# Prevention of Marine Biofouling Using the Natural Allelopathic Compound Batatasin-III and Synthetic Analogues

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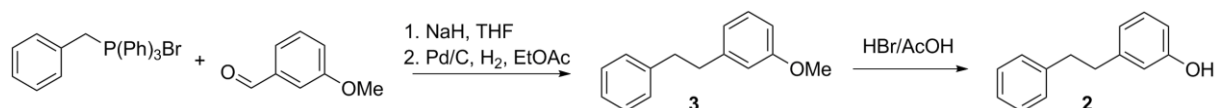
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**Synthetic Procedures for Compounds 2-22**

Note. All compounds were isolated as amorphous white solids with the following exceptions: Compound **2** gummy solid, **3** colourless oil, **4** brown oil, **5** colourless oil and **6** brown gum. All the prepared compounds matched the previously reported spectroscopic data.
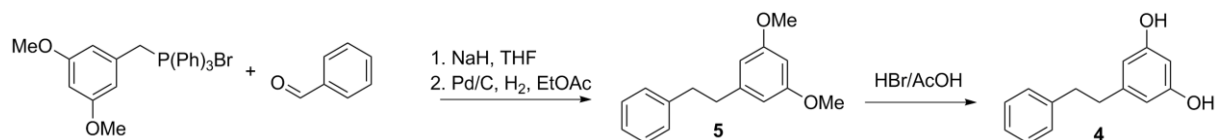
Compounds **3** and **2**.



*3-methoxybibenzyl* **3**.[1] Wittig reaction: 90% yield (0.4 mmol scale), *E:Z* = 1.5:1. Hydrogenation: 72% yield (0.4 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34 (2H, t, *J* = 7.2 Hz), 7.28 – 7.21 (4H, m), 6.85 (1H, d, *J* = 7.5 Hz), 6.83 – 6.78 (2H, m), 3.83 (3H, s), 2.97 (4H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.7, 143.5, 141.9, 129.4, 128.6, 128.5, 126.0, 121.0, 114.3, 111.4, 55.2, 38.1, 37.9; HRESIMS *m/z* 213.1270 [M + H]$^+$ (calcd for C$_{15}$H$_{17}$O, 213.1274).

*3-hydroxybibenzyl* **2**.[1] Demethylation: 68% yield (0.15 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.14 (1H, s), 7.29 – 7.14 (5H, m), 7.08 (1H, t, *J* = 7.8 Hz), 6.74 – 6.68 (2H, m), 6.66 (1H, ddd, *J* = 8.0, 2.4, 0.8 Hz), 2.92 – 2.80 (4H, m); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 158.3, 144.3, 142.8, 130.1, 129.3, 129.1, 126.6, 120.4, 116.2, 113.7, 38.6, 38.5; HRESIMS *m/z* 197.0974 [M + H]$^-$ (calcd for C$_{14}$H$_{13}$O, 197.0972).
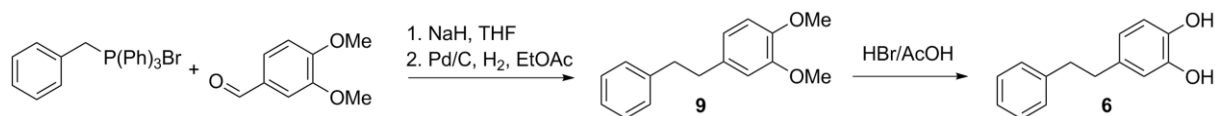
Compounds **5** and **4**.



*3,5-dimethoxybibenzyl* **5**.[2] Wittig reaction: 81% yield (1.2 mmol scale), *E:Z* = 2:1. Hydrogenation: 96% yield (1.0 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.27 (2H, m), 7.26 – 7.15 (3H, m), 6.44 – 6.30 (3H, m), 3.79 (6H, s), 3.03 – 2.78 (4H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.9, 144.3, 141.8, 128.6, 128.5, 126.1, 106.6, 98.1, 55.4, 38.4, 37.8; HRESIMS *m/z* 243.1376 [M + H]$^+$ (calcd for C$_{16}$H$_{19}$O$_2$, 243.1380).

*3,5-dihydroxybibenzyl* **4**.[3] Demethylation: 95% yield (0.4 mmol scale). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.25 (2H, m), 7.22 – 7.13 (3H, m), 6.27 – 6.23 (2H, m), 6.21 – 6.18 (1H, m), 2.89 – 2.74 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.6, 145.1, 141.7, 128.6, 128.5, 126.1, 108.4, 100.7, 37.7, 37.4; HRESIMS *m/z* 215.1061 [M + H]$^+$ (calcd for C$_{14}$H$_{15}$O$_2$, 215.1067).

Compounds **9** and **6**.



*3,4-dimethoxybibenzyl* **9**.[4] Wittig reaction: 83% yield (3 mmol scale), *E:Z* = 2:1. Hydrogenation: 95% yield (0.9 mmol scale). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.25 (2H, m,), 7.22 – 7.15 (3H, m), 6.79 (1H, d, *J* = 8.1 Hz), 6.72 (1H, dd, *J* = 8.1, 1.7 Hz), 6.64 (1H, d, *J* = 1.7 Hz), 3.86 (3H, s), 3.82 (3H, s), 2.98 – 2.79 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.8, 147.3, 141.8, 134.5, 128.6, 128.4, 126.0, 120.3, 112.0, 111.3, 56.0, 55.8, 38.2, 37.6; HRESIMS *m/z* 295.1305 [M + Na]$^+$ (calcd for C$_{17}$H$_{20}$NaO$_3$, 295.1305).

*3,4-dihydroxybibenzyl* **6**. Demethylation: 95% yield (0.3 mmol scale). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.33 (2H, m), 7.31 – 7.21 (3H, m), 6.85 (1H, d, *J* = 8.0 Hz), 6.78 (1H, s), 6.70 (1H, d, *J* = 8.2 Hz), 5.19 (1H, s), 5.08 (1H, s), 2.99 – 2.85 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.5, 141.9, 141.6, 135.2, 128.6, 128.5, 126.0, 121.1, 115.7, 115.4, 38.2, 37.3; HRESIMS *m/z* 213.0920 [M - H]$^-$ (calcd for C$_{14}$H$_{13}$O$_2$, 213.0916).

