Regular Article

Syntheses and Anti-inflammatory Activity of Natural 1,3-Diarylpropenes

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First syntheses of five natural 1,3-diarylpropenes (cinnamylphenols) 2–4, 7, and 8 along with synthesis of two other natural 1,3-diarylpropenes 1 and 5 and *E*-isomer of mucronulastyrene (6) were achieved by Friedel–Crafts alkylation as a key step. Subsequently, their anti-inflammatory effects were also investigated in lipopolysaccharide (LPS)-induced RAW264.7 macrophages. The compounds exhibited significant inhibition of inflammatory mediated nitric oxide (NO) production with no cytotoxicity except compound 8 (dalberatin B) at 10 μM concentration and IC_{50} values were found in the range from 4.05 to 16.76 μM.

Key words 1,3-diarylpropene; Friedel–Crafts alkylation; inflammation; nitric oxide (NO)

Flavonoids are naturally occurring low molecular weight phytochemicals possessing many biological properties useful to human health.[1] 1,3-Diarylpropenes (cinnamylphenols) acquire $C_6+C_3+C_6$ chemical subunit and belong to the flavonoid family, are distinguished class of naturally occurring bioactive compounds. These small templates have been shown to exhibit potential pharmacological properties including anticancer,[2–4] anti-oxidant,[5] anti-inflammatory,[6] anti-platelet,[7] and anti-malarial.[8] They can also serve as key intermediates in the synthesis of natural products and the evolution of biologically active compounds.[9–11] In recent years, there has been increasing interest around the globe in the synthesis of these privileged scaffolds.[12,13]

1,3-Diarylpropenes under the current study are depicted in Fig. 1. Isomucronustyrene (**1**) was isolated from the heartwood of *Dalbergia odorifera* (Leguminosae),[6] dalparvinene (**2**) isolated from *Dalbergia parviflora*[14] and dalberatins A–D (**7**, **8**, **3**, **4**) were also from the *Dalbergia* species.[15] Mucronustyrene (**5**) was isolated from the wood of *Machaerium mucronulatum* (Fabaceae) whereas compound **6** is synthetic *E*-isomer of mucronulastyrene.[16]

As part of our continuous interest in the synthesis of bioactive natural products and their analogues,[17–19] herein we describe an efficient synthesis and anti-inflammatory activity evaluation of natural 1,3-diarylpropenes **1**–**5**, **7**, and **8** along with a synthetic compound **6**.

Results and Discussion

Chemistry Syntheses of 1,3-diarylpropenes **1**–**8** were illustrated in Charts 1 and 2. Chart 1 deals with the synthesis of 1,3-diarylpropenes originated from 2,6-dimethoxyphenol (syringol) (**20**) (B ring) *i.e.*, compounds **1**–**4** whereas Chart 2 deals with the synthesis of 1,3-diarylpropenes generated from 2,3-dimethoxyphenol (**36**) *i.e.*, **5**–**8**. Synthesis of compounds **1**–**4** began with the protection of 4-hydroxybenzaldehyde (**9**), 2-methoxy 3-hydoxybenzaldehyde (**10**), and 2-hydroxy 5-methoxybenzaldehyde (**11**). Treatment of **9**–**11** with chloromethyl ethyl ether (EOM-Cl) using potassium carbonate (K_2CO_3)/tetrabutylammonium iodide (TBAI) system in acetone produced the ethoxymethyl (EOM)-protected aldehydes **12**–**14**, respectively.

Aldehydes **12**–**14** and benzaldehyde (**15**) were then subjected to Grignard reaction with vinylmagnesium bromide and the corresponding allyl alcohols **16**–**19** were obtained in high yields, respectively. Compound **20** was protected with acetyl group (electron withdrawing group) in order to avoid Friedel–Crafts (FC) alkylation at 4-position. Next, we considered the FC alkylation between compounds **17** and **21** as model reaction.

Treatment of 1.0 eq. of **17** with 2.0 eq. of **21** using 0.1 eq. of various metal triflates (Table 1) as catalysts and 4 Å molecular sieves (MS) as water scavengers to get the product **24** and the best results (60% yield) were obtained with copper(II) trifluoromethane sulfonate ($Cu(OTf)_2$). Lowering the catalyst loading led to the decrease of the yield. Next, the reaction was carried out in methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), tetrahydrofuran (THF) and diethyl ether solvents using 0.1 eq. of $Cu(OTf)_2$ as a catalyst and better yields were obtained in CH_2Cl_2. Hence, we utilized $Cu(OTf)_2$ as a catalyst with 0.1 eq. loading and CH_2Cl_2 as solvent for the remaining 1,3-diarylpropenes preparation. The allyl alcohols **19**, **17**, and **18** were underwent FC alkylation with **21** and the corresponding products **22**, **23**, and **25** were obtained in moderate yields. Deacetylation of **22**–**25** offered mucronustyrene (**1**) and compounds **26**–**28** in high yields, respectively. Finally, EOM-group deprotection of **26**–**28** using Dowex® resin in anhyd. MeOH led to the isolation of natural 1,3-diarylpropenes **2**–**4**, respectively.

Synthesis of 1,3-diarylpropenes **5**–**8** were commenced with the protection of 2-hydroxybenzaldehyde (**29**), **10**, and **11** with benzyl bromide and resulting benzyl protected aldehydes **30**–**32** were subjected to Grignard reaction with vinylmagnesim bromide to yield the allyl alcohols **33**–**35**, respectively (Chart 2). 2,3-Dimethoxyphenol (**36**) was protected with benzyl (–Bn) group.

