Concise total synthesis of 1,3-diphenylpropane derivatives griffithanes A, B and F

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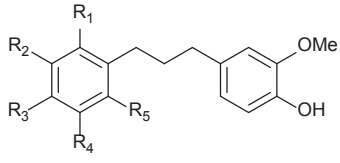
Concise and efficient total syntheses of diarylpropanes griffithane A, B and F, isolated from *Combretum griffithii*, have been accomplished from methoxybenzaldehyde. The Claisen–Schmidt condensation between aldehyde and acetophenone was applied to form chalcone as a key step. The structures of chalcones are confirmed by crystal X-ray crystallography.

Keywords: total synthesis, diarylpropane, *Combretum griffithii*, chalcone

Many unique natural products isolated from plants display different bioactivities that are very significant in phytochemistry.[1] Structures bearing the diarylpropane motif have a diverse range of biological properties including anti-inflammatory,[2, 3] antifungal,[4] anti-vascular,[5] anti-adipogenic,[6] anti-hCNT3 (human concentrative nucleoside transporter 3),[7] anti-proliferative,[8] inhibiting aromatase,[9] inducing TNF-α expression,[10] inhibiting DOPA decarboxylase,[11] and anti-tubercular activities.[12] The diphenylpropane broussonin A inhibited respiratory syncytial-virus (RSV) more effectively than the standard antiviral drug ribavirin, and its anti-aromatase activity has also been evaluated.[9] Broussonin B moderately inhibited chymotrypsin-like activity of the proteasome.[13]



1: R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OMe, R_5 = H
2: R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = H, R_5 = H
3: R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OH, R_5 = H

Fig. 1 Chemical structures of griffithanes A (**1**), B (**2**) and F (**3**).

Griffithane A, B and F (Fig. 1), are three novel diarylpropane-typed natural products, isolated from the stems of *Combretum griffithii* by Moosophon and co-workers in 2011 and 2013.[14, 15] They showed compounds **1**, **2** and **3** exhibited cytotoxicity towards one or more cancer cell lines (KB, MCF-7 and NCI-H187). The IC_{50} values of griffithanes A, B against KB cancer cell line are 6.7 and 17.8 μM, respectively; while those of griffithane F against KB and MCF-7 cancer cell lines are 24.6 and 23.1 μM, respectively.

Several methods have been reported for the synthesis of new diarylpropanes.[2, 3, 9, 16] We have initiated the total synthesis of the three new compounds in order to investigate the potential bioactivity of the derivatives. We now report the concise efficient total syntheses of griffithanes A, B and F from the accessible starting material methoxybenzaldehyde.

Results and discussion

Intermediates including aldehydes **7**, **10** and **13** and acetophenones **6** and **8** were synthesised according to literature.[17-23] The key intermediates 1,3-diphenylpropenones (chalcones) **14**–**16** were synthesised by Claisen–Schmidt condensation of acetophenones **6** and **8** with aldehydes **7**, **10** and **13** in 75–85% yields.[10, 24-26] The structures of **14** and **16** were confirmed by X-ray crystallography (Fig. 2). Using literature methods,[2, 16, 27] we attempted to obtain

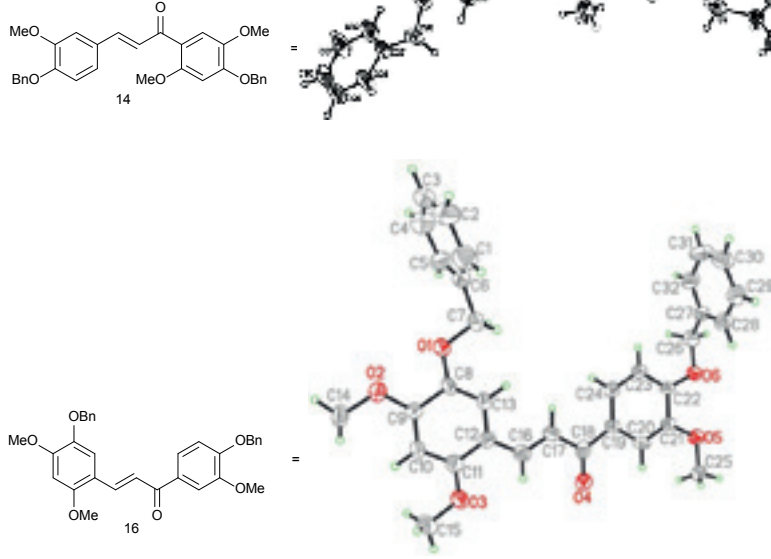


Fig. 2 Crystal X-ray crystallography of compound **14** at 33% probability and **16** at 38% probability.

