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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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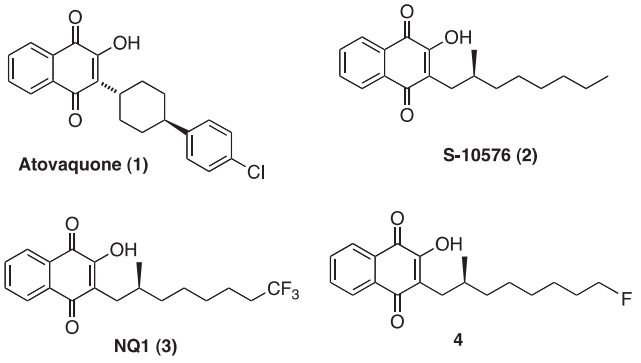
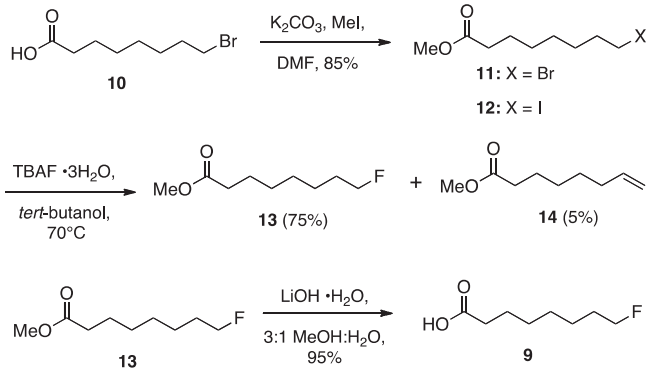
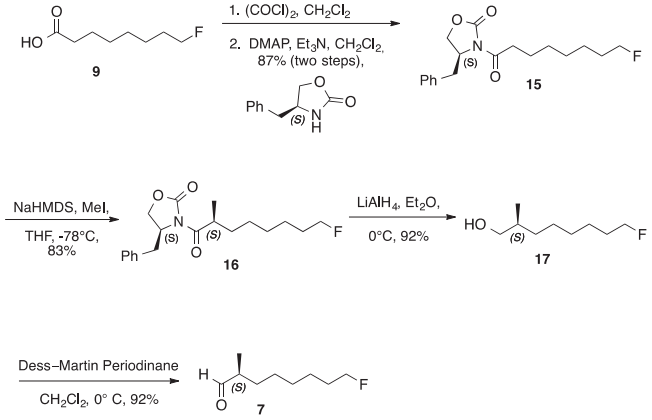


Figure 1. 3-Alkyl-2-hydroxy-1,4-naphthoquinones that inhibit the cytochrome bc_1 complex and our synthetic target **4**.



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



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

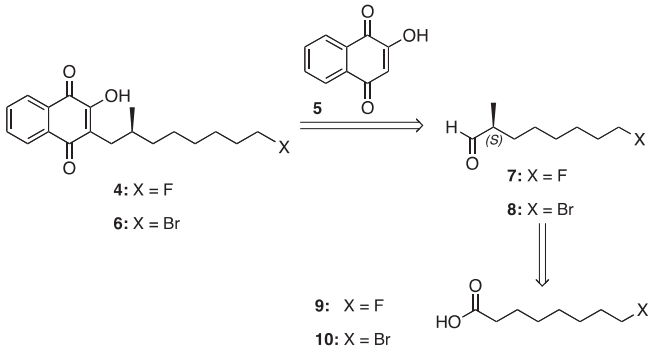
than that described in the literature, in which **9** was synthesized in 5 steps (61%).[13]

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]

