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Structural Studies on Herqueinone. The Configurations at C-4 of Herqueinone and at C-3 and C-4 of Dihydroherqueinone Monomethyl Ether

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On the basis of the ^{1}H NMR spectroscopy and the X-ray crystallography, the configuration at C-4 of herqueinone was determined to be *S* and the configurations at C-3 and C-4 of dihydroherqueinone monomethyl ether were elucidated to be *R* and *S*, respectively, with relation to the previously established *R*-configuration at the 2′-position of herqueinone.

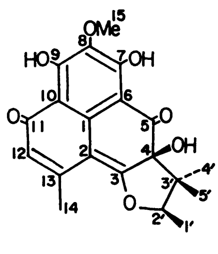
In the structural studies of herqueinone (**1**) which is a main red pigment isolated from the mycelia of *Penicillium herquei*,[1–5] its structure, except for the absolute configuration, was described as **1** by relating herqueinone to atrovenetin (**2**).[6,7] The configuration at C-2′ of **1** was reported to be *R* on the basis of the studies on the stereochemistry of the degradation product originating from its trimethylfuran ring.[8] On the other hand, the relative configurations at C-3, C-4, and C-5 of "glycol A" derived from dihydroherqueinone were shown as **3** on the basis of the long-range coupling between 3-H and 5-H in the ^{1}H NMR spectrum.[7] However, the relative configurations between C-2′ and C-4 of **1** and **3** have not been clarified yet.

For the biosynthetic studies of herqueinone (**1**),[9,10] it was necessary to determine the configuration at C-4 of **1** for clarifying the mechanism of the prenylation of the phenalenone skeleton. We therefore studied the configuration at C-4 of **1** and the configurations at C-3 and C-4 of dihydroherqueinone monomethyl ether (**4**) on the basis of the ^{1}H NMR spectroscopy and the X-ray crystallography. The results have been partly outlined in the form of the preliminary communications.[11,12] We will here report details of the results.

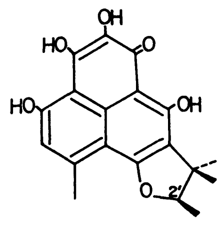
Results and Discussion

Herqueinone (1) and Dihydroherqueinone Monomethyl Ether (4). Herqueinone (**1**) was isolated from the mycelia of *Penicillium herquei* in the manner as described in the experimental part and identified by comparing its mp and ^{1}H NMR, IR, and UV spectra with those described in the literatures.[2,7] According to the method given in the literature,[7] dihydroherqueinone monomethyl ether (**4**) was prepared from the herqueinone (**1**) by hydrogenation followed by methylation. All the physical and spectral data of **4** are in fair agreement with the data described in the literature.[7] The configurations at C-4 of **1** and **4** were investigated by use of the ^{1}H NMR spectroscopy and the X-ray crystallography as follows.

^{1}H NMR Spectroscopic Study. The carbon atom at the 3′-position of herqueinone (**1**) has the geminal dimethyl groups which are composed of the C-4′ methyl group occupying the *pro-R* position and the C-5′ methyl group doing the *pro-S* position. The ^{1}H NMR signals at δ_H 1.00 and 1.40 were assigned to the C-4′ and C-5′ methyl groups, respectively, on the basis of the nuclear Overhauser effect (NOE),[13] which is shown in **1** of Fig. 1.[14]



1



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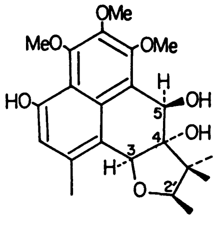

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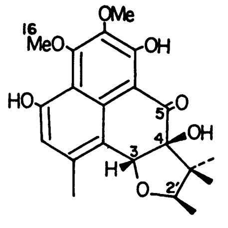

