Thymol Derivatives from *Eupatorium fortunei*

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Sixteen new thymol derivatives have been isolated from *Eupatorium fortunei* and their structures determined based on spectroscopic data. They were classified into three groups (i−iii) depending on the oxidation levels: (i) one oxygen function at the 9-position, (ii) two oxygen functions at the 8- and 9-positions, and (iii) three oxygen functions at the 8-, 9-, and 10-positions. The hydroxyl groups are acylated with tigloyl, angeloyl, acetyl, isobutyryl, 3-methyl-2-butenoyl, or 2-methylbutyryl moieties. The compounds having chiral centers showed no specific rotation and exist as racemic mixtures.

Eupatorium fortunei was once distributed in fields or at riversides in Japan; however, this species is now rarely found in the field. It has a pleasant odor when the stem is cut and has been called "a scent plant". There are some reports on the constituents of *E. fortunei*.[1] A Japanese group has reported the isolation of eupafortunin, a germacrane-type sesquiterpene,[2] and a Chinese group has found pyrrolizidine alkaloids.[3] However, no other report on the isolation of thymol derivatives has appeared, but thymol derivatives have been found in other *Eupatorium* species.[4−8] We have investigated the chemical constituents of *Petasites*,[9] *Farfugium*,[10] *Eupatorium*,[11] and other plants[12] classified to Compositae. In the present study the methanol extract of *E. fortunei* has been separated and the structures of the isolated compounds have been determined. Now we describe the details of this work.

Results and Discussion

A MeOH extract of the aerial parts of *E. fortunei* was separated into three fractions: an EtOAc-soluble fraction, a $CHCl_3$-soluble fraction, and an *n*-BuOH-soluble fraction. The EtOAc-soluble fraction was further purified by repeated silica gel column chromatography to yield 16 new compounds (**1**−**16**, Chart 1). The ^{13}C assignments for **1**−**16** are shown in Tables 1 and 2.Compounds **1**−**3** were tiglate[13] derivatives of thymol. Compound **1** showed a peak at *m*/*z* 231 as the largest value of *m*/*z* (CIMS), and the IR spectrum showed an absorption at 1740 cm^{-1}. The ^1H NMR spectrum exhibited the typical pattern of a 1,2,4-trisubstituted phenyl group, a proton characteristic of an α,β-unsaturated system, exomethylene protons, and four methyl groups attached to an aromatic ring and sp^2 carbons, respectively. Therefore, it was concluded that compound **1** was 8,9-dehydrothymol 3-*O*-tiglate.

Compound **2** exhibited the presence of a tiglate,[13] an acetate, and an exomethylene group. Two protons at δ 4.79 (s) had an HMBC correlation peak to the carbonyl group at δ 170.6 assignable to the acetate moiety. Therefore, and by comparison with the data of **1**, compound **2** was determined to be 9-acetoxy-8,10-dehydrothymol 3-*O*-tiglate. The NMR data of compound **3** resembled those of **2**, except that it had no exomethylene group. As it had a secondary methyl group instead, **3** was identified as 9-acetoxythymol 3-*O*-tiglate.

Compounds **4** and **5** had an epoxide at the 8,10-position. Compound **4** showed the presence of a tiglate,[13] a primary hydroxyl, and two proton signals at δ 3.18 and 2.81, each a doublet (J = 5.2 Hz) assigned to the 10-position of the epoxide. The tiglate moiety was obviously attached to the 3-hydroxyl group due to the chemical shifts of the protons at the 9-positions.

Compound **5** exhibited the presence of an angeloyl group.[13] The proton at δ 6.28 (H-3′) had NOEs into both methyl groups at δ 2.04 (dq, J = 1.5 and 1.5 Hz, H-5′) and 2.07 (dq, J = 7.4 and 1.5 Hz, H-4′). There were only two aromatic proton signals at δ 6.89 (s) and 6.86 (d, J = 0.5 Hz), which indicated their *para* positioning. The HMBC spectrum did not indicate the position of the angeloyl group (either 3- or 6-position). Therefore, **5** was reacted with MOMCl to prepare the MOM derivative **5a** (Figure 1). The NOESY spectrum of **5a** clearly showed the proximity of the methylene group doublets at δ 5.17 and 5.21 to H-5 (δ 7.14).[14] Further NOEs were detected between H-5 and H-10 and between H-2 and H-7, as in the case of compound **5**. Therefore, compound **5** was determined to be 9-acetoxy-8,10-epoxy-6-hydroxythymol 3-*O*-angelate.

