The Structure and Total Synthesis of Cassaic Acid[1,2]

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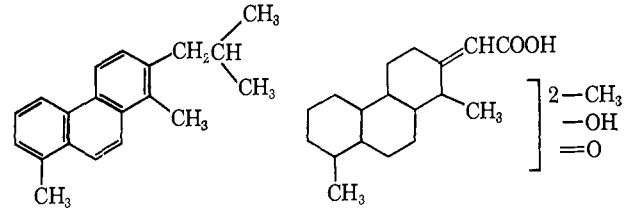
Abstract: Evidence is presented which establishes the structure of cassaic acid and, hence, also the structures of the *Erythrophleum* alkaloids cassaine, cassaidine, and coumingine. The question of stereochemistry is discussed. The total synthesis of cassaic acid which was carried out as part of this investigation, coupled with conversions described in the literature, constitutes a formal synthesis of cassaine and cassaidine. Of special interest is the method that was employed for establishing and maintaining a thermodynamically unfavorable configuration in an α-methyl ketone which served as a key intermediate.

The *Erythrophleum* alkaloid cassaine was first isolated in pure form by Dalma in 1935.[3] The substance possesses the molecular formula $C_{24}H_{39}O_4N$. On hydrolysis with dilute mineral acid, it affords β-dimethylaminoethanol and cassaic acid, $C_{20}H_{30}O_4$,[4] from which cassaine may be regenerated by treatment of the sodium salt with β-dimethylaminoethyl chloride.[5] Functional group analysis indicated the presence of one hydroxyl and one keto group,[4] and ultraviolet absorption spectra of cassaic acid (λ_{max} 215 mμ (log ε 4.3)) and of cassaine (λ_{max} 223 mμ (log ε 4.26)) indicate that the carboxyl functions in these substances (acid and ester, respectively) are α,β-unsaturated.[6] This conclusion was confirmed by the fact that on catalytic hydrogenation cassaic acid and cassaine furnish dihydro derivatives, which retain the keto group, but which show no discrete absorption in the 220-mμ region of the ultraviolet. On the basis of this evidence the substances were inferred to be tricyclic.

Information regarding nuclear structure was provided by selenium dehydrogenation of various derivatives of dihydrocassiac acid, from which reactions 1,2,8-trimethylphenanthrene could be isolated.[6,7] Further evidence was obtained by removal of the hydroxyl and keto functions in the dihydro acid and labeling of the carboxyl group in the latter compound by reaction of the corresponding methyl ester (cassanic acid methyl ester) with methylmagnesium bromide. Successive dehydration and dehydrogenation of the Grignard product afforded a crystalline hydrocarbon, $C_{20}H_{22}$.[8] Detailed comparison of the ultraviolet spectrum of the latter substance with spectra of various model compounds suggested that the $C_{20}H_{22}$ hydrocarbon was a trisubstituted phenanthrene derivative,[9] and the product was ultimately identified as 1,8-dimethyl-2-isobutylphenanthrene (**1**) by Humber and Taylor.[10] Barring rearrangement in the steps leading to **1**, part structure **2** could, therefore, be assigned to cassaic acid. This structure was then expanded to the nonisoprenoid formulation **3** by Humber and Taylor



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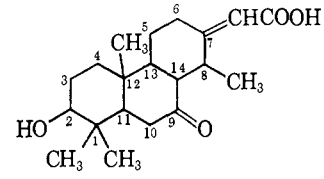
on the basis of considerations of the general behavior of the keto group and of an assumed analogy to other diterpenes.



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The work that has been carried out in this laboratory had as its initial objective a rigorous demonstration of the location of the keto group in cassaic acid. If the details of structure suggested by Humber and Taylor for the ring A system are provisionally accepted as correct, the keto group in question can be located only at C-9 or C-10, for cassaic acid is not an α- nor a β-hydroxy ketone, it does not possess the properties of a vinylogous β-keto ester, and does not exhibit conjugated ketonic absorption in the ultraviolet or infrared. The argument receives additional support from the observation of Engel[11] that ozonolysis of the diketone dehydrocassaic acid affords oxalic acid and a triketone in which the carbonyl groups are isolated and, hence, presumably situated in different rings.

Preliminary attempts to differentiate between the C-9 and C-10 alternatives by partial dehydrogenation of

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(2) A preliminary account of a portion of this work appeared in *Tetrahedron Letters*, No. 2, 7 (1959).

(3) G. Dalma, *Ann. Chim. Appl.*, 25, 569 (1935). For reviews of earlier work see T. A. Henry, "The Plant Alkaloids," 4th ed, J. and A. Churchill, Ltd., London, 1949, p 725, and E. L. McCawley in "The Alkaloids," Vol. V, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1955, Chapter 39.

(4) G. Dalma, *Helv. Chim. Acta*, 22, 1497 (1939).

(5) F. Faltis and L. Holzinger, *Ber.*, 72, 1443 (1939).

(6) L. Ruzicka and G. Dalma, *Helv. Chim. Acta.*, 22, 1516 (1939).

(7) L. Ruzicka, G. Dalma, and W. E. Scott, *ibid.*, 24, 179E (1941); see also A. Ronco, "Zur Kenntnis der Erythrophleum-Alkaloide, Ueber die Konstitution der Cassainsäure," Kommerzdruck und Verlags, A. G., Zurich, 1945.

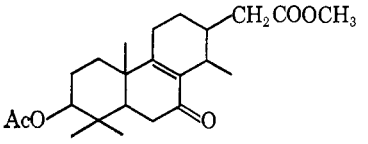
(8) L. Ruzicka, B. G. Engel, A. Ronco, and K. Berse, *Helv. Chim. Acta*, 28, 1038 (1945).

(9) B. G. Engel, A. Ronco, K. Berse, Pl. A. Plattner and L. Ruzicka, *ibid.*, 32, 1713 (1949).

(10) L. G. Humber and W. I. Taylor, *J. Chem. Soc.*, 1044 (1955).

(11) B. G. Engel, *Helv. Chim. Acta*, 42 131 (1959).

cassaic acid acetate methyl ester to an α- or a β-tetralone failed to yield any crystalline dehydrogenation products, although oils showing ultraviolet absorption reminiscent of α-tetralone were occasionally encountered. On the other hand, bromination and dehydrobromination of dihydrocassaic acid acetate methyl ester afforded in excellent yield an α,β-unsaturated ketone showing ultraviolet absorption, λ_{max} 247.5 mμ (ϵ 8700), consistent with structure **4**.[12] Moreover, treatment of **4** with acetic anhydride–acetyl chloride furnished an enol acetate with ultraviolet absorption, λ_{max} 242 mμ (ϵ 17,500), corresponding to that expected for **5**.[13] It follows that, subject to reservations regarding the ring A structure, the keto group in cassaic acid is most probably located at C-9. Definitive evidence



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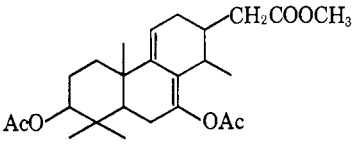

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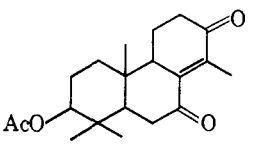

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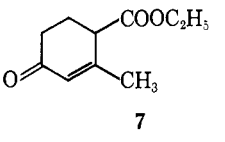
for the C-9 assignment was obtained as follows.

Ozonization of cassaic acid acetate methyl ester yields an acetoxy diketone (**26a**) which is readily converted into an epimeric product (**27a**) by the action of base or by chromatography on certain types of alumina. Reaction of **27a** with bromine followed by collidine dehydrobromination of the resulting bromo derivative yielded a compound (**6**) which showed typical enedione absorption, λ_{max} 266.5 mμ (ϵ 10,800).[14] A 1,4 relationship between the two carbonyl groups is thereby established. Since one of these groups arises by oxidative cleavage of the unsaturated acid side chain, known to be attached at C-7, the only position available for the second keto group, originally present in cassaic acid, is C-9.

With the general structural aspects of the B–C ring system fully established, attention was next directed toward the problem of the constitution of ring A. In view of limited supplies of natural material available for degradative work, a synthetic approach was undertaken.

In preliminary experiments Hagemann's ester (**7**)[15] was condensed with 1-chloropentanone-3 in the presence of triethylamine to afford a liquid product (**8**), characterized as the bissemicarbazone. Cyclization of **8** with sodium hydride, or alternatively with boron trifluoride etherate, gave an amorphous product (**9**), from which a crystalline semicarbazone could be obtained. Addition of a third ring was attempted by condensation (sodium hydride) of **9** with 1-chloropentanone-3,



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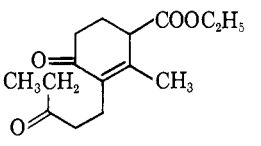

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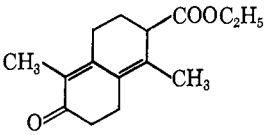

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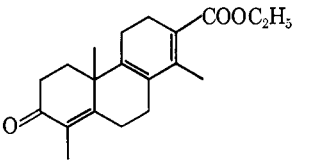

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followed by sodium hydride promoted cyclization. The crude product underwent extensive decomposition on attempted distillation, and no characterizable fractions could be obtained by chromatography. Since no crystalline derivatives could be obtained by any means, the material was finally reduced with lithium aluminum hydride and submitted to selenium dehydrogenation. In this case 15% of 1,2,8-trimethylphenanthrene was obtained. Thus, although a substantial amount of the desired product (**10**), or double bond isomers thereof, may have been formed, the failure of all attempts to isolate the key tricyclic intermediate in pure form appeared to preclude any useful application of this approach in the present investigation.

