

0.43 ml (0.0080 mole) of bromine in 25 ml of carbon tetrachloride added in portions over a period of 2 hr, with magnetic stirring. A few crystals of iodine were added at first, but very little hydrogen bromide evolution was observed. About 1 g of iron powder was then added in portions so that the evolution went at a good rate at 25°. After 4 hr the brown color gave way to the purple of iodine; the reaction was continued for 1 hr, giving a total time of 5 hr since the start of bromine addition. The solution was washed once with water, twice with aqueous potassium hydroxide, and twice more with water; evaporation gave 3.27 g of nearly colorless solids. Chromatography on 130 g of Merck 71707 basic alumina with 15% benzene in petroleum ether gave 3.20 g of a solid (not thoroughly dried) containing I and monobromojanusenes; elution with 40–95% benzene gave another 0.20 g of material, probably containing dibromojanusenes, as indicated by the infrared spectrum. Recrystallization of the former material from acetone–alcohol gave 1.55 g of the pure F_{β} isomer, mp 271–273°, and 1.03 g of solid. The latter was chromatographed on 150 g of Woelm Grade I neutral alumina using 5–10% benzene in petroleum ether; partial separation of I from monobromojanusenes was obtained, allowing most

of the I and another 0.3 g of pure F_{β} -bromojanusene to be harvested after recrystallization, giving a total of 1.88 g (52%) of the F_{β} isomer, mp 271–273°. The infrared spectrum of the F_{β} isomer (potassium bromide pellet) had a sharp band at 1408 cm^{-1} (m), an unsymmetrical doublet at 1058–1069 cm^{-1} (m), and a broad band at 800 cm^{-1} (m); these absorptions were the most useful in detecting this monobromo isomer in the presence of I or other monobromides in chromatography fractions. *Anal.* Calcd for $\text{C}_{30}\text{H}_{21}\text{Br}$: C, 78.09; H, 4.59. Found: C, 77.75; H, 4.37.

Further chromatography and recrystallization from acetone–alcohol allowed isolation of 10 mg of impure F_{α} -bromojanusene, mp 244–245°. The analysis below indicates that this isomer was probably contaminated with I. *Anal.* Calcd for $\text{C}_{30}\text{H}_{21}\text{Br}$: C, 78.09; H, 4.59. Found: C, 80.33; H, 5.07.

Acknowledgments. The authors are indebted to the National Science Foundation and to the Institute of General Medical Sciences (Public Health Service Grant GM-12139) for support of this work.

Total Synthesis of *dl*-Atisine^{1,2}

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Abstract: The first total synthesis of atisine in a racemic form is described. The synthesis of the pentacyclic compound **42c** having the fundamental skeleton of the alkaloid was achieved in a stereochemically unequivocal and highly selective manner starting from the tricyclic conjugated ketone **2**, implying that the suggested configuration of the atisine skeleton is substantiated synthetically. The new hydrocyanation reaction using alkylaluminum and hydrogen cyanide was successfully applied for building up both the A–E and C–D bridged ring system. The pentacyclic compound was further transformed by a three-step reaction sequence to the final compound **46**, which is connected with the six-step, partial synthesis of Pelletier in the natural series to complete the total synthesis of atisine.

The diterpene alkaloids widely distributed throughout the plant world have long been noted for their high toxic properties. In the past decade, the chemistry in this field has been markedly advanced despite the limited availability of the materials in quantity and complexity of the structures.³ Abundant evidence³ has been accumulated by the extensive degradative and synthetic work in support of the structure **1**⁴ suggested for the first representative aconite alkaloid, atisine. The stereochemistry^{3,5–9} of this

alkaloid, including the absolute configuration, has also been elucidated as depicted in the formula by interrelating the degradation products with those of the related diterpene alkaloids and diterpenes with some ambiguities remaining in points of the configuration^{3c,5,10,11} of the hydroxyl group at C-19 and of the conformation^{3c,d,5,10,12} of the E ring.¹³

Since the structure and configuration had been defined, total synthesis of atisine, because of its relative simplicity, has become a target of many synthetic organic chemists. The success is of importance also as a means of providing a definitive proof of the suggested formula **1**. The main difficulty for the synthesis was presumed to be in constructing two bridged ring systems, A–E and C–D, one of the bridge

(1) Studies on Total Syntheses of Diterpenes and Diterpene Alkaloids I.

(2) For a preliminary communication on this work see W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963). An outline of this work was also presented at the 3rd International Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 1964.

(3) For the reviews: (a) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, p 26; (b) E. S. Stern, "The Alkaloids, Chemistry and Physiology," Vol. VII, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1960, p 473; (c) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961); (d) S. W. Pelletier, *Experientia*, **20**, 1 (1964).

(4) K. Wiesner, R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. Ind. (London)*, 132 (1954); *J. Am. Chem. Soc.*, **76**, 6068 (1954).

(5) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **42**, 137 (1964); *Chem. Ind. (London)*, 623 (1958); see also references cited therein.

(6) R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962).

(7) H. Vorbrüggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

(8) (a) S. W. Pelletier, *ibid.*, **82**, 2398 (1960); (b) S. W. Pelletier and P. C. Parthasarathy, *ibid.*, **87**, 777 (1965); (c) S. W. Pelletier and D. M. Locke, *ibid.*, **87**, 761 (1965).

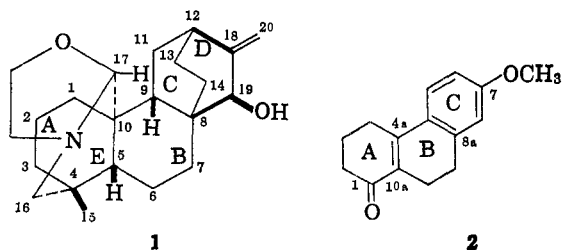
(9) A. J. Solo and S. W. Pelletier, *Chem. Ind. (London)*, 1108 (1960).

(10) W. B. Whalley, *Tetrahedron*, **18**, 43 (1962).

(11) Pelletier^{3c} and Whalley¹⁰ have proposed the 19 β configuration of the hydroxyl group on the basis of the fact that atisine is less strongly adsorbed on alumina than its 19 epimer. However, Dvornik and Edwards⁵ have considered this basis to be tenuous, although they showed other evidence which might lead to the same conclusion. We adopt this tentative assignment of the allylic hydroxyl group in the present paper.

(12) A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.*, 14 (1961).

(13) Argument on this point has been advanced. See ref 3c,d, 5, and 10. Our work, however, has no concern with this problem.



ends of each being located at the angular C-10 and C-8 position of the A-B-C tricyclic system. Thus the various pioneering works,¹⁴⁻²¹ which were published before or soon after our first successful² total synthesis of atisine, were directed to solving these difficulties. However, the approaches were confined to attainment of the tetracyclic skeletons only with either the A-E or C-D ring system. Syntheses of the partial skeleton of the A-B-C-E ring system were reported by ApSimon and Edwards,¹⁴ Iwai and his co-workers,¹⁵ and Findlay, *et al.*,¹⁶ and those of the A-B-C-D ring skeleton by Pelletier and Parthasarathy,¹⁷ Bell and Ireland,¹⁸ Zalkow and Girotra,¹⁹ Othman and Rogers,²⁰ and Ayer, *et al.*²¹

Recently, a new method for hydrocyanation using an alkylaluminum compound and hydrogen cyanide or a dialkylaluminum cyanide was found in this laboratory and has been proved to be quite useful, especially for introduction of a cyano group even into a highly hindered angular position of polycyclic ring systems.²² Since the cyano group thus introduced provides a suitable basis for construction of any of the bridged rings, it appeared highly promising to achieve the total synthesis of atisine or other diterpene alkaloids by applying this method. The synthesis was successful and represented the first total synthesis in the field of diterpene alkaloids. An outline of the work was already reported in a form of rapid communication in 1963,² and the present paper provides a full account of this work. After our publication, two successful syntheses have been reported by Masamune,²³ and Tahara and Hirao.²⁴

(14) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962); *cf.* W. L. Meyer and A. S. Levinson, *Proc. Chem. Soc.*, 15 (1963).

(15) (a) I. Iwai, A. Ogiso, and B. Shimizu, *Chem. Ind. (London)*, 1288 (1962); A. Ogiso, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull. (Tokyo)*, **11**, 770, 774 (1963); (b) I. Iwai and A. Ogiso, *Chem. Ind. (London)*, 1084 (1963); A. Ogiso and I. Iwai, *Chem. Pharm. Bull. (Tokyo)*, **12**, 820 (1964).

(16) J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 869 (1962); *cf.* R. W. Guthrie, A. Phillip, Z. Valenta, and K. Wiesner, *ibid.*, 2945 (1965).

(17) S. W. Pelletier and P. C. Parthasarathy, *ibid.*, 205 (1963).

(18) R. A. Bell and R. E. Ireland, *ibid.*, 269 (1963).

(19) (a) L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2037 (1963); **29**, 1299 (1964); *cf.* R. B. Turner, G. D. Diana, G. E. Fodor, K. Gebert, D. L. Simmons, A. S. Rao, O. Roos, and W. Wirth, *J. Am. Chem. Soc.*, **88**, 1786 (1966); (b) N. N. Girotra and L. N. Zalkow, *Tetrahedron*, **21**, 101 (1964); (c) L. H. Zalkow and N. N. Girotra, *Chem. Ind. (London)*, 704 (1964).

(20) A. A. Othman and N. A. J. Rogers, *Tetrahedron Letters*, 1339 (1963).

(21) W. A. Ayer, C. E. McDonald, and G. G. Iverach, *ibid.*, 1095 (1963).

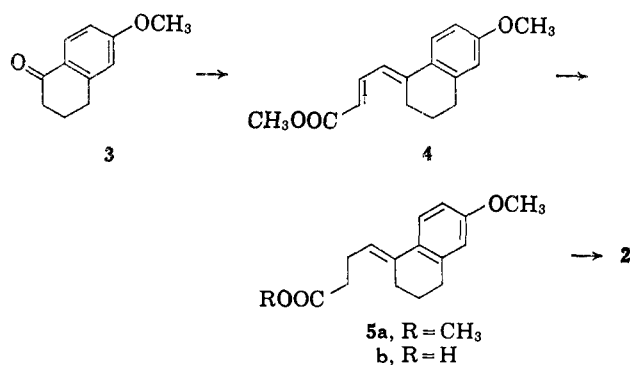
(22) (a) W. Nagata, M. Yoshioka, and S. Hirai, *ibid.*, 461 (1962); (b) W. Nagata, M. Yoshioka, and T. Okumura, *ibid.*, 847 (1966); (c) W. Nagata and M. Yoshioka, *ibid.*, 1913 (1966); (d) W. Nagata and M. Yoshioka, Proceedings of the 2nd International Congress on Hormonal Steroids, Milan, Italy, May 1966, Excerpta Medica Foundation, Amsterdam, 1966, in press. A full description of the work will be published soon.

(23) S. Masamune, *J. Am. Chem. Soc.*, **86**, 291 (1964).

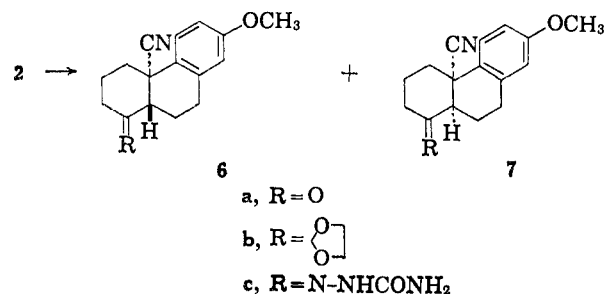
(24) A. Tahara and K. Hirao, *Tetrahedron Letters*, 1453 (1966); *cf.* A. Tahara, K. Hirao, and Y. Hamazaki, *Chem. Ind. (London)*, 850

As mentioned above, our synthesis was designed on the basis of a building principle that the angular cyano-²² should be most effectively utilized for construction of two bridged ring systems as a key reaction. With this principle in mind, the work was started from initial building up of the nitrogen-containing E ring on the A-B-C ground skeleton, followed by the construction of the C-D bridged ring system in the correct stereochemical manner, and was completed by introducing the desired functional groups into the D ring.

Synthesis of the A-B-C-E Ring System. Tricyclic conjugated ketone **2** was selected as the suitable starting material because the compound has a conjugated enone system needed for building up the E ring and also an anisole ring affording, after lithium-ammonia reduction, the same functional group suitable for construction of the D ring. This compound was already synthesized by Robinson and Schlittler,²⁵ Stork,²⁶ and Birch, *et al.*²⁷ We followed the Stork process consisting of the reaction sequence starting from 6-methoxy-1-tetralone (**3**). However, some improvements in the experimental conditions²⁸ were made for obtaining the material in quantity. Even at the



first step of the synthesis we encountered some difficulty. An attempted conjugate addition of a cyanide anion to the conjugated enone **2** by following the earlier method²⁹ using potassium cyanide and ammonium chloride in dimethylformamide failed, and the greater part of the starting enone remained unchanged. Application of the new hydrocyanation method²² using



(1965). Dr. Tahara's work consists of transformation of *l*-abietic acid to the optically active form of our tetracyclic intermediate **13a** and presents, therefore, a formal total synthesis. After completion of this manuscript we noted another successful synthesis of atisine reported by R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 4645 (1966).

(25) R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1288 (1935).

(26) G. Stork, *J. Am. Chem. Soc.*, **69**, 2936 (1947).

(27) A. J. Birch, H. Smith, and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957).

(28) See Experimental Section.

(29) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).

triethylaluminum and hydrogen cyanide gave a desired crude cyano ketone but only in low yield (11%).

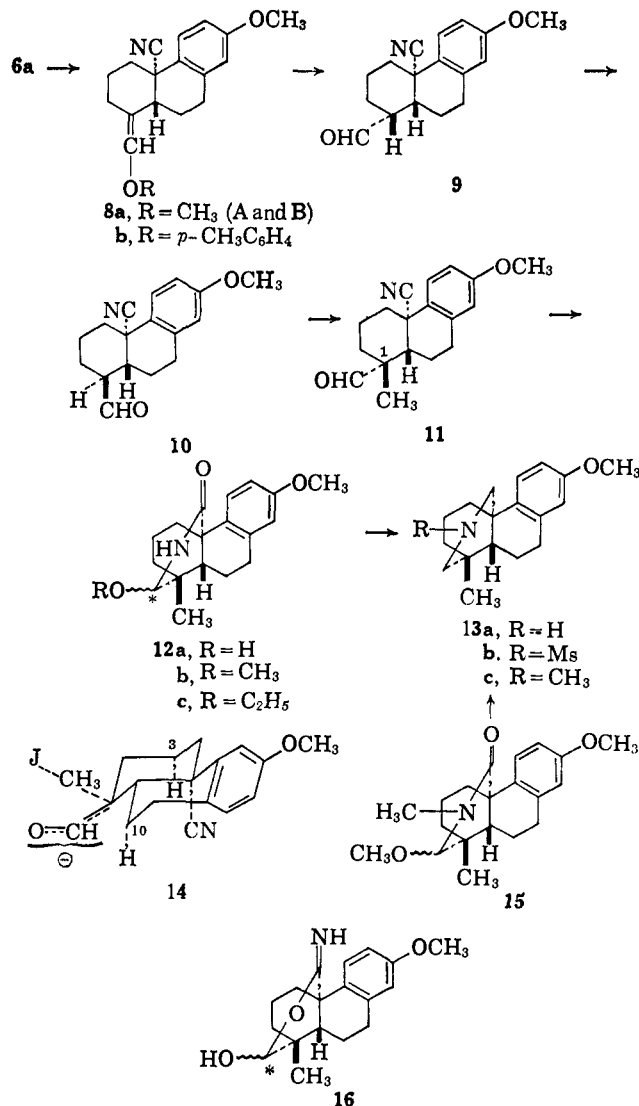
These unsatisfactory results indicated that the reagent system to be applied to this enone should be less basic and still efficient, because the **4a** carbon atom is not sufficiently electrophilic owing to electron supply from the adjacent anisole ring and moreover a base-induced reverse reaction of the products **6a** and **7a** to the starting enone **2** will occur with increased facility in this case through an additional conjugation of the double bond with the aromatic ring. Therefore, less basic diethylaluminum chloride was substituted for triethylaluminum. As expected, hydrocyanation of **2** with the former reagent and hydrogen cyanide in tetrahydrofuran at room temperature was quite successful and gave a crystalline mixture of *trans*- and *cis*-cyano ketone **6a**³⁰ and **7a** in 72–75% yield. While the pure *trans* isomer, mp 148–150°, could be obtained by direct crystallization of the initially formed mixture, the *cis* isomer could not be obtained in a pure form at the initial attempt. The residue enriched with the latter was, therefore, ketalized in a usual manner giving a pure sample of the *cis*-cyano ketal **7b**, mp 165.5–167°, from which the pure *cis*-cyano ketone **7a**, mp 134–135°, was obtained by mild acid hydrolysis. With the pure samples in hand it also became possible to separate both isomers by fractional crystallization through a semicarbazone mixture. Both isomers were found to be convertible without any serious epimerization at 10a into the corresponding ethylene ketal derivatives, **6b** and **7b**, which were then returned to the original cyano ketones quite safely by treatment with aqueous acetic acid.

