being cyclobutadienoid, affords a bifunnel for decay[2b,11,12] to S_0 diradical. This should then adopt a crosswise p orbital orientation of a Möbius system which is ground-state preferred and leads onward to product.

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Total Synthesis of Qinghaosu

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Since ancient times *Artemisia annua* L. has been used as a traditional Chinese herbal medicine known as Qinghao for treating fever. The effective constituent was isolated by Chinese investigators in 1972 and shown to be the sesquiterpene lactone **1**,[1] named qinghaosu (Chart I). It was found to be a potent plasmodicidal agent, and extensive clinical trials in China have revealed that **1** has considerable promise for the treatment of drug-resistant malaria.[2] The combination of an outstanding biological activity and an intriguing chemical structure having no precedent in the field of antimalarials incited us to develop a synthetic route toward this novel natural product.

(-)-Isopulegol (**2**) was converted into methoxymethyl ether **3**[3] ($ClCH_2OCH_3$, $PhN(CH_3)_2$, CH_2Cl_2, room temperature), which was hydroborated (B_2H_6, THF, 0 °C) to give after oxidative workup with alkaline hydrogen peroxide the 8*R* alcohol **4** in 80% yield along with 10% of the 8*S* epimer. This transformation was modeled after the stereoselective hydroboration of **2**.[4] After benzylation of the primary hydroxyl group ($PhCH_2Br$, KH, 4:1 THF:DMF, 0 °C) the methoxymethyl ether was cleaved (CH_3OH, HCl, 40 °C, 5 h) and the resulting alcohol **5** oxidized (PCC,[5] CH_2Cl_2, room temperature) to the (benzyloxy)menthone **6**. The overall yield for the conversion of (-)-isopulegol (**2**) into **6** was 58%.

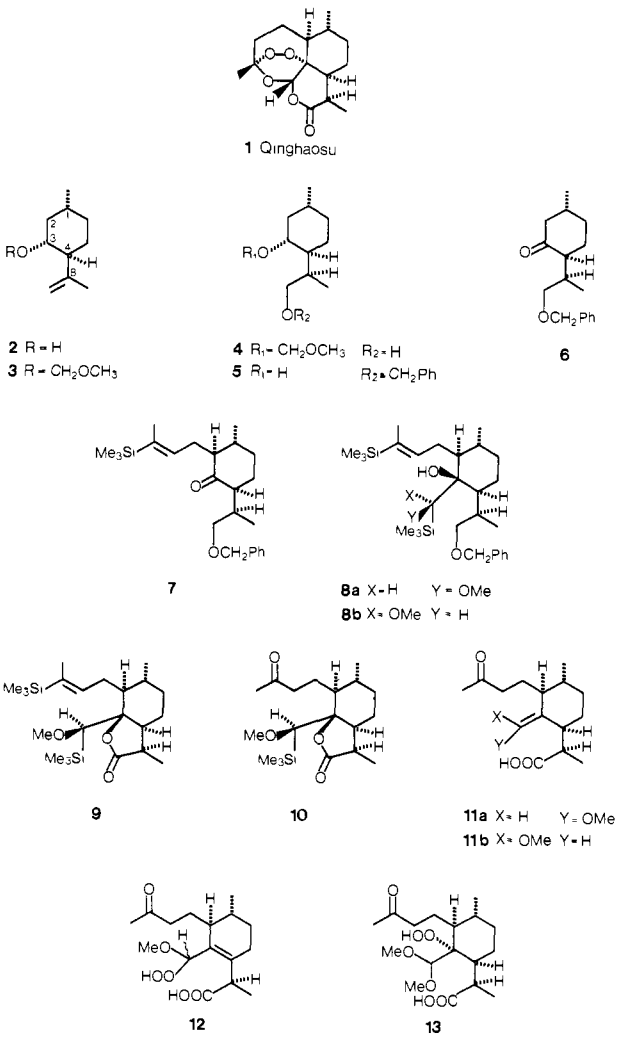
Kinetic deprotonation of **6** (LDA, THF, 0 °C) and treatment of the resulting enolate with (*E*)-(3-iodo-1-methyl-1-propenyl)-trimethylsilane[6] provided a 6:1 mixture of epimeric alkylation products from which the major isomer **7**[7] was isolated in 62% yield.