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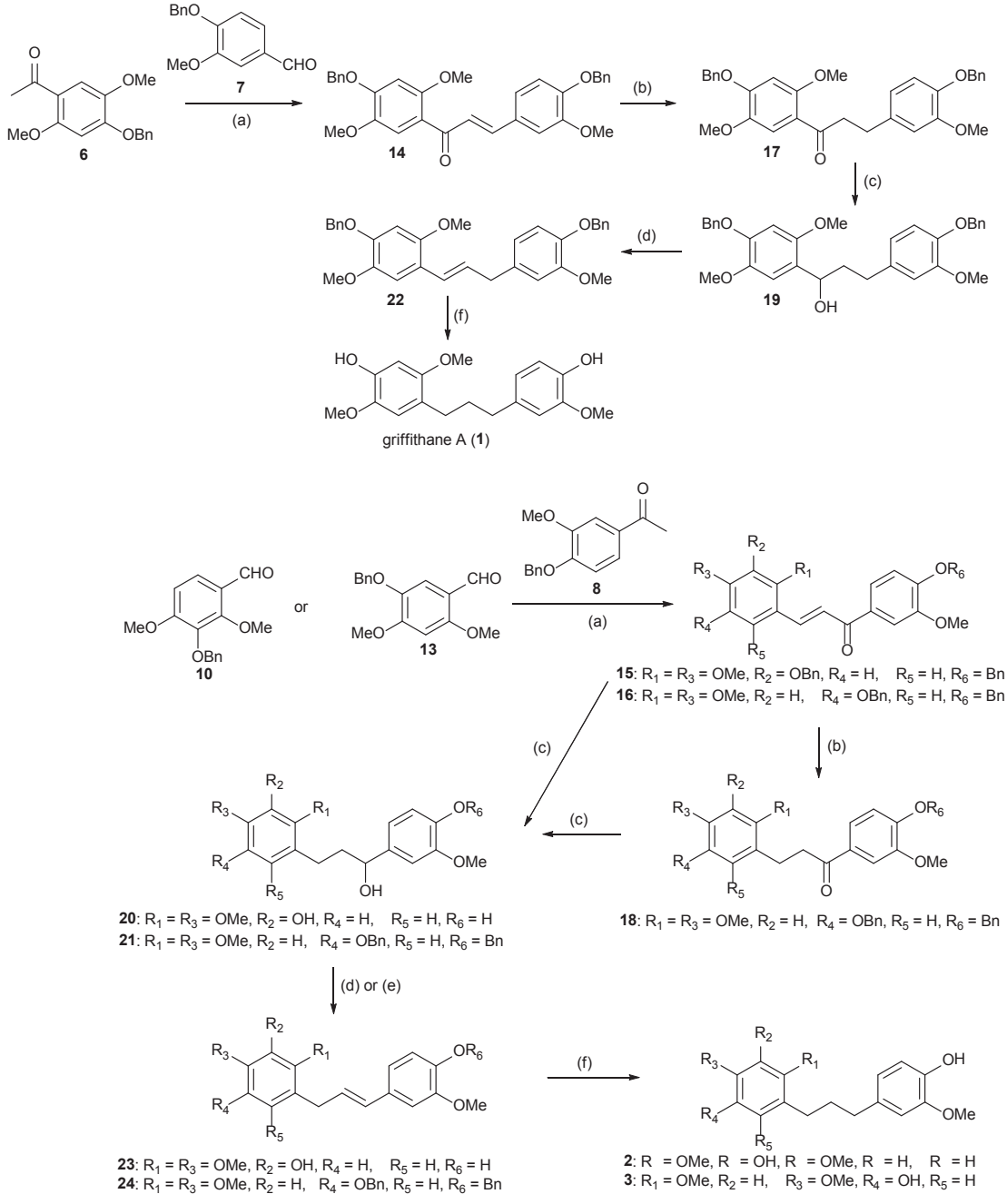
diphenylpropanes **1**–**3** by a one-step reduction of compounds **14**–**16**, but did not succeed. Starting with compounds **14**–**16**, we succeeded in obtaining three natural product griffithanes A, B and F in four steps. Firstly, 1,3-diphenylpropanones **18** and **19** were obtained by selectively reduction of double bonds of chalcones **14** and **16** in 77–80% yields.[16] Then, reduction of compounds **18** and **19** with $NaBH_4$ smoothly gave 1,3-diphenylpropan-1-ols **19** and **21** in 83–84% yields;[10] while compound **20** was available through atmospheric pressure hydrogenation of chalcone **15** in ethyl acetate in 82% yield.[10] After that, dehydration of compounds **19**–**21** with concentrated H_2SO_4/dioxane or 2M HCl/THF afforded 1,3-diphenylpropenes **22**–**24** in 85–86% yields.[10, 28]

Finally, the target compounds griffithanes A, B, and F were obtained by atmospheric pressure hydrogenation of 1,3-diphenylpropenes **22**–**24** for 12–24h in 85–86% yields (Scheme 1). Spectral data of **1**–**3** are consistent with those described for the natural products.[14, 15]

Conclusions

In summary, we have completed the first total syntheses of griffithanes A, B and F starting from accessible methoxybenzaldehyde (overall yields: 27% for griffithane A; 42% for griffithane B and 32% for griffithane F). The mild reaction conditions and operational simplicity make this method attractive for a practical synthesis of these natural products and their derivatives; this facilitates further biological experiments. Studies towards the structure modifications of these natural products for further pharmacological investigation are ongoing.