The configurational assignment of both cyano ketones **6a** and **7a** was based upon the following evidence. The relative rates of lithium aluminum hydride reduction of the ethylene ketal derivatives,³¹ **6b** and **7b**, were determined³² and found to be roughly 1 and 8 for **6b** and **7b**. The more difficultly reduced isomer **6b** should be *trans* and another isomer **7b** should be *cis* on the ground that a cyano group axial to both the A and B ring in the *trans* isomer should suffer more slowly from the nucleophilic attack than a cyano group equatorial to the A or B ring in the *cis* isomer.²⁹ The second proof was furnished by comparison of the cyano band intensities in the cyano ketones, **6a** and **7a**, in the infrared. The method, discovered in our laboratory and believed to be quite reliable, is based upon the fact that an ϵ value observed for an axial cyano group on a frozen cyclohexane ring as well as on its condensed ring system is generally smaller than that for an equatorial one.³³ From the ϵ values of 17.4 for **6a** and 24.2 for **7a** measured in chloroform solution, the former was assigned the *trans* form and the latter the *cis*.

After the configurations of both cyano ketones were clarified, conversion of the *cis* isomer into the

desired *trans* isomer was attempted. Owing to less solubility of the latter compound in acetone, the problem was readily solved as follows. After isolation of the *trans* isomer **6a** by direct crystallization of a crude isomeric mixture from acetone, the mother liquor, enriched with the *cis* isomer **6b**, was refluxed briefly in the presence of hydrochloric acid giving a solution of an approximately 1:1 equilibrium mixture³⁴ of both isomers. An additional crop of the *trans* isomer was obtained from this solution, and repetition of the process finally afforded the *trans* isomer as the sole product in 92–94% yield.

As the desired *trans*-cyano ketone **6a** became thus available in quantity, we next aimed at elaboration of another bridge end of the E ring of the alkaloid. For this purpose, homologation and subsequent methylation at the C-1 position were undertaken. The *trans*-cyano ketone **6a** was treated with methoxymethyl-triphenylphosphorane³⁵ giving a mixture of two geo-



(30) All the formulas in this paper are represented in the racemic forms, unless otherwise specified.

(31) Because of the facile elimination of hydrocyanic acid, a comparison of alkaline hydrolysis rates using the cyano ketones **6a** and **7a** was considered not to be suitable.

(32) Since the ethylene ketal derivatives **6b** and **7b** resist strongly alkaline hydrolysis, the lithium aluminum hydride reduction was selected for comparison.

(33) W. Nagata, M. Yoshioka, M. Narisada, and H. Watanabe, *Tetrahedron Letters*, 3133 (1964). Further studies confirming the conclusion is now in progress and will be published soon.

(34) In a separate experiment an equilibrium mixture obtained by refluxing a dioxane solution of each isomer in the presence of hydrochloric acid was determined to be composed of the *trans* and the *cis* isomer in roughly a 1:1 ratio. The determination was carried out using the characteristic band at 1370 cm⁻¹ of the *trans*-cyano ketone in the infrared. Birch, *et al.*,²⁷ reported the ratio of 4:1 for the *trans* and the *cis* isomer in an equilibrium solution of the corresponding descyano analogs.

(35) S. G. Levine, *J. Am. Chem. Soc.*, **80**, 6150 (1958); G. Wittig and E. Knauss, *Angew. Chem.*, **71**, 127 (1959).

ethylene glycol dimethyl ether) to complete the reduction. The yield amounted to about 86% from both starting materials. The secondary amine **13a** was then converted smoothly into the N-mesyl derivative **13b** of mp 143–144° and the N-methyl derivative **13c** of mp 85–86° with methanesulfonyl chloride in pyridine and with methyl iodide, respectively. The latter compound was identified with a sample synthesized by Iwai, *et al.*, by a different route.^{15,42}

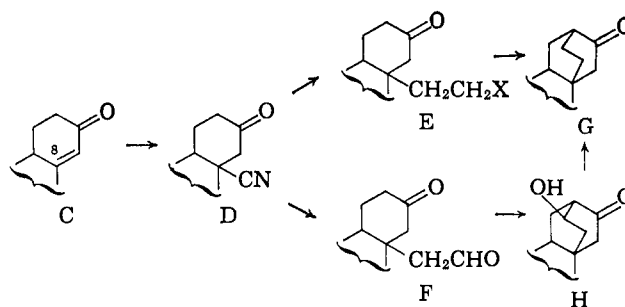
The secondary anisole amine **13a** underwent lithium-ammonia reduction in the presence of *t*-butyl alcohol⁴³ to afford the crystalline dienol ether **17a** in 83% yield. The base was acylated either with mesyl chloride in the presence of alkali or with acetic anhydride in pyridine giving the N-mesyl or the N-acetyl dienol ether **17b** or **c**. Both **17b** and **c** were converted by acid treatment into the corresponding N-acyl α,β -unsaturated ketones **18a**, mp 200–202°, and **18b**, mp 162–164°, in good yields. The hydrochloric acid treatment produced an equilibrium mixture of the conjugated enone **18a** and the nonconjugated enone **19** in preponderance of the former. Therefore, after isolation of the conjugated ketone **18a**, repeated treatment of the mother liquor with aqueous hydrochloric acid was needed for raising its yield.²⁸ On the other hand the nonconjugated enone **19**, mp 150–152°, was prepared by treatment of **17** with oxalic acid in 81% yield and converted likewise into **18a**. The N-mesyl anisole amine **13b** was also subjected to lithium-ammonia reduction in the presence of ethanol,⁴⁴ affording in 88% yield the demesylated dienol ether **17a** which likewise was converted into **18a** by remesylation and subsequent acid treatment. In one experiment under similar reduction conditions, we observed formation of the nondemesylated dienol ether **17b**, which was confirmed by transformation to the conjugated ketone **18a**. The over-all yield was 59%. This selective reduction process was considered to be highly advantageous when the alternative route described later was adopted for the synthesis. Unfortunately, however, this result was found to be unreproducible after some examination. Configurational assignment of the newly produced asymmetric carbon-9 of the compound **18** as depicted in the formula was based upon the well-accepted view that in such a thermodynamically controlled process, an alternative *trans,syn,trans* configuration can be safely eliminated because of its enormously high energy arising from a boat conformation of ring B. The first objective, to synthesize the A-B-C-E ring system containing the piperidine ring of the alkaloid, was thus achieved. The 76 and 36% over-all yield of the N-mesyl conjugated ketone **18a** from the crystalline mixture of **12a** and **b**, and from the *trans*-cyano ketone **6a** through four and eight steps, respectively, was attained by working without purification of the intermediates. The yields are quite excellent, indicating high uniformity and stereoselectivity of the reactions used. Of the two acylamides, the N-mesyl derivative **18a** was found to be more advantageous for further elaboration be-

cause of its good crystallizability and stability in the later reactions (*vide infra*).

The alternative route leading to the N-mesyl conjugated ketone **18a** via the N-mesyl anisole amine **13b** is now discussed. The starting methyl cyano aldehyde **11** was reduced with a large excess of lithium aluminum hydride in boiling tetrahydrofuran, giving the primary amino alcohol **20a** of mp 138–139.5, 149–150° in 67% yield, which was converted into the dimesyl derivative **20b** by mesylation. In this reduction initial attack of the reagent was presumed to take place at the tertiary formyl group giving an alkoxide which, on its participation in the angular cyano group and subsequent reduction, was converted into a 1,5-epoxide such as **21a** as an intermediate. This view was supported by formation of this compound, isolated as its N-mesyl derivative **21b**, when milder reduction conditions were employed.²⁸ The structure of the latter compound was evidenced by transformation to the N,O-dimesyl derivative **20b** via the ring-opened product **20c** by reduction with lithium aluminum hydride and subsequent mesylation. The dimesyl derivative **20b** was cyclized to the desired product **13b** by refluxing a dimethylformamide solution in the presence of potassium carbonate in excellent yield. Although the over-all yield of the key compound **18a** through this alternative route was comparably good, the first route was judged superior to the second one in that the intermediate lactamols **12a** and their alkyl ethers **12b** and **c** are easier to be worked up because of their high crystallizability as mentioned above.

Synthesis of the C-D Bridged Ring System. Building up the C-D bridged system was our second objective. As a favorable approach to this subject starting from the enone **18a** or **b** we selected a general plan shown in Scheme I. The first step is again to introduce a cyano group into the angular position producing a cyano ketone D and the second is to convert the cyano

Scheme I



group thus introduced into a β -functionalized ethyl group such as $\text{CH}_2\text{CH}_2\text{X}$ (X represents an appropriate leaving group) or CH_2CHO yielding E or F. The compound E or F is finally cyclized to form a desired bicyclo[2.2.2]octane ring system. That in this case our hydrocyanation method²² would give a *trans*-cyano ketone preponderantly was anticipated, but was subject to examination. Apparently the first route is not adequate when a cyano ketone D with the B-C *cis* juncture is a predominant product. Therefore the choice of the first $\text{D} \rightarrow \text{E} \rightarrow \text{G}$ or the second route $\text{D} \rightarrow \text{F} \rightarrow \text{H} \rightarrow \text{G}$ should depend upon the configuration of the cyano group in D. Before putting the plan into execution we made some model experiments using steroids and succeeded in building up the desired

(42) We are very grateful to Dr. Iwai for sending us the physical data of this compound.

(43) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(44) (a) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953); (b) W. S. Johnson, B. Bannister, and R. Pappo, *ibid.*, **78**, 6331 (1956).

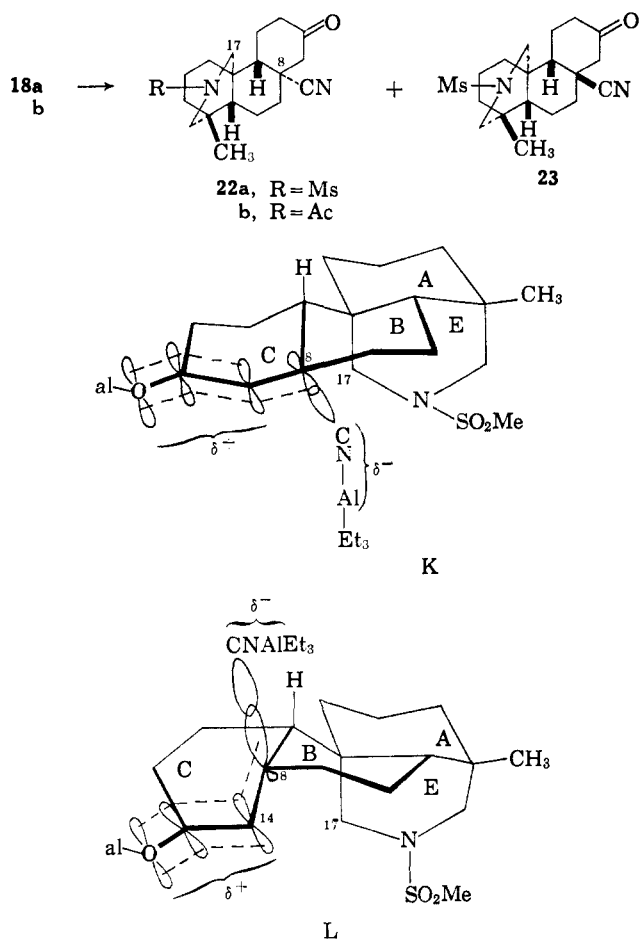


Figure 1.

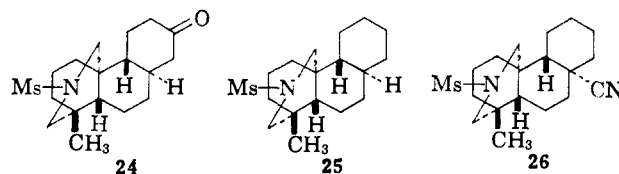
bicyclo[2.2.2]octane ring system on the A ring starting from 5 α -cyanocholestan-3-one.⁴⁵

With informations obtained in the model experiments in hand, hydrocyanation of the N-mesyl conjugated ketones **18a** and **b** was undertaken. Treatment of **18a** with excess of hydrogen cyanide and triethylaluminum in tetrahydrofuran at room temperature gave the cyano ketone **22a**, mp 222–223.5°, in 60% yield together with a small amount of the isomer **23**, mp 209–211°. At first insight it appears likely that in this case attack of a cyanide anion at the C-8 trigonal carbon would take place from the less hindered β side and give a *cis* isomer predominantly. However transition states deciding steric course of the reaction are believed to be different from the reactant and rather near the product depicted as **K** and **L** leading to the *trans* and the *cis* isomer, respectively (Figure 1). In **K**, a 1,3-diaxial interaction between the entering cyano group and the C-17 methylene is not considered to be serious as suggested by the small conformational energy⁴⁶ of a cyano group on a cyclohexane ring. On the other hand, 1,3-diaxial interaction between the C-14 methine and the C-17 methylene in **L** seems to be rather serious. Moreover, an additional large energy arising from the ring C boat conformation, brought about by keeping maximum overlap of the cyan-

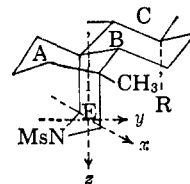
(45) The study on construction of the bridged ring systems related to the diterpene alkaloids using steroids will be reported separately.

(46) The conformational energy of 0.15–0.25 kcal/mole has been allotted to a cyano group: B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4606 (1962); N. L. Allinger and W. Szkrybalo, *ibid.*, **27**, 4601 (1962).

ide anion with the developing p orbital of the C-8 carbon from the β side, will make the transition state **L** more unstable than **K**. In accordance with this view, the major product was proved to be the *trans* isomer **22a** from the following evidence. The ϵ values of 12.1 and 20.0 of the band intensity of the cyano group were obtained for the major and the minor products, **22a** and **23**, respectively. According to the rule,³³ configuration of the cyano ketone with a smaller value was assigned as *trans* and that with a larger value as *cis*. Other evidence is based upon the dipole moment determination for each isomer. The values of 6.32 and 5.20 D. were obtained for the major and the minor products **22a** and **23**. Calculation of the dipole moment of the *trans*- and the *cis*-cyano ketone was made using Dreiding models on the assumption that both molecules possess all-chair conformation. The group moments of the keto and the cyano group, 3.06⁴⁷ and 3.70 D., used for calculation were obtained from cholestan-3-one and 5 α -cyanocholestan-3-one, respectively. For determination of the group moment of the methanesulfonylamino group in the E ring, the following three compounds, **24**, **25**, and **26**, served as reference. The ketone **24** was prepared from the enone **18a** by lithium-



ammonia reduction followed by remesylation and oxidation, and the desoxy compound **25** was obtained by Wolff-Kishner reduction of **24**. The B-C *trans* juncture in **24** and therefore in **25** can be deduced from the mode⁴⁸ of their formation. The compound **26** was prepared from the cyano ketone **22a** in question by Wolff-Kishner reduction and the B-C juncture of **26** was, therefore, at the moment unknown. Using the values of the dipole moments of 4.89, 4.86, and 6.13 D. obtained for the compounds **24**, **25**, and **26**, the group moment of the methanesulfonylamino group was calculated to give either imaginary roots or real values⁴⁹



depending upon the *cis* and *trans* fusion of the B-C ring of compound **26**. Obtaining the imaginary roots indicates that the assumption of the B-C *cis* junction is wrong. Using the real values we obtained the dipole moments of 6.73 and 6.12 D. for the *trans*- and the *cis*-cyano ketone, respectively. When some conformational change of the C ring from an ideal chair to a flattened chair or a twist form in the *cis*-cyano ketone arising from marked interactions between

(47) Cf. N. L. Allinger, J. G. D. Carpenter, and M. A. DaRooge, *ibid.*, **30**, 1423 (1965).

