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The Structure of Paeoniflorigenone, A New Monoterpene isolated from Paeoniae Radix

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A biologically active monoterpene, paeoniflorigenone (**2**), was isolated from the roots of *Paeonia albiflora* PALLAS. The structure of **2** was elucidated by means of chemical and spectral studies and its absolute structure was determined by X-ray analysis, by the direct method.[1)]

Keywords——monoterpene; paeoniflorigenone; Paeoniae Radix; *Paeonia albiflora*; neuromuscular-blocking effect; X-ray analysis

Paeoniae Radix, "Shakuyaku" in Japanese, is the root of *Paeonia albiflora* PALLAS and has been used in traditional Chinese medicine as an anodyne, sedative, astringent and antispasmodic.[2)] Paeoniflorin (PF) (**1**) isolated by Shibata *et al.*[3)] is well known as an active principle in paeony root but shows no inhibition of ACh-induced contraction in rectus abdominis muscle preparations from *Rana nigromaculata*.[4)]

In the course of our study on pharmacologically active principles of Paeoniae Radix, the ether-soluble fraction of the water extract of paeony roots was found to inhibit the contraction induced by ACh.[5)] From this fraction, a new monoterpene, named paeoniflorigenone (PFG) (**2**), was isolated along with benzoic acid (**3**) and *p*-hydroxybenzoic acid (**4**) and found to show a blocking effect on the neuromuscular junction in phrenic nerve diaphragm preparations of mice.[6)] This paper deals with the isolation and structure elucidation of **2**.

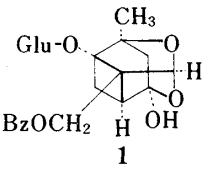
The ether-soluble fraction was subjected to silica gel column chromatography as described in the experimental section to furnish compounds **2**, **3**, and **4**.

Compounds **3** and **4** were identified by comparison with authentic samples. PFG (**2**) is a colorless viscous oil, $[\alpha]_D$ +4.3°, which shows infrared (IR) bands at 3400, 1725 and 1600 cm^{-1} and ultraviolet (UV) absorption maxima at 220, 258 (sh), 263 and 270 nm. Its mass spectrum (MS) shows fragment ions at m/z 319 $(M+1)^+$, 196 (M^+ − benzoic acid), 122, 105 and 77. The proton nueclear magnetic resonance (^{1}H-NMR) spectrum of **2** shows signals due to five aromatic protons in the region of δ 7.30—8.19, an acetal proton at δ 5.52 (s), tertiary methyl protons at δ 1.32 (s) and methyleneoxy protons at δ 4.14 and 4.42 (each dd, J=12.0, 9.6 Hz and J=12.0, 6.0 Hz). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **2** shows signals assignable to a ketonic carbonyl (δ 210.2), an ester carbonyl (166.1), a methyl (22.2), three methylenes (35.6, 47.7, 63.5), three methines (43.7, 47.2, 100.0), two quaternary carbons (79.4, 102.4) and six aromatic carbons (128.8, 129.9, 130.6, 133.3). These spectral data resemble those of PF[3,7)] except for the presence of a ketonic carbonyl and the absence of a glucose moiety.

Acetylation of **2** with Ac_2O in pyridine gave a monoacetate (**5**) as a colorless oil, $C_{19}H_{20}O_7$, $[\alpha]_D$ −13.7°, the ^{1}H-NMR spectrum of which shows a new signal due to an acetoxy group at δ 2.16. As acetylation of **2** causes no remarkable shift of proton signals, the hydroxyl group presumably occupies a tertiary position.

Methylation of **2** with diazomethane in Et_2O yielded a monomethyl ether (**6**) as colorless prisms, $C_{18}H_{20}O_6$, mp 121—122°C, $[\alpha]_D$ −14.0°. The IR spectrum of **6** shows two carbonyl absorptions at 1730 and 1715 cm^{-1} which are assignable to an ester carbonyl and a ketonic

