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Improved Procedure for the Enantiometric Synthesis of 1-Hydroxy/acetoxy-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane Lignans: Total Syntheses of (+)-Paulownin, (+)-Phrymarin I and (+)-Phrymarin II

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Short enantiomeric syntheses of the 1-hydroxy/acetoxy-3,7-dioxabicyclo[3.3.0]octane lignans, (+)-paulownin, and (+)-phrymarin I and II, were accomplished by starting from the chiral synthon, (*R*)-(+)-3-hydroxybutanolide, and employing photocyclization as the key step.

Key words: enantiomeric synthesis; (+)-paulownin; (+)-phrymarin I; (+)-phrymarin II; photocyclization

Lignans of the 3,7-dioxabicyclo[3.3.0]octane (furofuran) type have been challenging targets for organic synthesis[1] due to the important biological activities[2] exhibited by some members of this class. While several methods for the asymmetric synthesis of non-oxidized 3,7-dioxabicyclo[3.3.0]octane lignans have been reported,[3] only a few syntheses of lignans of the 1-hydroxy/acetoxy-3,7-dioxabicyclo[3.3.0]octane subgroup have appeared. We have reported in a recent paper[4] the first but lengthy enantiomeric synthesis of (+)-paulownin starting from the chiral synthon, (*R*)-(+)-3-hydroxybutanolide.

In this paper, we describe an improved and more efficient method for enantiomeric syntheses of the 1-hydroxy/acetoxy-3,7-dioxabicyclo[3.3.0]octane lignans, (+)-paulownin[5] (**1a**), (+)-phrymarin I[6] (**2**) and (+)-phrymarin II[6] (**3**) by a modification of our previous synthesis.

Kraus and Chen have reported[7] the synthesis of racemic **1a** by using type II photocyclization of (±)-**4a** as the key step (**Scheme 1, Route A**). Thus, the enantiometric synthesis of **1a** should be accomplished if intermediate **4a** were provided in its optically active form. In our previous synthesis of (+)-**1a**,[4] we developed a method for stereoselectively constructing 2-aryl-4-hydroxy-3-hydroxymethyltetrahydrofuran (**6a**)[8] from (*R*)-(+)-3-hydroxybutanolide (**5**)[9] (**Scheme 1, Route B**). In the present synthesis, tetrahydrofuran **6a** was transformed to Kraus intermediate **4a** and the photocyclization reaction was applied.

Materials and Methods

General methods. All melting point (mp) data are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard by a Varian Gemini 200 or Gemini 300 spectrometer at 200 and 300 MHz, respectively. Mass spectra were measured with a Jeol JMS-DX303 spectrometer, and optical rotation values were measured with a Jasco DIP-370 polarimeter.

2 - Methoxy - 4,5 - methylenedioxyphenylmethyl trichloroacetimidate (9b). To a stirred suspension of 60% NaH in oil (25 mg, 0.63 mmol, washed with dry hexane) in dry ether (5 ml), a solution of 2-methoxy-4,5-methylenedioxyphenylmethyl alcohol (0.50 g, 2.75 mmol) in dry THF (10 ml) was added dropwise. After stirring for 20 min at room temperature, trichloroacetonitrile (0.276 ml, 2.75 mmol) was added at 0°C. The mixture was stirred for 2 h at 20°C and concentrated *in vacuo*. Dichloromethane (10 ml) containing a few drops of MeOH was added to the resulting residue, and the whole was stirred for a short period before being filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford the imidate as a pale viscous oil (0.65 g, 1.99 mmol, 72%), this being used for the next step without further purification. ^{1}H-NMR (200 MHz) δ: 3.79 (3H, s, OCH_3), 5.28 (2H, s, Ar-CH_2-OC(=NH)CCl_3), 5.94 (2H, s, -OCH_2O-), 6.55 (1H, s, Ar-*H*), 6.93 (1H, s, Ar-*H*), 8.35 (1H, br s, C=N*H*).

