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).

Acknowledgement.—Partial support for this work in the form of a grant from the Public Health Service (GM-09067) is gratefully acknowledged. The authors are grateful to Professor L. H. Briggs and Dr. S. Rutledge for samples of (−)-kaurene and several of its derivatives. An exchange of spectral information with Professor Dev is acknowledged.

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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Received January 24, 1966

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-

(1) Preliminary accounts containing portions of this work appeared in *Tetrahedron Letters*, 269 (1963); 2627 (1965).

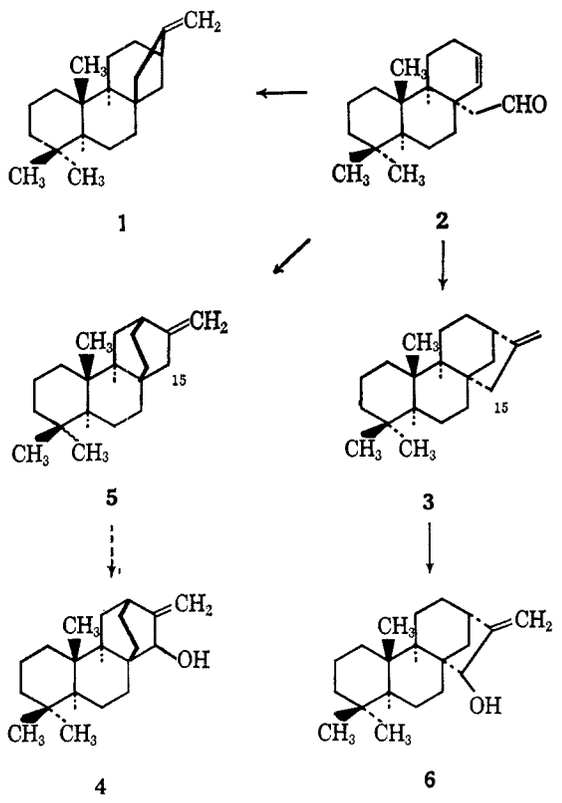
(2) Alfred P. Sloan Research Fellow, 1962–1966. To whom correspondence should be addressed: Gate and Crellin Laboratories of Chemistry California Institute of Technology, Pasadena, Calif. 91109.

(3) (a) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966); (b) R. A. Bell, R. E. Ireland, and R. A. Partyka, *ibid.*, **31**, 0000 (1966).

(4) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Fegdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801, 6633 (1955).

(5) K. Wiesner, J. R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. Ind.*, (London), 132 (1954); *Experientia*, **11**, 255 (1955).

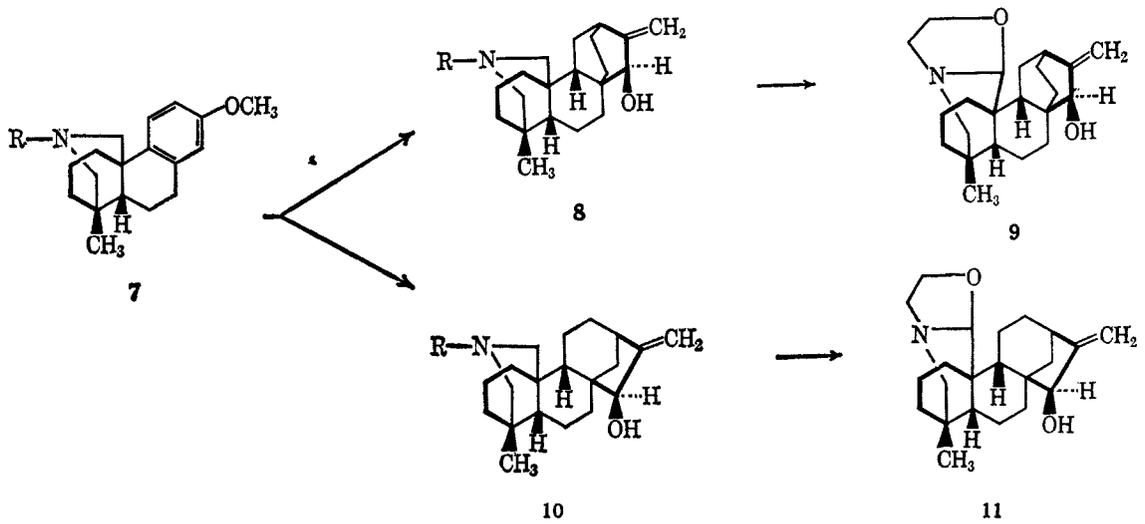
CHART I



cedure cannot be expected to be as specific as the structural results. The allylic hydrogen atom that must be removed during the process is on a freely rotating methyl group, and as such can satisfy the stereochemical requirements of the mechanism when the oxygen molecule attacks the system from either side. We would therefore expect to obtain two epimeric alcohols from this process after reduction of the initially formed hydroperoxide.[8] This is not a serious drawback, for if the process were applied to the corresponding alkaloid olefin precursor, one of the two alcohols generated would be the natural isomer and the other could be oxidized to a ketone and then reduced so as to generate the desired isomer. Therefore, the photosensitized oxygenation sequence appeared to provide all the aspects desired for the introduction of a hydroxyl function at C_{15} of the olefins **3** and **5**. This rationale was rendered to practice as outlined in Charts III and IV.

