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Synthesis of 1,2,4-trioxepanes via application of thiol-olefin Co-oxygenation methodology

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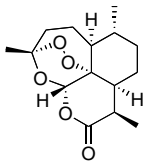
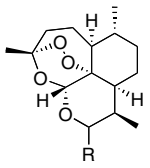
Abstract—Thiol-olefin co-oxygenation (TOCO) of substituted allylic alcohols generates β-hydroxy peroxides that can be condensed in situ with various ketones, to afford a series of functionalised 1,2,4-trioxepanes in good yields. Manipulation of the phenylsulfenyl group in **8a**–**8c** allows for convenient modification to the spiro-trioxepane substituents. Surprisingly, and in contrast to the 1,2,4-trioxanes examined, 1,2,4-trioxepanes are inactive as antimalarials up to 1000 nM and we rationalize this observation based on the inherent stability of these systems to ferrous mediated degradation. FMO calculations clearly show that the σ^* orbital of the peroxide moiety of 1,2,4-trioxane derivatives **4a** and **14b** are lower in energy and more accessible to attack by Fe(II) compared to their trioxepane analogues **8b** and **9b**.

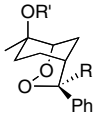
Malaria is a preventable disease caused by *Plasmodium species* the most lethal of which is *Plasmodium falciparum*. *P. falciparum* malaria has developed resistance to the most widely used regimens such as chloroquine and sulfadoxine/pyrimethamine.[1] As a result of the spread of multi-drug resistant Plasmodia we urgently require novel antimalarial pharmacophores.[2] In the early 1970s, Chinese chemists reported isolation and structure elucidation of the sesquiterpene 1,2,4-trioxane artemisinin (qinghaosu, **1**), the highly active antimalarial component of the ancient *Artemisia annua* (sweet wormwood) Chinese herbal remedy for fevers.[3] This important discovery represented a breakthrough in finding an effective antimalarial that was not quinoline-based. Sodium artesunate (**2**) is a succinic acid half-ester of the reduced lactol form of artemisinin (**1**) that, although prone to hydrolysis, is fast-acting, water-soluble, effective and widely used in areas of the world where malaria is endemic. Few examples of resistance to such trioxanes have been seen in the field or in the research laboratory. In combination with other antimalarial drugs, sodium artesunate (**2**) is rapidly becoming the drug of choice in most third-world cases of malaria.[4,5] The disadvantage of all semi-synthetic compounds is that their production requires **1** as starting material and currently the plant yields of artemisinin remain relatively low.



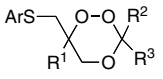
Artemisinin
(qinghaosu, (**1**))



Sodium artesunate, **2**
R = α-OC(O)$CH_2CH_2CO_2Na$



3a: R = CH_2SPh R' =H
3b: R = CH=CHPh R' = Ac



4a: R^1 = Me; R^2 and R^3 = $(CH_2)_5$; Ar=*p*-Cl-Ph
4b: R^1 = Ph; R^2 and R^3 = $(CH_2)_5$

To address the supply issue, a number of groups have attempted to produce totally synthetic peroxide analogues, some of which demonstrate remarkable antimalarial activity.[6a] During the course of our recent work on the synthesis of new antimalarial endoperoxides, we

