Prenylated Benzoic Acids from *Rapanea myricoides*

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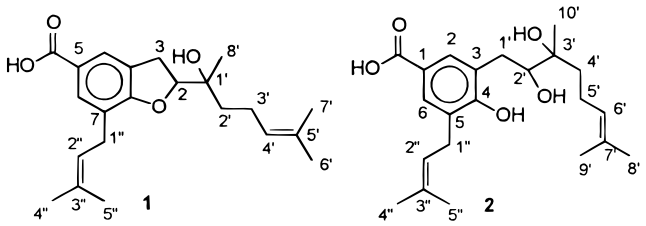
Investigation of leaves from the shrub *Rapanea myricoides* led to the isolation of two diprenylated benzoic acids. One was the known compound 5-carboxy-7-(3″,3″-dimethylallyl)-2-(1′-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran (**1**), while the other was assigned as the new diol **2** (3-(2′,3′-dihydroxy-3′,7′-dimethyloct-6′-enyl)-4-hydroxy-5-(3″,3″-dimethylallyl)benzoic acid, myricoidiol). These compounds were initially characterized through analysis of their spectroscopic data and comparison with some simpler synthetic analogues led to the final structure assignment for diol **2**.

Leafcutter ants are considered to be major agricultural pests over a geographical area ranging from Texas to Argentina. Although many important crops suffer severe defoliation from these ants, a wide variety of native vegetation is left relatively unscathed.[1] In the course of our studies on plant chemical defenses against leafcutter ants, a collection of plant species in diverse plant families has been examined.[2−5] Field and laboratory bioassays indicated that the Costa Rican plant *Rapanea myricoides* Schltdl. (Myrsinaceae) is seldom attacked by leafcutter ants.[1,6] As a result, we began investigating the secondary chemistry of this plant. In this paper, we report the isolation of two prenylated benzoic acids from *R. myricoides* extracts. Prenylated aromatic compounds isolated from plant sources are common in the literature, including some that are diprenylated benzoic acids.[7−12] Members of the diprenylated benzoic acid family include 3-geranyl-4-hydroxy-5-(3″,3″-dimethylallyl)benzoic acid and 6-carboxy-8-(3″,3″-dimethylallyl)-3α-hydroxy-2α-methyl-2-(4′-methylpent-3′-enyl)-3,4-dihydrobenzopyran.[13] From *R. myricoides*, we isolated another known member of this family, 5-carboxy-7-(3″,3″-dimethylallyl)-2-(1′-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran (**1**),[13] and a novel diol (**2**) that we have named myricoidiol. The structures of compounds **1** and **2** were established by spectroscopic methods, with the synthesis of various analogues employed to clarify the structure of diol **2**.



Air-dried aerial parts of *R. myricoides* were steeped in $CHCl_3$ overnight, and the resulting $CHCl_3$ extract was subjected to dry column chromatography (CC) over silica gel. The fraction that eluted with 30% hexanes in CH_2Cl_2 contained interesting downfield signals in its ^1H NMR spectrum and became the focus of further investigation. This fraction was sequentially purified by dry CC, flash CC, radial dispersion chromatography, and reversed-phase HPLC. This sequence afforded two pure UV-active compounds (50 and 4 mg). The more abundant and less polar of these compounds proved to be the prenylated benzoic acid **1**, which was previously reported as the methyl ester from *R. umbellata*, but without defined stereochemistry.[13,14] The second, more polar compound showed sets of related resonances in its NMR spectra (Table 1) but appeared to be a new member of this family.

Table 1. ^1H NMR and ^{13}C NMR Data (δ) for Compounds 1 and 2.[a]