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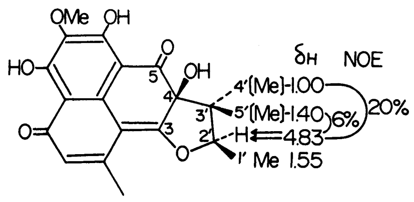
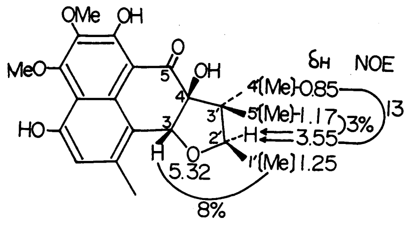
The configuration at C-4 of **1** was determined by the application of the anisotropic effect[15–17] to the C-4′ and C-5′ methyl groups, as follows. Models[18] for **1** were examined; the distances between the center of the carbonyl double bond and the geminal dimethyl groups are estimated to be 2.5 Å and 3.5 Å, and the angles between the vectors from the center of the carbonyl double bond to the geminal dimethyl groups and the vector of the carbonyl dipole moment are about 35° and 75°. These data indicate that these methyl groups suffer from the anisotropic effect of the carbonyl group at the 5-position. On the other hand, the contribution of the anisotropic effect of the C-4 hydroxyl group to the geminal dimethyl groups may be excluded, because a shift of a ^{1}H NMR signal of a methyl group due to the introduction of a hydroxy group at its neighboring carbon atom is known to be less than 0.1 ppm in ^{1}H NMR spectra of hydroxy steroids.[17,19] Owing to the anisotropic effect of the carbonyl group at the 5-position, an upfield shift would be expected for the C-4′ methyl group in **1a** with the 4*S*-configuration, whereas a downfield one for the C-4′ methyl group in **1b** with the 4*R*-configuration, as shown in Fig. 2. Appearance of the C-4′ methyl signal in a higher field than methyl signal as described above indicated the configuration at C-4 of herqueinone (**1**) to be *S* as in **1a**.

Incidentally, the NOE measurement (Fig. 1) of

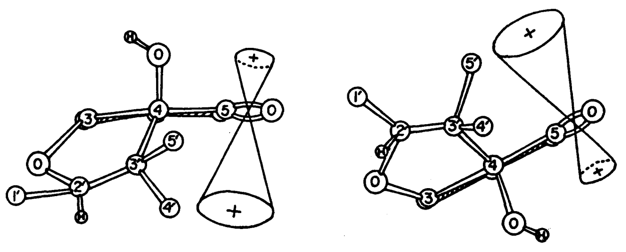


1



4

Fig. 1. Nuclear Overhauser effect observed for **1** and **4**.



1a: 2′*R*, 4*S* **1b**: 2′*R*, 4*R*

Fig. 2. Anisotropic effect of the carbonyl group at the 5-position of **1**.

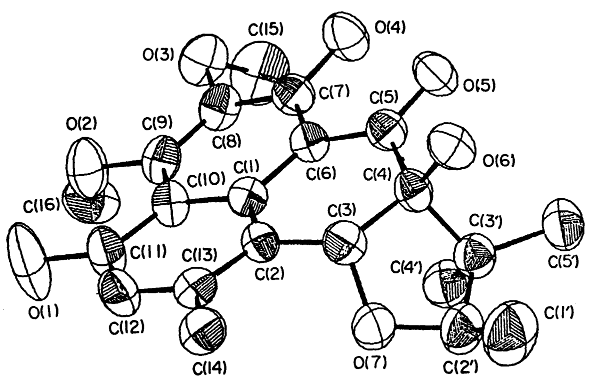


Fig. 3. ORTEP drawing[21] of the molecular structure of dihydroherqueinone monomethyl ether (**4**).

dihydroherqueinone monomethyl ether (**4**) showed also that the C-2′ hydrogen atom is *cis* to the C-4′ methyl group, while the hydrogen atom is *trans* to the C-3 hydrogen atom. This indicates that the configurations at C-3 and C-4 of **4** are *R* and *S*, respectively.