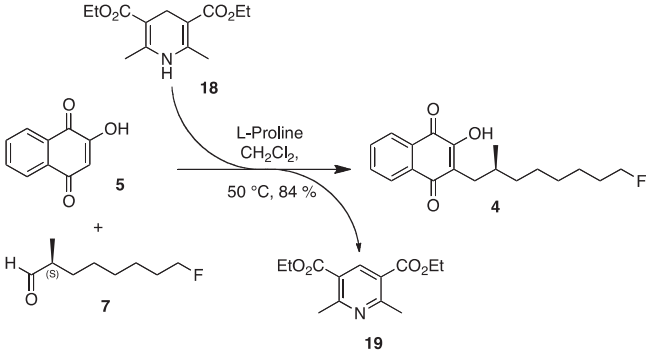
The α-methylation using NaHMDS and iodomethane furnished the oxazolidinone **16** in 83% yield.[14] Reductive cleavage of the chiral auxiliary from **16** using $LiAlH_4$ produced the alcohol **17** in a yield of 92%.[15] Dess–Martin oxidation provided aldehyde **7** (92%) that was used without further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

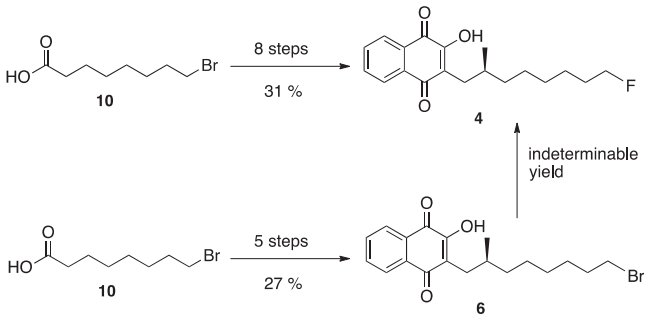
The alternative strategy, which delayed the introduction of the terminal fluorine until the final step, achieved the synthesis of brominated 3-alkyl-2-hydroxy-1,4-naphthoquinone **6** in five steps from bromooctanoic acid **10** (Scheme 5). This approach essentially mirrored the sequence of steps presented 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.



Scheme 5. Summary of two different approaches to the total synthesis of **4**.

different reaction conditions: CsF in *tert*-amyl alcohol,[22] TBAF in *tert*-amyl alcohol,[11] and TBAF in acetonitrile in 'wet' conditions.[23,24] All these conditions invariably produced mixtures consisting of the product **4**, alkene elimination product, and other unidentified side products that were inseparable by chromatographic techniques. Also, vacuum distillation, which had completely removed the fluorination side products in the first synthetic approach (vide supra), could not be employed in this case due to the solid nature of **4**. Thus, even though the second approach with fluorination at the last step would have shortened the total synthesis by two steps, the first approach with early fluorination was ultimately used to obtain pure and reliable quantities of the target compound **4**.

In conclusion, we have synthesized monofluorinated 3-alkyl-2-hydroxy-1,4-naphthoquinone **4** in 8 steps in 31% overall yield from 8-bromooctanoic acid (**10**).[25–31] Biological evaluation of this compound as an inhibitor of the cytochrome bc_1 complex of the malaria parasite is in progress and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.054.