	1			**2**	
position	^1H	^{13}C	position	^1H	^{13}C
1			1		130.2
2	4.69 dd (9.4, 8.5)	89.6	2	7.71 s[b]	129.8
3	3.21 m	29.9	3		118.6
4	7.75 br s	131.4	4		155.5
5		127.1	5		121.9
6	7.75 br s	125.0	6	7.73 s[b]	130.2
7		123.1	1′	3.10 dd (16.8, 6.4) 2.84 dd (16.8, 4.8)	31.1
8		162.4	2′	3.92 dd (6.4, 4.8)	67.9
9		121.8	3′		79.7
1′		73.7	4′	1.63 m	37.6
2′	1.54 m	37.1	5′	2.16 m	21.7
3′	2.13 m	21.9	6′	5.10 tq (7.0, 1.2)	123.8
4′	5.12 tq (7.1, 1.3)	124.0	7′		132.3
5′		133.2	8′	1.72 s	25.6
6′	1.73 s	25.7	9′	1.59 s	17.8
7′	1.63 s	17.6	10′	1.34 s	19.0
8′	1.30 s	22.6			
1″	3.30 m	28.3	1″	3.31 d (7.2)	28.5
2″	5.29 tq (7.3, 1.3)	121.3	2″	5.29 tq (7.5, 1.3)	121.9
3″		132.2	3″		132.8
4″	1.74 s	25.7	4″	1.73 s	25.8
5″	1.69 s	17.8	5″	1.67 s	17.8
CO_2H		171.9	CO_2H		171.3

[a] *J* values are given in parentheses (Hz). [b] Assignments may be interchanged.

The highest ion in the EIMS of compound **2** was observed at *m/z* 358, corresponding to a molecular formula of $C_{22}H_{30}O_4$ and eight degrees of unsaturation. Both the ^1H and ^{13}C NMR spectra contained well-separated and easily assigned resonances. Analysis of the ^{13}C NMR and DEPT spectra revealed the presence of five methyl groups, four methylene carbons, two oxygenated sp^3 carbons, one carboxylic acid, four sp^2-hybridized methines, five sp^2-hybrid-

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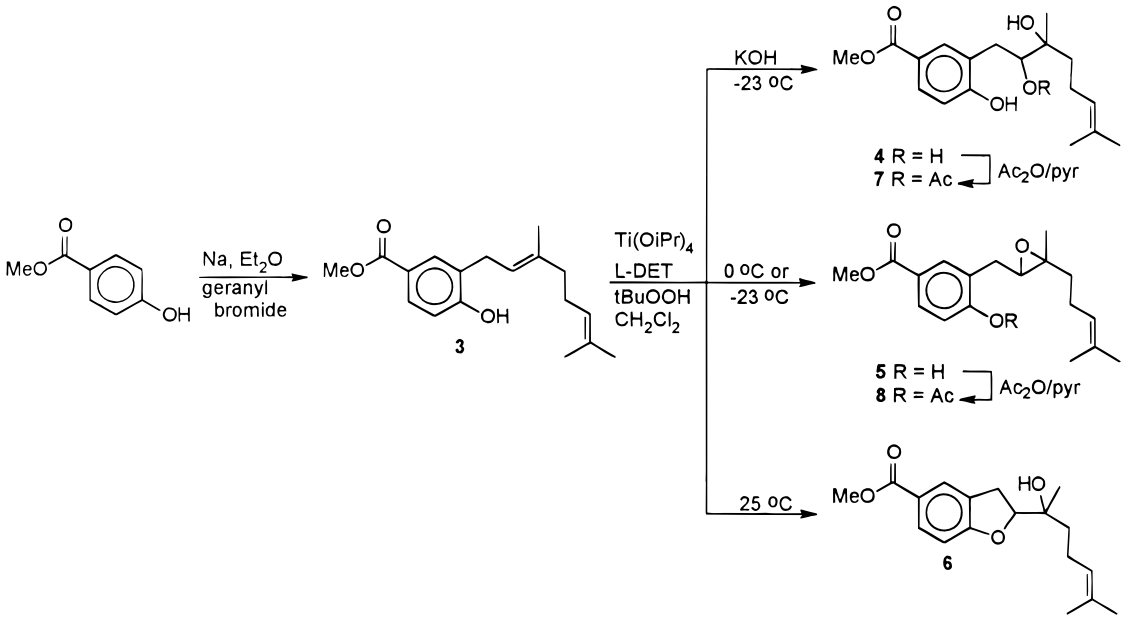
Scheme 1



ized quaternary carbons, and one sp^2 carbon that was both oxygenated and quaternary. Broad ^{1}H NMR resonances at δ 7.73 and 7.71 represented two aromatic hydrogens, indicating a 1,3,4,5-tetrasubstituted aromatic ring, and the intensity of this signal implied that the aromatic system was symmetrical or very nearly so. With the exception of the oxygenated aromatic carbon resonance, the ^{13}C NMR shifts of the aromatic carbons were almost identical to those of the benzofuran **1**, implying that the ring substituents were similar but that this compound might incorporate a phenolic −OH instead of the furan ether.

