TOTAL SYNTHESIS OF THE MAJOR METABOLITES OF GOMISIN A. SYNTHESIS OF HOMOCHIRAL MET A-II, MET A-III, MET D, AND MET F

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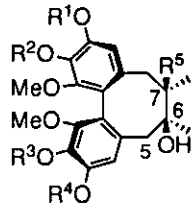
Abstract - The total syntheses of the metabolites of gomisin A (**1**) were achieved. By the Mukaiyama hydration or the successive double bond migration, lactone ring reduction, glycol formation, and reduction, the homochiral lactones (**10a-c**) provided met A-III (**3**), A-II (**2**), D (**5**), and F (**7**).

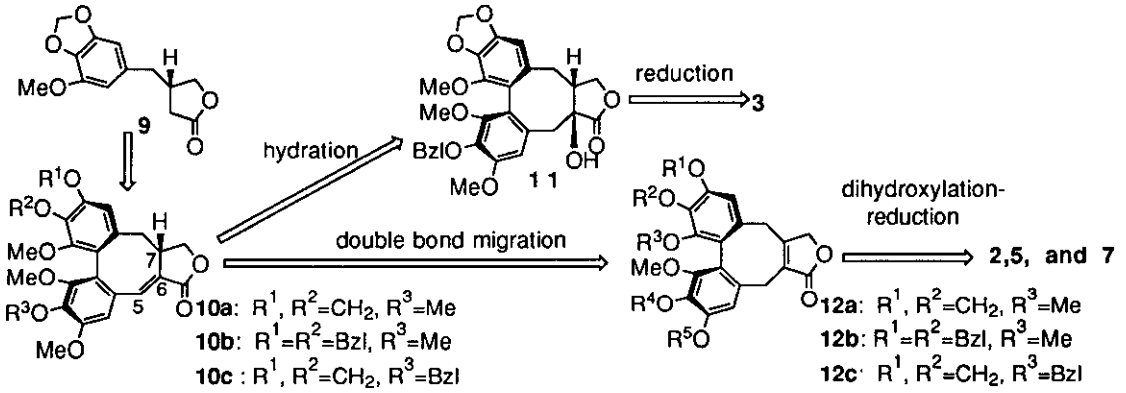
Gomisin A (**1**) is one of the components isolated from the fruits of *Schisandra chinensis* Bail.[1] (Schisandraceae), and pharmacologically **1** shows a antihepatotoxic action.[2] By the study of the metabolisms of **1** *in vitro* and *in vivo* by Ikeya and co-workers,[3] the metabolic transformations were found to cause the dealkylation of aromatic ether moiety and/or hydroxylation of eight membered ring at C7 position affording the variety of metabolites (met A-II (**2**), met A-III (**3**), met B (**4**), met D (**5**), met E (**6**), met F (**7**), met G (**8**)). In the course of our synthetic research of lignans isolated from *Schisandra chinensis*,[4,5] the synthesis of these metabolites attracted our concern. In this paper we report the total synthesis of the representative four metabolites (met A-II (**2**), met A-III (**3**), met D (**5**),met F (**7**)) in optically pure forms.[6]



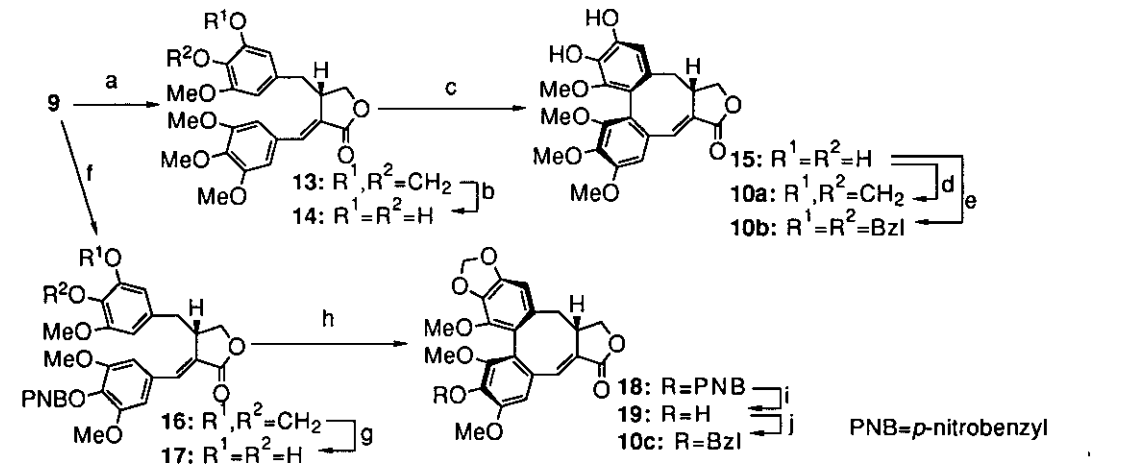
1: R^1, R^2=CH_2, R^3=R^4=Me, R^5=H; gomisin A
2: R^1, R^2=CH_2, R^3=R^4=Me, R^5=OH; met A-II
3: R^1, R^2=CH_2, R^4=Me, R^3= R^5=H; met A-III
4: R^1=R^2=R^5=H, R^3=R^4=Me; met B
5: R^1, R^2=CH_2, R^4=Me, R^3=H, R^5=OH; met D
6: R^1, R^2=CH_2, R^3=Me, R^4= R^5=H; met E
7: R^1=R^2=H, R^3=R^4=Me R^5=OH; met F
8: R^1, R^2=CH_2, R^3=Me, R^4=H, R^5=OH; met G

For the synthesis of the optically pure metabolites of **1**, we adopted the strategy originally developed by Robin and co-workers[6f] and successfully extended by our group for the total synthesis of variety of dibenzocyclooctene

lignans (gomisin A,[6j] gomisin N,[6n] kadsurin,[6p] *etc.*[6g,k]). In this strategy, the tetracyclic lactones (**10a-c**) were the key intermediates. The introduction of hydroxyl group at C6 position by the hydration reaction would lead to the synthesis of **3** through hydroxy lactone (**11**). On the other hand, double bond migration of **10a-c** to the butenolides (**12a-c**) followed by the dihydroxylation reaction was expected to offer the route to the other metabolites (**2**, **5**, and **7**) (Scheme 1)



Scheme 1. Strategy for the synthesis of the metabolites of gomisin A.



a) LDA, 3,4,5-trimethoxybenzaldehyde, THF, -78 °C; Ac_2O, Et_3N, CH_2Cl_2, room temperature; DBU, toluene, 60 °C: b) BCl_3, CH_2Cl_2, 0 °C; HCl, MeOH, room temperature (91% from **9**): c) $Fe(ClO_4)_3{\cdot}6H_2O$, CF_3CO_2H, CH_2Cl_2, room temperature: d) CH_2Br_2, K_2CO_3, DMF, 80 °C (62% from **14**): e) BzlBr, K_2CO_3, DMF, 60 °C (72% from **14**): f) LDA, 3,5-dimethoxy-4-(4-nitrobenzyloxy)benzaldehyde, THF, -78 °C; Ac_2O, Et_3N, CH_2Cl_2, room temperature; DBU, toluene, 60 °C (88%): g) BCl_3, CH_2Cl_2, -50 °C; HCl, THF, room temperature (52%): h) $Fe(ClO_4)_3{\cdot}6H_2O$, CF_3CO_2H, CH_2Cl_2, room temperature; CH_2I_2, K_2CO_3, DMF, 75 °C (46%): i) H_2, Pd-C, AcOEt, room temperature (100%): j) BzlBr, K_2CO_3, DMF, 60 °C (83%).

