New Diterpenes of *Torreya nucifera* Sieb. et Zucc.

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Three new labdane type diterpenes; 4-epiagathadiol (named kayadiol), 18-hydroxymanool (named torreferol), 18-hydroxy-13-epimanool (named 13-epitorreferol), were isolated from the non-steam-volatile fraction of leaves of *Torreya nucifera* Sieb. et Zucc. *(Taxaceae, Japanese name “Kaya”).

This is the first reported isolation these three diterpenes in a natural source.

In a previous paper we reported isolation and proof of the structures of 6-hydroxydehydroabietol and hinokiol from the non-steam-volatile fraction of leaves of *Torreya nucifera* Sieb. et Zucc.

Further investigation of the remaining portion has confirmed the presence of three new labdane type diterpenes.

A new diterpene alcohol named kayadiol (Ia), C_{20}H_{34}O_{2}, mp 114.5-115.5°C, [α]_{D}^{25} +45.8° (c=0.8, CHCl_{3}), shows signals at δ 1.67 (3H, s, an allylic methyl), δ 2.98-3.51 (2H, ABq, -CH_{2}O), δ 4.16 (2H, d, =C-CH_{2}OH), δ 4.51, 4.82 (each 1H, s, >C=CH_{2}), δ 5.38 (1H, br. t, >C-C=H) in its NMR spectrum. Spectral data indicate the presence of a primary alcoholic hydroxy group, a >C=CH_{2} group and an exocyclic methylene group. NMR and Mass spectra of the compound show marked similarity to those of agathadiol (Δ^{8(12)},13-labdadiene-15,19-diol). Therefore, it seems reasonable to suggest that the compound has the Δ^{8(12)},13-labdadiene skeletal structure. On hydrogenation with 2% palladium on a barium carbonate catalyst it was selectively reduced to give dihydro derivatives, one of which was identical with a synthetic specimen derived from pinifolic acid. 

![Chart 1](http://example.com/chart.png)

**Chart 1.**

- Ia R_{1}=CH_{3}, R_{2}=R_{3}=CH_{2}OH
- Ib R_{1}=CH_{2}OH, R_{2}=CH_{3}, R_{3}=CH_{2}OH
- IIa R_{1}=CH_{3}, R_{2}=CH_{2}OH, R_{3}=OH, R_{4}=CH_{3}
- IIb R_{1}=CH_{3}, R_{2}=CH_{2}OH, R_{3}=CH_{3}, R_{4}=OH
- Ic R_{1}=CH_{2}OH, R_{2}=CH_{3}, R_{3}=OH, R_{4}=CH_{3}
- IIc R_{1}=R_{2}=CH_{2}OH, R_{3}=OH, R_{4}=CH_{3}
- IIId R_{1}=R_{2}=CH_{3}, R_{3}=OH, R_{4}=CH_{3}
- IIe R_{1}=R_{2}=R_{3}=CH_{3}, R_{4}=OH

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2) We corrected its name. A paper on the common and systematic nomenclature of cyclic diterpenes was prepared by J. W. Rowe.
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CHART 2.

$\Delta_{8(20)}$-labdene-15, 18-dioic acid) by LiAlH$_4$ reduction. Since the tertiary carboxyl group of pinifolic acid has been shown to be in the $\alpha$-position, the structure ((Ia), $\Delta_{8(20)}$-$\Delta_{13}$-labdadiene-15,18-diol) is proposed for this compound. Also a comparison of NMR spectra of kayadiol and agathadiol (Ib) provided additional evidence for the $\alpha$-orientation of the C(4)-CH$_2$OH group of kayadiol. The stereochemistry of the hydroxyl group$^6$ was resolved by observing that the NMR spectrum of agathadiol showed signals at $\delta$3.21 to 3.81 due to a quartet of the axial $\beta$-CH$_2$OH group. However, kayadiol showed signals at $\delta$2.98 to 3.51 due to a quartet of equatorial $\alpha$-CH$_2$OH. In addition, signals of the 4-methyl of both compounds displayed a different chemical shift (Ia: 0.75, Ib: 0.95). These properties are explainable if kayadiol is epimeric with agathadiol at C-4. Mass spectra$^7$-$^8$ of bicyclic as well as tricyclic diterpenes.

