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Asymmetric syntheses of potential anti-malarial drugs designed from Fieser's 2-hydroxy-3-(2-methyloctyl)naphthalene-1,4-dione

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In celebration of the outstanding chemistry of Jan Bergman and for 50 years of his friendship and in memory of Bernard L. Trumpower

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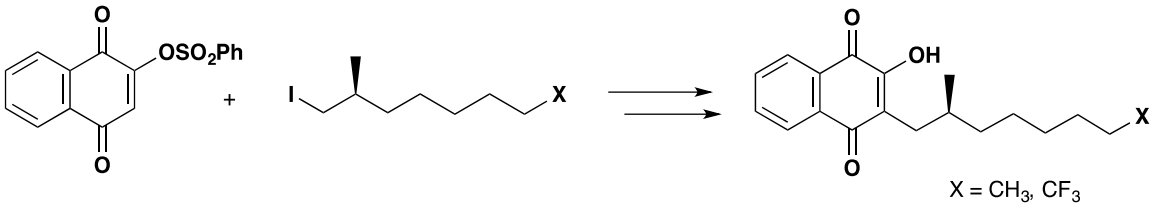
Abstract

We describe asymmetric syntheses of the potential anti-malarial drugs (*S*)-2-(8-fluoro-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione, (*S*)-2-hydroxy-3-(8-trifluoromethyl-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione, and (*S*)-2-hydroxy-3-(2-methyloctyl)naphthalene-1,4-dione, which are patterned after Fieser's "10576," known to be active against the mosquito borne parasite *Plasmodium falciparum.*



Keywords: Atovaquone, anti-malarials, asymmetric synthesis, 2-hydroxynaphthalene-1,4-dione

Introduction

Malaria, a disease transmitted by the mosquito borne parasite *Plasmodium falciparum*, is generally considered to be the most serious infectious disease in the world. It has been estimated by some parasitologists that 50% of the human beings *ever born* were killed by this parasite.[1] It currently kills more than 400,000 people annually, more than half of whom are children under the age of 5 in sub-Saharan Africa.[2] Unfortunately, the malaria parasite, through mutations has become resistant to known drugs, including atovaquone (**1**), a 2-hydroxynaphthalene-1,4-dione (2-hydroxy-1,4-naphthoquinone), which is an active component in Proguanil, a drug used to treat parasitic infections since the 1990s.[3] Moreover, naphthoquinones, such as derivatives of lawsone (**2**), lapachol (**3**), and β-lapachone (**4**), and others, have been of great interest in recent years as possible new agents to treat parasitic, fungal, and other infections, including malaria (Figure 1).[4-10]

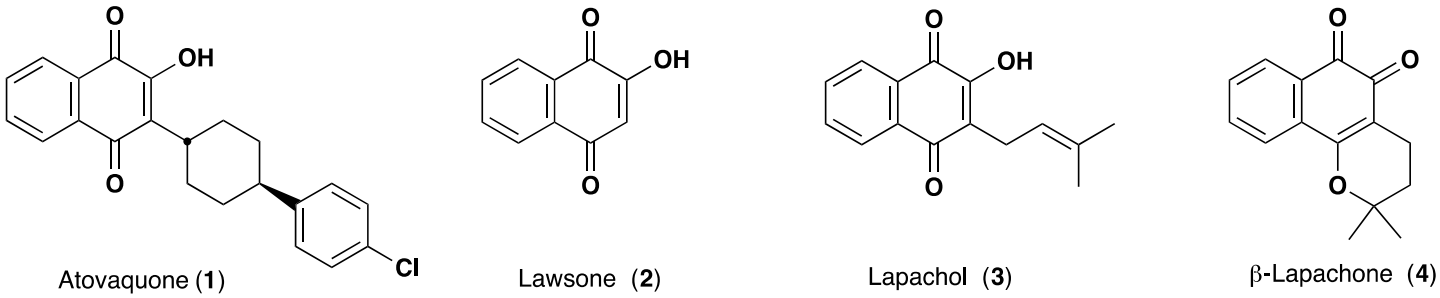


Figure 1. Structures of antimalarial naphthoquinones **1-4**

In connection with our interest in developing novel anti-malarial drugs based on lapachones and related 2-hydroxynaphthalene-1,4-diones[11-13] as inhibitors of the cytochrome bc_1 complex,[14] which is a respiratory enzyme essential for the *Plasmodium falciparum* parasite, we prepared the atovaquone analogue *(S)*-2-hydroxy-3-(2-methyloctyl)naphthalene-1,4-dione ("S-10576") (**5**), which was first synthesized and screened in 1948 by Fieser in racemic form ("M-285") and found to have curative action against malarial infections.[15] Although **5** is more potent than atovaquone, it undergoes rapid metabolism in humans by bis-hydroxylation of the two terminal alkyl groups to give a 2-methylheptyl carboxylic acid side chain.[16] To preclude this oxidative metabolism of **5**, we synthesized the fluorinated analogues *(S)*-2-(8-fluoro-2-methyloctyl)-3-hydroxy-naphthalene-1,4-dione (**6**)[17] and *(S)*-2-hydroxy-3-(8,8,8-trifluoro-2-methyloctyl)naphthalene-1,4-dione ("NQ1") (**7**)[12,13] (Figure 2). The *S* configuration was predicated by a protein modeling study of the interaction of **5** with the Rieske iron-sulfur protein.[12] Both **6** and **7** are more active than atovaquone, and **7** strongly inhibits atovaquone-resistant *Plasmodium falciparum* sporozoites. The IC_{50} data against *Plasmodium berghei* are shown for **5** and **7** in Figure 2.[13] However, **7** exhibits significantly lower species selectivity than **5.**[12,13] Atovaquone has IC_{50} = 19.7 nM, and **6** has not yet been tested.

