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Elena Cesar Rodo,[a] Liwen Feng,[a] Mouhamad Jida,[a] Katharina Ehrhardt,[a,b],§ Max Bielitza,[a] Jérémy Boilevin,[a] Michael Lanzer,[b,c] David Lee Williams,[d] Don Antoine Lanfranchi*,[a] and Elisabeth Davioud-Charvet*,[a]

Abstract: A platform of synthetic methodologies was established to access a focused library of polysubstituted 3-benzylmenadione derivatives functionalized at the aromatic ring of the naphthoquinone core. Two main routes were explored: (i) the naphthol route, via either an α-tetralone, or a propiophenone, and (ii) 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 two 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 has 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 with bio-inspired representatives in Figure 1. Owing to the broad occurrence of the *1,4*-naphthoquinone motif in compounds of natural origin and to their peculiar redox properties,[4] there is a growing interest in the chemistry of polysubstituted *1,4*-naphthoquinones as final mole-cules or key synthetic intermediates. Numerous *1,4*-naphthoquinones[5] do not contain the 2-methyl substituent, rendering the synthesis easy and straightforward from substituted benzenes.[5a] Also, among the menadione derivatives, the substitution pattern has to be considered (Figure 1): functionalization (i) at the east part of the molecule, affords the vitamin K series upon isoprenylation of vitamin K3 (menadione).[6] Using solid- and solution-phase synthesis, a library of synthetic menadione, juglone and plumbagin derivatives has been prepared allowing introduction of broad structural diversity at the east part of the quinone core.[7] Functionalization (ii) in the west part of menadione is also commonly found in plants, as exemplified by chimaphilin derivatives[8] (Figure 1). Larger (biaryls, macrocycles, *etc*) ring systems, although less common, appear in natural products, as exemplified by bivitamin K,[9] gossypolone,[10] and the

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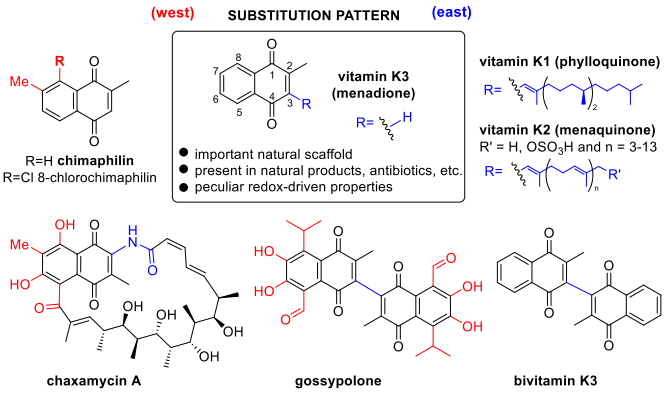
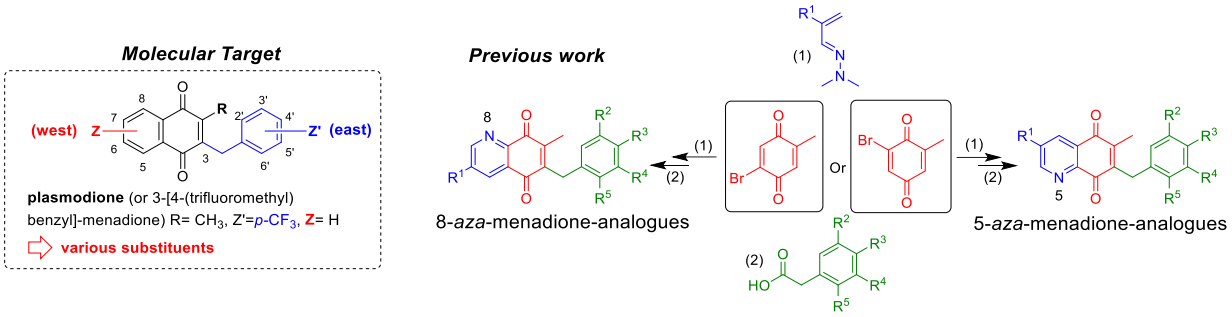


Figure 1. Natural and synthetic polysubstituted menadione derivatives.



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

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

In contrast to the previous east-substituted series, general methods for regioselective transformations to prepare synthetic menadione derivatives substituted both at the phenyl ring (west part) and at the quinone part (east) of the 1,4-naphthoquinone core are rare. Although numerous reports have described the synthetic routes to various menadione derivatives, large collections with a diversity of substitutions in the west ring are not commercially available in bulk. Although the regioselective annulations of quinones by the Diels-Alder strategy are commonly used to build the *1,4*-naphthoquinone nucleus in total synthesis of natural products,[12] it remains challenging to control the regioselectivity of the reaction when cycloaddition is applied to moderately reactive dienes with unsymmetrical 2-methylquinones.[13] Many factors increasing the regioselectivity of the [4+2] cycloadditions have been reported: i) the presence of Lewis[14] and Brønsted[15] acid catalysts, ii) 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 cycloadditions can produce highly selective results but, these approaches depend on structural features of the substrates, resulting in unpredictable outcomes of the reaction.

The recent discovery of the antimalarial lead 3-[4-(trifluoromethyl)benzyl]-menadione (Scheme 1), henceforth called plasmodione (compound **1c** in[17-19]), has led to reassessment of the synthetic methodologies used to prepare large numbers of diverse analogs and potential metabolites, that are functionalized at both the east and west 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- *aza*-menadione analogues).[20] The methodology used a two-step sequence through 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).

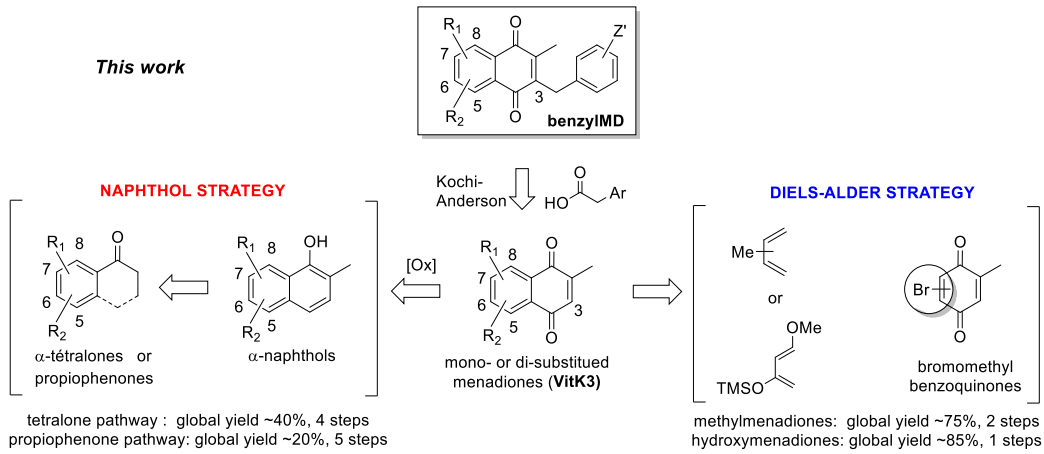
Thus, identification of plasmodione, currently a first lead/early hit, highlights the potential of redox-active 3-benzylmenadiones (benzylMD) with the following properties: a large chemical space for derivatization, and a wide range of redox potentials. The generation of more effective analogues can only be approached by total synthesis of 2-methyl-*1,4*-naphthoquinones substituted at the phenyl ring of menadione that necessitates the total regiocontrol of the synthetic reactions. Due to the lack of versatile and general methodologies to prepare polysubstituted 2-methyl-3-benzyl-*1,4*-naphthoquinones derivatives, these studies focused on the development and application of efficient methods to overcome these short-comings (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, 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 reaction starting from *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: (i) it leads to the dissymmetry of the molecule, and (ii) its acidic hydrogens 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 in any locus of the aromatic ring, in particular at C-6 or C-7 of the menadione core.

