December, 1988] © *1988 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn., 61, 4361—4366 (1988)* 4361

Synthesis and Absolute Configuration of the Acetalic Lignan (+)-Phrymarolin I

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(Received June 24, 1988)

The natural (+)-phrymarolin I was stereoselectively synthesized and its absolute configuration was unequivocally determined as being (1*S*,2*S*,5*R*,6*S*)-1-acetoxy-2-(2-methoxy-4,5-methylenedioxyphenoxy)-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

The unique lignans of *Phryma leptostachya* L., phrymarolin I and II, are the first examples of naturally occurring 1,2-dioxygenated 3,7-dioxabicyclo-[3.3.0]octanes.[1)] Recently, their congeners, including desacetylphrymarolin III and higher insecticidal sesquilignans,[2)] were isolated from the same plant. Concerning the development of new pesticides, we are interested in their absolute configurations and syntheses.

A structure involving the relative configuration of phrymarolin I (**1a**) was proposed on the basis of chemical and spectroscopic information.[1)] A total synthesis and a consequent establishment of the whole stereochemistry of (+)-phrymarolin I have recently been communicated.[3)] Full details of this work will be described herein.

The strategy for the synthesis is basically the same as that for the syntheses of racemic phrymarolin II and its stereoisomers[4)] (Fig. 1); the 1-hydroxy-6-aryl-2-aryloxy-3,7-dioxabicyclo[3.3.0]octane skeleton (**1a**) was constructed from β-vinyl-γ-butyrolactone, 2-methoxy-4,5-methylenedioxybenzaldehyde and 2-methoxy-4,5-methylenedioxyphenol. However, we found that cadmium carbonate-catalyzed condensation[5)] of the chloride (**2**) with 2-methoxy-4,5-methylenedioxyphenol (**4**), not as well as sesamol, only gave the undesirable 2α-epimer (**1b**) in low yield (14%). A synthesis of 2β-epimer was achieved by extending the stereocontrolled glycosylation method, developed by Mukaiyama et al., using glycosyl fluoride and tin(II) chloride.[6)] The new method improved 2β-isomer production and prevented an epimerization at the C-6 position.

The chiral starting substance, (*S*)-(+)-β-vinyl-γ-butyrolactone, was prepared from its racemate[7)] by optical resolution, as shown in Fig. 2. Aminolysis of (±)-**5** with (*S*)-(−)-α-methylbenzylamine in the presence of trimethylaluminium[8)] in dichloromethane gave an oily mixture of the hydroxy amides (**7a** and **7b**) in 56% combined yield. The diastereomers were separated by repeated liquid chromatography on silica gel with 3 vol% isopropyl alcohol in benzene as the eluent. Purely isolated **7a** was subjected to alkaline hydrolysis followed by lactonization with an azeotropic removal of the water to afford (+)-**5** in 58% yield. In the same manner as mentioned above, another diastereomer (**7b**) was converted to (−)-**5** in 64% yield. The absolute stereochemistry of the two enantiomeric lactones was unknown at this stage. Hydrogenation of the lactone [(+)-**5**], followed by reduction with lithium aluminium hydride gave the enantiomer, (*R*)-(+)-**8**, $[\alpha]_D$ $+14.3°$ ($CHCl_3$), whereas another lactone [(−)-**5**] led to the opposite enantiomer, (*S*)-(−)-**8**, $[\alpha]_D$ $-13.0°$ ($CHCl_3$). Their absolute configurations were assigned by a comparison of their optical rotations with that of

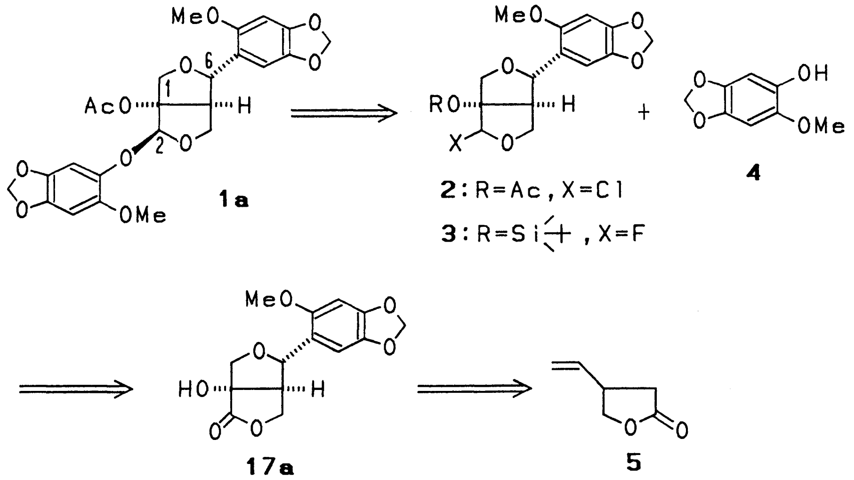

Fig. 1.

