ORGANIC LETTERS

2007
Vol. 9, No. 21
4327−4329

# Conversion of Antimalarial Drug Artemisinin to a New Series of Tricyclic 1,2,4-Trioxanes[1]

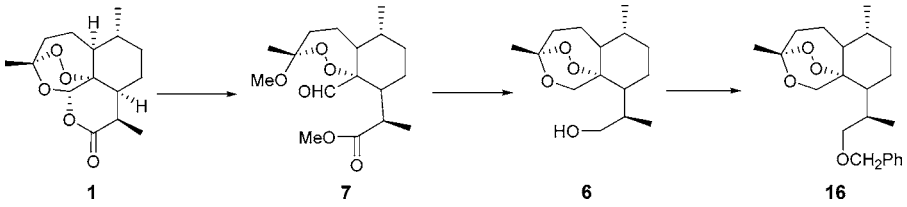
**Chandan Singh,*,† Sandeep Chaudhary,† Rani Kanchan,† and Sunil K. Puri‡**

*Division of Medicinal & Process Chemistry and Division of Parasitology, Central Drug Research Institute, Lucknow-226001, India*

*chandancdri@yahoo.com*

**Received August 3, 2007**

## ABSTRACT




**A highly efficient route for the conversion of the antimalarial drug artemisinin to a novel hydroxy-functionalized tricyclic 1,2,4-trioxane 6 is reported. Neither the trioxane 6 nor its derivatives 14–16, all of which lack the hydrolytically unstable acetal–lactone linkage, show antimalarial activity comparable with that of artemisinin.**

The discovery of artemisinin **1** as the active principle of the Chinese traditonal drug *Artemisia annua* is a major milestone in malaria chemotherapy.[2] Artemisinin and its more potent semisynthetic derivatives, e.g., artemether **2**, arteether **3**, and artesunic acid **4**, are active against both chloroquine-sensitive and -resistant malaria (Figure 1). These compounds are fast acting and are currently the drugs of choice for the treatment of cerebral/complicated malaria caused by multidrug-resistant *Plasmodium falciparum*.[2] While these drugs show excellent activity by the parenteral route, they show poor absorption by the oral route.[3] While the 1,2,4-trioxane moiety is believed to be essential for antimalarial activity of these drugs,[4] the extra acetal−lactone or acetal−acetal linkages are linked with their poor hydrolytic stability and therefore poor absorption by the oral route. Several derivatives of artemisinin prepared by replacement of oxygen at C-10 with carbon, e.g., **5a** and **5b**, have shown a better activity profile than the parent oxygen-containing compounds, and the improved activity has been attributed to their improved hydrolytic stability.[5]

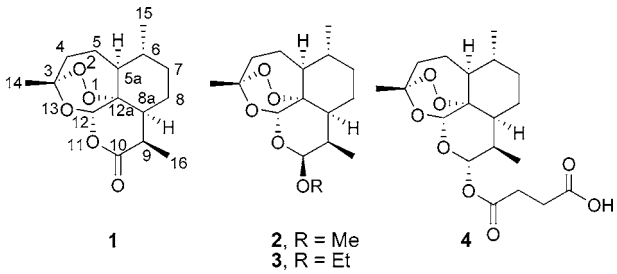



**Figure 1.** Artemisinin and its clinically useful derivatives.

Posner et al. have reported the synthesis of tricyclic 1,2,4-trioxanes **5c**,**d** which are very close analogues of artemisinin.

† Division of Medicinal & Process Chemistry.
‡ Division of Parasitology.

(1) C.D.R.I. communication no. 7162.

(2) (a) Klayman, D. L. *Science* **1985**, *228*, 1049−1055. (b) Luo, X. D.; Shen, C. C. *Med. Res. Rev.* **1987**, *7*, 29−52. (c) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253−297. (d) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1651−1681. (e) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661−1667. (f) Ploypradith, P. *Acta Trop.* **2004**, *89*, 329−342. (g) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945−2964. (h) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425−448. (i) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487−494.

(3) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301−315.

(4) Butler, A. R.; Yu, Y. L. *Chem. Soc. Rev.* **1992**, *21*, 85−90.

