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Efficient syntheses of streptocarpone and (±)-α-dunnione

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Abstract—An efficient divergent synthesis of both streptocarpone and racemic α-dunnione from lawsone are described. A one-pot, formal [3+2] cyclization to form a furanonaphthoquinone directly provided a common intermediate.

We have been interested in the chemistry of naphthoquinones for some time due to their interesting structure and activities.[1] A series of related naphthoquinone pigments (streptocarpone, α-dunnione, dunniol and dunnione) from *Streptocarpus dunnii* (Mast.)[2,3] have been isolated and characterized to contain an isoprenylated naphthoquinone structure (Fig. 1). The furanonaphthoquinone α-dunnione has also been isolated from *Streptocarpus pole-euonsii* (Gesneriaceae),[4] and from the Scrophulariaceae plants *Calceolaria andina*,[5] and *C. integrifolia*.[6] Recently, hydroxylated derivatives of α-dunnione have been isolated from *Chirita eburnea* Hance.[7]

Most of these compounds have very potent insecticidal and fungicidal activity[8] and they all probably have antioxidant activity.[7] However, the activity of streptocarpone is not known, even though a quaternary carbon on the side chain connected to a naphthoquinone nucleus was found to be important for some activity. Although the natural compounds are available, a synthetic preparation would allow formation of the desired compound in large quantities. Furthermore, chemical construction would allow the formation of other analogs which may be more effective in certain aspects (e.g., solubility).

All previous syntheses to form α-dunnione derive from dunniol.[9] Acidic cyclization of dunniol **3** forms racemic 1,2-naphthoquinone **4** which is isomerized in base to α-dunnione **2** (Scheme 1). This synthesis is inefficient and depends on easy access to dunniol, which is not commercially available. To the best of our knowledge, the total synthesis of streptocarpone has not been previously reported.

We were curious if the biosynthetic route (and our synthetic approach) to these compounds could be traced to a common intermediate enol ether (Scheme 2). Hydrolysis of ether **5** would provide streptocarpone **1**, whereas reduction of the exocyclic alkene directly provides α-dunnione **2**. Furthermore, we envisioned the direct

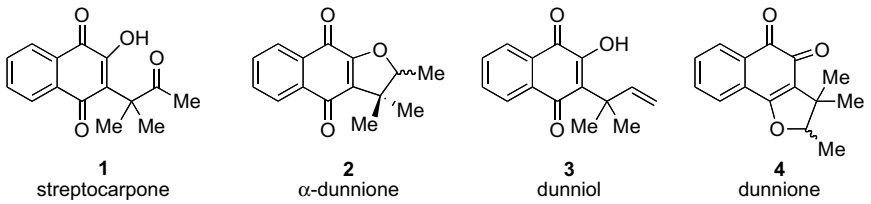

Figure 1. Prenylated naphthoquinones.

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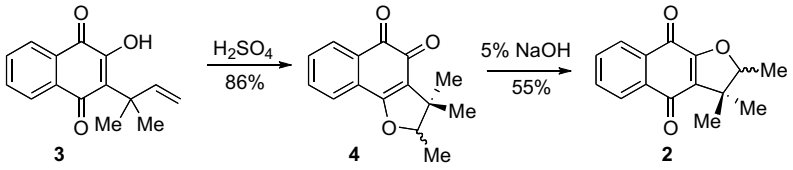
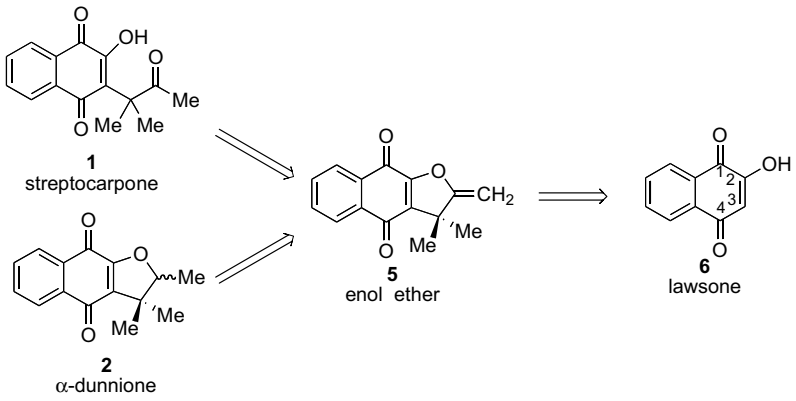


Scheme 1. Previous synthesis of α-dunnione.