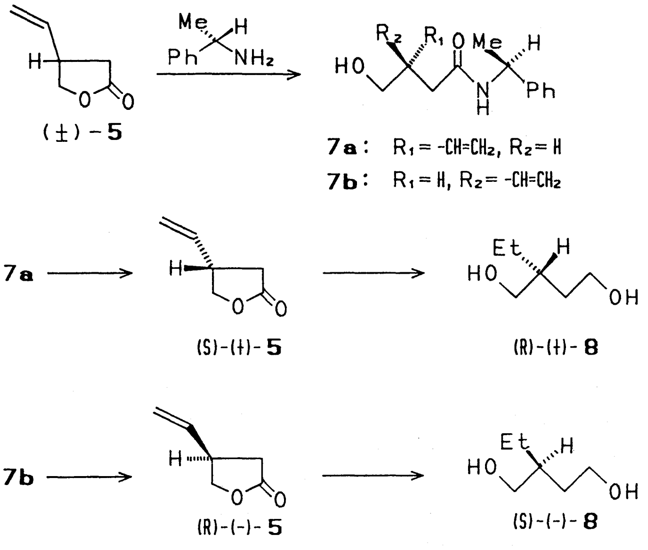

Fig. 2.

the diol (R)-(+)-**8** of which configuration was known, $[\alpha]_D$ +7.7° (neat).[9] The stereochemistries of (+)-**5** and (−)-**5** were defined as an (S)- and (R)-configuration, respectively.

The addition of the lithium enolate of (S)-(+)-**5** generated by lithium diisopropylamide (LDA) to 2-methoxy-4,5-methylenedioxybenzaldehyde (**6**) in tetrahydrofuran at −75 °C afforded the erythro and threo aldols (**9**) in 98% yield in the ratio of 65/35 (based on NMR), respectively. Due to the steric repulsion of the vinyl moiety of **5**, the reaction was supposed to be favorable to the (2R, 3S)-*trans* isomers. Without separation, the mixture was silylated with *t*-butyldimethylsilyl triflate[10] in the presence of 2,6-lutidine in dichloromethane at −30 °C (92% yield), and the silylated lactone was reduced with lithium aluminium hydride in a mixture of ether and tetrahydrofuran (2 : 1) at −10 °C to give the diol (**11**) in 82% yield. The terminal olefin of **11** was oxidized to the carbonyl function by successive oxidation with a catalytic amount of osmium tetraoxide and N-methylmorpholine N-oxide[11] in a

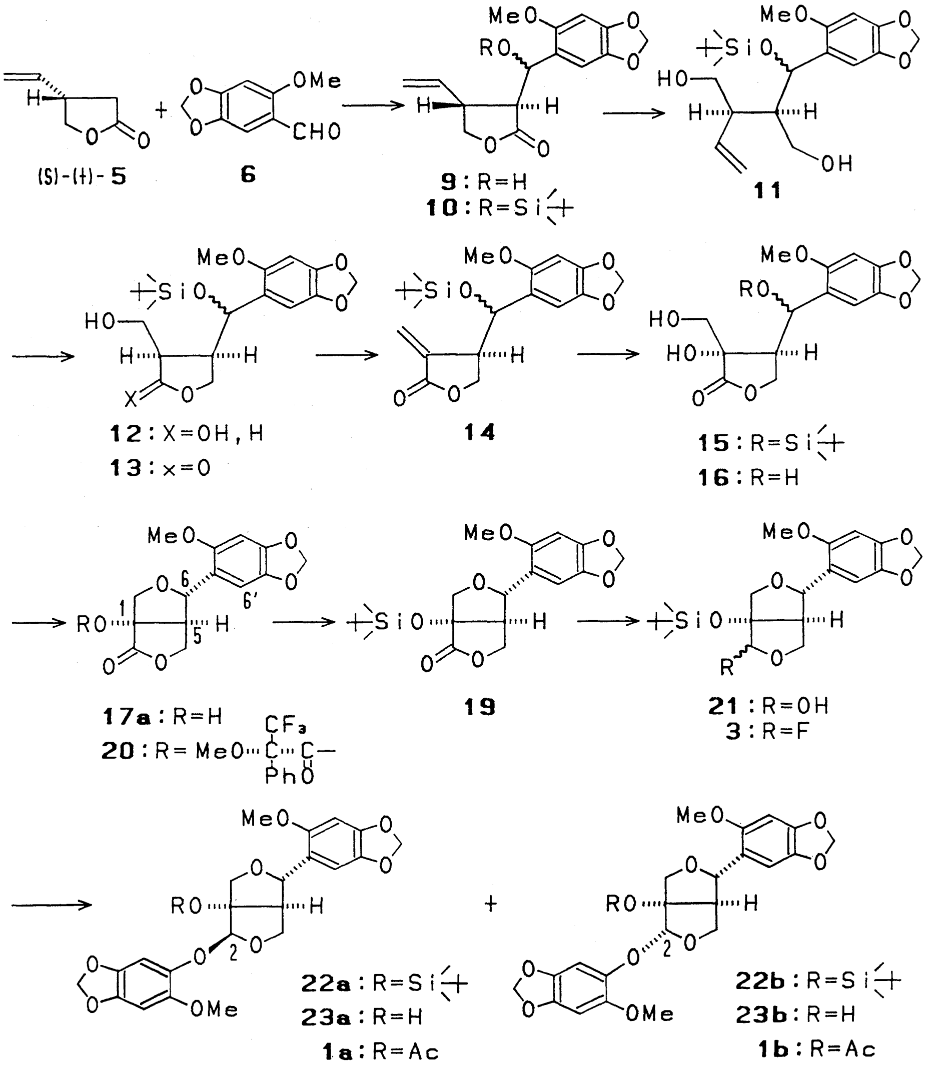

Fig. 3.