carbonyl, respectively. These were also confirmed by the ^{13}C-NMR spectum of **6** (δ 166.1, 209.5). The signals in the 200 MHz ^{1}H-NMR spectum of **6** are clearly separated: δ 1.26 (3H, s, $-\underset{|}{\overset{|}{C}}-CH_3$), 2.06 and 2.61 (each 1H, dd, J=12.8, 2.4 Hz; J=12.8, 3.2 Hz, $-C\underline{H}_2-\underset{|}{\overset{|}{C}}H-$), 2.37 (1H, m, $-O-CH_2-\underset{|}{\overset{|}{C}}\underline{H}-$), 2.66 (2H, AB q, J=18.0 Hz, $-\underset{|}{\overset{|}{C}}-C\underline{H}_2-$), 2.95 (1H, m, $-CH_2-\underset{|}{\overset{|}{C}}\underline{H}-$), 3.56 (1H, s, OCH_3), 4.08 and 4.42 (each 1H, dd, J=12.0, 9.6 Hz; J=12.0, 6.0 Hz, $-O-C\underline{H}_2-\underset{|}{\overset{|}{C}}H-$), 5.55 (1H, s, $\underset{-O}{\overset{-O}{>}}C\underline{H}-$), 7.40—7.64 (3H, m, arom. protons), 8.08 (2H, dd, J=8.4, 2.0 Hz, arom. protons). Since the ^{1}H-NMR signals of the methyleneoxy group appear as a pair of double doublets at δ 4.08 and 4.42, this group is presumably attached to a methine carbon. On irradiation at δ 2.37, both double doublets at δ 4.08 and 4.42 changed to doublets (each J=12.0 Hz) and the multiplet at δ 2.95 was sharpened. On irradiation at δ 2.95, both double doublets



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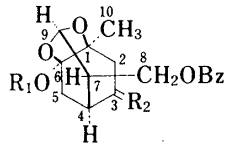

2 : R_1=H, R_2=O
5 : R_1=Ac, R_2=O
6 : R_1=Me, R_2=O
7 : R_1=Me, R_2=$\overset{OH}{H}$

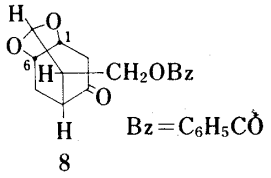

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Chart 1

TABLE I. Atomic Coordinates and Equivalent Isotopic Temperature Factors (Beq)

Atom	$X(10^4)$	$Y(10^4)$	$Z(10^4)$	Beq(Å^2)
C1	5110(3)	5370(2)	4475(5)	3.93(0.05)
C2	6171(3)	5022(2)	4819(7)	6.52(0.06)
C3	7009(3)	5554(2)	5122(5)	6.84(0.05)
C4	6644(3)	6222(2)	6064(5)	3.92(0.04)
C5	5739(2)	6044(2)	7457(4)	3.74(0.04)
C6	4794(2)	5842(1)	6230(4)	3.68(0.04)
C7	6243(2)	6742(2)	4506(5)	4.63(0.04)
C8	7056(3)	6864(2)	2921(6)	6.20(0.05)
C9	5186(3)	6514(2)	3694(5)	5.07(0.04)
C10	4246(4)	4875(2)	3871(8)	4.05(0.07)
C11	3580(3)	5926(2)	8853(6)	6.25(0.06)
C12	7172(3)	7515(2)	21(6)	3.83(0.04)
C13	6604(2)	7971(1)	−1349(5)	3.94(0.04)
C14	5527(2)	8061(2)	−1222(5)	5.32(0.04)
C15	5020(3)	8470(2)	−2554(8)	7.17(0.06)
C16	5571(4)	8792(2)	−3998(7)	7.47(0.07)
C17	6646(4)	8700(2)	−4150(7)	7.23(0.07)
C18	7157(3)	8291(2)	−2851(6)	5.26(0.05)
O1	5271(2)	5847(1)	2874(3)	4.27(0.04)
O2	7925(2)	5460(2)	4674(5)	9.46(0.05)
O3	3963(2)	5550(1)	7224(4)	4.62(0.03)
O4	4448(2)	6450(1)	5206(3)	5.03(0.03)
O5	6593(2)	7348(1)	1563(4)	6.58(0.03)
O6	8056(2)	7309(2)	−236(5)	8.57(0.05)
Atom	$X(10^3)$	$Y(10^3)$	$Z(10^3)$	B(Å^2)
HC2	620(3)	474(1)	614(5)	4.43(0.67)
H'C2	643(3)	457(2)	381(6)	5.99(0.82)
HC4	726(3)	646(2)	674(7)	5.81(0.85)
HC5	589(3)	572(1)	839(4)	3.98(0.62)
H'C5	561(3)	646(2)	831(5)	5.00(0.75)
HC7	610(3)	718(1)	518(5)	4.03(0.63)
HC8	722(3)	643(2)	228(7)	5.81(0.84)
H'C8	773(3)	712(2)	364(6)	5.69(0.87)
HC9	481(3)	679(2)	265(6)	4.68(0.65)

