Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2991–2995

Diels–Alder/thiol–olefin co-oxygenation approach to antimalarials incorporating the 2,3-dioxabicyclo[3.3.1]nonane pharmacophore

Paul M. O'Neill,[a,*] Edite Verissimo,[a] Stephen A. Ward,[b] Jill Davies,[b] Edward E. Korshin,[c] Nuna Araujo,[d] Matthew D. Pugh,[a] M. Lurdes S. Cristiano,[d] Paul A. Stocks[a] and Mario D. Bachi[c,*]

[a]*Department of Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK*
[b]*Department of Organic Chemistry, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK*
[c]*The Weizmann Institute of Science, Rehovot 76100, Israel*
[d]*University of the Algarve, FCT, Faro P-8000, Portugal*

Received 11 January 2006; revised 22 February 2006; accepted 22 February 2006
Available online 9 March 2006

Abstract—A Diels–Alder/thiol–olefin co-oxygenation approach to the synthesis of novel bicyclic endoperoxides **17a**–**22b** is reported. Some of these endoperoxides (e.g., **17b**, **19b**, **22a** and **22b**) have potent nanomolar in vitro antimalarial activity equivalent to that of the synthetic antimalarial agent arteflene. Iron(II)-mediated degradation of sulfone-endoperoxide **19b** and spin-trapping with TEMPO provide a spin-trapped adduct **25** indicative of the formation of a secondary carbon centered radical species **24**. Reactive C-radical intermediates of this type may be involved in the expression of the antimalarial effect of these bicyclic endoperoxides.

The 2,3-dioxabicyclo[3.3.1]nonane system **1** was first identified in the naturally occurring antimalarial yingzhaosu A **2**.[1,2] It was subsequently incorporated into synthetic antimalarials as Hoffmann LaRoche's arteflene **3**,[3] endoperoxides **4** synthesized by O'Neill et al.[4] β-sulfanyl and β-sulfonyl-endoperoxides **5**–**9b** synthesized by Bachi and co-workers,[5–8] and related cyclic peroxides synthesized by Nojima and co-workers,[9] to become a well-established pharmacophore. C(4)-Methyl-substituted β-sulfanyl- and β-sulfonyl-2,3-dioxabicyclo[3.3.1]nonane derivatives such as **5**–**8** are now readily available by a useful method based on the adaptation of the thiol–olefin co-oxygenation (TOCO) reaction[10] to limonene.[5–8] This method proved to be particularly efficient in a key step of the synthesis of C(4)-phenyl-substituted benzylidene endoperoxides like **10** and **11**[11] (Fig. 1).

More than 50 compounds of types **5**–**8** have been screened for in vitro activity.[12] Ten of the β-sulfonyl-endoperoxides of types **6** and **8** have IC_{50} values lower than 25 nM against *Plasmodium falciparum* (NF54).[12] Upon subcutaneous administration, four β-sulfonyl endoperoxides were shown to be highly active antimala-

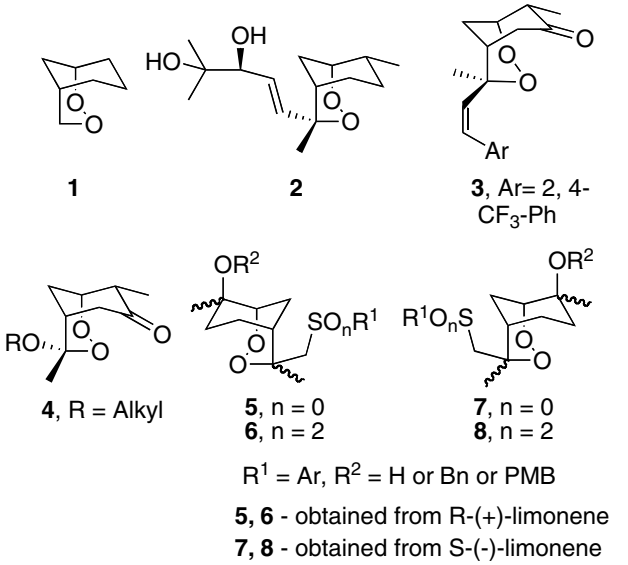
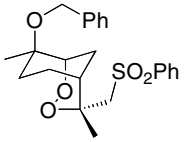


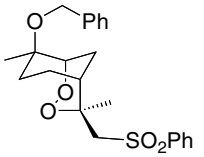
Figure 1. Bicyclic endoperoxides based on the 2,3-dioxabicyclo[3.3.1]nonane pharmacophore.

