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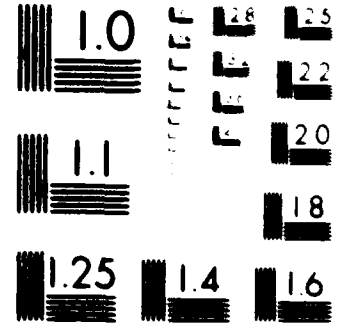
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ANTIMALARIAL CYCLIC PEROXIDE LACTONES

ANNUAL REPORT

KUO-HSIUNG LEE

November 14, 1986

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Antimalarial Agents, Total Synthesis of Qinghaosu

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Total synthesis of qinghaosu (1) based upon Zhou's method as shown in Scheme-2 has been achieved. New improved synthesis of 1 as well as synthesis of new analogs related to 1 are in progress.

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FIGURE 2

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ANNUAL REPORT

(1) List of structures of all target compounds that have been submitted to the Walter Reed Army Institute of Research for screening between October 15, 1985 - October 14, 1986.

None. The reason for this was stated in my previous Annual Report dated May 29, 1986. In this period, our efforts were directed entirely toward the total synthesis of qinghaosu (1) according to Scheme-1.

(2) Synthetic procedures for the total synthesis of qinghaosu (1)
As described in our previous Annual Report (dated 5/29/86) as well as four Quarterly Reports (dated 1/15/86, 4/15/86, 7/15/86 and 10/15/86), we have achieved the total synthesis of qinghaosu (1) based upon Zhou's method (Scheme-1).[1] Our synthesis of 1 is described below (Scheme-2). We are currently working on the new improved synthesis of 1 as well as the synthesis of new simpler analogs related to 1.

1. Compound b from Oxidation of a - 250 ml of an aqueous solution (300 ml) containing CrO_3 (70 g) and H_2SO_4 (112 g) was added dropwise to a solution of silylbutenol (a) (129.1 g) in acetone (220 ml) with stirring in an ice-water bath over 3 hrs. After completion of the addition, isopropyl alcohol was added to the reaction mixture. The mixture was poured into ether (500 ml), and 300 ml of aqueous saturated sodium chloride was added. The aqueous layer was extracted with ether (4 x 200 ml). The combined ether solutions were washed with saturated aqueous sodium chloride (2 x 200 ml), dried over anhydrous magnesium sulfate, and concentrated by distillation at atmospheric pressure through a 30 cm Vigreaux column. Continued distillation under reduced pressure gave silylbutenone (b) (3-trimethylsilyl-3-buten-2-one) (40.6 g; yield 31.9%; bp 81-84°C/92-93 mmHg; lit. bp 98-103°C/100 mmHg) as a pale yellow liquid: NMR ($CDCl_3$ 250 MHz) δ 6.479 (1H, d, J = 1.9 Hz, olefinic H), 6.149 (1H, d, J = 1.9 Hz, olefinic H), 2.270 (3H, s, CH_3CO-), and 0.123 (9H, s, $Si(CH_3)_3$).

2. Compound 5 from Alkylation of 4 - n-BuLi (1.55 M/L, 81.8 ml) was added dropwise to a solution of diisopropylamine (18.7 ml) in anhydrous tetrahydrofuran (THF) (130 ml) at -78°C with stirring for 30 min, and the mixture was stirred for an additional hour. To the mixture was added dropwise a solution of keto-benzyl ether (4) (27.5 g) in anhydrous THF (40 ml) for 30 min. After stirring for 30 min, 3-trimethylsilyl-3-buten-2-one (b) (22.5 g) in anhydrous THF (25 ml) was added dropwise. The mixture was stirred at -78°C

for 1 hr, then warmed to 0°C and further stirred at 0°C for 3 hrs. The reaction mixture was acidified with 10% HCl and stirred for 15 min, then neutralized with 5% $NaHCO_3$, and extracted with ether. The ether layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a crude product (47.0 g). Column chromatography of the crude product on silica gel (1 kg) with elution with 10% ether-hexane afforded the diketone (5) (19.6 g, yield 56.0%) as a colorless oil: IR ($CHCl_3$) 1705 (C = O) cm^{-1}; and NMR ($CDCl_3$, 200 MHz) δ 7.390-7.210 (5H, aromatic protons), 4.477 (2H, s, ϕ-$\underline{CH_2}$-O), 3.459 (1H, dd, J = 5.0 and 9.1 Hz), 3.373 (1H, dd, J = 5.6 and 9.1 Hz, AB part of ABX, O-$\underline{CH_2}$-CH<), 2.117 (3H, s, -C(=O)-CH_3), 1.060 (3H, d, J = 5.9 Hz, sec-CH_3), and 1.000 (3H, d, J = 6.8 Hz, sec-CH_3).

