Cysteine Protease Inhibitors

Design and Synthesis of Endoperoxide Antimalarial Prodrug Models**

Paul M. O'Neill, Paul A. Stocks, Matthew D. Pugh, Nuna C. Araujo, Edward E. Korshin, Jamie F. Bickley, Stephen A. Ward, Patrick G. Bray, Erica Pasini, Jill Davies, Edite Verissimo, and Mario D. Bachi**

There has been an increase in support for combination chemotherapy as a rational strategy to combat malaria.[1] It is anticipated that, in addition to pharmacodynamic benefits such as the synergistic effect of drugs, combination therapy will delay the development of drug resistance in the malaria parasite *P. falciparum*. For malaria chemotherapy it was suggested that one component of such a drug combination should be a 1,2,4-trioxane-containing artemisinin derivative, as these compounds show fast antiparasitic action.[2,3] Very recently, an extension of this approach resulted in the elaboration of new potent modular antimalarial agents. These active compounds each contain two antimalarial pharmacophores, such as 1,2,4-trioxane and aminoquinoline[4,5] or an aliphatic diamine,[6] within the same molecule.

Herein, we describe a paradigm for a masked combination chemotherapy which relies on the embedding of a number of active components, in a latent form, within a single endoperoxidic chemical entity. Following penetration as a "Trojan horse" into the ferrous-rich food vacuole (FV) of the malaria parasite, these endoperoxidic prodrugs will be unmasked by in situ iron(II)-mediated fragmentation thus releasing multiple parasiticidal entities.[7]

Our approach is illustrated by means of the purposely designed bicyclic endoperoxide prodrug prototypes **1** and subsequently proved through the study of model compounds **2**. The substituents at position 4 in **1** should secure the in situ generation of chalcones of type **3** alongside additional noxious species as shown in Scheme 1. Some of these active

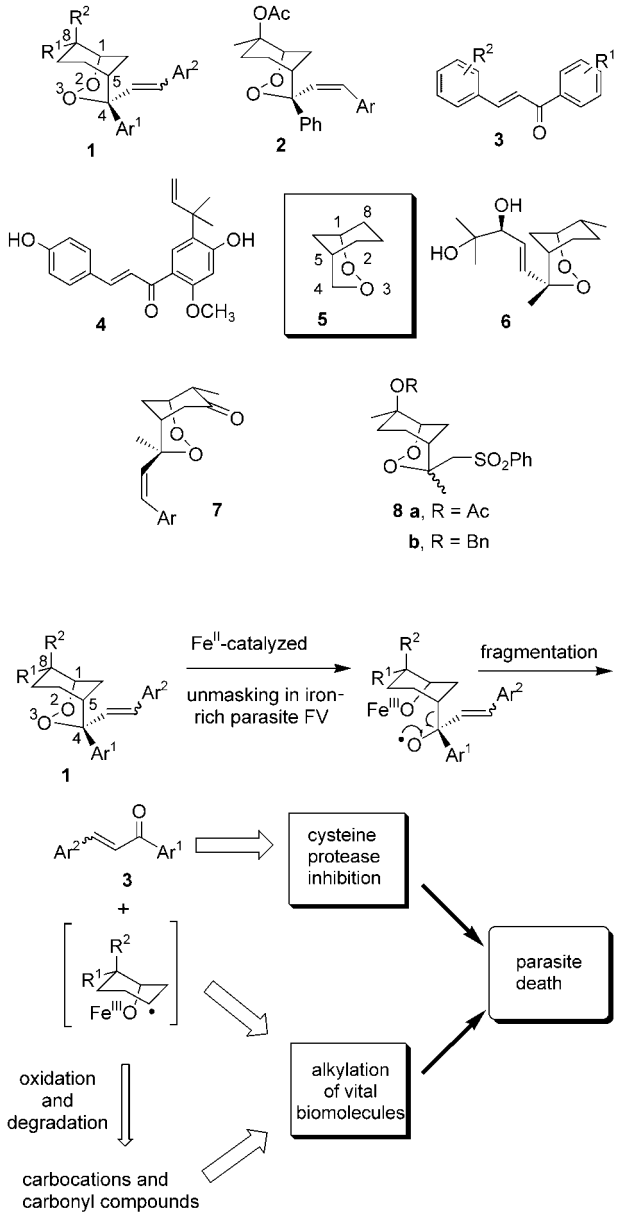
[*] Dr. P. M. O'Neill, Dr. P. A. Stocks, Dr. M. D. Pugh, N. C. Araujo, J. F. Bickley, J. Davies, E. Verissimo
Department of Chemistry
The Robert Robinson Laboratories
University of Liverpool
Liverpool L69 7ZD (UK)
Fax: (+44) 151-794-3588
E-mail: p.m.oneill01@liv.ac.uk

