Regular Article

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

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Received January 27, 2016; accepted March 8, 2016; advance publication released online March 30, 2016

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 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 + C₆ + C₁ 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,7 and anti-malarial.9 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 parviflora14 and dalberatins A–D (7, 8, 9, 10) were also from the Dalbergia species.15 Mucronustyrene (5) was isolated from the wood of Machaerium mucronatum (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-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. Decacylation 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 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. CH₂Cl₂ 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 –O Me 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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**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.

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

<table>
<thead>
<tr>
<th>S. No</th>
<th>Catalyst</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(OTf)₂</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OTf)₃</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>La(OTf)₃</td>
<td>26</td>
</tr>
</tbody>
</table>

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.

Chart 2. Synthesis of Diarylpropenes 5–8

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>NO Production (% Inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 µM</td>
</tr>
<tr>
<td>Medium</td>
<td>1.21 ±0.01 (98.79)***</td>
</tr>
<tr>
<td>1</td>
<td>80.28 ±0.73 (19.72)***</td>
</tr>
<tr>
<td>2</td>
<td>70.57 ±1.87 (24.43)***</td>
</tr>
<tr>
<td>3</td>
<td>99.12 ±1.20 (0.88)</td>
</tr>
<tr>
<td>4</td>
<td>92.73 ±1.04 (7.27)</td>
</tr>
<tr>
<td>5</td>
<td>75.64 ±2.50 (24.36)***</td>
</tr>
<tr>
<td>6</td>
<td>68.42 ±0.28 (31.58)***</td>
</tr>
<tr>
<td>7</td>
<td>88.80 ±1.72 (11.2)</td>
</tr>
<tr>
<td>8</td>
<td>69.80 ±1.12 (30.2)</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>79.1 ±4.1 (20.9)</td>
</tr>
</tbody>
</table>

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.

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...
1,3-diarylp propane 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-diarylprenes 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 inhibitory effects of inflammatory mediator NO production with no cytotoxicity except compound 8 (dalberatin B) at 10 µM concentration and IC50 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-Plastifolien 60, F254 (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). 1H-NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for 13C, 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 CDCl3/CD3OD 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. CH2Cl2 (8 mL) were added Cu(O2)Cl2 (0.04 g, 0.1 mmol) and molecular sieves 4Å (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. NH4Cl solution (2 mL) was added slowly and extracted with CH2Cl2 (2×30 mL). The combined organic layer was washed with brine (2×30 mL), dried over anhyd. Na2SO4 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-dimethoxyphe nylacetate (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=8.17 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-(Ethoxymethoxy)phenyl)allyl)-2,6-dimethoxyphe nylacetate (23) Yield: 61%; Colorless liquid; Rf=0.48 (EtOAc–hexane=1:2); 1H-NMR (300 MHz, CDCl3, 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, t, 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); 13C-NMR (75 MHz, CDCl3, δ): 168.8, 156.7, 152.5, 150.1, 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.

Table 3. Proliferation Effect and IC50 (µM) Values of 1,3-Diarylpropenes (1–8)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Proliferationa</th>
<th>IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1µM</td>
<td>10µM</td>
</tr>
<tr>
<td>Medium (MED)</td>
<td>100.0±2.06</td>
<td>100.0±2.06</td>
</tr>
<tr>
<td>1</td>
<td>105.3±11.82</td>
<td>11.48</td>
</tr>
<tr>
<td>2</td>
<td>112.7±9.62</td>
<td>8.98</td>
</tr>
<tr>
<td>3</td>
<td>95.60±2.72</td>
<td>15.28</td>
</tr>
<tr>
<td>4</td>
<td>117.7±9.70</td>
<td>12.96</td>
</tr>
<tr>
<td>5</td>
<td>93.08±2.03</td>
<td>10.48</td>
</tr>
<tr>
<td>6</td>
<td>105.5±7.56</td>
<td>4.05</td>
</tr>
<tr>
<td>7</td>
<td>100.3±9.97</td>
<td>16.76</td>
</tr>
<tr>
<td>8</td>
<td>94.36±3.12</td>
<td>5.04</td>
</tr>
<tr>
<td>l-NMMA</td>
<td>98.6±2.9</td>
<td>2.69</td>
</tr>
</tbody>
</table>

a) The results are reported as the mean values±S.E.M. for n=3. Statistical significance is based on the difference when compared with medium groups (⁎p<0.01).
(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); 13C-NMR (75 MHz, CDCl3): 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, 70.6, 64.1, 61.2, 33.8.

(1-(Benzyl)-oxy)-4-(3-(benzyl)-2-methoxyphenyl)-2,6-dimethoxyphenol (2) Yield: 32%; Colorless liquid; Rf: 0.50 (EtOAc–hexane=1:5); 1H-NMR (300 MHz, CDCl3): 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=6.9 Hz); δ: 7.45, 7.35, 7.28, 7.23, 7.19, 7.12, 7.09, 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); 13C-NMR (75 MHz, CDCl3): δ: 156.0, 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, 33.4, 14.4.

General Procedure for EOM-Deprotection To a stirred solution of EOM-protected 1,3-diarylpropane (0.4 mmol) in MeOH (4 mL) was added Dowex ® resin (150% w/w) under nitrogen atmosphere at room temperature. The reaction was stirred at 40°C for 3–8 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.
General Procedure for Benzyl Deprotection  To a stirred solution of benzyl protected 1,3-diarylp propane (0.15 mmol) in anhyd. CH₂Cl₂ (5 mL) was added BCl₃ solution (1.0 M in 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 preparation from 38, 1.5 eq. of BCl₃ used instead of 2.5 eq.]

4-Cinnamyl-2,3-dimethoxyphenol (Mucronasturene) (5) Yield: 89%; Colorless liquid; Rf=0.49 (EtOAc–hexane=1:1); ¹H-NMR (300 MHz, CDCl₃) δ: 7.34–7.13 (5H, m), 6.18 (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); ¹³C-NMR (75 MHz, CDCl₃) δ: 150.7, 147.1, 137.6, 135.4, 120.5, 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 C₁₇H₁₁O₃ (M⁺): 270.1256. Found: 270.1263.

(E)-4-(3-(2-Hydroxyphenyl)allyl)-2,3-dimethoxyphenol (Mucronasturene) (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, 1.5Hz), 7.08 (1H, t, J=7.8, 1.5Hz), 6.81 (1H, d, J=8.4 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, 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 C₁₇H₁₆O₃ (M⁺): 286.1205. Found: 286.1203.

Acknowledgments  This research was financially supported by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2009-0094071), and by the Hallym University Research Fund (HRF-G-2015-2).

Conflict of Interest  The authors declare no conflict of interest.

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

References