Total Synthesis of the Antimalarial Sesquiterpene Peroxide Qinghaosu and Yingzhaosu A

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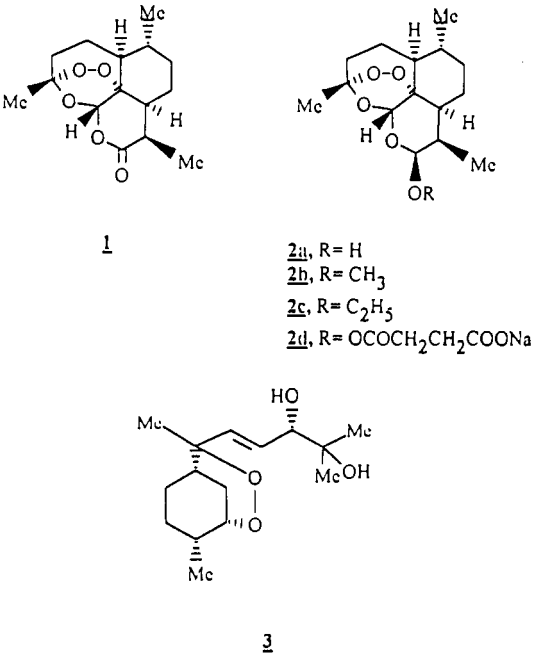
The Chinese herbal medicine Qinghao (*Artemisia annua* L. *Compositae*) is abundant and grows indigenously all over China. It has been used in practice for treatment of malaria in China for more than 1000 years, but its therapeutic effect in traditional form was not definite and consistent. Further studies on the antimalarial effect of Qinghao were done, and an active antimalarial constituent of Qinghao was isolated.[1a] On the basis of pharmacological[2] and chemical[1a] studies, as well as X-ray structure analysis,[1b] the antimalarial principle is a sesquiterpene peroxide named qinghaosu (arteannuin or artemisinin, **1**), which has recently been used as a new type of nontoxic antimalarial drug with rapid action against chloroquine-resistant malaria. The antimalarial activity of this unusual natural compound, especially against the *Plasmodium falciparum* strains responsible for more severe forms of the disease, provided a major lead in an area where resistance to existing drug treatments is increasing alarmingly. However, clinical trials revealed that in treatment with qinghaosu the disease recurred sooner than with chloroquine, despite complete disappearance of parasite from the patient's blood.

Derivatives of qinghaosu, for example, β-artemether (**2b**)[3] and β-arteether (**2c**)[3,4] as well as sodium artesunate (**2d**),[5] have been prepared from **2a** which was obtained from $NaBH_4$ reduction of qinghaosu.[1a] Many of them have the advantage of being more oil and water soluble and more potent than the parent compound qinghaosu. Sodium artesunate acts rapidly in restoring to consciousness comatose patients with cerebral malaria. Thus qinghaosu and its derivatives offer promise as a totally new class of antimalarial.

Yingzhaosu A (**3**) is also an antimalarial constituent, isolated from Yingzhao (*Artabotrys uncinatus* L. *Merr.*) a Chinese traditional medicine for treatment of malaria, and was shown to be a peroxy-containing sesquiterpene[6] similar to qinghaosu (**1**). The intriguing molecular architecture and unprecedented antimalarial activity have prompted a number of organic chemists to develop



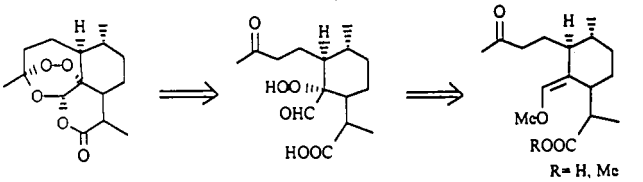
1

2a, R = H
2b, R = CH_3
2c, R = C_2H_5
2d, R = $OCOCH_2CH_2COONa$

3

Figure 1.

Scheme 1



1 **4** **5**

R = H, Me

synthetic routes toward these natural products (Figure 1).

Total Synthesis of Qinghaosu

The most unusual feature of the chemical structure of qinghaosu is the 1,2,4-trioxane ring, which may also be regarded as a bridging peroxide group. Qinghaosu is the only known 1,2,4-trioxane occurring in nature, although compounds with peroxide bridges are common, particularly in marine organisms.

Since qinghaosu may also be visualized as a ketal–acetal–lactone system formed by loss of water from the hydroperoxy–aldehyde **4**, the enol methyl ether **5** might serve as a key intermediate for the total synthesis of **1** (Scheme 1). In order to achieve the transformation of **5** to **4**, which could be cyclized to **1**, photooxygenation

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Xing-Xiang Xu was born in Yixing, Jiangsu, China, in 1941 and graduated from Beijing University in 1965. He then conducted research at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, and was appointed associated professor in 1986 and professor in 1992. His research interests are synthetic chemistry and methodology.

