

Structure–Activity Relationships of Synthetic Tricyclic Trioxanes Related to Artemisinin: The Unexpected Alkylative Property of a 3-(Methoxymethyl) Analog

Olivier Provot,^{*,[a]} Boris Camuzat-Dedenis,^[a] Mohamed Hamzaoui,^[a] Henri Moskowicz,^[a] Joëlle Mayrargue,^[a] Anne Robert,^[b] Jérôme Cazelles,^[b] Bernard Meunier,^[b] Fatima Zouhiri,^[c] Didier Desmaële,^[c] Jean d'Angelo,^{*,[c]} Jacqueline Mahuteau,^[c] Frédérick Gay,^[d] and Liliane Cicéron^[d]

Keywords: Antiprotozoals / Artemisinin / Trioxanes / Heme / Structure–activity relationships / Drug research

A clear-cut correlation between antimalarial potency and the alkylative property of synthetic tricyclic trioxanes **5–10** is reported. Thus, trioxanes **5** and **7**, substituted at the C-5a angular position by a methyl or a cyano group, proved to be completely devoid of antimalarial activity, and did not alkylate the heme model Mn^{II}TPP. In contrast, both the anti-*Plasmodium* activity and the alkylative property were

restored in the C-5a-unsubstituted analog **8**, bearing a methoxymethyl group at C-3. Reaction of **8** with Mn^{II}TPP furnished the covalent adduct **18**, resulting from trapping of the methoxymethyl radical by the heme model. All these results reinforce the hypothesis that the metalloporphyrin closely interacts with the peroxide bond of the drug to bring about activation of these trioxane antimalarial agents.

Introduction

The protozoan *Plasmodium falciparum* is the pathogen responsible for the most life-threatening form of malaria, causing the deaths of in excess of 2 million people annually. As the present deterioration in malaria control is largely due to the fact that this parasite is acquiring multidrug resistance, there is a great impetus for the development of new effective antimalarials. Currently used in China and South-East Asia, the sesquiterpene lactone 1,2,4-trioxane artemisinin (**1**) (*Qinghaosu*), isolated from *Artemisia annua* L., constitutes the prototype of endoperoxides, a new class of promising antimalarial agents. Artemisinin and semi-synthetic derivatives clear the peripheral blood of the parasite at nanomolar concentrations, and have proved to be highly selective, safe antimalarials.^[1] There is strong evidence to suggest that once inside the *Plasmodium*, artemisinin reacts first with intraparasite heme, giving rise to free radicals.^[2] Computational studies have shown that artemisinin and heme first dock in configuration **2**, which allows the heme iron center to cleave the endoperoxide bridge.^[3] This activation phase is followed by homolytic cleavage of the per-

oxide moiety, which initially gives rise to oxyl radicals. These radicals then rearrange to produce the C-centered radicals **3** and/or **4**. The latter species would seem very likely to be the entities responsible for antimalarial activity, which function by ultimately alkylating nearby macromolecules within the *Plasmodium*.^[4] Specific alkylations of proteins have thus been identified at pharmacologically relevant concentrations of artemisinin derivatives.^[5] Supporting evidence that these alkylation reactions involve the generation of drug radicals in the vicinity of heme was recently provided by the unambiguous characterization of a coval-

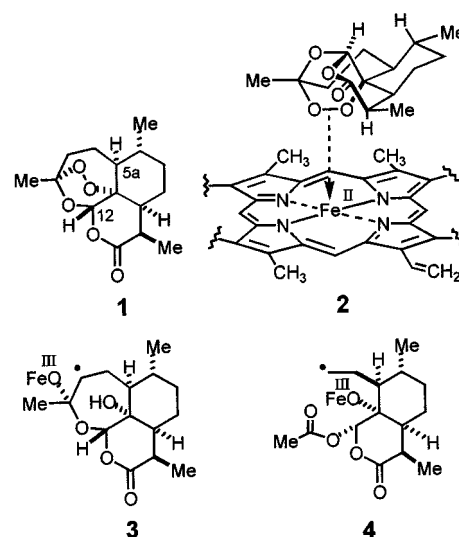


Figure 1. Proposed heme–artemisinin interaction

ent adduct between radical **4** and an Mn^{II} heme model.^[6–8]