Scheme 2. The synthesis of the tetracyclic intermediates (**10a-c**).

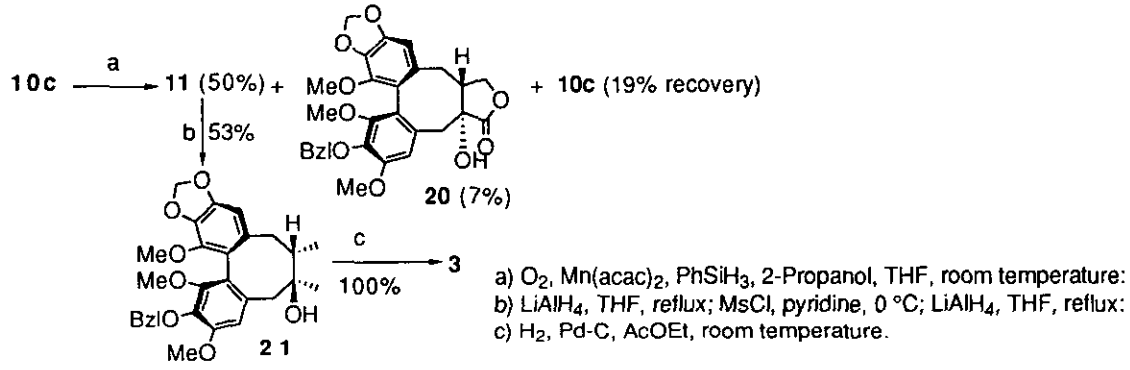
The Synthesis of the Tetracyclic Key Intermediates (10a-c)

As the synthesis of **10a** has already been reported,[6j] our synthesis started with the preparation of **10b** and **10c** from the readily available optically pure benzylbutyrolactones (**9**).[6j,7,8] (Scheme 2). Aldol condensation of

3,4,5-trimethoxybenzaldehyde with **9** followed by the demethylenation provided **14**. Then, **14** was transformed into **10b** by the successive oxidative coupling[6j,9] and the protection of the hydroxyl group as the benzyl ether. Similarly, use of 3,5-dimethoxy-4-(4-nitrobenzyloxy)benzaldehyde instead of 3,4,5-trimethoxybenzaldehyde and methylenation of the oxidative coupling product provided **18**. Then, the replacement of the 4-nitrobenzyl group with benzyl group afforded **10c**.[10]

The Synthesis of met A-III (3)

For the introduction of hydroxyl group to **10c** at C6 position, the Mukaiyama hydration reaction was utilized (Scheme 3).[11] In the presence of manganese(II) acetylacetonate, **10c** was hydrated with oxygen and phenylsilane in 2-propanol providing **11** and **20** in 50% and 7% yields, respectively. By the reduction of lactone ring to dimethyl group, **11** was converted into benzyl ether of met A-III (**21**), which was debenzylated finishing the total synthesis of **3**. The physical data of synthetic **3** were completely identical with those of **3** which was isolated by Ikeya by the treatment of **1** with S9-mix.[3]

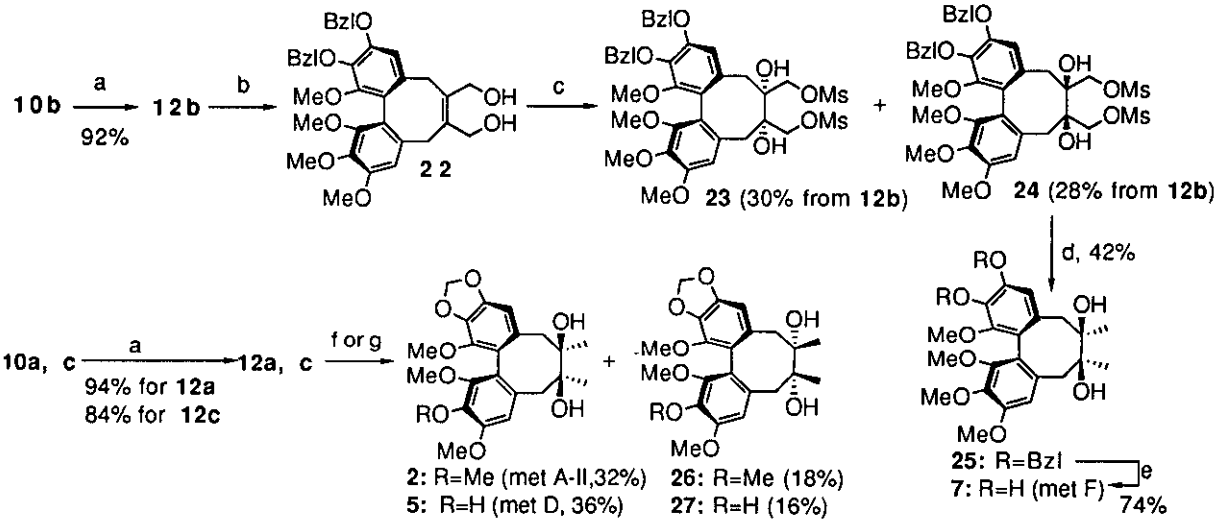


Scheme 3. The total synthesis of met A-III (**4**) from **10c**.

The Synthesis of met A-II (2), met D (5), and met F (7)

The synthesis of the metabolites which possess C6,7-diol unit can be represented by that of met F (**7**). The isomerization of **10b** to the corresponding butenolide (**12b**) was attained by the rhodium complex-triethylsilane catalyzed reaction developed by our group (Scheme 4).[12] The reaction proceeded in high yield (92%) affording the desired butenolide (**12b**). Then, **12b** was reduced to the corresponding allylic diol (**22**), which was treated with osmium tetroxide for the introduction of C6,7 diol moiety. After methanesulfonylation, the resultant dimesylates were separated affording two isomeric products (**23** and **24**) in the ratio of 1:1 reflecting the nonfaceselective nature of the glycol formation step. Lithium aluminum hydride reduction of the desired isomer (**24**) provided met F dibenzyl ether (**25**), and finally, deprotection of benzyl group finished the synthesis of **7**. The spectroscopic data of synthetic **7** were completely identical with those of naturally derived **7**.

In a identical manner, the syntheses of **2** and **5** were achieved. **10a** and **10c** were isomerized to **12a**, and **12c** (94% and 84%, respectively). Each butenolide was reduced, dihydroxylated, mesylated, reduced, and deprotected (only for the synthesis of **5**) to establish the synthesis of **2** and **5**. The spectroscopic data of synthetic **2** and **5** were identical with those of naturally derived **2** and **5**, respectively.[3]



a) $Rh(PPh_3)_3Cl$, Et_3SiH, toluene, reflux: b) DIBAH, THF, reflux: c) OsO_4, NMO, acetone-H_2O, room temperature; MsCl, pyridine, 0 °C: d) $LiAlH_4$, THF, reflux: e) H_2, Pd-C, AcOEt, room temperature: f (for **12a**)) DIBAH, THF, reflux; OsO_4, NMO, acetone-H_2O, room temperature; MsCl, pyridine, 0 °C; $LiAlH_4$, THF, reflux: g (for **12c**)) DIBAH, THF, reflux; OsO_4, NMO, acetone-H_2O, room temperature; MsCl, pyridine, 0 °C; $LiAlH_4$, THF, reflux; H_2, Pd-C, AcOEt, room temperature.

