Concise Synthesis of Biologically Interesting Mollugin and Its Analogues

Yong Rok Lee,* Xue Wang, Yun Mi Kim, Jae Jin Shim, Byung Nam Kim, and Do Hung Han

*School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea. *E-mail: yrlee@yu.ac.kr*
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The synthesis of naturally occurring mollugin and its analogues, 3,4-dihydromollugin, *cis*-3,4-dihydroxy-3,4-dihydromollugin, and *trans*-3,4-dihydroxy-3,4-dihydromollugin was achieved starting from 1,4-dihydroxynaphthalene-2-carboxylic acid. The key reaction is an electrocyclization for pyranyl ring formation in the presence of $PhB(OH)_2$/AcOH.

Key Words : Mollugin, 3,4-Dihydromollugin, Electrocyclization, $PhB(OH)_2$/AcOH

Introduction

Naturally occurring benzochromenes have a variety of interesting biological activities and physiological properties.[1] Among these, mollugin (**1**) and 3,4-dihydromollugin (**2**) were isolated from the medicinal plant *Rubia cordifolia* in China and India (Figure 1).[2] The dried roots and rhizomes of this plant are used officially as herbal medicine in the Chinese Pharmacopeia for treating arthritis, dysmenorrhea, hemostasis, and other diseases.[3] In India, this plant has been used for treatment of rheumatism, menstrual pain, and urinary disorders.[4] Mollugin (**1**) was also isolated from rhizome of *Galium mollugo*, which is found in many rubiaceous herbs in Europe and Africa.[5] Mollugin (**1**) and its analogue, 3,4-dihydromollugin (**2**), have biologically interesting properties such as antitumor,[2a] antimutagenic,[6] anti-leukemia,[7] anti-inflammatory,[8] and antiallergic activities.[8] In, particular, mollugin (**1**) has shown potent antiviral activity with an IC_{50} value of 2.0 μg/mL in human hepatoma Hep3B cells[9] and antiproliferative activity with an IC_{50} value of 3.5 μg/mL in human colon cancer cell line.[10] 3,4-Dihydromollugin (**2**) has also shown potent antiviral activity with an IC_{50} value of 2.0 μg/mL in human hepatoma Hep3B cells.[9] In addition, mollugin (**1**) has been shown to strongly inhibit the arachdonic acid-induced and collagen-induced platelet aggregation.[11] Recently, *cis*-3,4-dihydroxy-3,4-dihydromollugin (**3**) and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**4**) were isolated from *Pentas longiflora*, which is an important medicinal plant in Tropical East Africa.[12] "Nekilango" or "Segimbe" in Kenya and its root are used as a cure for tapeworm, itchy rashes, malaria, and pimples.[13] In Rwanda, this plant is also known as "Isagara", and is used as an ointment to treat scabies and the skin disease, pityriasis versicolar.[14] Their absolute configurations were not determined, but the specific optical rotation value ($[\alpha]_D^{21}$) of **3** was known as -12.9^o (c 0.35, $CHCl_3$). This wide range of biological activities and undefined absolute stereochemistry of these natural products **3** and **4** prompted studies for a rapid and efficient synthetic route to mollugin (**1**) and its analogues.

We recently reported that $Yb(OTf)_3$ or ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyl compounds or resorcinol with α,β-unsaturated aldehydes are a rapid route for synthesizing 2*H*-pyrans or benzopyrans.[15] These reactions involve an elctrocyclization for constructing 2*H*-pyrans or benzopyrans. These methodologies appear ideal for synthesizing natural products such as mollugin (**1**) and its analogues. We report the very efficient concise synthesis of mollugin (**1**) and 3,4-dihydromollugin (**2**) using an electrocyclization reaction as a key-step. We also report the first total synthesis of its analogues, *cis*-3,4-dihydroxy-3,4-dihydromollugin (**3**) and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**4**) as racemates from commercially available 1,4-dihydroxynaphthalene-2-carboxylic acid.