mixture of acetone, *t*-butyl alcohol and water at room temperature, followed by sodium periodate in a mixture of ethyl acetate and water. The lactol (**12**) was oxidized to the lactone (**13**) with silver carbonate on Celite in refluxing benzene in 91% overall yield from **11**. After sulfonylation of the primary hydroxyl group in **13** with mesyl chloride, the unstable mesylate was immediately treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature to furnish the methylene lactone (**14**) in 87% yield. Dihydroxylation with catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide[11] in a mixture of acetone, *t*-butyl alcohol and water quantitatively gave the 2α-diol (**15**) in high stereoselectivity, resulting from an exclusive attack of the reagent to the less hindered α-face of the molecule.

After removing the *t*-butyldimethylsilyl group with tetrabutylammonium fluoride in tetrahydrofuran at 0 °C, the resulting triol (**16**) was subjected to dehydrative cyclization with a catalytic amount of 10-camphorsulfonic acid (CSA) in dichloromethane at room temperature to afford the key intermediate (**17a**) in 59% yield, along with a 10% recovery of **15**.

It should be noted that both erythro and threo isomers of **16** afforded **17a** (6α) as the sole product via the thermodynamically preferable common transition state (**18a**), since the alternative transition state (**18b**), leading to **17b** (6β), was destabilized by the 1,3-diaxial interaction between the aromatic ring and the C-4 methylene group (Fig. 4). Under strongly acidic conditions, e.g., with diethyl ether-boron trifluoride (1/1) in dichloromethane or hydrogen chloride in tetrahydrofuran, the cyclization gave a mixture of **17a** and **17b**, probably due to the isomerization of **17a** under the conditions.

After recrystallizing **17a** from a mixture of benzene and diisopropyl ether, the lactone alcohol, $[\alpha]_D$ +67.3° ($CHCl_3$), was derivatized to the ester of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) according to Mosher et al.[12] The ^1H NMR spectrum of the (*S*)-(−)-MTPA ester was measured at 400 MHz; the aromatic proton (6′-H) of the (1*S*, 5*R*, 6*S*)-(*S*)-ester resonated at a higher field (6.73 ppm) than that of the diastereomeric (1*R*, 5*S*, 6*R*)-(S)-ester (6.97 ppm), indicating the optical purity (96% e.e.).

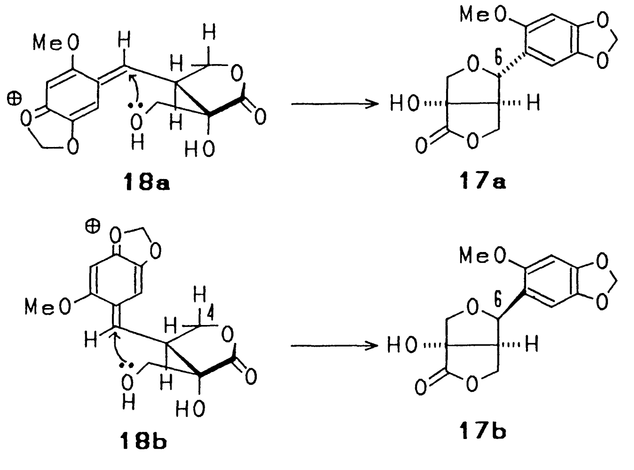

Fig. 4.

The crude sample of (+)-**17a** was treated with *t*-butyldimethylsilyl triflate and 2,6-lutidine[10] in dichloromethane (85% yield), and the resulting silyl ether (**19**) was reduced to the lactol (**21**) in 98% yield with diisobutylaluminium hydride (DIBAL) in toluene at −75 °C. The lactol was fluorinated in 92% yield with 2-fluoro-1-methylpyridinium tosylate and triethylamine[6] in dichloromethane, and the unstable fluoride (**3**) was immediately reacted with 2-methoxy-4,5-methylenedioxyphenol (**4**)[13] in the presence of tin(II) chloride, trityl perchlorate[6] and 4A Molecular Sieves in ether at 0 °C. A mixture of 2β-/2α-isomer, **22a** and **22b**, was obtained in 50% combined yield (**22a**/**22b**=33/67, based on NMR). Desilylation of the mixture with tetrabutylammonium fluoride in tetrahydrofuran and separation of the products by preparative TLC on silica gel furnished (+)-**23a** and (−)-**23b** in 11 and 29% yields from **3**, respectively (Fig. 3). The optical purity of (+)-**23a** was estimated to be 85% e.e. on the basis of the 400 MHz ^1H NMR spectrum of its (*S*)-(−)-MTPA ester.

The rather low optical yield may have resulted from contamination due to the unseparated diastereomer, (2*S*, 3*S*)-*cis*-**9**, produced by the aldol condensation of the benzaldehyde and vinylbutyrolactone during the first step of the synthesis. The (2*S*, 3*S*)-*cis* isomer should give the enantiomeric intermediate, (1*S*, 5*S*, 6*R*)-**17a** and (1*R*, 2*R*, 5*S*, 6*R*)-(−)-phrymarolin I in the following reactions.

