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1,4-Naphthoquinone Synthesis

A Platform of Regioselective Methodologies to Access Polysubstituted 2-Methyl-1,4-naphthoquinone Derivatives: Scope and Limitations

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Abstract: A platform of synthetic methodologies has been established to access a focused library of polysubstituted 3-benzylmenadione derivatives functionalized on the aromatic ring of the naphthoquinone core. Two main routes were explored: 1) The naphthol route, starting from either an α-tetralone or a propiophenone, and 2) the regioselective Diels–Alder reaction, starting from various dienes and two 2-bromo-5(or 6)-methyl-1,4-benzoquinones. 6-Substituted 2-methylnaphthols were synthesized by using a xanthate-mediated free-radical addition/cyclization sequence for the construction of the 6-substituted menadione subunit. Furthermore, an efficient and simple new pathway that allows the formation of 6- or 7-substituted 3-(substituted-benzyl)menadione regioisomers from a common commercial scaffold has also been developed by the naphthol route, advantageous with regard to step economy. Our synthetic methodologies exemplified by 34 compounds have allowed structure–activity relationships to be deduced for use as the basis for the development of new antimalarial redox-active polysubstituted benzylmenadione derivatives.

Introduction

1,4-Naphthoquinones are ubiquitously distributed throughout all kingdoms of life, including eubacteria, archaebacteria, fungi, protists, plants, and animals.[1] They have been used for centuries in folk medicine, cosmetics, and industrial dye applications.[2] Well-known examples[3] of 1,4-naphthoquinones are the menadione (2-methyl-1,4-naphthoquinone, also called vitamin K3) and plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone) derivatives, exemplified by the bio-inspired representatives in Figure 1. Owing to the broad occurrence of the 1,4-naphthoquinone motif in compounds of natural origin and their peculiar redox properties,[4] there is a growing interest in the chemistry of polysubstituted 1,4-naphthoquinones as final products or key synthetic intermediates. Numerous 1,4-naphthoquinones[5] do not contain the 2-methyl substituent, rendering their synthesis easy and straightforward from substituted benzenes.[5a] Also, among the menadione derivatives, the substitution pattern has to be considered (Figure 1). Functionalization of the eastern part of the molecule affords the vitamin K series upon isoprenylation of vitamin K3 (menadione).[6] By using solid- and solution-phase synthesis, a library of synthetic menadione, juglone, and plumbagin derivatives has been prepared allowing the introduction of broad structural diversity into the eastern part of the quinone core.[7] Functionalization of the western part of menadione is also commonly found in plants, as exemplified by chimaphilin derivatives[8] (Figure 1). Larger ring systems (e.g., biaryls, macrocycles), although less common, appear in natural products, as exemplified by bivitamin K,[9] gossypol-

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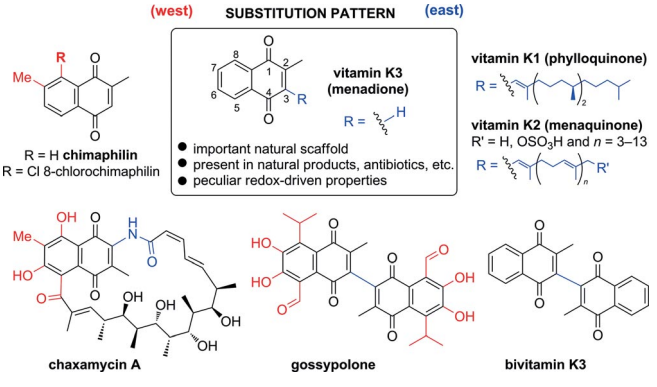
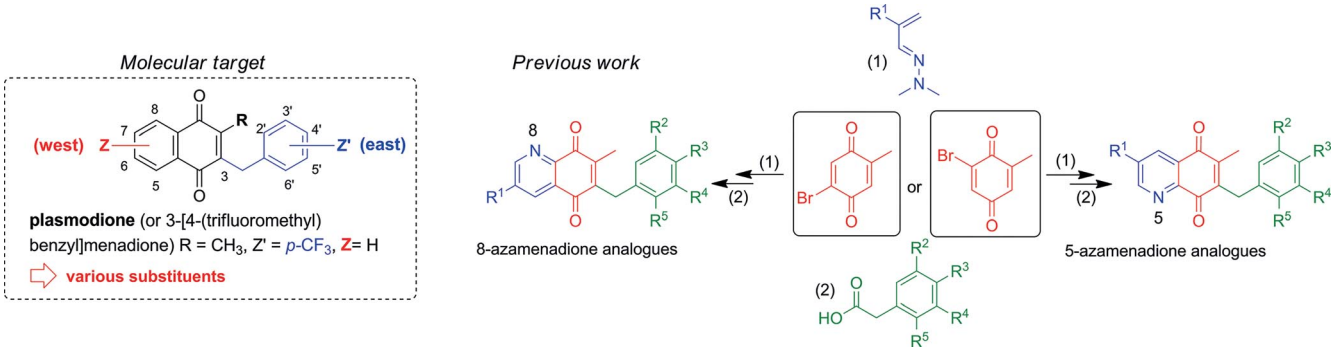


Figure 1. Natural and synthetic polysubstituted menadione derivatives.



Scheme 1. Synthesis of synthetic 3-benzylmenadione derivatives and aza analogues.

one,[10] and the antibiotic chaxamycin A,[11] which result from biotransformations of low-weight menadione-, plumbagin-, and chimaphilin-based scaffolds upon dimerization, isoprenylation of mevalonate, and macrocyclization, etc. (Figure 1). Therefore, the synthetic methodologies have to be highly regioselective for the preparation of menadione derivatives.

In contrast to the previous eastern-substituted series, general methods for regioselective transformations to prepare synthetic menadione derivatives substituted at both the phenyl ring ("western" part) and quinone moiety ("eastern" part) of the 1,4-naphthoquinone core are rare. Although numerous reports have described synthetic routes to various menadione derivatives, large collections with a diversity of substitutions in the western ring are not commercially available in bulk. Although regioselective annulations of quinones by the Diels–Alder strategy are commonly used to build the 1,4-naphthoquinone nucleus in the total synthesis of natural products,[12] it remains a challenge to control the regioselectivity of the reaction when moderately reactive dienes with unsymmetrical 2-methylquinones are used in the cycloaddition reaction.[13] Many factors increasing the regioselectivity of [4+2] cycloaddition reactions have been reported: 1) The presence of Lewis[14] and Brønsted[15] acid catalysts, 2) the presence of a halogen atom such as a bromine at the quinone dienophilic double bond, which also facilitates HBr elimination and the recovery of the quinone moiety following the cycloaddition.[16] Various combinations of factors governing the regioselectivity of cycloaddition reactions can produce highly selective results, but these approaches depend on structural features of the substrates, which results in unpredictable reaction outcomes.

The recent discovery of the antimalarial lead 3-[4-(trifluoromethyl)benzyl]menadione (Scheme 1), henceforth called plasmodione (compound **1c** in refs.[17–19]), has led to reassessment of the synthetic methodologies used to prepare large numbers of diverse analogues and potential metabolites functionalized on both the eastern and western parts of the molecule (Scheme 1). As a first step to access the target molecules, we reported a methodology for the preparation of polysubstituted 6-methylquinoline-5,8-dione scaffolds (5- and 8-azamenadione analogues).[20] The methodology consisted of a two-step sequence involving a regioselective (hetero) Diels–Alder reaction followed by radical alkylation of the 1,4-naphthoquinone core with a carboxylic acid in the presence of Ag^{I} nitrate and ammonium peroxydisulfate[21] to afford the corresponding alkylated product in good yields (Scheme 1).

