Bio-inspired dimerisation of prenylated quinones directed towards the synthesis of the meroterpenoid natural products, the scabellones

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Abstract – Stirring 2-geranyl-6-methoxy-1,4-hydroquinone in pyridine/O_2 or 2-geranyl-6-methoxy-1,4-benzoquinone in pyridine/N_2 affords the dimeric meroterpenoid natural products scabellones A–C in modest to low yields and also identifies 2-methoxy-6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone (scabellone E) as a new natural product. The corresponding reaction of the des-methoxy analogue 2-geranyl-1,4-benzoquinone in degassed pyridine for three days afforded the natural product cordiachromene A (15% yield) and 6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone (12%), the latter being a likely biosynthetic precursor to the marine meroterpenoid alkaloids conicaquinones A and B.

Keywords – meroterpenoid; dimerisation; bio-inspired; marine natural product; scabellone

Ascidians belonging to the genus *Aplidium* (Order Enterogona, Family Polyclinidae) are known to produce a variety of bioactive marine natural products.[1] We recently described the isolation of a series of meroterpenoid natural products including scabellones A (**1**) and B (**2**), 2-geranyl-6-methoxy-1,4-hydroquinone-4-sulfate (**3**) and 8-methoxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-1-benzopyran-6-ol (**4**) (Figure 1) from a New Zealand collection of *Aplidium scabellum*.[2] Scabellone B was identified as a moderately active antimalarial agent, making it of interest for structure-activity relationship studies. The pseudodimeric structures of the scabellones suggested that their biogenesis proceeds via dimerisation of hydroquinone **5** and/or quinone **6**. In continuation of our studies on the biomimetic synthesis of natural products[3,4] we herein report on our investigations of bio-inspired coupling reactions of **5** and **6** that afforded scabellones A–C, and which identified the structurally-related 2-methoxy-6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone (**7**, scabellone E) as a new natural product.

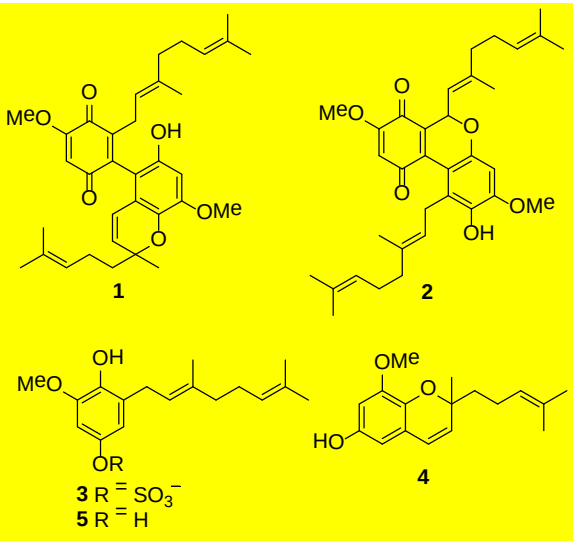
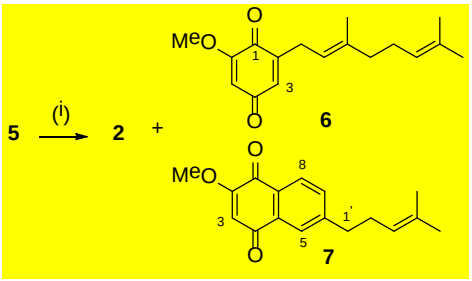


Figure 1. Structures of natural products scabellones A (**1**) and B (**2**) quinol sulfate **3** and chromenol **4** and related hydroquinone **5**.

