Synthesis of Biologically Active (−)-Dehydroiso-β-lapachone and the Determination of Its Absolute Configuration

Tetsutaro KIMACHI,* Eri TORII, Yusuke KOBAYASHI, Misae DOE, and Motoharu JU-ICHI

School of Pharmaceutical Sciences, Mukogawa Women's University; 11–68 Koshien Kyubancho, Nishinomiya, Hyogo 663–8179, Japan. Received December 31, 2010; accepted March 7, 2011; published online March 10, 2011

Synthesis of dehydoriso-β-lapachone (1) in both racemic and enantioenriched forms is achieved starting from reduced naphthoquinone equivalents. As for the synthesis of enantioenriched dehydroiso-β-lapachone, introduction of the asymmetric center was carried out by catalytic asymmetric epoxidation of the unfunctionalized trisubstituted olefin using Shi epoxidation diketal catalyst. The construction of isopropenylfurano-1,2-(β)-naphthoquinone was carried out by acidic ring-opening reaction of the epoxynaphthalene and the following diammonium cerium(IV) nitrate (CAN) oxidation. The absolute configuration of naturally occurring (−)-dehydroiso-β-lapachone was finally determined as (*R*) by comparing the measured optical rotation value of the synthetic (*R*)-dehydroiso-β-lapachone.

Key words synthesis; naphthoquinone; dehydroiso-β-lapachone; anti tumor activity; 2-alkoxy-1,4-dimethoxynaphthalene

We recently reported the total synthesis of two biologically active natural products, Rhinacanthin A and Rhinacanthin C.[1,2] In the synthesis of both compounds, we accomplished highly regioselective and stereoselective construction of α-lapachone or 1,4-naphthoquinone structures using 2-alkoxy-1,4-dimethoxynapthalenes, which we refer to as reduced naphthoquinone equivalents.[1] In the continuous study on the synthesis and evaluation of novel biologically active natural products, we describe herein the convenient and selective synthesis of racemic dehydroiso-β-lapachone and the asymmetric synthesis of (−)-dehydroiso-β-lapachone (**1**), which we also establishes the absolute configuration as (*R*).

(−)-Dehydroiso-β-lapachone (**1**), which racemic structure has been constructed and confirmed by the chemical modification of naturally occurring Lomatiol isolated from *Lomatia ilicifolia* and *Lomatia longifolia* in 1895[3] and has been reinvestigated by Hooker in 1936,[4] recently isolated from extracts of the rainforest plants, *Lantana involucrata*, shows significant *in vitro* cytotoxic activity against various human tumor cell lines. (Fig. 1)[5] The non-selective synthesis of racemic dehydroiso-β-lapachone (*rac*-**1**)[6] has been reported but its absolute configuration has not been established to date. Regarding the recent studies on the synthesis of 1,2-furanonaphthoquinones, Kongkathip *et al.* showed the acid catalyzed cyclization of 2-substituted-1,4-naphthoquinones affords various furano- or pyranonaphthoquinones in moderate to good yield.[7] Most recently, Singh *et al.* reported the chemical transformation of lapachol to its related derivatives including dehydroiso-β-lapachone.[8] In this study, Singh reported that the treatment of lapachol with nitrous acid afforded *rac*-**1** with equal amounts of three other isomers.

Inspired by these results, we first undertook the selective synthesis of racemic dehydroiso-β-lapachone (*rac*-**1**), which gave us knowledge to undertake the asymmetric synthesis of this natural product. As for the synthetic strategy, we envisaged a 1,2-furanonaphthoquinone formation by the ring-opening reaction of the epoxynaphthlene (**2**) and the subsequent oxidative ring closure to obtain *rac*-**1**. (Fig. 2).

