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An Effective Synthesis of 3-Methoxyflavones *via* 1-(2-Hydroxyphenyl)-2-methoxy-3-phenyl-1,3-propanediones

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The 3-methoxyflavones are widely distributed in plants of diverse families[1] and are currently of interest due to their various biological activities. They suppress superoxide generation in human neutrophils[2] and exhibit radical-scavenging activities[3] on 1,1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radicals. They also show cytotoxic effects[4] in medulloblastoma tumors and human cancer cells, act as anti-inflammatory agents[5] to inhibit nitric oxide production, and show hepatoprotective activity[6] against CCl_4.

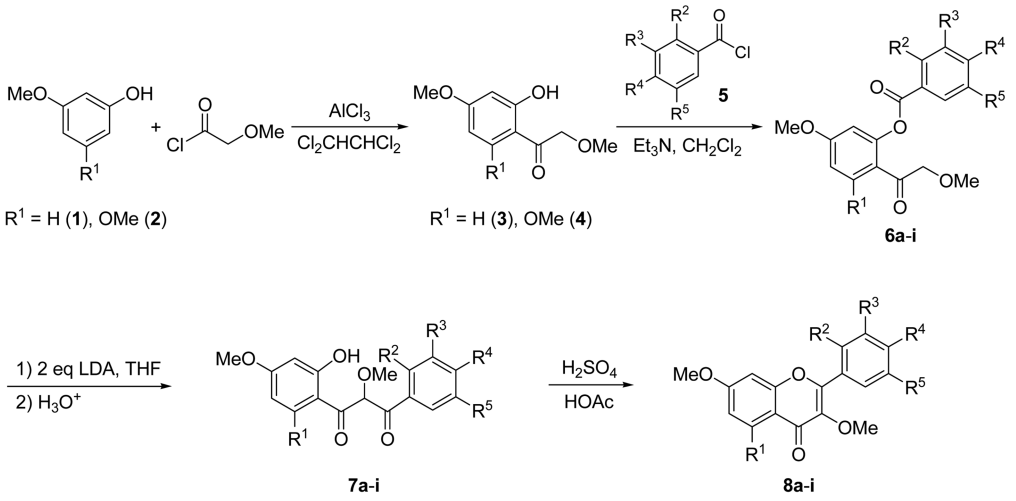
The initial synthesis of 3-methoxyflavones involves Allan-Robinson condensation,[7] in which 2'-hydroxy-2-methoxyacetophenones are heated with benzoic anhydrides and the metal salts of benzoic acids at 180-185 °C, followed by the hydrolysis of benzoates. However, the yields of this reaction are low to moderate. The use of amine solvents such as triethylamine and *N*-ethylpiperidine reduces the reaction temperature, allowing the reaction to be performed at the refluxing temperature of amines.[8] Furthermore, the reaction of 2'-hydroxy-2-methoxyacetophenones with benzoyl chlorides using a combination of potassium carbonate and a phase-transfer catalyst such as tetrabutylammonium bromide proceeds in refluxing toluene to afford 3-methoxyflavones.[9]

Alternatively, 2'-hydroxychalcones derived from 2'-hydroxyacetophenones and benzaldehydes in an alkaline medium undergo transformation to 3-methoxyflavones *via* single electron transfer processes utilizing 9,10-dicyanoanthracene, but yields are very low.[10] Similarly, two oxidation processes of 2'-hydroxychalcones with alkaline hydrogen peroxide[11] or flavones with dimethyldioxirane[12] afford 3-hydroxyflavones, which are then transformed into 3-methoxyflavones with dimethyl sulfate, but the former proceeds with overall low yields, and the latter requires multiple steps.

Although some methods for preparing 3-methoxyflavones have been reported, the scope of the problem has not yet been fully investigated. As part of our extending studies of flavones,[13] we describe an effective synthesis of 3-methoxyflavones *via* 1-(2-hydroxyphenyl)-2-methoxy-3-phenyl-1,3-propanediones as key intermediates under relatively mild conditions with high yields.

