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A Total Synthesis of the Antimalarial Natural Product (+)-Qinghaosu

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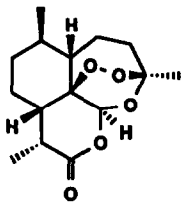
Abstract: Starting from (-)-β-pinene, an efficient total synthesis of the title antimalarial agent has been accomplished using an intermolecular Diels-Alder approach.

Malaria continues to be one of the most widespread health hazards. Over two hundred million people worldwide are currently estimated to be suffering from this infectious disease.[1] As a consequence, effective therapeutic agents against malaria are continuously being sought, especially against those strains which are resistant to conventional quinoline and acridine based drugs. In 1972, a sesquiterpenoid (+)-qinghaosu (**1**) was isolated from the Chinese medicinal plant qinghao (*Artemisia annua* L.) which has been used for the treatment of malaria in China since ancient times.[2] This highly oxygenated sesquiterpene peroxide was found to be superior to the conventional antimalarial drugs, such as chloroqine and quinine, against several strains of malaria without obvious adverse reactions or side effects in patients.[3,4] Because of its intriguing chemical structure and the promising prospects as a lead compound for the new class of antimalarial agents, (+)-qinghaosu (**1**) has been the subject of extensive synthetic efforts[5-16] and several elegant syntheses[10-16] have been accomplished during the past decade. We wish to report herein a fundamentally different approach to this antimalarial natural product.



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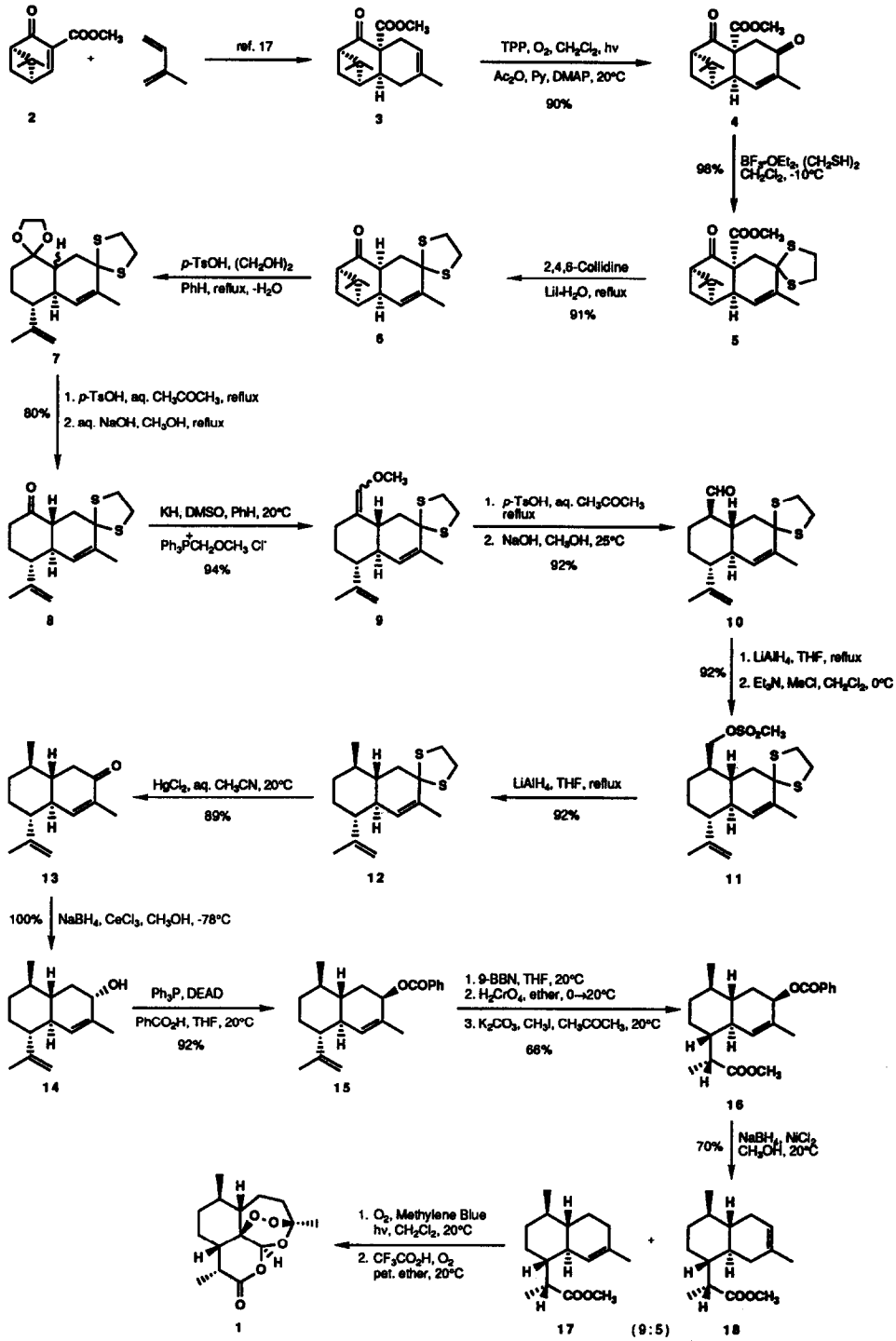
The synthesis began with the zinc chloride catalyzed Diels-Alder addition of (+)-enone ester **2** (≥ 92% ee), readily prepared from (-)-β-pinene in 65% yield over three steps, to isoprene.[17] The reaction proceeded with complete regioselectivity and facial selectivity to give, in virtually quantitative yield, adduct **3** which contains all the carbon atoms of the target molecule except the methyl group attached to the cyclohexane ring. Photooxygenation (tungsten lamps) of **3** with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in dichloromethane in the presence of acetic anhydride, pyridine, and dimethylaminopyridine[18]