Keywords: Artemisinin; Arteflene; Endoperoxide; Malaria; Mechanism of action.
* Corresponding authors. E-mail: P.M.oneill01@liv.ac.uk

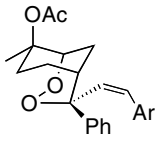
0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.02.059



9a. IC50 = 6.5 nM (NF54)
Artemisinin IC50 = 8.9 nM
ED50 = 0.8 mg/kg
Artemisinin ED50 = 0.95 mg/kg



9b. IC50 = 9.4 nM (NF54)
Artemisinin IC50 = 8.9 nM
ED50 = 0.43 mg/kg
Artemisinin ED50 = 0.95 mg/kg



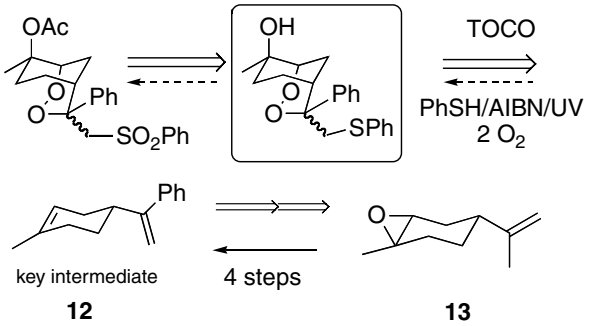
10. Ar = Ph
IC50 = 34 nM (K1)
11. Ar = *p*-Cl-Ph
IC50 = 23 nM (K1)

Figure 2. Structures and antimalarial activities of lead endoperoxides **9a**, **9b**, **10** and **11**.

rials in vivo against *Plasmodium yoelii* and *Plasmodium berghei* strains of malaria parasites. Relative to artemisinin, the most potent compounds **9a** and **9b** (Fig. 2) were about two times more efficacious against chloroquine-sensitive *P. berghei* and 3–5 times more efficacious against chloroquine-resistant *P. yoelii*. Thus, the potency of the endoperoxides **9a** and **9b** is comparable to those of some of the best currently used antimalarial drugs, including artemether and arteether. The benzyloxy derivative **9b** (Fig. 2) exhibits also a reasonable oral antimalarial efficacy about twice the level of arteflene. Antimalarial benzylidene endoperoxides, such as compounds **10** and **11**, have been shown to liberate chalcones following iron-dependent bioactivation of the endoperoxide bridge within isolated digestive vacuoles of *P. falciparum*. Such compounds are considered as pro-drug prototypes.[11]

In this paper, we report on the synthesis of a new series of bicyclic C(4)-phenyl-substituted β-sulfanyl/sulfonyl endoperoxides and the assessment of their antimalarial activity.

The key intermediate in our earlier[11] synthesis of pro-drug prototypes **10** and **11** was the phenyl limonene derivative **12** prepared in four steps from the unsaturated epoxide **13** (Scheme 1). We decided to investigate a more direct and flexible synthesis of **12** by employing a $Sc(OTf)_3$-catalysed Diels–Alder reaction of 1-phenyl-prop-2-en-1-one (**15**) with isoprene. Studies by Kobayashi have shown that scandium perfluoroalkane sulfonates catalyse the reaction of vinyl ketones with isoprene leading to excellent yields of the corresponding cycloadducts with very high levels of regioselectivity.[13]