Next, FC alkylation of **37** with **19** and **33**–**35** using $Cu(OTf)_2$/4 Å MS system in anhyd. CH_2Cl_2 produced the benzyl-protected 1,3-diarylpropenes **38**–**41** as major products, respectively. Due to the bulkiness of the benzyl group, FC alkylation favored at *ortho* to –OMe group rather than *ortho* to –OBn. We tried the FC alkylation with *tert*-butyldimethylsilyl (TBS)- and trityl-protected components, but, lower yields

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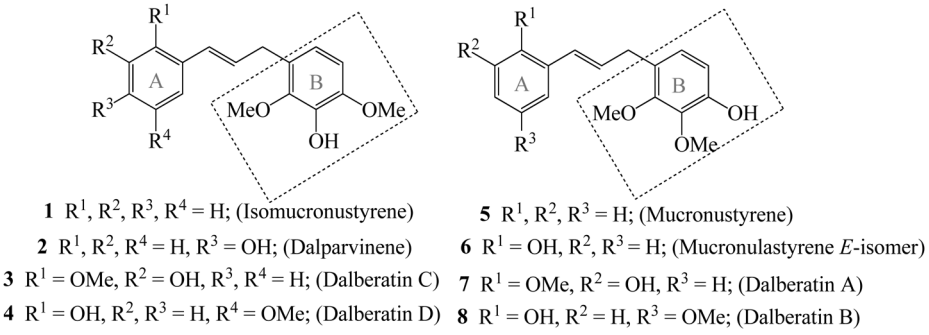
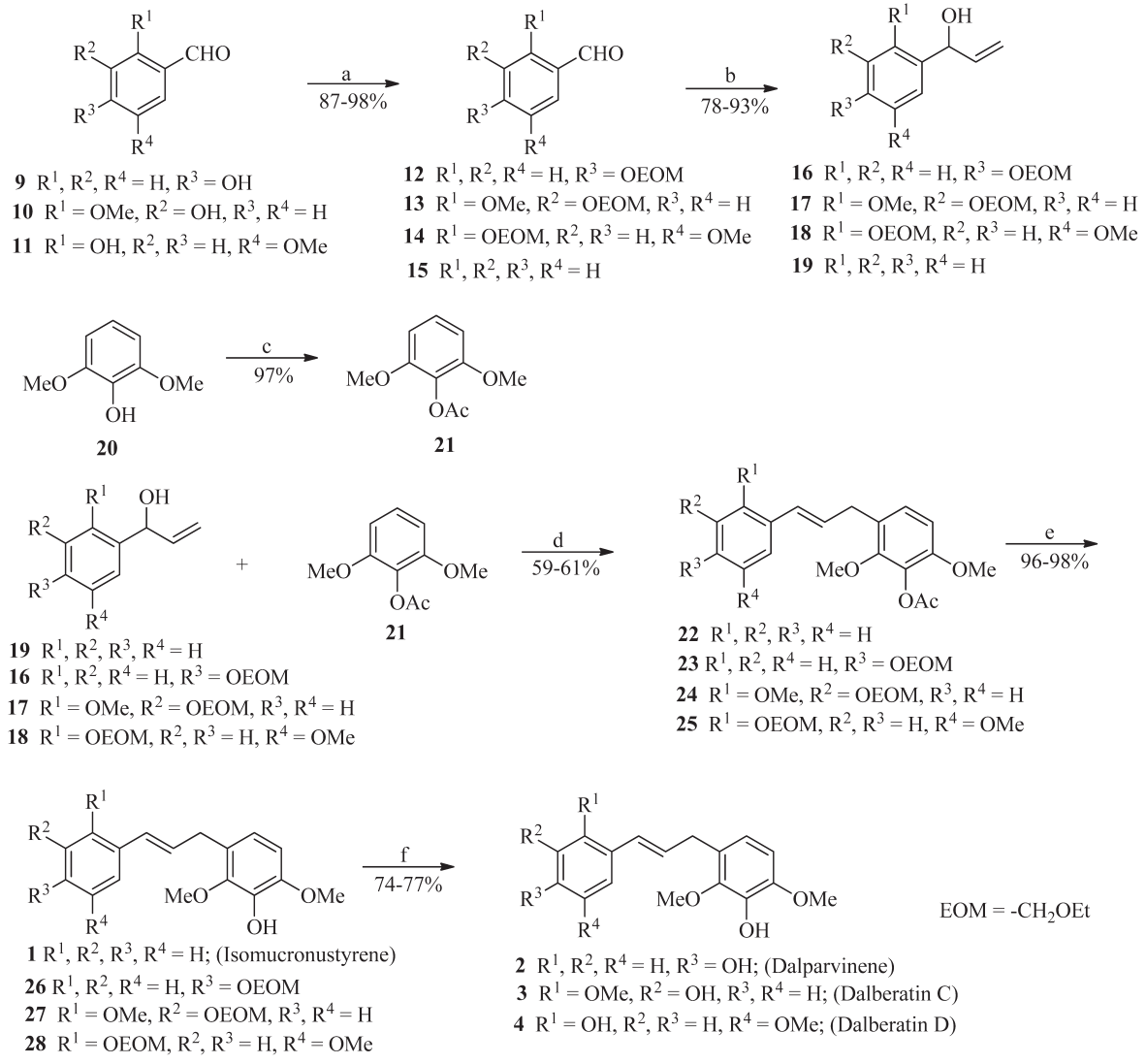


Fig. 1. Structures of 1,3-Diarylpropenes (**1**–**8**)

