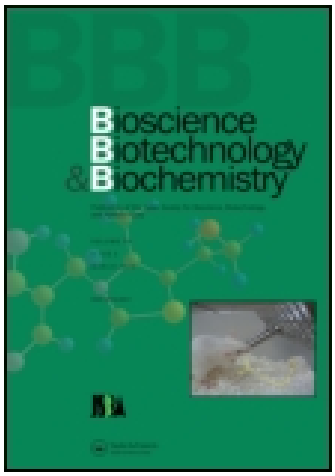

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Total Synthesis of (+)-Phrymarolin I from (+)-Malic Acid

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Total Synthesis of (+)-Phrymarolin I from (+)-Malic Acid

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(+)-Phrymarolin I was stereoselectively synthesized from (*R*)-(+)-3-hydroxybutanolide that had been prepared from (+)-malic acid. The procedure is more efficient than our previous synthesis in terms of fewer reaction steps and the easier availability of the starting material.

Key words: stereoselective synthesis; (+)-phrymarolin I; furofuran lignan; (*R*)-(+)-3-hydroxybutanolide

The herbaceous perennial plant, *Phryma leptostachya* L., is the only known source of unique 1-hydroxy/acetoxy-2-aryloxy-6-aryl-3,7-dioxabicyclo[3.3.0]octane lignans,[1] including such highly insecticidal sesquilignans as haedoxan A (**3**).[2] The first construction of the framework was accomplished by us in the synthesis of the simplest member, (±)-phrymarolin II (**2**),[3] and the strategy was extended to the synthesis of the sesquilignans, (±)-haedoxan A, D, and E.[4] We also succeeded in synthesizing optically active (+)-phrymarolin I (**1**)[5] from (*S*)-(+)-3-vinylbutanolide which enabled us to establish the (1*S*,2*R*,5*R*,6*S*) configuration for natural **1**. However, the synthesis required many steps and an optical resolution procedure for preparing the chiral synthon. In this paper, we will describe an alternative and shorter approach to (+)-**1** from (*R*)-(+)-3-hydroxybutanolide (**4**) which is readily accessible *via* regioselective reduction of (*R*)-(+)-malate[6a] or microbial reduction of 4-*tert*-butoxyacetoacetate.[6b]

The lithium enolate of (*R*)-(+)-**4**, which had been prepared from (*R*)-(+)-dimethyl malate according to Saito's procedure,[6a] was generated with 2.2 equiv. of diisopropylamide (LDA) in THF at −78°C and then by the reaction with 2-methoxy-4,5-methylenedioxybenzaldehyde to give a mixture of *erythro* ($J_{3,1'}$ = 3.1 Hz) and *threo* ($J_{3,1'}$ = 7.5 Hz) aldol products (**5a** and **5b**) in an 83% combined yield in the respective ratio of 71:29 (based on NMR data). As suggested by Shieh and Prestwitch,[7] the condensation exclusively gave 2,3-*trans*-disubstituted lactones ($J_{3,4}$ = 0.8 Hz for **5a** and $J_{3,4}$ = 5.5 Hz for **5b**) due to electrostatic repulsion of the alkoxy anion at the 4-position. Without separation, the diastereometric mixture of **5a** and **5b** was reduced with lithium aluminum hydride (LAH), and resulting tetraols **6** were treated *in situ* with aqueous hydrochloric acid to give cyclized product **7** in a 73% yield. It should be noted that the acid-catalyzed dehydrative cyclization solely gave thermodynamically preferable 2,3-*trans*-disubstituted **7**, irrespective of the stereochemistry at the benzylic carbon of tetraols **6**. After protecting the primary hydroxy group with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP),[8] the secondary hydroxy group was oxidized under Swern's condition,[9] giving 3-furanone **9** in an 86% yield from **7**.

The conversion of furanone **9** to furofuran system **13** required the stereoselective incorporation of a formyl unit and a hydroxy group on the carbonyl function of **9**. It is evident that directly additing a formyl anion equivalent to furanone **9** would predominantly give undesired 4β-hydroxyaldehyde **12b** due to steric repulsion of the bulky siloxymethyl substituent at the 3-position. Thus, the conversion was performed by a stepwise methylenation-osmium dihydroxylation-oxidation sequence. The methylenation of **9**, however, unexpectedly proved to be troublesome due to the relatively labile property of the 3-furanone system under strongly basic conditions. After various unsuccessful attempts, including the Wittig reaction, the Peterson reaction and Julia's olefination, the methylenation step was finally effected by using Tebbe reagent.[10] Thus, furanone **9** was treated with this reagent in THF at −78°C to furnish methylene furan **10** in a good yield (73%). A similar reaction with the CH_2Br_2–$TiCl_4$–Zn system[11] resulted in a low yield of **10** (18%). Dihydroxylation of