As part of a systematic program devoted to the development of new simplified artemisinin analogs, we recently synthesized tricyclic trioxanes **5** and **6** bearing a methyl group

[a] Laboratoire de Chimie Organique Associé au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud, 5 rue J.-B. Clément, F-92296 Châtenay-Malabry, France
Fax: (internat.) + 33-1/46835223
E-mail: provot@pop.u-psud.fr

[b] Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, F-31077 Toulouse cedex 4, France

[c] Unité de Synthèse Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud, 5 rue J.-B. Clément, F-92296 Châtenay-Malabry, France
Fax: (internat.) + 33-1/46835652
E-mail: jean.dangelo@cep.u-psud.fr

[d] Laboratoire d'Epidémiologie et de Chimiorésistance du Paludisme, Service de Parasitologie, Groupe Hospitalier Pitié-Salpêtrière, 47–83 Boulevard de l'Hôpital, F-75651 Paris, France

at the C-5a angular position and reported that these compounds were devoid of antimalarial activity.^{[9][10]} In this paper, we now report that compound **7**, bearing a cyano group at C-5a,^{[11][12]} is also inactive, whereas analogs **8**, **9**, and **10**, lacking the angular C-5a substituent, show substantial anti-*Plasmodium* potencies. Accordingly, the 5a-unsubstituted analog **8**, after reductive activation, was found to be capable of alkylating a heme model, namely Mn^{II}tetraphenylporphyrin, to give the covalent adduct **18**. On the contrary, when 5a-substituted trioxanes **5** and **7** were used under similar conditions, no porphyrin–drug adducts could be identified.

Results and Discussion

Trioxanes **7**, **8**, and **9** were prepared by the photooxidation of enol ethers **13**, according to the method of Jefford and Posner,^[13] involving acidic rearrangement of the intermediate dioxetanes **14**. The requisite starting enol ethers **13** were in turn prepared by addition of Wittig reagent **12** to oxo nitriles **11**.^{[11][12]} Configurational assignments for trioxanes **8** and **9** were established by ¹H-NMR spectroscopy, including long-range coupling between 5a-H and 12-H in isomer **8** ($J = 1.5$ Hz).

Antimalarial Activities

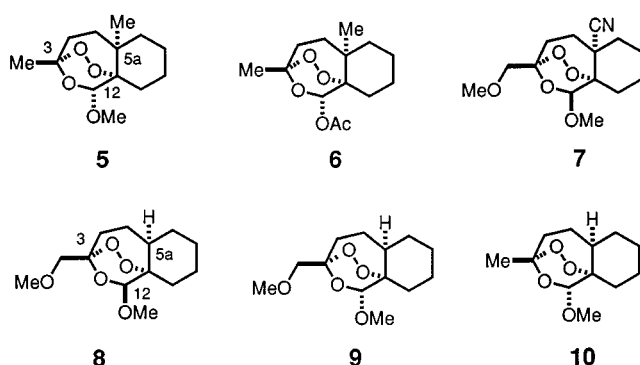
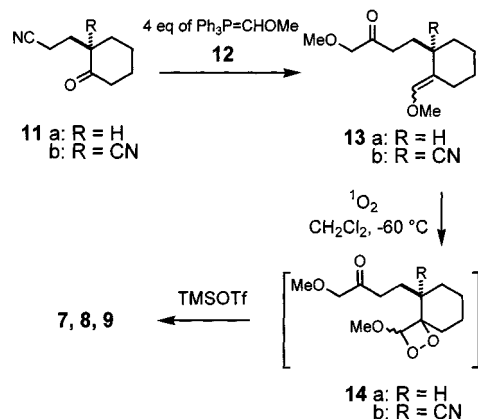