The intensity of the m/e 135 (153-H$_2$O) peak, which is about three times as great as ($\Sigma$ % basis) that of the peak at the m/e 153 in Kayadiol, is particularly significant. But the intensity of the m/e 135 peak is lower than that of the m/e 153 peak in agathadiol. Because of this we posited that the peak at m/e 135 is due to an ion, originating by dehydration, which is more favorable for an equatorial $\alpha$-CH$_2$OH group. Differences in the spectral data of $\alpha$-CH$_2$OH and $\beta$-CH$_2$OH diterpenes are attributed to steric hindrance of the 10$\beta$-angular methyl.$^8$

Two new hydroxymanool type diterpenes were also isolated: X) C$_{20}$H$_{34}$O$_2$, mp 125.0 to 126.0°C, $\left[\alpha\right]_D^{22} +50.8^\circ$, MS M$^+$/m/e 306, and Y) C$_{20}$H$_{34}$O$_2$, mp 145.0 to 146.0°C, $\left[\alpha\right]_D^{22} +58.5^\circ$, M$^+$/m/e 306. NMR and Mass spectra of both compounds show the same ion fragmentation patterns (Figs. 1, 2).

Peaks corresponding to ion obtained from ring A by rupture of the C(6)-(7) and C(9)-C(10) bonds and removal of hydrogen—fragmentation A (m/e153)—occurred in the Mass spectra$^7$-$^8$ of bicyclic as well as tricyclic diterpenes.

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(IId) and 13-epimanool (IIe), by comparison of 3,5-dinitrobenzoate derivatives (Table I) and their IR spectra were identical with those of the authentic samples.  

TABLE I. COMPARISON OF 3,5-DINITROBENZOATE DERIVATIVES

<table>
<thead>
<tr>
<th>3,5-Dinitrobenzoate of</th>
<th>mp, °C</th>
<th>[α]D 0°</th>
</tr>
</thead>
<tbody>
<tr>
<td>The reaction product of IIA</td>
<td>94.5−95.5</td>
<td>+6.2°</td>
</tr>
<tr>
<td>Authentic manool</td>
<td>95.0−96.0</td>
<td>+8.0°</td>
</tr>
<tr>
<td>The reaction product of IIB</td>
<td>116.0−117.5</td>
<td>+30.0°</td>
</tr>
<tr>
<td>Authentic 13-epimanool</td>
<td>116.5−118.5</td>
<td>+33.0°</td>
</tr>
</tbody>
</table>

Thus, these characteristics suggest that X is epimeric with Y at C-13. This correlation, therefore, established the structures and stereochemistry at the centres of X and Y, except for the position of the extra oxygen atoms.

On an allylic rearrangement11 X produced kayadiol in a yield of 40%, with some other products.

It follows that the extra oxygen atoms of both compounds are located at C-18 as well as in kayadiol. Thus, we proposed the structures (IIa) and (IIb) for X (named torreferol, epimer of torulosol8) (IIc)) and Y (named 13-epitorreferol).

This is the first report of 4-epiagathadiol, 18-hydroxymanool (torreferol) and 18-hydroxy-13-epimanool in a natural source. All these diterpenes are correlated to biosynthesis. Kayadiol is, in particular, a precursor of 6-hydroxydehydroabietol.

Isolation of kayadiol, torreferol and 13-epitorreferol. The residual portion (5.1 g, yellow resin-like material) separated 6-hydroxydehydroabietol and hinokiol was chromatographed on a silica gel column with hexane-acetone, and the three crystalline compounds (A, B, C) were isolated.

a) Kayadiol (Ia). A was repeatedly recrystallized from hexane-acetone to give 2.5 g of kayadiol (Ia), mp 114.5−115.5°C, [α]D 0° +45.8° (c=1.40, CHCl3). Anal. Found: C, 78.43; H, 11.02. Calcd. for C25H24O2: C, 78.38; H, 11.13%. MS M+m/e 306 and base peak m/e 81. λmax MeOH (log ε): 210 (3.38). λmax cm−1: 3300 (−OH), 3038, 1648, 900 (exocyclic methylene), 1042, 1066 (−CH2OH), 1670 (C=C−). NMR δ: 0.71, 0.75 (each 3H, s, two tertiary methyls) of 1.67 (3H, s, an allylic methyl), 2.98−3.51 (2H, unsymmetrical ABq, J=11.0 cps −CH2O), 4.16 (2H, d, J=7.0 cps =C-CH2OH) and 4.51, 4.82 (each 1H, C=CH2), 5.38 (1H, br. t, J=7.0 cps C=CH2OH).

