Structure of a New Ionone Derivative, Nigakialcohol from *Picrasma ailanthoides* PLANCHON[1)]

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A new ionone derivative, nigakialcohol, was isolated from the leaves of *Picrasma ailanthoides* PLANCHON (Simaroubaceae), the structure being found to be (4*R*,5*S*)-4-[(*R*)-3-hydroxybutyl]-5-hydroxymethyl-3,3-dimethyl-1-cyclohexanone. Nigakilactones E, F, and H and vomifoliol were also isolated from the leaves.

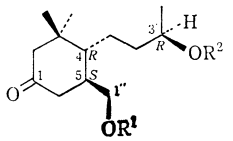
Bitter principles isolated from Simaroubaceae have been extensively investigated.[2-4)] Some of them show antileukemic activity.[5)] *Picrasma ailanthoides* PLANCHON (Japanese name: Nigaki) is one of two species belonging to Simaroubaceae grown in Japan. A number of bitter principles were isolated from the bark and stem of the plant and their structures elucidated.[3,4)] In connection with these studies, we examined constituents of the leaves of the plant and isolated vomifoliol[6)] (blumenol A[7)]) and a new ionone derivative (**1**, named nigakialcohol) as non-bitter principles, as well as three bitter principles, nigakilactones E,[3a)] F,[3a)] and H.[3b)] In this paper we wish to report on the determination of the structure of nigakialcohol (**1**).

Dried leaves of the plant were extracted with hot water. The aqueous extract was concentrated and extracted with benzene. The benzene extract was subjected to separation by chromatography to afford a new compound (**1**; yield 0.003%, $[\alpha]_D^{24}$ 0°), which is not bitter. The IR and ^{1}H NMR spectra suggested the presence of two tertiary methyls (δ 0.80 and 1.08, each 3H, s), a secondary methyl (δ 1.23, 3H, d), two hydroxyls (δ 2.26, 2H, s-like; disappeared on addition of D_2O; ν_{OH} 3400 cm^{-1}), three protons (δ 3.30—4.10, 3H, m) attached to carbon atoms bearing hydroxyls, a saturated carbonyl group ($\nu_{C=O}$ 1700 cm^{-1}), and α- and α'-methylene protons (δ 2.00—2.60, 4H, m) adjacent to the carbonyl group. The molecular formula, $C_{13}H_{24}O_3$, was inferred from elemental analysis and high resolution mass spectrum which gave no molecular ion peak but a fragment ion peak at *m/e* 210.1620 ($C_{13}H_{22}O_2$) due to dehydration.

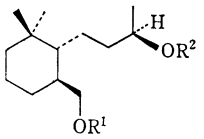
The presence of a primary alcohol and a secondary alcohol was suggested for **1** from the spectral data. This is supported by the following evidence. Acetylation of nigakialcohol (**1**) with acetic anhydride and pyridine afforded nigakialcohol diacetate (**2**) and monoacetate I (**3**). The NMR spectrum of the diacetate (**2**) showed that one acetoxyl is attached to a methylene carbon and another to a methine carbon, while the spectrum of the monoacetate I (**3**) revealed the presence of a secondary alcohol and an acetoxyl group on methylene carbon. On the other hand, another monoacetate, nigakialcohol monoacetate II (**4**) could be obtained by partial hydrolysis of diacetate (**2**) with alumina. The NMR spectrum of **4** showed the presence of a primary alcohol and an acetoxyl group on methine carbon (*cf.* Experimental).

In the NMR measurement of **1** using Eu(dpm)$_3$ as a shift reagent, one of three protons (due to –C<u>H</u>OH and –C<u>H</u>$_2$OH) giving a multiplet at δ 3.30—4.10, appeared at δ 13.85—14.65, the doublet corresponding to the secondary methyl being observed at δ 4.78 (d, J= 6 Hz). On irradiation at δ 14.28 (due to –C<u>H</u>OH), the doublet changed into a singlet. This shows the presence of the partial structure CH_3–C<u>H</u>–OH for nigakialcohol (**1**).

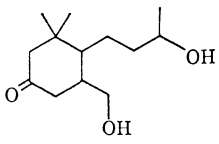
The molecular formula, $C_{13}H_{24}O_3$, of nigakialcohol and a comparison of the IR and NMR spectra of nigakialcohol with those of vomifoliol[6,7)] suggest the presence of an ionone skeleton for nigakialcohol. The above observation could lead to a structure **1a** for nigakialcohol.



	R^1	R^2
1	H	H
2	Ac	Ac
3	Ac	H
4	H	Ac



	R^1	R^2
5	H	H
11	Ac	Ac
12	Ac	H
13	H	Ac



1a

The presence of the ionone skeleton for **1** was shown as follows. Nigakialcohol (**1**) was subjected to Huang-Minlon reduction to afford deoxonigakialcohol (**5**) as an oil, $[\alpha]_D^{30}$ –28°. (±)-Deoxonigakialcohol was synthesized from (±)-γ-ionone (**6**) in four steps. (±)-γ-Ionone (**6**)[8,9)] was epoxidized with *m*-chloroperbenzoic acid in chloroform to afford a mixture of epoxy ketones (**7**) quantitatively.[10)] The mixture of epoxy ketones (**7**) gave one spot on TLC and a single peak on GLC examination. However, NMR measurement revealed that the product consists of two isomeric epoxy ketones in a ratio of 2:1 (*cf.* Experimental). The coupling constant values of the olefinic protons in the side chain for two isomers are identical, indicating that they are

configurational isomers between the side chain and the oxirane ring.

A mixture of **7** was treated with boron trifluoride etherate in toluene at 0 °C. An unsaturated keto aldehyde (**8**) obtained in 70% yield was found to be a mixture of two isomers in a ratio of 3:2 (by NMR measurement) which, without further separation, was subjected to reduction with sodium borohydride.

