Experiments Directed toward the Total Synthesis of Terpenes. XII. A Stereoselective Synthesis of (±)-Desoxypodocarpic Acid and (±)-13-Methoxydesoxypodocarpic Acid[1]

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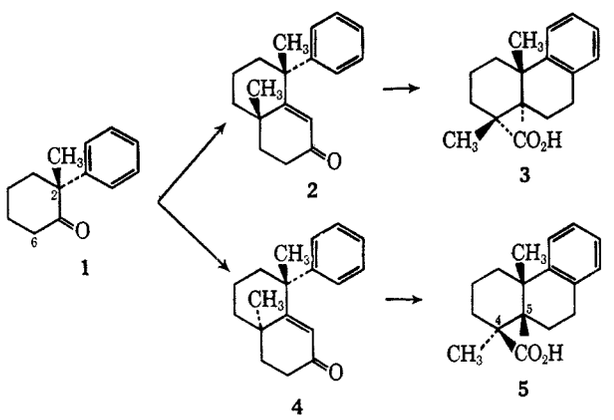
A stereoselective synthesis of (±)-desoxypodocarpic acid (9) and (±)-13-methoxydesoxypodocarpic acid (10) is described. A 21% over-all yield of the acid 10 from 2,6-dimethyl-6-phenylcyclohexanone (11) in 11 stages provides adequate quantities of this key synthetic intermediate for further transformations. The conversion of the acid 9 into podocarpic acid (6) is a well-known transformation.

Earlier we reported a stereoselective scheme for the synthesis of the abietic acid type resin acids[3] (3) from 2-methyl-2-phenylcyclohexanone (1) *via* the octalone 2. In this work, it was found that the attachment of the requisite C-6 methyl and C-6 oxobutyl groups to the starting cyclohexanone 1 could be accomplished stereoselectively and was dependent on the order in which the

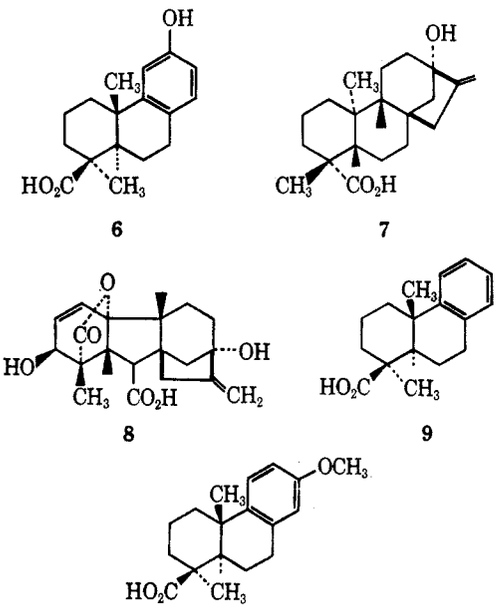
SCHEME I



groups were added. In particular, if the C-6 methyl group is attached first and then a precursor of the C-6 oxobutyl group, the ultimate tricyclic acid 5 that results is a member of the 4,5-iso series *via* the octalone 4. The reverse order of attachment leads to the natural arrangement exemplified by the acid 3 (Scheme I).

The acid 5 attracted our further attention, for not only does it belong to the 4,5-isoabietic acid series, but it may also be looked upon as a 5-isopodocarpic acid derivative. This synthetic scheme might therefore be adaptable to the synthesis of podocarpic acid (6) derivatives, if a suitable means were devised to invert the configuration of the C-5 hydrogen. In principle this is a much easier task than the initial control of the configuration of the C-4 methyl and carboxyl groups.

The podocarpic acid (6) system is equally as attractive an objective as the abietic acid arrangement 3, as a large number of naturally occurring substances are stereochemically related to the same or similar A/B ring system. Notable among these are steviol (7)[4] and gibberellic acid (8)[5] as well as podocarpic acid (6)[6] itself. To gain entry into this series of compounds we elected to modify our previously described synthesis so as to prepare (±)-desoxypodocarpic acid (9)[7] and (±)-13-



methoxypodocarpic acid (10).[8] The former is suitable for the synthesis of podocarpic acid (6) itself and the latter acid 10 might be a key intermediate for the synthesis of the related substances 7 and 8. Indeed both of these acids have been synthesized previously[7-9] with the stated ultimate objectives in mind, but it was felt that the present investigation was valuable in the interest of exploring the versatility of the synthetic sequence described earlier.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Dow Chemical Co. Fellow, 1963–1964; University of Michigan Fellow, 1965.

(3) R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **31**, 2543 (1966).

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

(5) F. McCapra, A. I. Scott, G. A. Sun, and D. W. Young, *Proc. Chem. Soc.*, 1851 (1962); J. A. Hartsuck and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **85**, 3414 (1963).

(6) W. P. Campbell and D. Todd, *ibid.*, **64**, 928 (1942).

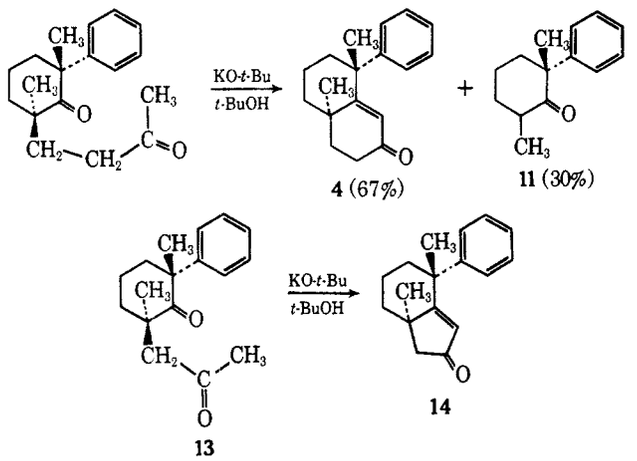
(7) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964), and earlier papers referred to therein.