Finally, the target molecule (1*S*, 2*S*, 5*R*, 6*S*)-**1a**, $[\alpha]_D$ +106.9° (dioxane), was obtained by acetylation of (+)-**23a** in acetic anhydride containing a small excess of 4-(dimethylamino)pyridine (DMAP). The optical rotation of natural **1a** was $[\alpha]_D$ +131.3° (dioxane). Although the synthesized (+)-**1a** was optically impure, the present synthesis unambiguously established the (1*S*, 2*S*, 5*R*, 6*S*)-configuration of the natural and dextrorotatory phrymarolin I.

Experimental

All melting points and boiling points are uncorrected. IR spectra were determined on a Shimadzu IR-420 spectrophotometer. Unless stated otherwise, ^1H NMR spectra were measured in $CDCl_3$ on a JEOL FX-100 spectrometer. Mass spectra were performed by an ESCO FMD-05A spectrometer at 70 ev. Optical rotations were determined on a Union Giken PM-101 polarimeter.

Gravity column chromatography and medium-pressure liquid chromatography were performed with Merck silica gel 60 (70—230 mesh ASTM) and Merck LiChroprep Si 60 (40—63 μm), respectively. TLC was performed on precoated silica-gel plates 60 F_{254} (0.25 mm or 0.5 mm thickness) supplied by E. Merck. Anhydrous sodium sulfate was used for drying solutions.

Optical Resolution of β-Vinyl-γ-butyrolactone. To a solution of (*S*)-(−)-α-methylbenzylamine (10.82 g, 89.2 mmol) in dry CH_2Cl_2 (300 ml) was added a 1 mol dm^{-3} solution of Et_3Al in hexane (90.0 ml, 90.0 mmol). After 30 min, (±)-**5** (10.00 g, 89.2 mmol) was added. The mixture was heated under reflux for 5 h and then poured into a mixture of 2 mol dm^{-3} aqueous HCl and crushed ice. The CH_2Cl_2 layer was separated, washed with water, dried, and concentrated in vacuo. The crude product was purified by medium-pressure liquid chromatography on silica gel eluted with 3 vol% *i*-PrOH in EtOAc to give **7a** (5.38 g, 23.1 mmol) and **7b** (6.37 g, 27.3 mmol) in 56% combined yield. **7a**: mp 97—99 °C; $[\alpha]_D^{14}$ −100.0° (*c* 2.3, $CHCl_3$). **7b**: A viscous oil; $[\alpha]_D^{14}$ −78.2° (*c* 2.2, $CHCl_3$).

A solution of **7a** (5.25 g, 22.5 mmol) in 1 mol dm^{-3} KOH in ethylene glycol (35 ml) was heated at 175 °C under an atmosphere of nitrogen for 10 h. The mixture was then cooled to room temperature, acidified with 2 mol dm^{-3} aqueous HCl (20 ml), diluted with brine, and extracted three times with EtOAc. The organic extracts were combined, dried, and concentrated in vacuo. The crude product was dissolved in benzene (50 ml) and a catalytic amount of *p*-TsOH was added. The resulting solution was heated under reflux with a concominant removal of water. After the mixture had been cooled to room temperature and concentrated in vacuo, the oily residue was chromatographed on silica gel. Elution with hexane-ether (1 : 1) gave crude (+)-**5**, which was distilled using micro Kugelrohr to afford pure (*S*)-(+)-**5** (1.39 g, 58%) as a colorless oil: bp 170 °C (bath)/2666 Pa; $[\alpha]_D^{19}$ +4.9° (*c* 4.3, EtOH). In the same manner as above, the amide (**7b**) gave (*R*)-(−)-**5** in 64% yield: $[\alpha]_D^{22}$ −5.2° (*c* 2.3, EtOH).

A Mixture of (3*R*,4*S*)-4-Ethenyl-3-[(1*R*/*S*)-1-hydroxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]dihydro-2(3*H*)-furanones (9). To a solution of LDA [prepared from butyllithium (15 wt% in hexane, 5.90 ml, 9.5 mmol) and diisopropylamine (1.33 ml, 9.5 mmol) at −10 °C for 15 min in dry THF (30 ml)] was added as drops a solution of (*S*)-(+)-**5** (1.00 g, 8.9 mmol) in dry THF (5 ml) at −75 °C under an atmosphere of dry argon. After 30 min, a solution of 2-methoxy-4,5-methylenedioxybenzaldehyde (1.76 g, 9.8 mmol) in dry THF (20 ml) was added as drops. After 3 h at −75 °C, the reaction was quenched by 10 wt% aqueous NH_4Cl. The solution was then allowed to warm up to room temperature and was extracted twice with ether. The combined organic layers were washed with 5 wt% aqueous $NaHCO_3$ and brine, dried, and evaporated. The crude product was chromatographed on silica gel eluted with EtOAc-benzene (1 : 9) to afford the diastereomeric aldols (**9**) (2.52 g, 8.63 mmol, 97%) as a slightly yellow viscous oil: IR ($CHCl_3$) 1040, 1150, 1185, 1483, 1760, and 3350 cm^{-1}; MS *m*/*z* 292 (M$^+$), 181, 166, 165, 151, 123, 95, and 53. Found: C, 61.51; H, 5.60%. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%.

