

to be 7-methoxycoumarin. It had mp 116–117° [lit. (for 7-methoxycoumarin) mp 115–116°<sup>19</sup> and 117–118°<sup>20</sup>].

*Anal.* Calcd for C<sub>10</sub>H<sub>8</sub>O<sub>2</sub>: C, 68.18; H, 4.55. Found: C, 67.83; H, 4.47.

The ultraviolet spectrum ( $\lambda_{\max}$  322 m $\mu$ ,  $\lambda_{\min}$  259 m $\mu$ ) was nearly identical with that of umbelliferone, and an infrared spectrum of the compound was identical with that of an authentic sample of 7-methoxycoumarin.<sup>27</sup>

(26) B. B. Dey, R. H. R. Rao, and T. R. Seshadri, *J. Indian Chem. Soc.*, **11**, 743 (1934).

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(27) Grateful acknowledgment is made to Mr. M. A. Irwin, who prepared the specimen of herniarin and measured its infrared spectrum.

## Experiments Directed toward the Total Synthesis of Terpenes. VII. The Synthesis of ( $\pm$ )-8 $\beta$ -Carbomethoxy-13-oxopodocarpanone, a Degradation Product of Phyllocladene<sup>1</sup>

ROBERT F. CHURCH,<sup>2</sup> ROBERT E. IRELAND,<sup>3</sup> AND JAMES A. MARSHALL<sup>4</sup>

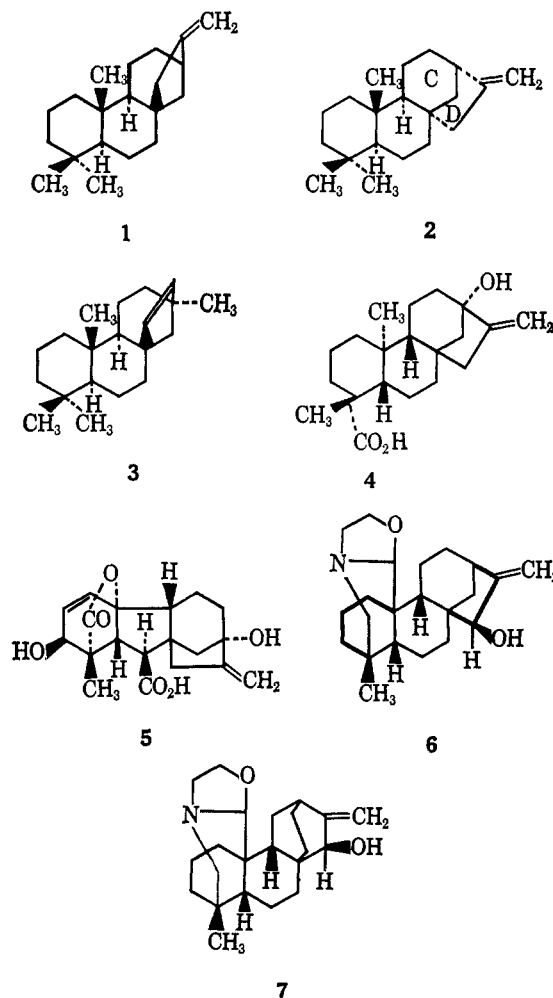
*Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48106*

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The synthesis of ( $\pm$ )-8 $\beta$ -carbomethoxy-13-oxopodocarpanone (**23**) via the Claisen rearrangement of the vinyl ether of 13 $\alpha$ -hydroxy podocarpan-8(14)-ene (**18**) is discussed.

