Supplementary Material (ESI) for Chemical Communications

Supporting Information

Enhanced Radical-Scavenging Activity of Naturally-Oriented Artepillin C Derivatives

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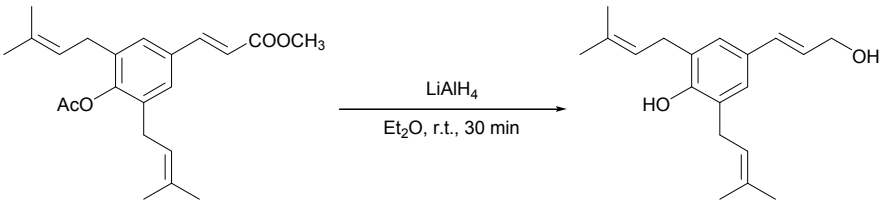
General Methods for synthesis

^{1}H NMR spectra were recorded on a JEOL JNM-EX400 spectrometer (400 MHz) with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm. Coupling constants are reported in Hz. Mass spectra were measured on a Shimazu GC-MS QP-1000 mass spectrometer using electron ionization (EI) method. Elemental analyses were performed with a Yanako CHN recorder MT-5. Reactions were monitored by analytical thin-layer chromatography (TLC) with use of Merck silica gel 60F_{254} glass plates. Column chromatography was performed on Kanto Chemical silica gel 60N (230-400 mesh). All the chemicals were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan), Kanto Chemical Co., Inc. (Tokyo, Japan), Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and Sigma Aldrich Japan (Tokyo, Japan).
3-[4-Acetoxy-3,5-(3-methyl-2-butenyl)-phenyl]-(2*E*)-propenoic acid methyl ester **1** have been synthesized as already described.[14] 4-Iodo-2-methylphenol **2** and Guaiacol **6** is commercially available.

