The Structure and Stereochemistry of Four New Sesquiterpenes Isolated from the Wood Oil of "Kaya" (*Torreya nucifera*)

By Tsutomu SAKAI, Kiichi NISHIMURA and Yoshio HIROSE

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In a previous communication,[1] we reported on the composition of volatile oil obtained from the leaves of *Torreya nucifera* Sieb. et Zucc. and on the identity of the torreyol isolated by Shinozaki[2] with δ-cadinol. We have subsequently studied the composition of the volatile wood oil of this species. As has previously been described in a short paper,[3] the wood oil was quite different from the leaf oil, containing four new sesquiterpenes without even trace amounts of ordinary terpenes.

The Composition of the Neutral Volatile Oil.—The following components were isolated by the adsorption chromatography of the wood oil on silica gel.

The first eluate was pure dendrolasin (I), which had been isolated previously from the ant *Lasius (Dendrolasius) fuliginosus* Latr. by Quilico et al.[4] and from the sweet potato fusel oil in our laboratory.[5] From the second and third fraction, two new sesquiterpene aldehydes were isolated; for these we propose the names nuciferal (II) and torreyal (III). Two new sesquiterpene alcohols were eluted after the aldehyde fractions. Since it was found that they were the alcohols corresponding to nuciferal and torreyal, they are named nuciferol (IV) and neotorreyol* (V). The last fraction consisted of *o*-methoxycinnamic aldehyde (VI), which had been isolated by Chiba[6] from this oil in the past.

For purposes of comparison, the composition of the root oil of this species was investigated at the same time. These results are listed on Table I.

TABLE I. THE COMPOSITION OF THE TRUNK AND ROOT OILS

Compound	Trunk oil		Root oil
	Nara Pref.	Hyōgo Pref.	Takarazuka City
Yield	%	%	%
	0.46	0.13	0.09
Dendrolasin (I)	4	11	—
Nuciferal (II)	8	—	6
Torreyal (III)	27	17	2
Nuciferol (IV)	28	4	11
Neotorreyol (V)	2	5	—
o-Methoxycinnamic aldehyde (VI)	21	18	71
Rest	10	45	10

The Structures of Nuciferal and Nuciferol.—The molecular formula of nuciferal was determined to be $C_{15}H_{20}O$ by mass spectrometry (molecular weight=216) and by the elemental analysis of its 2,4-dinitrophenylhydrazone (m. p. 138—139°C) and semicarbazone (m. p. 160—161°C). Nuciferal shows the characteristics of an α,β-unsaturated aldehyde group in the ultraviolet (λ_{max}^{EtOH} 222.5 mμ (ε, 15700)) and infrared spectra (ν_{max}^{film} 2720 (C–H), 1690 (conj. C=O) and 1645 cm^{-1} (conj. C=C)), and gives a positive Tollens reagent test. Since the other ultraviolet bands (λ_{max}^{EtOH} 264.5 mμ (ε, 950); 266.5 (880); 273 (800) and 279.5 (370)) and infrared bands (ν_{max}^{film} 1519 and 818 cm^{-1}) are similar to those of α-curcumene, it may be considered that nuciferal is an α,β-unsaturated aldehyde containing the α-curcumene skeleton.

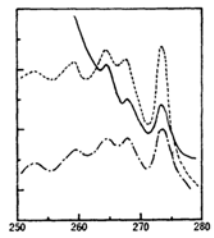
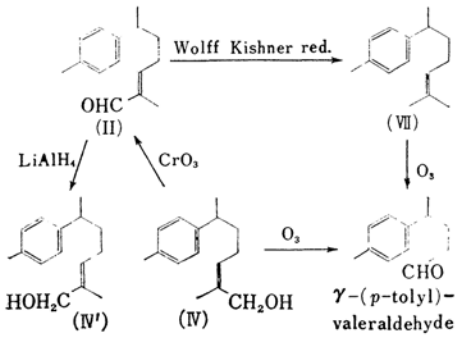


