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 **(±)-N-acetyl-16,17-imino-8α,12α-ethano-13-methylene-5β,9β,10α-podocarpan-14β-ol (46)**, mp 198–199°, 203°, ν_{max} 3604, 1625, 1046, and 906 cm^{-1}.

Anal. Calcd for $C_{22}H_{33}NO_2$: 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[55] 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 **(±)-N-acetyl-16,17-imino-8α,12α-ethano-13-methylene-5β,9β,10α-podocarpan-14a-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 $C_{22}H_{33}NO_2$: 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[55] of **47**.

(±)-N-Acetyl-16,17-imino-13-methylene-8α,12α-ethano-5β,9β,-10α-podocarpan-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 mμ (ε 13,100), 232 mμ (shoulder).

Anal. Calcd for $C_{22}H_{31}N_2O$: 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[55] of **48**.

Acknowledgments. The authors are very grateful to Professor Emeritus Dr. Ochiai and Dr. Takeda for their courtesy in support this work and encouragement. Thanks are also forwarded to Dr. Watanabe of this laboratory for measurement and calculation of the dipole moments, and to Mr. Sasakura for his technical assistance in preparing the starting material.

Total Synthesis of *dl*-Veatchine and *dl*-Garryine[1,2]

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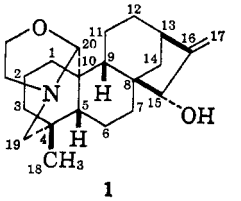
Contribution from the Shionogi Research Laboratory, Fukushima-ku, Osaka, Japan. *Received October 18, 1966*

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 the configurational elucidation was advanced, many synthetic organic chemists started to challenge the



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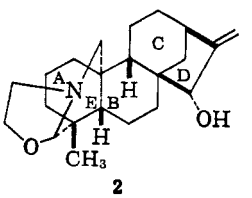


2

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

(2) For a preliminary communication on this work, see W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Am. Chem. Soc.*, **86**, 929 (1964). An outline of this work was also presented at the 3rd International Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 1964.

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

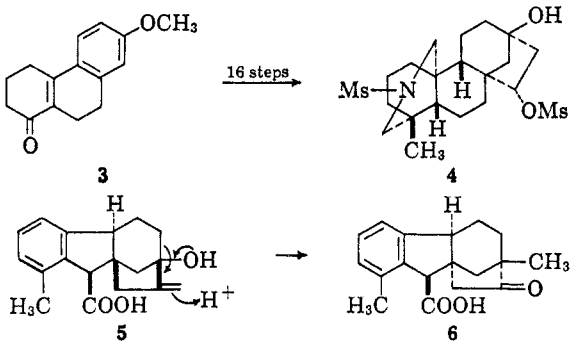
(4) For reviews see: (a) S. W. Pelletier, *Experientia*, **20**, 1 (1964); (b) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961); (c) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna 1958, p 26; (d) E. S. Stern in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, p 473; (e) H. G. Boit, "Ergebnisse der Alakloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 851.

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

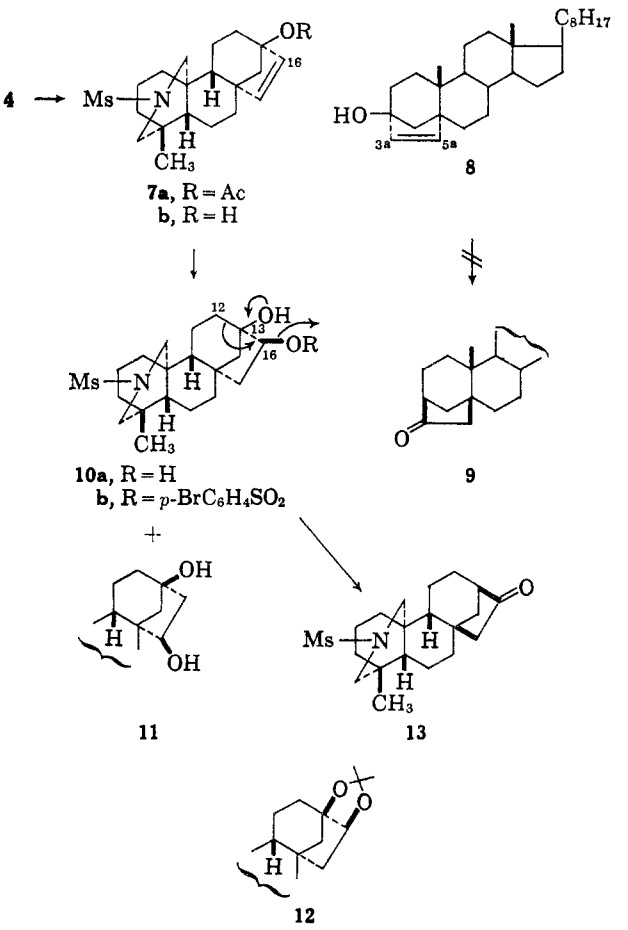
total synthesis of the alkaloids. Thus, a number of pioneering works[6-13] approaching this objective have been published before or after our success.