The procedure that ultimately proved successful followed more conventional lines in which 6-methoxy-2-tetralone[16] served as starting material. Methylation of this material by the enamine method[17] afforded 6-methoxy-1-methyl-2-tetralone (**11**), also obtainable by an alternate route devised by Howell and Taylor.[18] Condensation of **11** with dimethylaminobutanone methiodide gave the tricyclic ketone **12**,[19] which was converted by standard procedures through derivatives **13** and **14** into the required intermediate **15a**.[20] The latter substance was then reduced with lithium and alcohol in liquid ammonia,[21] and the resulting dihydroanisole (**16a**) was obtained in good yield in nicely crystalline form. This substance afforded an acetyl derivative (**16b**), and both compounds were smoothly cleaved to the corresponding β,γ-unsaturated ketones (**17a** and **17b**, respectively) by the action of

(12) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942); *cf.* E. E. Royals, *J. Org. Chem.*, **23**, 151 (1958).

(13) *Cf.* L. F. Fieser, Wei-Yuan Huang and J. C. Babcock, *J. Am. Chem. Soc.*, **75**, 116 (1953).

(14) W. P. Campbell and G. C. Harris, *ibid.*, **63**, 2721 (1941); L. Ruzicka, E. Rey, and A. C. Muhr, *Helv. Chim. Acta*, **27**, 472 (1944).

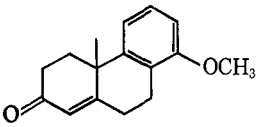
(15) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893).

(16) R. Robinson and P. Weygand, *J. Chem. Soc.*, 386 (1941); J. W. Cornforth, R. H. Cornforth, and R. Robinson, *ibid.*, 689 (1942).

(17) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(18) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1248 (1958).

(19) The ultraviolet absorption of this compound, λ_{max} 231 mμ (ϵ 25,000) (subtraction of the spectrum of **15a** from that of **12** gives λ_{max} 231 mμ (ϵ 20,700) as the contribution of the carbonyl chromophore in the latter compound), is anomalous in that maximum absorption at 240 mμ is predicted by the Woodward rules.[12] Similar shifts have been noted in the Cornforth–Robinson ketone (i), and in numerous compounds of type ii where x or y represents a heteroatom: see C. B. Clarke and A. R. Pinder, *J. Chem. Soc.*, 1967 (1958); E. M. Kosower and D. C. Remy, *Tetrahedron*, **5**, 281 (1959).



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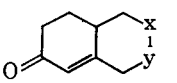
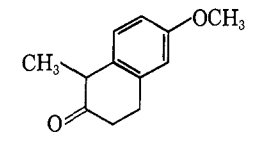


ii

(20) The same sequence was developed independently by Stork and his associates in their synthesis of α-onocerin: G. Stork, J. E. Davies, and A. Meisels, *J. Am. Chem. Soc.*, **81**, 5516 (1959). The details of our work will be found in the Experimental Section.

(21) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360, 5366 (1953).



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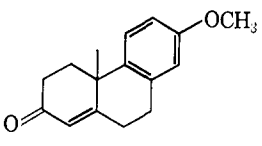

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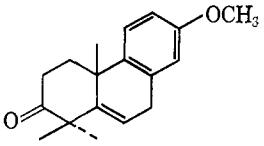

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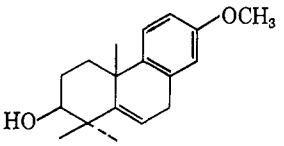

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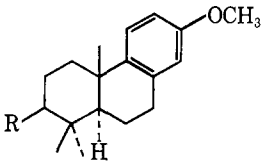
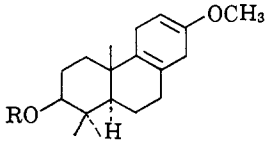
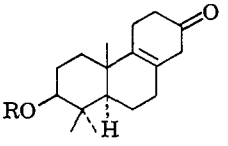


15a, R=OH
15b, R=OAc
15c, R=O

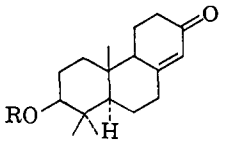
oxalic acid. The related α,β-unsaturated ketones (**18a** and **18b**) could be prepared through the use of mineral acid.



16a, R=H
b, R=Ac

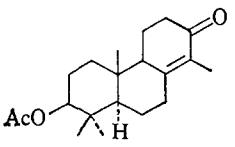


17a, R=H
b, R=Ac



18a, R=H
b, R=Ac

The acetoxy β,γ-unsaturated ketone was next treated with approximately 1 equiv of methyl iodide in the presence of potassium *t*-butoxide.[22,23] The crude reaction product, on reacetylation and chromatography, afforded the monomethylated α,β-unsaturated ketone **19**, λ_{max} 249 mμ (ϵ 17,500), in about 30% yield. The infrared spectrum of this substance, measured in carbon disulfide solution, was identical with that of an



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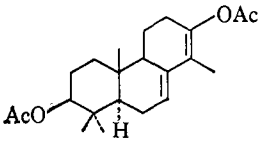

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optically active (dextrorotatory) compound of this constitution obtained by *p*-toluenesulfonic acid–toluene dehydration of hydroxyketone **29a** from natural sources. The structural features of the ring A system, and hence of cassaic acid itself, are thereby established.[24]

(22) N. W. Atwater, *J. Am. Chem. Soc.*, **79**, 5315 (1957).
(23) F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957).
(24) After this phase of the work had been completed W. J. Gensler and G. M. Sherman, *Chem. Ind.* (London), 223 (1959), reported

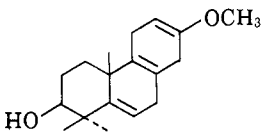
Further correlations of compounds in the synthetic series with those of natural derivation require introduction of a C-9 keto function in **19**. The plan originally devised for accomplishing this transformation involved conversion of **19** into an enol acetate **20** followed by peracid treatment of the latter derivative with subsequent hydrolysis and oxidation according to well-established procedures.[13,25] Compound **19** was therefore treated with acetic anhydride and acetyl chloride, and the resulting oily reaction product was examined in the ultraviolet. No high-intensity absorption attributable to the diene system of **20** was observed.[26] Similar results were obtained when acetic anhydride–*p*-toluenesulfonic acid and isopropenyl acetate–*p*-toluenesulfonic acid were used as acetylating agents. Direct bromination of **19** with N-bromosuccinimide likewise failed to yield any characterizable product.

In view of these difficulties an attempt was made to retain the ring B double bond of **14** through Birch reduction and to employ this function for introduction of a carbonyl group in the desired position. Reduction of **14** proceeded smoothly, and the resulting unsaturated enol derivative **21** was converted into **22** by the action of oxalic acid. However, the results of attempts to effect monomethylation of **22**, either directly or after acetylation of the free hydroxyl group, were unsuccessful.

The acetoxy ketone **19** was finally treated with chromic acid in acetic acid in the hope that direct introduction of the C-9 keto group might be accomplished. Repeated recrystallization of the crude oxidation product afforded a pure sample of the desired enedione (*d,l*-**6**), λ_{max} 266.5 mμ (ϵ 10,800), although in poor yield. The infrared spectra (solution) of the synthetic product and of the optically active degradation product **6** from cassaic acid were identical. Reduction of *d,l*-**6** with zinc dust and acetic acid gave the corresponding saturated acetoxydiketone as the *thermodynamically unstable epimer*[27] *d,l*-**26a**, which was likewise identified by infrared comparison with authentic naturally derived material.

Before proceeding with a discussion of experiments that lead to the total synthesis of cassaic acid, it will be well to consider the evidence that bears on the question of stereochemistry. Our conclusions in this regard are embodied in structure **23**. The argument for an equatorial assignment of the C-2 hydroxyl group is based upon studies, not here reported, of the retropinacol rearrangement of the ring A system of cassaic acid and upon the fact that lithium aluminum hydride reduction of **13** is expected, on the basis of ample analogy,[28] to furnish the equatorial alcohol. The

establishment of the C-2 position for the hydroxyl group by the Grignard dehydrogenation method. Subsequently, evidence permitting assignment of the keto group to C-9 has been obtained by the same general method: W. H. Gensler and G. M. Sherman, *J. Am. Chem. Soc.*, **81**, 5217 (1959).
(25) C. Djerassi, O. Mancera, G. Stork, and G. Rosenkranz, *ibid.*, 73, 4496 (1951).
(26) The appearance of weak absorption in the 280-mμ region suggested the possibility that enol acetylation furnished a homoannular diene which then underwent oxidation or disproportion to the aromatic system.
(27) In our early work[2] we reported the thermodynamically *stable* epimer (*d,l*-**27a**) as the product of this reaction. We have no reason to doubt this observation and suspect that slight differences in reaction conditions or in work-up procedure may have resulted in epimerization of the initially formed unstable product.



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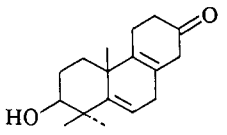

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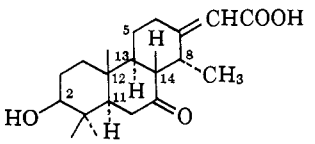

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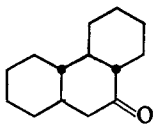
orientation, α or β, of an equatorial substituent at C-2 is determined by the nature of the A–B ring fusion and will be β if these rings are *trans* fused. That this is indeed the case is suggested by the close analogy between the catalytic hydrogenation of **14** to **15a** and the similar reduction step in the total synthesis of dehydroabietic acid,[29] which leads unambiguously to a *trans*-fused product. A stronger argument is provided by the correlation of cassanic acid with vinhaticoic acid,[30] in which the A–B *trans* arrangement has been established.

