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First Total Synthesis of (±)-Elatadihydrochalcone and Its Derivatives

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Pyranochalcones and pyranodihydrochalcones are an abundant subclass of the flavonoids and are widely found in nature.[1] Members of the pyranochalcones and pyranodihydrochalcones have been associated with a wide variety of biological activities such as antimutagenic, antimicrobial, anti-ulcer, antitumor, anti-leishmania, and antimalarial activities. Furthermore, some plants are used as traditional medicines in China and Europe.[2]

Recently, naturally occurring elatadihydrochalcone bearing pyranodihydrochalcone moiety was isolated from seedpods of *Tephrosia elata*, which was distributed in East Africa (Figure 1).[3] This plant is also used as traditional medicine to treat infectious diseases.[4] The crude extract from the seedpods of this plant showed anti-plasmodia activity with IC_{50} values of 2.8 ± 0.3 and 5.5 ± 0.3 μg/mL against chloroquine-sensitive Sierra Leone I and chloroquine-resistant Indochina I strains, respectively.[3] It is the first report on the occurrence of a β-hydroxydihydrochalcone in the genus *Tephrosia* species. The potent anti-plasmodia activity has stimulated interest in the synthesis of naturally occurring elatadihydrochalcone.[3]

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes.[5] This methodology provided a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl ring.[5] Our efforts in developing these methodologies led to the synthesis of biologically interesting natural products bearing pyranochalcone moiety.[6] As an expansion and ongoing study of our previous work, we report herein the first total synthesis of elatadihydrochalcone (**1**) as a racemate, along with its unnatural derivatives.

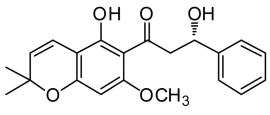
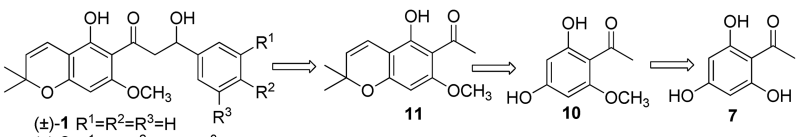


Figure 1. Naturally occurring elatadihydrochalcone (**1**) isolated from *Tephrosia elata*.

Results and Discussion

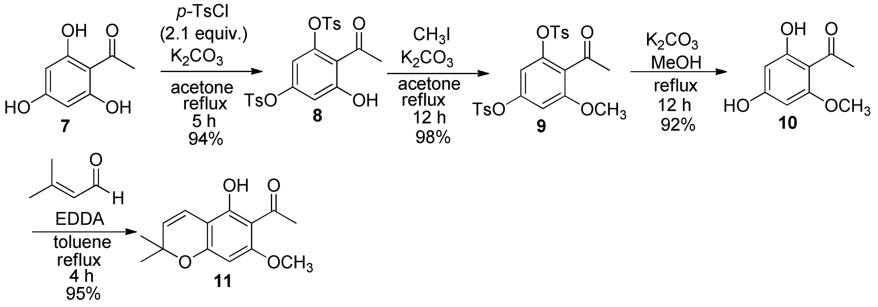
The retrosynthetic approaches for synthesizing (±)-elatadihydrochalcone (**1**) and its unnatural derivatives (±)-**2-6** were analyzed as shown in Scheme 1. (±)-Elatadihydrochalcone (**1**) and its derivatives (±)-**2-6** could be prepared by base-catalyzed aldol reactions of **11** to the corresponding aryl aldehydes. The key intermediate benzopyran **11** could be also generated from **10** through benzopyran formation reaction. The compound **10** could be derived from commercially available 2,4,6-trihydroxyacetophenone (**7**) by selective *ortho*-methylation.