(48) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

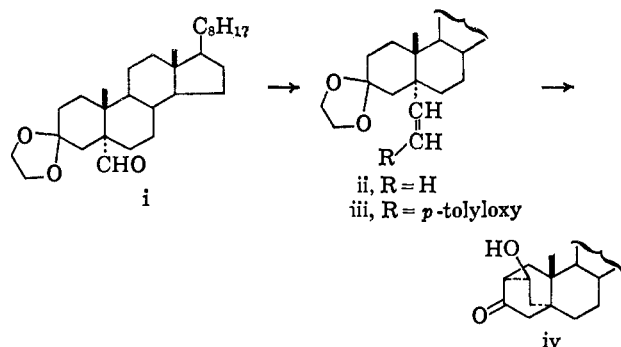
(49) The x, y, and z components [$\mu_{\text{MsN}}(x, y, z)$] obtained on assumption of the B-C *trans* junction of **26** are either -4.771, 0.925, and 0.0361 D. or 3.187, -3.670, and 0.0361 D., respectively, where the Cartesian axes are taken as depicted in the figure.

the C-17 and the C-12 as well as the C-14 methylene is taken into account (see Figure 2), the bond moment of the carbonyl group becomes parallel to the z axis giving a smaller value of 5.31 D. for the *cis*-cyano ketone, in better accordance with the observed value.⁶⁰ Comparison of the observed and the calculated values led to the same assignment as obtained by the study of the infrared band intensities. The N-acetyl conjugated ketone **18b** was likewise hydrocyanated giving the cyano ketone **22b**, mp 198–200°, in 28% yield. Assignment of *trans* configuration to this compound is based upon analogy with the case of the N-mesyl analog.

The next step is to convert the highly hindered cyano group into the β -functionalized ethyl group. One of the difficulties encountered in the present synthesis was this conversion. Various attempts using 5 α -cyanocholestan-3-one,⁴⁵ for instance, application of the Arndt-Eistert process to the corresponding angular carboxylic acid and of the Wittig reaction to the aldehyde, failed.⁵¹ Haworth, *et al.*,⁵² reported a successful conversion of an angular cyano group into a methyl ketone in a bicyclic system by treatment with methyl-lithium. Although it was not known whether the method was applicable also to a more rigid tetracyclic system, the same reaction was examined with the cyano ketal **27a** derived in good yield from the cyano ketone **22a** and found to be successful. On prolonged treatment with methyl-lithium at 13–14°, compound **27a** was converted into the methyl ketimine **28a**, which without isolation was treated with aqueous sulfuric acid giving the diketone **29a**, mp 228–230°, in 46% yield. Transportation of the oxygen of the methyl ketone side chain from the α to the β position was a problem. In view of the fact that an angular functional group of neopentyl type strongly resists an intermolecular reaction and in contrast undergoes an intramolecular one with great facility, it was considered to be wise to carry out the transformation with the help of a neighboring

(50) The calculated values of 8.42 and 6.84 D. for the *trans*- and *cis*-cyano ketone reported in a preliminary communication² were obtained by assuming a model with a freely rotating sulfonyl group on tetrahedral nitrogen. In this case the group moments of 4.44 and 0.79 D. for dimethyl sulfone and triethylamine were used for calculation.

(51) After completion of this work we reexamined the Wittig reaction of 5 α -formylcholestan-3-one (i) and succeeded in obtaining the desired olefins ii and iii in good yield. The failure in the initial attempt is probably due to incorrectly settled experimental conditions. Compound iii was converted into the bicyclo[2.2.2]octane iv by treatment with perchloric acid (see ref 45). The success opens a new way to the synthesis of



the atisine C–D ring. Refer also to compound **36** in the text. A successful olefination of the C-19 oxo steroids has been reported: O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963); J. A. Edwards, M. C. Calzada, L. C. Ibanez, and A. Bowers, *Steroids*, 6, 371 (1965).

(52) R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rodgers, *J. Chem. Soc.*, 2720 (1962).

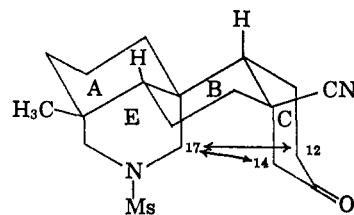
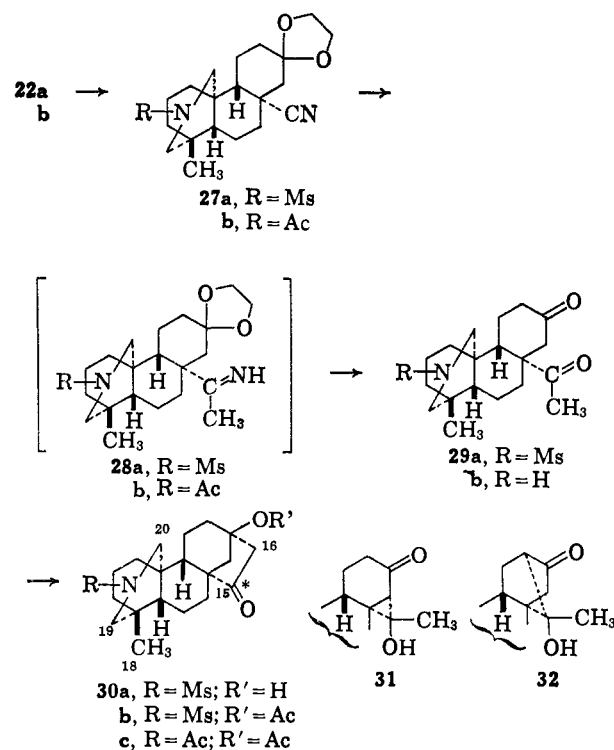
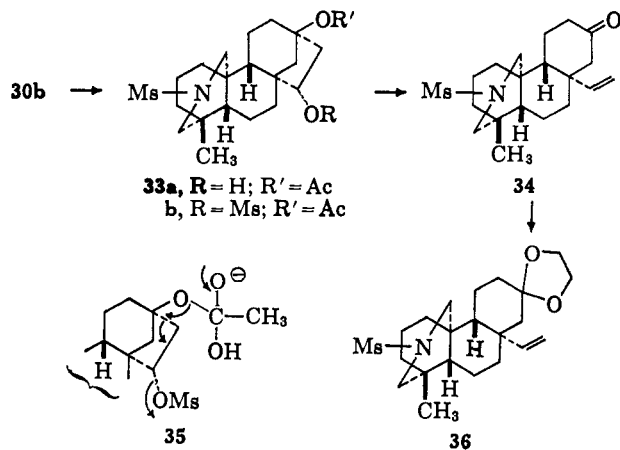


Figure 2.

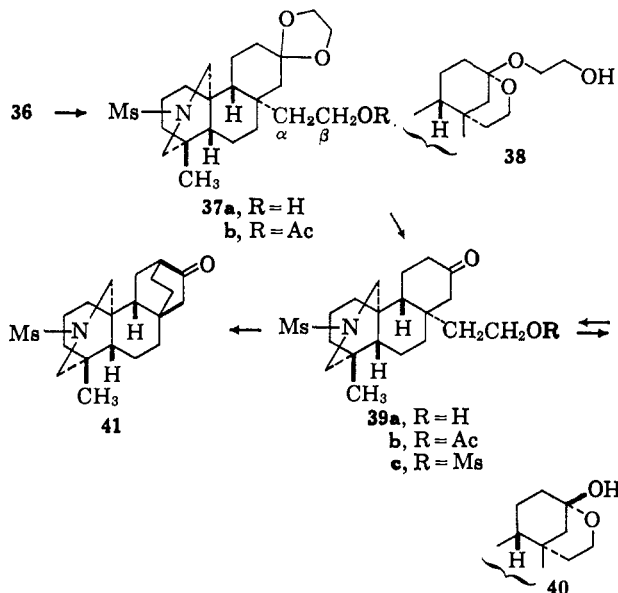
group. Thus the diketone **29a** was readily cyclized with dilute alkali to the hydroxy ketone **30a** with a ring system of the phyllocladene type.⁵² The other possible ring systems, **31** and **32**, could be excluded by the absence of an additional methyl group in the nmr spectrum and the presence of the band at 1732 cm^{-1} owing to the five-membered ring ketone in the infrared. The same conversions were done in the N-acetyl series. Compound **22b** was first ketalized to compound **27b** which was transformed to the acetoxy ketone **30c** *via* the amorphous diketone **29b** by successive treatment with methyl-lithium, aqueous sulfuric acid, dilute alkali, and acetic anhydride in pyridine. Throughout the transformation the yields were low, and the route using the N-acetyl derivatives was, therefore, abandoned.



Synthesis of the compound of type E in Scheme I from the hydroxy ketone **30a** was not difficult when a fragmentation reaction was applied. The hydroxy ketone **30a** was acetylated by heating a pyridine solution with acetic anhydride to give the acetoxy ketone **30b** which was then reduced with sodium borohydride. The *endo* configuration of the hydroxy group of the resulting 1,3-diol monoacetate **33a**, mp 206–207°, was based on analogy with the model experiment⁴⁵ and on the principle of *exo* attack of the reagent. The diol monoacetate **33a** was treated with methanesulfonyl chloride and pyridine to give the acetoxy mesylate **33b**, mp 237–238°. This compound was led success-

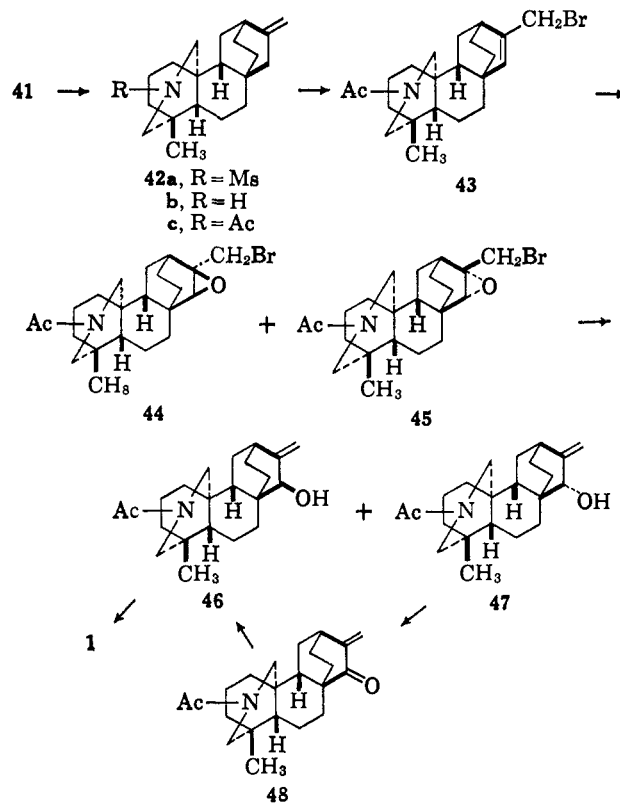


fully not only to *dl*-atisine, but also to garryine and veatchine⁵³ and, therefore, is the important common intermediate for our total synthesis of both types of alkaloids. The compound **33b** was now subjected to fragmentation.⁵⁴ Refluxing a methanolic dioxane solution of **33b** with aqueous potassium hydroxide gave, in excellent yield, the vinyl ketone **34**, mp 207–209°. The fragmentation reaction was sensitive to the solvent polarity, and it was observed in the model experiment⁴⁵ that in a more polar solvent, the reaction appeared not to proceed in a concerted manner and produced a considerable amount of undesired substitution and 1,2-elimination products.⁵⁴ The fragmentation is considered to be of a 1,6 type as illustrated in **35**, and the major driving force of this facile reaction is apparently the release of both compression of the highly hindered mesyloxy group and strain of the bridged ring system. The vinyl ketone **34** was then ketalized to give the vinyl ketal **36**, mp 196–197°. The 75% over-all yield of this compound from the diketone **29a** through six steps is excellent. Hydroboration and subsequent oxidation of the vinyl ketal **36** afforded the hydroxy ketal **37a**, mp 190–193°, in 80% yield. No α -hydroxy isomer was



formed as expected. A possible alternative structure such as **38** for this compound is eliminated by the fact that the acetyl group of its acetate **37b** was not removed on mild hydrolysis with aqueous acetic acid giving the acetoxy ketone **39b**. Acid hydrolysis of **37a** gave the keto alcohol **39a**. Although this compound exists in equilibrium with the bridged form **40** as judged by the weak intensity of the carbonyl band in the infrared, **39a** gave the keto mesylate **39c** as a sole product on mesylation. Cyclization of this compound to the desired pentacyclic ketone **41**, mp 183–185°, was effected by treatment with potassium *t*-butoxide. The over-all yield was 54% from the vinyl ketal **36** through four steps. Construction of the skeleton of the alkaloid was now accomplished.

Introduction of the Allyl Alcohol Function into the D Ring. The final stage of the present synthesis is to introduce the allyl alcohol function into the D ring. Again a model experiment using steroids⁴⁵ indicated a suitable route to the final goal. Olefination of the pentacyclic ketone **41** with methylenetriphenylphosphorane gave the *exo* olefin **42a**, mp 127–128°, in 73% yield. For connecting our final compound to the Pelletier compound **46**⁵⁵ it is necessary to change the



protecting group from mesyl to acetyl. Birch reduction of **42a** removed smoothly the mesyl group giving the secondary base **42b**, mp 78–81°, hydrochloride mp 126–129°, which was then converted into the N-acetyl derivative **42c**, 152.5–153°, in 86% over-all yield. Facile migration of an *exo* double bond into an *endo* position by various acidic or radical reagents was already known in the chemistry of the related natural products.^{3,56} Thus, Wohl-Ziegler bromination of the

(53) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Am. Chem. Soc.*, **89**, 1499 (1967). For the preliminary communication, see W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Am. Chem. Soc.*, **86**, 929 (1964).

(54) C. A. Grob, *Experientia*, **13**, 126 (1957).

(55) (a) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, 1339 (1963). We are very grateful to Professor S. W. Pelletier for authentic samples of the natural compounds, **46**, **47**, and **48**, a copy of the paper prior to publication, and kind discussions. (b) S. W. Pelletier, *Chem. Ind. (London)*, 1116 (1958).

olefin **42c** using N-bromosuccinimide in carbon tetrachloride in the presence of a trace of benzoyl peroxide afforded mainly the rearranged allylic bromide **43**. The migration of the double bond was judged by disappearance of the characteristic vinyl band at 880 cm^{-1} . The crude product was then subjected to epoxidation to give a mixture of the β and the α epoxides **44** and **45**, which was treated with zinc in boiling ethanol. Alumina chromatography of the crude product afforded, besides 28% of the recovered starting olefin **42c**, the desired allylic alcohol **46** and the epimer **47** in 14 and 10% yields, respectively, based upon the consumed starting material. Assignment of the configuration of the hydroxyl group at C-19 of each epimer was made based upon the polarity on alumina according to Pelletier's view.¹¹ The ratio of each epimer indicates the formation of the epimeric epoxides in about equal amount. The lower yield of 24% compared with the model experiment,⁴⁵ where a 53% over-all yield was obtained, may partly be ascribable to some loss of the acetamino group during the three-step reaction sequence. Pure samples of **46**, mp 198–199°, and **47**, mp 198–200°, obtained by further careful purification were proved to be the racemic forms of the naturally derived materials⁵⁵ by the complete identity of both the infrared spectra and the thin layer chromatograms. The 19 α -hydroxy compound **47** was oxidized with chromic anhydride in pyridine to give the conjugated enone **48** melting at 160–168°, $\lambda_{\text{max}}^{\text{EtOH}}$ 208 m μ (ϵ 13,100), 232 m μ (shoulder). The complete identity of the infrared and the ultraviolet spectra as well as the thin layer chromatogram of this enone with those of an authentic sample of the optically active compound⁵⁵ again established the suggested configuration of the skeleton of atisine. Since reconversion of the enone to the allylic 19 β -alcohol **46** and its epimer **47** and transformation of the former to atisine in the natural series have already been performed by Pelletier and co-workers^{55,57} through six steps, the present work represents a stereoselective total synthesis of *dl*-atisine.

Experimental Section

All melting points were measured on a Kofler hot-stage apparatus and are corrected. Unless otherwise stated, ultraviolet spectra were taken in 95% ethanol with a Hitachi EPS-2 spectrophotometer and infrared spectra in chloroform by use of a Koken DS-201B spectrophotometer. All nmr spectra were taken on deuterated chloroform solutions with a Varian A-60 spectrometer. Unless otherwise specified, the extracts were dried on anhydrous sodium sulfate and column chromatography was performed according to the method reported by Reichstein and Shoppee⁵⁸ using Woelm alumina (activity II).

