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A SIMPLE BIOGENETIC-TYPE SYNTHESIS OF MAGNOSALICIN, A NEW NEOLIGNAN WITH ANTIALLERGY ACTIVITY ISOLATED FROM MAGNOLIA SALICIFOLIA†

KENJI MORI,*[a] MAKOTO KOMATSU,††[a] MASARU KIDO[b] and KAZUYUKI NAKAGAWA[b]

[a]Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

[b]Laboratory of Natural Products Chemistry, Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kawauchi, Tokushima 771-01, Japan

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Abstract -- Magnosalicin [(±)-(2R*,3S*,4R*,5R*)-2,4-dimethyl-3,5-bis(2',4',5'-trimethoxyphenyl)tetrahydrofuran] was synthesized in a single step in 15.6 % yield from α-asarone by peracetic acid oxidation. The stereochemistry of (±)-2,4-dimethyl-3,5-bis(4'-methoxyphenyl)tetrahydrofuran, a product of peracetic acid oxidation of anethole, was shown to be same as that of magnosalicin (2R*,3S*,4R*,5R*) by X-ray crystallographic analysis.

As a part of their studies on Chinese medicinal drug, Sankawa and his co-workers isolated a new racemic neolignan named magnosalicin **1a** from Magnolia salicifolia Maxim. as an antiallergy compound.[1] Buds of M. salicifolia (Japanese name: tamushiba, kamushiba or satoshiba) are known as an oriental medicinal drug (Japanese name: shin-i), which has been used for nasal allergy and nasal empyema. Magnosalicin showed a significant inhibitory effect to histamine release from rat peritoneal mast cells. Its structure as (±)-**1a** was established by X-ray crystallographic method.[1] The novelty of its structure coupled with its biological activity made us to undertake a synthetic work on magnosalicin.

As a phenylpropane dimer, a biogenetic precursor of magnosalicin **1a** might be α-asarone **2** as suggested by Sankawa.[1] We therefore attempted the oxidation of α-asarone **2** with peracetic acid, and obtained magnosalicin **1a** in a single step as shown in Fig. 1. In 1979, Schmauder et al. isolated 2,4-dimethyl-3,5-bis(4'-methoxyphenyl)tetrahydrofuran as a racemic by-product of an industrial oxidation of anethole **3** with peracetic acid, and proposed its stereochemistry as the all-trans form **A** on the basis of its ^{1}H NMR analysis.[3] The yield of the neolignan-type compound was 5~10 % from anethole **3**. Although the yield was poor and the stereochemistry **A** assigned to the product was different from that of magnosalicin **1a**, we decided to attempt an analogous oxidation of α-asarone **2**, hoping the isolation of **1a** as one of the oxidation products. α-Asarone **2**[2] in AcOH was oxidized with 0.5 eq of 40 % AcOOH at room temp. The product was purified by SiO_2 chromatography and recrystallized to give slightly reddish crystals, m.p. 133~135°, in 15.6 % yield. This was identified as magnosalicin itself by comparing its IR and 400 MHz ^{1}H NMR spectra with those of authentic **1a**. The identity was further confirmed by a mixed m.p. determination with an authentic sample of **1a**, which showed no m.p. depression. With this gratifying result, our synthesis of magnosalicin **1a** was completed in a single step from α-asarone.

†Synthesis of Lignans -- II. Part I, Y. Takei, K. Mori and M. Matsui, Agric. Biol. Chem. 37, 637 (1973). The chemical experimental part of this work was taken from a part of the forthcoming doctoral dissertation of M. Komatsu. The X-ray crystallographic work was done by M. Kido and K. Nakagawa.

††Research Fellow on leave from Otsuka Pharmaceutical Co., Ltd. (1985-1987).