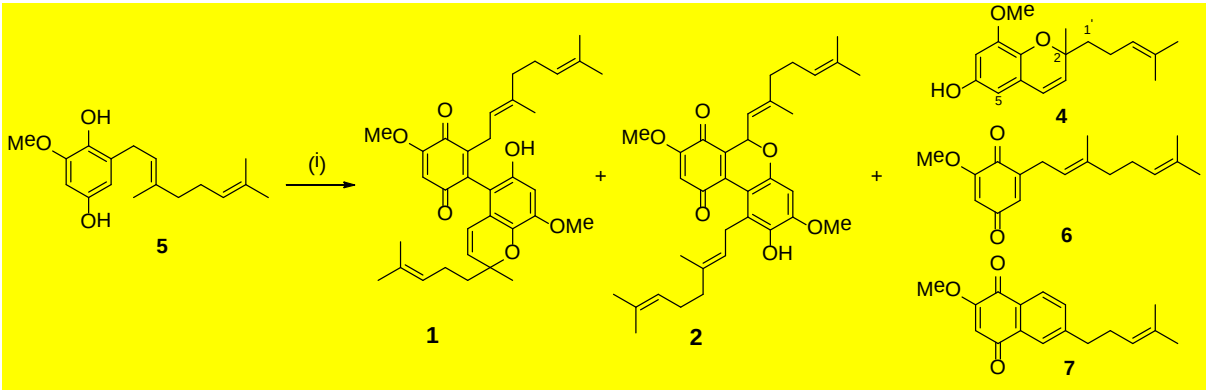
The combination of copper(I) chloride, pyridine and oxygen has been reported to mimic metal-centred oxidase enzymes as catalysts for the oxidation and coupling of phenolic compounds.[5] Reaction of hydroquinone **5** with O_2–CuCl–pyridine at room temperature gave quinone **6** (26%) and 2-methoxy-6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone (**7**)[6] (1%), while reaction undertaken at 0 °C (ice bath) afforded **6** (24%), **7** (1%) and dimeric products scabellone B (**2**) (3%) and C (1%) (Scheme 1).



Scheme 1. Reagents and conditions: (i) CuCl, pyridine, O_2, 0ºC, 30 min., **2** (3%), **6** (24%), **7** (1%).

The formation of naphthoquinone **7** under these reaction conditions, albeit in very low yield, was surprising. Previous efforts to construct such functionalised naphthoquinones typically utilise a Diels-Alder reaction between benzoquinone and α-cumene,[7] though an earlier publication by Burnett and Thomson reported that BF_3 diethyletherate effected the cyclisation of 2-methyl-5-(3-methylbut-2-enyl)-l,4-benzoquinone to give chimaphilin.[8] The transformation of **5** into **7** can be considered biomimetic as the biosynthesis of 2-(4-methylpent-3-en-1-yl)anthraquinone (MPAQ) has been shown to proceed via 2-geranyl-1,4-naphthoquinone[9] and there are numerous reports in the literature of the co-isolation of prenylated benzoquinones and the corresponding ring-closed naphthoquinones.[10] Indeed, with an authentic sample of naphthoquinone **7** in hand, re-examination of the extract fractions of *Aplidium scabellum* derived from our previous efforts to isolate naturally occurring scabellones A–D led to identification of the presence of the compound. Thus we have assigned the trivial name scabellone E to **7**.

Further experiments established pyridine as the only necessary component for the formation of dimeric products. Thus stirring hydroquinone **5** in pyridine under O_2 at room temperature for 30 minutes yielded dimeric products scabellones A (**1**) and B (**2**), as well as chromenol **4**, quinone **6**, and naphthoquinone **7** (Scheme 2).



Scheme 2. Reagents and conditions: (i) pyridine, O_2, rt, 30 min., **1** (11%), **2** (3%), **4** (trace), **6** (1.5%), **7** (1.5%),

The corresponding reaction of quinone **6** in pyridine, degassed and under nitrogen and stirred overnight, afforded scabellone A (**1**) (9%), chromenol **4** (10%), but only trace amounts of dimeric products scabellone B (**2**), scabellone C, and dichromenol **8**[11] (Figure 2).

