TOTAL SYNTHESIS OF (-)-QINGHAOSU IV (ARTEMISININ D, ARTEANNUIN D)[1]

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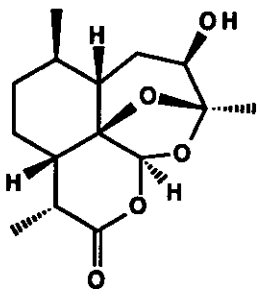
Abstract — Starting from (-)-β-pinene (**3**), a total synthesis of (-)-qinghaosu IV (**1**) has been accomplished.

(-)-Qinghaosu IV (**1**) (also known as artemisinin D and arteannuin D) is a highly oxygenated sesquiterpene of the cadinane family. This natural alcohol was first isolated in 1982 by Liang and coworkers[2] from the Chinese medicinal plant qinghao (*Artemisia annual* L.), which also produces a large number of cadinane-type terpenoids including (+)-qinghaosu (**2**),[3] a structural isomer of **1** which is responsible for the antimalarial activity of the herb. Qinghaosu IV (**1**) was identified as a key metabolite in the microbial metabolism studies carried out by Hufford *et al.*[4] and could serve as a marker in the investigation of the metabolic pathway of (+)-qinghaosu (**2**) in humans.



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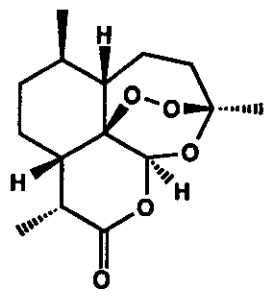

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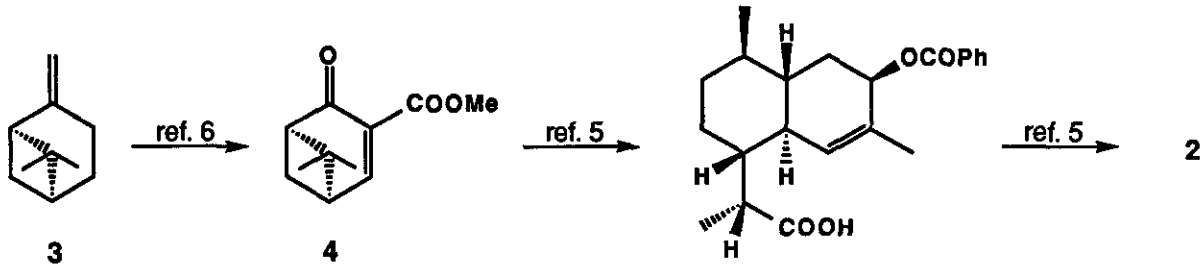
Recently, we reported an efficient total synthesis of qinghaosu (**2**) starting from (-)-β-pinene (**3**).[5] In the synthesis, β-pinene (**3**) was converted to enone ester (**4**),[6] from which the key intermediate (**5**) was prepared *via* a Diels-Alder process[5]

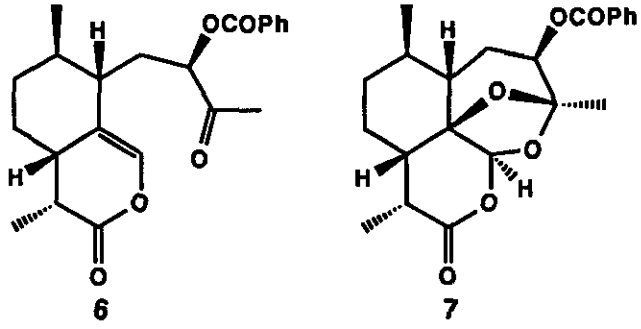
(Scheme 1). We have now extended this approach to the total synthesis of qinghaosu IV (**1**)[7] in the natural form. Results are described herein.

Scheme 1

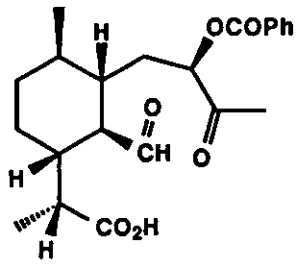


3 **4** **5**

Our original synthetic plan was to transform acid (**5**) into enol lactone (**6**), which could then be converted to the target molecule *via* an oxidative cyclization (**6** → **7**). This approach proved to be impractical. In spite of extensive efforts, the desired enol lactone (**6**) could not be formed. Ozonolysis of acid (**5**) in methylene chloride and in a combination of methylene chloride and methanol followed by reductive work-up using dimethyl sulfide gave aldehyde (**8**) and lactone (**9**), respectively. Both of these products were formed in poor yields and neither could be converted to enol lactone (**6**) under a variety of conditions applied. The cleavage of the double bond in **5** was also attempted using Lemieux-Johnson oxidation[8] but without much success. Treatment of acid (**5**) with sodium periodate and a catalytic amount of osmium tetroxide gave the unexpected alcohol (**10**), whereas reaction of **5** with an equal amount of osmium tetroxide resulted in extensive decomposition.