The reduction product was purified by column chromatography to give two diols **9** (R_f 0.36) and **9'** (R_f 0.30) in a ratio of 3:1. The IR and MS spectra of **9** and **9'** were almost the same. On GLC examination, each diol was found to be a mixture of two isomeric diols. NMR measurement also revealed that each diol consists of two isomers (*cf.* Experimental). In the NMR measurement using Eu(fod)$_3$-d_{27} as a shift reagent for **9** and **9'**, a doublet appearing at δ 1.26, changed into a pair of doublets at δ 2.25 (d, J=6 Hz) and δ 2.30 (d, J=6 Hz), and at δ 2.20 (d, J=6 Hz) and δ 2.25 (d, J=6 Hz), respectively.

Finally, the unsaturated diols **9** and **9'** were catalytically hydrogenated to afford saturated diols **10** and **10'**, respectively. **10** and **10'** gave almost the same IR spectra, minute differences being observed in the MS and NMR spectra. Each diol was found to be a mixture of two isomeric diols by NMR, GLC, and HPLC examinations. Their retention times on GLC and HPLC together with those of deoxonigakialcohol (**5**) are given in Table 1. Diol **10** was subjected to separation by preparative HPLC to give diols **10a** and **10b**. The synthetic diol **10a** was identical with deoxonigakialcohol (**5**) with respect to IR, MS, NMR, R_f on TLC, and R_t on GLC and HPLC (Table 1).

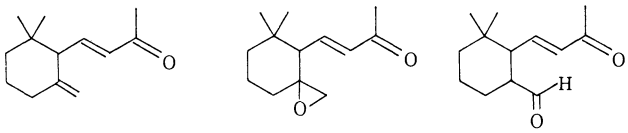
Table 1. R_f and R_t values on TLC, GLC, and HPLC for **5**, **10**, **10'**, **10a**, **10b**

	5	**10**	**10'**	**10a**	**10b**
R_f[a]	0.34	0.34	0.32	0.34	0.34
R_t on GLC[b] (min)	16.75	16.83 17.78	16.47 17.60		
R_t on HPLC[c] (min)	31.0	27.5 30.8	33.2 35.1	30.8	27.5

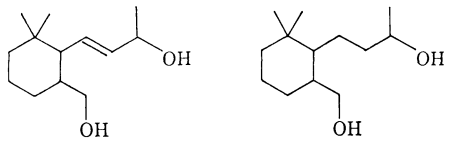
a) Developed with ether. b) Column: 10% FFAP Uniport B, 1.5 m, temperature 200 °C, a flow rate of N_2: 60 ml/min. c) Column: μ-Porasil 1/8 (inch) × 1 (foot), solvent system: 2.5% methanol–dichloromethane, flow rate: 0.5 ml/min, pressure: *ca.* 450 psi, detection: an RI detector.

The absolute configurations of chiral centers at C-5 and C-3' for nigakialcohol (**1**) were determined by an MTPA ester method; this method was recently developed by Yamaguchi and Yasuhara in order to determine the absolute configurations of secondary alcohols[11] and primary alcohols with the chiral center at the 2-position.[12]

Acetylation of deoxonigakialcohol (**5**) yielded a diacetate (**11**), which was partially hydrolyzed over alumina to afford deoxonigakialcohol monoacetate I and II (**12** and **13**). Nigakialcohol monoacetate I and II (**3** and **4**) and deoxonigakialcohol monoacetate II

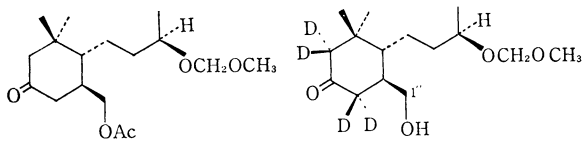


6 **7** **8**



9 **10**

(**13**) were converted into the corresponding (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid [(*R*)-(+)-MTPA; Mosher's reagent] esters (**A**) and (*S*)-(−)-MTPA esters (**B**), respectively, by Mosher's method.[13] The LIS (lanthanoid induced shift) values of the three pairs of diastereomeric esters are given in Table 2. The ΔLIS_{OMe} values[11,12] (−0.46 and −0.60) for MTPA esters of nigakialcohol monoacetate II (**4**) and deoxonigakialcohol monoacetate II (**13**) show a negative sign, indicating that the chiral center at C-5 of **4** is in *S*-configuration.[12] On the other hand, the positive sign of ΔLIS_{OMe} value (+2.06) was observed for MTPA esters of nigakialcohol monoacetate I (**3**). This indicates that the chiral center at C-3' is in *R*-configuration.[11] This is in line with the absolute configuration determination by Horeau's method.[14]



14 **15**-d_4

Table 2. Lanthanoide induced shift (LIS) values of the methoxyl group in the acid moiety for (*R*)-(+)- and (*S*)-(−)-MTPA esters[a]

Monoacetate	LIS_{OMe} value for (*R*)-(+)-MTPA ester, **A**	LIS_{OMe} value for (*S*)-(−)-MTPA ester, **B**	ΔLIS_{OMe} value ($LIS_A - LIS_B$)	Absolute configuration
3	4.89	2.83	+2.06	*R*(C-3')
4	1.09	1.55	−0.46	*S*(C-5)
13	3.33	3.93	−0.60	*S*(C-5)

a) Determined at the molar ratio of Eu(fod)$_3$-d_{27}/each ester (1:1) for a *ca.* 1.3 mmol/ml solution of each ester in CCl_4.