The total synthesis of (±)-elatadihydrochalcone (**1**) and its derivatives (±)-**2-6** was next attempted starting from 2,4,6-trihydroxyacetophenone (**7**) (Scheme 2). Conversion of **7** to **10** was first investigated through a literature survey. Previously reported *ortho*-methylation of **7** was achieved by using excess of (trimethylsilyl)diazomethane ($TMSCHN_2$)[7] or dimethyl sulfate in the presence of potassium carbonate.[8] Under these conditions, the desired product **10** was only obtained in 3-10% yield, together with the other products. As another synthetic route, Tsukayama prepared compound **10** in 3 steps starting from **7** by selective dibenzylation followed by *O*-methylation and subsequent dedibenzylation.[9] We previously used this method for the synthesis of **10**.[10] Although the overall yield is satisfactory (3 steps, 60%), more facile and general synthetic routes to **10** are



(±)-**1** $R^1=R^2=R^3=H$
(±)-**2** $R^1=H$, $R^2=CH_3$, $R^3=H$
(±)-**3** $R^1=OCH_3$, $R^2=R^3=H$
(±)-**4** $R^1=H$, $R^2=OCH_3$, $R^3=H$
(±)-**5** $R^1=R^2=OCH_3$, $R^3=H$
(±)-**6** $R^1=OCH_3$, $R^2=H$, $R^3=OCH_3$

Scheme 1. Retrosynthetic analysis for a racemic elatadidydrochalcone (**1**) and its derivatives.



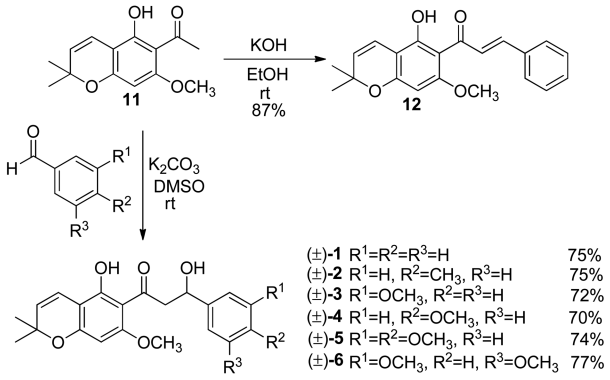
Scheme 2

needed. In order to efficiently synthesize **10** with high yields (3 steps, 85%), we modified Tsukayama's method with *p*-TsCl. As shown in Scheme 2, selective diprotection of **7** with 2.1 equivalents of *p*-TsCl in the presence of K_2CO_3 afforded **8** in 94% yield, which reacted with methyl iodide to give **9** in 98% yield. Deprotection of ditosyl groups on **9** in the presence of K_2CO_3 in refluxing methanol gave **10** in 92% yield. Treatment of **10** with 3-methyl-2-butenal in the presence of 20 mol % of ethylenediamine diacetate in refluxing toluene for 4 h provided isoevodionol (**11**) in 95% yield, which was isolated from *Evodia lepta*.[11]

To complete the total synthesis of (±)-elatadihydrochalcone (**1**) and its derivatives (±)-**2-6**, an aldol reaction was next attempted (Scheme 3). A reaction of compound **11** with benzaldehyde using KOH in ethanol at room temperature for 24 h provided compound **12** with chalcone moiety in 87% yield. Although several successful aldol reactions of acetophenone with aryl aldehydes in the presence of strong base such as NaOH, $Ca(OH)_2$, or KOH to give β-hydroxydihydrochalcones have been reported in moderate yield,[12] but reactions of **11** with benzaldehyde in the presence of NaOH or KOH in ethanol or water to give β-hydroxydihydrochalcones were unsuccessful. In 2004, Wang reported that reactions of acetophenone with aryl aldehydes in the presence of Na_2CO_3 (0.25 equiv.) in water gave β-hydroxy ketones in very high yields.[13] Using this reaction condition, we tried aldol reaction of **11** with benzaldehyde. Treatment of **11** with benzaldehyde in the presence of Na_2CO_3 (0.5 equiv.) in water at room temperature for 8 h gave the desired product (±)-**1** in 65% yield, together a trace of chalcone. Instead of Na_2CO_3, treatment of **11** with benzaldehyde in the presence of K_2CO_3 (0.5 equiv.) in DMSO at room temperature for 8 h afforded (±)-**1** in increased yield (75%), together with a trace of chalcone. The spectral data of synthetic material (±)-**1** were in agreement with those of the natural product reported in the literature.[3]

Similarly, reaction of **11** with the corresponding aryl aldehydes in the presence of K_2CO_3 (0.5 equiv.) in DMSO at room temperature for 8-15 h provided β-hydroxydihydrochalcones (±)-**2-6** in 75, 72, 70, 74 and 77% yield, respectively.

