



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



Susanna T. S. Chan<sup>†</sup>, Michael A. Pullar, Iman M. Khalil, Emmanuelle Allouche, David Barker, Brent R. Copp<sup>\*</sup>

School of Chemical Sciences, University of Auckland, 29 Symonds St, Auckland 1142, New Zealand

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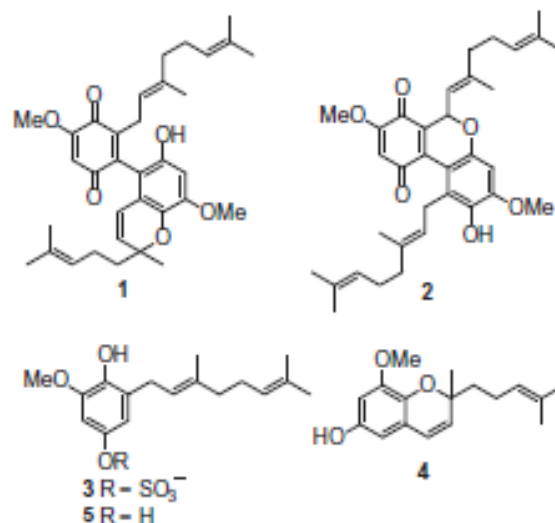
### ABSTRACT

Stirring 2-geranyl-6-methoxy-1,4-hydroquinone in pyridine/O<sub>2</sub> or 2-geranyl-6-methoxy-1,4-benzoquinone in pyridine/N<sub>2</sub> 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.

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Ascidians belonging to the genus *Aplidium* (Order Enterogona, Family Polyclinidae) are known to produce a variety of bioactive marine natural products.<sup>1</sup> 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)-2H-1-benzopyran-6-ol (4) (Fig. 1) from a New Zealand collection of *Aplidium scabellum*.<sup>2</sup> 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,<sup>3,4</sup> 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.

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.<sup>5</sup> Reaction of hydroquinone 5 with O<sub>2</sub>–CuCl–pyridine at room temperature gave quinone 6 (26%) and 2-methoxy-6-(4-methylpent-



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

3-en-1-yl)-1,4-naphthoquinone (7)<sup>6</sup> (1%), while the reaction undertaken at 0 °C (ice bath) afforded 6 (24%), 7 (1%) and the dimeric products, scabellone B (2) (3%) and C (1%) (Scheme 1).

The formation of naphthoquinone 7 under these reaction conditions, albeit in very low yields, was surprising. Previous efforts to

<sup>\*</sup> Corresponding author. Tel.: +64 9 373 7599; fax: +64 64 373 7422.

E-mail address: [b.copp@auckland.ac.nz](mailto:b.copp@auckland.ac.nz) (B.R. Copp).

<sup>†</sup> Current address: Molecular Targets Laboratory, Center for Cancer Research, National Cancer Institute, Building 562, Frederick, MD 21702, USA.