HC10	408(3)	449(2)	515(5)	6.01(0.84)
H′C10	367(3)	510(2)	385(6)	5.07(0.75)
H″C10	444(0)	465(0)	265(0)	5.53(0.0)
HC11	338(4)	636(2)	865(7)	7.51(1.05)
H′C11	411(3)	598(1)	995(5)	5.07(0.73)
H″C11	297(3)	569(1)	948(5)	4.74(0.69)
HC14	515(3)	785(2)	−6(5)	5.79(0.81)
HC15	421(3)	855(2)	−227(7)	6.89(0.94)
HC16	516(4)	919(2)	−478(6)	7.08(0.97)
HC17	699(3)	895(2)	−537(6)	5.72(0.80)
HC18	797(3)	815(2)	−295(7)	6.01(0.86)

TABLE II. Temperature Factors[a)]

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C1	83(2)	35(1)	224(7)	−1(1)	−4(4)	−26(2)
C2	97(3)	34(1)	343(11)	11(1)	23(5)	−20(3)
C3	70(2)	43(1)	241(7)	17(1)	1(4)	13(2)
C4	61(2)	37(1)	205(6)	1(1)	−27(3)	0(2)
C5	67(2)	35(1)	174(5)	3(1)	−18(3)	−9(2)
C6	59(2)	30(1)	198(6)	4(1)	−20(3)	−6(2)
C7	64(2)	33(1)	224(7)	4(1)	−7(3)	2(2)
C8	70(2)	42(1)	271(8)	5(1)	−5(4)	18(3)
C9	66(2)	41(1)	201(6)	5(1)	−15(3)	9(2)
C10	95(3)	49(1)	407(14)	−14(2)	−20(6)	−46(4)
C11	82(3)	61(2)	239(8)	−1(2)	21(4)	−15(3)
C12	59(2)	32(1)	255(7)	−8(1)	−3(3)	−3(2)
C13	60(2)	30(1)	237(7)	−9(1)	3(3)	3(2)
C14	60(2)	33(1)	280(8)	−4(1)	11(3)	17(2)
C15	72(2)	43(1)	383(10)	2(1)	−6(4)	30(3)
C16	104(3)	48(1)	334(10)	−5(2)	−23(5)	43(3)
C17	102(3)	53(1)	317(10)	−21(2)	10(6)	41(3)
C18	68(2)	45(1)	263(8)	−15(1)	16(4)	13(3)
O1	92(2)	48(1)	171(4)	−6(1)	−9(3)	−17(2)
O2	74(2)	55(1)	396(8)	23(1)	18(3)	17(3)
O3	69(1)	37(1)	235(5)	−4(1)	4(2)	−3(2)
O4	58(1)	35(1)	223(5)	8(1)	−8(2)	7(2)
O5	69(1)	41(1)	254(5)	4(1)	9(3)	25(2)
O6	63(2)	64(1)	343(8)	10(1)	12(3)	25(3)
HC2	44(7)					
H′C2	60(8)					
HC4	58(8)					
HC5	40(6)					
H′C5	50(7)					
HC7	40(6)					
HC8	58(8)					
H′C8	57(9)					
HC9	47(7)					
HC10	60(8)					
H′C10	51(8)					
H″C10	55(0)					
HC11	75(10)					
H′C11	51(7)					
H″C11	47(7)					
HC14	58(8)					
HC15	69(9)					
HC16	71(10)					
HC17	57(8)					
HC18	60(9)					

a) $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$ for heavier atoms and $T=\exp[-\beta_{11}(\sin\theta/\lambda)^2]$ for hydrogen atoms.

