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Syntheses of Carba-Analogues of Qinghaosu

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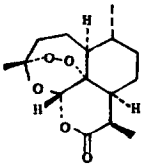
The syntheses of carba-analogues of qinghaosu **7** ,**8** ,**9** are first described. Arteannuic acid **11** was converted into key intermediate cyclic enol ether **14** in four steps. Reaction of **14** with paraformaldehyde under the catalysis of Lewis acid $BF_3 \cdot OEt_2$ afforded **7**. Oxidation of **7** with RuO_4 gave **8** and **9**.

Qinghaosu(Arteannuin) **1** is an effective antimalarial agent isolated from the Chinese traditional medicine Qinghao(Artemisia annua L)[1]. Its interesting biological activity and novel chemical structure have prompted three total syntheses[2,3,4], an attempted semi-synthesis[5], the preparation of analogues[6,7], and a model study[8]. However, when used as antimalarial medicine, it still has some shortcomings such as high recurrence of the disease and lower solubility in water and oil. In order to find a better antimalarial medicine, chemists synthesized a lot of its analogues 2[9],3[6],4[7], and succeeded in getting some more powerful medicine from these analogues. But these compounds still remain the peroxide functional group of qinghaosu.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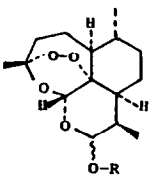
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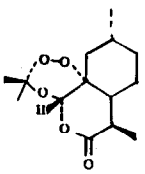
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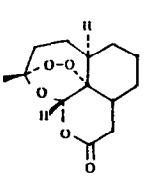
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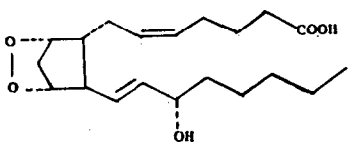
It is known[10] in the synthetic studies of prostaglandin when peroxide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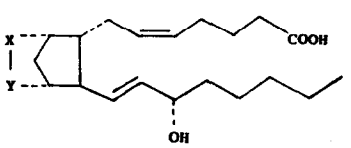
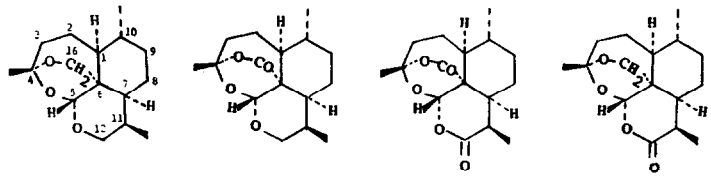
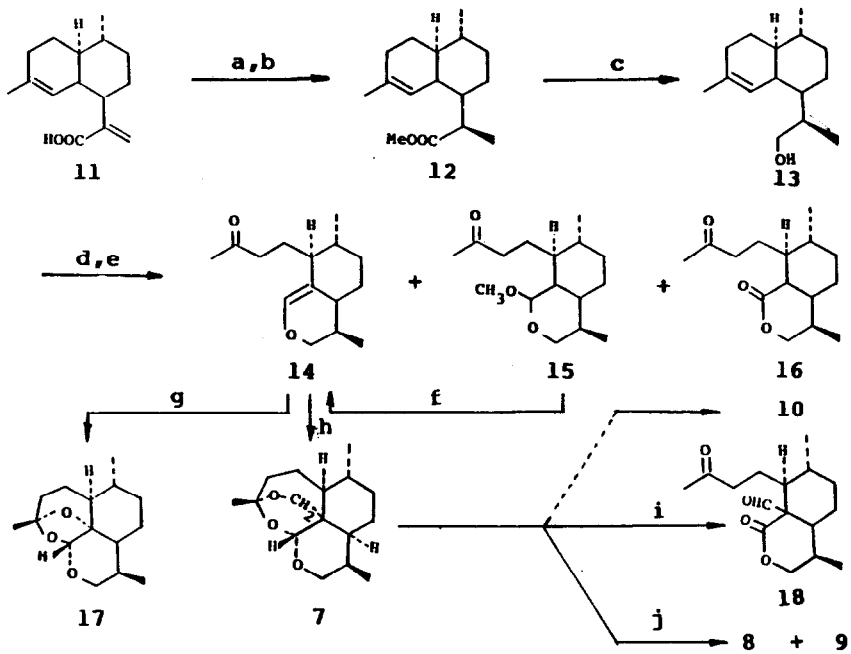

6 a.X=O,Y=CH_2;
b.X=CH_2,Y=O;

functional group in PGH_2 **5** is replaced by the other groups like **6**, it still has biological activity. Considering these successful examples, we designed and synthesized corresponding analogues of qinghaosu **7**, **8**, **9**, **10**.