In the preceding paper we reported the first total synthesis of atisine.[14] In continuation of the work, synthesis of veatchine and garryine was undertaken, and the successful result was already published in a form of a communication in 1964.[2] In the present paper, we describe a full account of this work. Almost at the same time, Masamune[15] and a little later Valenta, *et al.*,[16] also announced total syntheses of the same alkaloids based upon different building principles.

The pentacyclic compound **4**[17] was selected as a suitable starting material, because it already involves a bicyclo[3.2.1]octane ring system, though of phyllocladene type, in the molecule. As described in the preceding paper[14] the compound was prepared from the tricyclic conjugated ketone **3** through 16 steps in a highly stereoselective manner. With this compound **4**, the only remaining major problem was to convert its C–D bridged system of the phyllocladene type into that of the kaurene type, an opposite bridge configuration. It did not appear difficult to solve the matter, since this type of conversion was already known in gibberelline chemistry, as exemplified by a conversion in which allogibberic acid (**5**), a phyllocladene-type bridged system, was rearranged to gibberic acid (**6**), a kaurene type, by treatment with hydrochloric



acid.[18] The work was, therefore, initiated so as to follow this type of rearrangement. The compound **4** was refluxed with collidine to afford in 78% yield the acetoxy olefin **7a**, mp 200–200.5°, which was hydrolyzed to compound **7b**. It was anticipated that with this compound, a similar acid rearrangement giving compound **13** with the desired bridge configuration would take place. However, in a model experiment,[19] 3α,5α-ethenocholestan-3β-ol (**8**) could not be rearranged to compound **9** by treatment of the acid. The result clearly indicates that the rearrangement of



the pentacyclic hydroxy olefin **7b** will also be unsuccessful. One of the reasons for this failure may be that protonation may take place preferably at C-3a rather than at C-5a producing a sterically more favorable C-5a carbonium ion which cannot induce the desired rearrangement. The method, therefore, was abandoned and another more promising way to definitely induce the plus charge at the C-3a carbon was sought. This goal was realized by placing a suitable leaving group with a favorable *exo* orientation at the C-16 position in compound **7**, and the following two routes became available.

Sterically controlled hydroboration[20] of the olefin **7a** with bis(3-methyl-2-butyl)borane followed by oxidation and hydrolysis afforded the desired 1,2-diol **10a**, mp 242–245°, in 53% yield together with 18%

(6) 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).

(7) (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).

(8) J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 869 (1962).

(9) 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).

(10) R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, 1 (1960); *cf.* R. B. Turner and P. E. Shaw, *ibid.*, 24 (1960); R. B. Turner and K. H. Gänshirt, *ibid.*, 231 (1961); R. B. Turner, K. H. Gänshirt, P. E. Shaw, and J. D. Tauber, *J. Am. Chem. Soc.*, **88**, 1776 (1966).

(11) R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962); **31**, 2530 (1966).

(12) R. A. Bell and R. E. Ireland, *Tetrahedron Letters*, 269 (1963).

(13) S. Masamune, *J. Am. Chem. Soc.*, **83**, 1009 (1961).

(14) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *ibid.*, **89**, 1483 (1967); **85**, 2342 (1963).

(15) S. Masamune, *ibid.*, **86**, 290 (1964).

(16) Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 2437 (1964); R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Collection Czech. Chem. Commun.*, **31**, 602 (1966).

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

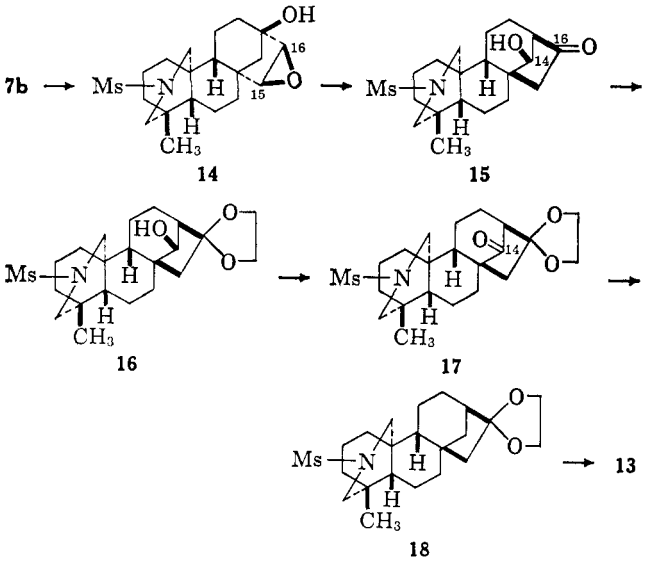
(18) A. J. Birch, R. W. Rickards, H. Smith, J. Winter, and W. B. Turner, *Chem. Ind.* (London), 401 (1960); *cf.* N. Takahashi, H. Kitamura, A. Kawarada, Y. Seta, M. Takai, S. Tamura, and Y. Sumiki, *Bull. Agr. Chem. Soc., Japan*, **19**, 267 (1955).

(19) This work will be published separately.