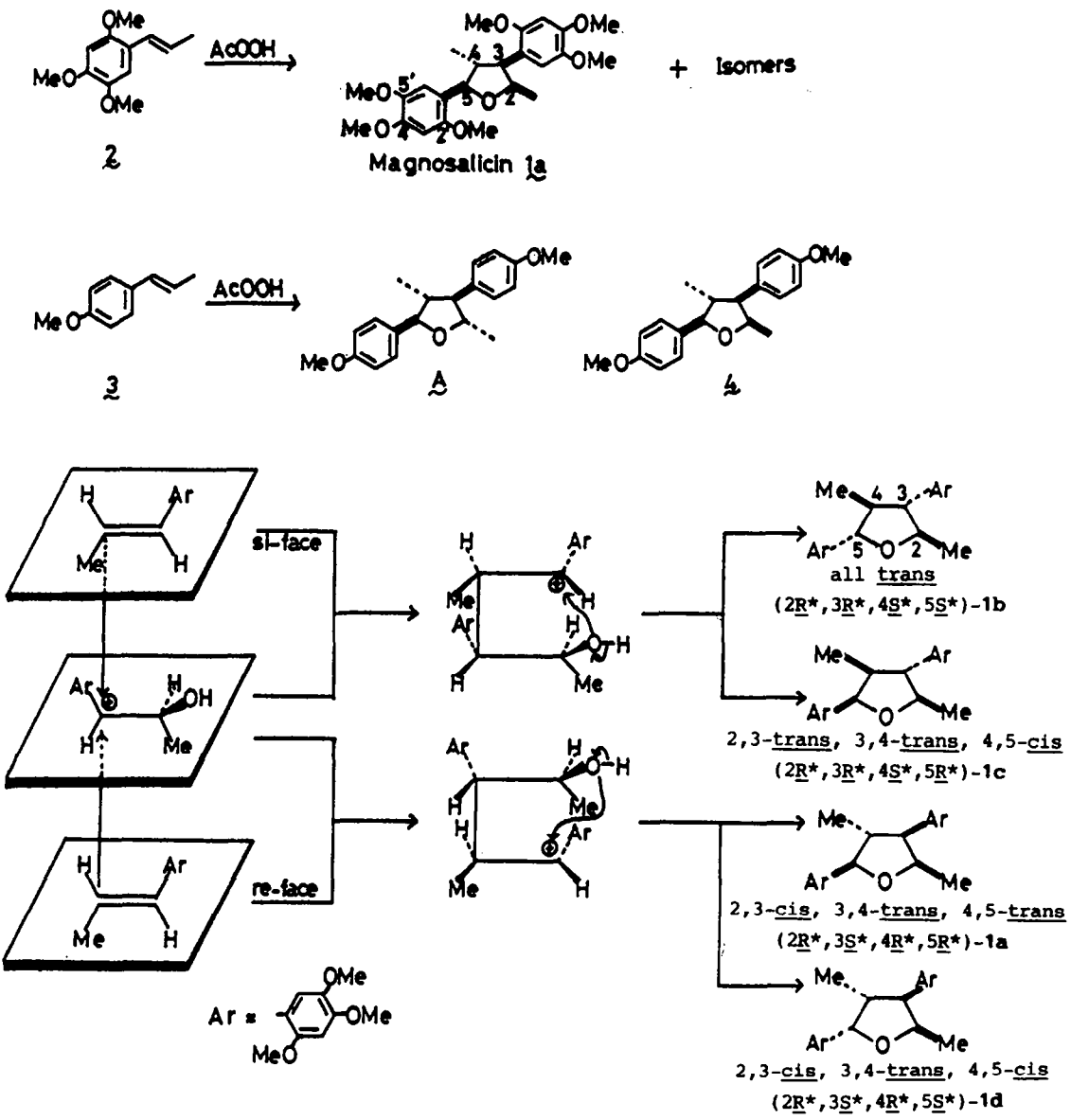


Fig. 1. Synthesis of magnosalicin and related compounds.

In spite of the moderate yield, isolation of **1a** from the reaction mixture was not so difficult because **1a** was the only crystalline product generated by this oxidation reaction.

The present oxidative coupling of α-asarone **2** should yield four diastereomers **1a**~**1d** (each as a racemate) as shown in Fig. 1. It was hardly believable to assume the desired **1a** to be the sole product. We therefore turned our attention to scrutinize other stereoisomers **1b**~**1d** in the reaction mixture, and attempted the separation of an oily residue left after isolation of the crystalline magnosalicin **1a**. Neither TLC nor medium pressure LC gave useful results. However, HPLC separation of the residual oil was successful in furnishing the expected three diastereomers, all of which showed very similar MS with M^+ at m/z=432 (=$C_{24}H_{32}O_7$) and a base peak at m/z=388. The ratio of the products in a crude mixture of products before the removal of crystalline **1a** was, in the increasing order of the HPLC retention time, magnosalicin **1a**:I:II:III=13:13:23:10. In addition, a trace

amount of another isomer I' was found to be present in I. The HPLC retention time of I' was only very slightly longer than that of I, and the separation of I from I' was impossible. The isomer I' was presumably generated from β-asarone [(Z)-isomer of 2], which was present as an impurity in our sample of α-asarone 2.

