

# Photooxygenation of 3-aryl-2-cyclohexenols: synthesis of a new series of antimalarial 1,2,4-trioxanes<sup>☆</sup>

Chandan Singh,<sup>a,\*</sup> Nitin Gupta<sup>a</sup> and Sunil K. Puri<sup>b</sup>

<sup>a</sup>Division of Medicinal & Process Chemistry, Central Drug Research Institute, Lucknow 226001, India

<sup>b</sup>Division of Parasitology, Central Drug Research Institute, Lucknow 226001, India

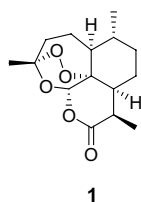
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**Abstract**—Using easily accessible 3-aryl-2-cyclohexenols, a photooxygenation route for the preparation of bicyclic 1,2,4-trioxanes is reported. Several of these trioxanes have shown significant antimalarial activity against multidrug resistant *Plasmodium yoelii* in mice by the oral route.

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Artemisinin **1**, since its isolation and characterization in the early 1970s from *Artemisia annua*, has been a subject of much investigation, not only due to its unique structure but also because of its potent antimalarial activity.<sup>1</sup> With the establishment of 1,2,4-trioxane as the antimalarial pharmacophore of artemisinin, various successful attempts have been made to prepare derivatives<sup>1</sup> as well as simple 1,2,4-trioxanes with varying orders of antimalarial activity.<sup>2,3</sup>

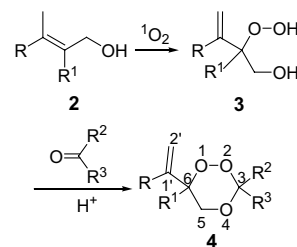


As a part of our endeavour to develop structurally simple synthetic substitutes of artemisinin, we earlier developed a new, convenient and high yielding method for the preparation of 1,2,4-trioxanes.<sup>2h</sup> Preparation of  $\beta$ -hydroxyhydroperoxides by photooxygenation of allylic alcohols and the acid-catalyzed condensation of the

hydroperoxides with aldehydes or ketones are the key steps of this method (Scheme 1). Several monocyclic 1,2,4-trioxanes prepared using this procedure have shown promising antimalarial activity in vitro and in vivo.<sup>4</sup>

Using easily accessible 3-aryl-2-cyclohexenols we have explored the scope of this photooxygenation route for the preparation of bicyclic 1,2,4-trioxanes and report herein the synthesis of a new series of 1,2,4-trioxanes some of which show significant antimalarial activity against multidrug resistant *Plasmodium yoelii* in mice by the oral route. There are only a few reports on photooxygenation of allylic cyclohexenols,<sup>5</sup> and the hydroperoxides were isolated only in one study.<sup>5c</sup> This is the first report on the synthesis of trioxanes using  $\beta$ -hydroxyhydroperoxides derived from photooxygenation of cyclohexenols.

3-Aryl-2-cyclohexenones **5a–c**, prepared by a literature procedure,<sup>6</sup> were reduced with NaBH<sub>4</sub> in MeOH or



Scheme 1.

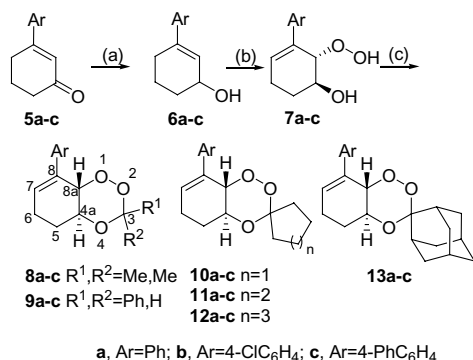
**Keywords:** Antimalarial; 1,2,4-Trioxane; Photooxygenation; *Plasmodium yoelii*.