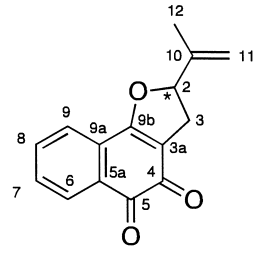


Fig. 1. Structure of (−)-Dehydroiso-β-lapachone

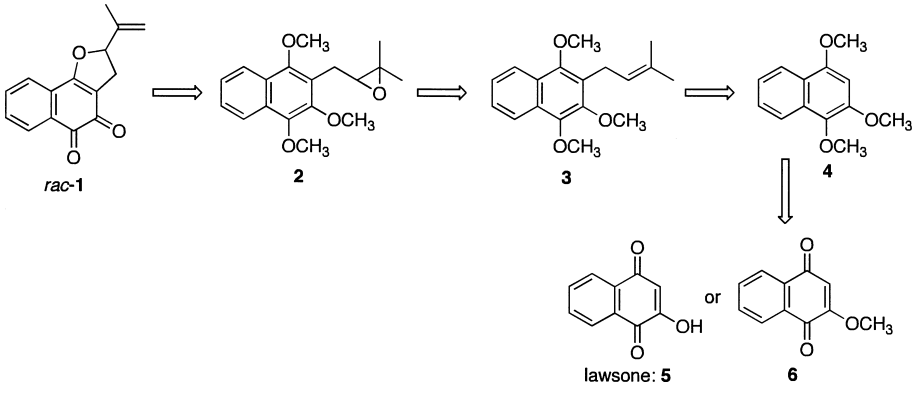
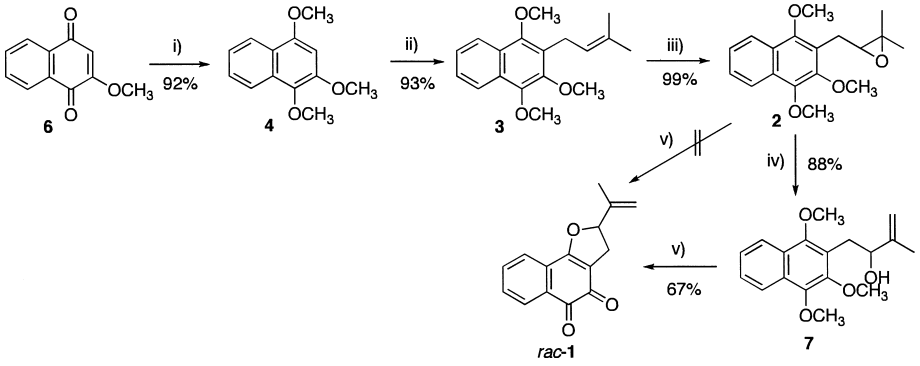


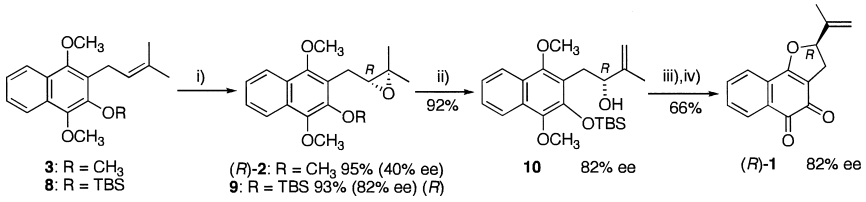
Fig. 2. Synthetic Strategy for the Racemic Dehydroiso-β-lapachone (*rac*-**1**)

* To whom correspondence should be addressed. e-mail: tkimachi@mukogawa-u.ac.jp



Reagents and conditions: i) 1) $Na_2S_2O_4$ dioxane/H_2O=1/1, 1 h, then solid KOH (6 eq), Me_2SO_4 (6 eq), rt, 3 h. ii) 1) *n*-BuLi, THF, rt, 2 h; 2) 1-bromo-3-methyl-2-butene, −80 °C. iii) *m*-CPBA, $NaHCO_3$ aq., rt, $CHCl_3$, 1 h. iv) 1 M aqueous solution of CSA, *n*-Bu_4N^+ Br^-, CH_2Cl_2. v) CAN, CH_3CN–H_2O.