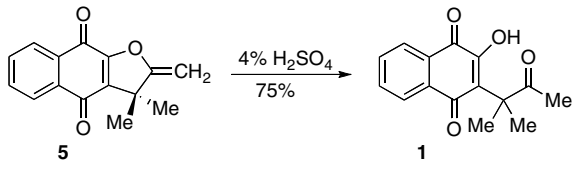
Scheme 2. Retrosynthetic analysis.

alkylation of the commercially available 2-hydroxy-1,4-naphthoquinone (lawsone, **6**) at the C-3 as the most efficient route to this common intermediate.

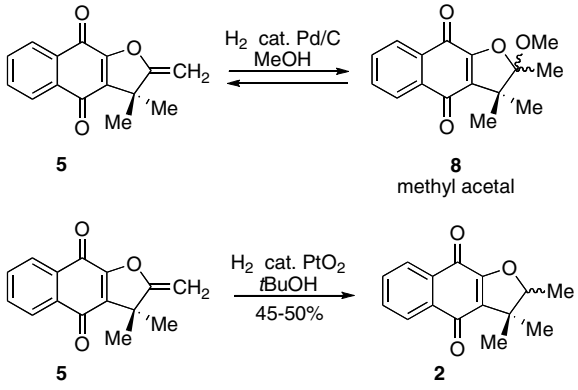
We began our synthesis with the regioselective alkylation of lawsone. According to the literature precedent, phenols[10] and carboxylic acids[11] are alkylated at the oxygen with tertiary propargylic halides. However, we did find one example of C-alkylation with ethyl cyanoacetate.[12] Since lawsone can be considered as the stable enol form of a β-diketone, we anticipated that the copper catalyzed reaction would be regioselective. As we discovered, the major product produced between lawsone and 3-chloro-3-methyl-1-butyne **7** was identified as enol ether **5** (Scheme 3). A one-pot, formal [3+2] cyclization to form the furanonaphthoquinone directly provided our common intermediate.

With a ready supply of dehydro-α-dunnione **5**, we first investigated the formation of streptocarpone **1** (Scheme 4). Stirring a suspension of furanonaphthoquinone **5** in hot aqueous sulfuric acid until the compound dissolves and then cooling and filtering the yellow product gave a good yield of pure streptocarpone. The melting point and NMR spectra correspond to the natural product.[3]

The reduction of the exocyclic double bond of **5** should be straightforward. However, we were surprised to find

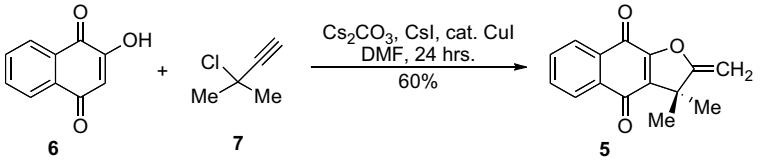


Scheme 4. Hydrolysis of enol ether.