Scheme 4. The total synthesis of met A-II (**2**), met D (**5**), and met F (**7**).

EXPERIMENTAL

General Methods. Melting Points were measured using Buchi 535 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-360 polarimeter. Ir spectra were taken with a Hitachi 270-30 spectrophotometer. Nmr spectra were taken in deuteriochloroform with a JEOL FX-200 Spectrometer at 200 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (ms) and high resolution mass spectra (HR-ms) were taken with a KRATOS CONCEPT 32 1H and 1S mass spectrometers. Flash chromatography was performed with silica gel 60 (230-400 mesh).

***(S)-(E)*-3-(5-Methoxy-3,4-methylenedioxybenzyl)-2-(3,4,5-trimethoxybenzylidene)-butanolide (13)** To solution of diisopropylamine (3.5 ml, 24 mmol) in tetrahydrofuran (THF) (20 ml) under argon (Ar) at -70 °C was added *n*-butyllithium (BuLi) (1.66 M in hexane, 14.8 ml, 24.6 mmol). Stirring at -70 °C was continued for 10 min, followed by the addition of **9** (5.0 g, 20 mmol) in THF (50 ml). The mixture was

stirred at -70 °C for 30 min, followed by the addition of the 3,4,5-trimethoxybenzaldehyde (4.7 g, 20 mmol) in THF (20 ml). Stirring was continued for 5 min, followed by the addition of a saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (AcOEt), the combined extracts were washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was dissolved in CH_2Cl_2 (50 ml), triethylamine (Et_3N) (7 ml), acetic anhydride (Ac_2O) (5 ml), and dimethylaminopyridine (DMAP) (100 mg) were added, and the mixture was stirred at room temperature for 1 h. The mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in toluene (70 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.5 ml) was added, and the mixture was stirred at 80 °C for 1.5 h. The reaction mixture was taken up into AcOEt, washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:2) to afford **13** (8.0 g, 94%) as a pale yellow solid; mp 79-81 °C (colorless prisms from AcOEt-hexane); $[\alpha]_D^{24}$ +67.5° (*c* 0.835, $CHCl_3$); ^1H nmr: 2.64 (1H, dd, J = 10, 14 Hz), 3.01 (1H, dd, J = 5, 14 Hz), 3.83-3.90 (1H, m), 3.86 (3H, s), 3.89 (6H, s), 3.90 (3H, s), 4.22-4.36 (2H, m), 5.93 (2H, s), 6.28 (1H, d, J = 1.5 Hz), 6.33 (1H, d, J = 1.5 Hz), 6.77 (2H, s), 7.51 (1H, d, J = 1.7 Hz); ir ($CHCl_3$): 1746, 1644, 1582 cm^{-1}; ms (m/z) 428 (M^+). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.20; H, 5.66.

(*S*)-(*E*)-3-(3,4-Dihydroxy-5-methoxybenzyl)-2-(3,4,5-trimethoxybenzylidene)butanolide (14) To a stirred solution of **13** (0.84 g, 1.96 mmol) in CH_2Cl_2 (10 ml) was added BCl_3 (1.0 M in CH_2Cl_2, 4 ml, 4 mmol), and the mixture was stirred at 0 °C for 30 min. After evaporation of the solvent, the residue was taken up into methanol (MeOH) (20 ml), and 2N HCl (6 ml) was added. After stirring at room temperature for 2 h, the reaction mixture was taken up into AcOEt, washed successively with H_2O and brine, and dried over $MgSO_4$. After evaporation of the solvent, **14** was obtained as a colorless amorphous solid (790 mg, 97%); $[\alpha]_D^{27}$ +50.3° (c 0.7, $CHCl_3$); ^1H nmr: 2.60 (1H, dd, J = 10, 14 Hz), 3.04 (1H, dd, J = 5, 14 Hz), 3.83 (3H, s), 3.89 (6H, s), 3.90 (3H, s), 3.78-3.90 (1H, m), 4.24-4.30 (2H, m), 5.31 (1H, s), 5.36 (1H, s), 6.43 (1H, d, J = 2 Hz), 6.23 (1H, d, J = 2 Hz), 6.79 (2H, s), 7.51 (1H, d, J = 2 Hz); ir ($CHCl_3$): 3556, 1746, 1646, 1620, 1582 cm^{-1}; ms (m/z) 416 (M^+); HR-ms (m/z) for $C_{22}H_{24}O_8$ (M^+): 416.14702. Found: 416.14652.

(3a*S*,*R*-Biar)-3a,4-Dihydro-8,9,10,11-tetramethoxy-6,7-methylenedioxydibenzo[4,5:6,7]-cycloocta[1,2-*c*]furan-1(3*H*)-one (10a) A solution of **14** (4.18 g, 10 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (9.64 g, 21 mmol), and CF_3CO_2H (100 ml) in CH_2Cl_2 (100 ml) was stirred at room temperature for 2.5 h. The mixture

was taken up into AcOEt, washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue (**15**) was dissolved in dimethylformamide (DMF) (20 ml), K_2CO_3 (13 g, 94 mmol) and CH_2Br_2 (3.2 ml, 46 mmol) were added, and the mixture was stirred at 80 °C for 1.5 h. The reaction mixture was taken up into AcOEt, washed successively with H_2O and brine, then dried over $MgSO_4$. The evaporation of the solvent and chromatography of the residue (AcOEt-hexane=1:1) gave **10a** as a colorless solid (2.66 g, 62% from **14**); mp 179.0-180.0 °C; $[\alpha]_D^{27}$ -359° (c 1.10, $CHCl_3$); ir (KBr): 1746, 1666, 1642, 1590 cm^{-1}; ^1H nmr: 2.43 (1H, d, J = 14 Hz), 2.99 (1H, dd, J = 6, 14 Hz), 3.40-3.60 (1H, m), 3.63 (3H, s), 3.81 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 4.44 (1H, t, J = 9 Hz), 4.09 (1H, dd, J = 9, 10 Hz), 5.96 (1H, d, J = 1.5 Hz), 5.98 (1H, d, J = 1.5 Hz), 6.58 (1H, s), 6.34 (3H, s), 7.51 (1H, d, J = 3 Hz); ms (m/z) 426 (M^+). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.49; H, 5.06.