Chart 1. Synthesis of Racemic Dehydroiso-β-lapachone (*rac*-**1**)



Reagents and conditions: i) Shi cat. Oxone, 0.05 M $Na_2B_4O_7 \cdot 10H_2O/4\times10^{-4}$ M Na_2(EDTA)aq, 5 h, −10 °C. ii) 1 M aqueous solution of CSA, *n*-$Bu_4N^+Br^-$, CH_2Cl_2. iii) TBAF, AcOH, THF, rt. iv) CAN, CH_3CN.

Chart 2. Asymmetric Synthesis of (*R*)-Dehydroiso-β-lapachone ((*R*)-**1**)

Results and Discussion

The commercially available 2-methoxy-1,4-naphthoquinone (**6**) was initially converted to 1,2,4-trimethoxynaphthalene (**4**) by the reductive methylation in high yield (92%).[9]

As shown in Chart 1, racemic epoxynaphthalene (**2**) was synthesized by the oxidation of olefin (**3**) obtained by *ortho*-lithiation followed by alkylation. The oxidative ring closure of **2** to *rac*-**1** resulted in the formation of a complex mixture. After brief investigations on the stepwise ring construction, it was found that the heterogeneous reaction of **2** in methylene chloride and aqueous camphorsulfonic acid (CSA) promoted ring opening and led to naphthalene alcohol (**7**) in excellent yield with the help of phase transfer catalyst tetrabutylammonium bromide (TEBABr).[10] Finally, conversion of naphthalene alcohol (**7**) to *rac*-**1** was achieved in 67% by diammonium cerium(IV) nitrate (CAN) oxidation.[11] The obtained *rac*-**1** showed analytical and spectroscopic data consistent with those reported except for the optical rotation value. Especially ^{1}H-NMR and ^{13}C-NMR assingnments of *rac*-**1** were established by heteronuclear multiple bond connectivity (HMBC) correlations and were listed in Experimental.

There are many reports concerning the absolute configuration of optically active naphthoquinone natural products as (*R*).[12,13] Perusal of these reports prompted us to carry out the epoxidation of **3** with the Shi catalyst and Oxone in buffered media.[1,14] We obtained (*R*)-**2** in good chemical yield with modest enantioselectivity (40% ee) (Chart 2). After brief investigations to improve the enantioselectivity of the epoxide (*R*)-**2**, we found that the enantioenriched **9**, which we already used in the total synthesis of Rhinacanthin A, was a suitable candidate for the preparation of **10**, instead of (*R*)-**7**.

As can be seen from Chart 2, the enantioenriched compound (**9**) was exposed to the acidic ring-opening reaction to afford **10** in good yield (92%). The thus obtained naphthalene alcohol (**10**) was converted to the desired (*R*)-**1** by CAN oxidation of the desilylated naphthol derivative, which was obtained from the naphthalene alcohol (**10**) by *in situ* treatment with acidic tetrabutylammonium fluoride (TBAF), in 59% over 3 steps from **9** without the loss of ee (Chart 2) As for the synthetic (*R*)-**1**, the value of the optical rotation exhibited $[\alpha]_D^{23}$ −52.3 (c=0.3, chloroform) {lit.[5] $[\alpha]_D$ −45.1, (c=0.40, chloroform)}, and the enantiomeric excess was found to be 82% by the chiral HPLC analysis. From the consideration on the sign of the optical rotation of (*R*)-**1**, we established the absolute configuration of the reported (−)-dehydroiso-β-lapachone as (*R*).

Conclusion

We established the convenient route for the synthesis of racemic dehydroiso-β-lapachone (*rac*-**1**) in 48% yield over 5 steps from commercially available **6**. Using a similar method, we also achieved the asymmetric synthesis of (*R*)-**1** in 59% from **9**, whose preparation has been previously reported in connection with the asymmetric synthesis of rhinacanthin A. Furthermore, we determined the absolute configuration of naturally occurring (−)-dehydroiso-β-lapachone as (*R*).