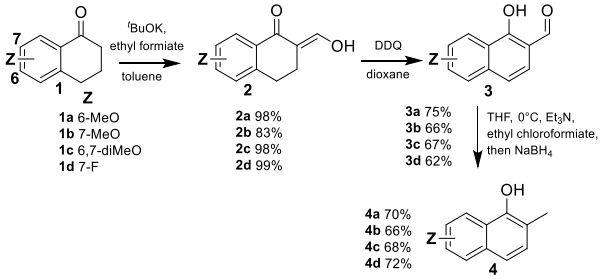
As a continuation of our studies into antiplasmodial drug development, we envisaged that polysubstituted 2-methyl-*1,4*-naphthoquinones could also be synthesized through two key strategies (Scheme 2), Diels-Alder or naphthol routes. Toward this end, it was decided to prepare these scaffolds starting 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-*1,4*-benzoquino-ne (**12a**), or 2-bromo-6-methyl-*1,4*-benzoquinone (**12b**) (*vide infra*). In this study, a small library of menadione analogues was built as key-intermediates in order to prepare benzylMD derivatives that might be useful as templates both in drug discovery and medicinal chemistry. Herein, we report new synthetic regioselective methods to obtain polysubstituted menadiones via two routes through: (i) naphthol strategy and (ii) Diels-Alder strategy (Scheme 2).



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

Naphthol route: Synthesis of methylnaphthols 4 and 9

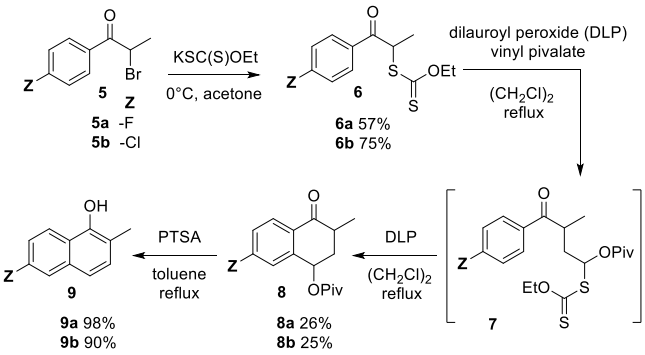
Two methods were employed to synthesize the polysubstituted methylnaphthols using commercially available tetralones or propiophenones.



Scheme 3. Preparation of 2-methyl-naphthols from starting tetralones.

***Via* a tetralone** (Scheme 3)**:** the commercial 1-tetralones **1** were quantitatively transformed in the presence of ethyl formate and *t*-BuOK into the corresponding 2-hydroxymethylene derivative **2**.[23] These compounds were aromatized with DDQ in dioxan[24] to afford the intermediates **3** with good yields. Then, the formyl group was reduced under mild conditions using a known protocol.[25] 1-hydroxy-2-naphthaldehyde **3** was reacted with $ClCO_2Et$ in the presence of Et_3N giving quantitatively the carbonate derivative, whose treatment with $NaBH_4$ in aqueous THF at 0 °C directly afforded the desired 2-methylnaphthol **4** derivatives in good yields.

***Via* a propiophenone** (Scheme 4)**:** Since the pioneering work of Zard *et al.*, extensive research efforts have focused on the construction of diverse polysubstituted naphthols as starting-blocks for 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 2-methyl-6,7-substituted tetralones was developed 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] and then by others.[28b] Thus, bromopropiophenones **5** were easily synthesized from commercial propiophenones by bromination with Br_2 in AcOH.[29] Treatment of the latter with potassium ethyl xanthate in acetone at 0 °C afforded the desired radical precursor **6** in good yield. The Zard procedure was used for the preparation of the key bicyclic intermediate **8**, starting with the radical addition of the xanthate onto vinyl pivalate using dilauroyl peroxide (DLP) as initiator in 1,2-dichloroethane (DCE), yielding the protected xanthate **7** which can be used as a starting point for another radical sequence. When the xanthate **7** solution was refluxed in DCE and treated with 1.2 equiv of DLP (added portionwise), tetralones **8** were obtained in 25% and 26% yield.



Scheme 4. Preparation of 2-methyl-naphthols via xanthates.

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 in order to facilitate the last step of the route. Next, tetralones **8** were treated with *p*-toluenesulfonic acid (PTSA)[27b] in refluxing toluene to obtain the corresponding naphthols **9** in excellent yields (Scheme 4).

Synthesis of polysubstituted menadiones 10 and 11

In order to find the best reaction conditions for the synthesis of the prototype menadione derivatives, 6-methoxy-2-methylnaphthol **4a** was chosen as model substrate to optimize the reaction conditions. In the literature, many oxidizing agents have been employed for that purpose including copper or copper(II) chloride ($CuCl_2$),[22a] hypervalent iodine derivatives (PIDA),[30] Fremy's salt,[31] manganese dioxide (MnO_2),[32] chromium trioxide (CrO_3)[33] and radical oxidation (CAN)[34] to cite a few. In our case, several conditions were tested to carried out 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 48h. Oxidation by CAN, NBS,[36] and $CuCl_2$ gave the desired menadione after 1 to 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 quantity. However, this reagent is unstable and expensive. For this reason, we selected PIDA as the most appropriate oxidizing agent and pragmatic choice for large scale preparation.

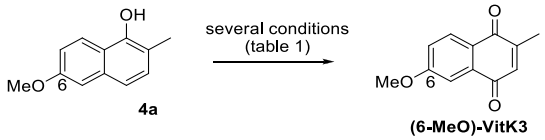
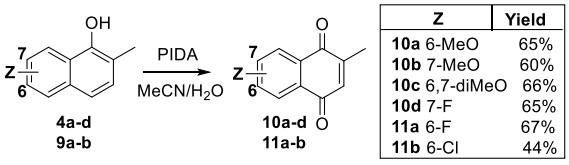


Table 1. Oxidation tests

Conditions	Yield
MnO_2 (5 equiv), CH_2Cl_2, 48 h, rt	(starting material)
Ag_2O (5 equiv), CH_2Cl_2, 48 h, rt	(starting material)
CuCl (3 equiv), air, rt, 2 h	40%
NBS (4 equiv), AcOH/ H_2O, 1 h, 65 °C	40%
CAN (3 equiv), MeCN/H_2O, 1 h, rt	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 reaction with PIDA was successfully performed and moderate to good yields were obtained for **10a-d** and **11a-b** when the reaction was conducted on a multigram scale to prepare a large variety of menadione analogues (Scheme 5).

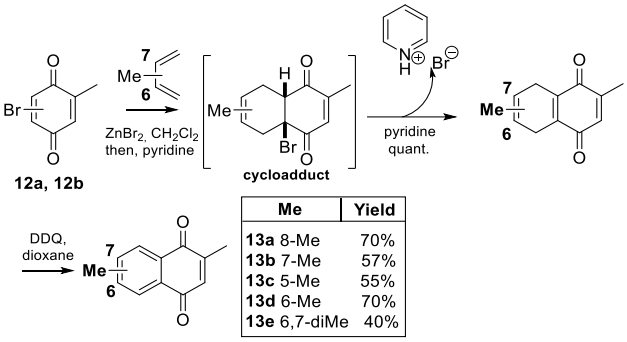


Z	Yield
10a 6-MeO	65%
10b 7-MeO	60%
10c 6,7-diMeO	66%
10d 7-F	65%
11a 6-F	67%
11b 6-Cl	44%

Scheme 5. Oxidation of the corresponding α-naphthols to menadione analogues.

