Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d5ob01430a

Biomimetic synthesis of *Sinularia* meroterpenoids and photochemical reactivity of capillobenzopyranol

Sarah A. French,[a,b] Ricardo A. Peralta [a,c] and Jonathan H. George *[a,d]

Received 5th September 2025,
Accepted 29th October 2025

DOI: 10.1039/d5ob01430a

rsc.li/obc

Motivated by a biosynthetic proposal which suggests a chemical relationship between capilloquinol and capillobenzopyranol, our studies report the first synthesis of their probable biogenetic precursors, furanoquinol and furanoquinone. A bioinspired cascade using an *ortho*-quinone methide intermediate derived from furanoquinone was attempted to construct the spirocyclic moiety of capilloquinol but instead led to the formation of capillobenzopyranol *via* an oxa-6π-electrocyclisation. Subsequent photochemical transformations of capillobenzopyranol resulted in a formal 1,3-hydrogen shift followed by intramolecular [2 + 2]-cycloaddition to construct an unusual 6–6–6–4 fused polycyclic compound.

Introduction

Cascade reactions involving *ortho*-quinone methide (*o*-QM) intermediates are valuable strategies for constructing complex secondary metabolites.[1] Owing to their partially dearomatised nature, *o*-QMs are highly electrophilic and susceptible to a diverse array of transformations, including hetero-Diels–Alder reactions, oxa-6π-electrocyclisations and conjugate additions. Moreover, the emergence of chemoenzymatic methods that proceed through *o*-QMs provides evidence that naturally occurring processes also make use of these privileged intermediates.[2] As a result, *o*-QMs are often featured in biosynthetic proposals that have been verified through biomimetic total synthesis endeavours.[3]

Marine organisms like the *Sinularia* genus of soft corals, are renowned for producing structurally complex meroterpenoid natural products.[4] For example, capilloquinol (**1**, Fig. 1) was isolated from *S. capillosa* and features a spirocyclic dihydrofuran with three contiguous stereocenters embedded within a 6–5–5–11 ring system.[5] In addition, several related meroterpenoids have been isolated from various *Sinularia* species, including the 2*H*-chromene capillobenzopyranol (**2**),[6] furanoquinol (**3**)[7,8] and furanoquinone (**4**).[7,8] Despite the isolation and synthesis of many marine meroterpenoids, capilloquinol remains an intriguing target due to its intricate structure and moderate cytotoxicity (ED_{50}: 3.8 μg mL^{-1} in P-388 cancer cell line), and we speculate that the related natural products shown in Fig. 1 might be biosynthetic precursors to capilloquinol.

Biosynthetically, as outlined in Scheme 1, we propose that capilloquinol (**1**) arises *via* the *ortho*-quinone methide (*o*-QM) intermediate (***E*)-5** from either capillobenzopyranol (**2**) or furanoquinone (**4**). Starting from capillobenzopyranol (**2**), a retro-oxa-6π electrocyclization[9] would generate *o*-QM (***Z*)-5**, then alkene isomerisation could occur to achieve the requisite (*E*)-alkene geometry for macrocyclisation. Alternatively, furanoquinone (**4**) could deliver (***E*)-5** directly by tautomerisation. In either case, the *o*-QM (***E*)-5** could undergo intramolecular conjugate addition of the pendant furan to forge the 11-membered ring of intermediate **7** *via* the oxocarbenium **6**. Conversion of **7** (as the hydroquinone) to capilloquinol (**1**) would then proceed