3,4-Methylenedioxyphenylmethyl trichloroacetimidate (9a). The title compound was prepared by the same procedure as that applied for **9b** and used

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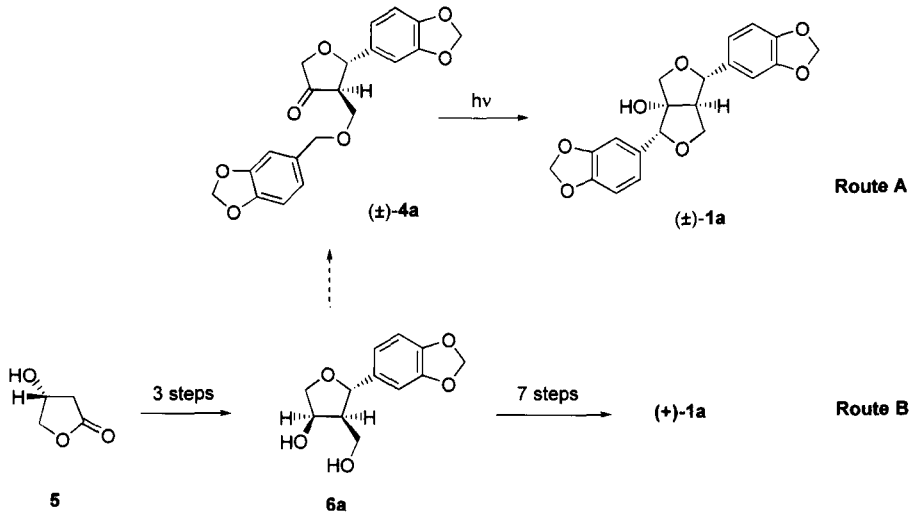
Abbreviations: LDA, lithium diisopropylamide; THF, tetrahydrofuran; *p*-Ts, *p*-toluenesulfonyl; DMSO, dimethylsulfoxide; DMAP, *N*,*N*-dimethylaminopyridine



Scheme 1.

without purification.

(2S, 3S, 4R)-4-Hydroxy-2-(3,4-methylenedioxyphenyl)-3-[(3,4-methylenedioxyphenyl)methoxymethyl]tetrahydrofuran (10a). A solution of diol **6a**[4] (0.7343 g, 3.802 mmol), imidate **9a** (1.4550 g, 4.908 mmol) and a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (50 ml) was stirred at room temperature for 17 h. A few drops of Et_3N was added, and the mixture was concentrated. The residue was chromatographed on silica gel (hexane:EtOAc = 2:1–1:1) to give **10a** as a pale viscous oil (0.790 g, 2.14 mmol, 69%). ^{1}H-NMR (300 MHz) δ: 2.18 (1H, m, H-3), 2.93 (1H, d, J = 3.7 Hz, -O*H*), 3.69–3.56 (2H, m, -CH_2OCH$_2$Ar), 3.87 (1H, dd, J = 9.7, 1.9 Hz, H-5), 4.27 (1H, dd, J = 9.7, 4.6 Hz, H-5), 4.34 (1H, d, J = 11.6 Hz, ArC*H*-O-), 4.46 (1H, d, J = 11.6 Hz, ArC*H*-O-), 4.59 (1H, m, H-4), 4.73 (1H, d, J = 10.0 Hz, H-2), 5.94 (2H, s, -OCH_2O-), 5.96 (2H, s, -OCH_2O-), 6.71–6.80 (6H, m). *Anal.* Found: C, 64.23; H, 5.51%. Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

(2S,3S,4R)-4-Hydroxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-3-[(3,4-methylenedioxyphenyl)methoxymethyl]tetrahydrofuran (10b). The title compound was synthesized from **6b**[8] and **9a** by the same procedure as that used for **10a** in a 48% yield. ^{1}H-NMR (300 MHz) δ: 2.34–2.55 (1H, m, H-3), 2.87 (1H, br, -O*H*), 3.63 (1H, dd, J = 9.60, 4.41 Hz, -C*H*-OCH$_2$Ar), 3.72 (3H, s, -OCH$_3$), 3.73 (1H, m, C*H*-OCH$_2$Ar), 3.87 (1H, dd, J = 9.6, 2.5 Hz, H-5), 4.26 (1H, dd, J = 9.6, 4.7 Hz, H-5), 4.37 (1H, d, J = 11.3 Hz, ArC*H*-O-), 4.44 (1H, d, J = 11.3 Hz, ArC*H*-O-), 4.59 (1H, m, H-4), 5.14 (1H, d, J = 9.4 Hz, H-2), 5.90 (2H, s, -OCH_2O-), 5.95 (2H, s, -OCH_2O-), 6.50 (1H, s, H-3′), 6.77–6.81 (3H, m, H-2″, 5″, 6″), 6.85 (1H, s, H-6′). *Anal.* Found: C, 62.30; H, 5.57%. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51%.