Diels-Alder route: Synthesis of methylmenadiones (14a-e)

Regioselective annulations of quinones by Diels-Alder reactions are achieved when haloquinones reacted with dienes bearing electron-donor groups in the presence of Lewis acids.[37] 5-, 6-, 7-, 8-, or 6,7-di- Methylmenadione derivatives (**13a-e**) were obtained using $ZnBr_2$ catalyzed Diels-Alder reaction 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 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 methyl-menadione scaffolds. Refluxing the cycloadduct intermediate in toluene for 24 h, or treating it with oxidizing agents such as CAN or DDQ[38] afforded the starting material. Furthermore, addition of bases such as Et_3N or i-Pr_2NEt did not promote the desired elimination but a degradation of the intermediate. In fact, the cycloadduct product displayed an unusual sensitivity to basic conditions. Finally, the reaction was optimised by addition of one equivalent of pyridine as a base. Noteworthy is to mention that pyridine addition followed the cycloaddition in order to favour HBr elimination, and to prevent product degradation. Next, treatment with pyridine and dehydrogenation with DDQ in dioxane afforded the corresponding methylmenadiones (**13a-e**) in satisfactory yields (Scheme 6).

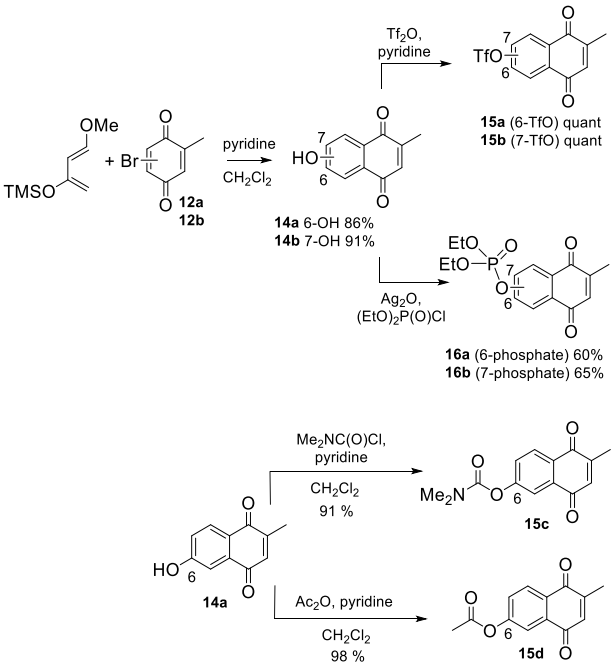


Me	Yield
13a 8-Me	70%
13b 7-Me	57%
13c 5-Me	55%
13d 6-Me	70%
13e 6,7-diMe	40%

Scheme 6. Synthesis of methylated menadiones via Diels-Alder reaction.

Synthesis and functionalization of 6- and 7-hydroxymenadiones

6- and 7-Hydroxymenadiones **14a** and **14b** were synthesized via a Diels-Alder reaction using Danifshefsky diene[39] and bromo-*1,4*-benzoquinones **12a** and **12b** as substrates (Scheme 7).



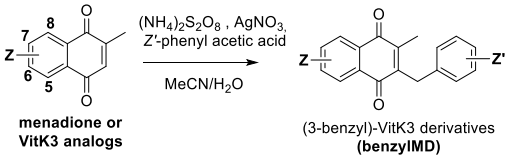
Scheme 7. Synthesis and functionalization of hydroxymenadione derivatives via Diels-Alder reaction.

Cycloadducts of 1,3-dioxybutadienes and bromoquinones undergo aromatization with the loss of one equivalent of MeOH. The reactions were carried out in CH_2Cl_2 using pyridine as a base to promote the elimination of HBr. Indeed, deprotonation of the hydroxyl group with pyridine and reaction with triflic anhydride, carbamoyle chloride and acetic anhydride in CH_2Cl_2 afforded the desired menadione derivatives **15a-d**, respectively, with excellent yields (Scheme 7). Nevertheless, 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 60% and 65% yield, respectively (Scheme 7). Diversely-functionalized menadiones can be easily synthesized in excellent yield from readily prepared hydroxymenadiones, as it was exemplified with 6-hydroxymenadione **14a** (Scheme 7).

Synthesis of 3-[substituted-benzyl]-menadione derivatives

The synthesis of 3-substituted-benzylMD derivatives was achieved by using the Jacobsen–Torssell procedure[41] (better known as Kochi–Anderson reaction[21]) between commercial phenylacetic acids and synthetized menadione analogs (2-methyl-*1,4*-naphthoquinones) as shown in Scheme 8.



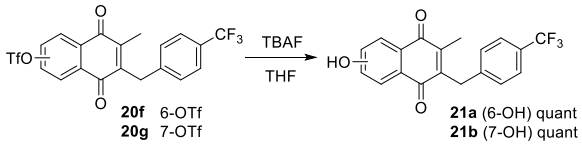
Scheme 8. Synthesis of 3-benzylmenadione derivatives.

Table 2. Synthesis of 3-[substituted-benzyl]-menadione derivatives via 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%

This synthetic methodology is the most useful pathway to prepare alkylated menadiones in bulk. The scope of this versatile reaction is illustrated with various 4'-Br, 4'-CF_3, 2',5'-diMeO, or 3',5'-diMeO -functionalized phenylacetic acids and a wide array of substituted menadiones involved in the reaction. Only alcohols and amino groups were 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 is an attractive methodology for efficient synthesis of 3-[substituted-benzyl]-menadione derivatives. Furthermore, Z and Z' could be electron-donating or electron-withdrawing functionalities at different positions on 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 diversity of substituents, such as halogens, methyl, methoxy and protected hydroxyls to provide the corresponding products with good purity. In all cases, the results showed the excellent reactivity of Ag(II)-mediated radical decarboxylation between the menadiones and commercial phenylacetic acids affording 33 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.

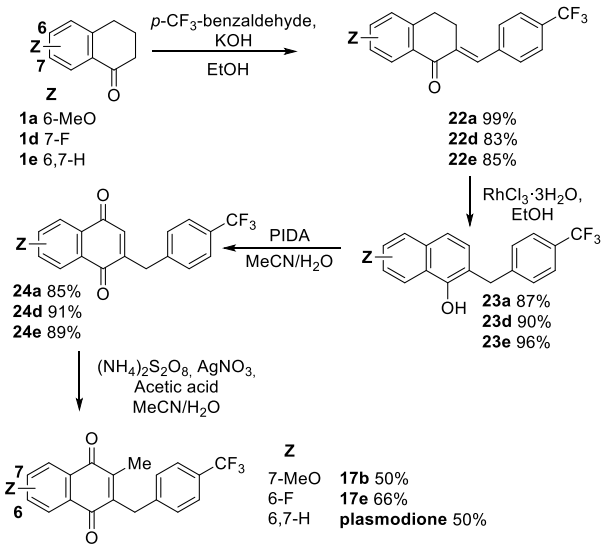
Pursuing our ongoing interest to increase the diversity of available 3-benzylMD derivatives, we decided to regenerate the hydroxyl substituent group by deprotection of the triflate present in both menadione substrates **20f** and **20g**. TBAF-promoted triflate removal (in THF at room temperature)[42]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



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

Expeditious and high-yielding route to access 3-[substituted-benzyl]-menadione derivatives

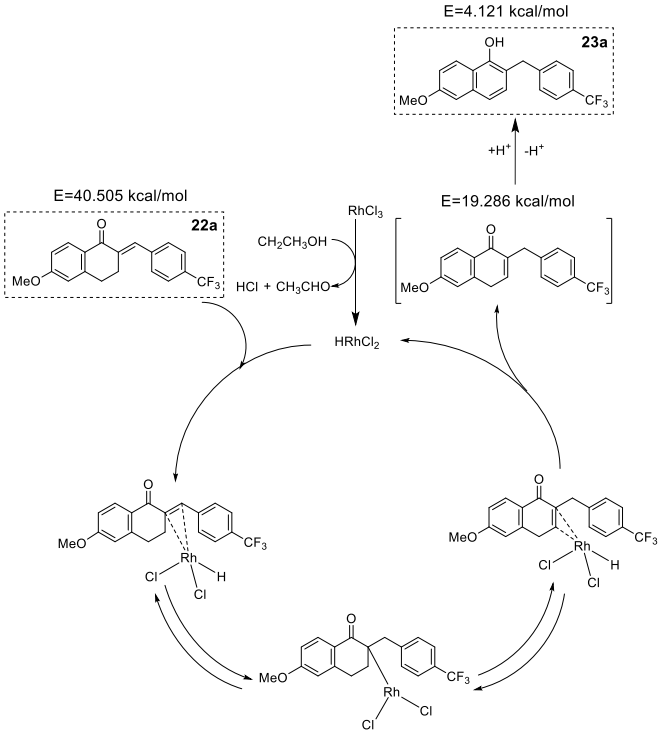
An elegant pathway that allows the formation of two 3-(substituted-benzyl)menadione regioisomers at C-6 or C-7 from the same starting material has also been envisioned. In the new process, the final benzylic chain is proposed to be introduced in the first step through the coupling of benzaldehydes to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