The ^{1}H NMR data of the diastereomers I~III as listed in Table 1 gave the clue to deduce their stereochemistries. Of course, the unambiguously established 2,3-cis, 3,4-trans, 4,5-trans configuration of magnosalicin 1a enabled us to use its NMR data as our standard for stereochemical argument. Difference between the chemical shift of the corresponding proton(s) of the diastereomers I~III and that of magnosalicin 1a afforded information on the stereochemistries of I~III. In the case of the isomer I, both an up-field shift ($\Delta\delta$= -0.36) of the signal due to C-4 CH_3 and a down-field shift ($\Delta\delta$= +0.62) of the signal due to C-4 H could be explained by its 3,4-trans configuration, considering the long-range shielding effect of the aromatic ring at C-5. Other parts of the spectrum of I is similar to that of 1a. Therefore the structure 1d (2,3-cis, 3,4-trans, 4,5-cis) was assigned to the isomer I. In the case of the isomer II, the signal due to C-2 CH_3 suffered a down-field shift ($\Delta\delta$= +0.32), while an up-field shift was observed for the signal due to C-4 CH_3. Consideration of the shielding effects of the aromatic rings enabled us to assign 1c (2,3-trans, 3,4-trans, 4,5-cis) to the isomer II. To the remai-

Table 1. ^{1}H NMR spectral data of magnosalicin 1a, its stereoisomers 1b~1d, and (2R*,3S*,4R*,5R*)-2,4-dimethyl-3,5-bis(4'-methoxylphenyl)tetrahydrofuran 4.

Protons	Chemical shifts δ and J values (Hz) of				
	1a[a]	I[b] (=1d)	II[b] (=1c)	III[b] (=1b)	4[a]
C-2 CH_3	0.90 (d, 6.5)	0.90 (d, 6.8)	1.22 (d, 6.5)	1.27 (d, 6.0)	0.94 (d, 6.5)
C-4 CH_3	1.04 (d, 6.5)	0.68 (d, 6.8)	0.68 (d, 6.8)	0.90 (d, 6.5)	0.98 (d, 6.5)
C-2 H[c]	4.60 (dq, 8.5, 6.5)	4.80 (dq, 7.5, 6.8)	4.77 (dq, 4.5, 6.5)	4.35 (dq, 9.5, 6.0)	4.43 (dq, 8.5, 6.5)
C-3 H	3.60 (dd, 8.5, 10.5)	non-observable due to an OCH_3 signal	non-observable due to an OCH_3 signal	3.13 (dd, 9.5, 10.5)	3.19 (dd, 8.5, 10.5)
C-4 H[d]	2.31 (ddq, 10.5, 9.0, 6.5)	2.93 (ddq, 8.5, 8.5, 6.8)	2.70 (ddq, 10.0, 7.2, 6.8)	2.45 (ddq, 10.5, 9.5, 6.5)	2.30 (ddq, 10.5, 9.5, 6.5)
C-5 H	4.97 (d, 9.0)	5.65 (d, 8.5)	5.05 (d, 10.0)	5.02 (d, 9.5)	4.42 (d, 9.5)
Ar-O-CH_3	3.79 (3H) 3.81 (3H) 3.82 (3H) 3.87 (3H) 3.90 (3H) 3.91 (3H)	3.75~3.91	3.77 (3H) 3.81 (3H) 3.91 (9H) 3.93 (3H)	3.82 (3H) 3.84 (3H) 3.86 (3H) 3.91 (9H)	3.80 (3H) 3.82 (3H)
Ar-H	6.535 (1H) 6.540 (1H) 6.69 (1H) 7.14 (1H)	2H non-observable due to the signals of I' 6.86 (1H) 7.06 (1H)	6.51 (1H) 6.58 (1H) 6.99 (1H) 7.05 (1H)	6.53 (1H) 6.56 (1H) 6.76 (1H) 7.08 (1H)	6.87 (2H, d, 7) 6.91 (2H, d, 7) 7.10 (2H, d, 7) 7.36 (2H, d, 7)

a) Measured as a $CDCl_3$ soln at 400 MHz.

b) Measured as a $CDCl_3$ soln at 100 MHz.