Fig. 1. UV spectra of nuciferal, nuciferol and α-curcumene.
——— Nuciferal ····· α-Curcumene
—·—· Nuciferol

1) T. Sakai, K. Nishimura, H. Chikamatsu and Y. Hirose, This Bulletin, **36**, 1261 (1963).
2) E. Shinozaki, *J. Soc. Chem. Ind.* (*Kōgyō-Kwagaku Zasshi*), **25**, 768 (1922).
3) T. Sakai, K. Nishimura and Y. Hirose, *Tetrahedron Letters*, No. 18, p. 1171 (1963).
4) A. Quilico, F. Piozzi and M. Pavan, *Tetrahedron*, **1**, 177 (1957).
5) Y. Hirose, M. Abu and Y. Sekiya, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 725 (1961).
6) K. Chiba, *Nippon Kagaku Sōran*, **1**, 6, 185 (1923).

* Since a sesquiterpene alcohol isolated from the leaves of the same plant had already been named "torreyol,"[2] the name of the present alcohol has been revised from "torreyol"[3] to neotorreyol. We wish to thank Professor H. Erdtman and Dr. V. Herout for their suggestions.

The Wolff-Kishner reduction of nuciferal afforded a hydrocarbon, which was identical with α-curcumene* (VII) as checked by infrared spectrometry and gas chromatography. Thus, it may be concluded that nuciferal is 2-methyl-6-(*p*-tolyl)hepten-2-al.



Nuciferol (IV) also shows the characteristic absorptions of a *p*-disubstituted benzene ring and a hydroxy group in the infrared (ν_{max}^{film} 3340 (OH), 1518 and 819 cm^{-1} (aromatic)) and ultraviolet spectra (Fig. 1). On oxidation with chromium trioxide in pyridine, nuciferol afforded the corresponding aldehyde, which was identical with natural nuciferal. On the other hand, the reduction of nuciferal with lithium aluminum hydride in tetrahydrofuran afforded an alcohol (IV') the infrared, ultraviolet and MS spectra of which were superimposable on those of natural nuciferol. NMR evidence (mentioned below) indicated natural nuciferol (IV) and the alcohol (IV') obtained from nuciferal to be cis-trans isomers with regard to the double bond. These results demonstrate that nuciferol is the corresponding alcohol of nuciferal, and that an isomerization of the double bond occurs upon treatment with chromium trioxide and can be represented by formula IV.

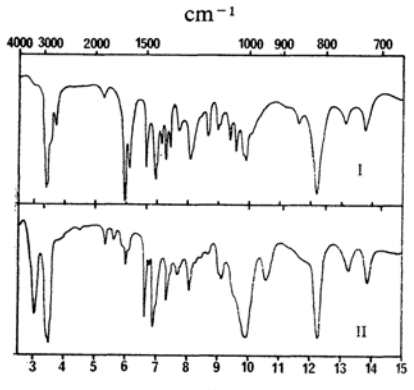


Fig. 2. IR spectra of nuciferal and nuciferol.
I, Nuciferal II, Nuciferol

* This compound was isolated by fractional distillation and adsorption chromatography from a commercial ginger oil (Polack & Schwarz Co.).

The structures of nuciferal and nuciferol were confirmed by their mass spectra, in which the presence of a series of prominent peaks at *m/e* 77, 91, 105, 119 and 133 supported the α-curcumene skeleton, for these peaks are also predominant in the fragmentation pattern of α-curcumene.