Methyl γ -(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotionate (4). A mixture of 360 g of granulated zinc, cleaned and dried as described in the literature,²⁶ and 19 g of dry mercuric chloride in 450 ml of anhydrous benzene was vigorously stirred under nitrogen for 80 min. To the stirred mixture was added at once a solution of 360 g of 6-methoxy-1-tetralone (**3**) and 350 g of methyl γ -bromocrotionate, bp 80–92° (13 mm), in a mixture of 250 ml of anhydrous benzene and 500 ml of anhydrous ether, and the resulting mixture was refluxed under stirring. After 20 min, 180 g of zinc and 113 g of bromo ester were added twice at 20-min intervals and 90 min later an additional 90 g of zinc and 113 g of bromo ester were added. After being refluxed for 180 min, the reaction mixture was cooled,

acidified with a mixture of 265 ml of acetic acid and 450 g of ice-water, and extracted with ether. The organic layer was washed with 3 *N* sodium hydroxide and with saturated salt solution and dried, and the solvent was evaporated to give an oily residue, which was distilled under reduced pressure to afford 185 g (51%) of unchanged **2**, bp 140–160° (0.9–1.0 mm), and 245 g (46%) of conjugated ester **4**, bp 181–185° (0.9–1.0 mm) [lit.²⁶ bp 182–188° (1.3 mm)] (96% yield based on the consumed **2**).

γ -(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric Acid (5b). A mixture of 211 g (0.82 mole) of conjugated ester **4** in 910 ml of pure dioxane and 62 ml (37 g) of Raney nickel (W-2) was shaken with hydrogen at atmospheric pressure and at room temperature to absorb 0.86 mole of hydrogen. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 215 g of syrup, which showed an ultraviolet maxima at 265 m μ ($\log \epsilon$ 4.1) and 330 m μ ($\log \epsilon$ 2.4). The crude ester **5a** in 2.5 l. of methanol was mixed with a solution of 420 g of potassium bicarbonate in 1.1 l. of water, and the mixture was refluxed under nitrogen for 7 hr, concentrated under reduced pressure, diluted with ice-water, and extracted with ether to remove neutral substances. The alkaline aqueous layers were combined, acidified with 380 ml of concentrated hydrochloric acid, and extracted with ether. The ether solution was washed with water and dried, and the ether was evaporated. The resulting residue was recrystallized from ether-petroleum ether to afford 111.4 g of acid **5b**, mp 79–79.5°, and 41.4 g of the second crop, mp 74–76° (76% from **4**).

1,2,3,4,9,10-Hexahydro-7-methoxy-1-oxophenanthrene (2). A solution of 172.5 g of γ -(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid (**5b**) in 1980 ml of glacial acetic acid and 496 ml of acetic anhydride was mixed with a solution of 33.3 g of fused zinc chloride in 991 ml of glacial acetic acid, and the resulting solution was refluxed under nitrogen for 2.5 hr to afford a brown-red solution. To the solution was added 777 ml of methanol with cooling. After removal of the solvent under reduced pressure, the residue was treated with 1.8 l. of 10% sodium hydroxide solution at 70° for 0.5 hr. The mixture was cooled and extracted with ether-chloroform (5:1). The organic layer was washed with water and dried, and the solvent was evaporated. The residue was recrystallized from ether to afford 102.1 g of enone **2**, mp 73.5–75.5° (lit.²⁶ mp 75–76°), and 3.6 g as the second crop, mp 68–74°, in a yield of 66%.

Hydrocyanation of 1,2,3,4,9,10-Hexahydro-7-methoxy-1-oxophenanthrene (2). a. **With Triethylaluminum and Hydrogen Cyanide.** To a solution of triethylaluminum (163 mg, 1.43 mmoles) in 1.16 ml of dry tetrahydrofuran was added a solution of hydrogen cyanide (30 mg, 1.1 mmoles) in 1.80 ml of absolute tetrahydrofuran in a nitrogen atmosphere under ice cooling. The solution was added to a solution of conjugated ketone **2** (136.9 mg, 0.64 mmole) in 2.0 ml of dry tetrahydrofuran in a nitrogen atmosphere under ice cooling. The mixture, in a stoppered flask, was kept at room temperature for 42 hr, treated with a small volume of methanol, acidified with 2 *N* hydrochloric acid, and extracted with ether. The ether solution was washed with water and dried. After removal of the solvent, the residue was purified by silica gel chromatography. The fractions eluted with benzene-chloroform-ethyl acetate (4.5:4.5:1) gave 16.7 mg (11%) of crude material of *trans*-cyano ketone **6a**, mp 119–133°, which showed a similar infrared spectrum with that of pure *trans*-cyano ketone **6a** described in the case of b.

b. **With Diethylaluminum Chloride and Hydrogen Cyanide.** To a solution of conjugated ketone **2** (43.7 g, 0.192 mole) in 280 ml of dry tetrahydrofuran was added slowly a tetrahydrofuran solution of hydrogen cyanide-diethylaluminum chloride, prepared by a gradual addition of a solution of hydrogen cyanide (36.2 ml, 0.958 mole) in 250 ml of dry tetrahydrofuran to a solution of diethylaluminum chloride (161.5 g, 1.34 moles) in 376 ml of dry tetrahydrofuran, at 0° under ice cooling in a nitrogen atmosphere. The resulting mixture was allowed to stand at room temperature in a reaction flask fitted with a mercury trap. After 45 hr, the mixture was cautiously poured into ice-water (10.5 kg) containing sodium hydroxide (148 g, 2 molar equiv of diethylaluminum chloride and 1 molar equiv of hydrogen cyanide) with vigorous stirring under ice cooling in a period of 5 min and, after being stirred for 5 min, the mixture was extracted with a mixture of chloroform and ether (3:1). The organic layers were washed with water and dried, and the solvent was evaporated under reduced pressure. The residue (53 g) gave a crystalline mixture of cyano ketones **6a** and **7a** (23.9 g) on recrystallization from acetone. The mother liquor was treated with semicarbazide hydrochloride and sodium acetate in the usual way to give a crystalline mixture of semicarbazones of **6a** and **7a** (21 g), mp 219–225°, which were refluxed with 3 *N* hydro-

(56) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *J. Chem. Soc.*, 1850 (1962).

(57) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, **78**, 4144 (1956).

(58) T. Reichstein and C. W. Shoppee, *Discussions Faraday Soc.*, 305 (1949).

chloric acid (790 ml) in benzene (206 ml) with vigorous stirring for 2 hr. Extraction with chloroform and the subsequent recrystallization of the residue (19.1 g) gave the additional mixture of cyano ketones (14.42 g). The combined crystalline mixture of cyano ketones (36.3 g, 75%), on recrystallization from acetone, gave (\pm)-4 α -cyano-7-methoxy-1,2,3,4,4a,9,10,10a-10 α -octahydro-1-oxophenanthrene (6a, 9.3 g), mp 151.5–154.5°. The mother liquor was concentrated under reduced pressure and dissolved in 180 ml of acetone and 15 ml of 1 *N* hydrochloric acid, and the resulting solution was refluxed for 20 min. After concentration of the solution under reduced pressure, *trans*-cyano ketone 6a was crystallized from the solution. The crystals were filtered off, and the filtrate was concentrated to give an additional crop of 6a. Repetition of this procedure afforded totally 24.2 g of 6a, mp 149–155°. The total yield was 33.5 g (68.6%). A sample melting at 148–150° was analyzed, ν_{\max} 2237 and 1724 cm^{-1} , $\epsilon_{\text{C}=\text{N}}$ 17.4.

Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{N}$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.74; H, 6.68; N, 5.49.

Semicarbazone 6c was prepared in the usual manner and recrystallized from chloroform–methanol, mp 235–237° dec, ν_{\max} 3502, 3374, 3172, 2228, 1680, and 1609 cm^{-1} .

Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{N}_4$: C, 65.36; H, 6.45; N, 17.94. Found: C, 65.17; H, 6.41; N, 17.84.

In another experiment, 4 α -cyano-7-methoxy-1,2,3,4,4a,9,10,10a-10 α -octahydro-1-oxophenanthrene (7a), mp 134–135°, was obtained besides 6a (37%) by fractional recrystallization of a mixture of cyano ketones from acetone in a yield of 5%. An analytical sample melting at 130–132° showed ν_{\max} at 2228 and 1714 cm^{-1} , $\epsilon_{\text{C}=\text{N}}$ 24.2.

Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{N}$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.81; H, 6.82; N, 5.47.

Semicarbazone 7c was prepared in the usual manner and recrystallized from chloroform–methanol, mp 232–234° dec, ν_{\max} 3263, 2239, 1693, 1614, 1576, and 1497 cm^{-1} .

Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{N}_4$: C, 65.36; H, 6.45; N, 17.94. Found: C, 65.00; H, 6.37; N, 17.97.

Ketalization of *trans*-Cyano Ketone 6a. The *trans*-cyano ketone 6a (600 mg) was dissolved in 30 ml of anhydrous benzene containing 0.78 ml of ethylene glycol and 30 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was gently refluxed for 4.5 hr under removal of water formed as an azeotropic distillate. The usual work-up and recrystallization of the crude product from acetone–ether afforded 237 mg (48%) of *trans*-cyano ketal 6b, mp 160–163°. A sample melting at 157–158.5° was analyzed, ν_{\max} 2239 and 1100 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{O}_3\text{N}$: C, 72.21; H, 7.06; N, 4.68. Found: C, 72.40; H, 7.22; N, 4.63.

The *trans*-cyano ketal (188 mg) was deketalized by heating in 75% acetic acid at 100° for 0.5 hr to give 88 mg (55%) of *trans*-cyano ketone 6a, mp 155–157°, which was identified with the authentic sample described above.

Ketalization of *cis*-Cyano Ketone 7a. *cis*-Cyano ketone 7a (43 mg) was ketalized in the same manner described above to give 34 mg (67%) of *cis*-cyano ketal 7b melting at 169–170° on recrystallization from acetone. A sample melting at 164–166.5° was analyzed, ν_{\max} 2248 and 1088 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{O}_3\text{N}$: C, 72.21; H, 7.06; N, 4.68. Found: C, 72.36; H, 7.16; N, 4.50.

The *cis*-cyano ketone ketal (39 mg) was deketalized in the same way as described above to give 30 mg (70%) of *cis*-cyano ketone 7a, mp 130–132°, which was identified with the authentic sample described above.

Reduction Rate of the *cis*- and the *trans*-Cyano Ketal with Lithium Aluminum Hydride. *trans*-Cyano ketone ketal 6b (57 mg, 0.19 mmole) was dissolved in 65 ml of 0.058 *M* tetrahydrofuran solution of lithium aluminum hydride maintained at $10 \pm 1^\circ$. Each aliquot (about 15 ml) of the reaction solution was taken out after 14, 30, and 62 min, destroyed with a tartrate–tartaric acid solution, and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated under reduced pressure to dryness. The amount of the unconsumed cyano ketal for each aliquot was calculated from the band intensity of the $\text{C}\equiv\text{N}$ stretching vibration in chloroform in the infrared spectrum. In the same manner, *cis*-cyano ketone ketal 7b (63 mg) was treated with 65 ml of 0.058 *M* tetrahydrofuran solution of lithium aluminum hydride at $10 \pm 1^\circ$. The obtained data are shown in Table I.

(\pm)-4 α -Cyano-7-methoxy-1-methoxymethylene-1,2,3,4,4a,9,10,10a-10 α -octahydrophenanthrene (8a). To a vigorously stirred suspension of methoxymethyltriphenylphosphonium chloride (8.05 g, 23.6 mmoles) in 50 ml of absolute ether was added dropwise 7.35

Table I. Reduction Rate of the Cyano Ketals with Lithium Aluminum Hydride

Reaction time, min	Percentage of the recovered cyano ketone ketal	
	<i>trans</i> -6b	<i>cis</i> -7b
14	78	13
30	70	5
62	48	5

ml of 1.6 *N* hexane solution of butyllithium (11.7 mmoles) at -10° within 3 min under nitrogen. The reaction mixture was kept at -3° for 20 min and then cooled to -30° . To this mixture a solution of 1.5 g of *trans*-cyano ketone 6a (5.86 mmoles) in 50 ml of dry tetrahydrofuran was added dropwise within 3 min. The temperature was raised to -20° , and the mixture was stirred for 60 min at -20 to -25° under nitrogen. The reaction mixture was poured onto ice–water and extracted with ether–methylene chloride (3:1). The organic layer was washed twice with a saturated salt solution, dried, and evaporated to give 4.12 g of an oily residue. The residue was chromatographed on alumina to remove phosphor compounds. The fractions eluted with petroleum ether–benzene (9:1 ~ 4:1) were combined (2.19 g) and again chromatographed on alumina giving 167 mg of 8a-A and 106 mg of 8a-B from fractions eluted with petroleum ether–benzene (19:1) and with petroleum ether–benzene (9:1 ~ 2:1), respectively. A pure sample of 8a-A melts at 97–99° (from methanol), ν_{\max} 2225 and 1679 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{N}$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.55; H, 7.59; N, 5.02.

A pure sample of 8a-B melts at 156–157° (from methanol), ν_{\max} 2232 and 1683 cm^{-1} .

Anal. Found: C, 76.21; H, 7.37; N, 5.09.

(\pm)-4 α -Cyano-1 α -formyl-7-methoxy-1,2,3,4,4a,9,10,10a-10 α -octahydrophenanthrene (9). **a.** From 8a-A. A solution of 30.4 g of methoxymethylene derivative (8a-A) in 1 ml of tetrahydrofuran containing 0.25 ml of 30% perchloric acid was allowed to stand at room temperature for 80 min. The reaction mixture was poured onto ice–water and extracted with methylene chloride. The organic layer was washed with water, dried, and evaporated under reduced pressure to give 28.4 mg of an oily residue. Preparative thin layer chromatography of this residue gave crude 9 (16 mg) together with a trace amount of 10 (0.8 mg) and unchanged starting 8a-A (3.8 mg). Repeated crystallization of the crude 9 from acetone–ether gave a pure sample of 9 melting at 110–112° (3 mg), ν_{\max} 2753, 2221, and 1721 cm^{-1} .

Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.92; H, 7.17; N, 5.20.

b. From 8a-B. A solution of 30.9 mg of 8a-B in 1 ml of tetrahydrofuran containing 0.25 ml of 30% perchloric acid was treated similarly. Working up as described in a gave 27.3 mg of crude 9. This product gave after two crystallizations from acetone–ether 2 mg of a pure sample of 9 melting at 110–112°, which was proved to be identical with an authentic sample obtained in a. Another crop of 9 melting at 109–112° (1.8 mg) was yielded by two crystallizations of fractions (14.3 mg) obtained from preparative thin layer chromatography of the mother liquor together with 1.2 mg of unchanged 8a-B.

c. Directly from *trans*-Cyano Ketone 6a. A solution of 1.5 g (5.86 mmoles) of *trans*-cyano ketone 6a in 50 ml of anhydrous tetrahydrofuran was treated with an ethereal solution of methoxymethylenetriphenylphosphorane, prepared from 8.05 g of methoxymethyltriphenylphosphonium chloride (23.6 mmoles) and 7.35 ml of 1.6 *N* hexane solution of butyllithium (11.74 mmoles) in the same manner as described above. Work-up of the reaction mixture in a similar manner gave 1.66 g of a crystalline mixture of two geometrical isomers of methoxymethylene derivative 8a. This mixture was dissolved in 22 ml of tetrahydrofuran and treated with 5.5 ml of 30% perchloric acid at room temperature for 3.5 hr. Work-up in a similar way to that described in a or b gave 1.42 g of crude 9, which was crystallized from acetone–ether to yield 755 mg of cyano aldehyde 9, mp 99–104°, and 132 mg of the second crop, mp 95–102° (56% total yield). A pure sample was obtained by further recrystallization and melted at 110–112°, identical with the authentic sample obtained in a or b.

(\pm)-4 α -Cyano-1 β -formyl-7-methoxy-1,2,3,4,4a,9,10,10a-10 α -octahydrophenanthrene (10). **a.** Epimerization of the 1 α -Formyl Derivative 9 to the 1 β -Formyl Derivative 10. A solution of 287 mg

of 1 α -formyl derivative **9** in 16 ml of methanol was treated with 1.6 ml of 2 *N* sodium hydroxide at room temperature under nitrogen for 1 hr. The reaction mixture was poured into a saturated salt solution and extracted with methylene chloride. The organic layer was washed with a salt solution and dried. Removal of the solvent afforded 280 mg of a residue which was crystallized from acetone-ether to give 142 mg of the 1 β -formyl derivative **10** melting at 137–138°. The second (68 mg, mp 135–136.5°) and the third crops (39 mg, mp 129–133°) were obtained from the mother liquor (82% total yield). Further crystallization gave a pure sample of **10** melting at 138–140°, ν_{\max} 2732, 2222, and 1712 cm⁻¹.