2'-Hydroxy-2,4'-dimethoxyacetophenone (**3**) and 2'-hydroxy-2,4',6'-trimethoxyacetophenone (**4**) were prepared from 3-methoxyphenol (**1**) and 3,5-dimethoxyphenol (**2**), respectively, with methoxyacetyl chloride in the presence of aluminum chloride in 1,1,2,2-tetrachloroethane (Scheme 1). The electrophilic aromatic substitution by 2-methoxyacetylium cation occurred exclusively in the 6-position of **1** and the 2-position of **2** and afforded **3** and **4** with 82% and 73% yields, respectively, after acidic workup and chromatographic separation. The ^{1}H NMR spectra of **3** and **4** showed OH signals at 12.41 and 13.71 ppm, respectively, which are characteristic of *ortho*-hydroxyl protons.

The direct preparation of 1-(2-hydroxy-4,6-dimethoxy-



Scheme 1

phenyl)-2-methoxy-3-phenyl-1,3-propanedione (**7c**) was initially attempted through the condensation of the dilithiated anion, generated from **4** and two equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF), with *N*-methoxy-*N*-methyl benzamide according to our previous report.[13a] However, the reaction did not proceed even after 24 h at room temperature. The corresponding reaction using other benzoylating reagents such as benzoyl chloride, benzoyl cyanide, or 2-pyridyl benzoate afforded **7c** with yields of only 10-15%. This may occur because the 2-methoxy substituent in **4** seems to hamper the formation of lithium enolate and the condensation with benzoylating reagents. Therefore, the preparation of **7** from **3** or **4** was carried out *via* 2-methoxyacetophenyl benzoates (**6**). The benzoylation of **3** and **4** with benzoyl chlorides (**5**) proceeded well in the presence of triethylamine in dichloromethane for 3-5 h between 0 °C and room temperature to produce **6a-i** in 89-97% yields.

The rearrangement of **6** to **7** was initially attempted by the treatment of 2-methoxyacetophenyl benzoate (**6c**) as a model compound with one equiv of LDA in THF, and the desired **7c** was obtained in 56% yield after 24 h at room temperature. However, the treatment of **6c** with two equiv of LDA in THF afforded **7c** within 0.5 h at temperatures between −15 °C and 0 °C in 78% yield. An additive equimolar amount of LDA seemed to shift the equilibrium to the more stabilized conjugate intermediate through the abstraction of the C_2 proton. The ^{1}H NMR spectra of **7c-i** showed C_2 proton signals at 5.78-6.13 ppm as singlets, indicating their primary existence as keto forms.

The cyclodehydration of **7c** was attempted using one equiv of sulfuric acid in various solvents such as HOAc, CH_3CN, EtOH, and THF. With these solvents, the desired 3,5,7-trimethoxyflavone (**8c**) was obtained with 94%, 92%, 90%, and 57% yields, respectively, after reacting at 80 °C for 0.5 h, 80 °C for 4 h, 78 °C for 48 h, and 65 °C for 48 h, respectively. Thus, HOAc was chosen as a suitable solvent for the cyclodehydration of **7**, and the same reaction conditions were adopted for the synthesis of other products. As shown in Table 1, various 3-methoxyflavones were synthesized in overall high yields from the starting compounds **1** or **2**. The reaction proceeded well both for the electron-withdrawing substituents such as the chloro group (**8a**, **8e**) and the electron-donating substituents such as the methyl (**8f**) and methoxy groups (**8b**, **8g-i**) of the 2-substituted phenyl ring. The *ortho*-substituted methoxy group (**8d**) hardly influenced the benzoylation, rearrangement, and cyclodehydration.

