STEREOSPECIFIC SYNTHESIS OF (+)-HOMODEOXOARTEMISININ

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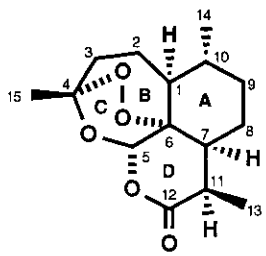
Abstract-The synthesis of (+)-homodeoxoartemisinin, **3**, was achieved from artemisinic acid, **4**, in eight steps.

Today, malaria infects up to 300 million people and kills up to 2 million each year.[4] This shocking reality is due largely to the emergence of drug resistant strains of Plasmodium falciparum. Artemisinin (Qinghaosu, **1**) isolated from Artemisia annua L. has recently been used in China as a new type of antimalarial drug with rapid action and low toxicity against chloroquine-resistant malaria.[5,6]

The combination of a novel chemical structure, a low yield from natural sources and urgency to develop a more ideal drug with enhanced antimalarial activity prompted us to search for a synthesis of new artemisinin-related compounds. Recently, we reported synthesis of (+)-deoxoartemisinin **2**, a new and more active antimalarial agent devoid of the carbonyl function at C-12 while retaining the biologically active endoperoxide.[7] Deoxoartemisinin, **2**, shows several fold increased antimalarial activity in vitro against chloroquine-resistant malaria as compared to artemisinin.[8] As nothing was known about the effect of size of ring D of artemisinin analogs on antimalarial activity, we elected



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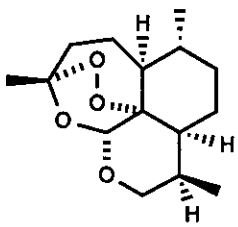

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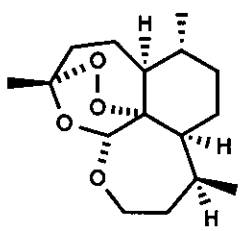

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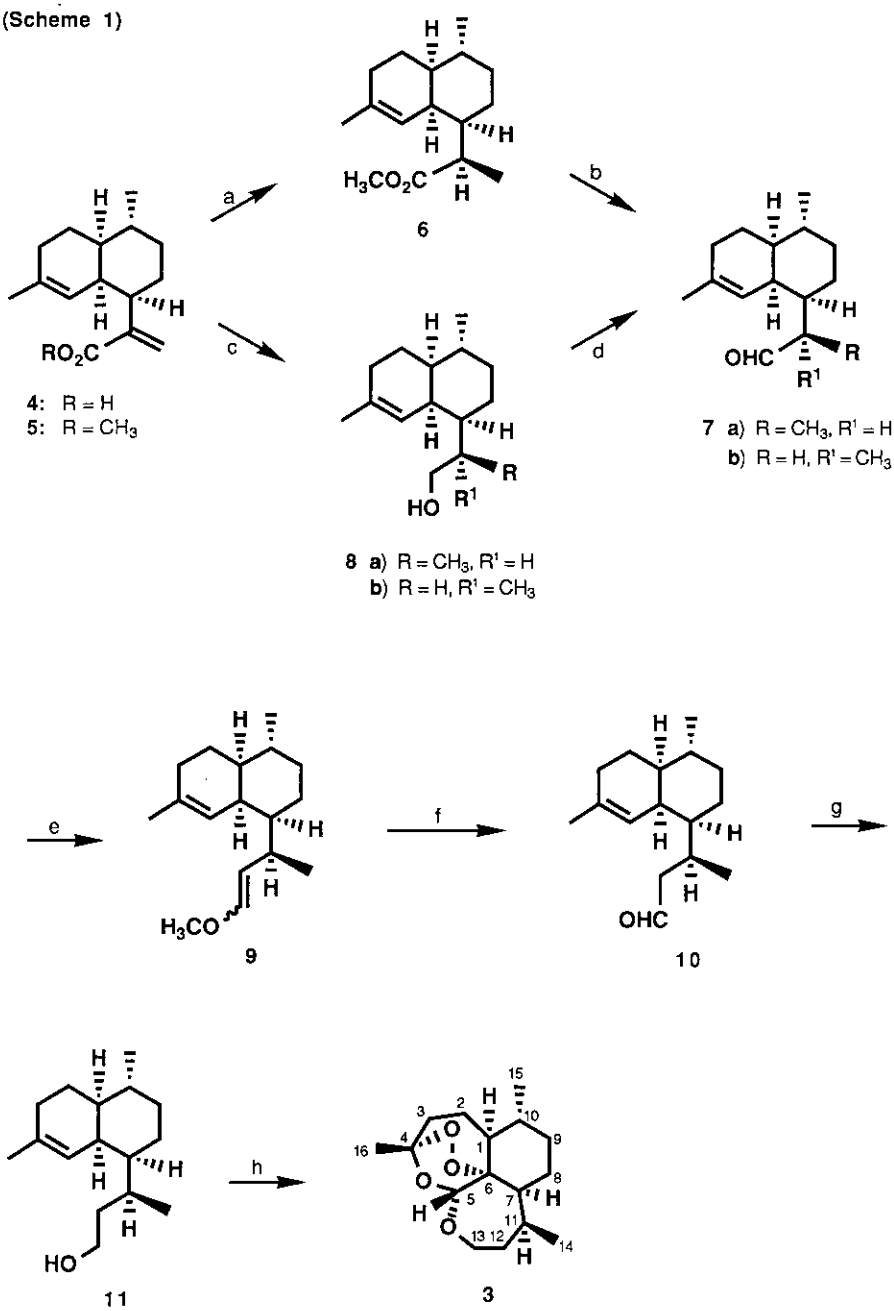
to prepare the seven membered ring analog of deoxoartemisinin to evaluate the role of ring size for antimalarial activity. We report here a successful stereospecific conversion of artemisinic acid **4**