3. Compound 6 from Cyclization of 5 via 6a - To a solution of diketone (5) (19.0 g) in ethanol (750 ml) was added $Ba(OH)_2.8H_2O$ (20.7 g). After the mixture was stirred at room temperature for 2.5 hrs, it was neutralized with 10% HCl and concentrated under reduced pressure (by vacuum pump, room temperature). The residue was extracted with dichloromethane, washed with water, dried over anhydrous magnesium sulfate, and concentrated to afford a crude product (23.1 g): IR ($CHCl_3$) 3400 (OH) and 1710 (C = O) cm^{-1}.

A mixture of the above products (23.0 g) and 2% oxalic acid in ethanol (800 ml) was refluxed for 2.5 hrs. The reaction mixture was neutralized with 5% $NaHCO_3$ and concentrated under reduced pressure (by vacuum pump, room temperature) to furnish a residue. Extraction of the residue with dichloromethane followed by washing with water, drying over anhydrous magnesium sulfate, and evaporation afforded a crude oily product (21.9 g). This product was chromatographed on silica gel (410 g) to yield an α,β-unsaturated ketone) (6) (12.0 g, 66.8% in 2 steps; recrystallized from hexane) as colorless prisms: mp 75-76°C; IR($CHCl_3$) 1660 and 1610 (α,β-unsaturated ketone) cm^{-1}; and NMR ($CDCl_3$, 200 MHz) δ 7.373-7.230 (5H, aromatic H), 5.861 (1H, s,olefinic H), 4.514, 4.442 (each 1H, ABq, J = 12.1 Hz, $\phi\underline{CH_2}$-O), 3.470 (1H, dd, J = 3.2 and 9.0 Hz), 3.343 (1H, dd, J = 5.9 and 9.0 Hz, AB part of ABX, O-$\underline{CH_2}$-CH<), 1.061 (3H, d, J = 6.3 Hz, sec-CH_3), and 1.023 (3H, d, J = 6.4 Hz, sec-CH_3).

This compound was proven to be 1α-Δ^5-10α-methyl-7β-[2'β-(1'-benzyloxy)-propane]-decalone-4 by an x-ray analysis as shown in Figure-1.

4. Compound 7 from Reduction and Oxidation of 6 and its Intermediate - To a solution of sodium borohydride (8.27 g) in pyridine (110 ml) was added dropwise a solution of the α,β-unsaturated ketone (6, 11.6 g) in pyridine (140 ml) in an ice-water bath. After the mixture was stirred at room temperature for 7 hrs., water (18 ml) was added, and the mixture was further stirred for 30 min. The mixture was diluted with ether (500 ml) and acidified with 10% HCl.

The ether layer thus separated was added with a solution of sodium iodate (79.8 g) in water (800 ml). After the mixture was further stirred for 15 hrs. at room temperature, the organic layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed successively with 5% $Na_2S_2O_3$, H_2O, 10% HCl, 5% $NaHCO_3$, H_2O, dried over anhydrous magnesium sulfate, and concentrated to give the oily residue (12.3 g).

To a solution of the foregoing residue (12.3 g) in acetone (70 ml) was added dropwise an aqueous solution (30 ml) containing CrO_3 (7.8 g) and H_2SO_4 (9 ml) in an ice-water bath. After the mixture was stirred for 15 min., isopropanol was added until the color of the reagent disappeared. The mixture was extracted with ether and the ether extract was washed with 5% $NaHCO_3$, and water, dried over anhydrous magnesium sulfate, and evaporated to give an oily residue (11.6 g). Column chromatography of the residue on silica gel (200 g) afforded the saturated ketone (7) (4.47 g, 38.2% in 2 steps; recrystallized from ether-hexane) as colorless needles: mp 62-64°C; IR ($CHCl_3$) 1700 (6-membered ketone); and NMR ($CDCl_3$, 250 MHz) δ 7.345-7.230 (5H, aromatic H), 4.508, 4.435 (each 1H, ABq., J = 12.1 Hz, O-$\underline{CH_2}$-ϕ), 3.431 (1H, dd, J = 3.2 and 9.2 Hz), 3.326 (1H, dd, J = 5.3 and 9.2 Hz, AB part of ABX, O-$\underline{CH_2}$-CH<), 0.974 (3H, d, J = 6.6 Hz, sec-CH_3), and 0.942 (3H, d, J = 6.3 Hz, sec-CH_3).

5. Compound 8 from Grignard Addition followed by Dehydration of 7 - A 200 ml three-necked flask was charged with magnesium turnings (560 mg) and absolute ether (35 ml), and iodomethane (3.6 g) was slowly added dropwise to the stirred mixture under nitrogen atmosphere. After the addition was complete, the mixture was cooled to room temperature. Then a solution of the saturated ketone (7, 546 mg) in absolute ether (25 ml) was added dropwise and stirred at room temperature for 1.5 hrs.

