Enantioselective Total Syntheses and Stereochemical Studies of All Four Stereoisomers of Yingzhaosu C†

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The enantioselective total syntheses and the stereochemistry of all four stereoisomers of yingzhaosu C, an antimalarial peroxy-containing sesquiterpene isolated from yingzhao [*Artabotrys uncinatus (L.) Merr.*], are described. The key to the syntheses was the combination of Sharpless asymmetric epoxidation and the intramolecular nucleophilic epoxy-opening with a benzylic peroxy group to construct the 1,2-dioxane skeleton. The configurations of the 1,2-dioxanes in four stereoisomers were assigned by spectroscopy and chemical transformation.

Introduction

The plant yingzhao [*Artabotrys uncinatus (L.) Merr.*] is known as a traditional Chinese herbal medicine for treatment of malaria, from which four sesquiterpenes were isolated and identified[1] as shown in Figure 1. Among them, yingzhaosu A and yingzhaosu C contained a peroxy group which was shown to be the antimalarial principle. The interesting molecular architecture and outstanding antimalarial activity prompted us to develop the synthetic routes toward these natural products. In previous work, we have completed the syntheses of yingzhaosu A,[2] B,[3] and D.[4] In this paper we will describe the enantioselective total syntheses of all four stereoisomers of yingzhaosu C[5] and the assignment of the absolute configuration of C-8 as well.

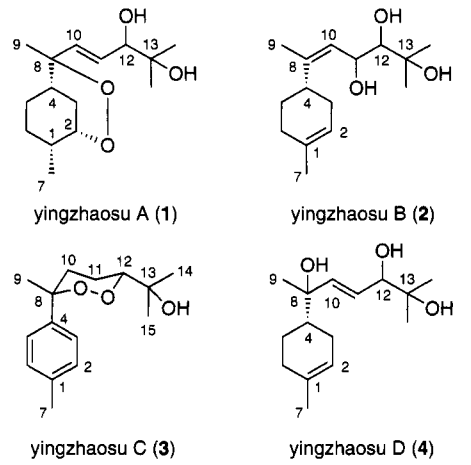
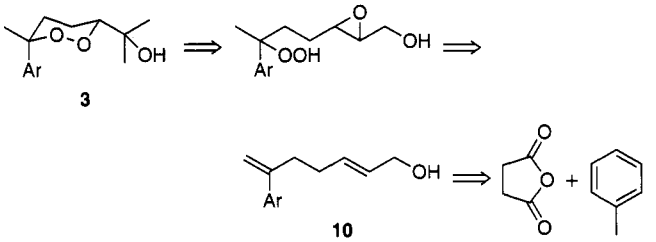


Figure 1.

Syntheses

From a retrosynthetic standpoint, the inherent synthetic challenge for yingzhaosu C lies in the preparation of the chiral 1,2-dioxane skeleton. For this purpose, we abandoned the common [4 + 2] cycloaddition of singlet oxygen to diene and adopted the Sharpless asymmetric epoxidation and intramolecular epoxy opening with a benzylic peroxy group. In the preparation of the benzylic peroxide, we extended Isayama's method[6] to accomplish the introduction of (triethylsilyl)peroxy at the benzylic position in the presence of the epoxide. On the basis of the above consideration, 6-(4′-methylphenyl)-2,6- heptadien-1-ol (**10**) could be used as our synthetic precursor as shown in Scheme 1. In continuation of our analysis from compound **10**, a plausible approach was the Friedel–Crafts reaction of toluene and succinic anhydride followed by two Wittig reactions.

Scheme 1



According to the known procedure,[7] 4-(4′-methylphenyl)-4-oxobutyric acid methyl ester (**5**) was prepared in 92% yield (Scheme 2). Transformation of the ketonic group of compound **5** into a methylene double bond was first completed by treatment with methylenetriphenylphosphorane in 75% yield. Then, another Wittig reaction of compound **8**, which was obtained from the ester **6**, with [(ethoxycarbonyl)methylene]triphenylphosphorane gave 6-(4′-methylphenyl)-2,6-heptadienoic acid ethyl ester (**9**) in 98% yield. On the basis of the chemical shifts and the coupling constant (J = 16.0 Hz) of compound **9**, the new carbon–carbon double bond was assigned as the *trans* configuration. Reduction of the α,β-unsaturated ester **9** with DIBAL-H at −78 °C afforded the intermediate **10** in 98% yield.

†In order that the nomenclature is identical to our earlier paper the skeletal numbering of yingzhaosu C would shift and relate to yingzhaosu compounds when the 1,2-dioxane skeleton was formed, as indicated in Figure 1 and Scheme 3.

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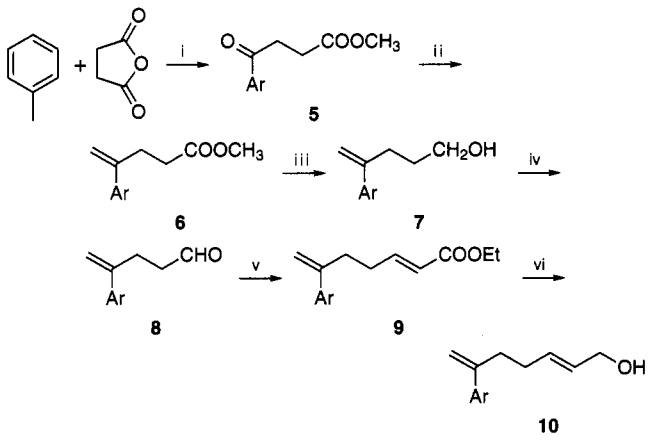
Scheme 2[a]



[a] Conditions: (i) (a) $AlCl_3$, then H_3O^+, (b) CH_3OH/H^+, reflux; (ii) Ph_3PCH_3I, t-BuOK, benzene, rt; (iii) $LiAlH_4/Et_2O$, rt; (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (v) $Ph_3P{=}CHCO_2Et$, benzene, reflux; (vi) DIBAL-H, −78 °C.