(3a*S*,*R*-Biar)-6,7-Dibenzyloxy-3a,4-dihydro-8,9,10,11-tetramethoxydibenzo[4,5:6,7]-cycloocta[1,2-*c*]furan-1(3*H*)-one (10b) To a solution of **14** (1.15 g, 2.76 mmol) in CF_3CO_2H (30 ml) and CH_2Cl_2 (30 ml) was added $Fe(ClO_4)_3 \cdot 6H_2O$ (3.0 g, 6.5 mmol), and the resultant mixture was stirred at room temperature for 30 min. AcOEt was added, the resultant mixture was successively washed with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in acetone (30 ml), benzyl bromide (1.7 ml, 14.3 mmol) and K_2CO_3 (3.6 g, 26 mmol) were added, the resultant mixture was heated under reflux for 3 h, and cooled to room temperature. Et_3N (10 ml) was added, the resultant mixture was stirred at room temperature for 1 day, and the solvent was removed under reduced pressure. The residue was taken up into AcOEt, the organic layer was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:2) to give **10b** as a colorless oil (1.18 g, 72%); $[\alpha]_D^{24}$ -222° (c 0.46, $CHCl_3$); ^1H nmr: 2.38 (1H, d, J = 14 Hz), 3.03 (1H, dd, J = 7, 14 Hz), 3.38-3.60 (1H, m), 3.61 (3H, s), 3.63 (3H, s), 3.83 (3H, s), 3.92 (3H, s), 3.82 (1H, dd, J = 9, 10 Hz), 4.34 (1H, t, J = 9 Hz), 5.00-5.18 (4H, m), 6.39 (1H, s), 6.59 (1H, s), 7.26-7.42 (10H, m), 7.52 (1H, d, J = 3 Hz); ir ($CHCl_3$): 3012, 1754, 1674, 1594 cm^{-1}; ms (m/z) 594 (M^+); HR-ms (m/z) Calcd for $C_{36}H_{34}O_8$ (M^+): 594.22537. Found: 594.22506.

(*S*)-(*E*)-3-(5-Methoxy-3,4-methylenedioxybenzyl)-2-[4-(4-nitrobenzyloxy)-3,5-dimethoxy-benzylidene]butanolide (16) BuLi (1.66 M in hexane, 9 ml, 14.9 mmol) was added to a solution of diisopropylamine (2.1 ml, 14.6 mmol) in THF (30 ml) at -70 °C, and the mixture was stirred at -70 °C for 10 min. A solution of **9** (3.0 g, 12 mmol) in THF (30 ml) was added to this mixture, and the resultant mixture was

stirred at -70 °C for 30 min. A solution of 3,5-dimethoxy-4-(4-nitrobenzyloxy)benzaldehyde (4.5 g, 14 mmol) in THF (75 ml) was added, the mixture was stirred at -70 °C for 5 min, and the reaction was quenched by saturated NH_4Cl. AcOEt was added, the separated organic layer was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was taken up into CH_2Cl_2 (30 ml), Ac_2O (3.0 ml), Et_3N (4.5 ml), and DMAP (50 mg) were added, and the resultant mixture was stirred at room temperature for 15.5 h. The mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was heated with DBU (4.5 ml) in toluene (50 ml) at 70 °C for 3 h. AcOEt was added, and the organic layer was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The solvent was evaporated, then the residue was chromatographed (AcOEt-hexane=1:2) to give **16** as a pale yellow solid (9.2 g, 88%); mp 93.5-95.0 °C (yellow prisms from AcOEt); $[\alpha]_D^{24}$ +43.1° (c 1.06, $CHCl_3$); ^{1}H-nmr: 2.64 (1H, dd, J = 10, 14 Hz), 2.99 (1H, dd, J = 5, 14 Hz), 3.70-3.90 (1H, m), 3.86 (3H, s), 3.87 (6H, s), 4.20-4.38 (2H, m), 5.17 (2H, s), 5.93 (2H, s), 6.27 (1H, d, J = 1.5 Hz), 6.32 (1H, d, J = 1.5 Hz), 6.76 (2H, s), 7.52 (1H, d, J = 1.7 Hz), 7.68 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz); ir (KBr): 1742, 1644, 1606, 1582 cm^{-1}; ms (m/z) 549 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{27}NO_{10}$ (M^+): 549.16250. Found: 549.16332. Anal. Calcd for $C_{29}H_{27}NO_{10}\cdot 1/2H_2O$: C, 62.36; H, 5.05; N, 2.51. Found: C, 62.39; H, 5.27; N, 2.41.

(*S*)-(*E*)-3-(3,4-Dihydroxy-5-methoxybenzyl)-2-[4-(4-nitrobenzyloxy)-3,5-dimethoxybenzylidene]butanolide (17) To a stirred solution of **16** (3.24 g, 5.9 mmol) in CH_2Cl_2 (100 ml) was added a solution of BCl_3 (1.0 M in CH_2Cl_2, 55 ml, 55 mmol) at -50 °C, the mixture was stirred at -50 °C for 15 min, and then H_2O (20 ml) was added. After evaporation of the solvent, the residue was taken up into THF (80 ml), and 12N HCl (20 ml) was added. After stirring at room temperature for 2.5 h, the reaction mixture was taken up into AcOEt, washed with H_2O and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:1) to give **17** as a colorless foam (1.66 g, 52%); $[\alpha]_D^{24}$ +36.7° (c 0.395, $CHCl_3$); ^{1}H nmr: 2.60 (1H, dd, J = 10, 15 Hz), 3.02 (1H, dd, J = 4, 15 Hz), 3.70-3.90 (1H, m), 3.83 (3H, s), 3.87 (6H, s), 4.20-4.30 (2H, m), 5.17 (2H, s), 5.25-5.44 (2H, br), 6.23 (1H, d, J = 2 Hz), 6.42 (1H, d, J = 2 Hz), 6.79 (2H, s), 7.51 (1H, d, J = 2 Hz), 7.68 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz); ir ($CHCl_3$): 3552, 1746, 1648, 1610 cm^{-1}; ms (m/z) 537 (M^+); HR-ms (m/z) Calcd for $C_{28}H_{27}NO_{10}$ (M^+): 537.16350. Found: 537.16247.

(3a*S*,*R*-Biar)-3a,4-Dihydro-8,9,11-trimethoxy-6,7-methylenedioxy-10-(4-nitrobenzyloxy)-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (18) A solution of **17** (1.60 g, 2.98 mmol), $Fe(ClO_4)_3 \cdot 6H_2O$ (3.0 g, 6.5 mmol), and CF_3CO_2H (20 ml) in CH_2Cl_2 (20 ml) was stirred at room temperature for 25 min. The mixture was taken up into AcOEt, and the organic layer was washed with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, successively and dried over $MgSO_4$. After evaporation of solvent, the residue was dissolved in DMF (15 ml), K_2CO_3 (1.8 g, 13 mmol) and CH_2I_2 (1.0 ml, 12.4 mmol) were added, and the mixture was stirred at 75 °C for 2 h. The reaction mixture was taken up into AcOEt, washed with H_2O and brine, then dried over $MgSO_4$. The evaporation of the solvent and chromatography of the residue (AcOEt-hexane=1:2) gave **18** as colorless foam (0.752 g, 46%); $[\alpha]_D^{24}$ -215.4° (c 0.565, $CHCl_3$); ^1H nmr: 2.43 (1H, dd, J = 1.4, 14 Hz), 2.96 (1H, dd, J = 6.6, 14 Hz), 3.38-3.60 (1H, m), 3.59 (3H, s), 3.78 (3H, s), 3.87 (3H, s), 4.09 (1H, dd, J = 9, 10 Hz), 4.46 (1H, t, J = 9 Hz), 5.20 (2H, s), 5.97 (1H, d, J = 1.5 Hz), 5.99 (1H, d, J = 1.5 Hz), 6.35 (1H, s), 6.60 (1H, s), 7.51 (1H, d, J = 3.4 Hz), 7.68 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz); ir ($CHCl_3$): 3004, 1752, 1676, 1608 cm^{-1}; ms (m/z) 547 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{25}NO_{10}$ (M^+): 547.14785. Found; 547.14736.

