SUPPORTING INFORMATION

Phytotoxic activity of quinones and resorcinolic lipid derivatives

Cassia S. Mizuno, Agnes M. Rimando,* Stephen O. Duke

United States Department of Agriculture, Agricultural Research Service,

Natural Products Utilization Research Unit, P.O. Box 8048

University, MS 38677-8048

*Corresponding Author:

Agnes M. Rimando

P.O. Box 8048

University, MS 38677

Phone: 662-915-1037; Fax: 662-915-1035

E-mail: agnes.rimando@ars.usda.gov

Preparation and synthesis of resorcinol analogs

1,3-dimethoxy-5-pentadecylbenzene **4**. To a cold solution (-78°C) of phosphonium salt **3** (500 mg, 0.92 mmol) in THF was added *n*-butyllithium (1.6 mol in hexanes, 580 µL, 0.92 mmol), and the resulting solution was stirred under an inert atmosphere for 2 h (Scheme 1). A solution of aldehyde **2** (154 mg, 0.92 mmol) in THF was added dropwise, and the mixture was allowed to warm to room temperature and stirred for 12 h. The resulting suspension was poured into water and extracted with ethyl acetate. The organic phase were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified through automated flash purification eluting with hexanes/ethyl acetate (9: 1). The resulting *cis* and *trans* isomers (174 mg, 0.5 mmol) were hydrogenated using Pd/C in MeOH affording 132 mg of **4**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 2H, *J* = 8 Hz); 1.27 (s, 25H); 1.60 (s, 2H); 2.55 (t, 2H, *J* = 8 Hz); 3.78 (s, 6H); 6.30 (s, 1H); 6.35 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 29.6, 29.7, 29.8, 29.9 (7C), 31.5, 32.1, 36.5, 55.4 (2C); 97.7, 106.6 (2C), 145.6, 160.8 (2C). GCMS: *m/z* 348.4

5-pentadecylbenzene-1,3-diol **5**. To a cold solution (-40 °C) of **4** (50 mg, 0.14 mmol) in DCM was added BBr_3 (70 µL, 0.72 mmol) (*1*) (Scheme 1). The reaction was stirred for 12 h at room temperature then poured into ice water. The aqueous layer was extracted with DCM (3 x 10 mL), and the organic solvent was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified through flash chromatography using hexanes/ethyl acetate (75:25) and afforded 36 mg of **5**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 8Hz); 1.27 (s, 24H); 1.54 (s, 2H); 2.42 (t, 2H, *J* = 8 Hz); 4.90 (s, 2H); 6.08 (s, 1H); 6.11 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 22.6,

29.3, 29.4, 19.5, 29.7 (7 C), 31.3, 31.9, 35.9, 99.7, 106.7 (2C), 145.1, 158 (2C). HRMS: calcd for $C_{21}H_{37}O_2$ [M+ H] 321.2793, found 321.2769.

3-methoxy-5-pentadecylphenol **6**. To a cold solution (-40 °C) of **4** (20 mg, 0.05 mmol) in DCM was added BBr_3 (11 µL, 0.11 mmol) (Scheme 1). The reaction was stirred for 12h at room temperature then poured into ice water. The aqueous layer was extracted with DCM (3 x 10 mL), and the organic solvent was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified through flash chromatography using hexanes/ethyl acetate (75:25) and afforded 16 mg of **6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 8 Hz); 1.25 (s, 24 H); 1.57 (t, 2H, *J* = 8 Hz); 2.50 (t, 2H, *J* = 8 Hz); 3.76 (s, 3H); 6.25 (d, 2H, J = 8 Hz); 6.32 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9 (7C), 31.4, 32.1, 36.3, 55.4, 98.8, 106.9 (2C), 108.0, 146.0, 160.9 (2C). HRMS: calcd for $C_{22}H_{39}O_2$ [M+ H] 335.295, found 335.2957.

tert-butyl(3-decyl-5-methoxyphenoxy)dimethylsilane **9**. Aldehyde **7** was synthesized from methylation (*2*) of the 3,5 dihydroxy aldehyde followed by protection of the hydroxyl group with TBSCl (*3*). To a cold solution (-78°C) of phosphonium salt **8** (700 mg, 1.44 mmol) in THF was added *n*-butyllithium (1.6 mol in hexanes, 905 µL, 1.44 mmol), and the resulting solution was stirred under inert atmosphere for 2h (Scheme 2). A solution of aldehyde **7** (385 mg, 1.44 mmol) in THF was added dropwise, and the mixture was allowed to warm to room temperature and stirred for 12 h. The resulting suspension was poured into water and extracted with ethyl acetate. The organic phase were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified through automated flash purification eluting with

hexanes/ethyl acetate (9:1) and gave 82 mg of **9**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.20 (s, 6H); 0.88 (t, 3H, *J* = 8Hz); 0.98 (s, 9H); 1.26 (s, 16H); 1.58 (s, 2H); 2.51 (t, 2H, *J* = 8 Hz); 3.76 (s, 3H); 6.23 (s, 1H); 6.28 (s, 1H); 6.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.15 (2C), 14.3, 22.9, 25.8, 25.9 (3C), 29.5 (2C), 29.7, 29.8 (2C); 29.9, 31.5, 32.1, 36.3, 55.3, 103.5, 107.4, 113.0, 145.3, 156.7, 160.5.