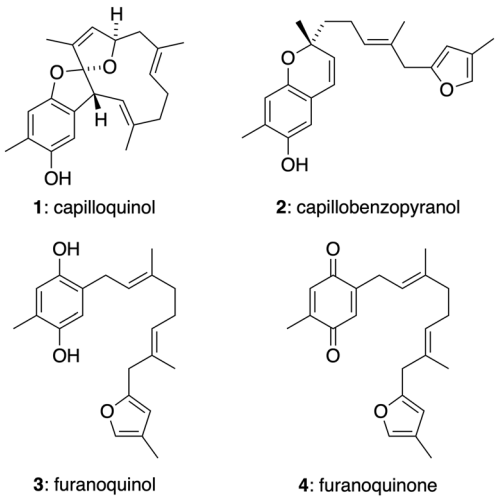
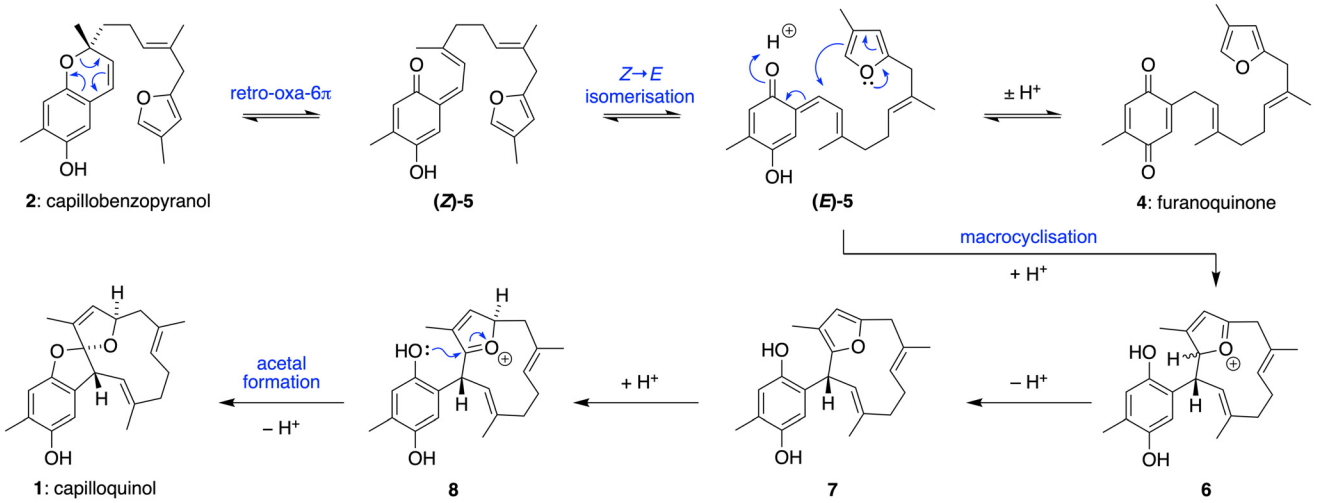


Fig. 1 Meroterpenoids isolated from *Sinularia* soft corals.

[a]*Department of Chemistry, University of Adelaide, Adelaide, SA 5005, Australia*
[b]*Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, USA*
[c]*Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, 09340 Ciudad de México, Mexico*
[d]*School of Chemistry and Chemical Engineering, University of Southampton, Highfield, Southampton SO17 1BJ, UK. E-mail: jonathan.george@southampton.ac.uk*



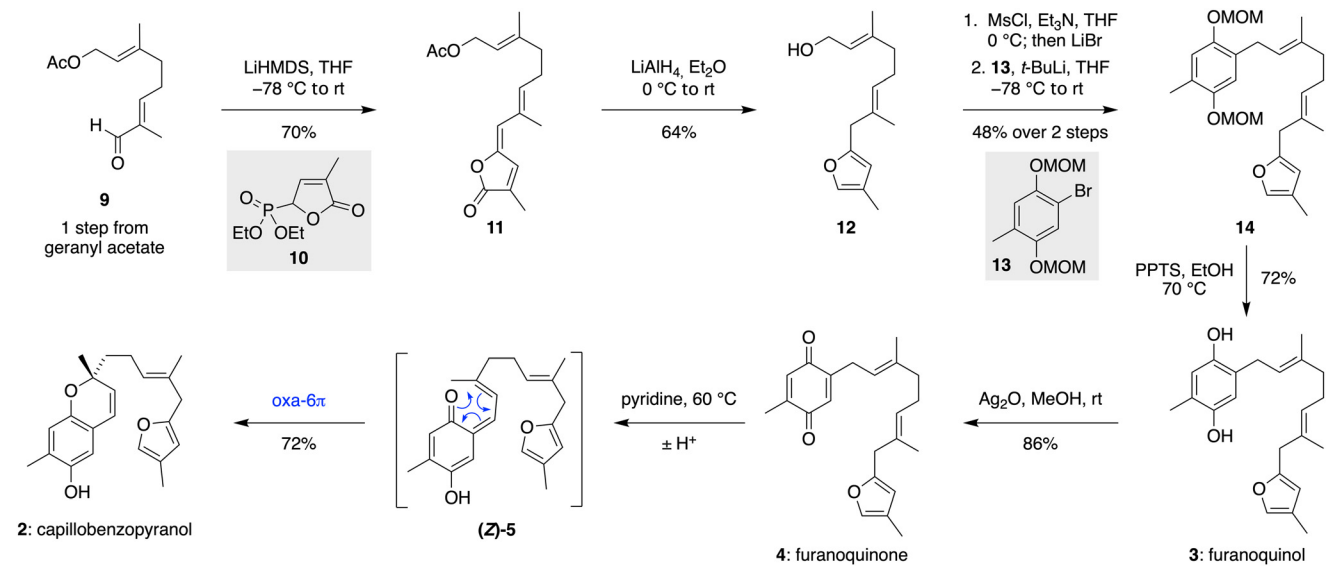
Scheme 1 Proposed biosynthesis of capillobenzopyranol (**2**) and capilloquinol (**1**) from a common *ortho*-quinone methide intermediate **5**.

through acetalisation of oxocarbenium ion **8** to install the spiroketal. This biogenetic proposal is consistent with known furan/*o*-QM reactivity: Ryu and co-workers reported low-temperature, Lewis acid-catalysed conjugate additions between *o*-QMs and furans,[10] and three recent paeoveitol total syntheses independently reported by the groups of Zhao,[11] Xie,[12] and Chen[13] employ an efficient intermolecular [4 + 2] cycloaddition between an *o*-QM and a benzofuran to assemble the natural product scaffold.