(3a*S*,*R*-Biar)-10-Benzyloxy-3a,4-dihydro-8,9,11-trimethoxy-6,7-methylenedioxydibenzo-[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (10c) **18** (277 mg, 0.51 mmol) was hydrogenated over 10% palladium on carbon (Pd-C) (20 mg) in AcOEt (20 ml) under H_2 (1 atm) for 45 min. The catalyst was filtered off, the filtrate was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. Evaporation of the solvent gave **19** as a colorless solid (214 mg, 100%). **19** (204 mg, 0.495 mmol) was heated at 60 °C with benzyl bromide (0.12 ml, 1 mmol) and K_2CO_3 (140 mg, 1.0 mmol) in DMF (5 ml) for 1.5 h, and cooled to room temperature. Et_3N (1 ml) was added, the mixture was stirred at room temperature for 30 min, and AcOEt was added. The resultant mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=2:3) to give **10c** as a colorless foam (212 mg, 83%); $[\alpha]_D^{25}$ -241.4° (c 0.215, $CHCl_3$); ^1H nmr: 2.42 (1H, d, J = 14 Hz), 2.97 (1H, dd, J = 7, 14 Hz), 3.35-3.60 (1H, m), 3.62 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.09 (1H, dd, J = 9, 10 Hz), 4.44 (1H, t, J = 9 Hz), 5.07 (1H, d, J = 10 Hz), 5.10 (1H, d, J = 10 Hz), 5.96 (1H, d, J = 1.5 Hz), 5.97 (1H, d, J = 1.5 Hz), 6.34 (1H, s), 6.57 (1H, s), 7.26-7.53 (6H, m); ir ($CHCl_3$): 1750, 1674, 1620 cm^{-1}; ms (m/z) 502 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{26}O_8$ (M^+): 502.16277. Found: 502.16278.

(3a*R*,13a*S*,*R*-Biar)-10-Benzyloxy-3a,4,13,13a-tetrahydro-13a-hydroxy-8,9,11-trimethoxy-6,7-methylenedioxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (11) and (3a*R*,13a*R*,*R*-Biar)-10-Benzyloxy-3a,4,13,13a-tetrahydro-13a-hydroxy-8,9,11-trimethoxy-6,7-methylenedioxydibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (20) To a mixture of **10c** (150 mg, 0.3 mmol) and manganese acetylacetonate ($Mn(acac)_2$) (90 mg, 0.35 mmol) in 2-propanol (6 ml) and THF (5 ml) was added phenylsilane ($PhSiH_3$) (0.25 ml, 2.0 mmol) under O_2 (1 atm), and the resultant mixture was stirred at room temperature for 44 h. AcOEt was added, the resultant mixture was washed with 2N-HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:2) to give **20** as a colorless oil (11 mg, 7%), **11** as a colorless solid (78 mg, 50%), and recovered **10c** (28 mg, 19% recovery). **20**; $[\alpha]_D^{24}$ +56.55° (c 0.55, $CHCl_3$); ^1H nmr: 1.90 (1H, s), 1.95-2.12 (1H, m), 2.56 (1H, d, J = 13 Hz), 2.59 (1H, dd, J = 11, 16 Hz), 2.88 (1H, dd, J = 9, 16 Hz), 3.42 (1H, d, J = 13 Hz), 3.71 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 4.02-4.18 (2H, m), 5.08 (2H, s), 5.96 (1H, d, J = 1.5 Hz), 5.98 (1H, d, J = 1.5 Hz), 6.38 (1H, s), 6.48 (1H, s), 7.26-7.48 (5H, m); ir (KBr): 3567, 1778, 1620, 1598 cm^{-1}; ms (m/z) 520 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{28}O_9$ (M^+): 520.17333. Found: 520.17374. **11**; mp 165-167 °C (colorless prisms from AcOEt-hexane); $[\alpha]_D^{24}$ -16.3° (c 0.245, $CHCl_3$); ^1H nmr: 2.50-2.84 (6H, m), 3.62 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 3.90 (1H, dd, J = 9, 11.5 Hz), 4.37 (1H, dd, J = 8, 9 Hz), 5.04 (1H, d, J = 11 Hz), 5.11 (1H, d, J = 11 Hz), 5.99 (2H, s), 6.30 (1H, s), 6.72 (1H, s), 7.26-7.52 (5H, m); ir (KBr): 3480, 1762, 1620, 1598 cm^{-1}; ms (m/z) 520 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{28}O_9$ (M^+): 520.17333. Found: 520.17242.

(6*S*,7*S*,*R*-Biar)-2-Benzyloxy-5,6,7,8-tetrahydro-6,7-dimethyl-1,3,12-trimethoxy-10,11-methylenedioxydibenzo[*a*,*c*]cycloocten-6-ol (21) To a refluxing solution of $LiAlH_4$ (70 g, 1.84 mmol) in THF (5 ml) was added a solution of **11** (70 mg, 0.135 mmol) in THF (5 ml), and the resultant mixture was heated under reflux for 15 min, and cooled to room temperature. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, the resultant mixture was stirred at room temperature for 10 min, and the insoluble material was filtered off. After evaporation of the solvent, the residue (79 mg) was dissolved in pyridine (1.0 ml), methanesulfonyl chloride (MsCl) (0.5 ml) was added, and the resultant mixture was stirred at 0 °C for 1 h. AcOEt was added, the mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue (80 mg) was dissolved in THF (5 ml) and the resulting mixture was added to a refluxing solution of $LiAlH_4$ (100 mg, 2.63 mmol) in THF (5 ml), the resultant mixture was heated under reflux for 5 min, and cooled to room temperature. The reaction was

quenched with $Na_2SO_4 \cdot 10H_2O$, the resultant mixture was stirred at room temperature for 15 min, and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:2) to give **21** as a colorless foam (35 mg, 53%); $[\alpha]_D^{26}$ +62.6° (c 0.115, $CHCl_3$); ^1H nmr: 0.82 (3H, d, J = 7 Hz), 1.25 (3H, s), 1.76-1.92 (2H, m), 2.33 (1H, dd, J = 7, 14 Hz), 2.35 (1H, d, J = 14 Hz), 2.56 (1H, dd, J = 2, 14 Hz), 2.69 (1H, d, J = 14 Hz), 3.55 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 5.06 (1H, d, J = 11 Hz), 5.10 (1H, d, J = 11 Hz), 5.95 (1H, d, J = 1.5 Hz), 5.97 (1H, d, J = 1.5 Hz), 6.48 (1H, s), 6.59 (1H, s), 7.26-7.51 (5H, m); ir ($CHCl_3$): 3564, 1620, 1594 cm^{-1}; ms (m/z) 492 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{32}O_7$ (M^+): 492.21480. Found: 492.21580.

