The Total Synthesis of Phyllocladene[1,2]

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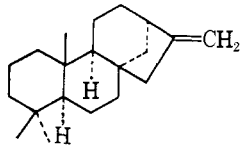
Abstract: A stereospecific, total synthesis of phyllocladene is described. In the course of this investigation an interesting example of *trans* opening as the net result of catalytic hydrogenolysis of an oxide was observed. Sodium–alcohol reduction of phyllocladene norketone yields the thermodynamically less stable alcohol as the preponderant product.

Phyllocladene (**1**) was first isolated from the essential oil of the leaves of *Phyllocladus rhomboidalis* by Baker and Smith[3] and has since been obtained from numerous other sources.[4] The early structural work of Brandt[5] and the more recent investigations of Briggs and his colleagues[6] serve to establish the structural features of the C–D ring system. The correlation of



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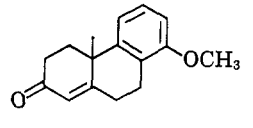
phyllocladene with manool, carried out by Grant and Hodges,[7] supplied the missing details of the A–B structure, including *trans* stereochemistry at the ring junction, and settled the question of absolute configuration as well.[8]

The present paper describes a stereospecific, total synthesis of phyllocladene, which at the same time clarifies certain ambiguities in the previous work concerning the stereochemical arrangement at the B–C ring fusion.

The starting point for synthesis was the Cornforth–Robinson ketone (**2**),[9] which was obtained from 5-methoxy-2-tetralone by conventional methods. Dimethylation of **2**[10] furnished the expected derivative **3**, which was reduced to the corresponding alcohol **4**



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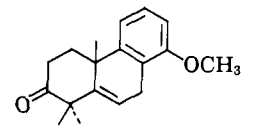

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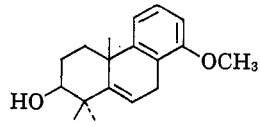

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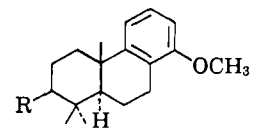
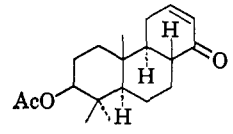


5a, R = H
b, R = OAc
c, R = O

by treatment with lithium aluminum hydride. Catalytic hydrogenation of **4** over palladized charcoal afforded the dihydro compound **5a**, from which derivatives **5b** and **5c** could be obtained by routine transformations. The *trans* stereochemistry assigned to the A–B ring fusion is based upon ample precedent.[11] More importantly, the synthesis of phyllocladene in itself provides definitive evidence on this point.

Further reduction of **5a** by the Birch method as employed by Johnson, Pappo, and Jones[12] yielded a mixture of two α,β-unsaturated ketones, which was separable into pure components **6**, λ_{max} 229 mμ, and **7**, λ_{max} 244 mμ, by acetylation and chromatography on alumina. However, the reduction was accompanied by extensive hydrogenolysis of the methoxyl group, and the combined yield of the two ketones was only



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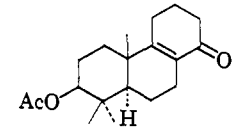

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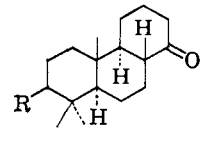


8a, R = OAc
b, R = OH
c, R = O

about 25%. Hydrogenation of **6** gave the saturated acetoxy ketone **8a**, from which the corresponding

(1) The financial support of the Eli Lilly Co. and the Robert A. Welch Foundation is gratefully acknowledged. One of the authors (K. H. G.) is indebted to the Dr. Carl Duisberg-Stiftung, Leverkusen, Germany, for a travel grant.

(2) For preliminary accounts of this work see R. B. Turner and P. Shaw, *Tetrahedron Letters*, No. 18, 24 (1960), and R. B. Turner and K. H. Gänshirt, *ibid.*, No. 7, 231 (1961).

(3) R. T. Baker and H. G. Smith, "The Pines of Australia," Technological Museum, Sydney, 1910, p 419.

(4) *Cf.* L. H. Briggs, *J. Chem. Soc.*, 79 (1937); L. H. Briggs and W. I. Taylor, *J. Org. Chem.*, 12, 551 (1947); L. H. Briggs and J. A. Loe, *J. Chem. Soc.*, 958 (1950).

(5) C. W. Brandt, *New Zealand J. Sci. Technol.*, 20B, 8 (1938); 34B, 46 (1952).

(6) L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmshurst, *Tetrahedron Letters*, No. 8, 8 (1959); L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *J. Chem. Soc.*, 1840 (1962).

(7) P. K. Grant and R. Hodges, *Tetrahedron*, 8, 261 (1960).

(8) *Cf.* L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmshurst, *Tetrahedron Letters*, No. 8, 13 (1959); L. H. Briggs, B. F. Cain, and R. C. Cambie, *ibid.*, No. 8, 17 (1959); C. Djerassi, M. Cais, and L. A. Mitscher, *J. Am. Chem. Soc.*, 81, 2386 (1959).

(9) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949). The anomaly in the ultraviolet spectrum of this substance (λ_{max}^{MeOH} 228 mμ (ϵ 19,500)) is noted in the preceding paper: R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Am. Chem. Soc.*, 88, 1766 (1966), footnote 19.

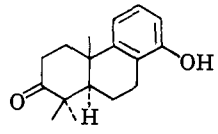
(10) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelley, *J. Chem. Soc.*, 1131 (1957).

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

(12) W. S. Johnson, R. Pappo, and W. F. Jones, *ibid.*, 78, 6339 (1956).

hydroxy ketone **8b** was obtained by alkaline hydrolysis. Acetylation of **8b** resulted in regeneration of **8a**, showing that no configurational change accompanied hydrolysis, while oxidation furnished a base-stable diketone **8c**. Acetoxy ketone **8a** was also obtained in poor yield, as was anticipated, by palladium–charcoal reduction of **7**.

The poor results experienced in Birch reduction of **5a** prompted an investigation of catalytic hydrogenation of the aromatic ring. For this purpose the phenol rather than the methyl ether was desired, and the methoxy ketone **5c** was accordingly demethylated with hydriodic acid in acetic acid. The phenolic product **9** was then



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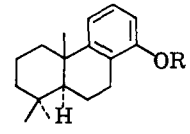
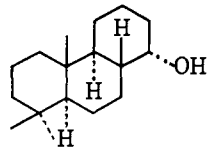


10a, R = H
b, R = Ac
c, R = CH_3

subjected to high-pressure hydrogenation in the presence of Raney nickel, and the resulting diol was oxidized directly with chromic acid. The product of this series of reactions was identical with a sample of **8c** obtained as indicated previously, and the yield was substantially improved.

Since the ring A oxygen function present in compounds thus far described is absent in phyllocladene, its removal at an early stage of synthesis seemed desirable. Of various alternative routes explored, Huang-Minlon reduction of **9** proved to be the most satisfactory, and the phenol **10a** was readily available by this procedure. Hydrogenation of this product over Raney nickel yielded two stereoisomeric alcohols, **11** and **12**, in an approximate ratio of 3:2. Platinum-catalyzed reduction afforded the same substances with about 20% of attendant hydrogenolysis.[13]

The fact that **11** and **12** differ only in the configuration of the hydroxyl group is evident from the facts (a) that both products give the same base-stable ketone (**13**) on oxidation with chromium trioxide in acetic acid and (b) that catalytic hydrogenation of **13** yields a mixture



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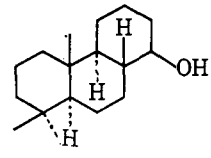

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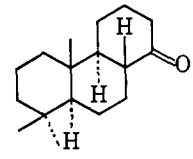

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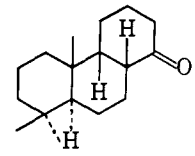
of **11** and **12** in approximately the same ratio as does hydrogenation of **10a**.

The orientations assigned to the hydroxyl groups of **11** and **12** are based upon the observation that the axial[14] epimer **11** is more easily eluted from alumina than is the equatorial isomer **12**,[15] that **12** is the major product of lithium aluminum hydride reduction of **13**, and that **11** absorbs at shorter wavelength (2.79 μ) than **12** (2.81 μ) in the hydroxyl region of the infrared.[16] Appropriate bands are also observed in the C–O stretching region (9.6–10.0 μ),[17] but the spectra are sufficiently complicated in this latter region to render structural arguments somewhat hazardous.

The stereochemistry at the B–C ring fusion must now be considered. The base stability of the tricyclic ketone **13** implies that the backbone arrangement is either *trans,anti,trans* or *trans,syn,cis* as in **14**.[18] Although the latter configuration might ordinarily be taken as



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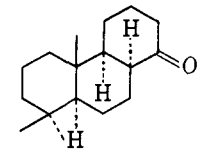

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inherently more probable in view of the expectation for *cis* hydrogenation,[19] the formation of a ketone, for example **15**,[20] at an intermediate stage in the hydrogenation process[21] would provide an opportunity for *cis* → *trans* isomerization[20] to give **13**, which would afford **11** and **12** on further reduction as demonstrated. This possibility, together with the fact that hydrogenation of a compound closely related to **10a** has been reported by Bible[22] to proceed cleanly with addition of hydrogen *trans* to the axial methyl groups, *i.e.*, α in accordance with the principle of catalyst hindrance, provides strong presumptive evidence for the *trans,anti,trans* structure indicated. A further argument in support of this contention is drawn from optical rotatory dispersion data for the levorotatory form of ketone **13**, which was obtained as follows.

