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THE TOTAL SYNTHESIS OF (+)-ARTEMISININ AND (+)-9-DESMETHYLARTEMISININ

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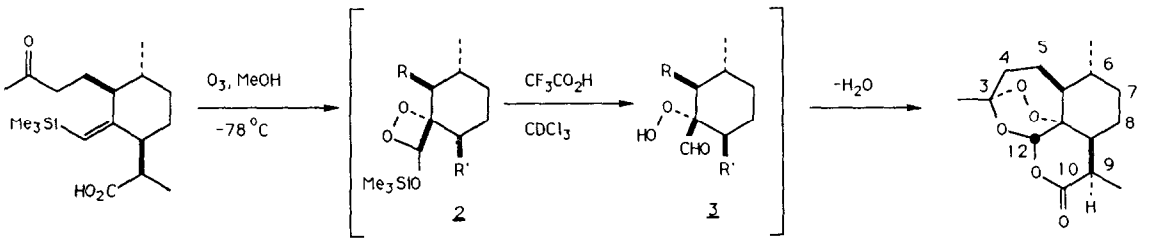
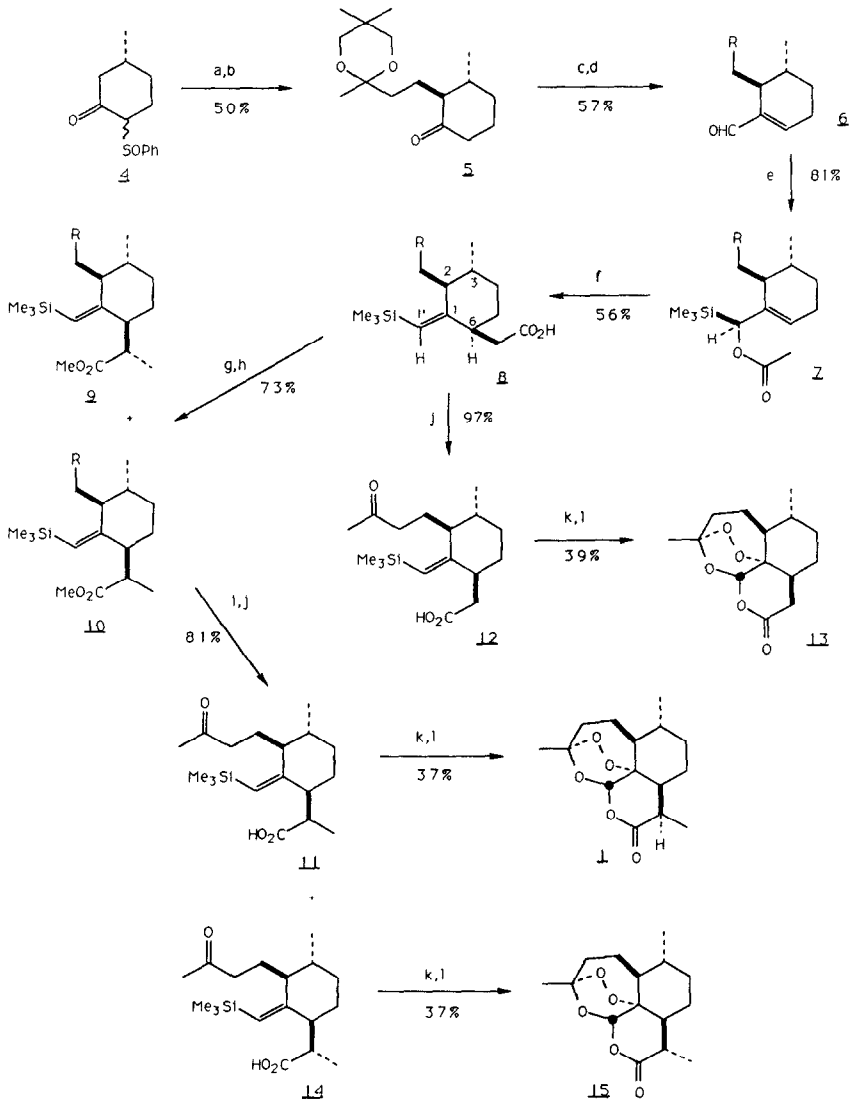
Abstract: (+)-Artemisinin has been synthesized from the 3R-methylcyclohexanone **4** in 12 steps.

(+)-Artemisinin, which has been commonly referred to as qinghaosu, is an effective antimalarial agent isolated from *Artemisia annua L.* An X-ray crystallographic analysis has shown that artemisinin possesses the unusual tetracyclic structure **1**, which represents a highly oxygenated example of a cadinane sesquiterpene[1].