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21. A mixture of the aldehyde **7** (100 mg, 0.624 mmol), 2-hydroxy-1,4-naphthoquinone (54.0 mg, 0.312 mmol), the Hantzsch ester (79.0 mg, 0.312 mmol), and L-Proline (18.0 mg, 0.156 mmol) in CH_2Cl_2 (30 mL) was refluxed for 12 h. After cooling to room temperature, SiO_2 (1 g) was added to the reaction mixture, which was concentrated in vacuo, then purified via dry-pack column chromatography (SiO_2, 10:1 hexanes/ethyl acetate). ^{1}H NMR confirmed **4** as the major product contaminated with diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**19**). LiOH·H_2O (82 mg, 1.2 mmol) was added, and the mixture was allowed to stir in 3:1 MeOH/H_2O (10 mL) for 4 h. After the removal of MeOH under reduced pressure, the mixture was washed with CH_2Cl_2 and the organic extracts were discarded. The aqueous layer was covered with CH_2Cl_2 and acidified with 2 N HCl. After the two layers were separated, the aqueous layer was further extracted with CH_2Cl_2 three times and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **4** as a yellow solid (50 mg, 63%). R_f = 0.70 (3:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.13 (dd, J = 7.81, 0.79 Hz, 1H), 8.08–8.09 (dd, J = 7.61, 0.79 Hz, 1H), 7.74–7.77 (td, J = 7.75, 1.26 Hz, 1H), 7.67–7.70 (td, J = 7.55, 1.26 Hz, 1H), 7.29 (s, 1H), 4.38–4.48 (dt, J = 47.40, 6.27 Hz, 2H), 2.58–2.62 (dd, J = 12.58, 6.15 Hz, 1H), 2.43–2.46 (dd, J = 12.63, 8.33 Hz, 1H), 1.81–1.86 (m, 1H), 1.64–1.73 (m, 2H), 1.21–1.44 (m, 8H), 0.88 (d, J = 6.61 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.1, 181.6, 153.7, 135.1, 133.2, 133.1, 129.7, 127.1, 126.3, 124.2, 85.0, 83.9, 37.4, 33.0, 31.0, 30.7, 30.5, 29.7, 27.2, 25.4, 25.4, 19.9. FT-IR (CH_2Cl_2, cm^{-1}) estim. 2922, 2851, 1640, 1589, 1363, 1272, 1223, 726. ^{19}F NMR (565 MHz, $CDCl_3$) δ −217.95. HRMS (ESI) calcd for $C_{19}H_{24}O_3F$ [M+H]$^+$: 319.1709, found 319.1702. $[\alpha]_D^{23}$ +7.9 (CH_2Cl_2).
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25. Methyl 8-fluorooctanoate (**13**). Clear oil. R_f = 0.75 (3:1 hexanes/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37–4.49 (dt, J = 47.47, 6.26 Hz, 2H), 3.67 (s, 3H), 2.29–2.32 (t, J = 7.52 Hz, 2H), 1.60–1.73 (m, 4H), 1.33–1.40 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 84.9, 83.8, 51.7, 34.2, 30.6, 30.5, 29.2, 29.1, 27.8, 25.2, 25.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.15.
26. 8-Fluorooctanoic acid (**9**). Clear oil. R_f = 0.45 (3:1 hexanes/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38–4.49 (dt, J = 47.42, 6.13 Hz, 2H), 2.34–2.37 (t, J = 7.59 Hz, 2H), 1.62–1.74 (m, 4H), 1.35–1.43 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 84.9, 83.8, 34.0, 30.6, 30.5, 29.1, 25.2, 24.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.16.
27. (*S*)-4-Benzyl-3-(8-fluorooctanoyl)oxazolidin-2-one (**15**). Clear oil. R_f = 0.50 (3:1 hexanes/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5H), 4.65–4.70 (m, 1H), 4.38–4.50 (dt, J = 47.49, 6.41 Hz, 2H), 4.15–4.22 (m, 2H), 3.28–3.31 (dd, J = 13.29, 3.08 Hz, 1H), 2.87–3.01 (m, 2H), 2.74–2.79 (dd, J = 13.90, 9.72 Hz, 1H), 1.65–1.75 (m, 4H), 1.37–1.45 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 153.7, 135.5, 129.6, 129.2, 127.6, 84.9, 83.8, 66.4, 55.4, 38.2, 35.7, 29.2, 25.3, 25.2, 24.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.10. FT-IR (CH_2Cl_2, cm^{-1}) estim. 2932, 1781, 1698, 1387, 1212, 703. HRMS (ESI) calcd for $C_{18}H_{24}NO_3FNa$ [M+Na]$^+$: 344.1638, found 344.1634.