Anal. Calcd for C₁₇H₁₉O₂N: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.76; H, 7.12; N, 5.17.

b. *Via* (\pm)-4 α -Cyano-7-methoxy-1-*p*-tolylloxymethylene-1,2,3,4,4a,9,10,10a-10 β -octahydrophenanthrene (**8b**). To a suspension of *p*-tolylloxymethyltriphenylphosphonium chloride (16.4 g, 39.2 mmoles) in 115 ml of dry ether, cooled at -35 to -40°, was added 24 ml of 1.39 *N* ethereal solution of butyllithium with stirring under dry nitrogen. The resulting mixture was warmed to 0° and stirred at the temperature for 15 min. To the red ylide solution, cooled again to -40°, was added dropwise a solution of *trans*-cyano ketone **6a** (5.00 g, 19.6 mmoles) in 100 ml of dry tetrahydrofuran during 2 min. The mixture was stirred at -40° for 30 min, poured onto ice-water, and extracted with ether. The ethereal solution was washed with water and dried and the ether was removed under reduced pressure to give the residue (15.2 g). The residue containing *p*-tolylloxymethylene **6** was suspended in a mixture of 150 ml of ether, 30 ml of benzene, and 58 ml of 60% perchloric acid and heated for 90 min at 70–80°. After cautious neutralization with 20 g of sodium carbonate under ice cooling, the products were extracted with ether. The ether solution was washed successively with 2 *N* sodium hydroxide and water and dried. The ether was evaporated under reduced pressure to give the crystalline mixture (14.2 g). In order to effect isolation of the aldehyde, the crude material was dissolved in 100 ml of ether and 50 ml of ethanol and shaken with 100 ml of 20% sodium bisulfite solution at room temperature for 30 min to precipitate the sodium bisulfite adduct (about 5 g), which was filtered off. The filtrate was again shaken with 20% sodium bisulfite solution, and the aqueous layer was washed with ether. This aqueous layer and the sodium bisulfite adduct described above were combined and mixed with 16 g of sodium hydroxide under ice cooling. The mixture was stirred at room temperature for 30 min to decompose the adduct and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was distilled off under reduced pressure to afford 3.65 g (69%) of the crude aldehyde **9** as a crystalline residue, which on recrystallization from acetone gave plates (3.257 g, 63%), mp 138–140°. This was proved to be identical with an authentic sample obtained in a.

In another experiment, a mixture of two geometrical isomers of *p*-tolylloxymethylene derivative **8b** was chromatographed on alumina. Elution with light petroleum ether-benzene (9:1 to 3:1) gave 445 mg (75%) of crude **8a**, which, on repeated recrystallizations from chloroform-methanol, gave pure *p*-tolylloxymethylene derivative, mp 161–167°. This showed one spot on the thin layer chromatogram, ν_{\max} 2225 and 1679 cm⁻¹.

Anal. Calcd for C₂₄H₂₅O₂N: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.43; H, 7.08; N, 4.05.

Methylation of (\pm)-4 α -Cyano-1 β -formyl-7-methoxy-1,2,3,4,4a,9,10,10a-10 β -octahydrophenanthrene (10**).** Aldehyde **10** (1.503 g) was dissolved in a hot mixture of 19.0 ml of anhydrous benzene and 4.8 ml of anhydrous *t*-butyl alcohol, diluted with 33 ml of anhydrous *t*-butyl alcohol, cooled to 20°, and mixed with 1.39 ml of methyl iodide. To the stirred mixture was added dropwise 1.25 g of sublimed potassium *t*-butoxide in 25 ml of *t*-butyl alcohol at 21–22° under nitrogen over a period of 10 min. The mixture was stirred for 2.5 hr at 22°, poured into ice-water, and extracted with methylene chloride. The organic layers were washed with salt solution and dried. The solvent was evaporated under reduced pressure to afford 1.637 g of crystalline residue. Part of the residue (0.741 g) was chromatographed on neutral alumina (30 g). The eluates with petroleum ether-benzene (1:1 to 1:2) were recrystallized from acetone-ether to give 294 mg of aldehyde **11**, mp 165–166°, and 164 mg of the second crop, mp 158–161° (yield 65%). A sample melting at 163–164° was analyzed: ν_{\max} 2746, 2240, and 1726 cm⁻¹; nmr spectrum showed peaks at τ 0.02 and 0.05 (doublet, 1 H), 6.22 (singlet, 3 H), and 8.69 (singlet, 3 H).

Anal. Calcd for C₁₈H₂₁O₂N: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.02; H, 7.63; N, 4.82.

The eluates with benzene-methylene chloride (9:1 to 4:1) were

recrystallized from acetone to give 32 mg (4.5%) of **O,N**-dimethyl lactamol (**15**), mp 151–152°. A pure sample melts at 154–155°, ν_{\max} 1636 and 1612 cm⁻¹; nmr spectrum showed peaks at τ 6.27 (singlet, 3 H), 6.38 (singlet, 3 H), 7.12 (singlet, 3 H), and 8.83 (singlet, 3 H).

Anal. Calcd for C₂₀H₂₇O₃N: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.55; H, 8.21; N, 4.26.

The eluate with methylene chloride-methanol (9:1) was recrystallized from methylene chloride-methanol to give 27 mg (3.6%) of the lactamol **12a**, mp 213–214°, which was identified with an authentic sample described below.

In another run, 6.39 g of **10** was methylated in a similar way and work-up of the reaction mixture yielded 7.55 g of a crystalline residue. The residue was crystallized from acetone-ether to give 3.25 g of crude **11**, mp 140–148°, and 0.47 g of the second crop, mp 142–148°. Chromatography of the mother liquor gave an additional 1.4 g of crude **11** melting at 142–155°. The yield of the crude **11** was 76%. Several crystallizations from acetone-ether raised the melting point to 163–164°.

Hydrolysis of (\pm)-4 α -Cyano-1 α -formyl-7-methoxy-1 β -methyl-1,2,3,4,4a,10,10a-10 β -octahydrophenanthrene (11**).** a. **In Water.** A suspension of the methyl aldehyde **11** (98 mg) in 21 ml of 2 *N* sodium hydroxide was refluxed with stirring for 10 hr. Precipitates were collected by filtration, washed well with water, then with ethanol and ether, and dried to afford 78 mg (75%) of lactamol **12a**, mp 208–210°, which showed no band arising from the cyano or aldehyde group in its infrared spectrum. On recrystallization from methylene chloride-acetone, it afforded an analytical sample, mp 209–211°, $\nu_{\max}^{\text{Nalol}}$ 3501, 3217, and 1657 cm⁻¹; nmr spectrum showed peaks at τ 6.30 (singlet, 3 H; 13-methoxy) and 8.82 (singlet, 3 H; 15-methyl).

Anal. Calcd for C₁₈H₂₃O₃N: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.97; H, 8.02; N, 4.75.

b. **In Ethanol.** The methyl aldehyde **11** (42 mg) in 5 ml of 95% ethanol containing 500 mg of powdered potassium hydroxide was heated under reflux in a nitrogen atmosphere for 3 hr. The resulting mixture was diluted with water and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure. The residue (47 mg) was chromatographed on alumina (1.5 g). The fractions (19.2 mg) eluted with benzene-chloroform (9:1 to 2:1) were recrystallized from chloroform-ether to give a less polar lactam derivative (15 mg), mp 237–244°, which was identified with the ethoxy lactam **12c** described below. The further fractions (22.0 mg) eluted with chloroform and chloroform-methanol (49:1) were recrystallized from chloroform-ether to afford a more polar lactam derivative (19 mg), mp 208–210°, which was identified with the lactamol **12a** described above.

c. **In Methanol.** A solution of the crude methyl aldehyde **11** (15.20 g) in 575 ml of methanol and 87 ml of 6 *N* sodium hydroxide was refluxed under nitrogen for 4 hr. The reaction solution was concentrated under reduced pressure, diluted with ice-water, and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure. The crystalline residue obtained was recrystallized from chloroform-ether to give 11.79 g of a crystalline mixture (mp 188–212°) of the lactamol **12a** described above and methoxy lactam **12b**. The presence of the methoxy lactam **12b** in this product was shown by nmr signals at τ 8.90 (3 H, 15-methyl), 6.32 (3 H, 13-methoxy), 6.57 (0.42 H, 14% of an epimer of methoxy lactam), and 6.72 (1.17 H, 39% of another epimer of methoxy lactam).

Ethylation of Hydroxyl Lactam **12a.** A mixture of hydroxyl lactam **12a** (60 mg), 3 ml of dry benzene, 1 ml of absolute ethanol, 1 ml of dry chloroform, 1 ml of ethyl orthoformate, and 5 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr. After being cooled, the mixture was poured into 6 ml of 2 *N* sodium carbonate and extracted with chloroform. The chloroform solution was washed with a saturated sodium chloride solution and dried, and the chloroform was evaporated under reduced pressure to dryness. The residue was recrystallized from chloroform-ether to afford 45 mg (69%) of ethoxy lactam **12c**, mp 234–245°, ν_{\max} 3384 and 1660 cm⁻¹; nmr spectrum showed peaks at τ 6.25 (singlet, 3 H; 13-methoxy), 4.5 (multiplet, 2 H; -OCH₂), 8.80 (triplet, *J* = 7 cps, CH₂CH₃), 8.90 (weak, 15-methyl), and 8.91 (strong, 15-methyl). The sample showed one spot on a thin layer chromatogram and no spot corresponding to a starting material.

Anal. Calcd for C₂₀H₂₇O₃N: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.18; H, 8.00; N, 4.14.

Methylation of the Mixture of **12a and **b**.** A solution of the crystalline mixture of **12a** and **b** (4.14 g) described above in

methanol (15 ml) and chloroform (30 ml) was mixed with 38% of methanolic hydrogen chloride (75 ml), and the mixture was kept at room temperature for 23 hr. The mixture was diluted with ice-water and extracted with chloroform. The chloroform solution was washed and dried. After removal of the solvent, the residue was recrystallized from methylene chloride-ether to give 1.63 g (38%) of the crystalline methoxy lactam **12b**, mp 210–218°. A sample melting at 208–220° was analyzed, $\nu_{\max}^{\text{Nujol}}$ 3380 and 1662 cm^{-1} ; nmr spectrum showed peaks at τ 8.90 (3 H, 15-methyl), 6.73 (0.85 H, 28% of an epimer of methoxy lactam), 6.57 (2.15 H, 72% of another epimer of methoxy lactam), and 6.23 (3 H, 13-methoxy).

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{O}_3\text{N}$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.15; H, 7.90; N, 4.52.

Ethylation of the Mixture of 12a and b. A crystalline mixture composed of **12a** and **b** (2.585 g), 250 ml of dry benzene, 50 ml of absolute ethanol, 50 ml of dry chloroform, 100 ml of ethyl orthoformate, and 500 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr. After being cooled, the solution was poured into an excess of 2 *N* sodium carbonate solution and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure. On crystallization from chloroform-methanol, the residue gave 2.491 g of a crystalline product, mp 198–238°, which showed no spot attributable to lactamol **12a** and was found to be a mixture of methoxy lactam **12b** and ethoxy lactam **12c**. This material was used for preparation of anisole amine **13a** (see below).

(±)-16,17-Imino-13-methoxy-5 β ,10 α -podocarpene-8,11,13-triene (13a). a. To a solution of the crystalline mixture of **12b** and **c** (2.532 g) in 250 ml of anhydrous diglyme was added 1.9 g of lithium aluminum hydride, and the reaction mixture was heated at 110° with stirring under nitrogen. After 2.5 hr an additional 1.9 g of lithium aluminum hydride was added, and the solution was heated at the same temperature for 2 hr more. The excess of the reagent was decomposed by gradual addition of a mixture of 50 ml of tetrahydrofuran and 20 ml of water under ice cooling, and the precipitates were filtered off and washed three times with ether. The filtrate was diluted with water and extracted with the ether washings. The ethereal solution was washed with water and dried, and the ether was removed. The crystalline residue (2.18 g) on recrystallization from ether gave 1.650 g (86%) of anisole amine **13a**, mp 91–93°. The pure sample melts at 92–93°; the spectrum showed nmr peaks at τ 9.18 (3 H, 15- CH_3) and 6.23 (3 H, 13- OCH_3).

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{ON}$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.57; H, 9.35; N, 5.32.

The hydrochloride of **13a** was recrystallized from methanol, mp 274–275°.

Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{ONCl}$: C, 70.23; H, 8.84; N, 4.27. Found: C, 69.29; H, 8.51; N, 4.55.

b. To a stirred solution of the mixture of **12a** and **b** (28.30 g) in anhydrous diglyme (2.8 l.) was added lithium aluminum hydride (28.30 g) under nitrogen, and the mixture was heated with stirring at 100–110° under nitrogen for 2.5 hr. An additional amount (14.15 g) of the hydride was added to the mixture, which was stirred at 100–110° for 2.5 hr more. The diglyme was removed under reduced pressure [bp 63–67° (14–17 mm)]. Wet ether was gradually added to the concentrate at 0° to decompose excess reagent. The precipitates were filtered off and washed with ether. The filtrate and ether washings were combined, washed with water, and dried. The solvent was evaporated under reduced pressure to dryness to give 24.91 g (97%) of a crystalline residue, which showed an almost identical infrared spectrum with the authentic sample and without purification was employed for preparation of dienol ether amine **17a** (see below).

(±)-N-Mesyloxy-16,17-imino-13-methoxy-5 β ,10 α -podocarpene-8,11,13-triene (13b). a. By Cyclization of the O,N-Dimesyl Alcohol Amine **20b**. The O,N-dimesyl alcohol amine **20b** (1.497 g) in 10 ml of dimethylformamide was heated under reflux with 1.5 ml of 4% potassium carbonate for 3 hr. The resulting solution was concentrated under reduced pressure, diluted with water, and extracted with chloroform. The extract was washed with water and dried, and the chloroform was evaporated under reduced pressure. The residue was recrystallized from acetone-ether to afford 875 mg (75%) of the anisole mesyl amide **13b**, mp 143–145°, ν_{\max} 1337 and 1155 cm^{-1} .

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{O}_3\text{NS}$: C, 65.29; H, 7.79; N, 4.01. Found: C, 65.46; H, 7.95; N, 4.11.

b. **Mesylation of the Anisole Amine 13a.** To the anisole amine **13a** (1.834 g, 6.77 mmoles) in 45 ml of dry pyridine was added

1.1 ml (14 mmoles) of methanesulfonyl chloride at 0°, and the mixture was kept at room temperature overnight. A small amount of ice and water were added to decompose the excess of the reagent, and after standing for 1.5 hr at room temperature, the mixture was poured into ice-water and extracted with ether-chloroform (3:1). The organic solution was washed with 3 *N* hydrochloric acid and water and dried, and the solvent was distilled under reduced pressure to give a residue, which was filtered through an alumina column as a benzene solution. The residue of the filtrate was recrystallized from acetone-ether to afford 2.065 g (88%) of anisole mesyl amide **13b**, mp 141–143°. This was identified with the authentic sample of anisole mesyl amide **13b** described in a by a mixture melting point test and comparison of infrared spectra.

(±)-N-Methyl-16,17-imino-13-methoxy-5 β ,10 α -podocarpene-8,11,13-triene (13c). A solution of anisole amine **13a** (65 mg) in 2 ml of absolute ethanol, 2 ml of absolute methanol mixed with 1 ml of methyl iodide, and 100 mg of potassium carbonate was refluxed for 0.5 hr. The reaction mixture was cooled, diluted with ice-water, and extracted with a mixture of ether-methylene chloride (3:1). The organic layers were washed with water and dried. The residue (66 mg) obtained after removal of the solvent was crystallized from pentane to give 41 mg of N-methyl anisole amine **13c**, mp 85–87°; ν_{\max} 2793 cm^{-1} ; the nmr spectrum showed peaks at τ 9.13 (C- CH_3), 7.95 (N- CH_3), and 6.25 (O- CH_3).

Anal. Calcd for $\text{C}_{15}\text{H}_{27}\text{ON}$: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.95; H, 9.47; N, 4.96.

The picrate of **13c** melts at 229–230° with decomposition.

Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{O}_8\text{N}_4$: C, 58.36; H, 5.88; N, 10.89. Found: C, 58.38; H, 5.82; N, 10.47.