Compound **7**
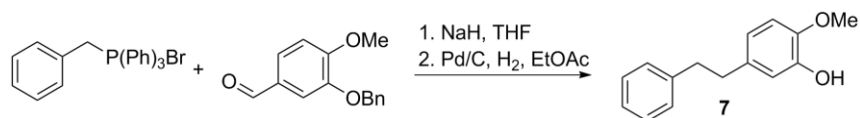


*3-hydroxy-4-methoxybibenzyl* **7**. Wittig reaction: 70% yield (0.5 mmol scale), *E:Z* = 2:1. Hydrogenation: 94% yield (0.3 mmol scale). ^{1}H NMR (400 MHz, (CD$_3$)$_2$CO) δ 7.36 (1H, s), 7.29 – 7.20 (4H, m), 7.19 – 7.12 (1H, m), 6.82 (1H, d, *J* = 8.2 Hz), 6.73 (1H, d, *J* = 2.0 Hz), 6.63 (1H, dd, *J* = 8.1, 2.0 Hz), 3.80 (3H, s), 2.90 – 2.84 (2H, m), 2.80 – 2.76 (2H, m); ^{13}C NMR (101 MHz, (CD$_3$)$_2$CO) δ 147.3, 146.6, 142.9, 135.7, 129.3, 129.1, 126.6, 120.1, 116.2,

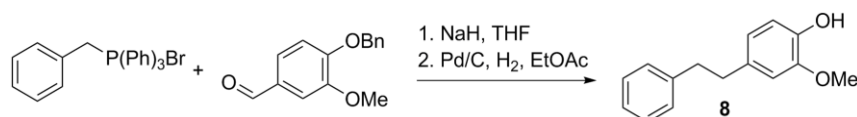112.4, 56.3, 38.8, 38.0; HRESIMS $m/z$ 251.1042 [M + Na]$^+$ (calcd for $C_{15}H_{16}NaO_2$, 251.1043).

Compound **8**



*4-hydroxy-3-methoxybibenzyl* **8**.[5] Wittig reaction: 73% yield (2 mmol scale), *E:Z* = 1:1. Hydrogenation: 86% yield (0.6 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.27 (2H, m), 7.24 – 7.17 (3H, m), 6.85 (1H, d, *J* = 8.0 Hz), 6.70 (1H, dd, *J* = 8.0, 1.9 Hz), 6.62 (1H, d, *J* = 1.9 Hz), 5.49 (1H, s), 3.84 (3H, s), 2.95 – 2.84 (4H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.4, 143.9, 141.9, 133.8, 128.7, 128.4, 126.0, 121.1, 114.3, 111.3, 56.0, 38.4, 37.8; HRESIMS $m/z$ 229.1219 [M + H]$^+$ (calcd for $C_{15}H_{17}O_2$, 229.1223).
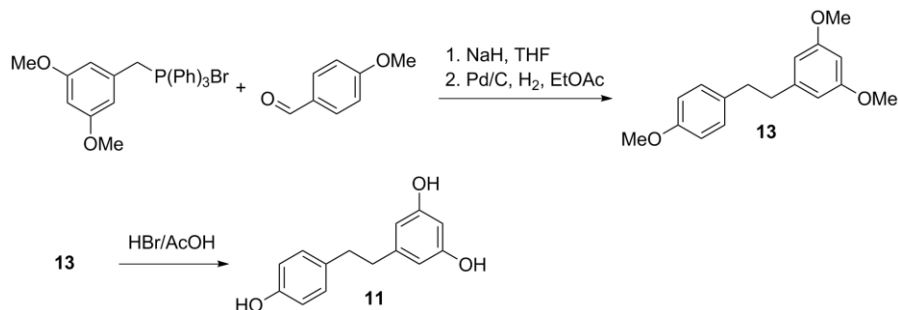
Compounds **12** and **10**.
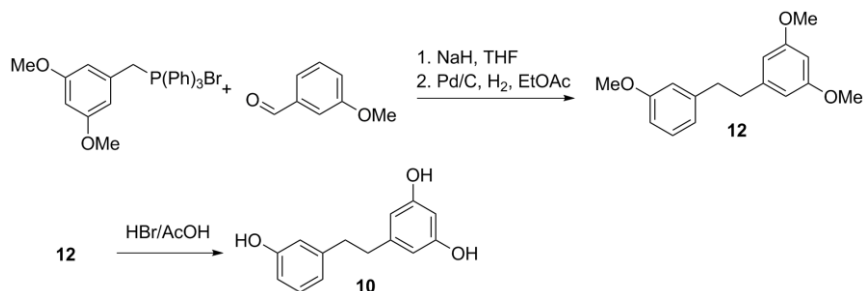


*3,3',5-trimethoxybibenzyl* **12**.[6] Wittig reaction: 77% yield (0.5 mmol scale), *E:Z* = 2.5:1. Hydrogenation: 89% yield (0.4 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 (1H, t, *J* = 8.3 Hz), 6.82 (1H, d, *J* = 7.5 Hz), 6.79 – 6.73 (2H, m), 6.37 (2H, s), 6.34 (1H, s), 3.81 (3H, s), 3.78 (6H, s), 2.90 (4H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.9, 159.8, 144.3, 143.5, 129.4, 121.0, 114.3, 111.4, 106.6, 98.1, 55.4, 55.3, 38.2, 37.9; HRESIMS $m/z$ 295.1305 [M + Na]$^+$ (calcd for $C_{17}H_{20}NaO_3$, 295.1305).

*3,3',5-trihydroxybibenzyl* **10**.[6] Demethylation: 84% yield (0.1 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.13 (1H, s), 8.03 (2H, s), 7.08 (1H, t, *J* = 7.7 Hz), 6.74 – 6.67 (2H, m), 6.65 (1H, d, *J* = 8.3 Hz), 6.23 (2H, s), 6.19 (1H, s), 2.82 – 2.69 (4H, m); $^{13}$C NMR (101 MHz,

(CD$_3$)$_2$CO) δ 159.3, 158.2, 145.1, 144.4, 130.0, 120.4, 116.2, 113.6, 107.7, 101.2, 38.5, 38.2; HRESIMS *m/z* 231.1012 [M + H]$^+$ (calcd for C$_{14}$H$_{15}$O$_3$, 231.1016).

Compounds **13** and **11**.



*3,4',5-trimethoxybibenzyl* **13**.[7] Wittig reaction: 83% yield (0.5 mmol scale), *E:Z* = 3:1. Hydrogenation: 87% yield (0.4 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.11 (2H, d, *J* = 8.6 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 6.35 – 6.30 (3H, m), 3.79 (3H, s), 3.77 (6H, s), 2.92 – 2.77 (4H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.9, 158.0, 144.4, 134.0, 129.5, 113.9, 106.7, 98.1, 55.4, 55.4, 38.6, 36.9; HRESIMS *m/z* 273.1485 [M + H]$^+$ (calcd for C$_{17}$H$_{21}$O$_3$, 273.1485).

*3,4',5-trihydroxybibenzyl* **11**.[8] Demethylation: 84% yield (0.2 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.02 (1H, s), 7.04 (2H, d, *J* = 8.2 Hz), 6.73 (2H, d, *J* = 8.5 Hz), 6.24 – 6.15 (2H, m), 6.19 – 6.17 (1H, m), 2.81 – 2.65 (4H, m); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 159.3, 156.3, 145.2, 133.6, 130.1, 115.9, 107.8, 101.1, 39.1, 37.5; HRESIMS *m/z* 231.1013 [M + H]$^+$ (calcd for C$_{14}$H$_{15}$O$_3$, 231.1016).

