

STEREOSPECIFIC SYNTHESIS OF (+)-HOMODEOXOARTEMISININ

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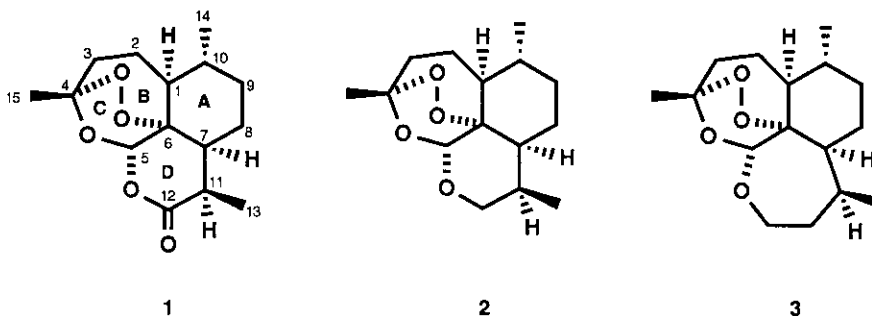
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Abstract—The synthesis of (+)-homodeoxoartemisinin, **3**, was achieved from artemisinic acid, **4**, in eight steps.

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*.

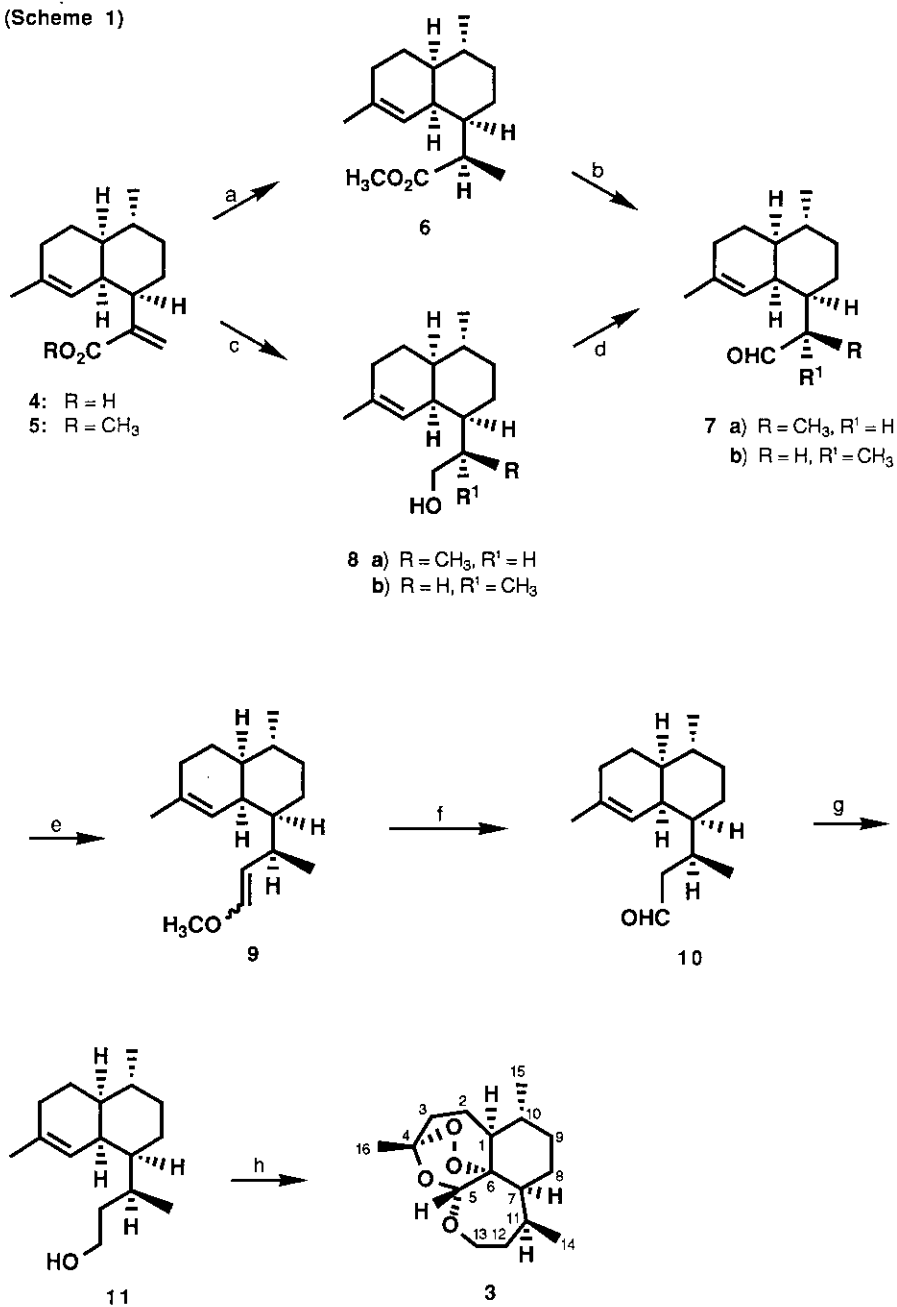
Artemisinin (Qinghaosu, **1**) isolated from *Artemisia annua* L. has recently been used in China as a new type of antimalarial drug with rapid action and low toxicity against chloroquine-resistant malaria.^{5,6}

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



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) LiBH₄, NiCl₂, CH₃OH, r.t., 1.5 h (b) DIBAL-H, CH₂Cl₂, -78°C, 2 h (c) LAH, NiCl₂, (C₂H₅)₂O, r.t., 1 h (d) PCC, CH₂Cl₂, r.t., 2 h (e) CH₃OCH₂P⁺Ph₃Cl⁻, PhLi, (C₂H₅)₂O, r.t., 15 h (f) 37% HCl, THF, r.t., 15 min (g) LAH, (C₂H₅)₂O, r.t., 10 min (h) O₂, hν, methylene blue, CH₂Cl₂, -78°C, 2 h, then Dowex-resin (strongly acidic), hexane, r.t., 4 h.