Reduction of O,N-Dimethyl Lactamol 15 with Lithium Aluminum Hydride. A mixture of the O,N-dimethyl lactamol **15** (50.2 mg) and lithium aluminum hydride (50 mg) in 5.0 ml of dry diglyme was heated at 100 \pm 3° with stirring under nitrogen. After 2 hr, an additional portion of lithium aluminum hydride (25 mg) was added, and the mixture was heated for 3.5 hr more with stirring. The mixture was cooled; the excess of the reagent was decomposed by addition of wet ether, and the precipitates were filtered off and washed with ether. The ether layer of the filtrate was separated, and the aqueous layer was extracted with the ether washings. All the ether extracts were combined and washed with water, and the solvent was evaporated well under reduced pressure. The residue was shaken with 6% tartaric acid solution to separate a basic product from a neutral one. The base (35 mg) obtained by the usual work-up was crystallized from ether to give 25 mg (58%) of N-methyl anisole amine **13c**, mp 84–85°, which was identified with an authentic sample described above by mixture melting point and comparison of infrared spectra.

(±)-16,17-Imino-13-methoxy-5 β ,10 α -podocarpene-8,12-diene (17a). To a stirred solution of 11.50 g (1.66 g-atoms) of lithium in 400 ml of liquid ammonia, distilled over sodium, was added dropwise a solution of crude anisole amine **13a** (5.750 g, 21.2 mmoles) in 142 ml of a 1:1 mixture of dry tetrahydrofuran and dry *t*-butyl alcohol at –60 to –70° over a period of 30 min and the resulting solution stirred at the same temperature for 2 hr. The excess of lithium was destroyed by addition of 150 ml of anhydrous methanol; the ammonia was distilled off, and, after dilution with water, the residue was extracted with ether. The ethereal solution was washed with water and dried, and the ether was evaporated under reduced pressure. The residue was recrystallized from ethanol to afford 4.722 g (83%) of dienol ether amine **17a**, mp 106–108°. An analytical sample melts at 117–118°; ν_{\max} 1695 and 1668 cm^{-1} .

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{ON}$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.20; H, 9.92; N, 5.22.

(±)-N-Mesyloxy-16,17-imino-13-methoxy-5 β ,10 α -podocarpene-8,12-diene (17b). To a solution of 12.70 g (46.5 mmoles) of crude dienol ether amine **17a** in 260 ml of tetrahydrofuran were added two solutions of 21 ml (272 mmoles) of methanesulfonyl chloride in 200 ml of tetrahydrofuran and 21 g (525 mmoles) of sodium hydroxide in 200 ml of water at the same rate over a period of 30 min under ice cooling with vigorous stirring. The mixture was stirred at room temperature for 1 hr, poured onto ice-water, and extracted with ether. The ethereal solution was washed with water and dried, and the ether was removed under reduced pressure to give 16.32 g of crude dienol ether mesyl amide **17b**, mp 152–160°. Recrystallization from acetone-ether gave a pure sample, mp 164–165°; ν_{\max} 1696, 1668, 1337, and 1155 cm^{-1} .

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{O}_3\text{SN}$: C, 64.92; H, 8.32; N, 3.99; S, 9.12. Found: C, 64.97; H, 8.39; N, 4.05; S, 9.11.

(±)-N-Acetyl-16,17-imino-13-methoxy-5 β ,10 α -podocarpene-8,12-diene (17c). A solution of dienol ether amine **17a** (199 mg) in 4

ml of pyridine was mixed with 2 ml of acetic anhydride, and the solution was allowed to stand at room temperature overnight. The usual work-up yielded 196 mg (85%) of dienol ether acetamide **17c**, recrystallized from methylene chloride-ether, mp 175–177°; ν_{\max} 1697, 1670, and 1630 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}$: C, 76.15; H, 9.27. Found: C, 75.94; H, 9.42.

(±)-**N-Mesyl-16,17-imino-5 β ,9 β ,10 α -podocarp-8(14)-en-13-one (18a)**. To a stirred and boiling solution of 15.97 g of crude dienol ether mesyl amide **17b** in 200 ml of tetrahydrofuran and 1 l. of methanol was added dropwise 240 ml of 4 *N* hydrochloric acid, and the mixture was stirred under reflux for 30 min, concentrated under reduced pressure, diluted with water, and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure to give a crystalline residue (14.95 g). Recrystallization from acetone-ether gave 8.50 g of conjugated ketone **18a**, mp 195–196°, and 1.05 g of the second crop contaminated with a small amount of unconjugated ketone **19**, mp 180–185°. The residue (5.80 g) of the mother liquor was treated again with 4 *N* hydrochloric acid in a similar manner, and the additional conjugated ketone **18a** (1.55 g), mp 195–196°, was obtained. Repetition of the procedure gave an additional crop of **18a** (0.80 g), mp 190–195°. The total yield was 11.9 g (78%). Recrystallization from acetone-ether gave a pure sample, mp 200–202°; ν_{\max} 1666, 1621, 1336, and 1147 cm^{-1} , λ_{\max} 234 $\text{m}\mu$ (ϵ 15,400).

Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3\text{NS}$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.00; H, 8.12; N, 4.15.

In one experiment, the conjugated ketone **18a** was obtained in 76% over-all yield from the mixture of lactamol **12a** and its methyl ether **12b** through four steps, when the intermediate conversions were carried out without purification of the products.

Reduction of the Anisole Mesyl Amide 13b with Lithium in Liquid Ammonia. a. To a solution of 3.5 g of lithium in 50 ml of liquid ammonia was added dropwise a solution of anisole mesyl amide **13b** (1.982 g) in 16 ml of dry tetrahydrofuran and 16 ml of absolute ethanol with stirring at –65° over a period of 30 min. After 5 min, 40 ml of absolute ethanol was added to the mixture over 10 min, and ammonia was evaporated off. The residue was diluted with water and extracted with ether. The ether solution was washed with water and dried, and the solvent was evaporated to afford 1.67 g of a residue, which on crystallization from ether-petroleum ether gave 1.145 g of the dienol ether amine **17a**, mp 112–117.5°, and 0.163 g of the second crop, mp 105–114°.

A pure sample was obtained by recrystallization of the first crop from methanol-ether, mp 117–118°. This sample was identified with the authentic one described above.

b. To a solution of 1.07 g of lithium in 13 ml of liquid ammonia was added dropwise 532 mg of anisole mesyl amide **13b** in 4 ml of dry tetrahydrofuran and 4 ml of absolute ethanol with stirring over a period of 30 min. After 5 min, 10 ml of absolute ethanol was added to the mixture over a period of 5 min, and then an additional 10 ml of absolute ethanol and 7.5 ml of methanol were added to the mixture. Ammonia was evaporated off and extracted with ether. Work-up in the usual way gave 546 mg of crude dienol ether mesyl amide **17b**, which showed infrared bands at 1338 and 1156 cm^{-1} ascribable to a mesyl amido group. A solution of this dienol ether mesyl amide **17b** in 5 ml of pure tetrahydrofuran and 15 ml of methanol was treated with 3 *N* HCl (7 ml) at reflux temperature for 1 hr. After being cooled, the mixture was diluted with water and extracted with chloroform. Work-up in the usual way gave 514 mg of a residue, which was crystallized from acetone-ether to give 301 mg (59%) of conjugated ketone **18a**, mp 192–196°, which was identified with an authentic sample described above.

(±)-**N-Acetyl-16,17-imino-5 β ,9 β ,10 α -podocarp-8(14)-en-13-one (18b)**. A solution of **17c** (154 mg) in 9 ml of methanol was refluxed with 2.4 ml of 4 *N* hydrochloric acid under nitrogen for 20 min, poured into ice-water, and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure to give 110 mg (73%) of acetyl enone **18b**, mp 161–164°, on crystallization from acetone-ether. Further recrystallization yielded a pure sample, mp 162–164°; ν_{\max} 1670 and 1630 cm^{-1} .

Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{O}_2\text{N}$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.73, H, 9.15; N, 4.52.

(±)-**N-Mesyl-16,17-imino-5 β ,10 α -podocarp-8-en-13-one (19)**. A mixture of a solution of the enol ether mesyl amide **17b** (112 mg) in 110 ml of ethanol and a solution of oxalic acid bishydrate (240 mg) in 0.30 ml of water was kept at room temperature for 65 min, poured into water, and extracted with ether. The ether solution

was washed several times with saturated sodium bicarbonate solution and then with water. The ether was evaporated, and the residue was crystallized from acetone-ether to give 87 mg (81%) of unconjugated enone **19**, mp 150–153°. A sample melting at 150–152° was analyzed; ν_{\max} 1715, 1339, and 1155 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3\text{SN}$: C, 64.07; H, 8.06; N, 4.15. Found: C, 64.23; H, 8.20; N, 4.21.

(±)-**4 α -Aminomethyl-1 α -hydroxymethyl-7-methoxy-1 β -methyl-1,2,3,4,4a,9,10,10a-10 β -octahydrophenanthrene (20a)**. To a solution of methyl aldehyde **11** (1.926 g) in 50 ml of dry tetrahydrofuran was added dropwise a solution of 2 g of lithium aluminum hydride in 50 ml of dry tetrahydrofuran with stirring over a period of 20 min. The resulting solution was heated under reflux with stirring for 2 hr. An additional 2 g of the reagent was added, and the reaction mixture was heated for 3 hr more. After being cooled, 23 ml of water was added under ice cooling to decompose the excess of the reagent, and the precipitates were filtered off and washed well with ether-chloroform. The filtrate was diluted with water and extracted with the organic washings. The organic solution was washed successively with water, 2 *N* hydrochloric acid, and water, and dried, and the solvent was distilled under reduced pressure to afford 233 mg of neutral substances. The acid washings were made alkaline with 2 *N* sodium hydroxide and extracted with chloroform-ether. The chloroform-ether solution was washed with water and dried, and the solvent was evaporated under reduced pressure to afford a basic product (1.76 g), which on crystallization from methylene chloride-ether afforded 1.428 g (67%) of the bisprimary alcohol amine **20a**, mp 127–138° (residue: 149°), as crude crystals. A pure sample melts at 138–139.5°, solidifies, and melts again at 149–150°; ν_{\max} 3649 and 3320 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_2\text{N}$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.79, H, 9.35; N, 4.76.

(±)-**N-Mesyl-17-amino-16,17-epoxy-13-methoxy-5 β ,10 α -podocarpene-8,11,13-triene (21b)**. Methyl aldehyde **11** (5.124 g) in 100 ml of dry tetrahydrofuran was mixed with a suspension of 4 g of lithium aluminum hydride in 100 ml of dry tetrahydrofuran. The mixture was refluxed with stirring for 2 hr. Work-up as described above gave 553 mg of a neutral and 3.90 g of a basic product. The basic product was crystallized from methanol-ether to afford 1.678 g (32%) of a crystalline mixture of bisprimary alcohol amine **20a** and 1,5 epoxide **21a**, mp 123–135°; 1.627 g of this mixture was mesylated in the usual way to give 2.47 g of a mesyl amide mixture **20b** and **21b**. This mixture was treated with potassium carbonate in dimethylformamide as described above to convert **20b** into cyclic anisol mesyl amide **13b**. The crude product was chromatographed on neutral alumina (60 g). The fractions eluted with petroleum ether-benzene (1:1) and benzene afforded 741 mg of cyclic anisol mesyl amide **13b** on crystallization from acetone. The eluates with benzene-chloroform (4:1) on recrystallization from acetone-ether gave 502 mg of 1,5-epoxide mesyl amide **21b**, mp 197–199°; ν_{\max} 3368, 1348, and 1157 cm^{-1} .

Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{O}_4\text{NS}$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.65; H, 7.56; N, 3.88.

Reduction of 21b with Lithium Aluminum Hydride. To a solution of 1.3 g of lithium aluminum hydride in 40 ml of dry tetrahydrofuran was added dropwise 634 mg of **21b** in 25 ml of dry tetrahydrofuran over a period of 10 min. The mixture was refluxed for 10 hr and an additional 600 mg of lithium aluminum hydride was added to the reaction mixture. After being refluxed further for 2 hr, the reaction mixture was cooled, and the excess of the reagent was decomposed by addition of 5.4 ml of water and extracted with methylene chloride. The solution was washed with water, dried, and evaporated to give 530 mg of a residue, which was recrystallized from acetone-ether to give 317 mg of *N*-mesyl bisprimary alcohol amine **20c**, mp 167–168.5°, and 93.4 mg of the second crop (total 65%), mp 164–168°. The first crop was analyzed.

Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{O}_4\text{NS}$: C, 62.10; H, 7.96; N, 3.81. Found: C, 62.23; H, 7.96; N, 3.87.

(±)-**4 α -Aminomethyl-1 α -hydroxymethyl-7-methoxy-1 β -methyl-1,2,3,4,4a,9,10,10a-10 β -octahydrophenanthrene O,N-Dimesyl Derivative (20b)**. a. Mesylation of the Bisprimary Alcohol Amine **20a**. The alcohol amine **20a** (346 mg, 1.21 mmoles) in 3.5 ml of dry pyridine was treated with 0.46 ml (6.0 mmoles) of methanesulfonyl chloride at room temperature overnight and work-up in the usual way gave 469 mg (87%) of *O,N*-dimesyl derivative **20b**, mp 147–149° (recrystallized from methanol-ether); ν_{\max} 3377, 1362, 1331, 1171, and 1153 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_6\text{NS}_2$: C, 53.92; H, 7.01; N, 3.14. Found: C, 54.18; H, 7.10; N, 3.08.

b. **Mesylation of 20c.** N-Mesyl derivative **20c** (351 mg) was mesylated with methanesulfonyl chloride and pyridine in the usual way. The residue obtained by the usual work-up was recrystallized from methanol-ether to give 408 mg (94%) of the O,N-dimesyl derivative **20b**, mp 147–149°. This was identified by comparison with an authentic sample described in a.

Hydrocyanation of Conjugated Ketone 18a. (\pm)-N-Mesyl-16,17-imino-8 α -cyano-5 β ,9 β ,10 α -podocarpan-13-one (**22a**) and (\pm)-N-Mesyl-16,17-imino-8 β -cyano-5 β ,9 β ,10 α -podocarpan-13-one (**23**). To a solution of 11.32 g, 35.5 mmoles, of conjugated ketone **18a**, contaminated with a small amount of unconjugated ketone **19**, in 320 ml of dry tetrahydrofuran was added under ice cooling a solution of hydrogen cyanide-triethylaluminum prepared by gradual mixing of a solution of hydrogen cyanide (3.94 ml, 0.104 mole) in 30 ml of dry tetrahydrofuran with an ice-cold solution of 23.6 ml (0.172 mole) of triethylaluminum in 120 ml of dry tetrahydrofuran. The mixture, placed in a reaction flask equipped with a mercury trap, was allowed to stand at room temperature for 48 hr. It was poured cautiously with vigorous stirring into a mixture of 17.9 g of sodium hydroxide and 4 kg of ice and water and extracted with chloroform-ether (4:1). The organic solution was washed with water and dried, and the solvent was evaporated under reduced pressure to afford 6.849 g of *trans*-cyano ketone **22a**, mp 223–225°, on recrystallization from acetone-ether. The residue (5.2 g) of the mother liquors was chromatographed on neutral alumina (60 g). The eluate with benzene-chloroform (9:1), on fractional recrystallization from acetone-ether, gave an additional 526 mg of **22a**, mp 219–224°, and 261 mg of the starting conjugated ketone **18a**, mp 198–201°. The total yield of **22a** was 60%. The residue of the mother liquors and the further eluates with benzene-chloroform (4:1 to 2:1) were combined and chromatographed again on alumina (60 g). Fractions eluted with light petroleum-benzene (1:4) on crystallization from acetone afforded 287 mg of unconjugated ketone **19**, mp 148–152°, which was identified with an authentic sample. Fractions eluted with benzene-methylene chloride (4:1) yielded 117 mg (1%) of *cis*-cyano ketone **23**, mp 204–210°, on recrystallization from acetone. *trans*-Cyano ketone **22a** had mp 222–223.5°, ν_{\max} 2238, 1725, 1342, and 1152 cm⁻¹; $\epsilon_{\text{C}=\text{N}}$ 12.1.

Anal. Calcd for C₁₉H₂₈O₃N₂S: C, 62.62; H, 7.74; N, 7.69; dipole moment, 6.73 D. Found: C, 62.64; H, 7.92; N, 7.37; dipole moment, 6.32 D.

cis-Cyano ketone **23** had mp 209–211°, ν_{\max} 2234, 1720, 1342, and 1152 cm⁻¹, $\epsilon_{\text{C}=\text{N}}$ 20.0.

Anal. Calcd for C₁₉H₂₈O₃N₂S: C, 62.62; H, 7.74; N, 7.69; dipole moment, 5.31 D. Found: C, 62.77; H, 7.80; N, 7.56; dipole moment, 5.20 D.