Compound **14**
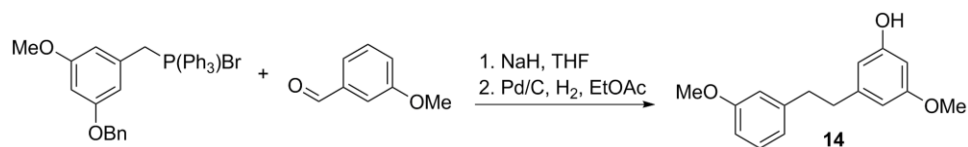


*3-hydroxy-3',5-dimethoxybibenzyl* **14**.[9] Wittig reaction: 57% yield (0.25 mmol scale), *E:Z* = 2.5:1. Hydrogenation: 65% yield (0.1 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.21 (1H, t, *J* = 7.7 Hz), 6.79 (1H, d, *J* = 7.5 Hz), 6.77 – 6.71 (2H, m), 6.36 – 6.32 (1H, m), 6.29 – 6.23 (2H, m), 4.80 (1H, s), 3.79 (3H, s), 3.76 (3H, s), 2.99 – 2.72 (4H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.0, 159.7, 156.7, 144.6, 143.4, 129.5, 121.0, 114.4, 111.5, 108.1, 106.9, 99.2, 55.4, 55.3, 38.0, 37.7; HRESIMS *m/z* 257.1182 [M - H]$^-$ (calcd for C$_{16}$H$_{17}$O$_3$, 257.1183).

6

Compound **15**
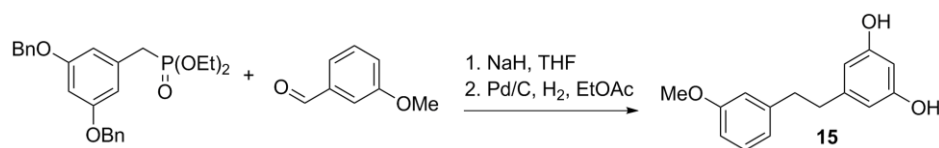


*3,5-dihydroxy-3'-methoxybibenzyl* **15**.[10] Horner-Wadsworth-Emmons reaction: 76% yield (0.1 mmol scale). Hydrogenation: 67% yield (0.1 mmol scale). ^{1}H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.04 (2H, s), 7.17 (1H, t, *J* = 8.0 Hz), 6.82 – 6.78 (2H, m), 6.73 (1H, ddd, *J* = 8.3, 2.6, 1.1 Hz), 6.24 (2H, d, *J* = 2.2 Hz), 6.19 (1H, t, J = 2.2 Hz), 3.76 (3H, s), 2.88 – 2.70 (4H, m); ^{13}C NMR (101 MHz, (CD$_3$)$_2$CO) δ 160.7, 159.3, 145.0, 144.4, 130.0, 121.5, 114.9, 112.1, 107.8, 101.2, 55.3, 38.5, 38.3; HRESIMS *m/z* 243.1027 [M + H]$^+$ (calcd for C$_{15}$H$_{15}$O$_3$, 243.1027).
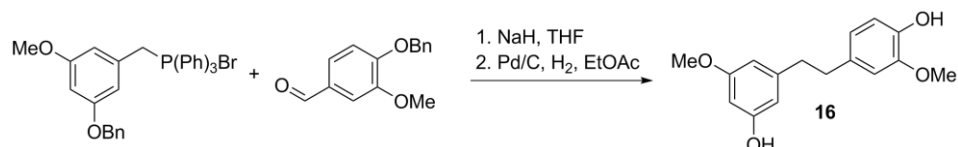
Compound **16**



*3',4-dihydroxy-3,3'-dimethoxybibenzyl* **16**.[11] Wittig reaction: 77% yield (0.35 mmol scale). Hydrogenation: 78% yield (0.1 mmol scale). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (1H, d, *J* = 8.0 Hz), 6.68 (1H, dd, *J* = 8.0, 1.8 Hz), 6.63 (1H, d, *J* = 1.7 Hz), 6.35 – 6.30 (1H, m), 6.27 – 6.23 (2H, m), 3.84 (3H, s), 3.75 (3H, s), 2.97 – 2.58 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.0, 156.7, 146.4, 144.7, 143.9, 133.8, 121.1, 114.3, 111.3, 108.2, 107.0, 99.1, 56.0, 55.4, 38.4, 37.4; HRESIMS *m/z* 273.1132 [M - H]$^-$ (calcd for C$_{16}$H$_{17}$O$_4$, 273.1132).

Compounds **22** and **17**.
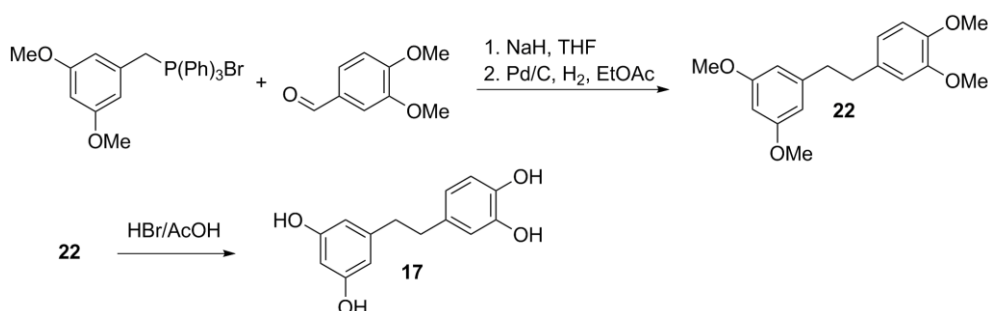
*3,3',4,5'-tetramethoxybibenzyl* **22**.[3] Wittig reaction: 91% yield (1.3 mmol scale). Hydrogenation: 92% yield (1.1 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.80 (1H, d, $J$ = 8.1 Hz), 6.73 (1H, dd, $J$ = 8.1, 1.9 Hz), 6.68 (1H, d, $J$ = 1.8 Hz), 6.37 – 6.29 (3H, m), 3.86 (3H, s), 3.85 (3H, s), 3.77 (6H, s), 2.90 – 2.81 (4H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.9, 148.9, 147.4, 144.3, 134.5, 120.4, 112.0, 111.4, 106.7, 98.0, 56.1, 55.9, 55.4, 38.6, 37.4; HRESIMS $m/z$ 325.1409 [M + Na]$^+$ (calcd for C$_{18}$H$_{22}$NaO$_4$, 325.1410).