Dr. E. E. Korshin, Prof. Dr. M. D. Bachi
Department of Organic Chemistry
The Weizmann Institute of Science
Rehovot 76100 (Israel)
Fax: (+972) 8-934 4142
E-mail: mario.bachi@weizmann.ac.il

Prof. Dr. S. A. Ward, Dr. P. G. Bray, E. Pasini
Liverpool School of Tropical Medicine
Pembroke Place, Liverpool L3 5QA (UK)

[**] This work was supported by grants from the BBSRC (UK) for P.A.S., P.O'N., and S.A.W. (26/B13581) and from the EPSRC (UK) for M.D.P.

 DOI: 10.1002/ange.200453859

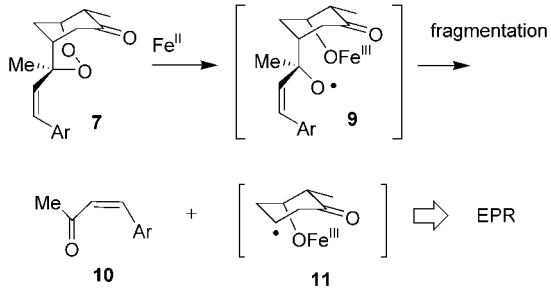


Scheme 1. The designed ferrous-catalyzed degradation of the generic prodrug **1**.

species are reminiscent of those generated by artemisinin and related trioxanes and presumably kill the parasite through a similar mode of action.[7–9] In contrast, chalcones **3** cannot be formed by ferrous-mediated degradation of the currently known 1,2,4-trioxanes. On the other hand, a series of chalcones have been found to be effective antimalarial cysteine protease (CP) inhibitors.[10] Moreover, natural licochalcone A (**4**) was reported to provide efficacious protection against *P. berghei* malaria in mice.[11] Falcipain 2, a CP of the papain family, is a *P. falciparum* FV hemoglobinase; it acts in concert with some aspartic proteases to degrade hemoglobin, thus enabling the malaria parasite to acquire amino acids for its protein biosynthesis.[12] Therefore, plasmodium CPs constitute an attractive target for antimalarial drug research.[1,12,13]

The designed prodrugs **1** are new representatives of an emerging class of promising antimalarial endoperoxides which contain the 2,3-dioxabicyclo[3.3.1]nonane framework **5** and are structurally related to naturally occurring yingzhaosu A (**6**).[14,15] Synthetic endoperoxides, such as arteflene (**7**, Ar = 2,4-bis(trifluoromethyl)phenyl) and its analogues,[16] as well as the β-sulfonyl endoperoxides **8a** and **8b** and related compounds,[15,17,18] were found to be potent and nontoxic antimalarial agents in vivo. In vitro antimalarial activity was reported for 4-acetal, 1,4-diacetal, and 1- or 4-iodomethyl derivatives of **8**.[19–21]

Biomimetic Fe^{II}-induced degradation reactions of arteflene (**7**) provided some clues on the mode of action of these endoperoxides.[22,23] Thus, on being subjected to ferrous-mediated fragmentation in water/MeCN, arteflene (**7**) gave the stable enone **10** and the transient carbon-centered cyclohexyl radical **11** (Scheme 2).[22] This latter species was

