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Synthetic studies toward 1,2-dioxanes as precursors of potential endoperoxide-containing antimalarials

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ABSTRACT

Introduction in therapy of the naturally occurring trioxane artemisinin opened a new era in malaria treatment and prompted the development of semisynthetic and synthetic derivatives characterized by the presence of the key peroxide bridge. The 1,2-dioxane ring is present in some natural endoperoxides such as plakortin and dihydroplakortin, which are endowed with interesting antimalarial properties. Here we describe the development of a versatile stereocontrolled synthetic strategy to 1,2-dioxanes functionalized at the critical C3, C4, and C6 positions, potentially useful for the development of innovative antimalarials.

Malaria is a severe world-wide health problem mainly affecting developing countries and causing high social and economic costs.[1] Due to the lack of a vaccine and to the emergence of parasites resistant to well-established antimalarial therapies, there is an urgent need for new, effective, and affordable drugs.[2] The introduction in therapy of artemisinin (**1**, Fig. 1), a naturally occurring endoperoxide sesquiterpene lactone, and of its semisynthetic derivatives, represented a breakthrough in the malaria treatment. To overcome the problems related to resistance, the World Health Organization recommends the use of artemisinin-based combination therapies (ACTs) in all malaria-endemic regions since artemisinins are among the few molecules active in the treatment of multidrug resistant *Plasmodium falciparum* malaria.[3,4]

Although still matter of debate,[5] considerable evidences suggest that the peroxide bond of **1** has a key role in antimalarial activity, being reductively activated by heme iron(II),[6–10] and leading to the formation of carbon-centered free radicals, toxic for the parasite. A number of synthetic cyclic peroxides are being developed as low cost alternatives to the expensive artemisinins.[11,12] Among the six-membered cyclic peroxide scaffolds explored, 1,2,4,5-tetraoxanes and spiro 1,2,4-trioxanes provided highly potent antimalarials (e.g., **2** and **3**),[13–17] while the 1,2-dioxane ring, although occurring in several natural compounds such as peroxyplakoric acids,[18,19] Yingzhaosu A (**4**),[20] Yingzhaosu C,[21] and plakortin (**5**),[22] was not

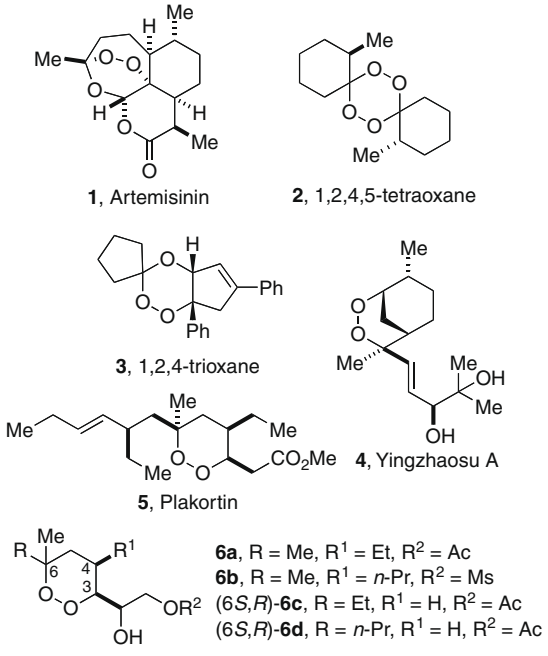

Figure 1. Examples of natural and synthetic antimalarials (**1**–**5**) and target 1,2-dioxanes (**6a**–**d**).