With the allylic alcohol **10** in hand, a pair of enantiomeric epoxides **11a** and **11b** was obtained in excellent yield (ca. 90%) and enantioselectivity (>95% ee) by the Sharpless asymmetric epoxidation.[8] Starting with this pair of enantiomers, the reaction sequences as shown in Scheme 3 were executed in a parallel fashion. After the hydroxy group of **11a** was protected as acetate, the (triethylsilyl)peroxy group was introduced[6] by the reaction with oxygen and triethylsilane in the presence of a catalytic amount of Co(modh)$_2$ [bis(1-morpholino-5,5-dimethyl-1,2,4-hexanetrionato)cobalt (II)] in 93% yield. Desilylation of **13a** with KF/18-crown-6 in anhydrous THF, in order that the resulting peroxy anion may attack the epoxide to construct the six-membered ring, gave instead **14a** with a free −OOH. Nucleophilic attack of peroxy group on the epoxide, after examination of various reagents, was finally realized by using the strongly acidic resin Amberlyst-15 to give the desired 1,2-dioxane **15a** in 65% yield. The ^{1}H NMR spectra of **13a**, **14a**, and **15a** all revealed that each of them was an epimeric mixture in approximately a 1:1 ratio. Fortunately, the hydrolytic products **16a$_1$** and **16a$_2$** obtained from **15a** showed subtle differences on TLC, so that the C-8 epimers **16a$_1$** and **16a$_2$** could be carefully separated by column chromatography. Paralleling this scheme, the other two C-8 epimers **16b$_1$** and **16b$_2$** were generated from **11b.**

Subsequent oxidative cleavage of the four optically pure 1,2-dioxanediols **16a$_1$**, **16a$_2$**, **16b$_1$**, and **16b$_2$** with $NaIO_4/RuCl_3$ (CCl_4:CH_3CN:H_2O 2:2:3, v/v) followed by esterification with CH_2N_2 led to four optically active esters **17a$_1$**, **17a$_2$**, **17b$_1$**, and **17b$_2$** in 60−80% yield, respectively. Treatment of the esters **17** with 2 equiv of MeLi at low temperature (−78 °C) eventually afforded all four stereoisomers of yingzhaosu C **18a$_1$**, **18a$_2$**, **18b$_1$**, and **18b$_2$** in 30−60% yield, respectively.

Stereochemical Studies

As shown in Scheme 3, **16a$_1$** and **16b$_1$**, **17a$_1$** and **17b$_1$**, and **18a$_1$** and **18b$_1$** are enantiomers, and so are **16a$_2$** and **16b$_2$**, **17a$_2$** and **17b$_2$**, and **18a$_2$** and **18b$_2$**. Because the absolute configuration of C-12 has been established by asymmetric Sharpless epoxidation and the S_N2 epoxide opening, the configuration of C-8 may be assigned by spectroscopic and conformational analysis.

Based on the fact that six-membered cyclic peroxides exist in a stable chair conformation,[9] the relative stereochemistry at the C-8 and C-12 positions in the ring could be deduced by judging the orientations of C-8 methyl and C-12 hydrogen (i.e., equatorial or axial). Obviously, it is convenient to assign the orientation of the C-12 hydrogen by its splitting pattern in ^{1}H NMR. As for the C-8 methyl, earlier workers had proposed that the orientation of C-8 methyl could be determined by consideration of the ^{13}C NMR shift for C-8 methyl (i.e., C-9) and that an axial methyl on a six-membered ring adopting a chair conformation resonates ca. 5 ppm upfield of the equatorial isomer.[10] Thus, it was of great importance to analyze carefully their ^{1}H NMR and ^{13}C NMR spectra. In order to recognize the C-8 methyl (i.e., C-9), the DEPT-135 technique was used to differentiate CH_3 from CH_2. The ^{13}C NMR data of the six compounds of the 12-R series **16a$_1$**, **16a$_2$**, **17a$_1$**, **17a$_2$**, **18a$_1$**, and **18a$_2$** are shown in Table 1 and their ^{1}H NMR shown in Table 2.

Table 1. ^{13}C NMR (75 MHz, $CDCl_3$) Data for 16a$_1$, 16a$_2$, 17a$_1$, 17a$_2$, 18a$_1$, and 18a$_2$

C no.	16a$_1$	16a$_2$	17a$_1$	17a$_2$	18a$_1$	18a$_2$
1	136.4	137.0	136.8	136.8	136.1	137.1
2, 6	129.1	129.0	129.2	129.1	128.9	129.0
3, 5	125.5	124.9	125.4	125.4	125.6	124.6
4	140.6	141.7	140.6	140.7	140.6	142.4
7	21.0	21.0	21.1	21.0	21.0	21.0
8	82.6	81.9	82.5	82.8	82.4	81.4
9	29.8	25.9	28.5	29.0	30.1	23.9
10	32.2	31.4	32.0	29.9	33.0	33.5
11	22.3	21.2	23.1	21.6	20.8	20.3
12	81.7	80.6	79.1	78.1	86.9	86.9
13	72.1	71.6	169.4	170.5	71.6	72.2
14	63.2	63.6	52.3	52.4	26.0	26.3
15					24.7	25.0

Table 2. ^{1}H NMR Data for 12-H of 16a$_1$, 16a$_2$, 17a$_1$, 17a$_2$, 18a$_1$, and 18a$_2$

compd	12-H
16a$_1$	4.23 (m)
16a$_2$	4.00 (m)
17a$_1$	4.75 (dd, J = 3.4, 8.5 Hz)
17a$_2$	4.54 (t, J = 4.2 Hz)
18a$_1$	3.99 (dd, J = 3.5, 10.2 Hz)
18a$_2$	3.92 (dd, J = 3.8, 10.3 Hz)

The ^{1}H NMR spin system for the C-12 peroxymethine proton provided evidence for the relative stereochemistry about this center. Taking **18a$_1$** and **18a$_2$** for example, the large $J_{12,11a}$ (ca. 10.2 Hz) was taken as indicative of an axial−axial coupling and therefore confirmed that the 12-H of **18a$_1$** and **18a$_2$** were both in axial orientation. By comparison of the ^{13}C NMR chemical shift values of the C-8 methyl group (**18a$_1$**: 30.1 ppm, **18a$_2$**: 23.9 ppm), it was suggested that the C-8 methyl has the equatorial orientation in **18a$_1$** and axial in **18a$_2$**. Their stable conformations are shown in Scheme 3; as a result, the C-8 configuration is *S* for **18a$_1$** and *R* for **18a$_2$**.