Scheme 10. Express tetralone's synthesis

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 various oxidation catalysts reacted with the starting α-methylene

ketone **22a**. These conditions are: i) PIDA, MeCN, 12 h, rt; or ii) TFA, CH_2Cl_2, 12 h, rt; or iii) *t*BuOK, DMSO, 12 h, rt;[43] or iv) $RuCl_3$, EtOH, 24 h, reflux; or v) DDQ, dioxan, 24 h, reflux; or vi) trimethylphenol, TFA, 90 °C, 24 h;[44] or vii) MnO_2 (5 equiv), CH_2Cl_2, 48 h, rt; or viii) Ag_2O (5 equiv), CH_2Cl_2, 48 h, rt; or ix) CrO_3, H_2O, AcOH, 90 °C, 12 h; or x) Ag_2O (16 equiv), 6M HNO_3, dioxan, rt; or xi) $CuCl_2$, THF, H_2O, 24 h, rt; or xii) $RhCl_3$, (10% mol) EtOH, reflux, 6h.[45] Only $RhCl_3$ efficiently catalyzed the aromatization of the α-methylene tetralone **22a** to the desired naphthol **23a** with a very satisfactory yield (87%); all other reactions led to the recovery of the starting material.



Scheme 11. Proposed mechanism of Rhodium-catalyzed olefin isomerization.

However, the reactivity of the Rh catalyst was highly dependent on the stability of Rh(I) species. According to the mechanism study described by Paiaro *et al*.,[45a] $Rh^{III}Cl_3$ was first reduced by ethanol, to form $HRh^{I}Cl_2$ and then coordinated with the olefin function group, and finally completed the catalytic cycle (Scheme 11). Subsequently, oxidative addition and *β*-elimination forced the double bond to shift through the proposed catalytic cycle (Schema 11) and finally, aromatization to the most thermodynamically stable naphthol **23a** (the calculated free enthalpy energies were estimated by ChemBioOffice 2012). Indeed, the active Rh^{I} intermediate was found to be sensitive to oxygen in open air and lost efficiency. Using well degased dry solvents and strict anaerobic conditions, both the yield (to 95%) and reproducibility of this reaction were optimized.

Then, the oxidation reaction of **23a**, **23d**, and **23e** with PIDA followed by Kochi-Anderson reaction was successfully performed and moderate to good yields were obtained for the three benzylMD: plasmodione, **17b** and **17d**.

In the final step, the methylation with acetic acid was thought to be feasible; however, yields of preliminary attempted reactions were not satisfactory. By using a phenylacetic acid as partner in the coupling reactions with menadiones, the yields of 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 stability of the methyl radical was much lower[46] than that of benzyl radical, and the more reactive methyl radical might destroy the desired product. In order to increase the yield of this reaction, the equivalent numbers of acetic acid, silver nitrate and ammonium persulfate were varied without impacting the outcome of the reaction.

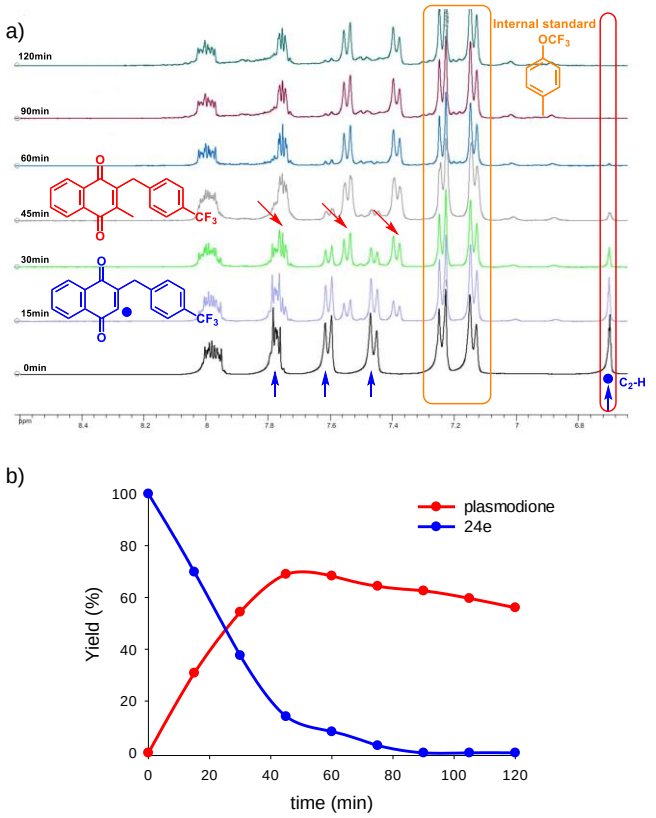


Figure 2. a) Kinetic ^{1}HNMR spectroscopy studies of the Kochi-Anderson reaction between desmethyl-menadione **24e** and acetic acid. b) Kinetic profile of the Kochi-Anderson reaction from **24e** leading to plasmodione, determined by ^{19}F NMR analysis experiments. Both 2 NMR studies were performed in a mixture of CD_3CN/D_2O, using 1-methyl-4-(trifluoromethoxy)benzene as an internal standard.

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 one hour, the starting material was almost completely consumed and the benzylMD was almost exclusively the final product shown by the complete disappearance of the proton (6.70 ppm) at C-2 position present in the starting material (see the kinetics of the reaction by NMR traces over time for the aromatic part, in Figure 2a). However, after 1 h, the generation of side products was observed and the yield of the reaction was decreased (Figure 2b). Based on kinetic profile determined by ^{19}F NMR in a mixture of CD_3CN/D_2O, the protocol of this reaction was optimized to give 50%-60% yield after 2 purification steps (chromatography followed by precipitation). The preparation of plasmodione and the analogs **17b** and **17e** (Scheme 10) reflects the optimized process.