One of the aromatic substituents was identified as a prenyl group by comparison of the ^{1}H resonances at δ 5.29, 3.31, 1.73, and 1.67, and ^{13}C resonances at δ 132.8, 121.9, 28.5, 25.8, and 17.8, with those of compound **1** (Table 1). A second olefinic resonance at δ 5.10 also was characteristic of the olefinic hydrogen of a terpene. Along with a methylene resonance at δ 2.16, methyl resonances at δ 1.59 and 1.72, and corresponding ^{13}C NMR resonances (δ 132.3, 123.8, 25.6, 21.7, 17.8), these signals indicated that there was an additional prenyl unit not directly connected to the aromatic ring. An oxygenated methine was confirmed by a resonance at δ 3.92 (J = 16.8, 6.4 Hz) and the ^{13}C NMR signal at δ 67.9. This resonance was quite different in chemical shift from those of the benzofuran **1** and 6-carboxy-8-(3″,3″-dimethylallyl)-3α-hydroxy-2α-methyl-2-(4′-methylpent-3′-enyl)-3,4-dihydrobenzopyran, distinguishing myricoidiol (**2**) from these other prenylated benzoic acids.

The ^{1}H resonance of the oxygenated methine was coupled to resonances at δ 3.10 and 2.84, which were in turn geminally coupled (J = 16.8 Hz). These chemical shifts, and that of the associated carbon (δ 31.1), established a benzylic position adjacent to the oxygenated methine. Selective INEPT data correlated the benzylic methylene at δ 3.10 to the as yet unassigned oxygenated quaternary carbon. These data suggested a partial structure corresponding to $ArCH_2CH(O-)C(O-)RR'$, with one of the alkyl substituents identified as a methyl group corresponding to a signal observed at δ 1.34 with a ^{13}C NMR shift at δ 19.0 and the second alkyl substituent incorporating the remaining prenyl chain.

Our initial analysis of the MS data suggested a compound with eight degrees of unsaturation, and seven could be readily identified in the benzene ring, carbonyl group, and two olefins. An epoxide ring spanning the oxygenated methine and quaternary carbons of the side chain (C-2′ and C-3′) would account for the remaining unsaturation. However, if this were the case, both the ^{1}H and ^{13}C resonances would be further upfield than those observed. An alternate explanation could be based on assignment of the *m*/*z* 358 ion as an ($M^+ - H_2O$) peak for a diol such as compound **2**, suggesting a true molecular formula of $C_{22}H_{32}O_5$ and only seven degrees of unsaturation for the true natural product. However, repeated MS analyses failed to detect an *m*/*z* 376 ion.

To distinguish between the two proposed structures, synthesis of three simpler analogues was undertaken. Methyl 4-hydroxybenzoate was alkylated with geranyl bromide in the presence of sodium metal to give the known geranylated product **3** (Scheme 1).[9,15] The geranylated phenol **3** then was subjected to epoxidation under Sharpless conditions.[16] Even though there is little precedent for Sharpless epoxidation of prenylated phenols, this strategy worked quite well. By variation of either the reaction temperature or the workup procedures, we were able to obtain three new oxidation products, the diol **4**, the epoxide **5**, and the benzofuran **6**. Comparison of the ^{1}H NMR data for these three compounds with that of the natural product indicated that the natural product was indeed the diol **2**. The distinguishing ^{1}H NMR resonances of the products were the oxygenated methine hydrogen and the two benzylic hydrogens. In diol **4**, the methine doublet of doublets was found at δ 3.92 (J = 6.1, 5.1 Hz), and the benzylic methylene hydrogens were at δ 3.10 (J = 16.8, 5.9 Hz) and 2.83 (J = 16.8, 6.1 Hz). These signals were considerably different from the corresponding methines of epoxide **5** and benzofuran **6** but compared nicely to those of the natural product (Table 1). In epoxide **5**, the methine resonated as a doublet of doublets at δ 3.06 (J = 9.8, 2.8 Hz) and the benzylic hydrogens as doublet of doublets at δ 2.98 (J = 14.8, 2.8 Hz) and 2.85 (J = 14.8, 9.8 Hz). The methine resonance of the benzofuran **6** appeared at δ 4.72 (J = 9.4, 8.8 Hz), with the two benzylic hydrogens at δ 3.26 (J = 15.9, 8.7 Hz) and δ 3.12 (J = 15.9, 9.5 Hz). Analysis of the ^{13}C NMR also supported this assignment. In the diol **4**, the methine carbon appeared at δ 67.8 and the oxygenated quaternary carbon appeared at δ 79.7, correlating perfectly