In each case both the exocyclic and endocyclic olefins were oxygenated in order to be certain of the placement of the new hydroxyl group. Both of the exocyclic olefins behaved exactly as predicted and gave only primary alcohols; there was no migration of the double bond observed prior to oxygenation. In the case of the bicyclo[2.2.2]octane derivatives, the endocyclic olefin **15** was prepared in pure condition only by hydride reduction of the bromide **14**. Acid-catalyzed isomerization of the exocyclic double bond led to an

CHART II



tion procedure that has been so thoroughly investigated by Schenck[6] and Nickon.[7] These workers have not only shown that the oxygenation of olefins invariably takes place with allylic-type rearrangement of the double bond, but also that the process is highly stereoselective. The first of these characteristics necessitate that we employ the endocyclic olefins **12** and **15** in order to obtain the desired secondary alcohols **6** and **4**. Thus, oxygenation of the endocyclic olefins **12** and **15** with allylic-type rearrangement of the double bond can only give the desired secondary alcohols **6** and **4**, by virtue of the bridged character of the C and D rings. The stereochemical consequences of this process cannot be expected to be as specific as the structural results. The allylic hydrogen atom that must be removed during the process is on a freely rotating methyl group, and as such can satisfy the stereochemical requirements of the mechanism when the oxygen molecule attacks the system from either side. We would therefore expect to obtain two epimeric alcohols from this process after reduction of the initially formed hydroperoxide.[8] This is not a serious drawback, for if the process were applied to the corresponding alkaloid olefin precursor, one of the two alcohols generated would be the natural isomer and the other could be oxidized to a ketone and then reduced so as to generate the desired isomer. Therefore, the photosensitized oxygenation sequence appeared to provide all the aspects desired for the introduction of a hydroxyl function at C_{15} of the olefins **3** and **5**. This rationale was rendered to practice as outlined in Charts III and IV.

In each case both the exocyclic and endocyclic olefins were oxygenated in order to be certain of the placement of the new hydroxyl group. Both of the exocyclic olefins behaved exactly as predicted and gave only primary alcohols; there was no migration of the double bond observed prior to oxygenation. In the case of the bicyclo[2.2.2]octane derivatives, the endocyclic olefin **15** was prepared in pure condition only by hydride reduction of the bromide **14**. Acid-catalyzed isomerization of the exocyclic double bond led to an unresolvable mixture of the two olefins **5** and **15**. A similar situation existed in the case of the bicyclo[3.2.1]octane derivatives, (±)-kaurene → (±)-isokaurene. In spite of the published report[9] that kaurene **3** is isomerized to isokaurene **12** by iodine in benzene, we were only able to obtain an equilibrium mixture of the two olefins **3** and **12**. This mixture is rich in (±)-isokaurene **12**, but chromatography and crystallization failed to remove all of the (±)-kaurene **3**. Further iodine–benzene treatment did not improve the concen-

(6) G. O. Schenck, H. Eggert, and W. Denk, *Ann.*, **584**, 177 (1953); G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

(7) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).

(8) A referee has pointed out that a mixture of isomeric alcohols might also arise from decomposition of the initially formed hydroperoxide to the ketone. Subsequent hydride reduction would then produce the observed mixture of isomeric alcohols. Except for the presence of peroxides detected in one experiment, we have no evidence that excludes this possibility.

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

CHART III

THE BICYCLO[3.2.1]OCTANE DERIVATIVES

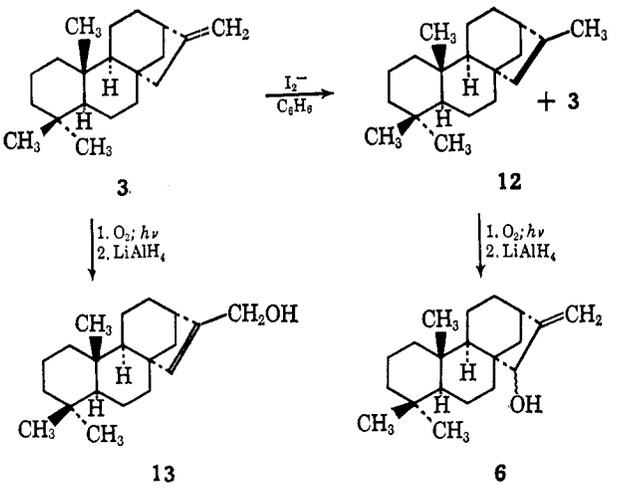
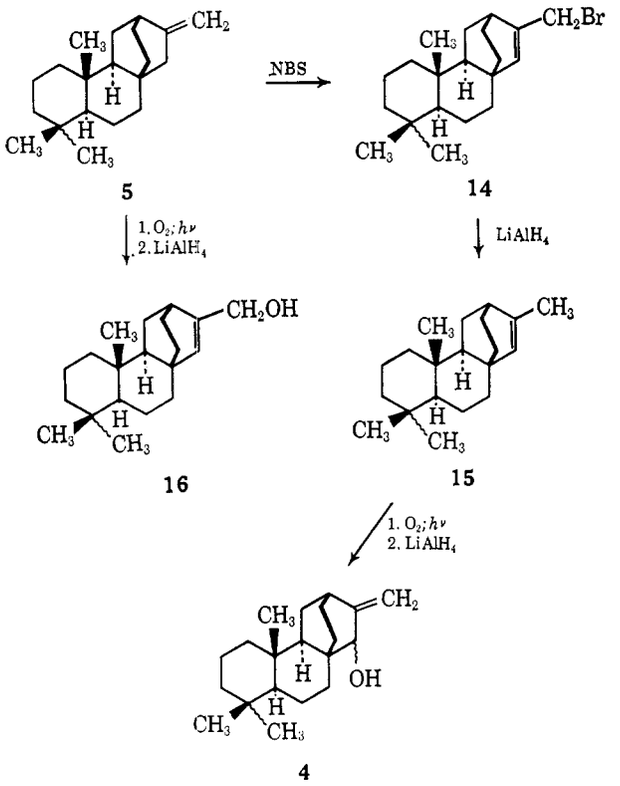


CHART IV

THE BICYCLO[2.2.2]OCTANE DERIVATIVES



tration of isokaurene **12**. Therefore, oxygenation experiments were carried out on the mixture of olefins **3** and **12** and the secondary alcohols readily separated from the primary alcohol.