(8) K. Mori and M. Matsui, *Tetrahedron*, **22**, 879 (1966).

(9) As well as the syntheses referred to above,[7,8] podocarpic acid derivatives have been prepared by (a) R. D. Haworth and R. L. Baker, *J. Chem. Soc.*, 1299 (1939); (b) R. D. Haworth and B. P. Moore, *ibid.*, 633 (1946); (c) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945); (d) F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind.* (London), 113 (1965); (e) J. A. Barltrop and A. C. Day, *J. Chem. Soc.*, 671 (1959); (f) O. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Amer. Chem. Soc.*, **82**, 1728 (1960); (g) C. T. Mathew, G. Sen Gupta, and P. C. Dutta, *Proc. Chem. Soc.*, 336 (1964); (h) W. E. Parham, E. L. Wheeler, and R. M. Dodson, *J. Amer. Chem. Soc.*, **77**, 1166 (1955); (i) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.*, 2175 (1964).

At first sight the most efficient entry into the podocarpic acid (**6**) system might appear to be the epimerization of the C-5 hydrogen of the acid **5**. While such a process is probably possible either through an oxidative process[7,9h] or a palladium-catalyzed epimerization,[9g] the low yield of the tricyclic acid **5** obtained in our earlier work[3] made this approach unattractive. The step in this previous scheme[3] that was primarily responsible for the low over-all yield of the tricyclic acid **5** was the aldol-type cyclization of the diketone precursor of the octalone **4**. Even in the best experiments this cyclization reaction (Scheme II) was accompanied

SCHEME II

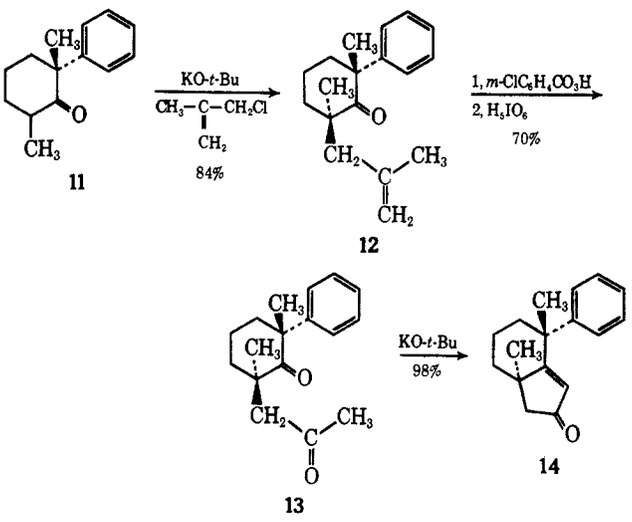


by significant amounts of reverse Michael-type side products, and the starting cyclohexanone **1** was isolated in up to 30% yield. An effective method that might prevent this undesirable side reaction and yet still fit within the framework of the over-all synthetic scheme would be to shorten the ketonic side chain by one carbon. Thus the reverse Michael-type reaction pathway is not open to the lower homolog **13** of the previous[3] diketone, and aldol-type cyclization should be uncomplicated. The hydrindenone **14** that would result from this sequence appeared as amenable to our ultimate purposes as the previous octalone **4**. To investigate the applicability of this concept, then, the authors set out to prepare the diketone **13** and to pursue its conversion into the tricyclic acids **9** and **10** of the podocarpic acid (**6**) system.

The hydrindenone **14** was available in 58% overall yield from 2,6-dimethyl-2-phenylcyclohexanone (**11**) by essentially the same procedures used earlier[3] for the synthesis of the analogous octalone **4**. In the present case, however, methallyl chloride was used as the initial alkylating agent in place of 1,3-dichloro-2-butene used earlier (Scheme III). The close similarity between the two alkylation reactions assured the desired stereochemical outcome, and the three-carbon side chain allowed entry into the hydrindenone system. The greatly increased over-all yield of the bicyclic ketone **14** over that observed earlier[3] in the synthesis of the bicyclic ketone **4** (29%) may primarily be ascribed to the efficiency of the final aldol-type cyclization step. This was a gratifying result of the shift to the hydrindenone system.

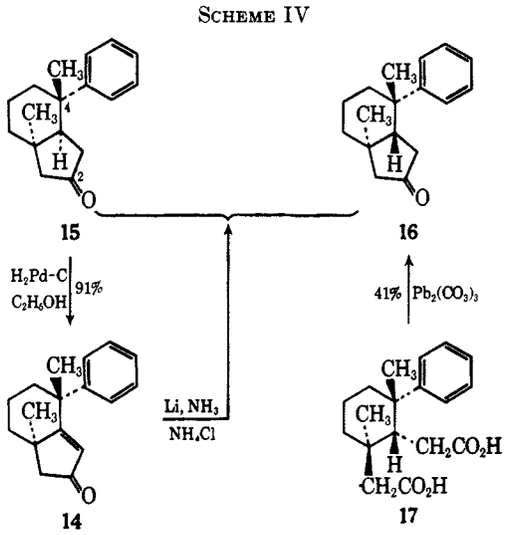
Having thus readily secured the desired intermediate enone **14**, the next concern was for its conversion into a

SCHEME III



tricyclic acid within the framework of the previously[3] described synthetic scheme. Our first task was then the stereoselective reduction of the double bond. It was initially felt that the methyl and phenyl groups at C-4 of the saturated *cis* ketone **15** would greatly hinder oxidative cleavage of the cyclopentanone ring between C-2 and C-3. Hence, the authors envisaged conversion of the saturated ketone **15** into the requisite diacid **22** directly. While this did not prove to be the case in the sequel, observations on the reduction of the enone **14** were informative.

