Tricyclic Analogues of Artemisinin: Synthesis and Antimalarial Activity of (+)-4,5-Secoartemisinin and (−)-5-Nor-4,5-secoartemisinin

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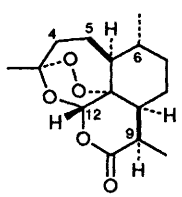
Two ring-A cleaved analogues of the natural product artemisinin have been synthesized and examined for *in vitro* antimalarial activity.

The sesquiterpene (+)-artemisinin[1] **1** has been shown to possess significant antimalarial activity against drug-resistant strains of *Plasmodium falciparum*.[2] Since quantities of **1** are limited, considerable synthetic effort has been expended in total syntheses[3–5] and related model studies.[6,7] In addition, the search for analogues of **1** having superior pharmacological properties has culminated in studies of the 1,2,4-trioxane ring system,[8,9] the essential pharmacophore of **1**, as well as dihydroartemisinin[10] and derivatives thereof.[11–13] Interesting additions to artemisinin structure-activity relationships (SAR) have been reported, including desethanoqinghaosu,[13] 9-desmethyl,[5] and 6,9-desmethylartemisinin,[14] 10-deoxoartemisinin[15] and 8*a*,9-secoartemisinin.[16]



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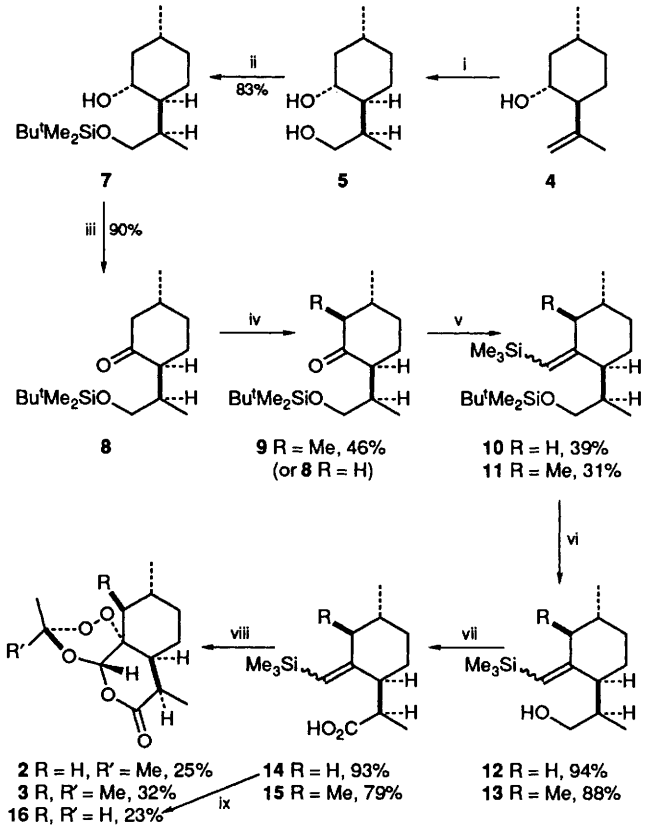

Scheme 1 *Reagents and conditions*: i, B_2H_6, tetrahydrofuran; H_2O_2, NaOH; ii, Bu^{t}Me$_2$SiCl, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2; iii, $(COCl)_2$, dimethyl sulphoxide; Et_3N; iv, lithium diisopropylamide, tetrahydrofuran, −78 °C; then MeI; v, MeO(Me)$_2$SiCHLiSiMe$_3$ **6**, pentane; vi, Bu$^n_4$NF, tetrahydrofuran; vii, pyridinium dichromate, *N*,*N*-dimethylformamide; viii, O_3–O_2, CH_2Cl_2, −78 °C; then acetone, Amberlyst-15, 22 °C; ix, O_3–O_2, CH_2Cl_2, −78 °C; then acetaldehyde, Amberlyst-15, 22 °C

We report the synthesis of (−)-5-nor-4,5-secoartemisinin **2** ('desmethanoqinghaosu'), and (+)-4,5-secoartemisinin **3**. It is expected that these analogues will provide useful information regarding the effects on activity of different relative orientations of the peroxy grouping compared to that in **1**. Furthermore, it is hoped that the methodology described herein can be advantageously employed in an alternative total synthetic route to the natural product **1**.