(2S,3S,4R)-4-Hydroxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-3-[(2-methoxy-4,5-methylenedioxyphenyl)methoxymethyl]tetrahydrofuran (10c). The title compound was synthesized from **6b**[8] and **9b** by the same procedure as that used for **10a** in a 41% yield. ^{1}H-NMR (300 MHz) δ: 2.37–2.23 (1H, m, H-3), 3.29 (1H, br, -O*H*), 3.60–3.80 (2H, m, -CH_2OCH$_2$Ar), 3.74 (3H, s, -OCH$_3$), 3.79 (3H, s, -OCH$_3$), 3.85 (1H, dd, J = 9.6, 4.1 Hz, H-5), 4.27 (1H, dd, J = 9.6, 5.0 Hz, H-5), 4.42 (2H, s, Ar-CH_2-O-), 4.61–4.56 (1H, m, H-4), 5.09 (1H, d, J = 9.3 Hz, H-2), 5.84 (2H, s, -OCH_2O-), 5.86 (2H, s, -OCH_2O-), 6.50 (1H, s, H-3″), 6.55 (1H, s, H-3′), 6.76 (1H, s, H-6″), 6.86 (1H, s, H-6′). *Anal.* Found: C, 61.27; H, 5.71%. Calcd. for $C_{22}H_{24}O_9$: C, 61.11; H, 5.59%.

(4R, 5S)-5-(3,4-Methylenedioxyphenyl)-4-[(3,4-methylenedioxyphenyl) methoxymethyl]dihydro-3(2H)-furanone (4a). To a cooled (−78°C) and stirred solution of oxalyl chloride (0.37 ml, 4.20 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise a solution of DMSO (0.52 ml, 7.30 mmol) in CH_2Cl_2 (3 ml) under Ar. After 10 min, alcohol **10a** (779 mg, 2.09 mmol) dissolved in CH_2Cl_2 (8 ml) was added dropwise. After stirring at −78°C for 15 min, the mixture was gradually warmed to −45°C and kept at that temperature for 1 h. Triethylamine (2.10 ml, 15.2 mmol) was then added, and the mixture was stirred at 0°C for 20 min. The reaction was quenched by adding a 4 M HCl solution (30 ml), and the whole was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 extract was washed with a 5% $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hex-