When ketone **7** was added to 1 equiv of lithium methoxy(trimethylsilyl)methylide[8] (THF, -78 °C), two diastereomeric alcohols, **8a** and **8b**, were obtained in a 1:1 ratio and almost quantitative yield. Since large nucleophiles are known to attack preferentially from the equatorial side of cyclohexanones,[9] both **8a** and **8b** must have the hydroxyl group in the axial position. By use of a 10-fold excess of the reagent the ratio of **8a** to **8b** was shifted to 8:1, and **8a** could be isolated in 89% yield. This stereoselectivity is the result of a kinetic resolution of the racemic organolithium reagent by the chiral ketone. At this point of the synthesis it was not possible to establish unambiguously the configuration of the newly formed exocyclic asymmetric center of **8a** and **8b**. However, the assignment of configuration **8a** to the major isomer followed from the result of the subsequent transformations.

Compound **8a** was debenzylated (Li, NH_3) and the resulting alcohol oxidized (excess PCC,[5] CH_2Cl_2, 15 h) to lactone **9** in 75% yield. Conversion of the vinylsilane group to a ketone[6] (*m*-CPBA, CH_2Cl_2; TFA, CH_2Cl_2, 0 °C, 3 min) was achieved in 72% yield. When the resulting ketone **10** was reacted with fluoride ion (*n*-Bu_4NF, THF, room temperature, 2 h), smooth desilylation occurred with simultaneous generation of the enol ether and carboxylic acid functions of **11a** in 95% yield. The same reaction sequence applied to isomer **8b** produced selectively enol ether **11b** with opposite configuration. The complementary formation of **11a** and **11b** is convincing evidence that the fluoride ion induced β elimination is stereospecific. A synthronous antiperiplanar process as in the acid-catalyzed E2 β elimination of β-(hydroxyalkyl)silanes[10] seems most likely.

When **11a** was reacted with $^1O_2$ (methylene blue, CH_2Cl_2, room temperature), an ene reaction led to hydroperoxide **12** isolated

Chart I



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in over 60% yield as 5:1 mixture of epimers. Because methoxy groups are known to have a cis-directing effect on the ene reaction of enol ethers,[11] the location of the double bond in **12** directly established the *Z* configuration of **11a**, which in turn allowed assignment of configuration **8a** to the "major" addition product formed from **7**.

On the basis of results reported by Asveld and Kellog[12] we could expect that by changing the reaction condition the introduction of a hydroperoxide function at C(3) of **11** and the formation of **13** would become possible. When the photooxygenation was carried out in methanol at −78 °C (solution of the sodium salt of **11a**), a complex mixture of products was formed. Although none of these could be identified, we assume that **13** was a major product. Indeed, when the crude mixture of oxygenation products was treated with acid (HCOOH, CH_2Cl_2, 0 °C, 24 h), crystalline qinghaosu (**1**) was obtained in 30% yield. Our synthetic material was identical (mp, $[\alpha]_D$, CD, NMR, IR) with an authentic sample of the natural product.[13]

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Registry No. 1, 63968-64-9; **2**, 89-79-2; **3**, 84051-29-6; **4**, 84051-30-9; **5**, 84051-31-0; **6**, 84051-32-1; **7**, 84051-33-2; **8a**, 84051-34-3; **8b**, 84064-31-3; **9**, 84051-35-4; **10**, 84051-36-5; **11a**, 84051-37-6; **11b**, 84064-32-4; **12** (isomer 1), 84051-38-7; **12** (isomer 2), 84064-33-5; **12**, 84051-39-8.