Configuration at the B–C fusion is less well defined. That this fusion represents a thermodynamically stable arrangement seems firmly established by the numerous instances in which cassaic acid derivatives have been subjected to the action of base without inversion at the epimerizable center C-14. For example, cassaic acid is obtained from coumingic acid after a 1.5-hr reflux period with 0.4 *N* aqueous alcoholic potassium hydroxide.[7] The failure of deliberate attempts to epimerize the ketoketal **31** (see below) by the action of base constitutes a strong additional argument. The regeneration of cassaine from cassaic acid[5] demonstrates the important fact that no configurational change is involved in the hydrolytic cleavage of the parent alkaloid. These observations, coupled with the proof of *trans* stereochemistry at the A–B ring junction, limit the possible sets of configurations at C-13 and C-14 to two, indicated for the analogous 9-ketoperhydrophenanthrenes by structures **24** and **25**. The greater stability of the *trans,anti,trans* compound **24** as compared with



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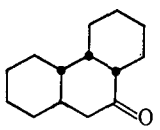


25

the corresponding *trans,anti,cis* derivative is well known,[31] and the failure of the *trans,syn,cis* product **25** to epimerize to the *trans,syn,trans* isomer[32] is satisfactorily explained by Johnson's observation that the latter arrangement requires a "boat" conformation in ring B.[33]

(28) E. R. H. Jones and T. G. Halsall in "Progress in the Chemistry of Organic Natural Products," Vol. 12, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1955, Chapter 2.

(29) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956).

(30) F. E. King, T. J. King, and J. M. Uprichard, *J. Chem. Soc.*, 3428 (1958).

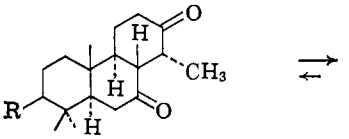
(31) R. P. Linstead, W. von E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942), *et seq.*

(32) R. P. Linstead and R. R. Whetstone, *J. Chem. Soc.*, 1428 (1950).

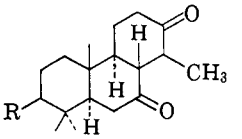
(33) W. S. Johnson, *Experientia*, 7, 315 (1951).

The stable *trans,anti,trans* and *trans,syn,cis* configurations for cassaic acid differ only in the orientation of the C-13 hydrogen atom. The conclusion that this atom is α oriented in the great majority of diterpenoids has been drawn by Klyne from studies of optical rotatory properties.[34] In the present case the best available argument appears to rest on the observation that the synthetic acetoxyketone **19** is formed under strongly basic conditions that ensure equilibration of configuration at C-13. The C-13 hydrogen atom in this compound, in the enedione **6**, and in the diketones **26a** and **27a** is therefore assigned an α orientation, since only this arrangement permits the C-5–C-13 bond to assume an equatorial disposition with respect to ring B. Since **26a** is obtained from cassaic acid by operations that do not involve the center of asymmetry at C-13, it follows that, to a high degree of probability, the *trans,anti,trans* structure assigned to cassaic acid **23** is correct.

The orientation of the C-8 methyl group may now be considered. As noted previously, cassaic acid acetate methyl ester affords on ozonization an acetoxy diketone **26a** which undergoes ready isomerization into **27a**. Since the B–C ring fusion has been shown to possess a



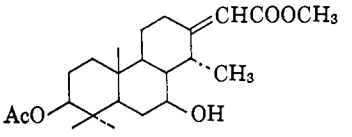
26a, R = OAc
b, R = OH
c, R = =O



27a, R = OAc
b, R = OH
c, R = =O

thermodynamically stable configuration, the transformation **26a** → **27a** can be explained only by a change in configuration of the C-8 methyl group, which might be from axial (α) to equatorial (β), or, in unusual circumstances, from equatorial to axial.

A decision in favor of the first of these possibilities may be drawn from consideration of the behavior of monoketals **31** and **34** prepared and correlated as follows. Sodium borohydride reduction of cassaic acid acetate methyl ester affords a single hydroxy derivative (**28**) which yields on ozonolysis an acetoxy hydroxy ketone (**29a**). The latter substance is stable in the face of epimerizing conditions. Thus, the compound is not epimerized by mineral acid and is transformed by



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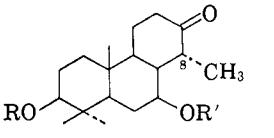


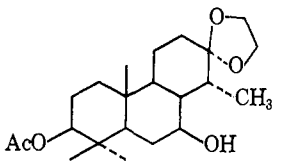
29a, R = Ac; R′ = H
b, R, = Ac; R′ = Ac
c, R, = H; R′ = H

vigorous treatment with base and subsequent oxidation into triketone **26c** which differs from, but is convertible into, triketone **27c**, obtained from the stable hydroxy diketone **27b**. The stability of the hydroxyketone **29a** is readily explained in terms of the assigned structure, since a change in configuration at C-8 would lead to an unfavorable 1,3 interaction between the methyl and hydroxyl groups. This argument can, of course, be applied with equal force to the alternate 8β,9α arrange-

(34) W. Klyne, *J. Chem. Soc.*, 3072 (1953).

ment (**38**). It should be noted, however, that oxidation of **29a** with chromium trioxide–acetic acid leads to the *unstable* diketone **26a**, and thus the methyl group in **29a** retains the configuration it possesses in cassaic acid. The use of an appropriately oriented C-9 hydroxyl group in maintaining during synthesis what would otherwise be an unfavorable configuration at C-8 is referred to again below.

When **29a** is subjected to exchange with 2-butanone ethylene ketal in the presence of *p*-toluenesulfonic acid,[35] the corresponding ketal **30** is obtained. Oxidation of the latter substance affords monoketal **31**, which is re-



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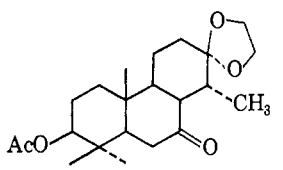
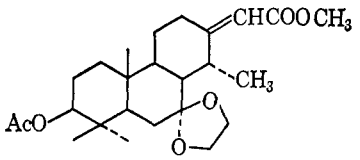


31

converted to **30**, and thence to **29a**, by sodium borohydride reduction and ketal exchange with acetone.

A second monoketal is obtained by ozonolysis of the cassaic acid derivative **32** and is assigned structure **33**. The two remaining monoketals were obtained as fol-



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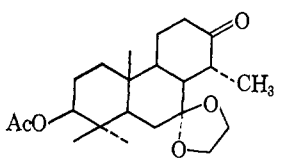
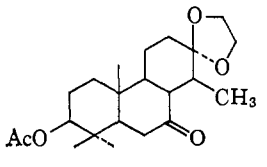


33

lows. Partial dioxolanation[35] of the stable acetoxy diketone **27a** involving attack on the less hindered carbonyl group (C-7) affords monoketal **34**, which is further converted into a bisketal for which structure **35** is suggested. Under mild conditions of exchange with acetone **35** furnishes the final member of the series **36**. It is of interest to note that sodium borohydride reduction of ketoketal **34** yields a substance (**37**) which is



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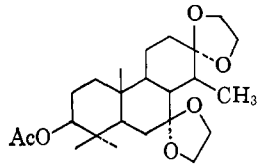

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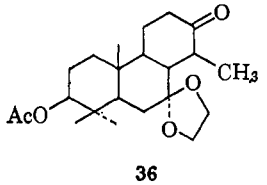

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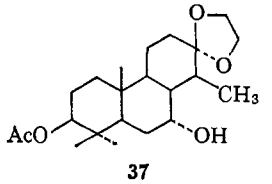

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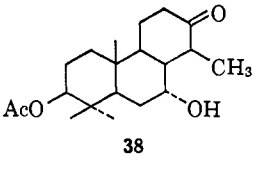

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cleaved to a configurationally stable hydroxy ketone differing from product **29a**. Although this material was available in an amount insufficient for hydrolysis and oxidation to the corresponding triketone (*cf.* **27c**), it seems reasonable to suppose that the substance possesses structure **38**.

A correlation between monoketals **31** and **34** has been established by prolonged treatment of each substance with *p*-toluenesulfonic acid in benzene. In both cases an equilibrium mixture consisting of approximately equal quantities of the two compounds **31** and **34** is produced. We assume that equilibrium is established by acid-catalyzed opening of the ketal ring and formation of a common enol–ether intermediate.[36] From these results it follows that the methyl configuration which is strongly favored in acetoxy diketone **27a** is to some extent destabilized in the corresponding monoketal **34**. In terms of classical steric effects this should be true if the configurational assignment in **34** is correct, since the equatorial methyl group, but not the axial one, is expected to encounter hindrance from the adjacent ethylene ketal ring.