The selective demethylation of **8c** was briefly attempted using boron tribromide. The reaction of **8c** with one equiv of boron tribromide in dichloromethane for 4 h between 0 °C and room temperature afforded 3,7-dimethoxy-5-hydroxyflavone (**9**) in 78% yield (Scheme 2). The formation of a complex between two oxygen atoms of the 4-carbonyl/6-methoxy group in **8c** and a boron atom may be ascribed to the selective demethylation of the 6-methoxy group. However, the treatment of **8c** with four equiv of boron tribromide for 24 h at room temperature afforded 3,5,7-trihydroxyflavone (**10**, Galangin) in 83% yield.

In conclusion, this method provides an effective synthesis of 3-methoxyflavones from the readily avaliable starting materials **1** and **2**. This procedure has the advantages of high yields at each step as well as the versatility of the reaction under the relatively mild conditions.

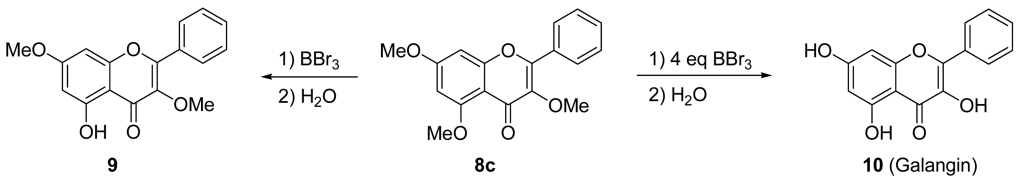
Table 1. Preparation of compounds **6**, **7**, and 3-methoxyflavones **8**

Entry	R^1	R^2	R^3	R^4	R^5	Isolated yields, %[a]		
						6[b]	**7**[c]	**8**[c]
a	H	H	Cl	H	H	97	85	89 (73)
b	H	H	H	OMe	H	94	87	91 (74)
c	OMe	H	H	H	H	94	78	94 (69)
d	OMe	OMe	H	H	H	97	70	85 (58)
e	OMe	H	H	Cl	H	90	86	82 (63)
f	OMe	H	H	Me	H	94	86	92 (74)
g	OMe	H	H	OMe	H	95	82	90 (70)
h	OMe	H	OMe	OMe	H	95	81	87 (67)
i	OMe	H	OMe	OMe	OMe	89	71	91 (58)

[a]The numbers in parentheses indicate the overall yields in three steps from **3** or **4**. [b]Chromatographic yields. [c]Recrystallized yields.

Experimental Section

Preparation of 2'-Hydroxy-2,4',6'-trimethoxyacetophenone 4 (General Procedure). To a solution of aluminum chloride (1.34 g, 10.0 mmol) in 1,1,2,2-tetrachloroethane (40 mL) was added 3,5-dimethoxyphenol (1.54 g, 10.0 mmol) and methoxyacetyl chloride (914 μL, 10.0 mmol) at room temperature. The resulting brownish solution was stirred overnight and then quenched with 1 N HCl (5 mL). After evaporation of the solvent, the mixture was poured into 1 N HCl (30 mL), extracted with dichloromethane (3 × 25 mL), and washed in a saturated $NaHCO_3$ solution (40 mL). The condensed residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane to give **4** (1.65 g, 73%). mp 101-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.71 (s, 1H), 6.08 (d, J = 2.4 Hz, 1H), 5.91 (d, J = 2.4 Hz, 1H), 4.60 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H); ^{13}C NMR



Scheme 2

(75 MHz, $CDCl_3$) δ 201.1, 167.5, 166.4, 162.6, 104.2, 93.8, 90.7, 78.0, 59.4, 55.6 (overlapped); FT-IR (KBr) 1630 (C=O) cm^{-1}; Ms *m/z* (%) 226 (M^+, 6), 181 (100).