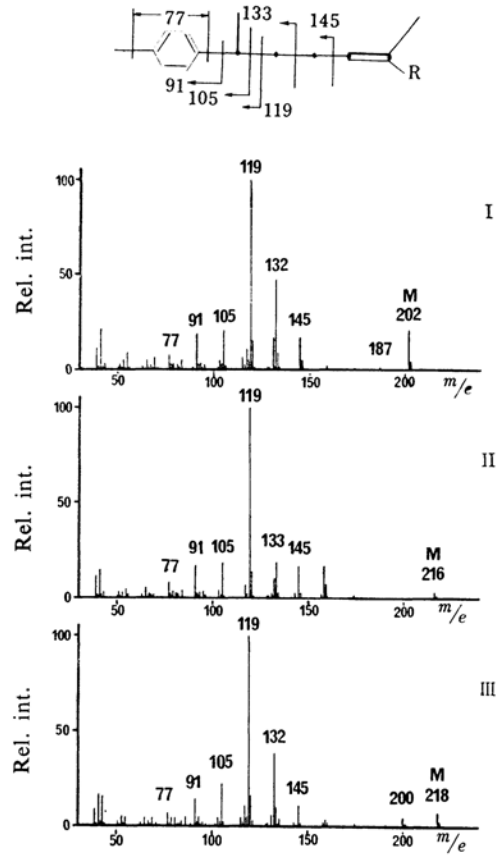
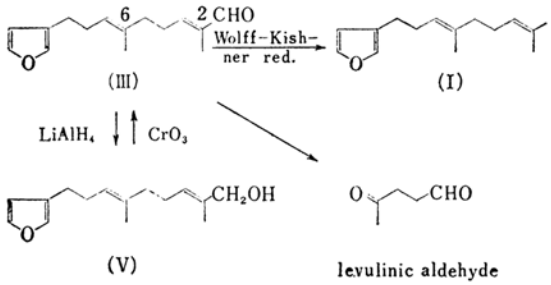


Fig. 3. Mass spectra of α-curcumene type compounds.
I, α-Curcumene II, Nuciferal III, Nuciferol

The Structures of Torreyal and Neotorreyol. —Molecular weight determination by mass spectrometry (parent peak at *m/e* 232) and the elemental analysis of its crystalline derivatives (2, 4-dinitrophenylhydrazone, m. p. 111—112°C; semicarbazone, m. p. 132—133°C) established the formula $C_{15}H_{20}O_2$ for torreyal. The ultraviolet (λ_{max}^{EtOH} 224 mμ (ε, 15940)) and infrared spectra (ν_{max}^{film} 2720 (C–H), 1690 (conj. C=O) and 1645 cm^{-1} (conj. C=C)) and the positive Tollens reagent test showed the presence of an α,β-unsaturated aldehyde group. The characteristic infrared bands at 1570, 1504, 1164, 1028, 874 and 779 cm^{-1} (similar to dendrolasin) and

the positive Ehrlich's color test suggested the presence of a furan ring in torreyal.

When torreyal was also subjected to Wolff-Kishner reduction, it afforded dendrolasin in an excellent yield. On the ozonolysis of torreyal, levulinic aldehyde was isolated as its bis-2, 4-dinitrophenylhydrazone (m. p. 238—239°C), but acetone was not detected. These results demonstrate that the aldehyde group conjugated with the ethylenic double bond is not located at C-6 but at C-2. Therefore, the structure of torreyal was deduced to be 2, 6-dimethyl-9(3-furyl)nonadien-2, 6-al.



Neotorreyol (V) is the corresponding alcohol of torreyal, because oxidation with chromium trioxide in pyridine led to torreyal, and the reduction of torreyal with lithium aluminum hydride in tetrahydrofuran yielded neotorreyol. Unlike the case of nuciferal-nuciferol, no isomerization about the double bond took place upon treatment with chromium trioxide. Its infrared spectra data are ν_{max}^{film} 3360 (OH), 1670 $\left(\begin{matrix}R\\R'\end{matrix}\right)$>C=C<$\left(\begin{matrix}R''\\H\end{matrix}\right)$, 1570, 1504, 1164, 1028, 874 and 779 cm^{-1} (furan).