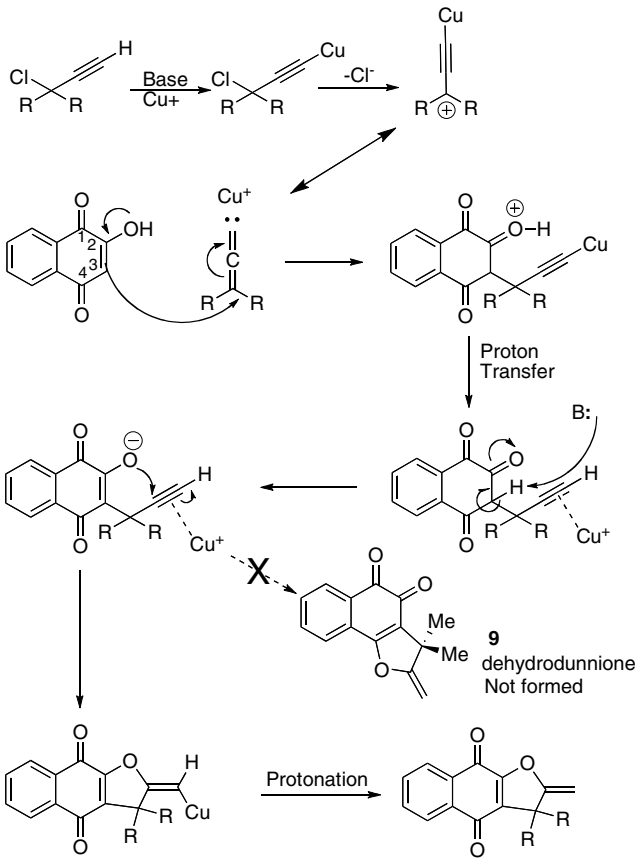


Scheme 5. Attempted and successful hydrogenation of enol ether.

that TLC analysis of the hydrogenation reaction of **5** in MeOH using Pd/C with pressurized H_2 gas showed no



Scheme 3. Selective alkylation of lawsone.



Scheme 6. Proposed mechanism of the formation of furanonaphthoquinone.

change over several days or weeks. NMR analysis of the crude reaction mixture following a rapid work-up showed the reason: the compound readily forms methyl acetal **8**, blocking the hydrogenation. The reaction is reversible and the acetal on a TLC plate (or during work-up) reverts to the starting material. Changing the solvent to *t*-butanol and the catalyst to PtO_2 (Adam's catalyst) allowed the hydrogenation to take place rapidly at room temperature under balloon pressure of H_2 (Scheme 5). The physical and spectroscopic properties of synthetically prepared racemic **2** match the literature data published.[3]

The mechanism of the interesting transformation of lawsone to enol ether **5** is still under investigation. We suggest that under the conditions of the coupling, a zwitterion-vinyl carbene intermediate is formed (Scheme 6).[13] This species couples with lawsone at C-3. Proton transfer (intramolecular or intermolecular) provides the terminal alkyne, π-activated by the copper ions present. Cyclization by the nucleophilic oxygen at C-2 on the activated alkyne thus forms the exocyclic enol 'vinylcuprate', which is protonated in situ or during the aqueous work-up. The formation of a carbocyclic 5-membered ring by intramolecular cuprate addition to an alkyne is known;[14] this would be the first oxygen variation of the process. Many questions are still unanswered by this mechanism: Why is the reaction selective for alkylation C-3? Why is the O-2 most nucleophilic and not O-4 (dehydrodunnione **9** is a known natural product,[3] whereas dehydro-α-dunnione **5** is an apparently new compound)? We hope to address these mechanistic concerns by forming the uncyclized C-alkylated intermediate by another route and submitting this compound to the conditions of the reaction to see if we have a viable intermediate.

In summary, we have presented a very efficient and easily accessible synthesis of streptocarpone and (±)-α-dunnione. Of note is the unprecedented transformation of lawsone **6** into furano enol ether **5** by copper catalyzed propargylation. The reactions have not been optimized and are sure to provide higher yields on a larger scale. Because the two products are produced from a common intermediate, which is formed by the coupling of two common substrates, the synthesis is both convergent and divergent and allows flexibility to form various congeners that vary, for example, by replacing different groups at the quaternary center. We are continuing to investigate the mechanistic aspects of the cyclization and the biological properties of these compounds which will be reported in separate articles.

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Supplementary data

Supplementary data (experimental procedures and full spectroscopic data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.090.

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