with those of the natural product. The corresponding shifts in epoxide **5** were δ 64.2 and 63.8, while the parallel resonances of benzofuran **6** were δ 89.9 and 73.6. Interestingly, the diol **4** did not give a molecular ion in repeated MS experiments. Instead, it consistently gave an ($M^+ - 18$) peak as the highest mass ion.

Confirmation of the structures of the synthetic products was obtained by derivatization of diol **4** and epoxide **5** with acetic anhydride in pyridine, giving the monoacylated products **7** and **8**.[17] The methyl shift of the acetate **7** was observed as a singlet at δ 2.10, demonstrating formation of an aliphatic ester. In the aromatic acetate **8**, the methyl singlet of the acetate resonated farther downfield at δ 2.36, differentiating it from the methyl singlet of acetate **7**. Furthermore, two exchangeable hydrogens, a phenol and an alcohol hydrogen, were seen in the ^{1}H NMR of compound **7**, but none was observed in the spectrum of acetate **8**. Thus, formation of the acetate esters **7** and **8** made clear that compounds **4** and **5** were the diol and epoxide respectively, and the correspondence between the spectra for compounds **4** and **2** confirmed the structure proposed for myricoidiol.

Through synthesis of the prenylated benzoic acid derivatives **4**−**6**, we were able to establish the structure of diol **2**. The directing effect of the phenol in the Sharpless epoxidation reaction appears to be the first example of this kind. Unfortunately, this epoxidation reaction showed no stereoselectivity, giving a racemic mixture as proven by subsequent formation of *O*-methyl mandelate esters. Thus, the general structure of myricoidiol can be assigned as shown in structure **2**, but the absolute stereochemistry of this compound must still be addressed.

Experimental Section

General Experimental Procedures. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. NMR spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards, unless otherwise noted. Both low- and high-resolution mass spectra were obtained at an ionization potential of 70 eV; only selected ions are reported here.

Plant Material. Leaves of *R. myricoides* were collected near Rincon de la Vieja, Costa Rica. The leaves were air-dried and then chopped in a Waring blender before storage in plastic bags. Voucher specimens have been deposited in the Jerome J. Howard collection.

Extraction and Isolation. The *R. myricoides* leaves (150 g) were steeped in $CHCl_3$ for 24 h and then concentrated in vacuo. The resulting residue (15 g) was partitioned between 30% CH_2Cl_2/hexanes and water. The organic extract was further purified by dry column chromatography eluting with 50% EtOAc/hexanes, followed by a 85% MeOH/H_2O Sep-Pak purification and then radial dispersion chromatography (5−40% EtOAc/hexanes/1% AcOH). Radial dispersion chromatography (5−40% EtOAc/hexanes/1% AcOH) yielded pure compound **1** (50 mg) and crude myricoidiol (**2**). Pure diol **2** (4 mg) was obtained after final purification by HPLC with an 80−100% MeOH/H_2O gradient.

Myricoidiol (2). colorless oil; $[\alpha]^{25}_D$ −12.8°($CHCl_3$, *c* 0.2); ^{1}H NMR see Table 1; ^{13}C NMR see Table 1; EIMS *m/z* [$M^+ - H_2O$] 358.