Treatment of the racemic alcohol **12** with the acid chloride derived from 3α-acetoxy-11-ketoetiocholanic acid afforded a mixture which was readily separated by chromatography on alumina into two pure diastereoisomeric steroid esters, mp 237–238°, $[\alpha]_D$ +28°, and mp 176–177°, $[\alpha]_D$ +88°. Saponification of the higher melting form gave the levorotatory antipode of **12**, $[\alpha]_D$ −29°, which on chromium trioxide oxidation furnished *l*-**13**, $[\alpha]_D$ −18°. The infrared spectra of the optically active derivatives, *l*-**12** and *l*-**13**, in carbon disulfide solution were identical with those of the corresponding racemic products measured in the same solvent.

The optical rotatory dispersion curve for *l*-**13**[23] shows a negative Cotton effect. Since the octant rule[24] predicts a negative Cotton effect for a ketone

(13) Although hydrogenolysis with nickel was less severe, the platinum product proved cleaner and easier to separate.

(14) The assumption of *trans* stereochemistry at the B–C fusion is implicit in this suggestion.

(15) *Cf.* S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).

(16) I. L. Allsop, A. R. H. Cole, D. E. White, and R. L. S. Willix, *J. Chem. Soc.*, 4868 (1956).

(17) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 5571 (1952).

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

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

(20) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963), have subsequently reported the preparation of **15** by ruthenium-catalyzed hydrogenation of **10a** and oxidation. Isomerization of **15** into **13** was also demonstrated. In an attempt to influence product stereochemistry by excluding the possibility of ketone formation, phenol acetate **10b** was reduced in the presence of platinum. No trace of acetate (or hydroxyl) absorption was observed in the infrared spectrum of the total crude product, and it is assumed that in this case complete hydrogenolysis occurs.

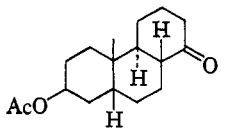
(21) *Cf.* P. Sabatier and A. Mailhe, *Compt. Rend.*, **140**, 350 (1905).

(22) R. H. Bible and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

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

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

possessing the relative and absolute configuration depicted in **13**,[25] but a positive Cotton effect for a ketone of structure **14**, it would appear that structure **13** assigned to the levorotatory tricyclic ketone is correct. The argument is strengthened by the fact that a negative Cotton effect has also been observed[26] for tricyclic ketone **16** which served as a key intermediate in the Robinson steroid synthesis.[27]



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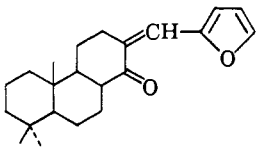
The further synthetic reactions which led ultimately to phyllocladene are now described. Condensation of the racemic tricyclic ketone **13** with furfuraldehyde furnished the furfurylidene ketone **17**, which was smoothly converted into the allyl derivative **18** by the action of allyl bromide and potassium *t*-butoxide. Alkylation with bromoacetic ester proved unsatisfactory. Since alkylation of arylidene α-decalones



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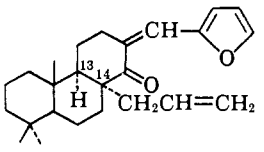

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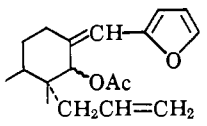

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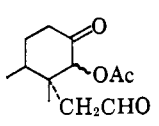

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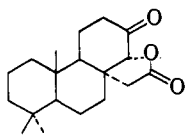

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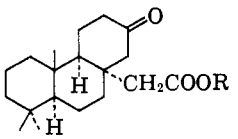


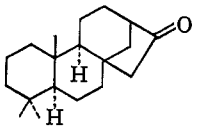
22a, R = H
b, R = CH_3

yields predominantly *cis*-fused products,[28] and since the presence of an axially oriented methyl group at C-12 provides considerable hindrance to β-alkylation,[29] a *cis* arrangement at carbon atoms 13 and 14 in product **18** is indicated.

Attention was next directed toward the problem of removing the keto group in **18**. Assuming an all-chair arrangement in the ring system, this function is badly hindered by the C-12 angular methyl group, and treatment with sodium borohydride, even under forcing conditions, was without effect. However, lithium aluminum hydride reduction proceeded without difficulty and afforded a crystalline alcohol in good yield. The latter product deteriorated rapidly on standing, and the material was therefore characterized as the more stable acetyl derivative **19**. The expectation that hydrogenolysis of the corresponding *p*-toluenesulfonyl derivative could be accomplished with lithium aluminum hydride was not fulfilled, since reduction of the amorphous tosylate gave back material showing strong hydroxyl absorption in the infrared. Attempts to replace the oxygen function by a halogen atom led to the formation of intractable tars.

The acetate **19** was accordingly ozonized, and an acetoxy keto aldehyde **20** was obtained, which was oxidized directly to the corresponding acid. Treatment of the latter compound with mineral acid in aqueous dioxane yielded the expected keto lactone **21**, which showed characteristic absorption in the infrared at 5.56 and 5.76 μ. On prolonged exposure to the action of zinc dust in acetic acid[30] compound **21** furnished keto acid **22a** along with some recovered starting material. The applicability of the calcium–liquid ammonia method[31] was not investigated.

At this point comparison of synthetic material with a degradation product from natural sources was possible, since keto acid **26a** had meanwhile been prepared as indicated below. It should be noted that at the time when this problem was under investigation the configuration of phyllocladene at C-14 was uncertain and was regarded by Wenkert[32] as corresponding to that of **22**.



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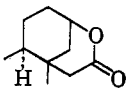

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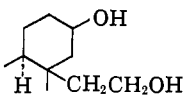

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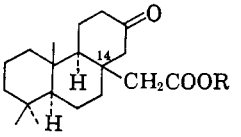


26a R = H
b R = CH_3

Phyllocladene norketone (**23**)[33,34] was converted into lactone **24** by oxidation with perbenzoic acid. Although attempts to accomplish direct transformation of **24** into keto acid **26a** by the method of Corey and Ursprung[35] were unsuccessful, lithium aluminum hydride reduction afforded a crystalline glycol (**25**) which gave the desired keto acid,[36] together with a substantial amount of lactone **24**, on oxidation with chromium trioxide.

Careful comparison of the infrared spectra (solution) of keto acids **22a** and **26a** and of the derived methyl

(25) The absolute configuration shown in formula 13 and assigned specifically to 1-13 follows from the transformation of 1-13 into phyllocladene.

(26) C. Djerassi and W. Klyne, *Chem. Ind.* (London), 988 (1956).

(27) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(28) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, 78, 6331 (1956); W. S. Johnson and D. S. Allen, *ibid.*, 79, 1261 (1957).

(29) *Cf.* L. H. Sarett, W. F. Johnson, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth, *ibid.*, 75, 2112 (1953).

(30) R. B. Woodward, F. F. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 2, 1 (1958).

(31) J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956); C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 76, 4092 (1954).

(32) E. Wenkert, *Chem. Ind.* (London), 282 (1955).

(33) H. Uota, *J. Dept. Agr. Kyushu Imp. Univ.*, 5, 118 (1937).

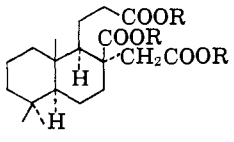
(34) We are greatly indebted to Dr. J. Murray, University of Otago, Dunedin, New Zealand, for the supplies of phyllocladene used in this work.

(35) E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, 78, 5041 (1956).

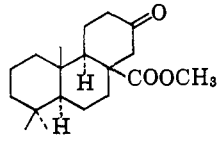
(36) This reaction has been carried out independently by H. Vorbrueggen and C. Djerassi, *ibid.*, 84, 2990 (1962).

esters **22b** and **26b** revealed many points of similarity, but the conclusion that the compounds were different was inescapable. Assuming that this difference could be ascribed solely to opposite orientations of the C-14 side chain, it was clear that at least two mechanisms were available for the base-catalyzed interconversion of esters **22b** and **26b**. In view of the small amount of **22b** that was available, the naturally derived substance **26b** was employed as test material and was treated with sodium methoxide in methanol under scrupulously anhydrous conditions. Unfortunately keto acid **26a** was the only product that could be isolated, a result we are inclined to attribute to acyl oxygen fission.[37] It is of interest to note that the transformation of the optical antipode of **22b**, obtained from *l*-kaurene, into the antipode of **26b** was subsequently accomplished by Briggs and his associates[38] and the point in question was thereby secured.

The procedure finally adopted for epimerization of the asymmetric center at C-14 involved ozonolysis of the allylfurfurylidene derivative **18** and further oxidation with chromium trioxide to triacid **27a**. Treatment of the latter substance with diazomethane afforded the corresponding ester **27b**. Neither the acid nor the ester could be obtained in crystalline form, but chromatography of the ester gave homogeneous material suitable for further manipulation.