*3,3',4,5'-tetrahydroxybibenzyl* **17**.[12] Demethylation: 85% yield (0.4 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 7.81 (2H, br s), 6.73 – 6.68 (2H, m), 6.54 (1H, dd, $J$ = 7.9, 2.0 Hz), 6.21 (2H, d, $J$ = 2.1 Hz), 6.18 (1H, t, $J$ = 2.1 Hz), 2.75 – 2.64 (4H, m); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 159.3, 145.7, 145.2, 143.9, 134.6, 120.4, 116.3, 115.9, 107.8, 101.1, 39.0, 37.7; HRESIMS $m/z$ 269.0787 [M + Na]$^+$ (calcd for C$_{14}$H$_{14}$NaO$_4$, 269.0784).

Compound **18**
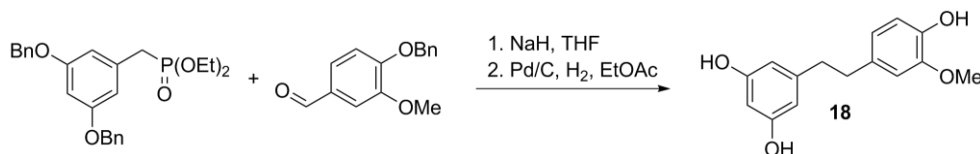


*3',4,5'-trihydroxy-3-methoxybibenzyl* **18**.[13] Horner-Wadsworth-Emmons reaction: 63% yield (0.3 mmol scale). Hydrogenation: 90% yield (0.04 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.00 (2H, s), 7.24 (1H, s), 6.80 (1H, d, $J$ = 1.7 Hz), 6.72 (1H, d, $J$ = 8.0 Hz), 6.65 (1H, dd, $J$ = 8.0, 1.8 Hz), 6.21 (2H, d, $J$ = 2.1 Hz), 6.18 (1H, t, $J$ = 2.1 Hz), 3.80 (3H, s), 2.80 – 2.68 (4H, m); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 159.3, 148.1, 145.6, 145.2, 134.2, 121.6, 115.5, 112.9, 107.8, 101.1, 56.2, 39.0, 38.0; HRESIMS $m/z$ 283.0944 [M + Na]$^+$ (calcd for C$_{15}$H$_{16}$NaO$_4$, 283.0941).

Compound **19**
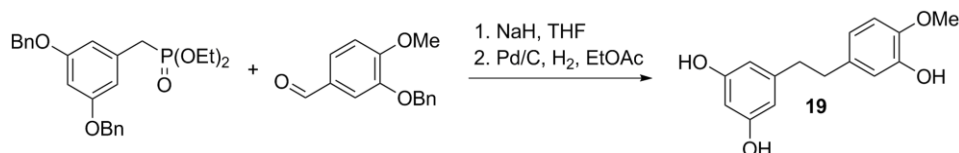


*3,3',5'-trihydroxy-4-methoxybibenzyl* **19**.[6] Horner-Wadsworth-Emmons reaction: 60% yield (0.1 mmol scale). Hydrogenation: 73% yield (0.1 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ 8.02 (2H, s), 7.36 (1H, s), 6.82 (1H, d, $J$ = 7.8 Hz), 6.73 (1H, s), 6.63 (1H, d, $J$ =

8.4 Hz), 6.23 (2H, s), 6.18 (1H, s), 3.79 (3H, s), 2.81 – 2.64 (4H, m); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) $\delta$ 159.3, 147.3, 146.6, 145.2, 135.9, 120.1, 116.1, 112.4, 107.8, 101.1, 56.3, 38.8, 37.7; HRESIMS $m/z$ 283.0945 [M + Na]$^+$ (calcd for C$_{15}$H$_{16}$NaO$_4$, 283.0941).
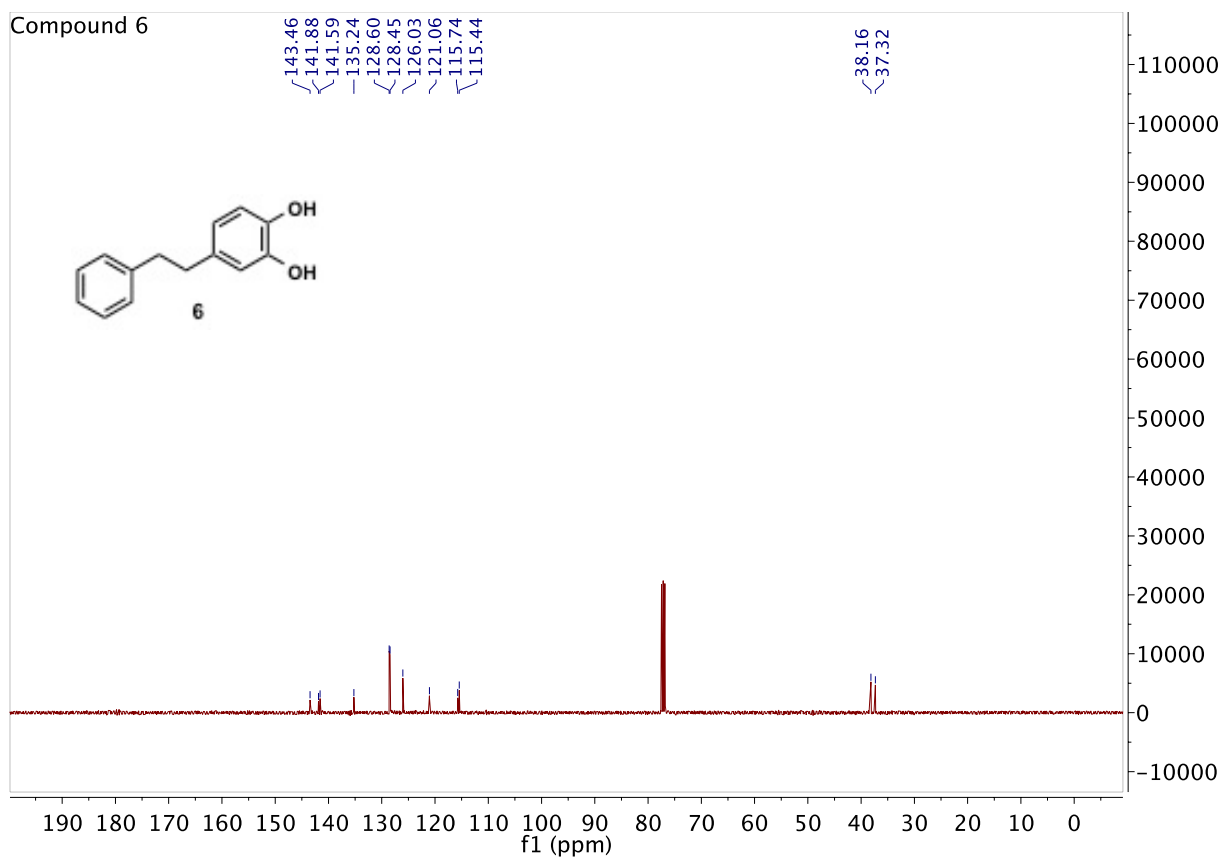
Compound **20**
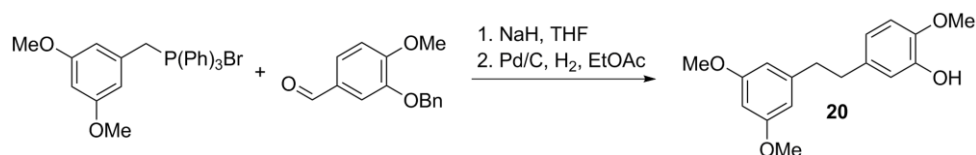