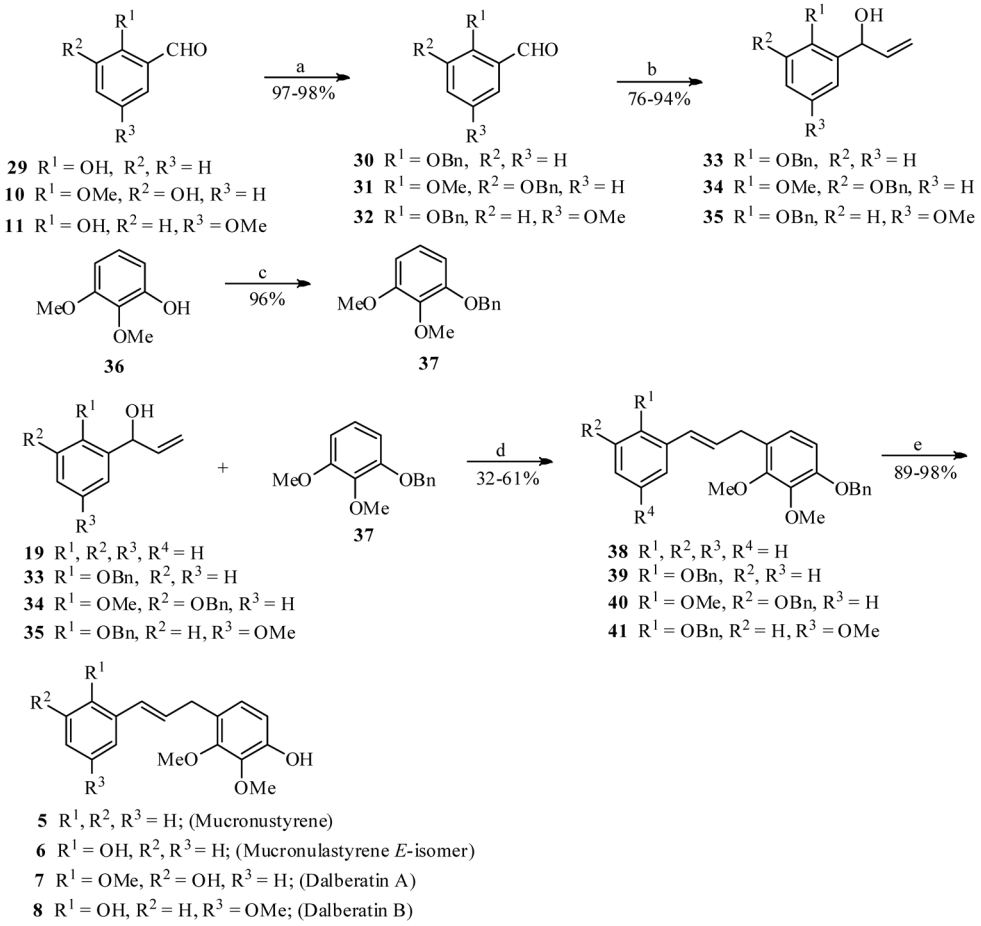


Reagents and conditions: a) chloromethyl ethyl ether (EOM–Cl), TBAI, K_2CO_3, anhyd. acetone, rt 4 h. b) 1.0 M vinylMgBr solution, anhyd. THF, 0°C–rt 2 h. c) acetic anhydride, 4-(dimethylamino)pyridine (DMAP), triethylamine (Et_3N), anhyd. CH_2Cl_2, rt overnight. d) $Cu(OTf)_2$, 4 Å MS, anhyd. CH_2Cl_2, 0°C, 5–6 h. e) aq. K_2CO_3, MeOH, rt 2 h, f) Dowex® resin, anhyd. MeOH, 40°C, 48 h.

Chart 1. Synthesis of Diarylpropenes **1**–**4**

were obtained than benzyl-protection FC alkylation. The lower yields with TBS- and trityl-protected components were due to their partial deprotection during the reaction. Finally, benzyl-deprotection of **39**–**41** was carried out by treatment with 1.0 M boron trichloride (BCl_3) solution at −40°C and the products **5**–**8** were obtained in high yields, respectively. All the target compounds **1**–**8** were settled from their NMR (^{1}H- and ^{13}C-) and MS data.

Anti-inflammatory Activity Inflammation is part of the body's immune response and it is a protective attempt of the host to remove the injurious stimuli including damaged cells, irritants or pathogens that leads to the restoration of the nor-



29 R^1 = OH, R^2, R^3 = H
10 R^1 = OMe, R^2 = OH, R^3 = H
11 R^1 = OH, R^2 = H, R^3 = OMe

30 R^1 = OBn, R^2, R^3 = H
31 R^1 = OMe, R^2 = OBn, R^3 = H
32 R^1 = OBn, R^2 = H, R^3 = OMe

33 R^1 = OBn, R^2, R^3 = H
34 R^1 = OMe, R^2 = OBn, R^3 = H
35 R^1 = OBn, R^2 = H, R^3 = OMe

36

37

19 R^1, R^2, R^3, R^4 = H
33 R^1 = OBn, R^2, R^3 = H
34 R^1 = OMe, R^2 = OBn, R^3 = H
35 R^1 = OBn, R^2 = H, R^3 = OMe

37

38 R^1, R^2, R^3, R^4 = H
39 R^1 = OBn, R^2, R^3 = H
40 R^1 = OMe, R^2 = OBn, R^3 = H
41 R^1 = OBn, R^2 = H, R^3 = OMe

5 R^1, R^2, R^3 = H; (Mucronustyrene)
6 R^1 = OH, R^2, R^3 = H; (Mucronulastyrene *E*-isomer)
7 R^1 = OMe, R^2 = OH, R^3 = H; (Dalberatin A)
8 R^1 = OH, R^2 = H, R^3 = OMe; (Dalberatin B)

Reagents and conditions: a) Benzyl bromide, K_2CO_3, dimethylformamide (DMF), 40°C, 4 h. b) 1.0 M vinylMgBr solution, anhyd. THF, 0°C–rt 2 h. c) Benzyl bromide, K_2CO_3, acetone, 40°C, 6 h. d) $Cu(OTf)_2$, 4 Å MS, anhyd. CH_2Cl_2, rt 3 h. e) 1.0 M BCl_3 solution, anhyd. CH_2Cl_2, −40°C, 1 h.

Chart 2. Synthesis of Diarylpropenes **5**–**8**

Table 1. Catalyst Screening for Friedel–Crafts Alkylation Reaction between **17** and **21**[a)]

S. No	Catalyst	% Yield[b)]
1	$Zn(OTf)_2$	50
2	**$Cu(OTf)_2$**	**60**
3	$Yb(OTf)_3$	25
4	AgOTf	37
5	$La(OTf)_3$	26

a) Reaction conditions: **17** (1.0 eq.), **21** (2.0 eq.), 4 Å MS and catalyst (0.1 eq.) in CH_2Cl_2 at 0°C for 6 h. *b*) Isolated yields after column chromatography.