Met A-III (3) **21** (32 mg, 0.065 mmol) was hydrogenated over 10% Pd-C (15 mg) in AcOEt (5 ml) under H_2 (1 atm) for 2 h. The catalyst was filtered off, then the filtrate was concentrated to give **3** as a colorless foam (28 mg, 100%); $[\alpha]_D^{26}$ +68.58° (c 0.155, $CHCl_3$); ^1H nmr: 0.82 (3H, d, J = 7 Hz), 1.25 (3H, s), 1.80-1.95 (2H, m), 2.33 (1H, d, J = 13 Hz), 2.34 (1H, dd, J = 7, 14 Hz), 2.60 (1H, dd, J = 1.7, 14 Hz), 2.68 (1H, d, J = 13 Hz), 3.41 (3H, s), 3.83 (3H, s), 3.94 (3H, s), 5.61 (1H, s), 5.89 (2H, s), 6.49 (1H, s), 6.63 (1H, s); ir ($CHCl_3$): 3540, 1618 cm^{-1}; ms (m/z) 402 (M^+); HR-ms (m/z) Calcd for $C_{22}H_{26}O_7$ (M^+): 402.16785. Found: 402.16792. [Natural product;[3] $[\alpha]_D^{24}$ +65° (c 0.48, $CHCl_3$); ^1H nmr: 0.82 (3H, d, J = 7 Hz), 1.25 (3H, s), 1.60 (1H, s), 1.87 (1H, s), 2.33 (1H, d, J = 13.5 Hz), 2.35 (1H, dd, J = 7, 14 Hz), 2.59 (1H, dd, J = 2, 14 Hz), 2.68 (1H, d, J = 13.5 Hz), 3.40 (3H, s), 3.83 (3H, s), 3.94 (3H, s), 5.60 (1H, s), 5.87 (2H, s), 6.49 (1H, s), 6.63 (1H, s)].

(*R*-Biar)-6,7-Dibenzyloxy-4,13-dihydro-8,9,10,11-tetramethoxy-6,7-methylenedioxy-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (12b) A solution of **10b** (1.10 g, 1.85 mmol), tris(triphenylphosphine)rhodium chloride ($Rh(PPh_3)_3Cl$) (70 mg, 0.076 mmol, 4 mol%), and triethylsilane (Et_3SiH) (0.02 ml, 0.13 mmol, 6.8 mol%) in toluene (25 ml) was heated under reflux for 17 h, and then the solvent was evaporated off. The residue was chromatographed (AcOEt-hexane=1:2) to give **12b** as a colorless foam (1.01 g, 92%); $[\alpha]_D^{24}$ +213.7° (c 0.655, $CHCl_3$); ^1H nmr: 2.92 (1H, dd, J = 4, 15 Hz), 3.11 (1H, d, J = 16 Hz), 3.32 (1H, dd, J = 4, 15 Hz), 3.55 (1H, d, J = 16 Hz), 3.70 (3H, s), 3.71 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 4.67 (2H, d, J = 3 Hz), 5.03-5.30 (4H, m), 6.56 (1H, s), 6.54 (1H, s), 7.25-7.56 (10H, m); ir ($CHCl_3$): 1746, 1668, 1596 cm^{-1}; ms (m/z) 594 (M^+); HR-ms (m/z) Calcd for $C_{36}H_{34}O_8$ (M^+): 594.22537. Found: 594.22665.

(6*S*,7*R*,*R*-Biar)-2,3-Dibenzyloxy-5,6,7,8-tetrahydro-6,7-bis(methanesulfonyloxymethyl)-1,10,11,12-tetramethoxydibenzo[*a*,*c*]cyclooctene-6,7-diol (23) and (6*R*,7*S*,*R*-Biar)-2,3-Di-

benzyloxy-5,6,7,8-tetrahydro-6,7-bis(methanesulfonyloxymethyl)-1,10,11,12-tetramethoxydibenzo[*a*,*c*]cyclooctene-6,7-diol (24) *To a refluxing solution of diisobutylaluminum hydride* (DIBAH) (1.5 M in toluene, 15 ml, 22.4 mmol) in THF (30 ml) was added a solution of **12b** (1.6 g, 2.7 mmol) in THF (30 ml), and the resultant mixture was heated under reflux for 20 min, and cooled to room temperature. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, the resultant mixture was stirred at room temperature for 30 min, and the insoluble material was filtered off. After evaporation of the solvent, the crude **22** (1.93 g) was *dissolved in acetone* (20 ml) *and* H_2O (5 ml), OsO_4 (30 mg) and *N*-methylmorpholine-*N*-oxide (NMO) (500 mg, 4.3 mmol) were added, and the resultant mixture was stirred at room temperature for 36 h. After addition of $NaHSO_3$, the mixture was concentrated and AcOEt was added. The separated organic layer was successively washed with H_2O, 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue (1.64 g) was dissolved in pyridine (15 ml), MsCl (3 ml) was added, and the resultant mixture was stirred at room temperature for 2 h. AcOEt was added, the mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=3:2) to give **23** (638 mg, 30%, colorless oil) and **24** (597 mg, 28%, colorless oil), which were used in the next reaction without further purification. **23**; ^{1}H nmr: 1.40-2.10 (2H), 2.52-2.84 (4H, m), 3.08 (3H, s), 3.12 (3H, s), 3.58 (3H, s), 3.65 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 4.21 (1H, d, J = 10 Hz), 4.22 (2H, s), 4.35 (1H, d, J = 10 Hz), 5.07 (1H, d, J = 11 Hz), 5.12 (1H, d, J = 11 Hz), 5.13 (2H, s), 6.61 (1H, s), 6.95 (1H, s), 7.26-7.52 (10H, m); ms (m/z) 692 (M^+-$MeSO_3H$). **24**; ^{1}H nmr: 1.30-1.90 (2H, br), 2.04-2.89 (4H, m), 3.11 (3H, s), 3.12 (3H, s), 3.57 (3H, s), 3.65 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 4.19 (2H, s), 4.26 (1H, d, J = 10 Hz), 4.37 (1H, d, J = 10 Hz), 5.10 (2H, s), 5.12 (1H, d, J = 10 Hz), 5.21 (1H, d, J = 10 Hz), 6.58 (1H, s), 7.00 (1H, s), 7.27-7.49 (10H, m); ms (m/z) 692 (M^+-$MeSO_3H$).