Antimalarial activities of 3-[substituted-benzyl]-menadione derivatives

1,4-Naphthoquinones are widely distributed among naturally-occuring quinones. Their role in biochemistry has often been highlighted because of the electron-transfer properties in numerous important pathways from the respiratory chain of living cells to maintaining of the redox equilibrium in the cytosol. In the first part of our investigations on menadione properties, we evaluated the oxidant character of newly synthesized 2-methyl-*1,4*-naphtoquinones by cyclic voltammetry in order to evaluate and set-up a predictive structure-redox potential model (QSPR: Quantitative Structure-Property Relationship) based on electrochemical and physicochemical properties of various redox-active compounds.[4b] With these new tools in hands, we made available an on-line evaluation (via 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 that have been reported for the synthetic atovaquone (as main active principle of Malarone®),[48] and by us, for the synthetic 2-methyl-*1,4*-naphthoquinone (or menadione) derivatives like plasmodione.[17-19] In the present study, we explored the consequences of incorporation of halogen, methyl, methoxy, and hydroxyl groups on the phenyl ring of the menadione core, on antimalarial activity of the privileged benzylMD structure. Therefore, the structure-activity relationships of the poly-substituted benzylMD series were assessed – through the importance of the functionalization of both the phenyl ring of menadione core (Z) and of the 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 in 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 (H, 4'-CF_3) and its 4-bromo-benzyl derivative (H, 4'-Br), called benzylMD **1a** in the previous report,[17] were lower than the value of the antimalarial drug chloroquine, attesting for a slightly superior antiplasmodial activity (58 nM and 82 nM versus 99 nM) against the multidrug-resistant *P. falciparum* strain Dd2. Interestingly, among the newly synthesized benzylMD derivatives (Z, Z'), the most potent antimalarial compounds were the 6-fluoro- and the 7-fluoro-analogues of plasmodione, **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 versus 58 nM with plasmodione), suggesting that introduction of fluorine at C-6 or at C-7 might be a favorable/tolerant substitution to maintain the antimalarial activity. In contrast to substitution with halogens, the antimalarial activities of the methylated and the methoxylated Z-analogues of the lead plasmodione are significantly reduced regardless of the substitution position on the phenyl ring, but with the substitution at C-6 always being the most favorable when Z' is an electron-withdrawing group (4'-CF_3, 4'-Br). For instance, the values ranged from 171 nM (for the 6-MeO and 6-Me substituted benzylMD **18a** and **20d** with a 4'-Br benzyl chain, respectively) to 186 nM and 215 nM (for the 6-MeO and 6-Me substituted benzylMD **17a** and **19d** with a 4'-CF_3 benzyl chain, respectively). Furthermore, methylation at C-5 or C-8 dramatically reduced the activity, with the IC_{50} values increased to 3638 nM for the 5-Me substituted benzylMD **19c** (4'-CF_3), 3004 nM and 3761 nM for the 8-Me substituted benzylMD **19a** and **20a** (4'-CF_3 and 4'-Br). Finally, 2-desmethyl-plasmodione **24e** – with a hydrogen atom instead of the methyl group at C-2 – displayed a very weak antimalarial activity attesting to the essential requirement of the 2-methyl group present in menadione core.

Conclusions

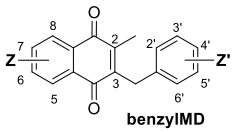
In summary, this study provides new insights into synthetic methodologies that can be used to prepare various biologically active polysubstituted 2-methyl-3-benzyl-*1,4*-naphthoquinones by efficient and versatile strategies through (i) the naphthol route, starting from either a tetralone, or a propiophenone,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

Experimental Section

Detailed descriptions of experimental procedures, spectral data and ^{1}H and ^{13}C NMR spectra of all new compounds 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. 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 solution 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 solid compound).

Typical procedure for 2-(hydroxymethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (2a): Commercially available 6-methoxytetralone (12.0 g, 68.14 mmol, 1 equiv) was used as 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 (lit.[24] 68-69 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.91 (d, 1H, *J* = 8.6 Hz), 6.82 (dd, 1H, *J* = 8.6 Hz, 2.4 Hz), 6.68 (d, 1H, *J* = 2.4 Hz), 3.82 (s, 3H), 2.82 (t, 2H, *J* = 7.3 Hz), 2.51 (t, 2H, *J* = 7.3 Hz) 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.



benzylMD

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

BenzylMD code	Z	Z'	IC_{50} values (nM) (n)[a]	BenzylMD code	Z	Z'	IC_{50} values (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** (from ref. 17)	H	4'-Br	82 ± 20 (7)
19d	6-Me	4'-CF_3	215 ± 68 (3)	plasmodione[b]	H	4'-CF_3	58 ± 11 (9)
19e	6,7-diMe	4'-CF_3	3243 ± 260 (3)	2-desmethyl plasmodione **24e**	H	4'-CF_3	3698 ± 191 (2)
20a	8-Me	4'-Br	3761 ± 972 (3)	**CQ**[c]	-	-	82.4 ± 1.6 (3)

[a] Activity against cultured parasites of *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] **Plasmodione** – named benzylMD **1c** in ref. 17, 18, and 19, and its *4*-bromo analog – 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 analog against the drug-multiresistant *P. falciparum* Dd2 strain were evaluated in a distinct assay based on tritiated hypoxanthine incorporation (ref. 17). [c] **MB**, methylene blue (IC_{50} = 3.6 ± 0.4 (4)); **CQ**, chloroquine, were used as standard drugs.

General procedure 2 for the aromatisation of α-formyl-tetralone to α-formyl naphthol: To a solution of *α*-formyl tetralone in dioxane (1.0 equiv, 0.2 M) was added 2,3-Dichloro-5,6-dicyano-*1,4*-benzoquinone (or DDQ) (1.0 equiv) 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 1-hydroxy-6-methoxy-2-naphthaldehyde (3a): 2a was used as 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 (lit.[24] 133 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.70 (s, 1H), 9.90 (s, 1H), 8.35 (d, 1H, *J* = 9.2 Hz), 7.45 (d, 1H, *J* = 8.8 Hz), 7.26 (d, 1H, *J* = 8.8 Hz), 7.18 (dd, 1H, *J* = 9.2 Hz, 2.6 Hz), 7.09 (d, 1H, *J* = 2.6 Hz), 3.96 (s, 3H) 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: To a solution of 2-formyl-1-naphthol in tetrahydrofuran (1.0 equiv, 1 mmol.mL^{-1}) was added triethylamine (1.2 equiv). 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 left under stirring during 30-60 min (white precipitate formation). The precipitates (triethylamine hydrochloride) were removed by filtration and washed with tetrahydrofuran (twice less than the amount used for the reaction). To the combined filtrates was added, at 5-15 °C, an aqueous solution of $NaBH_4$ (4.0 equiv, 2.6 M). When the addition was completed, 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 dilute solution of NaOH (10%), dried (brine, $MgSO_4$) and concentrated *in vacuo* to yield methylnaphthol (usually as a solid or oil which crystallized on standing).

Typical procedure for 6-methoxy-2-methylnaphthalen-1-ol (4a): 3a was used as starting material (1.32 g, 6.47 mmol) and treated according to the general procedure 3 to give **4a** (0.85g, 4.53 mmol); Yield = 70%; deliquescent white powder; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.03 (d, *J* = 9.8 Hz, 1H), 7.24 (AB system, *J* = 8.1 Hz, 2H), 7.11 (m, 2H), 5.19 (s, 1 O*H*), 3.90 (s, 3H), 2.37 (s, 3H) 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 ([M]$^+$, 100), 145.0 (83), 115.0 (62), 189.1 ([M + H]$^+$, 15).

General procedure 8 for the oxidation of methylnaphthols into 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. Saturated $NaHCO_3$ solution was added to the reaction orange mixture and the reaction mixture extracted with Et_2O (3 x 120 mL). The combined organic extracts were washed with brine and dried over 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 6-methoxy-2-methylnaphthalene-*1,4*-dione (10a): 4a was used as starting material (2.0 g, 10.63 mmol) and treated according to the general procedure 8 to give **10a** (1.40g, 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, 1H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.18 (dd, *J* = 8.6 Hz, *J* = 2.8 Hz, 1H), 6.79 (q, *J* = 1.8 Hz, 1H), 3.94 (s, 3H), 2.18 (d, *J* = 1.8 Hz, 3H) 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: [M+Na]$^+$ calcd for $C_{12}H_{10}O_3Na$ 225.0522; found 225.0522. ;

General procedure 9 for the preparation of menadiones by 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 minutes and the appropriated 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 solubilized in dioxane (0.3 M) and to this solution was added 2,3-Dichloro-5,6-dicyano-*1,4*-benzoquinone (DDQ) (1.0 equiv) 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 2,8-dimethylnaphthalene-*1,4*-dione (13a): 2-bromo-6-methyl-*1,4*-benzoquinone (**12b**, 2.50 g, 13.55 mmol) and pyperilene (10 mL, 135.5 mmol) were used as starting material 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 Hz, *J* = 2.4 Hz, 1H), 7.61-7.49 (m, 2H), 6.81 (q, *J* = 2.1 Hz, 1H), 2.75 (s, 3H), 2.18 (d, *J* = 2.1 Hz, 3H) 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: [M+H]$^+$ calcd for $C_{12}H_{11}O_2$ 187.0754; found 187.0761.