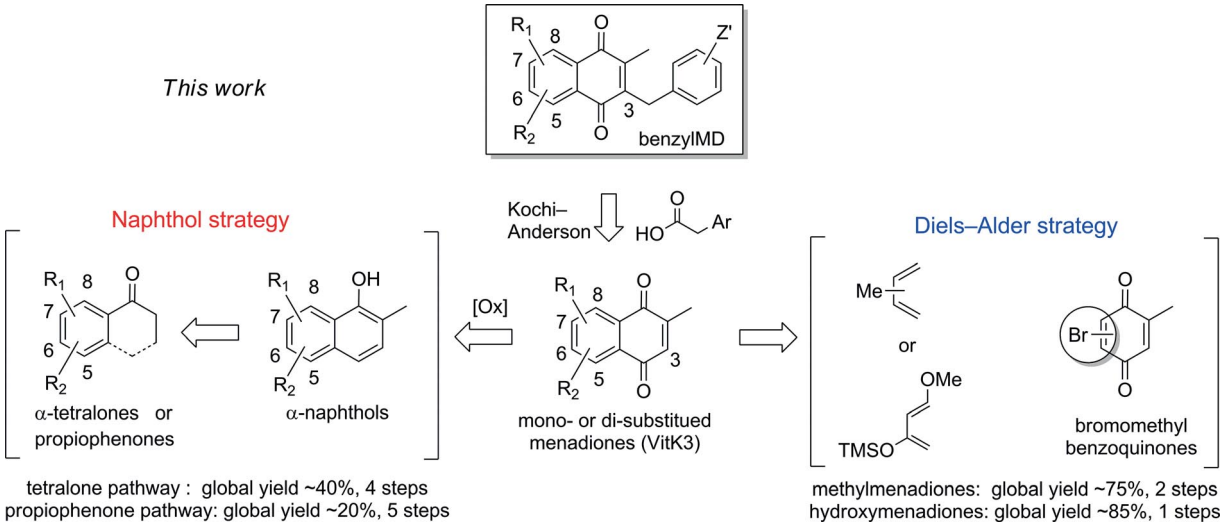
Thus, identification of plasmodione, currently a first antimalarial lead/early hit, highlights the potential of redox-active 3-benzylmenadiones (benzylMDs) with the following properties: A large chemical space for derivatization and a wide range of redox potentials. The generation of more effective analogues can only be approached by the total synthesis of 2-methyl-1,4-naphthoquinones substituted on the phenyl ring, which necessitates the total regiocontrol of the synthetic reactions. Owing to the lack of versatile and general methodologies to prepare polysubstituted 3-benzyl-2-methyl-1,4-naphthoquinone derivatives, the study described herein focused on the development and application of efficient methods to overcome these shortcomings (see Scheme 2).

Results and Discussion

Chemistry

Many methodologies for the preparation of synthetic and natural 1,4-naphthoquinone derivatives have been reported in the literature. In general, these synthetic routes utilize a naphthol intermediate, which, upon oxidation, affords the related 1,4-naphthoquinone. A more direct and regioselective approach is based on the Diels–Alder reactions of 1,4-benzoquinones and dienes.[13,14,16] However, in the case of menadione, the 2-methyl group presents two major difficulties that need to be overcome: 1) It leads to dissymmetry of the molecule and 2) its acidic hydrogen atoms are responsible for the instability of the menadione core in basic media. For these reasons, and aside from a few examples,[22] there are no general methodologies to prepare polysubstituted menadiones with various substituents introduced regioselectively at any locus of the aromatic ring, in particular, at C-6 or C-7 of the menadione core.

As a continuation of our studies into antiplasmodial drug development, we envisaged that polysubstituted 2-methyl-1,4-naphthoquinones could also be synthesized through two key strategies (Scheme 2): the Diels–Alder and naphthol routes. Toward this end, it was decided to prepare these scaffolds starting from various commercially available 4-substituted propiophenones **5a** and **5b**, 6- and/or 7-substituted tetralones **1a**–**d**, or dienes in the presence of the corresponding 2-bromo-5-methyl-



Scheme 2. Platform of synthetic methodologies to prepare a large number of diverse polysubstituted menadiones and analogues of the redox-active antimalarial lead 3-[4-(trifluoromethyl)benzyl]menadione, called plasmodione (Scheme 1).

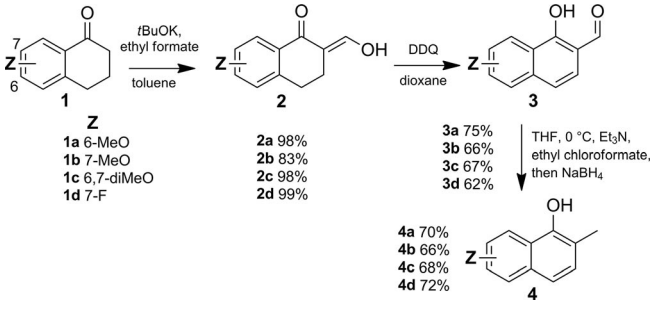
1,4-benzoquinone (**12a**) or 2-bromo-6-methyl-1,4-benzoquinone (**12b**). In this study, a small library of menadione analogues was built as key intermediates for the preparation of benzylMD derivatives that might be useful as templates both in drug discovery and medicinal chemistry. Thus, we report herein new regioselective synthetic methods to obtain polysubstituted menadiones by both the naphthol and Diels–Alder strategies (Scheme 2).

Naphthol Route – Synthesis of Methylnaphthols 4 and 9

Two methods were employed to synthesize the polysubstituted methylnaphthols using commercially available tetralones or propiophenones.

Synthesis of Methylnaphthols 4 From Tetralones

The commercially available 1-tetralones **1** were quantitatively transformed in the presence of ethyl formate and *t*BuOK into the corresponding 2-hydroxymethylene derivatives **2** (Scheme 3).[23] These compounds were aromatized with dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane[24] to afford the intermediates **3** in good yields. Then the formyl group was reduced under mild conditions using a known protocol.[25] 1-Hydroxy-2-naphthaldehydes **3** were treated with $ClCO_2Et$ in the presence of Et_3N to give quantitatively the carbonate derivative, the treatment of which with $NaBH_4$ in aqueous THF at 0 °C directly afforded the desired 2-methylnaphthols **4** in good yields.

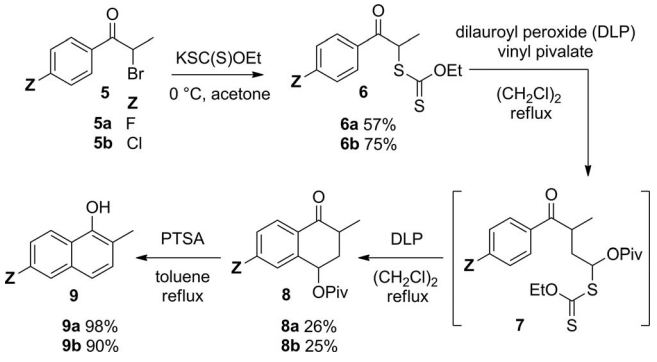


Scheme 3. Preparation of 2-methylnaphthols **4** starting from tetralones.

Synthesis of Methylnaphthols 9 from Propiophenones

Since the pioneering work of Quiclet-Sire and Zard, extensive research efforts have focused on the construction of diverse polysubstituted naphthols as starting blocks for the synthesis of complex natural products.[26] Few examples of naphthoquinones have been reported; the synthesis of (±)-10-norparvulenone and (±)-*O*-methylasparvenone were developed starting from commercially available *m*-methoxyphenol, hinging on a xanthate-mediated addition/cyclization sequence for the construction of the α-tetralone subunit, but lacking the methyl group.[27] Furthermore, the synthesis of 6,7-substituted 2-methyltetralones was also developed by using a xanthate-mediated free-radical addition/cyclization sequence for the construction of the α-methyltetralone subunit starting from 4-substituted propiophenones, first by us,[28a–c] and then by others.[28d] Thus, bromopropiophenones **5** were easily synthesized from commercial propiophenones by bromination with Br_2 in AcOH.[29] The treatment of propiophenones **5** with potassium ethyl xanthate in acetone at 0 °C afforded the desired radical precursors **6** in good yields (Scheme 4). Zard's procedure was used for the preparation of the key bicyclic intermediates **8**, starting with the radical addition of the xanthates **6** to vinyl pivalate using dilauroyl peroxide (DLP) as initiator in 1,2-dichloroethane (DCE) to yield the protected xanthates **7**, which can be used as a starting point for another radical sequence. When the xanthate **7** solutions were heated at reflux in DCE and treated with 1.2 equiv. of DLP (added portionwise), tetralones **8** were obtained in yields of 25 and 26 %.

The selection of vinyl pivalate as the radical trap was not arbitrary. It was anticipated that the OPiv group could serve as a leaving group for the aromatization in acidic media to facilitate the last step of the route. Next, tetralones **8** were treated with *p*-toluenesulfonic acid (PTSA)[27b] in toluene at reflux to



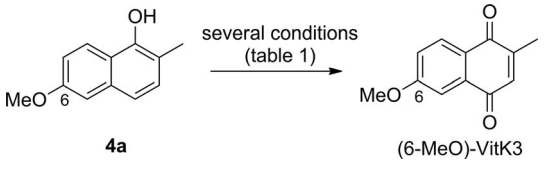
Scheme 4. Preparation of 2-methylnaphthols via xanthates.

give the corresponding naphthols **9** in excellent yields (Scheme 4).