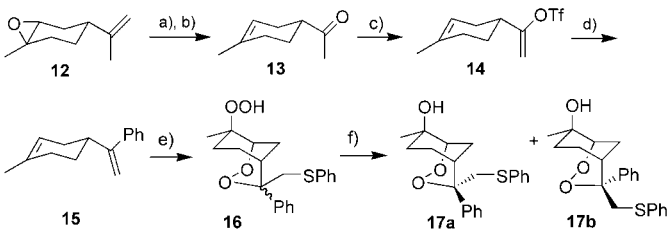


Scheme 2. Fe^{II}-catalyzed degradation of arteflene (**7**).

directly detected by EPR[23] and trapped with TEMPO (2,2,6,6-tetramethylpiperidinyloxy) in a degradation induced by Mn^{II}–tetraphenylporphyrin (TPP).[24] (Parallel biomimetic studies with the sulfonyl endoperoxide **8a** demonstrated that secondary C-centred radicals, related to **11**, can also readily undergo oxidation by Fe^{III} to potentially toxic carbocations.[25]) Whereas the enone **10** liberated from arteflene is inactive against *Plasmodium falciparum*,[22] the prodrugs described herein have the capacity to liberate an enone of the chalcone class with antimalarial activity.[10,11,26]

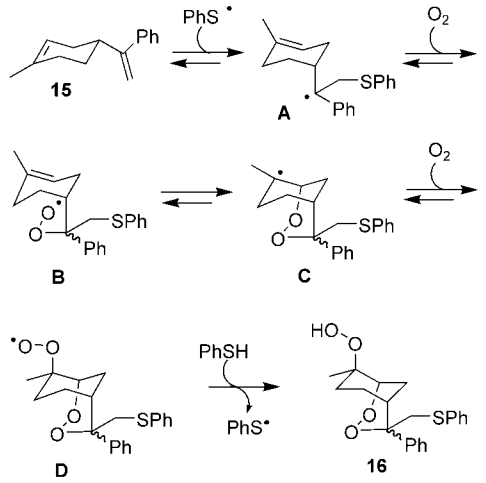
The synthesis of the model endoperoxides **2** is depicted in Schemes 3 and 5. Ozonolysis of commercially available (*R*)-limonene oxide (**12**) followed by in situ reduction and transformation of the internal epoxide into the corresponding alkene[27] afforded the unsaturated ketone **13** (50%; Scheme 3). The subsequent formation of the kinetic enol triflate **14** was initially attempted with trifluoromethanesulfonic anhydride. However, the unsatisfactory yield (8%) prompted us to use $PhNTf_2$[28] as the triflating agent and KHMDS as the base, which provided the triflate **14** in 64% yield. The triflate **14** was then subjected to a nickel-catalyzed cross-coupling[29] with phenyl magnesium bromide to give **15**, a phenyl analogue of (*R*)-limonene (75%; Scheme 3).

Recently we applied the free-radical, four-component, sequential thiol–olefin co-oxygenation (TOCO) reaction to limonene and similar monoterpenes, thus providing an efficient tool for the construction of the 2,3-dioxabicyclo[3.3.1]nonane system **5**.[30,31] This reaction was found to



Scheme 3. a) O_3, −78 °C, CH_2Cl_2; b) NaI, AcOH, AcONa, Zn (50% from **12**); c) KHMDS (1.5 equiv, 1.0 M in THF), $PhNTf_2$ (1.5 equiv), THF, −78→−40 °C, 64%; d) PhMgBr (2 equiv), $[Ni(acac)_2]$ (0.1 equiv), Et_2O, room temperature, 75%; e) PhSH (1.2 equiv), AIBN (0.07 equiv), O_2 (excess), *hν*, 0 °C, CH_3CN; f) Ph_3P (1.6 equiv), CH_3CN, CH_2Cl_2, 0 °C to room temperature (70% from **16**; **17a**/**17b** ca. 4:3). KHMDS = potassium hexamethyldisilazane; $PhNTf_2$ = *N*-phenyltrifluoromethanesulfonimide; acac = acetylacetonate; AIBN = azabisisobutyronitrile.