(Scheme 1)



Key : (a) $LiBH_4$, $NiCl_2$, CH_3OH, r.t., 1.5 h (b) DIBAL-H, CH_2Cl_2, -78°C, 2 h (c) LAH, $NiCl_2$, $(C_2H_5)_2O$, r.t., 1 h (d) PCC, CH_2Cl_2, r.t., 2 h (e) $CH_3OCH_2P^+Ph_3Cl^-$, PhLi, $(C_2H_5)_2O$, r.t., 15 h (f) 37% HCl, THF, r.t., 15 min (g) LAH, $(C_2H_5)_2O$, r.t., 10 min (h) O_2, hν, methylene blue, CH_2Cl_2, -78°C, 2 h, then Dowex-resin (strongly acidic), hexane, r.t., 4 h.

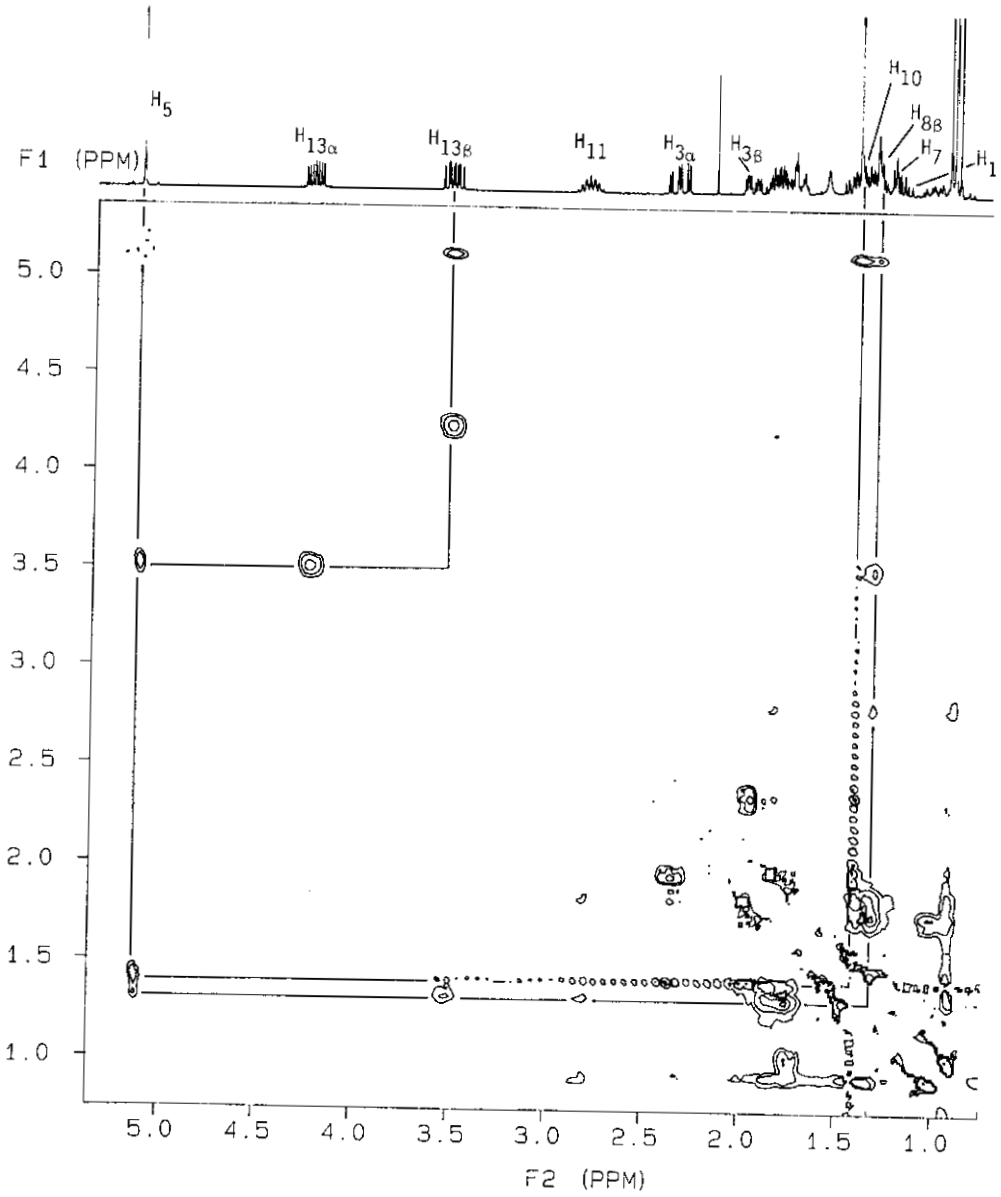
into (+)-homodeoxoartemisinin **3**.

Since artemisinic acid **4** obtained from Artemisia annua L. is approximately 8 to 10 times more abundant than artemisinin, **4** was chosen as a chiral starting material.[9] Initial reduction of **5** (prepared from **4**[9]) by $LiBH_4$ in the presence of $NiCl_2$ in anhydrous methanol (r.t., 1.5 h) gave **6** in 95% yield, which was then exposed to a second reduction (DIBAL-H, methylene chloride, -78°C, 2 h) to afford the dihydroaldehydes, **7a** and **7b**, in a ratio of 5 to 1 (yield 67%) (Scheme 1). The (11R)-diastereomer, **7a**, was also prepared from **8a**. Thus, one-step double reduction of **5** by LAH and $NiCl_2$ in anhydrous ethyl ether(r.t.,1 