The bridged bicyclic C/D ring structure is common to several members of the tetracyclic diterpenes. This structural unit, in the form of a substituted bicyclo[3.2.1]octane system, is present in phyllocladene **1**,<sup>5</sup> kaurene **2**,<sup>6</sup> and hibaene **3**.<sup>7</sup> Oxygenated variants of the same bicyclo[3.2.1]octane system can be found in steviol **4**,<sup>8</sup> gibberellic acid **5**,<sup>9</sup> and the alkaloid garryine **6**,<sup>10</sup> while the oxygenated bicyclo[2.2.2]octane system is present in the alkaloid atisine **7**.<sup>11</sup> The wide distribution of this structural feature made a scheme of general utility for the synthesis of such bridged bicyclic systems appear quite useful to ultimate total synthesis efforts in this area. The structural simplicity of the phyllocladene **1** system appeared to offer the logical substrate on which to practice and initial efforts were launched in this direction.

Inspection of the phyllocladene molecule **1** reveals the presence of the familiar *trans-anti-trans*-perhydrophenanthrene system (boldface in structure **1**) that is so prevalent among the diterpenes. The presence of this ring system suggested that formation of the bridged



(1) A preliminary report of this work appeared in *Tetrahedron Letters*, No. **17**, 1 (1960).

(2) Edgar G. Britten Fellow in Organic Chemistry, 1958–1959; Sun Oil Co. Fellow, 1959–1960.

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

(4) Public Health Service Research Fellow, National Heart Institute, 1958–1960.

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

(6) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *ibid.*, No. **24**, 18 (1960).

(7) Y. Kitahara and A. Yoshikoshi, *ibid.*, 1771 (1964).

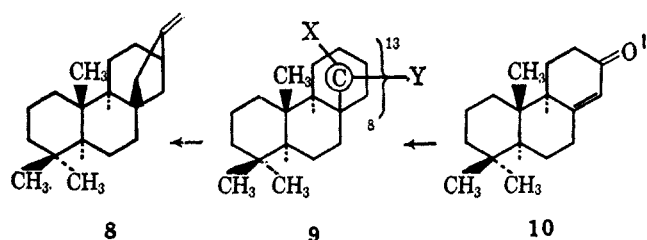
(8) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

(9) F. McCapra, A. I. Scott, G. A. Sim, and D. W. Young, *Proc. Chem. Soc.*, 1851 (1962); J. A. Hartuck and W. N. Lipscomb, *J. Am. Chem. Soc.*, **85**, 3914 (1963).

(10) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Fegdor, and J. Herzan, *ibid.*, **77**, 4801, 6633 (1955).

(11) K. Wiesner, J. R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. Ind. (London)*, 132 (1954); D. Dvorink and O. E. Edwards, *Tetrahedron*, **14**, 54 (1961); J. W. Apsimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962); S. W. Pelletier and D. M. Locke, *J. Am. Chem. Soc.*, **87**, 761 (1965); S. W. Pelletier and P. C. Parthasarathy, *ibid.*, **87**, 777 (1965).

component of the structure **8** might be accomplished through a generalized intermediate such as that represented by structure **9**. The concept involves introduction of a functionalized carbon atom, C–X, at C<sub>8</sub> of the perhydrophenanthrene nucleus, and the retention of sufficient functionality, Y, in ring C to allow ultimate closure of the carbon bridge to C<sub>13</sub>. The exact type of