After the foregoing reaction mixture was added dropwise with saturated aqueous ammonium chloride, it was extracted with ether. The ether extract was washed successively with 10% HCl, 5% sodium bicarbonate and H_2O, dried over anhydrous magnesium sulfate, and evaporated to give an oily residue (605 mg), whose IR spectrum showed the absence of carbonyl functions.

A solution of p-toluenesulfonic acid (550 mg) in tetrahydrofuran (1 ml) was added to a solution of the above oily residue (595 mg) in benzene (60 ml). The mixture was refluxed using a Dean-Stark apparatus for 2 hrs. The reaction mixture was cooled to room temperature and washed with dil. Na_2CO_3 and H_2O, dried over anhydrous magnesium sulfate, and evaporated to provide an oily residue (560 mg). This was subjected to preparative TLC using silver nitrate-impregnated silica gel plates (detection by spraying water and elution with 5% methanol-chloroform mixture) to yield 8 (110) mg) and 8a (90 mg). Compound 8 showed NMR ($CDCl_3$, 250 MHz) δ 7.367-7.220 (5H, aromatic H), 5.216 (1H, br.s, olefinic

H), 4.537, 4.454 (each 1H, ABq, J = 12.2 Hz, Ph-$\underline{CH_2}$-O-), 3.533 (1H, dd, J = 3.4 and 9.0 Hz), 3.301 (1H, dd, J = 6.8 and 9.0 Hz, AB part of ABX, O-$\underline{CH_2}$-CH<), 1.620 (3H, br. s, C=C-CH_3), 1.015 (3H, d, J = 6.8 Hz, sec-CH_3), and 0.856 (3H, d, J = 6.4 Hz, sec-CH_3).

6. Compound 8a from Debenzylation of 8 with Na/NH_3 - To a two-necked 1 liter flask was introduced liquid ammonia (300 ml) in a dry ice-acetone bath. This was then added with a solution of 8 (3.90 g) in ether (30 ml) and several pieces of metallic sodium (ca 5 g) with stirring. After 1 hr., the reaction was quenched by addition of aqueous ammonium chloride. The mixture was warmed up to room temperature, and then evaporated to dryness. The residue was extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to afford a crystalline residue (2.76 g, 99%), which was recrystallized from hexane to give 8a as colorless needles: mp 77-78°C. IR ($CHCl_3$) 3630 and 3450 (OH) cm^{-1}; NMR ($CDCl_3$, 250 MHZ) δ 5.213 (1H, br.s, olefinic H), 3.742 (1H, d.d, J = 3.3 and 10.6 Hz) 3.522 (1H, dd, J = 6.1 and 10.6 Hz, AB part of ABX, HO-CH_2-CH<), 1.632 (3H, br.s, C=C-CH_3), 0.998 (3H, d, J = 6.8 Hz, sec-CH_3) and 0.865 (3H, d, J = 6.5 Hz, sec-CH_3).

7. Compound 9 from Oxidation of 8a with Jones' Reagent - To a solution of 8a (2.75 g) in acetone (50 ml) was added dropwise Jones' reagent at 0°C until the color of the reagent did not disappear. After stirring for 40 min., isopropyl alcohol was added to the mixture to reduce the excess reagent. The mixture was then diluted with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to afford an oily residue (2.95 g). The residue was dissolved in ether and extracted with dil. K_2CO_3. The alkaline layer was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over $MgSO_4$, and evaporated to give a crystalline residue (2.60 g, 89%), which was recrystallized from acetone-hexane to yield 9 as colorless prisms: mp 130-132°C; IR ($CHCl_3$) 3400-3000 and 1700 (OH) cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 5.116 (1H, s, C=CH), 1.635 (3H, br.s, C=C-CH_3), 1.192 (3H, d, J = 6.9 Hz, sec-CH_3), and 0.870 (3H, d, J = 6.3 Hz, sec-CH_3).

8. Compound 10 from Methylation of 9 with CH_2N_2 - To a solution of 9 (2.57 g) in ether (50 ml) was added on ethereal diazomethane at 0° C. The mixture was allowed to stand for 5 min. The excess diazomethane was decomposed with acetic acid. The ether solution was washed with dil. K_2CO_3 and water, dried over anhydrous $MgSO_4$, and evaporated to furnish 10 as an oily residue (2.30 g, 94%): IR ($CHCl_3$) 1720 and 1170 (COO-) cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 5.121 (1H, br.s, olefinic H), 3.674 (3H, s, -$COOCH_3$), 1.134 (3H, d, J = 6.9 Hz, sec-CH_3), and 0.862 (3H, d, J = 6.4 Hz, sec-CH_3).

9. Ozonization of 10 to 11 - Ozone was introduced into a solution of 10 (185 mg) in MeOH (0.7 ml) and CH_2Cl_2 (4 ml) in a dry ice-acetone

bath for 135 sec until the starting material disappeared on TLC. After purging the excess ozone with Argon, Me_2S (0.7 ml) was added to the reaction solution with stirring at 0°-20°C for 2 hrs, and then at room temperature for 1 hr. The reaction solution was concentrated in vacuo to give the aldehyde-ketone (11), which shows almost one spot on TLC [Rf = 0.31, silica gel, benzene-acetone (10:1)].