Supplementary Material Available: IR, ^1H NMR, melting point, and optical rotation data for key intermediates and final product (2 pages). Ordering information is given on any current masthead page.

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Synthesis of the Cytotoxic Germacranolide Eucannabinolide

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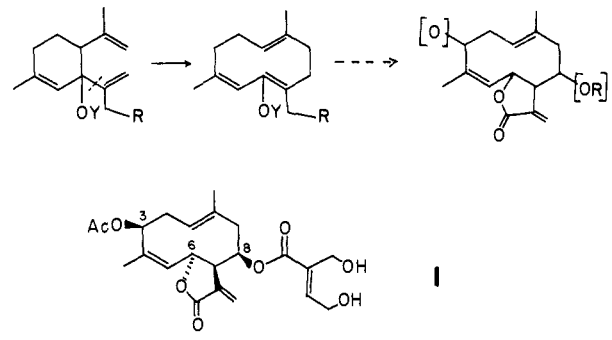
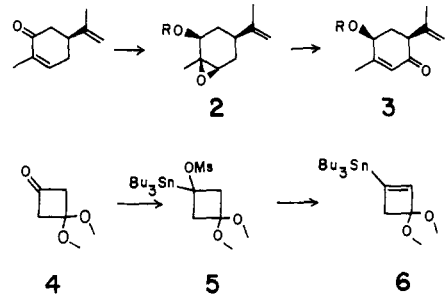
Previous results[1] from our laboratory have demonstrated that the oxy-Cope rearrangement provides a smooth pathway from monoterpenoid starting materials to appropriately functionalized germacrane-like intermediates as shown in Scheme I. Application of the route to germacranolide synthesis, however, is problematic because of the characteristic oxygenation at C8 which threatens β elimination after the ring expansion takes place. Stereochemical and regiochemical uncertainties are also present since the configurations at C6 and C7 (at least) and the direction of lactonization of the acrylic acid appendage would need to be set while on a conformationally flexible macrocyclic framework. Effective solutions to these problems have been found that allow rational construction of the germacranolide eucannabinolide (**1**).[2] An account of these solutions follows.

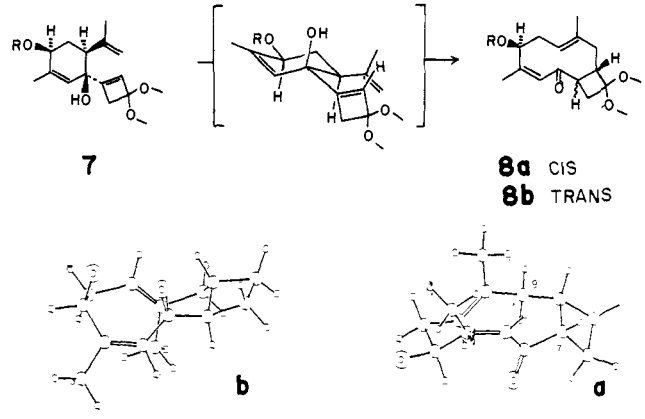
Scheme I



Scheme II



Scheme III



Our synthesis began with (+)-carvone. Reduction ($LiAlH_4$, Et_2O, 0 °C), epoxidation (MCPBA, CH_2Cl_2, 25 °C), and protection ($PhCH_2OCH_2Cl$, *i*-Pr_2NEt, 25 °C) yielded **2** in >70% yield (Scheme II).[3] The epoxide was eliminated via the selenoxide ((1) PhSeK–LiBr, THF, 25 °C; (2) 30% H_2O_2, $NaHCO_3$, NaOAc, THF, 60 °C, 16 h)[4] to a tertiary allylic alcohol, which was oxidized (Jones' reagent, 0 °C, 1.5 h) to the required enone **3** (53% yield from **2**).[5]

An appropriate equivalent of the required (alkoxyvinyl)acrylic acid appendage was found to be a cyclobutenone acetal which was prepared from the known acetal of the ketene/ethoxyacetylene

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