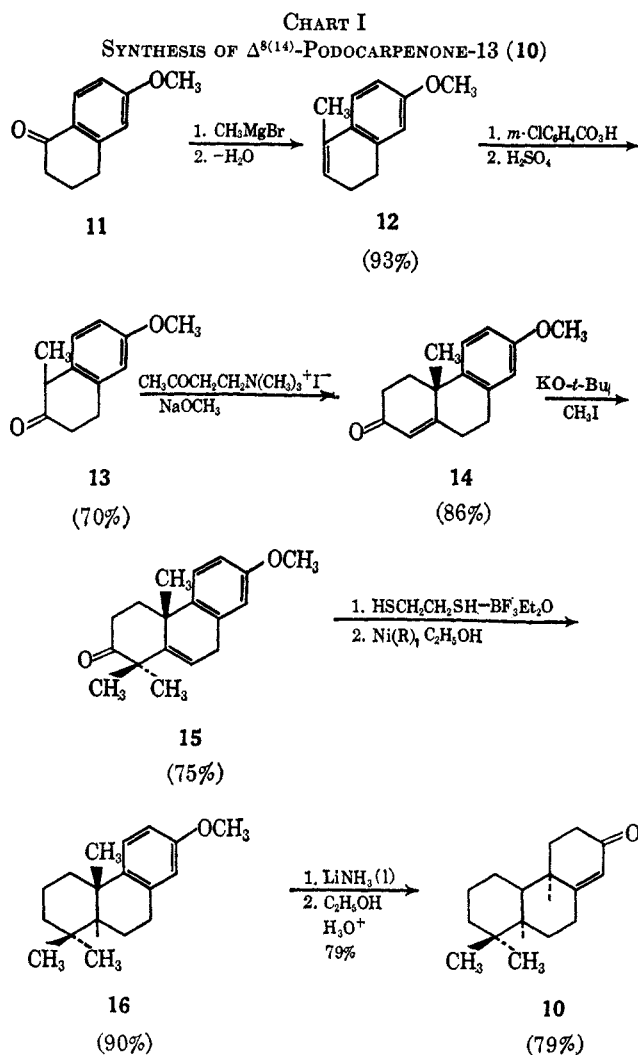


functionality used will depend to some measure on how the system represented by **9** is constructed. Ideally, this arrangement will be such that not only will the bridge construction be possible, but also further modification of the system toward phyllocladene **8** will be provided. It was recognized as well that the complete stereochemical features of phyllocladene **8** are embodied in the intermediate **9**. Therefore, the C<sub>8</sub>-functionalized carbon atom must be introduced in the  $\beta$  orientation (preferably highly stereoselectively), and, to be of the utmost utility, the method employed should also be capable of modification to form the C<sub>8</sub> epimer as a potential kaurene **2** precursor.

The logical conclusion to this "perhydrophenanthrene" reasoning process is, then, to devise a method whereby the intermediate **9** can be formed from a suitable C<sub>8</sub>-unsubstituted tricyclic compound. Such a starting material might be the  $\alpha,\beta$ -unsaturated ketone **10**. This compound offers activation of C<sub>8</sub> through conjugation with the C<sub>13</sub> carbonyl as well as the potential of retaining functionality in ring C through the C<sub>13</sub> ketone. Another important advantage is the ready accessibility of the ketone **10**, for not only is it known in both the active<sup>12</sup> and racemic forms,<sup>13</sup> but syntheses of the precursors<sup>13b,c</sup> of the desired racemic material are convenient and amenable to large-scale production. Thus, the scheme through which we hoped to elaborate the bicyclo[3.2.1]octane system of phyllocladene **1** had as its foundation these intermediates, and we now progress to the details of the individual stages.

Several routes were explored for the preparation of sufficiently large quantities of  $\Delta^{8(14)}$ -podocarpone-13 (**10**), and, while each of these led to the desired product, that elaborated in Chart I was by far the most convenient. The over-all yield of the unsaturated ketone **10** was 27%, and the material was available in quantities of 20–30 g as a result of one run. The experimental details for the conversion of 6-methoxy- $\alpha$ -tetralone **11** to the unsaturated ketone **15** are essentially those reported by Stork<sup>13b</sup> and require no further comment. Wolff-Kishner reduction of the ketone **15** was found to be unsatisfactory and the thioketal desulfurization sequence proved to be much superior.

The problem of inserting a functionalized carbon at C<sub>8</sub> in the  $\beta$  orientation has also been overcome in several ways. The Claisen rearrangement of the vinyl ether of an allylic alcohol appeared to us to have many advantages. First, the readily available unsaturated ketone **10** required little modification in order to prepare for the reaction. Particularly important were the high yields and stereospecificity reported by Burgstahler and Nordin<sup>14</sup> for this type of rearrangement. It



appeared highly likely that if the quasi-equatorially ( $\alpha$ ) oriented allylic alcohol **18** derived from the unsaturated ketone **10** could be obtained in favorable yield, the rearrangement of the corresponding vinyl ether would introduce a C<sub>8</sub>  $\alpha$ -acetaldehyde residue very efficiently.