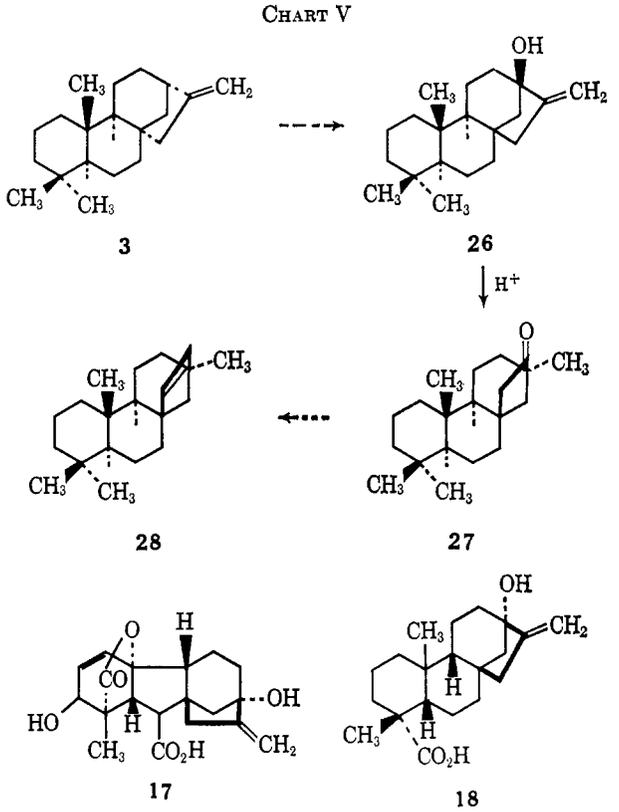
In each series the secondary alcohols were found to be a mixture of epimers, and in the bicyclo[2.2.2]octane derivatives, it was possible to resolve this epimeric mixture into its two component racemic alcohols. No attempt was made to prove the stereochemistry of the alcohols. The oxygenation procedure was successful for accomplishing the desired objective and was later employed by Masamune[10] in his synthesis of garryine.

(10) S. Masamune, *J. Am. Chem. Soc.*, **86**, 290 (1964).

We next turned our attention to the *a priori* more difficult problem of the introduction of a hydroxyl grouping at the bridgehead C_{13} position of the bicyclo[3.2.1]octane (kaurene) skeleton. There was a twofold purpose in this interest. First, the C_{13} hydroxylated derivative **26** served as a model for the construction of the C/D ring system of such diterpenoid materials as steviol **18**[11] and gibberellic acid **17**.[12] Secondly, acid-catalyzed rearrangement of the hydroxy olefin **26** itself could be expected to rearrange the kaurene-type carbon skeleton and provide synthetic entry into the hibaene[13] system **28**.

The direct introduction of oxygen at the bridgehead of kaurene **3** seemed like an unrewarding path to traverse, as the bridged character of the system precluded any activation of the C_{13} position by adjacent functionality. While it might be possible to utilize a radical-type reaction to accomplish the transformation, a more convenient approach appeared to be to construct the bridged system with the potential hydroxyl group already in place. Such an approach appeared to be offered by the same synthetic route (see Chart V) that had led to construction of **3** itself. Thus,

CHART V



the aldol-type cyclization that leads to the bicyclo[3.2.1]octane system of kaurene **3** requires the C_{14} ketone to activate the adjacent C_{13} position and thereby provide the necessary carbanionic site for cyclization with the side-chain aldehyde. The ketone function, however, need not be specifically at C_{14} in the carbon skeleton so long as it is adjacent to the C_{13} carbon atom. This reasoning led us to believe that an acetyl

(11) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *ibid.*, **83**, 3720 (1961).

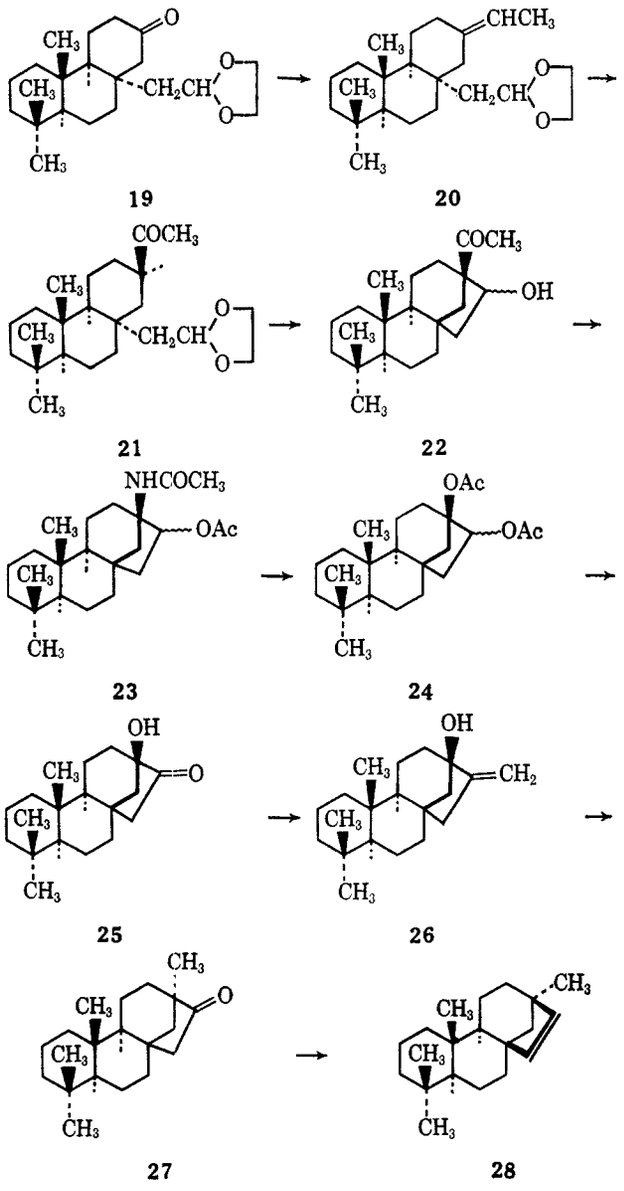
(12) F. McCapra, A. I. Scott, G. A. Sim, and D. W. Young, *Proc. Chem. Soc.*, 1851 (1962); J. A. Hartruck and W. N. Lipscomb, *J. Am. Chem. Soc.*, **85**, 3414 (1963).