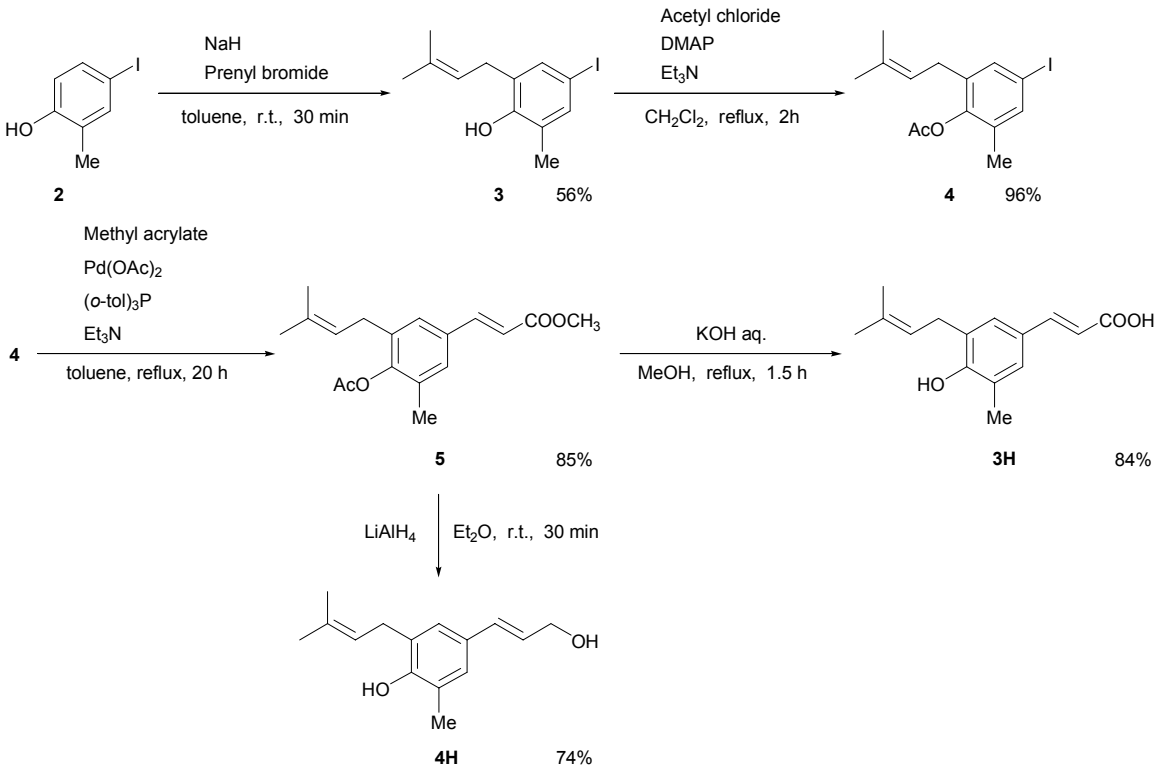
Scheme S1



1 **2H** 74%

4-[3-Hydroxy-2-propenyl-2,6-di(3-methyl-butenyl)phenol (2H)
To a solution of 3-[4-Acetoxy-3,5-(3-methyl-2-butenyl)-phenyl]-(2*E*)-propenoic acid methyl ester **1** (145 mg, 0.407 mmol) in dry Et_2O (5 mL) was added a 1.0 M solution of $LiAlH_4$ in Et_2O (0.50 mL, 0.50 mmol) at 0^{o}C. The resulting mixture was stirred at room temperature for 20 min. The reaction mixture was quenched with water and then acidified with 2N H_2SO_4. The solution was extracted with Et_2O, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (2:1, hexane/EtOAc) to afford **2H** (85.7 mg, 0.299 mmol, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H,), 6.50 (d, J = 15.9 Hz, 1H), 6.24-6.17 (m, 1H), 5.40 (s, 1H) , 5.31 (tquint, J = 7.2, 1.5 Hz, 2H), 4.28 (dd, J = 6.1, 1.2 Hz, 2H), 3.33 (d, J = 7.1 Hz, 4H), 1.77 (s, 12H); EI-MS *m/z* 286 (M^+); Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.45; H, 9.08.

Scheme S2



4-Iodo-2-methyl-6-(3-methyl-2-butenyl)phenol (3)

To a solution of **2** (601 mg, 2.49 mmol) in dry toluene (5 mL) was added NaH (105 mg, 2.63 mmol) and 1-bromo-3-methyl-2-buten (300 μL, 2.60 mmol) at 0°C. After the resulting mixture was stirred at room temperature for 30 min, the mixture was poured into water and then neutralized with 5% CH_3COOH. The mixture was extracted with Et_2O three times and washed with saturated aqueous $NaHCO_3$ followed by brine and dried over anhydrous $MgSO_4$. After solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (10:1, hexane/EtOAc) to afford compound **3** (420 mg, 1.39 mmol, 56%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 1.7 Hz, 1H), 7.24 (m ,1H), 5.28-5.24 (m, 1H), 5.17 (s, 1H), 3.29 (d, J = 7.3 Hz, 2H), 2.17 (s, 3H), 1.78 (s, 6H); EI-MS m/z 302 (M^+).

4-Iodo-2-methyl-6-(3-methyl-2-butenyl)phenyl acetate (4)

To a solution of **3** (417 mg, 1.38 mmol) and DMAP (16 mg, 0.13 mmol) in dry CH_2Cl_2 (3 mL) was added acetyl chloride (140 μL, 1.97 mmol) at 0°C. The resulting mixture was refluxed for 2 h, the mixture was cooled to room temperature and evaporated. The residue was purified by silica gel column chromatography (12:1, hexane/EtOAc) to afford compound **4** (453 mg, 1.32 mmol, 96%) as a light yellow oil. ^{1}H NMR (400 MHz ,$CDCl_3$) δ 7.41 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 1.5 Hz, 1H), 5.17 (tquint, J = 7.2 Hz, 1.5 Hz, 1H), 3.14 (d, J = 7.3 Hz, 2H), 2.31 (s, 3H), 2.10 (s, 3H), 1.74 (d, J = 1.0 Hz, 3H), 1.67 (s, 3H); EI-MS m/z 344 (M^+).