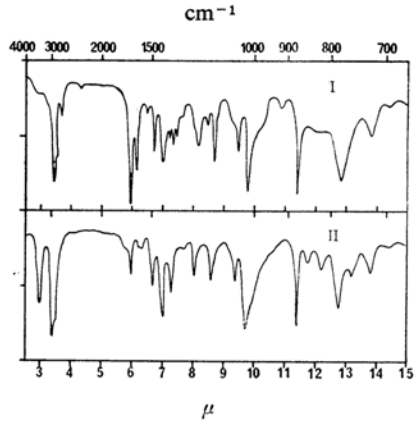
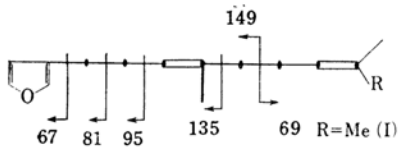


Fig. 4. IR spectra of torreyal and neotorreyol.
I, Torreyal II, Neotorreyol

The structures of torreyal and neotorreyol can be further confirmed by mass spectrometry. The predominance of the peaks at *m/e* 67, 81, 95 are common in alkylated furan compounds.[7] The peak at *m/e* 69, which, in dendrolasin and many other familiar terpenes containing the dimethylallyl group, often constitutes the base peak, is weak in the fragmentation of torreyal and neotorreyol; this suggests that the functional groups are located at the terminal position in both cases.



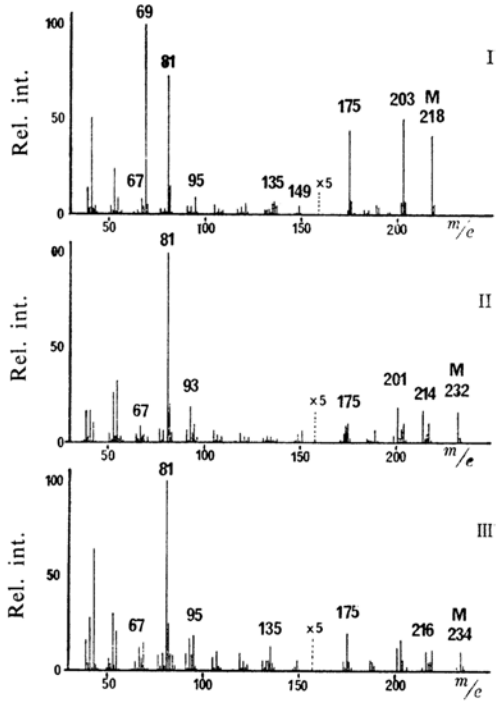


Fig. 5. Mass spectra of dendrolasin type compounds.
I, Dendrolasin II, Torreyal
III, Neotorreyol

The Stereochemistry of Nuciferal and Nuciferol.—There are two points of stereochemical interest in nuciferal and nuciferol, namely, the configurations at the asymmetric center, C-6, and at the ethylenic double bond.

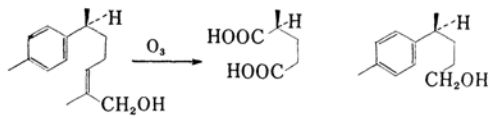
The configuration of the asymmetric center was established by the ozonization of nuciferol, which yielded *S*-(+)-α-methylglutaric acid (VIII), which was identical with an authentic sample.*

As nuciferal, nuciferol and α-curcumene isolated from ginger oil show a positive optical

7) Unpublished observation.

* We wish to thank Dr. H. Minato, Shionogi Pharmaceutical Institute, for his kind supply of (+)-α-methylglutaric acid.

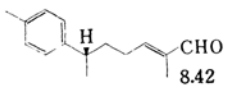
rotation, it may be suggested that they have the same S configuration. This conclusion was further supported by the calculations using the conformational asymmetry method of Brewster,[8] which was used by Marvell and Wiman[9] for the determination of the configuration of the 4-(*p*-tolyl)-1-pentanol (IX) isolated from the product of pulping Douglas fir.