General procedure10 for the Diels-Alder reaction with Danishefsky's diene: 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene (2.0 equiv) was added dropwise to a 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 0ºC. 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 eluting with (ethyl acetate/toluene: 1/2) gave the hydroxy-2-methylnaphthalene-*1,4*-dione.

Typical procedure for 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 Danishfsky's diene (2.9 mL, 14.85 mmol, 1.5 equiv) were used as starting material 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, DMSO-d6): δ = 10.96 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.19 (dd, *J* = 8.4 Hz, *J* = 2.8 Hz, 1H), 6.93 (q, *J* = 1.6 Hz, 1H), 2.15 (d, *J* = 1.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d6): 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; HRMS-ESI: [M+H]$^+$ calcd for $C_{11}H_9O_3$ 189.0546; 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 phenyl acetic acid derivative (2 equiv) were added to a stirred solution of MeCN/H_2O (3/1) and heated at 85 °C (70 °C in the flask). $AgNO_3$ (0.35 equiv) was first

added, and then $(NH_4)_2S_2O_8$ (1.3 equiv, 0.36 mmol.mL^{-1}) in MeCN/H_2O (3/1) was added dropwise. The reaction mixture was then heated for 2-3 h 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 a mixture of diethyl ether and cyclohexane as eluent. When necessary, the benzyl menadione compound was re- crystallised from hexane or a mixture of EtOAc/hexane to give the desired analytically pure benzylMD derivatives in good to excellent yields.

Typical procedure for 2,6-dimethyl-3-(4-(trifluoromethyl)benzyl) naphthalene-*1,4*-dione (19d): Yield = 65%; Yellow needles; m.p. 93-94 ºC (hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 7.98 (d, *J* = 7.4 Hz, , 1H), 7.87 (s, 1H), 7.53-7.48 (m, 3H), 7.17 (d, *J* = 7,4, 2H), 4.07 (s, 2H), 2.48 (s, 3H) 2.23 (s, 3H) 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 (2xCH) ; 128.58 (q, *J*= 28,9 Hz, C_q); 126.88 (CH) ; 126.62 (CH); 125.6 (q, *J* =3.8 Hz, 2xCH), 124.18 (q, *J*= 269.7 Hz, CF_3); 32.34 (CH_2) ; 21.85 (CH_3) 13.33 (CH_3) ppm; HRMS-ESI: $[M+Na]^+$ calcd for $C_{20}H_{15}F_3O_2Na$ 367.0916; found 367.0911.

General procedure for the condensation of *4*-trifluorobenzaldehyde and commercial tetralone's: 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 onto water and a white solid precipitated. The solid was filtered, washed with water (2x50 mL) and dried under vacuum to give the desired alkene compounds in excellent yields.

Typical procedure for (*E*)-2-(4-(trifluoromethyl)benzylidene)-3,4-dihydronaphthalen-1(2H)-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 Hz, *J* = 1.5 Hz, 1H), 7.75 (s , 1H), 7.52 ($(AB)_2$ system, *J* = 8.1 Hz, 4H), 7.40, (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.31-7.28 (m, 1H), 7.26-7.16 (m, 1H), 3.01-2.97 (m, 2H), 2.91-2.85 (m, 2H) 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 MHz, C_q); 129.91 (2xCH); 129.42 (CH) ; 128.31 (CH); 127.18 (CH); 125.60 (q, *J*=3.3 Hz, 2xCH); 124.07 (q, *J*= 270.3, CF_3); 28.81 (CH_2), 27.20 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.69 ppm; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{14}F_3O$ 303.0991; 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 RhI to RhIII* species, accounting for the arrest of the isomerization reaction. Thus, well degased 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 over $MgSO_4$ and concentrated. Chromatography (cyclohexane/EtOAc, 5:1) gave the pure products in excellent yields.

Typical procedure for 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, 1H), 7.65-7.61 (m, 1H), 7.37-7.26 (m, 5H), 7.20-7.14 (m, 2H), 7.10-7.05 (m, 1H), 4.99 (s, 1H, OH), 4.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ =148.63 (C_q); 144.05 (C_q); 133.82 (C_q); 128.90 (2xCH); 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, 2xCH); 124.59(C_q); 124.2 (q, *J*= 264.23, CF_3); 120.98 (CH); 120.72 (CH); 119.57 (C_q); 36.2 (CH_2) ppm; MS (EI) :*m/z* (%) : 302.1 ($[M^+]$, 100); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.39 ppm; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{14}F_3O$ 303.0991; found 303.0996.

General procedure for the oxidation of benzylnaphthol derivates into 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. Saturated $NaHCO_3$ (15 mL) solution was added to the reaction orange mixture and the reaction mixture extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine and dried over 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 the desired benzylMD compounds in excellent yields.

Typical procedure for 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, 2H), 7.76-7.71 (m, 2H), 7.49 ($(AB)_2$ system, *J* = 8.1 Hz, $\Delta\nu$ = 61.8 Hz, 4H) 6.63 (t, *J*=1.5 Hz, 1H), 3.96 (s,2H) 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 (2xCH); 129.41 (q, *J*=32.48 Hz, C_q); 126.75 (CH); 126.22 (CH); 125.78 (q, *J*=3.83Hz, 2xCH); 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 (m/z): $[M+H]^+$ calcd for $C_{18}H_{12}F_3O_2$ 317.0784; found 317.0791.

General procedure for the Kochi-Anderson reaction of 2-benzyl-*1,4*-naphthoquinones derivatives to the corresponding 3-benzylmenadiones: The 2-benzyl-*1,4*-naphthoquinones (0.316 mmol, 1 equiv) and acetic acid (1.58 mmol, 5 equiv) were added to a stirred solution of MeCN/H_2O (3/1, 9.19 mL) and heated at 85 °C. $AgNO_3$ (0.11 mmol, 0.35 equiv) was first added, and then $(NH_4)_2S_2O_8$ (0.411 mmol, 1.3 equiv) in MeCN/H_2O (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 eluant. When necessary, the compound was recristallised from hexane or a mixture of EtOAc/hexane to give the analytically pure benzylMD derivatives.

BIOLOGICAL ASSAYS

Inhibitors: Chloroquine diphosphate salt and methylene blue trihydrate were purchased from Sigma-Aldrich. The lead plasmodione was prepared as previously described (as benzylMD **1c**).[17] Stock solutions of methylene blue and chloroquine were prepared in pure water. All stock solutions of 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 of 3.3% under a low-oxygen atmosphere (3% CO_2, 5% O_2, 92% N_2 and 95% humidity). Cultures were synchronized using the sorbitol method.[50] Growth inhibition was determined in a SYBR green assay as previously described.[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. Final inhibitor concentrations in each assay ranged from 22 pM to 5 µM.

***In vitro* anti-*Plasmodium* activity assays:** Inhibition of intraerythrocytic parasite development by benzylMD derivatives and control agents (CQ, MB) was determined in microtiter tests according to standard protocols. *In vitro*

antimalarial activity is expressed as 50% inhibitory concentration (IC_{50}). Activities of the lead plasmodione, methylene blue, and chloroquine against the *P. falciparum* Dd2 strains (as presented in Table 3) were determined 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 a three-fold serial dilution in duplicates and at least three independent repetitions.