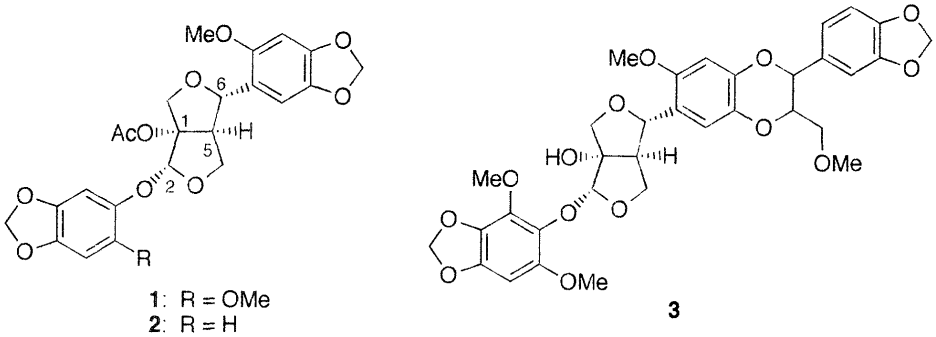
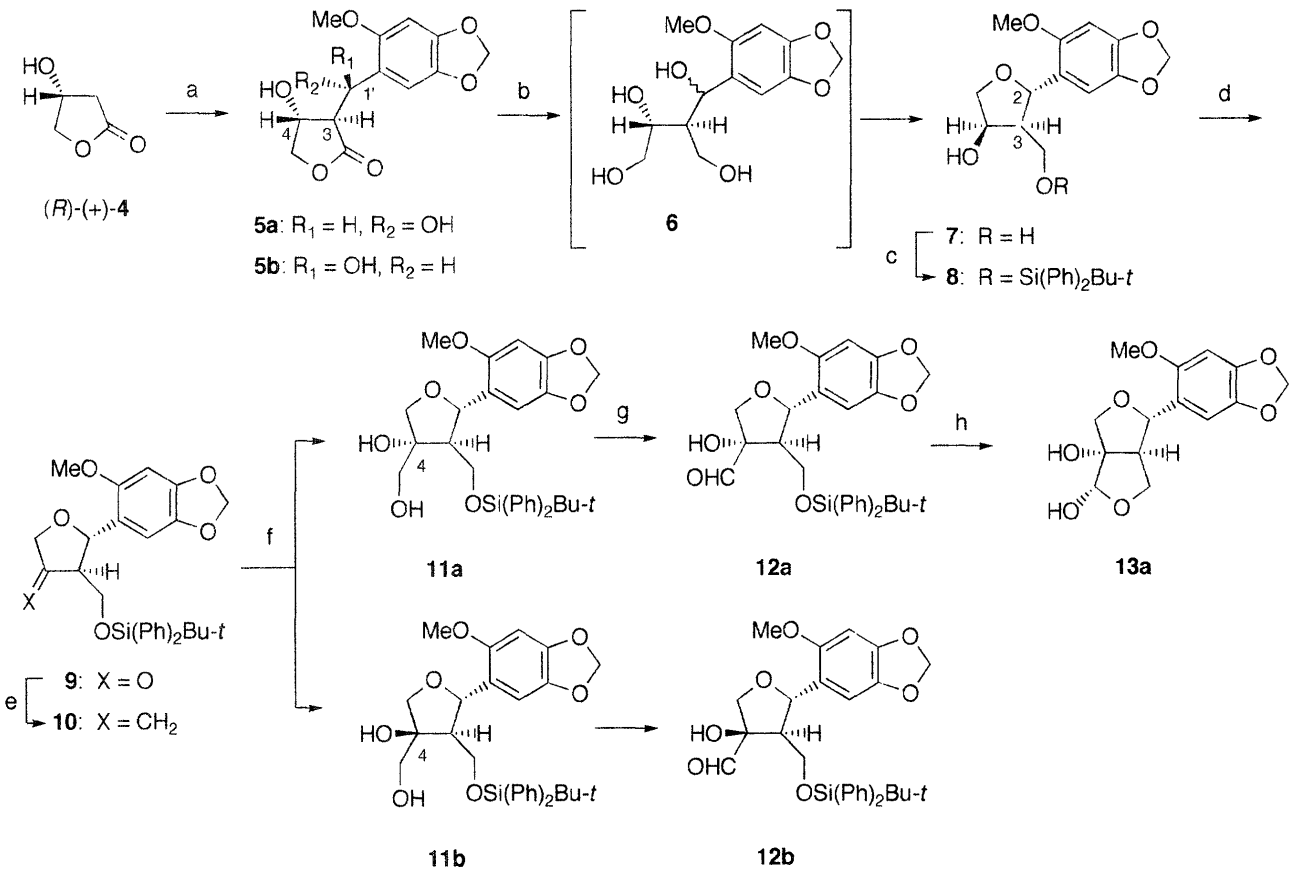
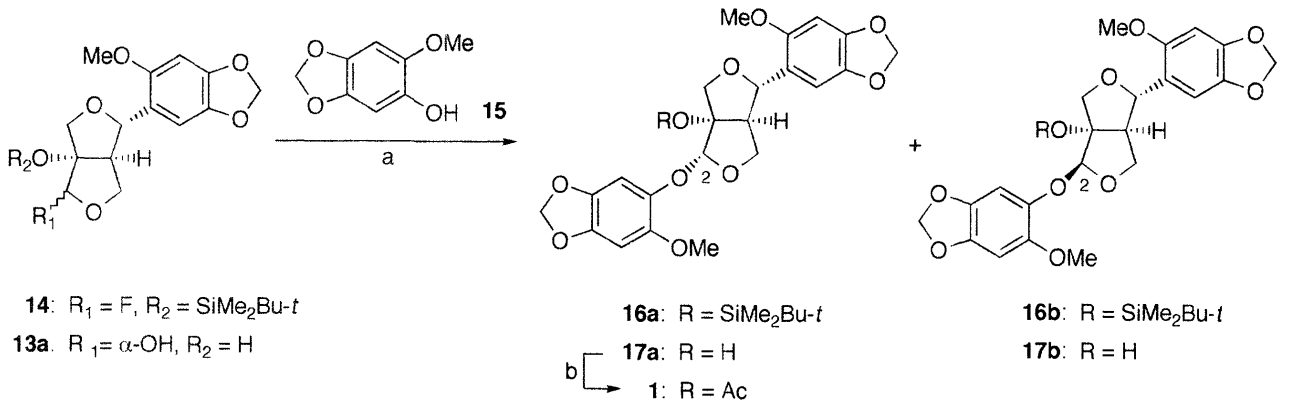