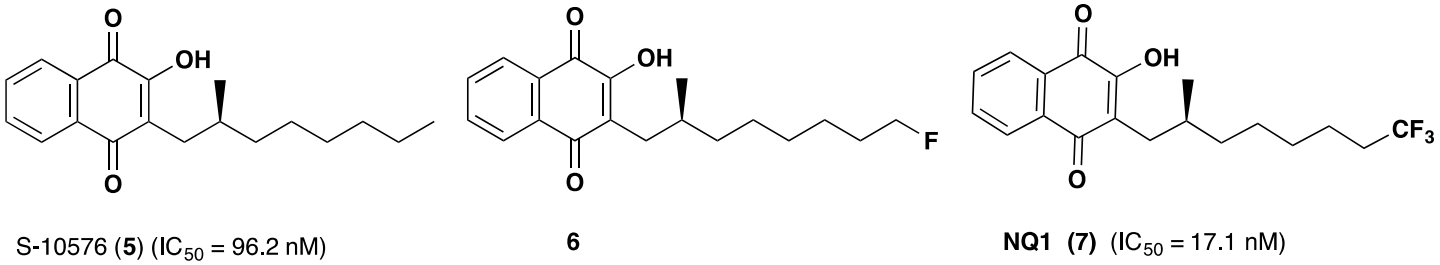
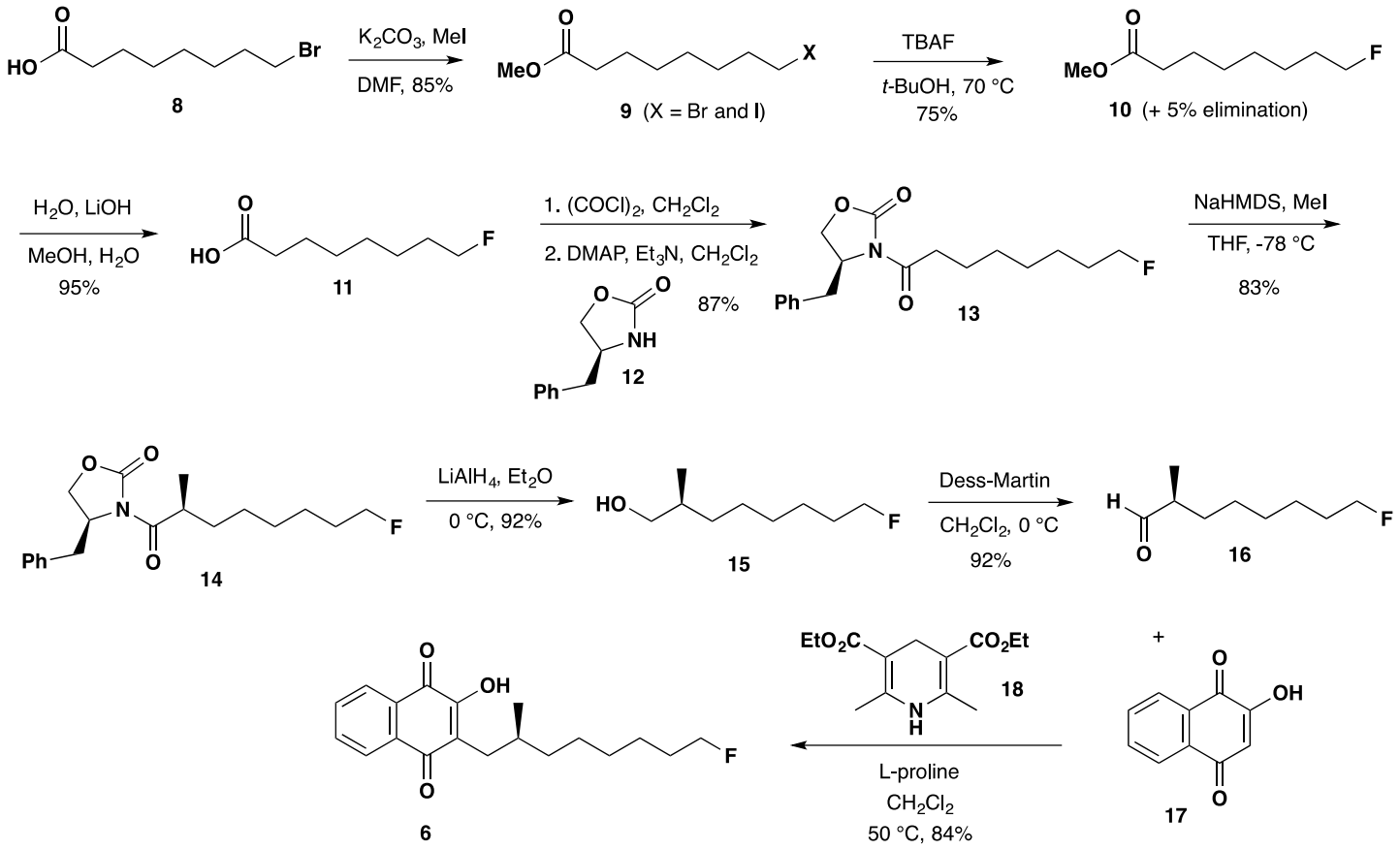