Synthesis of Polysubstituted Menadiones 10 and 11

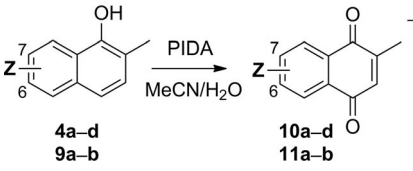
To find the best reaction conditions for the synthesis of the prototype menadione derivatives, 6-methoxy-2-methylnaphthol (**4a**) was chosen as the model substrate to optimize the reaction conditions. In the literature, many oxidizing agents have been employed for this purpose, including copper or copper(II) chloride ($CuCl_2$),[22a] hypervalent iodine derivatives (phenyliodonium diacetate, PIDA),[30] Fremy's salt,[31] manganese dioxide (MnO_2),[32] chromium trioxide (CrO_3),[33] and radical oxidation [cerium(IV) ammonium nitrate, CAN],[34] to cite but a few. We tested several conditions for the oxidation of 6-methoxy-2-methylnaphthol to 6-methoxymenadione (Table 1). The reaction did not proceed when performed with MnO_2 or Ag_2O[35] for 48 h. Oxidation by CAN, NBS (*N*-bromosuccinimide),[36] and $CuCl_2$ gave the desired menadione after 1–2 h in poor yields. Using Fremy's salt as the oxidizing reagent gave the 6-methoxymenadione in quantitative yield when the reaction was performed on a small scale. However, Fremy's salt is unstable and expensive. For this reason, we selected PIDA, which gave a yield of 60 %, as the most appropriate oxidizing agent and pragmatic choice for the large-scale preparation of the 6-methoxymenadione.

Table 1. Optimization of the oxidation of 2-methylnaphthols **4a**.



Conditions	Yield [%]
MnO_2 (5 equiv.), CH_2Cl_2, 48 h, r.t.	(starting material)
Ag_2O (5 equiv.), CH_2Cl_2, 48 h, r.t.	(starting material)
CuCl (3 equiv.), air, r.t., 2 h	40
NBS (4 equiv.), AcOH/H_2O, 1 h, 65 °C	40
CAN (3 equiv.), MeCN/H_2O, 1 h, r.t.	24
Fremy's salt (2.8 equiv.), KH_2PO_4 (0.8 equiv.), acetone/H_2O, 2 h, 0 °C	99
PIDA, (2.5 equiv.), MeCN/H_2O, 2 h, –5 to 10 °C	60

The oxidation reactions of naphthols **4** and **9** with PIDA were successfully performed, and moderate-to-good yields of **10a**–**d** and **11a**,**b** were obtained when the reactions were conducted on a multigram scale. Thus, a large variety of menadione analogues can be prepared by this approach (Scheme 5).

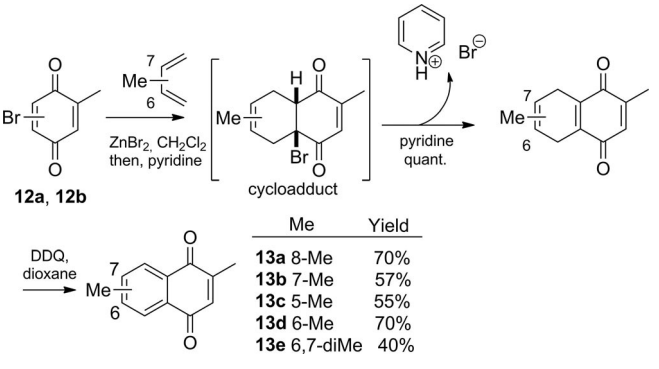


Z	Yield
10a 6-MeO	65%
10b 7-MeO	60%
10c 6,7-diMeO	66%
10d 7-F	65%
11a 6-F	67%
11b 6-Cl	44%

Scheme 5. Oxidation of the corresponding α-naphthols **4** and **9** to menadione analogues **10** and **11**.

Diels–Alder Route – Synthesis of Methylmenadiones 14a–e

Regioselective annulations of quinones by Diels–Alder reactions can be achieved when haloquinones react with dienes bearing electron-donating groups in the presence of Lewis acids.[37] In this work, 5-, 6-, 7-, 8-methyl or 6,7-dimethylmenadione derivatives **13a**–**e** were obtained by $ZnBr_2$-catalyzed Diels–Alder reactions with piperylene, isoprene, or 2,3-dimethylbuta-1,3-diene as the diene and 2-bromo-5-methylbenzoquinone (**12a**) or 2-bromo-6-methylbenzoquinone (**12b**) as the dienophile. The oxidation of the Diels–Alder adducts was not anticipated to be difficult: Treatment of the reaction mixture under basic conditions is a common method for generating oxidized naphthoquinones. Disappointingly, in contrast to the examples reported in the literature, elimination of HBr did not occur in situ and several conditions had to be tested to find a convenient method to synthesize the methylmenadione scaffolds. Heating the cycloadduct intermediate in toluene at reflux for 24 h or treating it with oxidizing agents such as CAN or DDQ[38] afforded the starting material. Furthermore, the addition of bases such as Et_3N or iPr_2NEt did not promote the desired elimination, but degradation of the intermediate. In fact, the cycloaddition product displayed an unusual sensitivity to basic conditions. Finally, the reaction was optimized by the addition of 1 equivalent of pyridine as base. Note that the addition of pyridine following the cycloaddition favors HBr elimination and prevents product degradation. In this way, treatment of the cycloadduct with pyridine and dehydrogenation with DDQ in dioxane af-



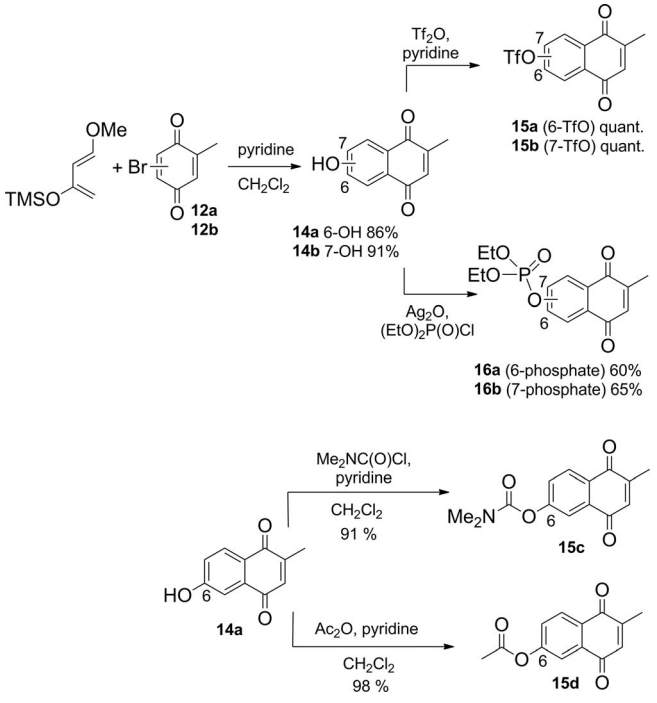
Me	Yield
13a 8-Me	70%
13b 7-Me	57%
13c 5-Me	55%
13d 6-Me	70%
13e 6,7-diMe	40%

Scheme 6. Synthesis of methylated menadiones by Diels–Alder reactions.

forded the corresponding methylmenadiones **13a**–**e** in satisfactory yields (Scheme 6).

Synthesis and Functionalization of 6- and 7-Hydroxymenadiones

6- and 7-Hydroxymenadiones **14a** and **14b** were synthesized by Diels–Alder reactions using Danishefsky's diene[39] and bromo-1,4-benzoquinones **12a** and **12b** as substrates, respectively (Scheme 7).

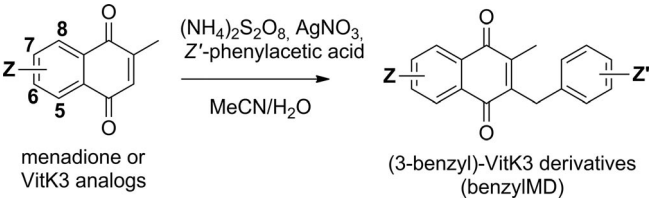


Scheme 7. Synthesis and functionalization of hydroxymenadione derivatives by Diels–Alder reactions.

The cycloadducts of 1,3-dioxybutadienes and bromoquinones underwent aromatization with the loss of 1 equivalent of MeOH. The reactions were carried out in CH_2Cl_2 by using pyridine as a base to promote the elimination of HBr. Indeed, deprotonation of the hydroxy group with pyridine and subsequent reaction with triflic anhydride, carbamoyl chloride, or acetic anhydride in CH_2Cl_2 afforded the desired menadione derivatives **15a**–**d**, respectively, in excellent yields (Scheme 7). However, the reaction did not proceed when pyridine was used in the reaction with diethyl chlorophosphate.[40] Finally, after further optimization using Ag_2O in CH_2Cl_2, 6- and 7-phosphate diethyl esters **16a** and **16b** were obtained in yields of 60 and 65 %, respectively (Scheme 7). Thus, diversely functionalized menadiones can be easily synthesized in excellent yields starting from readily prepared hydroxymenadiones, as exemplified by 6-hydroxymenadione **14a** (Scheme 7).

Synthesis of 3-(Substituted-benzyl)menadione Derivatives

3-(Substituted-benzyl)MD derivatives were synthesized by Jacobsen–Torssell reactions[41] (better known as the Kochi–Anderson reaction[21]) between commercial phenylacetic acids and the synthesized menadione analogues (2-methyl-1,4-naphthoquinones), as shown in Scheme 8.