Fig. Structures of Lignans from *Phryma leptostachya* L.



Scheme 1. Synthesis of Lactol **13**.

Reagents and conditions: a) 2.2 eq. LAD, THF −78°C, 2 h, then 2-methoxy-4,5-methylenedioxybenzaldehyde, −78°C, 3 h, 83%; b) $LiAlH_4$, THF, −10°C to rt, then 2 N HCl, rt, 3 h, 73%; c) *tert*-$BuPh_2SiCl$, Et_3N, cat. DMAP, CH_2Cl_2, 93%; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 1 h, then Et_3N, −78°C to rt, 30 min, 92%; e) Tebbe reagent, −78°C to rt, 73%; f) cat. OsO_4, NMO, acetone-H_2O, 5°C, 12 h, then chromatography on silica gel, 83%; g) DCC, TFA, pyr, DMSO–benzene, 88%; h) TBAF, THF, 89%.



Scheme 2. Synthesis of (+)-Phrymarolin I (**1**).

Reagents and conditions: a) cat. PPTS, Al_2O_3, benzene, reflux, 15%; b) Ac_2O, pyr, cat. DMAP, rt, 79%.

the *exo*-methylene by using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) as the reoxidant[12] gave a mixture of 4α- and 4β-diols, **11a** and **11b**, in a ratio of **11a**:**11b** = 89:11 in a 92% combined yield. Although there was no direct evidence to enable an assignment of the two stereoisomers, the stereochemistry of each product was predictable from the steric cource of dihydrogenation, in which the oxidant might predominantly approach from the less-hindered side of the molecule due to steric hindrance of the bulky *tert*-butyldiphenylsilyloxymethyl moiety. Oxidation of the primary hydroxy group to give a formyl function was next examined. Pfitzner–Moffatt oxidation (DMSO, DCC)[13] of **11a** gave hydroxyaldehyde **12a** in a good yield (88%), while Swern oxidation gave an inferior result (20%). Chromic acid species (PCC and PDC) were totally ineffective for this oxidation.

In our previous synthesis of (+)-phrymarolin I,[3] the 2-aryloxy moiety was introduced to the furofuran system by tin(II) chloride-trityl perchlorate-promoted acetalization of fluoride **14** with phenol **15** (Scheme 2), in which desired 2α-**16a** was obtained as the minor product (2α-**16a**:2β-**16b** = 33:67). In the present synthesis, the acid-catalized 2α-selective acetalization employed in Takano's asymmetric synthesis of (+)-sesamolin[14] was successfully applied for condensation of the lactol (**13a**) with phenol **15**. Thus, after desilylating **12a** with tetrabutylammonium fluoride (TBAF) in THF, lactol **13a** was obtained in an 89% yield. Lactol **13a** was refluxed together with 2-methoxy-4,5-methylene-

dioxyphenol (**15**) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in benzene, after removing any concomitant water (Al_2O_3) to furnish desacetylphrymarolin I (**17a**) and a trace of its 2β-epimer (**17b**) (based on NMR data). The isolated yield of (+)-**17a** separated by preparative TLC was 15% from **13a**. The value for the optical rotation of **17a**, $[\alpha]_D^{25}$ +154.5° (*c* 0.44, $CHCl_3$) was observed to be close to that of natural **17a**, $[\alpha]_D^{24}$ +163.6° (*c* 1.58, $CHCl_3$). Finally, the synthesis of (+)-phrymarolin I was accomplished by acetylating **17a** with acetic anhydride and a catalytic amount of DMAP. The physical and spectroscopic properties of synthetic **1** agree with those of natural **1**.