ref. 17
TPP, O2, CH2Cl2, hv
Ac2O, Py, DMAP, 20°C
90%
98%
BF3·OEt2, (CH2SH)2
CH2Cl2, -10°C
2,4,6-Collidine
LiI-H2O, reflux
91%
p-TsOH, (CH2OH)2
PhH, reflux, -H2O
80%
1. p-TsOH, aq. CH3COCH3, reflux
2. aq. NaOH, CH3OH, reflux
KH, DMSO, PhH, 20°C
Ph3P+CH2OCH3 Cl-
94%
1. p-TsOH, aq. CH3COCH3
reflux
2. NaOH, CH3OH, 25°C
92%
92%
1. LiAlH4, THF, reflux
2. Et3N, MsCl, CH2Cl2, 0°C
LiAlH4, THF, reflux
92%
HgCl2, aq. CH3CN, 20°C
89%
100%
NaBH4, CeCl3, CH3OH, -78°C
Ph3P, DEAD
PhCO2H, THF, 20°C
92%
1. 9-BBN, THF, 20°C
2. H2CrO4, ether, 0→20°C
3. K2CO3, CH3I, CH3COCH3, 20°C
66%
70%
NaBH4, NiCl2
CH3OH, 20°C
1. O2, Methylene Blue
hv, CH2Cl2, 20°C
2. CF3CO2H, O2
pet. ether, 20°C
(9:5)

effected the migration of the double bond to the strategic position for the eventual incorporation of the peroxy ketal moiety. The sterically less congested ketone carbonyl of the resulting enedione **4** (90% yield) was selectively protected in the form of a thioketal using 1,2-ethanedithiol and boron trifluoride etherate in dichloromethane at -10°C. The thioketal **5** thus obtained in 98% yield was subjected to decarbomethoxylation with lithium iodide monohydrate in refluxing 2,4,6-collidine. Treatment of the resulting ketone **6** (91% yield) with *p*-toluenesulfonic acid and ethylene glycol in benzene under reflux with removal of water induced the desired fragmentation of the cyclobutane ring with concomitant ketalization[17] to give a mixture of epimeric diene ketals **7** which, without purification, was treated sequentially with *p*-toluenesulfonic acid in acetone and sodium hydroxide in aqueous methanol to give dienone **8** in 80% overall yield.

The missing methyl group was installed with complete stereochemical control as follows. Wittig reaction of dienone **8** with methoxymethyltriphenylphosphonium chloride and potassium hydride in dimethyl sulfoxide and benzene at room temperature gave a mixture of enone ethers **9**. This mixture was subjected to hydrolysis with *p*-toluenesulfonic acid in refluxing aqueous acetone, and the epimeric aldehydes thus formed were treated with sodium hydroxide in aqueous methanol at room temperature to give the thermodynamically more stable aldehyde **10**. Lithium aluminium hydride reduction of **10** followed by mesylation with methanesulfonyl chloride and triethylamine gave mesylate **11** which was further reduced with lithium aluminium hydride to give the desired diene thioketal **12** in 73% overall yield from dienone **8**.

To elaborate the highly oxygenated region of the target molecule, diene thioketal **12** was first subjected to dethioketalization using mercuric chloride in aqueous acetonitrile. 1,2-Reduction of the resultant diene ketone **13** induced by sodium borohydride and cerium(III) chloride[19] gave the corresponding alcohol **14**, which was subjected to a Mitsunobu reaction[20] with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid to give benzoate **15** in 82% overall yield from **12**. Its isopropenyl group was subsequently converted to a propionate unit via a three-step synthetic sequence. Selective hydroboration was effected by 9-borabicyclo[3.3.1]nonane. This was followed by an oxidation with Jones reagent.[21] Esterification of the resulting carboxylic acid with potassium carbonate and methyl iodide in acetone gave rise to a 66% yield of ester **16** as a single stereoisomer. Subsequent removal of the benzoyloxy group was effected by nickel boride prepared from sodium borohydride and nickel(II) chloride.[22] A mixture of two inseparable regioisomers **17** and **18** was obtained in 70% yield and in a ratio of 9 : 5 with the desired isomer **17** predominating. It has been shown previously that both dihydroqinghao acid and its methyl ester (an epimer of compound **17** with a *cis*-fused ring system) were readily converted to qinghaosu (**1**) via a photooxygenation process.[5] To our delight, this procedure proved to be equally effective for the *trans* isomer. When the mixture of compounds **17** and **18** was subjected to photooxygenation at room temperature in methylene chloride using methylene blue as a photosensitizer followed by treatment of the crude product with trifluoroacetic acid in petroleum ether in the presence of oxygen, (+)-qinghaosu (**1**) was produced in 30% yield based on **17**. The synthetic compound thus obtained was found to be identical in all respects with an authentic sample of the natural product except slightly lower in the magnitude of the optical rotation (+63.3° vs. +64.53°).[23]

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