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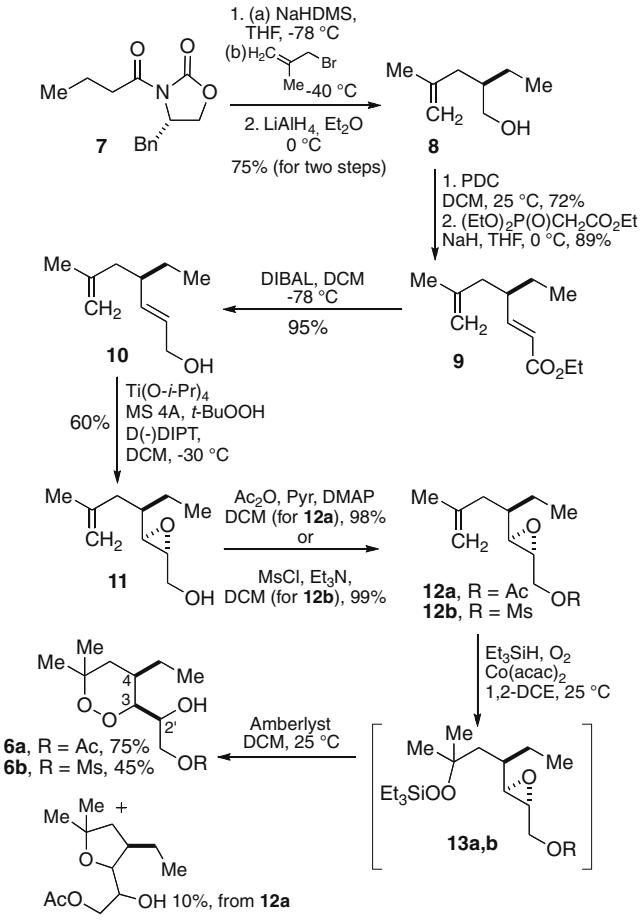
widely synthetically explored.[23] It has been reported that, in general, the 1,2-dioxane ring system may provide compounds less active than 1,2,4-trioxanes and 1,2,4,5-tetraoxanes.[24,25] Moreover, the 1,2-dioxane derivative arteflene (a synthetic analogue of **4**), has been discontinued during Phase II clinical trials due to high recrudescence rate.[26] However, appropriate decoration of the 1,2-dioxane system may lead to an increased antimalarial potency. Consequently, the development of appropriate synthetic strategies is required to explore the structure–activity relationships (SARs) for this scaffold. Previously, we reported the structural characterization and the antimalarial activity of plakortin,[22,27,28] an endoperoxide isolated from the Caribbean sponge *Plakortis simplex* and characterized by a relatively simpler skeleton with respect to artemisinins, although less potent. We attempted a semisynthetic approach to analogues of plakortin, but the reduced availability of the sponge, together with synthetic constrains linked to the poor stability of the 1,2-dioxane system during functional group elaboration, led to a limited number of semisynthetic derivatives. Furthermore, none of the analogues synthesized showed significantly higher in vitro activity against different *P. falciparum* strains with respect to the natural counterpart. Consequently, to explore SARs and to identify novel 1,2-endoperoxide antimalarials, we started some preliminary synthetic studies toward 1,2-dioxanes **6a**–**d**, described here, bearing alkyl moieties at C6 or C4 and a protected 1,2-diol functionality at C3. The latter is a versatile functional group whose activation to form reactive intermediates can be potentially exploited for the decoration of the 1,2-dioxane scaffold. Although the simplest route for the construction of the 1,2-dioxane ring could be the [4+2] cycloaddition of oxygen to 1,3-dienes,[29] this methodology does not provide control of the stereochemistry. Consequently, for the synthesis of compounds **6a**–**d**, we followed the strategy outlined by Xu et al. for the synthesis of Yingzhaosu C.[21] Accordingly, the peroxide functionality was introduced by using the Isayama peroxidation reaction,[30] followed by cyclization through an intramolecular peroxide-mediated stereoselective epoxy ring opening. In the case of derivatives **6c**,**d**, the Isayama hydroperoxydation reaction furnished epimeric mixtures at C6. However, due to the hypothesized radical-mediated mechanism of the Isayama reaction, no attempts were made to develop a stereoselective methodology based on this protocol (e.g., use of chiral cobalt(II) ligands).[31,32]