In summary, we accomplished a total synthesis of (+)-phrymarolin I from (*R*)-(+)-3-hydroxybutanolide through 11 steps in a 3% overall yield. The present synthesis is more efficient than our previous synthesis in terms of fewer reaction steps and the easy availability of the starting material. This strategy would be amenable to the synthesis of the other members of the lignans of this type involving highly insecticidal haedoxans.

Experimental

All melting point (mp) data are uncorrected. IR spectra were recorded with a Shimadzu IR-420 spectrometer, and ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM GSX-270 spectrometer at 270 MHz and 68 MHz, respectively. The internal references were TMS (0.00 ppm of ^{1}H for a solution in $CDCl_3$), acetone (2.23 ppm for ^{1}H and 31.00 ppm for ^{13}C for a solution in CD_3COCD_3), and $CDCl_3$ (77.00 ppm for ^{13}C for a solution in $CDCl_3$). Optical rotation values were measured at 25°C with a Horiba SEPA-200 polarimeter. Silica gel (Wakogel C-200 100–200 mesh) was obtained from Wako Pure Chemical Industries. TLC and preparative TLC were done by using Merck silica gel 60 F_{254} precoated plastic plates of 0.2 mm in thickness and Merck silica gel 60 F_{254} precoated glass plates of 0.5 mm in thickness, respectively.

(3R,4R)-4-Hydroxy-3-[(1R/S)-1-hydroxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]dihydro-2(3H)-furanones (**5**). A solution of (*R*)-(+)-3-hydroxybutanolide **4** (2.20 g, 21.6 mmol) in dry THF (15 ml) was added dropwise to a solution of LDA [prepared from 1.6 N *n*-BuLi in *n*-hexane (29.7 ml, 47.5 mmol) and diisopropylamine (6.72 ml, 48.0 mmol)] in dry THF (100 ml) at −78°C under nitrogen. After 2 h, 2-methoxy-4,5-methylenedioxybenzaldehyde (3.88 g, 21.6 mmol) in dry THF (50 ml) was added dropwise, and the resulting mixture was stirred at −78°C for 3 h before being worked up with 1 N aqueous HCl. The mixture was extracted with EtOAc (200 ml), and then successively washed with aqueous saturated sodium bicarbonate (150 ml) and brine (150 ml). The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 1 : 1 to 1 : 3) to provide 3.61 g of **5a** as white crystals, and further elution gave 1.44 g of **5b** as a colorless oil in a total yield of 5.05 g (83%). **5a**, *erythro*: mp 83–87°C; ^{1}H-NMR (270 MHz, CD_3COCD_3) δ: 7.05 (s, 1H), 6.64 (s, 1H), 5.89 (s, 2H), 5.37 (dd, 1H, J=4.6, 3.1 Hz), 4.74 (d, 1H, J=4.6 Hz), 4.49 (m, 1H), 4.41 (dd, 1H, J=9.4, 5.6 Hz), 4.27 (d, 1H, J=4.0 Hz), 4.01 (dd, 1H, J=9.4, 2.1 Hz), 3.77 (s, 3H), 2.77 (dd, 1H, J=3.1, 0.8 Hz); ^{13}C-NMR (68 MHz, CD_3COCD_3) δ: 178.32, 152.23, 148.63, 142.40, 124.58, 107.93, 102.47, 95.60, 76.92, 68.99, 67.93, 57.05, 56.09; IR ν_{max} (KBr) cm^{-1}: 3440, 1765, 1500, 1268, 1190, 1040, 1028. *Anal.* Found: C, 55.56; H, 4.89%. Calcd. for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00%. **5b**, *threo*: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.97 (s, 1H), 6.52 (s, 1H), 5.93 (s, 2H), 5.23 (dd, 1H, J=7.5, 1.0 Hz), 4.43 (m, 1H), 4.36 (dd, 1H, J=9.2, 6.4 Hz), 3.99 (dd, 1H, J=9.2, 4.9 Hz), 3.77 (d, 1H, J=5.4 Hz), 3.71 (s, 3H), 2.88 (dd, 1H, J=7.5, 5.4 Hz), 2.40 (br, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 177.89, 151.23, 148.11, 141.72, 120.39, 107.19, 101.28, 94.53, 72.94, 69.88, 66.91, 56.48, 54.95; IR ν_{max} ($CHCl_3$) cm^{-1}: 3495, 1774, 1491, 1256, 1196, 1046, 940. *Anal.* Found: C, 55.21; H, 5.11%. Calcd. for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00%.