Keywords: Artemisinin; 1,2,4-trioxane; Endoperoxide; Malaria; Mechanism of action.
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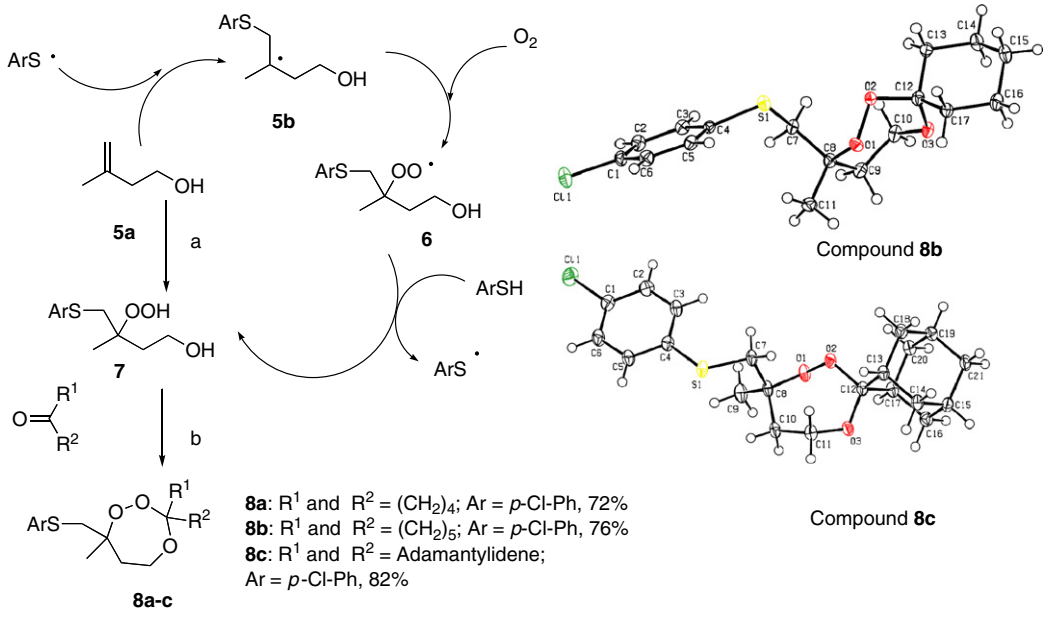
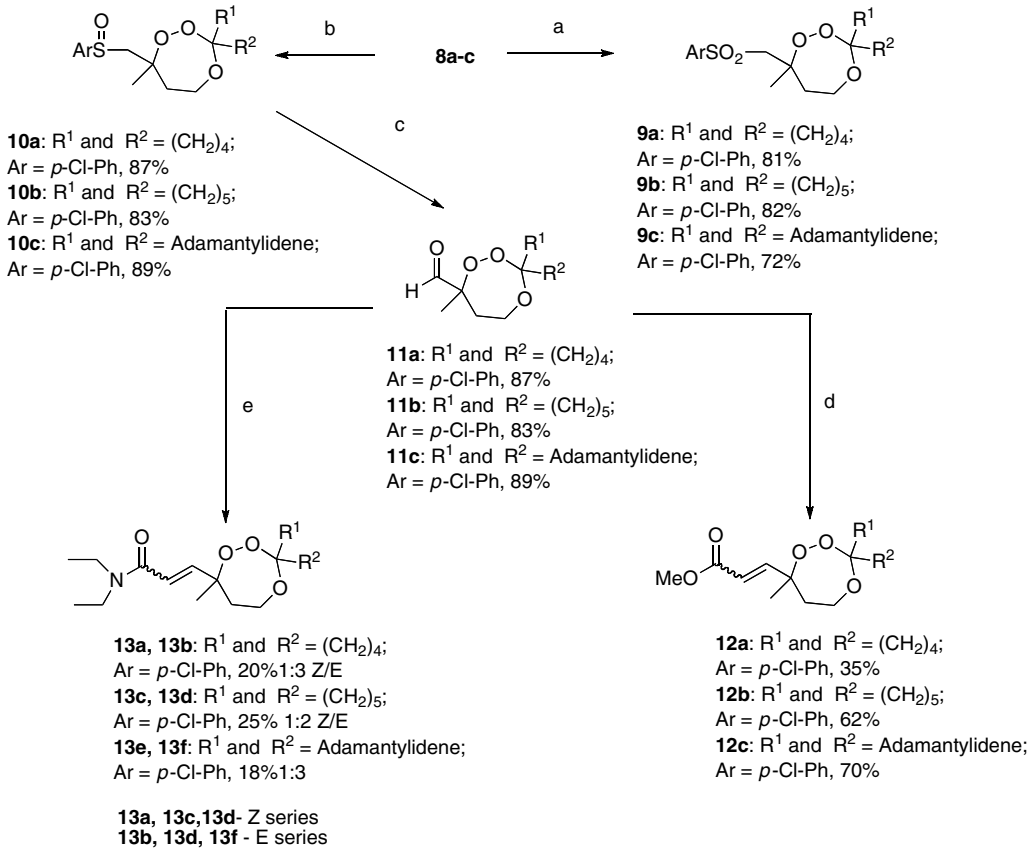
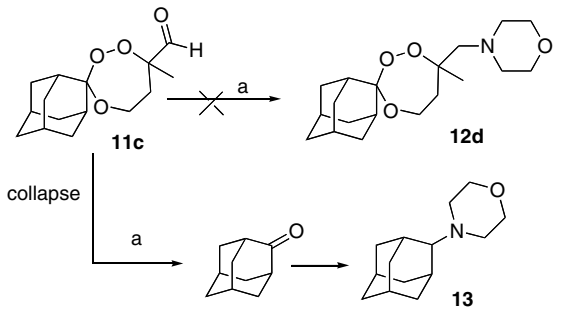


Scheme 1. Synthesis and crystal structures (ORTEP)[7] of substituted 1,2,4-trioxepanes by the TOCO reaction. Reagents and conditions: (a) PhSH (1.2 equiv), AIBN (0.07 equiv), O_2 (excess), hυ, 0 °C, CH_3CN; (b) ketone, cat. tosic acid.



