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Structure and Absolute Configuration of Campherenone and Campherenol, Sesquiterpenoids of *Cinnamomum camphora*[1]

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From camphor blue oil, the high boiling fraction of the essential oil of camphor tree, *Cinnamomum camphora* (Lauraceae), new sesquiterpenic ketone and alcohol, campherenone and campherenol, have been isolated. Both terpenoids can be interconverted by reduction-oxidation reactions. The physico-chemical properties of these substances and their derivatives and their transformation into β-santalene have established their stereostructures as I and II, respectively.

The essential oil from the wood of camphor tree, *Cinnamomum camphora* Siebold (Lauraceae), has been frequently investigated from an early date on account of its commercial importance.[3] Although the occurrence of oxygen-containing sesquiterpenoids has been recognized for long,[3] it is only quite recent that some sesquiterpenic alcohols have been isolated and adequately characterized.[4–7] During our survey on the constituents of camphor blue oil, the high boiling fraction of the essential oil, we have recently isolated two new sesquiterpenoids for which the names campherenone and campherenol are given. On the basis of chemical and physico-chemical evidence, we have proposed for campherenone and campherenol the stereostructures I and II, respectively.[8] The present paper describes the evidence in full detail.

Table I. NMR Signals of Ketones

Solvent	Campherenone (I)				Camphor (VII)		
	C-9	C-10	C-14,C-15	C-12	C-8	C-9	C-10
Carbon tetrachloride	0.96	0.85	1.64,1.59	5.03	0.81	0.94	0.84
Chloroform	0.96	0.88	1.64,1.57	5.04	0.83	0.97	0.91
Benzene	0.67	0.90	1.62,1.49	4.98	0.60	0.65	0.89
Pyridine	0.84	0.92	1.64,1.55	5.04	0.70	0.79	0.89

Campherenone analyzed for $C_{15}H_{24}O$. As the only oxygen function, campherenone contains a carbonyl group in a five-membered ring and with a methylene flanking it as evidenced by the infrared absorption at 1745 and 1415 cm^{-1}. In the nuclear magnetic resonance (NMR)

1) This paper form Part XXXVIII in the series on Sesquiterpenoids. Preceding paper, Part XXXVII, H. Hikino, K. Tori, I. Horibe, and K. Kuriyama, *J. Chem. Soc.* (C), in press.
2) Location: *Aoba-yama, Sendai.*
3) For historical aspects of the research, see E. Gildemeister and F. Hoffmann, "Die Ätherischen Öle," Vol. V, Academy Verlag, Berlin, 1959, p. 46.
4) N. Hirota and M. Hiroi, *Kōryō*, **No. 70**, 23 (1963).
5) S. Hayashi, K. Yano, N. Hayashi, and T. Matsuura, Abstract of the 8th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Sendai, 1964, p. 113.
6) S. Hayashi, N. Hayashi, T. Matsuura, and K. Yano, Abstract of the 9th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Kumamoto, 1965, p. 54.
7) H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 832 (1968).
8) The material presented herein has already been announced in part in *Tetrahedron Letters*, **1967**, 5069.

spectrum, signals for two tertiary methyls, two vinyl methyls, and a vinylic hydrogen are visible (Table I). Double resonance experiments revealed the latter three to be involved in an isopentenyl group. These data, together with the common occurrence of campherenone with α-santalene (XIII)[9] and β-santalene (VI)[10] in the same plant, lead to the assumption that campherenone may be 8- or 9-isopentenyl camphor. This was supported by the NMR evidence that the line positions of two methyl singlets in campherenone coincide with those of the C-9 and C-10 methyl proton signals in camphor (VII),[11] suggesting the isopentenyl grouping to be substituted at C-8 of the camphor skeleton. The mass spectrum of campherenone verified the structure I now postulated. Thus the cracking pattern is well explained in terms of an isopentenylcamphor, as discussed later in detail.