Table 2. Anti-inflammatory Activities of 1,3-Diarylpropenes (**1**–**8**)

Compound	NO Production (% Inhibition)	
	1 μM	10 μM
Medium (MED)	1.21±0.01 (98.79)***	1.21±0.01 (98.79)***
1	80.28±0.73 (19.72)***	60.73±1.00 (39.27)***
2	70.57±1.87 (24.43)***	63.48±0.42 (36.52)***
3	99.12±1.20 (0.88)	73.19±1.99 (26.81)***
4	92.73±1.04 (7.27)	65.91±2.69 (34.09)***
5	75.64±2.50 (24.36)***	62.07±3.40 (37.93)***
6	68.42±0.28 (31.58)***	41.34±1.83 (58.66)***
7	88.80±1.72 (11.2)	86.09±1.99 (13.91)**
8	69.80±1.12 (30.2)***	46.23±0.63 (53.77)***
L-NMMA	79.1±4.1 (20.9)	7.6±4.0 (92.4)***

The results are reported as the mean value±S.E.M. for n=3. Statistical significance is based on the difference when compared with LPS-treated groups. (**p<0.01, ***p<0.001). % Inhibition is based on LPS as shown in parenthesis.

mal tissue structure and function.[20)] In order to evaluate the anti-inflammatory effects of the prepared 1,3-diarylpropenes **1**–**8**, we measured the amount of nitric oxide (NO) which is one of the essential mediators on inflammation, in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages[21)] using N^G-monomethyl-L-arginine acetate (L-NMMA)[22,23)] as a positive control.

Effect of compounds **1**–**8** on NO generation by induced macrophages was monitored (Table 2). In this study, four compounds *i.e.*, compounds **6** (mucronulastyrene *E*-isomer), **8** (dalberatin B), **1** (isomucronustyrene), and **5** (mucronustyrene) showed significant activities at 10 μM. Among the 8 compounds, the maximum inhibitory activity was observed with compound **6** (58.7%) followed by compounds **8** (53.8%), **1** (39.3%), and **5** (37.9%). The cell viability assay at 10 μM concentration was not affected by any compound excluding compound **8** indicating no cytotoxicity as shown in Table 3. Compound **8** showed toxicity at 10 μM concentration. IC_{50} values of compounds **1**–**8** were evaluated by using GraphPad Prism 4.0 software and showed 11.48, 8.98, 15.28, 12.96, 10.48, 4.05, 16.76, and 5.04 μM, respectively (Table 3).

From these pharmacological results, we can conclude that

Table 3. Proliferation Effect and IC_{50} (μM) Values of 1,3-Diarylpropenes (**1**–**8**)

Compound	Proliferation[a)]		IC_{50} (μM)
	1 μM	10 μM	
Medium (MED)	100.0±2.06	100.0±2.06	
1	105.3±11.82	105.9±8.37	11.48
2	112.7±9.62	112.0±6.19	8.98
3	95.60±2.72	121.7±8.32	15.28
4	117.7±9.70	107.6±10.19	12.96
5	93.08±2.03	110.9±5.07	10.48
6	105.5±7.56	109.1±6.20	4.05
7	100.3±9.97	99.48±8.60	16.76
8	94.36±3.12	79.54±3.66**	5.04
L-NMMA	98.6±2.9	97.6±5.6	2.69

a) The results are reported as the mean value±S.E.M. for $n=3$. Statistical significance is based on the difference when compared with medium groups (** $p<0.01$).

1,3-diarylpropene **6** can be considered as a new lead to develop impressive anti-inflammatory agents.

Conclusion

We have developed an efficient approach for the synthesis of 1,3-diarylpropenes **1**–**8** using FC alkylation as a key step. Additionally, their anti-inflammatory effects were also investigated in LPS-induced RAW264.7 macrophages. The compounds exhibit significant inhibition of inflammatory mediated NO production with no cytotoxicity except compound **8** (dalberatin B) at 10 μM concentration and IC_{50} values are found in the range from 4.05 to 16.76 μM.

Experimental

Chemistry All chemicals were obtained from commercial suppliers and were used without further purification unless noted otherwise. All solvents used for reactions were freshly distilled from proper dehydrating agents under nitrogen gas. All solvents used for chromatography were purchased and directly used without further purification. TLC was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde and phosphomolybdic acid (PMA) stain. Chromatographic purification was carried out using Kieselgel 60 (60–120 mesh, Merck). ^{1}H-NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) and the coupling constants (J) quoted in Hz. Peak splitting patterns were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplet) and m (multiplet) and $CDCl_3$/CD_3OD was used as a solvent and an internal standard. Mass spectra were recorded on an Agilent-5977E spectrometer. High resolution mass spectra were recorded on a JMS-700 (JEOL, Japan) spectrometer. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected.

General Procedure for FC Alkylation To a stirred solution of allyl alcohol (1.0 mmol) and **21** (0.39 g, 2.0 mmol) in anhyd. CH_2Cl_2 (8 mL) were added $Cu(OTf)_2$ (0.04 g, 0.1 mmol) and molecular sieves 4 Å (0.39 g) at 0°C under nitrogen atmosphere. The reaction mixture was then stirred for 5–6 h. After completion of the reaction of the reaction, aq. sat. NH_4Cl solution (2 mL) was added slowly and extracted with CH_2Cl_2 (2×30 mL). The combined organic layer was washed with brine (2×30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc–Hexane=1 : 20–1 : 10) to afford the product [Note: FC reactions of allyl alcohol (**19**, **33**–**35**) and **37** were carried out at room temperature instead of 0°C and the reaction time was 3 h].