Scheme 8. Synthesis of 3-benzylmenadione derivatives.

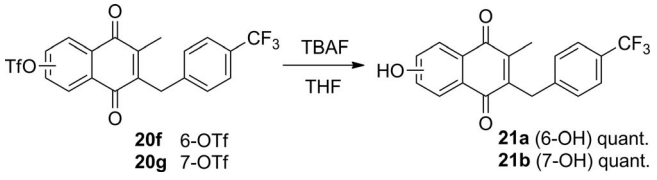
This synthetic methodology is the most useful pathway for the preparation of alkylated menadiones in bulk. The scope of this versatile reaction is illustrated by the successful use of 4′-Br, 4′-CF_3, 2′,5′-diMeO, and 3′,5′-diMeO-functionalized phenylacetic acids and a wide array of substituted menadiones in the reaction. Only alcohols and amino groups have been reported to stop the Ag^{II} catalysis under Kochi–Anderson reaction conditions.[17] The overall yields of this reaction are presented in Table 2. It is noteworthy that this procedure offers an efficient synthesis of 3-(substituted-benzyl)menadione derivatives. Furthermore, Z and Z′ could be electron-donating or -withdrawing functionalities at different positions of the substrate; they were well tolerated and gave the desired compounds in good-to-excellent yields. As expected, the reaction was compatible with a wide range of substituents, such as halogens, methyl, meth-

Table 2. Synthesis of 3-(substituted-benzyl)menadione derivatives **17**–**20** by the Kochi–Anderson reaction.

BenzylMD[a]	Z	Z′	Yield [%]
17a	6-MeO	4′-CF_3	80
17b	7-MeO	4′-CF_3	70
17c	6,7-diMeO	4′-CF_3	80
17d	7-F	4′-CF_3	65
17e	6-F	4′-CF_3	55
17f	6-Cl	4′-CF_3	71
18a	6-MeO	4′-Br	78
18b	7-MeO	4′-Br	63
18c	6,7-diMeO	4′-Br	75
18d	7-F	4′-Br	86
18e	6-F	4′-Br	85
19a	8-Me	4′-CF_3	75
19b	7-Me	4′-CF_3	68
19c	5-Me	4′-CF_3	76
19d	6-Me	4′-CF_3	65
19e	6,7-diMe	4′-CF_3	87
20a	8-Me	4′-Br	67
20b	7-Me	4′-Br	70
20c	5-Me	4′-Br	76
20d	6-Me	4′-Br	50
20e	6,7-diMe	4′-Br	82
20f	6-TfO	4′-CF_3	80
20g	7-TfO	4′-CF_3	70
20h	7-MeO	3′,5′-diMeO	77
20i	7-MeO	2′,5′-diMeO	65
20j	6,7-diMeO	3′,5′-diMeO	55
20k	6,7-diMeO	2′,5′-diMeO	72
20l	6-MeO	3′,5′-diMeO	71
20m	6-MeO	2′,5′-diMeO	65
20n	6-P(O)$_2$(EtO)$_2$	4′-CF_3	77
20o	7-P(O)$_2$(EtO)$_2$	4′-CF_3	70

oxy, and protected hydroxy groups, providing the corresponding products with good purity. In all cases, the results show excellent efficiency of the Ag(II)-mediated radical decarboxylation reaction between menadiones and commercial phenylacetic acids, affording 31 targeted products (**17a**–**f**, **18a**–**e**, **19a**–**e**, and **20a**–**o**) in good-to-excellent yields (50–87 %). In general, the reactions were clean, rapid, and efficient.

Pursuing our ongoing interest to increase the diversity of available 3-benzylMD derivatives, we decided to regenerate the hydroxy substituent group by deprotection of the triflate group in the menadione substrates **20f** and **20g**. TBAF-promoted triflate removal (in THF at room temperature)[42] was used for this reaction to yield the expected compounds **21a** and **21b** quantitatively (Scheme 9).



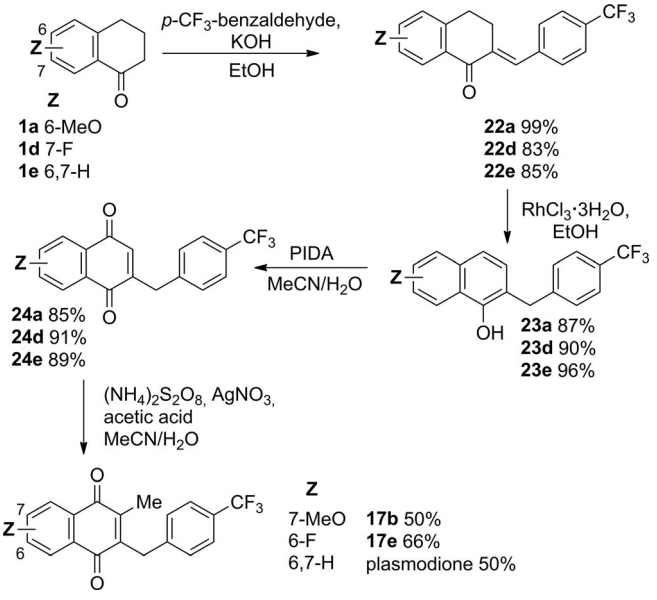
Scheme 9. Synthesis of 6- or 7-hydroxy-3-benzylmenadiones.

Expeditious and High-Yielding Route to 3-(Substituted-benzyl)menadione Derivatives

An elegant pathway that allows the formation of two 3-(substituted-benzyl)menadione regioisomers at C-6 or C-7 from the same starting material has also been envisioned. In this new process, the final benzylic chain is proposed to be introduced in the first step through the coupling of benzaldehydes to various commercial tetralones.

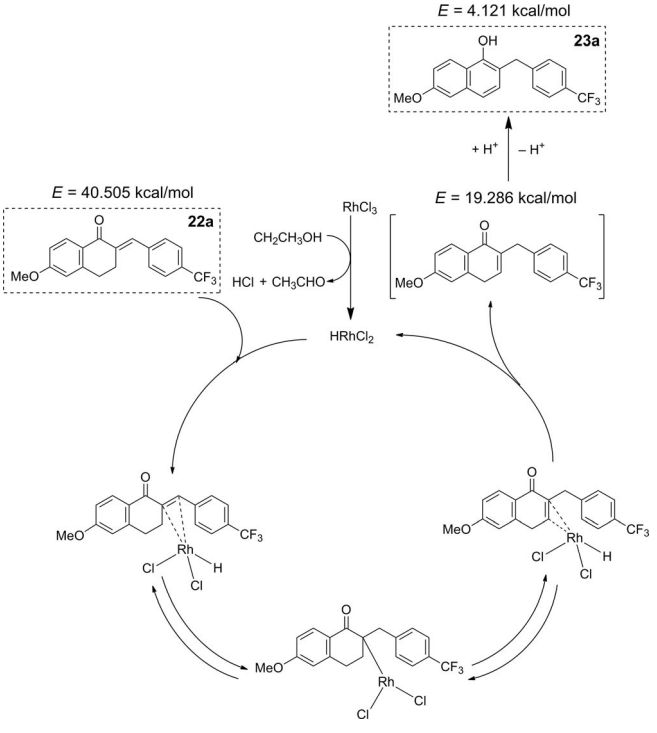
In this alternative scenario, the naphthol route is advantageous with regard to step economy, because 6- or 7-substituted 3-benzylMD regioisomers can be prepared in high yields by two pathways from the same tetralones **1a**, **1d**, or **1e**, that is, in five steps for the 6-regioisomers **17a** and **17e** (Schemes 3, 5, and 8), or only in four steps in the following expeditious route to plasmodione and the regioisomers **17b** and **17e**, respectively (Scheme 10). The conditions screened for aromatization included treatment of the starting α-methylene ketone **22a** with various oxidation catalysts. These conditions were 1) PIDA, MeCN, 12 h, room temperature, 2) TFA, CH_2Cl_2, 12 h, room temperature, 3) *t*BuOK, DMSO, 12 h, room temperature,[43] 4) $RuCl_3$, EtOH, 24 h, reflux, 5) DDQ, dioxane, 24 h, reflux, 6) trimethylphenol, TFA, 90 °C, 24 h,[44] 7) MnO_2 (5 equiv.), CH_2Cl_2, 48 h, room temperature, 8) Ag_2O (5 equiv.), CH_2Cl_2, 48 h, room temperature, 9) CrO_3, H_2O, AcOH, 90 °C, 12 h, 10) Ag_2O (16 equiv.), 6 M HNO_3, dioxane, room temperature, 11) $CuCl_2$, THF, H_2O, 24 h, room temperature, or 12) $RhCl_3$, (10 mol-%) EtOH, reflux, 6 h.[45] Only $RhCl_3$ efficiently catalyzed the aromatization of the α-methylenetetralone **22a** to the desired naphthol **23a** to give a very satisfactory yield (87 %); all the other reactions led to recovery of the starting material.