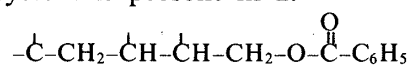
TABLE III. Bond Angles (°) with Standard Deviations in Parentheses

Atom 1	Atom 2	Atom 3	Angle (STD)
C2	−C1	−C6	111.9(3)
C2	−C1	−C10	113.4(3)
C2	−C1	−O1	106.1(3)
C6	−C1	−C10	113.3(3)
C6	−C1	−O1	103.4(2)
C10	−C1	−O1	107.9(3)
C3	−C2	−C1	109.8(3)
C4	−C3	−C2	115.7(3)
C4	−C3	−O2	121.7(3)
C2	−C3	−O2	122.5(3)
C5	−C4	−C3	107.1(3)
C5	−C4	−C7	109.0(3)
C3	−C4	−C7	111.8(3)
C6	−C5	−C4	108.2(2)
O3	−C6	−C1	109.2(2)
O3	−C6	−C5	116.4(2)
O3	−C6	−O4	110.1(2)
C1	−C6	−C5	111.8(2)
C1	−C6	−O4	101.2(2)
C5	−C6	−O4	107.0(2)
C8	−C7	−C4	111.4(3)
C8	−C7	−C9	112.9(3)
C4	−C7	−C9	110.3(3)
O5	−C8	−C7	106.3(3)
O1	−C9	−C7	110.1(3)
O1	−C9	−O4	105.0(2)
C7	−C9	−O4	110.5(3)
C13	−C12	−O5	112.3(3)
C13	−C12	−O6	124.4(3)
O5	−C12	−O6	123.4(3)
C14	−C13	−C12	121.4(3)
C14	−C13	−C18	119.3(3)
C12	−C13	−C18	119.3(3)
C15	−C14	−C13	119.9(3)
C16	−C15	−C14	120.4(4)
C17	−C16	−C15	120.2(4)
C18	−C17	−C16	120.1(4)
C13	−C18	−C17	120.1(4)
C1	−O1	−C9	106.5(2)
C6	−O3	−C11	115.7(3)
C6	−O4	−C9	103.0(2)
C8	−O5	−C12	116.3(3)

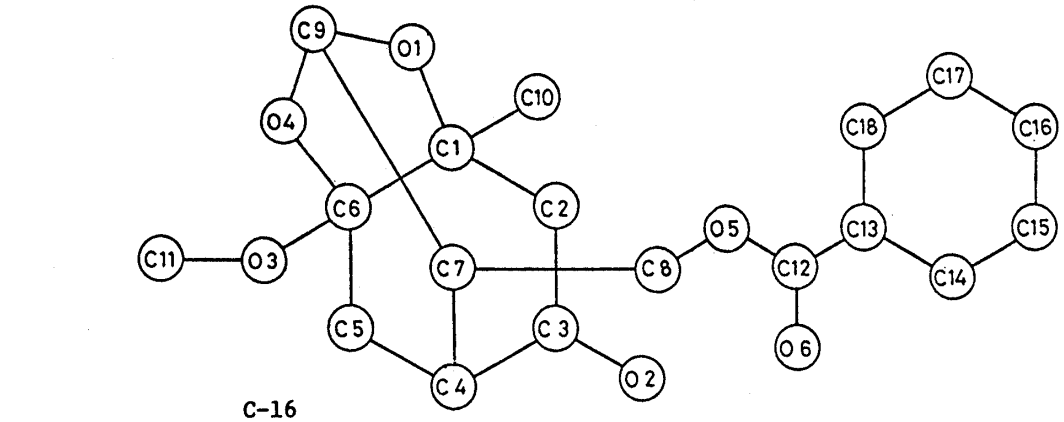
TABLE IV. Bond Lengths (Å) with Standard Deviations in Parentheses