Results and discussion

With two plausible synthetic starting points to study our bioinspired reaction cascade, we initially focused our efforts on the first total synthesis of furanoquinone (**4**). In a forward synthetic sense, a Horner–Wadsworth–Emmons olefination between the known enal **9**[14] and phosphonate **10**[15] gave butenolide **11** as a single (*E*)-stereoisomer (Scheme 2). Subsequent reduction of butenolide **11** (and concomitant deacetylation) with $LiAlH_4$ gave the known furan **12**.[16] Conversion of **12** into an allylic bromide facilitated its coupling to the aryllithium species derived from aryl bromide **13**[17] and *t*-BuLi to give **14**. Deprotection of **14** proceeded smoothly with pyridinium *p*-toluenesulfonate (PPTS) to furnish furanoquinol (**3**). Oxidation of furanoquinol with Ag_2O then gave furanoquinone (**4**) in good yield, thus completing the first total synthesis of these meroterpenoids.

With an efficient and scalable synthesis of furanoquinone (**4**), we next explored its proposed biomimetic conversion into

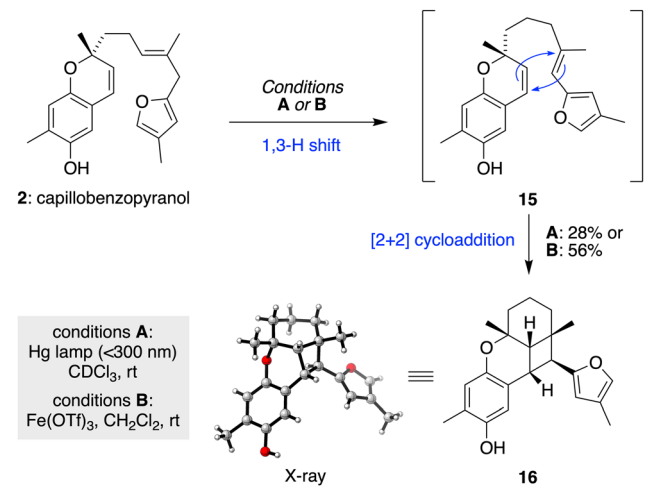


Scheme 2 Total synthesis of furanoquinol (**3**) and furanoquinone (**4**), and biomimetic conversion into capillobenzopyranol (**2**).

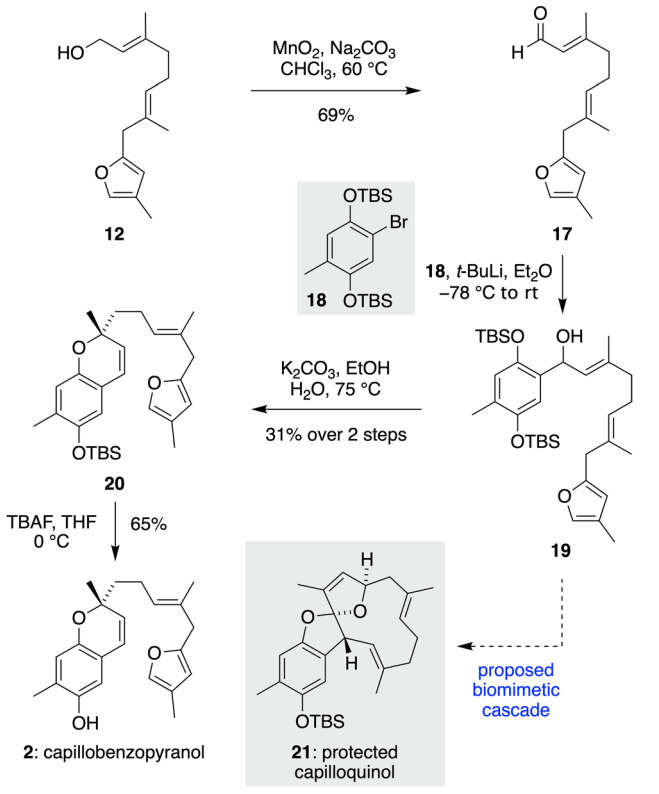
capilloquinol (**1**) *via* tautomerisation to *o*-QM (***E*)-5**. While exposure of **4** to several conditions known to tautomerise related quinones to *o*-QMs (*e.g.* acid, base and light, see SI for full details)[1] gave either no reaction or decomposition, heating it to 60 °C in pyridine formed the 2*H*-chromene of capillobenzopyranol (**2**) in good yield, presumably *via* oxa-6π-electrocyclisation of intermediate *o*-QM (***Z*)-5**.[18] Although undesired in this instance, the mild conversion of furanoquinone (**4**) to capillobenzopyranol (**2**) confirms this bioinspired transformation is chemically feasible. While a total synthesis of racemic capillobenzopyranol (**2**) has previously been disclosed by our group,[19] and more recently by Kundu in an enantioselective fashion,[20] this first bioinspired synthesis offers an efficient alternative with an overall yield of 10% over 7 steps.