Figure 2. Structures of trioxanes **5**–**10**



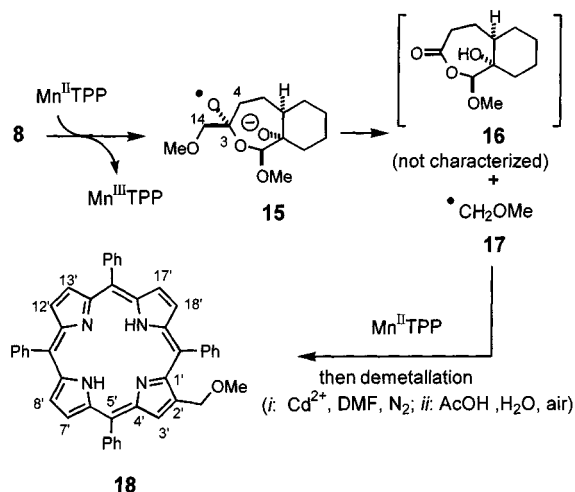
Scheme 1. Synthesis of trioxanes **7**–**9**

When tested against the “H” clone of *P. falciparum*,^[14] enantiomerically pure trioxanes **5**, **6** and **7** proved to be completely devoid of biological activity in the concentration range 20–500 nM. In comparison, artemisinin (**1**) exhibited an IC_{50} value of 19 nM on the same strain of *Plasmodium*. In sharp contrast, *racemic* trioxanes **8** and **9** display substantial antimalarial activities, having IC_{50} values of 0.7 μ M and 1.3 μ M, respectively, on the chloroquine-sensitive *Plasmodium falciparum* FCR3 (reference compound chloroquine showed an IC_{50} value of 0.19 μ M on this strain). A high antiprotozoal potency has also been reported for *racemic* trioxane **10**, structurally analogous to **5**, but lacking the methyl group at C-5a [IC_{50} value of 8 nM on the (W-2) Indochina clone of *P. falciparum*].^[13]

Alkylative Properties

The heme model used in the alkylation experiments was the hydrophobic complex Mn^{II}TPP, generated *in situ* by *n*Bu₄NBH₄ reduction of Mn^{III}tetraphenylporphyrin chloride [Mn^{III}(TPP)Cl].^[6–8] This synthetic analog of heme was expected to give a limited number of alkylated products owing to its four-fold symmetry. No covalent adducts could be characterized when trioxanes **5** and **7** were exposed to this heme model. In contrast, trioxane **8** furnished, after demetallation under mild conditions, adduct **18** in 20% yield. Formation of **18** can be rationalized by invoking initial one-electron reduction and homolytic cleavage of the peroxide bridge of **8**, giving oxyl radical **15**. However, subsequent rearrangement of **15** did not involve the breaking of C-3–C-4 bond to give a primary C-centered radical of type **4**, as observed for artemisinin (**1**),^[7] but rather cleavage of the C-3–C-14 bond, which furnished an unidentified neutral fragment (presumably lactone **16** or a derivative thereof) and methoxymethyl radical **17**. Trapping of this radical with Mn^{II}TPP, followed by demetallation of the porphyrin ring, finally afforded adduct **18**. This result indicates that trioxane **8** is able to generate C-centered radicals, acting as alkylating species toward the heme model, but in a different way from that reported for artemisinin and other trioxane analogs.^[8] Justification for the fragmentation [**15** $\rightarrow$ **16** + **17**] was provided by the difference in stability between the free ethyl radical (as a model for the primary C-centered radical of type **4**) and methoxymethyl radical **17**, namely 5 ± 1 kcal mol⁻¹ in favor of the latter, estimated on the basis of the homolytic dissociation energies of the corresponding alkanes.^[15]