b) Torreferol (IIa). B afforded a crystalline compound, which was repeatedly recrystallized from 1% acetone-hexane to give about 0.5 g of torreferol (IIa, 18-hydroxymanool), mp 125.0−126.0°C, [α]D 0° +51.8° (c=0.80, CHCl3). Anal. Found: C, 78.43; H, 11.01. Calcd. for C25H34O2: C, 78.38; H, 11.13%. λmax MeOH (log ε): 210 (3.06). MS M+m/e 306 and base peak m/e 81. λmax cm−1: 3340 (−OH), 1645 (C=C), 1036 (−CH2OH), 908 (exocyclic methylene). NMR δ: 0.70, 0.74 (each 3H, s, two tertiary methyls) and 2.98−3.52 (2H, unsymmetrical ABq, J=11.0 cps −CH2O), 4.50, 4.83 (each 1H, C=CH2), 4.92−6.22 (3H, -CH=CH2).

c) 13-Epitorreferol (IIb). Recrystallization of C with 1% acetone in hexane gave pure 13-epitorreferol (IIb), mp 145.0−146.0°C, [α]D 0° +58.5° (c=0.30, CHCl3). Anal. Found: C, 78.13; H, 11.39. Calcd. for C20H34O2: C, 78.38; H, 11.13%. λmax MeOH (log ε): 210 (2.16). MS M+m/e 306 and base peak m/e 81. λmax cm−1: 3340, 3080, 1640, 1040, 908, 886, 880. NMR δ: 0.71, 0.74, 1.27 (each 3H, s) and 2.98−3.52 (2H, ABq), 4.52, 4.83 (each 1H, C=CH2), 4.92−6.22 (3H, −CH=CH2).

Catalytic reduction of kayadiol. Kayadiol (400 mg)

EXPERIMENTAL

Melting points were uncorrected. Optical rotations were measured with a Yanagimoto Recording Spectropolarimeter Model ORD-185. IR spectra were recorded on a JASCO DS-301 spectrophotometer. NMR spectra were determined at 60 MHz in 10−15% solutions CDCl3 (unless otherwise stated) containing Me4Si as an internal standard using a Hitachi Model R-20 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6L spectrophotometer. Chromatography was carried out using a dry column method with silica gel, unless otherwise stated.

Isolation of kayadiol, torreferol and 13-epitorreferol. The residual portion (5.1 g, yellow resin-like material) separated 6-hydroxydehydroabietol and hinokiol was chromatographed on a silica gel column with hexane-acetone, and the three crystalline compounds (A, B, C) were isolated.

a) Kayadiol (Ia). A was repeatedly recrystallized from hexane-acetone to give 2.5 g of kayadiol (Ia), mp 114.5−115.5°C, [α]D 0° +45.8° (c=1.40, CHCl3). Anal. Found: C, 78.43; H, 11.02. Calcd. for C25H24O2: C, 78.38; H, 11.13%. MS M+m/e 306 and base peak m/e 81. λmax MeOH (log ε): 210 (3.38). λmax cm−1: 3300 (−OH), 3038, 1648, 900 (exocyclic methylene), 1042, 1066 (−CH2OH), 1670 (C=C−). NMR δ: 0.71, 0.75 (each 3H, s, two tertiary methyls) of 1.67 (3H, s, an allylic methyl), 2.98−3.51 (2H, unsymmetrical ABq, J=11.0 cps −CH2O), 4.16 (2H, d, J=7.0 cps =C-CH2OH) and 4.51, 4.82 (each 1H, C=CH2), 5.38 (1H, br. t, J=7.0 cps C=CH2OH).

b) Torreferol (IIa). B afforded a crystalline compound, which was repeatedly recrystallized from 1% acetone-hexane to give about 0.5 g of torreferol (IIa, 18-hydroxymanool), mp 125.0−126.0°C, [α]D 0° +51.8° (c=0.80, CHCl3). Anal. Found: C, 78.43; H, 11.01. Calcd. for C20H34O2: C, 78.38; H, 11.13%. MS M+m/e 306 and base peak m/e 81. λmax MeOH (log ε): 210 (3.06). MS M+m/e 306 and base peak m/e 81. λmax cm−1: 3340 (−OH), 1645 (C=C), 1036 (−CH2OH), 908 (exocyclic methylene). NMR δ: 0.70, 0.74 (each 3H, s, two tertiary methyls) and 2.98−3.52 (2H, unsymmetrical ABq, J=11.0 cps −CH2O), 4.50, 4.83 (each 1H, C=CH2), 4.92−6.22 (3H, -CH=CH2).

c) 13-Epitorreferol (IIb). Recrystallization of C with 1% acetone in hexane gave pure 13-epitorreferol (IIb), mp 145.0−146.0°C, [α]D 0° +58.5° (c=0.30, CHCl3). Anal. Found: C, 78.13; H, 11.39. Calcd. for C20H34O2: C, 78.38; H, 11.13%. MS M+m/e 306 and base peak m/e 81. λmax cm−1: 3340, 3080, 1640, 1040, 908, 886, 880. NMR δ: 0.71, 0.74, 1.27 (each 3H, s) and 2.98−3.52 (2H, ABq), 4.52, 4.83 (each 1H, C=CH2), 4.92−6.22 (3H, −CH=CH2).