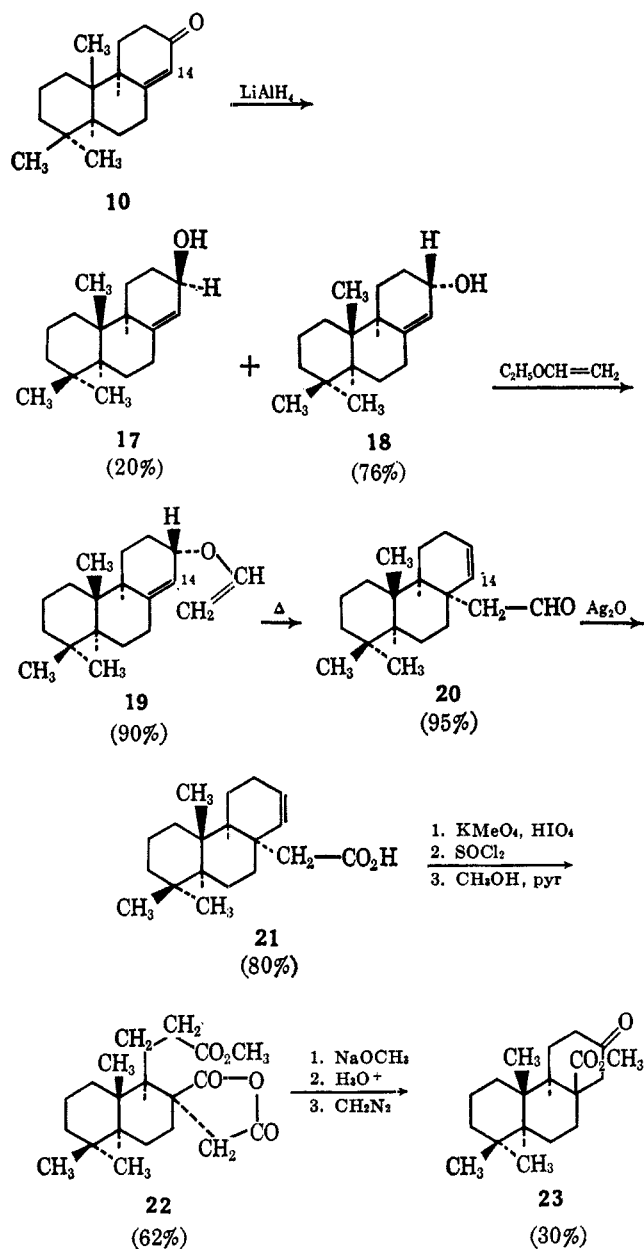
While a functionally substituted C<sub>8</sub> substituent should be available by this pathway, the stereochemical result is not that initially desired for phyllocladene **1**. Rather than to try to overcome this stereochemical barrier by employing the more labile, less readily available, quasi-axially ( $\beta$ ) oriented allylic alcohol **17**, the better solution appeared to be the utilization of C<sub>14</sub> of the rearrangement product **20** as the desired C<sub>8</sub>  $\beta$  substituent. The opportunity to make this change was inherent in the Claisen rearrangement sequence, for there remained a double bond in ring C and the C<sub>8</sub>  $\alpha$ -acetaldehyde side chain afforded the necessary carbon atoms to reconstitute the new C ring. Thus, the over-all plan for the conversion of the unsaturated ketone **10** to the desired phyllocladene intermediate **9** was to carry out the thermal rearrangement of the vinyl ether, oxidize the resulting olefinic aldehyde to a triacid, and recycle this material so as to leave a C<sub>8</sub>  $\beta$ -carboxyl group (formerly C<sub>14</sub> of the unsaturated ketone **10**) and a new C<sub>13</sub> ketone. The realization of this plan was accomplished as outlined in Chart II.