27a, R = H
b, R = CH_3



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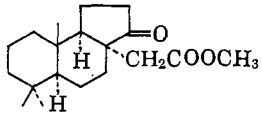
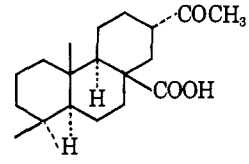


29

Dieckmann cyclization of **27b** can in principle yield either a six-ring or a five-ring β-keto ester. In general the five-ring product is preferred.[39] However, in the present instance the carbomethoxyl group attached directly to ring B is strongly hindered, and closure in the desired sense to a six-ring product under conditions of kinetic control was expected to be favored. Accordingly, triester **27b** was treated with potassium *t*-butoxide in benzene for 4 hr at reflux temperature and for 8 hr at room temperature. Acid-catalyzed hydrolysis, re-esterification, and chromatography gave a sample of the racemic keto ester (**28**)[40] along with some recovered starting material (**27b**). The infrared spectrum of a carbon disulfide solution of the substance was identical with that of the optically active keto ester *l*-**28**, a known degradation product of phyllocladene.[5,6] When the Dieckmann transformation was carried out in refluxing benzene for a period of 16 hr, approximately equal amounts of **28** and **29** were obtained. The suggestion can be made that **29** is derived by equilibrium control of the cyclization step.

Repetition of the experiments outlined above with substitution of resolved material (*l*-**13**) for the optically inactive tricyclic ketone **13** afforded the levorotatory modification of keto ester **28**, *i.e.*, *l*-**28**, mp 159–160°, $[\alpha]D$ −12°, identical in all respects with the degradation product of phyllocladene.

The further synthetic work leading to phyllocladene made use of *l*-**28** as a relay compound. Material was prepared by the conventional literature procedure[5] and also by Baeyer–Villiger oxidation of keto acid **30**[5,6] followed by hydrolysis and esterification to **31** and, finally, oxidation to the required keto ester. It is of interest to note that whereas the carbomethoxyl group of **31** is exceptionally resistant to hydrolysis,



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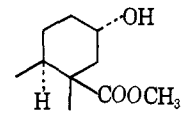

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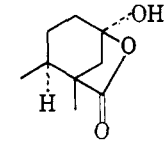
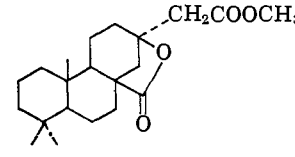


32

hydrolytic cleavage of the corresponding keto ester **28** proceeds with ease. Base attack on the ketonic carbonyl group with intermediate formation of lactol **32** provides a reasonable explanation for this phenomenon.

Condensation of *l*-**28** with methyl bromoacetate according to the Reformatsky procedure furnished the lactonic ester **33** in good yield. Treatment of the latter substance with sodium methoxide yielded amorphous acidic material (**34**) which was converted into a crystalline diacid (**35**) by catalytic hydrogenation and hydrolysis. Pyrolysis of **35** as the barium salt then afforded the tetracyclic ketone **36** which proved to be identical with a product of this constitution obtained from phyllocladene by the procedure of Henderson and



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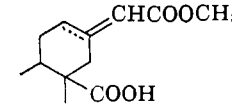

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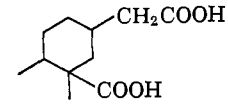

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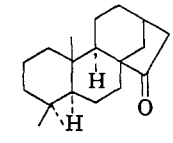


36

Hodges.[41]

In contrast to the behavior of phyllocladene norketone **23**, ketone **36** condenses smoothly with ethyl formate. The resulting hydroxymethylene ketone afforded an acetal **37** by the exchange procedure,[42]

(37) J. F. Bunnett, M. M. Robinson, and F. C. Pennington, *J. Am. Chem. Soc.*, 72, 2378 (1950).

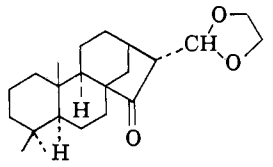
(38) L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 5374 (1963). Viewed in retrospect our choice of **26b** was unfortunate, since it appears that this isomer is heavily favored at equilibrium.

(39) N. N. Chatterjee, B. K. Das, and G. N. Barpujari, *J. Indian Chem. Soc.*, 17, 161 (1940); see also H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954), and references cited therin.

(40) An independent synthesis of this compound has been reported by R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, No. 17, 1 (1960).

(41) R. Henderson and R. Hodges, *Tetrahedron*, 11, 226 (1960).

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



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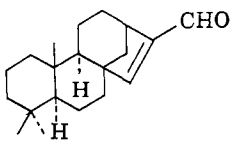
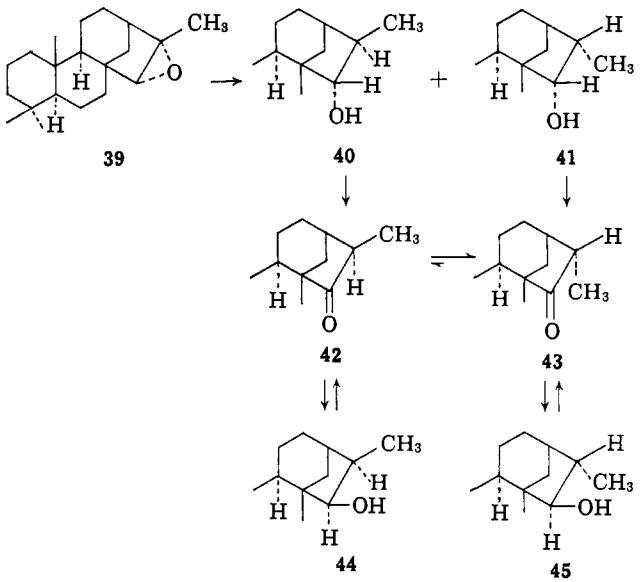


38

and successive treatment of the latter compound with lithium aluminum hydride and mineral acid gave an α,β-unsaturated aldehyde identical with the known product **38**.[43] Since **38** has been shown by Briggs and his associates[43] to yield phyllocladene (**1**) on Wolff–Kishner reduction, the synthesis of **38** reported in this paper completes the total synthesis of this diterpene.

In connection with the present investigation we have carried out a few experiments that supplement the published results of Henderson and Hodges.[41] Several of the compounds reported from the Glasgow laboratories have been obtained independently by us. In addition we have prepared the four epimeric alcohols **40**, **41**, **44**, and **45**, the structures of which were correlated as follows.

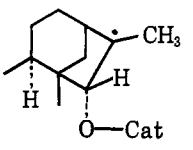
Catalytic hydrogenation of oxide **39** derived from isophyllocladene[41] yields a mixture of alcohols **40** and **41**, which are oxidized to ketones **42** and **43**, respectively. Treatment of **42** with base results in smooth isomerization into **43**, and arguments based upon examination of molecular models serve to establish configurations in these molecules. The parent



39 40 41 42 43 44 45

alcohols **40** and **41** therefore possess the stereochemistry indicated. The major product of the hydrogenolysis of **39** is the expected product **40**. A matter of considerable interest, however, is the simultaneous formation of some 12% epimer **41**. Although the mechanism of inversion cannot be clearly defined at this time, intermediacy of a bound radical **46**[44] and/or the allylic alcohol **47** represent(s) an attractive possibility.[45]

The carbonyl groups of **42** and **43** are subject to strong hindrance on the side of the C-12 angular methyl



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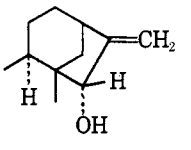
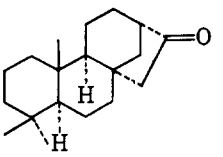


47

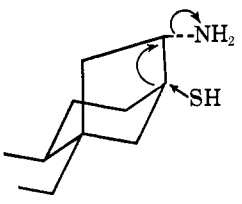
group, but lithium aluminum hydride reduction was carried out without incident. In this way the two remaining alcohols, **44** and **45**, were prepared. Oxidation of these substances regenerated the starting ketone in each case, and the configurations that are assigned would hence appear to be correct.

Mention is finally made of some experiments that were undertaken in an attempt to convert phyllocladene norketone **23** into *d*-kaurene norketone **48**[46] of opposite bridge configuration. Sodium–alcohol reduction of the oxime of **23** afforded an amine (**49**) which was isolated



48

as the hydrochloride and characterized as the N-acetyl derivative. The substance was then deaminated[47] with nitrous acid in aqueous acetic acid in the hope that rearrangement with solvent participation might lead to a kaurene derivative (**50**) convertible into the norketone **48**. The total crude product was treated with



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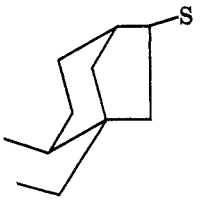

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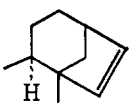


51

lithium aluminum hydride in order to cleave any acetate ester present, and the resulting material was oxidized directly with chromic acid. Chromatography furnished a small amount of material that was identified as unrearranged olefin **51**,[41] a major fraction consisting of phyllocladene norketone **23**, and lesser amounts of ketone **36** and an unidentified product which showed six-ring carbonyl absorption in the infrared. The latter two substances may arise by hydride transfer processes at an intermediate stage in the deamination reaction.