In conclusion, a concise synthetic route for biologically interesting elatadihydrochalcone (**1**) and its unnatural derivatives as racemates starting from commercially available 2,4,6-trihydroxyacetopheneone in 5 steps was developed.



Scheme 3

The key strategies involved benzopyran formation by ethylenediamine diacetate-catalyzed reactions and weak base-catalyzed aldol reactions to give β-hydroxydihydrochalcones. Further synthetic approaches for naturally occurring elatadihydrochalcone and its enantiomer are currently underway.

Experimental

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ using δ 77.0 ppm as the solvent. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS were carried out at the Korea Basic Science Institute.

4-Acetyl-5-hydroxy-1,3-phenylene bis(4-methylbenzenesulfonate) (8). To a solution of 2,4,6-trihydroxyacetophenone (**7**) (0.840 g, 5.0 mmol) in dry acetone (30 mL) was added K_2CO_3 (3.455 g, 25.0 mmol) and *p*-toluenesulfonyl chloride (2.002 g, 10.5 mmol). The reaction mixture was refluxed under N_2 for 8 h. Evaporation of acetone, addition of water (20 mL), extraction with EtOAc (3 × 30 mL), washing with brine (20 mL), and removal of the solvent followed by flash column chromatography on silica gel using hexane/EtOAc (10:1) gave **8** (2.226 g, 94%) as a solid: mp 69-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.73 (brs, OH), 7.70 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.36

(d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.42 (d, J = 2.4 Hz, 1H), 6.32 (d, J = 2.4 Hz, 1H), 2.65 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 164.4, 153.5, 150.6, 146.6, 146.2, 131.7, 131.5, 130.3, 130.1, 128.5, 128.3, 113.8, 110.2, 107.6, 32.5, 21.8, 21.7; IR (KBr) 3070, 2934, 1628, 1611, 1377, 1253, 1188, 1114, 1045, 801, 742 cm^{-1}; HRMS m/z [M$^+$] calcd for $C_{22}H_{20}O_8S_2$: 476.0600. Found: 476.0602.

4-Acetyl-5-methoxy-1,3-phenylene bis(4-methylbenzenesulfonate) (9). To a solution of **8** (2.0 g, 4.2 mmol) in dry acetone (30 mL) was added K_2CO_3 (1.452 g, 10.5 mmol) and methyl iodide (0.894 g, 6.3 mmol). The reaction mixture was refluxed under N_2 for 4 h. Evaporation of acetone, addition of water (20 mL), extraction with EtOAc (3 × 30 mL), washing with brine (20 mL), and removal of the solvent followed by flash column chromatography on silica gel using hexane/EtOAc (8:1) gave **9** (2.015 g, 98%) as a solid: mp 85-86 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.34-7.29 (m, 4H), 6.51 (d, J = 1.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.66 (s, 3H), 2.41 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 157.3, 150.3, 145.9, 145.8, 145.5, 131.4, 131.2, 129.8, 129.7, 128.2, 128.1, 123.8, 108.9, 104.5, 56.0, 31.5, 21.4, 21.4; IR (KBr) 3095, 3060, 2954, 1709, 1599, 1449, 1380, 1193, 1086, 994, 798, 675 cm^{-1}; HRMS m/z [M$^+$] calcd for $C_{23}H_{22}O_8S_2$: 490.0756. Found: 490.0755.

2,4-Dihydroxy-6-methoxyacetophenone (10).[7-9] To a solution of **9** (1.80 g, 3.7 mmol) in methanol (30 mL) was added K_2CO_3 (1.523 g, 11.0 mmol). The reaction mixture was refluxed for 4 h. Evaporation of methanol, addition of water (20 mL) and 1 N HCl (10 mL), extraction with EtOAc (3 × 30 mL), washing with brine (20 mL), and removal of the solvent followed by flash column chromatography on silica gel using hexane/EtOAc (4:1) gave **10** (0.617 g, 92%) as a solid: mp 203-204 ºC; ^{1}H NMR (300 MHz, acetone-d_6) δ 13.92 (s, 1H), 7.38 (brs, 1H), 6.03 (d, J = 2.0 Hz, 1H), 5.95 (d, J = 2.0 Hz, 1H), 3.90 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 203.4, 168.2, 165.7, 164.7, 105.9, 96.6, 91.7, 56.1, 33.0; IR (KBr) 3136, 1638, 1586, 1523, 1468, 1439, 1365, 1282, 1256, 1201, 1166, 1074, 959, 810 cm^{-1}.