The absolute configuration of the asymmetric center at C-4 could be determined by the measurement of coupling constant between $C_{(4)}$–H and $C_{(5)}$–H in a tetradeuterio derivative (**15**-d_4) derived from nigakialcohol (**1**). Nigakialcohol monoacetate I (**3**) was treated with dimethoxymethane[15] and phosphorus pentaoxide to afford nigakialcohol monoacetate I methoxymethyl ether (**14**). Deuteriation of **14** proceeded

with concomitant hydrolysis of the acetoxyl group at C-1″ to give **15**-d_4. In the NMR measurement of **15**-d_4 using Eu(fod)$_3$-d_{27} as a shift reagent, a broad signal due to a proton on C-5 and a broad signal due to methylene protons (-C$\underline{H}_2$OH) appeared at δ 2.20—2.50 and δ 4.25—4.66, respectively. On irradiation at δ 4.46, the broad signal due to the proton on C-5 collapsed into a doublet, coupled with a proton on C-4 with a coupling constant, J=11.5 Hz. Since the large coupling constant suggests a *trans*-relationship between $C_{(5)}$-H and $C_{(4)}$-H, the asymmetric carbon atom at C-4 position could be concluded to be in *R*-configuration.

The structure including the absolute configuration of nigakialcohol should be represented by (4*R*,5*S*)-4-[(*R*)-3-hydroxybutyl]-5-hydroxymethyl-3,3-dimethyl-1-cyclohexanone.

Experimental

General Procedure. IR spectra were taken on a Hitachi 260-30 or a JASCO JIR-10 spectrometer. ^{1}H NMR spectra were measured on a Hitachi R-20B (60 MHz) or a JNM PS-100 (100 MHz) spectrometer (JEOL). Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in Hz. CD and ORD curves were measured on a JASCO Model J-20 spectrometer. Measurements of optical rotation $[\alpha]_D$ were carried out using a JASCO DIP-SL polarimeter. Mass spectra (MS) were obtained on a Hitachi RMU-6-Tokugata mass spectrometer and high resolution mass spectra on a Hitachi RMH-2 mass spectrometer. Gas chromatography (GLC) was carried out using Shimadzu 4A-PF equipped with a hydrogen flame ionization detector (column A: SP-1000, 2 m, N_2 60 ml/min; column B: 10% FFAP Uniport B, 1.5 m, N_2 60 ml/min). Liquid Chromatograph Model ALC/GPC 202/401 (Waters Assoc.) was used for high performance liquid chromatography (HPLC); column: μ-Porasil 1/8 (inch)×1 (foot). Thin layer chromatography (TLC) was carried out on Kieselgel GF_{254} and Kieselgel G (E. Merck) of 0.25 mm thickness for analytical and 0.5 mm thickness for preparative. Wakogel C-200 (Wako) and Activated Alumina mesh 200—300 (Showakagaku) were used for column chromatography.

*Isolation of Nigakialcohol (**1**).* Dried leaves (12 kg) of *Picrasma ailanthoides* PLANCHON were pulverized and extracted with hot water (90 °C, 70 L) for 4 h. Extraction under the same conditions was repeated twice. The combined extracts (*ca.* 200 L) were concentrated under reduced pressure to *ca.* 40 L and extracted continuously with benzene for 4 days. The benzene extracts (36.5 g), dissolved in benzene, were passed through a column of neutral alumina (2 kg, pretreated with dilute hydrochloric acid, washed with water until the washings became neutral, and then activated) and eluted with the following solvents (each fraction: 1 L). Fractions 1—4, benzene; frs 5—20, benzene-ether 1:1; frs 21—31, ether; frs 32—40, ether-ethyl acetate 1:1; frs 41—92, ethyl acetate. Fractions 60—90 (4.7 g) were subjected to separation by column chromatography on silica gel (300 g). Elution (each fraction: 40 ml) was carried out with benzene (100 ml), benzene-acetone, 4:1 (500 ml), 3:1 (800 ml), 2:1 (1.2 L), and then with 1:1 (1 L). Nigakialcohol (**1**; 306 mg) was obtained from fractions 46—76. Fractions 77—95 (129 mg) were combined and purified by rechromatography on silica gel (20 g) to afford additional nigakialcohol (**1**; 67 mg). Nigakialcohol (**1**): IR (neat) 3400 and 1700 cm^{-1}; $[\alpha]_D^{24}$ 0° (*c* 0.21, $CHCl_3$); CD (*c* 0.083, EtOH, at 24 °C) $[\theta]_{340}$ −50, $[\theta]_{323}$ 0, $[\theta]_{294}$ +310, $[\theta]_{278}$ 0, $[\theta]_{255}$ −460; ORD (*c* 0.083, EtOH, at 24 °C) $[\Phi]_{360}$ −27°, $[\Phi]_{345}$ 0°, $[\Phi]_{314}$ +180°, $[\Phi]_{298}$ 0°, $[\Phi]_{277}$ −410°, $[\Phi]_{260}$ 0°; NMR (60 MHz) δ ($CDCl_3$) 0.80, 1.08 (each 3H, s, *t*-CH_3), 1.23 (3H, d, J=6 Hz, *s*-CH_3), 2.00—2.60 (4H, m, -CH_2-CO-CH_2-), 2.26 (2H, s-like, 2×-OH; disappeared on addition of D_2O), and 3.30—4.10 (3H, m, -C$\underline{H}_2$OH and -$\underline{C}$HOH); High resolution MS, Found: *m/e* 210.1628. Calcd for $C_{13}H_{22}O_2$ $(M-H_2O)^+$: *m/e* 210.1620. Found: *m/e* 213.1456. Calcd for $C_{13}H_{21}O_3$ $(M-CH_3)^+$: *m/e* 213.1491; Found: C, 65.99; H, 10.67%. Calcd for $C_{13}H_{24}O_3 \cdot 1/2\ H_2O$: C, 65.79; H, 10.62%. NMR measurement using Eu(dpm)$_3$ as a shift reagent was effected for a 9% (w/v) solution of **1** in $CDCl_3$ in a molar ratio [**1**/Eu(dpm)$_3$] of 1:0.69.

Isolation of Vomifoliol and Nigakilactones E, F, and H. The benzene extracts (45 g), obtained from the dried leaves (15 kg) by the same procedure as described above, were dissolved in benzene and chromatographed on a column of neutral alumina (3 kg) using the following solvents (each fraction: 1 L) as eluents: benzene (frs 1—7), benzene-ether (1:1, frs 8—65), ether (frs 66—165), ether-ethyl acetate (3:1, frs 166—187), ether-ethyl acetate (2:1, frs 188—220), ether-ethyl acetate (1:1, frs 221—254), and ethyl acetate (frs 255—265).