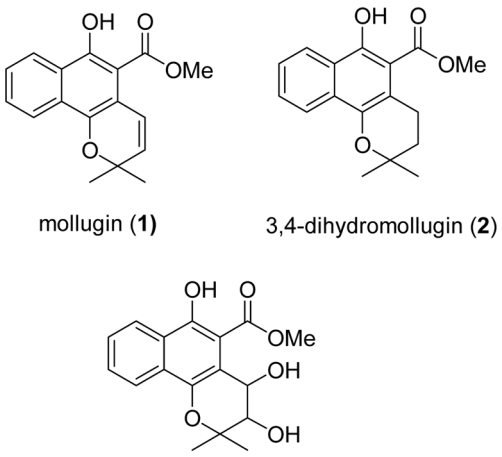
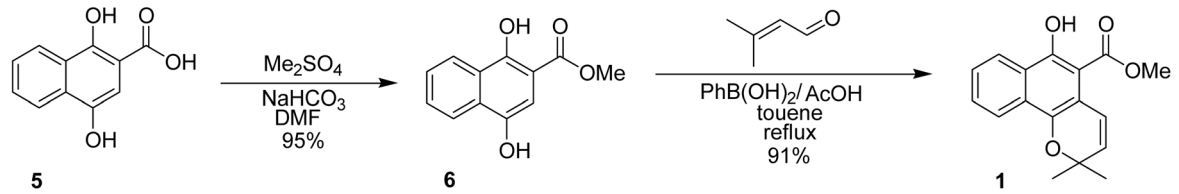


Figure 1

Results and Discussion

Several groups have reported the total synthesis of mollugin (**1**).[16-20] The first synthesis of mollugin was accomplished by Schildknecht[16] in 4 steps (10% overall yield) starting from the base-catalyzed condensation of diethyl-3,6-dihydroxyphthalate with diethyl succinate. Although this synthetic approach is only 4 steps, it has a low overall yield. The other synthesis of mollugin was also reported by Ho.[17] In this study, mollugin was accomplished in 3-steps (39% overall