Compound **6** has no methyl group attached to the aromatic ring, but the presence of a tertiary methyl group was indicated. The 1,2,4-trisubstituted pattern was indicated by the ^1H NMR spectrum. The HMBC spectrum suggested that the acetyl group was attached to the 7-position and the isobutyryl group to the 9-position. Therefore, **6** was determined to be 7-acetoxy-8-hydroxy-9-isobutyryloxythymol.

Compounds **7**−**13** had a methoxyl group at the 8-position. The position of the methoxyl group was determined by a HMBC long-range correlation peak between the methoxyl group and the carbon at the 8-position. Compound **7** was 8-methoxy-9-hydroxythymol, and compound **8** was a 3-*O*-isobutyryl derivative of **7**. Compound **9** was a 3-*O*-tiglate derivative of **7**, and compound **10** was a 3-*O*-(3-methyl-2-butenoyl) derivative of **7**. Compound **11** was assigned as a 9-*O*-angeloyl derivative of **7**, and compound **12** was a 9-*O*-isobutyryl derivative of **7**. Compound **13** showed the presence of a 2-methylbutyryloxy moiety attached to the 9-position and was a diastereomeric mixture. The structures of **7**−**13** were determined by analysis of the 2D NMR spectra.

Compounds **14** and **15** had three oxygen functions at the isopropyl group of thymol. Angeloyl and acetyl groups were detected for compound **14**, while there were a tigloyl and an acetyl group in compound **15**. The positions of these groups were determined by the 2D NMR spectra.

Compound **16** had a different skeleton. The NMR spectra showed the presence of a secondary hydroxyl [δ_H 5.17 (1H,

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Chart 1

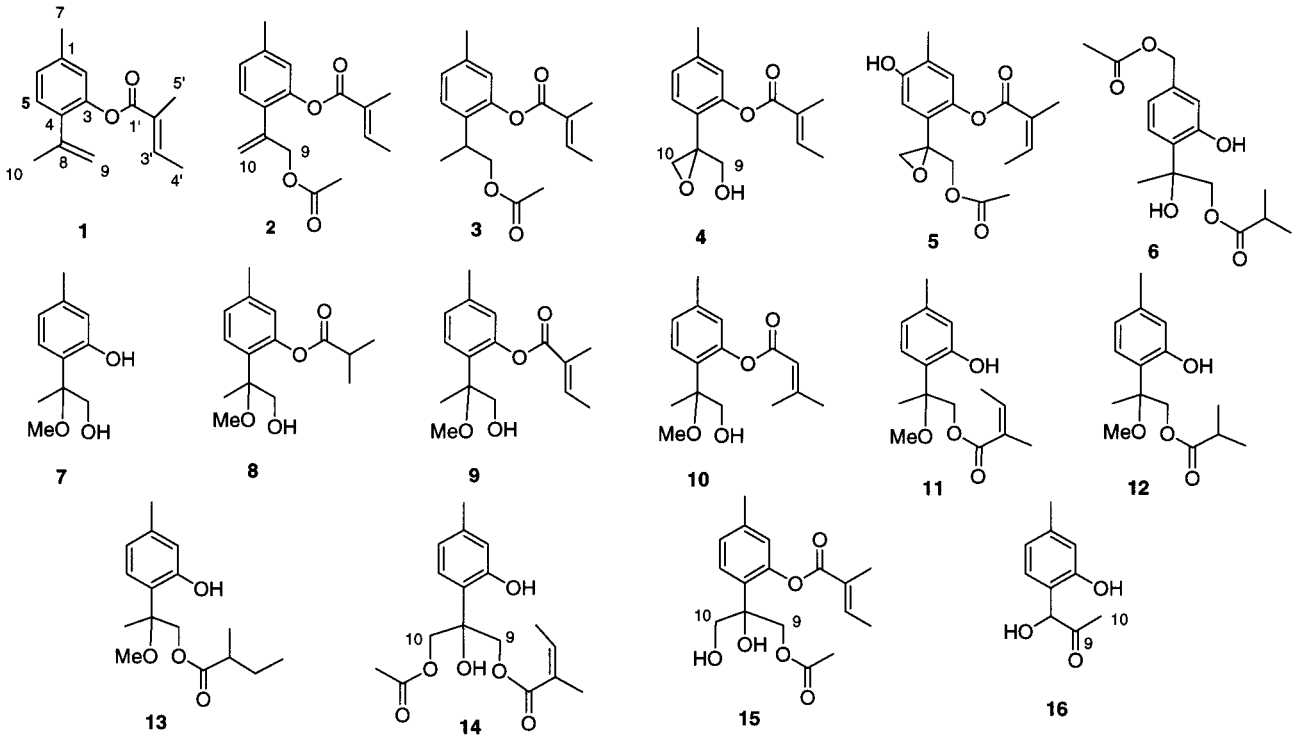

Table 1. ^{13}C NMR Spectral Data (δ) of Compounds **1**−**8** (100 MHz, in $CDCl_3$)