Fractions 66—75 were combined and the solvent was distilled off. The residue (2.3 g) was further chromatographed on silica gel [dry column, 250 g, eluent: benzene-ether (from 1:1 to 1:3), each fraction 50 ml]. Fractions 27—34 were combined and crystallized from benzene to afford vomifoliol (1.2 g).[6,7]

Fractions 101—116 gave a residue (1 g) which was chromatographed on silica gel [dry column, 150 g, eluent: ethyl acetate-ether (1:4), each fraction 50 ml]. Fractions 31—33 were combined and crystallized from benzene and then from benzene-light petroleum to give nigakilactone E.[3a]

Fractions 144—170 were combined and the solvents were removed. The residue (1.5 g) was further chromatographed on silica gel [dry column, 200 g, eluent: benzene-acetone (3:1), each fraction 50 ml]. Fractions 7—9 gave a residue which was crystallized successively from benzene and aqueous methanol to yield nigakilactone F (153 mg).[3a]

Fractions 182—195 were combined (1.8 g) and chromatographed on silica gel [dry column, 200 g, eluent: benzene-acetone (from 3:1 to 1:1), each fraction 100 ml]. Fractions 7 and 8 were combined and crystallized from benzene and then from methanol to give nigakilactone H (17 mg).[3b]

*Acetylation of Nigakialcohol (**1**).* Nigakialcohol (**1**; 41.0 mg) was treated with acetic anhydride (3 ml) and pyridine (5 drops) at room temperature for 25 min. After addition of methanol, the reaction mixture was treated as usual to give a residue, which was dissolved in benzene and passed through a dry column of silica gel (5 g). On elution (each fraction: 1 ml) with ether, fractions 8—12 gave nigakialcohol diacetate (**2**; 24.4 mg, yield 43%) and fractions 15—26 afforded nigakialcohol monoacetate I (**3**; 26.7 mg, yield 55%). Nigakialcohol diacetate (**2**): IR (neat) 1740 and 1715 cm^{-1}; $[\alpha]_D^{27}$ +30° (*c* 0.098, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.81, 1.09 (each 3H, *t*-CH_3), 1.24 (3H, d, J=6 Hz, *s*-CH_3), 2.03, 2.07 (each 3H, s, CH_3COO-), 2.10—2.50 (4H, m, -CH_2-CO-CH_2-) 3.80—4.40 (2H, m, -C$\underline{H}_2$OAc), and 4.50—5.10 (1H, m, -$\underline{C}$HOAc); MS *m/e* 252 $(M-60)^+$; Found: C, 65.36; H, 8.93%. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03%. Nigakialcohol monoacetate I (**3**): IR (neat) 3450, 1740, and 1715 cm^{-1}; $[\alpha]_D^{26}$ +3° (*c* 0.094, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.82, 1.10 (each 3H, s, *t*-CH_3), 2.07 (3H, s, CH_3COO-), 1.22 (3H, d, J=6 Hz, *s*-CH_3), 1.67 (1H, s-like, -OH; disappeared on addition of D_2O), 2.05—2.70 (4H, m, -CH_2-CO-CH_2-), 3.45—4.05 (1H, m, -$\underline{C}$HOH), and 3.95—4.30 (2H, m,

$-C\underline{H}_2OAc$); MS *m/e* 210 $(M-60)^+$; High resolution MS, Found: *m/e* 210.1558. Calcd for $C_{13}H_{22}O_2$ $(M-CH_3COOH)^+$: *m/e* 210.1620.

Partial Hydrolysis of Nigakialcohol Diacetate (2) into Nigakialcohol Monoacetate II (4). A solution of nigakialcohol diacetate (**2**; 57.3 mg) in benzene was adsorbed on the neutral alumina (6 g, prepared by the same pretreatment as before) for 6 days at room temperature. Elution with ether afforded nigakialcohol monoacetate II (**4**; 22.4 mg, yield 46%), IR (neat) 3450, 1735, and 1715 cm^{-1}; $[\alpha]_D^{26}$ +21° (*c* 0.14, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.80, 1.08 (each 3H, s, *t*-CH_3), 1.25 (3H, d, J=6 Hz, *s*-CH_3), 2.01 (1H, s-like, -OH; disappeared on addition of D_2O), 2.05 (3H, s, CH_3COO-), 2.05—2.60 (4H, m, $-CH_2-CO-CH_2-$), 3.40—3.90 (2H, m, $-C\underline{H}_2OH$), and 4.60—5.20 (1H, m, $-C\underline{H}OAc$); MS *m/e* 252 $(M-18)^+$; High resolution MS, Found: *m/e* 252.1727. Calcd for $C_{15}H_{24}O_3$ $(M-H_2O)^+$: *m/e* 252.1725, Found: *m/e* 210.1652. Calcd for $C_{13}H_{22}O_2$ $(M-CH_3COOH)^+$: *m/e* 210.1620.

Huang-Minlon Reduction of Nigakialchol (1). A mixture of nigakialcohol (**1**; 153.7 mg), diethylene glycol (16 ml), hydrazine hydrate (2.4 ml), and potassium hydroxide (1.6 g) was heated under reflux at 140 °C for 1 h under a nitrogen atmosphere, distillation being continued until the temperature of the vapor reached 218 °C. The reaction mixture was refluxed at 218 °C for 5 h, followed by extraction with chloroform and the usual treatment. The reaction product was dissolved in benzene and subjected to purification by chromatography on silica gel (5 g). Elution with ether afforded deoxonigakialcohol (**5**; 98.3 mg, yield 69%), IR (**5**; 3 mg/0.12 ml $CHCl_3$) 3380 cm^{-1}, (**5**; 12.5 mg/5.0 ml $CHCl_3$) 1450, 1388, 1088, 1061, and 945 cm^{-1}, $[\alpha]_D^{30}$ −28° (*c* 0.125, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.83, 0.94 (each 3H, s, *t*-CH_3), 1.19 (3H, d, J=6 Hz, *s*-CH_3), 2.27 (2H, s-like, 2× -OH; disappeared on addition of D_2O), and 3.35—4.05 (3H, m, $-C\underline{H}_2OH$ and $-C\underline{H}OH$); High resolution MS, Found: *m/e* 196.1745. Calcd for $C_{13}H_{24}O$ $(M-H_2O)^+$: *m/e* 196.1827; GLC and HPLC (Table 1).