(13) Y. Kitahara and A. Yoshikoshi, *Tetrahedron Letters*, 1771 (1964).

grouping attached directly to C_{13} would serve the same purpose as the C_{14} ketone and provide for the formation of the bicyclo[3.2.1]octane system. The important difference in this case is that the ketone function now occupies an extraannular position and is ideally situated for conversion to the desired C_{13} hydroxyl group. Chart VI shows how this concept was rendered to practice, as well as the conversion of the hydroxy olefin **26** to (±)-hibaene **28**.

CHART VI

THE SYNTHESIS OF (±)-HIBAENE **28** FROM THE KETO ACETAL **19**



Introduction of the C_{13} acetyl grouping was accomplished through hydroboration–oxidation of the C_{13} ethylene derivative **20** which in turn was obtained from the C_{13} keto acetal **19** with ethylidenetriphenylphosphorane. Aldol-type cyclization proceeded well after the C_{13} acetyl group had been epimerized to the more stable β (equatorial) position with base. However, the conversion of the C_{13} acetyl grouping to a hydroxyl group *via* the more obvious Baeyer–Villiger reaction sequence failed. Oxidation with peracid took place readily, but apparently rearrangement did not stop at the C_{13} acetate, for very little of this product could be isolated from the complex reaction mixture. The problem was admirably overcome, however, by utilization of the Beckmann rearrangement of the derived oxime and then replacement of the C_{13} nitrogen by acetate *via* rearrangement[14] of the N-nitroso derivative. After hydrolysis and oxidation of the derived diol, the hydroxy olefin **26** was readily obtained from the acyloin **25** by condensation with methylenetriphenylphosphorane. This process may be accomplished in a 46% over-all yield from the C_{13} keto acetal **19** to the hydroxy olefin **26** and serves as a quite satisfactory procedure for the generation of this bridgehead hydroxylated system.[15]

The conversion of the hydroxy olefin **26** to (±)-hibaene **28** *via* the ketone **26** follows familiar pathways.[16] The synthetic (±)-hibaene had solution infrared and proton magnetic resonance spectra that were identical with those of (+)-hibaene (stachene) which was obtained by Wolff–Kishner reduction of stachenone. Thus not only has it been possible to convert the C_{13} keto acetal **19** to a model for the C/D ring system of steviol **18** and gibberellic acid **17**, but also to achieve a carbon skeletal rearrangement such that the hibaene system is also available.

Experimental Section[17]

Allylic Bromide 14.—A solution of 350 mg (1.3 mmoles) of the (±)-atisirene **5** in 10 ml of carbon tetrachloride in which was suspended 230 mg (1.4 mmoles) of N-bromosuccinimide, was treated with a few crystals of benzoyl peroxide and heated under reflux for a 0.5 hour. The solution was then filtered to remove succinimide, and the carbon tetrachloride was removed at reduced pressure on the steam bath. The residue was dissolved in 1:1 ether–benzene, and the organic layer was washed with water, saturated aqueous sodium bicarbonate solution, water, and saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure on a steam bath. The crude crystalline bromide was crystallized from acetone and afforded 327 mg (73%) of the allylic bromide **14**, mp 117–120°, in three crops of 200 mg, 102 mg, and 25 mg each. The analytical sample, obtained after two further crystallizations from acetone, melted at 119–120°.

Anal. Calcd for $C_{20}H_{31}Br$: C, 68.36; H, 9.18; Br, 22.75. Found: C, 68.19; H, 9.22; Br, 22.81.

(±)-Isoatisirene 15.—To a slurry of 300 mg of lithium aluminum hydride in 25 ml of ether was added a solution of 300 mg (0.85 mmole) of the allylic bromide **14** in 10 ml of ether, and the suspension was stirred for 2 hr at room temperature. The reaction mixture was decomposed with saturated aqueous sodium sulfate solution; the precipitated salts were removed by filtration, and the filtrate was evaporated to dryness at reduced pressure on the steam bath. The crude, crystalline olefin was chromatographed on 6 g of alumina, whereupon elution with 100 ml of petroleum ether (30–60°) afforded 216 mg (93%) of (±)-isoatisirene **15**, mp 51–52°. The analytical sample, obtained

(14) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

(15) See also, G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *ibid.*, **87**, 1148 (1965).

(16) For example, see the steviol → isosteviol rearrangement: F. Dolder, H. Lichti, E. Mosettig, and P. Quitt, *ibid.*, **82**, 256 (1960).

(17) 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 Company, Tallahassee, Fla., 60–100 mesh.

after crystallization from ethanol and evaporative distillation at 120° (0.05 mm), melted at 51–52.5°.

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.00; H, 11.69.

Infrared showed $\nu_{max}^{HCCl_3}$ 1645 cm^{-1} (w) (>C=C<).

(±)-17-Hydroxyisoatisirene 16.—Through a solution of 54 mg (0.20 mmole) of the (±)-atisirene (**5**) in 3.5 ml of pyridine containing 1–2 mg of hematoporphyrin was passed a slow stream of oxygen while the reaction mixture was irradiated with a fluorescent desk lamp. After 96 hr the dark solution was diluted with ether and filtered through a pad of charcoal, and the solvents were removed at reduced pressure on the steam bath. The residue, which liberated iodine from starch–iodide test paper, was redissolved in ether and reduced by stirring with a slurry of 100 mg of lithium aluminum hydride in 10 ml of ether. After decomposition of the reaction mixture with saturated aqueous sodium sulfate solution, the precipitated salts were removed by filtration, and the ether was removed from the filtrate by distillation at reduced pressure on the steam bath. The crude, crystalline residue was crystallized from petroleum ether (30–60°) and afforded 43 mg (75%) of the (±)-17-hydroxyisoatisirene **16**, mp 114–115°. The analytical sample, obtained after sublimation at 110° (0.05 mm), melted at the same temperature.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.07; H, 11.30.