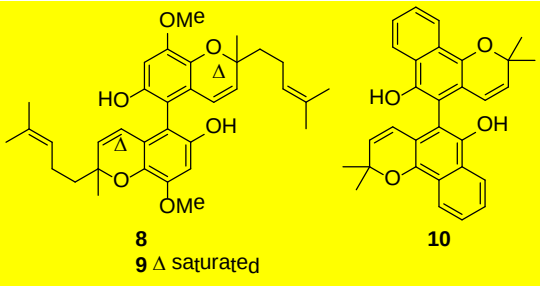
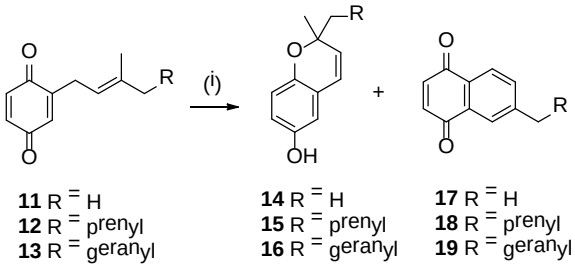


Figure 2. Structures of chromenol (**8**) and chroman (**9**) dimers and tectol (**10**).

Extending this latter reaction to three days using degassed pyridine afforded a complex mixture of products, from which chromenol **4** (5%) and naphthoquinone **7** (8%) were purified. The generality of the transformation of quinone **6** into naphthoquinone **7** in pyridine was investigated using structurally simpler benzoquinone analogues **11**, **12** and **13**.[4,12] In each case, stirring in degassed pyridine at room temperature for three days afforded complex mixtures, from which were isolated the corresponding chromenol **14** (32%)/**15** (52%)/**16** (44%)[13] and naphthoquinone **17** (2%)/**18** (7%)/**19** (1%)[14] (Scheme 3).



Scheme 3. Reagents and conditions: (i) degassed pyridine, N_2, rt, 72 h, **14** (32%), **17** (2%); **15** (52%), **18** (7%); **16** (44%), **19** (1%).

In the specific case of the reaction of 2-geranylbenzoquinone **12**, in addition to cordiachromene A (**15**) and 6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone (**18**), 2-geranyl-1,4-hydroquinone (9%) was identified in the product mixture. This observation suggested that quinone **12** was also an oxidant in the reaction, acting to oxidise a naphthoquinone precursor. Repeating each of the reactions of **11**–**13** with the addition of one equivalent of 1,4-benzoquinone as a sacrificial co-oxidant afforded slightly increased yields of naphthoquinones **17**–**19** (3%, 12% and 9%, respectively). Intriguingly, in each of these reactions, production of the corresponding chromenol **14**–**16** was suppressed. Trialing the addition of two equivalents of 1,4-benzoquinone to the reaction of **12** gave no further increase in yield of naphthoquinone **18**, but did lead to the production of benzo[*c*]chromene-7,10-dione **20**[15] (Figure 3) in 7% yield. Naphthoquinone **18** represents the terpenoid core of conicaquinones A and B, natural products previously reported from the Mediterranean ascidian *Aplidium conicum*.[16]

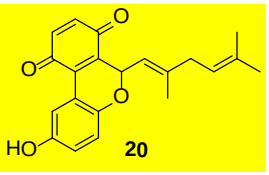


Figure 3. Structure of benzo[*c*]chromene-7,10-dione **20**

We have recently reported that the reaction of **12** with Et_3N in CH_2Cl_2 followed by overnight oxidation over silica gel affords dimers that can be elaborated into thiaplidiaquinones A and B, which are cytotoxic thiazinoquinones also isolated from *Aplidium conicum*.[4] Using similar reaction conditions with quinone **6** afforded only complex mixtures from which no individual products could be purified.

It has been previously reported that phenyliodine(III) bis(trifluoroacetate) (PIFA) can be activated with $BF_3.Et_2O$ to promote oxidative carbon-carbon bond formation.[17] Using hydroquinone **5** as starting material, reaction at 0 °C in dry acetonitrile yielded only benzoquinone **6** and no oxidative coupling products. However, when the temperature was decreased to –40 °C and the solvent changed to dry CH_2Cl_2, chroman dimer **9**[18] was formed (62%) (Figure 2). Repeating the reaction using chromenol **4** as the starting material afforded dichromenol **8** (89%). While we and others have found that reaction of the dichromenol tectol (**10**) with chloranil effects ring closure to yield the 9,10-dihydropyranobenzo[*c,f*]chromene-1,4-dione natural product tecomaquinone I,[3] efforts directed towards effecting a similar ring closure of **8** or **9** to yield scabellones C/D were unsuccessful.