SCHEME IV



Lithium–ammonia reduction of **14** (Scheme IV) led to a mixture of saturated ketones that was separated by column chromatography. While one ketone was a liquid and the other a solid, both provided crystalline, distinct semicarbazones. These saturated ketones were obtained in this manner in a ratio of 3:2 in which the liquid ketone was the major component. The stereochemistry of these saturated ketones was ascertained through independent synthesis of the *trans*-locked isomer from the diacid **17** of known[3] configuration. The *trans* ketone **16** obtained by pyrolysis of the lead salt of this diacid proved to be identical with the liquid ketone obtained on lithium–ammonia reduction of the enone **14** through direct spectral compari-

sons as well as mixture melting point determination of their semicarbazones. This conclusion meant that the crystalline saturated ketone from the lithium–ammonia reduction was the desired *cis*-locked ketone **15** and was available by this method in minor yield only.

With the configuration of the two saturated ketones **15** and **16** secured, the investigation turned to the catalytic hydrogenation of the enone **14**. Saturation of the conjugated double bond proceeded smoothly over palladium on carbon in ethanol solution in contrast to the earlier observations[3] on a similar reduction of the octalone **4**. In the present case only a single product was obtained in high yield, and this proved to be the desired *cis* ketone **15**. Thus through the agency of catalytic hydrogenation of the enone **14**, we were able to obtain a saturated ketone **15** with all of the asymmetric centers in the correct configuration for the conversion into the podocarpic acid (**6**) system. Unfortunately extensive effort to effect selective cleavage of the cyclopentanone ring system of the ketone **15** failed completely. Bromination, oxidation ($KMnO_4$, HNO_3, and CrO_3), and condensation ($HCO_2C_2H_5$–$NaOCH_3$) reactions all led to mixtures of products that could only be explained if one assumed that reaction took place on both methylene groups adjacent to the ketone.

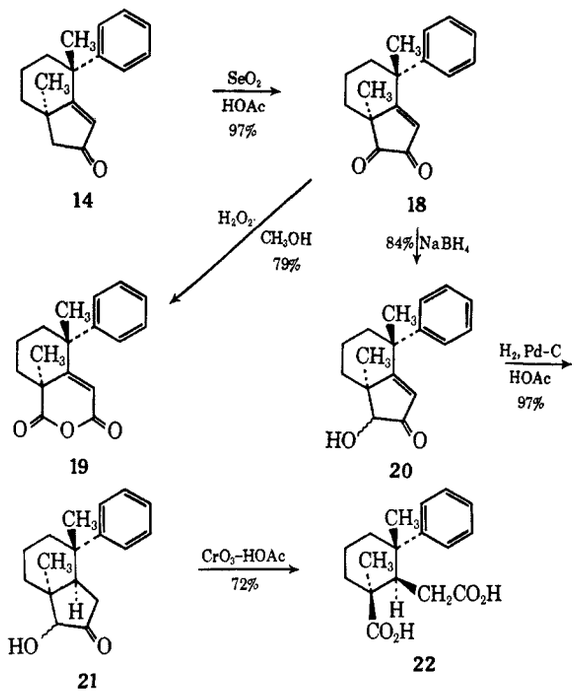
To overcome this lack of chemical selectivity at the ring cleavage stage, it was decided to take advantage of a unique feature of the hydrindenone **14**. By virtue of the location of the double bond in this molecule, the ketone can only enolize toward the C-1 position. Thus any reaction that involves ketone enolization will necessarily take place at the desired C-1 position and set the stage for subsequent ring cleavage between C-1 and C-2. It was thus elected to labilize the C-1 methylene first and then remove the double bond rather than the initially planned reverse order of reactions.

Functionalization of the C-1 methylene was most efficiently accomplished by selenium dioxide oxidation. The resulting dione **18** was obtained in high yield and readily oxidized further by hydrogen peroxide to the unsaturated anhydride **19**. Further efforts to convert this anhydride **19** into the desired saturated diacid **22** were thwarted by the resistance of the double bond to catalytic hydrogenation. Incomplete reduction was observed under the same conditions that effected rapid and complete reduction of the enone **14**. That the anhydride of the desired saturated acid **22** was indeed present in the mixture of reduction products was shown by treatment of the mixture with aluminum chloride and subsequent isolation of (±)-7-ketodesoxypodocarpic acid (**9**) in low yield.

We were finally able to overcome these synthetic problems by saturation of the double bond of the hydroxy ketone (**20**), which was readily available by sodium borohydride reduction of the dione **18**. Oxidation of the saturated hydroxy ketone **21** that results from these operations afforded the diacid **22** in a 58% over-all yield from the enone **14** (Scheme V).

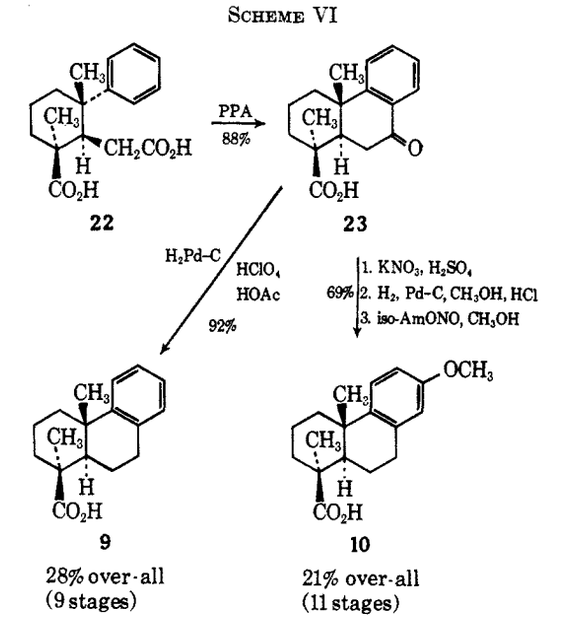
Having thus secured the required diacid **22** with all the stereochemical features of the podocarpic acid (**6**) system securely locked in, it was an easy matter to attain the desired goals. (±)-Desoxypodocarpic acid (**9**) was readily available by cyclization of the diacid **22** with polyphosphoric acid and then hydrogenolysis of the benzylic-type ketone of the tricyclic acid **23**.