Scheme 1 Synthesis of griffithanes A, B and F. Reagents and conditions: (a) 60% KOH, EtOH, room temperature (rt), 12 h, 75–85%; (b) $Pd(OAc)_2$, $NaBH_4$, $CHCl_3$, MeOH, 10 h, 77–80%; (c) 10% Pd/C, EtOAc, rt, 1 atm, 24 h, 82%; (d) $NaBH_4$, MeOH, rt, 30 min, 83–84%; (e) H_2SO_4, dioxane, reflux 4–5 h, 85–86%; (f) 1M HCl, THF, reflux 2 h, 85%; (g) 10% Pd/C, EtOAc, rt, 1 atm, 12–24 h, 85–95%.

Experimental

Melting points were measured on a microscopic melting point apparatus. The IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer with a KBr disk. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker AV 300 or AV 400 MHz and 75 or 100 MHz spectrometer in DMSO-d_6 or $CDCl_3$, chemical shift are given in ppm relative to TMS as an internal standard. Mass spectra and high resolution mass spectra were performed on Agilent Q TOF 6520 mass spectrometer with electron spray ionisation (ESI) as the ion mode.

Synthesis of 1,3-diarylpropenones (chalcones, **14–16***) by Claisen–Schmidt condensation of acetophenones with aldehydes; general procedure*

The appropriately substituted acetophenones **6** and **8** (0.77–0.86 g, 3 mmol) and the corresponding aldehydes **7**, **10** and **13** (0.73–0.82 g, 3 mmol) were dissolved in ethanol (30 mL), followed by the addition of a solution of 60% aq. KOH (3 mL). The reaction mixture was stirred for 12 h at room temperature and the progress of the reaction was monitored on TLC (petroleum ether/ethyl acetate, 3:1). After completion of the reaction, it was diluted with water (30 mL), acidified with 2M HCl (30 mL), and extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give 1,3-diarylpropenones (chalcones) **14–16** (1.15–1.30 g) in 75–85% yields.

*(*E*)-1-(4-(Benzyloxy)-2,5-dimethoxyphenyl)-3-(4-(benzyloxy)-3-methoxyphenyl)prop-2-en-1-one* (**14**): Yield 83%; yellow powder; m.p. 123–125 ºC; IR (KBr, cm^{-1}): ν 2941 (CH_2), 1645 (C=O), 1511 (CH=CH), 1265 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (d, *J* = 15.7 Hz, 1H, C3H), 7.25–7.46 (m, 12H, C2,C6",Cb-d,Cb'-d'H), 7.13 (s, 1H, C6'H), 7.10 (d, *J* = 1.7 Hz, 1H, C2"H), 6.87 (d, *J* = 8.7 Hz, 1H, C5"H), 6.54 (s, 1H, C2'H), 5.22 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 3.91 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.9 (C1), 154.2 (C4'), 152.4 (C2'), 150.1 (C3"), 149.7 (C4"), 143.9 (C3), 142.1 (C5'), 136.6 (Ca), 136.3 (Ca'), 128.8 (Cc), 128.6 (Cc'), 128.5 (Cb), 128.1 (Cb'), 127.9 (Cd), 127.2 (Cd'), 127.1 (C1"), 125.3 (C6"), 122.3 (C2), 121.2 (C5"), 113.8 (C1'), 113.6 (C2"), 111.0 (C6'), 99.8 (C3'), 71.2 (C4'-Ph$\underline{C}H_2$), 70.8 (C4"-Ph$\underline{C}H_2$), 56.6 (C5'O$\underline{C}H_3$), 56.4 (C3"O$\underline{C}H_3$), 56.0 (C5'O$\underline{C}H_3$); HRMS (ESI) calcd for $[C_{32}H_{30}O_6+H]^+$ *m/z* 511.2115, found 511.2139.

*(*E*)-1-(3-(Benzyloxy)-2,4-dimethoxyphenyl)-3-(4-(benzyloxy)-3-methoxyphenyl)prop-2-en-1-one* (**15**): Yield 75%; yellow powder; m.p. 128–130 ºC; IR (KBr, cm^{-1}): ν 2942 (CH_2), 1647 (C=O), 1512 (CH=CH), 1268 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, *J* = 14.1 Hz, 1H, C3H), 7.61–7.65 (m, 2H, C6',C6"H), 7.52–7.59 (m, 2H, C2,C5H), 7.32–7.50 (m, 10H, BnH), 6.94 (d, *J* = 8.6 Hz, 1H, C5'H), 6.72 (d, *J* = 8.6 Hz, 1H, C5"H), 5.26 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 3.98 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.0 (C1), 155.9 (C4"), 154.1 (C4'), 152.1 (C3'), 149.6 (C2"), 141.4 (C3), 139.3 (C3"), 137.4 (Ca), 136.3 (C1"), 128.6 (Cc), 128.3 (Cd), 128.0 (Cb), 127.2 (C6'), 122.6 (C6",C1'), 121.0 (C2), 112.1 (C5'), 111.2 (C2'), 107.6 (C5"), 75.2 (C3"-Ph$\underline{C}H_2$), 70.8 (C4'-Ph$\underline{C}H_2$), 61.5 (C2"O$\underline{C}H_3$), 56.1 (C4"O$\underline{C}H_3$), 56.0 (C3'O$\underline{C}H_3$); HRMS (ESI) calcd for $[C_{32}H_{30}O_6+H]^+$ *m/z* 511.2115, found 511.2160.