position	1	2	3	4	5	6	7	8
1	138.2	139.2	137.5	139.8	125.8	137.5	140.1	139.2
2	123.3	123.4	123.2	123.3	124.8	117.4	117.7	124.9
3	147.4	147.8	148.5	148.5	141.3	156.5	156.0	149.0
4	133.6	129.7	131.8	126.7	127.2	125.7	127.8.	129.8
5	129.0	129.7	127.1	128.8	114.7	126.4	121.1	129.0
6	126.6	126.7	127.0	126.9	151.7	119.0	120.8	126.6
7	21.0	21.1	20.9	21.1	15.8	65.6	21.0	20.7
8	141.6	140.5	31.9	59.2	56.7	77.6	83.1	79.4
9	115.5	66.3	68.6	63.2	65.4	70.5	68.7	68.9
10	23.5	117.2	17.4	50.2	51.2	25.9	19.2	20.1
1′	166.3	166.1	166.2	166.0	166.2	177.6		175.6
2′	127.4	127.1	127.1	126.6	126.7	33.9		34.3
3′	140.1	140.7	140.9	141.5	141.4	18.9		18.8
4′	15.9	15.9	16.0	16.0	16.0	18.9		18.8
5′	20.6	20.6	20.9	20.7	20.7			
CH_3CO		170.6	171.0		170.0	170.8		
CH_3CO		20.9	20.9		20.7	21.0		
OMe							50.7	50.8

Table 2. ^{13}C NMR Spectral Data (δ) of Compounds **9**−**16** (in $CDCl_3$)

position	9[a]	10[a]	11[b]	12[b]	13[a]	14[b]	15[b]	16[b]
1	139.1	138.9	140.1	140.0	140.1	140.1	139.4	140.7
2	125.1	125.1	117.8	120.6	117.8	118.6	124.4	118.0
3	148.6	148.4	156.1	156.1	156.1	156.6	147.4	154.9
4	130.0	130.1	121.0	120.8	120.7	118.9	128.7	119.2
5	129.0	128.8	127.5	127.4	127.4	126.3	128.6	129.3
6	126.7	126.6	120.7	117.7	120.7	120.5	126.9	121.7
7	20.8	20.8	21.0	20.2	21.0	20.9	20.8	25.0
8	79.4	79.5	81.2	81.2	81.3	78.5	76.2	78.8
9	69.1	69.1	68.2	68.4	68.3[c]	67.3	68.2	207.4
10	20.2	20.4	20.6	18.9	20.3	67.6	66.4	21.2
1′	166.4	165.1	167.4	176.5	176.2	168.1	166.5	
2′	127.1	115.2	127.5	33.9	41.0	126.9	126.7	
3′	141.1	160.3	138.6	18.8	26.6[d]	140.2	142.2	
4′	15.9	27.7	15.7	18.8	11.5	15.8	16.0	
5′	20.7	20.5	20.6		16.5	20.4	20.6	
CH_3CO						171.2	171.6	
CH_3CO						20.7	20.7	
OMe	50.9	50.9	50.8	50.8	50.8			

[a] 150 MHz. [b] 100 MHz. (Signals due to the presence of the distereoisomer. [c] 68.2. [d] 26.7).

s); δ_C 78.8 (CH)], an acetyl [δ_H 2.11 (3H, s); δ_C 21.2 (CH_3) and 207.4], and a methyl group [δ 2.30 (s)] attached to the aromatic ring. The substitution pattern of the aromatic ring was the same as that of thymol. Therefore, it was concluded that compound **16** is 2-(1′-hydroxy-2′-oxopropyl)-5-methylphenol.