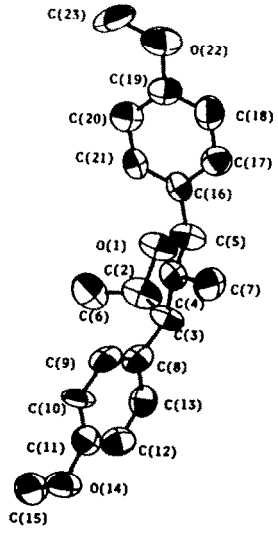
c) Assignments were made by decoupling experiments irradiating a signal due to C-2 CH_3.

d) Assignments were made by decoupling experiments irradiating a signal due to C-4 CH_3.

ning isomer III, the structure **1b** (all trans) was assigned, taking into account of a down-field shift ($\Delta\delta$= +0.37) of the C-2 CH_3 signal and an up-field shift ($\Delta\delta$= -0.47) of the C-3 H signal. These stereochemical conclusion must be taken as tentative, because our deduction was based entirely on the analysis of the shielding effects caused by the aromatic rings. The all-trans isomer **1b** was not the major product, although it seemed to be the most stable one. Since the stereochemical conclusion was tentative, we dared not discuss the steric course of the reaction basing on the mechanism proposed in Fig. 1.

Finally it occurred to us that the stereochemical assignment **A** of Schmauder et al.[3] might be wrong. They assigned the structure **A** to their oxidation product considering its ^{1}H NMR data only. We therefore repeated their oxidative coupling of anethole **3**, and obtained a crystalline product, m.p. 96~97° (lit.[3] m.p. 96~97°), in 3.8 % yield. Its IR and mass spectra were in accord with the published data,[3] and its gross structure as 2,4-dimethyl-3,5-bis(4'-methoxyphenyl)tetrahydrofuran was supported by its ^{13}C NMR spectrum and elemental analysis. Its 400 MHz ^{1}H NMR data are listed in table 1. There was remarkable similarity between this product and magnosalicin **1a** concerning the splitting patterns of the protons attached to the tetrahydrofuran ring. This strongly suggested that the oxidation product was not **A** but **4** with (2R*,3S*,4R*,5R*)-stereochemistry. This suggestion was unambiguously proved to be true by a single-crystal X-ray analysis of the oxidation product as described below.

The compound **4**, $C_{20}H_{24}O_3$, formed monoclinic crystals from i-PrOH, space group $P2_1/c$, with Z=4 in unit cells of dimensions a=10.313(5)Å, b=16.519(9)Å, c=10.447(4)Å, β=98.20(4)°, Dx=1.18 g/cm^3 and μ(Mo Kα)=0.8 cm.$^{-1}$ The cell dimensions and intensities were measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo Kα radiation with ω-scan mode within 2θ less than 40°. A total of 1639 independent reflections were collected, among which 1172 reflections [I≥1.96σ(I)] were stored as observed. The structure was solved by the direct method using MULTAN in Syntex XTL program.[4] All H atoms except 5 atoms were found on difference Fourier maps. The refinement of atomic parameters was carried out by a block-diagonal least-squares method. Thermal parameters were refined anisotropically for all non-H atoms and isotropically for the H atoms. The



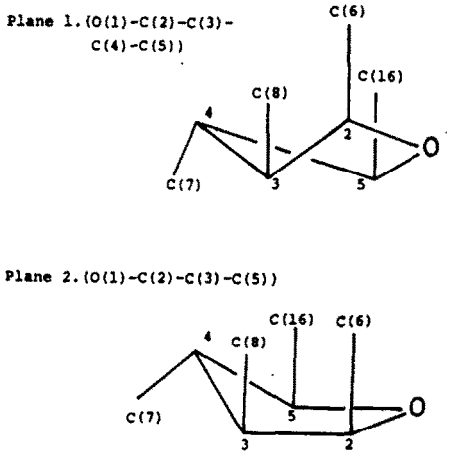


Fig. 2. a. (left) The molecular structure of (2R*,3S*,4R*,5R*)-**4** and
b. (right) the stereochemistry of the tetrahydrofuran ring moiety of **4**.