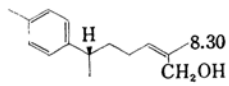
(IV) (VIII) (IX)

The configuration at the side-chain double bond was deduced from the NMR spectral data. Natural nuciferol shows in the NMR spectrum a singlet peak at 8.30 τ, due to the methyl group attached to the double bond, and triplet peaks at 4.87 τ, the vinyl proton. These peaks of the alcohol reduced from nuciferal shift to 8.50 and 4.72 τ, respectively. Usually, in a system of the $X \cdot CH_2C(CH_3)=CHCH_2 \cdot Y$ type, the τ value of *cis*-methyl (the cis relationship between the methyl group and the vinyl proton) is 8.32 (J=1.0—1.5 c. p. s.), lower (by τ 0.07) than that of *trans*-methyl.[10]

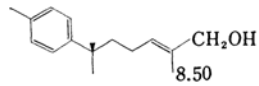
Thus, natural nuciferol was assigned a cis-isomer configuration, and the alcohol reduced from nuciferal, a trans-isomer configuration, they are illustrated by the following formulas:*



Natural nuciferal (II)

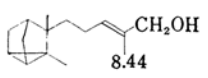


Natural nuciferol (IV)

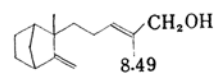


Alcohol reduced from nuciferal (IV')

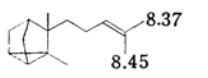
8) J. M. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).
9) E. N. Marvell and R. Wiman, *J. Org. Chem.*, **28**, 1542 (1963).
10) R. B. Bates, R. H. Carinighan, R. O. Rakutis and J. H. Schauble, *Chem. & Ind.*, **1962**, 1020.
* The configuration of α- and β-santalol was determined by Brieger[11] by an NMR spectral comparison of the corresponding hydrocarbons, α- and β-santalene. They are in good agreement with our assignment.



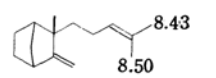
α-Santalol



β-Santalol



α-Santalene



β-Santalene

(τ values in CS_2 with Me_4Si internal reference)
11) G. Brieger, *Tetrahedron Letters*, No. 30, p. 2123 (1963).

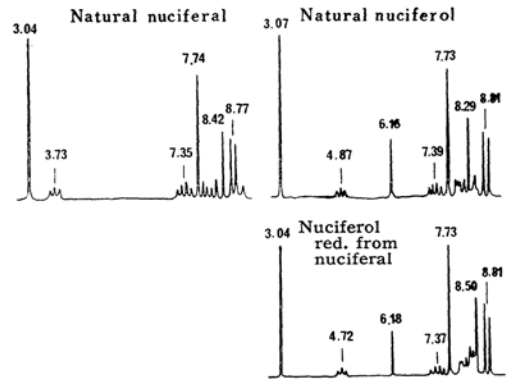
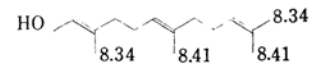


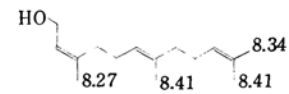
Fig. 6. NMR spectra of nuciferal and nuciferol.

The Stereochemistry of Torreyal and Neotorreyol.—As the interconversions between torreyal and neotorreyol involved no isomerization with respect to the configuration of the ethylenic double bond, it is suggested that they have the same configuration.

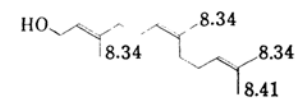
Recently, Bates et al.[12] examined the NMR spectra of four isomeric farnesols; the assigned methyl signals are shown in the following formulas:



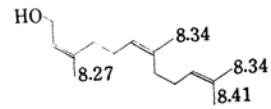
trans-trans



cis-trans

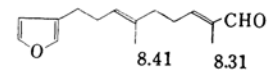


trans-cis



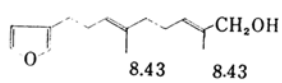
cis-cis

On the basis of these results and by comparison with dendrolasin, it may be concluded that torreyal and neotorreyol are trans-trans isomers which are represented by the following formulas:

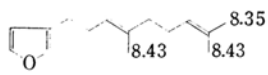


Torreyal (III)

12) R. B. Bates, D. M. Gale and B. J. Gruner, *J. Org. Chem.*, **28**, 1086 (1963).