*(*E*)-3-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-1-(4-(benzyloxy)-3-methoxyphenyl)prop-2-en-1-one* (**16**): Yield 85%; yellow powder; m.p. 126–128 ºC; IR (KBr, cm^{-1}): ν 2937 (CH_2), 1649 (C=O), 1512 (CH=CH), 1263 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, *J* = 15.7 Hz, 1H, C3H), 7.64 (d, *J* = 1.8 Hz, 1H, C2'H), 7.57 (dd, *J* = 8.4, 1.8 Hz, 1H, C6'H), 7.30–7.49 (m, 11H, C2,BnH), 7.19 (s, 1H, C2"H), 6.94 (d, *J* = 8.4 Hz, 1H, C5'H), 6.53 (s, 1H, C5"H), 5.25 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 3.98 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.1(C1), 155.0 (C4'), 153.3 (C3'), 152.0 (C4"), 149.6 (C3"), 142.2 (C3), 139.2 (C6"), 137.2 (Ca), 136.5 (Ca'), 132.2 (Cc), 128.7 (Cc'), 128.6 (Cd), 128.1 (Cd'), 128.0 (Cb), 127.6 (Cb'), 127.2 (C6'), 122.6 (C1'), 120.1 (C2), 115.9 (C5'), 115.6 (C2"), 112.3 (C1"), 111.4 (C2'), 97.2 (C5"), 72.4 (C3"-Ph$\underline{C}H_2$), 70.9 (C4'-Ph$\underline{C}H_2$), 56.3 (C6"O$\underline{C}H_3$), 56.1 (C3',C4"-O$\underline{C}H_3$); HRMS (ESI) calcd for $[C_{32}H_{30}O_6+H]^+$ *m/z* 511.2115, found 511.2154.

*Synthesis of 1,3-diphenylpropanones (*__17__ *and* __18__*); general procedure*

A mixture of 1,3-diphenylpropenones **14** and **16** (1.02 g, 2.0 mmol) in chloroform (4 mL), then $NaBH_4$ (0.076 g, 2.0 mmol), $Pd(OAc)_2$ (0.023g, 0.01 mmol) was combined in a round-bottomed flask with magnetic stirrer capped with a rubber septum that had a deflated balloon attached to it. Methanol (20 mL) was added into the flask slowly through a syringe. The mixture was stirred at room temperature for 10 h, based on TLC monitoring. The resulting mixture was filtered, and methanol was evaporated using rotary evaporator. Brine solution was added, and the product was extracted with $CHCl_3$. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give 1,3-diphenylpropanones **17** and **18** (0.79–0.82 g) in 77–80% yields as yellow solids.

1-(4-(Benzyloxy)-2,5-dimethoxyphenyl)-3-(4-(benzyloxy)-3-methoxyphenyl)propan-1-one (**17**): Yield 77%; off-white powder; m.p. 120–122 ºC; IR (KBr, cm^{-1}): ν 3060 (CH), 2958 (CH_2), 1669 (C=O), 1518 (CH=CH), 1216 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.44 (m, 11H, C6',BnH), 6.78–6.81 (m, 2H, C2",C5"H), 6.69 (d, *J* = 8.2 Hz, 1H, C6"H), 6.49 (s, 1H, C3'H), 5.21 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 3.86 (s, 6H), 3.73 (s, 3H), 3.21–3.26 (m, 2H, C2H), 2.90–2.95 (m, 2H, C3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.9 (C1), 154.7 (C4'), 152.7 (C2'), 149.5 (C3"), 146.3 (C4"), 143.6 (C5'), 137.4 (Ca), 136.2 (Ca'), 135.3 (C1"), 128.6 (Cc), 128.4 (Cc'), 128.1 (Cd), 127.6 (Cd'), 127.2 (Cb,Cb'), 120.1(C6"), 119.4 (C2"), 114.3 (C1'), 113.3 (C5"), 112.5 (C2"), 98.9 (C3'), 71.1 (C4',C4"-Ph$\underline{C}H_2$), 56.3 (C2'O$\underline{C}H_3$), 55.9 (C5',C3"-O$\underline{C}H_3$), 45.5 (C2), 30.2 (C3); HRMS (ESI) calcd for $[C_{32}H_{32}O_6+H]^+$ *m/z* 513.2272, found 513.2246.