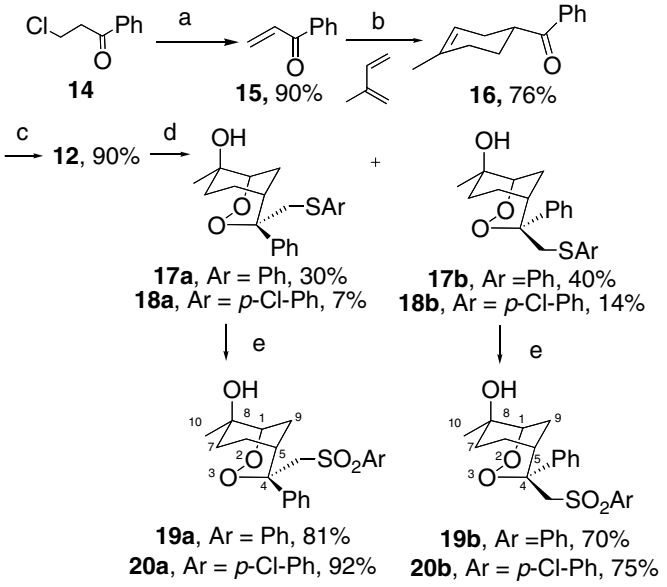


Scheme 1. Retrosynthetic analysis on sulfone endoperoxides to limonene epoxide **13**.

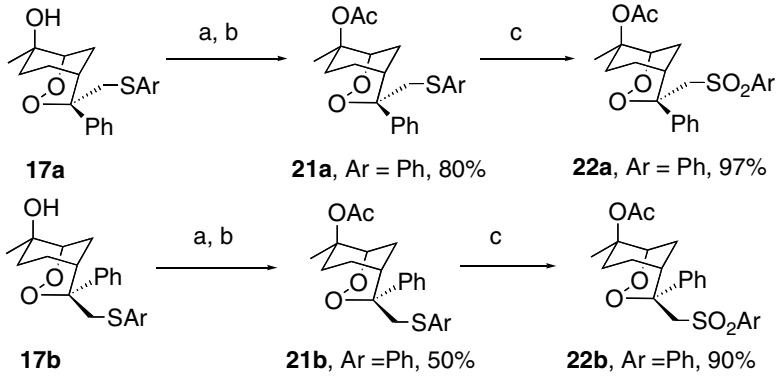
Enone **15** was prepared from 3-chloropropiophenone **14** by base-catalysed elimination of HCl in 90% yield. The enone product was used immediately in the Diels–Alder reaction with isoprene; the Kobayashi protocol gave the desired product **16** in 76% yield following purification by flash column chromatography; only minor quantities (<2%) of the regioisomeric 1,3-adduct could be detected. Compound **16** was subjected to a Wittig reaction, with methyl triphenyl phosphonium bromide and potassium *tert*-butoxide as base, to give the desired product **12** in 90% yield. Exposure of **12** to optimised conditions for the TOCO reaction gave a mixture of two diastereomers **17a**[14] and **17b**[15] in yields of 70% on a 2g scale.[11] The individual racemic diastereomers were separated by column chromatography and oxidised with *m*-CPBA to give the corresponding sulfones **19a**[16] and **19b**[17] in excellent yields. The TOCO reaction of **12,** performed using *p*-chlorothiophenol instead of phenylthiol, afforded the *p*-chloro-substituted analogues **18a** and **18b**, although in lower yields.

Since previous SAR studies involving C(4) methyl-substituted endoperoxides like **5**–**8** of both the '**a**' and '**b**' diastereomeric series revealed that acetylation of the tertiary alcohol led to improvement in antimalarial activity both in vitro and in vivo;[12] hydroxy endoperoxides **17a** and **17b** were transformed in good overall yield into the corresponding acetoxy sulfides **21a** and **21b** as shown in Scheme 3. The corresponding sulfones **22a** and **22b** were obtained as before, by the use of *m*-CPBA as oxidant. The assignment of stereochemistry at the C-4 position for **22b** has previously been confirmed by a combination of NMR spectroscopy and X-ray crystallography.[7,11]

Prior to testing, we considered the issue of enantiomeric purity since all of the compounds prepared in this study are racemic. Previously, several studies have confirmed that enantiomeric pairs of endoperoxides have identical antimalarial activity; these compounds include antimalarially potent 1,2,4-trioxanes,[18a,b] endoperoxides[18c] and analogues of the present series of bicyclic endoperoxides.[12] Thus, for the purposes of identifying lead endoperoxides, we note that many papers in the literature have employed primary screening of racemic endoperoxides and feel that this is a validated approach to antimalarial lead compound discovery.[18a–c] The antimalarial activity of selected endoperoxides was measured in red blood cell-based assays. Efficacy was monitored by parasite {^{3}H}-hypoxanthine incorporation