(12) R. Hodges and R. A. Raphael, *J. Chem. Soc.*, 50 (1960).

(13) (a) J. A. Barltrop and N. A. J. Rogers, *ibid.*, 2566 (1958); (b) G. Stork, A. Meisels, and J. E. Davies, *J. Am. Chem. Soc.*, **85**, 3419 (1963); (c) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1607 (1959).

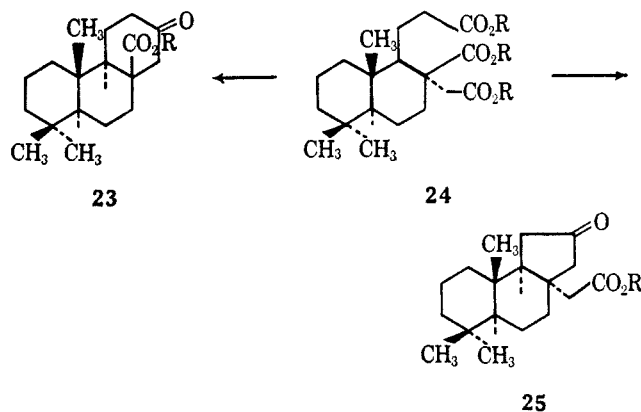
(14) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).

CHART II  
THE SYNTHESIS OF 8 $\beta$ -CARBOMETHOXYPODOCARPANONE-13

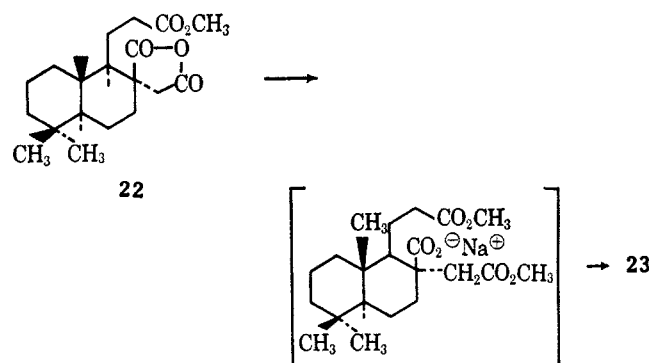


Several comments concerning individual steps in this transformation are appropriate. First, by analogy to the hydride reduction<sup>15</sup> of  $\Delta^4$ -cholestenone-3 in which the predominant allylic alcohol that results in the quasi-equatorially oriented  $\beta$  epimer, we took the major product 18 of the reduction of the ketone 10 to be the desired  $\alpha$ -oriented alcohol. This assumption was supported by the chromatographic behavior of the two alcohols 17 and 18, the inability to form a vinyl ether of the alcohol formed in minor proportion due to diene formation, and finally the correlation of the final keto ester 23 with material of proven stereochemistry.

Second, in order to overcome the possibility of a mixture of products from the Dieckmann-type cyclization and decarboxylation of the triacid 24 that results from oxidation of the olefinic acid 21, we formed the ester anhydride 22. Thus, by carrying the triacid 24 through this cyclization process, it appeared possible



to form both the desired cyclohexanone derivative 23 and the cyclopentanone derivative 25. On the other hand, the triacid 24 could be expected to form only the substituted succinic anhydride ester 22 when treated with thionyl chloride and then methanol at low temperature. This ester anhydride 22 can be expected to yield only the desired cyclohexanone derivative 23, for methanolysis of the anhydride by methoxide attack at the less hindered carbonyl will render



the potential angular carboxyl group inert toward base-catalyzed cyclization as a result of its conversion to a carboxylate anion. In point of fact when the reaction sequence was carried out, there was indeed no evidence of cyclopentanone carbonyl absorption in the infrared spectrum of the crude product. That this precaution was not entirely necessary was later shown by Turner and co-workers,<sup>16</sup> who successively carried out the Dieckmann-type cyclization sequence on the triacid 24.