*2,4-Diamino-7-chloro-5-(*p*-tolylthio)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile* (**18**): Yield 83%; off-white powder; m.p. 122–124 ºC; IR (KBr, cm^{-1}): ν 3061 (CH), 2961 (CH_2), 1667 (C=O), 1517 (CH=CH), 1212 (OCH_3); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, *J* = 1.5 Hz, 1H, C2'H), 7.49 (d, *J* = 8.4 Hz, 1H, C6'H), 7.28–7.43 (m, 10H, BnH), 6.87 (d, *J* = 8.4 Hz, 1H, C5'H), 6.78 (s, 1H, C6"H), 6.51 (s, 1H, C5"H), 5.21 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 3.92 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.08–3.11 (m, 2H, C2H), 2.89–2.92 (m, 2H, C3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.6 (C1), 152.3 (C2"), 149.5 (C4"), 149.1 (C4'), 142.0 (C3'), 137.6 (C3"), 136.4 (Ca,Ca'), 128.6 (C1'), 128.4 (Cc), 128.1 (Cc'), 127.7 (Cd), 127.5 (Cd'), 127.2 (Cb,Cb'), 122.5 (C1"), 121.4 (C6'), 118.3 (C6"), 112.3 (C5'), 110.8 (C2'), 98.3 (C5"), 72.5 (C3"-Ph$\underline{C}H_2$), 70.8 (C4'-Ph$\underline{C}H_2$), 56.6 (C2"O$\underline{C}H_3$), 56.1 (C3',C4"-O$\underline{C}H_3$), 38.8 (C2), 25.4 (C1); HRMS (ESI) calcd for $[C_{32}H_{32}O_6+H]^+$ *m/z* 513.2272, found 513.2294.

*Synthesis of 1,3-diphenylpropan-1-ols (*__19__–__21__*); general procedure*

Powdered $NaBH_4$ (0.30 g, 7.9 mmol) was added to a stirred solution of 1,3-diphenylpropanones **17** and **18** (0.72 g, 1.4 mmol) in MeOH (28 mL) and the reaction mixture was stirred at room temperature for 30 min. After completion of the reaction, MeOH was removed *in vacuo*. The oily residue was washed with $NaHCO_3$ and water, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel to give compounds **19** and **21** (0.60 g) as oils in 83–84% yields. A solution of 1,3-diphenylpropenone **15** (1.02 g, 2.0 mmol) in 20 mL of ethyl acetate was placed in the reaction bottle of the atmospheric pressure hydrogenation apparatus and to that was added 0.25 g (25 w/w %) of palladium-charcoal (10%). The air was displaced with hydrogen and the mixture was shaken for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the palladium-charcoal was filtered and ethyl acetate was removed under reduced pressure. The solid obtained was purified by column chromatography on silica gel to obtain the compound **20** (0.55 g, 82%) as an oil.

1-(4-(Benzyloxy)-2,5-dimethoxyphenyl)-3-(4-(benzyloxy)-3-methoxyphenyl)propan-1-ol (**19**): Yield 77%; off-white powder; m.p. 130–132 ºC; IR (KBr, cm^{-1}): ν 3035 (CH), 2931 (CH_2), 1517 (ArH), 1205 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.42 (m, 10H, BnH), 6.89 (s, 1H, C6'H), 6.84 (d, *J* = 8.2 Hz, 1H, C5"H), 6.74–6.80

(m, 1H, C2"H), 6.66 (dd, *J* = 8.2, 1.5 Hz, 1H, C6"H), 6.50 (s, 1H, C3'H), 5.13 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 4.84 (br s, 1H, C1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.67 (s, 3H), 2.55–2.79 (m, 2H, C3H), 2.48 (br s, 1H, C1OH), 1.95–2.11 (m, 2H, C2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.6 (C2'), 149.6 (C3"), 147.8 (C4'), 146.3 (C4"), 143.9 (C5'), 137.4 (Ca), 137.1 (Ca'), 135.5 (C1"), 128.5 (Cc), 128.4 (Cc'), 127.9 (Cd), 127.6 (Cd'), 127.3 (Cb), 127.2 (Cb'), 125.0 (C6"), 120.2 (C1'), 114.4 (C5"), 112.5 (C6'), 111.9 (C2"), 100.7 (C3'), 71.7 (C4'-Ph$\underline{C}H_2$), 71.2 (C4"-Ph$\underline{C}H_2$), 69.7 (C1), 56.9 (C2'O$\underline{C}H_3$), 55.9 (C5',C3"-O$\underline{C}H_3$), 39.0 (C2), 31.9 (C3); HRMS (ESI) calcd for $[C_{32}H_{34}O_6+Na]^+$ *m/z* 537.2248, found 537.2203.