10. Selective protection of the ketonic carbonyl group of 11 to 12 - To a solution of crude 11, obtained from 185 mg of 10, in CH_2Cl_2 (6 ml) was added dropwise 1,3-propanedithiol (138 mg) with stirring, and then BF_3-ether (90 mg). After the reaction mixture was stirred at room temperature for 3 hrs, CH_2Cl_2 (50 ml) was added. The solution was washed with 5% $NaHCO_3$ (25 ml x 2) and water (20 ml x 3), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oily residue, which was purified by P-TLC [silica gel, benzene-acetone (10:0.7)] to afford the desired product (12, 76.8 mg, Rf = 0.53) together with three other compounds [Rf = 0.61 (13 mg), Rf = 0.42 (38.2 mg), Rf = 0.36 (14.5 mg)].

11. Transformation of the aldehydic carbonyl group of 12 into the enol methyl ether (13) -A mixture of 12 (76 mg), trimethyl orthoformate (0.5 ml), MeOH (1 ml) and catalytic amount of p-TsOH.H_2O was stirred at room temperature for 12 hrs. The reaction solution was added to a boiling solution of xylene (5 ml) and refluxed with a water-separator for 1.5 hrs. After cooling, the solution was worked up in the usual way to give the enol ether [13, 47.6 mg, Rf = 0.50 (silica gel, benzene-acetone (10:0.5), 62.3%], which was purified by column chromatography [silica gel, n-hexane → n-hexane-benzene (1:1) → benzene → benzene-acetone (10:0.5)]. Compound 13 was isolated from benzene-acetone (10:0.5): IR: 1730 (COOMe) and 1652 (enol ether) cm^{-1}; NMR δ 0.95 (3H, d, J = 6.9 Hz, 10-Me), 1.11 (3H, d, J = 6.9 Hz, 11-Me), 1.63 (3H, s, 4-Me), 2.60-2.90 [4H, m, $(SCH_2)_2$], 3.556, 3.562 (3H, 2s, -OMe, mixture of 1:1.6), 3.69 (3H, s, COOMe) and 5.889, 5.949 (1H, 2s, $=\!\!\diagdown_H$, mixture of 1:1.6).

12. Conversion of the thioketal (13) into the carbonyl group (14) - To a stirred solution of $HgCl_2$ (66 mg) and powdered $CaCO_3$ (40 mg) in 80% aq. MeCN (1.5 ml) was added a solution of 13 (20 mg) in 80% aq. MeCN (1 ml) at room temperature. The mixture was stirred and refluxed under N_2 for 1.5 hrs, cooled and filtered. The filtered cake was washed with CH_2Cl_2 (50 ml). The organic layer was washed successively with 5M aq. NH_4OAc (20 ml) and water (20 ml x 3), and concentrated in vacuo to give 14 [14.6 mg, Rf = 0.24, silica gel, benzene-acetone (10:0.5), 94.8%]: IR 1725 (COOMe), 1710 (C = O) and 1652 (enol ether) cm^{-1}; NMR δ 0.92 (3H, d, J = 6.7 Hz, 10-Me), 1.05 (3H, d, J = 6.7 Hz, 11-Me), 2.125, 2.142 (3H, 2s, CH_3CO-, mixture of 1:1.6), 3.530, 3.545 (3H, 2s, OMe, mixture of 1:1.6), 3.67 (3H, s, COOMe) and 5.843, 5.950 (1H, 2s, $=\!\!\diagdown_H$, mixture of 1:1.6).

13. Synthesis of Qinghaosu (1) from 14 via 15 - To a solution of 14 (17 mg) in MeOH (20 ml) was added Rose Bengal (4 mg). The resulting red solution through which oxygen was bubbled using 1% $Na_2Cr_2O_7$-H_2O as filter, was cooled to -70 -60°C, irradiated with a high pressure mercury lamp (200 W) for 6 hrs, and then passed the HCl gas until the red color disappeared. After further stirring at room temperature for 2 hrs., the solution was neutralized with 5% $NaHCO_3$ and concentrated in vacuo to give an aqueous solution, which was extracted with ether (20 ml x 2). The ethereal layer was washed with water, dried over $MgSO_4$ and evaporated to give a residue (12 mg), which showed no starting material (14) on TLC [Silica gel, benzene-acetone (10:1)]. To a solution of the residue (12 mg) in ether (1.5 ml) was added a solution of 60% $HClO_4$ (0.3 ml) and water (0.6 ml). The mixture was stirred at 20-25°C for 40 hrs. The ethereal layer was separated and water (10 ml) was added to the aqueous layer. The combinued aqueous solution was further extracted with ether (20 ml x 2). The ethereal solution was washed, dried over $MgSO_4$ and evaporated to give a residue (10 mg), which showed the presence of the target compound (1, Rf = 0.43) together with three spots on TLC [Silica gel, benzene-acetone (10:1)]. The product was purified to give the target compound (1, Ca.* 1.1 mg, 7.3%) together with major compound (Ca.* 2.7 mg) by HPLC [solvent MeOH, Partisil M9 10/15 ODS-2, Col. No 4H, Whatman]. The nmr spectrum [400 MHz, $CDCl_3$ δ 1.01 (3H, d, J = 5.7 Hz, Me-10), 1.22 (3H, d, J = 7.5 Hz, Me-11), and 5.87 (1H, s, H-5)] of this synthetic compound is identical with that of an authentic sample of qinghaosu (1) isolated from Artemisia annua.