10.1021/ol701887x CCC: $37.00 
**Published on Web 09/18/2007**

These compounds have been shown to be less active than artemisinin against *Plasmodium berghei* in mice (Figure 2).[6]

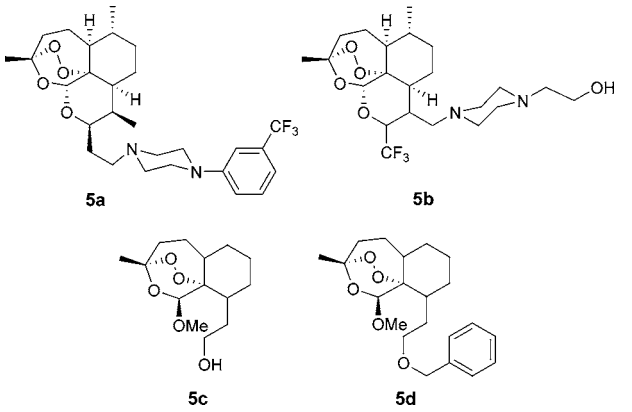
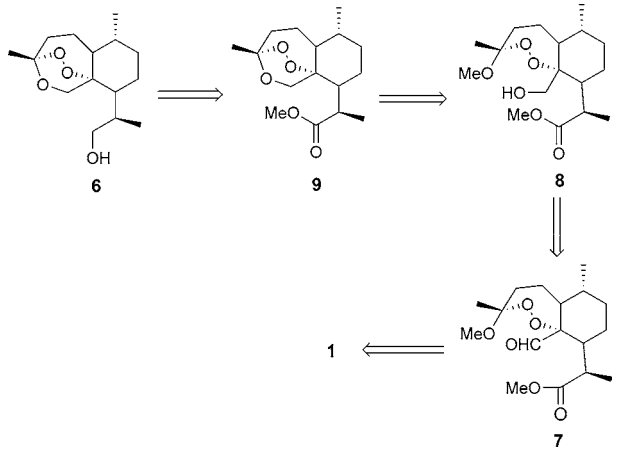



**Figure 2.** Artemisinin-derived antimalarials lacking $C_{10}-O$ linkage.

All of these compounds, however, have the C-12 acetal linkage and, therefore, still carry an element of hydrolytic instability. Herein, we report, for the first time, a three-step conversion of artemisinin to hydroxy-functionalized tricyclic 1,2,4-trioxane **6** which lacks extra acetal linkages both at C-10 and C-12. We also report the synthesis of ester and ether derivatives of this novel 1,2,4-trioxane.

Our initial strategy to prepare the required tricyclic 1,2,4-trioxane **6** is shown in Scheme 1. Accordingly, using the

**Scheme 1**

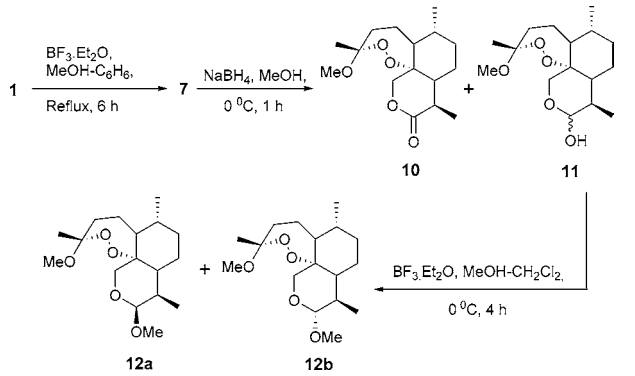



published procedure,[7] artemisinin was reacted with methanol in presence of $BF_3{\cdot}OEt_2$ to furnish bicyclic peroxide **7** in 70% yield.

Reaction of **7** with $NaBH_4$ in MeOH furnished a mixture of peroxides **10** and **11** instead of the desired bicyclic peroxy alcohol **8**. The reaction of **7** with other derivatives of $NaBH_4$ such as $NaB(OAc)_3H$ or $NaBH_3CN$ furnished the same products. The ratio of the peroxy products varied with reaction conditions and reagent used.

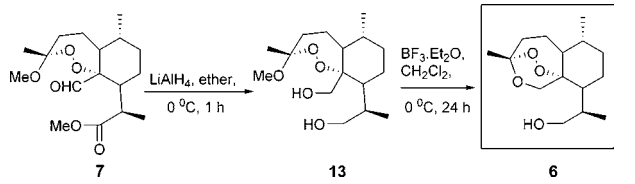
Compound **11** on reaction with MeOH in the presence of $BF_3{\cdot}OEt_2$ furnished the corresponding ethers **12a** and **12b**, both of which were separated and characterized. **12a** and **12b** are incidently the ring-B seco analogues of the antimalarial drug artemether (Scheme 2).