(1) (a) Liu, J. M.; Ni, M. Y.; Fan, J. F.; Tu, Y. Y.; Wu, Z. H.; Wu, Y. L.; Zhou, W. S. *Huaxue Xuebao* **1979**, *37*, 129. (b) Institute of Biophysics Academic Sinica. Sci. Sin. **1979**, *22*, 1114; **1980**, *23*, 380.

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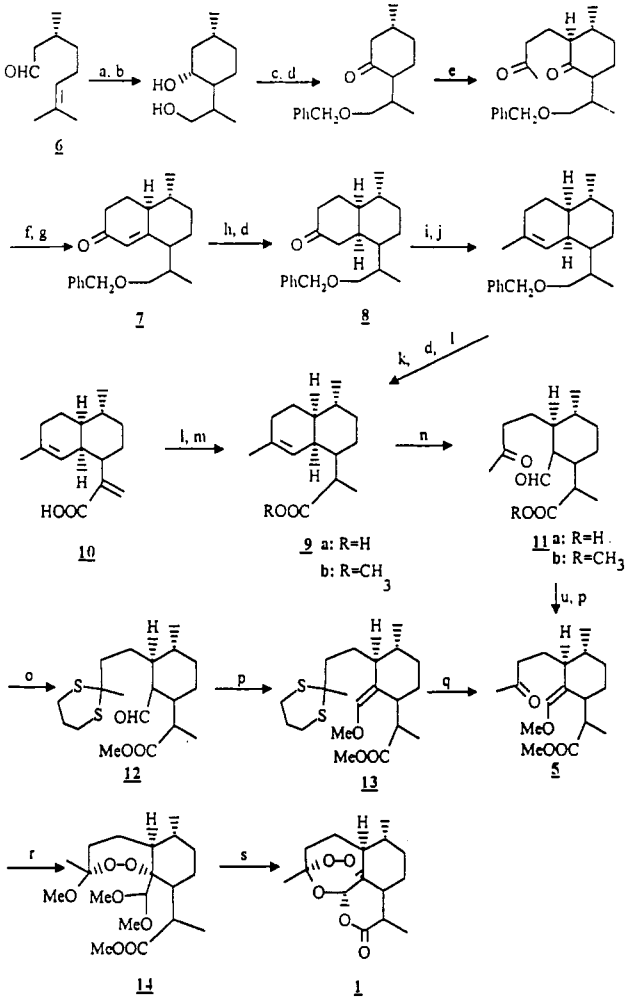
Scheme 2. Xu, Zhu, Huang, and Zhou: Total Synthesis of Qinghaosu[a]



[a] (a) $ZnBr_2$; (b) B_2H_6, H_2O_2–NaOH; (c) $PhCH_2Cl$–NaH; (d) Jones oxidation (e) LDA, $CH_2{=}C(Me_3Si)COCH_3$; (f) $Ba(OH)_2{\cdot}8H_2O$; (g) $(COOH)_2$; (h) $NaBH_4$–Py; (i) MeMgI; (j) *p*-TsOH; (k) Na–liquid NH_3; (l) CH_2N_2; (m) $NaBH_4$–$NiCl_2{\cdot}6H_2O$; (n) O_3, Me_2S; (*o*) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (p) $HC(OMe)_3$, *p*-TsOH; xylene, Δ, (q) $HgCl_2$–$CaCO_3$; (r) O_2, MeOH, Rose Bengal, *hν*, −78 °C; (s) 70% $HClO_4$.

of **5** was expected to provide a synthetically equivalent dioxetane. The key intermediate **5** (R = Me) was obtained from (*R*)-(+)-citronellal (**6**) through the reaction sequence outlined in Scheme 2.[7]

Both **7** and **8** showed a positive Cotten effect (CE) in their CD spectra; therefore the α-orientation of 1-H in **7** and of 6-H in **8** was assigned, respectively. **8** was successively converted into the compound **9**, which could be converted into the natural qinghao acid (**10**)[8]

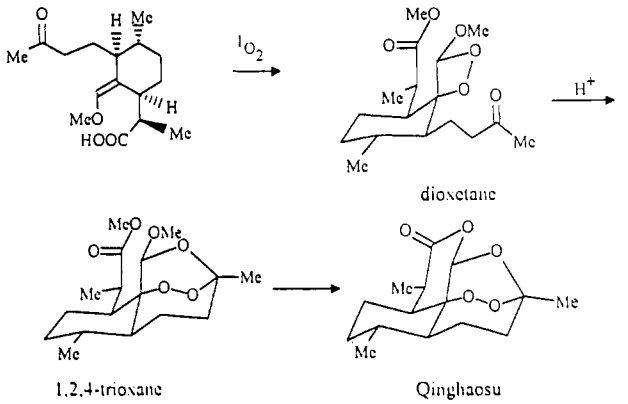
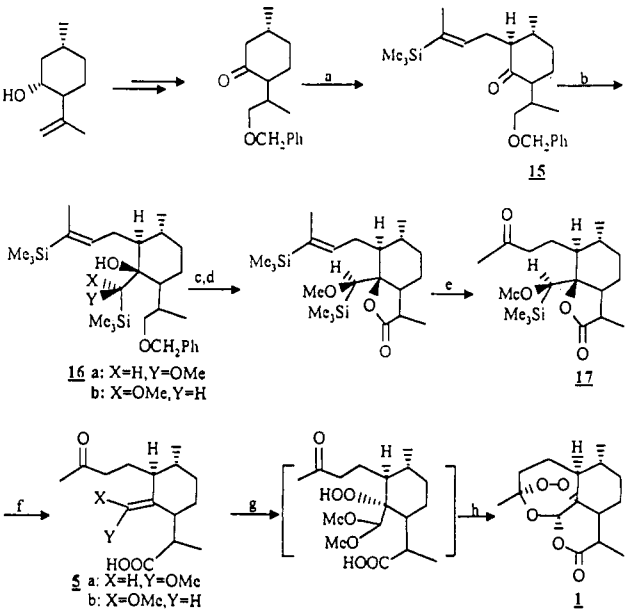