When comparisons of the ^{1}H NMR and ^{13}C NMR of **17a$_1$** and **17a$_2$** were made, the same deduction was

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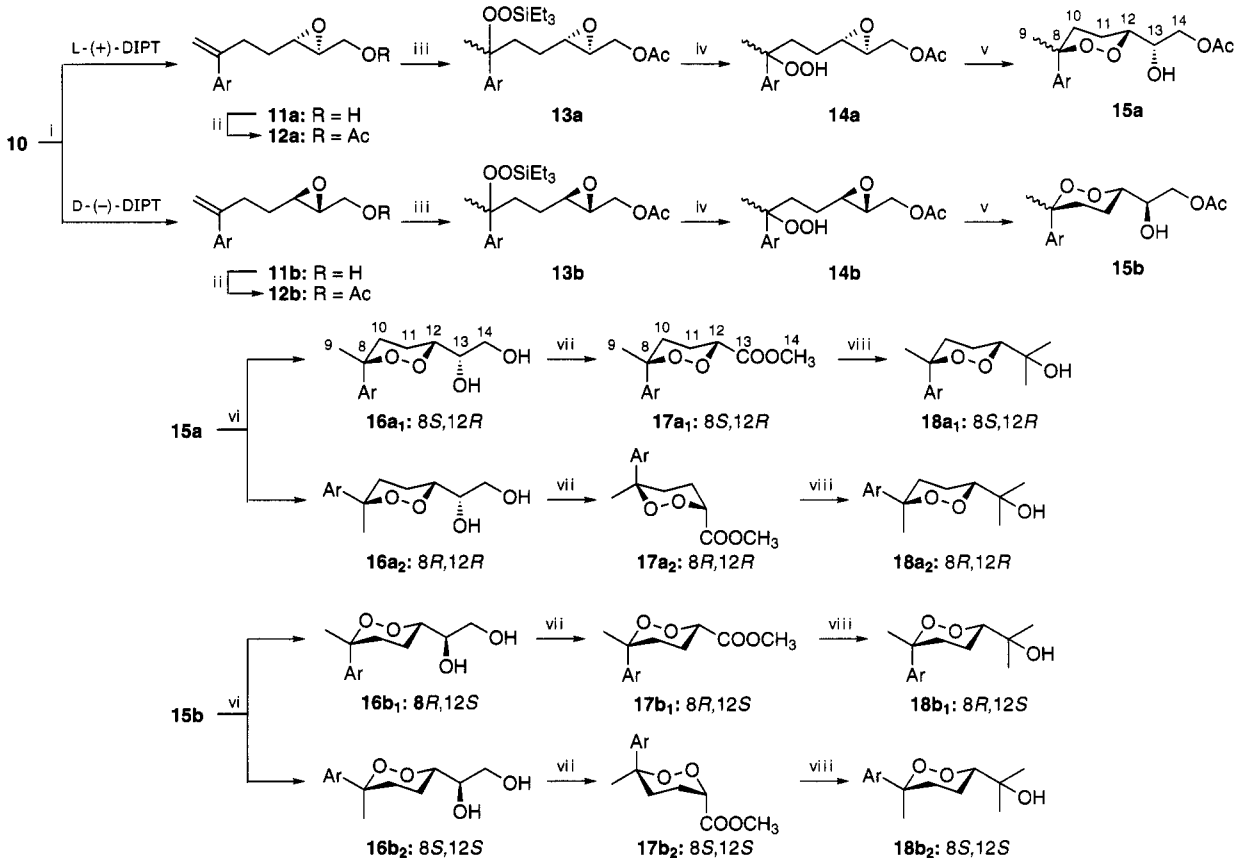
Scheme 3[a]



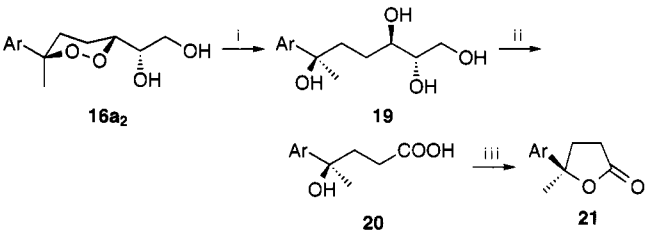
[a] Conditions: (i) $Ti(OPr^i)_4$, 4 Å molecular sieves, t-BuOOH, CH_2Cl_2, −20 °C; (ii) Ac_2O/pyridine, rt; (iii) Et_3SiH, O_2, $Co(modh)_2$, $(CH_2Cl)_2$, rt; (iv) KF/18-crown-6/THF, rt; (v) Amberlyst-15, CH_2Cl_2, rt; (vi) K_2CO_3/MeOH, 0 °C, then $H_2C_2O_4{\cdot}2H_2O$; (vii) $NaIO_4/RuCl_3$, CH_3CN:CCl_4:H_2O (2:2:3, v/v), rt, then CH_2N_2/Et_2O; (viii) 2 equiv of MeLi/Et_2O, −78 °C, then aqueous NH_4Cl.

obtained. A large $J_{12,11a}$ (8.5 Hz) in **17a**$_1$ confirmed an axial−axial coupling and hence an axial 12-H, while a small $J_{12,11a}$ (4.2 Hz) indicated that the orientation of 12-H was equatorial in **17a**$_2$. In the ^{13}C NMR spectra, the shift values of C-8 methyl (**17a**$_1$: 28.5 ppm, **17a**$_2$: 29.0 ppm), which were similar and close to that of **18a**$_1$, confirmed their equatorial orientation. On the basis of the same analysis, the stable conformations of **16a**$_1$ and **16a**$_2$ are also represented in Scheme 3.

