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STRUCTURE OF NIGAKIALCOHOL, A NEW IONONE DERIVATIVE FROM *PICRASMA AILANTHOIDES* PLANCHON

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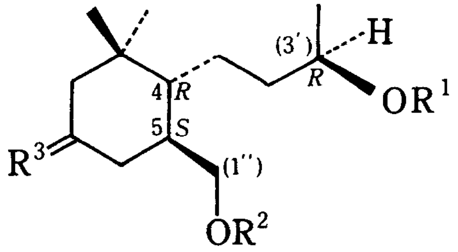
In the course of studies[1)] on the bitter principles of *Picrasma ailanthoides* Planchon (Simaroubaceae; Japanese name, Nigaki), a new ionone derivative, named nigakialcohol, was isolated together with vomifoliol[2)] (blumenol A[3)]). We now report the spectral and chemical evidence leading to the structure including absolute configuration (1) for this natural product.

A concentrated aqueous extract of the dry leaves of the plant was further extracted with benzene and the benzene extract was subjected to separation by repetition of column chromatography to afford nigakialcohol (1 ; yield 0.003%), $(\alpha)_D^{24}$ 0° ($CHCl_3$), a colorless oil, which is not bitter to the taste. The IR (neat) and PMR ($CDCl_3$) spectra of 1 suggest the presence of two tertiary methyls (δ 0.80 and 1.08, each 3H, s), a secondary methyl (δ 1.23, 3H, d, J = 6Hz), 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 hydroxyl-bearing carbon atoms, α- and α'-methylene protons (δ 2.00-2.60, 4H, m) adjacent to a carbonyl group ($\nu_{C=O}$ 1700 cm^{-1}).

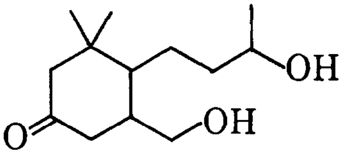


1 $R^1 = R^2 = H$, $R^3 = O$
2 $R^1 = R^2 = Ac$, $R^3 = O$
3 $R^1 = R^2 = H$, $R^3 = H_2$
5 $R^1 = H$, $R^2 = Ac$, $R^3 = O$
6 $R^1 = Ac$, $R^2 = H$, $R^3 = O$
7 $R^1 = R^2 = Ac$, $R^3 = H_2$
8 $R^1 = Ac$, $R^2 = H$, $R^3 = H_2$
9 $R^1 = CH_2OCH_3$, $R^2 = H$, $R^3 = O$
10 $R^1 = CH_2OCH_3$, $R^2 = Ac$, $R^3 = O$

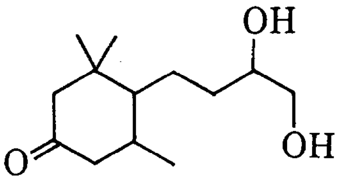
Acetylation of 1 in pyridine with acetic anhydride at room temperature overnight yielded a diacetate (2), an oil, $C_{17}H_{28}O_5$[4], $(\alpha)_D^{27}$ +30° ($CHCl_3$), PMR ($CDCl_3$) δ 2.03, 2.07 (each 3H, s, CH_3COO-), 3.80-4.40 (2H, m, CH_3COO-CH_2-), and 4.50-5.10 (1H, m, CH_3COO-CH-). The mass spectrum of 2 gave no molecular ion peak, but a fragment peak due to elimination of acetic acid at m/e 252 ($(M-60)^+$) From these observations, nigakialcohol (1) was suggested to be a ketone with a primary and a secondary hydroxyl, and represented by a molecular formula, $C_{13}H_{24}O_3$, although no molecular ion peak was obasrved in the mass spectrum (the highest peak is corresponding to a dehydration peak at m/e 210 $(M-18)^+$).

The compound (1), on the Huang-Minlon reduction, afforded a diol (3), an oil, $(\alpha)_D^{30}$ -28° ($CHCl_3$), IR (neat) 3359 cm^{-1}; PMR ($CDCl_3$) δ 0.83, 0.94 (each 3H, s), 1.19 (3H, d, J = 6Hz), 2.27 (2H, s-like; disappeared on addition of D_2O), and 3.35-4.05 (3H, m); MS m/e 196 ($(M-18)^+$); HPLC retention time 31.0 min (column: μ-Porasil, solvent system: 2.5% CH_3OH-CH_2Cl_2, flow rate: 0.5 ml/min); VPC retention time 16.8 min (column: 10% FFAP Uniport B, 1.5 m, column temperature: 200 °C, flow rate: 60 ml/min).