In view of the suggestion of Corey and his associates[48] that deamination of *exo*- and of *endo*-norbornylamine produces a classical carbonium ion, whereas a symmetrical bridged ion is obtained by solvolysis of *exo*-

(43) L. H. Briggs, B. F. Cain, and B. R. Davis, *Tetrahedron Letters*, No. 17, 9 (1960).

(44) G. C. Bond, *Quart. Rev.* (London), **8**, 279 (1954), and cited references.

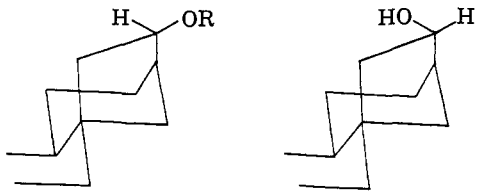
(45) It will be recalled that phyllocladene yields both epimeric dihydro derivatives on catalytic hydrogenation.[6]

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

(47) Deamination was first carried out in a closed system filled with air and connected to a buret system. Rapid *absorption* instead of evolution of gas was observed. We ascribe this result to air oxidation of reagent, and subsequent runs in which the apparatus was first purged with nitrogen proceeded normally. Although it seems unlikely that this phenomenon has not been encountered previously, literature descriptions of deamination procedures make it evident that the desirability of excluding air is not generally recognized.

(48) E. J. Corey, J. Casanova, P. A. Vatakencherry, and R. Winter, *J. Am. Chem. Soc.*, **85**, 169 (1963); *cf.* J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 (1964).

norbornyl arenesulfonates, acetolysis of the tosylate **52b** was also investigated. Sodium–alcohol reduction of phyllocladene norketone was regarded as an attractive route to this substance. However, both alcohols **52a**[41] and **53**[41] were obtained, and epimer **53** predominated by a factor of about 3.[49,50] Equilibration of



52a, R = H
52b, R = Ts

53

53 by prolonged treatment with a refluxing solution of sodium *n*-butoxide in *n*-butyl alcohol[51] afforded a mixture containing 63% **52a** and 37% **53**. Recycling provided a method for satisfactory conversion of **53** to the desired epimer **52a**. Tosylate **52b** could not be induced to crystallize and was hence subjected to direct acetolysis in acetic acid containing small amounts of acetic anhydride and sodium acetate.[52] The total crude product showed only traces of acetate on infrared analysis and furnished besides some unsolvolyzed starting material an olefin fraction that appeared to be largely **51**.

Experimental Section

Preparation of 2,3,4,9,10,12-Hexahydro-8-methoxy-12-methyl-2-oxophenanthrene (2).[9] A solution of 58.7 g of 1-methyl-5-methoxy-2-tetralone (prepared by enamine methylation of 5-methoxy-2-tetralone) in 300 ml of dry benzene was treated with diethylaminobutanone methiodide (from 44.1 g of diethylaminobutanone)[53] and 11.2 g of sodium in 220 ml of absolute ethanol according to the procedure of Cornforth and Robinson.[9] Distillation of the crude product furnished a fraction boiling between 160 and 188° (0.05 mm) which crystallized on standing. Recrystallization of this material from acetone–hexane gave 29.3 g of tricyclic ketone **2**: mp 114–117°, λ_{max}^{MeOH} 228 mμ (ε 19,500), $\lambda_{max}^{CS_2}$ 5.99 μ. The material proved satisfactory for subsequent operations, and more thorough purification was normally carried out in the next step.

Preparation of 1,2,3,4,9,12-Hexahydro-8-methoxy-1,1,12-trimethyl-2-oxophenanthrene (3). Methylation of the tricyclic ketone **2** was carried out by the Woodward–Patchett method.[10] Ten grams of **2** was dissolved in 200 ml of anhydrous *t*-butyl alcohol, and a solution of 4.9 g of potassium in 100 ml of *t*-butyl alcohol was added, followed immediately by 17 ml of methyl iodide. This operation and the subsequent manipulations were carried out in a nitrogen atmosphere. The mixture was stirred for 2 hr at room temperature, at the end of which time 41 ml of 10% aqueous sulfuric acid was added. The product was isolated by ether extraction with the usual washing and drying procedures. Crystallization from methanol gave 7.4 g of **3** melting at 107–109°. Several recrystallizations from methanol gave the analytical sample: mp 109.5–110.5°, $\lambda_{max}^{CS_2}$ 5.84 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.66; H, 8.13.

Lithium Aluminum Hydride Reduction of 3. A solution of 5.7 g of the dimethylated ketone **3** in 100 ml of absolute ether was added dropwise with stirring to a suspension of 8.0 g of lithium aluminum hydride in 250 ml of dry ether. After stirring for 1 hr at room temperature, the excess lithium aluminum hydride was decomposed by careful addition of methanol. The reaction mixture was then acidified with dilute aqueous sulfuric acid, and the ether layer was washed with water, dilute sodium hydroxide, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated, and the product **4** was crystallized from methanol: yield 3.8 g, mp 119–122°. The sample for analysis melted at 121.5–122°, $\lambda_{max}^{CS_2}$ 2.78 μ.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.33; H, 8.98.

Preparation of *trans*-1,2,3,4,9,10,11,12-Octahydro-8-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (5a). A sample of the unsaturated alcohol **4** (2.14 g) was hydrogenated in 50 ml of acetic acid in the presence of 928 mg of palladized charcoal. The catalyst was removed by filtration, and the acetic acid was then evaporated under reduced pressure. Crystallization from ether–petroleum ether (bp 30–60°) afforded 1.74 g of **5a** melting at 132–134°. Recrystallization from ether–petroleum ether gave the analytical sample: mp 133.5–134°, $\lambda_{max}^{CS_2}$ 2.78 μ.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.70; H, 9.51.

Treatment of **5a** with acetic anhydride and pyridine gave the corresponding **acetyl derivative 5b**: mp 110–112° (ether–petroleum ether), $\lambda_{max}^{CS_2}$ 5.79 μ.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.84; H, 8.67.

Catalytic Hydrogenation of Tricyclic Ketone 3. The unsaturated ketone **3** (4.29 g) was dissolved in 20 ml of acetic acid and hydrogenated in the presence of 925 mg of palladium–charcoal catalyst. The product was isolated by the usual procedure and, after crystallization from hexane, furnished 3.73 g of the saturated ketone **5c**, mp 80–84°. The analytical sample melted at 90–93°, $\lambda_{max}^{CS_2}$ 5.83 μ.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.30; H, 8.63.

A product possessing identical properties was obtained by oxidation of **5a** with the chromium trioxide–pyridine complex.

Birch Reduction of 5a. Small pieces of lithium totaling 4.5 g were added over a period of 2 hr to a stirred solution of 294 mg of **5a** in 38 ml of absolute ethanol and 80 ml of liquid ammonia.[12] During this period an additional 10 ml of ethanol was added in portions. The ammonia was then allowed to evaporate, and water and chloroform were added. The aqueous phase was twice extracted with chloroform, and the combined chloroform layers were washed, dried, and evaporated.

The residual material thus obtained was dissolved in 15 ml of ethanol and 3.5 ml of water. Concentrated hydrochloric acid (1.5 ml) was added, and the solution was heated under reflux in a nitrogen atmosphere for 30 min. The product was isolated by chloroform extraction and was finally acetylated with acetic anhydride and pyridine. Chromatography on alumina furnished early fractions consisting of 66 mg of crystalline material, which on recrystallization from ether–petroleum ether gave 32 mg of impure **6**, mp 113–117°. Three additional crystallizations raised the melting point to 133–134° (15 mg), λ_{max}^{MeOH} 229 mμ (ε 7200), $\lambda_{max}^{CS_2}$ 5.77 and 6.03 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.87; H, 9.35.

From later chromatographic fractions 25 mg of compound **7**, mp 93.5–97°, was obtained. The analytical sample melted at 96.5–98°, λ_{max}^{MeOH} 244 mμ (ε 7600), $\lambda_{max}^{CS_2}$ 5.77 and 6.00 μ.

Anal. Found: C, 74.93; H, 9.26.

Preparation of 2β-Acetoxypodocarpan-8-one (8a). Hydrogenation of a small sample of conjugated ketone **6** was carried out in acetic acid over palladized charcoal. The product was crystallized from petroleum ether and melted at 150–152°, $\lambda_{max}^{CS_2}$ 5.78 and 5.85 μ.

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.42; H, 9.92.

Saponification gave the corresponding hydroxy compound **8b** which was crystallized from ether–petroleum ether: mp 148–149°, $\lambda_{max}^{CS_2}$ 2.78 and 5.87 μ.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 76.93; H, 10.88.

Preparation of Podocarpane-2,8-dione (8c). From 8b. The hydroxy ketone **8b** (30 mg), obtained in the preceding experiment, was dissolved in 1 ml of acetic acid and added to 21 mg of chromium trioxide dissolved in 1 drop of water. The reaction mixture was

(49) For other examples of nonequilibrium reduction of ketones see J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962); G. Ourisson and A. Rassat, *Tetrahedron Letters*, **No. 21**, 16 (1960); K. D. Hardy and R. J. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).

(50) This result casts some doubt on the stereochemistry assigned to the amine **49**, which was also obtained by sodium–alcohol reduction. However, configuration in the amine is not particularly relevant if deamination involves a classical carbonium ion.