SCHEME V



(±)-Desoxypodocarpic acid (**9**), available in 28% over-all yield by this synthetic scheme, was converted to (±)-podocarpic acid (**6**) itself, by the procedures of Wenkert and coworkers,[7] and spectral comparison of this synthetic material with the naturally derived acid revealed their identity and reaffirmed our structural and stereochemical assignments (Scheme VI).

SCHEME VI



Finally, the synthetically important tricyclic acid **10** was prepared by a modification of the procedure first used by Wenkert and coworkers[7] and later by Mori and Matsui.[8] The reaction scheme employed is different only in detail but results in a higher over-all yield of the desired methoxylated tricyclic acid **10**. Employing procedures developed earlier[10] in these laboratories,

(10) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966); R. A. Bell, R. E. Ireland, and R. A. Partyka, *ibid.*, **31**, 2530 (1966).

Mori and Matsui[11] have made use of this acid **10** for the preparation of intermediates that may be suitable for the synthesis of steviol (**7**). Transformations along similar lines are in progress in these laboratories as well.

Experimental Section

Melting points were determined on a Kofler hot stage, infrared spectra were recorded with a Perkin-Elmer spectrophotometer, Model 237, and ultraviolet spectra were recorded with a Perkin-Elmer ultraviolet spectrophotometer, Model 202. A Varian Associates Model A-60 nuclear magnetic resonance spectrometer was used for nmr spectra. Petroleum ether, unless otherwise noted, refers to the fraction boiling in the range 30–60°. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

2α,6β-Dimethyl-2β-(3-methallyl)-6α-phenylcyclohexanone (12).—To a rapidly stirred solution of 16.4 g (0.081 mmol) of 2,6-dimethyl-2-phenylcyclohexanone (**11**)[3] and 13.7 g (0.122 mol) of powdered potassium *t*-butoxide in 200 ml of dry benzene under a nitrogen atmosphere was added 22.0 g (0.243 mol) of methallyl chloride. The mixture was stirred for 10 hr at room temperature and then stirred and heated under reflux for an additional 5 hr. The cooled reaction mixture was diluted with 200 ml of water and then extracted three times with ether. The combined organic layers were washed three times with water, once with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure on the steam bath. The residual oil was distilled at 0.05 mm of pressure. The fraction boiling in the range between 77 and 85° was collected and amounted to 17.2 g, 84% of which was taken to be the keto olefin **12**. Later experiments[12] have shown by nmr and vpc analyses that alkylation products of this type may contain as much as 15% of the epimeric keto olefin: infrared $\bar{\nu}_{max}^{film}$ 1695 (saturated carbonyl), 1635, 885 cm^{-1} (unsymmetrically substituted olefin).

Anal. Calcd for $C_{18}H_{24}O$: C, 84.34; H, 9.44. Found: C, 83.98; H, 9.64.

2β-Acetonyl-2α,6β-dimethyl-6α-phenylcyclohexanone (13).—To a stirred solution of the keto olefin (**12**, 500 mg, 1.90 mmol), and 7 ml of methylene chloride was added a 328-mg portion (1.90 mmol) of *m*-chloroperbenzoic acid. The reaction was stirred until a negative starch iodide test was obtained. The precipitated *m*-chlorobenzoic acid was separated by filtration. The filtrate was stirred while a solution of paraperiodic acid (H_5IO), 445 mg (1.90 mmol) in 25 ml of ether, was slowly added. Precipitation of HIO_3 started almost immediately. After 1 additional hr of stirring the precipitate was separated by filtration, and the organic layer was washed three times with 20-ml portions of water, once with 20 ml of saturated potassium bicarbonate solution, and finally with a saturated salt solution. The ether solution was dried (Na_2SO_4) and concentrated at reduced pressure. The residue was eluted from 20 g of alumina (Merck) with 350 ml of 10% ether–petroleum ether. In this manner there was obtained 341 mg (70%) of crystalline dione **13**, mp 89–92°. A small sample, obtained for analysis by two crystallizations from petroleum ether, melted at 91–93°: infrared $\bar{\nu}_{max}^{CHCl_3}$ 1710 (carbonyl), 1685 cm^{-1} (carbonyl).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.01; H, 8.54.

On larger scale runs of 25–50 g of the keto olefin **12**, the yields of the dione **13** of comparable purity varied from 40 to 60%. In experiments on these scales the precipitation of iodic acid caused some mechanical difficulties and may account for the lower yields obtained.