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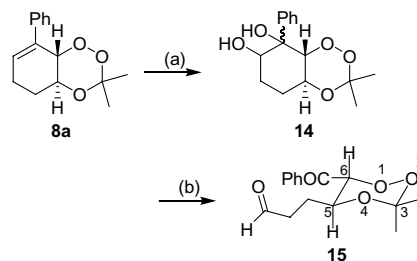
\* Corresponding author. Tel.: +91 522 2624273; fax: +91 522 2623405; e-mail: chandancdri@yahoo.com

$\text{CH}_2\text{Cl}_2$ – $\text{MeOH}$  (2:1) to yield 3-aryl-2-cyclohexenols **6a–c** in 95–98% yields. No double-bond reduction was observed under these conditions.<sup>7</sup> Methylene blue sensitized photooxygenation of these 3-aryl-2-cyclohexenols **6a–c** in  $\text{MeCN}$  gave 2-hydroperoxy-3-aryl-3-cyclohexenols **7a–c** in 22–35% yields. Hydroperoxides **7a–c** on acid catalyzed condensation with acetone furnished trioxanes **8a–c** in 25–37% yields.<sup>8,9</sup> Similar condensation with benzaldehyde, cyclopentanone, cyclohexanone, cycloheptanone and 2-adamantanone furnished trioxanes **9a–c**, **10a–c**, **11a–c**, **12a–c** and **13a–c** in 28–37%, 16–26%, 19–21%, 12–16% and 17–24% yields, respectively<sup>9</sup> (Scheme 2).

Though formation of both *cis* and *trans* fused trioxanes is possible, all the trioxanes isolated appeared to be single isomers by  $^1\text{H}$  and  $^{13}\text{C}$  NMR.<sup>9</sup> Also based on coupling constants it was not possible to assign unambiguously the stereochemistry. So an indirect approach was adopted. Thus trioxane **8a** was treated with catalytic  $\text{OsO}_4$  and 70% *t*-butyl hydroperoxide (TBHP) in the presence of triethylbenzylammonium acetate ( $\text{Et}_3\text{BnNOAc}$ ) to give diol **14**.<sup>10</sup> This diol appeared as a mixture of two isomers on TLC but homogeneous by  $^1\text{H}$  NMR. In the  $^1\text{H}$  NMR spectrum of **14** H-8a appeared as a doublet at 4.19 ppm with  $J = 9.4$  Hz, indicating that the stereochemistry at the ring junction is *trans*. This was further confirmed by  $\text{Pb}(\text{OAc})_4$  mediated cleavage of trioxane **14** to monocyclic trioxane **15**. In the  $^1\text{H}$  NMR spectrum of **15** H-6 appeared as a doublet at 5.20 ppm with  $J = 9.6$  Hz, confirming the *trans* stereochemistry. Since NMR spectra of all the trioxanes were similar it is assumed that the stereochemistry at the ring junction in all these trioxanes is *trans*. Also the  $^1\text{H}$  NMR spectra of these trioxanes deserves further comments. In the  $^1\text{H}$  NMR spectrum of **8a** (as well as all the other trioxanes), although signals for each proton were easily assigned, most of the signals appeared as multiplets and H-8a in particular gave rise to a very complex pattern. Thus H-8a which would be expected to be either a doublet (coupling with only H-4a) or at the most a doublet of doublets (direct coupling with H-4a and allylic coupling with H-7) appeared as a seven-line pattern. The 2D NMR ( $^1\text{H}$ – $^1\text{H}$  COSY) spectrum of **8a** revealed that H-8a was not only coupling with H-4a and H-7, but also with the C-6 protons (Scheme 3).



**Scheme 2.** Reagents and conditions: (a)  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , 1 h; (b)  $\text{O}_2$ ,  $h\nu$ , methylene blue,  $\text{MeCN}$ ,  $0^\circ\text{C}$ , 18 h; (c) aldehyde/ketone, concd  $\text{HCl}$  (cat.),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 3–6 h.



**Scheme 3.** Reagents and conditions: (a)  $\text{OsO}_4$  (cat.), 70% TBHP,  $\text{Et}_3\text{BnNOAc}$ ,  $\text{Me}_2\text{CO}$ , rt, 2 d, 64%; (b)  $\text{Pb}(\text{OAc})_4$ ,  $\text{PhH}$ , rt, stir, 1 h, 84%.