(51) W. von E. Doering, G. Cortes, and L. H. Knox, *J. Am. Chem. Soc.*, **69**, 1700 (1947).

(52) S. Winstein and J. Sonnenberg, *ibid.*, **83**, 3244 (1961).

(53) E. C. Spaeth, T. A. Geissman, and T. L. Jacobs, *J. Org. Chem.*, **11**, 399 (1946).

allowed to stand at room temperature for 3.5 hr. Dilution with water and ether extraction afforded crude material (20 mg) which was crystallized from ether–petroleum ether: yield 17 mg, mp 113–114°. The analytical sample melted at 115–116°, $\lambda_{max}^{CS_2}$ 5.87 μ.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.73; H, 9.75.

From 9. A solution of 148 mg of phenolic ketone **9** (see below) in 10 ml of ethanol containing 0.2 ml of 40% aqueous sodium hydroxide[54] was hydrogenated over W-2 Raney nickel[55] at 2000 psi and a temperature of 140–155°. After 3 hr, the bomb was cooled and rinsed out with ethanol. The product was isolated by standard procedures and was oxidized with chromium trioxide in acetic acid. After treatment with sodium methoxide to establish thermodynamic equilibrium at the B–C ring fusion, the oxidation product (72 mg) was crystallized from ether–petroleum ether. The material obtained in this way melted at 112–113° and did not depress the melting point of a specimen obtained as described in the preceding experiment. The infrared spectra of the two samples were identical.

Preparation of *trans*-1,2,3,4,9,10,11,12-Octahydro-8-hydroxy-1,1,12-trimethyl-2-oxophenanthrene (9). A solution of 2.20 g of compound **5c** in 100 ml of refluxing acetic acid was treated with 6 ml of 49% hydriodic acid. After heating for 1.5 hr, the reaction mixture was cooled and was poured into 200 ml of water containing a little sodium bisulfite. Ether was added, and the organic phase was washed, dried, and evaporated. Crystallization of the residue from methanol gave 1.21 g of **9**, mp 211–216°. An additional 0.44 g, mp 205–211°, was obtained from the mother liquor. One recrystallization raised the melting point to 216–219°. The analytical sample melted at 219–220°, $\lambda_{max}^{CH_2Cl_2}$ 2.80 and 5.87 μ.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.31; H, 8.80.

Preparation of *trans*-1,2,3,4,9,10,11,12-Octahydro-8-hydroxy-1,1,12-trimethylphenanthrene (10a). A solution of 1.48 g of **9** in 75 ml of diethylene glycol was treated with 11.3 g of 99% hydrazine and 2.3 g of potassium hydroxide,[56] and the mixture was heated to 120° under reflux for 6 hr. Nitrogen was bubbled slowly through the solution throughout the reaction period. The condenser was removed, and the temperature was raised to 195° where it was maintained for an additional 6-hr period. Isolation of the product by conventional procedures afforded 1.32 g of **10a**, mp 136–146°. Recrystallization from ether–petroleum ether gave a pure sample: mp 146–148°, λ_{max}^{EtOH} 274 mμ (ε 1200), $\lambda_{max}^{EtOH\ (NaOH)}$ 243 mμ (ε 7300) and 293 mμ (ε 3600), $\lambda_{max}^{CS_2}$ 2.79 μ.

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.62; H, 10.20.

The acetate **10b**, prepared as a derivative, melted at 123–124° (from ether–petroleum ether), $\lambda_{max}^{CS_2}$ 5.68 μ.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.87; H, 9.23.

Preparation of *trans*-1,2,3,4,9,10,11,12-Octahydro-8-methoxy-1,1,12-trimethylphenanthrene (10c). Zinc metal (62.5 g, 30 mesh) was amalgamated and added to a mixture of 75 ml of concentrated hydrochloric acid, 22 ml of water, and 7.48 g of methoxy ketone **5c** in 75 ml of ethanol.[57] The mixture was refluxed for 72 hr during which period 15-ml portions of concentrated hydrochloric acid were introduced at 6-hr intervals. The zinc was then removed by filtration, and the filtrate was diluted with a large volume of water and extracted with ether. After washing and drying, the ether was evaporated, and the product was crystallized from ethyl acetate: yield 4.59 g, mp 104–110°. Several recrystallizations afforded the analytical sample, mp 114–115°.

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.48; H, 10.17.

Preparation of Podocarpan-8-one (13). A solution of 1.19 g of phenol **10a** in 10 ml of ethanol containing 300 mg of sodium hydroxide was hydrogenated over W-2 Raney nickel[55] for 3 hr at 105° and a hydrogen pressure of 2300 psi. The catalyst was removed by filtration, and the filtrate was diluted with water and extracted with ether. Evaporation of the ether solution after routine washing and drying furnished 1.06 g of a colorless oil.

A 195-mg sample of the total crude product was reserved for chromatography (see below), and the remainder was oxidized directly with 850 mg of chromium trioxide in 10 ml of 90% acetic acid. The solution was allowed to stand at room temperature for 3 hr, at the end of which time water was added, and the product was extracted with ether. The crude material obtained in this way was crystallized from petroleum ether: yield 434 mg, mp 63–66°. The analytical sample obtained after several recrystallizations from petroleum ether melted at 67–68°.

Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, C, 82.09; H, 11.50.

Lithium aluminum hydride reduction of crude ketone afforded material from which the equatorial alcohol **12** could be readily isolated as the major product. Since this substance is more easily purified than the corresponding ketone **13**, and affords pure ketone directly by oxidation (see below), the lithium aluminum hydride route was normally followed for preparative purposes.

Preparation of Podocarpan-8α-ol (11) and Podocarpan-8β-ol (12). The 195-mg sample of hydrogenation product reserved in the previous experiment was chromatographed on 6 g of alumina. Elution with benzene afforded 75 mg of crude crystalline material, which gave 36 mg of pure podocarpan-8α-ol (**11**), mp 99–100°, $\lambda_{max}^{CS_2}$ 2.79 μ, after two recrystallizations from methanol.

Anal. Calcd for $C_{17}H_{30}O$: C, 81.53; H, 12.08. Found: C, 81.67; H, 11.99.

From later benzene eluates there was obtained, after crystallization from ether–petroleum ether, 24 mg of the epimeric alcohol **12**: mp 118–119°, $\lambda_{max}^{CS_2}$ 2.81 μ.

Anal. Found: C, 81.76; H, 12.37.

Both alcohols afforded podocarpan-8-one (**13**) on oxidation with chromium trioxide in acetic acid.

Catalytic Hydrogenation of Podocarpan-8-one (13). A sample of podocarpan-8-one (**13**, 100 mg) was hydrogenated in the presence of 100 mg of platinum oxide catalyst in 1 ml of acetic acid. Chromatography of the total crude reduction product on 3 g of alumina furnished 30 mg of **11**, mp 94–96°. Recrystallization from methanol gave a pure sample, mp 100–101°, that did not depress the melting point of material obtained in the preceding experiment. Later fractions afforded 21 mg of **12**, mp 118–120°, which likewise showed no depression with the sample obtained previously. The identity of the platinum reduction products was further confirmed by infrared spectral analysis.

Lithium Aluminum Hydride Reduction of Podocarpan-8-one (13). A solution of 331 mg of tricyclic ketone **13** in 5 ml of anhydrous ether was added dropwise with stirring to 75 mg of lithium aluminum hydride in 5 ml of dry ether. After stirring at room temperature for 1 hr, the excess reagent was decomposed with methanol, the mixture was acidified with dilute sulfuric acid, and the ether layer was thoroughly washed with water. Drying over anhydrous sodium sulfate, removal of the solvent, and crystallization from petroleum ether furnished 213 mg of podocarpan-8β-ol (**12**), mp 116–118°. Chromatography of the mother liquor yielded an additional 30 mg of **12** and a mixture containing the epimeric alcohol **11** which could be recycled through ketone **13**.

Resolution of Podocarpan-8β-ol (12). A 70-mg sample of alcohol **12** was treated in dry benzene (3 ml) with the acid chloride derived from 138 mg of 3α-acetoxy-11-ketoetiocholanic acid.[58] After standing at room temperature for 12 hr, ether and water were added, and the organic layer was washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. Removal of the solvent gave 201 mg of steroid ester that was chromatographed on alumina. In this way 41 mg of material was obtained that melted at 233–234°. Recrystallization to constant melting point and constant specific rotation gave a sample melting at 237–238°, $[\alpha]_D$ +28° (*c* 1.10, chloroform).

Anal. Calcd for $C_{39}H_{60}O_5$: C, 76.93; H, 9.93. Found: C, 76.69; H, 9.80.

Late chromatographic fractions afforded 12 mg of the diastereoisomer, mp 176–177°, $[\alpha]_D$ +88° (*c* 0.97, chloroform).

