to the oxidation of the olefins themselves.

The problem of the oxidation of these olefins without destruction of the double-bond linkage was neatly solved by application of the photosensitized oxygena-

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