The analogues **2** and **3** were synthesized from (−)-isopulegol **4** as shown in Scheme 1. Hydroboration of naturally derived **4** gave the known diol **5** in 80% yield.[17] Selective silylation of the primary hydroxy group of **5** with t-butyldimethylsilyl chloride in the presence of 4-dimethylaminopyridine[18] proceeded successfully to give **7**, which then underwent Swern oxidation to provide the ketone **8** in 75% overall yield. Kinetic deprotonation of this ketone went smoothly to afford regioisomerically pure enolate as evidenced by quenching with methyl iodide to furnish a single product **9**, in acceptable yield.

The recent finding that (dimethylmethoxysilyl)trimethylsilylmethyllithium **6** undergoes additions to simple unhindered ketones to afford trimethylsilylalkenes[19] allowed for a different approach than that which we had previously used to construct our vinyl silanes.[5,14,20] Thus, treatment of the ketones **8** or **9** with **6** in pentane furnished the requisite vinyl silanes **10** and **11** in reasonable yields. The by-product in these reactions consisted mainly of recovered ketone starting materials indicating that, in addition to Peterson alkenation,

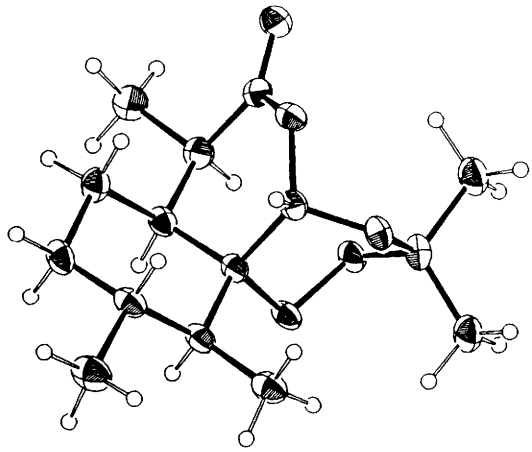

Fig. 1 Perspective drawing of $C_{15}H_{24}O_5$. Non-hydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density; hydrogen atoms are represented by arbitrarily small spheres that are in no way representative of their true thermal motion

these hindered ketones also underwent deprotonation. Next, the ketones were sequentially deprotected with tetrabutylammonium fluoride in tetrahydrofuran to provide the alcohols **12** and **13**, which were then oxidized to the corresponding acids **14** and **15** with pyridinium dichromate in dimethylformamide.

As in preceding syntheses, we depended on the penultimate ozonolysis of a vinyl silane for introduction of the labile α-hydroperoxyaldehyde moiety required for final construction of the trioxane ring. Hence, exposure of either acid **14** or **15** to ozone in dichloromethane at low temperature followed by warming and addition of acetone and Amberlyst-15 (acid source) led to the production of the targets **2** and **3** in good yield.† Proof for the structure **3** was obtained by single crystal X-ray crystallographic analysis as shown in Fig. 1.‡ The structure **2** was deduced in the following way. The structure of the known analogue desethanoqinghaosu **16** was previously determined by X-ray crystallography. Submission of the acid