The synthesis of 3,4,6-trisubstituted 1,2-dioxanes **6a**,**b** is described in Scheme 1. (*S*)-4-Benzyl-3-butyryloxazolidin-2-one **7**[33] was converted into the corresponding sodium enolate by treatment with NaHDMS in THF at −78 °C and the latter was alkylated with 3-bromo-2-methylpropene. $LiAlH_4$-promoted reductive cleavage of the chiral auxiliary afforded alcohol **8** in 75% overall yield. The primary alcohol of **8** was oxidized to the corresponding aldehyde by using an excess of PDC in dichloromethane (DCM). The resulting highly volatile aldehyde intermediate was converted into the corresponding α,β-unsaturated ester **9** via Wadsworth–Emmons olefination using triethylphosphonoacetate and sodium hydride. Reduction of **9** with DIBAL in DCM at −78 °C gave access to the allylic alcohol **10**, which was in turn submitted to a Sharpless asymmetric epoxidation using D-(−)-diisopropyl tartrate as the chiral auxiliary. (2*R*,3*R*)-Epoxy alcohol **11** was converted into the corresponding acetate **12a** by treatment with acetic anhydride in the presence of pyridine and *N*,*N*-dimethylaminopyridine. Following Isayama protocol,[34] regioselective hydroperoxysilylation of **12a** was achieved by treatment with cobalt(II) acetyl acetonate and triethylsilane under an oxygen atmosphere. In an attempt to reduce the number of steps, intermediate **13a** was not isolated, but the addition of acidic resin Amberlyst-15 directly to the reaction mixture resulted into deprotection of the silyl-protected hydroperoxide followed by a nucleophilic attack of the free hydroperoxy group on the epoxide.[35] Starting from

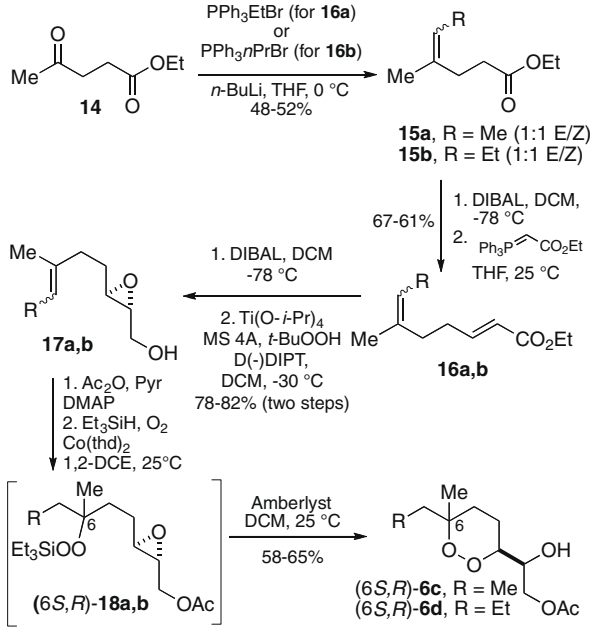


Scheme 1. Synthesis of 3,4,6-trisubstituted 1,2-dioxanes **6a**,**b**.

epoxide **12a**, the above described one-pot three-step procedure stereoselectively afforded the cyclization product **6a**[36] in 75% overall yield, along with a small amount (~10%) of a tetrahydrofuran derivative probably arising from a reduction of the peroxide group to the corresponding alcohol before intramolecular cyclization. In order to broaden the possibility of the diol functionalization at C3, mesylate **6b**[37] was also synthesized in 45% yield starting from intermediate **12b**, in turn prepared by treatment of alcohol **11** with mesyl chloride and triethylamine in DCM.

The synthesis of intermediates (6*S*,*R*)-**6c**,**d** is described in Scheme 2. Levulinic acid methyl ester **14** was selected as a suitable starting material for the synthesis of both (6*S*,*R*)-**6c** and (6*S*,*R*)-**6d**. Accordingly, compound **14** was easily converted into the corresponding olefins **15a** and **15b** through the standard Wittig protocol, using ethyltriphenylphosphonium bromide or *n*-propyltriphenylphosphonium bromide, respectively.