The promising antiparasitic activity of **1** against drug resistant strains of malaria combined with its synthetically challenging structure have prompted total syntheses by Zhou[2] and Hofheinz[3], an unsuccessful approach by Jung[4] and a model study by Clark[5]. We wish to report herein the successful outcome of our synthetic efforts directed towards the stereoselective total synthesis of (+)-artemisinin **1** (Scheme I). We have made use of the abnormal course of reaction of vinylsilanes with ozone as reported by Büchi[6]. Our key step involves the ring opening of a transient silyloxydioxetane **2** to a labile alpha-hydroperoxy- aldehyde **3**, which undergoes further selective cyclization as shown below:





Scheme I

a) 2.2 LDA, HMPA, THF, -78°C; then 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; b) Al(Hg), THF, H_2O; c) NH_2NHTs, pyr, THF; d) 4.0 equiv. n-BuLi, TMEDA; then DMF; e) $(Me_3Si)_3Al{\cdot}OEt_2$, Et_2O, pentane,-78°C, then Ac_2O, DMAP, 20°C; f) LICA, THF, -78°C to 20°C; g) Me_2SO_4, K_2CO_3, acetone; h) LICA, THF, 0°C; then CH_3I, 0°C; i) KOH, MeOH; j) aq. oxalic acid, silica gel, CH_2Cl_2, 20°C; k) O_3, MeOH, -78°C; l) $CHCl_3$, CF_3CO_2H, H_2O.

After exposure of the vinylsilane **11** to ozone at low temperature, the crude dioxetane **2** was observed by NMR (400 MHz, $CDCl_3$, 6.1 ppm for -O-O-C**H**R-OSiR_3). Acidification of the NMR sample with trifluoroacetic acid (TFA) led to opening of **2** to produce **3** along with partially cyclized by-products. After several hours the presence of **1** was apparent by NMR. Preparative TLC afforded the synthetic product **1** (37% yield from **11**), which was identical in all respects to naturally derived (+)-artemisinin.

The requisite keto-acid cyclization substrate **11** was prepared in optically active form according to Scheme I. The known **3R** chiral sulfoxide **4**[7] was converted to its dianion with LDA/HMPA and alkylated[7] with 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane to give a mixture of diastereomers at C6 and on sulfur which was desulfurized with aluminum amalgam to provide the ketone **5** in 50% yield, along with a small amount of isomer[8]. Treatment of **5** with pyridine and tosylhydrazide in refluxing THF gave a hydrazone in 94% yield, which was then converted to a vinyl anion upon reaction with four equivalents of n-butyllithium in TMEDA . After trapping the resultant vinyl anion with DMF[9], the product was flash chromatographed to afford diasteromerically pure aldehyde **6**, which had been separated from the C2 epimeric contaminant.

The aldehyde **6** was found to undergo a diastereoselective reaction with tris(trimethylsilyl)aluminum etherate, $(Me_3Si)_3Al{\cdot}OEt_2$[10]. Addition of acetic anhydride and DMAP to the reaction mixture gave rise to the diastereomerically pure silyl-acetate **7** (81%). The assignment of relative stereochemistry to the newly formed center (C-1') of **7** was assumed based on stereoelectronic considerations[11] and confirmed upon subsequent conversions to intermediates in the synthesis of the natural product, *vida infra*.

The silyl-acetate **7** was treated with lithium N-isopropylcyclohexylamide (LICA) in THF, whereupon the cyclohexylacetate **8**(6-beta) was the exclusive Ireland-Claisen ester enolate rearrangement product[12] afforded in 56% yield. The stereochemistry of **8** (6-beta vs. 6-alpha) was in turn proven by its conversion to 13-norartemisinin: careful deketalization of **8** without protodesilation was accomplished by reaction with a CH_2Cl_2 slurry of silica gel impregnated with aqueous oxalic acid to provide the keto-acid **12** in 97% yield. Successive treatment of the keto-acid **12** with ozone at low temperature and TFA in $CDCl_3$ gave (+)-9-desmethylartemisinin **13** in 39% yield. The regiochemistry about the double bond of **8** was expected based on the stereochemical assignment to **7**[11,12] and proven by NMR[13].

The acid **8** was converted to the corresponding methyl ester in 94% yield, which was deprotonated with LICA and alkylated with methyl iodide to provide a 7:3 mixture of **9** and **10**, respectively, in 78% yield. Alkaline hydrolysis of the ester mixture of **9** and **10** in KOH/MeOH, followed by deketalization as before led to the desired keto-acid **11**(56%) along with the isomer **14**(15%). As with the keto-acid **12**, the homologous keto-acids **11** and **14** were successively

exposed to ozone and acid in the same fashion to produce the tetracyclic products (+)-artemisinin and 9-isoartemisinin, repectively. In summary, artemisinin was obtained in 37% yield from **11** after chromatography, and was identical in all respects to the natural product (TLC, MS, IR, NMR, OR).

Acknowledgments

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8. A 9:1 ratio (beta:alpha at C-2), was observed by NMR(400MHz). We have since found that **5** does undergo equilibration at C-2 upon treatment with potassium hydroxide in methanol to a 1:1 epimeric mixture, and thus it can be assumed that the C-3 methyl directs the alkylation of **4** from the beta-face.
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11. The aldehyde **6** (R=Me) was shown to prefer the 2,3-diaxial twist chair (ene-al transoid) conformer by at least 3 Kcal/M (MMP2 calculations) over any cisoid (ene-al) conformer. Thus, approach of the TMS nucleophile would be expected to occur from the alpha-face of **6** (ene-al transoid) to give **7** exclusively.
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13. The C-2 (2.11 ppm, m, 1H) and C-6 (2.78 ppm, m, 1H) protons were identified by decoupling experiments. Irradiation of the C-1' vinyl proton (5.38 ppm, s, 1H) resulted in a N.O.E. enhancement of the C-6 proton (10%) but not the C-2 proton. Thus, the C-1' H and the C-6 H were shown to be cis.

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