† For **2**, m.p. 109–110 °C; $[\alpha]_D^{22}$ −94.5 (*c* 0.145, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) at 22 °C; δ 1.01 (d, *J* 6.4 Hz, 6 H), 1.22 (br s, 3 H), 1.42 (br s, 2 H), 1.56 (s, 3 H), 1.64 (br s, 2 H), 1.83 (br s, 2 H), 1.94 (m, 1 H), 2.01 (br, 0.3 H), 2.68 (m, 0.7 H), 3.10 (br, 0.7 H), 3.55 (br, 0.3 H), 5.60 (br, 1 H). However, at −10 °C, **2** displayed the following 7 : 3 mixture: δ 0.75 (m, 1 H), 0.99 (d, *J* 6.4 Hz, 1 H), 1.00 (d, *J* 6.4 Hz, 2 H), 1.19 (d, *J* 7.2 Hz, 2 H), 1.23 (d, *J* 7.3 Hz, 1 H), 1.41 (s, 2 H), 1.57 (s, 1 H), 1.64 (s, 2 H), 1.65 (s, 1 H), 1.82 (m, 2 H), 1.93 (m, 1 H), 2.09 (dddd, *J* 0.8, 1.6, 4.0, 13.5 Hz, 0.3 H), 2.68 (ddd, *J* 3.0, 4.0, 13.5 Hz, 0.7 H), 3.10 (dq, *J* 5.1, 7.2 Hz, 0.7 H), 3.55 (dq, *J* 4.4, 7.3 Hz, 0.3 H), 5.61 (s, 0.7 H), 5.70 (s, 0.3 H). For **3**, m.p. 102–103 °C; $[\alpha]_D^{22}$ +22.9 (*c* 0.520, dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) at 22 °C; δ 1.00 (d, *J* 6.4 Hz, 3 H), 1.05 (m, 1 H), 1.12 (d, *J* 6.7 Hz, 2 H), 1.24 (d, *J* 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.61 (s, 3 H), 1.77 (br, 1 H), 1.91 (br, 2 H), 3.72 (br, 1 H), 5.66 (s, 1 H). However, at −18 °C a single conformer of **3** was observed: δ 0.99 (d, *J* 6.4 Hz, 3 H), 1.04 (m, 2 H), 1.09 (d, *J* 7.2 Hz, 3 H), 1.20 (m, 1 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 1.36 (m, 1 H), 1.40 (s, 3 H), 1.61 (s, 3 H), 1.75 (m, 1 H), 1.90 (m, 2 H), 3.72 (dq, *J* 4.6, 7.2 Hz, 1 H), 5.66 (s, 1 H). The result of X-ray crystallographic analysis of **3** (single crystal) is shown in Fig. 1.

‡ *Crystal data*: $C_{15}H_{24}O_5$, compound **3**, monoclinic, space group $P2_1/n$, M_r = 284.35, *a* = 9.957(6), *b* = 9.212(10), *c* = 15.965(10) Å; β = 93.15(3)°, *U* = 1462.10 Å^3, *Z* = 4, D_m = 1.2918, D_c = 1.292 g cm^{-3}, *T* = 158 K, 1567 observed data with $F > 2.33\sigma(F)$, *R* = 0.034. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

14 to ozone as before, but with subsequent cyclization to acetaldehyde, afforded **16**, thus establishing the stereochemistry of **14** and **2**.

The analogues **2** and **3** have been tested *in vitro* against drug-resistant strains of *P. falciparum* at the Walter Reed Army Institute of Research. The IC_{50} values for these analogues ranged from 3 to 6 ng cm^{-3} while the IC_{50} for (+)-artemisinin was 0.2–0.8 ng cm^{-3}. Interesting conformational effects have been displayed by some members of this class of antimalarial analogues of **1** and are being further examined by NMR, molecular modelling, and X-ray crystallography in order to understand better the relative activities of these analogues.[21]§ Further work in progress focuses on the extension of Scheme 1 to provide (+)-artemisinin, **1**. As can be seen, if R in **14** were a 3-oxobutyl group, then the penultimate step (viii) would yield the natural product.

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§ Studies of a related analogue indicate that the minor conformational isomer observed at low temperature in chloroform solution (NMR) does not correspond exactly to the relative conformation of the natural product **1**. While the peroxy ring is in a boat conformation, it is in a different boat conformation than artemisinin. The major solution conformer appears to be in an 'unnatural' chair–chair–chair conformation as was also seen in the X-ray structure determination of this analogue. Neither conformer overlaps well with the natural product. The antimalarial potency of these analogues is apparently attenuated by this lack of overlap.

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