(2S,3R,4R)-4-Hydroxy-3-hydroxymethyl-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**7**). To a stirred suspension of LAH (1.01 g, 26.6 mmol) in dry THF (75 ml) was added dropwise a mixture of **5a** and **5b** (5.00 g, 17.7 mmol) dissolved in the same solvent (40 ml) while maintaining the temperature below −10°C. After stirring for 1 h at room temperature, the reaction mixture was carefully quenched with 2 N aqueous HCl (75 ml) at under 5°C. The resulting two phases were then vigorously stirred at room temperature for 3 h. The reaction mixture was extracted with EtOAc (3 × 30 ml), and the organic layer was successively washed with aqueous saturated sodium bicarbonate (75 ml) and brine (75 ml). The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was recrystallized from EtOAc to give 2.53 g of **7** as white crystals. The mother liquid was concentrated and purified by column chromatography on silica gel (EtOAc) to give 0.92 g of a second crop of **7**, the total yield being 73% from **5**, mp 141–143°C; ^{1}H-NMR (270 MHz, CD_3COCD_3) δ: 6.92 (s, 1H), 6.70 (s, 1H), 5.97 (s, 2H), 5.11 (d, 1H, J=9.8 Hz), 4.61 (m, 1H), 4.26 (dd, 1H, J=9.2, 4.3 Hz), 4.21 (d, 1H, J=4.3 Hz), 3.91 (ddd, 1H, J=14.2, 8.5, 5.7 Hz), 3.82 (dd, 1H, J=9.2, 1.8 Hz), 3.82 (s, 3H), 3.66 (ddd, 1H, J=14.2, 9.5, 5.2 Hz), 3.55 (dd, 1H, J=5.7, 5.2 Hz), 2.18 (m, 1H); ^{13}C-NMR (68 MHz, CD_3COCD_3) δ: 151.23, 148.03, 141.20, 121.38, 106.83, 101.05, 94.50, 75.52, 75.17, 73.94, 60.83, 55.86, 53.28; IR ν_{max} (KBr) cm^{-1}: 3250, 1480, 1425, 1190, 1055, 1030; $[\alpha]_D^{25}$ +40.7° (*c* 1.35, EtOH). *Anal.* Found: C, 58.36; H, 5.79%. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01%.

(2S,3R,4R)-3-[(tert-Butyldiphenylsilyl)oxy]methyl-4-hydroxy-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**8**). A mixture of **7** (3.18 g, 11.9 mmol), *tert*-butyldiphenylsilyl chloride (3.41 ml, 13.1 mmol), Et_3N (2.07 ml, 14.9 mmol) and a catalytic amount of 4-dimethylaminopyridine in dry DMF (2 ml) and dry CH_2Cl_2 (20 ml) was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with 10% aqueous ammonium chloride (20 ml) and extracted with EtOAc (2 × 15 ml), before being washed with brine (30 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was chromatographed on silica gel (*n*-hexane–EtOAc, 2 : 1 to 1 : 1) to provide 5.59 g of **8** (93%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.67–7.35 (m, 10H), 6.75 (s, 1H), 6.41 (s, 1H), 5.87 (dd, 2H, J=2.1, 0.7 Hz), 5.10 (d, 1H, J=8.9 Hz), 4.64 (m, 1H), 4.27 (dd, 1H, J=9.5, 4.4 Hz), 3.97–3.82 (m, 3H), 3.51 (s, 3H), 3.05 (br, 1H), 2.26 (m, 1H), 1.06 (s, 9H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 152.04, 147.28, 141.19, 135.50, 135.44, 129.86, 127.75, 121.74, 106.58, 101.03, 94.35, 75.41, 75.12, 73.94, 61.28, 55.96, 53.11, 26.75, 19.06; IR ν_{max} ($CHCl_3$) cm^{-1}: 3539, 2975, 1735, 1487, 1431, 1196, 1042, 825, 704. *Anal.* Found: C, 68.17; H, 6.76%. Calcd. for $C_{29}H_{34}O_6Si$: C, 68.75; H, 6.76%.