The ^{13}C NMR shift values confirm that the stable conformation of **17a**$_2$ is such a 1,4-diaxially substituted chair conformation. How to account for it? According to the previous work,[11] the most stable conformer of 1-methyl-1-phenylcyclohexane has the phenyl ring in the axial orientation, so we considered that the axial *p*-tolyl in **17a**$_2$ was the major control factor and the $-COOCH_3$ group was not large enough to invert the case, but the large $-CMe_2OH$ in **18a**$_2$ and $-CH(OH)CH_2OH$ in **16a**$_1$ played an important role for the stable conformations.

Further evidence for the above assignment was provided by chemical transformation. Compound **16a**$_2$ was subjected to catalytic hydrogenation, $NaIO_4$ oxidative cleavage, and lactonization to give compound **21**[12] in 53% overall yield as shown in Scheme 4. By comparison of its optical rotation ($[\alpha]_D$ +13.8°, $CHCl_3$) with a similar compound of *R*-configuration ($[\alpha]_D$ +72.4°, $CHCl_3$)[13] in which just a phenyl group replaces the *p*-tolyl group, the same configuration is assigned since they both have positive optical rotation. All the C-8 and C-12 absolute configurations in **16**−**18** are listed in Scheme 3.

Scheme 4[a]



[a] Conditions: (i) H_2, 10% Pd−C, EtOH, rt; (ii) $NaIO_4/RuCl_3$, CH_3CN:CCl_4:H_2O (2:2:3, v/v), rt; (iii) benzene, reflux.

The ^1H NMR spectra of the two pairs of synthetic enantiomers of yingzhaosu C showed remarkable differences between them. It was the spectra of enantiomers **18a**$_1$ and **18b**$_1$ that coincided with that of the natural yingzhaosu C. Since the optical rotation of the natural yingzhaosu C is only +2.89°(MeOH), the natural yingzhaosu C may be considered to be a mixture of enantiomeric **18a**$_1$ (8*S*,12*R*) and **18b**$_1$ (8*R*,12*S*) with the former being in excess.

Experimental Section

All anhydrous reactions were conducted with precautions for rigorous exclusion of air and moisture. Melting points were

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measured on a Büchi 535 melting apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200, Bruker AM-300, or AMX-600 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference. All chemical shifts (δ) are reported in parts per million and J values are in hertz. IR spectra were obtained on a Shimadzu IR-440 spectrometer. The low-resolution mass spectra (MS) were recorded on a VG-Quattro or HP-5989A and the high-resolution MS on a Finnigan MAT-95 spectrometer. Optical rotations were measured on a Perkin-Elmer 241MC spectrometer. Flash chromatography was carried out with silica gel (10–40 μm).

4-(4′-Methylphenyl)-4-pentenoic Acid Methyl Ester (6). A suspension of methyltriphenylphosphonium iodide (4.85 g, 12.0 mmol) and potassium *tert*-butoxide (1.35 g, 12.0 mmol) in dry benzene (50 mL) was stirred under nitrogen atmosphere at room temperature for 4 h, and then a solution of **5** (2.0 g, 9.7 mmol) in dry benzene (20 mL) was added dropwise. After being stirred for 12 h, the reaction mixture was filtered through a Celite pad, the filtrate was evaporated, and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (99:1) as eluent to give a colorless oil **6** (1.48 g, 75%): IR (film) 1745, 1630, 1515, 895, 825 cm^{-1}; ^1H NMR (200 MHz) δ 7.30, 7.14 (AA′BB′, 4H, J_{AB} = 8 Hz), 5.28 (s, 1H), 5.04 (s, 1H), 3.66 (s, 3H), 2.83 (t, 2H, J = 8 Hz), 2.48 (t, 2H, J = 8 Hz), 2.34 (s, 3H); MS (*m/e*) 205 (M^+ + 1, 25), 204 (M^+, 34), 173 (19), 145 (100), 130 (35), 117 (18). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.27; H, 7.87.

4-(4′-Methylphenyl)-4-penten-1-ol (7). To a solution of **6** (4.84 g, 23.7 mmol) in dry ether (100 mL) was added excess $LiAlH_4$ (1.0 g, 26.4 mmol). After being stirred for 2 h, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, and the clear solution was filtered, the filtrate was evaporated, and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (80:20) as eluent to give a colorless oil **7** (4.0 g, 96%): IR (film) 3350, 1630, 1515, 895, 825 cm^{-1}; ^1H NMR (300 MHz) δ 7.30, 7.12 (AA′BB′, 4H, J_{AB} = 8 Hz), 5.26 (s, 1H), 5.04 (d, 1H, J = 1.0 Hz), 3.63 (t, 2H, J = 6.5 Hz), 2.57 (t, 2H, J = 7.6 Hz), 2.33 (s, 3H), 1.70 (m, 3H); MS (*m/e*) 176 (M^+, 1.3), 132 (100), 117 (46), 91 (18). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.47; H, 9.27.