6 **7**



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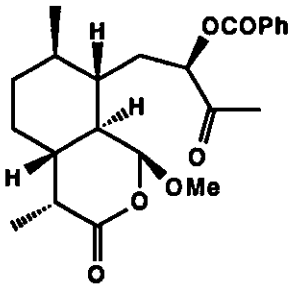

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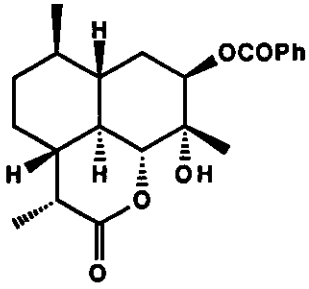

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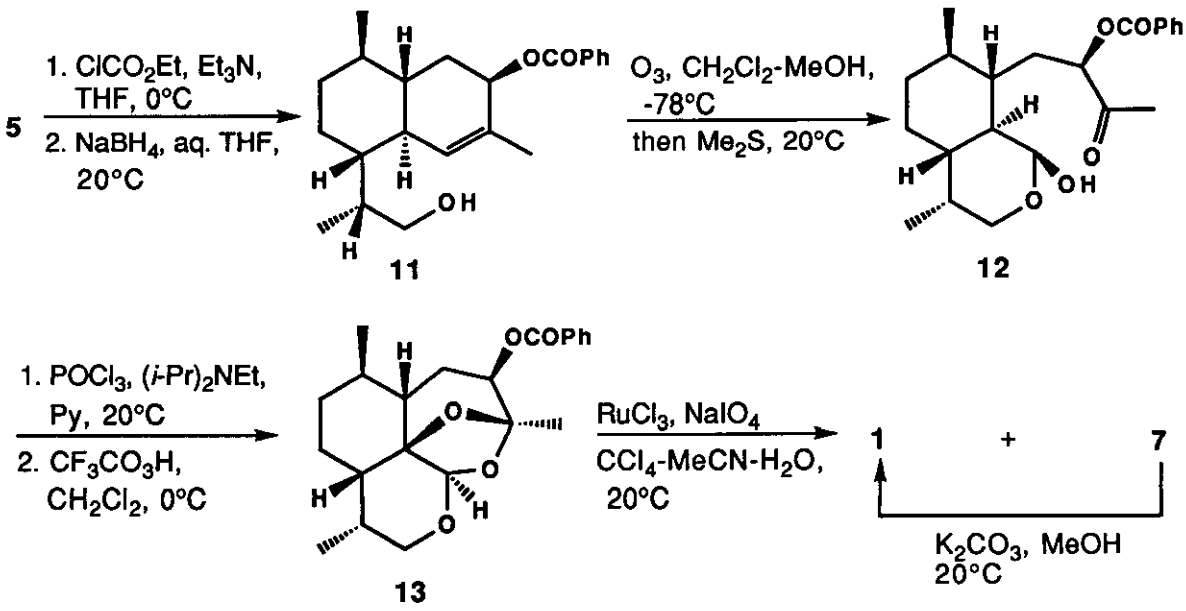
Several other approaches leading to 1 were also investigated, involving the methyl ester of 5 as an intermediate. These approaches, which would allow the retention of the existing carboxy group, also met with little success. Consequently, the carboxy group was selective reduced by treatment of acid (5) with ethyl chloroformate and triethylamine followed by reduction of the resulting anhydride with sodium borohydride. Alcohol (11), thus obtained in 87% yield, was shown to be a useful intermediate. The conversion of this compound to qinghaosu IV (1) could be effected *via* the synthetic sequence outlined in Scheme 2.

Scheme 2



Alcohol (**11**) was subjected to ozonolysis in methylene chloride and methanol at -78°C. Reductive work-up using dimethyl sulfide gave hemiacetal (**12**) in 77% yield. This compound was then treated with phosphorus oxychloride and ethyldiisopropylamine in pyridine at room temperature to effect dehydration. The unstable enol ether produced was immediately subjected to epoxidation with trifluoroperoxyacetic acid[9] in methylene chloride at 0°C to furnish a 33% yield of ketal (**13**). This compound on oxidation with sodium periodate and ruthenium(III) chloride in a mixture of carbon tetrachloride, acetonitrile, and water, standard conditions for converting ethers into esters,[10] gave (-)-qinghaosu IV (1) (9%) and the expected lactone (**7**) (3%).[11] The latter was readily hydrolyzed with aqueous potassium carbonate in methanol to provide an additional amount of **1**. The synthetic material displayed mp (189-190°C)[12] and spectroscopic properties[2,12] (ir, ^{1}Hnmr, and ms) consonant with those of the natural product.

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REFERENCES AND NOTES

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