BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1180—1184 (1968)

Stereochemical Studies of Monoterpene Compounds. VI.[1] The Stereochemistry of 2-Hydroxypinocamphone and Its Reduction Products[2]

Takayuki Suga, Tsuyoshi Shishibori, Toshifumi Hirata and Tamon Matsuura

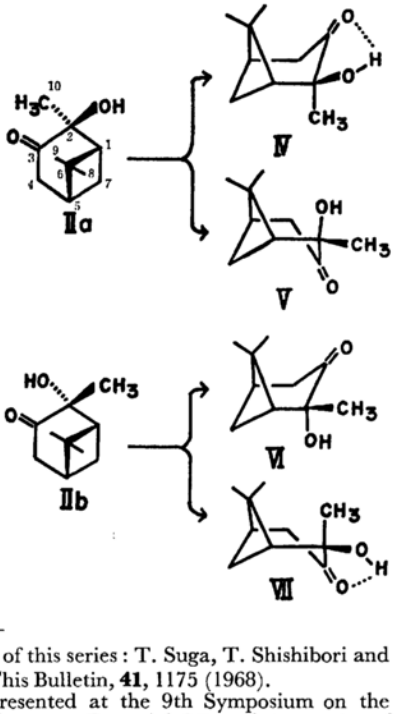
Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima

(Received October 18, 1967)

The stereochemical structure of (+)-2-hydroxypinocamphone (II), which was obtained from (−)-α-pinene (I) by the permanganate oxidation, was examined by a combination of physico-chemical methods. It was thus found that the C-2 methyl group is trans with respect to the C-6 bridge and that the preferred conformation is V having an axial hydroxyl group. In addition, the preferred conformation of *cis*-α-pinene glycol (IX) and *trans*-α-pinene glycol (X), which were produced from II by the lithium aluminum hydride reduction, was found to be IXa and Xa respectively.

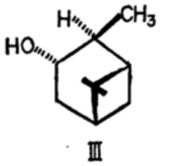
The configuration of C-2 in 2-hydroxypinocamphone (II) obtained by the potassium permanganate oxidation of α-pinene (I) is represented by IIa or IIb. Schmidt[3] has reported the configuration to be cis (IIb) on the basis of the fact that compound II gave isopinocampheol (III),[4] when reduced with sodium-ethanol. However, the assignment of this configuration seems not to be reliable, since the epimerization may occur at the 2-position during the sodium-ethanol reduction. In this paper the stereochemical structure of the hydroxyketone II was examined by a combination of such physico-chemical methods as ultraviolet, infrared and nuclear magnetic resonance spectra, optical rotatory dispersion, and circular dichroism measurements. In addition, an examination about the preferred conformation of a diastereoisomeric pair of α-pinene glycols (IX and X) was made, which were derived from II by the lithium aluminum hydride reduction.

I

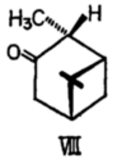


Results and Discussion

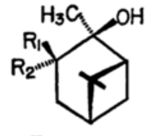
(+)-2-Hydroxypinocamphone (II) was prepared from (−)-α-pinene (I) in the same manner as in the case of Schmidt.[3] The lithium aluminum hydride reduction of II yielded a 63 : 37 mixture of α-pinene glycols, (IX) mp 55.5—56.0°C and (X) 160—161°C.



III



VIII



IX: R_1=OH, R_2=H
X: R_1=H, R_2=OH

These glycols coincided with those reported by Schmidt[3] as cis- and trans-forms concerning the hydroxyl groups respectively. Both the diols were converted into the original ketone II by the potassium permanganate oxidation or by the chromium trioxide-pyridine complex oxidation.

Stereochemistry of 2-Hydroxypinocamphone (II). The compound II in question is formulated either by IIa or IIb, and each of these epimers may take interconvertible conformations IV and V, and VI and VII, respectively, as shown above. In the

---

[1] Paper V of this series: T. Suga, T. Shishibori and T. Matsuura, This Bulletin, **41**, 1175 (1968).

[2] Partly presented at the 9th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics of the Chemical Society of Japan, Kumamoto, October, 1965.

[3] H. Schmidt, *Chem. Ber.*, **93**, 2485 (1960).