Scheme 2. Synthesis of substituted 1,2,4-trioxepanes by functional group manipulation of the phenylsulfenyl group. Reagents and conditions: (a) *m*-CPBA (2.2 equiv), CH_2Cl_2, room temperature, 24 h; (b) *m*-CPBA (1.0 equiv), CH_2Cl_2, room temperature, 6 h; (c) 2,6-lutidine (4.2 equiv), trifluoroacetic acid anhydride (3.8 equiv), acetonitrile, room temperature; (d) $Ph_3P{=}CHCO_2Me$ (1.1 equiv), CH_2Cl_2, room temperature, 3 h; (e) $Ph_3P{=}CHCONEt_2$ (1.1 equiv), $CHCl_3/H_2O$ (1:1 v/v), NaOH (1.5 equiv), room temperature, 3 h.

utilized a thiol-olefin co-oxygenation (TOCO) reaction to generate bicyclic peroxides (**3a**) and endoperoxide cysteine protease pro-drugs (**3b**)[6b] structurally related to yingzhaosu A. By replacement of the terpene with an allylic alcohol we have recently described the one-pot synthesis of some simplified 1,2,4-trioxane analogues (**4a**)

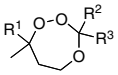


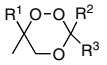
Scheme 3. Attempted synthesis of trioxane **12d** by reductive amination. Reagents and conditions: (a) aldehyde **11c** (1 equiv), morpholine (1.3 equiv) $NaBH(OAc)_3$ (1.3 equiv), CH_2Cl_2, 18 h, room temperature.

and (**4b**).[6c] In this communication, we report on the TOCO mediated synthesis of the 1,2,4-trioxepane pharmacophore, iron catalysed decomposition studies and preliminary in vitro antimalarial assessment.

The synthesis[6d] of target 1,2,4-trioxepanes **8a**–**8c** involves the in situ generation of a phenylthiol radical (AIBN/hv) which attacks the double bond of the homoallylic alcohol **5a** in a Markonikov fashion. The tertiary radical that is generated is trapped with molecular oxygen to form the peroxy radical **6**; radical hydrogen abstraction produces the α-hydroxyperoxide **7** and thiophenyl radical that continues the cycle. After consumption of the alcohol **5a** catalytic amounts of tosic acid and the requisite ketone are added to enable 1,2,4-trioxepane formation. In the free radical component of this chemistry high dilution is essential to prevent competitive formation of side products (Scheme 1).

Table 1. In vitro antimalarial activity versus the 3D7 strain of *Plasmodium falciparum*[14,15]