Interestingly compounds having a methoxyl group at the 8-position showed no specific rotation, except for **10**. Analysis using a chiral HPLC column (Chiralcel OD-H) revealed that **7**−**9** and **11**−**13** exist as racemic mixtures, while compound **10** showed only one peak under the same conditions. Therefore, we suspect that these may be artifacts formed during the isolation using methanol. However, the absolute configurations of compound **10** and other compounds having chiral centers have not been determined yet. Some thymol derivatives isolated from *E. stoechadosmum* showed no optical rotation, although they had chiral centers.[8] Furukawa and his group also reported that eupatriol had no optical rotation.[7]

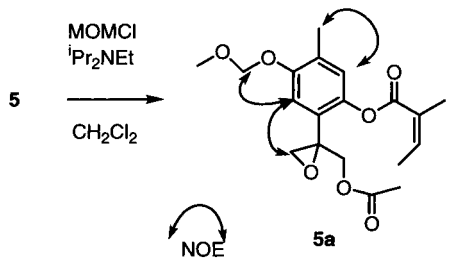

Figure 1. Methoxymethylation of compound **5** and the NOEs observed for **5a**.

Experimental Section

General Experimental Procedures. The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer. The ^1H, ^{13}C, and 2D NMR spectra were taken with a Varian Unity 600 (600 MHz), a JEOL GX400 (400 MHz), or a Varian Unity 200 (200 MHz) spectrometer. The mass spectra including high-

resolution mass spectra were taken with a JEOL JMS AX-500 spectrometer. GC−MS was measured with a HP GC6890-MS5973 system. Specific rotations were measured with a JASCO DIP-140. Chemcopak Nucleosil 50-5 and Chiralcel OD-H (Daisel) were used for HPLC (JASCO pump system). Silica gel 60 (70−230 mesh, Merck) was used for column chromatography, and silica gel 60 F_{254} plates (Merck) were used for TLC.

Plant Material. *E. fortunei* was cultivated in a garden in Tokushima City for five years (1994−1998). A voucher specimen (TBU-MT-199501) is deposited at the Herbarium of the Faculty of Pharmaceutical Sciences, Tokushima Bunri University. The plant was identified by Dr. Takayuki Kawahara, Hokkaido Research Center of Forestry and Forest Products Research Institute, Ministry of Agriculture, Forestry and Fisheries, Japan.

Extraction and Isolation. The methanol extract (161.2 g) of the aerial parts (half-dried, 1.29 kg) was partitioned between EtOAc, $CHCl_3$, and then *n*-BuOH, successively. The EtOAc-soluble fraction (48.95 g) was subjected to silica gel column chromatography and was eluted by hexane−AcOEt, followed by $CHCl_3$−MeOH, in gradient, Sephadex LH-20 ($CHCl_3$−MeOH = 1:1), and then HPLC (hexane−EtOAc or $CHCl_3$−EtOAc) to give 28 compounds: **1** (6.6 mg), **2** (72.0 mg), **3** (58.2 mg), **4** (20.9 mg), **5** (6.7 mg), **6** (2.1 mg), **7** (15.7 mg), **8** (17.5 mg), **9** (2.23 g), **10** (5.7 mg), **11** (22.4 mg), **12** (470.9 mg), **13** (4.8 mg), **14** (12.3 mg), **15** (28.0 mg), **16** (7.3 mg), (3*S*,4*S*)-3-hydroxy-*p*-menth-1-ene-6-one (1.3 mg),[15] thymol (3.2 mg),[4] thymol methyl ether (7.7 mg),[4] hydrothymoquinone dimethyl ether (10.3 mg),[16] thymol 3-*O*-tiglate (9 mg), thymol 3-*O*-(2-methylpropionate) (9.7 mg),[4] 8,9-dehydrothymol 3-*O*-(2-methylpropionate) (4.3 mg),[4] 9-hydroxy-8,10-dehydrothymol (9.5 mg),[15] 9-hydroxythymol (5.8 mg),[15] 8,9-dihydroxythymol (35.8 mg),[7] 9-acetoxy-8,10-epoxythymol 3-*O*-tiglate (324.9 mg),[17] and caryophyllene oxide (10.1 mg).[18]

1: IR (KBr) ν_{max} 1740, 1650, 1630 cm^{-1}; CIMS *m/z* 231 [M + H]$^+$, 213, 186, 149, 83 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (3H, s, H-10), 2.03 (3H, quint, J = 1.4 Hz, H-5′), 2.04 (3H, s, OCOCH_3), 2.04 (3H, dq, J = 8.0, 1.4 Hz, H-4′), 2.34 (3H, s, H-7), 4.99 (1H, quint, J = 1.8 Hz, H-9a), 5.11 (1H, quint, J = 1.8 Hz, H-9b), 6.21 (1H, qq, J = 8.0, 1.4 Hz, H-3′), 6.88 (1H, d, J = 1.1 Hz, H-2), 7.01 (1H, dd, J = 7.8, 1.1 Hz, H-6), 7.17 (11H, d, J = 7.8 Hz, H-5); HRCIMS *m/z* 231.1375 [M + H]$^+$ (calcd for $C_{15}H_{19}O_2$, 231.1385).