The absolute stereochemistry of campherenone was deduced by the optical rotatory dispersion (ORD) and circular dichroism (CD) curves which show a positive Cotton effect for n–π^* transition, indicating that it is identical with that of *d*-camphor (VII).[12]

As mentioned previously analysis of the mass spectrum of campherenone was instructive for its structural elucidation. The mass spectrum of campherenone is reproduced in Fig. 1, the elemental compositions of certain questionable peaks being confirmed by high resolution measurements. Recently the mass spectrum of camphor, a congener of campherenone, has extensively examined by Weinberg and Djerassi[13] and Dimmel and Wolinsky.[14] Therefore, the present interpretation of the fragmentation reactions of campherenone was performed in comparison with their conclusions regarding those of camphor. As a result, it was found that most of the mechanisms of its electron impact fragmentation reactions are parallel with those of camphor but some of them are different from those of camphor. The breakdown reactions leading to the principal mass spectral fragmentation peaks (represented in Fig. 2) are now discussed in terms of the structure (I) elucidated.

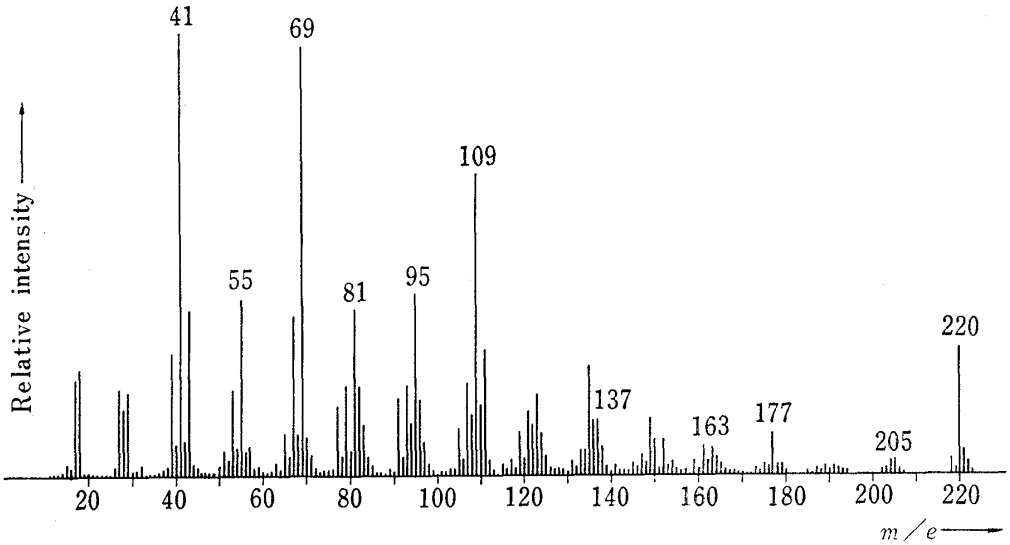

Fig. 1. Mass Spectrum of Campherenone (70 eV)

From the molecular ion (**1**), *m/e* 220, a methyl group or an isohexenyl group is lost to give a $C_{14}H_{21}O^+$ ion (**2** or **4**), *m/e* 205, or a $C_9H_{13}O^+$ ion (**5**), *m/e* 137. Two carbon atoms (C-2 and

9) T. Kato, T. Mukai, and T. Nozoe, Abstract of the 3rd Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Tokyo, 1959.
10) S. Hayashi, N. Hayashi, K. Yano, M. Okano, and T. Matsuura, *Bull. Chem. Soc. Japan*, **41**, 234 (1968).
11) J.D. Connolly and R. McCrindle, *Chem. Ind.* (London), **1965**. 379.
12) G. Jacob, G. Ourisson, and A. Rassat, *Bull. Soc. Chim. France*, **1959**, 1374.
13) D. S. Weinberg and C. Djerassi, *J.Org. Chem.*, **31**, 115 (1966).
14) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410 (1967).