3-[4-Acetoxy-3-methyl-5-(3-methyl-2-butenyl)-phenyl]-(2E)-propenoic acid methyl ester (5)

To a solution of **4** (449 mg, 1.30 mmol), methylacrylate (600 μL, 6.68 mmol), Et_3N (370 μl, 2.65 mmol), $Pd(OAc)_2$ (15 mg, 0.066 mmol) and (*o*-tol)$_3$P (40 mg, 0.13 mmol) in dry toluene (2.5 mL) was refluxed for 20 h. The mixture was cooled to room temperature, diluted with Et_2O, and filtrated through Celite. The filtrate was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (5:1, hexane/EtOAc) to afford compound **5** (335 mg, 1.11 mmol, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H,), 7.25 (s, 1H), 7.22 (s, 1H), 6.36 (d, *J* = 16.1 Hz, 1H), 5.21 (tquint, *J* = 7.2 Hz, 1.5 Hz, 1H), 3.80 (s, 3H), 3.20 (d, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.17 (s, 3H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.69 (s, 3H); EI-MS *m/z* 302 (M^+).

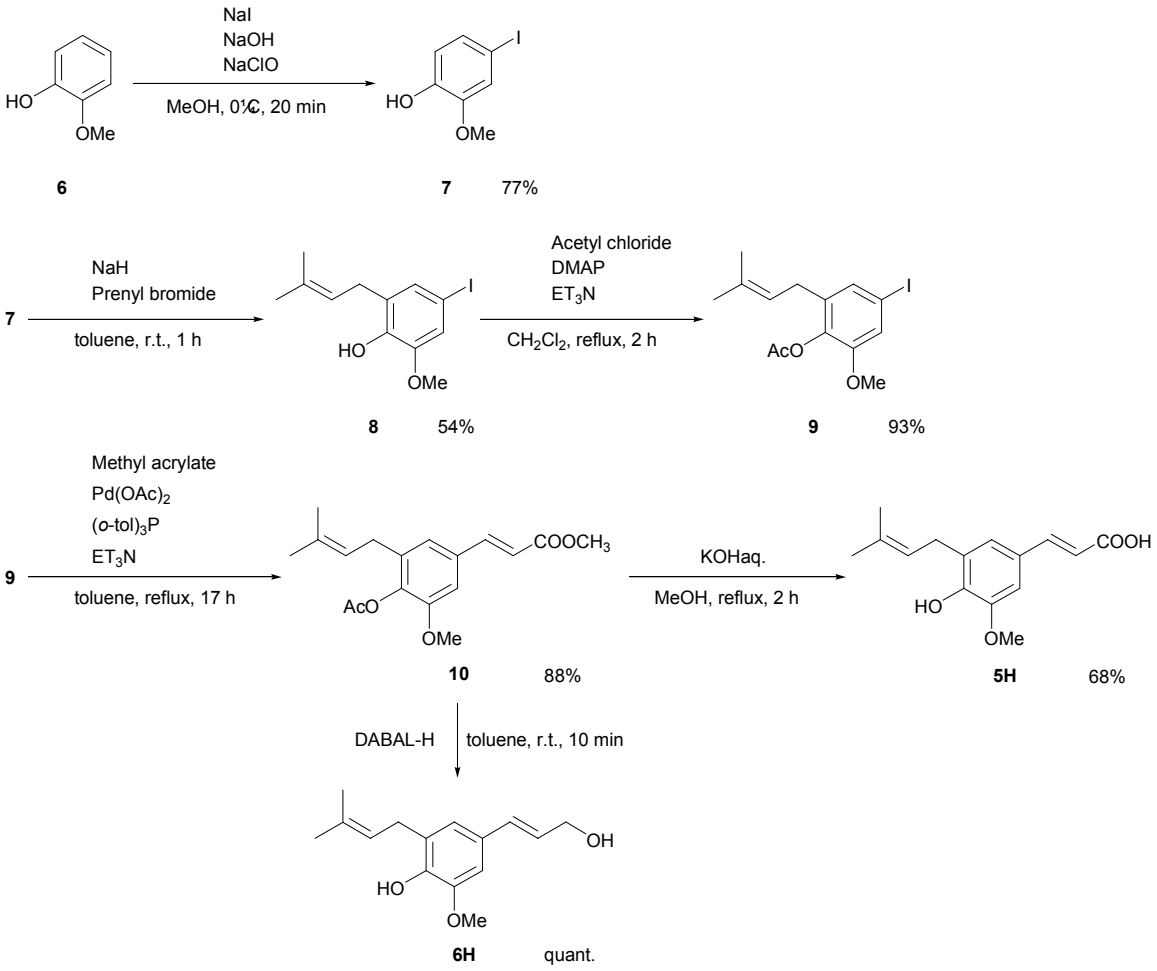
3-[4-Hydoroxy-3-methyl-5-(3-methyl-2-butenyl)-phenyl]-(2E)-propenoic acid (3H)