(20) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960); G. Zweifel, N. R. Aryangar, and H. C. Brown, *ibid.*, **85**, 2072 (1963).

yield of the isomeric 1,3-diol **11**, mp 262–263°. The *exo* configuration of the newly introduced hydroxyl group in both diols is based upon the view of the *exo* side attack of borane as well as formation of the acetonide **12** of the 1,2-diol **10a**. The isolation of the latter was conveniently carried out *via* its acetonide **12**. In this reaction no epimeric *endo*-hydroxy compounds were isolated. The preponderant and stereoselective formation of the 1,2-diol with the desired configuration was thus secured. Selective sulfonation of the 16-hydroxyl group was effected by treatment of **10a** with *p*-benzenesulfonyl chloride in pyridine for 40 hr at room temperature, giving the monobrosylate **10b**. Compound **10b** was now subjected to base-induced rearrangement. Refluxing an aqueous methanolic dioxane solution of crude **10b** with potassium hydroxide gave the rearranged ketone **13** having a desired bridge configuration, mp 215–217°, in 70% over-all yield from the diol **10a**. The band at 1739 cm^{-1} in the infrared clearly shows the formation of a five-membered ring ketone. The facile rearrangement of this system is obviously due to the favorable orientation of the C-16–OBs bond antiparallel to the migrating C-12–C-13 bond.

To secure this key compound **13** the following alternative route involving more reaction steps but with higher selectivity was also established. Epoxidation of alcohol **7b**, mp 181–191° (solidifies and melts at 203–204°), with perbenzoic acid stereoselectively gave the *exo*-epoxide **14**, mp 258–259.5°, in 71% yield. The



desired *exo* configuration of the epoxy function was again deduced from the well-established view of the favorable attack of reagents from the less hindered *exo* side in a bicyclo[3.2.1]octane ring system and supported by its facile Wagner–Meerwein type rearrangement shown below. The rearrangement was induced with diethylaluminum chloride more smoothly than with boron trifluoride etherate giving the ketol **15**, mp 242–243°, in 59% yield. The superiority of diethylaluminum chloride may be due to its less acidity to facilitate migration of electrons from the bridgehead oxygen in a metalated intermediate. The infrared spectrum of the product showed the presence of both the hydroxyl and the five-membered ring keto group as judged by bands at 3630 and 1744 cm^{-1}. Since no configurational change at the C-15 carbon takes place during the rearrangement, the resulting hydroxyl group should retain its configuration and therefore be *exo* oriented. To remove this unnecessary hydroxyl group at C-14, the ketol **15** was ketalized, and the resulting hydroxy ketal **16**, mp 220–221°, was oxidized with chromic anhydride in pyridine giving the keto ketal **17**, mp 205–206°, in 80% over-all yield. Elimination of a hindered C-14 ketone function in a similar ring system was reported[16] to be effected, but only in a low yield, by applying the Cram modification[21] for Wolff–Kishner reduction. Moreover an application of the enforced Barton condition,[22] successfully applied by Bell, *et al.*,[12] in the kaurene synthesis, to the present compound should be avoided because a severe change of the mesylamino group with strong alkali was expected. Recently a new and simple modification of the Wolff–Kishner reduction for hindered or masked ketones was found in this laboratory[23] and its efficiency has been verified also in other laboratories.[24] The method consists of effecting hydrazone formation using hydrazine dihydrochloride and subsequent heating with alkali in triethylene glycol. Application of this method to the ketone **17** gave the desoxo compound **18**, mp 198.5–200°, in 91% yield as expected. The latter was deketalized in the usual manner giving the pentacyclic ketone **13** described above. The 32% over-all yield of the last compound from the olefin **7a** by this route is also good and comparable to the 37% yield obtained by the first route. The synthesis of the ground skeleton of the garryia alkaloids was thus accomplished in a highly stereoselective manner.

Introduction of the allyl alcohol function was carried out by a similar manner to that used in the atisine synthesis (see below).[14]