A Mixture of (3*R*,4*S*)-3-[(1*R*/*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-4-ethenyldihydro-2(3*H*)-furanones (10). A solution of *t*-$BuMe_2SiOTf$ (3.0 ml, 12.9 mmol) in dry CH_2Cl_2 (7 ml) was added as drops to a solution of **9** (2.52 g, 8.63 mmol) and 2,6-lutidine (2.0 ml, 17.3 mmol) in the same solvent (30 ml) at −30 °C under an atmosphere of dry argon. After 40 min at that temperature, the mixture was poured into 5 wt% aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ether (75 ml). The combined organic layers were washed successively with 10 wt% aqueous $Cu(NO_3)_2$ and brine, dried, and evaporated. The oily residue was chromatographed on silica gel eluted with hexane-EtOAc (3 : 1) to give the silyl ether (**10**, 3.22 g, 7.93 mmol, 92%) as a mixture of diastereomers. A part of the mixture was separated by medium-pressure liquid chromatography on silica gel with EtOAc-benzene (1 : 19) as the eluant. *erythro*-**10**: A viscous oil; ^{1}H NMR δ=−0.09 (3H, s), 0.12 (3H, s), 0.93 (9H, s), 2.68 (1H, dd, *J*=3 and 8 Hz), 3.06 (1H, m), 3.73 (3H, s), 3.81 (1H, dd, *J*=8 and 9 Hz), 4.21 (1H, dd, *J*=8 and 9 Hz), 5.00—5.30 (3H, m), 5.52—5.84 (1H, m), 5.89 (2H, dd, *J*=3 and 1 Hz), 6.42 (1H, s), and 7.07 (1H, s); IR ($CHCl_3$) 830, 1040, 1150, 1185, 1481, 1762, and 2940 cm^{-1}; MS *m*/*z* 406 (M$^+$), 350, 349, 295, 169, and 75. *threo*-**10**: White crystals (mp 98—101 °C); ^{1}H NMR δ=−0.06 (3H, s), 0.12 (3H, s), 0.93 (9H, s), 2.81 (1H, dd, *J*=3 and 8 Hz), 3.10—3.48 (1H, m), 3.76 (3H, s), 3.88 (1H, dd, *J*=8 and 9 Hz), 4.38 (1H, t, *J*=8 Hz), 4.52—4.82 (2H, m), 5.12—5.44 (1H, m), 5.65 (1H, d, *J*=2 Hz), 5.89 (2H, q, *J*=1 Hz), 6.44 (1H, s), and 6.93 (1H, s). Found: C, 61.99; H, 7.48%. Calcd for $C_{21}H_{30}O_6Si$: C, 62.04; H, 7.44%.

A Mixture of (2*R*,3*R*)-2-[(1*R*/S)-1-[(*t*-Butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-3-vinyl-1,4-butanediols (11). A solution of **10** (3.22 g, 7.93 mmol) in dry THF (25 ml) was added as drops to a stirred slurry of lithium aluminium hydride (0.33 g, 8.68 mmol) in dry ether (50 ml) at −10 °C under an atmosphere of dry argon. After 30 min at −10 °C, the excess reagent was decomposed carefully by the addition of EtOAc followed by 10 wt% aqueous citric acid (100 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc. The two organic extracts were combined, washed with 5 wt% aqueous $NaHCO_3$, dried, and concentrated in vacuo. The oily residue was chromatographed on silica gel eluted with hexane-EtOAc (1 : 1) to give **11** (2.66 g, 6.49 mmol, 82%) as a colorless viscous oil: IR ($CHCl_3$) 835, 1040, 1050, 1070, 1185, 1255, 1462, 1480, 2930, and 3350 cm^{-1}; MS *m*/*z* 295 (M$^+$ −$SiMe_2Bu$-*t*), 278, 180, 179, 165, 163, 134, and 75. Found: C, 61.30; H, 8.36%. Calcd for $C_{21}H_{34}O_6Si$: C, 61.43; H, 8.34%.

A Mixture of (3*R*,4*R*)-3-Hydroxymethyl-4-[(1*R*/*S*)-1-[(*t*-butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]dihydro-2(3*H*)-furanones (13). A solution of **11** (2.66 g, 6.49 mmol), *N*-methylmorpholine *N*-oxide monohydrate (0.96 g, 7.10 mmol) and 2 wt% aqueous OsO_4 (1 ml) in a mixture of acetone (30 ml), *t*-BuOH (7 ml), and water (7 ml) was allowed to stand at room temperature under an atmosphere of argon for 15 h. Celite and aqueous $NaHSO_3$ (0.9 g/15 ml) were added and the mixture was filtered. The residue was washed well with acetone, and the filtrate was concentrated in vacuo. The oily residue was taken up in EtOAc and washed with brine.

To the EtOAc extract was added a solution of $NaIO_4$ (1.40 g, 6.55 mmol) in water (100 ml). The resulting two phases were vigorously stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, and concentrated in vacuo to leave practically pure **12** as a viscous oil, which was used for the next step without further purification.