Preparation of [2-(2-Methoxyacetyl)-3,5-dimethoxy]-phenyl 4-methoxybenzoate 6g (General Procedure). To a solution of **4** (905 mg, 4.0 mmol) in dichloromethane (16 mL) was added 4-methoxybenzoyl chloride (682 mg, 4.0 mmol) and triethylamine (558 μL, 4.0 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 5 h. The mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was purified by silica gel column chromatography using 50% EtOAc/*n*-hexane to give **6g** (1.37 g, 95%). mp 92-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.40 (d, *J* = 2.1 Hz, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 4.45 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 164.6, 164.0, 162.7, 159.3, 150.7, 132.5, 121.3, 114.2, 113.9, 100.5, 96.5, 78.3, 59.2, 56.0, 55.7, 55.5; FT-IR (KBr) 1727 (COO), 1691 (C=O) cm^{-1}; Ms *m/z* (%) 360 (M^+, 1), 135 (100).

Preparation of 1-(2-Hydroxy-4,6-dimethoxy)-2-methoxy-3-(4-methoxyphenyl)-1,3-propanedione 7g (General Procedure). To a solution of **6g** (1.08 g, 3.0 mmol) in THF (12 mL) was added LDA (1.8 M, 3.4 mL, 6.1 mmol) at −15 °C under an argon atmosphere. After being stirred for 1 h at temperatures between −15 °C and 0 °C, the mixture was quenched with 1 N HCl (5 mL). After the evaporation of THF, the mixture was poured into 0.5 N HCl (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was crystallized twice in 15% EtOAc/*n*-hexane to give **7g** (887 mg, 82%). mp 152-153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.67 (s, 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.93 (s, 1H), 5.79 (d, *J* = 2.3 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 191.0, 167.6, 166.6, 163.7, 161.5, 131.1, 128.3, 114.0, 105.0, 94.0, 90.9, 85.6, 59.0, 55.7, 55.5, 55.2; FT-IR (KBr) 1678 (C=O) cm^{-1}; Ms *m/z* (%) 360 (M^+, 1), 135 (100).

Preparation of 3,5,7,4'-Tetramethoxyflavone 8g (General Procedure). A solution of **7g** (721 mg, 2.0 mmol) and *conc* H_2SO_4 (107 μL, 2.0 mmol) in glacial acetic acid (15 mL) was heated at 80 °C for 0.5 h. After the evaporation of the glacial acetic acid, the mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was crystallized twice in 10% EtOAc/*n*-hexane to give **8g** (616 mg, 90%) as a colorless solid. mp 164-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 163.8, 161.1, 160.9, 158.8, 152.6, 141.0, 129.8, 123.2, 113.9, 109.4, 95.7, 92.3, 59.9, 56.4, 55.7, 55.4; FT-IR (KBr) 1627 (C=O) cm^{-1}; Ms *m/z* (%) 342 (M^+, 64), 341 (100).

3,7-Dimethoxy-3'-chloroflavone (8a): mp 163-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.98-8.09 (m, 2H), 7.41-7.50 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 6.93 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 164.2, 157.0, 153.3, 141.7, 134.6, 132.7, 130.5, 129.8, 128.1, 127.2, 126.6, 118.0, 114.7, 99.9, 60.2, 55.9; FT-IR (KBr) 1638 (C=O) cm^{-1}; Ms *m/z* (%) 318 (M^++2, 17), 317 (40), 316 (M^+, 50), 315 (100).

3,7,4'-Trimethoxyflavone (8b): mp 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.9 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 2H), 7.02 (d, *J* = 9.1 Hz, 2H), 6.96 (dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 164.3, 161.7, 157.3, 155.5, 141.0, 130.4, 127.5, 123.7, 118.5, 114.6, 114.3, 100.3, 60.3, 56.2, 55.8; FT-IR (KBr) 1636 (C=O) cm^{-1}; Ms *m/z* (%) 312 (M^+, 57), 311 (100).

3,5,7-Trimethoxyflavone (8c): mp 203-204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.09 (m, 2H), 7.46-7.52 (m, 3H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 6H, overlapped); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 164.0, 161.0, 158.9, 152.5, 141.8, 130.9, 130.3, 128.5, 128.1, 109.5, 95.8, 92.4, 60.1, 56.4, 55.8; FT-IR (KBr) 1635 (C=O) cm^{-1}; Ms *m/z* (%) 312 (M^+, 57), 311 (100).