Atom 1	Atom 2	Length (STD)
C1	−C2	1.531(5)
C1	−C6	1.566(4)
C1	−C10	1.523(6)
C1	−O1	1.452(4)
C2	−C3	1.506(5)
C2	−HC2	1.060(35)
C2	−H′C2	1.168(36)
C3	−C4	1.530(5)
C3	−O2	1.220(4)
C4	−C5	1.534(4)
C4	−C7	1.558(5)
C4	−HC4	1.017(39)
C5	−C6	1.519(4)
C5	−HC5	0.925(29)
C5	−H′C5	1.013(31)
C6	−O3	1.380(4)
C6	−O4	1.450(4)
C7	−C8	1.516(5)
C7	−C9	1.523(5)
C7	−HC7	0.994(28)
C8	−O5	1.451(5)
C8	−HC8	0.985(36)
C8	−H′C8	1.101(39)
C9	−O1	1.426(4)
C9	−O4	1.402(4)
C9	−HC9	1.014(35)
C10	−HC10	1.170(35)
C10	−H′C10	0.851(37)
C10	−H″C10	0.980(5)
C11	−O3	1.420(5)
C11	−HC11	0.899(36)
C11	−H′C11	1.013(33)
C11	−H″C11	1.001(34)
C12	−C13	1.481(5)
C12	−O5	1.326(4)
C12	−O6	1.209(4)
C13	−C14	1.385(4)
C13	−C18	1.393(5)
C14	−C15	1.373(6)
C14	−HC14	1.017(37)
C15	−C16	1.363(7)
C15	−HC15	1.060(44)
C16	−C17	1.384(7)
C16	−HC16	1.076(40)
C17	−C18	1.361(6)
C17	−HC17	1.061(39)
C18	−HC18	1.070(41)

at δ 2.06 and 2.61 changed to doublets (each J=12.8 Hz). These results suggest that the following system is present in **2**:



Reduction of **6** with sodium borohydride in EtOH–CH_2Cl_2 (2:1 v/v) afforded an alcoholic compound (**7**), $C_{18}H_{22}O_6$, mp 102—103 °C, $[\alpha]_D$ +64.6°. The ^{1}H-NMR spectrum of **7** showed a new signal due to an oxygen-bearing methine proton at δ 4.29 (1H, t, J=8.0 Hz) which was shifted downfield by acetylation. On irradiation at δ 4.29, the double doublet at δ 2.12 (1H, J=16.0, 8.0 Hz) was transformed to a doublet (J=16.0 Hz) and the multiplet at δ 2.81 was



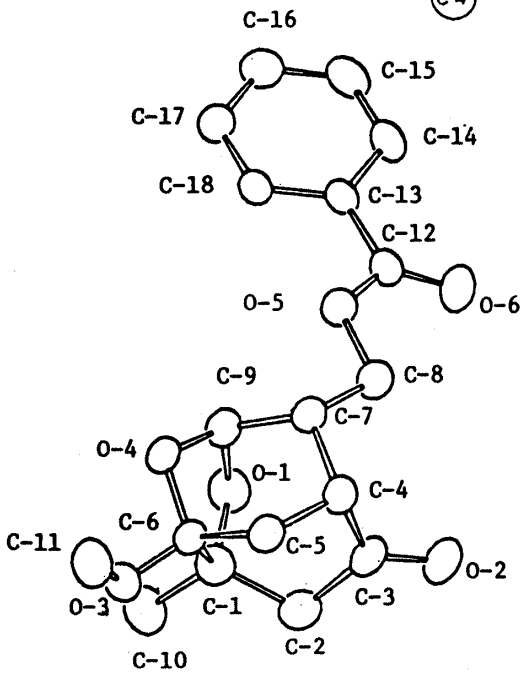


Fig. 1

sharpened, whereas the triplet at δ 4.29 was changed to a doublet (J=8.0 Hz) by irradiation at δ 2.12 or 2.81. The results of these decoupling experiments indicate that the hydroxyl group of **7** is located at a position between the methine group (at δ 2.81) and the methylene group (at δ 1.93 and 2.12).[8] From these findings, the partial structure **8** was deduced for **2**. The remaining methyl and hydroxyl groups were supposed to be located at C-1 and C-6, respectively, or *vice versa*.

The structure and relative stereochemistry of PFG were eventually established by a single-crystal X-ray analysis of **6** using the direct method. Details of the X-ray analysis are given in the experimental section and the final atomic parameters, bond angles and bond lengths are listed in Tables I—IV.

A perspective drawing of **6** is shown in Fig. 1.