(*E*)-3-Cinnamyl-2,6-dimethoxyphenyl Acetate (22) Yield: 61%; Colorless liquid; *Rf*=0.44 (EtOAc–hexane=1 : 4); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34–7.14 (5H, m), 7.02 (1H, d, *J*=8.7 Hz), 6.66 (1H, d, *J*=8.7 Hz), 6.41 (1H, d, *J*=15.6 Hz), 6.30 (1H, dt, *J*=15.6, 6.3 Hz), 3.78 (6H, s), 3.50 (2H, d, *J*=6.3 Hz), 2.35 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.9, 151.0, 137.7, 133.4, 131.2, 129.2, 128.8, 128.7, 127.3, 127.2, 126.5, 126.3, 107.7, 61.7, 56.5, 33.1, 21.0.

(*E*)-3-(3-(4-(Ethoxymethoxy)phenyl)allyl)-2,6-dimethoxyphenyl Acetate (23) Yield: 61%; Colorless liquid; *Rf*=0.48 (EtOAc–hexane=1 : 2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (2H, d, *J*=8.4 Hz), 6.94 (2H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.4 Hz) 6.59 (1H, d, *J*=8.4 Hz), 6.35 (1H, d, *J*=15.6 Hz), 6.17 (1H, dt, *J*=15.6, 6.3 Hz) 5.19 (2H, s) 3.79 (3H, s), 3.78 (3H, s), 3.70 (2H, q, *J*=7.1 Hz), 3.48 (2H, d, *J*=6.3 Hz), 2.35 (3H, s) 1.21 (3H, t, *J*=7.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.8, 156.7, 152.5, 151.0, 131.6, 130.5, 127.4, 127.3, 127.1, 126.5, 116.5, 107.7, 105.1, 93.4, 64.5, 61.6, 56.4, 33.0, 20.8, 15.5.

(*E*)-3-(3-(3-(Ethoxymethoxy)-2-methoxyphenyl)-allyl)-2,6-dimethoxyphenyl Acetate (24) Yield: 60%; Colorless liquid; *Rf*=0.32 (EtOAc–hexane=1 : 3); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.12 (1H, dd, *J*=7.8, 1.5 Hz), 7.05 (1H, d, *J*=8.7 Hz), 7.04 (1H, d, *J*=8.7 Hz), 6.96 (1H, t, *J*=7.8 Hz), 6.78 (1H, d, *J*=15.9 Hz), 6.69 (1H, d, *J*=7.8 Hz), 6.33 (1H, dt, *J*=15.9, 6.9 Hz), 5.27 (2H, s), 3.82 (9H, s), 3.77 (2H, q, *J*=6.9 Hz), 3.56 (2H, d, *J*=6.9 Hz), 2.37 (3H, s), 1.25 (3H, t, *J*=6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.4, 150.6, 150.4, 146.7, 132.9, 131.6, 130.1, 126.6, 126.0, 124.9, 123.8, 119.1, 114.9, 107.2, 93.6, 64.2, 61.1, 60.8, 56.1, 33.1, 20.5, 15.1.

(*E*)-3-(3-(2-(Ethoxymethoxy)-5-methoxyphenyl)-allyl)-2,6-dimethoxyphenyl Acetate (25) Yield: 59%; Colorless liquid; *Rf*=0.30 (EtOAc–hexane=1 : 5); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, *J*=8.4 Hz), 7.00 (1H, d, *J*=9.0 Hz), 6.95 (1H, d, *J*=8.4 Hz), 6.76 (1H, s), 6.70 (1H, d, *J*=9.0 Hz), 6.68 (1H, d, *J*=15.9 Hz), 6.27 (1H, dt, *J*=15.9, 6.9 Hz) 5.14 (2H, s), 3.79 (6H, s), 3.75 (3H, s), 3.71 (2H, q, *J*=6.9 Hz), 3.52 (2H, d, *J*=6.9 Hz), 2.36 (3H, s), 1.22 (3H, t, *J*=6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.5, 154.4, 150.6, 148.3, 133.0, 129.7, 128.3, 126.7, 126.1, 125.4, 116.8, 113.3, 111.0, 107.2, 94.4, 64.1, 61.3, 56.1, 55.6, 33.1, 20.6, 15.2.

1-(Benzyloxy)-4-cinnamyl-2,3-dimethoxybenzene (38) Yield: 61%; Colorless liquid; *Rf*=0.65 (EtOAc–hexane=1 : 5); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46–7.16 (10H, m), 6.87 (1H, d, *J*=8.7 Hz), 6.64 (1H, d, *J*=8.7 Hz), 6.35 (1H, d, *J*=15.6 Hz), 6.22 (1H, dt, *J*=15.6, 6.6 Hz), 5.06 (2H, s), 3.89 (3H, s), 3.86 (3H, s), 3.44 (2H, d, *J*=6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 151.7, 151.2, 137.4, 137.0, 130.5, 129.2, 128.4, 128.3, 127.7, 127.1, 126.8, 126.5, 126.3, 125.9, 123.8, 109.3, 70.9, 61.1, 60.8, 33.1

(*E*)-1-(Benzyloxy)-4-(3-(2-(benzyloxy)phenyl)allyl)-2,3-dimethoxybenzene (39) *Rf*=0.65 (EtOAc–hexane=1 : 5); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44-723 (11H, m), 7.13 (1H, td, *J*=8.4, 1.8 Hz), 6.90–6.78 (4H, m), 6.63 (1H, d, *J*=8.7 Hz), 6.33

(1H, dt, *J*=15.9, 6.9 Hz), 5.07 (2H, s), 5.05 (2H, s), 3.88 (3H, s), 3.85 (3H, s), 3.49 (2H, dd, *J*=6.9, 1.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 155.7, 152.1, 151.5, 143.3, 137.5, 137.4, 130.3, 129.1, 128.7, 128.5, 128.1, 128.0, 127.9, 127.5, 127.4, 127.3, 126.8, 125.7, 124.2, 121.2, 112.8, 109.9, 71.4, 70.7, 61.4, 61.2, 33.8.