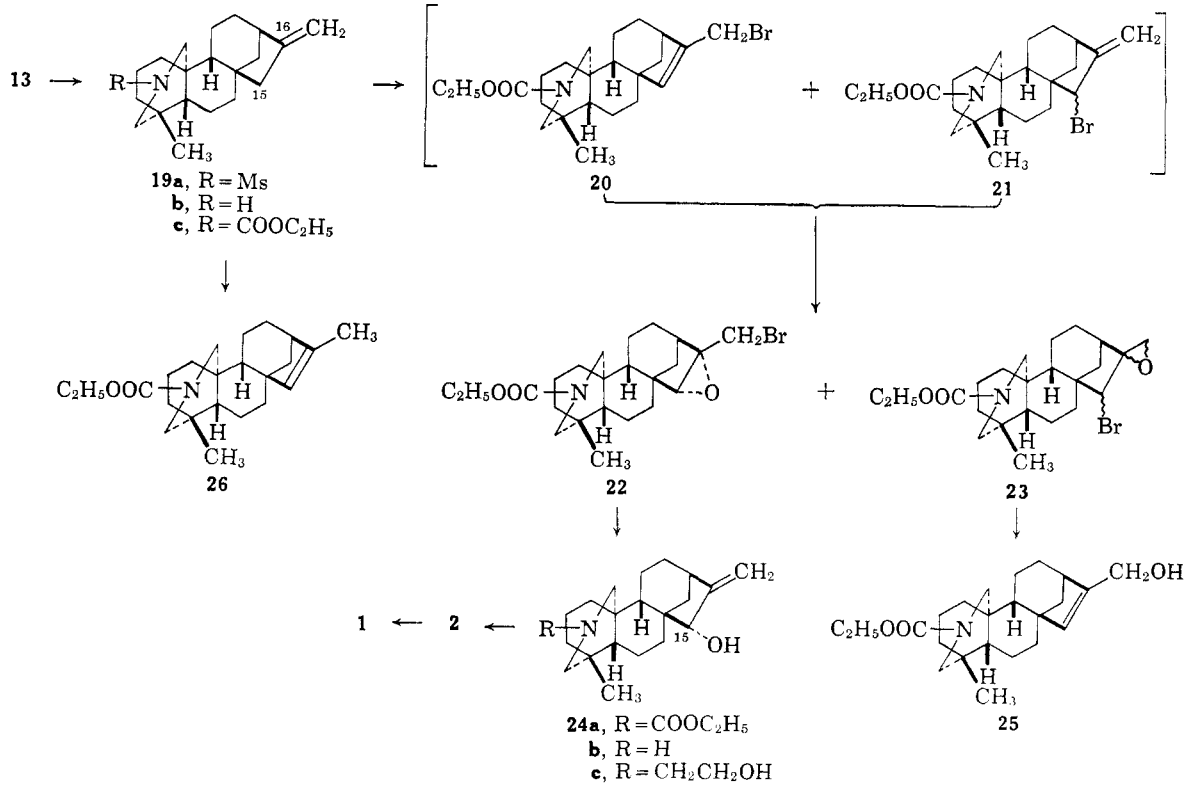
Wittig condensation of the pentacyclic ketone **13** afforded the *exo*-methylene derivative **19a**, mp 136–137°, in 90% yield. Before placing a hydroxyl group at C-15 the protecting N-mesyl group should be replaced by another suitable one which can be removed at a later stage without affecting the coexisting allylic alcohol function in the D ring. Thus, the N-mesyl olefin **19a** was at first subjected to lithium–ammonia reduction affording the demesylated secondary amine **19b**, mp 68–71°, which was then converted into an oily N-carbethoxy derivative **19c** by treatment with ethyl chloroformate and alkali. The compound **19c** could not be crystallized but was found to be uniform from thin layer chromatography. Wohl–Ziegler bromination of this compound using N-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide gave a mixture of allylic bromides **20** and **21**, which without purification was epoxidized giving the crystalline epoxy bromide **22**, mp 145–147°, and the oily isomer **23** after separation of the crude product by alumina chromatography. While the crystalline epoxy bromide was converted into the desired *exo*-methylene

(21) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

(22) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(23) W. Nagata and H. Itazaki, *Chem. Ind.* (London), 1194 (1964).

(24) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1019 (1965); G. V. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, **31**, 1026 (1966); private communication from Professor Tanaka in Tokyo University, who applied the method to elimination of a C-6 keto group in some trimethyl steroids.



alcohol **24a**, mp 151–152°, an oily isomer **23** gave the isomeric allylic alcohol **25**, mp 129–130.5°, by treatment with zinc in refluxing *t*-butyl alcohol or ethanol. The presence of a vinyl group in compound **24a** follows from the band at 906 cm^{-1} in the infrared. Since epoxidation should occur from the *exo* side, the secondary hydroxyl group of **24a** also should have a favorable *exo* orientation. The isomeric allyl alcohol **25** did not have a band corresponding to a vinyl group in the infrared, but did have a signal corresponding to one proton at τ 4.62 in the nmr, supporting structure **25**. In a separate experiment starting from the N-mesyl olefin **19a**, the five-step reaction process was carried out successively without purification of the intermediates in each step to give the desired secondary **24a** (9%) and the primary allylic alcohol **25** (10%) together with 23% yield of a desoxy olefin mixture. This mixture was found to be composed mainly of the *endo*-olefin **26** as evident from an almost identical infrared spectrum with that of the product obtained by isomerization of the starting *exo*-olefin with iodine.[25] Hydrolytic removal of the N-carbethoxy group was effected by refluxing a solution of **24a** in diethylene glycol with potassium hydroxide and a trace of hydrazine[26] to afford the secondary base **24b**, mp 182–182.5°. Finally, the base **24b** was alkylated with ethylene chlorohydrin according to the process described in the literature[27] to give *dl*-dihydroveatchine (**24c**), mp 138–141°, in 56% over-all yield from **24a**. Both bases **24b** and **24c** were proved to be the racemic forms of the naturally derived dihydropyrolysis base B[27–29] and dihydroveatchine[27,28] by the complete identity of infrared spectra ($CHCl_3$) and thin layer chromatograms. Since transformation of dihydroveatchine to garryine by treatment with osmium tetroxide[27] and further to veatchine by a two-step reaction sequence[30] has already been accomplished in the natural series, this work constitutes a total synthesis of racemic forms of these alkaloids and simultaneously establishes their suggested configuration except for the F ring. All the reactions employed in this synthesis, although not satisfactory in yield in a few steps of the last stage, proceeded in a desired stereochemical sense.

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 Shoppee[31] using Woelm alumina (activity II).