Additional support for the stereochemical assignments presented in this paper is obtained from optical rotatory dispersion measurements. It should first be noted that both the dispersion curve for the α,β-unsaturated ketone **19**, which exhibits a negative Cotton effect,[37] and the molecular rotation differences listed in Table I provide evidence for the absolute configurations

Table I. Molecular Rotation Differences

Hydroxy compound	ΔMD acetate, deg	ΔMD ketone, deg
4,4-Dimethylcholestan-3β-ol-7-one	+45	−35
Lanostan-3β-ol-7-one	+46	−101
Cassaic acid (**23**)	...	−135
Dihydrocassaic acid	...	−130
Cassaic acid methyl ester	+77	...
Dihydrocassaic acid methyl ester	+26	...
Hydroxydiketone **26b**	+52	−105
Hydroxydiketone **27b**	+71	−19

that we employ. The optical rotatory dispersion curves[38] of acetoxy diketones **26a** and **27a** show, respectively, strong negative and strong positive Cotton effects. Since the octant rule[39] predicts negative Cotton effects for both keto groups in **26a** and positive Cotton effects for both of these functions in **27a**, it would appear that the configurations are correctly assigned. Finally the results of a detailed nuclear magnetic resonance study of cassaic acid methyl ester recently published by Hauth, Stauffacher, Niklaus, and Melera[40] confirm the conclusions set forth in structure **23** and further lead to assignment of stereochemistry at the double bond, for which no evidence is available from our work.

(35) H. J. Dauben, B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(36) *Cf.* M. E. Wall and H. A. Walens, *ibid.*, 77, 5661 (1955). Transketalization, either inter- or intramolecular, is regarded as an unlikely alternative.

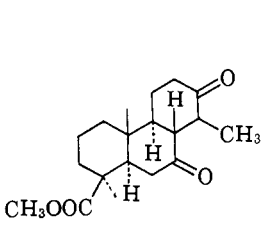
(37) *Cf.* C. Djerassi, R. Riniker, and B. Riniker, *ibid.*, **78**, 6362 (1956). We are indebted to Professor Djerassi for this result.

(38) Obtained through the courtesy of Mr. Max Marsh, Eli Lilly Co., Indianapolis, Ind.

(39) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(40) H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

In dealing with the structure and stereochemistry of cassamic acid, a substance closely related to cassaic acid, Chapman, *et al.*,[41] have tentatively arrived at a β arrangement for the C-8 methyl group in the parent acid and in the derived diketone **39**. Compound **39** is unstable with respect to its C-8 epimer and it is stated that the methyl group in **39** which is presumed to be equatorial and β, "is subject to considerable interaction with both (ketonic) oxygen atoms in consequence." Our own examination of the situation indi-



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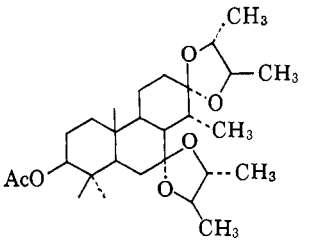


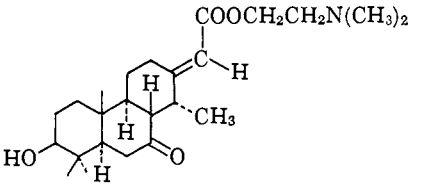
40

cates that an 8β-methyl group lies very nearly in the nodal plane of the C-7 carbonyl group,[42] and that the dispositions of the C-9 keto function with respect to either an 8α- or 8β-methyl group are essentially equivalent. Extrapolation of the suggestion of the British investigators to ketones **26** and **27** would imply that they are incorrectly formulated. Since epimerization in certain key steps of the British sequence[43] is not excluded by the experimental evidence, the point awaits future clarification. Regardless of the precise stereochemistry involved, it is clear that the conversions **27a** → **34** ⇄ **31** → **30** → **29a** → **26a** enumerated above constitute a method of passing from the thermodynamically stable acetoxy diketone **27a** to the thermodynamically unstable acetoxy diketone **26a** having the natural configuration at C-8. In particular it will be noted that the availability of hydroxy ketone **29a** by this route provides an intermediate in which the stereochemistry at C-8 required in cassaic acid is enforced.

We return now to the matter of synthesis. The preparation of racemic acetoxy diketone (*d,l*-**26a**) suggested the use of its optically active counterpart as a relay compound, which, however, imposed the formal requirement of resolution. The latter objective proved exceptionally difficult of attainment, but was finally accomplished by preparation of the bisketal **40** with levorotatory 2,3-butanediol.[44] The product obtained in this way proved identical in all respects with material prepared from a sample of naturally derived, optically active **26a** and differed from the corresponding bisketal of optically active **27a** which was also prepared for comparison purposes. In no case was there any evidence for C-8 epimerization, although the conditions required for obtaining complete conversion to the butanediol ketals were somewhat more vigorous (see the Experimental Section) than those required for the preparation of **35**. The presence of the extra methyl groups contributed by butanediol may impede the epimerization reaction.

Cleavage of **40** with acetone and *p*-toluenesulfonic acid furnished a mixture of monoketals and diketone **26a** identical with the product from natural sources, and convertible into the acetoxy hydroxy ketone **29a** by procedures that have already been discussed.

Reaction of **29a** with methyl bromoacetate according to the Reformatsky procedure, followed by oxidation of the crude material with chromium trioxide and dehydration with thionyl chloride, gave, after chromatography, a sample of cassaic acid acetate methyl ester identical with an authentic specimen. Hydrolysis of the acetate methyl ester gave material identical with cassaic acid. In view of the known conversions of cassaic acid into cassaine (**41**),[5] and of cassaine into cassaidine (**42**),[45] the present synthesis constitutes, also, a total synthesis of these two alkaloids.



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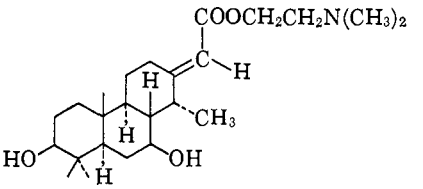

42

Experimental Section

Cassaine. Samples of dry, powdered bark from *Erythrophleum guineense* G. Don were thoroughly extracted with ethanol and with chloroform. The residue from concentration of the extracts was taken up in chloroform, and the total bases were isolated by washing with six portions of 0.5 *N* sulfuric acid. The aqueous washings were made basic (pH 8) with dilute ammonium hydroxide, and the alkaloidal material that separated was taken up in chloroform, treated with anhydrous sodium sulfate, and evaporated to dryness.[46] **Cassaine bisulfate,** mp 290–293° dec, was obtained from the amorphous residue by the fractionation procedure of Dalma.[4] The **free base** melted at 143–145° (lit[47] mp 142.5°).

Cassaic Acid and Its Derivatives. Cassaic acid, mp 217–219° (evacuated capillary) (lit[47] mp 223–224°), was obtained by acid-catalyzed hydrolysis of cassaine bisulfate. The **methyl ester,** mp 189–190° (lit[4] mp 189–190°), and **acetate methyl ester,** mp 149–151° (lit[47] mp 149–151°), were prepared by routine procedures.

Catalytic hydrogenation of cassaic acid over palladized charcoal furnished approximately 40% of **dihydrocassaic acid** which melted at 253–254° (lit[6] mp 253–255°) in an evacuated capillary. The **dihydro methyl ester** melted at 121–122° (lit[7] mp 121°) and gave **dihydro acetate methyl ester** melting at 188–189° (lit[7] mp 189°).

Preparation of Unsaturated Ketone 4. A mixture of 104 mg of dihydrocassaic acid acetate methyl ester and 47 mg of N-bromosuccinimide in 5 ml of carbon tetrachloride was heated to reflux

(41) G. T. Chapman, B. Jaques, D. W. Mathieson, and V. P. Arya, *J. Chem. Soc.*, 4010 (1963).

(42) This would appear to be the favored arrangement, since the methyl group in the stable form of 1-methyl-*trans*-2-decalone has been rigorously established to be *cis* to the adjacent ring junction hydrogen, *i.e.*, equatorial: R. B. Turner and J. Lin, unpublished results; see also N. L. Allinger and H. M. Blater, *J. Am. Chem. Soc.*, **83**, 994 (1961), and S. S. Butcher and E. B. Wilson, *J. Chem. Phys.*, 40, 1671 (1964). There is no reason at the present time to suppose that a "boat" ring is involved in this or in the other cases.

(43) Transformations (I, X = O) → (I, X = H_2) → (IV, X = H_2) of ref 41 are critical.

(44) *Cf.* J. Casanova and E. J. Corey, *Chem. Ind.* (London), 1664 (1961). We are indebted to Dr. D. R. Whitaker, National Research Council, Ottawa, Canada, for supplying us with a sample of (−)-butanediol.

(45) B. G. Engel, *Helv. Chim. Acta*, **42**, 1127 (1959).

(46) We are indebted to Dr. Norbert Neuss, Eli Lilly Co., for arranging for large-scale processing.

(47) L. Ruzicka, G. Dalma, and W. E. Scott, *Helv. Chim. Acta*, **24**, 63 (1941).

temperature with a 60-w light bulb for 20 min. Filtration and evaporation of the solvent afforded a residue that was dissolved in 4 ml of collidine and heated to boiling under nitrogen for 30 min. The mixture was then cooled, diluted with water, and extracted with ether. The organic layer was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed by evaporation, and the residue was crystallized from ether–petroleum ether (bp 30–60°) to yield 91 mg of **4**, mp 141–142°. Several recrystallizations gave the analytical sample: mp 145–146.5°, λ_{max}^{EtOH} 247.5 mμ (ε 8700), $\lambda_{max}^{CS_2}$ 5.78 and 6.02 μ, $[\alpha]D$ −39° (*c* 0.86, ethanol).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.97; H, 8.85.

Preparation of the Enol Acetate 5. A solution of 49 mg of the above ketone **4** in 3 ml of acetic anhydride and 1 ml of acetyl chloride was heated under reflux in a slow stream of nitrogen for 4 hr. The reaction mixture was then diluted with ether, and the solution was washed with dilute sodium hydroxide, water, and saturated sodium chloride, and was finally dried over anhydrous sodium sulfate. Removal of the solvent and crystallization from ether–petroleum ether gave 38 mg of enol acetate **5**, mp 160.5–163°. The analytical sample melted at 165–166°, λ_{max}^{EtOH} 242 mμ (ε 17,500), $\lambda_{max}^{CS_2}$ 5.75 μ, $[\alpha]D$ −155° (*c* 0.68, ethanol).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.41; H, 8.22.