Acetylation of Deoxonigakialcohol (5). Deoxonigakialcohol (**5**; 110.3 mg) was treated with acetic anhydride (8 ml) and pyridine (10 drops) at room temperature for 6 h. After decomposition of excess acetic anhydride by addition of methanol and the usual work-up, the reaction product was dissolved in benzene and passed through a column of silica gel (5 g). On elution with benzene–ether (2: 1), deoxonigakialcohol diacetate (**11**; 122.0 mg, yield 79%) was obtained, IR (neat) 1742 cm^{-1}; $[\alpha]_D^{20}$ −17° (*c* 1.06, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.82, 0.93 (each 3H, s, *t*-CH_3), 1.21 (3H, d, J=6 Hz, *s*-CH_3), 2.02, 2.05 (each 3H, s, CH_3COO-), 3.60—4.40 (2H, m, $-C\underline{H}_2OAc$), and 4.60—5.10 (1H, m, $-C\underline{H}$-OAc); MS *m/e* 238 $(M-60)^+$.

Partial Hydrolysis of Deoxonigakialcohol Diacetate (11). A solution of deoxonigakialcohol diacetate (**11**; 119.2 mg) in benzene was adsorbed on the neutral alumina (7 g, prepared by the same treatment as before) for 6 days. After benzene (20 ml) had been passed through the column, elution with benzene–ether (4: 1, each fraction: 10 ml) was followed. From fractions 1—5, the starting material (**11**; 26.0 mg) was recovered in 23% yield. Fractions 6—11 gave deoxonigakialcohol monoacetate II (**13**; 43.1 mg, yield 43%), IR (neat) 3430 and 1739 cm^{-1}; $[\alpha]_D^{30}$ −7° (*c* 0.40, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.81, 0.92 (each 3H, s, *t*-CH_3), 1.23 (3H, d, J=6 Hz, *s*-CH_3), 1.75 (1H, s-like, -OH; disappeared on addition of D_2O), 2.03 (3H, s, CH_3COO-), 3.30—3.90 (2H, m, $-C\underline{H}_2OH$), and 4.85 (1H, m, $-C\underline{H}OAc$); MS *m/e* 196 $(M-60)^+$. Fractions 13—17 afforded deoxonigakialcohol monoacetate I (**12**; 10.4 mg, yield 10%), IR (neat) 3420 and 1739 cm^{-1}; $[\alpha]_D^{30}$ −36° (*c* 0.104, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$); 0.83, 0.94 (each 3H, s, *t*-CH_3), 1.20 (3H, d, J=6 Hz, *s*-CH_3), 1.65 (1H, s-like, -OH; disappeared on addition of D_2O), and 3.55—4.40 (3H, m, $-C\underline{H}_2OAc$ and $-C\underline{H}OH$); MS *m/e* 196 $(M-60)^+$.

Epoxidation of (±)-γ-Ionone (6). (±)-γ-Ionone (**6**) was prepared from geraniol *via* Ψ-ionone[8] by the reported procedure.[9] The crude γ-ionone containing α- and β-ionones was chromatographed on a column of silica gel impregnated with 20% silver nitrate. Elution with 15% ether in hexane gave (±)-γ-ionone (**6**), the purity of which was examined by GLC (column: A, temperature 220 °C), IR (neat) 1676, 990, and 896 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.89, 0.93 (each 3H, s, *t*-CH_3), 2.27 (3H, s, CH_3CO-), 2.59 (1H, s, $-C\underline{H}-CH=CH-$), 4.57, 4.81 (each 1H, s, $-C=CH_2$), 6.10 (1H, d, J=16 Hz, $-CH=C\underline{H}-CO-$), and 6.97 (1H, dd, J=10 and 16 Hz, $-C\underline{H}-C\underline{H}=CH$); MS *m/e* 192 (M^+) and 43 (base peak).

(±)-γ-Ionone (**6**; 987.1 mg) in chloroform (100 ml) was treated with *m*-chloroperbenzoic acid (975.7 mg) at room temperature for 2 days with agitation. After addition of chloroform (100 ml), the reaction was stopped by addition of 10% sodium sulfite solution and the reaction product was extracted with chloroform. The usual treatment gave a mixture of isomeric epoxy ketones (**7**) in a quantitative yield, which showed a single peak on GLC (R_t 4.3 min, column: A, temperature 220 °C) and a single spot on TLC (R_f 0.38, developed with hexane–ether, 1: 1); IR (neat) 3030, 1662, 1250, and 900 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.92, 1.05 (each 3H×2/3, s, *t*-CH_3), 0.95, 1.01 (each 3H×1/3, s, *t*-CH_3), 2.24 (3H, s, CH_3CO-), 6.08 (1H×2/3, d, J=16 Hz, $-CH=C\underline{H}-CO-$), 6.05 (1H×1/3, d, J=16 Hz, $-CH=C\underline{H}-CO-$), 6.68 (1H×2/3, dd, J=10 and 16 Hz, $-C\underline{H}-C\underline{H}=CH-$), 6.66 (1H×1/3, dd, J=10 and 16 Hz, $-C\underline{H}-C\underline{H}=CH-$); MS *m/e* 208 (M^+) and 43 (base peak); Found: C, 74.68; H, 9.48%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%.