(±)-N-Mesyl-13β-acetoxy-19,20-imino-5β,8α9β,10α,13α-17-norphylloclad-15-ene (7a). A solution of 1.529 g of mesyl acetate **4**[14] in 15 ml of collidine was boiled for 15.5 hr, cooled, poured into a mixture of 2 *N* hydrochloric acid and ice, and extracted with chloroform. The chloroform solution was washed successively with water, 2 *N* sodium carbonate, and twice with water and dried, and the chloroform was evaporated under reduced pressure. Recrystallization of the residue from methylene chloride–ether gave 968 mg (78%) of olefin acetate **7a**, mp 200–200.5°, ν_{max} 1729, 1336, and 1149 cm^{-1}.

Anal. Calcd for $C_{22}H_{33}O_4NS$: C, 64.84; H, 8.16; N, 3.44. Found: C, 65.25; H, 8.35; N, 3.73.

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

(26) *Cf.* S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, 205 (1963).

(27) K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, *Chem. Ber.*, **86**, 800 (1953).

(28) We are very grateful to Professor Z. Valenta for his courtesy in supplying valuable authentic samples of natural compounds.

(29) The authors wish to thank Professor S. W. Pelletier for providing a sample of dihydropyrolysis base B.

(30) S. W. Pelletier and K. Kawazu, *Chem. Ind.* (London), 1879 (1963).

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

(±)-N-Mesyl-19,20-imino-5β,8α,9β,10α,13α-17-norphyllocladen-13β-ol (7b). A solution of 1.017 g of olefin acetate **7a** in 90 ml of ethanol was refluxed with 22 ml of 2 *N* potassium hydroxide for 1.6 hr. The usual work-up and recrystallization of the residue from acetone–ether gave 861 mg (94%) of hydroxy olefin **7b**, mp 185–186°. Further recrystallization raised the melting point to 189–191° (solidifies and melts at 203–204°), ν_{max} 3591, 1333, and 1148 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}O_3NS$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.97; H, 8.65; N, 4.06.

(±)-N-Mesyl-19,20-imino-5β,8α,9β,10α,13α-17-norphyllocladane-13β,16β-diol (10a), Its Acetonide (12), and (±)-N-Mesyl-19,20-imino-5β,8α,9β,10α,13α-17-norphyllocladane-13β,15β-diol (11). Diborane gas, generated from 13.20 g (93 mmoles) of boron trifluoride etherate and 1.59 g (42 mmoles) of sodium borohydride, was introduced into a solution of 7.43 g (106 mmoles) of pure 2-methyl-2-butene in 110 ml of dry tetrahydrofuran at 0° under nitrogen with stirring during 40 min. The mixture was kept at 0° for 2 hr and was mixed with 1.675 g (4.11 mmoles) of olefin acetate **7a** in 20 ml of dry tetrahydrofuran and the resulting mixture was allowed to stand at room temperature for 18 hr. This mixture was treated successively with 5 ml of water, 50 ml of 3 *N* sodium hydroxide, and 50 ml of 30% hydrogen peroxide at 0°, and the solution was vigorously stirred for 1.5 hr at the same temperature, poured into ice–water, and extracted with chloroform. The chloroform solution was washed with 2 *N* hydrochloric acid and water and dried, and the chloroform was evaporated to give a crystalline residue, which exhibited a weak band of an acetate in the infrared spectrum. The residue was dissolved in 160 ml of ethanol and 40 ml of 2 *N* potassium hydroxide and heated under reflux for 2.5 hr. Usual work-up gave a crystalline residue, which was dissolved in 200 ml of dry acetone containing 200 mg of toluene-*p*-sulfonic acid monohydrate and was refluxed for 4 hr with stirring. The reaction mixture was cooled, poured into ice-cold 1% sodium hydrogen carbonate, and extracted with chloroform. The chloroform solution was washed with water and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on alumina (60 g). The crystalline residue from eluates with benzene and benzene–chloroform (9:1) were recrystallized from methylene chloride–ether to afford 1.061 g (61%) of acetonide **12**, mp 226–227.5°. Further recrystallization raised the melting point to 228–230°, ν_{max} 1337, 1155, 1116, and 1061 cm^{-1}.

Anal. Calcd for $C_{23}H_{37}O_4NS$: C, 65.21; H, 8.80; N, 3.31. Found: C, 65.15; H, 8.84; N, 3.29.

Eluates with benzene–chloroform (2:1) gave crystals (13 mg), mp 190–196°, which could not be further purified.

Further elution with chloroform–methanol (49:1–9:1) yielded 290 mg (18%) of the 1,3-glycol **11**, mp 261–262°, on recrystallization from chloroform–methanol. A pure sample melts at 262–263°, ν_{max}^{Nujol} 3507, 3438, 1312, and 1142 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}O_4NS$: C, 62.63; H, 8.67; N, 3.65. Found: C, 62.33; H, 8.71; N, 3.69.

The acetonide **12** (1.035 g) described above was heated with 55 ml of 90% acetic acid at 100° for 30 min and the solvent was distilled under reduced pressure to dryness (codistilled with toluene). The residue was recrystallized from methylene chloride–ether to yield 821 mg (88%) of 1,2-glycol **10a**, mp 245.5–246°, ν_{max} 3590, 1336, and 1150 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}O_4NS$: C, 62.63; H, 8.67; N, 3.65. Found: C, 62.57; H, 8.71; N, 3.69.