Experimental

General All materials not explicitly mentioned were purchased from Wako Pure Chemical Products Co. (Osaka, Japan), Tokyo Kasei Kogyo Co. (Tokyo, Japan), Nacalai Tesque Co. (Kyoto, Japan), and Aldrich Chemical Co. (U.S.A.) ^{1}H-NMR spectra were recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are recorded in parts per million (ppm) relative to TMS. ^{13}C-NMR spectra were proton decoupled and recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometers using the carbon signal of the deuterated solvent as the internal standard. IR spectra were recorded in KBr using a PERKIN ELMER SPECTRUM 2000FT-IR spectrometer. MS were obtained on JEOL JMS-700 instruments. Optical rotations were measured on a P-1020 (Japan Spectroscopic Co.) polarimeter at the sodium D-line and ambient temperature. Analytical HPLC was performed on a Waters 600E/484 unit and the wavelength detector was operated at 254 nm. Chiral

HPLC analyses were performed using CHIRALPAK AD-H or CHIRALPAK-IC columns at room temperature unless stated otherwise. Enantiomeric purity assays using chiral HPLC columns were completed with both racemic and enantioenriched materials and repeated at least once in order to ensure accuracy of the method used. Melting points were measured on a Yanaco micro melting point apparatus without correction. Flash chromatography was performed with silica gel (Wakosil C-200) obtained from Wako Pure Chemical Products Co. Analytical thin layer chromatography was performed on Merck Silica gel 60 F_{254} alminium sheets and the visualization was accomplished by UV lamp.

3-(3-Methyl-2-butenyl)-1,2,4-trimethoxynaphthalene (3) To a 0 °C stirred solution of **4** (2.18 g, 10 mmol) in THF (tetrahydrofuran) (15 ml), *n*-butyllithium (7.3 ml, 12 mmol, 1.65 M solution in hexane) was added dropwise under argon atmosphere. After 2 h stirring at room temperature, the mixture was cooled to −80 °C, followed by dropwise addition of prenyl bromide (3.5 ml, 30 mmol). The mixture was allowed to warm up to room temperature in 30 min ethylacetate (AcOEt) and satd aq NH_4Cl was added to the mixture and separated. The aqueous layer was extracted three times with AcOEt. The combined organic layer was washed with 1% aq. $Na_2S_2O_3$, water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (3.40 g) was purified by flash chromatography (AcOEt : *n*-hexane=1 : 6) to provide 2.65 g of **3** as a yellow oil (93%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.70 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 3.54 (d, 2H, J=6.6 Hz, CH_2), 3.89 (s, 3H, OCH_3), 3.96 (s, 3H×2, OCH_3), 5.23—5.26 (m, 1H, CH=C), 7.34—7.46 (m, 2H, ArH), 8.00 (dd, 1H, J=1.8, 6.6 Hz, ArH), 8.08 (dd, 1H, J=1.8, 7.3 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.9 (CH_3), 24.1 (CH_2), 25.7 (CH_3), 60.7 (CH_3), 60.9 (CH_3), 62.2 (CH_3), 121.6 (CH), 122.1 (CH), 123.4 (CH), 124.8 (CH), 125.6 (CH), 127.2 (C), 128.3 (C), 131.5(2C) (C), 143.7 (C), 148.5 (C), 150.0 (C). High resolution-mass spectra (HR-MS) (EI^+) *m*/*z*: Calcd for $C_{18}H_{22}O_3$: 286.1569; Found: 286.1562.