However, the reactivity of the Rh catalyst was highly dependent on the stability of the Rh^I species. According to the mechanistic study described by Paiaro et al.,[45a] $Rh^{III}Cl_3$ is first reduced by ethanol to form HRh^ICl_2 and then coordinates to the olefin



Scheme 10. Express synthesis of 3-(substituted-benzyl)menadione derivatives starting from tetralones.

functional group (Scheme 11). Subsequently, oxidative addition and β-elimination forces a shift of the double bond (Scheme 11) and finally aromatization to the most thermodynamically stable naphthol **23a** (the calculated free energies were estimated by *ChemBioOffice 2012*[53]). Indeed, the active Rh^I intermediate was found to be sensitive to oxygen in open air and lost efficiency; however, the use of well-degassed dry solvents and strict anaerobic conditions, both the yield (increased to 95 %) and reproducibility of this reaction were optimized.



Scheme 11. Proposed mechanism for the rhodium-catalyzed olefin isomerization.

Compounds **23a**, **23d**, and **23e** were then successfully oxidized with PIDA followed by the Kochi–Anderson reaction to give the three benzylMDs, namely plasmodione, **17b**, and **17e** in moderate-to-good yields.

In the final step, methylation with acetic acid was thought to be feasible; however, the yields of the preliminary reactions were not satisfactory. By using a phenylacetic acid as partner in the coupling reactions with menadiones, the yields of the radical alkylation products ranged from 50 to 87 %. However, when using acetic acid instead of phenylacetic acid, the methylation yield was limited to 30 %, because the stability of the methyl radical is much lower[46] than that of the benzyl radical, and the more reactive methyl radical may destroy the desired product. To increase the yield of this reaction, the relative amounts of acetic acid, silver nitrate, and ammonium persulfate were varied without impacting the outcome of the reaction.

To follow the reaction kinetics and track the reaction products by NMR spectroscopy, we used 2-[4-(trifluoromethyl)benzyl]naphthalene-1,4-dione (**24e**) as the starting material for the reaction model. After stirring for 30 min, the reaction conversion reached over 50 % and we observed the rapid generation of 2-benzylMD. After 1 hour, the starting material had been almost completely consumed and the benzylMD was almost exclusively the final product, as shown by the complete disappearance of the proton (δ = 6.70 ppm) at C-2 present in the starting material (see the kinetics of the reaction by the change in the NMR spectra over time, Figure 2, a). However, after 1 h, the formation of side-products was observed and the yield of the reaction decreased (Figure 2, b). Based on the kinetic profile determined by ^{19}F NMR analysis in a mixture of CD_3CN/D_2O, the protocol of this reaction was optimized to give a yield of 50–60 % after two purification steps (chromatography followed by precipitation). The preparation of plasmodione and the analogues **17b** and **17e** (Scheme 10) reflects the optimized process.

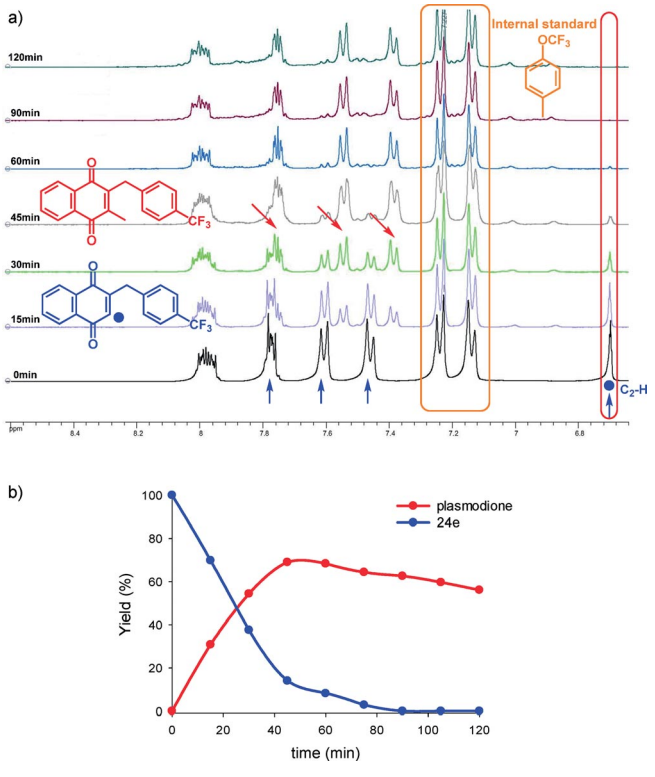
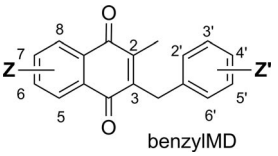


Figure 2. a) Kinetic ^{1}H NMR spectroscopy study of the Kochi–Anderson reaction between demethylmenadione **24e** and acetic acid. b) Kinetic profile for the Kochi–Anderson reaction of **24e** to plasmodione, determined by ^{19}F NMR analysis experiments. The two NMR studies were performed in a mixture of CD_3CN/D_2O using 1-methyl-4-(trifluoromethoxy)benzene as internal standard.

Antimalarial Activities of 3-(Substituted-benzyl)menadione Derivatives

1,4-Naphthoquinones are widely distributed in naturally occurring quinones. Their role in biochemistry has often been highlighted because of their electron-transfer properties in numerous important pathways from the respiratory chain of living cells to maintaining the redox equilibrium in cytosol. In the first part of our investigation of menadione properties, we evaluated the oxidant character of newly synthesized 2-methyl-1,4-naphthoquinones by cyclic voltammetry to evaluate and establish a predictive structure–redox potential model (QSPR: quantitative structure–property relationship) based on the electro- and physicochemical properties of various redox-active compounds.[4b] With these new tools in hand, we made available an on-line evaluation (through the Web interface) of the oxidant character of redox agents to help chemists targeting such desired redox properties. Also, seminal studies on several synthetic naphthoquinones found that these compounds possess antiprotozoal activities.[47] These include potent antimalarial properties, which have been reported for synthetic atovaquone (as the main active principle of Malarone®),[48] and by us, for synthetic 2-methyl-1,4-naphthoquinone (or menadione) derivatives like plasmodione.[17–19] In the present study, we explored the consequences of the incorporation of halogen, methyl, methoxy, and hydroxy groups into the phenyl ring of the menadione core on the antimalarial activity of the privileged benzylMD structure. Therefore, the structure–activity relationships of the polysubstituted benzylMD series were assessed through a study of the effect of the functionalization of both the phenyl ring of the menadione core (Z) and benzyl chain (Z′) on the antimalarial activities in comparison with the lead plasmodione, which has been reported previously.[17] The 50 % inhibitory concentration (IC_{50}) was determined for each compound by using the SYBR green assay in the presence of *P. falciparum* strain Dd2 parasitized red blood cells in culture (Table 3). In parallel, the IC_{50} values of positive controls, chloroquine (82.4 nM) and Methylene Blue (3.6 nM), were determined to be of the same order of magnitude as the values reported elsewhere.[18] In the data presented in Table 3, the IC_{50} values of the lead plasmodione (Z = H, Z′ = 4′-CF_3) and its 4-bromobenzyl derivative (Z = H, Z′ = 4′-Br), called benzylMD **1a** in the previous report,[17] are lower than the value of the antimalarial drug chloroquine, attesting to a slightly superior antiplasmodial activity (58 and 82 vs. 99 nM) against the multidrug-resistant *P. falciparum* strain Dd2. Interestingly, among the newly synthesized benzylMD derivatives (Z, Z′), the most potent antimalarial compounds are the 6- and 7-fluoro analogues of plasmodione,

Table 3. Averaged IC_{50} values for polysubstituted 3-benzylmenadione derivatives determined from growth inhibition assays with *Plasmodium falciparum* strain Dd2.



