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Studies on Coumarins from the Root of *Angelica pubescens* Maxim. V.[1] Stereochemistry of Angelols A—H

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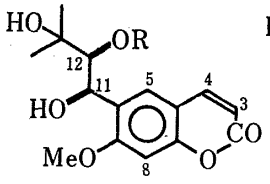
The absolute configurations of angelols A—H (**1**—**8**) isolated from *Angelica pubescens* Maxim. (Umbelliferae) were determined to be as shown in Chart 1 by means of chemical, spectral and X-ray analysis. Furthermore, the stereostructure of angelol B(**2**) was determined to be as shown in Fig. 1 on the basis of X-ray analysis.

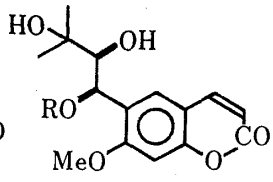
Keywords——*Angelica pubescens* Maxim.; Umbelliferae; coumarin; angelols A—H; X-ray analysis

In our preceding paper, we reported the isolation of seven new angelol-type coumarins, namely angelols B—H (**2**—**8**), from the root of *Angelica pubescens* Maxim., together with a known coumarin, angelol A (**1**), and we elucidated their plane structures and relative configurations by means of chemical and spectral studies. In the present paper, we report on the absolute configurations at the C-11 and C-12 positions in these compounds and on the results of X-ray crystallographic analysis of angelol B (**2**).

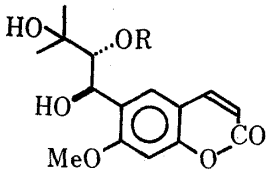
Previously, Hata and Kozawa had deduced that the configuration at the C-12 position in **1** was *R* by comparison of the optical rotatory dispersion (ORD) spectrum of a ketone (**19**) derived from **1** with that of a synthesized ketone (**23**) whose configuration at the C-12 position was known to be *R*. But in this case, there is still the problem that **19** had an α,β-unsaturated lactone ring, whereas **23** did not. That is to say, since the α,β-unsaturated lactone moiety and benzene ring in the coumarin ring do not lie in the same plane, and the group having an asymmetric center is present on the benzene ring, there is a possibility that conformational distortion occurs, and such distortion among the lactone ring, double bond and benzene ring could contribute greatly to the optical rotation. Therefore, we measured the ORD spectrum of **19**, 3,4-dihydro-**19** (**24**) and **25**, in which the lactone ring in **24** was cleaved and then the product was methylated. It became evident that the ORD spectrum of showed a negative Cotton effect like that of **19**, whereas **25** showed a positive Cotton effect (Table I). Hence it was inappropriate to deduce the absolute configuration at the C-12 position in **1** by comparison of the Cotton effects of **19** and **23**, and it was presumed that the configuration at the C-12 position in **1** was *S* in view of the Cotton effect of **25**. However, this result was still insufficient to establish the configuration, because **25** contains a carboxyl group, whereas **23** does not, that is, they do not have the same structure. Furthermore, it had been deduced that the configuration at the C-11 position in **1** was *R* by comparison of the ORD spectra of an aldehyde (**21**) obtained from **1** and an alcohol (**26**) prepared from the isopropylidene derivative of **1** with those of analogous compounds.[2] In this case, there still remains the problem that **21** has a coumarin ring. Therefore, we tried to determine the absolute configuration at the C-11 and C-12 positions by the synthesis of derivatives (**29** and **30**) from **2**. Two alcohols **10** and **11** derived from **2** gave **29** and **30** *via* alcohols **27** and **28** which were formed through methylation followed by lithium aluminium hydride reduction, and by catalytic hydrogenation, respectively. On the other hand, **9** also afforded a methyl ether (**29**) *via* the lithium aluminium hydride reduction product (**31**).



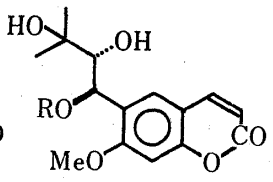
1: R=angeloyl
2: R=tigloyl
3: R=2-methyl-butyryl



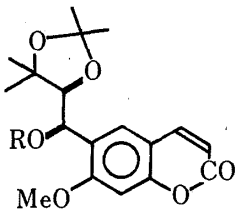
4: R=tigloyl



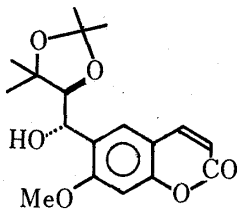
5: R=isovaleryl
6: R=2-methyl-butyryl



7: R=angeloyl
8: R=isovaleryl



9: R=tigloyl
10: R=H



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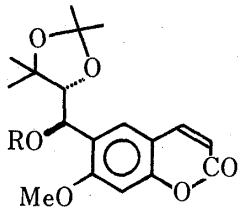
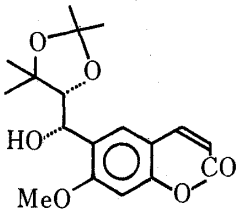


14: R=2-methyl-butyryl
15: R=isovaleryl
17: R=H
20: R=angleoyl



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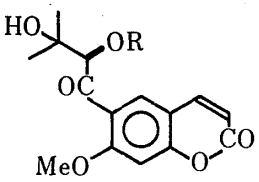
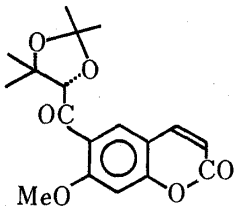


13: R=tigloyl



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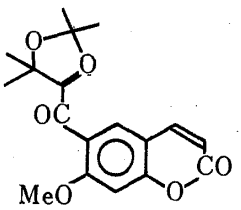