4-(4′-Methylphenyl)-4-pentenal (8). A solution of dimethyl sulfoxide (4.02 g, 51.5 mmol) in dichloromethane (10 mL) was added slowly to a cooled (−60 °C) solution of oxalyl chloride (3.31 g, 26.0 mmol) in dichloromethane (50 mL). After 5 min at −60 °C, a solution of **7** (4.0 g, 22.7 mmol) in dichloromethane (20 mL) was added and stirring continued for a further 30 min, triethylamine (16 mL) was then added and the resulting mixture was allowed to warm to room temperature, the solution was washed sequentially with 5% oxalic acid, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (97:3) as eluent to give a colorless oil **8** (3.85 g, 97%): IR (film) 1730, 1630, 1515, 895, 825 cm^{-1}; ^1H NMR (300 M Hz) δ 9.78 (t, 1H, J = 1.3 Hz), 7.29, 7.15 (AA′BB′, 4H, J_{AB} = 8 Hz), 5.30 (s, 1H), 5.05 (d, 1H, J = 1.1 Hz), 2.83 (t, 2H, J = 7.4 Hz), 2.60 (t, 2H, J = 7.4 Hz), 2.35 (s, 3H); MS (*m/e*) 174 (M^+, 5.1), 145 (6.2), 131 (100), 117 (31); HRMS calcd for $C_{12}H_{14}O$ 174.1045, found 174.1059.

6-(4′-Methylphenyl)-2,6-heptadienoic Acid Ethyl Ester (9). A solution of **8** (4.5 g, 25.9 mmol) and [(ethoxycarbonyl)-methylene]triphenylphosphorane (27.0 g, 77.6 mmol) in dry benzene (100 mL) was refluxed for 2 h, and then the reaction mixture was evaporated and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (99:1) as eluent to give a colorless oil **9** (6.17 g, 98%): IR (film) 1725, 1660, 1630, 1515, 975, 895, 825 cm^{-1}; ^1H NMR (200 MHz) δ 7.30, 7.16 (AA′BB′, 4H, J_{AB} = 8 Hz), 6.97 (dt, 1H, J = 16.0, 7.0 Hz), 5.81 (dt, 1H, J = 16.0, 2.0 Hz), 5.29 (d, 1H, J = 1 Hz), 5.04 (d, 1H, J = 1 Hz), 4.19 (q, 2H, J = 7.2 Hz), 2.65 (t, 2H, J = 8 Hz), 2.35 (m, 5H), 1.28 (t, 3H, J = 7.2 Hz); MS (*m/e*) 245 (M^+ + 1, 1.9), 244 (M^+, 13), 215 (8.6), 199 (19), 171 (82), 170 (100), 131 (36), 117 (16), 91 (60). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.61; H, 8.32.

6-(4′-Methylphenyl)-2,6-heptadien-1-ol (10). To a solution of **9** (625 mg, 2.6 mmol) in dry ether (100 mL) at −78 °C under nitrogen atmosphere was added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 5.6 mL, 5.6 mmol). The solution was stirred at −78 °C for 1 h and then quenched with 10% sulfuric acid (8 mL). After the resulting mixture was allowed to warm to room temperature, the aqueous phase was extracted with ether (3 × 5 mL), the combined organic extracts were washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (70:30) as eluent to give a colorless oil **10** (505 mg, 98%): IR (film) 3350, 1630, 1515, 975, 895, 830 cm^{-1}; ^1H NMR (200 MHz) δ 7.30, 7.14 (AA′BB′, 4H, J_{AB} = 8 Hz), 5.68 (m, 2H), 5.27 (d, 1H, J = 1 Hz), 5.03 (d, 1H, J = 1 Hz), 4.08 (d, 2H, J = 6 Hz), 2.58 (t, 2H, J = 8 Hz), 2.35 (s, 3H), 2.22 (m, 2H), 1.37 (s,1H); MS (*m/e*) 203 (M^+ + 1, 0.8), 202 (M^+, 4.7), 184 (27), 171 (27), 132 (100), 131 (53), 117 (41), 91 (49); HRMS calcd for $C_{14}H_{18}O$ 202.1358, found 202.1389.

(2*S*,3*S*)-2,3-Epoxy-6-(4′-methylphenyl)-6-hepten-1-ol (11a). An oven-dried flask, charged with 1.0 g of 4 Å powdered activated molecular sieves, a magnetic stir bar, and 50 mL of dry dichloromethane, was cooled to −20 °C under nitrogen atmosphere, and then titanium(IV) isopropoxide (0.96 g, 3.39 mmol) and L-(+)-diisopropyl tartrate (1.11 g, 4.74 mmol) were sequentially added. After the mixture was stirred for 15 min, a solution of **10** (1.4 g, 6.93 mmol) in dichloromethane (5 mL) was added followed by anhydrous *tert*-butyl hydroperoxide in dichloromethane (5.86 N, 2.4 mL, 14.1 mmol). The resulting mixture was refrigerated (−20 °C) for 12 h and then quenched with water (20 mL). After the mixture warmed to room temperature, a 10% aqueous solution of NaOH saturated with sodium chloride (15 mL) was added to effect the hydrolysis of the tartrate, the aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) as eluent to give a colorless oil **11a** (1.35 g, 89%): $[\alpha]_D$ −19.7° (c 0.93, EtOAc); IR (film) 3400, 1630, 1515, 890, 825 cm^{-1}; ^1H NMR (200 MHz) δ 7.30, 7.14 (AA′BB′, 4H, J_{AB} = 8 Hz), 5.30 (s, 1H), 5.07 (s, 1H), 3.86, 3.57 (ABX system, 2H, J_{AB} = 13 Hz, J_{AX} = 4 Hz, J_{BX} = 5 Hz), 2.98 (m, 1H), 2.87 (m, 1H), 2.66 (m, 2H), 2.34 (s, 3H), 1.73 (m, 2H), 1.62 (s,1H); MS (*m/e*) 219 (M^+ + 1, 12), 218 (M^+, 28), 201 (36), 187 (16), 157 (100), 145 (42), 131 (51), 117 (31), 91 (26); HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1264.

