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 mucronulastrene (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 IC50 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.1–3 1,3-Diarylpropenes (cinnamylphenols) acquire C6+ C3+ C6 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 anti-cancer,4–6 anti-oxidant,7 anti-inflammatory,8 anti-platelet,9 and anti-malarial.10 They can also serve as key intermediates in the synthesis of natural products and the evolution of biologically active compounds.8–10 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. Iso mocronustrene (1) was isolated from the heartwood of Dalbergia odorifera (Leguminosae),6 dalparvinene (2) isolated from Dalbergia parviflora10 and dalberatins A–D (7, 8, 3, 4) were also from the Dalbergia species.15 Mucronustrene (5) was isolated from the wood of Machaerium mucronulatum (Fabaceae) whereas compound 6 is synthetic E-isomer of mucronulastrene.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-hydroxybenzaldehyde (10), and 2-hydroxy 5-methoxybenzaldehyde (11). Treatment of 9–11 with chloromethyl ethyl ether (EOM-Cl) using potassium carbonate (K2CO3)/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 (CH2Cl2), chloroform (CHCl3), tetrahydrofuran (THF) and diethyl ether solvents using 0.1 eq. of Cu(OTf)2 as a catalyst and better yields were obtained in CH2Cl2. Hence, we utilized Cu(OTf)2 as a catalyst with 0.1 eq. loading and CH2Cl2 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 mucronustrene (1) and compounds 26–28 in high yields, respectively. Finally, EOM-group deprotection of 26–28 using Dowex6 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 vinylmagnesium 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. CH3Cl2 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-butylmethylsilyl (TBS)- and trityl-protected components, but, lower yields
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 (BCl₃) 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 (¹H- and ¹³C-) 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-

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

Reagents and conditions: a) chloromethyl ethyl ether (EOM–Cl), TBAI, K₂CO₃, 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 (Et₃N), anhyd. CH₂Cl₂, rt overnight. d) Cu(OTf)₂, 4 Å MS, anhyd. CH₂Cl₂, 0°C, 5–6 h. e) aq. K₂CO₃, MeOH, rt 2 h, f) Dowex® resin, anhyd. MeOH, 40°C, 48 h.

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

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1. R₁, R₂, R₃, R₄ = H; (Isomucronustiren)
2. R₁, R₂, R₃ = H, R₄ = OH; (Dalparvinene)
3. R¹ = OMe, R₂ = OH, R₃, R₄ = H; (Dalberatin C)
4. R¹ = OH, R₂, R₃ = H, R₄ = OMe; (Dalberatin D)
5. R¹, R₂, R₃ = H; (Mucronustirene)
6. R¹ = OH, R₂ = H; (Mucronylstirene E-isomer)
7. R¹ = OMe, R₂ = OH, R₃ = H; (Dalberatin A)
8. R¹ = OH, R₂ = H, R₃ = OMe; (Dalberatin B)

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1. R¹ = OMe, R₂ = OH, R₃, R₄ = H; 87–98%
2. R¹ = OH, R₂, R₃ = H, R₄ = OMe; 78–93%
3. R¹ = OH, R₂, R₃ = H, R₄ = OMe
4. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
5. R¹ = OMe, R₂ = OMe, R₃ = H, R₄ = OMe
6. R¹ = OMe, R₂ = OMe, R₃ = H, R₄ = OMe
7. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
8. R¹ = OMe, R₂ = OMe, R₃ = H, R₄ = OMe
9. R¹ = OMe, R₂ = OMe, R₃ = H
10. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
11. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
12. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
13. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
14. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
15. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
16. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
17. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
18. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
19. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
20. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
21. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
22. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
23. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
24. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
25. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
26. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
27. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
28. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
29. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
30. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
31. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
32. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
33. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
34. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
35. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
36. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
37. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
38. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
39. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
40. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
41. R¹ = OMe, R₂ = OMe, R₃, R₄ = H
mal tissue structure and function. 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 using NG-monomethyl-L-arginine acetate (L-NMMA) 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

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

| S. No | Catalyst | % Yield |
|-------|----------|---------|
| 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 CH2Cl2 at 0°C for 6 h. b) Isolated yields after column chromatography.

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**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 (11.12)          | 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.

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Reagents and conditions: a) Benzyl bromide, K2CO3, dimethylformamide (DMF), 40°C, 4 h. b) 1.0 M vinylMgBr solution, anhyd. THF, 0°C–rt 2 h. c) Benzyl bromide, K2CO3, acetone, 40°C, 6 h. d) Cu(OTf)2, 4 Å MS, anhyd. CH2Cl2, rt 3 h. e) 1.0 M BCl3 solution, anhyd. CH2Cl2, −40°C, 1 h.

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**Chart 2. Synthesis of Diarylpropenes 5–8**
dic acid (PMA) stain. Chromatographic purification was carried out using column chromatography (EtOAc–Hexane=1:2–10) 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 3h].