TABLE V. Comparisons of $|Fc(h)|^2/|Fc(\bar{h})|^2$ and $Io(h)/Io(\bar{h})$

h	k	l	Fo	$\frac{\lvert Fc(h)\rvert^2}{\lvert Fc(\bar{h})\rvert^2}$	$Io(h)/Io(\bar{h})$
6	5	1	3.3	0.96	1.07
6	10	1	4.2	1.05	0.96
8	15	1	2.3	1.05	0.94
9	2	2	4.2	0.95	1.06
7	4	2	2.7	1.07	0.98
13	4	2	2.4	0.96	1.03
7	5	2	2.2	0.94	1.01
9	8	2	3.7	1.04	0.91
11	12	2	3.1	1.05	0.94
6	13	2	2.0	1.09	0.80
6	19	2	2.1	0.96	1.11
10	9	3	2.3	1.08	0.91
4	12	3	3.7	0.94	1.21
12	5	4	2.3	1.04	0.98
11	9	4	2.3	1.04	0.89
10	5	5	2.5	1.05	0.89
9	5	6	2.7	0.95	1.01
6	10	6	2.6	0.96	1.09
1	4	7	3.5	1.05	0.94

An attempt was made to determine the absolute configuration of **6** by making use of anomalous dispersion of the O atom with Cu-$K\alpha$ radiation. The intensities of 19 Friedel pairs with high enough intensities ($I>2\sigma(I)$) and with $|Fc(hkl)|^2/|Fc(\bar{h}\bar{k}\bar{l})|^2$ values differing by more than 4% from unity were measured as follows. $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$ as well as their equivalents, $I(\bar{h}\bar{k}l)$ and $I(\bar{h}k\bar{l})$ for $I(hkl)$, and $I(\bar{h}kl)$ and $I(h\bar{k}l)$ for $I(\bar{h}\bar{k}\bar{l})$, were measured with a scan speed of $2°\,min^{-1}$ in θ and each reflection was scanned four times. The average intensities of each group were compared and are shown in Table V, which indicates that the absolute configuration must be represented by a reversed coordinate system with respect to that adopted in the intensity measurement. The absolute configuration thus determined is closely related to that of PF.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. For column chromatography, Wakogel C-200 was used and for thin-layer chromatography (TLC) and preparative layer chromatography (PLC), Merck Kieselgel G (Typ 60) and 60 PF_{254}, respectivcly. The developing solvent system was a mixture of $CHCl_3$ and MeOH (9:1), and spots were visualized by exposure to ioding vapor or by spraying 10% H_2SO_4 followed by heating. The UV spectra were recorded with a Hitachi 124 spectrophotometer and IR spectra with a Hitachi 260-10 infrared spectrophotometer. The NMR spectra were taken with a Varian EM-390 (^1H, 90 MHz) or XL-200 (^1H, 200 MHz; ^{13}C, 50.3 MHz) NMR spectrometer with tetramethylsilane as an internal standard. Mass spcctra (MS) were measured with a JEOL JMS-D200 mass spectrometer. The specific rotations were measured with a Union PM-101 automatic digital polarimeter.

Extraction and Isolation———Dried roots of *Paeonia albiflora* PALLAS(260 g), collected in Toyama in 1977, were cut into pieces and homogenized with cold water (700 ml). The homogenized mixture was allowed to stand overnight at room temperature and filtered. The residue was percolated twice with cold water (each 500 ml). The combined filtrate was extracted three times with Et_2O and the solvent was distilled off under reduced pressure to give a brown residue (960 mg). This was chromatographed on a silica gel column (20 g, 1.7×17 cm), which was developed successively with (a) petroleum benzin, (b) petroleum benzin–Et_2O (9:1), and (c) petroleum benzin–Et_2O (4:1).

Fraction (a): This fraction, showing a colorless parabolic spot on exposure to iodine vapor, gave a crystalline residue after concentration. The residue was recrystallized from a mixture of petroleum benzin and Et_2O, yielding 580 mg of colorless needles (3), mp 123—125°C, which were identified as benzoic acid by comparisons of the IR and ^1H-NMR spectra with those of an authentic sample. *Anal.* Calcd for $C_7H_6O_2$: C, 68.84; H, 4.95. Found: C, 68.77; H, 5.05.