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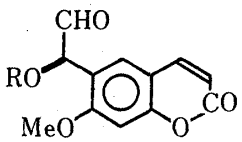
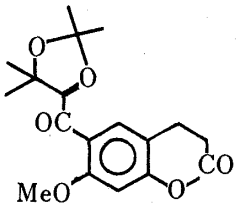


12: R=tigloyl
21: R=angeloyl
22: R=isovaleryl



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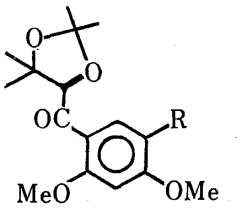

23: R=C_2H_5
25: R=C_2H_4COOMe

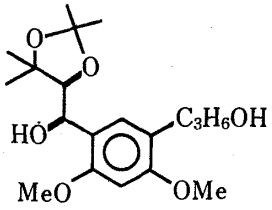

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Chart 1

From the above results, it became clear that, of the products **10** and **11** obtained by saponification of **9**, **10** retained the original configuration, whereas **11** was inverted at the C-11 position. Consequently, if the asymmetric synthesis of either **29** or **30** is possible, the configurations of the C-11 and C-12 positions of **2** could be decided. A methyl ether (**33**) prepared from herniarin (**32**) readily gave a bromide (**34**) upon addition of Br_2 in $CHCl_3$ under cooling. On reaction with butyllithium, **34** afforded a lithio derivative, which upon further condensation with a methyl ester (**35**) prepared from D(−)-α,β-dihydroxyisovaleric acid, gave a ketone (**36**). The lithium aluminium hydride reduction of **36** afforded only one alcohol (**37**). The methyl ether of **37** was identical with **30** in all respects including the optical activity. Accordingly, the absolute configuration at the C-12 position in **2** was concluded to be *S*. On the other hand, as

Table I. ORD Data for Derivatives

Compd.	*c*	Solvent	°C	[α] (nm)			
10	0.503	Ethanol	24	−95.4° (589)	−143.1° (500)	−270.4° (400)	−548.7° (375)
11	0.419	Ethanol	24	+19.1° (589)	+23.9° (500)	+66.8° (400)	+105.5° (375)
16	0.550	Ethanol	25	+80.0° (589)	+130.9° (500)	+298.2° (400)	+589.1° (375)
17	0.598	Ethanol	25	−13.4° (589)	−20.1° (500)	−60.4° (400)	−107.4° (375)
18	0.177	Dioxane	22	+22.6° (500)	+56.5° (400)	+146.9° (370)	+237.3° (360)
				+508.5° (351, p)	+372.9° (349)		
19	0.111	Dioxane	22	−18.0° (500)	−54.1° (400)	−144.1° (370)	−234.3° (360)
				−486.5° (351, tr)	−414.4° (349)		
24	0.185	Dioxane	21	−21.6° (400)	−64.9° (370, tr)	−43.2° (364)	−270.3° (350)
				−464.9° (340, tr)	−400.0° (335)		
25	0.165	Dioxane	21	+42.4° (400)	+193.9° (360)	+254.5° (353, p)	+181.8° (345)
				+193.9° (340, p)	+97.0° (335)		
29	0.481	Ethanol	20	−75.0° (589)	−100.0° (500)	−166.7° (400)	−325.0° (350)
				−650.0° (310)			
30	0.668	Ethanol	25	+77.8° (589)	+113.8° (500)	+233.6° (400)	+335.4° (350)
				+389.2° (332)			

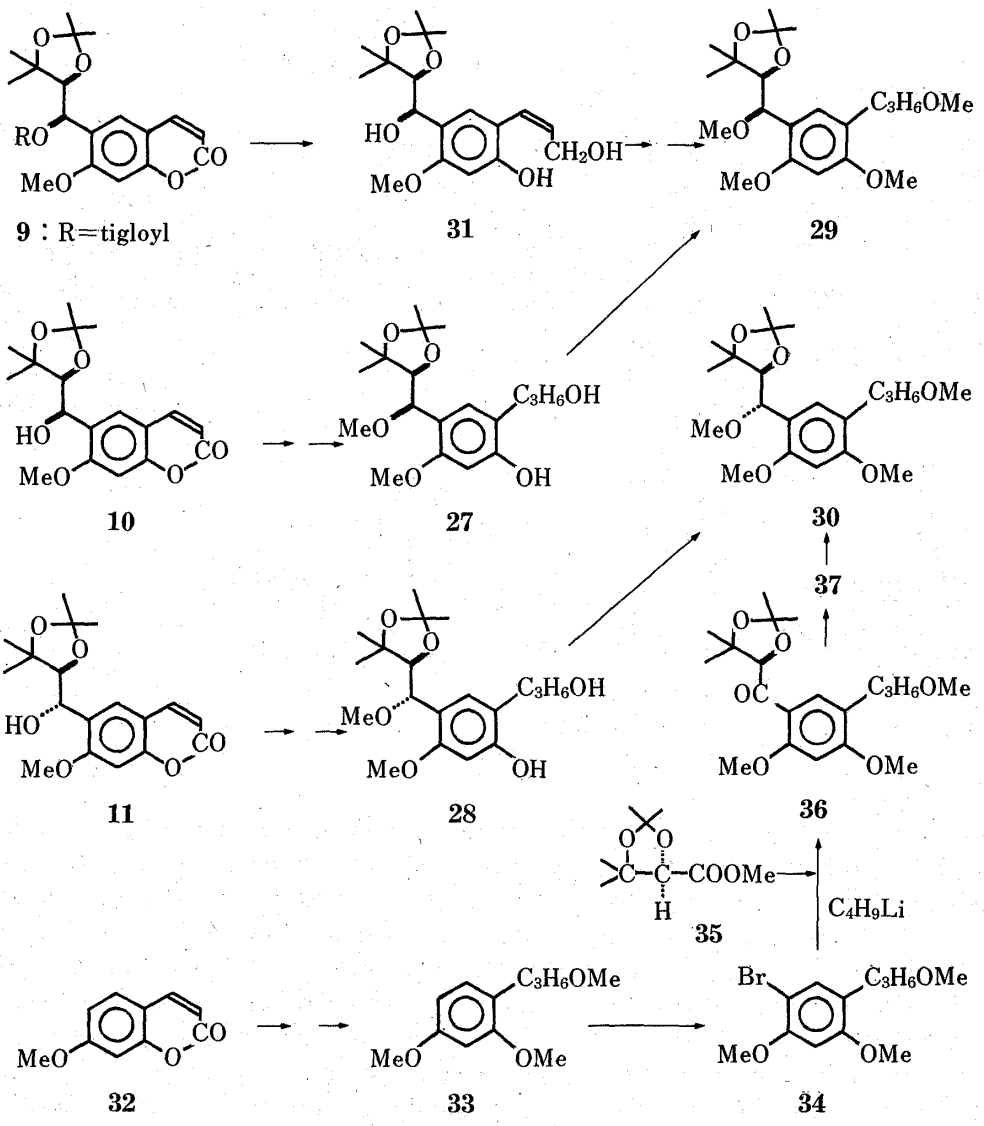
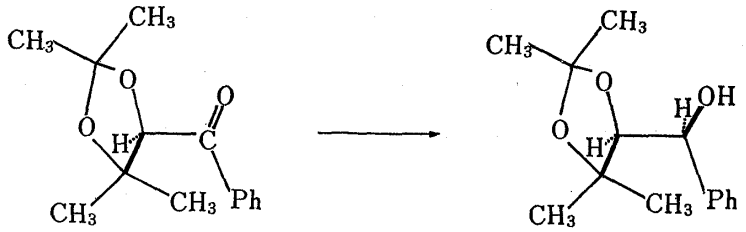