Scheme 2. Reagents and conditions: (a) potassium acetate, EtOH, reflux, 3 h; (b) isoprene, $Sc(OTf)_3$, 5 Å molecular sieves, CH_2Cl_2, −20 °C, 3 h; (c) methyl triphenyl phosphonium bromide, potassium *tert*-butoxide, THF, rt; (d) PhSH (1.2 equiv), AIBN (0.07 equiv), O_2 (excess), hν, 0 °C, CH_3CN; Ph_3P (1.6 equiv), CH_3CN, CH_2Cl_2, 0 °C to rt (Ar = Ph, ratio **17b/17a** ca. 4:3); (e) *m*-CPBA, CH_2Cl_2, rt.



Scheme 3. Reagents and condition: (a) TMSOTf (2 equiv), 2,6-lutidine (2.75 equiv), CH_2Cl_2; (b) neat AcCl; (c) *m*-CPBA (1.1 equiv), CH_2Cl_2, 0 °C.

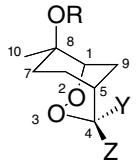
using parasite-infected human erythrocytes.[19,20] All compounds were assayed in triplicate against the chloroquine-resistant parasite, K1 and data are recorded in Table 1.

The endoperoxides **17a**–**22b** have a broad range of IC_{50}s versus the K1 strain with the two most potent compounds expressing equivalent activity to arteflene. Apart from analogues **18a** and **18b**, compounds of the '**b**' series tend to be more potent than compounds of the '**a**' series (see **17b**, **19b**, **20b** and **22b** vs **17a**, **19a**, **20a** and **22a**). In line with previous SAR work on C(4)-methyl analogues of types **5**–**8**,[12] acetylation of the 8-hydroxyl function and oxidation of the sulfide group to a sulfone enhance activity for this class of endoperoxide. It is apparent that the incorporation of the phenyl group at the C(4) position in place of the C(4) methyl group of previous analogues (**5**–**8**) provides no advantage in terms of enhancing antimalarial activity.

In order to gain insight into potential antimalarial mechanisms of action of these endoperoxides, we performed an iron(II)-mediated degradation of sulfone **19b** in the presence of the spin-trapping agent TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (Scheme 4).[21,22] Following column chromatography of the reaction mixture, a major product (40%) was identified as β-ketosulfone **23**.[23a] The residual complex mixture was analysed by LCMS and several products were identified including the spin-trapped TEMPO adduct **25**.[23b] The formation of these products is consistent with the mechanism depicted in Scheme 4 whereby association of oxygen O_2 with reducing Fe(II) provides an oxyl radical by homolytic cleavage of the endoperoxide bridge. The intermediate oxyl radical species fragments to produce the secondary carbon centered radical species **24** in tandem with the sulfone **23**.

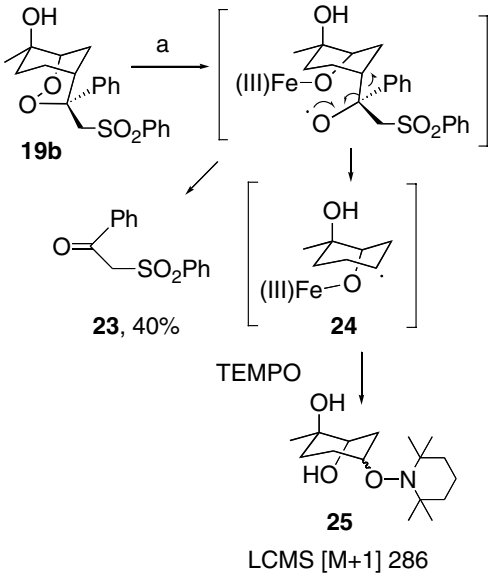
Although in vitro antimalarial assessment of the 'potentially protein reactive **23**' revealed that it is inactive, we have no knowledge about its potential activity if released within the parasite's food vacuole or cytosol[24a] through iron-induced degradation of the parent peroxide. Nevertheless, by analogy to the mode of action of