**Table 1.** In vivo antimalarial activity results of trioxanes against *Plasmodium yoelii* in mice by the oral route<sup>a</sup>

Compound	Dose (mg/kg/day)	% Suppression on day 4 <sup>b</sup>
<b>10c</b>	96	96.2
<b>11c</b>	96	98.5
<b>12c</b>	96	100.0
<b>13b</b>	96	96.3
$\beta$ -Arteether	48	100.0

<sup>a</sup> See Ref. 11.

<sup>b</sup> Percent suppression =  $[(C - T)/C] \times 100$ ; where  $C$  = parasitaemia in the control group, and  $T$  = parasitaemia in the treated group.

These trioxanes were subjected to in vivo antimalarial activity against multidrug-resistant *P. yoelii* in mice at a dose of 96 mg/kg by the oral route.<sup>11</sup> Trioxanes **10c**, **11c**, **12c** and **13b** showed more than 95% suppression of parasitaemia at this dose (Table 1). As can be seen in Table 1, trioxane **12c** was the most active of the series. It shows complete suppression of parasitaemia on day 4.

In conclusion, we have developed a photooxygenation route for the preparation of *trans*-fused bicyclic 1,2,4-trioxanes. Stereoselective photooxygenation of 3-aryl-2-cyclohexenols and acid catalyzed condensation of *trans*-2-hydroperoxy-3-aryl-3-cyclohexenols with aldehydes and ketones are the key steps of this method. Several new trioxanes prepared by this method have shown significant antimalarial activity against multidrug resistant *P. yoelii* in mice by the oral route.