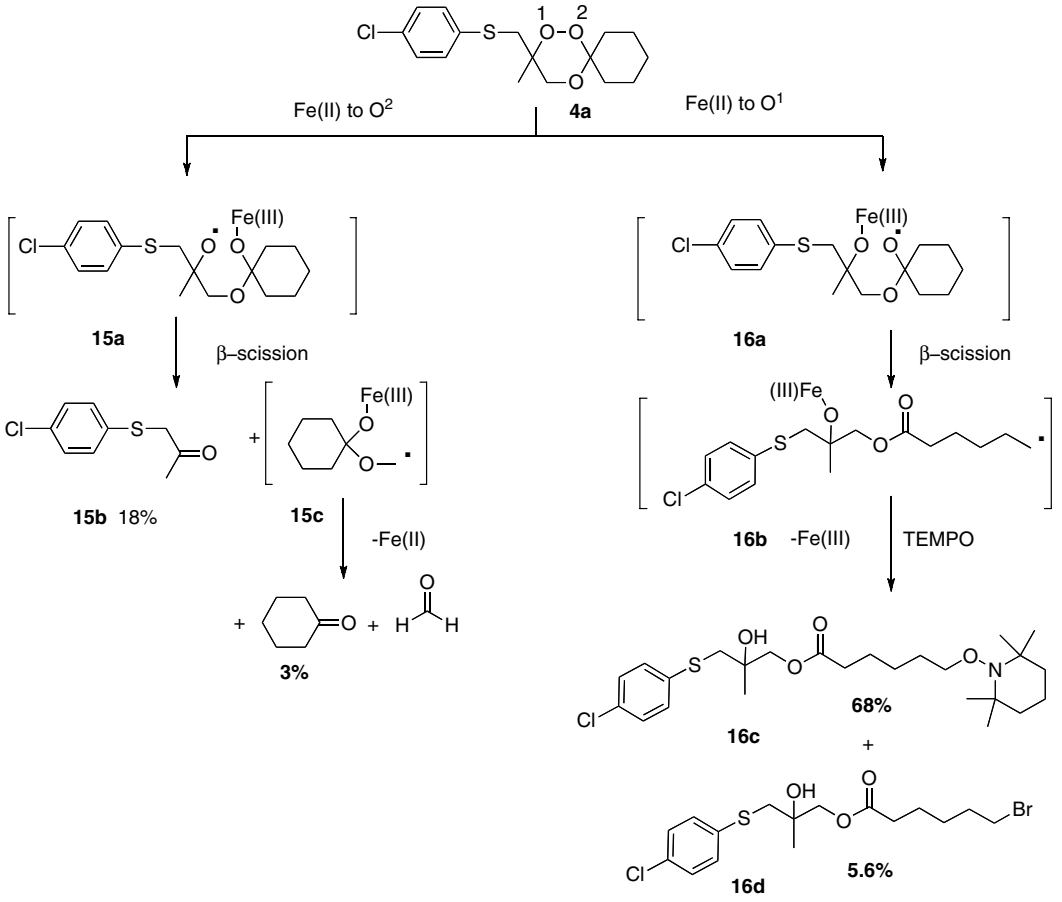

9a-9d


14a-14d

Compound	R^1	R^2 and R^3	IC_{50} (nM)
9a	*p*-Cl–Ph–SO_2–CH_2–	$(CH_2)_4$	>1000
9b	*p*-Cl–Ph–SO_2–CH_2–	$(CH_2)_5$	>1000
9c[16a]	*p*-Cl–Ph–SO_2–CH_2–	Adamantylidine	>1000
12c[16b]	–CH=$CHCO_2CH_3$–	Adamantylidine	>1000
14a[6c,17]	*p*-Cl–Ph–SO_2–CH_2–	$(CH_2)_4$	99.8
14b[6c,17]	*p*-Cl–Ph–SO_2–CH_2–	$(CH_2)_5$	136.9
14c[6c,17]	*p*-Cl–Ph–SO_2–CH_2–	Adamantylidine	188.7
14d[6c,17]	*p*-Cl–Ph–S–CH_2–	$(CH_2)_4$	110.5
Artemisinin			12.6

Parasites were maintained in continuous culture according to the method of Trager and Jensen.[14] IC_{50} values were measured according to the methods described by Desjardins.[15]

Previous studies with bicyclic endoperoxides and 1,2,4-trioxanes have revealed that endoperoxide sulfones



Scheme 4. Ferrous mediated degradation of trioxane **14e** and TEMPO spin-trapping of primary carbon-centred radical **16b**. Reagents and conditions: (a) Trioxane **14e** (1 equiv), $FeBr_2$ (1 equiv) TEMPO (1.3 equiv), THF, 24 h, room temperature.

display potent activity both in vitro and in vivo.[8–11] The sulfides were converted into the corresponding sulfones using excess amount of *m*-chloroperbenzoic acid in dichloromethane in excellent yields. The presence of the sulfenyl group within the trioxepane skeleton also provided us with the opportunity to prepare the aldehydes **11a**–**11c** from the corresponding sulfides by the Pummerer reaction. The sulfides **8a**–**8c** were converted to the corresponding sulfoxides **10a**–**10c** using stoichiometric amount of mCPBA in dichloromethane. The two diastereomers of the intermediate sulfoxides formed could be separated by column chromatography but they were used in situ for the Pummerer reaction as shown in Scheme 2. The aldehydes could then be converted to vinyl esters and amides by Wittig chemistry with the appropriate ylide. The rationale for the synthesis of **12a**–**13c** is based on the observation by Singh et al.[12] that several vinyl ester 1,2,4-trioxane derivatives have excellent in vivo activity profiles. For esters **12a**–**12c**, only the *E*-configured esters were produced [as evidenced by the large vinylic coupling constant (J_{H-H} = 16.2 Hz)]. For the vinyl amides **13a**–**13c**, a mixture of products was obtained with isomer ratios varying from 1:2 to 1:3 Z/E. The isomers could be readily separated by flash column chromatography.