[4] T. Kuwata, *J. Am. Chem. Soc.*, **59**, 2509 (1937).

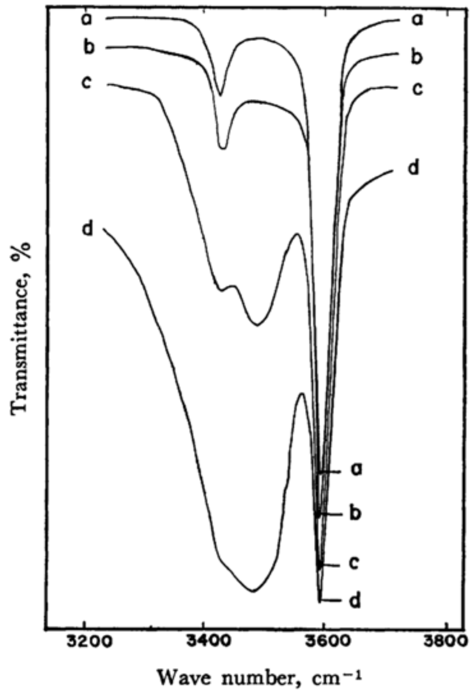


Fig. 1. Infrared spectra of 2-hydroxypinocamphone (II) in a carbon tetrachloride solution of various concentrations: a, 0.0025 M; b, 0.01 M; c, 0.05 M; d, 0.25 M.

first place, the preferred conformation of the hydroxyketone II was examined by IR, UV and NMR spectral measurements.

Intramolecular hydrogen bonding between the hydroxyl and carbonyl groups is possible in conformers IV and VII which have an equatorial hydroxyl group, whereas such bonding is impossible in V and VI having an axial one. The infrared spectra of II in the hydroxyl stretching region showed the concentration-depending bands at 3594 and 3474 cm^{-1} as shown in Fig. 1.[*1] The nuclear magnetic resonance in a carbon tetrachloride solution exhibited a pronounced high-field shift of 1.36 ppm of the hydroxyl signal on dilution, and also this signal was shifted to the higher field by 0.67 ppm when the temperature was varied from 20°C to 60°C. These facts showed the hydroxyl group at the C-2 not to be intramolecularly bonded, and the group appeared to be axial.

This assignment of the hydroxyl group was confirmed by the fact that the carbonyl $n \rightarrow \pi^*$ band of II in the ultraviolet absorption spectrum (*cf.* Fig. 4) exhibited the bathochromic shift[5-7] by 13 mμ in methanol, as compared to the band of (−)-pinocamphone (VIII) lacking in the hydroxyl group. Furthermore, the axial orientation of the hydroxyl group of II was emphasized by the effect of benzene[8,9] on the C-2 methyl resonance in the nuclear magnetic resonance. When the nuclear magnetic resonance of II was measured on passing from deuteriochloroform to benzene solution, each of 8- and 9-methyl resonances suffered an upfield shift by 0.30 ppm, whereas the signal of the C-2 methyl group moved to the higher field by only 0.04 ppm as shown in Fig. 2. This fact indicates the C-2 methyl to be equatorial, and therefore the C-2 hydroxyl group must be axial. Thus, the preferred conformation of 2-hydroxypinocamphone (II) has been assigned as either V or VI, where the configuration of V is *S*-configuration[10] at C-2 and that of VI must be *R*-configuration.

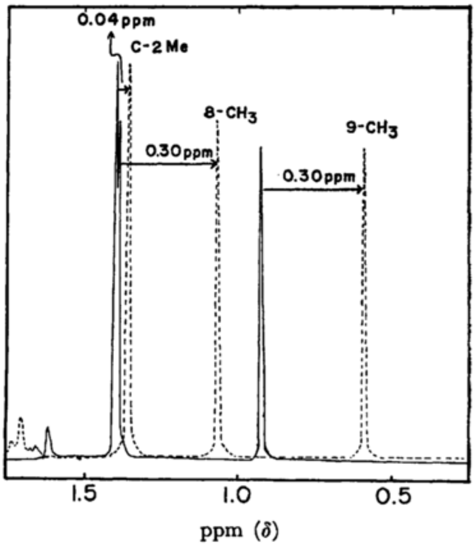


Fig. 2. The methyl resonances in the NMR spectra of 2-hydroxypinocamphone (II) in deuteriochloroform (the full line) and in benzene (the broken line).