(6*R*,7*S*,*R*-Biar)-2,3-Dibenzyloxy-5,6,7,8-tetrahydro-1,10,11,12-tetramethoxy-6,7-dimethyldibenzo[*a*,*c*]cyclooctene-6,7-diol (25) To a refluxing suspension of $LiAlH_4$ (500 mg, 13 mmol) in THF (10 ml) was added a solution of **24** (590 mg, 0.75 mmol) in THF (20 ml) during 10 min, the resultant mixture was heated under reflux for 30 min, and cooled to room temperature. $Na_2SO_4 \cdot 10H_2O$ was added, and the resultant mixture was stirred at room temperature for 1.5 h. After removal of insoluble material by filtration, the filtrate was concentrated, and the residue was chromatographed (AcOEt-hexane=1:2) to give **25** as a colorless oil (190 mg, 42%); $[\alpha]_D^{27}$ +88.72° (c 0.195, $CHCl_3$); ^{1}H nmr: 0.94 (3H, s), 1.30 (3H, s), 2.35 (1H, d, J = 15 Hz), 2.53 (1H, d, J = 15 Hz), 2.64 (1H, d, J = 15 Hz), 2.72 (1H, d, J = 15 Hz), 1.80-2.80 (2H, br), 3.57

(3H, s), 3.69 (3H, s), 3.94 (3H, s), 3.95 (3H, s), 5.04-5.21 (4H, m), 6.63 (1H, s), 6.69 (1H, s), 7.24-7.52 (10H, m); ir ($CHCl_3$): 3544, 1594 cm^{-1}; ms (m/z) 600 (M^+); HR-ms (m/z) Calcd for $C_{36}H_{40}O_8$ (M^+): 600.27232. Found: 600.27112.

Met F (7) **25** (100 mg, 0.17 mmol) was hydrogenated over 10% Pd-C (10 mg) in AcOEt (5 ml) under H_2 (1 atm) for 24 h. The catalyst was filtered off, then the filtrate was concentrated to give **7** as a colorless solid (52 mg, 74%); mp 246.5-248.5 °C; $[\alpha]_D^{27}$ +118.4° (c 0.255, $CHCl_3$); ^1H nmr: 1.13 (3H, s), 1.33 (3H, s), 1.62 (2H, br), 2.37 (1H, d, J = 14 Hz), 2.58 (1H, d, J = 14 Hz), 2.65 (1H, d, J = 14 Hz), 2.80 (1H, d, J = 14 Hz), 3.30 (3H, s), 3.48 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 5.49 (1H, br), 5.65 (1H, br), 6.65 (1H, s), 6.76 (1H, s); ir (KBr): 3464, 3356, 1600 cm^{-1}; ms (m/z) 420 (M^+). Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.66; H, 6.66. [Natural product;[3] mp 217.5-220 °C (colorless prisms from Et_2O); $[\alpha]_D^{23}$ +107° (c 1.10, $CHCl_3$); ^1H nmr: 1.13 (3H, s), 1.33 (3H, s), 2.14 (2H, s), 2.37 (1H, d, J = 13.4 Hz), 2.58 (1H, d, J = 13.7 Hz), 2.66 (1H, d, J = 13.4 Hz), 2.80 (1H, d, J = 13.7 Hz), 3.31 (3H, s), 3.47 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 5.94 (2H, br), 6.66 (1H, s), 6.76 (1H, s)].

(*R*-Biar)-4,13-Dihydro-8,9,10,11-tetramethoxy-6,7-methylenedioxydibenzo[4,5:6,7]cyclo-octa[1,2-*c*]furan-1(3*H*)-one (12a). A solution of **10a** (1.27 g, 2.98 mmol), $Rh(PPh_3)_3Cl$ (100 mg, 0.11 mmol, 3.6 mol%), and Et_3SiH (0.05 ml, 0.31 mmol, 10 mol%) in toluene (25 ml) was heated under reflux for 14 h, and then the solvent was evaporated off. The residue was chromatographed (AcOEt-hexane=1:2) to give **12a** as a colorless solid (1.2 g, 94%); mp 171.5-172.5 °C (colorless needles from AcOEt); $[\alpha]_D^{24}$ +299.4° (c 0.315, $CHCl_3$); ^1H nmr: 2.98 (1H, dd, J = 3, 16 Hz), 3.30 (1H, dd, J = 3, 16 Hz), 3.09 (1H, d, J = 16 Hz), 3.53 (1H, d, J = 16 Hz), 3.72 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 4.66 (2H, d, J = 3 Hz), 6.00 (1H, d, J = 1.5 Hz), 5.97 (1H, d, J = 1.5 Hz), 6.39 (1H, s), 6.56 (1H, s); ir (KBr): 1756, 1740, 1672, 1620, 1600 cm^{-1}; ms (m/z) 426 (M^+). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.51; H, 5.43.

Met A-II (2) and (6*S*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6,7-dimethyl-1,10,11,12-tetramethoxy-2,3-methylenedioxydibenzo[*a*,*c*]cyclooctene-6,7-diol (26) To a refluxing solution of DIBAH (1.5 M in toluene, 2.5 ml, 3.75 mmol) in THF (5 ml) was added a solution of **12a** (133 mg, 0.26 mmol) in THF (5 ml), and the resultant mixture was heated under reflux for 10 min, and cooled to room temperature. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, the resultant mixture was stirred at room temperature for 30 min, and the insoluble material was filtered off. After evaporation of the solvent, the residue (146 mg) was dissolved in acetone (5 ml) and H_2O (1.5 ml), OsO_4 (5 mg), and NMO (70 mg, 0.6 mmol) were added, and the resultant mixture was stirred at room temperature for 17 h. After addition of AcOEt, the organic layer was successively

washed with H_2O, 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue (175 mg) was dissolved in CH_2Cl_2 (2.0 ml), pyridine (1 ml) and MsCl (0.5 ml) were added, and the resultant mixture was stirred at room temperature for 2 h. AcOEt was added, the mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the solution of the residue (370 mg) in THF (5 ml) was added to a refluxing suspension of $LiAlH_4$ (500 mg, 13.2 mmol) in THF (5 ml), the resultant mixture was heated under reflux for 20 min, and cooled to room temperature. $Na_2SO_4 \cdot 10H_2O$ was added, and the resultant mixture was stirred at room temperature for 0.5 h. After removal of insoluble material by filtration, the filtrate was concentrated, and the residue was chromatographed (AcOEt-hexane=1:1) to give **26** as colorless prisms (20 mg, 18%) and **2** as colorless needles (36 mg, 32%). **26**; mp 184-185 °C (colorless prisms from Et_2O-hexane); $[\alpha]_D^{23}$ +106.7° (c 0.135, $CHCl_3$); ^1H nmr: 1.14 (3H, s), 1.29 (3H, s), 2.04 (1H, s), 2.39 (1H, d, J = 14 Hz), 2.50 (1H, d, J = 14 Hz), 2.71 (1H, d, J = 14 Hz), 2.72 (1H, d, J = 14 Hz), 3.22 (1H, s), 3.57 (3H, s), 3.83 (3H, s), 3.89 (6H, s), 6.00 (2H, s), 6.56 (1H, s), 6.67 (1H, s); ir (KBr): 3392, 1622, 1594 cm^{-1}; ms (m/z) 432 (M^+). Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H 6.53. Found: C, 64.01; H, 6.68. **2**; mp 164.5-165 °C (colorless needles from Et_2O-hexane); $[\alpha]_D^{23}$ +94.12° (c 0.17, $CHCl_3$); ^1H nmr: 1.12 (3H, s), 1.31 (3H, s), 2.06 (1H, s), 3.20 (1H, s), 2.36 (1H, d, J = 14 Hz), 2.53 (1H, d, J = 14 Hz), 2.63 (1H, d, J = 14 Hz), 2.78 (1H, d, J = 14 Hz), 3.20 (1H, s), 3.53 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 5.97 (1H, d, J = 1.5 Hz), 5.972 (1H, d, J = 1.5 Hz), 6.60 (1H, s), 6.62 (1H, s); ir (KBr): 3488, 1620, 1598 cm^{-1}; ms (m/z) 432 (M^+). Anal. Calcd for $C_{23}H_{28}O_8$: C, 65.88; H, 6.53. Found: C, 65.59; H, 6.70. [Natural product;[3] mp 163-165 °C (colorless needles from EtOH-H_2O); $[\alpha]_D^{24}$ +71° (c 0.21, $CHCl_3$); ^1H nmr: 1.12 (3H, s), 1.30 (3H, s), 2.05 (1H, s), 2.36 (1H, d, J = 13.5 Hz), 2.53 (1H, d, J = 14 Hz), 2.63 (1H, d, J = 13.5 Hz), 2.78 (1H, d, J = 14 Hz), 3.19 (1H, s), 3.52 (3H, s), 3.85 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 5.97 (1H, d, J = 1.5 Hz), 5.972 (1H, d, J = 1.5 Hz), 6.60 (1H, s), 6.61 (1H, s)].