A mixture of **12** and silver carbonate on Celite (10.0 g, containing ca. 10 mmol of the silver salt) in benzene (75 ml) was heated under reflux for 45 min. After cooling to room temperature, the mixture was filtered through a pad of Celite with more of benzene. After removing the solvent, the oily residue was chromatographed on silica gel eluted with hexane-EtOAc (1 : 1) to give **13** (2.43 g, 5.93 mmol, 91%) as a viscous oil: IR ($CHCl_3$) 835, 1005, 1040, 1150, 1170, 1185, 1260, 1465, 1482, 1760, 2850, and 3500 cm^{-1}; MS *m/z* 335 (M^+ −Bu-*t*), 295, 278, 268, 259, 208, 165, and 75. Found: C, 58.49; H, 7.36%. Calcd for $C_{20}H_{30}O_7Si$: C, 58.51; H, 7.37%.

A Mixture of (4*R*)-4-[(1*R*/*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-3-methylenedihydro-2(3*H*)-furanones (14). Methanesulfonyl chloride (0.69 ml, 8.90 mmol) was added to a solution of **13** (2.43 g, 5.93 mmol) and Et_3N (1.65 ml, 11.86 mmol) in dry benzene (50 ml) at ca. 5 °C. The mixture was stirred at room temperature for 4 h before the addition of DBU (1.35 g, 8.90 mmol). After 30 min, the mixture was washed with water and the aqueous layer was extracted with EtOAc. The two organic layers were combined, washed successively with 10 wt% aqueous citric acid and 5 wt% aqueous $NaHCO_3$, and dried. After removing the solvent, the oily residue was chromatographed on silica gel eluted with hexane-EtOAc (4 : 1) to afford **14** (2.02 g, 5.15 mmol, 87%) as a viscous oil: IR ($CHCl_3$) 1040, 1100, 1185, 1480, and 1755 cm^{-1}. Found: C, 61.14; H, 7.18%. Calcd for $C_{20}H_{28}O_6Si$: C, 61.20; H, 7.19%.

A Mixture of (3*S*,4*R*)-4-[(1*S*/*R*)-1-[(*t*-Butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-3-hydroxy-3-(hydroxymethyl)dihydro-2(3*H*)-furanones (15). A solution of **14** (2.02 g, 5.15 mmol), *N*-methylmorpholine *N*-oxide monohydrate (0.80 g, 5.92 mmol) and 2 wt% aqueous OsO_4 (1 ml) in a mixture of acetone (30 ml), *t*-BuOH (7 ml) and water (7 ml) was allowed to stand at room temperature under an atmosphere of argon for 12 h. Celite and aqueous $NaHSO_3$ (1.0 g/20 ml) were then added and the mixture was filtered through a pad of Celite. The residue was washed well with acetone, and the filtrate was concentrated in vacuo. The oily residue was taken up in EtOAc and washed with brine. The extract was dried, concentrated in vacuo, and chromatographed on silica gel eluted with hexane-EtOAc (1 : 2) to give **15** (2.12 g, 4.98 mmol, 97%) as a gummy oil: IR ($CHCl_3$) 835, 1040, 1070, 1100, 1150, 1185, 1480, 1600, 1770, and 3350 cm^{-1}; MS *m/z* 369 (M^+−Bu-*t*), 295, 294, 277, 191, 181, 180, 165, 161, 133, and 75. Found: C, 56.41; H, 7.09%. Calcd for $C_{20}H_{30}O_8Si$: C, 56.31; H, 7.09%.

(1*S*,5*R*,6*S*)-(+)-1-Hydroxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one (17a). A 1 mol dm^{-3} solution of *n*-Bu_4NF in THF (6.00 ml, 6.00 mmol) was added to a solution of **15** (2.12 g, 4.98 mmol) in dry THF (20 ml) at 0 °C. After 2 h at 0 °C the mixture was poured into 10 wt% aqueous NH_4Cl and extracted twice with EtOAc. The extracts were combined, dried, concentrated in vacuo, and chromatographed on silica gel eluted with EtOAc to give **16** as a gummy oil. Found: C, 53.74; H, 5.30%. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16%.

The triol **16** was dissolved in dry CH_2Cl_2 (50 ml) containing a catalytic amount of 10-camphorsulfonic acid. The solution was stirred at room temperature for 3 h before being quenched with a few drops of Et_3N. After removing the solvent, the oily residue was chromatographed on silica gel eluted with hexane-EtOAc (1 : 1) to afford **17a** (0.86 g, 2.93 mmol, 59%) as white crystals. An analytically pure sample was obtained by recrystallization from *i*-Pr_2O-benzene: mp 136—137.5 °C; $[\alpha]_D^{25}$ +67.3° (*c* 2.02, $CHCl_3$); ^{1}H NMR (acetone-d_6) δ=2.84 (1H, s), 2.93 (1H, dt, *J*=8 and 5 Hz), 3.81 (3H, s), 4.11 (2H, s), 4.38 (1H, dd, *J*=5 and 10 Hz), 4.63 (1H, dd, *J*=8 and 10 Hz), 5.07 (1H, d, *J*=5 Hz), 5.92 (2H, s), 6.67 (1H, s), and 6.97 (1H, s); IR ($CHCl_3$) 1040, 1115, 1160, 1187, 1481, 1774, and 3400 cm^{-1}; MS *m/z* 294 (M^+), 277, 180, 165, and 133. Found: C, 57.06; H, 4.81%. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80%.