In order to determine the configuration at the 2-position of II through ORD and CD measurements, models[11] were constructed for two conformers V and VI, the octant projection diagrams of which are shown in Fig. 3. The sign of the Cotton effect was predicted from this diagrams on assuming the octant

---

[*1] A small peak at 3426 cm^{-1} is due to the overtone of the carbonyl stretching absorption.

5) C. Djerassi, " Optical Rotatory Dispersion : Applications to Organic Chemistry," Chapter 8, McGraw-Hill Book Co., Inc., New York, N. Y. (1960).

6) G. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, **1955**, 352.

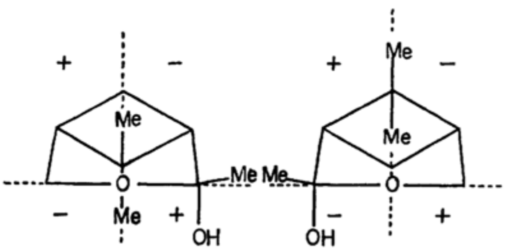
7) G. Baumgartner and C. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955).

8) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif. (1965), p. 163.

9) N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, **42**, 3127 (1964).

10) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1965).

11) " HGS Molecular Structure Model," Maruzen Co., Tokyo, was applied.



V VI

Fig. 3. The octant projections of conformers V and VI.

rule[12] to be applicable to the pinane skeleton. The conformer V was thus expected to exhibit a positive Cotton effect, whereas the conformer VI a negative one.

The ORD and CD curves of II in carbon tetrachloride showed the positive Cotton effect as shown in Fig. 4. The solvent-independent, positive ORD and CD curves were also observed in the other solvents, isooctane, dioxane, acetonitrile, dimethyl sulfoxide and methanol (see experimental section). These results imply that the C-2 methyl group is trans to the C-6 bridge, in contrast with Schmidt's report[8] in which the methyl group has been assigned to be cis to the C-6 bridge. Consequently, it was confirmed that the stereochemical structure of (+)-2-hydroxypinocamphone (II) is V.

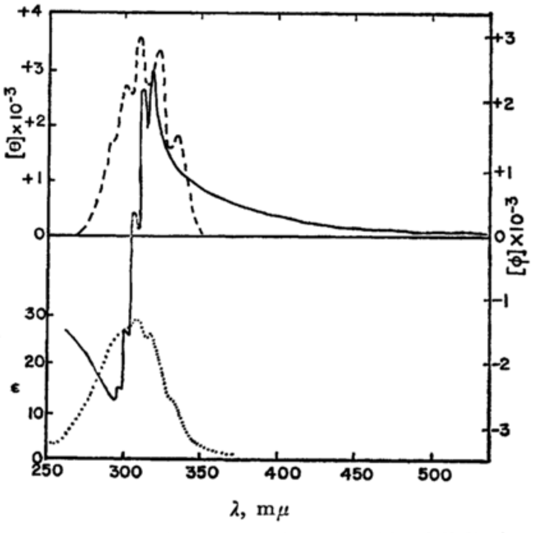


Fig. 4. Optical rotatory dispersion (the full line) and circular dichroism curves (the broken line) and ultraviolet spectrum (the dotted line) of (+)-2-hydroxypinocamphone (II) in carbon tetrachloride.

Conformation of *cis*- and *trans*-α-Pinene Glycols (IX and X). (−)-*cis*-α-Pinene glycol (IX) may take two interconvertible forms IXa and IXb (Fig. 5). The hydroxyl stretching absorption in a dilute, carbon tetrachloride solution was found at 3614 and 3545 cm^{-1}. The former peak was attributed to a free hydroxyl group and the latter to an intramolecularly bonded one. In this case, the conformational preference between IXa and IXb cannot be determined only on the basis of $\Delta\nu$ in the infrared spectrum, because of the equality of the OH···O distance[11] (*ca.* 2.2 Å) in both IXa and IXb.