Chart 2

regards the absolute configuration at the C-11 position, the result that the lithium aluminium hydride reduction of **36** only gave **37** as an alcohol indicated that **36** underwent asymmetric reduction in the definite conformation in this reaction. If this reduction is explained on the basis of the Cram,[3] Carabatsos[4] and Stocker[5] rules, it seems reasonable to assume that **36** was reduced in the conformation shown in Chart 3. Consequently, the absolute configuration of the newly formed asymmetric carbon was assumed to be *S*.

From the above chemical and spectral data, and the relationships of **1**—**8** described in the preceding paper, it was concluded that the absolute configurations in **1**—**4** were C-11 (*R*) and C-12 (*S*), whereas in **5**—**8** they were C-11 (*R*) and C-12 (*R*). There is no question about the absolute configuration of C-12, but that of C-11 is open to some uncertainty in that we presumed that **36** was reduced in the conformation shown in Chart 3.



36 **37**

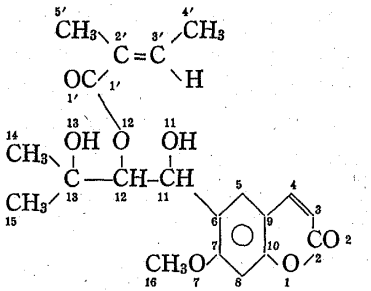
Chart 3

In order to confirm the absolute configuration at the C-11 position, and to investigate further the stereostructure of angelol B (**2**), which was subject to acyl migration, and whose ^{1}H-nuclear magnetic resonance (NMR) spectrum showed a high-field shift of the signals due to the acyl moiety at C-12, the authors carried out an X-ray diffraction analysis of **2**.

Needle-shaped colorless crystals of **2** were grown at room temperature by slow evaporation of a hexane–EtOAc solution of **2**. A single crystal (0.2 mm×0.6 mm×0.2 mm) was used for the X-ray study. Preliminary oscillation and Weisenberg photographs indicated the crystal to be monoclinic and the space group to be $P2_1$ from the systematic absent reflections. All subsequent X-ray measurements were made with a Rigaku automated four-circle diffractometer employing a graphite monochrometer and Cu $K\alpha$ radiation. The unit cell parameters, as determined by least-squares analysis of the general positions of 22 independent reflections, are a=9.902 (3), b=11.239 (2), c=9.916 (3) Å, β=117.05 (3)° and V=982.8 (6)Å^3. The density of crystals, which was determined by flotation in a benzene–CCl_4 mixture, was found to be 1.278 (1)g·cm^{-3}. This is in good agreement with the density of 1.272 g·cm^{-3} calculated for the existence of two formula weights per unit cell. X-ray diffraction peak counts were measured using a θ-2θ scan mode and a scan rate of 4°/min. Stationary background counts (5 s each) were taken at both limits of each scan. A total of 1746 unique reflections was measured to the limit 2θ=130°. The X-ray intensities of four standard reflections monitored at 100 reflection intervals showed no evidence of structural deterioration during data collection. Lorentz and polarization corrections were applied, but no absorption correction was made due to the small size of the crystal.