Neotorreyol (V)



Dendrolasin (I)

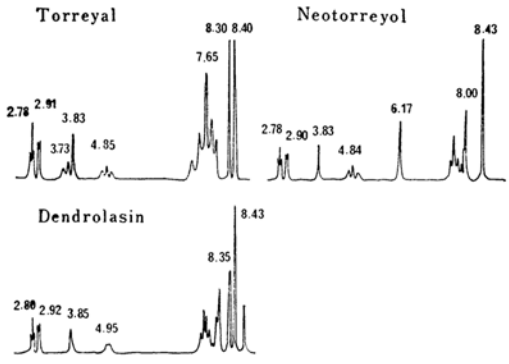


Fig. 7. NMR spectra of dendrolasin, torreyal and neotorreyol.

Experimental*1

The Preparation of the Volatile Oil. — Crushed chips of a trunk of Kaya (498 kg.) which grew in Nara Prefecture were steam-distilled. The steam-volatile oil (2.3 kg.) was obtained in a yield of 0.46%. This oil was diluted with ether, washed with 5% potassium hydroxide, and dried over sodium sulfate. After the removal of the solvent, the neutral volatile oil (2.1 kg.) was obtained.

Another sample of a trunk (5 kg.) which grew in Hyōgo Prefecture were extracted with methanol. The methanol was evaporated off, and the residue was steam-distilled to give the volatile oil (6.5 g.).

The volatile oil (3.2 g.) from the root (3.4 kg.) was obtained by the same procedure.

The Separation of the Oil.—The neutral volatile wood oil (5 g.) was chromatographed on a silica gel column (70 g.). An example of the course of isolation is shown in Table II.

Their properties are recorded and presented below.

Nuciferal (II), b. p. 107.5—108.5°C/0.03 mmHg, $[\alpha]_D^{20}$ +62.07° (*c* 16.55, $CHCl_3$), 2,4-dinitrophenylhydrazone, m. p. 138—139°C (Found: C, 63.60; H, 6.06; N, 14.04. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13%.), semicarbazone, m. p. 160—161°C (Found: C, 70.24; H, 8.50; N, 15.30. Calcd. for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.48; N, 15.34%.).*3

Torreyal (III), b. p. 124—126°C/0.05 mmHg, $[\alpha]_D^{20}$ +1.90°, 2,4-dinitrophenylhydrazone, m. p. 111—112°C (Found: C, 61.67; H, 5.67; N, 13.74. Calcd. for $C_{21}H_{24}N_4O_5$: C, 61.15; H, 5.87; N, 13.59%.), semicarbazone, m. p. 132—133°C (Found: C, 67.09; H, 8.13; N, 14.48. Calcd. for $C_{16}H_{23}N_3O$: C, 66.41; H, 8.01; N, 14.52%.).

Nuciferol (IV), b. p. 131—132°C/0.05 mmHg, $[\alpha]_D^{20}$ +41.06°.

Neotorreyol (V), b. p. 117—119°C/0.03 mmHg, $[\alpha]_D^{20}$ 0°.

Attempts to prepare crystalline derivatives of the two alcohols were both unsuccessful.

The Kishner Reduction of Nuciferal.—The Cook and Linstead procedure[13] was followed. Nuciferal (0.8 g.) was converted into the semicarbazone, which was then heated with a free flame in a distilling flask with solid potassium hydroxide (2 g.). The mass fused, ammonia and nitrogen were given off, and then oily droplets of hydrocarbon began to distill. The residue was dissolved in water and extracted with ether. The distillate and the ether extract were combined, the solvent was removed in vacuo, leaving an oil, and the oil was purified by chromatography over silica gel to yield α-curcumene (0.5 g.), which was identical with an authentic sample isolated from ginger oil. The specific retention time relative to β-elemene (1.00) was 1.76 in GLC at 170°C.