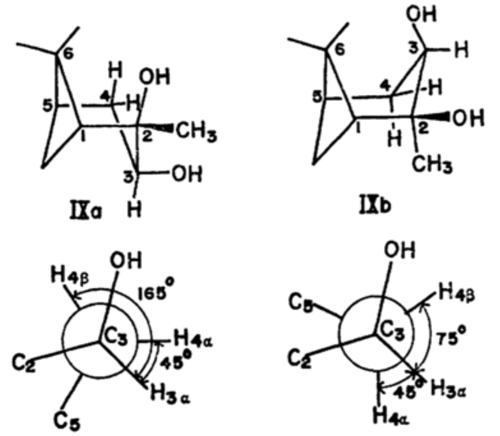
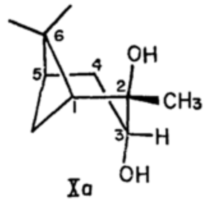


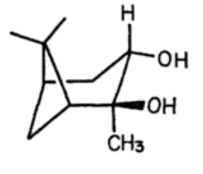
Fig. 5. The possible conformations for *cis*-α-pinene glycol (IX), and the dihedral angles between the C-3 proton and the C-4 protons in the conformers IXa and IXb.

However, the NMR spectrum of the *cis*-diol IX afforded the reliable evidence for the conformational assignment. The C-3 proton of the *cis*-glycol IX exhibited a signal at 3.94 ppm (double doublets, J=5.4 and 9.3 cps). The coupling constants for the C-3 proton of the two possible conformations were calculated by the equation of Karplus.[13] The dihedral angles used in the calculation were estimated from the models[11] and are shown in Fig. 5. The calculated coupling constants for IXa were $J_{3\alpha,4\alpha}=3.9$ cps and $J_{3\alpha,4\beta}=8.5$ cps, and the constants for IXb were $J_{3\alpha,4\alpha}=3.9$ cps and $J_{3\alpha,4\beta}=0.1$ cps. The observed spectrum agrees nearly with the calculated coupling constants for IXa. Therefore, the preferred conformation of (−)-*cis*-α-pinene glycol (IX) was found to be IXa.

On the other hand, (−)-*trans*-α-pinene glycol (X) may take two interconvertible forms Xa and Xb.



Xa



Xb

---

[12] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

[13] M. Karplus, *ibid.*, **85**, 2870 (1963).

Since the OH···O distances[11] are *ca.* 4.0 Å in Xa and *ca.* 2.5 Å in Xb, intramolecular hydrogen bonding is possible in conformer Xb having two equatorial hydroxyl groups, but such bonding is impossible in conformer Xa having two axial hydroxyl groups. The hydroxyl stretching absorption of *trans*-α-pinene glycol (X) in a dilute, carbon tetrachloride solution was found at 3610 and 3626 cm^{-1}, which would be attributed to the free, tertiary and secondary hydroxyl groups, respectively. It may be said *trans*-glycol X not to form the intramolecular hydrogen bond. Thus, the orientation of two hydroxyl group of glycol X was diaxial. As the C-2 configuration of the hydroxyketone II is retained in the lithium aluminum hydride reduction, it was seen that the conformation of (−)-*trans*-α-pinene glycol (X) is shown as Xa.

Experimental

The IR spectra were recorded by a Hilger H-800 Spectrophotometer (calcium fluoride prism) and a Perkin-Elmer Model 621 Grating Infrared Spectrometer. The ORD and CD spectra were measured at 25°C with a Japan Spectroscopic Co., Ltd. Model ORD/UV-5 Spectropolarimeter. The NMR spectra were recorded with a Hitachi Perkin-Elmer, R-20, and a Varian Associates, A-60, high-resolution spectrometers using tetramethylsilane as an internal standard. The variable-temperature NMR spectra were measured with a Japan Electron Optics Lab., JNM-C-60H. Microanalysis was done at the Microanalytical Center in the Faculty of Pharmacy of Kyoto University.