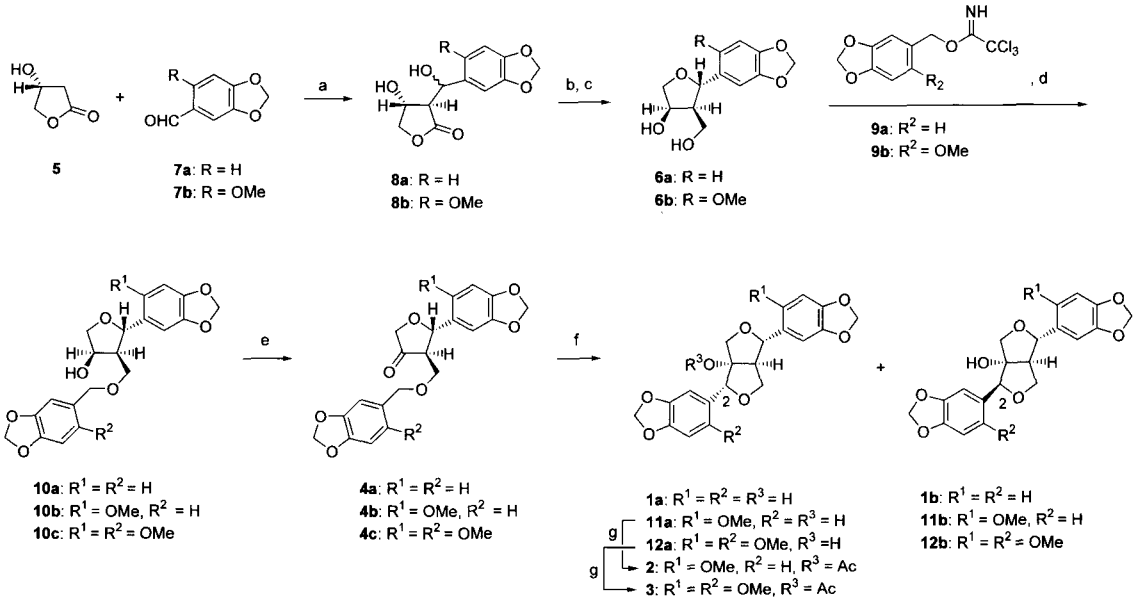
ane:EtOAc = 3:1) to give furanone **4a** (736 mg, 2.01 mmol, 96%) as a pale oil. ^{1}H-NMR (300 MHz) δ: 2.40–2.44 (1H, m, H-4), 3.50 (1H, dd, J = 9.7, 3.3 Hz, -C*H*OCH$_2$Ar), 3.84 (1H, dd, J = 9.7, 3.8 Hz, -C*H*OCH$_2$Ar), 3.98 (1H, d, J = 17.0 Hz, Ar-C*H*-O-), 4.31 (1H, dd, J = 17.0, 1.0 Hz, Ar-C*H*-O-), 4.32 (1H, d, J = 11.5 Hz, H-2), 4.43 (1H, d, J = 11.5 Hz, H-2), 5.11 (1H, d, J = 9.9 Hz, H-5), 5.96 (2H, s, -OC*H*$_2$O-), 5.97 (2H, s, -OC*H*$_2$O-), 6.86–6.73 (6H, m, Ar-*H*s). *Anal.* Found: C, 64.42; H, 5.08%. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%.

(4R,5S)-5-(2-Methoxy-4,5-methylenedioxyphenyl)-4-[(3, 4-methylenedioxyphenyl)methoxymethyl]dihydro-3(2H)-furanone (4b). The title compound was obtained from **10b** in an 85% yield by the same procedure as that used for **4a** as a pale viscous oil. ^{1}H-NMR (300 MHz) δ: 2.64–2.54 (1H, m, H-4), 3.58 (1H, dd, J = 9.5, 3.3 Hz, -C*H*OCH$_2$Ar), 3.75 (3H, s, -OC*H*$_3$), 3.81 (1H, dd, J = 9.5, 4.2 Hz, -C*H*OCH$_2$Ar), 4.00 (1H, d, J = 17.0 Hz, Ar-C*H*-O-), 4.28 (1H, dd, J = 17.0, 1.0 Hz, Ar-C*H*-O-), 4.36 (1H, d, J = 11.7 Hz, H-2), 4.42 (1H, d, J = 11.7 Hz, H-2), 5.53 (1H, d, J = 8.9 Hz, H-5), 5.94 (2H, s, -OC*H*$_2$O-), 5.95 (2H, s, -OC*H*$_2$O-), 6.54 (1H, s, H-3′), 6.80–6.68 (3H, m, H-2″, 5″, 6″), 6.92 (1H, s, H-6′). *Anal.* Found: C, 62.93; H, 5.07%. Calcd. for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03%.