3-(3-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)propyl)-2,6-dimethoxyphenol (**20**): Yield 82%; off-white powder; m.p. 158–160 ºC; IR (KBr, cm^{-1}): ν 3039 (CH), 2932 (CH_2), 1519 (ArH), 1206 (OCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.91 (d, *J* = 1.7 Hz, 1H, C2"H), 6.86 (d, *J* = 8.1 Hz, 1H, C5"H), 6.79 (dd, *J* = 8.1, 1.7 Hz, 1H, C6"H), 6.65 (d, *J* = 8.4 Hz, 1H, C6'H), 6.60 (d, *J* = 8.4 Hz, 1H, C3'H), 5.59 (br s, 1H, C4'OH), 5.57 (br s, 1H, C4"OH), 4.53–4.57 (m, 1H, C1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H, C3H), 2.38 (br s, 1H, C1OH), 1.92–2.06 (m, 2H, C2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5 (C2'), 146.1 (C3"), 145.2 (C4'), 144.8 (C4"), 138.5 (C5'), 136.6 (C1"), 127.6 (C6"), 119.5 (C1'), 118.9 (C5"), 114.0 (C2"), 108.4 (C6'), 106.6 (C3'), 73.3 (C1), 60.6 (C2'O$\underline{C}H_3$), 56.2 (C3"O$\underline{C}H_3$), 55.8 (C5'O$\underline{C}H_3$), 40.0 (C2), 25.9 (C3); HRMS (ESI) calcd for $[C_{18}H_{22}O_6+Na]^+$ *m/z* 357.1309, found 357.1309.

3-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-1-(4-(benzyloxy)-3-methoxyphenyl)propan-1-ol (**21**): Yield 84%; off-white powder; m.p. 133–135 ºC ; IR (KBr, cm^{-1}): ν 3033 (CH), 2930 (CH_2), 1518 (ArH), 1202 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.46 (m, 4H, Cc,Cc'H), 7.28–7.39 (m, 6H, Cb,Cb',Cd,Cd'H), 6.93 (d, *J* = 1.5 Hz, 1H, C2'H), 6.84 (d, *J* = 8.2 Hz, 1H, C5'H), 6.73–6.76 (m, 2H, C6',C2"H), 6.54 (s, 1H, C5"H), 5.14 (s, 2H, C3"PhC$\underline{H}_2$), 5.07 (s, 2H, C4'PhC$\underline{H}_2$), 4.46 (dd, *J* = 8.5, 4.7 Hz, 1H, C1H), 3.89 (s, 6H, C3',C6"OMe), 3.80 (s, 3H, C4"OMe), 2.61–2.67 (m, 2H, CH_2, C3H), 1.85–2.00 (m, 2H, CH_2, C2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.1 (C6"), 149.7 (C3'), 148.9 (C4"), 147.4 (C4'), 142.0 (C3"), 138.0 (C1'), 137.6 (Ca), 137.2 (Ca'), 128.4 (Cc), 128.3 (Cc'), 127.7 (Cd), 127.6 (Cd'), 127.5 (Cb,Cb'), 127.2 (C6'), 121.6 (C2"), 118.2 (C1"), 118.1 (C5'), 109.7 (C2'), 98.3 (C5"), 73.0 (C1), 72.3 (C3"-Ph$\underline{C}H_2$), 71.1 (C4'-Ph$\underline{C}H_2$), 56.4 (C6"O$\underline{C}H_3$), 56.2 (C4"O$\underline{C}H_3$), 55.9 (C3'O$\underline{C}H_3$), 39.4 (C2), 25.7 (C3); HRMS (ESI) calcd for $[C_{32}H_{34}O_6+Na]^+$ *m/z* 537.2248, found 537.2248.

*Synthesis of 1,3-diphenylpropenes (***22**–**24***); general procedure*

Two drops of concentrated H_2SO_4 were added to a solution of compounds **19** and **21** (0.51 g, 1.0 mmol) in dioxane (4 mL). The reaction mixture was refluxed for 4–5 h and the progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured over ice-cold water with vigorous stirring. The reaction mixture was extracted with petroleum ether and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give compounds **22** and **24** (0.42–0.43 g) as oils in 85–86% yields. 1M HCl (3 mL, 3 mmol) was added to a solution of compound **20** (0.50g, 1.5 mmol) in THF (10 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 10 min and refluxed for 2 h and the progress of reaction was monitored by TLC. After completion of the reaction, THF was removed under reduced pressure, cooled and extracted with ethyl acetate and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give compounds **23** (0.40 g, 85%) as an oil.

*(*E*)-1-(Benzyloxy)-4-(3-(4-(benzyloxy)-3-methoxyphenyl)prop-1-en-1-yl)-2, 5-dimethoxybenzene* (**22**): Yield 85%; off-white syrup; IR (film, cm^{-1}): ν 3026 (CH), 2925 (CH_2), 1516 (CH=CH), 1209 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22–7.44 (m, 10H, 2BnH), 6.97 (s, 1H, C6'H), 6.68–6.83 (m, 4H, C1,C2",C5",C6"H,), 6.49 (s, 1H, C3'H), 6.16–6.21 (m, 1H, C2H), 5.13 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 3.86 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 3.47 (d, *J* = 6.7 Hz, 2H, C3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9 (C4'), 149.7 (C3"), 148.1 (C4"), 146.6 (C5'), 144.1 (C2'), 137.4 (Ca), 137.1 (Ca'), 133.9 (C1"), 128.5 (C1), 128.4 (Cc), 128.0 (Cc'), 127.8 (Cd), 127.7 (Cd'), 127.3 (Cb), 127.2 (Cb'), 124.9 (C2), 120.5 (C6"), 119.2 (C1'), 114.4 (C2"), 112.6 (C5"), 110.7 (C6'), 100.9 (C3'), 71.6 (C4'-Ph$\underline{C}H_2$), 71.2 (C4"-Ph$\underline{C}H_2$), 56.8 (C2'O$\underline{C}H_3$), 56.4 (C5'O$\underline{C}H_3$), 56.0 (C3"O$\underline{C}H_3$), 39.4 (C3); HRMS (ESI) calcd for $[C_{32}H_{32}O_5+H]^+$ *m/z* 497.2323, found 497.2286.