The above results clearly established that the replacement of the hydrogen atom at C-5a by a methyl or a cyano group in our synthetic trioxanes was detrimental to their biological activity and also, under the present conditions, to their alkylative property. Thus, the inactive 5a-substituted trioxanes **5** and **7** did not alkylate the heme model. In contrast, both anti-*Plasmodium* activity and alkylative property were restored in the 5a-unsubstituted analog **8**. This lack of reactivity of 5a-substituted trioxanes can be rationalized by examining the activation phase of these endoperoxides. In-

Scheme 2. Reaction of trioxane **8** with heme model Mn^{II} TPP

spection of complex **19** indeed reveals that close docking of the drug onto the metalloporphyrin should be impeded, owing to the destabilizing steric interaction between the *ax*-ial substituent at C-5a (*syn* to the endoperoxide bridge) and the porphyrin nucleus.

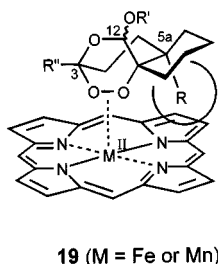


Figure 3. Presumed interaction of 5a-substituted trioxanes with the porphyrin ring

Conclusion

Characterization of the covalent adduct **18** between trioxane **8** and the heme model Mn^{II} TPP confirms that the alkylative property of artemisinin is not limited to this natural compound, but is a common feature probably required for the antimalarial activity of most endoperoxide-containing drugs. The foregoing results provide an understanding of the mode of action of 1,2,4-trioxanes. Moreover, the insights so gained are likely to aid the design and development of new artemisinin-like antimalarials.

Experimental Section

General: Infrared (IR) spectra were obtained with a Perkin–Elmer 841 spectrometer using neat films between NaCl plates or KBr pellets. Only significant absorptions are listed. The ^1H - and ^{13}C -NMR spectra were recorded with Bruker AC 200 P (200 MHz and 50 MHz, for ^1H and ^{13}C , respectively), Bruker AM 250, or Bruker ARX 400 (400 MHz and 100 MHz, for ^1H and ^{13}C , respectively) spectrometers. Methyl, methylene, methine, and quaternary carbon

nuclei in ^{13}C -NMR spectra were recognized on the basis of the *J*-modulated spin-echo sequence. Optical rotations were measured at 20°C with a Perkin–Elmer 241 MC polarimeter in a 1-dm cell. Analytical thin-layer chromatography was performed on Merck silica gel 60F₂₅₄ precoated glass plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230–400 mesh ASTM). Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride under nitrogen. All reactions involving air- or moisture-sensitive compounds were routinely conducted in glassware that had been flame-dried under a positive pressure of argon. Organic layers were dried with anhydrous MgSO_4 . Chemicals obtained from commercial suppliers were used without further purification. Mass-spectral analyses were recorded by electron impact at 70 eV or DCI/ NH_3^+ with a Nermag R10–10H spectrometer. All elemental analyses were performed by the Service de Microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

(E)- and (Z)-1-Methoxy-4-(2-methoxymethylencyclohexyl)butan-2-one (13a): To an ice-cooled solution of (methoxymethyl)triphenylphosphonium chloride (3.4 g, 10 mmol) in dry THF (50 mL), a solution of phenyllithium (2 M in benzene/diethyl ether, 3:1, 5 mL, 10 mmol) was added dropwise. The red solution was stirred at 0°C for 2 h and then nitrile **11a**^[12] (2.5 mmol) in THF (10 mL) was added dropwise. After stirring at 20°C for 24 h, the solution was poured into water and extracted with diethyl ether. The combined organic phases were washed with brine, dried, and concentrated under reduced pressure. Chromatographic purification on silica gel (cyclohexane/ethyl acetate, 50:50) afforded 330 mg of enol ethers **13a** as a colorless oil (58%). – IR (neat): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1680 (C=C). – ^1H NMR (CDCl_3 , 200 MHz) [the presence of an (*E*)/(*Z*) mixture of isomers in a 30:70 ratio complicates the spectrum]: Less polar (*Z*) isomer: δ = 1.40–2.00 (m, 10 H), 2.25–2.55 (m, 2 H), 2.80 (m, 1 H), 3.41 (s, 3 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 3.50 (s, 3 H, $=\text{CHOCH}_3$), 4.00 (s, 2 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 5.80 (d, J = 1.0 Hz, 1 H, $=\text{CHOMe}$). – ^{13}C NMR (CDCl_3 , 50 MHz): Less polar (*Z*) isomer: δ = 21.6 (CH_2), 24.8 (CH_2), 26.4 (CH_2), 28.3 (CH_2), 31.6 (CH_2), 32.5 (CH), 37.0 (CH_2), 59.1 (2 CH_3), 77.5 (CH_2 , $\text{CH}_3\text{OCH}_2\text{CO}$), 128.0 (C, $\text{MeOCH}=\text{C}$), 140.4 (CH, $\text{MeOCH}=\text{C}$), 201.8 (C, CO). – $\text{C}_{13}\text{H}_{22}\text{O}_3$ (226.3): calcd. C 68.99, H 9.82; found C 69.01, H 9.63.

