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Synthesis of a monofluoro 3-alkyl-2-hydroxy-1,4-naphthoquinone: a potential anti-malarial drug

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ABSTRACT

Monofluorinated 3-alkyl-2-hydroxy-1,4-naphthoquinone **4** was prepared in eight steps from commercially available 8-bromooctanoic acid (**10**). The key step involved L-proline-catalyzed three-component reductive alkylation (TCRA) of 2-hydroxy-1,4-naphthoquinone (**5**) with the optically active aldehyde **7**.

Atovaquone (**1**, Fig. 1) is a 2-hydroxynaphthoquinone that is a potent anti-malarial compound in current clinical use, and which competitively inhibits the cytochrome bc_1 complex of the malaria parasite *Plasmodium falciparum*.[1]

Due to the resistance developed to atovaquone,[2] other hydroxynaphthoquinones have been investigated for comparable anti-malarial properties.[3–5] For example, we found that S-10576 (**2**) is a potent inhibitor of the yeast cytochrome bc_1 complex that exhibits species selectivity higher than that of atovaquone.[3] Despite its efficacy, S-10576 (**2**) is readily metabolized in human cells via hepatic P450-mediated hydroxylation and subsequent oxidative carboxylation at the terminal position of the alkyl chain.[6] On the other hand, NQ1 (**3**), the trifluorinated analog of **2**, is metabolically stable and strongly inhibits atovaquone-resistant *P. falciparum* sporozoites. However, its species selectivity is significantly lower than that of S-10576 (**2**).[4,7] Based on molecular modeling studies and biological assays, we and others believe that the bulkiness of the trifluoromethyl group may be responsible for this reduced selectivity.[5,7] Thus, we surmised that a monofluorinated 8-carbon side chain would enhance the poor species selectivity of **3**, while retaining its metabolic stability, and would also recover the inhibition potency of **2**.[5,7] This led us to pursue the synthesis of monofluorinated 3-alkyl-2-hydroxy-1,4-naphthoquinone derivative **4**.

The retrosynthetic analysis of **4** is outlined in Scheme 1. Our target molecule **4** can be partitioned into 2-hydroxy-1,4-naphthoquinone (**5**) and *S*-aldehyde **7**. We envisioned that **4** might be generated by L-proline-catalyzed three-component reductive alkylation (TCRA) of **5** with **7**. The optically active aldehyde **7** would be obtained by chiral auxiliary-mediated asymmetric α-methylation of commercially available 8-bromocarboxylic acid **10** or 8-fluorocarboxylic acid **9,** itself obtained by fluorination of **10**.

We initially attempted the synthesis of 8-fluorocarboxylic acid **9** by treating the commercially available 8-bromooctanoic acid (**10**) with TBAF at 70 °C in *tert*-butanol. However, this reaction gave an inseparable mixture consisting majorly of the corresponding nine-membered lactone (not shown) and only a trace of the desired product **9**. A search of the literature revealed a precedent for TBAF-induced intramolecular S_N2-type cyclization/lactonization of halo-carboxylic acids.[8] To circumvent this side reaction, the carboxylic acid moiety in **10** was masked as its methyl ester **11** (Scheme 2). In the event, treating **10** with K_2CO_3 and iodomethane afforded a 2:1 mixture (85%) of the desired product **11** and its iodo-analog **12**, respectively.[9] No attempt was made to separate the mixture of **11** and **12** since both were anticipated to undergo fluorination in the next step.[10] The fluorination of the mixture of **11** and **12** gave the desired product **13** (75%) and a small amount of the Hoffmann elimination side product **14** (5%).[11] Attempts to separate the mixture by column chromatography were not successful. Fortunately, though, pure fluoro ester **13** was obtained by vacuum distillation using a Vigreux column.[12] Finally, saponification (LiOH, H_2O/MeOH) of fluoro ester **13** furnished the corresponding fluoro acid **9** in 95% yield. Overall, even with two additional steps for the protection of the carboxylic acid moiety and subsequent deprotection, this three-step fluorination method is a more efficient alternative for the preparation of fluoro acid **9**

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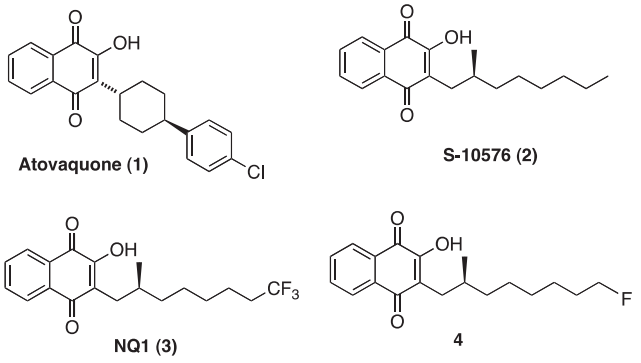
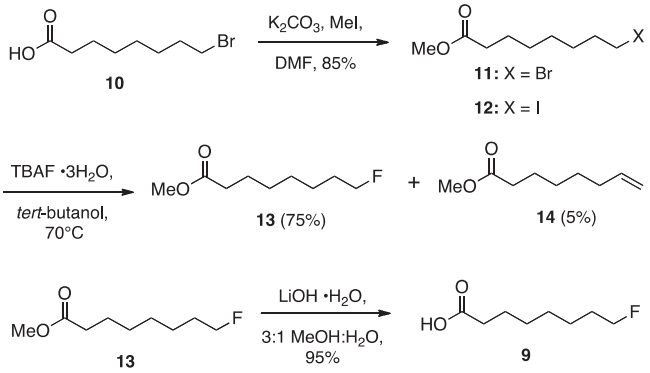


Figure 1. 3-Alkyl-2-hydroxy-1,4-naphthoquinones that inhibit the cytochrome bc_1 complex and our synthetic target **4**.