(*E*)-1-(Benzyloxy)-4-(3-(3-(benzyloxy)-2-methoxyphenyl)allyl)-2,3-dimethoxybenzene (40) Yield: 32%; Colorless liquid; *Rf*=0.52 (EtOAc–hexane=1 : 5); ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 7.49–7.31 (10H, m), 7.11 (1H, dd, *J*=7.8, 0.9 Hz), 6.96 (1H, t, *J*=7.8 Hz), 6.88 (1H, d, *J*=8.4 Hz), 6.83 (1H, dd, *J*=7.8, 0.9 Hz), 6.82 (1H, d, *J*=15.9 Hz), 6.70 (1H, d, *J*=8.4 Hz), 6.38 (1H, dt, *J*=15.9, 7.0 Hz), 5.14 (4H, s), 3.95 (6H, s), 3.88 (3H, s), 3.57 (2H, d, *J*=7.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 152.0, 151.8, 151.3, 147.0, 143.0, 137.2, 137.1, 132.0, 128.3, 127.7, 127.2, 127.1, 126.8, 124.9, 123.8, 123.7, 118.6, 113.1, 109.7, 71.2, 70.9, 61.1, 61.0, 60.8, 33.5.

(*E*)-1-(Benzyloxy)-4-(3-(2-(benzyloxy)-5-methoxyphenyl)allyl)-2,3-dimethoxybenzene (41) Yield: 32%; Colorless liquid; *Rf*=0.56 (EtOAc–hexane=1 : 5); ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 7.48–7.30 (10H, m), 7.02 (1H, d, *J*=2.7 Hz), 6.85 (1H, d, *J*=8.4 Hz), 6.85 (1H, d, *J*=8.4 Hz), 6.81 (1H, d, *J*=15.3 Hz), 6.71 (1H, dd, *J*=8.4, 2.7 Hz), 6.36 (1H, dt, *J*=15.6, 6.9 Hz), 6.67 (1H, d, *J*=8.4 Hz), 5.11 (2H, s), 5.02 (2H, s), 3.93 (3H, s), 3.89 (3H, s), 3.78 (3H, s), 3.53 (2H, d, *J*=6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 154.3, 152.1, 151.6, 150.2, 143.3, 137.6, 137.5, 130.6, 128.7, 128.6, 128.6, 128.0, 127.9, 127.5, 127.4, 127.1, 125.5, 124.2, 114.7, 113.3, 112.1, 109.9, 71.8, 71.5, 61.4, 61.1, 56.0, 33.7.

General Procedure for Acetyl Deprotection To a stirred solution of acetyl protected 1,3-diarylpropene (0.4 mmol) in MeOH (4 mL) was added aq. 0.7 M K_2CO_3 (3.43 mL) and stirred for 2 h at room temperature. After completion of the reaction, MeOH was removed under reduced pressure and the pH was adjusted to 6 with 1 N HCl. The crude was extracted with EtOAc (2×25 mL). The combined organic layer was washed with brine (2×30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc–Hexane=1 : 4–1 : 2) to afford the product.

3-Cinnamyl-2,6-dimethoxyphenol (Isomucronustylene) (1) Yield: 98%; Colorless oil; *Rf*=0.42 (EtOAc–hexane=1 : 2); ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 7.30 (5H, m), 6.63 (1H, d, *J*=8.4 Hz), 6.59 (1H, d, *J*=8.4 Hz), 6.36 (1H, d, *J*=15.6 Hz), 6.29 (1H, dt, *J*=15.6, 5.4 Hz), 4.90 (1H, s), 3.79 (6H, s), 3.43 (2H, d, *J*=5.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 147.5, 146.0, 139.4, 137.9, 130.4, 129.5, 128.3, 126.7, 126.0, 125.8, 119.2, 107.1, 59.8, 55.6, 32.9; electron ionization (EI)-MS *m/z* 270 (M^+, base), 239, 207; high resolution (HR)-MS: Calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found: 270.1250.

(*E*)-3-(3-(4-(Ethoxymethoxy)phenyl)allyl)-2,6-dimethoxyphenol (26) Yield: 98%; Pale yellow color oil; *Rf*=0.50 (EtOAc–hexane=1 : 2); ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 7.25 (2H, d, *J*=8.4 Hz), 6.94 (2H, d, *J*=8.4 Hz), 6.66 (1H, d, *J*=8.7 Hz) 6.56 (1H, d, *J*=8.7 Hz), 6.35 (1H, d, *J*=15.9 Hz), 6.19 (1H, dt, *J*=15.9, 6.3 Hz) 5.55 (1H, s) 5.19 (2H, s) 3.86 (3H, s), 3.85 (3H, s), 3.70 (2H, q, *J*=6.9 Hz), 3.47 (2H, d, *J*=6.3 Hz), 1.21 (3H, t, *J*=6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 156.7, 146.5, 145.5, 138.9, 131.7, 130.2, 127.8, 127.3, 126.7, 119.3, 116.5, 106.7, 93.5, 64.5, 61.0, 56.6, 33.2, 15.5.

(*E*)-3-(3-(3-(Ethoxymethoxy)-2-methoxyphenyl)-allyl)-2,6-dimethoxyphenol (27) Yield: 98%; Colorless oil; *Rf*=0.65 (EtOAc–hexane=1 : 2); ^{1}H-NMR (300 MHz, CD_3OD) *δ*: 7.09 (1H, dd, *J*=7.8, 1.8 Hz), 6.98 (1H, dd, *J*=7.8, 1.8 Hz), 6.92 (1H, t, *J*=7.8 Hz), 6.68–6.60 (3H, m), 6.34 (1H, dt, *J*=16.2, 6.6 Hz), 5.21 (2H, s), 3.81 (3H, s), 3.80 (3H, s), 3.73 (3H, s), 3.66 (2H, q, *J*=7.0 Hz), 3.47 (2H, d, *J*=6.6 Hz), 1.19 (3H, t, *J*=7.0 Hz); ^{13}C-NMR (75 MHz, CD_3OD) *δ*: 150.6, 147.5, 147.0, 146.0, 139.4, 132.0, 131.0, 126.0, 124.4, 123.9, 119.1, 115.2, 107.0, 93.7, 64.4, 60.1, 59.8, 55.5, 33.3, 14.4.