The structure was solved by a direct method using the MULTAN 78 program.[6] An *E*-map, calculated using 208 reflections ($|E|\geqq 1.50$) with the phase set of the highest combined figure of merit (2.77), revealed the locations of all the nonhydrogen atoms. The structure was refined by a full-matrix least-squares method with isotropic temperature factors and then by a block-diagonal least-squares method with anisotropic ones for all the nonhydrogen atoms. All hydrogen atoms could be located from a difference Fourier map and these were included in a further refinement with isotropic temperature factors. The final R value was 0.047 including Fo=0 reflections. The final positional parameters with the estimated standard

Table II. Atomic Coordinates ($\times 10^4$), Isotropic Temperature Factors ($\times 10^1$) and Their Standard Deviations of Nonhydrogen Atoms



Atom	x	y	z	B_{eq} (Å^3)[a]
O (1)	12426(3)	2007[b]	4491(4)	39(2)
C (2)	13748(5)	1764(5)	4389(6)	45(3)
C (3)	14567(6)	708(5)	5168(6)	54(3)
C (4)	14103(5)	5(5)	5981(6)	41(3)
C (5)	12134(5)	−383(4)	6862(5)	32(2)
C (6)	10805(5)	−74(4)	6883(4)	29(2)
C (7)	10029(5)	950(4)	6087(5)	32(2)
O (7)	8737(3)	1205(3)	6200(4)	38(2)
C (8)	10556(5)	1636(4)	5273(5)	35(3)
C (9)	12714(5)	301(4)	6059(5)	31(2)
C (10)	11919(5)	1293(4)	5289(5)	34(3)
C (11)	10187(5)	−771(4)	7783(5)	32(2)
O (11)	10894(4)	−1913(3)	8114(4)	39(2)
C (12)	10501(4)	−88(4)	9238(4)	27(2)
O (12)	12122(3)	−110(3)	10198(3)	31(2)
C (13)	9704(5)	−594(5)	10136(5)	31(2)
C (14)	10317(6)	−19(5)	11695(5)	44(3)
C (15)	7997(5)	−396(5)	9233(6)	42(3)
C (16)	8025(6)	2330(5)	5621(7)	49(4)
C (1′)	12924(5)	860(4)	10218(5)	30(2)
O (1′)	12363(3)	1789(3)	9615(4)	36(2)
C (2′)	14599(5)	650(5)	11061(5)	36(3)
C (3′)	15136(5)	−363(6)	11785(6)	47(3)
C (4′)	16759(6)	−693(7)	12688(7)	53(4)
C (5′)	15518(6)	1702(6)	11012(8)	57(4)

[a] The equivalent isotropic temperature factors for nonhydrogen atoms have been calculated as $B_{eq}=4/3\ (a^2B_{11}+2ab\cos\gamma B_{12}+\cdots)$.
[b] O(1) was fixed at an arbitrary position along the y axis to define the origin.

deviations of nonhydrogen atoms are listed in Table II. The atomic scattering factors for all atoms were taken from "International Tables for X-ray Crystallography"[7] All numerical calculations were carried out on an ACOS-700 computer at the Computation Center of Osaka University using programs of "The Universal Crystallographic Computing System."[8]

From the results of this X-ray diffraction analysis, it became clear that angelol B (**2**) has the stereostructure shown in Fig. 1. In this structure, the hydroxy group is linked by a hydrogen bond to the acyloxyl group. The positional relation of these two groups accounts well for the fact that **2** was liable to acyl migration. Furthermore, this structure linked by the hydrogen bond locates the acyl group at C-12 in a position above the benzene ring. This explains the result that in the ^{1}H-NMR spectrum of **2**, the signals arising from the acyl group were shifted to high field.

Since the absolute configuration at the C-12 position of **2** was decided to be *S* as described earlier, from this X-ray diffraction analysis the absolute configuration at the C-11 position was concluded to be *R*. This result justified our presumption that the reduction from **36** to **37** in the process of synthesis of the derivatives of **2** proceeded in the conformation shown in Chart 3.

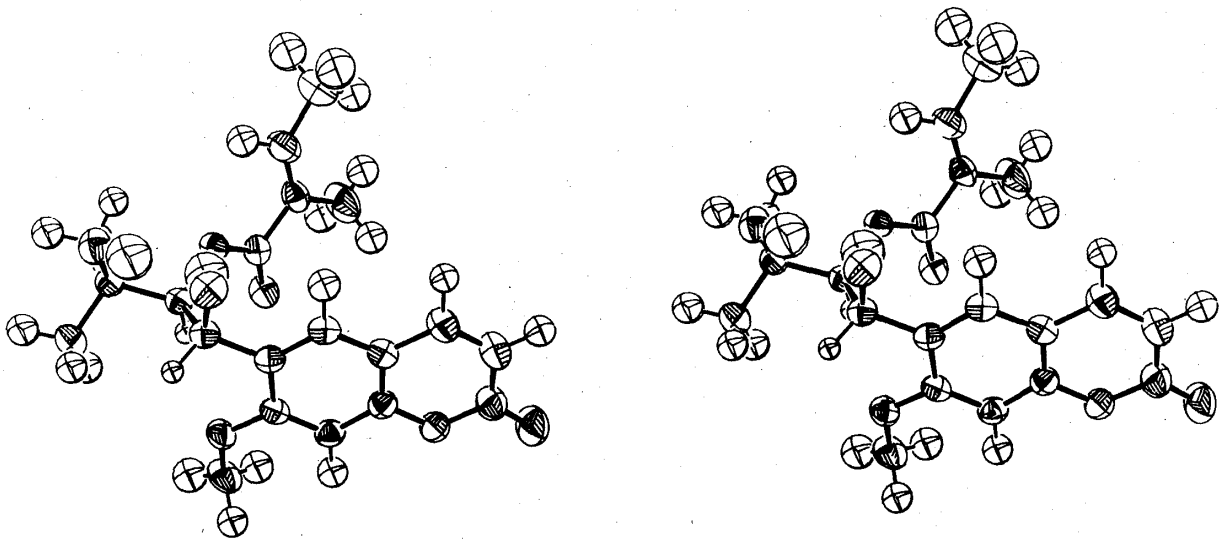


Fig. 1. A Stereoscopic View of the Molecular of **2**

All atoms are represented by thermal elipsoids defined by the principal axes of thermal vibration and scaled to include 50% probability.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi EPI-G2 spectrometer, and the ORD spectra with a JASCO ORD/UV-5 spectrometer. The ^{1}H-NMR spectra were taken with a Hitachi R-40 (90 MHz) spectrometer with tetramethylsilane as an internal standard. For medium pressure column chromatography on silica gel and for column chromatography on silica gel, we used Merck silica gel 60 (230—400 mesh) and silica gel 60 (70—230 mesh), respectively. For thin layer chromatography and preparative thin layer chromatography, we used Merck plate silica gel $60F_{254}$ (0.25 and 2 mm).