The Reduction of Nuciferal with Lithium Aluminum Hydride.—A solution of nuciferal (0.8 g.) in dry tetrahydrofuran (10 ml.) was stirred drop

Table II. The separation of the neutral volatile wood oil

Eluting solvent	Fr. No.	Eluate, g.	Component
3% Ether in hexane	1— 2	0.20	Dendrolasin (I)
3% Ether in hexane	6—10	0.40	Nuciferal (II)
3% Ether in hexane	11—20	1.34	Torreyal (III)
10% Ether in hexane	24—40	1.38	Nuciferol (IV)
20% Ether in hexane	41—43	0.12	Neotorreyol (V)
30% Ether in hexane	44—51	1.05	*o*-Methoxycinnamic aldehyde (VI)
Methanol	52	0.50	Rest

*1 M. ps. and b. ps. are uncorrected. The IR spectra were taken with a Perkin-Elmer (Model 137) and a Hitachi (Model EPI-2) infracord spectrophotometer. The UV absorption spectra were measured in an ethanol solution with a Hitachi (Model FPS-2) spectrophotometer. The NMR spectra were determined in a CCl_4 solution with Me_4Si as an internal standard, using a Varian (Model A-60) spectrometer.*2 The mass spectra were measured with a Hitachi (Model RMU-6) mass spectrometer: ionizing voltage, 80 eV.; ion-accelarating voltage, 2 kV.; temp. of ionization chamber, 250°C; vaporizing temp. of sample, 150°C. The GLC was carried out with a Shimadzu (Type GC-2B) gas chromatograph: column, Celite-Carbowax 1500 (10:2), 3 m.; temp., 170°C; carrier gas, N_2. For adsorption chromatography Mallinckrodt's silica gel was used.

*2 We wish to thank the Shionogi Pharmaceutical Institute and the Research Laboratory of Takeda Pharmaceutical Industries for their NMR measurements.

*3 The analyses were performed in the Microanalytical Laboratory of the Institute of Polytechnics, Osaka City University.

13) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, **1934**, 946.

by drop into a suspension of lithium aluminum hydride (0.4 g.) in dry tetrahydrofuran (10 ml.), and then the mixture was heated under reflux for 30 min. The mixture was decomposed by the addition of water in a ice bath and extracted with ether. The solvent was evaporated, and the residue was chromatographed on silica gel to yield a colorless oil (0.68 g.), the infrared and MS spectra of which were identical with that of nuciferol.

The Oxidation of Nuciferol with Chromium Trioxide. — (a) A solution of nuciferol (2 g.) in glacial acetic acid (6 ml.) was stirred drop by drop into a solution of chromium trioxide (0.8 g.) in glacial acetic acid (6 ml.) at room temperature. The mixture was then heated on a water bath for 20 min., cooled, poured into water (100 ml.), and extracted with ether. The ether extract was washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulfate, and evaporated to leave an oil. This residual oil was then dissolved in hexane and chromatographed on silica gel. Elution with 3% ether in hexane yielded an aldehyde (0.6 g.). Its infrared and MS spectra were identical with those of nuciferal, and the melting point of its semicarbazone was undepressed on admixture with an authentic sample.

(b) Chromium trioxide (2 g.) was stirred into pyridine (20 ml.) in an ice bath to give a chromium trioxide-pyridine complex. A solution of nuciferol (1 g.) in pyridine (10 ml.) was added to the complex prepared above in an ice bath and left overnight at room temperature. The reaction mixture was then poured into ice-water and extracted with ether. The ether extract was washed with dilute hydrochloric acid and water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel to yield nuciferal (0.8 g.).

The Ozonolysis of Nuciferol. — (a) Nuciferol (3 g.) was dissolved in methyl acetate (10 ml.) and ozonized at 0°C. The ozonide was decomposed by heating it with water (10 ml.) for 10 min., and methyl acetate was distilled off. The distillation residue was extracted with ether and then evaporated in vacuo to leave an aldehyde (1.5 g.). Its 2,4-dinitrophenylhydrazone had a m. p. of 94—95°C (Found: C, 60.13; H, 5.77; N, 15.70. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72%.), which was identical with that of an authentic sample of γ-(*p*-tolyl)valeraldehyde 2,4-dinitrophenylhydrazone (prepared from α-curcumene).