(4R,5S)-5-(2-Methoxy-4,5-methylenedioxyphenyl)-4-[(2-methoxy-4,5-methylenedioxyphenyl)methoxymethyl]dihydro-3(2H)-furanone (4c). The title compound was obtained from **10c** in a 98% yield in the same procedure as that used for **4a** as white crystals, mp 111–112°C (ether). ^{1}H-NMR (300 MHz) δ: 2.62–2.58 (1H, m, H-4), 3.63 (1H, dd, J = 9.5, 3.4 Hz, -C*H*OCH$_2$Ar), 3.74 (6H, s, -OC*H*$_3$ × 2), 3.85 (1H, dd, J = 9.2, 4.4 Hz, -C*H*OCH$_2$Ar), 4.01 (1H, d, J = 16.8 Hz, Ar-C*H*-O-), 4.28 (1H, d, J = 16.8 Hz, Ar-C*H*-O-), 4.44 (2H, s, H-2), 5.54 (1H, d, J = 8.8 Hz, H-5), 5.94–5.90 (4H, m, -OC*H*$_2$O- × 2), 6.50 (1H, s, H-3″), 6.54 (1H, s, H-3′), 6.79 (1H, s, H-6″), 6.91 (1H, s, H-6′). *Anal.* Found: C, 61.11; H, 5.13 %. Calcd. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15%.

(+)-Paulownin (1a). Furanone **4a** (193 mg, 0.521 mmol) was dissolved in distilled benzene (230 ml), and a few drops of a solution of rose bengal in MeOH (*ca.* 50 mg/ml) were added. The solution was thoroughly degassed by sonicating under Ar for 5 min. The solution was charged in a photoreaction vessel (Riko-kagaku Sangyo Co.) and irradiated with a 100 W high-pressure mercury lump (Riko-kagaku Sangyo Co.) at room temperature under a stream of Ar for 2 h. The solution was concentrated *in vacuo*, and the resulting residue was chromatographed on silica gel (hexane:EtOAc = 2:1) to give a mixture (2α:2β = 91:9, based on NMR) of **1a** and **1b** (80.2 mg, 0.217 mmol, 42%) along with unreacted **4a** (64.4 mg, 33%). This epimeric mixture was separable by silica gel TLC ($CHCl_3$:MeOH = 98:2). (+)-Paulownin (**1a**): White needles, mp 106–107°C (EtOAc-hexane), $[\alpha]_D^{26}$ +26.5° (*c* 0.92, $CHCl_3$) [lit.[5] $[\alpha]_D$ +29.0° (*c* 1.0, $CHCl_3$)]. ^{1}H-NMR (300 MHz) δ: 1.74 (1H, s, -O*H*), 2.99–3.06 (1H, m, H-5), 3.81 (1H, dd, J = 9.2, 6.2 Hz, H-4β), 3.88 (1H, d, J = 9.4 Hz, H-8β), 4.02 (1H, d, J = 9.4 Hz, H-8α), 4.49 (1H, dd, J = 9.2, 8.1 Hz, H-4α), 4.79 (1H, s, H-2), 4.83 (1H, d, J = 5.1 Hz, H-6), 5.95 (2H, s, -OC*H*$_2$O-), 5.97 (2H, s, -OC*H*$_2$O-), 6.77–6.94 (6H, m, Ar-*H*s). EIMS *m/z*: 370 (M^+, 20), 235 (5), 220 (11), 205 (68), 164 (23), 149 (100), 131 (72), 103 (52). *Anal.* Found: C, 64.65; H, 4.95%. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%. 2β-Epimer (**1b**, neopaulownin): Yellow gum, $[\alpha]_D^{26}$ +42.0° (*c* 0.10, $CHCl_3$). ^{1}H-NMR (300 MHz) δ: 2.29 (1H, br, OH), 2.63 (1H, m, H-5), 3.49 (1H, d, J = 10.9 Hz, H-8β), 3.63 (1H, d, J = 10.9 Hz, H-8α), 4.00 (1H, dd, J = 9.7, 1.4 Hz, H-4β), 4.11 (1H, dd, J = 9.7, 6.5 Hz, H-4α), 4.43 (1H, d, J = 7.9 Hz, H-6), 4.70 (1H, s, H-2), 5.96 (2H, s, -OC*H*$_2$O-), 5.97 (2H, s, -OC*H*$_2$O-), 6.76–6.86 (3H, m, Ar-*H*s), 6.90–6.99 (3H, m, Ar-*H*s).