be particularly suitable for the formation of the bicyclic endoperoxidic backbone of model compounds **2**. Optimization of this reaction led to the following protocol: a solution of PhSH was added during 30 min to a solution of the 1,5-diene **15** and AIBN in acetonitrile at 0 °C under small positive pressure of pure oxygen and under UV irradiation, to afford the hydroperoxy endoperoxides **16**. The reactive hydroperoxy group was reduced selectively in the same vessel with Ph_3P to give the rather stable hydroxy endoperoxides **17**. The diastereomeric compounds **17a**,**b** (**a**/**b** ca. 4:3) were isolated after flash chromatography in 70% yield (average yield per newly formed bond: >93%). The mechanism of the sequential TOCO reaction is illustrated in Scheme 4.



Scheme 4. Mechanism of the TOCO reaction.

It has been noted for the case of the parent limonene that it is necessary to maintain a low concentration of PhSH and a high monoterpene/PhSH ratio throughout the TOCO reaction to obtain the bridged bicyclic endoperoxides in good yield.[31] However, because of the supporting effect of the phenyl group in the phenyl analogue **15**, addition of the sulfanyl radical to the terminus of the exocyclic C=C bond in **15** to generate radical **A** is faster (Scheme 4). The phenyl group stabilizes radical **A**, thus shifting the equilibrium **15**⇄**A** to the right and accelerating the whole chain process. As a result, the TOCO reaction gave the hydroperoxy endoperoxides **16** in high yield, even in a more concentrated solution, in shorter reaction times, and with close to stochiometric ratios of the reagents.

The configuration of the diastereomeric sulfides **17a** and **17b** was assigned based on their NMR spectra in accordance with the previously formulated empirical rules.[30,31] Some relevant ^{1}H NMR data are shown in Figure 1. The assignment for **17a** by NMR spectroscopy was corroborated by the crystal structure of the corresponding crystalline acetoxy sulfone **17c** (Figure 1),[32] which was obtained in a silylation, acetylation, and oxidation process.[18,31]

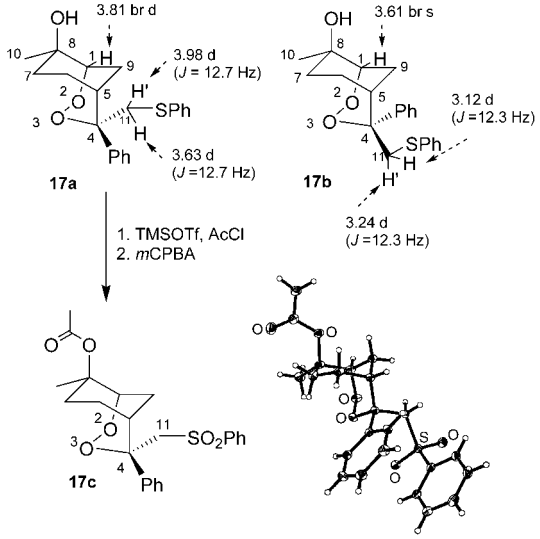
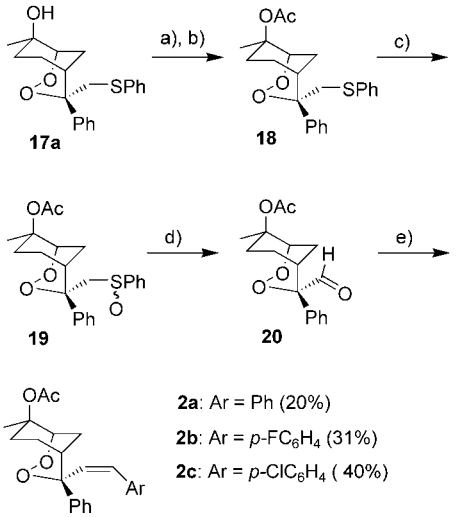


Figure 1. Distinctive ^{1}H NMR data for sulfides **17a** and **17b**, and synthesis and X-ray crystal structure of the sulfone **17c** (ORTEP).[32]