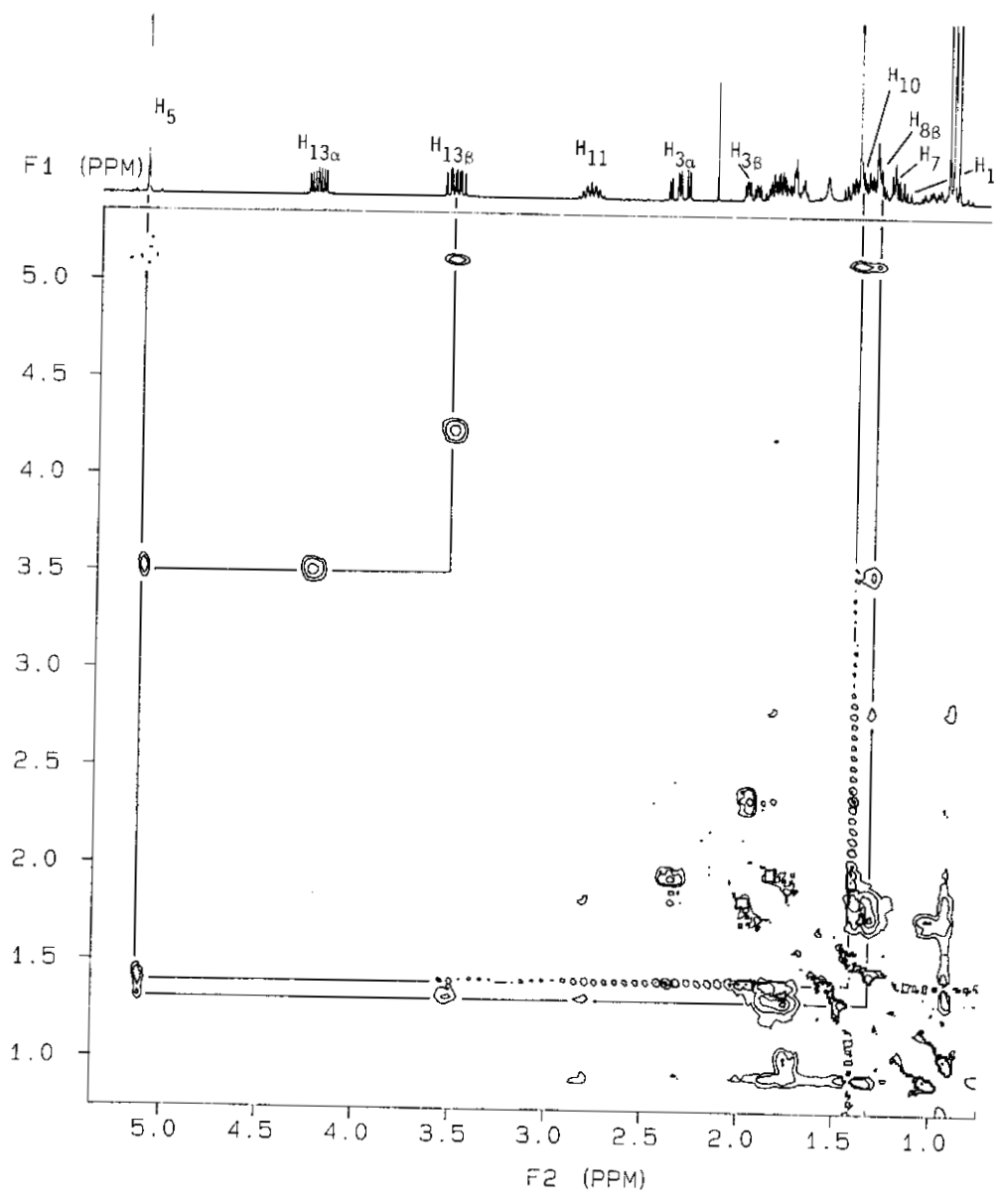
into (+)-homodeoxoartemisinin 3.

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 4⁹) by LiBH₄ in the presence of NiCl₂ 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 NiCl₂ 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 photooxidative 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 3¹⁰ (21% yield) in one step and of natural configuration.⁷⁻⁹

The assignments of the ¹H-nmr and ¹³C-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-H_β (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-H_α (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-H_α observed (δ2.35, m) compared to the 3-H_β (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). $[\alpha]_D^{25} = +65.8^\circ$ (c 1.2, CHCl₃), ¹H-nmr (CDCl₃, δ, ppm, 300MHz): 0.91 (3H, d, J=7.1 Hz, H₃C-14), 0.94 (3H, d, J=6.4 Hz, H₃C-15), 1.41 (3H, s, H₃C-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), C¹³-nmr (CDCl₃, 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 (CHCl₃, 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 C₁₆H₂₆O₄: 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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