The higher melting ester (480 mg), obtained from several runs, was heated under reflux for 12 hr in 100 ml of 10% methanolic potassium hydroxide. The bulk of the methanol was then removed by distillation. Water was added, and distillation was continued until the temperature of the distillate reached 100°. The mixture was then cooled and extracted with ether. The ether layer was finally washed with dilute sodium hydroxide, dried over anhydrous sodium sulfate, and concentrated to dryness. The product *l*-**12**

(54) G. Stork, *J. Am. Chem. Soc.*, 69, 576 (1947).
(55) A. A. Pavlic and H. Adkins, *ibid.*, 68, 1471 (1946).
(56) Huang-Minlon, *ibid.*, 71, 3301 (1949).
(57) E. L. Martin, *Org. Reactions*, 1, 155 (1942).
(58) J. von Euw, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, 27, 1287 (1944); R. B. Turner, V. R. Mattox, W. F. McGuckin, and E. C. Kendall, *J. Am. Chem. Soc.*, 74, 5814 (1952).

(143 mg, mp 108–109°) was isolated by crystallization from petroleum ether. A purified sample melted at 109–110°, $[\alpha]D$ −29° (*c* 0.84, chloroform). The infrared absorption spectrum of the optically active material, measured in carbon disulfide, was identical with that of the racemic alcohol (*d,l*-**12**).

Preparation of *l*-Podocarpan-8-one (*l*-13). A solution of 238 mg of *l*-**12** in 2 ml of acetic acid was treated with 125 mg of chromium trioxide in 1 ml of acetic acid containing a few drops of water. After standing overnight at room temperature, the reaction mixture was diluted with water and extracted with ether. The ether was removed under reduced pressure. The resulting white crystalline residue was recrystallized from petroleum ether: yield 156 mg, mp 87–88°. A second recrystallization from the same solvent gave a pure sample of *l*-**13**, mp 87.5–88°, $[\alpha]D$ −18° (*c* 0.90, chloroform), negative Cotton effect.[23] The infrared absorption spectrum (CS_2) was identical with that of optically inactive ketone.

Reaction of Podocarpan-8-one (13) with Furfuraldehyde. A solution of 600 mg of racemic podocarpan-8-one (**13**) in 20 ml of methanol was treated with 3 ml of freshly distilled furfuraldehyde and 11 ml of 33% aqueous sodium hydroxide solution. The mixture was allowed to stand in the dark at room temperature for 4 hr. At the end of this time a mass of crystals had separated. Filtration and recrystallization from methanol yielded 716 mg of furfurylidene derivative **17**: mp 87.5–88°, $\lambda_{max}^{CS_2}$ 5.96 μ.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.99; H, 9.42.

Repetition of this experiment using *l*-podocarpan-8-one (*l*-**13**) as starting material gave *d*-**17**: mp 122.5–123°, $[\alpha]D$ +41° (*c* 0.88, chloroform). The infrared spectra (CS_2) of the optically active and optically inactive products were identical.

Alkylation of Furfurylidene Derivative 17 with Allyl Bromide. A solution of potassium *t*-butoxide prepared from 687 mg of potassium and 20 ml of dry *t*-butyl alcohol was added to a stirred solution of 617 mg of racemic furfurylidene ketone **17** in 30 ml of sodium hydride dried benzene. Freshly distilled allyl bromide (7.2 ml) was then added, and the reaction mixture was stirred at room temperature under nitrogen for 4 hr. At the end of this time the mixture was acidified with acetic acid, diluted with water, and extracted with ether. The organic layer was thoroughly washed and, after filtering through anhydrous sodium sulfate, was concentrated to dryness. The residue, on crystallization from methanol, furnished 604 mg of racemic **18**, mp 104–105°. The sample for analysis melted at 108–108.5°, $\lambda_{max}^{CS_2}$ 3.24, 5.96, 10.08, and 10.91 μ.

Anal. Calcd for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 81.71; H, 9.30.

When dextrorotatory **17** was employed *l*-**18**, mp 88–88.5°, $[\alpha]D$ −115° (*c* 0.89, chloroform), was obtained. The infrared spectrum of this substance (CS_2 solution) was identical with that of the *d,l* modification.

Preparation of Compound 19. A solution of 462 mg of the allyl derivative **18** in 25 ml of anhydrous ether was added dropwise to a stirred suspension of 400 mg of lithium aluminum hydride in 25 ml of anhydrous ether. After stirring at room temperature for 2 hr under nitrogen, the excess reagent was destroyed by the cautious addition of methanol, and 100 ml of ether and 75 ml of 10% aqueous sodium hydroxide[59] were added. The ether solution was washed with water and saturated sodium chloride solution and was finally dried and evaporated. The crude crystalline alcohol obtained in this way showed an ultraviolet absorption maximum at 269 mμ (ε 17,000) and exhibited characteristic bands in the infrared at 2.78 and 2.82 μ (doublet) and at 10.08, 10.95, and 13.78 μ. The material darkened rapidly on exposure to air and was in general acetylated directly (acetic anhydride–pyridine) without purification. The acetyl derivative **19** was stable, and 240 mg of this product, mp 99–100°, was obtained by crystallization from ether–petroleum ether. The sample for analysis melted at 103–104°, λ_{max}^{MeOH} 269 mμ (ε 26,600), $\lambda_{max}^{CS_2}$ 5.73 μ.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 79.10; H, 9.66.

Conversion of Compound 19 to Keto Lactone 21. The acetyl derivative **19** (240 mg) was ozonized at −10° in a mixture of 8 ml of ethyl acetate and 4 ml of acetic acid. After standing in the cold for 20 min, the reaction mixture was treated with 300 mg of zinc dust and 1 ml of water and was stirred until a negative starch–iodide test was obtained. The zinc was removed by filtration, and the filtrate was diluted with ether and washed with water and dilute sodium hydroxide. The neutral product **20**, 153 mg, $\lambda_{max}^{CS_2}$ 3.69, 5.71, 5.81, and 8.10 μ, crystallized, but was oxidized directly with chromium trioxide–acetic acid without further purification. After standing overnight at room temperature the oxidation mixture was worked up in the usual way, and yielded 111 mg of crude acetoxy keto acid suitable for lactonization to compound **21**. The presence of some lactone in the product was indicated by the appearance of a weak band at 5.57 μ in the infrared.

The acid was dissolved in 10 ml of purified dioxane containing 2 ml of concentrated hydrochloric acid, and the resulting mixture was refluxed overnight in a nitrogen atmosphere. The product **21** was then taken into ether, washed with dilute sodium hydroxide, and crystallized from methylene chloride–petroleum ether: yield 38 mg, mp 194–195°, $\lambda_{max}^{CS_2}$ 5.57 and 5.78 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.96; H, 9.09.

Preparation of Keto Ester 22b. The keto lactone **21** (50 mg) obtained by the procedure of the preceding experiment and 500 mg of acid-washed[60] zinc dust were heated to 100° with 10 ml of acetic acid for 84 hr. Fresh zinc dust was added in 200-mg portions at 12-hr intervals during the heating period. The product was then separated into neutral and acidic fractions. The neutral fraction afforded 20 mg of unreacted keto lactone **21**. From the acidic fraction 30 mg of keto acid **22a**, mp 88–91°, $\lambda_{max}^{CS_2}$ 5.87 μ, was obtained.

Esterification with diazomethane yielded the corresponding keto ester **22b**: mp 82.5–83.5°, $\lambda_{max}^{CS_2}$ 5.78 and 5.86 μ.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.07. Found: C, 75.03; H, 10.10.

Preparation of Lactone 24. A 4.30-g sample of norketone **23**, mp 100–101° $\lambda_{max}^{CS_2}$ 5.75 μ, $[\alpha]D$ +72° (*c* 1.15, chloroform), was dissolved in 100 ml of dry benzene, and 38 ml of a benzene solution of perbenzoic acid containing 19.0 mmoles of peracid was added. The reaction mixture was allowed to stand at room temperature for 7 days. The solution was then washed with dilute sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the product was crystallized from methanol: yield 3.35 g, mp 150–154°. The analytical sample melted at 153–154°, $\lambda_{max}^{CS_2}$ 5.78 μ, $[\alpha]D$ +9.0° (*c* 0.83, chloroform).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.70; H, 10.31.

Lithium Aluminum Hydride Reduction of Lactone 24. Lactone **24** (2.74 g) was reduced with 2.0 g of lithium aluminum hydride in ether according to the usual procedure. Crystallization of the reduction product from a small volume of ether gave 1.95 g of glycol **25**, mp 155–159°. Several recrystallizations from ether afforded the analytical sample melting at 167–169°, $\lambda_{max}^{CS_2}$ 3.08 μ (broad), $[\alpha]D$ −6.5° (*c* 1.02, chloroform).

Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.30; H, 11.80.

Preparation of Keto Acid 26a and of Keto Ester 26b. The glycol **25** (1.85 g) in 30 ml of acetic acid was added slowly at 18° to a solution of 1.70 g of chromium trioxide in 1 ml of water and 10 ml of glacial acetic acid. After 3 hr at room temperature, the reaction mixture was diluted with water and extracted with ether. In this way there was obtained 238 mg of lactone **24** and 466 mg of keto acid **26a**, mp 157–158° (from methylene chloride–petroleum ether), $\lambda_{max}^{CH_2Cl_2}$ 2.81, 2.88 (shoulder), and 5.81 μ, $[\alpha]D$ +8.2° (*c* 1.09, chloroform).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.58; H, 9.96.