The completion of the synthesis of the model prodrugs **2** is described in Scheme 5. The acetylation of the sterically hindered tertiary hydroxy group in **17a** to give the sulfide **18** was achieved by 1) silylation with TMSOTf, and 2) acylation of the crude TMS derivative with neat AcCl.[18,31] The key aldehyde intermediate **20** was obtained by a Pummerer-type oxidative desulfurization as reported for similar endoperoxidic sulfoxides:[15] selective oxidation of **18** with *m*CPBA afforded a mixture of the epimeric sulfoxides **19**; treatment of **19** with TFAA[33] afforded the desired aldehyde **20** (40%). Finally, this aldehyde was converted into the prototypic prodrugs **2a–c** through a Wittig *cis* olefination.[16a,b]

The endoperoxidic prodrug prototypes **2a–c** were assayed for in vitro antimalarial activity against the chloroquine-resistant K1 strain of *Plasmodium falciparum* (Table 1). The data are encouraging in the sense that all of the prepared analogues **2** have superior activity to the Hoffmann LaRoche antimalarial drug candidate arteflene (**7**).

A biomimetic Fe^{II}-mediated degradation of the model endoperoxide **2a** in H_2O/MeCN at room temperature according to the previously described protocol[22,23] afforded the expected *trans* chalcone **3a** (45%) as the major product (Scheme 6),[34] along with a smaller amount of the diol **21**

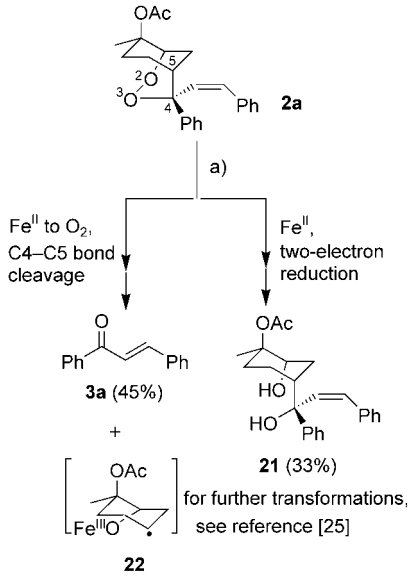


Scheme 5. a) TMSOTf (2 equiv), 2,6-lutidine (2.75 equiv), CH_2Cl_2, 95%; b) neat AcCl (60% from **17a**); c) *m*CPBA (1.1 equiv), CH_2Cl_2, 0°C, 85%; d) TFAA (2 equiv), morpholine, CH_3CN, 40%; e) $(ArCH_2)Ph_3P^+Br^-$ (1.4 equiv), KHMDS (1.4 equiv), THF, −10→25°C, 2 h. TMSOTf = trimethylsilyl triflate; TFAA = trifluoroacetic anhydride.

Table 1: In vitro antimalarial activity of prototype endoperoxides **2a–c** against the K1 strain of *P. falciparum*.

Compound	IC_{50} [nM]	SD ±
2a	34	4
2b	29	5
2c	23	4
arteflene (**7**)	47	8
artemisinin	15	4

(33%), the product of a two-electron reduction.[22] (The chalcone **3a** is a surrogate marker for the generation of the secondary C-centered radical **22**.) More significantly, LC–MS analysis of ethyl acetate extracts of isolated FVs of mid-term trophozoites exposed to 50 μM prodrug clearly demonstrated the presence of parent chalcone **3a**. Quantification was achieved by LC–MS monitoring of $[M+H]$ at m/z 209.3. The chalcone **3a** was identified by matching the MS/MS spectrum of the parent ion and by comparing the retention times with those of an authentic sample.



Scheme 6. a) $FeCl_2 \cdot 4H_2O$ (1 equiv), CH_3CN/H_2O (1:1), room temperature.