3-methoxy-5-undecylphenol **10**. Tetrabutyl ammonium fluoride (290 µM, 0.29 mmol) was added to a solution of **9** (54 mg, 0.19 mmol) in THF, and the mixture was stirred at room temperature for 45 min (Scheme 2). The reaction was poured into water, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic solvent was removed under reduced pressure. The crude product was purified through flash chromatography eluting with hexanes/ethyl acetate (7:3) and gave 22 mg of **10**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 8 Hz); 1.25 (s, 15H); 1.57 (m, 3H); 2.50 (t, 2H, *J* = 8Hz); 3.76 (s, 3H); 4.99 (s, 1H); 6.24 (s, 1H); 6.26 (s, 1H); 6.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 29.5 (2C), 29.7, 29.8 (2C), 29.9, 31.4, 32.1, 36.2, 55.4, 98.8, 107.0, 108.1, 146.0, 156.6, 160.9. HRMS: calcd for $C_{18}H_{31}O_2$ [M+ H] 279.2324, found 279.2319.

*General procedure for acetylation. Preparation of compounds **11** and **12***. Triethylamine (2 mmol) was added to a solution of phenol (**6** or **10**) (1 mmol) in dichloromethane (Scheme 3). The reaction was stirred for 10 min and acetyl chloride (1.5 mmol) was added at 0 °C (*4*). The mixture was stirred overnight at room temperature. The reaction was poured into water and extracted with ethyl acetate (3 x 10 mL). The organic phase were combined and dried over $MgSO_4$. The solvent was concentrated, and

the crude product was purified by column chromatography using hexanes/ethyl acetate (7:3) as eluent.

3-methoxy-5-pentadecylphenyl acetate ***11***. 92% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, *J* = 8 Hz); 1.26 (s, 24H); 1.59 (m, 2H); 2.27 (s, 3H); 2.56 (t, 2H, *J* = 8 Hz); 3.77 (s, 3H); 6.46 (s, 1H); 6.51 (s, 1H); 6.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 21.3, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9 (6C), 31.2, 32.1, 36.2, 55.5, 104.8, 112.1, 114.0, 145.6, 151.7, 160.5, 169.6. HRMS: calcd for $C_{24}H_{40}Na_1O_3$ [M + Na] 399.2875, found 399.2876.

3-methoxy-5-undecylphenyl acetate ***12***. 94% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, 2H, *J* = 8 Hz); 1.28 (s,); 1.61 (m, 2H); 2.29 (s, 3H); 2.58 (t, 2H, *J* = 8 Hz); 3.79 (s, 3H); 6.48 (s, 1H); 6.53 (s, 1H); 6.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 21.3, 22.9, 29.5, 29.6, 29.7, 29.8 (2C), 29.9, 31.3, 32.1, 36.2, 55.5, 104.8, 112.1, 114.0, 145.6, 151.6, 160.4, 169.7. HRMS: calcd for $C_{20}H_{32}Na_1O_3$ [M + Na] 343.2249, found 343.2219.

General procedure for alkylation. *Preparation of* ***13*** *and* ***14***. Alkylation was performed using a modified procedure described by Orsini *et al* (*5*) (Scheme 3). Potassium carbonate (2 mmol) was added to a solution of phenol (**6** or **10**) (1 mmol) in DMF. The reaction was stirred for 30 min, and ethyl iodide (1.5 mmol) was added dropwise. The reaction was stirred for 12 h and quenched with water. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and concentrated to a crude product which was purified on a column of silica gel (hexanes/ethyl acetate (9:1).