(*R*-Biar)-10-Benzyloxy-4,13-dihydro-8,9,11-trimethoxy-6,7-methylenedioxydibenzo-[4,5:6,7]cycloocta[1,2-*c*]furan-1(3*H*)-one (12c) A solution of **10c** (58 mg, 0.12 mmol), $Rh(PPh_3)_3Cl$ (10 mg, 0.01 mmol), and Et_3SiH (0.005 ml, 0.03 mmol) in toluene (5 ml) was heated under reflux for 22.5 h. After evaporation of the solvent, the residue was chromatographed (AcOEt-hexane=1:2) to give **12c** as a colorless solid (48.7 mg, 84%); $[\alpha]_D^{24}$ +223° (c 0.13, $CHCl_3$); ^1H nmr: 2.99 (1H, dd, J = 3, 15 Hz), 3.07 (1H, d, J = 15 Hz), 3.10 (1H, dd, J = 3, 15 Hz), 3.61 (1H, d, J = 15 Hz), 3.72 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 4.66 (2H, d, J = 3 Hz), 5.06 (2H, s), 5.97 (1H, d, J = 1.5 Hz), 5.99 (1H, d, J = 1.5 Hz),

6.39 (1H, s), 6.54 (1H, s), 7.26-7.51 (5H, m); ir ($CHCl_3$): 1748, 1670, 1598 cm^{-1}; ms (m/z) 502 (M^+); HR-ms (m/z) Calcd for $C_{29}H_{26}O_8$ (M^+): 502.16277. Found: 502.16269.

Met-D (5) and **(6*S*,7*R*,*R*-Biar)-5,6,7,8-Tetrahydro-6,7-dimethyl-1,10,12-trimethoxy-2,3-methylenedioxydibenzo[*a*,*c*]cyclooctene-6,7,11-triol (27)** To a refluxing solution of DIBAH (1.5 M in toluene, 3 ml, 4.5 mmol) in THF (10 ml) was added a solution of **12c** (273 mg, 0.55 mmol) in THF (5 ml), and the resultant mixture was heated under reflux for 15 min, and cooled to room temperature. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, the resultant mixture was stirred at room temperature for 30 min, and the insoluble material was filtered off. After evaporation of the solvent, the residue was dissolved in acetone (10 ml) and H_2O (2 ml), OsO_4 (5 mg), and NMO (200 mg) were added, and the resultant mixture was stirred at room temperature for 5 days. After addition of AcOEt, the organic layer was successively washed with H_2O, 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (8 ml), pyridine (4 ml) and MsCl (2 ml) were added, and the resultant mixture was stirred at room temperature for 3 h. AcOEt was added, the mixture was washed successively with 2N HCl, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography (AcOEt-hexane=3:2) to give a colorless foam (154 mg). The solution of this foam (154 mg, 0.22 mmol) in THF (5 ml) was added to a refluxing suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (5 ml), the resultant mixture was heated under reflux for 15 min, and cooled to room temperature. $Na_2SO_4 \cdot 10H_2O$ was added, and the resultant mixture was stirred at room temperature for 0.5 h. After removal of insoluble material by filtration, the filtrate was concentrated, the residue was chromatographed (AcOEt-hexane=1:1), and the residue was hydrogenated in AcOEt (5 ml) over 10% Pd-C (10 mg) under H_2 (1 atm) at room temperature for 3 h. After filtration, the filtrate was concentrated and purified by chromatography (AcOEt-hexane=1:1) to give **27** as colorless prisms (15 mg, 16%) and **5** as colorless prisms (33 mg, 36%). **5**; mp 131-132.5 °C (colorless prisms from Et_2O-hexane); $[\alpha]_D^{24}$ +117.33° (c 0.15, $CHCl_3$); ^1H nmr: 1.13 (3H, s), 1.31 (3H, s), 2.05 (1H, s), 2.37 (1H, d, J = 14 Hz), 2.52 (1H, d, J = 14 Hz), 2.63 (1H, d, J = 14 Hz), 2.78 (1H, d, J = 14 Hz), 3.23 (1H, s), 3.41 (3H, s), 3.85 (3H, s), 3.95 (3H, s), 5.64 (1H, s), 5.98 (2H, s), 6.61 (1H, s), 6.62 (1H, s); ir (KBr): 3424, 1616 cm^{-1}; ms (m/z) 418 (M^+); HR-ms (m/z) Calcd for $C_{22}H_{26}O_8$ (M^+): 418.16277. Found: 418.16285. [Natural product;[3] mp 128-130 °C (colorless prisms from MeOH-H_2O); $[\alpha]_D^{23}$ +80.5° (c 1.49, $CHCl_3$); ^1H nmr: 1.13 (3H, s), 1.31 (3H, s), 1.74 (1H, s), 2.08 (1H, s), 2.37 (1H, d, J = 13.5 Hz), 2.52 (1H, d, J = 14 Hz), 2.64 (1H, d, J = 13.5 Hz), 2.77 (1H, d, J = 14 Hz), 3.23 (1H, s), 3.41 (3H, s), 3.84 (3H, s), 3.95 (3H, s), 5.80 (1H, s), 5.98 (2H, s), 6.61 (1H, s), 6.62 (1H, s)]. **27**; mp 215-217

°C (colorless prisms from Et_2O-hexane); $[\alpha]_D^{24}$ +98.57° (c 0.28, $CHCl_3$); ^1H nmr: 1.10 (3H, s), 1.29 (3H, s), 2.03 (1H, s), 2.37 (1H, d, J = 14 Hz), 2.44 (1H, d, J = 14 Hz), 2.72 (2H, d, J = 14 Hz), 3.16 (1H, s), 3.47 (3H, s), 3.82 (3H, s), 3.93 (3H, s), 5.55 (1H, s), 6.01 (2H, s), 6.57 (1H, s), 6.67 (1H, s); ir (KBr): 3492, 1614 cm^{-1}; ms (m/z) 418 (M^+); HR-ms (m/z) Calcd for $C_{22}H_{26}O_8$ (M^+): 418.16277. Found: 418.16265.

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