Methyl 3-Geranyl-4-hydroxybenzoate (3).[9] To a solution of methyl 4-hydroxybenzoate (2.05 g, 13.5 mmol) in anhydrous Et_2O (30 mL) were added small pieces of Na (0.9 g, 39.1 mmol). The mixture was stirred for 3 h at ∼25 °C under nitrogen, and then geranyl bromide (3 mL, 15.1 mmol) was added dropwise. The resulting mixture was heated at reflux for 48 h until all sodium had disappeared. The solution was allowed to cool to ∼25 °C, 10% HCl (10 mL) was added, and the separated aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with H_2O (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc/hexanes) to give compound **3** (1.44 g, 37%) as a yellow oil: ^{1}H NMR δ 7.83 (m, 2H), 6.83 (d, J = 8.9 Hz, 1H), 5.31 (tq, J = 7.1, 1.2 Hz, 1H), 5.07 (tq, J = 6.8, 1.3 Hz, 1H), 3.87 (s, 3H), 3.40 (d, J = 7.1 Hz, 2H), 2.10 (m, 4H), 1.78 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR δ 167.3, 158.8, 138.9, 131.9, 131.8, 129.6, 126.9, 123.8, 122.3, 121.0, 115.4, 51.9, 39.7, 29.4, 26.4, 25.6, 17.6, 16.2.

Diol 4. To a solution of compound **3** (0.64 g, 2.2 mmol) in CH_2Cl_2 (20 mL, distilled from CaH_2) at −23 °C was added L-(+)-diethyl tartrate (0.52 g, 1.1 mmol) followed by Ti(O-*i*-Pr)$_4$ (0.75 g, 1.2 mmol). This solution was stirred for 5 min before addition of 3.3 M *t*-BuOOH in toluene (1.5 mL, 2.2 mol), and the resulting solution was then stored in a freezer at ∼20 °C. After 24 h, the flask was placed in a −23 °C bath, and 10% aqueous tartaric acid (5 mL) was added with stirring. The cold bath was removed after 30 min, and the mixture was stirred until the aqueous layer melted and became clear. The aqueous layer was separated, and the organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was then diluted with Et_2O (15 mL) and cooled to 0 °C, and 1 N NaOH (6 mL) was added. After the reaction mixture was stirred for 30 min, the ether layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was purified by column chromatography (25% EtOAc/hexanes) to give the desired product **4** as a pale yellow oil (0.13 g, 68% yield based on recovered starting material): ^{1}H NMR δ 7.79, (m, 2H), 6.85 (d, J = 9.1 Hz, 1H), 5.08 (tq, J = 7.1, 1.4 Hz, 1H), 3.92 (dd, J = 6.1, 5.9 Hz, 1H), 3.87 (s, 3H), 3.10 (dd, J = 16.8, 5.1 Hz, 1H), 2.83 (dd, J = 16.8, 6.1 Hz, 1H), 2.10 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.50 (m, 2H), 1.34 (s, 3H); ^{13}C NMR δ 166.9, 157.1, 132.3, 132.2, 129.5, 123.7, 122.4, 118.9, 117.2, 79.7, 67.8, 51.8, 37.3, 30.9, 25.6, 21.6, 19.2, 17.6; HRFABMS *m/z* [$M - H_2O + H$]$^+$ 305.1783 (calcd for $C_{18}H_{25}O_4$, 305.1753).

Epoxide 5. According to the procedure described for preparation of compound **4**, compound **3** (99 mg, 0.34 mmol) was treated with L-(+)-diethyl tartrate (130 mg, 0.63 mmol), Ti(O-*i*-Pr)$_4$ (160 mg, 0.57 mmol), and *t*-BuOOH (0.2 mL, 0.72 mmol) at 0 °C. After treatment with saturated aqueous $NaHCO_3$, standard workup and purification by column chromatography (25% EtOAc/hexanes) gave compound **5** as a pale yellow oil (51 mg, 48%): ^{1}H NMR δ 7.85 (m, 2H), 6.94 (d, J = 8.7 Hz, 1H), 5.06 (tq, J = 7.2, 1.3 Hz, 1H), 3.88 (s, 3H), 3.06 (dd, J = 9.8, 2.8 Hz, 1H), 2.98 (dd, J = 14.9, 2.8 Hz, 1H), 2.85 (dd, J = 14.9, 9.8 Hz, 1H), 2.09 (dt, J = 7.6, 7.6, Hz, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.50 (m, 2H), 1.49 (s, 3H); ^{13}C NMR δ 167.0, 160.1, 132.6, 132.4, 130.7, 124.1, 123.0, 122.2, 117.0, 64.2, 63.8, 51.8, 38.3, 31.7, 25.6, 23.5, 17.6, 16.8; HRFABMS *m/z* [$M + H$]$^+$ 305.1748 (calcd for $C_{18}H_{25}O_4$, 305.1753).