3,5,7,2'-Tetramethoxyflavone (8d): mp 154-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.49 (m, 2H), 7.00-7.08 (m, 2H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 6H, overlapped), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 164.1, 161.5, 159.9, 157.7, 153.4, 142.6, 132.1, 131.1, 120.8, 120.5, 111.7, 110.4, 96.1, 92.9, 60.8, 56.8, 56.1 (overlapped); FT-IR (KBr) 1643 (C=O) cm^{-1}; Ms *m/z* (%) 342 (M^+, 47), 311 (100).

3,5,7-Trimethoxy-4'-chloroflavone (8e): mp 185-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 164.5, 161.4, 159.2, 151.7, 142.3, 136.7, 129.8, 129.7, 129.1, 109.9, 96.3, 92.7, 60.5, 56.8, 56.2; FT-IR (KBr) 1631 (C=O) cm^{-1}; Ms *m/z* (%) 348 (M^++2, 22), 347 (44), 346 (M^+, 63), 345 (100).

3,5,7-Trimethoxy-4'-methylflavone (8f): mp 140-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 164.3, 161.4, 160.8, 159.3, 153.3, 141.9, 141.1, 129.6, 128.4, 109.9, 96.1, 92.8, 60.4, 56.8, 56.1, 21.9; FT-IR (KBr) 1630 (C=O) cm^{-1}; Ms *m/z* (%) 326 (M^+, 58), 325 (100).

3,5,7,3',4'-Pentamethoxyflavone (8h): mp 154-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.72 (m, 2H), 6.98 (d, *J* = 9.2 Hz, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 3.97 (s, 9H, overlapped), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 164.3, 161.4, 159.2, 152.9, 151.2, 149.0, 141.6, 123.8, 122.0, 111.6, 111.1, 109.8, 96.1, 92.8, 60.3, 56.8, 56.4, 56.3, 56.2; FT-IR (KBr) 1625 (C=O) cm^{-1}; Ms *m/z* (%) 372 (M^+, 100).

3,5,7,3',4',5'-Hexamethoxyflavone (8i): mp 156-157 °C (lit.[7] 154-155 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 2H), 6.50 (d, *J* = 2.1 Hz, 1H), 6.36 (d, *J* = 2.1 Hz, 1H), 3.97

(s, 3H), 3.95 (s, 6H), 3.94 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 164.0, 161.0, 158.8, 153.0, 152.4, 141.6, 140.0, 126.0, 109.5, 105.8, 95.8, 92.4, 61.0, 60.1, 56.4, 56.3, 55.8; FT-IR (KBr) 1627 (C=O) cm^{-1}; Ms *m/z* (%) 402 (M^+, 89), 387 (100).

3,7-Dimethoxy-5-hydroxyflavone (9): mp 143-145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.04-8.09 (m, 2H), 7.48-7.56 (m, 3H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 3.87 (s, 6H, overlapped); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 165.6, 162.0, 156.9, 155.9, 139.7, 131.0, 130.5, 128.6, 128.4, 106.2, 98.0, 92.2, 60.4, 55.8; FT-IR (KBr) 3317 (OH), 1662 (C=O) cm^{-1}; Ms *m/z* (%) 298 (M^+, 78), 297 (100).

3,5,7-Trihydroxyflavone (10): mp 216-218 °C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 12.08 (s, 1H), 9.84 (s, 1H), 8.23-8.28 (m, 2H), 8.22 (s, 1H), 7.46-7.58 (m, 3H), 6.55 (d, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 176.0, 164.4, 161.5, 157.1, 145.2, 137.1, 131.2, 130.0, 128.5, 127.6, 103.4, 98.4, 93.7; FT-IR (KBr) 3315 (OH), 1656 (C=O) cm^{-1}; Ms *m/z* (%) 270 (M^+, 100).

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