X-Ray Crystallographic Study. The absolute configuration of **4** is finally confirmed by the X-ray crystallography. A total of 1892 independent reflections were collected by use of Mo *Ka* radiation and 1811 reflections were used for structural determination. The structure of **4** was solved by the direct method by use of MULTAN[20] and the positional coordinates were refined by block-diagonal least-squares techniques to $R=0.058$.

Table 1. Final atomic coordinates of **4**, with standard deviations in parentheses

(1) The non-hydrogen atoms

Atom	$10^4 x$	$10^4 y$	$10^4 z$	B_{eq}[a]/Å^2
O(1)	2195(5)	12002(12)	4993(5)	8.0
O(2)	804(4)	9557(10)	5668(3)	5.7
O(3)	541(4)	5900(9)	6624(3)	4.9
O(4)	2639(4)	3577(8)	7655(3)	4.8
O(5)	5012(4)	3159(8)	8260(3)	4.6
O(6)	7274(4)	4271(8)	8157(3)	4.6
O(7)	7257(4)	9449(9)	8240(3)	5.0
C(1)	4166(5)	8058(11)	6824(4)	3.3
C(2)	5378(5)	8780(10)	6858(4)	3.2
C(3)	6564(5)	7776(11)	7573(5)	3.9
C(4)	6420(5)	5914(11)	8213(4)	3.6
C(5)	5098(5)	4964(10)	7935(4)	3.6
C(6)	4026(5)	6180(10)	7348(4)	3.3
C(7)	2819(5)	5434(11)	7255(4)	3.8
C(8)	1727(5)	6644(12)	6729(4)	3.9
C(9)	1858(5)	8432(13)	6234(4)	4.0
C(10)	3064(5)	9165(12)	6221(4)	3.8
C(11)	3193(6)	10887(13)	5630(5)	4.7
C(12)	4380(6)	11484(12)	5642(5)	4.6
C(13)	5472(5)	10448(11)	6247(4)	3.7
C(14)	6732(6)	11152(13)	6173(4)	4.7
C(15)	253(6)	5776(19)	7536(6)	6.8
C(16)	43(6)	10488(14)	6178(6)	5.8
C(1′)	9116(7)	7972(20)	9453(7)	7.6
C(2′)	7791(6)	8609(14)	9239(5)	5.2
C(3′)	6832(5)	6915(12)	9290(4)	4.0
C(4′)	5745(6)	8129(13)	9458(5)	4.9
C(5′)	7368(6)	5246(13)	10096(5)	5.0

a) $B_{eq}=(B_{11}+B_{22}+B_{33})/3$.

(2) The hydrogen atoms

Atom	$10^3 x$	$10^3 y$	$10^3 z$	B/Å^2
H(1)	739(5)	1086(10)	698(4)	7.8
H(2)	671(5)	1151(10)	561(4)	5.0
H(3)	704(5)	1246(10)	652(4)	7.4
H(4)	441(5)	1290(10)	527(4)	3.0
H(5)	158(5)	1151(10)	495(4)	9.5
H(6)	957(5)	533(10)	746(4)	2.4
H(7)	102(5)	488(10)	816(4)	9.5
H(8)	57(5)	691(10)	801(4)	12.5
H(9)	53(5)	1064(10)	701(4)	8.7
H(10)	962(5)	938(10)	633(4)	7.9
H(11)	967(5)	1162(10)	582(4)	8.5
H(12)	335(5)	272(10)	791(4)	7.6
H(13)	705(5)	315(10)	845(4)	6.8
H(14)	514(5)	728(10)	947(4)	6.2
H(15)	603(5)	898(10)	1005(4)	4.3
H(16)	538(5)	927(10)	893(4)	4.0
H(17)	803(5)	413(10)	993(4)	4.9
H(18)	684(5)	412(10)	1017(4)	5.1
H(19)	770(5)	570(10)	1058(4)	6.6
H(20)	938(5)	747(10)	1023(4)	7.7
H(21)	965(5)	984(10)	936(4)	8.8
H(22)	859(5)	658(10)	894(4)	9.3
H(23)	832(5)	990(10)	988(4)	0.4
H(24)	704(5)	724(10)	739(4)	7.1