*3-hydroxy-3',4,5'-trimethoxybibenzyl* **20**.[11] Wittig reaction: 76% yield (0.5 mmol scale), *E:Z* = 2.5:1. Hydrogenation: 92% yield (0.4 mmol scale). $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) $\delta$ 7.36 (1H, s), 6.82 (1H, d, *J* = 8.2 Hz), 6.75 (1H, d, *J* = 2.0 Hz), 6.65 (1H, dd, *J* = 8.1, 2.0 Hz), 6.41 (2H, d, *J* = 2.2 Hz), 6.31 (1H, t, *J* = 2.2 Hz), 3.80 (3H, s), 3.74 (6H, s), 2.80 (4H, s); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) $\delta$ 161.8, 147.3, 146.6, 145.2, 135.7, 120.1, 116.2, 112.4, 107.3, 98.6, 56.3, 55.4, 39.0, 37.7; HRESIMS $m/z$ 311.1257 [M + Na]$^+$ (calcd for C$_{17}$H$_{20}$NaO$_4$, 311.1254).

Compound **21**
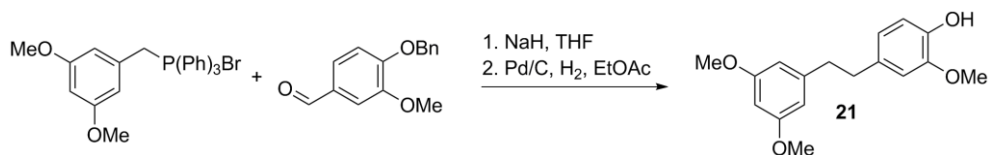


*4-hydroxy-3,3',5'-trimethoxybibenzyl* **21**.[14] Wittig reaction: 66% yield (0.5 mmol scale), *E:Z* = 1.4:1. Hydrogenation: 83% yield (0.2 mmol scale). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.84 (1H, d, *J* = 8.0 Hz), 6.70 (1H, dd, *J* = 8.0, 1.8 Hz), 6.64 (1H, d, *J* = 1.8 Hz), 6.37 – 6.29 (3H, m), 5.49 (1H, s), 3.85 (3H, s), 3.77 (6H, s), 2.84 (4H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 160.9, 146.4, 144.3, 143.9, 133.8, 121.1, 114.3, 111.3, 106.7, 98.0, 56.0, 55.4, 38.7, 37.5; HRESIMS $m/z$ 289.1435 [M + H]$^+$ (calcd for C$_{17}$H$_{21}$O$_4$, 289.1434).

$^1$H-NMR and $^{13}$C NMR spectrum of compound **6** in CDCl$_3$.

Compound 6

7.38, 7.36, 7.34, 7.29, 7.27, 7.26, 7.24, 6.86, 6.84, 6.78, 6.71, 6.69, 5.19, 5.19, 5.08, 2.98, 2.98, 2.96, 2.95, 2.94, 2.91, 2.90, 2.89, 2.88, 2.87



Compound 6

143.46, 141.88, 141.59, 135.24, 128.60, 128.45, 126.03, 121.06, 115.74, 115.44, 38.16, 37.32
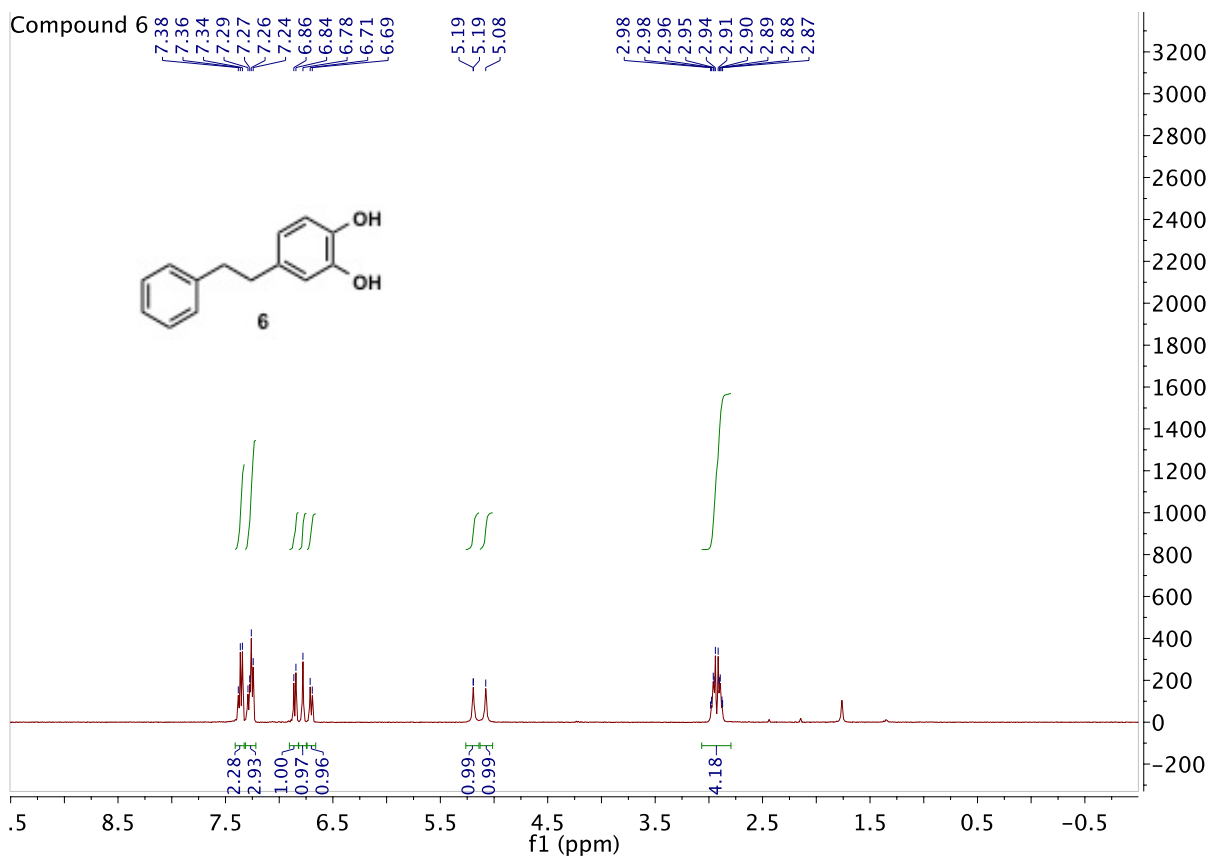
$^1$H-NMR and $^{13}$C NMR spectrum of compound **7** in (CD$_3$)$_2$CO.

