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Enantioselective Total Synthesis of All Four Stereoisomers of Yingzhaosu C

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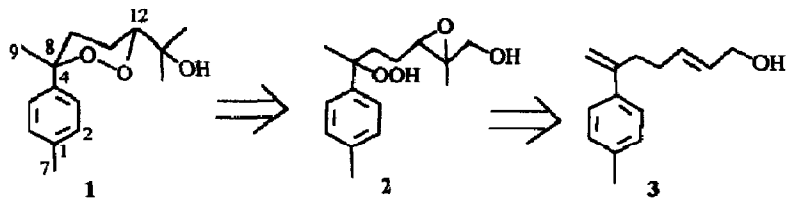
Abstract: An enantioselective total synthesis of all four stereoisomers of Yingzhaosu C, an antimalarial peroxy-containing sesquiterpene isolated from Yingzhao [*Artabotrys uncinatus*(L.) Merr.], is described.

Yingzhaosu C **1**, isolated from a traditional Chinese herbal medicine Yingzhao [*Artabotrys uncinatus*(L.) Merr.], like Yingzhaosu A[1], is another antimalarial principle and shown to be a sesquiterpene possessing a characteristic cyclic peroxide and a *p*-tolyl terminus.[2] Furthermore, there are two chiral centers (C-8 and C-12) in the six-membered cyclic peroxide and only the C-12 configuration was assigned as R.[2] The combination of its interesting biological activity, unusual structure and stereochemistry prompted us to study its synthesis, particularly the enantioselective synthesis of all four stereoisomers. Herein we present the results.



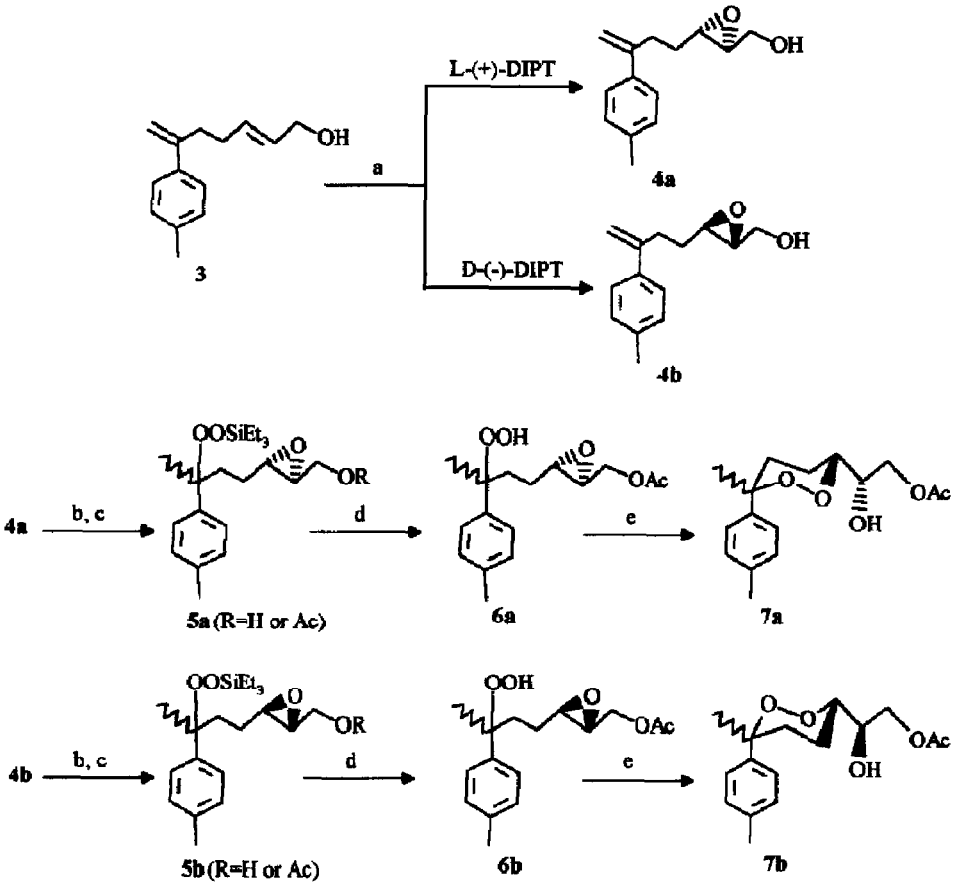
1 **2** **3**

Scheme 1

Although the [4+2] cycloaddition of singlet oxygen to diene may construct the six-membered cyclic peroxide, it is more proper for our purpose to use an intramolecular nucleophilic substitution of hydroperoxide to the epoxide whose configuration has been established. Our synthetic strategy was shown in scheme 1. Obviously the desired epoxy group acting as the acceptor of hydroperoxide would be easily prepared when a hydroxy group was introduced into one of the isopropyl methyl groups (see compound **2**). Further analysis indicated that with the formation of cyclic peroxide, the resulting C-13 secondary hydroxy should be preferable to the tertiary one since the former may possibly be used to separate the C-8 epimers by derivation. Recently, a new method reported by Isayama and co-workers[3] has provided an effective approach to introduce the hydroperoxide. As a result, compound **3** was used as our synthetic precursor which could be

prepared by Friedel-Crafts reaction[4] starting from toluene and succinic anhydride followed by two steps of Wittig reaction.