A sample of the keto acid was esterified with diazomethane to give keto ester (**26b**): mp 179–180°, $\lambda_{max}^{CS_2}$ 5.79 and 5.83 μ, $[\alpha]D$ +17.4° (*c* 1.11, chloroform).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.93; H, 10.12.

Preparation of Keto Ester 28. A solution of 223 mg of the racemic furfurylidene ketone **18** in 5 ml of ethyl acetate was treated with excess ozone at −10°. Acetic acid (2 ml), water (1 ml), and 30% hydrogen peroxide (0.6 ml) were then added, and the mixture was allowed to stand overnight at room temperature. Dilution with water and ether extraction furnished 218 mg of material, which was taken up in 5 ml of acetic acid and treated directly with 225 mg of chromium trioxide in a small volume of water. The oxidation reaction was allowed to proceed overnight at room temperature, and the mixture was then diluted with water and

(59) Sodium hydroxide was employed for dissolving the aluminum hydroxide in view of the expected sensitivity of the product to acid.

(60) R. L. Shriner and F. W. Neumann, "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p 73.

extracted with ether. After thorough washing with water to remove the acetic acid, the ether layer was extracted with dilute sodium hydroxide. Acidification followed by extraction with ether and the usual washing and drying operations gave 165 mg of crude triacid **27a** as a colorless oil. The product could not be induced to crystallize.

The total crude acidic product was esterified with diazomethane, and the resulting neutral material (158 mg) was chromatographed on alumina. Elution with petroleum ether–benzene mixtures gave a homogeneous sample, 97 mg, $\lambda_{max}^{CS_2}$ 5.77 μ (broad), of triester **27b**. The material failed to crystallize and was employed in the next step without further attempts at purification.

Dieckmann cyclization of triester **27b** was carried out as follows. Potassium (246 mg) was dissolved in 20 ml of dry *t*-butyl alcohol. The excess solvent was evaporated under reduced pressure, and the residual potassium *t*-butoxide was purged twice with benzene, dried over sodium hydride, to remove the last traces of alcohol. A solution of 97 mg of **27b** in 16 ml of dry benzene was then added. The mixture was refluxed for 4 hr (dry nitrogen atmosphere), and after stirring at room temperature for an additional 8 hr was finally acidified with dilute sulfuric acid. The product was taken up in ether, washed with water and saturated sodium chloride solution, filtered through anhydrous sodium sulfate, and concentrated to dryness.

The residual oil was dissolved in 5 ml of acetic acid, 2 ml of concentrated hydrochloric acid and 0.5 ml of water were added, and the solution was refluxed for 1 hr under nitrogen. The product was isolated by water dilution and ether extraction, and after treatment with excess diazomethane was chromatographed on alumina. In addition to about 20 mg of recovered oily triester, 45 mg of crude crystalline material was obtained. Recrystallization from methanol yielded 25 mg of keto ester **28**, mp 120–125°. Further recrystallization from the same solvent afforded the analytical sample: mp 130–131°, $\lambda_{max}^{CS_2}$ 5.80 μ. The infrared absorption spectrum of this compound (carbon disulfide) was identical with that of an optically active sample obtained by degradation of isophyllocladene (see below).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.78; H, 9.94.

When the cyclization of 520 mg of triester **27b** was carried out in benzene in the presence of alcohol-free potassium *t*-butoxide with a 16-hr reflux period, chromatography (after hydrolysis, decarboxylation, and reesterification) afforded two crystalline keto esters. In addition to 42 mg of **28**, mp 128–131°, there was obtained an isomeric five-ring keto ester, 30 mg, mp 115–116°, $\lambda_{max}^{CS_2}$ 5.74 μ, to which structure **29** is assigned.

Anal. Found: C, 74.71; H, 9.81.

Repetition of the 4-hr reflux procedure using triester derived from 180 mg of *l*-**18** gave, after purification, 11 mg of *l*-**28**, mp 158–159°. One final recrystallization from methanol furnished the sample for comparison, mp 159–160°, $[\alpha]D$ −12° (*c* 0.53, chloroform). A mixture melting point with an authentic specimen, mp 159–161°, $[\alpha]D$ −11° (*c* 0.60, chloroform), obtained by degradation of isophyllocladene, showed no depression. The infrared spectra of the two samples were superposable.

Preparation of Hydroxy Ester 31. A 208-mg sample of keto acid **30**, obtained by permanganate oxidation of isophyllocladene according to the literature procedure,[5] was dissolved in 4 ml of benzene and treated with 1.6 ml of a benzene solution of perbenzoic acid containing 0.715 mmole of peracid. After 6 days at room temperature, the mixture was diluted with ether, washed thoroughly with water, and dried. Esterification with diazomethane followed by saponification and crystallization from methanol afforded a pure sample of hydroxy ester **31**: mp 111–112°, $\lambda_{max}^{CS_2}$ 2.79 and 5.81 μ.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.88; H, 10.23.

Oxidation of 31 to Keto Ester 28. The hydroxy ester **31** (50 mg) was oxidized with 50 mg of chromium trioxide in 2 ml of acetic acid. The product *l*-**28** was isolated in the usual way: yield 34 mg, mp 160–162°, $\lambda_{max}^{CS_2}$ 5.81 μ. The substance was identical in all respects with an authentic sample prepared by the literature procedure[5,6] and with the synthetic sample of *l*-**28** described previously.

Preparation of Lactonic Ester 33. The levorotatory keto ester *l*-**28** was condensed with methyl bromoacetate under the Reformatsky conditions employed by Bachmann, Cole, and Wilds.[61] The keto ester (175 mg) was dissolved in a mixture of 2.5 ml of anhydrous ether and 2.5 ml of dry benzene, 600 mg of acid-washed,[60] granulated zinc (30 mesh), and 0.25 ml of freshly distilled methyl bromoacetate were added. The mixture was heated under reflux in an atmosphere of dry nitrogen. Reaction was initiated by the introduction of a small crystal of iodine. After 45 min, additional portions of zinc (100 mg) and of methyl bromoacetate (0.1 ml) were added, and these additions were repeated at the end of a second 45-min interval. After a total reaction time of 3 hr, the mixture was cooled and diluted with 25 ml of ether containing 0.5 ml of acetic acid. The residual zinc was finally washed with an ether–methylene chloride mixture containing 0.5% of acetic acid, and the combined organic fractions were washed with water and dilute sodium hydroxide solution. After drying over anhydrous magnesium sulfate, the solvents were evaporated and the crude, crystalline product was recrystallized from ether–petroleum ether. Chromatography of the mother liquor afforded additional material which was combined with the main fraction. A final recrystallization gave a pure sample of lactonic ester **33**: 113 mg, mp 133–134°, $\lambda_{max}^{CS_2}$ 5.63 and 5.74 μ, $[\alpha]D$ +17° (*c* 1.0, chloroform).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.25; H, 9.27.

Preparation of Diacid 35. A solution of 131 mg of lactonic ester **33** in 10 ml of dry methanol was treated with a solution of sodium methoxide prepared from 0.1 g of sodium and 2 ml of methanol. After heating under reflux for 30 min (nitrogen atmosphere), the reaction mixture was concentrated to small volume, diluted with water, and acidified with acetic acid. Ether extraction afforded 131 mg of crude half-ester **34** which was hydrogenated directly over 75 mg of platinum oxide catalyst in 2 ml of acetic acid. The reduction product was then saponified by heating with 2 ml of 2 *N* methanolic sodium hydroxide for 1 hr. Dilution with water, acidification, and ether extraction afforded 91 mg of crude diacid. Recrystallization from aqueous methanol yielded analytically pure material: 52 mg, mp 204.5–205°, $\lambda_{max}^{CS_2}$ 5.87 μ, $[\alpha]D$ +7.2° (*c* 0.7, chloroform).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.96.

Conversion of Diacid 35 into Ketone 36. A 40-mg sample of diacid **35** in 4 ml of methanol and 1 ml of water was titrated with 0.15 *N* sodium hydroxide to the phenolphthalein end point. A solution of 39 mg of barium hydroxide octahydrate in 6 ml of water was then added, and after 30 min the precipitated barium salt was filtered, washed thoroughly with water, and dried in a vacuum desiccator. The resulting salt (50 mg) was then heated under a cold finger for 20 min at 420–440° (0.05 mm). The material that collected on the cold finger (22 mg) was crystallized from aqueous methanol: yield 16 mg, mp 133.5–134°, $\lambda_{max}^{CS_2}$ 5.76 μ, $[\alpha]D$ −36° (*c* 0.75, chloroform). A mixture melting point determination with a sample of ketone **36** prepared from phyllocladene by the method of Henderson and Hodges[41] (mp 132–133°, $[\alpha]D$ −33°) showed no depression, and the infrared absorption spectra of the two specimens were completely identical.