4β,8α-Dimethyl-4α-phenylhexahydro-3(9)-inden-2-one (14).—Under a nitrogen atmosphere a solution of 2.00 g (7.72 mmol) of the dione **13** in 10 ml of dry benzene was added dropwise to a stirred suspension of 2.62 g (23.2 mmol) of potassium *t*-butoxide in 15 ml of *t*-butyl alcohol. The reaction was stirred at room temperature for 20 hr. The mixture was acidified with 25 ml of 3 *N* hydrochloric acid, and most of the *t*-butyl alcohol was removed at reduced pressure. The residue was partitioned between ether and water. The organic layer was washed three times with water and once with a saturated salt solution. The dried (Na_2SO_4) ether solution was concentrated at reduced pressure on the steam bath. The residual oil was evaporatively distilled at 130° (0.1 mm) and the distillate induced to crystallize by trituration in ether. After crystallization of this material from ether–petroleum ether (bp 60–75°), there was attained 1.82 g (97.5%) of the unsaturated ketone (**14**), mp 87–90°, in three crops. An analytical sample, obtained after two further crystallizations from ether–petroleum ether (bp 60–75°), melted at 91.5–92°: ir, $\bar{\nu}_{max}^{CHCl_3}$ 1680 cm^{-1} (unsaturated carbonyl); uv, λ_{max}^{MeOH} 239 mμ (ε 10,390); nmr, $\delta_{TMS}^{CCl_4}$ 0.62 (hydrogens on methyl at C-9), 1.40 (hydrogens on methyl at C-7), 6.10 ppm (vinyl hydrogen).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.89; H, 8.45.

Lithium–Ammonia Reduction of the Enone 14.—The unsaturated ketone **14** was reduced using the procedure of Ireland and Kierstead.[3] To a solution of 71 mg (9.9 mmol) of lithium wire in 400 ml of liquid ammonia (previously distilled from sodium) was added dropwise with stirring a solution of 1.0 g (4.15 mmol) of the unsaturated ketone **14** in 150 ml of anhydrous ether. The blue color faded after 7 min, and then excess solid ammonium chloride was added. The liquid ammonia was concentrated to approximately 0.1 of the volume with the aid of the steam bath. At this point 100 ml of ether was added, and the remaining ammonia was evaporated. The remaining mixture was diluted with 100 ml of ether, decanted, and washed three times with 100-ml portions of water and once with a saturated salt solution. The dried (Na_2SO_4) organic solution was concentrated at reduced pressure, and the residue which amounted to 950 mg of an oil was chromatographed on 125 g of alumina (Merck). Elution with 2.0 l. of 10% ether–petroleum ether afforded 361 mg of the pure *trans*-locked ketone **16** as an oil which resisted crystallization. A middle 500-ml fraction contained a mixture of the *trans*-locked ketone **16** and the *cis*-locked ketone **15**. Another 2.0 l. of the same eluent mixture afforded 230 mg of the pure *cis*-locked ketone **15** as white crystals.

Both of the ketones were converted into their semicarbazone derivatives by the procedure of Fieser.[13]

An analytical sample of the semicarbazone of the *trans*-locked ketone **16**, prepared by two crystallizations from methanol–ethanol, melted at 221–223°: ir, $\bar{\nu}_{max}^{Nujol\ mull}$ 3460 (s), 3340–3050 (b) (N–H), 1690 (s), 1575 (s) cm^{-1} (semicarbazone).

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04. Found: C, 72.25; H, 8.36; N, 13.91.

An analytical sample of the semicarbazone of the *cis*-locked ketone **15**, prepared by crystallization from large volumes of methanol, melted at 241–243°: ir, $\bar{\nu}_{max}^{Nujol\ mull}$ 3450 (m), 3350 (w), 3310 (w), 3200 (m) (N–H), 1670 (s), 1640 (s), 1585 (m), 1550 (m) cm^{-1} (semicarbazone).

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04. Found: C, 72.28; H, 8.26; N, 14.18.

4β,8α-Dimethyl-4α-phenylhexahydro-9βH-indan-2-one (16).—An intimate mixture of the diacid[3] **17** (94 mg, 0.31 mmol) and 100 mg of lead carbonate, contained at the sealed end of a 7-mm Pyrex tube, was heated to 270–290° for 10 min. The ketone **16** distilled through a glass wool plug as it was formed. The oily pyrolysate amounted to 31 mg (41%) of the *trans*-locked ketone **16**: ir, $\bar{\nu}_{max}^{film}$ 1750 cm^{-1} (s) (carbonyl); nmr, $\delta_{TMS}^{CCl_4}$ 0.33 (hydrogens on methyl at C-9), 1.28 ppm (hydrogens on methyl at C-7).

The semicarbazone of the *trans*-locked ketone **16** was prepared in the same manner as in previous examples. A sample, obtained after crystallization from methanol–ethanol, melted at 218–221° alone or on admixture with the semicarbazone, mp 221–223°, of the ketone **16** that resulted from lithium–ammonia reduction of the enone **14**.

4β,8α-Dimethyl-4α-phenylhexahydro-9αH-indan-2-one (15).—A mixture of 500 mg (2.07 mmol) of the unsaturated ketone **14** and 100 mg of 10% palladium on carbon in 20 ml of absolute ethanol was stirred in a hydrogen atmospheric pressure until hydrogen uptake had ceased (2 hr, 40 min). The catalyst was removed by filtration, and the liquid portion was concentrated at reduced pressure. The residue crystallized and after crystallization from petroleum ether (bp 60–75°) amounted to 459 mg (91%) of the saturated ketone **15**, mp 95–97°. The analytical sample, prepared by two crystallizations of a portion of this material from hexane, melted at 99.5–101°: ir, $\bar{\nu}_{max}^{CHCl_3}$ 1730 cm^{-1} (s) (saturated carbonyl); nmr, $\delta_{TMS}^{CCl_4}$ 0.53 (hydrogens on methyl at C-9), 1.06 ppm (hydrogens on methyl at C-7).

(11) K. Mori and M. Matsui, *Tetrahedron Lett.*, 2347 (1965).

(12) P. A. Grand, observations made in these laboratories and to be published.

(13) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 85.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.02; H, 8.94.