(b) A stream of ozone was passed into a solution of nuciferol (2 g.) in 90% acetic acid (10 ml.) at room temperature for 50 hr. To the mixture was then added 30% hydrogen peroxide (2 ml.), and the mixture was allowed to stand overnight at room temperature. After water (20 ml.) had been added, the excess hydrogen peroxide was decomposed by heating it with a small amount of a Pd-C catalyst on a water bath for 2 hr. After the usual work-up α-methylglutaric acid (0.2 g., m. p. 79—80°C, $[\alpha]_D^{29}$ +17.0° (*c* 0.10, MeOH), was obtained. Its melting point was not depressed by admixture with an authentic sample.

The Kishner Reduction of Torreyal. — By the reduction of semicarbazone prepared from torreyal (1.2 g.) in the manner described above for nuciferal, dendrolasin (0.6 g.) was obtained. It was identified by a comparison of its infrared spectra and gas chromatographic retention times with those of an authentic sample. The specific retention time relative to β-elemene (1.00) is 2.97 in GLC at 170°C.

The Reduction of Torreyal with Lithium Aluminum Hydride. — Torreyal (1 g.) in tetrahydrofuran was reduced with lithium aluminum hydride by the procedure described above for nuciferal. When it was worked-up in the usual manner, an alcohol (0.83 g.) was obtained. This was found to be identical with neotorreyol by infrared and MS spectroscopy.

The Oxidation of Neotorreyol with Chromium Trioxide. — A mixture of neotorreyol (1 g.) and a chromium trioxide - pyridine complex was allowed to stand overnight at room temperature. The reaction mixture was then treated in the same manner as nuciferol, thus yielding torreyal (0.6 g.).

The Ozonolysis of Torreyal.—Torreyal (1 g.) in chloroform (10 ml.) was ozonized at 0°C. After the addition of water (10 ml.) to decompose the ozonide, the mixture was heated on a water bath for 10 min. By distillation on a water bath, a chloroform solution (A) was obtained, while distillation on a free flame produced an aqueous solution (B). From A, no carbonyl derivatives were obtained at all, but from B the presence of levulinic aldehyde was proved as its bis-2,4-dinitrophenylhydrazone (0.2 g., m. p. 238—239°C. Found: C, 44.40; H, 3.54; N, 23.61. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.35; H, 3.50; N, 24.34%.). The melting point of this derivative was not depressed by admixture with an authentic sample prepared from α-methylfuran.

The Identification of *o*-Methoxycinnamic Aldehyde.—*Oxidation with Silver Oxide.*—A hot solution of aldehyde (1.7 g.) in ethanol (5 ml.) was added to a suspension of silver oxide prepared from silver nitrate (1.7 g.) in aqueous 10% sodium hydroxide (20 ml.) heated at 55—60°C. The mixture was then heated while being stirred for 10 min. The black precipitate was filtered off and washed with hot water. The filtrate was acidified with hydrochloric acid, and the precipitated acid was collected by filtration. The product was recrystallized from ethanol to furnish needles (0.8 g.; m. p. 184—185°C), identified as *o*-methoxycinnamic acid by mixed melting point determination with an authentic sample.

Oxidation with Potassium Permanganate.—To a suspension of *o*-methoxycinnamic aldehyde (1 g.) in water (10 ml.), an alkaline 10% potassium permanganate solution was added; the mixture was then heated while being stirred on a water bath for 30 min. The reaction mixture was worked up by the usual manner to give a crude acid. The crude crystall was recrystallized from hot water to yield *o*-methoxybenzoic acid, m. p. 94—95°C, which was identified by a mixed melting point determination with an authentic specimen.

Summary

Four new sesquiterpenes, nuciferal (II), nuciferol (III), torreyal (IV) and neotorreyol (V),

together with dendrolasin and *o*-methoxycinnamic aldehyde, have been isolated from the neutral volatile wood oil of Kaya (*Torreya nucifera* Sieb. et Zucc.) by adsorption chromatography on silica gel.

The structures and stereochemistry of these new compounds have been confirmed by infrared, ultraviolet, NMR and MS spectrometry, as well as by chemical methods.

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