2: IR (KBr) ν_{max} 1740, 1650, 1620 cm^{-1}; EIMS *m/z* 288 [M]$^+$, 160, 145, 83 (100), 55; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (3H, dq, J = 1.1, 1.1 Hz, H-5′), 2.04 (3H, s, OCOCH_3), 2.05 (1H, dq, J = 7.3, 1.1 Hz, H-4′), 2.36 (3H, s, H-7), 4.79 (2H, s, H-9), 5.23 (1H, d, J = 1.5 Hz, H-10a), 5.39 (1H, d, J = 1.5 Hz, H-10b), 6.23 (1H, qq, J = 7.3, 1.5 Hz, H-3′), 6.91 (1H, d, J = 1.1 Hz, H-2), 7.04 (1H, dd, J = 8.0, 1.1 Hz, H-6), 7.20 (1H, d, J = 8.0 Hz, H-2); HREIMS *m/z* 288.1333 [M]$^+$ (calcd for $C_{17}H_{20}O_4$, 288.1362).

3: $[\alpha]_D^{24}$ −10.5 (*c* 0.57, $CHCl_3$); IR (KBr) ν_{max} 1740, 1650, 1630 cm^{-1}; CIMS *m/z* 291 [M + H]$^+$, 231, 186, 149, 83 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (3H, d, J = 7.0 Hz, H-10), 2.07 (3H, dq, J = 7.0, 1.5 Hz, H-4′), 2.07 (3H, dq, J = 1.5, 1.5 Hz, H-5′), 2.34 (3H, s, H-7), 3.23 (1H, sext, J = 7.0 Hz, H-8), 4.12 (2H, d, J = 7.0 Hz, H-9), 6.27 (1H, qq, J = 7.0, 1.0 Hz, H-3′), 6.89 (1H, d, J = 1.5, Hz, H-2), 7.03 (1H, dd, J = 8.1, 1.5 Hz, H-6), 7.19 (1H, d, J = 8.1 Hz, H-5); HRCIMS *m/z* 291.1598 [M + H]$^+$ (calcd for $C_{17}H_{23}O_4$, 291.1596).

4: $[\alpha]_D^{23}$ −32.0° (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} 3500, 1740, 1660, 1640, 1590 cm^{-1}; CIMS *m/z* 263 [M + H]$^+$, 261, 244, 215, 162, 145, 133, 83 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (1H, dq, J = 1.4 Hz, H-5′), 2.08 (3H, dq, J = 6.0, 1.4 Hz, H-4′), 2.36 (3H, s, H-7), 2.81 (1H, d, J = 5.2 Hz, H-10b), 3.18 (1H, d, J = 5.2 Hz, H-10a), 3.84 (1H, d, J = 12.6 Hz, H-9b), 3.91 (1H, d, J = 12.6 Hz, H-9a), 6.29 (1H, qq, J = 6.0, 1.4 Hz, H-3′), 6.93 (1H, br s, H-2), 7.06 (1H, br d, J = 8.0 Hz, H-6), 7.35 (1H, d, J = 8.0 Hz, H-5); HRCIMS *m/z* 263.1281 [M + H]$^+$ (calcd for $C_{15}H_{19}O_4$, 263.1283).

5: $[\alpha]_D^{23}$ −8.5° (*c* 0.68, $CHCl_3$); IR (KBr) ν_{max} 3450, 1740, 1670, 1630 cm^{-1}; CIMS *m/z* 321 [M + H]$^+$, 320, 260, 220, 178, 161, 83 (100); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.01 (3H, s, OCOCH_3), 2.04 (1H, dq, J = 1.5, 1.5 Hz, H-5′), 2.07 (3H, dq, J = 7.4, 1.5 Hz, H-4′), 2.23 (3H, s, H-7), 2.83 (1H, d, J = 5.5 Hz, H-10a), 3.02 (1H, d, J = 5.5 Hz, H-10b), 4.18 (1H, d, J = 12.2 Hz, H-9a), 4.54 (1H, d, J = 12.2, Hz, H-9b), 6.28 (1H, qq, J = 7.4, 1.5 Hz, H-3′), 6.86 (1H, d, J = 0.5 Hz, H-2), 6.89 (1H, s, H-5); HRCIMS *m/z* 320.1241 [M]$^+$ (calcd for $C_{17}H_{20}O_6$, 320.1260).

