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Convenient, scalable synthesis of 2-methyl-3-(3',3'-carboxymethylpropyl)-1,4-naphthoquinone, the principal vitamin K urinary metabolite

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ABSTRACT

The ultimate metabolite of vitamin K, 2-methyl-3-(3',3'-carboxymethylpropyl)-1,4-naphthoquinone (**1**), has been shown to be biologically active and may be used as a measure of vitamin K levels in the body. We report a facile, five-step synthesis of **1** that requires only two isolated intermediates and a single chromatographic purification, and provides the title product in 26% overall yield. The structure of one of the intermediates was confirmed by X-ray crystallography.

1. Introduction

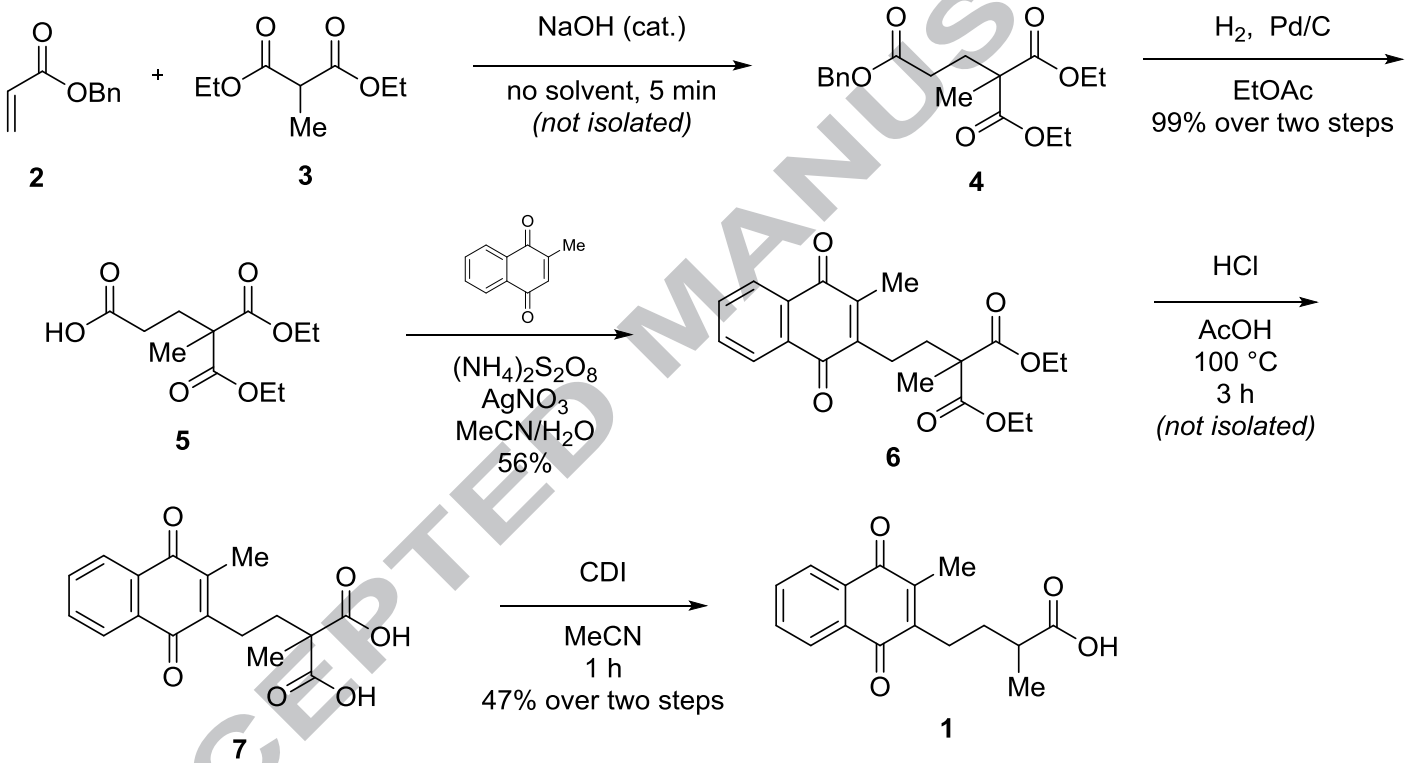
Vitamin K[1] refers to a family of molecules based upon the 2-methyl-1,4-naphthoquinone moiety[2], with variability of the side-chain at the 3-position. This family is divided into the plant-derived phylloquinone (vitamin K_1), having a phytyl side-chain, and the menadiones (vitamin K_2), which have isoprenoid side-chains of varying lengths. In humans, vitamin K is essential for blood coagulation and bone health, [3] as well as further functions.[4] The title compound (**1** in Scheme 1) is a human metabolite formed from vitamin K, and has been shown to be biologically active.[5,6,7]

This paper reports a convenient and scalable synthesis of **1** that uses only inexpensive reagents and catalysts. Literature routes to **1** entail long synthetic routes,[8] complex product mixtures, and relatively poor overall yields.[9] After our studies were underway, Teitelbaum and coworkers[10] reported the most straightforward route to date for synthesis of **1**, but their method still requires an expensive starting material and catalyst; their overall yield was 6% encompassing five steps, including one particularly low-yielding (17%) step.