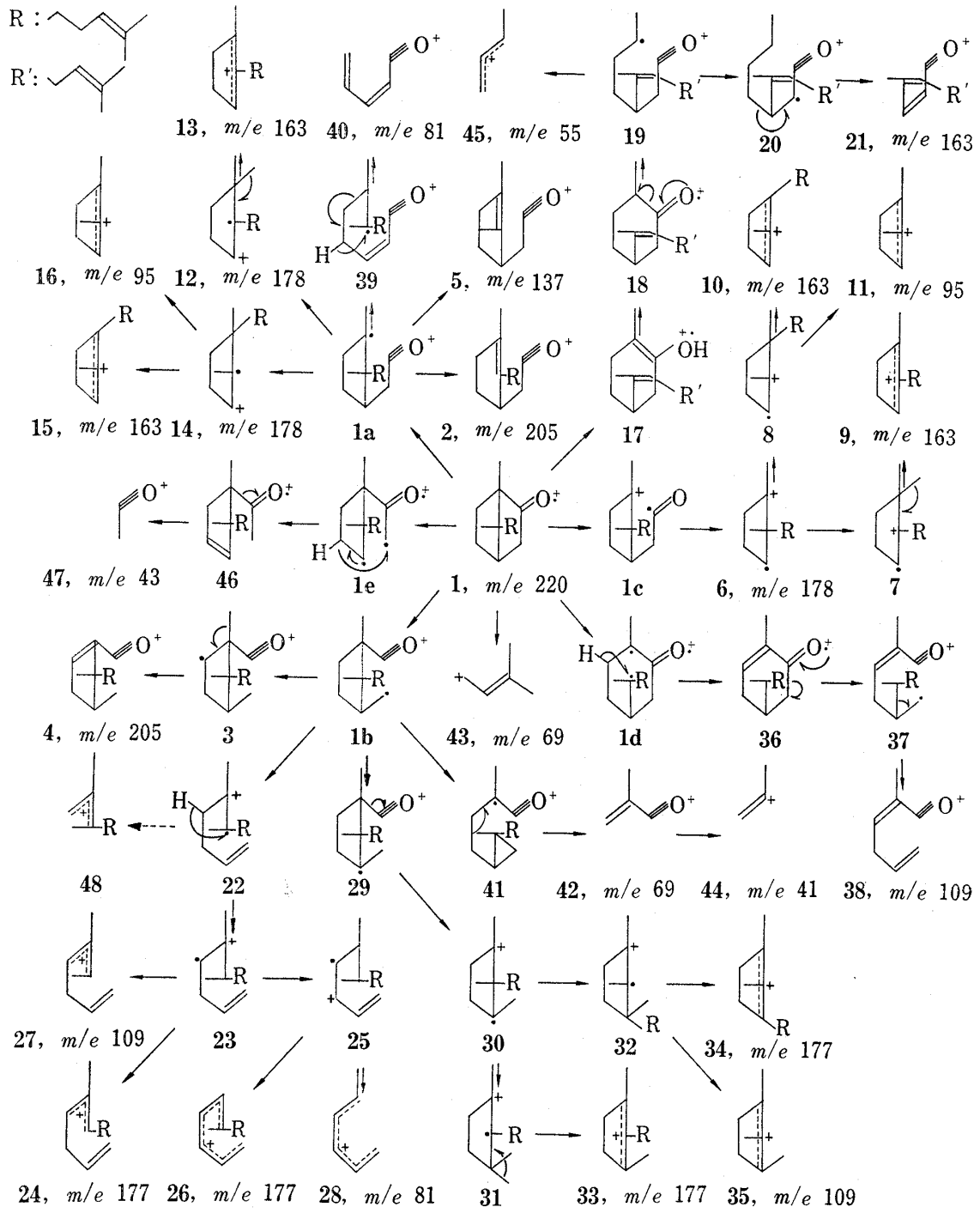

Fig. 2. Fragmentation Reactions of Campherenone on Electron Impact

C-3) are lost as ketene to afford a $C_{13}H_{22}^+$ ion (**6**), *m/e* 178, in which the C-7 isohexenyl group or the C-7 methyl group is migrated to the adjacent carbon positively charged (C-1) to form the ion (**7** or **8**). The former (**7**) can then lose either methyl group at C-1 to give the ion (**9**), *m/e* 163. The latter (**8**) can also lose either methyl group or isohexenyl group at C-1 giving the stable species (**10** or **11**), *m/e* 163 or 95. For generation of a $C_{12}H_{19}^+$ ion, *m/e* 163, and a $C_7H_{11}^+$ ion, *m/e* 95, the alternative pathways (**1**→**1a**→**12**→**13** and **1**→**1a**→**14**→**15** and **16**) may operate simultaneously. However, since the *m/e* 95 peak is intense (fourth abundant in the spectrum) while the *m/e* 163 is very weak, the breakdown reactions seem to proceed almost exclusively by the scheme (**1**→**1c**→**6**→**8**→**11** and **1**→**1a**→**14**→**16**). Moreover, high resolution measurements showed that the *m/e* 163 peak is due to not only a $C_{12}H_{19}^+$ ion (53%) but also a $C_{11}H_{15}O^+$