(E)-3-Cinnamyl-2,6-dimethoxyphenyl Acetate (22) Yield: 61%; Colorless liquid; Rf=0.44 (EtOAc–hexane=1:4); ¹H-NMR (300 MHz, CDCl₃) δ: 7.34–7.14 (5H, m), 7.02 (1H, d, J=8.71 Hz), 6.66 (1H, d, J=8.7 Hz), 6.41 (1H, t, 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), 1³C-NMR (75 MHz, CDCl₃) 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-(Ethoxy methoxyphenyl)allyl)-2,6-dimethoxyphenylacetate (23) Yield: 85%; Colorless liquid; Rf=0.62 (EtOAc–hexane=1:3); ¹H-NMR (300 MHz, CDCl₃) δ: 7.12 (1H, dd, J=7.8, 1.5 Hz), 7.05 (1H, d, J=8.71 Hz), 7.04 (1H, d, J=8.7 Hz), 6.96 (1H, t, J=7.81 Hz), 6.78 (1H, d, J=15.9 Hz), 6.69 (1H, d, J=8.71 Hz), 6.33 (1H, dt, J=15.9, 6.9 Hz), 5.27 (2H, s), 3.82 (9H, s), 3.77 (2H, q, J=6.91 Hz), 3.56 (2H, d, J=6.91 Hz), 2.37 (3H, s), 1.25 (3H, t, J=6.91 Hz), 1³C-NMR (75 MHz, CDCl₃) 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-(3-(Ethoxy methoxy)-7-methoxyphenyl)-2,6-dimethoxyphenylacetate (24) Yield: 98%; Colorless liquid; Rf=0.52 (EtOAc–hexane=1:5); ¹H-NMR (300 MHz, CDCl₃) δ: 7.03 (1H, d, J=8.4 Hz), 7.00 (1H, d, J=9.01 Hz), 6.95 (1H, d, J=8.4 Hz), 6.76 (1H, d, J=7.01 Hz), 6.70 (1H, d, J=9.01 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=6.91 Hz), 3.52 (2H, d, J=6.91 Hz), 2.36 (3H, s), 1.22 (3H, t, J=6.91 Hz), 1³C-NMR (75 MHz, CDCl₃) 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-(Benzoyl oxy)-4-cinnamyl-2,3-dimethoxybenzene (38) Yield: 61%; Colorless liquid; Rf=0.65 (EtOAc–hexane=1:5); ¹H-NMR (300 MHz, CDCl₃) δ: 7.46–7.16 (10H, m), 6.87 (1H, d, J=8.71 Hz), 6.64 (1H, d, J=8.7 Hz), 6.35 (1H, d, J=15.6 Hz), 6.22 (1H, dt, J=15.6, 6.1 Hz), 5.06 (2H, s), 3.83 (3H, s), 3.86 (3H, s), 3.44 (2H, d, J=6.6 Hz), 1³C-NMR (75 MHz, CDCl₃) 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-[(Benzyl oxy)-4-(3-(2-benzoyl phenyl)allyl)-2,3-dimethoxybenzene (39) Rf=0.65 (EtOAc–hexane=1:5); ¹H-NMR (300 MHz, CDCl₃) δ: 7.44–7.23 (11H, m), 7.13 (1H, td, J=8.4, 1.8 Hz), 6.90–6.78 (4H, m), 6.63 (1H, d, J=8.71 Hz), 6.33
E)-1-(Benzyl)-4-(3-(3-benzyl)-2-methoxyphenyl)-2,3-dimethoxybenzene (40) Yield: 32%; Colorless liquid; \( R_f = 0.52 \) (EtOAc–hexane=1:5); \( \delta \)-NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.49\)–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, dd, \( J = 8.4, 1.2 \) Hz), 3.83 (3H, s), 3.47 (2H, d, \( J = 7.8, 15.6 \) Hz), 3.01 (2H, q, \( J = 6.6, 17.1 \) Hz), 2.86 (1H, d, \( J = 8.4, 1.2 \) Hz), 1.19 (3H, s), 1.17 (3H, s), 1.16 (3H, s), 1.15 (3H, s), 1.14 (3H, s), 1.13 (3H, s), 1.12 (3H, s), 1.11 (3H, s), 1.10 (3H, s), 0.62 (9H, s), 0.42 (EtOAc–hexane=1:5); \( \delta \)-C-NMR (75 MHz, CDCl\(_3\)): \( \delta = 157.5, 151.2, 146.3, 137.1, 137.0, 130.6, 127.4, 127.1, 127.1, 127.0, 126.8, 124.2, 121.2, 115.9, 70.1, 67.4, 61.2, 33.8.

General Procedure for Acetyl Deprotection
To a stirred solution of acetylated 1,3-dianilipropene (0.4 mmol) in MeOH (4 mL) was added aq. 0.7% K\(_2\)CO\(_3\) (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\(_2\)SO\(_4\) and concentrated in vacuo. The crude was purified by column chromatography (EtOAc–hexane=1:4–1:2) to afford the product.