Figure 2.

Scheme 3. Schmid and Hofheinz: Total Synthesis of Qinghaosu[a]



[a] (a) LDA, THF; $TMS(Me)C{=}CHCH_2I$; (b) $TMS(Li)C(OMe)H$, THF, −78 °C; (c) Li–liquid NH_3; (d) excess PCC, CH_2Cl_2, (e) *m*-CPBA, THF; TFA; (f) *n*-Bu_4NF, THF; (g) O_2, Methylene Blue, MeOH, *hν*, −78 °C; (h) HCOOH, CH_2Cl_2.

and in turn was obtained from the latter. The absolute configuration of **8** and **9** was thus unambiguously confirmed. Ozonization of **9** afforded the aldehyde–ketone **11**. The selective protection of the ketonic carbonyl of **11** was realized by treatment with 1,3-propanedithiol in CH_2Cl_2. Then the aldehydic carbonyl of **12** was reacted with trimethyl orthoformate followed by refluxing in xylene to give the enol ether unit. Removal of the thioketal afforded the key intermediate **5**. Without protection of the ketonic carbonyl, the aldehydic carbonyl of **11** could also react with MeOH in the presence of acid to form acetal and to give the same key intermediate **5**.[9] Photooxidation of a methanolic solution of **5** in the presence of oxygen and Rose Bengal at −78 °C[10] followed by treatment with gaseous HCl led to the trapped intermediate **14**, which on treatment with acid gave qinghaosu (**1**) in 28% overall yield from **5**.

The formation of **1** may be considered as a result of singlet oxygen ($^1O_2$) addition to the exocyclic methyl

(2) Qinghaosu Antimalarial Coordinating Research Group. *Chin. Med. J.* **1979**, *92*, 811.
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(4) Brossi, A.; Venugopalan, B.; Dominguez Gerpe, L.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.
(5) Li, Y.; Yu, P. L.; Cheng, Y. X.; Ji, R. Y. *Huaxue Xuebao* **1982**, *40*, 557.
(6) Liang, X. T.; Yu, D. Q.; Wu, W. L.; Deng, H. C. *Huaxue Xuebao* **1979**, *37*, 215.
(7) (a) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Huaxue Xuebao* **1983**, *41*, 574. (b) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Huaxue Xuebao* **1984**, *42*, 940. (c) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819.
(8) Deng, D. A.; Zhu, D. Y.; Gao, Y. L.; Dai, J. Y.; Xu, R. S. *Kexue Tongbao* **1981**, 1209.
(9) Zhu, J.; Xu, X. X.; Zhou, W. S. *Huaxue Xuebao* **1987**, *45*, 150.
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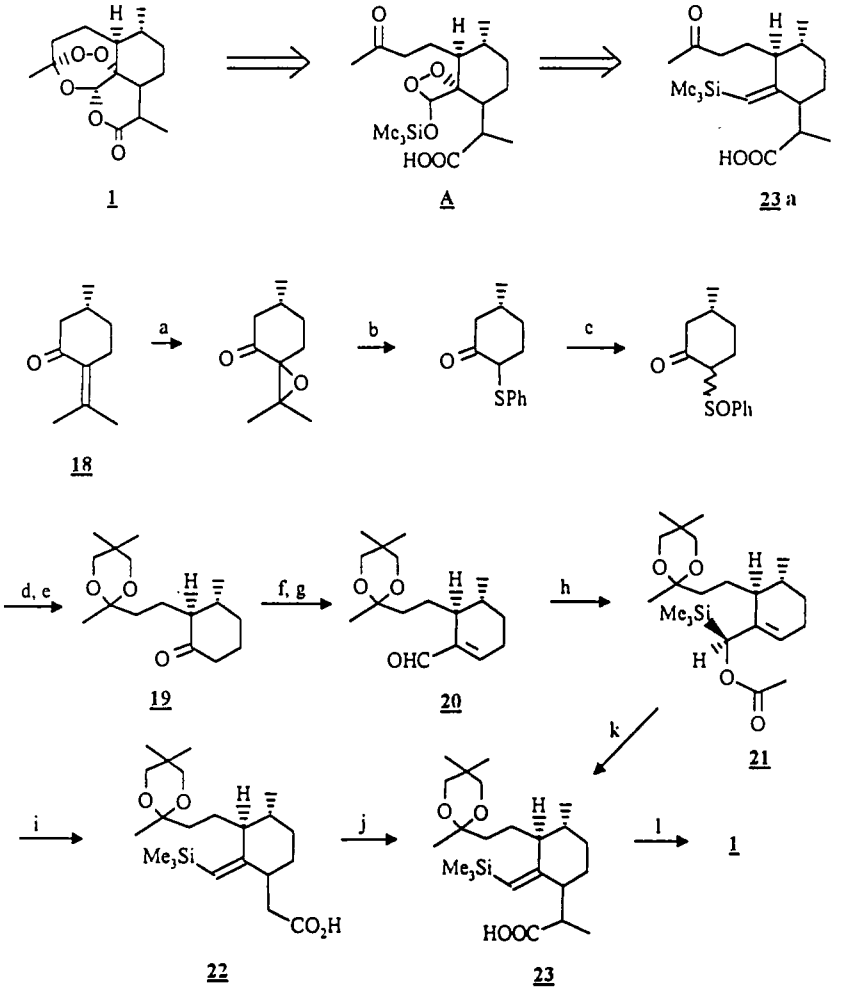
Scheme 4. Avery, Chong, and Jennings-White: Total Synthesis of Qinghaosu[a]