Figure 2. Structures of antimalarial naphthoquinones **5-7**

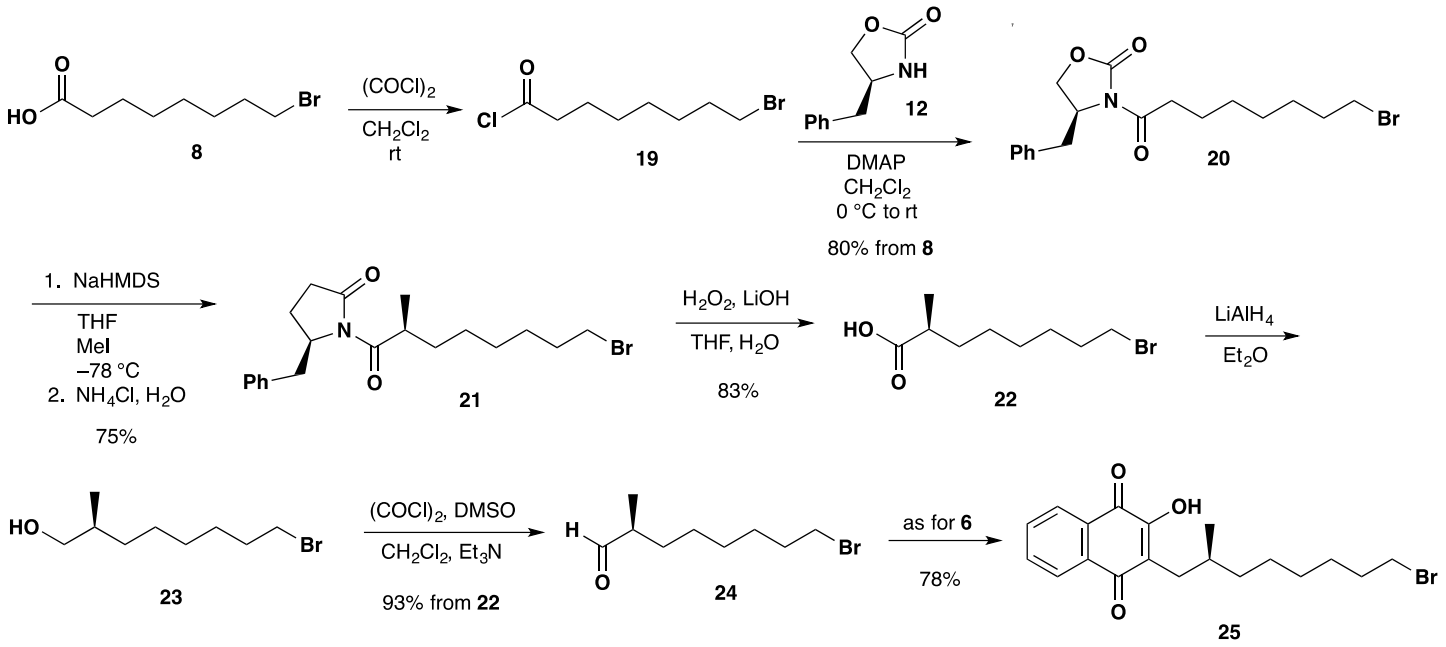
Results and Discussion

Our initial synthesis of **6**[17] involved the preparation of (*S*)-8-fluoro-2-methyloctanal (**16**) and subsequent condensation with 2-hydroxy-1,4-naphthoquinone (**17**) using our three-component reductive alkylation method,[19] to afford **6** in excellent yield (Scheme 1). Thus, synthesis of the known 8-fluorooctanoic acid (**11**),[18] acid chloride formation, and the Evans chiral auxiliary methodology[20] with (*S*)-4-benzyl-2-oxazolidinone (**12**), and asymmetric C-2 methylation[20-22] of **13**, afforded **14** in good overall yield from **11**. Interestingly, ester formation from the commercially available 8-bromooctanoic acid (**8**) gave **9** as a mixture of bromide and iodide, which was converted into fluoride **10**. Reduction of **14** and oxidation of alcohol **15** gave the desired (*S*)-8-fluoro-2-methyloctanal (**16**).[17]



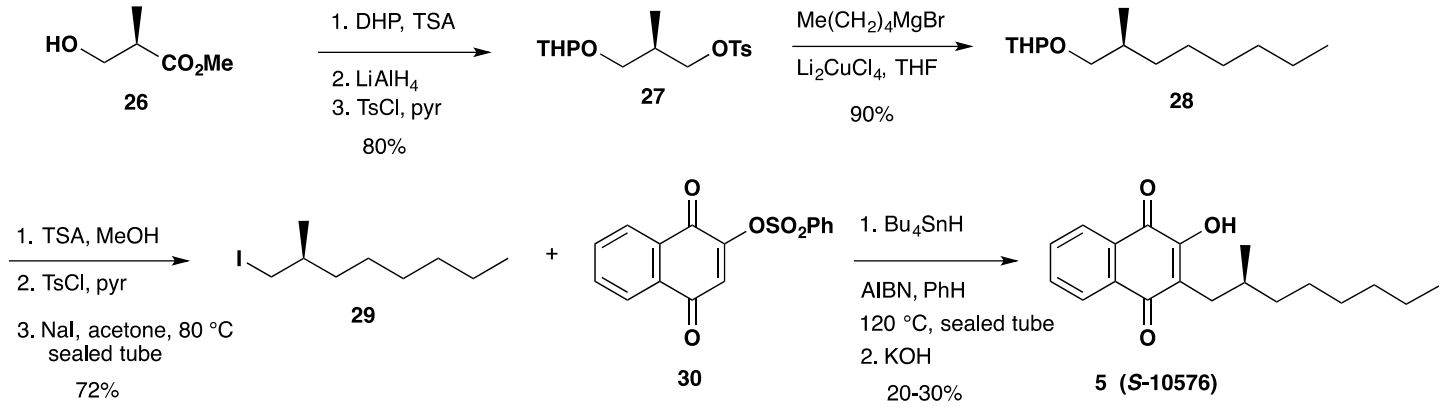
Scheme 1. Synthesis of (*S*)-2-(8-fluoro-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**6**)[17]

We now describe an alternative synthesis of **6** via the new compounds (*S*)-8-bromo-2-methyloctanal (**24**) and *(S)*-2-(8-bromo-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**25**) (Scheme 2), which avoids the intermediacy of the toxic octyl fluorides **10** and **11** (Krebs cycle poisons comparable to fluoroacetic acid).[18] Furthermore, substitution of bromine should allow for further functionalization of this ω-position. The chemistry follows that in Scheme 1 starting with 8-bromooctanoic acid (**8**) and affords **25** in good overall yield.