(±)-N-Mesyl-19,20-imino-17-norkauran-16-one (13). A solution of 1,2-glycol **10a** (730 mg) in 10 ml of dry pyridine was treated with 1.45 g of *p*-bromobenzenesulfonyl chloride at 0°, and the mixture was allowed to stand at room temperature for 40 hr. The excess of the chloride was decomposed by treating it with a small amount of water at 0° for 30 min, and the mixture was poured into a mixture of ice and 100 ml of 2 *N* hydrochloric acid and extracted with chloroform. The chloroform solution was washed twice with water and dried, and the solvent was removed under reduced pressure to yield crude monobrosylate **10b** (1.22 g). A solution of the crude **10b** in 240 ml of a mixture of dioxane–methanol (1:1) was heated with 40 ml of 5 *N* potassium hydroxide (40 ml) under reflux for 3 hr. After being cooled, the resulting mixture was neutralized with acetic acid, concentrated under reduced pressure, diluted with ice–water, and extracted with chloroform. The chloroform layer was washed with water and dried, and the solvent was evaporated under reduced pressure to give a residue, which was chromatographed on alumina (30 g). Elution with petroleum ether–benzene (1:4) gave 489 mg (70%) of ketone **13**, mp 215–217°, on recrystallization from methylene chloride–ether. A pure sample showed the same melting point, ν_{max} 1739, 1339, and 1153 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}O_3NS$: C, 65.71; H, 8.55; N, 3.83. Found: C, 65.38; H, 8.55; N, 3.82.

From eluates with chloroform–methanol (9:1), 16 mg of the starting material **10a**, mp and mmp 243–245°, was recovered.

(±)-N-Mesyl-19,20-imino-5β,8α,9β,10α,13α-15β,16β-epoxy-17-norphyllocladan-13β-ol (14). A solution of 834 mg (2.28 mmoles) of **7b** in 35 ml of benzene was mixed with 11.6 ml of 0.295 *M* benzene solution of perbenzoic acid, and the mixture was allowed to stand at room temperature. After 38 hr, the reaction solution was poured into ice–water and extracted with chloroform. The organic layer was washed with ice-cold 2 *N* sodium hydroxide and water and dried, and the solvent was removed under reduced pressure. The residue was recrystallized from acetone–ether to give 780 mg (90%) of epoxy alcohol **14**, mp 260.5–262°, ν_{max} 3592, 1340, 1149, and 897 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}O_4NS$: C, 62.97; H, 8.19; N, 3.67. Found: C, 62.56; H, 8.27; N, 3.78.

(±)-N-Mesyl-19,20-imino-17-norkauran-14β-ol-16-one (15). To a solution of 755 mg of epoxy alcohol **14** in 45 ml of dry tetrahydrofuran was added slowly 1.41 g of diethylaluminum chloride in 5 ml of dry tetrahydrofuran at 0°, and the mixture was allowed to stand at room temperature overnight. The solution was carefully poured into a mixture of 2 *N* sodium hydroxide and ice under stirring and extracted with chloroform. The chloroform solution was washed twice with water and dried, and the chloroform was removed under reduced pressure. The residue was chromatographed on alumina (30 g). Elution with benzene–chloroform (2:1–1:1) afforded 402 mg (59%) of ketol **15**, mp 241–242°, on recrystallization from acetone–ether. Further recrystallization raised the melting point to 242–243°, ν_{max} 3630, 1744, 1337, and 1151 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}O_4NS$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.03; H, 8.24; N, 3.65.

(±)-N-Mesyl-19,20-imino-16,16-ethylenedioxy-17-norkauran-14β-ol (16). A solution of ketol **15** (419 mg) in 150 mg of ethylene glycol containing 23 mg of toluene-*p*-sulfonic acid monohydrate was slowly distilled under reduced pressure (3 mm) over a period of 3 hr. The usual work-up of the reaction mixture yielded 416 mg (89%) of hydroxy ketal **16**, mp 219–220.5°, on recrystallization from methylene chloride–ether. A pure sample melts at 220–221°, ν_{max} 3533, 1346, 1148, and 1095 cm^{-1}.

Anal. Calcd for $C_{22}H_{35}O_5NS$: C, 62.09; H, 8.29. Found: C, 61.75; H, 8.27.

(±)-N-Mesyl-19,20-imino-16,16-ethylenedioxy-17-norkauran-14-one (17). Hydroxy ketal **16** (400 mg) in pyridine was treated with a pyridine–chromic anhydride complex prepared from 1 g of chromic anhydride and 1 ml of dry pyridine at room temperature for 14 hr. The mixture was poured into ice–water and extracted with ether–methylene chloride (3:1). The extracts were washed with water and dried. Evaporation of the solvent gave a residue, which was crystallized from methylene chloride–ether to give 373 mg (94%) of keto ketal **17**, mp 204–205°. An analytical sample melts at 205–206°, ν_{max} 1738, 1337, 1151, and 1109 cm^{-1}.

Anal. Calcd for $C_{22}H_{33}O_5NS$: C, 62.38; H, 7.85; N, 3.31. Found: C, 62.28; H, 7.86; N, 3.56.