Keto Aldehyde (8). A few drops of boron trifluoride etherate solution were added with stirring to an ice-cooled solution of the epoxy ketone (**7**; 280.5 mg) in toluene (2.5 ml). After 15 min, 5% sodium hydroxide solution was added. The reaction product was then extracted with toluene and the extract was treated as usual to give a residue. The residue was subjected to purification by chromatography on a column of silica gel (6 g). Elution with ether afforded a mixture of isomeric keto aldehydes (**8**; 200.5 mg, yield 71.4%). The product showed one spot on TLC (R_f 0.44, developed with hexane–ether, 2: 3) and one peak on GLC (R_t 6.1 min, column: A, temperature 220 °C); IR (neat) 2830, 1715, and 1662 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.94 (6H×3/5, s, *t*-CH_3), 0.87, 1.10 (each 3H×2/5, *t*-CH_3), 2.24 (3H, s, CH_3CO-), 2.45—2.80 (2H, m, $-CH-$), 6.05 (1H×3/5, d, J=16 Hz, $-CH=C\underline{H}-CO-$), 6.12 (1H×2/5, d, J=16 Hz, $-CH=C\underline{H}-CO-$), 6.66 (1H×3/5, dd, J=8 and 16 Hz, $-C\underline{H}-C\underline{H}=CH-$), 6.70 (1H×2/5, dd, J=8 and 16 Hz, $-C\underline{H}-C\underline{H}=CH-$), 9.45 (1H×3/5, d, J=3.5 Hz, -CHO), and 9.56 (1H×2/5, s-like, -CHO); MS *m/e* 208 (M^+) and 43 (base peak); High resolution MS, Found: *m/e* 208.1464. Calcd for $C_{13}H_{20}O_2$: *m/e* 208.1463.

Reduction of Keto Aldehyde (8) into Unsaturated Diol (9). A solution of the keto aldehyde (**8**; 40.8 mg) in methanol (1.5 ml) was cooled with an ice bath and sodium borohydride (7.7 mg) was added to the solution. After 30 min, the reaction was stopped by addition of aqueous acetic acid, methanol was removed and extraction with ether was followed. The ether extract was treated as usual and the reaction product was chromatographed on a column of silica gel (10 g) eluting with ether to afford isomeric diols **9** (7.3 mg) and **9′** (2.4 mg). **9**: TLC R_f 0.36 (developed with ether); GLC R_t 24.4 and 25.8

min with peak area in a ratio of 3:2 (column: A, temperature 200 °C), R_t 18.3 and 19.0 min with peak area in a ratio of 3:2 (column: B, temperature 210 °C); IR (neat) 3330 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.85 (6H×3/5, s, *t*-CH_3), 0.80, 1.02 (each 3H×2/5, s, *t*-CH_3), 1.26 (3H, d, J=6 Hz, *s*-CH_3), 2.41 (2H, s-like, -OH), 3.15—3.65 (2H, m, -$C\underline{H}_2OH$), 4.05—4.50 (1H, m, -$C\underline{H}OH$), and 5.40—5.70 (2H, m, -CH=CH-); MS *m/e* 194 $(M-18)^+$ and 82 (base peak). **9′**: TLC R_f 0.30 (developed with ether); GLC R_t 26.1 and 27.1 min with peak area in a ratio of 5:3 (column: A, temperature 200 °C), R_t 18.4 and 18.8 min with peak area in a ratio of 5:3 (column: B, temperature 210 °C); IR (neat) 3330 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.82 (6H×5/8, s, *t*-CH_3), 0.77, 1.02 (each 3H×3/8, s, *t*-CH_3), 1.26 (3H, d, J=6 Hz, *s*-CH_3), 2.82 (2H, s-like, -OH), 3.20—3.75 (2H, m, -$C\underline{H}_2OH$), 4.00—4.40 (1H, m, -$C\underline{H}OH$), and 5.18—5.78 (2H, m, -CH=CH-); MS *m/e* 194 $(M-18)^+$ and 82 (base peak). The NMR measurement using Eu(fod)$_3$-d_{27} as a shift reagent was carried out for a 10% (9%) solution of **9** (**9′**) in $CDCl_3$ in a molar ratio [**9** (**9′**)/Eu(fod)$_3$-d_{27}] of 1:0.25 (0.17).

Hydrogenation of Unsaturated Diols (9 and 9′). Unsaturated diol (**9**; 59.8 mg) in ethanol (4 ml) was hydrogenated in the presence of 5% palladium charcoal (4.9 mg) at room temperature overnight. The reaction product was purified by chromatography on a column of silica gel (7 g). Elution with ether gave a mixture of saturated diols (**10a** and **10b**; 20.1 mg, yield 33.3%), R_f value on TLC, R_t value on GLC, and R_t values on HPLC are listed in Table 1; IR (neat) 3320 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.82, 0.90, 0.93, 1.00 (each s, total 6H, *t*-CH_3), 1.19 (3H, d, J=6 Hz, *s*-CH_3), 2.01 (2H, m, 2× -OH), and 3.55 (3H, m, -$C\underline{H}OH$ and -$C\underline{H}_2OH$); MS *m/e* 196 $(M-18)^+$ and 69 (base peak).

Unsaturated diol (**9′**; 24.0 mg) in ethanol (4 ml) was hydrogenated in the presence of 5% palladium charcoal (4.9 mg) under the same conditions as above to afford a mixture of saturated diols (**10′a** and **10′b**; 9.8 mg, yield 40.5%), R_f value on TLC, R_t values on GLC, and R_t values on HPLC are shown in Table 1; IR (neat) 3320 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.82, 0.90, 0.93, 1.00 (each s, total 6H, *t*-CH_3), 1.19 (3H, d, J=6 Hz, *s*-CH_3), 2.06 (2H, s-like, 2× -OH), 3.40—4.20 (3H, m, -$C\underline{H}OH$ and -$C\underline{H}_2OH$); MS *m/e* 196 $(M-18)^+$ and 69 (base peak).