(1S, 2R, 5R, 6S)-1-Hydroxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-2-(3, 4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (11a). A degassed (sonicated) solution of furanone **4b** (48.8 mg, 0.123 mmol) in benzene (230 ml) containing a trace amount of rose bengal was irradiated for 30 min at room temperature under Ar as just described for **1a**. The solution was concentrated, and the resulting residue was purified by silica gel TLC (benzene:EtOAc = 5:1) to give an epimeric mixture of **11a** and **11b** (α/β = 71/29, based on NMR, 14.2 mg, 29%). This mixture was separated by silica gel TLC ($CHCl_3$:MeOH = 95:5). **11a**: White crystals, mp 67–68°C. ^{1}H-NMR (300 MHz) δ: 1.68 (1H, br, -O*H*), 2.92–2.85 (1H, m, H-5), 3.76 (1H, dd, J = 6.5, 5.0 Hz, H-4β), 3.77 (3H, s, -OC*H*$_3$), 3.92 (1H, d, J = 9.3 Hz, H-8β), 3.95 (1H, dd, J = 9.4, 6.5 Hz, H-4α), 4.05 (1H, d, J = 9.3 Hz, H-8α), 4.77 (1H, s, H-2), 5.09 (1H, d, J = 5.0 Hz, H-6), 5.91 (1H, d, J = 1.4 Hz, -OC*H*O-), 5.92 (1H, d, J = 1.4 Hz, -OC*H*O-), 5.97 (2H, s, -OC*H*$_2$O-), 6.54 (1H, s, H-3′), 6.80–6.68 (3H, m, H-2″, 5″, 6″), 6.92 (1H, s, H-6′). EIMS *m/z*: 400 (M^+), 266, 191, 165, 151, 150, 149 (base), 135, 84. HRMS *m/z* (M^+): calcd. for $C_{21}H_{20}O_8$, 400.116; found, 400.115. **11b**: Yellow gum. ^{1}H-NMR (300 MHz) δ: 2.40 (1H, br, O*H*), 2.52–2.60 (1H, m, H-5), 3.49 (1H, d, J = 10.3 Hz, H-8β), 3.60 (1H, d, J = 10.3 Hz, H-8α), 3.79 (3H, s, OCH_3), 4.13 (1H, dd, J = 9.6, 6.9 Hz, H-4β), 4.20 (1H, dd, J = 9.6, 2.0 Hz, H-4α), 4.69 (1H, s, H-2), 4.77 (1H, d, J = 7.2 Hz, H-6), 5.91 (2H, s,



Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C (80% for **8a**, 83% for **8b**); (b) $LiAlH_4$, THF, −10°C to rt; (c) for **6a**, cat. *p*-TsOH, CH_2Cl_2, rt (73%); for **6b**, 2 M HCl, rt (84%); (d) cat. *p*-TsOH, CH_2Cl_2 (69% for **10a**, 48% for **10b**, 41% for **10c**); (e) $(COCl_2)$, DMSO, CH_2Cl_2, −78°C to −45°C then Et_3N, 0°C (96% for **4a**, 85% for **4b**, 98% for **4c**); (f) *hν*, benzene, cat. rose bengal (42% for **1a** and **1b**, 29% for **11a** and **11b**, 40% for **12a** and **12b**); (g) Ac_2O, cat. DMAP.

-OC*H*$_2$O-), 5.97 (2H, s, -OC*H*$_2$O-), 6.52 (1H, s, H-3′), 6.79 (1H, d, *J*=8.2 Hz, H-2″), 6.93-7.01 (2H, m, H-5″, 6″), 7.00 (1H, s, H-6′).