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[1] a) T. J. Schmidt, S. A. Khalid, A. J. Romanha, T. M. Alves, M. W. Biavatti, R. Brun, F. B. Da Costa, S. L. de Castro, V. F. Ferreira, M. V. de Lacerda, J. H. Lago, L. L. Leon, N. P. Lopes, R. C. das Neves Amorim, M. Niehues, I. V. Ogungbe, A. M. Pohlit, M. T. Scotti, W. N. Setzer, M. de N C Soeiro, M. Steindel, A. G. Tempone, *Curr. Med. Chem.* **2012**, *19*, 2176-2228; b) H. Eilenberg, S. Pnini-Cohen, Y. Rahamim, E. Sionov, E. Segal, S. Carmeli, A. Zilberstein, *J. Exp. Bot.* **2010**, *61*, 911-922; c) C. M. Holsclaw, K. M. Sogi, S. A. Gilmore, M. W. Schelle, M. D. Leavell, C. R. Bertozzi, J. A. Leary, *ACS Chem. Biol.* **2008**, *3*, 619-624.

[2] a) A. Fournet, A. Angelo, V. Muñoz, F. Roblot, R. Hocquemiller, A. Cavé, *J. Ethnopharmacol.* **1992**, *37*, 159-164 ; b) V. P. Papageorgiou, A. N. Assimopoulou, E. A. Couladouros, D. Hepworth, K. C. Nicolaou, *Angew. Chem. Int. Ed.* **1999**, *38*, 270-301.

[3] S. Padhye, P. Dandawate, M. Yusufi, A. Ahmad, F. H. Sarkar, *Med. Res. Rev.* **2012**, *32*, 1131-1158.

[4] a) E.A. Hillard, F. Caxico de Abreu, D.C. Melo Ferreira, G. Jaouen, M. Oliveira Fonseca Goulart, C. Amatore, *Chem. Commun*. **2008**, 2612-2628; b) M. Elhabiri, P. Sidorov, E. Cesar-Rodo, G. Marcou, D. A. Lanfranchi, E. Davioud-Charvet, D. Horvath, A. Varnek, *Chemistry Eur. J.* **2015**, *21*, 3415-3424; c) K. W. Wellington, *RSC Advances* **2015**, *5*, 20309-20338.

[5] a) A. Mahapatra, S. P. Mativandlela, B. Binneman, P. B. Fourie, C. J. Hamilton, J. J. Meyer, F. van der Kooy, P. Houghton, N. Lall, *Bioorg Med Chem.* **2007**, *15*, 7638-7646; b) J.-S. Yu. *Synlett* **2014**, *25*, 2377-2378.

[6] a) M. J. Shearer, P. Newman, *J. Lipid Res.* **2014**, *55*, 345-362.

[7] a) L. Salmon-Chemin, A. Lemaire, S. De Freitas, B. Deprez, C. Sergheraert, E. Davioud-Charvet, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 631-635; b) L. Salmon-Chemin, E. Buisine, V. Yardley, S. Kohler, M.-A. Debreu, V. Landry, C. Sergheraert, S. L. Croft, R. L. Krauth-Siegel, E. Davioud-Charvet, *J. Med.* Chem. **2001**, *44*, 548-565.

[8] G. Saxena, S. W. Farmer, R. E. Hancock, G. H. Towers, *J. Nat. Prod.* **1996**, *59*, 62-65.

[9] R. B. Gupta, R. N. Khanna, N. N. Sharma, *Indian J. Chem.* **1977**, 15B, 394-5 ; b) R. B. Gupta, R. N. Khanna, V. P. Manchanda, *Indian J. Chem.* **1979**, 18B, 217-218.

[10] Y. Gu, P. K. Li, Y. C. Lin, Y. Rikihisa, R. W. Brueggemeier, *J. Steroid Biochem. Mol. Biol.* **1991**, *38*, 709-715.

[11] M. E. Rateb, W. E. Houssen, M. Arnold, M. H. Abdelrahman, H. Deng, W. T. Harrison, C. K. Okoro, J. A. Asenjo, B. A. Andrews, G. Ferguson, A. T. Bull, M. Goodfellow, R. Ebel, M. Jaspars, *J. Nat. Prod.* **2011**, *74*, 1491-1499.

[12] C. C. Nawrat, C. J. Moody, *Angew Chem Int Ed Engl.* **2014**, *53*, 2056-2077.

[13] a) L. Boisvert, P. Brassard, *J. Org. Chem.* **1988**, *53*, 4052-4059; b) M. Miyashita, T. Yamasaki, T. Shiratani, S. Hatakeyama, M. Miyazawaa, H. Irie, *Chem. Commun.* **1997**, 1787-1788.

[14] a) J. Tou, W. Reusch, *J. Org. Chem.* **1980**, *45*, 5012-14; b) R. L. Nunes, L. W. Bieber, *Tetrahedron Lett*. **2001**, *42*, 219-221.

[15] a) Y.-F. Ji, Z.-M. Zong, X.-Y. Wei, G.-Z. Tu, L. Xu, L.-T. He, *Synth. Commun*. **2003**, *33*, 763-772; b) J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc*. **2007**, *129*, 9536-9537.

[16] a) J. G. Bauman, R. Hawley, H. Rapoport, *J. Org. Chem*. **1985**, *50*, 1573-1577; b) B. Kesteleyn, N. De Kimpe, *J. Org. Chem*. **2000**, *65*, 640-644.

[17] T. Müller, L. Johann, B. Jannack, M. Bruckner, D.A. Lanfranchi, H. Bauer, C. Sanchez, V. Yardley, C. Deregnaucourt, J. Schrevel, M. Lanzer, R.H. Schirmer, E. Davioud-Charvet, *J. Am. Chem. Soc*. **2011**, *133*, 11557-11571.

[18] K. Ehrhardt, E. Davioud-Charvet, H. Ke, A. Vaidya, M. Lanzer, M. Deponte, *Antimicrob. Agents Chemother.* **2013**, *57*, 2114-2120.

[19] M. Bielitza, D. Belorgey, K. Ehrhardt, L. Johann, D. A. Lanfranchi, V. Gallo, E. Schwarzer, F. Mohring, E. Jortzik, D. L. Williams, K. Becker, P. Arese, M. Elhabiri, E. Davioud-Charvet, *Antioxid. Redox Signal.* **2015**, *22*, 1337-1351.

[20] D. A. Lanfranchi, E. Cesar-Rodo, B. Bertrand, H-H. Huang, L. Day, L. Johann, M. Elhabiri, K. Becker, D. L. Williams, E. Davioud-Charvet, *Org. Biomol. Chem.* **2012***, 10,* 6375-6387.

[21] J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc*. **1970**, *92*, 1651-1659.

[22] a) G. Bringmann, G. Zhang, A. Hager, M. Moos, A. Irmer, R. Bargou, M. Chatterjee, *Eur. J. Med. Chem*. **2011**, *46*, 5778-5789 ; b) D. Mal, K. Ghosh, S. Jana, *Org Lett.* 2015, *17*, 5800-5803.

[23] B. C. Pearce*,* R. A. Parker, M. E. Deason, D. D. Dischino, E. Gillespie, A. A. Qureshi, K. Volk, J. J. Wright, *J. Med. Chem.* **1994**, *37*, 526-541.

[24] S. H. Kim*,* J. R. Gunther, J. A. Katzenellenbogen, *Org. Lett.,* **2008**, *10*, 4931-4934.

[25] N. Minanmi, S. Kikima, *Chem. Pharm. Bull.,* **1979***, 6,* 1490-1494.

[26] B. Quiclet-Sire, S. Z. Zard, *Top Curr. Chem*. **2006**, *264*, 201-236.

[27] a) A. Cordero-Vargas, B. Quiclet-Sire, S. Z. Zard, *Org. Lett.*, **2003**, *5*, 3717-3719 ; b) A. Cordero-Vargas, I. Pérez-Martín, B. Quiclet-Sire, S. Z. Zard, *Org. Biomol. Chem.* **2004**, *2*, 3018-3025.

[28] a) D. A. Lanfranchi, L. Johann, D. L. Williams, E. Davioud-Charvet, Eur. Pat. Appl., EP 11305346, 2011; b) D. A. Lanfranchi, L. Johann, D. L. Williams, E. Davioud-Charvet, E. Cesar-Rodo, PCT Int. Appl. WO 2012131010 A1 20121004, 2012; c) R. Guignard, *Synlett* **2013**, *24*, 157-160.