(+)-**2-Hydroxypinocamphone (II).** To a mixture of 579 g of (−)-α-pinene (I) (bp 71.0°C/51 mmHg, n_{D}^{25} 1.4626, d_4^{25} 0.8556, $[\alpha]_{\mathrm{D}}^{25}$ −39.92°) and 5570 m*l* of 90% aqueous acetone was added 300 g of powdered potassium permanganate in small portions in a period of 8.5 hr at −5—5°C. The mixture was stirred for further 24 hr at 5°C. The filtrate free from manganese dioxide was treated as performed by Kuwata,[4] and gave 142 g of a neutral product boiling at 115—125°C/12.5 mmHg. This product solidified as a crystalline mass in a refrigerator. 2-Hydroxypinocamphone (II) was obtained by recrystallization from *n*-hexane and showed the following properties: mp 32.5—34.0°C (lit.[3] mp 34.5—35.3°C); $[\alpha]_{\mathrm{D}}^{25}$ +21.1° (*c* 4.64, ethanol) (lit.[4] $[\alpha]_{\mathrm{D}}^{25}$ −18.56° (*c* 14.44, ethanol), from (+)-α-pinene), $[\alpha]_{\mathrm{D}}^{25}$ +38.1° (*c* 3.12, chloroform) (lit.[3] $[\alpha]_{\mathrm{D}}$ −41.2° (chloroform), from (+)-α-pinene). UV: $\lambda_{max}^{\mathrm{CCl_4}}$ 309 mμ (ε 29.6), $\lambda_{max}^{\mathrm{isooctane}}$ 309 mμ (ε 24.6), $\lambda_{max}^{\mathrm{dioxane}}$ 309 mμ (ε 27.8), $\lambda_{max}^{\mathrm{acetonitrile}}$ 307 mμ (ε 26.1), $\lambda_{max}^{\mathrm{dimethyl\ sulfoxide}}$ 309 mμ (ε 30.0), $\lambda_{max}^{\mathrm{methanol}}$ 308 mμ (ε 28.0). ORD: $[\phi]_{336}^{\mathrm{CCl_4}}$ +2410, $[\phi]_{288}$ −2501; $[\phi]_{338}^{\mathrm{isooctane}}$ +2457, $[\phi]_{290}$ −2319; $[\phi]_{338}^{\mathrm{dioxane}}$ +2227, $[\phi]_{289}$ −2014; $[\phi]_{337}^{\mathrm{acetonitrile}}$ +2034, $[\phi]_{228}$ −1979; $[\phi]_{337}^{\mathrm{dimethyl\ sulfoxide}}$ +2212, $[\phi]_{288}$ −2240; $[\phi]_{337}^{\mathrm{methanol}}$ +1684, $[\phi]_{296}$ −1943. CD: $[\theta]_{310}^{\mathrm{CCl_4}}$ +3793, $[\theta]_{310}^{\mathrm{isooctane}}$ +3281, $[\theta]_{311}^{\mathrm{dioxane}}$ +3281, $[\theta]_{310}^{\mathrm{acetonitrile}}$ +3083, $[\theta]_{321}^{\mathrm{dimethyl\ sulfoxide}}$ +3326, $[\theta]_{311}^{\mathrm{methanol}}$ +2736.

The IR spectra in the hydroxyl stretching region were measured in 0.0025, 0.01, 0.05 and 0.25 M carbon tetrachloride solutions using salt absorption cells of 40.0, 10.0, 2.0 and 0.4 mm in length respectively.

The hydroxyl proton signal of the NMR spectrum appeared at δ 3.57 ppm in 20% carbon tetrachloride solution and at δ 2.21 ppm in 2.5% solution. This signal in 10% carbon tetrachloride solution was observed at δ 3.05 ppm at 20°C and at δ 2.38 ppm at 60°C. The methyl proton signal appeared at δ 0.88 ppm (C-9, 3H), 1.38 (C-8, 3H) and 1.39 (C-2 methyl, 3H) in 10% deuteriochloroform, and 0.58 (C-9, 3H), 1.08 (C-8, 3H) and 1.35 (C-2 methyl, 3H) in 10% benzene at 20°C.

(−)-***cis*- and (−)-*trans*-α-Pinene Glycols (IX and X).** To 3.5 g of lithium aluminum hydride suspended in 200 m*l* of dry ether was added 22.0 g of II in a period of 3 hr at room temperature. Then, the reaction mixture was refluxed for 4 hr. After being left at room temperature for a day, the mixture gave 21.0 g of a crude diol, which was chromatographed on silica gel column with a mixture of ethyl acetate and *n*-hexane to separate into two components. The first eluate gave 9.6 g of a diol and the second eluate afforded 5.6 g of another diol. The homogeneity of these glycols separated was checked by chromatostrip analysis.