6: $[\alpha]_D^{23}$ −13.6° (*c* 0.24, $CHCl_3$); IR (KBr) ν_{max} 3300, 1740, 1630, 1580 cm^{-1}; CIMS *m/z* 310 [M]$^+$, 293, 251, 233, 222, 205, 163 (100), 145, 89; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.15 (3H, d, J = 7.1 Hz, H-3′), 1.16 (3H, d, J = 7.1 Hz, H-4′), 1.63 (3H, s, H-10), 2.11 (3H, s, OCOCH_3), 2.59 (1H, sept, J = 7.1 Hz, H-2′), 4.27 (1H, d, J = 12.0 Hz, H-9a), 4.44 (1H, d, J = 12.0 Hz, H-9b), 5.04 (2H, s, H-7), 6.87 (1H, d, J = 1.7 Hz, H-2), 6.99 (1H, d, J = 8.0 Hz, H-5), 6.81 (1H, dd, J = 8.0, 1.7 Hz, H-6), 9.06 (1H, s, O*H*); HRCIMS *m/z* 310.1417 [M]$^+$ (calcd for $C_{16}H_{22}O_6$, 310.1416).

7: $[\alpha]_D^{24}$ 0° (*c* 1.71, $CHCl_3$); IR (KBr) ν_{max} 3300, 1630, 1570 cm^{-1}; CIMS *m/z* 196 [M]$^+$,165, 147 (100), 135; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.67 (3H, s, H-10), 1.93 (br s, O*H*), 2.29 (3H, s, H-7), 3.29 (3H, s, OCH_3), 3.56 (1H, dd, J = 11.6, 5.8 Hz, H-9a), 3.84 (1H, d, J = 11.6 Hz, H-9b), 6.68 (1H, dd, J = 7.7, 0.8 Hz, H-6), 6.70 (1H, d, J = 0.8 Hz, H-2), 6.98 (1H, d, J = 7.7 Hz, H-5), 8.52 (1H, s, O*H*); HRCIMS *m/z* 196.1101 [M]$^+$ (calcd for $C_{11}H_{16}O_3$, 196.1099).

8: $[\alpha]_D^{24}$ 0° (*c* 1.9, $CHCl_3$); IR (KBr) ν_{max} 3400, 1750, 1620, 1570 cm^{-1}; CIMS *m/z* 266 [M]$^+$, 235, 165, 147 (100), 135; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.32 (6H, d, J = 7.1 Hz, H-3′, 4′), 1.66 (3H, s, H-10), 2.33 (3H, s, H-7), 2.79 (1H, sept, J = 7.1 Hz, H-2′), 3.08 (3H, s, OCH_3), 3.58 (1H, br d, J = 11.0 Hz, H-9a), 3.89 (1H, d, J = 11.0 Hz, H-9b), 6.78 (1H, d, J = 1.1 Hz, H-2), 7.04 (1H, dd, J = 7.9, 1.1 Hz, H-6), 7.18 (1H, d, J = 7.9 Hz, H-5); HRCIMS *m/z* 266.1526 [M]$^+$ (calcd for $C_{15}H_{22}O_4$, 266.1518).

9: $[\alpha]_D^{20}$ 0° (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} 3450, 1740, 1650, 1620 cm^{-1}; CIMS *m/z* 278 [M]$^+$, 247, 179, 165, 147 (100); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.60 (3H, s, H-10), 2.05 (1H, br s, O*H*), 2.06 (3H, dq, J = 1.6, 1.6 Hz, H-5′), 2.08 (3H, dq, J = 7.2, 1.6 Hz, H-4′), 2.35 (3H, s, H-7), 3.13 (3H, s, OCH_3), 3.60 (1H, dd, J = 11.0, 8.2 Hz, H-9a), 3.84 (1H, dd, J = 11.0, 2.7 Hz, H-9b), 6.26 (1H, qq, J = 7.2, 1.6 Hz, H-3′), 6.85 (1H, d, J = 0.8 Hz, H-2), 7.06 (1H, dd, J = 8.0, 0.8 Hz, H-5), 7.32 (1H, d, J = 8.0 Hz, H-6); HRCIMS *m/z* 278.1511 [M]$^+$ (calcd for $C_{16}H_{22}O_4$, 278.1508).