(*E*)-3-(3-(2-(Ethoxymethoxy)-5-methoxyphenyl)-allyl)-2,6-dimethoxyphenol (28) Yield: 96%; Colorless oil; *Rf*=0.38 (EtOAc–hexane=1 : 3); ^{1}H-NMR (300 MHz, CD_3OD) *δ*: 6.95 (1H, d, *J*=8.7 Hz), 6.94 (1H, d, *J*=3.0 Hz), 6.67 (1H, dd, *J*=8.7, 3.0 Hz), 6.65 (1H, d, *J*=15.9 Hz), 6.62 (1H, d, *J*=8.4 Hz), 6.61 (1H, d, *J*=8.4 Hz), 6.31 (1H, dt, *J*=15.9, 6.6 Hz) 5.08 (2H, s), 3.80 (3H, s), 3.79 (3H, s), 3.70 (3H, s), 3.64 (2H, q, *J*=7.0 Hz), 3.44 (2H, dd, *J*=6.6, 1.2 Hz), 1.15 (3H, t, *J*=7.0 Hz); ^{13}C-NMR (75 MHz, CD_3OD) *δ*: 155.9, 149.5, 148.5, 147.0, 140.4, 131.5, 130.0, 127.1, 126.0, 120.3, 118.1, 114.1, 112.0, 108.1, 95.6, 65.3, 60.9, 56.6, 55.9, 34.3, 15.5.

General Procedure for EOM-Deprotection To a stirred solution of EOM-protected 1,3-diarylpropene (0.15 mmol) in anhyd. MeOH (4 mL) was added Dowex® resin (150% w/w) under nitrogen atmosphere at room temperature. The reaction was stirred at 40°C for 31–48 h. After completion of the reaction, filtered, washed with MeOH (5 mL) and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc–Hexane=1 : 4–1 : 3) to afford the product.

(*E*)-3-(3-(4-Hydroxyphenyl)allyl)-2,6-dimethoxyphenol (Dalparvinene) (2) Yield: 76%; Pale yellow color liquid; *Rf*=0.33 (EtOAc–hexane=1 : 2); ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 7.20 (2H, d, *J*=8.4 Hz), 6.73 (2H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.1 Hz) 6.59 (1H, d, *J*=8.1 Hz), 6.33 (1H, d, *J*=16.2 Hz), 6.16 (1H, dt, *J*=16.2, 6.3 Hz) 5.57 (1H, s) 5.13 (1H, s) 3.87 (3H, s), 3.86 (3H, s), 3.47 (2H, d, *J*=6.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 154.6, 146.2, 145.1, 138.6, 130.5, 130.0, 127.3, 127.1, 126.5, 119.6, 115.3, 106.5, 60.8, 56.3, 32.9; EI-MS *m/z* 286 (M^+, base), 255, 223; HR-MS: Calcd for $C_{17}H_{18}O_4$ (M^+): 286.1205. Found: 286.1213.

(*E*)-3-(3-(3-Hydroxy-2-methoxyphenyl)allyl)-2,6-dimethoxyphenol (Dalberatin C) (3) Yield: 74%; Pale yellow color liquid; *Rf*=0.23 (EtOAc–hexane=1 : 1); ^{1}H-NMR (300 MHz, CD_3OD) *δ*: 6.89 (1H, dd, *J*=7.8, 1.2 Hz), 6.82 (1H, t, *J*=7.8 Hz), 6.67 (1H, dd, *J*=7.8, 1.2 Hz), 6.63 (1H, d, *J*=8.1 Hz), 6.62 (1H, d, *J*=8.1 Hz), 6.60 (1H, d, *J*=17.1 Hz), 6.32 (1H, dt, *J*=17.1, 6.6 Hz), 3.81 (3H, s), 3.80 (3H, s), 3.68 (3H, s), 3.46 (2H, d, *J*=6.6 Hz); ^{13}C-NMR (75 MHz, CD_3OD) *δ*: 150.1, 147.5, 146.0, 145.0, 139.4, 131.6, 130.7, 126.0, 124.7, 124.31, 119.2, 116.8, 114.7, 107.0, 60.1, 59.8, 55.5, 33.2; EI-MS *m/z* 316 (M^+, base), 285, 253; HR-MS: Calcd for $C_{18}H_{20}O_5$ (M^+): 316.1311. Found: 316.1314.

(*E*)-3-(3-(2-Hydroxy-5-methoxyphenyl)allyl)-2,6-dimethoxyphenol (Dalberatin D) (4) Yield: 77%; Pale yellow color liquid; *Rf*=0.20 (EtOAc–hexane=1 : 4); ^{1}H-NMR (300 MHz, CD_3OD) *δ*: 6.85 (1H, d, *J*=3.0 Hz), 6.73 (1H, d, *J*=8.1 Hz), 6.68 (1H, d, *J*=8.1 Hz), 6.66 (1H, dd, *J*=8.1, 3.0 Hz), 6.60 (1H, d, *J*=15.6 Hz), 6.59 (1H, d, *J*=8.1 Hz), 6.28 (1H, dt, *J*=15.6, 6.9 Hz), 3.80 (3H, s), 3.79 (3H, s), 3.67 (3H, s), 3.44 (2H, dd, *J*=6.9, 1.8 Hz); ^{13}C-NMR (75 MHz, CD_3OD) *δ*: 153.2, 148.2, 147.4, 146.0, 139.3, 129.4, 126.3, 125.5, 125.4, 119.3, 116.1, 113.4, 110.9, 107.1, 59.9, 55.5, 55.0, 33.4; EI-MS *m/z* 316 (M^+, base), 285, 253; HR-MS: Calcd for $C_{18}H_{20}O_5$ (M^+):