ion (47%), which may be formed by the pathway (**1**→**17**→**18**→**19**→**20**→**21**). Carbon monoxide is lost from the molecular ion (**1b**) to afford a $C_{14}H_{24}^+$ ion (**22**) which undergoes further rearrangements and fragmentations shown furnishing the *m/e* 177 peak (**24** or **26**), the *m/e* 109 peak (**27**), and the *m/e* 81 peak (**28**). The *m/e* 109 fragment in the spectrum of camphor is known to occur also by loss of carbon monoxide and the C-3 carbon. Therefore, the alternative side pathways (**1**→**1b**→**29**→**30**→**31**→**33** and **1**→**1b**→**29**→**30**→**32**→**34** and **35**) to give the *m/e* 177 and 109 peaks, may also be possible. Contrary to camphor's spectrum where a hydrocarbon ion ($C_8H_{13}^+$) composes 95% of the *m/e* 109 peak, in campherenone's spectrum it consists of 52% of a hydrocarbon ion ($C_8H_{13}^+$) (**27** or **35**) and 48% of an oxygenated ion ($C_7H_9O^+$), which may be produced by the sequence (**1**→**1d**→**36**→**37**→**38**). Since the *m/e* 81 fragment was shown by high resolution measurements to contain, along with 88% of a hydrocarbon ion ($C_6H_9^+$) (**28**), 12% of an oxygen-containing species ($C_5H_5O^+$) whose formation is considered to follow the mechanism (**1**—**1a**—**39**—**40**). Since the *m/e* 151 peak was revealed by high resolution measurements to be attributed to an oxygen-containing ion ($C_{10}H_{15}O^+$), the fragmentation of an ion (**22**, R=CH_3) to a hydrocarbon ion (**48**, R=CH_3) observed in the breakdown of camphor, does not occur in that of campherenone. Dimmel and Wolinsky[13] suggested that the *m/e* 69 fragment, third abundant in camphor's spectrum, is due to the four-carbon oxygenated ion ($C_4H_5O^+$) (**42**). However, high resolution measurements demonstrated that, in campherenone spectrum, an oxygen-containing ion (**42**) composes only 17% of the *m/e* 69 peak and the remaining 83% is associated with a hydrocarbon ion ($C_5H_9^+$) (**43**), which is simply formed by the cleavage of an allylic carbon-carbon bond (C-8:C-10). The abundance of the oxygen-containing ion (**42**) may probably decreased by further loss of carbon monoxide to give a $C_3H_5^+$ ion (**44**), *m/e* 41, forming the base peak.

Campherenol analyzed for $C_{15}H_{26}O$. The infrared (IR) spectrum showed hydroxyl bands at 3650 and 3410 cm^{-1} and the NMR spectrum exhibited a carbinyl hydrogen signal at 3.97 ppm, indicating it to be a secondary alcohol. In the NMR spectrum, two tertiary methyl signals (0.81, 0.87 ppm), two vinyl methyl signals (1.58, 1.63 ppm), and a vinyl hydrogen signal (5.02 ppm) were visible. These data suggest that campherenol is similar in structure to campherenone. Acetylation yielded the acetate (III) from which campherenol was regenerated on hydrolysis. When campherenol was oxidized with chromic acid, campherenone was obtained, establishing the stereostructure of campherenol except for the configuration at C-2. Reduction of campherenone with lithium aluminum hydride afforded, together with a small amount of campherenol, the epimer of campherenol, 2-*epi*-campherenol (IV), which on acetylation gave the acetate (V). When the fact that hydride reduction of camphor (VII) proceeds under the steric approach control of the reagent to give mainly isoborneol (X) along with a minute amount of borneol (VIII), is taken into consideration, this observation indicates the C-2 hydroxyl group in campherenol to be α-oriented. In order to establish the configuration at C-2 of campherenol, the NMR spectra of the derivatives thus prepared were compared. As a result, it was revealed that the chemical shifts and splitting patterns of the C-2 hydrogen signals of campherenol and its acetate (III) are consistent with those of borneol (VIII) and its acetate (IX), while those of 2-*epi*-campherenol (IV) and its acetate (V) are compatible with those of isoborneol (X) and its acetate (XI) (Table II), a fact which indicates that the C-2 hydroxyl group of campherenol is α-oriented. In the NMR spectra, no downfield shift of the methyl group at C-7 caused by the spatial interaction with the 2β-hydroxyl group is observed in 2-*epi*-campherenol (IV), and consequently, no acetylation effect on the methyl resonance in 2-*epi*-campherenyl acetate (V) is found, confirming the isopentenyl group in campherenone and campherenol to be substituted at the π-*cis* position of the bornane skeleton.