1-ethoxy-3-methoxy-5-pentadecylbenzene ***13***. 67% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, *J* = 8 Hz); 1.26 (s, 24H); 1.40 (t, 3H, *J* = 8 Hz); 1.60 (m, 2H); 2.54

(t, 2H, J = 8Hz); 3.77 (s, 3H); 4.0 (dd, 2H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 12Hz); 6.30(s, 1H); 6.34 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 15.1, 22.9, 29.6, 29.8 (2C); 29.9 (7C), 31.5, 32.2, 36.5, 55.4, 63.5, 98.2, 106.6, 107.2, 145.5, 160.2, 160.8. GCMS: *m/z* 362.3

1-ethoxy-3-methoxy-5-undecylbenzene **14**. 41% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, 3H, J = 8 Hz); 1.28 (s,); 1.41 (t, 3H, *J* = 8 Hz); 1.61 (m, 2H); 2.55 (t, 2H, *J* = 8 Hz); 3.79 (s, 3H); 4.02 (dd, 2H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 16 Hz); 6.31 (s, 1H); 6.35 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 15.1, 22.9, 29.5, 29.7, 29.8 (2C), 29.9 (2C), 31.5, 32.1, 36.5, 55.4, 63.5, 98.1, 106.6, 107.2, 145.5, 160.2, 160.8. HRMS: calcd for $C_{20}H_{35}O_2$ [M+ H] 307.2637, found 307.2633.

General procedures for the preparation of ***21-25***. To a solution of tetramethoxybenzene **15** (1 eq) and HMPA (0.1 eq) in THF was added n-BuLi (1 eq) at -40°C. The reaction was warmed to -10 °C and stirred at this temperature for one hour. The alkyl bromide (1.1 eq) was added dropwise, and the reaction was stirred overnight. Saturated NH_4Cl was added to the reaction, and the aqueous phase was extracted with ethyl acetate. The organic phase were combined and dried over $MgSO_4$. Removal of the organic solvent under reduced pressure afforded crude mixture that was purified through flash chromatography eluting with hexanes/ethyl acetate.

1,2,4,5-tetramethoxy-3-methylbenzene ***21***. 55% yield. Reaction of tetramethoxy benzene **15** (500 mg, 2.53 mmol) and methyl iodide **16** (341 µL, 2.78 mmol) afforded 244 mg of **21**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H); 3.72 (s, 6H); 3.83 (s, 6H); 6.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.53, 56.4 (2C), 60.6 (2C), 96.5 (2C), 126.4, 141.3, 149.1 (2C).

1,2,4,5-tetramethoxy-3-pentylbenzene ***22***. 73% yield. Reaction of tetramethoxy benzene **15** (400 mg, 2.01 mmol) and bromopentane **17** (277 µL, 2.21 mmol) afforded 244 mg of **22**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 8 Hz); 1.34 (m, 4H); 1.49-1.54 (m, 2H); 2.60 (t, 2H, *J* = 8 Hz); 3.76 (s, 6H); 3.83 (s, 6H); 6.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 22.7, 24.8, 30.6, 32.3, 56.4 (2C), 61.1 (2C), 96.7 (2C), 131.3, 141.2, 149 (2C).

3-decyl-1,2,4,5-tetramethoxybenzene ***23***. 29% yield. Reaction of tetramethoxy benzene **15** (300 mg, 1.51 mmol) and bromodecane **18** (347 µL, 1.66 mmol) afforded 150 mg of **23**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, 3H, *J* = 8Hz); 1.25 (s, 12H); 1.36 (m, 2H); 1.52 (m, 2H); 2.60 (t, 2H, *J* = 8 Hz); 3.76 (s, 6H); 3.83 (s, 6H); 6.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 24.9, 29.6, 29.7, 29.8, 29.9, 30.2, 31.0, 32.1, 56.4 (2C), 61.1 (2C), 96.7 (2C), 131.3, 141.2, 149.0 (2C).

1,2,4,5-tetramethoxy-3-undecylbenzene ***24***. 64% yield. Reaction of tetramethoxy benzene **15** (200 mg, 1.0 mmol) and bromoundecane **19** (249 µL, 1.1 mmol) afforded 148 mg of **24**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, *J* = 8 Hz), 1.25 (s, 14H), 1.36 (m, 2H); 1.52 (m, 2H); 2.60 (t, 2H, *J* = 8 Hz); 3.76 (s, 6H); 3.83 (s, 6H); 6.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 24.8, 29.5, 29.7, 29.8 (2C), 29.9, 30.2, 31.0, 32.1, 56.4 (2C), 61.1 (2C), 96.8 (2C), 131.3, 141.2, 149.0 (2C).

1,2,4,5-tetramethoxy-3-tetradecylbenzene **25**. 41% yield. Reaction of tetramethoxy benzene **15** (235 mg, 1.18 mmol) and bromotetradecane **20** (389 µL, 1.29 mmol) afforded 200 mg of **25**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, *J* = 8 Hz); 1.25 (s, 20); 1.42 (m, 2H); 1.51 (m, 2H), 2.60 (t, 2H, *J* = 8 Hz); 3.76 (s, 6H); 3.83 (s, 6H);

6.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 24.9, 29.6, 29.7, 29.8, 29.9 (5C), 30.2, 31.0, 32.1, 56.4 (2C), 61.1 (2C), 96.7 (2C), 131.3, 141.2, 149.0 (2C).