Preparation of 2β-Acetoxy-8-methylpodocarp-8(14)-ene-7,9-dione (6). Acetoxy diketone **27a** (72 mg) was dissolved in 2 ml of acetic acid and was treated by dropwise addition with 4.5 ml of 0.05 *M* bromine in acetic acid. After standing at room temperature for 15 min, the reaction mixture was diluted with ether and was washed with water, dilute sodium hydroxide, water, dilute hydrochloric acid, and saturated sodium chloride solution. Drying over anhydrous sodium sulfate and evaporation of the solvent afforded 84 mg of crystalline bromide, which, without further purification, was heated under reflux for 30 min with 3 ml of collidine (nitrogen atmosphere). Crystallization of the product from ether–petroleum ether gave 20 mg of enedione **6** melting at 183–185°. An additional 8 mg of slightly less pure material, mp 177–180°, was obtained from the mother liquor. The analytical sample melted at 186.5–187.5°, λ_{max}^{EtOH} 266.5 mμ (ε 10,800), $\lambda_{max}^{CHCl_3}$ 5.82 and 4.96 μ, $[\alpha]D$ −7° (*c* 0.82, ethanol).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.54.

Preparation of 8 from Hagemann's Ester 7. 1-Chloropentanone-3[48] (90 g) was added over a period of 4 hr to a refluxing solution of 68 g of Hagemann's ester **7**[15] in 150 ml of triethylamine. After refluxing for an additional 16 hr, the reaction mixture was concentrated under reduced pressure, and water and ether were added. Dilute sulfuric acid was added until the aqueous layer was acidic to congo red. The organic phase was then washed with water and saturated sodium chloride and was dried over anhydrous sodium sulfate. Distillation afforded 72 g of **8**: bp 143–145° (0.03 mm), $n^{25}D$ 1.4927, d^{25} 1.081, λ_{max}^{EtOH} 241 mμ (ε 10,700), $\lambda_{max}^{CS_2}$ 5.83 and 6.02 μ.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.31; H, 8.23.

The **bissemicarbazone** prepared as a derivative melted at 207–208.5° dec.

Anal. Calcd for $C_{17}H_{28}O_4N_6$: C, 53.67; H, 7.42; N, 22.09. Found: C, 53.23; H, 7.80; N, 22.04.

Preparation of the Bicyclic Keto Ester 9. Compound **8** was treated with sodium hydride in benzene solution, and the reaction mixture was stirred at room temperature until the evolution of hydrogen ceased. The excess sodium hydride was destroyed by addition of methanol, and the benzene solution was washed with water, dried, and distilled. The product **9** boiled at 131–132° (0.03 mm), $n^{25}D$ 1.5483, λ_{max}^{EtOH} 295 mμ (ε 19,000), $\lambda_{max}^{CS_2}$ 5.82 and 6.05 μ.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.26; H, 8.21.

The **semicarbazone** was prepared as a derivative, mp 184°.

Anal. Calcd for $C_{16}H_{23}O_3N_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.95; H, 7.74; N, 13.88.

Preparation of 6-Methoxy-1-methyl-2-tetralone (11). 2,6-Dihydroxynaphthalene[49] was converted into the corresponding dimethyl ether, which was reduced by the literature procedure to 2,6-dimethoxy-1,4-dihydronaphthalene.[16] The latter compound (50 g) was hydrolyzed to 6-methoxy-2-tetralone,[16] and the ketone was dissolved directly without purification in 500 ml of benzene to which 100 ml of pyrrolidine was added. The reaction mixture was refluxed under a water separator in a nitrogen atmosphere for 1.5 hr during which time 5 ml of water was collected. The solution was then cooled and was concentrated under reduced pressure at room temperature.

The residue was dissolved immediately in 500 ml of methanol, 25 ml of methyl iodide was added, and the resulting solution was refluxed under nitrogen for 30 min. At the end of this time an additional 50 ml of methyl iodide was added, and refluxing was continued for 1 more hr. The excess methyl iodide was removed by distillation. Acetic acid (50 ml) and sodium acetate (50 g) in 100 ml of water were added, and the mixture was heated under reflux for 45 min. The solution was finally concentrated *in vacuo* and then diluted with ether and washed successively with dilute sodium hydroxide, dilute hydrochloric acid, water, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate the ether was removed by evaporation, and the residue was distilled under reduced pressure yielding 30 g of 6-methoxy-1-methyl-2-tetralone (**11**), bp 110–112° (0.05 mm). The semicarbazone melted at 202–204° dec and proved to be identical with a sample prepared by the method of Howell and Taylor.[18]

Preparation of 2,3,4,9,10,12-Hexahydro-7-methoxy-12-methyl-2-oxophenanthrene (12). 6-Methoxy-1-methyl-2-tetralone (**11**) was condensed with dimethylaminobutanone methiodide according to the procedure of Howell and Taylor.[18] Crystallization of the product from ether–petroleum ether gave 50% of tricyclic ketone **12**: mp 105–107.5°, λ_{max}^{EtOH} 231 mμ (ε 25,000).

Catalytic Hydrogenation of 12. The tricyclic ketone obtained in the preceding experiment (243 mg) was hydrogenated over 600 mg of 10% palladized charcoal in 10 ml of acetic acid. After the uptake of hydrogen ceased, the catalyst was removed by filtration, the filtrate was diluted with water, and the product was isolated by ether extraction. Crystallization from ether–petroleum ether afforded 164 mg of ***cis*-1,2,3,4,9,10,11,12-octahydro-7-methoxy-12-methyl-2-oxophenanthrene**, mp 62–64°. The analytical sample melted at 68–69°, $\lambda_{max}^{CS_2}$ 5.82 μ.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.51; H, 8.13.

Conversion of 12 to 1,2,3,4,9,10-Hexahydro-1,1,12-trimethyl-2-oxophenanthrene (13). A solution of 4.60 g of tricyclic ketone **12** in 100 ml of dry *t*-butyl alcohol was purged with nitrogen and treated with potassium *t*-butoxide prepared by addition of 2.0 g of potassium to 50 ml of dry *t*-butyl alcohol. Methyl iodide (6.5 ml) in 10 ml of *t*-butyl alcohol was then added, and the mixture was stirred for 1.5 hr at 30° and then for 10 min at reflux temperature. Dilute hydrochloric acid was added to the cooled suspension, and the product was taken up in ether. After washing and drying, the solvent was removed under reduced pressure, and the residual oil was dissolved in petroleum ether–benzene (4:1) and filtered through a short column of neutral alumina (Woelm, activity II–III). The material from the petroleum ether–benzene washings was crystallized from dilute methanol and furnished 1.70 g of **1,2,3,4,9,12-hexahydro-7-methoxy-1,1,12-trimethyl-2-oxophenanthrene (13)** as colorless prisms, mp 78–80°. A second crop, 400 mg, mp 75–77°, was obtained from the mother liquors.

Four recrystallizations from ether–petroleum ether gave the analytical sample: mp 80–81°, λ_{max}^{EtOH} 277 mμ (ε 1800), 284 mμ (ε 1700), $\lambda_{max}^{CS_2}$ 5.83 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.92; H, 8.20.

Careful chromatography of crude material gave besides compound **13** small amounts of impure starting material **12** and a substance which crystallized from ether in colorless plates: mp 175.5–176°, λ_{max}^{EtOH} 224 mμ (ε 22,000), 262 (12,000), 325 (3000); $\lambda_{max}^{CS_2}$ 5.88 and 6.05 μ. The latter product was not further investigated.

Lithium Aluminum Hydride Reduction of 13 to 14. A solution of 1.70 g of dimethylated ketone **13** in 50 ml of anhydrous ether was added dropwise over 1 hr to 700 mg of lithium aluminum hydride in 100 ml of dry ether at reflux temperature. After further refluxing for 1 hr, the excess reagent was destroyed with methanol, and dilute hydrochloric acid was then added. The ether layer was washed with dilute sodium hydroxide, water, and saturated sodium chloride, and was dried over anhydrous sodium sulfate. Evaporation of the solvent and crystallization of the residue from ether–petroleum ether furnished 1.31 g of **1,2,3,4,9,12-hexahydro-7-methoxy-1,1,12-trimethyl-2β-hydroxyphenanthrene (14)**, mp 126–127°. The mother liquor gave a second crop, 255 mg, mp

(48) E. M. McMahon, J. N. Roper, W. P. Untermohlen, R. C. Harris, and J. H. Brandt, *J. Am. Chem. Soc.*, 70, 2971 (1948); G. Baddeley, H. T. Taylor, and W. Pickles, *J. Chem. Soc.*, 124 (1953).

(49) L. F. Fieser, *J. Am. Chem. Soc.*, 50, 461 (1928).

121–123°. The sample for analysis was obtained by recrystallization from ether–petroleum ether: mp 127–128°, $\lambda_{max}^{CH_2Cl_2}$ 2.82 μ.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.35; H, 8.64.

