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TOTAL SYNTHESIS OF (+)-YINGZHAOSU A

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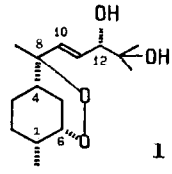
Abstract: The first total synthesis of (+)-Yingzhaosu A, an antimalarial constituent isolated from Yingzhao (Artabotrys uncinatus (L.) Merr.), was achieved starting from R-(-)-carvone

Yingzhaosu A **1** is an antimalarial constituent[1] isolated from Yingzhao Artabotrys uncinatus (L.) Merr., a traditional Chinese herbal medicine for treatment of malaria,and was shown to be a peroxy-containing sesquiterpene, similar to Qinghaosu **2**[2-4] which possesses the prominent antimalarial activity. The structure of Yingzhaosu A reveals an unique dioxabicyclo[3,3,1]-nonane ring system bearing a dihydroxy olefinic side chain, three chiral centers at C-6, C-4 and C-1 have been preliminarily deduced as S, S and R, however, the other two at C-8 and C-12 remain unsolved[1]. Herein we report the first total synthesis and stereochemistry of natural (+)-Yingzhaosu A.



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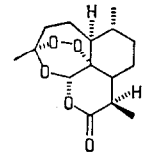

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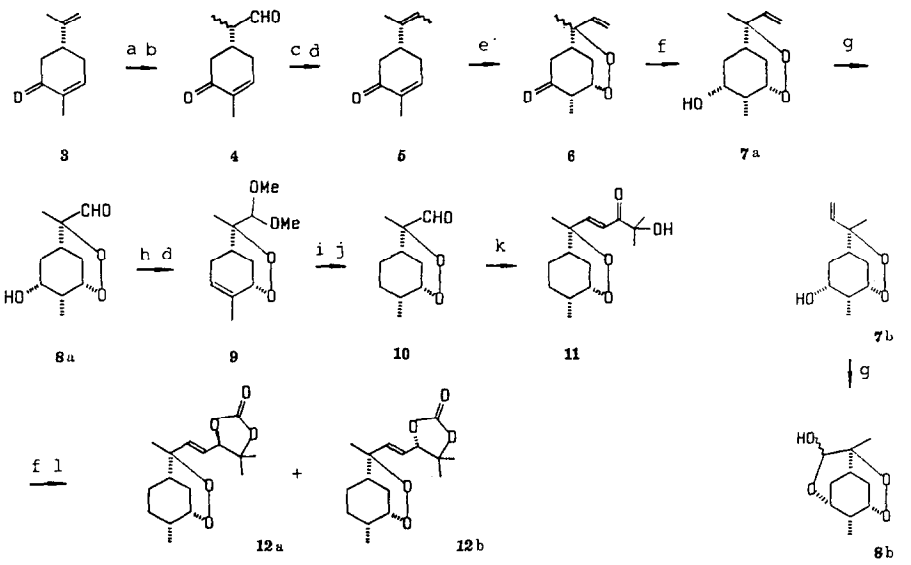
We had developed an efficient and convergent strategy. In order to construct the major framework **10**, compound 5 containing a "temporary" α,β-unsaturated ketone function was employed to investigate the formation of a peroxy bridge at the proper position. An arsenical ylid can be adopted for construction of the side chain with E double bond.

We chose R-(-)-carvone **3**($[\alpha]_D^{25}$-60.5°) as starting material. Epoxidation of which with m-CPBA followed by rearrangement of the resulting epoxide with $BF_3 \cdot Et_2O$ yielded the aldehyde **4**. Reaction of the latter with methyl Grignard reagent followed by dehydration of the product gave a mixture of geometrical isomers **5**. The overall yield of four steps from **3** to **5** was ca.15%[5]. When 5

Scheme 1.



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-MeOH,-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. $Ph_3AsCH_2CO(OH)Me_2Br$, K_2CO_3-H_2O,CH_2Cl_2. l. $COCl_2$,Py.

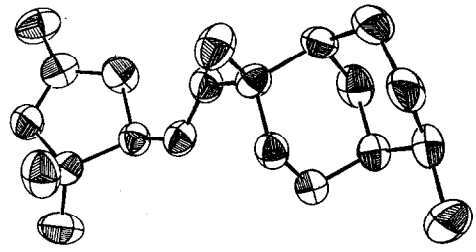
was reacted with $^1O_2$ in presence of p-TsOH, an ene reaction product was formed which then underwent an intramolecular Michael addition, forming the peroxy bridge, to give a mixture[6] of C-8 methyl epimers **6** in 1:1 ratio in 57% yield. Although the determination of C-8 configuration is an important problem, it is difficult to separate the mixture **6** by chromatography. Interestingly, reduction of the carbonyl group of **6** with lithium borohydride furnished a separable mixture of **7a** and **7b** in 51% yield. It is obvious that the hydride ion would attack on C-2 from the out-flank of the semi-cage to afford an α-hydroxy group selectively. Based on their ^{1}HNMR, the configuration of C-8 in **7a** and **7b** could be deduced[7]. Upon ozonolysis **7a** gave the aldehyde **8a**, whereas **7b** gave hemiacetal **8b**. Thus the configuration of C-8 in **8a** was established to be desired S[8].