7 8 9 10

Arteannuic acid **11**, which exists together with qinghaosu in the same plant, was converted into artennuinol **13** by esterification with CH_2N_2, hydrogenation with $NaBH_4$ in the presence of $NiCl_2\ 6H_2O$[3], and reduction with $LiAlH_4$. Ozonolysis of arteannuinol **13** afforded three compounds **14**,**15** and **16** in 15.8%,63.5% and 10.5% yield respectively. Compound **16** may be yielded through overoxidation of **13** followed by lactonization. Thermolysis of **15** may also give cyclic enol ether **14**.



a.CH_2N_2;b.$NiCl_2 \cdot 6H_2O$,$NaBH_4$;c.$LiAlH_4$;d.O_3/MeOH-CH_2Cl_2;e.Me_2S;f.xylene, PTS, ;g.m-CPBA;h.$BF_3\ OEt_2$,(HCHO)n;i.Jones reagent;j.$RuCl_3$-$NaIO_4$

Oxidation of **14** with m-CPBA furnished compound **17**, which was the same as that obtained by degradation of qinghaosu[11]. The desired carba-analogue **7** was obtained by the reaction of **14** with paraformaldehyde under the catalysis of Lewis acid $BF_3 \cdot OEt_2$[12]. We were unsuccessful in oxidizing the C-12 position of **7** selectively with RuO_4, but obtained the C-16 position oxidized compound **8** instead. The compound **9**, in which both the C-12 and C-16 position were oxidized, could be also obtained under longer oxidation time. When Jones reagent was used, compound **18** was yielded. This result may be due to

the oxidation of the C-16 position and ester transfer.

Studies of the synthesis of compound **10** and the testing of pharmacological activity of all the above three compounds are in progress.

Experimental

All m.p.were uncorrected. IR spectra were measured as a film for oils or as a nujol mull for solids on a Shimadzu 440 spectrometer. ^{1}HNMR spectra were recorded with TMS as an internal standard at 60 MHz on a EM 360A spectrometer or at 200MHz on a Varian XL-200 spectrometer. MS spectra were obtained on a Finnigan 4021 GC-MS spectrometer. High Resolution(HR)MS was determined on a Finnigan-MAT 8430 HRMS. Optical rotations were measured on a Antopol polarimeter. All column chromatographies were performed on silica gel H(10-40u), and with petroleum ether-ethyl acetate system as an eluent.

11-R-methyl arteannuinol 13: A solution of **12**(7.56 g) in absolute ether(20 mL) was added dropwise to a suspension of $LiAlH_4$(2.80 g) in 150 mL of absolute ether. After refluxing for an hour, the reaction was quenched with ethyl acetate, and was diluted with ether, washed with brine, dried over Na_2SO_4, and evaporated to give a white solid **13**(5.72 g ,85.2%). Recrystallization from hexane-acetone gave needle crystals. mp 83°C(lit.[3], 81°C); $[\alpha]_D^{25}$-11.06°(C, 0.75, MeOH)[lit.[3], $[\alpha]_D^{25}$-8.47°(C, 0.55, $CHCl_3$)]; IR: 3400, 1640cm^{-1}; ^{1}HNMR: 5.30(1H, br), 4.90(1H, dd, J=12, 4Hz), 4.79(1H, dd, J=12, 7Hz), 1.58(3H, s,4-CH_3), 1.07(3H,d, J=6Hz, 11-CH_3), 0.91(3H, d, J=6Hz, 10-CH_3); m/z: 222(M^+), 205(M^+-OH), 191(M^+-CH_2OH); Anal.Calcd.for $C_{15}H_{26}O$: C, 81.02; H, 11.79; Found: C, 80.78; H, 11.91.

Ozonolysis of arteannuinol 13: Ozone was passed into a solution of arteannuinol **13**(1.701 g) in MeOH(18 mL) and CH_2Cl_2(80 mL) at -78°C until the color of the solution turned blue. After purging the ozone with a stream of N_2, Me_2S(2 mL) was added to the reaction solution with stirring at room temperature for 2 h. The solvent was removed in vacuum. Flash chromatography of the residue afforded three products: **14**, 300 mg; **15**, 1.26 g; **16**, 240 mg. Compound **14**: IR: 1720, 1660cm^{-1}; ^{1}HNMR: 6.07(1H, S), 3.48(2H, br); 2.05(3H, s, 4-CH_3), 0.90(3H, d, J=6Hz, 11-CH_3), 0.82(3H, d, J=7Hz, 10-CH_3); m/z: 236(M^+), 165(M^+-$CH_2COCH_2CH_3$). Compound **5**: mp 45°C; $[\alpha]_D^{25}$-50.8°(C,1.66,$CHCl_3$); IR: 1715cm^{-1}; ^{1}HNMR: 4.58(1H, d, J=4Hz, 5-H), 3.52(2H, m, 12-H), 3.04(3H, S, -OCH_3), 2.08(3H, s, 4-CH_3), 0.89(3H, d, J=6Hz, 11-CH_3), 0.84(3H, d, J=7Hz, 10-CH_3); m/z: 267(M^+-1), 237(M^+-OCH3); Anal.Calcd.for $C_{16}H_{28}O_3$: C, 71.59; H, 10.53; Found: C, 71.55; H, 10.40. Compound 16: mp 105°C; $[\ ]_D^{25}$-67.3°(C, 0.73, $CHCl_3$); IR: 1760, 1720cm^{-1}; ^{1}HNMR: 4.28(1H, ABX, J_{AB}=12Hz, J_{BX}=10Hz, 12-H_A), 4.01(1H, ABX, J_{AB}=12Hz, J_{AX}=16HZ, 12-H_B); 2.08(3H, s, 4-CH_3), 0.98(3H, d, J=6Hz, 11-CH_3), 0.90(3H, d, J=6Hz, 10-CH_3); m/z: 253(M^++1), 181(M^++1--$CH_2COCH_2CH_3$); Anal.Calcd.for $C_{15}H_{24}O_3$: C, 71.38; H,9.60; Found: C, 70.98; H, 9.95.