Finally, the racemic keto ester 23 that was the result of these transformations was shown to be identical with its optically active counterpart<sup>5</sup> obtained by degradation of phyllocladene 1 through a comparison of their solution infrared spectra. This identity demonstrated the validity of the approach to the construction of these bridged bicyclic diterpene derivatives and provided the key intermediate for the final construction of phyllocladene 1. Thus, the keto ester 23 satisfies all the requirements set forth in a general form in the intermediate 9. That this was indeed the case was shown when Turner and his collaborators prepared the keto ester 23 by a different route<sup>16</sup> and employed<sup>17</sup> it to complete the construction of the bridged system of phyllocladene 1.

(15) Pl. A. Plattner, A. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949).

(16) R. B. Turner and P. E. Shaw, *Tetrahedron Letters*, **No. 18**, 24 (1960).

(17) R. B. Turner and K. H. Ganschirt, *ibid.*, 231 (1961).

Experimental Section<sup>18</sup>

*trans*-1,2,3,4,9,10,11,12-Octahydro-7-methoxy-1,1,12-trimethylphenanthrene (16).—A stirred solution of 23.9 g of the ketone 15 in 100 ml of glacial acetic acid and 25 ml of ethane-1,2-dithiol was cooled to 5° and treated dropwise with 10 ml of boron trifluoride etherate over a 10-min period. The reaction mixture developed a deep orange color and the dithioketal began to crystallize. Stirring was continued at room temperature for 1 hr; the mixture was cooled to 5° and filtered. The product was washed with two 50-ml portions of ice-cold 90% methanol and sucked dry at the pump. This treatment afforded 27.7 g of a colorless thioketal (90%, mp 103–106°) sufficiently pure for the next reaction. Two recrystallizations from acetone afforded an analytically pure sample that melted at 105–106.5°.

*Anal.* Calcd for C<sub>20</sub>H<sub>28</sub>SO<sub>2</sub>: C, 69.34, H, 7.57. Found: C, 69.39; H, 7.53.

A solution of 27.7 g of dithioketal in 500 ml of absolute ethanol was added to a suspension of approximately 330 g of W2 Raney nickel in 1 l. of absolute ethanol. The mixture was then stirred and heated under reflux in an atmosphere of nitrogen for 16 hr. The cooled mixture was filtered under nitrogen; the nickel was washed exhaustively with ethanol, and the combined filtrates were taken to dryness under reduced pressure. Crystallization of the residue from ethanol gave in three crops 18.2 g (80% from the ketone) of the ether 16 as colorless needles, mp 83–85° (lit.<sup>13a</sup> mp 85–86°).

**8(14)-Podocarpone-13 (10).**—To a solution of 3.78 g (0.54 g-atom) of lithium in 600 ml of liquid ammonia was added a solution of 4.6 g (0.018 mole) of the tricyclic ether 16 in 250 ml of ether. After the reaction mixture was stirred for 20 min, 150 ml of ethanol was added dropwise with stirring to discharge the blue color. The solvents were evaporated, and the residue was partitioned between ether and water. The ethereal solution was separated, washed successively with water, 5% aqueous hydrochloric acid, 10% aqueous potassium bicarbonate, water, 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 crystalline residue was dissolved in 200 ml of alcohol. The resulting solution was treated with 160 ml of 5 *N* aqueous hydrochloric acid, and then the reaction mixture was stirred and heated at 65–67° under a nitrogen atmosphere for 35 min. The reaction mixture was diluted with water and then extracted three times with 100-ml portions of ether. The combined ethereal extracts were washed twice with water, once with 10% aqueous potassium bicarbonate, once with water, and once with saturated salt solution. After the ethereal solution was dried over anhydrous sodium sulfate, the ether was removed at reduced pressure, and the solid residue was crystallized from petroleum ether (30–60°). In this fashion there was obtained 3.45 g (79%) of the unsaturated ketone 10, mp 92.5–93.5° with softening at 86° (lit.<sup>13a</sup> mp 89–91°, in two crops).