The resulting esters were obtained as 1:1 mixture of *E* and *Z* olefins. In the subsequent steps of the synthetic pathway, reduction of the ester group performed by using DIBAL in DCM at −78 °C furnished the corresponding aldehydes which were immediately reacted with (carbomethoxymethylidene)triphenylphosphorane to afford the α,β-unsaturated esters **16a**,**b**. In this case, the olefination reaction resulted into the selective formation of the conjugated *E*-olefins (98:2 *E*/*Z* ratio). Following the synthetic sequence already described for the synthesis of **6a**, DIBAL promoted reduction of the esters **16a**,**b** afforded the corresponding allylic alcohols which were submitted to the Sharpless epoxidation protocol, stereoselectively furnishing the epoxide intermediates **17a**,**b**. Protection of the primary alcohol of **17a**,**b** as the corresponding acetate ester was followed by the hydroperoxysilylation reaction, firstly attempted

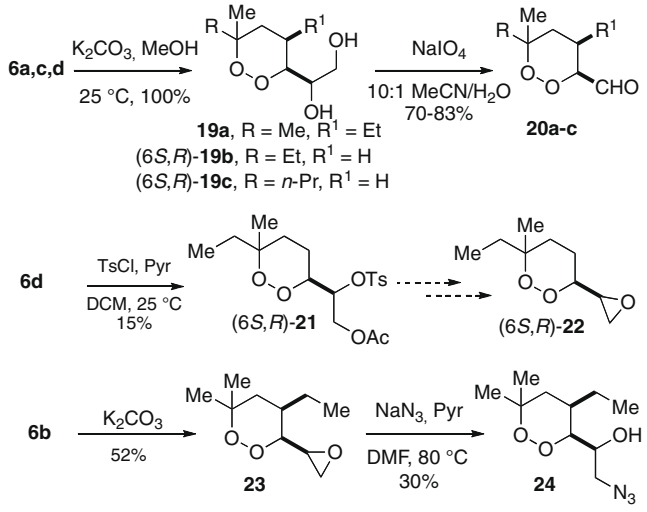


Scheme 2. Synthesis of 3,6-disubstituted 1,2-dioxanes (6*S*,*R*)-**6c**,**d**.

by using cobalt(II) acetylacetonate as the catalyst. However, in this case, the trisubstituted olefin had a lower reactivity than the previously used disubstituted olefin. As reported in the literature,[31] the use of cobalt(II) bis[2,2,6,6-tetramethylheptane-3,5-dienoate] resulted in the formation of the desired intermediates. Following our developed protocol, cyclization of (6*S*,*R*)-**18a**,**b** to afford 1,2-dioxanes (6*S*,*R*)-**6c**,**d** was performed without preliminary isolation of the silylated intermediates and resulted in good overall yield.

As shown in Scheme 3, intermediates **6a–d** were further elaborated to furnish reactive intermediates potentially useful for the decoration of the 1,2-dioxane moiety. Intermediates **6a**,**c**,**d** were converted into the corresponding diols **19a–c**[38] by potassium carbonate-promoted hydrolysis of the ester group, performed in methanol at 25 °C. The diol moiety was then converted into aldehydes **20a–c**[39] by treatment with sodium periodate in a 5:1 mixture of acetonitrile and water.

Another versatile functional group, which could allow the chemical derivatization of C3 position, is represented by the epoxide ring. In a first attempt to obtain this ring, secondary alcohol **6d** was converted into the corresponding tosylate with the final aim of hydrolyzing the ester functionality of **21** affording, under basic conditions, epoxide **22**. However, due to steric constrain, the tosylation reaction occurred in low yield. Consequently, an alternative synthetic pathway for the construction of the epoxide ring was pursued. At this purpose, the synthesis of mesylate **6b** was undertaken, and the latter was cyclized under alkaline conditions affording epoxide **23**.[40] Finally, epoxide **23** was treated with an excess of sodium azide in *N*,*N*-dimethylformamide to afford azide **24**.



Scheme 3. Synthesis of diols **19a–c** and further elaboration of the *cis*-diol moiety.

