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Artemisinin Tricyclic Analogs: Role of a Methyl Group at C-5a

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Abstract: New artemisinin tricyclic analogs, bearing a methyl group at C-5a were synthetized through ozonation of vinylsilanes. Presence of such a substituent was detrimental to the antimalarial activity of these trioxanes, thus reinforcing the hypothesis that tight hemin-trioxane complexes are involved in the activation phase of these compounds. © 1998 Elsevier Science Ltd. All rights reserved.

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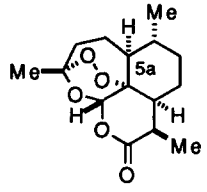
The sesquiterpene lactone, 1,2,4-trioxane artemisinin **1** (*Qinghaosu*), isolated from *Artemisia annua* L. (*Compositae*), constitutes one the most promising antimalarial drugs [1]. Interestingly, the activity of artemisinin is significantly maintained in most of simplified tricyclic analogs **2** (where R" = H) [2,3,4,5]. It has been postulated that interaction of 1,2,4-trioxanes, such as **2**, with the target hemin in the Fe (II) oxidation state proceeds through the complexes **3**, in which the peroxide bridge of trioxane coordinates with the metal center of hemin [6].



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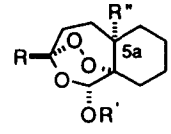

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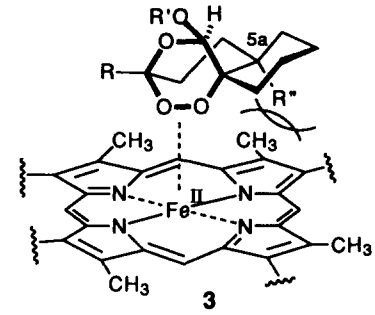

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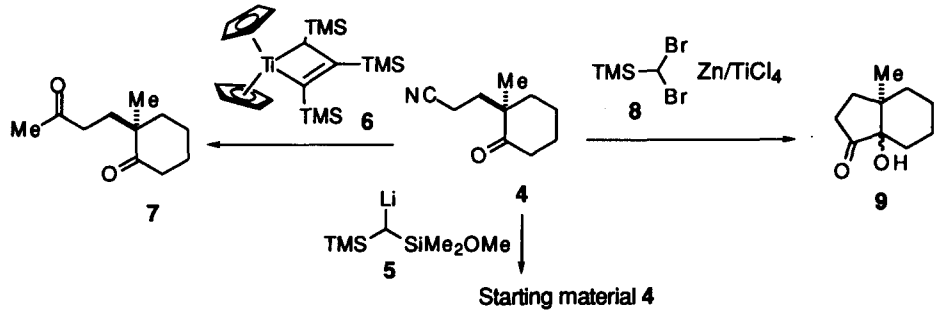
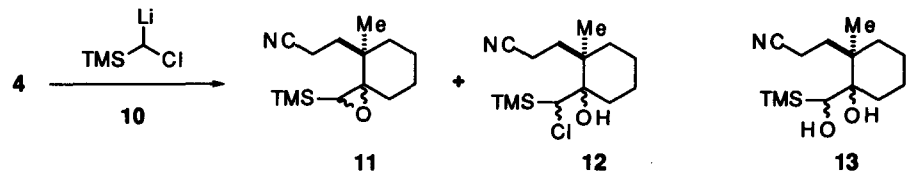
This activation phase is followed by the generation of free-radical species that ultimately damage specific macromolecules within the *Plasmodium* parasite, a hypothesis recently reinforced by the characterization of a covalent adduct between artemisinin and a heme model [7]. We reasoned that, in the case of C-5a substituted trioxanes **2** (where R" ≠ H)[1], the activation phase **3** should be thwarted, because of the destabilizing steric interaction between the *axial* R" group of **2** and heme nucleus; consequently a notable decrease of the antimalarial activity was expected for such molecules, compared with the non-substituted counterparts.

With the aim to support the above putative mechanism, the tricyclic 1,2,4-trioxanes **18a** and **18b** bearing a methyl group at the C-5a angular position (**2**, R = R" = Me) were synthetized through the vinylsilane route [9], and their antimalarial potencies were evaluated. The common starting material in these approaches was enantiomerically pure ketonitrile (*R*)-**4** [10]. Direct introduction of a vinylsilyl moiety to **4** (**4** → **15**) was first examined. While attempted addition of [(methoxydimethylsilyl)(trimethylsilyl)methyl] lithium **5** [11] to **4** returned only starting material, the condensation of titanacyclobutene **6** [12] to **4** (toluene, 8 h, 80 °C) gave unexpectedly diketone **7**, resulting from the addition of reagent **6** to the nitrile function of **4**, with a 65 % yield. Another unexpected result was obtained in the treatment of **4** with (dibromomethyl)trimethylsilane **8** in the presence of zinc and titanium tetrachloride (CH_2Cl_2, 3 h at 25 °C) [13]: reductive cyclization of **4** took place, furnishing the bicyclic derivative **9** in 45 % yield.[2]