316.1311. Found: 316.1306.

General Procedure for Benzyl Deprotection To a stirred solution of benzyl protected 1,3-diarylpropene (0.15 mmol) in anhyd. CH_2Cl_2 (5 mL) was added BCl_3 solution (1.0 M in CH_2Cl_2, 0.375 mL, 0. 375 mmol, 2.5 eq.) slowly under nitrogen atmosphere at −40°C. The reaction was stirred for 1 h at −40°C. After completion of the reaction, excess BCl_3 was quenched by the slow addition of MeOH (1 mL) and then solvent was removed under reduced pressure. H_2O (5 mL) and CH_2Cl_2 (15 mL) were added to the crude and two layers separated. Aqueous layer was extracted with CH_2Cl_2 (2×25 mL) dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc–Hexane=1 : 4–1 : 3) to afford the product [Note: For compound **5** preparation from **38**, 1.5 eq. of BCl_3 used instead of 2.5 eq.].

4-Cinnamyl-2,3-dimethoxyphenol (Mucronustyrene) (5) Yield: 89%; Colorless liquid; *Rf*=0.49 (EtOAc–hexane=1 : 1); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34–7.13 (5H, m), 6.81 (1H, d, *J*=8.4 Hz), 6.43 (1H, d, *J*=15.6 Hz), 6.40 (1H, d, *J*=8.4 Hz), 6.35 (1H, dt, *J*=15.6, 5.7 Hz), 5.92 (1H, s), 3.89 (3H, s), 3.82 (3H, s), 3.49 (2H, d, *J*=5.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.7, 147.1, 137.6, 135.4, 130.5, 128.7, 128.3, 126.8, 126.0, 127.1, 119.2, 103.6, 60.9, 55.9, 32.8; EI-MS *m/z* 270 (M^+, base), 239, 207; HR-MS: Calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found: 270.1263.

(*E*)-4-(3-(2-Hydroxyphenyl)allyl)-2,3-dimethoxyphenol (Mucronulastyrene) (6) Yield: 98%; Pale yellow color liquid; *Rf*=0.18 (EtOAc–hexane=1 : 3); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30 (1H, dd, *J*=7.8, 1.5 Hz), 7.08 (1H, td, *J*=7.8, 1.5 Hz), 6.86 (1H, d, *J*=7.8 Hz), 6.84 (1H, d, *J*=8.4 Hz), 6.77 (1H, dd, *J*=7.8, 1.2 Hz), 6.68 (1H, d, *J*=8.4 Hz), 6.60 (1H, d, *J*=15.6 Hz), 6.29 (1H, dt, *J*=15.6, 6.9 Hz), 5.68 (1H, s), 5.20 (1H, s), 3.93 (3H, s), 3.86 (3H, s), 3.50 (2H, dd, *J*=6.9, 1.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.8, 150.9, 148.4, 140.1, 132.2, 128.3, 127.7, 125.5, 125.2, 125.1, 124.9, 121.0, 115.9, 110.5, 60.9, 60.7, 33.8; EI-MS *m/z* 286 (M^+, base), 255, 223; HR-MS: Calcd for $C_{17}H_{18}O_4$ (M^+): 286.1205. Found: 286.1203.

(*E*)-4-(3-(3-Hydroxy-2-methoxyphenyl)allyl)-2,3-dimethoxyphenol (Dalberatin A) (7) Yield: 91%; Colorless liquid; *Rf*=0.56 (EtOAc–hexane=1 : 1); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.95 (1H, dd, *J*=7.8, 2.4 Hz), 6.91 (1H, t, *J*=7.8 Hz), 6.81 (1H, d, *J*=8.4 Hz), 6.80 (1H, dd, *J*=7.8, 2.4 Hz), 6.66 (1H, d, *J*=8.4 Hz), 6.58 (1H, d, *J*=15.9 Hz), 6.34 (1H, dt, *J*=15.9, 6.6 Hz), 5.81 (1H, s), 5.77 (1H, s), 3.90 (3H, s), 3.85 (3H, s), 3.74 (3H, s), 3.49 (2H, dd, *J*=6.6, 0.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.6, 148.9, 148.1, 144.2, 139.8, 131.4, 130.8, 125.1, 124.6, 124.5, 118.0, 114.0, 110.3, 61.4, 60.7, 60.5, 33.3; EI-MS *m/z* 316 (M^+, base), 285, 253; HR-MS: Calcd for $C_{18}H_{20}O_5$ (M^+): 316.1311. Found: 316.1308.

(*E*)-4-(3-(2-Hydroxy-5-methoxyphenyl)allyl)-2,3-dimethoxyphenol (Dalberatin B) (8) Yield: 94%; Colorless liquid; *Rf*=0.52 (EtOAc–hexane=1 : 1); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.84 (1H, d, *J*=3.0 Hz), 6.82 (1H, d, *J*=8.4 Hz), 6.69 (1H, d, *J*=8.4 Hz), 6.66 (1H, d, *J*=8.4 Hz), 6.65 (1H, dd, *J*=8.4, 3.0 Hz), 6.57 (1H, d, *J*=15.6 Hz), 6.27 (1H, dt, *J*=15.6, 6.6 Hz), 5.64 (1H, s), 4.76 (1H, s), 3.92 (3H, s), 3.85 (3H, s), 3.74 (3H, s), 3.49 (2H, d, *J*=6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.0, 150.9, 148.4, 146.9, 140.1, 132.3, 125.7, 125.4, 125.2, 124.9, 116.7, 114.1, 112.6, 110.5, 60.9, 60.7, 56.1, 33.7; EI-MS *m/z* 316 (M^+, base), 285, 253; HR-MS: Calcd for $C_{18}H_{20}O_5$ (M^+): 316.1311. Found: 316.1316.

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Supplementary Materials The online version of this article contains supplementary materials (experimental procedures and characterization data).

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