The semicarbazone derivative, prepared in the same manner as described above, was crystallized from large volumes of methanol and melted at 243–245°. A mixture of a sample of this material and the semicarbazone, mp 241–243°, of the ketone **15** that resulted from lithium–ammonia reduction of the enone **14** also melted at 243–245°: ir, $\nu_{max}^{Nujol\ mull}$ 3450 (w), 3350 (w), 3310 (w), 3200 (m) (N–H), 1670 (s), 1640 (s), 1585 (m), 1550 (m) cm^{-1} (semicarbazone).

4β,8α-Dimethyl-4α-phenylhexahydro-3(9)-indene-1,2-dione (18).—A solution of 5.23 g (20.5 mmol) of the unsaturated ketone **14** and 8.50 g (66.0 mmol) of selenous acid in 150 ml of glacial acetic acid was heated under reflux for 4 hr. Filtration of the cooled reaction mixture and removal of the acetic acid from the filtrate on the rotary evaporator at reduced pressure left a semicrystalline residue. This material was dissolved in ether. The ethereal solution was washed six times with water and dried (Na_2SO_4), and the ether was removed at reduced pressure on the steam bath. The orange crystalline residue was sublimed at 150° (0.005 mm) and afforded 6.38 g (97%) of the dione **18**, mp 112–113°.

A sample of the yellow crystals, prepared for analysis by crystallization from ether–petroleum ether, melted at 114–114.5°: ir, $\nu_{max}^{CHCl_3}$ 1765 (s) (carbonyl), 1715 cm^{-1} (s) (unsaturated carbonyl); λ_{max}^{MeOH} 285 mμ (ε 6450); nmr, $\delta_{max}^{CCl_4}$ 0.63 (hydrogens on methyl at C-9), 1.47 (hydrogens on methyl C-7), 6.67 ppm (vinyl hydrogen).

Anal. Calculated for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.20; H, 7.25.

2β-Carboxy-2α,6β-dimethyl-6α-phenylcyclohexylideneacetic Acid Anhydride (19).—A solution of 1.35 g (5.30 mmol) of the dione **18** and 3.33 ml of 30% hydrogen peroxide in 25 ml of methanol was heated under reflux until the solution became colorless (approximately 30 min). The reaction mixture was diluted with 150 ml of water and extracted with three 100-ml portions of ether. The combined organic layers were washed three times with water and once with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure. One crystallization of the residue from ether–petroleum ether (bp 60–75°) afforded 1.15 g (79%) of the crystalline unsaturated anhydride **19**, mp 134–137°.

A sample, prepared for analysis by two crystallizations from ethyl acetate–petroleum ether (bp 60–75°), melted at 139–140°: ir, $\nu_{max}^{CHCl_3}$ 1785 (s), 1740 (s) (anhydride), 1625 (m) cm^{-1} (double bond); nmr, $\delta_{TMS}^{DCCl_3}$ 0.95 (hydrogens on methyl at C-1), 1.41 (hydrogens on methyl at C-3), 6.49 ppm (vinyl hydrogen).

Anal. Calculated for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.61; H, 6.77.

4β,8α-Dimethyl-1ξ-hydroxy-4α-phenylhexahydro-3(9)-inden-2-one (20).—A solution of 334 mg (8.86 mmol) of sodium borohydride in 35 ml of water was slowly added (15 min) to a solution of 8.89 g (34.9 mmol) of the unsaturated dione **18** in 190 ml of methanol. The reaction mixture was stirred for an additional 3 hr at room temperature and diluted with 600 ml of water, and the product was isolated by three extractions with 250-ml portions of ether. The combined organic layers were washed three times with water and once with a saturated salt solution and dried (Na_2SO_4). Removal of the ether at reduced pressure on the steam bath afforded an oily crystalline residue which was crystallized from methanol–petroleum ether (bp 60–75°). In this manner there was obtained 5.12 g (57.5%) of the keto alcohol **20**, mp 117–118.5°. After chromatographic purification of the mother liquor from this crystallization on 150 g of silicic acid, there was obtained an additional 2.36 g (26.5%), mp 123–125°, of the keto alcohol **20**, which was eluted with 2 l. of ether. The spectra of these samples indicated that the variation in melting point was probably due to the presence of epimeric keto alcohols, for in subsequent transformations either sample gave the same results. In practice no effort was made to separate the epimers.

The analytical sample, prepared by three crystallizations from ether–petroleum ether, melted at 123–125°: ir, $\nu_{max}^{CHCl_3}$ 3530, 3390 (hydroxyl), 1705 cm^{-1} (s) (unsaturated carbonyl); uv, λ_{max}^{MeOH} 237 mμ (ε 14,200); nmr $\delta_{TMS}^{CCl_4}$ 0.58 (hydrogens on methyl at C-9), 1.39 (hydrogens on methyl at C-7), 3.42 (doublet, J = 4 cps, hydroxyl hydrogen), 3.87 (doublet, J = 4 cps, hydrogen on carbon 3), 6.22 ppm (vinyl hydrogen).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.72; H, 7.75.

4β,8α-Dimethyl-1ξ-hydroxy-4α-phenylhexahydro-9αH-indan-2-one (21).—To a suspension of 150 mg of 10% palladium on carbon in 25 ml of glacial acetic acid was added 456 mg (1.77 mmol) of the keto alcohols **20**, and the mixture was stirred under a hydrogen atmosphere at room temperature for 6 hr. Hydrogen uptake ceased after 5.5 hr. The catalyst was removed by filtration, and the filtrate was diluted with 300 ml of water and extracted with three 100-ml portions of ether. The combined organic layers were washed three times with water, once with 5% sodium bicarbonate, and twice with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue amounted to 446 mg (97%) of crystalline hydroxy ketone **21**, mp 155–168°. Three successive crystallizations of a portion from acetone–petroleum ether afforded analytically pure material which melted at 173–174°: ir, $\nu_{max}^{CHCl_3}$ 3600–3400 (hydroxyl), 1735 cm^{-1} (s) (saturated carbonyl); nmr, $\delta_{TMS}^{DCCl_3}$ 0.67 (hydrogens on methyl at C-9), 1.14 (hydrogens on methyl at C-7), 3.72 ppm (doublet, J = 3 cps, hydrogen on carbon 3).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.15; H, 8.59.