Table 1. Antimalarial activities of bicyclic endoperoxides



Compound	Y	Z	R	IC_{50}[a] (nM)
17a	CH_2SPh	Ph	H	298
17b	Ph	CH_2SPh	H	81
18a	CH_2S–*p*-Cl–Ph	Ph	H	247
18b	Ph	CH_2S–*p*-Cl–Ph	H	541
19a	CH_2SO_2Ph	Ph	H	230
19b	Ph	CH_2SO_2Ph	H	92
20a	CH_2SO_2–*p*-Cl–Ph	Ph	H	225
20b	Ph	CH_2SO_2–*p*-Cl–Ph	H	107
21a	CH_2SPh	Ph	Ac	164
21b	Ph	CH_2SPh	Ac	124
22a	CH_2SO_2Ph	Ph	Ac	72
22b	Ph	CH_2SO_2Ph	Ac	42
Arteflene				76
23				1000

[a] Parasites were maintained in continuous culture according to the method of Trager and Jensen.[18] IC_{50} values were measured according to the methods described by Desjardins.[19]



Scheme 4. Reagents: (a) Iron(II) acetate (2 equiv) TEMPO, (3 equiv), CH_3CN.

other antimalarial endoperoxides,[24b,c] it is expected that the activity of the peroxides described in Table 1 is mediated by the secondary carbon centered radical **24**, generated by iron-mediated bioactivation in the vicinity of one or more key parasite protein targets.[24b] It is also feasible, based on previous observations,[24c] that this radical species can also form potentially protein reactive carbocations via radical oxidation with ferric iron (generated through the initial SET-mediated cleavage of the endoperoxide bridge).

In conclusion, we have developed a novel and efficient approach to antimalarial endoperoxides that is based on a Diels–Alder reaction and a TOCO reaction. It follows a protocol that should allow a variety of structural modifications on the 1,3-diene and on the vinyl ketone participating in the Diels–Alder reaction as well as in the arylthiol participating in the TOCO reaction (Scheme 2). Consequently in addition to possible manipulations of the group 'R,' also groups 'Y' and 'Z' of the endoperoxides (**17a**–**22a**) reported in Table 1 should be prone to changes required for SAR studies. The best compounds from the present series are obtained in good yields and have equivalent activity to arteflene. Further work in this area will continue.

Acknowledgments

The authors thank the EPSRC (M.P.), the BBSRC (S.A.W., P.O.N., P.A.S., Grants BB/C006321/1 and 26/B13581) and the FCT (Fundação para a Ciência e a Tecnologia) Portugal, for funding this work. We also thank Dr. J. L. Maggs (Department of Pharmacology, University of Liverpool) for carrying out the LCMS study on analogue **19b**.

References and notes

1. Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211.
2. Xu, X. X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron Lett.* **1991**, *32*, 5785.
3. Hofheinz, W.; Burgin, H.; Gocke, E.; Jaquet, C.; Masciadri, R.; Schmid, G.; Stohler, H.; Urwyler, H. *Trop. Med. Parasitol.* **1994**, *45*, 261.
4. O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065.
5. Bachi, M. D.; Korshin, E. E. *Synlett* **1998**, 122.