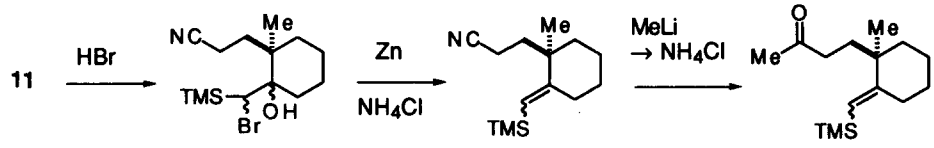


In view of these results, an original, indirect route for the preparation of vinylsilanes **15**, based on the two-step deoxygenation of epoxysilanes **11** was next developed.[3] Addition of chloromethyl(trimethylsilyl) lithium **10** [16] to ketonitrile **4** (*i* : 1 eq of $TMSCH_2Cl$; *ii* : 3 eq of LiCl; *iii* : 1.2 eq of *s*-BuLi; *iv*: 2 eq of TMEDA, *v*: 0.6 eq of **4**, THF, -78 °C, 3 h) gave a mixture of epoxysilanes **11** (11: 8: 5: 1 mixture of diastereomers, 35 % yield), of chlorhydrines **12** (20 % yield), and of unreacted starting material **4** (35 % yield).



1- For a recent synthesis of a tricyclic 1,2,4-trioxane bearing a nitrile group at C-5a, see [8].
2- For a related electroreductively-promoted intramolecular coupling of ketones with nitriles, see [14].
3- For a related method, see [15].

The above mixture was separated by flash chromatography over silica gel. During this operation, chlorhydrines **12** were converted into α-diols **13**, which were next transformed with a 75 % yield into desired epoxysilanes **11** (PPh_3, diethyl diazodicarboxylate, toluene, 2 h at 60 °C). Treatment of **11** with 48 % aqueous HBr (CH_2Cl_2, 5 min at 20 °C) [17,18] afforded bromhydrines **14** (76 % yield), which upon zinc reduction gave key vinylsilanes **15**[4] as a 1.5:1 mixture of stereomers (20 eq of zinc powder, NH_4Cl, EtOH/H_2O, 10 min at 20 °C, 92 % yield). Addition of MeLi to **15** then led to pivotal keto-vinylsilanes **16**[5] (stereomers in the ratio 1.5: 1) (4 eq MeLi, Et_2O, -78 °C → 20 °C, 10 min, then aqueous NH_4Cl, 65 % yield).



14 **15** **16**

Ozonation of **16** [9], followed by treatment with boron trifluoride-etherate complex gave peroxide aldehyde **17**[6] as a 3: 1 mixture of diastereomers (O_3, MeOH-CH_2Cl_2, -78 °C, then BF_3-OEt_2, 2 h at 20 °C, 80 % yield of crude product), which was finally converted into our goals trioxanes **18a**[7] (MeOH, BF_3-OEt_2, $HC(OMe)_3$, 1 h at 20 °C, 35 % overall yield from **16**) and **18b**[8] (Ac_2O, BF_3-OEt_2, 12 h at 20 °C, 42 % overall yield from **16**). Structure of **18b** was unequivocally established through an X-ray crystallographic analysis.[9]

4-**15**: colorless oil; IR (film, cm^{-1}) 2238, 1604; ^1H NMR ($CDCl_3$, 200 MHz), *major isomer* δ: 0.08 (s, 9H), 0.98, (s, 3H), 1.20-1.80 (m, 9H), 1.90-2.25 (m, 2H), 2.39 (dt, *J* = 13.3, 4.5 Hz, 1H), 5.13 (s, 1H); *minor isomer* δ: 0.13 (s, 9H), 1.12 (s, 3H), 1.20-1.80 (m, 10H), 1.90-2.40 (m, 2H), 5.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz), *major isomer* δ: 0.2 (3 CH_3), 12.2 (CH_2), 21.6 (CH_2), 25.3 (CH_3), 28.1 (CH_2), 31.4 (CH_2), 32.9 (CH_2), 39.9 (C), 40.6 (CH_2), 120.5 (C), 121.9 (CH), 161.6 (C); Anal. Calcd. for $C_{14}H_{25}NSi$: C, 71.42; H, 10.69; N, 5.94. Found: C, 71.21; H, 10.77; N, 5.83.

5-**16**: colorless oil; IR (film, cm^{-1}) 1722, 1594; ^1H NMR ($CDCl_3$, 200 MHz), *major isomer* δ: 0.01 (s, 9H), 0.87 (s, 3H), 1.17-1.70 (m, 8H), 1.90-2.30 (m, 4H), 2.04 (s, 3H), 5.05 (s, 1H); *minor isomer* δ: 0.07 (s, 9H), 1.02 (s, 3H), 1.17-1.70 (m, 8H), 1.90-2.30 (m, 4H), 2.04 (s, 3H), 5.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz), *major isomer* δ: 0.22 (3 CH_3), 21.6 (CH_2), 25.6 (CH_3), 28.3 (CH_2), 30.5 (CH_3), 31.3 (2 CH_2), 38.6 (CH_2), 40.0 (C), 40.8 (CH_2), 119.9 (CH), 163.2 (C), 209 (C); Anal. Calcd. for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 71.14; H, 11.24.