Properties of the First Eluate (*cis-Glycol*): mp 55.5—56.0°C (from petroleum benzine), $[\alpha]_{\mathrm{D}}^{25}$ −0.89° (*c* 7.91, chloroform) (lit.[3] mp 55.5—56.0°C, $[\alpha]_{\mathrm{D}}$ +3.3° (ethanol), from (−)-II).

The hydroxyl stretching absorption in 0.0021 M carbon tetrachloride solution was found at 3614 and 3545 cm^{-1}.

The NMR spectrum of the glycol was measured in 5 w/v% deuteriochloroform solution at 20°C.

The solution of 2.5 g of the glycol dissolved in 27 m*l* of 90% aqueous acetone was oxidized with 2.4 g of potassium permanganate for 12 hr at −5°C, and the original ketol II (1.7 g) was obtained, which was confirmed by comparison of the IR spectrum. Thus, the first eluate is *cis*-α-pinene glycol (IX).

Properties of the Second Eluate (*trans-Glycol*): mp 160—161°C (from ethanol), $[\alpha]_{\mathrm{D}}^{25}$ −33.13° (*c* 4.8, ethanol) (lit.[3] mp 159—160°C, $[\alpha]_{\mathrm{D}}^{25}$ +49° (ethanol), from (−)-II).

Found: C, 69.74; H, 10.68%. Calcd for $C_{10}H_{16}O_2$: C, 70.55; H, 10.66%.

The hydroxyl stretching absorption in 0.00079 M carbon tetrachloride solution appeared at 3626 and 3610 cm^{-1}.

A sample of 0.2 g of the second eluate was oxidized with a solution of 0.5 g of chromium trioxide in 5 m*l* of pyridine for 2 hr at room temperature, and 0.1 g of the original ketol II was obtained, which was confirmed by comparison of the IR spectrum. Thus, the second eluate is *trans*-α-pinene glycol (X).

(−)-**Pinocamphone (VIII).** Following the procedure reported,[14] 20 g of (+)-isopinocampheol (III) (mp 55—57°C, $[\alpha]_{\mathrm{D}}^{25}$ +31.6° (*c* 10, benzene)), which was prepared from (−)-α-pinene (I) ($[\alpha]_{\mathrm{D}}^{25}$ −39.32°) through hydroboration,[15] was oxidized with sodium dichromate to produce 17.8 g of (−)-isopinocamphone: bp 66°C/5 mmHg, n_{D}^{25} 1.4725, d_4^{25} 0.9618, $[\alpha]_{\mathrm{D}}^{25}$ −9.77° (neat) (lit.[15] bp 54—56°C/1 mmHg, n_{D}^{25} 1.4745, α_{D}^{25} +10.3°, from (−)-III); 2,4-dinitrophenylhydrazone, mp 153°C (lit.[16] mp 151—152°C); semicarbazone, mp 227—228°C (lit.[4] mp 228°C).

---

[14] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

[15] G. Zweifel and H. C. Brown, *ibid.*, **86**, 393 (1964).

[16] A. Kergomard, *Bull. Soc. chim. France*, **1958**, 394.

Furthermore, following the method reported,[15] 0.50 g of (—)-isopinocamphone was added to the solution prepared by dissolving 0.12 g of metallic sodium in 25 m*l* of absolute ethanol, and then a mixture was stood for 24 hr at room temperature. The usual treatment of the mixture gave 0.35 g of the ketone VIII: $[\alpha]_D^{25}$ $-18.56°$ (*c* 1.99, ethanol) (lit.[16] α_J $-15°$), λ_{max}^{MeOH} 295 mμ (ε 26.7).

The authors wish to express their hearty thanks to Takasago Perfumery Co., Ltd., Tokyo, for a gift of (—)-α-pinene, to Professor Shô Ito of Tohoku University, for measuring the NMR spectra by a Varian Associates, A-60, spectrometer, and to Japan Electron Optics Lab., Tokyo, for the variable-temperature NMR spectra measurement.