(4R,5S)-4-[(tert-Butyldiphenylsilyl)oxy]methyl-5-(2-methoxy-4,5-methylenedioxyphenyl)dihydro-3(2H)-furanone (**9**). To a solution of DMSO (1.04 ml, 14.7 mmol, distilled from CaH_2) in dry CH_2Cl_2 (30 ml) was added dropwise oxalyl chloride (0.55 ml, 6.31 mmol) dissolved in CH_2Cl_2 (6 ml) at −78°C under nitrogen. The reaction mixture was stirred for 10 min before additing **8** (2.91 g, 5.74 mmol) dissolved in dry CH_2Cl_2 (10 ml). After 1 h, Et_3N (3.20 ml, 23.0 mmol) was added, and the resulting mixture was allowed to warm to 0°C and then stirred for 30 min. The mixture was quenched with 10% aqueous ammonium chloride (20 ml) and extracted with CH_2Cl_2 (2 × 20 ml). The organic layer was washed with brine (30 ml), the dried (Na_2SO_4) organic layer being concentrated under reduced pressure. The crystalline residue was recrystallized from 2-propanol to give 2.32 g of **9** as white crystals. The mother liquid was concentrated, and the residue was chromatographed on silica gel (*n*-hexane–EtOAc, 3 : 1) to afford 0.33 g of **9** in a total yield of 92%, mp 144–146°C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.38–7.36 (m, 10H), 6.91 (s, 1H), 6.52 (s, 1H), 5.90 (dd, 2H, J=3.6, 1.5 Hz), 5.77 (d, 1H, J=8.6 Hz), 4.31 (d, 1H, J=16.8 Hz), 4.11 (dd, 1H, J=10.2, 3.7 Hz), 4.05 (d, 1H, J=16.8 Hz), 3.77 (dd, 1H, J=10.2, 2.8 Hz), 3.65 (s, 3H), 2.50 (m, 1H), 1.03 (s, 9H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 215.18, 152.54, 148.04, 141.36, 135.62, 135.58, 129.72, 129.69, 127.66, 127.64, 120.63, 107.25, 101.28, 94.51, 76.53, 72.42, 60.20, 56.07, 55.99, 26.63, 19.24; IR ν_{max} ($CHCl_3$) cm^{-1}: 2962, 1769, 1495, 1201, 1120, 1051, 709. *Anal.* Found: C, 69.05; H, 6.47%. Calcd. for $C_{29}H_{32}O_6Si$: C, 69.02; H, 6.39%.

(2S,3R)-3-[(tert-Butyldiphenylsilyl)oxy]methyl-2-(2-methoxy-4,5-methylenedioxyphenyl)-4-methylenetetrahydrofuran (**10**). Tebbe reagent (8.80 ml and 0.5 M in toluene from Aldrich Chemical Co., 4.40 mmol) was added dropwise to a stirred and cooled (−78°C) solution of 3-furanone **9** (2.11 g, 4.18 mmol) in dry THF (150 ml). After removing the cold bath, the mixture was stirred for 4 h. Diethyl ether (150 ml) was added, and then 1 N aqueous NaOH was added dropwise until no more gas evolved. After additing

water (200 ml), the organic phase was dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (*n*-hexane–EtOAc, 4:1 to 3:1) provided 1.52 g of **10** (73%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.67–7.34 (m, 10H), 6.87 (s, 1H), 6.47 (s, 1H), 5.90 (s, 2H), 5.25 (d, 1H, J=6.1 Hz), 5.02 (d, 1H, J=1.1 Hz), 5.01 (d, 1H, J=1.1 Hz), 4.56 (dd, 1H, J=12.7, 1.1 Hz), 4.43 (dd, 1H, J=12.7, 3.4 Hz), 3.81 (d, 1H, J=5.7 Hz), 3.71 (d, 1H, J=5.7 Hz), 3.63 (s, 3H), 2.79 (m, 1H), 1.01 (s, 9H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 151.99, 149.55, 141.11, 135.60, 129.53, 127.57, 127.54, 122.54, 106.91, 106.78, 105.12, 101.04, 94.37, 77.94, 71.62, 64.63, 56.13, 53.31, 26.71, 19.23; IR ν_{max} ($CHCl_3$) cm^{-1}: 2962, 1739, 1496, 1436, 1222, 1115, 1047, 760, 709. *Anal.* Found: C, 70.98; H, 6.99%. Calcd. for $C_{30}H_{34}O_6Si$: C, 71.68; H, 6.82%.

(2S,3R,4R)-3-[(tert-Butyldiphenylsilyl)oxy]methyl-4-hydroxy-4-hydroxymethyl-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**11a**). To a solution of **10** (0.77 g, 1.53 mmol) in a mixture of acetone (12 ml) and water (3 ml) were added *N*-methylmorpholine *N*-oxide (0.40 g, 3.41 mmol) and 1% aqueous OsO_4 (1 ml), and the resulting mixture was vigorously stirred overnight at 5°C under nitrogen. Two ml of 5% aqueous $NaHSO_3$ was added, and the resulting mixture was concentrated under reduced pressure. The oily residue was taken up in EtOAc (10 ml), washed with brine (10 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was filtered through a short silica gel column, eluting with *n*-hexane–EtOAc (1:2). The filtrate was concentrated and the residue was purified by chromatography on silica gel (benzene–EtOAc, 2:1 to 1:1) to give a mixture of 0.69 g of **11a** (83%) as a colorless oil and 0.08 g of **11b** (9%) as a colorless oil. **11a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.67–7.25 (m, 10H), 6.92 (s, 1H), 6.40 (s, 1H), 5.90 (s, 2H), 4.72 (d, 1H, J=6.7 Hz), 4.01 (d, 1H, J=10.4 Hz), 3.85 (dd, 1H, J=10.8, 4.2 Hz), 3.74 (d, 1H, J=10.4 Hz), 3.72 (dd, 1H, J=10.8, 9.0 Hz), 3.71–3.64 (m, 2H), 3.45 (s, 3H), 3.23 (br, 1H), 3.19 (br, 1H), 2.36 (m, 1H), 1.06 (s, 9H). **11b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.65–7.30 (m, 10H), 6.79 (s, 1H), 6.31 (s, 1H), 5.93 (s, 2H), 4.98 (d, 1H, J=7.4 Hz), 4.13 (d, 1H, J=10.1 Hz), 3.89 (dd, 1H, J=6.4, 2.0 Hz), 3.86 (dd, 1H, J=8.9, 2.8 Hz), 3.77 (br, 1H), 3.73 (d, 1H, J=10.1 Hz), 3.70 (dd, 1H, J=10.0, 2.8 Hz), 3.65 (dd, 1H, J=6.4, 3.1 Hz), 3.40 (br, 1H), 3.38 (s, 3H), 2.02 (m, 1H), 1.06 (s, 9H).