Infrared showed bands at $\nu_{max}^{HCCl_3}$ 3620, 3450 (free and associated OH), 1640 cm^{-1} (w) (>C=C<).

(±)-15-Hydroxyatisirene 4.—In a similar manner to that described for the oxygenation of the (±)-atisirene **5**, 190 mg (0.66 mmole) of the (±)-isoatisirene **15** was oxygenated in 6.0 ml of pyridine containing 1–2 mg of hematoporphyrin, and the crude hydroperoxide product was reduced through the agency of 100 mg of lithium aluminum hydride in ether slurry. The crude allylic alcohol product, which was a brown oil (179 mg), was combined with 57 mg of oily product obtained from a similar oxygenation of 60 mg of the (±)-isoatisirene **15**, and the resulting 236 mg of crude material was chromatographed on 20 g of alumina.

Elution with 60 ml of petroleum ether afforded 68 mg of recovered isoatisirene **15**, which was identified by its infrared spectrum and mobility on thin layer chromatograph. The material solidified and after crystallization from ethanol amounted to 50 mg of isoatisirene **15**, mp 51–52°.

Continued elution of the column with 180 ml of 25% ether–petroleum ether (30–60°) afforded 37 mg [19% based on (±)-isoatisirene **15** consumed] of one epimer of the secondary allylic alcohol **4**, mp 123–126°. The analytical sample, obtained after one crystallization from petroleum ether (30–60°) and sublimation at 110° (0.05 mm), melted at 126–127°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.37; H, 11.30.

Infrared showed $\nu_{max}^{HCCl_3}$ 3610, 3450 (free and associated OH), 3060 (vinyl H), 1655, 900 cm^{-1} (terminal >C=CH_2).

Continued elution of the column with 180 ml of 50% ether–petroleum ether (30–60°) afforded 55 mg (29% based on (±)-isoatisirene **15** consumed) of the other epimer of the secondary allylic alcohol **4**, mp 146–148°. The analytical sample was prepared by two crystallizations from petroleum ether (30–60°) and sublimation at 135° (0.05 mm), and melted at 153–154°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.09; H, 11.13.

Infrared bands showed $\nu_{max}^{HCCl_3}$ 3610, 3450 (free and associated OH), 3060 (vinyl H), 1655, 900 cm^{-1} (terminal >C=CH_2).

The combined yield of (±)-15-hydroxyatisirene **4** was 92 mg and represents a 48% yield of oxygenation based on the recovery of 68 mg of (±)-isoatisirene **15**.

(±)-17-Hydroxyisokaurene 13.—A solution of 75 mg (0.28 mmole) of (±)-kaurene **3** in 5.0 ml of dry pyridine containing 1–2 mg of hematoporphyrin was subjected to a slow stream of oxygen for 96 hr while the mixture was irradiated with a standard, fluorescent desk lamp situated one inch from thereaction vessel. After this period the reaction mixture was diluted with ether, filtered through charcoal, and then the solvents were removed at reduced pressure in a 35° water bath. The crude residue was taken up in ether and added to a slurry of 100 mg of lithium aluminum hydride in 20 ml of ether. After stirring for 1 hr, the reaction mixture was decomposed with saturated sodium sulfate solution, and filtered to remove the precipitated salts; the filtrate was evaporated to dryness in a jet of nitrogen on the steam bath. The crude alcohol so obtained was adsorbed onto 5 g of alumina, and 50 mg (63%) of (±)-17-hydroxyisokaurene **13**, mp 119–121°, was eluted with 100 ml of 1:1 ether–petroleum ether (30–60°). The analytical sample, obtained after two crystallizations from petroleum ether (30–60°), melted at 122.5–123.5°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.17; H, 11.17.

Infrared showed $\nu_{max}^{HCCl_3}$ 3620, 3450 (free and associate OH), 1640 cm^{-1} (w) (>C=C<).

(±)-15-Hydroxykaurene 6.—A solution of 130 mg (0.48 mmole) of (±)-isokaurene **13** in 10.0 ml of benzene was treated with a few crystals of iodine, and the mixture was heated under reflux for 6 hr. The reaction mixture was diluted with ether and then washed with saturated aqueous sodium bisulfite solution, saturated aqueous sodium bicarbonate solution, water, saturated salt solution, and dried over anhydrous sodium sulfate. After removal of the solvents at reduced pressure on the steam bath, the residue was chromatographed on 6 g of alumina. Elution with 100 ml of petroleum ether (30–60°) afforded 127 mg of a crystalline (mp 34–37°) mixture of (±)-kaurene **3** and (±)-isokaurene **12**, as judged by the presence of an 875-cm^{-1} band (>C=CH_2) in the infrared spectrum. While this material was richer in (±)-isokaurene **12**, longer reaction times or repeated crystallization from ethanol did not afford pure (±)-isokaurene **12**. Therefore, the mixture was employed directly in the oxygenation reaction and the respective allylic alcohols separated.