(1S, 2R, 5R, 6S)-1-Hydroxy-2,6-bis(2-methoxy-4,5-methylenedioxyphenyl) - 3, 7 - dioxabicyclo[3.3.0] octane (12a). By the same procedure as that used for **11a**, the photoreaction of furanone **4c** gave an epimeric mixture of **12a** and **12b** (α/β=79/21, based on NMR) in a 40% yield. This mixture was separated by silica gel TLC (toluene:EtOAc=4:1). **12a**: Yellow gum. ^{1}H-NMR (300 MHz) δ: 1.85-1.92 (1H, br, -O*H*), 2.84 (1H, m, H-5), 3.77 (3H, s, -OC*H*$_3$), 3.79 (3H, s, -OC*H*$_3$), 3.92 (1H, dd, *J*=6.9, 9.3 Hz, H-4β), 3.96 (1H, d, *J*=9.6 Hz, H-8β), 4.23 (1H, d, *J*=9.6 Hz, H-8α), 4.46 (1H, dd, *J*=9.3, 8.1 Hz, H-4α), 5.06 (1H, d, *J*=5.1 Hz, H-6), 5.12 (1H, s, H-2), 5.90 (1H, d, *J*=1.5 Hz, -OC*H*O-), 5.91 (1H, d, *J*=1.5 Hz, -OC*H*O-), 5.92 (1H, d, *J*=1.5 Hz, -OC*H*O-), 5.94 (1H, d, *J*=1.5 Hz, -OC*H*O-), 6.52 (1H, s, H-3′), 6.55 (1H, s, H-3″), 7.04 (1H, s, H-6′), 7.08 (1H, s, H-6″). HRMS *m/z* (M$^+$): calcd. for $C_{22}H_{22}O_9$, 430.126; found, 430.124. **12b**: Yellow gum. ^{1}H-NMR (300 MHz) δ: 2.60 (1H, m, H-5), 3.40 (1H, d, *J*=9.8 Hz, H-8β), 3.68 (1H, d, *J*=9.8 Hz, H-8α), 3.78 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 4.00 (1H, s, O*H*), 4.11 (1H, dd, *J*=9.5, 6.5 Hz, H-4β), 4.25 (1H, dd, *J*=9.5, 1.8 Hz, H-4α), 4.83 (1H, d, *J*=7.8 Hz, H-6), 4.93 (1H, s, H-2), 5.90 (2H, s, -OC*H*$_2$O-), 5.96 (2H, s, -OC*H*$_2$O-), 6.51 (1H, s, H-3′), 6.57 (1H, s, H-3″), 7.09 (1H, s, H-6′), 7.11 (1H, s, H-6″).

(+)-Phrymarin II (2). The second title compound was synthesized by standard acetylation (Ac_2O, cat. DMAP) of **11a**, $[\alpha]_D^{27}$ +8.9° (*c* 0.38, $CHCl_3$). ^{1}H-NMR (200 MHz) δ: 1.72 (3H, s, COC*H*$_3$), 3.08-3.20 (1H, m, H-5), 3.79 (3H, s, OC*H*$_3$), 3.92 (1H, dd, *J*=9.4, 5.1 Hz, H-4β), 4.28 (1H, d, *J*=10.7 Hz, H-8β), 4.44 (1H, dd, *J*=9.4, 8.1 Hz, H-4α), 4.44 (1H, d, *J*=10.7 Hz, H-8α), 4.99 (1H, s, H-2), 5.02 (1H, d, *J*=4.8 Hz, H-6), 5.93 (2H, s, -OC*H*$_2$O-), 5.94 (2H, s, -OC*H*$_2$O-), 6.54 (1H, s, H-3′), 6.75 (1H, d, *J*=8.4 Hz, H-2″), 6.79-6.88 (2H, m, H-5″, 6″), 6.99 (1H, s, H-6′). EIMS *m/z*: 442 (M$^+$), 202 (base), 191, 161, 135, 84, 49, 43. HRMS *m/z* (M$^+$): calcd. for $C_{23}H_{22}O_9$, 442.126; found, 442.125.