[a] (a) Alkaline, H_2O_2, THF; (b) NaSPh, THF; (c) *m*-CPBA, CH_2Cl_2, −78 °C; (d) 2 equiv of LDA, HMPT or DMTP, THF, then 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; (e) Al(Hg) amalgam, wet THF, (*f*) *p*-$CH_3C_6H_4SO_2NHNH_2$; (g) 4 equiv of *n*-BuLi, TMEDA, 0 °C, then DMF; (h) $Mc_3Si)_3Al{\cdot}OEt_2$, then Ac_2O, DMAP, −78 to 23 °C; (i) 2 equiv of LDEA, THF, −78 to 23 °C; (j) 2 equiv of LDA, THF, 50 °C; CH_3I, −78 °C; (k) 3 equiv of LDEA, THF, −78 to 50 °C, 2.5 equiv of LDA, 0–45 °C; CH_3I, −78 °C to ambient temperature; (l) O_3/O_2, CH_2Cl_2, −78 °C, then SiO_2; 3 M aqueous H_2SO_4.

vinyl ether followed by acid-induced rearrangement of the resultant dioxetane to afford the 1,2,4-trioxane substructure,[10] which leads eventually to product by loss of methanol (Figure 2).

Schmid and Hofheinz[11] used low-temperature photoxidation for introducing the hydroperoxy group to the C-6 position in the same key intermediate **5** (R = H), as shown in Scheme 3.

The enol ether unit of **5** was directly prepared from the reaction of ketone **15** with the silyl reagent. When ketone **15** was treated with 1 equiv of lithium methoxy(trimethylsilyl)methylide, two diastereomeric alcohols, **16a** and **16b**, were obtained in a 1:1 ratio and almost quantitative yield. By use of a 10-fold excess of the reagent, the ratio of **16a** and **16b** was shifted to 8:1, and **16a** could be isolated in 89% yield. Since bulky nucleophiles should attack preferentially from the equatorial side of cyclohexanone, both **16a** and **16b** must have the hydroxyl group in the axial position. When **17** was treated with fluoride ion, smooth desilylation occurred with simultaneous generation of the enol ether and carboxylic acid function of **5a** (R = H) in 95% yield. When the same reaction sequence was applied to the isomer **16b**, the enol ether **5b** was produced selectively with the opposite configuration. The complementary formation of **5a** and **5b** convincingly proved that the fluoride-induced β-elimination is stereospecific. When **5a** was reacted with $^1O_2$, an ene reaction led to the formation of hydroperoxide. On treatment of the crude mixture with acid, crystalline qinghaosu was obtained in 30% yield in two steps.

Avery and co-workers[12] have made use of the abnormal course of reaction of the vinylsilane **23** with ozone as reported by Buchi[13] for total synthesis of qinghaosu. The procedure could be considered to be the ring opening of a transient (silyloxy)dioxetane **A**, resulting in the formation of the known α-hydroperoxy–aldehyde unit. The key intermediate **23** was prepared according to Scheme 4.