A solution of the above hydrocarbon mixture (120 mg, 0.44 mmole) in 6.0 ml of pyridine containing 1–2 mg of hematoporphyrin was irradiated for 96 hr with a fluorescent desk lamp while a slow stream of oxygen was passed through the solution. The reaction mixture was diluted with ether and passed through a pad of charcoal, and the solvents were removed at reduced pressure in a 35° water bath. The crude residue was taken up in ether, and the ethereal solution was added to a slurry of 200 mg of lithium aluminum hydride in ether. After decomposition of the reaction mixture with saturated sodium sulfate solution, filtration, and evaporation of the filtrate to dryness, the residue was shown to contain at least four components by thin layer chromatography on silica gel in 9:1 hexane–ethyl acetate: (±)-17-hydroxyisokaurene **13**, the epimeric (±)-15-hydroxykaurenes **6**, and starting hydrocarbon mixtures. Chromatography of this mixture on 15 g of alumina afforded 20 mg (16%) hydrocarbons eluted with 100 ml of petroleum ether (30–60°); 56 mg (44%), mp 124–126°, of a mixture of epimeric (±)-15-hydroxykaurenes **6** eluted with 600 ml of 25% ether–petroleum ether (30–60°); and 32 mg (25%), mp 120–122°, of (±)-17-hydroxykaurene **13** eluted with 400 ml of ether.

The fraction shown to contain a mixture of epimeric (±)-15-hydroxykaurenes by thin layer chromatography on silica gel in 9:1 hexane–ethyl acetate was crystallized twice from petroleum ether and then sublimed at 110° (0.05 mm). This process afforded 28 mg (22%) of an analytically pure epimer, mp 126–127°, as judged by the presence of only one spot on thin layer chromatography. The companion epimer was not obtained in pure condition.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.46; H, 11.12.

Infrared showed $\nu_{max}^{CHCl_3}$ 3610, 3450 (OH), 3060 (vinyl H), 1655 (C=C), 1050, 1020, 1000 (C=O), and 900 cm^{-1} (>C=CH_2).

The fraction containing (±)-17-hydroxyisokaurene **13** was crystallized from petroleum ether (30–60°) and melted at 121–122.5° alone or in admixture with authentic material obtained by oxygenation of (±)-kaurene **3**.

Ethylidene Acetal 20.—A solution of 1.8 g (16 mmoles) of potassium *t*-butoxide in an anhydrous mixture of 20 ml of *t*-butyl alcohol and 20 ml of tetrahydrofuran in an atmosphere of nitrogen was treated with 3.0 g (8.08 mmoles) of ethyl triphenyl phosphonium bromide, and the mixture was stirred at 24° for 1 hr. A solution of 0.9 g (2.7 mmoles) of the keto acetal **19** in 80 ml of tetrahydrofuran was then added, and stirring was continued for a further 16 hr. The solvent was then removed (bath temperature 30°), and the residue was fractionated between 200 ml of petroleum ether and 50 ml of 80% methanol. The methanol layer was extracted with two 50-ml portions of petroleum ether, and the combined hydrocarbon layers were washed with 30 ml of 80% methanol and 30 ml of water. After drying over anhydrous sodium sulfate, the solution was filtered through 20 g of alumina; the alumina was washed with a further

500 ml of 2% ether in petroleum ether yielding, on removal of the solvent, 937 mg of the ethylidene acetal **2**. Recrystallization from methanol afforded needles, mp 86–88.5°.

Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.75; H, 10.94.

Infrared showed ν_{max}^{film} 1663 cm^{-1} (w) (>C=CHCH$_3$).

Keto Acetal 21.—A stirred suspension of 0.9 g (25 mmoles) of sodium borohydride in 70 ml of dry tetrahydrofuran at 0° in an atmosphere of nitrogen was treated with 4 ml of boron trifluoride etherate (32 mmoles) in 30 ml of tetrahydrofuran over a 5-min period. After a further 5 min, 0.930 g of the ethylidine acetal **20** (2.7 mmoles) in 50 ml of tetrahydrofuran was added in a slow stream, and the mixture was stirred for 3.5 hr, the temperature rising from 0 to 27° over this period. The reaction mixture was then cooled to 0° and treated cautiously with 22 ml of 10% potassium hydroxide (vigorous evolution of hydrogen), followed by 22 ml of 30% hydrogen peroxide (highly exothermic!). The mixture was then heated under reflux for 1.25 hr, cooled, and extracted with 200 ml of benzene–ether (1:1). The organic layer was washed with three 50-ml portions of water, dried over anhydrous sodium carbonate, and evaporated to dryness. The colorless oily residue was dissolved in 150 ml of acetone; the solution was cooled to 5° and treated dropwise (with "swirling") with 1.40 ml of Jones reagent[18] (5.6 mmoles). Ether (300 ml) was then added, and the mixture was quickly washed with 100 ml of water, 100 ml of 5% potassium hydroxide, and two 50-ml portions of brine. After drying over anhydrous sodium sulfate and removal of solvent, the residue was crystallized from methanol to give 0.84 of colorless needles, mp 116–119° (86%), of the α (axially) oriented acetyl acetal.

Anal. Calcd for $C_{23}H_{38}O_2$: C, 76.19; H, 10.57. Found: C, 76.27; H, 10.51.

Infrared showed ν_{max}^{Nujol} 1695 cm^{-1} (s) (–COCH$_3$).

A solution of 0.84 g of this acetyl acetal in 100 ml of 5% methanolic sodium methoxide was maintained at 25° in an atmosphere of nitrogen for 16 hr. After dilution with 100 ml of water, the mixture was extracted with two 100-ml portions of ether–benzene (5:1). The combined extracts were washed with 50 ml of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from pentane to yield 0.77 g (92%) of colorless needles of the β (equatorially) oriented keto acetal **21**. Two further crystallizations from pentane yielded clumps of needles, mp 84–87°.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.24; H, 10.66.

Infrared showed ν_{max}^{Nujol} 1705 cm^{-1} (–COCH$_3$).

(±)-13β-Acetyl-17-norkauran-16ξ-ol 22.—A solution of 1.5 g of the keto acetal **21** in 100 ml of acetone was treated with 30 ml of 3 *N* hydrochloric acid, and the mixture was heated under reflux for 30 min. Benzene–ether (100 ml of 1:1) was added to the cooled solution; the organic layer was separated and washed with two 30-ml portions of water. After drying over anhydrous sodium sulfate and removal of solvent, the residue was crystallized from hexane to give colorless needles (1.15 g, 87%) of the hydroxy ketone **9**, mp 148–157°. Repeated crystallization from hexane afforded fine needles, mp 153–163° (constant).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.04; H, 10.72.