To a solution of **5** (332 mg, 1.10 mmol) in MeOH (3.0 mL) was added to a solution of KOH (359 mg, 5.50 mmol) in water (2.5 mL). The mixture was refluxed for 1.5 h, cooled to 0^{o}C, and neutralized with 5%CH_3COOH. The MeOH was evaporated under pressure and acidified with 6N HCl and the aqueous residue was extracted with Et_2O three times. The organic layer was washed with saturated aqueous $NaHCO_3$ followed with brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was washed with hexane afford **3H** (227 mg, 0.920 mmol, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.9 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H,), 5.53 (brs, 1H), 5.33-5.29 (m, 1H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.81 (s, 6H); EI-MS *m/z* 246 (M^+); Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.92. H, 7.24.

4-[(*E*)-3-hydroxy-1-propenyl]-2-methyl-6-(3-methyl-2-butenyl)phenol (4H)

To a solution of **5** (174 mg, 0.575 mmol) in dry Et_2O (5 mL) was added a 1.0 M solution of $LiAlH_4$ in Et_2O (0.70 mL, 0.70 mmol) at 0^{o}C. The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with water and then acidified with 2N HCl. The solution was extracted with Et_2O, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (2:1, hexane/EtOAc) to afford **4H** (99 mg, 0.43 mmol, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 1.7 Hz, 1H), 6.99 (d, *J* = 2.0 Hz,1H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.24-6.17 (m, 1H), 5.33-5.29 (m, 1H), 5.23 (s, 1H), 4.29 (dd, *J* = 6.0 Hz, 1.1 Hz, 2H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.22 (s, 3H), 1.80 (s, 3H), 1.78 (s, 3H); EI-MS m/e: 232 (M^+); Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.36; H, 8.68.

Scheme S3



4-Iodo-2-methoxyphenol (7)

Guaiacol **6** (2.48 g, 20.0 mmol) was dissolved in MeOH (50 mL) and then NaI (4.50 g, 29.9 mmol) and NaOH (1.25 g, 30.0 mmol) was added on ice and NaClO (40 mL, 29 mmol) was added dropwise over 40 min at 0-2°C. The mixture was stirred for 20 min at 0°C. The mixture was acidified with 4 N HCl and then treated with 10% $Na_2S_2O_3$. The MeOH was evaporated under reduced pressure and the aqueous residue was extracted with Et_2O three times. The organic layer was saturated aqueous $NaHCO_3$ followed by brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (7:2, hexane/EtOAc) to afford compound **7** (3.84 g, 15.4 mmol, 77%) as a reddish brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 8.3, 2.0 Hz, 1H), 7.11 (d, J = 1.7 Hz, 1H,), 6.68 (d, J = 8.3 Hz, 1H), 5.57 (s, 1H), 3.88 (s, 3H); EI-MS *m/z* 250 (M^+).

4-Iodo-2-methoxy-6-(3-methyl-2-butenyl)phenol (8)

To a solution of **7** (815 mg, 3.26 mmol) in dry toluene (5 mL) was added NaH (143 mg, 3.58 mmol) and 1-bromo-3-methyl-2-buten (410 μL, 3.56 mmol) at 0°C. After the resulting mixture was stirred at room temperature for 1h, the mixture was poured into water and then neutralized with 5%

CH_3COOH. The mixture was extracted with Et_2O three times and washed with saturated aqueous $NaHCO_3$ followed by brine and dried over anhydrous $MgSO_4$. After solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (8:1, hexane/EtOAc) to afford compound **8** (559 mg, 1.76 mmol, 54%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 1.7 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 5.64 (s, 1H), 5.26 (tquint, *J* = 7.3 Hz, 1.5 Hz, 1H), 3.85 (s, 3H), 3.28 (d, *J* = 7.3 Hz, 2H), 1.74 (d, *J* = 1.0 Hz, 3H),1.70 (s, 3H); EI-MS *m/z* 318 (M^+).