28. (*S*)-4-Benzyl-3-((*S*)-8-fluoro-2-methyloctanoyl)oxazolidin-2-one (**16**). Clear oil. R_f = 0.60 (3:1 hexanes/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21–7.35 (m, 5H), 4.65–4.70 (m, 1H), 4.37–4.49 (dt, J = 47.26, 6.19 Hz, 2H), 4.16–4.22 (m, 2H), 3.69–3.73 (m, J = 6.85 Hz, 1H), 3.25–3.28 (dd, J = 13.24, 3.44 Hz, 1H), 2.74–2.79 (dd, J = 13.54, 9.54 Hz, 1H), 1.63–1.79 (m, 3H), 1.30–1.44 (m, 7H), 1.21 (d, J = 7.05 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 153.3, 135.5, 129.2, 127.6, 84.9, 83.8, 66.2, 55.6, 38.1, 37.9, 33.5, 30.6, 29.4, 27.3, 25.3. FT-IR (CH_2Cl_2, cm^{-1}) estim. 2931, 1774, 1697, 1386, 1208. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.10. HRMS (ESI) calcd for $C_{19}H_{26}NO_3FNa$ [M+Na]$^+$: 358.1794, found 358.1787. $[\alpha]_D^{23}$ +76.3 (CH_2Cl_2).
29. (*S*)-8-Fluoro-2-methyloctan-1-ol (**17**). Clear oil. R_f = 0.50 (3:1 hexanes/ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38–4.49 (dt, J = 47.40, 6.26 Hz, 2H), 3.49–3.52 (dd, J = 10.43, 5.87 Hz, 1H), 3.40–3.44 (dd, J = 10.41, 6.48 Hz, 1H), 1.64–1.74 (m, 2H), 1.58–1.63 (m, 1H), 1.24–1.41 (m, 8H), 0.91 (d, J = 6.76, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.1, 85.0, 83.9, 68.6, 36.0, 33.2, 29.7, 27.1, 25.4, 25.3, 16.8. FT-IR (CH_2Cl_2, cm^{-1}) estim. 3355, 2930, 2858, 2360, 1458, 1038. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.05. $[\alpha]_D^{23}$ −11.7 (CH_2Cl_2).
30. (*S*)-8-Fluoro-2-methyloctanal (**7**). Clear oil. R_f = 0.80 (3:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61–9.62 (d, J = 2.04 Hz, 1H), 4.38–4.49 (dt, J = 47.25, 6.11 Hz, 2H), 2.30–2.37 (m, 1H), 1.69–1.74 (m, 2H), 1.63–1.68 (m, 2H), 1.33–1.43 (m, 7H), 1.09 (d, J = 7.18 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.5, 85.0, 83.7, 46.5, 30.6, 30.4, 29.4, 27.0, 25.3, 13.6. FT-IR (CH_2Cl_2, cm^{-1}) estim. 2936, 2860, 2359, 1811, 1706, 1457, 1004. ^{19}F NMR (565 MHz, $CDCl_3$) δ −218.26. HRMS (ESI) calcd for $C_9H_{11}OF$ [M+H]$^+$: 159.1174, found 159.1184. $[\alpha]_D^{23}$ +11.7 (CH_2Cl_2).
31. (*S*)-2-(8-Bromo-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**6**). Yellow solid. Mp 81–82 °C. R_f = 0.70 (3:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–8.12 (dd, J = 7.63, 0.83 Hz, 1H), 8.07–8.08 (dd, J = 7.57, 0.91 Hz,

1H), 7.73–7.76 (td, J = 7.48, 1.33 Hz, 1H), 7.66–7.69 (td, J = 7.45, 1.21 Hz, 1H), 7.33 (s, 1H), 3.39 (t, J = 7.21 Hz, 2H), 2.57–2.61 (dd, J = 12.31, 5.96 Hz, 1H), 2.42–2.45 (dd, J = 12.51, 8.41 Hz, 1H), 1.81–1.85 (m, J = 7.56 Hz, 3H), 1.29–1.42 (m, 8H), 0.88 (d, J = 6.52 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.1, 181.6, 153.7, 135.1, 133.2, 133.1, 129.7, 127.0, 126.3, 124.2, 37.3, 34.2, 33.0, 33.0, 30.9, 29.1, 28.4, 27.1, 19.9. FT-IR (CH_2Cl_2, cm^{-1}) estim. 3350, 2900, 1630, 1600, 1350, 1250, 700. HRMS (ESI) calcd for $C_{19}H_{24}O_3Br$: 379.0909, found 379.0894. $[\alpha]_D^{23}$ +0.9 (CH_2Cl_2).

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