TABLE 2. INTERATOMIC DISTANCES OF **4**, WITH STANDARD DEVIATIONS IN PARENTHESES

Interatomic distance	l/Å		l/Å
C(1)–C(2)	1.416(8)	C(8)–O(3)	1.367(8)
C(1)–C(6)	1.426(9)	C(9)–C(10)	1.434(9)
C(1)–C(10)	1.418(8)	C(9)–O(2)	1.371(8)
C(2)–C(3)	1.505(8)	C(10)–C(11)	1.401(10)
C(2)–C(13)	1.383(9)	C(11)–C(12)	1.376(10)
C(3)–C(4)	1.518(9)	C(11)–O(1)	1.363(9)
C(3)–O(7)	1.443(8)	C(12)–C(13)	1.390(9)
C(4)–C(5)	1.516(9)	C(13)–C(14)	1.517(9)
C(4)–C(3′)	1.570(8)	C(15)–O(3)	1.455(9)
C(4)–O(6)	1.423(8)	C(16)–O(2)	1.422(9)
C(5)–C(6)	1.423(8)	C(1′)–C(2′)	1.465(12)
C(5)–O(5)	1.232(8)	C(2′)–C(3′)	1.526(11)
C(6)–C(7)	1.393(9)	C(2′)–O(7)	1.438(8)
C(7)–C(8)	1.413(9)	C(3′)–C(4′)	1.522(10)
C(7)–O(4)	1.336(9)	C(3′)–C(5′)	1.513(10)
C(8)–C(9)	1.354(10)		

TABLE 3. BOND ANGLES OF **4**, WITH STANDARD DEVIATIONS IN PARENTHESES

Bond angle	ϕ/°		ϕ/°
C(2)–C(1)–C(6)	121.4(5)	C(9)–C(8)–O(3)	119.8(6)
C(2)–C(1)–C(10)	119.4(5)	C(8)–C(9)–C(10)	122.8(6)
C(6)–C(1)–C(10)	119.1(5)	C(8)–C(9)–O(2)	120.1(6)
C(1)–C(2)–C(3)	120.3(5)	C(10)–C(9)–O(2)	117.0(6)
C(1)–C(2)–C(13)	119.9(5)	C(1)–C(10)–C(9)	117.8(6)
C(3)–C(2)–C(13)	119.9(5)	C(1)–C(10)–C(11)	119.2(6)
C(2)–C(3)–C(4)	118.2(5)	C(9)–C(10)–C(11)	123.0(6)
C(2)–C(3)–O(7)	107.1(5)	C(10)–C(11)–C(12)	120.0(6)
C(4)–C(3)–O(7)	107.5(5)	C(10)–C(11)–O(1)	124.0(6)
C(3)–C(4)–C(5)	116.0(5)	C(12)–C(11)–O(1)	116.0(6)
C(3)–C(4)–C(3′)	103.1(5)	C(11)–C(12)–C(13)	121.5(6)
C(3)–C(4)–O(6)	107.6(5)	C(2)–C(13)–C(12)	119.9(6)
C(5)–C(4)–C(3′)	110.0(5)	C(2)–C(13)–C(14)	122.4(6)
C(5)–C(4)–C(6)	108.7(5)	C(12)–C(13)–C(14)	117.7(6)
C(3′)–C(4)–O(6)	111.3(5)	C(1′)–C(2′)–C(3′)	118.9(7)
C(4)–C(5)–C(6)	119.8(5)	C(1′)–C(2′)–O(7)	110.6(7)
C(4)–C(5)–O(5)	117.0(5)	C(3′)–C(2′)–O(7)	103.8(6)
C(6)–C(5)–O(5)	123.2(6)	C(4)–C(3′)–C(2′)	101.7(5)
C(1)–C(6)–O(5)	121.4(5)	C(4)–C(3′)–C(4′)	111.7(5)
C(1)–C(6)–C(7)	120.2(5)	C(4)–C(3′)–C(5′)	112.0(5)
C(5)–C(6)–C(7)	118.3(5)	C(2′)–C(3′)–C(4′)	106.3(6)
C(6)–C(7)–C(8)	120.6(6)	C(2′)–C(3′)–C(5′)	114.2(6)
C(6)–C(7)–O(4)	122.2(6)	C(4′)–C(3′)–C(5′)	110.6(6)
C(8)–C(7)–O(4)	117.2(6)	C(9)–O(2)–C(16)	117.1(6)
C(7)–C(8)–C(9)	119.1(6)	C(8)–O(3)–C(15)	115.5(6)
C(7)–C(8)–O(3)	120.7(6)	C(3)–O(7)–C(2′)	109.5(5)