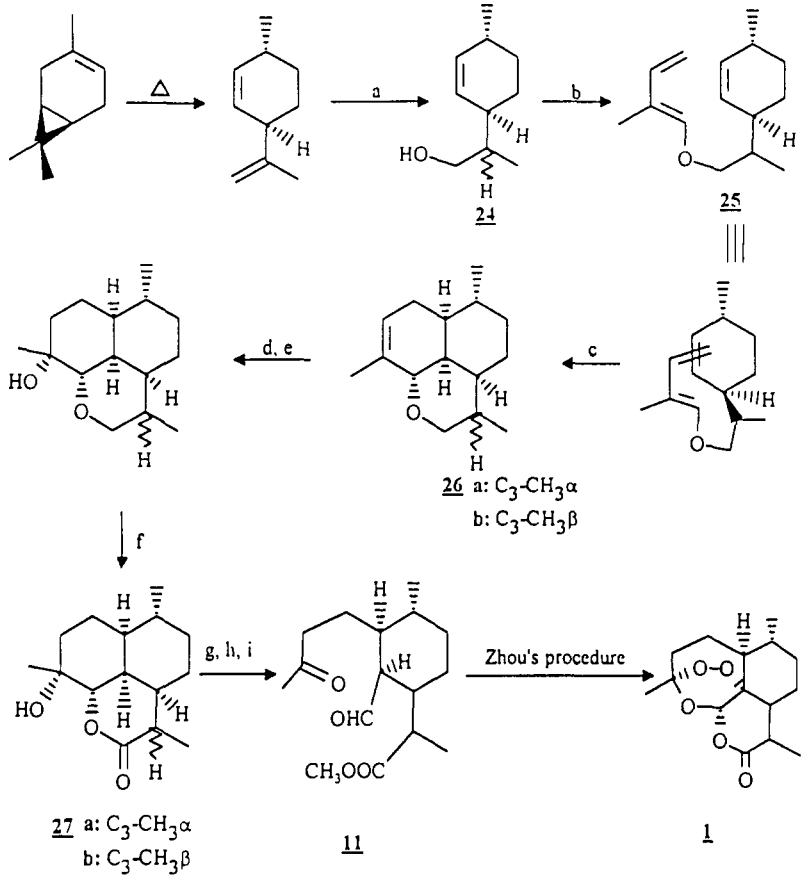
(R)-(+)-Pulegone (**18**) was used as starting material and transformed into the optically active ketone **19** through five steps. Reaction of the ketone **19** with tosylhydrazine followed by treatment with 4 equiv of *n*-BuLi and trapping of the resultant vinyl anion with DMF afforded α,β-unsaturated aldehyde **20**. The 1,2-addition of tris(trimethylsilyl)aluminum etherate to

(11) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624.

(12) (a) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629. (b) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974.

(13) Buchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294.

Scheme 5. Ravindranathan, Kumar, Menon, and Hiremath: Formal Total Synthesis of Qinghaosu[a]



[a] (a) 1.0 equiv of 9-BBN; 3 N NaOH; (b) 1-ethoxy-2-methyl-1,3-butadiene, $Hg(OAc)_2$, NaOAc; (c) toluene, 210 °C sealed tube, 72 h; (d) *m*-CPBA, CH_2Cl_2, 0 °C; (e) $LiAlH_4$, Et_2O; (f) $RuCl_3 \cdot 3H_2O$, $NaIO_4$; (g) 1 equiv of NaOH; (h) $NaIO_4$; (i) CH_2N_2.

aldehyde **20** and subsequent quenching with acetic anhydride yielded a single silyl acetate **21**. Upon treatment of **21** with lithium diethylamide (LDEA), an Ireland–Claisen rearrangement took place, forming regioselectively the vinylsilane moiety and connecting stereoselectively the acetic acid function through a chair-like transition state, to give the desired product **22**. Methylation of **22** with 2 equiv of lithium diisopropylamide (LDA) led to a single diastereomerically pure homologous acid **23** in nearly quantitative yield. The transformation of **21** to **23** could also be carried out in one pot by successive treatment of **21** with LDEA and LDA. Finally acid **23** was converted in a one-pot procedure involving sequential treatment with ozone followed by wet acidic silica gel to effect a complex process of dioxetane **A** formation, ketal deprotection, and cyclization to the natural product qinghaosu in 33–39% yield.

A stereoselective formal total synthesis of qinghaosu (Scheme 5) based on an intramolecular Diels–Alder reaction of the triene **25** was achieved by Ravindranathan and co-workers,[14] as shown in Scheme 5.