All nmr spectra corresponding to each synthetic intermediate described in this report have been sent to Dr. A. J. Lin, my Contracting Officer's Technical Representative on October 20, 1986.

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*The yield was calculated from the intensity curve of HPLC compared with an authentic sample of qinghaosu.

(3) Literature References

1. X. X. Xu, J. Zhu, D. Z. Huang and W. S. Zhou, 1984 Hawaii Am. Chem. Soc. Meeting Abstract, 10E102.
2. Ibid., Tetrahedron, 42, 819 (1986).

(4) Biological Test Data

None

(5) Publications and Patents

"Antimalarial Agents 4. Synthesis and Biological Activity of Brusatol Related Compounds," by K. H. Lee, S. Tani and Y. Imakura, J. Med. Chem., submitted.

(6) List of Personnel Receiving Contract Support

a. Dr. Junko Koyama (10/25/85-4/08/86), Instructor of Synthetic Organic Chemistry, Kobe Women's College of Pharmacy, was appointed as a postdoctoral fellow working on the alternative synthesis of qinghaosu.

b. Dr. Toshio Yokoi (10/15/85-9/30/86), Assistant Professor of Pharmaceutical Chemistry on leave from Kobe Gakuin University (Ph.D. from Kyoto University) did an excellent job on this contract.

c. Dr. Hiroshi Irie (7/1/86-7/31/86), Professor of Pharmaceutical Chemistry and Dean of Faculty of Nagasaki University, Japan participated in the total synthesis of qinghaosu. Dr. Irie is an internationally well-known synthetic organic chemist with nearly 100 publications in synthetic natural products chemistry.

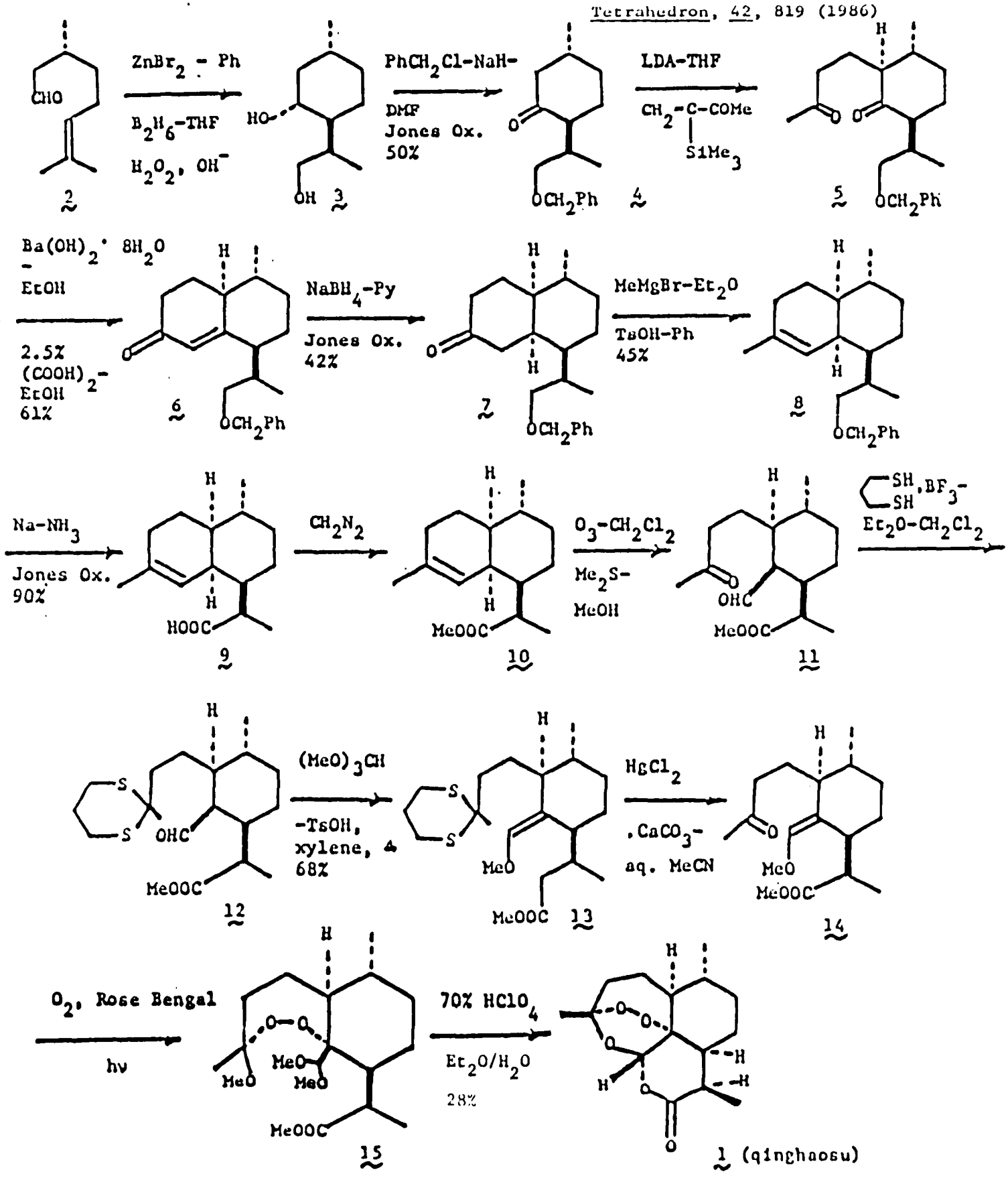
d. Dr. Venkataraman Amarnath (4/1/86-7/1/86), a Research Assistant Professor of Medicinal Chemistry, participated in the synthesis of qinghaosu. Dr. Amarnath is an experienced synthetic organic chemist.