Compound 7

7.36
7.36
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.21
7.21
7.18
7.18
7.17
7.16
7.16
7.15
7.15
7.14
6.83
6.81
6.73
6.73
6.65
6.64
6.63
6.62
3.80
2.89
2.89
2.87
2.87
2.86
2.85
2.85
2.81
2.79
2.79
2.77
2.77
2.77

OMe

OH

7

0.72
3.81
0.83
1.01
0.89
0.96
3.22
2.11
2.49

f1 (ppm)

Compound 7

147.31
146.60
142.91
135.72
129.28
129.05
126.58
120.10
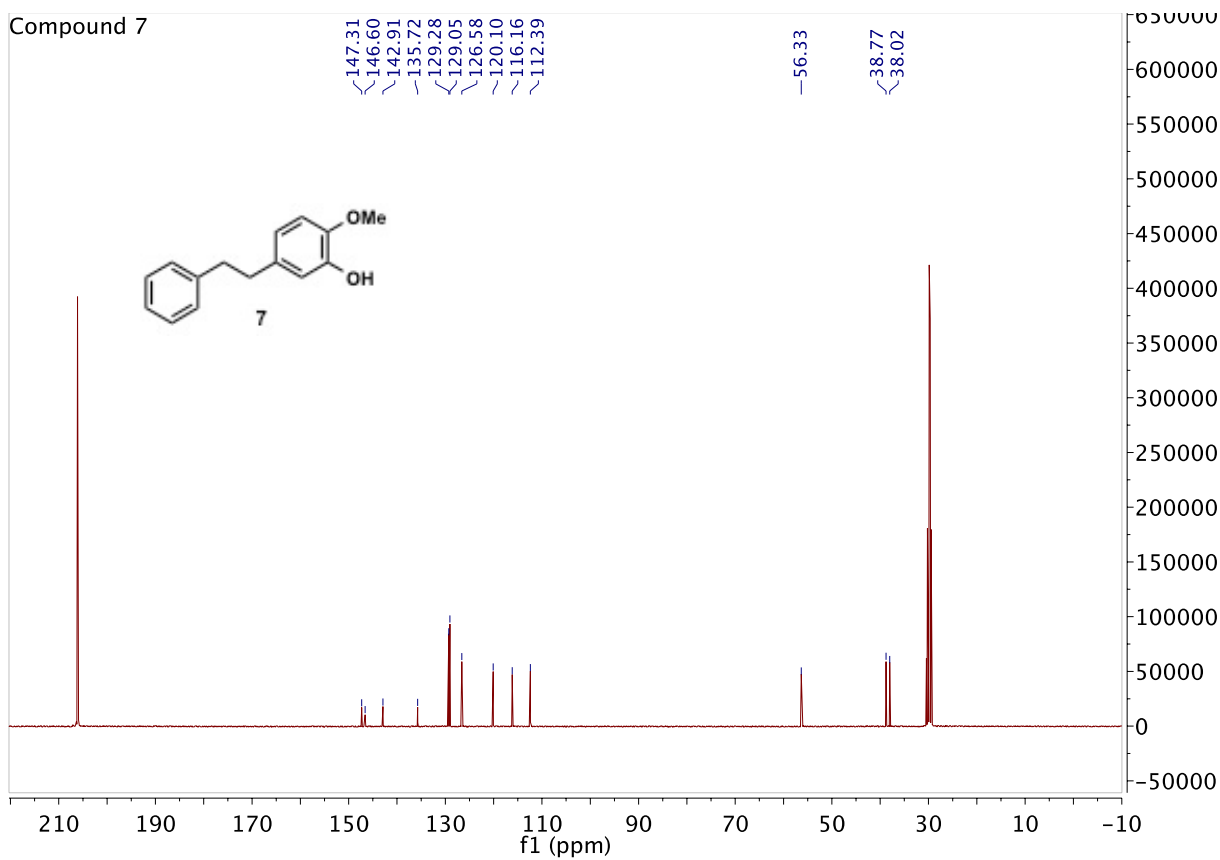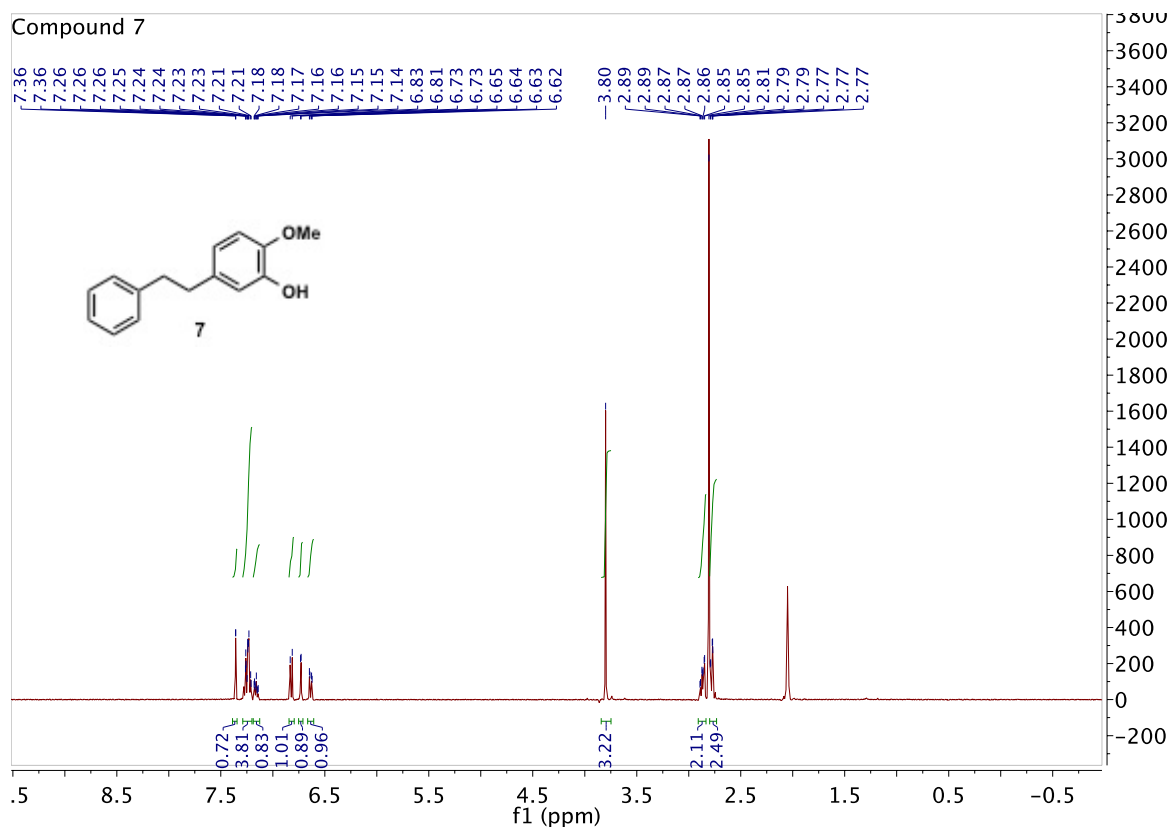116.16
112.39
56.33
38.77
38.02