Thermolysis of 15: A solution of **15**(563 mg) in xylene(20 mL) containing a catalytic amount of P-TsOH was heated at reflux for 2 h. After cooling, the solution was worked up in the usual manner to afford the crude product. Flash chromatography of the residue gave **14**(490 mg, 98%).

Synthesis of compound 17: To a solution of **14**(96 mg) in CH_2Cl_2(15 mL) , m-CPBA(104 mg) was added at 25°C. After 3 h, ether was added and the solution was washed with 10% $NaHSO_3$, $NaHCO_3$(sat.), brine, dried over Na_2SO_4, and evaporated to give a white solid **17**(95 mg, 93%). Recrystallization from petroleum ether-acetone gave plate crystals. mp 102-103°C. All spectra were identical with that in the literature[11].

Synthesis of compound 18: Jones reagent(1.5 mL) was added dropwise into a solution of **7**(40 mg) in acetone(10 mL) at 0°C. After 5 h, i-PrOH was added to quench the reaction. The reaction mixture was worked up in the usual manner and purified by flash chromatography to give **7**(10 mg) and **18** (20 mg). Compound **18**: IR: 2720, 1760, 1720 cm^{-1}; ^{1}HNMR: 9.48(1H, S, -CHO), 4.27(1H, ABX, J_{AB}=10Hz, J_{BX}=18Hz, 12-H), 2.03(3H, s, 4-CH_3), 0.98(3H, d, J=7Hz, 11-CH_3), 0.82(3H,J=7Hz, 10-CH_3); m/z: 281(M^++1), 180(M^+-$CH_2CH_2COCH_3$ -CHO)

Synthesis of compound 7: To a solution of **14**(370 mg) in CH_2Cl_2(10 mL) and parafomaldehyde(300 mg) under N_2 at 0°C, BF_3•Et_2O(0.2 mL) was added dropwise. After 4 h, the reaction mixture was worked up as usual and purified by chromatography to afford crystals 7(263 mg,63.1%). mp 131-133°C; $[\alpha]_D^{25}$ -18.0°(C, 0.75, $CHCl_3$); IR: no characteristic absorptions; ^{1}HNMR: 5.14(1H, S, 5-H), 4.21(1H, AB ,J_{AB}=12Hz, 16-H), 3.68(1H, J_{AB}=12Hz, 16-H), 3.65(1H, ABX, J_{AB}=10Hz, J_{AX}=16Hz, 12-H), 3.38(1H, ABX, J_{AB}=10Hz, J_{BX}=17Hz,12-H), 1.41(3H, s, 4-CH_3), 0.90(3H, d, J=7Hz, 11-CH_3), 0.78(3H, d,J=6Hz, 10-CH_3); m/z: 267(M^++1), 237(M^++1-CH3); Anal.Calcd.for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84 Found: C, 72.29; H,9.58.

Synthesis of 8 and 9: To a solution of 7(187 mg) in CCl_4(10 mL),CH_3CN(5 mL) were added $RuCl_3$•nH_2O(20 mg) and $NaIO_4$(3.08 g). After the mixture had been stirred for two weeks, water(5 mL) and CH_2Cl_2(20 mL) were added. The mixture was worked up as usual. Chromatography of the residue gave starting material 7(15 mg); **8**(51 mg); and **9**(72 mg). Compound **8**: mp 92°C; $[\alpha]_D^{25}$-95.7° (C, 0.89 ,$CHCl_3$); IR: 1760cm^{-1}; ^{1}HNMR: 5.36(1H,s,5-H), 3.63(1H, ABX, J_{AB}=10 Hz, J_{BX}=18Hz, 12-H), 3.40(1H, ABX, J_{AB}=10Hz, J_{AX}=16Hz,12-H), 1.62(3H, S, 4-CH_3), 1.00(3H, d, J=7Hz,11-CH_3), 0.82(3H, J=6Hz, 10-CH_3); m/z: 281(M^++1), 252(M^+--CO-); Anal.Calcd.for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63 Found: C, 68.57; H ,8.87. Compound **9**: mp 145°C; $[\alpha]_D^{25}$ -104.3°(C, 0.39, $CHCl_3$); IR: 1768cm^{-1}; ^{1}HNMR: 6.06(1H, S, 5-H), 1.62(3H, S, 4-CH_3), 1.22(3H, d, J=6Hz, 11-CH_3), 1.04(3H, d, J=7Hz, 10-CH_3); m/z: 295(M^++1); HRMS Calcd.for: $C_{16}H_{22}O_5$: 294.3468; Found: 294.3461.

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