Table 2. Deviations (Å) of atoms from the least-squares planes

Plane 1. (O(1)-C(2)-C(3)-C(4)-C(5))

O(1)	0.04 Å		
C(2)	0.12	C(6)	1.48 Å
C(3)	-0.25	C(8)	0.40
C(4)	0.28	C(7)	-0.24
C(5)	-0.20	C(16)	0.59

Plane 2. (O(1)-C(2)-C(3)-C(5)) (Excluding C(4) atom from plane 1)

O(1)	0.03 Å		
C(2)	0.03	C(6)	1.24 Å
C(3)	-0.02	C(8)	0.68
C(4)	0.67	C(7)	0.47
C(5)	0.02	C(16)	0.83

final R-value was 0.089. The ORTEP computer drawing of **4** is shown in Fig. 2a. Deviations of atoms from the least-squares planes 1 and 2 of the tetrahydrofuran ring of **4** are listed in Table 2 (see also Fig. 2b). Evidently, the stereostructure **4** was the correct one and **A** was excluded. It became clear that the crystalline product **4** obtained by oxidative coupling of anethole possesses the same (2R*,3S*,4R*,5R*)-stereochemistry as that of magnosalicin **1a**.

In summary, we synthesized magnosalicin **1a** by a biomimetic single-step synthesis from α-asarone.

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra were measured on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Jeol JMN FX-100 spectrometer or at 400 MHz on a Jeol JMN FX-400 spectrometer. ^{13}C-NMR spectra were recorded at 25 MHz on a Jeol JNM FX-100 spectrometer. Mass spectra were measured on a Jeol JMS DX-300 spectrometer at 70 eV. Fuji Davison BW-820 MH was used for SiO_2 column chromatography.

(2R*,3S*,4R*,5R*)-2,4-Dimethyl-3,5-bis(2',4',5'-trimethoxyphenyl)tetrahydrofuran (magnosalicin) **1a**. To a stirred and ice-cooled soln of **2** (0.8 g, 3.8 mmol) in AcOH (3 ml) was added dropwise a soln of 40 % AcOOH in AcOH (0.37 ml, 1.9 mmol; 0.5 eq). After the addition, the mixture was stirred for 40 min at room temp. It was then diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with sat $NaHCO_3$ soln(x2), water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with n-hexane-EtOAc-CH_2Cl_2 (4:1:2) gave crude **1a**, which was recrystallized twice from ether to give slightly reddish prisms of **1a** (0.13 g, 15.6 %), m.p. 133~135° (authentic **1a**, m.p. 133~134°; m.m.p. 132~134°. No m.p. depression was observed); νmax (nujol) 1615 (w), 1520 (s), 1470 (s), 1445 (m), 1405 (m), 1350 (w), 1335 (w), 1320 (m), 1290 (w), 1265 (w), 1255 (m), 1205 (vs), 1185 (m), 1155 (w), 1140 (w), 1120 (m), 1110 (w), 1070 (m), 1055 (s), 1045 (s), 1035 (s), 1015 (w), 1005 (w), 950 (w), 920 (w), 910 (w), 885 (w), 860 (w), 820 (w), 815 (m), 770 (w), 750 (w), 720 (w), 710 (w), 700 (w), 690 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.5 Hz), 2.31 (1H, ddq, J=10.5, 9.0 and 6.5 Hz), 3.60 (1H, dd, J=8.5 and 10.5 Hz), 3.79 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 4.60 (1H, dq, J=8.5 and 6.5 Hz), 4.97 (1H, d, J=9 Hz), 6.535 (1H, s), 6.540 (1H, s), 6.69 (1H, s), 7.14 (1H, s); ^{13}C NMR (25 MHz, $CDCl_3$) δ 15.1, 19.0, 44.6, 49.5, 56.2 (2C), 56.4, 56.6, 56.7, 57.1, 76.0, 80.7, 97.6, 97.8, 111.5, 113.2, 119.7, 121.7, 142.8, 143.5, 148.2, 149.0, 151.8, 152.4; MS: m/z 432 (M^+), 388, 357, 224, 220, 207, 205, 181 (base peak), 165, 151. The spectral data were identical with those of an authentic sample. (Found: C, 66.75; H, 7.50. Calc for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46 %).