The stereostructures I and II thus deduced for campherenone and campherenol were established chemically by the following reaction. Thus, 2-*epi*-campherenol (IV) was treated with *p*-toluenesulfonyl chloride in pyridine to give no expected tosylate but a hydrocarbon

Table II. NMR Signals of C-2 Hydrogen of Alcohols and Acetates (CCl_4)

Campherenol (II)	3.97 ddd (J=10,3,1)
Campherenyl acetate (III)	4.86 ddd (J=9,3,1)
2-*epi*-Campherenol (IV)	3.51 dd (J=5,5)
2-*epi*-Campherenyl acetate (V)	4.62 dd (J=7,5)
Borneol (VIII)	3.94 ddd (J=10,4,2)
Bornyl acetate (IX)	4.81 ddd (J=10,3,2)
Isoborneol (X)	3.51 dd (J=5,5)
Isobornyl acetate (XI)	4.62 dd (J=5,5)

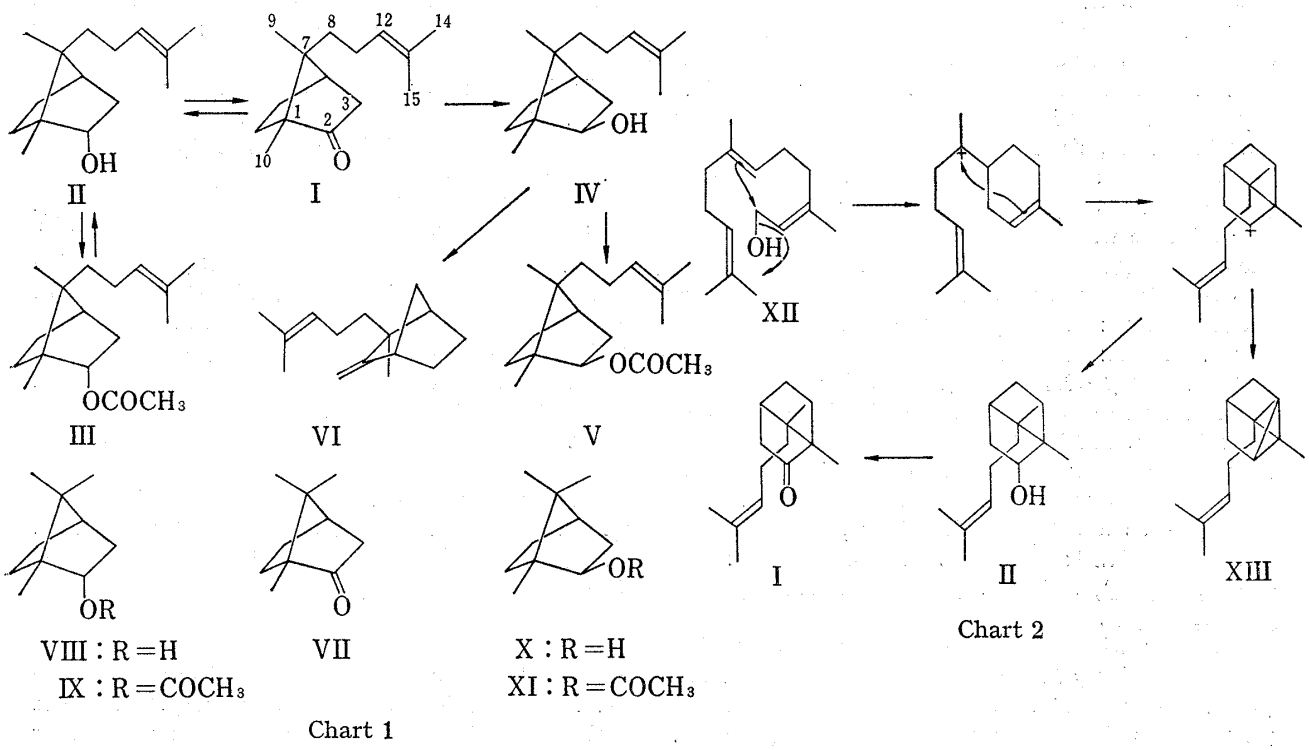

Chart 1

Chart 2

which from the NMR spectrum was shown to possess an isopentenyl, a tertiary methyl, and a vinylidene group. Comparison of the hydrocarbon with β-santalene (VI) revealed the identity.

Campherenone and campherenol provide the first sesquiterpenoids having the extended bornane skeleton, which we propose to designate as the campherane skeleton with the numbering shown. It appears most probable that these sesquiterpenoids are biosynthesized from farnesol (XII) through the pathway illustrated in the Chart 2.

Experimental[15]

Isolation of Campherenone——Camphor blue oil was fractionally distilled through a spinning band column to give a high-boiling fraction, bp_4 150—170°, which was submitted to alumina chromatography followed by repeated silica gel chromatography to give a ketone fraction which was distilled under reduced pressure affording campherenone (I) as a colorless oil, $[\alpha]_D$ −33.0° (c=10.0). ORD (c=0.1097, MeOH): $[\Phi]_{334}$ 0, $[\Phi]_{308}^{peak}$ +320, $[\Phi]_{296}$ 0, $[\Phi]_{274}^{trough}$ −540. CD (c=0.1097, MeOH): $[\theta]_{298}^{max}$ +600. *Anal.* Calcd. for $C_{15}H_{24}O$: C, 81.76;

15) Melting points are uncorrected. Specific rotations were taken in $CHCl_3$ solution. NMR spectra were measured at 60 MHz in CCl_4 solution unless otherwise indicated. Chemical shifts are expressed in ppm from Me_4Si as internal reference, and coupling constants (J) in Hz. Abbreviations: s=singlet, d=doublet, and dd=doublet of doublets.