With capillobenzopyranol (**2**) in hand, we next sought to probe its biogenetic link to capilloquinol (**1**). Retro-oxa-6π-electrocyclisations of 2*H*-pyrans with similar structures to capillobenzopyranol have been reported to proceed under both photochemical and thermal conditions.[1,21] While no reactivity of our system was observed under thermal conditions, photochemical excitation of capillobenzopyranol (**2**) with a broad spectrum high-pressure Hg lamp gave cyclobutane **16** in a 28% yield (Scheme 3). X-ray analysis of **16** confirmed the fused tetracycle was comprised of a 6–6–6–4 ring system and established the relative stereochemistry of the cyclobutane.[22] Presumably, a formal 1,3-H shift occurs to give a conjugated furan **15** as an *E*-stereoisomer, prior to a stereospecific, intramolecular [2 + 2] cycloaddition. Notably, some furanosesquiterpenes with the same conjugated furan system as the putative intermediate **15** have been isolated from *Sinularia* soft corals.[23] Natural products with 6–6–6–4 polycyclic ring systems derived from intramolecular [2 + 2] cycloaddition of 2*H*-chromenes are rare, but some examples with embedded orcinol moieties are known.[24] An attempt to form the more common 6–6–5–4 ring system found in many natural product families by a direct [2 + 2] cycloaddition using catalytic $Fe(OTf)_3$ instead gave **16** as the only isolated product in 56% yield.[25] Given the ease with which capillobenzopyranol (**2**) undergoes alkene isomerisation and [2 + 2]-cycloaddition on exposure to UV light or a mild Lewis acid catalyst, it is plausible that cycloadduct **16** is a meroterpenoid natural product that has yet to be isolated.[26]

A final attempt to trigger the desired biosynthetic cascade to protected capilloquinol **21** *via* dehydration of benzylic alcohol **19** is outlined in Scheme 4. Oxidation of allylic alcohol **12** with MnO_2 gave aldehyde **17** in good yield, which was treated with the aryllithium derived from aryl bromide **18** to give **19**. Surprisingly, on exposure to mildly acidic conditions (*e.g.* standing in $CDCl_3$ or purification on silica gel), decomposition of **19** was observed. However, treatment with K_2CO_3 in H_2O-EtOH, the desired furnished TBS-protected capillobenzopyranol **20** in a 30% yield over two steps, rather than the desired TBS protected capilloquinol **21**. The observed reaction could occur *via* migration of a TBS group from a phenol to the benzylic alcohol position, and elimination of TBSOH from the resultant phenolate to give an *o*-QM, which cyclises to form **20**. To complete an alternative total synthesis of capillobenzopyranol (**2**), deprotection of **20** was achieved with TBAF in good yield.



Scheme 3 Olefin migration and intramolecular [2 + 2] cycloaddition of capillobenzopyranol (**2**).



Scheme 4 An alternative synthesis of capillobenzopyranol (**2**) from benzylic alcohol **19**.

Conclusion

In summary, our proposed biosynthesis of capilloquinol inspired the first synthesis of two probable biogenetic precursors, furanoquinol and furanoquinone. When attempting the desired cascade reaction to generate capilloquinol from either furanoquinone or benzylic alcohol **19**, the biomimetic oxa-6π-electrocyclisation of an *o*-QM intermediate instead gave capillobenzopyranol as the sole product. When assessing whether capillobenzopyranol was itself a viable precursor to capilloquinol, photoexcitation instead resulted in olefin isomerisation and intramolecular [2 + 2] cycloaddition to give a 6–6–6–4 tetracycle which may aid the future discovery of related natural products.

Author contributions

S. A. F. designed and performed the experiments, analysed the experimental data and wrote the manuscript. R. A. P. collected the X-ray data. J. H. G. directed the investigations and prepared the manuscript with S. A. F.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures and full characterisation data for all new compounds. See DOI: https://doi.org/10.1039/d5ob01430a.

CCDC 2101324 contains the supplementary crystallographic data for this paper.[22]

Acknowledgements

This work was supported by the Australian Research Council (Discovery Project, DP200102964).

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