Isomers **1b**, **1c** and **1d** of magnosalicin. Before removing crystalline **1a**, a crude mixture of the products was analyzed by HPLC (Column, Nucleosil® 50-5, 250 mm x 4.6 mm; Solvent, n-hexane-EtOAc-MeOH = 25,000:10,000:1; Flow rate, 1.2 ml/min; Detection at 254 nm): Rt 19.5 min (22 % **1a**), 21.0 min (22 %, I = **1d** containing a small amount of I' at Rt = 21.6 min), 23.8 min (39 %, II = **1c**), 26.4 min (17 %, III = **1b**). These isomers were separated by HPLC, and their IR, ^1H NMR and MS were measured. ^1H NMR data of **1b**, **1c** and **1d** are listed in Table 1. IR and MS of I (=**1d**): νmax (nujol) 1615 (w), 1520 (m), 1215 (m), 1205 (m), 1050 (m), 1035 (m) cm^{-1}; MS: m/z 432 (M^+), 414, 388 (base peak), 357, 220, 205, 181, 165, 151. IR and MS of II (=**1c**): νmax (nujol) 1615 (m), 1530 (s), 1450 (s), 1220 (s), 1050 (s) cm^{-1}; MS: m/z 432 (M^+), 414, 388 (base peak), 357, 220, 205, 181, 165, 151. IR and MS of III (=**1b**): νmax (nujol) 1615 (m), 1520(s), 1210 (s), 1040 (s) cm^{-1}; MS: m/z 432 (M^+), 388 (base peak), 357, 220, 205, 181, 165, 151.

(2R*,3S*,4R*,5R*)-2,4-Dimethyl-3,5-bis(4'-methoxyphenyl)tetrahydrofuran 4. To a stirred and ice-cooled soln of 3 (14.8 g, 100 mmol) in AcOH (20 ml) was added 40 % AcOOH in AcOH (9.5 ml, 50 mmol; 0.5 eq) at <20°. The mixture was stirred for 2 h at that temp, and an additional amount of 40 % AcOOH in AcOH (4.7 ml, 25 mmol; 0.25 eq) was added. After stirring for 1.5 h, the mixture was diluted with CH_2Cl_2. The soln was washed with water, sat $NaHCO_3$ soln and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue (17.6 g) was chromatographed over SiO_2 (700 g). Elution with n-hexane–EtOAc–CH_2Cl_2 (4:1:2) first eluted recovered 3 and then 4.1 g of an oil containing 4. Further elution yielded 10.1 g of more polar major product (diol monoacetate). The fraction containing 4 was distilled to give 3.0 g of an oil, b.p. 135–160°/0.15 Torr. The oil crystallized after storage in a refrigerator. This was twice recrystallized from i-PrOH to give 0.6 g (3.8 %) of 4 as colorless needles, m.p. 96–97° (lit.[3] m.p. 96–97°); νmax (KBr) 1620 (m), 1590 (w), 1520 (vs), 1470 (w), 1455 (w), 1445 (w), 1385 (w), 1305 (w), 1250 (vs), 1235 (m), 1170 (m), 1145 (w), 1120 (w), 1105 (w), 1070 (s), 1040 (s), 1020 (w), 1010 (w), 950 (w), 900 (w), 870 (w), 840 (m), 830 (m), 810 (w), 780 (w), 760 (w), 720 (w), 690 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J=6.5 Hz), 0.98 (3H, d, J=6.5 Hz), 2.30 (1H, ddq, J=10.5, 9.5 and 6.5 Hz), 3.19 (1H, dd, J=8.5 and 10.5 Hz), 3.80 (3H, s), 3.82 (3H, s), 4.42 (1H, d, J=9.5 Hz), 4.43 (1H, dq, J=8.5 and 6.5 Hz), 6.87 (2H, d, J=7 Hz), 6.91 (2H, d, J=7 Hz), 7.10 (2H, d, J=7 Hz), 7.36 (2H, d, J=7 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 14.6, 19.1, 46.7, 55.2 (2C), 56.1, 77.4, 87.5, 113.8 (4C), 127.6 (2C), 129.6(2C), 131.4, 133.4, 158.3, 159.2; MS: m/z 312 (M^+), 268 (base peak), 253, 237, 176, 161, 147, 145, 135, 121. These spectral data were in accord with those reported.[3] (Found: C, 76.85; H, 7.53. Calc for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74 %). The isomers of 4 were not examined in detail.

X-ray crystallographic analysis of 4. Summary of the work is described in the text. Supplementary materials are available on request.[4]

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