Final atomic coordinates, bond lengths, and bond angles are given in Tables 1—3. The relative configuration of **4** is shown in Fig. 3. Attempt to solve the absolute configuration of **4** on the basis of the anomalous dispersion effect of oxygen atoms for Cu $K\alpha$ radiation[22] failed, because the effect on the R index[23] and the Bijvoet inequalities[24] was too small to determine the absolute configuration. However, the 3R- and 4S-configurations of **4** were determined with relation to the previously established absolute configuration of R at the 2′-position.[8]

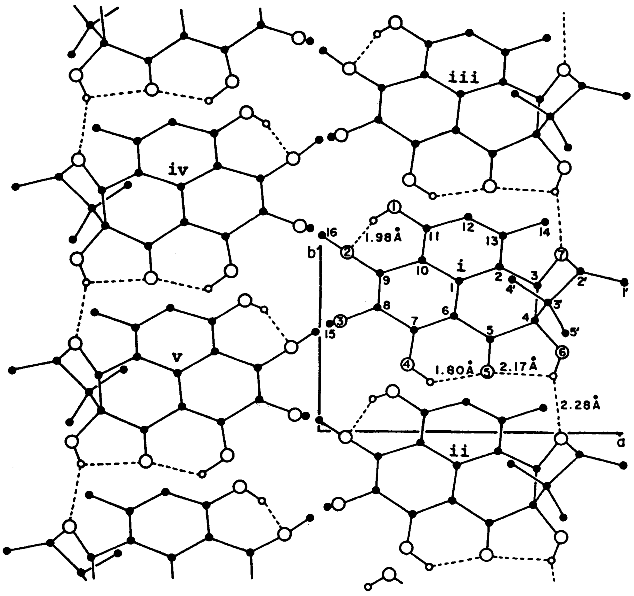


Fig. 4. The projection of dihydroherqueinone monomethyl ether (**4**) along the c axis. The atoms indicated with ●, ◯, and ○ denote carbon, oxygen, and hydrogen atoms, respectively. The hydrogen bondings are shown by a broken line. Symmetry codes: (i) x, y, z; (ii) $x, -1+y, z$; (iii) $x, 1+y, z$; (iv) $-x, 1/2+y, -z$; (v) $-x, -1/2+y, -z$. The other molecules related by a 2_1 axis are omitted in order to avoid overlapping.

The molecular arrangement and the hydrogen bond networks in the crystal are shown in Fig. 4. The molecules are packed along the c axis and are linked by the long intermolecular hydrogen bonding between O(6)–H and O(7′)[25] (furan ring) along the b direction. On the other hand, three intramolecular hydrogen bondings between O(1)–H and O(2) (methoxy group), O(4)–H and O(5) (carbonyl group), and O(6)–H and O(5) (carbonyl group) are formed.

The determination of the configuration at C-4 of herqueinone (**1**) and the configurations at C-3 and C-4 of dihydroherqueinone monomethyl ether (**4**) leads to the establishment of the absolute configuration of all the herqueinone- and dihydroherqueinone-type phenalenones.