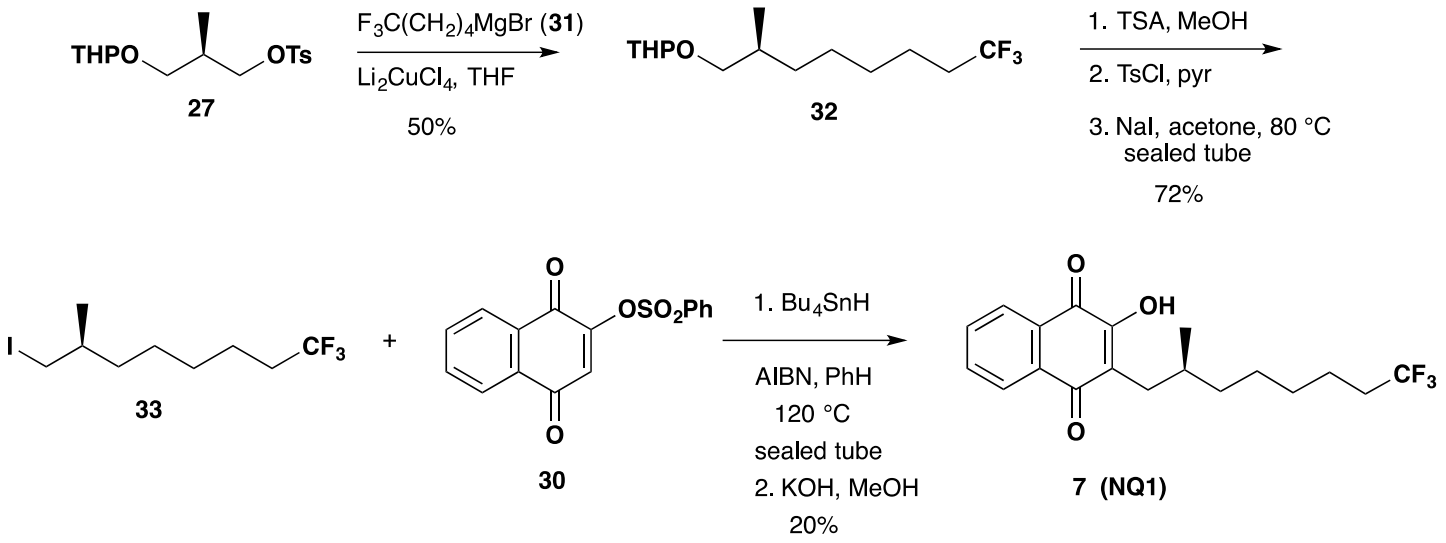
Scheme 2. Synthesis of (*S*)-2-(8-bromo-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**25**)

Our syntheses of **5** and **7** take a different path from those of **6** and **25**, and are described in Schemes 3 and 4, respectively. In place of our three-component reductive alkylation of an aldehyde (i.e., **16** + **17** + **18,** Scheme 1), we employed tin-mediated coupling of the requisite alkyl iodide to 2-hydroxy-1,4-naphthalene-1,4-dione sulfonate **30.** The conversion of propanoate **26** to iodide **29** is known[23] and sulfonate **30** was prepared from 2-hydroxy-1,4-naphthalene-1,4-dione (**17**) (using $PhSO_2Cl$, K_2CO_3, DMF, rt) in 78% yield. Whereas Fieser synthesized racemic **5** in 1948 ("10576"), our synthesis of (*S*)-**5** is the first to be described of this biologically active stereoisomer (Scheme 3).



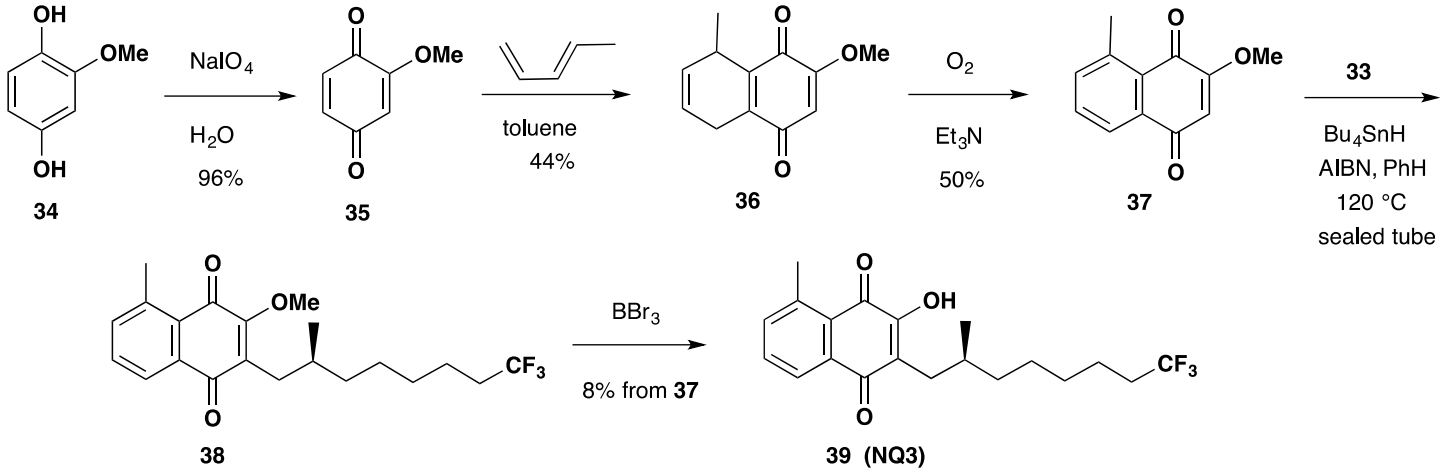
Scheme 3. Synthesis of (*S*)-2-hydroxy-3-(2-methyloctyl)naphthalene-1,4-dione (**5**) (*S*-10576)

Similar methodology was used to synthesize **7** (NQ1) (Scheme 4).[11] Tosylate **27** was treated with Grignard **31,** as prepared from 5-bromopentanoic acid in two steps with sulfur tetrafluoride[24,25] and Mg, to afford **32** in 50% yield. Conversion of **32** to iodide **33** and coupling with quinone sulfonate **30** gave the desired **7** (NQ1) in low yield. We prepared iodide **33** from **32** as we described in Scheme 3 for iodide **29.**