h) afforded **8a** and **8b** with less stereoselectivity (**8a**:**8b**=2:1) in 51% yield. Alcohol **8a** was separated from alcohol **8b** by column chromatography (silica gel for tlc without gypsum). Oxidation of **8a** by PCC in anhydrous methylene chloride (r.t., 2 h) gave (11R)-dihydroartemaldehyde **7a** in 90% yield. Subsequent Wittig homologation of **7a** by methoxymethyl-triphenylphosphonium chloride and phenyllithium in anhydrous ether (r.t.,15 h) afforded the vinyl methyl ether **9** in 90% yield (cis/trans=2/1). No epimerization at C-11 had occurred during this homologation. Treatment of the cis/trans mixture **9** with a few drops of 37% HCl (THF, r.t., 15 min) cleanly gave the homoaldehyde **10** in 70% yield. Further reduction of **10** into homoalcohol **11** was achieved by LAH in anhydrous ethyl ether (r.t.,10 min) (90% yield). Stereospecific photoxidative cyclization (oxygen, methylene blue and irradiation in methylene chloride at -78° for 2 h) of **11**, followed by in situ treatment with Dowex-resin (strongly acidic) afforded (+)-homodeoxoartemisinin **3**[10] (21% yield) in one step and of natural configuration.[7-9]