6. Bachi, M. D.; Korshin, E. E.; Ploypradith, P.; Cumming, J. N.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903.
7. Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449.
8. Szpilman, A. M.; Korshin, E. E.; Rozenberg, H.; Bachi, M. D. *J. Org. Chem.* **2005**, *70*, 3618.
9. (a) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H. S.; Wataya, Y. *Tetrahedron* **2001**, *57*, 5979; (b) Kim, H.-S.; Begum, K.; Ogura, N.; Wataya, Y.; Nojima, M.; McCulloough, K. J. *J. Med. Chem.* **2002**, *45*, 4732.
10. Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099.
11. O'Neill, P. M.; Stocks, P. A.; Pugh, M. D.; Araujo, N. C.; Korshin, E. E.; Bickley, J. F.; Ward, S. A.; Bray, P. G.; Pasini, E.; Davies, J.; Verissimo, E.; Bachi, M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4193.
12. Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem.* **2003**, *46*, 2516.
13. Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.
14. Compound **17a**: ν_{max} (neat)/cm^{-1} 3520 (OH), 2922 (C–H), 1709, 1583 (C=C, Ar), 1305 (C–O), 1151 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.10 (m, 10H, Ar), 3.98 (d, J = 12.7 Hz, 1H, C(11)H′), 3.81 (br s, 1H, C(1)H), 3.64 (d, J = 12.7 Hz, 1H, C(11)H), 2.37–2.17 (m, 4H), 1.73–1.61 (m, 2H), 1.45 (s, 3H, C(10)H_3), 1.37 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 129.0, 128.4, 127.6, 124.7, 86.1 (C(4)), 82.4 (C(1)), 71.7 (C(8)), 42.7 (C(11)), 35.8, 32.1 (C(5)), 28.6 (C(10)), 24.7, 24.3. MS *m/z* (CI) $[M+NH_4]^+$ 374 (6), 339 (47), 246 (31), 235 (100), 229 (17), 217 (16) 105 (5). Found $[M+H^+]$ 357.15325 $C_{21}H_{25}O_3S$ requires 357.15244.
15. Compound **17b**: ν_{max} (neat)/cm^{-1} 3425 (OH), 2924 (C–H), 1583 (ArC=C), 1490, 1461 (ArC=C), 1375 (OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.02 (m, 10H, Ar), 3.60 (br s, 1H, C(1)H), 3.24 (d, J = 12.3 Hz, 1H, C(11)H′), 3.12 (d, J = 12,4 Hz, 1H, C(11)H), 2.60–2.58 (m, 1H, C(5)H), 2.53–2.43 (m, 1H), 2.00–1.93 (m, 2H), 1.92–1.60 (m, 2H), 1.43 (s, 3H, C(10)H_3), 1.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 130.3, 130.0, 129.95, 129.9, 129.0, 129.0, 128.4, 128.4, 127.7, 127.6, 126.9, 126.5, 125.1, 87.4 (C(4)), 82.5 (C(1)), 71.8 (C(8)), 43.5 (C(11)), 36.2, 29.4 (C(5)), 28.6 (C(10)), 24.8, 23.4, 23.3, 22.6. (Ar). MS *m/z* (CI) $[M+NH_4]^+$ 374 (6), 356 (10), 339 (82), 235 (100), 229 (32), 217 (52), 157 (11), 123 (34). Found $[M+Na]^+$ 379.1362 for $C_{21}H_{24}SO_3Na$, requires 379.1344.
16. Compounds **19a** and **19b** were purified by flash column chromatography using 50–70% ethyl acetate/hexane. Compound **19a**: ν_{max} (nujol)/cm^{-1} 3494 (OH), 2920, 1704, 1583 (Ar), 1459, 1377, 1305 (C–O), 1278 (S=O), 1192 (S=O), 1081 (–C–O–), 1052, 779, 784. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.18 (m, 10H, Ar), 4.27 (d, J = 14.8 Hz, 1H, C(11)H′, 4.03 (d, J = 14.8 Hz, 1H, C(11)H), 3.80 (br d, J = 2.8 Hz, 1H, C(1)H), 2.41 (m, 1H, C(5)H), 2.29–1.54 (m, 5H), 1.39 (s, 3H, C(10)H), 1.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.05, 133.5, 130.2, 129.0, 128.4, 127.6, 126.2, 124.8, 86.0 (C(1)), 82.5 (C(4)), 71.8 (C(8)), 42.7 (C(5)), 35.9, 31.9 (C(9)), 28.6, 24.3 (C(10)), 23.0. Anal. Calcd for $C_{21}H_{24}SO_5$: C, 64.93; H, 6.23. Found: C, 64.44; H, 6.18. MS *m/z* (CI, +ve) 388 ($[M^+]$, 6), 406 $([M+NH_4]^+$, 9), 278 (100), 371(3). Found $[M+NH_4]^+$ 406.16787, $C_{21}H_{28}O_5SN$ requires 406.16882. 6), 146 (16), 138 (10), 104 (12).