benzylMD

BenzylMD	Z	Z′	IC_{50} [nM] (*n*)[a]	BenzylMD	Z	Z′	IC_{50} [nM] (*n*)[a]
17a	6-MeO	4′-CF_3	186 ± 58 (3)	**20b**	7-Me	4′-Br	992 ± 107 (3)
17b	7-MeO	4′-CF_3	3187 (1)	**20c**	5-Me	4′-Br	1820 ± 71 (3)
17c	6,7-diMeO	4′-CF_3	3685 (1)	**20d**	6-Me	4′-Br	171 ± 66 (3)
17d	7-F	4′-CF_3	83 ± 12 (4)	**20e**	6,7-Me	4′-Br	2706 ± 26 (2)
17e	6-F	4′-CF_3	59 ± 11 (3)	**20f**	6-OTf	4′-CF_3	236 ± 37 (4)
17f	6-Cl	4′-CF_3	242 ± 60 (4)	**20g**	7-OTf	4′-CF_3	3546 ± 902 (3)
18a	6-MeO	4′-Br	171 ± 69 (3)	**20h**	7-MeO	3′,5′-diMeO	778 ± 89 (4)
18b	7-MeO	4′-Br	3230 (1)	**20i**	7-MeO	2′,5′-diMeO	2187 (1)
18c	6,7-diMeO	4′-Br	881 ± 129 (4)	**20j**	6,7-diMeO	3′,5′-diMeO	2704 (1)
18d	7-F	4′-Br	74 ± 32 (4)	**20k**	6,7-diMeO	2′,5′-diMeO	1365 ± 521 (4)
18e	6-F	4′-Br	83 ± 23 (3)	**20m**	6-MeO	2′,5′-diMeO	104 ± 58 (4)
19a	8-Me	4′-CF_3	3004 ± 941 (2)	**20n**	6-$P(O)_4(Et)_2$	4′-CF_3	157 ± 49 (2)
19b	7-Me	4′-CF_3	439 ± 205 (5)	**20o**	7-$P(O)_4(Et)_2$	4′-CF_3	518 ± 231 (3)
19c	5-Me	4′-CF_3	3638 ± 193 (2)	BenzylMD **1a**[b]	H	4′-Br	82 ± 20 (7)
19d	6-Me	4′-CF_3	215 ± 68 (3)	Plasmodione[c]	H	4′-CF_3	58 ± 11 (9)
19e	6,7-diMe	4′-CF_3	3243 ± 260 (3)	2-Demethylplasmodione **24e**	H	4′-CF_3	3698 ± 191 (2)
20a	8-Me	4′-Br	3761 ± 972 (3)	CQ[d]	–	–	82.4 ± 1.6 (3)

[a] Activity against cultured parasites of the *P. falciparum* Dd2 strain is presented as mean IC_{50} values ± standard deviation (SD) determined from *n* independent growth inhibition assays in triplicate using the SYBR® green technique. [b] From ref.[17] [c] Plasmodione, named benzylMD **1c**, in ref.[17–19], and its 4-bromo analogue, named benzylMD **1a** in ref.[17], were used as internal references. The lower nanomolar IC_{50} values previously reported for plasmodione and its 4-bromo analogue against the drug-multiresistant *P. falciparum* Dd2 strain were evaluated in a distinct assay based on tritiated hypoxanthine incorporation (ref.[17]). [d] Methylene Blue [MB, IC_{50} = 3.6 ± 0.4 (4)] and chloroquine (CQ) were used as standard drugs.

17e (6-F, 4′-CF_3), **18e** (6-F, 4′-Br), **17d** (7-F, 4′-CF_3), and **18d** (7-F, 4′-Br), respectively (**17e**: 59 nM, **18e**: 83 nM, **17d**: 83 nM, and **18d**: 74 nM vs. 58 nM with plasmodione), which suggests that the introduction of fluorine at C-6 or C-7 might be a favorable/tolerant substitution to maintaining antimalarial activity. In contrast to the substitution by halogens, the antimalarial activities of the methylated and methoxylated Z analogues of the lead plasmodione are significantly reduced, regardless of the substitution position on the phenyl ring, but with substitution at C-6 always being the most favorable when Z′ is an electron-withdrawing group (4′-CF_3, 4′-Br). For instance, the IC_{50} values range from 171 nM (for the 6-MeO- and 6-Me-substituted benzylMDs **18a** and **20d** with a 4′-Br-benzyl chain, respectively) to 186 nM and 215 nM (for the 6-MeO- and 6-Me-substituted benzylMDs **17a** and **19d** with a 4′-CF_3-benzyl chain, respectively). Furthermore, methylation at C-5 or C-8 dramatically reduces the activity, with the IC_{50} values increasing to 3638 nM for the 5-Me-substituted benzylMD **19c** (4′-CF_3) and to 3004 nM and 3761 nM for the 8-Me-substituted benzylMDs **19a** and **20a** (4′-CF_3 and 4′-Br). Finally, 2-demethylplasmodione **24e**, with a hydrogen atom instead of a methyl group at C-2, displays a very weak antimalarial activity, attesting to the essential requirement of the 2-methyl group in the menadione core.

Conclusions

This study has provided new insights into the synthetic methodologies that can be used to prepare various biologically active polysubstituted 2-methyl-3-benzyl-1,4-naphthoquinones by efficient and versatile strategies, namely the naphthol route, starting from either a tetralone or a propiophenone, or regioselective Diels–Alder reactions. These original procedures were found to be useful for the synthesis of focused chemical libraries of benzylMD analogues with broad structural diversity. The structural complexity, ease of synthesis, and variation in substitution patterns present in these molecules will allow quantitative structure–activity relationship studies, useful for various biological applications. In this work we have found compounds displaying a wide variation of activity against *P. falciparum* parasites. These synthetic templates may be employed as an important class of "privileged scaffolds" in redox medicinal chemistry.

Experimental Section

Detailed descriptions of experimental procedures are given in the Supporting Information.

General Procedure 1 for the α-Formylation of Tetralone: A mixture of tetralone in toluene (1 equiv., 0.45 mmol mL^{-1}) and ethyl formate (2.0 equiv.) was prepared. The solution was cooled to –78 °C under argon and mechanically stirred while potassium *tert*-butoxide (2.0 equiv.) was added in portions: The solution became milky and pinky in color. The solution was warmed to –5 °C until TLC monitoring (petroleum ether/Et_2O, 3:1) indicated the completion of the reaction. The solution was quenched with 10 % HCl (the pink color disappeared) and the mixture extracted with Et_2O. The organic phases were dried (brine, $MgSO_4$) and concentrated in vacuo to yield α-formyl tetralone (usually as a solid).

Typical Procedure for the Synthesis of 2-(Hydroxymethylene)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (2a): Commercially available 6-methoxytetralone (12.0 g, 68.14 mmol, 1 equiv.) was used as the starting material and treated according to the general procedure 1 to give **2a** (13.62 g, 66.8 mmol), yield 98 %; light-brown solid; m.p. 66–67 °C (ref.[24] 68–69 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.6 Hz, 1 H), 6.82 (dd, J = 8.6, 2.4 Hz, 1 H), 6.68 (d, J = 2.4 Hz, 1 H), 3.82 (s, 3 H), 2.82 (t, J = 7.3 Hz, 2 H), 2.51 (t, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.1 (C=O), 175.1 (CH), 163.5 (C_q), 144.5 (C_q), 128.8 (CH), 126.2 (CH), 113.1 (CH), 112.6 (C_q), 108.21 (CH), 55.5 (OCH_3), 29.4 (CH_2), 23.3 (CH_2) ppm.

General Procedure 2 for the Aromatization of α-Formyltetralone to α-Formylnaphthol: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.0 equiv.) was added to a solution of α-formyltetralone in dioxane (1.0 equiv., 0.2 M) at room temperature. A white precipitate appeared rapidly. After completion of the reaction (TLC monitoring), the white precipitate was removed by filtration. The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (silica gel, cyclohexane/Et_2O, 3:1) to give the desired compound.

Typical Procedure for the Synthesis of 1-Hydroxy-6-methoxy-2-naphthaldehyde (3a): Compound **2a** was used as the starting material (4.08 g, 19.69 mmol) and treated according to the general procedure 2 to give **3a** (2.86 g, 14.2 mmol), yield 75 %; white powder; m.p. 128–129 °C (ref.[24] 133 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.70 (s, 1 H), 9.90 (s, 1 H), 8.35 (d, J = 9.2 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.18 (dd, J = 9.2, 2.6 Hz, 1 H), 7.09 (d, J = 2.6 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6 (C=O), 162.0 (C_q), 161.5 (C_q), 139.6 (C_q), 127.5 (CH), 126.1 (C_q), 119.0 (CH), 116.4 (CH), 116.2 (CH), 113.2 (C_q), 106.3 (CH), 55.5 (OCH_3) ppm.

General Procedure 3 for the Reduction of 2-Formyl-1-naphthols: Triethylamine (1.2 equiv.) was added to a solution of 2-formyl-1-naphthol in tetrahydrofuran (1.0 equiv., 1 mmol mL^{-1}). The solution was cooled to 0 °C and then ethyl chloroformate (1.2 equiv.) was added over a period of 30 min. The solution was stirred during 30–60 min (white precipitate formed). The precipitate (triethylamine hydrochloride) was removed by filtration and washed with tetrahydrofuran (twice less than the amount used for the reaction). An aqueous solution of $NaBH_4$ (4.0 equiv., 2.6 M) was added to the combined filtrates at 5–15 °C. When the addition was complete, the reaction mixture was stirred at room temperature for 1–2 h and then diluted with water. The solution was cooled to 0 °C and made acidic by the slow addition of aqueous HCl (10 %). The aqueous solution was extracted with Et_2O. The organic phases were washed with a dilute solution of NaOH (10 %), dried (brine, $MgSO_4$), and concentrated in vacuo to yield methylnaphthol (usually as a solid or oil that crystallized on standing).