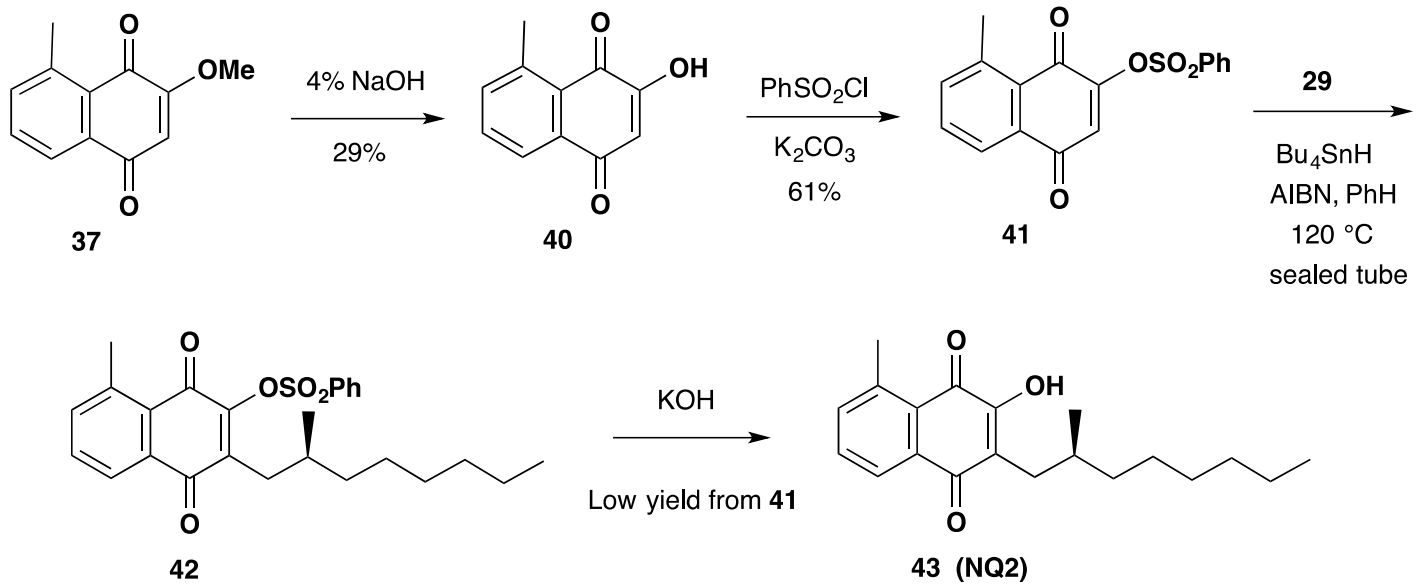
Scheme 4. Synthesis of (*S*)-2-hydroxy-3-(8,8,8-trifluoro-2-methyloctyl)naphthalene-1,4-dione (**7**) (NQ1)

Protein modeling studies suggested that the 8-methyl analogues might show improved activity, via non-covalent interactions between this methyl group and Cys-180 of the Rieske iron-sulfur protein and cytochrome *b* in the ubiquinol oxidation pocket.[11] We have prepared *(S)*-3-hydroxy-5-methyl-2-(8,8,8-trifluoro-2-methyl-octyl)naphthalene-1,4-dione (**39**) (NQ3**)**[11] using the tin coupling method shown in Schemes 3 and 4. Thus, we synthesized 2-methoxy-8-methylnaphthalene-1,4-dione (**37**) from 2-methoxyhydroquinone (**34**) via known chemistry (oxidation,[26,27] Diels-Alder cycloaddition,[28] and aerial oxidation[28]) and coupled it with **33** as shown in Scheme 5. Demethylation with BBr_3[29] afforded **39** in low yield. Interestingly, the sulfonate corresponding to **38** could not be hydrolyzed with KOH to **39,** in contrast to the results in Schemes 3 and 4. Disappointingly, analogue **39** (NQ3) shows much weaker activity against *Plasmodium berghei* (IC_{50} >4400 nM) than we expected.[13]



Scheme 5. Synthesis of (*S*)-3-hydroxy-5-methyl-2-(8,8,8-trifluoro-2-methyloctyl)naphthalene-1,4-dione (**39**) (NQ3)

Finally, we synthesized compound **43** (NQ2**)**, the defluorinated version of **39,** as shown in Scheme 6. 2-Methoxy-8-methylnaphthalene-1,4-dione (**37**) was converted into sulfonate **41** and coupled with iodide **29** as described in Scheme 3 for **5** to give **43** (NQ2) in low yield. As was the case for **39** (NQ3), analogue **43** (NQ2) shows much weaker activity (IC_{50} 247 nM) than (*S*)-**5** against *Plasmodium berghei* than we expected based on the protein modeling mentioned above.[13]



Scheme 6. Synthesis of (*S*)-3-hydroxy-5-methyl-2-(2-methyloctyl)naphthalene-1,4-dione (**43**) (NQ2)

Conclusions

We describe the first synthesis of *(S)*-2-hydroxy-3-(2-methyloctyl)naphthalene-1,4-dione (*S*-**5**), the biologically active enantiomer of the racemate "10576" ("M-285") that Fieser synthesized more than 70 years ago. This compound shows improved activity over atovaquone, which has been used to treat malaria and pneumonia *(Pneumocystis)* pathogens since the mid 1990s as "Malarone," a combination drug containing atovaquone and proguanil. In fact, the Center for Disease Control (CDC) has recommended Malarone for Americans traveling to nearly all malaria-endemic countries. However, these pathogens soon became resistant to atovaquone and new drugs are greatly needed.[30,31]

By blocking the terminal oxidative metabolism of *S*-**5** with a trifluoromethyl group (**7**) (NQ1) we have show that this latter compound is a new lead in the design of improved hydroxy-naphthalene-1,4-dione therapeutics, with 5-6 times greater activity against *Plasmodium berghei* than *S*-**5**. Both **6** and **7** are more active than atovaquone, and **7** strongly inhibits atovaquone-resistant *Plasmodium falciparum* sporozoites. The precise activity of (*S*)-2-(8-fluoro-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**6**) remains to be established, but it too would be expected to block terminal group metabolism. We have also shown that the presence of an 8-methyl group in these compounds (**39** and **43**) does not lead to improved activity as our protein modeling seemed to suggest.