The assignments of the ^{1}H-nmr and ^{13}C-nmr signals were made on the basis of 2D-COSY and HETCOR spectra of (+)-homodeoxoartemisinin **3**. The relative configuration at the new chiral centers, C-4, 5, 6 and 11 of **3** was unambiguously determined by utilization of the two dimensional nOe (NOESY)[11] technique. The NOESY spectrum (Figure 1) showed interactions between 5-H (δ5.11, s), the 10-Hβ (δ1.42, m) and one of the 8-H protons (δ1.29, m) and one of the 13-H protons (δ3.52, m), demonstrating that the 5-H is β. No nOe enhancement was observed between 5-H and the 7-Hα (δ1.24, m) and between 5-H and 11-H (δ2.82, m), establishing that the 11-H is α. The strong deshielding of the 3-Hα observed (δ2.35, m) compared to the 3-Hβ (δ1.98, m) supports an assignment of the stereochemistry of C-4 and C-6[11b] as depicted in **3**.

(+)-Homodeoxoartemisinin **3** is found to show approximately 20 times less in vitro antimalarial activity compared to artemisinin **1** against chloroquine-resistant malaria. Enlargement of the D-ring which would allow greater flexibility of the overall ring system including the biologically active endoperoxide decreases significantly the in vitro antimalarial activity. The increased flexibility of the polycyclic structure may lead to poorer receptor fit or more probably decreased reactivity of the endoperoxide.

In conclusion, (+)-homodeoxoartemisinin **3**, a novel antimalarial agent, was synthesized in eight steps (overall yield, 7.6%) from artemisinic acid.



(Figure I) NOESY Spectra of (+)-Homodeoxoartemisinin 3

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10. Compound **3**: mp 86-87°C (hexane). $[\alpha]_D^{25}$ = +65.8° (c 1.2, $CHCl_3$), ^{1}H-nmr ($CDCl_3$, δ ,ppm, 300MHz): 0.91 (3H, d, J=7.1 Hz, H_3C-14), 0.94 (3H, d, J=6.4Hz, H_3C-15), 1.41 (3H, s, H_3C-16), 1.98 (1H, 2dd, J=3.1, 4.7 and 14.6 Hz, H-3β), 2.35 (1H, 2dd, J=3.97, 13.4 and 14.6 Hz, H-3α), 2.82 (1H, m, H-11), 3.52 (1H, 2dd,J=6.76, 8.8 and 13.0 Hz, H-13β), 4.23 (1H, 2dd, J=4.3, 8.4 and 13.0 Hz, H-13α), 5.11 (1H, s, H-5), C^{13}-nmr ($CDCl_3$, δ ,ppm,75 MHz):20.13 (C-14), 21.09 (C-15), 22.20 (C-8), 25.01 (C-2), 25.94 (C-16), 26.34 (C-11), 33.56 (C-9), 35.07 (C-12), 35.93 (C-3), 37.58 (C-10), 50.90 (C-7), 52.98 (C-1), 65.74 (C-13), 85.34 (C-6), 99.29 (C-5), 103.58 (C-4). ir ($CHCl_3$, ν, cm^{-1}):2950,2880,1440,1380,1100,1050,930,880, 840,660, ms m/z:163,107,95,93,91,81,79,77,69, 67,55 (100%),53. Anal. Calcd for $C_{16}H_{26}O_4$: C,68.08;H,9.22;O,22.7. Found: C,68.45; H,9.11; O,23.43.
11. For NOESY experiments of artemisinin and its analogs, see
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