[29] M. Van der Mey, K. M. Bommelé, H. Boss, A. Hatzelmann, M. Van Slingerland, G. J. Sterk, H. Timmerman, *J. Med. Chem.* **2003**, *46*, 2008-2016.

[30] a) A. Pelter, S. M. A. Elgendy, *J. Chem. Soc. Perkin 1* **1993**, *16*, 1891-1896; b) P. Bachu, J. Sperry, M. A. Brimble, *Tetrahedron* **2008**, *64*, 3343-3350.

[31] H.-J. Teuber, W. Rau, *Chem. Berichte* **1953**, *86*, 1036-1047.

[32] a) L. Krishna Kumari, M. Pardhasaradhi, *Indian J. of Chem. Sec. B* **1982**, *21*, 1067- 1070; b) N. Kakusawa, K. Inui, J. Kurita, T. Tsuchiya, *Heterocycles* **1996**, *43*, 1601-1604.

[33] a) G. Fawaz, L. F. Fieser, *J. Am. Chem. Soc.* **1950**, *72*, 996-1000; b) R. Schmid, F. Goebel, A. Warnecke, A. Labahn, *J. Chem. Soc*., *Perkin Trans. 2*, **1999**, 1199-1202; c) A. Bohle, A. Schubert, Y. Sun, W. R. Thiel, *Adv*. *Synth*. *Catal*. **2006**, *348*, 1011-1015.

[34] V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862-1891.

[35] Y. Tanoue, K. Sakata, M. Hashimoto, S. Morishita, M. Hamada, N. Kai, T. Nagai, *Tetrahedron* **2002**, *58*, 99-104.

[36] J. R. Grunwell , A. Karipides , C. T. Wigal , S. W. Heinzman , J. Parlow , J. A. Surso , L. Clayton , F. J. Fleitz, M. Daffner , J. E. Stevens, *J. Org. Chem.* **1991**, *56*, 91-95.

[37] a) B. M. Trost, W. H. Pearson, *Tetrahedron Lett.* **1983**, *24*, 269-272; b) D. A., Lanfranchi, G. Hanquet, *J. Org. Chem*. **2006**, *71*, 4854-4861.

[38] M. C. Venuti, B. E. Loe, G. H. Jones, J. M. Young, *J. Med. Chem,* **1988**, *31*, 2132-2136.

[39] S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc*. **1974**, *96*, 7807-7808.

[40] K. P. Mandal, F. Gao, Z. Lu, Z. Ren, Z. Ramesh, J. S. Birtwistle, K. Kaluarachchi, X. Chen, R. C. Bast, W. Liao, J. S. McMurray, *J. Med. Chem*. **2011**, *54*, 3549-3563.

[41] a) N. Jacobsen, K. Torssell, *Liebigs Ann. Chem.* **1972**, *763*, 135-147; b) N. Jacobsen, K. Torssell, *Acta. Chem. Scand.* **1973**, *27*, 3211-3216.

[42] T. Ohgiya, S. Nishiyama, *Tetrahedron Letters* **2004**, *45*, 6317-6320.

[43] A. Martínez, J. C. Barcia, A. M. Estévez, F. Fernández, L. González, J. C. Estévez, R. J. Estévez, *Tetrahedron Lett.* **2007**, *48*, 2147-2149.

[44] K. F. Eidman, P. J. Nichols, In e-EROS *Encyclopedia of Reagents for Organic Synthesis*, (Eds: John Wiley & Sons, Ltd), **2001**, DOI: 10.1002/047084289X.rt236.pub2.

[45] a) G. Paiaro, A. Musco, G. Diana, *J. Organometal. Chem.* **1965**, *4*, 466-474; b) J. Andrieux, D. H. R. Barton, H. Patin, *J. Chem. Soc., Perkin Trans. 1* **1977**, 359-363; c) D. G. Batt, G. D. Maynard, J. J. Petraitis, J. E. Shaw, W. Galbraith, R. R. Harris, *J. Med. Chem.* **1990**, *33*, 360-370; d) M. Taniura, Y.Tamai, "Process for Producing 2-Methyl-1-naphthol by Isomerization of 2-Methylene-1-tetralone", Eur. Pat. Appl. EP 558069 A1 19930901, **1993**.

[46] G. Leroy, D. Peeters, C. Wilante, *J. Mol. Structure: THEOCHEM* **1982**, *5*, 217-233.

[47] a) L. F. Fieser, E. Berliner, F. J. Bondhus, F. C. Chang, W. G Dauben, M. G. Ettlinger, G. Fawaz, M. Fields, M. Fieser, C. Heidelberger, H. Heymann, A. M. Seligman, W. R. Vaughan, A. G. Wilson, E. Wilson, M. Wu, M. T. Leffler, K. E. Hamlin, R. J. Hathaway, E. J. Matson, E. E. Moore, M. B. Moore, R. T. Rapala, H. E. Zaugg. *J. Am. Chem. Soc.* **1948**, *70*, 3151-3155; b) L. F. Fieser, A. P. Richardson, *J. Am. Chem. Soc.* **1948**, *70*, 3156-3165; c) L. Salmon-Chemin, A. Lemaire, S. De Freitas, B. Deprez, C. Sergheraert, E. Davioud-Charvet, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 631-635; d) L. Salmon-Chemin, E. Buisine, V. Yardley, S. Kohler, M.-A. Debreu, V. Landry, C. Sergheraert, S. L. Croft, R. L. Krauth-Siegel, E. Davioud-Charvet, *J. Med.* Chem. **2001**, *44*, 548-565.

[48] a) K. Lopez-Shirley, F. Zhang, D. Gosser, M. Scott, S. R. Meshnick, *J. Lab. Clin. Med.* **1994**, *123*, 126-130; b) J. J. Kessl, B. B. Lange, T. Merbitz-Zahradnik, K. Zwicker, P. Hill, B. Meunier, H. Pálsdóttir, C. Hunte, S. Meshnick, B. L. Trumpower, *J. Biol. Chem.* **2003**, *278*, 31312-31318.

[49] W. Trager, J. B. Jensen. *Science* **1976**, *193*, 673-675.

[50] C. Lambros, J. P. Vanderberg. *J. Parasitol.* **1979**, *65*, 418-420.

[51] M. Smilkstein, N. Sriwilaijaroen, J. X. Kelly, P. Wilairat, M. Riscoe, *Antimicrob. Agents Chemother.* **2004**, *48*, 1803-1806.

[52] D. Beez, C. P. Sanchez, W. D. Stein, M. Lanzer. *Antimicrob. Agents Chemother.* **2011**, *55*, 50-55.

[53] ChemBioOffice 2012, PerkinElmer, Inc., **2012**.

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Entry for the Table of Contents

Catch Phrase

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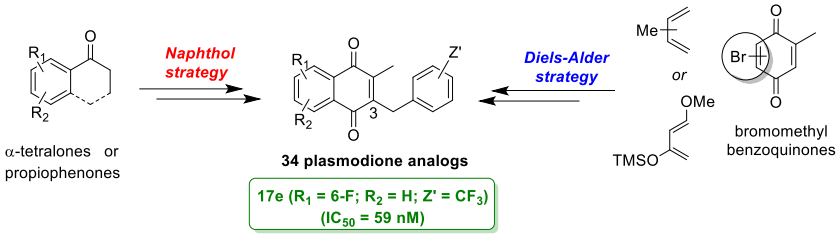
Page – Page

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



A platform of synthetic methodologies to prepare potent antimalarial polysubstituted 3-benzylmenadione derivatives were established by regioselective strategies (i) *via* the naphthol route, starting from either a α-tetralone, or a propiophenone, or (ii) *via* the regioselective Diels-Alder reaction.