In conclusion, we have developed a general synthetic route for the preparation of a promising class of antimalarial prodrug candidates of the general structure **1**. Compound **2a** was chosen as a prototype. It was expected that for a variety of substituents R^1 and R^2 at C8 of the bridged bicyclic framework **5**, different compounds of type **1** ($Ar^1 = Ar^2 = Ph$) would act as precursors to the chalcone **3a**, which is the prototype of the known CP inhibitors **3** and **4**. Indeed, it was proved that the endoperoxide **2a** liberates, through iron(II) mediation, the chalcone **3a** and additional potential parasiticidal species. Not only did all three model compounds **2** exhibit significant antimalarial activity but definitive proof that these systems are capable of liberating a chalcone in the living parasite was provided by LC–MS analysis of prodrug-exposed parasites. It is planned to extend the present work by studying compounds of type **1** with masked chalcone units endowed with varying CP-inhibition potential and antimalarial potencies.

Received: January 27, 2004 [Z53859]

Keywords: antimalarial agents · chalcones · combination chemotherapy · cysteine protease inhibitors · endoperoxides

[1] P. J. Guerin, P. Olliaro, F. Nosten, P. Druilhe, R. Laxminarayan, F. Binka, W. L. Kilama, N. Ford, N. J. White, *Lancet Infect. Dis.* **2002**, *2*, 564–573.
[2] M. Frederich, J. M. Dogne, L. Angenot, P. De Mol, *Curr. Med. Chem.* **2002**, *9*, 1435–1456.
[3] S. Pukrittayakamee, N. J. White, *Pharm. News* **2001**, *8*, 21–26.
[4] a) A. Robert, O. Dechy-Cabaret, J. Cazelles, B. Meunier, *Acc. Chem. Res.* **2002**, *35*, 167–174; b) O. Dechy-Cabaret, F. Benoit-Vical, A. Robert, B. Meunier, *ChemBioChem* **2000**, *1*, 281–283; c) L. K. Basco, O. Dechy-Cabaret, M. Ndounga, F. S. Meche, A. Robert, B. Meunier, *Antimicrob. Agents Chemother.* **2001**, *45*, 1886–1888.
[5] O. Dechy-Cabaret, A. Robert, B. Meunier, *C. R. Chim.* **2002**, *5*, 297–302.
[6] S. Hindley, S. A. Ward, R. C. Storr, N. L. Searle, P. G. Bray, B. K. Park, J. Davies, P. M. O'Neill, *J. Med. Chem.* **2002**, *45*, 1052–1063.
[7] a) G. H. Posner, S. B. Park, L. Gonzalez, D. Wang, J. N. Cumming, D. Klinedinst, T. A. Shapiro, M. D. Bachi, *J. Am. Chem. Soc.* **1996**, *118*, 3537–3538; b) J. N. Cumming, P. Ploypradith, G. H. Posner, *Adv. Pharmacol.* **1997**, *37*, 253–297; c) G. H. Posner, J. N. Cumming, M. Krasavin in *Biomedicinal Chemistry: Applying Chemical Principles to the Understanding and Treatment of Disease* (Ed.: P. F. Torrence), Wiley-Interscience, New York, **2000**, pp. 289–309; d) K. Borstnik, I.-H. Paik, G. H. Posner, *Mini-Rev. Med. Chem.* **2002**, *2*, 573–583.
[8] a) A. Robert, J. Cazelles, B. Meunier, *Angew. Chem.* **2001**, *113*, 2008–2011; *Angew. Chem. Int. Ed.* **2001**, *40*, 1954–1957; b) A. Robert, B. Meunier, *J. Am. Chem. Soc.* **1997**, *119*, 5968–5969; c) Y. Wu, *Acc. Chem. Res.* **2002**, *35*, 255–259; d) Y. Wu, Z.-Y. Yue, Y.-L. Wu, *Angew. Chem.* **1999**, *111*, 2730–2733; *Angew.*

Chem. Int. Ed. **1999**, *38*, 2580 – 2583; e) C. W. Jefford, *Curr. Med. Chem.* **2001**, *8*, 1803 – 1826.