(+)-Phrymarin I (3). The third title compound was synthesized by standard acetylation (Ac_2O, cat. DMAP) of **12a**, $[\alpha]_D^{27}$ +28.2° (*c* 0.99, $CHCl_3$). ^{1}H-NMR (300 MHz) δ: 1.71 (3H, s, COC*H*$_3$), 3.13-3.21 (1H, m, H-5), 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.86 (1H, dd, *J*=9.0, 6.0 Hz, H-4β), 4.23 (1H, d, *J*=10.5 Hz, H-8β), 4.48 (1H, t, *J*=9.0 Hz, H-4α), 4.62 (1H, d, *J*=10.5 Hz, H-8α), 5.01 (1H, d, *J*=4.2 Hz, H-6), 5.40 (1H, s, H-2), 5.88 (2H, s, -OC*H*$_2$O-), 5.92 (2H, s, -OC*H*$_2$O-), 6.50 (1H, s, H-3′), 6.54 (1H, s, H-3″), 6.88 (1H, s, H-6′), 7.00 (1H, s, H-6″). MS *m/z*: 472 (M$^+$), 232 (base), 221, 179, 165, 147, 73, 57, 43. HRMS *m/z* (M$^+$): calcd. for $C_{24}H_{24}O_{10}$, 472.137; found, 472.136.

Results and Discussion

Diols **6a** and **6b** were prepared by the respective

Table 1. Photo-cyclization of Furanones **4a–c**
All reactions were performed in a photoreaction vessel illuminated by a 100 W high-pressure mercury lamp (Riko-Kagaku Sangyo Co.).

Run	Compound	Solvent	Time	Sensitizer	Products	Yield (%)	2α/2β
1	**4a**	benzene	2 h	none	**1a, b**	10	ND
2	**4a**	benzene	2 h	rose bengal	**1a, b**	42	91/9
3	**4a**	benzene	1 h	rose bengal	**1a, b**	26	89/11
4	**4b**	benzene	0.5 h	rose bengal	**11a, b**	29	71/21
5	**4b**	benzene	1 h	rose bengal	**11a, b**	23	61/39
6	**4b**	benzene	3 h	rose bengal	**11a, b**	17	ND
7	**4b**	benzene	3 h	none	**11a, b**	9	ND
8	**4b**	acetone	1 h	rose bengal	**11a, b**	0	ND
9	**4c**	benzene	0.5 h	rose bengal	**12a, b**	40	79/21
10	**4c**	benzene	1 h	rose bengal	**12a, b**	25	76/24

ND: not determined.

condensation of (*R*)-(+)-3-hydroxybutanolide (**5**) with aldehydes **7a** and **7b**, and subsequent reduction and dehydrative cyclization in the same manner as that described previously.[4,8] The primary hydroxyl groups of **6a** and **6b** were selectively benzylated by the imidate method[10] to afford **10a–c** in good yields. The usual etherification procedure, using (3,4-methylenedioxy)benzyl bromide in the presence of potassium hydride and a catalytic amount of 18-crown-6, showed no selectivity between the two hydroxyl groups and resulted in a mixture of benzyl ethers. The secondary hydroxyl groups of **10a–c** were oxidized by Swern's procedure to respectively give 3-furanones **4a–c** in high yields.

The 1-hydroxy-3,7-dioxabicyclo[3.3.0]octane framework was constructed by the photoreaction of furanons **4a–c**. Although Kraus and Chen[7] have employed a medium-pressure Hanovia lamp in the photocyclization process, we used an easily available 100 W high-pressure mercury lamp instead, and performed the reactions by varying the solvent and reaction time with or without a sensitizer (Table 1). Although some loss in yield was observed compared with the result of Kraus and Chen (68% yield for the reaction of racemic **4a**), we demonstrated that a high-pressure mercury lamp is also suitable for this reaction. We also found that the addition of a sensitizer such as rose bengal accelerated the reaction. Prolonging the reaction time and using acetone as the solvent instead of benzene resulted in a markedly lower yield due to decomposition of the product. The specific rotation value of (+)-paulownin (**1a**) thus obtained was $[\alpha]_D^{27}$ +26.5° [lit.[5] $[\alpha]_D^{25}$ +29.0°], showing high optical purity (91% ee). (+)-Phrymarin II (**2**) and (+)-phrymarin I (**3**) were also synthesized by acetylating **11a** and **12a**, respectively.

In conclusion, we improved our previous synthesis of (+)-paulownin and developed an efficient and short enantiomeric synthesis of 1-hydroxy/acetoxy-3,7-dioxabicyclo[3.3.0]octane lignans.

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