2. Results and Discussion

The present synthesis begins with Michael addition of diethyl methyl malonate (**2**) onto benzyl acrylate (**3**). The reaction is run neat in the presence of catalytic NaOH, and gives product **4** quickly (5 min at rt). The NaOH is removed by simple filtration through a plug of silica, using EtOAc as eluent, to provide a solution of **4** that is used directly in the next reaction, i.e., hydrogenolysis utilizing a low loading of Pd/C catalyst (0.5 mol % Pd) under 1 atm of H_2. Thus, free acid **5** is obtained in 99% yield, over two steps, on a multi-gram scale, without the need for purification. Radical coupling between **5** and menadione is accomplished by an adaptation of the Kochi-Anderson reaction,[11,12,13] with pure product **6** obtained readily after workup by simple trituration. The malonate ester moiety of **6** is then saponified to produce the diacid species as an

intermediate. While continued application of heat provides the decarboxylation product **1** directly, we find that treatment with *N*,*N*'-carbonyldiimidazole (CDI) is a milder way (fewer side products) to effect decarboxylation.[14] Upon completion of all chemical steps, the single chromatographic purification of the entire route is accomplished on silica gel, providing pure **1** in an overall yield of 26%.



Scheme 1. Synthesis of vitamin K metabolite (1).

Note that the structure of intermediate **6** was confirmed by x-ray crystallography **(Figure 1**). Bond lengths and angles were within expected ranges.

3. Conclusion

This synthesis of vitamin K metabolite **1** uses only inexpensive starting materials and reagents, and avoids protecting groups. The synthesis is readily scalable, and can be conducted with no special precautions to exclude air. Upon completion of all synthetic steps, only one chromatographic purification step is required. Due to its simplicity and robust nature, we expect this approach to become the primary method to produce **1**, along with numerous analogous compounds.

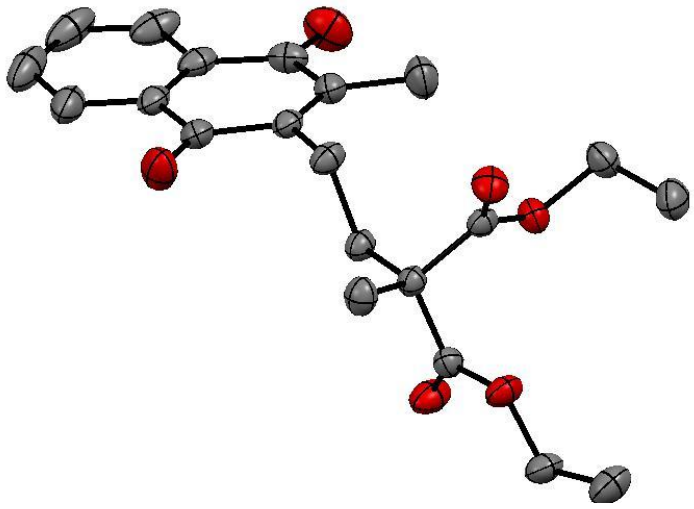


Figure 1. Crystal structure of 2-methyl-3-(3',3'-dicarboxybutyl)-1,4-naphthoquinone diethyl ester (6). For clarity, hydrogens are not shown.

4. Acknowledgments

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6. We acknowledge helpful discussions with both Dr. Victor G. Young, Jr. and Mr. Christopher Roberts. This work was supported by Occhem Labs, LLC and the Barany Research Fund.

5. Supplementary data

Supplementary data (synthetic procedures, analytical data, and NMR spectra) associated with this article can be found, in the online version, at: Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1503070. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.Uk).

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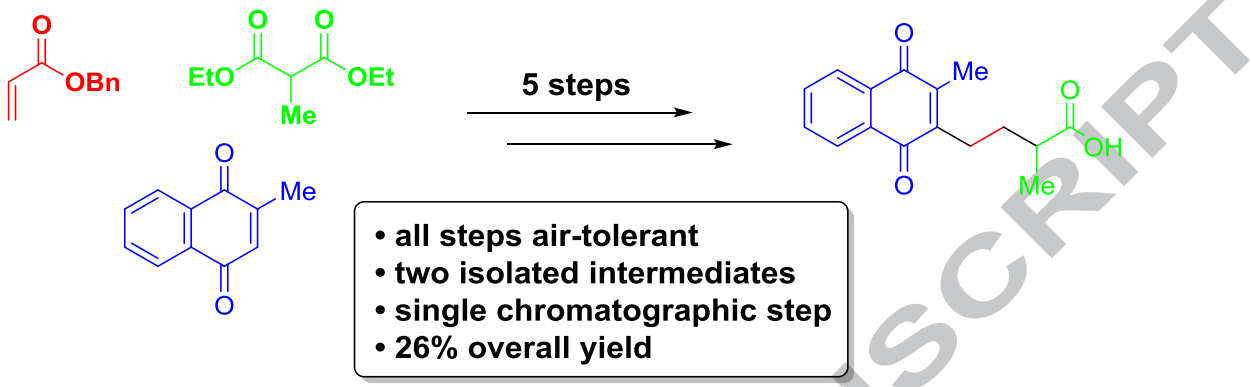
Graphical abstract



Highlights

- all steps air-tolerant
- two isolated intermediates
- single chromatographic step
- 26% overall yield