2β-Carboxy-2α,6β-dimethyl-6α-phenylcyclohexylacetic Acid (22).—A 2.35-ml portion of a chromium trioxide solution (prepared by the addition of 10 g of chromium trioxide to 20 ml of water and subsequent dilution with glacial acetic acid to produce a total volume of 100 ml) was added dropwise to a stirred solution of 221 mg (0.86 mmol) of the keto alcohols **20** in 6 ml of acetic acid. After 12 hr at room temperature, the mixture was shaken with ether and water, and the ethereal solution was separated. Two additional ether extractions were performed, and the combined ethereal layers were extracted three times with 5% NAOH (150 ml total). Addition of the combined basic layers to iced, concentrated hydrochloric acid produced a white precipitate which was immediately extracted with ether. The organic solution was washed four times with water and once with saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue amounted to 180 mg of crystalline diacid (72%), mp 203–207°. An analytical sample, obtained by three crystallizations from ether–hexane, melted at 207–209°: ir $\nu_{max}^{CHCl_3}$ 3550–2400 (b), 1695 cm^{-1} (s) (carboxyls).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.33; H, 7.72.

An anhydride was made of the diacid **22** by heating a small amount in acetic anhydride.

A sample, prepared for analysis by evaporative distillation at 175° (0.02 mm) and two crystallizations from ether–hexane, melted at 127–128°: ir, $\nu_{max}^{CHCl_3}$ 1805 (s), 1765 (s) cm^{-1} (anhydride).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.96; H, 7.49.

(±)-7-Ketodesoxypodocarpic Acid (23). A. From the Diacid 22.—The pulverized diacid **22** (103 mg, 0.36 mmol) was covered with 11 ml of polyphosphoric acid and 4 ml of 85% phosphoric acid. After stirring under a nitrogen atmosphere for 45 min, the mixture was stirred and heated with an oil bath maintained at 90° for another 45 min. While still warm, the reaction was poured over approximately 20 g of crushed ice, and the precipitate was extracted into ether. The ether solution was washed with three 50-ml portions of water and once with a saturated salt solution and dried (Na_2SO_4). After removal of the ether at reduced pressure on the steam bath, there remained 85 mg (88%) of nearly white crystalline (±)-7-ketodesoxypodocarpic acid (**23**), mp 218–220°.

An analytical sample, prepared by crystallization from ethyl acetate, melted at 221–222.5°: ir, $\nu_{max}^{CHCl_3}$ 3500–2600 (carboxyl hydroxyl), 1680 (carboxyl), 1670 cm^{-1} (unsaturated carbonyl); uv, λ_{max}^{MeOH} 249 mμ (ε 10,720); 294 (1485); nmr, $\delta_{TMS}^{DCCl_3}$ 1.21 (hydrogens on methyl at C-10), 1.32 ppm (hydrogens on methyl C-4).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.70; H, 7.39.

B. From the Unsaturated Anhydride 19.—To a suspension of 330 mg of 10% palladium on carbon in 25 ml of ethanol was added a solution of 660 mg (2.41 mmol) of the unsaturated anhydride **19** in 50 ml of ethanol, and the mixture was shaken in a hydrogen atmosphere at 3 psi on a Parr apparatus for 6.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated at reduced pressure. The residual oil was partitioned between ether and water. The organic solution was washed three times with a 5% bicarbonate solution and three times with water, dried (Na_2SO_4), and concentrated at reduced pressure on the steam

bath. There resulted 586 mg of an oil which was shown to be a mixture by thin layer chromatography and infrared spectroscopy. This oil was not further purified.

The product mixture from the above reduction was dissolved in a 20-ml portion of methylene chloride. This solution was added dropwise to a nitrogen protected, externally cooled (0°), stirred mixture of 900 mg of anhydrous aluminum chloride and 40 ml of methylene chloride. The reaction mixture was stirred at 0° for 2.5 hr and then allowed to come to room temperature. The mixture was poured onto 10 ml of iced concentrated hydrochloric acid and extracted with ether. The organic layer was extracted with three 50-ml portions of 10% potassium hydroxide, and the combined basic layers were poured onto 35 ml of iced concentrated hydrochloric acid. The precipitated acid was extracted into three 100-ml portions of ether and the combined organic layers were washed three times with water and once with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure on the steam bath. Evaporation distillation at 200° (0.005 mm) of the residue afforded 241 mg (37%) of (±)-7-ketodesoxypodocarpic acid (**23**), mp 215–218°. A sample, crystallized from methanol–petroleum ether (bp 60–75°), melted at 218–220°. A mixture of this keto acid and that obtained by polyphosphoric acid cyclization of the diacid **22**, mp 221–222.5°, melted at 218–221°, and the two acids showed identical solution infrared spectra: $\nu_{max}^{CHCl_3}$ 3500–2600 (carboxyl hydroxyl), 1680 (s) (carbonyl), 1670 cm^{-1} (s) (unsaturated carbonyl).