[9] a) S. R. Meshnick, T. E. Taylor, S. Kamchonwongpaisan, *Microbiol. Rev.* **1996**, *60*, 301 – 315; b) S. R. Meshnick, *Int. J. Parasitol.* **2002**, *32*, 1655 – 1660; c) Y.-L. Hong, Y.-Z. Yang, S. R. Meshnick, *Mol. Biochem. Parasitol.* **1994**, *63*, 121 – 128; d) W. Asawamahasakda, I. Ittarat, Y.-M. Pu, H. Ziffer, S. R. Meshnick, *Antimicrob. Agents Chemother.* **1994**, *38*, 1854 – 1858; e) J. Bhisutthibhan, X.-Q. Pan, P. A. Hossler, D. J. Walker, C. A. Yowell, J. Carlton, J. B. Dame, S. R. Meshnick, *J. Biol. Chem.* **1998**, *273*, 16192 – 16198; f) A. V. Pandey, B. L. Tekwani, R. L. Singh, V. S. Chauhan, *J. Biol. Chem.* **1999**, *274*, 19383 – 19388; g) U. Eckstein-Ludwig, R. J. Webb, I. D. A. van Goethem, J. M. East, A. G. Lee, M. Kimura, P. M. O'Neill, P. G. Bray, S. A. Ward, S. Krishna, *Nature* **2003**, *424*, 957 – 961.

[10] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. J. Rosenthal, J. H. McKerrow, *J. Med. Chem.* **1995**, *38*, 5031 – 5037.

[11] a) M. Chen, T. G. Theander, S. B. Christensen, L. Hviid, L. Zhai, A. Kharazmi, *Antimicrob. Agents Chemother.* **1994**, *38*, 1470 – 1475; b) L. Nadelmann, J. Tjornelund, S. H. Hanse, C. Cornetti, U. G. Sidelmann, *Xenobiotica* **1997**, *27*, 667 – 680.

[12] a) P. J. Rosenthal, *Emerging Infect. Dis.* **1998**, *4*, 49 – 57; b) P. J. Rosenthal, *Adv. Parasitol.* **1999**, *43*, 105 – 159; c) P. J. Rosenthal, J. H. McKerrow, M. Aikawa, H. Nagasawa, J. H. Leech, *J. Clin. Invest.* **1988**, *82*, 1560 – 1566; d) D. E. Goldberg, A. F. G. Slater, R. Beavis, B. Chait, A. Cerami, G. B. Henderson, *J. Exp. Med.* **1991**, 173, 961 – 969; e) N. D. Gamboa de Dominguez, P. J. Rosenthal, *Blood* **1996**, *87*, 4448 – 4454; f) M. Dua, P. Raphael, P. S. Sijwali, P. J. Rosenthal, M. Hanspal, *Mol. Biochem. Parasitol.* **2001**, *116*, 95 – 99.

[13] a) R. G. Ridley, *Nature* **2002**, *415*, 686 – 693; b) G. H. Coombs, D. E. Goldberg, M. Klemba, C. Berry, J. Kay, J. Mottram, *Trends Parasitol.* **2001**, *17*, 532 – 537; c) P. Olliaro, J. Cattani, D. Wirth, *JAMA* **1996**, *275*, 230 – 233.

[14] a) X. T. Liang, D. Q. Yu, W. L. Wu, H. C. Deng, *Acta Chim. Sin. (Engl. Ed.)* **1979**, *37*, 215 – 230; b) X. Liang in *Advances in Chinese Medicinal Materials* (Eds.: H. M. Chang, H. W. Yeung, W. W. Tso, A. Koo), World Scientific, Singapore, **1985**, pp. 427 – 432; c) X. X. Xu, J. Zhu, D.-Z. Huang, W.-S. Zhou, *Tetrahedron Lett.* **1991**, *32*, 5785 – 5788.

[15] M. D. Bachi, E. E. Korshin, R. Hoos, A. M. Szpilman, *J. Heterocycl. Chem.* **2000**, *37*, 639 – 646.