H, 10.98. Found: C, 81.86; H, 10.95. IR (CCl_4)cm^{-1}: 1745 (cyclopentanone), 1415 (methylene α to carbonyl), 825 (trisubstituted ethylene bond). NMR: described previously (Table I).

Isolation of Campherenol——In the above silica gel chromatography, a mixture of campherenol and valerianol (kusunol)[7] was eluted immediately after the elution of guaiol.

The mixture (311 mg) in pyridine (2 ml) was treated with Ac_2O (2 ml) at room temperature overnight. Upon isolation in the usual manner, the product (207 mg) was chromatographed over silica gel (5 g). The fractions (70 mg) eluted with light petroleum were combined and distilled under reduced pressure to yield campherenyl acetate (III) as a colorless oil, $[\alpha]_D-23.2°$ ($c=5.7$). *Anal.* Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.44; H, 10.92. IR (CCl_4)cm^{-1}: 1733, 1238 (acetoxyl). NMR: 0.82, 0.88 (two 3H, s's, $C_{(9)}\underline{H}_3$, $C_{(10)}\underline{H}_3$), 1.59, 1.64 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 1.97 (3H, s, $C\underline{H}_3$–COO–), 4.86 (1H, ddd, $J=9,3,1$, $C_{(2)}\underline{H}$), 5.03 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}$).

Campherenyl acetate (III) (55 mg) in ethanolic NaOH solution (1%, 4 ml) was stirred at room temperature for 5 hr. Evaporation of the solvent, dilution with water, and extraction into ether gave the product (45 mg). Chromatography over silica gel (2 g) and elution with light petroleum–benzene (2:1) followed by distillation under diminished pressure afforded campherenol (II) as a colorless oil (40 mg), $[\alpha]_D-62.1°$ ($c=3.9$). *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.92; H, 11.71. IR(CCl_4)cm^{-1}: 3650, 3410 (hydroxyl), 833 (trisubstituted ethylene bond). NMR: 0.81, 0.87 (two 3H, s's, $C_{(9)}\underline{H}_3$, $C_{(10)}\underline{H}_3$), 1.58, 1.63 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 3.97 (1H, ddd, $J=10,3,1$, $C_{(2)}\underline{H}$), 5.02 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}$).