Separation of Diols (10a and 10b) by HPLC. A mixture of the diols (**10a** and **10b**; 12.6 mg) was subjected to separation by preparative HPLC under the same conditions as given in Table 1 to give diols **10a** (2.5 mg) and **10b** (3.0 mg). **10a**: R_f value on TLC, R_t value on GLC, and R_t value on HPLC given in Table 1; IR (**10a**; 2.5 mg/0.12 ml $CHCl_3$) 3380 cm^{-1}, (**10a**; 2.5 mg/1.5 ml $CHCl_3$) 1450, 1388, 1088, 1061, and 945 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.90, 1.00 (each 3H, s, *t*-CH_3), 1.21 (3H, d, J=6 Hz, *s*-CH_3), 1.80 (2H, s-like, 2× -OH), and 3.35—4.05 (3H, m, -$C\underline{H}OH$ and -$C\underline{H}_2OH$); High resolution MS, Found: *m/e* 196.1830. Calcd for $C_{13}H_{24}O$ $(M-H_2O)^+$: *m/e* 196.1827. **10b**: R_f and R_t values given in Table 1; IR (**10b**; 3 mg/0.12 ml $CHCl_3$) 3380 cm^{-1}, (**10b**; 3.0 mg/1.5 ml $CHCl_3$) 1450, 1388, 1076, 1061, and 937 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.83, 0.94 (each 3H, s, *t*-CH_3), 1.19 (3H, d, J=6 Hz, *s*-CH_3), 1.74 (2H, s-like, 2× -OH), 3.35—4.05 (3H, m, -$C\underline{H}OH$ and -$C\underline{H}_2OH$); High resolution MS, Found: *m/e* 181.1590. Calcd for $C_{12}H_{21}O$ $(M-H_2O-CH_3)^+$: *m/e* 181.1592.

(R)-(+)-MTPA Ester of Nigakialcohol Monoacetate I (3). Pyridine (0.3 ml) and (+)-MTPACl (25 μl) were added to a solution of nigakialcohol monoacetate I (**3**; 17.8 mg) in carbon tetrachloride (0.3 ml). The mixture was stirred for 2 h at room temperature and then *N,N*-dimethyl-1,3-propanediamine (50 μl) was added. After the usual treatment, the reaction product was dissolved in benzene and subjected to purification by chromatography on a column of silica gel (2 g). Elution with ether gave (*R*)-(+)-MTPA ester of **3** (24.0 mg, yield 74%), IR (neat) 1742 and 1720 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.77, 1.02 (each 3H, s, *t*-CH_3), 1.30 (3H, d, J=6 Hz, *s*-CH_3), 2.01 (3H, s, CH_3COO-), 3.49 (3H, -OCH_3), 3.90—4.15 (2H, m, -$C\underline{H}_2OAc$), 4.70—5.20 (1H, m, -$C\underline{H}$-OMTPA), and 7.20—7.70 (5H, m, arom H's); MS *m/e* 253 and 189 (base peak).

(S)-(−)-MTPA Ester of Nigakialcohol Monoacetate I (3). The same treatment of nigakialcohol monoacetate I (**3**; 23.1 mg) with (−)-MTPACl (25 μl) gave (*S*)-(−)-MTPA ester of **3** (29.2 mg, yield 70%); IR (neat) 1740 and 1720 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.65, 0.88 (each 3H, s, *t*-CH_3), 1.37 (3H, d, J=6 Hz, *s*-CH_3), 2.01 (3H, s, CH_3COO-), 3.55 (3H, -OCH_3), 3.85—4.05 (2H, m, -$C\underline{H}_2OAc$), 4.80—5.20 (1H, m, -$C\underline{H}$-OMTPA), and 7.20—7.65 (5H, m, arom H's); MS *m/e* 253 and 189 (base peak).

(R)-(+)- and (S)-(−)-MTPA Esters of Nigakialcohol Monoacetate II (4). (*R*)-(+)-MTPA ester (17.0 mg, yield 67%) and (*S*)-(−)-MTPA ester (24.3 mg, yield 89%) were prepared by the same procedure from nigakialcohol monoacetate II (**4**; 14.1 mg and 15.0 mg), respectively. (*R*)-(+)-MTPA ester: IR (neat) 1740 and 1720 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.78, 1.03 (each 3H, s, *t*-CH_3), 1.18 (3H, d, J=6 Hz, *s*-CH_3), 1.97 (3H, s, CH_3COO-), 3.50 (3H, -OCH_3), 3.90—4.40 (2H, m, -$C\underline{H}_2OAc$), 4.45—4.95 (1H, m, -$C\underline{H}$-OMTPA), and 7.20—7.60 (5H, m, arom H's); MS *m/e* 253 and 189 (base peak). (*S*)-(−)-MTPA ester: IR (neat) 1742 and 1720 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.78, 1.03 (each 3H, s, *t*-CH_3), 1.17 (3H, d, J=6 Hz, *s*-CH_3), 1.98 (3H, s, CH_3COO-), 3.52 (3H, -OCH_3), 4.20—4.40 (2H, m, -$C\underline{H}_2OAc$), 4.45—5.00 (1H, m, -$C\underline{H}$-OMTPA), and 7.20—7.70 (5H, m, arom H's); MS *m/e* 253 and 189 (base peak).