Preparation of *trans*-1,2,3,4,9,10,11,12-Octahydro-7-methoxy-1,1,12-trimethyl-2β-hydroxyphenanthrene (15a). A solution of 277 mg of the lithium aluminum hydride reduction product **14**, obtained in the preceding experiment, in 5 ml of acetic acid was stirred with 190 mg of palladium–charcoal in a hydrogen atmosphere. When the absorption of hydrogen ceased, the mixture was filtered through Celite, diluted with ether, and washed successively with water, dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate the solvent was removed by evaporation, and the residue was crystallized from ether–petroleum ether, yield 210 mg of **15a**, mp 139–140°. A second crop consisting of 26 mg, mp 138–139°, was obtained from the mother liquor. The analytical sample was prepared by three recrystallizations from ether–petroleum ether, mp 140–141°, $\lambda_{max}^{CS_2}$ 2.78 μ.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.84; H, 9.60.

The **acetyl derivative 15b** melted at 103–103.5°, $\lambda_{max}^{CS_2}$ 5.78 and 8.08 μ.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.74; H, 9.10.

Oxidation of 67 mg of the hydroxy derivative **15a** with 66 mg of chromium trioxide in 2.5 ml of pyridine gave 46 mg of ***trans*-1,2,3,4,9,10,11,12-octahydro-7-methoxy-1,1,12-trimethyl-2-oxophenanthrene (15c)** melting at 70–71°. Recrystallization from ether–petroleum ether afforded the analytical sample, mp 73–73.5°, $\lambda_{max}^{CS_2}$ 5.85 μ.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.52; H, 8.86.

Preparation of 16a by Birch Reduction of 15a. Lithium wire (390 mg) was added in small pieces to a solution of 100 mg of **15a** in 50 ml of liquid ammonia, 20 ml of ether, and 2 ml of ethanol over a period of 45 min with mechanical stirring. Thirty minutes after addition of the lithium was complete the blue color disappeared, and water and ether were added. The organic layer was washed and dried, and the solvent was removed by evaporation. Crystallization of the residue from ether–petroleum ether gave 81 mg of ***trans*-1,2,3,4,5,8,9,10,11,12-decahydro-7-methoxy-1,1,12-trimethyl-2β-hydroxyphenanthrene (16a)**; mp 129–131°. The analytical sample melted at 139–139.5°, $\lambda_{max}^{CS_2}$ 2.78, 5.90, and 6.00 μ.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.21.

Treatment of this product with acetic anhydride and pyridine gave the corresponding acetate **16b**; mp 107.5–108.5°, $\lambda_{max}^{CS_2}$ 5.79, 5.90, 6.00, and 8.04 μ.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.08; H, 9.38.

Preparation of 2β-Hydroxypodocarp-13-en-7-one (17a). The dihydro anisole derivative **16a** (25 mg) and 67 mg of oxalic acid were dissolved in 2 ml of ethanol containing 0.1 ml of water. After 1.5 hr at room temperature the solution was diluted with water and extracted with ether. The ethereal extract was washed with dilute sodium hydroxide and water and was finally dried over anhydrous sodium sulfate. Removal of the solvent and crystallization of the product from ether–petroleum ether gave 17 mg of β,γ-unsaturated ketone **17a**; mp 150–152°, $\lambda_{max}^{CH_2Cl_2}$ 2.79 and 5.88 μ.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.70; H, 10.09.

Preparation of 2β-Acetoxypodocarp-13-en-7-one (17b). A solution of 197 mg of enol-ether acetate **16b** was cleaved with oxalic acid as described for the corresponding hydroxy derivative. Crystallization of the crude product furnished 160 mg of β,γ-unsaturated ketone **17b**, mp 101–102.5°. The sample for analysis melted at 103.5–104.5°, $\lambda_{max}^{CS_2}$ 5.82 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.06; H, 9.01.

Treatment of **17a** with acetic anhydride and pyridine yielded an oil which failed to crystallize.

Preparation of 2β-Hydroxypodocarp-8(14)-en-7-one (18a). Enol-ether **16a** (168 mg) in 5 ml of methanol was treated with 2 ml of water and 2 ml of concentrated hydrochloric acid. After a reflux period of 30 min, the bulk of the methanol was removed on a nitrogen stream, and the product was isolated by ether extraction. Crystallization from ether–petroleum ether yielded 123 mg of **18a**, mp 148.5–149.5°. The analytical sample melted at 151–152°, λ_{max}^{EtOH} 241 mμ (ε 15,500), $\lambda_{max}^{CH_2Cl_2}$ 2.79 and 6.03 μ.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.43; H, 9.85.

The acetate **18b**, mp 115–115.5°, λ_{max}^{EtOH} 240 mμ (ε 16,000), $\lambda_{max}^{CS_2}$ 5.78, 6.00, and 8.10 μ, was obtained by acetylation of **18a** with acetic anhydride and pyridine.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.74; H, 9.13.

Preparation of *d,l*-2β-Acetoxy-8-methylpodocarp-8(14)-en-7-one (19). The β,γ-unsaturated ketone **17b** (677 mg) was dissolved in 25 ml of dry *t*-butyl alcohol, and 7.3 ml of a solution of potassium *t*-butoxide prepared from 178 mg of potassium and 10.0 ml of dry *t*-butyl alcohol was added after the system had been purged with nitrogen. The mixture was then heated to reflux temperature, and 0.14 ml of methyl iodide in 60 ml of dry *t*-butyl alcohol was dropped in (nitrogen atmosphere) over a period of 2 hr. After refluxing for an additional 30 min, the reaction mixture was diluted with ether and acidified with dilute hydrochloric acid. The organic layer was washed with water and dilute sodium hydroxide, and was dried over anhydrous sodium sulfate. The solvent was then removed, and the residue was reacetylated with acetic anhydride and pyridine. The product (618 mg) was chromatographed over neutral alumina (Woelm, activity II–III). The fraction (315 mg) eluted with petroleum ether–benzene (9:1) was crystallized from ether–petroleum ether and afforded 208 mg of **19**, mp 126–128°. Further recrystallization from the same solvent pair gave the analytical sample: mp 136–137°, λ_{max}^{EtOH} 249 mμ (ε 17,500), $\lambda_{max}^{CS_2}$ 5.78 and 6.02 μ.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.25; H, 9.46.

Preparation of *d*-2β-Acetoxy-8-methylpodocarp-8(14)-en-7-one (*d*-19). A 352 mg-sample of acetoxy hydroxy ketone **29a** (see below) was dissolved in 20 ml of toluene containing 211 mg of dry *p*-toluenesulfonic acid. The mixture was heated under reflux for 6 hr (nitrogen atmosphere) and was then cooled, diluted with ether, and washed successively with water, dilute sodium hydroxide, and again with water. The total crude product after chromatography on alumina furnished 152 mg of *d*-**19**, mp 150–152°. Two recrystallizations from ether–petroleum ether gave a sample melting at 152.5–153.5°, $[\alpha]_D$ +64.3° (*c* 1.126, ethanol). The infrared spectrum (CS_2) was identical with that obtained for the racemic modification **19**.

Birch Reduction of 14 to 21. Four-hundred milligrams of **14** in 80 ml of ether, 300 ml of liquid ammonia, and 20 ml of absolute ethanol was treated with 1.2 g of lithium according to the procedure employed for reduction of **15a**. The product was isolated in the usual way, and after crystallization from ether–petroleum ether furnished 320 mg of **21**, mp 131–132°. An additional 36 mg, mp 124–126°, was obtained from the mother liquors. Recrystallization from ether–petroleum ether yielded the analytical sample: mp 134–136°, $\lambda_{max}^{CS_2}$ 2.79, 5.90, and 6.00 μ.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.77; H, 9.34.

Preparation of 2β-Hydroxypodocarpa-10,13-dien-7-one (22). The enol–ether **21** (168 mg) was cleaved with 480 mg of oxalic acid in 10 ml of ethanol and 3 ml of water by the previously described procedure. Crystallization of the product from ether–petroleum ether gave 106 mg of **22**, mp 121–123°. The analytical sample melted at 120–121°, $\lambda_{max}^{CS_2}$ 2.70 and 5.83 μ.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.17; H, 9.30.

Preparation of *d,l*-2β-Acetoxy-8-methylpodocarp-8(14)-ene-7,9-dione (*d,l*-6). To a solution of 155 mg of **19** in 8 ml of acetic acid there was added 150 mg of chromium trioxide in 6 ml of 90% acetic acid. The reaction mixture was heated to 60° for 2 hr, at the end of which time ice was added, and the product was extracted with ether. After washing and drying, the solvent was removed, and the residue was recrystallized three times from ether–petroleum ether yielding 17 mg of *d,l*-**6**, mp 158–161°. The analytical sample melted at 165–165.5°, λ_{max}^{EtOH} 266 mμ (ε 11,000), $\lambda_{max}^{CHCl_3}$ 5.82 and 5.96 μ. The infrared spectrum in chloroform solution was completely identical with that of the optically active derivative **6**.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.38.

Preparation of *d,l*-2β-Acetoxy-8α-methylpodocarpane-7,9-dione (*d,l*-26a). A mixture of 335 mg of zinc dust and 45 mg of enedione *d,l*-**6** in 6 ml of acetic acid was heated to reflux temperature for 2 hr. The mixture was then diluted with ether and filtered, and the filtrate was washed with dilute sodium hydroxide, water, and a saturated solution of sodium chloride. Removal of the solvent and chromatography of the residue gave 16 mg of crude *d,l*-**26a**, $\lambda_{max}^{CHCl_3}$ 5.80, 5.85, and 8.00 μ. The infrared spectrum of this product and that of the optically active acetoxy diketone **26a**, when meas-

ured in chloroform solution, were identical. The analytical sample, obtained in a second experiment, melted at 163–164.5°.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.60; H, 8.73.