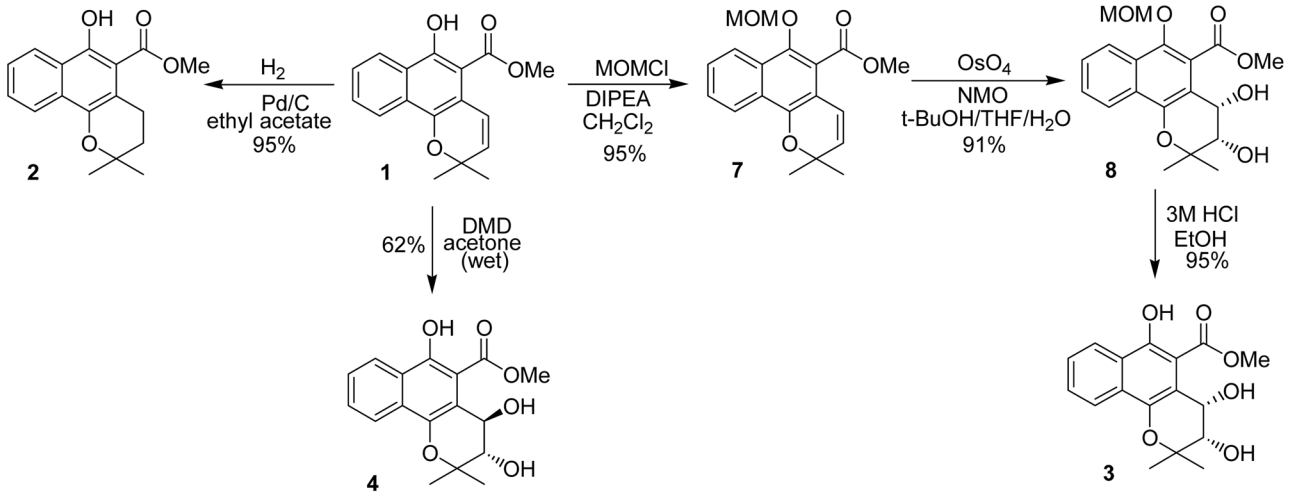


Scheme 1

yield) starting from 1,4-dihydroxynaphthalene-2-carboxylic acid. The key step in the synthetic strategy involves the boron trifluoride diethyl etherate-catalyzed electrophilic aromatic substitution of 2-methyl-3-buten-2-ol to methyl 1,4-dihydroxy-2-naphthoate. The other synthesis of compound **1** was accomplished by Trauner in 5 steps (26% overall yields) from carbomethoxy naphthoquinone using the Sakurai-type allyation, methylation, and subsequent Grubbs cross-methathesis.[18] The key reaction in this synthetic strategy is the pyranyl ring formation through the 6π-electrocyclization in the presence of triethylamine. More recently, mollugin was synthesized by De Kimpe in 9-steps (11%, overall yields) from 1,4-naphthoquinone.[19] In a related study, another concise and new pathway towards mollugin in 3-steps (61%, overall yields) was also reported by De Kimpe.[20] The key reaction is the boron trifluoride diethyl etherate-catalyzed prenylation of methyl 1,4-dihydroxy-2-naphthoate. Although several synthetic approaches to mollugin have been reported,[16-20] there is still a demand for a concise and general route. Above all, the syntheses of its analogues, **3** and **4** have not been reported.

This synthesis of mollugin (**1**) begins with commercially available compound **5** as shown in Scheme 1. The pyranyl ring on mollugin was introduced directly without making a detour using a formal [3+3] cycloaddition reaction of compound **6** and 3-methyl-2-butenal.[15] The esterification of compound **5** with dimethylsulfate in DMF instead of the hazardous diazomethane gave compound **6** in a 95% yield.[21] Treatment of compound **6** with 3-methyl-2-butenal in the presence of ethylenediamine diacetate (20 mol%) in refluxing toluene for 10 h gave the desired product compound **1** in 25% yield along with unidentified materials. Efforts to improve the yield of mollugin (**1**) in this reaction by varying the solvents were unsuccessful. An attempt to improve the yield through a reaction using pyridine or triethylamine in refluxing toluene was unsuccessful. Fortunately, the reaction between compound **6** and 3-methyl-2-butenal using $PhB(OH)_2$/AcOH in refluxing toluene for 7 h afforded compound **1** in 91% yield.[22] The spectral data of the synthetic material **1** are in agreement with those reported in the literature.[19]

The catalytic hydrogenation of compound **1** over Pd/C (20 psi) in ethyl acetate for 1 h gave 3,4-dihydromollugin **2** in 95% yield (Scheme 2). The spectroscopic data of compound **2** were the same with that reported in the literature.[2a] The direct catalytic dihydroxylation of compound **1** with osmium tetroxide using 2 equiv. of NMO in *t*-BuOH/THF/H_2O (10:3:1) at room temperature for 12 h gave the *cis*-diol **3** in low yield (10%) with unidentified products.[23] Attempts to improve the yield of cis-diol **3** in this reaction by varying the solvents and reagents were unsuccessful. Fortunately, after protection of the phenolic group of **1** with MOMCl, treatment of **7** with osmium tetroxide using 2 equiv. of NMO in *t*-BuOH/THF/H_2O (10:3:1) at room temperature for 12 h afforded product **8** in 91% yield. Deprotection of MOM ether of **8** with 3 M HCl in refluxing methanol for 30 mim gave *cis*-diol **3** in 95% yield. The spectral data of the synthetic material **3** are in agreement with those reported in the literature.[12] On the other hand, an attempt using 2 equiv of DMD in wet acetone at room temperature for 3 h led to the *trans*-diol **4** in 62% yield. The stereochemical assignment of the *cis* and *trans* products was easily defined by



Scheme 2

observing the coupling constants between the vicinal protons of H3-H4. The *J* value for H3-H4 vicinal coupling in the *cis*-3,4-dihydroxy-3,4-dihydromollugin (**3**) is 4.8 Hz, while it is 6.4 Hz for the *trans*-3,4-dihydroxy-3,4-dihydromollugin (**4**). The spectral data of the synthetic materials **3** and **4** were identical to those reported in the literature.[12]

In conclusion, a concise total synthesis of mollugin (**1**) was achieved in only 2-steps (86%, overall yield) from a commercially available material **5**. The reaction sequence was based upon a formal [3+3] cycloaddition of compound **6** to 3-methyl-2-butenal in the presence of $PhB(OH)_2$/AcOH. The synthesis of its analogues, 3,4-dihydromollugin (**2**), *cis*-3,4-dihydroxy-3,4-dihydromollugin (**3**), and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**4**), was also effectively achieved through catalytic hydrogenation, *cis*-dihydroylation or *trans*-hydroxylation, respectively. Further synthetic approaches of mollugin analogues and attempts to determine the undefined absolute stereochemistry using osmium-catalyzed asymmetric dihydroxylation are currently in progress.[24]

Experimental Section

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS and MS spectra were carried out by Korea Basic Science Institute.