Isoevodionol (11). To a solution of **10** (0.182 g, 1.0 mmol) and 3-methyl-2-butenal (0.168 g, 2.0 mmol) in toluene (10 mL) was added ethylenediamine diacetate (0.018 g, 0.1 mmol) at room temperature. The reaction mixture was refluxed for 10 h and then cooled to room temperature. H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). Evaporation of the solvent and purification by column chromatography on silica gel hexane/EtOAc (7:1) gave **11** (0.236 g, 95%) as a solid; mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.28 (s, 1H), 6.62 (d, J = 10.0 Hz, 1H), 5.85 (s, 1H), 5.38 (d, J = 10.0 Hz, 1H), 3.81 (s, 3 H), 2.56 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 162.8, 161.7, 160.0, 125.2, 115.9, 105.5, 102.5, 90.5, 78.0, 55.4, 32.9, 28.2; IR (KBr) 2924, 2855, 1620, 1464, 1362, 1269, 1206, 1159, 1124, 891, 831, 731 cm^{-1}; HRMS: m/z [M$^+$] calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1047.

General Procedure for the Synthesis of β-Hydroxydihydrochalcones 1-6. To a solution of **11** (100 mg, 0.40 mmol) in DMSO (5 mL) was added anhydrous K_2CO_3 (28 mg, 0.20 mmol) and aryl aldehydes (0.48 mmol). The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC for 8-15 h. After the reaction was completed, addition of water (10 mL) and 1 N HCl (2 mL), extraction with EtOAc (3 × 20 mL), washing with brine (20 mL), and removal of the solvent followed by flash column chromatography on silica gel using hexane/EtOAc (4:1) gave the corresponding β-hydroxydihydrochalcones **1-6**.

(±)-Elatadihydrochalcone (1): Yield 75%, a solid, mp 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.93 (brs, OH), 7.36-7.17 (m, 5H), 6.58 (d, J = 9.9 Hz, 1H), 5.79 (s, 1H), 5.38 (d, J = 9.9 Hz, 1H), 5.19 (dd, J = 9.0, 3.0 Hz, 1H), 3.69 (s, 3H), 3.42 (dd, J = 18.3, 3.0 Hz, 1H) 3.27 (dd, J = 18.3, 9.0 Hz, 1H), 1.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 162.9, 161.8, 160.6, 143.3, 128.4, 127.3, 125.8, 125.4, 115.8, 105.5, 102.7, 91.3, 78.3, 70.1, 55.6, 52.7, 28.3; IR (KBr) 3566, 2973, 2935, 1608, 1383, 1281, 1198, 1136, 873, 699 cm^{-1}; HRMS m/z [M$^+$] calcd for $C_{21}H_{22}O_5$: 354.1467. Found: 354.1469.

(±)-3-Hydroxy-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-*p*-tolylpropan-1-one (2): Yield 75%, an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.43 (brs, OH), 7.33 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 6.56 (d, J = 10.2 Hz, 1H), 6.03 (s, 1H), 5.43 (d, J = 10.2 Hz, 1H), 5.36 (dd, J = 12.9, 2.7 Hz, 1H), 3.87 (s, 3H), 2.97 (dd, J = 16.5, 12.9 Hz, 1H), 2.77 (dd, J = 16.5, 2.7 Hz, 1H), 2.36 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 162.0, 159.9, 158.8, 138.3, 135.9, 129.3, 126.2, 125.9, 115.9, 105.6, 102.8, 93.6, 78.8, 78.0, 56.1, 45.5, 28.4, 28.1, 21.2; IR (neat) 3456, 3444, 3053, 2973 , 2931, 1674, 1634, 1604, 1571, 1466, 1348, 1202, 1150, 1119, 911, 817, 734 cm^{-1}; HRMS m/z [M-H_2O]$^+$ calcd for $C_{22}H_{22}O_4$: 350.1518. Found: 350.1515.