In conclusion, we described herein synthetic studies toward 1,2-dioxane rings functionalized at C3, C4, and C6 positions. Control of stereochemistry was achieved at both C3 and C4. Chemical derivatization at the C3 has been performed by the synthesis of aldehydes and epoxides. With the final aim of synthesizing potential antimalarials, the versatile aldehyde and epoxide functional groups can be exploited for the decoration of the 1,2-dioxane scaffold.

Acknowledgment

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35. A mixture of **12a** (0.25 mmol) and $Co(acac)_2$ (11 mg) in 1,2-dichloroethane (5 mL), was stirred under an oxygen atmosphere. To the resulting pink solution, triethylsilane (82 μL, 0.52 mmol) was added, followed by a catalytic amount of *t*-BuOOH (6 M in nonane). The resulting dark green solution was stirred at 25 °C until the starting material disappeared. Amberlyst-15 (20 mg) was subsequently added to the reaction mixture which was stirred at 25 °C for 3 h. The resin was removed by filtration and the solvent was evaporated to afford a crude product which was purified by flash chromatography (1:2 diethyl ether/petroleum ether) to afford **6a** as a colorless oil (75%).
36. (3*S*,4*R*,2′*S*)-**6a**: ^{1}H NMR ($CDCl_3$) δ 4.24 (dd, 1H, J = 2.7, 11.9 Hz), 4.12–4.01 (m, 2H), 3.82 (dd, 1H, J = 3.2, 9.4 Hz), 2.37 (d, 1H, J = 7.0 Hz), 2.04 (s, 3H), 1.75 (m, 2H), 1.53 (m, 1H), 1.23 (s, 3H), 1.20 (m, 2H), 1.14 (s, 3H), 0.84 (t, 3H, J = 7.3 Hz). MS-ESI (m/z) 269 $(M+Na)^+$.
37. (3*S*,4*R*,2′*S*)-**6b**: ^{1}H NMR ($CDCl_3$) δ 4.44 (dd, 1H, J = 3.5, 11.9 Hz, 4.27 (m, 1H), 4.18 (m, 1H), 3.83 (m, 1H), 3.07 (s, 3H), 2.60 (d, 1H, J = 7.6 Hz), 1.85–1.52 (m, 3H), 1.28 (s, 3H), 1.26 (m, 1H), 1.21 (s, 3H), 0.92 (t, 3H, J = 7.2 Hz). MS-ESI (m/z) 305 $(M+Na)^+$.
38. (3*S*,4*R*,2′*R*)-**19a**: ^{1}H NMR ($CDCl_3$) δ 3.90 (m, 2H), 3.72 (m, 2H), 2.58 (d, 1H, J = 8.5 Hz), 2.10 (m, 1H), 1.82–1.73 (m, 2H), 1.55 (m, 1H), 1.29 (s, 3H), 1.27 (m, 2H) 1.21 (s, 3H), 0.91 (t, 3H, J = 7.3 Hz). ^{13}C NMR (CD_3OD) δ 87.1, 78.8, 72.1, 62.3, 39.2, 33.9, 26.6, 24.4, 22.6, 9.8. MS-ESI (m/z) 227 $(M+Na)^+$.
39. (3*S*,4*R*)-**20a**: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 4.01 (d, 1H, J = 7.33 Hz), 1.78 (dd, J = 4.7, 13.2 Hz), 1.72–1.63 (m, 1H), 1.42–1.33 (m, 3H), 1.31 (s, 3H), 1.23 (s, 3H), 0.92 (t, 3H, J = 7.3 Hz). MS-ESI (m/z) 195 $(M+Na)^+$.
40. (3*S*,4*R*,2′*S*)-**23**: ^{1}H NMR ($CDCl_3$) δ 3.31 (dd, 1H, J = 6.2, 9.7 Hz), 2.86–2.83 (m, 1H), 2.73 (m, 1H), 1.84–1.78 (m, 3H), 1.36 (s, 3H), 1.35 (m, 1H), 1.18 (s, 3H), 0.95 (t, 3H, J = 7.4 Hz). MS-ESI (m/z) 209 $(M+Na)^+$.