In conclusion, we have achieved a bio-inspired synthesis of the meroterpenoids scabellone A–C, finding that reaction of 2-geranyl-6-methoxy-1,4-hydroquinone in pyridine under O_2 or 2-geranyl-6-methoxy-1,4-benzoquinone in pyridine under N_2 affords the dimeric natural products in modest to low yields. The study also identified 2-methoxy-6-(4-methylpent-3-en-1-yl)-1,4-naphthoquinone as a new natural product (scabellone E).

Acknowledgments

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References and notes

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6. Data for **7**: R_f (CH_2Cl_2) 0.57; IR ν_{max} (ATR) 1683, 1652, 1609, 1243 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, d, *J* = 8.0 Hz, H-5), 7.90 (1H, d, *J* = 1.6 Hz, H-6), 7.51 (1H, dd, *J* = 8.0, 1.6 Hz, H-8), 6.14 (1H, s, H-2), 5.12 (1H, m, H-3'), 3.90 (3H, s, 3-OCH_3), 2.77 (2H, t, *J* = 7.5 Hz, H_2-1'), 2.35 (2H, td, *J* = 7.5 Hz, H_2-2'), 1.67 (3H, s, H_3-6'), 1.53 (3H, s, H_3-5'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.3 (C-1), 180.0 (C-4), 160.6 (C-3), 150.0 (C-7), 133.6 (C-8), 133.2 (C-4'), 132.0 (C-8a), 129.1 (C-4a), 126.9 (C-5), 126.1 (C-6), 122.6 (C-3'), 109.7 (C-2), 56.4 (3-OCH_3), 36.3 (C-1'), 29.3 (C-2'), 25.6 (C-6'), 17.7 (C-5'); (+)-HRESIMS *m/z* 271.1322 $[M+H]^+$ (calcd for $C_{17}H_{19}O_3$, 271.1329).
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11. Data for **8**: R_f (MeOH: CH_2Cl_2, 1:9) 0.63; IR (ATR) ν_{max} 3446, 2929, 1583, 1443, 1198 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.55 (2H, s, H-7), 5.89 (2H, d, *J* = 9.9 Hz, H-4), 5.58 (2H, d, *J* = 9.9 Hz, H-3), 5.08 (2H, t, *J* = 7.1 Hz, H-3'), 4.55 (2H, s, OH), 3.88 (6H, s, OCH_3-10), 2.12 (4H, m, H_2-2'), 1.76 (2H, m, H_2-1'a), 1.67 (2H, obscured, H_2-1'b), 1.66 (6H, s, H_3-5'), 1.57 (6H, s, H_3-6'), 1.43 (6H, s, H_3-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.0 (C-8), 148.2 (C-6), 136.5 (C-8a), 132.0 (C-3, 4'), 124.2 (C-3'), 122.0 (C-4a), 120.4 (C-4), 105.8 (C-5), 100.3 (C-7), 77.9 (C-2), 56.3 (C-10), 40.4 (C-1'), 26.0 (C-9), 25.8 (C-5'), 22.8 (C-2'), 17.7 (C-6'); (+)-HRESIMS $[M+H]^+$ 547.3065 (calcd for $C_{34}H_{43}O_6$, 547.3054).
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14. Data for **17**: R_f (hexane:CH_2Cl_2, 1:2) 0.61; IR (ATR) ν_{max} 2925, 1662, 1598, 1305, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, d, *J* = 8.0 Hz, H-8), 7.89 (1H, d, *J* = 2.0 Hz, H-5), 7.55 (1H, dd, *J* = 8.0, 2.0 Hz, H-7), 6.94 (2H, s, H-2/H-3), 2.51 (3H, s, H_3-1'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.4 (C-1/C-4), 145.1 (C-6), 138.8 (C-2), 138.5 (C-3), 134.6 (C-7), 131.8 (C-4a), 130.1 (C-8a), 126.8 (C-5), 126.6 (C-8), 21.9 (C-1'). Data for **18**: R_f (hexane:CH_2Cl_2, 1:2) 0.72; IR (ATR) ν_{max} 3682, 2923, 2866, 1664, 1601, 1304, 1055, 1033, 1012, 833, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (1H, d, *J* = 8.0 Hz, H-8), 7.90 (1H, d, *J* = 2.0 Hz, H-5), 7.56 (1H, dd, *J* = 8.0, 2.0 Hz, H-7), 6.95 (2H, s, H-2/H-3), 5.13 (1H, m, H-3'), 2.78 (2H, t, *J* = 8.0 Hz, H_2-1'), 2.35 (2H, dt, *J* = 8.0, 7.5 Hz, H_2-2'), 1.67 (3H, s, H_3-5'), 1.53 (3H, s, H_3-6'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.4 (C-4), 185.0 (C-1), 149.5 (C-6), 138.8 (C-2), 138.5 (C-3), 134.2 (C-7), 133.2 (C-4'), 131.8 (C-4a), 129.9 (C-8a), 126.6 (C-5), 126.2 (C-8), 122.6 (C-3'), 36.3 (C-1'), 29.3 (C-2'), 25.7 (C-5'), 17.7 (C-6'); (+)-HRESIMS $[M+H]^+$ *m/z* 241.1225 (calcd for $C_{16}H_{16}O_2$, 241.1223). Data for **19**: R_f (hexane: CH_2Cl_2, 1:2) 0.68; IR