(±)-N-Mesyl-19,20-imino-16,16-ethylenedioxy-17-norkaurane (18). A mixture of 267 mg of keto ketal **18**, 3.5 ml of hydrazine (95%), 848 mg of hydrazine dihydrochloride, and 8.5 ml of triethylene glycol was heated at 120° for 2 hr. After addition of 1.6 g of potassium hydroxide, the temperature of the reaction mixture was slowly raised to 215° over a period of 1 hr to remove an excess of hydrazine. After being heated for 1 hr further at the same temperature, the reaction mixture was poured into ice–water and extracted with methylene chloride. The methylene chloride solution was washed successively with water, twice with ice-cold 2 *N* hydrochloric acid, and twice with water and dried, and the solvent was evaporated under reduced pressure to afford a neutral residue (256 mg). This was crystallized from ether to give 241 mg of crude ketal **18**, mp 187–193°, and from the mother liquors, an additional crop (5 mg) of **18**, mp 193–196°, was obtained after alumina chromatography. The total yield of **18** is 91%. A pure sample melts at 198.5–200°, ν_{max} 1339, 1152, and 1114 cm^{-1}.

Anal. Calcd for $C_{22}H_{35}O_4NS$: C, 64.52; H, 8.62. Found: C, 64.62; H, 8.50.

Deketalization of the Ketal 18. The ketal (24.8 mg) was heated with 2.5 ml of 80% acetic acid at 100° for 1 hr. The usual work-up gave 19.6 mg (89%) of a ketone, which was identified with an authentic sample of the ketone **13** described above, mp and mmp 215–216°. The identity of both specimens was also confirmed by comparison of the infrared spectra.

(±)-N-Mesyl-19,20-iminokaur-16-ene (19a). To an ethereal solution of methylenetriphenylphosphorane, prepared by treating 1.65 g (4.62 mmoles) of methyltriphenylphosphonium bromide with 3.08 ml of 1.36 *N* ethereal solution of butyllithium (4.20 mmoles) at room temperature for 2 hr under stirring, was added 512 mg (1.40 mmoles) of **13** in 20 ml of dry tetrahydrofuran. The ether was distilled off and replaced with dry tetrahydrofuran, and the reaction solution was refluxed for 5 hr, diluted with water, and extracted with chloroform. The chloroform solution was washed twice with water, dried, and concentrated to dryness under reduced pressure. The residue was chromatographed on alumina (30 g). The less-polar fractions eluted with petroleum ether–benzene (4:1) were recrystallized from ether–pentane to afford 456 mg (90%) of olefin mesyl amide **19a**, mp 134–135°. A pure sample melts at 136–137°, ν_{max} 3060, 1659, 1336, 1149, and 882 cm^{-1}.

Anal. Calcd for $C_{21}H_{33}O_2NS$: C, 69.38; H, 9.15; N, 3.85. Found: C, 69.65; H, 9.30; N, 4.15.

(±)-19,20-Iminokaur-16-ene (19b) and Its Ethyl Carbonate 19c. A solution of 434 mg of the olefin mesyl amide **19a** in 20 ml of dry tetrahydrofuran and 3 ml of absolute ethanol was added dropwise to a solution of 874 mg of lithium in 90 ml of liquid ammonia with stirring. The reaction mixture was stirred at a bath temperature of −70° for 30 min and then treated with 10 ml of absolute ethanol to destroy excess lithium. The ammonia was evaporated, and the residue was diluted with water and extracted with ether. The ether layer was separated, washed with water, and dried, and the ether was removed to afford 331 mg (97%) of crude free base **19b**. Crystallization from ether gave crystalline monohydrate of the free base, mp 67–70°, ν_{max} 3386 (weak), 3066, 1658, and 879 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}N \cdot H_2O$: C, 79.15; H, 10.96. Found: C, 79.28; H, 10.66.

To a stirred solution of 314 mg (1.1 mmoles) of crude free base **19b** in 10 ml of ether were added two solutions of 8.22 ml (11 mmoles) of 2 *N* sodium hydroxide and 8.22 ml of ethereal solution of 1.194 g (16.5 mmoles) of ethyl chloroformate at the same rate over a period of 50 min under ice cooling. The mixture was stirred at room temperature for 2 hr, poured into water, and extracted with ether. The ether solution was washed successively with water, 2 *N* hydrochloric acid, and twice with water and dried, and the ether was removed under reduced pressure to dryness to afford a theoretical amount (394 mg) of an oily ethyl carbonate **19c**. Attempts to crystallize the material failed; infrared spectrum: 3067, 1675 (strong), and 880 cm^{-1}. This material exhibited only one spot on a thin layer chromatogram (silica gel G, benzene–ethyl acetate, 1:1).