In Figure 3, we show some additional non-fluorinated compounds that we have synthesized (unpublished) and their IC_{50} activity. Activity below 200 nM is considered to be significant. Importantly, the activity of *R*-**5** is nearly 30 times less that that of *S*-**5** against the yeast *bc1* complex. The difference in activity between the two epimers of **5** is believed to involve different interactions of the 2-methyloctyl side chain with the binding groove of the yeast cytochrome *bc1* complex. Whereas both the *S* and *R* isomers of **5** show a strong hydrophobic interaction with valine-146 in the protein complex, the *S*-**5** interaction constrains the rotation of the "loose end" of the side chain in the protein binding groove and allows for stronger binding than does the *R*-**5** epimer by nearly a factor of 30.[11]

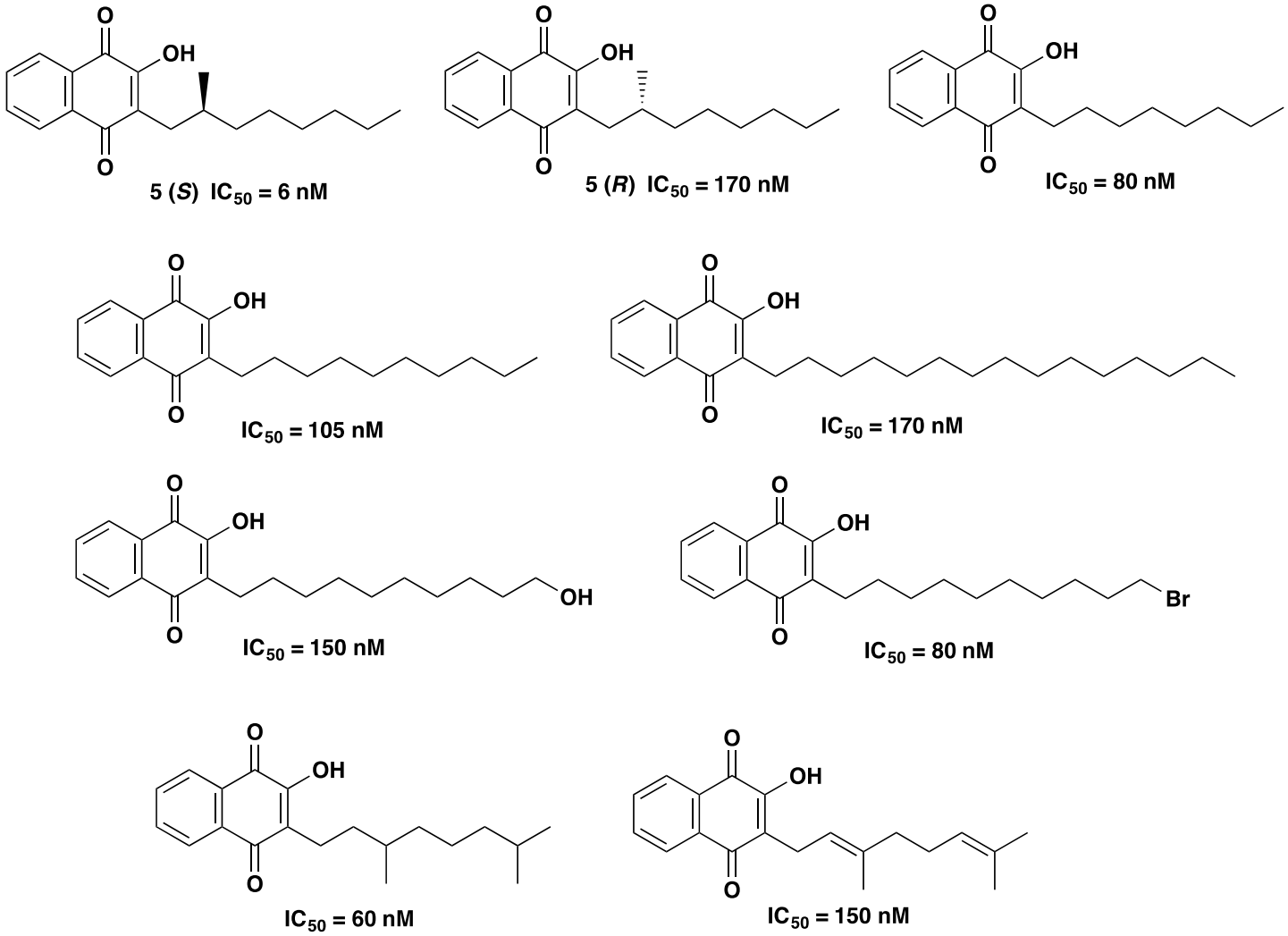


Figure 3. Structures of 2-hydroxynaphthalene-1,4-diones and IC_{50} (nM) against the yeast *bc1* complex

Experimental Section

General. All reactions were performed under positive nitrogen pressure in oven-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (0.25 mm) and visualized under shortwave UV light at 254 nm or by staining with *p*-anisaldehyde or $KMnO_4$ and heating. Unless otherwise noted, all organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* as a standard work-up procedure. Column chromatography was run using silica gel with particle size 40-63 µm. Melting points were measured using the Mel Temp apparatus of Laboratory Devices with samples prepared in open capillary tubes. Mass spectra were performed by the SCS Mass Spectrometry lab at the University of Illinois. IR spectra were obtained by using a Jasco FT/IR-4100 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz, respectively, using Bruker Avance III HD 600 spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) using the residual signal of the solvent as an internal reference ($CDCl_3$, δ_H 7.26; δ_C 77.23). Multiplicities were reported using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br).