(2*R*,3*R*)-2,3-Epoxy-6-(4′-methylphenyl)-6-hepten-1-ol (11b). The title compound was prepared from **10** following the procedure described for its enantiomer **11a** with D-(−)-diisopropyl tartrate replacing L-(+)-diisopropyl tartrate: yield 91%; $[\alpha]_D$ +19.5° (*c* 1.455, EtOAc); IR and ^1H NMR, see compound **11a**.

(2*S*,3*S*)-2,3-Epoxy-6-(4′-methylphenyl)-6-heptenyl Acetate (12a). To a solution of **11a** (2.67 g, 12.2 mmol) in pyridine (15 mL) was added acetic anhydride (3.68 g, 36.1 mmol). After being stirred at room temperature for 3 h, the solution was cooled in an ice bath and 10% HCl (30 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate (4 × 60 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated, and the crude product was purified by flash chromatography with petroleum ether–ethyl acetate (95:5) as eluent to give a colorless oil **12a** (2.97 g, 93%): $[\alpha]_D$ −30.2° (*c* 1.24, $CHCl_3$); IR (film): 1745, 1630, 1515, 1230, 890, 825 cm^{-1}; ^1H NMR (300 MHz) δ 7.30, 7.14 (AA′BB′, 4H, J_{AB} = 8.1 Hz), 5.29 (d, 1H, J = 1.2 Hz), 5.06 (d, 1H, J = 1.2 Hz), 4.30, 3.87 (ABX system, 2H, J_{AB} = 12.2 Hz, J_{AX} = 3.1 Hz, J_{BX} = 6.3 Hz), 2.92 (m, 1H), 2.85 (m, 1H), 2.65 (m, 2H), 2.35 (s, 3H), 2.08 (s, 3H), 1.72 (m, 2H); MS (*m/e*) 260 (M^+, 3.5), 200 (20), 187 (16), 170 (100), 145 (28), 131 (46), 117 (50), 91 (58). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.66; H, 8.03.

(2*R*,3*R*)-2,3-Epoxy-6-(4′-methylphenyl)-6-heptenyl Acetate (12b). The title compound was prepared from **11b**

following the procedure described for its enantiomer **12a**: yield 93%; $[\alpha]_D$ +30.3° (*c* 1.37, $CHCl_3$); IR and ^1H NMR, see compound **12a**.

(2*S*,3*S*)-2,3-Epoxy-6-(4′-methylphenyl)-6-[(triethylsilyl)peroxy]heptyl Acetate (13a). A solution of **12a** (600 mg, 2.3 mmol), triethylsilane (540 mg, 4.6 mmol), and $Co(modh)_2$ (62 mg, 0.12 mmol) in 1,2-dichloroethane (10 mL) was stirred vigorously under an oxygen atmosphere at room temperature (25 °C) for 3 h, and then the volatile materials were evaporated under reduced pressure and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (98:2) as eluent to give a colorless oil **13a** (873 mg, 93%): IR (film) 1745, 1515, 1230, 810 cm^{-1}; ^1H NMR (300 MHz) δ 7.11–7.26 (m, 4H), 4.29, 3.84 (m, 2H, two ABX systems overlapping), 2.86 (m, 1H), 2.76 (m, 1H), 2.33 (s, 3H), 2.07 (s, 3H), 1.80–2.15 (m, 2H), 1.59,1.58 (2 × s, 3H), 1.30–1.65 (m, 2H), 0.98 (t, 9H, *J* = 7.8 Hz), 0.70 (q, 6H, *J* = 7.8 Hz); MS (*m/e*) 409 (M^+ + 1, 0.3), 262 (18), 261 (100), 201 (99), 145 (53), 131 (33), 91 (28). Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.66; H, 8.88. Found: C, 64.77; H, 9.30.

(2*R*,3*R*)-2,3-Epoxy-6-(4′-methylphenyl)-6-[(triethylsilyl)peroxy]heptyl Acetate (13b). The title compound was prepared from **12b** following the procedure described for its enantiomer **13a**: yield 91%; IR and ^1H NMR, see compound **13a**.

(2*S*,3*S*)-2,3-Epoxy-6-hydroperoxy-6-(4′-methylphenyl)-heptyl Acetate (14a). To a solution of **13a** (3.84 g, 9.4 mmol) in tetrahydrofuran (40 mL) was added KF (600 mg, 10.3 mmol) and 18-crown-6 (124 mg, 0.47 mmol). After being stirred at room temperature for 1 h, the mixture was evaporated under reduced pressure and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (80:20) as eluent to give a colorless oil **14a** (2.48 g, 90%): IR (film) 3350, 1740, 1515, 1240, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.50, 7.48 (2 × s, 1H, exchangeable with D_2O), 7.15–7.35 (m, 4H), 4.31, 3.89 (m, 2H, two ABX systems overlapping), 2.93 (m, 1H), 2.83 (m, 1H), 2.34 (s, 3H), 2.07 (s, 3H), 1.85–2.20 (m, 2H), 1.60, 1.59 (2 × s, 3H), 1.40–1.75 (m, 2H); MS (*m/e*) 295 (M^+ + 1, 1.0), 262 (9.0), 261 (56), 201 (60), 200 (46), 145 (18), 131 (21), 118 (100), 91 (58); HRMS calcd for $C_{16}H_{21}O_3$ (M^+ − OOH) 261.1491, found 261.1493.

(2*R*,3*R*)-2,3-Epoxy-6-hydroperoxy-6-(4′-methylphenyl)-heptyl Acetate (14b). The title compound was prepared from **13b** following the procedure described for its enantiomer **14a**: yield 91%; IR and ^1H NMR, see compound **14a**.