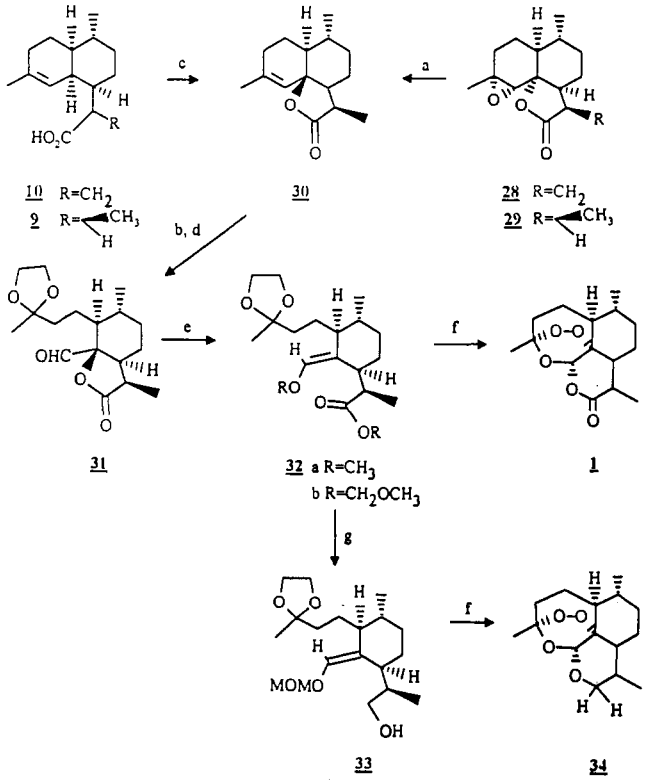
The epimeric mixture of alcohol **24**, which was obtained from (+)-car-3-ene, was converted to the enol ether **25** by transetherification with 1-ethoxy-2-methyl-1,3-butadiene. The triene **25** underwent an intramolecular Diels–Alder reaction to furnish an epimeric mixture of ethers **26a** and **26b** in 25–30% yield. The mixture of **26** was epoxidized with *m*-CPBA, reduced with $LiAlH_4$, and oxidized with $RuCl_3$–$NaIO_4$ to give an epimeric mixture (7:3) of lactones **27a** and **27b**, which could be separated and characterized by NMR and X-ray analysis. Pure **27a** could be equilibrated with NaOAc–MeOH to obtain an equilibrium mixture of **27a** and **27b** in a 6:4 ratio. The lactone **27b** was converted into the known keto aldehyde compound **11** by cleavage with $NaIO_4$. Since the conversion of the **11** to qinghaosu is known,[7] this work represents another total synthesis of qinghaosu.

An efficient partial synthesis of qinghaosu **1** through enol ether **32** was reported by Lansbury and Nowak,[15] in which qinghao acid (**10**) and qinghaosu B (**28**) were used as the starting material and separately converted into **30** (Scheme 6). Ozonization of **30** and selective protection of the resulting ketonic carbonyl afforded **31**. Reductive cleavage of **31** with sodium naphthalenide followed by in situ reaction with alkylating agents (CH_3I, CH_3OCH_2Cl) produced enol ether–esters **32a** and **32b**. $^1O_2$ reaction of **32a** and **32b** was performed with Rose Bengal as a sensitizer to give 30–35% isolated yields of qinghaosu (**1**). $^1O_2$ reaction of the alcohol **33** produced deoxoqinghaosu (**34**), which has been known to possess in vitro and in vivo antimalarial activity superior[16] to that of qinghaosu.

Recently, starting from (−)-β-pinene, another total synthesis of qinghaosu has been accomplished using an

(14) Ravindranathan, T.; Anil Kumar, M.; Memon, R. B.; Hiremath, S. V. *Tetrahedron Lett.* **1990**, *31*, 755.
(15) Lansbury, P. T.; Nowak, D. M. *Tetrahedron Lett.* **1992**, *33*, 1029.
(16) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D.; Milhous, W. K. *J. Med. Chem.* **1990**, *33*, 1516.
(17) Liu, H.-J.; Yeh, W.-L.; Chew, S.-Y. *Tetrahedron Lett.* **1993**, *34*, 4435.
(18) Roth, R. J.; Acton, N. *J. Nat. Prod.* **1989**, *52*, 1183.
(19) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron Lett.* **1991**, *32*, 5785.

Scheme 6. Lansbury and Nowak: Partial Synthesis of Qinghaosu and Deoxoqinghaosu[a]



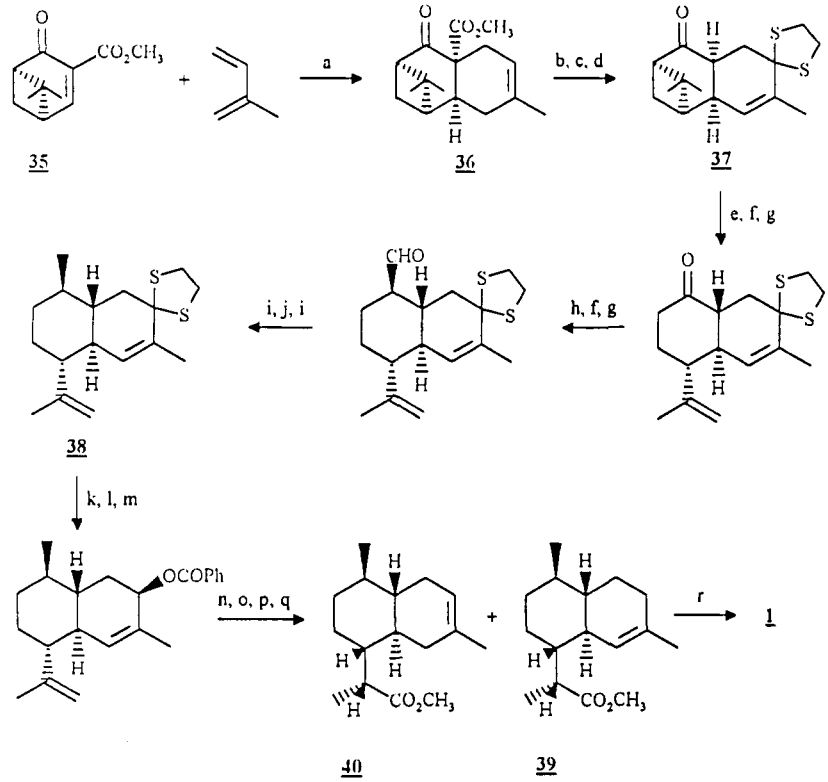
[a] (a) 2:1 *n*-BuLi/tungsten hexachloride, THF; (b) O_3; (c) CrO_3–3,5-dimethylpyrazole, CH_2Cl_2; (d) 1,2-bis[(trimethylsilyl)oxy]ethane, TMS triflate, CH_2Cl_2; (e) 2 equiv of sodium naphthalenide, THF, then CH_3I, CH_3OCH_2Cl; (f) $^1O_2$, Rose Bengal; camphorsulfonic acid; (g) $LiAlH_4$.