17. Compound **19b**: ν_{max} (nujol)/cm^{-1} 3499 (OH), 1715, 1584 (Ar), 1305 (C–O), 1284 (S=O), 1132 (S=O), 752, 698, 684. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.22 (m, 10H, Ar), 3.68 (d, J = 14.6 Hz, 1H, C(11)H′), 3.56 (br s, 1H, C(1)H), 3.50 (d, J = 14.7 Hz, 1H, C(11)H), 2.84 (m, 1H, C(5)H), 2.38–1.51 (m, 6H), 1.38 (s, 3H, C(10)H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 138.9, 133.4, 129.2, 128.5, 128.2, 127.7, 127.6, 85.9 (C(1)), 82.8 (C(4)), 71.7 (C(8)), 62.9 (C(11)), 36.0 (C(5)), 29.9, 28.5, 24.1 (C(10)), 23.9. Anal. Calcd for $C_{21}H_{24}SO_5$: C, 64.93; H, 6.23. Found: C, 64.76; H, 6.27. MS *m/z* (CI, +ve) 388 ($[M^+]$, 6), 406 $([M+NH_4]^+$, 1), 278 (100), 232 (9).
18. (a) O'Neill, P. M.; Rawe, S. L.; Borstnik, K.; Miller, A.; Storr, R. C.; Ward, S. A.; Bray, P. G.; Davies, J.; Ho Oh, C.; Posner, G. H. *ChemBioChem* **2005**, *6*, 2048; (b) Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timari, G.; Rossier, J. C.; Rudaz, M.; Barbuzzi, O.; Gerard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G.; Manzanares, I.; Canfield, C. J.; Fleck, S. L.; Robinson, B. L.; Peters, W. *Helv. Chim. Acta* **1995**, *78*, 647; (c) Najjar, T.; Gorrichon, L.; Baltas, M.; Andre-Barres, C.; Vial, H. *Org. Biomol. Chem.* **2005**, *3*, 1612.
19. Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673.
20. Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
21. Cazelles, J.; Robert, A.; Meunier, B. *J. Org. Chem.* **1999**, *64*, 6776.
22. Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y. X.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Tomas, J. S.; Scheurer, C.; Scorneaux, B.; Tang, Y. Q.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900.
23. (a) Compound **23**: ν_{max} (nujol)/cm^{-1} 1725 (C=O), 1670 (Ar), 1597 (Ar), 1581 (Ar), 1307 (S=O), 1227, 1155 (S=O), 1083, 1005, 902, 744, 684. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 4H), 7.89–7.45 (m, 6H), 4.74 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 139.2, 134.7, 134.6, 129.6, 129.5, 129.2, 129.0, 63.9. MS *m/z* (CI, +ve) 261 ($[M+H]^+$, 8), 278 ($[M+NH_4]^+$, 94), 138(100), 121 (71), 105 (78), 94 (22), 78 (21). For $C_{14}H_{12}SO_3$: C, 64.60; H, 4.65. Found: C, 64.24; H, 4.71; (b) The column used in LCMS studies was a Waters Symmetry 5-micron, C-8. The eluent was a gradient of acetonitrile in formic acid (0.1%): 10% for 10 min, 10% to 85% over 5 min; 0.9 mL/min. t_R = 2 min 9 s and 2 min 45 s. MS *m/z* 286($[M+H]^+$, 100), 158 (9), 126 (10).
24. For studies implicating the enzyme PfATP6, see: (a) Eckstein-Ludwig, U.; Webb, R. J.; van Goethem, I. D. A.; East, J. M.; Lee, A. G.; Kimura, M.; O'Neill, P. M.; Bray, P. G.; Ward, S. A.; Krishna, S. *Nature* **2003**, *424*, 957; For a recent review on iron(II) triggered antimalarial activity of peroxides, see: (b) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397; (c) Szpilman, A. M.; Korshin, E. E.; Hoos, R.; Posner, G. H.; Bachi, M. D. *J. Org. Chem.* **2001**, *66*, 6531.