e. Dr. Yasuhiro Imakura (7/15/86-10/15/86), Visiting Assistant Professor on leave from Faculty of Pharmaceutical Science, The University of Tokushima, Japan, replaced Dr. Toshio Yokoi's position. Dr. Imakura is author and co-author of more than 35 publications in the area of isolation and synthesis of natural products. He succeeded in the synthesis of qinghaosu (1) from 10.

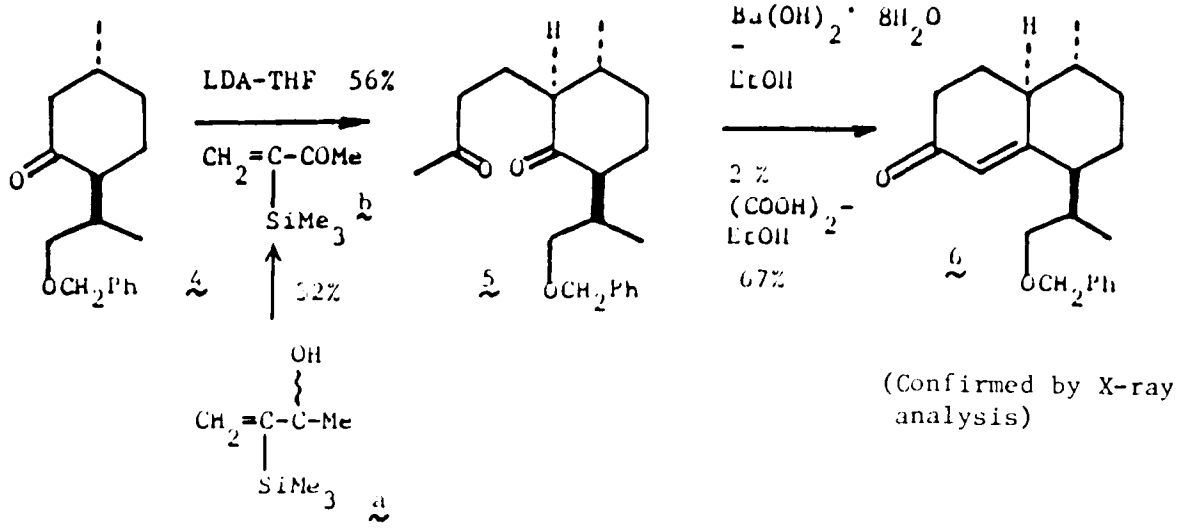
f. Dr. Forrest Smith (9/1/86-10/15/86), a synthetic medicinal chemist has replaced Dr. Amarnath's position to work on the new method for the synthesis of qinghaosu.