Preparation of Compound 37. The tetracyclic ketone **36** (94 mg) was dissolved in 30 ml of dry benzene containing 2 ml of freshly distilled ethyl formate. Sodium hydride (200 mg) was added, and the mixture was stirred at room temperature under nitrogen for 8 hr. The excess sodium hydride was then destroyed by the addition of a small quantity of methanol. Dilution with ether and extraction with water and cold, dilute sodium hydroxide solution furnished 88 mg of crude, base-soluble hydroxymethylene derivative, $\lambda_{max}^{CS_2}$ 5.85 and 5.97 μ, which was treated directly with 5 ml of 2-methyl-2-ethyl-1,3-dioxolane and 1 mg of *p*-toluenesulfonic acid.[42] After refluxing for 3.5 hr (nitrogen atmosphere), the bulk of the solvent was removed under reduced pressure. The product was finally taken up in ether and washed with dilute sodium hydroxide and water. After drying over anhydrous sodium sulfate, the ether was evaporated, and the residual material was chromatographed on alumina. In this way 39 mg of acetal **37** melting at 117–119° was obtained. Several recrystallizations from dilute methanol gave the sample for analysis, mp 124–125°, $\lambda_{max}^{CS_2}$ 5.78 μ, $[\alpha]D$ −17.7° (*c* 0.9, chloroform).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.45, 76.42; H, 9.89, 9.86.

Preparation of the α,β-Unsaturated Aldehyde 38. A solution of 18 mg of keto acetal **37** in 2 ml of anhydrous ether was added dropwise to a suspension of 30 mg of lithium aluminum hydride in 8 ml of dry ether. The mixture was stirred under nitrogen at room temperature for 5 hr, at the end of which time the excess reagent was destroyed with methanol. Dilute sulfuric acid was then added, and,

(61) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

after a period of 1 hr, the organic material was extracted with ether. Chromatography of the crude product (19 mg) on alumina furnished 8 mg of conjugated aldehyde **38**: mp 127–128°, $\lambda_{max}^{CS_2}$ 3.70 and 5.96 μ, $[\alpha]D$ −63.3° (*c* 0.6, chloroform). A mixture melting point with an authentic specimen,[41,43] mp 125–127°, $[\alpha]D$ −62.4°, was undepressed, and the infrared spectra of the two samples were identical.

Preparation of Alcohols 40 and 41. A sample of epoxide **39** (208 mg), obtained from isophyllocladene by a procedure closely similar to that employed by Henderson and Hodges,[41] was hydrogenated over 104 mg of platinum oxide catalyst in 3 ml of acetic acid. The catalyst was removed by filtration, and the filtrate was diluted with water and extracted with ether. The ether solution was then washed with dilute sodium hydroxide, dried, and evaporated. The oily residue (187 mg) obtained in this way was chromatographed on alumina. Elution with benzene–petroleum ether mixtures gave 26 mg of crude **41** which was recrystallized from aqueous methanol to constant melting point, 81–82°, $[\alpha]D$ −35° (*c* 0.6, chloroform).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.29; H, 11.51.

After several intermediate mixed chromatographic fractions a second alcohol (**40**), 86 mg, was eluted. The recrystallized (aqueous methanol) material melted at 114.5–115.5°, $[\alpha]D$ −6.6° (*c* 0.6, chloroform).

Anal. Found: C, 82.60; H, 11.79.

Oxidation of Alcohol 40. A solution of 57 mg of compound **40** in 1 ml of acetic acid was treated with 30 mg of chromium trioxide in a small amount of aqueous acetic acid. The reaction was allowed to proceed overnight at room temperature. Crystallization of the product from dilute methanol furnished a sample of ketone **42**: mp 103.5–104°, $\lambda_{max}^{CS_2}$ 5.78 μ (lit[41] mp 101–102°).

Preparation of Ketone 43. A 12-mg sample of alcohol **41** was oxidized by the procedure employed above. Crystallization from aqueous methanol gave ketone **43**: mp 120–121°, $\lambda_{max}^{CS_2}$ 5.78 μ (lit[41] mp 127.5–129°).

When 22 mg of ketone **42** was heated with 3 ml of 1% sodium methoxide solution for 3 hr, a sample of ketone **43** was obtained, mp 120–120.5°, that did not depress the melting point of material obtained by the procedure of the previous paragraph. The infrared spectra of the two specimens were identical.

Preparation of Alcohol 44. This substance was obtained by lithium aluminum hydride reduction of ketone **42**. The analytical sample melted at 104–105° (dilute methanol), $[\alpha]D$ +13.2° (*c* 0.75, chloroform).

Anal. Found: C, 82.57; H, 11.60.

Chromium trioxide oxidation regenerated ketone **42**.

Preparation of Alcohol 45. Lithium aluminum hydride reduction of **43** afforded a sample of alcohol **45**, mp 94–95°, reconvertible to ketone **43** by chromium trioxide oxidation.

Anal. Found: C, 82.42; H, 11.70.

Preparation of Amine 49. The oxime (46 mg), mp 176–178°, derived from phyllocladene norketone (**23**), was dissolved in 7 ml of isopropyl alcohol. The reaction mixture was heated under reflux for 3 hr, during which time small pieces of sodium wire were added. The excess sodium was finally destroyed by addition of ethanol and water, and the product was isolated by ether extraction. The organic layer was thoroughly washed with water and was dried over anhydrous magnesium sulfate. Evaporation of the solvent furnished 40 mg of amorphous amine which was separated from nonbasic contaminants by conversion into a crystalline hydrochloride. The purified amine regenerated from this salt was characterized as the N-acetyl derivative obtained by routine acetylation with acetic anhydride. The analytical sample melted at 217–218°, $\lambda_{max}^{CS_2}$ 5.98 μ.

Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.68; H, 11.11; N, 4.10.

Nitrous Acid Deamination of Amine 49. A solution of 93 mg of amine hydrochloride, obtained as described in the preceding experiment, in 3 ml of water and 3 ml of acetic acid was placed in a flask connected to a gas measuring buret, and the entire system was purged with nitrogen. Sodium nitrite (52 mg) was then added and the reaction mixture was stirred at room temperature. Although nitrogen evolution had essentially stopped after 2 hr, the reaction was allowed to proceed overnight in order to ensure completion. The solvent was removed under vacuum at 25°, and the product was taken into ether and washed successively with dilute sodium hydroxide, water, and saturated sodium chloride solution. Evaporation of the dried ethereal solution furnished 76 mg of oily product that showed both hydroxyl and acetate absorption in the infrared.

The crude product was subjected to ester cleavage by reaction with 100 mg of lithium aluminum hydride in 10 ml of anhydrous ether for 3 hr at room temperature. The excess lithium aluminum hydride was then destroyed with wet ether, and the product (40 mg) was isolated by extraction with ether and methylene chloride. The partially crystalline material obtained in this way showed no carbonyl absorption in the infrared.

In order to avoid problems of stereoisomerism, the total crude alcohol was oxidized (2.5 min) with 0.25 ml of the Jones reagent[62] in 3 ml of acetone. The crude oxidation product (37 mg) was finally chromatographed on alumina. Elution with petroleum ether afforded 4.7 mg of a substance which showed infrared absorption characteristics essentially identical with those of olefin **51**.[41] Material was unfortunately not available to permit direct comparison. Further elution with benzene–petroleum ether mixtures yielded successively 5.7 mg of ketone **36**, mp 129.5–131°, 15.5 mg of phyllocladene norketone (**23**), mp 100–101°, and 6.7 mg of an unidentified substance, mp 125–127°, $\lambda_{max}^{CS_2}$ 5.81 μ.

Sodium–Alcohol Reduction of Phyllocladene Norketone. A solution of 85 mg of phyllocladene norketone in 10 ml of ethanol was heated under reflux (nitrogen atmosphere) in the presence of excess sodium metal for 2.5 hr. When the sodium had finally dissolved the mixture was concentrated, diluted with water, and extracted with ether. The ethereal layer was washed with water, dried, and evaporated to yield 83 mg of crystalline residue. Chromatography on Florisil gave 58.5 mg of alcohol **53**, mp 152° (lit[41] mp 150–151.5°), and 17.5 mg of the corresponding epimer **52a**, mp 157° (lit[41] mp 156–157°).

Butoxide-Catalyzed Equilibration of Alcohol 53. Sodium metal (550 mg) was dissolved in 7 ml of *n*-butyl alcohol, and 55 mg of alcohol **53** in 3 ml of *n*-butyl alcohol was then added. The reaction mixture was then heated in an oil bath at 140° for 45 min. Chromatography (Florisil) of the product obtained in this way furnished 19 mg of unaltered starting material **53** and 32 mg of alcohol **52a**.

Acetolysis of Tosylate 52b. Alcohol **52a** (60 mg) in 1 ml of dry pyridine was treated with 120 mg of *p*-toluenesulfonyl chloride for 4 days at room temperature. The reaction mixture was processed in the usual way and afforded 90 mg of tosylate **52b** as a clear oil which showed no tendency to crystallize.

The crude tosylate in 2 ml of acetic acid (0.1 *M* in sodium acetate and 0.01 *M* in acetic anhydride) was sealed under nitrogen in an ampoule which was immersed in an oil bath at 49° for 48 hr. Dilution with water and extraction with ether gave 66 mg of material that showed insignificant absorption in the acetate region of the infrared. Addition of *n*-hexane caused the separation of 20 mg of crystals which appeared on the basis of nmr examination to be unreacted tosylate. The residual soluble fraction was identified as olefin **51** by infrared analysis.

The results of this preliminary experiment did not provide encouragement sufficient to warrant further study of the reaction.

(62) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).