(ATR) ν_{max} 2922, 2856, 1666, 1601, 1303, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (1H, d, *J* = 7.9 Hz, H-8), 7.90 (1H, d, *J* = 1.6 Hz, H-5), 7.56 (1H, dd, *J* = 7.9, 1.6 Hz, H-7), 6.94 (2H, s, H-2/H-3), 5.14 (1H, m, H-3'), 5.06 (1H, m, H-7'), 2.79 (2H, t, *J* = 7.5 Hz, H_2-1'), 2.36 (2H, q, *J* = 7.5 Hz, H_2-2'), 2.03 (2H, m, H_2-6'), 1.98 (2H, m, H_2-5'), 1.67 (3H, d, *J* = 1.0 Hz, H_3-9'), 1.59 (3H, s, H_3-10'), 1.53 (3H, s, H_3-11'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.4 (C-4), 185.0 (C-1), 149.5 (C-6), 138.8 (C-3), 138.5 (C-2), 136.8 (C-4'), 134.2 (C-7), 131.8 (C-4a), 131.5 (C-8'), 129.9 (C-8a), 126.6 (C-5), 126.3 (C-8), 124.2 (C-7'), 122.4 (C-3'), 39.7 (C-5'), 36.3 (C-1'), 29.2 (C-2'), 26.6 (C-6'), 25.7 (C-9'), 17.7 (C-10'), 16.0 (C-11'); (+)-HRESIMS $[M+Na]^+$ *m/z* 331.1673 (calcd for $C_{21}H_{24}NaO_2$, 331.1669).

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18. Data for **9**: R_f (MeOH: CH_2Cl_2, 1:9) 0.56; IR (ATR) ν_{max} 3462, 2937, 1606, 1442, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.52 (1H, s, H-7), 5.10–5.07 (1H, m, H-3'), 3.86 (3H, s, OCH_3-10), 2.36–2.27 (1H, m, H_2-4a), 2.19–2.14 (1H, m, H_2-4b), 2.12–2.06 (3H, m, H_2-2' and H_2-1'a), 1.78–1.73 (2H, m, H_2-3), 1.67 (1H, m, H_2-1'b), 1.66 (3H, s, H_3-6'), 1.58 (3H, s, H_3-5'), 1.33 (3H, s, H_3-9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.6 (C-8), 147.3 (C-6), 138.1 (C-8a), 131.8 (C-4'), 124.3 (C-3'), 122.0 (C-4a), 108.7 (C-5), 98.2 (C-7), 75.8 (C-2), 56.1 (C-10), 39.9 (C-1'), 31.0 (C-3), 25.8 (C-6'), 24.4 (C-9), 22.6 (C-2'), 20.8 (C-4), 17.6 (C-5'); (+)-HRESIMS $[M+H]^+$ 551.3367 (calcd for $C_{34}H_{47}O_6$, 551.3347).