Methyl 1,4-dihydroxy-2-naphthoate (6). To a solution of **5** (2.042 g, 10.0 mmol) in DMF (20 mL) was added sodium bicarbonate (0.840 g, 10.0 mmol) and dimethyl sulfate (1.324 g, 10.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was quenched by addition of 1 N HCl (30 mL) solution and the aqueous solution was extracted with ethyl acetate (40 mL × 3). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (3:1) afforded **6** (2.072 g, 95%) as a solid: mp 198-199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.45 (1H, s), 8.32 (1H, d, J = 8.4 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.60-7.55 (1H, m), 7.52-7.47 (1H, m), 7.09 (1H, s), 3.91 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 154.3, 144.7, 129.5, 128.3, 125.8, 125.2, 123.4, 122.1, 104.5, 104.4, 52.0; IR (KBr) 3387, 2953, 1647, 1599, 1516, 1478, 1441, 1356, 1298, 1256, 1150, 1100, 1073, 1026, 992, 847 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{10}O_4$: 218.0579. Found: 218.0581.

Mollugin (1). A solution of **6** (0.218 g, 1.0 mmol), 3-methyl-2-butenal (0.126 g, 1.5 mmol), phenylboronic acid (0.122 g, 1.0 mmol) and glacial AcOH (0.8 mL) in toluene (30 mL) was refluxed for 7 h in an apparatus connected to with a Dean-Stark trap. After cooling, the reaction mixture was quenched by addition of sodium bicarbonate (30 mL) solution and the aqueous solution was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (15:1) afforded **1** (0.258 g, 91%) as a solid: mp 129-130 °C (lit.[12] mp 129.5-131 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.15 (1H, s), 8.35 (1H, d, J = 8.4 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.63-7.57 (1H, m), 7.53-7.46 (1H, m), 7.09 (1H, d, 10.0 Hz), 5.65 (1H, d, J = 10.0 Hz), 4.0 (3H, s), 1.47 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.4, 141.6, 129.3, 129.1, 128.9, 126.3, 125.1, 124.0, 122.3, 121.9, 112.5, 102.2, 74.6, 52.3, 28.6; IR (KBr) 2972, 1651, 1582, 1451, 1362, 1343, 1248, 1194, 1163, 1132, 1098, 1013, 957, 889, 806, 770 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{16}O_4$: 284.1049. Found: 284.1051.

3,4-Dihydromollugin (2). To a solution of **1** (57 mg, 0.2 mmol) in ethyl acetate (10 mL) in a Parr bottle was added 10% Pd/C (20 mg). The bottle was shaken for 1 h at 20 psi of H_2. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (15:1) to give **2** (55 mg, 95%) as a solid: mp 98-99 °C (lit.[2c] mp 99-100 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.17 (1H, s), 8.34 (1H, d, J = 8.2 Hz), 8.16 (1H, d, J = 8.3 Hz), 7.60-7.55 (1H, m), 7.47-7.43 (1H, m), 3.95 (3H, s), 3.04 (2H, t, J = 6.8 Hz), 1.81 (2H, t, J = 6.8 Hz), 1.39 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 156.3, 141.6, 129.4, 129.0, 125.6, 124.3, 123.7, 121.5, 111.7, 105.3, 73.1, 52.0, 33.2, 26.5, 23.4; IR (KBr) 2975, 1649, 1589, 1445, 1383, 1339, 1236, 1123, 1098, 997, 804, 770 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{18}O_4$: 286.1205. Found: 286.1202.