E)-3-(3-(4-Hydroxyphenyl)allyl)-2,6-dimethoxyphenol (Dalparvinene) (2) Yield: 76%; Pale yellow color liquid; \( R_f = 0.33 \) (EtOAc–hexane=1:1); \( \delta \)-NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.20 \) (2H, d, \( J = 8.4, 1.2 \) Hz), 6.73 (2H, d, \( J = 8.4, 1.2 \) Hz), 6.67 (1H, d, \( J = 8.1, 1.2 \) Hz), 5.99 (1H, d, \( J = 8.1, 1.2 \) Hz), 5.39 (1H, d, \( J = 8.1, 1.2 \) Hz), 5.34 (1H, d, \( J = 8.1, 1.2 \) Hz), 3.84 (3H, s), 3.83 (3H, s), 3.82 (3H, s), 3.44 (2H, d, \( J = 6.6, 1.2 \) Hz), 1.15 (3H, t, \( J = 7.0, 1.2 \) Hz); \( \delta \)-NMR (75 MHz, CDCl\(_3\)); \( \delta = 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, 56.5, 53.9, 34.3, 15.5.

General Procedure for EOM-Deprotection
To a stirred solution of EOM-protected 1,3-dianilipropene (0.15 mmol) in anhyd. MeOH (4 mL) was added Dowex\(^{\circ}\) 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-(2-Ethoxyethoxy)-5-methoxyphenyl)-2,6-dimethoxyphenol (28) Yield: 96%; Colorless oil; \( R_f = 0.38 \) (EtOAc–hexane=1:3); \( \delta \)-NMR (300 MHz, CDCl\(_3\)): \( \delta = 6.95 \) (1H, d, \( J = 8.7, 1.2 \) Hz), 6.94 (1H, d, \( J = 3.0, 1.2 \) Hz), 6.67 (1H, dd, \( J = 8.7, 3.0, 1.2 \) Hz), 6.65 (1H, d, \( J = 15.9, 1.2 \) Hz), 6.62 (1H, d, \( J = 8.4, 1.2 \) Hz), 6.11 (1H, d, \( J = 8.4, 1.2 \) Hz), 3.01 (2H, q, \( J = 6.6, 1.2 \) Hz), 1.15 (3H, t, \( J = 7.0, 1.2 \) Hz); \( \delta \)-C-NMR (75 MHz, CDCl\(_3\)): \( \delta = 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, 56.5, 53.9, 34.3, 15.5.
General Procedure for Benzyl Deprotection
To a stirred solution of benzyl protected 1,3-diarylpropene (0.15 mmol) in anhyd. CH₂Cl₂ (5 mL) was added BCl₃ solution (1.0 M in anhyd. CH₂Cl₂, 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 BCl₃ was quenched by the slow addition of MeOH (1 mL) and then solvent was removed under reduced pressure. H₂O (5 mL) and CH₂Cl₂ (15 mL) were added to the crude and two layers separated. Aqueous layer was extracted with CH₂Cl₂ (2×25 mL) dried over anhyd. Na₂SO₄ 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 BCl₃ used instead of 2.5 eq.].

4-Cinnamyl-2,3-dimethoxyphenol (Mucronusteryne) (5) Yield: 89%; Colorless liquid; Rf = 0.49 (EtOAc–hexane=1:1); ¹H-NMR (300 MHz, CDCl₃) 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), 3.89 (3H, s), 3.82 (3H, s), 3.49 (2H, d, J = 5.7 Hz); ¹³C-NMR (75 MHz, CDCl₃) 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 C₁₇H₁₈O₃ (M⁺): 270.1256. Found: 270.1263.

(E)-4-(3-(2-Hydroxyphenyl)allyl)-2,3-dimethoxyphenol (Mucronulasteryne) (6) Yield: 98%; Pale yellow color liquid; Rf = 0.18 (EtOAc–hexane=1:3); ¹H-NMR (300 MHz, CDCl₃) δ: 7.30 (1H, dd, J = 7.8, 1.5 Hz), 7.08 (1H, td, J = 7.8, 1.5 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); ¹³C-NMR (75 MHz, CDCl₃) δ: 152.8, 150.9, 148.4, 140.1, 132.2, 128.3, 127.7, 125.5, 125.2, 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 C₁₇H₂₀O₃ (M⁺): 286.1205. Found: 286.1203.

(E)-4-(3-(3-Hydroxy-2-methoxyphenyl)allyl)-2,3-dimethoxyphenol (Dalberatin A) (7) Yield: 9%; Colorless liquid; Rf = 0.56 (EtOAc–hexane=1:1); ¹H-NMR (300 MHz, CDCl₃) 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); ¹³C-NMR (75 MHz, CDCl₃) δ: 150.6, 148.9, 148.1, 144.2, 139.8, 131.4, 130.8, 125.1, 124.5, 124.8, 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 C₁₇H₂₀O₃ (M⁺): 316.1310. 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); ¹H-NMR (300 MHz, CDCl₃) 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); ¹³C-NMR (75 MHz, CDCl₃) 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 C₁₇H₂₀O₃ (M⁺): 316.1311. Found: 316.1316.