Oxidation of Campherenol with Chromium Trioxide–Pyridine Complex——To a CrO_3-pyridine complex (made from CrO_3 (70 mg) and pyridine (0.3 ml)) was added campherenol (II) (22 mg) in pyridine (0.5 ml). The mixture was left standing at room temperature overnight. After isolation in the customary manner, the product (21 mg) was chromatographed over silica gel (1 g). Light petroleum eluted an oil (11 mg) which on distillation under reduced pressure furnished campherenone (I) as a colorless oil, $[\alpha]_D-19.6°$ ($c=2.3$). IR (CCl_4)cm^{-1}: 1745 (cyclopentanone), 1415 (methylene adjacent to carbonyl), 825 (trisubstituted double bond). NMR: 0.85, 0.96 (two 3H, s's, $C_{(9)}\underline{H}_3$, $C_{(10)}\underline{H}_3$), 1.59, 1.64 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 5.03 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}$). Identity with the natural campherenone was confirmed by theusual criteria.

Reduction of Campherenone with Lithium Aluminum Hydride——Campherenone (79 mg) in ether (10 ml) was stirred with $LiAlH_4$ (10 mg) at room temperature for 1 hr. Upon isolation in the usual way, the product (79 mg) was chromatographed over silica gel (3 g).

Elution with light petroleum–benzene (5:1) and distillation under reduced pressure gave 2-*epi*-campherenol (IV) as a colorless oil (67 mg), $[\alpha]_D+15.3°$ ($c=2.6$). *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.21; H, 11.90. IR (CCl_4) cm^{-1}: 3650, 3490 (hydroxyl). NMR: 0.82, 0.87 (two 3H, s's, $C_{(9)}\underline{H}_3$, $C_{(10)}\underline{H}_3$), 1.57, 1.63 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 3.51 (1H, dd, $J=5,7$, $C_{(2)}\underline{H}$), 5.02 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}$).

Elution with benzene afforded campherenol (II).

Acetylation of 2-*epi*-Campherenol——2-*epi*-Campherenol (IV) (34 mg) in pyridine (0.1 ml) and Ac_2O (0.05 ml) was left standing at room temperature for 2 days. After isolation in the usual manner, the product (47 mg) was chromatographed over silica gel (1 g). Elution with light petroleum and distillation under diminished pressure yielded 2-*epi*-campherenyl acetate (V) as a colorless oil (41 mg), $[\alpha]_D+39.2°$ ($c=3.8$). *Anal.* Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.10; H, 10.62. IR (CCl_4)cm^{-1}: 1732, 1232 (acetoxyl). NMR: 0.81, 0.84 (two 3H, s's, $C_{(9)}\underline{H}_3$, $C_{(10)}\underline{H}_3$), 1.58, 1.66 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 1.97 (3H, s, $C\underline{H}_3$–COO–), 4.61 (1H, dd, $c=5,7$, $C_{(2)}\underline{H}$), 5.04 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}_3$).

Dehydration of 2-*epi*-Campherenol with *p*-Toluenesulfonyl Chloride in Pyridine——To 2-*epi*-Campherenol (IV) (294 mg) in pyridine (2 ml) was added tosyl chloride (300 mg) and the mixture set aside at room temperature for 2 days. Isolation in the customary way gave the product (271 mg) which was chromatographed over silica gel (10 g).

Elution with light petroleum furnished β-santalene (VI) as a colorless oil. IR (CCl_4)cm^{-1}: 3075, 1654, 877 (vinylidene). NMR: 1.03 (3H, s, $C_{(9)}\underline{H}_3$), 1.58, 1.63 (two broad 3H, s's, $C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 4.40, 4.64 (two 1H, s's, $C_{(10)}\underline{H}_2$), 5.00 (1H, dd, $J=7,7$, $C_{(12)}\underline{H}$). The identity was confirmed by comparison of the IR and NMR spectra with the authentic data.[16,17]

Elution with light petroleum-benzene (5:1) gave the recovered 2-*epi*-campherenol (IV).

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