10: $[\alpha]_D^{23}$ +18.2° (*c* 0.8, $CHCl_3$); IR (KBr) ν_{max} 3450, 1740, 1650, 1620 cm^{-1}; CIMS *m/z* 278 [M]$^+$, 247 (100), 165, 147, 83; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.60 (3H, s, H-10), 2.00 (3H, q, J = 1.1 Hz, H-4′), 2.23 (3H, q, J = 1.1, H-5′), 2.34 (3H, s, H-7), 3.15 (3H, s, OCH_3), 3.63 (1H, br d, J = 11.3, H-9a), 3.79 (1H, d, J = 11.3 Hz, H-9b), 5.91 (1H, sept, J = 1.1 Hz, H-2′), 6.84 (1H, br s, H-2), 7.04 (1H, br d, J = 8.0 Hz, H-6), 7.33 (1H, d, J = 8.0 Hz, H-5); HRCIMS *m/z* 278.1480 [M]$^+$ (calcd for $C_{16}H_{22}O_4$, 278.1518).

11: $[\alpha]_D^{20}$ 0° (*c* 0.97, $CHCl_3$); IR (KBr) ν_{max} 3330, 1720, 1630, 1580 cm^{-1}; EIMS *m/z* 278 [M]$^+$, 246, 165, 146 (100), 131, 83; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (3H, s, H-10), 1.88 (3H, dq, J = 1.5, 1.5 Hz, H-5′), 1.95 (3H, dq, J = 7.3, 1.5, H-4′), 2.29 (3H, s, H-7), 3.29 (3H, s, OCH_3), 4.28 (1H, d, J = 11.7 Hz, H-9a), 4.43 (1H, d, J = 11.7 Hz, H-9b), 6.07 (1H, qq, J = 7.3, 1.5, H-3′), 6.67 (1H, br d, J = 7.7 Hz, H-6), 6.70 (1H, br s, H-2), 6.93 (1H, d, J = 7.7, H-5), 8.51 (1H, s, OH); HREIMS *m/z* 278.1502 [M]$^+$ (calcd for $C_{16}H_{22}O_4$, 278.1518).

12: $[\alpha]_D^{20}$ 0° (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} 3330, 1740, 1630, 1580 cm^{-1}; EIMS *m/z* 266 [M]$^+$, 234, 165, 146 (100), 135, 117, 91; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (3H, d, J = 7.0 Hz, H-3′), 1.15 (3H, d, J = 7.0 Hz, H-4′), 1.63 (3H, s, H-10), 2.28 (3H, s, H-7), 2.56 (1H, sept, J = 7.0 Hz, H-2′), 3.27 (3H, s, OCH_3), 4.21 (1H, d, J = 12.0 Hz, H-9a), 4.34 (1H, d, J = 12.0 Hz, H-9b), 6.66 (1H, d, J = 7.7 Hz, H-6), 6.69 (1H, s, H-2), 6.91 (1H, d, J = 7.7 Hz, H-5), 8.46 (1H, s, OH); HREIMS *m/z* 266.1535 [M]$^+$ (calcd for $C_{15}H_{22}O_4$, 266.1518).

13: $[\alpha]_D^{20}$ 0° (*c* 0.9, $CHCl_3$); IR (KBr) ν_{max} 3330, 1740, 1630, 1580, 1510 cm^{-1}; CIMS *m/z* 280 [M]$^+$, 249 (100), 179, 165, 147; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.86 (3H, t, J = 7.0 Hz, H-4′), 1.12 (3H, d, J = 7.0 Hz, H-5′), 1.45 (1H, sept, J = 7.0 Hz,

H-3′a), 1.64 (3H, s, H-10), 1.65 (1H, m, H-3′b), 2.29 (3H, s, H-7), 2.40 (1H, sext, J = 7.0 Hz, H-2′), 3.28 (3H, s, OCH_3), 4.21 and 4.23 (1H, d, J = 11.6 Hz, H-9a),* 4.34 and 4.36 (1H, d, J = 11.6 Hz, H-9b),* 6.70 (1H, br s, H-2), 6.67 (1H, br d, J = 7.7 Hz, H-6), 6.91(1H, d, J = 7.7 Hz, H-5), 8.48 (1H, s, OH); HRCIMS m/z 280.1688 $[M]^+$ (calcd for $C_{16}H_{24}O_4$, 280.1675) (*due to the presence of the diastereoisomers).