Experimental

The fungal culture of *Penicillium herquei* Bainier and Sartory (IFO 7904) was purchased from the Institute for Fermentation.[26] The ^{1}H NMR spectra for 60 and 90 MHz were taken on a Varian T-60 and a Hitachi R-22 spectrometers by use of TMS as an internal standard. The ^{13}C NMR spectra were obtained on a Hitachi R-42 FT NMR (22.6 MHz) spectrometer ($\delta_{\mathrm{TMS}}=0$). The X-ray intensity data were collected on a Syntex R3 and a Rigaku AFC-5 diffractometers with graphite-monochromated Mo $K\alpha$ and Cu $K\alpha$ radiations, respectively.

Incubation of P. herquei. A spore suspension of *P. herquei* precultured on a malt extract agar medium were inoculated to 200 ml of a Raulin-Thom solution[2] in a 1 L Erlenmeyer flask (total 25 flasks), and incubated at 25 °C in the dark. After cultivation for 5 d, light yellow mycelia covered over the surface of the medium, and then the mycelia produced spores and became yellow-green. Then, droplets of reddish liquid appeared on the surface of the culture, and the medium became brown after cultivation for 15 d.

Isolation of Herqueinone (1). After incubation for 25 d, the mycelia were filtered off, and the mycelia were immersed in EtOAc. The filtrate was acidified to pH 5 with 10% hydrochloric acid and extracted with EtOAc. Removing EtOAc from the combined EtOAc extract afforded the residue (*ca.* 5 g), which wa ssubjected to centrifugal liquid chromatography on a silica-gel plate (3 mm in thickness and 10 cm in radius) with EtOAc–hexane (1 : 4 v/v) to give a red powder (310 mg). Recrystallization of this powder from EtOH gave herqueinone (**1**) (275 mg): red needles, mp 217—218 °C (lit,[7] 218—222 °C); $[\alpha]^{25}_{D}$ +374° (*c* 1.68, $CHCl_3$); UV (EtOH) λ_{max} 410 (log ε 4.02) and 300 nm (4.25); IR(Nujol) ν_{max} 3300 (OH) and 1640 and 1620 cm^{-1} (C=O); ^{1}H NMR ([^{2}H]-DMSO) δ_H=1.00 (3H, s, 4′-H_3), 1.40 (3H, s, 5′-H_3), 1.55 (3H, d, J=6.5 Hz, 1′-H_3), 2.50 (3H, d, J=1.5 Hz, 14-H_3), 3.80 (3H, s, 15-H_3), 4.83 (1H, q, J=6.5 Hz, 2′-H), and 6.28 (1H, d, J=1.5 Hz, 12-H); ^{13}C NMR ([^{2}H]DMSO) δ_C=197.0 and 186.4 (each s, C-5 and C-11), 122.8 (d, C-12), 95.9 (d, C-2′), 78.9 (s, C-4), and 59.9 (q, C-15); MS (70 eV), *m/z* (rel intensity), 372 (M$^+$, 100), 356 (40), 341 (68), 329 (36), and 274 (52); Found: C, 64.51; H, 5.49%.