(1S,2E)- and (1S,2Z)-[2-Methoxymethylene-1-(4-methoxy-3-oxobutyl)cyclohexyl-1-carbonitrile (13b): Treatment of nitrile **11b**^[12] as described above afforded enol ether **13b** (60%) as a 65:35 mixture of (*Z*)/(*E*) isomers. – Less polar (*E*) isomer, R_f = 0.59 (petroleum ether/ethyl acetate, 1:1), colorless oil. – $[\alpha]_{\text{D}}^{22}$ = +15 (c = 1.4, CH_2Cl_2). – IR (neat): $\tilde{\nu}$ = 2250 cm^{-1} (CN), 1715 (C=O), 1675 (C=C). – ^1H NMR (CDCl_3 , 200 MHz): δ = 1.10–1.90 (m, 8 H), 2.00–2.60 (m, 4 H), 3.30 (s, 3 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 3.50 (s, 3 H, $=\text{CHOCH}_3$), 3.90 (s, 2 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 6.10 (s, 1 H, $=\text{CHOMe}$). – $\text{C}_{14}\text{H}_{21}\text{NO}_3$ (251.3): calcd. C 66.90, H 8.42, N 5.57; found C 66.75, H 8.47, N 5.54. – More polar (*Z*) isomer, R_f = 0.53 (petroleum ether/ethyl acetate, 1:1), colorless oil. – $[\alpha]_{\text{D}}^{22}$ = +42.5 (c = 1.7, CH_2Cl_2). – IR (neat): $\tilde{\nu}$ = 2250 cm^{-1} (CN), 1715 (C=O), 1675 (C=C). – ^1H NMR (CDCl_3 , 200 MHz): δ = 1.20–1.90 (m, 8 H), 2.20–2.70 (m, 4 H), 3.30 (s, 3 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 3.45 (s, 3 H, $=\text{CHOCH}_3$), 4.00 (s, 2 H, $\text{CH}_3\text{OCH}_2\text{CO}$), 5.85 (s, 1 H, $=\text{CHOMe}$).

[3R*-(3 α ,5 α ,9 α ,10R*)]- and [3R*-(3 α ,5 α ,9 α ,10S*)]-3,9a-(Epoxy-methano)-5a,6,7,8,9a-hexahydro-10-methoxy-3-methoxymethyl-9aH-1,2-benzodioxepin (8 and 9): A solution of enol ether **13a** (321 mg, 1.42 mmol) in anhydrous CH_2Cl_2 (30 mL) was placed in a