Catalytic Hydrogenation of 10——A solution of **10** (5.6 g) in AcOH (10 ml) was added to prereduced Adams catalyst (PtO_2 1 g) in AcOH (50 ml), and the mixture was stirred in the presence of hydrogen for 5 h at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane–EtOAc to give the 3,4-dihydro product (3.9 g), colorless needles, mp 154—155°C. IR ν_{max}^{Nujol} cm^{-1}: 3480 (OH), 1665 (CO), 1620, 1585 (arom.). ORD (c=0.595, EtOH) $[\alpha]^{21}$ (nm): −33.6° (589), −47.1° (500), −67.2° (450), −100.8° (400), −181.5° (350), −571.4° (300). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.30 (1H, s), 6.63 (1H, s), 5.06 (1H, dd, J=6.0 and 6.0 Hz, +D_2O d, J=6.0 Hz), 4.30 (1H, d, J=6.0 Hz), 3.84 (3H, s), 2.95 (1H, d, J=6.0 Hz), 2.99 (2H, m), 2.77 (2H, m), 1.51, 1.39, 1.22, 1.01 (each 3H, s). *Anal.* Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.36.

Formation of 24 and 25——A solution of the above 3,4-dihydro product (2 g) in dry pyridine (4 ml) was added dropwise to a CrO_3-pyridine complex which was prepared from dry pyridine (16 ml) and CrO_3 (2 g) under ice cooling. After being stirred for a while, the mixture was allowed to stand at room temperature overnight, then diluted with ice water (500 ml), acidified with 20% H_2SO_4 and extracted with EtOAc. The extract was separated into neutral and acidic portions in the usual way. The neutral portion was purified by chromatography on silica gel, using hexane–EtOAc (1: 1) as a solvent, and recrystallized from hexane–EtOAc to give **24** (55 mg), colorless needles, mp 135—136°C. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1680 (CO), 1610, 1575 (arom.). The ORD data are summarized in Table I. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.52 (1H, s), 6.68 (1H, s), 5.35 (1H, s), 3.89 (3H, s), 2.98 (2H, m), 2.80 (2H, m), 1.55, 1.45, 1.37, 1.08 (each 3H, s). *Anal.* Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.46; H, 6.34. The acidic portion was recrystallized from hexane–EtOAc to afford colorless needles (700 mg), mp 118—119°C. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1740, 1700, 1670 (CO), 1610, 1580 (arom.). ORD (c=0.150, dioxane) $[\alpha]^{21}$ (nm): +26.7° (370), +200.0° (360), +306.9° (354) (peak), +226.7° (348) (trough), +333.3° (340) (peak), +120.0° (335). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.98 (2H, br s), 7.50 (1H, s), 6.52 (1H, s), 5.49 (1H, s), 3.83 (3H, s), 2.83 (2H, m), 2.70 (2H, m), 1.56, 1.45, 1.33, 1.04 (each 3H, s). *Anal.* Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.25; H, 6.75. This product (500 mg) was dissolved in MeOH (10 ml), and methylated with CH_2N_2–Et_2O in the usual way. The product was purified by chromatography on silica gel with hexane–EtOAc (2: 1) as a solvent, and recrystallized from hexane to give **25** (450 mg), colorless needles, mp 100—101°C. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1675 (CO), 1600, 1570, 1500 (arom.). The ORD data are summarized in Table I. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.50 (1H, s), 6.45 (1H, s), 5.44 (1H, s), 3.92 (6H, s), 3.67 (3H, s), 2.90 (2H, m), 2.58 (2H, m), 1.58, 1.45, 1.34, 1.07 (each 3H, s). *Anal.* Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 62.98; H, 7.28.

Methylation of 10 with CH_3I and Ag_2O——**10** (4.1 g) was dissolved in CH_3I (10 g) under ice cooling, and Ag_2O (10 g) was added with stirring under ice cooling. The mixture was refluxed on a boiling bath for 1 h. After addition of Et_2O (60 ml), the mixture was stirred for 10 min, and Ag_2O was removed by filtration. The filtrate was concentrated to dryness. The residue was purified by chromatography on silica gel with hexane–EtOAc (3: 1) to give **10**-monomethyl ether (2.5 g), colorless crystalline powder. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.69 (1H, d, J=9.5 Hz), 7.54 (1H, s), 6.86 (1H, s), 6.28 (1H, d, J=9.5 Hz), 4.76 (1H, d, J=7.5 Hz), 4.08 (1H, d, J=7.5 Hz), 3.95, 3.23 (each 3H, s), 1.53, 1.41, 1.17, 0.87 (each 3H, s).

Methylation of 11 with CH_3I and Ag_2O——**11** (3.6 g) was methylated with CH_3I (8.5 g) and Ag_2O (8.5 g) in the same way as for **10**. The product was purified by chromatography on silica gel with hexane–EtOAc (3: 1) to give **11**-monomethyl ether (2.2 g), colorless viscid oil. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.69 (1H, d, J=9.5 Hz), 7.52 (1H, s), 6.82 (1H, s), 6.24 (1H, d, J=9.5 Hz), 4.77 (1H, d, J=9.0 Hz), 3.91 (1H, d, J=9.0 Hz), 3.92, 3.17 (each 3H, s), 1.44 (3H, s), 1.35 (6H, s), 1.23 (3H, s).