(1*S*,5*R*,6*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one (19). A solution of *t*-$BuMe_2SiOTf$ (0.70 ml, 2.30 mmol) in dry CH_2Cl_2 (2 ml) was added as drops to a solution of (+)-**17a** (0.48 g, 1.63 mmol) and 2,6-lutidine (0.57 ml, 4.89 mmol) in the same solvent (10 ml) at −10 °C under an atmosphere of dry argon. The reaction mixture was gradually warmed up to room temperature and kept at this temperature for 18 h. The mixture was then diluted with ether (30 ml) and washed successively with 5 wt% aqueous $NaHCO_3$, 20 wt% aqueous $Cu(NO_3)_2$, brine, and again 5 wt% aqueous $NaHCO_3$. The ethereal extract was dried, concentrated in vacuo, and chromatographed on silica gel eluted with hexane-EtOAc (4 : 1) to give **19** (0.57 g, 1.39 mmol, 85%) as a colorless oil: ^{1}H NMR δ=0.04 (3H, s), 0.17 (3H, s), 0.81 (9H, s), 2.92 (1H, m), 3.76 (3H, s), 4.08 (1H, d, *J*=10 Hz), 4.21 (1H, d, *J*=10 Hz), 4.33 (1H, dd, *J*=5 and 10 Hz), 4.57 (1H, dd, *J*=8 and 10 Hz), 5.05 (1H, d, *J*=5 Hz), 5.90 (2H, s), 6.49 (1H, s), and 6.97 (1H, s); IR ($CHCl_3$) 843, 1043, 1160, 1195, 1487, 1780, and 2960 cm^{-1}; MS *m/z* 408 (M^+), 352, 351, 181, 165, 127 (base), and 75. Found: C, 58.73; H, 6.90%. Calcd for $C_{20}H_{28}O_7Si$: C, 58.80; H, 6.91%.

A Mixture of (1*S*,2*R*/*S*,5*R*,6*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-2-hydroxy-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octanes (21). A 1 mol dm^{-3} solution of DIBAL in toluene (1.60 ml, 1.60 mmol) was added as drops to a solution of **19** (566 mg, 1.39 mmol) in dry toluene (12 ml) at −70 °C under an atmosphere of dry argon. After 1 h at −75 °C, the mixture was diluted with ether and washed successively with 1 mol dm^{-3} aqueous HCl and 5 wt% aqueous $NaHCO_3$. The ethereal extract was dried, concentrated in vacuo, and chromatographed on silica gel eluted with hexane-EtOAc (2 : 1) to give **21** (567 mg, 1.38 mmol, 99%) as a viscous oil: ^{1}H NMR δ=0.04—0.28 (6H, s×4), 0.84—0.96 (9H, s×2), 2.28—2.68 (1H, m), 3.48—4.32 (5H, m), 3.75 (3H, s), 4.68—4.98 (1H, d×2, *J*=7 and 8 Hz), 5.02—5.24 (1H, d×2, *J*=6 and 8 Hz), 5.91 (2H, s), 6.49 (1H, s), and 6.94—7.06 (1H, s×2); IR ($CHCl_3$), 840, 910, 1045, 1190, 1260, 1487, 2970, and 3150—3650 cm^{-1}; MS *m/z* 410 (M^+), 394, 353, 191, 173, 165 (base), 161, and 75. Found: C, 58.70; H, 6.85%. Calcd for $C_{20}H_{30}O_7Si$: C, 58.51; H, 7.37%.

A Mixture of (1*S*,2*R*/*S*,5*R*,6*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-2-fluoro-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octanes (3). A solution of **21** (146 mg, 0.36 mmol), 2-fluoro-1-methylpyridinium tosylate (150 mg, 0.54 mmol) and Et_3N (0.10 ml, 0.72 mmol) in dry CH_2Cl_2 (3 ml) was stirred at room temperature for 50 min. The mixture was then concentrated in vacuo and the residue was chromatographed on silica gel. Elution with hexane-EtOAc (3 : 1) afforded **3** (134 mg, 0.33 mmol, 92%) as a viscous oil: ^{1}H NMR δ=0.10 (6H, s), 0.84—0.88 (9H, s×2), 2.36—2.90 (1H, m), 3.48—4.48 (4H, m), 3.74 (3H, s), 4.74—5.06 (1H, d×2, *J*=7 Hz each), 5.06—5.90 (1H, d×2, *J*=64 Hz each), 5.90 (2H, s), 6.47 (1H, s), and 7.00—7.06 (1H, s×2); IR ($CHCl_3$) 838, 1035, 1042, 1105, 1145, 1160, 1190, 1260, 1485, and 2950 cm^{-1}; MS *m/z* 412 (M^+), 355 (base), 191, 175, 165, and 75.