(±)-3-((3,3-Dimethyloxiran-2-yl)methyl)-1,2,4-trimethoxynaphthalene (2) 0.5 M aq. $NaHCO_3$ (1.0 ml) was added to a stirred solution of **3** (286 mg, 1.0 mmol) in CH_2Cl_2 (methylene chloride) (3.0 ml). *m*-Chloroperbenzoic acid (*m*-CPBA) (271 mg, 1.1 mmol; a commercially available 70% *m*-CPBA was used) was slowly added to the mixture at 0 °C, and the mixture was stirred for 30 min at room temperature. After the completion of the reaction, monitored by tlc, the reaction mixture was worked up by addition of $CHCl_3$ (chloroform) and water at 0 °C, and extracted with $CHCl_3$. The organic layer was washed with 1% aq. $Na_2S_2O_3$, 0.5 M aq. $NaHCO_3$, and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **2** (300 mg, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.02 (dd, 1H, J=5.1, 12.0 Hz, CH_2), 3.06 (dd, 1H, J=5.1, 4.7 Hz, CH_2), 3.13 (dd, 1H, J=4.7, 12.0 Hz, CH), (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.43 (td, 1H, J=14.0, 7.0 Hz, ArH), 8.01 (dd, 1H, J=1.4, 7.0 Hz, ArH), 8.09 (dd, 1H, J=1.4, 7.0 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 19.0 (CH_3), 24.8 (CH_3), 24.9 (CH_2), 59.1 (C), 60.7 (CH_3), 60.9 (CH_3), 62.4 (CH_3), 64.1 (CH), 121.6 (CH), 122.2 (CH), 123.5 (C), 125.0 (CH), 125.4 (C), 125.9 (CH), 128.8 (C), 143.5 (C), 148.3 (C), 150.8 (C). HR-MS (EI^+) *m*/*z*: Calcd for $C_{18}H_{22}O_4$: 302.1518; Found: 302.1517.

(±)-3-Methyl-1-(1,3,4-trimethoxynaphthalen-2-yl)but-3-en-2-ol (7) To a stirred solution of **2** (262 mg, 0.87 mmol) in CH_2Cl_2 (8.0 ml) at 0 °C, 1 M aqueous solution of CSA (1.0 ml) was added dropwise. After 30 min stirring at room temperature, TEBABr (16 mg, 5 mol%) was added to the mixture, and stirred for 1.5 h. Worked up by addition of $CHCl_3$ and satd aq NH_4Cl, the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **7** (230 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.89 (t, 3H, J=0.9 Hz, CH_3), 2.98 (dd, 1H, J=9.2, 13.5 Hz, CH_2), 2.99 (bs, 1H, OH), 3.20 (dd, 1H, J=3.3, 13.5 Hz, CH_2), 3.94 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.32 (td, 1H, J=3.3, 9.2 Hz, CH(OH)), 4.86 (quint, 1H, J=0.9 Hz, C=CH_2), 5.06 (quint, 1H, J=0.9 Hz, C=CH_2), 7.42—7.49 (m, 2H, ArH), 7.99—8.01 (m, 1H, ArH), 8.09—8.11 (m, 1H, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.1 (CH_3), 31.8 (CH_2), 60.8 (CH_3), 60.9 (CH_3), 62.1 (CH_3), 76.4 (CH), 110.2 (C=CH_2), 121.7 (CH), 122.2 (CH), 124.1 (C), 125.1 (CH), 125.3 (C), 126.0 (CH), 128.8 (C), 143.7 (C), 147.8 (C), 148.0 (C), 150.7 (C=CH_2). HR-MS (EI^+) *m*/*z*: Calcd for $C_{18}H_{22}O_4$: 302.1518; Found: 302.1518.

(±)-2-Isopropenyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (Dehydroiso-β-lapachone) (*rac*-1) To a stirred solution of **7** (115 mg, 0.38 mmol) in CH_3CN (acetonitrile) (6.0 ml) at 0 °C, CAN (548 mg, 1.0 mmol) in water (3.6 ml) was added dropwise. Red-orange solution was stirred at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed three times with water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt : *n*-hexane=1 : 1) to provide *rac*-**1** as a red solid (61 mg, 67%). mp 98 °C (lit. 97 °C).[5] ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.81 (t, 3H, J=0.9 Hz, H-12), 2.97 (dd, 1H, J=7.8, 15.6 Hz, H-3), 3.30 (dd, 1H, J=10.5, 15.6 Hz, H-3), 5.03 (quint, 1H, J=0.9 Hz, H-11), 5.14 (quint, 1H, J=0.9 Hz, H-11), 5.49 (dd, 1H, J=7.8, 10.5 Hz, H-2), 7.59 (td, 1H, J=1.4, 7.3 Hz, H-7), 7.66 (td, 1H, J=1.4, 7.3 Hz, H-8), 7.69 (dd, 1H, J=1.4, 7.3 Hz, H-9), 8.10 (dd, 1H, J=1.4, 7.3 Hz, H-6). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 16.9 (C-12), 31.2 (C-3), 90.0 (C-2), 113.8 (C-11), 115.3 (C-3a), 124.5 (C-9), 127.5 (C-5a), 129.6 (C-6), 130.9 (C-9a), 132.0 (C-7), 134.5 (C-8), 142.0 (C-10), 169.7 (C-9b), 175.4 (C-4), 181.1 (C-5). IR (KBr) cm^{-1}: 1699, 1656, 1635, 1616, 1586. HR-MS (EI^+): *m*/*z* Calcd for $C_{15}H_{12}O_3$: 240.0786; Found: 240.0781.