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8. Typical procedure for the preparation of trioxanes: To a precooled solution (0°C) of hydroperoxide (**7a–c**, 1 equiv) and aldehyde or ketone (5–6 equiv) in CH<sub>2</sub>Cl<sub>2</sub> was added concentrated HCl (4–5 drops) and the solution stirred at 0°C for 3–6 h. The reaction mixture was poured over satd aq NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Standard workup gave the crude trioxane, which was chromatographed over silica gel (60–120 mesh) using EtOAc–hexane (1:99) as eluent to furnish the pure trioxane.
9. Selected characteristic data. Hydroperoxide **7a**: IR (neat, cm<sup>−1</sup>) 3354; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.70–1.88 (m, 1H), 1.95–2.09 (m, 1H), 2.30 (m, 2H), 2.60 (br s, 1H, OH), 4.36 (m, 1H), 4.82 (m, 1H), 6.18 (t, 1H, *J* = 3.4 Hz), 7.32 (m, 5H), 8.43 (br s, 1H, OOH); FAB-MS (*m/z*) 207 [M+H]<sup>+</sup>. Trioxane **8a**: mp 88–89°C; IR (KBr, cm<sup>−1</sup>) 1605; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.40 (s, 3H), 1.66 (s, 3H), 1.76–1.98 (m, 2H), 2.40 (m, 2H), 4.18 (m, 1H), 5.15 (m, 1H), 5.89 (m, 1H), 7.21–7.36 (m, 5H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 21.14 (q), 25.21 (t), 25.85 (t), 26.41 (q), 70.67 (d), 82.76 (d), 104.67 (s) 127.13 (2 × d), 127.76 (d), 128.52 (3 × d), 135.03 (s), 137.05 (s); FAB-MS (*m/z*) 247 [M+H]<sup>+</sup>; HR EIMS (*m/z*) calcd for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub> 246.1256 (M)<sup>+</sup>, found 246.1263. Trioxane **9a**: mp 135–136°C; IR (KBr, cm<sup>−1</sup>) 1597; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 2.01–2.17 (m, 2H), 2.47 (m, 2H), 4.16 (m, 1H), 5.42 (m, 1H), 5.95 (m, 1H), 6.31 (s, 1H), 7.23–7.40 (m, 8H), 7.49–7.54 (m, 2H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 25.24 (t), 25.55 (t), 77.90 (d), 82.61 (d), 105.70 (d) 127.22 (2 × d), 127.46 (2 × d), 127.87 (d), 128.81 (2 × d), 128.87 (3 × d), 130.39 (d), 134.56 (s), 134.86 (s), 136.94 (s); FAB-MS (*m/z*) 295 [M+H]<sup>+</sup>. Trioxane **11a**: IR (neat, cm<sup>−1</sup>) 1600; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.46–1.65 (m, 9H), 1.75–1.99 (m, 2H), 2.24–2.45 (m, 3H), 4.22 (m, 1H), 5.17 (m, 1H), 5.88 (m, 1H), 7.30 (m, 5H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 22.71 (t), 22.82 (t), 25.24 (t), 25.95 (t), 25.99 (t), 29.90 (t), 35.72 (t), 69.78 (d), 82.93 (d), 104.88 (s), 127.10 (2 × d), 127.71 (d), 128.54 (3 × d), 135.19 (s), 137.15 (s); FAB-MS (*m/z*) 287 [M+H]<sup>+</sup>. Trioxane **13a**: mp 138–140°C; IR (KBr, cm<sup>−1</sup>) 1604; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.55–2.19 (m, 15H), 2.40 (m, 2H), 2.97 (br s, 1H), 4.18 (m, 1H), 5.18 (m, 1H), 5.88 (m, 1H), 7.30 (m, 5H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) 25.30 (t), 26.03 (t), 27.65 (2 × d), 30.08 (d), 33.48 (t), 33.74 (t), 33.81 (t), 34.11 (t), 37.18 (d), 37.66 (t), 69.18 (d), 82.81 (d), 106.91 (s), 127.10 (2 × d), 127.67 (d), 128.56 (2d), 128.66 (d), 135.35 (s), 137.28 (s); FAB-MS (*m/z*) 339 [M+H]<sup>+</sup>; HR EIMS (*m/z*) calcd for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub> 338.1882 (M)<sup>+</sup>, found 338.1851. Trioxane **14**: mp 146–148°C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.32 (s, 3H), 1.67 (s, 3H), 1.69–2.10 (m, 4H), 2.68 (s, 1H, OH), 3.90 (dd, 1H, *J* = 10.6, 4.8 Hz), 4.19 (d, 1H, *J* = 9.4 Hz), 4.47 (ddd, 1H, *J* = 11.2, 9.4, 4.2 Hz), 7.30–7.51 (m, 5H); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>/D<sub>2</sub>O): δ 1.32 (s, 3H), 1.67 (s, 3H), 1.69–2.10 (m, 4H), 3.90 (dd, 1H, *J* = 10.6, 4.8 Hz), 4.19 (d, 1H, *J* = 9.4 Hz), 4.47 (ddd, 1H, *J* = 11.2, 9.4, 4.2 Hz), 7.30–7.51 (m, 5H); FAB-MS (*m/z*) 281 [M+H]<sup>+</sup>. Trioxane **15**: IR (neat, cm<sup>−1</sup>) 1688; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.40 (s, 3H), 1.64 (s, 3H), 1.69–1.96 (m, 2H), 2.61 (m, 2H), 4.40 (td, 1H, *J*<sub>t</sub> = 9.6 Hz, *J*<sub>d</sub> = 3.0 Hz), 5.20 (d, 1H, *J* = 9.6 Hz), 7.50 (t, 2H, *J* = 7.2 Hz), 7.63 (t, 1H, *J* = 7.2 Hz), 8.05 (d, 2H, *J* = 7.2 Hz), 9.76 (t, 1H, *J* = 1.2 Hz); FAB-MS (*m/z*) 279 [M+H]<sup>+</sup>.
10. A slight modification of the Sharpless' procedure was used: Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, 43, 2063–2066.
11. The in vivo efficacy of compounds was evaluated against *Plasmodium yoelii* (MDR) in the Swiss mice model. The colony of bred Swiss mice (25 ± 1 g) were inoculated with 1 × 10<sup>6</sup> parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions were prepared in groundnut oil, so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg) in 0.1 mL and administered orally for each dose. Parasitaemia level were recorded from thin blood smears between days 4–28.<sup>12</sup> Mice treated with β-artether served as a positive control.
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