Pyrex photochemical apparatus. Methylene Blue (2 mg, 0.03 mmol) was added and the reaction mixture was cooled to -60°C . Oxygen was then bubbled into the solution under irradiation by a 400-W high-pressure sodium lamp set at a distance of 10 cm. After 2 h, TMSOTf (115 mg, 0.52 mmol) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 10 min, triethylamine (150 mg, 1.5 mmol) was added and the reaction mixture was filtered through Celite. The filtrate was washed with water, dried with MgSO_4 , and concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane then cyclohexane/ethyl acetate, 95:5) to give 142 mg of trioxane **8** (40%) as a colorless oil. — ^1H NMR ($[\text{D}_6]$ benzene, 400 MHz): δ = 1.05 (m, 1 H, 6- H_{ax}), 1.28 (td, J = 13.8, 5.0 Hz, 1 H, 9- H_{ax}), 1.42–1.75 (m, 6 H, 7-H, 8- H_{ax} , 5- H_{eq} , 4a-H, 6- H_{eq}), 1.74 (m, 1 H, 8- H_{eq}), 1.81 (br. d, J = 13.8 Hz, 1 H, 9- H_{eq}), 1.95 (dddd, J = 14.5, 13.4, 13.4, 4.4 Hz, 1 H, 5- H_{ax}), 2.22 (td, J = 14.5, 4.4 Hz, 1 H, 4- H_{eq}), 2.41 (td, J = 14.5, 3.7 Hz, 1 H, 4- H_{ax}), 3.20 (s, 3 H, CH_3OCH_2), 3.30 (s, 3 H, 10- COCH_3), 3.40 (s, 2 H, CH_3OCH_2), 5.04 (d, 1 H, J = 1.5 Hz, 10a-H). — ^{13}C NMR (CDCl_3 , 50 MHz): δ = 24.1 (CH_2 , C-8), 25.4 (CH_2 , C-6), 26.6 (CH_2 , C-5), 31.1 (CH_2 , C-7), 34.1 (CH_2 , C-4), 36.0 (CH_2 , C-9), 47.8 (CH, C-5a), 56.5 (CH_3 , CH_3OCH_2), 59.5 (CH_3 , 10- COCH_3), 76.3 (CH_2 , CH_3OCH_2), 83.7 (C, C-9a), 105.0 (C, C-10), 105.8 (C, C-3). — $\text{C}_{13}\text{H}_{22}\text{O}_5$ (258.3): calcd. C 60.44, H 8.58; found C 60.58, H 8.42. — Further elution gave 40 mg of trioxane **9** as a colorless oil (12%). — ^1H NMR ($[\text{D}_6]$ benzene, 200 MHz) (only the most significant resonances are listed): δ = 2.20–2.50 (m, 2 H), 3.00 (s, 3 H, CH_3OCH_2), 3.15 (s, 3 H, 10- COCH_3), 3.20 (s, 2 H, CH_3OCH_2), 4.70 (s, 1 H, 10a-H).