$LiAlH_4$ Reduction followed by Catalytic Hydrogenation of 10-Monomethyl Ether (Formation of 27)——A solution of **10**-monomethyl ether (2.5 g) in dry Et_2O (200 ml) was added dropwise to a suspension of $LiAlH_4$ (500 mg) in dry Et_2O (50 ml) with vigorous stirring in a stream of N_2 under ice cooling, then the whole was stirred at room temperature for 2 h. After decomposition of the excess $LiAlH_4$ by addition of Et_2O saturated with water, the mixture was acidified with 20% H_2SO_4 and extracted with Et_2O. The extract was washed with water, dried and concentrated to afford a crystalline product (1.15 g). This product (1 g) was hydrogenated over PtO_2 (300 mg) in EtOH (100 ml) in the usual way. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane–EtOAc to give **27** (860 mg), colorless needles, mp 201—202°C. ^{1}H-NMR ($CDCl_3$) δ ppm: 8.65 (1H, br s), 7.00 (1H, s), 6.45 (1H, s), 4.64 (1H, d, J=9.0 Hz), 4.12 (1H, d, J=9.0 Hz), 3.76, 3.15 (each 3H, s), 3.55 (2H, t, J=6.0 Hz), 2.69 (2H, t, J=7.5 Hz), 1.82 (2H, m), 1.48, 1.40, 1.05, 0.71 (each 3H, s). *Anal.* Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.38; H, 8.45.

Methylation of 27 with CH_3I and Ag_2O (Formation of 29)——**27** (500 mg) was methylated with CH_3I (1 g) and Ag_2O (1.5 g) in the same way as described above. The product was purified by chromatography on silica gel with hexane–EtOAc (2: 1) as a solvent and recrystallized from petroleum ether to give **29** (320 mg), colorless needles, mp 78—79°C. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1590, 1500 (arom.). The ORD data are summarized in Table I. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.07 (1H, s), 6.40 (1H, s), 4.65 (1H, d, J=9.0 Hz), 4.15 (1H, d, J=9.0 Hz), 3.83 (6H, s), 3.33, 3.25 (each 3H, s), 3.38 (2H, t, J=6.0 Hz), 2.64 (2H, t, J=7.5 Hz), 1.82 (2H, m), 1.51, 1.42, 1.08, 0.73 (each 3H, s). *Anal.* Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.15; H, 8.75.

$LiAlH_4$ Reduction followed by Catalytic Hydrogenation of 11-Monomethyl Ether (Formation of 28)——A solution of **11**-monomethyl ether (2 g) in dry Et_2O (200 ml) was added dropwise to a suspension of $LiAlH_4$ (500 mg) in dry Et_2O (50 ml) with vigorous stirring in a stream of N_2 under ice cooling, and the mixture was treated in the same way as for **10**-monomethyl ether. The product (1.8 g) was hydrogenated over PtO_2 (300 mg) in EtOH (100 ml) in the usual way. The product was recrystallized from hexane–EtOAc to give **28** (1.7 g), colorless needles, mp 128—129°C. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.30 (1H, br s), 7.05 (1H, s), 6.35 (1H, s), 4.65 (1H, d, J=9.0 Hz), 4.00 (1H, d, J=9.0 Hz), 3.71, 3.10 (each 3H, s), 3.60 (2H, t, J=6.0 Hz), 2.69 (2H, t, J=7.5 Hz), 1.83 (2H, m), 1.42, 1.36, 1.31, 1.28 (each 3H, s). *Anal.* Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.51; H, 8.35.

Methylation of 28 with CH_3I and Ag_2O (Formation of 30)——**28** (1.5 g) was methylated with CH_3I (1.5 g) and Ag_2O (2 g) in the same way as described above. The product was purified by chromatography on silica gel, using hexane–EtOAc (2: 1) as a solvent and recrystallized from petroleum ether to give **30** (450 mg), colorless needles, mp 58—60°C. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1580, 1500 (arom.). The ORD data are summarized in Table I. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.13 (1H, s), 6.46 (1H, s), 4.66 (1H, d, J=9.0 Hz), 3.97 (1H, d, J=9.0 Hz), 3.84 (6H, s), 3.34, 3.10 (each 3H, s), 3.39 (2H, t, J=6.0 Hz), 2.67 (2H, t, J=7.5 Hz), 1.87 (2H, m), 1.43, 1.35, 1.32, 1.26 (each 3H, s). *Anal.* Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.05; H, 8.99.

$LiAlH_4$ Reduction of 9 (Formation of 31)——A solution of **9** (1 g) in dry Et_2O (30 ml) was added dropwise to a suspension of $LiAlH_4$ (400 mg) in dry Et_2O (30 ml) with vigorous stirring in a stream of N_2 under ice cooling, and the mixture was treated in the same way as described above. The product was purified by chromatography on silica gel with hexane–EtOAc (1: 2) to afford **31** (270 mg), colorless crystalline powder, mp 195—197°C. IR ν_{max}^{Nujol} cm^{-1}: 3505, 3320, 3150 (OH), 1610, 1510 (arom.). ORD (c=0.585, EtOH) $[\alpha]^{21}$ (nm): −34.2° (589), −41.0° (500), −102.6° (400), −188.0° (350), −273.5° (330). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.10 (1H, s), 6.45 (1H, s), 6.51 (1H, dd, J=16 and 1.5 Hz), 5.72 (1H, dd, J=16 and 7.0 Hz), 4.28 (2H, dd, J=7.0 and 1.5 Hz), 4.96 (1H, d, J=9.0 Hz), 4.15 (1H, d, J=9.0 Hz), 3.80 (3H, s), 1.45, 1.38, 1.10, 0.82 (each 3H, s). *Anal.* Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 63.66; H, 7.83.