**Scheme 2**




Our failure to achieve the conversion of **7** to the target alcohol **8** required a change in our original plan. Accordingly, peroxide **7** was reacted with $LiAlH_4$ in dry ether at 0 °C to furnish diol **13** in 80% yield. Diol **13** on reaction with a catalytic amount of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ furnished the required tricyclic 1,2,4-trioxane alcohol **6** in 80% yield (Scheme 3).

**Scheme 3**




Having achieved an efficient conversion of artemisinin to tricyclic alcohol **6**, we prepared several ester and ether derivatives of this compound.

(5) (a) Hindley, S.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052−1063. (b) Avery, M. A.; Alvim-Gaston, M.; Vroman, J. A.; Wu, B.; Ager, A.; Peters, W.; Robinson, B. L.; Charman, W. *J. Med. Chem.* **2002**, *45*, 4321−4335. (c) Posner, G. H.; Paik, I.-H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060−1065. (d) Grellepois, F.; Chorki, F.; Ourevitch, M.; Charneau, S.; Grellier, P.; McIntosh, K. A.; Charman, W. N.; Pradines, B.; Crousse, B.; Bonnet-delpon, D.; Begue, J. P. *J. Med. Chem.* **2004**, *47*, 1423−1433. (e) Paik, I.-H.; Xie, S.; Shapiro, T. A.; Labonte, T.; Narducci Sarjeant, A. A.; Baege, A. C.; Posner, G. H. *J. Med. Chem.* **2006**, *49* (9), 2731−2734. (f) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. *J. Med. Chem.* **2007**, *50* (10), 2516−2519.

(6) (a) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459. (b) Posner, G. H.; Oh, C. H.; Webster, K.; Ager, A. L., Jr.; Rossan, R. N. *Am. J. Trop. Med. Hyg.* **1994**, *50*, 522−526.

(7) Singh, C.; Kanchan, R. *Indian J. Chem.* **1999**, *38B*, 1368−1370.

Trioxane **6** on reaction with $Ac_2O/Et_3N$ and succinic anhydride/$Et_3N$ furnished acetate **14** (99% yield) and hemisuccinate **15** (98% yield), respectively. Trioxane **6** on reaction with $PhCH_2Br/NaH$ furnished the benzyl derivative **16** (Figure 3).

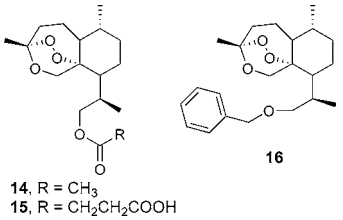



**Figure 3.** Derivatives of tricyclic trioxane **6**.

Peroxides **7**, **10**, **11**, **12a**,**b**, and trioxane **6** and its derivatives **14**−**16** were assessed for their antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in mice by intramuscular route.[8] The antimalarial data of some of the selected compounds are given in Table 1.

As can be seen from Table 1, these compounds are less active than arteether, thus emphasizing the importance of the tetracyclic system of artemisinin.

In conclusion, we have developed an efficient process for conversion of artemisinin to hydrolytically stable tricyclic 1,2,4-trioxane **6** and its derivatives. We have also prepared several seco analogues of artemisinin and evaluated them for their antimalarial activity.

Our results show that all of these seco analogues are less active than artemisinin, thus emphasizing the importance of the tetracyclic system present in artemisinin.

(8) For an in vivo antimalarial efficacy test procedure, see: Singh, C.; Chaudhary, S.; Puri, S. K. *J. Med. Chem.* **2006**, *49* (24), 7227−7233.

**Table 1.** Antimalarial Activity of Trioxane **6** and Its Derivatives **14**−**16**

| compd | log *P* | dose (mg/kg/day) | % suppression of parasitaemia on day 4[a] | cured/ treated |
|---|---|---|---|---|
| **6** | 2.74 | 96 | 71.98 | 0/5 |
| **14** | 2.97 | 96 | 14.10 | 0/5 |
| **15** | 2.64 | 96 | 38.46 | 0/5 |
| **16** | 4.84 | 96 | 53.57 | 0/5 |
| **3** | 3.84 | 6 | 100 | 5/5 |

[a] Percent suppression = $[(C - T)/C]100$; where $C$ = parasitaemia in control group and $T$ = parasitaemia in treated group.

**Acknowledgment.** S.C. and R.K. are grateful to the Council of Scientific & Industrial Research (CSIR), New Delhi, for the award of Senior Research Fellowships.

**Supporting Information Available:** Experimental details and characterization data, purity/characterization table, and $^1H$ NMR and $^{13}C$ NMR spectra of compounds **6**, **7**, **12a**,**b**, and **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701887X