Ultraviolet showed  $\lambda_{\text{max}}^{\text{EtOH}}$  242 m $\mu$  ( $\epsilon$  15,900) [lit.<sup>13a</sup>  $\lambda_{\text{max}}^{\text{EtOH}}$  241.5 m $\mu$  ( $\epsilon$  16,150)].

Infrared showed  $\lambda_{\text{max}}^{\text{HCCl}_3}$  6.1 (s) (conjugated >C=O), 6.18  $\mu$  (conjugated >C=C<).

**13-Hydroxypodocarp-8(14)-enes (17 and 18).**—To a solution of 3.15 g (0.013 mole) of unsaturated ketone 10 in 200 ml of ether was added 17.4 ml of a 1.2 *M* ethereal lithium aluminum hydride solution, and the reaction mixture was stirred at room temperature for 2 hr. After treatment of the solution with 1.6 ml of water and then 1.3 ml of 10% aqueous sodium hydroxide, the precipitated salts were removed by filtration, and the ether was evaporated at reduced pressure on the steam bath. Crystallization of the crude reduction product from petroleum ether (60–75°) afforded 2.42 g (76%) of the 13 $\alpha$ -hydroxy isomer 18, mp 127–128°, as colorless prisms. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 127.5–128°.

(18) 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 bands 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.

*Anal.* Calcd for C<sub>17</sub>H<sub>28</sub>O: C, 82.53; H, 11.00. Found: C, 82.33; H, 11.19.

Infrared showed  $\lambda_{\text{max}}^{\text{HCCl}_3}$  2.90 (s) (O–H), 6.0 (>C=C<), 9.55  $\mu$  (s) (C–OH).

Chromatography of the residue (700 mg) from the mother liquors from the above crystallizations on 80 g of Florisil afforded first 570 mg (18%) of the 13 $\beta$ -hydroxy isomer 17, mp 109–111°, by elution with 100 ml of 5% ether–petroleum ether (30–60°). Further elution with 1500 ml of the same solvent pair afforded 100 mg of the 13 $\alpha$ -hydroxy isomer 18, mp 125–128°.

The analytical sample of the 13 $\beta$ -hydroxy isomer 17 was obtained by crystallization from petroleum ether (30–60°) and melted at 110–111°.

*Anal.* Calcd for C<sub>17</sub>H<sub>28</sub>O: C, 82.53; H, 11.00. Found: C, 82.66; H, 11.21.

**Vinyl Ether 19.**—In a typical run, 5.0 g (20.16 mmoles) of allylic alcohol 18 was dissolved in 300 ml of ethyl vinyl ether, freshly distilled from sodium, containing 5.20 g of mercuric acetate which had been recrystallized from ethanol containing 0.02% glacial acetic acid. The solution was heated under reflux in a nitrogen atmosphere for 16 hr, cooled, and then treated with 0.25 ml of glacial acetic acid. After stirring for another 3 hr at room temperature (29°), the reaction mixture was diluted with an equal volume of petroleum ether (30–60°), washed with 30 ml of 5% aqueous potassium hydroxide, and dried over anhydrous potassium carbonate. After removal of the solvent, the residue was chromatographed on 150 g of alumina. Elution with light petroleum gave 5.6 g of crystalline vinyl ether 19 (96%). Crystallization of this material from ether–methanol afforded 4.92 g (90%) of analytically pure ether 19 as prismatic needles, mp 45.5–46.5°.

*Anal.* Calcd for C<sub>19</sub>H<sub>30</sub>O: C, 83.15; H, 11.02. Found: C, 83.24; H, 10.88.

Infrared showed  $\nu_{\text{max}}^{\text{film}}$  3105, 3025 (w) (C=C–H), 1625, 1598 (s) (C=C), 960, 825 cm<sup>-1</sup> (s) (vinyl).