14: $[\alpha]_D^{23}$ −7.9° (c 1.2, $CHCl_3$); IR (KBr) ν_{max} 3300, 1740, 1720, 1650, 1640 cm^{-1}; CIMS m/z 322 $[M]^+$, 305, 244, 209, 162, 145 (100), 101, 83; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85 (3H, dq, J = 1.5, 1.5 Hz, H-5′), 1.92 (3H, dq, J = 7.3, 1.5, H-4′), 2.07 (3H, s, OCOCH_3), 2.27 (3H, s, H-7), 4.47 (2H, s, H-9), 4.51 (1H, d, J = 12.1 Hz, H-10a), 4.54 (1H, d, J = 12.1 Hz, H-10b), 6.13 (1H, qq, J = 5.9, 1.5 Hz, H-3′), 6.65 (1H, dd, J = 8.1, 1.1 Hz, H-6), 6.70 (1H, d, J = 1.1 Hz, H-2), 6.92 (1H, d, J = 8.1 Hz, H-5), 8.77 (1H, s, OH); HRCIMS m/z 322.1391 $[M]^+$ (calcd for $C_{17}H_{22}O_6$, 322.1416).

15: $[\alpha]_D^{21}$ −1.6° (c 1.5, $CHCl_3$); IR (KBr) ν_{max} 3450, 1730, 1640 cm^{-1}; CIMS m/z 322 $[M]^+$, 305, 222, 209, 191, 162 (100), 145, 133, 101; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.99 (3H, s, OCOCH_3), 2.07 (3H, dq, J = 1.5, 1.5 Hz, H-5′), 2.08 (3H, dq, J = 7.3, 1.5 Hz, H-4′), 2.34 (3H, s, H-7), 3.81 (2H, s, H-10), 4.43 (1H, d, J = 11.7 Hz, H-9a), 4.50 (1H, d, J = 11.7 Hz, H-9b), 6.33 (1H, qq, J = 7.3, 1.5 Hz, H-3′), 6.86 (1H, d, J = 1.1 Hz, H-2), 7.07 (1H, dd, J = 8.0, 1.1 Hz, H-6), 7.56 (1H, d, J = 8.0 Hz, H-5); HRCIMS m/z 322.1391 $[M]^+$ (calcd for $C_{17}H_{22}O_6$, 322.1416).

16: $[\alpha]_D^{21}$ −13.1° (c 0.64, $CHCl_3$); IR (KBr) ν_{max} 3300, 1710, 1620, 1590 cm^{-1}; CIMS m/z 181 $[M + H]^+$, 179, 163, 161, 135 (100); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.11 (3H, s, H-10), 2.30 (3H, s, H-7), 5.17 (1H, s, H-8), 6.68 (1H, s, H-2), 6.75 (1H, d, J = 7.7 Hz, H-6), 7.10 (1H, d, J = 7.7 Hz, H-5); HRCIMS m/z 181.0854 $[M + H]^+$ (calcd for $C_{10}H_{13}O_3$, 181.0865).

Preparation of MOM-Protected Derivative of 5. A solution of compound **5** (3 mg) in CH_2Cl_2 (0.3 mL) was treated with iPr$_2$NEt (0.1 mL) and CH_3OCH_2Cl (0.1 mL) at room temperature for 5 h. A saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to afford a crude product (9.5 mg), which was purified by HPLC (hexane−AcOEt 15%) to give pure **5a** (1.6 mg).

5a: IR (KBr) ν_{max} 1740, 1640 cm^{-1}; CIMS m/z 364 $[M]^+$ 304, 273, 264, 243, 222, 205, 191, 160, 83 (100); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (3H, s, OCOCH_3), 2.07 (3H, dq, J = 1.5, 1.5 Hz, H-5′), 2.08 (3H, dq, J = 7.4, 1.5 Hz, H-4′), 2.24 (3H, d, J = 0.6 Hz, H-7), 2.84 (1H, d, J = 5.2 Hz, H-10a), 3.02 (1H, d, J = 5.2 Hz, H-10b), 3.49 (3H, s, OCH_3), 4.18 (1H, d, J = 12.3 Hz, H-9a), 4.52 (1H, d, J = 12.3 Hz, H-9b), 5.17 (1H, d, J = 6.6 Hz, OCH_2O), 5.21 (1H, d, J = 6.6 Hz, OCH_2O), 6.28 (1H, qq, J = 7.4, 1.5 Hz, H-3′), 6.90 (1H, d, J = 0.6 Hz, H-2), 7.14 (1H, s, H-5); HRCIMS m/z 365.1587 $[M + H]^+$ (calcd for $C_{19}H_{25}O_7$, 365.1601).

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