OMe

OH

7

f1 (ppm)

11

Table S1. Trivial Names and Sources of the Natural Compounds Included in the Current
Study

| Trivial name | Natural Product[a] | Initial plant source[b] |
|---|---|---|
| **1** (Batatasin III) | Y | *Dioscorea batatas*[15] |
| **2** -[c] | N | n.a.[d] |
| **3** - | Y | *Radula complanata*[16] |
| **4** (Dihydropinosylvin) | Y | *Pinus sp.*[17] |
| **5** (Dihydropinosylvin dimethyl ether) | Y | *Pinus armandii*[18] |
| **6** - | N | n.a. |
| **7** - | N | n.a. |
| **8** - | N | n.a. |
| **9** - | N | n.a. |
| **10** - | Y | *Orchidaceae sp.*[19] |
| **11** (Dihydroresveratrol) | Y | *Cannabis sativa*[8] |
| **12** (Batatasin III dimethyl ether) | Y | *Bletilla striata*[20] |
| **13** - | N | n.a. |
| **14** (3'-O-Methylbatatasin III) | Y | *Coelogyne Ovalis*[21] |
| **15** - | Y | *Oncidium sp.*[10] |
| **16** (Gigantol) | Y | *Lusia indivisa*[22] |
| **17** (Dihydropiceatannol) | Y | *Cassia garrettiana*[23] |
| **18** (Tristin) | Y | *Bulbophyllum triste*[24] |
| **19** - | Y | *Glycyrrhiza glabra*[25] |
| **20** - | Y | *Combretum caffrum*[26] |
| **21** - | N | n.a. |
| **22** - | N | n.a. |

[a]Has the synthetic compound also been identified as a natural product, Y = yes, N = no. [b]Several of the prepared compounds have been isolated from numerous and diverse plants. Only the initial isolation of the actual natural product is listed in the current table. Some compounds have been described in earlier references but then as reduced versions of stillbenoids. [c]Compound does not have a trivial name. [d]n.a. Non applicable.
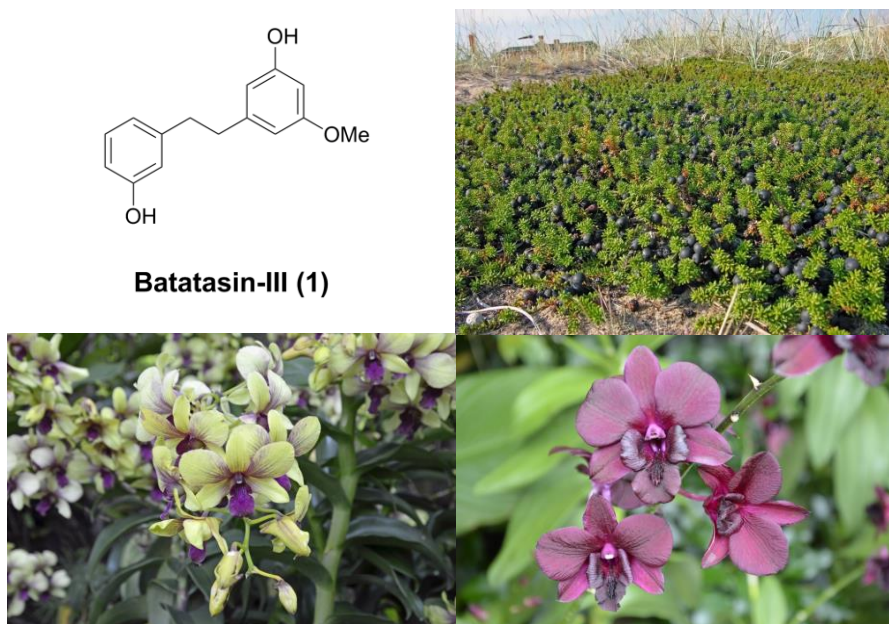
**Figure S1.** Top panels: Structure of the dihydrostilbene batatasin-III (**1**) and an example of the dense colonies formed by *Empetrum nigrum* (the common crowberry), which is a prolific producer of **1**. *E. nigrum* is believed to suppress the growth of competing species due to the production and release of **1**, both by direct interference with germination and seedling growth of co-occurring species and through apparent competition in that herbivores seldom select crowberry as a forage plant. Bottom panels: Members of *Dendrobium* orchids (Orchidaceae), a family from which compound **1** and numerous related analogues have also been isolated. (Photo by J. Svenson and J. Lehmuskallio).

**Figure S2.** Examples of biofouling and biofouling species found on man-made and natural structures. Left panel: Illustration of the massive growth of macrofoulers such as barnacles, blue mussels and algae on the underside of the plastic flotation elements of a jetty submerged for six months in the waters off the Swedish west coast. Top right panel: Illustration of natural fouling of barnacles on the shell of a *Chlamys islandica* scallop. Bottom right panel: the microfouling diatom *Cylindrotheca closterium* (each organism is 60-70 µm) common in marine biofilms. (Photo by J. Svenson and R. A. Ingebrigtsen).

**Stilbenoid Structure Activity Relationship.** Numerous studies have described the diverse bioactivities displayed by natural and synthetic stilbenoids. Several of these analyzes have been dedicated to establishing the structure activity relationships via analogue synthesis. The extensive studies by Mata et al. reports the phytotoxic, spasmolytic and cytototxic activity of bibenzyl derivatives isolated from the orchids *Epidendrum rigidum* and *Nidema boothii* alongside synthetic analogues.[27,28] The studies suggests that a methoxy substituent at the C-3 or C-5 position is beneficial for phytotoxicity (*Lemna paucicostata*), while there appeared to be no apparent link between the cytotoxic activities against four mammalian cell lines and the structure of the eight analyzed compounds.[27] The spasmolytic activity of **1** and 15 analogues was assessed by recording their ability to inhibit spontaneous contractions in guinea-pig ileum. The $IC_{50}$-values for inhibition ranged from 0.14 to 2.36 µM indicating a high general inhibitory activity, seemingly independent on the nature and pattern of hydroxyl and methoxy substituents on the bibenzylic scaffold.[28] $Ca^{2+}$-calmodulin sensitive phosphodiesterase (PDE) was identified as a plausible biological target for the spasmolytic activity and was further studied with additional analogues (also including substituted 1,3-diphenylpropanes) and via docking studies.[28,29] Neither the experimental or the computational docking studies revealed any conclusive binding mode for the active compounds and no chemical feature on the dibenzylic scaffold could be assigned as crucial for activity.[29] Most of the compounds analyzed displayed similar $IC_{50}$ values for PDE binding (9-146 µM).[29] The dibenzylic scaffold has also been investigated for its ability to inhibit tyrosinase by Nihei and co-workers,[30] as COX-2 inhibitors[31] and recently as inhibitors of phytopathogenic fungi.[32] None of those studies have yielded definite SARs illustrating that this family of compounds is not only capable of binding to several relevant biological targets but they appear to be able to do so in numerous ways that are challenging to predict.