Preparation of *l*-2β-Acetoxy-8α-methylpodocarpane-7,9-dione (26a). A solution of 134 mg of cassaic acid acetate methyl ester in a mixture of 5 ml of ethyl acetate and 5 ml of glacial acetic acid was cooled to −10° in a salt-ice bath. Four molar equivalents of ozone was passed into the solution, which was then allowed to stand in the cooling bath for 1 hr. Zinc dust (300 mg) and water (0.2 ml) were added, and the resulting mixture was stirred for 30 min. The product was isolated by ether extraction and after two recrystallizations from ether–petroleum ether gave 65 mg of diketone **26a**, mp 163–168°. The analytical sample melted at 169–170°, $\lambda_{max}^{CS_2}$ 5.78, 5.88, and 8.10 μ, $[\alpha]D$ −16° (*c* 0.95, ethanol).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.03; H, 8.74.

Preparation of *l*-2β-Hydroxy-8α-methylpodocarpane-7,9-dione (26b). Cassaic acid (44 mg) in 5 ml of ethyl acetate and 5 ml of methanol was ozonized by the procedure of the previous experiment. The crude product (33 mg) was crystallized from methylene chloride–petroleum ether and gave a sample of **26b**: mp 176–180°, $\lambda_{max}^{CH_2Cl_2}$ 3.00 and 5.86 μ, $[\alpha]D$ −36° (*c* 1.02, ethanol). The melting point was not sharp and was variable, possibly owing to thermal isomerization to the 8β epimer.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.25; H, 9.49.

Preparation of *l*-8α-Methylpodocarpane-2,7,9-trione (26c) from 26b. A solution of 14 mg of chromium trioxide in 1 ml of 90% acetic acid was added to 50 mg of **26b** in 0.5 ml of acetic acid. The mixture was allowed to stand at room temperature for 2.5 hr, and the product was isolated by the usual procedure. As in the case of **26b** the melting point was variable, the highest value being 185–187°, with sintering at 180°, $\lambda_{max}^{CH_2Cl_2}$ 5.86 μ, $[\alpha]D$ −73° (*c* 0.93, ethanol).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.40; H, 9.04.

From 29c. Oxidation of 33 mg of **29c** with 20 mg of chromium trioxide as described above gave 15 mg of **26c**, mp 181–185°. The material showed infrared absorption characteristics identical with the sample of the preceding experiment and a mixture melting point with **27c** was depressed to 157–165°.

Preparation of *l*-2β-Acetoxy-8β-methylpodocarpane-7,9-dione (27a). A solution of 20 mg of **26a** in 2 ml of methanol containing 0.2 mmole of sodium methoxide was heated under reflux for 2 hr. The reaction mixture was diluted with water, and the product was taken into ether. Removal of the solvent followed by reacetylation with acetic anhydride and pyridine gave 13 mg of **27a**, mp 144–146° (from ether–petroleum ether). The melting point of the substance was depressed to 135° on admixture with a sample of **26a**, and the infrared spectra of the two products were distinctly different in the fingerprint region. Epimerization also occurred when **26a** was chromatographed on alumina which had been "neutralized" by treatment with ethyl acetate.

The sample for analysis melted at 150.5–151.5°, $\lambda_{max}^{CS_2}$ 5.76, 5.83, and 8.06 μ, $[\alpha]D$ −26° (*c* 0.93, ethanol).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.86; H, 9.23.

Saponification of **27a** (methanolic sodium hydroxide) afforded ***l*-2β-hydroxy-8β-methylpodocarpane-7,9-dione (27b)**: mp 173–174° (marked depression with the corresponding 8α epimer), $\lambda_{max}^{CH_2Cl_2}$ 3.00 and 5.86 μ, $[\alpha]D$ −54° (*c* 0.75, ethanol). This product was also obtained by treatment of **26b** with base.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.83; H, 9.71.

Preparation of *l*-8β-Methylpodocarpane-2,7,9-trione (27c). Oxidation of 50 mg of ***l*-2β-hydroxy-8β-methylpodocarpane-7,9-dione (27b)** under conditions described for **26b** afforded 27 mg of **27c**, mp 198–200.5°, after crystallization from methylene chloride–petroleum ether. The analytical sample melted at 200–201.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.86 μ, $[\alpha]D$ −61° (*c* 0.77, ethanol). This product was also obtained by base-catalyzed epimerization (sodium methoxide at room temperature) of **26c**.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.52; H, 8.96.

Sodium Borohydride Reduction of Cassaic Acid Acetate Methyl Ester to 28. A solution of 820 mg of cassaic acid acetate methyl ester and 310 mg of sodium borohydride in 25 ml of methanol was allowed to stand at room temperature for 6 hr. After neutralization with acetic acid, the mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The combined organic extracts were washed, dried, and evaporated. Crystallization of the residue from ether–petroleum ether gave 625 mg of **28**, mp 140–142°. The analytical sample melted at 145.5–146°, λ_{max}^{EtOH} 222.5 mμ (ε 18,000); $\lambda_{max}^{CS_2}$ 2.80, 5.80, 5.88, 6.01, and 8.08 μ; $[\alpha]D$ −90° (*c* 0.92, ethanol).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.20; H, 9.02.

Preparation of 2β-Acetoxy-9β-hydroxy-8α-methylpodocarpan-7-one (29a) from 28. The sodium borohydride reduction product **28** of the preceding experiment (603 mg) in 10 ml of ethyl acetate and 10 ml of methanol was ozonized by the procedure described above for the preparation of **26a**. The crude product was crystallized from ether–petroleum ether and yielded 323 mg of **29a** melting at 132–133°. A second crop (55 mg), mp 130–131°, was isolated from the mother liquor. The analytical sample melted at 135–136°, $\lambda_{max}^{CS_2}$ 2.76, 5.76, 5.84, and 8.10 μ, $[\alpha]D$ −5° (*c* 0.70, ethanol).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.57; H, 9.56.

From 31. Treatment of 33 mg of ketal **31** (see below) with 14 mg of sodium borohydride in 1.5 ml of methanol for 30 min afforded 30 mg of amorphous material, the infrared absorption characteristics of which were identical with those of compound **30**. Cleavage of this material with 2.4 mg of *p*-toluenesulfonic acid in 3 ml of acetone (1 hr at reflux temperature) gave 26 mg of oil which was chromatographed on alumina. Two recrystallizations (ether–petroleum ether) of the chromatographed product afforded 6.3 mg of material, mp 135–135.5°, identical with compound **29a** (mixture melting point and infrared).

Standard acetylation of acetoxy hydroxy ketone **29a** furnished the corresponding diacetoxy ketone **29b**: mp 142–143°, $\lambda_{max}^{CS_2}$ 5.76, 5.82, and 8.07 μ, $[\alpha]D$ −8.9° (*c* 1.25, ethanol).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.01; H, 9.15.

Hydrolysis of **29a** with aqueous methanolic sodium hydroxide gave the dihydroxy ketone **29c**, mp 186–186.5°, $\lambda_{max}^{CH_2Cl_2}$ 2.79 and 5.86 μ, $[\alpha]D$ −10° (*c* 0.91, ethanol).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.19; H, 10.04.

Preparation of Ketal 30. The acetoxy hydroxy ketone **29a** (150 mg) was dissolved in 6 ml of 2-ethyl-2-methyl-1,3-dioxolane[35] containing 12 mg of *p*-toluenesulfonic acid. The solvent was then slowly distilled, the volume of the solution being reduced by approximately one-half over a period of 10 hr. The reaction mixture was diluted with ether and washed with dilute sodium hydroxide, water, and saturated sodium chloride. After drying, the solvent was evaporated, and the resulting oily residue was chromatographed on alumina. An initial amorphous fraction (30 mg), which showed no hydroxyl absorption in the infrared, was discarded. Further elution gave 150 mg of **30** as a colorless oil, $\lambda_{max}^{CS_2}$ 2.78, 5.76, and 8.05 μ.

Preparation of Monoketal 31 from 30. A solution of 150 mg of **30** and 40 mg of chromium trioxide in 3.5 ml of acetic acid was allowed to stand at room temperature for 2.5 hr. The product was isolated in the usual way and furnished 73 mg of **31** melting at 169–171°. The analytical sample prepared by recrystallization from ether–petroleum ether melted at 172.5–173°, $\lambda_{max}^{CS_2}$ 5.75, 5.86, and 8.05 μ, $[\alpha]D$ +5° (*c* 1.20 ethanol).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.93; H, 9.05.

A solution of 19 mg of this substance in 4 ml of 0.1 *N* sodium methoxide in methanol was allowed to stand at room temperature for 20 hr. Acetylation of the product and recrystallization from ether–petroleum ether gave material, mp 173–174°, identical with the starting material, showing that epimerization at the B–C ring fusion had not occurred.

From 34. Fifty milligrams of monoketal **34** (see below) in 10 ml of dry benzene containing 5 mg of *p*-toluenesulfonic acid was heated under reflux (nitrogen atmosphere) for 22 hr. The reaction product was chromatographed on alumina and yielded 19 mg of monoketal **31**, 19 mg of starting material **34**, and a terminal fraction consisting of 13 mg of oil. Recrystallization from ether–petroleum ether afforded 13 mg of **31**, mp 170–171.5°, and 10 mg of **34**, mp 158–160°. The infrared spectra of these samples were identical, respectively, with those of authentic specimens. The same mixture was obtained when **31** was employed as starting material.