*Derivation of **4** from **1**.* A slurry of herqueinone (**1**) (206 mg) in EtOAc (20 ml) was hydrogenated in the presence of 10% Pd–C (80 mg). After 1 molar equivalent of hydrogen had been taken up, the hydrogen uptake ceased, and the catalyst was filtered off. The filtrate was treated with ethereal CH_2N_2 (*ca.* 1 molar equiv.) at 0 °C for 30 min. The excess of CH_2N_2 was quenched with a few drops of acetic acid. The solvent was evaporated *in vacuo* to afford a crystalline residue (148 mg). This residue was purified by preparative TLC (silica gel GF_{254}; 0.5 mm thick) with EtOAc–hexane (1 : 1 v/v). The green-yellow fluorescent band at R_f 0.66 under UV light, on extraction with EtOAc, afforded yellow needles (121 mg). Recrystallization of this needles from EtOH gave yellow rods of dihydroherqueinone monomethyl ether (**4**): mp 173—174 °C (lit,[7] 172—174 °C); $[\alpha]^{25}_{D}$+39.0° (*c* 7.28, EtOH); UV (EtOH) λ_{max} 399 (log ε 3.78), 357 (3.62), and 290 nm (4.09); IR (Nujol) ν_{max} 3460 and 3366 (OH) and 1632 cm^{-1} (C=O); ^{1}H NMR ([^{2}H]CHCl$_3$) δ_H=0.80 (3H, s, 4′-H_3), 1.17 (3H, s, 5′-H_3), 1.34 (3H, d, J=6.5 Hz, 1′-H_3), 2.53 (3H, s, 14-H_3), 3.68 (1H, q, J=6.5 Hz, 2′-H), 3.98 (3H, s, 15-H_3), 4.28 (3H, s, 16-H_3), 5.44 (1H, s, 3-H), and 6.72 (1H, s, 12-H); ^{13}C NMR ([^{2}H]DMSO) δ_c=202.9 (s, C-5), 113.5 (d, C-12), 82.0 (s, C-4), 81.5 (2×d, C-3 and C-2′), 60.9 (q, C-15), and 62.4 (q, C-16); MS (70 eV), *m/z* (rel intensity), 388 (M$^+$, 100), 302 (74), 287 (38), 259 (34), 244 (15), and 216 (22); Found: C, 64.65; H, 6.33%.

*X-Ray Crystallographic Analyses of Dihydroherqueinone Monomethyl Ether (**4**).* *(i) Analysis by Use of Mo* Kα *Radiation*: The crystal used was about 0.5 mm×0.4 mm×0.7 mm in size. Cell dimensions were derived by the least-squares calculations from 2θ values of 25 well-centered diffraction peaks for **4**. Crystal data are; $C_{21}H_{24}O_7$; M=388.45; monoclinic (space group $P2_1$); Z=2 per unit cell with dimensions a=11.213(4), b=6.229(3), c=14.252(5)Å, β=110.21(3)°; U=934.3 Å^3; D_c=1.38 g cm^{-1}; D_m=1.40 g cm^{-1}; μ(Mo $K\alpha$) =1.1 cm^{-1}. A total of 1892 reflections were collected by use of ω-scan technique ($2\theta_{max}$=50.0°); 1811 reflections with intensity greater than 1.96 times the standard deviations were used as observed reflections. The phases of 244 reflections with $|E|>1.40$ were determined by use of MULTAN.[20] An E map for the best solution yielded positions for all the atoms except hydrogen atoms, followed by a difference map to find the positions for all the hydrogen atoms. Anisotropic refinement for carbon and oxygen atoms and isotropic refinement for hydrogen atoms reduced the R index to 0.058.

(ii) Analysis by Use of Cu Kα *Radiation*: A total 2784 reflections with the Friedel pair of (h, k, l) and (h, $\bar{k}$, l) were collected by use of ω-scan technique ($2\theta_{max}$=125°); 2697 reflections with $I_o>4.0\sigma(I_o)$ were used as observed reflections. The positional coordinates for the enantiomeric pair were refined by use of two sets of coordinates: (a) the same atomic coordinates determined as above and (b) the atomic coordinates translated by the code of (x, $-y$, z). Final refinement by use of the anomalous dispersion effect of oxygen atoms for Cu $K\alpha$ radiation[22] reduced the R index to 0.0662 for the coordinates (a) and 0.0668 for the coordinates (b). All the $||F_c(h,k,l)|-|F_c(h,\bar{k},l)||/\sigma(F_o)$ values were smaller than 0.8.

The complete F_o-F_c data and the table of anisotropic thermal parameters for **4** are deposited as Document No. 8261 at the Chemical Socity of Japan.

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