1,2-Dioxane 15a (8*RS*,12*R*,13*S*). To a solution of **14a** (200 mg, 0.68 mmol) in dichloromethane (20 mL) was added 30 mg of Amberlyst-15. After being stirred at room temperature for 12 h, the mixture was filtered and the filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) as eluent to give a white solid **15a** (130 mg, 65%): IR (CH_2Cl_2) 3450, 1740, 1510, 1245, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.14–7.35 (m, 4H), 3.60–4.45 (m, 4H), 2.34 (s, 3H), 2.10, 2.06 (2 × s, 3H), 1.55–2.60 (m, 5H), 1.50, 1.37 (2 × s, 3H); MS (*m/e*) 295 (M^+ + 1, 0.2), 294 (M^+, 3.2), 278 (1.4), 263 (1.2), 234 (2.5), 191 (10), 165 (100), 159 (4.5), 145 (46), 132 (55), 119 (71), 91 (4.8). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.06; H, 7.03.

1,2-Dioxane 15b (8*RS*,12*S*,13*R*). The title compound was prepared from **14b** following the procedure described for its enantiomer **15a**: yield 64%; IR and ^1H NMR, see compound **15a**.

1,2-Dioxanediol 16a$_1$ (8*S*,12*R*,13*S*) and 16a$_2$ (8*R*,12*R*,13*S*). To a solution of **15a** (1.27 g, 4.32 mmol) in methanol (40 mL) was added K_2CO_3 (40 mg, 0.29 mmol) in an ice bath. After the completion of the reaction, $H_2C_2O_4{\cdot}2H_2O$ (80 mg, 0.63 mmol) was added to neutralize the reaction mixture. Then the solvent was removed under reduced pressure and the residue was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated, and the crude products were separated by flash chromatography with petroleum ether–ethyl acetate (80:20) as eluent to give a white solid **16a$_1$** (469 mg), **16a$_2$** (463 mg), and a mixture of **16a$_1$** and **16a$_2$** (115 mg). The total yield is 1.05 g (97% yield).

For **16a$_1$**: mp 69–71 °C; $[\alpha]_D$ +175.4° (*c* 1.12, $CHCl_3$); IR (CH_2Cl_2) 3400, 1515, 1270, 1080, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.31, 7.17 (AA′BB′, 4H, J_{AB} = 8.2 Hz), 4.23 (m, 1H), 3.58, 3.51 (A_2B system, 3H, J_{AB} = 6.0 Hz), 2.53 (dt, 1H, *J* = 13.8, 3.8 Hz), 2.34 (s, 3H), 1.55–2.05 (m, 5H, two of them exchangeable with D_2O), 1.36 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 252 (M^+, 2.4), 237 (1.6), 221 (2.4), 191 (6.0), 159 (7.6), 145 (49), 132 (47), 119 (100), 91 (48), 61 (12). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.55; H, 7.99.

For **16a$_2$**: mp 98–99 °C; $[\alpha]_D$ −49.2° (c 1.08, $CHCl_3$); IR (CH_2Cl_2) 3400, 1515, 1270, 1070, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.30, 7.17 (AA′BB′, 4H, J_{AB} = 8.2 Hz), 4.00 (m, 2H), 3.86, 3.77 (ABX system, 2H, J_{AB} = 11.6 Hz, J_{AX} = 3.4 Hz, J_{BX} = 5.8 Hz), 2.34 (s, 3H), 1.85–2.25 (m, 6H, two of them exchangeable with D_2O), 1.52 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 252 (M^+, 0.8), 237 (1.5), 221 (1.2), 191 (5.2), 159 (6.0), 145 (43), 132 (34), 119 (100), 91 (47), 61 (16). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.36; H, 8.04.

1,2-Dioxanediol 16b$_1$ (8*R*,12*S*,13*R*) and 16b$_2$ (8*S*,12*S*,13*R*). The title compounds were prepared from **15b** following the procedure described for their enantiomers **16a$_1$** and **16a$_2$**: yield 96%. For **16b$_1$**: mp 68–70 °C; $[\alpha]_D$ −172.3° (*c* 1.09, $CHCl_3$); IR and ^1H NMR, see compound **16a$_1$**. For **16b$_2$**: mp 96–98 °C; $[\alpha]_D$ +47.0° (*c* 1.07, $CHCl_3$); IR and ^1H NMR, see compound **16a$_2$**.

1,2-Dioxane Ester 17a$_1$ (8*S*,12*R*). To a biphasic solution of acetonitrile (2 mL), carbon tetrachloride (2 mL), and water (3 mL) was added **16a$_1$** (156 mg, 0.62 mmol) followed by sodium periodate (543 mg, 2.54 mmol) and a catalytic amount of ruthenium trichloride hydrate. After the resulting mixture was stirred vigorously for 1 h at room temperature, 10 mL of dichloromethane was added, the aqueous phase was extracted with dichloromethane (4 × 5 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated. The crude product (acid) was then dissolved in ether (15 mL), the solution of diazomethane was added dropwise until the completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography with petroleum ether–ethyl acetate (98:2) as eluent to give a white solid **17a$_1$** (105 mg, 68%): mp 69.5–71.5 °C; $[\alpha]_D$ +151.9° (*c* 1.19, $CHCl_3$); IR (KBr) 1740, 1515, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.32, 7.16 (AA′BB′, 4H, J_{AB} = 8.0 Hz), 4.75 (dd, 1H, *J* = 3.4, 8.5 Hz), 3.71 (s, 3H), 2.48 (m, 1H), 2.34 (s, 3H), 1.85–2.15 (m, 3H), 1.45 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 250 (M^+, 2.2), 235 (4.2), 218 (23), 191 (3.3), 159 (14), 145 (17), 132 (100), 119 (67), 91 (37), 59 (7.1). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.67; H, 7.17.