Infrared showed ν_{max}^{Nujol} 3400 (s) (–OH), 1700, 1680 cm^{-1} (s) (–COCH$_3$); $\nu_{max}^{CCl_4}$ 3400 (s), 1680 cm^{-1} (s).

The acetate prepared from the hydroxy ketone **22** by treatment of material, mp 148–157°, with acetic anhydride–pyridine crystallized from hexane as needles, mp 183–185°.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.60; H, 9.95.

Infrared showed ν_{max}^{Nujol} 1725 (s) (–OCOCH$_3$), 1705 cm^{-1} (s) (–COCH$_3$).

(±)-13β-Acetyl-17-norkauran-16ξ-ol Oxime.—A solution of 0.25 g of the hydroxy ketone **22** acetate in 10 ml of methanol was added to a solution of 1 g of hydroxylamine hydrochloride and 1.5 g of sodium acetate in 40 ml of methanol, and the mixture was heated under reflux for 2 hr. The cooled solution was diluted with 50 ml of water, and the mixture was extracted with two 100-ml portions of ether–benzene (5:1). The combined extracts were washed with 30 ml of water (twice), dried over anhydrous sodium sulfate, and evaporated to dryness. The residual, colorless, crystalline oxime amounted to 0.26 g. A portion was recrystallized three times from hexane to afford needles, mp 184–186°.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93. Found: C, 73.92; H, 10.02.

Infrared showed ν_{max}^{Nujol} 3250 (s) (=NOH), 1730 cm^{-1} (s) (–OCOCH$_3$).

(±)-16ξ-Acetoxy-13β-acetamido-17-norkaurane 23.—A solution of 240 mg of the above crude oxime in 20 ml of pyridine at −10° was treated with 300 mg of *p*-toluene sulphonyl chloride, and the mixture was maintained at −8° overnight. Excess reagent was decomposed by the addition of ice and water, and the product was extracted with 100 ml of ether–benzene (10:1). The extract was washed with 30 ml of 5 *N* hydrochloric acid, 30 ml of 1 *N* sodium hydroxide, 30 ml of water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The crystalline residue was dissolved in 20 ml of dioxane, 12 ml of water was added, and the solution was heated under reflux for 20 min. The product was extracted with 200 ml of ether–benzene (1:1); the extract was washed with two 30-ml portions of sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of solvent left a crystalline residue which on recrystallization from acetone–hexane afforded 224 mg (93% from the ketol **22**) of the acetamide **23** as needlelike prisms, mp 190, 210–212°. Recrystallization from acetone produced analytically pure material as needles, mp 212–213°.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93. Found: C, 73.65; H, 9.94.

Infrared showed ν_{max}^{Nujol} 3300 (s), 3075 (w), 1648, 1550 (s) (NHCOCH$_3$), 1730, 1720 cm^{-1} (s) (OCOCH$_3$).

(±)-13β,16ξ-Diacetoxy-17-norkaurane 24. A. From the Acetamide 23.—A solution of 118 mg of the acetamide **23** in 10 ml of glacial acetic acid was added to a saturated solution of 1 g of anhydrous sodium acetate in 10 ml of glacial acetic acid. The stirred mixture was then treated with a solution of 0.5 g of nitrogen dioxide in 10 ml of acetic acid and the stirring was continued for 1.5 hr at 26°. The reaction mixture was diluted with 100 ml of ether–benzene (5:1), and the organic layer was separated and washed with 50 ml of water, two 50-ml portions of 1 *N* sodium hydroxide, 20 ml of water, and dried over anhydrous sodium sulfate. Removal of solvent left a pale yellow-crystalline residue (118 mg), which was sufficiently pure for the next reaction. A sample recrystallized from pentane at 0° had mp 164–166°.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.20; H, 9.53.

Infrared showed ν_{max}^{Nujol} 1733, 1250, 1230 cm^{-1} (all s) (–OCOCH$_3$).

B. From the Ketol 22 Acetate.—In a typical run, 0.51 ml (3.6 mmoles) of trifluoroacetic anhydride was added to a stirred suspension of 0.08 ml (3.0 mmoles) of 85% hydrogen peroxide in 20 ml of methylene chloride at 0°. The mixture was warmed to room temperature over 1 hr and was then treated with a solution of 125 mg (0.35 mmole) of the ketol **22** acetate in 5 ml of methylene chloride. The resulting solution was heated under reflux for 1.5 hr, cooled, and diluted with 100 ml of ether. The ethereal layer was separated and washed with two 30-ml portions of 1% sodium hydroxide. The extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The residue was chromatographed on 4 g of neutral alumina (Woelm, grade I). Successive elution with hexane–benzene afforded 12 mg (10%) of the diacetate **24**, 80 mg of starting ketone, and 26 mg of unidentified oily material.

(±)-13β,16ξ-Dihydroxy-17-norkaurene.—A solution of 115 mg of crude diacetate **24** in 30 ml of 5% methanolic sodium hydroxide was heated under reflux in an atmosphere of nitrogen for 1.5 hr. The cooled solution was diluted with excess water and extracted with two 50-ml portions of ether–benzene (1:1). The combined extracts were washed with 50 ml of water and then dried over anhydrous sodium sulfate. Removal of solvent and recrystallization of the residue from acetone–hexane afforded colorless prisms (84 mg, 96%), mp 160–165° (polymorphic change to needles), 168–171°. Recrystallization from acetone produced prisms, mp 160–165°, 171–173°.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.08; H, 10.97.