Our current study included 22 synthetic dibenzylic compounds, ranging from mono- to tetrasubstituted, in an attempt to establish the features that dictate the antifouling activity of this promising class of natural compound. Given the ranging biological targets available in the different test species and the flexible nature of the molecules, it is not possible to assign a single general antifouling SAR. For some organisms, such as the bacteria and the microalgae, we are not able to conclude a defined SAR supported by our experimental data. Interestingly, the *L. sativa* root elongation inhibition was coupled to the polarity of the compounds in a fashion that was opposite to that documented for *B. improvisus*. The link between cyprid toxicity was coupled to compound hydrophobicity and this appeared also to be valid to some extent against *C. savignyi* metamorphosis inhibition. However, in the inhibition assays we were not able to detect a narrow, defined substitution pattern responsible for the observed bioactivity. This suggests that these molecules are small and flexible enough to bind receptors in multiple modes. This correlates well with other studies reported for this family of compounds (vide supra).

# REFERENCES

(1)     Blangetti, M.; Fleming, P.; O'Shea, D. F. *J. Org. Chem.* **2012**, *77*, 2870-2877.

(2)     Azzena, U.; Dettori, G.; Idini, M. V.; Pisano, L.; Sechi, G. *Tetrahedron* **2003**, *59*, 7961-7966.

(3)     Alonso, E.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417-421.

(4)     Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579-2588.

(5)     Learmonth, D. A.; Vieira-Coelho, M. A.; Benes, J.; Alves, P. C.; Borges, N.; Freitas, A. P.; Soares-Da-Silva, P. *J. Med. Chem.* **2002**, *45*, 685-695.

(6)     Hernández-Romero, Y.; Rojas, J. I.; Castillo, R.; Rojas, A.; Mata, R. *J. Nat. Prod.* **2004**, *67*, 160-167.

(7)     Reyes-Ramirez, A.; Leyte-Lugo, M.; Figueroa, M.; Serrano-Alba, T.; Gonzalez-Andrade, M.; Mata, R. *Eur. J. Med. Chem.* **2011**, *46*, 2699-2708.

(8)     Elferaly, F. S. *J. Nat. Prod.* **1984**, *47*, 89-92.

(9)     Sachdev, K.; Kulshreshtha, D. K. *Phytochemistry* **1986**, *25*, 499-502.

(10)    Williams, R. B.; Martin, S. M.; Hu, J. F.; Garo, E.; Rice, S. M.; Norman, V. L.; Lawrence, J. A.; Hough, G. W.; Goering, M. G.; O'Neil-Johnson, M.; Eldridge, G. R.; Starks, C. M. *Planta Med.* **2012**, *78*, 160-165.

(11)    Crombie, L.; Jamieson, S. V. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1467-1475.

(12)    Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem.* **1993**, *36*, 2950-2955.

(13)    Talvitie, A.; Mannila, E.; Kolehmainen, E. *Liebigs Ann. Chem.***1992**, *1992*, 399-401.

(14)    Wang, X. L.; Liu, D.; Xia, Y. M.; Cao, X. P.; Pan, X. F. *Chin. J. Chem.* **2004**, *22*, 467-472.

(15)    Hashimoto, T.; Hasegawa, K.; Kawarada, A. *Planta* **1972**, *108*, 369-374.

(16) Asakawa, Y.; Kusube, E.; Takemoto, T.; Suire, C. *Phytochemistry* **1978**, *17*, 2115-2117.

(17) Lindstedt, G. *Acta Chem. Scand.* **1950**, *4*, 448-455.

(18) Fang, J. M.; Su, W. C.; Cheng, Y. S. *Phytochemistry* **1988**, *27*, 1395-1397.

(19) Fritzemeier, K. H.; Kindl, H. *Eur. J. Biochem.* **1983**, *133*, 545-550.

(20) Yamaki, M.; Kato, T.; Bai, L.; Inoue, K.; Takagi, S. *Phytochemistry* **1991**, *30*, 2759-2760.

(21) Sachdev, K.; Kulshreshtha, D. K. *Phytochemistry* **1986**, *25*, 499-502.

(22) Majumder, P. L.; Lahiri, S. *Indian J. Chem. B* **1989**, *28*, 771-774.

(23) Hata, K.; Baba, K.; Kozawa, M. *Chem. Pharm. Bull.* **1979**, *27*, 984-989.

(24) Majumder, P. L.; Pal, S. *Phytochemistry* **1993**, *32*, 1561-1565.

(25) Biondi, D. M.; Rocco, C.; Ruberto, G. *Journal of Natural Products* **2005**, *68*, 1099-1102.

(26) Pettit, G. R.; Singh, S. B.; Schmidt, J. M.; Niven, M. L.; Hamel, E.; Lin, C. M. *J. Nat. Prod.* **1988**, *51*, 517-527.

(27) Hernández-Romero, Y.; Acevedo, L.; de Los Ángeles Sánchez, M.; Shier, W. T.; Abbas, H. K.; Mata, R. *J. Agric. Food Chem.* **2005**, *53*, 6276-6280.

(28) Hernández-Romero, Y.; Rojas, J. I.; Castillo, R.; Rojas, A.; Mata, R. *J. Nat. Prod.* **2004**, *67*, 160-167.

(29) Reyes-Ramírez, A.; Leyte-Lugo, M.; Figueroa, M.; Serrano-Alba, T.; González-Andrade, M.; Mata, R. *Eur. J. Med. Chem.* **2011**, *46*, 2699-2708.

(30) Oozeki, H.; Tajima, R.; Nihei, K. I. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5252-5254.

(31) Trombetta, D.; Giofre, S. V.; Tomaino, A.; Raciti, R.; Saija, A.; Cristani, M.; Romeo, R.; Siracusa, L.; Ruberto, G. *Nat. Prod. Commun.* **2014**, *9*, 1761-1764.

(32)     Zhou, X. M.; Zheng, C. J.; Gan, L. S.; Chen, G. Y.; Zhang, X. P.; Song, X. P.; Li, G.

N.; Sun, C. G. *J. Nat. Prod.* **2016**, *79*, 1791-1797.