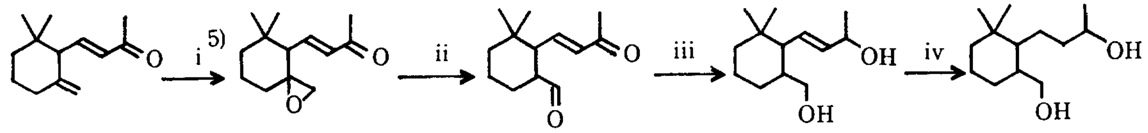
The spectral investigation of 1, 2, and 3, and comparison of the IR and PMR spectra of 1 with those of vomifoliol could lead to the structure (a) or (b) for 1, provided that nigakialcohol has an ionone skeleton. Combination of lanthanide induced shift (LIS) technique using $Eu(dpm)_3$ and double irradiation applied to PMR measurement for 1 showed the presence of the partial structure, CH_3-CH-OH. This presents convincing support for the structure a, 3,3-dimethyl-4-(3-hydroxybutyl)-5-hydroxymethylcyclohexan-1-one for 1. The proposed struc-



a



b



4 **3**

i) m-CPBA, $CHCl_3$ ii) BF_3 OEt_2, PhMe, at 0 °C
iii) $NaBH_4$, MeOH, at 0 °C iv) H_2-Pt, EtOH

ture a for 1 was confirmed by an unambiguous synthesis of the diol (3), corresponding to the deoxo derivative of 1, from (±)-γ-ionone (4). A mixture of isomeric diols thus obtained gave four peaks on HPLC. Separation of the mixture by column chromatography followed by HPLC gave a diol, which was found to be completely identical with the diol (3) derived from the natural product (1) by the Huang-Minlon reduction. The asymmetric centers at C-5, C-4, and C-3' were determined for 1 as follows.

Recently, Yamaguchi and Yasuhara have developed a new convenient method for determining absolute configurations of secondary carbinols$^{6)}$ and of primary carbinols with the chiral center at the 2-position$^{7)}$. This method was applied to determine the chiral centers at C-5 and C-3' for 1. Partial acetylation of 1 in pyridine with acetic anhydride at room temperature for 20 min gave a monoacetate (5, 43% yield), as an oil, $[\alpha]_D^{26}$ +3° ($CHCl_3$), MS *m/e* 210 [$(M-60)^+$], together with the diacetate (2). In the PMR spectrum ($CDCl_3$) of 5, the presence of the secondary hydroxyl group at C-3' was shown by the appearance of signals at δ 1.67 (1H, s-like; disappeared on addition of D_2O) and δ 3.45-4.05 (1H, m; HO-C̍H-). On the other hand, another monoacetate (6), an oil, $[\alpha]_D^{26}$ +21° ($CHCl_3$), MS *m/e* 252 [$(M-18)^+$], was formed by partial hydrolysis of the diacetate (2) in benzene over alumina,$^{8)}$ and was shown to possess a primary alcohol moiety by the PMR spectrum ($CDCl_3$) [δ 2.01 (1H, s-like; disappeared on addition of D_2O) and δ 3.40-3.90 (2H, m)]. Similarly, 3 was acetylated to give a diacetate (7), an oil, $[\alpha]_D^{20}$ -17° ($CHCl_3$). Partial hydrolysis of 7 gave a monoacetate (8), an oil $[\alpha]_D^{30}$ -7° ($CHCl_3$), PMR ($CDCl_3$) δ 1.75 (1H, s-like; disappeared on addition of D_2O) and δ 3.30-3.90 (2H, m).

Each monoacetate (5, 6, and 8) was converted to the corresponding (*R*)-(+)-

Table : Lanthanide Induced Shift (LIS) Values of the Methoxy Group in the Acid Moiety for (*R*)-(+)- and (*S*)-(-)-MTPA Esters*

	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
Esters of monoacetate (5)	4.89	2.83	+2.06	*R* (C-3')
Esters of monoacetate (6)	1.09	1.55	-0.46	*S* (C-5)
Esters of monoacetate (8)	3.33	3.93	-0.60	*S* (C-5)

* 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.

α-methoxy-α-trifluoromethylphenylacetic acid ((*R*)-(+)-MTPA: Mosher's reagent) esters (A), and (*S*)-(-)-MTPA esters (B), respectively, according to the Mosher's method[9]. The LIS values of the two pairs of diastereomeric esters were shown in Table. In the light of positive sign of ΔLIS_{OMe} value[6,7] for MTPA esters of **5**, and negative sign for those of **6** and **8**, *R*- and *S*-configurations could be assigned to the asymmetric centers at C-3' and C-5, respectively. The absolute stereochemistry at C-3' was also shown to be *R* by the Horeau's method[10]. Experiments using MTPA esters of **6** and **8** gave the same result (5*S*-configuration); this shows that the result is not altered by the presence of the carbonyl group at C-1.

Finally, the absolute configuration of C-4 was determined by the LIS technique coupled with double irradiation applied to PMR measurement of deuteriated alcohol (**9**-d_4), which was derived from the monoacetate (**5**) via methoxymethylether (**10**)[11]. A broad signal due to a proton on C-5 collapsed into a doublet (J = 11.5Hz) on irradiation at the methylene protons on C-1". The large coupling constant suggests a *trans* relationship between $C_{(5)}$-H and $C_{(4)}$-H, that is to say *R*-configuration for C-4.

In conclution, nigakialcohol must be represented by (4*R*,5*S*,3'*R*)-3,3-dimethyl-4-(3'-hydroxybutyl)-5-hydroxymethylcyclohexan-1-one.

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