4-Iodo-2-methoxy-6-(3-methyl-2-butenyl)phenyl acetate (9)

To a solution of **8** (559 mg, 1.76 mmol) and DMAP (22 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) was added acetyl chloride (175 μL, 2.46 mmol) at 0^{o}C. The resulting mixture was refluxed for 2 h, the mixture was cooled to room temperature and evaporated. The residues were purified by silica gel column chromatography (8:1, hexane/EtOAc) to afford compound **9** (589 mg, 1.64 mmol, 93%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 5.17-5.14 (m, 1H), 3.78 (s, 3H), 3.16 (d, *J* = 7.3 Hz, 2H), 2.30 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H); EI-MS *m/z* 360 (M^+).

(*E*)-3-[4-(Acetyloxy)-3-methoxy-5-(3-methyl-2-butenyl)-phenyl]-2-propenoic acid methyl ester (10)

To a solution of **9** (589 mg, 1.64 mmol), methylacrylate (0.74 mL, 8.2 mmol), Et_3N (0.46 ml, 3.3 mmol), $Pd(OAc)_2$ (19 mg, 0.082 mmol) and (*o*-tol)$_3$P (51 mg, 0.16 mmol) in dry toluene (5 mL) was refluxed for 17 h. The mixture was cooled to room temperature, diluted with Et_2O, and filtrated through celite. The filtrate was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (8:1, hexane/EtOAc) to afford compound **10** (457 mg, 1.44 mmol, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 16.1 Hz, 1H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.95 (d, *J* = 1.7 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.21-5.17 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.22 (d, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.74 (d, *J* = 1.0 Hz, 3H), 1.69 (s, 3H); EI-MS *m/z* 318 (M^+).

(*E*)-3-[4-Hydroxy-3-methoxy-5-(3-methyl-2-butenyl)-phenyl]-2-propenoic acid (5H)

To a solution of **10** (457 mg, 1.44 mmol) in MeOH (10 mL) was added to a solution of KOH (403 mg, 7.18 mmol) in water (10 mL). Reaction mixture was refluxed for 2h and then neutralized by 5% CH_3COOH aq. The MeOH was evaporated under pressure and acidified with 4N HCl and the aqueous residue was extracted with Et_2O three times. The organic layer was washed with saturated aqueous $NaHCO_3$ followed with brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography(1:1 hexane/EtOAc) to afford **5H** (255 mg, 0.972 mmol, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.9 Hz, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 5.99 (brs, 1H), 5.32-5.29 (m, 1H), 3.92 (s, 3H), 3.35 (d, *J* = 7.3 Hz, 2H), 1.76 (s, 3H),1.73 (s, 3H); EI-MS *m/z* 262 (M^+); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.70; H, 6.93.

4-((*E*)-3-hydroxy-1-propenyl)-2-methoxy-6-(3-methyl-2-butenyl)phenol (6H)

To a solution of **10** (200 mg, 0.628 mmol) in dry Et_2O (5 mL) was added a 1.5 M solution of DIBAL-H in toluene (2.0 mL, 3.0 mmol) at 0^oC. The resulting mixture was stirred at room temperature for 10 min. The reaction mixture was quenched with water, the solution was extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solution was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (3:2, hexane/EtOAc) to afford **6H** (141 mg, 0.782 mmol, quant.) as a colorless oil.^{1}H NMR (400 MHz $CDCl_3$) δ 6.78 (d, J = 4.1 Hz, 2H), 6.51 (d, J = 15.6 Hz, 1H), 6.21 (dt, J = 15.9 Hz, 6.0 Hz, 1H), 5.71 (s, 1H), 5.31 (tquint, J = 7.3 Hz, 1.5 Hz, 1H), 4.29 (dd, J = 6.1 Hz, 1.5 Hz, 2H), 3.89 (s, 3H), 3.33 (d, J = 7.3 Hz, 2H), 1.74 (m ,6H); EI-MS *m/z* 248 (M^+); Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.34; H, 8.09.