2,5-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione ***26***. 41% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89 (s, 3H); 3.76 (s, 3H); 4.00 (s, 3H); 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.7, 56.6, 61.3, 105.5, 126.3, 156.0, 159.0, 182.8, 183.5. HRMS: calcd for $C_9H_9O_4$ [M- H] 181.0500, found 181.0549.

2,5-dimethoxy-3-undecylcyclohexa-2,5-diene-1,4-dione ***29***. 32%yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (t, 3H, *J* = 8 Hz); 1.20 (s, 16H); 1.34 (s, 2H); 2.37 (t, 2H, *J* = 8 Hz); 3.76 (s, 3H); 3.99 (s, 3H); 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.8, 23.2, 28.8, 29.5 (2C), 29.7, 29.8 (3C), 32.1, 56.5, 61.5, 105.5, 130.8, 156.0, 158.9, 182.6, 183.7. HRMS: calcd for $C_{19}H_{31}O_4$ [M+ H] 323.2222, found 323.2210.

2,5-dimethoxy-3-tetradecylcyclohexa-2,5-diene-1,4-dione ***30***. 33% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, 3H, *J* = 8 Hz); 1.21 (s, 22H); 1.36 (s, 2H); 2.39 (t, 2H, *J* = 8 Hz); 3.77 (s, 3H); 4.01 (s, 3H); 5.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.8, 23.5, 28.8, 29.5, 29.7 (7C), 29.8, 32.1, 56.5, 61.5, 105.5, 130.8, 156.0, 158.9, 182.6, 183.7. HRMS: calcd for $C_{22}H_{37}O_4$ [M+ H] 365.2691, found 365.2650.

2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione ***31***. 6.8% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.93 (s, 3H); 3.84 (s, 3H); 5.82 (s, 1H); 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.66, 56.5, 61.3, 105.5, 126.2, 156.0, 159.0, 183.4.

3-decyl-2-hydroxy-5-methoxycyclohexa-2,5-diene-1,4-dione ***33***. 24% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, 3H, *J* = 8 Hz); 1.25 (s, 14H); 1.42 (s, 2H); 2.41 (t, 2H, *J* = 8 Hz); 3.83 (s, 3H); 5.82 (s, 1H); 7.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ

14.3, 22.8, 22.9, 28.2, 29.5, 29.6, 29.7, 29.8 (2C), 32.1, 56.9, 102.4, 119.5, 151.8, 161.2, 181.9, 183.1. HRMS: calcd for $C_{17}H_{25}O_4$ [M- H] 293.1752, found 293.1744.

2-hydroxy-5-methoxy-3-undecylcyclohexa-2,5-diene-1,4-dione ***34***. 35% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, 3H, *J* = 8 Hz); 1.21 (s, 16H); 1.41 (s, 2H); 2.39 (t, 2H, *J* = 8 Hz); 3.81 (s, 3H); 5.80 (s, 1H); 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 22.8 (2C), 28.2, 29.2, 29.5 (2C), 29.7, 29.8 (2C); 32.0, 56.8, 102.4, 119.5, 151.8, 161.3, 181.8, 183.0. HRMS: calcd for $C_{17}H_{27}O_4$ [M- H] 307.1909, found 307.1898.

References

(1) Gehringer, L.; Bourgogne, C.; Guillon, D.; Donnio, B. Liquid-Crystalline Octopus Dendrimers: Block Molecules with Unusual Mesophase Morphologies. *J. Am. Chem. Soc*. **2004**, *126*, 3856–3867.

(2) Oyama, K.; Kondo, T. Total Synthesis of Flavocommelin, a Component of the Blue Supramolecular Pigment from *Commelina communis*, on the Basis of Direct 6-C-Glycosylation of Flavan. *J. Org. Chem*. **2004**, 69, 5240-5246.

(3) Pettit, G. R.; Grealish, M. P.; Jung, M. K.; Hamel, E.; Pettit, R. K.; Chapuis, J. C.; Schmidt, J. M. Antineoplastic Agents. 465. Structural Modification of Resveratrol Sodium Resverastatin Phosphate. *J. Med. Chem*. **2002**, 45, 2534-2542.

(4) Mal, D.; Pahari, P.; De, S. R. Regiospecific synthesis of 3-(2,6-dihydroxyphenyl)phthalides: application to the synthesis of isopestacin and cryphonectric acid. *Tetrahedron*. **2007**, 63, 11781-11792.

(5) Orsini, F.; Verotta, L.; Lecchi, M.; Restano, R.; Curia, G.; Redaelli, E.; Wanke, E. Resveratrol Derivatives and Their Role as Potassium Channels Modulators. *J. Nat. Prod*. **2004**, 67, 421-426.