Preparation of Reference Compounds, 24, 25, and 26. a. (\pm)-N-Mesyl-16,17-imino-13-oxo-5 β ,9 β ,10 α -podocarpane (**24**). To a solution of lithium (0.70 g) in 70 ml of liquid dry ammonia was added dropwise 700 mg of enone **18a** in 35 ml of dry tetrahydrofuran at a bath temperature of -78° over a period of 10 min, and the mixture was stirred for 20 min at that temperature. The excess lithium was destroyed by addition of 8.0 g of ammonium chloride with occasional swirling. The mixture, after evaporation of the ammonia, was poured into ice-water and extracted with ether-methylene chloride (3:1) and then with methylene chloride-methanol (3:1). The extracts, after washing with water and drying, were evaporated under reduced pressure to give 598 mg of a crystalline residue.

To a solution of this residue in 17 ml of tetrahydrofuran were added under ice cooling and stirring two solutions of 1 ml of methanesulfonyl chloride in 10 ml of tetrahydrofuran and 1 g of sodium hydroxide in 10 ml of water at the same rate over a period of 20 min, and the resulting solution (two layers) was stirred for 1 hr at room temperature, poured into ice-water, and extracted with ether-methylene chloride (3:1). The extracts were washed with water, dried, and evaporated in reduced pressure to give 677 mg of a residue.

This residue was dissolved in 70 ml of acetone, and the solution was treated with 0.8 ml of Jones' reagent⁵⁹ at 0° for 10 min. The mixture was poured onto ice-water and extracted with ether-methylene chloride (3:1). The extracts were washed with ice-cold 2 N sulfuric acid, water, 2 N sodium carbonate solution, and water, dried, and evaporated in reduced pressure to give 610 mg of a residue which was subjected to alumina chromatography. The fractions eluted with benzene and benzene-chloroform (9:1) gave 378 mg (54%) of **24**, mp 196–199°, on recrystallization from methylene chloride and ether containing a small amount of pentane. Re-

crystallization from the same solvent gave a pure sample of **24** melting at 197–200°, ν_{\max} 1711, 1335, and 1150 cm⁻¹.

Anal. Calcd for C₁₈H₂₆O₃NS: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.24; H, 8.46; N, 4.09; dipole moment, 4.89 D.

b. (\pm)-N-Mesyl-16,17-imino-5 β ,9 β ,10 α -podocarpane (**25**). A mixture of 213 mg of **24**, 10 ml of triethylene glycol, 2.5 ml of 80% hydrazine hydrate, and 300 mg of potassium hydroxide was heated at 90–100° for 1 hr, and the temperature was slowly raised to 190–200° for distilling off the excess of hydrazine and maintained at that temperature for 0.5 hr. After being cooled, the mixture was poured into water and extracted with ether-methylene chloride (3:1). The extracts were washed with water, dried, and evaporated under reduced pressure to give 199 mg of a residue. This was purified by filtration of its benzene solution (500 ml) through an alumina column (5 g) and crystallized from methylene chloride and ether to give 167 mg (81%) of **25**, mp 140–141.5°. Recrystallization from the same solvent gave a pure sample of **25**, melting at 141–142°.

Anal. Calcd for C₁₈H₃₁O₂NS: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.16; H, 9.54; N, 4.41; dipole moment, 4.86 D.

c. (\pm)-N-Mesyl-16,17-imino-8 α -cyano-5 β ,9 β ,10 α -podocarpane (**26**). A mixture of 457 mg (1.25 mmoles) of cyano ketone **22a**, 1.05 g of hydrazine dihydrochloride, 5 ml of 85% hydrazine hydrate, and 25 ml of triethylene glycol was heated at 100–110° for 1 hr to afford a clear solution. To this solution was added 1.82 g of potassium hydroxide (85%), and the temperature of the mixture was slowly raised to 200 ± 5° in a period of 20 min to distil off the excess hydrazine, and it was maintained at the same temperature for 0.5 hr. Work-up in a similar way to that described in b gave 433 mg of a syrup, which was chromatographed on alumina. The fractions eluted with petroleum ether-benzene (1:1) and benzene gave 281 mg (64%) of **26**, mp 162–162.5°. Recrystallization from methylene chloride and ether gave a pure sample melting at 162.5–163°, ν_{\max} 2224, 1337, and 1152 cm⁻¹.

Anal. Calcd for C₁₉H₃₀O₂N₂S: C, 65.11; H, 8.63; N, 7.99. Found: C, 65.10; H, 8.81; N, 7.79; dipole moment, 6.13 D.

Measurements of Dipole Moments. The measurements were carried out at 25° on dilute solutions in benzene. The dielectric constants were measured by means of a heterodyne beat apparatus provided with a platinum cell.⁶⁰ For each solute, determinations were made on solutions of four different concentrations appropriately chosen below wt 2%. The graphical plot of the dielectric constant as well as the density of solutions against the concentration in weight per cent gave linear dependence within experimental errors. The slopes of these straight lines were evaluated by the least-squares method, and the molar polarization of the solute was calculated by a method similar to that introduced by Halverstadt and Kumler,⁶¹ differing in that densities were used rather than the specific volumes. The deformation polarization of each compound was assumed to be 1.05 times the molar refraction approximated with the sum of atomic refractions for the D line. Since the values of moments are great, no serious errors are introduced by this assumption, probable errors being estimated at less than 0.05 D.

(\pm)-N-Mesyl-16,17-imino-8 α -cyano-13,13-ethylenedioxy-5 β ,9 β ,10 α -podocarpane (**27a**). A solution of *trans*-cyano ketone **22a** (1.61 g) in 90 ml of anhydrous benzene was slowly distilled with 1 ml of ethylene glycol and 140 mg of toluene-*p*-sulfonic acid monohydrate to remove water formed during the reaction as an azeotropic mixture. After 3.5 hr, the reaction mixture was cooled, poured into 5 ml of ice-cold 2 N sodium carbonate solution, and extracted with chloroform. The organic layer was washed with water and dried, and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform-methanol to yield 1.670 g (93%) of the *trans*-cyano ketal **27a**, mp 261–264°. A pure sample melts at 267–268°, ν_{\max} 2230, 1339, 1149, and 1120 cm⁻¹, $\epsilon_{\text{C}=\text{N}}$ 26.3.

Anal. Calcd for C₂₁H₃₂O₄N₂S: C, 61.74; H, 7.90; N, 6.86. Found: C, 61.92; H, 7.87; N, 7.25.

(\pm)-N-Mesyl-16,17-imino-8 α -acetyl-5 β ,9 β ,10 α -podocarpan-13-one (**29a**). To a solution of **27a** (7.77 g, 19 mmoles) in 250 ml of dry tetrahydrofuran and 200 ml of anhydrous ether was added 52 ml of 1.80 N ethereal solution of methylolithium (93 mmoles) under ice cooling. The mixture was kept at 13–14° or 11 hr. After being poured cautiously into ice-water, the mixture was extracted with chloroform-ether (3:1). The organic solution was washed with water and dried, and the solvent was evaporated under reduced pres-

(59) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(60) Y. Kurita and M. Kubo, *J. Am. Chem. Soc.*, 79, 5460 (1957); B. Eda, K. Tsuda, and M. Kubo, *ibid.*, 80, 2426 (1958).

(61) I. F. Halverstadt and W. D. Kumler, *ibid.*, 64, 2988 (1942).

sure. The basic crude ketimine **28a** (7.84 g), showing a C=N band at 1638 cm^{-1} and no band arising from a cyano group in its infrared spectrum, was dissolved in 550 ml of 2 *N* sulfuric acid and 50 ml of ethanol. The solution was refluxed for 7 hr depositing a neutral product. After being cooled, the mixture was extracted with chloroform-ether (3:1). The extract was washed with 1 *N* sodium carbonate and water and dried, and the solvent was removed under reduced pressure to leave a crystalline residue, which was recrystallized from methylene chloride-methanol affording 3.296 g (46%) of acetyl ketone **29a**, mp 222–228°. An analytical sample melts at 228–230°, ν_{max} 1713, 1341, and 1151 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_4\text{NS}$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.22; H, 8.22; N, 3.81.

(±)-*N*-Mesyl-19,20-imino-5 β ,8 α ,9 β ,10 α ,13 α -17-norphyllocladan-13 β -ol-15-one (**30a**). A solution of acetyl ketone **29a** (657 mg) in 40 ml of ethanol and 40 ml of 1 *N* potassium hydroxide was refluxed under nitrogen for 2.5 hr. After being concentrated under reduced pressure, the mixture was diluted with ice-water and extracted with chloroform. The chloroform solution was washed with water and dried, and the chloroform was evaporated under reduced pressure to afford a crystalline product, which was recrystallized from methanol-ether to give 553 mg (84%) of ketol **30a**, mp 209–211°. An analytical sample melts at 207–210°, ν_{max} 3617, 1732, 1335, and 1149 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_4\text{NS}$: C, 62.97; H, 8.19; N, 3.67. Found: C, 62.75; H, 8.15; N, 3.53.

(±)-*N*-Mesyl-19,20-imino-5 β ,8 α ,9 β ,10 α ,13 α -17-norphyllocladan-13 β -ol-15-one 13-Acetate (**30b**). A solution of ketol **30a** (455 mg) in 3 ml of dry pyridine was heated with 1 ml of acetic anhydride in an oil bath (130–140°) for 2 hr. After being cooled the reaction solution was diluted with ice, poured into water, and extracted with chloroform. The chloroform extracts were washed successively with 2 *N* sodium carbonate solution, water, 2 *N* hydrochloric acid, and water and dried, and the solvent was removed under reduced pressure to dryness. The residue, on recrystallization from chloroform-methanol, gave 484 mg (96%) of ketol acetate **30b**, mp 254–256°, ν_{max} 1735, 1337, and 1149 cm^{-1} ; the nmr showed peaks at τ 7.30 (singlet, 3 H), 8.00 (singlet, 3 H), 9.15 (singlet, 3 H), and no sharp signal between 8.1 and 9.0.

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{O}_5\text{NS}$: C, 62.39; H, 7.85; N, 3.31. Found: C, 62.11; H, 7.77; N, 3.38.

(±)-*N*-Acetyl-16,17-imino-8 α -cyano-5 β ,9 β ,10 α -podocarpin-13-one (**22b**). A solution of acetyl enone **18b** (1.082 g, 3.6 mmoles) in 20 ml of dry tetrahydrofuran was treated with a solution of triethylaluminum (3 ml, 22 mmoles) and hydrogen cyanide (0.7 ml, 18 mmoles) in 20 ml of dry tetrahydrofuran in a similar manner described in hydrocyanation of the *N*-mesyl analog **18a**. The reaction mixture, in a stoppered flask, was allowed to stand at room temperature for 17 hr, poured into a mixture of 20 ml of 2 *N* sodium hydroxide and ice, and extracted with chloroform-ether (3:1). The organic solution was washed with water and dried, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on neutral alumina (30 g). Fractions eluted with benzene-chloroform (9:1 to 4:1) were recrystallized from acetone-ether to afford 332 mg (28%) of *trans*-cyano ketone **22b**, mp 194–198°. A pure sample melts at 198–200°, ν_{max} 2241, 1726, and 1635 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.91; H, 8.62; N, 8.47.

(±)-*N*-Acetyl-16,17-imino-8 α -cyano-13,13-ethylenedioxy-5 β ,9 β ,10 α -podocarpin (**27b**). *N*-Acetyl cyano ketone **22b** (233 mg) was treated with ethylene glycol (0.0851 ml) and toluene-*p*-sulfonic acid monohydrate (20 mg) in absolute benzene (15 ml) in a similar manner described in ketalization of the *N*-mesyl analog **22a**. After 3 hr, the mixture was poured into a mixture of 2 *N* sodium carbonate and ice and extracted with ether. The organic layer was washed with water and dried, and the solvent was removed under reduced pressure. The residue was recrystallized from methanol-ether to afford 188 mg (71%) of cyano ketal **27b**, mp 125–130°. An analytical sample melts at 126–128°, ν_{max} 2258, 1630, and 1125 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{O}_2\text{N}$: C, 70.93; H, 8.66; N, 7.52. Found: C, 69.22; H, 8.67; N, 7.91.

(±)-*N*-Acetyl-19,20-imino-5 β ,8 α ,9 β ,10 α ,13 α -17-norphyllocladan-13 β -ol-15-one 13-Acetate (**30c**). To a solution of **27b** (140 mg, 0.378 mmole) in 3.5 ml of dry tetrahydrofuran was added an ethereal solution of methylolithium (3.78 mmoles, in 4.9 ml), and the solution was allowed to stand at room temperature overnight. The reaction solution was cautiously poured into ice-water and extracted with ether and then with chloroform. The extracts were washed with

water and dried, and the solvent was evaporated under reduced pressure to afford crude ketimine **28b** (122 mg), which was dissolved in 4 ml of ethanol and 2 ml of 2 *N* hydrochloric acid. The resulting mixture was refluxed for 5 hr, concentrated under reduced pressure, and extracted with chloroform. The chloroform solution was washed with water and dried, and after evaporation of the solvent, the residue (93 mg) was treated with 0.3 ml of acetic anhydride and 2 ml of pyridine at room temperature overnight. The acetylated product (95 mg) on chromatography on alumina gave 68 mg (52%) of crude diketone **29b** (ν_{max} 1710 and 1630 cm^{-1}) which was dissolved in 2 ml of ethanol and 2 ml of *N* potassium hydroxide, and the mixture was refluxed under nitrogen for 2 hr. Work-up in the usual way gave crude ketol (59 mg), which was heated with 0.2 ml of acetic anhydride and 1 ml of pyridine at 120–130° for 2 hr. Work-up in the usual way gave 64 mg of a residue, which was chromatographed on alumina. Fractions eluted with benzene and chloroform (9:1 to 2:1) were recrystallized from ether to give 9 mg of ketol acetate **30c**, mp 185–188°, $\nu_{\text{max}}^{\text{CHCl}_3}$ 1738, 1642, and 1230 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{O}_4\text{N}$: C, 71.29; H, 8.58. Found: C, 70.58; H, 8.83.

(±)-*N*-Mesyl-19,20-imino-5 β ,8 α ,9 β ,10 α ,13 α -17-norphyllocladan-13 β ,15 α -diol 13-Acetate (**33a**). To a boiling solution of 430 mg of **30b** in 25 ml of pure tetrahydrofuran and 6 ml of water was added 500 mg of sodium borohydride with stirring in five portions over a period of 6 hr. The reaction mixture was concentrated under reduced pressure and extracted with chloroform. The chloroform extracts were washed with water and dried, and the chloroform was evaporated under reduced pressure to dryness. The residue was recrystallized from methanol-ether to give 329 mg (75%) of *exo*-1,3-glycol monoacetate **33a**, mp 205–207°. Further recrystallization raised the melting point to 206–207°, ν_{max} 3614, 3514, 1730, 1332, and 1149 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{O}_5\text{NS}$: C, 62.09; H, 8.29; N, 3.29. Found: C, 62.19; H, 8.32; N, 3.14.

(±)-*N*-Mesyl-13 β -acetoxo-15 α -mesyloxy-19,20-imino-5 β ,8 α ,9 β ,10 α ,13 α -17-norphyllocladan (**33b**). To a solution of 277 mg of **33a** in 2 ml of dry pyridine was added 0.2 ml of methanesulfonyl chloride under ice cooling, and the mixture was allowed to stand at room temperature overnight. The excess of the reagent was destroyed by addition of ice at 0°. After 40 min the reaction mixture was poured into ice-water and extracted with chloroform. The chloroform solution was washed successively with 2 *N* sodium carbonate, water, 2 *N* hydrochloric acid, and water and dried, and the chloroform was evaporated under reduced pressure. The residue was recrystallized from chloroform-methanol to yield 316 mg (97%) of **33b**, mp 231–233°. An analytical sample melts at 237–238°, ν_{max} 1732, 1360, 1322, 1170, and 1148 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{37}\text{O}_7\text{NS}_2$: C, 54.85; H, 7.42; N, 2.78. Found: 54.93; H, 7.32; N, 2.79.

(±)-*N*-Mesyl-16,17-imino-8 α -vinyl-5 β ,9 β ,10 α -podocarpin-13-one (**34**). To a solution of **33b** (289 mg) in 10 ml of dioxane was added successively 10 ml of methanol, 10 ml of water, and 3.0 g of potassium hydroxide. The mixture was refluxed under nitrogen for 2 hr. After being concentrated under reduced pressure, the solution was diluted with ice-water and extracted with chloroform. The chloroform solution was washed with 2 *N* hydrochloric acid and water and dried; the chloroform was removed under reduced pressure. The crystalline residue was recrystallized from chloroform-methanol to afford 182 mg (87%) of vinyl ketone **34**, mp 208–209°, ν_{max} 3029, 1712, 1638, 1334, 1148, 1005, and 923 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3\text{NS}$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.83; H, 8.47; N, 4.13.