6-Methoxymethoy-2,2,dimethyl-2*H*-benzo[*h*]chromene-5-carboxylic acid methyl ester (7). Methoxymethyl chloride (40 mg, 0.50 mmol) was added to a solution of **1** (100 mg, 0.35 mmol) and diisopropyl ethylamine (226 mg, 1.75 mmlo) in dry methylene chloride (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h, and then water (20 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 20 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (20:1) afforded **7** (109 mg, 95%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.17 (1H, m), 8.07-8.04 (1H, m), 7.52-7.46 (2H, m), 6.41 (1H, d, J = 9.9 Hz), 5.67 (1H, d, J = 9.9 Hz), 5.10 (2H, s), 3.96 (3H, s), 3.59 (3H, s), 1.49 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 145.3, 144.7, 130.2, 128.2, 126.9, 126.7, 122.9, 122.3, 121.2, 119.9, 112.3, 101.2, 76.5, 57.7, 52.4, 29.7, 27.8, 27.7; IR (neat) 2975, 1730, 1439, 1370, 1292, 1229, 1163, 1132, 1061, 1013, 961, 774 cm^{-1}; MS (EI) 328 (M^+), 313, 283, 252, 251, 238, 237, 224, 223, 209, 205, 195, 165, 152; HRMS m/z (M^+) calcd for $C_{19}H_{20}O_5$: 328.1311. Found: 328.1313.

3,4-Dihydroxy-6-methoxymethoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylic acid methyl eser (8). To a solution of osmium tetroxide (10 mg, 0.04

mmol) and *N*-methylmorpholine-*N*-oxide (82 mg, 0.7 mmol) in *t*-BuOH/THF/H_2O (10:3:1, 5 mL) was added **7** (115 mg, 0.35 mmol) and the reaction mixture was stirred at room temperature for 12 h. Saturated $NaHSO_3$ solution (30 mL) was added, the mixture was stirred for 1 h, and extracted with CH_2Cl_2. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) to give **8** (116 mg, 91%) as a solid: mp 40-41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23-8.21 (1H, m), 8.20-8.07 (1H, m), 7.59-7.51 (2H, m), 5.11 (2H, m), 4.96 (1H, d, J = 4.7 Hz), 3.97 (3H, s), 3.79 (1H, d, J = 4.7 Hz), 3.60 (3H, s), 1.54 (3H, s), 1.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 145.8, 145.0, 128.8, 127.7, 127.5, 127.1, 123.9, 123.2, 113.6, 101.5, 78.6, 71.3, 64.6, 58.1, 53.1, 24.2, 23.9, 21.4; IR (KBr) 3461, 2951, 1732, 1628, 1591, 1435, 1362, 1290, 1252, 1173, 1100, 1022, 961, 889, 802 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{22}O_7$: 362.1366. Found: 362.1364.

***cis*-3,4-Dihydroxy-3,4-dihydromollugin (3).** To a solution of **8** (50 mg, 0.14 mmol) in methanol (10 mL) was added 3 M HCl (5 drops) and the reaction mixture was heated at 50 °C for 30 mim. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution, water (30 mL), and dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) to give **3** (42 mg, 95%) as a solid: mp 110-111 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.7, 140.8, 129.6, 128.9, 127.0, 125.8, 123.9, 122.6, 112.8, 104.5, 77.3, 72.3, 52.9, 24.9, 22.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.31 (1H, s), 8.32 (1H, d, J = 8.2 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.62-7.51 (2H, m), 4.95 (1H, d, J = 4.8 Hz), 3.99 (3H, s), 3.92 (1H, d, J = 4.8 Hz), 1.49 (3H, s), 1.43 (3H, s); IR (KBr) 3443, 2953, 1660, 1593, 1446, 1381, 1238, 1154, 1102, 1017, 770 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{18}O_6$: 318.1103. Found: 318.1104.

***trans*-3,4-Dihydroxy-3,4-dihydromollugin (4).** To a solution of **1** (100 mg, 0.35 mmol) in acetone (10 mL) was added 7.7 mL of dimethyldioxirane (0.09 M in acetone) at room temperature and the reaction mixture was stirred at room temperature for 3 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel afforded **4** (69 mg, 62%) as a solid: mp 60-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.46 (1H, s), 8.34 (1H, d, J = 8.2 Hz), 8.17 (1H, d, J = 8.2 Hz), 7.65-7.52 (2H, m), 5.04 (1H, d, J = 6.4 Hz), 4.03 (3H, s), 3.77 (1H, d, J = 6.4 Hz), 1.49 (3H, s), 1.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 156.5, 141.1, 129.6, 129.1, 127.1, 125.3, 124.1, 122.6, 112.9, 104.0, 76.2, 70.0, 52.9, 25.6, 19.9; IR (KBr) 3426, 2955, 1659, 1593, 1447, 1381, 1155, 1100, 907, 806, 770 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{18}O_6$: 318.1103. Found: 318.1105.

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