Catalytic reduction of kayadiol. Kayadiol (400 mg)
in ethyl acetate (30 ml) and pyridine (2 ml) was hydrogenated over 2% palladium on barium carbonate (400 mg) and consumed 1 double bond equivalent of hydrogen in one hour, after which hydrogenation ceased.

Filtration, evaporation of the solvent and purification by chromatography with hexane-acetone gave two crystalline products, one of which showed the following physical properties and spectral data

**mp 102.0–103.0°C, [α]_D^20 +17.8° (c=0.60, CHCl_3). Anal.**

Filtration, evaporation of the solvent and purification by chromatography with hexane-acetone gave two crystalline products, one of which showed the following physical properties and spectral data

**mp 90–91°C, [α]_D^22 +13.6° (c=0.30, CHCl_3), showed the same NMR spectrum as the former derivative. We believe that the former is epimeric with the latter at C-13. The former was identical with a reduced compound (III) derived from pinifolic acid.**

**LiAlH_4 reduction of pinifolic acid (IV).** Pinifolic acid (100 mg) dissolved in dry dioxane (5 ml) was added to a suspension of lithium aluminum hydride (40 mg) in dry dioxane (10 ml), then this mixture was boiled under reflux for 6 hr. Recrystallization of the crystalline product (65 mg) from hexane-acetone gave a pure compound (III), **mp 102.5–103.5°C, [α]_D^22 +20.1° (c=0.31, CHCl_3). Anal.**

**Chromium trioxide oxidation and Huang-Minlon reduction of torreferol (IIa) and 13-epitorreferol (IIb)**

A solution of IIa (50 mg) in pyridine (5 ml) was added to the chromium trioxide-pyridine complex, prepared by adding chromium trioxide (100 mg) to pyridine (10 ml), and this was left at room temperature for 10 hr. Methanol (5 ml) was added and, after an additional hour, the reaction mixture was diluted with ice cold aqueous sodium hydroxide (5%, 50 ml), then it was extracted with ether. The ether solution was extracted with ice cold hydrochloric acid (10%) to remove pyridine, then was washed with water and dried (Na_2SO_4). The residues (45 mg), obtained from oxidation of IIa, potassium hydroxide (100 mg) and hydrazine hydrate (about 100%, 0.30 ml) in diethylene glycol (5 ml, redistilled) were refluxed for 1 hr at 200–240°C. The reaction product was diluted with water and extracted with ether. The extract was dried (Na_2SO_4) and the solvent was removed leaving an oil (40 mg). Purification by chromatography on silica gel with hexane-ether gave a crystalline material (35 mg); mp 49.5–51.5°C, [α]_D^20 +28.6° (c=0.31, CHCl_3). **Anal.**

**3,5-Dinitrobenzoate of manool and 13-epimanool derived from torreferol and 13-epitorreferol.** These derivatives were prepared in the usual fashion, using an excess of 3,5-dinitrobenzoyl chloride in pyridine at room temperature for 3 days. Products were recrystallized from methylene chloride-methanol. 3,5-Dinitrobenzoate of manool: **Anal.**

**Allylic rearrangement of torreferol.** Torreferol (100 mg) was boiled under reflux with a mixture of glacial acetic acid (1.0 ml) and acetic anhydride (1.0 ml) for 8 hr. The reaction mixture was poured onto ice, made alkaline (5% aq. KOH) and extracted with ether. The ether solution was concentrated and its residue boiled under reflux with ethanolic potassium hydroxide (5%, 10 ml) for 8 hr. Purification by chromatography with hexane-ether gave crystalline products, one of which was identical with kayadiol (Ia) in all respects (40 mg, mp 114.0–115.0°C, [α]_D^20 +41.3°, (c=0.30 CHCl_3)).
Acknowledgement. We wish to thank Dr. J.W. Rowe (3,5-dinitrobenzoate of manool and 13-epimanool) and Dr. C. Enzell, Dr. O. Theander (Pinifolic acid) and Prof. R. A. Marty (agathadiol) for kindly supplying the authentic samples. We are also grateful to Prof. K. Minami and Dr. Y. Hirose (Tokyo University) for their kind advice, and are indebted to S. Uehara, President of this company for permission to publish this paper.