The aldehyde function of **8a** was protected and following dehydration gave compound **9**. The hydrogenation of double bond of **9** was realized, without affecting the peroxy group, using a properly activated platinum oxide and an equi-

valent amount of hydrogen in a yield of 80%. Hydrolysis of the acetal protecting group gave the free aldehyde **10**. Compound **10** was reacted with arsonium ylid $Ph_3AsCHCOC(CH)Me_2$[9], prepared from 3-hydroxy-3-methyl-2-butanone, to yield α,β- unsaturated ketone **11**, which was reduced with $LiBH_4$ followed by treatment with phosgene to give a mixture of the C-12 isomeric carbonates **12a** and **12b** in a ratio of 3:2. The isomers were seperated by flash chromatography to give **12a**: m.p 97-98°C, $[\alpha]_D^{25}$+204°($CHCl_3$) and **12b**: m.p 99-100°C, $[\alpha]_D^{25}$+201° ($CHCl_3$) in overall 62% yield. The structure of **12a** and **12b** were further supported by ^{1}HNMR[10].

Owing to the lack an authentic sample, the C-12 configuration of natural product was only established through comparison of ^{1}HNMR spectrum between the synthetic carbonate **12a** or **12b** and natural carbonate. It is worthwhile to note that there is remarkable difference between **12a** and **12b** in chemical shift of 10-H and 11-H ($\delta_{10H} - \delta_{11H}$: **12a**: 0.19 ppm; **12b**: 0.25 ppm) and coupling constant of 11-H and 12-H (**12a**: J=5.9 Hz; **12b**: J=6.9 Hz), it was these values of **12b** which coincided with that of the natural carbonate. Thus **12b** was assigned as the carbonate of natural Yingzhaosu A. The S-configuration of C-12 in **12a** was finally confirmed by X-ray diffraction analysis[11](Fig. 1). Treatment of **12b** and **12a** with $LiBH_4$ afforded Yingzhaosu A 1 and its C-12 epimer[12] respectively, 1:m.p 95-96°C, $[\alpha]_D^{25}$+226°($CHCl_3$); C-12 epimer:m.p 55-56°C, $[\alpha]_D^{25}$+234°($CHCl_3$).

Figure 1



Perspective drawing of the X-ray structure of **12b**

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5. Compound **5** was initially prepared by controlled ozonization and Wittig reaction, but partial racemization occurred in the Wittig reaction.
6. Hofheinz, W. et al, presented on the 7th international congress for Tropical Medicine and Malaria in Amsterdam, private communication.
7. ^{1}HNMR shows that there is remarkable difference between **7a** and **7b** in chemical shift of 9-CH_3(**7a**: 1.35 ppm; **7b**: 1.6 ppm), which could be attributed to the deshield effect of double bond to 9-CH_3 in **7b**, where the endo vinyl group situates in the same side with 9-CH_3.
8. The value of chemical shift of 9-CH_3 of **7a** was close to that of natural Yingzhaosu A.
9. Huang, Y. Z.; Shi, L. L.; Yang, J. H.; Xiao, W. J., Youji Huaxue, 1988, **8**, 10.
10. ^{1}HNMR ($CDCl_3$, 200MHz): **12a**: δ: 1.11(3H, d, J=6.4Hz, 7-CH_3), 1.22(3H, s, 9-CH_3), 1.37 (3H, s, 14-CH_3), 1.54 (3H, s, 15-CH_3), 3.79-3.83 (1H, br., 6-H), 4.77 (1H, dd, J=5.9Hz, J=1Hz, 12-H), 5.83(1H, dd, J=15.8Hz, J=5.9 Hz, 11-H), 6.02 (1H, dd, J=15.8Hz, J=1Hz, 10-H). **12b**: δ: 1.12(3H, d, J= 6.4Hz, 7-CH_3), 1.23 (3H, s, 9-CH_3), 1.36 (3H, s, 14-CH_3), 1.54 (3H, s, 15-CH_3), 3.80-3.83 (1H, br., 6-H), 4.78 (1H, dd, J=6.9Hz, J=1Hz, 12-H), 5.83(1H, dd, J=15.8Hz,J=6.9Hz, 11-H), 6.08(1H, dd, J=15.8Hz,J=1Hz, 10-H).
11. The crystal of **12b** was found to be orthorhombic system with space group $P_{1/2}1_{/2}1_{/2}$ and the unit cell parameter are precisely determined as a=7.710(2), b=9.502(3), c=21.570(3) Å, Vc=1580.4 $Å^3$, Z=4. R_1=0.047,R_2=0.051. Final crystallographic coordinates have been deposited in Cambridge Crystallographic Data Center.
12. ^{1}HNMR ($CDCl_3$, 200MHz): 1: δ: 1.13 (3H, d, J=6.4Hz, 7-CH_3), 1.19 (3H, s, 9-CH_3), 1.22(3H, s, 14-CH_3), 1.27(3H, s, 15-CH_3), 3.81-3.83 (1H, br, 6-H), 4.00 (1H, d, J=6.8Hz, 12-H), 5.81 (1H, dd, J=15.8Hz, J=6.8Hz, 11-H), 5.99(1H, d, J=15.8Hz, 10-H). C-12 epimer: δ: 1.13(3H, d, J=6.4Hz, 7-CH_3), 1.20 (3H, s, 9-CH_3), 1.23 (3H, s, 14-CH_3), 1.27 (3H, s, 15-CH_3), 3.80-3.83 (1H, br, 6-H), 3.99 (1H, dd, J=6.3Hz, J=0.6Hz, 12-H), 5.82 (1H, dd, J=15.8Hz, J=6.3Hz, 11-H), 6.02 (1H, dd, J=15.8Hz, J=0.6Hz, 10-H).

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