**Aldehyde 20.**—A Carius tube containing 4.0 g (14.60 mmoles) of crystalline vinyl ether 19 under nitrogen was placed in an oil bath at 190°, and this temperature was maintained for 3 hr. The product was removed from the cooled tube and chromatographed on 200 g of Florisil. Elution with petroleum ether (30–60°) gave a small amount of diene (84 mg) and elution with the same solvent containing 5% ether afforded 3.82 g of the aldehyde 20 (95%). A portion of the aldehyde was crystallized from pentane at –50° and formed poorly defined needles, mp 35–36°. The sample for analysis was prepared by evaporative distillation at 100° (0.05 mm).

*Anal.* Calcd for C<sub>19</sub>H<sub>30</sub>O: C, 83.15; H, 11.02. Found: C, 82.96; H, 10.99.

Infrared showed  $\nu_{\text{max}}^{\text{film}}$  2720 (w) (CH, aldehyde), 1718 cm<sup>-1</sup> (s) (C=O, aldehyde).

**Unsaturated Acid 21.**—The oxidation was carried out according to a procedure of Robinson and co-workers.<sup>19</sup> To a well-stirred solution of 650 mg (2.37 mmoles) of the aldehyde 20 and 4.3 ml (410 mg, 2.37 mmoles) of a solution of 1.24 g of silver nitrate in 13 ml of water in 25 ml of alcohol was added dropwise 16.5 ml (410 mg, 10 mmoles) of a solution of 1.24 g of sodium hydroxide in 50 ml of water. The reaction mixture was stirred vigorously for 2.5 hr, and then filtered to remove the precipitated silver. After the addition of 50 ml of water, the aqueous alcoholic filtrate was extracted three times with ether and then made strongly acid with concentrated hydrochloric acid. The solid acid 21 was filtered and crystallized from methanol. There resulted 550 mg (80%) of the acid 21, mp 150–152°, as a white, microcrystalline solid. The analytical sample, obtained after one further crystallization from the same solvent, melted at 151–152°.

*Anal.* Calcd for C<sub>19</sub>H<sub>30</sub>O<sub>2</sub>: C, 78.57; H, 10.41; neut equiv, 290. Found: C, 78.63; H, 10.31; neut equiv, 278.

Infrared showed  $\lambda_{\text{max}}^{\text{HCCl}_3}$  3.2–3.7 (s, broad) (C–H and associated O–H), 5.90  $\mu$  (s) (carboxyl >C=O).

**Ester Anhydride 22.**—According to the procedure of Lemieux and Rudloff,<sup>20</sup> a solution of 500 mg (1.72 mmoles) of the unsaturated acid 21, 720 mg (5.18 mmoles) of potassium carbonate, 2.96 g (13.8 mmoles) of sodium periodate, and 36.5 mg (0.231 mmole) of potassium permanganate in 690 ml of water was stirred at room temperature for 20 hr. The reaction mixture

(19) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(20) R. E. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

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  $\lambda_{\max}^{\text{film}}$  5.4, 5.6 (s) (anhydride  $>C=O$ ), 5.79  $\mu$  (s) (ester  $>C=O$ ).

**8 $\beta$ -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, and treated 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  $\bar{\nu}_{\max}^{\text{KCl}}$  1724 (s, broad) (ester and ketone  $>C=O$ ), 1200  $\text{cm}^{-1}$  (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 ( $\pm$ )-Kaurene and ( $\pm$ )-Atisirene<sup>1</sup>

RUSSELL A. BELL, ROBERT E. IRELAND,<sup>2</sup> AND RICHARD A. PARTYKA

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48106

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The synthesis of ( $\pm$ )-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  $C_{18}$  keto acetal **2** from the hydroboration and leads to ( $\pm$ )-atisirene **17**.

In the preceding paper<sup>3</sup> 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**.<sup>4</sup> 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 avail-

ability 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**<sup>5</sup> via a similar sequence of reactions to those used by Turner and co-workers<sup>6</sup> for the keto ester **20**  $\rightarrow$  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).

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

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