When Sharpless asymmetric epoxidation[5] was performed on compound **3**, a couple of enantiomeric epoxides **4a** and **4b** was obtained in ca.90% yield upon treatment with L-(+) and D-(-)-diisopropyl tartrate, respectively. The C-12 configuration of **4a** and **4b** was unambiguously assigned as shown in scheme 2. Their optical purity was determined by comparing the ^{1}H NMR spectra of corresponding Mosher's esters[5] and shown to be >95%e.e.



Reagents and Conditions: a)Ti(OPr^i)$_4$, 4ÅMS, t-BuOOH, CH_2Cl_2, -20^{0}C, b)Ac_2O/Pyridine, r.t., c) Et_3SiH, O_2, Co(modp)$_2$, $(CH_2Cl)_2$, r.t., d) KF/18-crown-6/THF, r.t., e) Amberlyst-15, CH_2Cl_2, r.t.

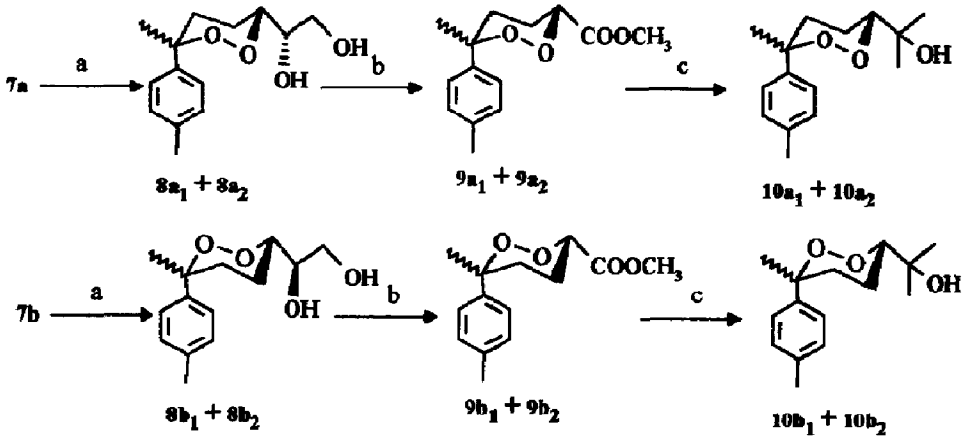
Scheme 2

With the optically pure epoxides in hand, we then pursued the introduction of the triethylsilylperoxy group at C-8 position of compound 4 by Isayama's procedure[3]. The experimentation showed that the result is dependent on the catalyst and Co(modp)$_2$ was remarkably superior to Co(acac)$_2$. When the compound **4b** was reacted with molecular oxygen and triethylsilane in the presence of a catalytic amount of Co(modp)$_2$,

compound **5b** (R=H) was obtained in 54% yield as anticipated. If the hydroxy group of **4** was converted into acetate, the yield of compound **5** (R=Ac) was greatly raised to 90%. The result showed clearly that this step is substantially improved by the protection of hydroxy group and the epoxide actually remained intact. The ^{1}H NMR of **5a** and **5b** (R=Ac) revealed that they were an epimeric mixture of C-8 methyl in about 1:1 ratio.[6]

Subsequent treatment of **5** (R=Ac) with KF/18-crown-6 in anhydrous tetrahydrofuran produced compound **6** with a free -OOH. It is suggested that the nucleophilic epoxide-opening would be assisted by an acidic catalyst. Lewis acids, such as $BF_3{\cdot}Et_2O$ and $AlCl_3$, were first tried, but as a result the weak peroxy bond was unexpectedly damaged. Silica gel also proved to be not effective. Finally, under the catalysis of the strongly acidic resin Amberlyst-15, compounds **6a** and **6b** were cyclized, forming the peroxy-containing six-membered ring to give compounds **7a** and **7b** in 65% yield, respectively. Both **7a** and **7b** were again C-8 epimeric mixtures. Fortunately, the hydrolytic products $\mathbf{8a_1}$ and $\mathbf{8a_2}$ obtained from **7a** showed subtle difference on TLC, so that the resulting dihydroxy cyclic peroxides $\mathbf{8a_1}$ and $\mathbf{8a_2}$ not only made the further transformation possible, but also made the C-8 epimers separable by column chromatography. Compound **7b** gave the same result and the C-8 epimers $\mathbf{8b_1}$ and $\mathbf{8b_2}$ were also separated. Compounds $\mathbf{8a_1}$ and $\mathbf{8b_1}$ are enantiomers, and so are $\mathbf{8a_2}$ and $\mathbf{8b_2}$. The $[\alpha]_D(CHCl_3)$ was +175.4° for $\mathbf{8a_1}$, -49.2° for $\mathbf{8a_2}$, -172.3° for $\mathbf{8b_1}$ and +47.0° for $\mathbf{8b_2}$.