Formation of 29 from 31——**31** (200 mg) was dissolved in MeOH (5 ml), and methylated with CH_2N_2–Et_2O in the usual way. The product was purified by chromatography on silica gel with hexane–EtOAc (1: 1) as a solvent and recrystallized from hexane–EtOAc to give colorless needles (250 mg), mp 119—120°C. ORD (c=0.278, MeOH) $[\alpha]^{20}$ (nm): −35.9° (589), −107.9° (400), −194.2° (350), −345.3° (320). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.16 (1H, s), 6.43 (1H, s), 6.59 (1H, dd, J=16 and 1.5 Hz), 5.85 (1H, dd, J=16 and 7.0 Hz), 5.00 (1H, d, J=9.0 Hz), 4.08 (1H, d, J=9.0 Hz), 4.28 (2H, dd, J=7.0 and 1.5 Hz), 3.87, 3.85 (each 3H, s), 2.80 (1H, br s), 1.80 (1H, br s), 1.50, 1.39, 1.18, 0.92 (each 3H, s). *Anal.* Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01.

Found: C, 64.63; H, 8.00. This product (230 mg) was hydrogenated over PtO_2 (50 mg) in AcOH (40 ml) in the usual way. The product was purified by chromatography on silica gel with hexane–EtOAc (2: 1) as a solvent to afford a colorless viscid oil (190 mg). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.14 (1H, s), 6.42 (1H, s), 4.99 (1H, d, J=9.0 Hz), 4.12 (1H, d, J=9.0 Hz), 3.85 (6H, s), 3.58 (2H, t, J=6.0 Hz), 2.90 (1H, br s), 2.30 (1H, br s), 2.66 (2H, t, J=7.5 Hz), 1.80 (2H, m), 1.50, 1.40, 1.15, 0.86 (each 3H, s). *Anal.* Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.38; H, 8.45. This product (160 mg) was methylated with CH_3I (300 mg) and Ag_2O (200 mg) in the same way as described above. The product was purified by chromatography on silica gel with hexane–EtOAc (2: 1) as a solvent and recrystallized from hexane to give colorless needles (98 mg), mp 78—79°C. The IR, ORD and ^{1}H-NMR spectra were identical with those of **29**. The melting point showed no depression an admixture with **29**.

(±)-α,β-Dihydroxyisovaleric Acid——NaOEt (3.5 g) was added in small portions to a solution of $CH_2ClCOOC_2H_5$ (130 ml) in acetone (65 ml) with stirring in a stream of N_2 at −10°C, and the mixture was further stirred at room temperature for 4 h. The mixure was poured into ice water (300 ml) and extracted with Et_2O. The extract was washed with water, dried and concentrated. The residue gave colorless oil (55 g), bp_{20} 75—85°C, on fractional distillation under reduced pressure. A solution of this product (50 g) in AcOH (140 ml), H_2O (140 ml) and HCl (20 ml) was heated on a boiling water bath for 1.5 h. After removal of the ethyl ether–soluble part, the mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, then the extract was concentrated *in vacuo*, and purified by chromatography on silica gel with $CHCl_3$–MeOH (5: 1) as a solvent to afford a colorless viscid oil (21 g).

D(−)-α,β-Dihydroxyisovaleric Acid——A mixture of (±)-α,β-dihydroxyisovaleric acid (20 g) and quinine (50 g) in EtOH (350 ml) was heated on a boiling water bath until the quinine was completely dissolved, then the solution was allowed to stand in a refrigerator overnight. The precipitate was collected by filtration and recrystallized from EtOH to give colorless needles (21 g), mp 213—215°C (dec.), which were subjected to column chromatography on Amberlite IR-120B (H^+ form) with 15% MeOH as a solvent to affords a colorless viscid oil (10 g). ORD (c=1.087, MeOH) $[\alpha]^{22}$ (nm): −9.2° (589), −16.6° (500), −31.3° (400), −47.9° (350), −97.5° (300), −165.6° (270).

Formation of 35——P_2O_5 (1 g) was added to a solution of D-(−)-α,β-dihydroxyisovaleric acid (8 g) in dry acetone (500 ml) and the mixture was stirred at room temperature for 24 h. The solution was concentrated to half the initial volume *in vacuo*, then Na_2CO_3 was added. The mixture was stirred for a while, then filtered. The filtrate was dissolved in Et_2O (1000 ml), and the solution was washed with water, dried and concentrated to dryness. The residue was purified by chromatography on silica gel with $CHCl_3$–MeOH (10: 1) as a solvent and recrystallized from petroleum ether to give D-(−)-2,2,5,5-tetramethyl-1,3-dioxolane-4-carboxylic acid (4.2 g), colorless prisms, mp 72—73°C. IR ν_{max}^{Nujol} cm^{-1}: 3500—2500 (OH), 1720 (CO). ORD (c=0.467, MeOH) $[\alpha]^{20}$ (nm): 0° (500), +8.6° (400), +12.8° (330), +10.7° (300), 0° (270), −38.5° (250), −162.7° (235) (trough), −120.0° (230). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.20 (1H, br s), 4.38 (1H, s), 1.53, 1.50, 1.39, 1.25 (each 3H, s). *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.11; H, 7.95. This product (4 g) was methylated with CH_2N_2–Et_2O in the usual way to afford **35** (3.9 g), colorless viscid oil. ORD (c=1.336, MeOH) $[\alpha]^{20}$ (nm): +7.5° (589), +22.5° (500), 0° (330), −52.4° (270), −224.6° (250), −636.2° (230) (trough), −329.0° (220). ^{1}H-NMR ($CDCl_3$) δ ppm: 4.37 (1H, s), 3.80 (3H, s), 1.53, 1.48, 1.39, 1.17 (each 3H, s).