***(S)*-4-Benzyl-3-(8-bromooctanoyl)oxazolidin-2-one** (**20**). To a solution of 8-bromooctanoic acid (**8**) (4.13 g, 18.5 mmol) in CH_2Cl_2 (200 mL), oxalyl chloride (8 mL, 93 mmol) was added. The reaction mixture was stirred

overnight. The crude acyl chloride **19** was concentrated *in vacuo* and stored under vacuum. In a separate round-bottomed flask, a solution of *(S)*-4-benzyloxazolidin-2-one (**12**) (4.26 g, 18.5 mmol) and DMAP (0.27 g, 2.2 mmol) in CH_2Cl_2 (200 mL) was stirred at 0 °C. Then Et_3N (9.7 mL, 69 mmol) was added dropwise into the reaction mixture, followed by the above acyl chloride in CH_2Cl_2 (10 mL). The reaction was stirred overnight, and after TLC confirmed completion, the reaction was concentrated *in vacuo* and covered with EtOAc (100 mL). The solution was extracted with EtOAc, washed with 3% HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), and dried. It was finally concentrated *in vacuo*, then purified using flash chromatography to give **20** as a thick oil, 5.67 g (80% from **8**): $[\alpha]_D$ +37°; ^{1}H NMR ($CDCl_3$) δ 7.20-7.34 (5H, m), 4.67 (1H, m), 4.15-4.21 (2H, m), 3.41 (2H, t, *J* 7 Hz), 3.28-3.31 (1H, dd, *J* 13, 3 Hz), 2.90 (1H, m), 2.95 (1H, m), 2.75-2.79 (1H, dd, *J* 13, 10 Hz), 1.87 (2H, m, 7 Hz), 1.70 (2H, m, 6 Hz), 1.37-1.46 (6H, m); ^{13}C NMR ($CDCl_3$) δ 173.5, 153.7, 135.5, 129.6, 129.2, 127.6, 66.4, 55.4, 38.1, 35.7, 34.1, 32.9, 29.1, 28.7, 28.2, 24.3; IR: ν_{max} (cm^{-1}) 2930, 1780, 1700, 1390, 1210, 701. *Anal.* HRMS *m/z* Calcd for $C_{18}H_{25}BrNO_3$ (M + H): 382.1018. Found: 382.1013.

(*S*)-4-Benzyl-3-((*S*)-8-bromo-2-methyloctanoyl)oxazolidin-2-one (**21**). To a solution of NaHMDS (26 mL, 26.3 mmol) in THF (200 mL) while stirred at -78 °C, a pre-cooled solution of the oxazolidinone **20** (8.37 g, 21.9 mmol) in THF (50 mL) was added dropwise. After an hour of stirring, methyl iodide (6.8 mL, 110 mmol) was added dropwise, and the reaction mixture was stirred for 4 h at the same temperature. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl (aq). After the solvent was removed *in vacuo,* the mixture was extracted with CH_2Cl_2, washed consecutively with 5% $KHSO_4$, saturated $Na_2S_2O_3$, and brine, dried, and concentrated *in vacuo*. The crude product was purified by flash chromatography using ethyl acetate and hexanes, affording 6.51 g (75%) of **21** as a thick, colorless oil: $[\alpha]_D$ +33°; ^{1}H NMR ($CDCl_3$) δ 7.20-7.33 (5H, m), 4.68 (1H, m), 4.17-4.20 (2H, m); 3.70 (1H, m, *J* 7 Hz), 3.41 (2H, t, *J* 6 Hz), 3.27 (1H, dd, *J* 13, 4 Hz), 2.77 (1H, dd, 13, *J* 9 Hz), 1.84 (2H, m, *J* 7 Hz), 1.75 (1H, m, *J* 6.17 Hz), 1.42 (3H, m, *J* 6.17 Hz), 1.32 (4H, m, *J* 2.94 Hz), 1.21 (3H, d, *J* 6.81 Hz); ^{13}C NMR ($CDCl_3$) δ 177.4, 153.3, 135.5, 129.7, 129.2, 127.6, 66.2, 55.6, 38.1, 37.9, 34.1, 33.5, 32.9, 29.0, 28.2, 27.3, 17.6; IR: ν_{max} (cm^{-1}) 2930, 2360, 1780, 1700, 1390, 1210. *Anal.* HRMS *m/z* Calcd for $C_{19}H_{27}BrNO_3$ $(M + H)^+$: 396.1174. Found: 396.1165.

(*S*)-8-Bromo-2-methyloctanoic acid (**22**). To a solution of **21** (0.66 g, 1.67 mmol) in THF-water (40 mL) in 3:1 ratio stirring at 0 °C, H_2O_2 (30%, 1.6 mL, 16 mmol) was added. After 10 min, $LiOH{\cdot}H_2O$ (0.14 g, 3.33 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with Na_2SO_3. The solution was washed with EtOAc and separated. The aqueous solution was covered with EtOAc and acidified to pH 2 with 5% $KHSO_4$. The organic layer was extracted with EtOAc, washed with brine, dried, and concentrated *in vacuo* to give **22** (0.33 g, 83%), as a colorless liquid, which was used in the next step without further purification: $[\alpha]_D$ +4.4°; ^{1}H NMR ($CDCl_3$) δ 11.2 (1H, br s), 3.40 (2H, t, *J* 7 Hz), 2.47 (1H, m, *J* 7 Hz), 1.85 (2H, m, *J* 7 Hz), 1.66 (1H, m, *J* 7 Hz), 1.43 (3H, m, *J* 7 Hz), 1.33 (4H, m, *J* 5 Hz), 1.18 (3H, d, *J* 8 Hz); ^{13}C NMR ($CDCl_3$) δ 182.5, 39.4, 34.1, 33.6, 32.9, 28.9, 28.2, 27.2, 17.1; IR: ν_{max} (cm^{-1}) 2935, 2858, 1704, 1464, 1241, 941. *Anal.* HRMS *m/z* Calcd for $C_9H_{18}BrO_2$: 237.0490. Found: 237.0489.

(*S*)-8-Bromo-2-methyl-1-octanol (**23**). To a stirred solution of **22** (1.0 eq) in dry ether at 0 °C, $LiAlH_4$ (3.0 eq, 4.0 M solution in dry ether) was added dropwise. The mixture was stirred overnight. After quenching with water, the mixture was extracted with diethyl ether, washed with brine, dried, and concentrated *in vacuo*. The crude product **23,** as a colorless liquid, was used in the next step without further purification: $[\alpha]_D$ +88°; ^{1}H NMR ($CDCl_3$) δ 3.49- 3.52 (1H, dd, *J* 10, 6 Hz), 3.40-3.44 (3H, m), 1.83-1.87 (2H, m, *J* 7 Hz), 1.26-1.45 (9H, m); IR: ν_{max} (cm^{-1}) 3340, 2928, 1464, 1260, 1040, 646.