(2S,3R,4S)-3-[(tert-Butyldiphenylsilyl)oxy]methyl-4-formyl-4-hydroxy-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**12a**). To a solution of **11a** (0.24 g, 0.446 mmol) in dry DMSO (1 ml) and dry benzene (1 ml) were added trifluoroacetic acid (26 µl, 0.335 mmol), pyridine (72 µl, 0.892 mmol) and dicyclohexylcarbodiimide (0.37 g, 1.78 mmol) at 0°C, and the mixture was stirred for 20 h at room temperature. After filtration, the reaction mixture was diluted with 1 N aqueous HCl (5 ml) and extracted with Et_2O (5 ml). The organic phase was successively washed with aqueous saturated sodium bicarbonate (15 ml) and brine (15 ml). The dried (Na_2SO_4) organic layer was concentrated under reduced pressure, and the residue was chromatographed on silica gel (*n*-hexane–EtOAc, 3:1) to afford 0.21 g of **12a** (88%) as a colorless oil. **12a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 7.63–7.28 (m, 10H), 6.91 (s, 1H), 6.45 (s, 1H), 5.91 (s, 2H), 5.27 (d, 1H, J=8.4 Hz), 4.22 (d, 1H, J=10.2 Hz), 4.04 (d, 1H, J=10.2 Hz), 3.82 (dd, 1H, J=10.9, 3.9 Hz), 3.73 (dd, 1H, J=10.9, 6.3 Hz), 3.51 (s, 3H), 3.34 (br, 1H), 2.64 (m, 1H), 1.03 (s, 9H). Similarly, **11b** afforded **12b** as a colorless oil. **12b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 7.75–7.31 (m, 10H), 6.84 (s, 1H), 6.37 (s, 1H), 5.92 (s, 2H), 5.06 (d, 1H, J=10.9 Hz), 4.41 (d, 1H, J=9.5 Hz), 3.95 (d, 1H, J=9.5 Hz), 3.66 (dd, 1H, J=5.1, 2.6 Hz), 3.47 (dd, 1H, J=5.1, 3.2 Hz), 3.45 (s, 3H), 3.03 (br, 1H), 2.59 (m, 1H), 0.97 (s, 9H).

(1S,2S,5R,6S)-1,2-Dihydroxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (**13a**). To a solution of **12a** (140.0 mg, 0.261 mmol) in THF (5 ml) was added tetrabutylammonium fluoride (0.34 ml and 1.0 M in THF, 0.339 mmol) at 0°C, and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc (3×7 ml). The organic layer was successively washed with 1 N HCl (10 ml), aqueous saturated sodium bicarbonate (10 ml) and brine (10 ml). The dried (Na_2SO_4) organic layer was concentrated under reduced pressure, and the residue was chromatographed on silica gel (*n*-hexane–EtOAc, 1:2) to afford 61.3 mg of **13a** (89%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.08 (s, 1H), 6.49 (s, 1H), 5.91 (d, 1H, J=9.9 Hz), 5.90 (s, 2H), 5.15 (s, 1H), 4.85 (d, 1H, J=6.7 Hz), 4.28 (dd, 1H, J=10.1, 7.0 Hz), 4.21 (d, 1H, J=9.8 Hz), 3.95 (dd, 1H, J=10.1, 2.2 Hz), 3.76 (d, 1H, J=9.9 Hz), 3.74 (s, 3H), 3.67 (d, 1H, J=9.8 Hz), 2.46 (m, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 151.68, 146.93, 141.79, 121.61, 106.50, 101.95, 97.39, 94.16, 92.08, 83.65, 77.08, 69.99, 58.69, 55.99; IR ν_{max} ($CHCl_3$) cm^{-1}: 3453, 1496, 1436, 1252, 1047, 778. *Anal.* Found: C, 57.13; H, 5.40%. Calcd. for $C_{14}H_{16}O_7$: C, 56.76; H, 5.44%.