(R)-(+)- and (S)-(−)-MTPA Esters of Deoxonigakialcohol Monoacetate II (13). (*R*)-(+)-MTPA ester (16.7 mg, yield 65%) and (*S*)-(−)-MTPA ester (30.7 mg, yield 87%) were prepared from deoxonigakialcohol monoacetate II (**13**; 13.8 mg and 19.1 mg). (*R*)-(+)-MTPA ester: IR (neat) 1740 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.82, 0.92 (each 3H, s, *t*-CH_3), 1.17 (3H, d, J=6 Hz, *s*-CH_3), 1.96 (3H, s, CH_3COO-), 3.52 (3H, -OCH_3), 3.70—4.95 (3H, m, -$C\underline{H}_2OAc$ and -$C\underline{H}$-OMTPA), 7.20—7.70 (5H, m, arom H's); MS *m/e* 280 and 189 (base peak). (*S*)-(−)-MTPA ester: IR (neat) 1740 cm^{-1}; NMR (60 MHz) δ (CCl_4) 0.82, 0.92 (each 3H, s, *t*-CH_3), 1.16 (3H, d, J=6 Hz, *s*-CH_3), 1.97 (3H, s, CH_3COO-), 3.53 (3H, -OCH_3), 3.90—4.50 (2H, m, -$C\underline{H}_2OAc$), 4.50—5.00 (1H, m, -$C\underline{H}$-OMTPA), and 7.20—7.65 (5H, m, arom H's); MS *m/e* 280 and 189 (base peak).

Determination of the Configuration at C-3′ in Nigakialcohol Monoacetate I (3) by Horeau's Method. Racemic α-phenylbutyric anhydride (60.3 mg, 0.194 mmol) and nigakialcohol monoacetate I (**3**; 20.0 mg; 0.074 mmol) were dissolved in pyridine (0.3 ml). After the solution had been allowed to stand at room temperature overnight, water (0.5 ml) was added and the mixture was left to stand for 1.5 h at room temperature. Benzene was added, followed by extraction with saturated sodium hydrogencarbonate solution. The benzene layer was washed with dilute hydrochloric acid and then with brine, and dried over sodium sulfate. Concentration *in vacuo* afforded 28.5 mg (0.069 mmol, yield 93%) of an α-phenylbutyrate of **3**. An NMR spectrum of this ester indicated that **3** was totally esterified. The sodium hydrogencarbonate extract was acidified with 3M hydrochloric acid and the acidified solution was extracted with chloroform. The chloroform extract was

washed with brine and treated as usual to yield 47.1 mg (0.287 mmol, yield 91%) of α-phenylbutyric acid, which showed $[\alpha]_D^{28}$ +2.1° (*c* 0.471, $CHCl_3$, optical yield 12%), suggesting that the asymmetric center (C-3′) of the secondary alcohol possesses *R*-configuration.

*Preparation of Tetradeuterionigakialcohol Methoxymethyl Ether (**15**-d_4).* Phosphorus pentaoxide (*ca.* 500 mg) was added to a solution of nigakialcohol monoacetate I (**3**; 26.7 mg) in chloroform (3 ml, freshly distilled from phosphorus pentaoxide) and dimethoxymethane (1.5 ml), and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with cold saturated sodium carbonate solution and then with brine, dried over sodium sulfate, and evaporated to afford a residue. The residue was dissolved in hexane and purified by column chromatography over silica gel (4 g). On elution (each fraction: 1 ml) with hexane–ether (2: 3), fractions 7—21 gave nigakialcohol monoacetate I methoxymethyl ether (**14**; 20.5 mg, yield 66%); IR (neat) 1740 and 1715 cm^{-1}; $[\alpha]_D^{26}$ +5° (*c* 0.140, $CHCl_3$); NMR (60 MHz) δ ($CDCl_3$) 0.82, 1.10 (each 3H, s, *t*-CH_3), 1.19 (3H, d, J=6 Hz, *s*-CH_3), 2.10—2.50 (4H, m, $-CH_2-CO-CH_2-$), 2.18 (3H, s, CH_3COO-), 3.40—3.80 (1H, m, $-\underline{C}\underline{H}-O-CH_2-$), 3.48 (3H, s, $-OCH_3$), 4.00—4.20 (2H, m, $-C\underline{H}_2OAc$), and 4.46, 4.60 (2H, ABq, J=7.5 Hz, $-O-CH_2-O-$); MS *m/e* 299 $(M-15)^+$.

The methoxymethyl ether (**14**; 30.0 mg) was deuteriated by treatment with sodium methoxide [prepared from sodium (*ca.* 60 mg) and deuterium oxide (1.2 ml)] in methanol-*d* (9 ml). The reaction mixture was heated under reflux for 4 days under nitrogen atmosphere. Neutralization with dilute hydrochloric [*D*] acid, extraction with dichloromethane, and the usual work-up gave a residual oil. The same deuteriation procedure was repeated twice to afford a deuteriated nigakialcohol methoxymethyl ether (**15**-d_4; 23.1 mg); IR (neat) 3440 and 1700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 0.79, 1.08 (each 3H, s, *t*-CH_3), 1.20 (3H, d, J=6 Hz, *s*-CH_3), 2.17 (1H, s-like, –OH), 3.40—4.00 (3H, m, $-C\underline{H}_2OH$ and $-\underline{C}\underline{H}-O-CH_2-$), 3.38 (3H, s, $-OCH_3$), and 4.58, 4.68 (2H, ABq, J= 7.5 Hz, $-O-CH_2-O-$); δ (CCl_4) 0.78, 1.08 (each 3H, s), 1.26 (3H, d, J=6 Hz), 2.60 (1H, s-like; disappeared on addition of D_2O), 3.30—3.90 (1H, m), 3.31 (3H, s), and 4.47, 4.61 (2H, ABq, J=7.5 Hz); NMR (100 MHz) [**15**-d_4/Eu(fod)$_3$-d_{27} =1: 0.07; for 7% (w/v) solution of **15**-d_4 in $CDCl_3$] δ 1.03, 1.24 (each 3H, s, *t*-CH_3), 1.31 (3H, d, J=6 Hz, *s*-CH_3), 2.20 —2.50 (1H, m, $-\underline{C}\underline{H}-CH_2O\cdots Eu$), 3.58 (3H, s, $-OCH_3$), 3.75—4.10 (1H, m, $-\underline{C}\underline{H}-O-CH_2-$), 4.25—4.66 (2H, m, $-C\underline{H}_2O\cdots Eu$), and 4.87, 4.94 (2H, ABq, J=7.5 Hz, $-O-CH_2-O-$).

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