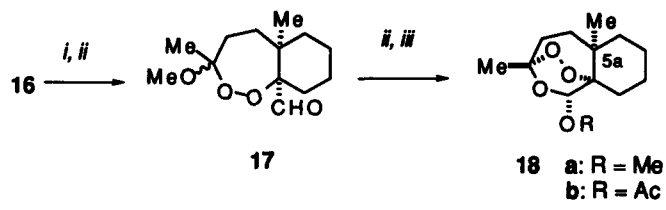
6-**17**: oil; IR (film, cm^{-1}) 2945, 1740; ^1H NMR ($CDCl_3$, 200 MHz) *major isomer* δ: 0.98 (s, 3H), 1.11 (s, 3H), 1.33-2.30 (m, 9H), 1.41 (s, 3H), 3.28 (s, 3H); 9.37 (s, 1H).

7-**18a**: white solid; mp 42-48 °C; $[\alpha]_D^{20}$ = +16.2 (EtOH, c = 1.5); IR (KBr, cm^{-1}) 1470, 1376; ^1H NMR (C_6D_6, 400 MHz) δ: 0.99 (s, 3H), 1.05-1.23 (m, 4H), 1.29 (s, 3H), 1.20-1.35 (m, 2H), 1.35-1.41 (m, 2H), 1.60-1.68 (m, 2H), 2.26 (ddd, *J* = 17.6, 14.2, 2.6 Hz, 1H), 2.38-2.46 (m, 1H), 3.36 (s, 3H), 4.95 (s, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ: 20.9 (CH_3), 21.2 (CH_2), 23.2 (CH_2), 26.4 (CH_3), 29.5 (CH_2), 35.5 (CH_2), 36.4 (CH_2), 39.6 (CH_2), 40.7 (C), 54.9 (CH_3), 83.8 (C), 95.8 (CH), 102.6 (C); MS (CI, NH_3), m/z (%): 260 ($M^{+\cdot}$ + NH_4, 19), 243 (2), 228 (10), 210 (67), 139 (100).

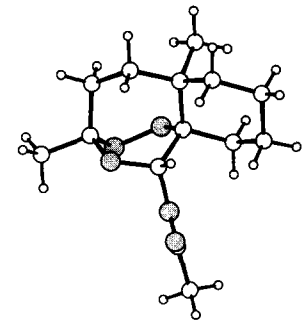
8-**18b**: colorless crystals; mp 88-90 °C; $[\alpha]_D^{20}$ = +26.6 (EtOH, c = 1.2); IR (KBr, cm^{-1}) 1748, 1454, 1379; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.07 (s, 3H), 1.21-1.32 (m, 3H) 1.38 (s, 3H), 1.45-1.99 (m, 8H), 2.18 (s, 3H), 2.44 (td, *J* =14.7, 1.9 Hz, 1H), 6.55 (s, 1H), Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.02; H, 8.27.

9-Crystal data of **18b**: M_W = 270.32, crystal of 0.30 x 0.30 x 0.50 mm, orthorhombic P $2_12_12_1$, Z = 4, a = 7.613 (2), b = 8.135 (3), c = 22.604 (8) Å, V = 1400 $Å^3$, d_{calc} = 1.28 g cm^{-3}, F(000) = 584, λ (CuKα) = 1.5418 Å, μ = 0.80 mm^{-1}. Nonius CAD4 diffractometer. 5814 collected reflexions, 2547 unique, 2501 observed ($I \geq 2\sigma(I)$). The structure refined by full-matrix least square with *SHELX*93, R = 0.049 for 2501 observed reflexions and wR_2 = 0.115 for 2547 unique reflexion. Residual electron density between -0.27 and 0.31 e $Å^3$.

Unambiguous stereochemical assignment of **18a** was ensured by converting **18b** into **18a** (MeOH, BF_3-OEt_2, 20 °C, 12 h).



i: O_3, MeOH, *ii*: BF_3-OEt_2, *iii*: MeOH (**18a**) or Ac_2O (**18b**)



X-ray crystal structure of **18b**

The *in vitro* antimalarial effectivenesses of **18a** and **18b** were evaluated against *Plasmodium falciparum* by using the method developed by Desjardins and coworkers involving the uptake of tritiated hypoxanthine [19]. Both compounds proved to be completely devoid of biological activity in the range of 0.02-0.5 μM (in comparison, on the same strain of *Plasmodium falciparum* [20], artemisinin **1** and artemether exhibited IC_{50} of 19 nM and 11 nM, respectively). *Thus, in line with our original assumption, the presence of a methyl substituent at C-5a in trioxanes 2 dramatically reduced their antimalarial activity.*

To conclude, the fact that the replacement of the hydrogen atom at C-5a by a methyl group in trioxanes **2** was detrimental to activity reinforces the hypothesis that tight hemin-trioxane complexes of type **3** are involved in the activation phase of these antimalarial agents.

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