Conversion of Cassaic Acid Acetate Methyl Ester into Ketal 32. A solution of 281 mg of cassaic acid acetate methyl ester in 7 ml of 2-ethyl-2-methyl-1,3-dioxolane containing 60 mg of *p*-toluenesul-

fonic acid was heated under reflux with slow distillation of the solvent for a period of 17 hr. The crude product was chromatographed on alumina. Crystallization from methylene chloride–petroleum ether furnished 130 mg of ketal **32**, mp 201–203°. The analytical sample melted at 204–205°; $\lambda_{max}^{CS_2}$ 5.78, 5.81, 6.09, and 8.07 μ; $[\alpha]D$ −114° (*c* 1.24, chloroform).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.14; H, 8.79.

Preparation of Monoketal 33. A sample (101.8 mg) of ketal **32** obtained in the preceding experiment was dissolved in a mixture of 3 ml of methanol and 3 ml of ethyl acetate, and the solution was cooled to −10°. Ozone was passed in for 5 min, and the reaction mixture was allowed to stand in the cold for 30 min. At the end of this time 2 ml of acetic acid, 2 ml of water, and a small portion of zinc dust were added. After stirring for 10 min the zinc was removed by filtration, and the filtrate was diluted with water and extracted with ether. The ethereal layer was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was removed, and the product was crystallized from methylene chloride–petroleum ether to yield 68.3 mg, mp 183–186°. Several recrystallizations gave the analytical sample: mp 186–187°; $\lambda_{max}^{CS_2}$ 5.77, 5.82, and 8.07 μ; $[\alpha]D$ −5.6° (*c* 1.26, ethanol).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.09; H, 9.03.

Preparation of Monoketal 34. A mixture of 150 mg of 2β-acetoxy-8β-methylpodocarpane-7,9-dione (**27a**) and 22 mg of *p*-toluenesulfonic acid in 10 ml of 2-ethyl-2-methyl-1,3-dioxolane was heated under reflux for 1 hr. Ether was added, and, after washing with dilute sodium hydroxide and drying, the solvent was evaporated. Two recrystallizations from ether–petroleum ether gave 75 mg of compound **34**, mp 156–159°. The sample prepared for analysis melted at 163–164°; $\lambda_{max}^{CS_2}$ 5.76, 5.85, and 8.06 μ; $[\alpha]D$ −38° (*c* 1.09, ethanol). The infrared spectrum of this material differed markedly from that of monoketal **31** in the 8.5–11-μ region.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.80; H, 8.72.

Preparation of Bisketal 35 from 27a. A solution of 150 mg of acetoxy diketone **27a** and 42 mg of *p*-toluenesulfonic acid in 10 ml of 2-ethyl-2-methyl-1,3-dioxolane was heated under reflux for 5.5 hr. The solution was cooled, ether was added, and the mixture was washed thoroughly with water and was dried over anhydrous sodium sulfate. Evaporation of the solvent and crystallization of the residue from ether–petroleum ether afforded 150 mg of **35**, mp 198–200°. The analytical sample melted at 206.5–207.5°, $\lambda_{max}^{CS_2}$ 5.78 and 8.05 μ, $[\alpha]D$ −26° (*c* 0.98, ethanol).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.23; H, 9.06.

Preparation of Monoketal 36 from 35. A sample of bisketal **35** (42.5 mg) was dissolved in 3 ml of acetone, and 9 mg of *p*-toluenesulfonic acid was added. After standing at room temperature for 15 min the reaction mixture was diluted with ether and was washed with water, dilute sodium hydroxide, water, and saturated sodium chloride. Removal of the solvent gave 38.2 mg of crude material, which was chromatographed on alumina. In this way there was obtained 4 mg of starting material **35**, 4 mg of acetoxy diketone **27a**, and 12 mg of monoketal **36**, mp 153–155°. The sample for analysis melted at 153–154°; $\lambda_{max}^{CS_2}$ 5.78, 5.84, and 8.06 μ, $[\alpha]D$ −47.2°(*c* 0.57, ethanol).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.73; H, 9.20.

Sodium Borohydride Reduction of Monoketal 34. Monoketal **34**, 58 mg, in 2 ml of methanol was treated with 25 mg of sodium borohydride for 45 min at room temperature. The product was isolated in the usual way and gave, after crystallization from ether–petroleum ether, 40 mg of the acetoxy hydroxy ketal **37**, mp 193–195°. The analytical sample melted at 197–198°; $\lambda_{max}^{CS_2}$ 2.79, 2.85, 5.78, and 8.06 μ, $[\alpha]D$ −24° (*c* 1.44, ethanol).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.49; H, 9.54.

Preparation of the Acetoxy Hydroxy Ketone 38. A 17-mg sample of compound **37** was dissolved in 3 ml of acetone containing 1.4 mg of *p*-toluenesulfonic acid, and the mixture was heated under reflux for 10 hr. Dilution with water and extraction with ether gave crude product which was crystallized from ether–petroleum ether: 9.8 mg, mp 142–144°, $[\alpha]D$ −19.3° (*c* 0.66, ethanol). A mixture melting point with acetoxy hydroxy ketone **29a**, mp 135–136°, was depressed to 105–115°. Material for combustion analysis was, unfortunately, not available.

Resolution of *d,l*-26a. A solution of 15.8 mg of synthetic, racemic acetoxy diketone ***d,l*-26a**, 508 mg of D-(−)-2,3-butanediol, and 4 mg of *p*-toluenesulfonic acid in 5 ml of dry benzene was heated under reflux for a period of 10 hr and was then allowed to stand over night at room temperature. The product was isolated in the usual way and was chromatographed on alumina. There was obtained in this way 8.2 mg of material that showed no ketonic carbonyl absorption in the infrared. A considerable amount of monoketal (identified by infrared) was also obtained and could be recycled. Several recrystallizations from ether–petroleum ether afforded 3 mg of bisketal **40**, mp 173–175°. The infrared spectrum of this material was identical with that of an authentic sample of **40** (see below) and a mixture melting point with **40** was undepressed. A mixture melting point with the corresponding 8β-methyl bisketal was 143–154°, and the infrared comparison in this case revealed marked differences.

Cleavage of bisketal **40** (24.8 mg) was accomplished by treatment of the material with 2 mg of *p*-toluenesulfonic acid in 3 ml of acetone at reflux temperature for 27 hr. The product was taken into ether, washed, dried, and chromatographed on neutral alumina (prepared by acid wash). In addition to various monoketal fractions, there was obtained 6.2 mg of material which showed infrared absorption superimposable on that of **26a**. Recrystallization from ether–petroleum ether gave a sample, mp 168.5–170°, which was completely identical with an authentic specimen.

Preparation of Bisketal 40. A solution of 40 mg of optically active acetoxy diketone **26a**, 480 mg of D-(−)-2,3-butanediol, and 7.4 mg of *p*-toluenesulfonic acid in 7 ml of dry benzene was heated under reflux for 29 hr. Chromatography of the crude reaction product on alumina furnished 40.5 mg of crystalline material, which was recrystallized from ether–petroleum ether, mp 173.5–174°. Repeated recrystallization from the same solvent gave the analytical sample, mp 175.5–176.5°.

Anal. Calcd for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69. Found: C, 70.30; H, 9.58.

The same procedure as applied to optically active acetoxy diketone **27a** gave a bisketal, mp 196.5–197°. A mixture melting point with bisketal **40** was depressed to 143–154°.

Conversion of 29a to Cassaic Acid Acetate Methyl Ester and Cassaic Acid. Two hundred milligrams of granulated zinc (30 mesh) was heated on a steam bath for 15 min with concentrated sulfuric acid containing a few drops of nitric acid. The acid was then decanted, and the metal was washed with water, acetone, and ether and was finally dried under vacuum at 100°. The zinc was then added to a solution of 40.2 mg of acetoxy hydroxy ketone **29a** in 0.5 ml of sodium-dried ether containing 0.1 ml of freshly distilled methyl bromoacetate. The mixture was heated under reflux, and a trace of iodine was added. After about 5 min the solution became cloudy. Three fresh portions of zinc (100 mg), cleaned as described above, were added at 45-min intervals, and an additional 0.1 ml of methyl bromoacetate was introduced with the second portion of zinc. After a total reaction time of 3 hr the product was extracted into ether containing a small amount of acetic acid. The ethereal solution was then washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. Removal of the solvent gave 49.4 mg of crystalline material showing strong hydroxyl absorption in the infrared.

The crude Reformatsky product was oxidized directly without further purification by treatment with 40 mg of chromium trioxide in 2 ml of acetic acid. After standing overnight at room temperature the reaction mixture was worked up in the usual way and afforded 35.6 mg of product showing strong hydroxyl absorption and carbonyl bands at 5.75 and 5.85 μ in the infrared.

Dehydration of the crude oxidation product was accomplished by the action of thionyl chloride (0.15 ml) in pyridine (1 ml) at 0° for 30 min. The material resulting from this treatment (26.8 mg) was chromatographed on alumina. In this way 12.5 mg of cassaic acid acetate methyl ester, mp 147–149.5°, was obtained. Recrystallization from ether–petroleum ether gave a pure specimen, mp 148–149°, $[\alpha]D$ −102° (*c* 0.513, ethanol), identical in all respects with an authentic sample.

There was also obtained from the chromatogram 16.5 mg of material melting at 180–182° which showed acetate, ketone, and conjugated ester absorption in the infrared. Although the matter was not pursued further, it is not unlikely that this product represents the geometric isomer (double bond) of cassaic acid acetate methyl ester.

Mild alkaline hydrolysis of cassaic acid acetate methyl ester furnished a sample of cassaic acid that was indistinguishable from the authentic naturally derived substance.