1,2-Dioxane Ester 17a$_2$ (8*R*,12*R*). The title compound was prepared from **16a$_2$** following the procedure described for its C-8 epimer **17a$_1$**: yield 78%; mp 99.5–101 °C; $[\alpha]_D$ −197.0° (*c* 1.19, $CHCl_3$); IR (KBr) 1740, 1515, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.35, 7.19 (AA′BB′, 4H, J_{AB} = 8.2 Hz), 4.54 (t, 1H, *J* = 4.2 Hz), 3.86 (s, 3H), 2.35 (s, 3H), 1.95–2.35 (m, 4H), 1.38 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 250 (M^+, 1.6), 235 (6.9), 218 (18), 191 (7.3), 159 (14), 145 (22), 132 (100), 119 (84), 91 (50), 59 (9.7). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.39; H, 7.39.

1,2-Dioxane Ester 17b$_1$ (8*R*,12*S*). The title compound was prepared from **16b$_1$** following the procedure described for its enantiomer **17a$_1$**: yield 60%; mp 70–71 °C; $[\alpha]_D$ −148.4° (*c* 1.17, $CHCl_3$); IR and ^1H NMR, see compound **17a$_1$**.

1,2-Dioxane Ester 17b$_2$ (8*S*,12*S*). The title compound was prepared from **16b$_2$** following the procedure described for its C-12 epimer **17a$_1$**: yield 75%; mp 98–99.5 °C; $[\alpha]_D$ +193.0° (*c* 1.25, $CHCl_3$); IR and ^1H NMR, see compound **17a$_2$**.

Yingzhaosu C 18a$_1$ (8*S*,12*R*). To a solution of **17a$_1$** (60 mg, 0.24 mmol) in dry ether (5 mL) at −78 °C under nitrogen atmosphere was added dropwise a solution of methyllithium (1.5 M in diethyl ether, 0.32 mL, 0.48 mmol). The solution was stirred at −78 °C for 10 min and then quenched at low temperature with saturated aqueous ammonium chloride (3 mL). After the resulting mixture was allowed to warm to room temperature, the aqueous phase was extracted with ether (3 × 2 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography with petroleum ether–ethyl

acetate (92:8) as eluent to give a colorless oil **18a$_1$** (36 mg, 60%): $[\alpha]_D$ +189.3° (*c* 0.93, $CHCl_3$); IR (film) 3450, 1515, 820 cm^{-1}; ^1H NMR (600 MHz) δ 7.32, 7.15 (AA'BB', 4H, J_{AB} = 8.0 Hz), 3.99 (dd, 1H, J = 3.5, 10.2 Hz), 2.54 (dt, 1H, J = 13.9, 3.4 Hz), 2.34 (s, 3H), 1.95 (dt, 1H, J = 5.4, 13.0 Hz), 1.75 (s, 1H), 1.55–1.65 (m, 2H), 1.34 (s, 3H), 1.12 (s, 3H), 1.00 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 233 (2.5), 232 (14), 199 (18), 186 (28), 159 (51), 145 (86), 132 (64), 119 (39), 91 (32), 59 (100); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1548.

Yingzhaosu C (18a$_2$) (8*R*,12*R*). The title compound was prepared from **17a$_2$** following the procedure described for its C-8 epimer **18a$_1$**: yield 35%; $[\alpha]_D$ +36.9° (*c* 1.06, $CHCl_3$); IR (film) 3450, 1520, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.30, 7.16 (AA'BB', 4H, J_{AB} = 8.1 Hz), 3.92 (dd, 1H, J = 3.8, 10.3 Hz), 2.34 (s, 3H), 1.75–2.25 (m, 5H), 1.61 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR see Table 1; MS (*m/e*) 233 (2.0), 232 (12), 199 (2.0), 186 (2.6), 159 (2.3), 145 (98), 132 (13), 119 (3.3), 91 (12), 59 (100); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1544.

Yingzhaosu C (18b$_1$) (8*R*,12*S*). The title compound was prepared from **17b$_1$** following the procedure described for its enantiomer **18a$_1$**: yield 50%; $[\alpha]_D$ −185.4° (*c* 0.78, $CHCl_3$); IR and ^1H NMR, see compound **18a$_1$**.

Yingzhaosu C (18b$_2$) (8*S*,12*S*). The title compound was prepared from **17b$_2$** following the procedure described for its C-12 epimer **18a$_1$**: yield 30%; $[\alpha]_D$ −33.3° (*c* 0.7, $CHCl_3$); IR and ^1H NMR, see compound **18a$_2$**.

Chemical Transformation of 16a$_2$ to the Lactone 21. A solution of **16a$_2$** (55 mg, 0.22 mmol) in ethanol (2 mL) was hydrogenated over palladium charcoal (10%, 20 mg) for 2 h, and the solution was filtered and concentrated. The crude product **19** was dissolved in 0.5 mL of acetonitrile, 0.5 mL of carbon tetrachloride, and 0.75 mL of water, and then sodium periodate (191 mg, 0.89 mmol) and a catalytic amount of ruthenium trichloride hydrate were added. After the resulting mixture was stirred vigorously for 40 min at room temperature, 2 mL of dichloromethane was added, the aqueous phase was extracted with dichloromethane (3 × 2 mL), the combined organic extracts were dried over Na_2SO_4 and evaporated, the crude product **20** was passed through a short silica gel column to remove the ruthenium compounds and then dissolved in dry benzene (5 mL), the solution was gently heated in a distilled set, and the solvent was nearly completely removed. This operation was repeated for four times, and the crude product was purified by flash chromatography with petroleum ether–ethyl acetate (96:4) as eluent to give a colorless oil **21** (22 mg, 53% yield overall): $[\alpha]_D$ +13.8° (*c* 0.74, $CHCl_3$); IR (film) 1780, 1520, 820 cm^{-1}; ^1H NMR (300 MHz) δ 7.15–7.30 (m, 4H), 2.35–2.65 (m, 4H), 2.35 (s, 3H), 1.70 (s, 3H); MS (*m/e*) 191 (M^+ + 1, 7.1), 190 (M^+, 13), 176 (12), 175 (100), 91 (33).

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