(*R*)-3-((3,3-Dimethyloxiran-2-yl)methyl)-1,2,4-trimethoxynaphthalene [(*R*)-2] The compound **3** (286 mg, 1.0 mmol) was dissolved in acetonitrile/dimetoxymethane (CH_3CN/DMM) (15 ml, 1 : 2 v/v). Buffer [10 ml, 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aq. Na_2 ethylenediamine tetraacetate (EDTA)], tetrabutylammonium hydrogen sulfate (14 mg, 0.04 mmol) and Shi epoxidation diketal catalyst (78 mg, 0.3 mmol) were added with stirring. The mixture was cooled to −10 °C. A solution of Oxone (853 mg, 1.4 mmol) in 4×10^{-4} M aq. Na_2(EDTA) (7 ml) and 0.83 M aq. K_2CO_3 (7 ml) were added dropwise separately over a period of 3.5 h. After stirring for 30 min, the mixture was quenched by addition of $CHCl_3$ and water. The mixture was extracted with $CHCl_3$ (30 ml×3), washed with water, dried over $MgSO_4$, purified by flash chromatography to afford enantioenriched (*R*)-**2** as a yellow oil (287 g, 95% yield). The enantiomeric excess was found to be 40% and was obtained by HPLC on a Chiralpak IC column (250×4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 97/3 as eluent (flow rate 1.0 ml/min) at 254 nm. The major enantiomer was eluted after 6.7 min, and the minor enantiomer was eluted after 11.3 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.02 (dd, 1H, J=5.1, 12.0 Hz, CH_2), 3.06 (dd, 1H, J=5.1, 4.7 Hz, CH_2), 3.13 (dd, 1H, J=4.7, 12.0 Hz, CH), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.43 (td, 1H, J=14.0, 7.0 Hz, ArH), 8.02 (dd, 1H, J=1.4, 7.0 Hz, ArH), 8.10 (dd, 1H, J=1.4, 7.0 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 19.0 (CH_3), 24.8 (CH_3), 24.9 (CH_2), 59.1 (C), 60.7 (CH_3), 60.9 (CH_3), 62.4 (CH_3), 64.1 (CH), 121.6 (CH), 122.2 (CH), 123.5 (C), 125.0 (CH), 125.4 (C), 125.9 (CH), 128.8 (C), 143.5 (C), 148.3 (C), 150.8 (C). HR-MS (EI^+) *m*/*z*: Calcd for $C_{18}H_{22}O_4$: 302.1518; Found: 302.1517. $[\alpha]_D^{25}$ −12.04 (c=0.96, $CHCl_3$).