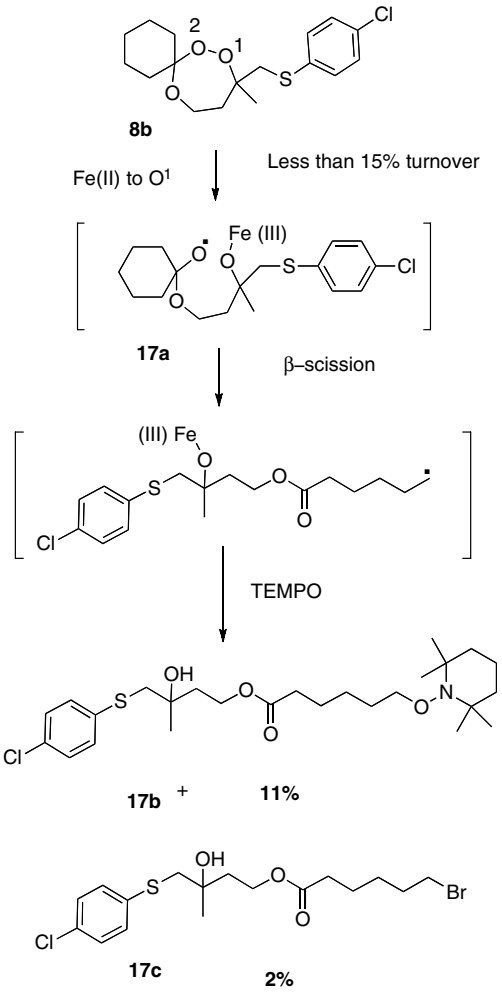
Attempts to enhance water solubility of the trioxepanes by either reductive amination to produce **12d** or oxidation of the aldehyde **11c** were unsuccessful. In the former case we observed decomposition of the trioxepane ring system to 2-adamantanone. For substrate **11c** the major product of the reaction was **13**, the reductive amination product of 2-adamantanone and morpholine (Scheme 3).

Selected 1,2,4-trioxepanes depicted in Scheme 2 were subjected to in vitro antimalarial assessment versus the 3D7 strain of *P. falciparum* according to a published procedure and the data are recorded in Table 1. For comparison several 1,2,4-trioxanes were also included in the screen. Remarkably, all of the 1,2,4-trioxepanes synthesized were inactive as antimalarials up to a concentration of 1000 nM. This is stark contrast to the corresponding spiro 1,2,4-trioxanes where activities as low as 99.8 nM were recorded.

Recent studies in the Dussault group have described the use of the 1,2,4-trioxepanes as a carbonyl protecting group due to the exceptional stability of this ring system under a range of different reaction conditions.[13a] Since the interaction of endoperoxide antimalarials with iron is key to their biological mechanism of action[13b] we reasoned that the poor activity of this series may be down to inherent lack of reactivity and enhanced stability of the 1,2,4-trioxepane ring compared with the 1,2,4-trioxane heterocycle. Thus, we decided to the compare the ferrous mediated degradation of a selected 1,2,4-trioxane with the corresponding 1,2,4-trioxepane.

Exposure of 1,2,4-trioxane **4a** to 1 equivalent of ferrous bromide in the presence of the spin-trapping agent TEMPO produced several products that were characterized by standard techniques (Scheme 4). Notably, all of **4a** was consumed during the 24 h reaction period. The mechanistic pathway depicted in Scheme 4 can rationalize the formation of isolated iron degradation products; the major product of this reaction was the TEMPO spin-trapped adduct **16c** that is produced by association of ferrous iron with O^1 to form the oxy radical intermediate that fragments by β-scission to produce the primary carbon-centred radical. This radical species is intercepted by TEMPO to produce the adduct **16c**;[18] in addition, small quantities of alkyl bromide **16d** are also produced. The alternative pathway proceeds through the formation of the alternative oxyl radical species **15a** by association of O^2 with ferrous iron (Scheme 4). Fragmentation produces ketone **18** and cyclohexanone (from the carbon-centred radical species **15c**). Our results are consistent with the recent iron degradation studies on cyclohexyl functionalized 1,2,4-trioxanes where both products of the O^1 and O^2 pathways were observed.[19]

The reaction of the corresponding 1,2,4-trioxepane **8b** under the same conditions led to poor turnover of substrate (<15%) (Scheme 5). No products of the O^2



Scheme 5. Ferrous mediated degradation of trioxepane **8b** and TEMPO spin-trapping. Reagents and conditions: (a) Trioxepane **8b** (1 equiv), $FeBr_2$ (1 equiv) TEMPO (1.3 equiv), THF, 24 h, room temperature.