*(*E*)-3-(3-(4-Hydroxy-3-methoxyphenyl)allyl)-2,6-dimethoxyphenol* (**23**): Yield 81%; off-white powder; m.p. 134–136 ºC; IR (film, cm^{-1}): ν 3028 (CH), 2928 (CH_2), 1519 (CH=CH), 1210 (OCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.83–6.87 (m, 3H, C1,C6',C2"H), 6.69 (d, *J* = 8.4 Hz, 1H, C6"H), 6.62 (d, *J* = 8.4 Hz, 1H, C5"H), 6.34 (d, *J* = 15.7 Hz, 1H, C2H), 6.16–6.21 (m, 1H, C3'H), 5.60 (br s, 1H, C4'OH), 5.59 (br s, 1H, C4"OH), 3.88 (s, 3H, C2'OMe), 3.87 (s, 6H, C5',3"OMe), 3.49 (dd, *J* = 6.6, 1.0 Hz, C3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5 (C3"), 146.3 (C4'), 145.2 (C4"), 144.9 (C5'), 138.6 (C2'), 130.3 (C1"), 130.2 (C1), 127.0 (C2), 126.4 (C6"), 119.6 (C5"), 114.3 (C1'), 107.9 (C2",C5'), 106.4 (C3'), 60.7 (C2'O$\underline{C}H_3$), 56.2 (C5'O$\underline{C}H_3$), 55.8 (C3"O$\underline{C}H_3$), 32.8 (C3); HRMS (ESI) calcd for $[C_{18}H_{20}O_5+Na]^+$ *m/z* 339.1203, found 339.1225.

*(*E*)-1-(Benzyloxy)-5-(3-(4-(benzyloxy)-3-methoxyphenyl)allyl)-2,4-dimethoxybenzene* (**24**): Yield 86%; off-white syrup; IR (film, cm^{-1}): ν 3023 (CH), 2923 (CH_2), 1513 (CH=CH), 1208 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.43 (m, 10H), 6.76–6.79 (m, 3H, C2,C2',C6'H), 6.54 (s, 1H, C2"H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H, C5"H), 6.27 (d, *J* = 15.7 Hz, 1H, C1H), 6.07–6.16 (m, 1H, C5'H), 5.13 (s, 2H, CH_2, C4'PhC$\underline{H}_2$), 5.04 (s, 2H, CH_2, C3"PhC$\underline{H}_2$), 3.87 (s, 6H, C3',C6"OMe), 3.80 (s, 3H, C4"OMe), 3.39 (d, *J* = 8.5 Hz, 2H, C3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.1 (C6"), 149.7 (C3'), 149.1 (C4"), 147.4 (C4'), 142.1 (C3"), 137.6 (Ca'), 137.2 (Ca), 131.5 (C1'), 130.1 (C1), 128.4 (Cc'), 128.3 (Cc), 127.7 (Cd'), 127.6 (Cd), 127.5 (Cb'), 127.4 (Cb), 127.2 (C2), 120.5 (C1"), 118.9 (C6'), 118.0 (C5'), 114.2 (C2'), 109.5 (C2"), 98.5 (C5"), 72.4 (C3"-Ph$\underline{C}H_2$), 71.1 (C4'-Ph$\underline{C}H_2$), 56.5 (C6"O$\underline{C}H_3$), 56.4 (C4"O$\underline{C}H_3$), 56.0 (C3'O$\underline{C}H_3$), 33.9 (C3); HRMS (ESI) calcd for $[C_{32}H_{32}O_5+H]^+$ *m/z* 497.2323, found 497.2328.

*Synthesis of griffithanes A (**1**), B (**2**) and F (**3**); general procedure*

A solution of compounds **22**–**24** (0.25-0.40 g, 0.8 mmol) in 8 mL of ethyl acetate was placed in the reaction bottle of atmospheric pressure hydrogenation apparatus and to that was added 0.063–0.1 g (25 w/w %) of palladium-charcoal (10%). The air was displaced with hydrogen and the mixture was shaken for 12–24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the palladium-charcoal was filtered and ethyl acetate was removed under reduced pressure. The solid obtained was purified by column chromatography on silica gel to afford natural products **1**–**3** (0.22–0.24 g) as yellow oils in 85–95% yields. The structures of the synthesised compounds above were characterised by their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectra.