intermolecular Diels–Alder approach by Hsing-Jang Liu and co-workers[17] as shown in Scheme 7. The zinc chloride catalyzed Diels–Alder addition of (+)-enone ester **35** prepared from (−)-β-pinene proceeded with regioselective and facial selectivity to give adduct **36**, which then underwent a series of functional group transformations involving the fragmentation of the cyclobutane ring in compound **37**, the installation of the methyl group with stereochemical control in compound **38**, and the conversion of the isopropenyl group into a propionate unit with 9-BBN to furnish a mixture of two inseparable regioisomers **39** and **40** in a ratio of 9:5. Experiment has proved that the desired isomer **39** with a trans-fused ring system was equally converted to qinghaosu via a photooxygenation process.[18]

Total Synthesis of Yingzhaosu A

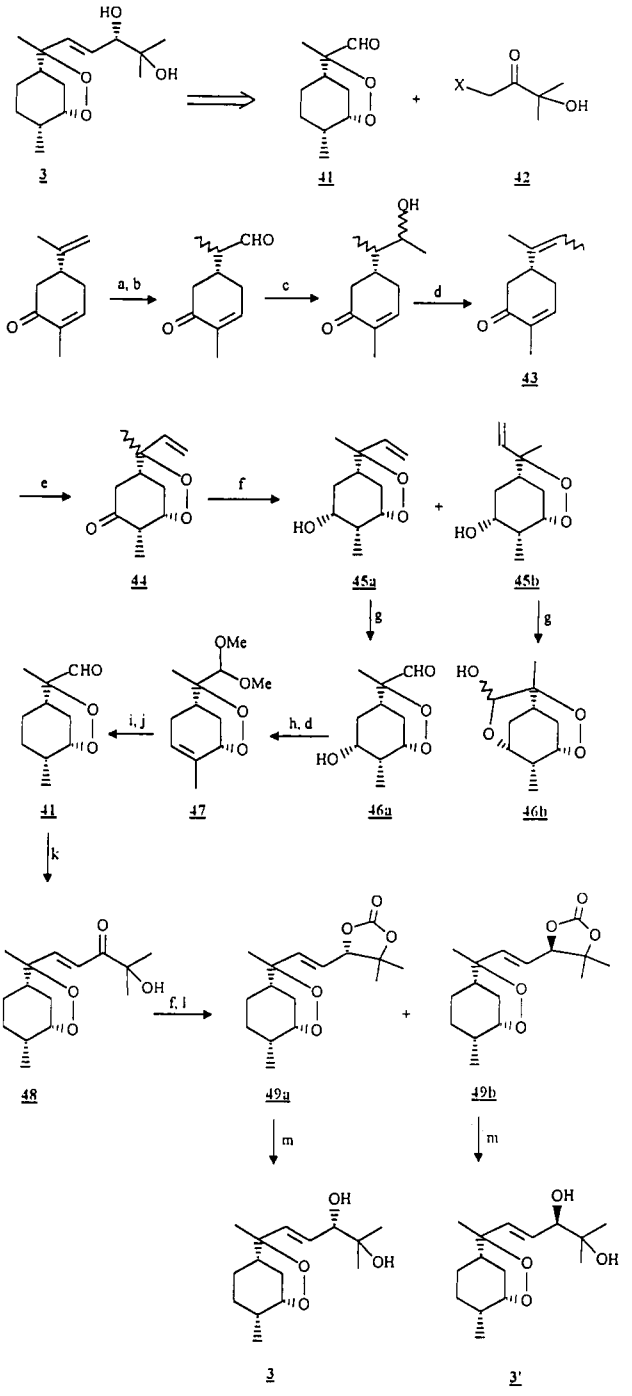
Yingzhaosu A (**3**) is also a peroxy-containing antimalarial constituent, isolated from Yingzhao (*A. uncinatus* L. *Merr.*). Its structure reveals a unique dioxabicyclo[3.3.1.]nonane ring system bearing a dihydroxyolefinic side chain. Three chiral centers at C-6, C-4, and C-1 have been preliminarily deduced as *S*, *S*, and *R*, while the other two at C-8 and C-12 remain unsolved.[6] In order to construct the major framework **41**, compound **43** containing a temporary α,β-unsaturated ketone function was used to build a peroxy bridge at the proper position, and then the ketone group was removed after the peroxy bridge was formed. An arsenical ylide was adopted for the construction of the side chain with an *E* double bond. (*R*)-(−)-Carvone was used as starting material as shown in Scheme 8.[19]