(1*S*,2*S*,5*R*,6*S*)-(+)-1-Hydroxy-2-(2-methoxy-4,5-methylenedioxyphenoxy)-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane and Its (1*S*,2*R*,5*R*,6*S*)-Isomer [23a (Desacetyl Phrymarolin I) and 23b]. A mixture of the fluoride **3** (130 mg, 0.32 mmol), 2-methoxy-4,5-methylenedioxyphenol (62 mg, 0.38 mmol), $TrClO_4$ (0.13 g, 0.38 mmol), $SnCl_2$ (0.12 g, 0.64 mmol) and pulverized 4A Molecular Sieve in dry ether (10 ml) was stirred at 0—5 °C for 2.5 h. After the reaction had been quenched by 0.5 mol dm^{-3} aqueous NaOH, the resulting mixture was filtered through a pad of Celite with the aid of ether. The ethereal layer was separated, washed with 0.5 mol dm^{-3} NaOH, dried, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel developed with benzene-EtOAc (19 : 1) to give a mixture of **22a** and **22b** (88 mg, 0.16 mmol, 50%).

The crude product was dissolved in dry THF (2 ml) and a 1 mol dm^{-3} solution of n-Bu_4NF in THF (0.35 ml, 0.35 mmol) was added. After 1.5 h at room temperature, the mixture was diluted with CH_2Cl_2, washed with 10 wt% aqueous NH_4Cl, dried, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel developed with 20 vol% EtOAc in benzene to give **23a** (15.5 mg, 0.034 mmol, 21%) and **23b** (41.6 mg, 0.093 mmol, 58%). **(1*S*,2*S*,5*R*,6*S*)-23a:** mp 133—134 °C (lit. mp 133—134 °C); $[\alpha]_D^{23}$ +128.6° (c 0.49, $CHCl_3$); ^1H NMR δ=2.57 (1H, m), 3.72 (1H, d, J=10 Hz), 3.74 (3H, s), 3.75 (3H, s), 3.70—3.90 (1H, br), 4.06 (1H, dd, J=3 and 10 Hz), 4.31 (1H, d, J=10 Hz), 4.40 (1H, dd, J=7 and 10 Hz), 4.91 (1H, d, J=6 Hz), 5.16 (1H, s), 5.88 (2H, s), 5.89 (2H, s), 6.48 (1H, s), 6.53 (1H, s), 6.76 (1H, s), and 7.12 (1H, s); IR ($CHCl_3$) 1040, 1070, 1165, 1185, 1485, 1503, 2900, and 3150—3650 cm^{-1}; MS m/z 446 (M^+), 278, 181, 180, 168 (base), 165, and 153. **(1*S*,2*R*,5*R*,6*S*)-23b:** $[\alpha]_D^{24}$ −38.1° (c 1.39, $CHCl_3$); ^1H NMR δ=2.64 (1H, q, J=7 Hz), 2.80—3.20 (1H, br), 3.74 (3H, s), 3.78 (3H, s), 4.05 (1H, d, J=11 Hz), 4.18 (2H, d, J=7 Hz), 4.53 (1H, d, J=11 Hz), 5.02 (1H, d, J=7 Hz), 5.30 (1H, s), 5.87 (2H, s), 5.89 (2H, s), 6.47 (1H, s), 6.54 (1H, s), 6.74 (1H, s), and 7.05 (1H, s); IR ($CHCl_3$), 865, 940, 1005, 1040, 1162, 1185, 1430, 1483, 1502, 2900, and 3150—3650 cm^{-1}; MS m/z 446 (M^+), 278, 181, 180, 168 (base), 165, and 153.

(1*S*,2*S*,5*R*,6*S*)-(+)-1-Acetoxy-2-(2-methoxy-4,5-methylenedioxyphenoxy)-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane [1a (Phrymarolin I)]. A mixture of **23a** and a catalytic amount of DMAP in Ac_2O (ca. 1 ml) was allowed to stand at room temperature for 12 h before being poured onto crushed ice. After the ice had melted, the precipitated solids were collected and dissolved in EtOAc. The extract was washed successively with 1 mol dm^{-3} aqueous HCl and 5 wt% aqueous $NaHCO_3$, dried, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel developed with benzene-EtOAc (9 : 1) to give **1a** as white crystals: mp 155—157 °C (lit. mp 155—157 °C); $[\alpha]_D^{25}$ +106.9° (c 0.11, dioxane); ^1H NMR δ=2.12 (3H, s), 2.88 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 3.80 (1H, d, J=11 Hz), 4.03 (1H, dd, J=2 and 9 Hz), 4.49 (1H, dd, J=7 and 9 Hz), 4.60 (1H, d, J=11 Hz), 4.87 (1H, d, J=7 Hz), 5.66 (1H, s), 5.86 (2H, s), 5.91 (2H, s), 6.51 (2H, s), 6.82 (1H, s), and 7.03 (1H, s).

This work was partially supported by a a Grant-in-Aid for Research No. 59470113 from Ministry of Education, Science and Culture.

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13) Compound **4** was synthesized by Baeyer-Villiger oxidation of 2-methoxy-4,5-methylenedioxybenzaldehyde (**6**) with m-chloroperbenzoic acid and potassium fluoride in dichloromethane, followed by alkaline hydrolysis.