[16] a) W. Hofheinz, G. Schmid, H. Stohler, Eur. Pat. Appl. 311955, **1989** [*Chem. Abstr.* **1990**, *112*, 20999]; b) W. Hofheinz, H. Burgin, E. Gocke, C. Jaquet, R. Masciadri, G. Schmid, H. Stohler, H. Urwyler, *Trop. Med. Parasitol.* **1994**, *45*, 261 – 265; c) C. Jaquet, H. R. Stohler, J. Chollet, W. Peters, *Trop. Med. Parasitol.* **1994**, *45*, 266 – 271.

[17] M. D. Bachi, E. E. Korshin, P. Ploypradith, J. N. Cumming, S. J. Xie, T. A. Shapiro, G. H. Posner, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903 – 908.

[18] M. D. Bachi, E. E. Korshin, R. Hoos, A. M. Szpilman, P. Ploypradith, S. Xie, T. A. Shapiro, G. H. Posner, *J. Med. Chem.* **2003**, *46*, 2516 – 2533.

[19] P. M. O'Neill, N. L. Searle, K. J. Raynes, J. L. Maggs, S. A. Ward, R. C. Storr, B. K. Park, G. H. Posner, *Tetrahedron Lett.* **1998**, *39*, 6065 – 6068.

[20] a) T. Tokuyasu, A. Masuyama, M. Nojima, H.-S. Kim, Y. Wataya, *Tetrahedron Lett.* **2000**, *41*, 3145 – 3148; b) T. Tokuyasu, A. Masuyama, M. Nojima, K. J. McCullough, H.-S. Kim, Y. Wataya, *Tetrahedron* **2001**, *57*, 5979 – 5989.

[21] H.-S. Kim, K. Begum, N. Ogura, Y. Wataya, T. Tokuyasu, A. Masuyama, M. Nojima, K. J. McCullough, *J. Med. Chem.* **2002**, *45*, 4732 – 4736.

[22] P. M. O'Neill, L. P. Bishop, N. L. Searle, J. L. Maggs, S. A. Ward, P. G. Bray, R. C. Storr, B. K. Park, *Tetrahedron Lett.* **1997**, *38*, 4263 – 4266.

[23] P. M. O'Neill, L. P. Bishop, N. L. Searle, J. L. Maggs, R. C. Storr, S. A. Ward, B. K. Park, F. Mabbs, *J. Org. Chem.* **2000**, *65*, 1578 – 1582.

[24] J. Cazelles, A. Robert, B. Meunier, *J. Org. Chem.* **1999**, *64*, 6776 – 6781.

[25] A. M. Szpilman, E. E. Korshin, R. Hoos, G. H. Posner, M. D. Bachi, *J. Org. Chem.* **2001**, *66*, 6531 – 6540.

[26] A variety of peptidyl aldehydes are also potent in vitro inhibitors of protozoan CP; see: K. A. Scheidt, W. R. Roush, J. H. McKerrow, P. M. Selzer, E. Hansell, P. J. Rosenthal, *Bioorg. Med. Chem.* **1998**, *6*, 2477 – 2494, and references therein.

[27] H. Takikawa, Y. Yamazaki, K. Mori, *Eur. J. Org. Chem.* **1998**, 229.

[28] T. Hayashi, Y. Katsuro, M. Kumada, *Tetrahedron Lett.* **1980**, *21*, 3915.

[29] P. M. O'Neill, M. D. Pugh, A. V. Stachulski, S. A. Ward, J. Davies, B. K. Park, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2682.

[30] M. D. Bachi, E. E. Korshin, *Synlett* **1998**, 122 – 124.

[31] E. E. Korshin, R. Hoos, A. M. Szpilman, L. Konstantinovski, G. H. Posner, M. D. Bachi, *Tetrahedron* **2002**, *58*, 2449 – 2469.

[32] CCDC 228984 (**17c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[33] For these modified Pummerer reaction conditions, see: Y. Arroyo-Gomez, J. F. Rodriguez-Amo, M. Santos-Garcia, M. A. Sanz-Tejedor, *Tetrahedron: Asymmetry* **2000**, *11*, 789 – 796.

[34] A partial *cis*-to-*trans* isomerization of enone **10** upon Mn^{II}TPP-induced fragmentation of arteflene (**7**) has been reported in reference [24].