Benzofuran 6. According to the procedure described for preparation of compound **4**, compound **3** (77 mg, 0.27 mmol) was treated with L-(+)-diethyl tartrate (94 mg, 0.7 mmol), Ti-(O-*i*-Pr)$_4$ (94 mg, 0.49 mmol), and *t*-BuOOH (0.2 mL, 0.72 mmol) at 25 °C. Standard workup and purification by flash column chromatography (25% EtOAc/hexanes) gave compound **6** as a pale yellow oil (41 mg, 51%): ^{1}H NMR δ 7.85 (m, 2H), 6.78 (d, J = 9.0 Hz, 1H), 5.12 (tq, J = 7.0, 1.3 Hz, 1H), 4.72 (dd, J = 9.4, 8.8 Hz, 1H), 3.87 (s, 3H), 3.26 (dd, J = 15.9, 8.7 Hz, 1H), 3.12 (dd, J = 15.9, 9.5 Hz, 1H), 2.10 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.50 (m, 2H), 1.31 (s, 3H); ^{13}C NMR δ 166.9, 163.6, 132.3, 131.0, 127.6, 126.7, 124.0, 122.8, 108.8, 89.9, 73.6, 51.8, 36.9, 29.7, 25.7, 22.8, 21.9, 17.7; HREIMS *m/z* [M]$^+$ 304.1684 (calcd for $C_{18}H_{24}O_4$, 304.1675).

Acetate 7. To a solution of compound **4** (38 mg, 0.12 mmol) in pyridine (10 mL) was added acetic anhydride (60 μL), and the resulting solution was heated at 80 °C for 18 h. The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (20% EtOAc/

hexanes) to afford the acetate **7** as a colorless oil (37 mg, 85%): ^{1}H NMR δ 7.80 (m, 3H, 1 exchangeable), 6.86 (d, J = 8.6 Hz, 1H), 5.12 (dd, J = 5.1, 5.0 Hz, 1H), 5.04 (tq, J = 7.1, 1.4 Hz, 1H), 3.87 (s, 3H), 3.16 (dd, J = 17.3, 5.0 Hz, 1H), 2.82 (dd, J = 17.3, 5.2 Hz, 1H), 2.24 (br s, 1H, exchangeable), 2.12 (m, 2H), 2.07 (s, 3H), 1.65 (s, 3H), 1.60 (m, 2H), 1.57 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 170.4, 166.9, 156.9, 132.3, 131.8, 129.5, 123.3, 122.3, 118.2, 117.2, 77.9, 69.3, 51.8, 37.1, 27.9, 25.6, 21.5, 21.0, 20.0, 17.5; HRFABMS m/z [M − H_2O + Na]$^+$ 369.1679 (calcd for $C_{20}H_{26}O_5Na$, 369.1678).

Acetate 8. The epoxide **5** (24 mg, 0.08 mmol) was treated with acetic anhydride (40 μL) in pyridine (10 mL) as described for compound **7** to obtain the aromatic acetate **8** in quantitative yield (27 mg): ^{1}H NMR δ 8.02 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.4, 2.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 5.03 (tq, J = 7.2, 1.3 Hz, 1H), 3.91 (s, 3H), 2.94 (dd, J = 5.9, 5.8 Hz, 1H), 2.88 (dd, J = 14.7, 6.1 Hz, 1H), 2.76 (dd, J = 14.6, 5.6 Hz, 1H), 2.36 (s, 3H), 2.07 (m, 2H), 1.63 (s, 3H), 1.58 (s, 3H), 1.45 (m, 2H), 1.37 (s, 3H); ^{13}C NMR δ 168.8, 166.3, 152.7, 132.0, 131.9, 130.6, 129.4, 128.1, 123.4, 122.7, 62.2, 61.0, 52.2, 38.5, 29.8, 25.6, 23.7, 21.0, 17.6, 16.8; HRFABMS m/z [M + H]$^+$ 347.1833 (calcd for $C_{20}H_{27}O_5$, 347.1858).

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