(±)-3-Hydroxy-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(3-methoxyphenyl)propan-1-one (3): Yield 72%, an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.76 (brs, OH), 7.31 (d, J = 7.8 Hz, 1H), 7.01-6.98 (m, 2H), 6.89-6.86 (m, 1H), 6.58 (d, J = 9.9 Hz, 1H), 6.03 (s, 1H), 5.44 (d, J = 9.9, Hz, 1H), 5.36 (dd, J = 12.9, 3.0 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.95 (dd, J = 16.5, 12.9 Hz, 1H), 2.78 (dd, J = 16.5, 3.0 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 162.0, 159.9, 159.7, 158.7, 140.5, 129.8, 126.3, 118.1, 115.9, 113.6, 111.6, 105.5, 102.9, 93.7, 78.7, 78.0, 56.2, 55.3, 45.6, 28.4, 28.1; IR (Neat) 3442, 3054, 2970, 2936, 1673, 1635, 1604, 1463, 1348, 1266, 1201, 1151, 1118, 1047, 884, 779, 735 cm^{-1}; HRMS m/z [M-H_2O]$^+$ calcd for $C_{22}H_{22}O_5$: 366.1467. Found: 366.1465.

(±)-3-Hydroxy-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)propan-1-one (4): Yield 70%, an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.98 (brs, OH), 7.36 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 10.2 Hz, 1H), 6.03 (s, 1H), 5.44 (d, J = 10.2 Hz, 1H), 5.34 (dd, J = 12.9, 3.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H),

2.98 (dd, J = 16.5, 12.9 Hz, 1H), 2.76 (dd, J = 16.5, 3.0 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 162.1, 160.0, 159.7, 158.9, 130.9, 127.5, 126.2, 116.0, 114.0, 105.6, 102.8, 93.7, 78.7, 78.0, 56.2, 55.3, 45.4, 28.5, 28.1; IR (neat) 3583, 3467, 3055, 2970, 2933, 1674, 1604, 1570, 1513, 1464, 1347, 1202, 1150, 1118, 1034, 884, 830, 735 cm^{-1}; HRMS *m/z* [M-H_2O]$^+$ calcd for $C_{22}H_{22}O_5$: 366.1467. Found: 366.1465.

(±)-3-(3,4-Dimethoxyphenyl)-3-hydroxy-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (5): Yield 74%, an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.96 (brs, OH), 6.97 (s, 1H), 6.90 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 9.9 Hz, 1H), 5.84 (s, 1H), 5.43 (d, J = 9.9 Hz, 1H), 5.19 (dd, J = 8.7, 3.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.40 (dd, J = 18.3, 3.0 Hz, 1H), 3.30 (dd, J = 18.3, 8.7 Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 162.9, 161.8, 160.6, 148.9, 148.2, 136.0, 125.5, 117.9, 115.7, 110.9, 109.0, 105.5, 102.7, 91.3, 78.3, 69.9, 55.8, 55.7, 55.6, 52.8, 28.3; IR (neat) 3513, 2959, 1612, 1512, 1443, 1422, 1261, 1205, 1140, 1033, 876, 817, 737 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{23}H_{26}O_7$: 414.1679. Found: 414.1681.

(±)-3-(3,5-Dimethoxyphenyl)-3-hydroxy-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (6): Yield 77%, a solid, mp 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.96 (brs, OH), 6.62 (d, J = 9.9 Hz, 1H), 6.56 (d, J = 2.1 Hz, 2H), 6.35 (d, J = 2.1 Hz, 1H), 5.84 (s, 1H), 5.43 (d, J = 9.9 Hz, 1H), 5.18 (dd, J = 9.0, 3.0 Hz, 1H), 3.77 (s, 6H), 3.76 (s, 3H), 3.40 (dd, J = 18.0, 3.0 Hz, 1H), 3.28 (dd, J = 18.0, 9.0 Hz, 1H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 162.9, 161.8, 160.7, 160.5, 145.9, 125.4, 115.7, 105.4, 103.7, 102.7, 99.2, 91.2, 78.2, 70.1, 55.6, 55.2, 52.7, 28.3; IR (neat) 3522, 2970, 2939, 2839, 1610, 1461, 1424, 1285, 1150, 1060, 884, 841, 735 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{23}H_{26}O_7$: 414.1679. Found: 414.1679.

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