4-(3-(4-Hydroxy-3-methoxyphenyl)propyl)-2, 5-dimethoxyphenol (griffithane A, **1**): Yield 86%; Viscous oil; IR (film, cm^{-1}): ν 3417 (OH), 3002 (CH), 2932 (CH_2), 1511 (ArH), 1267 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.85 (br d, *J* = 8.4 Hz, 1H, C5"H), 6.70–6.72 (m, 2H, C2",C6"H), 6.67 (s, 1H, C6'H), 6.56 (br s, 1H, C4"OH), 5.60 (br s, 1H, C4'OH), 5.55 (s, 1H, C3'H), 3.88 (s, 3H, C3"OMe), 3.83 (s, 3H, C5'OMe), 3.76 (s, 3H, C2'OMe), 2.62 (t, *J* = 8.0 Hz, 2H, C3H), 2.58 (t, *J* = 8.0 Hz, 2H, C1H), 1.87 (quint, *J* = 8.0 Hz, 2H, C2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.0 (C2'), 146.3 (C3"), 144.2 (C4'), 143.5 (C4"), 140.0 (C5'), 134.6 (C1"), 121.6 (C6"), 120.9 (C1'), 114.1 (C5"), 113.2 (C6'), 111.0 (C2"), 99.4 (C3'), 56.7 (C5'O$\underline{C}H_3$), 56.0 (C2'O$\underline{C}H_3$). 55.8 (C3"O$\underline{C}H_3$), 35.5 (C3), 32.1 (C2), 29.5 (C1); HRMS (ESI) calcd for $[C_{18}H_{22}O_5+H]^+$ *m/z* 319.1540, found 319.1536.

3-(3-(4-Hydroxy-3-methoxyphenyl)propyl)-2,6-dimethoxyphenol (griffithane B, **2**): Yield 95%; Viscous oil; IR (film, cm^{-1}): ν 3424 (OH), 3004 (CH), 2936 (CH_2), 1512 (ArH), 1269 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (d, *J* = 8.4 Hz, 1H, C5"H), 6.69–6.71 (m, 2H, C2",C6"H), 6.64 (d, *J* = 8.4 Hz, 1H, C6'H), 6.59 (d, *J* = 8.4 Hz, 1H, C5'H), 5.61 (br s, 1H, OH, C4"OH), 5.54 (br s, 1H, OH, C3'OH), 3.87 (s, 6H, C4', C3"OMe), 3.85 (s, 3H, C2'OMe), 2.58–2.64 (m, 4H,

C1,C3H), 1.89 (quint, J = 8.0 Hz, 2H, C2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.3 (C2'), 145.9 (C3'), 145.4 (C3"), 143.5 (C4"), 138.5 (C4'), 134.4 (C1"), 128.4 (C1'), 120.9 (C6'), 119.3 (C6"), 114.1 (C5"), 111.0 (C2"), 106.3 (C5'), 60.5 (C4'O$\underline{C}H_3$), 56.2 (C2'O$\underline{C}H_3$), 55.8 (C3"O$\underline{C}H_3$), 35.3 (C3), 32.5 (C2), 29.2 (C1); HRMS (ESI) calcd for $[C_{18}H_{22}O_5+Na]^+$ *m/z* 341.1359, found 341.1376.

5-(3-(4-Hydroxy-3-methoxyphenyl)propyl)-2,4-dimethoxyphenol (griffithane F, **3***)*: Yield 85%; viscous oil; IR (film, cm^{-1}): ν 3382 (OH), 3003 (CH), 2934 (CH_2), 1512 (ArH), 1265 (OCH_3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (d, J = 8.4 Hz, C5"H), 6.75 (s, C6'H), 6.70-6.71 (m, C2",6"H), 6.50 (s, C3'H), 5.56 (br s, 1H, C5'OH), 5.29 (br s, 1H, C4"OH), 3.88 (s, 3H, C4'OMe), 3.87 (s, 3H, C3"OMe), 3.79 (s, 3H, C2'OMe), 2.55–2.62 (m, 4H, C1,C3H), 1.86 (quint, J = 8.0 Hz, 2H, C2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9 (C2'), 146.3 (C3"), 144.6 (C4'), 143.5 (C4"), 139.2 (C5'), 134.5 (C1"), 123.4 (C1'), 120.9 (C6"), 115.8 (C6'), 114.1 (C5"), 111.0 (C2"), 97.1 (C3'), 56.5 (C2'O$\underline{C}H_3$), 56.2 (C4'O$\underline{C}H_3$), 55.8 (C3"O$\underline{C}H_3$), 35.2 (C3), 31.9 (C2), 29.0 (C1); HRMS (ESI) calcd for $[C_{18}H_{22}O_5+H]^+$ *m/z* 319.1540, found 319.1548.

Electronic Supplementary Information

Electronic Supplementary information including the data and ^{1}H NMR and ^{13}C NMR spectra of **14**–**24**, **1**–**3**, can be found, in the online version available from at stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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