Fraction (b): The concentrated residue from this fraction was dissolved in a small amount of Et_2O and chromatographed on a silica gel column (5 g, 1.5×8.5 cm) with a mixture of petroleum benzin and Et_2O (85:15). The fractios showing a single spot, *Rf* 0.42 on TLC ($CHCl_3$–MeOH, 3:1), were combined and concentrated. Recrystallization of the residue from a mixture of petroleum benzin and Et_2O gave colorless prisms (4), mp 212—213°C, which began to sublime at around 170°C; this product was identified as *p*-hydroxybenzoic acid by comparisons of the IR and ^1H-NMR spectra with those of an authentic sample. *Anal.* Calcd for $C_7H_6O_3$: C, 60.87; H. 4.38. Found: C, 60.71; H, 4.47.

Fraction (c): This fraction was divided into two parts (c-1 and c-2). From fraction (c-1), showing a single spot, *Rf* 0.60 on TLC, viscous oily PFG (**2**) was obtained (118 mg). Fraction (c-2), showing more than two spots including a sot of *Rf* 0.60, was concentrated and the residue was rechromatographed on silica gel (15 g, 1.8×14.5 cm) with a mixture of petroleum benzin and Et_2O (9:1). The fractions showing a spot of *Rf* 0.60 on TLC were combined and concentrated. The residue was further purified by PLC to give 19 mg of **2**. **2**: $[\alpha]_D^{25}$ +4.3° (c=0.69, MeOH). UV λ_{max}^{MeOH} nm (log ϵ): 220 (3.94), 258 (sh 2.84), 263 (2.90), 270 (2.82). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1725, 1605. ^1H-NMR ($CDCl_3$) δ: 1.32 (3H, s, –C(OH)–CH_3), 2.93 (1H, m, $-CH_2CH-$), 4.14 and 4.42 (each 1H, dd, J=12.0, 9.6 Hz; J=12.0, 6.0 Hz, $-O-CH_2CH-$), 5.52 (1H, s, $-O-CH-O-$), 7.30—7.72 (3H, m, arom. protons), 8.10 (2H, dd, J=8.4, 2.0 Hz, arom. protons). MS m/z: 319 $(M+1)^+$, 196, 150 (base), 122, 105, 77, 69, 44.

Acetylation of 2———Compound **2** (60 mg) was dissolved in 0.5 ml each of Ac_2O and pyridine and the solution was left to stand overnight. The reaction mixture was poured into ice-water and extracted with Et_2O. The Et_2O layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (10 g, 1.5×16.5 cm) with a petroleum benzin–Et_2O solvent system. The fractions eluted with petroleum benzin–Et_2O (4:1) and showing a single spot of *Rf* 0.92 on TLC were combined and concentrated *in vacuo* to give 23 mg of a colorless oily substance (**5**). UV λ_{max}^{MeOH} nm (log ϵ): 229 (4.14), 268 (sh 2.94), 272 (2.99), 280 (2.89). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1600. ^1H-NMR ($CDCl_3$) δ: 1.29 (3H, s, –C(OAc)–CH_3), 2.16 (3H, s, –OAc), 4.04 and 4.42 (each 1H, dd, J=12.0, 9.6 Hz; J=12.0, 6.0 Hz, $-O-CH_2CH-$), 5.56 (1H, s, $-O-CH-$), 7.27—7.62 (3H, m, arom. protons), 8.03 (2H, dd, J=8.4, 2.0 Hz, arom. protons). *Anal.* Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 65.48; H, 5.54.

Methylation of 2———Ethereal diazomethane was added to **2** (28 mg) and the reaction mixture was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* and the residue was subjected to chromatography on silica gel (5 g, 1.5×8.5 cm), with petroleum benzin–Et_2O (9:1) to afford colorless prisms (**6**) after crystallization from Et_2O. **6**: mp 121—122°C. Yield 12 mg. $[\alpha]_D^{25}$ −14.0° (c=1.0, MeOH). UV λ_{max}^{MeOH} nm (log ϵ): 228 (4.27), 268 (sh 3.21), 275 (3.22), 280 (sh 3.20). ^{13}C-NMR (pyridine-d_5) δ: 21.8 (q), 30.9 (t), 43.6 (d), 46.7 (d), 47.6 (t), 52.2 (q), 63.3 (t), 80.6 (s), 101.1 (d), 104.7 (s), 128.8 (d). 129.9 (d), 130.5 (s), 133.4 (d), 166.1 (s), 209.5 (s). MS m/z: 333 $(M+1)^+$,, 210, 164, 143, 122, 105 (base), 77, 69, 44. *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C. 65.00; H, 6.09.