Introduction of a Hydroxyl Group at the 15 Position of 19c. Crude ethyl carbonate **19c** (354 mg, 0.99 mmole) was dissolved in 20 ml of pure dry carbon tetrachloride and 5 ml of the solvent was distilled off to remove moisture as an azeotropic mixture. To this solution was added 185 mg (1.04 mmoles) of N-bromosuccinimide and 13 mg (0.05 mmole) of benzoyl peroxide, and the mixture was refluxed for 30 min. After being cooled, the separated succinimide was filtered off and washed with carbon tetrachloride. The filtrates were combined, washed with water, and dried, and the solution was concentrated to about 2 ml under reduced pressure at 27°. This concentrate was dissolved in 5 ml of benzene containing 1.48 mmoles of perbenzoic acid, and the solution was allowed to stand at 15–18° for 43 hr in the dark. The organic solvent was evaporated to about 1.5 ml under reduced pressure at 30°. This concentrate was dissolved in 10 ml of *t*-butyl alcohol, and the solution was refluxed with 4.2 g of zinc dust with vigorous stirring for 4 hr. After being cooled, zinc and zinc salt were removed by decantation and washed with ether–methylene chloride (3:1). The combined organic solutions were washed with ice-cold 2 *N* sodium hydroxide and water and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on alumina (15 g). Eluates with petroleum ether–benzene (9:1–2:1) gave 82 mg (23%) of an oil, which showed an identical infrared spectrum with that of a crude sample of *endo*-olefin **26** prepared by heating the starting olefin **19c** with iodine.[25] Eluates with petroleum ether–benzene (1:2) and benzene gave 32 mg (9%) of **(±)-N-carbethoxy-19,20-iminokaur-16-en-15α-ol (24a)**, mp 141–149°, on crystallization from ether–pentane. A pure sample melts at 150–151°, ν_{max} 3618, 1675, and 906 cm^{-1}.

Anal. Calcd for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.45. Found: C, 73.96; H, 9.42.

Further elution with benzene–chloroform (9:1–4:1) gave 38 mg (10%) of **(±)-N-carbethoxy-19,20-iminokaur-15-en-17-ol (25)**, mp 120–128.5°, on crystallization from ether–pentane. A pure sample melts at 129–130.5°, ν_{max} 3624, 1676 and 1012 cm^{-1}; the nmr spectrum showed a peak at τ 4.62 (1 H).

Anal. Calcd for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.45. Found: C, 73.81; H, 9.63.

In another run, a crude material of epoxy bromides was chromatographed on alumina. Elution with petroleum ether–benzene (2:1–1:1) gave **(±)-N-carbethoxy-19,20-imino-15α,16α-epoxy-17-bromokaurane (22)** in a yield of 9%, mp 145–147° on recrystallization from ether–pentane, ν_{max} 1676 and 936 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}O_3NBr$: C, 61.06; H, 7.58; N, 3.10. Found: C, 61.68; H, 7.75; N, 3.42.

Further elution with benzene gave another oily **epoxy bromide 23** (9%), which was found to be homogeneous on a thin layer plate but could not be crystallized.

These epoxides **22** and **23** were separately treated with zinc and ethanol in a similar way described above and crystals obtained after similar work-up of the reaction mixtures were identified with authentic samples of **24a** and **25**, respectively.

(±)-19,20-Iminokaur-16-en-15α-ol (24b). N-Carboethoxy allyl alcohol **24a** (30.4 mg) was dissolved in 2.0 ml of diethylene glycol containing 0.5% hydrazine, and the solution was refluxed with 240 mg of potassium hydroxide under nitrogen for 30 min. After being cooled, the reaction mixture was diluted with water and extracted with ether. The ethereal solution was shaken several times with 10% tartaric acid solution, and the aqueous layer was made alkaline with 2 *N* sodium hydroxide and extracted with ether. The ether solution was washed with water and dried, and the ether was removed under reduced pressure to give a residue (19.9 mg), which was crystallized from methanol and ether to afford 12.4 mg (51%) of base **24b**, mp 179–180°. A pure sample melts at 182–182.5°, ν_{max} 3603, 3393 (weak), 3077, 1161, and 906 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}ON$: C, 79.67; H, 10.37. Found: C, 79.41; H, 10.65.

This sample showed an infrared spectrum (in chloroform) and a thin layer chromatogram (silica gel G; developed with benzene–ethanol–concentrated ammonia, 50:50:1) completely identical with those of an authentic specimen[29] of naturally derived dihydropyrolysis base B (mp 168–171°).

(±)-N-(2′-Hydroxylethyl)-19,20-iminokaur-16-en-15α-ol (24c). A mixture of 16 mg of **24b**, 3 ml of absolute methanol, 1.0 ml of ethylene chlorohydrin, and 100 mg of dry sodium carbonate powder was gently refluxed for 18 hr with stirring. The reaction mixture was diluted with a saturated sodium chloride solution and extracted with chloroform. The chloroform solution was washed with water and dried, and the solvent was distilled under reduced pressure to dryness. The residue was dissolved in ether and extracted with 10% tartaric acid. The aqueous solution was neutralized with 2 *N* sodium hydroxide and extracted with ether. The ether solution was washed with water and dried. Removal of the ether under reduced pressure left a residue (15.4 mg), which was crystallized from acetone–water to afford 12.7 mg (69%) of alkylamine **24c**, mp 134–138°. Further crystallization raised the melting point to 138–141°, ν_{max} 3618, 3479, 1660, and 905 cm^{-1}.

Anal. Calcd for $C_{22}H_{35}O_2N$: C, 76.47; H, 10.21. Found: C, 76.67; H, 10.21.

This sample showed an infrared spectrum (in chloroform) and a thin layer chromatogram (alumina, developed with ethyl acetate) indistinguishable from those of an authentic sample[28] of optically active dihydroveatchine (mp 149–151°).

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