Typical Procedure for the Synthesis of 6-Methoxy-2-methylnaphthalen-1-ol (4a): Compound **3a** was used as the starting material (1.32 g, 6.47 mmol) and treated according to the general procedure 3 to give **4a** (0.85 g, 4.53 mmol), yield 70 %; deliquescent white powder. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.03 (d, J = 9.8 Hz, 1 H), 7.24 (AB system, J = 8.1 Hz, 2 H), 7.11 (m, 2 H), 5.19 (s, 1 O*H*), 3.90 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 158.1 (C_q), 15.7 (CH_3), 55.8 (OCH_3), 149.4 (C_q), 135.3 (C_q), 130.3 (CH), 123.2 (CH), 120.1 (C_q), 119.5 (CH), 118.3 (CH), 114.8 (C_q), 106.2 (CH) ppm. MS (EI): m/z (%) = 188.1 (100) $[M]^+$, 145.0 (83), 115.0 (62), 189.1 (15) $[M + H]^+$.

General Procedure 8 for the Oxidation of Methylnaphthols to Menadiones: (Diacetoxyiodo)benzene (PIDA) (12.1 mmol, 2.1 equiv.) was added portionwise to a stirred solution of the methylnaphthol (5.8 mmol, 1 equiv.) in acetonitrile (70 mL) and water (30 mL) at –5 °C over 20–30 min. After stirring for 30 min at –5 °C, the reaction mixture was stirred at room temperature for 1 h. A saturated $NaHCO_3$ solution was added to the orange reaction mixture and the reaction mixture extracted with Et_2O (3 × 120 mL). The combined organic extracts were washed with brine and dried with anhydrous $MgSO_4$. The crude was purified by flash chromatography on silica gel (hexane/Et_2O, 2:3) to give the desired compound.

Typical Procedure for the Synthesis of 6-Methoxy-2-methylnaphthalene-1,4-dione (10a): Compound **4a** was used as the starting material (2.0 g, 10.63 mmol) and treated according to the general procedure 8 to give **10a** (1.40 g, 6.91 mmol), yield 65 %; yellow powder; m.p. 146–148 °C (Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.6 Hz, 1 H), 7.49 (d, J = 2.8 Hz, 1 H), 7.18 (dd, J = 8.6, J = 2.8 Hz, 1 H), 6.79 (q, J = 1.8 Hz, 1 H), 3.94 (s, 3 H), 2.18 (d, J = 1.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.06 (C=O), 184.56 (C=O), 163.96 (C_q), 148.52 (C_q), 135.25 (CH), 134.33 (C_q), 129.02 (CH), 125.77 (C_q), 120.21 (CH), 109.29 (CH), 55.91 (OCH_3), 16.52 (CH_3) ppm. HRMS (ESI): calcd. for $C_{12}H_{10}O_3Na$ 225.0522 $[M + Na]^+$; found 225.0522.

General Procedure 9 for the Preparation of Menadiones by the Diels–Alder Reaction: A solution of 2-bromo-5-methyl-1,4-benzoquinone (**12a**) or 2-bromo-6-methyl-1,4-benzoquinone (**12b**; 1.0 equiv.) in dry CH_2Cl_2 (0.15 mmol mL^{-1}) was added to a suspension of $ZnBr_2$ (1.2 equiv.) in dry CH_2Cl_2 (1.5 mmol mL^{-1}). The mixture was stirred for 5 min and the appropriate diene was added (10 equiv.). After stirring overnight the reaction mixture was quenched with a solution of saturated NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were washed with brine and dried with $MgSO_4$. Pyridine (2 equiv.) was added and the mixture was stirred at room temperature for 4 h. CH_2Cl_2 was evaporated to yield the quinone as a yellow oil. The quinone (1.0 equiv.) was dissolved in dioxane (0.3 M) and DDQ (1.0 equiv.) was added at room temperature. After completion of the reaction (TLC monitoring), the white precipitate was removed by filtration. The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (silica gel, cyclohexane/EtOAc, 4:1) to give the desired compound.

Typical Procedure for the Synthesis of 2,8-Dimethylnaphthalene-1,4-dione (13a): 2-Bromo-6-methyl-1,4-benzoquinone (**12b**; 2.50 g, 13.55 mmol) and piperylene (10 mL, 135.5 mmol) were used as the starting materials and treated according to the general procedure 9 to give **13a** (1.76 g, 9.48 mmol), yield 70 %; yellow needles; m.p. 132 °C (hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (dd, J = 10.5, J = 2.4 Hz, 1 H), 7.61–7.49 (m, 2 H), 6.81 (q, J = 2.1 Hz, 1 H), 2.75 (s, 3 H), 2.18 (d, J = 2.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.51 (C=O), 185.34 (C=O), 149.45 (C_q), 141.28 (C_q), 137.65 (CH), 134.27 (CH), 133.76 (C_q), 132.79 (CH), 129.84 (C_q), 124.99 (CH), 22.89 (CH_3), 16.86 (CH_3) ppm. HRMS (ESI): calcd. for $C_{12}H_{11}O_2$ 187.0754 $[M + H]^+$; found 187.0761.

General Procedure 10 for the Diels–Alder Reaction with Danishefsky's Diene: 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene (2.0 equiv.) was added dropwise to 2-bromo-5-methyl-1,4-benzoquinone (**12a**) or 2-bromo-6-methyl-1,4-benzoquinone (**12b**; 1.0 equiv.) in CH_2Cl_2 (0.2 M) at 0 °C. The solution was stirred at room temperature for 2 h, then pyridine (1.5 equiv.) was added, and the suspension stirred under air at room temperature for 6 h. Concentration and flash column chromatography (ethyl acetate/toluene, 1:2) gave hydroxy-2-methylnaphthalene-1,4-dione.

Typical Procedure for the Synthesis of 6-Hydroxy-2-methylnaphthalene-1,4-dione (14a): 2-Bromo-6-methyl-1,4-benzoquinone (**12b**; 2.00 g, 9.90 mmol, 1 equiv.) and Danishefsky's diene (2.9 mL, 14.85 mmol, 1.5 equiv.) were used as the starting materials and treated according to the general procedure 10 to give **14a** (1.60 g, 8.50 mmol), yield 86 %; orange solid; m.p. 175 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.96 (s, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.29 (d, J = 2.8 Hz, 1 H), 7.19 (dd, J = 8.4, J = 2.8 Hz, 1 H), 6.93 (q, J = 1.6 Hz, 1 H), 2.15 (d, J = 1.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 185.18 (C=O), 184.31 (C=O), 163.07 (C$_q$), 148.75 (C$_q$), 135.27 (CH), 134.49 (C$_q$), 129.56 (CH), 124.44 (C$_q$), 121.03 (CH), 111.82 (CH), 16.45 (CH$_3$) ppm. HRM (ESI): calcd. for $C_{11}H_9O_3$ 189.0546 [M + H]$^+$; found 189.0557.

General Procedure 13 for the Synthesis of Benzyl Menadione Derivatives: The corresponding menadione derivative (1 equiv., 0.05 mmol mL^{-1}) and phenylacetic acid derivative (2 equiv.) were added to a stirred solution of MeCN/H$_2$O (3:1) and heated at 85 °C (70 °C in the flask). AgNO$_3$ (0.35 equiv.) was first added and then (NH$_4$)$_2$S$_2$O$_8$ (1.3 equiv., 0.36 mmol mL^{-1}) in MeCN/H$_2$O (3:1) was added dropwise. The reaction mixture was then heated for 2–3 h at 85 °C. MeCN was evaporated and the mixture extracted with DCM. The crude mixture was purified by flash chromatography on silica gel using a mixture of diethyl ether and cyclohexane as eluent. When necessary, the benzylmenadione was recrystallized from hexane or a mixture of EtOAc/hexane to give the desired analytically pure benzylMD derivatives in good-to-excellent yields.

Typical Procedure for the Synthesis of 2,6-Dimethyl-3-[4-(trifluoromethyl)benzyl]naphthalene-1,4-dione (19d): Yield 65 %; yellow needles; m.p. 93–94 °C (hexane/EtOAc). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.98 (d, J = 7.4 Hz, 1 H), 7.87 (s, 1 H), 7.53–7.48 (m, 3 H), 7.17 (d, J = 7.4 Hz, 2 H), 4.07 (s, 2 H), 2.48 (s, 3 H) 2.23 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 184.98 (C=O), 184.81 (C=O), 144.82 (C$_q$), 144.74 (C$_q$), 144.17 (C$_q$), 142.31 (C$_q$), 134.38 (CH), 131.81 (C$_q$), 129.87 (C$_q$), 128.87 (2 × CH), 128.58 (q, J = 28.9 Hz, C$_q$), 126.88 (CH), 126.62 (CH), 125.6 (q, J = 3.8 Hz, 2 CH), 124.18 (q, J = 269.7 Hz, CF$_3$), 32.34 (CH$_2$), 21.85 (CH$_3$) 13.33 (CH$_3$) ppm. HRM (ESI): calcd. for $C_{20}H_{15}F_3O_2Na$ 367.0916 [M + Na]$^+$; found 367.0911.