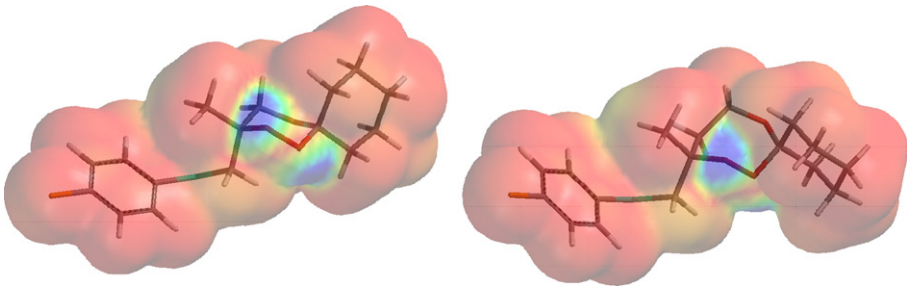


Figure 1. Low energy conformations of 1,2,4-trioxane **4a** and 1,2,4-trioxepane **8b** with the σ^* orbital mapped onto the electron density molecular surface.

pathway were observed; only products of the O^1 pathway were detected with 11% of the spin-trapped adduct **17b** constituting the major product of the reaction.

In order to rationalize this difference in reactivity molecular modelling studies were performed. A conformational search using a Monte-Carlo method using the MMFF94 forcefield[20] was performed on molecules **4a**, **14b** and **8b**, **9b**. Each conformer generated was subjected to a single point energy calculation at a semi-empirical level using PM3 parameters and the energy of the σ^* orbital of the peroxide bond was calculated. The Boltzmann weighted average energy of the orbital was compared for the trioxane and trioxepane molecular pairs **4a**/**14b** and **8b**/**9b**. The Boltzmann weighted average of the exposed surface area of the oxygen atoms in the peroxide bond was also calculated for each compound in order to assess the accessibility of the peroxide to attack by Fe(II). Interestingly, the energy of the σ^* orbital of the peroxide bond for the trioxane compounds was markedly lower than that of the corresponding trioxepanes for both the sulfide (~0.44 kcal/mol difference) and sulfone (~3 kcal/mol difference). Figure 1 displays a low energy conformation of **4a** and **8b** with the σ^* orbital mapped onto the molecular electron density surface. It is noteworthy that the accessibility to σ^* for the trioxane would appear to be much greater than that of σ^* of the trioxepane. Additionally, the trioxane molecules have a larger exposed surface area (~18 $Å^2$) of the peroxide oxygen atoms compared to the corresponding trioxepanes (~16 $Å^2$). Thus, the two factors of the accessibility and energy of the σ^* orbital of the peroxide bond could account for the surprisingly low biological activity observed and very poor turnover in the spin-trapping experiments of the 1,2,4-trioxepane compounds compared to the 1,2,4-trioxanes.

In summary, thiol-olefin co-oxygenation (TOCO) of substituted allylic alcohols generates β-hydroxy peroxides that can be condensed in situ with various ketones, to afford a series of functionalised 1,2,4-trioxepanes in good yields. Surprisingly, endoperoxides in this class are inactive up to 1000 nM and we rationalize this observation based on the inherent stability of these systems to ferrous mediated degradation.[21] FMO calculations support the degradation studies in the sense that the σ^* orbital of the peroxide bridge in 1,2,4-trioxanes is lower in energy and more accessible to attack by Fe(II) compared to their trioxepane analogues.

Acknowledgments

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7. Crystallographic data (excluding structure factors) for the structures **8b** and **8c** have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication numbers CCDC616381 and CCDC616382. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ca.uk).
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endoperoxide class of drug. The paper supports the idea of a non-haem iron mediated mechanism of bioactivation for the artemisinins see; (b) Eckstein-Ludwig, U.; Webb, R. J.; Van Goethem, I. D.; East, J. M.; Lee, A. G.; Kimura, M.; O'Neill, P. M.; Bray, P. G.; Ward, S. A.; Krishna, S. *Nature* **2003**, *424*, 957.