Formation of 33 from Herniarin (32)——A solution of **32** (9.6 g) in dry Et_2O (300 ml) was added dropwise to a suspension of $LiAlH_4$ (4 g) in dry Et_2O (50 ml) with vigorous stirring in a stream of N_2 under ice cooling. After refluxing for 1 h, the mixture was allowed to stand at room temperature overnight and treated in the same way as described above. The product was extracted with EtOAc, then the extract was washed with water, dried and concentrated *in vacuo*. The residue (6 g) was methylated with CH_2N_2–Et_2O in the usual way. The product was purified by chromatography on silica gel with $CHCl_3$ as a solvent and recrystallized from hexane–EtOAc to give colorless needles (4.5 g), mp 85—87 °C. This product (4 g) was hydrogenated over PtO_2 (500 mg) in EtOH to afford a colorless viscid oil (4.5 g). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.05 (1H, d, J=8.5 Hz), 6.48 (1H, d, J=1.5 Hz), 6.45 (1H, dd, J=8.5 and 1.5 Hz), 3.81 (6H, s), 3.61 (2H, t, J=6.0 Hz), 2.67 (2H, t, J=7.5 Hz), 1.87 (1H, br s), 1.83 (2H, m). This product (4.3 g) was methylated with CH_3I (8 g) and Ag_2O (8 g) in the same way as described above. The product was purified by chromatography on silica gel with hexane–EtOAc (4: 1) as a solvent to give **33** (2.5 g), colorless viscid oil. ^{1}H-NMR ($CDCl_3$) δ ppm: 6.99 (1H, d, J=8.5 Hz), 6.40 (1H, d, J=1.5 Hz), 6.38 (1H, dd, J=8.5 and 1.5 Hz), 3.75 (6H, s), 3.38 (2H, t, J=6.0 Hz), 3.32 (3H, s), 2.62 (2H, t, J=7.5 Hz), 1.81 (1H, m).

Formation of 34 from 33——A solution of Br_2 (2 g) in $CHCl_3$ (20 ml) was added dropwise to a solution of **33** (2.5 g) in $CHCl_3$ (50 ml) with stirring. After being stirred for a while, the mixture was evaporated to dryness. The residue was extracted with Et_2O, the extract was washed with water, dried and concentrated to dryness. The residue was purified by chromatography on silica gel with hexane–EtOAc (4: 1) as a solvent and recrystallized from hexane to give **34** (3 g), colorless crystalline powder, mp 44—45°C. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.27 (1H, s), 6.47 (1H, s), 3.89, 3.83, 3.35 (each 3H, s), 3.39 (2H, t, J=6.0 Hz), 2.61 (2H, t, J=7.5 Hz), 1.82 (2H, m). *Anal.* Calcd for $C_{12}H_{17}O_3Br$: C, 49.83; H, 5.88. Found: C, 49.72; H, 5.74.

Condensation of 34 and 35 (Formation of 36)——A solution of **34** (3 g) in dry Et_2O (30 ml) was added dropwise to *n*-butyllithium (abt. 15% in hexane) (15 ml) with stirring in a stream of N_2 under ice cooling. The mixture was added dropwise to a solution of **35** (3 g) in dry Et_2O (50 ml) with vigorous stirring in a stream

of N_2 under ice cooling. After being stirred at room temperature for 1 h, the whole was refluxed for 30 min, poured into ice water (300 ml), acidified with 20% H_2SO_4 and extracted with Et_2O. The extract was washed with water, dried and concentrated to dryness. The residue was purified by chromatography on silica gel with hexane–EtOAc (4: 1) as a solvent to give **36** (530 mg), colorless viscid oil, which gave a positive 2,4-dinitrophenylhydrazine reaction. ORD (c=0.25, dioxane) $[\alpha]^{13}$ (nm): −7.9° (589), −32.0° (500), −36.0° (470), −32.0° (450), 0° (405), +60.0° (370), +208.0° (355) (peak), +168.0° (350), +186.0° (345). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.46 (1H, s), 6.39 (1H, s), 5.41 (1H, s), 3.89 (6H, s), 3.32 (3H, s), 3.37 (2H, t, J=6.0 Hz), 2.61 (2H, t, J=7.5 Hz), 1.81 (2H, m), 1.57, 1.45, 1.33, 1.06 (each 3H, s). *Anal.* Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.37; H, 8.06.

$LiAlH_4$ Reduction of 36 (Formation of 37)——A solution of **36** (400 mg) in dry Et_2O (50 ml) was added dropwise to a suspension of $LiAlH_4$ (400 mg) in dry Et_2O (50 ml) with vigorous stirring in a stream of N_2 under ice cooling. The mixture was treated as described above, and the product was purified by chromatography on silica gel with hexane–EtOAc (3: 1) as a solvent to give **37** (310 mg), colorless viscid oil. ORD (c=0.508, EtOH) $[\alpha]^{22}$ (nm): +13.8° (589), +17.7° (550), +19.7° (500), +13.8° (450), +7.8° (400), +11.8° (350), +13.8° (330). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.10 (1H, s), 6.41 (1H, s), 4.82 (1H, dd, J=9.0 and 7.0 Hz, +D_2O d, J=9.0 Hz), 4.05 (1H, d, J=9.0 Hz), 3.83, 3.79, 3.30 (each 3H, s), 3.37 (2H, t, J=6.0 Hz), 3.02 (1H, d, J=7.0 Hz), 2.62 (2H, t, J=7.5 Hz), 1.82 (2H, m), 1.38 (3H, s), 1.36 (6H, s), 1.29 (3H, s). *Anal.* Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.34; H, 8.65.

Formation of 30 from 37——**37** (250 mg) was methylated with CH_3I (1 g) and Ag_2O (1 g) in the same way as described above. The product was purified by chromatography on silica gel with hexane–EtOAc (2: 1) as a solvent and recrystallized from petroleum ether to give colorless prisms (230 mg), mp 58—60°C, which were identical with **30**.

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