Scheme 7. Liu, Yeh, and Chew: Total Synthesis of Qinghaosu[a]



[a] (a) $ZnCl_2$; (b) TPP, O_2, CH_2Cl_2, *hν*, Ac_2O, Py, DMAP; (c) BF_3·OEt_2, $(CH_2SH)_2$, CH_2Cl_2, −10 °C; (d) LiI·H_2O, 2,4,6-collidine; (e) *p*-TsOH, $(CH_2OH)_2$, PhH, reflux; (f) *p*-TsOH, aqueous acetone, reflux; (g) aqueous NaOH, CH_3OH, reflux; (h) $Ph_3P^+CH_2OCH_3Cl^-$, KH, DMSO, PhH; (i) LAH, THF, reflux; (j) Et_3N, MsCl, Ch_2Cl_2; (k) $HgCl_2$, aqueous CH_3CN: (l) $NaBH_4$, $CeCl_3$, CH_3OH, −78 °C; (m) Ph_3P, DEAD, $PhCO_2H$, THF; (n) 9-BBN, THF; (o) H_2CrO_4, ether; (p) K_2CO_3, CH_3I, acetone, (q) $NaBH_4$, $NiCl_2$, CH_3OH; (r) $^1O_2$, Methylene Blue, *hν*, CH_2Cl_2, then CF_3CO_2H, O_2, petroleum ether.

Scheme 8[a]



[a] (a) *m*-CPBA, CH_2Cl_2; (b) BF_3·OEt_2, PhH; (c) MeMgBr, Et_2O, −78 °C; (d) $POCl_3$, Py; (e) O_2, *hν*, Methylene Blue, MeCN, *p*-TsOH; (f) $LiBH_4$, Et_2O; (g) O_3, CH_2Cl_2–CH_3OH, −78 °C; Me_2S; (h) $HC(OMe)_3$, MeOH, *p*-TsOH; (i) PtO_2, H_2, AcOEt; (j) *p*-TsOH, Me_2CO–H_2O, 55 °C; (k) $Ph_3AsCH_2COC(OH)Me_2$·Br, K_2CO_3–H_2O, CH_2Cl_2; (l) $COCl_2$, Py; (m) $LiBH_4$.

When **43** was reacted with $^1O_2$ in the presence of *p*-TsOH, an ene reaction product was formed and the resulting compound underwent an intramolecular Michael addition, forming the peroxy bridge, to give an inseparable mixture of C-8 methyl epimer **44** in a 1:1 ratio. Reduction of the carbonyl group of **44** from the less hindered convex face with $LiBH_4$ furnished a separable mixture of **45a** and **45b**. Based on ^1H NMR data, the configuration of C-8 at **45a** and **45b** could be deduced. Upon ozonolysis, **45a** gave the aldehyde **46a** whereas **45b** gave the hemiacetal **46b**. The configuration in **46a** was firmly established. The hydrogenation of the double bond of **47** was realized without affecting the peroxy group, using a properly activated platinum oxide and an equivalent amount of hydrogen, in a yield of 80%. Compound **41** was reacted with the appropriate arsenical ylide to yield the α,β-unsaturated ketone **48**. The latter was reduced using $LiBH_4$ followed by treatment with phosgene to give a separable mixture of C-12 isomeric carbonates **49a** and **49b** in a ratio of 3:2. Owing to the lack of an authentic sample, the C-12 configuration of the natural product was only established through comparison of the ^1H NMR data between the synthetic carbonate **49a** or **49b** and the natural carbonate. The *S* configuration of C-12 in **49a** was finally confirmed by X-ray diffraction analysis.[19] Treatment of **49a** and **49b** with $LiBH_4$ afforded yingzhaosu A (**3**) and its C-12 epimer **3′**. Thus the first total synthesis of (+)-yingzhaosu A was achieved, and its C-8 and C-12 configurations were established.

Conclusion

Although different monoterpenes were used as starting materials in the total syntheses of qinghaosu, the key step, introduction of the peroxy function to form the known labile hydroperoxy–aldehyde, was realized either by adding singlet oxygen ($^1O_2$) to an exocyclic methyl vinyl ether followed by an acid-induced rearrangement of the resultant methoxydioxetanes or by using the abnormal ozonolysis of vinylsilane followed by a similar (silyloxy)dioxetane rearrangement. In the total synthesis of yingzhaosu, the ene reaction of singlet oxygen was followed by an intramolecular Michael addition of the resultant hydroperoxy group to the α,β-unsaturated carbonyl moiety to form the peroxy bridge in the early fifth step of the 14-step synthesis.

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