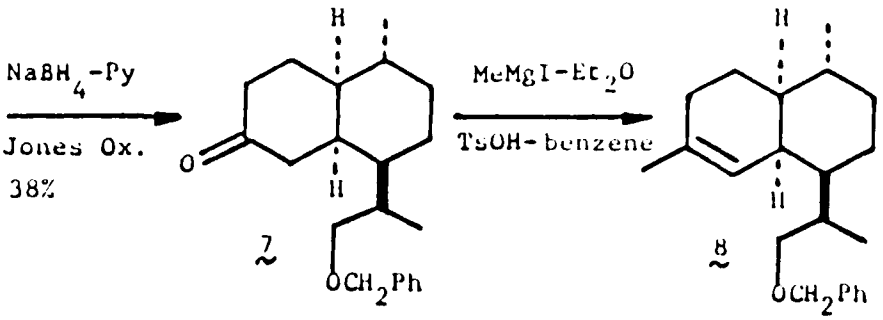
Scheme - 1 : Zhou's Total Synthesis of Qinghaosu

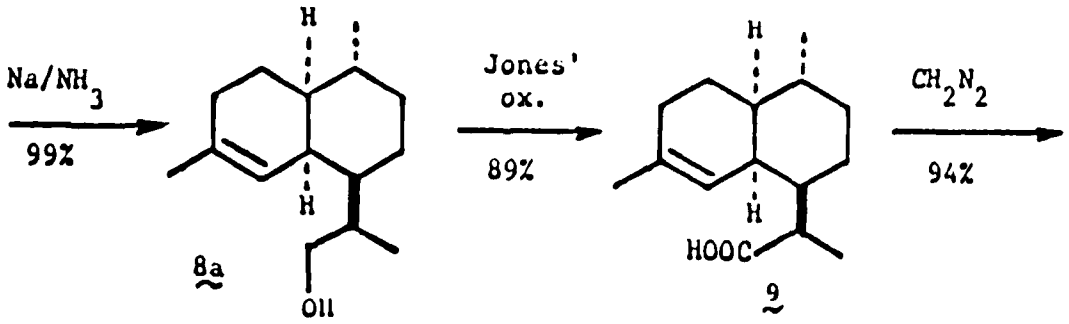
(X. X. Xu, J. Zhu, D. Z. Huang, and W. S. Zhou, 1984 Hawaii ACS Meeting Abstract)
Tetrahedron, 42, 819 (1986)