(±)-13β-Hydroxy-17-norkauran-16-one 25.—A solution of 84 mg (0.28 mmole) of the above diol in 100 ml of acetone at

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

−24° was treated dropwise with 0.12 ml (0.48 mmole) of Jones reagent,[18] and the mixture was maintained at −24 ± 1° for 3 min. Then 1 drop of propan-2-ol was added to destroy any excess oxidant. The solution was diluted with 50 ml of benzene and washed with 20 ml of water (thrice), 10 ml of 1% sodium hydroxide (twice) and water (20 ml), and dried over anhydrous sodium sulfate. Removal of solvent and recrystallization of the residue from hexane (charcoal) afforded irregularly shaped needles (71 mg, 90%), mp 170–172°, of the acyloin **25**. Two more crystallizations gave needles, mp 174–176°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.55; H, 10.46.

Infrared showed ν_{max}^{Nujol} 3425 (s) (–OH), 1748 cm^{-1} (s) (cyclopentanone).

(±)-13β-Hydroxykaurene 26.—A solution of 225 mg (2 mmoles) of potassium *t*-butoxide in an anhydrous mixture of 10 ml of *t*-butyl alcohol and 50 ml of tetrahydrofuran was treated with 750 mg (2.1 mmoles) of methyltriphenylphosphonium bromide, and the mixture was stirred in an atmosphere of nitrogen for 1 hr. A solution of 92 mg of the acyloin **25** (0.32 mmole) in 20 ml of dry tetrahydrofuran was then added, and stirring was continued for a further 15 hr. The solvent was removed under reduced pressure, and the residue was fractionated between 200 ml of hexane and 50 ml of 80% methanol. The methanol layer was separated and extracted with a further 50-ml portion of hexane. The hydrocarbon fractions were combined and washed with 20 ml of 80% methanol, 20 ml of water, and dried over anhydrous sodium sulfate. Removal of solvent and chromatography of the residue on 5 g of alumina afforded the hydroxy olefin **26** (82 mg, 89%) [hexane–benzene (10–50%) eluates]. Two recrystallizations from hexane gave needles, mp 151–153°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.24; H, 11.03.

Infrared showed ν_{max}^{Nujol} 3250 (s) (–OH), 3080 (w), 1660 (m), 877 cm^{-1} (s) (>C=CH_2).

The results of the following reaction indicate that this material was contaminated with 5 mg of a phosphorus compound and 2 mg of a compound that is probably the 8,13 epimer of **26** corresponding to a base-catalyzed "benzilic acid" type rearrangement of the acyloin **25**. The yield of the hydroxy olefin **26** should therefore be 81.5%.

(±)-Hiban-16-one 27.—A solution of 68 mg of the hydroxy olefin **26** in 30 ml of methanol was treated with 10 ml of 10 *N* hydrochloric acid, and the mixture was heated under reflux for 1 hr. The cooled solution was diluted with 40 ml of water and extracted with two 50-ml portions of ether–benzene (5:1). The combined extracts were washed with two 10-ml portions of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on 8 g of alumina and elution with benzene–petroleum ether (1:4) yielded the ketone **27** (37 mg, 55%); subsequent elution with pure benzene afforded, respectively, phosphorus-containing material (5 mg) and a semicrystalline ketone, ν_{max}^{film} 1741 cm^{-1} (2 mg), whose infrared spectrum bore a marked similarity to that of the ketone **27** and which was presumed to be the 8,13 epimer resulting from base-catalyzed rearrangement in the previous step.

Recrystallization of the ketone **27** from pentane at −70° gave colorless prisms, mp 117–119°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.03; H, 11.17.

Infrared showed ν_{max}^{film} 1739 cm^{-1} (s) (cyclopentanone).

(±)-16β-Hydroxyhibane.—A solution of 40 mg of the ketone **27** in 20 ml of absolute ethanol was treated with 20 mg of sodium borohydride, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with 50 ml of water and extracted with two 50-ml portions of benzene–ether (1:5). The combined extracts were washed with two 20-ml portions of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residual alcohol (40 mg) was purified by evaporative distillation at 125° (0.01 mm).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.61; H, 11.67.

Infrared showed ν_{max}^{film} 3380 cm^{-1} (s) (–OH).

(±)-Hibaene 28.—A solution of 24 mg of the above alcohol in 1 ml of pyridine at 0° was treated with 50 mg of *p*-toluenesulfonyl chloride, and the mixture was kept at room temperature for 16 hr. Ice water was then added, and the mixture was extracted with two 25-ml portions of ether. The ether extracts were combined, washed with 10 ml of 1 *N* hydrochloric acid and two 10-ml portions of 10% potassium carbonate, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was dissolved in 5 ml of collidine, and the solution was heated under reflux for 30 hr. The reaction mixture was then cooled, diluted with 50 ml of water, and extracted with two 50-ml portions of ether. The combined ether extracts were washed with two 30 ml portions of 1 *N* hydrochloric acid, 10 ml of water, 10 ml of 10% potassium carbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was adsorbed onto 5 g of neutral alumina (Woelm grade I) and (±)-hibaene **28** (8 mg, 30% from ketone **27**) was eluted with hexane. Evaporative distillation at 120° (0.01 mm) yielded a colorless, mobile oil whose infrared and nmr spectra were identical with those of (+)-hibaene prepared from stachenone by the method of Wenkert and co-workers.[19]

Anal. Calcd for $C_{20}H_{32}$: C, 88.16, H, 11.84. Found: C, 87.92; H, 11.74.

Infrared showed ν_{max}^{film} 3040 (w) (C=CH), 1361, 1370, 1380 (all ms) (CCH_3), 750 cm^{-1} (ms) (*cis*-CH=CH–).

Acknowledgment.—The authors are indebted to Dr. Baarschers for a sample of (+)-stachenone from which (+)-hibaene (stachene) was obtained by Wolff–Kishner reduction. The support of this work by a grant from the National Institutes of Health (GM-09067) is gratefully acknowledged.

(19) E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Am. Chem. Soc.*, **86**, 2218 (1964).