$NaBH_4$ Reduction of 6———$NaBH_4$ (25 mg) was added in portions to a solution of **6** (50 mg) in 2 ml of EtOH–CH_2Cl_2 (2:1). The mixture was stirred for 1 h at room temperature, then a small amount of AcOH was added. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O and dried over Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on a silica gel column (5 g, 1.5×8.5 cm) with $CHCl_3$. The fractions showing a spot of *Rf* 0.74 on TLC ($CHCl_3$–MeOH 3:1) were combined and concentrated *in vacuo*, giving 32 mg of colorless prisms (**7**), mp 102—103°C. $[\alpha]_D^{25}$ +64.6° (c=1.33, MeOH). UV λ_{max}^{MeOH} nm (log ϵ): 228 (4.18), 267 (sh 3.08), 272 (3.11), 279 (3.02). IR ν_{max}^{KBr} cm^{-1}: 3530, 1720, 1640, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, -C(CH$_3$)-), 1.43 and 2.28 (each 1H, dd, J=12.8, 2.4 Hz; J=12.8, 4.8 Hz, -CH$_2$CH-), 1.93 and 2.12 (each 1H, d, J=16.0 Hz; dd, J=16.0, 8.0 Hz, -CH(OH)CH$_2$-), 2.38 (1H, m, -O-CH$_2$CH-), 2.81 (1H, m, -CH-CH(OH)-), 3.52 (3H, s, -OCH_3), 4.29 (1H, t, J=8.0 Hz, -CHCH(OH)-), 5.56 (1H, s, -O-CH-O-), 7.38—7.73 (3H, m, arom. protons), 8.08 (2H, dd, J=8.4, 2.0 Hz, arom. protons). ^{13}C-NMR (pyridine-d_5) δ: 23.0 (q), 32.2(t), 37.9 (d), 42.4 (t), 47.6 (d), 52.1 (q), 66.4 (t), 69.6 (d), 82.9 (s), 101.1 (d), 105.5 (s), 129.6 (d), 130.7 (d), 132.0 (s), 134.1 (d), 167.8 (s). *Anal.* Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.37; H, 6.72.

Acetylation of 7———Compound **7** (32 mg) was dissolved in 0.5 ml each of Ac_2O and pyridine and the solution was allowed to stand overnight. The reaction mixture was worked up as usual. The residue was subjected to column chromatography on silica gel (10 g, 1.3×16.5 cm), with $CHCl_3$ to afford a colorless oil. Yield 33 mg. $[\alpha]_D^{25}$ +32.1° (c= 1.28, MeOH). UV λ_{max}^{MeOH} nm (log ϵ): 228 (4.10), 268 (sh 3.04), 273 (3.06), 280 (3.00). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, -C(CH$_3$)-), 2.11 (3H, s, -OAc), 2.90 (1H, m, -CH$_2$CH-), 3.51 (3H, s, -OCH_3), 4.51 (2H, m, -O-CH$_2$CH-), 5.28 (1H, dt, J=7.5, 3.0 Hz, -CH(OAc)-), 5.54 (1H, s, -O-CH-O-), 7.35—7.75 (3H, m, arom. protons), 8.07 (2H, dd, 8.0, 2.0 Hz, arom. protons). *Anal.* Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.78; H, 6.77.

Crystal Data for 6———Orthorhombic, space group $P2_12_12_1$, a=12.735(5), b=19.582(7), c=6.826(3) Å, Z=4, V=1702.2 Å^3, Dx=1.296 g·cm^{-1}. The intensity data were collected by the θ—2θ scanning technique with a θ scan speed of 6° min^{-1} using graphite-monochromated Cu-$K\alpha$ radiation on a Philips PW1100 four-circle diffractometer. 1789 unique reflections were measured in a θ range of 3 to 78°.

Determination of the Structure of 6———The structure was solved by the direct method and refined by the block-diagonal least-squares method. The final R index was 0.052. The final atomic parameters and their standard deviations, bond angles and bond lengths are shown in Tables I—IV.

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References and Notes

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8) Since the alcoholic compound (**7**) is formed by addition of a hydride ion from the less hindered side, the orientation of the hydroxyl group should be the same as that of the benzoyl group.