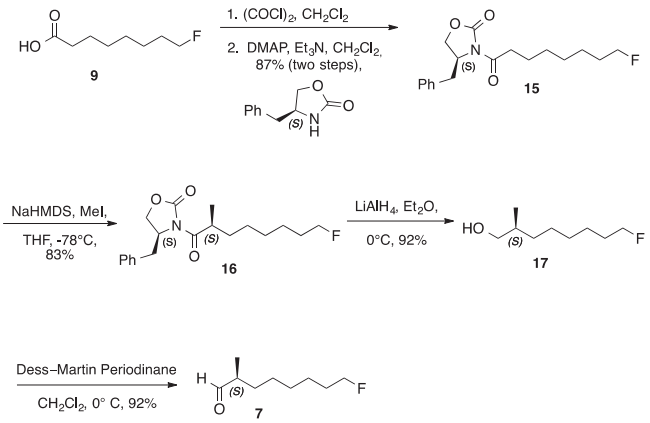
Scheme 2. Synthesis of 8-fluorooctanoic acid (**9**).

than that described in the literature, in which **9** was synthesized in 5 steps (61%).[13]

The enantioselective α-methylation was performed as shown in Scheme 3. The ω-fluorocarboxylic acid **9** was first treated with oxalyl chloride to form 8-fluorooctanoyl chloride, followed by the addition of (*S*)-4-benzyl-2-oxazolidinone using triethylamine and DMAP to give **15** in 87% yield.[14]

The α-methylation using NaHMDS and iodomethane furnished the oxazolidinone **16** in 83% yield.[14] Reductive cleavage of the chiral auxiliary from **16** using $LiAlH_4$ produced the alcohol **17** in a yield of 92%.[15] Dess–Martin oxidation provided aldehyde **7** (92%) that was used without further purification.[16]

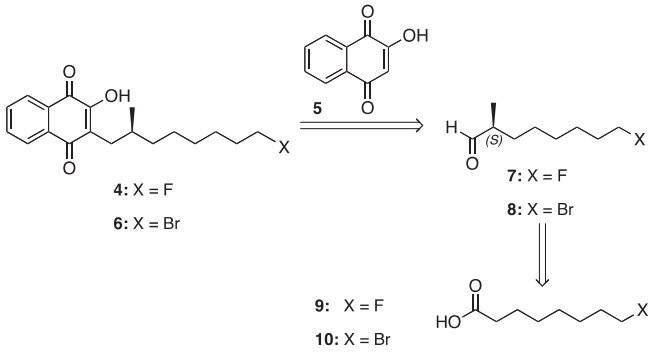
We conducted the L-proline-catalyzed three-component reductive alkylation of naphthoquinone **5** with aldehyde **7** and the Hantzsch ester (**18**) under the conditions reported by Ramachary.[17–19] Even though the authors reported good yields during the synthesis of several 3-substituted 2-hydroxy-1,4-naphthoquinones at room temperature,[17] in our case, the reactions at room temperature furnished the desired product **4** in only 33% yield even with extended reaction times (more than 48 h). However, refluxing CH_2Cl_2 not only accelerated the reaction but also improved the yield from 33% to 84% (Scheme 4).[20,21] Overall, the best yields were obtained by using 2 equiv of the aldehyde **7**, consistent with the examples reported by Ramachary.[17] Purification of the final product **4** was complicated by the presence of the pyridine by-product (**19**) from the oxidation of the Hantzsch ester (**18**), which exhibited the same R_f value as **4**. Attempts to remove **19** by washing the mixture with 2 N HCl failed. Alternatively, stirring the mixture with LiOH in H_2O/MeOH at room temperature for 4 h followed by acid work up afforded the desired product **4** as a pale yellow solid. It is important to note that the addition of LiOH to the H_2O/MeOH solution of the crude reaction mixture could have certainly furnished the final product **4**; however, we ran column



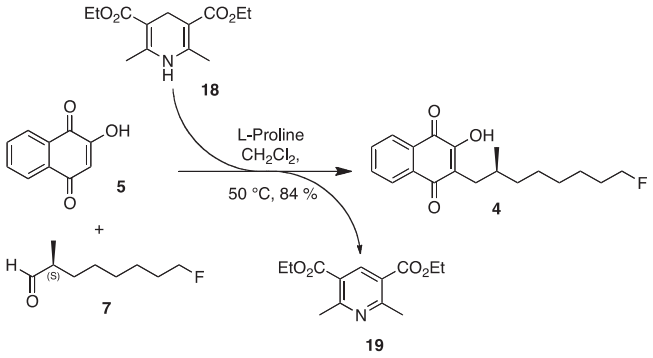
Scheme 3. Synthesis of aldehyde **7**.

chromatography prior to hydrolysis in order to recover and recycle the excess aldehyde **7**.

The alternative strategy, which delayed the introduction of the terminal fluorine until the final step, achieved the synthesis of brominated 3-alkyl-2-hydroxy-1,4-naphthoquinone **6** in five steps from bromooctanoic acid **10** (Scheme 5). This approach essentially mirrored the sequence of steps presented in Scheme 3. Moreover, the TCRA reaction of naphthoquinone **5** with aldehyde **8** (Scheme 1), the bromo analog of the aldehyde **7**, furnished the bromide **6** in 78% yield. Crystallization gave needle crystals of **6**, enabling us to assign its structure and absolute configuration using X-ray crystallography. However, the conversion of **6** to **4** using TBAF and *tert*-butanol was plagued by purification issues, in which **4** could not be separated from its mixture with other side products. In an attempt to optimize nucleophilic fluorination, we screened



Scheme 1. Retrosynthetic analysis.



Scheme 4. Synthesis of target compound **4** via a TCRA method.