Scheme - 2 : Compounds Synthesized During This Reporting Period







Scheme - 2 : Compounds Synthesized During This Reporting Period - Continued

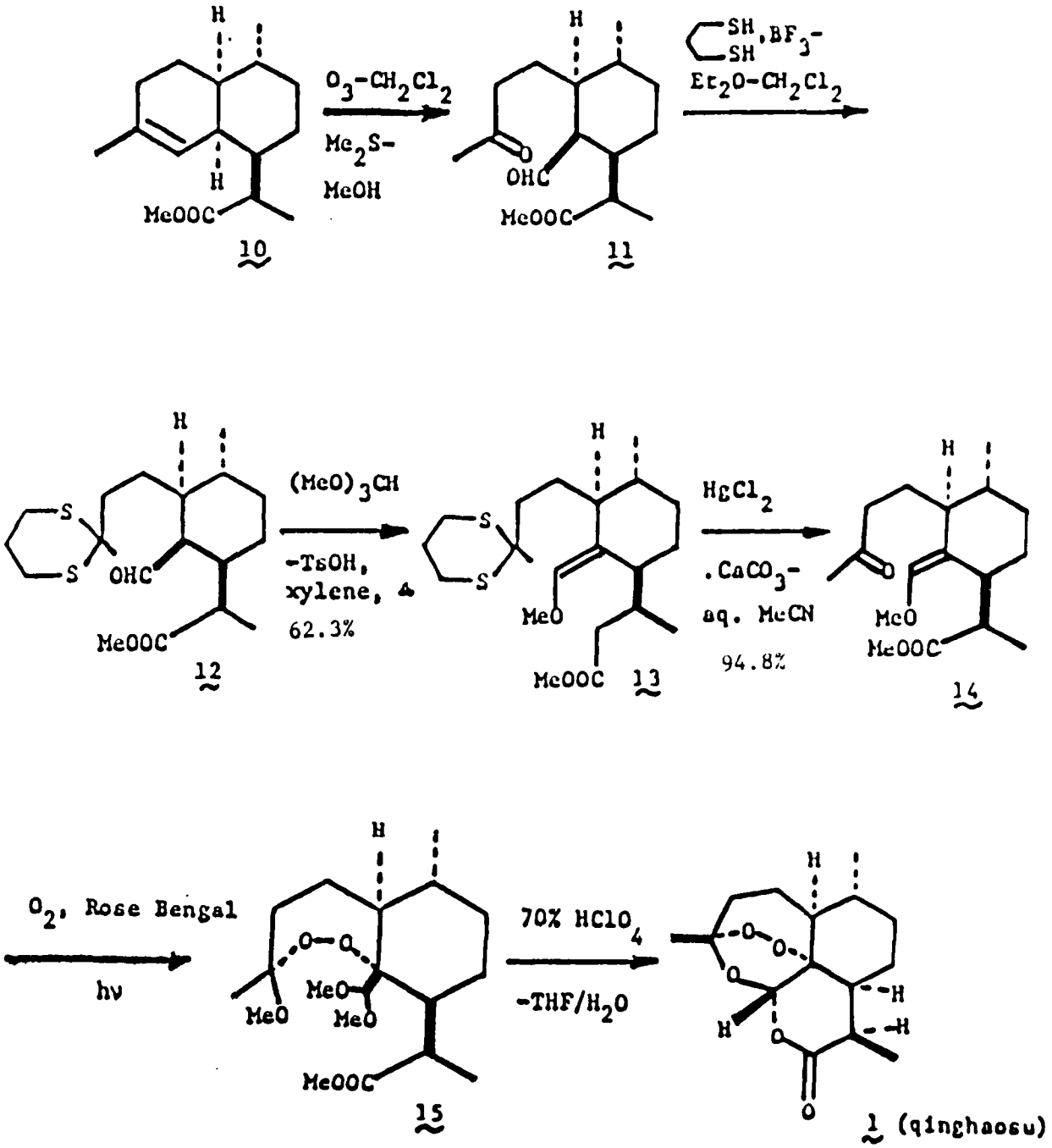
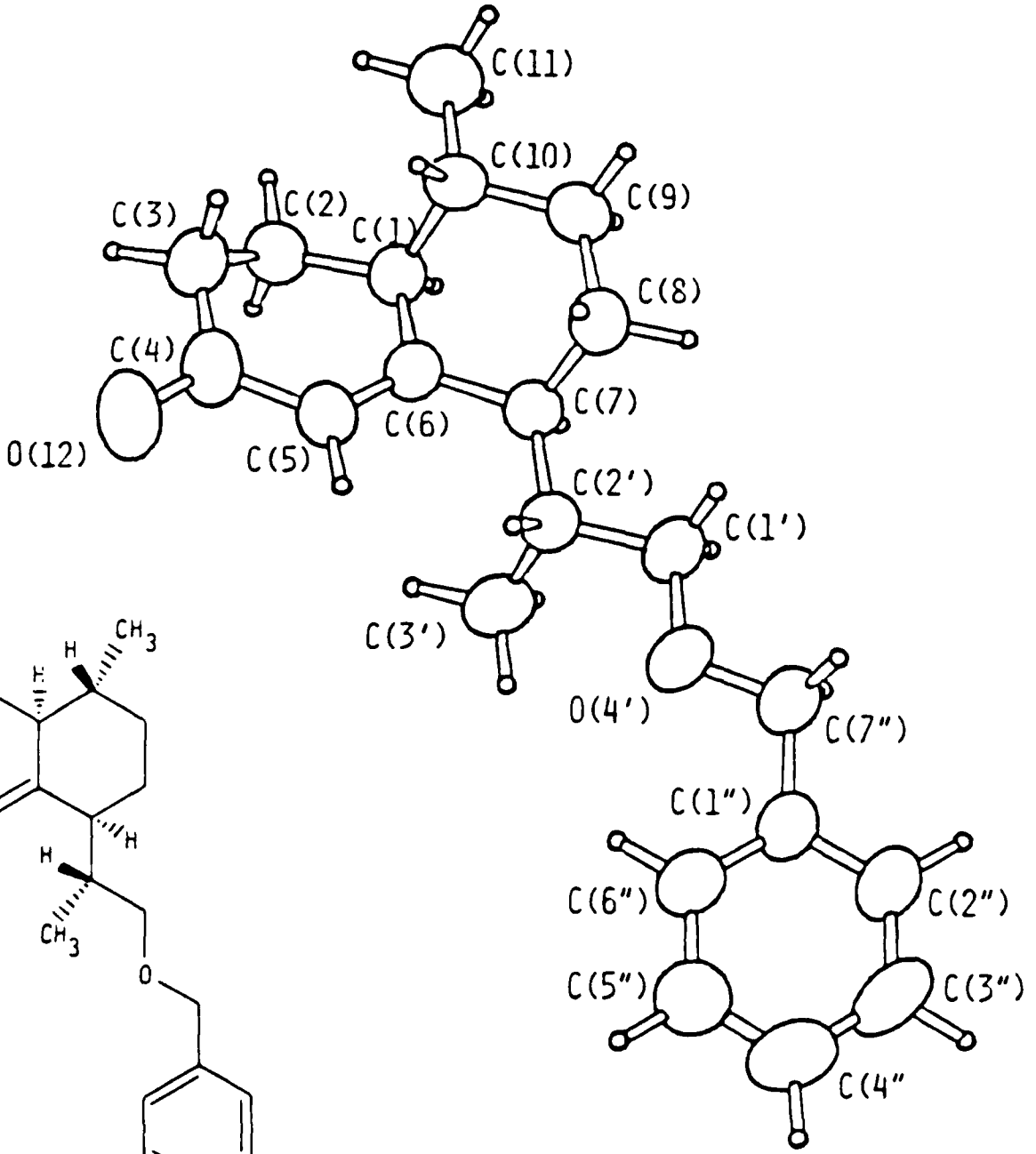


Figure 1

X-Ray Structure of Compound 6



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