As shown in scheme 3, all four optically pure dihydroxy compounds $\mathbf{8a_1}$, $\mathbf{8a_2}$, $\mathbf{8b_1}$ and $\mathbf{8b_2}$ underwent the oxidative cleavage with $NaIO_4/RuCl_3$ (CCl_4:CH_3CN:H_2O, 2:2:3, v/v) and esterification with CH_2N_2 to give four optically active esters $\mathbf{9a_1}$, $\mathbf{9a_2}$, $\mathbf{9b_1}$and $\mathbf{9b_2}$ in 60-80% yield, respectively. Treatment of the esters **9** with 2eq. MeLi at low temperature (-78^{0}C) eventually afforded the target compounds $\mathbf{10a_1}$, $\mathbf{10a_2}$, $\mathbf{10b_1}$ and $\mathbf{10b_2}$[7] in 30-60% yield, respectively.



Reagents and Conditions: a) K_2CO_3/MeOH, 0^{0}C, then $H_2C_2O_4{\cdot}2H_2O$, b) $NaIO_4/RuCl_3$, CH_3CN:CCl_4:H_2O (2:2:3, v/v), r.t., then CH_2N_2/Et_2O, c) 2eq. MeLi/Et_2O, -78^{0}C, then aq. NH_4Cl.

Scheme 3

The ^1H NMR spectra of two couples of the synthetic enantiomers of Yingzhaosu C showed that there was remarkable difference between them. It was found that the values of enantiomers **10a$_1$** and **10b$_1$** coincided with that of the natural Yingzhaosu C[8]. But the optical rotation of the natural Yingzhaosu C is only +2.89°(MeOH). Thus, the natural Yingzhaosu C could be considered as a mixture of enantiomeric **10a$_1$** and **10b$_1$** with the former being in excess. The research on the stereochemistry of **8**, **9** and **10** is in progress and the result will be discussed elsewhere.

Acknowledgement

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6. The ^1H NMR($CDCl_3$, 300MHz) spectra of **5a** and **5b** (R=Ac) both revealed two singlet peaks (δ: 1.58, 1.59ppm) for C-8 methyl with the integral area of about 1:1 ratio.
7. **10a$_1$** and **10b$_1$** were enantiomers, the $[\alpha]_D$($CHCl_3$) was +189.3° for **10a$_1$** and -185.4° for **10b$_1$**, their ^1H NMR($CDCl_3$, 600MHz) spectra were identical. δppm: 7.32, 7.15(4H, AA'BB', J_{AB}=8.0Hz, Ar-H), 3.99(1H, dd, J=3.5, 10.2Hz, 12-H), 2.54(1H, dt, J=13.8, 3.5Hz, 10-He), 2.34(3H, s, 1-CH_3), 1.95(1H, dt, J=5.4, 12.9Hz, 10-Ha), 1.79(1H, b, -OH), 1.55-1.65(2H, m, 11-H), 1.34(3H, s, 8-CH_3), 1.12, 1.00(2 x 3H, 2 x s, 14, 15-H).
   10a$_2$ and **10b$_2$** were enantiomers, too. The $[\alpha]_D$($CHCl_3$) was +36.9° for **10a$_2$** and -33.3° for **10b$_2$**. ^1H NMR($CDCl_3$, 300MHz) δppm: 7.30, 7.16(4H, AA'BB', J_{AB}=8.1Hz, Ar-H), 3.92(1H, dd, J=3.8, 10.3Hz, 12-H), 2.34(3H, s, 1-CH_3), 1.75-2.25(5H, m, -CH_2CH_2- and -OH), 1.61(3H, s, 8-CH_3), 1.28, 1.25(2 x 3H, 2 x s, 14, 15-H).
8. ^1H NMR($CDCl_3$, 200MHz) data of the natural Yingzhaosu C was extracted from reference 2. δppm: 7.13-7.34(4H, m, Ar-H), 4.00(1H, m, 12-H), 2.34(3H, s, 1-CH_3), 2.14(1H, -OH), 1.34(3H, s, 8-CH_3), 1.12, 1.00(2 x 3H, 2 x s, 14, 15-H).

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