[3S-(3 α ,5 α ,9 α ,10S*)]-3,9a-(Epoxy-methano)-5a,6,7,8,9,9a-hexahydro-10-methoxy-3-methoxymethyl-9aH-1,2-benzodioxepin-5a(3H)-carbonitrile (7): Treatment of enol ether **13b** as described above afforded trioxane **7** (50%) as a colorless oil. — $[\alpha]_{\text{D}}^{22}$ = +62 (CH_2Cl_2 , c = 0.6). — IR (neat): $\tilde{\nu}$ = 2250 cm^{-1} (CN). — ^1H NMR (CDCl_3 , 400 MHz): δ = 1.60–1.75 (m, 5 H, 7-H, 8-H, 6- H_{ax}), 1.82–1.96 (m, 3 H, 4- H_{eq} , 9- H_{eq} , 6- H_{eq}), 2.10 (ddd, J = 13.7, 11.7, 4.8 Hz, 1 H, 9- H_{ax}), 2.22 (td, J = 13.7, 3.8 Hz, 1 H, 4- H_{ax}), 2.26 (dt, 15.3, 3.8 Hz, 1 H, 5- H_{eq}), 2.51 (ddd, J = 15.3, 13.5, 3.8, 1 H, 5- H_{ax}), 3.39 (d, J = 11.7 Hz, 1 H, $\text{CH}_3\text{OCH}_2\text{C}$), 3.40 (s, 3 H, $\text{CH}_3\text{OCH}_2\text{C}$), 3.45 (d, J = 11.7 Hz, 1 H, $\text{CH}_3\text{OCH}_2\text{C}$), 3.52 (s, 3 H, 10- COCH_3), 4.99 (s, 1 H, H-10). — ^{13}C NMR (CDCl_3 , 100 MHz): δ = 21.4 (CH_2 , C-7 or C-8), 22.6 (CH_2 , C-8 or C-7), 30.8 (CH_2 , C-4), 32.2 (CH_2 , C-5), 33.3 (CH_2 , C-6), 34.3 (CH_2 , C-9), 50.3 (C, C-5a), 57.1 (CH_3 , 10- COCH_3), 60.0 (CH_3 , $\text{CH}_3\text{OCH}_2\text{C}$), 75.4 (CH_2 , $\text{CH}_3\text{OCH}_2\text{C}$), 81.5 (C, C-9a), 103.0 (CH, C-10), 105.1 (C, C-3), 121.7 (CN). — $\text{C}_{14}\text{H}_{21}\text{NO}_5$ (283.3): calcd. C 59.35, H 7.47, N 4.94; found C 59.21, H 7.32, N 4.97.

Reaction of Trioxane **8 with $\text{Mn}^{\text{II}}(\text{TPP})$:** Mn^{III} tetraphenylporphyrin chloride (15.5 mg, 22 μmol) and trioxane **8** (17.8 mg, 0.07 mmol) were dissolved in CH_2Cl_2 (4 mL). This solution was carefully degassed, and then solid tetra-*n*-butylammonium borohydride (60.3 mg, 235 μmol) was added. The resulting solution was stirred at 25°C under nitrogen for 1 h. A solution of $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (138 mg, 447 μmol) in deoxygenated DMF (1 mL) was then added and the resulting mixture was stirred under nitrogen for 15 min in order to achieve transmetallation from the manganese(II) to the

cadmium(II) porphyrin. Air was then admitted into the flask and 10% aqueous acetic acid (5 mL) was added. After stirring for 5 min to ensure complete demetallation of the cadmium(II) porphyrin, the mixture was extracted with CH_2Cl_2 , the organic layer was washed with water, dried with MgSO_4 , and concentrated under reduced pressure. The covalent adduct was purified by chromatography on silica gel (CH_2Cl_2 , R_f = 0.60) to give ca. 3 mg of adduct **18** (ca. 20%). — UV/Vis (CH_2Cl_2): λ_{max} (rel. ϵ) = 418 nm (100), 514 (6). — ^1H NMR (CD_2Cl_2 , 250 MHz): δ = 3.37 (s, 3 H, OCH_3), 4.58 (d, J = 1.5 Hz, 2 H, CH_2OCH_3), 7.79 (m, 12 H, phenyl), 8.09 (m, 2 H, phenyl), 8.21 (m, 6 H, phenyl), 8.64 (d, J = 5.0 Hz, 1 H, 18'-H), 8.79 (d, J = 5 Hz, 2 H, 8'-H and 17'-H), 8.84 (d, J = 5.0 Hz, 1 H, 7'-H), 8.88 (br. s, 3 H, 3'-H, 12'-H and 13'-H). — Upon irradiation of the broad singlet at δ = 8.88, containing the 3'-H resonance, the doublet at δ = 4.58 assigned to the methylene resonance of the CH_3OCH_2 fragment collapsed to a sharp singlet. — MS (DCI/NH_3); m/z (%): 662 (5), 661 (19), 660 (56), 659 (100) $[\text{MH}^+]$, 627 (3) $[\text{M} - (\text{OCH}_3)^+]$.