(*R*)-1-[3-(*tert*-Butyldimethylsilyloxy)-1,4-dimethoxynaphthalen-2-yl]-3-methylbut-3-en-2-ol (10) To a stirred solution of **9**[1] (100 mg, 0.25 mmol) in CH_2Cl_2 (2.5 ml) at 0 °C, 1 M aqueous solution of CSA (0.25 ml) was added dropwise. After 30 min stirring at room temperature, TEBABr (7 mg, 5 mol%) was added to the mixture, and stirred for 1.5 h. Worked up by addition of $CHCl_3$ and satd aq NH_4Cl, the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to provide **10** (92 mg, 92%). The enantiomeric excess was found to be 82% and was obtained by HPLC on a Chiralpak IC column (250×4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 97/3 as eluent (flow rate 1.0 ml/min) at 254 nm. The major enantiomer was eluted after 5.5 min, and the minor enantiomer was eluted after 5.1 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.25 (t, 3H, J=0.9 Hz, CH_3), 0.27 (s, 3H, CH_3), 1.03 (s, 9H, $C(CH_3)_3$) 1.87 (t, 3H, J=0.9 Hz, CH_3), 2.88 (d, 1H, J=3.3 Hz, OH), 3.06 (dd, 1H, J=9.5, 13.5 Hz, CH_2), 3.20 (dd, 1H, J=3.3, 13.5 Hz, CH_2), 3.81 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.35 (td, 1H, J=3.3, 9.5 Hz, CH), 4.84 (quint, 1H, J=0.9 Hz, C=CH_2), 5.02 (quint, 1H, J=0.9 Hz, C=CH_2), 7.40 (td, 2H, J=1.5, 7.0 Hz, ArH), 7.46 (td, 1H, J=1.5, 7.0 Hz, ArH), 7.99 (dd, 1H, J=1.5, 7.0 Hz, ArH), 8.20 (dd, 1H, J=1.5, 7.0 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ −3.91 (CH_3), −3.80 (CH_3), 18.0 (CH_3), 18.8 (C), 26.2(3C) (CH_3), 31.8 (CH_2), 61.1 (CH_3), 62.1 (CH_3), 76.2 (CH), 110.8 (C=CH_2), 121.6 (CH), 122.3 (CH), 123.7 (C), 124.3 (CH), 124.4 (C), 126.0 (CH), 128.4 (C), 141.7 (C), 144.0 (C), 147.7 (C), 151.2 (C=CH_2). HR-MS (EI^+) *m*/*z*: Calcd for $C_{23}H_{34}O_4Si$: 402.2226; Found: 402.2208. $[\alpha]_D^{25}$ +31.85 (c=0.98, $CHCl_3$).

(*R*)-(−)-Dehydroiso-β-lapachone [(*R*)-1] To a stirred solution of **10** (643 mg, 1.6 mmol) in THF (18 ml), AcOH (acetic acid) (0.18 ml, 3.1 mmol) and TBAF (2.2 ml, 2.2 mmol) was slowly added at 0 °C. The reaction was completed within a few minutes, and the mixture was poured into water with crushed ice. The mixture was extracted twice with AcOEt, and the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide the enantioenriched desilylated naphthol derivative

(461 mg, quant.). The enantiomeric excess was found to be 82% and was obtained by HPLC on a Chiralpak IA column (250×4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 90/10 as eluent (flow rate 1.0 ml/min) at 254 nm. The major enantiomer was eluted after 10.3 min, and the minor enantiomer was eluted after 9.8 min. mp 98—101 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.90 (t, 3H, J=0.9 Hz, CH_3), 2.61 (d, 1H, J=3.3 Hz, OH), 3.03 (dd, 1H, J=9.2, 13.9 Hz, CH_2), 3.27 (dd, 1H, J=3.3, 13.9 Hz, CH_2), 3.92 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.43 (td, 1H, J=3.3, 9.2 Hz, CH), 4.88 (quint, 1H, J=0.9 Hz, C=CH_2), 5.06 (quint, 1H, J=0.9 Hz, C=CH_2), 6.95 (s, 1H, OH), 7.35 (dd, 1H, J=1.4, 7.3 Hz, ArH), 7.46 (dd, 1H, J=1.4, 7.3 Hz, ArH), 7.97 (dd, 1H, J=1.4, 7.3 Hz, ArH), 7.99 (dd, 1H, J=1.4, 7.3 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.1 (CH_3), 31.3 (CH_2), 61.4 (CH_3), 62.3 (CH_3), 76.9 (CH), 110.7 (CH_2), 120.4 (C), 120.8 (CH), 122.5 (CH), 123.1 (C), 123.6 (CH), 126.1 (CH), 127.9 (C), 137.5 (C), 145.1 (C), 147.3 (C), 151.1 (C). HR-MS (EI^+) m/z: Calcd for $C_{17}H_{20}O_4$: 288.1362; Found: 288.1364. $[\alpha]_D^{23}$ +38.83 (c=1.0, $CHCl_3$).