(±)-*N*-Mesyl-16,17-imino-8 α -vinyl-13,13-ethylenedioxy-5 β ,9 β ,10 α -podocarpin (**36**). A solution of vinyl ketone **34** (154 mg) in 30 ml of dry benzene containing ethylene glycol (56 mg) and toluene-*p*-sulfonic acid monohydrate (15 mg) was gently refluxed, and water formed during the reaction was distilled off as an azeotropic mixture. After 3 hr, the mixture was concentrated under reduced pressure, poured into ice-cold 2 *N* sodium carbonate, and extracted with chloroform. The chloroform solution was washed with water and dried. After evaporation of the chloroform, the residue was recrystallized from methanol to give 138 mg (79%) of vinyl ketal **36**, mp 194–196°. A pure sample melts at 196–197°, ν_{max} 3030, 1628, 1335, 1148, 1117, 1013, and 925 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{O}_4\text{NS}$: C, 64.52; H, 8.62; N, 3.42. Found: C, 64.52; H, 8.57; N, 3.65.

When the six-step process was carried out without purification of the intermediates, diketone **29a** gave vinyl ketal **36** in an over-all yield of 75%.

(±)-N-Mesyl-16,17-imino-8 α -(2'-hydroxy)ethyl-13,13-ethylene-dioxy-5 β ,9 β ,10 α -podocarpene (37a). Into a solution of 36 (2.549 g, 622 μ moles) in 50 ml of dry tetrahydrofuran was introduced diborane gas, prepared from 4.85 g (34.2 μ moles) of boron trifluoride etherate in diglyme (45 ml) and 873 mg (23.1 μ moles) of sodium borohydride in diglyme (30 ml), with stirring in a nitrogen atmosphere at 0° during 20 min. The reaction mixture was stirred at room temperature for 2 hr and treated successively with 5.7 ml of water, 11.4 ml of 2 N sodium hydroxide, and 11.4 ml of 30% hydrogen peroxide, with stirring under ice cooling. The reaction mixture was stirred at room temperature for 30 min more, diluted with ice-water, and extracted with chloroform. The chloroform layer was washed with water and dried, and the chloroform was removed under reduced pressure. The residue was recrystallized from methanol to afford 2.150 g (80%) of hydroxy ketal 37a, mp 193–195°. On repeated crystallization from methanol-ether, an analytical sample, mp 190–193°, was obtained. An attempt to effect further purification of the sample by alumina chromatography did not change the melting point, ν_{\max} 3622, 3420, 1336, 1148, and 1119 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{O}_5\text{NS}$: C, 61.79; H, 8.72; N, 3.28. Found: C, 62.09; H, 8.80; N, 3.41.

Acetylation of the Hydroxy Ketal 37a and Deketalization of the Ketal Acetate 37b. A solution of hydroxy ketal 37a (34.6 mg) in 1 ml of pyridine was treated with 0.3 ml of acetic anhydride at room temperature overnight. The solution was treated with ice-water and extracted with methylene chloride. The organic solution was washed successively with ice-cold 1 N hydrochloric acid, water, 2 N sodium carbonate, and water, and dried; the solvent was removed under reduced pressure. The residue gave 18.8 mg of acetoxy ketal 37b, mp 174–184°, on recrystallization from acetone. Further recrystallization raised the melting point to 191.5–192.5°, ν_{\max} 1730, 1336, 1149, and 1084 cm^{-1} .

Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{O}_6\text{NS}$: C, 61.39; H, 8.37; N, 2.98. Found: C, 61.41; H, 8.55; N, 3.16.

Acetoxy ketal 37b (15 mg) was heated with 20 ml of 70% acetic acid at 100° for 20 min. The mixture was concentrated under reduced pressure, poured into ice-cold 2 N sodium carbonate, and extracted with methylene chloride. The extracts were washed with water and dried, and the solvent was evaporated under reduced pressure. The residue was recrystallized from acetone-ether to afford 10.2 mg of acetoxy ketone 39a, mp 168–169°, ν_{\max} 1730, 1714, 1338, and 1151 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{O}_5\text{NS}$: C, 62.09; H, 8.29; N, 3.29. Found: C, 61.51; H, 8.31; N, 3.51.

Deketalization of Hydroxy Ketal 37a. Hydroxy ketal 37a (2.02 g) was heated with 100 ml of 70% acetic acid at 100° for 20 min. The solution was concentrated under reduced pressure, diluted with ice-water, and extracted with chloroform. The chloroform solution was washed with water and dried, and the solvent was distilled off under reduced pressure. On recrystallization from acetone-ether, the residue gave 1.745 g of crude hydroxy ketone 34a. A pure sample was obtained on recrystallization from acetone-ether, mp 167–169°, ν_{\max} 3590, 1708 (weak, carbonyl), 1340, and 1150 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{33}\text{O}_4\text{NS}$: C, 62.64; H, 8.67; N, 3.65. Found: C, 62.57; H, 8.71; N, 3.52.

(±)-N-Mesyl-16,17-imino-8 α ,12 α -ethano-5 β ,9 β ,10 α -podocarpene-13-one (41). A solution of crude hydroxy ketone 39a (1.745 g) in 20 ml of dry pyridine was treated at 0° with 1.81 ml of methanesulfonyl chloride and the mixture was kept at 21° for 9 hr. The excess of the chloride was decomposed by adding a small amount of ice. After 1 hr, the mixture was poured into ice-water and extracted with chloroform. The chloroform solution was washed successively with ice-cold 2 N hydrochloric acid, water, 2 N sodium carbonate, and water, and dried; the solvent was removed under reduced pressure at a temperature below 40° to give crude keto mesylate 39c (2.00 g), which was used for the next conversion without purification, ν_{\max} ca. 1710, 1360, 1340, 1175, and 1150 cm^{-1} .

A solution of crude 39c (2.00 g) in 50 ml of anhydrous benzene was stirred with potassium *t*-butoxide in *t*-butyl alcohol (5.22 μ moles in 55 ml) at room temperature for 2 hr. The resulting colloidal mixture was diluted with ice-water and extracted with chloroform. The chloroform solution was washed with water and dried. After evaporation of the chloroform under reduced pressure, the residue was crystallized from acetone-ether giving 434 mg of pentacyclic ketone 41, mp 179–181°. The residue of the mother liquor was chromatographed on alumina (33 g), and benzene fractions afforded an additional 502 mg of 41, mp 185–187°, on recrystallization from acetone-ether. The total yield is 54% from

hydroxy ketal 39a, ν_{\max} 1724, 1714 (doublet), 1339, and 1150 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3\text{NS}$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.92; H, 8.52; N, 3.87.

(±)-N-Mesyl-16,17-imino-13-methylene-8 α ,12 α -ethano-5 β ,9 β ,10 α -podocarpene (42a). To an ethereal solution of methylenetriphenylphosphorane, prepared by treating a suspension of 1.465 g (4.104 μ moles) of methyltriphenylphosphonium bromide in 10 ml of dry ether with 1.11 N butyllithium in ether (3.70 ml, 4.1 μ moles) with stirring at room temperature for 2 hr, was added dropwise a solution of 41 (500 mg, 1.365 μ moles) in 10 ml of pure tetrahydrofuran. After being refluxed for 25 min, the ether was removed and replaced with 5 ml of dry tetrahydrofuran. The solution was refluxed for 2.5 hr, poured into ice-water, and extracted with chloroform. The chloroform layer was washed with water and dried, and the chloroform was evaporated under reduced pressure. The residue was chromatographed on alumina (30 g). Eluates with light petroleum-benzene (2:1) were recrystallized from ether-pentane to give 365 mg (73%) of *exo*-olefin 42a, mp 126–127°. A pure sample melts at 127–128°, ν_{\max} 3006, 1648, 1337, 1147, and 882 cm^{-1} .

Anal. Calcd for $\text{C}_{21}\text{H}_{33}\text{O}_2\text{NS}$: C, 69.38; H, 9.15; N, 3.85. Found: C, 69.32; H, 9.23; N, 4.03.

(±)-16,17-Imino-13-methylene-8 α ,12 α -ethano-5 β ,9 β ,10 α -podocarpene (42b). To a solution of 388 mg of lithium in 50 ml of liquid ammonia was added dropwise a solution of 159 mg of 42a in 4 ml of dry tetrahydrofuran and 0.8 ml of absolute ethanol at a bath temperature of –73°. The solution was stirred for 30 min and the excess of lithium was destroyed by addition of 6 ml of absolute ethanol. After the ammonia was evaporated some amount of ice-water was added to the residue. The resulting mixture was then extracted with ether, and the ether layer was washed with water and dried. The solvent was removed under reduced pressure. The crystalline residue (124 mg) was recrystallized from ether to afford the base 42b, mp 78–81°, ν_{\max} 3068, 1645, and 881 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{N}$: C, 84.14; H, 10.95; N, 4.91. Found: C, 84.10; H, 11.00; N, 4.86.

The hydrochloride of 42b, mp 126–129°, was obtained by treatment of an ethereal solution of the free base with hydrogen chloride and by recrystallization from ethyl acetate, ν_{\max} 2699–2477, 1587, and 884 cm^{-1} .

Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{N}\cdot\text{HCl}\cdot 2.5\text{H}_2\text{O}$: C, 65.45; H, 10.16; N, 3.82; H₂O, 12.27. Found: C, 65.81; H, 10.21; N, 4.01; H₂O, 11.37.

(±)-N-Acetyl-16,17-imino-13-methylene-8 α ,12 α -ethano-5 β ,9 β ,10 α -podocarpene (42c). To a solution of 114 mg of 42b in 3 ml of tetrahydrofuran were added 3.5 ml of 3 N sodium hydroxide and a solution of 0.39 ml of acetic anhydride in 3.5 ml of tetrahydrofuran at the same rate over a period of 10 min with stirring under ice cooling. The reaction mixture was stirred at room temperature for 30 min, diluted with ice water, and extracted with chloroform. The chloroform solution was washed with water, dried, and concentrated under reduced pressure to dryness. On recrystallization from acetone-ether, the residue yielded 112 mg (86% from 42a) of *exo*-olefin acetamide 42c, mp 153–154.5°, ν_{\max} 1623 and 880 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{NO}$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.59; H, 10.30; N, 4.63.

Introduction of a Hydroxyl Group at the Allylic Position of 42c. A mixture of 227 mg (0.695 μ mole) of *exo*-olefin acetamide 42c in 4 ml of dry carbon tetrachloride, 136 mg (0.762 μ mole) of N-bromosuccinimide, and 1.3 mg of benzoyl peroxide was heated at a bath temperature of 80–90°. After 10 min, the mixture was cooled, poured into ice-water, and extracted with ether. The ether solution was washed with water and dried, and the solvent was removed under reduced pressure. The residue (crude allylic bromide 43, 288 mg) was dissolved in 10.7 ml of a benzene solution of perbenzoic acid (0.81 μ mole), and the solution was allowed to stand at room temperature in the dark. After 90 hr, 87% of the theoretical amount of perbenzoic acid was consumed (iodometry), and the mixture was poured into ice-water and extracted with ether. The organic solution was washed with ice-cold 2 N sodium hydroxide and water and dried, and the solvent was evaporated under reduced pressure to give a crude mixture of epoxy bromides 44 and 45 (284 mg), which were refluxed with 2.80 g of zinc dust in 18 ml of absolute ethanol with vigorous stirring for 5 hr. Zinc and zinc salt were filtered off and washed repeatedly with methanol. The filtrate was concentrated under reduced pressure, diluted with water, and extracted with ether. The ether solution was washed with water and dried, and the ether was removed under reduced

pressure. The amorphous residue (223 mg) was chromatographed on alumina (7 g) to give three main fractions.

(a) Elution with benzene yielded 62.6 mg (28%) of the starting *exo*-olefin **42c**, melting at 145–147°.

(b) The fractions (69 mg) eluted with benzene–chloroform (19:1) were rechromatographed on alumina (8 g), and the fractions eluted with the same solvent gave 23.3 mg (9.8%, 14% based upon the consumed olefin **42c**) of crude crystals, mp 160–180°. The crude crystals and the mother liquors were separately purified by using preparative thin layer chromatography (silica gel G, benzene–ethyl acetate–ethanol, 20:80:0.5) to remove a small amount of polar by-products. Crystals obtained from less polar fractions (total 10.5 mg) were repeatedly recrystallized from acetone–ether to afford 3.9 mg of (\pm)-*N*-acetyl-16,17-imino-8 α ,12 α -ethano-13-methylene-5 β ,9 β ,10 α -podocarpin-14 β -ol (**46**), mp 198–199°, 203°, ν_{\max} 3604, 1625, 1046, and 906 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2$: C, 76.92; H, 9.68. Found: C, 76.67; H, 9.62.

This sample showed an infrared spectrum and a thin layer chromatogram indistinguishable from those of the optically active specimen^{5b} of **46**.

(c) The fractions eluted with benzene–chloroform (9:1 to 4:1) on crystallization from acetone–ether gave crude crystals (16.5 mg, 6.9%, 10% based upon the consumed olefin **42c**) of (\pm)-*N*-acetyl-16,17-imino-8 α ,12 α -ethano-13-methylene-5 β ,9 β ,10 α -podocarpin-14 α -ol (**47**), which were recrystallized from the same solvent to give 1.5 mg of a pure sample melting at 198–200°, and the second crop (6.0 mg), 192–195°, ν_{\max} 3611, 1627, 1042, and 907 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.47; H, 9.88; N, 4.45.

This sample showed an infrared spectrum and a thin layer chromatogram (silica gel G, ethyl acetate–benzene, 2:1) completely identical with those of the naturally derived specimen^{5b} of **47**.

(\pm)-*N*-Acetyl-16,17-imino-13-methylene-8 α ,12 α -ethano-5 β ,9 β ,10 α -podocarpin-14-one (**48**). The first mother liquors obtained from the fractions in c were combined (14 mg) and were dissolved in 0.9 ml of dry pyridine and treated with 48 mg of chromic anhydride and 0.5 ml of pyridine. The mixture was allowed to stand at room temperature overnight, poured into ice–water, and extracted with ether. The ether solution was washed successively with water, ice-cold 2 *N* hydrochloric acid, and water, and dried, and the ether was removed under reduced pressure. The residue (11 mg) was chromatographed on alumina (1 g). Fractions eluted with benzene–ether (9:1 to 4:1) on recrystallization from acetone–ether gave enone **48** (1.6 mg), mp 154–165°. In another run, the crude crystals of **47** (12 mg, one portion of the second crop and the residual crystals described above) were oxidized in the same way described above. An ethereal solution of the residue (9 mg) in petroleum ether–benzene (1:1) was filtered through alumina (200 mg). The eluates (4 mg) were recrystallized to afford 1.5 mg of enone **48**, mp 156–160°. Further recrystallization gave a pure sample, mp 160–168°, ν_{\max} 1703, 1628, and 942 cm^{-1} , λ_{\max} 208 $\text{m}\mu$ (ϵ 13,100), 232 $\text{m}\mu$ (shoulder).

Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}$: C, 77.37; H, 9.15. Found: C, 77.20; H, 9.45.

This sample showed an infrared spectrum, an ultraviolet spectrum, and a thin layer chromatogram completely identical with those of the optically active specimen^{5b} of **48**.

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Total Synthesis of *dl*-Veatchine and *dl*-Garryine^{1,2}

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Abstract: The total synthesis of veatchine and garryine in a racemic form is described. The synthesis is started from the pentacyclic compound **4**, the same intermediate for the synthesis of atisine. The major problem treated in the present work is to convert the C–D bridged ring system of the phyllocladene type in **4** into the opposite bridge configuration of the kaurene type in **13**. For this conversion two routes involving the Wagner–Meerwein type rearrangement are established. Introduction of the allyl alcohol function into the D ring is carried out in the same manner as employed in the atisine synthesis. The final compound of the present synthesis is *dl*-dihydroveatchine (**24c**). The transformation of **24c** to garryine and further to veatchine by a few-steps synthesis is already recorded in the natural series.

The alkaloids veatchine **1** and garryine **2** isolated from *Garrya veatchii* Kellogg, together with atisine, are found to be the first representatives of a new class of diterpene alkaloids. The structure and the stereochemistry including the absolute configuration have been clarified as depicted in formulas **1** and **2**.^{3–5} As

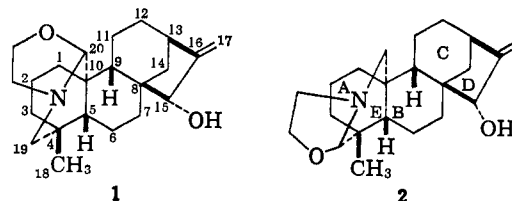
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