Methyl (±)-7-Ketodesoxypodocarpate.—The methyl ester of (±)-7-ketodesoxypodocarpic acid **23** was prepared by treating the acid with ethereal diazomethane. A sample for analysis, prepared by crystallization from ether–methanol, melted at 124–126° (lit.[9f] mp 124–125°): ir $\nu_{max}^{CHCl_3}$ 1720 (ester carbonyl), 1675 cm^{-1} (unsaturated carbonyl); uv, λ_{max}^{MeOH} 249 mμ (ε 10,010), 294 (1315); nmr, $\delta_{TMS}^{CCl_4}$ 1.11 (hydrogens on methyl at C-4), 1.27 (hydrogens on methyl at C-10), 3.68 ppm (hydrogens of ester).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.36; H, 7.58.

(±)-Desoxypodocarpic Acid (9).—A mixture of 43 mg (0.158 mmol) of keto acid **23**, 30 mg of 10% palladium on carbon, four drops of 72% perchloric acid, and 4 ml of glacial acetic acid was stirred in a hydrogen atmosphere until the uptake of hydrogen gas ceased (2 hr). The reaction mixture was filtered, and the filtrate was partitioned between ether and water. The combined organic layers were washed three times with water and once with saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure on the steam bath. The residual white crystalline solid amounted to 38 mg (92%) of (±)-desoxypodocarpic acid (**9**), mp 232–234°. A portion, obtained for analysis by three crystallizations from methanol, melted at 234–235° (lit. mp 232–233°;[7,9f] 225–230°[8]): ir, $\nu_{max}^{Nujol\ mull}$ 3400–2400 (acid hydroxyl), 1680 cm^{-1} (carboxyl).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.90; H, 8.64.

Methyl (±)-desoxypodocarpate was prepared by the treatment of the acid with ethereal diazomethane. An analytical sample was prepared by crystallization from methanol and melted at 127.5–128.5° (lit.[7] mp 130–131°; 126–127°;[8] 128–129°[9a]): ir, $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (s) (ester carbonyl); nmr, $\delta_{TMS}^{CCl_4}$ 0.98 (hydrogens on methyl at C-4), 1.24 (hydrogens on methyl at C-10), 3.60 ppm (hydrogens of ester).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.23; H, 8.74.

Methyl (±)-O-methylpodocarpate was prepared according to the procedure of Wenkert from 100 mg (0.35 mmol) of methyl (±)-desoxypodocarpate in 20% over-all yield. The solution infrared spectrum of this material and that of an authentic sample obtained from podocarpic acid (**6**) were identical.

(±)-13-Nitro-7-ketodesoxypodocarpic Acid.—To a stirred mixture of 1.0 g (3.66 mmol) of pulverized (±)-7-ketodesoxypodocarpic acid (**23**) and 540 mg (5.40 mmol) of pulverized potassium nitrite was added 17 ml of concentrated sulfuric acid (previously cooled to −5°). The reaction mixture was stirred for 30 min, poured onto crushed ice, and extracted three times with ether. The combined organic layers were washed three times with water and once with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from ethyl acetate and there was obtained 1.0 g (86%) of the nitro keto acid, mp 275–276°.

A small sample, prepared for analysis by crystallization from ethyl acetate, melted at 276–277°: ir, $\nu_{max}^{Nujol\ mull}$ 3500–2400 (b) (carboxyl OH), 1705 (s) (carboxyl), 1670 (s) (unsaturated carbonyl), 1520, 1370 cm^{-1} (s) (nitro); uv, λ_{max}^{MeOH} 236 mμ (ε 19,200), 270 (8900).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04. Found: C, 64.23; H, 5.95.

(±)-13-Methoxydesoxypodocarpic Acid (10).—A mixture of the nitro keto acid (1.05 g, 3.31 mmol), 500 mg of 10% palladium on carbon, ten drops of concentrated hydrochloric acid, and 800 ml of methanol was stirred in a hydrogen atmosphere until the uptake of hydrogen ceased (2 hr). The catalyst was removed by filtration, and the liquid portion was cooled to 0°. To this solution was added 4.8 ml of isoamyl nitrite, and the reaction mixture was allowed to warm to room temperature overnight. The solution was concentrated at reduced pressure and then partitioned between water and ether. The ether layer was extracted with three portions of a 5% sodium hydroxide solution, and the combined basic layers were added to an excess of iced, concentrated hydrochloric acid. The precipitate acid was extracted into ether, and the organic solution was washed three times with water and once with a saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure on the steam bath. After evaporative distillation of the residue at 170° (0.005 mm), the distillate crystallized on trituration with ether and amounted to 765 mg (80%), mp 191–193°, of the methoxy acid **10**.

An analytical sample, prepared by crystallization from ether–petroleum ether, melted at 192.5–194° (lit.[8] mp 193–194°): ir, $\nu_{max}^{CHCl_3}$ 3400–2400 (b) (carboxyl OH), 1700 (s) (carboxyl), 1605 cm^{-1} (s) (methoxy phenyl); nmr, $\delta_{max}^{DCCl_3}$ 1.09 (hydrogens on methyl at C-4), 1.32 (hydrogens on methyl at C-10), 3.74 ppm (hydrogens on methoxy carbon).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.33.

Registry No.—**9**, 5708-75-8; methyl ester of **9**, 16957-27-0; **10**, 5749-13-3; **12**, 16957-29-2; **13**, 16957-30-5; **14**, 16957-31-6; **15**, 16957-32-7; semicarbazone of **15**, 16957-33-8; **16**, 16957-34-9; semicarbazone of **16**, 16957-35-0; **18**, 16957-36-1; **19**, 16957-37-2; **20**, 16957-38-3; **21**, 16957-39-4; **22**, 16957-40-7; anhydride of **22**, 16957-41-8; **23**, 16957-42-9; methyl ester of **23**, 5708-77-0; (±)-13-nitro-7-ketodesoxypodocarpic acid, 16957-44-1.