To a stirred solution of the naphthol derivative (72 mg, 0.25 mmol) described above in CH_3CN (4.2 ml) at 0 °C, CAN (343 mg, 0.63 mmol) in water (2.5 ml) was added dropwise. Red-orange solution was stirred for 1 h at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to provide (*R*)-**1** (39.8 mg, 66% yield). mp 97 °C. The enantiomeric excess was found to be 82% and was obtained by HPLC on a Chiralpak AD-H column (250×4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 60/40 as eluent (flow rate 1.0 ml/min) at 254 nm. The major enantiomer was eluted after 5.7 min, and the minor enantiomer was eluted after 5.2 min. $[\alpha]_D^{23}$ −52.3 (c=0.3, $CHCl_3$).

References and Notes

1) Kimachi T., Torii E., Ishimoto R., Sakue A., Ju-ichi M., *Tetrahedron: Asymmetry*, **20**, 1683—1689 (2009).
2) Gotoh A., Sakaeda T., Kimura T., Shirakawa T., Wada Y., Wada A., Kimachi T., Kakemoto Y., Iida A., Hirai M., Tomita H., Okamura N., Nakamura T., Okumura K., *Biol. Pharm. Bull.*, **27**, 1070—1074 (2004).
3) Rennie E. H., *J. Chem. Soc.*, **67**, 784—793 (1895).
4) Hooker S. C., *J. Am. Chem. Soc.*, **58**, 1181—1190 (1936).
5) Hayashi K., Chang F.-R., Nakanishi Y., Bastow K. F., Cragg G., McPhail A. T., Nozaki H., Lee K.-H., *J. Nat. Prod.*, **67**, 990—993 (2004).
6) Gupta R. B., Khanna R. N., *Indian J. Chem.* **19B**, 17—19 (1980).
7) Kongkathip N., Kongkathip B., Siripong P., Sangma C., Luangkamin S., Niyomdecha M., Pattanapa S., Piyaviriyagu S., Kongsaeree P., *Bioorg. Med. Chem.*, **11**, 3179—3191 (2003).
8) Singh P., Krishna V., Khandelwal P., Sharma K. K., Sharma M. C., *J. Indian Chem. Soc.*, **87**, 85—95 (2010).
9) The compound **4** was also prepared from lawsone (**5**) by the known procedure. See Kraus G. A., Man T. O., *Synth. Commun.*, **16**, 1037—1042 (1986).
10) Without addition of TEBABr, compound **7** was obtained in 3—4% yield. It is obvious that the addition of TEBABr facilitates the acid-catalyzed epoxide ring-opening reaction, but we need further investigation to confirm the actual role of TEBABr.
11) A trace amount of *rac*-**1** isomer, (isopropenylfurano-2,3-naphthoquinone, dehydroiso-α-lapachone) was also obtained. We are proposing that the acidic cyclization of the naphthoquinone alcohol intermediate derived from initial CAN oxidation of **7** provided the desired *rac*-**1**. Kongkathip's results that acid catalyzed cyclization of 1,4-naphthoquinone precursors preferentially afforded furano-1,2-naphthoquinones are consistent with our results. See ref. 7.
12) Kizu H., Habe S., Ishida M., Tomimori T., *Yakugaku Zasshi,* **114**, 492—513 (1994).
13) Heltzel C. E., Gunatilaka A. A. L., Glass T. E., Kingston D. G. I., *J. Nat. Prod.*, **56**, 1500—1505 (1993).
14) Wong O. A., Shi Y., *Chem. Rev.*, **108**, 3958—3987 (2008), and references cited therein.