- [1] For recent reviews, see: [1a] H. Ziffer, R. J. Highet, D. L. Klayman *Prog. Chem. Org. Nat. Prod.* **1997**, 72, 121–214. — [1b] S. R. Meshnick, T. E. Taylor, S. Kamchonwongpaisan, *Microbiol. Rev.* **1996**, 301–315. — [1c] T. T. Hien, N. J. White, *Lancet* **1993**, 341, 603–608. — [1d] S. Kamchonwongpaisan, S. R. Meshnick, *Gen. Pharmac.* **1996**, 27, 587–592. — [1e] G. H. Posner, *Expert Opin. Ther. Pat.* **1998**, 8, 1487–1493.
- [2] S. R. Meshnick, Y.-Z. Yang, V. Lima, F. Kuypers, S. Kamchonwongpaisan, Y. Yuthavong, *Antimicrob. Agents Chemother.* **1993**, 37, 1108–1114.
- [3] M. A. Avery, S. Mehrota, J. D. Bonk, J. A. Vroman, D. K. Goins, R. Miller, *J. Med. Chem.* **1996**, 39, 2900–2906.
- [4] [4a] G. H. Posner, C. H. Oh, *J. Am. Chem. Soc.* **1992**, 114, 8328–8329. — [4b] G. H. Posner, J. N. Cumming, P. Ploypradith, C. H. Oh, *J. Am. Chem. Soc.* **1995**, 117, 5885–5886. — [4c] C. W. Jefford, M. G. H. Vicente, Y. Jacquier, F. Favarger, J. Mareda, P. Millasson-Schmidt, G. Brunner, U. Burger, *Helv. Chim. Acta* **1996**, 79, 1475–1487.
- [5] [5a] Y.-Z. Yang, W. Asawamahasakda, S. R. Meshnick, *Biochem. Pharmacol.* **1993**, 46, 336–339. — [5b] W. Asawamahasakda, I. Itarat, Y.-M. Pu, H. Ziffer, S. R. Meshnick, *Antimicrob. Agents Chemother.* **1994**, 38, 1854–1858.
- [6] A. Robert, B. Meunier, *J. Am. Chem. Soc.* **1997**, 119, 5968–5969.
- [7] A. Robert, B. Meunier, *Chem. Soc. Rev.* **1998**, 27, 273–279.
- [8] A. Robert, B. Meunier, *Chem. Eur. J.* **1998**, 4, 1287–1296.
- [9] F. Zouhiri, D. Desmaële, J. d'Angelo, C. Riche, F. Gay, L. Cicéron, *Tetrahedron Lett.* **1998**, 39, 2969–2972.
- [10] F. Zouhiri, D. Desmaële, J. d'Angelo, J. Mahuteau, C. Riche, F. Gay, L. Cicéron, *Eur. J. Org. Chem.* **1998**, 2897–2906.
- [11] M. Hamzaoui, O. Provot, F. Grégoire, C. Riche, A. Chiaroni, F. Gay, H. Moskowitz, J. Mayrargue, *Tetrahedron: Asymmetry* **1997**, 8, 2085–2088.
- [12] M. Hamzaoui, O. Provot, B. Camuzat-Dedenis, H. Moskowitz, J. Mayrargue, L. Cicéron, F. Gay, *Tetrahedron Lett.* **1998**, 39, 4029–4030.
- [13] [13a] C. W. Jefford, J. A. Velarde, G. Bernardinelli, D. H. Bray, D. C. Warhurst, W. K. Milhous, *Helv. Chim. Acta* **1993**, 76, 2775–2788. — [13b] G. H. Posner, C. H. Oh, L. Gerena, W. K. Milhous, *Heteroatom Chem.* **1995**, 6, 105–116.
- [14] P. Mirovsky, F. Gay, D. Bustos, D. Mazier, M. Gentilini, *Trans. R. Soc. Trop. Med. Hyg.* **1990**, 84, 511–515.
- [15] D. M. Golden, S. W. Benson, *Chem. Rev.* **1969**, 69, 125–134.

Received February 1, 1999
[O99056]