***(S)*-8-Bromo-2-methyloctanal** (**24**). To a stirred solution of oxalyl chloride (1.37 mL, 16.0 mmol) in 5 mL of CH_2Cl_2 at -78 °C, DMSO (2.27 mL, 32.0 mmol) was added dropwise. After stirring for 15 min, a solution of **23** (1.19 g, 5.33 mmol) in 10 mL CH_2Cl_2 and Et_3N (6.69 mL, 48.0 mmol) were added consecutively. The solution was stirred for 45 min while warming up to room temperature. The solution was quenched with water, extracted with CH_2Cl_2, washed with brine, dried, and concentrated *in vacuo*. The crude product was purified via flash chromatography, affording 1.1 g (93%) of **24** as a colorless liquid, $[\alpha]_D$ +9°; ^{1}H NMR ($CDCl_3$) δ 9.61 (1H, d, *J* 2 Hz), 3.40 (2H, t, *J* 7 Hz), 2.33 (1H, m), 1.85 (2H, m, *J* 7 Hz), 1.71 (1H, m, *J* 6 Hz), 1.33-1.46 (7H, m), 1.10 (3H, d, *J* 7 Hz); ^{13}C NMR ($CDCl_3$) δ 182.2, 161.1, 71.2, 39.4, 35.9, 34.1, 33.6 32.9, 28.9, 28.2, 27.2, 25.3, 20.2, 17.1; IR: ν_{max} (cm^{-1}) 2933, 2858, 1703, 1463. *Anal.* HRMS *m/z* Calcd for $C_9H_{16}BrO$ $(M + H)^+$: 219.0385. Found: 219.0383.

(*S*)-2-(8-Bromo-2-methyloctyl)-3-hydroxynaphthalene-1,4-dione (**25**). In a round-bottom flask equipped with a stirring bar, aldehyde **24** (2.0 eq), 2-hydroxynaphthalene-1,4-dione (**17**) (1.0 eq), the Hantzsch ester (1.0 eq), and L-proline (0.5 eq) were all combined together in CH_2Cl_2 and stirred at rt for 48 h. The reaction mixture was concentrated *in vacuo*, then purified via flash column chromatography using hexanes and EtOAc to give **25** (78%) as a yellow solid: mp 81-82 °C; $[\alpha]_D$ = +0.9°; ^{1}H NMR ($CDCl_3$) δ 8.07-8.12 (2H, dd, *J* 7 Hz), 7.66-7.76 (2H, dt, *J* 8 Hz), 7.33 (1H, s), 3.39 (2H, t, *J* 7 Hz), 2.57-2.61 (1H, dd, *J* 6 Hz), 2.42-2.45 (1H, dd, *J* 8 Hz), 1.81-1.85 (3H, m, *J* 8 Hz), 1.29-1.42 (8H, m), 0.88 (3H, d, *J* 7 Hz); ^{13}C NMR ($CDCl_3$) 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, 32.95, 30.9, 29.1, 28.4, 27.06, 19.9; IR: ν_{max} (cm^{-1}) 3350, 2900, 1630, 1600, 1350, 1250, 700. *Anal.* HRMS *m/z* Calcd for $C_{19}H_{24}BrO_3$ $(M + H)^+$ 379.0909. Found: 379.0894.

(*S*)-2-Hydroxy-3-(8,8,8-trifluoro-2-methyloctyl)naphthalene-1,4-dione (**7**) (**NQ1**)**.** Yield 20 mg (4%); mp 87–89 °C.; $[\alpha]_D$ CH_2Cl_2 –1.3 (c = 1); ^{1}H NMR ($CDCl_3$) δ 8.14–8.09 (dd, *J* 8.0 Hz, 2H, H-5, H-8), 7.68–7.79 (2H, H-6, H-7), 7.79–7.68 (m, 2H, H-6, H-7), 7.30 (br, 1H, OH), 2.43–2.63 (m, 4H), 2.09–2.04 (m, 2H, CH_2), 1.86 (br, 1H, CH), 1.36–1.24 (br, 10H, $(CH_2)_5$); ^{19}F NMR ($CDCl_3$) δ –66.8 (t, *J* 11.8 Hz); (EI) *m/z* 354 (88%) $(M)^+$. *Anal.* HRMS Calcd for $C_{19}H_{21}F_3O_3$ 354.1443. Found: 354.1442.

(*S*)-3-Hydroxy-5-methyl-2-(8,8,8-trifluoro-2-methyloctyl)naphthalene-1,4-dione (**39**) (**NQ3**). Yield 1 mg (4%); ^{1}H NMR ($CDCl_3$) δ 8.19–8.18 (d, *J* 2 Hz, 1H, H-5), 7.64–7.62 (2H, H-6, H-7), 7.57 (br, 1H, OH), 2.93 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.41–2.58 (m, 4H), 2.11–2.04 (m, 2H, CH_2), 1.86 (br, 1H, CH), 1.36–1.24 (br, 10H, $(CH_2)_5$). ^{19}F NMR ($CDCl_3$) δ –66.8 (t, *J* 12 Hz). (EI) *m/z* 368 (88%) (M^+H^+). *Anal.* HRMS Calcd for $C_{20}H_{23}F_3O_3$: 368.1599. Found: 368.1604.

***S*-2-Hydroxy-3-(2-methyloctyl)-8-methylnaphthalene-1,4-dione (43) (NQ2)**. Yield 5 mg (11%): mp 53–55 °C; ^{1}H NMR ($CDCl_3$) δ 8.19–8.18 (d, *J* 2 Hz, 1H, H-5), 7.64–7.62 (2H, H-6, H-7), 7.57 (br, 1H, OH), 2.67–2.43 (m, 2H, CH_2), 1.86 (br, 1H, CH), 1.40–1.19 (br, 10H, $(CH_2)_5$), 0.93–0.88 (m, 6H, CH_3, CH_3); (EI) *m/z* 314 (82%); *Anal.* HRMS Calcd for $C_{20}H_{26}O_3$: 314.1882. Found: 314.1880.

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