(1S,2R,5R,6S)-1-Hydroxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)oxy-3,7-dioxabicyclo[3.3.0]octane (**17a**, desacetylphrymarolin I). A solution of **13a** (48.3 mg, 0.162 mmol), 2-methoxy-4,5-methylenedioxyphenol (**15**; 0.15 g, 0.972 mmol) and a catalytic amount of PPTS in dry benzene (20 ml) was refluxed for 8 h while removing the water with aluminum oxide. After removing the solvent under reduced pressure, the residue was filtered through a short silica gel column that was eluted with benzene–EtOAc (4:1). The filtrate was concentrated, and the residue was purified by preparative TLC (benzene–EtOAc, 9:1) to afford 10.7 mg of **17a** (15%) as colorless crystals and 0.8 mg of **17b** (1%) as a colorless oil. **17a**: mp 133–134°C (lit.[5] mp 133–134°C); ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.15 (s, 1H), 6.80 (s, 1H), 6.56 (s, 1H), 6.51 (s, 1H), 5.96 (s, 2H), 5.91 (s, 2H), 5.18 (s, 1H), 4.93 (d, 1H, J=6.1 Hz), 4.45 (dd, 1H, J=9.3, 7.3 Hz), 4.34 (d, 1H, J=9.7 Hz), 4.08 (dd, 1H, J=9.3, 2.6 Hz), 3.83 (br, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 (d, 1H, J=9.7 Hz), 2.59 (m, 1H); $[\alpha]_D^{25}$ +154.5° (c 0.44, $CHCl_3$) {natural **17a**, $[\alpha]_D^{24}$ +163.6° (c 1.58, $CHCl_3$)}. **17b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.05 (s, 1H), 6.74 (s, 1H), 6.54 (s, 1H), 6.47 (s, 1H), 5.89 (s, 2H), 5.87 (s, 2H), 5.30 (s, 1H), 5.02 (d, 1H, J=7.1 Hz), 4.53 (dd, 1H, J=11.2, 2.3 Hz), 4.18 (d, 1H, J=6.8 Hz), 4.05 (dd, 1H, J=11.2, 2.3 Hz), 3.83 (d, 1H, J=6.8 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 3.01 (br, 1H), 2.64 (m, 1H).

(1S,2R,5R,6S)-1-Acetoxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)oxy-3,7-dioxabicyclo[3.3.0]octane (**1**, phrymarolin I). A mixture of **17a** (10.7 mg, 0.024 mmol) and a catalytic amount of DMAP in acetic anhydride (0.5 ml) and pyridine (0.5 ml) was allowed to stand at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to afford 9.3 mg of **1** (79%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.05 (s, 1H), 6.86 (s, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 5.93 (s, 2H), 5.88 (s, 2H), 5.68 (s, 1H), 4.88 (d, 1H, J=6.7 Hz), 4.62 (d, 1H, J=11.0 Hz), 4.40 (dd, 1H, J=9.1, 7.3 Hz), 4.05 (dd, 1H, J=9.1, 1.7 Hz), 3.82 (d, 1H, J=11.0 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 2.90 (m, 1H), 2.14 (s, 3H); $[\alpha]_D^{25}$ +120.28° (c 0.98, dioxane) {natural **1**, $[\alpha]_D^{25}$ +131.3° (c 0.12, dioxane)}.

References

1) E. Taniguchi and Y. Oshima, *Agric. Biol. Chem.*, **36**, 1013–1025 (1972); E. Taniguchi and Y. Oshima, *ibid.*, **36**, 1489–1496 (1972).
2) E. Taniguchi, K. Imamura, F. Ishibashi, T. Matsui, and A. Nishio, *Agric. Biol. Chem.*, **53**, 631–643 (1989).
3) F. Ishibashi and E. Taniguchi, *Agric. Biol. Chem.*, **50**, 3119–3125 (1986).
4) F. Ishibashi and E. Taniguchi, *Agric. Biol. Chem.*, **53**, 1565–1573 (1989).
5) F. Ishibashi and E. Taniguchi, *Bull. Chem. Soc. Jpn.*, **61**, 4361–4366 (1988); F. Ishibashi and E. Taniguchi, *Chem. Lett.*, **1986**, 1771–1774.
6) a) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, *Chem. Lett.*, **1984**, 1389–1392; b) D. Seebach and M. Eberle, *Synthesis*, **1986**, 37–40.
7) H. M. Shieh and G. D. Prestwich, *J. Org. Chem.*, **46**, 4319–4321 (1981); H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310–3324 (1973).
8) R. E. Ireland and D. M. Obrecht, *Helv. Chim. Acta*, **69**, 1273–1286 (1986).
9) A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480–2482 (1978).
10) F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.*, **100**, 3611–3613 (1978); D. L. J. Clive, P. L. Wickens, and L. Wikens, *J. Org. Chem.*, **60**, 5532–5536 (1995).
11) L. Lombardo, *Tetrahedron Lett.*, **23**, 4293–4296 (1982); K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **53**, 1698–1702 (1980).
12) V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, **1976**, 1973–1976.
13) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661–5670 (1965); K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5670–5678 (1965).
14) S. Takano, T. Ohkawa, S. Tamori, S. Satoh, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1988**, 189–191.