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16. (a) Procedure for the synthesis of compounds **8c** and **9c**; A 2-necked 500 ml round-bottomed flask was charged with a solution of 3-methyl-but-3-en-1-ol (0.5 g, 5.8 mmol) and AIBN (77.5 mg, 4.72 mmol) in acetonitrile (115 ml). The reaction vessel was flushed with oxygen for several minutes at 0 °C then stoppered and kept under a positive pressure of pure oxygen, with the aid of two oxygen balloons. The reaction mixture was vigorously stirred and UV irradiated at 0 °C using an externally mounted 100 W BLACK-RAY UV lamp at a distance of 5–7 cm, with the simultaneous addition of 4-chlorothiophenol (1250 mg, 8.64 mol) solution in acetonitrile (32 ml) over a period of 30 min. After completion of the addition, the reaction was left to continue stirring at 0 °C, for 4–6 h or until consumption of starting materials (monitored by tlc). The reaction vessel was then allowed to warm to −10 °C, flushed with nitrogen and a solution of 2-adamantanone (2.61 mg, 17.35 mmol) in dichloromethane (32 ml) was added followed by catalytic amount of tosic acid (25 mg). The mixture was left stirring at −10 °C and allowed to cool slowly to room temperature overnight. The solvent was removed by rotary evaporation and column chromatography on the crude mixture gave the product **8c** in 80% as a colourless solid; mp 62–64 °C; IR; V_{max} ($CHCl_3$)/cm^{-1}1011.2, 1090.2, 1112.2, 1450.1, 1472.0, 2840.6, 2901.3, 2980.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H, CH_3), 1.60 (m, 6H, adamantylidene), 1.76 (m, 3H, adamantylidene), 1.94 (m, 5H, adamantylidene), 2.20 (s, 1H, CH_2), 2.40 (s, 1H, CH_2), 3.20 (d, 1H, J = 13.18 Hz, SCH_2), 3.45 (d, 1H, J = 13.18 Hz, SCH_2), 3.65–3.85 (m, 2H, OCH_2), 7.20 (d, 2H, J = 8.46 Hz, Ar), 7.35 (d, 2H, J = 8.31 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.15, 130.14, 128.89, 127.07, 109.64, 106.38, 70.32, 58.15, 56.39, 51.74, 40.13, 40.05, 35.59, 32.65, 32.19, 32.15, 31.73, 31.36 25.36, 21.80, 20.78; MS (ES+) $[M+Na]^+$ (100), 417/419, $[2M+Na]^+$ 811/814, HRMS calculated for 417.1267 $C_{21}H_{27}O_3NaSCl$. Found: 417.1280 (Caution): since vapours of organic solvents may form explosive mixtures with oxygen in closed systems, all such reactions should be conducted behind safety shields. A solution of **8c** (0.43 g, 1.1 mmol) and *m*-CPBA (0.56 g, 3.3 mmol) in CH_2Cl_2 (17 ml) was stirred for 4–6 h at room temperature. After consumption of the more polar intermediate (monitored by tlc), the mixture was poured into a saturated solution of 5% K_2CO_3 solution. The mixture was then extracted with dichloromethane, the organic layer separated, dried over $MgSO_4$ and evaporated. Purification of the residue by column chromatography gave the desired sulfone **9c** compound in 72% yield; mp 100–102 °C; IR; V_{max}($CHCl_3$)/cm^{-1}821.4, 912.3, 1010.8, 1090.3, 1113.1, 1143.4, 1272.2, 1317.6, 1374.4, 1442.6, 1472.9, 1579.0, 2847.8, 2908.4, 2999.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–2.00 (m, 14H, adamantylidene), 1.55 (s, 3H, CH_3), 2.10 (s, 1H, CH_2), 2.25 (m, 1H, CH_2), 3.45 (d, 1H, J = 14.66 Hz, SO_2CH_2), 3.75 (m, 2H, OCH_2), 3.82 (d, 1H, J = 14.66 Hz, SO_2CH_2), 7.50 (d, 2H, J = 8.57 Hz, Ar), 7.95 (d, 2H, J = 8.55 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.92, 27.63, 35.32, 37.59, 44.21, 58.19, 61.93, 81.73, 108.87, 129.60, 130.40, 139.77, 140.56. MS (ES+) $[M+Na]^+$ (100), 449/451, $[2M+Na]^+$ (<5%) 875 HRMS calculated for 449.1165/451.1136, $C_{21}H_{27}NO_4NaS^{35}Cl$/$C_{21}H_{27}NO_4NaS^{37}Cl$. Found: 449.1169/451.1152, respectively.; (b) Preparation of **12c**; to a solution of the sulfoxide **10c** (1.17 g, 2.9 mmol) at 0 °C in CH_3CN (12 ml), 2,6-lutidine (1.30 g, 12.3 mmol) and trifluoro acetic anhydride (TFAA) (2.40 g, 11.2 mmol), in CH_3CN (12 ml) were added. The mixture was stirred at room temperature for 3 h and extracted with