General Procedure for the Condensation of 4-Trifluorobenzaldehyde and Commercial Tetralones: A solution of KOH (41.04 mmol, 1.2 equiv.) in EtOH (105.5 mL) was added to a mixture of α-tetralone (4.562 mL, 34.2 mmol, 1 equiv.) and 4-CF$_3$-benzaldehyde (37.62 mmol, 1.1 equiv.). The solution was stirred at room temperature for 4 h. The reaction mixture was poured into water and a white solid precipitated. The solid was filtered, washed with water (2 × 50 mL), and dried under vacuum to give the desired alkenes in excellent yields.

Typical Procedure for the Synthesis of (*E*)-2-[4-(trifluoromethyl)benzylidene]-3,4-dihydronaphthalen-1(2*H*)-one (22e): Yield 85 %; white solid; m.p. 170–172 °C (from EtOH). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.05 (dd, J = 7.8, J = 1.5 Hz, 1 H), 7.75 (s, 1 H), 7.52 [(AB)$_2$ system, J = 8.1 Hz, 4 H], 7.40, (dd, J = 7.8, 1.5 Hz, 1 H), 7.31–7.28 (m, 1 H), 7.26–7.16 (m, 1 H), 3.01–2.97 (m, 2 H), 2.91–2.85 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 187.49 (C=O), 143.19 (C$_q$), 139.47 (C$_q$), 137.41 (C$_q$), 134.66 (CH), 133.56 (CH), 133.23 (C$_q$), 130.02 (q, J = 31.57 Hz, C$_q$), 129.91 (2 CH), 129.42 (CH), 128.31 (CH), 127.18 (CH), 125.60 (q, J = 3.3 Hz, 2 CH), 124.07 (q, J = 270.3 Hz, CF$_3$), 28.81 (CH$_2$), 27.20 (CH$_2$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –62.69 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}F_3O$ 303.0991 [M + H]$^+$; found 303.0971.

General Procedure for the Isomerization to the Corresponding Benzylnaphthol Derivatives: A solution of the corresponding alkene (3.31 mmol, 1 equiv.) and RhCl$_3$ (0.331 mmol, 0.1 equiv.) was heated at reflux in ethanol (70 mL) for 6 h. During this process, when the reaction was carried out in open air, oxygen was observed to interfere in the catalytic cycle by oxidizing Rh(I) to Rh(III)* species, accounting for the arrest of the isomerization reaction. Thus, well-degassed solvent and strict anaerobic conditions were necessary for this reaction to occur. After concentration, the residue was partitioned between water and ethyl acetate, and the organic phase was dried with MgSO$_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 5:1) gave the pure products in excellent yields.

Typical Procedure for the Synthesis of 2-[4 (trifluoromethyl)benzyl]naphthalen-1-ol (23e): Yield 96 %; white solid; m.p. 83.5–84 °C (cyclohexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.87–7.84 (m, 1 H), 7.65–7.61 (m, 1 H), 7.37–7.26 (m, 5 H), 7.20–7.14 (m, 2 H), 7.10–7.05 (m, 1 H), 4.99 (s, 1 H, OH), 4.03 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 148.63 (C$_q$), 144.05 (C$_q$), 133.82 (C$_q$), 128.90 (2 CH), 128.81 (q, J = 33.42 Hz, C$_q$), 128.63 (CH), 128.00 (CH), 126.79 (CH), 125.71 (CH), 125.63 (q, J = 3.83 Hz, 2 CH), 124.59 (C$_q$), 124.2 (q, J = 264.23 Hz, CF$_3$), 120.98 (CH), 120.72 (CH), 119.57 (C$_q$), 36.2 (CH$_2$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –62.39 ppm. MS (EI): *m/z* (%) = 302.1 (100) [M]$^+$. HRMS (ESI): calcd. for $C_{18}H_{14}F_3O$ 303.0991 [M + H]$^+$; found 303.0996.

General Procedure for the Oxidation of the Benzylnaphthol Derivatives to 2-Benzyl-1,4-naphthoquinones: (Diacetoxyiodo)-benzene (PIDA) (5.29 mmol, 2.1 equiv.) was added portionwise to a stirred solution of naphthol (2.65 mmol, 1 equiv.) in acetonitrile (35 mL) and water (12 mL) at –5 °C over 20–30 min. After stirring for 30 min at –5 °C, the reaction mixture was stirred at room temperature for 1 h. A saturated NaHCO$_3$ (15 mL) solution was added to the orange reaction mixture and the mixture was extracted with Et$_2$O (3 × 50 mL). The combined organic extracts were washed with brine and dried with anhydrous MgSO$_4$. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 1:10 to 1:5) to give the corresponding desired benzylMDs in excellent yields.

Typical Procedure for the Synthesis of 2-[4-(Trifluoromethyl)benzyl]naphthalene-1,4-dione (24e): Yield 89 %; yellow needles; m.p. 98–100 °C (hexane/EtOAc). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.13–8.02 (m, 2 H), 7.76–7.71 (m, 2 H), 7.49 [(AB)$_2$ system, J = 8.1 Hz, $\Delta\nu$ = 61.8 Hz, 4 H] 6.63 (t, J = 1.5 Hz, 1 H), 3.96 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 184.87 (C=O), 184.72 (C=O), 149.78 (CH), 141.00 (C$_q$), 135.90 (CH), 133.96 (CH), 133.87 (C$_q$), 132.05 (C$_q$), 129.74 (2 CH), 129.41 (q, J = 32.48 Hz, C$_q$), 126.75 (CH), 126.22 (CH), 125.78 (q, J = 3.83 Hz, 2 CH), 125.77 (C$_q$), 124.12 (q, J = 269.18 Hz, CF$_3$), 35.67 (CH$_2$) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –62.54 ppm. HRMS (ESI): calcd. for $C_{18}H_{12}F_3O_2$ 317.0784 [M + H]$^+$; found 317.0791.

General Procedure for the Kochi–Anderson Reaction of 2-Benzyl-1,4-naphthoquinone Derivatives to the Corresponding 3-Benzylmenadiones: The 2-benzyl-1,4-naphthoquinone (0.316 mmol, 1 equiv.) and acetic acid (1.58 mmol, 5 equiv.) were added to a stirred solution of MeCN/H$_2$O (3:1, 9.19 mL) and heated at 85 °C. AgNO$_3$ (0.11 mmol, 0.35 equiv.) was first added, and then (NH$_4$)$_2$S$_2$O$_8$ (0.411 mmol, 1.3 equiv.) in MeCN/H$_2$O (3:1, 3.94 mL) was added dropwise in 5 min. The reaction mixture was then heated for 60 min at 85 °C. MeCN was evaporated and the mixture was extracted with DCM. The crude mixture was purified by flash chromatography on silica gel using toluene as eluent. When necessary, the compound was recrystallized from hexane or a mixture of EtOAc/hexane to give the analytically pure benzylMD derivatives.

Biological Assays

Inhibitors: The chloroquine diphosphate salt and Methylene Blue trihydrate were purchased from Sigma–Aldrich. The lead plasmodione was prepared as described previously (as benzylMD **1c** in ref.[17]). Stock solutions of Methylene Blue and chloroquine were prepared in pure water. Stock solutions of the benzylMD derivatives (6 mM) were prepared in DMSO and stored in aliquots at –20 °C.

Growth Inhibition Assays: *P. falciparum* wild-type strain Dd2 was cultured at 37 °C according to standard protocols[49] in RPMI medium containing 9 % human serum and type A erythrocytes at a hematocrit level of 3.3 % under a low-oxygen atmosphere (3 % CO_2, 5 % O_2, 92 % N_2, and 95 % humidity). The cultures were synchronized by using the sorbitol method.[50] Growth inhibition was determined in a SYBR green assay as described previously.[51,52] Inhibitors were added to synchronized ring stage parasite cultures in microtiter plates (0.5 % parasitemia, 1.25 % hematocrit) and incubated for 72 h. The final inhibitor concentrations in each assay ranged from 22 pM to 5 μM.

In Vitro Anti-*Plasmodium* Activity Assays: The inhibition of intraerythrocytic parasite development by benzylMD derivatives and control agents (CQ, MB) was determined in microtiter tests according to standard protocols. The in vitro antimalarial activity is expressed as 50 % inhibitory concentration (IC_{50}). The activities of the lead plasmodione, Methylene Blue, and chloroquine against the *P. falciparum* Dd2 strain (as presented in Table 3) were determined by using the SYBR® green I assay as described before.[51,52] Briefly, synchronous ring stage parasites were incubated for 72 h in the presence of decreasing drug concentrations in microtiter plates (0.5 % parasitemia, 1.5 % hematocrit final). Each inhibitor was analyzed in three-fold serial dilution in duplicates and with at least three independent repetitions.

Supporting Information (see footnote on the first page of this article): General Procedures 4–7, 11, and 12; detailed descriptions of experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra of all new compounds.

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