ethyl acetate. The organic layer was dried in $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography gave the product **11c** in 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.53–1.86 (m, 4H, adamantyl), 1.90–3.13 (m, 10H, adamantyl), 2.55 (br s, 2H, CH_2), 2.74 (t, 1H, J = 7.31 Hz, OCH_2), 3.11 (t, 1H, J = 7.16 Hz, OCH_2), 9.57 (s, 1H, CHO); (100 MHz, $CDCl_3$): δ 27.86, 36.71, 39.64, 43.30, 47.37, 129.51, 131.29, 218.57. To a solution of the aldehyde **11c** (0.37 g, 1.4 mmol) in CH_2Cl_2(12 ml) was added $Ph_3P{=}CHCO_2Me$ (0.5 g, 1.5 mmol) at room temperature and the solution was allowed to stir at this temperature for 3 h. The reaction mixture was concentrated and chromatographed on a silica gel to give the desired product **12c** in 70% yield as a colourless oil; IR V_{max} (neat) cm^{-1} 1108.7, 1161.3, 1319.3, 1446.6, 1653.3, 1722.2, 2854.6, 2919.5; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.53–1.75 (m, 6H, adamantylidene), 1.80 (br s, 3H, adamantylidene), 1.86–2.20 (m, 5H, adamantylidine), 2.36 (s, 1H, CH_2), 2.44 (s, 1H, CH_2), 3.60–4.00 (m, 2H, CH_2O), 3.79 (s, 2H, OCH_3), 5.98 (d, 1H, CH, J = 16.21 Hz), 7.20 (d, 1H, J = 16.19 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.11, 27.97, 34.33, 38.24, 43.10, 52.51, 59.16, 84.07, 109.35, 120.63, 152.62, 167.72. MS (ES+) $[M+Na]^+$ (100) 345, HRMS calculated for 345.1678 $C_{18}H_{26}NO_5Na$. Found: 345.1675.
17. All additional new compounds in Table 1 provided satisfactory ^{1}H and ^{13}C NMR and elemental analysis data. Details can be found in: O' Neill, P.M.; Amewu, R.; Mukhtar, A.; Ward, S.A.; Publication number WO2006016903; PCT/US2005/012236.
18. To a solution of **4a** (0.3 g, 0.91 mmol) in THF (15 ml) ferrous bromide (0.40 g, 1.82 mmol) and TEMPO (0.3 g, 1.82 mmol) were added and the reaction mixture was allowed to stir at ambient temperature under nitrogen atmosphere for more than 16 h. Following rotary evaporation of THF the crude product was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography to afford **16c** as the major product in 58%; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.09(br s, 6H, CH_3), 1.14 (br s, 6H, CH_3), 1.23–1.27 (m, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.35–1.57 (m, 8H, CH_2), 1.59–1.70 (m, 2H, CH_2), 2.31 (t, 2H, J = 7.4 Hz, $COCH_2$), 3.07 (d, 1H, J = 13.47 Hz, SCH_2), 3.17 (d, 1H, J = 13.48 Hz, SCH_2), 3.72 (t, 2H, J = 6.45 Hz, CH_2O), 4.02 (d, 1H, J = 11.39 Hz, CH_2O), 4.09 (d, 1H, J = 11.20 Hz, CH_2O), 7.24 (d, 2H, J = 8.54 Hz, Ar), 7.34 (d, 2H, J = 8.54 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.57, 24.53, 25.40, 26.51, 28.81, 32.75, 34.50, 40.05, 44.75, 69.74, 72.32, 76.90, 129.58, 131.71, 133.05, 135.58, 173.80 MS (ES+), $[M+H]^+$ (100) 486.1 and $[M+Na]^+$ 508.2, HRMS calculated for 486.2445 $C_{25}H_{41}O_4NSCl$. Found: 86.2459.The minor fraction was identified as **16d** MS (ES+), (100) $[M+Na]^+$ 431/433/435. HRMS calculated for 431.0058/433.0039/435.0009 $C_{16}H_{22}O_3NS^{35}ClBr$/ $C_{16}H_{22}O_3NS^{35}ClBr$/$C_{16}H_{22}O_3NS^{37}ClBr$. Found: 431.0053/433.0013/435.0000.
19. Tang, Y. Q.; Dong, Y. X.; Wang, X. F.; Sriraghavan, K.; Wood, J. K.; Vennerstrom, J. L. *J. Org. Chem.* **2005**, *70*, 5103.
20. Spartan'04, Wavefunction Inc, Irvine, CA, <http://www.wavefun.com//>.

21. For studies on the iron mediated degradation of diastereomers of 10-(2-hydroxy-1-naphthyl)-deoxoqinghaosu, (-deoxoartemisinin) see Wang, D.-Y.; Wu, Y.; Wu, Y.-L.; Li, Y.; Shan, F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1827; this paper suggests that the antimalarial potency of a given trioxane is directly related to the ease with which the peroxide bond is cleaved by iron. For detailed studies to the contrary, see Haynes, R. K.; Ho, W. Y.; Chan, H.-W.; Fugmann, B.; Stetter, J.; Croft, S. L.; Vivas, L.; Peters, W.; Robinson, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1381.